# ISOXAZOLES

## Part One

*This is a part of the forty-ninth volume in the series*

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

**EDWARD C. TAYLOR**, *Editor*

**ARNOLD WEISSBERGER**, *Founding Editor*

# ISOXAZOLES

## Part One

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University of Pavia,
Pavia, Italy



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*To the memory of*
ADOLFO QUILICO
*the great pioneer*
*of isoxazole renaissance*

# The Chemistry of Heterocyclic Compounds
## Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

*The Chemistry of Heterocyclic Compounds*, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has 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 which impinge on almost all aspects of modern organic and medicinal chemistry, 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 heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes are of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction created as many problems as it solves, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry*, and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

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# Preface

In the seventeenth volume of the series *The Chemistry of Heterocyclic Compounds*, published in 1962, Part I was devoted to *Isoxazoles and Related Compounds*. The authors, Adolfo Quilico and Giovanni Speroni, covered the entire chemistry of this nucleus in 232 pages, elaborating about 880 references up to 1958. Nowadays, more than 15,500 papers, dealing with the same nucleus, are known in the literature. This huge increase in published work in the past 30-year period necessitated a complete reelaboration of the monograph on this important class of heterocyclic compounds. The material has been divided into three parts, to be published in separate volumes.

This volume, Part 1, is devoted to mononuclear isoxazoles and to their dihydro- and tetrahydro derivatives. Each chapter represents a survey on physical properties, syntheses, and reactions of the three classes of compounds. Owing to the increasing importance of isoxazoles as intermediates in the synthesis of complex molecules, special paragraphs on this subject are added at the end of each chapter. In this volume the literature reported in *Chemical Abstracts* through 1984 (Volume 101) has been covered. Although every reasonable effort has been made to include in the text all significant material, no attempt has been made to incorporate all available data, deferring the task to the forthcoming tabular survey. Treatment of theoretical and mechanistic aspects has been kept to a minimum. References have been collected in a single list at the end of the volume; see page 1 of Chapter 1 for an explanation of their numbering.

In Parts 2 and 3 of this monograph, chapters on isoxazolones, benzisoxazoles, anthranils, and other polynuclear isoxazole derivatives, as well as the tabular survey, an updating of Part 1, and a chapter on applications of isoxazole compounds, will be provided.

We have been greatly helped in the preparation of this manuscript over several years by many people. First, we wish to acknowledge the continued encouragement and valuable assistance of the late Professor A. Quilico and the constant advice of the late Professor G. Speroni. Outstanding help in collecting data and typing the manuscript has been provided by Drs. G. D'Alò, P. Comotti, and C. Montepiani. Careful reading and critical supervision of the text by our colleagues Professors K. N. Houk, P. Caramella, G. Bianchi, R. Gandolfi, F. Marinone Albini, A. Gamba Invernizzi, A. Corsico Coda, and Dr. G. Mellerio are gratefully acknowledged. Warm thanks are due especially to Professor Franca Marinone Albini also for his attentive check of the proofs and of the camera-ready material, as well as for preparation of the subject index. Grateful thanks are also due to the Consiglio Nazionale delle Ricerche (Rome) for financial support of our multidecade research work on isoxazole chemistry. Our thanks are also due to the series editor Professor E. C. Taylor and to the

staff of John Wiley & Sons for their help in improving the language and in solving printing problems.

P. GRÜNANGER
P. VITA-FINZI

*Pavia, Italy*
*June 1990*

# Contents


**1. ISOXAZOLES** **1**

1.1 Introduction . . . . . 1
1.2 Physicochemical Properties . . . . . 3
1.2.1 Infrared Spectra . . . . . 3
1.2.2 Ultraviolet Spectra . . . . . 7
1.2.3 Nuclear Magnetic Resonance Spectra . . . . . 24
1.2.3.1 PMR Spectra . . . . . 24
1.2.3.2 $^{13}$C-NMR Spectra . . . . . 45
1.2.3.3 $^{14}$N- and $^{15}$N-NMR Spectra . . . . . 55
1.2.3.4 Other Nuclei NMR Spectra . . . . . 58
1.2.4 Mass Spectra . . . . . 59
1.2.5 Other Spectra . . . . . 88
1.2.5.1 Microwave Spectra . . . . . 88
1.2.5.2 Photoelectron Spectra . . . . . 88
1.2.5.3 Electron Paramagnetic Resonance Spectra . . . . 90
1.2.5.4 Electron Spin Resonance Spectra . . . . . 90
1.2.5.5 Nuclear Quadrupole Resonance Spectra . . . . . 91
1.2.5.6 Other Spectra . . . . . 92
1.2.6 Crystal and Molecular Structure . . . . . 92
1.2.7 Dipole Moments . . . . . 98
1.2.8 Theoretical Calculations . . . . . 103
1.2.8.1 Reactivity, Aromaticity, and Electron Density . . . 103
1.2.8.2 Molecular Geometry . . . . . 106
1.2.8.3 Basicity and Dipole Moments . . . . . 107
1.2.8.4 Ionization Potentials . . . . . 109
1.2.8.5 Molecular Core Binding Energy . . . . . 110
1.2.8.6 Spectroscopic Data and Conformational Analysis . 110
1.2.9 Basicity . . . . . 114
1.2.10 Miscellaneous Data . . . . . 118
1.2.11 Analytical Methods . . . . . 121
1.3 Methods of Preparation . . . . . 125
1.3.1 [CCC + NO] Processes . . . . . 126
1.3.1.1 Oximation of 1,3-Dicarbonyl (and Related) Compounds . . . . . 126
1.3.1.2 Oximation of $\alpha,\beta$-Acetylenic Carbonyl (and Related) Compounds . . . . . 149
1.3.1.3 Oximation of $\alpha,\beta$-Dihalocarbonyl (and Related) Compounds . . . . . 155
1.3.1.4 Oximation of $\alpha,\beta$-Ethylenic Carbonyl (and Related) Compounds $\beta$-Substituted with Electron-

Withdrawing Groups . . . . . 157
1.3.1.5 Oximation of α,β-Ethylenic Carbonyl (and Related) Compounds . . . . . 171
1.3.1.6 Other Oximation Reactions . . . . . 173
1.3.1.7 Synthesis from Unsaturated Compounds and Nitric (Nitrous) Acid . . . . . 176
1.3.1.8 Nitrosation of Ketodicarboxylic Esters . . . . . 182
1.3.2 [CNO + CC] Processes . . . . . 183
1.3.2.1 Cycloaddition of Nitrile Oxides (or Their Precursors) to Acetylenic Compounds . . . . . 183
1.3.2.2 Cycloaddition of Nitrile Oxides (or Their Precursors) to Ethylenic Compounds . . . . . 196
1.3.2.3 Cycloaddition of Nitrile Oxides (or Their Precursors) with Active Methylene Compounds . . . . . 203
1.3.2.4 Cycloaddition of Nitrile Oxides (or Their Precursors) with Sodium Acetylides or Acetylenic Grignard Reagents . . . . . 207
1.3.2.5 Other [CNO + CC] Processes . . . . . 209
1.3.3 [CNO + 2C] Processes: Syntheses from Nitro Derivatives . 209
1.3.4 [CCNO + C] Processes . . . . . 215
1.3.4.1 Synthesis from Oxime Dilithium Salts and Carboxylic Acid Derivatives . . . . . 215
1.3.4.2 Reaction of α-Chloroketoximes with Ylides . . . . 218
1.3.5 [CCCN + O] Process . . . . . 218
1.3.6 Cyclization Processes . . . . . 218
1.3.6.1 [OCCCN] Processes . . . . . 218
1.3.6.2 [CCCON] Processes . . . . . 220
1.3.6.3 [CCNOC] Processes . . . . . 221
1.3.6.4 [CCCNO] Processes . . . . . 221
1.3.7 From Heterocyclic Compounds . . . . . 227
1.3.7.1 From Other 1,2-Oxazole Derivatives . . . . . 227
1.3.7.2 From Other Heterocycles . . . . . 248
1.4 Chemical Properties . . . . . 264
1.4.1 Protonation and Quaternization . . . . . 265
1.4.2 Complexation . . . . . 268
1.4.2.1 Metallic Complexes . . . . . 268
1.4.2.2 Molecular Complexes . . . . . 273
1.4.3 Reduction Reactions . . . . . 273
1.4.3.1 Hydrogenolytic Ring Cleavage . . . . . 273
1.4.3.2 Reductions without Ring Cleavage . . . . . 281
1.4.4 Oxidation Reactions . . . . . 284
1.4.5 Thermolysis and Photolysis . . . . . 285
1.4.6 Reactions with Nucleophiles . . . . . 298
1.4.6.1 Reactions with Ring Cleavage . . . . . 298

1.4.6.2 Reactions Without Ring Cleavage . . . . . 319
1.4.7 Carbanionic Condensations . . . . . 324
1.4.7.1 Metallation . . . . . 324
1.4.7.2 Other Base-Promoted Condensations . . . . . 331
1.4.8 Grignard Reagents . . . . . 333
1.4.9 Electrophilic Substitutions . . . . . 334
1.4.9.1 Nitration . . . . . 335
1.4.9.2 Sulfonation . . . . . 337
1.4.9.3 Halogenation . . . . . 337
1.4.9.4 Other Substitutions . . . . . 340
1.4.10 Ring Transformations into Other Heterocyclic Systems . . . . . 341
1.4.10.1 Transformations into Three-Membered Heterocycles . . . . . 342
1.4.10.2 Transformations into Four-Membered Heterocycles . . . . . 343
1.4.10.3 Transformations into Five-Membered Heterocycles, Containing One Heteroatom . . . . . 343
1.4.10.4 Transformations into Five-Membered Heterocycles, Containing Two Heteroatoms . . . . . 347
1.4.10.5 Transformations into Five-Membered Heterocycles, Containing Three or Four Heteroatoms . . . . . 354
1.4.10.6 Transformations into Six-Membered Heterocycles, Containing One Heteroatom . . . . . 359
1.4.10.7 Transformations into Six-Membered Heterocycles, Containing More than One Heteroatom . . . . . 366
1.4.10.8 Transformations into Seven-Membered Heterocycles . . . . . 369
1.4.10.9 Transformations into Heterocyclic Condensed Systems . . . . . 370
1.4.11 Other Reactions Without Ring Cleavage . . . . . 371
1.4.12 Use of Isoxazoles as Key Intermediates in Synthetic Design 391
1.4.12.1 Syntheses of Aliphatic Compounds . . . . . 393
1.4.12.2 Syntheses of Alicyclic Compounds . . . . . 400
1.4.12.3 Syntheses of Aromatic Compounds . . . . . 408
1.4.12.4 Syntheses of $\beta$-Lactones and $\beta$-Lactams . . . . . 413
1.4.12.5 Syntheses of $\gamma$-Butyrolactams . . . . . 413

**2. ISOXAZOLINES (DIHYDROISOXAZOLES) 417**

2.1 Introduction . . . . . 417
2.2 2-Isoxazolines . . . . . 418
2.2.1 Physicochemical Properties . . . . . 418
2.2.1.1 Infrared Spectra . . . . . 418

2.2.1.2 Ultraviolet and Fluorescence Spectra . . . . . 419
2.2.1.3 Nuclear Magnetic Resonance Spectra. . . . . 421
2.2.1.4 Mass Spectrometry. . . . . 441
2.2.1.5 Other Spectra: Circular Dichroism . . . . . 452
2.2.1.6 Crystal and Molecular Structure . . . . . 452
2.2.1.7 Dipole Moments. . . . . 456
2.2.1.8 Theoretical Calculations . . . . . 457
2.2.1.9 Miscellaneous Data . . . . . 458
2.2.1.10 Chromatographic Analysis . . . . . 459
2.2.2 Syntheses . . . . . 460
2.2.2.1 [CCC + NO] Processes. . . . . 461
2.2.2.2 [CNO + CC] Processes: Cycloaddition of Nitrile Oxides and Their Precursors to Ethylenic Compounds . . . . . 475
2.2.2.3 [CNO + C + C] Process: Reaction of Nitrile Oxides with Ylides . . . . . 523
2.2.2.4 [CCNO + C] Processes. . . . . 524
2.2.2.5 [CCCNO] Processes . . . . . 525
2.2.2.6 Syntheses from Heterocyclic Compounds . . . . . 530
2.2.2.7 Miscellaneous Methods. . . . . 539
2.2.3 Reactions . . . . . 540
2.2.3.1 Reactions without Ring Cleavage . . . . . 541
2.2.3.2 Reactions with Ring Cleavage . . . . . 557
2.2.3.3 Use of 2-Isoxazolines as Key Intermediates in Synthetic Design . . . . . 572

2.3 2-Isoxazoline *N*-Oxides . . . . . 603
2.3.1 Physical Properties. . . . . 603
2.3.2 Methods of Preparation . . . . . 607
2.3.2.1 From 1,3-Dinitroalkanes (**353**: X = $NO_2$) or Their Precursors. . . . . 607
2.3.2.2 From 3-Halo-1-nitroalkanes (**353**: X = Br) (Pathway *e*) . . . . . 610
2.3.2.3 From Diazoalkanes (**353**: X = $N_2^+$) (Pathway *f*) . . . . . 612
2.3.2.4 From Ylides [**353**: X = $R_2S(O)^+$] (Pathway *g*) . . . . . 612
2.3.2.5 Miscellaneous Methods. . . . . 613
2.3.3 Chemical Properties . . . . . 614
2.3.3.1 Deoxygenation . . . . . 615
2.3.3.2 Dehydration. . . . . 615
2.3.3.3 Reduction. . . . . 617
2.3.3.4 Oxidation . . . . . 618
2.3.3.5 Reaction with Grignard Reagents . . . . . 618
2.3.3.6 Rearrangement Reactions. . . . . 619

2.3.3.7 Miscellaneous Reactions . . . . . 620

2.4 3-Isoxazolines . . . . . 621
2.5 4-Isoxazolines . . . . . 625
2.5.1 Physical Properties . . . . . 626
2.5.2 Methods of Preparation . . . . . 630
2.5.2.1 [CNO + CC] Cycloaddition Reaction . . . . . 630
2.5.2.2 [CCC + NO] Process . . . . . 637
2.5.2.3 Syntheses from Isoxazole or Isoxazolidine Derivatives . . . . . 638
2.5.2.4 Miscellaneous Methods . . . . . 640
2.5.3 Chemical Properties . . . . . 641
2.5.3.1 Thermolysis . . . . . 641
2.5.3.2 Other Ring-Opening Reactions . . . . . 646
2.5.3.3 Addition Reactions to the CC Double Bond . . . 647

**3. ISOXAZOLIDINES (Tetrahydroisoxazoles) 649**

3.1 Introduction . . . . . 649
3.2 Physicochemical Properties . . . . . 649
3.2.1 Infrared Spectra . . . . . 650
3.2.2 Ultraviolet Spectra . . . . . 650
3.2.3 Nuclear Magnetic Resonance Spectra . . . . . 650
3.2.3.1 PMR Spectra . . . . . 651
3.2.3.2 $^{13}$C-NMR Spectra . . . . . 666
3.2.3.3 $^{15}$N-NMR Spectra . . . . . 669
3.2.3.4 $^{19}$F- and $^{31}$P-NMR Spectra . . . . . 669
3.2.4 Mass Spectra . . . . . 670
3.2.5 Other Spectra . . . . . 674
3.2.6 Crystal and Molecular Structure . . . . . 675
3.2.7 Dipole Moments . . . . . 678
3.2.8 Invertomers . . . . . 679
3.2.9 Theoretical Calculations . . . . . 683
3.2.10 Basicity . . . . . 683
3.2.11 Miscellaneous Data . . . . . 684
3.2.12 Analysis . . . . . 684
3.3 Synthesis 685
3.3.1 [CNO + CC] Processes . . . . . 686
3.3.1.1 Cycloaddition of Nitrones to Ethylenic Compounds 686
3.3.1.2 Cycloaddition of Nitronic Esters to Double-Bond Compounds . . . . . 710
3.3.1.3 Dimerization of Nitrones . . . . . 721
3.3.1.4 Cycloaddition of Oximes to Ethylenic Compounds . . . . . 722
3.3.2 [CCC + NO] Processes . . . . . 725

3.3.2.1 Syntheses from 1,3-Dihalo Compounds . . . . . 725
3.3.2.2 Oximation of $\alpha,\beta$-Ethylenic Carbonyl Compounds . . . . . 725
3.3.2.3 Other Processes . . . . . 727
3.3.3 [CCCN + O] Process . . . . . 728
3.3.4 Cyclization Processes . . . . . 728
3.3.4.1 [OCCCN] Process . . . . . 728
3.3.4.2 [NOCCC] Process . . . . . 729
3.3.4.3 [CCCNO] Processes . . . . . 729
3.3.5 From Heterocyclic Compounds . . . . . 730
3.3.5.1 From Other 1,2-Oxazole Derivatives . . . . . 730
3.3.5.2 From Other Heterocycles . . . . . 732
3.4 Chemical Properties . . . . . 733
3.4.1 Formation of Salts and Quaternization . . . . . 733
3.4.2 Hydrogenolysis . . . . . 734
3.4.3 Oxidation . . . . . 737
3.4.4 Thermolysis . . . . . 738
3.4.4.1 1,3-Dipolar Cycloreversion . . . . . 738
3.4.4.2 N—O Bond Cleavage . . . . . 740
3.4.4.3 Elimination Reactions . . . . . 742
3.4.4.4 Decomposition to Carbonyl Compounds . . . . . 742
3.4.5 Photolysis . . . . . 743
3.4.6 Decomposition by Acids . . . . . 744
3.4.7 Decomposition by Bases . . . . . 747
3.4.8 Nucleophilic Reactivity . . . . . 750
3.4.9 Other Reactions in Side Chains . . . . . 752
3.4.10 Use of Isoxazolidines as Key Intermediates in Synthetic Design . . . . . 753
3.4.10.1 Alkaloids via Intermolecular Nitrone Cycloadditions . . . . . 754
3.4.10.2 Alkaloids via Intramolecular Nitrone Cycloadditions . . . . . 761
3.4.10.3 Other Nitrogen-Containing Products . . . . . 765
3.4.10.4 Nitrogen-Free Systems . . . . . 774

**References . . . . . 779**

**Index . . . . . 867**

# List of Tables


Table 1.1. Isoxazole fundamental IR vibrations and assignments, 4
Table 1.2. IR data for the CH vibrations of methyl- and dimethyl-isoxazoles, 5
Table 1.3. UV data of isoxazole and alkylisoxazoles, 8
Table 1.4. UV data of arylisoxazoles, 10
Table 1.5. UV data of 3-(3,5-dichloro-2,4,6-trimethyl)-5-arylisoxazoles, 13
Table 1.6. UV data of polyisoxazoles, 14
Table 1.7. UV data of isoxazoles with unsaturated substituents, 15
Table 1.8. UV data of alkylarylisoxazoles, 17
Table 1.9. UV data of isoxazole carboxylic acids and derivatives, nitriles and carbonyl compounds, 18
Table 1.10. UV data of 5-isoxazolepolyenealdehydes, 19
Table 1.11. UV data of nitroisoxazoles, 20
Table 1.12. UV data of hydroxy-, alkoxy- and aminoisoxazoles, 21
Table 1.13. PMR data of isoxazole, 25
Table 1.14. PMR data of alkylisoxazoles, 26
Table 1.15. PMR data of aryl-, diaryl-, and arylheteroarylisoxazoles, 27
Table 1.16. PMR data of alkylarylisoxazoles, 29
Table 1.17. PMR data of 3,5-diarylisoxazoles, 30
Table 1.18. PMR data of 3-, 4-, and 5-monosubstituted isoxazoles, 32
Table 1.19. PMR data of disubstituted isoxazoles, 33
Table 1.20. PMR data of hydroxy- and methoxyisoxazoles, 35
Table 1.21. PMR data of aminoisoxazoles and derivatives, 36
Table 1.22. PMR chemical shifts of methyl and other groups in trisubstituted isoxazoles, 38
Table 1.23. PMR data of isoxazolium salts, 42
Table 1.24. PMR coupling constants of isoxazole and methyl derivatives, 44
Table 1.25. $^{13}$C-NMR chemical shifts of isoxazole and derivatives, 46
Table 1.26. $^{13}$C-NMR chemical shifts and $^{13}$C-$^{15}$N coupling constants, 48
Table 1.27. $^{13}$C-NMR chemical shifts of the isoxazole ring carbon atoms for 3,5-diarylisoxazoles, 49
Table 1.28. $^{13}$C-NMR chemical shifts of the isoxazole ring carbon atoms for isoxazolium salts, 50
Table 1.29. $^{13}$C-NMR chemical shifts of the isoxazole ring carbon atoms of 3-phenoxymethylisoxazolinones and derivatives, 52
Table 1.30. $^{13}$C-NMR chemical shifts at 30° of 3-aryl-1-(3,4-dimethyl-5-isoxazolyl)triazenes, 52
Table 1.31. Calculated EHT net charges for isoxazole, 53
Table 1.32. Coupling constants $J_{C-H}$ of isoxazoles, 54
Table 1.33. Nitrogen chemical shifts of isoxazole and derivatives, 55

Table 1.34. $^{2}J(^{15}N\text{-}H_3)$ coupling constants, 58
Table 1.35. $^{17}O$-NMR chemical shifts and line widths of furan, isoxazole, and furazan derivatives, 59
Table 1.36. MIKE spectrum of isoxazole and stable fragment ions, 60
Table 1.37. Mass spectra of isoxazole and methyl derivatives, 62
Table 1.38. Mass spectra of alkylarylisoxazoles, 65
Table 1.39. Mass spectra of arylisoxazoles, 68
Table 1.40. Mass spectra of haloisoxazoles, 75
Table 1.41. Mass spectra of isoxazolecarboxylic acids and esters, 77
Table 1.42. Mass spectra of hydroxylated isoxazoles, 78
Table 1.43. Mass spectra of isoxazolylketones, 79
Table 1.44. Mass spectra of nitroisoxazoles, 82
Table 1.45. Mass spectra of alkoxyisoxazoles, 84
Table 1.46. Experimental and calculated (CNDO/S-CI) shake-up energy and intensity of isoxazole, 90
Table 1.47. Bond lengths and angles for the rings of isoxazole derivatives, 93
Table 1.48. Bond lengths and angles of a methylenetriisoxazole, 94
Table 1.49. Bond lengths and angles of diisoxazoles, 96
Table 1.50. Electric dipole moments of substituted isoxazoles, 99
Table 1.51. Calculated $\pi$-electron densities and $\pi$-bond orders of isoxazole, 105
Table 1.52. Calculated bond lengths and bond angles of the isoxazole molecule, 106
Table 1.53. Geometries of N-protonated isoxazole, 106
Table 1.54. Calculated dipole moment of isoxazole, 108
Table 1.55. MINDO/3 calculations of molecular vibration frequencies of isoxazole, 111
Table 1.56. $^{14}N$ Quadrupole coupling constants, 112
Table 1.57. $pK_a$ values of isoxazole derivatives, 115
Table 1.58. $pK_a$ values of isoxazole monocarboxylic acids, 116
Table 1.59. Base strengths ($pK_a$ values of conjugated acids) of isoxazolinones and hydroxyisoxazoles, 117
Table 1.60. Thermodinamic parameters of isoxazole and derivatives, 120
Table 1.61. Magnetic susceptibility of metal complexes of isoxazole and derivatives, 121
Table 1.62. Isoxazoles from asymmetrically substituted $\beta$-diketones, 133
Table 1.63. Synthesis of 3- and 5-alkyl-isoxazoles, 160
Table 1.64. Synthesis of isoxazoles from $\beta$-OR-$\alpha,\beta$-ethylenic ketones and aldehydes, 162
Table 1.65. Synthesis of isoxazoles from $\beta$-NRR′-$\alpha,\beta$-ethylenic ketones and aldehydes, 165
Table 1.66. Synthesis of isoxazoles from $\beta$-halo-$\alpha,\beta$-ethylenic nitriles, 169
Table 1.67. Synthesis of isoxazoles from $\beta$-substituted $\alpha,\beta$-ethylenic nitriles, 170

Table 1.68. Reaction of benzonitrile oxides with arylacetylenes: percentage yield of acetylenic oximes in the reaction mixture, 184
Table 1.69. Cycloaddition of nitrile oxides to monosubstituted alkynes, 185
Table 1.70. Cycloaddition of nitrile oxides to 1,2-disubstituted alkynes, 186
Table 1.71. Synthesis of isoxazoles from functionalized nitrile oxides, 190
Table 1.72. Cycloaddition of nitrile oxides to β-haloalkenes, 197
Table 1.73. Synthesis of isoxazoles from β-azidovinyl ketones and related compounds, 219
Table 1.74. Synthesis of 3-haloisoxazoles from β-nitroketones, 222
Table 1.75. Oxidative conversion of 2-isoxazolines to isoxazoles, 228
Table 1.76. Synthesis of isoxazoles from 5-amino-2-isoxazolines, 235
Table 1.77. Synthesis of 3-arylisoxazoles and of dimethyl 3-arylisoxazole-4,5-dicarboxylates from norbornadiene derivatives and nitrile oxides, 243
Table 1.78. Synthesis of isoxazoles from 3-acylbenzofurans, 249
Table 1.79. Metallic complexes of isoxazole derivatives, 270
Table 1.80. Reduction of isoxazoles to β-enaminoketones, 275
Table 1.81. Selected catalytic hydrogenations of isoxazoles, 282
Table 1.82. Thermal isomerization of 5-aminoisoxazoles to azirines, 290
Table 1.83. Photochemical conversion of isoxazoles into 1-azirines and oxazoles, 294
Table 1.84. Base-promoted isomerization of 3-unsubstituted isoxazoles, 300
Table 1.85. Isomerization of 3-unsubstituted isoxazoles to α-cyanocarbonyl compounds, 303
Table 1.86. Reactions of isoxazolium salts with Grignard reagents, 313
Table 1.87. Action of bases on 2,3,5-tri- or tetra-substituted isoxazolium salts, 318
Table 1.88. Nucleophilic substitutions in isoxazole side chain, 323
Table 1.89. Synthesis of styrylisoxazolium salts, 332
Table 1.90. Reactivities toward deuteriodeprotonation, 335
Table 1.91. Nitration of aryl-substituted isoxazoles, 336
Table 1.92. Ring rearrangements of isoxazole derivatives, 355
Table 1.93. Transformations of 5-acylaminoisoxazoles into pyrimidin-4-ones, 367
Table 1.94. Synthesis of aminoisoxazoles through Hofmann or Curtius reaction, 383
Table 2.1. UV data of 2-isoxazolines, 420
Table 2.2. PMR data of 3-unsubstituted 2-isoxazolines, 422
Table 2.3. PMR data of 3-substituted 2-isoxazolines, 423
Table 2.4. PMR data of 3-substituted-4-methoxycarbonyl-2-isoxazolines, 424
Table 2.5. PMR data of 3,5-disubstituted 2-isoxazolines, 425
Table 2.6. PMR data of 3,4,5-trisubstituted 2-isoxazolines, 428
Table 2.7. PMR data of 4-acyl- and 5-acyl-2-isoxazolines, 430

Table 2.8. PMR data of 3,5,5-trisubstituted 2-isoxazolines, 432
Table 2.9. PMR data of 3,4,5,5-tetrasubstituted 2-isoxazolines, 433
Table 2.10. PMR data of 5-amino-3-aryl-4-methylene-2-isoxazolines, 434
Table 2.11. $^{13}$C-NMR chemical shifts of 2-isoxazoline carbon atoms, 437
Table 2.12. $^{13}$C-NMR chemical shifts of methyl groups on 2-isoxazoline ring, 439
Table 2.13. Optimum geometries (STO-3G) for 2-isoxazoline, 458
Table 2.14. Ring-chain tautomerism of 5-hydroxy-2-isoxazolines, 472
Table 2.15. Relative reactivities of dipolarophiles toward benzonitrile oxide, 492
Table 2.16. Regioisomer ratios for the cycloaddition of nitrile oxides to CC double bond compounds, 494
Table 2.17. Cycloaddition of nitrile oxides to chiral allylic ethers and alcohols, 499
Table 2.18. Cycloaddition of nitrile oxides to vinylglycine derivatives, 500
Table 2.19. Site-specificity in the cycloaddition of nitrile oxides to azaeptafulvene derivatives, 502
Table 2.20. Cycloaddition of nitrile oxides to 1,2-dialkylethylenes, 506
Table 2.21. Cycloaddition of nitrile oxides to 5-vinylisoxazole derivatives, 508
Table 2.22. Cycloaddition of nitrile oxides to *trans*-$\beta$-methylstyrenes, 510
Table 2.23. Cycloaddition of nitrile oxides to allenic ethers, 512
Table 2.24. Cycloaddition of nitrile oxides to acyclic sulfur-containing olefins, 518
Table 2.25. Competition between cyclization and elimination in base treatment of quaternary salts $[ArC(=NOH)CHRCHR'NR_2''(Me)]^+$, 527
Table 2.26. Oxidative cyclization of phenolic oximes to spiroisoxazolines, 528
Table 2.27. Alkylation of 2-isoxazolines, 532
Table 2.28. Synthesis of 2-isoxazolines from 2-methoxyisoxazolidines, 534
Table 2.29. Synthesis of 2-isoxazolines from 4-methylenepyrans, 539
Table 2.30. Monocyclic 2-isoxazolinium salts, 542
Table 2.31. Nucleophilic substitution at position 3 of 2-isoxazolines, 549
Table 2.32. Thermolysis of 2-isoxazoline derivatives, 558
Table 2.33. Photolysis products from monocyclic 2-isoxazolines, 560
Table 2.34. $\gamma$-Amino alcohols from reduction of hydrocarbyl-substituted 2-isoxazolines, 563
Table 2.35. $\gamma$-Amino alcohols from reduction of oxygenated 2-isoxazolines, 564
Table 2.36. Treatment of 5-chloromethyl-2-isoxazoline derivatives with bases, 568
Table 2.37. IR and PMR data of 2-isoxazoline *N*-oxides, 604
Table 2.38. Rearrangement reactions of 4-aryl-2-isoxazoline-3,5-dicarboxylate *N*-oxide, 620

Table 2.39. PMR data of 4-isoxazolines, 627
Table 2.40. $^{13}C$ NMR data of 4-isoxazolines, 629
Table 2.41. Cycloaddition of nitrones to methyl propiolate and cyanoacetylene, 632
Table 2.42. Thermolysis of monocyclic 4-isoxazolines, 645
Table 3.1. PMR data of simple isoxazolidines, 652
Table 3.2. PMR chemical shifts of methyl groups in polymethylated isoxazolidines, 657
Table 3.3. PMR chemical shifts of spiroisoxazolidine derivatives, 660
Table 3.4. PMR data of 2,3,3,5-tetrasubstituted isoxazolidine invertomers, 661
Table 3.5. PMR data of 2,3,4,5-tetrasubstituted isoxazolidine invertomers, 662
Table 3.6. PMR data of 2,3,5-trisubstituted isoxazolidines, 663
Table 3.7. $^{13}C$-NMR chemical shifts of isoxazolidines, 667
Table 3.8. Coupling constants of 2-methoxy-4,5-dicyano-3-methoxycarbonylisoxazolidine invertomers, 669
Table 3.9. Bond lengths and angles of some isoxazolidines, 677
Table 3.10. Dipole moments of isoxazolidines, 678
Table 3.11. Dipole moments of isoxazolizidines, 679
Table 3.12. Kinetic measurements of N-substituted isoxazolidines, 680
Table 3.13. Relative rate constants for the cycloaddition of nitrones to ethylenic dipolarophiles, 688
Table 3.14. Regioisomeric ratios of isoxazolidines, 690
Table 3.15. Synthesis of isoxazolidines from a chiral nitrone, 692
Table 3.16. Cycloaddition of *C,N*-diarylnitrones to 1,2-disubstituted olefins, 703
Table 3.17. Synthesis of 2-methoxyisoxazolidine derivatives, 713
Table 3.18. Synthesis of N-substituted isoxazolidines from oximes and olefins, 723

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CHAPTER 1

# Isoxazoles

## 1.1 INTRODUCTION

The chemistry of isoxazole dates from 1888, when Claisen[2/888*] proposed the correct structure (3-methyl-5-phenylisoxazole) for the compound isolated some years before[1/884] from the action of hydroxylamine on benzoylacetone. He suggested the name *monoazole* for the five-membered ring $C_3NO$, which was modified by Hantsch[1/888] to *isoxazole*, a name derived from the already known isomeric ring *oxazole*. In 1891, Claisen published his classical paper "Ueber Isoxazole,"[9/891] in which the fundamental outline of the isoxazole chemistry was reported. The parent compound of the series, the unsubstituted isoxazole, was synthesized by the same author in 1903[7/03] by oximation of propargylaldehyde acetal.

From a historical point of view, it is interesting to note that two isoxazole compounds (i.e., *eulite* and *dislite*) had been isolated as early as 1852[1/852] from the reaction of concentrated nitric acid with citraconic acid. Nevertheless, their structures remained unknown for a long time, and were not demonstrated to be polynitro derivatives of isoxazole and 3,3′-diisoxazole, respectively, until 1946[2/46,8/46] (see also § 1.3.1.7b, pp. 178–179).

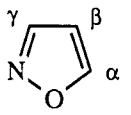
After the fundamental work of Claisen and co-workers on the oximation of $\beta$-dicarbonyl compounds, a few other authors, notably Dunstan and Dymond,[15/891] Moureu,[8/03,9/03,3/04] Wieland,[3/03,4/03] and Schmidt, [3/08,6/09] explored different methods of synthesis of the isoxazole ring (from nitroalkanes, unsaturated carbonyl or $\gamma$-dicarbonyl compounds, and nitrous or nitric acid). The synthesis from hydroximoyl chlorides and sodium acetylides was discovered in 1927,[3/27] but the reemergence of interest in isoxazole chemistry must be ascribed to Quilico and co-workers, as a consequence of their research on the action of nitric acid on acetylenic compounds during the period 1930–1946 (see § 1.3.1.7c, pp. 179–181).

The discovery by the same authors of the new synthesis from fulminic acid[11/39] and nitrile oxides,[5/46,5/50,16/50] later included by Huisgen[25/60] in the general scheme

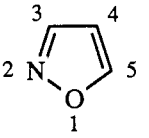
*Editor's note: References are listed chronologically in the Reference list and are numbered as follows: reference number within year/last two or three digits of year. Thus 2/888 is the second reference in 1888; 2/46 is the second reference in 1946.

of the 1,3-dipolar cycloadditions, led to a lively revival of interest in this heterocyclic ring. Its peculiar and almost unique properties favored a steadily increasing utilization of this ring as a synthon of various functionalities for the synthesis of heterocycles (see §1.4.10) and complex molecules (see § 1.4.12). On the other hand, the discovery of the interesting pharmacological activities of some isoxazole derivatives, such as sulfa drugs, modified penicillins, antibiotics, and others (see Part 2 of this work), has contributed notably to the development of isoxazole chemistry.

The trivial name *isoxazole*, originally proposed by Hantsch, has been adopted by IUPAC and is used in *Chemical Abstracts*, although the more systematic name *1,2-azole* is utilized occasionally by some authors. The three ring positions available for substitution were originally indicated as in structure **A** below, utilizing the Greek letters $\alpha$, $\beta$, and $\gamma$ starting from the position next to the oxygen atom. This nomenclature persisted until the 1950s, after which numbering beginning at oxygen atom, as depicted in structure **B**, predominated and is now used exclusively.

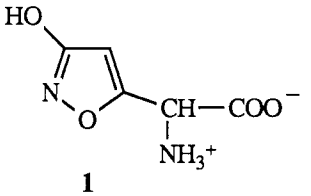



**A**

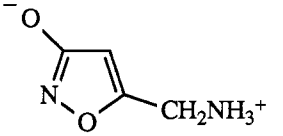



**B**

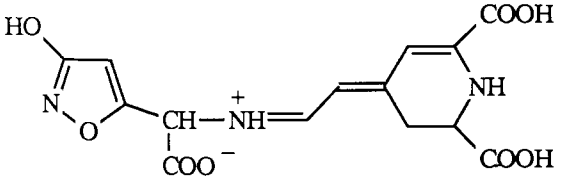
A few compounds with the isoxazole ring have recently been found in natural sources: the dipolar compounds ibotenic acid (**1**) and muscimol (**2**), isolated from *Amanita muscaria*,[122/65,123/65] *A. pantherina*,[25/64,116/64] and *A. cothurnata*[205/76] (Agaricaceae), which have insecticidal and central nervous system (CNS) de-



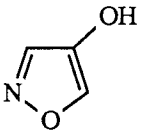

**1**




**2**




**3**




**4**

pressant activity;[64/69] the pigment musca-aurin I (**3**) from *A. muscaria*;[12/82] and the plant growth regulator triumferol or 4-hydroxyisoxazole (**4**), isolated from the leaves of *Triumfetta rhomboidea* (Tiliaceae).[236/81] Furthermore, 4,5-dimethylisoxazole has been detected in the volatile oil of tomato juice[206C/74] and in the volatile compounds from commercial soybean lecithin,[63/84] and trimethylisoxazole is present in the ether-soluble portion of cigarette smoke condensate.[266/78]

## 1.2 PHYSICOCHEMICAL PROPERTIES

Sections on physicochemical properties are included in reviews on the chemistry of isoxazoles.[78/62,7C/79,243/79,314/80,203/84] Some topics can be found in *Physical Methods in Heterocyclic Chemistry*: solubility,[100/63] ionization constants,[99/63] dipole moments,[220/71] x-ray diffraction,[265/72] ultraviolet (UV),[101/63, 218/71] infrared (IR),[102/63, 221/71] photoelectron (PE),[281/74] nuclear quadrupole resonance (NQR),[222/71] and microwave[282/74] spectroscopy, and mass spectrometry.[219/71]

### 1.2.1 Infrared Spectra

The infrared and Raman spectra of isoxazole and isoxazole-$d_3$ have been thoroughly investigated.[25/59,52/59,64/61,77/63,113/65,67/68,185/68,134/74,179/76] Based on the planar structure of isoxazole, belonging to the symmetry group $C_s$, comparison with the spectra of other heterocyclic compounds (furan, pyrrole, etc.), and theoretical calculations, full assignments of the absorption frequencies of isoxazole have been made. The IR spectra have been recorded in both vapor[25/59,52/59,134/74] and liquid phases[25/59,52/59] and in solutions.[64/61,134/74,179/76]

The eight-atom molecule of isoxazole gives rise to 18 normal vibrations: 13 of A′ class and five of A″ class. The 13 A′ vibrations can be classified as seven ring vibrations (four for stretching and three for bending modes) and six CH vibrations (three for stretching and three for bending modes). The five A″ vibrations involve three CH out-of-plane bending and two ring deformations.[52/59] The 18 fundamental vibrations of isoxazole and their more recent assignments[134/74,179/76] are reported in Table 1.1. Furthermore, overtones and combination bands for isoxazole[25/59,52/59] and isoxazole-$d_3$ [77/63] have been assigned.

Some differences in the assignments of the vibration frequencies in the region 1200 to 1000 $cm^{-1}$, attributed to either the ring or the CH deformation mode, are given in various papers.[25/59,52/59,64/61,113/65] Absolute IR intensities of isoxazole have been determined experimentally and compared with semiempirical Complete Neglect of Differential Overlap (CNDO/2) molecular orbital (MO) calculations.[179/76] Raman spectra of isoxazole, methyl- and phenylisoxazoles[8B/40,25/59,52/59,134/74] have also been reported, with assignments, but they have rarely been used when solving structural problems or identifying isoxazoles.

TABLE 1.1. ISOXAZOLE FUNDAMENTAL IR VIBRATIONS AND ASSIGNMENTS

| Symmetry | ν ($cm^{-1}$) 179/76 | Assignment 134/74 , 179/76 |
|---|---|---|
| A' | 3161 | $\nu_{C5\text{-}H}$ |
| | 3131 | $\nu_{C4\text{-}H}$ |
| | 3089 | $\nu_{C3\text{-}H}$ |
| | 1557 | $\nu_{ring\ (C=N)}$ |
| | 1429 | $\nu_{ring\ (C=C)}$ |
| | 1366 | $\nu_{ring}$ |
| | 1260 | $\nu_{ring} + \delta_{CH}$ |
| | 1217 | $\delta_{CH} + \nu_{ring}$ |
| | 1128 | $\delta_{CH} + \nu_{ring}$ |
| | 1091 | $\nu_{ring} + \delta_{CH}$ |
| | 1026 | $\nu_{ring} + \delta_{CH}$ |
| | 916 | $\delta_{ring}$ |
| | 845 | $\delta_{ring}$ |
| A'' | 891 | $\gamma_{C3\text{-}H}$ |
| | 792 | $\gamma_{C4\text{-}H}$ |
| | 765 | $\gamma_{C5\text{-}H}$ |
| | 632 | Γ |
| | 595 | Γ |

C-H vibrations: ν = stretching
δ = in-plane bending
γ = out-of-plane bending
Ring vibrations: ν = stretching
δ = in-plane bending
Γ = out-of-plane bending

IR spectra of methyl-,[64/61,134/74] dimethyl-,[25/59,64/61,134/74] and trimethylisoxazoles,[64/61] in both the gaseous and liquid states and in solutions, have been measured between 4000 and 200 $cm^{-1}$. The frequencies of CH bonds of methyl- and dimethylisoxazoles are reported in Table 1.2.[77/66,134/74]

In the vapor state, 3,5-dimethylisoxazole shows the following ring frequencies:[25/59] 1621 (*v*), 1558 (*v*), 1374 (*v*), 1415 (*v*), 1145 (*δ*), 893 (*δ*), 700 (*δ*), 612 (Γ), and 584 (Γ), which have been attributed by comparison with those of isoxazole and 3,5-dimethyl-4-nitroisoxazole. The methyl groups on the isoxazole ring show different bands depending on their ring position: 3-methyl at 1386–1372 $cm^{-1}$ and 4-methyl at 1396–1391 and 963–936 $cm^{-1}$. The higher-frequency bands (at ca. 1380–1390 $cm^{-1}$) have been attributed to Me symmetrical bending modes, and that at ca. 940 $cm^{-1}$ to the $\nu_{C\text{-}C}$ vibrations. Other absorptions, at 1200–1100 $cm^{-1}$ and 1030 $cm^{-1}$, are probably due to methyl rocking modes.[64/61]

A typical band at 2994–2962 $cm^{-1}$ has been found in the IR spectra of 10 substituted 3-methylisoxazoles. Electron acceptor groups in the 4-position raise the vibration frequency of the asymmetric methyl bands, in agreement with the

TABLE 1.2. IR DATA ($cm^{-1}$) FOR THE CH VIBRATIONS OF METHYL- AND DIMETHYLISOXAZOLES (LIQUID PHASE)

| Compound | $\nu_{C_5H}$ | $\nu_{C_4H}$ | $\nu_{C_3H}$ | $\delta_{CH}$ | $\delta_{CH}$ | $\delta_{CH}$ | $\gamma_{C_3H}$ | $\gamma_{C_4H}$ | $\gamma_{C_5H}$ |
|---|---|---|---|---|---|---|---|---|---|
| 3-Me | 3156 m | ca. 3120 m | - | - | 1117 s | 1055 s | - | ca. 862[a] | 767 s[a] |
| 4-Me | - | - | - | ca. 1160 s | ca. 1090 s | - | ca. 870 s | - | ca. 820 s |
| 5-Me | - | 3140 m | 3111 m | 1180 s | - | 1032 s | 887m[a] | 781 vs[a] | - |
| 3,4-$Me_2$ | 3156 m | - | - | 1182 s | - | - | - | - | 778 s[a] |
| 3,5-$Me_2$ | - | 3129 m | - | - | 1130 m | - | - | 783 s | - |
| 4,5-$Me_2$ | - | - | 3080 m | 1175 s | - | - | 876m[a] | - | - |

m = medium; s = strong; vs = very strong.
[a]Measured in the gas phase.

electronegativity of the substituents.[98/63] The amounts of 3- and 5-methylisoxazole in synthetic mixtures have been evaluated by IR absorptions: 3-methylisoxazole shows bands at 1571, 1447, 1412, 1122, and 1058 $cm^{-1}$ and 5-methylisoxazole shows bands at 1605, 1476, 1339, 1232, 1185, 1032, 1000, and 916 $cm^{-1}$.[40/63]

The additivity of electronic contributions due to ring heteroatoms and substituents has been calculated for the methyl IR absorptions of four substituted methylisoxazoles and other polysubstituted azoles. The calculated values for the band $\nu_{CH}$ at 2935 $\pm$ 10 $cm^{-1}$ have been compared with the measured values.[195/77]

The infrared spectra of di- and trisubstituted isoxazoles (amino, alkoxy, nitro, chloro, and esters) have been studied, and the band shifts have been discussed in relation to the number and position of substituents.[64/61] Similarly, the spectra of 5-halogeno mono- and disubstituted isoxazoles have been studied.[29/64,113/65]

The most characteristic bands related to the various substitution pattern of the isoxazole ring have been discussed.[64/61,113/65] For example, the ring stretching frequencies increase with the number of substituents: monosubstituted, 1599–1576 $cm^{-1}$; disubstituted, 1636, 1518–1473, 1473–1427, and 1435–1405 $cm^{-1}$; and trisubstituted, 1666–1610, 1537–1487, 1480–1440, and 1451–1407 $cm^{-1}$. In-plane CH deformation modes absorb in the region 1200–1100 $cm^{-1}$: at 1178–1116 for CH at the 4-position and at 1155 $cm^{-1}$ for CH at the 5-position.[64/61] However, the band at 1128 $cm^{-1}$ has sometimes been considered as a ring vibration of isoxazole derivatives.[113/65] In-plane ring deformation bands can be found in the region 1050–800 $cm^{-1}$ [64/61,113/65] and the two out-of-plane deformations in the region 600–400 $cm^{-1}$. Discussion of the CH out-of-plane absorptions has also been reported.[25/59,52/59,64/61,113/65]

Infrared absorption bands attributed to isoxazole ring vibrations have sometimes been indicated along with those due to functional groups, usually without a full interpretation of the data. In most papers absorption bands in the range 1580–1675 $cm^{-1}$ have been attributed to the C=N bond, and those in the range 970–950 $cm^{-1}$ to the N–O bond. Other ring absorptions are reported in the ranges 1465–1490, 1400–1450, 872–810, and 597–685 $cm^{-1}$. In the case of 3-

or 5-(2′-hydroxyphenyl)isoxazole and derivatives, the N–O band has been reported at 1110–1120 $cm^{-1}$.[200/79] The ring and CH absorptions of optically active isomeric 3-, 4-, and 5-*sec*-butylisoxazoles,[92/68] as well as of fluorinated 3,5-disubstituted isoxazoles,[199/79] have been assigned.

The basicity of isoxazole and methylisoxazoles has been studied by IR spectroscopy either by evaluation of the $\nu_{OH}$ of the various alcohols used as solvents or by evaluation of the $\nu_{CH}$ of the isoxazoles in basic solvents.[75/78] The first method indicates that isoxazole is less basic than oxazole and that the $pK_a$ of isoxazoles increases in the following sequence:

isoxazole < 5-Me < 3-Me < 3,5-diMe ≤ 4,5-diMe < 3,4,5-triMe-isoxazole

As far as the substituent absorptions are concerned, the bands assigned to phenyl groups in differently substituted phenylisoxazoles have been tabulated.[64/61,113/65] On the contrary, the stretching *C*-halogen in the spectra recorded at 400 $cm^{-1}$ of haloisoxazoles could not be singled out.[113/65]

The infrared absorptions of alkoxycarbonyl groups in isoxazole esters have been investigated and compared with those of alkyl benzoates. Since the isoxazole ring releases electrons from all its positions less readily than does the phenyl ring, the frequencies of the 3-, 4-, and 5-alkoxycarbonyl compounds are, respectively, 9–12, 2–8 and 17–18 $cm^{-1}$ higher than those of the corresponding alkyl benzoate.[64/61] Similar results can be found for ketones or aldehydes, which show CO absorption bands at higher frequencies than those of the corresponding phenyl derivatives.

Along with other spectroscopic methods, IR spectroscopy has been used in the study of tautomerism of aminoisoxazoles,[52/61,67/61,42/66,78/66,274/80] 5-isoxazolinones,[26/59,66/61,31/70,36/70,134/81] 4-hydroxyisoxazoles,[14/56,187/71,222/72] 3-hydroxyisoxazoles,[27/61,21/62,97/64,42/66,78/66,34/67,26/70] 3,5-dihydroxy-4-phenylisoxazole,[80/71] 3-mercaptoisoxazoles,[47/80] and the corresponding methylated derivatives. The infrared spectrum of muscimol (**2**)[25/64] and IR data of analogues of muscimol and ibotenic acid (**1**) have also been reported.[34/67,1/74,3/74,1/80]

Infrared data of 5,5′-diisoxazole and its deuterated derivative have been studied in the crystal state, in solution, and in the liquid state. Raman spectra have been recorded in $CHCl_3$, $CS_2$, and MeCN.[44B/66, 228/70] Full data for the infrared spectrum in polarized light of 5,5′-diisoxazole-$H_4$ and 5,5′-diisoxazole-$D_4$ in the liquid phase at 120°C have been reported. Almost complete assignment of fundamental frequencies has been discussed for IR and Raman spectra.

Full spectra of 3,4′-[77/66] 4,4′-,[49/64] 3,5′-[49/59] 3,3′- and 5,5′-diisoxazoles,[47/59, 49/59] 3,3′,5′3″-triisoxazole, 3,3′,5′,5″,3″,3‴-tetraisoxazole, 3,3′,5′,5″,3″,3‴,5‴,5⁗, 3⁗,3⁗⁗-hexaisoxazole[54/59] and two octaisoxazoles,[30/60] as well as those of some intermediate 4-substituted isoxazoles[77/66] have been reproduced. Infrared data for nitro,[25/59, 78/66, 308/80] azo,[89/72, 80C/75] sulfonamido,[41/66, 32/71, 45B/72, 129/81] and sulfohydrazido[129/81] derivatives have been studied.

In the cases of 5-methyl-3-methylsulfonamidoisoxazole, 5-methyl-3-phenylsulfonamidoisoxazole, and 3-4-dimethyl-5-phenylsulfonamidoisoxazole, analysis of the bands in the region 1600–1500 $cm^{-1}$ has demonstrated that in the solid state these compounds are in the amido tautomeric form. In fact, almost no changes occur on N-deuteration, by contrast with many other heterocyclic sulfonamides.[41/66] Infrared spectra have also proved to be a valuable tool in the structure elucidation of in vivo metabolites of $N^1$-(5-methyl-3-isoxazolyl)sulfanilamide (sulfisomezole); for example, $N^1$-(5-hydroxymethyl-3-isoxazolyl)sulfanilamide has been isolated and the most characteristic IR bands discussed.[32/71]

Along with those of some antibiotics of interest, the infrared spectra of some isoxazolylpenicillins, as sodium salts, have been presented.[75/65] All the bands of the IR spectrum (4000–200 $cm^{-1}$) of the antibiotic Syntarpen [dicloxacillin = 3-(2-chlorophenyl)-5-methyl-4-isoxazolylpenicillin] and of its sodium salt have been assigned and discussed.[39/73] The carbonyl infrared absorption frequencies of several other isoxazolylpenicillins have also been reported.[191/80] The infrared spectra of the polymorphic forms of sulfisoxazole and sulfamethoxazole have been discussed. In the latter case the IR spectra of the two polymorphs were shown to be different.[181/72]

Isomeric 3- and/or 5-substituted isoxazoles show almost identical IR spectra; however, in some cases differences have been evidenced. For example, 3-ethyl-5-methylisoxazole shows two bands at 1261 and 1245 cm,$^{-1}$ which are absent in 5-ethyl-3-methylisoxazole.[72/64] 17$\beta$-(3-Isoxazolyl)- and 17$\beta$-(5-isoxazolyl)androstene derivatives show a sharp band at 1562 and 1592 cm,$^{-1}$ respectively.[116/66] These bands have been attributed to 3-alkyl- and 5-alkyl substituted isoxazoles.

The lack of coplanarity between the benzoyl group and the isoxazole ring for 4-benzoyl-2,3,5-trimethylisoxazolium methosulfate has also been deduced, from the IR carbonyl absorption (at 1687 $cm^{-1}$), showing a higher value than that expected for a diaryl ketone.[111/83] The infrared absorptions of complex cations such as ($Me_3NH$-isoxazole)[172/75] or (triazole H-isoxazole)[138/75] have been reported and discussed.

In the case of metal complexes with isoxazole derivatives as ligands, in addition to the infrared data, absorptions in the far-infrared region (400–100 $cm^{-1}$) have been recorded and the assignments discussed.[167/74, 207B/74, 136/75, 136B/75, 136C/75, 138/75, 172/75, 172/76, 174/76, 175/76, 222/76, 242/76, 243/76, 244/76, 107/77, 173/77, 174/77, 175/77, 243/78, 253/80 276B/80, 210/81, 210B/81, 182/83, 267/83, 149/84] The 1558 $cm^{-1}$ ring stretching band of isoxazole shifts to 1565 $cm^{-1}$ in the infrared spectrum of $(NH_3)_5Co$(isoxazole)$(ClO_4)_3$.[132/82] The IR data of ferrocenylisoxazoles[332/83] and of $(ylide)_2.PdCl_2$ containing an isoxazole ring[182/76] have been reported.

### 1.2.2 Ultraviolet Spectra

As for other five-membered heterocyclic compounds, the UV spectra of isoxazoles show only absorption bands corresponding to $\pi \rightarrow \pi^*$ transitions.

However, depending on the relative position of the bands, the unsaturated heterocyclic derivatives can be divided into two groups:

1. Thiophene, thiazole, isothiazole, and selenophene, absorbing, as cyclopentadiene, at 230–240 nm (43,500–41,600 $cm^{-1}$)

2. Furan, pyrrole, imidazole, pyrazole, oxazole, and isoxazole, absorbing at 200–210 nm (50,000–47,600 $cm^{-1}$)[117B/65, 129B/67]

Isoxazole belongs to the second group, showing an absorption maximum at 211 nm (log $\varepsilon$ = 3.6) (47,300 $cm^{-1}$, $\varepsilon$ = 3981) in the ultraviolet spectrum [8B/54, 9B/55] in both aqueous and ethanolic solutions. Isoxazole does not obey Beer's law, as demonstrated by the absorptions in ethanolic and cyclohexane solutions,[186/68, 79/77] and exhibits hypochromism (decrease in band intensity) by increasing concentration. This effect has been connected with the high dipole moment[186/68] and with antiparallel sandwich-type selfassociation, via dipole–dipole interactions, [79/77] shown by isoxazole.

TABLE 1.3. UV DATA OF ISOXAZOLE AND ALKYLISOXAZOLES

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log $\varepsilon$) | Solvent | References |
|---|---|---|---|---|---|
| H | H | H | 211 (3.6) | EtOH | 9B/55 |
| Me | H | H | 210 | $H_2O$ | 8B/54 |
| | | | 217 (3.74) | $H_2O$ | 9B/55 |
| H | Me | H | 221 (3.50) | $H_2O$ | 8B/54, 9B/55 |
| H | H | Me | 217 | $H_2O$ | 8B/54 |
| | | | 213 (3.19) | $H_2O$ | 9B/55 |
| Me | Me | H | 219 (3.52) | $H_2O$ | 8B/54 |
| H | Me | Me | 226 (3.68) | $H_2O$ | 8B/54 |
| | | | 221 (3.63) | isooctane | 8B/54 |
| Me | H | Me | 215 | $H_2O$ | 8B/54 |
| | | | 212 (3.76) | MeOH | 182/69 |
| Me | Me | Me | 224 (3.70) | $H_2O$ | 8B/54 |
| Me | H | $n$-$C_8H_{17}$ | <220 | EtOH | 118C/65 |
| Et(Me)CH | H | H | 210-211 (3.60) | MeOH | 51/72 |
| $Et(Me)CHCH_2$ | H | H | 210-211 (3.61) | MeOH | 51/72 |
| H | Et(Me)CH | H | 220-221 (3.50) | MeOH | 51/72 |
| H | $Et(Me)CHCH_2$ | H | 220-221 (3.48) | MeOH | 51/72 |
| H | H | Et(Me)CH | 217 (3.79) | MeOH | 51/72 |
| H | H | $Et(Me)CHCH_2$ | 218 (3.80) | MeOH | 51/72 |

It is interesting to note that $n \rightarrow \pi^*$ transitions for isoxazole have been calculated by the CNDO-Configuration Interaction (CI) method[147/72] and related to the $^{14}N$ chemical shift,[147/77] but have remained undetected until now. Methylisoxazoles in aqueous solution exhibit absorption maxima between 210 and 230 nm, depending on the substituent position. In isooctane solution a shift toward higher frequencies is noticeable.[8B/54, 6B/53]

The strongest bathochromic shift is produced by the presence of a methyl group at $C_4$ (2–10 nm), and usually higher than at $C_5$ (5–6 nm). A methyl group at $C_3$ causes a blue shift of 1–2 nm. The UV data of methylisoxazoles and of some other alkylisoxazoles are reported in Table 1.3.

Alkyl groups show the same behavior as that of methyl groups.[92/68,51/72] The small differences in the UV absorption maximum of isomeric alkyl isoxazoles make this method useless for their identification in a reaction mixture.[30/69] In some cases the UV spectra of substituted isoxazoles show a bathochromic shift in comparison with those of the corresponding pyrazoles.[6B/53]

A phenyl group, conjugated with the double bonds of the ring, shifts the absorption maximum toward longer wavelengths with a considerable hyperchromic effect.[2B/32,1B/34,1B/48] The absorption maxima in different solvents of 3-phenyl-,[18B/55,118C/65,202/76,214/78,183/81] 4-phenyl-,[18B/55] and 5-phenylisoxazole,[18B/55,27/63, 118C/65,58/67,202/76,214/78,105/81] reported in Table 1.4, show that the largest shift occurs for the 5-phenylisoxazoles. This effect is strong when complete conjugation of phenyl and isoxazole rings occurs, but decreases when substituents on the phenyl groups (such as 2-methyl or 2,4-dimethyl groups) prevent coplanarity of the two rings.[27/63,10B/69]

The UV spectrum of 5-(2,4,6-tri-*tert*-butylphenyl)isoxazole shows a maximum at 273 nm, corresponding to the nonconjugated tri-*tert*-butylbenzene.[27/63] The same hypochromic and hypsochromic effects are reported for 4-substituted 5-arylisoxazoles.[27/63,10B/69]

A close similarity has been observed in the UV spectra of the following compounds: 3-phenylisoxazole and acetophenone oxime,[1B/34] 4-phenylisoxazole and α-methylstyrene,[2B/32] 5-phenylisoxazole, and the β-form of the *trans*-cinnamic aldehyde oxime,[1B/48] where full conjugation occurs. By contrast, the UV absorptions in an alkaline medium of 5-arylisoxazoles and the isomeric substituted β-cyanoacetophenones, differing by about 30–40 nm, make it possible to determine the concentration of the latter compound in the presence of the starting isoxazole derivative.[58/67] In the case of diphenyl-[18B/55,118C/65,202/76,214/78] and triphenylisoxazoles,[78/62,202/76] absorptions at higher wavelengths can be attributed to conjugation of the 5-phenyl group. Selected examples of UV data of arylisoxazoles are reported in Table 1.4.

It is noteworthy that 3,5-diphenylisoxazole shows two absorption bands, at 243–245 and 266–267 nm, corresponding to the maxima of 3-phenyl- (240 nm) and 5-phenylisoxazole (260 nm). Depending on the substituent effect of one or both aryl groups, 3,5-diarylisoxazoles often show only one absorption maximum, due to the merging of the two bands. The values of the UV data have also been used to assign the structures to isomeric isoxazoles containing

TABLE 1.4. UV DATA OF ARYLISOXAZOLES

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| Ph | H | H | 238 (4.01) | isooctane | 18B/55 |
| | | | 239.5 (4.09) | MeOH | 18B/55 |
| | | | 251 (3.88) | MeCOOH | 202/76 |
| | | | 275 (4.17) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| 4-$NO_2C_6H_4$ | H | H | 279 (4.13) | MeCOOH | 214/78 |
| | | | 281 (4.28) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| 3-$NO_2C_6H_4$ | H | H | 232 (4.31) | EtOH | 249/82 |
| 4-$BrC_6H_4$ | H | H | 249 (4.09) | EtOH | 249/82 |
| 4-$ClC_6H_4$ | H | H | 249 (4.17) | EtOH | 249/82 |
| 3-$ClC_6H_4$ | H | H | 240 (4.10) | EtOH | 249/82 |
| H | Ph | H | 238 (4.01) | isooctane | 18B/55 |
| | | | 237 (4.08) | MeOH | 18B/55 |
| H | H | Ph | 260 (4.26) | $H_2O$ | 18B/55 |
| | | | 260 (4.25) | MeOH | 18B/55 |
| | | | 206 (4.11) fl, 261 (4.28) | 4% MeOH in $H_2O$ | 58/67 |
| | | | 206 (4.15), 260 (4.26) | isooctane | 58/67 |
| | | | 262 (4.27) | MeCOOH | 202/76 |
| | | | 290 (4.32) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| H | H | 2-$MeC_6H_4$ | 257 (4.17) | isooctane | 27/63 |
| | | | 256 (4.15) | 4% MeOH in $H_2O$ | 27/63 |
| H | H | 4-$MeC_6H_4$ | 209 (4.12), 264 (4.29) | isooctane | 58/67 |
| | | | 211 (4.09), 267 (4.31) | 4% MeOH/$H_2O$ | 58/67 |
| H | H | 2,4,6-$Me_3C_6H_2$ | 239.5 (3.94) | isooctane | 27/63 |
| | | | 253 (3.85) | MeCOOH | 214/78 |
| | | | 295 (3.87) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| H | H | 2,4,6-*t*-$Bu_3C_6H_2$ | 273 (2.89) | isooctane | 27/63 |
| H | H | 3-$BrC_6H_4$ | 217 (4.25), 261 (4.26) | isooctane | 58/67 |
| | | | 214 (4.20), 261 (4.27) | 4% MeOH/$H_2O$ | 58/67 |
| H | H | 3-$ClC_6H_4$ | 215 (4.28), 261 (4.26) | isooctane | 58/67 |
| | | | 214 (4.22), 261 (4.27) | 4% MeOH/$H_2O$ | 58/67 |
| H | H | 4-$BrC_6H_4$ | 212 (4.07), 268 (4.38) | isooctane | 58/67 |
| | | | 208 (4.07), 269 (4.37) | 4% MeOH/$H_2O$ | 58/67 |
| H | H | 4-$ClC_6H_4$ | 212 (4.05), 265 (4.31) | isooctane | 58/67 |
| | | | 211 (4.06), 266 (4.33) | 4% MeOH/$H_2O$ | 58/67 |
| H | H | 4-$NO_2C_6H_4$ | 280 (4.05) | MeCOOH | 214/78 |
| | | | 282 (4.33) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| | | | 306 (4.4) | MeOH | 29/63 |
| H | H | 2-$HOC_6H_4$ | 219 (4.60), 261 (4.61), 272 (4.49), 306 (4.43) | EtOH | 184/77 |
| 2-$HOC_6H_4$ | H | H | 217 (4.35), 249 (4.06), 298 (3.56) | EtOH | 184/77 |
| H | Ph | Ph | 224 (4.3), 273 (4.1) | isooctane | 78/62 |
| H | Ph | 2-$HOC_6H_4$ | 263 (4.03) | EtOH | 2/80 |

TABLE 1.4. *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| H | Ph | 2-HO-5-$MeC_6H_3$ | 265 (4.09) | EtOH | 2/80 |
| H | Ph | 2-HO-4-$MeOC_6H_3$ | 276 (3.90) | EtOH | 2/80 |
| H | 2-$MeOC_6H_4$ | 2-$HOC_6H_4$ | 291 (3.83) | EtOH | 2/80 |
| H | 4-$MeOC_6H_4$ | 2-$HOC_6H_4$ | 279 (3.96) | EtOH | 2/80 |
| H | 4-$MeOC_6H_4$ | 2-HO-4-$MeOC_6H_3$ | 279 (3.96) | EtOH | 2/80 |
| H | 4-$NO_2C_6H_4$ | 2,4-$(HO)_2C_6H_3$ | 257 (4.05) | EtOH | 2/80 |
| H | Ph | 2,4-$(HO)_2C_6H_3$ | 280 (3.84) | EtOH | 2/80 |
| Ph | H | Ph | 243 (4.30), 266 (4.37) | isooctane | 18B/55 |
| | | | 245 (4.25), 267 (4.32) | 95% EtOH | 118C/65 |
| | | | 268 (4.39) | MeCOOH | 202/76 |
| | | | 312 (4.42) | 16.8 *M* $H_2SO_4$/MeCOOH | 202/76 |
| Ph | H | 4-$ClC_6H_4$ | 248 (4.27), 272 (4.43) | MeOH | 153/70 |
| | | | 248 (4.26) fl, 273 (4.44) | 95% EtOH | 118C/65 |
| | | | 274 (4.47) | MeCOOH | 214/78 |
| | | | 317 (4.48) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| Ph | H | 4-$HOC_6H_4$ | 242 (4.30), 281-287 (4.40) | EtOH | 18/68 |
| Ph | H | 3-$NO_2C_6H_4$ | 258 (4.41) | MeCOOH | 214/78 |
| | | | 300 (4.37) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| Ph | H | 4-$NO_2C_6H_4$ | 305 (4.27) | MeCOOH | 214/78 |
| | | | 3.17 (4.45) | 16.8 *M* $H_2SO_4$/MeCOOH | 214/78 |
| Ph | H | 4-$MeOC_6H_4$ | 246 (4.26), 284 (4.40) | MeOH | 153/70 |
| Ph | H | 3-$MeOC_6H_4$ | 268 (4.26) | MeOH | 153/70 |
| Ph | H | 3,4-$(CH_2O_2)C_6H_3$ | 238 (4.34), 284 (4.18), 307 (4.20) | MeOH | 153/70 |
| Ph | H | 4-$BrC_6H_4$ | 244 (4.27), 274 (4.45) | MeOH | 153/70 |
| Ph | H | 3-$BrC_6H_4$ | 248 (4.31), 266 (4.39) | MeOH | 153/70 |
| Ph | H | 1-naphthyl | 225 (4.72), 301.5 (4.10) | 95% EtOH | 118C/65 |
| Ph | H | 2-naphthyl | 236 (4.54), 256 (4.62), 298 (4.33) | 95% EtOH | 118C/65 |
| 2-$HOC_6H_4$ | H | Ph | 243 (4.69), 261 (4.51), 305 (4.20) | EtOH | 18/68 |
| 4-$HOC_6H_4$ | H | Ph | 261-271 (4.71) | EtOH | 18/68 |
| 4-$MeOC_6H_4$ | H | Ph | 270 (4.49) | MeOH | 153/70 |
| 3-$MeOC_6H_4$ | H | Ph | 268 (4.28) | MeOH | 153/70 |
| 3,4-$(CH_2O_2)C_6H_3$ | H | Ph | 265 (4.36) | MeOH | 153/70 |
| 4-$BrC_6H_4$ | H | Ph | 260 (4.49) | MeOH | 153/70 |
| 3-$BrC_6H_4$ | H | Ph | 247 (4.35), 270 (4.34) | MeOH | 153/70 |

Table 1.4. *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| 4-$ClC_6H_4$ | H | Ph | 257 (4.44) | MeOH | 153/70 |
| 4-$MeC_6H_4$ | H | 4-$MeOC_6H_4$ | 250 (4.29), 282 (4.43) | MeOH | 153/70 |
| 4-$MeOC_6H_4$ | H | 4-$MeC_6H_4$ | 275 (4.51) | MeOH | 153/70 |
| 4-$HOC_6H_4$ | H | 4-$HOC_6H_4$ | 250 (3.91), 280 (4.22) | EtOH | 18/68 |
| 2-$HOC_6H_4$ | H | 4-$HOC_6H_4$ | 243 (4.42), 272 (4.75), 305 (4.34) | EtOH | 18/68 |
| 2-$HOC_6H_4$ | H | 2-$HOC_6H_4$ | 247 (4.16), 260 (4.09), 310 (4.03) | EtOH | 18/68 |
| 4-$MeC_6H_4$ | H | 2-$HOC_6H_4$ | 249 (4.19), 265 (4.13), 310 (3.92) | EtOH | 222/77 |
| 2-$HOC_6H_4$ | H | 4-$MeC_6H_4$ | 248 (4.34), 275 (4.45) | EtOH | 222/77 |
| 2-$HOC_6H_4$ | H | 4-$ClC_6H_4$ | 249 (4.22), 273 (4.40) | EtOH | 200/81 |
| 4-$ClC_6H_4$ | H | 2-$HOC_6H_4$ | 252 (4.37), 276 (4.10), 311 (4.02) | EtOH | 200/81 |
| Ph | Ph | Ph | 230 (4.40), 274 (4.25) | isooctane | 78/62 |
| | | | 275 (4.23) | MeCOOH | 202/76 |
| | | | 318 (4.26) | 16.8 *M* $H_2SO_4$/MeCOOH | 202/76 |

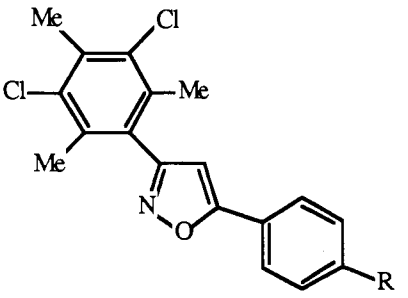
heterocyclic substituents.[88/68,52C/70] Interestingly enough, triphenylisoxazole obeys Beer's law, by contrast with the behavior of isoxazole and 3,5-diphenylisoxazole.[186/68] It has been assumed that for triphenylisoxazole the self-association is sterically hindered.[79/77]

The substituent effect on the UV spectra in connection with the formation of the isoxazole ring by oximation of β-diketones[153/70] and by cycloaddition of benzonitrile oxides to acetylenic compounds has been studied.[95/67] In the latter case the UV data of a series of 5-aryl-3-(3,5-dichloro-2,4,6-trimethylphenyl)isoxazoles have been reported in comparison with those of the corresponding 4-substituted arylacetylenes. All substituents show a bathochromic shift of the longer-wavelength bands, which is largest for the extreme cases of 4-$NO_2$ and 4-$NMe_2$[95/67] (see Table 1.5).

The presence of a hydroxyphenyl group in 3,5-diarylisoxazoles may induce a different number of bands in the UV spectra, depending on the substituent position.[18/68] 3-Phenyl-5-(4-hydroxyphenyl)-5-phenylisoxazole shows two well-separated absorption bands, whereas 3-(4-hydroxyphenyl)-5-phenylisoxazole shows only one broad band corresponding to the overlapping of the maxima at λ 268 nm and at λ 242 nm, the latter being shifted here to longer wavelengths. Three UV bands appear at λ 243, 261, and 305 nm for 3-(2-hydroxyphenyl)-5-phenylisoxazole and for all 3-(2-hydroxyphenyl)-5-arylisoxazoles.[18/68,222/77,200/81]

The band at λ 260 nm may be due to the usual conjugated 5-phenylisoxazole chromophore, while the other two bands can be related with those of 2-

TABLE 1.5. UV DATA OF

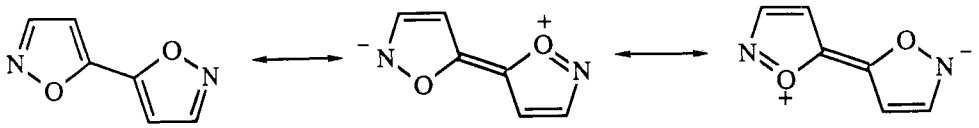



| R | $\lambda_{max}$ (nm) (MeOH) | Shift (nm) |
|---|---|---|
| H | 264 | 0 |
| Cl | 270.5 | 6.5 |
| Br | 274 | 10 |
| $NO_2$ | 301 | 37 |
| Me | 271 | 7 |
| MeO | 282.5 | 17.5 |
| $Me_2N$ | 331 | 67 |

hydroxyacetophenone oxime (at $\lambda$ 251 and 304 nm). The band at 305 nm has been attributed to chelation between the OH and C=N groups since it is absent in 4-hydroxyphenyl derivatives.[18/68] Similar behavior is shown by 3- and 5-(2′-hydroxyphenyl)isoxazoles[184/77] and the corresponding methyl, 2′-hydroxyphenylisoxazoles.[219/74,222/74,184/77]

UV spectra of 3,5-diarylisoxazoles[214/78] and some other isoxazole derivatives[202/76] have been recorded in acidic media (MeCOOH and $H_2SO_4$/MeCOOH) for the determination of $pK_a$ values. Some examples of UV data in acidic solutions are reported in Table 1.4. 1,3-Bis- and 1,4-bis(3-isoxazolyl)benzenes show absorption bands in agreement with those of 3-phenylisoxazole but with a bathochromic shift in the case of the latter compound, for stronger conjugation of 1,4-disubstituted benzenes.[28/61]

Striking evidence of the different capacity for conjugation of the isoxazole ring with the substituent in positions 3 and 5 can be found in the UV spectra of 3,3′-diisoxazole[13B/57,17B/59] and 5,5′-diisoxazole.[53B/58,17B/59,29/63] The former compound shows a maximum at 214 nm, at almost the same wavelength of isoxazole (211 nm) but with an intensity ($\varepsilon$ = 7500) about double that of simple isoxazole ($\varepsilon$ = 3600). By contrast, the latter compound shows a maximum at 260.5 nm (log $\varepsilon$ = 4.25), similar to that of 5-phenylisoxazole [260 nm (log $\varepsilon$ = 4.25)] but different for the presence of a vibrational structure.[29/63] In fact, rather unresolved maxima at about 251, 256, 260.5, 266, 271, and 277 nm could be recorded. This behavior indicates a fully conjugated planar rigid structure without repulsive effects and was attributed to a *trans* configuration. This structure is stabilized by resonance, as indicated in the following mesomeric formulas, with a strong character of double bond in the region between the two rings:



It is noteworthy that the unsymmetrical diisoxazoles (3,4′-[77/66] and 3,5′-diisoxazoles[49/59]) show intermediate values for UV absorption (222 nm[77/66] and 242 nm,[49/59] respectively), indicating a partial interaction of the two rings—stronger, however, than that of 3,3′-diisoxazole. By contrast, 3,3′,5,5′-tetramethyl- and 3,3′,5,5′-tetraphenyl-4,4′-diisoxazole show UV spectra similar to those of trimethylisoxazole and 3,5-diphenylisoxazole, respectively.[49/64] The lack of coplanarity of the rings is also shown by the higher values of log ε for 4,4′-diisoxazoles than for the corresponding isoxazoles. Selected examples of UV data of polyisoxazoles are reported in Table 1.6.

The UV spectra of 3- and 5-styrylisoxazoles have been studied and compared with those of benzylideneacetone oxime and 1-phenylhexatriene or cinnamylidene oxime, respectively.[73/73] The spectrum of 3,5-distyrylisoxazole is nearly identical to the spectrum obtained by superimposing those of 3- and 5-styrylisoxazole. All these spectra show a vibrational structure. The absorption maxima of substituted styrylisoxazoles have also been discussed in relation to the double-bond configuration.[73/73] UV spectra of some 4-nitro- or 4-amino-5-styrylisoxazoles have also been reported without discussion.[110/73,175/80] In Table 1.7, UV data of some styryl-, vinyl-,[148/76] and ethynylisoxazoles are collected. Stilbenyl derivatives of pyrazoles containing isoxazole rings have been prepared and their UV spectra recorded.[73/79]

TABLE 1.6. UV DATA OF POLYISOXAZOLES

| Compound | $\lambda_{max}$ (nm) (log ε, EtOH) | References |
|---|---|---|
| 3,3'-Diisoxazole | 214 (3.88)[a] | 18B/55 |
| | 210 (3.90) | 54/59 |
| 5,5'-Diphenyl-3,3'-diisoxazole | 273 (4.68) | 22/59 |
| 5,5'-Diisoxazole | 260 (4.23) | 17B/59 |
| 3,3'-Diphenyl-5,5'-diisoxazole | 235 (4.46), 268 (4.49) | 22/59 |
| 3,5'-Diisoxazole | 242 (4.08) | 49/59 |
| 3,4'-Diisoxazole | 222 (3.87) | 77/66 |
| 5-Phenyl-3,4'-diisoxazole | 265 (4.31) | 77/66 |
| 3,3',5,5'-Tetramethyl-4,4'-diisoxazole | 224 (3.88) | 49/64 |
| 3,3',5,5'-Tetraphenyl-4,4'-diisoxazole | 240 (4.52), 268 (4.58) | 49/64 |
| 5-Chloro-3,3'-dimethyl-4,5'-diisoxazole | 249 (4.03) | 43/67 |
| 5-Methoxy-3,3'-dimethyl-4,5'-diisoxazole | 257 (4.20) | 43/67 |
| 3,3',5',3"-Triisoxazole | 239 (4.175) | 54/59 |
| 3,3',5',5"-Triisoxazole | 263 (4.28) | 54/59 |
| 3,3',5',5",3",3"'-Tetraisoxazole | 267 (4.335) | 54/59 |
| 3,3',5',5",3", 3"', 5"', 5"", 3"", 3""'-Hexaisoxazole | 267 (4.335) | 54/59 |

[a] Solvent not reported.

TABLE 1.7. UV DATA OF ISOXAZOLES WITH UNSATURATED SUBSTITUENTS

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| Ph-CH=CH | H | H | 207 (4.11), 214 (4.12), 219 (4.17), 226 (4.07), 233 sh, 279 (4.36), 290 sh, 300 (4.08), 307 sh | cyclohexane | 73/73 |
| | | | 206 (4.16), 213 (4.15), 218 (4.20), 225 (4.08), 276 (4.41), 290 sh, 300 sh | MeOH | 73/73 |
| Ph-CH=CH | H | Me | 204 (4.25), 213 (4.20), 219 (4.22), 226 (4.08), 275 (4.41), 290 sh, 300 (3.91) | cyclohexane | 73/73 |
| | | | 202 (4.28), 213 (4.20), 220 (4.24), 226 (4.12), 278 (4.43), 290 sh, 300 sh | MeOH | 73/73 |
| Ph-CH=CH | H | Ph | 207.5 (4.46), 212 sh, 218 (4.33), 226 (4.11), 275 sh, 281 (4.62), 294 sh, 300 sh | cyclohexane | 73/73 |
| | | | 207 (4.48), 212 sh, 216 sh, 225 (4.14), 275 sh, 281 (4.63), 294 sh, 300 sh | MeOH | 73/73 |
| H | H | $CH_2$=CH | 247 (4.14) | EtOH | 139/68 |
| H | H | Ph-CH=CH | 220 (3.95), 226 (3.99), 233 (3.84), 290 sh, 298 (4.46), 305 sh, 320 sh | cyclohexane | 73/73 |
| | | | 220 sh, 225.5 (3.99), 231 (3.86), 298 (4.46), 305 sh | MeOH | 73/73 |
| Me | H | Ph-CH=CH | 221 (3.98), 226 (4.01), 234 (3.89), 292 sh, 298 (4.46), 309 (4.43), 320 sh | cyclohexane | 73/73 |
| | | | 220 (3.96), 226 (4.01), 233 (3.89), 300 (4.49), 305 sh, 320 sh | MeOH | 73/73 |
| Ph | H | Ph-CH=CH | 222 sh, 227 (4.33), 235 (4.27), 247 (4.04), 255 sh, 302.5 (4.54), 310 sh, 325 sh | cyclohexane | 73/73 |
| | | | 221 sh, 227 (4.32), 233 (4.24), 246.5 (4.08), 305 (4.55), 310 sh, 325 sh | MeOH | 73/73 |
| PhCH=CH | H | PhCH=CH | 204 (4.35), 214 (4.30), 220 (4.35), 226.5 (4.32), 234 (4.03), 285 sh, 298 sh, 304 (4.67), 310 sh, 325 sh | cyclohexane | 73/73 |
| | | | 207.5 (4.34), 213.5 (4.29), 219 (4.33), 226 (4.31), 233 (4.05), 285 sh, 305 (4.70), 325 sh | MeOH | 73/73 |
| H | H | Ph-C≡C | 265 (3.94) infl, 280 (4.07), 288 (3.95) infl, 297 (3.94) | EtOH | 105/81 |
| H | H | MeOOC-CH=CH-C≡C | 255 (3.79) infl, 275 (3.91) infl, 291 (4.00), 307 (3.88) infl | EtOH<br>EtOH | 105/81<br>105/81 |
| H | H | MeOOC-CH=CH(C≡C)$_2$ | 251, 264, 278.5, 294, 311, 330 | $Et_2O$ | 105/81 |
| H | H | OHC-CH=CH | 276 (4.3)<br>270 (4.15) | cyclohexane<br>MeOH | 145/67<br>145/67 |
| H | H | OHC-(CH=CH)$_2$ | 306 (4.57)<br>306 (4.57) | cyclohexane<br>MeOH | 145/67<br>145/67 |
| Me | $CH_2$=CH | Me | 230 (4.07) | isooctane | 148/76 |
| Me | $NO_2$ | PhCH=CH | 244 sh (4.04), 265 (4.13), 352 (4.36) | MeOH | 175/80 |
| Me | $NO_2$ | 4-Me$C_6H_4$CH=CH | 250 sh (3.92), 265 (3.95), 357 (4.20) | MeOH | 175/80 |
| Me | $NO_2$ | 4-MeO$C_6H_4$CH=CH | 252 (4.02), 280 (4.05), 387 (4.39) | MeOH | 175/80 |

Methylphenylisoxazoles[6/53,27/63,118C/65,202/76,183/81] and alkylarylisoxazoles[27/63,34/65,118C/65,10B/69,219/74,222/74] behave as the corresponding phenyl- or arylisoxazoles in the UV region, as deducible from the data collected in Table 1.8. In the case of 5-aryloxymethyl-3-phenylisoxazoles, three bands at 218 ± 2 nm (due to the anisole moiety), 225 ± 5 nm (attributed to the 5-methylisoxazole chromophore), and 245 ± 5 nm have been observed. The last maximum has been assigned to a chromophore of acetophenone oxime type.[86/72]

The UV spectra of variously substituted isoxazolecarboxylic acids have been investigated[6B/53,11B/57,15/61,53/62,53/63] (see Table 1.9). By comparison of these data with those of isoxazole, methyl- and phenylisoxazoles, it appears that the carboxylic group shows only a slight conjugation with the isoxazole ring,[11B/57] depending on the position of the substituent. Shifts toward longer wavelengths of about 14–20 nm have been observed; in the case of isoxazole 3-carboxylic acids, the absorptions have been attributed to the HOOC–C = N- chromophore. Often there is also a variation in the intensity of the bands,[11B/57,53/62] due to the influence of the acidic group. For example, the presence of a 4-carboxylic group in 5-methyl-3-phenylisoxazole carboxylic acid hinders the phenyl ring to assume a coplanar conjugated configuration with the isoxazole ring. This fact is indicated by the very low molar extinction coefficient ($\varepsilon$ = 541) of the 264-nm band, by contrast with the corresponding absorption (240 nm) of 5-methyl-3-phenylisoxazole ($\varepsilon$ = 14,850).[53/62] Similar behavior is shown by the corresponding ethyl 5-methyl-3-phenylisoxazole-4-carboxylate ($\varepsilon$ = 416 at 266 nm), the major UV absorption lying below 220 nm for the ester and at 230 nm ($\varepsilon$ = 11,150) for the acid (see Table 1.9). Such strong steric interaction is absent for the 3-methyl-5-phenylisoxazole-4-carboxylic acid ($\varepsilon$ = 15,440 at 268 nm) and for its ethyl ester ($\varepsilon$ = 13,120 at 265).[53/62]

In Table 1.9 the UV data of some acids and their derivatives—nitriles and carbonyl compounds—are reported. UV spectra of some 4-acyl- or 4-cyano-3-carbethoxyisoxazoles in ethanol and cyclohexane have also been studied.[54/65] 3-Phenyl-5-aroylisoxazoles show two bands in the UV region: at 230–245 nm as for 3-phenylisoxazole and 3-phenyl-5-acylisoxazoles and at 266–288 nm for the aroyl chromophore.[11/64]

Noteworthy is the behavior of 5-isoxazolecarboxaldehyde in various solvents as found by UV spectroscopy.[31/64,145/67] In apolar solvents such as cyclohexane, it shows only one absorption maximum (244 nm), while in polar solvents the main absorption band is at shorter wavelengths (214 nm), sometimes with a shoulder at about 245 nm. The maximum at 214 nm in MeOH, similar to the UV absorption of simple isoxazoles, has been attributed to the corresponding hemiacetal of the aldehyde.[31/64,145/67] Similarly, 5-isoxazolepolyenealdehydes show different absorptions depending on the likelihood of the solvent to form hemiacetals. However, it has been noted that each conjugated double bond increases the absorption maximum of about 30 nm (see Table 1.10). A linear relationship between $\lambda^2_{max}$ and the number of double bonds has been found,[145/67] as in the case of 2-furanepolyenealdehydes.

An investigation of the UV absorptions of alkyl-4-nitroisoxazoles in different

TABLE 1.8. UV DATA OF ALKYLARYLISOXAZOLES

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| Me | H | Ph | 261.5 (4.27)<br>262 (4.27)<br>287 (4.37) | 95% EtOH<br>MeCOOH<br>16.8 *M* $H_2SO_4$/MeCOOH | 118C/65<br>202/76<br>202/76 |
| H | Me | Ph | 263 (4.21)<br>261 (4.20) | 4% MeOH/$H_2O$<br>isooctane | 27/63<br>27/63 |
| Ph | H | Me | 240 (4.15)<br>253 (4.03)<br>273 (4.28) | 95% EtOH<br>MeCOOH<br>16.8 *M* $H_2SO_4$/MeCOOH | 118C/65<br>202/76<br>202/76 |
| Me | H | 4-$MeC_6H_4$ | 267 (4.33) | EtOH | 34/65 |
| Et | H | 4-$MeC_6H_4$ | 267 (4.33) | EtOH | 34/65 |
| Me | H | 4-$ClC_6H_4$ | 268 (4.35) | EtOH | 34/65 |
| Et | H | 4-$ClC_6H_4$ | 268 (4.37) | EtOH | 34/65 |
| Me | H | 4-$MeOC_6H_4$ | 277 (4.36) | EtOH | 34/65 |
| Et | H | 4-$MeOC_6H_4$ | 277 (4.37) | EtOH | 34/65 |
| Me | H | 2-$HOC_6H_4$ | 221 (4.13), 261 (4.22),<br>272 (3.93), 306 (4.10) | MeOH | 219/74 |
| Me | H | 2-HO-3-$MeC_6H_3$ | 220 (4.13), 263 (4.18),<br>273 (4.09), 304 (3.84) | MeOH | 222/74 |
| Me | H | 2-HO-5-$MeC_6H_3$ | 223 (4.06), 262 (4.12),<br>273 (3.97), 314 (3.82) | MeOH | 222/74 |
| 2-HO-3-$MeC_6H_3$ | H | Me | 223 (4.05), 250 (4.01),<br>259 (3.97), 300 (3.53) | MeOH | 222/74 |
| 2-HO-5-$MeC_6H_3$ | H | Me | 226 (3.98), 249 (3.86),<br>258 (3.71), 305 (3.55) | MeOH | 222/74 |
| H | Me | 2-$MeC_6H_4$ | 245.5 (4.01)<br>245 (4.00) | 4% MeOH/$H_2O$<br>isooctane | 27/63<br>27/63 |
| H | Me | mesityl | 234 (4.02)<br>232 (4.03) fl | 4% MeOH/$H_2O$<br>isooctane | 10B/69<br>10B/69 |
| H | *i*-Pr | Ph | 260 (4.17)<br>259 (4.17) | 4% MeOH/$H_2O$<br>isooctane | 10B/69<br>10B/69 |
| H | *i*-Pr | 2-$MeC_6H_4$ | 240 (3.94)<br>240 (3.95) | 4% MeOH/$H_2O$<br>isooctane | 10B/69<br>10B/69 |
| Ph | H | *n*-Bu | 241 (4.10) | 95% EtOH | 118C/65 |
| Ph | H | *n*-$C_8H_{17}$ | 240 (4.17) | 95% EtOH | 118C/65 |
| Ph | H | $CH_2Cl$ | 242 (4.08) | 95% EtOH | 118C/65 |
| Ph | H | $CH_2Br$ | 227 (4.20) | 95% EtOH | 118C/65 |

TABLE 1.9. UV DATA OF ISOXAZOLE CARBOXYLIC ACIDS AND DERIVATIVES, NITRILES AND CARBONYL COMPOUNDS

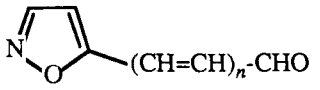
| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| *Acids* | | | | | |
| COOH | H | H | 226 (3.35) | MeOH | 78/62 |
| COOH | H | Me | 234 (3.49) | MeOH | 11B/57 |
| COOH | H | Ph | 268 (4.23) | MeOH | 11B/57 |
| COOH | COMe | Me | 230 (3.87) | HCl 2 *N* | 91/68 |
| COOH | COPh | Me | 258 (4.15) | HCl 2 *N* | 91/68 |
| COOH | COPh | Ph | 261 (4.35) | HCl 2 *N* | 91/68 |
| COOH | CN | Ph | 277 (4.22) | HCl 2 *N* | 91/68 |
| COOH | COOEt | $NH_2$ | 245 (4.11) | HCl 2 *N* | 91/68 |
| H | H | COOH | 224 (3.90) | MeOH | 78/62 |
| Me | H | COOH | 224 (3.95) | MeOH | 11B/57 |
| Ph | H | COOH | 226 (4.35) | MeOH | 11B/57 |
| Me | $NH_2$ | COOH | 293 (3.86) | MeOH | 159/82 |
| H | COOH | H | 206 (3.81) | EtOH | 77/66 |
| Me | COOH | Me | 215 (3.83) | MeOH | 11B/57 |
| Me | COOH | Ph | 268 (4.19) | MeOH | 53/62 |
| Me | COOH | 2-$ClC_6H_4$ | 240 br sh (3.85) | MeOH | 53/63 |
| Ph | COOH | H | 230.5 (3.95) | MeOH | 53/63 |
| Ph | COOH | Me | 230 (4.05), 264 (2.73) | MeOH | 53/62 |
| 2-$ClC_6H_4$ | COOH | Me | 219 (4.11) | MeOH | 53/63 |
| Ph | COOH | Ph | 232 (4.23), 268 (4.25) | MeOH | 15/61 |
| Ph | COOH | $NH_2$ | 231 (4.31) | MeOH | 15/61 |
| *Esters* | | | | | |
| Me | COOEt | Ph | 265 (4.12) | MeOH | 53/62 |
| Me | COOEt | CN | 234 (3.90) | MeOH | 159/82 |
| Ph | COOEt | Me | 266 (2.62) | MeOH | 53/62 |
| H | COOEt | $NH_2$ | 242 (4.24) | MeOH | 186/71 |
| Ph | COOEt | $NH_2$ | 232 (4.21) | MeOH | 186/71 |
| Me | H | COOMe | 226 (3.98) | 95% EtOH | 118C/65 |
| Me | $NH_2$ | COOMe | 222 (3.67), 298 (3.94) | MeOH | 159/82 |
| Ph | H | COOMe | 227.5 (4.24) | 95% EtOH | 118C/65 |
| Ph | $NO_2$ | COOMe | 221 (4.20) | EtOH | 159/82 |
| COOMe | H | COOMe | 210 (3.85), 230 sh (3.75) | EtOH | 63/81 |
| 2-Quinolinyl | COOMe | COOMe | 210 ( 2.25), 246 infl (1.97), 263 (2.23), 308 (1.16) | MeOH | 119/79 |
| | | | 270 (2.67), 348 (1.88) | MeOH/$HClO_4$ 2 :1 | 119/79 |
| *Amides* | | | | | |
| Me | $CONH_2$ | $CONH_2$ | 230 (3.98) | MeOH | 159/82 |
| Me | $CONH_2$ | COOH | 223 (3.92), 228 (3.92) | MeOH | 159/82 |
| Me | COOH | $CONH_2$ | 226 (4.04) | MeOH | 159/82 |
| *Nitriles* | | | | | |
| Ph | CN | H | 239 (4.01) | EtO | 258/82 |
| H | CN | 2-$NH_2C_6H_4NH$ | 204 (3.90), 219 (4.22), 255 (4.05), 312 (4.33) | MeOH | 48/80 |
| Ph | H | CN | 225 (4.36) | 95% EtOH | 118C/65 |
| *Hydrazides and Azides* | | | | | |
| Me | $CONHNH_2$ | $CH_2OH$ | 212 (3.91) | EtOH | 213/81 |
| Me | $CONHNH_2$ | CHOHMe | 212 (3.91) | EtOH | 213/81 |
| Me | $CONHNH_2$ | $C(OH)Me_2$ | 212 (3.92) | EtOH | 213/81 |
| Me | $CON_3$ | $CH_2OH$ | 216 (3.76) | EtOH | 213/81 |
| Me | $CON_3$ | CHOHMe | 216 (3.80) | EtOH | 213/81 |
| Me | $CON_3$ | $C(OH)Me_2$ | 216 (3.81) | EtOH | 213/81 |
| *Ketones* | | | | | |
| H | COMe | Me | 232 (3.80), 275 (3.07) | 95% EtOH | 173/83 |
| H | $COCHMe_2$ | $CHMe_2$ | 238 (3.87) | 95% EtOH | 173/83 |

TABLE 1.9. *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| H | $COCMe_3$ | $CMe_3$ | 227 (3.72), 280 (2.60) | 95% EtOH | 173/83 |
| H | COPh | Ph | 252 (4.18), 284 (4.04) | 95% EtOH | 173/83 |
| Ph | H | COMe | 238 (4.33) | 95% EtOH | 118C/65 |
| Ph | H | COPh | 242 sh (4.21), 266 (4.25) | EtOH | 11/64 |
| Ph | H | $COC_6H_4Cl$-4 | 233 (4.24), 276 (4.31) | EtOH | 11/64 |
| Ph | H | $COC_6H_4Br$-4 | 233 (4.28), 281 (4.31) | EtOH | 11/64 |
| Ph | H | $COC_6H_4NO_2$-4 | 242 sh (4.22), 270 (4.38) | EtOH | 11/64 |
| Ph | H | $COC_6H_4Me$-4 | 234 (4.24), 275 (4.25) | EtOH | 35/64 |
| Ph | H | 2-naphthoyl | 261 (4.50), 303 (4.20) | EtOH | 35/64 |
| Ph | H | 2-thienoyl | 237 (4.14), 310 (4.12) | EtOH | 35/64 |
| Ph | Ph | COMe | 225.0 (4.12), 261.5 (3.81) | EtOH | 50/65 |
| Ph | Ph | COPh | 261.5 (4.01), 288 infl (3.80) | EtOH | 50/65 |
| COPh | H | Me | 261 (4.09) | EtOH | 193/79 |
| Ph | $NH_2$ | COMe | 229 (4.10), 330 (3.81) | EtOH | 14/80 |
| Ph | $NH_2$ | COPh | 226 (4.31), 257 (4.16), 361 (4.21) | EtOH | 14/80 |
| COOEt | $NH_2$ | COPh | 230 (3.91), 259 (3.87), 364 (3.90) | EtOH | 14/80 |
| $CONH_2$ | $NH_2$ | COMe | 263 (3.45), 342 (3.82) | EtOH | 14/80 |
| $CONH_2$ | $NH_2$ | COPh | 265 (3.69), 360 (3.73) | EtOH | 14/80 |
| CN | $NH_2$ | COPh | 230 (4.06), 310 (3.95), 362 sh (3.52) | EtOH | 14/80 |
| CN | $NH_2$ | $COC_6H_4NO_2$-4 | 264 (4.15), 299 (4.03) 382 (3.54) | EtOH | 14/80 |
| Ph-N=N | $NH_2$ | COPh | 228 (4.15), 261 sh (3.91), 318 (3.80), 377 (2.93) | EtOH | 14/80 |
| *Aldehydes* | | | | | |
| H | H | CHO | 244 (3.9) | cyclohexane | 145/67 |
| H | H | MeOCHOH | 214 (3.8) | MeOH | 145/67 |

solvents revealed, in addition to a band in the range 215–225 nm, a band between 240 and 270 nm which has been attributed to the conjugation of the nitro group and the isoxazole ring. Furthermore, most 4-nitroisoxazoles show a band at 300–350 nm (ε = 100) which shifts to a longer wavelength either by increasing the solvent polarity or by steric interactions of bulky substituents in the 3- and 5-positions. In the latter case an increase in band intensity is also evident.[21/61,50/64] In Table 1.11 the UV data of a number of 4-nitroisoxazoles and 3-nitroisoxazoles are reported.

TABLE 1.10




| *n* | $\lambda_{max}$ (cyclohexane) | log ε |
|---|---|---|
| 0 | 244 | 3.09 |
| 1 | 276 | 4.03 |
| 2 | 306 | 4.57 |
| 3 | 334 | 4.66 |

TABLE 1.11. UV DATA OF NITROISOXAZOLES

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| H | $NO_2$ | H | 216 (3.77), 239 (3.75) | isooctane | 21/61, 50/64 |
| | | | 217 (3.69), 250 (3.70) | $H_2O$ | 50/64 |
| Me | $NO_2$ | H | 224.5 (3.78), 243 (3.72) infl | isooctane | 21/61, 50/64 |
| | | | 226 (3.72), 250 (3.73) | $H_2O$ | 50/64 |
| H | $NO_2$ | Me | 253 (3.75) | isooctane | 21/61, 50/64 |
| | | | 263 (3.74) | $H_2O$ | 50/64 |
| Me | $NO_2$ | Me | 259 (3.76) | isooctane | 50/64 |
| | | | 267 (3.75) | $H_2O$ | 50/64 |
| | | | 218 (4.05), 265 (4.10) | EtOH | 110/73 |
| | | | 264 (3.74) | MeCOOH | 202/76 |
| | | | 223 (4.00) | 16.8 *M* $H_2SO_4$/MeCOOH | 202/76 |
| Me | $NO_2$ | CH=CHPh | 217 (4.20), 255 (4.05), 350 (4.20) | EtOH | 110/73 |
| Me | $NO_2$ | CHBr-CHBrPh | 217 (4.32), 255 (4.05) | EtOH | 110/73 |
| Me | $NO_2$ | 4-$NO_2C_6H_4$CH=CH | 216 (4.02), 334 (4.49) | EtOH | 110/73 |
| $CMe_3$ | $NO_2$ | H | 224 (3.73), 244 (3.67) infl, 326 (2.01) infl | isooctane | 21/61, 50/64 |
| | | | 220 (3.74), 247 (3.67) infl, 325 (2.17) | MeOH | 50/64 |
| H | $NO_2$ | $CMe_3$ | 213 (3.80), 261 (3.77), 322 (2.20) infl | isooctane | 21/61, 50/64 |
| | | | 269 (3.72), 337 (2.36) infl | $H_2O$ | 50/64 |
| $CMe_3$ | $NO_2$ | $CMe_3$ | 257 (3.26), 341 (2.39) | isooctane | 50/64 |
| | | | 259 (3.22), 343 (2.42) | MeOH | 50/64 |
| Ph | $NO_2$ | H | 252 (3.78) | MeCOOH | 202/76 |
| | | | 283 (3.98) | 16.8 *M* $H_2SO_4$/MeCOOH | 202/76 |
| $NO_2$ | H | Ph | 253 (4.24) | EtOH | 78/66 |
| $NO_2$ | H | $CH_2O$-tetrahydro-pyranyl | 205 (4.15) | EtOH | 78/66 |
| Me | $NO_2$ | OMe | 282 (3.89) | MeOH | 41/63 |

3,5-Dimethyl-4-(arylazo)isoxazoles[89/72,80C/75] show two absorption maxima in the ranges 226–240 nm and 330–348 nm in ethanolic solution, while 3,5-diphenyl-4-arylazoisoxazoles[258/79] show one only at 343–372 nm. By contrast, 3,3′-diphenyl-5,5′-diamino-4,4′-azodiisoxazole also absorbs in visible light at 413 nm.[119/78]

The UV spectra of some variously substituted 5-halogenoisoxazoles have been reported and the shift of the bands discussed.[17/65] Ultraviolet absorption spectroscopy has been used, together with other spectroscopic methods, to study the

TABLE 1.12. UV DATA OF HYDROXY-, ALKOXY-, AND AMINOISOXAZOLES

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| H | H | OMe | 222 (3.78) | cyclohexane | 116/71 |
| Me | H | OMe | 223 (3.77) | EtOH | 31/70 |
| Me | Me | OMe | 209 (3.75) | cyclohexane | 66/61 |
| | | | 215 (3.79) | $H_2O$ | 66/61 |
| | | | 227 (3.97) | 20 *N* $H_2SO_4$ | 66/61 |
| *t*-Bu | Ph | OMe | 231 (3.94) | MeOH | 26/59 |
| Ph | H | OMe | 236 (4.19) | cyclohexane | 66/61 |
| | | | 239 (4.20) | $H_2O$ | 66/61 |
| | | | 239 (4.14) | EtOH | 31/70 |
| Ph | Me | OMe | 228 (4.10) | cyclohexane | 66/61 |
| | | | 231 (4.03) | $H_2O$ | 66/61 |
| | | | 275 (4.21) | 20 *N* $H_2SO_4$ | 66/61 |
| | | | 252 (3.80) | EtOH | 31/70 |
| H | H | $NH_2$ | 245.5 (4.19) | EtOH | 42/66 |
| Me | H | $NH_2$ | 227 (3.68) | cyclohexane | 67/61 |
| | | | 239 (3.96) | $H_2O$ | 67/61 |
| | | | 254 (4.09) | 2 *N* $H_2SO_4$ | 67/61 |
| *i*-Pr | H | $NH_2$ | 243 (4.06) | EtOH | 75/84 |
| *sec*-Bu | H | $NH_2$ | 243 (3.99) | EtOH | 75/84 |
| Ph | H | $NH_2$ | 206 (4.23), 233 (4.08) | EtOH | 75/84 |
| Me | Me | $NH_2$ | 233 (3.80) | cyclohexane | 67/61 |
| | | | 244 (3.92) | $H_2O$ | 67/61 |
| | | | 263 (4.14) | 2 *N* $H_2SO_4$ | 67/61 |
| OH | Me | Me | 213 (3.82) | cyclohexane | 97/64 |
| | | | 224 (3.80) | $H_2O$ | 97/64 |
| | | | 236 (3.94) | 20 *N* $H_2SO_4$ | 97/64 |
| OH | Et | Me | 214 (3.82) | cyclohexane | 97/64 |
| | | | 224 (3.80) | $H_2O$ | 97/64 |
| OMe | Me | Me | 209 (3.75) | cyclohexane | 97/64 |
| | | | 218 (3.79) | $H_2O$ | 97/64 |
| | | | 229 (3.97) | 20 *N* $H_2SO_4$ | 97/64 |
| OH | H | Ph | 261 (4.27) | cyclohexane | 27/61 |
| | | | 261 (4.30) | $H_2O$ | 97/64 |
| | | | 277 (4.30) | 20 *N* $H_2SO_4$ | 97/64 |
| OMe | H | Ph | 260 (4.27) | cyclohexane | 27/61 |
| | | | 260 (4.32) | $H_2O$ | 97/64 |
| | | | 279 (4.33) | 20 *N* $H_2SO_4$ | 97/64 |
| | | | 260 (4.27) | EtOH | 78/66 |
| OEt | H | Ph | 258 (4.12) | EtOH | 78/66 |
| Cl | H | Ph | 261 (4.28) | cyclohexane | 27/61 |
| OMe | H | $(CH_2)_2NHCOOMe$ | 212 (3.81) | EtOH | 1/74 |

TABLE 1.12. *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| OH | H | $(CH_2)_2NH_3^+Br^-$ | 209 (3.85) | EtOH | 1/74 |
| O⁻ | H | $(CH_2)_2NH_3^+$ | 210 (3.78) | EtOH | 1/74 |
| OMe | H | $(CH_2)_2CONH_2$ | 211 (3.84) | EtOH | 3/74 |
| OMe | H | $(CH_2)_3NH_3^+Cl^-$ | 211 (3.75) | EtOH | 3/74 |
| OH | H | $(CH_2)_3NH_3^+Br^-$ | 209 (3.78) | EtOH | 3/74 |
| O- | H | $(CH_2)_3NH_3^+$ | 211 (3.79) | EtOH | 3/74 |
| $NH_2$ | H | H | 228.5 (3.45) | EtOH | 42/66 |
| $NH_2$ | H | Me | 209 (3.83) | cyclohexane | 67/61 |
| | | | 230 (3.91) | 2 *N* $H_2SO_4$ | 67/61 |
| $NH_2$ | H | Ph | 206 (4.20), 260 (4.16) | EtOH | 42/66 |
| $NH_2$ | H | 4-$BrC_6H_4$ | 267 (4.38) | EtOH | 42/66 |
| $NH_2$ | H | 4-$MeOC_6H_4$ | 272 (4.40) | EtOH | 42/66 |
| $NH_2$ | Ph | Ph | 268 | EtOH | 12/74 |
| Me | OH | Me | 236 (3.62) | Buffer pH = 3 | 187/71 |
| | | | 253 (3.76) | 20 *N* $H_2SO_4$ | 187/71 |
| | | | 270 (3.64) | 0.1 *N* NaOH | 187/71 |
| Me | OH | Ph | 217 sh, 277 (4.25) | Buffer pH = 3 | 187/71 |
| | | | 220 (3.76), 300 (4.15) | 20 *N* $H_2SO_4$ | 187/71 |
| | | | 230 (3.90), 322 (4.13) | 0.1 *N* NaOH | 187/71 |
| Ph | OH | Me | 239 (3.89), 267 sh | Buffer pH = 3 | 187/71 |
| | | | 216 sh, 245 sh, 282 (4.11) | 20 *N* $H_2SO_4$ | 187/71 |
| | | | 233 (3.90), 310 (3.72) | 0.1 *N* NaOH | 187/71 |
| Ph | OH | Ph | 218 sh, 241 sh, 283 (4.20), 289 (4.21) | Buffer pH = 3 | 187/71 |
| | | | 225 (4.07), 322 4.35) | 20 *N* $H_2SO_4$ | 187/71 |
| | | | 225 (4.26), 343 (4.17) | 0.1 *N* NaOH | 187/71 |
| Me | OMe | Me | 230 (3.59) | Buffer pH = 3 | 187/71 |
| | | | 248 (3.65) | 20 *N* $H_2SO_4$ | 187/71 |
| Me | OMe | Ph | 215 sh, 272 (4.20) | Buffer pH = 3 | 187/71 |
| | | | 217 sh, 294 (4.21) | 20 *N* $H_2SO_4$ | 187/71 |
| Ph | OMe | Ph | 221 sh, 237 (4.15), 276 (4.26), 281 sh | 50% EtOH | 187/71 |
| | | | 223 (4.10), 314 (4.30) | 20 *N* $H_2SO_4$ | 187/71 |
| Me | $NH_2$ | Me | 239 (3.48) | cyclohexane | 67/61 |
| | | | 242 (3.58) | $H_2O$ | 67/61 |
| | | | 212 (3.67) | 2 *N* $H_2SO_4$ | 67/61 |
| Me | $NH_2$ | CH=CHPh | 220 (4.15), 300 (4.40) | EtOH | 110/73 |
| OH | Ph | OH | 254 (4.32) | $H_2O$ (pH = 1-8) | 80/71 |
| | | | 277 (4.10) | $H_2O$ (pH = 12-14) | 80/71 |
| | | | 258 (4.30) | MeOH | 80/71 |
| | | | 261 (4.20) | EtOH | 80/71 |

TABLE 1.12. *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $\lambda_{max}$ (nm) (log ε) | Solvent | References |
|---|---|---|---|---|---|
| | | | 263 (3.86) | $CHCl_3$ | 80/71 |
| | | | 270 (4.23) | DMSO | 80/71 |
| OMe | Ph | OMe | 251 (4.47) | EtOH | 80/71 |
| $NH_2$ | H | $NH_2$ | 244 (4.40) | MeOH/HCl | 89/65 |
| | | | 228 (4.11) | $MeOH/OH^-$ | 89/65 |
| $NH_2$ | H | NHAc | 239 (4.23) | MeOH | 89/65 |
| | | | 248 (4.28) | MeOH/HCl | 89/65 |
| NHAc | H | NHAc | 227 (4.06), 246 (4.06) | MeOH | 89/65 |
| $NH_2$ | $CHOHC_6H_4NO_2$-4 | $NH_2$ | 232 (4.03), 269 (3.92) | MeOH | 89/65 |
| | | | 249 (4.40) | MeOH/HCl | 89/65 |
| $NH_2$ | $CH_2C_6H_4NO_2$-4 | $NH_2$ | 234 (4.03), 272 (3.94) | MeOH | 89/65 |
| | | | 252 (4.23) | MeOH/HCl | 89/65 |

tautomerism of 3-hydroxy-[27/61,21/62,97/64] and 4-hydroxyisoxazoles,[187/71,222/72] 5-isoxazolinones,[26/59.66/61.31/70,36/70.116/71] and the corresponding amino-isoxazoles.[67/61,11/63,30/64,18/65.42/66,75/84]

Spectra have been recorded in solvents of different polarities and pH values. Usually, the absorption values have been compared with those of model compounds, such as the methylated derivatives.[31/59,27/61,66/61,21/62,97/64,187/71] Some examples of hydroxy-, alkoxy-, and aminoisoxazoles, including 3,5-dihydroxy-isoxazole[80/71,181/75] and 3,5-diaminoisoxazole[89/65] and derivatives, are reported in Table 1.12. UV data of musca-aurin I (**3**)[12/82] and of some muscimol homologues or analogues have also been reported.[67/67,1/74,3/74,2/76,3/76]

The tautomerism and stability of 3-mercaptoisoxazoles[47/80] have been studied. The process of protonation of 3-amino-5-methyl- and 5-amino-3-methylisoxazole, investigated by UV spectroscopy, has been found to be similar to that of the corresponding sulfonamides (sulfamethoxazole and sulfisoxazole).[187/73]

Furthermore, 3-, 4-, and 5-aminodimethylisoxazoles can also be determined quantitatively in mixtures with sulfonamides, hydroxylamine, and ammonium hydrate by reaction with sodium 1,2-naphthoquinone-4-sulfonate, which affords various dyes absorbing at 425–480 nm.[5B/74] The spectrophotometric characteristics of the dyes obtained by diazotation and coupling of sulfamethoxazole,[206/72] and the UV spectra of sulfamethoxazole,[160B/76,229/78] sulfisoxazole,[160B/76] and isocarboxazide,[160B/76] have been investigated to find a sensitive method for drug control.

The determination of sulfamethoxazole and trimethoprim in pharmaceutical preparations can be carried out simultaneously by a spectrophotometric method

at 240.5 nm in a solution of pH 7.2.[158C/79] UV data, together with other spectroscopic methods, have been used to elucidate the structure of $N^1$-(5-hydroxymethyl-3-isoxazolyl)sulfanilamide, a metabolic product of sulfisomezole.[32/71] From the UV and nuclear magnetic resonance (NMR) spectra the stoichiometry and the stability constants of the formation of complexes of sulfonamides (such as sulfisoxazole) and the cyclic polyether 18-crown-6 have been studied.[34/79] Colorimetric[266/81] and fluorometric[27/81] methods for the detection of small quantities of the herbicide isouron have been established.

Isoxazole derivatives can form complexes with metals (Pd, Pt, Fe, Ni, Co, Cr, Mn, Cu, Cd, etc.),[167/74,207B/74,136/75,136B/75,136C/75,172/76,222/76,242/76,243/76,244/76,174/77,253/80,276B/80,210B/81,182/83] iodine,[285/76] or nitrophenols and nitroanisole[161/75,54B/76,118/76,285/77,286/77] (see § 1.4.1). UV absorptions recorded in different solvents or in solid state gave useful indications for complex geometries or structures. The electronic absorptions of $Cr(CO)_5$-isoxazole in $CH_2Cl_2$ and in isooctane have been reported and the data discussed.[91C/79] In the UV spectrum, $(NH_3)_5Co(isoxazole)(ClO_4)_3$ shows two maxima at 469 and 333 nm, recorded in 0.5 *M* $HClO_4$.[132/82]

The stability and structure of some transition-metal complexes of 5-methylisoxazole have been studied by potentiometric methods. UV spectra are reported and discussed.[222B/77] The UV maxima of meso-ionic compounds of some azoles have been reported.[144/74] In the case of 3,5-dimethyl-4-tosylaminoisoxazole perchlorate and of the free base, the UV data have been used to demonstrate the stability of the sulfonamidate in diluted solution.[144/74]

### 1.2.3 Nuclear Magnetic Resonance Spectra

Due to the presence of two different vicinal heteroatoms, the dissymmetry of the isoxazole nucleus affects the values of chemical shifts of either the protons or the carbon atoms of the ring. The differences in chemical shifts are nearly always sufficiently marked to allow the assignment of the structure to unknown isoxazoles on the basis of nuclear magnetic resonance (NMR) data alone. However, for correct interpretation of the spectra, one has to be acquainted with the effects exerted on the proton and carbon atom signals by the substituents. Also, the chemical shifts of the substituents, as methyl or phenyl groups, can sometimes give valuable informations regarding the structure. Data in the literature for proton magnetic resonance (PMR), $^{13}$C-NMR, and $^{14}$N-NMR and other nuclei will be reported and discussed in various sections below.

#### *1.2.3.1 PMR Spectra*

The chemical shifts of the protons of the unsubstituted isoxazole are connected strictly to the distribution of the electron density on the ring as calculated for this heterocyclic compound[90/66] (see also § 1.2.8). The PMR data of isoxazole, neat or dissolved in various solvents, have been reported in many

TABLE 1.13. PMR DATA OF ISOXAZOLE (δ, TMS = 0, $J$ in Hz)

| $H_3$ | $H_4$ | $H_5$ | $J_{3-4}$ | $J_{4-5}$ | $J_{3-5}$ | Solvent | References |
|---|---|---|---|---|---|---|---|
| 8.34 | 6.41 | 8.51 | 1.5 | 1.5 | - | $CDCl_3$ | 3/67 |
| 8.44 | 6.53 | 8.64 | 1.8 | 1.8 | - | neat | 168/68 |
| 8.40 | 6.40 | 8.61 | 1.7 | 1.7 | 0.5 | neat | 11/69 |
| 8.19 | 6.32 | 8.44 | 1.6 | 1.6 | - | $CCl_4$ | 259/70 |
| 8.46 | 6.75 | 8.69 | - | - | - | neat | 28B/64 |
| 8.15 | 6.28 | 8.39 | 1.78 | 1.69 | 0.27 | $CS_2$ | 28/74 |
| 8.19 | 6.31 | 8.44 | 1.6 | 1.6 | 0 | liq.cryst. | 149/70 |

papers[28B/64,3/67,168/68,11/69,149/70,259/70,28/74] (see Table 1.13). In all the reported conditions the signals of $H_4$ proton absorb at a higher field (δ 6.31–6.75) than do $H_3$ (δ 8.15–8.46) and $H_5$ (δ 8.39–8.69), but all in the aromatic proton region.

In isoxazole and its derivatives the $H_3$ signal usually appears broad, owing to an interaction between the proton and the ring nitrogen atom, ascribed to the quadrupole relaxation of the $^{14}N$ nucleus.[28B/64,168/68,11/69] This fact is sometimes diagnostic in differentiating the close signals of $H_3$ and $H_5$. For isoxazole it has been shown that the $H_3$ signal sharpens up at −46°C or when a viscous solution of triethylene glycol or a saturated aqueous solution is used.[168/68]

From an accurate analysis of the isoxazole PMR spectrum in a liquid-crystal solution the following dipole–dipole coupling constants could be determined:[149/70] $D_{35} = -64 \pm 2$ Hz; $D_{45} = -300 \pm 2$ Hz; $D_{34} = -487 \pm 2$ Hz. Furthermore, the PMR spectrum of isoxazole, including $^{13}C$ satellites in natural abundance in two nematic phases (IV and ZLI 1167), have been studied.[144/81] The molecular geometries obtained, eventually corrected for harmonic vibrations, have been discussed in comparison with data obtained by microwave spectroscopy.[144/81] The spin density distribution of isoxazole induced by addition of nickelbis(acetylacetonate) has also been measured.[163C/81]

Conformational studies of 3,3′-diisoxazole and 5,5′-diisoxazole by means of PMR spectra in nematic phases are known.[33/71,130/72] In the former case, spectra in the nematic and isotropic phases have been compared. In the latter, four different nematic phases have been employed. Both compounds show a preferential *transoid* conformation. Results have been compared with calculated data and discussed.

The presence of an electron-donating substituent, such as a methyl group, causes an upfield shift of the protons in the isoxazole ring.[28/74] This effect exerted on $H_4$ is stronger when the substitution occurs in position 5[40/63,28B/64,11/69,259/70] than when it occurs in position 3[40/63,28B/64,259/70] (in $CCl_4$: 0.47 ppm upfield for 5-methylisoxazole and 0.30 ppm for 3-methylisoxazole). The upfield shift of $H_4$ in the case of 3,5-dimethylisoxazole[28B/64,72/64,259/70,110/73] is identical with that of 5-methylisoxazole, thus indicating that the substituent in 5 probably has the greatest influence. Similar results have been obtained for other variously substituted alkyl isoxazoles; even the signals of $H_3$ and $H_5$ are shielded by the presence of an alkyl group on the isoxazole ring (see Table 1.14).

TABLE 1.14. PMR DATA OF ALKYLISOXAZOLES (δ, TMS = 0, *J* in Hz)

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $H_4$ | $H_5$ | $R_3$ | $R_4$ | $R_5$ | $J_{vic}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Me | H | H | - | 6.29 | 8.79 | 2.26 | - | - | - | neat | 28B/64 |
| | | | - | 6.02 | 8.13 | 2.28 | - | - | $1.6_{4-5}$ | $CCl_4$ | 259/70 |
| H | Me | H | 8.23 | - | 8.35 | - | 2.00 | - | - | neat | 28B/64 |
| H | H | Me | 8.21 | 6.05 | - | - | - | 2.36 | $1.8_{3-4}$ | neat | 28/64, 11/69 |
| | | | 7.90 | 5.85 | - | - | - | 2.42 | $1.6_{3-4}$ | $CCl_4$ | 259/70 |
| | | | 8.02 | 5.93 | - | - | - | 2.39 | $1.75_{3-4}$ | $CS_2$ | 28/74 |
| Me | H | Me | - | 5.89 | - | 2.13 | - | 2.31 | - | neat | 28B/64 |
| | | | - | 5.85 | - | 2.24 | - | 2.41 | - | $CCl_4$ | 259/70 |
| | | | - | 5.91 | - | - | - | - | - | $(CD_3)_2CO$ | 28B/64 |
| | | | - | 5.90 | - | 2.20 | - | 2.35 | - | $CDCl_3$ | 110/73 |
| | | | - | 5.73 | - | 2.11 | - | 2.26 | - | $CS_2$ | 28/74 |
| H | Me | Me | 8.08 | - | - | - | 1.86 | 2.26 | - | neat | 28B/64 |
| | | | 7.95 | - | - | - | 1.88 | 2.23 | - | $CS_2$ | 28/74 |
| Me | Me | H | - | - | 8.06 | 2.22 | 1.97 | - | - | $CDCl_3$ | 28/74 |
| Me | Me | Me | - | - | - | 2.12 | 1.85 | 2.25 | - | $CCl_4$ | 259/70 |
| | | | - | - | - | 2.05 | 1.81 | 2.18 | - | $CS_2$ | 28/74 |
| Me | H | Et | - | 5.80 | - | 2.20 | - | 1.2 t<br>2.6 q | - | neat | 72/64 |
| Et | H | Me | - | 5.80 | - | 1.2 t<br>2.6 q | - | 2.30 | - | neat | 72/64 |
| Et | H | Et | - | 5.70 | - | 1.2 t<br>2.6 q | - | 1.2 t<br>2.6 q | - | neat | 72/64 |
| Et(Me)CH- | H | H | - | 6.02 | 8.15 | - | - | - | $1.8_{4-5}$ | $CCl_4$ | 51/72 |
| $Et(Me)CHCH_2$ | H | H | - | 6.05 | 8.19 | - | - | - | $2.0_{4-5}$ | $CCl_4$ | 51/72 |
| H | Et(Me)CH | H | 7.93 | - | 8.03 | - | - | - | - | $CCl_4$ | 51/72 |
| H | $Et(Me)CHCH_2$ | H | 7.92 | - | 8.06 | - | - | - | - | $CCl_4$ | 51/72 |
| H | H | Et(Me)CH | 7.90 | 5.80 | - | - | - | - | $1.6_{3-4}$ | $CCl_4$ | 51/72 |
| H | H | $Et(Me)CHCH_2$ | 7.95 | 5.85 | - | - | - | - | $1.6_{3-4}$ | $CCl_4$ | 51/72 |
| Me | H | C≡C-R | - | 6.07 | - | 2.08 | - | - | - | $C_6D_6$ | 201/66 |

The PMR spectra have been used as a tool to calculate the ratio of 3- and 5-methylisoxazoles in some reaction mixtures,[40/63,111/66] or the isomeric purity of products[51/72] or to determine the structures in isoxazole steroids.[22/63,183/71] 3,5-Dialkyl- or cycloalkylisoxazoles have been used as intermediates in the synthesis of prostanoic derivatives; structure determination and purity of these intermediates were based essentially on PMR data.[159/81] Variously substituted

TABLE 1.15. PMR DATA OF ARYL-, DIARYL-, AND ARYLHETEROARYLISOXAZOLES
(δ, TMS = 0, *J* in Hz)

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $H_4$ | $H_5$ | $J_{vic}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|
| Ph | H | H | - | 6.62 | 8.48 | - | neat | 28B/64 |
| | | | - | 6.58 | 8.39 | $1.6_{4-5}$ | $CCl_4$ | 259/70 |
| | | | - | 6.96 | 8.79 | $1.5_{4-5}$ | $(CD_3)_2CO$ | 259/70 |
| | | | - | 6.74 | 8.49 | $1.73_{4-5}$ | $CD_3NO_2$ | 249/82 |
| H | Ph | H | 8.43 | - | 8.58 | - | $CCl_4$ | 259/70 |
| H | H | Ph | 8.29 | 6.44 | - | $1.7_{3-4}$ | neat | 11/69 |
| | | | 8.15 | 6.39 | - | $2.0_{3-4}$ | $CCl_4$ | 259/70 |
| | | | 8.28 | 6.48 | - | $1.9_{3-4}$ | $CDCl_3$ | 3/67 |
| | | | 8.49 | 6.83 | - | $1.7_{3-4}$ | $(CD_3)_2CO$ | 259/70 |
| 4-$ClC_6H_4$ | H | H | - | 6.56 | 8.39 | $1.7_{4-5}$ | $CCl_4$ | 259/70 |
| | | | - | 6.95 | 8.77 | $1.6_{4-5}$ | $(CD_3)_2CO$ | 259/70 |
| | | | - | 6.74 | 8.52 | $1.75_{4-5}$ | $CD_3NO_2$ | 249/82 |
| 4-$NO_2C_6H_4$ | H | H | - | 7.14 | 8.89 | $1.7_{4-5}$ | $(CD_3)_2CO$ | 259/70 |
| | | | - | 7.15 | 8.92 | - | DMSO-$d_6$ | 52D/81 |
| 3-$NO_2C_6H_4$ | H | H | - | 6.88 | 8.60 | $1.75_{4-5}$ | $CD_3NO_2$ | 249/82 |
| 2,6-$Cl_2C_6H_3$ | H | H | - | 6.40 | 8.41 | $1.8_{4-5}$ | $CDCl_3$ | 52D/81 |
| 2-$HOC_6H_4$ | H | H | - | 6.70 | 8.40 | $2.0_{4-5}$ | - | 184/77 |
| H | H | 4-$MeC_6H_4$ | 8.22 | 6.43 | - | $2.0_{3-4}$ | $CDCl_3$ | 205B/80 |
| H | H | 2-$MeOC_6H_4$ | 8.20 | 6.26 | - | $1.9_{3-4}$ | neat | 11/69 |
| H | H | 4-$ClC_6H_4$ | 8.17 | 6.43 | - | $2.0_{3-4}$ | $CCl_4$ | 259/70 |
| | | | 8.45 | 6.84 | - | $1.7_{3-4}$ | $(CD_3)_2CO$ | 259/70 |
| H | H | 4-$NO_2C_6H_4$ | 8.54 | 7.12 | - | $2.0_{3-4}$ | $(CD_3)_2CO$ | 259/70 |
| H | H | 2-$HOC_6H_4$ | 8.40 | 6.90 | - | $1.5_{3-4}$ | - | 184/77 |
| H | H | mesityl | 8.21 | 6.14 | - | $1.8_{3-4}$ | neat | 11/69 |
| Ph | Ph | H | - | - | 9.08 | - | $CDCl_3$ | 176/74 |
| Ph | $C_6F_5$ | H | - | - | 7.33 | - | - | 334/83 |
| H | Ph | 2-$HOC_6H_4$ | 9.12 | - | - | - | DMSO-$d_6$ | 2/80 |
| H | Ph | 2-HO-3-$MeC_6H_3$ | 9.06 | - | - | - | DMSO-$d_6$ | 2/80 |
| H | Ph | 2-HO-4-$MeOC_6H_3$ | 9.07 | - | - | - | DMSO-$d_6$ | 2/80 |
| H | 2-$MeOC_6H_4$ | 2-$HOC_6H_4$ | 8.86 | - | - | - | DMSO-$d_6$ | 2/80 |
| H | 4-$MeOC_6H_4$ | 2-$HOC_6H_4$ | 9.06 | - | - | - | DMSO-$d_6$ | 2/80 |
| H | 4-$MeOC_6H_4$ | 2-HO-4-$MeOC_6H_3$ | 8.93 | - | - | - | DMSO-$d_6$ | 2/80 |
| H | 4-$NO_2C_6H_4$ | 2-HO-4-$MeOC_6H_3$ | 9.14 | - | - | - | DMSO-$d_6$ | 2/80 |
| H | Ph | 2-HO-4-$MeOC_6H_3$ | 8.95 | - | - | - | DMSO-$d_6$ | 84/78 |

TABLE 1.15 *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $H_4$ | $H_5$ | $J_{vic}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|
| 2-HO-4-$MeOC_6H_3$ | Ph | H | - | - | 8.21 | - | $CDCl_3$ | 84/78 |
| Ph | H | Ph | - | 6.74 | - | - | $CCl_4$ | 259/70 |
| | | | - | 6.80 | - | - | $CDCl_3$ | 95/67 |
| | | | - | 6.83 | - | - | TFA | 174/70 |
| Ph | H | 3-$BrC_6H_4$ | - | 6.84 | - | - | $CDCl_3$ | 160/70 |
| Ph | H | 3-$NO_2C_6H_4$ | - | 7.04 | - | - | $CDCl_3$ | 160/70 |
| Ph | H | 2-$MeC_6H_4$ | - | 6.60 | - | - | $CDCl_3$ | 25/77 |
| Ph | H | 2-$HOOCC_6H_4$ | - | 7.30 | - | - | DMSO-$d_6$ | 25/77 |
| Ph | H | 2-$EtOOCC_6H_4$ | - | 6.80 | - | - | $CDCl_3$ | 172/82 |
| 2-$MeC_6H_4$ | H | Ph | - | 6.6 | - | - | $CDCl_3$ | 25/77 |
| Mesityl | H | Ph | - | 6.51 | - | - | $CDCl_3$ | 160/70 |
| 3-$ClC_6H_4$ | H | Ph | - | 6.73 | - | - | $CDCl_3$ | 160/70 |
| 2,6-$Cl_2C_6H_3$ | H | Ph | - | 6.53 | - | - | $CDCl_3$ | 38B/79 |
| $CBr_5$ | H | Ph | - | 6.53 | - | - | $CDCl_3$ | 104/81 |
| 4-$ClC_6H_4$ | H | mesityl | - | 6.54 | - | - | $CDCl_3$ | 160/70 |
| 4-$MeC_6H_4$ | H | 2-$HOC_6H_4$ | - | 6.74 | - | - | $CDCl_3$ | 222/77 |
| 2-$HOC_6H_4$ | H | 4-$MeC_6H_4$ | - | 6.47 | - | - | $CDCl_3$ | 222/77 |
| 3-$CF_3C_6H_4$ | H | 2-$EtOOCC_6H_4$ | - | 6.77 | - | - | $CDCl_3$ | 172/82 |
| 4-$MeOC_6H_4$ | H | 3-pyridyl | - | 6.85 | - | - | TFA | 174/70 |
| Ph | H | 5-$NH_2$-3,4-$Me_2$-1-pyrazolyl | - | 6.78 | - | - | DMSO-$d_6$ | 154B/72 |
| Ph | H | 5-$NH_2$-3-Ph-1-pyrazolyl | - | 7.00 | - | - | DMSO-$d_6$ | 154B/72 |
| Ph | H | 5-$NH_2$-3-Me-4-Ph-1-pyrazolyl | - | 7.10 | - | - | DMSO-$d_6$ | 154B/72 |
| Ph | H | 3-HO-2-thienyl | - | 7.00 | - | - | DMSO-$d_6$ | 166/82 |
| Ph | H | 3-HO-2-benzo[*b*]thienyl | - | 7.10 | - | - | DMSO-$d_6$ | 166/82 |

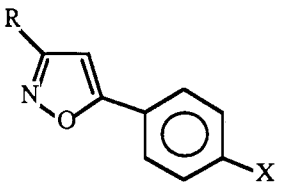
methylene diisoxazoles show the signals expected in the PMR spectrum, depending on substitution.[66/76,67/76,13/79,16/82]

It is known that the descreening effect of the benzene ring on the neighboring protons is maximum when the ring and the protons lie on the same plane and that the effect is decreased by increasing the torsional angle. Examination of the chemical shifts of protons in 3-, 4-, and 5-phenylisoxazole and 3,5-diphenylisoxazole recorded in the same solvent (see Table 1.15) led to finding the strongest deshielding effect for $H_4$ in 3-phenylisoxazole and for $H_3$ in 4-phenylisoxazole and the weakest for $H_5$ in the latter compound. A weak effect for $H_4$ is also observed for 5-phenylisoxazoles. These data seem to indicate a different preferred conformation for the three monophenyl-substituted isoxazoles in which the angles between the planes of the two rings are different, 5-phenylisoxazole showing the greatest angle.

TABLE 1.16. PMR DATA OF ALKYLARYLISOXAZOLES (δ, TMS = 0)

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $H_4$ | $H_5$ | $Me_{ring}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|
| H | Me | Ph | 8.12 | - | - | 2.05 | neat | 11/69 |
| | | | 8.00 | - | - | 2.21 | $CCl_4$ | 259/70 |
| H | *i*-Pr | Ph | 8.29 | - | - | - | neat | 11/69 |
| H | Me | 2-$MeC_6H_4$ | 8.16 | - | - | 1.89 | neat | 11/69 |
| H | *i*-Pr | 2-$MeC_6H_4$ | 8.33 | - | - | - | neat | 11/69 |
| H | Me | mesityl | 8.16 | - | - | 1.89 | neat | 11/69 |
| Ph | H | Me | - | 6.20 | - | 2.25 | $CCl_4$ | 259/70 |
| Ph | H | Et | - | 6.25 | - | - | $CCl_4$ | 95/67 |
| | | | - | 6.22 | - | - | $CDCl_3$ | 38B/79 |
| 2-$HOC_6H_4$ | H | Me | - | 6.20 | - | 2.36 | $CCl_4$ | 200/79 |
| 2,6-$Cl_2C_6H_3$ | H | Et | - | 5.98 | - | - | $CDCl_3$ | 38B/79 |
| 4-$ClC_6H_4$ | H | *n*-Bu | - | 6.27 | - | - | $CDCl_3$ | 160/70 |
| 4-$ClC_6H_4$ | H | *i*-Bu | - | 6.29 | - | - | $CDCl_3$ | 13/65 |
| Me | H | Ph | - | 6.27 | - | 2.31 | $CCl_4$ | 259/70 |
| Me | H | 1-Me-2-$NO_2$-4-pyrrolyl | - | 6.47 | - | 2.26 | $(CD_3)_2CO$ | 55B/80 |
| Ph | Et | H | - | - | 8.18 | - | $CDCl_3$ | 38B/79 |
| 2,6-$Cl_2C_6H_3$ | Me | H | - | - | 8.32 | 1.91 | $CDCl_3$ | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | Et | H | - | - | 8.29 | - | $CDCl_3$ | 38B/79 |

TABLE 1.17



| R | X | $H_4$ (δ, $CDCl_3$) | References |
|---|---|---|---|
| 3,5-$Cl_2$-2,4,6-$Me_3C_6$ | $NMe_2$ | 6.29 | 95/67 |
| | OMe | 6.30 | 95/67 |
| | Me | 6.36 | 95/67 |
| | H | 6.44 | 95/67 |
| | Cl | 6.44 | 95/67 |
| | Br | 6.44 | 95/67 |
| | $NO_2$ | 6.71 | 95/67 |
| 4-$MeOC_6H_4$ | H | 6.77 | 160/70 |
| Ph | H | 6.77 | 160/70 |
| 4-$ClC_6H_4$ | H | 6.74 | 160/70 |
| 4-$MeC_6H_4$ | H | 6.74 | 160/70 |
| 3-$ClC_6H_4$ | H | 6.73 | 160/70 |
| Ph | OMe | 6.71 | 160/70 |
| Ph | Me | 6.77 | 160/70 |
| Ph | Cl | 6.84 | 160/70 |
| Ph | $NO_2$ | 7.04 | 160/70 |

A conformational study of the three monophenylisoxazoles has been carried out by means of PMR spectroscopy in liquid-crystal solvent. The results showed that all three compounds are in a twisted conformation around the bond connecting the phenyl and the isoxazole rings: 3-phenyl- and 5-phenylisoxazole showing a twist angle of 18° and 4-phenylisoxazole one of 20°.[123/79]

The strong downfield shift of $H_4$ in 3,5-diphenylisoxazole[95/67,259/70] indicates that in this compound the phenyl linked at $C_5$ is less inclined to the plane of the isoxazole ring than for 5-phenylisoxazole.[95/67,259/70] In monoarylisoxazoles[259/70,205B/80,52D/81] only a strong withdrawing substituent on the phenyl, mainly at $C_5$, as a $NO_2$ group causes a substantial downfield shift of $H_4$ and also of $H_3$[259/70] as in *p*-nitrophenylisoxazole.

As examples of the values of chemical shifts of the isoxazole ring protons, selected PMR data on aryl-, diaryl, and arylheteroarylisoxazoles are reported in Table 1.15, and data on alkylarylisoxazoles in Table 1.16. The inductive effect of the substituents made it possible in some cases to explain the chemical shifts of the protons in alkyl- and arylisoxazoles.[12/71]

Studies on the mechanism of 1,3-dipolar cycloaddition have led to the synthesis of a series of variously substituted 3,5-diarylisoxazoles. Some authors examined changes in the chemical shift of $H_4$ in PMR spectra due to different substituents on the phenyl groups.[95/67,160/70] For 3-(3′,5′-dichloro-2′,4′,6′-trimethylphenyl)-5-arylisoxazoles a roughly linear correlation of the $H_4$ chemical shift with the Hammett σ-constants of *p*-substituents on the benzene

ring in position 5 could be obtained by the least-squares method (see Table 1.17).[95/67]

The PMR data of the aromatic protons of these isoxazoles have been used as good examples for studying the substituent effect in a series of 1,4-disubstituted benzenes that contain a constant composite substituent (the isoxazole ring) and a variable simple substituent.[205/77] For the variable substituent the chemical shifts of *ortho* and *meta* protons are well described by the nonaddictive relationship

$$\delta_{calc} = \delta_{benzene} + a_{ortho} + a_{meta} + Ka_{ortho}a_{meta}$$

where $\delta_{benzene} = 7.27$ ppm, while for the constant composite substituent, a good graphical correlation can be expressed as

$$\delta_{calc} = 7.27 + a_{meta} + a_{ortho}(1 + Ka_{meta})$$

This graphical method can be of assistance in the correct assignment of aromatic signals.

In another series of 3,5-diarylisoxazoles the effects on $H_4$ chemical shifts of the substituents *para* to the phenyl groups in the 3- and 5-positions have been evaluated.[160/70] As shown in Table 1.17, the chemical shift of $H_4$ is almost unaffected by the *para* (and *meta*)-substituted phenyl groups at position 3. By contrast, the shifts caused by the *para*-substituted phenyl at position 5 can again be correlated as a linear function of Hammett $\sigma$-constants through a least-squares treatment of the data.

The chemical shifts in trifluoroacetic acid (TFA) of $H_4$ in a series of diarylisoxazoles have been recorded.[174/70] In many cases the structure or presence of regioisomeric diarylisoxazoles formed from the reaction of asymmetric $\beta$-diketones with hydroxylamine has also been established on the basis of PMR data.[116/66,30/69,219/74,222/74,25/77,221/77,25/80] Very few examples of PMR data of monosubstituted isoxazoles with electron-withdrawing groups are reported. However, 3-cyanoisoxazole, 3-isoxazolecarboxyaldehyde, and 3,3′-diisoxazole[48/61] are known to show a downfield shift for both $H_4$ and $H_5$ with respect to the chemical shift of isoxazole:[259/70] $H_4$ shifts of 0.74, 0.40, and 0.67 ppm and $H_5$ shifts of 0.50, 0.20, and 0.58 ppm, respectively, for the three compounds. The chemical shifts are reported in Table 1.18, revised relative to the first assignment of the authors in the very early paper on PMR data.

In 3-glycosylisoxazoles[44/73] or other 3-monosubstituted compounds[32/80,47/80] the chemical shifts of $H_4$ are at $\delta$ 6.1–6.55 and of $H_5$ are at $\delta$ 8.2–8.43. Also, 4-nitro and 4-methoxycarbonylisoxazole show a downfield shift for $H_3$ (0.54 and 0.36 ppm) and $H_5$ (0.80 and 0.64 ppm) relatively to isoxazole (recorded in the same solvent). Generally, the $C_4$ substituent influences the chemical shift of $H_5$ more strongly than that of $H_3$. The chemical shift of some variously 5-substituted isoxazoles are also reported in Table 1.18, showing that depending on the substituents, $H_3$ absorbs at $\delta$ 7.98–8.69 and $H_4$ at $\delta$ 5.75–6.80.

TABLE 1.18. PMR DATA OF 3-, 4-, AND 5-MONOSUBSTITUTED ISOXAZOLES (δ, TMS = 0, $J$ in Hz)

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $H_4$ | $H_5$ | $J_{vic}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|
| 3-Monosubstituted isoxazoles | | | | | | | | |
| $NO_2$ | H | H | - | 7.05 | 8.80 | $1.7_{4-5}$ | $CDCl_3$ | 197/72 |
| NHOH | H | H | - | 6.10 | 8.30 | $2.0_{4-5}$ | $CD_3OD$ | 197/72 |
| CN | H | H | - | 7.14 | 9.11 | $2.3_{4-5}$ | neat | 48/61 |
| CHO | H | H | - | 6.86 | 8.81 | $1.9_{4-5}$ | neat | 48/61 |
| SH | H | H | - | 6.55 | 8.43 | $2.0_{4-5}$ | $CCl_4$ | 47/80 |
| SAc | H | H | - | 6.67 | 8.52 | $2.0_{4-5}$ | $CDCl_3$ | 47/80 |
| $(CH_2)_3OH$ | H | H | - | 6.1 | 8.2 | $2.0_{4-5}$ | $CCl_4$ | 32/80 |
| 3-Isoxazolyl | H | H | - | 7.07 | 9.19 | $2.0_{4-5}$ | $CDCl_3$ | 48/61 |
| 4-Monosubstituted isoxazoles | | | | | | | | |
| H | Et | H | 8.07 | - | 8.18 | - | $CCl_4$ | 191/76 |
| H | CHBrMe | H | 8.20 | - | 8.35 | - | $CCl_4$ | 191/76 |
| H | $CH_2Br$ | H | 8.23 | - | 8.35 | - | $CCl_4$ | 77/66 |
| H | CHOHMe | H | 8.85 | - | 8.95 | - | $D_2O$ | 139/68 |
| H | COOMe | H | 8.70 | - | 9.15 | - | $CDCl_3$ | 3/67 |
| H | $NO_2$ | H | 8.73 | - | 9.24 | - | $CCl_4$ | 259/70 |
| H | 2-benzo-thiazolyl | H | 7.15 | - | 7.33 | - | $CDCl_3$ | 143/72 |
| 5-Monosubstituted isoxazoles | | | | | | | | |
| H | H | $(CH_2)_9CH=CH_2$ | 8.12 | 5.95 | - | $1.6_{3-4}$ | $CDCl_3$ | 276/80 |
| H | H | $CH=CH_2$ | 8.15 | 6.17 | - | - | $CDCl_3$ | 139/68 |
| H | H | C≡CPh | 8.31 | 6.50 | - | $1.9_{3-4}$ | $CDCl_3$ | 105/81 |
| H | H | C≡CCH=CHCOOMe | 8.32 | 6.55 | - | $1.9_{3-4}$ | $CDCl_3$ | 105/81 |
| H | H | CHOHMe | 8.80 | 6.80 | - | - | $D_2O$ | 139/68 |
| H | H | CH=NOH | 8.69 | 6.80 | - | $2.4_{3-4}$ | DMSO-$d_6$ | 166/70 |
| H | H | COOMe | 8.53 | 7.07 | - | $1.8_{3-4}$ | $CDCl_3$ | 3/67 |
| H | H | $CH_2SiMe_3$ | 7.98 | 5.75 | - | $2.0_{3-4}$ | $CCl_4$ | 20/79 |
| H | H | $SiMe_3$ | 8.14 | 6.46 | - | $1.5_{3-4}$ | $CCl_4$ | 20/79 |

Some examples of chemical shifts of the isoxazole protons in disubstituted isoxazoles with functionalized substituents are reported in Table 1.19. The shift due to the substituent can be evaluated relative to the chemical shift of the parent alkyl- or arylisoxazole obtained in similar conditions (i.e., in the same solvent). Strong deshielding shifts due to the negative inductive effects can be observed in nitro,[78/66,11/69,259/70,308/80,149/81,115/83] cyano,[48/61,258/82,94/84] and aldehydo[48/61] derivatives, for esters,[3/67,80/67,160/70,259/70,63/81,22/82,138/83,124/84] amides,[259/70,22/82] and ketones.[259/70,213/80,77/83,173/83,338/83] Small downfield shifts are caused by halogenated substituents.[11/69,259/70,213/80] Some examples of sulfurated and phosphorated derivatives[47/80,197/80,52C/81] are also reported in Table 1.19.

PMR data have been used to recognize regioisomeric isoxazoles[32/70,53/70,171/78,77/83,124/84] as well as to evaluate their ratio in reaction mixtures.[166/71,12/73,28C/73] The formation of 3-aryl-5-substituted isoxazoles from α-nitroketones and isopropenyl acetate has been followed and studied by PMR data.[174B/72] The results of the homolytic bromination of a number of 3,5-

TABLE 1.19. PMR DATA OF DISUBSTITUTED ISOXAZOLES (δ, TMS = 0)

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $R_4$ | $R_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|
| 4,5-Disubstituted isoxazoles | | | | | | | |
| H | $NO_2$ | Me | 8.87 | - | 2.91 | neat | 11/69 |
| H | $NO_2$ | 4-$NO_2C_6H_4$ | 9.35 | - | - | $(CD_3)_2CO$ | 259/70 |
| H | Br | Me | 8.15 | - | 2.36 | neat | 11/69 |
| H | Cl | Me | 8.16 | - | 2.35 | neat | 11/69 |
| H | Cl | Ph | 8.20 | - | - | $CCl_4$ | 259/70 |
| H | I | Ph | 8.57 | - | - | $(CD_3)_2CO$ | 259/70 |
| H | COMe | Me | 8.57 | 2.50 | 2.76 | $CDCl_3$ | 173/83 |
| H | $COCHMe_2$ | $CHMe_2$ | 8.52 | - | - | $CDCl_3$ | 173/83 |
| H | $COCMe_3$ | $CMe_3$ | 8.50 | - | - | $CDCl_3$ | 173/83 |
| H | COPh | Ph | 8.52 | - | - | $CDCl_3$ | 173/83 |
| $R_3$ | $R_4$ | $R_5$ | $H_4$ | $R_3$ | $R_5$ | Solvent | References |
| 3,5-Disubstituted isoxazoles | | | | | | | |
| CN | H | Ph | 6.9 | - | - | $CDCl_3$ | 94/84 |
| $NO_2$ | H | Me | 6.67 | - | 2.63 | - | 308/80 |
| $NO_2$ | H | $CH_2OH$ | 6.95 | - | 3.06 | - | 308/80 |
| $NO_2$ | H | Ph | 7.06 | - | - | $CDCl_3$ | 78/66 |
| COOMe | H | Me | 6.47 | - | - | $(CD_3)_2CO$ | 259/70 |
| CONHCl | H | Me | 6.64 | - | 2.66 | $CDCl_3$ | 22/82 |
| $CONH_2$ | H | Ph | 7.11 | - | - | $(CD_3)_2CO$ | 259/70 |
| COOEt | H | 4-$MeC_6H_4$ | 7.37 | - | - | DMSO-$d_6$ | 138/83 |
| COOH | H | 4-$MeC_6H_4$ | 7.30 | - | - | DMSO-$d_6$ | 138/83 |
| Me | H | COOMe | 6.93 | - | - | $(CD_3)_2CO$ | 259/70 |
| Ph | H | COOMe | 7.30 | - | - | $CDCl_3$ | 258/82 |
| 4-$ClC_6H_4$ | H | COOEt | 7.23 | - | - | $CDCl_3$ | 160/70 |
| COOMe | H | COOMe | 7.30 | - | - | $CDCl_3$ | 63/81 |
| COPh | H | COOMe | 7.44 | - | - | $CDCl_3$ | 124/84 |
| Me | H | COPh | 6.78 | 2.36 | - | $CCl_4$ | 259/70 |
| Mesityl | H | $COCH_2CH_2Br$ | 6.90 | - | - | $CDCl_3$ | 77/83 |
| Ph | H | Cl | 6.37 | - | - | $CCl_4$ | 259/70 |
| Cl | H | Ph | 6.75 | - | - | $(CD_3)_2CO$ | 259/70 |
| Br | H | COOH | 7.17 | - | - | $CDCl_3$ | 213/80 |
| Br | H | COMe | 6.93 | - | - | $CDCl_3$ | 213/80 |
| Br | H | $COCH_2Br$ | 7.10 | - | - | $CDCl_3$ | 213/80 |
| Br | H |  | 6.32 | - | - | $CDCl_3$ | 213/80 |
| SAc | H | Me | 6.35 | - | - | $CDCl_3$ | 47/80 |
| SAc | H | Ph | 6.82 | - | - | $CDCl_3$ | 47/80 |
| SH | H | Me | 5.93 | - | 2.73 | $CDCl_3$ | 47/80 |
| SH | H | Ph | 6.38 | - | - | $CDCl_3$ | 47/80 |
| Ph | H | P(OMe)(Me)O | 7.41 | - | - | $CDCl_3$ | 197/80 |
| 4-$ClC_6H_4$ | H | P(OH)(Me)O | 7.02 | - | - | $CDCl_3$ | 197/80 |
| $R_3$ | $R_4$ | $R_5$ | $H_5$ | $R_3$ | $R_4$ | Solvent | References |
| 3,4-Disubstituted isoxazoles | | | | | | | |
| Ph | CN | H | 8.98 | - | - | $CDCl_3$ | 258/82 |
| Ph | $NO_2$ | H | 9.29 | - | - | $CCl_4$ | 259/70 |
| | | | 9.93 | - | - | $(CD_3)_2CO$ | 259/70 |
| 2-Acetoxy-2-bornylCO | $NO_2$ | H | 9.33 | - | - | $CDCl_3$ | 149/81 |
| $CH_2CH(OMe)_2$ | $NO_2$ | H | 9.25 | - | - | $CDCl_3$ | 115/83 |
| $CH_2CHO$ | $NO_2$ | H | 9.86 | - | - | $CDCl_3$ | 115/83 |
| Me | COOEt | H | 9.92 | 2.45 | - | - | 80/67 |

TABLE 1.19. *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $H_5$ | $R_3$ | $R_4$ | Solvent | References |
|---|---|---|---|---|---|---|---|
| Ph | COOMe | H | 9.00 | - | - | $CDCl_3$ | 258/82 |
| 4-$ClC_6H_4$ | COOEt | H | 8.95 | - | - | $CDCl_3$ | 160/70 |
| COPh | COOMe | H | 9.03 | - | - | $CDCl_3$ | 124/84 |
| Mesityl | $COCH_2CH_2Br$ | H | 9.09 | - | - | $CDCl_3$ | 77/83 |
| Ph | $COCH_3$ | H | 8.86 | - | - | - | 338/83 |
| Ph | Cl | H | 8.93 | - | - | $(CD_3)_2CO$ | 259/70 |
| Ph | I | H | 8.45 | - | - | $CCl_4$ | 259/70 |
| | | | 8.92 | - | - | $(CD_3)_2CO$ | 259/70 |
| 2,6-$Cl_2C_6H_3$ | $CH_2SPh$ | H | 8.25 | - | - | $CDCl_3$ | 52C/81 |
| 4-$NO_2C_6H_4$ | $CH_2SPh$ | H | 8.13 | - | - | $CDCl_3$ | 52C/81 |
| Mesityl | $CH_2SPh$ | H | 8.20 | - | - | $CDCl_3$ | 52C/81 |
| 4-$FC_6H_4$ | P(Me)(OH)O | H | 9.40 | - | - | DMSO-$d_6$ | 197/80 |

dimethylisoxazoles have been evaluated by PMR spectroscopy. The characteristic values of the chemical shifts of the methyl groups provided evidence of the higher reactivity of the $C_5$-methyl.[186/74]

The mechanism of formation of isoxazoles by reaction of nitrile oxides and monoacetylenic compounds has been studied by deuterium incorporation. In two cases the ratio of the 4-deuterated isoxazoles has been evaluated by a PMR method along with mass spectrometry.[194B/70] The synthesis of trimethylisoxazole from nitroethane has been studied similarly. Acetaldehyde-$d_4$ has been used as an intermediate, and partial deuteration of $C_4$-Me has been found and discussed.[37/69]

The shielding effect of hydroxy, methoxy, and amino groups can probably be explained better by a positive mesomeric effect. In Table 1.20 some examples of chemical shifts of simple 3-hydroxyisoxazoles are reported. The fact that the upfield shift of 3-hydroxy-5-phenylisoxazole is smaller than expected could be explained by intermolecular hydrogen bonds in solution.

Some methoxy derivatives[97/64,259/70,116/71,159/81] have been studied as models to check the presence of tautomeric forms in isoxazolinones. Tautomerism will be discussed in Part 2 of the present work, but here we remind readers that these studies make it possible to assert that 3-isoxazolinones are primarily 3-hydroxyisoxazoles.[97/64] Moreover, it is worth noting the shielding influence of methoxy and ethoxy groups on the vicinal protons.[97/64]

One of the best known 3-hydroxyisoxazoles is muscimol (**2**),[122/65] which was isolated from *Amanita* species. Owing to their interesting neuropharmacological properties, much synthetic work, including PMR data of muscimol (**2**) and analogues, has been reported.[130/68,3/74,1/80.33/80,162/80.103/82] Selected examples of PMR data of muscimol derivatives or analogues are reported in Table 1.20.

Another bioactive natural isoxazole is triumferol (**4**),[236/81] whose 4-hydroxyisoxazole structure was assigned by analysis of the very simple NMR spectra of the parent compound, as well as of its O-acyl and O-methyl derivatives, and

TABLE 1.20. PMR DATA OF HYDROXY- AND METHOXYISOXAZOLES (δ, TMS = 0)

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $H_4$ | $H_5$ | $R_3$ | $R_4$ | $R_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|
| OH | H | H | - | 6.13 | 8.57 | 11.1 | - | - | DMSO-$d_6$ | 23/81 |
| | | | | $J_{4,5}$ = 2.0 Hz | | | | | | |
| OH | H | $cyC_3H_5$ | - | 5.70 | - | - | - | - | $(CD_3)_2CO$ | 23/67 |
| | | | - | 5.67 | - | - | - | - | DMSO-$d_6$ | |
| OH | H | Me | - | 5.66 | - | 11.75 | 2.32 | - | $CDCl_3$ | 214/83 |
| OH | H | Ph | - | 6.18 | - | - | - | - | $CCl_4$ | 259/70 |
| | | | | 6.58 | - | 11.40 | - | - | DMSO-$d_6$ | 97/64 |
| OH | H | $CH_2NH_2$ | - | 5.85 | - | - | - | 4.18 | $D_2O$ | 122/65 |
| OH | H | $CH_2OH$ | - | 5.92 | - | 7.10 | - | 4.60 | DMSO-$d_6$ | 162/80 |
| | | | | | | | | | $CDCl_3$ (1:8) | |
| OH | H | COOMe | - | 6.70 | - | - | - | 3.87 | DMSO-$d_6$ | 33/80 |
| OH | H | $CH_2COOH$ | - | 6.00 | - | 7.72 | - | 3.80 | $(CD_3)_2CO$ | 214/83 |
| OMe | H | Ph | - | 6.43 | - | - | - | - | $(CD_3)_2CO$ | 259/70 |
| | | | - | 6.06 | - | 3.97 | - | - | $CCl_4$ | 97/64 |
| | | | - | 6.10 | - | 3.85 | - | - | $CDCl_3$ | 78/66 |
| OEt | H | Ph | - | 6.03 | - | 4.30 | - | - | $CCl_4$ | 97/64 |
| OMe | H | $CH_2Br$ | - | 5.80 | - | 3.87 | - | 4.23 | $CCl_4$ | 162/80 |
| OTs | H | Me | - | 6.09 | - | - | - | - | $CDCl_3$ | 103/82 |
| OTs | H | Ph | - | 6.58 | - | - | - | - | $CDCl_3$ | 103/82 |
| H | OH | H | 8.25 | - | 8.33 | - | 8.18 | - | $(CD_3)_2CO$ | 236/81 |
| H | OAc | H | 8.34 | - | 8.76 | - | 2.28 | - | $CDCl_3$ | 236/81 |
| H | OMe | H | 8.34 | - | 8.50 | - | 3.80 | - | $(CD_3)_2CO$ | 236/81 |
| H | H | OMe | 8.11-8.15 | 5.26-5.29 | - | - | - | - | $CHCl_3$ | 116/71 |
| | | | 8.12-8.15 | 5.28-5.32 | - | - | - | - | dioxane | 116/71 |
| | | | 8.15-8.18 | 5.36-5.40 | - | - | - | - | *M* HCl | 116/71 |
| | | | 8.78-8.83 | 6.08-6.14 | - | - | - | - | 70% $HClO_4$ | 116/71 |
| Me | H | OMe | - | 5.08 | - | 2.10 | - | 3.91 | $CCl_4$ | 61/62 |
| | | | - | 5.10 | - | 2.17 | - | 3.93 | $CDCl_3$ | 31/70 |
| $cyC_5H_9$ | H | OMe | - | 5.08 | - | - | - | 3.96 | $CDCl_3$ | 31/70 |
| Ph | H | OMe | - | 5.37 | - | - | - | 3.94 | $CCl_4$ | 61/62 |
| | | | - | 5.54 | - | - | - | 4.03 | $CDCl_3$ | 31/70 |
| | | | - | 6.17 | - | - | - | 4.08 | DMSO-$d_6$ | 31/70 |
| | | | - | 5.87 | - | - | - | - | $(CD_3)_2CO$ | 259/70 |
| COOMe | H | OMe | - | 5.64 | - | - | - | - | $CDCl_3$ | 22/81 |
| $CH_2OPh$ | H | OMe | - | 5.20 | - | - | - | 3.80 | $CDCl_3$ | 198/79 |
| | | | - | 5.60 | - | - | - | 4.00 | DMSO-$d_6$ | 198/79 |

definitively assured by synthesis. The $H_3$ signal was identified by its broadness due to the quadrupole effect of the neighboring nitrogen atom.

Studies on tautomerism showed that in general the 4-hydroxyisoxazole structure is preferred to that of 4-isoxazolinone.[187/71,222/72] Tautomerism of 3,5-dihydroxy-4-phenylisoxazole (phenyldisic acid) has also been studied by PMR. Data on the corresponding methoxy derivatives have been reported.[80/71]

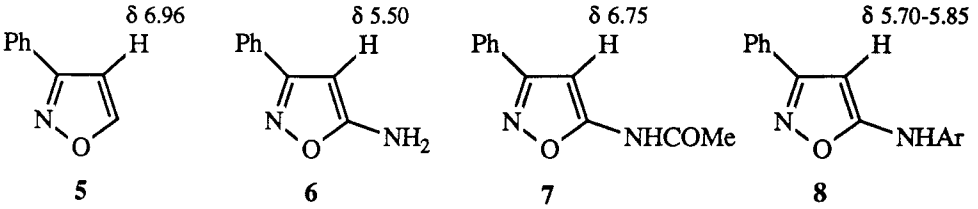
Other 4-aryl-3,5-dihydroxyisoxazoles show different chemical shifts of the acid protons, depending on the amount of water in the solution: 12.0 ppm in

TABLE 1.21. PMR DATA OF AMINOISOXAZOLES AND DERIVATIVES (δ, TMS = 0)

| $R_3$ | $R_4$ | $R_5$ | $H_3$ | $H_4$ | $H_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|
| H | H | $NH_2$ | 7.98 | 5.11 | - | $CDCl_3$ | 42/66 |
| Me | H | $NH_2$ | - | 4.28 | - | $(CD_3)_2CO$ | 259/70 |
| *i*-Pr | H | $NH_2$ | - | 4.95 | - | $CDCl_3$ | 75/84 |
| *sec*-Bu | H | $NH_2$ | - | 4.94 | - | $CDCl_3$ | 75/84 |
| $NH_2$ | H | H | - | 5.77 | 7.88 | $CDCl_3$ | 42/66 |
| $NH_2$ | H | Me | - | 5.60 | - | $(CD_3)_2CO$ | 259/70 |
| NHAc | H | Me | - | 6.65 | - | $(CD_3)_2CO$ | 259/70 |
| Ph | H | $NH_2$ | - | 5.50 | - | $(CD_3)_2CO$ | 259/70 |
| Ph | H | NHAc | - | 6.75 | - | $(CD_3)_2CO$ | 259/70 |
| Ph | H | NHPh | - | 5.85 | - | $CDCl_3$ | 28/72 |
| $NH_2$ | H | Ph | - | 6.32 | - | $(CD_3)_2CO$ | 259/70 |
| NHAc | H | Ph | - | 7.28 | - | $(CD_3)_2CO$ | 259/70 |
| $CH_2CH(OMe)_2$ | $NH_2$ | H | - | - | 7.95 | $CDCl_3$ | 115/83 |
| $CH_2CH(OMe)_2$ | NHAc | H | - | - | 9.04 | $CDCl_3$ | 115/83 |

dimethyl sulfoxide (DMSO-$d_6$), 9.5 ppm for the "semihydrate," and 6.6 ppm for the dihydrate. Furthermore, the chemical shifts of the aromatic protons show that in this case the isoxazole ring behaves as a strong electron-withdrawing group, comparable to the nitro group.[181/75]

As expected, the amino group also gives rise to a strong upfield shift of the neighboring protons (Table 1.21). However, it is worth noting that the corresponding acetylamino groups show the opposite effect. For example, considering 3-phenylisoxazole (**5**)($H_4$ in $Me_2CO$-$d_6$ δ 6.96) as the parent compound, in the same solvent $H_4$ absorbs at δ 5.50 in 5-amino-3-phenylisoxazole (**6**) and at δ 6.75 in 5-acetamino-3-phenylisoxazole (**7**). This fact can be explained when the C=O group lying in the same plane of the ring influences the neighboring protons by its anisotropic effect. Similarly, 5-arylamino-3-phenylisoxazoles (**8**) show an $H_4$ downshift signal (at δ 5.70–5.85) due to the anisotropic effect of the phenyl ring.[28/72]




**5** **6** **7** **8**

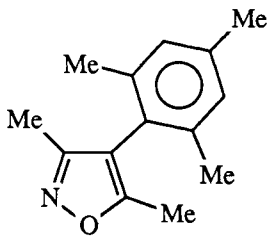
Information on the structure can also be obtained by examination of the chemical shifts of some substituents of the isoxazole ring, such as the methyl and phenyl groups. In fact, the chemical shifts of the methyl groups in methyl-

isoxazoles are again, as for the protons, determined by their position on the ring and by the influence of the neighboring substituents.

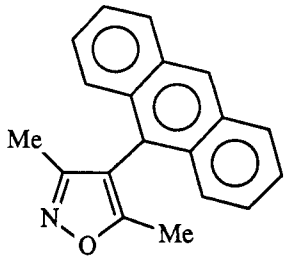
Although the differences in chemical shifts are not as marked as for the protons, the methyl groups absorb from the high to the weak field in the following sequence: $C_4$-Me, $C_3$-Me, and $C_5$-Me. For instance, the monomethyl isoxazoles show (as reported in Table 1.14) the following chemical shifts for the methyl groups: $\delta$ 2.00 ($C_4$-Me in 4-methylisoxazole), $\delta$ 2.26 ($C_3$-Me in 3-methylisoxazole), and $\delta$ 2.36 ($C_5$-Me in 5-methylisoxazole). In trimethylisoxazole the mutual shielding effect is indicated by the following chemical shifts: $\delta$ 2.12 (3-Me), $\delta$ 1.85 (4-Me), and $\delta$ 2.26 (5-Me).

The influence of a phenyl group on the methyls is not very strong, as on the protons, and seems to be due to conjugation effects. Furthermore, the chemical shift of a methyl in the 4-position is more affected by the presence of a phenyl in position 5 than in position 3. Compare, for example, the chemical shifts of 4-methyl-5-phenyl isoxazole (Table 1.16) and 3,5-diphenyl-4-methylisoxazole (Table 1.22).

The magnetic anisotropy of aromatic systems has also been studied in the case of two aryl-substituted 3,5-dimethylisoxazoles: **9** and **10**.[14/76] The chemical shift differences ($\Delta\delta$) of the PMR signals of the *p*- and *o*-methyl groups in the case of the mesityl substituent and that of $H_1$ and $H_4$ for the 9-anthranyl substituent are considered a measure of the anisotropic phenomenon. The data obtained for **9** ($\Delta\delta$ = 0.31) and for **10** ($\Delta\delta$ = 0.46) are, as expected, not very high compared to those of other aromatic systems. However, they are similar to those of the corresponding pyrazoles.




**9**




**10**

From the point of view of methyl chemical shifts it is interesting to note that the lacking of coplanarity of the aromatic substituent and the isoxazole ring induces an upfield shift for the isoxazole $C_3$ and $C_5$ methyls: $\delta$ 1.98 and $\delta$ 2.17, respectively. Probably for similar reasons, an even larger upfield shift has been detected for a $Ph_2C$–OH substituent at $C_4$: $\delta$ 1.57 ($C_3$-Me) and $\delta$ 1.82 ($C_5$-Me).[42/66] Similar behavior is shown in the case of 3,5-dimethyl-4-phenylazo- and 3,5-dimethyl-4-(2′-benzoyl-4′-chlorophenylazo)isoxazole (see Table 1.22).

The influence on the chemical shifts of the methyl groups of other functionalized substituents, also depending on their position, can be deduced by the large number of examples reported in Tables 1.16 and 1.19 for disubstituted

TABLE 1.22. CHEMICAL SHIFTS OF METHYL GROUPS AND OF OTHER GROUPS IN TRISUBSTITUTED ISOXAZOLES (δ, TMS = 0)

| $R_3$ | $R_4$ | $R_5$ | $R_3$ | $R_4$ | $R_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|
| Me | Me | Me | 2.12 | 1.85 | 2.25 | $CCl_4$ | 259/70 |
| Me | $CH_2Ph$ | Me | 1.98 | - | 2.23 | $CCl_4$ | 259/70 |
| Me | Ph | Me | 2.22 | - | 2.37 | $CCl_4$ | 259/70 |
| Me | 4-$NO_2C_6H_4$ | Me | 2.35 | - | 2.53 | $CDCl_3$ | 259/70 |
| Me | mesityl | Me | 1.99 | - | 2.17 | $CDCl_3$ | 14/76 |
| Me | 9-anthranyl | Me | 1.98 | - | 2.17 | $CDCl_3$ | 14/76 |
| Me | Me | Ph | 2.27 | 2.13 | - | $CDCl_3$ | 98/76 |
| Me | Me | 4-$NO_2C_6H_4$ | 2.30 | 2.21 | - | $CDCl_3$ | 98/76 |
| Me | Me | 2-thienyl | 2.25 | 2.13 | - | $CDCl_3$ | 98/76 |
| Me | Me | 2-pyridyl | 2.27 | 2.11 | - | $CDCl_3$ | 98/76 |
| Me | Me | 4-Me-2-pyridyl | 2.28 | 2.10 | - | $CDCl_3$ | 98/76 |
| Me | Me | 3,5-$Me_2$-2-pyridyl | 2.32 | 2.20 | - | $CDCl_3$ | 98/76 |
| Ph | Me | Ph | - | 2.21 | - | $CDCl_3$ | 259/70 |
| Me | $CH_2OH$ | Me | 2.21 | - | 2.33 | $CDCl_3$ | 259/70 |
| Me | $CH_2OAc$ | Me | 2.18 | - | 2.34 | $CCl_4$ | 259/70 |
| Me | $C(Ph)_2OH$ | Me | 1.57 | - | 1.82 | $CDCl_3$ | 259/70 |
| Me | COPh | Me | 2.24 | - | 2.32 | $CCl_4$ | 259/70 |
| Me | CHO | Ph | 2.48 | - | - | $CDCl_3$ | 177/83 |
| Me | CN | Me | 2.38 | - | 2.62 | $CCl_4$ | 259/70 |
| Me | COCl | Me | 2.43 | - | 2.77 | $CCl_4$ | 259/70 |
| Me | COOH | Me | 2.37 | - | 2.42 | $CDCl_3$ | 259/70 |
| Me | COOEt | Me | 2.50 | - | 2.75 | $CDCl_3$ | 80/67 |
| Me | COOH | Ph | 2.54 | - | - | $CDCl_3$ | 53/62 |
| Me | COOEt | Ph | 2.55 | - | - | $CDCl_3$ | 53/62 |
| Ph | COOH | Me | - | - | 2.75 | $CDCl_3$ | 53/62 |
| Ph | COOEt | Me | - | - | 2.53 | $CDCl_3$ | 53/62 |
| Me | Me | I | 2.24 | 1.93 | - | $CDCl_3$ | 98/76 |
| Me | Cl | Me | 2.17 | - | 2.33 | $CCl_4$ | 259/70 |
| Me | Br | Me | 2.21 | - | 2.37 | $CCl_4$ | 259/70 |
| Me | I | Me | 2.22 | - | 2.45 | $CCl_4$ | 259/70 |
| Me | Cl | Ph | 2.28 | - | - | $CCl_4$ | 259/70 |
| Me | Br | Ph | 2.28 | - | - | $CCl_4$ | 259/70 |
| Me | I | Ph | 2.29 | - | - | $CCl_4$ | 259/70 |
| Ph | Br | Me | - | - | 2.42 | $CCl_4$ | 259/70 |
| Ph | I | Me | - | - | 2.49 | $CCl_4$ | 259/70 |
| Me | N=NPh | Me | 2.46 | - | 2.74 | $CCl_4$ | 259/70 |
| Me | 2-benzoyl-4-Cl-phenylazo | Me | 2.49 | - | 1.98 | $CDCl_3$ | 80C/75 |
| Me | $NO_2$ | Me | 2.49 | - | 2.77 | $CCl_4$ | 259/70 |
| | | | 2.61 | - | 2.88 | $CDCl_3$ | 259/70 |
| | | | 2.55 | - | 2.80 | $CDCl_3$ | 110/73 |
| Me | $NO_2$ | CH=CHPh | 2.60 | - | - | $CDCl_3$ | 110/73 |
| Me | $NO_2$ | CH=CHC$_6$H$_4$OMe-4 | 2.60 | - | - | $CDCl_3$ | 110/73 |
| Mesityl | Me | SPh | - | 1.78 | - | $CDCl_3$ | 52C/81 |
| 4-$NO_2C_6H_4$ | Me | SPh | - | 2.20 | - | $CDCl_3$ | 52C/81 |
| 2,6-$Cl_2C_6H_3$ | Me | SPh | - | 1.86 | - | $CDCl_3$ | 52C/81 |
| 2,6-$Cl_2C_6H_3$ | SPh | Me | - | - | 2.52 | $CDCl_3$ | 52C/81 |
| Me | $NH_2$ | Me | 2.00 | 2.68 | 2.10 | $CDCl_3$ | 67/61 |
| Me | Me | $NH_2$ | 2.03 | 1.65 | 4.63 | $CDCl_3$ | 67/61 |
| | | | 2.00 | 1.70 | - | DMSO-$d_6$ | 98/76 |
| Ph | COOEt | $NH_2$ | 7.2-7.8 | - | 6.37 | $CDCl_3$ | 186/71 |

TABLE 1.22. *(Continued)*

| $R_3$ | $R_4$ | $R_5$ | $R_3$ | $R_4$ | $R_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|
| Me | Ph | $NH_2$ | 2.2 | 7.3 | 4.6 | $CDCl_3$ | 31/80 |
| Ph | Ph | $NH_2$ | - | - | 4.6 | $CDCl_3$ | 31/80 |
| OH | Me | Me | - | 1.83 | 2.22 | $CDCl_3$ | 23/67 |
| | | | - | 1.73 | 2.14 | DMSO-$d_6$ | 23/67 |
| OH | Et | Me | 11.80 | 1.15<br>2.32 | 2.23 | $CDCl_3$ | 23/67 |
| OH | Ph | Me | 11.70 | 7.2-7.7 | 2.41 | $CDCl_3$ | 103/82 |
| OMe | Me | Me | - | 1.74 | 2.20 | $CCl_4$ | 97/64 |
| OMe | $CH_2OH$ | Me | 3.92 | 4.33 | 2.31 | $CDCl_3$ | 162/80 |
| OMe | $CH_2Cl$ | Me | 3.97 | 4.27 | 2.35 | $CDCl_3$ | 162/80 |
| Ph | Me | OMe | - | 1.60 | - | $CCl_4$ | 61/62 |
| Me | Me | OMe | 2.13 | 1.75 | - | $CDCl_3$ | 31/70 |
| Me | COOEt | OMe | 2.29 | - | - | $CCl_4$ | 61/62 |
| OMe | 3-MeO-5-Ph-4-isoxazolyl | Ph | 3.95 | - | 7.60 | $CDCl_3$ | 78/66 |
| Me | $SiMe_3$ | Me | 2.26 | 0.32 | 2.38 | $CDCl_3$ | 193/80 |
| Me | $SnMe_3$ | Me | 2.20 | 1.32 | 2.33 | $CDCl_3$ | 193/80 |
| Me | H | $CH_2SiMe_3$ | 2.16 | 5.56 | 2.10($CH_2$) | $CDCl_3$ | 193/80 |
| Me | Me | $CH_2SiMe_3$ | 2.12 | 1.77 | 2.04($CH_2$) | $CDCl_3$ | 193/80 |
| Me | Me | $CH_2SnMe_3$ | 2.14 | 1.80 | 2.22($CH_2$) | $CDCl_3$ | 193/80 |
| Me | 1-pyperidinyl$SO_2$ | Me | 2.43 | - | 2.60 | DMSO-$d_6$ | 129/81 |
| Me | 4-$ClC_6H_4NHSO_2$ | Me | 2.24 | - | 2.40 | DMSO-$d_6$ | 129/81 |

isoxazoles and in Table 1.22 for trisubstituted isoxazoles. The PMR data of a noteworthy variety of 4-substituted 3,5-dimethylisoxazoles[67/61,53/62,80/67,259/70,110/73,80C/75,14/76,129/81] and 5-substituted 3,4-dimethylisoxazoles have been studied.[67/61,98/76] Also in these cases, strong deshielding effects can be observed for the electron-withdrawing substituents (such as CN, COCl, COOH, COOR, $NO_2$, and Ph–N=N–) and shielding effects for electron-donating substituents (such as OMe, $NH_2$, and OH).[67/61,186/71,98/76] No effects can be observed for the halogenoisoxazoles (see Table 1.22).[259/70] As described for the protons, the 4-substituents influence the $C_5$ substituents more intensely than the $C_3$ substituents. Some examples of 3-aryl-4-methyl-5-phenylthioisoxazoles and of the regioisomeric 3-aryl-5-methyl-4-phenylthioisoxazoles[52C/81] are also reported in Table 1.22.

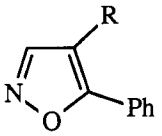
The PMR data of 3,4-disubstituted 5-aminoisoxazoles show that the compounds are in the amino form, owing to the presence of a singlet (2H) at $\delta$ 4.6 which exchanges with $D_2O$.[31/80] The structure of the acetylation product of 3,4-diphenyl-5-aminoisoxazole has been established to be 3,4-diphenyl-5-diacetylaminoisoxazole through the equivalence of the two acetyl groups in the PMR spectrum recorded in different solvents.[152B/74] Synthetic intermediates and 4-substituted derivatives of muscimol (**2**) and ibotenic acid (**1**) have been synthesized. Their structure was confirmed by PMR data, as exemplified in Table 1.22

by 3-hydroxy-5-methyl-4-phenylisoxazole[103/82] and 4-chloromethyl-3-methoxy-5-methyl- and 4-hydroxymethyl-3-methoxy-5-methylisoxazoles.[162/80]

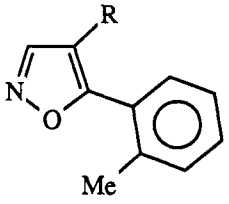
The chemical shifts of the methyl and methylene groups are not affected greatly by the presence of metals of group IV (Si or Sn), as shown by the examples reported in Table 1.22. The principal rule of the additivity of the substituent effect on spectroscopic data of methyl groups, known for toluene derivatives, has also been used to calculate the chemical shift of methylazoles.[195/77] Fourteen variously substituted isoxazoles have been considered. Differences from the calculated and observed chemical shifts were in the range 0–0.26 ppm.

Sometimes the chemical shifts of protons not directly linked to the isoxazole ring can be indicative of the relative position of the substituents. For example, the two isomeric compounds 4-carbethoxy-3-methyl-5-phenylisoxazole and 4-carbethoxy-5-methyl-3-phenylisoxazole show different chemical shifts for the protons of the ethoxy group: $\delta$ 1.30 (t, Me), $\delta$ 4.33 (q, $CH_2O$) for the former compound and $\delta$ 1.17 (t, Me), $\delta$ 4.30 (q, $CH_2O$) for the latter compound. The shift at the lower field (0.13 ppm) for the methyl group of the first compound indicates that the phenyl group at $C_5$ can exert its anisotropic effect on the neighboring ethoxy group.[53/62] Similar results have been reported in other cases of variously substituted 4- or 5-carbomethoxyisoxazoles.[117/80,200/80]

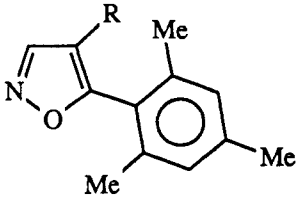
It has been suggested that even the shape of the phenyl signals can be indicative for structural determination. For example, the alkylation in position 4 of the isoxazole ring or on the phenyl group in position 5 (as for **11–17**, see Tables 1.15 and 1.16) causes a hindrance to the rotation of the phenyl group, which affects the shape of the signal. In fact, the aromatic protons show two multiplets when a free rotation is possible (**11–13**) and only a broad singlet when the rotation is hindered[11/69] (**14–17**).




**11** R = Me
**12** R = $Me_2CH$

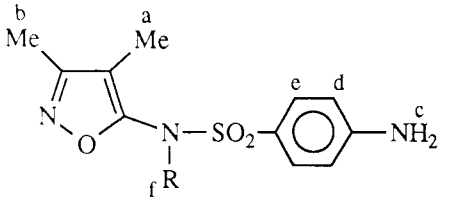



**13** R = H
**14** R = Me
**15** R = $Me_2CH$

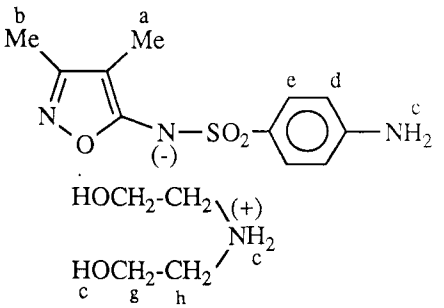



**16** R = H
**17** R = Me

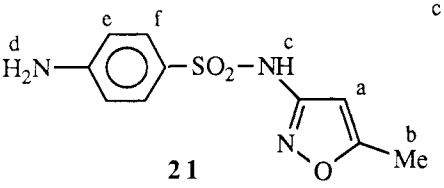
The structure of some regioisomeric glycosyl isoxazoles,[98/70,44/73,33/76,72/79,111/80] obtained by 1,3-dipolar cycloaddition reactions, and of some isoxazolylpenicillins[191/80,138/83] has been determined by a PMR technique. To find a rapid method of identifying thereapeutic sulfonamides, the PMR data in DMSO-$d_6$ of 21 commercial products have been recorded, among them sulfisoxazole (**18**),



**18** R = H
**19** R = Ac



**20**

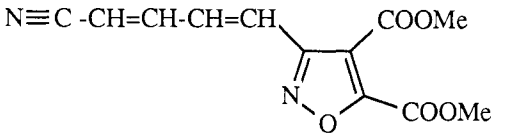


**21**

acetylsulfisoxazole (**19**), sulfisoxazole diolamine (**20**), and sulfamethoxazole (**21**).[182/72] The following data are diagnostic for **18–21**:

| | a | b | c | d | e | f | g | h |
|---|---|---|---|---|---|---|---|---|
| **18** | 1.67 | 2.08 | 6.1 | 6.58 | 7.42 | 10.1 | - | - |
| **19** | 1.88 | 2.25 | 6.40 | 6.68 | 7.62 | 1.88 | - | - |
| **20** | 1.58 | 1.92 | 5.75 | 6.50 | 7.40 | - | 3.67 | 2.97 |
| **21** | 6.13 | 2.30 | 6.00 | 6.65 | 7.57 | 10.9 | - | - |

By means of UV spectra and NMR data of the aromatic protons the stability constants of the complexes of sulfonamides (e.g., **18** and **19**) with the cyclic polyether 18-crown-6 have been studied.[34/79] The configuration of the side chain of **22–24** has been established by accurate NMR spectra and decoupling experiments.

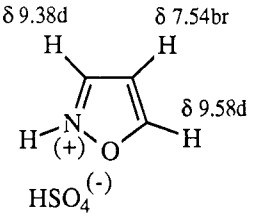


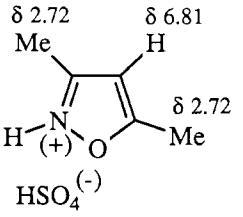
**22** *Z,Z*
**23** *E,Z*
**24** *E,E*

For the assignments of chemical shifts of the protons, the relative positions, either within the shielding cone of the anisotropic CN group or within the deshielding region of the isoxazole ring, have been taken into account.[147/75] By comparison of these data, the structure of 3,4-dimethyl-5-(4,5-biscarbomethoxyisoxazol-3-yl)pentadienonitrile has been established.[112/81] The PMR spectra of isoxazole and 3,5-dimethylisoxazole have also been recorded in concentrated sulfuric acid.[259/70] In these conditions the protonation of the

nitrogen atom of heterocyclic ring occurs, and hence changes in the PMR data are impressive.

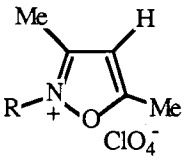
The isoxazolium salt shows a broad signal for $H_4$ and two doublets for $H_3$ and $H_5$:



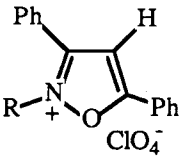




All the signals occur more downfield (1–1.2 ppm) than those of isoxazole. Also, the coupling constants are affected by the ring protonation: $J_{3-4}$ (1.9 Hz) differs from $J_{4-5}$ (2.8 Hz), the latter showing a higher value of about 1 Hz. 3,5-Dimethylisoxazolium salt again shows a deshielding of the signals with respect to the corresponding isoxazole.[259/70] It is worth noting the coincidence of the methyl chemical shift, probably due to the equalization of electronic density at $C_3$ and $C_5$.

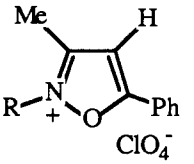
TABLE 1.23



**25**



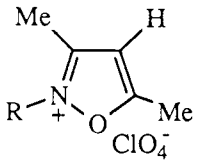
**26**



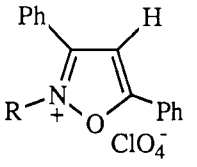
**27**

| | | R | Me-3 | Me-5 | H-4 | R | Solvent | References |
|---|---|---|---|---|---|---|---|---|
| **25** | **a** | $PhCH_2$ | 2.57 s | 2.70 s | 6.85 s | 5.72 s, 7.39 s | $CDCl_3$ | 151/68 |
| | **b** | $Me_3C$ | 2.62 s | 2.62 s | 6.74 br | 1.83 s | $CDCl_3$ | 151/68 |
| | **c** | PhCH(Me) | 2.05 s | 2.64 s | 6.82 s | 2.64 s, 6.10 m, 7.32 s | $CDCl_3$ | 151/68 |
| | **d** | $PhCMe_2$ | 2.07 s | 2.75 s | 6.84 s | 2.15 s, 7.44 s | $CDCl_3$ | 151/68 |
| | **e** | $(4\text{-Tolyl})_2CH$ | 2.17 s | 2.33 s | 6.04 s | 2.25 s, 5.61 s, 6.9-7.4 (ABq) | DMSO-$d_6$ | 163/80 |
| **26** | | Me | - | - | 8.31 s | 4.49 s | DMSO-$d_6$ | 163/80 |
| **27** | | $Ph_2CH$ | 2.29 s | - | 6.80 s | 5.63 s, 6.9-7.9 | DMSO-$d_6$ | 163/80 |

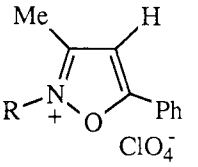
By contrast, the chemical shifts of the methyl groups in 2-substituted 3,5-dimethylisoxazolium perchlorate (**25**)[151/68,163/80] are sufficiently well separated (Table 1.23). The unusual upfield shift of the methyl protons at $C_3$ for **25c** and **d** is promoted by the anisotropic effect of the benzene ring of the quaternizing group.



25



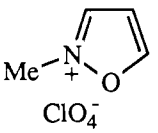
26



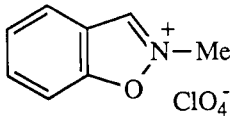
27

The chemical shifts of the methyls of 4-substituted-2,3,5-trimethylisoxazolium methosulfates have been reported:[111/83] 2-Me absorbs at 4.20–4.40 ppm; 3-Me at 2.60–3.00 ppm, 5-Me at 2.70–3.15 pøpm, and $Me_2SO_4$ at 3.75–3.80 ppm. The largest deshielding effect is shown by the 4-nitro derivative. The $C_3$ proton in 5-amino-2-methyl-4-phenylisoxazolium chloride shows a signal at 8.7 ppm.[10/74]

The *N*-methyl chemical shifts of a number of quaternized azoles have been studied to compare the reactivity of the ground state and the donating effect of the heteroatoms.[166/74] Data have been reported for 2-methylisoxazolium perchlorate and 2-methyl-1,2-benzisoxazolium perchlorate:



$\Delta\delta = 29$ Hz



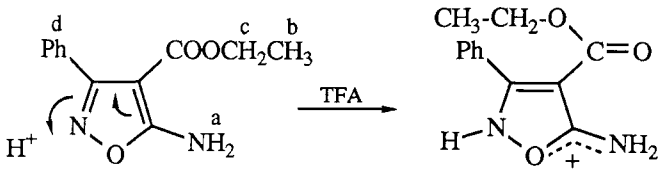
$\Delta\delta = 39$ Hz in sulfolane

(relative to $Me_2SO_4$ as internal reference at $\delta$ 4.00)

The strong downfield shift of the isoxazole derivatives with respect to other azoles indicates (1) that in the 1,2-azoles the donation order is NMe > S > O, as in the ground state; (2) that there is no parallel with the electrophilic substitution; and (3) that both resonance effects and electronic effects influence the chemical shifts.

The PMR data of 3-aryl-2-methyl-5-phenyl- and 5-aryl-2-methyl-3-phenylisoxazolium iodides have been studied[131/81] and compared with those of corresponding isoxazoles.[95/67,160/70] The chemical shifts of $H_4$ and the quaternary methyl group of the latter compounds have been found to correlate with $\sigma^*$ values. The $\rho$ value observed for $H_4$ in the latter group was 3.3 times that observed in the former group. Different treatments of the data have been considered. Results have been discussed to evaluate transmission of the substituent effect in quaternary systems.[131/81]

In studying the structure of heterocyclic $\beta$-enamino esters, protonation of ethyl 5-amino-4-isoxazolecarboxylates has been carried out.[208/70] The PMR data of ethyl 5-amino-3-phenylisoxazole-4-carboxylate recorded in $CDCl_3$ and TFA, particularly, indicate that protonation occurs in position 2, as for furan, thiophene, and pyrrole:




| | a | b | c | d |
|---|---|---|---|---|
| $CDCl_3$ | 6.37 | 1.13 | 4.20 | 7.2-7.8 |
| TFA | - | 0.79 | 3.87 | 7.1 |

The signals of the immonium protons are covered by that of solvent; however, the electron shift due to the protonation is evidenced by an upfield shift of the ester protons (0.34 ppm for the methylene and 0.33 ppm for the methyl), which moves them closer to the phenyl group. Furthermore, the phenyl, appearing in $CDCl_3$ as a large multiplet, is a broad singlet in TFA. This is another example of structure elucidation based on the shape and chemical shifts of the substituents. NMR spectra have shown that complexes of formula $(XY_2P{=}CHCOR)PdCl_2$, containing the 3-methyl-4-isoxazolyl radical, exist in solution as a mixture of *meso* and *d,l* forms, as do others in the same series.[182/76]

Spin-crossover complexes, including $[Fe(isoxazole)_6](ClO_4)_2$, have been studied using PMR. The spin-lattice relaxation times and the line width have been measured above and below the transition temperature. The distance of the hydrogen *ortho* to the nitrogen from the Fe(II) ion has been measured.[183/83] PMR studies on three transition-metal (Co, Cu, Ni) complexes of 3-amino-5-methylisoxazole[54/84] and PMR data for $[(NH_3)_5Co(isoxazole)](CClO_4)$,[132/82] ferrocenylmethylisoxazoles[332/83] have been reported.

The values of *coupling constants* of isoxazole have been measured[28B/64,75C/64,11/69,259/70] either for the pure product or in solution: $J_{3\text{-}4} = J_{4\text{-}5} = 1.6\text{–}1.7$ Hz. A long-range coupling constant, $J_{3\text{-}5}$, has also been reported (see Table 1.13). Similar coupling constants (1.6–2.0 Hz) have been observed (see Tables 1.14, 1.15, and 1.18) for some monosubstituted isoxazoles having two neighboring protons on the ring. The low values of the constants are common to other 1,2- and 1,3-azoles and are probably due to the strong bond polarization caused by the heteroatoms in the ring.[259/70]

More recently,[28/74] the signs and more precise values of the proton coupling

TABLE 1.24

| | $^3J_{3\text{-}4}$ | $^4J_{3\text{-}5}$ | $^3J_{4\text{-}5}$ | $^4J_o$H-Me | $^5J_m$H-Me | $^5J_o$Me-Me | $^5J_m$Me-Me |
|---|---|---|---|---|---|---|---|
| Isoxazole | 1.78 | 0.27 | 1.69 | - | - | - | - |
| 5-Me-isoxazole | 1.75 | - | - | -0.89 | 0.64 | - | - |
| 3,5-$Me_2$-isoxazole | - | - | - | -0.33(3) | - | - | -0.22 |
| 4,5-$Me_2$-isoxazole | - | - | - | -0.43 | 0.63 | 0.71 | - |
| TriMe-isoxazole | - | - | - | - | - | 0.0 + 0.03 | 0.20 |

constants of the isoxazole and its methyl derivatives have been reported in comparison with those of isothiazole (Table 1.24).

The magnitude of the coupling constant $^3J_{4-5}$ of 1.69 Hz is similar to that of furan (1.75 Hz) but is smaller than that of sulfur-containing heterocycles (4.90 Hz for thiophene and 4.66 Hz for isothiazole). By contrast, the presence of the electronegative nitrogen atom in the isoxazole strongly reduces the $^3J_{3-4}$ (1.78 Hz) and $^4J_{3-5}$ (0.27 Hz) values in comparison with those of furan (3.30 and 0.85 Hz, respectively).

The couplings between ring and methyl protons seem to depend on the difference in $\pi$-bond order[28/74] in the ring in the case of $^4J_o^{H,Me}$. Since the nitrogen polarizes mainly the $\sigma$-electron core at $C_3$, the value of $^4J_o^{H,Me}$ is reduced for 3-methylisoxazole but not for 4,5-dimethylisoxazole. The magnitude of $^5J_m^{H,Me}$ is larger for isoxazole than for furan and thiophene, a fact attributed to a stronger $\sigma$-electron effect, due to the presence of the nitrogen atom in the ring. Moreover, the difference between the value for the isoxazole (0.64) and the isothiazole (0.51) depends on the higher oxygen electronegativity. In the case of $^5J_o^{Me,Me}$ and $^6J_m^{Me,Me}$, both the $\pi$-bond order and the $\sigma$-electron effect have been invoked to explain the values measured.

### *1.2.3.2 $^{13}$C-NMR Spectra*

$^{13}$C-NMR data of isoxazole[28/75,38/77] and methylisoxazoles[38/77] have been studied in relation to those of isothiazole and derivatives. In the unsubstituted isoxazole, the three ring carbon atoms absorb at 104.5 ppm ($C_4$), 150.0 ppm ($C_3$), and 158.9 ppm ($C_5$).[28/75,209/76] Introduction of a methyl group on the ring shifts downfield (8–10 ppm) the signal of the carbon atom to which the methyl is linked.[209/76] The $C_4$-methyl signal (at ca. 6 ppm) is well differentiated from the $C_3$- and $C_5$-methyl signals (at ca. 10–11 ppm). $^{13}$C-NMR chemical shifts of isoxazole and some derivatives are reported in Table 1.25.

The structure of the reaction product between nitroethane and 6-bromopiperonal has been elucidated as 4-(6′-bromo-3′,4′-methylenedioxyphenyl)-3,5-dimethylisoxazole on the basis of $^{13}$C-NMR data compared with those of 3,4,5-trimethyl-, 3-phenyl-5-methyl-, and 3,5-dimethyl-4-phenylisoxazole (see the data in Table 1.25). The chemical shifts of $C_4$ (116 ppm) and methyl groups (10–11 ppm) provided evidence that an aryl, not a methyl group, was linked at $C_4$. In fact, a methyl at $C_4$, which would absorb at ca. 6 ppm, could be excluded.[122/75] Tentative assignments of aromatic carbon atoms have been reported.

$^{13}$C-NMR shifts have been used to determine the metallation site in 4-substituted 3,5-dimethylisoxazoles. Comparison of the $^{13}$C-NMR spectra of the starting materials with those of the products of electrophilic substitution on the organometallic compounds showed a downfield shift of 3.5–5.0 ppm of the $C_5$ signal. Metallation occurs only at $C_5$.[209/76] Some examples are reported in Table

TABLE 1.25. $^{13}$C-NMR CHEMICAL SHIFTS OF ISOXAZOLE AND DERIVATIVES (ppm)

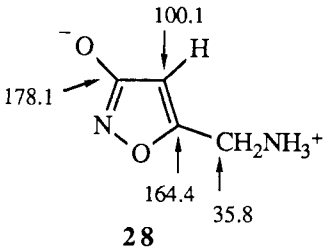
| $R_3$ | $R_4$ | $R_5$ | $C_3$ | $C_4$ | $C_5$ | $R_3$ | $R_4$ | $R_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | 150.0 | 104.5 | 158.9 | - | - | - | $(CD_3)_2CO$ | 28/75 |
| | | | 149.1 | 103.7 | 157.9 | - | - | - | $CHCl_3$ | 209/76 |
| Me | H | H | 159.2 | 105.7 | 159.2 | - | - | - | neat | 209/76 |
| H | H | Me | 150.9 | 101.4 | 169.2 | - | - | - | neat | 209/76 |
| Me | Me | H | 159.3 | 113.6 | 154.8 | 9.6 | 6.3 | - | $CDCl_3$ | 137/84 |
| Me | H | Me | 160.0 | 102.7 | 169.4 | - | - | - | neat | 209/76 147/75 |
| | | | 159.9 | 102.3 | 169.0 | 12.1 | - | 11.3 | $CDCl_3$ | 122/75 |
| Me | Me | Me | 159.9 | 109.0 | 164.2 | 10.7 | 6.6 | 10.0 | $CDCl_3$ | 122/75 |
| Ph | H | Me | 160.3 | 100.1 | 169.6 | - | - | 11.6 | $CDCl_3$ | 122/75 |
| Me | Ph | Me | 158.6 | 116.7 | 165.1 | 11.4 | - | 10.7 | $CDCl_3$ | 122/75 |
| Me | 2-Br-4,5-dioxo-methylene-$C_6H_2$ | Me | 158.5 | 115.9 or 116.4 | 166.1 | 11.6 | - | 10.5 | $CDCl_3$ | 122/75 |
| Ph | H | Ph | 164.0 | 97.5 | 170.5 | - | - | - | DMSO-$d_6$ | 179/74 |
| 2,3,5,6-$Me_4C_6H$ | H | Ph | 164.0 | 101.2 | 169.9 | - | - | - | $CDCl_3$ | 23/82 |
| Ph | Me | Ph | 163.4 | 108.4 | 165.4 | - | - | - | $CDCl_3$ | 200/83 |
| Me | $CH_2NMe_2$ | Me | 159.5 | 111.4 | 165.9 | - | - | - | neat | 209/76 |
| Me | $CH_2NMe_2$ | Et | 159.6 | 110.7 | 170.5 | - | - | - | $CDCl_3$ | 209/76 |
| Me | $CH_2NMe_2$ | $CH_2COOH$ | 162.3 | 108.2 | 171.3 | - | - | - | $D_2O$ | 209/76 |
| Me | $CH_2NHCOOBu$ | Me | 159.4 | 111.9 | 166.5 | - | - | - | $CDCl_3$ | 209/76 |
| Me | $CH_2NHCOOBu$ | Et | 159.4 | 110.9 | 171.1 | - | - | - | neat | 209/76 |
| Me | $CH_2NHCOOBu$ | $CH_2COOH$ | 159.8 | 114.1 | 171.0 | - | - | - | $CDCl_3$ | 209/76 |
| Me | $CH_2N(Et)COOBu$ | Et | 159.1 | 110.4 | 171.0 | - | - | - | neat | 209/76 |
| Me | $CH_2N(Et)COOBu$ | $CH_2COOH$ | 159.8 | 113.4 | 170.0 | - | - | - | $CDCl_3$ | 209/76 |
| Me | $(CH_2)_2NHCOOBu$ | Me | 159.6 | 110.9 | 165.7 | - | - | - | $CDCl_3$ | 209/76 |
| Me | $(CH_2)_2NHCOOBu$ | $CH_2COOH$ | 159.6 | 113.2 | 169.4 | - | - | - | DMSO | 209/76 |
| Me | $CH_2N(Et)CH_2COOBu$ | Me | 159.1 | 111.8 | 166.5 | - | - | - | neat | 209/76 |
| Me | $CH_2OH$ | Me | 159.9 | 114.2 | 166.7 | - | - | - | $CDCl_3$ | 209/76 |
| Me | $CH_2OH$ | $CH_2COOH$ | 160.8 | 117.1 | 170.6 | - | - | - | DMSO | 209/76 |
| Me | $SiMe_3$ | Me | 163.3 | 106.9 | 173.5 | - | - | - | $CDCl_3$ | 193/80 |
| Me | $SnMe_3$ | Me | 164.0 | 105.7 | 173.5 | - | - | - | $CDCl_3$ | 193/80 |
| Me | H | $CH_2SiMe_3$ | 159.8 | 100.1 | 172.0 | - | - | - | $CDCl_3$ | 193/80 |
| Me | Me | $CH_2SiMe_3$ | 159.7 | 106.44 | 167.4 | - | - | - | $CDCl_3$ | 193/80 |
| Me | $CH_2SiMe_3$ | Me | 158.9 | 110.9 | 162.1 | - | - | - | $CDCl_3$ | 193/80 |
| Me | $CH_2SnMe_3$ | Me | 158.6 | 113.5 | 160.9 | - | - | - | $CDCl_3$ | 193/80 |
| $CH_2SiMe_3$ | H | Me | 161.9 | 101.8 | 168.4 | - | - | - | $CDCl_3$ | 193/80 |
| $CH_2SnMe_3$ | H | Me | 164.2 | 101.3 | 168.4 | - | - | - | $CDCl_3$ | 193/80 |
| Me | H | 1-Me-2-$NO_2$-4-pyrrolyl | 160.0 | 100.0 | 163.6 | 11.0 | - | - | DMSO-$d_6$ | 55B/80 |
| Ph | COOMe | COOMe | 156.9 | 116.5 | 159.9 | - | - | - | $CDCl_3$ | 147/75 |
| (*Z,Z*)$(CH=CH)_2CN$ | COOMe | COOMe | 157.1 | 115.8 | 158.2 | - | - | - | $CDCl_3$ | 147/75 |
| (*E,E*)$(CH=CH)_2CN$ | COOMe | COOMe | 157.0 | 117.5 | 158.6 | - | - | - | $CDCl_3$ | 147/75 |
| Ph | COPh | H | 161.6 | 119.3 | 163.6 | - | - | - | DMSO-$d_6$ | 179/74 |
| Me | CHO | Ph | 159.6 | 115.3 | 175.2 | 11.2 | 184.3 | - | $CDCl_3$ | 177/83 |
| Ph | CHO | Ph | 163.0 | 114.1 | 175.0 | - | 183.7 | - | $CDCl_3$ | 177/83 |
| $NH_2$ | H | Me | 164.8 | 95.0 | 168.6 | - | - | 12.2 | DMSO-$d_6$ | 56/78 |
| $N_3$ | H | Me | 161.1 | 96.1 | 172.9 | - | - | 12.5 | DMSO-$d_6$ | 56/78 |
| 4-$MeOC_6H_4$ | NHOH | H | 160.1 | 132.6 | 146.5 | - | - | - | DMSO-$d_6$ | 52/81 |
| $NMe_2$ | NHCOPh | $CF_3$ | 163.4 | 110.1 | 153.4 | - | - | 115 | DMSO-$d_6$ | 166/76 |
| Me | SEt | $NH_2$ | 163.8 | 81.4 | 171.1 | - | - | - | $CDCl_3$ | 274/80 |
| *i*-Pr | SMe | $NH_2$ | 171.0 | 82.2 | 170.6 | - | - | - | $CDCl_3$ | 274/80 |
| Ph | SMe | $NH_2$ | 163.7 | 80.7 | 171.9 | - | - | - | $CDCl_3$ | 274/80 |
| Ph | SPh | $NH_2$ | 164.2 | 77.8 | 172.1 | - | - | - | $CDCl_3$ | 274/80 |
| 4-$ClC_6H_4$ | SPh | $NH_2$ | 163.2 | 77.7 | 172.0 | - | - | - | $CDCl_3$ | 274/80 |

TABLE 1.25. *(Continued)*

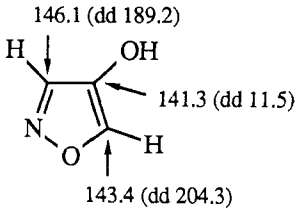
| $R_3$ | $R_4$ | $R_5$ | $C_3$ | $C_4$ | $C_5$ | $R_3$ | $R_4$ | $R_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Ph | Me | NHCOPh | 163.6 | 103.8 | 159.5 | - | - | - | DMSO-$d_6$ | 179/74 |
| Ph | Ph | NHAc | 162.4 | 110.0 | 159.1 | - | - | - | DMSO-$d_6$ | 179/74 |
| Ph | Ph | $NH_2$ | 161.7 | 91.4 | 167.7 | - | - | - | DMSO-$d_6$ | 179/74 |
| CN | H | Me | 139.5 | 104.2 | 172.9 | - | - | 12.1 | $CDCl_3$ | 107/82 |
| Me | CN | Me | 159.7 | 92.3 | 176.6 | 10.3 | - | 12.3 | $CDCl_3$ | 107/82 |
| Me | H | CN | 160.7 | 114.7 | 142.3 | 11.1 | - | - | $CDCl_3$ | 107/82 |
| COOMe | H | OMe | 157.8 | 78.3 | 175.4 | - | - | - | $CDCl_3$ | 22/81 |

1.25, showing that $C_5$ absorbs at ca. 170 ppm when substituted by an ethyl or a $CH_2COOH$ group.

Several silylated and stannylated isoxazoles, either in the ring or in the side chain, have been examined by means of $^{13}$C-NMR to study the electronic substituent effect of the $MR_3$ and $CH_2MR_3$ groups. Shifts in the signals of the ring carbon atoms have been studied.[193/80] Photochemical reactions of benzofurazans in the presence of dimethyl acetylenedicarboxylate yielded a mixture of isomeric products.[147/75,112/81] Structures such as **22–24** were also assigned by the $^{13}$C-NMR chemical shifts of three signals (at ca. 158, 157, and 116 ppm) attributed to the ring carbon atoms of a trisubstituted isoxazole. The $^{13}$C-NMR spectra of two isoxazole derivatives found in nature, muscimol (**28**)(in $D_2O$)[13/82] and triumferol (**29**)(in $Me_2CO$-$d_6$),[236/81] have been reported. The three very close $^{13}$C signals in triumferol could be assigned by means of an off-resonance gated decoupling technique.



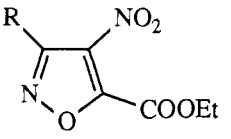

**28**




**29**

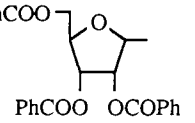
The structure of the actual regioisomer obtained in the synthesis of trisubstituted isoxazoles such as **30**[273/80] could be established by comparison of the calculated[209/76] $^{13}$C-NMR chemical shift, for both isomers, with those measured: The structure of some other *C*-glycosylisoxazoles has been revised or assigned on the basis of the $^{13}$C-NMR spectrum.[65B/81]

The structure of natural $\beta$-ketoaldehydes, defensive secretions of termites,[276/80,154/81] and $\alpha$-pyrone derivatives[202/80] has been confirmed by reaction with hydroxylamine, leading to isoxazole derivatives. The structures of these



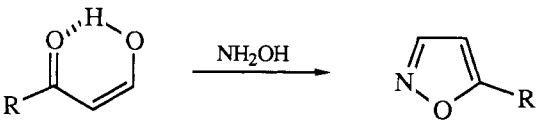
**30 a** R = cyclo-$C_6H_{11}$

**b** R = PhCOO



| | Measured | | Calculated | | Calculated | |
|---|---|---|---|---|---|---|
| | $C_4$ | $C_5$ | $C_4$-$NO_2$ | $C_5$-COOEt | $C_4$-COOEt | $C_5$-$NO_2$ |
| 30 a | 133.0 | 157.4 | 130-140 | 150-160 | 100-110 | 180-190 |
| b | 132.5 | 157.6 | | | | |

isoxazoles have been established by spectroscopic data mainly on the chemical shifts of the ring carbon atoms, as exemplified here:



| | $C_3$ | $C_4$ | $C_5$ | Solvent | References |
|---|---|---|---|---|---|
| R = $CH_2$=$CH(CH_2)_9$ | 150.2 | 99.9 | 173.2 | $CDCl_3$ | 276/80 |
| R = $CH_3(CH_2)_5CH$=$CH(CH_2)_5$ | 149.7 | 99.5 | 172.5 | $C_6D_6$ | 154/81 |

Comparison of the $^{13}$C-NMR data of 2,4,6-trimethylbenzonitrile, 2,4,6-trimethylbenzonitrile oxide, 2,4,6-trimethylbenzaldoxime, and the corresponding 3-mesitylisoxazoline and 3-mesitylisoxazole is reported in Table 1.26. Note the high-field absorption of the carbon in the nitrile oxide compared with that of nitrile. The absorption of the heterocyclic derivatives is as expected: the C = N signal moves downfield (12.1 ppm) in the isoxazoline relative to the benzaldehyde oxime because of the presence of a carbon atom ($C_4$) instead of a hydrogen, and further, to 3.4 ppm, in the "aromatic" isoxazole. However, the higher chemical shift of $C_4$ and the lower one of $C_5$ compared to the carbon

TABLE 1.26. $^{13}$C-NMR CHEMICAL SHIFTS (ppm) AND $^{13}$C-$^{15}$N COUPLING CONSTANTS (Hz)

| | Compound | CN | $C_4$ | $C_5$ | $^{13}C$-$^{15}N$: $J$(Hz) |
|---|---|---|---|---|---|
| a | Mesityl-CN | 117.5 | - | - | - |
| b | Mesityl-CN—>O | 35.7 | - | - | 77.5 ± 0.5 |
| c | Mesityl-CH=NOH | 145.1 | - | - | 28 ± 0.1 |
| d | 3-Mesitylisoxazoline | 156.3 | 39.9 | 68.5 | - |
| e | 3-Mesitylisoxazole | 160.6 | 105.7 | 158.7 | 4.0 ± 0.5 |

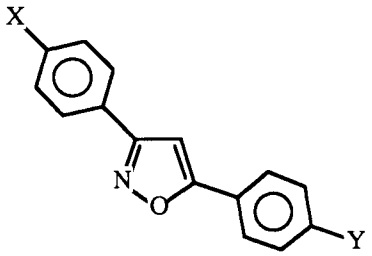
atoms of the furan ring (143.0 ppm for $C_2$ and $C_5$ and 109.9 ppm for $C_3$ and $C_4$) might indicate that the isoxazole ring is less aromatic than the furan ring.

In the case of 3-amino- and 3-azido-5-methylisoxazole (Table 1.25), a stronger substituent effect is observed on the chemical shift of the ring atoms, especially in the nitrogen $\alpha$ position, as for thiazole derivatives.[56/78] The $^{13}$C-NMR data of some aminoisoxazoles and derivatives have also been reported (see Table 1.25). It is interesting to note that in these compounds no imino-tautomeric form could be detected.[274/80]

The transmission of the substituent effects in the isoxazole system has been studied to find an easy method to identify isomeric 3,5-diarylisoxazoles.[187/80,128/81] In all the reported $^{13}$C-NMR data of the 3,5-diarylisoxazoles the $C_4$ signal appears as the most upfield signal of the aromatic carbons, with the $C_3$ and $C_5$ signals as the two most downfield ones.

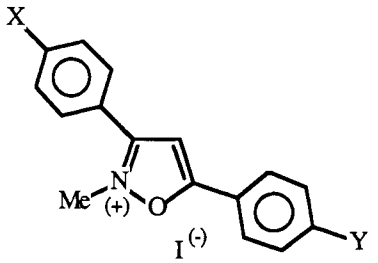
As reported previously, the $C_3$ absorbs at a higher field than does the $C_5$.

TABLE 1.27. $^{13}$C-NMR CHEMICAL SHIFTS (ppm) OF THE ISOXAZOLE RING CARBON ATOMS FOR **31** AND **32** (DMSO-$d_6$)




| | X | Y | $C_3$ | $C_4$ | $C_5$ |
|---|---|---|---|---|---|
| **31** | H | H | 162.2 | 98.3 | 169.3 |
| | OMe | H | 161.8 | 98.0 | 168.9 |
| | OEt | H | 161.8 | 98.0 | 168.9 |
| | NHAc | H | 161.8 | 98.1 | 169.1 |
| | Me | H | 162.1 | 98.2 | 169.2 |
| | F | H | 161.3 | 98.3 | 169.2 |
| | Cl | H | 161.2 | 98.3 | 169.5 |
| | Br | H | 161.3 | 98.3 | 169.5 |
| | $CF_3$ | H | 161.2 | 98.6 | 169.9 |
| | CN | H | 161.0 | 98.6 | 169.9 |
| | $NO_2$ | H | 160.8 | 98.8 | 170.1 |
| **32** | H | $NMe_2$ | 161.9 | 94.9 | 170.3 |
| | H | OMe | 162.0 | 96.8 | 169.3 |
| | H | OEt | 162.0 | 96.7 | 169.3 |
| | H | NHAc | 162.1 | 97.2 | 169.3 |
| | H | Me | 162.1 | 97.6 | 169.4 |
| | H | F | 162.2 | 98.2 | 168.3 |
| | H | Cl | 162.3 | 98.9 | 168.1 |
| | H | Br | 162.3 | 98.9 | 168.2 |
| | H | $CF_3$ | 162.4 | 100.3 | 167.7 |
| | H | CN | 162.4 | 100.6 | 167.4 |
| | H | $NO_2$ | 162.5 | 101.3 | 167.1 |

TABLE 1.28. $^{13}$C-NMR CHEMICAL SHIFTS (ppm) OF THE ISOXAZOLE RING CARBON ATOMS FOR **33** AND **34** (DMSO-$d_6$)




| | X | Y | $C_3$ | $C_4$ | $C_5$ |
|---|---|---|---|---|---|
| **33** | H | H | 159.2 | 104.9 | 169.0 |
| | OMe | H | 158.6 | 104.2 | 168.3 |
| | Me | H | 159.0 | 104.5 | 168.7 |
| | F | H | 158.3 | 104.8 | 168.9 |
| | Cl | H | 158.2 | 104.9 | 169.0 |
| | Br | H | 158.3 | 104.9 | 169.0 |
| | $CF_3$ | H | 158.2 | 105.3 | 169.5 |
| | CN | H | 158.0 | 105.4 | 169.4 |
| | $NO_2$ | H | 157.8 | 105.6 | 169.5 |
| **34** | H | OMe | 159.0 | 103.0 | 169.2 |
| | H | NHAc | 159.0 | 103.5 | 168.9 |
| | H | Me | 159.1 | 104.1 | 169.2 |
| | H | F | 159.1 | 104.6 | 168.0 |
| | H | Cl | 159.1 | 105.3 | 167.8 |
| | H | Br | 159.1 | 105.3 | 168.0 |
| | H | $CF_3$ | 159.2 | 106.6 | 167.2 |
| | H | CN | 159.2 | 106.8 | 167.0 |
| | H | $NO_2$ | 159.3 | 107.2 | 166.6 |

However, the definitive assignment for these carbon atoms was achieved by studying the coupling constants of the 3-[3′-fluorophenyl]-5-phenylisoxazole and of the 5-[3′-fluorophenyl]-3-phenylisoxazole and the $^{13}$C-enriched derivative of the latter. Coupling constants $J_{CF}$ and chemical shifts have been reported for all the aromatic carbon atoms.[187/80] In Tables 1.27 and 1.28 the chemical shifts of the isoxazole ring carbon atoms of 3-aryl-5-phenyl- (**31**) and 5-aryl-3-phenylisoxazoles (**32**) are reported together with those of some corresponding *N*-methylisoxazolium iodides[145/82] (**33** and **34**).

In the case of 3-aryl-5-phenylisoxazoles the electron-withdrawing substituents exert a shielding effect on $C_3$ and a deshielding effect on $C_4$ and $C_5$, similar to that revealed in the case of 3-(4′-aryl)-1-phenylpropenones. However, for **31**, this substituent effect from a strong electron donor to a strong electron-withdrawing groups is quite small, in the range of 1 ppm. By contrast, for 3-phenyl-5-arylisoxazoles a stronger substituent effect causes a deshielding of $C_3$ and $C_4$ and a shielding of $C_5$. The ring carbon atom chemical shifts of some 3,5-diaryl- and 4-methyl-3,5-diarylisoxazoles have been reported without discussion.[200/83]

Correlation between the $^{13}$C-NMR chemical shifts and the Hammett $\sigma$ values

are reported for $C_4$ and $C_5$ in both series of compounds. Dual substituent parameter (DSP) treatment improves the correlation. By comparison with the data for furans, the formal introduction of a nitrogen atom, as in isoxazoles, seems to decrease the substituent effect. Transmission of the substituent effects in the isoxazole ring is more comparable with those of the benzothiazole system.[128/81]

Similar studies on the $^{13}$C-NMR chemical shift of 3-aryl-2-methyl-5-phenyl- and 5-aryl-2-methyl-3-phenylisoxazolium[145/82] iodide using the single parameter correlation and DSP showed the following:

1. In the **33** series the substituents show a minimal effect on $C_3$ and $C_5$ with a larger shift (1.4 ppm) on $C_4$. Electron-donating substituents cause a shielding effect, whereas electron-withdrawing substituents cause a deshielding of $C_4$ and $C_5$ and an upfield shift of $C_3$.
2. The effect of substituents is larger (4.2 ppm) for $C_4$ in the **34** series and very modest for $C_5$; $C_3$ is almost unaffected. Also in this case, $C_4$ is shifted upfield by electron-donating substituents and downfield by electron-withdrawing substituents.
3. Comparison of the corresponding isoxazole and isoxazolium derivatives shows that the charged system transmission of substituent effects is little enhanced.
4. The very small differences of chemical shift in the 2-methyl group did not permit a correlation.

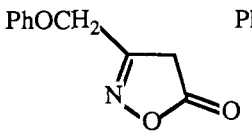
$^{13}$C-NMR spectra have also been used to study tautomerism in the case of isoxazolin-5-ones and 5-hydroxyisoxazoles (see Part 2 of the present work). Recently, the spectra of 3-phenoxymethylisoxazolinones and their methyl derivatives recorded in different solvents have been reported[198/79] (see Table 1.29).

These data and a mathematical analysis for the tautomeric ring proton exchange in pyridine as solvent showed that the NH, CH, and OH tautomers are present in the ratios 10 $\pm$ 5, 15 $\pm$ 3, and 10 $\pm$ 8% and that the remaining 65 $\pm$ 8% is represented by the anionic form. Similarly, the tautomerism of 3-aryl-1-(3,4-dimethyl-5-isoxazolyl)triazenes has been studied on the basis of the $^{13}$C-NMR spectra of the triazenes, their methylated derivatives, and some simpler diaryl- or arylmethyltriazenes[243/80] (see Table 1.30).

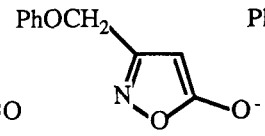
The most stable tautomer is **39A**, with the azo group conjugated with the heterocyclic ring. The substituents on the aryl group weakly affect the tautomeric equilibrium. Theoretical calculations [Hückel molecular orbitals (HMO) and CNDO/2] were in agreement with these results. A discussion of the more stable configurations of structures **A** and **B** is also reported.

The reactivity of heteroaromatic nitriles has been correlated with a $^{13}$C-NMR chemical shift. Enamino ketones are easily obtained from nitriles, which show signals of the C$\equiv$N group in the range 109–118 ppm and of C–CN greater than 133 ppm. A formula correlating the $^{13}$C chemical shift and reactivity has been calculated and discussed. Electron density on the heteroaromatic ring and

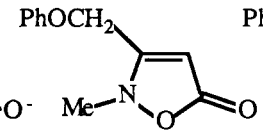
TABLE 1.29



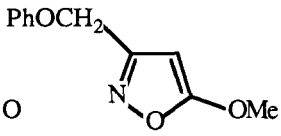
35



36



37



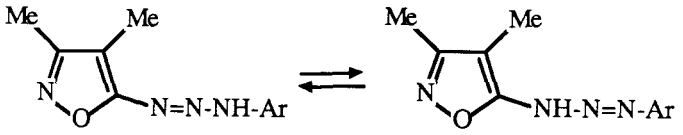
38

| Compound | $C_3$ | $C_4$ | $C_5$ | $CH_2$ | C-O | Me | Solvent |
|---|---|---|---|---|---|---|---|
| **35** | 163.8 | 34.3 | 174.2 | 63.3 | 157.4 | - | $CDCl_3$ |
| | 163.5 | 79.5 | 173.6 | 62.1 | 157.7 | - | DMSO-$d_6$ |
| | 163.7 | 69.0 | 176.1 | 63.3 | 158.8 | - | pyridine-$d_5$ |
| **36** | 161.2 | 70.7 | 178.0 | 62.5 | 157.1 | - | $NEt_3$-$CDCl_3$ |
| | 163.6 | 72.2 | 178.9 | 62.2 | 157.1 | - | NaOH-$H_2O$ |
| **37** | 162.6 | 89.5 | 170.0 | 60.8 | 157.1 | 38.1 | $CDCl_3$ |
| | 164.5 | 89.4 | 170.3 | 61.3 | 158.0 | 38.3 | DMSO-$d_6$ |
| | 164.3 | 88.1 | 169.4 | 60.7 | 157.2 | 38.1 | pyridine-$d_5$ |
| **38** | 163.0 | 76.7 | 174.6 | 62.6 | 158.0 | 58.9 | $CDCl_3$ |
| | 163.4 | 77.2 | 175.3 | 62.6 | 158.7 | 59.2 | DMSO-$d_6$ |
| | 163.1 | 77.3 | 175.0 | 61.8 | 157.0 | 59.2 | pyridine-$d_5$ |

results of MO calculations have also been taken into account. Three cyano-isoxazoles have been considered: two (3-cyano-5-methyl- and 5-cyano-3-methyl-isoxazole) show a medium reactivity; the third (4-cyano-3,5-dimethylisoxazole) seems to be unreactive.[107/82] Data are reported in Table 1.25.

Structure and side-chain conformation of $\beta$-lactamase-resistant penicillins were analyzed by experimental and theoretical methods. In this context full

TABLE 1.30. $^{13}$C-NMR CHEMICAL SHIFTS (ppm) AT 30° C OF **39** IN DMSO-$d_6$



A B

39

| Ar | $C_3$ | $C_4$ | $C_5$ | 3-Me | 4-Me |
|---|---|---|---|---|---|
| $C_6H_5$ | 161.4 | 101.7 | 166.1 | 10.1 | 6.9 |
| 4-Me$C_6H_4$ | 161.3 | 101.5 | b | 10.1 | 6.8 |
| 4- $FC_6H_4$ | 161.3 | 101.5 | 165.8 | 10.1 | 6.8 |
| 4-$ClC_6H_4$ | 158.6 | a | a | 10.1 | 6.8 |
| 4-EtOCO$C_6H_4$ | 161.5 | 103.7 | 165.4 | 10.1 | 6.8 |

[a] Not observable.

[b] Intensity too low due to a long relaxation time.

assignments for the $^{13}$C-NMR signals of five isoxazolepenicillins have been reported.[191/80] The $\sigma$ and $\pi$ bonding between metal and nitrogen donor ligand in complexes, including isoxazole-$Cr(CO)_5$, have been studied by means of $^{13}$C-NMR and other techniques.[91C/79]

Nickel bis(acetylacetonate), $Ni(acac)_2$, is known to be a shift reagent acting specifically on nitrogen lone pairs and is largely independent of other functional groups present in the molecule. In a study of the substituent effect on the $Ni(acac)_2$-induced proton and carbon NMR shift of some anilines and nitrogen heterocycles, data relative to isoxazole have been reported.[163C/81] The shifts are expressed as relative apparent spin density and show that the greater influence is on the atoms in positions $\alpha$ to the nitrogen.

| $C_3$ | $C_4$ | $C_5$ | $H_3$ | $H_4$ | $H_5$ |
|---|---|---|---|---|---|
| 494 ± 39 | 223 ± 8 | 221 ± 8 | 36 ± 5 | 61 ± 3 | (100) |

In the case of isoxazole the EHT (extended Hückel theory) calculations gave a good correlation between the total ($\sigma + \pi$) calculated electron density and the experimental proton and $^{13}$C-NMR chemical shifts.[156B/67] Calculated EHT net charges for isoxazole are reported in Table 1.31. Many studies on the $J_{CH}$ of isoxazole[75C/64,11/69,266/72,28/75,38/77] and substituted isoxazoles[75C/64,11/69,38/77] have been reported. Some values for the coupling constants are given in Table 1.32.

It is worth noting that $J_{C_4-H_4} < J_{C_3-H_3} < J_{C_5-H_5}$. This sequence could be predicted correctly by MO calculation (Intermediate Neglect of Differential Overlap, INDO)[38/77] and is related to the electronic density on the ring.[11/69] All these coupling constants are larger than those of furan, that is, of a symmetric five-membered heterocyclic.

In the case of isoxazole and derivatives the $^nJ_{CH}$ ($n > 1$) values are large, as for other five-membered heterocyclic compounds. Furthermore, it is also interesting to note that the $^2J_{CH}$ are larger than the $^3J_{CH}$, by contrast to what happens with six-membered heterocycles and that the ring dissymmetry due to the presence of the –N–O– group causes important differences in both kinds of long-range coupling constants.[28/75] NMR spectral analysis of isoxazole in liquid-crystal solvents has also been performed taking into account the $J_{^{13}C-H}$ coupling constants obtained from $^{13}$C-NMR spectra in isotropic $CDCl_3$ solution and assuming that their sign is positive. Results have been discussed.[144/81]

Several 3-unsubstituted isoxazoles have been examined to correlate the NMR

TABLE 1.31

| Position | $\rho_\sigma$ | $\rho_\pi$ | $\rho_{\sigma+\pi}$ | $\rho_H$ |
|---|---|---|---|---|
| 1 | - 0.68 | +0.19 | -0.49 | - |
| 2 | -0.04 | -0.56 | -0.60 | - |
| 3 | +0.15 | +0.25 | +0.40 | +0.114 |
| 4 | -0.12 | -0.07 | -0.19 | +0.114 |
| 5 | +0.34 | +0.19 | +0.53 | +0.122 |

TABLE 1.32. COUPLING CONSTANTS $J_{C-H}$ (Hz) OF ISOXAZOLES

| $R_3$ | $R_4$ | $R_5$ | $^1J(C_3-H_3)$ | $^1J(C_4-H_4)$ | $^1J(C_5-H_5)$ | $^2J(C_3-H_4)$ | $^2J(C_4-H_3)$ | $^2J(C_3-H_5)$ | $^2J(C_5-H_4)$ | References |
|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | 188.1 | 184.6 | 203.5 | 6.2 | 14.2 | 4.4 | 11.3[a] | 28/75 |
| H | H | H | 187.6 | 184.6 | 203.5 | 6.2 | 9.6 | 14.3 | 10.9[b] | 38/77 |
| H | H | H | 186.7 | 182.8 | 202.1 | - | - | - | - | 156B/67 |
| H | H | H | 188.0 | 184.3 | 203.3 | - | - | - | - | 75C/64 |
| Me | H | H | - | 181.8 | 201.3 | 6.2 | - | 14.0 | 10.0[c] | 38/77 |
| H | H | Me | 185.3 | 181.8 | - | 6.0 | 9.3 | - | 10.2[d] | 38/77 |
| H | H | Me | 185.3 | 182.0 | - | - | - | - | - | 11/69 |
| Me | H | Me | - | 178.8 | - | - | - | - | - | 75C/64 |
| Me | H | 1-Me-2-$NO_2$-4-pyrrolyl | - | 182.0 | - | - | - | - | - | 55B/80 |
| H | Br | Me | 191.7 | - | - | - | - | - | - | 11/69 |
| H | Cl | Me | 191.6 | - | - | - | - | - | - | 11/69 |
| H | $NO_2$ | Me | 197.6 | - | - | - | - | - | - | 11/69 |
| H | H | Ph | 186.1 | 181.9 | - | - | - | - | - | 11/69 |
| H | Me | Ph | 183.1 | - | - | - | - | - | - | 11/69 |
| H | *i*-Pr | Ph | 182.3 | - | - | - | - | - | - | 11/69 |
| H | H | 2-$MeC_6H_4$ | 185.9 | 182.5 | - | - | - | - | - | 11/69 |
| H | Me | 2-$MeC_6H_4$ | 183.6 | - | - | - | - | - | - | 11/69 |
| H | *i*-Pr | 2-$MeC_6H_4$ | 183.0 | - | - | - | - | - | - | 11/69 |
| H | H | mesityl | 185.6 | 181.2 | - | - | - | - | - | 11/69 |
| H | Me | mesityl | 182.4 | - | - | - | - | - | - | 11/69 |
| COOMe | H | OMe | - | 189.5 | - | - | - | - | - | 22/81 |

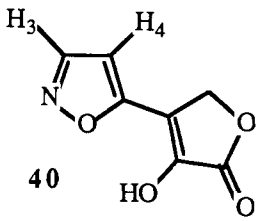
[a] $^3J(C_3-H_5) = 6.2$; $^3J(C_5-H_3) = 4.3$

[b] $^3J(C_3-H_5) = 6.2$; $^3J(C_5-H_3) = 4.4$

[c] $^3J(C_3-H_5) = 6.2$

[d] $^3J(C_5-H_3) = 4.5$

parameters with the effects of the substituents in positions 4 and 5.[11/69] It has been shown that the $^1J_{C_3-H_3}$ and some $^1J_{C_4-H_4}$ values are affected[11/69] (see Table 1.32) by the electronic effects of the substituents. For example, the electron-donating effect of a methyl group at $C_5$ causes a decrease in $^1J_{C_3-H_3}$ and $^1J_{C_4-H_4}$ of 1.4 and 0.8 Hz, respectively. A minor decrease is noted for 5-phenylisoxazole: 0.6 and 0.9 Hz. By contrast, the $^1J_{C_3-H_3}$ values increase of 6.3, 6.4, and 12.3 Hz for 4-chloro-, 4-bromo-, and 4-nitro-5-methylisoxazole, due to the electron-withdrawing effect of the 4-substituents.[11/69] Furthermore, other examples of the substituent effects on $J_{13_{C-H}}$, and a relationship between $J_{13_{C-H}}$ and the rate constants of the ring opening by bases of 3-unsubstituted isoxazoles have been




**40**

$C_3$ 151.3 ppm dd $^1J_{C3-H3} = 189.5$ Hz $^2J_{C3-H4} = 5.9$ Hz

reported.[11/69] The values of coupling constants $^1J_{CH}$ and $^2J_{CH}$ have been used to establish the actual structure of the isoxazole compound (**40**) obtained by oximation of γ-pyrone.[231/81]

### *1.2.3.3 $^{14}N$- and $^{15}N$-NMR Spectra*

The nitrogen ($^{15}N$ and $^{14}N$) chemical shifts of isoxazole and some derivatives have been determined using various reference compounds, as reported in Table 1.33. The values of $^{15}N$ chemical shifts for enriched $^{15}N$-isoxazole and $^{15}N$-3-mesitylisoxazole are unusual in the series of azoles since the *N*-resonances appear at 70–125 ppm for "pyrrole-like" nitrogens, at 215–280 ppm for "pyridine-like" nitrogens, and at a somewhat lower field (about 10 ppm) for azoles

TABLE 1.33. NITROGEN CHEMICAL SHIFTS (ppm) OF ISOXAZOLE AND DERIVATIVES

| Compound | Solvent | Chemical shifts (reference) $^{15}N$ | $^{14}N$ | Resonance half-height width, Hz $^{14}N$ | π charge density at N from SCF-PPP method ($q_N^{\pi}$) | References |
|---|---|---|---|---|---|---|
| $^{15}N$-isoxazole | neat | 339.6($Me_4N^+Cl^-$) | - | - | - | 125B/73 |
| $^{15}N$-isoxazole | neat | - | 358($NH_4^+$)[a] | - | - | 147/77 |
| Isoxazole | neat | - | -2 ± 1($MeNO_2$)[a] | 220 ± 10 | 1.3058 | 223/72 |
| | neat | - | 0 ± 1($MeNO_2$)[b] | 220 ± 10 | 1.3058 | 46/78 |
| | DMF(1:1) | - | -4 ± 2($MeNO_2$)[a] | 290 ± 20 | - | 223/72 |
| | MeOH(1:1) | - | +6 ± 2($MeNO_2$)[a] | 335 ± 10 | - | 223/72 |
| | DMSO[e] | -2.7($MeNO_2$)[b] | - | - | - | 138/84 |
| | DMSO-$d_6$ | +2.2($MeNO_2$)[b](14.7)[d] | - | - | - | 104/83 |
| | $CDCl_3$ | +0.6($MeNO_2$)[b](14.6)[d] | - | - | - | 104/83 |
| 5-Me-isoxazole | DMSO-$d_6$ | +0.1($MeNO_2$)[b](14.4)[d] | - | - | - | 104/83 |
| | $CDCl_3$ | -2.4($MeNO_2$)[b] | - | - | - | 104/83 |
| 3,5-$Me_2$-isoxazole | DMSO-$d_6$ | -9.2($MeNO_2$)[b] | - | - | - | 104/83 |
| | $CDCl_3$ | -12.0($MeNO_2$)[b] | - | - | - | 104/83 |
| $^{15}N$-3-mesityl-isoxazole | $CH_2Cl_2$ | 335.9; 339.6($Me_4N^+Cl^-$) | - | - | - | 125B/73 |
| Benzo[d]isoxazole | neat | - | +27 ± 1($MeNO_2$)[a] | 1250 ± 25 | 1.2760 | 46/78 |
| | DMSO[e] | -3.3 | - | - | - | 138/84 |
| | $D_2O$[e] | -3.2(14.6)[d] | - | - | - | 138/84 |
| Benzo[c]isoxazole | neat | - | +8 ± 1($MeNO_2$)[a] | 1500 ± 25 | 1.3424 | 46/78 |
| | DMSO[e] | +7.5- | - | - | - | 138/84 |

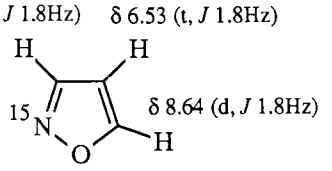
[a] Positive downfield from reference.
[b] Relative to external neat $MeNO_2$.
[c] Indicates spectrum taken with proton decoupler.
[d] The value in parentheses corresponds to $^2J(^{15}N\text{-}^1H)$ in hertz.
[e] Indicates 0.5 *M* DMSO with 0.01 *M* increment of $Cr(acac)_3$ for N atom.

with a heteroatom near the nitrogen.[125B/73] The $^{15}N$-$^{13}C$ coupling constants for $^{15}N$-3-mesitylisoxazole have been measured: $J_{^{15}N-C_3}$, 4.0 ± 0.5 Hz, and $J_{^{15}N-C_1}$, 7.0 ± 0.5 Hz.[125B/73] All these data are discussed in relation to those of nitriles, nitrile oxides, and aldoximes.

Correlation of the $^{14}N$ chemical shift with the reciprocal energy of the $N \rightarrow \pi^*$ wavelength electronic absorption of two coordinate nitrogens (as for C=N–O groups) has been studied. Data for isoxazole have been reported.[147/77] The $^{14}N$ chemical shift of isoxazole is very low with respect to $MeNO_2$, as is usual for azoles with a pyridine-like nitrogen (0–140 ppm), but is in the lower range because in this case nitrogen is near an oxygen atom.[223/72] For example, isoxazole shows a $^{14}N$ chemical shift at −2 to +6 ppm; by contrast, oxazole shows the same at 125 ppm and pyrazole at ca. 80 ppm, all from $MeNO_2$.[223/72,46/78] These differences, as well as those of the azoles with a pyrrole-like nitrogen (100–260 ppm), have been correlated with the $\pi$ charge density ($q_N^{\pi}$) by the SCF-PPP (Pariser–Parr–Pople)-MO method.[223/72,46/78] The shifts have also been explained by the average excitation energy (AEE) approximation for many azoles, including isoxazole.[223/72] Additivity rules as a sum of increments have been provided for the spectral assignments of the nitrogen shifts in azoles.[46/78]

It is noteworthy that a methyl group at $C_3$ leads to the shielding of $^{15}N$ resonance by 9 ppm in DMSO-$d_6$ and 10 ppm in $CDCl_3$ as for imidazoles and pyrazoles. Compare the values of 5-methyl- and 3,5-dimethylisoxazole in Table 1.33.[104/83] It is also interesting to note the difference in the $^{15}N$ and $^{14}N$ chemical shifts of two benzoisoxazoles (see Table 1.33), the latter in relation to the $\pi$ charge density ($q_N^{\pi}$).

The $^{14}N$ chemical shifts of isoxazoles have also been reported in a paper relative to tetracoordinate boron–nitrogen compounds.[14/74] The origin of the broadening of the PMR signal of the proton $\alpha$ to the nitrogen atom in azoles, including isoxazole, has been studied:[168/68]




The broadened unresolved doublet at $\delta$ 8.44 sharpens either at −46°C or in a saturated aqueous or viscous triethylene glycol solution.

The contributions of the various relaxation mechanisms to the spin-lattice $T_1$, and spin-spin $T_2$ relaxation times of hydrogen $\alpha$ to the nitrogen were taken into account and it was concluded that the broadening arises from incomplete washing out of $N–H_a$ spin-spin coupling by $^{14}N$ quadrupolar relaxation. The effects of temperature variations, solvents, and protonation were discussed and parameters reported.[168/68]

From $^{15}N$–H couplings $J_{^{14}N-H}$ values have been calculated using the relation

$$J_{^{14}N-H}N\text{–}H = -0.7129 J_{^{15}N-H}$$

For $^{15}N$-enriched isoxazole, the following data have been obtained:

| | $J^{15}N\text{-}H_a$ | $J^{14}N\text{-}H_a$ | $J^{15}N\text{-}H_b$ | $J^{14}N\text{-}H_b$ |
|---|---|---|---|---|
| Pentane | 14.90 Hz | 10.60 Hz | 1.70 Hz | 1.20 Hz |
| $CDCl_3$ | 14.40 Hz | 10.30 Hz | 1.80 Hz | 1.30 Hz |
| $H_2O$ | 14.25 Hz | 10.15 Hz | 1.80 Hz | 1.30 Hz |

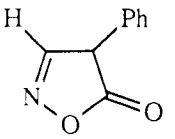
It has been reported that protonation or quaternarization leads to a marked decrease in magnitude of the $J_{N-H_a}$. Furthermore, these coupling constants depend strongly on the nitrogen-lone-pair orientation.[198/74]

The $^{15}N=C_3H$ coupling constant of isoxazole has been measured (15.0 Hz in DMSO) in order to assign the configuration to oximes.[30/67] In fact, oximes with an *anti* configuration show a coupling constant of 16 Hz, similar to that of isoxazole. By contrast, those with a *syn* configuration show a $^2J_{^{15}N-H_3}$ value of 3 Hz. $^3J_{^{15}N-H}$ of 1.3–1.8 Hz and $^4J_{^{15}N-H} < 1$ have also been measured for isoxazole and its methyl derivatives.[104/83]

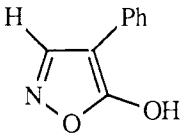
On the basis of $^2J_{^{15}N-H_3}$ coupling constants in different solvents, the tautomerism of $^{15}N$-4-phenyl-2-isoxazolin-5-one (**41**) has been studied.[198/74] In Table 1.34 the coupling constants of **41** and those of $^{15}N$-5-methoxy-4-phenylisoxazole (**42**) and 2-$^{15}N$-methyl-4-phenylisoxazolin-5-one (**43**) are reported. Structure **42** shows a $J$ value similar to that of simple isoxazole, while that of **43** is smaller. Comparison of the data reported in Table 1.34 indicates that in protic solvent, **41** exists in the form **41c**, while the form **41b** is stabilized in the basic solvent.[198/74]

TABLE 1.34

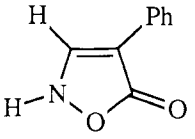
| Compound | Solvent | $^2J(^{15}N\text{-}H_3)$(Hz) |
|---|---|---|
| **41** | MeOH/$H^+$ | 8.6 |
| | EtOH/$H^+$ | 8.8 |
| | DMSO | 9.4 |
| | DMSO/Py | 11.6 |
| | MeOH/$OH^-$ | 13.0 |
| | $CDCl_3$ | insoluble |
| **42** | $CDCl_3$ | 14.1 |
| | $Et_2O$ | 14.3 |
| **43** | $CDCl_3$ | 7.4 |
| | $Et_2O$ | 7.4 |



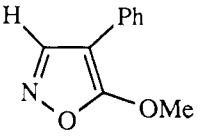

**41a**



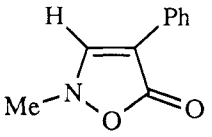

**41b**




**41c**



**42**



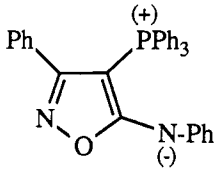
**43**

### *1.2.3.4 Other Nuclei NMR Spectra*

Many papers related to fluorinated isoxazoles report $^{19}$F-NMR data. $^{19}$F chemical shift in 3,5-bisdimethylamino-4-fluoro-isoxazole was found at $-190$ ppm[55/78] relatively to $CCl_3F$. Isomeric 4- and 5-trifluoromethylisoxazoles, showing different signals for the $CF_3$ group, could be quantitatively evaluated in reaction mixtures.[333/83] In fact, in $^{19}$F-NMR, $C_4$-$CF_3$ and $C_5$-$CF_3$ absorb at ca. $-14$ and $-22$ ppm, respectively, relative to trifluoroacetic acid. Isomeric 3,4- and 3,5-perfluoroalkylated isoxazoles could be identified similarly by means of $^{19}$F-NMR a-$CF_2$ signals: at about 106 ppm for $C_4$-$CF_2$ and at 112–115 ppm for $C_5$-$CF_2$ groups[171/78] relative to $CCl_3F$. Other $^{19}$F-NMR data for $CF_3$- and $C_6F_5$-substituted isoxazoles have been reported.[257/79.149/81.334/83]

Protonation of the isoxazole ring, by dissolution in fluorosulfonic acid, has been evidenced by the chemical shift values of fluorine atoms in 3-pentafluorophenyl-4-nitro-3-phenylisoxazole.[257/79] The signals are deshielded by 4–9 ppm in acidic media. Substituted 5-$CF_3$-isoxazole shows the following coupling constants: $^2J_{CF} = 39.5$ Hz and $^3J_{CF} = 2$ Hz.[166/76]

$^{31}$P chemical shift in **44** has been found at $+9.35$ ppm relative to phosphoric acid,[232/81] and a $^{199}$Hg chemical shift in 3-cyano-4-methylmercurio-5-phenylisoxazole at $-344$ ppm (q, $J_{^{199}Hg-H_1} = 138.7$ Hz) from neat dimethylmercury.[94/84]



**44**

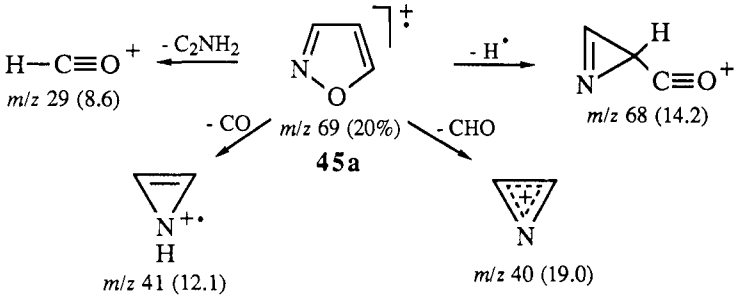
$^{17}$O-NMR data of furan, isoxazole, and their methyl derivatives have been reported and discussed.[137/84] The chemical shifts, influenced primarily by the electronegativity of the atoms linked directly to the oxygen atom, are also affected by alkylation on the various ring positions: $\beta$ and $\gamma$ effects are observed as for simple aliphatic ethers. In Table 1.35 the $^{17}$O chemical shifts and line widths of some heterocycles are listed.

TABLE 1.35. $^{17}$O-NMR CHEMICAL SHIFTS AND LINE WIDTHS OF FURAN, ISOXAZOLE, AND FURAZAN DERIVATIVES

| Compound | $^{17}$O chemical shift (ppm) | Line width (Hz) |
|---|---|---|
| Furan | 240 | 60 |
| 2-Me-furan | 247.5 | 60 |
| 2,5-$Me_2$-furan | 255.5 | 80 |
| Isoxazole | 350 | 90 |
| 3-Me-isoxazole | 344 | 90 |
| 5-Me-isoxazole | 356 | 100 |
| 3,4-$Me_2$-isoxazole | 338 | 110 |
| 3,5-$Me_2$-isoxazole | 350 | 150 |
| 3,4,5-$Me_3$-isoxazole | 340 | 180 |
| 3,4-$Me_2$-furazan | 446 | 210 |

## 1.2.4 Mass Spectra

Since 1968 the mass spectra of isoxazole derivatives have been studied widely; however, the mass spectrum of isoxazole was reported for the first time in 1972.[194/72] The fragmentation pathway proposed for isoxazole recalls that of the isoxazoles studied previously and is shown in the following scheme:




More recently, isoxazole fragmentation by electron impact has been studied in a modern way by means of metastable ion analysis and thermodynamic properties.[194B/81] In Table 1.36 the mass-analyzed ion kinetic energy (MIKE) spectra of the isoxazole molecular ion are reported.[194B/81]

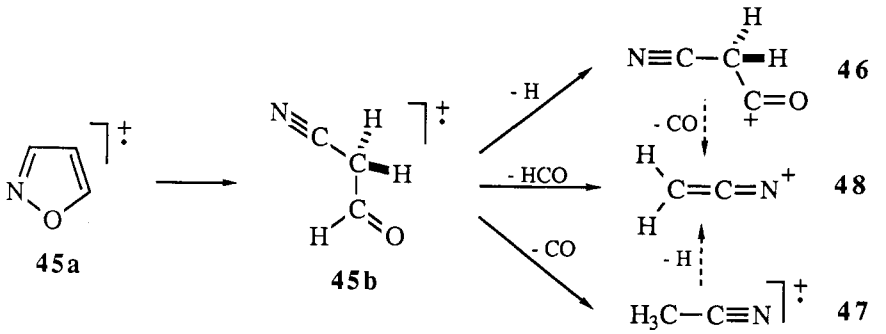
The heat of formation of some of the predictable radical ions, or ions in the fragmentation of isoxazole, have been calculated using the Modified Intermediate Neglect of Differential Overlap (MINDO)/3 method. On this basis each step of the fragmentation pathway has been discussed. The results can be rationalized as follows, where the higher-energy pathways are indicated by dashed arrows (see scheme at p. 60).

It is noteworthy that two of the major decomposition pathways of the isoxazole molecular ion, loss of H· and of CHO·, are rearrangement reactions.

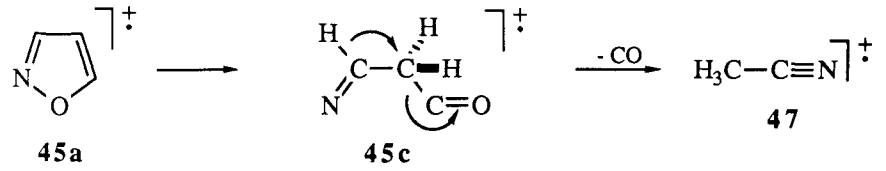
TABLE 1.36. MIKE SPECTRUM OF ISOXAZOLE AND STABLE FRAGMENT IONS

| Parent ion | *m/z*, Fragment ion | Intensity | Kinetic energy released, $T_{50\%}$ (meV) |
|---|---|---|---|
| $[C_3H_3NO]^{+\cdot}$ (*m/z* 69) isoxazole | 68 | 100 | 348 |
| | 42 | 0.07 | - |
| | 41 | $1.1_6$ | 110 ± 2 |
| | 40 | $1.1_8$ | 47 ± 7 |
| $[C_3H_2NO]^+$ (*m/z* 68) (M-H) | 67 | (100)[a] | - |
| | 40 | 51 | 30 ± 2 |
| $[C_2H_3N]^{+\cdot}$ (*m/z* 41) (M-CO) | 40 | 100 | 153 ± 1 |
| | 39 | $0.2_1$ | - |
| | 38 | 0.35 | - |
| $[C_2H_2N]^+$ (*m/z* 40) (M-CHO) | 39 | (100)[a] | - |
| | 38 | 25 | 410 ± 3 |

[a] Composite metastable peak (one component being an interference peak).

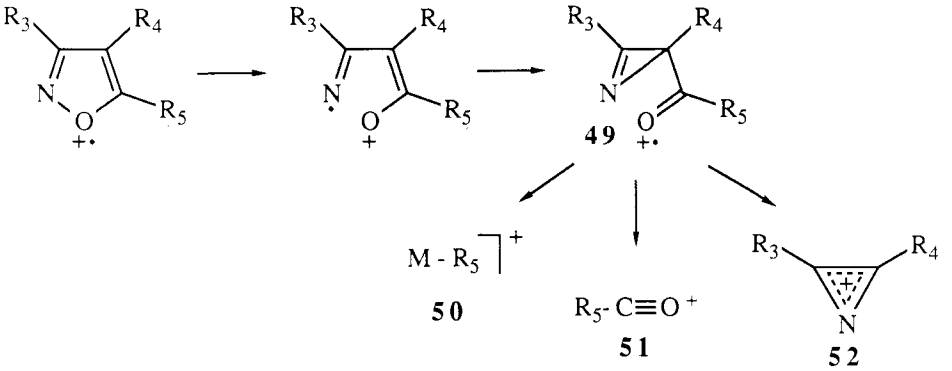



These two reactions and the CO elimination involve ring opening by cleavage of the N–O bond and 1,2-hydrogen migrations. However, from these data, the formation of an azirine-like structure seems to be unnecessary to explain these processes. The following alternative pathway can also be considered:[194B/81]



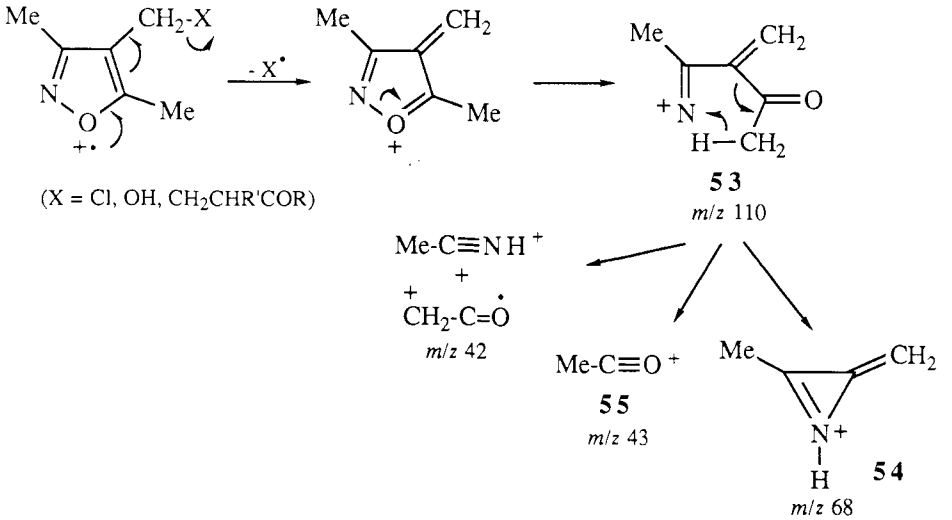

It has been established that the loss of hydrogen occurs from position 5, since the mass spectrum of 4-*D*-isoxazole does not show a loss of deuterium. Furthermore, 3-methylisoxazole exhibits a strong peak at *m/z* 82 $[M-H]^+$, which is absent in the mass spectrum of 5-methylisoxazole.

The lability of the N–O bond of isoxazoles is characteristic of the chemical behavior of the ring opening, as well as of the fragmentation induced by electron impact. In alkylisoxazoles, particularly, the general scheme of fragmentation involves, by cleavage of the N–O bond, formation of an acylazirine (**49**). The acylazirine then gives rise to the following ions:[204/68,175/69] **50**, by loss of $C_5$ substituent as radical; **51**, by cleavage of the acyl ion; and **52**, the azirine ion.




The ions **50** and **51** are very useful in singling out the substituent at the 5-position.

Usually, mass spectra of alkylisoxazoles show quite strong molecular ions, not always $[M - 1]^+$ ions, due to the cleavage of the benzylic carbon–hydrogen bond, cleavage which, by contrast, is very peculiar to many other methyl heterocycles. The isoxazole ring opening is probably easier than cleavage of the hydrogen–carbon bond.[175/69] Studies with labeled isoxazoles demonstrated that the $[M - 1]^+$ ions arise mainly by the loss of hydrogen from the ring.




Scheme 1.1.

TABLE 1.37. MASS SPECTRA OF ISOXAZOLE AND METHYL DERIVATIVES

| Compound | eV | *m/z* (%) | References |
|---|---|---|---|
| Isoxazole | 50 | 70(5); 69($M^+$,100); 68(71); 42(17); 41(60); 40(95); 39(25); 38(22); 37 (9); 30(7); 29(43); 27(12); 26(13) | 194/72 |
| 5-Me-isoxazole | 70 | 84(9); 83($M^+$,55); 82(7); 68(39); 55(6); 54(11); 51(7); 43(100); 42(7); 41(23); 40(21); 39(8); 38(6); 28(8); 27(10) | 12/69 |
| 3,5-$Me_2$-isoxazole | 70 | 97($M^+$,60); 82(77); 54(83); 43(100); 42(14) | 204/68 |
| | 70 | 98(11); 97($M^+$,93); 83(8); 82(100); 68(6); 55(53); 54(93); 52(8); 51(10); 43(95); 42(16); 41(16); 40(9); 39(10); 28(32); 27(30); 26(12) | 12/69 |
| $Me_3$-isoxazole | 70 | 111($M^+$,100); 110(16); 96(86); 68(85); 55(58); 43(85); 42(71) | 204/68 |
| | 70 | 111($M^+$,100); 110(16); 97(18); 96(86); 82(23); 68(85); 55(58); 54(44); 43(85); 42(72); 41(35) | 175/69 |

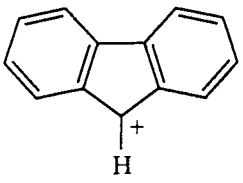
In 4-alkyl-substituted 3,5-dimethylisoxazoles[175/69] the mass spectra show characteristic ions (**53–55**) at *m/z* 110, 68, and 43. The formation of these ions is explained by the initial cleavage of the substituent X, as a radical, followed by the fragmentation depicted in Scheme 1.1. Noteworthy is the hydrogen transfer from the methyl group at $C_5$ to the nitrogen in the case of ion **53**. Some examples of mass spectra of methylisoxazoles are reported in Table 1.37.

Many specific skeletal rearrangements have been reported to explain the formation of either single ions or general characteristic losses of molecules or radicals from the molecular ion,[172/68,197B/68,12/69,177/69,15B/70,164/75] mainly for diphenyl- or triphenylisoxazoles and methylphenylisoxazoles.

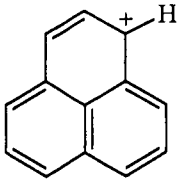
In the mass spectra of triphenyl- and diphenylisoxazoles, as in those of other diphenylheterocycles, a fragment ion at *m/z* 165 (corresponding to $C_{13}H_9$) is always present. The abundance of this ion is larger when the two phenyl groups are adjacent:[177/69]

| | |
|---|---|
| 3,4-diphenylisoxazole | 42% intensity |
| 3,5-diphenylisoxazole | 4% intensity |
| 4,5-diphenylisoxazole | 36% intensity |
| 3,4,5-triphenylisoxazole | 20% intensity |

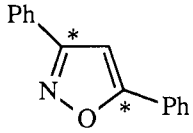
According to the rearrangements of the molecular ion, structures of fluorenyl ion (**56**) or phenalenyl ion (**57**) have been assigned to $C_{13}H_9^+$. Many studies have been carried out[197B/68,12/69,177/69,15B/70,164/75] to explain the formation of this fragment ion, in an effort to understand the skeletal rearrangement of the isoxazole ring under electron impact. In fact, the molecular ion must, first, lose CO and $H_2CN\cdot$ (or HCN and H·) to give $C_{13}H_9^+$. Metastable ions indicate that the first rearrangement involves loss of CO from carbon 5 as shown for the 3,5-$^{13}$C-labeled 3,5-diphenylisoxazole (**58**).[164/75] Subsequent cleavage from $[M-{}^{13}CO]^{+\cdot}$ involves losses of $H_2CN$ and $H_2{}^{13}CN$ in the ratio 1:1. This means that after the



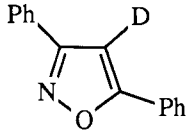
56



57



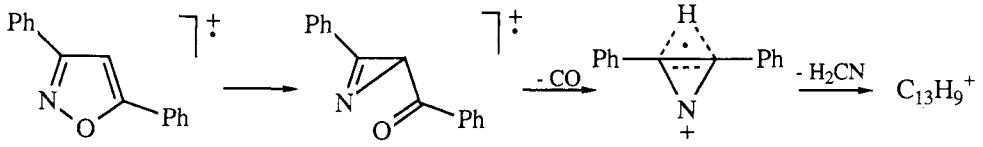
58



59

loss of CO, each of two remaining isoxazole carbon atoms is lost to the same extent by elimination of $H_2CN$, probably from a symmetrical intermediate.

With regard to the hydrogen atoms of the $H_2CN$ radical, the mass spectrum of 4-deutero-3,5-diphenylisoxazole (**59**) shows that the $[M-CO]^{+\cdot}$ ion eliminates HCN, (DCN + $H_2CN$) and HDCN in the ratio 0.1:9.9:90. This clearly indicates that the primary loss involves the isoxazole ring hydrogen together with a hydrogen from the phenyl rings. The phenomenon of scrambling with the phenyl hydrogens, which is very intensive in many other heterocyclic nuclei, is minimal for isoxazoles. As the behavior described above recalls that of 2,3-diphenylazirine by electron impact, the most probable fragmentation pattern should be as depicted in the following scheme:

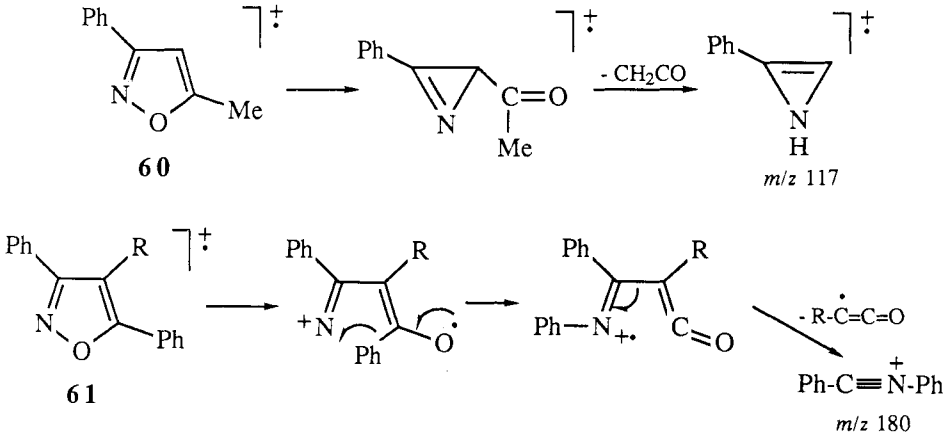


Comparison of the thermal and photochemical products of diphenylisoxazole with the mass spectra ions leads to an assumption of analogous behavior for the isoxazole ring with all the reactions that proceed through the benzoylazirine intermediate[147/76] (see § 1.4.5). The loss of (CO + HCN) from the molecular ion also occurs for haloisoxazoles such as 5-chloro-3-phenylisoxazole and 4-iodo-3-phenylisoxazole.[12/69] 3,5-Diphenyl-4-(*p*-fluorophenyl)isoxazole has been used to study the scrambling pattern of the principal fragmentations in the mass spectrometer.[177/72] In this case scrambling seems to occur for formation of the $C_{13}H_9^+$ ion.

As already mentioned, by contrast with many other heterocyclic systems, the isoxazole nucleus usually does not show, by electron impact, randomization of

the hydrogens of the ring with those of the possible phenyl[177/69] or methyl substituents. This fact was clearly demonstrated by the spectra of 3-$d_3$-phenylisoxazole, 3-methyl-5-$d_3$-phenylisoxazole, 3-phenyl-5-*d*-methylisoxazole and 3-methyl-4-deutero-5-phenylisoxazole.[12/69] This hydrogen specificity is comparable to that observed in oxazoles. For this reason some authors assume the rearrangement isoxazole → oxazole via acylazirine.[172/68]

A shift of hydrogen or phenyl has been observed in 5-methylisoxazoles and 5-phenylisoxazoles, respectively. For example, 5-methyl-3-phenylisoxazole (**60**) gives 3-acetyl-2-phenylazirine, which loses ketene by the shift of one hydrogen from the methyl to the nitrogen.[12/69] Similarly, a shift of the phenyl[12/69] occurs in **61**:




Another skeletal rearrangement involving loss of CHO has been observed in many methyl- and methylphenylisoxazoles[12/69] [i.e., 5-methyl-, 3,5-dimethyl-, and trimethylisoxazole, and 4-phenyl-5-methyl-, 3-methyl-5-phenyl (**62**), 4-methyl-5-phenyl-, and 3,5-diphenyl-4-methylisoxazole].[206B/79] Also, in these cases the shift of the substituent at $C_5$ and a subsequent hydrogen shift can be assumed, as depicted for the following example:[12/69]

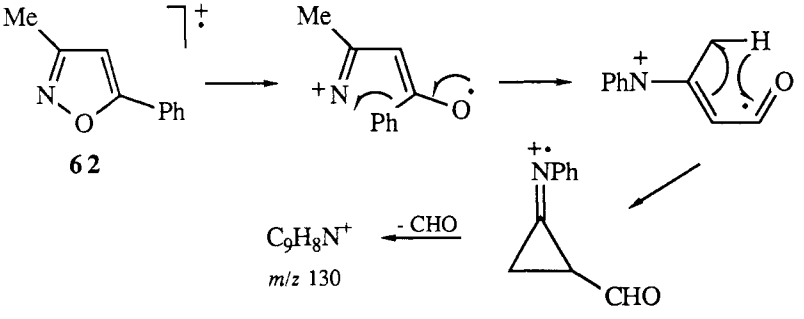
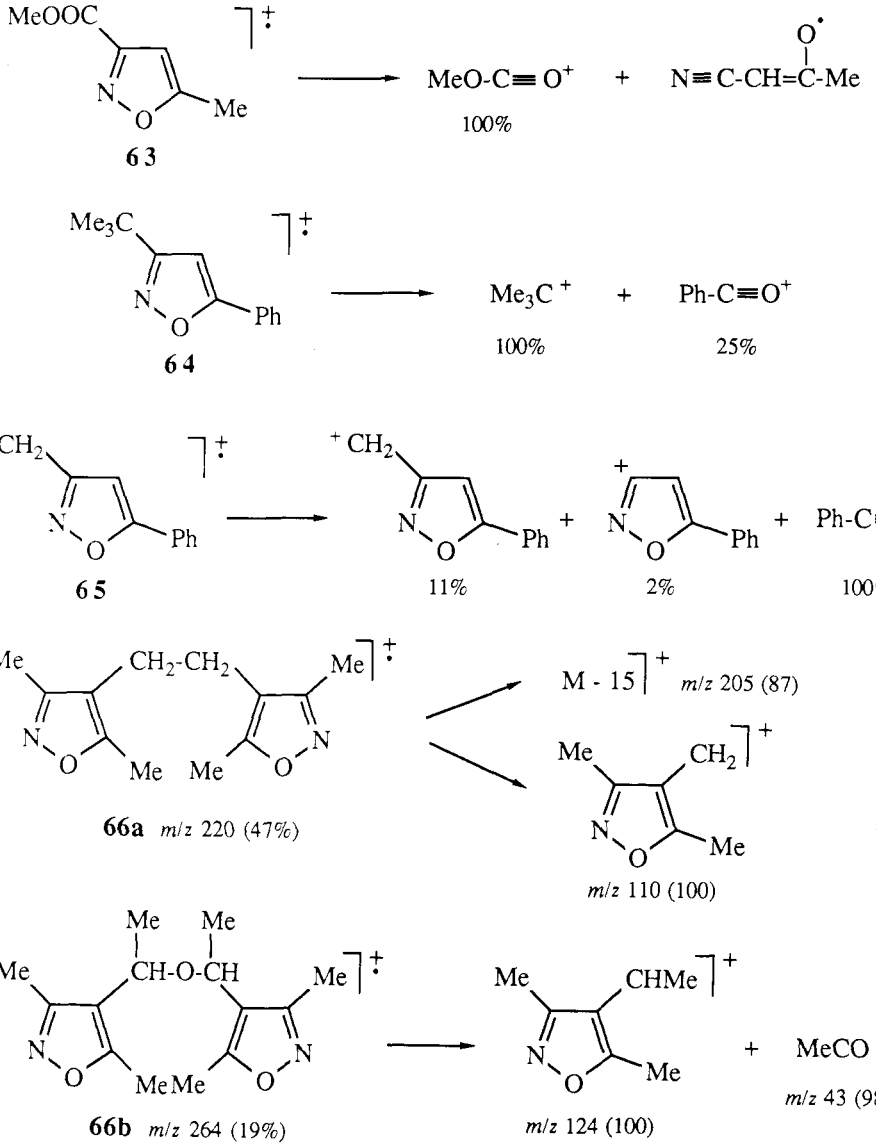


TABLE 1.38. MASS SPECTRA OF ALKYLARYLISOXAZOLES

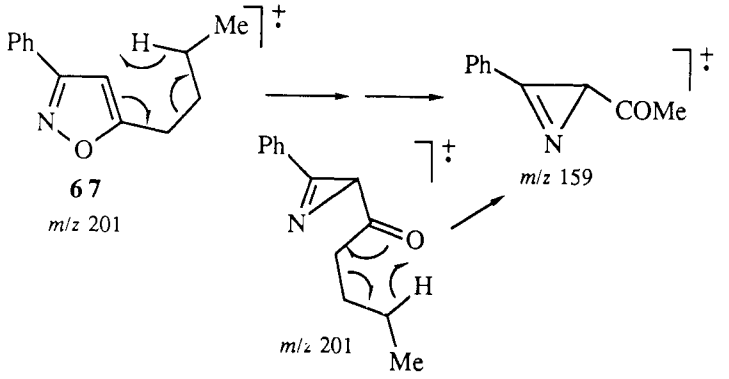
| Compound | eV | *m/z* (%) | References |
|---|---|---|---|
| 5-Me-3-Ph-isoxazole | 70 | 159($M^+$,67); 144(100); 117(22); 116(31); 90(12); 89(13); 77(52); 51 (21); 43(21) | 12/69 |
| 5-Me-4-Ph-isoxazole | 70 | 159($M^+$,100); 144(21); 130(14); 117(95); 116(55); 104(38); 103(31); 90(33); 89(55); 78(28); 77(15);, 63(29); 43(64) | 12/69 |
| 3-Me-5-Ph-isoxazole | 70 | 159($M^+$,90); 130(19); 105(100); 104(39); 90(18); 89(21); 82(28); 77 (90); 51(45) | 12/69 |
| 4-Me-5-Ph-isoxazole | 70 | 159($M^+$,74); 130(21); 105(100); 104(21); 90(19); 78(21); 77(90); 51 (49) | 12/69 |
| 3-Et-5-Ph-isoxazole | 70 | 173($M^+$,66); 172(11); 158(11); 131(19); 117(10); 105(100); 103(23); 91 (16); 89(16); 78(32); 77(94); 76(16); 68(20); 63(15); 51(56); 41(16); 39(23) | 12/69 |
| 4-Et-3-Ph-isoxazole | 70 | 173($M^+$,59); 158(99); 146(16); 145(15); 144(36); 130(62); 118(71); 104(21); 103(28); 77(100) | 38B/79 |
| 3-*t*-Bu-5-Ph-isoxazole | 70 | 201($M^+$,36); 186(17); 145(10); 144(39); 116(6); 105(26); 104(6); 78 (8); 77(41); 57(100); 51(23); 41(41); 39(18) | 12/69 |
| 5-*n*-Bu-3-Ph-isoxazole | 70 | 201($M^+$,50); 159(46); 145(14); 144(100); 117(16); 116(28); 105(14); 103(12); 91(10); 89(14); 77(48); 51(12); 41(7) | 12/69 |
| 3-Me-5-(*o*-$HOC_6H_4$)-isoxazole | 70 | 175($M^+$,100); 147(5); 134(12); 133(5); 121(33); 119(8); 105(25); 93(9); 77(12); 65(12); 63(7); 55(72); 51(6); 39(11) | 219/74 |
| 3-(2,6-$Cl_2C_6H_3$)-4-Me-isoxazole | 70 | 227($M^+$,37); 226(10); 199(22); 198(33); 172(39); 164(100); 145(16); 136(26); 128(15); 123(12); 109(30); 100(22); 75(40); 74(32); 54(37) | 52D/81 |
| 3,4-$Me_2$-5-Ph-isoxazole | 80 | 173($M^+$,100); 132(5); 131(5); 130(4); 116(9); 115(14); 105(50); 104 (50); 103(15); 78(14); 77(50); 71(6); 68(28); 51(18); 43(7); 42(12); 41(12); 40(6) | 98/76 |
| 4,5-$Me_2$-3-Ph-isoxazole | 70 | 173($M^+$,100); 158(45); 131(24); 130(36); 77(26); 51(14); 43(14) | 38B/79 |
| 3,4-$Me_2$-5-(*o*-$MeC_6H_4$) isoxazole | 80 | 187($M^+$,100); 172(2); 158(5); 146(10); 145(16); 144(11); 131(22); 130(13); 129(9); 128(9); 119(47); 118(29); 117(45); 116(6); 115 (18); 103(9); 91(49); 90(9); 89(10); 77(6); 68(33); 65(24); 63(8); 51(8); 43(6); 42(14); 41(16); 40(9) | 98/76 |
| 3,4-$Me_2$-5-(*m*-$MeC_6H_4$) isoxazole | 80 | 187($M^+$,100); 158(7); 146(4); 145(2); 144(5); 131(3); 130(8); 129(4); 128(4); 120(4); 119(38); 118(28); 117(24); 115(9); 103(5); 92(5); 91 (34); 77(5); 68(17); 65(12); 44(7); 43(9); 41(10); 40(9) | 98/76 |
| 3,4-$Me_2$-5-(*p*-$MeC_6H_4$) isoxazole | 80 | 187($M^+$,100); 173(5); 158(9); 146(4); 144(6); 131(6); 130(12); 129 (10); 128(6); 127(6); 120(7); 119(60); 118(35); 117(45); 116(8); 115 103(7); 93(7); 92(5); 91(40); 89(9); 78(8); 77(7); 71(7); 68(14); (35); 65(19); 63(8); 51(7); 43(8); 42(10); 41(20) | 98/76 |
| 3,4-$Me_2$-5-(*p*-*t*$BuC_6H_4$) isoxazole | 80 | 229($M^+$,31); 214(100); 186(9); 174(6); 173(7); 172(4); 161(8); 157(6); 145(7); 131(2); 130(3); 129(4); 128(4); 117(8); 115(8); 105(9); 77(9); 68(7); 55(7); 44(4); 43(9); 42(10); 41(17) | 98/76 |
| 3,4-$Me_2$-5-(*m*-*t*$BuC_6H_4$) isoxazole | 80 | 229($M^+$,60); 214(100); 186(14); 174(14); 173(12); 172(10); 161(12); 157(12); 145(15); 117(15); 115(15); 105(10); 91(15); 77(15); 55(10); 43(10); 42(11); 41(21) | 98/76 |
| 3,5-$Me_2$-4-(*p*-$NO_2C_6H_4$) isoxazole | 50 | 218($M^+$,100); 203(18); 189(11); 188(58); 175(18); 172(15); 146(15); 145(15); 131(12); 130(25); 129(17); 119(75); 118(29); 117(12); 105 (11); 104(26); 103(54); 102(23); 91(42); 89(21); 88(22); 87(12); 78 (16); 77(58); 75(17); 65(15); 64(14); 63(27); 62(19); 55(11); 52(12); 51(25); 50(15); 43(100); 42(12); 41(19); 40(19); 39(26) | 182/74 |

Some examples of mass spectra of arylalkylisoxazoles are reported in Table 1.38.

Although skeletal rearrangements are an important feature of the mass spectra of isoxazoles, it must be pointed out that no rearrangement or migration occurs when the substituents of the isoxazole ring can give easy cleavage or stable ions. Some examples are reported here for 3-methoxycarbonyl-5-methylisoxazole (**63**),[172/68,175/69] 3-*tert*-butyl-5-phenylisoxazole (**64**),[12/69] 3-ethyl-5-phenylisoxazole (**65**),[12/69] or **66a**[287/82] and **66b**:[148/76]



A $\beta$-scission, with hydrogen rearrangement, may occur when the 5-alkyl substituent has a chain longer than two carbon atoms, as for 3-phenyl-5-*n*-butyl-isoxazole (**67**):[12/69]




Hydrogen rearrangement may proceed through the isoxazole or the azirine, ultimately producing the ion *m/z* 159.

Mass spectra have been used as a very effective tool for structure elucidation when the synthetic methods lead to isomeric isoxazoles, as for example through the 1,4-dianions of oximes[174/70] or by oximation of asymmetric $\beta$-diketones,[155/69,27/70,192/70,219/74,222/74,169/75,36/76,231/76,25/77,221/77,224/77,249/80] chalcones,[249/80,200/81] pyrones,[184/77] and benzo-$\gamma$-pyrones.[216/76,200/79,248/80,201F/81,123/84] By these methods, one or both of the 3,5-disubstituted isoxazoles can be obtained. Usually, the structure of the products is clearly established by electron impact fragmentation.

Most products obtained as described are alkyl-, aryl-, or diaryl-substituted isoxazoles. In same cases mass spectrometry permits us to revise erroneous structures. The assignment of the isomeric structure was based primarily on formation of the $R_5$-C≡O$^+$ ion. In the fragmentation pattern of asymmetrically trisubstituted or 3,5-disubstituted isoxazoles,[174/70,192/70,219/74,222/74,169/75,216/76,25/77,221/77,249/80] the most prominent peaks are those reported in the following scheme:

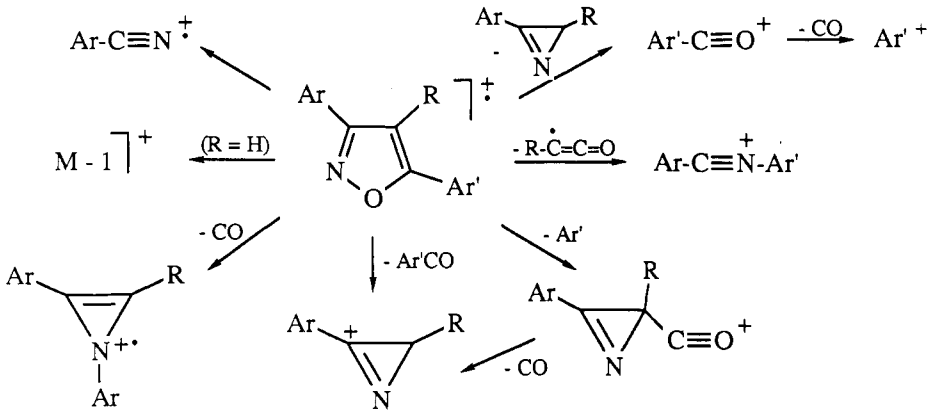


TABLE 1.39. MASS SPECTRA OF ARYLISOXAZOLES

| Compound | eV | *m/z* (%) | References |
|---|---|---|---|
| 3-Ph-isoxazole | 70 | 145($M^+$,98); 144(100); 117(14); 116(26); 90(16); 89(22); 77(79); 63 (10); 51(42) | 12/69 |
| 5-Ph-isoxazole | 70 | 145($M^+$,100); 105(83); 90(14); 89(12); 77(60); 51(17) | 12/69 |
| 3-(*p*-$NO_2C_6H_4$)-isoxazole | 50 | 190($M^+$, 100); 189(97); 162(12); 143(31); 132(10); 116(16); 102(15); 90(13); 89(68); 88(10); 77(12); 76(29); 75(30); 74(12); 63(28); 62 (14); 51(15); 50(34); 39(13) | 182/74 |
| | 70 | 190($M^+$, 100); 189(81); 162(9); 143(28); 116(13); 89(55); 76(29); 75 (23); 63(27); 50(33) | 52D/81 |
| 5-(*p*-$NO_2C_6H_4$)-isoxazole | 70 | 190($M^+$,100); 189(13); 160(38); 150(41); 132(27); 120(22); 116(10); 104(36); 92(23); 89(84); 77(25); 76(48); 75(28); 74(16); 68(11); 63 (34); 62(14); 52(12); 51(20); 50(44); 39(19) | 182/74 |
| 3-(2,6-$Cl_2C_6H_3$)-isoxazole | 70 | 213($M^+$,73); 212(100); 185(42); 184(35); 157(26); 150(25); 149(13); 145(18); 123(45); 114(37); 109(42); 87(23); 75(47); 74(48); 73(32); 63(24); 61(21) | 52D/81 |
| 3,5-$Ph_2$-isoxazole | 70 | 221($M^+$,55); 144(15); 105(100); 89(15); 77(66); 63(10); 51(27) | 172/68 |
| 4,5-$Ph_2$-isoxazole | 70 | 221($M^+$,47); 193(16); 165(36); 105(100); 77(42) | 177/69 |
| 3,4-$Ph_2$-isoxazole | 70 | 221($M^+$,100); 193(58); 165(42); 116(24); 90(87); 89(84); 77(47); 63(26); 51(26) | 177/69 |
| 3-(*o*-$MeC_6H_4$)-5-Ph-isoxazole | 70 | 235($M^+$,100); 234(82); 158(47); 130(40); 105(84); 91(33); 77(89) | 25/77 |
| 5-(*o*-$MeC_6H_4$)-3-Ph-isoxazole | 70 | 235($M^+$,100); 234(53); 132(28); 119(47); 103(10); 91(39); 77(20) | 25/77 |
| 5-(*p*-$MeOC_6H_4$)-3-Ph-isoxazole | 70 | 251($M^+$,59); 135(100); 132(12); 105(16); 103(53); 92(12); 77(41) | 192/70 |
| 3-(*p*-$MeOC_6H_4$)-5-Ph-isoxazole | 70 | 251($M^+$,77); 174(17); 146(10); 133(57); 105(100); 103(29); 102 (30); 90(28); 77(55) | 192/70 |
| 3-(*p*-$ClC_6H_4$)-5-Ph-isoxazole | 70 | 257(16); 255($M^+$,48); 178(10); 139(12); 137(28); 105(100); 77(89) | 192/70 |
| 5-(*p*-$ClC_6H_4$)-3-Ph-isoxazole | 70 | 257(16); 255($M^+$,43); 144(13); 141(30); 139(100); 113(10); 111(30); 103(32); 77(20) | 192/70 |
| 5-(*p*-$NO_2C_6H_4$)-3-Ph-isoxazole | 70 | 267(17); 266($M^+$,100); 265(35); 220(10); 219(12); 192(8); 191(6); 165(6); 151(7); 150(71); 145(8); 144(83); 120(20); 116(13); 105(9); 104(31); 89(14); 77(32); 76(16); 63(9); 51(12); 50(7) | 187/74 |
| 3-(*p*-$NO_2C_6H_4$)-5-Ph-isoxazole | 50 | 267(9); 266($M^+$, 67); 106(9); 105(100); 95.5(5); 77(33); 51(6) | 187/74 |
| 3-(*m*-$NO_2C_6H_4$)-5-Ph-isoxazole | 50 | 267(13); 266($M^+$,56); 189(5); 162(5); 106(9); 105(100); 95.5(6); 78 (9); 77(32); 51(5) | 187/74 |
| 5-(*m*-$NO_2C_6H_4$)-3-Ph-isoxazole | 70 | 267(18); 266($M^+$,100); 265(12); 220(6); 219(6); 192(6); 165(5); 150 (62); 145(11); 144(100); 133(6); 121(13); 116(13); 105(6); 104(30); 103(5); 92(5); 89(14); 77(24); 76(17); 75(6); 63(9); 51(11); 50(6); 43(21); 39(6) | 187/74 |
| 3-(2,6-$Cl_2C_6H_3$)-5-Ph-isoxazole | 70 | 289($M^+$,60); 261(50); 199(17); 191(18); 190(18); 125(18); 116(25); 109(18); 90(95); 89(100); 53(36) | 52D/81 |

TABLE 1.39. *(Continued)*

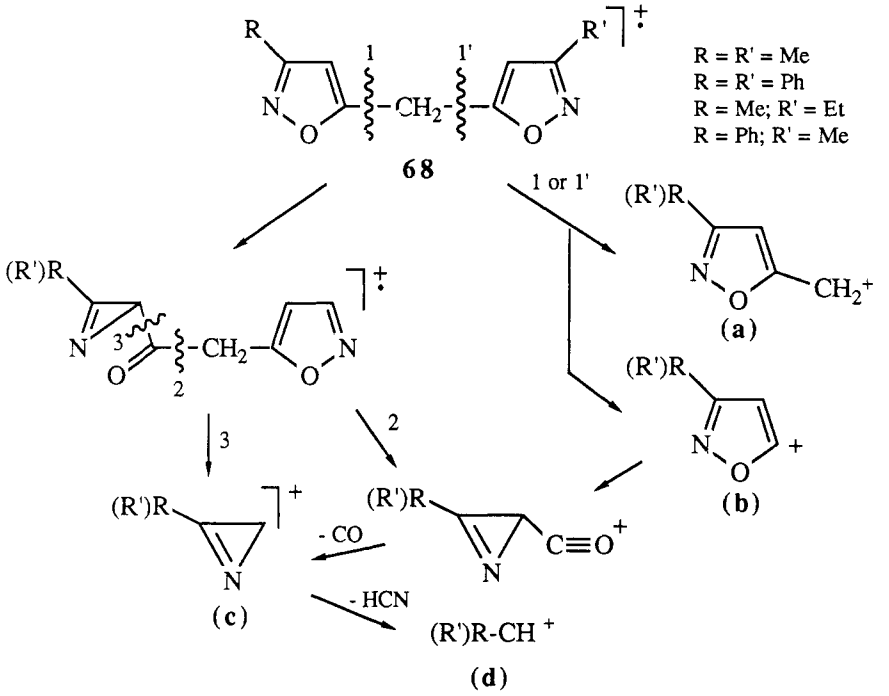
| Compound | eV | *m/z* (%) | References |
|---|---|---|---|
| 3,5-($p$-$ClC_6H_4$)$_2$ isoxazole | 70 | 291($M^+$,18); 290(6); 289(31); 219(9); 141(34); 140(8); 139(100); 113(9); 113(9); 111(27); 75(12) | 187/74 |
| 3-($p$-$BrC_6H_4$)-5-Ph-isoxazole | 50 | 301(25); 299($M^+$,24); 106(8); 105(100); 77(30). | 187/74 |
| 5-($p$-$BrC_6H_4$)-3-Ph-isoxazole | 70 | 302(9); 301(57); 300(22); 299($M^+$,54); 298(15); 273(6); 271(7); 220 (5); 186(8); 185(100); 184(9); 183(95); 165(7); 157(30); 155(27); 155 (27); 144(28); 116(9); 105(13); 89(15); 77(20); 76(15); 75(12); 63(7); 57(6); 51(12); 50(7); 43(7); 39(5) | 187/74 |
| 3,5-($p$-$NO_2C_6H_4$)$_2$-isoxazole | 70 | 312(3); 311($M^+$,55); 190(7); 189(16); 151(7); 150(100); 143(7); 120 (18); 117(6); 104(22); 92(10); 89(6); 76(17); 75(8); 63(5); 59(7); 57 (8); 50(5); 43(6) | 187/74 |
| 3,4,5-$Ph_3$-isoxazole | 70 | 297($M^+$,39); 180(32); 165(20); 105(100); 89(21); 77(58); 51(10) | 177/69 |
| | | 297($M^+$,100); 192(2); 180(33); 166(6); 165(14); 106(7); 105(92); 89(10); 77(33); 51(6) | 174/70 |

Usually, the base peak corresponds to $ArC{\equiv}O^+$ ion, which is diagnostic for the substituent in position 5. Sometimes the base peak is the molecular ion. The cleavage of Ar occurs when the aryl group gives rise to a stable radical. Then the $[M-Ar]^+$ ion loses CO to afford the azirine. The substituent in position 3 can sometimes be identified by presence of the ArCN ion.[192/70,171/73,159/80,16/82] By contrast with the substituent at $C_5$, the substituent at $C_3$ is never cleaved by electron impact. In 3,5-disubstituted isoxazoles, loss of hydrogen from 4 gives rise to the $[M-H]^+$ ion. Together with the ions depicted in the foregoing scheme, the mass spectrum shows peaks arising from fragmentation of the aryl groups. Often, ions corresponding to doubly charged molecular ions ($M^{2+}$) have been detected.[174/70] Mass spectra of selected arylisoxazoles are reported in Table 1.39.

Mass spectra of nine isoxazolylmethyl- and two bis(isoxazolylmethyl) isoxazoles have been studied and discussed in detail.[13/79] These compounds can be gathered into two main groups: 5,5′-diisoxazolylmethanes (**68**) and 5,3′-diisoxazolylmethanes (**69**). All the compounds show intense molecular ions. The most characteristic ions for **68** are, as indicated in Scheme 1.2, (**a**) and (**b**), arising from the cleavage around the methylene group [(**a**) usually shows an easy loss of ketene]; (**c**) and (**d**) are the already reported ions formed by electron impact on 3,5-disubstituted isoxazoles. When $R \neq R'$ these ions show different *m/z* values in the same spectrum, depending on the substituent.

Compounds **69** show the same fragmentation pathways described for **68**, but in addition they show [M–RCN], [M–RCN–CO], and R′–C≡O ions (Scheme 1.3). Most of these processes have been determined by metastable transition. Bis(isoxazolylmethyl)isoxazoles show the same fragmentation patterns but more complicated spectra.

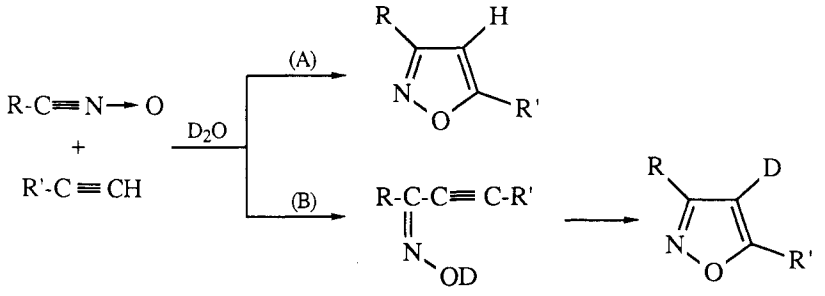
Also, the mass spectra of some tetrasubstituted 4,4′-methylene diisoxazoles

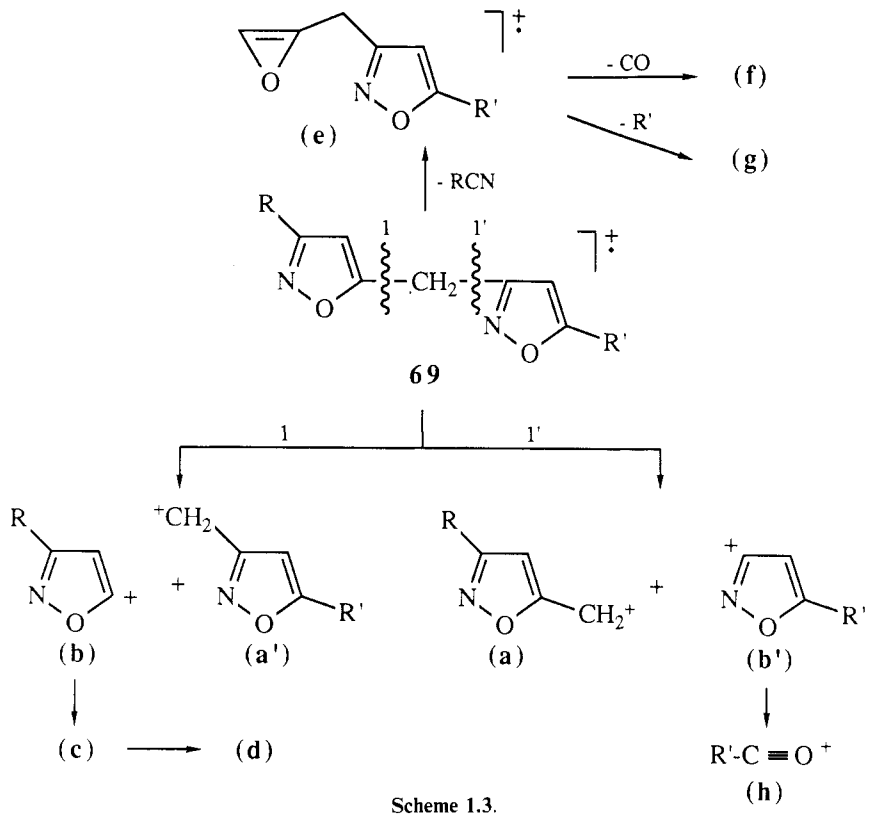



**Scheme 1.2.**

have been discussed together with those of 4,4′-diisoxazoles.[44/77,16/82,140/84] Tautomerism of the 3-methylisoxazolin-5-one has also been studied by mass spectrometry.[134/69] Fragmentation of the methyl derivatives has been followed by deuteration.

The mechanism of formation of 3,5-disubstituted isoxazoles from nitrile oxides and monosubstituted acetylenes has been studied by deuterium incorporation.[194B/70] The ratio between the 4*H*- and 4*D*-isoxazoles, measured from the mass spectrum of the reaction mixture, showed which pathway has been followed: direct 1,3-cycloaddition (A) without deuterium incorporation or intermediate formation of an α-acetylenic oxime (B) with incorporation:



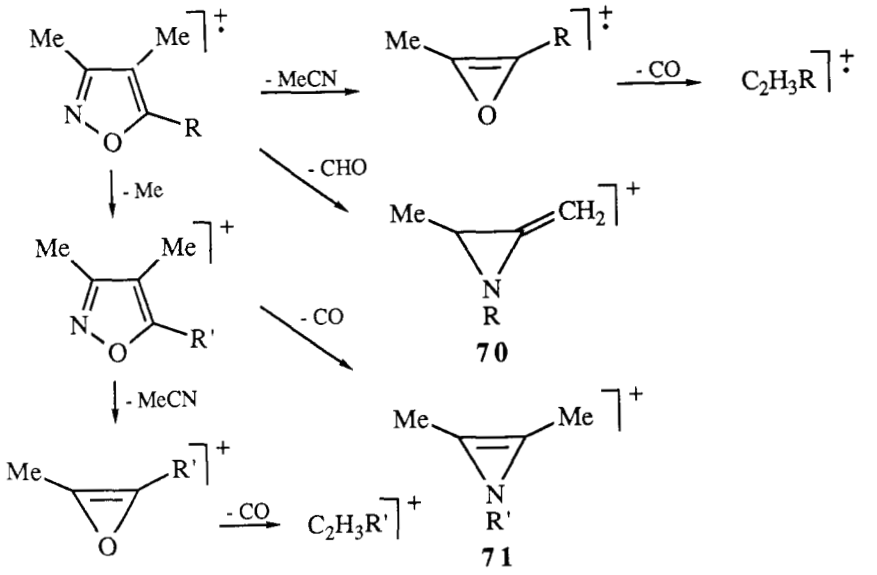



Scheme 1.3.

It has thus been demonstrated that the reaction pathway depends on the nature of the substituents.[194B/70]

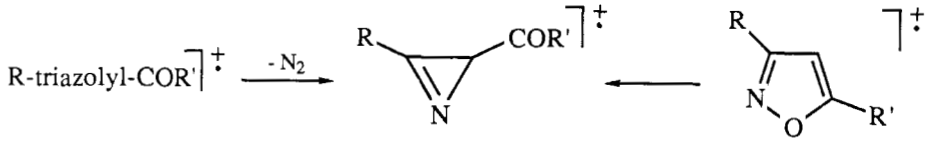
Twenty-five mass spectra of 3,4-dimethyl-5-arylisoxazoles and 3,4-dimethyl-5-heteroarylisoxazoles have been reported and discussed.[98/76] The most characteristic fragmentations involve loss of acetonitrile and CO and, if possible, of a methyl radical from the substituent at position 5, as reported in Scheme 1.4. The fragments from the loss of acetonitrile are not always present in the mass spectra of 3,4-dimethyl-5-pyridylisoxazoles, while the loss of CHO and CO gives rise to ions such as **70** and **71**.

The mass spectra of some other heteroarylisoxazoles (thienyl,[98/76,166/82] benzothienyl,[166/82] thiazolyl,[98/76] benzothiazolyl,[143/72] triazolyl,[113/79] 1,2,4-oxadiazolyl,[159/80,86/81] morpholino,[9/81] thiazolidinyl-4-ones,[130/82] 1,4,2-dioxazolyl[177/83]) have been reported and discussed as a tool for structure elucidation. Usually, the main fragmentations are related to the cleavage of the N–O bond of the isoxazole ring and subsequent formation of the azirine for 3-substituted isoxazoles[166/82] or loss of CO and HCN[143/72] for 3-unsubstituted isoxazoles. 1,2,4-Oxadiazolylisoxazoles show as the base peak the benzonitrile[159/80] or benzoyl[86/81] cations, probably arising from the oxadiazole ring.

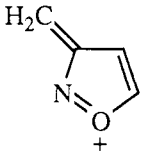



**Scheme 1.4.**

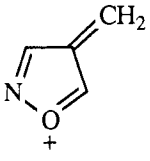
The mass spectra of 3-methyl-5-(4-methyltriazolyl)- and 3-phenyl-5-(4-phenyltriazolyl)isoxazole show an interesting analogy with triazolylcarbonyl compounds (R-triazolyl-COR′) for the fragmentation pattern since their composition differs by $N_2$. Therefore, the loss of $N_2$ by the triazole ring can be related to the ring opening of the isoxazole by electron impact:[113/79]



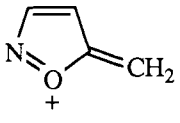

The effect of the substituent in arylisoxazoles on the decomposition of the molecular ion has also been extensively studied at different temperatures and voltages.[89/71,182/74,187/74] It has been established that the shift of positive charge from the substituent at $C_3$ to the ring oxygen depends on the electronic effect of the substituent, and precedes isomerization of the molecular ion and ring cleavage. Furthermore, in the case of *p*-nitrophenylisoxazoles, for the formation of the [M–NO] cations, cyclic conjugated forms with the positive charge on the oxygen, such as **72–74**, can be assumed. Since the three forms are not energetically equivalent, the probability of formation of the [M–NO] ion is different and is increasing in the order **72** < **74** < **73**.



72

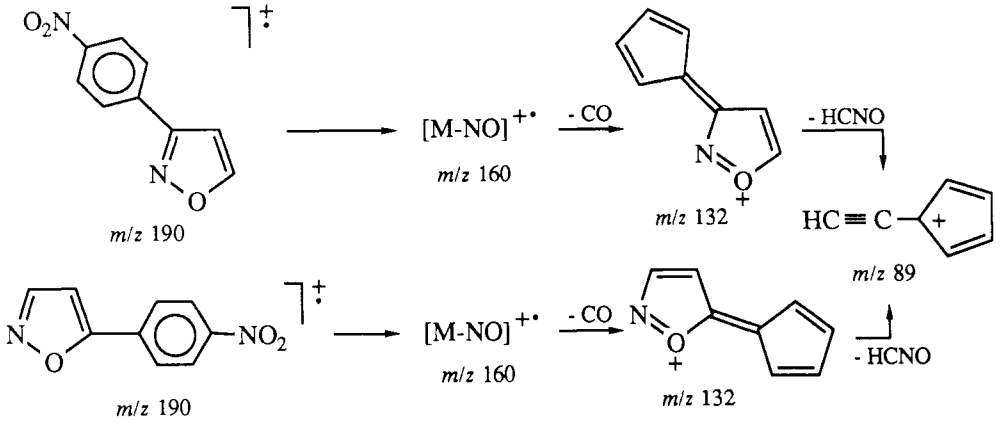


73



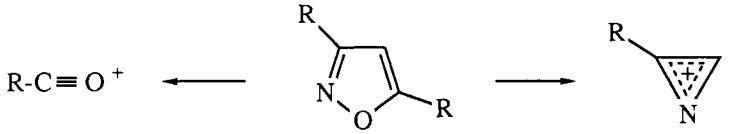
74

As an example, the main fragmentations of 3-*p*-nitrophenyl and 5-*p*-nitrophenylisoxazole are reported in the following scheme:[182/74]




The intensity of the $[Ar-C{\equiv}O]^+$ ion in 3,5-diarylisoxazoles or 5-substituted 3-arylisoxazole is connected with the ease of the ring oxygen to accommodate a positive charge shifted from the molecular ion.

As an example, the intensities of the acylion and the azirine ion in isoxazole, 3,5-dimethylisoxazole, and 3,5-diphenylisoxazole are reported here:

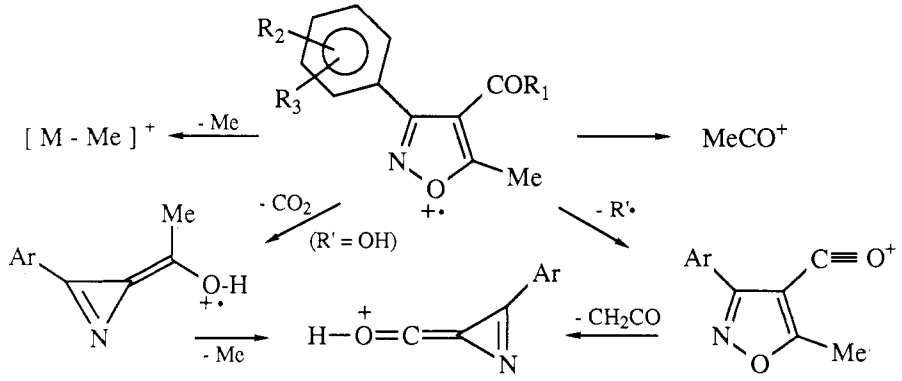



| | | |
|---|---|---|
| 43.0% | R = H | 95.0 |
| 72.5 | R = Me | 71.5 |
| 100.0 | R = Ph | 6.7 |

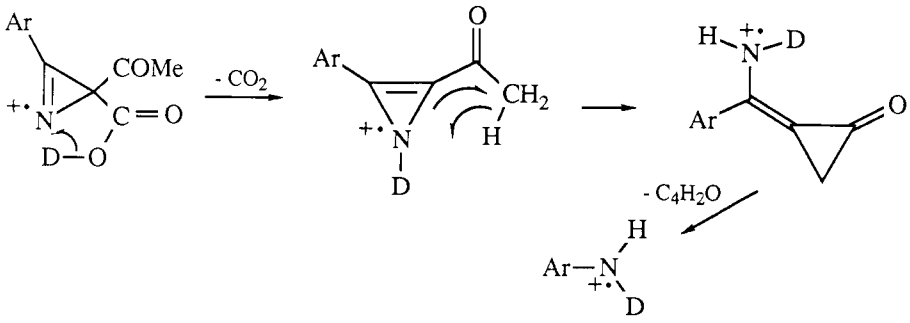
The spectra of fifteen 3,5-diarylisoxazoles have been reported and discussed from this point of view.[187/74]

Similarly, the rearrangement and stability of the molecular ions of several 3-aryl-5-methyl-4-isoxazolecarboxylic acids have been studied.[193/72,183/74] The intensity and stability of the molecular ion depend on the electronic effect of the substituent on the aryl group at $C_3$ and on the position of this substituent with respect to the carboxylic group. The loss of $CO_2$ may occur by participation of either the oxygen atom of the carboxylic group, through a hexacyclic inter-

mediate, or the ring nitrogen through a rearrangement. Deuterated derivatives have shown that both pathways are feasible. The corresponding methyl esters and amides show the same fragmentation pattern:




Loss of $CO_2$ and hydrogen shifts, the latter studied by deuteration, can be visualized in the following way:




The influence of the substituent position on the aryl group for the fragmentation can be exerted if the interaction between the substituent and the carboxylic group leads to stable cyclic intermediates, as for 3-*o*-chlorophenyl-5-methyl-4-isoxazolecarboxylic acid[193/72] and derivatives:[183/74]

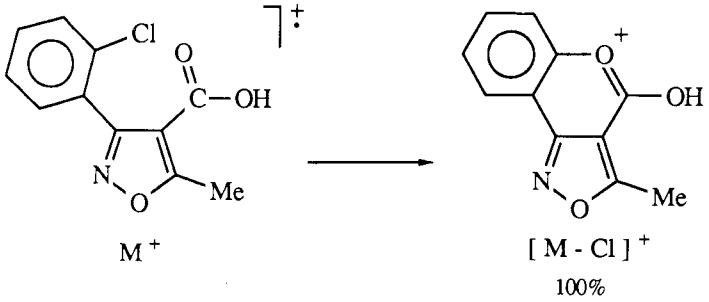
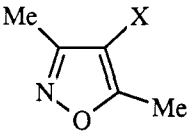


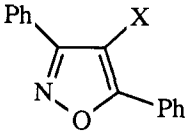
TABLE 1.40. MASS SPECTRA OF HALOISOXAZOLES

| Compound | *m/z* (%) | References |
|---|---|---|
| 5-Cl-3-Ph-isoxazole | 181(16); 180(5); 179($M^+$,48); 153(5); 151(14); 145(13); 144(100); 126 (4); 124(10); 117(6); 116(40); 103(8); 89(24); 78(6); 77(74); 76(11); 63(14); 62(8); 51(34); 50(15) | 12/69 |
| 4-I-3-Ph-isoxazole | 271($M^+$,12); 270(100); 269(11); 242(9); 143(16); 116(41); 115(6); 114 (10); 104(6); 103(13); 89(34); 88(9); 78(6); 77(54); 76(11); 75(6); 74(5); 65(6); 64(5); 63(15); 62(7); 52(6); 51(30); 50(12) | 12/69 |
| 5-I-3,4-$Me_2$-isoxazole | 223($M^+$,100); 127(10); 96(15); 68(35); 58(25); 54(30); 53(60); 44(5); 43(100); 42(45); 41(55) | 98/76 |
| 4-Cl-3,5-$Ph_2$-isoxazole | 257(11.0); 255($M^+$,31.1); 230(1.6); 229(2.8); 228(1.2); 227(5.0); 223 (1.6); 222(2.9); 221(2.9); 220(8.6); 219(2.6); 193(1.5); 192(3.3); 191 (1.5); 190(2.8); 189(2.9); 181(2.2); 180(11.1); 178(1.6); 166(1.6); 165 (4.5); 164(1.1); 163(1.6); 152(1.2); 150(2.2); 146(1.6); 143(1.1); 139 (1.3); 138(1.1); 137(1.1); 136(1.8); 129(2.2); 128(1.5); 126(1.1); 125 (1.2); 124(1.7); 123(2.1); 122(1.7); 121(1.1); 119(1.1); 117(2.0); 116 (1.3); 115(1.8); 114(1.3); 111(1.6); 110(1.3); 109(1.5); 107(1.4); 106 (8.1); 105(100); 104(2.4); 103(8.7); 102(1.5); 101(1.3); 99(1.1); 98 (2.2); 97(2.8); 96(2.1); 95(2.9); 94(1.2); 93(1.5); 91(3.1); 90(1.9); 89 (7.3); 88(1.6); 87(2.1); 85(1.8); 84(2.1); 83(3.9); 82(2.9); 81(3.8); 80 (1.2); 79(2.8); 78(6.7); 77(62.0); 76(6.4); 75(2.7); 74(2.9); 73(4.0); 71 (2.8); 70(2.1); 69(4.5); 68(1.7); 67(3.3); 65(1.7); 64(1.2); 63(4.0); 62 (1.8); 61(1.5); 60(3.5); 57(4.5); 56(2.6); 55(7.6); 54(2.0); 53(1.3); 51 (17.8); 50(5.6); 45(2.2); 42(2.6); 41(8.6) | 257/70 |
| 4-I-3-Me-5-Ph-isoxazole | 285($M^+$,53); 158(6); 130(19); 106(10); 105(100); 103(10); 102(6); 89 (29); 77(36); 63(11); 51(12); 50(6) | 12/69 |
| 4-Br-3,5-$Ph_2$-isoxazole | 301(21.0); 299($M^+$,21.1); 222(2.2); 221(4.6); 220(15.0); 219(1.2); 193 (1.5); 192(6.2); 191(1.5); 190(3.0); 189(4.7); 181(1.9); 180(13.0); 166 (1.3); 165(4.5); 163(1.7); 150(1.0); 143(1.5); 116(1.1); 115(2.6); 114 (1.3); 106(8.3); 105(100); 103(3.5); 95(1.3); 91(1.2); 90(1.3); 89(8.1); 88(2.1); 87(1.5); 81(1.1); 79(1.0); 78(5.4); 77(50); 76(2.8); 75(2.0); 74(1.5); 69(1.2); 63(4.1); 62(1.7); 55(2.0); 51(15.0); 50(4.2); 41(3.0) | 257/70 |
| 4-I-3,5-$Ph_2$-isoxazole | 349(1.1); 347($M^+$,48.0); 223(1.4); 222(3.3); 221(7.1); 220(9.3); 193 (1.5); 192(3.5); 191(1.8); 190(5.0); 189(7.1); 188(1.7); 187(1.8); 181 (1.4); 180(8.6); 166(1.4); 165(4.0); 163(1.8); 146(1.3); 144(1.3); 143 (2.5); 129(1.3); 128(4.5); 117(1.4); 116(1.7); 115(3.8); 114(1.3); 106 (8.8); 105(100); 104(1.3); 103(5.3); 98(1.3); 97(1.3); 95(1.9); 94(1.3); 91(2.1); 90(1.9); 89(9.6); 88(2.5); 87(1.7); 83(1.3); 81(1.5); 79(1.3); 78(5.7); 77(42.0); 76(3.8); 75(2.2); 74(1.9); 73(1.3); 69(1.6); 67(1.4); 65(1.3); 64(1.3); 63(5.0); 62(1.9); 60(1.4); 57(1.6); 55(2.7); 51(13.8); 50(4.5); 41(3.8) | 257/70 |
| 4-$ClCH_2$-3,5-$Me_2$-isoxazole | 145($M^+$,15); 110(100); 68(94); 43(80); 42(65) | 204/68, 175/69 |
| 5-$BrCH_2$-3-Ph-isoxazole | 239(29); 237($M^+$,29); 159(6); 158(31); 145(14); 144(100); 128(7); 127 (6); 105(19); 103(6); 102(6); 89(9); 79(6); 77(40); 76(6); 63(7); 51(18); 50(7) | 12/69 |

Furthermore, the influence of the substituents on the stability and on the decomposition pathway of the molecular ion has been studied for 4-halo-3,5-dimethyl- (**75**)[154/71] and 4-halo-3,5-diphenylisoxazoles (**76**).[257/70,48/71] The intensity of the molecular ion of **75** increases in the order 4-Cl ⩽ 4-Br < 4-H < 4-I. The first two compounds show similar intensity and behavior. Abundance of the




**75**




**76**

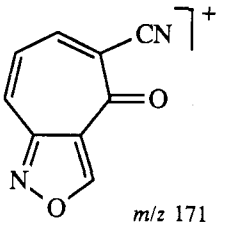
peak $[M-Me]^+$ in **75** is minor than in 3,5-dimethylisoxazole, while the acetyl cation is always intense. For **76** the intensity of $M^+$ is 4-Cl < 4-H ⩽ 4-Me < 4-Br < 4-I.

The most probable structures of the molecular ion and of the charge distribution are discussed.[257/70,48/71,154/71] Structures of isomeric 4- and 5-perfluoroalkylated isoxazoles have also been determined on the basis of their mass spectra.[171/78] Mass spectra of haloisoxazoles are reported in Table 1.40.

The mass spectra of some alkyl isoxazolecarboxylates have been reported without discussion. Data have been collected in Table 1.41. In some cases the metastable ions provided evidence for the fragmentation pathways.[135/72,119/79,112/81] Moreover, the fragmentation pattern of *tert*-butyl-5-phenylisoxazole-3-peroxycarboxylate has been reported and discussed.[135/72]

The mass spectra of the three geometric isomeric dimethyl 3-(4′-cyano-buta-1′,3′-dienyl)isoxazole-4,5-dicarboxylates (**22–24**) have been studied by comparison with those of dimethyl 3-phenyl- and dimethyl 3-formylisoxazole-4,5-dicarboxylate. The fragmentation pattern, identical for the three isomers, is discussed and supported by metastable ions.[142/84]

The base peak (*m/z* 171) has been suggested to arise from ion at *m/z* 203 by loss of MeOH, and ring closure of the $C_3$ butadiene moiety with the carboxylate at $C_4$. The following tropane structure has been proposed for the ion at *m/z* 171:




*m/z* 171

The fragmentation patterns of some isoxazoles with hydroxylated side chain have sometimes been studied by deuteration[194/72] (see Table 1.42). In Scheme 1.1 (p. 61) the most important and characteristic peaks of the mass spectrum of 3,5-dimethyl-4-hydroxymethylisoxazole[204/68,175/69,194/72] are shown. The spectra of

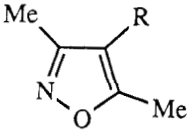
TABLE 1.41. MASS SPECTRA OF ISOXAZOLECARBOXYLIC ACIDS AND ESTERS

| Compound | *m/z* (%) | References |
|---|---|---|
| 4-HOOC-3,5-$Me_2$-isoxazole | 141($M^+$,24.0); 126(6.8); 99(28.4); 97(33.0); 84(55.0); 82(56.0); 81(8.5); 68(8.5); 55(21.0); 54(41.5); 53(7.6); 52(10.2); 51(7.6); 45(8.5); 43(100); 42(50.0); 41(35.0) | 194/72 |
| 4-HOOC-5-Me-3-Ph-isoxazole | 204(11.8); 203($M^+$,100); 188(15.6); 161(8.5); 160(8.5); 159(56.2); 145 (12.3); 144(100); 143(30.4); 117(12.8); 116(17.0); 105(7.5); 104(7.1); 94(5.7); 93(52.2); 89(9.9); 78(9.9); 77(87.0); 76(11.8); 75(8.0); 74(6.6); 69(7.1); 63(13.2); 52(5.4); 51(56.6); 50(17.5); 43(100) | 193/72 |
| 4-HOOC-5-Me-3-(*p*-$NH_2C_6H_4$)-isoxazole | 219($M^+$,15.1); 218(100); 174(6.2); 160(6.0); 159(54.3); 158(8.3); 134 (7.2); 132(9.3); 131(7.6); 120(11.2); 108(8.6); 104(5.9); 92(48.2); 91 (5.3); 66(5.9); 65(57.8); 64(5.8); 52(5.9); 43(36.8) | 193/72 |
| 4-HOOC-3-(*o*-$ClC_6H_4$)-5-Me-isoxazole | 237($M^+$,1.4); 203(14.6); 202(100); 180(6.2); 178(19.2); 177(5.5); 160 (13.2); 150(10.1); 129(5.0); 127(12.8); 123(5.5); 113(7.8); 111(7.8); 75(16.0); 50(8.2); 43(41.3) | 193/72 |
| 4-HOOC-3-(*m*-$NO_2$ $C_6H_4$)-5-Me-isoxazole | 248($M^+$,34.6); 231(7.4); 230(8.7); 204(24.7); 189(18.3); 188(12.3); 143 (8.9), 77(6.2); 76(14.0); 75(9.6); 63(6.7); 50(11.9); 43(100) | 193/72 |
| 5-Me-3-MeOOC-isoxazole | 141($M^+$,9); 110(9); 82(22); 59(100); 43(50); 42(7) | 204/68 175/69 |
| 5-MeOOC-3-Ph-isoxazole | 203($M^+$,88); 116(72); 104(100); 77(83) | 36/80 |
| 4-MeOOC-3,5-$Ph_2$-isoxazole | 279($M^+$,8); 142(100); 115(95); 77(78) | 36/80 |
| 5-MeO-3-MeOOC-isoxazole | 157($M^+$,57); 126(31); 82(24); 68(15); 59(100) | 22/81 |
| 3,5-$(MeOOC)_2$-isoxazole | 185($M^+$,9); 154(25); 82(18); 67(8); 59(100); 43(3) | 63/81 |
| 4,5-$(MeOOC)_2$-3-[NC-CH=C(Me)-C(Me)C=CH]-isoxazole | 290($M^+$,15); 231(60); 199(100); 131(45) | 112/81 |
| 4,5-$(MeOOC)_2$-3-(2-quinolinyl)-isoxazole | 312($M^+$,22); 237(13); 223(38); 156(10); 142(14); 140(14); 129(16); 128(100); 101(18) | 119/79 |
| 3,5-[$HOCH_2(CH_2OCH_2)_3$ $CH_2OCO]_2$-isoxazole | 509($M^+$,1); 378(3); 272(5); 155(80); 140(100) | 134/81 |
| 3,5-[$HOCH_2(CH_2)_{11}$ OCO]-isoxazole | 525($M^+$,1); 324(5); 296(9); 266(14); 55(100) | 134/81 |

TABLE 1.42. MASS SPECTRA OF HYDROXYLATED ISOXAZOLES

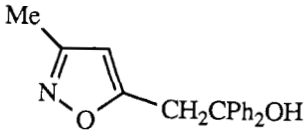
| Compound | eV | *m/z* (%) | References |
|---|---|---|---|
| 4-HOCH$_2$-3,5-Me$_2$-isoxazole | 70 (200°C) | 127(M$^+$,100); 112(12); 110(25); 109(36); 84(64); 82(64); 68(75); 43(88); 42(82) | 204/68 |
| | 50 (200-250°C) | 127(M$^+$,36); 126(10); 112(6); 110(11); 109(16); 84(27); 82(27); 71(11); 70(7.5); 68(10); 67(10); 66(11); 57(9); 56(10); 55(7); 54 (8); 53(6); 52(7); 43(100); 42(34); 41(13) | 194/72 |
| 4-DOCH$_2$-3,5-Me$_2$-isoxazole | 50 | 128(M$^+$,40); 127(16); 113(7); 110(11); 109(16); 85(30); 83(27); 72(13); 68(13); 57(6); 55(7); 54(6); 53(7); 43(100); 42(30); 41(13) | 194/72 |
| 3,5-Me$_2$-4-PhCHOH-isoxazole | 50 | 204(10); 203(M$^+$,70); 202(17); 187(10); 186(34); 170(7); 161(17); 160(20); 147(16); 145(13); 144(30); 131(9); 129(8); 126(47); 125 (13); 124(100); 115(16); 108(22); 105(34); 103(15); 102(13); 91 (17); 84(41); 82(27); 80(8); 79(33); 78((75); 77(53); 76(6); 69(13); 65(8); 56(8); 51(21); 43(63); 42(12); 41(11) | 194/72 |
| 3,5-Me$_2$-4-Ph$_2$COH-isoxazole | 50 | 279(M$^+$,11); 262(11); 261(12); 246(27); 218(15); 217(8); 203(15); 202(100); 201(10); 182(8); 178(9); 177(7); 176(10); 165(9); 160 (19); 155(10); 152(7); 151(6); 145(6); 124(8); 105(63); 91(6); 82 (18); 78(10); 77(52); 76(6); 51(18); 42(37); 41(12) | 194/72 |
| 3-Me-5-[Ph$_2$(HO)C CH$_2$-]-isoxazole | 70 | 279(M$^+$,<1); 261(8); 184(35); 183(100); 106(21); 105(98); 96(95); 82(6); 77(99) | 217/74 |
| 3-[HO-(CH$_2$)$_3$-]-isoxazole | 70 | 126(M$^+$,3); 97(54); 83(95); 68(26); 55(41); 54(41); 41(61); 31(100); 29(30) | 32/80 |

compounds **77**[194/72] and **78**[217/74] have also been discussed.



**77**

**a** R = PhCHOH
**b** R = Ph$_2$COH



**78**

The data for mass spectra of some ketones are reported in Table 1.43. The fragmentation path of 4-benzoyl-3,5-dimethylisoxazole is shown here as an example:

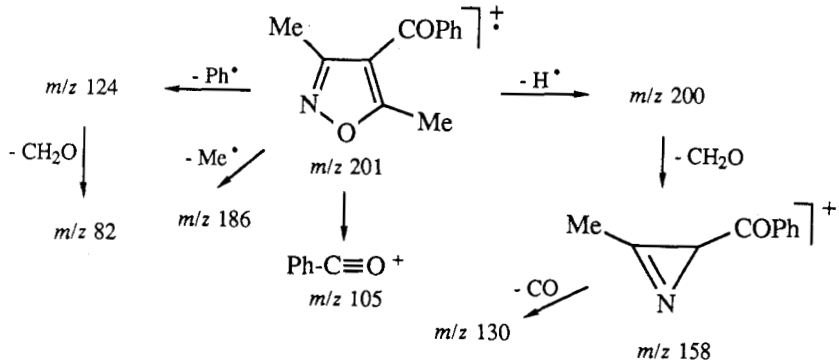
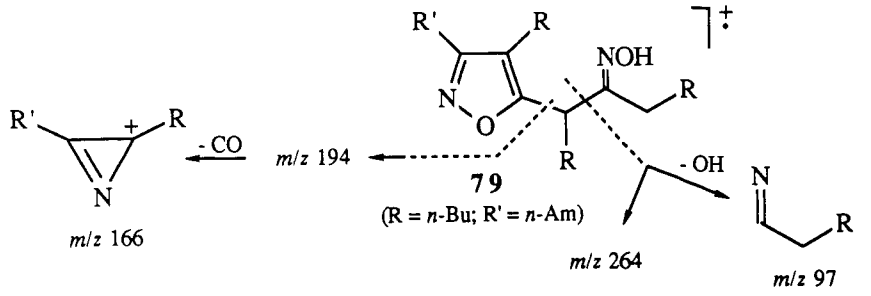


TABLE 1.43. MASS SPECTRA OF ISOXAZOLYL KETONES

| Compound | *m/z* (%) | References |
|---|---|---|
| 3,5-$Me_2$-4-PhCO-isoxazole | 201($M^+$,6); 200(7); 186(5); 158(2); 130(2); 124(2); 105(13); 82(3) | 89/71 |
| 5-Me-4-MeCO-3-Ph-isoxazole | 201($M^+$,100); 186(21); 159(56); 144(92); 117(12); 116(10); 105(6); 77(24); 43(32) | 73/78 |
| 5-Me-3-Ph-4-PhCO-isoxazole | 263($M^+$,90); 248(5); 235(11); 234(13); 221(10); 220(9); 193(8); 144 (15); 105(100); 77(45); 43(17) | 73/78 |
| 4-$MeCOCH_2CH_2$-3,5-$Me_2$-isoxazole | 167($M^+$,16); 126(13); 124(8); 110(33); 97(11); 82(18); 68(44); 43 (100) | 175/69 |
| 4-$(MeCO)_2CH$-$CH_2$-3,5-$Me_2$-isoxazole | 209($M^+$,3); 167(9); 166(73); 124(29); 110(41); 97(4); 83(10); 82(11); 68(45); 43(100) | 175/69 |
| 4-[(MeCO)(EtOCO)$CHCH_2$-]-3,5-$Me_2$-isoxazole | 239($M^+$,7); 221(3); 196(36); 166(15); 150(50); 124(21); 110(72); 97 (10); 82(16); 68(58); 43(100) | 175/69 |
| 4-(2-cy-pentanonyl-$CH_2$-)-3,5-$Me_2$-isoxazole | 193($M^+$,32); 150(6); 110(100); 68(59); 43(41); 42(12) | 204/68 |
| 4-(2-cy-hexanonyl-$CH_2$-)-3,5-$Me_2$-isoxazole | 207($M^+$,23); 150(6); 136(5); 110(100); 98(9); 95(17); 68(46); 43(35); 42(10) | 175/69 |
| 4-(2-tetralonyl-$CH_2$-)-3,5-$Me_2$-isoxazole | 255($M^+$,45); 238(4); 214(12); 212(29); 171(7); 158(9); 146(46); 145 (24); 143(12); 138(12); 118(14); 115(18); 111(12); 110(100); 90(25); 68(64); 43(58); 42(12) | 175/69 |

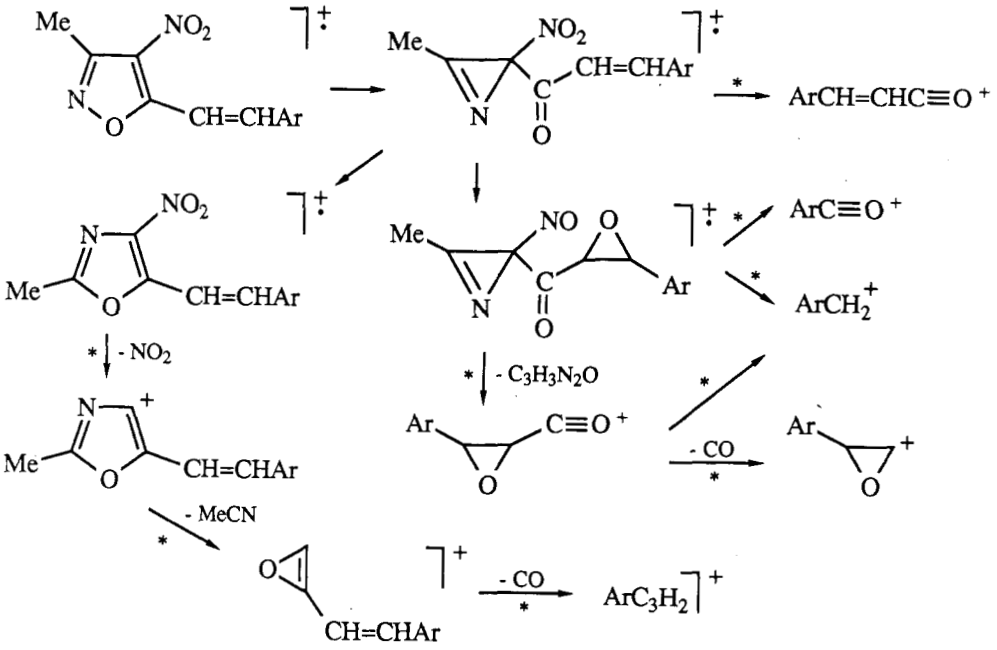
The main peaks of the mass spectra of some 3,5-diacylisoxazoles have been reported.[54/75] The electron impact fragmentation of the oxime, 2,4-dinitrophenylhydrazone, and semicarbazone of 5-benzoyl-3,4-diphenylisoxazole has also been discussed.[146/77] By reaction with $NH_2OH \cdot HCl$ in acetic acid, elasnin yields the isoxazole derivative **79** ($M^+$ 378)[202/80] (the values of the main fragments are reported on the formula):




For 3,5-dimethyl-4-nitroisoxazole the initial fragmentation occurs by loss of the nitro group; therefore, the loss of a methyl is less evident than for other

4-substituted-3,5-dimethylisoxazoles.[12/69] However, in more complex isoxazole derivatives, the influence on the fragmentation pattern in mass spectrometry of a nitro group at position 4 has been discussed.[173B/80,241B/80,74/81,82/81]

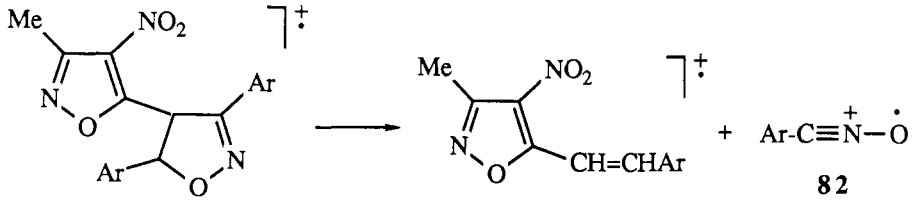
The fragmentation by electron impact of 3-methyl-4-nitro-5-styrylisoxazoles has been reported either through the azirine–oxazole pathway[241B/80] (as in Scheme 1.5) or through an anomalous pathway.[173B/80] However, both fragmentations involve interaction of the nitro group with the styryl double bond, either by OH elimination or by transfer of an oxygen atom forming an epoxy ketone[241B/80] or a phenyl ketone.[173B/80] The chemical ionization mass spectra of these compounds, with $H_2$ and $CH_4$ reagent gases, showed that the rearrangement to azirine still occurs with the former gas, while the energy available seems to be too low to allow this process under the latter conditions.




**Scheme 1.5.**

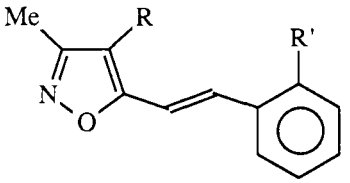
The cinnamoyl ion is the second peak for intensity (64% of the $[MH]^+$, which is the base peak) with $H_2$, since oxidation of the double bond is prevented by protonation of the nitro group. However, $H_2$ chemical ionization spectra also show $[MH-NO_2]$ $[MH-OH]$, $[MH-C_3H_3N_2O]$, [ArCO], and $[ArCH_2]$ ions. $CH_4$ chemical ionization spectra show only [MH] and $[MH-NO_2]$ ions, the first being the base peak.

3,5-Diaryl-4-(3′-methyl-4′-nitro-5-isoxazolyl)-2-isoxazolines[82/81] (**80**), which can be synthesized by cycloaddition of benzonitrile oxides with 3-methyl-4-nitro-5-styrylisoxazoles, by electron impact give rise to a retro-cycloaddition reaction yielding the ions corresponding to the 1,3-dipole and the dipolarophile (**81** and **82**) used in the synthesis.




Thus, along with the usual fragmentation ions of the two rings (see also § 2.1.4), the ions of the styryl derivatives discussed previously (**81**)(see Scheme 1.5)[82/81] can be found in the mass spectra. The mass spectra of 3-methyl-4-nitro-5-(1,3-diaryl-1-keto-4-*n*-butyl)isoxazoles, used for the synthesis of isoxazoloazepines, have been discussed.[74/81] Some mass spectra of nitroisoxazoles are reported in Table 1.44.

Mass spectra of some 3-alkyl-5-aminoisoxazoles have been studied and the fragmentation pathway for 5-amino-3-isopropylisoxazole has been proposed in detail.[75/84] Similarly, the mass spectra of 4-amino-3-methyl-5-styrylisoxazoles (**83a**),[124B/81] 4-benzylidene-3-methyl-5-styrylisoxazoles (**83b**),[178B/80] and the imidoximes (**83c**)[83/81] have been studied by metastable transitions. In all




**83 a** R = $NH_2$
**b** R = N=CHAr
**c** R = NHC(=NOH)Ar

compounds **83** the fragmentation path involves interaction of the substituent at $C_4$, the double bond of the styryl group, and the *ortho* substituent of the aryl group. The azirine ion is the intermediate that better explains rearrangements and cleavages. 4-Aminoisoxazoles (**83a**) are relatively stable under electron impact, as demonstrated by the high intensity of the molecular ions (44–100%). Strong peaks are always the cinnamoyl and the tropilium ions. Scheme of fragmentation patterns are reported and discussed.[178B/80,83/81,124B/81]

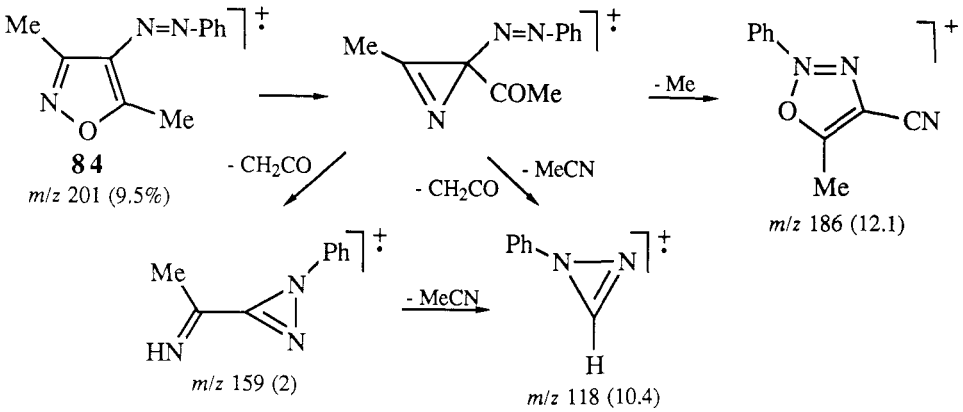
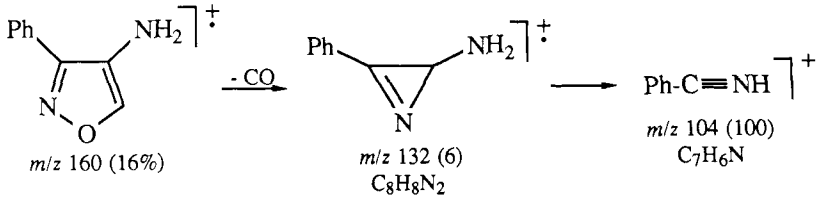


TABLE 1.44. MASS SPECTRA OF NITROISOXAZOLES

| Compound | *m/z* (%) | References |
|---|---|---|
| 3,5-$Me_2$-4-$NO_2$-isoxazole | 142($M^+$,49); 96(9); 83(82); 81(9); 80(9); 71(13); 67(13); 65(6); 63(7); 54(11); 53(8); 52(8); 44(6); 43(100); 42(52) | 12/69 |
| 3-Me-5-(*o*-$MeC_6H_4CH$=CH)-4-$NO_2$-isoxazole | 244($M^+$,97); 227(3); 198(4); 157(13); 145(31); 133(16); 129(28); 119 (36); 117(31); 115(100); 105(36); 92(8); 91(85); 77(25); 76(8); 69(42); 65(31); 63(26); 51(26); 39(37); 30(7) | 173B/80 |
| 5-(*o*-$H_2NC_6H_4CH$=CH)-3-Me-4-$NO_2$-isoxazole | 245($M^+$,13); 228(8); 158(4); 146(2); 134(7); 130(5); 120(5); 118(7); 106(3); 92(3); 91(10); 77(8); 76(3); 69(3); 65(6); 63(8); 51(7); 43(100); 39(7); 30(1) | 173B/80 |
| 5-(*o*-$HOC_6H_4CH$=CH)-3-Me-4-$NO_2$-isoxazole | 246($M^+$,35); 229(49); 200(1); 152(2); 147(7); 145(100); 135(3); 131(4); 121(9); 119(4); 107(10); 93(3); 92(4); 91(33); 77(18); 76(4); 69(2); 65 (20); 63(10); 51(17); 39(3); 30(3) | 173B/80 |
| 3-Me-5-(*p*-$NCC_6H_4CH$=CH)-4-$NO_2$-isoxazole | 255($M^+$,100); 209(5); 172(19); 168(5); 156(17); 144(8); 140(12); 130 (33); 116(21) | 241B/80 |
| 3-Me-5-(*o*-$MeOC_6H_4CH$=CH)-4-$NO_2$-isoxazole | 260($M^+$,100); 243(1); 214(1); 173(6); 161(32); 149(25); 145(22); 135 (81); 133(15); 121(51); 107(24); 92(14); 91(87); 77(80); 76(17); 69 (7); 65(15); 63(34); 51(32); 39(21); 30(6) | 173B/80 |
| 3-Me-5-(*p*-$MeOC_6H_4CH$=CH)-4-$NO_2$-isoxazole | 260($M^+$,100); 214(2); 177(2); 173(2); 161(10); 149(6); 145(3); 135(9); 121(8) | 241B/80 |
| 5-(*o*-$ClC_6H_4CH$=CH)-3-Me-4-$NO_2$-isoxazole | 264($M^+$,35); 247(1); 218(1); 177(5); 165(19); 153(20); 149(17); 139 (72); 137(37); 125(49); 111(15); 101(100); 91(1); 77(23); 76(16); 69 (33); 65(1); 63(19); 51(44); 39(10); 30(4) | 173B/80 |
| 5-(*o*-$HOOCC_6H_4CH$=CH)-3-Me-4-$NO_2$-isoxazole | 274($M^+$,1); 257(1); 149(2); 147(1); 135(1); 91(1); 84(100); 77(14); 76 (3); 69(2); 65(1); 63(1); 51(9); 39(16); 30(20) | 173B/80 |
| 5-(3,4-$CH_2O_2C_6H_3CH$=CH)-3-Me-4-$NO_2$-isoxazole | 274($M^+$,100); 228(1); 191(1); 187(6); 175(15); 163(2); 159(6); 149(10); 135(6) | 241B/80 |
| 3-Me-4-$NO_2$-5-(*o*-$NO_2C_6H_4CH$=CH)-isoxazole | 275($M^+$,3); 229(3); 188(1); 176(1); 160(1); 150(25); 148(2); 92(100); 91(37); 77(53); 76(61); 69(10); 65(46); 63(53); 51(81); 39(42); 30(21) | 173B/80 |
| 3-Me-4-$NO_2$-5-(*p*-$NO_2C_6H_4CH$=CH)-isoxazole | 275($M^+$,100); 229(2); 192(17); 176(7); 164(4); 150(19); 136(3) | 241B/80 |
| 5-(3,5-$Cl_2C_6H_3CH$=CH)-3-Me-4-$NO_2$-isoxazole | 298($M^+$,100); 252(11); 215(10); 211(24); 199(13); 187(4); 183(20); 173(21); 159(11) | 241B/80 |
| 5-(*m*-$BrC_6H_4CH$=CH)-3-Me-4-$NO_2$-isoxazole | 308($M^+$,83); 262(2); 225(7); 221(3); 209(12); 197(6); 193(5); 183 (100); 169(8) | 241B/80 |

For 3,5-dimethyl-4-phenylazoisoxazole (**84**) the losses and rearrangements shown at p. 81 are invoked to rationalize the mass spectrum.[89/71]
Rearrangement to azirine and hydrogen shifts also occur in 3-phenyl-4-amino-isoxazole[12/69] and 3-amino-5-methylisoxazole,[204/68,175/69] as demonstrated by exact mass measurements and deuteration.




*m/z* 160 (16%) *m/z* 132 (6) $C_8H_8N_2$ *m/z* 104 (100) $C_7H_6N$

Tautomerism of 1-(3,4-dimethyl-5-isoxazolyl)-3-aryltriazenes has also been studied by mass spectrometry: the presence of 3,4-dimethyl-5-isoxazolyldiazonium, as an intense peak, indicates that in the vapor phase the azo group is conjugated with the heterocyclic ring;[28B/79] the structure of fragment ions is included in the discussion.

Rearrangements are also assumed in the fragmentation of 5-diacetylamino-3,4-diphenylisoxazole, which shows a loss of acetic anhydride.[152B/74] The mass spectrum of 5-(*o*-aminoanilino)-4-cyanoisoxazole, reported without discussion,[48/80] can be explained only by rearrangements of the molecular ion. The fragmentation scheme of the isomeric 3-phenyl-4-cyanoisoxazole and 3-phenyl-5-cyanoisoxazole has been reported and the intermediate formation of an azirine ion has been assumed.[248/82]

The mass spectra of isoxazoles linked at $C_5$ to a heteroatom (oxygen as alkoxy group, nitrogen as $NH_2$, and sulfur as thioalkyl) have been studied extensively by high-resolution mass measurements, metastable transitions, and comparison with labeled compounds in order to understand the rearrangements due to electron impact.[194/69,163/71,208/77] In some cases different voltages have also been used.[194/69]

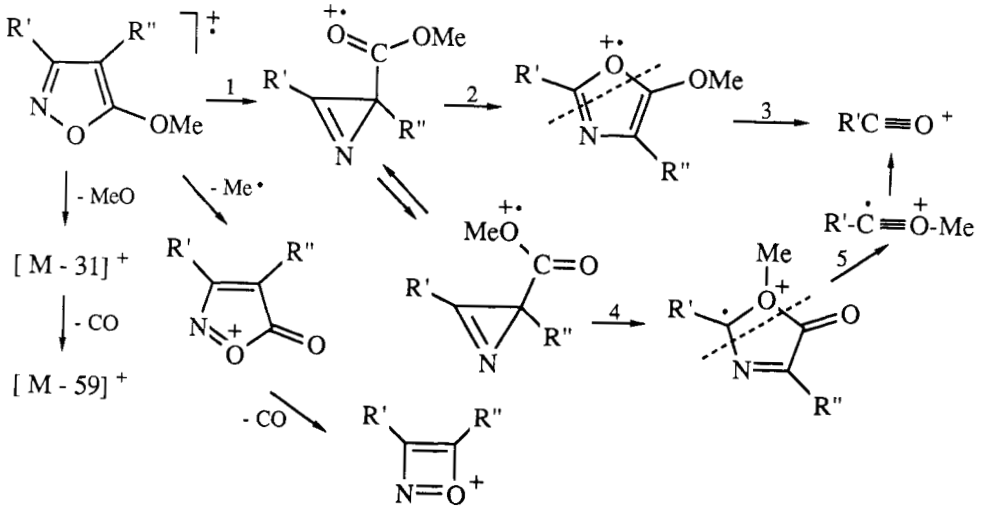
The most characteristic ions of 5-methoxyisoxazoles, which are also recorded at different voltages, can be indicated as [M–Me], [M–Me–CO], [M–MeO], [M–MeO–CO], and [$C_3$-substituent + CO].

Their formation can be explained only by molecular ion rearrangements: cleavage of the weak N–O bond gives rise to azirine ring closure, which then undergoes a ring enlargement to oxazole. All these intermediates are quite unstable under electron collision and are the origin of the reported fragment ions. It has been demonstrated that 5-alkoxyisoxazoles undergo a thermally induced skeletal rearrangement to azirine carboxylates,[203/69] which show, in mass spectrometry, behavior similar to that of 5-alkoxyisoxazoles,[202/70] also in metastable transition. Azirines are therefore considered the first intermediates in these rearrangements. Furthermore, a photochemical transformation isoxazole → azirine → oxazole is known,[95/66] supporting the latter rearrangement, the only one that can explain the [$C_3$-substituent + CO] ions.

TABLE 1.45. MASS SPECTRA OF ALKOXYISOXAZOLES

| Compound | *m/z* (%) | References |
|---|---|---|
| 3-Me-5-MeO-isoxazole | 114(1.5); 113($M^+$,23); 112(0.7); 98(1); 92(1); 91(1); 88(1); 86(7); 85(9); 84(11); 83(4); 82(78); 81(1); 78(3); 70(2); 68(3); 67(2); 59(6); 58(68); 57(2); 56(2); 15 (15); 54(60); 53(5); 52(9); 51(4); 50(1); 49(2); 47(3); 46(4); 45(7); 44(3); 43 (100); 42(20); 41(8) | 208/77 |
| 3,4-$Me_2$-5-MeO-isoxazole | 128(0.6); 127($M^+$,7); 126(0.7); 112(1.5); 99(77); 98(1); 97(1); 96(10); 86(5); 85(1); 84(8); 72(2); 69(3); 68(33); 67(2); 66(2); 59(4); 58(13); 57(3); 56(33); 55(13); 54(3); 53(5); 52(3); 51(2); 50(1); 49(1); 47(2); 45(1); 44(3); 43(100); 42(47); 41(10) | 208/77 |
| 5-MeO-3-Ph-isoxazole | 176(7); 175($M^+$,55); 174(1); 160(0.6); 147(3); 146(5); 145(11); 144(100); 133 (2);132(7); 131(1); 130(5); 129(3); 120(2); 119(4); 118(10); 117(39); 116(35); 115(2); 108(2); 107(12); 106(5); 105(14); 104(7); 103(11); 102(26); 101(2); 91(11); 90(6); 89(21); 88(3); 87(2); 78(8); 77(100); 76(16); 75(8); 74(8); 69 (5); 65(6); 64(3); 63(17); 62(7); 61(3); 59(4); 57(3); 56(2); 55(2); 52(7); 51(48); 50(20); 41(5) | 208/77 |
| | 175($M^+$,1.5); 160(0.7); 147(2); 144(10); 120(5); 117(5); 116(10); 105(100); 91(8); 77(7); 51(9) | 194/69 |
| 4-Me-5-MeO-3-Ph-isoxazole | 190(5); 189($M^+$,34); 188(6); 175(1); 174(10); 161(8); 160(9); 159(3); 158(21); 147(2); 146(14); 134(3); 132(3); 131(12); 130(42); 129(4); 128(7); 120(14); 119(4); 118(3); 117(3); 116(8); 115(13); 106(3); 105(92); 104(20); 103(31); 102(3); 93(2); 91(9); 89(7); 88(2); 87(2); 78(9); 77(100); 76(9); 75(8); 74(6); 65(3); 64(3); 63(13); 62(5); 61(2); 59(4); 56(4); 55(9); 54(2);53(3); 52(9); 51 (46); 50(21); 49(2); 45(3); 43(11); 41(2) | 208/77 |

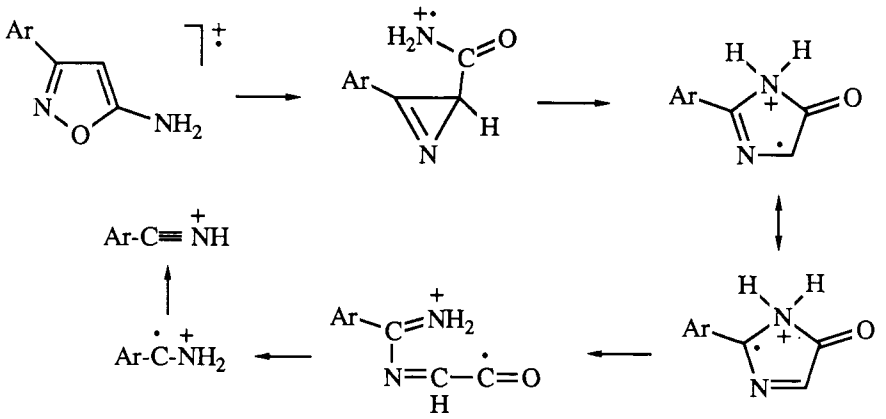
This last ion corresponds to *m/z* 105 ($C_7H_5O$) for 3-phenyl-5-alkoxyisoxazoles and to *m/z* 43 ($C_2H_3O$) for 3-methyl-5-alkoxyisoxazoles. The precursors are ions at *m/z* 120 and 58, respectively, arising from an oxazole methylated at the ring oxygen. The fragmentation shown in Scheme 1.6 has been proposed[194/69.208/77] for 5-methoxyisoxazoles[208/77] (see Table 1.45).




Scheme 1.6.

The formation of two azirine ions differing in the charge position can explain, through two different oxazole ions, the presence of the methylated acyl ions, which easily collapse into the acyl ions. A similar fragmentation pattern has been assumed for 5-amino and 5-alkylmercaptoisoxazoles.[163/71]

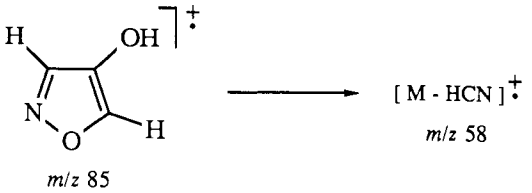
It is interesting to note that 5-amino-3-phenylisoxazole shows a base peak at *m/z* 105, as observed in the same conditions for 5-methoxy-3-phenylisoxazole. However, this ion has a different composition: $C_7H_7N$, not $C_7H_5O$. Also, in this case the molecular ion gives rise to the azirine, which rearranges to an imidazolone ring:



A thiooxazole ion is the intermediate in the fragmentation pathway of 5-alkylmercaptoisoxazole, leading to the characteristic [Ar–C$^{\cdot}$ = S$^{+}$–R] and [Ar–C≡S]$^{+}$ ions.[163/71] The mass spectra of 3-alkoxy-5-substituted isoxazoles[224/69] have been studied and compared with those of ibotenic acid and related compounds[222/69] and with those of 2-substituted-4-isoxazolin-3-ones.[223/69]

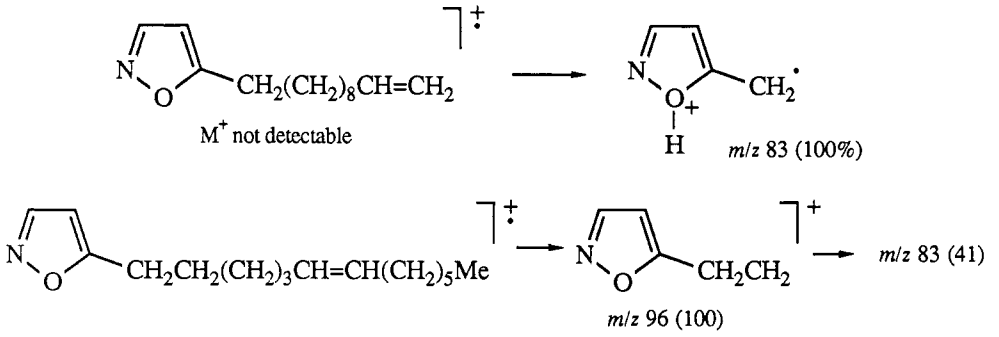
Trimethylsilyl derivatives have been used to identify ibotenic acid (**1**) and muscimol (**2**) in extracts of *Amanita pantherina* by means of gas chromatography/mass spectrometry (GC-MS). Fragmentation of trimethylsilylmuscimol is reported.[207/78] The mass spectrum of *N*-trifluoroacetyldimethylibotenic acid has been studied in connection with structure determination of musca-aurin I (**3**).[12/82]

High-resolution electron impact (EI)-MS data showed that triumferol (**4**)(4-hydroxyisoxazole) loses HCN from the molecular ion, giving a stable ion:[236/81]

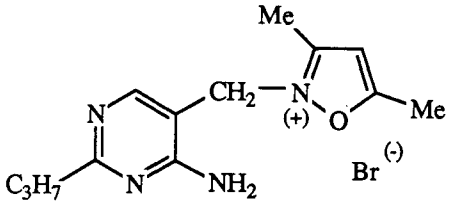


*m/z* 85

The structures of termite defense secretions have been determined by oximation of a β-ketoaldehyde system to 5-alkenylisoxazoles.[276/80,154/81] The cleavage of the side chain occurs by hydrogen shifts:

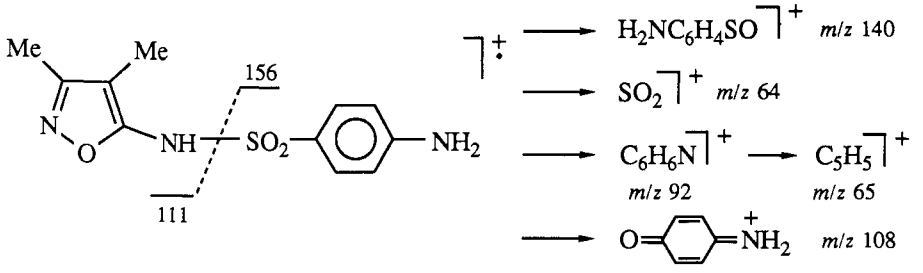



The mass spectra of vitamin $B_1$ and analogues, one of them containing the isoxazole ring **85**, have been studied.[67B/67] The base peak corresponds to the dimethylisoxazole ion. Fragmentation of 5-isoxazolylmethyltriphenylphosphonium bromides by EI has also been described.[66/76]




**85**

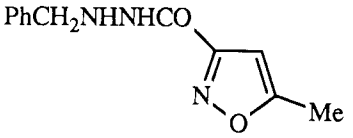
Mass spectrometry has been used as a tool for the determination of pharmaceutical products. Sulfonamides, which undergo characteristic fragmentations, can also be detected easily in drugs by means of mass spectrometry.[130/77,40C/78] For example, sulfisoxazole (**18**)[72/63] is cleaved into two ions (*m/z* 156 and 111) by EI: Sulfamethoxazole (**21**) and sulfisoxazole (**18**) are two of the few sulfonamides that do not exhibit the $[M-SO_2]$ ion.



Recently, the use of collision-induced dissociation mass-analyzed ion kinetic energy spectrometry (CID/MIKES) for the identification of sulfonamide drug residues in swine liver has been described.[8/83] Sulfonamides [A–$SO_2$–$C_6H_4$–$NH_2$–*p*] are identified by the CID/MIKES spectrum of the $(M + H)^+$ ion produced under chemical ionization with isobutane. The most characteristic ions are $(M + H - 66)^+$, that is, $(M + H - H_2SO_2)^+$; at *m/z* 156 $(H_2NC_6H_4SO_2)^+$, *m/z* 140 ($C_6H_6NOS$), *m/z* 108 ($C_6H_6NO$), *m/z* 92 ($C_6H_6N$), and $[AH_2]^+$.

Data for sulfisoxazole (**18**) and 17 sulfonamides have been reported.[8/83] Some data on fragments of 3,5-dimethyl-4-sulfonylderivatives have also been indicated.[129/81] The molecular ion in the mass spectrum of the *N'*-(5-hydroxymethyl-3-isoxazolyl)sulfanilamide, a metabolite of sulfisomezole, could not be detected because of the thermal decomposition. However, the presence of very abundant *m/z* 31 and *m/z* 18 peaks indicated the presence of a $CH_2OH$ group.[32/71]

Mass spectra of 1-(ethoxycarbonylmethyl)-3-(4-*N*-*R*-sulfamoyl)phenylthioureas, including a derivative of sulfisoxazole, have been discussed.[24/84] A detailed study of the fragmentation pathway of isocarboxazide (**86**)(Marplan) by high-resolution measurements and metastable transition shows that in this case also, the molecular ion rearranges to an azirine ring, which gives rise to the main fragment ions.[19B/75]




**86**

The molecular ion corresponding to oxacillin-free acid has been detected from its potassium salt, using the ammonium chloride addition technique[201/82] to enhance ionization. Mass spectra of isoxazolylpenicillins and of their metabolites have been obtained by the FAB (fast atom bombardment) technique. Adduct ions [$M + H^+$, $M + Na^+$, etc.] and some significant fragment ions have been indicated. Mass spectra are reported and discussed.[8/85]

Isoxicam [4-hydroxy-2-methyl-*N*-(5-methyl-3-isoxazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide], a nonsteroidal anti-inflammatory agent, and its principal urinary metabolites have also been studied by means of mass spectrometry: mass spectra are reported.[27G/84] References on GC-MS analysis are given in § 1.2.11.

The flash photolysis of isoxazole has been monitored by means of time-of-flight mass spectrometry. Descriptions of the apparatus and mass spectra at various times are reported. Evidence is given for the formation of an azirine intermediate in the transformation isoxazole–oxazole.[55/84]

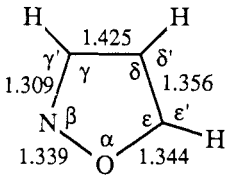
Quasi-equilibrium statistical theory was applied to the negative-ion mass spectra of diphenylisoxazoles; electron capture by the isoxazoles leads to mole-

cular ions having excited vibrations of the ring and of bonds attached to it.[236/77] The dissociation rate constants were also calculated.[217B/75]

### 1.2.5 Other Spectra

#### *1.2.5.1 Microwave Spectra*

Microwave spectroscopy has been used to obtain information on the molecular geometry, electron distribution, barriers to internal rotations, and molecular force field. Often, the experimental data have been compared with the results of theoretical calculations (see § 1.2.8). Data on the rotational spectra indicated a planar structure of isoxazole[35/66,31B/75,117/75] with the parameters reported in the formula[117/75]




α 108.8°
β 105.3°
γ 112.3°
γ' 118.6°
δ 103.6°
δ' 128.5°
ε 110.6°
ε' 133.4°

The most accurate data have been obtained with the microwave–microwave double-resonance modulation of monosubstituted isotopic species: $^{13}C$, $^{15}N$, and $^{18}O$ in their natural abundance.[31B/75,117/75] The molecular structure, corrected for harmonic vibrations ($r^z$ structure), of isoxazole in two nematic solvents has been studied by means of $^1H$-NMR spectra and compared with a microwave "best structure."[144/81]

Microwave spectra of $^{15}N$-isoxazole and oxazole have been assigned, and the molecular Zeeman effect observed and measured to establish the aromatic character of the molecules through the magnetic properties.[99/74] The nuclear quadrupole coupling tensors of $^{14}N$, $^{15}N$, $^{13}C$, and $^{18}O$ in isoxazole have been determined from microwave spectra of 4*D*-isoxazole and monosubstituted isotopic species (see § 1.2.5.4).[31B/75,71/78]

The microwave spectrum of 5-methylisoxazole has been measured in the region 18–36 GHz and transitions of the A and E species, in the ground torsional state, have been assigned.[229/75,106/77] The rotation constants reported are: A, 9230.831 MHz; B, 3559.334 MHz. The threefold barrier to internal rotation of the methyl group was calculated to be 772.2 cal/mol.[229/75] Similar results have been obtained by double resonance measurement and by application of the internal axis method, which is useful for low barriers.[106/77]

#### *1.2.5.2 Photoelectron Spectra*

The photoelectron spectra (PES) of isoxazole have been measured, along

with those of many other heterocycles.[3/70.45/70.179/77.140/79] This type of spectrum affords the energies of the occupied orbitals, and was employed primarily to determine the $\pi$-ionization potentials. The isoxazole spectrum shows two bands in the region 8–12 eV, with a vibrational fine structure comparable to those of the other heteroaromatic compounds.

The first band has been assigned to a $\pi$ band, while the second band is composed by the overlapping of $\pi$ and $n$ (nonbonding nitrogen lone pair) ionizations. The second band shows an intensity about twice that of the first band. These spectra can be used as fingerprints to recognize the class of the heterocycle. The measured vertical ionization potentials are 10.17 and 11.29 eV. These values are higher than those of furan, thiophene, pyrrole, and pyrazole.[3/70]

It has been noticed that the first ionization potentials of five-membered rings are lower by about 1 eV than those of six-membered ring heterocycles.[180/69] The adiabatic ionization potentials for isoxazole have also been reported: 9.99 and 11.13 eV.[3/70] A value of 9.93 eV has been indicated for the energy measured in the photoelectron spectrum of isoxazole for the first adiabatic transition, in a study related to the fragmentation mechanism of isoxazole in mass spectrometry.[194B/81]

An empirical correlation between the basicity and ionization potential of the nitrogen lone pair have been discussed for several heterocycles. The heterocycles have been divided in three groups. Isoxazole belongs to the imidazole, pyrazole, and oxazole group.[85/84] The vapor-phase He(I) photoelectron spectra of isoxazole, 5-methylisoxazole, and 3,5-dimethylisoxazole have been reported. These spectra have been studied by the technique of photoelectron angular distribution measurements combined with a first-order perturbation theoretical approach.[31/82]

The first three bands of isoxazoles have been assigned to the $\pi$, $\pi$, and $n$ bands from the top. By contrast, the similar oxazoles bands have been attributed to the $\pi$, $n$, and $\pi$ bands. The photoelectron spectrum of a $Cr(CO)_5$–isoxazole complex has been compared with that of free isoxazole in order to evaluate the $\sigma$ and $\pi$ bonding between the metal and the nitrogen donor ligand. The following vertical ionization potentials (in eV) with assignments have been reported and discussed along with those of other azoles.[91C/79]

| | Metal *d*-orbitals | | $\pi_3$ | $\pi_2$ | $\sigma_N$ |
|---|---|---|---|---|---|
| Isoxazole | - | - | 10.20 | 11.38 | 11.38 |
| $Cr(CO)_5$-isoxazole | 7.42 | 7.65 | 10.92 | 11.85 | - |

Also, the x-ray PES of isoxazole has been studied[140/79.193B/81.262/82] to measure the core binding energies. The experimental data have been compared with calculations of the core orbital energies. Low-energy, low-intensity shake-up satellites are observed in the various energy regions for isoxazole and other five-membered ring heterocycles.[262/82] The experimental data are supported by CNDO/S-CI calculations. Results are reported in Table 1.46.

TABLE 1.46. EXPERIMENTAL AND CALCULATED (CNDO/S-CI) SHAKE-UP ENERGY ($E_{sh}$ eV), AND INTENSITY ($I_{sh}$ PERCENT OF THE MAIN LINE) OF ISOXAZOLE

| | Transition | Theoretical | | Experimental | |
|---|---|---|---|---|---|
| | | $I_{sh}$ | $E_{sh}$ | $I_{sh}$ | $E_{sh}$ |
| $O_{1s}$ | (2a"----> 4a") | 2.6 | 7.5 | 3.0 | 9.0 |
| $N_{1s}$ | (3a"----> 4a") | 5.2 | 4.9 | 2.0 | 5.7 |
| | (2a"----> 4a") | 10.5 | 6.3 | 6.0 | 7.7 |
| $C_{1s}$ | (3a"----> 4a") | 7.0 | 4.7 | 8.0 | 8.0 |
| | (2a"----> 4a") | 2.3 | 5.3 | | |

### *1.2.5.3. Electron Paramagnetic Resonance Spectra*

Electron paramagnetic resonance spectroscopy (EPR) of some isoxazole complexes has been studied. Hexakis(isoxazole)iron(II) bisperchlorate, which contains a monodentate ligand, exhibits a high spin–low spin transition. The magnetic moment is 5.28 $\mu$B at room temperature and 1.3 $\mu$B at temperatures below 200 K.[207/74]

EPR studies of some copper complexes of isoxazole,[141/79] 3-methyl-5-phenylisoxazole,[126B/80,190/80] 3,5-dimethylisoxazole,[141/79,126B/80,190/80] and 3-amino-5-methylisoxazole (AMI)[139/81,143/81] in different solvents, such as dimethylformamide (DMF), pyridine, and MeCN, have been reported. It has been shown that the species formed in DMF and pyridine are entirely different. The latter are similar to the structure determined from powders or polycrystalline form, probably due to the anisotropic molecular reorientation in solutions.

The complexes of isoxazole and 3,5-dimethylisoxazole show four hyperfine lines in pyridine and only one line in DMF. Values of $g_{11}$ and $A_{11}$ of complexes are reported. The spin-Hamiltonian constants in DMF solutions indicate the existence of $CuO_6$ chromophores for all complexes, except $Cu(3\text{-AMI})_4Cl_2$, which shows a $CuO_4$ chromophore. The same compound shows a $CuN_4$ chromophore in pyridine. These data indicate strong metal–ligand $\sigma$ bonding.

### *1.2.5.4 Electron Spin Resonance Spectra*

The anion radicals of isoxazole, 5-methylisoxazole, and other heterocycles have been generated in the presence of sodium in argon matrices. The examination of the electron spin resonance (ESR) spectra showed that the radical possesses a structure resulting from the cleavage of an oxygen bond, the negative charge being localized on the oxygen atom and the spin density on the nitrogen in the case of isoxazole. These results are supported by calculations of the isotropic coupling constants using the INDO molecular orbital methods.[126/73]

By contrast, the ESR spectra of the radicals obtained by reaction of isoxazole with a HO radical showed that the radical is added to the $C_5$ carbon atoms.

Abstraction of hydrogen was not detected.[190/73] The structure of the radical is discussed. ESR spectra of a number of complexes of isoxazole derivatives have been reported and discussed in order to understand the nature of coordination around the metal ion.[253/80.276B/80.267/83.149/84]

The presence of at least two types of stable free radicals in poly(phenylene-isoxazole) was demonstrated by ESR spectroscopy. The formation of a charge transfer complex with the phenylene group as electron donor, and the isoxazole ring as electron acceptor, has been suggested.[165/71]

### *1.2.5.5 Nuclear Quadrupole Resonance Spectra*

Nuclear quadrupole coupling constants ($\chi = e^2qQ/h$) result from interaction of the nuclear quadrupole, $eQ$, with the electric field gradient, $eq$, at the site of the nucleus. Along with the corresponding asymmetry parameters $\eta$, these data indicate the electronic charge distributions in the vicinity of the nucleus considered. They have been measured and calculated (see § 1.2.8) for $^{14}N$ for many heterocycles, including isoxazole.[35/66.54/69.195/71.155/73.262/79] Some data for isoxazole are reported here:

| $\chi_{xx}$ (MHz) | $\chi_{yy}$ (MHz) | $\chi_{zz}$ (MHz) | $\eta$ (%) | Conditions | References |
|---|---|---|---|---|---|
| <1 | <1 | <1 | - | gas phase (MW) | 35/66 |
| ±0.404 | ±5.024 | +5.428 | 0.8511 | 77 K | 155/73 |
| 0.020 | 5.296 | -5.316 | 0.9811 | 77 K | 262/79 |
| 0.02 | 5.37 | -5.39 | 0.9925 | MW | 31B/75 |

The second experimental values obtained by the NQR spectrum of isoxazole ($\nu_+ = 5.226$ MHz; $\nu_- = 2.916$ MHz; $\nu_d = 2.310$ MHz) are different from those obtained in gaseous-phase microwave measurements; however, they are closer to the theoretical values (§ 1.2.8).[155/73] These results would imply a $\sigma_{N\text{-}O}$ bond highly polarized toward the oxygen atom, owing to the lone pair of the oxygen conjugating with the ring system. This causes a positive net $\pi$ charge on the oxygen. Comparison of these results with those of oximes and nitro derivatives has been reported.[155/73]

Orientation of the inertial principal axis system is also discussed.[54/69.195/71.262/79] Later the principal value and axis of the nuclear quadrupole coupling tensor were determined by means of the microwave spectrum of 4*D*-isoxazole.[71/78] The values with regard to axes in the nuclear plane are almost numerically identical, − 5.42 and + 5.34 MHz. The axis of the most negative coupling constant makes an angle of 26° with the bisector of the ring angle at the nitrogen atom.[71/78]

$^{35}Cl$-NQR spectra of a number of 5-aryl-3-(*p*-chlorophenyl)- and 3-aryl-5-(*p*-chlorophenyl)isoxazoles and their 4-chloro derivatives have been reported and discussed.[106/70.306/80] These data provided evidence for a partial positive charge at $C_5$ and a partial negative charge at $C_3$ of the isoxazole ring. The inductive effect

acts much more at $C_3$ than in other positions. By contrast, the mesomeric effect acts more strongly on $C_5$.[106/70]

### *1.2.5.6 Other Spectra*

Fluorescence spectra of a number of stilbenyl derivatives of isoxazoles, prepared by the anyl synthesis, have been reported and discussed. Maxima for 3-phenyl-5-(substituted-stilbenyl)isoxazoles are in the range 408 to 470 nm, for 5-phenyl-3-(substituted-stilbenyl)isoxazoles between 397 and 443 nm, and for 3-stilbenylbenzoisoxazoles between 400 and 464 nm.[68/79]

Phosphorescence spectra of isocarboxazide and other drugs have been studied in ethanol solution. Isocarboxazide (**86**) shows excitation maximum at 320 nm and phosphorescence maxima at 410 to 435 nm with a lifetime shorter than 0.2 second. The phosphorescence of isocarboxazide is too feeble to be of analytical value.[235/77]

Radioluminescence and photoluminescence of some organic compounds, including triphenylisoxazole, have been studied.[190/70]

Mössbauer effect[207/74,107/77,210B/81] and reflectance spectra,[107/77,182/83,267/83,149/84] together with other spectroscopic techniques, gave useful information to characterize metal complexes of isoxazole and derivatives.

Circular dichroism (CD), has been employed to establish the absolute configuration (as S) of the chiral center of 3-, 4-, and 5-*sec*-butylisoxazoles.[92/68] The CD spectrum of musca-aurin I (**3**) has also been reported.[28D/73]

## 1.2.6 Crystal and Molecular Structure

Substituted isoxazoles are often in a crystalline form suitable for x-ray analysis. However, this technique has been utilized mainly to determine tautomeric forms in the solid state of hydroxyisoxazoles, the preferred conformation of a number of diisoxazoles, complexes, and other variously substituted unknown isoxazoles. Pharmaceutical drugs such as sulfonamides and isoxazolylpenicillins have also been studied with this technique in order to correlate structure and activity. Bond lengths and angles of some substituted isoxazoles described in this section and measured by means of x-ray diffraction are reported in Table 1.47.

The x-ray powder diffraction pattern of the isoxazole hydrate has been recorded.[59B/73,30/74] It shows the known structure II clathrate hydrate of tetrahydrofuran, but containing 34 molecules of water per mole of isoxazole.[59B/73] However, analysis on a sample of composition $C_3H_3NO \cdot 14.7H_2O$ also showed the characteristics of the structure II hydrate lattice, Fd3m, $a = 17.17 \pm 0.09$ Å at about 120 K.[30/74] Several weak lines due to ice Ih were also observed.[30/74] Data are also discussed on the basis of NMR and dielectric studies.[30/74]

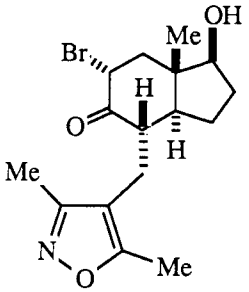
TABLE 1.47. BOND LENGTHS (Å) AND ANGLES (DEGREES) FOR THE SUBSTITUTED ISOXAZOLE RING OF **87-90, 93-96, AND 98-100**

| | N-O | N-$C_3$ | $C_3$-$C_4$ | $C_4$-$C_5$ | $C_5$-O | $C_3$-$R_3$ | $C_5$-$R_5$ | References |
|---|---|---|---|---|---|---|---|---|
| Bond lengths | | | | | | | | |
| **87α** | 1.426 | 1.315 | 1.417 | 1.353 | 1.353 | 1.332 | 1.475 | 145/69 |
| **87β** | 1.417 | 1.313 | 1.408 | 1.372 | 1.372 | 1.341 | 1.439 | 6/69 |
| **88** | 1.43 | 1.33 | 1.39 | 1.34 | 1.37 | 1.70 | 1.45 | 122/79 |
| **89** | 1.407 | 1.332 | 1.384 | 1.384 | 1.332 | 1.465 | 1.465 | 42/79 |
| **90** | 1.406 | 1.334 | 1.429 | 1.361 | 1.351 | 1.450 | 1.415 | 152B/74 |
| **93** | 1.403 | 1.320 | 1.419 | 1.356 | 1.336 | 1.474 | 1.477 | 258/82 |
| **94** | 1.427 | 1.331 | 1.440 | 1.338 | 1.358 | - | - | 2/72 |
| **95** | 1.423 | 1.315 | 1.433 | 1.328 | 1.346 | 1.285 | 1.488 | 1/74 |
| **96** | 1.428 | 1.319 | 1.440 | 1.337 | 1.353 | 1.300 | 1.488 | 3/74 |
| **98** | 1.420 | 1.303 | 1.398 | 1.361 | 1.375 | 1.488 | 1.280 | 12/78 |
| **99** | 1.434 | 1.327 | 1.447 | 1.320 | 1.338 | 1.289 | 1.500 | 4/76 |
| **100** | 1.441 | 1.321 | 1.435 | 1.353 | 1.370 | 1.332 | 1.495 | 1/80 |
| | $ONC_3$ | $NC_3C_4$ | $C_3C_4C_5$ | $C_4C_5O$ | $C_5ON$ | $R_3C_3N$ | $R_3C_3C_4$ | $OC_5R_5$ | $C_4C_5R_5$ |
| Bond angles | | | | | | | | | |
| **87α** | 105.0 | 112.2 | 104.4 | 110.3 | 108.2 | 122.8 | 125.0 | 116.5 | 135.4 |
| **87β** | 105.2 | 112.4 | 105.2 | 108.1 | 109.0 | 121.7 | 125.8 | 116.5 | 135.4 |
| **88** | 103.0 | 113.7 | 105.4 | 109.5 | 108.4 | 117.0 | 129.3 | 117.7 | 132.9 |
| **89** | 107.2 | 110.5 | 102.7 | 112.4 | 107.1 | 117.9 | 131.6 | 117.9 | 131.6 |
| **90** | 106.4 | 111.5 | 102.7 | 112.4 | 107.1 | 120.4 | 128.1 | 116.8 | 130.7 |
| **93** | 107.5 | 108.3 | 106.8 | 108.7 | 108.7 | 120.2 | 131.4 | 121.6 | 129.6 |
| **94** | 106.1 | 109.5 | 106.2 | 109.9 | 108.3 | - | - | - | - |
| **95** | 106.1 | 109.8 | 105.7 | 110.8 | 107.6 | 122.2 | 127.9 | 115.3 | 134.1 |
| **96** | 106.0 | 110.2 | 105.3 | 110.5 | 107.9 | 121.0 | 128.7 | 114.3 | 135.1 |
| **98** | 105.4 | 112.5 | 105.6 | 108.2 | 108.3 | 118.0 | 129.5 | 116.5 | 135.3 |
| **99** | 105.7 | 109.8 | 104.9 | 112.1 | 107.5 | 122.8 | 127.4 | 115.1 | 132.8 |
| **100** | 103.9 | 123.5 | 103.8 | 110.3 | 108.6 | 123.2 | 113.3 | 115.5 | 134.2 |

The crystal and molecular structures of 3-hydroxy-5-phenylisoxazole (**87**)[114/65,6/69,145/69,1B/71] and 3-chloro-5-phenylisoxazole (**88**)[122/79] have been determined. Two crystalline forms of (**87**) were identified ($\alpha$[114/65,145/69] and $\beta$[6/69]), both showing the same isoxazole tautomeric structure. The molecules are planar and the values of bond distances suggested a conjugation effect between isoxazole and benzene rings. The two forms differ for packing: in the $\alpha$ form, due to the near-perpendicularity of the longest molecular dimension of the twofold axis, molecules are packed almost parallel to one other. By contrast, in the $\beta$-form molecules are packed almost perpendicular to each other. The planarity of these molecules, formed by two rings linked by a simple C–C bond, is analogous to that of diphenyl 3,3′-diisoxazoles,[170B/67] and 5,5′-diisoxazole,[222/68] as reported later.

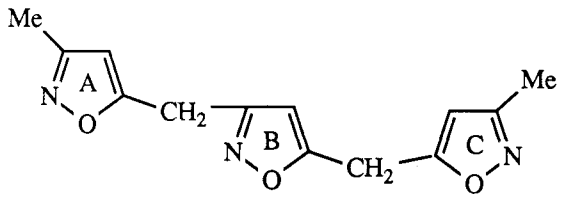
By contrast, in **88** as well as in 3,5-diphenylisoxazole (**89**),[42/79] in the crystal state the rings are not coplanar: isoxazole and benzene rings are twisted by 15° in **88**[122/79] and by 25.6° in **89**.[42/79] CNDO/II calculations for the configuration of **88** were in agreement with the x-ray analysis; **89** consists of a symmetrical structure with a twofold axis running through a $C_4$–$H_4$ bond. The structure of 5-diacetylamino-3,4-diphenylisoxazole (**90**) has also been elucidated by x-ray

analysis.[152B/74] The stereochemistry of the hydrogenation product of 4-(3′,5′-dimethyl-4′-isoxazolylmethyl)-7,7a-dihydro-1β-hydroxy-7a-β-methyl-5(6*H*)indanone, intermediate in the steroid synthesis, could be assigned only on x-ray data[174/74] of its α-bromoderivative (**91**).




**91**

The crystal structure of a methylene-polyisoxazole, 3-(3-methyl-5-isoxazolyl)-methyl-5-(3-methyl-5-isoxazolyl)methylisoxazole (**92**), has been elucidated.[123/81] The molecule is not planar since the two external isoxazole rings are rotated in opposite directions along the $C_5$–$CH_2$ bonds, as can be established by




**92**

the values of the dihedral angles $C_5$–$CH_2$–$C_{5'}$–$C_{4'}$ and $C_{3'}$–$CH_2$–$C_{5''}C_{4''}$: 127.2° and 124.0°, respectively. The geometry of the isoxazole rings, similar to that found in the examples listed in Table 1.47, is reported in Table 1.48.

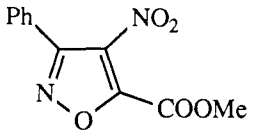
TABLE 1.48. BOND LENGTHS (Å) AND ANGLES (DEGREES) OF **92**

| | N-O | N-$C_3$ | $C_3$-$C_4$ | $C_4$-$C_5$ | $C_5$-O | R-$C_3$ | $C_5$-R' |
|---|---|---|---|---|---|---|---|
| Bond lengths | | | | | | | |
| Ring A | 1.419 | 1.297 | 1.411 | 1.328 | 1.362 | 1.506 | 1.494 |
| Ring B | 1.424 | 1.316 | 1.385 | 1.350 | 1.351 | 1.509 | 1.486 |
| Ring C | 1.423 | 1.310 | 1.422 | 1.324 | 1.354 | 1.488 | 1.498 |

| | $ONC_3$ | $NC_3C_4$ | $C_3C_4C_5$ | $C_4C_5O$ | $C_5ON$ | $NC_3R_3$ | $R_3C_3C_4$ | $OC_5R_5$ | $R_5C_5C_4$ | C-$CH_2$-C |
|---|---|---|---|---|---|---|---|---|---|---|
| Bond angles | | | | | | | | | | |
| A | 104.8 | 112.6 | 104.7 | 109.9 | 108.0 | 119.8 | 127.6 | 116.2 | 133.8 | - |
| B | 105.7 | 111.4 | 105.8 | 109.8 | 107.3 | 118.6 | - | 117.4 | 132.8 | 113.5 |
| C | 106.0 | 110.1 | 106.4 | 109.7 | 107.8 | 119.6 | 130.3 | 116.6 | 133.7 | 113.0 |

Cycloaddition reaction of benzonitrile oxide and methyl (*E*)-3-nitropropenoate led to three products: 3-phenyl-4-isoxazolecarboxylic esters and 3-phenyl-5-isoxazolecarboxylic ester, formed by loss of nitrous acid from the two regioisomeric cycloadducts, and 3-phenyl-5-methoxycarbonyl-4-nitroisoxazole (**93**).

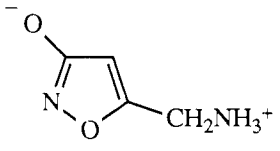
The structure of this last unexpected product has been elucidated by x-ray crystallography.[258/82] The most characteristic feature that emerged for **93**



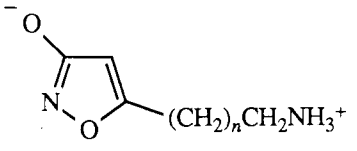
**93**

depends on the steric congestion due to the three vicinal substituents: the plane containing the nitro group is in fact orthogonal to the plane containing the two aromatic rings and the ester group. The loss of mesomeric overlap with the nitrogroup is compensated by the minor steric hindrance. Full data are reported. In Table 1.47 bond lengths and angles relative to the isoxazole ring are reported.

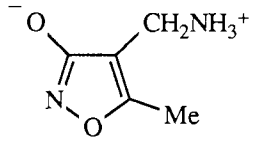
Investigation on isoxazole enol-betaines, which are structural analogues to γ-aminobutyric acid (GABA) or related amino acids with similar pharmacological activity, led to study of the crystal structure of muscimol (**94**),[2/72] homomuscimol (**95**)[1/74] and its homologue (**96**),[3/74] 4-aminomethyl-5-methyl-3-isoxazolol (**97**),[7/77] isomuscimol (**98**),[12/78] and 5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*]azepin-3-ol (**99**).[4/76]



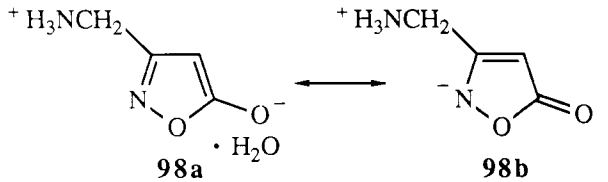
**94**



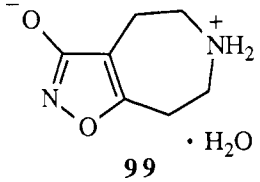
**95** $n = 1$
**96** $n = 2$



**97**



**98a** **98b**

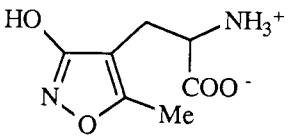


**99**

The compounds **94–97** all show a zwitterionic structure with a planar isoxazole ring and a chain out of the ring plane with a different torsional angle for each structure: 60° for **94**, 83.1° for **95**, 11.3° for **96**, and 80.3° for **97**. For most

of them the angle is similar to that of muscarine (73°) and analogous derivatives. All these compounds adopt a conformation in which the side chain is directed toward the ring oxygen. The crystal structures of **95** and **97** are all stabilized by a system of hydrogen bonds. From the bond-length values of **98** it is evident that there is a significant resonance effect within the isoxazolol ring, the two forms, **98a** and **98b**, making important contributions to the hybrid molecule.[12/78]

X-ray analysis of the crystal monohydrate of (*R,S*)-α-amino-β-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA)(**100**), an analogue of ibotenic acid, has been carried out.[1/80] In this case, too, the isoxazole ring is planar, and AMPA crystallizes in a zwitterionic form with the hydroxy group of the isoxazole nucleus nonionized. From the bond lengths the nonionized 3-hydroxyisoxazole group can be considered to be a marked carboxylic acid function.




**100**

The crystalline structures of the following diisoxazoles have been reported:

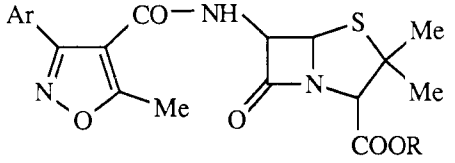
TABLE 1.49. BOND LENGTHS (Å) AND ANGLES (DEGREES) OF DIISOXAZOLES

| | 5,5'- 222/68 | 3,3'- 170B/67 | 3,4'- 4/69 A | 3,4'- 4/69 B |
|---|---|---|---|---|
| Bond lengths | | | | |
| O-N | 1.418 | 1.40 | 1.422 | 1.422 |
| N-$C_3$ | 1.291 | 1.31 | 1.322 | 1.321 |
| $C_3$-$C_4$ | 1.423 | 1.44 | 1.428 | 1.394 |
| $C_4$-$C_5$ | 1.323 | 1.34 | 1.341 | 1.372 |
| $C_5$-O | 1.343 | 1.38 | 1.346 | 1.342 |
| $C_5$-$C_{5'}$ | 1.483 | - | - | - |
| $C_3$-$C_{3'}$ | - | 1.44 | - | - |
| $C_3$-$C_{4'}$ | - | - | 1.477 | - |
| Bond angles | | | | |
| O-N-$C_3$ | 105.4 | 106.6 | 105.10 | 105.57 |
| N-$C_3$-$C_4$ | 112.3 | 111.0 | 111.22 | 112.85 |
| $C_3$-$C_4$-$C_5$ | 101.7 | 104.9 | 104.63 | 103.02 |
| $C_4$-$C_5$-O | 113.4 | 108.8 | 110.65 | 111.66 |
| $C_5$-O-N | 106.1 | 109.1 | 108.39 | 106.89 |
| $C_4$-$C_5$-$C_{5'}$ | 132.8 | - | - | - |
| $C_4$-$C_3$-$C_{3'}$ | - | 129.5 | - | - |
| $C_{5'}$-$C_{4'}$-$C_3$ | - | - | 128.40 | - |
| $C_{3'}$-$C_{4'}$-$C_3$ | - | - | 128.54 | - |
| $C_4$-$C_3$-$C_{4'}$ | - | - | 129.22 | - |
| N-$C_3$-$C_{4'}$ | - | - | 119.56 | - |

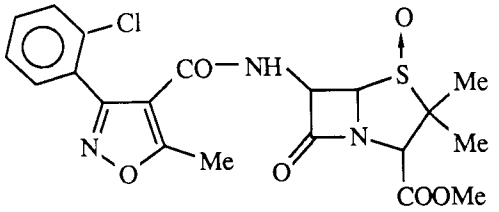
5,5′-,[75/63,222/68,3/72] 3,3′-,[170B/67] 3,5′-[176/78] and 3,4′-diisoxazole.[4/69,1B/71] In Table 1.49 bond lengths and angles of three diisoxazoles are reported. It is noteworthy that the symmetrical diisoxazoles (5,5′ and 3,3′) show planar structure with a *trans* configuration. In both molecules the simple C–C bonds are shortened because of the resonance. 3,4′-Diisoxazole shows different bond lengths and angles for the two rings. In fact, rings are not coplanar, the angle between their planes being 2.8°. A *cis* configuration has been assumed as for 3,5′-diisoxazole.

In the literature, crystal data, methods and parameters for structure analysis, and refinement are reported and discussed. In the case of 5,5′-diisoxazole three kinds of twinning crystal have been studied.[3/72] Shomaker and Trueblood's analysis of the rigid body motion of molecules in term of three tensors has been applied to 3,4′-diisoxazole, 3-hydroxy-5-phenylisoxazole, and 2-methyl-4-phenyl-5-isoxazolinone.[1B/71] Cell dimensions and space group of two substituted 4,4′-diisoxazoles and of 3,5-dimethyl- and 4-hydroxy-3,5-diphenylisoxazole have been reported. The last compound shows polymorphism.[166B/71]

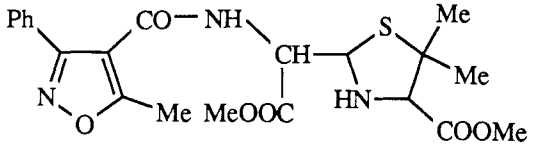
In the course of studies on the structure–activity relationship of biological active products, the crystal structures of a series of isoxazolylpenicillins (**101**–




| | | | |
|---|---|---|---|
| **101** | oxacillin [37/77] | Ar = Ph | R = Na |
| **102** | cloxacillin [51B/76] | Ar = 2-$ClC_6H_4$ | R = Me |
| **103** | dicloxacillin [45/77] | Ar = 2,6-$Cl_2C_6H_3$ | R = Me |
| **104** | flucloxacillin [191/80] | Ar = 2-Cl,6-$FC_6H_3$ | R = Me |




**105** cloxacillinsulfoxide [51C/76]




**106** oxacillin penicilloic methyl diester [37/77]

**106**) have been reported and discussed. In cloxacillin (**102**) and dicloxacillin (**103**) the exocyclic amide group and the isoxazole ring are nearly coplanar and perpendicular to the $\beta$-lactam ring; moreover, the phenyl ring is located above the bicyclic nucleus,[51B/76,45/77] unlike the ring in oxacillin.[37/77] In the case of the corresponding sulfoxide (**105**), the side chain of the thiazolidine ring is more extended than for cloxacillin, probably because of the steric hindrance of the sulfoxide group.[51C/76] The structural features of the first five isoxazolepenicillins have been compared and discussed.[191/80]

The crystal and molecular structure of sulfisoxazole (**18**)[182B/72,91B/79,5/82,19/82] and sulfamethoxazole (**21**)[30/80,222/80,61/82] has been studied along with the structure of the complexes of the latter compound with crown ethers[41/77] and trimethoprim.[85B/80] Sulfamethoxazole shows polymorphism, and the crystal structures of the two polymorphs have been compared with that of the trimethoprim complex.[61/82] In both sulfonamides the two planar aromatic rings linked by the $SO_2NH$ group show torsional angles of 56–60°. Crystal structures are stabilized by several different hydrogen bondings. Full data are reported and discussed.

Polymorphism of sulfisoxazole (**18**) and sulfamethoxazole (**21**) has also been studied by x-ray powder diffraction data[181/72] and thermal data. By means of this technique the former shows two polymorphs and the latter three polymorphic forms. Metal(II) isoxazole complexes[107/77] and complexes of 3-amino-5-methylisoxazole (AMI) and 5-amino-3,4-dimethylisoxazole (ADI) with nickel, copper, calcium, and barium have been analyzed by x-ray powder diagrams[233B/79,210/81] to elucidate the structures.

The structure of *catena*-3,5-dimethylisoxazole-$\mu$-dichlorodicopper(I) has been analyzed by x-ray diffraction methods in order to understand its sensitivity to atmospheric oxygen. Full data are reported. The sensitivity to oxygen has been attributed to the compound relationship with CuCl rather than to the presence of the isoxazole.[107B/77]

A quantitative comparison was carried out on the three-dimensional geometry of a number of organic molecules which present various phase states or polymorphic modifications. 3-Hydroxy-5-phenylisoxazole, 3,3′-diisoxazole, and 5,5′-diisoxazole have also been considered.[312/80] The structure and crystallinity of polyphenyleneisoxazole has been studied also by x-ray powder diffraction analysis.[165/71]

### 1.2.7 Dipole Moments

The electric moment of isoxazole has been obtained by dielectric measurements in both benzene ($\mu$ 2.76 D,[16/47] 2.83 D[9/43]) and dioxane ($\mu$ 3.01 D[14/52]), the latter solvent giving here, as in other cases, dipole moment values higher than in benzene solution. More recently, a value of 2.90 D has been measured for isoxazole by microwave spectroscopy.[35/66,71/78]

Different approaches and methods have been used to study the physical properties of isoxazole, including the electric moment. The first attempt[5C/40]

TABLE 1.50. ELECTRIC DIPOLE MOMENTS OF SUBSTITUTED ISOXAZOLES

| Compound | $\mu_{expt}$ (D) | Solvent | $\mu_{calc}$ (D) | References |
|---|---|---|---|---|
| 3-Me-isoxazole | 2.86 | benzene | - | 5C/40 |
| | 2.86 | benzene | 2.80 | 14/52, 6/50 |
| | 2.89 | dioxane | - | 14/52, 6/50 |
| | - | - | 2.88 | 196/68 |
| 4-Me-isoxazole | 3.12 | benzene | 3.20 | 15/52 |
| | 3.12 | benzene | 2.975 | 103/63, 196/68 |
| 5-Me-isoxazole | 3.13 | benzene | - | 5C/40 |
| | 3.04 | benzene | 3.17 | 14/52, 6/50 |
| | 3.13 | dioxane | - | 14/52, 6/50 |
| | - | - | 3.00 | 196/68 |
| 4-Br-isoxazole | 1.88 | benzene | 1.8 | 78/62 |
| | 1.99 | dioxane | - | 78/62 |
| 3-Ph-isoxazole | 2.98 | benzene | - | 5C/40 |
| | 2.80 | benzene | 2.98 | 18B/55 |
| | - | - | 2.9 | 39/62 |
| | - | - | 2.99 | 196/68 |
| | - | - | 2.92 | 75B/65 |
| 4-Ph-isoxazole | 2.96 | benzene | - | 18B/55 |
| | - | - | 2.70 | 196/68 |
| | - | - | 2.6 | 39/62 |
| | - | - | 2.85 | 75B/65 |
| 5-Ph-isoxazole | 3.34 | benzene | - | 5C/40 |
| | 3.16 | benzene | 3.28 | 18B/55 |
| | - | - | 3.12 | 196/68 |
| | - | - | 3.3 | 39/62 |
| | - | - | 2.99 | 75B/65 |
| 3-*p*-$NO_2C_6H_4$-isoxazole | 4.53 | benzene | 4.87 | 191/72 |
| 5-*p*-$NO_2C_6H_4$-isoxazole | 3.72 | benzene | 3.35 | 191/72 |
| 3,4-$Me_2$-isoxazole | 3.15 | benzene | 3.13 | 14/52, 6/50 |
| | 3.18 | dioxane | - | 14/52, 6/50 |
| | - | - | 3.05 | 196/68 |
| 4,5-$Me_2$-isoxazole | 3.23 | benzene | 3.50 | 14/52, 6/50 |
| | 3.34 | dioxane | - | 14/52, 6/50 |
| | - | - | 3.16 | 196/68 |
| 3,5-$Me_2$-isoxazole | 3.18 | benzene | - | 5C/40 |
| | 3.08 | benzene | - | 14/52, 6/50 |
| | 3.10 | dioxane | - | 14/52, 6/50 |
| | - | - | 3.04 | 196/68 |
| 3-Me-4-Ph-isoxazole | - | - | 2.77 | 196/68 |
| 3-Me-5-Ph-isoxazole | 3.21 | benzene | 3.08 | 5C/40 |
| 4-Me-3-Ph-isoxazole | - | - | 3.17 | 196/68 |
| 5-Me-3-Ph-isoxazole | 3.18 | benzene | 3.08 | 5C/40 |
| 3,5-$Ph_2$-isoxazole | 3.33 | benzene | 3.08 | 5C/40 |
| | 2.99 | benzene | 3.00 | 18B/55 |
| 5-Cl-3-Ph-isoxazole | 2.97 | benzene | 2.32 | 191/72 |
| 4-$NO_2$-3-Ph-isoxazole | 1.10 | benzene | 1.55 | 191/72 |
| 3-$NH_2$-5-Ph-isoxazole | 3.20 | benzene | 3.23 | 191/72 |

TABLE 1.50. *(Continued)*

| Compound | $\mu_{expt}$ (D) | Solvent | $\mu_{calc}$ (D) | References |
|---|---|---|---|---|
| 5-$NH_2$-3-Ph-isoxazole | 3.57 | benzene | 3.90 | 191/72 |
| | 3.60 | benzene | - | 18/65 |
| 5-$Me_2N$-3-Ph-isoxazole | 3.66 | benzene | - | 18/65 |
| 5-$NH_2$-4-Ph-isoxazole | 3.43 | benzene | - | 18/65 |
| 5-MeO-3-Ph-isoxazole | 3.80 | benzene | 2.02/3.89 | 196/68 |
| | 3.896 | dioxane | - | 196/68 |
| 5-MeO-4-Ph-isoxazole | 2.065 | benzene | 1.79/3.49 | 196/68 |
| 3-HOOC-5-Me-isoxazole | 3.06 | dioxane | 3.83 | 6C/52 |
| 5-HOOC-3-Me-isoxazole | 3.32 | dioxane | 2.99 | 6C/52 |
| 3-HOOC-5-Ph-isoxazole | 2.85 | dioxane | 3.99 | 6C/52 |
| 5-HOOC-3-Ph-isoxazole | 3.25 | dioxane | 2.98 | 6C/52 |
| 3,4,5-$Me_3$-isoxazole | 3.42 | benzene | - | 5C/40 |
| | 3.39 | benzene | - | 14/52, 6/50 |
| | 3.40 | dioxane | - | 14/52, 6/50 |
| | - | - | 3.21 | 196/68 |
| 3,5-$Me_2$-4-$NO_2$-isoxazole | 1.39 | benzene | 1.36 | 191/72 |
| 4-Cl-3,5-$Me_2$-isoxazole | 1.89 | benzene | 1.57 | 191/72 |
| 4-Br-3,5-$Me_2$-isoxazole | 1.99 | benzene | 1.59 | 191/72 |
| 4-I-3,5-$Me_2$-isoxazole | 2.28 | benzene | 1.73 | 191/72 |
| 4-Cl-3,5-$Ph_2$-isoxazole | 1.87 | benzene | 1.33 | 191/72 |
| 4-Br-3,5-$Ph_2$-isoxazole | 1.99 | benzene | 1.40 | 191/72 |
| 4-I-3,5-$Ph_2$-isoxazole | 2.49 | benzene | 1.54 | 191/72 |
| 4-Me-5-$NH_2$-3-Ph-isoxazole | 3.73 | benzene | - | 18/65 |
| 4-Me-5-$Me_2N$-3-Ph-isoxazole | 3.53 | benzene | - | 18/65 |
| 3-Me-5-$NH_2$-4-Ph-isoxazole | 3.41 | benzene | - | 18/65 |
| 3-Me-5-$Me_2N$-4-Ph-isoxazole | 3.53 | benzene | - | 18/65 |
| 3,4-$Me_2$-5-MeO-isoxazole | 2.468 | benzene | 2.11/3.93 | 196/68 |
| | 2.521 | dioxane | - | 196/68 |
| 4-Me-5-MeO-3-Ph-isoxazole | 2.83 | dioxane | 2.19/4.07 | 78/62, 196/68 |
| 3-Me-5-MeO-4-Ph-isoxazole | 2.32 | dioxane | 1.79/3.59 | 78/62, 196/68 |
| 4,5-$Me_2$-3-MeO-isoxazole | 2.16 | dioxane | - | 78/62 |
| 3-HO-4,5-$Me_2$-isoxazole | 2.02 | dioxane | - | 78/62 |
| 3,5-$(HO)_2$-3-Ph-isoxazole | 4.8 | dioxane | - | 233/72 |
| 4-HOOC-3,5-$Me_2$-isoxazole | 3.28 | dioxane | 3.18 | 6B/52 |
| 4-EtOOC-3,5-$Me_2$-isoxazole | 3.10 | dioxane | 3.12 | 6B/52 |

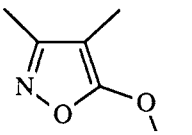
TABLE 1.50. *(Continued)*

| Compound | $\mu_{expt}$ (D) | Solvent | $\mu_{calc}$ (D) | References |
|---|---|---|---|---|
| 4-HOOC-5-Me-3-Ph-isoxazole | 3.23 | dioxane | 3.22 | 6B/52 |
| 4-EtOOC-5-Me-3-Ph-isoxazole | 3.08 | dioxane | 3.15 | 6B/52 |
| 4-HOOC-3-Me-5-Ph-isoxazole | 3.32 | dioxane | 3.36 | 6B/52 |
| 4-EtOOC-3-Me-5-Ph-isoxazole | 3.18 | dioxane | 3.30 | 6B/52 |
| 4-HOOC-3,5-$Ph_2$-isoxazole | 3.39 | dioxane | 3.23 | 6B/52 |
| 4-EtOOC-3,5-$Ph_2$-isoxazole | 3.19 | dioxane | 3.16 | 6B/52 |

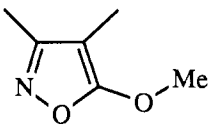
using a vectorial method gave a value of 2.8 D for the dipole moment forming an angle of 105° with the nitrogen–oxygen bond and of 2.85 D for an angle of 120°.[6/50] These data are in good agreement with the values 2.7 D and 127° calculated from electronic distribution data.[15/51] The dipole moment of isoxazole has been calculated by a different approach and methods, as reported in § 1.2.8. The value of the dipole moment of 5,5′-diisoxazole (1.76 D in benzene at 25°C) provided other evidence, in addition to IR and Raman data, that the molecule exists in solution in a single distorted configuration.[228/70]

The experimental dipole moments of many variously substituted isoxazoles have been measured and are mostly reported in Table 1.50. Some of the observed values are compared with the theoretical ones.[6B/52,6C/52,78/62,196/68, 147/72,191/72] Also, the electric dipole moments of a number of isoxazolecarboxylic acids and esters have been measured and theoretically calculated.[6B/52,6C/52,8/52] These data have been discussed to establish the most stable conformation of the molecules and nicely reviewed.[78/62]

Tautomerism of 5-isoxazolinones, 3-hydroxyisoxazoles, and 5-amino-isoxazoles has also been studied on the basis of dipole moments, by comparison of the values measured and calculated of the free isoxazolinones or isoxazoles and their methyl derivatives, in which tautomeric changes are inhibited.[78/62,18/65,196/68] The two values calculated for each of the 5-methoxyisoxazoles reported in Table 1.50 are referred to the two possible conformations for the methoxy group (**A** and **B**), respectively.




**A**



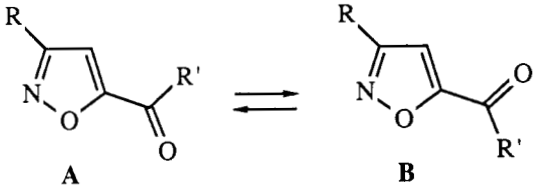

**B**

The $\mu$ values for these compounds have also been calculated by vector addition. The results obtained by this method differ at most by 0.3 D from those

calculated by theoretical methods. Configuration **A** seems to be preferred, especially when the 4-position is substituted.[196/68]

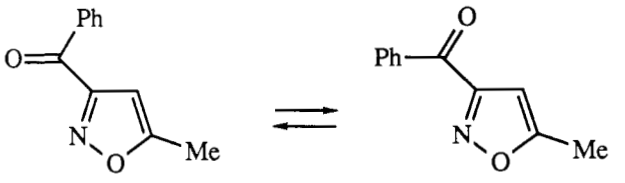
Conjugation of the phenyl and isoxazole rings in 3-, 4-, and 5-phenylisoxazoles has been evaluated by charge distributions and electric dipole moments.[39/62] It has been concluded that interaction of the phenyl with the isoxazole ring is small, close to that with an open $\pi$ system. The reactive positions in the phenyl ring have been discussed.[39/62]

Effects of the substituents in the isoxazole ring on the electric dipole moments can be correlated to the Hammett constants, for example, for 4-substituted-3,5-dimethylisoxazole.[191/72] The conformations in solution of some isoxazole carbonyl derivatives have been established by measurements of the dipole moments of the molecules and calculation of those of the *cis*-N,O and *trans*-N,O forms[193/79] (**A** and **B**).



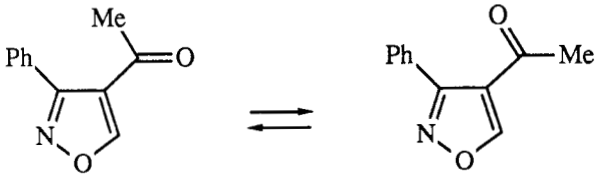
**A** **B**

| | | | | | | |
|---|---|---|---|---|---|---|
| **107 A** | R = Me, | R' = Ph | $\mu_{exp}$ 2.26 D | $\mu_A$ 5.66 D | $\mu_B$ 1.02 D | 87% B |
| **107 B** | R = Ph, | R' = Me | $\mu_{exp}$ 2.21 D | $\mu_A$ 5.38 D | $\mu_B$ 1.81D | 94% B |



**A** **B**

| | | | | |
|---|---|---|---|---|
| **108** | $\mu_{exp}$ 1.92 D | $\mu_A$ 6.03 D | $\mu_B$ 1.97 D | 100% B |



**A** **B**

| | | | | |
|---|---|---|---|---|
| **109** | $\mu_{exp}$ 2.54 D | $\mu_A$ 2.71 D | $\mu_B$ 2.14 D | 32% B |

The tautomeric structure of 3,5-dihydroxy-4-phenylisoxazole, named disic acid, has also been assigned to the reaction product of diethyl phenylmalonate

with hydroxylamine on the basis of the high value of the dipole moment ($\mu$ = 4.8 D).[233/72] Moreover, the structure of *N*-arylidene-4-phenylisoxazol-5-onium-3-enolate was assigned to the reaction product of disic acid with aromatic aldehydes because its higher dipole moment ($\mu$ = 6.5 D for Ar = cinnamylidene).[233/72]

In azole complexes with iodine, increases in dipole moments depend on the charge transfer and on the stability constant of the complexes. The complex of 3,5-dimethylisoxazole has also been studied.[157/75,285/76] An experimental and theoretical study of the dipole moments of 1-(5-isoxazolyl)-3-aryltriazenes has been reported.[192/80] It has been established that *N*-methylation causes an increment of about 0.8 D of the dipole moment.

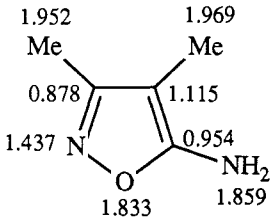
## 1.2.8 Theoretical Calculations

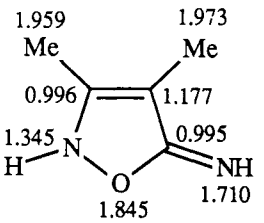
### *1.2.8.1 Reactivity, Aromaticity, and Electron Density*

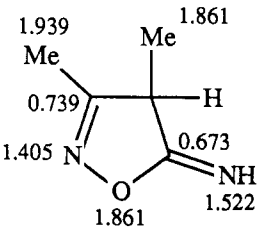
In the last two decades a number of papers dealing with molecular orbital calculations on isoxazole and its derivatives have been published. In the earlier papers the $\pi$-electron density distribution on the isoxazole[15/51,75B/65] and phenylisoxazoles[39/62,75B/65] was calculated by molecular orbital and refined semiempirical molecular orbital methods. The purpose was to investigate the chemical reactivity of the heterocyclic ring. The results were consistent for the case of electrophilic substitution on the 4-position rather than on the other ring positions,[15/51] as well as for a low aromaticity value of the isoxazole ring and weak interaction of the phenyl substituent on the isoxazole ring in phenylisoxazoles.[39/62,75B/65] Moreover, the isoxazole ring behaved on the phenyl ring as an *ortho-para* substituent.[39/62,75B/65]

More recently it has been stated that the positional selectivity observed in the electrophilic attack on heterocyclic molecules may be explained, according to frontier orbital theory, by the magnitude of the highest occupied molecular orbital (HOMO) electron density of each atomic center. The HOMO coefficients calculated by *ab initio* SCF wave functions of double-zeta quality and by PRDDO (partial retention of diatomic differential overlap) methods[140/79] predicted the reactivity order for electrophilic substitution for isoxazole ($C_4 > C_5 > C_3$), and for other heterocyclic compounds, in agreement with the experimental data.[140/79]

The charge density of 5-amino-3,4-dimethylisoxazole and its tautomeric

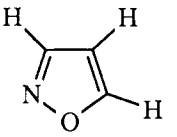


forms has been calculated by the HMO method to explain the formation of 4-arylazo-3,4-dimethylisoxazolin-5-ones by reaction with aryldiazonium salts. The charge density values are shown on the formulas at p. 103.[71/79]

The charge density of 5-amino-3,4-dimethylisoxazole and its tautomeric forms has been calculated by the HMO method to explain the formation of 4-arylazo-3,4-dimethylisoxazolin-5-ones by reaction with aryldiazonium salts. The charge density values are shown on the formulas at p. 103.[71/79]



| | | |
|---|---|---|
| $C_3$-H | -1.8 kcal/mol | points in the plane |
| $C_4$-H | -2.8 kcal/mol | points in the plane |
| $C_5$-H | +2.0 kcal/mol | points in the plane |
| $O_1$ | -37.0 kcal/mol | points 2 Å above the ring plane |
| $N_2$ | -66.8 kcal/mol | points 2 Å above the ring plane |

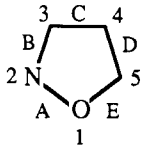
In this case, as for the other heterocycles, the N heteroatoms are clearly more reactive toward electrophilic reagents than are the O atoms. The attack is not limited to the ring plane, because the negative region spread throughout such a plane gives rise to a larger space for the electrostatically favored approach of the positively charged reagent. Furthermore, position 4 is most favored for electrophilic attack.[236/72]

Anion radicals of isoxazole and other heterocycles, generated in argon matrices, were found to possess an open structure. To explain the ring opening, the overlap populations between the neighboring first-row atoms of the heterocyclic anions in the cyclic form have been calculated by an Extended Hückel Theory (EHT)-MO method. Coefficients of the LCAO descriptions of the semifilled $\pi$-type molecular orbitals of cyclic anions have also been reported.[126/73]

The $\pi$-electron densities, bond orders, frontier electron densities, and localization energy have also been calculated by the Hückel molecular orbital (HMO) method,[28/66.196/68] the MO-LCAO method,[90/66] the Pariser–Parr–Pople SCF method,[223/72] and the same combined with configuration interaction[35/70] and all electron calculation[29/67] methods. Results relative to the $\pi$-electron densities and bond orders of isoxazole are reported in Table 1.51. These data led to prediction of the chemical reactivity of isoxazole, but some contradictory values of the charge distribution were obtained. However, the very low value of the $\pi$-bond order of the N–O bond, by comparison with those of the other ring bonds, and the largest localized dipole due to the N–O bond, indicated that this bond can

*Linear combination of atomic orbitals—Gaussian type orbitals.

TABLE 1.51. CALCULATED π-ELECTRON DENSITIES AND π-BOND ORDERS OF ISOXAZOLE



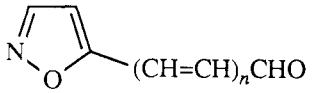

| $O_1$ | $N_2$ | $C_3$ | $C_4$ | $C_5$ | A | B | C | D | E | Method | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.85 | 1.28 | 0.87 | 0.99 | 1.02 | 0.285 | 0.795 | 0.546 | 0.817 | 0.342 | HMO | 28/66 |
| 1.719 | 1.189 | 1.019 | 1.104 | 0.968 | 0.412 | 0.772 | 0.580 | 0.776 | 0.458 | MO-LCAO | 90/66 |
| 1.686 | 1.357 | 0.907 | 1.063 | 0.986 | 0.371 | 0.512 | 0.741 | 0.603 | 0.751 | PPP-SCF-CI | 35/70 |
| 1.657 | 1.323 | 0.937 | 1.086 | 0.997 | 0.404 | 0.735 | 0.617 | 0.738 | 0.526 | PPP-SCF-CI | 35/70 |
| 1.91 | 1.13 | 0.96 | 1.05 | 0.95 | - | - | - | - | - | impr.LCAO | 141/71 |
| 1.784 | 1.256 | 0.903 | 1.096 | 0.962 | - | - | - | - | - | CNDO-CI | 147/72 |
| -0.13110.0873 | | 0.1187 | -0.1104 | 0.1924 | 0.296 | 0.858 | 0.452 | 0.833 | 0.448 | CNDO/2 | 28/74 |
| | | | | | 1.361 | 1.957 | 1.501 | 1.955 | 1.498 | MO-SINDO1 | 199/83 |

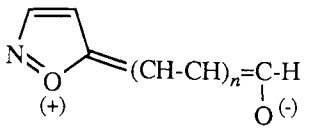
be the preferred point of attack for hydrolytic reagents. These data are in agreement with the experimental reactivity.

The index of aromaticity has been considered to be the value of the lowest bond order, since this indicates the weakest bond that is related to the magnitude of the ring current. The bond orders of 40 ring systems have been calculated with the semiempirical MO method SINDO1. Isoxazole, with a value of 1.361, is in the range of moderately aromatic compounds (1.548–1.332), being less aromatic than oxazole (1.392).[199/83] The calculated bond orders are reported in Table 1.51.

On the basis of the experimentally measured bond lengths of a variety of compounds, including 3-hydroxy-5-phenylisoxazole, as well as diisoxazoles, anthranil, and isoxazolinone derivatives, the empirical resonance integral parameters for the various types of N–O bonds have been calculated.[20/70]

The charge distribution and energies of molecular orbitals have been calculated by the LCAO-MO method for isoxazole and related 5-isoxazolepolyenealdehydes in order to explain their experimental UV absorptions.[145/67] By the introduction at position 5 of an aldehyde group, the net charge at position 4 becomes positive, that on the nitrogen has a less negative value than in isoxazole, and the charge on the ring oxygen decreases but is still similar to the value calculated for isoxazole. It is interesting to note that in the higher members of 5-isoxazolepolyenealdehyde, the charge on nitrogen again tends rapidly to assume the value found for isoxazole, showing that the contribution of the following dipolar form decreases with increasing polyene chain length. The data calculated are in agreement with the UV absorptions in the series of isoxazole and furan derivatives.



### *1.2.8.2 Molecular Geometry*

Molecular geometries (bond lengths and bond angles) of isoxazole have been estimated by several methods.[210/68,36/69,141/71,147/72,28/74,278/74,90C/75,12/76,179/76,140/80,16/81,132/81] The results are summarized in Table 1.52. In the same table are reported for comparison the experimental data obtained from rotation spectra of eight isotopic forms of isoxazole, in their natural abundance, by double-resonance-modulated microwave spectroscopy.[117/75] The molecular geometries obtained by x-ray analysis of some isoxazole derivatives are reported in § 1.2.6.

TABLE 1.52. CALCULATED BOND LENGTHS (Å) AND ANGLES (DEGREES) OF THE ISOXAZOLE MOLECULE

| N-O | N-$C_3$ | $C_3$-$C_4$ | $C_4$-$C_5$ | $C_5$-O | $C_3$-H | $C_4$-H | $C_5$-H | Method | References |
|---|---|---|---|---|---|---|---|---|---|
| Bond lengths | | | | | | | | | |
| 1.38 | 1.30 | 1.43 | 1.36 | 1.36 | - | - | - | VESCF | 210/68 |
| 1.36 | 1.34 | 1.33 | 1.41 | 1.31 | - | - | - | LCAO-SCF-MO | 36/69 |
| 1.38 | 1.30 | 1.44 | 1.35 | 1.36 | - | - | - | improved LCAO | 141/71 |
| 1.39 | 1.33 | 1.42 | 1.37 | 1.39 | - | - | - | CNDO-CI | 147/72 |
| 1.40 | 1.29 | 1.50 | 1.32 | - | - | - | - | CNDO | 278/74 |
| 1.277 | 1.328 | 1.418 | 1.355 | - | 1.112 | 1.108 | 1.112 | CNDO/2 | 179/76 |
| 1.391 | 1.316 | 1.438 | 1.335 | 1.380 | - | - | - | ab initio | 12/76 |
| 1.301 | 1.351 | 1.449 | 1.387 | 1.373 | 1.082 | 1.077 | 1.083 | MNDO SCF-MO | 132/81 |
| 1.383 | 1.316 | 1.436 | 1.349 | 1.372 | 1.082 | 1.076 | 1.083 | STO-3G | 16/81 |
| 1.399 | 1.309 | 1.425 | 1.356 | 1.344 | 1.077 | 1.074 | 1.075 | microwave | 117/75 |

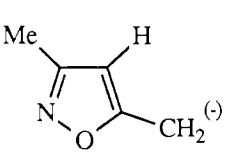
| $C_5ON$ | $ONC_3$ | $NC_3C_4$ | $C_3C_4C_5$ | $C_4C_5O$ | $C_3C_4H$ | $C_4C_5H$ | $NC_3H$ | $C_5C_4H$ | $C_4C_3H$ | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Bond angles | | | | | | | | | | |
| 106.2 | 111.1 | 107.2 | 106.0 | 109.5 | - | - | - | - | - | 210/68 |
| 110 | 105 | 112°46' | 103°44' | 108°30' | - | - | - | - | - | 36/69 |
| 108 | 106 | 112 | 102 | 111 | - | - | - | - | - | 141/71 |
| 107 | 110 | 108 | 107 | 108 | - | - | - | - | - | 147/72 |
| - | 108.4 | 110.8 | 101.9 | - | - | - | - | - | - | 278/74 |
| - | 109.0 | 110.2 | 101.2 | - | 128.8 | 134.6 | - | - | - | 179/76 |
| - | - | - | 104.3 | 109.8 | - | - | - | - | - | 12/76 |
| 110.5 | 109.2 | 108.4 | 103.4 | 108.5 | 127.6 | 133.8 | 122.6 | - | - | 132/81 |
| 109.3 | 105.8 | 111.5 | 104.2 | 109.2 | 127.2 | 133.6 | 120.7 | 128.6 | 127.8 | 16/81 |
| 108.8 | 105.3 | 112.3 | 103.0 | 110.6 | 128.5 | 133.4 | 118.6 | 128.5 | 129.1 | 117/75 |

TABLE 1.53. GEOMETRIES OF N-PROTONATED ISOXAZOLE

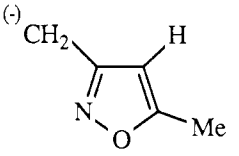
| Bond lengths (Å) | | Bond angles (degrees) | |
|---|---|---|---|
| N-O | 1.320 | $C_5$-O-N | 107.8 |
| N-$C_3$ | 1.377 | O-N-$C_3$ | 112.0 |
| $C_3$-$C_4$ | 1.429 | N-$C_3$-$C_4$ | 105.8 |
| $C_4$-$C_5$ | 1.407 | $C_3$-$C_4$-$C_5$ | 105.1 |
| $C_5$-O | 1.366 | $C_4$-$C_5$-O | 109.4 |
| N-H | 1.022 | $C_3$-N-H | 131.0 |
| $C_3$-H | 1.090 | N-$C_3$-H | 122.5 |
| $C_4$-H | 1.083 | $C_3$-$C_4$-H | 127.5 |
| $C_5$-H | 1.091 | $C_4$-$C_5$-H | 133.5 |

The geometry of the transition state in the 1,3-dipolar cycloaddition of fulminic acid and acetylene has been calculated,[90C/75] along with the size of isoxazole,[278/74,12/76,140/80] for discussing the reaction mechanism. The optimized geometries of the *N*-protonated isoxazole have also been reported[132/81] (Table 1.53).

The stability of carbanions **111** and **112** has been evaluated through the total energies, calculated as $-1252.483$ and $-1252.149$ eV, respectively, by means of the MINDO/2 method. Full geometries of the molecules used for calculations have been reported.[23/76] The excited states of isoxazole, oxazole, and 2*H*-azirine-2-carbaldehyde have been calculated within the single excited configuration interaction (SECI) procedure for study of the photoisomerization mechanism for isoxazole.[16/81]




**111**




**112**

### *1.2.8.3 Basicity and Dipole Moments*

The technique of the partitioning of energy in the MNDO method has been used to determine the factors involved in the great difference in basicity of imidazole ($pK_a = 6.95$) and oxazole ($pK_a = 0.8$) relative to pyrazole ($pK_a = 2.47$) and isoxazole ($pK_a = -2.03$), respectively.[132/81] The different degrees of destabilization of the five-membered ring $\pi$ bonding, upon protonation, in these azoles have been ascribed to the amount of $\pi$-electron charge density localized on the heteroatoms after protonation. The lack of participation of the $\pi$-electron charge density of the oxygen in isoxazole to the delocalization of the positive charge at the vicinal nitrogen atom is due mainly to the mutual electrostatic field effect between both heteroatoms. To this fact has been related the low basicity of the isoxazole ring. The calculated heat of formation for isoxazole (19.2 kcal/mol) with the MNDO SCF-MO method is similar to the experiment value (18.8 kcal/mol).[132/81]

The value of the dipole moment of simple isoxazole has been obtained by different approaches or calculation methods and are summarized in Table 1.54. The calculated value of the dipole moment, which could be easily compared with the experimental one, has often been used as a test to establish the goodness of the theoretical approach employed.

It is noteworthy that the EHT method[156B/67] gave too-high values for the dipole moments for many other heterocycles. It has been noted that calculations by the CNDO-CI (Del Bene–Jaffe) method[147/72] overestimate (about 30%) the electric moment values, but were in agreement with the experimental data for

TABLE 1.54. CALCULATED DIPOLE MOMENT OF ISOXAZOLE

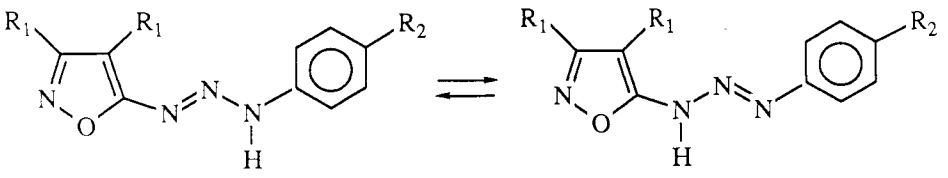
| Method | $\mu_{calc}$ (D) | References | $\mu_{obs}$ (D) | References |
|---|---|---|---|---|
| Hückel molecular orbital | 2.85 | 28/66 | 2.81 | 7/48 |
| Hückel molecular orbital | 2.81 | 196/68 | 2.76, 2.84 | 103/63 |
| Hückel molecular orbital | 2.50 | 191/72 | 2.82 | 191/72 |
| EHT (extended Hückel theory) | 7.63 | 156B/67 | 2.76 | 103/63 |
| Semiempirical MO-LCAO | 2.78 | 75B/65 | 2.76 | 103/63 |
| PPP-MO (Pariser-Parr-Pople) | 3.11 | 29/67 | 2.90 | 35/66 |
| VESCF-BJ | 2.45 | 210/68 | - | - |
| Improved LCAO | 2.95 | 141/71 | 3.07 | 141/71 |
| Addictive calculations | 2.90 | 43/75, 220/75 | 2.90 | 35/66 |
| LCGO calculations | 3.64 | 179/77 | - | - |
| CNDO-CI (Del Bene-Jaffe) | 3.45 | 147/72 | 3.01, 2.90 | 103/63, 35/66 |
| CNDO/2 (Pople-Segal) | 3.07 | 31/67 | 2.90 | 35/66 |
| CNDO/2-SCF | 3.17 | 82B/67 | 3.01 | 103/63 |
| CNDO/2 | 3.150 | 28/74 | 2.90 | 35/66 |
| CNDO/2 | 2.84 | 179/76 | 2.76, 2.84, 2.90 | 103/63, 9/43, 35/66 |
| INDO | 3.050 | 28/74 | 2.90 | 35/66 |
| MNDO-SCF-MO | 2.73 | 132/81 | 2.8 | 220/71 |

electronic absorption spectra and ground-state properties (i.e., chemical reactivity, $^{1}$H-, $^{13}$C-NMR spectra, etc.). Better results seem to be obtained by CNDO/2 (Pople–Segal),[31/67] CNDO-SCF,[82B/67] and improved LCAO calculations.[141/71] The values of dipole moments calculated by *ab initio* SCF wave functions of double-zeta quality were 20–30% higher than the experimental values.[140/79]

In general, the calculated dipole moments are overestimated by an extended *sp* basis set without polarization functions and underestimated when a minimal basis set is employed.[140/79] By the Hückel method the values of the dipole moments of isoxazole and many variously substituted isoxazoles have been calculated.[196/68,191/72] The results are reported in § 1.2.7 (Table 1.50, p. 99) in comparison with measured values. A CNDO/2 molecular orbital study of the electronic and conformational forms of ibotenic acid also reported the calculated dipole moments of the three possible molecular states (nonionic, zwitterion, and monoanion).[180/76]

The ratio of conformers in the solution of four isoxazole ketones has been evaluated by comparison of the experimental and calculated dipole moments.[193/79] In the most preferred form the carbonyl group is cisoid to the next

double bond of the ring. The dipole moments of some 1-(5′-isoxazolyl)-3-phenyltriazenes (**113**) have been calculated by the CNDO/2 method for the two tautomeric forms.[192/80]



**A** **113** **B**

| | | μ(D) | |
|---|---|---|---|
| $R_1$ | $R_2$ | **A** | **B** |
| H | H | 3.46 | 3.63 |
| Me | H | 3.65 | 3.60 |
| H | Me | 3.45 | 3.61 |
| H | $NO_2$ | 8.02 | 7.64 |

However, small differences in the values for the two forms are not sufficient for us to determine by dipole moments which predominates.

### *1.2.8.4 Ionization Potentials*

The first ionization potential of isoxazole has been calculated with LCAO-SCF-MO (8.78 eV)[36/69] and CNDO-CI[147/72] [9.78 ($\pi$), 11.25 ($\pi$), 12.27 ($n$) eV] methods. Experimental measurements of the ionization potential by photoelectron spectrometry[3/70,45/70] gave for isoxazole 10.17 and 11.29 eV for the vertical and 9.99 and 11.13 eV for the adiabatic values.[3/70] The fine structure of UV photoelectron spectra of isoxazole and some oxadiazoles has been studied and assignments have been made by *ab initio* calculations.[179/77]

The ionization potential ($IP_1$) at 10.26 eV shows nine members, which appear to be two progressions with intervals at 1480 and 550 $cm^{-1}$. The band at 11.42 eV ($IP_{vert}$) consists of a double progression (970, 1230 $cm^{-1}$) probably attributable to $\pi$ overlaying the broad nitrogen-lone-pair level, for which no fine structure was observed. Assignments through calculated energy levels have been reported[179/77] and discussed[179/77,140/79] in comparison with those of other five-membered ring heterocycles. The population analysis data for isoxazole show considerable similarity to those of furan and the corresponding azoles.[179/77]

A comparison of the vertical ionization energy measured by means of the He(I) photoelectron angular distribution spectra of isoxazole, 5-methylisoxazole, and 3,5-dimethylisoxazole and those obtained by CNDO/S calculation has been reported. From these data the first three bands from the top of the

isoxazoles have been assigned to $\pi$, $\pi$, and $n$ bands.[31/82] These results compare well with those of oxazole and furan derivatives.

### *1.2.8.5 Molecular Core Binding Energy*

The molecular core binding energy have been measured by x-ray photoelectron spectroscopy and compared with nonempirical calculations for the assignments:[33B/71]

| | $C_3$ | $C_4$ | $C_5$ | $N_{1s}$ | $O_{1s}$ or $N_{1s}$ | |
|---|---|---|---|---|---|---|
| (eV): | 286.9 | 285.9 | 287.4 | 402.1 | 536.6 | Isoxazole |
| (eV): | 286.3 | 285.5 | 287.1 | 402.4 | 401.1 | Pyrazole |

The molecular and orbital energies for isoxazole and some other five-membered-ring heterocycles have been calculated by two different methods[140/79] (SCF wave functions of double-zeta quality and PRDDO) and compared with previously calculated values.[180/69,179/77] The total SCF energies obtained by PRDDO calculations lie 0.3–0.5 a.u. higher than those from double-zeta calculations.[140/79] The core orbital energies calculated with both methods,[140/79] compared with the experimental core binding energies,[33B/71] showed too-large absolute values but a similar relative shift for binding energies for $C_{1s}$, $N_{1s}$, and $O_{1s}$ levels.

Experimental and calculated (CNDO/S-CI) energy and intensity values of shake-up $\pi \rightarrow \pi^*$ transitions in the region of x-ray/PES of some five-membered heterocycles containing two heteroatoms have been reported.[262/82] A comparison between the calculated ESCA (electron spectroscopy for chemical analysis) chemical shifts by the self-consistent charge (SCC)-MO method and the corresponding experimental data for carbon and nitrogen atoms has been reported for isoxazole and other heterocycles, and the influence of the intramolecular reorganization and solid polarization energies on inner-core energy levels discussed briefly.[193B/81]

### *1.2.8.6 Spectroscopic Data and Conformational Analysis*

The energy calculated by different methods for the first $\pi \rightarrow \pi^*$ transition of isoxazole[75B/65,35/70,141/71,147/72] are almost in agreement with the experimental datum: 5.88 eV.[9B/55] The various parameters taken into account are discussed in the papers.

In the case of the CNDO-CI method of Del Bene and Jaffe,[147/72] four tran-

sitions have been calculated:

$$\Delta E: \quad 4.61 \text{ eV } (n \rightarrow \pi^*)$$
$$5.63 \text{ eV } (\pi \rightarrow \pi^*)$$
$$6.09 \text{ eV } (\pi \rightarrow \pi^*)$$
$$6.99 \text{ eV } (n \rightarrow \pi^*)$$

Some of them should occur in the far UV but have not yet been detected.[147/72]

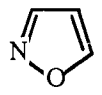
In the case of phenylisoxazoles, calculations showed that the bands of the 3- and 4-phenylisoxazole are very close to each other, whereas that of 5-phenylisoxazole is shifted toward the red end of the spectrum.[39/62] These data are in agreement with the maxima reported for the phenylisoxazoles.[18B/55]

Similar results have been obtained by a refined semiempirical MO-LCAO method[75B/65] for the UV spectra of isoxazole, phenylisoxazoles, and benzoisoxazoles:

| | $\lambda_{max}$ (nm) | eV |
|---|---|---|
| Isoxazole | 211 | 5.88 |
| 3-Phenylisoxazole | 240 | 5.17 |
| 4-Phenylisoxazole | 236 | 5.25 |
| 5-Phenylisoxazole | 260 | 4.77 |

MINDO/3 calculations of molecular vibration frequencies are reported for 34 molecules, including isoxazole, for which the experimental data were avail-

TABLE 1.55



Point group $C_s$

| | | | MINDO/3 | Exptl.[134/74] |
|---|---|---|---|---|
| *a'* | CH | stretch | 3582 | 3160 |
| | CH | stretch | 3489 | 3128 |
| | CH | stretch | 3486 | 3086 |
| | i.p. | ring I | 1659 | 1560 |
| | i.p. | ring II | 1525 | 1432 |
| | i.p. | ring III | 1437 | 1373 |
| | i.p. | ring IV | 1317 | 1260 |
| | CH | bend | 1173 | 1217 |
| | CH | bend | 1072 | 1128 |
| | i.p. | ring V | 1024 | 1089 |
| | i.p. | ring VI | 984 | 1021 |
| | i.p. | ring VII | 729 | 917 |
| | i.p. | ring VIII | 714 | 840 |
| *a''* | CH | bend | 816 | 898 |
| | CH | bend | 781 | 792 |
| | CH | bend | 689 | 763 |
| | o.p. | ring I | 526 | 630 |
| | o.p. | ring II | 495 | 588 |

able (Table 1.55). The agreement was satisfactory, becoming good if allowance is made for systematic deviations for specific types of vibration.[114/77]

The absolute IR band intensities of isoxazole have been measured and calculated by the semiempirical CNDO/2 method. Discussion of the theoretical and observed values has been reported.[179/76] The extended Hückel theory, an LCAO-MO method, calculates $\sigma$- and $\pi$-electron distributions simultaneously. By this method, a good correlation is observed between the total ($\sigma + \pi$) calculated electron densities and the experimental proton and $^{13}C$ chemical shifts.[156B/67]

By the all-electron calculations on five-membered ring heterocycles, including isoxazole, a linear correlation between the $\sigma$ or total electron distribution and the proton and $^{13}C$ chemical shifts has been evidenced.[180/69] The charge density for isoxazole calculated by the modified CNDO-CI method proposed by Del Bene and Jaffe ($C_5 < C_3 < C_4$) is in good agreement with the chemical shift values of the three protons ($H_4 > H_3 > H_5$).[147/72] Furthermore, the calculated[147/72] $J^{13}_{C-H}$ showed the same decreasing order as that of the experimental data.

| | $J^{13}_{C-H}$ (Hz) | | |
|---|---|---|---|
| | CNDO-CI | Exptl. | By increments method [75C/64] |
| $C_3$-H | 170.9 | 188.0 | 185.5 |
| $C_4$-H | 162.1 | 184.3 | 182.0 |
| $C_5$-H | 176.1 | 203.3 | 201.5 |

The proton spin-spin coupling constants of isoxazole and its alkyl derivatives have been determined and discussed in terms of the coupling mechanism.[28/74] Furthermore, it has been noted that the chemical shifts of the ring protons and methyl protons are not simply related to the electron density, calculated by molecular orbital theory at the CNDO/2 level of approximation.[28/74]

$^{14}$Nitrogen nuclear quadrupole coupling constants in isoxazole have been calculated using the Pariser–Parr–Pople (PPP) technique,[29/67] the method of

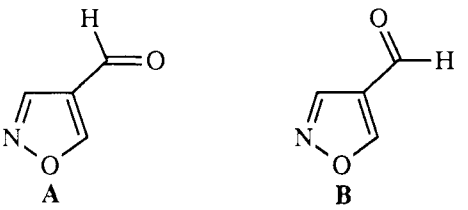
TABLE 1.56. $^{14}N$ QUADRUPOLE COUPLING CONSTANTS (IN MHz)

| | Calculated | | | | Experimental | | | |
|---|---|---|---|---|---|---|---|---|
| | PPP 29/67 | CNDO/2 31/67 | SCF-LCAO-MO 54/69, 195/71 | *ab initio* DZ 140/79, 262/79 | Microwave 35/66, 31B/75 | | $^{14}$NNQR 155/73, 262/79 | |
| $\chi_{aa}$ | -0.94 | +0.97 | +5.12 | 4.93 | <1 | 5.37 | +5.024 | 5.296 |
| $\chi_{bb}$ | +0.72 | -1.08 | +0.89 | +0.082 | <1 | 0.02 | +0.404 | 0.020 |
| $\chi_{cc}$ | +0.22 | +0.11 | -6.01 | -5.00 | <1 | -5.39 | -5.428 | -5.316 |
| $\eta$ (%) | - | - | 0.704 | 0.9674 | - | 0.9925 | 0.8511 | 0.9811 |

Pople and Segal involving complete neglect of differential overlap (CNDO/2), including all the valence electron[31/67] and *ab initio* SCF-LCAO-MO wave functions using Gaussian basis sets,[54/69.195/71] and the double-zeta *ab initio* wave functions.[140/79.262/79] The results of the first two methods agree rather well, better the second, with the first microwave data reported[35/66] (see Table 1.56). The low values of the quadrupole coupling constants for isoxazole have been attributed to the influence on the nitrogen of the neighboring oxygen.[31/67] By contrast, the theoretical values of the other methods are reasonably close to the experimental data obtained either by successive microwave measurements or by the $^{14}N$ nuclear quadrupole resonance (NQR) spectrum.[155/73.262/79] It is worth recalling that the microwave data are gas-phase values, whereas NQR is referred to the solid state.

It has been found that the largest compound of $|\chi|$ lies approximately in the direction of the classically localized nitrogen lone pair.[195/71] The isoxazole molecule shows the largest asymmetry parameter (0.991).[140/79] Calculated values of the total energy of isoxazole and other heterocycles have been reported.[179/77.262/79]

A study involving the quantum-chemical calculation of the stability of the conformers and of the sizes of the energy barrier in acetyl and formyl derivatives of azoles made by the EHT method and Dewar $\sigma$-$\pi$ method has also reported the data for 4-formylisoxazole (**114**).[291/77] From the calculations, the O,O-*cis* (**A**) conformer is shown to be more favored (by $\Delta = -0.2$ kcal/mol) than the O,O-*trans* (**B**) conformer, while the latter is more stable in the case of 3-formyl-




**114**

furan. Theoretical calculations of the electronic structure and conformational modes of muscimol (**94**),[59/70.186E/79.228/82] ibotenic acid (**1**), and related neurotransmitter drugs[150C/75.180/76.181/76.180/77.228/82] have been reported both in the solid state and in solution. The preferred calculated conformations have been related to the biological activity and to the binding to the receptor.

A study of the suitability of various theoretical molecular orbital methods [EHT, *ab initio*, perturbative configuration interaction using localized orbitals (PCILO), and CNDO/2] for studying zwitterionic molecules has also been reported,[180/77] CNDO/2 being considered to give the best results. Later, the *ab initio* calculation procedure was used for muscimol and aza analogues.[228/82]

The potential energy barriers for rotation around the $C_5$ side-chain bond in

muscimol (**2**) and analogues have been calculated (using the MINDO-3 method) for the preferred conformations in connection with their pharmacological activity.[186E/79] To find the relation between the conformation of the side chain of isoxazolepenicillins (such as oxacillin, **101**) and the enzymatic mechanism connected with their biological activity, their molecular structure has been analyzed by spectroscopic and theoretical methods.[191/80] The conformational map for oxacillin (**101**) obtained by the PCILO method reports the preferred and forbidden regions for the side chain in this compound.

The various conformations of 5,5′-diisoxazole, along with those of 2,2′-dipyridyl and diphenyl, have been studied by nonbonded interactions and by PPP[229/70] and CNDO/2 calculations.[227B/70] The latter method gave the best results. Calculations show that the *trans* configuration is more stable than the *cis* by 1 kcal/mol for 5,5′-diisoxazole.[227B/70] Good agreement has been found between these results and conformational studies carried out by means of NMR spectra recorded in nematic phases.[130/72]

The chromophores of a series of probes of membrane potential have been subjected to molecular orbital calculation to characterize the charge distribution and excitation-induced shift of electron density in the chromophore.[39/78] Some of these dyes contain isoxazole and isoxazolinone rings. Quantum-chemical study of the structure of complexes of azoles, including isoxazole, has been reported.[251B/79]

### 1.2.9 Basicity

Isoxazole is a very weak base[6/50,133/69,115/71] ($pK_a = -2.03$ measured spectroscopically at 260 nm),[133/69] weaker than that of other heterocyclic compounds (i.e., *N*-methylimidazole, $pK_a = 7.33$; pyridine, 5.23; thiazole, 2.54; *N*-methylpyrazole, 2.04; oxazole, 0.8). This feeble basic strength indicates the dominating inductive effect of the powerfully electronegative ring oxygen. This effect appears strongest when the heteroatoms are vicinal (e.g., isoxazole and oxazole).[133/69] The $pK_a$ values of isoxazole and its methyl derivatives were taken into account in the study of the hydrogen exchange rates catalyzed by acids.[115/71,150/74]

The acid-base properties of isoxazole and methylisoxazoles were studied either in protic solvents or in basic solvents or DMSO-$d_6$ by IR procedures. In the former case the differences in the $\nu_{OH}$ values of the solvent in the presence of isoxazoles have been considered. In the latter, stretching vibrations of the CH bonds have been measured[75/78] and discussed. Ionization constants of several variously substituted phenylisoxazoles have been measured in acetic acid by spectrophotometric methods.[202/76,214/78] The electronegativity and position of the substituents influence the basicity of the isoxazole derivatives, the influence decreasing in the sequence $C_3 > C_4$.[202/66]

$pK_a$ values of 4-substituted-3,5-diphenylisoxazoles and 4-substituted-3,5-dimethylisoxazoles correlate well with $\sigma_M$ constants in the Hammett

TABLE 1.57. $pK_a$ VALUES OF ISOXAZOLE DERIVATIVES

| Compound | $pK_a$ | References |
|---|---|---|
| Isoxazole | -2.03 | 133/69 |
| 3-Me-isoxazole | -1.67 | 150/74 |
| 5-Me-isoxazole | -2.01 | 150/74 |
| 3-Ph-isoxazole | -3.19 | 202/76 |
| 5-Ph-isoxazole | -2.96 | 202/76 |
| 3-(4-$NO_2C_6H_4$)-isoxazole | -4.48 | 214/78 |
| 5-(4-$NO_2C_6H_4$)-isoxazole | -4.39 | 214/78 |
| 5-Mesityl-isoxazole | -2.81 | 214/78 |
| 3,5-$Me_2$-isoxazole | -1.26 | 298/78 |
| 3-Me-5-Ph-isoxazole | -2.08 | 202/76 |
| 5-Me-3-Ph-isoxazole | -2.38 | 202/76 |
| 3,5-$Ph_2$-isoxazole | -3.05 | 202/76 |
| 3-(4-Cl-$C_6H_4$)-5-Ph-isoxazole | -3.26 | 214/78 |
| 3-(3-$NO_2C_6H_4$)-5-Ph-isoxazole | -4.05 | 214/78 |
| 3-(4-$NO_2C_6H_4$)-5-Ph-isoxazole | -3.87 | 214/78 |
| 3-Mesityl-5-Ph-isoxazole | -2.89 | 214/78 |
| 5-(4-Cl-$C_6H_4$)-3-Ph-isoxazole | -3.10 | 214/78 |
| 5-(3-$NO_2C_6H_4$)-3-Ph-isoxazole | -3.73 | 214/78 |
| 5-(4-$NO_2C_6H_4$)-3-Ph-isoxazole | -3.63 | 214/78 |
| 3-Cl-5-Ph-isoxazole | -6.01 | 202/76 |
| 4-Cl-5-Ph-isoxazole | -5.16 | 202/76 |
| 5-Cl-3-Ph-isoxazole | -4.90 | 202/76 |
| 4-$NO_2$-3-Ph-isoxazole | -7.90 | 202/76 |
| 3,4,5-$Me_3$-isoxazole | -1.00 | 137/77 |
| 4-Me-3,5-$Ph_2$-isoxazole | -2.70 | 202/76 |
| 3,4,5-$Ph_3$-isoxazole | -3.14 | 202/76 |
| 3,5-$Me_2$-4-$PhCH_2$-isoxazole | -1.60 | 202/66 |
| 3,5-$Me_2$-$AcOCH_2$-isoxazole | -1.82 | 202/66 |
| 3,5-$Me_2$-4-Cl-isoxazole | -2.48 | 202/66 |
| 3,5-$Me_2$-4-Br-isoxazole | -2.32 | 202/66 |
| 3,5-$Me_2$-4-I-isoxazole | -2.06 | 202/66 |
| 3,5-$Me_2$-4-$NO_2$-isoxazole | -3.72 (-6.17) | 202/66, 202/76 |
| 3,4-$Cl_2$-5-Ph-isoxazole | -7.70 | 202/76 |
| 4-Cl-3,5-$Ph_2$-isoxazole | -4.68 | 202/76 |
| 4-Br-3,5-$Ph_2$-isoxazole | -4.67 | 202/76 |

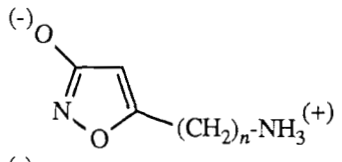
equation.[202/66,202/76] A substituent effect on the $pK_a$ values in the isoxazole series can be observed in the data reported in Table 1.57. Methyl groups increase the basicity. By contrast, phenyls decrease the basicity because of the electron-donating effect and the conjugation effect. An empirical relationship between basicity and ionization potential, measured by means of photoelectron spectroscopy of 11 azoles and benzoazoles, including isoxazole, has been studied and discussed.[85/84] The $pK_a$ value for isoxazole has been corrected to $-3.27$. The separation of isomeric isoxazole derivatives by thin-layer chromatography using the complex formation has been discussed in relationship to the $pK_a$ values.[298/78]

The dissociation constants of isoxazole monocarboxylic acids showed higher values for the 5- and 3-isomer than for the 4-isomer (see Table 1.58).[78/62] Similar

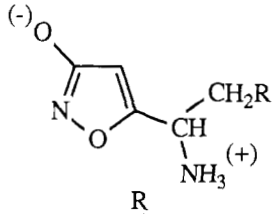
TABLE 1.58

| Isoxazole | $K_a$ |
|---|---|
| 5-COOH | $9.1 \times 10^{-3}$ |
| 4-COOH | $3.8 \times 10^{-4}$ |
| 3-COOH | $2 \times 10^{-3}$ |
| 5-Ph-3-COOH | $5.5 \times 10^{-3}$ |
| 3-Me-5-Ph-COOH | $2 \times 10^{-4}$ |

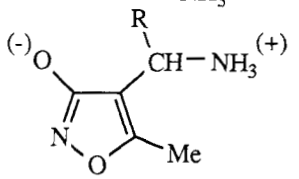
behavior is shown by the phenyl-substituted isoxazolecarboxylic acids. The $pK_a$ value (9.3) of 5-isoxazolecarboxaldoxime has been measured potentiometrically by comparison with carbaldoximes in the thiazole series[166/70] ($pK_a$ = 8.6–10.9). The zwitterionic structure of muscimol (**94**) and analogues (**95**, **96**, **115–117**) was evidenced by the $pK_a$ values determined by titration in aqueous solutions. It is



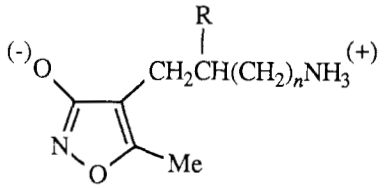
| | | $pK_a$ |
|---|---|---|
| **94** | $n = 1$ | 4.78, 8.43 [64/69] |
| **95** | $n = 2$ | 5.12, 9.46 [1/74] |
| **96** | $n = 3$ | 5.37, 10.36 [3/74] |



| | | |
|---|---|---|
| **115 a** | R = H | 4.69, 8.45 [3B/74] |
| **b** | R = Me | 4.65, 8.42 [3B/74] |
| **c** | R = Et | 4.69, 8.49 [3B/74] |



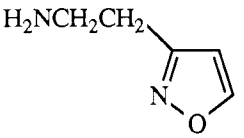
| | | |
|---|---|---|
| **116 a** | R = H | 4.74, 9.95 [7/77] |
| **b** | R = Me | 4.74, 9.73 [3/76] |



| | | |
|---|---|---|
| **117 a** | R = H, $n = 0$ | 5.12, 10.42 [3/76] |
| **b** | R = Me, $n = 0$ | 4.87, 10.06 [3/76] |
| **c** | R = H, $n = 1$ | 5.32, 10.6 [2/77] |

noteworthy that the $pK_a$ values of **117** are also quite different from those of the comparable homomuscimol (**95**).

The natural 4-hydroxyisoxazole (triumferol)(**4**) in aqueous solution showed a $pK_a$ value of 7.75 by spectrophotometry.[236/81] Contrary to 4-aminomethyloxazole, 3-(2-aminoethyl)isoxazole (**118**) shows histaminomimetic activity.[11/75] This property has been correlated with the basicity by comparison with the histamine value:



**118**

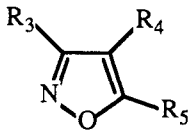
| | | |
|---|---|---|
| **(118)** | $pK_1$ 2.5 (ring N) | $pK_2$ 9.3 ($NH_2$) |
| histamine | $pK_1$ 6.0 (ring N) | $pK_2$ 9.8 ($NH_2$) |

Acid dissociation,[115B/64] microionization constants[262/80] of some sulfonamides, including sulfisoxazole and sulfamethoxazole, have been obtained, and the substituent effect on the values of the constants has been discussed.

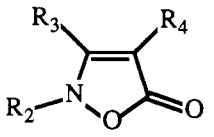
Basicity has been used, along with the spectroscopic data, to study the tautomerism of isoxazolinones.[66/61,97/64,187/71,222/72] Selected examples of $pK_a$ values of isoxazolinones and their methyl derivatives are reported in Table 1.59. The $pK_a$ data confirm the predominance of the hydroxy tautomers in the case of 3- and 4-isoxazolinones[97/64,187/71,222/72] (see also Part 2 of the present work).

The dissociation constants of 3,5-dihydroxy-4-phenylisoxazole have been determined either by potentiometric titration (2.10, 2.12, and 10.80) or by spectroscopic methods (1.86 and 9.98).[80/71] The $pK_a$ values of a series of 3,5-dihydroxy-4-arylisoxazoles have also been reported, the 4-nitrophenyl deriva-

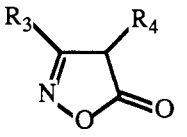
TABLE 1.59. BASE STRENGTHS ($pK_a$ VALUES OF CONJUGATED ACIDS) OF ISOXAZOLINONES AND HYDROXYISOXAZOLES



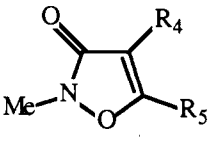
**A**



**B**



**C**



**D**

| Structure | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $pK_a$ | Method [a] | References |
|---|---|---|---|---|---|---|---|
| A | - | Me | Me | OMe | -1.47 | T | 66/61 |
| B | Me | Me | Me | - | -1.24 | T | 66/61 |
| | | | | | -1.58 | S | 66/61 |
| C | - | Me | Me | - | -0.66 | T | 66/61 |
| A | - | OMe | Me | Me | -2.08 | S | 97/64 |
| D | Me | - | Me | Me | -1.36 | S | 97/64 |
| A | - | Me | OH | Me | -1.71 | S | 187/71 |
| A | - | Me | OH | Ph | -2.75 | S | 187/71 |
| A | - | Ph | OH | Ph | -3.25 | S | 187/71 |
| A | - | Me | OMe | Me | -2.27 | S | 187/71 |
| A | - | Me | OMe | Ph | -3.03 | S | 187/71 |
| A | - | Ph | OMe | Ph | -3.36 | S | 187/71 |

[a] T = titration method; S = spectrophotometric method.

tive being shown to be one of the strongest organic acids, with a $pK_a$ of $-0.1$ lower than that of picric acid ($pK_a = 0.3$) and trifluoroacetic acid ($pK_a = 0.23$).[181/75]

Some $pK_a$ values for isoxazole salts or complexes have been reported.[42/75,138/75,172/75,288/76] It has been determined that in the case of trimethylamine (TMA) salts with heterocyclic derivatives (B)(isoxazole, thiazole, pyridines, etc.), the $\nu_s$ (NH stretching) in the IR spectra of complex cations $(TMAHB)^+$ shows a pronounced doublet structure when $\Delta pK_a$ ($pK_{aTMA} - pK_{aB}$) is in the range 4–8. Since in the case of isoxazole the $\Delta pK_a$ (11.84) has a large value, the $\nu_s$ band, which shows a Fermi resonance window effect, has a single main maximum with a shoulder.[172/75] When thiazolinium perchlorate was dissolved in isoxazole, a complex cation was obtained, as demonstrated by the infrared absorption.[138/75] In the $\nu_s$ range, two bands were observed and it is interesting to note that here the $\Delta pK_a$ is 4.58.

In the study of complexes the 3,5-dimethylisoxazole has been used as a donor with tetracyanoquinodimethane[42/75] and with $AlBr_3$.[150/74] In both cases the $pK_a$ of the complex was $-0.2$.[42/75,288/76] Azoles, including isoxazoles, give complexes with iodine[157/75] and nitrophenols.[118/76,285/77,286/77] For 3,5-dimethylisoxazole complexes in the former case, a $pK_a$ value of $-2$ and in the latter, with 2,4,6-trinitrophenol and 2,4,6-trinitroanisole, a $pK_a$ value of 1.3 have been measured.[285/77,286/77]

The lack of or very low reactivity of isoxazole[205/82] and derivatives[137/77] as nitrogen donors or nucleophilic reagents in some specific reactions has been explained by their very low basicity. The stability constants of the metal chelates of 3-(*o*-hydroxyphenyl)-5-arylisoxazoles with rare earth metal ions have been measured potentiometrically.[138C/79] A theoretical study of the factors that promote the very low basicity of isoxazole in relation to other azoles has been reported (see also § 1.2.8).[132/81]

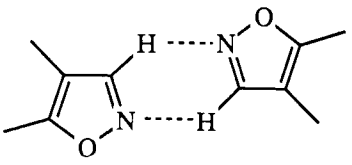
### 1.2.10 Miscellaneous Data

Unsubstituted isoxazole has been studied largely either by spectroscopic methods or by theoretical calculations (as reported in §§ 1.2.1–1.2.5 and § 1.2.8, respectively) because of its peculiar properties. Isoxazole, a colorless liquid with a characteristic smell, shows the following physical properties: b.p. 95–95.5°C, m.p. $< -80°$, $D_4^{20}$ 1.0795, $n_D^{20}$ 1.4268, critical temperature 552.04 K, $pK_a = -2.03$, and dipole moment $2.76 \pm 0.02$ D in benzene and $3.01 \pm 0.02$ D in dioxane. Alkylisoxazoles are usually liquid, and only the introduction on the ring of more than one substituent with a long chain led to solid compounds. Phenyl derivatives are usually solid.

A comparison of the boiling points of isoxazole and of other five-membered ring heterocycles shows that the boiling point of isoxazole is higher than that of oxazole (60–70°C) and furan (31°C) but lower than that of heterocycles containing two nitrogens and/or a NH group (pyrrole, 131°C; pyrazole, 188°C; imidazole, 256°C).[16/47] Boiling points and melting points of isoxazoles are reported

in a tabular survey. Also, the solubility of isoxazole and derivatives differs from that of oxazoles and other similar heterocycles.[100/63] Isoxazole is scarcely soluble in water (15 g per 100 ml at 25°C) and gives an azeotropic mixture, b.p. 88.5°C. By contrast, oxazole and its methyl derivatives dissolve easily in water. These facts indicate a greater association for isoxazoles than for oxazoles, but far less association than for pyrazole and imidazole derivatives.

The influence of temperature on density and surface tension, Eötvös constants, solubility curves, parachor values, molecular refractions, and cryoscopic studies have been reported and reviewed.[16/47,14B/52,78/62] From these studies it has been established that 3-unsubstituted isoxazoles behave differently from their isomers. These results have been interpreted in terms of an enhanced capacity for intermolecular association of the free position by the formation of hydrogen bonds between the nitrogen atom and $C_3$–H, represented as




Furthermore, cryoscopic measurements in benzene confirm the associative capacity of isoxazoles and indicate the following order: isoxazole, 5-Me, 4-Me, 4,5-$(Me)_2$ $\gg$ 3-Me $>$ 3,4-$(Me)_2$. 3,5-Dimethyl and 3,4,5-trimethylisoxazole are practically devoid of associative capacity. Data on dipole moments are reported in § 1.2.7.

Magnetochemical measurements on 3,5-dimethylisoxazole give a value of 59.7 for magnetic susceptibility. This indicates an increment $\lambda = +1.0$ for the isoxazole ring (including the double bonds). A measure of the aromaticity of the ring can be derived from the formula $\Delta = \lambda - 5.45l$, where $\lambda$ is the characteristic increment of the system inclusive the double bonds, and $l$ the increment for the double bond. For aromatic systems $\Delta$ is negative, whereas for polymethylene rings $\Delta$ is positive. The aromaticity of a ring is, therefore, enhanced proportionately to the higher negative value of $\Delta$. For isoxazole $\Delta$ is $-9.9$ and this ring is therefore ranked between the furan ($\Delta = -13.4$) and pyrimidine ($\Delta = -9.85$) rings.[1/46]

The enthalpy of combustion $\Delta H_c^\circ$ of isoxazole[174/78] was first determined in 1978 by precision oxygen-bomb calorimetry. From these data the enthalpy of formation in the gas and condensed phases [$\Delta H_f^\circ$(g) and $\Delta H_f^\circ$(c)] have been derived. Data for isoxazole and some substituted isoxazoles are reported in Table 1.60.

Thermodynamic parameters of isoxazole have been calculated from vibrational spectra using a rigid rotator harmonic oscillator as model.[67/68,185/68] A resonance energy of 50 kcal/mol has been calculated from the combustion heat data of different methyl- and phenylisoxazoles.[4B/40] By contrast, the empirical resonance energy (ERE) and conjugation energy of pyrazole and isoxazole

TABLE 1.60

| Compound | $\Delta H_c°$(298.15 K) (kcal/mol) | $\Delta H_f°$(g) (kcal/mol) | $\Delta H_f°$(c) (kcal/mol) | References |
|---|---|---|---|---|
| Isoxazole | -394.70 ± 0.12 | 18.78 ± 0.13 | 10.07 ± 0.13 | 174/78 |
| 3-Methylisoxazole | -546.00 ± 0.14 | 8.52 ± 0.16 | - | 169/78 |
| 5-Methylisoxazole | -545.65 ± 0.17 | 8.14 ± 0.18 | - | 169/78 |
| 3-Amino-5-methylisoxazole | -566.37 ± 0.13 | 5.0 ± 0.6 | -14.78 ± 0.14 | 154/73 |
| 5-Amino-3,4-dimethylisoxazole | -723.46 ± 0.30 | 1.24 ± 0.68 | -19.76 ± 0.31 | 153/73 |

derivatives have been deduced by heats of dehydration of the corresponding hydroxydihydro derivatives.[250/78]

The stability of complexes of 3,5-dimethylisoxazoles has been evaluated by their heats of formation.[42/75,288/76]. The ERE value calculated for phenylisoxazoles is 6 ± 5 kcal/mol lower than that reported previously. The isoxazole conjugation energy (1 kcal/mol) is rather less than that for furan (8 kcal/mol), pyrazole (14 kcal/mol), and benzene (22 kcal/mol), showing that isoxazole derivatives are very much less aromatic. Saturated vapor pressures and critical points of liquid for 48 heterocycles, including isoxazole, have been calculated and reported.[48/77]

Thermal data of sulfonamides showing whether or not polymorphism is present have been studied.[181/72] Two polymorphs of sulfisoxazole (**18**) have been found. Form I, obtained by recrystallization from water at room temperature, exhibits a transition peak at 145°C with a heat of transition of 294 cal/mol, and a m.p. at 196°C, with a heat of fusion of 7.46 kcal/mol. Form II is obtained simply by trituration of form I. Probably because of the ease of transformation, the two forms show identical IR and x-ray diffraction diagrams.

For acetylsulfisoxazole (**19**), polymorphism was not found. However, heat (8.16 kcal/mol), entropy (17.3 e.u.), and temperature of fusion (197°C) have been measured.[181/72] Three polymorphs of sulfamethoxazole (**21**) have been identified. The following thermal data have been reported: fusion temperature 170°C for all; heat 5.86, 6.03, and 5.48 kcal/mol and entropy 13.2, 13.6, and 12.4 e.u., respectively, for forms I, II, and III. Transition temperatures of 166°C for II and 123°C for III have been found. Furthermore, form III shows a transition heat of 457 cal/mol and an entropy of 1.1 e.u.[181/72]

The freezing-point diagrams of the isomeric pairs of some isoxazolecarboxylic acids have been determined. In all cases investigated, a wide zone of miscibility in the solid state has been found.[7/52]

A phase diagram of the binary sulfamethoxazole–trimethoprim system has been studied, showing a total dissociation in the melt phase.[86/78] The existence of a clathrate isoxazole·$34H_2O$ has been discovered by means of direct and differential thermic analysis of the water–isoxazole binary system.[37B/72] Dielectric, NMR, and x-ray diffraction studies on the hydrate of isoxazole have also been reported and discussed.[30/74]

Thermodynamic parameters involved in rotation of the partial C = N double

TABLE 1.61

| Complex | $\mu_{obs}$BM (25°C) | References |
|---|---|---|
| $Co(isox)_6(BF_4)_2$ | 4.74 | 107/77 |
| $Ni(isox)_6(BF_4)_2$ | 3.00 | 107/77 |
| $Cu(isox)_5(BF_4)_2$ | 1.77 | 107/77 |
| $Cu(isox)Cl_2$ | 1.76 | 167/74 |
| $Ni(isox)Cl_2 \cdot 1/2H_2O$ | 3.15 | 167/74 |
| $Co(isox)Cl_2$ | 4.93 | 167/74 |
| $Co(isox)Br_2$ | 4.56 | 167/74 |
| $Cr(isox)_3Cl_3$ | 4.0 | 222/76 |
| $Cr(3,5\text{-}Me_2\text{-}isox)_3I_3 \cdot 6H_2O$ | 3.9 | 222/76 |
| $Cu(3,5\text{-}Ph_2\text{-}isox)Cl_2 \cdot H_2O$ | 1.9 | 174/77 |
| $Ni(3,5\text{-}Ph_2\text{-}isox)Cl_2 \cdot H_2O$ | 3.4 | 174/77 |
| $Co(3,5\text{-}Ph_2\text{-}isox)Cl_2 \cdot H_2O$ | 4.5 | 174/77 |
| $Co[(3,5\text{-}Ph_2\text{-}isox)_4(H_2O)_2](ClO_4)_2 \cdot 2H_2O$ | 5.6 | 174/77 |
| $Mn(isox)_2Cl_2$ | 6.7 | 253/80 |
| $Mn(isox)_2Br_2$ | 5.8 | 253/80 |
| $Mn(3,5\text{-}Me_2\text{-}isox)_4(NCS)_2$ | 6.0 | 253/80 |
| $Mn(3,5\text{-}Ph_2\text{-}isox)_2Cl_2 \cdot 2.5H_2O$ | 6.5 | 276B/80 |
| $Mn(3\text{-}NH_2\text{-}5\text{-}Me\text{-}isox)_2Cl_2$ | 5.6 | 276B/80 |
| $Mn(5\text{-}NH_2\text{-}3,4\text{-}Me_2\text{-}isox)_2Cl_2 \cdot H_2O$ | 5.6 | 276B/80 |
| $[Fe(3,5\text{-}Ph_2\text{-}isox)_6]\ Cl_3$ | 5.5 | 210B/81 |
| $[Fe(3\text{-}NH_2\text{-}5\text{-}Me\text{-}isox)_4Cl_2]\ Cl$ | 6.1 | 210B/81 |
| $[Fe(3\text{-}NH_2\text{-}5\text{-}Me\text{-}isox)_6]\ Br_3$ | 5.9 | 210B/81 |

bond in a series of five-membered heteroaromatic *N,N*-dimethylcarboxamides (including 3-isoxazolyl-*N,N*-dimethylcarboxamide) have been measured by total line shape analysis of their NMR spectra.[237/77] A study of the thermal stability of bis(aryl)oligo(oxaalkanes) containing pyrazolyl- or isoxazolylazo groups in the *ortho* and *ortho'* positions has been reported.[292/82]

The magnetic susceptibility of a number of metal complexes of isoxazole and derivatives has been measured by the Gouy method and corrected for the diamagnetism of component atoms.[167/74,222/76,107/77,174/77,253/80,210B/81] The magnetic moments of some complexes are reported in Table 1.61. Conductivity measurements in various solvents have been reported for many complexes.[167/74,222/76,174/77,210/81]

### 1.2.11 Analytical Methods

Isoxazole, the isomeric monomethyl- and dimethylisoxazoles, trimethylisoxazole, and some aryl- and alkylarylisoxazoles give crystalline addition products with cadmium and mercuric chlorides, which are often used for their isolation and purification.[7/03,4/09,4/26,14/38,1/49,35/56,39/57,164/67,139/68,37/69,51/72]

Thin-layer chromatographic (TLC) analysis, described in most of the papers either for monitoring the reaction mixture or for the detection of isoxazole derivatives, has been performed on silica gel plates. Isomeric 17$\beta$-(isoxazolyl)-5-androsten-3$\beta$-ol acetates have been barely separable on a silica gel G plate; however, $R_f$ values relative to cholesterol have been determined.[116/66] Thin-layer silica gel plates impregnated with inorganic salts (Zn or Cd salts) or organic acceptors (*p*-benzoquinone, chloranil, trinitro- and tetranitrofluorene) have been used for the separation of isomeric aryl- and arylalkylisoxazoles.[298/78]

The differences in mobilities due to the eventual formation of donor-acceptor complexes depend on substituents of the isoxazole ring and on the differences in basicity of the isomers. The best results are obtained when the substituents are quite different: for 3- and 5-phenylisoxazoles in the case of inorganic salts, and for 5-aryl-3-phenyl- and 3-aryl-5-phenylisoxazoles in the case of organic complexes. Complexes are not formed when bulky substituents are present.[298/78]

Twelve 3,5-dimethyl-4-arylazoisoxazoles have been separated by TLC using as the eluant a $CHCl_3$/toluene/dioxane (6:3:1) mixture: $R_f$ values have been reported.[297/78] TLC spots of isoxazoles are usually evidenced under a UV lamp using fluorescent TLC plates. However, in some cases, they are detected by means of reagents. For example, Dragendorff reagent[11/61] has been used for hydroxyisoxazoles, acidic phosphomolibdic solution for *C*-glycosides,[44/73] iodine vapors for diisoxazoles,[49/64] and $FeCl_3$ solution for hydroxyarylisoxazoles.[200/79]

The last reagent can also be used for spot tests of isomeric (2-hydroxyphenyl)isoxazoles: 3-(2′-hydroxyphenyl)isoxazoles give a color reaction (red-violet) with $FeCl_3$ solution; by contrast, 5-(2′-hydroxyphenyl)isoxazoles, because of a strong hydrogen bond with the ring oxygen, do not enter into a reaction with alcoholic $FeCl_3$ solution.[200/79] 7-Hydroxy-6-isoxazolobenzoxazoles give coloration with neutral $FeCl_3$ (green), with concentrated sulfuric acid (pink), and with $TiCl_3$ (dark violet).[181/82]

Column chromatography for the separation and purification of isoxazole derivatives has been carried out mostly on silica gel; however, alumina has also been employed.[21/62,49/64,116/66,31/81,32/82] It is noteworthy that $\alpha,\beta$-acetylenic ketoximes can be purified only on silica gel column chromatography since on alumina they are transformed into the corresponding isoxazoles.[219/70] Some isoxazolylamino acids have been separated by paper chromatography.[4/57]

Gas-liquid chromatographic (GLC) analysis of isoxazole derivatives has been carried out mainly on different kinds of silicone grease columns: GE-SF 96,[72/64] XE-60,[27/70] SE-52,[27/70] and SE-30[37/69] for alkylisoxazoles; cyano XF-1150[27/65] and silicon rubber[161/66] (SE-30)[38B/79] for arylisoxazoles; DC-550[55/61] and SE-30[258/82] for esters; and silicone 702 for 4-bromomethylisoxazole;[77/66] 1% SE-30 on silanized Gas-Chrom P column has been used for analysis of isoxazolylandrosten-3-ols on a gas-chromatograph equipped with an argon ionization detector ($^{90}Sr$).[116/66] Polyethylene glycole succinate[40/73] and stearate columns[51/72] have been employed to purify and evaluate the purity of alkylisoxazoles by GLC.

GLC analysis has been reported either for preparative purposes[157/67,38B/79,287/82]

or for quantitative studies.[55/61,56/61,72/64,12/73,258/82] For example, the ratio of the methyl derivatives obtained by methylation of 4,5-dimethyl-3-hydroxyisoxazole has been evaluated by GLC (SF-96 column), the 4,5-dimethyl-3-methoxyisoxazole showing the shorter retention time.[21/62]

Retention times and Kovàts indexes of some 5-substituted 3,4-dimethylisoxazoles have been calculated using three different columns: silicone SE-30, Carbowax 20M, and Apiezon L, the last on alkaline chromosorb W HMDS.[98/76] GC-MS analyses of the same compounds have been, however, carried out on an OV-225 column.[98/76] 4,5-Dimethylisoxazole has been identified among 78 other products by means of GC-MS in the volatile fraction of commercial oil-free soybean lecithin.[63/84]

Methods for the isolation and purification of muscimol (**2**)[25/64,57/65] and ibotenic acid (**1**)[116/64,58/65,98/65,122/65,123/65,219/69] from natural sources (*Amanita* species) have been described in detail: paper chromatography,[25/64,116/64,57/65,58/65,98/65,122/65,123/66] paper electrophoresis,[25/64,116/64,57/65,58/65,98/65,122/65] column chromatography on alumina,[116/64,57/65] ion-exchange resins,[25/64,116/64,57/65,123/65] and cellulose[122/65] have been used. Chemotaxonomic studies on *Amanita* species by evaluation of their content in isoxazole derivatives have been carried out employing mainly paper chromatography,[123/66] electrophoresis,[205/76] and thin-layer chromatography.[145/81] GLC analysis did not give good results.[145/81]

However, GC analysis could be carried out on trimethylsilyl derivatives using SE-30 and OV-101 columns. Retention times have been reported, showing that quantitative analysis of the trimethylsilyl derivatives of muscimol and ibotenic acid can be afforded by this method.[207/78] This method made it possible to obtain the mass spectra of compounds by means of GC-MS apparatus. Quantitative analysis of muscimol and ibotenic acid was afforded by means of HPLC (Li-Chrosorb-$NH_2$ and Nucleosil 5 CN columns)[14/79] and an amino acid analyzer (microbore single column).[151/82] The sensitivity of the various methods was discussed. It is noteworthy that muscimol is often formed by decarboxylation of ibotenic acid during the extraction and separation procedures and is considered as an artifact.

Analytical methods for the purification of synthetic ibotenic acid (**1**),[38/66,34/67] homomuscimol (**95**),[1/74] and isoxazole analogues of GABA[3/74] have been described. Resolution of synthetic ibotenic acid in the enantiomers was made possible through *N*-(trifluoroacetyl)ibotenic acid by quinine.[123/69] By contrast, (*d,l*)-3-(1-hydroxy-2-piperidinoethyl)-5-phenylisoxazole has been resolved by (*l*)-tartaric acid or by α-10-camphosulfonic acid.[114/75]

Isoxazolylpenicillins have been analyzed by means of reversed-phase TLC and $R_f$ values.[138/83] A rapid modified ultrafiltration method connected with antibiotic binding to serum protein[82B/65] has also been used to analyze dicloxacillin (**103**). A gas chromatographic procedure for penicillins using SE-30 and QF-1 columns has been carried out on the methyl esters of the acids obtained by the hydrolysis of penicillins.[21B/64]

A pharmacokinetic study of metabolism and urinary excretions of isoxazolylpenicillins leading to the isolation of penicilloic acid, 5-hydroxy-

methyl derivative of penicillins, and its corresponding penicilloic acid has been carried out by means of HPLC. A reversed-phase Li-Chrosorb RP-18 column eluted with buffer solutions mixed with acetonitrile was used.[43B/83]

Some analytical methods for the determination of the herbicide 3-(5′-*t*-butyl-3′-isoxazolyl)-1,1-dimethylurea (Isouron) and its isomers or analogues have been described.[27/81,266/81,237/82,21/84,22/84] GC analysis could be carried out after an ethylation reaction: ethylated isouron and analogues were well separated on an OV-101 column.[237/82] Colorimetric determination of isouron and its analogues and the isomeric 1-(3′-*t*-butyl-5′-isoxazolyl)-3,3-dimethylurea was based on the products obtained after hydrolysis, by reaction with 4-dimethylaminocinnamaldehyde.[21/84,22/84]

A number of studies to identify pharmaceutical compounds have been reported; the compounds included Isocarboxazide (Marplan) (**86**),[75B/64,80B/65,1B/66,10B/66,52B/67,101B/67] Perisoxal,[49/80] Isoxicam,[27G/84] 5-phenyl-3-isoxazolecarboxylic acid (PIA),[49/80,53/80] 5-methyl-3-isoxazolecarboxylic acid (MIA),[49/80] and their derivatives. Isocarboxazide (**86**) has been identified mainly on silica gel TLC plates either containing bases or by elution with solvents containing a few percent of ammonia or amines. Often, $R_f$ values in the different solvent systems are reported. Several reagents have been used to visualize the spots: for example, triphenyltetrazolium chloride,[75B/64] potassium permanganate, iodoplatinate, Dragendorf reagent,[80B/65] iodine,[1B/66] Folin-Ciocalteau,[52B/67] Mandelin,[101B/67] and many other reagents. Structure and $R_f$ correlation in TLC have also been discussed.[1B/66] A cerimetric method for the determination of hydrazides was also shown to be suitable for Isocarboxazide (**86**).[10B/66]

By decomposition to the corresponding $\beta$-ketonitriles, followed by condensation with 4-dimethylaminobenzaldehyde,[49/80] 5-substituted isoxazole 3-carboxylic acids, such as PIA and MIA, can be quantitatively evaluated in the absorption spectra at 457 and 442 nm, respectively.[49/80] Similarly, by reaction with 2-hydroxynaphthalene carbaldehyde, the intermediate $\beta$-ketonitriles are transformed to benzocumarins, which can be detected by fluorescence spectra.[53/80] These colorimetric or fluorimetric tests can be carried out on all the products that, by hydrolysis or oxidation, can be transformed in 3-isoxazolecarboxylic acids.[49/80,53/80] The quantity of Perisoxal in plasma has been determined by this procedure.[53/80] Metabolic transformations of labeled Isoxicam have been studied and analytical methods (TLC, HPLC) have been reported.[27G/84]

A variety of methods for the qualitative and quantitative determination of sulfonamides, including sulfisoxazole (**18**),[44/59,4/60,70F/61,72/61,72C/61,72E/61,17B/62,60B/62,54B/63,66B/63,70B/63,86B/63,90B/63,40/64,134B/65,12B/66,149B/66,122B/67,43/70,159/70,149B/71,214B/76,215/77,283/77,13/78,61/78,66/78,175/78,178/78,108C/79,158D/79,199D/79,102/81,8/82,9/82,50/82,152/82,243/82,139/83] acetylsulfisoxazole (**19**),[72B/61,54B/63,134B/65,149B/71,158D/79,9/82] and sulfamethoxazole (**21**)[1C/65,32/71,149B/71,14B/75,8/77,132/77,13B/78,14/78,40B/78,141/78,177/78,178/78,108B/79,158C/79,158D/79,102/81,7/82,8/82,42/82,50/82,97/82,148/82,149/82,168/83,179/83] have been reported. Some papers deal with the identification of sulfonamides in drugs,[72/61,72E/61,17B/62,60B/62,70B/63,90B/63,159/70,149B/71,135/74,14B/75,214B/76,8/77,283/77,14/78,61/78,66/78,141/78,158C/79,102/81,7/82,8/82,97/82,139/83,168/83] in biological fluids,[44/59,70F/61,

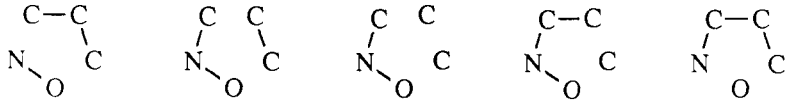
[72B/61,72C/61,12B/66,132/77,215/77,40B/78,177/78,108B/79,42/82,148/82,9/83] and in presence of metabolites.[43/70,32/71,42/82]

Polarographic methods,[72/61,72E/61,90B/81] potentiometric titration,[60B/62,14B/75,8/82] thin-layer chromatography,[54B/63,66B/63,70B/63,86B/63,90B/63,149B/71,13B/78,14/78,108C/79,2B/81,9/82,121/82,310/82] vapor programmed TLC,[159/70] paper chromatography,[66B/63,43/70,32/71] ion-exchange resins,[32/71,135/74] HPLC,[8/77,132/77,215/77,13/78,175/78,177/78,108B/79,158D/79,102/81,9/82,42/82,97/82,148/82,149/82,152/82,139/83,168/83] GLC of the methyl derivatives,[40B/78,178/78] and colorimetric,[4/60,70F/61,40/64,1C/65,149B/66,122B/67,214B/76,283/77,141/78,50/82] fluorimetric,[134B/65,9/83] and photometric[12B/66] methods have been used. Liquid-liquid extraction parameters for isolating organic compounds (including sulfisoxazole **18**) have been determined and discussed.[243/82]

Potentiometric titration has been used for the determination of either 3-(*o*-chlorophenyl)-5-methylisoxazole carboxylic acid and its chloride[60/78] or sodium hypochlorite and *N*-chloro-5-methyl-3-isoxazolecarboxamide in the Hofmann reaction.[28B/66] The polarographic behavior of a number of haloisoxazoles in anhydrous dimethylformamide has been discussed.[251/79] *N*-Ethyl-5-phenylisoxazolium-3′-sulfonate (Woodward's Reagent K) has been employed as a coupling reagent in the synthesis of peptides. This reaction for dipeptides has been followed by HPLC to determine the extent of racemization.[30/77]

## 1.3 METHODS OF PREPARATION

If we consider the starting materials, it is convenient to organize the several different methods of preparing the isoxazole ring according to the ring-closure pattern. The following two (3 + 2), one (3 + 1 + 1) and two (4 + 1) processes can be singled out:

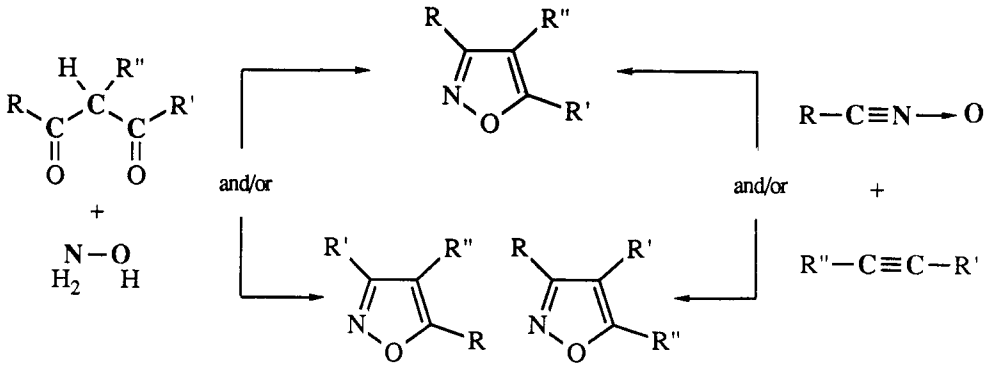


The first two methods (i.e., oximation of several classes of compounds, mostly provided with carbonyl groups, and cycloaddition of nitrile oxides to unsaturated compounds) are by far the most widely utilized syntheses. However, neither of them is completely unequivocal, and many efforts have been devoted to the problem of their site, regio, and stereo selectivities. In addition to those shown above, at least four cyclization (5 + 0) patterns are known. In addition, isoxazoles can be prepared starting either from other 1,2-oxazole derivatives (dihydro- and tetrahydroisoxazoles or isoxazolinones) or from other heterocyclic systems. In the latter case a ring-opening/ring-reclosure process is at work.

## 1.3.1 [CCC + NO] Processes

### *1.3.1.1 Oximation of 1,3-Dicarbonyl (and Related) Compounds*

The oximation of 1,3-dicarbonyl compounds (mainly β-ketoaldehydes and β-diketones) is the oldest known[1/884,2/888] synthetic route to the isoxazole ring, and was by far the most widely used method of synthesis of this heterocycle until the discovery[5/46] of the nitrile oxide route (see § 1.3.2.1). With asymmetrically substituted starting materials, neither method leads to isoxazole compounds of unequivocal structure. Only the identity between the products obtained from both methods allows us to establish the substitution pattern without uncertainty, as the following scheme shows:

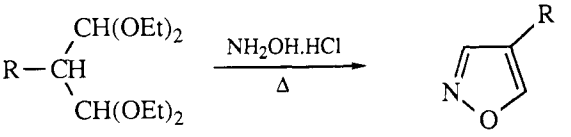



With symmetrical 1,3-dicarbonyl compounds the oximation reaction maintains its synthetic value entirely, and competes favorably with the nitrile oxide route, owing to the easy accessibility of the starting materials and to the high yields commonly attained. The main pattern of the reaction will be illustrated here according to the nature of the 1,3-dicarbonyl compound, and the involvement of some related compounds (e.g., β-ketonitriles or β-keto esters) will also be outlined briefly.

#### a. β-Dialdehydes

The free malondialdehyde[8/55] or, better, its tetraethylacetal,[8/55,16/57,26/57,39/57] easily obtainable from vinyl acetate and triethyl orthoformate, are an excellent source of isoxazole, which is produced in 70–90% yields by treatment with hydroxylamine hydrochloride in aqueous solution at 50–70°C. The same isoxazole has been obtained by oximation of other derivatives, which can be considered a masked malondialdehyde; for example, 1,1-dichloro-3-bromo-3-acetoxypropane.[35/56] 4-Monosubstituted isoxazoles have been prepared analogously by oximation (usually under acidic conditions) of malondialdehydes (or, most commonly, their tetraethylacetals) substituted for by an alkyl,[45/59,92/68,51/72]

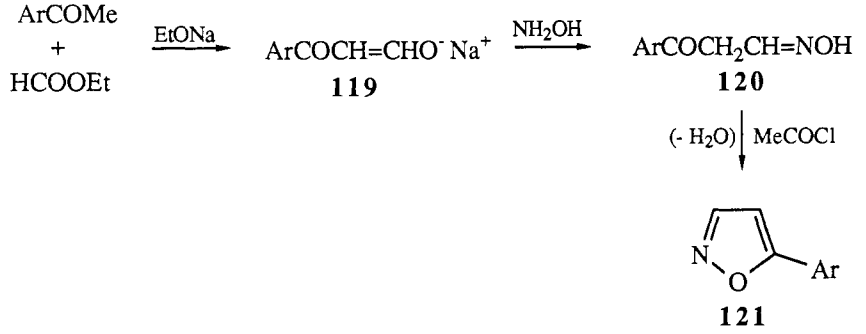
aryl,[8/27,45/59.230/68.151/77] heterocyclic,[88B/72,143/72,112/73] or other functional group:[8/899,2/47,4/47,57/66,77/66,111/66]



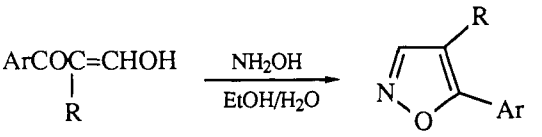
b. β-Ketoaldehydes

Oximation of the unsymmetrical acylacetaldehydes can a priori give rise to several products: monoximes, dioximes, the so-called "sesquioximes," and 3- or 5-unsubstituted isoxazoles. The formation of one or the other compound depends on the nature of the substituent, the pH of the medium, and the reaction solvent.

5-Arylisoxazoles (**121**) can be prepared relatively easily without contamination from the 3-substituted isomer. The earlier procedure,[3/891,3/10,9/30,2/34,1/37] checked more recently for large-scale production,[166/66] involves isolation of the unstable monoxime (**120**), obtained from the sodium salt (**119**) of an aroylacetaldehyde with buffered hydroxylamine solution, and subsequent dehydrative cyclization with acetyl chloride (or other reagents).[4/58,220/78]

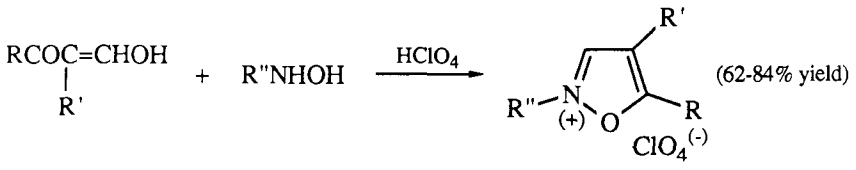


Overall yields from the sodium salts (**119**) are in the range 50–65%. Yields up to 97% have been reported for the synthesis of 5-aryl- or 5-aryl-4-alkyl (or aryl)-isoxazoles by oximation of the free β-ketoaldehyde under more or less feebly acidic conditions, in alcoholic or hydroalcoholic media without isolation of the intermediate oxime:[15/53,64/59,12/71]



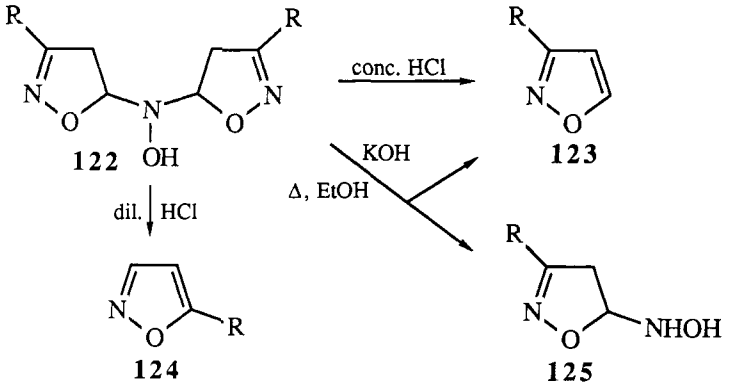
Experimental conditions must be controlled thoroughly, since the same reaction in a concentrated, strongly acidic solution is reported to lead to the isomeric 5-unsubstituted 3-arylisoxazoles.[12/71] The oximation of β-ketoaldehydes is easier when the keto group is hindered, as, for example, in mesitoylacetaldehyde, which furnishes only 5-mesitylisoxazole in 94% yield.[7/45]

An important variation of this type of synthesis is the direct preparation of 3-unsubstituted isoxazolium salts, employed in the synthesis of peptides (see also § 1.4.6.1e, pp. 313–314), by oximation of β-ketoaldehydes with phenyl (or benzyl)-hydroxylamine in the presence of perchloric acid:[156/69]




The oximation of aliphatic β-ketoaldehydes (or of their sodium salts) has led to somewhat contradictory results. Most often the formation of the sole 3-unsubstituted isoxazole[1/37,65/59,66/59,162/67,82/68,212/68,216/69,28/74,150/75,154/81] has been reported, usually operating under more or less neatly acidic conditions and sometimes under heating. In the case of a steroidal β-ketoaldehyde, the intermediate monoxime has been isolated.[108/67] In other cases formation of the two possible isomers is claimed.[4.09,14/38,116/66] Thus from the sodium salts of acetoacetaldehyde and hydroxylamine hydrochloride in strong aqueous hydrochloric acid, for example, isomeric 5- and 3-methylisoxazoles are obtained in a 70:30 ratio.[4/09]

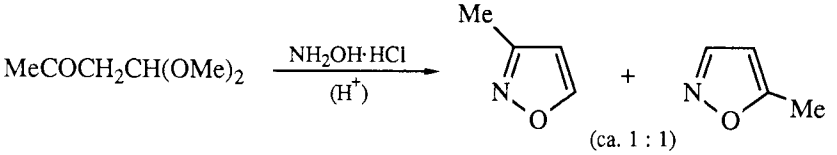
When hydroxylamine reacts with the sodium salts of benzoyl-,[3/891] aceto-,[4/891] or cinnamoylacetaldehyde[40/62] at room temperature, solid crystalline products, the so-called "sesquioximes," are obtained. Despite a different proposal,[8/41] their structures are generally accepted as bisisoxazolinylhydroxylamines (**122**):[1/34,14/40,15/40]



Acidic treatment of the sesquioxime gives either the 3- (**123**) or the 5-substituted (**124**) isoxazole, depending on the concentration of the acid used. For example, when acetoacetaldehyde sesquioxime is treated with hydrochloric acid (*d* 1.19), 80% of the 3-methylisoxazole is present in the reaction mixture. On the contrary, with 0.5 *N* hydrochloric acid, 87% of 5-methylisoxazole is formed.[15/40] In hot alcoholic potassium hydroxide the sesquioxime is split into 3-substituted isoxazole and 3-substituted isoxazolin-5-yl hydroxylamine (**125**). The latter compound is the only product when hydroxylamine is also present.[2/34,14/40]

In the case of cinnamoylacetaldehyde, oximation in aqueous solution gave, instead of the sesquioxime (prepared in ethanol), the monoxime, easily cyclizable to 5-styrylisoxazole (**124**: R = CH=CHPh) by heating in acidic methanol.[40/62] Direct formation of the same compound is achieved by oximation of the copper salt of the β-ketoaldehyde[40/62] and of other derivatives of the masked aldehyde group.[133/68] The isomeric 3-styrylisoxazole has been prepared by cyclization of the cinnamoylacetaldehyde 1-semicarbazone 3-oxime.[133/68]

With the aim of obtaining pure 3- or 5-unsubstituted isoxazoles, several attempts have been directed toward the use of appropriate functional derivatives of β-ketoaldehydes. Thus the use of enamines, enol ethers, or β-chlorovinyl ketones of the general structure RCOCH=CHY is illustrated in § 1.3.1.4, pp. 157–168. Despite a different claim,[58/71] oximation of both acetoacetaldehyde tetramethylacetal[5/53] and dimethylacetal[1/55,25/55,111/66] is not site specific, and yields a mixture of 3- and 5-methylisoxazole:

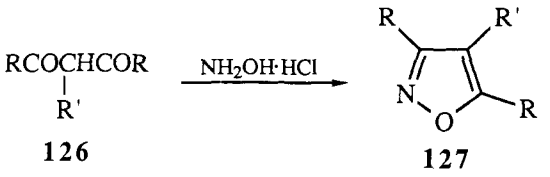



A prevalence of 5-methylisoxazole in large-scale preparation from acetoacetaldehyde dimethylacetal requires carefully selected experimental conditions.[40/63]

Use of the cyclic acetals of β-ketoaldehydes as starting materials has been claimed to give the 3-substituted isoxazole exclusively;[72/60] an intermediate oxime can be isolated under controlled conditions. Nevertheless, even this type of oximation has subsequently been demonstrated to give 3-alkylisoxazoles contaminated with appreciable amounts of the 5-substituted isomer.[92/68] Purification of the former can be achieved through alkaline treatment, which cleaves the 5-substituted ring only and leaves the 3-substituted isomer unaffected.

### c. Symmetrical β-Diketones

Oximation of symmetrically substituted β-diketones with the general structure **126** is unequivocal and can furnish only one isoxazole derivative (**127**):

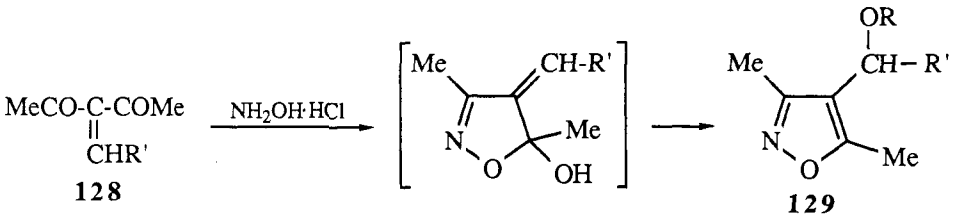



126 127

Because of the ready availability of starting materials, this route is still the most popular synthesis of 3,5-di- and 3,4,5-trisubstituted isoxazoles, especially when the substituent in positions 3 and 5 is an alkyl group. The reaction has wide applicability and is usually carried out by refluxing the alcoholic solution of the β-diketone and hydroxylamine hydrochloride (with or without the addition of potassium carbonate) in equimolar amounts. For example, from acetylacetone,[3/888,4/888,7/21.5/27,28/54,100/68,40/73] dibenzoylmethane,[2/899,5/01,100/68] and di-α-furoyl-[26/52] and di-β-indoloyl-[2/22] methane, excellent yields of 3,5-dimethyl-, 3,5-diphenyl-, 3,5-di-α-furyl-, or 3,5-di-β-indolylisoxazole, respectively, are obtained. A 3,5-diphenylisoxazole $^{13}C$-labeled in the 3 and 5 positions has been prepared successfully from labeled dibenzoylmethane.[147/76]

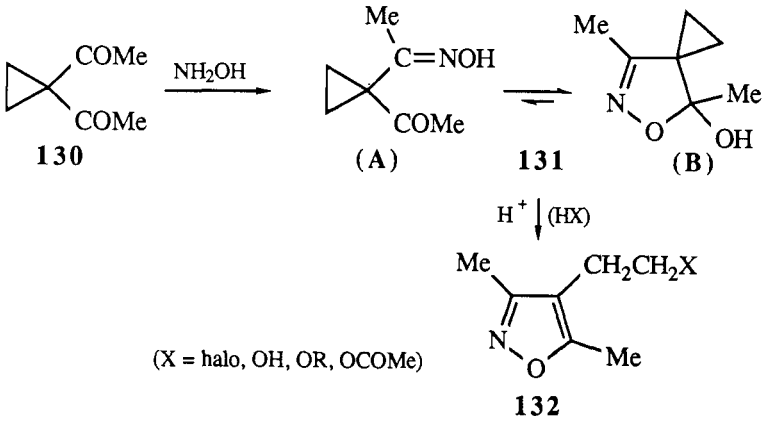
α (or *meso*)-Substituted β-diketones are also easily oximated to 3,4,5-trisubstituted isoxazoles, where the 4-substituent may assume the most variable structures. Thus in addition to alkyl[15/891,76/60,202/66,145/68,161/69,63/73,168/76] or aryl[6/15.3/21,13/56,46/62,89/64,14/76] substituents, several reactive groups, such as nitro,[176/75] chloro,[21/60,93/63] cyano,[175/82] arylazo,[3/25,55/63,106/66,167/70,195/76,137/81] phenacyl,[1/02] or carbalkoxy,[1/893,1/15] can be present in the 4-position of the isoxazole ring. Acidic oximation of tribenzoylmethane is reported to give 3,5-diphenylisoxazole instead of the 4-benzoylderivative expected.[16/73] α-Acetoxy-β-diketones furnish 4-hydroxy-3,5-disubstituted isoxazoles directly by refluxing in an ethanolic solution of hydroxylamine hydrochloride.[148/66,187/71] However, operating at room temperature or in pyridine solution allows isolation of the still acetylated monoxime[187/71] or dioxime,[148/66] which both cyclize readily by heating in an acidic medium. Occasionally, the monoxime or the dioxime has been isolated under controlled conditions.[89/64]

α,β′-Unsaturated β-diketones, such as alkylidene (or arylidene) acetylacetones (**128**), react with hydroxylamine hydrochloride in water or in acetonitrile to give 4-α-hydroxyethyl- (or benzyl)-3,5-dimethylisoxazoles (**129**: R = H).[148/76,165/76] In different solvents, such as methanol or acetic acid, the corresponding α-methoxy (**129**: R = Me) or α-acetoxy (**129**: R = COMe) derivatives are formed:[165/76,49/82]



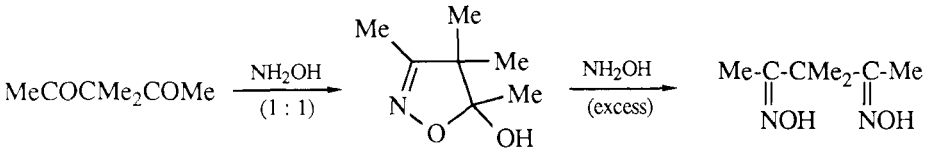

128 129

Oximation of 1,1-diacetylcyclopropane (**130**) proceeds with nucleophilic opening of the cyclopropane ring: when hydroxylamine sulfate is used in a 1% aqueous solution of HX, the corresponding 4-β-halogenoethyl-3,5-dimethylisoxazole (**132**: R = Cl, Br, or I) is obtained in 35–55% yields.[185/81,272/82] With other solvents a β-hydroxy, β-alkoxy, or β-acetoxy derivative can be obtained. The use of free hydroxylamine in absolute ethanol permits separation of the intermediate monoxime, stabilized in its tautomeric form (**131B**), which immediately rearranges to (**132**: X = Cl) upon acidic treatment:[272/82]




**130** (A) **131** (B) **132**

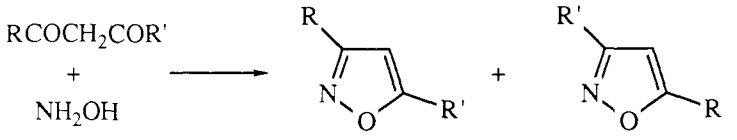
With other α,α-disubstituted β-diketones, the oximation reaction stops at the 5-hydroxy-2-isoxazoline stage, but excess hydroxylamine sometimes leads to the open-chain dioxime,[161/69,24/80] as, for example, in the case of 3,3-dimethylpentan-2,4-dione:[161/69]




The mechanism of the oximation of acetylacetone has been studied kinetically by a flow-NMR technique, and has been demonstrated to involve a nucleophilic addition of hydroxylamine to the carbonyl group, followed by rapid cyclization with subsequent dehydration.[123B/76,237/76] Similar results have been observed by following pH-metrically the oximation of acetylacetone and benzoylacetone with hydroxylamine hydrochloride using methanol–water as solvent.[203/81]

### d. Unsymmetrical β-Diketones

Unless the two terminal groups are very dissimilar for electronic and/or steric effects, the oximation of asymmetrically substituted β-diketones leads to a mixture of the two isomeric isoxazoles:



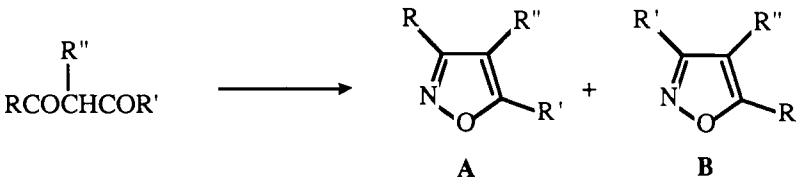

Its composition depends on two main factors, which interplay in a complex manner: the ambident nucleophilicity of hydroxylamine, which can attack the same center with either the nitrogen or the oxygen atom, and the nature of the terminal substituents, which influence the tautomeric equilibration between the two possible enolic forms and the reactivity of the adjacent carbonyl group through both their electronic and steric properties. Of course, both these factors can vary in dependence on the reaction medium and temperature and on the pH.

Whereas the composition of the crude isomeric mixture is relatively easy to determine through chromatographic (GC, TLC, or HPLC) or spectroscopic (MS, NMR, or UV) methods, the preparative separation of the two isomers is usually troublesome and sometimes involves severe losses. This drawback has contributed to the decline of this method in favor of more regioselective syntheses. Nevertheless, when one of the two isomers is formed in large excess, simple purification of the reaction mixture may furnish a single product in consistent yields. In these cases the easy availability of the starting materials makes the oximation of β-diketones very convenient from a preparative point of view. Selected examples of oximation of representative β-diketones are presented in Table 1.62.

The site selectivity of the reaction has often been tentatively related to the direction of enolization of the substrate. In fact, the more electronegative carbonyl group is expected to be the more enolized and should induce the corresponding carbon atom to assume position 5 in the predominant isoxazole isomer. This is, at least qualitatively, corroborated by the experimental results. Nevertheless, keto-enol tautomerism of β-diketones is a complex phenomenon,[227F/70,152B/84] which depends strongly on several factors not easily quantifiable. Moreover, one must take into account kinetic as well as thermodynamic effects, in particular the nucleophilicity of the hydroxylamine species. Therefore, despite the wealth of experimental results, a rigorous rationalization of the reaction mechanism is still lacking.

A somewhat naive rule states that the substituent linked to the more electropositively charged carbonyl group will occupy position 3 in the resulting isoxazole. When the two carbonyl groups possess more or less similar charges, a mixture of the two isomers will result. This rule seems to be valid *in primis* for oximations with hydroxylamine hydrochloride in refluxing alcohol and/or water, and usually holds also for buffered or neutral media. Under the latter conditions, however, the intermediate monoximes (or, more accurately, the ring

TABLE 1.62. ISOXAZOLES FROM ASYMMETRICALLY SUBSTITUTED β-DIKETONES




A B

| R | R' | R" | Reactant[a] | Isolated isoxazole (ratio) | Total yield (%) | References |
|---|---|---|---|---|---|---|
| Me | *n*-Pr | H | HH, excess $K_2CO_3$, Δ | A(77) + B(23) | | 4/02, 32/70 |
| Me | $CMe_3$ | H | HH, MeOH, Δ | A | | 26/56 |
| Et | cyclo-$C_6H_{11}$ | Me | HH, Py, ROH | A + B | | 30/69 |
| Me | 4-norbornenyl | H | HH, EtOH, 60° | A | 90 | 150/75 |
| Me | $CH_2OR$ | H | HH, EtONa, EtOH, Δ | A + B | 60.5 | 4/38, 157/67 |
| Me | $CH_2PPh_3^+Cl^-$ | H | HH, $H_2O$, Δ | A | 71 | 25/80 |
| Me | Ph | H | HH (orHH + Na salt) | A | | 1/884, 2/888, 4/26 |
| Me | Ph | Cl | HH, MeOH, Δ | A | 80 | 93/63 |
| Me | Ar | N=NAr' | HH, NaAc, EtOH/$H_2O$, Δ | A | 51-85 | 171/76, 90B/79, 137/81 |
| Me | 4-pyridyl | H | HH, $Na_2CO_3$, Δ | A | 84 | 143/68 |
| Me | 4-$C_5H_4NMe^+Cl^-$ | H | HH, EtOH, Δ | A(50) + B(50) | 53 | 143/68 |
| $C_6H_5CH_2$ | Ph | H | HH, EtOH, Δ | A | ca. 100 | 3B/01, 155/69 |
| Ph | $CMe_3$ | H | HH, EtOH, Δ | A | | 30/57 |
| 3-$NO_2C_6H_4$ | $CMe_3$ | H | HH, EtOH, Δ | A+B | | 30/57 |
| $CMe_3$ | 4-$MeOC_6H_4$ | H | HH, EtOH, Δ | A | | 30/57 |
| Ph | CH=CHPh | H | HH, EtOH, Δ | A | | 14/13, 2/19 |
| Ph | $CH_2PPh_3^+Cl^-$ | H | HH, EtOH/$H_2O$, 140° | A | 77 | 25/80 |
| Ph | 4-$MeC_6H_4$ | H | HH, MeOH, Δ | A | | 153/70 |
| 2-$HOC_6H_4$ | Ph | H | HH, Py, Δ | A | | 129/83 |
| 4-$NO_2C_6H_4$ | Ph | H | HH, AcOH, AcONa, Δ | A(80) + B(20) | 65 | 1B/04, 153/70, 249/80 |
| Ph | 4-$MeOC_6H_4$ | H | HH, MeOH, Δ | A(71) + B(29) | | 153/70 |
| Ph | 4-$BrC_6H_4$ | H | HH, MeOH, Δ | A(51) + B(49) | | 153/70 |
| Ph | 2-$C_{10}H_7$ | H | $NH_2OH$ | A(50) + B(50) | | 169/75 |
| 4-$NO_2C_6H_4$ | 2-$C_{10}H_7$ | H | $NH_2OH$ | A(75) + B(25) | | 169/75 |
| 2-$C_{10}H_7$ | 4-$MeOC_6H_4$ | H | $NH_2OH$ | A(75) + B(25) | | 169/75 |
| Ph | 2-furyl | H | HH, EtOH/$H_2O$, Δ | A(75) + B(25) | 90 | 88/68 |
| Ph | 2-thienyl | H | HH, MeOH, Δ | A(80) + B(20) | | 108/83 |
| Me | 2-$HOC_6H_4$ | H | HH, boiling Py | A | 79 | 219/74 |
| Ph | 2-$MeC_6H_4$ | H | HH, Py, Δ | A | 84 | 25/77 |
| Ph | 2-$HOOCC_6H_4$ | H | HH, AcOH, Δ | A | 82 | 25/77 |
| 2-$HOC_6H_4$ | 2-furyl | H | HH, Py, Δ | A | 50-60 | 126/82 |
| 2-$HOC_6H_4$ | 2-furyl | H | HH, MeOH, Δ | B | 50-60 | 126/82 |
| 3-pyridyl | 2-$HOC_6H_4$ | H | HH, EtOH, Δ | A(60) + B(40) | 63 | 224/77 |
| 4-pyridyl | 2,4-$(HO)_2C_6H_3$ | H | HH, various pH | A | 60 | 224/77 |
| Me | ferrocenyl | H | HH, Py, 70° | A | 81 | 332/83 |

[a] HH = hydroxylamine hydrochloride.

tautomers 5-hydroxy-2-isoxazolines) or even the dioximes can be obtained as exclusive or accompanying reaction products (see below).

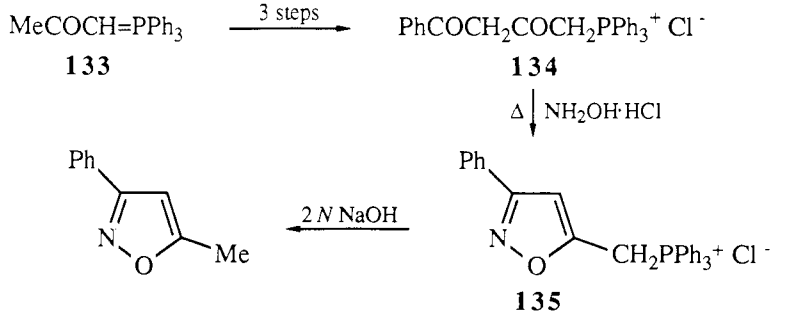
A rather comprehensive study of the oximation of benzoylaroylmethanes of general structure $PhCOCH_2COAr$ has revealed that indeed, the reaction product (or products) depends on the electronic nature of the substituents Ar in the direction stated above. Thus *p*-nitrodibenzoylmethane (−I and −M substituents) gives mainly 3-*p*-nitrophenyl-5-phenylisoxazole, whereas *p*-methyldibenzoylmethane (+I substituent) yields 3-phenyl-5-*p*-tolylisoxazole only. From diketones containing −I and +M substituents, mixtures of the two isomeric 3,5-disubstituted isoxazoles are obtained.[153/70] The isomer ratio has been measured by quantitative UV analysis. Analogous quantitative measurements have been made on the isomer mixtures obtained by oximation (e.g., of β-naphthoylaroylmethane,[169/75] of furoylbenzoylmethanes,[88/68,231/76] and of pyridyl-substituted β-diketones[108/83]).

The effect of the pH value on the oximation reaction should also be taken into account. As a general trend, treatment with hydroxylamine hydrochloride in hot alcoholic solution preferentially yields one isomer only, whereas operating in buffered solution often furnishes a mixture of isomers.

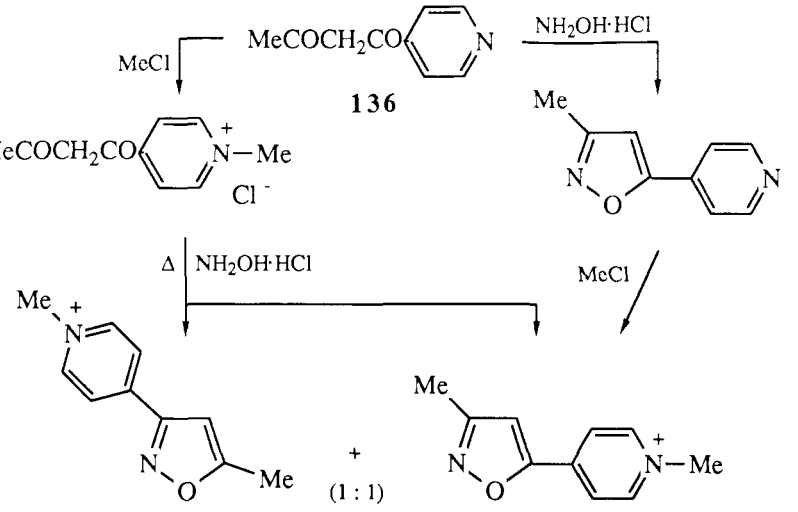
According to expectation, as a rule, aroyl (or acyl)-acetones of general structure $MeCOCH_2COAr(R)$ furnish by oximation 3-methyl-substituted isoxazoles only: for example, benzoylacetone and 4-(4′-pyridyl)butane-2,4-dione yield 3-methyl-5-phenyl-[1/884,2/888,4/26] and 3-methyl-5-(4′-pyridyl)isoxazole,[143/68] respectively. Complexation does not change the direction of the oximation: chromtricarbonylbenzoylacetone gives 3-methyl-5-chromtricarbonylphenylisoxazole.[17/62]

Some exceptions to the foregoing rule are known in the literature, especially when Ar is a heteroaryl group: in some cases formation of a 5-methyl-substituted isoxazole has been reported.[277/74,4/77,61/81,85B/81,125/81,136/81] A mixture of the two isomeric isoxazoles, with a 3-methyl/5-methyl ratio of 3:1, has been obtained by oximation of 2-ethoxy-5-acetoacetylquinoxaline.[12/73] Justified by the strong electron-attracting power of the heteroaryl group is the 3:1 ratio in favor of the 5-methyl isomer, observed in the oximation of 5-nitro-2-acetoacetylthiazole.[7/76] Only the 3-(5′-nitro)furyl-5-methylisoxazole seems to be produced from the nitrofuroylacetone.[102/68]

It is interesting to note that a "reversal" of the normal regiochemistry can be attained by using instead of the free benzoylacetone, for example, the diketophosphonium salt (**134**), which is easily prepared starting from the ylide (**133**):



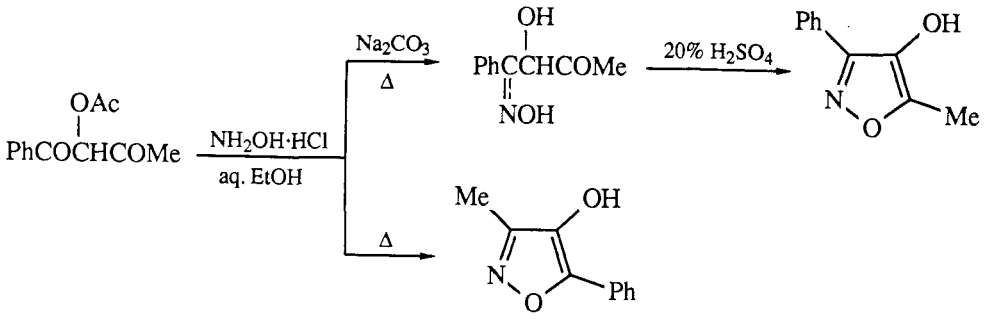
Subsequent treatment of the isoxazole phosphonium salt (**135**) with 2 *N* sodium hydroxide yields 5-methyl-3-phenylisoxazole, contaminated with only a minor amount of the regioisomer.[25/80] In the case of the diketone (**136**) already cited, preventive quaternarization with methyl chloride makes it possible to obtain a 1:1 mixture of the two isomeric methylisoxazolylpyridinium salts (Scheme 1.7).[143/68,24/70] Acetyl- and benzoylpivaloylmethane are oximated to 3-methyl-




**Scheme 1.7**

and 3-pheny-5-*t*-butylisoxazole exclusively, respectively. It is nevertheless enough to introduce a *p*-methoxy group in the latter diketone to invert the site chemistry, the 3-*t*-butyl-5-aryl compound thus being obtained.[30/57]

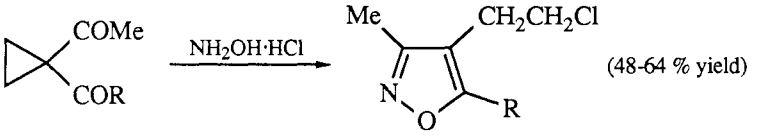
Even slight modification of the experimental conditions can change the site chemistry of the oximation reaction. In this context the example of 2-acetoxy-1-phenylbutane-1,3-dione is particularly noteworthy: treatment with hydroxylamine hydrochloride, neutralized with sodium carbonate, leads to 3-phenyl-5-methyl-4-hydroxyisoxazole through the intermediacy of the monoxime.[148/66] On the other hand, oximation in acidic pH directly gives the regioisomeric 3-methyl-5-phenyl-4-hydroxyisoxazole:[187/71]



When one of the two carbonyl groups is protected through acetalization, attack of the hydroxylamine nitrogen atom occurs on the free carbonyl group.[46/73]

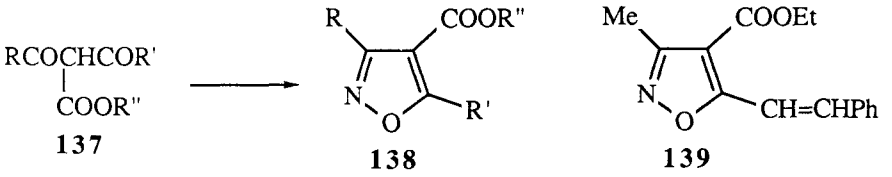
Treatment of aroylacetones with N-substituted hydroxylamines represents a simple direct method for the synthesis of 3,5-disubstituted isoxazolium salts, which are usually isolated as perchlorates in fairly good yields.[43/73] The same method has been utilized for the preparation of 3,5-dimethyl-4-arylazoisoxazolium salts.[195/76]

α,α-Disubstituted β-diketones usually cannot give isoxazoles by oximation, and 5-hydroxy-2-isoxazolines or dioximes are obtained (see § 2.2.2.1, pp. 471–473). Nevertheless, 1,1-diacylcyclopropanes are an exception to this rule, since acid-promoted scission of the cyclopropane ring makes it possible to pull the reaction toward the formation of isoxazole derivatives. Thus, for example, 4-(2-chloroethyl)isoxazoles are the final products of the oximation of 1-acetyl-1-acylcyclopropanes:[243/83]




e. β-Diketo Esters

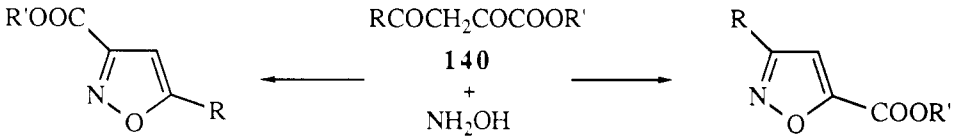
Two types of diketo esters have been used extensively as starting materials for isoxazole synthesis: 2-acyl-3-keto esters (**137**) and 2,4-diketo esters (**140**). α-Acyl-β-keto esters of general formula (**137**) are easily available compounds and contain two systems (i.e., a β-diketone and a β-keto ester moiety) susceptible of reacting with hydroxylamine to give a five-membered heterocycle. As a matter of fact, attack of the nucleophile occurs at the former system only, and alkyl 3,5-disubstituted isoxazole-4-carboxylates (**138**) are the sole product, at least under acidic or buffered conditions. The same result is obtained in the presence of an α,β-ethylenic ketone moiety: for example, a 97% yield of ethyl 3-methyl-5-styrylisoxazole-4-carboxylate (**139**) is obtained by oximation of ethyl α-cinnamoylacetacetate in acetic acid medium.[77/69]




The site selectivity of the oximation reaction follows the general pattern illustrated for simple β-diketones. In the case of unsymmetrical substitution on the two carbonyl groups, the methyl group or the more electron-attracting substituent is inclined to occupy position 3 in the predominant isoxazole deriva-

tive. Thus, for example, ethyl 2-benzoyl (or 2-α-furoyl)-acetacetate is transformed in ethyl 3-methyl-5-phenyl-[2/15,53/62] (or 5-α-furyl-[151/69])isoxazole-4-carboxylate, respectively, in excellent yields. A careful choice of experimental conditions is essential for optimizing yields. For example, pure ethyl 3-methyl-5-*o* (or *m* or *p*)-nitrophenylisoxazole-4-carboxylate is obtained by short heating of the corresponding diketo ester with hydroxylamine hydrochloride in ethanol solution,[12/47,24/60] whereas the same product produced in ethanolic pyridine is contaminated by notable amounts of a degradation product (i.e., 3-*o*-nitrophenyl-5-isoxazolinone).[139/69]

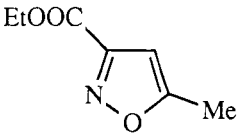
Acyl- or aroylpyruvic acids or esters have long been known to be preferentially oximated on the activated carbonyl adjacent to the carboxy or alkoxycarbonyl group, thus leading to 5-alkyl (or aryl)-isoxazole-3-carboxylic acids or esters. Under particular conditions, however, formation of the isomeric 3-substituted isoxazole-5-carboxylic acid can assume some importance or even become prevalent. Thus the free acetylpyruvic acid (**140**: R = Me; R′ = H) is known to react with hydroxylamine hydrochloride in aqueous solution to form mainly 5-methylisoxazole-3-carboxylic acid:[3/12]



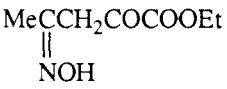

The same product is produced when the corresponding acetylpyruvic ester is heated with hydroxylamine hydrochloride in acetic acid solution.[9/891] Analogous results are obtained with other acylpyruvic acids.[15/46] Benzoylpyruvic acid in a slightly alkaline medium initially furnishes the monoxime, which subsequently cyclizes to 5-phenylisoxazole-3-carboxylic acid.[14/891] Acetylpyruvic acid in a strong acidic medium has, however, been claimed to give 3-methylisoxazole-5-carboxylic acid as the major product.[4/09.1B/10]

The oximation of the 2,4-diketo esters (**140**: R′ ≠ H) has been studied more extensively than that of the free acid. A short treatment of these esters with hydroxylamine hydrochloride in refluxing ethanol is the simplest and most convenient method for synthesizing 5-alkyl (or 5-aryl)-isoxazole-3-carboxylic esters in high yields.[169/82] The oximation of ethyl acetopyruvate has been studied most thoroughly, and the formation of minor amounts of the isomeric 5-carboxylic ester accurately evaluated. In acidic media (e.g., hydroxylamine sulfate in ethanol at room temperature) good to excellent yields of 5-methylisoxazole-3-carboxylic ester (**141**) are always attained.[34F/61.55/61,63/61,34/62,70/65,65/70,137/75,79/78,169/82] On passing from the methyl group to higher alkyl residues, the percentage of 3-alkylisoxazole-5-carboxylic ester in the reaction mixture diminishes with increasing inductive effect of the substituent.[69/63] When free hydroxylamine is used in aqueous solution, ethyl α-hydroxyiminoacetopyruvate (**142**) is formed, which cyclizes at 75°C in the presence of mineral acid to give ethyl 3-methylisoxazole-

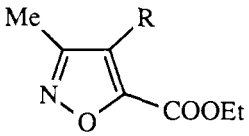
5-carboxylate (**143a**) in good yields.[48/63,68/63] Treatment of the oxime (**142**) with an excess hydroxylamine gives a mixture of the two regioisomers.[204/77]



**141**



**142**



**143 a** R = H
**b** R = Cl

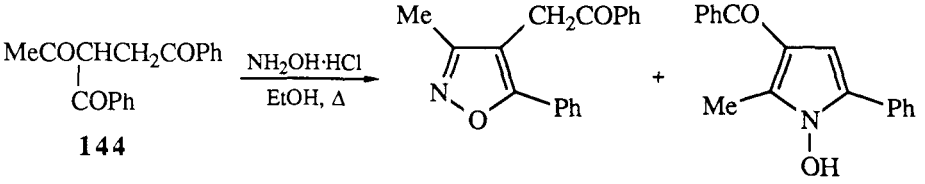
Similar results have been obtained in the oximation of ethyl 2,4-diketo-7-octenoate: hydroxylamine hydrochloride furnishes the 5-butenylisoxazole-3-carboxylate as sole product, whereas free hydroxylamine, followed by acidic treatment, leads to a 7:3 mixture of the two possible isomers, the 3-butenyl-isoxazole-5-carboxylate being the prevalent product.[197/83] Analogously, the pure 5-*n*-pentylisoxazole-3-carboxylate has been obtained in an acidic medium,[162/82,46/83] while a 1:1 mixture of the two isomeric esters is produced by alkaline oximation.[46/83] Furthermore, the two isomeric esters can be separately isolated by oximating under different pH values in the preparation of tridecylisoxazolecarboxylic acids.[19/84]

Surprisingly, reaction of 2-chloroacetopyruvic ester with hydroxylamine in acidic medium does not yield the expected 5-methyl-substituted ester but the isomeric ethyl 4-chloro-3-methylisoxazole-5-carboxylate (**143b**).[4/46] Cinnamoyl-[15/13,3/42,16/46,18/56,38/60] aroyl-,[1B/890,35/58,4/59,46/61,169/82] and heteroaroyl-[32/59,46/61,5/66,30/71,216/78] pyruvates are oximated in acidic (or buffered) medium to the corresponding 5-substituted isoxazole-3-carboxylic esters without exception.

A different claim[80/81] on a material derived from the methyl ester of visnaginone should be regarded as doubtful. Nevertheless, here too, slightly alkaline conditions favor the formation of the regioisomer, as in the preparation of isopropyl 3-phenylisoxazole-5-carboxylate.[208/66]

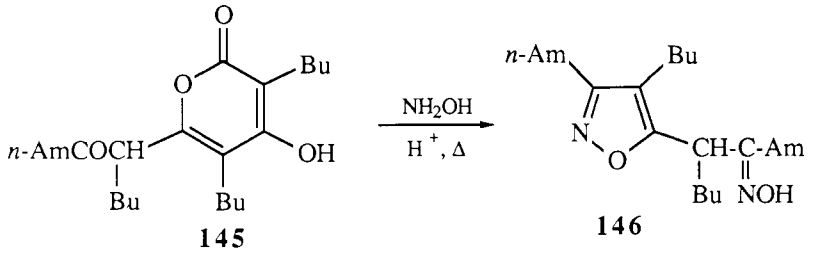
### f. Tri- and Polyketones

Of particular interest are the triketones, which contain both a superimposed $\beta$-diketone and a $\gamma$-diketone moiety. The latter functionality is also reactive toward hydroxylamine, leading to *N*-hydroxypyrrole derivatives. In fact, for example, acetyldiphenacyl (1-phenyl-3-benzoylpentane-1,4-dione, **144**) reacts with hydroxylamine hydrochloride in refluxing aqueous ethanol to give 40% of 3-methyl-4-phenacyl-5-phenylisoxazole and 40% of 1-hydroxy-2-methyl-5-phenyl-3-benzoylpyrrole:[6/66]



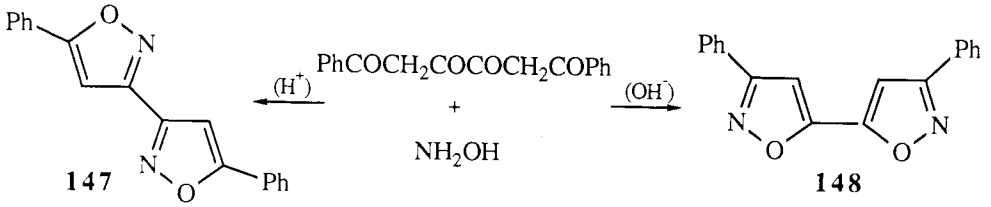
**144**

The structure of the natural product elasnin (**145**), a masked 3,5,7-triketo acid, was confirmed by cyclization to the isoxazole oxime (**146**) with hydroxylamine in acidic media, according to expectation:[202/80]



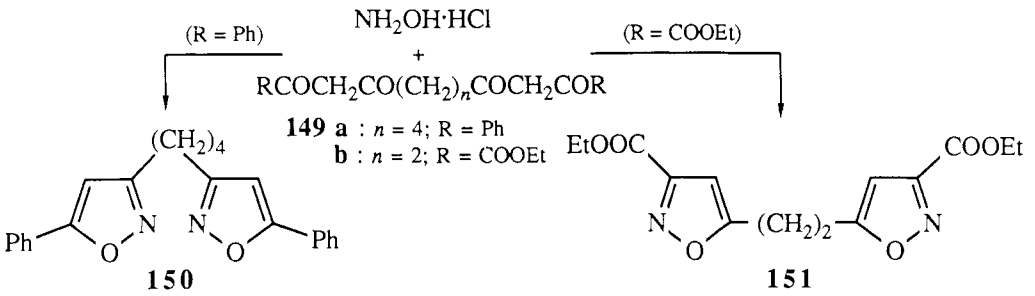

**145** **146**

Diisoxazoles can be prepared by oximation of tetraketones. For example, the reaction of oxalyldiacetone with hydroxylamine hydrochloride gives 5,5′-dimethyl-3,3′-diisoxazole as the main product, together with other products.[9/891,8/46] Under favorable conditions, the intermediate isoxazolyldiketone can be isolated.[9/891] Noteworthy is the behavior of oxalyldiacetophenone on oximation: in an acidic medium the 3,3′-diisoxazole (**147**) is produced, whereas under basic conditions the isomeric 5,5′-diisoxazole (**148**) is formed:[22/59]




**147** **148**

When the two β-diketone moieties are separated by an alkyl chain, they react independently and furnish the regioisomers predicted on the grounds of their presumed preferred enolization. For example, the oximation of adipyldiacetophenone (**149a**) furnishes the 3,3′-diisoxazolylbutane derivative (**150**),[22/59] and that of diethyl 2,4,7,9-tetraketodecandioate (**149b**) the 5.5′-diisoxazolylethane derivative (**151**):[12/56]




**150** **151**

4,4′-Diisoxazole[44/77] and 4,4′-diisoxazolylmethane derivatives[62/63,16/82] have been prepared from branched tetraketones. They are sometimes accompanied by monocyclic hydroxycyclohexanone derivatives, arising from an intramolecular aldol-type reaction.

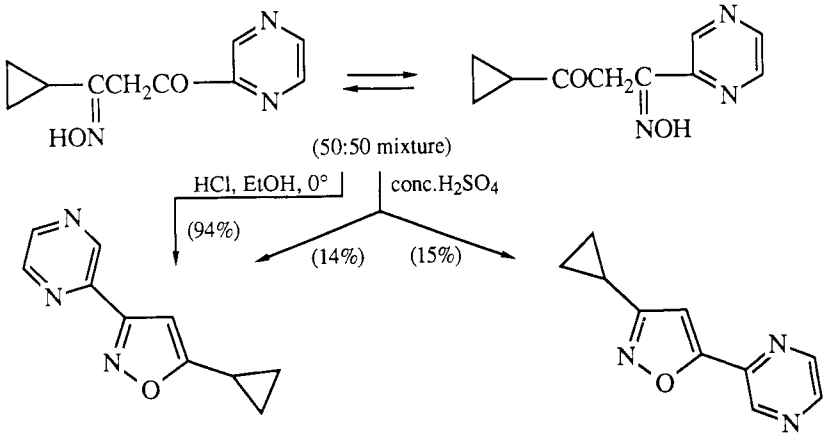
### g. Intermediates and Related Compounds

It is generally accepted that the monoximes of β-diketones are the intermediate products during the oximation process, and indeed sometimes they can be isolated under proper conditions, most commonly by operating in buffered solutions and at lower temperatures. The monoximes are usually unstable compounds, which readily cyclize to the corresponding isoxazoles by treatment with acid or alkali or by heating. When the isoxazole thus obtained in two steps corresponds to the product prepared directly by acidic oximation, there is obviously no real interest in isolating the oxime. However, the separation of the oxime often makes it possible to reach the regioisomeric isoxazole, as noted in earlier sections.

On the other hand, the monoximes are sometimes relatively stable and capable of existence. For example, the presence of a perfluoroalkyl group linked to one of the carbonyl functions stabilizes the intermediate monoxime or its valence tautomer 5-hydroxy-2-isoxazoline, which aromatizes to the corresponding isoxazole in a second step (see also § 1.3.7.1c, pp. 231–233).

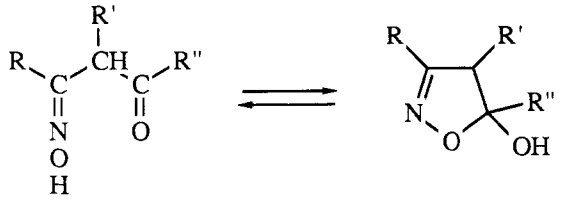
The site selectivity of the oximation reaction is still controversial. In some cases, for example when 4,4,4-trifluoro-1-phenylbutane-1,3-dione is employed as the starting material, final formation of 3-trifluoromethyl-5-phenylisoxazole is reported.[177/77] In other cases, the 5-perfluoroalkyl isomers have been reported.[143/68,129/75] In all these cases acetyl chloride and concentrated sulfuric or polyphosphoric acid[273/76] are the best reagents for accomplishing cyclodehydration to the isoxazole derivatives. Good to excellent yields are usually achieved.

In some cases cyclization is accompanied by ring opening; for example, the oxime of 2-acetyl-1,3-indandione, treated with concentrated sulfuric acid, affords 5-(2-carboxyphenyl)-3-methylisoxazole in 80% yield.[260/81] Peculiar behavior has been recorded for 1-cyclopropyl-1,3-propanediones bearing a pyridyl or a diazinyl residue in position 3. These β-diketones afford a nearby equivalent amount of the two regioisomeric monoximes in mutual equilibrium. Cyclodehydration in concentrated sulfuric acid leads to a mixture of regioisomeric 3,5-disubstituted isoxazoles, reflecting the initial isomeric oximes ratio. By contrast, when the heterocyclic group has a nitrogen in the *ortho* position, treatment of the oximes mixture in refluxing ethanol with a catalytic amount of hydrochloric acid gives 3-heteroaryl-5-cyclopropylisoxazole regiospecifically, as in the following example:[160/77]



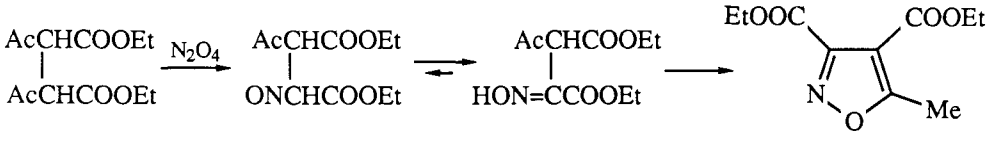

The explanation proposed involves the neighboring group assistance of the *ortho* nitrogen of the heterocyclic ring during the cyclodehydration process.

The ring-chain tautomerism between the two stereoisomeric β-diketone monoximes and the corresponding 5-hydroxy-2-isoxazolines has been studied by spectroscopic methods:[40/69,229/76]

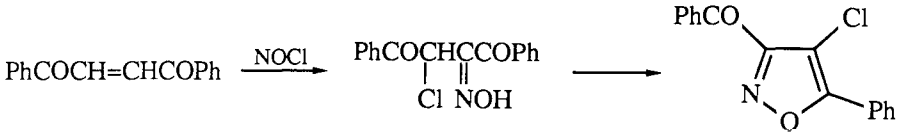


Increasing steric encumbrance of the substituents in position 3, 4, and/or 5 shifts the equilibrium toward the cyclic tautomer, whereas a 5-aryl group favors the chain tautomer, especially when an electron-repelling substituent on the aromatic ring causes the reactivity of the carbonyl group to drop further[229/76] (see also § 2.2.2.1e, p. 472).

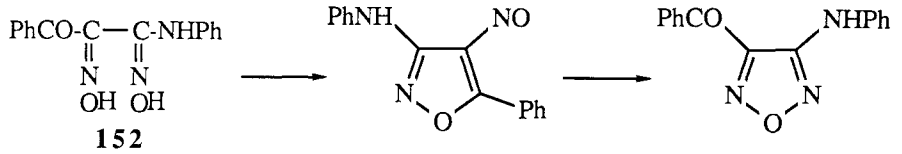
β-Diketone monoximes are not necessarily prepared only by oximation of β-diketones, as the following synthesis of diethyl 5-methylisoxazole-3,4-dicarboxylate from 2,3-diacetylsuccinic ester illustrates:[7/09]



The ability of nitrosyl chloride to add to double bonds is well known, and this reaction can be used for the synthesis of isoxazoles, as exemplified here:[6/54]



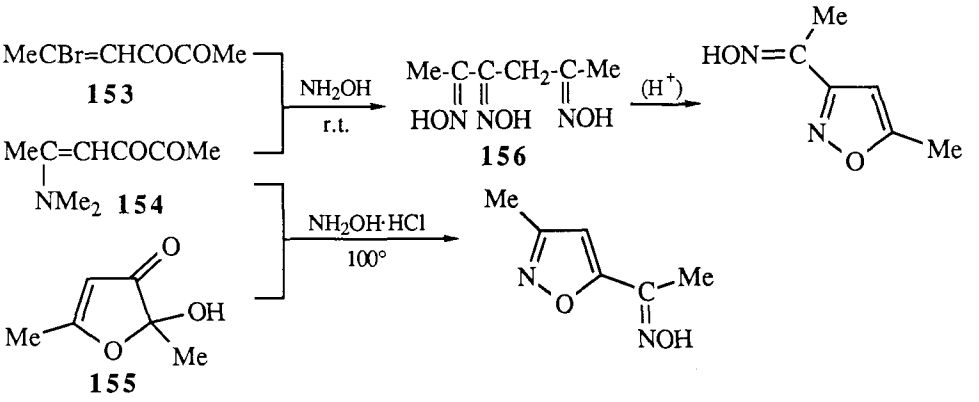

The anilidoxime (**152**), prepared by the reaction of dibenzoylfuroxan with aniline, rearranges in ethanol to the unstable 3-anilino-4-nitroso-5-phenylisoxazole, which spontaneously changes further to 4-anilino-3-benzoyl-1,2,5-oxadiazole:[143/69]



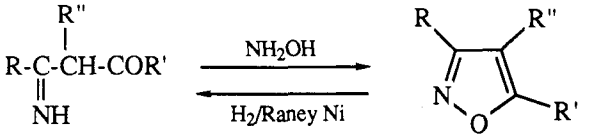

In some instances the isolation of dioximes in the reaction of hydroxylamine with β-diketones has been reported. These include, for example, the dioximes of acetylacetone[1/887,2C/899,6/03] and its α-monosubstituted derivatives,[148/66,118/71] benzoylacetone,[8/33] and difuroylmethane.[26/52] The dioximes yield isoxazoles on heating or when treated with alkali or acid. Thionyl chloride in liquid $SO_2$ has also been used.[19/66] With the same reagent *meso*-disubstituted acetylacetones furnish tetrasubstituted pyrazole-*N*-oxides instead of 5-hydroxyisoxazolines. Treatment of the dioximes with oxidizing phenyliodine-bistrifluoroacetate made it possible to isolate, in addition to the 3,5-disubstituted isoxazoles expected, lower amounts of 4-oxo-4*H*-pyrazole-1,2-dioxides.[57/82]

It is noteworthy that the regiochemistry of dioxime cyclization follows the general pattern already encountered for β-diketones. For example, benzoylacetone dioxime cyclizes to 3-methyl-5-phenylisoxazole in an acidic medium and to 3-phenyl-5-methylisoxazole under basic conditions.[8/33]

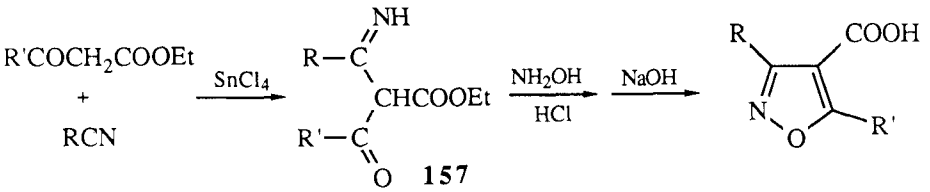
A further example of pH-dependent regiochemistry is shown by hexane-2,3,5-trione or its derivatives. The trioxime (**156**) thereof, available by neutral oximation of the β-enamino derivative (**154**) or of the β-bromoenedione (**153**) at room temperature,[5C/74] cyclizes to the oxime of 3-acetyl-5-methylisoxazole when treated with mineral acids.[5B/40,5C/74] On the contrary, the isomeric oxime of 5-acetyl-3-methylisoxazole is obtained when the enamino compound (**154**) or 2-hydroxyfuran-3-one (**155**)(the hemiacetalic form of hexane-2,3,5-trione) is oximated in an acidic medium at 100°C:[5C/74]




β-Diketone monoimines react with hydroxylamine site selectively; an isoxazole is formed that bears in position 3 the residue initially linked to the imino group:[7/892,4/38,6/41,8/70,248/78]




The method is limited by the low stability and poor accessibility of the starting material, whose most common method of synthesis is hydrogenolytic cleavage of the isoxazole itself (see § 1.4.3.1). Nevertheless, a successful approach to 3,5-disubstituted isoxazole-4-carboxylic acids, representing a useful alternative to the nitrile oxide route, involves the site-specific oximation of the imino tin$^{IV}$ chloride complexes of **157** obtained by $SnCl_4$-catalyzed condensation of aliphatic nitriles to β-keto esters:[248/78]



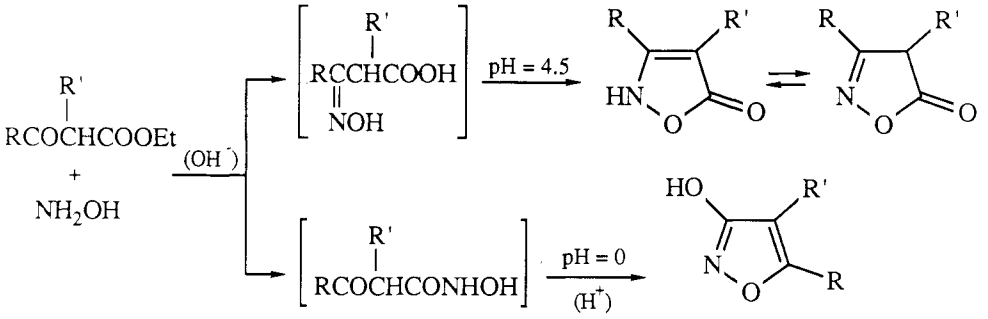

The relative reactivity of free carbonyl and thiocarbonyl groups toward hydroxylamine has been little studied. In monothiodibenzoylmethane the thiocarbonyl group is oximated preferentially.[158/68]

### h. β-Keto Esters and Related Compounds

It is well known that β-keto esters react with hydroxylamine to yield mainly

5-isoxazolinones; for appropriate details, see Part 2 of this work. It must be mentioned here that under proper conditions, the isomeric 3-hydroxyisoxazoles can be produced from the same starting materials. Contrary to the isomeric 5-isoxazolinones, the latter compounds invariably exist in their HO form (see Part 2 of this work).

Whereas α-unsubstituted β-keto esters, with the exception of ethyl γ-cyclopropyl-β-ketopropionate,[30/70] give only 5-isoxazolinones or their condensation products, α-substituted β-keto esters react with hydroxylamine in alkaline media (i.e., in the presence of a more or less large excess of sodium carbonate or hydroxide) to yield a mixture of 4,5-disubstituted 3-hydroxyisoxazoles and 3,4-disubstituted 5-isoxazolinones.[60/61,66/61,97/64,23/67,136/67,130/68,30/70,16/71,1/73] For example, ethyl α-methylacetoacetate yields a mixture of 40% 3-hydroxy-4,5-dimethylisoxazole and 55% 3,4-dimethylisoxazolin-5-one,[23/67] and ethyl α-methyl-β-ketovalerate yields a mixture of 52% 5-ethyl-3-hydroxy-4-methylisoxazole and 41% 3-ethyl-4-methylisoxazolin-5-one.[1/73] A simultaneous and competitive attack of the nucleophile on the carbonyl and on the ester group has been proposed, with formation of an oxime or a hydroxamic acid, respectively. The former cyclizes immediately, giving rise to 5-isoxazolinone when the solution is slightly acidified, and the latter requires strong acidic conditions in order to cyclize:[23/67]



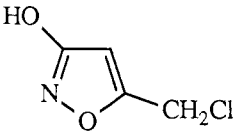
The intermediate β-ketohydroxamic acid is usually not isolated, but can be generated by other routes. 3-Hydroxy-5-methylisoxazole has conveniently been prepared from *O*-benzylacetacetohydroxamic acid, available in turn by condensation of diketene to *O*-benzylhydroxylamine, through catalytic hydrogenolysis and subsequent acid-promoted cyclization:[33/72]



Pure 3-hydroxyisoxazoles, free of isomeric 5-isoxazolinones, can be synthesized by alkaline oximation of ketalized β-keto esters.[124/65,67/67,191/68,26/70,2/74,263/83] The intermediate β-ketohydroxamic acid ketals are usually isolated here, and cyclize by treatment with acids. For example, the synthesis of 5-chloromethyl-3-hydroxyisoxazole, useful for preparing the zwitterionic muscimol, is accomplished through the following steps:[124/65]

$$ClCH_2COCH_2COOEt \xrightarrow{CH(OMe)_3} ClCH_2C(OMe)_2CH_2COOEt \longrightarrow$$

$$\xrightarrow{NH_2OH} ClCH_2C(OMe)_2CH_2CONHOH \xrightarrow[HCl]{AcOH}$$



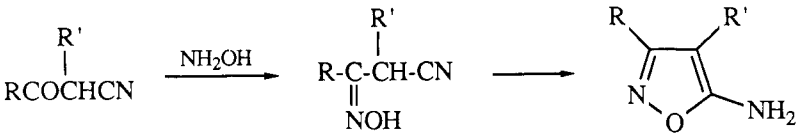
(34% overall yield)

Despite the poor yield obtained in one instance,[3/76] the method is simple and seems to offer large applicability.

When the ester group of the β-keto ester is substituted by a related nitrogen-containing functionality, the oximation reaction produces 5-aminoisoxazoles only. For example, 5-amino-3,4-dimethylisoxazole has been prepared by oximation of the following α-methylacetacetic acid derivatives: amide,[66/60] imino ether,[21/56] and amidine.[46/58] Its *N*-arylsulfonyl derivatives have been achieved analogously starting from the *N*-sulfonylamide[66/60,34B/61] or from the *N*-sulfonylamidine.[22/56]

### i. β-Ketonitriles and β-Iminonitriles

The oximation of β-ketonitriles is the oldest[2/891,10/891] and simplest method of preparing 5-aminoisoxazoles. The reaction initially affords the oxime, which can sometimes be isolated.[11/03] However, under the experimental conditions usually adopted, the oxime cyclizes to the isoxazole derivative:



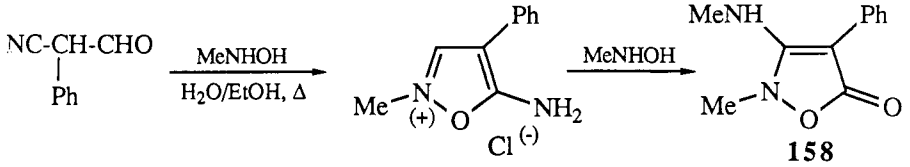
The original procedure[2/891] uses free hydroxylamine in absolute alcoholic (or aqueous)[9/07] solution, but hydroxylamine hydrochloride in pyridine[4/54,179/74] or aqueous ethanol[18/897] also gives good results. Owing to the low stability of 5-aminoisoxazoles toward hydrolytic conditions, the 5-isoxazolinone is sometimes obtained directly[11/03] (see also Part 2 of this work).

The reaction has wide applicability, and thus 3-alkyl-,[9/07,194/68,3/80,78/82] 5-aryl-,[2/891,129/71,149/74,36/76] and 3-heteroaryl-[83/68,52/71,129/71,133/72] 5-aminoisoxazoles have been

prepared with good to excellent yields. Even the 3-unsubstituted 5-aminoisoxazoles can conveniently be prepared by this method, starting from the cyanoacetaldehyde sodium salt and hydroxylamine hydrochloride.[68/82] Reported yields are good to excellent. With some derivatives, such as α-cyanopinacolone, the 3-aminoisoxazole has been claimed to be formed by oximation.[88/82]

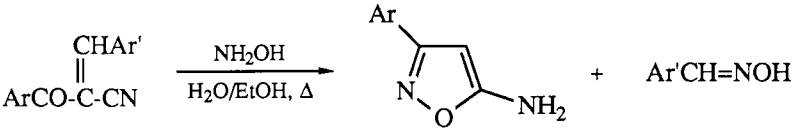
Use of α-monosubstituted β-ketonitriles produces 3,4-disubstituted 5-aminoisoxazoles. Owing to its importance as a starting material in the pharmaceutical industry, the 3,4-dimethyl derivative has been prepared under the most varied conditions.[1/47,14/51,24/52,25/54,1/57,114/80] Other 3,4-dialkyl-,[10/891,1/47] 3-alkyl-4-aryl-,[18/897,4/54,3/56,8/74] 3-aryl-4-alkyl-,[114/80] 3,4-diaryl-,[18/897,128/71,129/71,179/74] and 3-ethoxycarbonyl-4-phenyl-[13/74] 5-aminoisoxazoles have been prepared by this method.

5-Amino-2-methyl-4-phenylisoxazolium chloride has been synthesized by reaction of phenylcyanoacetaldehyde with *N*-methylhydroxylamine hydrochloride;[10/74] use of an excess of the nucleophile gives the isoxazolinone **158**:

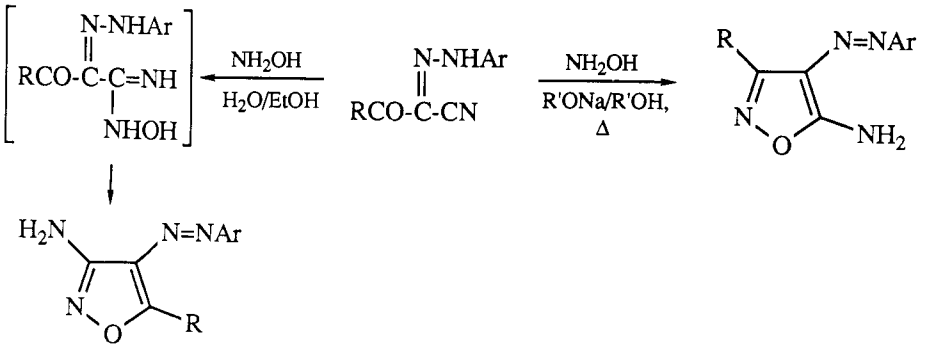



**158**

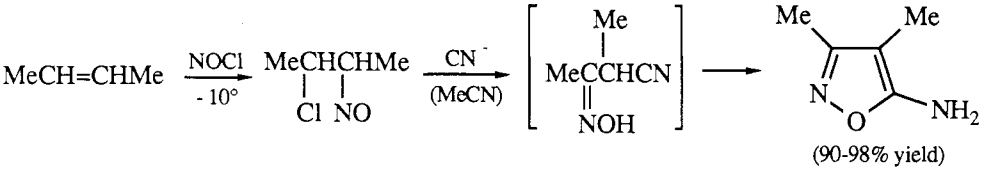
It is worth noting that oximation of the arylidene derivative of aroylacetonitrile under relatively mild conditions leads to the simple 5-amino-3-arylisoxazole, with loss of the corresponding benzaldehyde oxime:[10/52]




Moreover, sometimes either 3- or 5-aminoisoxazoles are formed, depending on experimental conditions. This is the case, for example, for 2-arylhydrazono-3-oxonitriles,[146/75] whose oximation under neutral conditions furnishes, through the intermediacy of the corresponding β-ketoamidoximes, 5-substituted 3-amino-4-arylazoisoxazoles. On the other hand, oximation in the presence of sodium alkoxides leads to the expected 3-substituted 5-amino-4-arylazoisoxazoles in fair yields:

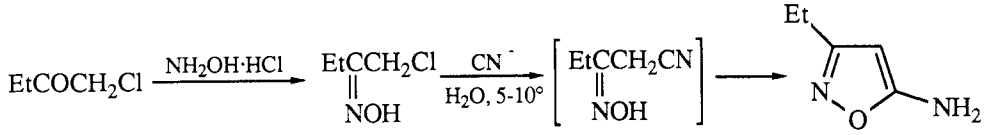


The β-ketonitrile oxime can also be prepared *in situ* and cyclized directly to a 5-aminoisoxazole derivative. Thus an easy, high-yield synthesis of 5-aminoisoxazoles is based on the treatment of α-chlorooximes (or the corresponding nitrosochlorides) with dry potassium or sodium cyanide in aprotic solvents;[85/68,210/69,109/72,135/73,102/74] since the former compounds are readily attainable from olefins and nitrosyl chloride, this method offers a convenient two-step conversion from 1,2-disubstituted olefins to 5-aminoisoxazoles, as, for example:



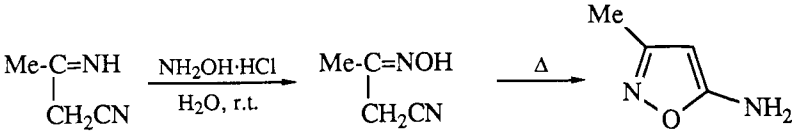
(90-98% yield)

The method is particularly valuable in preparing 3,4-condensed 5-aminoisoxazoles. Of course, the cyclization step requires the presence of a hydrogen atom on the carbon linked to the chloride. Furthermore, terminal olefins are not suitable as starting material because α-chloroaldoximes do not cyclize easily. 4-Unsubstituted 5-aminoisoxazoles can also be synthesized from α-chloroketoximes, as in the following example:[3/80]

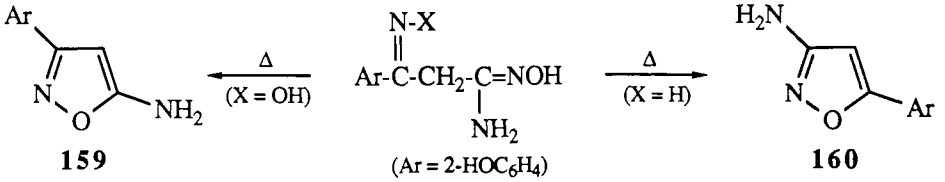


(54% yield)

5-Aminoisoxazoles have also been prepared by oximation of β-iminonitriles,[5/893,12/895,3/898,12/51,31/52,23/56,69/62] easily available by nitrile dimerization through the Thorpe reaction. The reaction conditions are very similar to those used for β-ketonitriles and the intermediate oxime is usually not isolated, as for example:[5/893]

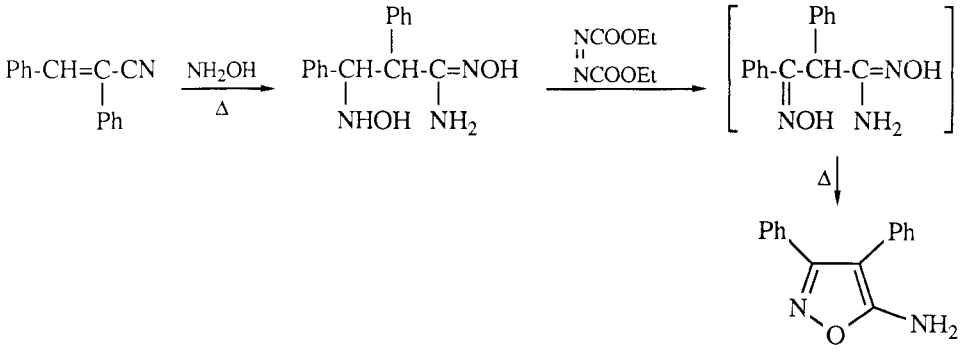



Other derivatives of β-ketonitriles, susceptible of transformation into aminoisoxazoles, are the β-oximinoamidoximes or their β-imino analogues. It is worth noting that in this case heating in ethanol produces the two isomers **159** and **160**, respectively, as shown by the following example:[36/76]

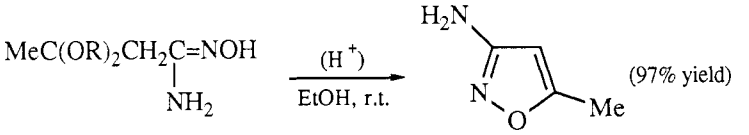


**159** (Ar = 2-HOC6H4) **160**

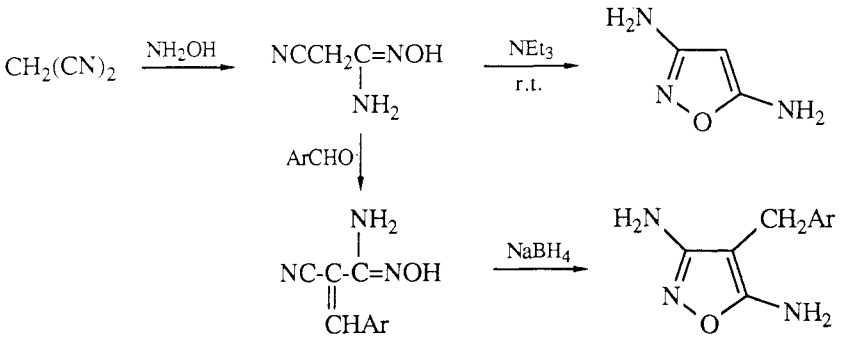
The β-oximinoamidoximes can be also prepared *in situ* by dehydrogenation of the corresponding hydroxylamino derivatives, as, for example:[12/74]



Excellent yields of 3-aminoisoxazoles have been reported by mild acidic treatment of the ketalized β-ketoamidoximes, as, for example:[227/83]



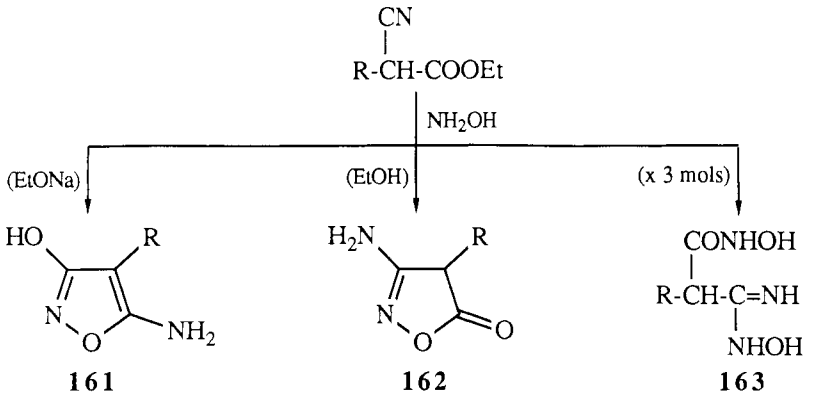
The synthesis of 3,5-diaminoisoxazole hydrochloride has been accomplished by base-promoted cyclization of 2-cyanoacetamidoxime, obtained in turn by carefully controlled oximation of malononitrile:[89/65]



Introduction of a benzyl group in position 4 could be achieved through the cyanoamidoxime arylidene derivative, whose treatment with sodium borohydride resulted in reduction and concomitant cyclization.

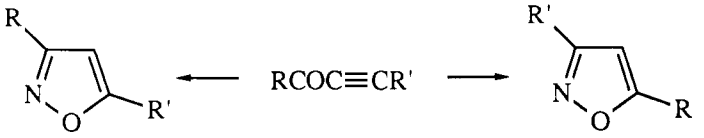
The oximation of α-cyanocarboxylic esters yields different products according to experimental conditions: the reaction in the presence of sodium ethoxide

leads to 5-amino-3-hydroxyisoxazoles (**161**), whereas the reaction in a neutral medium produces the isomeric 3-amino-5-isoxazolinone (**162**). Operating with a threefold excess of hydroxylamine causes the reaction to shift toward the amidoxime-hydroxamic acid (**163**):[51/61]



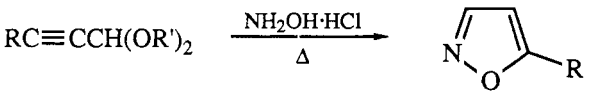

### *1.3.1.2 Oximation of α,β-Acetylenic Carbonyl (and Related) Compounds*

The oximation of α,β-acetylenic aldehydes or ketones is one of the longest known syntheses of isoxazole derivatives. However, the trouble with it is that hydroxylamine can attack both the carbonyl and the triple bond, giving rise to either a 1,2- or a 1,4-addition. Moreover, depending on the pH of the medium, hydroxylamine acts as a bidentate nucleophile. When the two functional groups of the unsaturated carbonyl compound are differently substituted, two isomeric 3,5-disubstituted isoxazoles are the possible products, and the formation of one or the other or a mixture of both depends mainly on the reaction medium and on the nature of the substituents:



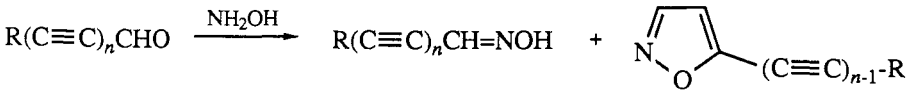

Although no systematic study has been undertaken, some preferential trends can be evidenced from the wealth of experimental data.

Acetylenic aldehydes or, better, their acetals, easily obtainable from acetylenic Grignard reagents and ethyl orthoformate, condense with hydroxylamine hydrochloride to give, without appreciable exceptions, 3-unsubstituted isoxazoles:[3/04,53B/58,49/59,54B/69,154/72,69/74,20/79]



Isoxazole itself has been produced starting from propargylaldehyde[1/49] or from its diethylacetal.[7/03] The phenylpropiolic aldoxime has been isolated as an apparent intermediate in the reaction of hydroxylamine with phenylpropiolaldehyde,[7/03] and is readily converted into 5-phenylisoxazole by treatment with a trace of alkali.[7/03,5/25]

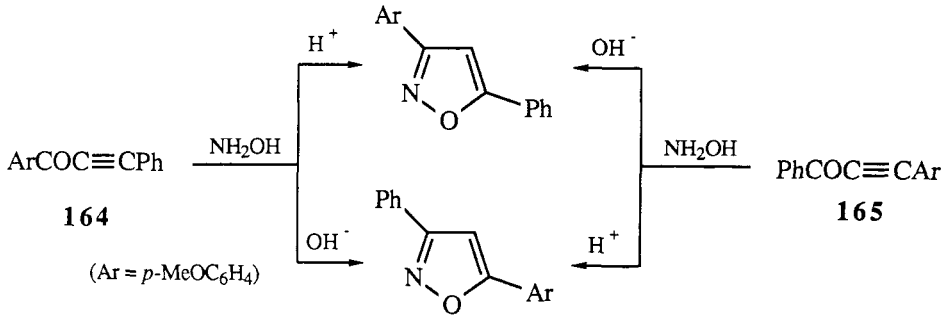
The behavior of the phenylpropiolic aldehyde and of other di- and triynals toward hydroxylamine has recently been investigated more thoroughly.[105/81] A mixture of the *E*- and *Z*-oximes and of 5-substituted isoxazoles is obtained under both acidic and basic conditions in comparable yields, as the following scheme shows:



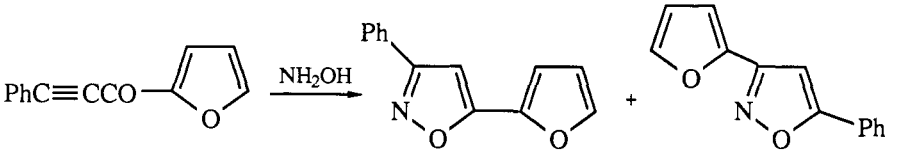
| | | Yield in: | | |
|---|---|---|---|---|
| *n* | | *E*-oxime | *Z*-oxime | Isoxazole |
| 1 | R = Ph | 20 | 13 | 4 |
| 2 | R = Ph | 21 | 17 | 17 |
| 2 | R = CH=CHCOOMe | 15 | 15 | 10 |
| 3 | R = CH=CHCOOMe | 15 | 18 | 5 |

The behavior of acetylenic ketones is less straighforward. As a broad general rule, treatment with a hot alcoholic solution of hydroxylamine hydrochloride (occasionally also in pyridine) furnishes, exclusively or predominantly, the isoxazole isomer arising from attack by the hydroxylamine nitrogen on the carbonyl group. In a basic solution ($Na_2CO_3$ or NaOH) attack on the $\beta$-carbon of the triple bond is preferred, and the other isomer is formed.

In some individual cases the formation of two isomers under different conditions is adequately documented. For example, 3-*p*-methoxyphenyl-5-phenylisoxazole is obtained by acidic oximation of **164** and neutral or basic oximation of **165**, whereas, conversely, the isomeric 5-*p*-methoxyphenyl-3-phenylisoxazole arises from **164** in basic or neutral or acetic media and from **165** in strong acidic media:[3/27]

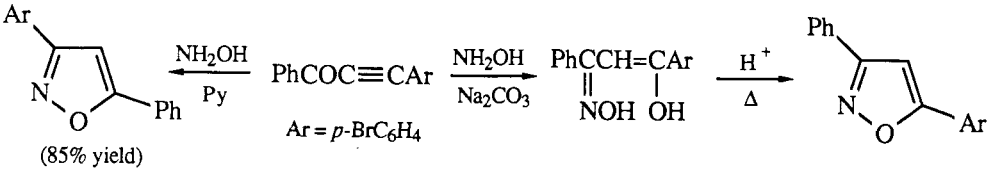


The two isomeric phenyl-α-furyl-isoxazoles are obtained by oximation of phenylfuroylacetylene in the following proportions:[88/68]

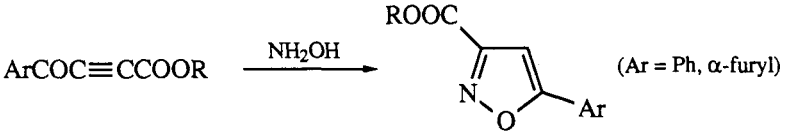


| conditions: | (HCl) | < 5% | 78% yield |
|---|---|---|---|
| | (KOH) | 46.5% | 15.5% yield |

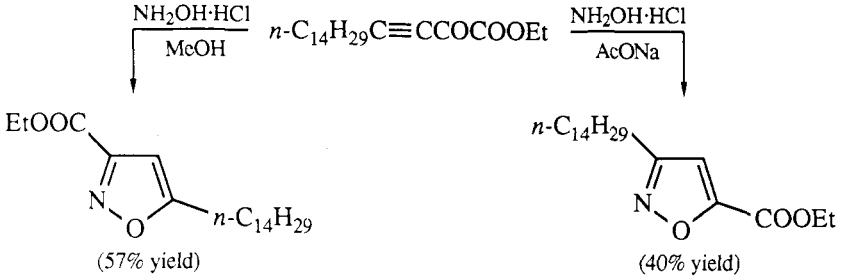
Furthermore, *p*-bromobenzoylphenylacetylene reacts with hydroxylamine in pyridine to give 3-*p*-bromophenyl-5-phenylisoxazole directly, whereas oximation in the presence of sodium carbonate allows the isolation of an intermediate hydroxychalcone oxime, easily cyclizable under acidic conditions to the isomeric isoxazole:[131/68]



Nevertheless, steric hindrance or electronic effects can reverse the site selectivity illustrated above. For example, oximation of phenyl-α-naphthoylacetylene (even in pyridine solution) affords 3-phenyl-5-α-naphthylisoxazole as the sole product.[131/68] Aroylpropiolic esters, at least in the two examples studied, are oximated to isoxazole-3-carboxylates in neutral or buffered solution:[12/50,30/71]



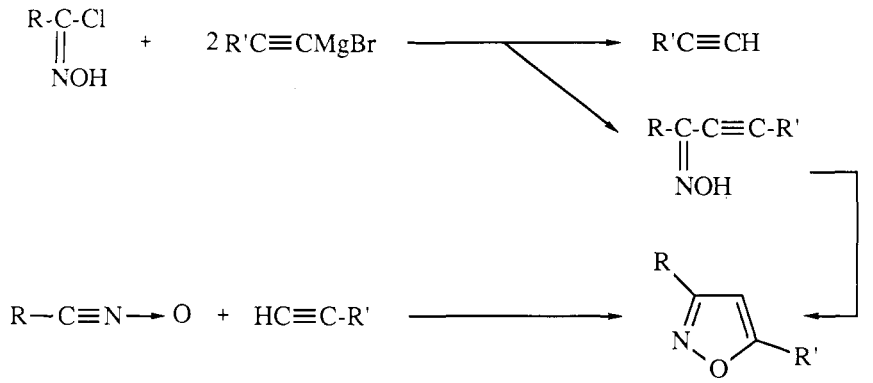
On the other hand, acetylenic α-keto esters behave normally, as the following example on ethyl 2-oxo-3-octadecynoate shows:[171/70]



The formation of a 5-hydroxyisoxazoline, which dehydrates thermally, has also been observed in the oximation of 1,5-diphenylpentadiyn-3-one;[3/68] the corresponding enynic ketone (i.e., 1,5-diphenylpentenyn-3-one) adds 2 mol of hydroxylamine, 1 mol giving the isoxazole ring and 1 mol adding to the double bond. The structural assignment is, however, still uncertain.[6/45,3/68] The two isomeric 3- and 5-ferrocenylisoxazoles have been prepared by operating under different pH values.[56/62]

In several other cases of oximation of acetylenic ketones, only one of the two isomers has been obtained. Attacks of hydroxylamine nitrogen on both the carbonyl group[8/03,9/03,2/04,6/04,6/45,176/67,100B/69,20/71,155/71,20/79] and the triple bond [12/46,208/66,109/68,220B/73,225/75] have been postulated and the corresponding structures asserted. Caution should be exerted in trusting these results, especially the older ones, since the structural assignments are not always supported by rigorous chemical and spectroscopic proofs.

The $\alpha,\beta$-acetylenic oximes, although often invoked as intermediates in the oximation reaction of acetylenic ketones, have been isolated only occasionally.[20/79] They can conveniently be prepared in their *syn*-triple-bond configuration by cautious addition of hydroximic acid chlorides to 2 mol of acetylenic Grignard reagents at 0°C,[219/70] and are also often present as by-products in the reaction of nitrile oxides with 1-alkynes[207/69,194B/70] (see also § 1.3.2.1, pp. 183–184). Acetylenic oximes are relatively stable compounds only at low temperatures, in a neutral or acidic medium. Traces of bases (inorganic or organic), long standing at room temperature, chromatography on alumina, or short heating induce easy cyclization to the corresponding 3,5-disubstituted isoxazoles:[89/69,207/69,194B/70,219/70,178/72,44/73]

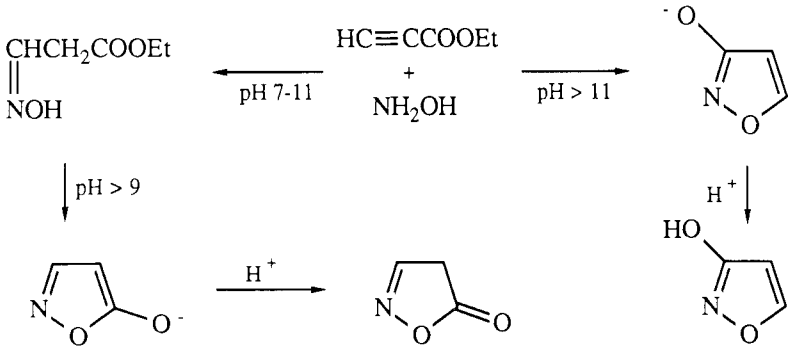



The cyclization reaction has been studied kinetically,[216/70,110/71,112/71] and was shown to be solvent dependent and base catalyzed.

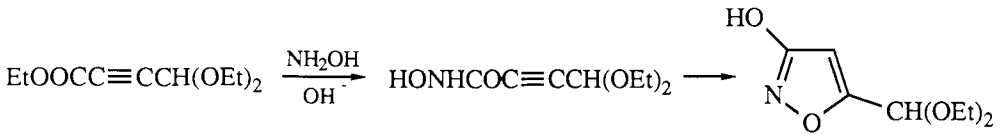
Both 1-alkoxy- and 1-dialkylaminobutenynes and their substituted homologues are masked ketoaldehydes and are consequently oximated in acidic medium to the corresponding 3 (or 5)-monosubstituted isoxazoles.[230/69,258/70,62/72,273/74] Oximation of $\alpha,\beta$-acetylenic carboxylic esters shows a twofold

aspect. In a neutral or slightly alkaline medium (pH < 11) attack occurs on the triple bond and 5-isoxazolinones are produced through the intermediacy of $\beta$-keto ester oximes (see Part 2 of this work); in an acidic medium the reaction is too slow to be useful.

By contrast, the reaction in the presence of bases is very fast, and after acidification affords 3-hydroxyisoxazoles, presumably formed through an intermediate acetylenic hydroxamate. Thus ethyl propiolate, for example, is oximated at about pH 8.3 to ethyl 3-hydroximinopropionate, which cyclizes to 5-isoxazolinone under basic treatment followed by acidification;[116/71] by contrast, use of aqueous ethanolic sodium or potassium hydroxide yields, after acidification, 3-hydroxyisoxazole:



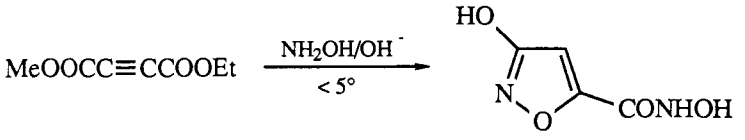

Several other 5-substituted 3-hydroxyisoxazoles have thus been prepared;[42/66,126/66,132/66,124/68,239/81] calcium hydroxide[74/70] has also been reported to act as a condenser instead of sodium or potassium hydroxides. It is worth noting that a triple bond, substituted on one side with an acetal function and on the other side with a carbethoxy group, when attacked by hydroxylamine, furnishes 3-hydroxyisoxazole-5-carboxaldehyde diethylacetal. The intermediate hydroxamic acid can be isolated by operating at 10–15°C instead of 30°C.[39/66,34/67,122/68]



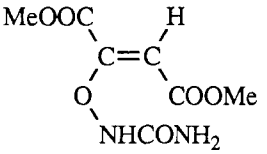

This reaction is the first step of a convenient synthesis of the important natural product ibotenic acid. A $^{14}C$-labeled 3-hydroxy-5-methylisoxazole (hymexazole, an important fungicide) has been prepared by this route, starting from sodium methylacetylide and labeled carbon dioxide.[214/73]

The reaction of dimethyl acetylenedicarboxylate with 2 mol of hydroxylamine in an alkaline medium proved rather sluggish and furnished a mixture of

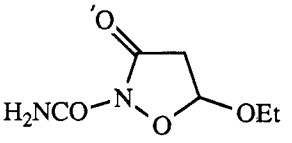
products;[178/77] however, under strictly controlled experimental conditions, the yield of 3-hydroxy-5-isoxazole hydroxamic acid is raised up to 51%, allowing a convenient two-step synthesis of the natural product muscimol (**2**), an important cyclic analogue of $\gamma$-aminobutyric acid:[263/82]



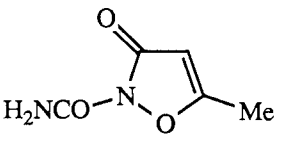

The use of *N*-hydroxyurea as a nucleophile modifies the results somewhat. This compound reacts under basic conditions through its anion $NH_2CONHO^-$, which attacks the $\beta$-position of the acetylenic bond. When dimethyl acetylenedicarboxylate is employed as a starting material, the intermediate (**166**) (isolable in low yields) cyclizes to methyl 3-hydroxyisoxazole-5-carboxylate,[33/80,13/82] and analogous results are obtained with methyl phenylpropiolate.[23/81] Ethyl propiolate or tetrolate also furnish 2-carbamido-3-isoxazolinone derivatives (**167** or **168**), respectively:[23/81]




**166**

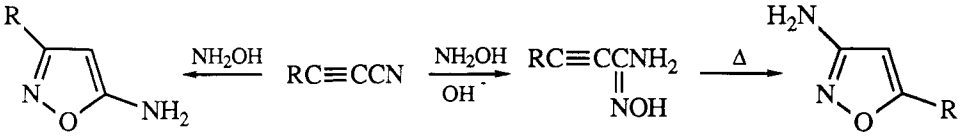



**167**




**168**

$\alpha,\beta$-Acetylenic nitriles (i.e., 1-cyanoalkynes) mimic the acetylenic esters in their behavior in the oximation. In acidic or neutral media the triple bond is attacked exclusively, leading to 5-aminoisoxazole derivatives. An excess of base, such as sodium hydroxide, switches on the nucleophilic attack prevailingly toward the cyano group, thus producing the amidoxime or, directly, the corresponding 3-aminoisoxazole:[9/07,42/66,59/66,60B/66,125/66,162/73]

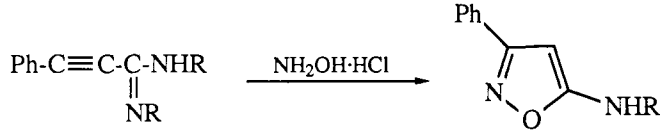



(R = H, Me, Ph, Ar)

Sometimes a mixture of the two isomers is obtained, the ratio depending sharply on the solvent, the pH of the medium, and the temperature.[75/84]

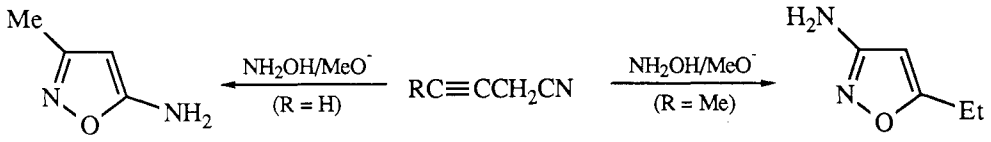
Here, too, *N*-hydroxyurea or *N*-hydroxyurethane can conveniently replace hydroxylamine in the preparation of 3-aminoisoxazoles.[180/71,203/74] Acetylenic

amidines are a convenient starting material for the synthesis of N-substituted 5-aminoisoxazoles, oximation under acidic conditions being adopted here:[28/72]




(37-55% yield)

It is worth noting that even β,γ-acetylenic nitriles can produce aminoisoxazoles by oximation. For example, propargyl cyanide is oximated in the presence of sodium methoxide to yield 5-amino-3-methylisoxazole; on the other hand, oximation of 3-pentynonitrile under the same conditions affords 3-amino-5-ethylisoxazole:[32/68]

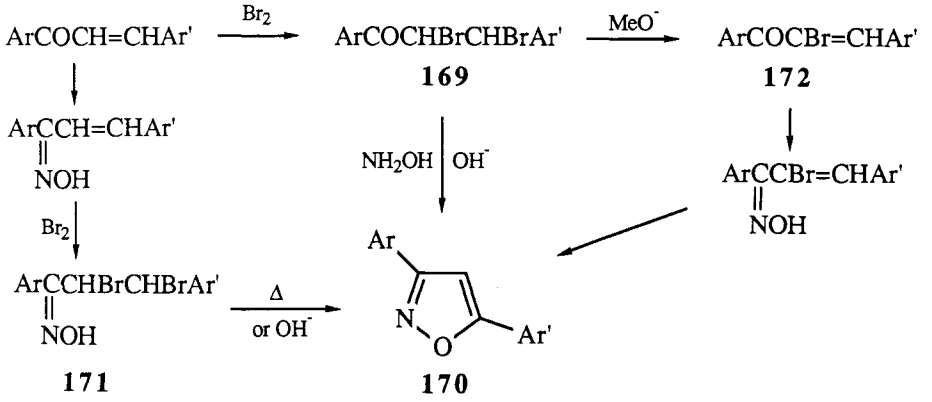



### *1.3.1.3 Oximation of α,β-Dihalocarbonyl (and Related) Compounds*

It has long been known[5/895,1B/900,3/27,10/27] that α,β-dihalo ketones readily give 3,5-disubstituted isoxazoles when heated with hydroxylamine in the presence of alkali. The more reactive dibromides, easily obtainable by bromination of the unsaturated ketones, have commonly been employed instead of the chlorides. This reaction has frequently been applied for the synthesis of unsymmetrical 3,5-diarylisoxazoles in order to prove the structure of the isoxazoles formed in the oximation reaction of asymmetrical 1,3-diketones. Because of their easy availability, chalcone dibromides (**169**) have most often been utilized. The reaction is generally considered highly site selective, since usually only the isoxazole (**170**), derived from the attack of hydroxylamine nitrogen to the carbonyl group, is obtained.[3/27,2/32,3/34,12/37,18/40,96/65,18/68,100/68,131/68,172/68,153/70,196/71,160/72,173/73,185/74,169/75,60B/76,25/77,11/79,125/80,187/80,249/80,77/81,204/81,1/83,57/83] As a matter of fact, this technique[8/49] makes it possible for us to rectify the incorrectly assigned structures of several 3,5-diarylisoxazoles obtained from 1,3-diketones.[5/43,6/43,3/45,4/45,5/45] Nevertheless, this method is not unequivocal, since some structures attributed to hydroxy-substituted diarylisoxazoles on this basis have later been found to be isomeric.[200/81,201/81]

Mononitro-substituted chalcone dibromides have been reported to yield a mixture of the two possible isomers.[249/80] This fact has been attributed to both the substituent effect and possibly the base-promoted formation of the β-diketone *prior* to cyclization. To assure the right structure, comparison with

isoxazoles obtained by another route is often useful,[131/68] for instance with those from the nitrile oxide synthesis, which possess an unequivocal substituent in the 3-position:

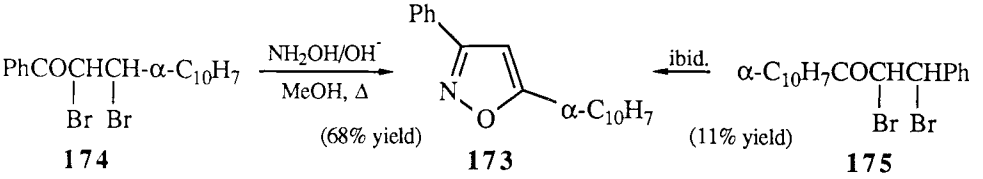



Mass spectrometric[192/70,249/80] and $^{13}$C-NMR[187/80] analyses can also be used to assign the correct structure to 3,5-diarylisoxazole.

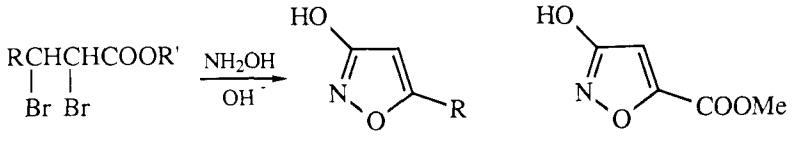
α-Bromochalcones (**172**) have been suggested to be intermediates in this reaction[10/27] and can in fact be isolated either by dehydrobromination of chalcone dibromides with sodium methoxide or by direct bromination of chalcones with tetrabromo-*o*-benzoquinone.[96/77] By treatment with hydroxylamine in the presence of alkali they give the same isoxazoles (**170**), which are formed on direct oximation of the dibromides.[8/49,96/77]

Use of pyridine as a base in the oximation reaction brings about complications, giving rise to the formation of isoxazolines and to nuclear bromination.[102/70] The oximes of chalcone dibromides (**171**), in turn, yield isoxazoles (**170**) on heating above their melting point or on treatment with alkali.[1/30,6/31,7/31,8/49]

Oximation of partially alkylated α,β-dibromo ketones (or aldehydes) does not change the site specificity of the reaction, and exclusive attack on the carbonyl group is observed.[30/57,18/59,56/68] However, steric hindrance can sometimes reverse the site selectivity, as the example of 3-phenyl-5-α-naphthylisoxazole (**173**) illustrates. This compound is obtained from both isomeric chalcone dibromides (**174** and **175**), the latter reacting more slowly and with lower yields:[131/68]



5-Substituted 3-hydroxyisoxazoles are produced in moderate yields by oximation of the suitable α,β-dihalogenopropionic esters in alkaline media:[12/70]

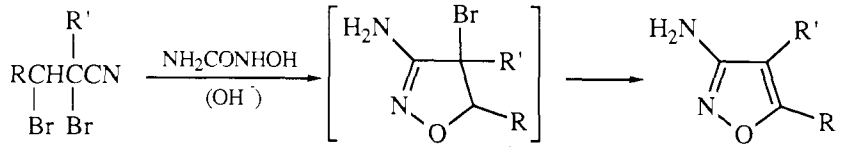



**176**

Excellent yields of methyl 3-hydroxyisoxazole-5-carboxylate (**176**) are, moreover, obtained by treatment of dimethyl 2,3-dibromosuccinate with *N*-hydroxyurea in the presence of sodium methoxide.[33/80]

α,β-Dibromocarbonitriles react with hydroxylamine in a neutral or alkaline medium to yield a mixture of 3- and 5-aminoisoxazole derivatives, which must be separated by chromatography; for example, a 50% yield of 3-amino-5-methylisoxazole is obtained starting from 2,3-dibromobutyronitrile,[32/73] whereas use of hydroxylamine and excess sodium hydroxide on 2,3-dibromo-3-phenylpropionitrile afforded a 36% yield of 5-amino-3-phenylisoxazole together with a 13% yield of the isomeric 3-amino-5-phenylisoxazole.[188/70]

Far better results are obtained with *N*-hydroxyurea, which in the presence of sodium hydroxide yields the 3-aminoisoxazole compound as the sole product,[102/65.105/65.180/66.188/70.92/74] presumably through an intermediate 4-bromoisoxazoline:[188/70]

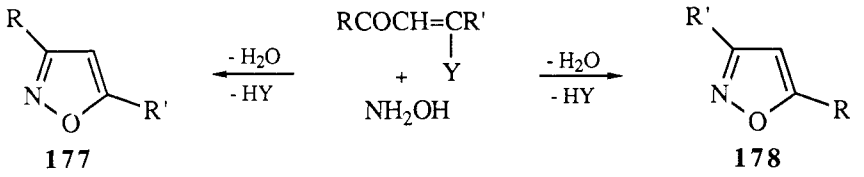



| R | R' | % |
|---|---|---|
| Me | H | 59-75 |
| H | H | 62 |
| H | Me | 61 |
| Ph | H | 56-58 |
| Ph | Ph | 25 |

### *1.3.1.4 Oximation of α,β-Ethylenic Carbonyl (and Related) Compounds β-Substituted with Electron-Withdrawing Groups*

α,β-Unsaturated aldehydes or ketones, carrying an electron-withdrawing group in the β-position, offer two sites prone to attack by nucleophiles: the carbonyl group and the positively charged carbon linked to the electron-withdrawing group. Consequently, this type of compound reacts readily with hyd-

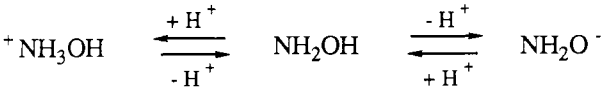
roxylamine, yielding isoxazoles of general formula **177** and/or isoxazoles (**178**) as follows:




The prevailing or exclusive formation of one or the other isomer depends on the nature of Y, R, and R′, and both electronic and steric factors seem to be involved.

The longest known starting materials for this isoxazole synthesis are the β-halogenated α,β-ethylenic aldehydes or ketones (Y = Cl or Br), but more recently β-alkoxy (Y = OR″) and β-dialkylamino or β-anilino derivatives (Y = $NR''_2$ or NHAr) are being used increasingly. Roughly, it can be stated that the site selectivity of the addition increases in the sequence halogen < OR″ < $NR''_2$, NHAr.

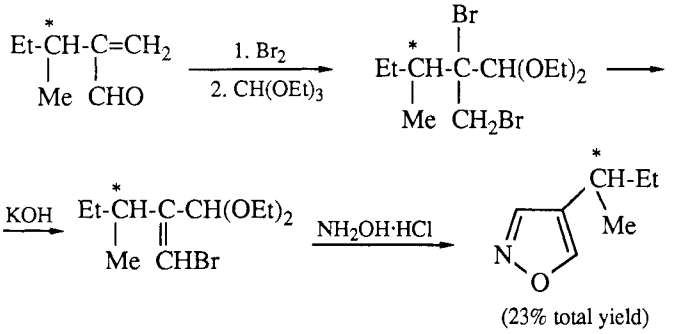
A noteworthy effort toward rationalization of the reaction has recently been made by attempting to correlate the site selectivity with both the nature of the leaving group Y and with a shift of the nucleophilic center in dependence on the pH of the reaction medium. In fact, hydroxylamine is an ambident nucleophile, owing to the following equilibrium:




An extensive and systematic investigation of the oximation of β-substituted enones under various conditions has demonstrated that a mixture of the two regioisomers is always obtained, although the site selection may be strong in some cases, especially when the substituents at the ends of the enone system are electronically very different. As a general rule, when the leaving group Y is OR or SR, an acidic or alkaline medium provokes a prevalence of the isoxazole **177**, having in position 3 the substituent initially linked to the carbonyl group, whereas under neutral conditions the isoxazole (**178**), which has the β-substituent in position 3, more or less prevails. When the leaving group Y is an amino residue (e.g., anilino, ethylamino, pyrrolidino), under any pH conditions the reaction gives the isoxazole **178**.[40/82] A reaction mechanism has been postulated involving, under any conditions, an attack on the β-carbon atom of β-enones either from the nitrogen or from the oxygen atom of hydroxylamine, with subsequent cyclization to an isoxazoline derivative and final elimination.[105/83]

### a. β-Halo-α,β-Ethylenic Aldehydes

When heated with aqueous hydroxylamine hydrochloride, β-chloroacrolein readily gives isoxazole,[26B/56] and α-methyl-β-bromoacrolein gives 4-methylisoxazole.[8/51] The method has been applied to the preparation of the optically active 4-*sec*-butylisoxazole, starting from the appropriate α-substituted acrolein:[37/67]



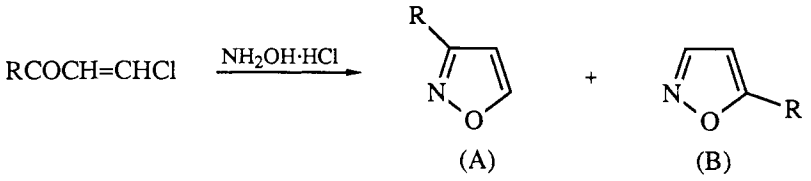

(23% total yield)

The ethoxychloromethyl group can be used instead of the free carbonyl group.[256/73]

α,β-Disubstituted acroleins yield only 4,5-disubstituted isoxazoles, the aldehyde group being attacked exclusively by the hydroxylamine.[120/64] The cyclization requires acidic conditions, whereas in an alkaline medium the reaction is reported to stop at the oxime step.[134/66] In another instance the intermediate oxime has been isolated and cyclized by treatment with methanolic sodium methoxide.[15/70]

### b. β-Halo-α,β-Ethylenic Ketones

As is well known, β-chlorovinyl ketones are readily available through condensation of acyl chlorides to acetylenes in the presence of aluminum trichloride. Oximation of aliphatic β-chlorovinyl ketones RCOCH=CHCl usually yields a mixture of two isomers, 3- and 5-alkylisoxazole:



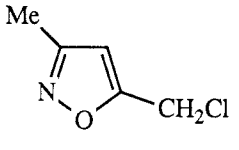

(A) (B)

The isomer ratio has not always been determined exactly, and no systematic study of the influence of electronic and/or steric factors is known; some data are reported in Table 1.63. A slight tendency toward 1,4- rather than 1,2-addition can be deduced, and acidic conditions are usually adopted. Some substituted

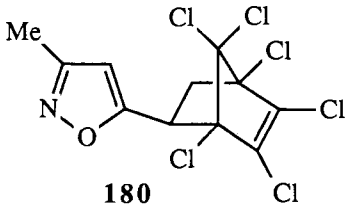
TABLE 1.63. SYNTHESIS OF 3-(A) AND 5-ALKYL(B)-ISOXAZOLES

| R | Conditions | Ratio: A | : | B | Total yield (%) | References |
|---|---|---|---|---|---|---|
| Me | $NH_2OH{\cdot}HCl$ in MeOH, Δ | 46 | : | 54 | 58 | 3/51, 22/52 |
| Et | $NH_2OH{\cdot}HCl$ in MeOH, Δ | 59 | : | 41 | 60 | 22/52 |
| Pr | $NH_2OH{\cdot}HCl$ in MeOH, Δ | 67 | : | 33 | 73 | 22/52 |
| $CH_2Cl$ | $NH_2OH{\cdot}HCl$ in MeOH, Δ | 100 | : | 0 | 85 | 22/52 |
| MeCHCl | $NH_2OH{\cdot}HCl$ in MeOH | 97 | : | 3 | 86 | 67/58 |
| (S-)Et(Me)CH | $NH_2OH{\cdot}HCl$ | 13 | : | 87 | | 92/68 |
| $MeOOC(CH_2)_4$ | $NH_2OH{\cdot}HCl$ in MeOH, Δ | 0 | : | 100 | 27 | 65/63 |
| 3-(2-Me-1,2-dicarba-dodecaboran-1-yl)methyl | $NH_2OH{\cdot}HCl$ | 60 | : | 40 | 83 | 226/69 |
| 1,4,5,6,7,7-$Cl_6$-5-norbornenyl | $NH_2OH{\cdot}HCl$ in $Et_2O$, Δ | 100 | : | 0 | 82 | 69/80 |

terms of general formula $RCOCH=C(Cl)R'$ have also been tested; when R′ is chloromethyl or heptachloro-*endo*-bicycloheptenyl, only the isomers **179**[198/77] and **180**,[32/78] respectively, have been obtained by acidic oximation.

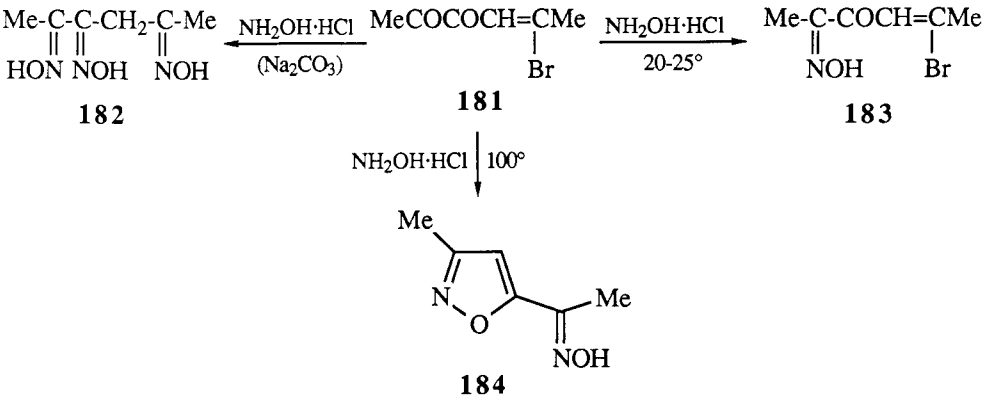



**179**




**180**

Sometimes the unsaturated carbonyl system shows different reactivity depending on the experimental conditions adopted. For example, the masked triketone **181** yields the trioxime **182** in a slightly alkaline medium, whereas in an acidic medium only one molecule of hydroxylamine adds to the most reactive carbonyl group, thus leading to the monoxime **183**; at higher temperatures the isoxazole derivative **184** is formed.[5C/74]




**182** **181** **183**

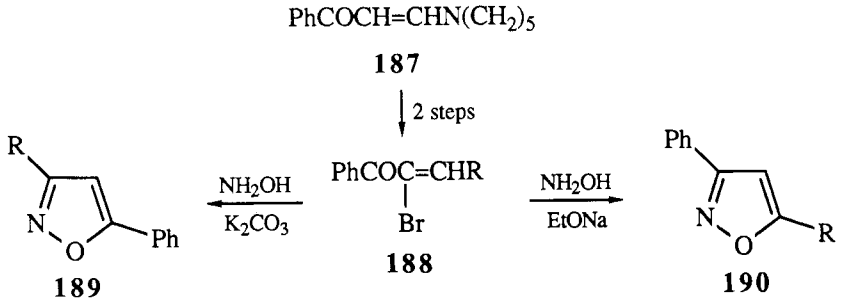
**184**

Aromatic β-chlorovinyl ketones usually furnish 5-arylisoxazole as the sole or prevalent product,[37/57.129/66.210/71] owing possibly to the diminished reactivity of the carbonyl group. The oximation reaction has also been applied to bromochalcones of general formula **185**:[3/27.3/29.3/45.8/49.96/77] in both cases the resulting diarylisoxazoles have been assigned structure **186**, possibly proceeding from an intermediate more or less stable 4-bromo-2-isoxazoline (see § 1.3.7.1, pp. 230–231). Bromo compounds (**185**) are also possible intermediates in the formation of isoxazoles from hydroxylamine and chalcone dibromides (see § 1.3.1.3, pp. 155–156).




**185** **186**

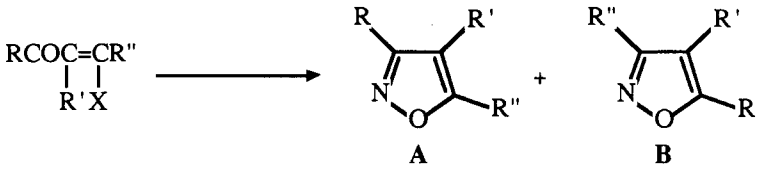
An interesting regiospecific synthesis of 3,5-disubstituted isoxazoles has been reported to occur by oximation of α-bromoenones (**188**)[easily available from β-pyrrolidinoenones (**187**)] under carefully controlled conditions: the reaction in 95% ethanol in the presence of potassium carbonate yields the 3-alkyl-5-phenylisoxazole (**189**), whereas the reaction in absolute ethanol in the presence of excess sodium ethoxide furnishes the isomeric 3-phenyl-5-alkylisoxazole (**190**).[156/80.68B/81]



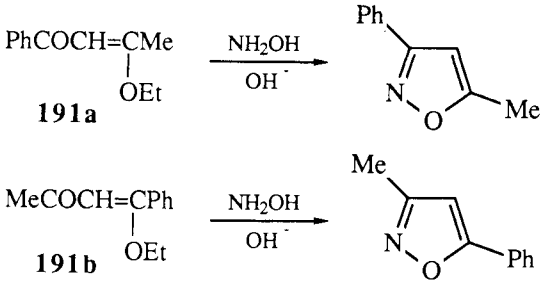

c. β-Alkoxy-α,β-Ethylenic Ketones or Aldehydes

Selected examples are listed in Table 1.64. Ethers of the enolic forms of β-ketoaldehydes or of unsymmetrical β-diketones are known to give one of the two possible isomeric isoxazoles by oximation under proper conditions. Thus the O-ethers **191a** and **191b** of the two isomeric enolic forms of benzoylacetone give 5-methyl-3-phenylisoxazole and 3-methyl-5-phenylisoxazole, respectively.[7/07.4/26] The reaction has been utilized for characterization of the O-methyl

TABLE 1.64



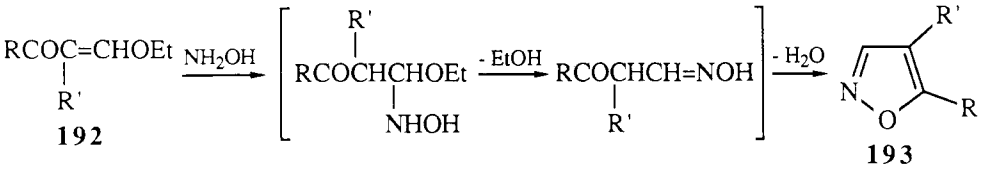

| X | R | R' | R" | Conditions | Product | Total yield (%) | References |
|---|---|---|---|---|---|---|---|
| OEt | H | H | H | aq. $NH_2OH$·HCl | A = B | 70 | 75/62 |
| OEt | H | Et | H | aq. $NH_2OH$·HCl | A = B | 66 | 75/62 |
| OMe | Me | H | H | aq. $NH_2OH$·HCl | A + B (1:2) | | 111/66 |
| OMe | Me | H | *t*-Bu | $NH_2OH$·HCl/MeONa, MeOH | A | | 26/56 |
| OMe | Me | H | Ph | $NH_2OH$/KOH, $H_2O$/MeOH | A | | 6/53 |
| OEt | Me | H | Ph | $NH_2OH$/KOH, $H_2O$/MeOH | A | 80-90 | 4/26 |
| OMe | Ph | H | Me | $NH_2OH$/KOH, $H_2O$/MeOH, Δ | A | | 6/53 |
| OMe | *t*-Bu | H | Ph | $NH_2OH$·HCl | A | | 30/57 |
| OEt | Ph | H | OEt | $NH_2OH$, EtOH, Δ | B | 85 | 11/63 |
| OEt | 4-$MeOC_6H_4$ | H | Ph | $NH_2OH$, MeOH, Δ | B | | 3/27 |
| OEt | Me | COMe | H | $NH_2OH$·HCl, MeOH, Δ | B | 60 | 3/65 |
| OEt | Me | COOEt | H | $NH_2OH$·HCl, EtOH, Δ | B | 60 | 66/59 |
| | | | | $NH_2OH$·HCl, AcONa, $H_2O$ | B | 96 | 38/84 |
| OEt | COOEt | Ph | H | $NH_2OH$, EtOH, Δ | B | 46 | 1/43 |
| OEt | $CH(OEt)_2$ | COOEt | H | $NH_2OH$, EtOH, 5° | B | 56 | 217/73 |
| OEt | COOEt | COOEt | H | $NH_2OH$, aq. EtOH | B | 66 | 17/55 |
| OCOMe | CH=CHPh | H | H | $NH_2OH$·HCl, AcONa, EtOH, Δ | B | | 133/68 |
| OCOPh | Ph | H | H | $NH_2OH$, AcOH, Δ | A | 87 | 3/43 |
| OCOPh | 2-furyl | H | H | $NH_2OH$, not spec. | A + B | | 54B/69 |




ethers (existing in stereoisomeric *cis* and *trans* forms) obtained from benzoylacetone and diazomethane.[6/53] Analogous results are reached by oximation of some O-methyl ethers of the enolic forms of acetyl- and aroylpinacone.[26/56,30/57]

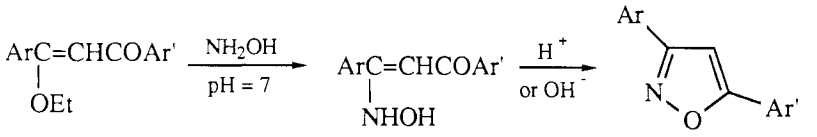
Enol ethers of β-ketoaldehydes of general formula RCOCH=CHOR′ usually yield a mixture of the two possible isomers where the 5-substituted isoxazole prevails,[111/66] although a different claim has also been made.[3/43] An acetoxy group instead of alkoxy (R′ = COMe in the formula above) also gives predominantly or exclusively the 5-substituted isoxazole.[133/68,54B/69]

Disubstituted enol ethers of general formula **192** give only isoxazoles (**193**) by treatment with hydroxylamine:[1/43,66/59,3/65,217/73,76/76,77/76,78/76]



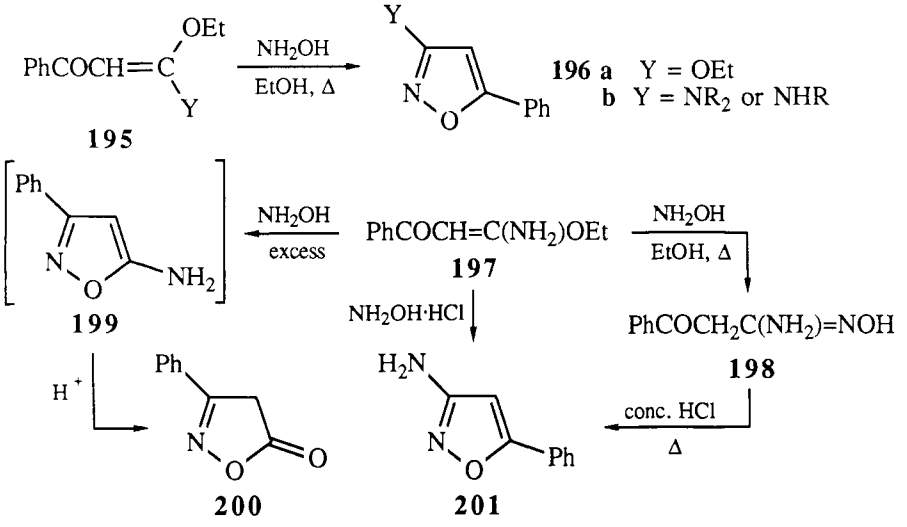
This rule is valid even when both R and R′ are carbethoxy groups, diethyl isoxazole-4,5-dicarboxylate thus being achieved,[17/55] but is not valid when R and R′ are closed into a ring, where a mixture of isomers is usually obtained (see Part 2 of this work).

By treating the two isomeric O-ethyl ethers of *p*-anisoylbenzoylmethane with neutral hydroxylamine, the two unstable products **194a** and **194b** are formed, respectively, which can easily be converted into isoxazoles in both acidic and alkaline media:[3/27]



| | Ar | Ar′ |
|---|---|---|
| (a) | Ph | *p*-$MeOC_6H_4$ |
| (b) | *p*-$MeOC_6H_4$ | Ph |

3-Ethoxy-5-phenylisoxazole (**196a**) is the sole product resulting from oximation of β,β-diethoxyvinyl phenyl ketone (**195a**). Starting from compounds **195b**, having both an alkoxy and a more or less substituted amino group in the β-position, only 1,4-addition has been observed, leading to 3-alkylamino-5-phenylisoxazole (**196b**)(Scheme 1.8).[11/63] This result was to be expected, because



Scheme 1.8.

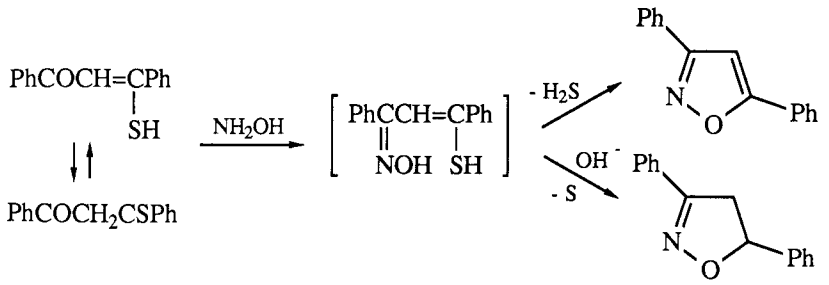
of the better leaving properties of the alkoxy compared with the alkylamino group. With compound **197** the product of the oximation reaction depends strongly on the experimental conditions: a theoretical amount of free hydroxylamine in slightly alkaline medium leads to the formation of the amidoxime **198**, which can be cyclized by treatment with concentrated HCl. 3-Amino-5-phenylisoxazole (**201**) is obtained directly under slightly acidic conditions, whereas heating with an excess of hydroxylamine causes cyclization in the opposite direction, forming the unstable 5-amino-3-phenylisoxazole **199**, readily hydrolyzable to the 5-isoxazolinone **200**.[11/63] An analogous general synthesis of 3-aminoisoxazoles without isolation of the amidoxime has also been reported.[116/78]

The utility and reliability of this method of isoxazole synthesis is limited by the difficulty in preparing the enol ethers in a pure form. Moreover, it is necessary to use free hydroxylamine in the presence of a slight excess of alkali. If hydroxylamine hydrochloride is used, the mineral acid set free causes hydrolysis of the enol ethers, and the reaction product is the same as that obtained by oximation of the free diketone. This fact explains some divergent results found in the literature.[4/25.5/26]

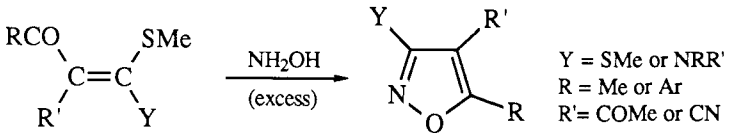
Of course, $\beta$-ethoxyacroleins of formula RC(OEt)=CHCHO yield only 5-substituted isoxazoles, as some examples, mainly in the steroidal field, show.[38D/64,52/70,246/70] Isoxazole itself has been obtained by oximation of $\beta$-ethoxyacrolein with hydroxylamine hydrochloride.[75/62]

Oximation of sulfur analogues of $\beta$-alkoxyvinyl ketones has been studied only occasionally. $\beta$-*p*-Tolylmercaptovinyl phenyl ketone is reported to give a 48% yield of a not-better-characterized phenylisoxazole.[38/57] A more substituted $\beta$-methylthiovinyl ketone is oximated to give a trisubstituted isoxazole through a 1,4-addition process.[273/83]

$\alpha$-Mercaptobenzalacetophenone has been reacted with hydroxylamine to give 3,5-diphenylisoxazole under evolution of hydrogen sulfide (the intermediate oxime may or may not be isolated). In an alkaline medium desulfurization occurs with the formation of isoxazoline:[14/58]




More attention has been paid to the oximation reaction of acylketene S,S- or S,N-acetals of general formula **202**: 1,4-addition of hydroxylamine is a rule here and 3-alkylthio- or 3-aminoisoxazoles (**203**) are obtained, respectively, in fair-to-excellent yields:[14/67,209/78,155/84]



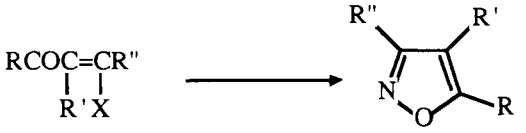

202 203

It is noteworthy that cyclization occurs on the carbonyl group with preference to the cyano group.[209/78]

d. β-Dialkylamino-α,β-Ethylenic Ketones or Aldehydes

Selected examples are listed in Table 1.65. β-Dialkylaminovinyl ketones,

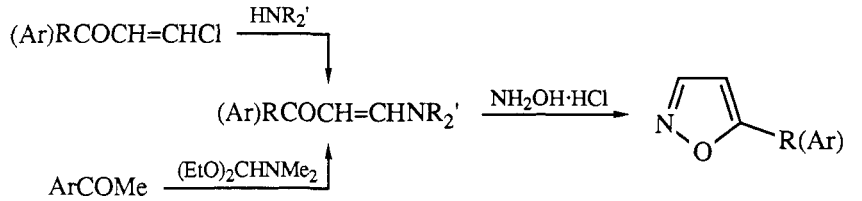
TABLE 1.65



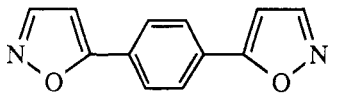

| X | R | R' | R" | Conditions[a] | Yield (%) | References |
|---|---|---|---|---|---|---|
| $NMe_2$ | H | Me | H | HH, AcOH ($H_2SO_4$), Δ 8 h | 95 | 9/60 |
| $NMe_2$ | H | Ph | H | HH, AcOH ($H_2SO_4$) or $H_2O$, Δ | 86-95 | 151/77 |
| $NEt_2$ | Me | H | H | HH, MeOH, Δ 5 h | 59 | 11/54 |
| NHPh | Me | H | H | HH, EtOH, Δ 1.5 h | 58 | 6/47 |
| 1-Piperidinyl | Me | H | H | HH, $H_2O$, Δ 2 h | 81; 61-77 | 111/66, 168/71 |
| $NMe_2$ | $Me_2CH$ | H | H | HH, $H_2O$ | 85 | 106/64, 109/66 |
| $NEt_2$ | EtCH(Me) | H | H | HH, MeOH, Δ 5 h | 61[b] | 92/68 |
| 1-Piperidinyl | $EtCHMeCH_2$ | H | H | HH, MeOH, Δ 5 h | 67 | 51/72 |
| $NEt_2$ | cyclo-hex | H | H | HH, EtOH, Δ 5 h | 70[c] | 213/71 |
| $NMe_2$ | Ph | H | H | HH, MeOH, Δ 6 h | 70-76; 89 | 37/57, 111/66 |
| $NMe_3^+Cl^-$ | Ph | H | H | HH, MeOH, Δ 10 h | 17 | 37/57 |
| NHPh | Ph | H | H | HH, EtOH, Δ 1 h | | 6/47 |
| NHPh | 4-$ClC_6H_4$ | H | H | HH, EtOH, Δ 5 h | 25[b] | 215/71 |
| NHPh | 3-$BrC_6H_4$ | H | H | H sulfate, EtOH, Δ 3 h | 97.5 | 58/67 |
| $NMe_2$ | 2-$HOC_6H_4$ | H | H | HH, $H_2O$/dioxane, r.t. 5-10 h | 65 | 157/77 |
| NHPh | 2-$MeC_6H_4$ | H | H | HH, $H_2O$/EtOH, Δ 3-8 h | 88 | 10B/69 |
| NHPh | mesityl | H | H | HH, $H_2O$/EtOH, Δ 3-8 h | 94 | 10B/69 |
| $NH_2$ | Me | H | Me | HH/$K_2CO_3$, EtOH, Δ 6 h | 59 | 34/77 |
| NHCOOMe | Et | H | Me | HH/$K_2CO_3$, EtOH, Δ 20 h | 81[d] | 34/77 |
| $NHCOCCl_3$ | *t*-Bu | H | Me | HH/$K_2CO_3$, EtOH, Δ 20 h | 46 | 34/77 |
| $NMe_2$ | COMe | H | Me | HH, HCl/$H_2O$, Δ 2 h | 76 | 5C/74 |
| NH | Ph | H | Me | HH/$K_2CO_3$, EtOH, Δ 6 h | 86 | 34/77 |
| NHMe | 2-$HOC_6H_4$ | H | Me | HH, AcONa, Δ | 60 | 109/73 |
| NHPh | Ph | Me | H | HH, $H_2O$/EtOH, Δ 3 h | 80 | 10B/69 |
| $NMe_2$ | Ph | COPh | H | HH, MeOH, Δ 1 h | 94 | 173/83 |

[a] HH = hydroxylamine hydrochloride.
[b] Impure of 3-substituted isoxazole.
[c] 3-substituted isoxazole.
[d] Mixture of the two isomeric isoxazoles.

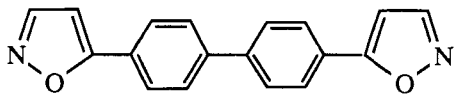
which can be prepared (eventually *in situ*) from β-chlorovinyl ketones and a secondary amine or from aryl methyl ketones and *N*,*N*-dimethylformamide diethylacetal, react with hydroxylamine in acidic media.[11/54,37/57,109/66,111/66,92/68,51/72] or with hydroxylamine-*O*-sulfonic acid[205B/80] to give 5-substituted isoxazoles in good yields and high selectivity:



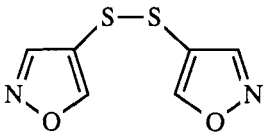

The use of piperidine instead of diethyl- or dimethylamine in the synthesis of the starting material seems to be convenient:[111/66] for example, in the synthesis of optically active 5-alkylisoxazoles, the diethylamino derivative led to isoxazoles containing up to 6–7% of the 3-alkyl-substituted isomers, whereas with the piperidino derivative pure 5-alkylisoxazoles were obtained.[51/72] Several diisoxazolyl derivatives, for example **204** and **205**, have been prepared by this method.[66/69,157/77] Contrary to all other known data, cyclohexyl β-diethylaminovinyl ketone has been reported to yield 3-cyclohexylisoxazole as the sole product of the oxiamation reaction.[213/71]



**204**



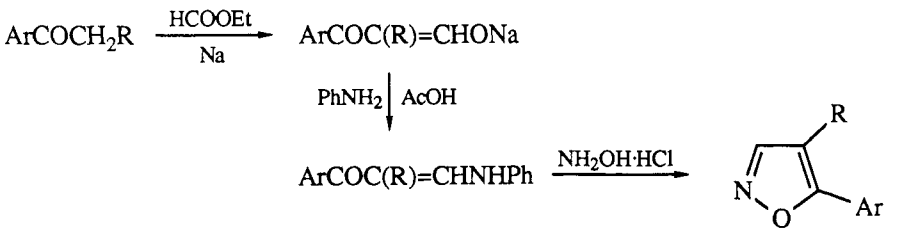
**205**



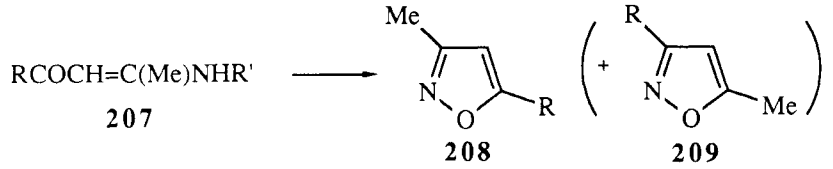
**206**

4-Alkyl (or aryl)-isoxazoles are obviously obtained by treatment of β-dimethylamino-α-substituted acroleins of general formula $Me_2NCH=C(R)CHO$ with hydroxylamine in acidic media.[9/60,117/66,151/77] The disulfide **206** has been prepared by this method.[5/64] Sometimes the solution containing the salt $Me_2NCH=C(R)CH=NMe_2^+$, produced from RMe by the Vilsmeier reaction, can be used to synthesize 4-substituted isoxazoles in excellent yields.[117/71]

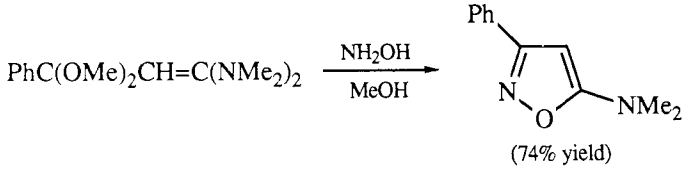
Other starting materials for the synthesis of 5-aryl- and 4,5-disubstituted isoxazoles are the β-anilinovinyl ketones, which can easily be prepared in two steps from allyl aryl ketones. They react promptly with hydroxylamine hydrochloride in refluxing alcoholic solution to give isomerically almost pure compounds:[6/47,58/67,10B/69,54B/69,215/71]



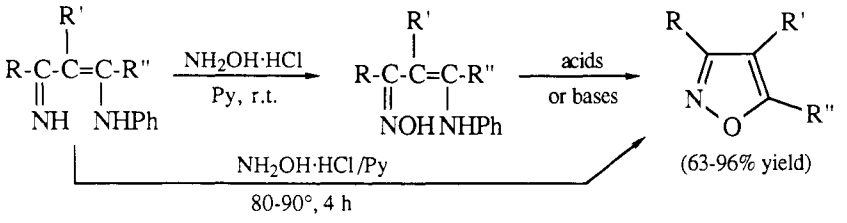
In one case (Ar = *p*-$ClC_6H_4$; R = H) a 9% impurity of isomeric 3-*p*-chlorophenylisoxazole was estimated from the PMR spectrum.[215/71] Michael-type addition also prevails in the oximation of β-methyl-β-aminosubstituted vinyl ketones (**207**), forming the isomer **208**, but here a minor amount of the isomer **209** is sometimes formed, which increases with increasing electron-attracting properties of the N-substituent group (e.g., when R′ = $COCCl_3$):[34/77]



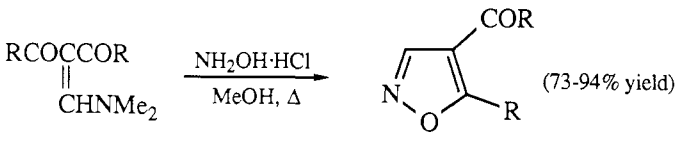
The presence of an aminomethyl instead of a methyl group in the β-position of **207** seems to induce exclusive attack by the nucleophile on the carbonyl group.[169B/75] An analogous result is achieved when β,β-dimethylaminoacrylophenone dimethylacetal is reacted with hydroxylamine in absolute methanol:[11/80]



A convenient regiospecific synthesis of isoxazoles employs the β-anilinovinyl ketone imines as a starting material, easily available by $AlCl_3$-catalyzed condensation of phenylimines to nitriles. In this case exclusive attack by hydroxylamine on the imine group occurs, as also evidenced by isolation of the corresponding intermediate oxime:[200/83]

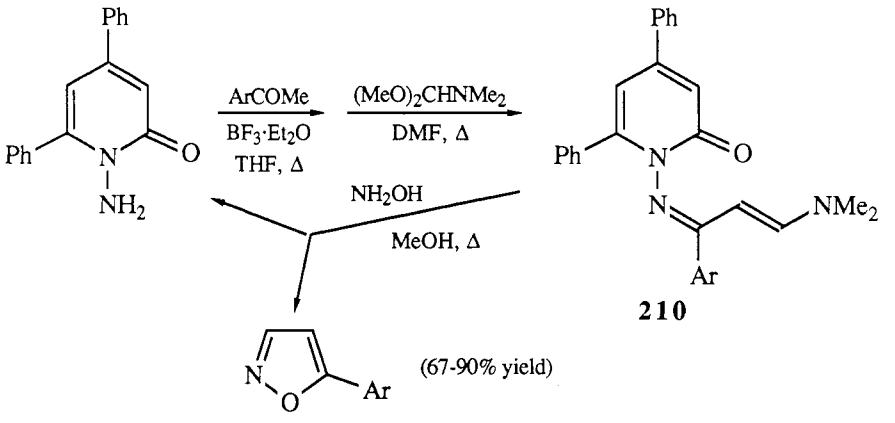


Symmetrically substituted 2-dimethylaminomethylene-1,3-diketones are attacked by hydroxylamine on the activated double bond, thus leading to 3-unsubstituted isoxazoles; for example:[173/83]




With asymmetrically substituted derivatives a mixture of the two possible isomers is obtained.[242C/79]

An interesting approach to pure 5-arylisoxazoles is provided by neutral oximation in refluxing dry methanol of the enaminimines (**210**), easily synthesized from 1-amino-4,6-diphenyl-2-pyridone; good to excellent yields have been reported:[86/84]



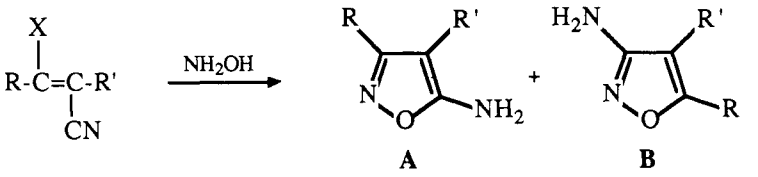

e. β-Substituted α,β-Ethylenic Nitriles

β-Bromocinnamonitrile is known to give excellent yields of 3-amino-5-phenylisoxazole by treatment with hydroxylamine in alkaline ethanolic solution, whereas in neutral solution yields are low and a mixture of isomers is obtained, the 5-amino-3-phenylisoxazole largely prevailing[42/66] (see Table 1.66).

Generally, an alkaline medium warrants the formation of a 3-amino isomer;[42/66,125/66,134/66,126/68,207/72] in addition to hydroxylamine, its *N*-ethoxycarbonyl or *N*-carboxamido derivatives can be used.[126/68,83/73] An intermediate amidoxime has never been reported. The same type of isomer (i.e., 3-amino-5-methylisoxazole) has been obtained starting from α-bromocrotononitrile.[180/66]

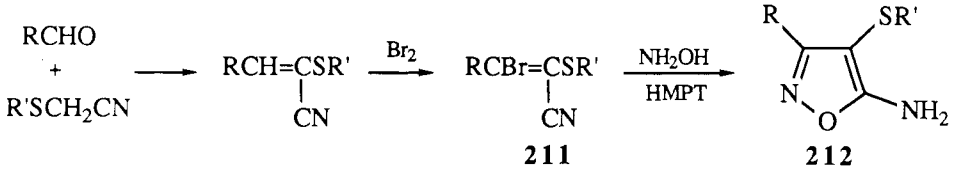
By contrast, neutral conditions privilege the Michael-type addition pattern to form the 5-amino isomer **212**, as has recently been demonstrated for α-alkylthio-β-bromoacrylonitriles (**211**), easily obtainable from the corresponding aldehydes:[274/80]

TABLE 1.66



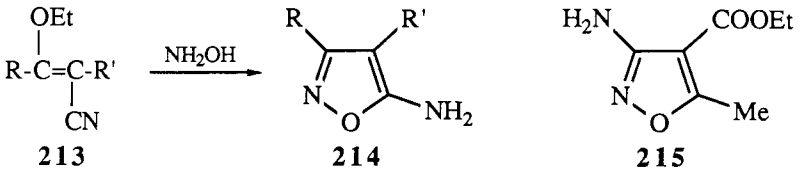
| X | R | R' | Conditions | Product | Total yield (%) | References |
|---|---|---|---|---|---|---|
| Cl | H | H | EtOOCNHOH or ROOCCH$_2$NHOH/EtONa | B | 69 | 126/68 180/71 |
| Cl | Me | OMe | $NH_2OH$ | B | | 134/66 |
| Cl | *n*-Pr | CN | $H_2NCONHOH/OH^-$ | B | | 83/73 |
| Cl | R | CN | $H_2NCONHOH/OH^-$ | B | | 207/72 |
| Br | Me | SEt | $NH_2OH$/HMPT, 60°, 1 h | A | 88 | 274/80 |
| Br | Et | SEt | $NH_2OH$/HMPT, 60°, 1 h | A | 88 | 274/80 |
| Br | $Me_2CH$ | SMe | $NH_2OH$/HMPT, 60°, 1 h | A | 85 | 274/80 |
| Br | $Me_2CH$ | SEt | $NH_2OH$/HMPT, 60°, 1 h | A | 85 | 274/80 |
| Br | *n*-Bu | SEt | $NH_2OH$/HMPT, 60°, 1 h | A | 95 | 274/80 |
| Br | Ph | H | $NH_2OH$/EtOH, 35-40° | A + B (72:28) | 19 | 42/66 |
| Br | Ph | H | $NH_2OH/OH^-$, r.t. | B | 94 | 42/66 |
| Br | *p*-$BrC_6H_4$ | H | $NH_2OH/OH^-$, r.t. | B | 57 | 42/66, 125/66 |
| Br | *p*-$MeOC_6H_4$ | H | $NH_2OH/OH^-$, r.t. | B | | 125/66 |
| Br | Me | $SC_6H_4Br$-*p* | $NH_2OH$/HMPT, 60°, 1 h | A | 90 | 274/80 |
| Br | Ph | SEt | $NH_2OH$/HMPT, 60°, 1 h | A | 81 | 274/80 |
| Br | *o*-$ClC_6H_4$ | SEt | $NH_2OH$/HMPT, 60°, 1 h | A | 13 | 274/80 |
| Br | *o*-$MeOC_6H_4$ | SEt | $NH_2OH$/HMPT, 60°, 1 h | A | 78 | 274/80 |
| Br | Ph | SPh | $NH_2OH$/HMPT, 60°, 1 h | A | 17[a] | 274/80 |
| Br | *p*-$ClC_6H_4$ | SPh | $NH_2OH$/HMPT, 60°, 1 h | A | 35[a] | 274/80 |

[a] Together with large amounts of amidoxime RCBr=C(SPh)C($NH_2$)=NOH.



**211** **212**

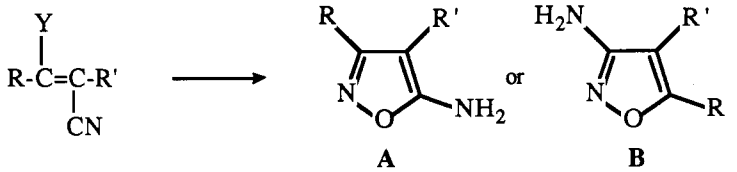
Monocyano- and dicyanoketene acetals show differing behavior: the former compounds react with hydroxylamine in an alkaline medium to yield 5-alkoxy-3-aminoisoxazoles;[146/70,180/71] by contrast the latter derivatives form 3-alkoxy-5-amino-4-cyanoisoxazoles,[44/58] showing a preferential attack by the nucleophile on the carbon atom carrying the alkoxy group. This last direction is fairly general and makes it possible to prepare a large variety of 5-aminoisoxazole derivatives (**214**)(see Table 1.67 for selected examples). Because of their reasonable availability, enol ethers of acylmalononitrile of general formula **213** are particularly useful as starting materials:[24/58,8/60,75/64,33/69,11/82]



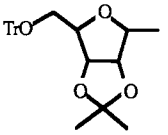

213 214 215

(R' = CN, COOEt or CONHAr)

TABLE 1.67



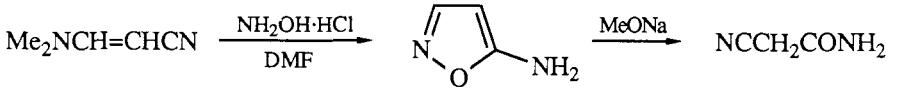

A B

| Y | R | R' | Conditions | Isox | Yield (%) | References |
|---|---|---|---|---|---|---|
| OMe | OMe | H | $NH_2OH$, MeOH, Δ 6 h | B | 77 | 146/70 |
| OMe | 4-$CF_3C_6H_4$ | H | $NH_2OH$·HCl | B | | 49/81 |
| OMe | H | $PhSO_2$ | aq. $NH_2OH$, r.t. | A | 63 | 217/78 |
| OEt | H | CN | $NH_2OH/OH^-$, < 50° | A | | 24/58 |
| OEt | H | COOEt | $NH_2OH/OH^-$, < 50° | A | | 24/58 |
| | | | $NH_2CONHOH/MeO^-$ | A | 70[a] | 78/64 |
| OEt | H | $CONHC_6H_4CF_3$-3 | $NH_2OH$, EtOH/$NEt_3$, 80° | A | | 11/82 |
| OEt | Me | CN | $NH_2OH/OH^-$ | A | 71 | 75/64 |
| OMe | Ph | CN | $NH_2OH$, $H_2O$, r.t. | A | 40 | 8/60 |
| OMe | 4-$ClC_6H_4$ | CN | $NH_2OH$, $H_2O$, r.t. | A | 72 | 8/60 |
| OEt | OEt | CN | aq. $NH_2OH$, r.t. | A | 73 | 44/58 |
| OEt | Me | COOEt | $NH_2OH$ | A | 97 | 78/64 |
| | | | $NH_2CONHOH/MeO^-$ | B | 54 | 78/64 |
| OMe | Ph | COOEt | $NH_2OH$, $H_2O$, r.t. | A | 95 | 8/60 |
| SH | Ph | H | $NH_2OH$·HCl | A | 59 | 9/73 |
| SMe | H | $PO(OEt)_2$ | $NH_2OH$, EtOH, r.t. | A | 86 | 14/75 |
| SMe | Me | $PO(OEt)_2$ | $NH_2OH$, EtOH, r.t. | A | 77 | 14/75 |
| SMe | SMe | CN | $NH_2OH$ | A | 32 | 6/62 |
| SMe | SMe | COOMe | $NH_2OH$ | A | 96 | 6/62 |
| 4-$MeC_6H_4SO_2$ | CN | 4-$MeC_6H_4SO_2$ | $NH_2OH$, AcOH, 80° | A | 33 | 43/63 |
| $NMe_2$ | H | H | $NH_2OH$·HCl | A | | 256/74 |
| $NMe_2$ | H |  | $NH_2OH$·HCl/Py, DMF | A | 86 | 180B/77 |
| $NH_2$ | Me | H | $NH_2OH/OH^-$, EtOH, r.t. | A | 83 | 167/73 |
| | | | $NH_2OH$/MeONa, MeOH | A | 60 | 32/73 |
| $NH_2$ | $C_2F_5$ | CN | $NH_2OH/OH^-$, r.t. | A | 87 | 121/81 |

[a] Isoxazole A not isolated; yield refers to the α-cyanocarboxamide obtained.

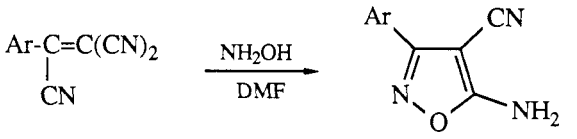
The use of *N*-hydroxyurea instead of hydroxylamine in an alkaline medium may invert the addition direction; for example, from ethyl β-ethoxy-α-cyanocrotonate the "anomalous" isomer **215** has been obtained with the former reagent, whereas the "normal" isomer **214** (R = Me; R′ = COOEt) is formed with hydroxylamine.[78/64] The same inversion of the site of attack on passing from hydroxylamine to *N*-hydroxyurea has been observed with some α-bromoacrylonitriles in the *C*-nucleosides field.[76/75,69/79] By contrast, β-(2-furyl)-α-haloacrylonitriles yield 3-amino-5-furylisoxazoles with both hydroxylamine and *N*-hydroxyurea.[196/84]

β-Alkylthio- and β,β-dialkylthioacrylonitriles invariably yield 5-aminoisoxazoles, at least in the few instances investigated.[6/62,9/73,14/75] The unsubstituted 5-aminoisoxazole, intermediate in the synthesis of cyanoacetamide, has been claimed to be formed by treatment of β-dimethylaminoacrylonitrile with hydroxylamine hydrochloride in dimethylformamide for 3.5 h at 65–70°C: [236/73,256/74,215/75]



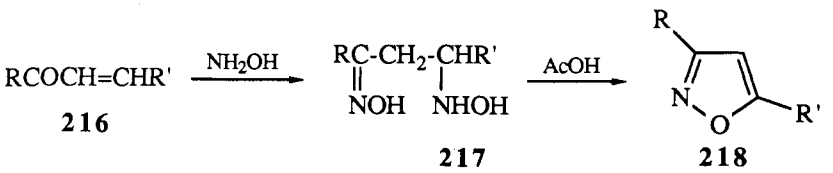

Analogously, 5-amino-3-methylisoxazole has conveniently been prepared by alkaline oximation of β-aminocrotononitrile.[32/73,167/73]

The cyano group can also act as a leaving group, as in the following example:[54/81]



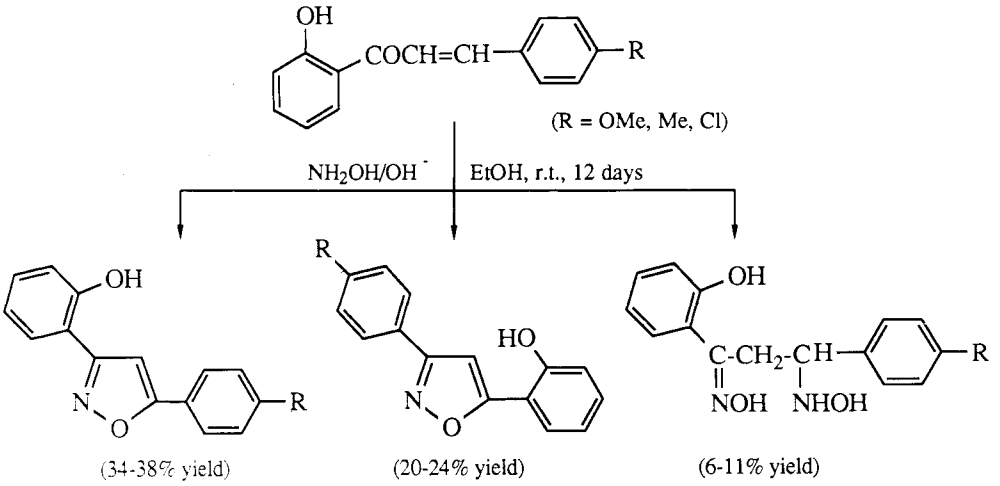

### *1.3.1.5 Oximation of α,β-Ethylenic Carbonyl (and Related) Compounds*

Hydroxylamine reacts in a very complex way with α,β-unsaturated ketones, RCOCH=CHR′. Among the different products formed, depending on the conditions under which the reaction has been carried out, isoxazoles have frequently been isolated. They are formed in oxidation processes that accompany the normal formation of isoxazolines, hydroxylaminooximes, and dioximes. Particularly straightforward is the formation of isoxazoles (**218**) from chalcones (**216**), carrying a heteroaromatic ring in one or both positions (R and/or R′). The intermediate hydroxylaminooximes (**217**) can usually be isolated and subsequently cyclized by treatment with acetic acid: [96/63,121/64,164/68,152/75]



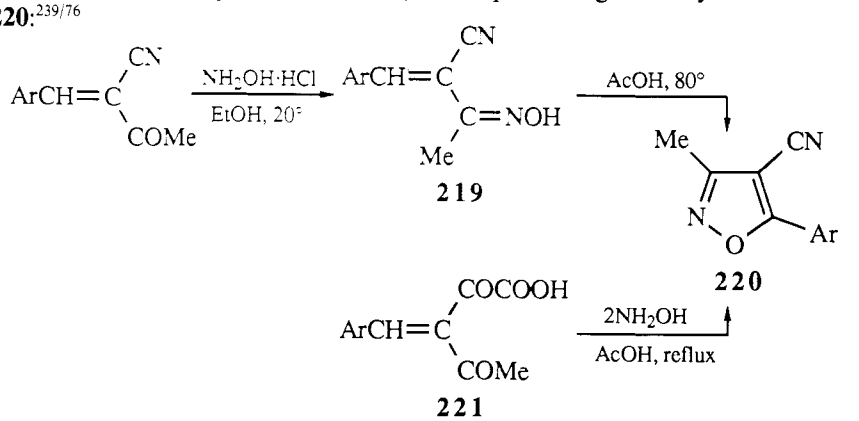

**216** **217** **218**

Also widely studied have been the chalcones (**216**), carrying on one side (R or R′) a 2′-hydroxyaryl group;[8/61,8/68,140B/69,169/71,205/74,218/74,217/76,222/77,200/81] in these cases various products can be formed, depending on medium, time of reaction, and nature of substituents. Reaction with hydroxylamine hydrochloride in ethanol or in dry pyridine usually yields chalcone oximes, hydroxylamino-oximes, dioximes, and 2-isoxazolines, but not isoxazole derivatives, at least as primary products. The latter compounds, on the other hand, are obtained directly in strong basic alcoholic solution at room temperature, commonly as a mixture of the two possible 3,5-disubstituted isomers, identified mainly by mass spectrometric analysis.[217/76,222/77,200/81] For example, the results shown in Scheme 1.9 have been recorded.[200/81]




**Scheme 1.9.**

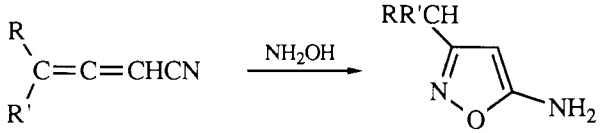
A dehydrogenation in hot acetic acid accompanies the cyclization of the α,β-unsaturated α-cyanoketone **219**, thus producing directly the isoxazole **220**:[239/76]




**219** **220** **221**

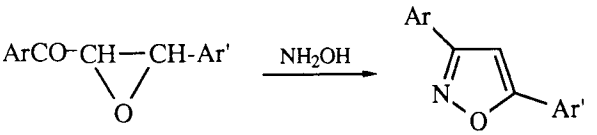
Interestingly enough, the same compound can be achieved by oximation of the diketo acid **221** with an excess of hydroxylamine in boiling acetic acid.[239/76,159/77] For a more detailed discussion of the oximation of α,β-unsaturated ketones, see § 2.2.2.1, pp. 461–468. For cyclization processes of α,β-ethylenic ketoximes, see § 1.3.6.1, pp. 225–226.

Allenic nitriles are oximated site specifically in more or less slightly alkaline media to give 3-alkyl-5-aminoisoxazoles with moderate to good yields:[2/59,75/84]



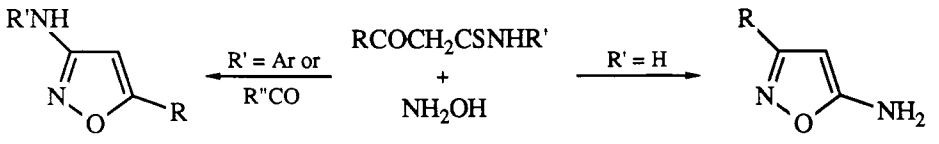

### *1.3.1.6 Other Oximation Reactions*

α,β-Dibromo ketones are known to yield, site specifically, the corresponding disubstituted isoxazoles (see § 1.3.1.3, pp. 155–156). A closely related reaction is the oximation of chalcone epoxides; here, too, the site of attack is the carbonyl group, and only one isoxazole is obtained:



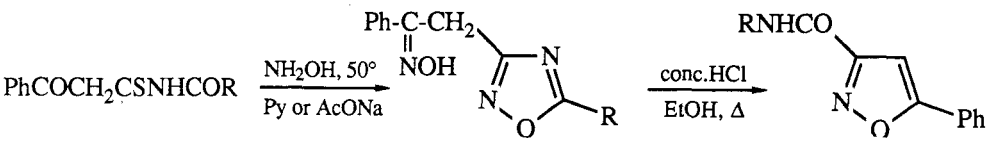

The reaction has general applicability;[4/16,7/16,65/73,138/78,71B/80,125/80] sometimes intermediate products can be isolated (i.e., oximes or 5- or 4-hydroxy-2-isoxazolines) which require an acidic treatment with sulfuric acid or *p*-toluenesulfonic acid for dehydration to the final product.[7/16,100/73] (see also §§ 1.3.7.1, p. 231, and 2.2.3.1b, p. 544). Furthermore, the reaction is not restricted to chalcones, but has also been applied to β-aroylacrylic acid epoxides, which are oximated to 3-arylisoxazole-5-carboxylic acids.[75/81] An easy entry into substituted 3- or 5-aminoisoxazoles is provided by the oximation of acylacetothioamides and some related compounds.

Benzoylacetothioamide condenses with hydroxylamine in buffered solution to yield 5-amino-3-phenylisoxazole.[2/20,22/62,5/63] However, with N-substituted thioamides the site of attack of the hydroxylamine nitrogen atom changes from the carbonyl to the thiocarbonyl group, and derivatives (**222**) of the 3-aminoisoxazole are obtained:[2/20,5/63]

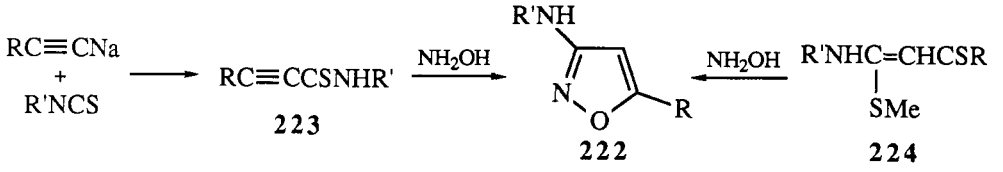



**222**

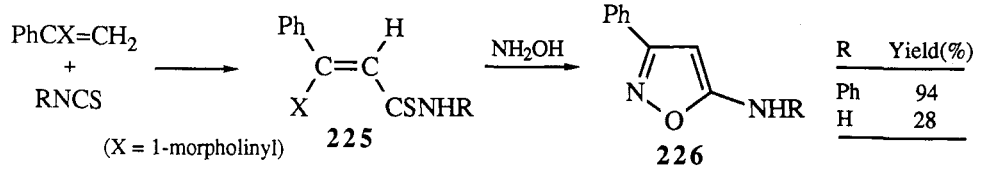
This corresponds to a higher reactivity of the C=S group than of the C=O group in an acidic medium. However, when the oximation is accomplished with *N*-acylthioamides in pyridine solution or in the presence of sodium acetate, both the carbonyl and the thiocarbonyl groups react, yielding the oxime of 3-phenacyl-5-methyl(or phenyl)-1,2,4-oxadiazole. This product is unstable in acidic medium and readily rearranges to 3-acylamino-5-phenylisoxazole:[221/81]




Similarly, N-substituted arylthiopropiolic acid amides (**223**), easily attainable from isothiocyanates and sodium arylacetylenes, condense with hydroxylamine to give substituted 3-aminoisoxazole derivatives (**222**) with moderate to poor yields.[2/17,9/37,11/37,11/38] Analogous results have been obtained by oximation of 3-methylthio-3-arylamino-2-propen-1-thiones (**224**):[7/73]

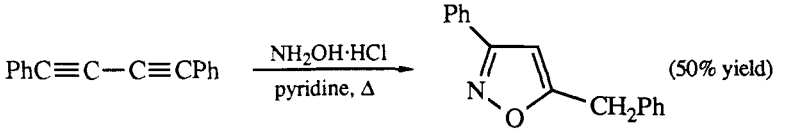



The behavior of 3-morpholinothiocinnamic acid amides (**225**) differs from that reported above and depends strongly on the experimental conditions. In contrast to previous claims,[126/65] excess hydroxylamine in refluxing methanol converts **225** into 5-amino-3-phenylisoxazoles (**226**) under loss of morpholine and $H_2S$; interestingly enough, the use of hydroxylamine hydrochloride on **225** (R = Ph) under milder conditions also affords 5-mercapto-3-phenylisoxazole as a by-product (28% yield):[6/70]

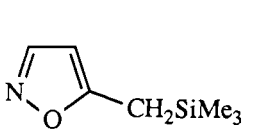



| R | Yield(%) |
|---|---|
| Ph | 94 |
| H | 28 |

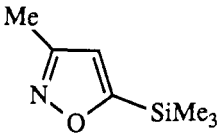
1,3-Butadiynes are known to undergo easy additions by mono- and bifunctional nucleophiles. It is therefore not surprising that 1,4-diphenyl-1,3-butadiyne is oximated to 5-benzyl-3-phenylisoxazole:[155/69]



Application of the same scheme to polydiethynylbenzene affords a polyisoxazole derivative,[183/72] whereas oximation of 1,4-bis(trimethylsilyl)-1,3-butadiyne in buffered medium is a convenient source of 5-(trimethylsilyl)methylisoxazole (**227**). If the latter reaction is carried out in excess pyridine, **227** and a minor amount of the isomeric compound **228** are obtained.[20/79]

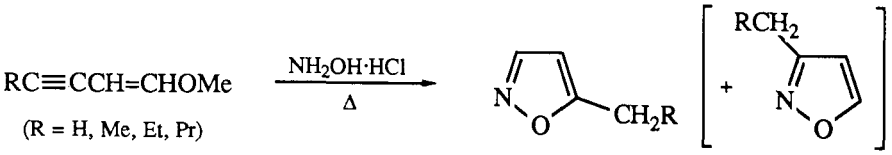


**227**

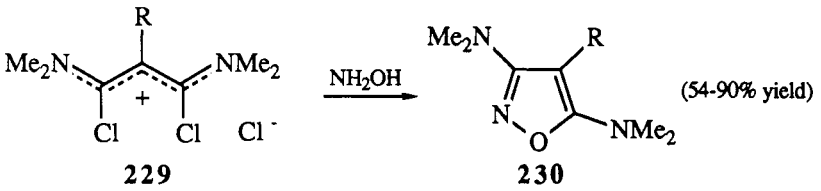


**228**

Oximation of 1-methoxybutenyne and its higher homologues yields 5-alkylisoxazoles, contaminated with the 3-alkyl isomer, especially in the case of lower alkyl groups (e.g., starting from methoxybutenyne itself):[258/70]

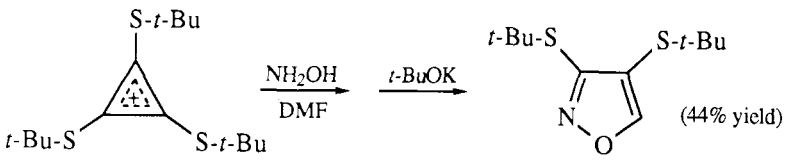


Some specially featured isoxazole derivatives are accessible by oximation of cationic compounds. For example, 3,5-bisdimethylaminoisoxazoles (**230**) have been prepared by reaction of the readily available 1,3-dichlorotrimethinecyanines (**229**)(a doubly activated malondiamide) with an alkaline or buffered aqueous solution of hydroxylamine:[47/76,55/78]



**229** **230**

3,4-Di(*t*-butylthio)isoxazole, which is otherwise difficult to obtain, has been synthesized by oximation of a trisubstituted cyclopropenium salt:[171/79]



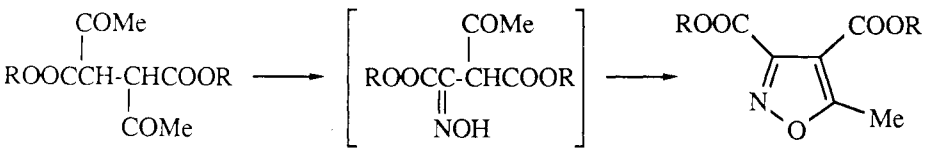
### *1.3.1.7 Synthesis from Unsaturated Compounds and Nitric (Nitrous) Acid*

The action of nitric acid on aliphatic compounds is complex because of accompanying secondary reactions. Besides nitration, oxidation processes always occur and the reduction products of nitric acid, principally nitrogen oxides, react with the reactants, products, and their oxidation products to give substances whose structure and mode of formation are sometimes difficult to explain. Some of these reaction products, reported in the early literature as being of unknown structure, have subsequently been characterized as isoxazole derivatives. These include eulite and dislite, obtained in 1852 from citraconic acid and nitric acid; the compound that Angeli and Schmidt prepared from acetonylacetone and nitric acid (1891); and some of the products formed from acetylene and nitric acid (1901–1902). As mentioned earlier, eulite and dislite were the first substances containing the isoxazole ring to be isolated.

These reactions, which very seldon attain a preparative significance, are discussed in the following three groups on the basis of the various possible reactions involved: (1) from $\gamma$-dicarbonyl compounds and nitric acid, (2) from ethylene derivatives and nitric acid, and (3) from acetylene derivatives and nitric acid.

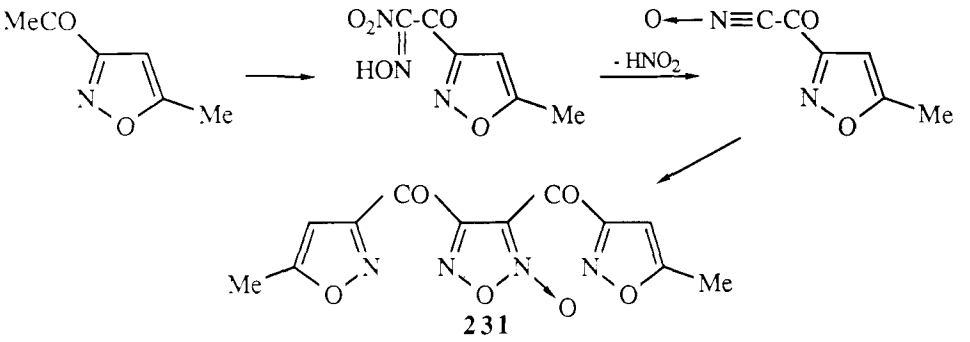
#### a. Isoxazoles from $\gamma$-Dicarbonyl Compounds and Nitric Acid

The mechanism of this reaction probably involves attack by nitrous acid, formed by the reduction of nitric acid, upon a methylene or methinyl group activated by the presence of a neighboring –CO– and subsequent ring closure of the $\beta$-isonitroso ketone thus formed. In this process, elimination of certain groups (such as carboxyl and acyl) and formation of a furoxan ring can also occur. The first reported[3/08,7/09] example of this type of reaction was the formation of 5-methylisoxazole-3,4-dicarboxylic ester from $\alpha,\beta$-diacetylsuccinic ester and fuming nitric acid:




The same isoxazole dicarboxylate is also formed from monoacetylsuccinic ester and nitrous acid.[6/09] $\alpha,\beta$-Diacetyl-$\beta$-oximinopropionic acid and oximinosuccinic acid have been isolated as secondary products of this reaction. The action of fuming nitric acid on acetonylacetone gives two different products.[6/09] The first is 3-acetyl-5-methylisoxazole, formed by cyclization of the 3-monoxime of hexane-2,3,5-trione. The second is a compound already described,[8/891] whose structure, after an erroneous assignment,[1/12] was demonstrated to be 3,4-bis(5-

methylisoxazol-3-ylcarbonyl)furoxan (**231**).[1/31] This compound is possibly formed by the action of nitric acid on acetylmethylisoxazole, formation of the nitrile oxide from the intermediate acylnitrolic acid, and subsequent dimerization:

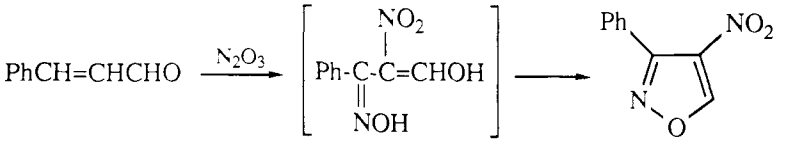



**231**

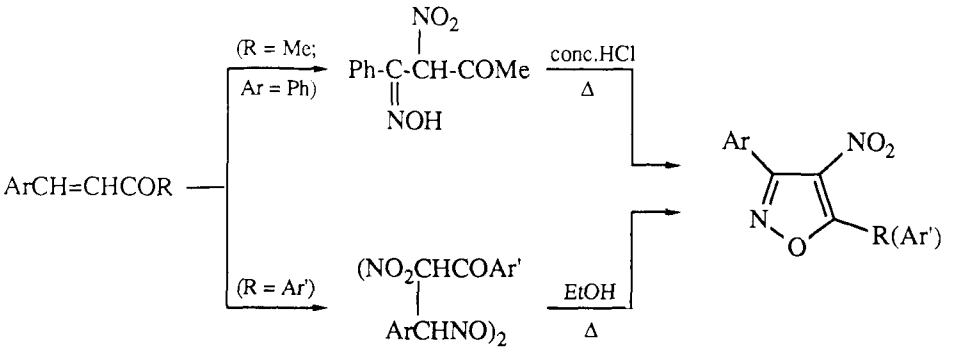
An example of this type of reaction is the action of concentrated nitric acid on phenacylacetone, which gives a mixture of 3-acetyl-5-phenylisoxazole and of 3-benzoyl-5-methylisoxazole;[10/38.2/48] on 1,2-dibenzoylethane, which yields 3-benzoyl-5-phenylisoxazole;[8/38.2/48] and on phenacylacetoacetic ester, which produces, by elimination of the acetyl group, 5-phenylisoxazole-3-carboxylic ester.[7/38] α,β-Dibenzoylpropionic ester and 1,2,4-triphenylbutan-1,4-dione react similarly to give ethyl 5-phenylisoxazole-3-carboxylate and 3-benzoyl-4,5-diphenylisoxazole, respectively.[3/48] In these reactions, isoxazolecarboxylic acids are frequently formed as oxidation products of the corresponding acetylisoxazoles.[1/31.2/48.62/59]

b. Isoxazoles from Ethylenic Derivatives and Nitrogen Trioxide or Nitric Acid

α,β-Unsaturated aldehydes or ketones add nitrogen trioxide to give monoximes of β-nitro ketones or the dimeric pseudonitrosites, which easily form 4-nitroisoxazoles. For example, cinnamaldehyde is transformed directly into 3-phenyl-4-nitroisoxazole:[3/03]

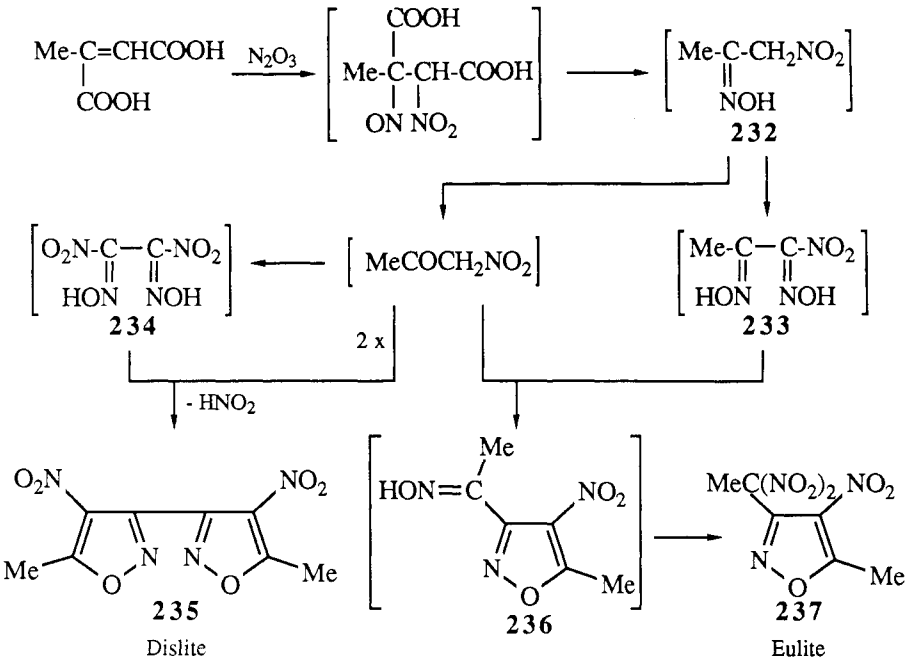



Starting from benzalacetone[4/03.4/46] and from chalcones,[3/03.2/05.120/78] the intermediate nitro-β-diketone monoxime and the pseudonitrosites, respectively, are isolable:




Much more complicated processes occur in the interaction of hot concentrated nitric acid with citraconic acid. From this reaction two well-crystallized products, eulite and dislite, were isolated by Baup in 1852[1/852] and studied without success by Bassett,[1/871,17/891] Ciamician,[1/889] and Angeli.[13/891,4/893] Subsequent investigations[3/35,2/36,3/36,4/36,5/38,2/46,4/46,8/46] have demonstrated that eulite (**237**) and dislite (**235**) are nitroderivatives of 3-ethyl-5-methylisoxazole and 5,5′-dimethyl-3,3′-diisoxazole, respectively. Possible reactions leading to their formation have been suggested[6/46,8/46] by these researchers. By analogy with the behavior of the unsaturated aldehydes and ketones, it is probable that the reaction starts with the addition of nitrogen trioxide to the double bond of citraconic acid. Two molecules of carbon dioxide are lost and nitroacetone oxime (**232**) is formed. Further action of nitrous and nitric acids on nitroacetone oxime would give oximinonitrolic acid (**233**), whereas hydrolysis would transform it into nitroacetone. From these the oxime of the acyl derivative (**236**) can be formed by reactions analogous to those described above and converted by nitric acid to eulite. The conversion of oximes to the *gem*-dinitro structures by action of nitric acid has been reported in the literature. This conversion could also occur in a previous stage. Other possible schemes can be considered. For example, the oxime of α-nitropropionic aldehyde could replace the oxime of nitroacetone as an intermediate.

Dislite could be formed from two molecules of nitroacetone and a molecule of the hypothetical bisnitrolic acid (**234**), possibly arising from nitroacetone.[8/46] Mesaconic acid, the *trans* stereoisomer of citraconic acid, does not give eulite on treatment with nitric acid. The structures of eulite and dislite have been confirmed by their conversion to 3-acetyl-5-methyl-4-nitroisoxazole and by synthesis, respectively.[4/46,8/46] The entire process is summarized in Scheme 1.10.

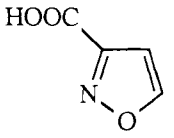



**Scheme 1.10.**

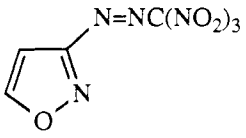
### c. Isoxazoles from Acetylenic Derivatives and Nitric Acid

Old studies[7/01.6/02.10/03] had demonstrated that bubbling acetylene through fuming nitric acid produced nitroform, a solid acid, and a crystalline explosive compound. A thorough investigation of these substances and of two ketones, which are formed in the same reaction when acetylene containing acetone vapor is employed, has been reported.[8/29.3/30.4/30.1/31.3/31.4/31.5/31.6/32.4/34] It was recognized that these compounds were isoxazole derivatives, and in this series of papers their structures and mechanism of formation have been reported. These investigations also led to the characterization of a number of simple isoxazole derivatives.

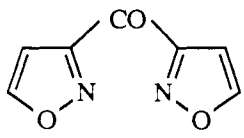
These products are all 3-monosubstituted isoxazole derivatives, although at first, on the basis of their behavior toward alkaline reagents, they were thought to be 5-substituted derivatives. They possess the structure of, respectively, isoxazole-3-carboxylic acid (**238**), 3-isoxazolylazotrinitromethane (**239**), 3,3′-diisoxazolylketone (**240**), and 3,4-bis(3-isoxazolylcarbonyl)furoxan (**241**). With them is associated compound **242**, which is formed with loss of dinitrogen tetroxide on cautious heating of the solution of **239** in an inert solvent or on long standing at ordinary temperature.



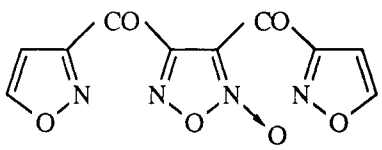

**238**



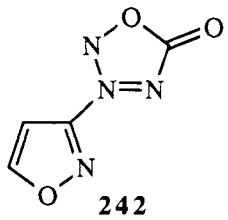

**239**




**240**

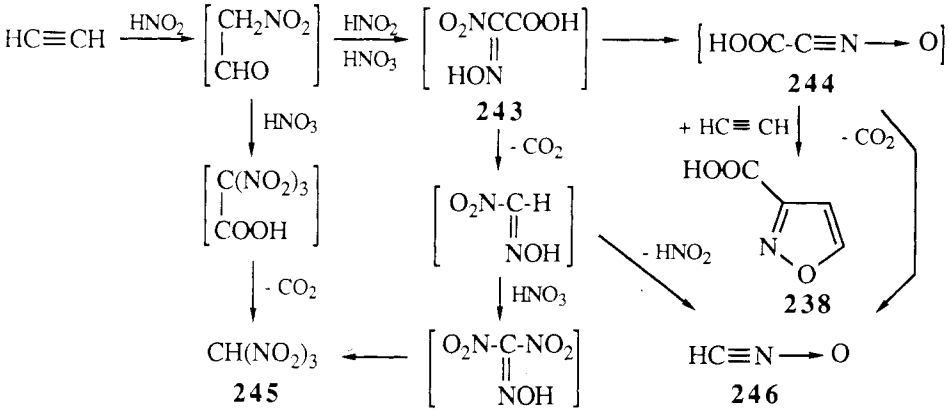



**241**




**242**

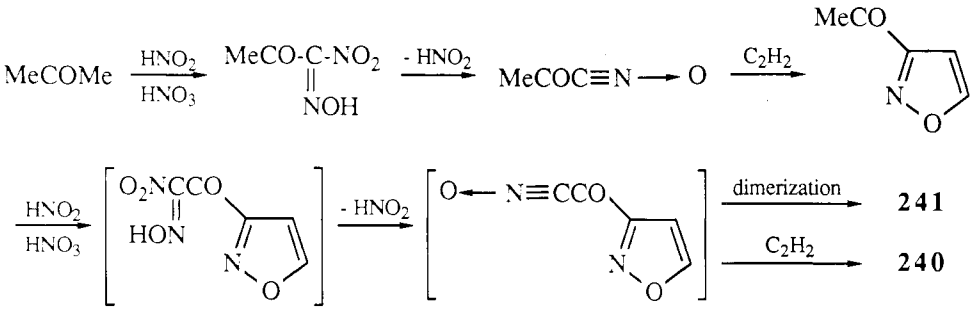
The formation of these compounds has been explained on the basis of their being addition reactions of nitrile oxides and fulminic acid, and the related nitrolic acids, to the acetylenic bond. Thus isoxazole-3-carboxylic acid (**238**) is formed according to the following scheme,[7/46.9/46] where the isolation of nitroform (**245**) is also accounted for:




This is closely related to the interpretation suggested by Wieland[4/07] for the formation of fulminic acid (**246**) from ethanol and nitric acid in the presence of mercury salts. Nitrolacetic acid (**243**), by loss of nitrous acid, yields the nitrile oxide **244**, which adds acetylene to give isoxazole-3-carboxylic acid and may loose carbon dioxide to form fulminic acid (**246**). In Wieland's scheme the latter compound would be formed through methylnitrolic acid by loss of nitrous acid.

Experimental support for this scheme is provided by the formation of isoxazole-3-carboxylic acid from acetylene and ethyl nitrolacetate at ordinary

temperature in nitric acid solution.[9/46] 3,3′-Diisoxazolyl ketone (**240**) is formed in a similar way from acetylene, acetone, and nitric acid:[1B/46]



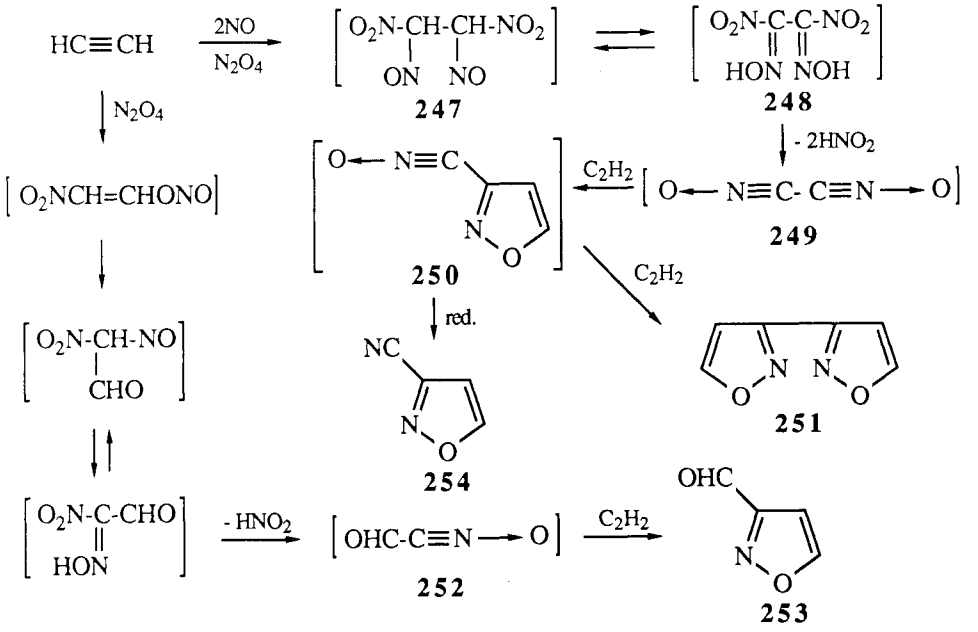

Acetylmethylnitrolic acid, a well-known product of the action of nitric acid on acetone, gives, by loss of nitrous acid, the nitrile oxide, which condenses with acetylene to produce 3-acetylisoxazole. From this, by the same sequence of reactions, the ketone **241**, which is always associated with the ketone **240**, is presumably formed by dimerization of the corresponding nitrile oxide. The scheme above is consistent with the fact that all the isoxazole derivatives formed belong to the 3-monosubstituted series.

Two of the various steps in the process have been checked experimentally: the synthesis of 3-acetylisoxazole from acetylmethylnitrolic acid and acetylene at ordinary temperature and the synthesis of diisoxazolyl ketone from 3-acetylisoxazole and acetylene in a nitric acid solution.[9/46] Furthermore, the intermediacy of pyruvonitrile oxide has been checked by intercepting it with dimethyl acetylenedicarboxylate, which yields the expected isoxazole derivative.[169/66] A similar reaction has been observed in the formation of 3-benzoylisoxazole on treating a solution of acetophenone in nitric acid with acetylene at room temperature.[9/46] The formation of diaroylfuroxan from methyl aryl ketones and nitric acid involves a similar formation of nitrile oxide and its dimerization.

The formation of 3-isoxazolylazonitroform (**239**) is more difficult to explain. This substance has been synthesized by coupling 3-isoxazolyldiazonium chloride with nitroform[6/32] and a similar reaction probably represents the last step in its formation. Possibly, the isoxazole-3-diazonium salt, needed for coupling with nitroform, is formed from the 3-nitroso compound by the action of nitric oxide. This type of formation of diazonium compounds is known in the benzene series.[4/897] The nitrosoisoxazole may be formed from the intermediate $O_2NC(=NOOH)NO$, from the 3-carboxylic acid by displacement of the carboxyl group by nitroso, or from 3-nitroisoxazole by reduction.

Under different experimental conditions the reactions of acetylene with a mixture of nitric oxide and nitrogen dioxide acquires synthetic importance for the preparation of 3,3′-diisoxazole (**251**). Heating the starting materials in a closed vessel in ethyl acetate solution at 50–65°C, a 60–70% yield of **251** is

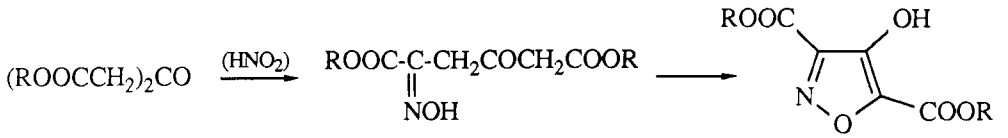
obtained, along with smaller quantities (in the order of 5–10% each) of 3-cyanoisoxazole (**254**) and 3-isoxazolecarboxaldehyde (**253**).[61/58,48/61] The mechanism shown in Scheme 1.11 accounts satisfactorily for the products formed, starting with a normal addition of nitric oxide and nitrogen dioxide to the triple bond to give the dipseudonitrole **247**, which rearranges to the dinitrolic acid **248**. Loss of nitrous acid gives the key intermediate cyanogen-*N*,*N*-dioxide (**249**), which would cycloadd to acetylene in two steps, yielding either the bis adduct **251** or the monoadduct **250**; the latter can be reduced to 3-cyanoisoxazole by the nitrous acid or the nitric oxide present in the reaction mixture.[48/61]



**Scheme 1.11.**

### *1.3.1.8 Nitrosation of Ketodicarboxylic Esters*

4-Hydroxyisoxazole-3,5-dicarboxylic esters are conveniently prepared by nitrosation of dialkyl acetonedicarboxylates (or their α-bromoderivatives) with isoamyl nitrite,[7/891] sodium[194/66] or silver nitrite,[106/69] or nitrosyl chloride:[190/78]



With the latter reagent the intermediate monoxime could be isolated.[190/78]

## 1.3.2 [CNO + CC] Processes

This section is concerned primarily with the 1,3-dipolar cycloaddition of nitrile oxides R–C≡N → O to CC triple-bond compounds to give isoxazoles directly. However, since nitrile oxides are mostly generated *in situ* from precursors such as hydroximoyl halides, primary nitroalkanes, aldoximes, furazan-*N*-oxides, and others, all reactions of these precursors with triple-bond compounds are also considered, provided that no definite open-chain intermediate is isolated and characterized.

On the other hand, dipolarophilic partners not containing CC triple bonds may sometimes be used conveniently. For example, CC double-bond compounds possessing a suitable substituent may undergo a cycloaddition to give a highly unstable 2-isoxazoline, which is transformed spontaneously onto an isoxazole through an elimination reaction (see also § 1.3.7.1, pp. 230–237).

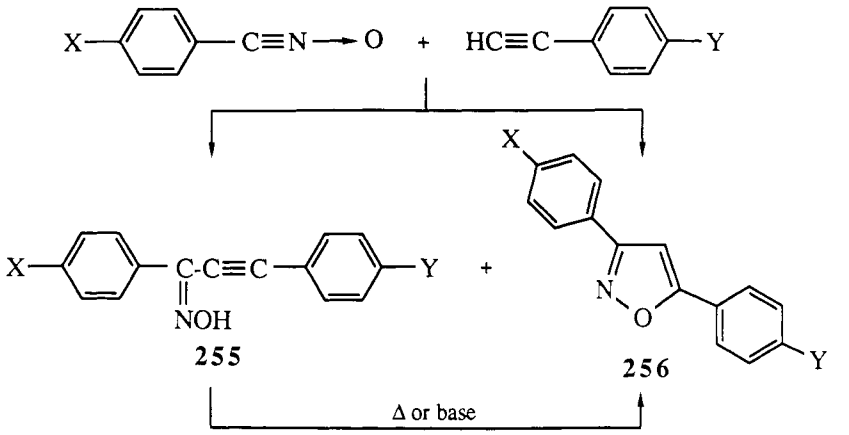
Nitrile oxides (and their precursors) are prone to nucleophilic attack and react in basic media with substrates that can behave as alkyne synthons, such as β-dicarbonyl compounds. In this case the intermediacy of an open-chain β-carbonyl monoxime may be hypothesized, the latter compound cyclizing immediately to the heterocyclic product. Provided that no definite intermediate is evidenced, these reactions are considered here, too. The cycloaddition of nitrile oxides to alkynes has been the object of some reviews.[36B/73.265E/78]

### *1.3.2.1 Cycloaddition of Nitrile Oxides (or Their Precursors) to Acetylenic Compounds*

#### a. General Mechanism

For a general discussion of the significance and mechanism of the 1,3-dipolar cycloaddition of nitrile oxides to unsaturated compounds, reference is made to § 2.2.2.2c, pp. 489–504, where the several sources of nitrile oxides are mentioned briefly. Here some general patterns pertaining particularly to cycloaddition with triple bonds are illustrated.

1. The 1,3-dipolar cycloaddition of nitrile oxides to arylacetylenes to give 3,5-diarylisoxazoles (**256**) has been shown to be in competition with the 1,3-addition to give acetylenic oximes (**255**):



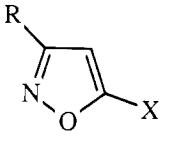
The latter compounds are not intermediates in the cycloaddition, but cyclize readily to isoxazoles either thermally or in a basic medium.[207/69,194B/70,216/70,110/71,112/71,178/72,153/74,278/74] The two reactions are concurrent, and electron-repelling groups on the arylacetylene as well as electron-withdrawing groups on the nitrile oxide increase the percentage of the acetylenic oxime in the reaction mixture, as shown in Table 1.68.

TABLE 1.68. REACTION OF BENZONITRILE OXIDE WITH ARYLACETYLENES: PERCENTAGE YIELD OF ACETYLENIC OXIMES (**255**) IN THE REACTION MIXTURE[194B/70] (SOME VALUES INTEGRATED BY THE REFERENCE'S AUTHORS)

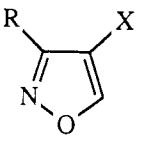
| Y : \ X : | $NO_2$ | Cl | H | OMe |
|---|---|---|---|---|
| Cl | 11 | 9 | 7 | 7 |
| H | 18 | 15 | 12 | 10 |
| OMe | 34 | 32 | 28 | 24 |
| $NMe_2$ | 74 | 65 | 53 | 52 |

2. The CC triple bond is a weaker dipolarophile than the corresponding CC double bond;[28B/73] styrene is more than 10 times more reactive than phenylacetylene, and methyl acrylate is more than 6 times more reactive than methyl propiolate (see Fig. 2.3 and Table 2.15, § 2.2.2.2, pp. 491–492). As far as the reactivity is concerned, some analogies and some differences of behavior toward the alkenes should be emphasized here. In analogy with the alkene dipolarophiles, monosubstitution with a conjugative ester group increases the reaction rate (methyl propiolate reacts three times faster than acetylene), but introduction of a second ester group increases it further, contrary to what happens in the alkene series. Substitution with a methyl group decreases the rate (methyl tetrolate reacts over 40 times more slowly than methyl propiolate), but conjugation with a phenyl group also slows down the rate (e.g., phenylacetylene reacts almost four times more slowly than acetylene).

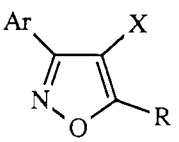
3. Monoalkyl- and monoarylacetylenes as well as other electron-rich monosubstituted alkynes yield the 5-substituted isoxazoles only, thus showing complete regiospecificity. However, with electron-deficient alkynes, mixtures of the two possible regioisomers **257** and **258** are usually obtained. As documented



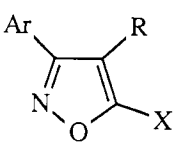

**257**




**258**




**259**




**260**

TABLE 1.69. CYCLOADDITION OF NITRILE OXIDES TO MONOSUBSTITUTED ALKYNES

| R | X | Ratio **257** : **258** | Total yield (%) | References |
|---|---|---|---|---|
| H | COOMe | 84 : 16 | 52 | 28/73 |
| H | CHOHMe | 90 : 10 | n.d. | 139/68 |
| Me | COOMe | 69 : 31 | 90 | 28C/73 |
| Me | *n*-$C_9F_{19}$ | 51 : 49 | 55 | 171/78 |
| $Me_3C$ | COOMe | 91 : 9 | 95 | 28C/73 |
| CN | COOMe | 66 : 34 | 78 | 28C/73 |
| Ph | COOMe | 72 : 28 | 98 | 27/73 |
| Ph | $CF_3$ | 14 : 86 | 78 | 333/83 |
| Ph | $C_6F_5$ | 0 : 100 | 84.5 | 334/83 |
| Ph | COPh | 85 : 15 | 82 | 178/71, 103/81 |
| Ph | CN | 82 : 18 | | 91/77 |
| *p*-$NO_2C_6H_4$ | COOMe | 70 : 30 | 92 | 28C/73 |
| *p*-$ClC_6H_4$ | COOEt | 69 : 31 | 90 | 160/70 |
| *p*-$MeOC_6H_4$ | COOMe | 60 : 40 | 100 | 28C/73 |
| 2,4,6-$Me_3C_6H_2$ | COOMe | 28 : 72 [a] | 97 | 28C/73 |
| 2,4,6-$Me_3C_6H_2$ | COOEt | 34 : 66 | | 91/77 |
| 2,4,6-$Me_3C_6H_2$ | $COOCH_2CH_2Br$ | 30 : 70 | 76 | 77/83 |
| 2,4,6-$Me_3C_6H_2$ | $CF_3$ | 57 : 43 | | 91/77 |
| 2,4,6-$Me_3C_6H_2$ | CN | 57 : 43 | | 91/77 |
| 2,4,6-$Me_3C_6H_2$ | COMe | 80 : 20 | 85 | 103/81 |
| 2,4,6-$Me_3C_6H_2$ | COPh | 59 : 41 | 96 | 103/81 |
| 2,3,5,6-$Me_4C_6H$ | COOMe | 34 : 66 | 100 | 28C/73 |
| PhCO | COOMe | 91 : 9 | 81 | 124/84 |
| $PhSO_2$ | COOMe | 94 : 6 | | 219/79 |

[a] A slight solvent dependance is observed here.

by Table 1.69, the amount of 4-substituted isoxazoles (**258**)(i.e., the isomers with "reversed" regiochemistry) is always far higher in the cycloaddition of nitrile oxides with alkynes than with alkenes. Furthermore, this trend toward the "reversed" product gets considerably stronger with electron-rich nitrile oxides, such as mesitonitrile oxide. For example, methyl propiolate reacts with benzonitrile oxide to yield a mixture of the two regioisomers with a large predominance of the 5-substituted isoxazole; with mesitonitrile oxide the ratio of the two regioisomeric products is exactly reversed in favor of the 4-substituted isomer. The simple frontier orbital theory has been used to explain the regiochemical pattern.[28C/73,128B/73,36D/73,91/77]

4. Although no systematic study of the subject has been undertaken, asymmetrically 1,2-disubstituted electron-deficient acetylenes react with nitrile oxides to yield (exclusively or prevailingly) the regioisomeric isoxazole of general formula **259**, that is, carrying the electron-withdrawing group in the 4-position. As exemplified in Table 1.70, in contrast to the isomer ratios obtained with the corresponding alkenes (see Table 2.15, § 2.2.2.2c, p. 492), a definite shift toward the 4-isomer (**259**) is also observed. This fact has been

TABLE 1.70. CYCLOADDITION OF NITRILE OXIDES TO 1,2-DISUBSTITUTED ALKYNES

| Ar | R | X | Ratio (259) : (260) | Total yield (%) | References |
|---|---|---|---|---|---|
| Ph | Me | COOMe | 99 : 1 | 83 | 27/73 |
| Ph | Me | COPh | 100 : 0 | 80 | 90/68 |
| Ph | Ph | COMe | 100 : 0 | 85 | 158/73, 89/75, 103/81 |
| Ph | Ph | COOMe | 99 : 1 | 94 | 27/73 |
| Ph | Ph | COOEt | 100 : 0 | 87 | 27/73 |
| Ph | Ph | $COOCMe_3$ | 100 : 0 | 40 | 180/70 |
| Ph | Ph | $COOCH_2Ph$ | 45 : 55 (in THF) | 66 | 36/80 |
| | | | 28 : 72 (in toluene) | 54 | |
| Ph | Ph | COPh | 98 : 2 | 55 | 103/81 |
| *p*-$MeC_6H_4$ | Ph | CHO | 100 : 0 | 30 | 153/76 |

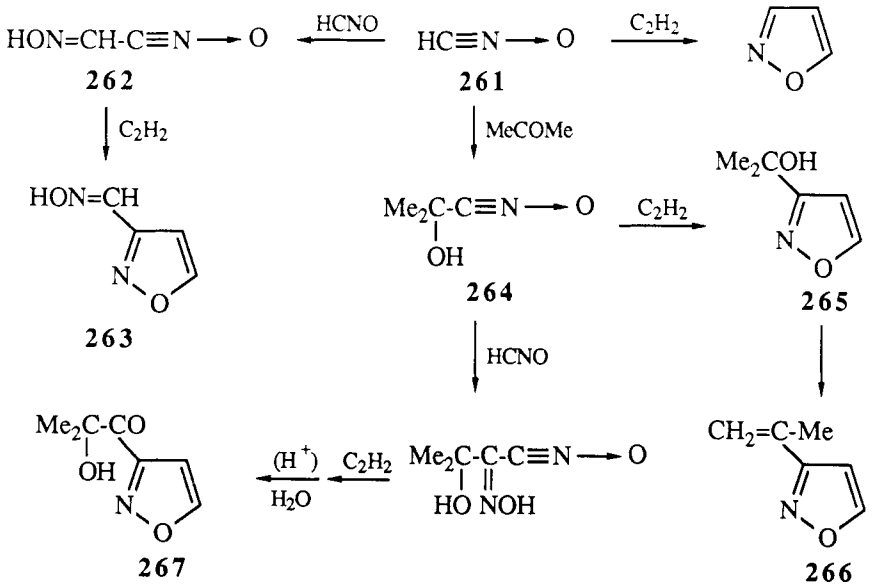
rationalized by invoking both the faster drop of the lowest unoccupied molecular orbital (LUMO)(alkyne) energy upon bending of the dipolarophile toward the transition-state geometry[97B/79] and the presence of secondary orbital interactions between the dipole and the carbonyl group, conceivable in the case of alkyne, but not alkene, derivatives.[153B/78,103/81]

From a preparative point of view, it should perhaps be emphasised that cycloaddition to alkynes, although slower and in moderate yields, most easily furnishes the isomerically pure isoxazole compound. An even more convenient method of preparing 4-isoxazolyl ketones or esters is based on the use of enamine derivatives (see below).

Regiospecific control of the amino group on the cycloaddition is also at work with alkynes; for example, diethylaminophenylacetylene reacts with aromatic nitrile oxides to give high yields of 5-diethylaminoisoxazoles,[2/64.110/65.156/68] and analogously dialkylaminopropiolonitrile cycloadds to give 4-cyano-5-dialkylaminoisoxazoles.[152/70]

### b. Synthetic Potentiality: Syntheses of Isoxazole and Its Monosubstituted Derivatives

The parent compound of the series, isoxazole itself, can be prepared only in poor yield by condensation of the simplest term of nitrile oxide [i.e., fulminic acid (**261**)] with acetylene. Generation of fulminic acid from sodium fulminate and sulfuric acid[7/49] or *in situ* from formohydroximic acid iodide and triethylamine[3/67.56B/69.28/73] led to low yields (1.4–2.6%) of isoxazole together with consistent yields of 3-isoxazolecarbaldehyde oxime (**263**) from the fulminic acid dimer [i.e., oximinoacetonitrile oxide (**262**)]. When the reaction is carried out to increase the concentration of acetylene, with acetone as the solvent, the more complex products **265**, **266**, and **267** have been obtained.[11/39,13/40,5/49] Their formation can be explained by assuming a preliminary attack of fulminic acid on acetone to yield the nitrile oxide **264**, which subsequently reacts with acetylene or with another molecule of fulminic acid according to Scheme 1.12.



Scheme 1.12.

Better conversion to isoxazole (39% overall yield) is realized by a more indirect route (i.e., by cycloadding fulminic acid to norbornadiene and then thermolyzing the condensed polycyclic isoxazoline)[28/73] (see also § 1.3.7.1, p. 245).

Acetylene has been utilized only occasionally as a dipolarophile in the cycloaddition with other nitrile oxides; 3-monosubstituted isoxazoles have been obtained in low to moderate yields.[7/47.7/49,92/68.56B/69.51/72.125B/73] Here, too, better yields are attainable by operating in two steps: first condensing the nitrile oxide with vinyl acetate or vinyl chloride, and then thermolyzing or hydrolyzing the 2-isoxazoline derivative (see below and § 1.3.7.1, pp. 230, 233).

Conversely, cycloaddition of fulminic acid with monosubstituted alkyne derivatives offers a general route for preparing 5-monosubstituted isoxazoles. Yields are satisfactory only when the fulminic acid, prepared *in situ* from either iodoformoxime[3/67,28/73] or sodium fulminate,[145/67] is generated very slowly in the presence of a large excess of dipolarophile. When this precaution is not observed, lower yields and/or products derived from the dimeric form of fulminic acid or from its reaction with acetone (used as solvent), analogous to **263** and **265–267**, are normally observed.[5/49.7/49.139/68.151/77] It should finally be remembered that whereas some alkyne derivatives (e.g., phenylacetylene[3/67,28/73] and propargyl alcohol[145/67]) yield only the 5-substituted isoxazole, others (e.g., methyl propiolate[3/67,28/73] and 1-butyn-3-ol[139/68]) lead to a mixture containing a small amount of the regioisomeric 4-monosubstituted isoxazole (see above). Therefore, on the whole, 5-monosubstituted isoxazoles are prepared more conveniently by oximation of the acetylenic aldehydes (see § 1.3.1.2, pp. 149–150).

### c. Synthetic Potentiality: Synthesis of Disubstituted Isoxazoles

The only example of cycloaddition of fulminic acid to a disubstituted alkyne involves the strong dipolarophilic dimethyl acetylenedicarboxylate, a 33% yield of the expected dimethyl isoxazole-4,5-dicarboxylate being reported.[28/73] Both aliphatic[34/65.147/67.68/78.183/78.71/80] and aromatic[5/46.9/56.3/58.29/60.48/64.118C/65.82/66.207/69.154/70.160/70.26/73.216/73.153/75.68/78] nitrile oxides, usually prepared *in situ* by dehydrohalogenation of hydroximic acid halides or by dehydration of nitroalkanes, easily react with monosubstituted alkynes to yield 3,5-disubstituted isoxazoles. In fact, this represents the best route to these compounds, and their structure can be assured by comparison with the products obtained by oximation of the suitable α-acetylenic or α,β-dihalo ketones (see §§ 1.3.1.2–1.3.1.3).[131/68] This last method, however, which should make it possible to exclude formation of the isomeric 3,4-disubstituted isoxazoles, sometimes leads to the isomeric 3,5-disubstituted derivatives, having the substituents in the reversed position. In this case, comparison with the product obtained by cycloaddition of the same nitrile oxides with the corresponding α-amino-substituted styrene may be useful, owing to the regiospecificity induced by the presence of the amino group (see § 1.3.2.2, p. 200).

In some cases thermal generation of nitrile oxides from hydroximic acid chlorides[86/64.116/65.195/73] or from nitrolic acids[7/46] may be convenient. Stable nitrile oxides (i.e., heavily substituted benzonitrile oxides or their analogous heterocyclic terms) react similarly.[17/59.3/64.88/65.95/67.113/67.158/69.8/72.7/75.170B/78]

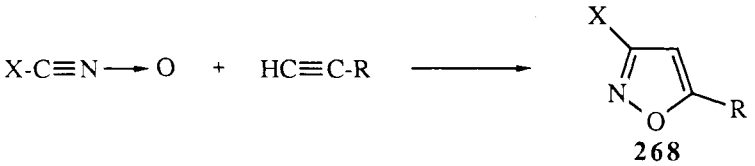
Kinetic studies on the 1,3-dipolar cycloaddition of aromatic nitrile oxides to arylacetylenes[31/66.95/67.151/67.56B/70.216/70.110/71.112/71.153/74] show a very small dependence of rate from solvent polarity, a relatively high entropy of activation ($\Delta S^{+} = -23$ to $-25$ e.u.), and a slightly positive $\rho$ value ($+0.52$) in the reaction between substituted nitrile oxides and phenylacetylene. Obtaining a nonlinear Hammett plot (V-shaped curve with approximate $\rho$ values of $+0.5$ and $-0.3$) in the cycloaddition of an aromatic nitrile oxide to *para*-substituted phenylacetylenes nicely corroborates the hypothesis that the dipolarophile undergoes both a nucleophilic and an electrophilic attack: that is, that both HOMO and LUMO energy differences are comparable in frontier orbital treatment (Sustmann's type II; see § 2.2.2.2c, pp. 490–492).[128B/73.41/74.246C/74] Changes in the transition-state geometries have also been proposed to explain these nonlinear Hammett correlations for some 1,3-dipolar cycloadditions.[180B/75.43B/78] Elaboration of kinetic data must take into account concurrence of the 1,3-addition reaction to give the corresponding acetylenic oximes (p. 183).

The versatility and general applicability of the nitrile oxide isoxazole synthesis is undoubtedly due to the fact that most functional groups do not interfere with the 1,3-dipolar cycloaddition reaction. Therefore, a large number of monosubstituted triple-bond compounds, containing a large variety of heteroatoms in the substituent, are reactive toward nitrile oxides to give 3,5-disubstituted isoxazoles with good to excellent yields. Thus aliphatic or aromatic nitrile oxides

react easily with propargyl halides,[3/57,29/60,107/66,56/72,88/78,52B/79,244/81] ethynylcarbinols,[3/53,22/59,33/61,11/64,82/66,107/66,89/67,106/67,147/67] included some steroidal derivatives,[214/68,21/69,182/69,222/75] alkoxyacetylenes,[50/58,31/59,16/60] and acetylenic amines.[47/64,100/65,106/67,216/73] In the latter case it should be remembered that propargylamine (and presumably other primary or secondary amines) is prevailingly reactive on its amino group, giving rise to a 1,3-addition product, that is, an unsaturated amidoxime (see § 2.2.2.2c, p. 487). The isoxazole amine is also obtained, but as a minor product.[51/66]

The behavior of electron-attracting substituted acetylenes is not as straightforward. In some cases, such as with propynal or its diethylacetal,[7/59] propiolic acid,[5/46,147/67,134/81] and propargylmalonate,[14/63,156/76] the 3,5-disubstituted isoxazole derivative has been reported to be the sole product of the cycloaddition. However, ethynyl ketones,[11/64,178/71,103/81] propiolic esters,[208/68,160/70,27/73,28C/73,186/76,91/77,68/78] propiolonitrile,[35/68,91/77] and polyfluorinated alkynes[91/77,177/77,171/78,333/83] react with nitrile oxides to give a mixture of the two possible regioisomeric 3,5-disubstituted and 3,4-disubstituted isoxazoles, where the latter compound is usually the minor component. Remarkably, the use of mesitonitrile oxide and other polymethylated benzonitrile oxides even reverses this regioselectivity in cycloaddition with methyl or ethyl propiolate.[28C/73,91/77] Furthermore, a moderate dependence of the regioselectivity on the solvent polarity has been recorded here.[28C/73] It should be added that benzyl propiolate is reported to cycloadd benzonitrile oxide regiospecifically.[36/80] For interpretation of the regioselectivity through frontier orbital considerations, see page 494.

Cycloaddition of nitrile oxides to dipolarophiles containing other hetero elements are also known. Trimethylsilylacetylene yields 3,5-disubstituted silicon-containing isoxazoles, contaminated with 3.5–5% of the 3,4-disubstituted regioisomer (NMR evaluation).[15/74] The cycloaddition of aromatic nitrile oxides to acetylenic boronate[120/66,152/66] or phosphinate[197/80] is reported to be regiospecific. On the other hand, several functional groups present in the nitrile oxides do not interfere with the cycloaddition reaction to monosubstituted alkynes, thus allowing easy preparation of isoxazoles (**268**) containing

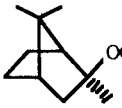
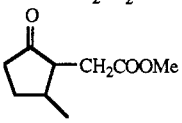



**268**

a reactive site in position 3. A series of typical examples has been collected in Table 1.71.

It is interesting to note that acyl- and sulfonylcarbonitrile oxides show a greater regioselectivity in favor of the 3,5-disubstituted isomer than that of their alkyl and aryl counterparts. Acyl nitrile oxides react with methyl propiolate

TABLE 1.71. SYNTHESIS OF ISOXAZOLES FROM FUNCTIONALIZED NITRILE OXIDES

| X | R | Yield of (268) (%) | References |
|---|---|---|---|
| $CH{\equiv}CCMe_2CH_2$ | $CMe_2CH_2CN$ | 65-70 | 193/75 |
| PhCH=CH | Ph | | 73/73 |
| EtOOC | Ph | 33 | 7/47, 116/65 |
| NC | Ph | 40 | 118/66 |
| MeCO | Ph | 70 | 7/46, 116/65 |
| PhCO | $CH_2Br$ | 80 | 18/71 |
| PhCO | Ph | 100 | 116/65, 18/71 |
|  | COOMe | 80 | 149/81 |
| $MeOOCCH_2CH(COOMe)C(CH_2CH_2COOMe)Me$ | Ph | 90 | 122/76 |
| $MeOOCCH_2CH_2$ | *n*-hexyl | 85 | 245/78 |
| $MeOOCCH_2CH_2$ | Ph | 70 | 148/79 |
|  | *n*-pentyl | 70 | 201/80 |
| $MeC(OCH_2)_2CH_2CH_2$ | *n*-Bu | 80 | 142/79 |
| PhS | COOEt | 65 | 193/81 |
| $PhSO_2$ | 1-phthalimidomethyl | - | 235/81 |

regiospecifically to give methyl 3-acyl-5-isoxazolecarboxylate;[149/81] phenylsulfonylcarbonitrile oxide yields a product contaminated with 6% of the regioisomeric methyl 3-phenylsulfonyl-4-isoxazolecarboxylate.[219/79] The contrast with benzonitrile oxide, which gives a 72:28 mixture of the 5- and 4-regioisomers, is evident and has been ascribed to substantial lowering of the dipole LUMO energy, which thus strengthens the HOMO (dipolarophile)–LUMO (dipole) interaction, leading to the 5-isomer.

The cycloaddition of functionalized aliphatic nitrile oxides (i.e., containing ketone or ester groups) with functionalized monosubstituted alkynes (i.e., containing one or more ketone or aldehyde or ester or cyano groups) regiospecifically furnishes excellent yields of crucially substituted 3,5-disubstituted isoxazoles, starting materials for the synthesis of corrins and related ligands. The versatility of the nitrile oxide synthesis in this field has been reviewed[230/76] and is illustrated in more detail in § 1.4.12, pp. 414–416.

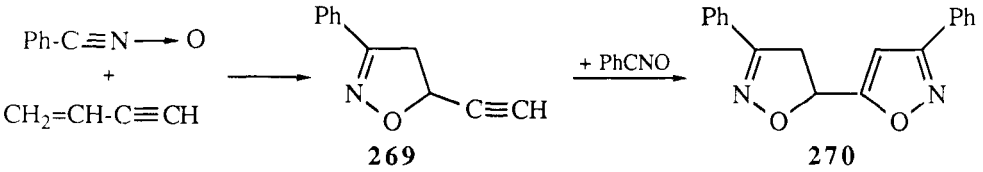
Polyheterocyclic systems can be synthesized when either the nitrile oxide or the alkyne moiety contains another heterocyclic nucleus. Heterocyclic nitrile oxides from the furan,[27/67,35/68,54B/69,132/69,30/71] thiophene,[36/68,54B/69] and pyridine[47/64,187/66,106/67] series are known and cycloadd normally. It has been claimed that with furancarbonitrile oxides, "thermal" generation gives better yields than does dehydrochlorination of hydroximic acid chloride with base.[27/67] Conversely, furyl-[88/68,54B/69] and thienylacetylenes[54B/69] are convenient starting materials for preparing 5-furyl- or 5-thienylisoxazole derivatives, respectively. A large variety of *C*-glucosides containing a disubstituted isoxazole ring (3- or

5-glycosylisoxazoles), and thus being of potential pharmacological interest, have been synthesized through the nitrile oxide route.[98/70.74/71.44/73.58B/73.91/73.32/74.90/74.143/75.33/76.111/80.65B/81]

Site selectivity is observed in the cycloaddition of nitrile oxides to conjugated enynes. The following general rules can be evinced from the experimental results:

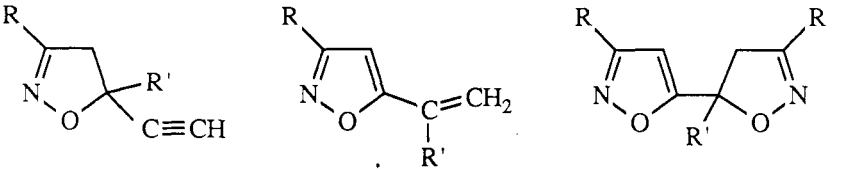
1. When double and triple bonds are substituted equally, competition between the two dipolarophilic sites occurs, the double bond being more reactive than the triple one.
2. A monosubstituted bond is always more reactive than a disubstituted unsaturated bond, irrespective of the nature (double or triple) of the unsaturation.
3. Monoadducts are usually isolable when cycloaddition is carried out in the presence of an excess of dipolarophile; bis adducts are also obtained if both bonds are dipolarophilic enough and when the ratio of the reactants is at least 1:1.

This general pattern is illustrated by the reaction of vinylacetylene with benzonitrile oxide:[20/55.22/60.67/63] with an excess of vinylacetylene only 5-ethynyl-3-phenyl-2-isoxazoline (**269**) is obtained, whereas with equimolar amounts of starting materials a mixture of **269** and the bis adduct **270** is formed.



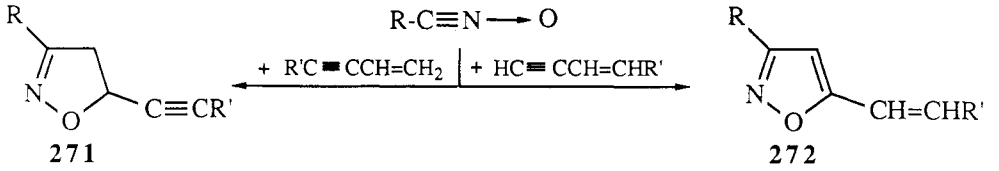

**269** **270**

When acetonitrile oxide is used, 3-methyl-5-vinylisoxazole has been isolated as a by-product.[200/66] As the following summary shows, the methyl substitution on the 2-position of the vinyl group[33/61,123/64,200/66] decreases the reactivity of the double bond in favor of the triple bond, which becomes even a higher reactive point in the case of acetonitrile oxide:




| R | R' | Yield (%) | Yield (%) | Yield (%) | References |
|---|---|---|---|---|---|
| Me | H | 17 | 6 | 15 | 200/66 |
| Ph | H | 18 | 11.5 | 48 | 33/61, 123/64 |
| Me | Me | 9 | 20 | 15 | 200/66 |

On one or the other side of the conjugative moiety, substitution totally suppresses the reactivity of the disubstituted bond, thus leading either to an isoxazoline (**271**) or an isoxazole (**272**) monoadduct:[20/55,22/60,33/61,91/63,97/63,123/64,135/65,81/66,200/66,145/67,226/68,73/73,228/75,161/77]




**271** **272**

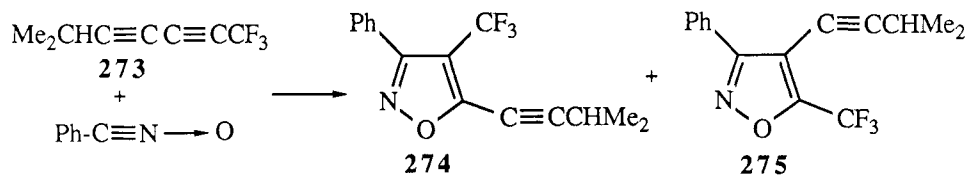
(R = H, Me, Ph; R' = Ph, CHO, $CH_2OH$, COOR", OR", alkyl, SR", SeR", TeR", $SiMe_3$, C≡CH)

The presence of a carbonyl or carbinol or methylene group inserted between the two unsaturated bonds does not affect the general reactivity pattern above.[174/67,69/73]

d. Synthetic Potentiality: Syntheses of Trisubstituted Isoxazoles

Dihydrocarbyl alkynes are very poor dipolarophiles and usually do not react at all with benzonitrile oxides. Attempts to force the reaction lead only to isomerization of nitrile oxides to isocyanates or to dimerization to furoxans. Nevertheless, diphenylacetylene, which has been reported to be unreactive toward benzonitrile oxide in ether,[5/46] gives a 28% yield of 3-(5′-nitro)furyl-4,5-diphenylisoxazole when faced with the thermal decomposition of 5-nitrofurohydroximoyl chloride.[27/67] By contrast, no isoxazole derivative is obtained by the usual dehydrohalogenation procedure. The very reactive phenylglyoxylonitrile oxide affords only 5% of the expected 3-benzoyl-4,5-diphenylisoxazole when reacted with tolan.[18/71]

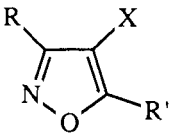
Activation of the triple bond by strong electron-attracting groups, such as in perfluoro-2-butyne, promoted the cycloaddition.[149/81] Coherently, the diyne **273** reacts with benzonitrile oxide only with its triple bond directly activated by the $CF_3$ group; a mixture of the two regioisomers **274** and **275** arises:[333/83]



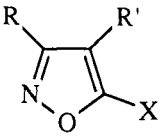

**274** **275**

Conjugation with carbonyl, cyano, or ester groups strongly enhances the reactivity, and moderate to good yields of trisubstituted isoxazoles (**276**) can easily be reached.[86/84,90/68,208/68,180/70,20/71,27/73,158/73,89/75,66/76,153/76,103/81,149/81] As shown by the data in Table 1.70, a very high regioselective control is operating, and the

regioisomers **277** are formed only occasionally as by-products in very low yields. A notable exception to this rule is the reaction with benzyl phenylpropiolate, which gives a mixture of the two regioisomers, where the "abnormal" isomer carrying the ester group in the 5-position predominates. However, cycloaddition with the polymer-supported acetylenic ester affords the isoxazole carrying the ester group in the 4-position as a unique product.[36/80]



**276**



**277**

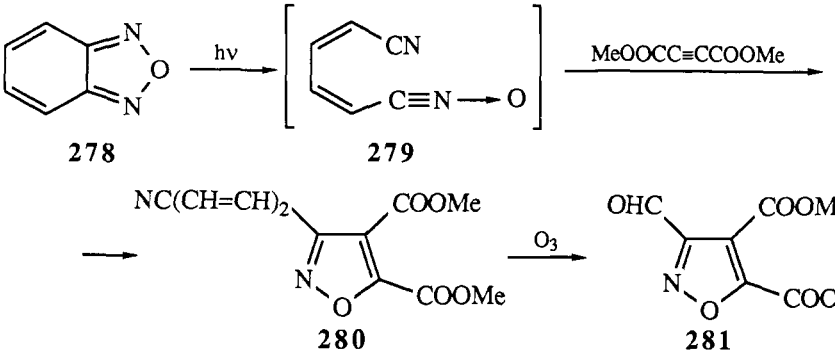
(X = COR" (Ar), CHO, COOR")

A phosphonate group shows the same regiospecific control and the same activating action as those of the methoxycarbonyl group.[72/79,65B/81] Nitro-*t*-butylacetylene also gives an isoxazole with the nitro group in 4-position.[4/70] Free arylpropiolic acids are reported to cycloadd nitrile oxides to give isoxazole-4-carboxylic acids.[5/46,7/46,9/56]

A large variety of semisynthetic penicillin derivatives containing the isoxazole nucleus [see, e.g., oxacillin (**101**) and their mono- (**102**) and dichloro (**103**) derivatives] are available through nitrile oxide synthesis.[91B/70,65/74,18/75,171/75,207/76] 2-Butynoylpenicillanic acid is usually utilized as a dipolarophilic partner.

By far the most active disubstituted dipolarophile seems to be dialkyl acetylenedicarboxylate, which cycloadds the very different nitrile oxides to give the corresponding isoxazole-4,5-dicarboxylic esters.[30/66,118/66,36/68,240/77,68/78, 149/81,193/81] Dimethyl acetylenedicarboxylate has sometimes been used as a scavenger to trap the presumed intermediate nitrile oxide.[169/66,236/74,186/76,33B/79,41/80, 200/80,281/83]

It seems worthwhile to mention the photoinduced ring opening of benzofurazan (**278**), leading to the highly reactive nitrile oxide **279**, which can be trapped with dimethyl acetylenedicarboxylate. The resulting 3-(δ-cyano)butadienylisoxazole (**280**), isolated as a mixture of diastereoisomers, is not easily prepared by other routes and gives the aldehydo diester **281** by ozonolysis:[147/75] An analogous result is obtained from 5,6-dimethylbenzofurazan.[112/81]




**278** **279** **280** **281**

Dicyanoacetylene is also a very active dipolarophile, and 3-phenyl-4,5-dicyanoisoxazole is reported to form in 84% yield by reaction with benzonitrile oxide in refluxing ether.[61/63] Analogous results are obtained with bistrimethylsilylacetylene,[44/64,15/74] where the use of mesitonitrile oxide at 50°C without solvent increases the yield up to 98%.[15/74]

The strong directing power of the amino group is evidenced by the fact that regiospecific cycloaddition of nitrile oxides to diethylaminophenylacetylene[156/68] or to diethylaminopropiolonitrile yields 5-aminoisoxazoles:[152/70,18/71]



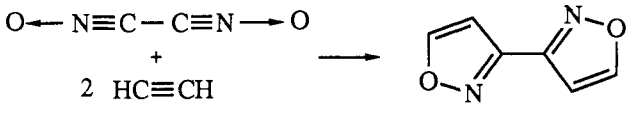

(R' = Ph or CN)

Conversely, phenyl propynyl thioether cycloadds an aromatic nitrile oxide regioselectively only: a 10:1 mixture of regioisomers is obtained, with prevalence of the 4-phenylthio-substituted isoxazole.[52C/81]

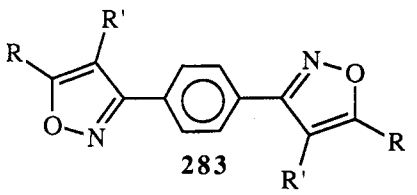
e. Synthetic Potentiality: Syntheses of Polyisoxazoles

Polynuclear systems containing two or more isoxazole rings can be built up conveniently through nitrile oxide synthesis. Two routes are a priori conceivable: either a bisnitrile oxide is condensed with an alkyne, leading to a 3,3′-linkage of the two isoxazole rings, or a nitrile oxide in excess is reacted with a diyne compound, in which case a 5,5′-linkage is created. Furthermore, when a bisnitrile oxide cycloadds to a diyne, polymeric compounds can arise.

An example of the former case is represented by the cycloaddition of oxalobisnitrile oxide, prepared *in situ*, to acetylene, which leads to 3,3′-diisoxazole (**282**) in 60–70% yield.[48/61] The same bisnitrile oxide has been isolated at very low temperature as an unstable solid[2/65] and reacts promptly with active dipolarophiles such as phenylacetylene[4/63,2/65,116/65] and dimethyl acetylenedicarboxylate.[2/65] However, with less reactive alkynes, such as tolan, dimerization to the furoxan bisnitrile oxide occurs first, leading to low yields of the corresponding 3,4-diisoxazolyl furoxan:[2/65]




**282**

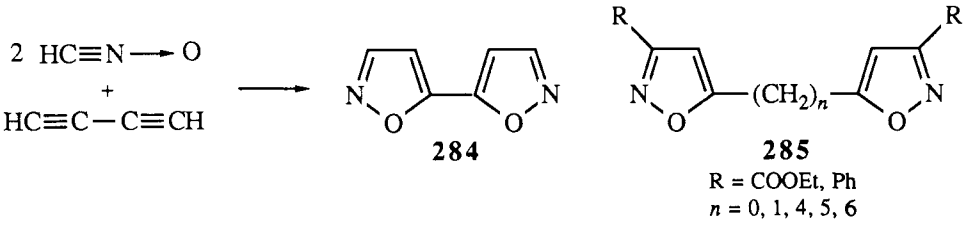



**283**

| R | R' |
|---|---|
| Ph | H |
| $CH_2OH$ | H |
| COOMe | H |
| $NEt_2$ | Ph |
| N*i*-$Bu_2$ | N*i*-$Bu_2$ |

Another bisnitrile oxide (i.e., terephthalonitrile di-*N*-oxide) is easily accessible and has often been utilized as a starting material for the preparation of bisisoxazole derivatives of general formula **283**.[2/64.20/64.92/65.2/66.33/68.157/68] Diisoxazole derivatives, derived from tetramethylated terephthalonitrile dioxide,[88/65] isophthalonitrile di-*N*-oxide,[113/67.33/68.271/78] thiophene 2,5-dinitrile dioxide,[96/71] pyridine 2,6-dinitrile dioxide,[269/78] or malonodinitrile di-*N*-oxide,[154/77] are also known.

Conversely, the cycloaddition of fulminic acid to butadiyne afforded 5,5′-diisoxazole (**284**), together with other by-products derived from the dimeric form of fulminic acid.[48/59] The deuterated compound **284** has been prepared by the same procedure.[87/64] More straightforward results and higher yields have been obtained by cycloaddition of carbethoxyfulmide[32/72] or of aromatic nitrile oxides[22/59.81/66] to butadiyne or to diethynylalkanes. Diisoxazoles or diisoxazolylalkanes of general formula **285** (i.e., linked through 5,5′-positions) are thus formed:

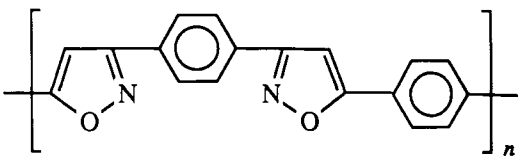



**284** **285**

R = COOEt, Ph
*n* = 0, 1, 4, 5, 6

The reaction has wide applicability, as demonstrated by the cycloaddition of several nitrile oxides to other diyne derivatives, such as 1,4-dihydroxy-1,4-diethynylcyclohexadienes,[33/61] 1,4-diethynyl-benzene or naphthalene,[60/62] siladiynes,[15/74] and diphenylpropiolylperoxide.[180/70] All these compounds have two terminal free ethynyl groups and can afford both the monoadduct and the more or less insoluble bis adduct, according to the reactants ratio. It is, however, worth noting that when one of the two triple bonds is disubstituted, as in compounds of general formula RC≡CC≡CH, only the monoadduct to the terminal triple bond is obtained.[201/66]

A considerable effort has been made to synthesize di- or polyisoxazolylmethanes having methylene groups connecting positions 5 and 5′ of the isoxazole rings. The synthesis of these $\beta$-polyketone synthons can be achieved through appropriate use of the nitrile oxide method, building the molecule stepwise one heterocyclic ring at a time.[81/66.161/77] Finally, polymers of type **286**




**286**

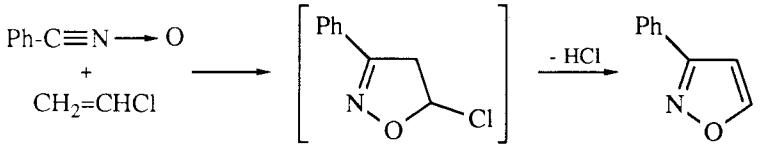
are obtained by polycycloaddition of terephthalonitrile oxide with 1,4-diethynylbenzene.[92/65.157/68.165B/71]

### *1.3.2.2 Cycloaddition of Nitrile Oxides (or Their Precursors) to Ethylenic Compounds*

As will be discussed in § 1.3.7.1 in more detail, several types of 2-isoxazolines, containing a suitable leaving group in the 4 or 5 position, can easily undergo an elimination reaction to yield the corresponding isoxazole. Since the foregoing 2-isoxazolines are usually attainable by the nitrile oxide synthesis, sometimes cycloadditions of nitrile oxides to double-bond dipolarophiles can directly afford the isoxazole derivatives, because of the lability of the intermediate 2-isoxazoline under experimental conditions.

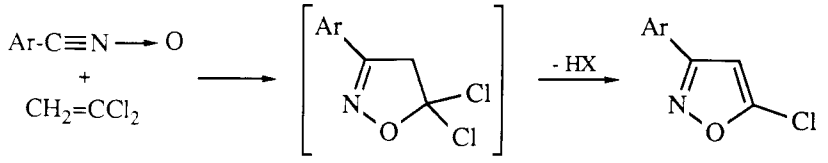
Although the division is somehow artificial, in this section we will deal with cycloaddition reactions where the 2-isoxazolines could not be isolated, deferring analogous reactions, where isolation of the intermediate primary cycloadduct is possible or demonstrated, to § 1.3.7.1. In these cases the isoxazole is obtained in a second step, under thermolytic, basic, or acidic treatment. Several electronegative groups, such as OH, OMe, SMe, OCOMe, halogens, $NO_2$, $NH_2$, $NR_2$, $N(CH_2)_4$, and $N(CH_2)_4O$, are suitable leaving groups and are spontaneously eliminated as HX from the primary 2-isoxazoline cycloadduct.

Vinyl chloride has long been known to react with benzonitrile oxide;[16/50] although the intermediacy of 3-phenyl-5-chloro-2-isoxazoline is only presumed, 3-phenylisoxazole has been obtained in iced ether in 90% yield:[26/73]



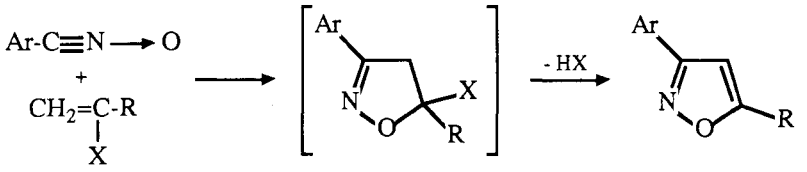

An analogous result has been obtained with vinyl bromide.[38/70]

The most direct synthesis of 3-aryl-5-chloroisoxazoles is based on the cycloaddition of nitrile oxides to vinylidene chloride:[193/70,185/84]



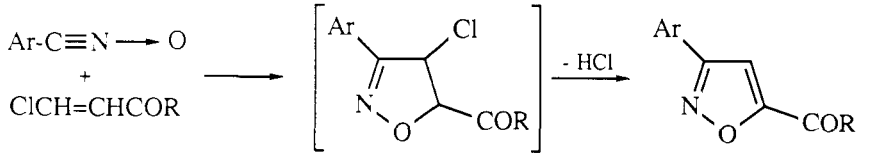

Several other 5-substituted isoxazoles are easily prepared by the cycloaddition of nitrile oxides to $\beta$-halogen-substituted alkenes or to double-bond compounds of general formula $CH_2=C(Cl)R$[8/54.42/70,244/73,13B/76] (see Table 1.72).

TABLE 1.72

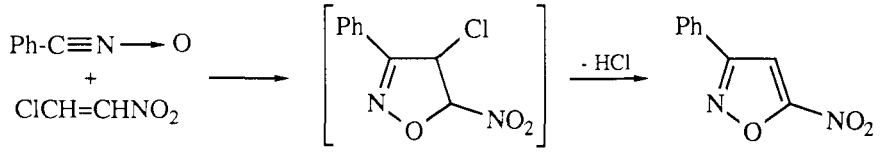


| X | Ar | R | References |
|---|---|---|---|
| Br | Ph | Me | 118C/65 |
| Br | Ph | Ph | 8/54 |
| Cl | Ph | *p*-$MeC_6H_4$ | 8/54 |
| Br | 2,6-$Cl_2C_6H_3$ | Me | 42/70 |
| Cl | 2,6-$Cl_2C_6H_3$ | CN | 42/70 |
| Cl | Ar | CN | 244/73 |
| Br | Ph | $NO_2$ | 252/82 |
| Cl | Ph | $CH_2Cl$ | 13B/76 |
| Br | Ph | $CH_2Br$ | 29/60 |

A change in the regioselectivity has been observed with β-chlorovinyl ketones, which invariably cycloadd to yield 3-aryl-5-acylisoxazoles;[32/58] when aryl β-chlorovinyl ketones are used, the intermediate chloroisoxazoline is generally stable enough to be isolated in the absence of bases:[11/64]



An analogous regiochemistry controls the reaction with 2-chloro-1-nitroethylene, only 5-nitro-3-phenylisoxazole being thus obtained; the chloroethylenic derivative is here a convenient synthon of the elusive nitroacetylene:[32/75]



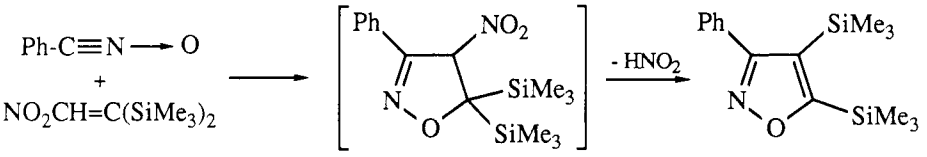
Both a monoadduct and a diisoxazole can be isolated from the cycloaddition of aryl nitrile oxides to 2,3-dichlorobutadiene.[199/66]

Usually, the 5- or 4-nitro-2-isoxazolines, obtained by cycloaddition of nitrile oxides to conjugated nitroalkenes, are sufficiently stable to be isolated as the primary product. Nevertheless, with 2-nitropropene or 2-nitro-2-butene this

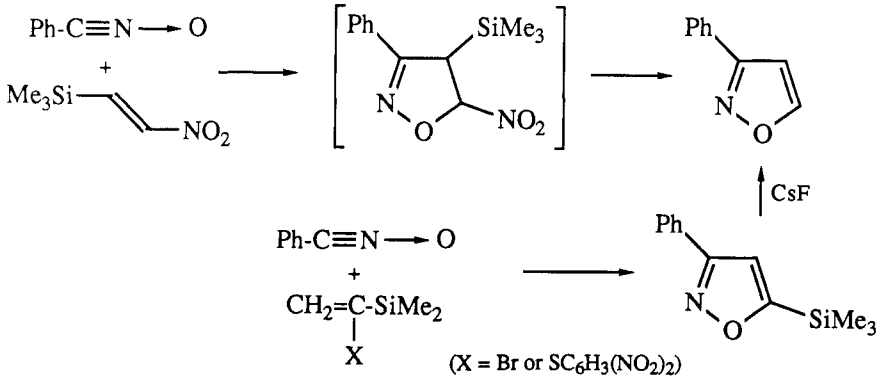
was not possible, and under the experimental conditions adopted (dry ether solution, 12 h at room temperature followed by 2 h of reflux), only 3-aryl-5-methyl- or 4,5-dimethylisoxazole, respectively, is formed directly through elimination of nitrous acid.[225/76] A mixture of regioisomeric isoxazoles is also obtained directly under spontaneous loss of nitrous acid in cycloaddition with nitroethylenes $\beta$-conjugated with electron-withdrawing groups, such as cyano, carboxy, or carbalkoxy; in this case, the 3,4-disubstituted isoxazole is largely predominant over the 3,5-disubstituted isomer.[249/82] Analogous behavior is noted with $\alpha$-nitrostilbene[8/54] but not with $\omega$-nitrostyrene, which yields a mixture of the stable 4-nitro-3,5-diphenyl-2-isoxazoline[9/50] and of the less stable regioisomer. The mixture of primary products is conveniently transformed into a mixture of 3,5- and 3,4-diphenylisoxazole.[26/73]

It is worth emphasizing that, both with halogens and with a nitro group, the ease of elimination is definitively higher when the leaving group is located in the isoxazoline 5-position compared with a regioisomer that has the leaving group in the 4-position. For example, at 150–170°C and 0.001 mm, only the 5-nitro-derivative loses nitrous acid, yielding 3,4-diphenylisoxazole; the regioisomeric 3,5-diphenyl-4-nitroisoxazoline is stable at these temperatures and aromatizes under more vigorous conditions.[26/73]

Loss of $NO_2^-$ from the isoxazoline 4-position is accompanied by a 1,2-migration of a trimethylsilyl group in the cycloaddition reaction of benzonitrile oxide to 1,1-bis(trimethylsilyl)-2-nitroethylene, which produces 3-phenyl-4,5-bis (trimethylsilyl)isoxazole:[281/82,209/83]



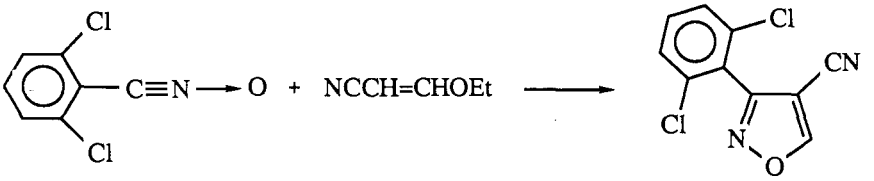

Moreover, 3-phenylisoxazole is produced directly, although in low yields, when benzonitrile oxide is cycloadded to 2-nitrovinyltrimethylsilane:[209/83]



The same product was obtained by desilylation of the 5-trimethylsilyl derivative, easily attainable through cycloaddition of the nitrile oxide to a suitable α-substituted vinyltrimethylsilane.[209/83]

The dehydration of the low-stable 5-hydroxy-2-isoxazolines is dealt with in § 1.3.7.1, pp. 231–232. Here we should mention that the enolic form of β-diketones or β-keto esters is believed to be the real dipolarophilic moiety in the cycloaddition of these compounds to nitrile oxide (see § 1.3.2.3, p. 203).

Vinyl ethers usually cycloadd nitrile oxides to furnish stable 5-alkoxy-2-isoxazolines; however, if an activating cyano group is also conjugated with the double bond, the 4-cyanoisoxazole has been obtained directly:[42/70]

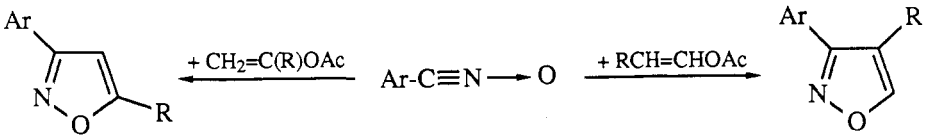



(60% yield)

Direct cycloaddition of the nitrile oxide to cyanoacetylene would have given the isomeric 5-cyanoderivative. A similar "reversion" of regiochemistry is accomplished with 3-nitroacrylonitrile, which reacts with benzonitrile oxide to yield 3-phenyl-4-cyanoisoxazole with high regioselectivity.[258/82] The reaction with methyl 3-cyanoacrylate is less straightforward and gives a mixture of isoxazole compounds.

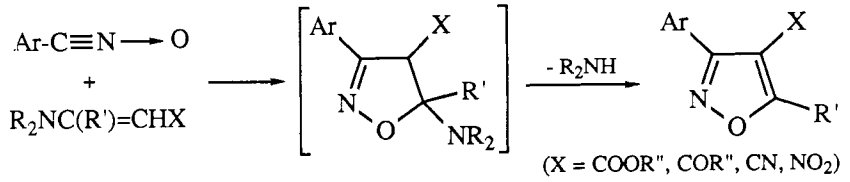
Vinyl acetate is an active dipolarophile and cycloadds nitrile oxide to give the corresponding 5-acetoxyisoxazoline derivatives. However, depending on both the experimental conditions and the nature of the nitrile oxide, a spontaneous elimination of acetic acid sometimes occurs, and the isoxazole derivative is directly isolated. Isoxazole itself[1/51] and several 3-substituted isoxazoles[37/65,27/69,38/70,215/71] have thus been synthesized.

The elimination reaction is easier when isopropenyl acetate or α-acetoxystyrene are utilized as dipolarophiles, the 3-aryl-5-methyl (or phenyl)-isoxazole being regiospecifically obtained.[56/67,89/68,38/70,174B/72] The directive power of the acetoxy group is evidenced by the fact that cycloaddition to propenyl acetate or to β-acetoxystyrene leads to regioisomeric 3-aryl-4-methyl (or phenyl)-isoxazole as the sole product:[51/69,141/72]



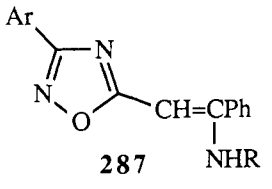

Enamines are known to be very active dipolarophiles, and promptly react with nitrile oxides to yield 5-amino-substituted isoxazolines, which can easily be transformed into isoxazoles by acidic or thermal treatment. The cycloaddition

is strictly regiospecific, the amino residue always occupying the 5-position. Consequently, the deamination opens a convenient route to 4-substituted isoxazoles, even those unsubstituted in the 5-position. Occasionally, direct synthesis of the isoxazole derivative has been reported,[37/63,27/69,51/69,26/73] even with amino-substituted alkenes. The elimination of the amine molecule (dialkylamines or cyclic amines such as pyrrolidine or morpholine are usually present) is strongly accelerated by the presence of a conjugated electron-attracting group, such as carbonyl, ester, cyano, or nitro. In such cases direct entry into the isoxazole 4-carboxylates,[37/63,80/67,114/69,125/69,27/73,204/73,240/79,205/80] 4-phosphinates,[197/80] or 4-acyl-,[37/63,178/71,219/72,158/73] 4-cyano-,[35/68,18/71] or 4-nitroisoxazoles[149/81,115/83] is available. The method has very wide applicability and gives moderate to good yields:

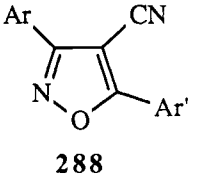



*Cis* elimination is easy here. Furthermore, the captodative olefins act as synthons of the corresponding acetylenic derivatives, which, however, if used as dipolarophiles, lead to a mixture of the two regioisomers or, more frequently, to the regioisomeric 5-substituted derivatives. For example, *m*-nitrobenzonitrile oxide reacts with 3-morpholinylacrylonitrile to yield the 3-aryl-4-cyanoisoxazole, and with propiolonitrile to give, in lower yields, the 3-aryl-5-cyanoisoxazole.[35/68]

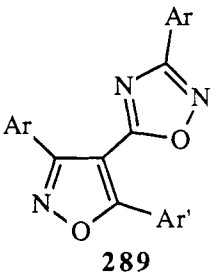
It is worth noting that in β-aminocinnamonitrile, carrying a free or a monosubstituted amino group, the cyano group becomes the most reactive dipolarophilic moiety, thus leading to the 1,2,4-oxadiazole derivatives (**287**).[143/77,159/80] Only in the presence of a cyclic amino group[143/77] or of β-amino-*p*-dimethylaminocinnamonitrile[159/80] are the isoxazole monoadduct **288** and bis adduct **289** respectively, obtained.




**287**

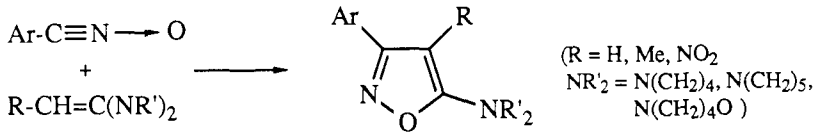



**288**



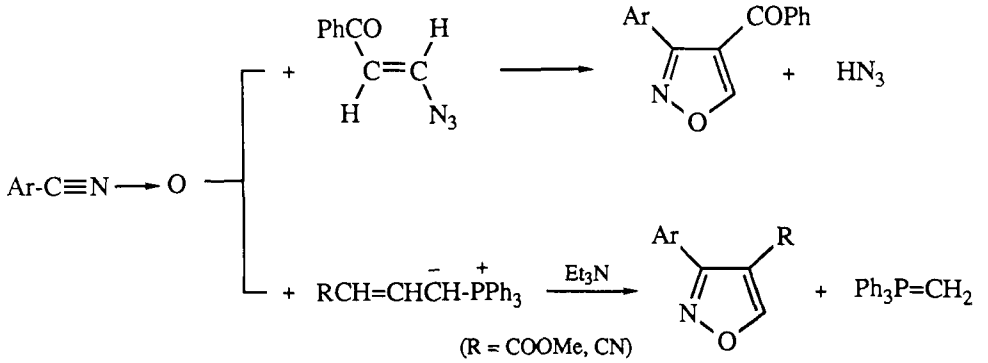

**289**

Ketene aminals are also active dipolarophiles, and here an easy general synthesis of 5-dialkylaminoisoxazoles is realized:[177/66,139/73,230/74]

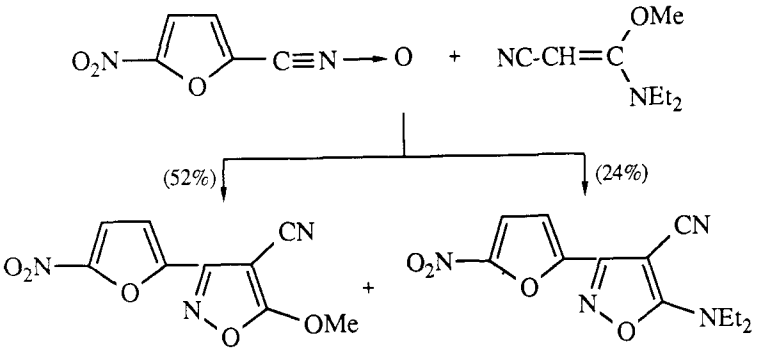



5,5-Dialkoxy-2-isoxazolines do not eliminate one molecule of alcohol spontaneously; only mild hydrolysis under controlled conditions makes it possible to achieve that goal.[26/59] By contrast, cycloaddition of nitrile oxides to ketene diethylmercaptal affords 3-aryl-5-ethylthioisoxazoles directly,[36/63] without isolation of the intermediate isoxazoline derivative. The reaction is more sensible to steric limitations than is a reaction with oxygen analogues; methylketene diethylmercaptal does not cycloadd at all.

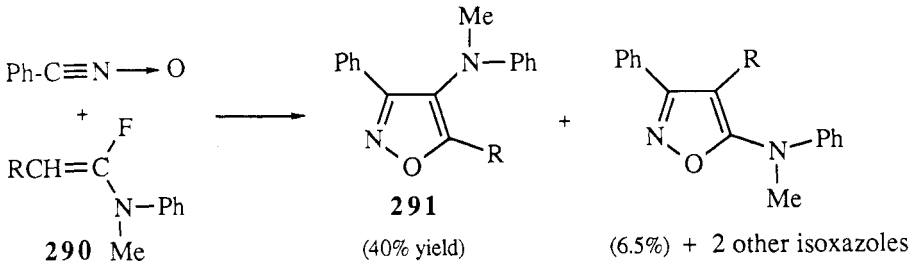
Other easily eliminated moieties are hydrazoic acid[176/74] and methylenetriphenylphosphorane,[149/76] as the following examples show:




When two good leaving groups are present simultaneously, a mixture of two isoxazoles can eventually arise, as evidenced by the following example:[152/70]

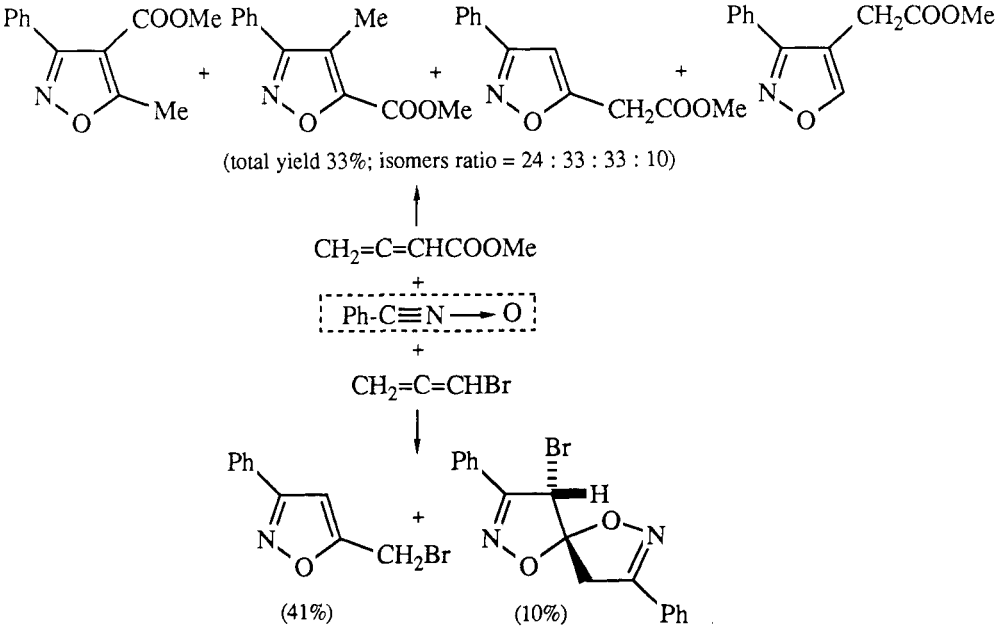



A different example is provided by the fluoroenamine **290** (R is a glycosyl residue), which cycloadds benzonitrile oxide to give a mixture of isoxazoles, where surprisingly, the major product is the 4-amino-substituted isoxazole **291**:[65B/81]




Two special cases of ethylenic compounds, which can cycloadd to nitrile oxides to yield isoxazoles directly, are quinones and some allenic derivatives. For the former compounds, which give rise to indoxazenequinones and their benzo derivatives, reference is made to Part 2 of this work.

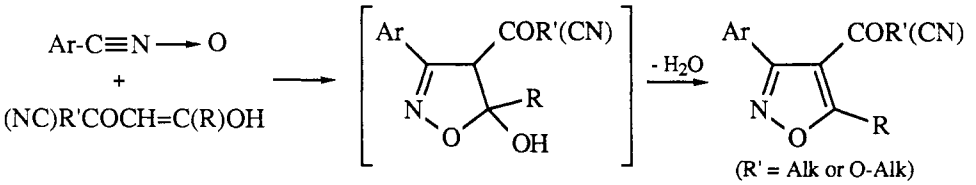
Unsubstituted allene or its alkyl (or aryl)-substituted terms are known to cycloadd 2 mol of nitrile oxides to give spirobisisoxazolines (see § 2.2.2.2e, p. 509). Nevertheless, the presumed intermediates 4- or 5-methyleneisoxazolines sometimes rearrange to isomeric substituted methylisoxazoles before cycloadding a second molecule of dipole. This occurs, for example, with allenic monocarboxylic esters[55/70,44/78] or with bromoallene,[143/74] as the examples in Scheme 1.13 shows.




**Scheme 1.13.**

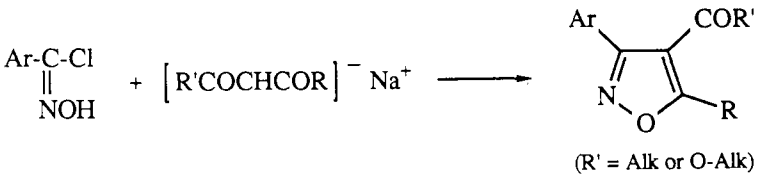
### *1.3.2.3 Cycloaddition of Nitrile Oxides (or Their Precursors) with Active Methylene Compounds*

Several compounds containing an active methylene group, such as β-keto esters, β-diketones, β-keto nitriles, or α-cyano esters, react readily with nitrile oxides to give isoxazole derivatives.[5/46] The reaction takes place only in the presence of catalytic amounts of a base (i.e., sodium hydroxide or alkoxide). A more or less concerted cycloaddition of the 1,3-dipole to the enolic form of the β-dicarbonyl derivative or to its resonance-stabilized carbanion has been suggested to occur:




The presumed intermediate 5-hydroxy-2-isoxazolines have never been evidenced under the experimental conditions adopted.

A longer known and more widely used method of preparing the same types of isoxazole compounds (i.e., having an ester, a ketone, or a cyano group in position 4) is the reaction of hydroximoyl chlorides, the usual precursors of nitrile oxides, with the sodium salts of active methylene compounds:[8/36,4/37]



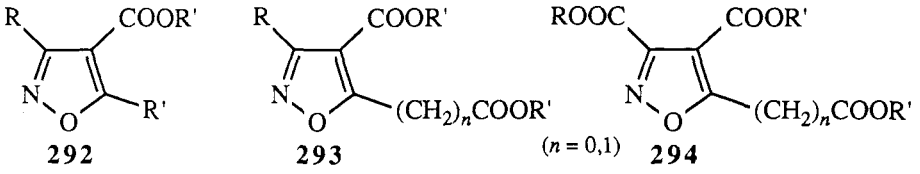

Rapid dehydrochlorination of the hydroximoyl chloride by the strong carbanion base should bring the reaction back to the cycloaddition pattern shown above (i.e., nitrile oxide + enolate). Although other mechanistic pathways cannot be excluded, the presence of furoxans as by-products and the occasional isolation of relatively stable nitrile oxides as intermediates seem to corroborate the view reported above.

A large variety of 3-aryl-5-methylisoxazole-4-carboxylates have thus been synthesized by treatment of the appropriate benzohydroximic acid chloride with an ethanolic solution of the sodium salt of alkyl acetacetate.[4/37,49/58,46/59,24/60,53/62,53/63,54/63,79/65,165/67,78/68] The condensation occurs in good yields at room temperature or below, and fairly good results are also obtained when nitrile oxide is used instead of the hydroximoyl chloride.[5/46,17/59,133/66,193/81]

Very wide variations of the isoxazole-4-carboxylate substitution pattern are possible, so that the general structure **292** is always attainable using the proper reactants. For example, an alkyl,[193/81] cycloalkyl,[46/75] alkoxycarbonyl,[8/39,193/81] or

heterocyclic[54/63,190/66,198/66,35/67,27/69,151/69,183/70] group can be introduced in position 3 if the appropriate hydroximic acid chloride or nitrile oxide is utilized.

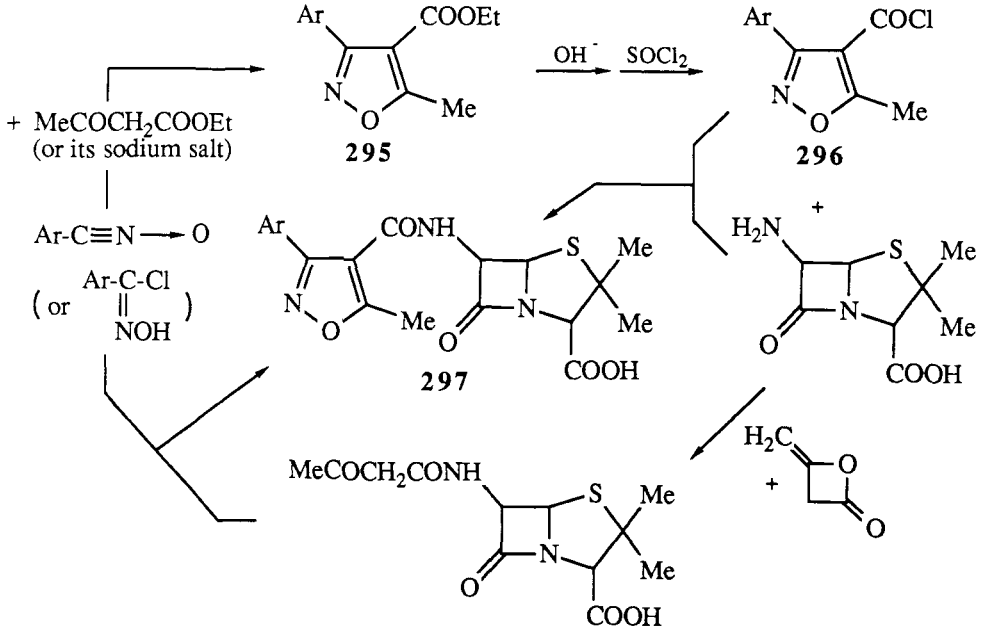
A 5-unsubstituted isoxazole-4-carboxylate can be prepared if the condensation is carried out with formyl acetate sodium salt;[27/69,151/69] furthermore, alkyl,[54/63,78/68] aryl,[8/39,53/63,54/63,27/69,151/69] formyl,[215/68] heterocyclic,[54/63,151/69,47/75] or styryl[54/63,77/69] substituents have been inserted in position 5. The use of oxalacetic ester or of acetonedicarboxylate as dipolarophilic moieties furnishes dicarboxylic (**293**)[4/37,4/40,5/46,124/69,126/69] or tricarboxylic esters (**294**), respectively:[5/40]




Similar results have been obtained using β-ketocarboxamides instead of esters.[233/78]

The reaction of β-keto esters or of malonic esters with hydroximoyl chloride in aqueous basic medium does not follow the same mechanism as the reaction in ethanolic solution, since intermediate open-chain sodium salts can be isolated. β-Cyano ketones react analogously to yield 4-cyanoisoxazole derivatives.[8/36,54/65,35/67,27/69]

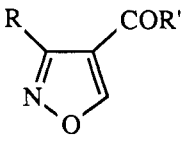
The condensation of nitrile oxides or hydroximoyl chlorides with active methylene compounds has been utilized widely for the synthesis of semisynthetic penicillins (**297**), some of which are employed in the pharmaceutical market [e.g., oxacillin (**101**), cloxacillin (**102**), and dicloxacillin (**103**) (see Part 2 of this work)]. Two different ways of proceeding may be adopted: either the proper 4-isoxazolecarboxylate (**295**) is transformed into the acid chloride **296** and this



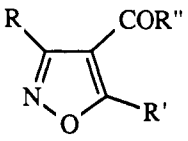

**Scheme 1.14.**

then condensed with 6-aminopenicillanic acid,[53/63,79/65,133/66,182/66,80/68,26/69,220/69,236/70,46/75] or the latter compound is first acetacetylated with diketene and subsequently cycloadded to the nitrile oxide or its precursor (Scheme 1.14).[99/73,213/77]

The sodium salts of β-ketoaldehydes, such as acetacetaldehyde and benzoylacetaldehyde, react with hydroximic acid chlorides to yield the 5-unsubstituted 4-acylisoxazoles of general structure **298**.[155/66,90/68,27/69] Condensation of β-diketones (or their sodium salts) with nitrile oxides (or their precursors, hydroximoyl chlorides) respresents an easy route to 3,5-disubstituted 4-acylisoxazoles of general formula **299**;[14/37,5/46,88/64,54/65,21/66,35/67,52/67,27/69,162/71,192/72,89/75,193/81] although yields are usually only moderate, starting materials are quite accessible. When the β-diketone is symmetrically substituted, as in acetylacetone or benzoylacetophenone, structural isomerism is not possible. However, when the groups bonded to the two carbonyls are different, two isomers are a priori conceivable, R′ and R″ being exchangeable in formula **299**. For example, with benzoylacetone only one isomer is obtained [i.e., the 3-substituted 4-benzoyl-5-methylisoxazole **299** (R′ = Me; R″ = Ph)[14/37,6/68,90/68,193/81]], although a discordant structural attribution has also been made in one case.[35/67]



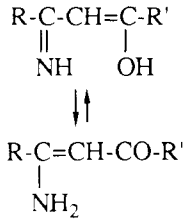

**298**



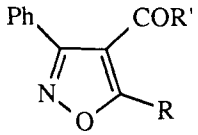

**299**

Under slightly different conditions the condensation between nitrile oxides and β-diketones takes different directions: thus an excess of the former reagent favors the formation of trisubstituted 4*H*-1,2,4-oxadiazines,[41/82] and an excess of the latter reagent opens an easy route to 2,4-diacylpyrroles.[45/82]

Monoimino-β-diketones show a peculiar behavior and give rise, depending on the substitution pattern, either to the isoxazole derivative **300**, possibly derived from the dipolarophilic activity of the enamino-keto form, and/or to the bis adduct **301**, derived from the imino-enol form:[36/67]

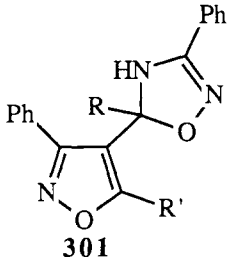



+ PhCNO




**300**

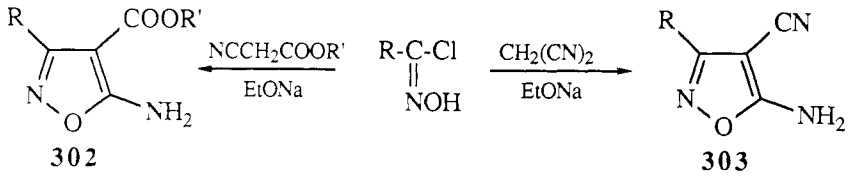
and/or




**301**

| R | R' | Yield (%): 300 | 301 |
|---|---|---|---|
| Me | Me | 5-10 | 10 |
| Me | Ph | 40 | -- |
| Ph | Me | -- | 20-30 |
| Ph | *n*-Bu | -- | 17 |

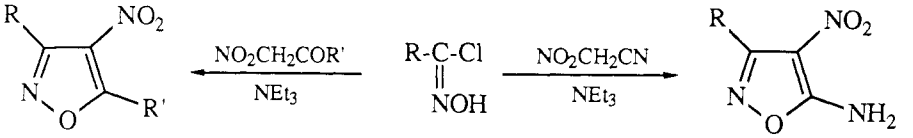
When the active methylene group is located between a cyano group on one side and an ester or an amide or another cyano group on the other side, condensation with nitrile oxides or their precursors furnishes a 5-aminoisoxazole derivative. Thus, starting from α-cyano esters or from malonodinitrile, 5-aminoisoxazole-4-carboxylates (**302**)[8/36.5/46.54/65.35/67.120C/67.135/67.233/70.140/71] or 4-cyano-5-aminoisoxazoles (**303**),[35/67.120C/67.135/67.158/69] respectively, are obtained:




**302** **303**

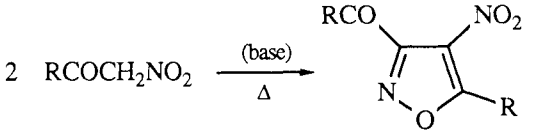
If a 4-unsubstituted 5-aminoisoxazole derivative is the desired product, the suitable *t*-butyl α-cyanoester is used as starting material. The *t*-butyl isoxazole-4-carboxylate thus obtained is smoothly decomposed on heating in concentrated sulfuric acid to give the 4-unsubstituted compound.[140/71] Cyanoacetamides[8/36.120C/67.141/67.102/71.11/73.82/73] and other activated acetonitrile derivatives[23/80] behave analogously in a strong basic medium. The phosphonate group can substitute for the carboxylic ester group of cyanoacetates in this type of condensation, but the yields of isoxazole compounds are definitively lower here.[7B/73]

The complex system $NCCH_2C(NH_2)=C(CN)Y$ (where Y = CN or COOMe) is attacked by hydroximoyl chloride on the active methylene, not on the tetrasubstituted double bond.[59/81.60/81] β-Nitroketones or β-nitrocarbonitriles also contain an active methylene group and are therefore capable of reacting with hydroximic acid chlorides in the presence of triethylamine to give 4-nitroisoxazole derivatives:[176/75.242/79]



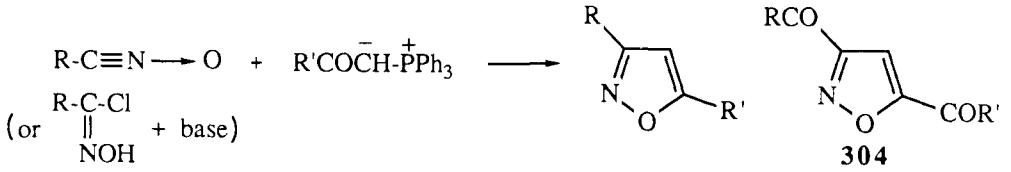

(yields 46-77%) (yield 38% for R = Ph)

It has been claimed that 3,5-disubstituted 4-nitroisoxazoles are formed simply by reacting β-nitroketones with a basic catalyst in a nonaqueous solvent.[277/77] Probably dehydration to the acyl carbonitrile oxide is accomplished first, followed by condensation of the latter compound with a second molecule of the β-nitroketone:



A related condensation of benzonitrile oxide with the sodium salts of β-ketosulfoxides furnishes 4-methylsulfinylisoxazole derivatives.[171/73]

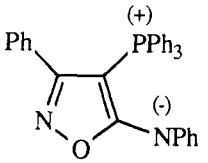
Another interesting isoxazole synthesis, relying on the nucleophilic attack of a carbanion to the nitrile oxide, applies to acylphosphoranes:[250/70,27/71,76/75,223/75]




**304**

This reaction also takes place directly with hydroximic acid chloride, but in this case 1 mol of triethylamine or 1 mol of the phosphorane acting as base must be added. Use of cyanomethylenetriphenylphosphorane leads to 5-aminoisoxazoles.[76/75] The method is particularly valuable for the preparation of 3,5-diacylisoxazoles (**304**) from acylcarbohydroximoyl chlorides and β-oxophosphorus ylides.[302/78]

It should be noted that the simple methylenephosphorane reacts with benzonitrile oxide in dimethyl sulfoxide to yield, besides the usual cycloadduct or its open-chain transformation product,[148B/67,17B/69] a reasonable amount of 3-phenyl-5-anilinoisoxazole, arising from the reaction of a second molecule of nitrile oxide with an intermediate phenylketene imine.[39/67] A peculiar dipolarophile is *N*-phenyliminoketenylidene triphenylphosphorane, which

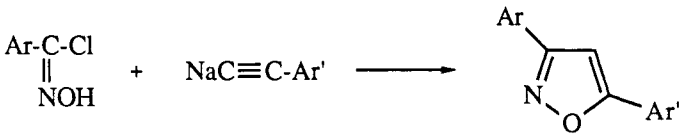



**305**

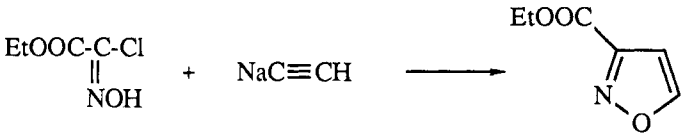
normally cycloadds to benzonitrile oxide to yield the isoxazole compound (**305**).[232/81] Sulfur and arson ylides give a complex reaction with nitrile oxides, and isoxazole derivatives have been isolated only occasionally as by-products.[44/67,64/67]

### *1.3.2.4 Cycloaddition of Nitrile Oxides (or Their Precursors) with Sodium Acetylides or Acetylenic Grignard Reagents*

The condensation of hydroximic acid chlorides with sodium arylacetylides is one of the oldest isoxazole syntheses, being known as early as 1927 to be an unequivocal method of preparing 3,5-diarylisoxazoles:[3/27]

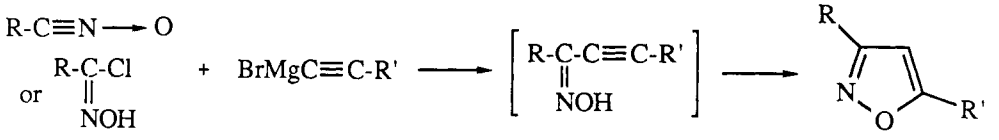


Since then the method has been applied to several types of hydroximoyl chlorides and to different acetylenic salts,[8/42,7/46,7/68] including the simple sodium acetylide, which allows us to prepare 3-monosubstituted isoxazoles; for example:

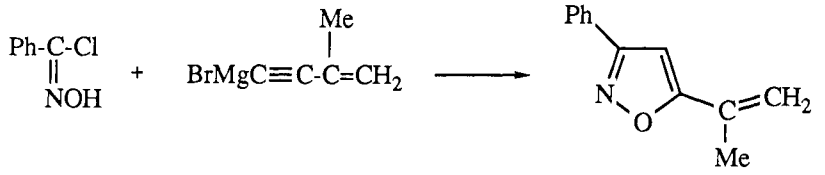


The suggestion[5/46] that the reaction involves a previous dehydrochlorination to nitrile oxide, which then reacts as usual with the alkyne, has been substantiated experimentally by trapping the intermediate nitrile oxide with norbornene.[67B/70]

A useful variation of this isoxazole synthesis makes use of acetylenic Grignard reagents instead of the sodium salts.[3/47] Both when the nitrile oxide is liberated *in situ* or when the hydroximic acid chloride is used directly, α,β-acetylenic ketoximes seem to be the most probable intermediate. They are unstable compounds, especially in a basic medium, which readily cyclize to isoxazoles (see also § 1.3.2.1, pp. 183–184). This view is supported by the occasional isolation of α,β-acetylenic ketoximes as by-products[89/69,44/73] and by their yield as sole products under proper experimental conditions:[219/70]



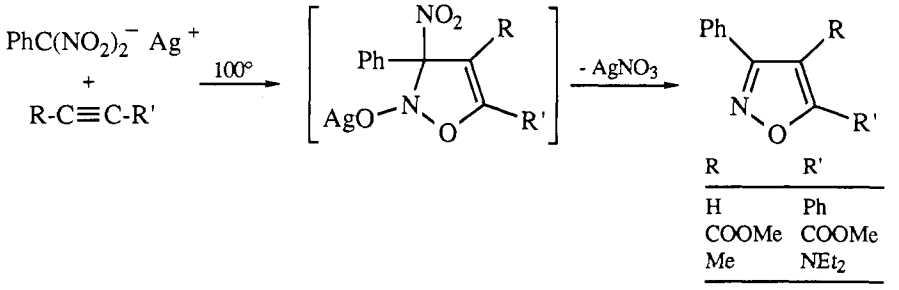
This method seems particularly advisable with the simple ethynylmagnesium bromide, which yields 3-monosubstituted isoxazoles,[37/65,44/73,73/73] or with Grignard reagents of the enynes,[33/61] which allow the triple bond to become the sole reacting moiety in the presence of the more active dipolarophilic double bond, as the following example shows:



On the whole, the method has general validity and has been applied to different hydroximoyl chlorides, leading to several 3,5-disubstituted isoxazoles.[3/47,33/59,27/61,30/63,72/64,78/66,78/69,213/80] It has been used preferentially in the building of di- and polyisoxazole derivatives.[13B/57,21/59,22/59,33/59,49/59,54/59,30/60,50/60,28/61,77/66]

### *1.3.2.5 Other [CNO + CC] Processes*

Low yields (5–15%) of isoxazoles are obtained by thermolysis of the silver salts of phenyldinitromethane at 100°C in the presence of the corresponding acetylenic compound; the reaction does not seem to involve the nitrile oxide as intermediate, but more presumably an isoxazolidine derivative, which loses silver nitrate:[203/80]

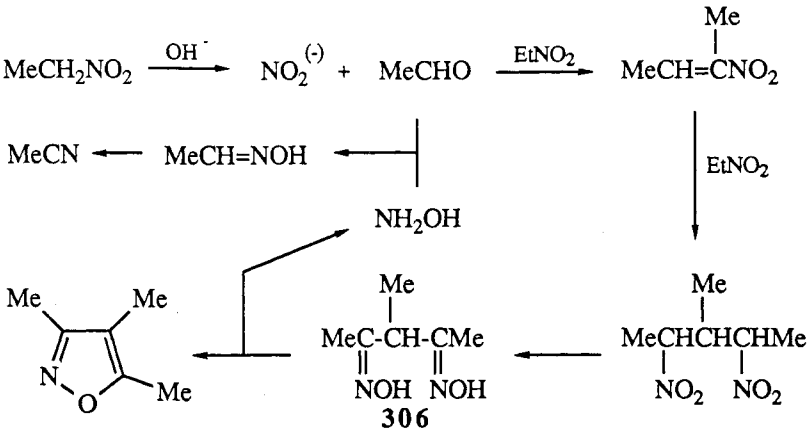



| R | R' |
|---|---|
| H | Ph |
| COOMe | COOMe |
| Me | $NEt_2$ |

## 1.3.3 [CNO + 2C] Process: Syntheses from Nitro Derivatives

It has long been observed that nitroethane, heated with aqueous solutions of alkali hydroxides or carbonates, forms a weakly basic, liquid product, $C_6H_9NO$.[7/888] This substance has been demonstrated[15/891] to be an isomer of the previously known trimethyloxazole and has been assigned the correct structure of trimethylisoxazole. This was confirmed by synthesis from methylacetylacetone and hydroxylamine. Under similar conditions, triethylisoxazole is formed from 1-nitropropane. The same treatment using nitromethane does not give the expected isoxazole, but methazonic acid (nitroacetaldoxime), especially when ammonia is used as the alkaline condensing agent.[2/900] 2-Nitropropane also does not produce isoxazoles.

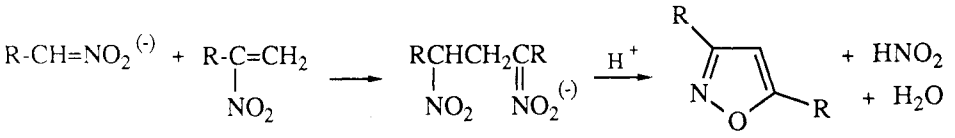
The action of alkalis on primary nitroalkanes, leading to isoxazoles, is a complex process. Besides the trialkylisoxazole, significant amounts of the nitrile (aceto- or propionitrile, respectively) and of the aldoxime are formed, whereas the solution contains alkali nitrite (up to 37% of the theory). Furthermore, if the reaction is stopped at an early stage, the free aldehyde (e.g., acetaldehyde from nitroethane) has been identified in the aqueous solution. A mechanism that accounts satisfactorily for all the facts reported above, has recently been formulated as in the following sequence, and has been supported further by experiments with labeled ($^{14}C$ and $d_4$) aldehydes:[37/69]




**306**

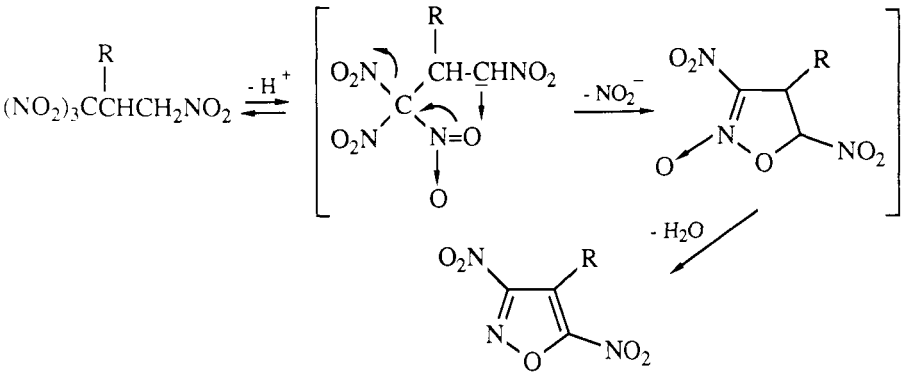
Other data corroborate this scheme: for example, when the reaction is performed in the presence of formaldehyde, the products are trimethylisoxazole and 3,5-dimethylisoxazole;[37/69] moreover, the use of organic bases, such as diethylamine, *n*-propylamine, or *n*-butylamine, instead of aqueous solutions of potassium carbonate, allows us to isolate the intermediate 1,3-dioximes, such as **306**,[16/40] which by acidic[8B/41] or basic[16/40.37/69] treatment readily cyclize to isoxazoles.

An independent study of the reaction of alkane nitronates with α-nitroolefins showed that whereas 2-alkane nitronates generally give good yields of the expected Michael-type adducts, 1-propane nitronate reacts with 2-nitro-1-butene, yielding 3,5-diethylisoxazole as the main product, in addition to only small amounts of the desired 3,5-dinitroheptane. In an aqueous medium the latter compound was not formed at all, and a 65% yield of the isoxazole was reached:[72/64]



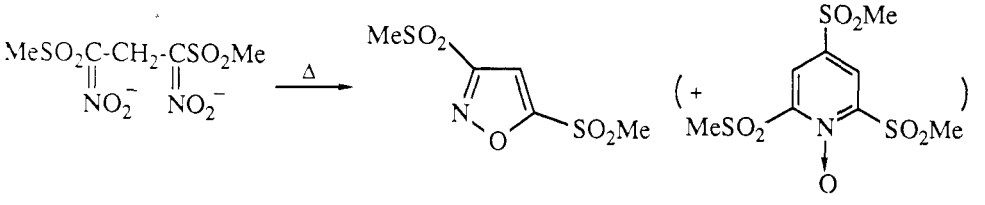

Similar results have been obtained with other 1-alkane nitronates. A mixture of the two possible isomers in equal amounts is obtained when the substituents on the nitronate and on the nitroolefin are different.

Occasionally, other 1,3-dinitro derivatives have been used as starting material for the preparation of isoxazole compounds. For example, 1,1,1,3-tetranitroalkanes are transformed into 3,5-dinitroisoxazoles by heating at 80°C in water or in 10% aqueous nitric acid:[255/73]



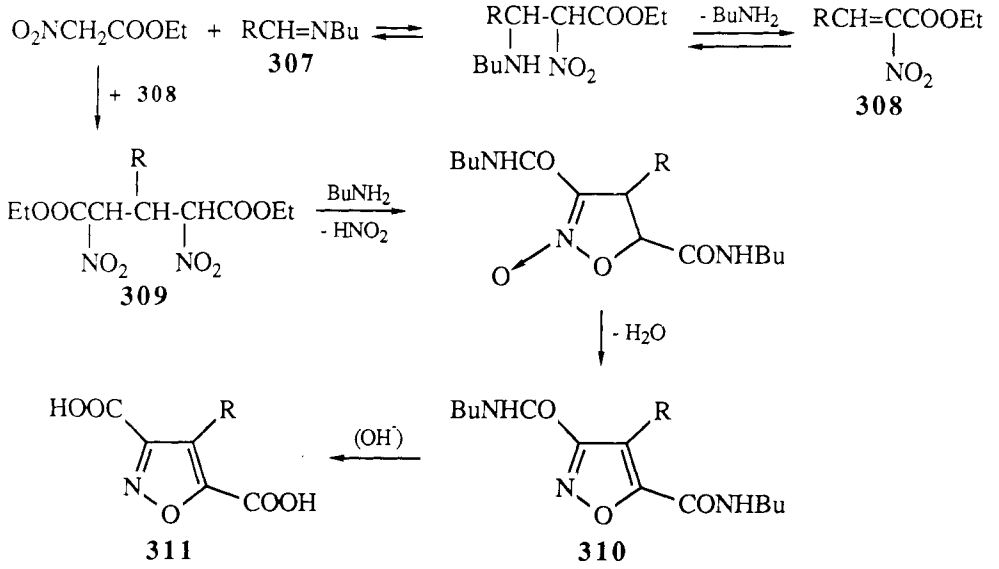
(R = H, Me; yields 70-50%)

1,3-Bis(methylsulfonyl)propane-1,3-dinitronates and other related compounds decompose in acidic medium either at room temperature or by heating to give low yields (about 20%) of 3,5-bis(methylsulfonyl)isoxazole, together with smaller quantities of 2,4,6-tris(methylsulfonyl)pyridine-*N*-oxide:[9/75]



Isoxazole-3,5-dicarboxylic acid is formed on boiling 2,4-dinitroglutaric acid with 10% hydrochloric acid.[2/53] Small quantities of trimethylisoxazole are also formed in the reaction of nitroethane with ethylene oxide in the presence of pyridine.[41/60]

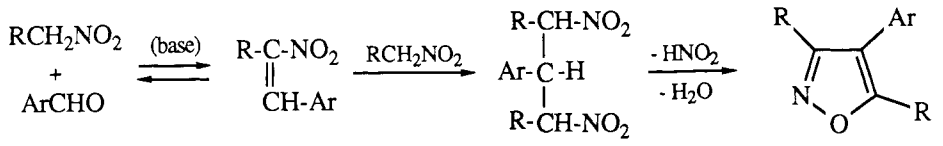
An important preparative application in this field is a general synthesis of isoxazole-3,5-dicarboxylic acids starting from ethyl nitroacetate. By refluxing either a mixture of ethyl nitroacetate with a Schiff base (**307**) or an $\alpha,\beta$-unsaturated $\alpha$-nitro ester (**308**), also prepared from ethyl nitroacetate,[20/63] with an excess of *n*-butylamine, fairly good yields of the isoxazole diamides (**310**) are obtained, which easily hydrolyze to the 4-substituted isoxazole-3,5-dicarboxylic acids (**311**)(Scheme 1.15).[15/60,18/61,20/63,21/63,44C/63,47/63]



Scheme 1.15.

The proposed mechanism of the reaction here also assumes the intermediacy of a 1,3-dinitro compound (**309**). As a matter of fact, the latter compound yields diamides (**310**) by treatment with excess *n*-butylamine.[21/71] An internal displacement of nitrite ion provokes cyclization to an isoxazoline *N*-oxide, which is usually too unstable to be isolated, and immediately dehydrates to the isoxazole compound. Under appropriate conditions, however, the isoxazoline *N*-oxide can be isolated (see § 2.3.2.1, pp. 607–610), and the isoxazole synthesis concerns their dehydration (see also § 1.3.7.1, p. 247). The aryltrinitromethanes and nitrostilbenes constitute another source of trisubstituted isoxazoles, and several efforts have been made to elucidate the complex reactivity of these types of compounds.

Triphenylisoxazole has long been known to be a by-product of the preparation of α-nitrostilbenes by condensing benzaldehyde and phenylnitromethane in the presence of an aliphatic amine,[6/11] as well as in other reactions of phenylnitromethane in basic media.[1/21,16/60] Better yields of triphenylisoxazole are obtained simply by heating α-nitrostilbene with aqueous concentrated potassium hydroxide.[6/11,10/24] The same derivative had been produced on heating α,α-dinitrodibenzyl in the same medium,[4/01,13/37] but its structure was later assured by degradative[3/21] and synthetic studies.[6/15] It was also noted that good yields of triphenylisoxazole are achieved when an equimolar mixture of nitrostilbene and phenylnitromethane is used in an alkaline medium.[3/21] This fact supports the following mechanism (p. 213), originally proposed only speculatively.[6/11,3/21] Furthermore, by action of potassium hydroxide on 4′-methoxy-7-nitrostilbene, 3,5-diphenyl-4-*p*-methoxyphenylisoxazole is obtained,[3/21] whose formation can be explained only by assuming a previous cleavage of the nitros-




tilbene derivative into anisaldehyde and phenylnitromethane, the required reactants.

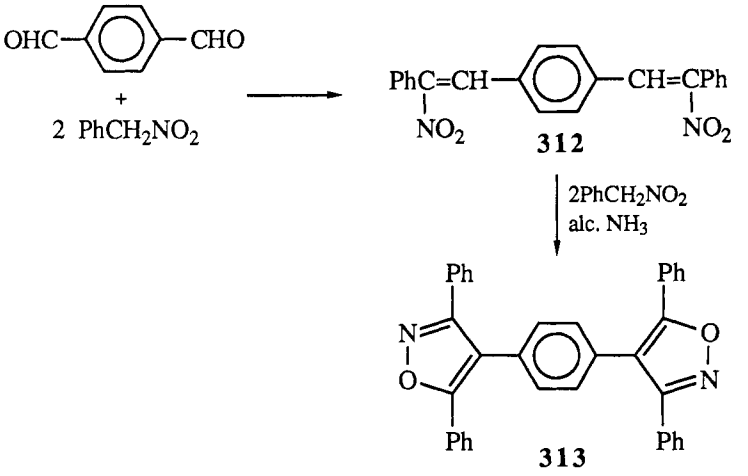
Formation of the heterocyclic ring from the 1,3-dinitro compound can follow one of these two mechanistic pathways: (1) preliminary elimination of nitrous acid to give a nitroolefin, which can either cyclize to a 2-isoxazoline *N*-oxide or isomerize to a 3-oximinoketone through an internal redox reaction (original Heim's proposal); or (2) direct intramolecular displacement of a nitrite ion by the nitronate oxygen atom to give the isoxazoline *N*-oxide, which promptly dehydrates to isoxazole, possibly through the open-chain 3-oximinoketone. This second mechanism has been substantiated by Nielsen and Archibald[154/69] by observing that an authentic sample of 1-nitro-1,2,3-triphenylpropene fails to cyclize to triphenylisoxazole or to 3,4,5-triphenyl-2-isoxazoline *N*-oxide under any conditions.

As a matter of fact, both triphenylisoxazoline *N*-oxide[10/24,4/35] and dibenzoylphenylmethane monoxime[4/35] were isolated as intermediates in the reaction of α-nitrostilbene (alone or in the presence of phenylnitromethane) with sodium methoxide or alcoholic ammonia. Both intermediates are easily converted to triphenylisoxazole by acids or alkali. Well-defined addition products of secondary amines to the nitrostilbene double bond have been isolated.[3/52] These compounds, too, on heating in alcoholic solution, give triphenylisoxazoline *N*-oxide and triphenylisoxazole.[4/52,5/52,6/52]

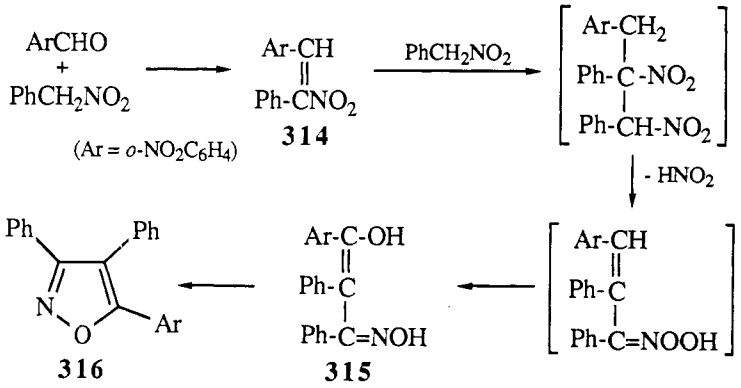
On the whole, isoxazole synthesis starting from arylnitromethane and/or α-nitrostilbene gives good results when the three aryl groups are identical (or at least the two in the 3- and 5-positions), but difficulties arise otherwise. Thus 3,5-diphenyl-4-(*o*-bromophenyl)isoxazole and 3,5-diphenyl-4-(*p*-bromophenyl) isoxazole have been prepared from *o*- and *p*-bromobenzaldehyde, respectively, and phenylnitromethane.[19/40] By contrast, *p*-bromophenylnitromethane and α-nitrostilbene in the presence of sodium methoxide gave a mixture of triphenylisoxazole and of the two 5(3)-*p*-bromophenyl-3(5),4-diphenylisoxazoles.[10/28] This has been attributed to the partial hydrolysis of nitrostilbene to phenylnitromethane, which participates in the condensation process. From the nitrostilbenes formed by condensation of benzaldehyde with *p*-tolylnitromethane and of *p*-tolualdehyde with phenylnitromethane, the isoxazoles expected according to the mechanism indicated above have also been obtained.[1/29]

Several other triarylisoxazoles, carrying substituents in the 4-aryl group, have been obtained by similar processes.[3/21,2/41,14/50] Aliphatic nitroalkanes may also be utilized: the condensation of nitroethane with 6-bromopiperonal gives a unique product in very low yield, for which the structure of 3,5-dimethyl-4-(2′-bromo-

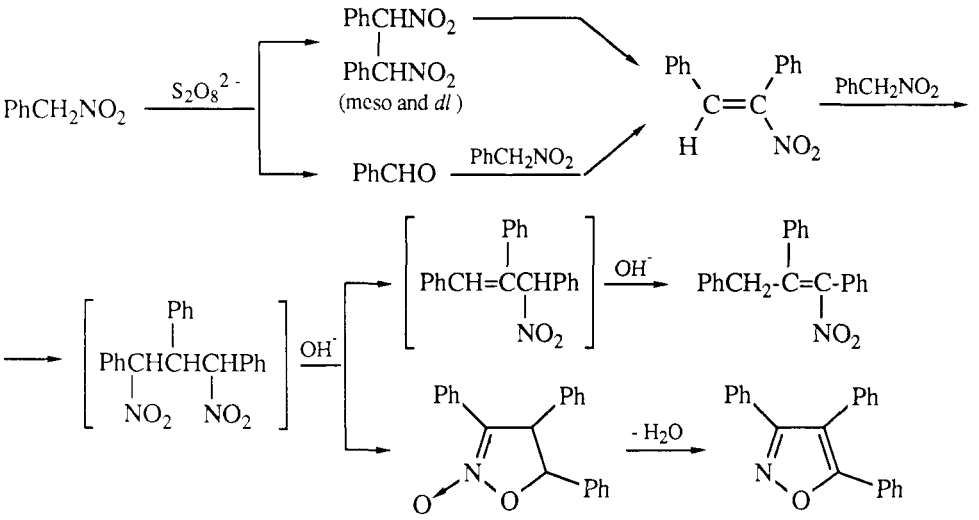
4′,5′-methylenedioxyphenyl)isoxazole has been proved by comparison of its $^{13}$C-NMR spectrum with those of model compounds.[122/75] Analogously, 3,5-dicylohexenyl-4-arylisoxazoles have been prepared by condensation of 1-cyclohexenylnitromethane and aromatic aldehydes in the presence of alkali.[27/54] Terephthaldehyde condenses with phenylnitromethane to give the bisnitrostilbene derivative (**312**), which with two further molecules of phenylnitromethane yields the tetrasubstituted *p*-phenylenediisoxazole (**313**):[17/40]




The formation of 3,4-diphenyl-5-*o*-nitrophenylisoxazole (**316**) by condensation of *o*-nitrobenzaldehyde with phenylnitromethane[16/39] requires a different mechanism. *o*,1′-Dinitrostilbene (**314**) and a small quantity of the monoxime of benzoyl-*o*-nitrobenzoylphenylmethane (**315**) are also isolated. The last product can be produced in good yield from the dinitrostilbene (**314**) and a second molecule of phenylnitromethane and, on boiling with alcoholic potassium hydroxide, it is transformed into 3,4-diphenyl-5-*o*-nitrophenylisoxazole. The reaction must therefore be formulated as in the following scheme. According to the Heim–Meisenheimer mechanism reported above, the isomeric 3,5-diphenyl-4-*o*-nitrophenylisoxazole would be formed:



Low yields (up to 25%) of trimethylisoxazole are also formed by oxidation of nitroethane with ammonium persulfate in aqueous sodium hydroxide;[11/53] under the same conditions, phenylnitromethane gives a mixture of several products, between them triphenylisoxazole and triphenylisoxazoline *N*-oxide in very small amounts.[170/70] The principal products in this case are the two 1,2-dinitro-1,2-diphenylethanes,[4B/57] especially if the reaction is carried out in the presence of a heterogeneous extractant (chloroform or benzene), or *cis*-α-nitrostilbene and benzaldehyde,[170/70] when lengthy reaction conditions are adopted. Nevertheless, *dl*-1,2-dinitro-1,2-diphenylethane itself gives a 67% yield of triphenylisoxazole when treated with 30% aqueous sodium hydroxide at 90–100°C. Based on these results, the mechanism shown in Scheme 1.16 has been proposed.[170/70]




**Scheme 1.16.**

A plain but rather low-yield (25%) preparation of triphenylisoxazole involves treatment of *aci*-phenylnitromethane sodium salt in DMSO solution with 2,2′-azobisisobutyronitrile and heating at 70°C. The reaction is a radical-initiated series of condensations of the anion to give the isoxazoline *N*-oxide, which dehydrates thermally.[30/82] For cyclization processes involving unsaturated nitrocompounds, see § 1.3.6.1, pp. 223–224.

## 1.3.4 [CCNO + C] Processes

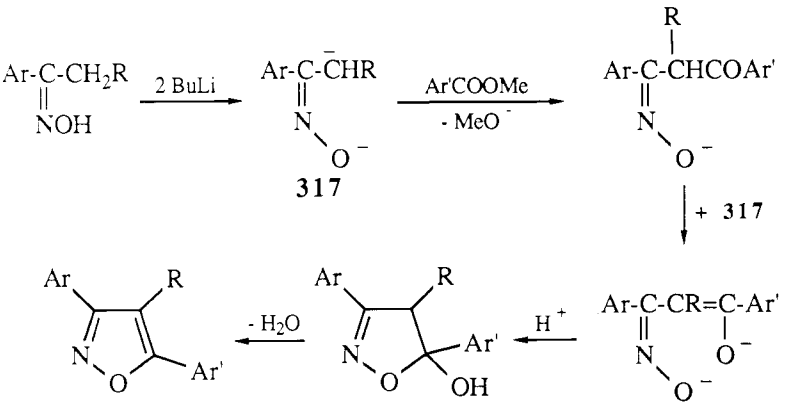
### *1.3.4.1 Synthesis from Oxime Dilithium Salts and Carboxylic Acid Derivatives*

Several oximes, carrying at least one hydrogen atom in the α-position, react with 2 mol of *n*-butyllithium to yield the corresponding 1,4-dilithium salts.[100C/69]

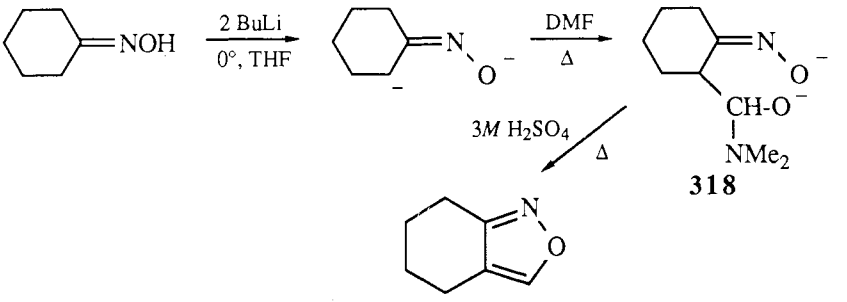
These salts condense with a variety of carboxylic acid derivatives or nitriles, and subsequently cyclize to the isoxazole ring under acidic conditions. (For analogous syntheses of 2-isoxazolines and 5-isoxazolinones, see § 2.2.2.5b and Part 2 of this work, respectively.)

This method of synthesis is fairly general for 3-mono-, 3,4- or 3,5-di-, and 3,4,5-trisubstituted isoxazoles, and offers some remarkable advantages. Contrary to the other two methods of most general applicability (oximation of β-diketones and nitrile oxide cycloaddition), it is an unequivocal route to unsymmetrically substituted derivatives; furthermore, starting materials are as a rule readily available, and the experimental procedure is simple and of "one-pot" type.

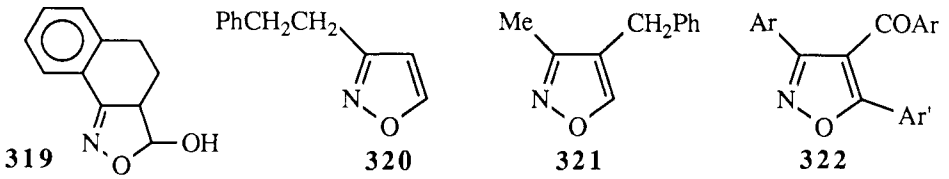
Originally, 1,4-dilithium salts (**317**) were condensed with carboxylic esters;[174/70,135/75,194/76,211/76,167/83] yields here are only moderate, owing to the consumption of a second mole of lithium salt before the cyclization step, according to the following scheme:




Better yields (referred to the ketone oxime) are obtained when nitriles[150/72] are used, owing to the possibility of using a 1:1 ratio of the starting materials. Nevertheless, two other more recent procedures greatly improved the yields: on one hand, the use of 3 mol of a less nucleophilic base (i.e., lithium diisopropylamide) instead of *n*-butyllithium avoids the waste of a second molecule of oxime;[173C/80,164/82] on the other hand, with the use of carboxamides instead of esters, yields up to 80–90% are easily attained.[204/78] 5-Unsubstituted isoxazoles (e.g., 3,4-tetramethyleneisoxazole) have thus been prepared using *N*,*N*-dimethylformamide;[204/78] the stability of intermediates such as **318** in the basic reaction medium has been demonstrated and is consistent with the high basic strength of the $Me_2N^-$ anion:




If a less concentrated sulfuric acid (e.g., 1.5 *M* instead of 3 *M*) is used in the cyclization step, the intermediate 5-hydroxyisoxazoline can sometimes be isolated: for example, starting from the α-tetralone oxime, a single diastereoisomer (**319**) has been isolated. Its dehydration to the isoxazole requires trifluoroacetic acid.[204/78] Since the geometry of the starting oxime is retained in the dilithium salt and the second proton abstracted is *syn* to the oxime oxygen atom,[184D/76] it is not surprising that the isomerically pure benzylacetone (*E*)-oxime regiospecifically gives the isoxazole **320** when treated with DMF, whereas the (*Z*)-oxime produces the isoxazole **321**.[204/78] Phthalic anhydride[265/77] and N-substituted phthalimides can also be utilized as a condensing partner.[93/76,229/77]

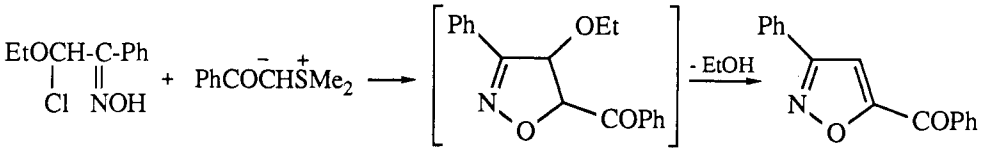



The use of 2 mol of an aroyl chloride in tetrahydrofuran at room temperature for 1 h makes it possible to prepare, with reasonable yields, 4-acyl derivatives (**322**) through bis-acylation of the starting dilithium salt of the appropriate acetophenone.[164/76]

A variation of the amide method, which uses the *O*-ethyl salts of $RC^+(OEt)$-$NBu_2BF_4^-$ or similar compound, makes possible regiospecific preparation of 5-alkyl-substituted isoxazoles in moderate yields.[210/82] Unfortunately, the method does not seem to be extendible to the synthesis of 3-unsubstituted isoxazoles.[204/78] Some substituents lower or completely cancel the reactivity of the possible dianions: for example, a nitro group on the phenyl ring or a chlorine atom or a dimethylamino group in the α-position of acetophenone oximes.[174/70]

### *1.3.4.2 Reaction of α-Chloroketoximes with Ylides*

Attack by benzoylsulfonium ylide on α-chloro-α-ethoxyacetophenone oxime affords 5-benzoyl-3-phenylisoxazole in 50% yield:[226/72]



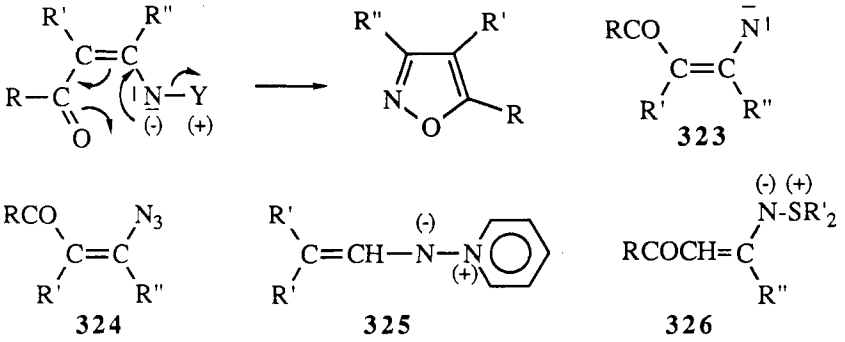

## 1.3.5 [CCCN + O] Process

Oxidation of 3-aminopropionitrile or of 3-aminoisobutyronitrile with 30% hydrogen peroxide, catalyzed by sodium wolframate, has been claimed to yield an unsubstituted or 4-methylated 5-aminoisoxazole, respectively.[127/68,113/69,180/71] On the basis of its mechanism and field of applicability, this method would appear to be very simple and deserving of more thorough study.

## 1.3.6 Cyclization Processes

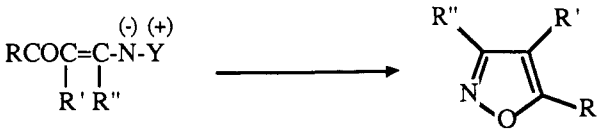
### *1.3.6.1 [OCCCN] Processes*

α,β-Ethylenic ketones, carrying an appropriate nitrogen-containing group in the β-position, can be induced to cyclize thermo- or photolytically to the corresponding isoxazole derivatives. As a matter of fact, the nitrogen atom present in the β-position can undergo a nucleophilic attack by the carbonyl oxygen atom if a good leaving group is present; of course, the formation of a true β-acylvinylnitrene (**323**) as intermediate cannot be excluded a priori:




Compounds utilized in this kind of synthesis are β-azidovinyl ketones (**324**), acyl-*N*-(1-pyridinio)vinylaminides (**325**), and acylvinylsulfinimines (**326**), and typical results are summarized in Table 1.73.

TABLE 1.73




| R | R' | R" | Y | Conditions | Isoxazole (% yield) | Other products (% yield) | References |
|---|---|---|---|---|---|---|---|
| Ph | H | H | $N_2$ | benzene, hν, 20° | 40 | $PhCOCH_2CN$(9.5) | 10/66 |
| | | | | DMF, 45-50°, 8 h | 3 | $PhCOCH_2CN$(50) | 10/66 |
| | | | | [b] from $PhCOC{\equiv}CH + NaN_3$ in $H_2O$, pH = 10 | 16 | PhCOMe (27) | 62/66, 209/66 |
| | | | | [b] from (*E*)-PhCOCH=$CHSO_2Ph$ + $NaN_3$ in MeOH | 12 | (*E*)-PhCOCH=$CHN_3$ (88) | 65/66 |
| 4-$MeOC_6H_4$ | H | H | $N_2$ | [b] from $ArCOC{\equiv}CH + HN_3$ in $CHCl_3$, r.t., 1 day | 45 | (*E*)-ArCOCH=$CHN_3$ (32) | 14/65 |
| Ph | Me | H | $N_2$ | toluene, 110° | 43 | PhCOCHMeCN (16) | 10/66 |
| | | | | benzene, hν, 20° | 43 | PhCOCHMeCN (9) | 10/66 |
| Ph | Ph | H | $N_2$ | DMF, 90° | 65 | | 10/66 |
| Ph | H | Ph | $N_2$ | [b] from $PhCOC{\equiv}CPh + HN_3$ in $CHCl_3$, r.t., 2 days | 67 | | 14/65 |
| Ph | H | COPh | $N_2$ | [b] from $PhCOC{\equiv}CCOPh + HN_3$ in $CHCl_3$, r.t., overnight | 76 | | 14/65 |
| | | | | [b] from *meso* -PhCOCHBrCHBrCOPh + $NaN_3$ in DMF, r.t., 3 h | 61 | | 90/71 |
| COOEt | OEt | H | $N_2$ | toluene, reflux 1 h | 70 | | 18/70 |
| OMe | H | COOEt | $N_2$ | benzene, reflux 20 h | 30 | 2,3-$(COOMe)_2$-aziridine (65) | 22/81 |
| Me | COMe | H | 1-Pyr[a] | benzene, reflux 1 h | 80 | | 164/73 |
| Me | COOEt | H | 2,6-$Me_2$-1-Pyr | benzene, reflux 20 min | 75 | | 164/73 |
| Ph | H | H | $SPh_2$ | $CHCl_3$, reflux 1 h | 73 | PhSPh (87) | 186/73 |
| Ph | H | COPh | $SPh_2$ | $CHCl_3$, reflux 1 h | 75 | PhSPh (98) | 186/73 |

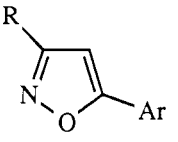
[a] Pyr = pyridinio.
[b] Generated *in situ*.

Moderate yields of 4,5-diphenyl- and 4-methyl-5-phenylisoxazole are obtained from 1,2-diphenyl- and 2-methyl-1-phenyl-3-azido-propen-1-one, respectively.[10/66] Of course, azido and carbonyl groups of compounds **324** must be in a *cis* relationship in order to achieve cyclization efficiently: the *trans* isomer of **324** leads to β-ketonitrile as the main product, together with the corresponding oxazole derivative and only traces of isoxazole.[95/69]

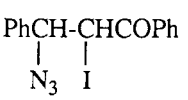
Substituted ethynyl ketones of general formula $ArCOC{\equiv}CR$ react at room temperature with a chloroform solution of hydrazoic acid to give the corresponding isoxazoles (**327**) in yields ranging from 50 to 80%.[14/65] Unsubstituted ethynyl ketones $ArCOC{\equiv}CH$[62/66.209/66] or β-sulfonyl vinyl ketones[65/66] seem to react somewhat differently with sodium azide: in both cases the *trans* isomer of

**324** is the main product, and in the former case the choice of solvent is essential, isoxazoles being produced only in an aqueous medium. In contrast, in dimethylformamide, primarily 4-acyl-1,2,3-triazoles are obtained. [10/66,209/66] Sometimes isoxazole derivatives are isolated as side products during the preparation of α-azidovinyl ketones.[90/71,179/72,11/79]

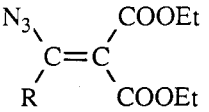
Also, chalcone dibromides or α-bromochalcones can produce β-azidovinyl ketones *in situ*; however, isoxazoles are the principal products only when the β-aryl is *para*-substituted with an electron-withdrawing group such as $NO_2$ or CN.[170/84] Other convenient starting compounds are 2-iodo-3-azido ketones



**327**



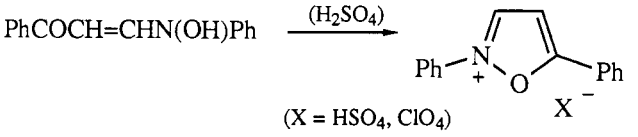
**328**



**329**

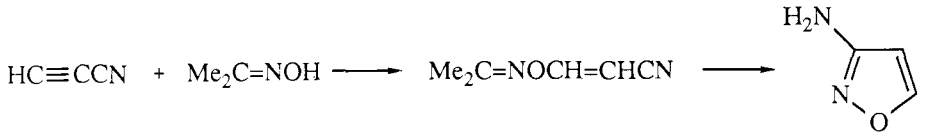
(**328**),[74/67] easily attainable from chalcones and iodine azide, and the unstable azidomethylenemalonates **329**,[18/70] which can be achieved in two steps from acylmalonates. The compounds **325**[164/73] and **326**[186/73] are less easily available (compound **325** from ethoxymethylene-pentane-2,4-dione or -acetoacetate and pyridine-*N*-imides, **326** from ethynyl ketones and diphenylsulfinimines), but their thermolytic behavior is more straightforward, and good yields of isoxazole derivatives are achieved.

A somewhat related closure to an isoxazole ring through formation of the N–O bond is the synthesis of *N*-arylisoxazolium salts discovered by Woodward and Woodman.[114/66] It is based on the acid-promoted cyclization of αβ-acylvinylphenylhydroxylamine; for example:



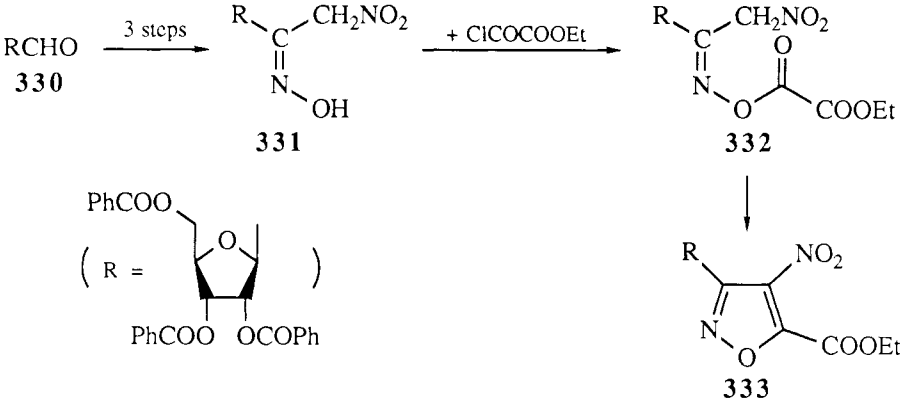
### *1.3.6.2 [CCCON] Processes*

Synthesis of 3-aminoisoxazole has been claimed to occur by reaction of cyanoacetylene with acetone oxime, through a vinyl-substituted oxime:[81/69] β-Chloroacrylonitrile may be used instead of cyanoacetylene.[135/70]

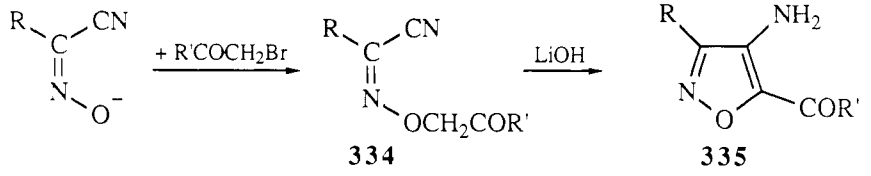


### *1.3.6.3 [CCNOC] Processes*

Photolysis of 2-diazo-2-phenylacetophenone is reported to yield a mixture of triphenylisoxazole (main product) and of *cis*- and *trans*-3,4,5-triphenyl-2-isoxazoline (by-products).[34/66] Far more important from a preparative standpoint is the recently developed synthesis of a benzoyl-protected 3-ribofuranosyl-4-nitro-5-isoxazolecarboxylate (**333**) by pyridine-promoted cyclization of the acyl derivative (**332**) of the α-nitro ketoxime (**331**). Since the latter compound is easily available from the corresponding aldehyde (**330**), the method seems promising, and isolation of **332** is not always necessary.[273/80]



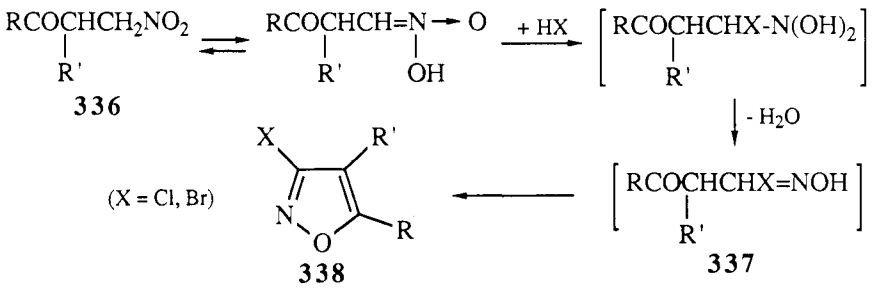

An interesting direct route to 4-aminoisoxazole derivatives (**335**) is based on the lithium hydroxide–catalyzed cyclization of α-alkyloxyiminonitriles (**334**); moderate yields are reported.[14/80]




### *1.3.6.4 [CCCNO] Processes*

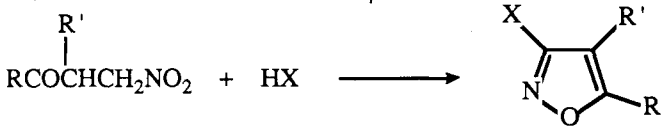
A convenient entry in the class of 3-halogenoisoxazoles (**338**) starts from the β-nitroketones (**336**), easily attainable from the corresponding β-chloro or β-bromo ketones and sodium nitrite in dimethylformamide (DMF). These compounds, when treated at about 150°C with concentrated hydrochloric or hydrobromic acid, are converted in moderate yields to 3-chloro- or 3-bromo-isoxazole derivatives,[1/09,11/57,52/60,117/67,177/77] probably through the following me-

chanism, which involves the intermediacy of the hydroximic acid halides (**337**):[1/09,52/60]



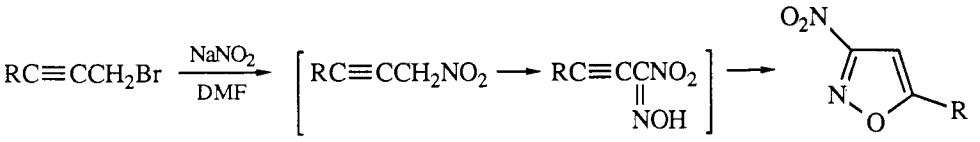

Reaction with hydrobromic acid is usually faster, but yields in chloro derivatives are frequently higher than in bromo analogues. 3-Nitro-1-phenylpropenone is also reactive toward hydrochloric acid, yielding 5-phenyl-3,4-dichloroisoxazole, but reaction with hydrobromic or hydroiodic acid yields 5-phenylisoxazole prevailingly or exclusively.[117/67] Reductive cyclization with hydroiodic acid is also known to occur in the case of a saturated $\beta$-nitro ketone.[177/77] 3-Haloisoxazoles prepared by this route are collected in Table 1.74.

TABLE 1.74. SYNTHESIS OF 3-HALOISOXAZOLES FROM β-NITROKETONES




| X | R | R' | Conditions | Yield (%) | References |
|---|---|---|---|---|---|
| Cl | H | Me | conc. HCl in sealed tube at 150°, 3 h | 30 | 11/57, 52/60 |
| Cl | H | Et | conc. HCl in sealed tube at 150°, 3 h | 31 | 11/57, 52/60 |
| Cl | H | Ph | conc. HCl in glass bomb on steam bath, 24 h | 50 | 177/77 |
| Cl | H | 4-$ClC_6H_4$ | conc. HCl in glass bomb on steam bath, 24 h | 60 | 177/77 |
| Cl | H | 2,4-$Cl_2C_6H_3$ | conc. HCl in glass bomb on steam bath, 24 h | 4 | 177/77 |
| Cl | H | 3,4-$Cl_2C_6H_3$ | conc. HCl in glass bomb on steam bath, 24 h | 20 | 177/77 |
| Cl | H | 4-$MeC_6H_3$ | conc. HCl in glass bomb on steam bath, 24 h | 10 | 177/77 |
| Cl | Cl | Ph | HCl | 33 | 117/67 |
| | | | from 3-nitro-1-phenylpropenone | 38 | 117/67 |
| Cl | H | $CH_2CH_2COOH$ | conc. HCl in sealed tube at 150°, 3 h | 35-55 | 1/09 |
| Br | H | Me | 48% HBr, reflux 10 min | 20 | 11/57, 52/60 |
| Br | H | Et | 48% HBr, reflux 10 min | 25 | 11/57, 52/60 |
| Br | H | Ph | 48% HBr, reflux 1 h | 45; 15 | 52/60, 177/77 |
| Br | H | 4-$ClC_6H_4$ | 48% HBr in glass bomb on s.b., 24 h | 30 | 177/77 |
| Br | H | $CH_2Br$ | 48% HBr, reflux 30 min | 100 | 52/60 |
| Br | Br | Me | 48% HBr, reflux 30 min | | 52/60 |
| Br | H | $CH_2CH_2COOH$ | 15% HBr/AcOH, 8 h on steam bath | | 1/09 |

A somewhat related reaction is the synthesis of 3-nitroisoxazoles by treatment of a propargyl bromide with an excess of sodium nitrite in DMF at 0–20°C:[130B/67,197/72,218/72,308/80]

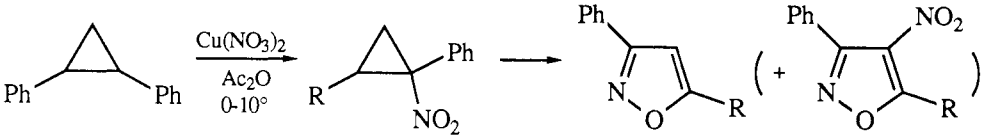


| R | Yield (%) |
|---|---|
| H | 32 |
| *n*-Bu | 30 |
| Ph | 63 |
| COOMe | 20 |

Propargyl alcohol is sometimes obtained as a by-product, owing to the formation of small amounts of isomeric nitrites instead of nitro derivatives.[130B/67,224/73]

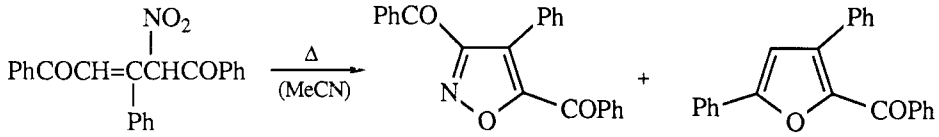
Yields are poor for the simple 3-nitroisoxazole, but the use of propargyl tosylate or of other solvents does not improve yields.[197/72,218/72] Propargyl chloride and iodide do not react or give only tars.[197/72] 3,3-Dinitro-5,5′-diisoxazole has been obtained by the same method.[224/73]

Nitration of 1,2-diphenylcyclopropane with copper nitrate and acetic anhydride gives 3,5-diphenylisoxazole (**340a**), together with smaller amounts of the product (**341**) of further nitration.[292/76,282/81] The reaction involves an initial nitration of the cyclopropyl ring to **339a**, which is supposed to transform into **340a** through two successive ring-opening/ring-reclosure steps. In fact, the separately prepared **339b** gives an excellent yield of 3-phenylisoxazole (**340b**) when treated with acetic acid:[282/81]



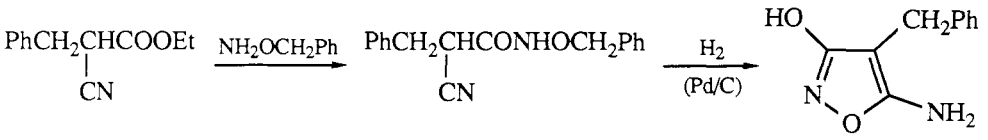
**339** **a** R = Ph **b** R = H **340** **a** R = Ph **b** R = H **341**

Thermolysis of the nitroolefin **342** produces both dehydration and loss of nitrous acid, leading, respectively, to 3,5-dibenzoyl-4-phenylisoxazole as the main product and to 2-benzoyl-3,5-diphenylfuran as the by-product:[2/75]

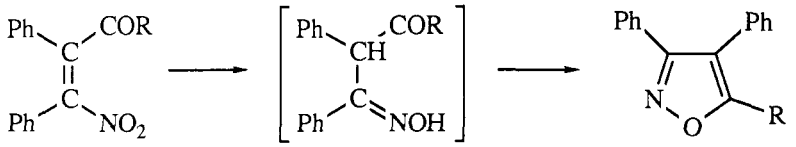


**342** (~52%) (~20%)

α-Cyanocarboxylic esters are known to be oximated to 5-amino-3-hydroxyisoxazoles (see § 1.3.1.1, pp. 148–149); the reaction can be also carried out in two steps, first preparing the *O*-benzylhydroxamic acid, which is subsequently hydrogenolyzed; for example:[51/61]



Chemical[138/79] or electrochemical reduction[138/79,24/81] of α,β-diphenyl-β-nitro-α,β-unsaturated ketones in acidic media leads to trisubstituted isoxazoles in good yields, presumably through the nitroso compound, the monoxime of the β-diketone, and the 5-hydroxy-2-isoxazoline:

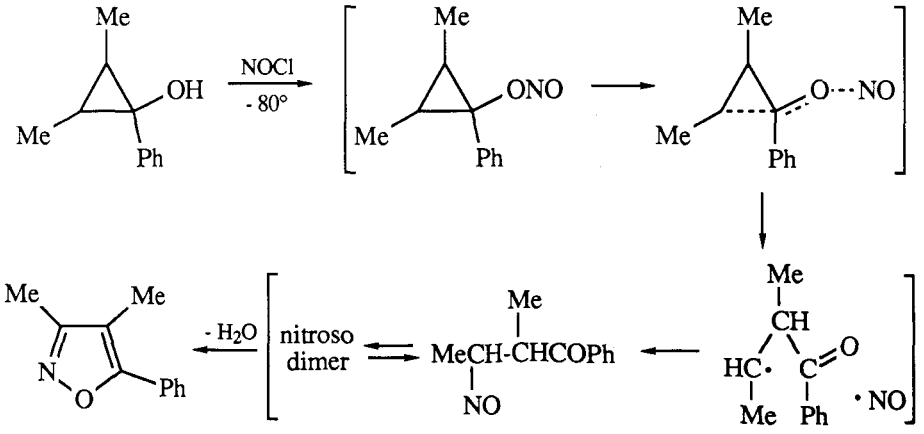


(60-76% yield)

By contrast, electrolysis in a neutral medium gives the 4,5-dihydroxy-2-isoxazoline derivative[24/81] (see § 2.2.2.5d, p. 530).

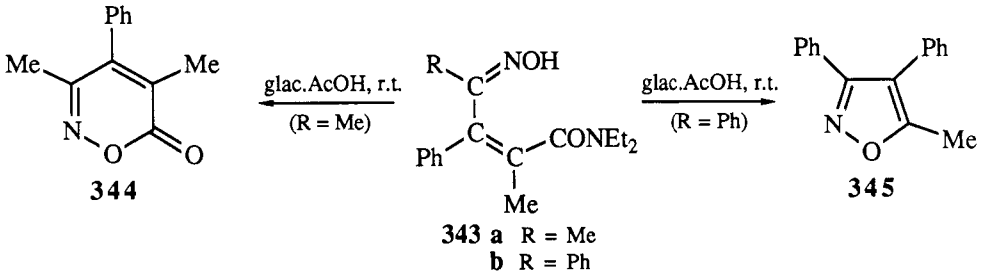
5-Aminoisoxazole derivatives are obtained analogously by electrolysis of *Z*-α-cyano-β-nitrostyrenes or *Z*-α-cyano-β-nitrostilbenes;[35/75] the intermediacy of the ene-hydroxylamine (tautomeric to the α-cyanoaldehyde oxime) has been demonstrated.[182/80] The same types of compounds can be prepared by chemical reduction using thiols as reducing agents.[31/80] Other reductants do not give heterocyclic products.[25B/79]

Although the method seems of little preparative value, it is interesting to note that isoxazoles (and 5-hydroxy-2-isoxazolines) are formed when appropriately substituted cyclopropyl nitrite esters are decomposed homolytically at low temperatures; for example, 3,4-dimethyl-5-phenylisoxazole is the final product of the thermolysis or photolysis of 2,3-dimethyl-1-phenylcyclopropanol nitrite:[93/72]

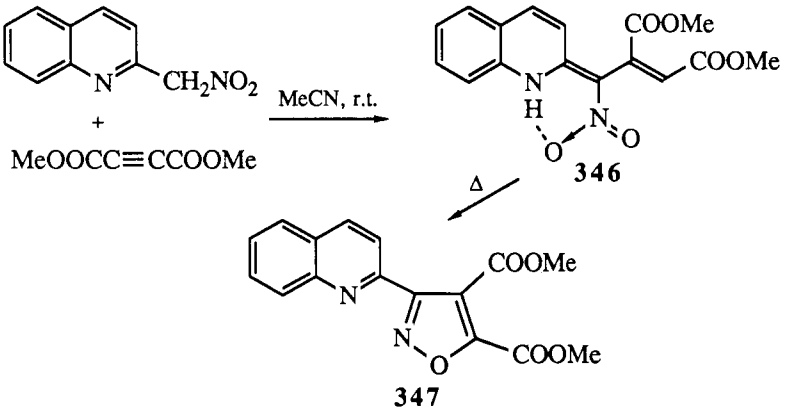


Of course, formation of the necessary intermediate monoxime requires that the nitroso group might migrate to a primary or a secondary carbon atom. The cyclization reaction of α,β-unsaturated ketoximes, substituted in the α or β position, has already been mentioned in our discussion dealing with oximation of the corresponding ketones, since the oximes are usually not isolable (see §§ 1.3.1.2, 1.3.1.4, and 1.3.1.5).

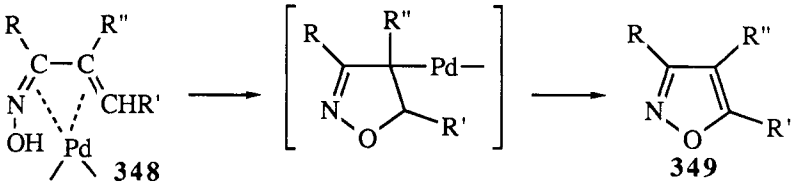
The behavior of the stable γ-hydroximino carboxamides of structure **343**, derived from four-membered cyclic nitrones, seems to be a special case. The phenylpentenecarboxamide **343a** gives the oxazinone **344** by acidic treatment, whereas the diphenylbutenecarboxamide **343b** forms 5-methyl-3,4-diphenylisoxazole (**345**), possibly derived from the unstable oxazinone by the elimination of carbon monoxide:[207/82]




The addition product from 2-nitromethylquinoline and dimethyl acetylenedicarboxylate, presumably having the structure of a nitroalkene (**346**), cyclizes in refluxing toluene to give the isoxazole derivative **347**:[119/79]

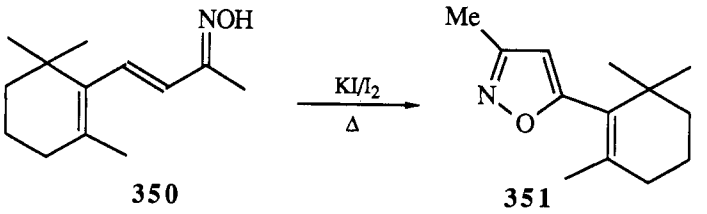



A more general procedure for isoxazoles is the intramolecular oxypalladation of the α,β-unsaturated ketoximes **348**: treatment either with $PdCl_2$-$(PPh_3)_2$ complex in the presence of PhONa in refluxing benzene for 8 h or with $PdCl_2$ in the presence of $Na_2CO_3$ at room temperature for 20 h gives relatively high yields of the corresponding isoxazoles (**349**):[234/73,77/75]




Not only are α,β-ethylenic oximes active, but β,γ- and γ,δ-ethylenic oximes can even be used with the latter reagent; however, the former palladium complex provokes cyclization to pyridine derivatives.[77/75,226C/76] A related procedure accomplished the synthesis of 3-hydroxyisoxazoles by treatment of α,β-unsaturated hydroxamic acid with lithium chloropalladite at room temperature. Yields are only moderate.[31/79]

Another interesting and widely used method of oxidative cyclization of α,β-ethylenic oximes has been applied to β-ionone oxime (**350**)(either the *E*- or *Z*-isomer), which was treated with a mixture of iodine–potassium iodide in hot aqueous tetrahydrofuran containing potassium bicarbonate, thus directly obtaining the isoxazole **351** in high yields:[96/72]




The reaction mechanism presumably involves the intermediacy of a 4-iodo-2-isoxazoline.

Several other 3,5-di- and 3,4,5-trisubstituted isoxazoles have been prepared by this route, usually in fairly good yields.[96/72,100/73,47/75,143/75,173/80] Aldoximes do not give satisfactory results because of the instability of the derived 3-unsubstituted isoxazole to base.[96/72]

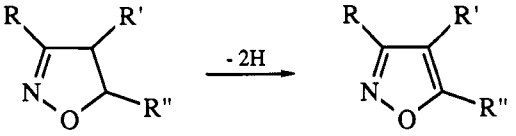
Another suitable reagent for the same oxidative cyclization is *N*-iodosuccinimide, operating in refluxing carbon tetrachloride: a 60% yield of 3-methyl-5-phenylisoxazole has thus been obtained from benzalacetone.[120/80] *N*-Bromosuccinimide has also been utilized for synthesis of the trisubstituted isoxazoles,[167/77,173/80] but yields are almost always lower than those reached with the iodine–potassium iodide method. Even lower yields and slower reactions have been ascertained when *N*-chlorosuccinimide was used as the oxidant.[173/80]

## 1.3.7 From Heterocyclic Compounds

### *1.3.7.1 From Other 1,2-Oxazole Derivatives*

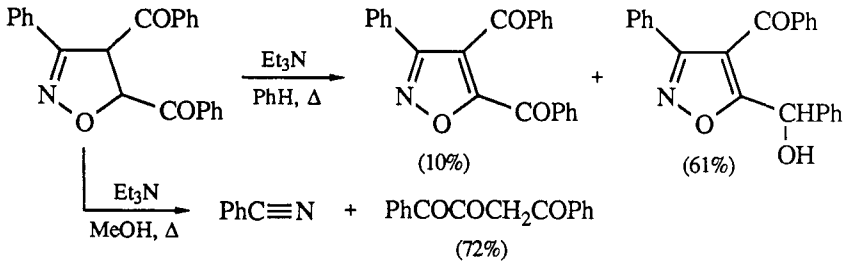
#### a. By Dehydrogenation of 2-Isoxazolines

Since 2-isoxazoline derivatives are more readily available than the corresponding isoxazoles, dehydrogenation of the former compounds sometimes represents a convenient method of preparation of the latter compounds:




Some selected examples are collected in Table 1.75. Simple air oxidation, at room temperature or under heating, occurs only with some 4-formyl-5-phenyl-2-isoxazolines, obtained by regioselective cycloaddition of nitrile oxides to cinnamaldehyde.[177/83]

Base-promoted dehydrogenation has been reported briefly for several 4-acyl-2-isoxazolines, whereas 5-acylisoxazolines as a rule suffer ring fragmentation (see § 2.2.3.2d, pp. 570–571) under the same conditions. Only 4,5-dibenzoyl-3-phenyl-2-isoxazolines, when heated with triethylamine in benzene, yield isoxazole derivatives, arising from both dehydrogenation and a redox reaction:[148/74]




The conversion of 2-isoxazolines to isoxazoles is generally more difficult than the oxidation of 2-pyrazolines to pyrazoles,[156C/67] and choice of the appropriate dehydrogenating agent is often critical. For example, bromine, selenium dioxide, dilute nitric acid, and ethyl nitrite do not affect 2-isoxazolines.[17/52,27/60] Chromic trioxide in acetic acid solution has long been known[2/896] to oxidize 3,5-diaryl-2-isoxazolines, but not its 3- or 5-alkyl-substituted derivatives.[8/33] This oxidative procedure has been widely used[6/31,3/45,4/45,5/45,9/47,10/47,11/47,8/49,2/54,8/54,47/58,30/59,3/65,92/65,155/66,183/75,201/81] for its experimental simplicity, but the yields are usually only moderate, and difficulties can sometimes be encountered in the separation of isoxazole from the unchanged 2-isoxazoline. Furthermore, it is

TABLE 1.75. OXIDATIVE CONVERSION OF 2-ISOXAZOLINES TO ISOXAZOLES

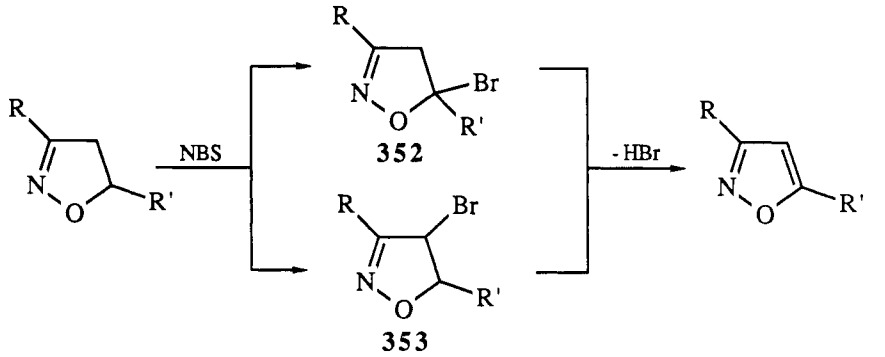
| R | R' | R" | Method[a] | Yield (%) | References |
|---|---|---|---|---|---|
| Ph | H | H | F | 88 | 118C/65 |
| H | H | Ph | F | 81 | 118C/65 |
| *n*-Pr | H | *n*-Hex | E | 83-90 | 107/79 |
| *n*-Hex | H | $CH{=}CH_2$ | E | 70 | 286/83 |
| Me | H | COOMe | D | 97 | 234/77 |
| | | | F | 85 | 118C/65 |
| $(CH_2)_2COOMe$ | H | *n*-Hex | D | 98 | 234/77 |
| | | | | | 245/78 |
| Me | H | Ph | D | 100 | 234/77 |
| Ph | H | Me | D | 98 | 234/77 |
| | | | F | 73 | 118C/65 |
| Me | H | β-naphthyl | F | 54 | 34/65 |
| Ph | H | $CH_2Br$ | F | 70 | 118C/65 |
| COOH | H | Ph | C | 43 | 43/60 |
| COOEt | H | Ph | F | 86 | 135/72 |
| Ph | H | COOMe | F | 66 | 118C/65 |
| Ph | H | CN | F | 80 | 118C/65 |
| Me | H | $4\text{-}MeC_6H_4CO$ | F | 83 | 89/68 |
| Ph | H | Ph | B | | 2/896, 8/33, 27/60 |
| | | | F | 90 | 118C/65 |
| Ph | H | $4\text{-}BrC_6H_4$ | B | 38 | 6/31, 3/45, 8/49 |
| | | | | | 2/54, 15/54 |
| $4\text{-}BrC_6H_4$ | H | $4\text{-}MeOC_6H_4$ | B | 75 | 11/47 |
| $2\text{-}HOC_6H_4$ | H | $4\text{-}HOC_6H_4$ | B | 61 | 201/81 |
| $4\text{-}MeOC_6H_4$ | H | $3\text{-}NO_2C_6H_4$ | B | 24 | 5/45 |
| $4\text{-}NO_2C_6H_4$ | H | mesityl | G | 40 | 9/47 |
| Ph | H | 2-furyl | E | 15-20 | 88/68 |
| | | | F | 44 | 88/68, 152/75 |
| 2-Furyl | H | Ph | F | 60 | 88/68 |
| Ph | H | CH=CHPh | F | 21 | 118C/65 |
| Ph | H | $CH_2OPh$ | F | 40 | 86/72 |
| PhCO | H | Ph | F | 50 | 18/71 |
| Ph | Me | Ph | B | | 183/75 |
| Me | CN | $2\text{-}ClC_6H_4$ | G | 61 | 159/77 |
| Ph | $NO_2$ | Ph | B | 58 | 316/82 |
| | | | C | 64 | 260/79 |
| | | | D | 99 | 234/77 |
| | | | H | 85-87 | 91/81 |
| Ph | CHO | Ph | A | 15 | 177/83 |
| R | COR' | R" | H | good | 148/74, 177/83 |
| Ph | COMe | Ph | E; F | 20; 10 | 158/73 |
| Ph | Ph | COPh | F | 95 | 158/73 |
| Ph | COOMe | Ph | F | 60 | 157/66 |
| Ph | COPh | COPh | H | 71 | 148/74 |

[a] Methods: A, air oxidation; B, $CrO_3$ in glacial AcOH at 80° or on steam bath; C, $KMnO_4$, $OH^-$ or $H^+$; D, γ-$MnO_2$ in refluxing benzene; E, chloranil or DDQ in refluxing benzene or dioxane; F, NBS, with AIBN in refluxing $CCl_4$, then base, or with (RO) G, acidic medium; H, basic medium.

noticeable that *cis*-3,4,5-trisubstituted 2-isoxazolines are oxidized, whereas the *trans* isomers remain unaffected under the same conditions.[27/60] Potassium permanganate has been successful in individual cases;[43/60,8/61,260/79,264/81] under mild conditions this oxidant does not affect the isoxazoline ring, and has therefore

been utilized to oxidize double or triple bonds[16/52] or even a furyl group[88/68] in the side chain. By contrast, chromic acid oxidizes both the isoxazoline to isoxazole and the furan ring to a carboxylic acid group.[4/56]

The first dehydrogenating agent to show general applicability has been *N*-bromosuccinimide;[118C/65] usually, the intermediate 5- or 4-bromo-substituted isoxazoline is too unstable to be isolated, and dehydrobromination is either spontaneous or promoted by direct treatment of the reaction mixture with weak bases (most often, fused potassium acetate in glacial acetic acid or triethylamine in dry tetrahydrofuran). With 5-aryl- or 5-acylisoxazolines, the unstable intermediate has been shown to be the 5-bromo derivative **352**; with 5-alkyl-substituted terms, both 4-bromo (**353**) or 5-bromo derivatives (**352**) may be formed:




Particularly striking is the very fast evolution of hydrogen bromide in the bromination of 5-acylisoxazolines, which provides an easy, high-yield entry to 5-acylisoxazoles;[35/64,89/68,158/73,148/74] the formation of 4-acylisoxazoles, however, seems much more difficult, since 3,5-diphenyl-4-acetylisoxazole has been prepared in only 10% yield by this route.[158/73] Both *cis* and *trans* isomers are oxidized,[157/66] and both aromatic or heteroaromatic[34/65,118C/65,33/67,116/69,18/71,47/75,115/78] and alkyl groups[118C/65,110/69,147/70,32/72,86/72,69/73,144/75] are feasible in the 5-position. Yields are usually moderate to good, and seldom are excellent. A carboxylic ester group in the 3- or 5-position does not interfere,[118C/65,137/72] whereas in the case of 3-phenyl-5-cyanoisoxazoline, a cyano group does not, but is claimed to prevent conversion to isoxazole when a benzoyl group is present in the 3-position.[18/71] It should be also mentioned that 3-phenyl-5-furyl-2-isoxazoline is at first brominated by *N*-bromosuccinimide (NBS) on the furan ring and only subsequently oxidized in the isoxazoline ring.[88/68,152/75]

Although in some cases[27/60] manganese dioxide has been used previously, a recent investigation[234/77,245/78] showed that yields of conversion depend strongly on the type of oxidant used and are optimized by means of active $\gamma$-manganese dioxide. Refluxing in dry benzene to remove water azeotropically leads to essentially quantitative conversion of 2-isoxazolines to the corresponding is-

oxazoles. The mild neutral conditions involved leave several functionalities and protective groups unaffected: for example, 3,5-diphenyl-4-nitroisoxazoline has been oxidized to 3,5-diphenyl-4-nitroisoxazole,[234/77] and similarly, a 1,3-dioxolane group in the side chain remained unaltered.[142/79] Chloranil in refluxing benzene or *t*-butanol (with or without triethylamine) has sometimes been used successfully for the aromatization of 2-isoxazolines, especially those carrying a carbonyl group in the 4-position, and yields are particularly high when the carbonyl belongs to a six- or seven-membered ring.[206/66,158/73,240/74,156/75,240/76,188/79]

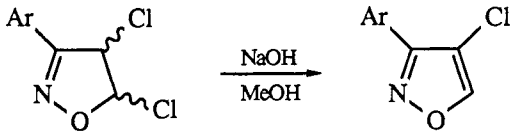
The use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) seems particularly promising, good conversions being obtained when the reagent is used in a 3:1 excess in refluxing benzene or dioxane.[107/79,115B/80,286/83] Nevertheless, at least in one instance chloranil or DDQ is reported to have failed, and resort to NBS treatment has been necessary.[32/72] A rather peculiar dehydrogenation is effected by refluxing 5-*o*-chlorophenyl-3-methylisoxazoline-4-carbonitrile in acetic acid, whereby nearly a 60% yield of the corresponding isoxazole nitrile is obtained.[159/77] An analogous oxidation is claimed to occur by refluxing some 3,5-diacylisoxazolines in an aqueous methanolic solution of hydrochloric acid.[4/45,9/47]

### b. By Dehydrohalogenation of Halo-2-Isoxazolines

4-Halo-2-isoxazolines, such as 4-bromo-3,5-diphenyl-2-isoxazoline or 3-phenyl-4-chloro-5-benzoyl-2-isoxazoline, easily dehydrohalogenate by treatment with alcoholic potassium hydroxide[9/50] or sodium methoxide,[11/64] respectively. As mentioned above, bromination of noncondensed 2-isoxazolines with NBS yields unstable and often nonisolable bromo derivatives; by contrast, when the isoxazolines are condensed at positions 4 and 5 with a five-membered ring such as in cyclopenta[*d*]-, indeno-, or acenaphtho-2-isoxazolines, the intermediate condensed 4-bromoisoxazolines are stable and easily obtainable (see Part 2 of this work).

An interesting dehydrobromination occurs with some 4-bromo-3,5,5-trisubstituted isoxazolines, that have at least one phenyl group in position 5. The formation of the 3,5-disubstituted 4-phenylisoxazole upon warming with ethanolic silver nitrate can be explained through a phenyl 1,2-migration in a carbonium ion–type rearrangement.[167/77,173/80]

5-Chloro- and 5-bromo-2-isoxazolines are usually very unstable and dehydrohalogenate spontaneously to isoxazoles even at room temperature. Thus, for example, in the cycloaddition of nitrile oxides to vinyl halides or to α-halostyrenes, isoxazoles are obtained directly.[8/54,38/70,26/73] Consistent with this finding, dehydrochlorination of the two stereoisomeric 3-(2,6-dichlorophenyl)-4,5-dichloro-2-isoxazolines with methanolic sodium hydroxide gives the 3-(2,6-dichlorophenyl)-4-chloroisoxazole as the sole reaction product:[42/70]

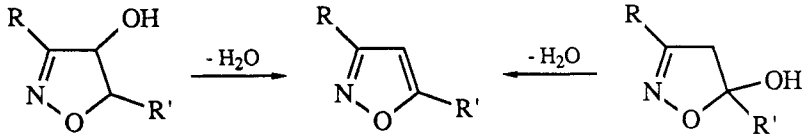



(Ar = 2,6-dichlorophenyl)

The *cis* isomer reacts faster than the *trans* isomer, just as required by an *anti*-elimination stereochemical mechanism. Very often 4-halo- or 5-halo-2-isoxazolines have been alleged as intermediates in various isoxazole syntheses, especially by the oximation of haloethylenic or of α,β-dihalocarbonyl compounds and by the cycloaddition of nitrile oxides to haloethylenic compounds, and reference is made to the appropriate sections (§§ 1.3.1.4, 1.3.1.3, and 1.3.2.2, respectively).

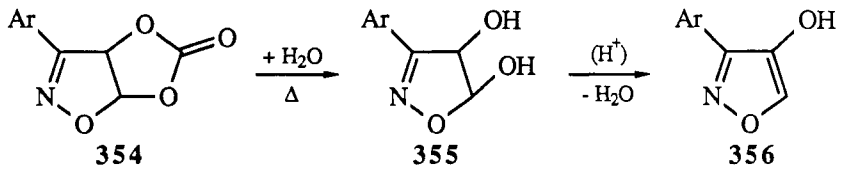
### c. By Dehydration of Hydroxy-2-isoxazolines

Both 4-hydroxy- and 5-hydroxy-2-isoxazolines dehydrate more or less easily to give the corresponding isoxazoles:




4-Hydroxy-2-isoxazolines are prepared either by oximation of chalcone epoxides or by oxidative cyclization of α,β-ethylenic ketoximes in the presence of transition-metal salts (see §§ 2.2.2.1e and 2.2.2.1a, respectively). Heating the hydroxy compound with a mixture of acetic acid–sulfuric acid affords the isoxazole in fair yields.[7/16,11/61,130/78] Thermolysis at 160–180°C in the presence of potassium bisulfate has also been used.[173/66]

The higher lability, due to its emiacetal character, of the 5-hydroxy toward the 4-hydroxy group is reflected in the formation of 3-aryl-4-hydroxyisoxazoles (**356**) by treatment of 3-aryl-4,5-dihydroxy-2-isoxazolines (**355**) or of their precursors (**354**) with sulfuric acid:[12/68]



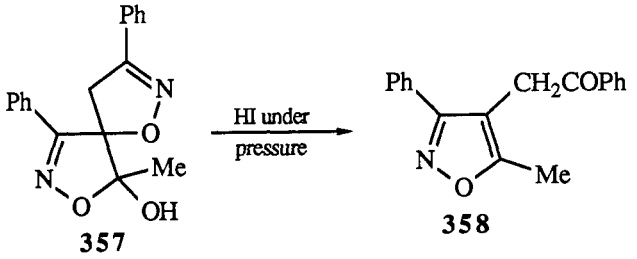

**354** **355** **356**

Calorimetric measurements of the heats of dehydration confirm the higher reactivity of the 5-hydroxy and 4,5-*cis* derivatives.[250/78]

5-Hydroxy-2-isoxazolines have frequently been invoked as labile intermediates in some syntheses of isoxazoles: for example, during the alkaline hydrolysis of 5-hydroxyisoxazoline acetates (see below) or during the oximation of β-diketones (see § 1.3.1.1), or in the cycloaddition of hydroximic acid chlorides or nitrile oxides to β-dicarbonyl compounds (see § 1.3.2.3). It is also possible that 5-hydroxyisoxazolines are involved as a first step in the chromic acid oxidation of 3,5-diarylisoxazolines to isoxazoles (see above).

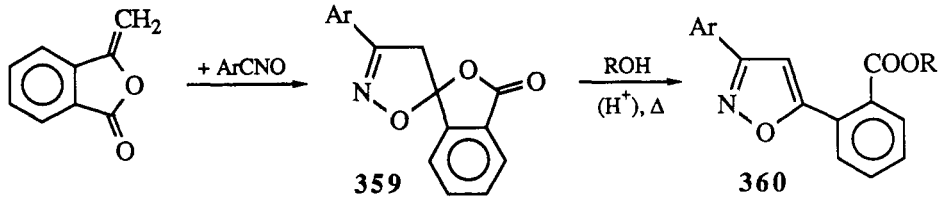
Nevertheless, under appropriate conditions, 5-hydroxy-2-isoxazolines, which are ring tautomers of β-diketone ketoximes, are relatively stable and can be isolated. These compounds dehydrate under various conditions: thermally at 180–200°C,[38/70,86/74,129/75] with or without the presence of polyphosphoric acid,[119/64] refluxing in xylene[3/68] or thionyl chloride,[38/70] or by treatment with acids,[7/16,78/71,50/72,158/74,146/78,101/83] with titanium tetrachloride,[76/75] or with phosphorus oxychloride in pyridine.[50/72] Some examples in the steroid field are also known.[42/69] A large variety of substituted isoxazoles have thus been prepared.

Some 3-amino-5-trifluoromethyl-5-hydroxy-2-isoxazolines were found to be stable toward dehydration even in concentrated sulfuric acid or trifluoroacetic acid, but were led to the isoxazoles expected by treatment with a mixture of the latter acid and its anhydride.[166/76] A special case of conversion of a 5-hydroxyisoxazoline to an isoxazole derivative is the acidic treatment of the spiro compound **357**, which leads to 5-methyl-4-phenacyl-3-phenylisoxazole (**358**):[102/64]




**357** **358**

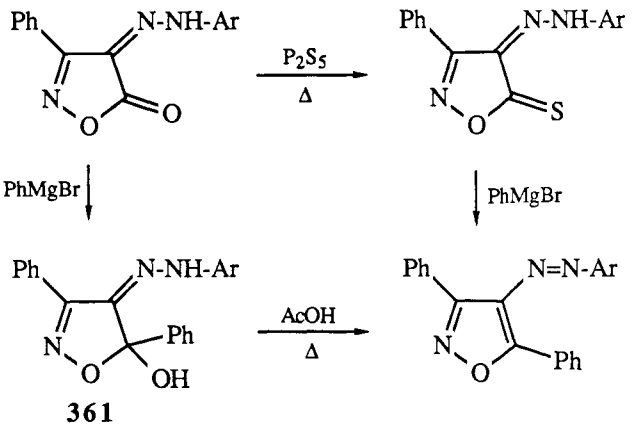
The alcoholysis of spiroisoxazoline (**359**), a masked 5-hydroxy compound easily obtainable by treatment of methylenephthalide with nitrile oxides, gives the isoxazolylbenzoates **360** directly:[82/80,216/83]




**359** **360**

The free acid can be obtained directly from **359** by thermolysis.[83/80,283/80,37/82]

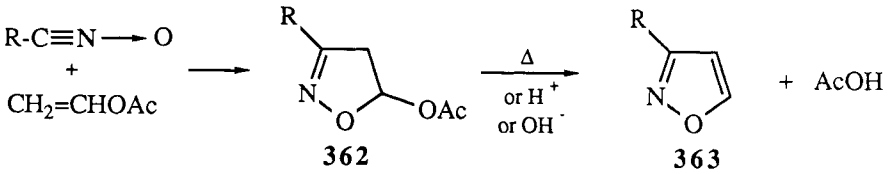
A 4-arylazo-3,5-diphenylisoxazole is easily obtained by acid-promoted dehydration of the 5-hydroxyisoxazoline derivative **361**, prepared in turn by treatment of 4-arylhydrazono-3-phenyl-2-isoxazolin-5-one with phenylmagnesium bromide. The thione analogue yields the isoxazole directly:[84/84]




**361**

d. By Elimination of Acetic Acid from 5-Acetoxy-2-isoxazolines

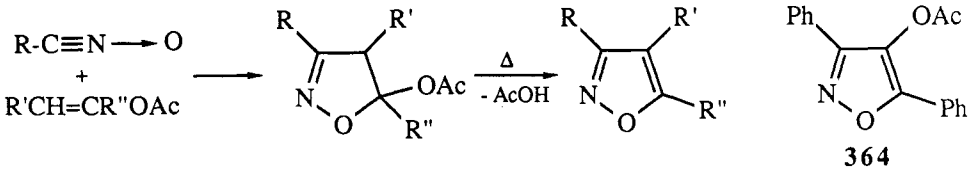
One of the most common routes to 3-monosubstituted isoxazoles is the cycloaddition of nitrile oxides to vinyl acetate to give the corresponding 5-acetoxy-2-isoxazolines (**362**) regiospecifically; a subsequent thermal[37/60.38/70.184/72.184/76] or acid- or base-promoted[8/50.1/51.9/62.120/66.200/68.183/71] elimination of acetic acid furnishes the isoxazole **363** in fairly good yields:




**362** **363**

If the goal is the synthesis of the isoxazole, it is unnecessary to isolate the acetoxyisoxazoline (see also § 1.3.2.2).

Analogously, 3,5-[184/72] or 3,4-disubstituted isoxazoles[199/72] have been obtained from the corresponding 5-acetoxy-2-isoxazolines, prepared by nitrile oxide condensation to the appropriately α- and/or β-substituted vinyl acetates:




**364**

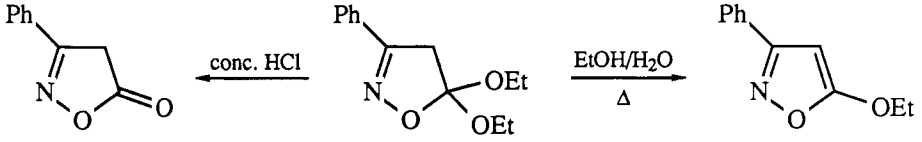
Even the parent isoxazole has been prepared by this route, although in low yields.[1/51]

The thermal elimination of acetic acid has been shown to be, as expected, a

*syn* process,[19B/80] following a first-order kinetics in DMF.[250/72] 3,5-Diphenyl-4-acetoxy-2-isoxazoline (**364**) decomposes less easily than the 3,4-diphenyl-5-acetoxy isomer, and the 4,5-*cis* compound decomposes more easily than the *trans* isomer.[199/72]

e. By Elimination of Alcohol from 5-Alkoxy-2-isoxazolines (and Related Reactions)

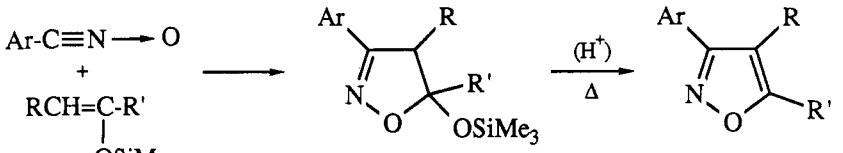
5-Alkoxyisoxazolines undergo elimination of alcohol on acidic treatment;[9/62,33/67,27/69] for example, 3-(5-nitro-2-furyl)-5-ethoxy-2-isoxazoline gives nearly quantitative yields of 3-(5-nitro-2-furyl)isoxazole.[33/67,27/69] 5,5-Dialkoxy-isoxazolines (i.e., 5-isoxazolinone-dialkylacetals; see also Part 2 of this work) readily eliminate one molecule of alcohol in mild hydrolytic medium (boiling 3 h in aqueous methanol or ethanol), whereas treatment with concentrated hydrochloric acid leads to the corresponding 5-isoxazolinone; for example:[26/59]




(85-90% yield) (85% yield)

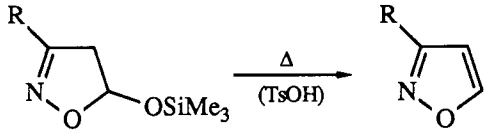
An analogous elimination reaction is reported from 5-isoxazolinone dialkylthioketals to 5-alkylthioisoxazoles.[36/63]

Other isoxazoline derivatives are too unstable to be isolated, and elimination occurs more or less spontaneously during the work up. For example, 3-(2,6-dichlorophenyl)-5-phenyl-5-trimethylsilyloxy-2-isoxazoline, prepared by cycloaddition of 2,6-dichlorobenzonitrile oxide to the silyl enol ether of acetophenone, is completely converted to 3,5-diarylisoxazole by simple preparative TLC or by acidic treatment:[73/78,38B/79]




(Ar = Ph or 2,6-$Cl_2C_6H_3$) (85% yield)

An acid-promoted elimination of trimethylsilanol afforded fairly good yields of the lower derivatives of the isoxazole series:[4/79,1/82]




(R = H, Me, Et, *n*-Am)

### f. By Deamination of 5-Amino-2-isoxazolines

2-Isoxazolines carrying a tertiary amine residue in the 5-position are easily available through the regiospecific cycloaddition of nitrile oxides to enamines (see § 2.2.2.2d, pp. 519–521). Heating with aqueous dilute mineral acids, usually hydrochloric or sulfuric acid, or with alcoholic hydrochloric acid, or, less frequently, simple pyrolysis convert these compounds into the corresponding isoxazoles (selected examples are collected in Table 1.76):

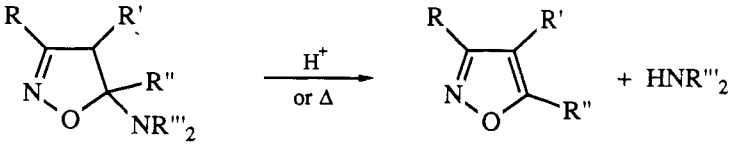
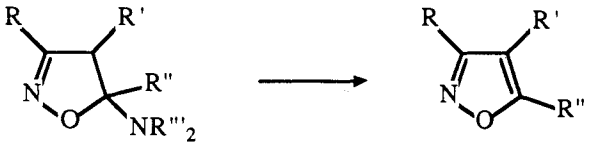


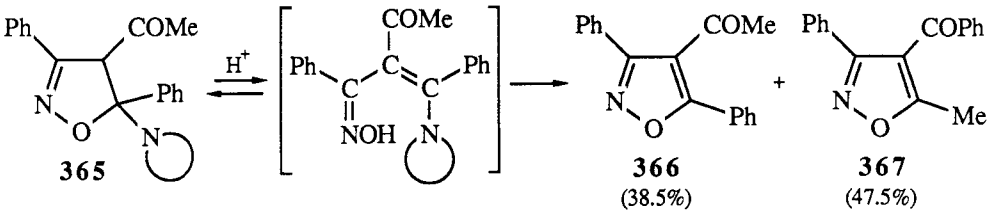

TABLE 1.76. SYNTHESIS OF ISOXAZOLES FROM 5-AMINO-2-ISOXAZOLINES



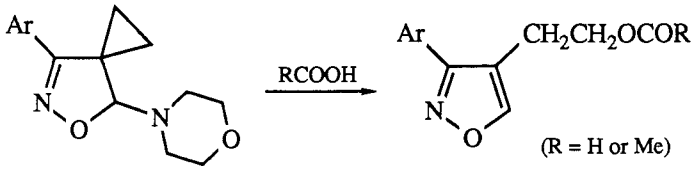

| R | R' | R" | $NR'"_2$ | Conditions | Yield (%) | References |
|---|---|---|---|---|---|---|
| Ph | H | H | NHCOOMe | AcOH, 50% $H_2SO_4$, reflux 1 h | 80 | 152/80 |
| 4-$NO_2C_6H_4$ | H | H | 1-morpholinyl | 20% HCl, 70°, 30 min | 90 | 57/67 |
| 5-$NO_2$-2-furyl | Me | H | 1-piperidinyl | conc. HCl, heat | 60 | 33/67 |
| Ph | $CH{=}CH_2$ | H | $NEt_2$ | 150-170°/25 mm | 73 | 210/70 |
| Ph | Ph | H | 1-pyrrolidinyl | conc. HCl, MeOH, reflux 3 min | 90 | 26/73 |
| 5-$NO_2$-2-furyl | H | Et | 1-piperidinyl | conc. HCl, heat | 85 | 33/67 |
| 4-$NO_2C_6H_4$ | H | Me | 1-morpholinyl | 20% HCl, 70°, 30 min | 40 | 68/70 |
| PhCH=CH | H | Ph | 1-morpholinyl | conc. HCl, EtOH, reflux 1 h | 95 | 28/67 |
| 5-$NO_2$-2-furyl | Me | Et | 1-morpholinyl | conc. HCl, heat | 85 | 33/67 |
| 4-$NO_2C_6H_4$ | Me | Et | 1-morpholinyl | 10% HCl, reflux 15 min | | 37/63 |
| Ph | COMe | Ph | 1-morpholinyl | 160° | 100 | 158/73 |

Morpholine, pyrrolidine, piperidine, or dialkylamine are the amino moieties encountered most frequently. 3-Monosubstituted,[57/67,128/68,119/69] 3,4-disubstituted,[37/63,33/67,128/68,27/69,119/69,210/70,26/73] 3,5-disubstituted,[37/63,28/67,33/67,35/68,128/68,27/69,119/69,68/70,85/77] or trisubstituted[37/63,33/67,128/68,119/69,158/73] isoxazoles have been obtained with fair to excellent overall yields.

Sometimes the elimination reaction is not as straightforward. For example, heating of 4-acetyl-5-morpholinyl-3,5-diphenyl-2-isoxazoline (**365**) with aqueous HCl gives a mixture of the two isomeric 4-acylisoxazoles **366** and **367**, presumably owing to a facile ring/open-chain tautomerism which permits the reclosure of the oxime group on two different carbonyls:[103/81]



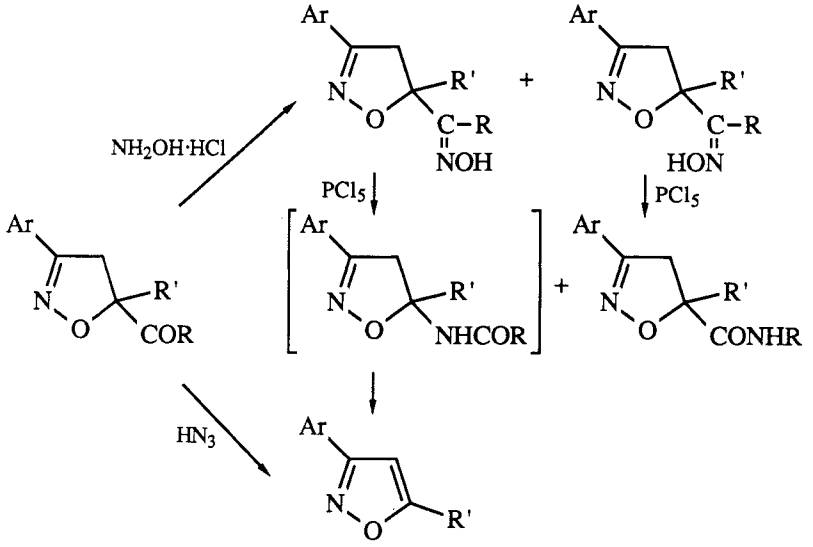

4,4-Disubstituted derivatives are usually unable to deaminate. Nevertheless, a 4-spirocyclopropane ring has been cleaved with formic or acetic acid to give 4-(2′-acyloxyethyl)isoxazole:[144/83]




Elimination of a hydroxylamine residue has also been recorded.[40/62]

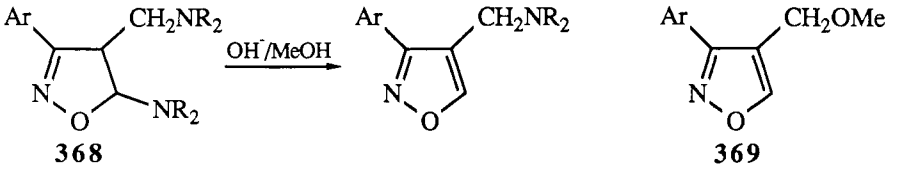
In some cases, elimination of the amine molecule occurs spontaneously at room temperature, in particular when enamines of β-diketones, β-keto esters, or β-ketonitriles are utilized as dipolarophiles in cycloaddition with nitrile oxides. Here, isoxazoles are isolated directly (see § 1.3.2.2, p. 200).

Noteworthy is the behavior of 5-acylisoxazolines in the Schmidt reaction or of their oximes in the Beckmann reaction; together with the 5-carboxamide derivative, the corresponding isoxazole is obtained, possibly through the intermediacy of 5-acetamidoisoxazoline, which loses the acetamide residue spontaneously in acidic media (Scheme 1.17).[149/66.89/68]




**Scheme 1.17.**

Base-promoted deamination, although slower, is reported to be more convenient with 5-amino-4-aminomethyl-2-isoxazolines (**368**); in this case acidic deamination is accompanied by substantial amounts of the 3-monosubstituted isoxazole, arising from a retro-Mannich reaction:[180/80]

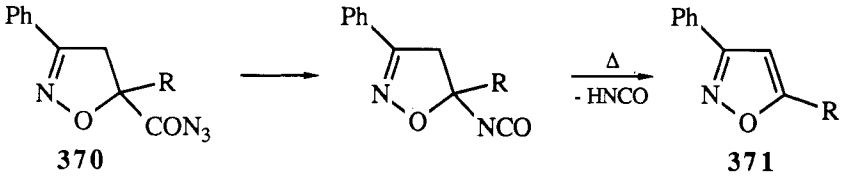



**368** **369**

Similarly, 4-methoxymethyl derivatives (**369**) are obtained under basic conditions.[181/80]

### g. Miscellaneous Elimination Reactions

Several other 2-isoxazoline derivatives can undergo an elimination reaction and thus aromatize to isoxazoles. For example, 5-isocyanato-2-isoxazolines (**371**), obtained through a Curtius reaction from the corresponding acyl azides (**370**), are reported to pyrolyze with elimination of isocyanic acid:[249/72]

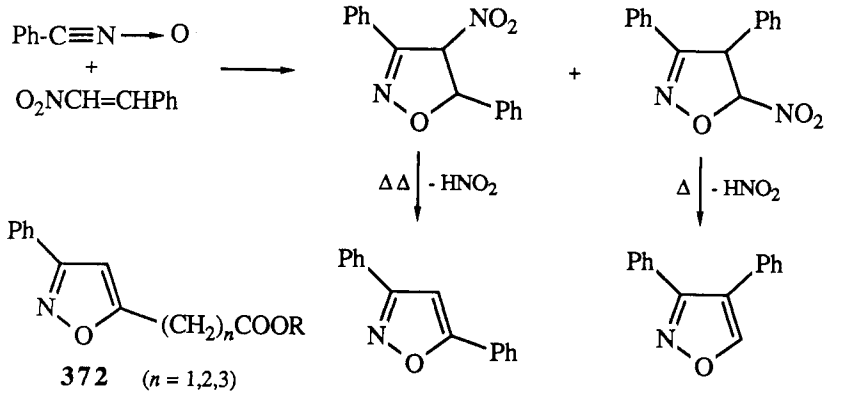



**370** **371**

A study of the pyrolysis of several 2-isoxazoline derivatives has established that the leaving group in the 5-position can be ordered in the following series of increasing difficulty of elimination: OCOMe < NCO < NHCOOEt < NHCONHPh < CN. Furthermore, the introduction of a methyl group in the same position lowers the elimination temperature to 50–100°C below that of the unsubstituted compound.[250/72]

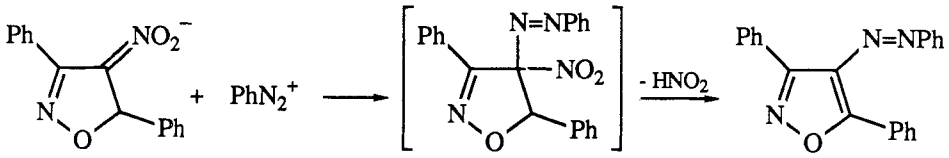
4-Nitro- and 5-nitro-2-isoxazolines are also known to lose nitrous acid, yielding isoxazoles. As usual, the ease of elimination differs in the two series of compounds; for example, 3,5-diphenyl-4-nitroisoxazoline is quantitatively transformed into 3,5-diphenylisoxazole when heated over its melting point at atmospheric pressure,[8/54.2/56.316/82] but survives unaltered a distillation at 150–170°C and 0.001 mm, whereas under the same conditions its isomer, 3,4-diphenyl-5-nitroisoxazoline, is aromatized to 3,4-isoxazole.[26/73] Moreover, cycloaddition of benzonitrile oxide to α-nitrostilbene in boiling diethyl ether directly produces triphenylisoxazole instead of the expected nitroisoxazoline.[8/54] It should also be remembered that thermolysis of 4-nitro-3,5-diphenylisoxazoline in boiling dimethylformamide does not yield the denitrated

product; instead, dehydrogenation occurs, yielding 4-nitro-3,5-diphenyl-isoxazole.[316/82]



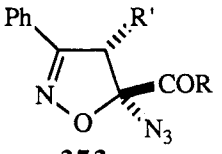

Analogously, 2-h refluxing in dry toluene is required to convert 3-aryl-5-nitro-2-isoxazolines into 3-arylisoxazoles in good yields; 6-h refluxing of 3-aryl-4-nitro-5-methyl-2-isoxazolines in dry xylene gives lower yields of 3-aryl-5-methylisoxazoles.[254/74,225/76,249/82] Easy preparation of the isoxazolyl alkanoates (**372**) can be achieved by simple distillation of the suitable 5-nitroisoxazoline derivatives.[151/71]

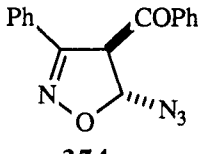
A peculiar synthesis of 4-nitroisoxazole derivatives is based on the reaction of tetranitromethane with the potassium salts of 4-nitroisoxazolines; the intermediacy of a dinitrocompound is possibly involved here.[91/81] An interesting synthesis of 4-arylazoisoxazoles uses 4-nitro-2-isoxazolines as the starting material.[258/79] Treatment of 3,5-diphenyl-4-nitro-2-isoxazoline sodium salt with phenyldiazonium salt gives 3,5-diphenyl-4-phenylazoisoxazole in 75% yield, owing to electrophilic attack on the 4-position and subsequent loss of nitrous acid:

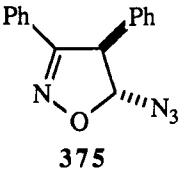


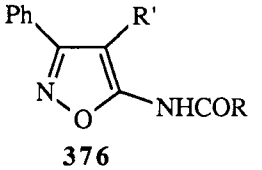

Unfortunately, far lower yields are reported for other aryldiazonium salts.

Loss of $HN_3$ from 5-azidoisoxazolines (**373**) is promoted by triethylamine at 50°C, whereas aromatization is spontaneous with compound **374**, possibly through an E1cb mechanism. With compound **375** the *syn* elimination of $HN_3$ is much slower and requires a 25-day treatment with triethylamine at 45°C or heating in dry toluene at 100°C for 1 month.[176/74] By contrast, thermolysis of compounds **373** under the latter conditions yields derivatives **376** via a concerted pathway involving a nitrenium ion:[179/74]


373

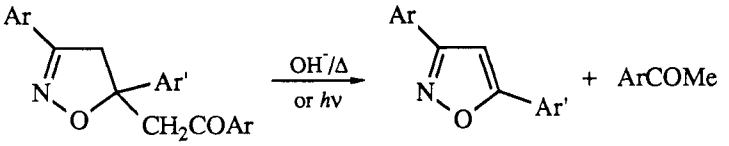

374


375

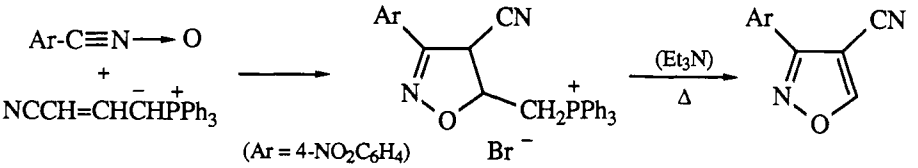

376

Acid-catalyzed elimination of methylmercaptan or of thiophenol easily transforms 5-methyl (or phenyl)thio-2-isoxazolines into the corresponding isoxazoles, whereas the isomeric 4-thiosubstituted isoxazolines are stable under the same conditions.[278/83,160/84] Since 4- or 5-isoxazolinyl sulfoxides, especially in their *trans* form, are highly unstable and undergo a desulfurating elimination reaction at room temperature, 3,4- or 3,5-disubstituted isoxazoles can be obtained directly by peracid oxidation of 5- or 4-isoxazolinyl sulfides, respectively.[52D/81,278/83]

Both *cis*- and *trans*-isoxazolinyl sulfones can be desulfonated to isoxazoles by treatment with more or less strong bases.[154/66,278/83] A suggested 3,5-diphenyl-4-nitrato-2-isoxazoline eliminates the elements of $HNO_3$ to give 3,5-diphenylisoxazole.[153/69] Even a molecule of acetophenone can be extruded from a 5-phenacyl-2-isoxazoline by heating with either bases or with acids, or photochemically:[1/68,199/68]



Elimination of a molecule of protonated acetonimine has been invoked to explain the fragmentation of a substituted 5-isoxazolinyl-1,3-oxazin-6-one into 3,5-diphenylisoxazole and a pyridine *N*-oxide.[106/79] Base-promoted elimination of a phosphonium salt has been used in the synthesis of 3-*p*-nitrophenylisoxazole-4-carbonitrile:[149/76]



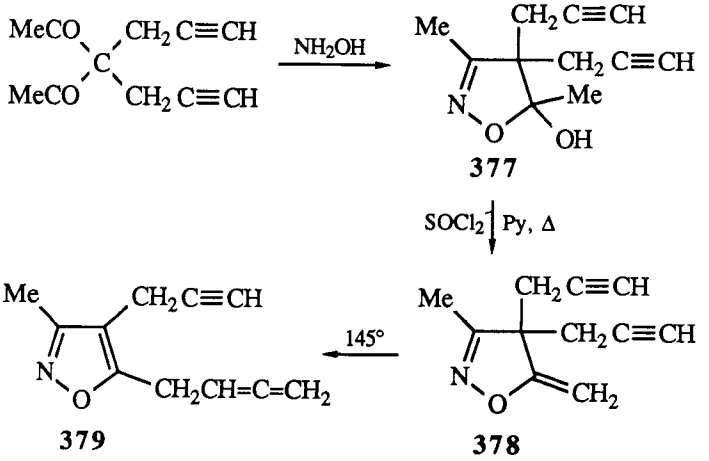
5α-Hydroxyalkyl-2-isoxazolines are usually dehydrated to 5-alkylisoxazoles in strong acidic conditions.[89/68,143/84]

h. Rearrangement of 4- or 5-Alkylidene-2-isoxazolines

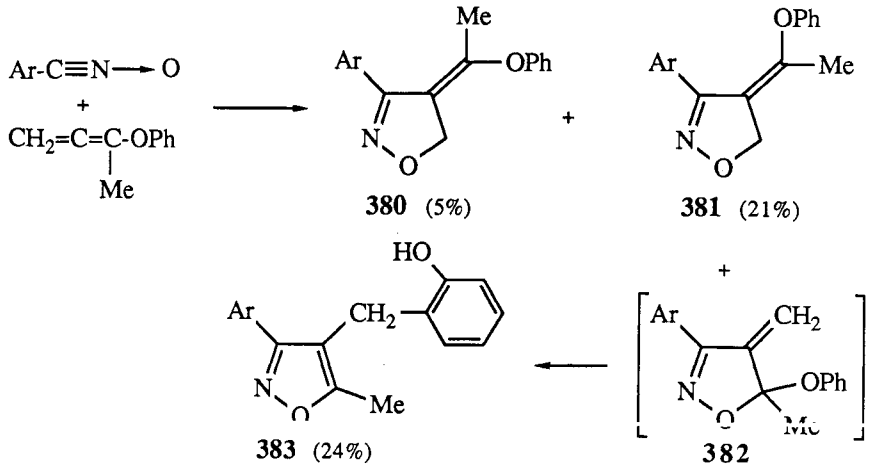
2-Isoxazolines having an *exo* double bond in the 5-position are usually very unstable, and rearrange spontaneously to the isomeric isoxazoles, owing to a

very rapid hydrogen 1,3-shift. Thus the elusive intermediate 5-methylene-2-isoxazoline has never been isolated and in its place a 5-methylisoxazole is always obtained[31/69,212/84] (see also § 1.3.2.2, p. 202).

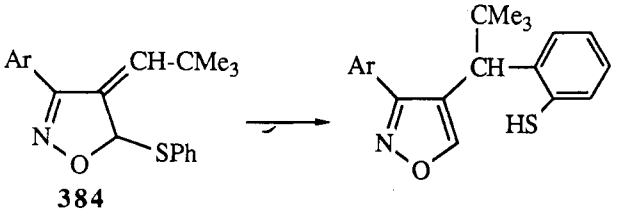
Nevertheless, in special cases the *exo*-methyleneisoxazolines can be isolated. For example, dehydration of 3,5-dimethyl-4,4-dipropargyl-5-hydroxy-2-isoxazoline (**377**) with thionyl chloride in pyridine gives the relatively stable *exo*-methylene compound **378**; heating of the latter at 145°C under nitrogen causes rearrangement to the air-sensitive 5-(2,3-butadienyl)-3-methyl-4-propargylisoxazole (**379**) in 77% yield:[161/69]



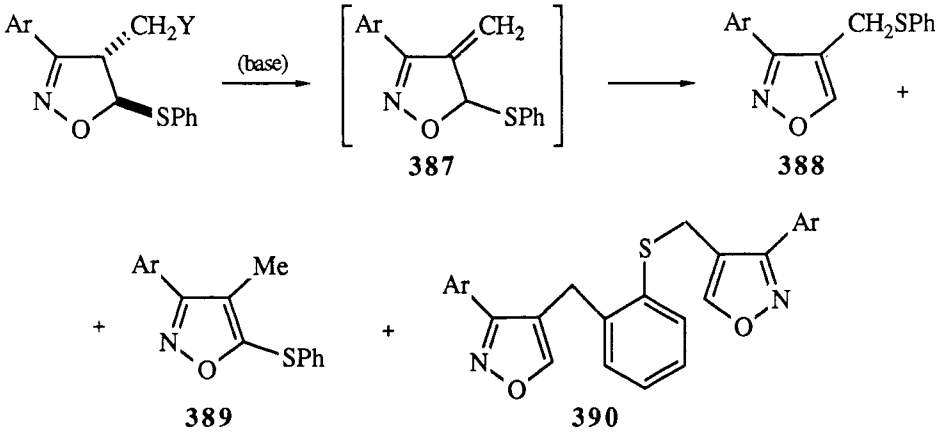

3-Aryl-4-diphenylmethylene-2-isoxazoline is fairly stable and rearranges to the isomeric 3-aryl-4-diphenylmethylisoxazole only by refluxing with methanolic sodium methoxide.[146/72,152/74] Whereas the phenoxy-substituted 4-methyleneisoxazoline compounds **380** and **381** are thermally stable, the isomeric unsubstituted 4-methyleneisoxazoline **382** could not be evidenced in the reaction mixture, but the Claisen-rearranged isomeric isoxazole **383** was isolated:[150/79]



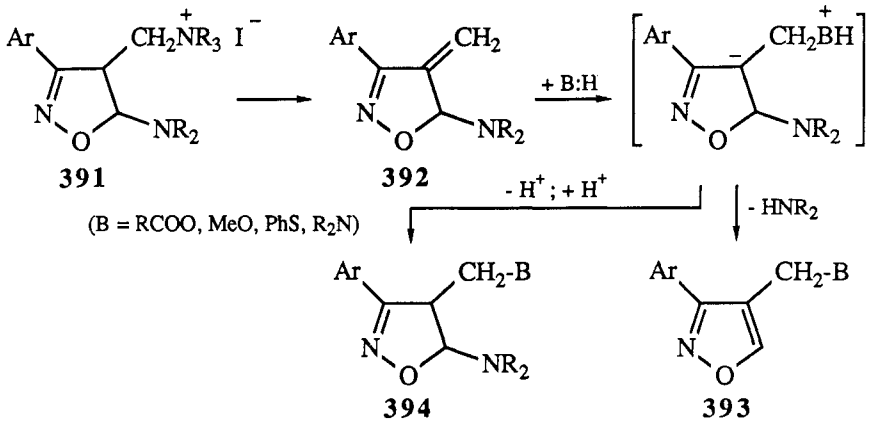
An analogous rearrangement occurs with the thio compound **384**, whereas its isomer (**385**) is slowly hydrolyzed with spontaneous oxidation to isoxazole-4-carboxaldehyde (**386**):[145/83]




The unsubstituted thio derivative **387** also is not isolable, and according to conditions, gives rise to the addition/elimination product **388** either alone or accompanied by minor amounts of the pure H-shifted isomer **389** and of the Claisen-rearranged bis adduct **390**:[52C/81]

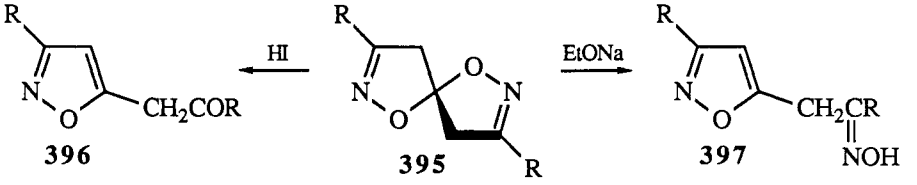



Another type of stable *exo*-unsaturated compounds is that of the 3-aryl-4-methylene-5-amino-2-isoxazolines (**392**), easily available from the quaternary salts (**391**) by Hofmann elimination:[180/80] upon reaction with carboxylic acids or with bases, such as methoxide, benzenethiolate, and secondary amines, an addition–elimination scheme leads to the 4-substituted isoxazoles **393**. In basic media, minor or major amounts of the pure addition product **394** are also present:[181/80]

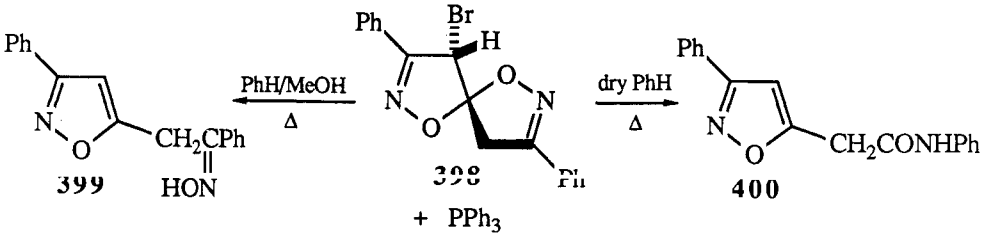



i. Ring Opening of Spirodiisoxazolines

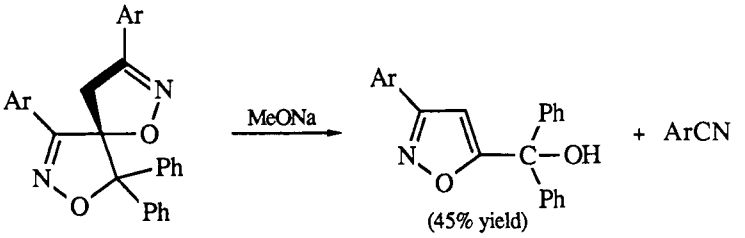
5,5′-Spiro-2,2′-diisoxazolines (**395**), obtained in the cycloaddition of nitrile oxides to allene, can be ring-opened under both acidic and basic conditions: refluxing with aqueous hydroiodic acid leads to the 5-acylmethylisoxazoles (**396**), whereas by treatment with hot ethanolic sodium ethoxide its oxime (**397**) is obtained:[29/60,88B/68]




More interesting, at least from a mechanistic point of view, is the behavior of the 4-bromo-5,5′-spirodiisoxazoline **398** toward triphenylphosphine: in refluxing benzene–methanol the *E*-oxime of 3-phenyl-5-phenacylisoxazole (**399**) is formed, whereas in dry benzene lower yields of the anilide **400** are obtained.[16B/75] Attack by triphenylphosphine on the bromine atom, assisted by solvent protonation of the oxygen in the same ring, would lead to the former compound: attack by the oxygen atom with intermediate formation of a quasi-phosphonium salt would produce the latter.



A 4,5′-spirodiisoxazoline is also known, and base-promoted fragmentation of one of the two rings yields an easy predictable isoxazole derivative:[146/72.152/74]




j. Cycloreversion of Condensed 2-Isoxazolines

The tricyclic cycloadduct **401** of arylnitrile oxides to cyclooctatetraene is thermally unstable and undergoes a high-yield symmetry-forbidden cyclo-reversion to 3-arylisoxazole and benzene:[40/67.208/68.209/70.26/73]

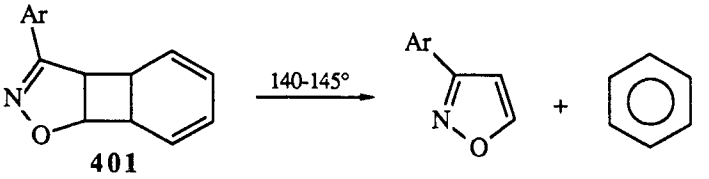
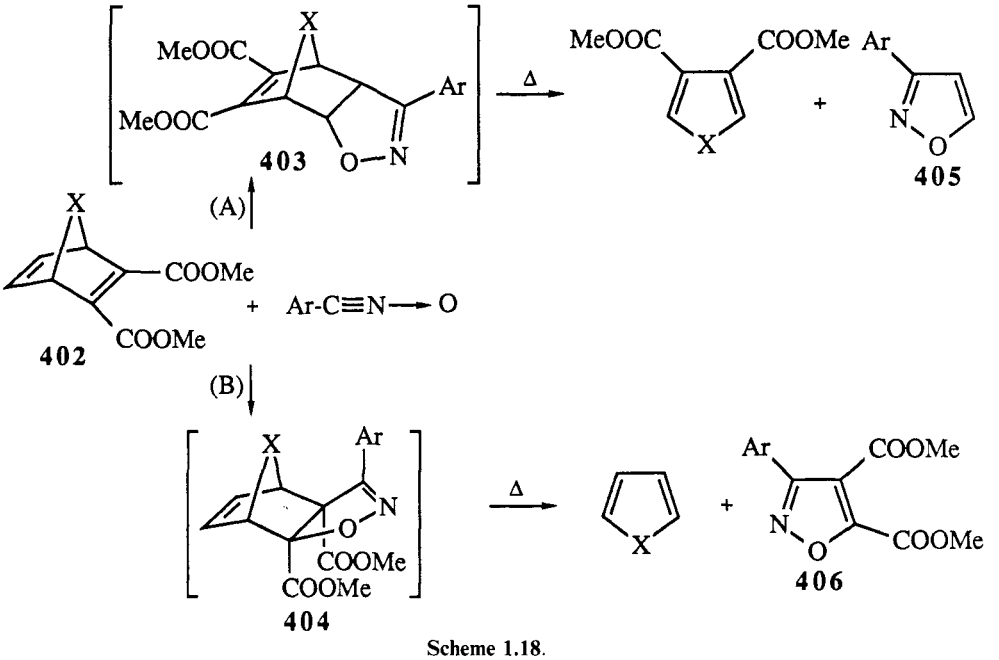



TABLE 1.77. SYNTHESIS OF 3-ARYLISOXAZOLES (PATHWAY A) AND OF DIMETHYL-3-ARYLISOXAZOLE-4,5-DICARBOXYLATES (PATHWAY B) FROM NORBORNADIENE DERIVATIVES (**402**) AND NITRILE OXIDES

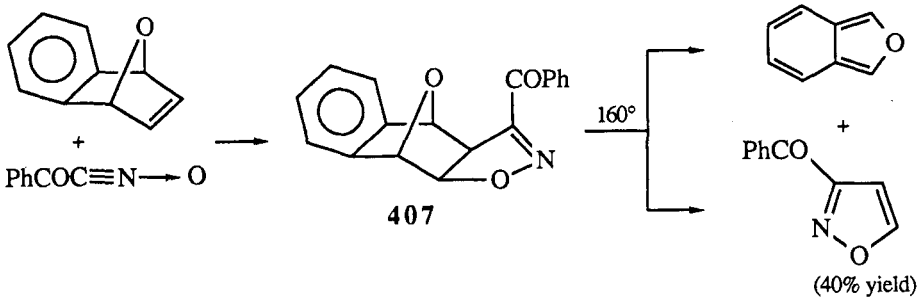
| (**402**) X | ArCNO where Ar is: | Solvent | Ratio A/B (**405** : **406**) | References |
|---|---|---|---|---|
| O | 4-$MeOC_6H_4$ | benzene | 0.15 | 220/81 |
| O | Ph | benzene | 0.33 | 220/81 |
| O | mesityl | DMF | 1.51 | 220/81 |
| | | MeCN | 1.27 | 220/81 |
| | | dioxane | 1.17 | 214/76 |
| | | $Et_2O$ | 0.80 | 220/81 |
| | | benzene | 0.75 | 220/81 |
| | | *n*-Hex | 0.64 | 220/81 |
| | | EtOH | 0.47 | 220/81 |
| O | 4-$NO_2C_6H_4$ | benzene | 0.77 | 220/81 |
| O | PhCO | $Et_2O$ | 1.22 | 52/83 |
| NCOOEt | mesityl | $Et_2O$ | 1.20 | 214/76 |
| $CH_2$ | 4-$MeOC_6H_4$ | benzene | 8.43 | 220/81 |
| $CH_2$ | Ph | benzene | 6.41 | 220/81 |
| $CH_2$ | 4-$NO_2C_6H_4$ | benzene | 25.32 | 220/81 |
| $C{=}CMe_2$ | 4-$MeOC_6H_4$ | benzene | 4.99 | 220/81 |
| $C{=}CMe_2$ | Ph | benzene | 8.62 | 220/81 |
| $C{=}CMe_2$ | 4-$NO_2C_6H_4$ | benzene | 17.87 | 220/81 |

Norbornadiene derivatives of type **402** (where X = $CH_2$, O, NR, $C{=}CR_2$) are known to act as masked acetylene derivatives, since their cycloaddition to nitrile oxides can involve either the disubstituted or the tetrasubstituted double bond. The condensed isoxazolines **403** and **404**, not always isolable, collapse thermally to a 3-monosubstituted isoxazole (**405**) or to a trisubstituted isoxazole dicarboxylate (**406**), respectively.[248/74,214/76,220/81,52/83] As Table 1.77 shows, pathways A and B of Scheme 1.18 are both effective, and a mixture of products are obtained, owing to the poor site selectivity of nitrile oxides toward compounds **402**. When X = O a slight prevalence of pathway B is usually observed, whereas with X = $CH_2$ or $C{=}CMe_2$, pathway A is largely dominant. A noticeable solvent dependency is observed, polar aprotic solvents favoring pathway A, and apolar solvents as well as ethanol or methanol favoring pathway B.[220/81]

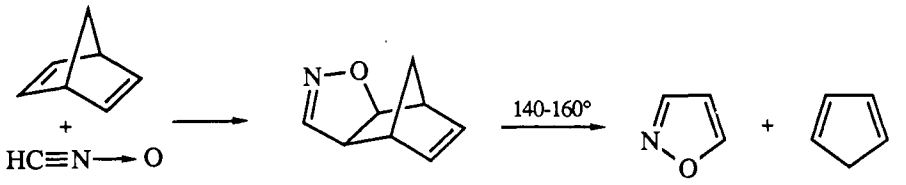



**Scheme 1.18.**

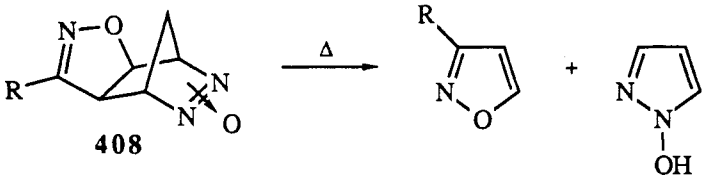
3-Benzoylisoxazole has been obtained in fair yield by thermolysis of the cycloadduct **407**, resulting from the cycloaddition of benzoylnitrile oxide to 1,4-epoxy-1,4-dihydronaphthalene:[142/72]



Isoxazole itself can be prepared in 37% overall yield by thermolysis of the cycloadduct from fulminic acid and norbornadiene:[28/73]



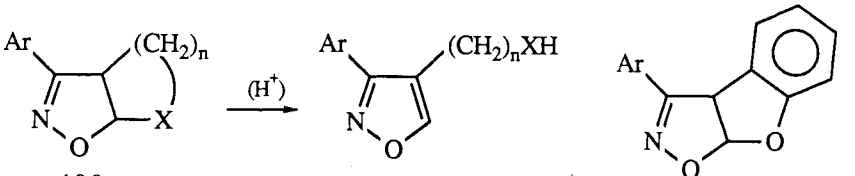

Another polycyclic system suitable for cycloreversion is **408**, also readily attainable through nitrile oxide synthesis, which thermally decomposes in high yields into an isoxazole and 1-hydroxypyrazole:[74/82]




**408**

k. Other Ring Openings of Condensed 2-Isoxazolines

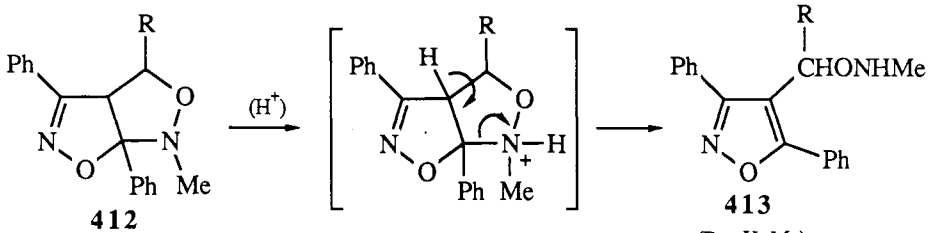
3,4-Disubstituted isoxazoles (**410**) with a functionalized 4-side chain are conveniently obtained by the acid-promoted cleavage of bicyclic 2-isoxazolines (**409**), easily attainable by nitrile oxide synthesis (see Part 2 of this work):[54/68,127/69]




**409** (X = O, NAc; n = 2, 3) **410** **411**

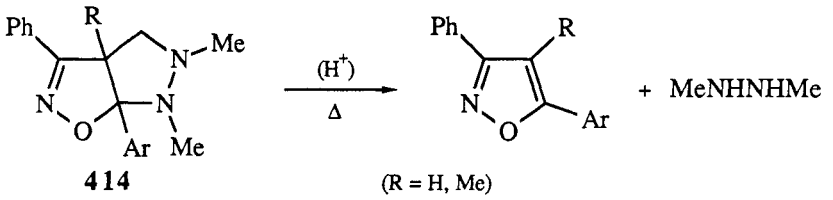
Yields are excellent, especially when X = O. The ring-opening process can be extended to benzoderivatives of general structure **411**.[203/78]

3*a*,4,6,6*a*-Tetrahydroisoxazolo[5,4-*c*]isoxazoles (**412**), also attainable by nitrile oxide synthesis, are smoothly cleaved to isoxazoles (**413**) by treatment with 12 *N* hydrogen chloride in dry chloroform; treatment with aqueous acid is



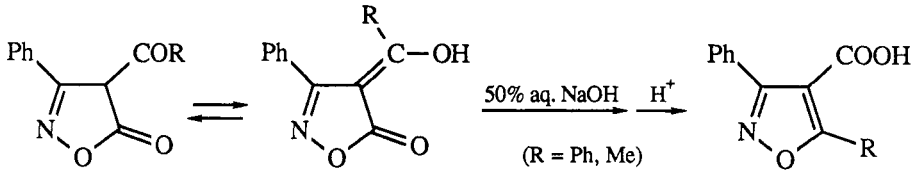

**412** **413** (R = H, Me)

less convenient, since a complicated mixture of products is obtained.[170/78] A similar ring scission has been observed with the pyrazolidino[4,3-*d*]isoxazoline system **414**, where, however, the fragmentation usually proceeds further, to give 3,5-disubstituted isoxazoles:[22/74,168/76,156/77]



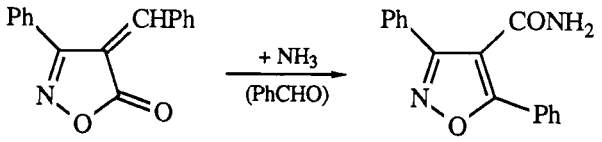

## l. Isomerization of Isoxazolinone Derivatives

4-Acyl-5-isoxazolinones rearrange to the isomeric 4-isoxazolecarboxylic acids under the influence of a concentrated solution of sodium hydroxide:[18/52,15/61]

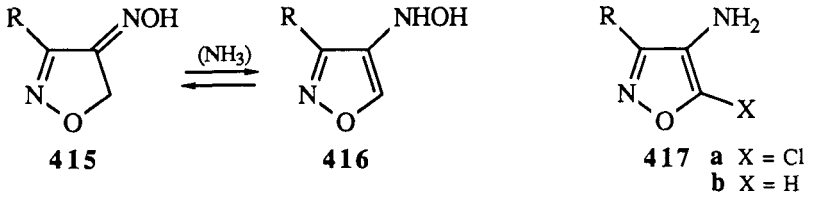



With 4-formyl-3-phenyl-5-isoxazolinone, the only product obtained was benzoic acid.[15/61] The driving force for the rearrangement is the higher stability of the isoxazole ring toward the isoxazolinone ring.

4-Benzylidene-3-phenyl-5-isoxazolinone or its ammonium salt, when treated for several days with anhydrous ammonia in ethanolic solution in the presence of benzaldehyde, is transformed into 3,5-diphenylisoxazole-4-carboxamide in good yields:[1/15,157/73]

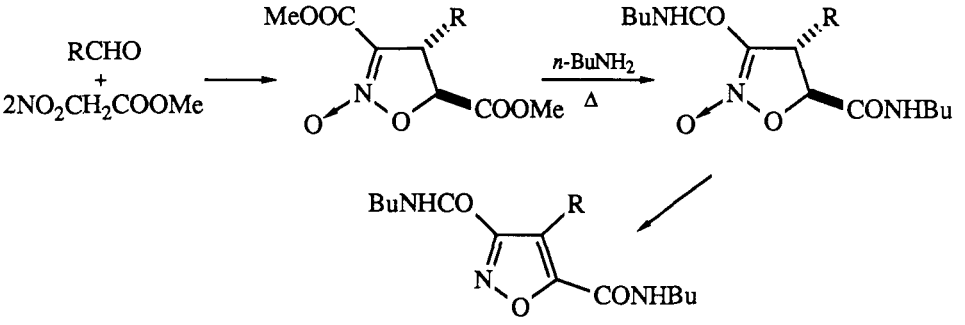



3-Substituted 2-isoxazolin-4-one oximes (**415**), available from 3-methyl-substituted furoxans through the so-called Angeli's rearrangement,[1/880,9/892,5/894] tautomerize in the presence of a weak base to 4-hydroxylaminoisoxazoles (**416**), which revert to the oxime form in a strongly basic medium.[6B/29,52/81] Hydrochloric acid causes the transformation of **415** to 4-amino-5-chloroisoxazoles (**417a**), whereas 5-unsubstituted 4-aminoisoxazoles (**417b**) are obtained by reduction with zinc and sodium hydroxide:[52/81]



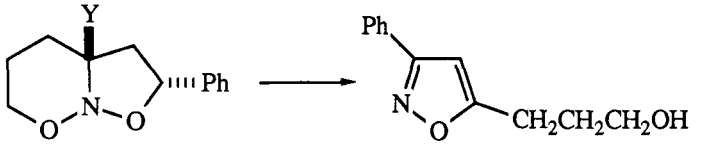

m. Dehydration of 2-Isoxazoline *N*-Oxides

The dehydration of 2-isoxazoline *N*-oxides, which is conveniently accomplished in the presence of strong bases, is dealt with in § 2.3.3.2, pp. 615–617. Since isoxazoline *N*-oxides are less accessible compounds than isoxazoles, this method has little preparative value. An exception is represented by the synthesis of 4-substituted isoxazole-3,5-dicarboxylic acid and its functional derivatives from aromatic or aliphatic aldehydes and methyl nitroacetate, where the intermediate isoxazoline *N*-oxide is usually not isolated (see § 1.3.4.1, pp. 211–212). Under suitable conditions the isoxazoline *N*-oxide can be isolated and subsequently dehydrated by heating for enough time in methanol:[21/71.37/74.45/80]




n. Rearrangement of Isoxazolidine Derivatives

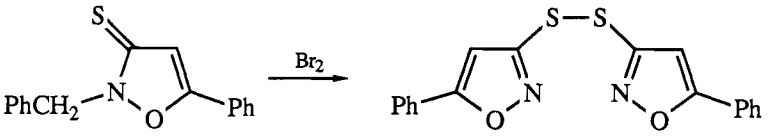
3-(5′-Isoxazolyl)-1-propanols can be achieved in variable yields by a complex acid-promoted rearrangement sequence from 6-substituted 8-phenyl-2,9-dioxa-1-azabicyclo[4.3.0]nonanes:[113/77.146/78.130/80]




(Y = $NO_2$, OMe, OH)

o. Miscellaneous Syntheses

The 4-isoxazoline-3-thione (**418**) has been oxidized by bromine to bis-3-isoxazolyldisulfide (**419**):[117/81]




**418** **419**

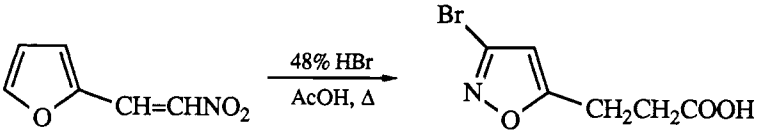
Analogous derivatives have also been prepared.

Finally, we should note the isomerization of 3,5-disubstituted isoxazoles through the formation of isoxazolium salt, followed by treatment with hydroxylamine in basic media (see § 1.4.6.1, pp. 317–318).

### *1.3.7.2 From Other Heterocycles*

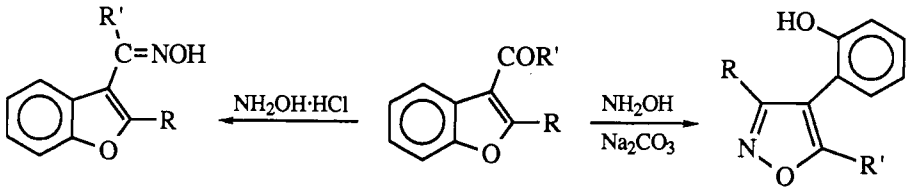
#### a. From Furan and Benzofuran Derivatives

3-(3-Bromoisoxazol-5-yl)propionic acid has been obtained directly by treatment of the readily available 2-(2-nitrovinyl)furan with hot concentrated hydrobromic acid:[8/65,138/66,139/66,213/68,219/69]




This reaction recalls the synthesis of 3-haloisoxazoles from β-nitro ketones (see § 1.3.6.4, pp. 221–222).

2-Acylbenzofurans (**420**) show a dual reactivity toward hydroxylamine: in an acidic medium normal oximes (**421**) are obtained, whereas in the presence of a weak base, such as sodium carbonate, attack by hydroxylamine on the 2-position of benzofuran largely prevails, and 4-(*o*-hydroxyphenyl)-substituted isoxazoles (**422**) are finally achieved, sometimes mixed with the oxime:[17/63,19/64,80/64,27/66]




**421** **420** **422**

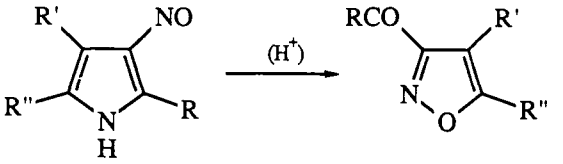
Table 1.78 presents some selected examples of the reaction. This behavior is reminiscent of that of chromones (see below), which possess the same structural moiety O–C=C–C=O (endocyclic instead of exocyclic). 2-Ethyl-3-cyanobenzofuran reacts with hydroxylamine to give a mixture of the corresponding amide and of 5-amino-3-ethyl-4-(2-hydroxyphenyl)isoxazole.[27/66]

TABLE 1.78. SYNTHESIS OF ISOXAZOLES FROM 3-ACYLBENZOFURANS

| R | R' | Conditions | Oxime **421** (%) | Isox **422** (%) | References |
|---|---|---|---|---|---|
| Et | H | $NH_2OH·HCl$/AcONa in EtOH, heating 8 h | 76 | 0 | 17/63 |
| | | $NH_2OH·HCl$ in pyridine, heating 8 h | 69.5 | 0 | 17/63 |
| | | $NH_2OH$/NaOH in EtOH, heating 24 h | 55 | 0 | 17/63 |
| | | $NH_2OH/Na_2CO_3$ in EtOH, heating 25 h | 35 | 34 | 17/63 |
| H | Et | $NH_2OH·HCl$ in aq. EtOH, reflux 2 h | 78 | 0 | 17/63 |
| | | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 15 h | 0 | 64.5 | 17/63 |
| H | Ph | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 3 h | low | 50.5 | 17/63 |
| Et | Et | $NH_2OH·HCl$/AcONa in aq. EtOH, reflux 5 h | 64 | 8 | 17/63 |
| | | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | 0 | 80 | 17/63 |
| Et | Ph | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | 0 | 56.5 | 17/63 |
| | | $NH_2OH$/AcONa in aq. EtOH, reflux 5 h | 9.5 | 30 | 17/63 |
| $CH_2Ph$ | Me | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 66 | 19/64 |
| Ph | Me | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 18 | 19/64 |
| Me | 4-$MeOC_6H_4$ | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 52 | 19/64 |
| Et | 4-$MeOC_6H_4$ | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 90 | 19/64 |
| *n*-Bu | 4-$MeOC_6H_4$ | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 84 | 19/64 |
| *n*-Bu | 4-$HOC_6H_4$ | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 73 | 19/64 |
| Et | 4-$HOC_6H_4CH$=CH | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 33 | 19/64 |
| Et | 2-thienyl | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 24 | 19/64 |
| Et | 4-pyridyl | $NH_2OH/Na_2CO_3$ in aq. EtOH, reflux 5 h | - | 67 | 19/64 |

### b. From 3-Nitrosopyrroles

2,5-Disubstituted or 2,4,5-trisubstituted 3-nitrosopyrroles, easily attainable by nitrosation of the corresponding pyrroles, are converted into 3-acylisoxazoles under the influence of hot, dilute mineral acids, according to the following general scheme:



The reaction was first applied to the formation of 3-benzoyl-4,5-diphenylisoxazole from triphenylisonitrosopyrrole and hydroxylamine hydrochloride.[1/35,6/37] Use of semicarbazide hydrochloride led to the semicarbazone of the same ketone.[2/37]

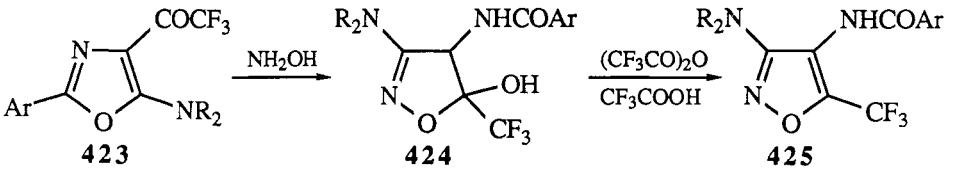
Prolonged treatment with hydroxylamine hydrochloride of the 3-acylisoxazoles thus formed leads to oximes of furoxan ketones (see § 1.4.10.5); these products had formerly been obtained by reacting an excess of hydroxylamine hydrochloride directly on 3-nitrosopyrroles.[3/05,2/07,1/08] The reaction does not progress beyond the stage of the isoxazole ketone when a mineral acid in boiling alcoholic solution is employed instead of a hydroxylamine salt.[6/37] The reaction probably involves cleavage of the isonitrosopyrrole to the oxime of the 1,3-diketone, followed by cyclization to isoxazole.

Disubstituted (2,5-diphenyl- or 5-methyl-2-phenyl)-3-nitrosopyrroles behave similarly. The reaction is particularly easy with 2,5-dimethyl-3-nitrosopyrrole, which is converted into 5-methyl-3-acetylisoxazole by simple dissolution of its sodium salt in water at room temperature.[6/39] For 3-nitrosotrimethylpyrrole, the transformation occurs only on prolonged boiling with 1 *N* hydrochloric acid. 2-Methyl-5-phenylpyrrole undergoes nitrosation to give a mixture of the two possible isomeric 3-nitrosopyrroles, which in turn can be transformed into 5-methyl-3-benzoylisoxazole and into 5-phenyl-3-acetylisoxazole, respectively.[7/71]

The reaction has been extended to 2,5-diphenyl-4-benzoyl-3-nitrosopyrrole and represents a convenient entry into the class of 3,4-diacylisoxazoles and of the related isoxazolo[3,4-*d*]pyridazine nucleus.[11/56] Even a trisubstituted 3-hydroxylaminopyrrole has been transformed by acidic treatment (and probably through an air oxidation step) to a 3,4-diacylisoxazole derivative.[4/62]

### c. From Oxazoles

The possibility of the system O–C=C–C=O, partly or totally inserted in a heterocyclic ring, to undergo nucleophilic 1,4-addition has already been illustrated in the field of 3-acylbenzofurans (see above) and will be reexamined below in the field of $\gamma$-pyrone derivatives. An extension of this principle to 5-amino-4-trifluoroacetyloxazoles (**423**) led to a convenient two-step synthesis of 3,4-diamino-5-trifluoromethylisoxazoles of general formula **425**:[166/76]




**423** **424** **425**

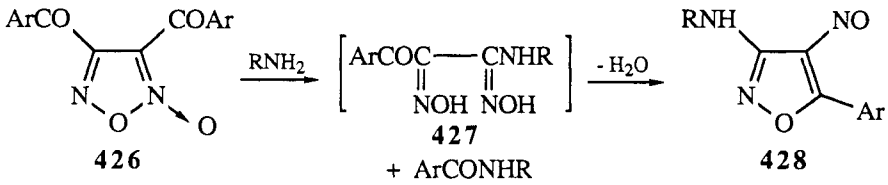
The isolable intermediate 5-hydroxyisoxazolines (**424**) might be a mixture of the two possible stereoisomers.

It should be noted that photorearrangement of oxazole can also give, among

several other products, the isomeric isoxazoles, presumably through the intermediacy of the appropriate acylazirines.[204B/69,49/73,138/77] The reaction usually has no preparative value, since the yields are rather low and the separation of the products is tedious and time consuming. Fairly convenient (44% yield) seems the preparation of 3,4-diphenylisoxazole as the main product of the irradiation of a benzene solution of 2,4-diphenyloxazole.[138/77]

d. From Diacylfuroxans

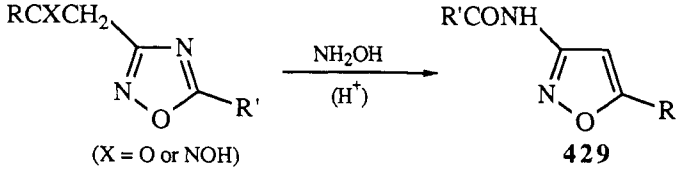
Diaroylfuroxans (**426**) react more or less exothermically with primary aromatic or aliphatic amines to yield a complicated mixture of products, from which the deeply colored 3-aryl (or 3-alkyl)amino-4-nitroso-5-arylisoxazoles (**428**) can be isolated in low yield, together with the monosubstituted benzamide.[21/897.1/10.10/10] The intermediacy of aroylaminoglyoximes (**427**) is generally admitted, although not demonstrated. Ammonia itself does not lead to isoxazole derivatives but to 3-amino-4-aroylfurazans:




On similar treatment with aryl hydrazines, orange-colored 3-arylhydrazino-4-nitroso-5-arylisoxazoles are formed, together with the corresponding arylhydrazides.[21/897.7/25.1/27.1/28.53/61.66/63.146/68] By contrast, methylhydrazine yields 3-methylhydrazino-4-benzoylfurazan.[215/78] Thermolysis of 3,4-disubstituted furoxans generates nitrile oxides *in situ*, which can cycloadd triple-bond compounds to give isoxazoles: the reaction is examined in §§ 1.3.2.1 and 2.2.2.2.

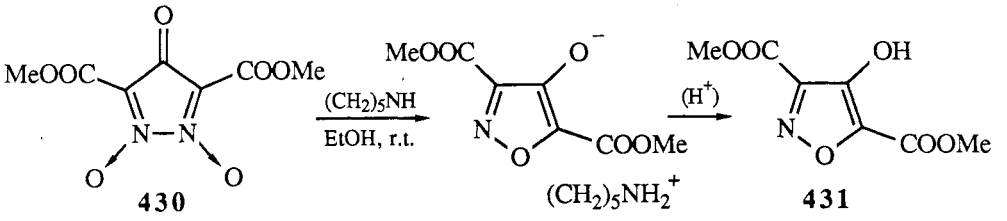
e. From Other Five-Membered Heterocycles

When a 1,2,4-oxadiazole derivative carries a carbonyl or an oxime functionality in the $\beta$-position of the 3-side chain, acid-catalyzed ring opening furnishes a $\beta$-diketone monoxime or dioxime, which immediately recloses to a 3-carbamidoisoxazole of general formula **429**:[221/81.90/82]



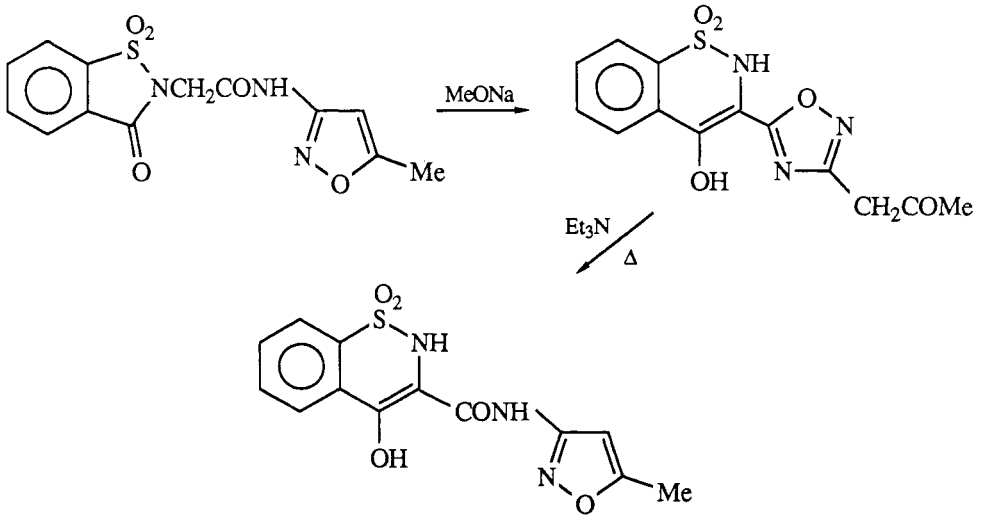

Starting from the ketone, the same ring transformation can be achieved by treatment with strong bases.[247/83] A base-promoted ring opening of the 3,4-

diazacyclopentadienone dioxide (**430**) makes it possible to synthesize the 4-hydroxyisoxazole derivatives (**431**) in low yields.[202/83]



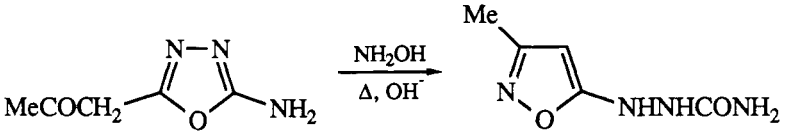

(20-25% yield)

The easiness of interconversion between isoxazoles and 1,2,4-oxadiazoles has been utilized in the synthesis of some hydroxy-1,2-benzothiazine-1,1-dioxides, as Scheme 1.19 shows.[264/76.261/77.266/77.94/83]




**Scheme 1.19.**

2-Acetonyl-5-amino-1,3,4-oxadiazole is oximated in basic medium, giving rise to a ring transformation to 3-methyl-5-isoxazolylsemicarbazide in 46% yield:[179/81]

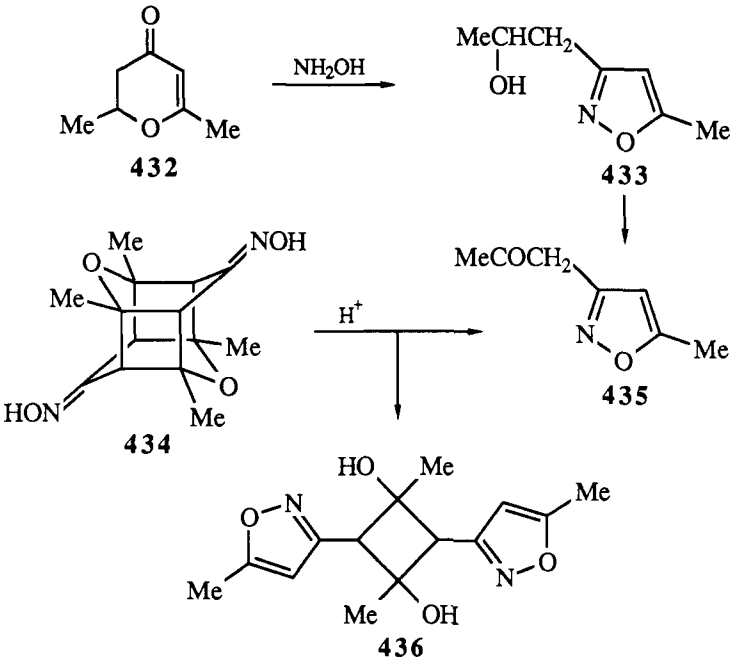



Of no preparative value is the occasional formation of 3,5-dimethylisoxazole by sodium dithionite reduction of 1-hydroxy-4-bromo-3,5-dimethylpyrazole-2-

oxide.[194/80] Low yields of isoxazole derivatives have been obtained by ring opening of 1,2-dithiolium salts under the influence of hydroxylamine.[161/66.12/67]

f. From γ-Pyrones and Their Benzoderivatives

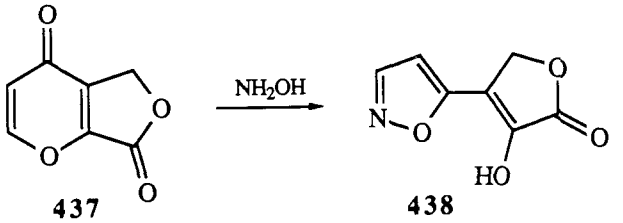
Simple γ-pyrones are known to react with hydroxylamine to yield the expected oximes. Nevertheless, it should be noted that 2,3-dihydro-2,6-dimethyl-4-pyrone (**432**) reacts with hydroxylamine hydrochloride in hot pyridine and ethanol to give a 51% yield of the isoxazole **433**, whose oxidation product (**435**) is also formed in 52% yield by treatment of the dioxime (**434**) of




**432** **433** **434** **435** **436**

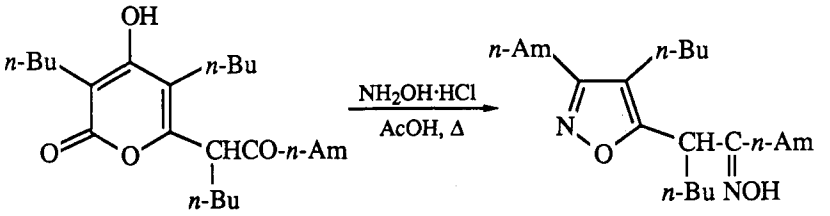
**Scheme 1.20.**

the cage photodimer of 2,6-dimethyl-4-pyrone with hot polyphosphoric acid (Scheme 1.20). A further 37% yield of compound **436**, a formal dimer of enolic **435**, is also obtained.[69/61.103/69] In both cases the intermediacy of a diketone monoxime has been assumed. A 1,4-attack of hydroxylamine (under both neutral and acidic conditions) to the γ-pyrone condensed butenolide (**437**) produces the 5-substituted isoxazole (**438**):[231/81]




**437** **438**

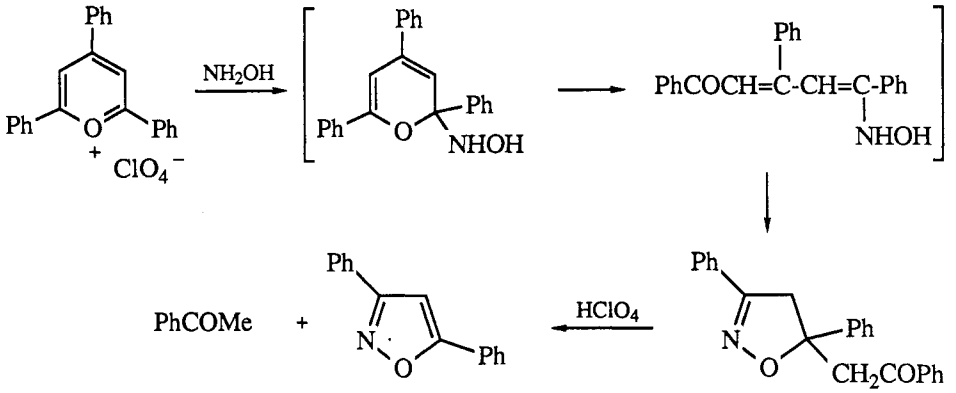
Recently, the structure of elasnin (**439**), a naturally occurring elastase inhibitor having a highly alkylated 4-hydroxy-α-pyrone skeleton, has been corroborated by transformation onto the isoxazole derivative **440**, possibly obtained through an intermediate "triketide" oxime:[100/79]




**439** **440**

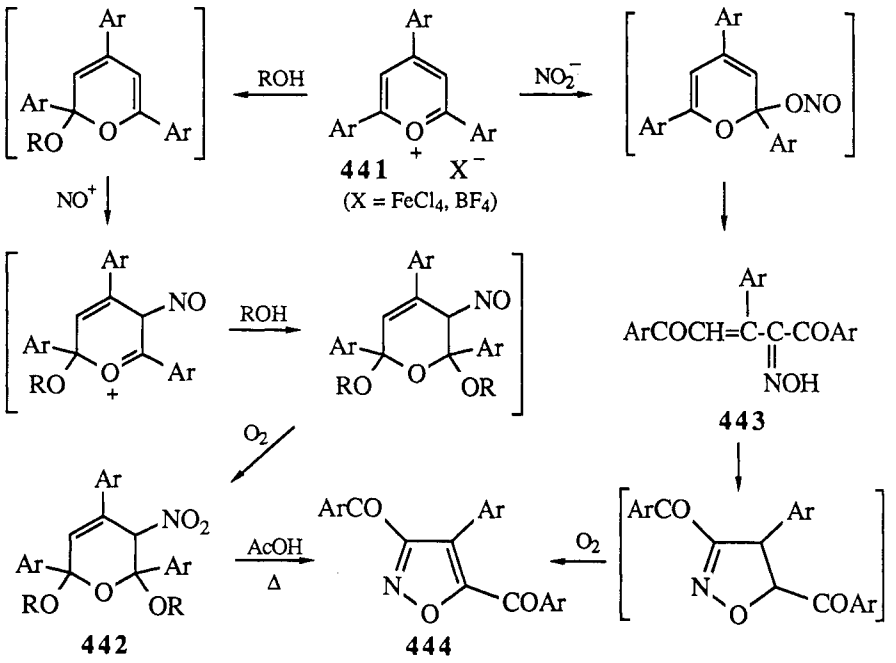
On the formation of isoxazolyl isoxazolinones by oximation of dehydroacetic acid and of analogous compounds having 4-hydroxy-2-pyrone structure, see Part 2 of this work.

Pyrylium salts are known to be ring-cleaved by several nucleophilic agents. Some of them are susceptible of inducing a reclosure with formation of an isoxazole ring. For example, 2,4,6-triphenylpyrylium perchlorate is attacked by hydroxylamine hydrochloride to give 5-phenacyl-3,5-diphenyl-2-isoxazoline at first, which in the presence of perchloric acid decomposes to acetophenone and 3,5-diphenylisoxazole:[199/68]




A similar reaction has been signaled for 2,6-dimethyl-4-(2-benzothiazolyl)pyrylium perchlorate.[194B/73]

The reaction between sodium nitrite and 2,4,6-triarylpyrylium salts (**441**) follows two distinct pathways, leading to 2,4,6-triaryl-2,6-dialkoxy-5-nitro-5,6-dihydro-2*H*-pyrans (**442**) or to 3,5-diaroyl-4-arylisoxazoles (**444**), respectively (Scheme 1.21).[227/73,2/75] When the reaction is carried out in alcoholic solvents, the main products are the dihydropyrans (**442**), whereas the best yields (26–65%) of isoxazoles (**444**) are obtained in refluxing acetonitrile as solvent and tetrafluo-

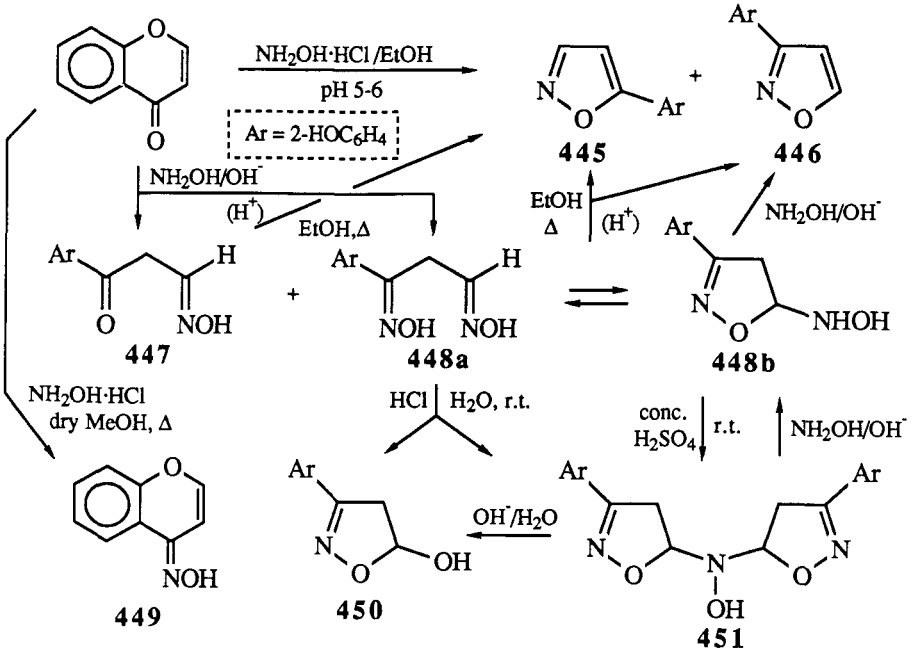



**Scheme 1.21.**

roborate as counterion. Furthermore, in the absence of air, the intermediate monoxime (**443**) could be isolated.

Several studies, sometimes contradictory (especially the older ones), have been devoted to the ring contraction of chromones and its derivatives (flavones, isoflavones, benzochromones, and others) under the nucleophilic attack of hydroxylamine, which can initiate at either position 2 or position 4. The products thereby obtained vary considerably, depending on the pH of the medium, the nature of the solvent, and the concentration of the reactants. A short review has appeared.[240C/77]

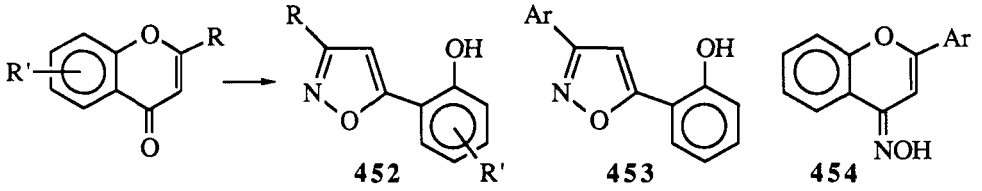
Chromone itself is transformed into its oxime (**449**) only when hydroxylamine hydrochloride is used in anhydrous acidic medium (e.g., boiling absolute methanol).[235/76,184/77,289/82] When the oximation is carried out in acidic nonanhydrous medium (e.g., boiling 95% ethanol), a mixture of the two isomeric (2-hydroxyphenyl)isoxazoles **445** and **446** is obtained.[184/77,226/77,200/79] Under neutral or alkaline conditions the reaction stops at the monoxime **447** or at the dioxime **448a**,[226/77,220/78,159/84] the choice depending on the experimental conditions. The latter compound equilibrates in protic or polar aprotic solvents with the cyclic isomer **448b**.[159/84] Pure 5-(2-hydroxyphenyl)isoxazole (**445**) is most conveniently prepared by acid-promoted cyclization of **447**,[220/78,200/79] whereas pure 3-(2-hydroxyphenyl)isoxazole (**446**) is formed by heating the dioxime **448** in aqueous alkali or in aprotic solvents.[159/84] Acidic treatment or




Scheme 1.22.

thermolysis of the dioxime **448** gives rise to cyclization to the 5-hydroxyisoxazoline **450** and/or the bisisoxazolinylhydroxylamine **451**.[200/79,159/84] The various reactions are summarized in Scheme 1.22.

Oximation of 2-substituted chromones usually follows the same pattern as with chromone, but showing a definite preference for a nucleophilic attack at position 2, leading, after cyclization, to the 5-(2-hydroxyphenyl)isoxazole derivatives **452**.[15/56,219/74,222/74,6/75,109/75,216/76,224/77,201/81] Some old results,[18/40,27/52,13C/57] claiming formation of the isomeric 3-(2-hydroxyphenyl) compounds, have recently been questioned, and structures **452** were assured mainly through mass spectrometric analysis.

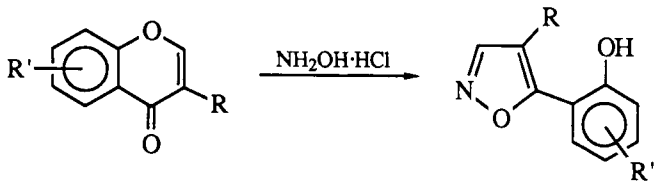



The best yields in isoxazoles are reached when hydroxylamine hydrochloride is used in boiling pyridine or in boiling ethanol in the presence of small amounts of pyridine. Here again, the use of an anhydrous solvent in the oximation of flavone or substituted flavones causes the formation, in addition to the is-

oxazoles expected (**453**), of the flavone oximes (**454**) as by-products.[219/74,216/76,201/81] Interestingly enough, oximation of 4-nitroflavone contradicts the general pattern reported above: a mixture of the open-chain monoxime and of both isomeric 3,5-diarylisoxazoles was formed in this case.[201/81]

Under alkaline conditions and excess hydroxylamine the intermediate open-chain dioxime (or its tautomer, 5-hydroxylamino-2-isoxazoline) can be isolated, for example, from 2-methylchromone.[219/74] 3-Hydroxyflavone is reported to be unreactive toward hydroxylamine, whereas 3-methoxyflavone reacts normally to give 5-(2-hydroxyphenyl)-4-methoxy-3-phenylisoxazole.[201F/81]

3-Substituted chromones (such as isoflavone) are oximated, at least under acidic or neutral conditions, to 4-substituted 5-(2-hydroxyphenyl)isoxazoles exclusively:[6/77,199/77,7/78,83/78,84/78,45/79,197B/79,2/80,228/80,251/82]

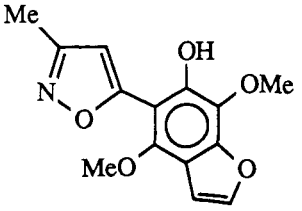



In an alkaline medium different products can arise, as, for example, the open-chain dioxime (or its cyclic tautomer), the bisisoxazolinylhydroxylamine, or a 2-aminochromone.

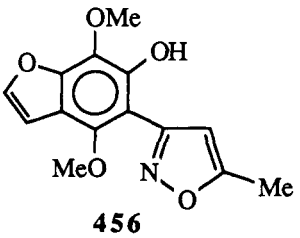
Chromone-3-carboxylic acid is oximated under both acidic and alkaline conditions to give, with decarboxylation, 5-(2-hydroxyphenyl)isoxazole.[251/82,123/84] The presence of a carbonyl group in the chromone 3-position can alter the site of the nucleophilic attack. For example, 3-formylchromone is oximated in acidic media to give the oxime or 3-cyanochromone as main products, depending on the experimental conditions used; reaction with two equivalents of hydroxylamine hydrochloride yields the oxime of 4-(2-hydroxybenzoyl) isoxazole.[247/74,249/78,248/80,259/83] Under alkaline conditions the reaction proceeds differently, yielding pyrazolone derivatives.[259/83]

Depending on the experimental conditions, 3-acylchromones afford either 4-(2-hydroxybenzoyl)-5-phenylisoxazole and/or the isomeric 4-benzoyl-5-(2-hydroxyphenyl)isoxazole.[218/70,15/73,3/83] It has been reported that 3-(2-hydroxyphenyl)-4-aroylisoxazoles are formed by oximation in pyridine.[88D/79] Furthermore, treatment of the 3-formylchromone oxime with excess guanidine in alkaline media yields 4-formyl-3-(2-hydroxyphenyl)isoxazole.[170/80]

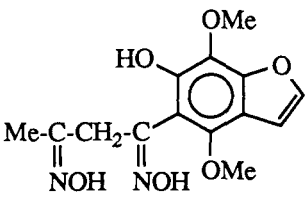
3,4-Disubstituted[83/78,84/78,45/79,197B/79,2/80,228/80,251/82] or condensed chromones[81/63,50/70,183/71,186/72,18/73,93/82] show the same behavior toward hydroxylamine hydrochloride as do the monosubstituted derivatives. In particular, khellin, notwithstanding a previous claim,[12/53] is oximated in refluxing pyridine to give the isoxazole **455** in 67% yield, along with the isomer **456** and the open-chain dioxime **457** as by-products.[184/77]




**455**




**456**

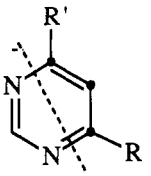



**457**

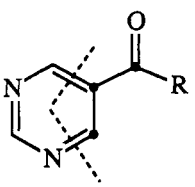
The sulfur analogues of chromone and its derivatives (i.e., chromone- or flavone-4-thiones) show a somewhat different behavior toward hydroxylamine, the nucleophilic attack at position 4 here becoming of some importance. For example, isoflavone-4-thiones give either a mixture of the two isomeric isoxazoles[200/77,84/78] or the sole 3-(2-hydroxyphenyl) derivative[83/78,84/78,45/79,228/80] (i.e., the isoxazole isomeric to the compound obtained from the oxygenated counterpart). Use of anhydrous pyridine as solvent here, too, allows isolation of the isoflavone oxime.[201F/81,251/82] Under alkaline conditions the open-chain dioxime can be isolated as the main product.[200/77] Other condensed systems, such as 5-phenylthieno[3.2-*b*]pyran-7-one, follow the same reaction pattern as that of flavones.[166/82]

### g. From Other Six-Membered Heterocycles

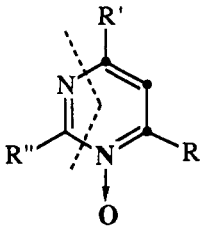
Thorough studies on the ring contraction from pyrimidine to isoxazole derivatives have, up to now, revealed three different fragmentation patterns of the pyrimidine ring, depending on the nature of the substituents and of the reactants. From structures such as **A** and **B**, isoxazoles, having as "building blocks" the carbon atoms originally in the 4-, 5-, and 6-positions (in **A**) or in 5- and 6-positions *plus* one carbon from an *exo*-carbonyl group (in **B**), are obtained, the N–O moiety being provided externally. Pyrimidine-*N*-oxides such as **C** may even provide all five isoxazole ring atoms ($C_4$, $C_5$, $C_6$, $N_1$, and oxide O).




**A**



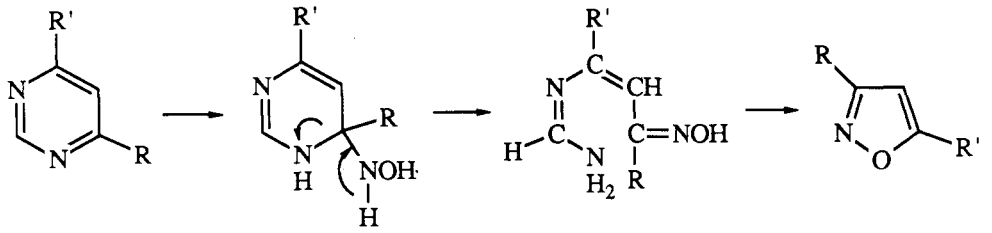

**B**



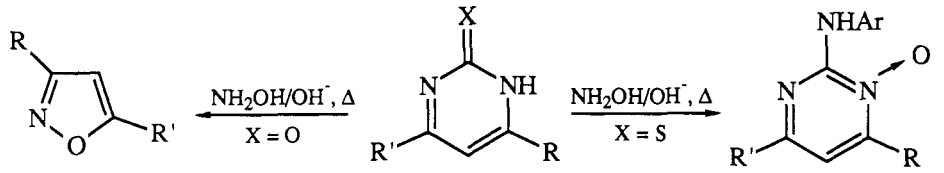

**C**

For example, by treatment of pyrimidine with an excess of aqueous hydroxylamine hydrochloride at 125°C, isoxazole itself is formed, although in low yields; far higher yields are obtained starting from compounds having one nitrogen atom positivized, such as pyrimidine *N*-oxide, 1-methylpyrimidinium

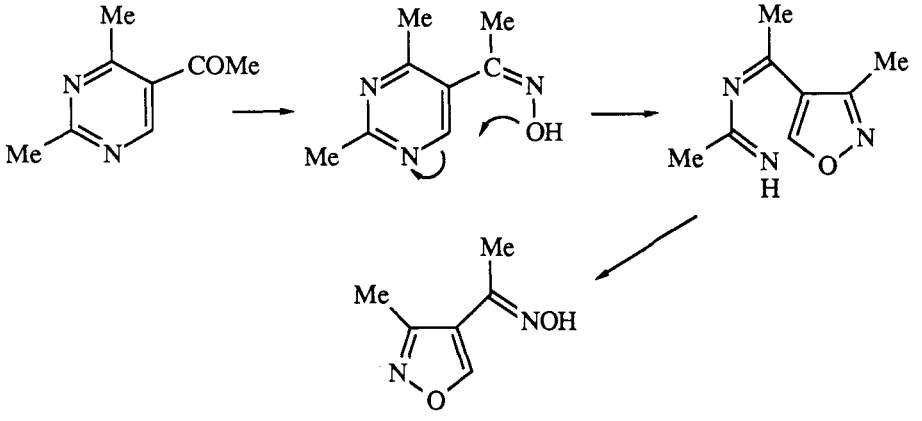
methosulfate, or 1,3-diethylpyrimidinium tetrafluoroborate, or starting from 4,6-disubstituted pyrimidines. From 6-methyl-4-phenylpyrimidine *N*-oxide, an 80–85% yield of 3-methyl-5-phenylisoxazole is achieved.[210/74] $^{15}$N-labeled experiments have demonstrated that the isoxazole N–O moiety is furnished by the hydroxylamine molecule and not by the pyrimidine N→O function, thus suggesting the following reaction mechanism:



Good yields of 3,5-disubstituted isoxazoles are also obtained by oxidation under basic conditions of 1,4,6-trisubstituted 2(1*H*)-pyrimidinones, whereas on the contrary the corresponding pyrimidinethiones (or their salts) undergo transformation to N-substituted 2-aminopyrimidine *N*-oxides as main products:[28/81]

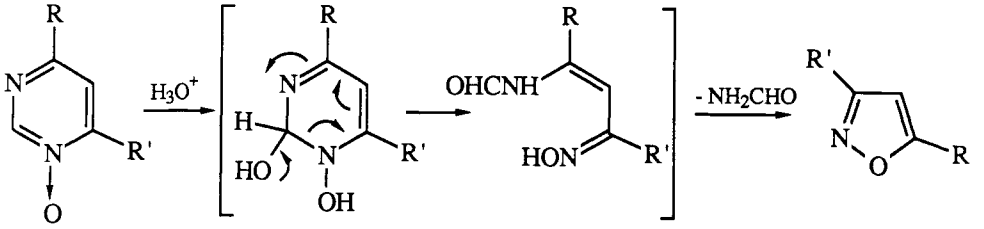


Introduction of an acetyl group in the pyrimidine 5-position shifts the attack by the hydroxylamine from $C_6$ to the carbonyl group, thus yielding the corresponding oxime; a prolonged reaction time (boiling for 40 h) caused the attack of the oxime nucleophilic end to the $C_6$ ring carbon atom, with simultaneous cleavage of the C–N bond, according to the following scheme:



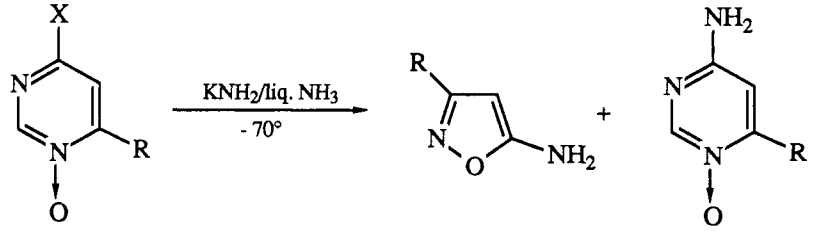
A 50% yield of a mixture of the two isomeric oximes of 4-acetyl-3-methylisoxazole has thus been obtained by oximation of 5-acetyl-2,4-dimethylpyrimidine.[213/74]

Acid-promoted hydrolysis of 4-aryl- or 4-alkyl-substituted pyrimidine *N*-oxides gives rise to nonisolable α,β-unsaturated monoximes, which readily cyclize to isoxazoles by loss of formamide:[114/67]

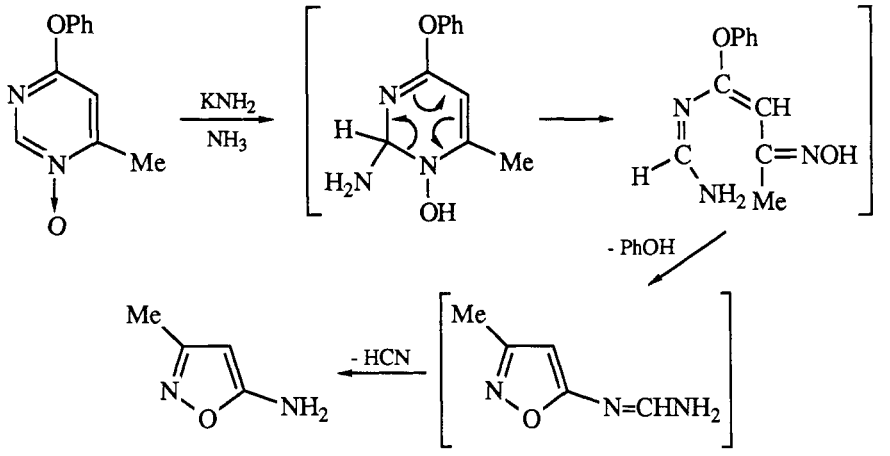



This ring transformation occurs even if the 2-position of the pyrimidine ring is occupied. The reaction has been taken advantage of for assuring the exact structures of 2,4,6-trisubstituted pyrimidine *N*-oxides.[93/77,37C/79]

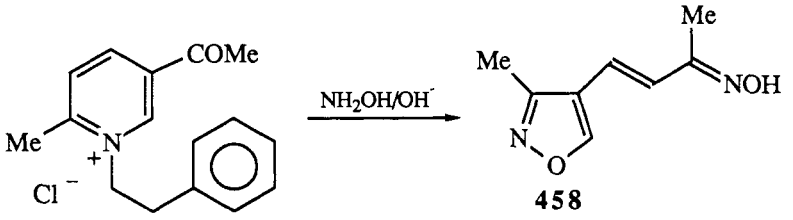
When the 6-*R*-pyrimidine *N*-oxide is substituted in the 4-position with a good leaving group, such as the halogens or phenoxy-, phenylthio-, or trimethylammonium, by treatment with potassium amide in liquid ammonia it undergoes both amination to 4-amino-6-*R*-pyrimidine *N*-oxide and ring contraction to 5-amino-3-*R*-isoxazole:[208/74]




The formation of the 4-amino compound occurs through an $S_N(AE)$ mechanism and is favored by good leaving groups, becoming the sole process observed in the case of 4-trimethylammonium salt. Conversely, ring contraction requires leaving groups having a low mobility:[212/74] for example, 6-methyl-4-phenoxypyrimidine *N*-oxide gives 3-methyl-5-aminoisoxazole exclusively in 62% yield. Attack of the nucleophile at the 2-position of the pyrimidine has been demonstrated to start the reaction according to the following mechanism:[211/74]

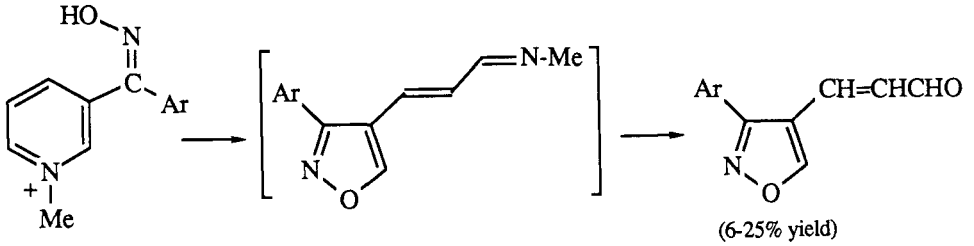



The oximation of pyridinium salts has been studied much less well. Nevertheless, some evidence is available that 3-acylpyridinium salts should behave as 3-acylpyrimidine. Thus 3-acetyl-6-methyl-1-$\beta$-phenylethylpyridinium chloride reacts with hydroxylamine in alkaline medium to give an oxime, whose structure could possibly be **458**:[12/63]




**458**

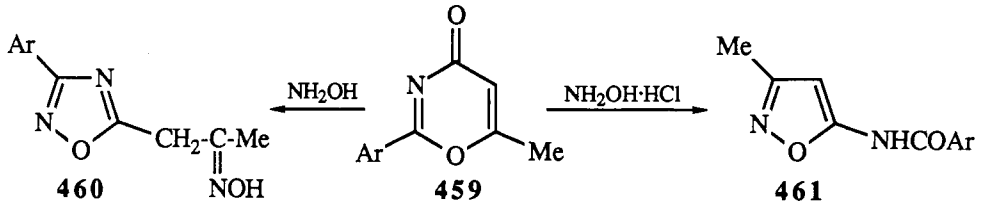
The same ring contraction is known for other pyridinium salts.[184D/79] A nitro-substituted imidazopyrimidine has also been reported to be cleaved by hydroxylamine to yield a 4-nitro-4-amino-substituted isoxazole.[136/74] Low yields of $\beta$-(3-aryl-4-isoxazolyl)acroleins are reported to form by alkaline treatment of the (*Z*)-oximes of *N*-methyl-3-aroylpyridinium iodides:[51/80]




(6-25% yield)

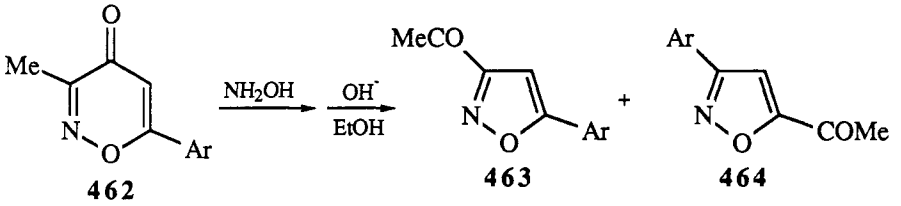
Another ring contraction starts from 2-phenyl (or pyridyl)-4*H*-6-methyl-1,3-oxazin-4-ones (**459**), which are readily attacked by hydroxylamine. The site

selectivity of the nucleophilic attack is markedly pH dependent: in neutral solution, position 2 of the heterocyclic ring is attacked, and the oxime of a 1,2,4-oxadiazole derivative (**460**) is finally formed, whereas treatment with hydroxylamine hydrochloride in ethanol directs the attack to the 6-position, thus leading to 5-aroylamino-3-methylisoxazoles (**461**):[124/78]

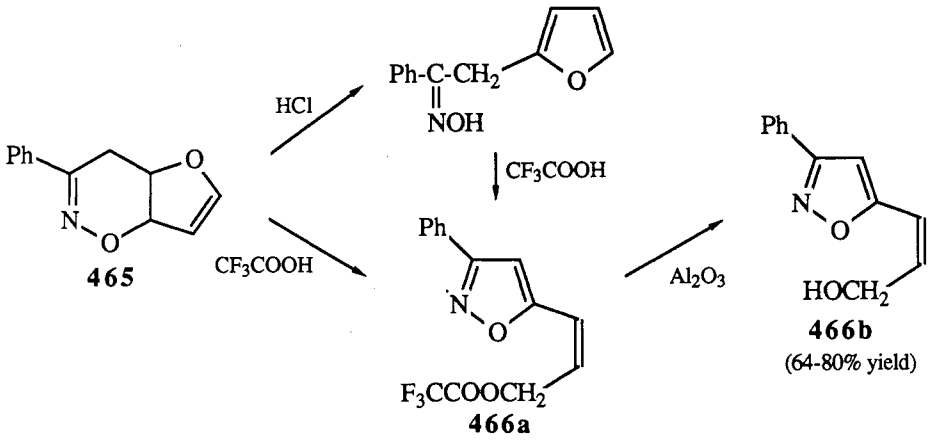



(Ar = Ph, 2-, 3-, 4-pyridyl; 16-65% yield)

The 3-methyl-6-substituted 1,2-oxazin-4-ones (**462**) are claimed to yield a mixture of the possible isoxazole derivatives **463** and **464** by oximation and subsequent alkaline hydrolysis:[100/72]



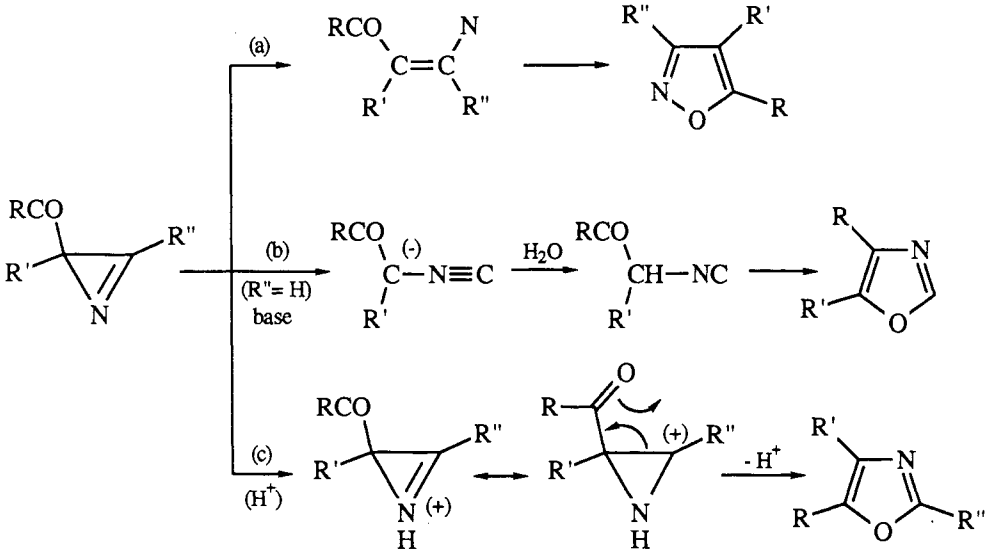

For an isoxazole synthesis involving a substituted 1,2-oxazin-6-one as the presumed intermediate, see § 1.3.6.4, p. 225. When the 5,6-dihydro-1,2-oxazine system is fused with a dihydrofuran ring, as in compound **465**, acidic treatment opens both rings, and the subsequent recyclization furnishes an isoxazole derivative of structure **466**.[116/79]



### h. From Miscellaneous Heterocycles

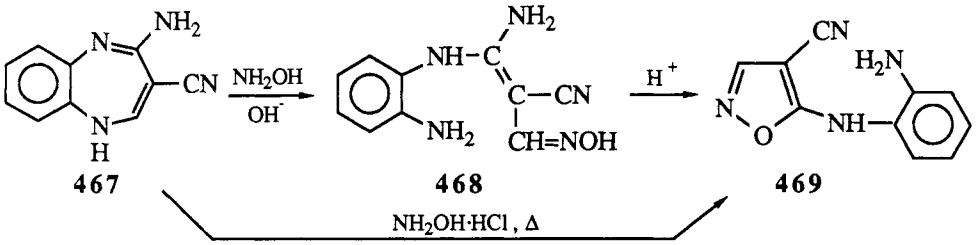
As already mentioned, acyl-2*H*-azirines seem to be intermediates in the photorearrangement of oxazole to isoxazole derivatives. The rearrangement acylazirines → isoxazoles usually occurs thermally. For example, heating of a toluene solution of 3-phenyl-2-formyl-2*H*-azirine in a sealed tube at 200°C for 3 days gives an 80% yield of 3-phenylisoxazole;[87/75] the same isomerization can be achieved at room temperature either in tetrahydrofuran in the presence of $Mo(CO)_6$ [115/77] or in dry benzene in the presence of cyclopentadienyliron dicarbonyl dimer.[29/79] Analogously, heating a benzene solution of 2-acetyl-3-phenyl-2*H*-azirine in a sealed tube at 200°C for 26 h gave rise to conversion to 5-methyl-3-phenylisoxazole in 61% yield.[138/77] This rearrangement clearly involves a C–N bond fission and possibly the intermediacy of a *β*-acylvinyl nitrene.

Similar transformations are known to 2-benzoyl-3-phenyl-2*H*-azirine, which gives by simple photoirradiation a 27% yield of 3,5-diphenylisoxazole; thermal or photochemical treatment in acetonitrile in the presence of $Fe_2(CO)_9$ or $Fe(CO)_5$, respectively, affords a mixture of the isoxazole (31–39%) and of the enamino ketone, arising from a reductive process.[282/82] But 2-acyl-2*H*-azirines are also known to rearrange thermally in some cases to oxazoles,[99/76,183/76] and this involves a C–C bond fission. It has recently been demonstrated that the rearrangement of 3-unsubstituted 2-acyl-2*H*-azirines to oxazoles is catalyzed by bases, and that the analogous conversion of the 3-substituted terms is, by contrast, catalyzed by acids[126/78] (benzoic acid or, better, borontrifluoride etherate) according to Scheme 1.23, which accounts for the formation of both isoxazoles and oxazoles.




**Scheme 1.23.**

It seems likely that base can catalyze the rearrangement of 3-substituted 2-acyl-2*H*-azirines to isoxazoles, as can be inferred from the formation of an isoxazole derivative as a side product in the synthesis of azirine-2-carboxamides by reduction of 2*H*-azirine compounds with sodium borohydride.[221/72] Isoxazole (**469**) has been obtained by a nucleophilic ring-opening attack of hydroxylamine onto the cyanobenzodiazepine (**467**); under appropriate experimental conditions, the intermediate α,β-unsaturated oxime (**468**) can be isolated:[48/80]




## 1.4 CHEMICAL PROPERTIES

The isoxazole ring system exhibits a characteristic chemical behavior, and occupies a unique position among the heterocyclic rings. Since it is fairly stable toward several common reagents and, on the other hand, is easily opened under well-defined conditions, the isoxazole ring is admirably suited to act as a synthon of several functionalities. Although the main features of isoxazole chemistry were known as early as the 1960s,[77/62.1/63] the importance of this ring as a key intermediate in the chemical synthesis has grown considerably in the past decade and is still expanding broadly. Therefore, a special paragraph is devoted to applications of isoxazole derivatives in synthetic design (see §1.4.12, pp. 391–416).

The general chemical behavior of the isoxazole ring depends strongly on its substitution pattern. Indeed, the three positions (3, 4, and 5) available for substitution show fairly different properties. As also justified by theoretical calculations (see § 1.2.8, pp. 103–105), the ring has some aromatic character, and position 4 is the preferred point of attack for electrophilic substitution. The hydrogen in position 3 is the most easily detachable by basic reagents, and this tendency is enhanced by quaternization of the ring nitrogen. The stability toward bases increases with increasing substitution: 3,5-di- and trisubstituted alkyl- or arylisoxazoles are extremely stable compounds. On the other hand, whatever the substitution pattern may be, the weak N–O bond of the ring (about 52 kcal/mol) is easily cleaved under well-controlled conditions, usually by hydrogenolytic methods.

### 1.4.1 Protonation and Quaternization

Isoxazoles are fairly weak bases and usually neither dissolve in dilute mineral acids, nor form definite isolable salts with them. However, a crystalline hydrochloride has been obtained from trimethylisoxazole and dry hydrogen chloride.[15/891] In some cases chloroaurates[15/891] and chloroplatinates[4/09] are known. More stable seem to be the perchlorates or hydrochlorides of 5-methyl-3-phenoxymethylisoxazoles.[5/41] This higher stability has been attributed to chelate ions. Protonation of several amino-substituted isoxazoles has been studied through UV and NMR spectroscopy;[67/61,208/70,187/73,188/73,12/83] for example, ethyl 5-amino-3-phenylisoxazole-4-carboxylate is protonated by trifluoroacetic acid at the ring nitrogen.[208/70]

The possibility of obtaining isoxazolium salts by alkylating isoxazoles with alkyl iodides was noted as early as 1891.[9/891] On heating 5-methylisoxazole with methyl iodide at 100°C a crystalline methiodide was obtained, whereas a methosulfate was formed with dimethyl sulfate at 70°C.[4/09] Analogous behavior is shown by 5-phenylisoxazole.[3/10] Although the remarkable reactivity of the 3-unsubstituted isoxazolium salts had been noted since the beginning of the century,[5B/02,9B/03] it was not until the discovery of their utilization in the synthesis of peptides (see § 1.4.6.1, pp. 313–314)[36/61,166/66] that the chemistry of isoxazolium salts received the general consideration it deserves from the chemical community.

General preparation of isoxazolium salts must take into account the low basicity of the isoxazole ring and the increased vulnerability to nucleophilic attack introduced in the ring by quaternization. The following principal methods have been employed:

1. Direct alkylation with alkyl halides or dialkyl sulfate requires relatively vigorous conditions and long reaction times. Kinetic data have confirmed the lower reactivity of the isoxazole ring compared with other azole or azine nitrogens;[19/73,9/74] there is a fairly good correlation between the rate of quaternization and the basicity of the nitrogen ring. For example, isoxazole itself is $10^4$ times less reactive than 1-methylimidazole.[19/73] Furthermore it is logical that 3-methyl-5-(3′-pyridyl)isoxazole is quaternized by methyl chloride on the pyridine nitrogen atom.[148/69]

For quaternization of isoxazole derivatives, reaction temperatures from 70 to 100°C and a large excess of alkylating agent are commonly employed. 3-Unsubstituted isoxazoles require more carefully controlled conditions than do 3,5-disubstituted or trisubstituted derivatives. 3,5-Dimethylisoxazole has been reacted with methyl iodide at 60°C in a sealed tube[115/71] and with ethyl iodide at 100°C;[22/55] 3,5-diarylisoxazoles are converted into *N*-methyl iodides by heating with dimethyl sulfate at 95–100°C and subsequently with hydroiodic acid.[131/81] It is interesting to note that contrary to what happens with the pyrazole and

isothiazole analogues, the presence of a nitro group in the 4-position is enough to suppress the possibility of quaternization.[115/71]

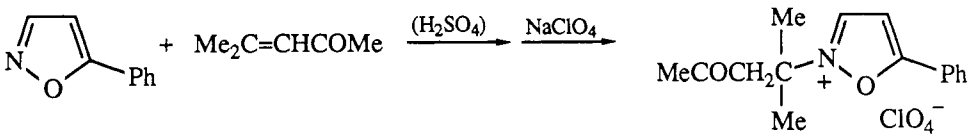
Isoxazoles (included the 3-unsubstituted) are N-methylated by cautious heating with dimethyl sulfate at three successive temperature steps from 60 to 100°C[5B/02,165/66,51/69,35/74] or in a sealed tube at 70–75°C for 3 days.[111/66] Sulfolane is claimed to be a convenient solvent for quaternization with dialkyl sulfate.[56/70]

The isoxazolium methosulfates or bisulfates are usually highly hygroscopic and noncrystallizable salts, and their transformation into nonhygroscopic perchlorates is often performed without isolation of the intermediate salts. The *N*-methyl perchlorate of the parent isoxazole has thus been isolated.[9/74] Isoxazolium perchlorates, however, must be handled with due care, since at least some of them are impact sensitive, and most of them detonate over the melting point. Isoxazolium perchlorates can also be obtained through the *p*-tosylates, whose formation occurs at 40–80°C,[111/66,128/75] or through the trifluorosulfonates, obtainable at room temperature in benzene.[128/75]

Other crystalline salts with definite melting points, soluble in most organic solvents and sparingly soluble in water, are the tetrachloroferrates, easily available by conversion of the intermediate, nonisolated methosulfates with ferric chloride and hydrochloric acid.[7/28,10/28,8/49,16/55,72/60,195/76] Isoxazolium hexachloroantimonates have also been reported.[157/78,36/79]

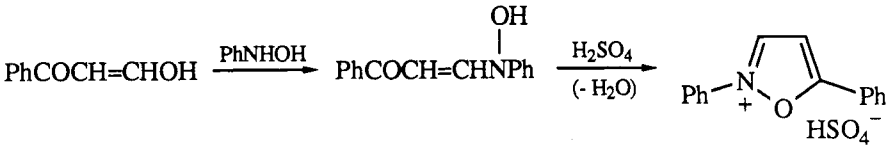
2. Far milder conditions are required to alkylate isoxazoles with trimethyl- or triethyloxonium fluoroborate: equimolar amounts of reagents, room temperature, and methylene chloride or acetonitrile as solvent are usually employed.[111/66,165/66,166/66,135/68,220/68,195/76,22/78,248/79] Crystalline fluoroborates are obtained in yields frequently reaching 70–90%. Less commonly, fluoroborates have been prepared either in two steps through the intermediacy of methosulfates[195/76,36/79] or by the combined action of ethyl bromide and anhydrous silver fluoroborate.[23/69] According to expectations, 3,5-dimethyl-4-methylthiomethylisoxazole is methylated first at the sulfur atom and only in a second step at the ring nitrogen atom.[152/77] Methyl fluorosulfonate was found to be the most suitable reagent for methylating the ring nitrogen atom of several 5-amino-substituted isoxazoles.[80/83]

3. Isoxazolium salts with bulky N-substituents are prepared most conveniently by quaternization of isoxazoles (3-unsubstituted and 3-methyl-substituted) with a suitable secondary or tertiary alcohol in the presence of 70% perchloric acid.[114/66,151/68,162/69,163/80,152/83] An $S_N1$ mechanism has been postulated.[40/63,151/68] In agreement with it, benzyl alcohol requires 10 months to give a 29% yield of the isoxazolium salt, whereas moderate-to-good yields are reached in 1–2 days with *t*-butyl, α-methylbenzyl, α,α-dimethylbenzyl alcohol, benzhydrol, or fluorenol. A steric factor is also effective, since, for example, trityl alcohol no longer reacts with 3,5-dimethylisoxazole.[151/68] A similar mechanism through a carbonium ion is possibly involved in the acid-catalyzed alkylation of 5-phenylisoxazole with mesityl oxide:[114/66]

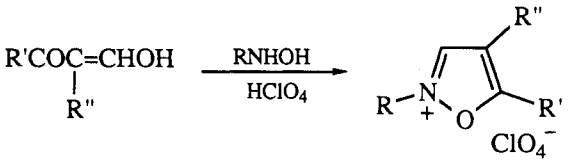


Another reaction, whose initial step might be an electrophilic attack on the isoxazole ring nitrogen, is condensation between isoxazoles and diphenylcyclopropenone; the reaction proceeds further, and a 4-pyridone is the final product.[48/73]

4. 2,5-Diphenylisoxazolium salts have been prepared by acid-promoted cyclization of 3-(*N*-hydroxyanilino)acrylophenone:[114/66]

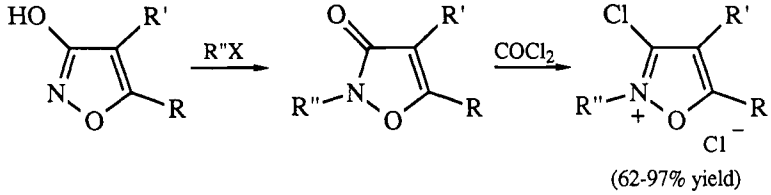


This method has been reduced to a one-step general procedure involving the simple addition of perchloric acid to a mixture of a β-ketoaldehyde and an N-substituted hydroxylamine:[156/69,145/71]



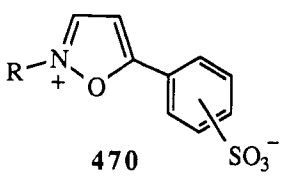
Extension to β-diketones made it possible to prepare 3,5-disubstituted *N*-alkylisoxazolium perchlorates.[43/73,195/76] Use of α-cyanophenylacetaldehyde and *N*-methylhydroxylamine hydrochloride afforded 5-amino-2-methyl-4-phenylisoxazolium hydrochloride.[10/74] On the whole, this method seems most convenient for preparing for *N*-arylisoxazolium salts.

5. 3-Chlorosubstituted isoxazolium chlorides are suitably prepared by treatment of *N*-alkyl-3-isoxazolinones with oxalyl chloride[220/68] or, better, with trichloroacetyl chloride[36/79] or, even better, with phosgene.[127/77,157/78,36/79] The starting material is in turn obtained by alkylation of 3-hydroxyisoxazoles:

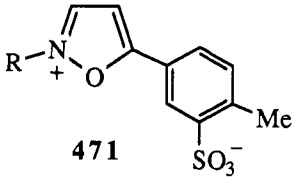


*N*-Methyl-5-isoxazolinones are alkylated to 5-alkoxyisoxazolium salts.[147/68,195/76]

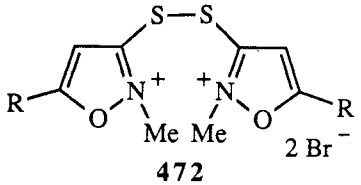
6. Zwitterionic isoxazolium salts such as **470** have found interesting applications in the synthesis of peptides, and their preparation has been the subject of several studies.[36/61,111/66,166/66] Three principal methods have been envisaged: (a) chlorosulfonation of 5-phenylisoxazole, followed by quaternization with trialkyloxonium fluoroborate or with dialkyl sulfate and finally by hydrolysis; (b) initial quaternization of the starting material, followed by chlorosulfonation of the quaternary salt and hydrolysis in unbroken sequence; and (c) chlorosulfonation of 5-phenylisoxazole, followed by esterification and thermolytic internal displacement. With all three procedures the chlorosulfonation affords a 2:1 mixture of the *meta*/*para*-substituted isomers, which must be separated by fractional crystallization at one step of the sequence.[111/66,166/66] When the synthesis starts from 5-*p*-tolylisoxazole, a single isomer of structure **471** is produced.




**470**



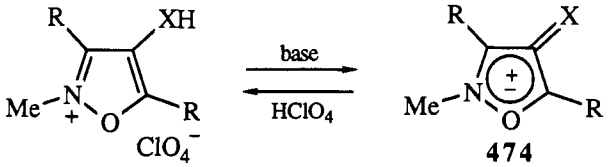

**471**




**472**

Occasionally, isoxazolium salts have been synthesized by other methods, as, for example, oxidation of *N*-methyl-3,5-diaryl-2-isoxazolinium chloroferrates with chromic trioxide,[50/63] or oxidation of 2-methyl-5-phenylisoxazolin-3-thione with bromine to give the bisisoxazolium disulfide **472**.[46/80]

Finally, it is interesting to note that deprotonation of the 4-hydroxyisoxazolium salt **473a** makes it possible to isolate the highly unstable mesoionic compound **474a**, which can revert to the starting salt by treatment with perchloric acid.[22/78] Formation of the analogous compound **474b** could be evidenced only in solution through UV spectroscopy:[144/74]




**474**

**473 a** X = O; R = Ph
**b** X = NTos; R = Me

### 1.4.2 Complexation

#### *1.4.2.1 Metallic Complexes*

Despite the low disposability of the electron pairs, isoxazole and its alkyl

(mono-, di-, and tri-), as well as some aryl and aralkyl derivatives, have long since been known to form microcrystalline or powderlike complexes with metallic salts.[7/03.4/09.4/26.6/26.5/27.14/38] Cadmium, zinc, and mercuric chlorides, especially, were used to give addition products with the aim of isolation and purification, since the complexes easily regenerate the isoxazole compound by pyrolysis. Thus isoxazole itself, which forms an azeotropic mixture with water, can be suitably separated from its aqueous or aqueous-ethanolic solutions through precipitation with a concentrated solution of cadmium chloride.[1/49.8/55.75/62] The insoluble double salt, after purification, is then pyrolyzed, the pure isoxazole distilling over. The same purification process has been adopted with monomethylisoxazoles;[5/11.258/70] for 3,5-dimethylisoxazole the zinc chloride complex,[6/26,5/27.9/63] and for tetramethyleneisoxazoles the mercuric chloride complex,[28/70] are more convenient for the same purpose.

The different formation rate of the cadmium complexes has sometimes been utilized for purifying an isoxazole compound containing small amounts of the regioisomer: this was, for example, the case of 5-methyl-3-phenylisoxazole, which is commonly obtained impure from 3-methyl-5-phenylisoxazole.[4/26] The latter isomer reacts much faster with cadmium chloride and can thus be removed. More recently, a large number of complexes of isoxazole derivatives with metal ions, particularly with transition metal (II) ions, have been described, and their spectral and magnetic properties thoroughly investigated to determine the stereochemistry of the complex and the nature of the coordinating link. The known complexes are listed in Table 1.79 with an indication of the most probable metal–ligand bond.

The metallic complexes are usually prepared by refluxing the metallic salts either in an excess of the ligand as solvent (especially for isoxazole and 3,5-dimethylisoxazole) or with stoichiometric amounts of the ligand in acetone or methanol (or in a mixture of both). Fluoborates are prepared by dissolving at room temperature the hydrated metal (II) fluoborate and the ligand in nitromethane as solvent and acetic anhydride as dehydrating agent. Generally speaking, the complexes are soluble in polar, chiefly aprotic, solvents and less soluble in nonpolar solvents. Some of them are highly hygroscopic and often contain water of crystallization. The ligand behaves in these complexes most frequently as monodentate N-bonded, but also in several cases as bidentate bridging through both the nitrogen and the oxygen ring atoms. In some cases, specially when zinc is involved, only metal–oxygen bonds are evidenced.

4-Aminoisoxazoles usually bind to the metal ion through the exocyclic nitrogen of the amino group, and often behave as bidentate ligands, the ring nitrogen or, less frequently, the ring oxygen also being involved. The donor center of 3-amino- and 5-amino-substituted derivatives depends strongly on the nature of the metal ion and on the mono- or polymeric structure of the complex. For example, 3-amino-5-methylisoxazole coordinates the metal either through the ring nitrogen [mainly in Co(II), Ni(II), or Cr(III) complexes] or through the ring oxygen [mainly in Zn(II), Cd(II), Pd(II), or Pt(II) complexes] or through both of them [as in Hg(II) and some Cu(II) complexes]. 5-Amino-3,4-dimethyl-

TABLE 1.79. METALLIC COMPLEXES OF ISOXAZOLE DERIVATIVES

| Ligand (L) | Complex | References |
|---|---|---|
| Isoxazole | $CrL_3Cl_3$,[a] $CrL_3Br_3$[a] | 222/76 |
| | $MnL_6(BF_4)_2$[a] | 107/77 |
| | $MnL_2Cl_2$, $MnL_2Br_2$, $MnL_2I_2 \cdot H_2O$, $MnL_2(NCS)_2$ | 253/80 |
| | $FeL_6(BF_4)_2$[a] | 107/77 |
| | $FeL_6(ClO_4)_2$[a] | 183/83 |
| | $Co(NH_3)_5L(ClO_4)_3$[a] | 132/82 |
| | $Co(CO)_5L$[a] | 91C/79 |
| | $CoL_6(BF_4)_2$[a] | 107/77 |
| | $CoLCl_2$,[b] $CoLBr_2$,[a] $CoL_2(NCS)_2 \cdot 0.5H_2O$[a] | 167/74 |
| | $NiL_6(BF_4)_2$[a] | 107/77 |
| | $NiLCl_2 \cdot 0.5H_2O$,[b] $NiL_3Br_4$,[a] $NiL_2(NCS)_2 \cdot 0.5H_2O$ | 167/74 |
| | $CuLCl_2$[b] | 167/74 |
| | $CuL_5(BF_4)_2$[a] | 107/77 |
| | $ZnLCl_2 \cdot 0.5H_2O$,[b] $ZnL_2Br_2$,[b] $ZnL_2I_2 \cdot 0.5H_2O$,[b] $ZnL(NCS)_2$[b] | 174/76 |
| | $ZnL_6(BF_4)_2$[a] | 107/77 |
| | $PdL_2Cl_2$,[a] $PdL_2Br_2$,[a] $PdL(SCN)_2$[b] | 136C/75 |
| | PdL(oxalato)[b] | 182/83 |
| | $CdLCl_2$[a] | 7/03, 1/49, 8/55, 167/74 |
| | $CdLBr_2 \cdot 2H_2O$,[a] $CdLI_2$,[a] $CdL(NCS)_2$[a] | 167/74 |
| | $CdL_6(BF_4)_2$[a] | 107/77 |
| | $PtL_2Cl_4$ | 7/03 |
| | $PtL_2Cl_2$,[a] $PtL_2Br_2$,[a] $PtL_2I_2$[a] | 136C/75 |
| | $HgLCl_2$,[c] $HgLBr_2$,[c] $HgL(NCS)_2 \cdot 2H_2O$[c] | 174/76 |
| 5-Methylisoxazole | $ML(NO_3)_2$, $ML_2(NO_3)_2$[M = Co,Ni, Cu] | 222B/77 |
| | $ZnL(NO_3)_2$ | 222B/77 |
| | $AgL(NO_3)$ | 222B/77 |
| | $CdLCl_2$ | 4/09, 5/11 |
| | $PtL_2Cl_4$ | 4/09 |
| | $HgLCl_2$ | 4/09 |
| 3,5-Dimethylisoxazole | $AlLBr_3$ | 288/76 |
| | $CrL_3Cl_3 \cdot 6H_2O$,[a] $CrL_3Br_3 \cdot 6H_2O$,[a] $CrL_3I_3 \cdot 6H_2O$[a] | 222/76 |
| | $MnLCl_2 \cdot 0.5H_2O$, $MnLBr_2$, $MnL_2I_2 \cdot 4H_2O$, $MnL_4(NCS)_2$ | 253/80 |
| | $CoL_2Cl_2$,[a] $CoL_2Br_2$,[a] $CoL_2I_2$,[a] $CoL_2(NCS) \cdot 3H_2O$,[a] $[CoL_4(H_2O)_2](ClO_4)_2 \cdot H_2O$[a] | 136/75 |
| | $NiL_2Cl_2 \cdot H_2O$,[b] $NiLBr_2 \cdot 0.5H_2O$,[b] $NiL_2(NCS)_2$,[b] $NiL_4(NCS)_2$,[a] $[NiL_4(H_2O)_2](ClO_4)_2 \cdot H_2O$[a] | 136/75 |
| | $Cu_2LCl_2$[a] | 107B/77 |
| | $Cu_2LBr_2$,[b] $CuLCl_2$[b] | 136/75 |
| | $CuLBr_2$[b] | 136/75, 190/80 |
| | $CuL_4(ClO_4)_2$[a, solid; b, solut. | 136/75, 126B/80 |
| | $ZnL_2Cl_2$ | 6/26, 5/27 |
| | $ZnLCl_2$,[c] $ZnL_2Br_2$,[c] $ZnL_2I_2$[c] | 174/76 |
| | $PdL_2Cl_2$,[a] $PdL_2Br_2$,[a] $PdLI_2$,[b] $PdL_2(NO_3)_2$[a] | 136C/75 |
| | PdL(oxalato)[b] | 182/83 |
| | $CdLCl_2$,[a] $CdLBr_2$,[a] $CdL_2I_2$[a] | 174/76 |
| | $SbLCl_5$ | 288/76 |
| | $PtL_2Cl_2$,[a] $PtL_2Br_2$,[a] $PtLI_2$[b] | 136C/75 |
| 4,5-Dimethylisoxazole | $CdLCl_2$ | 14/38 |
| | $HgLCl_2$ | 14/38 |
| 3-Methyl-4-isopropenylisoxazole | $HgLCl_2$ | 16/54 |
| Trimethylisoxazole | $AuLCl_3$ | 15/891 |

TABLE 1.79. *(Continued)*

| Ligand (L) | Complex | References |
|---|---|---|
| Trimethylisoxazole | $HgLCl_2$ | 15/891 |
| 3-Methyl-5-phenylisoxazole | $CrL_2$ | 299/78 |
| | $CrL_3Cl_3{\cdot}6H_2O$,[a] $Cr_2L_3Br_6{\cdot}6H_2O$[b] | 222/76 |
| | $MnL_2Br_2$, $MnL_2I_2{\cdot}H_2O$, $MnL_2(NCS)_2{\cdot}1.5H_2O$ | 253/80 |
| | $CoL_2Cl_2$,[a] $CoL_2Br_2$,[a] $CoL_2I_2$,[a] $CoL_2(NCS)_2{\cdot}2H_2O$,[a] | |
| | $CoL_4(NCS)_2$,[a] $[CoL_4(H_2O)_2](ClO_4)_2$[a] | 136B/75 |
| | $Ni_2LBr_4{\cdot}2H_2O$,[b] $NiL_3(NCS)_2$,[b] $NiL_4(NCS)_2{\cdot}H_2O$,[a] | |
| | $NiL_2(ClO_4)_2$[b] | 136B/75 |
| | $CuLBr_2$ | 136B/75, 190/80 |
| | $Cu_2LBr_2$,[b] $CuLCl_2$,[b] $CuL_3Br$[b] | 136B/75 |
| | $CuL_4(ClO_4)_2$[a,solid; b, solut. | 136B/75, 126B/80 |
| | $ZnL_2Cl_2$,[c] $ZnL_2Br_2$,[c] $ZnL_2I_2{\cdot}2H_2O$[c] | 175/76 |
| | $PdL_2Cl_2$,[a] $PdLBr_2$,[b] $PdLI_2{\cdot}H_2O$[b] $PdL_2(NO_3)_2$,[a] $PdL_2(SCN)_2$[b] | 243/76 |
| | $CdLCl_2$ | 4/26 |
| | $CdL_2Cl_2{\cdot}H_2O$,[b] $CdL_2Br_2{\cdot}2H_2O$,[b] $CdLI_2{\cdot}2H_2O$[b] | 175/76 |
| | $PtL_2Cl_2$,[a] $PtL_2Br_2$,[a] $PtL_2I_2$[a] | 243/76 |
| | $HgLCl_2$ | 4/26 |
| | $HgL_2Cl_2$,[b] $HgL_2Br_2{\cdot}2H_2O$[b] | 175/76 |
| 5-Methyl-3-phenylisoxazole | $CdLCl_2$ | 4/26 |
| 3,5-Diphenylisoxazole | $CrL_2$ | 299/78 |
| | $CrL_3Cl_3$,[a] $CrL_3Br_3{\cdot}3H_2O$[a] | 222/76 |
| | $MnL_2Cl_2{\cdot}2.5H_2O$,[a] $MnL_3(H_2O)Br_2{\cdot}2H_2O$[a] | 276B/80 |
| | $FeL_6Cl_3$,[a] $FeL_3Cl_3$,[a] $FeL_6Br_3$,[a] $FeL_3Br_3$,[a] $FeL_4(ClO_4)_6{\cdot}3H_2O$[a] | 210B/81 |
| | $CoL_2Cl_2{\cdot}H_2O$,[a] $CoL_2Br_2$,[a] $CoL_2I_2$,[a] $CoL_2(NCS)_2{\cdot}2H_2O$,[a] | |
| | $CoL_4(H_2O)_2](ClO_4)_2{\cdot}2H_2O$[a] | 174/77 |
| | $NiL_2Cl_2{\cdot}H_2O$,[b] $NiL_2Br_2{\cdot}2H_2O$,[b] $NiL_2I_2$,[b] $NiL_2(NCS)_2$,[b] | |
| | $NiL_4(NCS)_2$,[a] $[NiL_4(H_2O)_2](ClO_4)_2{\cdot}2H_2O$[a] | 174/77 |
| | $CuLCl_2{\cdot}H_2O$,[a] $CuL_2Br_2$,[a] $CuL_4(ClO_4)_2{\cdot}4H_2O$[a] | 174/77 |
| | $ZnLCl_2$,[a] $ZnL_2Br_2{\cdot}4H_2O$,[a] $ZnLI_2{\cdot}4H_2O$[a] | 175/76 |
| | $PdL_2Cl_2$,[a] $PdL_2Br_2$,[a] $PdL_2I_2$,[a] $PdL_2(NO_3)_2{\cdot}2H_2O$[a] | 243/76 |
| | $CdL_2Cl_2$,[a] $CdL_2Br_2$,[a] $CdL_2I_2{\cdot}4H_2O$[a] | 175/76 |
| | $PtL_2Cl_2$,[a] $PtL_2Br_2$,[a] $PtL_2I_2$[a] | 243/76 |
| | $HgL_2Cl_2$,[a] $HgL_2Br_2{\cdot}H_2O$[a] | 175/76 |
| 3-Amino-5-methylisoxazole | $CaL_2Cl_2{\cdot}H_2O$,[a] $CaL_3Cl_2{\cdot}2H_2O$,[a] $CaL_4Br_2{\cdot}3H_2O$[a] | 210/81 |
| | $CrL_2Cl_3$,[b] $CrL_3Cl_3{\cdot}L{\cdot}H_2O$,[a] $CrL_2Br_3{\cdot}5\ H_2O$,[b] $CrL_2(H_2O)Br_3{\cdot}2L{\cdot}H_2O$,[a] | |
| | $CrLI_3$,[a] $CrL_3(NO_3)_3{\cdot}2H_2O$[a] | 243/78 |
| | $MnL_2Cl_2$,[b] $MnL_2Br_2$,[b] $MnL_2I_2$,[b] $MnL_2(NCS)_2{\cdot}H_2O$[b] | 276B/80 |
| | $FeL_4Cl_3$,[a] $FeL_3Cl_3{\cdot}H_2O$,[a] $FeL_6Br_3$,[a] $FeL_6(ClO_4)_3{\cdot}2H_2O$[a] | 210B/81 |
| | $CoL_2Cl_2$,[a] $CoL_2Br_2$,[a] $CoL_4(NCS)_2{\cdot}2H_2O$,[a] $CoL_4(NO_3)_2{\cdot}3H_2O$,[a] | |
| | $CoL_4(NO_2)_2{\cdot}L$,[a] $[CoL_4(H_2O)_2](ClO_4)_2{\cdot}2H_2O$,[a] $CoL_6(ClO_4)_2$[a] | 250/77 |
| | $NiL_2Cl_2{\cdot}2H_2O$,[d] $NiL_4Cl_2{\cdot}0.5H_2O$,[a] $NiL_4Br_2$,[a] $NiL_4(NCS)_2$,[a] | |
| | $NiL_4(NCS)_2{\cdot}L{\cdot}H_2O$,[a] $NiL_4(NO_3)_2$,[a] $NiL_6(ClO_4)_2$[a] | 244/76, 233B/79 |
| | $CuL_2Cl_2$[b] | 250/77 |
| | $CuL_4(NO_3)_2$,[a] $CuL_4(ClO_4)_2$[a] | 250/77, 139/81 |
| | $CuL_4Br_2$[a] | 250/77, 233B/79 |
| | $CuL_4Cl_2$,[a] $CuL_2Br$,[b] $CuL_2(NO_3)_2$[b] | 250/77, 143/81 |
| | $ZnL_2Cl_2$,[c] $ZnL_2Br_2$,[c] $ZnL_2I_2$,[c] $ZnL_2(NCS)_2$[c] | 175/77 |
| | $PdL_2Cl_2$,[c] $PdL_2Br_2$,[c] $PdLI_2$,[b] $PdL_2(NCS)_2{\cdot}H_2O$,[c] $PdL_3(NO_3)_2$[c] | 242/76 |
| | $PdL_2$(oxalato)[c] | 253/80 |
| | $CdLCl_2$,[b] $CdLBr_2$,[c] $CdL_2I_2$,[c] $CdL_2(NCS)_2$[c] | 175/77 |

TABLE 1.79. *(Continued)*

| Ligand (L) | Complex | References |
|---|---|---|
| 3-Amino-5-methylisoxazole | $PtL_2Cl_2$,[c] $PtL_2Br_2$,[c] $PtL_2I_2$[c] | 242/76 |
| | $HgLCl_2$,[b] $HgLBr_2$[b] | 175/77 |
| 4-Amino-3,5-dimethylisoxazole | $CoL_2Cl_2$,[d] $CoL_2Br_2$,[d] $CoL_2I_2$,[d] $CoL_2(NCS)_2$[e] | 267/78 |
| | $NiL_2Cl_2{\cdot}2H_2O$,[e] $NiL_3Cl_2{\cdot}4H_2O$,[e] $NiL_2Br_2{\cdot}4H_2O$[e] | 267/78 |
| | $CuLCl_2{\cdot}2H_2O$,[e] $CuL_2Cl_2{\cdot}H_2O$,[e] $CuL_2Br_2{\cdot}2H_2O$,[e] $CuL_3(ClO_4)_2$[e] | 267/78 |
| | $ZnLCl_2{\cdot}H_2O$,[f] $ZnLBr_2$,[f] $ZnL_2I_2$,[c] $ZnL(NCS)_2{\cdot}H_2O$[f] | 173/77 |
| | $PdL_2Cl_2{\cdot}2H_2O$,[d] $PdL_2Br_2{\cdot}2H_2O$,[d] $PdL_2I_2$,[d] $PdL_2(NO_3)_2{\cdot}H_2O$,[d] $PdL_2(NCS)_2$[d] | 243/76 |
| | $CdLCl_2{\cdot}H_2O$,[e] $CdLBr_2{\cdot}H_2O$,[e] $CdL_2I_2{\cdot}2H_2O$,[e] $CdL(NCS)_2$[e] | 173/77 |
| | $PtL_2Cl_2$[d] | 243/76 |
| | $HgLCl_2$,[c] $HgLBr_2$,[a] $HgL(NCS)_2$[e] | 173/77 |
| 5-Amino-3,4-dimethylisoxazole | $CaL_2Cl_2{\cdot}4H_2O$, $CaL_3Br_2{\cdot}2H_2O$, $CaL_4I_2{\cdot}3H_2O$ | 210/81 |
| | $CrLCl_3{\cdot}4H_2O$,[c] $CrL_3Cl_3{\cdot}H_2O$,[c] $CrL_2(H_2O)Br_3{\cdot}5H_2O$,[a] $CrL_3(H_2O)Br]Br_2{\cdot}L{\cdot}4H_2O$,[a] $CrL_3(NO_3)_3{\cdot}2H_2O$[a] | 243/78 |
| | $MnL_2Cl_2{\cdot}H_2O$,[b] $MnL_2Br_2$,[b] $MnL_2I_2{\cdot}H_2O$,[b] $MnL_2(NCS)_2{\cdot}3H_2O$[b] | 276B/80 |
| | $CoL_2Cl_2$,[d] $CoL_2Br_2$,[d] $Co_2L_7I_4$,[e] $Co_4L_{11}I_8$,[e] $CoL_2(NO_3)_2$,[c] $[CoL_4(H_2O)_2](ClO_4)_2$[a] | 249/77 |
| | $[NiL_3(H_2O)]Cl_2{\cdot}H_2O$,[a] $[NiL_3(H_2O)]Br_2{\cdot}H_2O$,[a] $NiL_4I_2{\cdot}H_2O$,[a] $NiL_3(NCS)_2{\cdot}H_2O$,[c] $NiL_2(NO_3)_2{\cdot}2H_2O$,[c] $NiL_3(ClO_4)_2{\cdot}4H_2O$,[c] | 244/76 |
| | $Cu_2L_3Br_4$,[c] $Cu_4L_3I_8$,[c] $Cu_2L_5(NO_3)_4$,[c] $CuL_2(NCS)_2$[d] | 249/77 |
| | $ZnL_2Cl_2$,[d] $ZnL_2Br_2$,[d] $ZnL_2I_2$,[d] $ZnL_2(NCS)_2$[d] | 175/77 |
| | $PdL_2Cl_2$,[d] $PdL_2Br$,[d] $PdL_2I_2{\cdot}H_2O$,[d] $PdL_2(NCS)_2{\cdot}2H_2O$,[d] $Pd_2L_3(NO_3)_4$[f] | 242/76 |
| | $PdL_2$(oxalato)[c] | 253/80 |
| | $CdLCl_2$,[c] $CdLBr_2$,[a] $CdL_2I_2$,[f] $CdL_2(NCS)_2$ | 175/77 |
| | $BaL_3Cl_2$, $BaL_3I_2{\cdot}2H_2O$, $BaL_6(NCS)_2$ | 210/81 |
| | $PtL_2Cl_2$,[d] $PtL_2Br_2$,[c] $PtL_2(NCS)_2$[d] | 242/76 |
| | $HgLCl_2$,[f] $HgLBr_2$[c] | 175/77 |
| 4-Chloro-3,5-dimethylisoxazole | $CuLCl_2$,[a] $CuLBr_2$,[a] $CuL(ClO_4)_2{\cdot}2H_2O$[a] | 267/83 |
| 4-Chloro-3-methyl--5-phenylisoxazole | $CuL_2Cl_2$,[a] $CuLBr_2$,[a] $CuL_2(ClO_4)_2$,[a] $CuL(NO_3)_2{\cdot}H_2O$[b] | 149/84 |

[a] N-bonded ligand.
[b] Bridging N- and O-bonded ligand.
[c] O-bonded ligand.
[d] Exocyclic $NH_2$-bonded ligand.
[e] Bridging $NH_2$- and $N_{ring}$-bonded ligand.
[f] Bridging $NH_2$- and $O_{ring}$-bonded ligand.

isoxazole seems to be the most ecleptic, all types of metal–ligand bonds being represented. Both monodentate (through exocyclic amino group, as in all Zn and in most Pd or Pt complexes, or through the ring nitrogen, as in some Cr or Ni complexes, or through the ring oxygen, as in Cu and some Cr or Ni complexes) and bidentate (exocyclic N either with ring N, as in some Co complexes, or with ring oxygen, as in individual Cd, Hg, and Pd salts) links are present.

Different species of Cu(II) complexes in various solvents have been studied by EPR spectroscopy (§ 1.2.5.3),[141/79,126B/80,190/80,139/81,143/81] and sometimes a different nature of the metal–ligand bond has been evidenced. The stability constants of some isoxazole and 5-methylisoxazole metal complexes have been measured potentiometrically and compared with other azoles: the expected sequence of complex forming ability pyrazole > isothiazole > isoxazole has been evidenced.[222B/77,232/78] A higher stability for the complex of 3,5-dimethylisoxazole with aluminum bromide than with antimony pentachloride has been determined.[288/76]

Some metal [Cu(II), Co(II), and Ni(II)] complexes of sulfamethoxazole have been prepared, and their antibacterial activity has been evaluated in comparison with that of the parent compound.[85/78,133/78] The inhibitory activity of some Pd and Pt(II) complexes of isoxazole and its derivatives on the membrane-bonded ATPase has been found to be generally higher than that of the free ligands.[138/81]

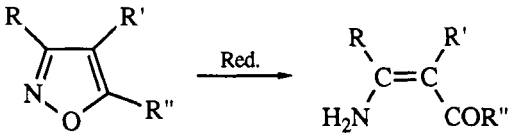
### *1.4.2.2 Molecular Complexes*

Despite the low donor ability of the isoxazole ring, some 1:1 molecular complexes of 3,5-dimethylisoxazole with trinitroanisole or trinitrophenol are known,[161/75,118/76,285/77,286/77] and their formation constants have been measured spectrophotometrically. The formation of a true 1:1 molecular complex in the widely used antibacterial mixtures of sulfamethoxazole and trimethoprim has been demonstrated.[50/77] $NH_3$ adducts of sulfamethoxazole and of sulfisoxazole have been described.[54/80] A study of the complex cation [thiazole···H···isoxazole]$^+$ confirms that the proton is more closely attached to the stronger basic thiazole.[138/75] Finally, H-bonding seems to be the driving force for the formation of complexes between some isoxazole sulfonamides and 18-crown-6.[41/77,34/79]

## 1.4.3 Reduction Reactions

### *1.4.3.1 Hydrogenolytic Ring Cleavage*

The isoxazole ring is readily cleaved at the N–O bond by several reducing agents:

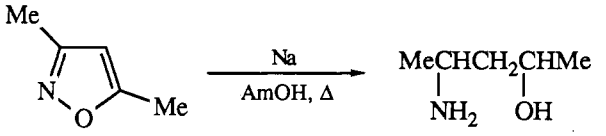



The $\beta$-enamino ketones generally obtained by this process exhibit a manifold reactivity, which, depending on the substitution pattern, offers an easy entry to a large variety of acyclic, homocyclic, and heterocyclic systems.

As illustrated more thoroughly in § 1.4.12, the use of isoxazole compounds as key intermediates in the synthesis of complex molecules is based primarily on the possibility of opening the heterocyclic ring by hydrogenolysis at the wanted stage of the synthetic design.

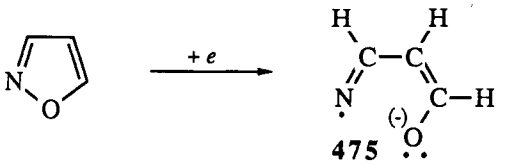
It was demonstrated as early as 1891 that the reduction of 3,5-dimethylisoxazole with sodium in amyl alcohol or in wet ether gives the monoimine of acetylacetone.[9/891] A similar result is obtained by reduction of trimethylisoxazole with metallic sodium in moist ether, a reaction previously known but misinterpreted.[15/891] Metallic sodium in ethanol is the reductant chosen for 3,5-dimethyl-4-phenylisoxazole.[89/64]

At a higher temperature (i.e., in refluxing 1-pentanol), sodium reduction can proceed further; thus, from 3,5-dimethylisoxazole a diastereomeric mixture of 4-amino-2-pentanols has been obtained in 40% yield:[17C/59,173B/72]




Sodium amalgam was used to reduce β-(3-halogenoisoxazol-5-yl)propionic acid: reductive dehalogenation and ring cleavage produced a mixture of 5-cyano-4-oxopentanoic acid and succinic acid.[1/09]

A step through an open-chain anion radical such as **475**, formed by rupture of the weakest N–O bond in consequence of the oxygen electronegativity, is substantiated by the ESR spectrum (§ 1.2.5.4) obtained by photo-induced generation in an argon matrix containing Na and isoxazole:[126/73]




**475**

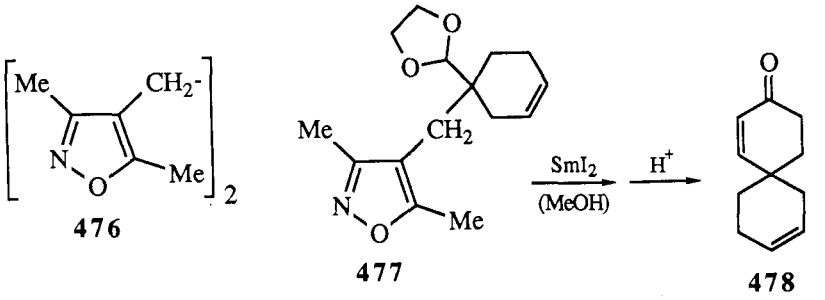
Other chemical reducing agents, leading to β-enamino ketones, are samarium diiodide[287/82] or transition-metal carbonyls such as molybdenum hexacarbonyl in the presence of water[156/82] or iron pentacarbonyl in the presence of water and photo-irradiation.[282/82] Some data on the reduction conditions and substitution pattern are presented in Table 1.80.

Note that samarium diiodide requires an excess of reagent (2 Eq) and methanol as a proton source; in the absence of the latter component, the dimeric product **476** is obtained from 4-chloromethyl-3,5-dimethylisoxazole.[287/82] A good yield of the spiro compound **478** is formed by reaction of the isoxazole acetal **477** and subsequent treatments with acids:[287/82]

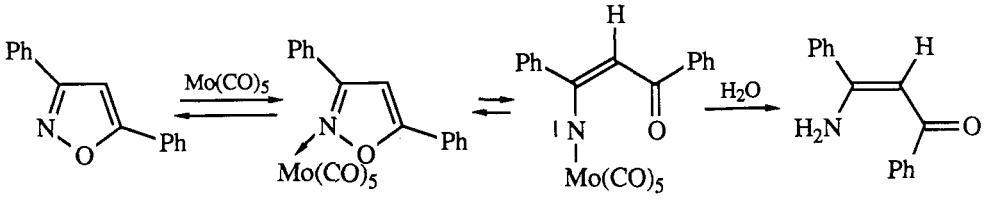
TABLE 1.80. REDUCTION OF ISOXAZOLES TO β-ENAMINOKETONES

| R | R' | R'' | Conditions | Yield (%) | References |
|---|---|---|---|---|---|
| Me | H | Me | $SmI_2$ (2 equiv.) in THF(MeOH), r.t. 1 h | 57 | 287/82 |
| | | | $Mo(CO)_6$ (0.5 eq.) in $MeCN(H_2O)$, reflux 4 h | 91 | 156/82 |
| | | | $Fe(CO)_5$ (1.2 eq.) in $MeCN(H_2O)$, 350 nm lamp, r.t. 6 h | 72 | 282/82 |
| Me | H | Ph | $Mo(CO)_6$ (0.5 eq.) in $MeCN(H_2O)$, reflux 4 h | 80 | 156/82 |
| | | | $Fe(CO)_5$ (1,2 eq.) in $MeCN(H_2O)$, sunlight, r.t. 24 h | 79 | 282/82 |
| Ph | H | Ph | $Mo(CO)_6$ (0.5 eq.) in $MeCN(H_2O)$, reflux 4 h | 90 | 156/82 |
| | | | $Fe(CO)_5$ (1.2 eq.) in $MeCN(H_2O)$, sunlight, r.t. 24 h | 74 | 282/82 |
| Me | COOH | Me | $SmI_2$ (2 eq.) in THF(MeOH), r.t., 1 h | 96 | 287/82 |
| Me | $CH_2OH$ | Me | $SmI_2$ (2 eq.) in THF(MeOH), r.t., 1 h | 80[a] | 287/82 |

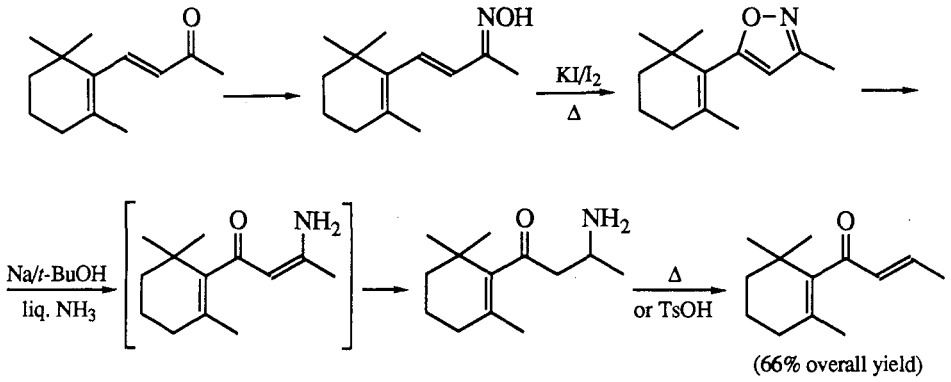
[a] Along with 13% trimethylisoxazole and 2% dimeric compound.



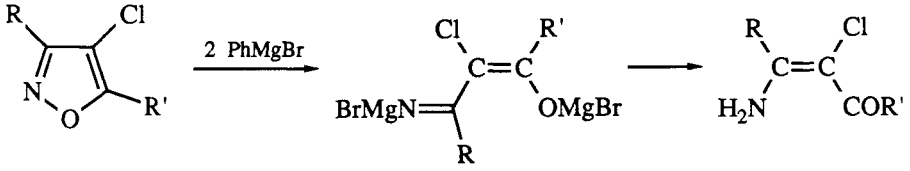

The reaction with metal carbonyls is presumed to proceed through a nitrene complex; for example:[156/82]




An important variation of this type of reduction is the reaction of isoxazoles with sodium and *t*-butyl alcohol in liquid ammonia. In this case the intermediate β-enaminoketone is further reduced to the saturated β-amino ketone. In turn, the latter compound, rather unstable, promptly decomposes, by thermolysis or by acidic treatment, into the α,β-enone.[96/72,100/73,159/81] This sequence is exemplified here by the transformation of β-ionone into β-damascone:[96/72]

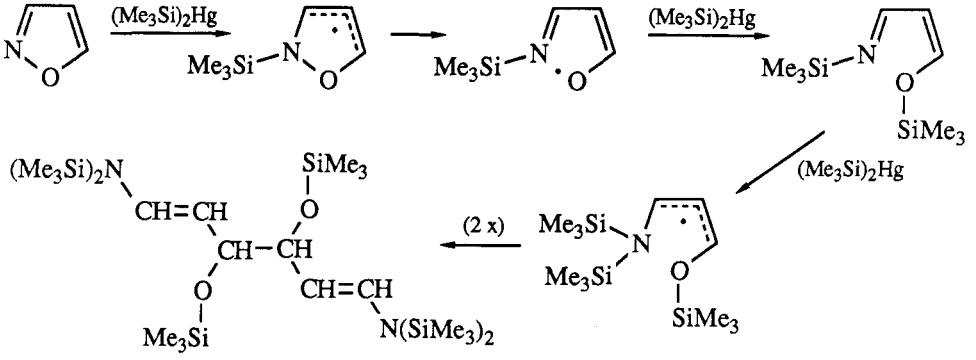



Reductive cleavage to β-enamino ketone has sometimes been effected by organomagnesium compounds: thus 3-methyl-5-phenylisoxazole reacts with excess phenylmagnesium bromide to give the monoimine of benzoylacetone, along with diphenyl.[4/26] Involvement of a six-membered cyclic complex may be envisaged here. Similarly, triphenylisoxazole is attacked by the same Grignard reagent or, better, by methylmagnesium iodide to yield the monoimino derivative of phenyldibenzoylmethane.[10/28] 3,5-Disubstituted 4-iodo (or 4-bromo)-isoxazoles are known to give organomagnesium compounds (see § 1.4.8, p. 333), but their 4-chloro analogues usually suffer ring cleavage, monoimines of the corresponding α-chloro-β-diketones being obtained:[21/60,95/63]

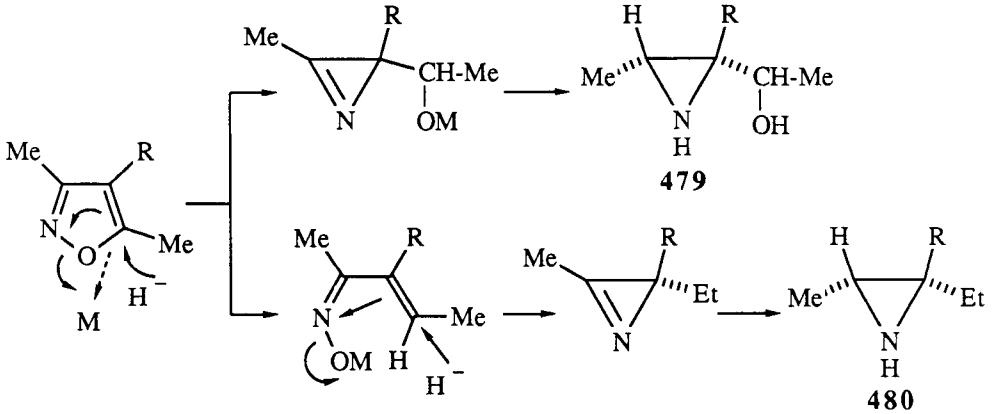



In this case the action of magnesium subhalides has been proved.[95/63]

Remarkable is the behavior of isoxazole and its methyl derivatives toward bis(trimethylsilyl)mercury in boiling benzene: a dimeric product derived from a 2:3 molar ratio of reagents is obtained.[236/76] The proposed mechanism is here exemplified for the parent compound:

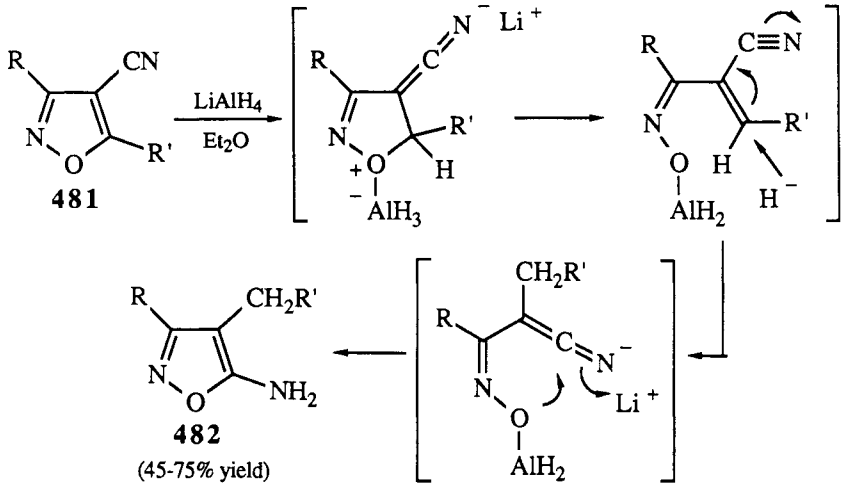


In most cases, however, organomagnesium compounds do not affect the ring, and so do other common reducing agents, such as lithium aluminum hydride or stannous chloride. Nevertheless, some exceptions are known. Whereas 3,4-diphenylisoxazole is reported to be stable toward the former reagent,[203/70] prolonged treatment of 3,5-dimethyl- or trimethylisoxazole with lithium aluminum hydride in refluxing tetrahydrofuran causes an 80% destruction of the heterocyclic ring with the formation of a mixture of products. The major product is the aziridine carbinol (**479**), and one minor product is the corresponding norhydroxyderivative (**480**). Both products are possibly produced through the azirine step, depending on whether the ring is opened through an N–O or an O–$C_5$ cleavage:[29/75]




3-Phenylpropylamine is reported to form by treatment of 5-phenylisoxazole with excess lithium aluminum hydride.[3/58]

An interesting rearrangement accompanies the $LiAlH_4$ reduction of 4-cyanoisoxazoles (**481**), which furnishes 5-aminoisoxazoles (**482**) in fair yields.[120/84] The cyano group favors both the initial nucleophilic attack at position 5, causing the ring cleavage, and the second hydride attack, causing the ring reclosure, according to Scheme 1.24.

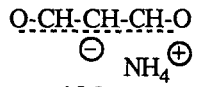



Scheme 1.24.

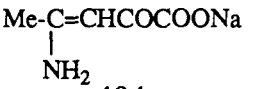
Reductive cleavage of the isoxazole ring sometimes also occurs under acidic conditions. Thus treatment of the *N*-phenylimidochloride of 5-methyl-3-phenylisoxazole-4-carboxylic acid with stannous chloride and hydrogen chloride gives, along with the expected aldehyde, some benzoylacetone, arising from the hydrolysis of the corresponding monoimine.[6/38] 1,3-Amino alcohols of general formula $R_5CH(OH)CHR_4CH(NH_2)R_3$ are the final products of the polarographic reduction of variously substituted arylisoxazoles.[284/76] Other polarographic studies are known.[39/65,230/80]

Apart from the occasional reductive ring cleavages mentioned, conversion of isoxazoles into β-enamino ketones is usually accomplished by catalytic hydrogenation. The reaction has very wide applicability and generally occurs with excellent or quantitative yields. Several catalysts have been employed successfully, and several functional groups in the side chain do not interfere with the reaction.

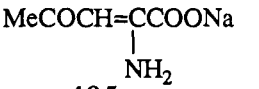
The most common catalyst is Raney nickel,[4/50,19/55,28/60,32/64,149/66,37/67,12/72,206B/79] used at ordinary pressure and temperature in ethanolic or aqueous solution. The latter solvent has proved convenient for reducing the isoxazolecarboxylic acids (as sodium salts).[4/50] Thus isoxazole itself yields the ammonium salt of malondialdehyde (**483**) and the isomeric 3-methylisoxazole-5-carboxylic and 5-methylisoxazole-3-carboxylic acid sodium salts (compounds **484** and **485**, respectively).



**483**



**484**

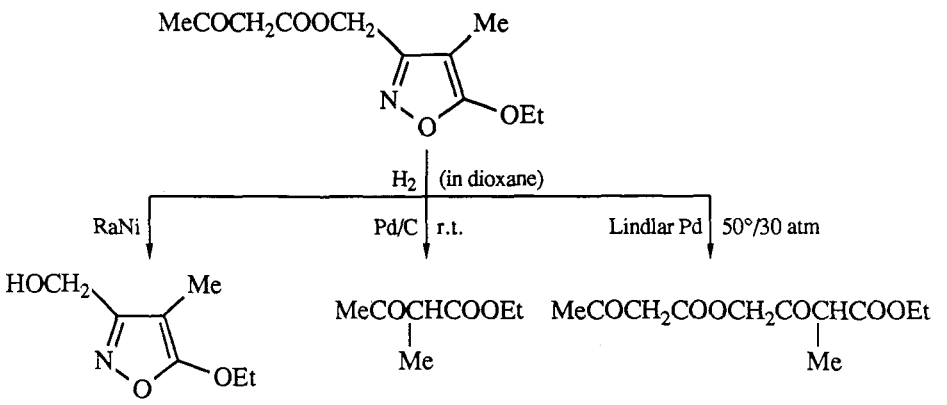


**485**

In some cases the addition of potassium hydroxide in small amounts may be useful.

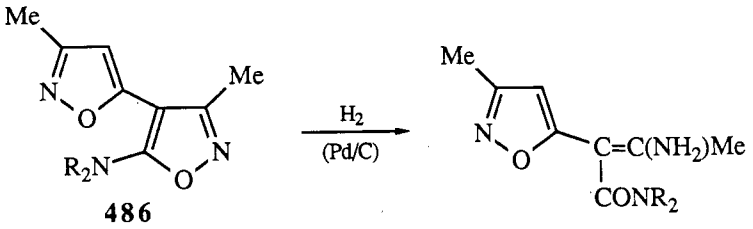
Hydrogenolysis to β-enamino ketones has also been carried out over platinum black,[17/54,96/72,40/73,42/73,52/73,180B/77,184/77] platinum activated with Raney nickel[159/81,184/84] or palladium–charcoal[147/73,36/76,205/80] catalysts. However, in some cases catalytic hydrogenolysis failed.[122/75,184/77]

Depending on the nature of the catalyst, a remarkable selectivity has sometimes been observed, as the following scheme shows:[193/83]



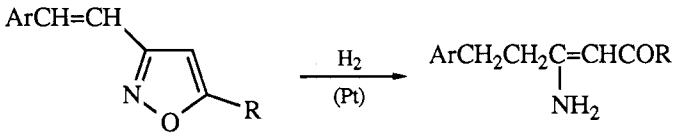
Another convenient procedure for obtaining β-keto esters from 5-alkoxyisoxazoles involves hydrogenation in the presence of Raney nickel and $BCl_3$ in methanol–water.[195/83]

A clear example of selective hydrogenolysis concerns the 4,5′-diisoxazole derivatives (**486**): catalysis with palladium–charcoal cleaves the activated 5-amino-substituted isoxazole ring only, whereas use of Raney nickel causes nonselective opening of both isoxazole rings:[182/71]



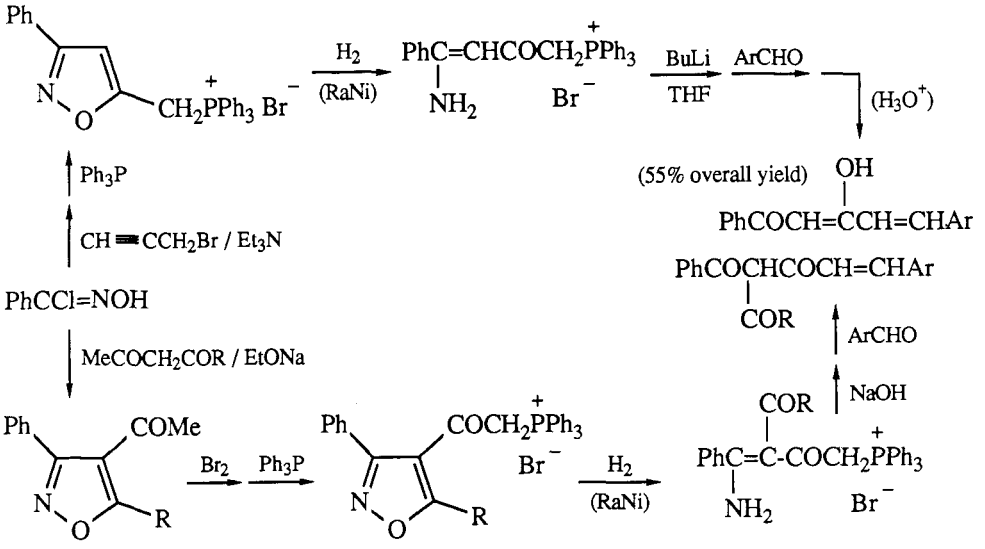

**486**

The isoxazole ring in 3-styrylisoxazoles has been found to be more resistant toward reductive cleavage: in fact, the heterocyclic ring remains unaltered by hydrogenation with Raney nickel, whereas ring opening is observed in the presence of platinum black; for example:[23/58,19/63,108/81]



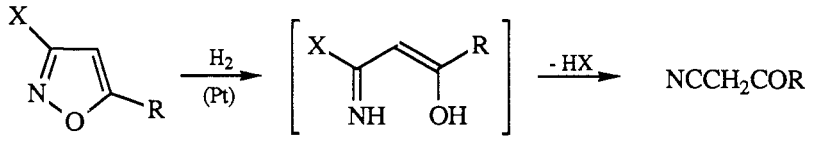

On the other hand, 5-*p*-methylstyryl-3-phenylisoxazole has been reported to give the saturated β-enamino ketone by hydrogenation in the presence of either Raney nickel (RaNi) or Lindlar catalyst.[39/74] By contrast, the C = N double bond of Schiff bases is not attacked during RaNi-catalyzed hydrogenation.[24/56] Other functional groups, such as carbonyl, cyano, carboxy or carbalkoxy, hydroxy, and amino groups, are usually unaffected as well as other heterocyclic rings, such as furan,[86/77] pyrazole,[134/71] or imidazole.[43/76] By contrast, a selective hydrogenation of a carbonyl group *prior* to isoxazole ring hydrogenolysis has been observed with bisisoxazolylacetone.[94/77]

The presence of a phosphorane moiety in the side chain allows a general entry into the classes of α,γ-dioxoolefins[39/74,66/76] and of an α,γ,γ′-trioxoolefins,[29B/75] as the examples in Scheme 1.25 shows.



Scheme 1.25.

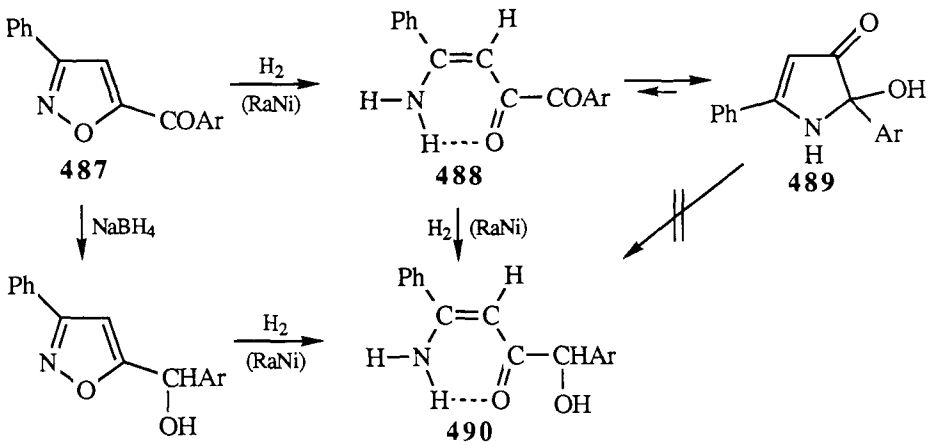
3-Chloroisoxazoles[27/61] or 3-bromoisoxazoles[78/69] undergo both hydrogenolysis of the N–O bond and dehalogenation, yielding β-cyanocarbonyl compounds:



4-Bromoisoxazole yields the expected bromomalondialdehyde monoimine if the hydrogenation is stopped after consumption of 0.8 mol of hydrogen; otherwise, the reduction proceeds further, finally giving 2-aminoethanol.[28/60]

3-Hydroxyisoxazoles or their *O*-benzyl ethers give, as expected, β-ketocarboxamides,[60/61,97/64,130/68,151/78,214/83] and 5-aminoisoxazole give the corresponding β-enaminocarboxamides.[161/67,10/72] Sometimes, these compounds are not isolable: thus catalytic hydrogenation of 5-amino-3-methyl-4-(2-quinolyl)isoxazole and subsequent purification by column chromatography on $Al_2O_3$ furnishes 2-quinolylacetacetamide.[67/78] On the other hand, selective hydrogenolysis of the 3-*O*-benzyl ether linkage without affecting the isoxazole ring can be accomplished in the presence of palladium/charcoal catalyst in ethanol or acetic acid solution.[139/66,189/68,192/68]

Interesting is the behavior of 5-aroylisoxazoles (**487**) toward catalytic hydrogenation: 1 mol of hydrogen affords the enamino-α-diketones (**488**), with 2 mol the hydrogenation proceeds further, yielding the hydroxyenamino ketone **490**. During isolation, compound **488** isomerizes into the stable cyclic tautomer **489**, which is resistant to hydrogenation:[148/74]




Finally, it should be remembered that occasionally reductive ring cleavage may also occur by photolysis of isoxazoles, and that with 5-alkoxyisoxazoles competition between rearrangement to 2*H*-azirine-2-carboxylates may arise under well-defined conditions (see § 1.4.5, p. 289). Selected examples of catalytic hydrogenations of isoxazoles to β-enaminoketone derivatives are collected in Table 1.81.

### *1.4.3.2 Reductions Without Ring Cleavage*

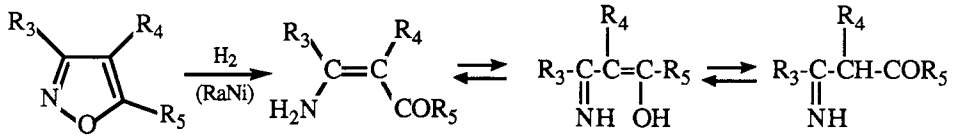
Several reducing agents operate only on functional groups present in the side chain, without touching the ring; the most significant are listed briefly here.

1. Lithium aluminum hydride, with some exceptions (see above) and sodium borohydride invariably do not cleave the ring. They are convenient reagents for reducing carbonyl groups[28/57,32/58,11/64,3/65,103/65,128/66,155/66,82/67,27/68,118/69,171/72,195/72,71/74,114/74,115/74,148/74,167B/74] or esters[65/65,82/67,106/67,54/68,50/69,26/71,49/72,6/78,169/82,92/84] to secondary or primary alcoholic functions, as well as C=N bonds to saturated secondary amino[24/56,75/66,177/72] or hydrazino[62/59,17/61,34/61,42/62,12B/64,5/66] moieties, or cyano to aminomethyl groups,[51/66] leaving unaltered the heterocyclic ring. The pellet form of $LiAlH_4$ has been reported to be particularly suitable for the reduction of isoxazolecarboxylic acids to the corresponding alcohols.[269/83]

Nevertheless, it is interesting to remark that 3,5-dialkylisoxazoles, carrying an electron-withdrawing substituent such as $NO_2$, CN, or $SO_2OR$ in the 4-position, are smoothly reduced to the corresponding 2-isoxazolines by lithium aluminum hydride or by sodium borohydride.[270/83]

The weakly stable 4,5-diamino-3-phenylisoxazole has been prepared by reduction of 5-amino-4-nitro-3-phenylisoxazole with sodium borohydride in the presence of Pd/C.[198/68] An analogous reduction has been accomplished with other 4-nitroisoxazole derivatives.[56/67] Reduction of benzoylisoxazoles up to benzylisoxazoles has been achieved by lithium aluminum hydride in the presence of aluminum chloride.[145/68]

TABLE 1.81. SELECTED CATALYTIC HYDROGENATIONS OF ISOXAZOLES



| $R_3$ | $R_4$ | $R_5$ | Conditions[a] | Yield (%) | References |
|---|---|---|---|---|---|
| VH | H | H | Ra-Ni, EtOH | | 4/50 |
| H | CH(Me)Et | H | Ra-Ni, MeOH | 60 | 37/67 |
| H | H | 2-$HOC_6H_4$ | Pt, EtOH | 89 | 184/77 |
| Me | H | Me | Ra-Ni, MeOH | | 4/50 |
| Me | H | *n*-Pr | Pt, EtOH | 42 | 40/73 |
| Me | H | $CH_2CH_2Ph$ | Pt, EtOH | 95 | 40/73 |
| *n*-$C_{15}H_{31}$ | H | *n*-$C_{13}H_{27}$ | Ra-Ni, EtOH | | 183/78 |
| $HOOCCH_2CH_2$ | H | *n*-$C_6H_{13}$ | Pt, MeOH | 90 | 245/78 |
| $HOOCCH_2CH_2$ | H | $CH_2CH_2COOH$ | Pt, MeOH, trace $NEt_3$ | 74 | 94/71 |
| Me | H | $CH(COOEt)_2$ | Pt, EtOH | | 52/73 |
| Me | H | $CH_2PPh_3Br$ | Ra-Ni, EtOH | 90 | 66/76 |
| Me | H | $CH{=}C(NH_2)Ph$ | Pt, EtOH | 52 | 42/73 |
| α-Furyl | H | Me | Ra-Ni | 65.5 | 86/77 |
| 2-$HOC_6H_4$ | H | $NH_2$ | 5% Pd/C, EtOH | 100 | 36/76 |
| Ph | H | $NH_2$ | Ra-Ni, EtOH | 89 | 17/54 |
| 2,6-$Cl_2C_6H_3$ | H | Me | Ra-Ni, 50 psi, EtOH | 88 | 193/69 |
| Ph | H | Ph | Ra-Ni, EtOH | | 4/50 |
| Ph | H | $CH_2PPh_3Br$ | Ra-Ni, EtOH | 92 | 66/76 |
| $HOOCCH_2CH_2$ | H | Ph | Pt, MeOH | | 148/79 |
| $(CH_2)NCH_2CH(OH)$ | H | Ph | Ra-Ni, EtOH | 83 | 12/72 |
| EtOOC | H | $CH_2PPh_3Br$ | Ra-Ni, EtOH | 40 | 66/76 |
| HO | H | COPh | Pt, AcOEt | 98 | 214/83 |
| HO | Me | Me | Pt, EtOH | | 60/61 |
| HO | $CH_2NHCOCF_3$ | Me | 10% Pd/C, press., EtOH | 79 | 130/68 |
| Me | $COCH_2PPh_3Br$ | Me | Ra-Ni, EtOH | | 29B/75 |
| Ph | Me | Ph | Ra-Ni, slight press., MeOH | 100 | 206B/79 |
| Me | COOMe | Me | Ra-Ni, 50 psi, MeOH | 80 | 193/69 |
| Et | COOEt | Ph | Pd/C, 50 psi, EtOH | 100 | 205/80 |
| 3-MeO,4-$PhCH_2O$-$C_6H_3CH{=}CH$ | H | *n*-Am | Pt, MeOH | 100[b] | 108/81 |
| Me | 2-$NO_2C_6H_4SO_2NH$ | Me | Ra-Ni, 45-50 psi, EtOH | 75[c] | 130/79 |
| Ph | 2-$NO_2C_6H_4NHCO$ | Me | Ra-Ni, 45-50 psi, EtOH | 75[c] | 159/74 |

[a] Atmospheric pressure and room temperature, if not otherwise specified.
[b] Double bond saturated.
[c] $NO_2$ reduced to $NH_2$.

Several isoxazolecarboxaldehydes have been prepared in good yields by reduction of the corresponding *N,N*-dimethylcarboxamides or ethyleneimides with lithium aluminum hydride ($CONMe_2 \rightarrow CHO$).[35/62,125/65,2/76,2/78,12/80] Under slightly different circumstances, carboxamides can furnish the appropriate saturated amines ($CON< \rightarrow CH_2N<$).[86/67,87/67,91/67,67/68,72/83]

Noteworthy is the addition of borohydride to the activated C=N bond of isoxazolium salts. The nature of the reaction products depends on the substitution pattern of the substrate and on the conditions adopted: thus 3-unsubstituted 5-phenylisoxazolium salts afford a mixture of 5-phenyl-4-isoxazolines and of their borane complexes, whereas 5-unsubstituted isoxazolium salts are also attacked by the hydride anion at position 5, giving both 4- and 3-isoxazolines and, finally, isoxazolidines[36/74] (see §§ 2.5, p. 638, and 2.4, p. 622).

3,5-Disubstituted *N*-methylisoxazolium salts are smoothly transformed into 4-isoxazolines (or their borane complexes) by treatment with either lithium aluminum hydride or sodium borohydride.[269/82] When an electron-withdrawing group is present in the 4-position, a mixture of 3- and 4-isoxazoline derivatives is formed, and the reduction can even proceed further to isoxazolidines, as in the case of 4-nitro-substituted derivatives.[157/84]

2. Selective hydrogenation of the ethylenic double bond in the side chain is possible by using a relatively less active catalyst, such as palladium on charcoal or on barium sulfate—and better if in the presence of an acidic medium.[78/67.82/67.171/72.174/74.275/76.49/82] Even a selective hydrogenation of a triple bond to a double bond[32/81] or a selective hydrogenolysis of a benzyloxy group[68/66] can be achieved by using the appropriate catalyst. Other functional groups have occasionally been reduced through catalytic hydrogenation, such as an azido group,[68/66.188/68] an aromatic nitro group,[54/63.17/67.131/75] or a cyano group[11/75] to the corresponding amino group. Catalytic deuteration of a 5-bromomethylisoxazole derivative resulted in a deuterium-labeled 5-methyl compound.[140/81]

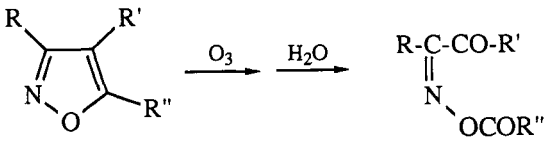
3. Reductions with stannous chloride have safely been carried out for transforming an aromatic or heteroaromatic (notably the isoxazole 4-nitro) nitro group[4/41.7/42.4/46.30/63.89/64.78/66.130B/67.85/72.218/72.224/73.173/76.163/77] or an azido group[4/31.5/31] into an amino group, a cyano into an aminomethyl group,[9/38] a diazonium salt into a hydrazino derivative,[5/31.94/64] a diazoamino into amino and hydrazino groups,[5/31.94/64] and a phenylimino acid chloride into an aldehyde[6/38] or anilinomethyl group.[9/38]

4. Other routine reducing agents used in the isoxazole field are: zinc dust and acetic acid (ketone → carbinol,[32/58] reductive dehalogenation,[3/19.76/60] or nitro → amino[2/05]); zinc and ammonium chloride[165/77.115/83] or amalgamated aluminum[3/03.7/21.162/71.167/73.3B/74.2/76.2/77.2/78.273/80.305/83] (nitro or hydroxyimino → amino); ammonium sulfide (azoxy → hydrazo[10/891] or nitro → amino[246/73]); diborane or diborane–methyl sulfide complex in refluxing tetrahydrofuran (carboxamide → primary amino group;[130/68.3/74.2/77.6/78] >NCHO → >NMe;[140/77] –CONHOH or CH=NOH → $CH_2NH_2$[139/66.263/82]); K selectride (keto acid → hydroxy acid);[201/80] diisobutylaluminum hydride (lactone → lactol).[201/80]

Hydrogenolysis of α-chloroalkylisoxazoles to the corresponding alkylisoxazoles has been achieved by zinc in ethanol.[39/58] An asymmetric reduction of some isoxazole ketones with microbiological methods has also been reported.[35/84] The polarographic reduction of 4-arylazoisoxazoles has been investigated.[261/83]

### 1.4.4 Oxidation Reactions

The isoxazole ring is fairly stable toward oxidizing agents, and the only general method of ring cleavage is ozonolysis, used in the past as structural proof. Ozone neatly cleaves the 4,5-double bond of the ring, and acyl derivatives of α-diketone monoximes are thus obtained from substituted isoxazoles:




In turn, the structure and configuration of the oxime are established by this method of formation. Thus triphenylisoxazole gives the low-melting *syn* benzil monoxime, not the isomeric *anti* oxime.[4/21] These and analogous results were useful in correcting earlier misconceptions of the steric course of the Beckmann rearrangements.[3/21.4/21] Many other examples of ozonolysis of trisubstituted isoxazoles are known.[3/24.10/28.1/29,77/64,157/66] Less substituted isoxazoles are further degraded. Thus the three isomeric (*S*)-*sec*-butylisoxazoles are oxidized by ozonolysis, followed by decomposition with aqueous alkaline hydrogen peroxide, to (*S*)-2-methylbutanoic acid without any loss of optical purity.[92/68]

Oxidation of isoxazoles often provokes ring cleavage, especially if carried out in alkaline media. Thus aqueous alkaline permanganate (but sometimes also neutral or acidic permanganate) oxidizes arylisoxazoles to easily identifiable aromatic acids. In many cases, this fact made it possible to determine the orientation of electrophilic substitution reactions, such as the nitration of arylisoxazoles.[7/39.4/46.4/51.37/57,66/58.76/61.89/64.37/65.198/68.66/73] For example, 3,5-dimethyl-4-*p*-nitrophenylisoxazole is oxidized to *p*-nitrobenzoic acid,[89/64] and the reaction products, obtained by nitration of 3-phenylisoxazole with nitric–sulfuric acids, are oxidized to a mixture of *para*- and *meta*-nitrobenzoic acids, along with minor amounts of the *ortho* isomer.[37/65]

Particularly easy is the oxidation of 3-unsubstituted arylisoxazoles: 5-phenylisoxazole is degraded to benzoic acid by heating with chromic acid in a strong acidic medium.[3/58] On the other hand, most oxidizing agents in neutral or acidic media leave the isoxazole ring unaffected. Therefore, several functional groups in the side chain can be prepared safely without opening the ring.

Isoxazolecarboxylic acids have frequently been prepared from alkenyl derivatives by oxidation with boiling chromic–sulfuric (or acetic) acid mixture [11/39.3/42.5/42.7/42.8/42.139/68.77/69] or with permanganate in various media,[8/39.7/42.8/59.33/61.81/66.56/67.54/68.166/71.148/76] from primary alcohols[5/49.68/58.27/61.78/69.103/82] or aldehydes,[6/38.4/42.7/49] or from acylisoxazoles with permanganate,[3/30.32/58.27/61] chromic acid,[13/40.2/46] or dilute nitric acid.[6/42.4/48] Aroylisoxazoles are more resistant to oxidation and do not give isoxazolecarboxylic acids.[4/48] 4-Chloro-3-*p*-hydroxyphenyl-5-methylisoxazole has been oxidized to 4-chloro-5-methylisoxazole-3-carboxylic acid by

treatment with alkaline permanganate,[4/46] and 3-alkoxymethyl derivatives yielded the corresponding isoxazole-3-carboxylic acids by oxidation with peracetic acid.[4/38,6/41]

Acetylisoxazoles are readily prepared by acidic permanganate or chromic trioxide oxidation of isopropenyl derivatives[11/39,13/40,3/41,4/46,5/49,7/49,33/61] or of a secondary alcohol.[32/58,106/67,131/75] Some isoxazole aldehydes have been obtained by cautious oxidation of the corresponding carbinols.[13/39,145/67,169/82,269/83]

No example of oxidation of methyl or alkyl to carboxylic group is known in the isoxazole field. An attempt to oxidize trimethylisoxazole with aqueous 45% nitric acid gave only 1% of 3,5-dimethylisoxazole-4-carboxylic acid.[233/69] However, oxidation of 3-(3-bromo-5-isoxazolyl)propionic acid with chromic acid in sulfuric acid is reported to furnish the 3-bromo-5-isoxazolecarboxylic acid.[8/65,138/66,139/66,213/68,219/69]

When the isoxazole is linked to another heterocyclic ring, the result of the oxidation depends on the nature of the heterocycle, the presence of substituents, and the type of oxidizing agent employed. Thus with 3-isoxazolylfurazaneacetic acid the isoxazole ring is attacked by alkaline permanganate and carboxyfurazaneacetic acid is formed, but boiling chromic–sulfuric acid gives isoxazole-3-carboxylic acid.[1B/46] In furylisoxazoles the furan ring is destroyed, giving isoxazolecarboxylic acids,[6/49,88/68] but in pyrazolylisoxazoles it is the pyrazole ring that resists oxidation, and pyrazolecarboxylic acids are obtained.[6/49]

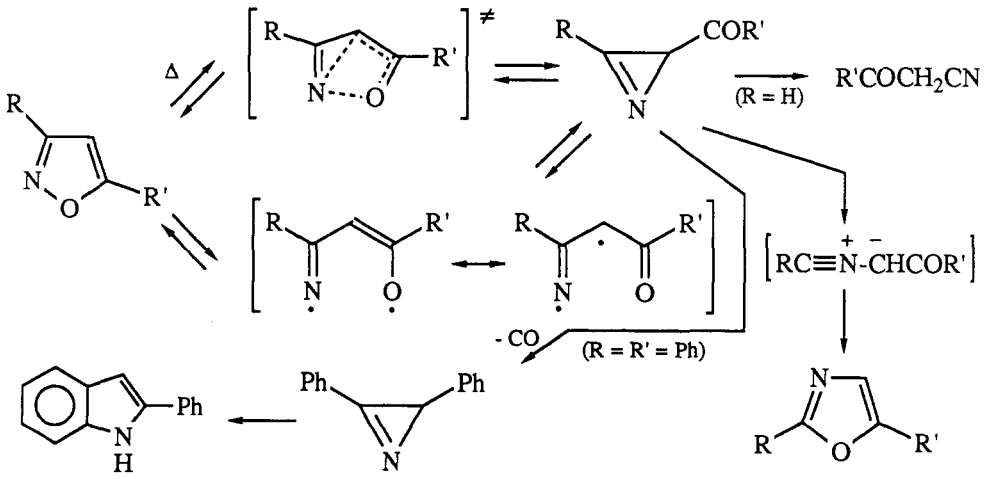
Although styrylisoxazoles are commonly oxidized to benzoic and isoxazolecarboxylic acids, the presence of a nitro group in position 4 completely changes the course of the reaction. 3-Methyl-4-nitro-5-styrylisoxazole is oxidized by permanganate in acetone solution to 3-methyl-4-nitroisoxazolin-5-one.[74/62]

Other oxidants that leave the isoxazole ring unaltered are Oppenhauer's oxidant (carbinol → ketone),[116/66,21/69] air (aldehyde → acid),[139/68] peracids (vinyl → aldehyde,[139/68] epoxidation,[41/84] or sulfide → sulfoxide or sulfone),[32/57,36/63,152/72,177/77] selenium dioxide (acetyl → α-ketoaldehyde or α-ketocarboxylic acid),[21/66,162/71] ozone (double bond → aldehyde),[215/68,147/75] and hydrogen peroxide (isoxazole boronic acid → hydroxyisoxazole).[115/67] Autooxidation (or hydrogen peroxide oxidation) of isoxazolethiols to diisoxazolyl disulfides is also known.[54/66,102/67,47/80]

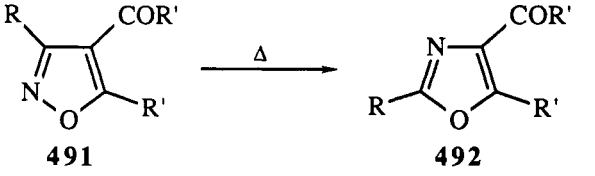
### 1.4.5 Thermolysis and Photolysis

The thermal stability of alkyl- or aryl-substituted isoxazoles is relatively high. Thus 3,5-diphenyl-, 3,5-diphenyl-4-methyl- and 5-acetyl-3,4-diphenylisoxazoles are perfectly stable on heating at 280°C for 10 days.[89/75] However, under more severe conditions, the weak N–O bond is cleaved, and several products may arise. Three examples are worth mentioning here. 3,5-Dimethylisoxazole is pyrolyzed in the gas phase at 600°C to give the isomeric 2,5-dimethyloxazole in 95% yield;[5/76] the 3-unsubstituted 5-methylisoxazole isomerizes at 550°C to cyanoacetone;[192/82] flash pyrolysis of 3,5-diphenylisoxazole

at 960°C furnishes, besides 56% starting material, a complex mixture of products, whose main components are 2,5-diphenyloxazole and 2-phenylindole.[147/76] Kinetic studies,[156/81,192/82] corroborated by theoretical considerations,[11/83] have established that in all cases the isoxazole at first isomerizes to the corresponding 1-azirine in a rate-determining step, either through a concerted 1,3-sigmatropic shift or through a stepwise diradical mechanism, as the following comprehensive scheme shows:



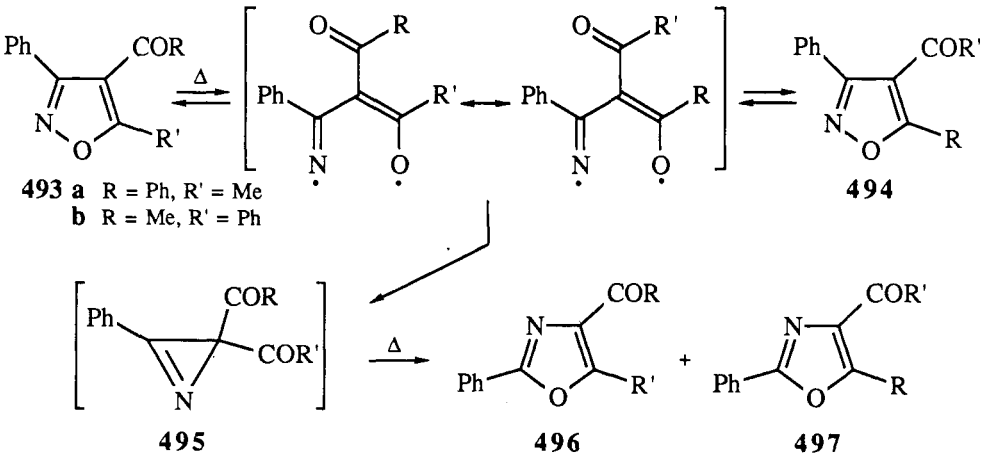

These results show that at least for these simple derivatives, the thermal behavior of 3,5-disubstituted isoxazoles closely corresponds to both the photochemical (see below) and electron-impact patterns (see § 1.2.4, pp. 61–65). The presence of a carbonyl group in the isoxazole 4-position strongly favors the cleavage of the ring N–O bond: thus, on heating a 4-acylisoxazole of structure **491** at 230–240°C, excellent yields of the isomeric 4-acyloxazoles (**492**) are obtained.[176B/74,89/75]




**491** **492**

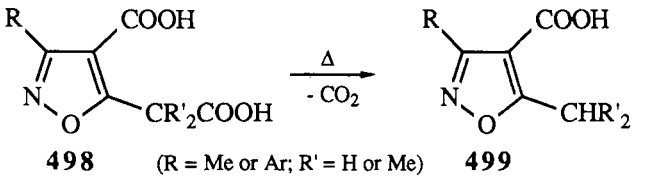
| R | R' | Yield(%) |
|---|---|---|
| Ph | Ph | 80 |
| Me | Me | 82 |
| Ph | Me | 96 |

When the isoxazole 5-substituent is dissimilar from the carbonyl substituent, as in 4-benzoyl-5-methyl-3-phenyl- (**493a**) or in 4-acetyl-3,5-diphenylisoxazole (**493b**), a mixture of three products is formed: the isomeric 4-acylisoxazole (**494**) along with the two isomeric acyloxazoles (**496** and **497**). An intermediacy of 3,3-diacyl-1-azirine (**495**) reasonably rationalizes the experimental results:[176B/74,89/75]

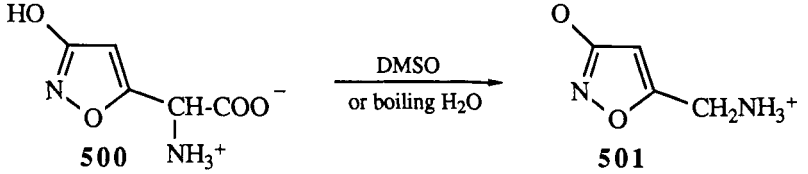



A relatively unexpected thermal instability has been reported for dimethyl 3-aryl(alkyl)isoxazole-4,5-dicarboxylate, which decomposes on distillation, furnishing the corresponding nitriles Ar(R)–CN.[311/82]

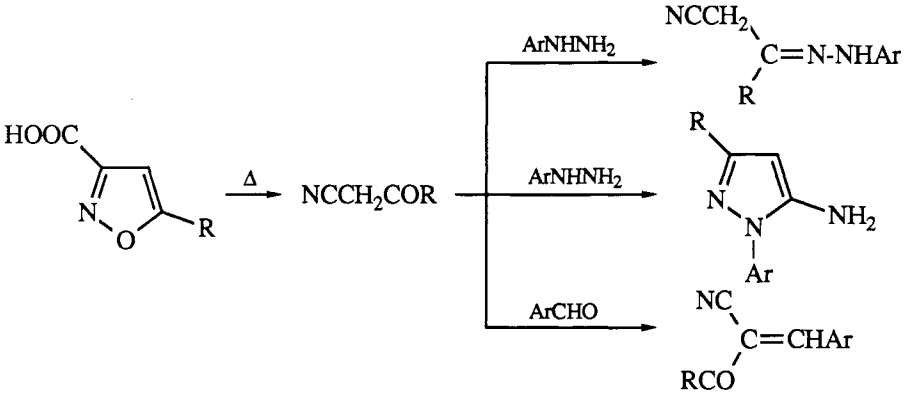
By contrast with the easy decarboxylation of the 2-isoxazoline counterparts (see § 2.2.3.2a, p. 553), isoxazole-4-carboxylic acids usually do not decarboxylate by pyrolysis. Exceptions are 5-*p*-nitrophenyl-3-phenyl-[9/56] and 5-methyl-3-phenyl-isoxazole-4-carboxylic acids,[37/63] which develop carbon dioxide on heating above melting point (180–200°C) or, better, in quinoline with traces of copper, giving the corresponding 4-unsubstituted isoxazoles in unstated yields. The thermal stability of the 4-carboxy group is also reflected in the thermal behavior of some dicarboxylic acids of structure **498**, which decarboxylate to compounds **499**:[14/62.128/70]




Another decarboxylation in the side chain is exemplified by the easy conversion of ibotenic acid (**500**) to muscimol (**501**):[125/65]



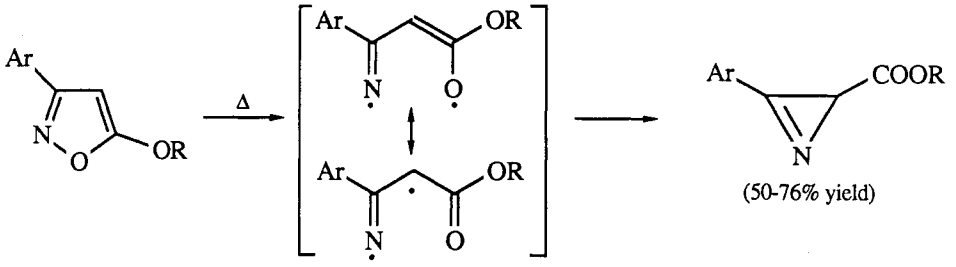
Far easier than decarboxylation with their isomers is the long known[9/891] thermal decarboxylation of 5-substituted isoxazole-3-carboxylic acids.[14/39.15/39,9/40,6/48,7/50.12/56,34/58.35/58.23/59.32/59] The α-cyano ketones initially formed are only weakly stable, and are usually identified as arylhydrazones, pyrazoles, or arylidene derivatives:




The thermolysis is carried out either in the melt or in solution with or without copper powder, and is best in the presence of the appropriate reagent. The presence of a 4-acyl[90/68] or nitro group[176/75] facilitates decarboxylation, which has been carried out by brief boiling in ethanol or water or at 55°C under vacuum, respectively.

Of course, a basic medium greatly enhances the reaction rate, owing to formation of the anion. Decarboxylation of the free acid seems to proceed through the zwitterion and requires more severe conditions, owing to the low basicity of the ring nitrogen. The decarboxylation has been utilized as a proof of structural assignments, since the isomeric isoxazole-5-carboxylic acids show far higher stability. A colorimetric method for the analytical determination of 5-substituted isoxazole-3-carboxylic acids and of other isoxazole derivatives of pharmacological relevance, which are easily convertible to these acids, is based on the thermal scission in the presence of *p*-dimethylaminobenzaldehyde.[49/80]

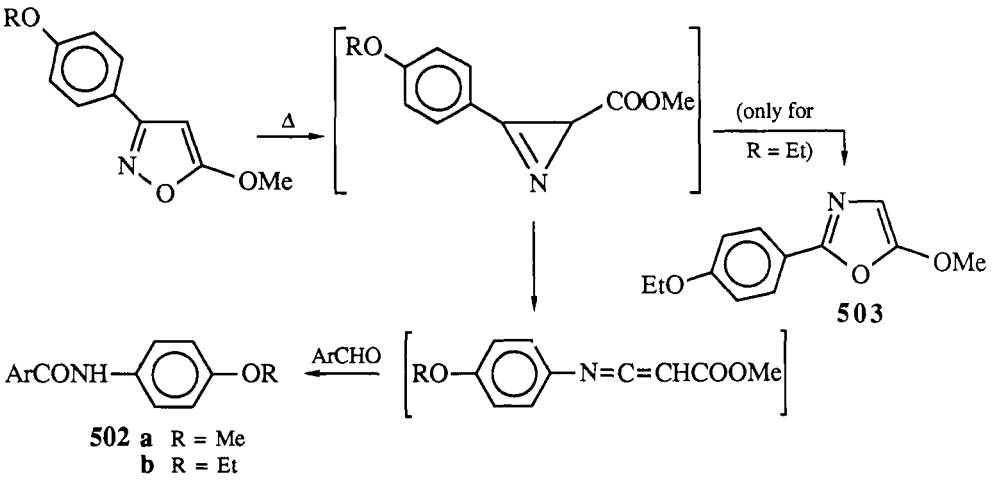
Isoxazoles, having a heteroatom (O,S,N) linked to the 5-position, are particularly prone to ring homolytic cleavage, leading to skeleton rearrangements and/or further transformations. Although stable to heat under vacuum distillation, 5-alkoxy-3-arylisoxazoles, when heated in refluxing decalin or at 200°C under atmospheric pressure, smoothly rearrange to alkyl 1-azirine-2-aryl-3-carboxylates:[203/69,202/70,29/77]



If catalyzed by copper stearate, this isomerization occurs in cyclohexane at 60°C.[160/75] Kinetic data support the biradical mechanism reported above.[248/77.218/78]

Almost quantitative yields of azirine carboxylates have recently been obtained when dioxane solutions of 5-alkoxyisoxazoles are briefly (5–8 min) heated at 80°C in the presence of hydrogen and poisoned palladium–charcoal.[143/83] Of course, more prolonged treatment causes reduction to open-chain enamino esters, which is complete within 60 min.

Certain substituents in the isoxazole 3-aryl group, such as a *p*-alkoxy, induce instability in the expected azirine carboxylate when the purely thermal rearrangement is used, and products of further transformation are obtained, yet in low yields. When 3-*p*-methoxyphenyl-5-methoxyisoxazole is heated with an aromatic aldehyde under reflux, the benzanilide **502a** is produced, presumably through cleavage of the azirine compound to a ketenimine. With the 3-*p*-ethoxyphenyl compound, partial isomerization to the oxazole derivative **503** is observed in addition, along with **502b**:[149/74]

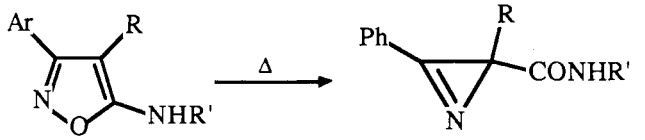



**502 a** R = Me
**b** R = Et

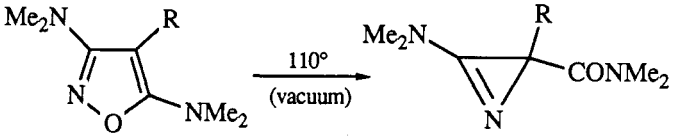
Attempts to extend the thermal synthesis of 1-azirine derivatives to 5-alkylthioisoxazoles have been just barely successful, owing to the higher stability of these compounds to heat. Only a 17% yield of an impure azirine thiolester was achieved by heating 5-*n*-butylthio-3-phenylisoxazole at 230°C.[202/70]

Better results have been obtained in the thermolysis of 5-amino-3-arylisoxazoles, which is somehow similar to that of 5-alkoxyisoxazoles but involves some significant differences. Under carefully chosen conditions, the chief product, here too, is the valence-bond isomeric 2-aryl-1-azirine-3-carboxamide, especially if the substrate is heated in high-boiling dilute solution. Table 1.82 reports some examples. Excellent yields of aminoazirines are also obtained from 3,5-bis(dimethylamino)isoxazoles by both thermolysis and photolysis:[47/76]

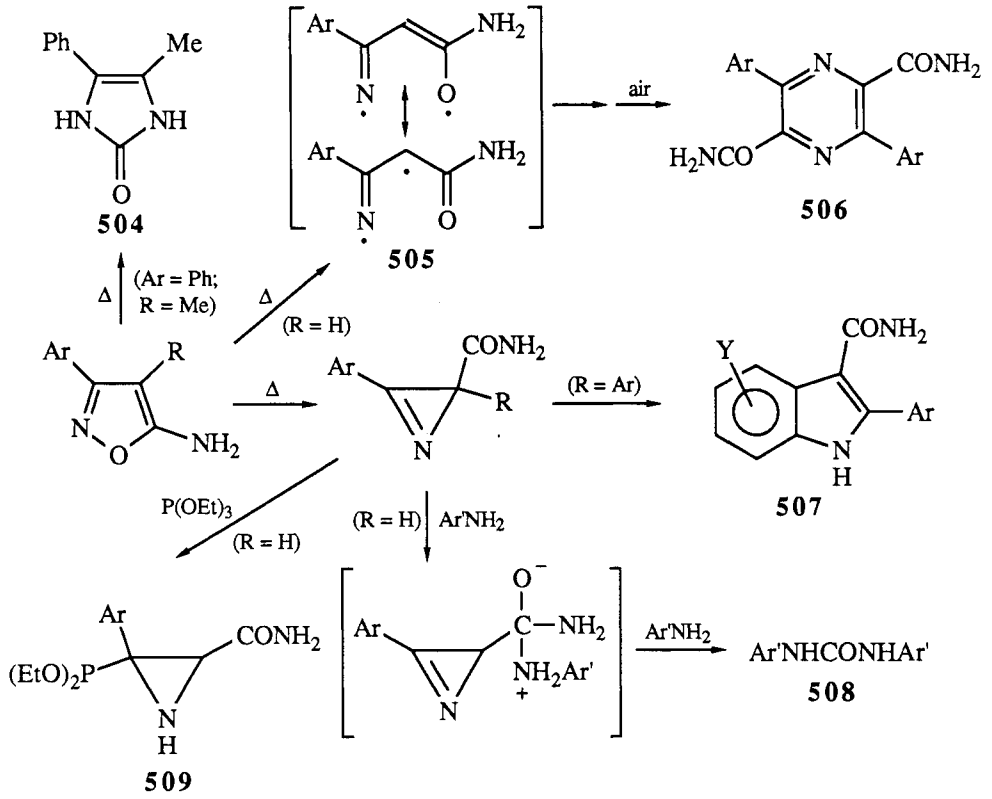
TABLE 1.82. THERMAL ISOMERIZATION OF 5-AMINOISOXAZOLES TO AZIRINES




| Ar | R | R' | Conditions | Yield (%) | References |
|---|---|---|---|---|---|
| Ph | H | H | Refluxing 2-ethoxyethanol, 1 h | 19 | 156/70 |
| Ph | Me | H | Refluxing tetralin, 3 h | 28 | 127/71 |
| Ph | Ph | H | Refluxing decalin, 2 h | 86 | 128/71 |
| | | | Refluxing tetralin, 2 h | 73 | 128/71 |
| 4-$MeC_6H_4$ | Ph | H | Refluxing decalin, 45 min | 52 | 128/71 |
| 4-$ClC_6H_4$ | Ph | H | Refluxing tetralin, 1 h | 36 | 128/71 |
| Ph | H | 4-$ClC_6H_4CH_2$ | Refluxing decalin, 1.5 h | 17 | 137/72 |
| Ph | H | 4-$MeC_6H_4CH_2$ | Refluxing decalin, 2 h | 58 | 137/72 |
| Ph | H | 4-$MeOC_6H_4CH_2$ | Refluxing decalin, 2 h | 12 | 137/72 |
| Ph | Ph | Me | Heating at 150-170° | 60-65 | 98/82 |
| Me | Ph | Me | Heating at 150-170° | 60-65 | 98/82 |
| Ph | Me | Me | Heating at 150-170° | 60-65 | 98/82 |

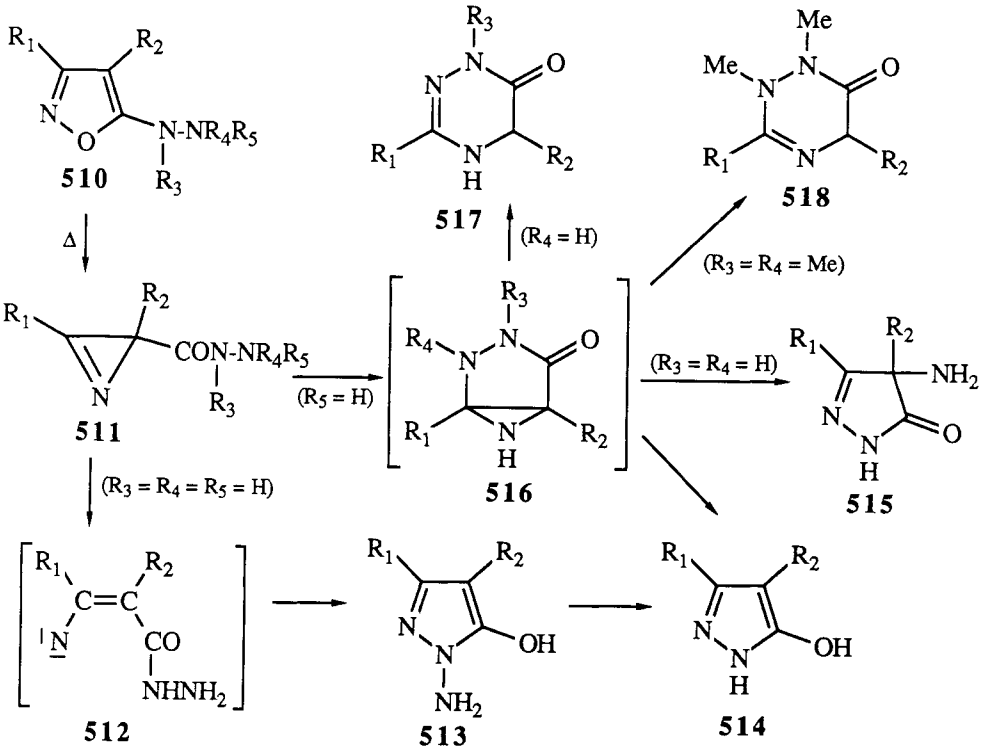



Under different conditions a mixture of products is generally produced, deriving either from another reaction pattern or from decomposition of the initially formed azirine derivative. When 5-amino-4-methyl-3-phenyl (or 3-methyl)-isoxazole was heated at 80°C, isomerization to the imidazolone **504** was observed,[31/52,32/52,127/71] whereas 5-amino-3-arylisoxazoles, when heated in neat-melt or in concentrated solution, dimerize to the pyrazine derivatives **506**, formed directly from the diradical **505** (or its ionic equivalent).[48/70,156/70] Other possible products, depicted in Scheme 1.26, derive from further transformation of the azirine intermediate. For example, starting from 5-amino-3,4-diaryl-isoxazoles, scission of the azirine N–C bond and reclosure to the *ortho* position of the aryl group lead to the indole derivative **507**.[149/74] Heating 5-aminoi-soxazoles in refluxing *o*-toluidine or in *p*-chloroaniline furnishes ureas of structure **508**[48/70,127/71] and boiling in triethyl phosphite results in the addition products **509**.[129/71]



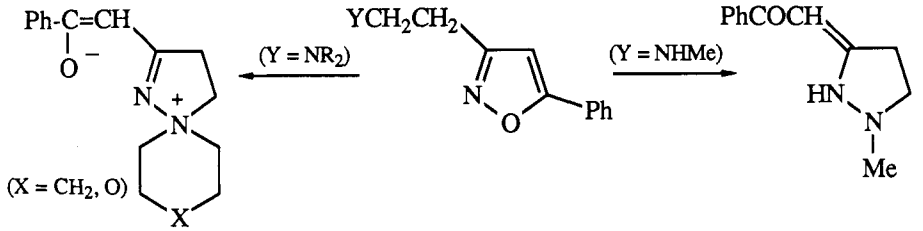

Scheme 1.26.

Remarkable is the behavior of 5-hydrazinoisoxazoles, more or less substituted in the hydrazino moiety. Only the trisubstituted derivative isomerizes to the azirine carbohydrazide **511** in good yields; thermolysis of di- and monomethylated or unsubstituted isoxazolylhydrazines (**510**) affords a mixture of products, containing variable amounts of 1-amino- (**513**), 4-amino- (**515**), or unsubstituted 5-pyrazolones (**514**) and/or of 1,2,4-triazin-6-ones (**517** and **518**)(Scheme 1.27). The intermediacy of the nitrene (**512**) and of the bicyclic aziridine (**516**) has been proposed.[157/72,140/77,98/82]

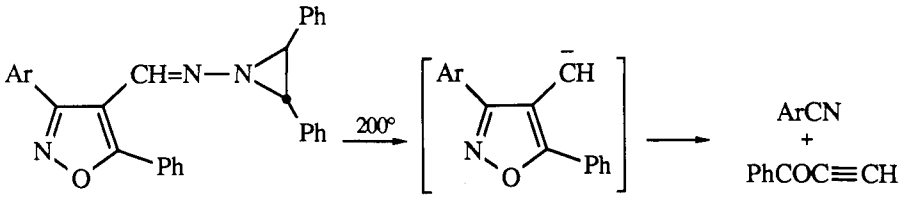


Scheme 1.27.

The presence of a $\beta$-amino substituent in the isoxazole 3-position promoted N–O ring scission with production of a 2-pyrazolinium betaine or of a 3-methylidene 1-methylpyrazolidine:[12/72]

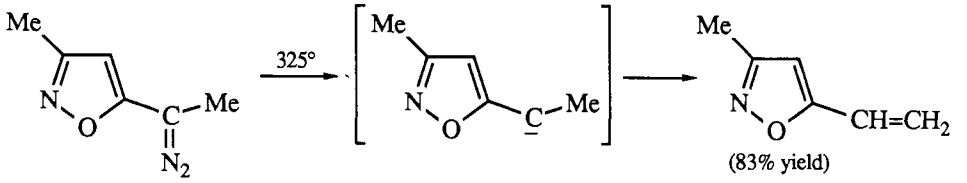


A group potentially able to produce a carbene or a nitrene moiety in the isoxazole 4-position also facilitates ring cleavage. Thus pyrolysis of the isoxazol-4-yl aziridinylimine **519** gives a mixture of the aromatic nitrile and benzoylacetylene;[153/76] a cinnamoyl cyanide has been obtained from 4-azido-3-methyl-5-styrylisoxazole.[229/79]



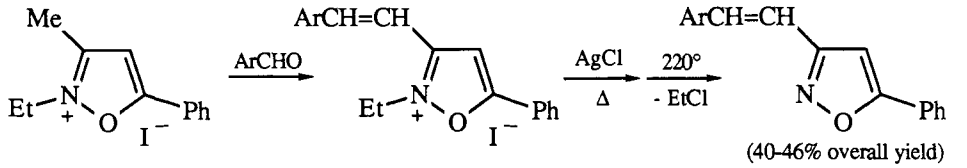

**519**

Similarly, pyrolysis or photolysis of a sodium 5-isoxazolylcarboxaldehyde *p*-tosylhydrazonate provokes scission into a nitrile and propiolaldehyde.[222/79] A carbene moiety in the isoxazole 5-position shows appreciable resistance to fragmentation, and sometimes a hydrogen shift is noted; for example:[222/79]




Thermolysis of 1-(3,4-dimethyl-5-isoxazolyl)-3-aryltriazenes in DMSO or chlorinated solvents gives good yields of 5-amino-3,4-dimethylisoxazole, besides arenes and biaryls.[71/79] The structures of the intermediate radicals have been investigated by $^1$H-CIDNP* spectroscopy.[225/78] For thermal valence isomerization of isoxazole derivatives, leading to different heterocyclic systems, see § 1.4.10.

Isoxazolium salt can be dequaternized by heat. This decomposition has been taken advantage of in the preparation of 3-styrylisoxazoles. As already noted, these compounds cannot be prepared directly by aldol-type condensation on the corresponding 3-methylisoxazoles, while the same condensation readily occurs on the activated 3-methylisoxazolium salt; for example:[19/63]




Other examples of this decomposition reaction involve the preparation of 3-chloro-,[36/79] 3-alkylthio-,[37/79] and 3-aminoisoxazoles.[18/84]

Several in-depth studies have been devoted to the photochemical behavior of isoxazole compounds. Most of them have been found to undergo isomerization

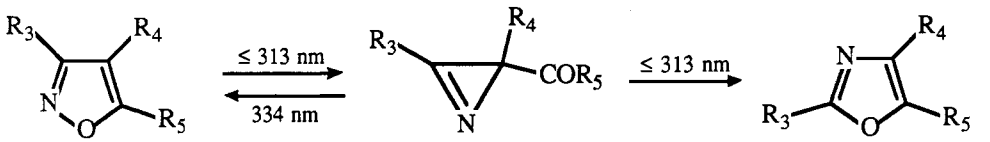
*Chemically induced dynamic nuclear polarization.

to 1-azirines, which, in turn, can rearrange further to different final products. The preparative yields of the photochemical process are usually only moderate. The subject has been briefly reviewed.[13/71,16/75,212/76] Flash-photolysis studies of the parent isoxazole are known.[55/84,150/84,152/84]

The rearrangement 3,5-disubstituted isoxazole → 1-azirine → oxazole shows a remarkable wavelength dependence: irradiation with 313 nm or shorter-wavelength radiation converts the isoxazole or the intermediate 3-acyl-1-azirine into the corresponding 2,5-disubstituted oxazole, whereas irradiation of the azirine at wavelengths greater than 313 nm causes a back-conversion to the isoxazole.[95/66,83/67,92/72,241/73] With 3,5-dimethyl-, 3(5)-methyl-5(3)-phenyl-, or 3,5-diphenylisoxazole, 25–40% conversions to 1-azirines can be obtained under controlled conditions, with quantum yields in the range 0.19–0.05.[92/72,5/76]

Emission spectroscopy, sensitization, and quenching experiments,[83/67,92/72] as well as extended Hückel[92/72] and *ab initio* CI[127/80,16/81] MO calculations, carried out for the parent compounds (isoxazole, 1-azirine-3-carboxaldehyde, oxazole),

TABLE 1.83. PHOTOCHEMICAL CONVERSION OF ISOXAZOLES INTO 1-AZIRINES AND OXAZOLES

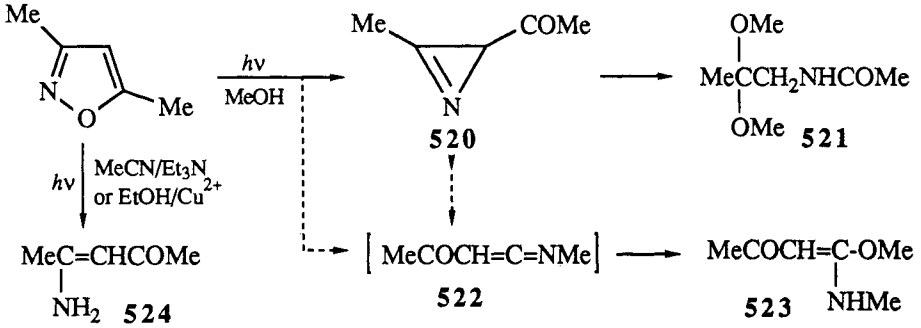



| $R_3$ | $R_4$ | $R_5$ | Conditions[a] | Yields (%) of azirine | Yields (%) of oxazole | References |
|---|---|---|---|---|---|---|
| Ph | H | H | LP, cyclohexane | 11 | 8 | 138/77 |
| COOEt | H | H | MP, diethyl ether | - | 8 | 122/71 |
| Me | H | Me | MP, diethyl ether | ca.40 | - | 5/76 |
| Ph | H | Me | LP, *n*-hexane | 25 | 5 | 92/72 |
| Me | H | Ph | LP, benzene | 25 | - | 92/72 |
| Ph | H | Ph | MP, diethyl ether (253.7 nm) | - | 65 | 83/67 |
| | | | MP, diethyl ether (> 280 nm) | 58 | 2 | 83/67, 241/73 |
| 4-$MeOC_6H_4$ | H | Ph | MP, diethyl ether (> 280 nm) | 35 | - | 83/67 |
| OH | H | Ph | LP, methanol | - | 18 | 5/74 |
| OH | H | $CH(NH_3^+)COO^-$ | | - | 35 | 67/67 |
| Ph | H | Ph | LP, diethyl ether | - | 30 | 18/71 |
| Ph | H | $NH_2$ | HP, diethyl ether | 42 | - | 156/70 |
| 4-$ClC_6H_4$ | H | $NH_2$ | HP, diethyl ether | 28 | - | 129/71 |
| Ph | H | $NHCH_2C_6H_4OMe$ | HP, diethyl ether | 71 | - | 137/72 |
| Ph | Ph | Ph | | - | ca.40 | 34/66 |
| Ph | COMe | Me | MP, benzene | - | 85 | 89/75 |
| Ph | $CMe=CH_2$ | Me | LP, dimethoxyethane | - | 48 | 99/76 |
| Ph | CMe=CHCOOMe | Me | LP, cyclohexane | - | 70 | 99/76 |
| Ph | $CMe=CHCOOCH_2CF_3$ | Me | LP, dimethoxyethane, 45' | 13 | 21 | 99/76 |
| Ph | $CMe=CHCOOCH_2CF_3$ | Me | LP, dimethoxyethane, 90' | - | 56 | 99/76 |
| Me | Me | $NH_2$ | MP, diethyl ether | 72 | - | 4/81 |
| Ph | Me | $NH_2$ | HP, diethyl ether | 18 | - | 127/71 |
| Ph | COOEt | $NH_2$ | HP, THF | - | 20 | 17/72 |

[a] LP = low-pressure Hg lamp; MP = medium-pressure Hg lamp; HP = high-pressure lamp.

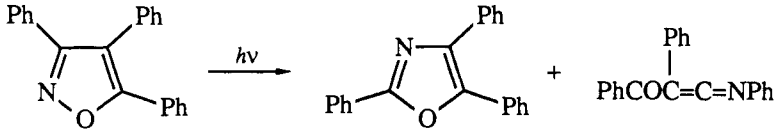
have reasonably clarified the reaction mechanism. The lower-energy excited state of the azirine is associated with a $(n,\pi^*)$ transition localized on the carbonyl chromophore, and the higher-energy excited state, with a $(n,\pi^*)$ transition involving the ketimine chromophore. Intersystem crossing from the singlet to the triplet states leads to azirine C–N bond cleavage and consequently to isoxazole formation in the former case, and to azirine C–C bond cleavage and oxazole formation in the latter case. Nearly concerted processess seem most probable. Some selected examples of preparatively significant photochemical conversions of isoxazoles into 1-azirines and/or oxazoles are presented in Table 1.83.

Solvent participation can alter the composition of the product mixture. Thus irradiation of 3,5-dimethylisoxazole in methanol furnishes the ketal amide **521** and methoxy enone **523**: the former compound has been proposed to proceed




from cleavage of an intermediate 1-azirine (**520**), the latter through an acylketenimine (**522**).[50/73,150/76]

As a matter of fact, the isolation of a benzoyldiphenylketenimine, along with the expected triphenyloxazole, has been reported in the photochemical rearrangement of triphenylisoxazole:[34/66]

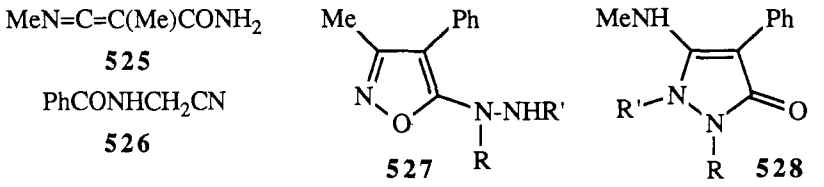



Furthermore, whereas in acetonitrile the main product of the irradiation of 3,5-dimethylisoxazole is the corresponding azirine (**520**), the same solvent in the presence of triethylamine or ethanol in the presence of copper(II) salts causes photoreductive ring cleavage to the amino enone **524** as the main product.[138/74,150/76] A mechanism involving exciplex formation has been proposed.[150/76]

Irradiation of 3,5-diphenylisoxazole in propylamine affords, along with 2,5-diphenyloxazole, small amounts of *N*-propylbenzamide, *N*,*N*′-dipropyl-

benzamidine, and *N*-propyl-2,5-diphenylimidazole, all proceeding from the action of the amine on a presumable intermediate 3-benzoyl-2-phenyl-1-azirine.[178/75]

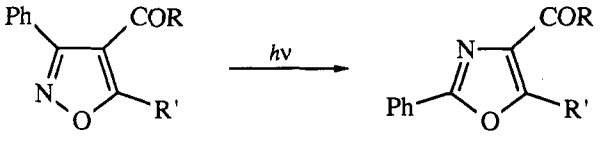
The presence of a functional group linked to the isoxazole ring exerts a more or less strong directive effect toward the formation of one or the other product. Thus, as a general rule, 5-aminoisoxazoles are photo-rearranged to 1-azirine-3-carboxamides in moderate to good yields.[156/70,127/71,128/71,137/72,4/81] The photo-induced process seems more suitable from a preparative standpoint for 4-unsubstituted or alkylsubstituted compounds, whereas thermal isomerization gives better results for 3,4-diaryl-5-aminoisoxazoles.[128/71,137/72] The ketenimine derivative **525** or the malondiamide, produced by hydration, are by-products in the photolysis of 5-amino-3,4-dimethylisoxazole.[4/81] A secondary photo-rearrangement product, benzoylaminoacetonitrile (**526**), can arise along with the expected azirinecarboxamide in the irradiation of 5-amino-3-phenylisoxazole, and its formation and amount are solvent- and wavelength-dependent.[156/70]



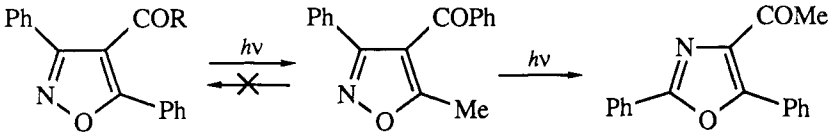

Irradiation of 5-hydrazinylisoxazoles of general structure **527** affords a complex mixture of products whose relative amounts depend on the nature of the substituents: along with compounds **515**, **517**, and **518**, already known to arise from thermolysis (p. 262), a new pyrazolone derivative of structure **528** is isolated, clearly proceeding from a methyl 1,2-shifted intermediate *N*-methylketenimine.[265/78]

Different results are achieved by photolysis of 5-arylideneaminoisoxazoles in triethylamine: albeit in low yields, products of reduction (i.e., bisisoxazolylaminodiarylethanes), oxidation (*N*-isoxazolylbenzamides), and cyclization (isoxazolo[5,4-*b*]pyridines) are formed.[26/76]

3-Hydroxyisoxazoles are photo-isomerized to 4-oxazolin-2-ones,[67/67.5/74] together with small amounts of other by-products. The presence of a carbonyl group, or even of a simple CC double bond, in isoxazole 3- or 4-positions also promoted formation of the isomeric oxazole as the sole product of the photolysis:[18/71,122/71,89/75,99/76]

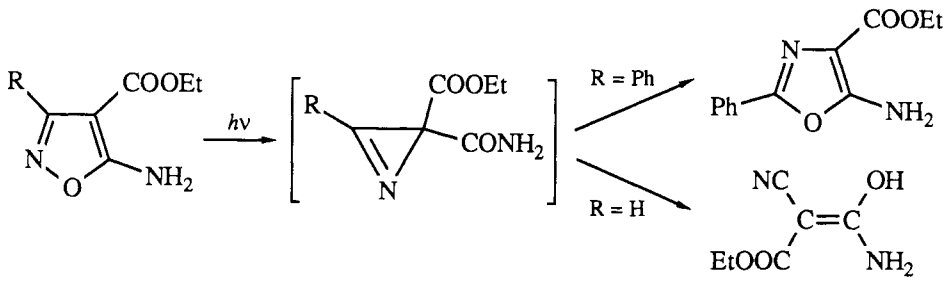


The reaction is not always straightforward, especially when R ≠ R′. For example, 4-acetyl-3,5-diphenylisoxazole (**529**) is rapidly and irreversibly photoisomerized to the 4-benzoyl derivative **530**, which is transformed more slowly into 4-acetyl-2,5-diphenyloxazole (**531**):[89/75]

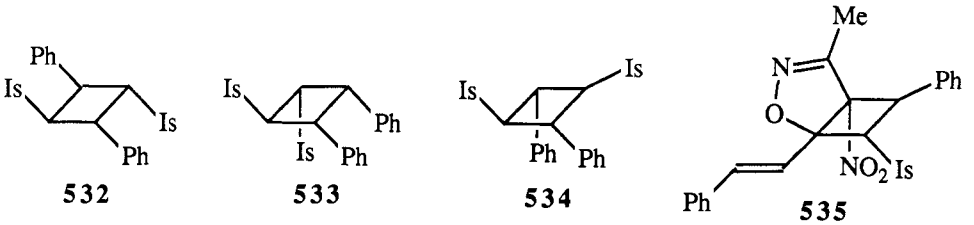



This behavior markedly differs from the thermal treatment of the same ketone, which affords two isomeric oxazole ketones (p. 287). By contrast, irradiation of the 4-trideuteroacetyl-5-methyl-3-phenylisoxazole resulted in a 4-acetyl-5-methyl-2-phenyloxazole that has the deuteration equally distributed between the acetyl and the methyl groups.[99/76] A definitively proved mechanism of these seemingly contradictory results is still lacking.

When both the carbethoxy and amino groups are present, the isomeric oxazole is the prevalent product of the photoisomerization; the absence of a 3-substituent alters the reaction pathway, and the same open-chain product is obtained as from the base-promoted ring cleavage:[17/72]

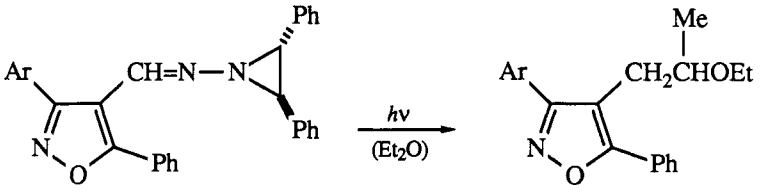



Sometimes the photochemical process concerns the side-chain functionalities and not the ring. 3-Methyl-4-nitro-5-styrylisoxazole was long known to dimerize when exposed to sunlight;[7/42] the structure **532**, of α-truxillic type, has been more recently assured through spectroscopic studies and chemical behavior.[163/77] Excellent yields of the dimer are attained in the solid state or in adsorption on solid silica gel; irradiation in benzene solution or in silica gel cyclohexane slurry furnishes, in addition to **532**, three other dimers, having the structures **533** (δ-truxinic type), **534** (ε-truxillic type) and **535**.[127/79] Formation of the latter dimer, albeit in low yields (0.5–4.5%), evidences the reactivity of the isoxazole 4–5 double bond in [2 + 2] photocycloadditions.




[Is = 3-Methyl-4-nitroisoxazol-5-yl]

The aziridinylimine **536** is photodecomposed by irradiation in diethyl ether into a mixture of *cis*/*trans* stilbene and of the ether **537**, arising from a 4-isoxazolylcarbene;[153/76] the difference with pyrolysis here is striking (p. 293):




(Ar = 4-MeC$_6$H$_4$)

### 1.4.6 Reactions with Nucleophiles

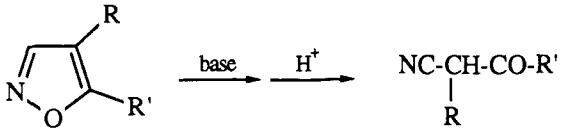
The isoxazole ring is fairly sensitive to the action of nucleophilic reagents, and its reactivity depends strongly on the position and nature of the substituents. As a general rule, the stability of the ring in basic media increases with increasing substitution: monosubstituted isoxazoles are more or less easily ring-cleaved, whereas trisubstituted isoxazoles are usually stable and are more prone to reactions with nucleophiles in the side chains. Quaternization increases the reactivity of the ring toward nucleophilic attack. Here the reactions will be considered separately, depending on whether or not they lead to ring cleavage.

#### *1.4.6.1 Reactions with Ring Cleavage*

##### a. 3-Unsubstituted Isoxazoles

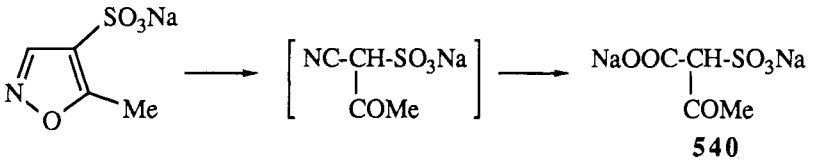
3-Unsubstituted isoxazoles have long been known to be cleaved by bases. As early as 1891, Claisen showed that treatment of 5-phenylisoxazole with sodium ethoxide in absolute ethanol or with aqueous sodium hydroxide at room temperature yields, after acidification, $\omega$-cyanoacetophenone.[3/891] Isoxazole itself is cleaved to the sodium salt of cyanoacetaldehyde;[7/03] when the ring opening is carried out with ammonia in an ethanol solution and a sealed tube at 70°C, a moderate yield of 3-aminoacrylonitrile is obtained as a mixture of stereoisomers.[142/74]

The isomerization of 3-unsubstituted isoxazoles to α-cyanocarbonyl compounds under the influence of bases takes place very easily at room temperature, and no exception is known to the general equation




**538** **539**

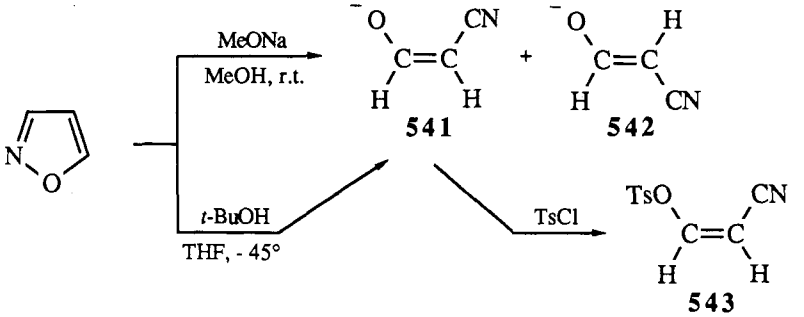
The reaction is carried out most frequently with sodium methoxide or ethoxide in alcohol, but potassium isopropoxide or *tert*-butoxide, sodium amide or hydride, lithium diisopropylamide in anhydrous solvents, as well as aqueous solutions of sodium or potassium hydroxides have also been used. In aqueous solutions, however, the reaction can sometimes proceed further. For example, 5-methylisoxazole-4-sulfonic acid is converted by 30% aqueous sodium hydroxide at room temperature to α-sulfoacetacetic acid disodium salt (**540**):[2/40]




**540**

4-Alkyl(or aryl)-5-arylisoxazoles (**538**: R′ = Ar) are isomerized to α-cyanoketones (**539**) by sodium ethoxide in anhydrous ethanol and subsequent cautious acidification, but with 10–15% aqueous NaOH, the decomposition products RCOONa and $R'CH_2CN$ are obtained.[64/59]

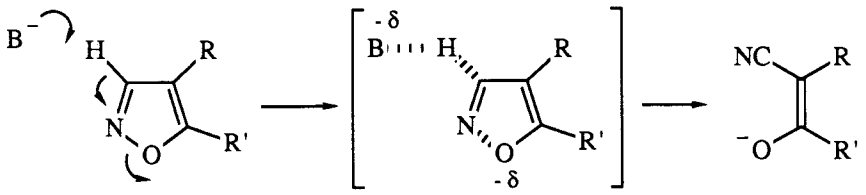
From a stereochemical point of view, the base-promoted isomerization of isoxazole, carried out under standard conditions (i.e., with sodium methoxide in methanol at room temperature) has long been known to yield an equilibrium mixture (45:55) of the stereoisomeric enolates **541** and **542**:[7/03]




Nevertheless, by operating at low temperature (−45°C in tetrahydrofuran) with potassium *t*-butoxide, it has been possible to demonstrate that the ring

cleavage at first furnishes the *cis*-enolate (**541**), which could be trapped by reaction with tosyl chloride to give pure *cis*-β-tosyloxyacrylonitrile (**543**) in high yields.[92/76,187/76] When the same reaction is carried out at −28°C, about 30% of the *trans*-enolate (**542**) is formed.

Kinetic studies[26/54,19/55,28/60,46/66,59/67,151/77] on the isomerization of 3-unsubstituted isoxazoles have established that the reaction is second order (first order in base and in substrate) and that the mechanism of the reaction belongs to a concerted one-stage E2 type rather than to a two-step E1cB type, in which the deprotonation precedes the fast ring opening:



This conclusion is corroborated by the following facts:

1. A primary deuterium isotope effect ($k_H/k_D$ = 3.1 for 5-phenylisoxazole) is observed in the 3-position.
2. Sharp isosbestic points are visible in the UV spectrum of the reaction mixtures on going from reactants to products.
3. Electron-withdrawing substituents in the 4- or 5-position increase the rate (e.g., 4-bromoisoxazole is cleaved 100 times faster than isoxazole).[28/60]
4. Aryl substituents in position 4 are more effective than those in position 5.

Some quantitative data on rate constants and activation parameters are given in Table 1.84.[151/77]

TABLE 1.84. BASE-PROMOTED ISOMERIZATION OF 3-UNSUBSTITUTED ISOXAZOLES[a]

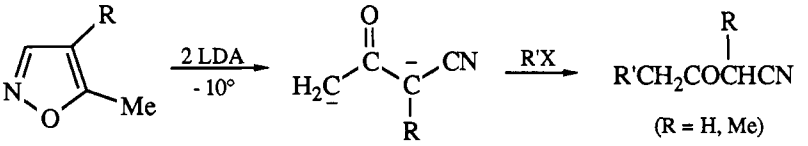
| Isoxazole | Rate constant (k/l mol$^{-1}$ s$^{-1}$) | $E$ (kcal mol$^{-1}$) | DS (cal mol$^{-1}$ K$^{-1}$) |
|---|---|---|---|
| 4-Phenyl | 1.06 x 10$^{-2}$ | 19.6 0.2 | - 3.6 |
| 5-Phenyl | 5.63 x 10$^{-4}$ | 22.1 0.1 | - 1.3 |
| 4-*p*-Bromophenyl | 1.81 x 10$^{-2}$ | 19.0 0.2 | - 4.6 |
| 5-*p*-Bromophenyl | 7.39 x 10$^{-4}$ | 22.0 0.1 | - 0.9 |
| 4-*p*-Nitrophenyl | 8.20 x 10$^{-2}$ | 17.0 0.2 | - 8.5 |
| 5-*p*-Nitrophenyl | 1.74 x 10$^{-3}$ | 20.5 0.2 | - 4.3 |

[a] Reaction with hydroxide ion at 25°C in 96:4 (v/v) water:methanol.

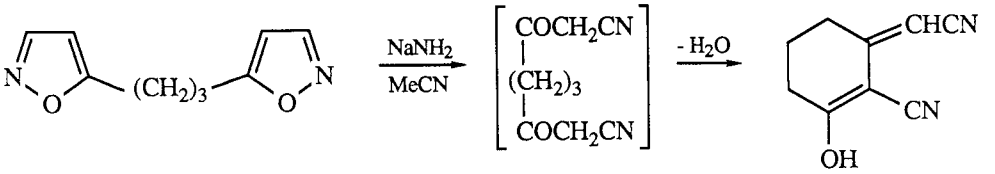
The effective isolation of the α-cyanoketone depends on the stability of the latter compound, which often is unstable and readily dimerizes and/or polymerizes. This is, for example, the case with cyanoacetone, which can be trapped

as its arylhydrazone. As a matter of fact, 5-methylisoxazole has been suggested as a suitable stable synthon to be used instead of cyanoacetone.[40/63,63/70,60/77] Thus it condenses in an alkaline medium with $\alpha,\beta$-unsaturated ketones in a Michael-type addition to give $\alpha$-cyanocyclanones, with aldehydes to give alkylidenecyano ketones, with $\alpha,\beta$-unsaturated ketones in acidic medium to yield six-membered 3-acyllactams, and so on (see also § 1.4.12, p, 393).

Use of 2 Eq of lithium diisopropylamide in tetrahydrofuran (THF) at $-10°C$ provokes the formation of the cyanoketone dianion, which reacts *in situ* with several reagents to give regiospecifically monosubstituted derivatives:[264/78]




Sometimes the expected $\alpha$-cyano ketone can further rearrange intramolecularly, and a different product is obtained. For example, 1,2-di(5-isoxazolyl)-ethane normally isomerizes to 3,6-dioxosuberonitrile,[12/56] whereas 1,3-di(5-isoxazolyl)propane reacts with base to give 2-cyano-3-hydroxy-2-cyclohexen-1-ylideneacetonitrile in quantitative yields:[154/72]

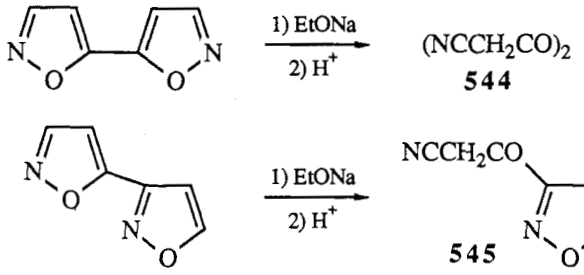



Although now outdated owing to the higher precision and convenience of spectroscopic methods, in the past the quantitative analysis of 3-monosubstituted isoxazoles in mixtures with their 5-isomers was based on the different stability of the two types of compounds toward bases at room temperature.[4/09,37/57,67/58]

On the other hand, treatment with cold alkoxides to purify the 3-monosubstituted isoxazoles from minor amounts of the 5-monosubstituted isomer can still be useful. The latter compound is readily converted into the water-soluble sodium salt of the cyanoketone, whereas the 3-monosubstituted isoxazole remains unaffected under these conditions and is recovered in pure form.

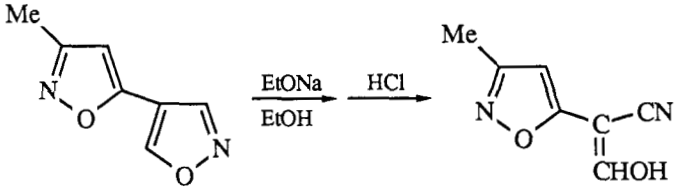
Several examples of base-promoted isomerization of 5-monosubstituted isoxazoles have long been known in which the 5-substituent is an alkyl,[3/892,22/52,11/54,65/59,40/63,230/69,264/78] alkenyl,[8/42,6/47,139/68] aryl,[7/45,11/54,37/57,72/60,27/65,12/71] hydroxyalkyl,[5/49] acyl,[9/42] carboxy, or carbalkoxy.[8/42]

The cleavage of 5,5′-diisoxazole involves both rings, yielding **544**;[53B/58] that of 3,5′-diisoxazole furnishes 3-cyanoacetylisoxazole (**545**):[49/59]

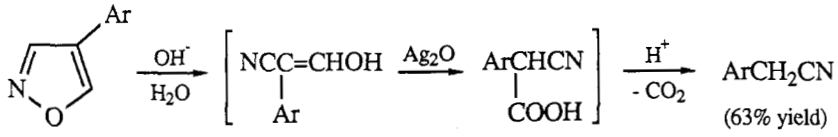



4-Monosubstituted isoxazoles behave similarly, giving α-substituted cyanoacetaldehydes. The substituent may be an alkyl,[19/55,37/67] aryl,[19/55] halogen,[28/60] nitro,[57/66,29/69] carboxy, or carbethoxy group,[8/42,2/47] and the ring cleavage is particularly easy when an electron-withdrawing group is present in the 4-position. In fact, heating of 4-nitroisoxazole with aniline suffices to produce the anil of nitrocyanoacetaldehyde.[1/03]

Treatment of 3′-methyl-4,5′-diisoxazole with sodium ethoxide quantitatively furnishes (3-methyl-5-isoxazolyl)cyanoacetaldehyde, thus emphasizing the different stabilities of 3,5-disubstituted and 3,5-unsubstituted isoxazole rings:[166/71] Heating in dimethyl sulfoxide at 140°C is enough to cleave the isoxazole ring of 4-(6-purinyl)isoxazole almost quantitatively.[117/71]




Sometimes α-cyanoaldehyde is too unstable to be isolated; in this case an oxidative ring cleavage gives directly α-cyanocarboxylic acid or its nitrile derived by decarboxylation. 4-(2′,4′-Dinitro)phenylisoxazole gives 2,4-dinitrobenzyl cyanide by treatment with 10% aqueous sodium hydroxide in the presence of silver oxide:[63/67]

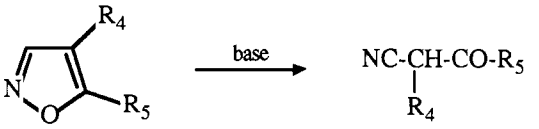



4,5-Disubstituted isoxazoles isomerize similarly to α-substituted α-cyanoketones, and the α-substituents include alkyl,[14/38,64/59,65/59,12/71,264/78] aryl,[64/59,65/59,72D/61,17/63] halogen,[1/36,205/78] sulfonic,[2/40] acyl,[3/65,175/82] or carboxylic residues.[12/13,1/43,24/58,66/59,18/70] The spontaneous ring opening of 3-unsubstituted

isoxazole-4-diazonium salts even in acidic medium should be recalled here (see § 1.4.6.2, p. 320).

Of course, 3-unsubstituted isoxazoles, carrying an amino or an alkoxy group in the 5-position, are transformed by alkoxides into α-cyanocarboxamides or α-cyanocarboxylic esters, respectively. A list of selected examples or ring opening of 3-unsubstituted isoxazoles is presented in Table 1.85.

TABLE 1.85. ISOMERIZATION OF 3-UNSUBSTITUTED ISOXAZOLES TO α-CYANOCARBONYL COMPOUNDS

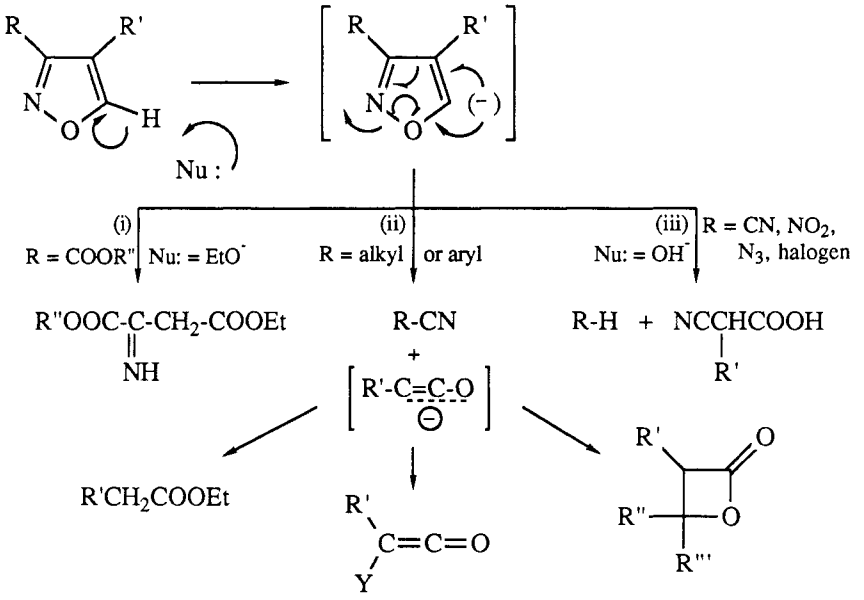



| $R_4$ | $R_5$ | Base and conditions | Product | Yield (%) | References |
|---|---|---|---|---|---|
| H | H | *t*-BuOK, THF, -45° | *cis*-NCCH=CHOK | > 90 | 92/76, 187/76 |
| H | Me | EtONa | NCCH=C(Me)ONa | | 230/69 |
| H | Me | *i*-$Pr_2NLi$, THF, -10°, then RX | $RCH_2COCH_2CN$ | 60 | 264/78 |
| H | $CH=CH_2$ | MeOK, $Et_2O$ | $NCCH=C(OK)CH=CH_2$ | | 139/68 |
| H | $CH_2CH(Me)Et$ | 10% aq. KOH, reflux, 2 days | $EtCH(Me)CH_2COOH$ | | 51/72 |
| H | $Ph_2CHCH_2$ | EtONa | $Ph_2CHCH_2COCH_2CN$ | | 65/59 |
| H | Ph | EtONa | $PhCOCH_2CN$ | | 37/57 |
| H | Ph | $NaNH_2$, xylene | $PhCOCH_2CN$ | 100 | 72/60 |
| H | Ph | NaH, monoglyme/PhH, r.t., then $H^+$ | $PhCOCH_2CN$ | 14 | 12/71 |
| H | 4-$NO_2C_6H_4$ | 0.5 *N* MeONa, MeOH, Δ, then $H^+$ | 4-$NO_2C_6H_4COCH_2CN$ | | 27/65 |
| H | 4-$MeOC_6H_4$ | NaH, monoglyme/PhH, r.t., then $H^+$ | 4-$MeOC_6H_4COCH_2CN$ | 40 | 12/71 |
| H | mesityl | MeONa, MeOH/PhH, then $H^+$ | mesityl-$COCH_2CN$ | 90 | 7/45 |
| Br | H | MeONa | NCCBr=CHONa | | 28/60, 69/59 |
| $NO_2$ | H | MeONa or KOH, MeOH | $NCC(NO_2)$=CHONa | | 57/66, 29/69 |
| $NO_2$ | H | alc. $PhNH_2$, Δ | $NCCH(NO_2)CHO$ | | 69/59 |
| COPh | H | MeONa, MeOH | PhCOCH(CN)CHO | | 4/47 |
| CH(Me)Et | H | 4 *N* KOH, Δ, then $H^+$ | $EtCH(Me)CH_2COOH$ | | 37/67, 56/68 |
| 2,4-$(NO_2)_2C_6H_3$ | H | 10% aq. NaOH, $Ag_2O$, r.t., then $H^+$ | 2,4-$(NO_2)_2C_6H_3CH_2CN$ | 68 | 63/67 |
| $CMe_3$ | $CMe_3$ | EtONa, Δ, then $H^+$ | *t*-BuCOCH(CN)*t*-Bu | | 212/70 |
| Cl | Me | NaOH | MeCOCHClCN | 76 | 205/78 |
| Cl | Me | Piperidine, EtOH, 0° | $^-OC(Me)=C(Cl)CN\ (CH_2)_5NH_2^+$ | 93 | 175/82 |
| $NO_2$ | Me | Pyridine, EtOH, - 5°/0° | $^-OC(Me)=C(NO_2)CN\ PyH^+$ | 98 | 175/82 |
| COMe | Me | EtONa, EtOH, then $H^+$ | $(MeCO)_2CHCN$ | 60 | 3/65 |
| COOEt | Me | EtONa, EtOH, Δ, then $H^+$ | EtOOCCH(CN)COMe | | 24/58 |
| COOEt | OEt | EtONa, EtOH, 5-10°, then $H^+$ | $NCCH(COOEt)_2$ | | 18/70 |
| COOEt | $NH_2$ | 1 *N* NaOH or 10% $Ba(OH)_2$, Δ, then $H^+$ | $EtOOCCH(CN)CONH_2$ | | 66/59 |
| Me | Ph | NaH, monoglyme/PhH, r.t., then $H^+$ | PhCOCH(CN)Me | 72 | 64/59, 12/71 |
| Me | Ph | NaOH | PhCOOH + EtCN | 10-12 | 64/59 |
| 2-$HOC_6H_4$ | Et | $PhNHNH_2$, 170-210° | 1-Ph-4-(2'-$HOC_6H_4$)-5-aminopyrazole | 20 | 17/63 |
| Ph | 2-furyl | EtOH, 45°, then $H^+$ | 2-furyl-COCH(CN)Ph | | 72D/61 |

## b. 5-Unsubstituted Isoxazoles

When isoxazole position 3 is substituted and position 5 is free, the nucleophilic attack occurs at the proton on the latter position. The result of the subsequent ring opening depends on the nature of the substituent in position 3. As a general rule, the reaction requires more severe conditions than does the nucleophilic attack on 3-unsubstituted derivatives: for example, heating with alkoxides or use of stronger bases, such as sodium amide or butyllithium.

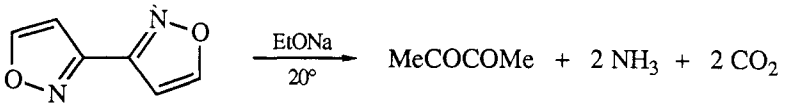
Three main courses of the reaction (Scheme 1.28) can be envisaged:[4/53]




**Scheme 1.28.**

(i) When isoxazole-3-carboxylic acid is heated briefly with sodium ethoxide solution, the sodium salt of an iminooxaloacetic ester is isolated.[8/42] Hydrolysis of this derivative gives carbethoxypyruvic acid. An analogous cleavage is shown by 3-furazanylisoxazoles.[1B/46]

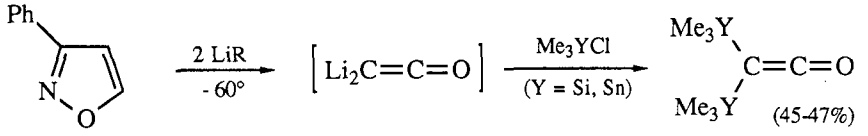
Sometimes the imino derivative can be degraded further; for example, 3,3′-diisoxazole is cleaved by sodium ethoxide even at room temperature to diacetyl, ammonia, and carbon dioxide:[47/59]




(ii) When the substituent in the 3-position is an alkyl or an aryl group, the imino derivative is unstable, and cleavage of both isoxazole N–O and $C_3$–$C_4$

bonds is observed. Of course, a one-step ($\pi_2 + \pi_4$) cycloreversion of the isoxazole 5-anion can also be envisaged (dashed lines in Scheme 1.28). In the presence of a boiling solution of sodium alkoxide, the corresponding nitrile and the acetic ester (substituted or not) are formed directly.[7/03,4/09.2/40,51/72] 3,4-Diphenylisoxazole is cleaved to benzonitrile and phenylacetic acid on prolonged heating with methanolic potassium hydroxide.[7/30] At room temperature 3-substituted isoxazoles are usually stable toward hydroxides or alkoxides. However, when an electron-attracting group is present in the 4-position, the ring cleavage is easier and sometimes proceeds under milder conditions. For example, 4-nitro-3-phenylisoxazole reacts with ethanolic potassium hydroxide on slight heating to give the potassium salt of ethyl nitroacetate.[3/03] Sodium amide in xylene solution at 100°C smoothly cleaves 3-alkyl (or aryl)-isoxazoles into nitriles and sodium acetate.[72/60]

Attack on 3,4-diphenylisoxazole by butyllithium or lithiodialkylamide in THF at −60°C enables the production of lithium phenylethinolate, which at such a low temperature can be trapped with trimethylchlorosilane, carbonyl compounds, or imines to give ketenes, β-lactones, or β-lactams, respectively.[12/79.158/82] The monosubstituted 3-phenylisoxazole, on the other hand, reacts with 2 Eq of lithiumtetramethylpiperidide and subsequently with trimethylchlorosilane or trimethylchlorostannate to yield bistrimethylsilyl (or stannyl)-ketene, possibly formed through the intermediacy of a dilithioketene:[6B/75,12/79]

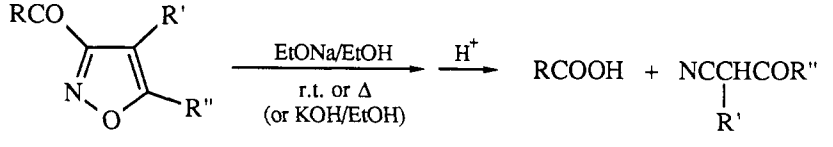



3,4-Dimethylisoxazole is reported to be stable even on long heating with sodium ethoxide solution.[14/38]

(iii) When position 3 is occupied by a good leaving group, such as halogen,[27/61] nitro,[218/71] cyano,[4/32] or azido,[4/31,9/46] removal of the corresponding anion facilitates the formation of a cyanoacetic acid (or ester). This reaction occurs readily with hot alkaline hydroxides or alkoxides, sometimes even at room temperature, as in the case of 3-cyanoisoxazole.

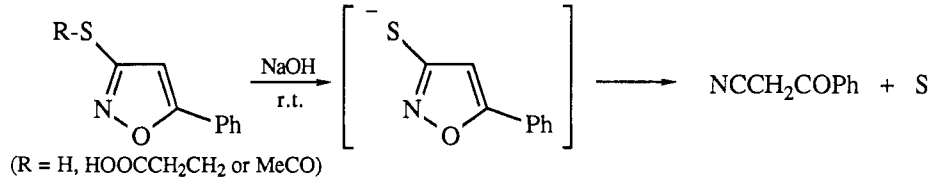
c. 3-Acylisoxazoles and Other Suitably 3-Substituted Isoxazoles

The carbonyl group of 3-acylisoxazoles is preferentially attacked by nucleophiles, independent of whether position 5 is substituted or not. The reaction follows the general pattern

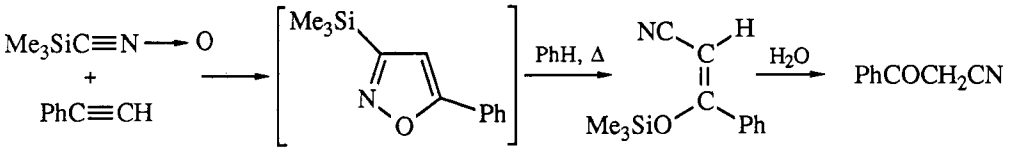


3-Acetyl,[4/32] 3-benzoylisoxazole,[7/47] and 3,3′-diisoxazolyl ketone,[1/46] where R′ and R″ are hydrogen atoms, are cleaved to the acid and to the unstable cyanoacetaldehyde, usually trapped as *p*-nitrophenylhydrazone. When the isoxazole is 5- or 4,5-substituted, more stable α-cyanoketones can be isolated along with the acid RCOOH.[2/46,7/46,5/48,11/56,4/62] For base-catalyzed decarboxylation and subsequent ring opening of isoxazole-3-carboxylic acids, see § 1.4.5, p. 288.

Other isoxazole derivatives prone to ring opening in alkaline medium are 3-mercapto-, 3-acetylthio-, and 3-β-carboxyethylthio-5-phenylisoxazoles:[47/80]




The trimethylsilyl group in position 3 is even more sensitive to thermal and hydrolytic conditions: the cycloadduct from trimethylsilanecarbonitrile oxide and phenylacetylene could not be characterized conveniently, because it decomposes on exposure to atmospheric moisture:[268/82,109/83]

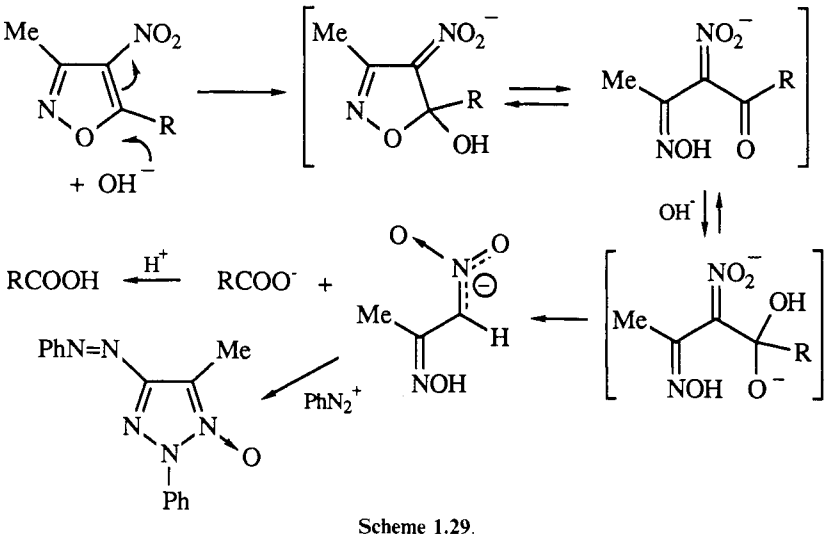



Analogous behavior has been observed for 3-(organomercurio)isoxazoles.[94/84]

### d. 3,5-Di- and Trisubstituted Isoxazoles

When positions 3 and 5 are both substituted, the isoxazole ring is generally stable to alcoholic or aqueous bases. For example, 3,5-dimethyl-, 3,5-diphenyl-, and trimethylisoxazole are not affected even by prolonged treatment with bases under drastic conditions. Moreover, esters, amides, or nitriles of isoxazole carboxylic acids can easily be saponified without cleaving the ring.

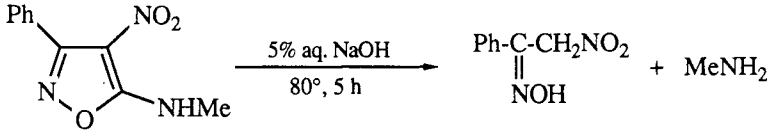
The presence of a strong electron-withdrawing substituent, such as the nitro group, in position 4 introduces a certain degree of lability into the isoxazole ring. Thus 3,5-dimethyl-4-nitroisoxazole is cleaved to acetic acid by prolonged reflux in alkaline solution,[186/80] and the other fragment, presumably the oxime of nitroacetone, can be trapped by treatment with phenyldiazonium chloride to form a triazole.[7/42] The reaction proceeds through a double attack of the hydroxide ions to the activated $C_5$ atom of the isoxazole ring, and has a general applicability, the 3-methyl-4-nitro-5-isoxazolyl moiety behaving as a "masked" carboxylic group (Scheme 1.29).[186/80]



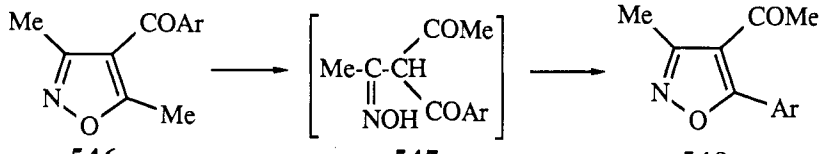
Scheme 1.29.

An interesting procedure for the synthesis of *trans*-cinnamic acids is indeed based on the alkaline hydrolysis (refluxing 1 *N* aqueous sodium hydroxide) of the easily available 3-methyl-4-nitro-5-styrylisoxazoles.[175/80] The same procedure has been extended to syntheses of coumaric[107/83] and arylpropiolic acids.[170/83]

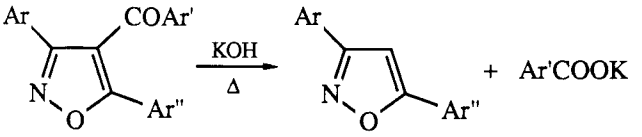
The higher stability of the oxime of $\omega$-nitroacetophenone permits its isolation, along with methylamine, from the alkaline treatment of 5-methylamino-3-phenyl-4-nitroisoxazole:[11/68]



The base-induced rearrangement from the 4-aroylisoxazole **546** to the 4-acetylisoxazole **548** presumably follows a similar mechanistic pattern: ring opening caused by nucleophilic attack at position 5, followed by ring closure of the doubly $\beta$-keto-substituted monoxime (**547**):[218/70]

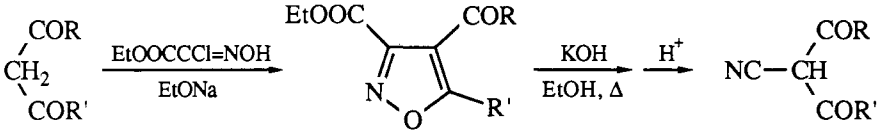


By contrast, 3,5-diaryl-4-aroylisoxazoles are cleaved by potassium hydroxide into 3,5-diarylisoxazoles and potassium benzoate, that is, under preservation of the heterocyclic ring:[145/68]

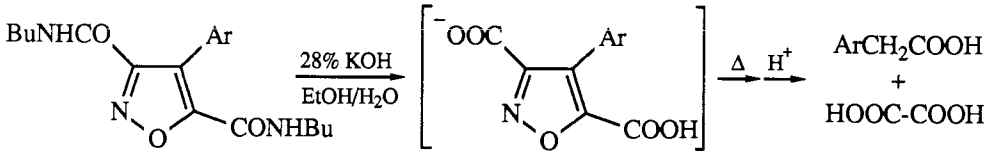



Analogous behavior has been reported for 3,4-diphenyl-5-*p*-methoxybenzoylisoxazole, which is converted in 88% yield to 3,4-diphenylisoxazole by alcoholic potassium hydroxide.[7/30]

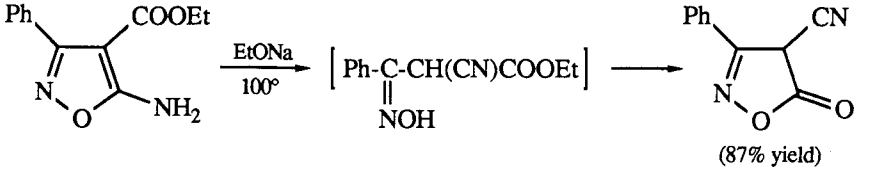
The simultaneous presence of a 3-carbethoxy and a 4-acyl group increases the lability of the isoxazole ring and causes ring opening when the compound is treated with boiling ethanolic potassium hydroxide. Since the isoxazole keto ester can easily be prepared from oxalohydroxamoyl chloride and the sodium salt of β-dicarbonyl derivatives, the entire sequence makes it possible to introduce an α-cyano group into the β-dicarbonyl compound:[12/39]




The alkaline treatment of 4-arylisoxazole-3,5-dicarboxylic acid, obtained *in situ* by saponification of the corresponding *n*-butylamides, follows a different fate: decarboxylation of the 3-carboxylate causes N–O scission, followed by a retro-aldol-type cleavage of the $C_4$–$C_5$ bond, which finally gives a mixture of arylacetic acid and oxalic acid:[20/63]

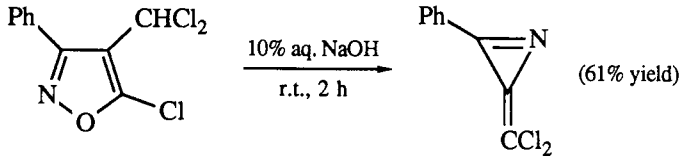



The presence of an amino group in the 5-position, joined with a 4-carbethoxy substituent, also favors the nucleophilic ring opening, followed by a reclosure to an isoxazolinone derivative:[8/60]

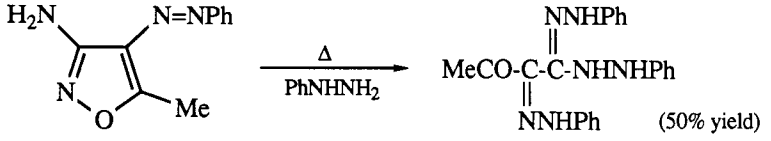



$LiAlH_4$-promoted reductive ring cleavage of 4-cyanoisoxazole with subsequent reclosure to 5-aminoisoxazole was reported in § 1.4.3.1, p. 277.

Remarkable is the formation of an unsaturated azirine derivative by aqueous alkaline treatment of 5-chloro-4-dichloromethyl-3-phenylisoxazole:[244/77]

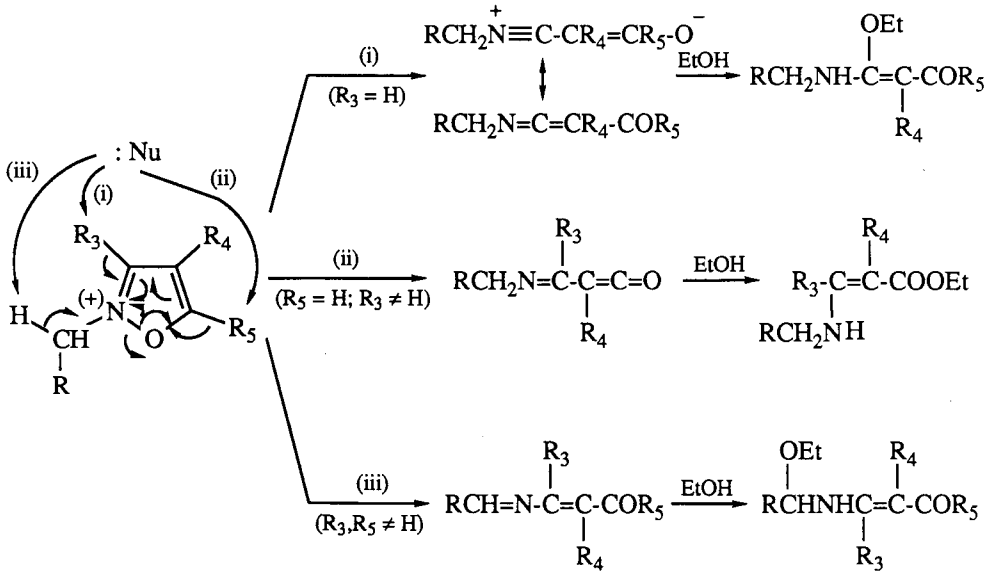



Ring opening has also been reported when 3-amino-5-methyl-4-phenylazoisoxazole is heated at 110°C with excess phenylhydrazine:[295/77]




e. Isoxazolium Salts

The positive charge introduced through quaternization strongly increases the lability of the isoxazole ring toward nucleophilic attack. The site of attack depends on the relative acidities of the protons, their ease of abstraction decreasing in the sequence 3-proton > 5-proton > (N)α-proton. The three mechanistic possibilities are summarized in Scheme 1.30, which exemplifies the reaction with alkaline ethoxide.

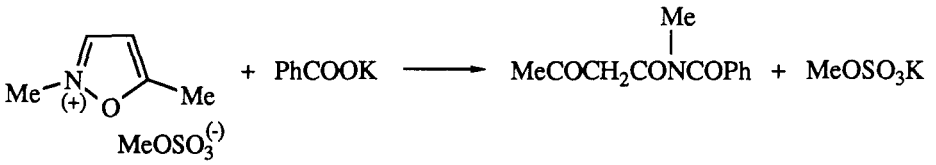



Scheme 1.30.

It is important to emphasize that proton abstraction with subsequent (or concurrent) ring opening is the privileged initial step when hard nucleophiles (such as hydroxides, alkoxides, carboxylates, amines, pyridine) are employed. On the other hand, soft nucleophiles (such as borohydride, butyllithium, or even Grignard reagents) seem to prefer to attack the carbon atom in position 3, yielding 4-isoxazolines or products of further transformation (see below). Of course, the product of primary cleavage, which is usually not separable, if provided with appropriate substituents, can rearrange further and give rise to a large variety of products, both acyclic and homo- or heterocyclic.

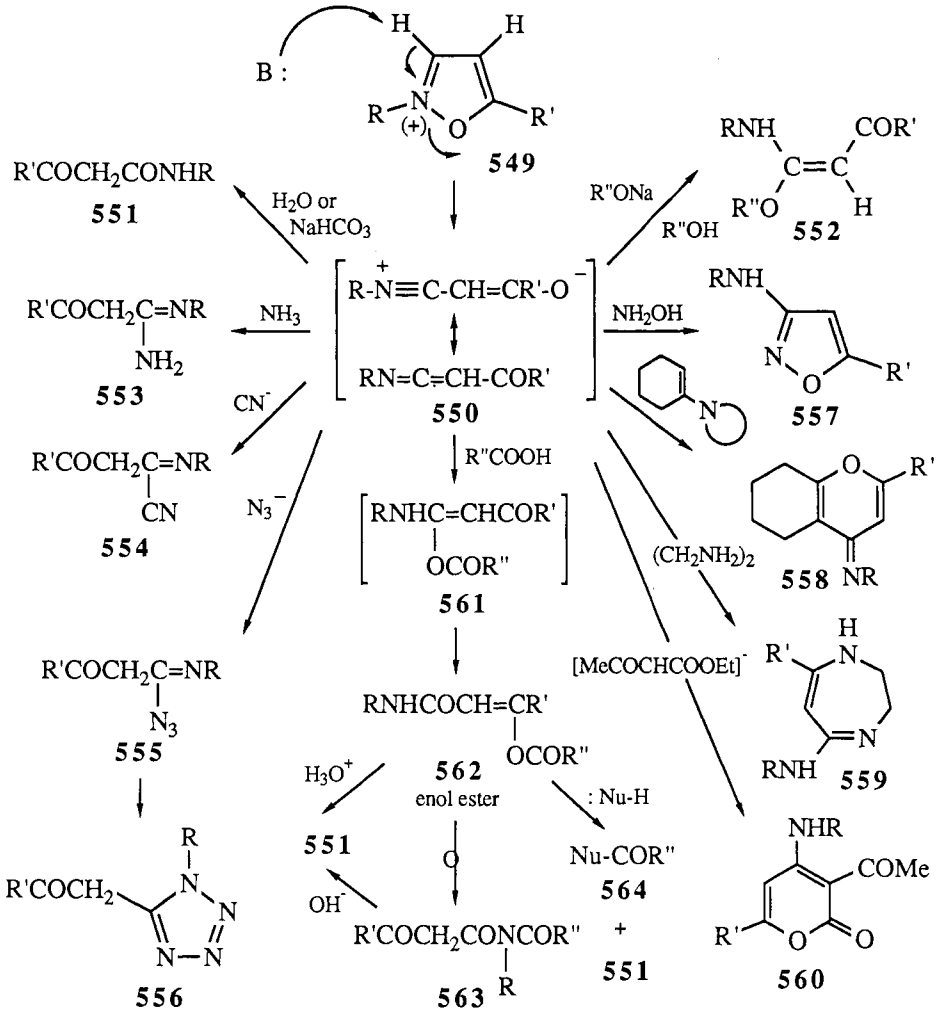
The three different cases are illustrated below.

(i) *3-Unsubstituted isoxazolium salts.* At the beginning of the twentieth century it was discovered that 3-unsubstituted isoxazolium salts are easily cleaved by a great number of strong as well as weak bases, even under the mildest conditions. For example, treatment of 2,5-dimethylisoxazolium methosulfate with potassium benzoate at room temperature in aqueous solution gives acetoacetic acid *N*-methyl-*N*-benzoylamide:[4/09]



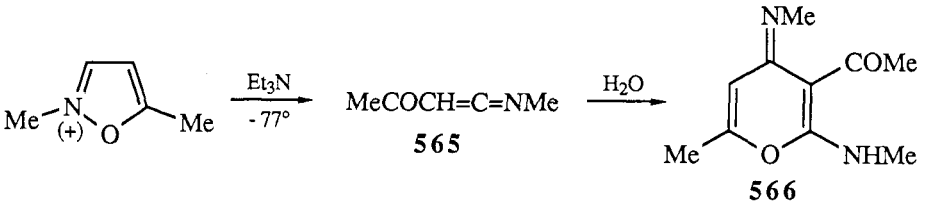

Analogously, 5-methylisoxazolium methiodide is transformed into acetoacetic acid *N*-methylamide by treatment with silver oxide.[4/09] A wide variety of other nucleophiles have also been used, and the utility of the reaction for synthesizing various types of compounds, notably heterocyclic systems, was quickly discovered.[3/10,3/12,4/12,1/16,1/17,1/37,35/61] Nevertheless, it was not until the 1960s that the mechanism of the reaction[35/61,165/66] and its utilization in peptide synthesis[36/61] were explored extensively and clarified by appropriate spectroscopic methods.

The first step of the reaction on a generalized 2,5-disubstituted isoxazolium salt (**549**)(see Scheme 1.31) is the concerted base-promoted proton abstraction and ring opening to give an α-oxoketene imine (**550**), which is highly reactive and usually nonseparable. Only in special cases has the intermediate acylketene imine (**550**) been isolated in a free state or in solution at a low temperature: appropriate examples are those obtained from 5-substituted *N*-*t*-butylisoxazolium perchlorate,[96/66,162/69] from 2,4,5-triphenylisoxazolium perchlorate,[186/78] and from a tricyclic *N*-ethyl (or *N*-methyl)-isoxazolium fluoroborate.[207B/70]



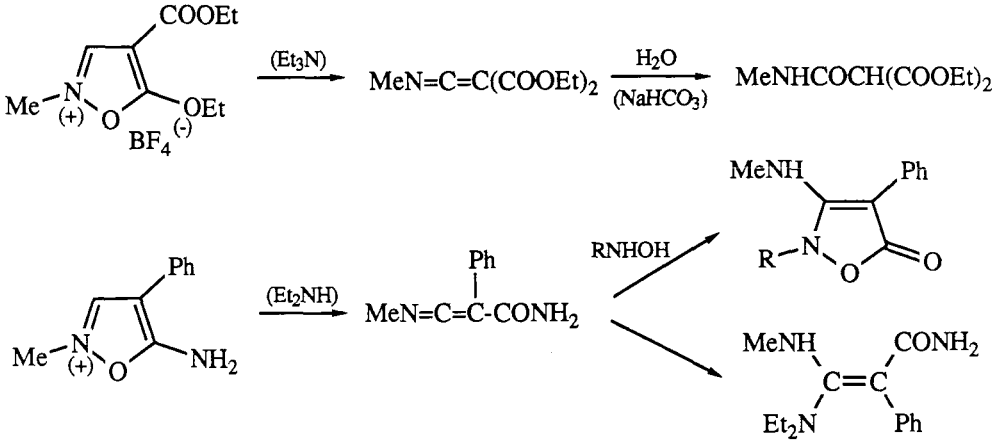

Scheme 1.31.

Attack by a nucleophile takes place on the carbon atom next to the nitrogen, and can be followed by rearrangement or reclosure processes. Thus hydrolysis with hydroxide or, better, with sodium bicarbonate gives the $\beta$-keto acid amide **551**, accompanied in the first case by variable amounts of a so-called "ketoketenimine dimer," possibly a 3-acyl-4-alkylamino-2-pyridone.[165/66] Thus, starting from 2,5-dimethylisoxazolium iodide, the ketenimine **565** could be spectroscopically identified in solution at $-77°C$; treatment with water afforded a 40% yield of the crystalline "dimer" **566**:[183/76]



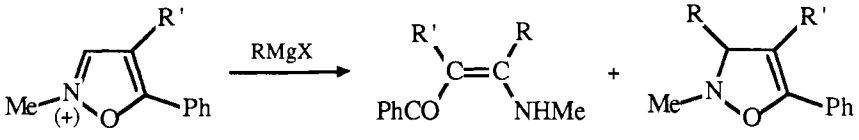

Addition of alkoxides,[3/10,1/17,165/66] ammonia,[181/77] cyanide,[3/10,3/12,1/37] or azide[165/66,204/80] ions is easily accomplished and yields compounds **552**, **553**, **554**, or **555**, respectively. The former compound has an *E*-configuration as indicated by spectroscopic evidence,[165/66] and the last compound, the iminoazide (**555**), is thermally unstable and promptly cyclizes to the tetrazole derivative **556**. Other heterocyclic derivatives can be obtained by treatment of the isoxazolium salts with appropriately substituted nucleophiles: thus hydroxylamine in alkaline solution originates, through a presumable *β*-ketoamidoxime, a 3-alkylamino-isoxazole (**557**),[135/66] whereas the cyclohexanone enamine,[147/68] ethylenediamine[72/75,278/78] or sodium methyl acetoacetate[1/17] give rise, respectively, to a 4-iminopyrone (**558**), 5-amino-2,3-dihydro-1,4-diazepine (**559**), or 4-amino-2-pyrone (**560**) system.

Similar behavior is shown by isoxazolium salts bearing substituents different from alkyl or aryl groups; two examples are shown here:[147/68,10/74]




Grignard reagents can attack 3-unsubstituted isoxazolium salts on either the 3-proton or the 3-carbon atom: competition between ring opening and addition is observed here, depending on the nature of the nucleophilic reagent and the substitution pattern of the substrate, as exemplified in Table 1.86.[211/69,35/74] However, the reaction partner studied far more, because of its implications in the peptide synthesis field, is carboxylic acid (or carboxylate). As usual with other nucleophilic reagents also, the reaction can be carried out in either one or

TABLE I.86



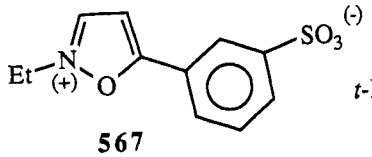

| R | R' | Yield (%) | Yield (%) |
|---|---|---|---|
| Me | Me | 21 | 41 |
| Me | H | 55 | 10 |
| Et | H | 75 | 15 |
| Ph | H | 29 | 57 |
| $CH_2Ph$ | H | - | 95 |
| $CH_2Ph$ | Me | - | 81 |
| $CH_2CH{=}CH_2$ | H | - | 85 |

two steps. In the former case the isoxazolium salt reacts directly with the carboxylate ion; in the latter case it is at first transformed with triethylamine into the ketenimine, which is subsequently condensed with free carboxylic acid. Although never intercepted, the *O*-acylisoamide **561** is supposed to form, which immediately rearranges to the enol ester **562** by transacylation. A concerted[165/66] or two-step process initiated by a rate-determining proton transfer from the undissociated acid[166/80] has been proposed for the addition of the carboxylic acid to the oxoketenimine. In the absence of other reactants, the enol ester **562** slowly rearranges to the imide **563** through an intramolecular *O*,*N*-acyl migration. This rearrangement depends strongly on the size of the N-substituent and is suppressed when the latter is the bulky *t*-butyl group.[110/68] On the contrary, *N*-arylisoxazolium salts are more prone to yield the rearranged imide **563** directly, especially under basic catalysis.[107/67,145/71]

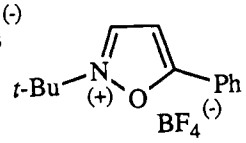
A different approach to preventing *O*,*N*-acyl rearrangement is based on conformational restrictions: for example, the enol esters derived from *N*-methyl (or *N*-ethyl)-4,5-tetramethyleneisoxazolium fluoroborate are stable when refluxed overnight in acetonitrile or dioxane.[207B/70] The kinetics of the rearrangement and of the acid- or base-catalyzed hydrolyses to the corresponding β-keto acid amides (**551**) have been studied and interpreted.[166/80]

Far more important is the availability of the "active" ester **562** to react with an amine (or another nucleophile), giving an amide **564** (or another carboxylic acid derivative, such as an ester or a hydrazide). If applied to protected amino acids, the entire sequence, which can be combined in a one-pot reaction, represents a convenient coupling procedure for peptide bond formation.[36/61,166/66]

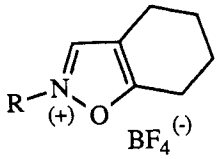
The most widely used isoxazolium salts for peptide synthesis are represented by formulas **567–569**. *N*-Ethyl-5-phenylisoxazolium-3′-sulfonate (**567**),[166/66] the well-known Woodward Reagent K, is a stable, nonhygroscopic inner salt, which is available commercially since several years. Its preparation involves the reaction of 5-phenylisoxazole with chlorosulfonic acid, followed by alkylation with triethyloxonium fluoroborate and subsequent acidic hydrolysis. The



567



568

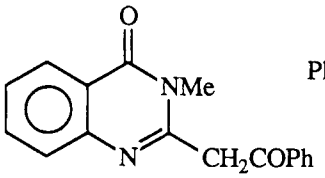


569
(R = Me, Et)

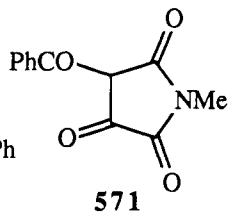
peptide synthesis is accomplished by treating Woodward Reagent K at 0–25°C in a well-stirred nitromethane or acetonitrile suspension with a protected amino acid in the presence of triethylamine. As soon as the isoxazolium salt is dissolved, the esterified second amino acid, generated *in situ* from the hydrochloride and triethylamine, is added.[209/77] The advantages of Woodward Reagent K are high yields, easy separation of the peptide from the water-soluble by-product (**551**: R = Et; R′ = $PhSO_3^-$-*m*), and a relatively low degree of racemization (occurring via azlactones),[166/66,77/67,101/69,159/69,118/75,30/77] albeit still superior to the azide procedure. Some disadvantages of this method should be mentioned: the limited solvent choice, the high cost of the reagent, and the formation of some inert water-insoluble imide (**563**) if the addition of the amino acid ester to the enol ester is not timed carefully. The latter drawback is eliminated by using the isoxazolium salt (**568**),[110/68,170/76] but the diminished reactivity and the intervention of different side reactions lower the utility of this reagent.[159/69,168/70,185/73] Reagent **569** seems to be free of rearrangement and racemization problems, but has been little used in peptide synthesis.[207B/70] It should also be mentioned that benzisoxazolium salts have shown some advantages for peptide synthesis (see Part 2 of this work).

The water solubility of Woodward Reagent K and its by-products has facilitated its use for cyclization of peptides,[38/65] for intermolecular cross-linking of polypeptides,[15B/65] and for protein modifications.[15C/67,15D/67,23/69,23C/69,10/71,10B/71] It has also been employed for the synthesis of glycopeptides,[31/74,19/75] and for esterification processes, as in the synthesis of 1-piperidyl esters of acylamino acids[129/68] or of internucleotide linkages.[57/64] Furthermore, activation with isoxazolium salts during the reduction of carboxylic groups to carbinols with sodium borohydride may be useful when the conventional methods are not applicable.[173/74]

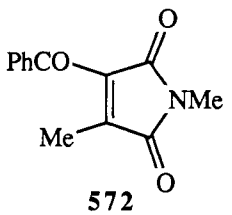
Of course, suitably functionalized carboxylates can react with isoxazolium salts, yielding heterocyclic systems, arising from subsequent recyclization of the primarily formed enol ester or imide: this is the case, for example, with quinazolones (**570**), pyrrolidinetriones (**571**), pyrrolinediones (**572**), and diazepinediones (**573**) obtained by treatment of *N*-methyl-5-phenylisoxazolium methosulfate with anthranilate,[4/12] oxalate,[4/12,1/17] pyruvate,[1/17] or glycine,[165/66] respectively.



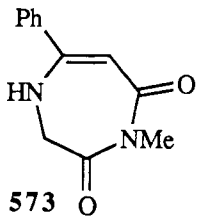

**570**




**571**

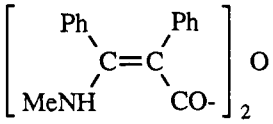



**572**

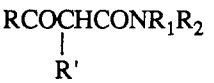



**573**

(ii) *5-Unsubstituted isoxazolium salts.* 2,3-Di- and 2,3,4-trisubstituted isoxazolium salts are deprotonated by strong bases, such as sodium alkoxides, at position 5; consequent ring-opening leads, through a nonisolable ketene intermediate, to β-enamino esters or to the corresponding β-keto esters by subsequent hydrolysis (see the scheme on p. 309).[51/69,175/82] For example, treatment of 2-methyl-3,4-diphenylisoxazolium chloroferrate with sodium methoxide in dry methanol smoothly furnishes methyl α-phenyl-β-methylaminocinnamate.[51/69] Under strictly controlled conditions the intermediate anhydride (**574**) could be isolated. β-Keto acid amides (**575**) are the main products of the reaction of 5-unsubstituted isoxazolium salts with primary and secondary amines.[51/69]



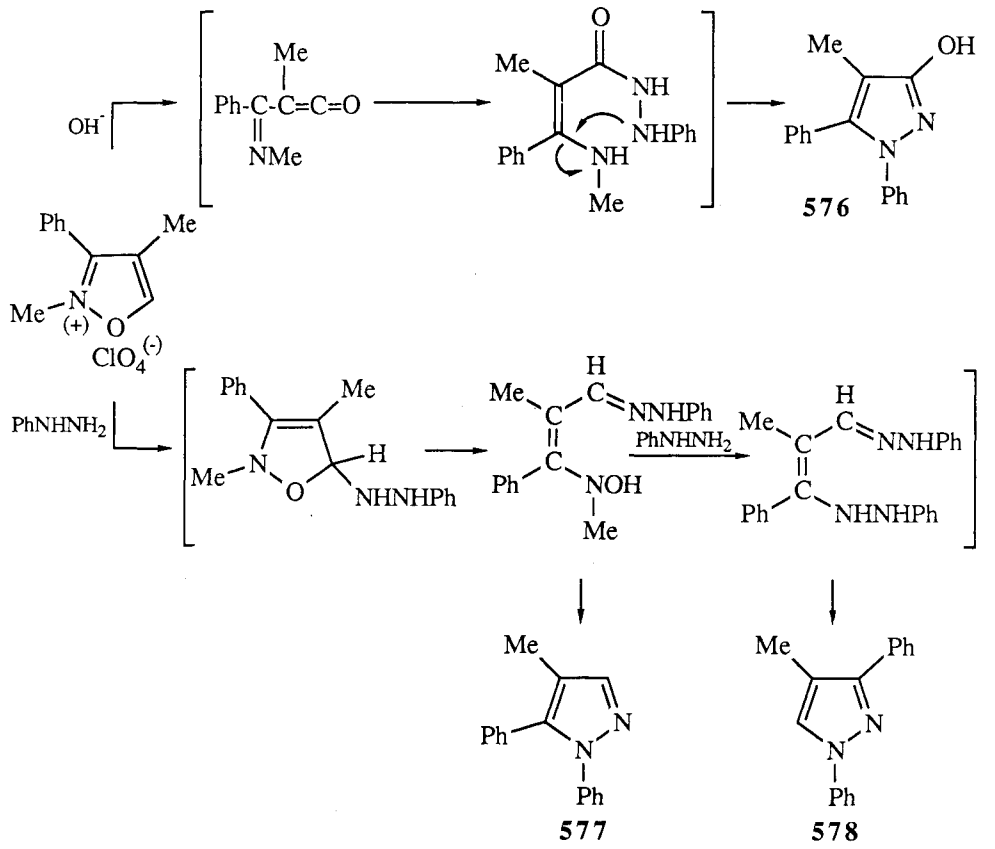

**574**



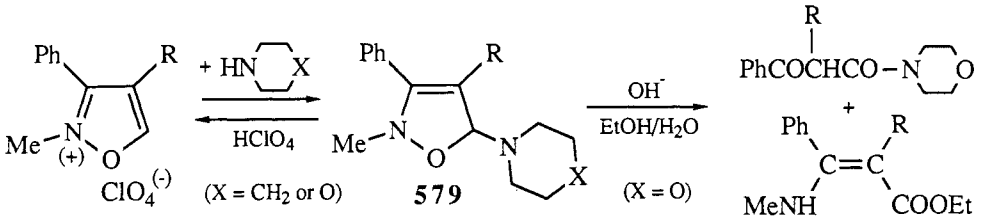

**575**

Weaker bases have been claimed to operate through a different mechanism: ring opening would here be originated by a nucleophilic attack on the carbon atom in position 5, leading to a presumed 3-isoxazoline intermediate. For example, 2,4-dimethyl-3-phenylisoxazolium perchlorate reacts with phenylhydrazine to give either 3-hydroxy-4-methyl-1,5-diphenylpyrazole (**576**)(when the reaction is carried out in the presence of sodium hydroxide) or a mixture of the isomeric pyrazoles **577** and **578** (when the reaction is performed in methylene chloride)(Scheme 1.32).[52/69] Similar results, with the formation of several heterocyclic systems, are obtained by action of carbanionic nucleophiles.[52/69]

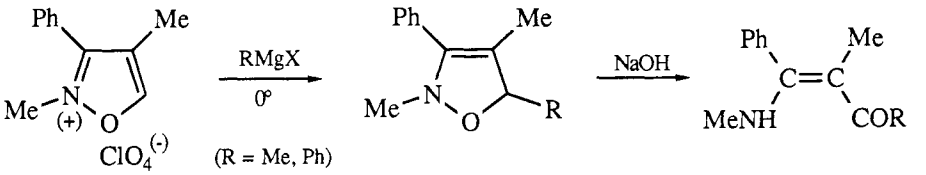
In special cases the 3-isoxazoline derivative could be isolated. Thus treatment of 5-unsubstituted isoxazolium salts with piperidine or morpholine at a low temperature makes it possible to obtain the 5-amino-substituted 3-isoxazoline (**579**) quantitatively, which reverts to the isoxazolium salt by treatment with perchloric acid:[51/69]



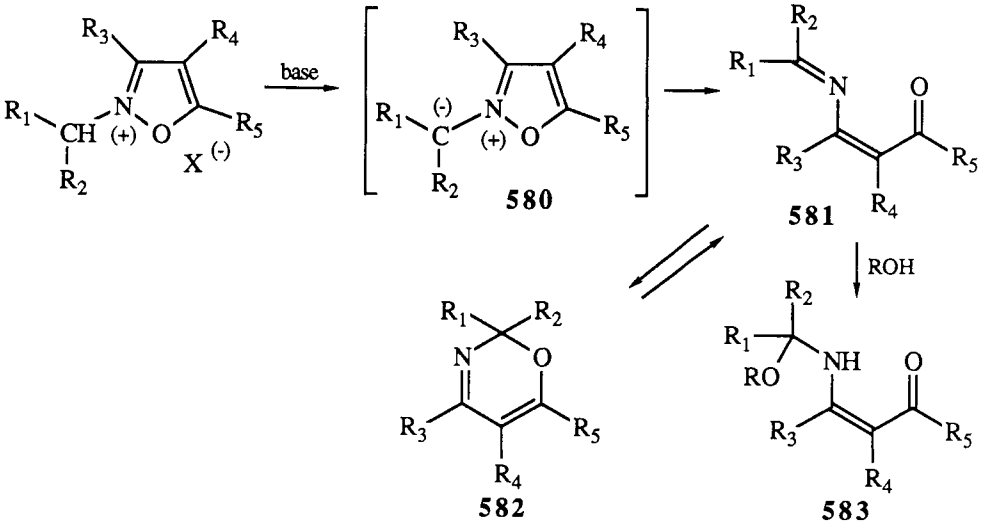
**Scheme 1.32.**



Similarly, addition of alkylmagnesium halides results in isolation of relatively stable 3-isoxazoline derivatives, which suffer ring opening by treatment with sodium hydroxide:[51/69]



(iii) *2,3,5-Tri- and tetrasubstituted isoxazolium salts.* Isoxazolium salts carrying a 3,5-disubstitution pattern (position 4 may be or not substituted) are cleaved by bases to yield the corresponding 3-imino-2-en-1-ones (**581**), which in turn can equilibrate to the tautomeric 2*H*-1,3-oxazines (**582**), or when this is used as a solvent, 1 mol of alcohol can be added to give **583**.[10/62,89/77,163/80] Initial



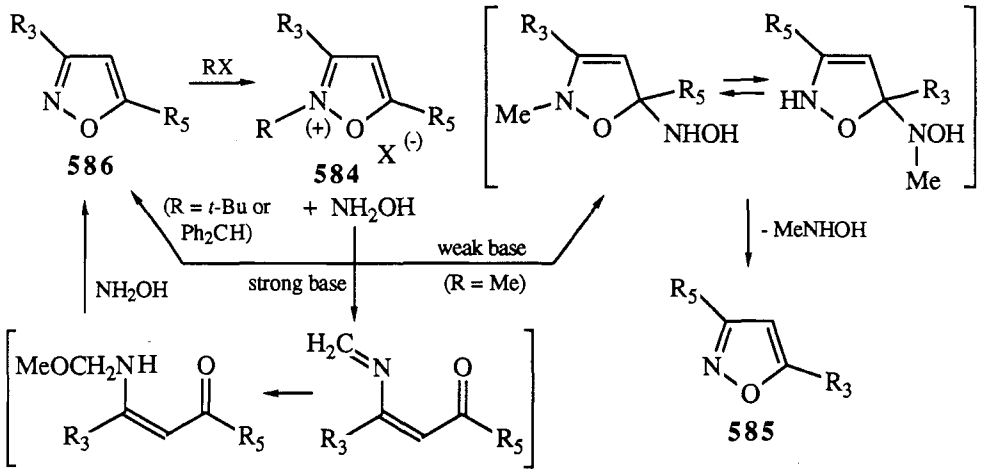

**Scheme 1.33.**

deprotonation at the nitrogen α-position with formation of the ylide **580** is considered the most logical mechanistic starting point (Scheme 1.33). Some examples of this reaction are collected in Table 1.87. It is interesting to note that with *N*-alkyl substitution the stable form is the cyclic 1,3-oxazine (**582**), whereas aryl substitution in the α-position ($R_1$ or $R_2$) make the acyclic form (**581**) more stable.

Of some preparative significance is the reaction of unsymmetrically 3,5-disubstituted *N*-alkylisoxazolium salts (**584**) with hydroxylamine in the presence of either a strong base (potassium methoxide) or a weak base (potassium carbonate). Competition between nitrogen α-proton abstraction and nucleophilic attack on the 5-carbon atom produces a mixture of the two isomeric 3,5-disubstituted isoxazoles. The isoxazole **585**, with inverted $C_3$ and $C_5$ substituents, is obtained primarily in the presence of a weak base, whereas the isolazole **586**, with retained $C_3$ and $C_5$ substituents, increases or becomes the sole product when the reaction takes place under the influence of a strong base or when the α-proton on the nitrogen substituent is absent or is benzylic.[50/78]

TABLE 1.87. ACTION OF BASES ON 2,3,5-TRI- OR TETRA-SUBSTITUTED ISOXAZOLIUM SALTS

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Base | Yields of products 581 | 582 | 583 | References |
|---|---|---|---|---|---|---|---|---|---|---|
| H | H | Me | H | Me | I | MeOK/MeOH | - | - | 48 | 89/77 |
| | | | | | | MeONa/MeOH | - | - | 67 | 89/77 |
| H | H | Me | H | Ph | I | MeOK/MeOH | - | - | 79 | 89/77 |
| | | | | | $ClO_4$ | MeONa/MeOH | - | - | 91 | 89/77 |
| | | | | | $ClO_4$ | MeOK/MeOH | - | - | 46 | 89/77 |
| H | H | Me | H | *t*-Bu | I | MeOK/MeOH | - | - | 75 | 89/77 |
| H | H | Me | H | $CH_2$=CH$(CH_2)_2$ | I | MeOK/MeOH | - | - | 49 | 89/77 |
| H | H | Me | H | $PhCH_2CH_2$ | I | MeOK/MeOH | - | - | 72 | 89/77 |
| | | | | | | *t*-BuOK/*t*-BuOH | - | - | 44 | 89/77 |
| H | H | Ph | H | Ph | $ClO_4$ | DBU | - | 63 | - | 163/80 |
| H | H | Ph | Ph | Ph | $FeCl_4$ | dil. NaOH | - | 50 | - | 10/62, 163/80 |
| Me | H | Me | H | $PhCH_2CH_2$ | I | MeOK/MeOH | - | - | 78 | 89/77 |
| Ph | Me | Me | H | Me | $ClO_4$ | MeOK | 83 | - | - | 163/80 |
| Ph | Me | Me | H | Ph | $ClO_4$ | MeOK | 73 | - | - | 163/80 |
| Ph | Ph | Me | H | Me | $ClO_4$ | DBU or MeOK | 87 | - | - | 163/80 |
| 4-$MeC_6H_4$ | 4-$MeC_6H_4$ | Me | H | Me | $ClO_4$ | MeOK | 89 | - | - | 163/80 |
| Ph | Ph | Me | H | Ph | $ClO_4$ | MeOK | 41 | - | - | 163/80 |
| 9-Fluorenyl | | Me | H | Me | $ClO_4$ | DBU | 75 | - | - | 163/80 |
| 9-Fluorenyl | | Me | H | Ph | $ClO_4$ | DBU | 46 | - | - | 163/80 |



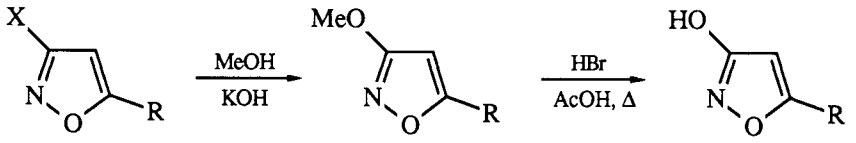

Thus isomerization of 3-methyl-5-*t*-butylisoxazole, the sole product obtained by oximation of the corresponding $\beta$-diketone, to 3-*t*-butyl-5-methylisoxazole can be accomplished through *N*-methylation and subsequent treatment with hydroxylamine hydrochloride in the presence of potassium carbonate. Finally, it should be remembered that the base-promoted ring opening of an isoxazolium salt is the key step in the Stork–Ohashi isoxazole aromatization reaction (see § 1.4.12, p. 408).

### *1.4.6.2 Reactions Without Ring Cleavage*

#### a. Substitution Reactions on Ring Atoms

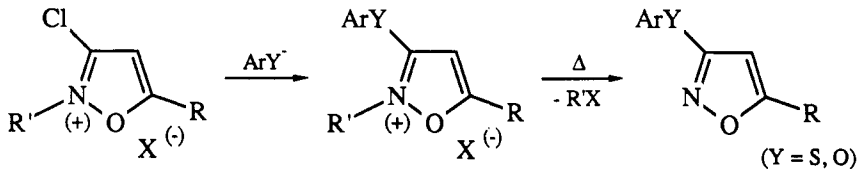
Halogen atoms and, more rarely, other electron-withdrawing groups in positions 3 and 5 of the isoxazole ring are more or less rapidly substituted by nucleophiles. Whereas halogen atoms in position 4 resemble the aryl halides in their stability toward nucleophiles, the displacement reaction is strongly activated in position 3 and especially in position 5, provided that the other position (5 or 3, respectively) is suitably substituted, in order to avoid ring opening (see above). As expected, bromine is substituted faster than chlorine.

The substitution of the 3-halogen by the methoxy group is a well-known reaction,[1/09] and is usually carried out by heating with methanolic potassium hydroxide. The reaction has been resumed and generalized more recently,[27/61,189/68,78/69] and has largely been used in connection with synthetic routes toward the important naturally occurring ibotenic acid (**1**) and muscimol (**2**). In fact, these 3-hydroxyisoxazole derivatives are easily obtained by acidic hydrolysis of the corresponding 3-methoxy (or benzyloxy) derivatives:[124/65.125/65,38/66]

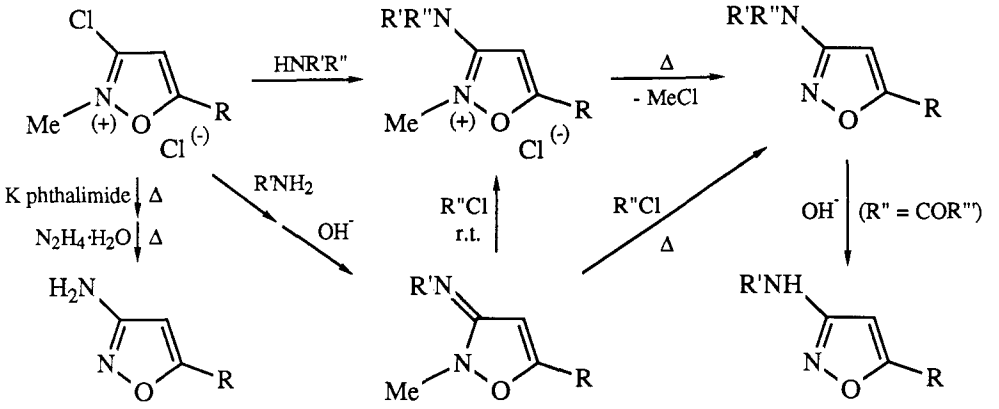



Analogously, 3-nitroisoxazoles can be transformed into 3-hydroxy- or 3-alkoxyisoxazoles.[30/63,78/66,130B/67,218/72,224/73]

3-Chloroisoxazolium salts are reported to be easily hydrolyzed with alkali to the corresponding 4-isoxazolin-3-one;[36/79] reactions with sodium hydrosulfide,[220/68,127/77,36/79] phenols,[37/79] thiophenols,[37/79] thiols,[37/79] or aniline[220/68,175/79,18/84] give rise to 4-isoxazolin-3-thiones, 3-phenoxy-, 3-phenyl-(or 3-alkyl)thio-, or 3-anilinoisoxazolium salts, respectively. In some cases pyrolysis of these compounds affords the isoxazoles:[36/79,37/79]

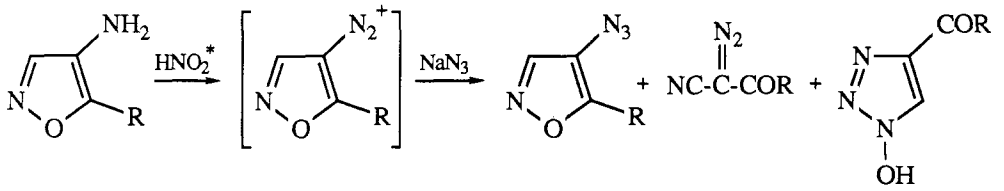



These reactions, expanded to other primary amines and to secondary amines, as well as to potassium phthalimide, have recently been applied in a versatile synthesis of unsubstituted, *N*-mono- and *N,N*-disubstituted 3-aminoisoxazoles, as illustrated in the following scheme:[18/84]



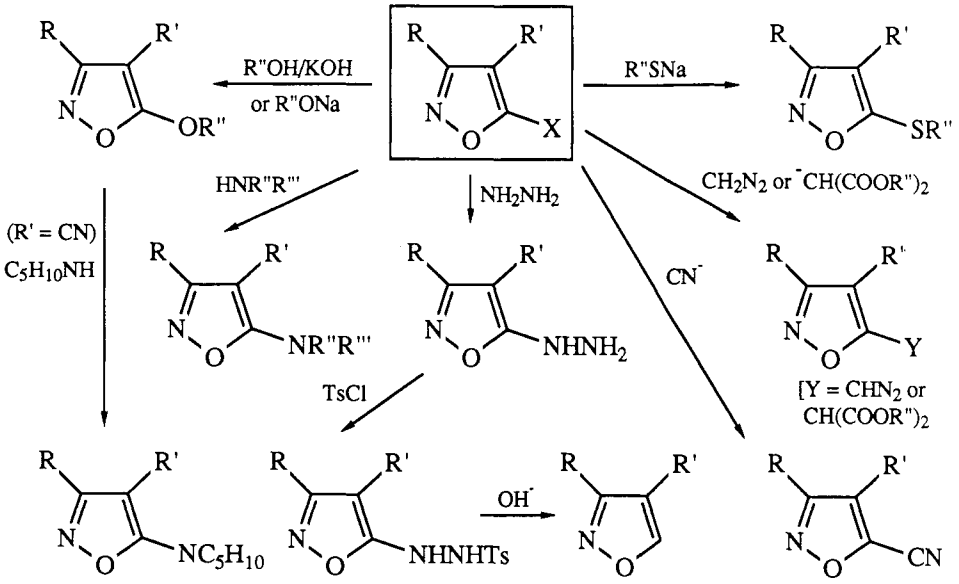

3-Iodo-5-phenylisoxazole has been prepared from the 3-amino derivative through nitrosation and subsequent treatment with potassium iodide.[177/77] 4-Diazonium salts have been used to prepare 4-iodo-,[8/21] 4-chloro,[4/41,4/46,8/46] or 4-hydroxyisoxazoles.[4/46]

The preparation of 3-unsubstituted 4-azidoisoxazoles through diazotization of the corresponding amines is made difficult by the high instability of the intermediate diazonium salts, which deprotonate and ring cleave spontaneously to give mainly the α-cyanodiazo ketone and a 1-hydroxy-4-aryl-1,2,3-triazole:[152/83,305/83]




| R | * | Products ratio(%) |
|---|---|---|
| Me | $NaNO_2/H_2SO_4$ | 8.5 : 72 : 0 |
| *t*-Bu | $NaNO_2/H_2SO_4$ | 0 : 44 : 35.5 |
| *t*-Bu | $(NO)_2SO_4/H^+$ | 30 : 20 : 0 |

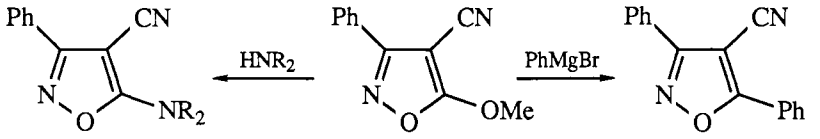
5-Haloisoxazoles are readily available from 5-isoxazolinones by treatment with phosphorus oxyhalides in the presence of a tertiary base or through a 1,3-dipolar cycloaddition of nitrile oxides to 1,1-dihaloethylenes. The halogen atom can be replaced by a variety of nucleophilic reagents. Thus isoxazol-5-thiols,[54/66,102/67] 5-alkoxy-,[17/65,40/70,202/70,177/77,67/78,185/84] 5-alkylthio-,[76/59,17/65,54/66,102/67,40/70,202/70,152/72,177/77,185/84] and 5-aminoisoxazoles[8/53,76/59,17/65,182/71,29/77,177/77,67/78,80/83,185/84] are easily prepared (Scheme 1.34).




**Scheme 1.34.**

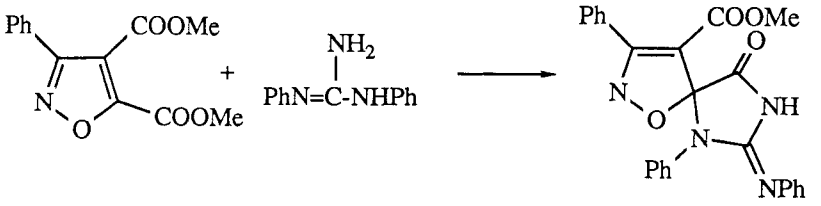
Sometimes other pathways become competitive: whereas use of dimethylamine in anhydrous benzene makes it possible to obtain excellent yields of the 5-dimethylamino compound, the same reaction in 95% ethanol leads to an open-chain product: the oxime of α-benzoylpropionic acid *N*,*N*-dimethylamide.[17/65] Carbanionic nucleophiles, such as diazomethane, sodium cyanide, or sodium diethylmalonate, also replace the halogen atom.[76/59,123/75,159/82]

Reaction with hydrazine hydrate furnishes the 5-hydrazino compound, which can be converted to the 5-unsubstituted isoxazole through tosylation and alkaline degradation.[144/69] 1,1-Dimethylhydrazine leads to slightly different results.[140/77] If suitably activated, for example, by a cyano group in position 4, even a 5-methoxy group can be displaced by dimethylamine or by phenylmagnesium bromide:[8/60,11/73]




By contrast, treatment of ethyl 5-methoxy-3-phenylisoxazole-4-carboxylate with dimethylamine furnishes 5-methoxy-3-phenylisoxazole, without displacement at the 5-position.[11/73]

A heterocyclic spiro compound is the result of the reaction of dimethyl 3-phenylisoxazole-4,5-dicarboxylate with 1,3-diphenylguanidine:[160/80]




The acid-promoted hydrolysis of 5-aminoisoxazoles to 5-isoxazolinones will be dealt with in Part 2 of this work.

### b. Substitution Reactions in Side Chains

Halogenomethylisoxazoles are readily attacked by several nucleophiles, the halogen atom being displaced under more or less mild conditions. A kinetic study of the solvolysis of 1-(4-isoxazolyl)ethyl bromide in 80% ethanol pointed out that the reactivity of the α-halogen in position 4 is very close to that of a benzylic halogen.[191/76] Preparatively, the carbinol is obtained by cautious treatment of the same bromide with a mixture of tetrahydrofuran and water. In other cases the same transformation has conveniently been accomplished with freshly precipitated lead oxide.[68/58,76/60]

Dichloromethylisoxazoles have been used to prepare 3- and 5-isoxazole aldehydes.[2/42.2/43,10/64] A 5-dibromoacetylisoxazole has been transformed into the corresponding α-hydroxy acid by treatment with aqueous base.[224/81]

Iodides,[22/52,107/66] ethers,[40/57,72/62,66/72,86/72,162/72] esters,[26/55] thio ethers,[22/75,152/77] and phosphoric[12/54] or thiophosphoric esters[195/70,56/77] containing the isoxazole nucleus have been prepared by attack of the appropriate nucleophile on the halogen-carrying carbon atom of the side chain in the 3-, 4-, or 5-position. Also, carbanionic nucleophiles such as sodium diethyl malonate,[14/63,162/80] sodium ethyl acetoacetate,[148B/71] and sodium cyanide,[26/55,106/67,54/68,151/76] readily displace a halogen atom, provided that the isoxazole ring is stable enough toward base-promoted ring cleavage (see above).

Treatment of 3,5-bis(chloromethyl)isoxazole with the appropriate dithiolates led to macrocyclic polyethers, containing isoxazole units.[198/83] Similar macrocyclic structures arose by treatment of 3-chloromethyl-5-hydroxymethylisoxazole with sodium hydride.[99B/79]

By far the most frequently utilized displacement reaction in isoxazole side chains has been ammonolysis. Formation of a primary amine can be accomplished either by aqueous ammonia (the method has proved especially valuable in the synthesis of muscimol and related compounds) or with the potassium phthalimide method. A further indirect method is based on the nucleophilic displacement by sodium azide, followed by selective catalytic hydrogenation.[68/66,188/68] Sometimes α-elimination can compete with substitution, and low yields of the dimeric alkene compound can result, instead of the expected amino derivative,[28/71,224/81] as in the following example:

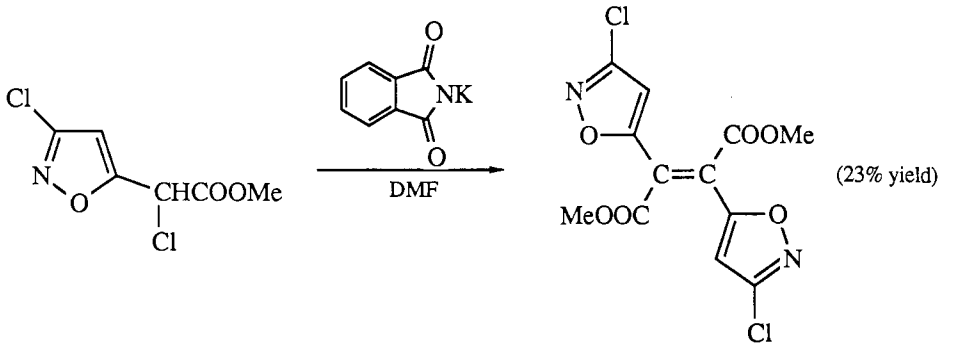
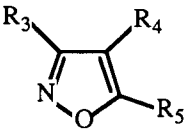



TABLE 1.88. NUCLEOPHILIC SUBSTITUTIONS IN ISOXAZOLE SIDE CHAINS




| $R_3$ | $R_4$ | $R_5$ | Modified side chain | Nucleophile and conditions | Yield (%) | References |
|---|---|---|---|---|---|---|
| H | CHBrMe | H | 4-CHOHMe | $H_2O$/THF (1:1), r.t., 2.5 h | 60 | 191/76 |
| H | H | CHBrCOOH | 5-CH($NH_3^+$)$COO^-$ | conc. $NH_4OH$, r.t. | 80 | 38/66 |
| OH | H | $CH_2Cl$ | 5-$CH_2NH_2$ | conc. $NH_4OH$, 90°, 16 h | 100 | 124/65 |
| $CH_2Cl$ | H | Me | 3-$CH_2CN$ | NaCN, $PhCH_2N^+Et_3Cl^-$ in $CH_2Cl_2$ | 47 | 151/76 |
| $CH_2Cl$ | H | Me | 3-$CH_2SnMe_3$ | $Me_3SnLi$, THF, -60° | 45 | 193/80 |
| H | $CH_2Cl$ | Me | 4-$CH_2OH$ | PbO in $H_2O$, 3 h reflux | 60 | 68/58 |
| Me | H | $CH_2Br$ | 5-$CH_2SMe$ | MeSNa, MeOH, <0°, then r.t. 12 h | 95 | 152/77 |
| $CH_2$-CH-(O) | H | Ph | 3-$CHOHCH_2N(CH_2)_5$ | $(CH_2)_5NH$,benzene, 3 h reflux | 91 | 137/73 |
| Ph | H | $CH_2Cl$ | 5-$CH_2ONH_2$ | PhthNOH, MeCN, $Et_3N$, reflux, then $N_2H_4{\cdot}H_2O$ in EtOH | 52 | 162/72 |
| Ph | H | $CH_2Br$ | 5-$CH_2NH_2$ | HMT, conc.HCl, $CHCl_3$/MeOH,1 h reflux | 73 | 51/66 |
| Ph | H | $CH_2Br$ | 5-$CH_2OPh$ | PhOH, $K_2CO_3$, acetone, 6 h reflux | 40 | 86/72 |
| Me | $CH_2Cl$ | Me | 4-$CH_2OAc$ | AcOK/AcOH, 100°, 5 h | 55 | 202/66 |
| Me | $CH_2Cl$ | Me | 4-$CH_2SnMe_3$ | $Me_3SnLi$, THF, - 60° | 40 | 193/80 |
| Me | $CH_2Cl$ | Me | 4-$CH_2CHAc_2$ | $CH_2(COMe)_2$, $K_2CO_3$, acetone, 17 h reflux | 61 | 148B/71 |
| Me | $CH_2Cl$ | Me | 4-$CH_2$-(Me, O) | Me-(OMgI) in $Et_2O$, HMPA, r.t. | 41 | 177/73 |
| Me | $CH_2Cl$ | Me | 4-[1-(6-nitro)benz-imidazolyl]methyl | 6-nitrobenzimidazole Na salt, DMF, 18 h reflux | 33 | 99/77 |
| Me | Br | $CH_2Br$ | 5-$CH_2C(NH_2)$=NH | thiourea, EtOH, | | 50/81 |
| Ph | $CH_2Cl$ | Me | 4-$CH_2NMe_2$ | $Me_2NH$, toluene, 110°, 10 h | 87.5 | 54/68 |
| $CH_2Cl$ | Ph | Ph | 3-$CH_2COOH$ | KCN, 90% EtOH, 2 h reflux, then KOH | 78 | 106/67 |
| Ph | $CH_2Br$ | Ph | 4-$CH_2OMe$ | MeONa, MeOH, reflux | | 72/62 |

Secondary amines are active nucleophiles and cause both substitution of halogen atoms and cleavage of epoxide rings to give amino alcohols.

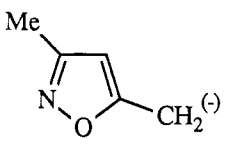
Sometimes, as with 3-bromoacetyl-5-methylisoxazole, yields of the direct ammonolysis (urotropine method) are low. Substitution with secondary amines occurs readily on the corresponding semicarbazones, which can subsequently be hydrolyzed. Ammonia, behaving as a base, does not give substitution, but gives rise to closure to isoxazolyltriazinone.[5/61] Selected examples of nucleophilic substitution reactions in isoxazole side chains have been collected in Table 1.88.

### 1.4.7 Carbanionic Condensations

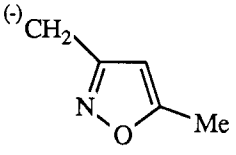
As in other nitrogen heterocyclic systems, such as pyridine and quinoline, protons at the α-position of alkylisoxazoles are relatively acidic and more or less easily removed by bases, giving rise to condensation reactions with a variety of electrophilic reagents. The α-proton abstraction is particularly easy for the 5-position, and is activated either by quaternization of the ring or by the presence of a suitable substituent in position 4. Nonactivated compounds require a strong base in order to produce the carbanion (metallation), whereas properly activated compounds enter the condensation reactions already under catalysis of tertiary amines or similar bases. The two mechanistic types are discussed separately below.

#### *1.4.7.1 Metallation*

The reactivity of 3,5-dimethylisoxazole has been well reviewed.[84/77,87B/79,224/80] Taking this compound as a typical example, MINDO/2 calculations show that formation of the 5-isoxazole carbanion **587** is favored over formation of the




**587**

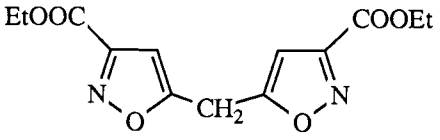



**588**

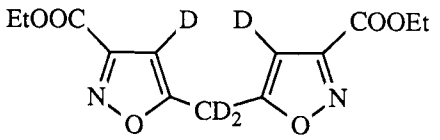
3-carbanion **588** by about 7 kcal/mol. In line with this prediction, deuteration experiments (treatment with butyllithium in THF, then quenching with deuterium oxide) demonstrated that deuterium is incorporated regioselectively at the 5-methyl group. Kinetic measurements show that the hydrogen–deuterium exchange is 280 times faster at the 5-methyl than at the 3-methyl position, although on the whole it appears to be slower than in the case of 2-picoline and quinaldine. Furthermore, the deuteration rate is slowed by the

presence of electron-repelling groups and accelerated by electron-withdrawing substituents in the 4-position of the isoxazole ring.[23/76] Similar results have been obtained in hydrogen–deuterium exchange studies for other 4-substituted 3,5-dimethylisoxazoles.[163/68,169/69]

From a preparative point of view, metallation can be performed by a variety of bases. Those used most frequently are butyllithium or lithium diisopropylamide in tetrahydrofuran at $-78°C$ and $-50°C$, respectively, and sodium or lithium amide in liquid ammonia. Sodium methoxide has been used with the doubly activated methylene group of the bisisoxazolylmethane **589**, which is even more acidic than the alcoholic OH hydrogen, giving an insoluble sodium salt. It is worth noting that in this case deuteration with $CD_3ONa$ and $CD_3OD$ furnishes the tetradeuterated compound **590**.[32/72]



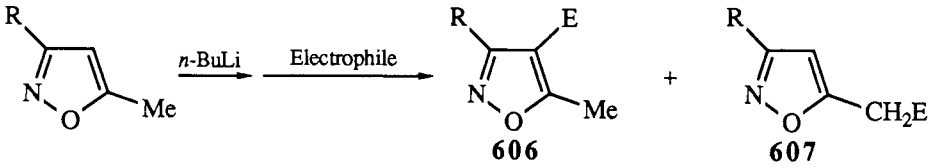
**589**



**590**

Normally, the carbanion formed in the 5α-position reacts with a large number of electrophiles. A summary of the possible products of these reactions is illustrated in Scheme 1.35.

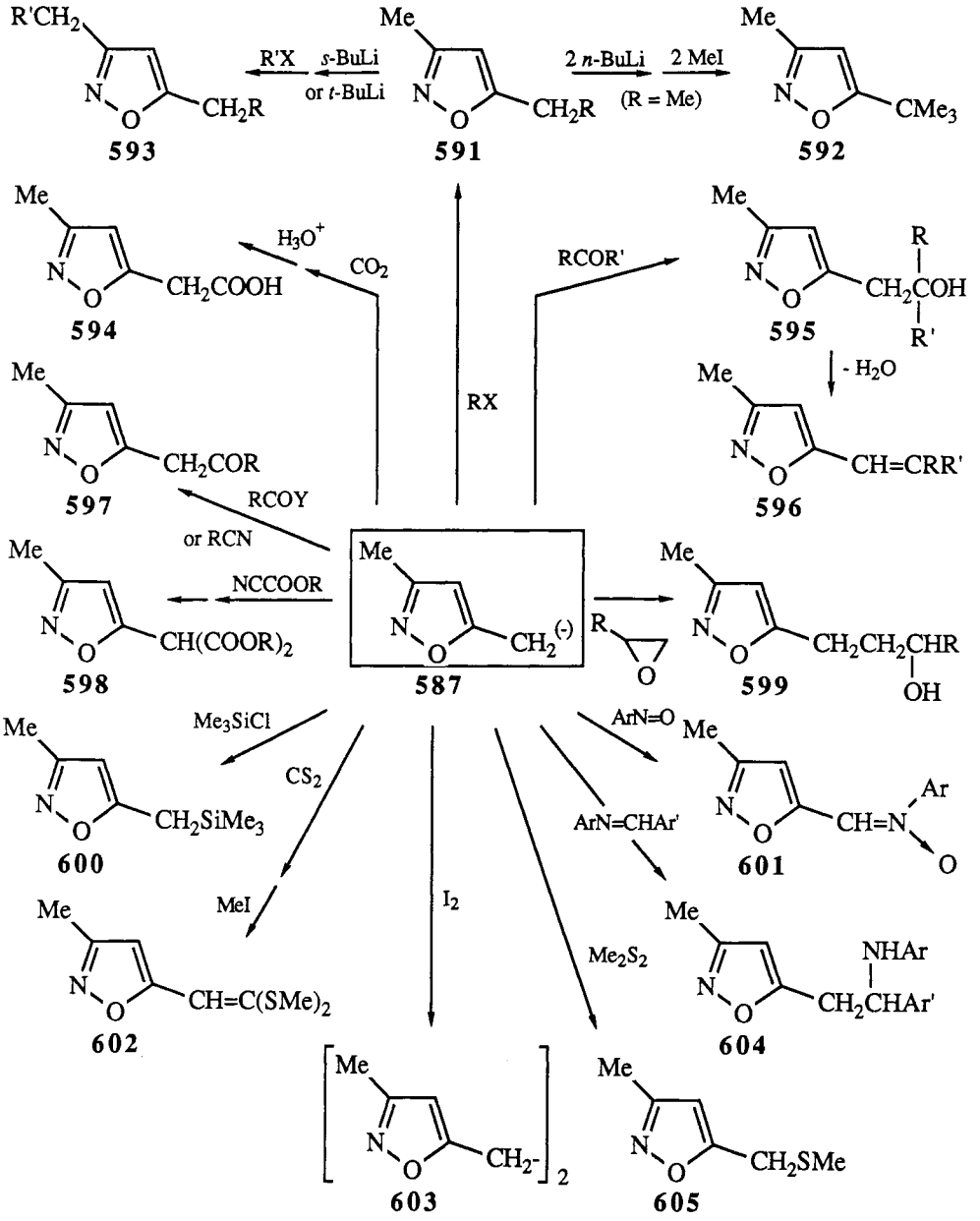
Sometimes other sites can compete with the 5α-position, depending on the substitution pattern and on the nature of the base employed in carbanion formation. When a substituent is present in the isoxazole 3-position, which is apt to coordinate the lithium reagent, metallation of the neighboring 4-position can be more or less pronounced. Such substituents are, for example, methoxy, methoxymethyl, or dimethylaminomethyl. As the following prospect shows, treatment of these compounds with butyllithium and then with an electrophile (carbon dioxide or methyl iodide) furnishes a mixture of two products, arising either from ring or side-chain metallation, respectively:[130/68,151/76]



**606** **607**

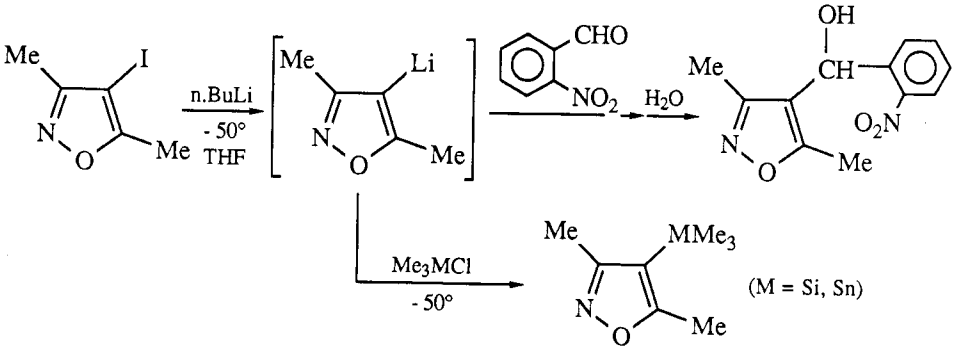
| R | E | Ratio **606** : **607** |
|---|---|---|
| MeO | COOH | 18 : 82 |
| $MeOCH_2$ | Me | 20 : 80 |
| $Me_2NCH_2$ | Me | 50 : 50 |

Metallation with the noncoordinating lithium diisopropylamide gives, as expected, compounds **607** exclusively.[151/76]


R'CH2
R'X
s-BuLi
or t-BuLi
Me
2 n-BuLi
2 MeI
(R = Me)
CH2R
CMe3
593
591
592
H3O+
CO2
RCOR'
CH2COOH
CH2COH
R
R'
594
595
- H2O
CH=CRR'
596
RX
CH2COR
597
RCOY
or RCN
NCCOOR
CH(COOR)2
598
587
CH2(-)
R
CH2CH2CHR
OH
599
Me3SiCl
ArN=O
CS2
CH2SiMe3
600
ArN=CHAr'
CH=N
Ar
O
601
MeI
I2
Me2S2
CH=C(SMe)2
602
NHAr
CH2CHAr'
604
CH2-
2
603
CH2SMe
605

Scheme 1.35.

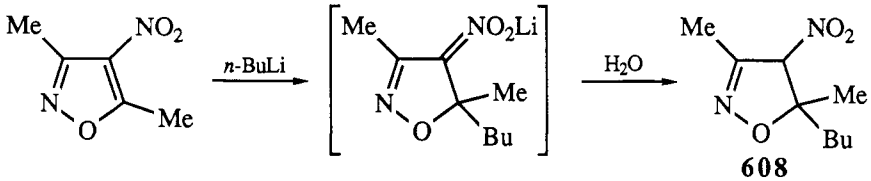
When position 5 is substituted by an aryl group, for example, only ring metallation occurs. Thus 3-methoxy-5-arylisoxazole or 3-aryl-5-alkoxy (or 5-alkylthio- or 5-chloro)isoxazoles react with *n*-butyllithium and then with carbon dioxide to yield the corresponding 3,5-disubstituted isoxazole-4-carboxylic acids; using iodine instead of $CO_2$, the corresponding 4-iododerivative is obtained.[40/70] When 3,5-dialkylisoxazoles are involved, metallation in position 4 can be achieved through the 4-iododerivative only by metal–halogen exchange, as the following example shows:[131/75,193/80]




For substitution in the 4-position through Grignard reagents, see § 1.4.8, p. 333.

The size of the reacting base is also critical for site selectivity: while *n*-butyllithium does not metallate 3-methyl-5-pentylisoxazole (**591**: R = *n*-$C_4H_9$), use of *s*-BuLi or *t*-BuLi in THF or ether at −78°C specifically metallates the 3α-position, thus leading to 3-alkylation only (i.e., to compounds of structure **593**).[237/81] By contrast, 3,5-dimethylisoxazole is reported to be di- and trialkylated at position 5α by increasing amounts of sodium amide and methyl iodide in liquid ammonia, first giving 3-methyl-5-isopropylisoxazole and finally, 5-*t*-butyl-3-methylisoxazole (**592**).[40/73]

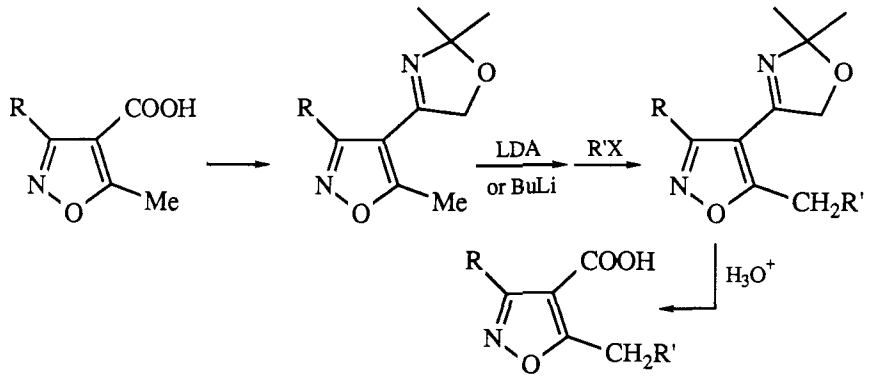
The insertion of a nitro group in the isoxazole 4-position cancels the side-chain lithiation in favor of a nucleophilic attack on the $C_5$ atom, which leads to isoxazoline (**608**) as the predominant product along with unaltered starting material:



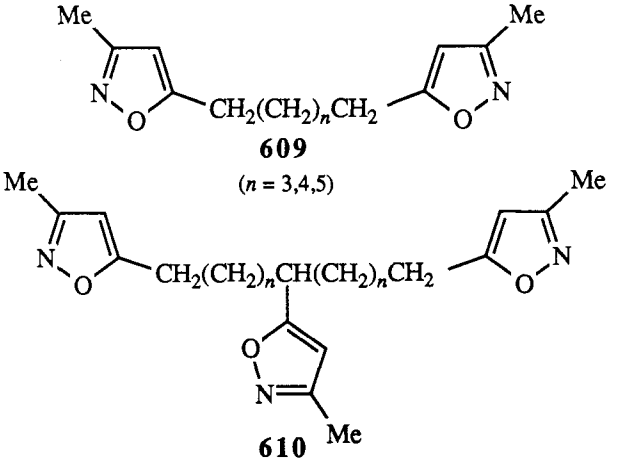

**608**

Apart from the deviations cited above, 5α-alkylation of 3- or 3,4-aryl- or alkyl-substituted 5-methylisoxazoles with a metallating agent and an alkyl halide is straightforward and gives excellent yields of 5-alkylisoxazoles, having

structure **591** or an analogous structure.[41/70,32/72,40/73,151/76,6/78,237/81,212/82] Protection of the carboxy group through use of the 2-oxazoline allows the 5α-alkylation of an isoxazole-4-carboxylic acid:[183/84]




Reaction of the carbanion (**587**) with α,ω-dibromoalkanes $Br(CH_2)_nBr$ yields bis-5-isoxazolylalkanes (**609**); when 2 mol of sodium amide is used, a mixture of **609** and the product of dialkylation (**610**) is obtained. A variance seems to be the parent compound (i.e., ethylene dibromide), which behaves as an oxidant, giving the anomalous product 1,2-bis(3-methyl-5-isoxazolyl)ethane (**603**).[40/73]

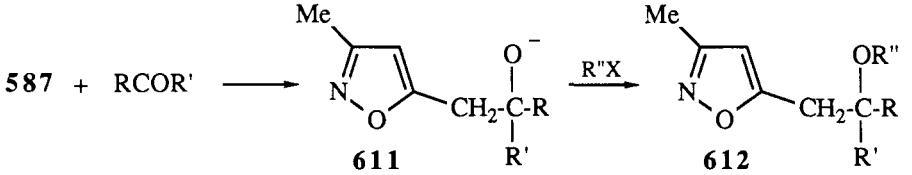



The same oxidative duplication product (**603**) can be obtained more conveniently by treating carbanion (**587**) with iodine.[41/70] An analogous reaction starting from bis(3-methyl-5-isoxazolyl)methane makes it possible to produce 1,1,2,2-tetrakis-(3-methyl-5-isoxazolyl)ethane.[67/76]

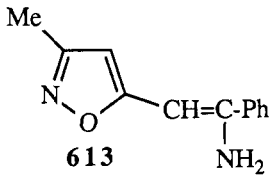
Carboxylation of 5α-carbanions with carbon dioxide, followed by acidification, is a general method for synthesizing 5-isoxazolylacetic acids, such as

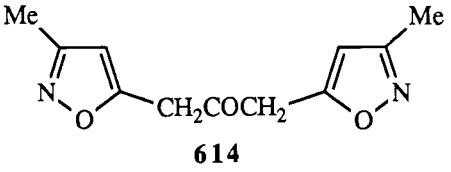
**594**,[130/68,41/70,151/78,42/81] usually with good to excellent yields. The use of ethyl cyanoformate as a carboxylating agent does not lead to the monocarboxylated product, but to 5-isoxazolylmalonate (**598**),[52/73] arising from dicarboxylation.

An obvious extension of the condensation reaction involves the carbonyl compounds. Aromatic aldehydes and ketones react readily with the 5α-carbanion produced by butyllithium or sodium amide to give the expected 5-β-hydroxyethylisoxazole derivatives,[41/70,25/76,285/80,237/81] such as **595**, which can easily be dehydrated to 5-alkenyl derivatives,[41/70,25/76,142/81] such as **596**, or oxidized to the corresponding 5-isoxazolylmethyl aryl ketones,[95/76,64/77,76/77,289/78,27/80,285/80] such as **597**. Aliphatic ketones require lithium amide to enter a reaction, whereas aliphatic aldehydes do not react at all.[25/76] Furthermore, if the alkoxide anion **611**, initially formed in anhydrous medium, is treated with an alkyl halide before neutralization, the corresponding ethers (**612**) are formed, although in rather low yields.[25/76]



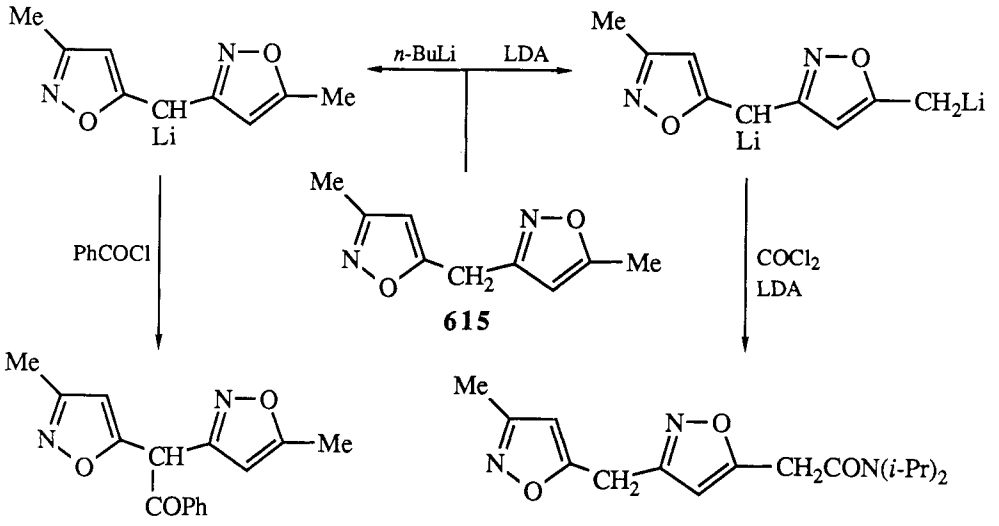

5-Isoxazolylmethyl ketones of type **597** can be prepared directly by reaction of the 5α-carbanion with the appropriate carboxylic ester[41/70,118/74,124/74,25/76,121/79] or with the nitrile.[41/70,42/73,284/78] In the latter case the intermediate unstable imine (e.g., **613**)[42/73] can sometimes be isolated by operating cautiously. Acyl chlorides can also be employed as acylating agents,[46/73,67/76] and phosgene is a suitable electrophilic partner for obtaining diisoxazolylacetones, such as **614**:[67/76]



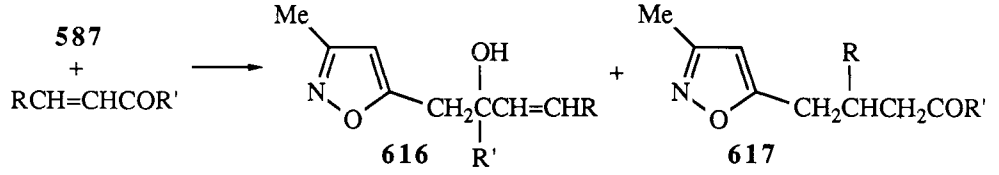




A diisoxazole compound such as **615**, containing two active 5α-centers, can be acylated site selectively, as the example in Scheme 1.36 shows.[67/76]

With α,β-unsaturated carbonyl compounds, competition between 1,2-addition and 1,4-addition (Michael addition) can occur. As illustrated below, in ethylenic aldehydes and ketones 1,2-addition seems to predominate,[25/76] whereas alkyl cinnamates give the Michael addition products exclusively:[32/72,25/76]




Scheme 1.36.



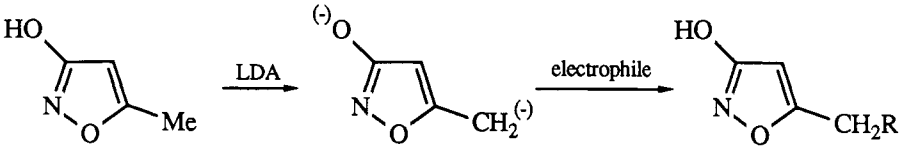

| R | R' | Yield of **616**(%) | Yield of **617**(%) |
|---|---|---|---|
| Me | H | 43 | - |
| Ph | H | 38 | trace |
| H | Me | 6 | 8 |
| Ph | Ph | 35 | 11 |
| Ph | OMe | - | 10 |

Trimethyl silylation or trimethyl stannylation of the isoxazole 5α-position through metallation is also known to give compounds such as **600**.[193/80,237/81] These compounds react with electrophiles in the presence of fluoride ions to give desilylated condensation products. For example, reaction of 3,4-dimethyl-5-trimethylsilylmethylisoxazole with benzaldehyde gave an 80% yield of 3,4-dimethyl-5-β-hydroxyphenethylisoxazole, and with δ-valerolactone a 45% yield of 1-(3,4-dimethylisoxazol-5-yl)-6-hydroxy-2-hexanone.[288/82]

Other electrophilic reagents are (1) carbon disulfide, which in the presence of methyl iodide yields thioketene acetals such as **602**;[41/70] (2) dimethyl disulfide, which gives the thioether **605**;[36/82] (3) the epoxide ring, which is cleaved to alcohols (**599**);[237/81] (4) nitrosoarenes, which condense to furnish nitrones of

structure **601** in low yields, along with azoxyarenes;[210/76] and (5) Schiff bases, whose addition produces arylamino derivatives of structure **604**.[42/73] It is worth noting that treatment of the metallated trimethylisoxazole with dimethyl disulfide is reported to give, besides the largely dominant 5α-substituted product, the isomeric 3α-methylthiomethyl derivative.[36/82]

Treatment of 3-hydroxy-5-methylisoxazole with 2 Eq of lithium diisopropylamide generates the dianion (**618**), which reacts exclusively at the 5α-position when treated with electrophiles:[214/83]

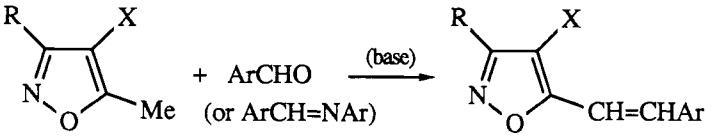



**618**

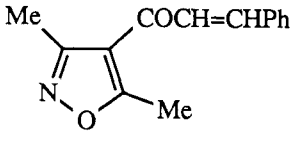
The use of *n*-butyllithium is less site selective, yielding a mixture of products.

### *1.4.7.2 Other Base-Promoted Condensations*

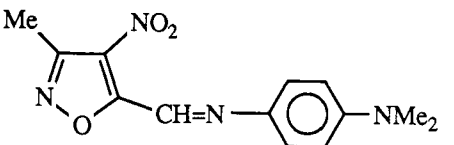
The presence of an electron-withdrawing substituent in the isoxazole 4-position greatly enhances the reactivity of the methyl group in the neighboring position 5 toward base-promoted condensations. Thus 3-substituted 5-methylisoxazoles, having a nitro,[7/42.4/43.8/46.74/62.56/67.85/72.66/73.110/73.175/80.19/81.107/83.170/83] arylazo,[194/79] amido,[66/73.270/77] cyano, carbalkoxy, or benzoyl group,[90/68.77/69.66/73] readily condense with an aromatic aldehyde in the presence of a base (secondary or tertiary amine, sodium hydroxide, or alkoxide) to give the corresponding 5-styryl derivatives:




Kinetic studies have been carried out on this reaction.[46/77.223/78] By contrast, condensation on the acetyl group is known for 4-acetyl-3,5-dimethylisoxazole, which furnishes 4-cinnamoyl-3,5-dimethylisoxazole (**619**) in 85% yield.[175/82]

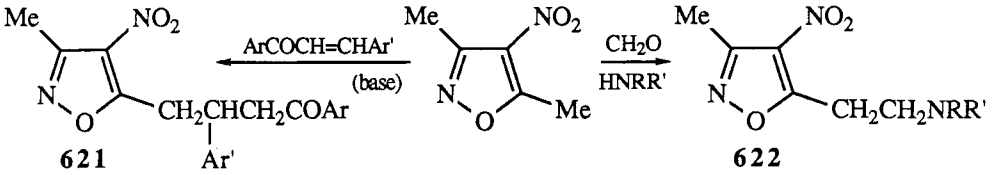



**619**



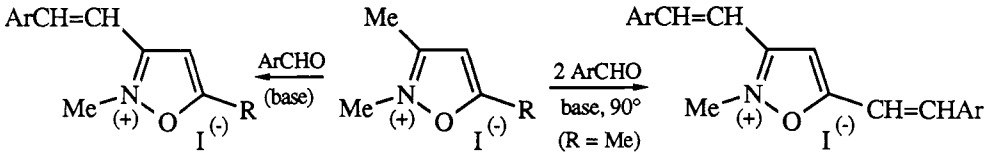

**620**

Other condensations are feasible for 3,5-dimethyl-4-nitroisoxazole: for example, condensation with *p*-nitrosodimethylaniline to give the anil **620**,[74/62] Michael reaction with chalcones in the presence of piperidine to give compounds **621**,[74/62,137/78,74/81] and the Mannich reaction, which yields the amines **622**.[208C/76,88F/79]



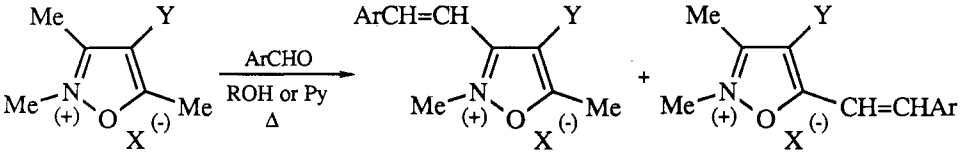

Of course, this reaction occurs with acetylisoxazoles as well.[106/67] Simple isoxazole carboxylic esters or ketones undergo Claisen condensation to give isoxazole β-diketones without difficulty.[10/40,134/71]

As already mentioned, quaternization of the isoxazole nucleus enhances the reactivity of the methyl groups in positions 3 and 5. Thus 3,5-dimethyl- and 3-methyl-5-phenylisoxazole methiodide react easily with several aromatic aldehydes in the presence of pyridine or piperidine: at low temperatures the 3-styryl derivative can be isolated, whereas in the former case heating favors the formation of substituted 3,5-distyrylisoxazoles:[28/54,22/55,23/58,19/63]




Interestingly enough, when position 4 bears an electron-withdrawing group, a 3-styryl and/or a 5-styryl derivative is formed, depending on the nature of the 4-substituent and of the aldehyde (aliphatic aldehydes or ketones do not react), as Table 1.89 shows.[111/83]

TABLE 1.89




| Y | Ar | Yield (%) | |
|---|---|---|---|
| $NO_2$ | Ph | 36 | - |
| $NO_2$ | PhCH=CH | 67[a] | - |
| $NO_2$ | 4-$Me_2NC_6H_4$ | 80 | - |
| Cl | Ph | 36 | 9 |
| Cl | PhCH=CH | 18 | 18 |
| COMe | 2-furyl | - | 85 |
| COMe | PhCH=CH | - | 68 |
| COMe | 4-$Me_2NC_6H_4$ | - | 11 |
| CN | Ph | - | 42 |

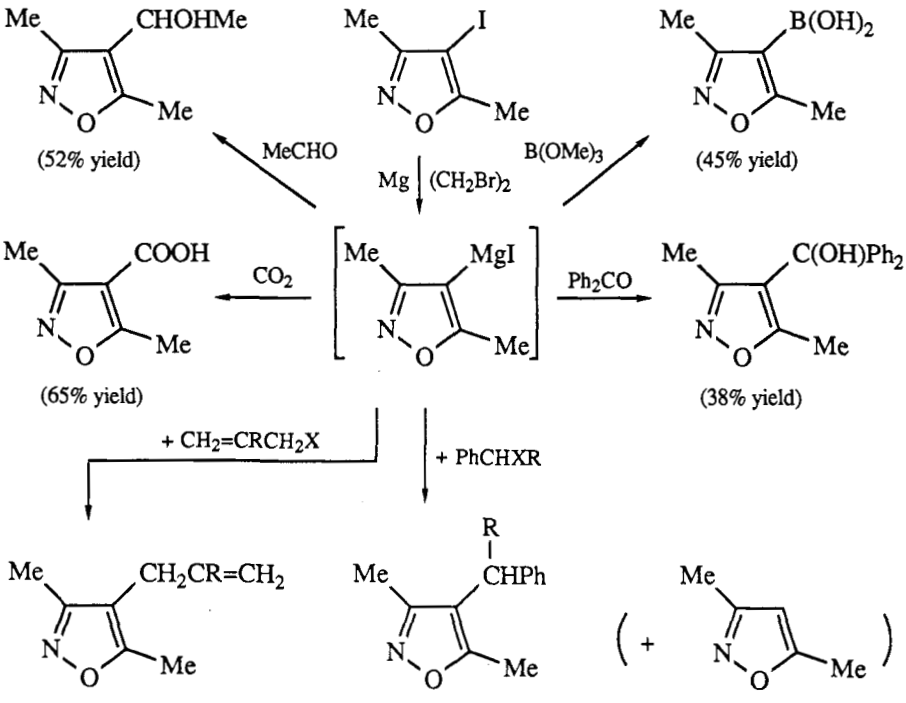
[a] Two stereoisomers.

### 1.4.8 Grignard Reagents

It has already been reported that Grignard reagents can sometimes reductively open the isoxazole ring (see § 1.4.3.1, p. 276). Furthermore, addition of Grignard reagents to isoxazolium salts leads to 3- or 4-isoxazolines (see §§ 2.4, p. 622, and 2.5.2.3, p. 638). Nevertheless, several functional groups in the side chains react in the normal way with various organomagnesium halides without affecting the nucleus. Thus isoxazole alcohols have successfully been prepared from the corresponding ketones[8/24,10/25,2/31,11/39] or esters,[4/46,122/69,184/72] as well as isoxazole ketones from nitriles[4/32,10/40,30/58,122/71,141/72,91/74] or esters.[122/69,101/74,260/80]

The coupling reaction of 3,5-dimethyl-4-halomethylisoxazole with allyl, benzyl, or phenyl magnesium halides or with aluminum trialkyls leads to higher 4-alkyl-substituted 3,5-dimethylisoxazoles. Even better results have been achieved with 4α-chlorobenzyl-3,5-dimethylisoxazole, which couples with alkylmagnesium halides without difficulty.[3C/84] By contrast, alkyl halides do not react at all, 3,5-dimethylisoxazole being obtained quantitatively after hydrolysis. Prolonged heating of 4-bromo-3,5-dimethylisoxazole with ethylmagnesium bromide forms 3,3′,5,5′-tetramethyl-4,4′-diisoxazole.[3C/84]

It is worth noting that 4-cyano-5-methoxy-3-phenylisoxazole is attacked by phenylmagnesium bromide not at the cyano group, but at ring position 5, with replacement of the methoxy with a phenyl group.[11/73] Addition to the carbonyl group, with simultaneous reductive cleavage of the ring, is known for 3,5-di-




Scheme 1.37.

acylisoxazoles.[302/78] More scanty are the hitherto known organomagnesium compounds, containing the isoxazole ring. Here, too, ring cleavage is the main competitive reaction. Moderately good results can be obtained by treating 3,5-dimethyl-4-iodoisoxazole with magnesium in the presence of ethyl iodide or, better, dibromoethane. The isoxazolylmagnesium iodide thus formed is stable enough to react with carbon dioxide, carbonyl compounds, or trimethyl borate, with formation of the expected addition products.[21/60,94/63,115/67,148/76] By contrast, a mixture of products is originated when the same organomagnesium compound reacts with trimethylsilyl chloride.[193/80]

Higher yields of substitution products are obtained by reaction with allyl or with benzyl halides (Scheme 1.37).[3B/84] By contrast, alkyl halides do not react at all, 3,5-dimethylisoxazole being quantitatively obtained after hydrolysis. Prolonged heating of 4-bromo-3,5-dimethylisoxazole with ethylmagnesium bromide forms 3,3′,5,5′-tetramethyl-4,4′-diisoxazole.[3C/84]

Replacement of iodine with bromine or chlorine or of the methyl with phenyl groups lowers the yields and complicates the process with side reactions. Even less successful is the reaction in the case of 4-chloromethyl-3,5-dimethylisoxazole, which reacts with magnesium and then with $CO_2$ under the aforementioned conditions to give only 7% of (3,5-dimethyl-4-isoxazolyl)acetic acid.[94/63] Better results are achieved when the same Grignard reagent condenses with trimethylsilyl chloride in THF; if the reaction is carried out in dry ether, bis(3,5-dimethylisoxazol-4-yl)ethane is formed.[193/80] The latter compound has also been obtained as a main product (40% yield) by reaction of the chloromethylisoxazole with *n*-butylmagnesium chloride.[3B/84] 3-Unsubstituted isoxazoles are conceivably unsuitable for preparing Grignard reagents.

Despite the rather low yields, it is interesting that 3-bromo-5-phenylisoxazole is apt to give the corresponding Grignard reagent by treatment with magnesium and dibromoethane. Subsequent addition of formaldehyde, acetone, or carbon dioxide furnishes the 3-isoxazolyl carbinols or the 5-phenylisoxazole-3-carboxylic acid; $\omega$-cyanoacetophenone is always a by-product.[78/69]

### 1.4.9 Electrophilic Substitutions

The susceptibility of the isoxazole ring toward an electrophilic attack corresponds roughly to what could be expected from the simultaneous presence of an activating oxygen atom and of an electron-withdrawing nitrogen atom. Isoxazole undergoes electrophilic substitution less readily than furan, but more rapidly than pyridine.

Quantitative evaluation of the reactivity of isoxazole, or its 3- or 5-methyl- and 3,5-dimethyl derivatives, toward electrophiles has been undertaken by studying the acid-catalyzed deuterio deprotonation[56/64,115/71,150/74] and the nitration in a strongly acidic medium.[115/71,127/75] Although no neat correlation has been found between the log $k_0$ values of the two substitution reactions,[185/75] some general common features could be ascertained. Only the 4-position of the

TABLE 1.90. REACTIVITIES TOWARD DEUTERIO DEPROTONATION[150/74]

| Compound | Ring position: | Log (partial rate factor) [a] 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Furan | | 8.2 | ca. 4.5 | ca. 4.5 | 8.2 |
| Thiophene | | 8.6 | 5.0 | 5.0 | 8.6 |
| 1-Methylpyrrole | | 10.6 | 10.3 | 10.3 | 10.6 |
| Isoxazole | | - | - | 4.3 | - |
| Isothiazole | | - | - | 3.6 | - |
| 1-Methylpyrazole | | - | 5.6 | 9.8 | 5.6 |
| Pyridine | | - | ca. -5 | - | - |
| 3-Methylisoxazole | | - | - | 5.4 | - |
| 5-Methylisoxazole | | - | - | 6.8 | - |
| 3,5-Dimethylisoxazole | | - | - | 7.6 | - |
| 3-Methylisothiazole | | - | - | 4.6 | - |
| 5-Methylisothiazole | | - | - | 4.8 | - |
| 3,5-Dimethylisothiazole | | - | - | 6.9 | - |
| 1,3-Dimethylpyrazole | | - | - | 10.7 | - |
| 1,5-Dimethylpyrazole | | - | - | 11.4 | - |
| 1,3,5-Trimethylpyrazole | | - | - | 13.4 | - |

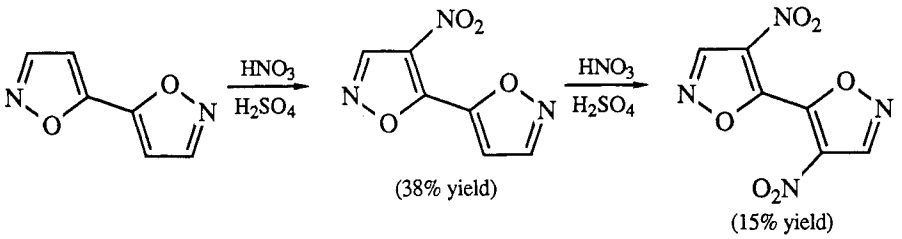
[a] Calculated with respect to one position of benzene = 1.

isoxazole ring is attacked by the electrophile; 4-methylisoxazole does not exchange hydrogen, but decomposes at 120°C in 40% $D_2SO_4$.[150/74] A rate profile makes it clear that both electrophilic substitutions occur on the free base. As Table 1.90 shows, inside a 1,2-azole series the reactivity order pyrazole $\gg$ isothiazole $\geqslant$ isoxazole is a general pattern.[115/71] Methyl substitution increases the reaction rate more significantly for the 5-methyl isomer than for the 3-methyl isomer. This rate increment is larger for isoxazole ($\Delta \log k_0 = 1.4$) than for pyrazole (0.7) and for isothiazole (0.2), thus leading to an aromaticity order for the 1,2-azoles which parallels that of five-membered monoheteroaromatic furan < pyrrole < thiophene.[150/74] From a preparative point of view, the specific observations that follow are worthy of mention.

### *1.4.9.1 Nitration*

Isoxazole itself is nitrated only with great difficulty. 4-Nitroisoxazole is obtained in only 3.7% yield under nitration with mixed nitric and sulfuric acids (1:5) at 35–40°C.[69/59] A 35% yield is reported in the nitration with nitronium tetrafluoroborate in sulfolane.[258/81] Far easier and more straightforward is the reaction with 3,5-dimethylisoxazole[7/21,115/71] and other 3,5-dialkylisoxazoles,[10/64] which invariably yields the 4-nitroderivative. For instance, the use of mixed acids at steam-bath temperature gives a 90% yield of 3,5-dimethyl-4-nitroisoxazole.[7/21,4/41] Under similar conditions the 2,3,5-trimethylisoxazolium salt does not react at all.[115/71] Both 3-methyl-[4/41] and 5-methylisoxazoles[4/41,168/71] are nitrated in the 4-position only. Interestingly enough, even the 3,5-dimethyl-4-halogenoisoxazoles are transformed by substitutive nitration into 3,5-dimethyl-4-nitroisoxazole, although in lower yields than in the case of the parent compound.[196/73]

The isoxazole nucleus seems to act as an activating substituent: for example, 5,5′-[47/59] and 3,3′-diisoxazole[8/46] are nitrated and dinitrated:




(38% yield)

(15% yield)

With aryl-substituted isoxazoles the reaction proceeds fast and under mild conditions, and competition between substitution in the isoxazole 4-position and in the aryl ring may occur. Theoretical calculations anticipated an activating effect of the isoxazole nucleus with respect to the benzene ring, especially for 5-phenylisoxazole, without excluding the possibility of a *meta* nitration for 3-phenylisoxazole.[39/62,75B/65]

In fact, nitration of 5-phenylisoxazole with mixed acids at room temperature furnishes a mixture of products, where the 5-*p*-nitrophenylisoxazole is the main isomer, along with far lower amounts of the 5-*m*-nitrophenyl derivative.[37/57.66/58.27/65.231/68] 4-Nitro-5-*p*-nitrophenylisoxazole is also present in fair

TABLE 1.91. NITRATION OF ARYL-SUBSTITUTED ISOXAZOLES

| Isoxazole | Exper. conditions | Nitration in position: | Yield (%) | References |
|---|---|---|---|---|
| 3- Phenyl | mixed acids, r.t. | *p*-Ph + *m*-Ph (traces *o*-Ph) | 90 | 37/65 |
| | $HNO_3/Ac_2O$, ca. 5° | 4-Isox | 57 | 215/71 |
| 3-*p*-Nitrophenyl | mixed acids, 70-80° | 4-Isox + *o*-Ar,4-Isox (80:20) | | 215/71 |
| | mixed acids (excess), 80° | *o*-Ar,4-Isox | 68 | 215/71 |
| 3-*p*-Chlorophenyl | mixed acids, r.t. | *m*-Ar + *o*-Ar + 4-Isox (80:13:7) | | 215/71 |
| | $HNO_3/Ac_2O$ | no reaction | | 215/71 |
| 3-Phenyl-5-methoxy | mixed acids, 0° | *m*-Ph (impure) | 100 | 31/59 |
| 3-Phenyl-5-methyl | $HNO_3/H_2SO_4$ 98%, 0° | *m*-Ph + *p*-Ph (92:8) | 78 | 128/75 |
| | $HNO_3/H_2SO_4$ 70%, 100° | *p*-Ph + *m*-Ph (95:5) | | 128/75 |
| | $HNO_3/Ac_2O$, r.t. | 4-Isox | ≥19 | 56/67 |
| | $HNO_3/Ac_2O$, 100° | *p*-Ph,4-Isox | 10 | 128/75 |
| 4-Phenyl | mixed acids, r.t. | *o,p*-Ph + *p*-Ph (75:24) | 99 | 63/67 |
| | mixed acids, 70° | *o,p*-Ph | 90 | 63/67 |
| | conc. $HNO_3$, 100° | *p*-Ph | 98 | 63/67 |
| 5-Phenyl | mixed acids, r.t. | *p*-Ph + *p*-Ph,4-Isox + *m*-Ph (50:30:6) | 86 | 231/68 |
| | mixed acids, r.t. | *p*-Ph | 50 | 27/65 |
| | mixed acids, 80° | *p*-Ph,4-Isox | | 27/65 |
| | $HNO_3/Ac_2O$ | *p*-Ph | 50 | 27/65 |
| 3-Methyl-5-phenyl | mixed acids, 5° | *p*-Ph | 58 | 128/75 |
| | $HNO_3/Ac_2O$, 75° | *p*-Ph,4-Isox | 12 | 128/75 |
| 3,5-Diphenyl | mixed acids, 0° | 5-*p*-Ph | | 185/74 |
| | mixed acids (excess), 0° | 3-*m*-Ph,5-*p*-Ph | | 185/74 |
| | $HNO_3/Ac_2O$ | 4-Isox | | 185/74 |

amounts,[231/68] and is the only product when nitration is carried out at a higher temperature (89% yield at 70–80°C) on deactivated 5-*p*-nitrophenylisoxazole.[215/71] The *meta* nitration is higher in the case of 3-arylisoxazoles,[4/51,31/59,37/65,215/71,128/75] where substitution in the presence of mixed acids occurs exclusively in the benzene ring (mainly *para* and *meta*, with traces of *ortho* substitution).

The 4-nitro derivatives are the exclusive or main products when the nitration is accomplished with fuming nitric acid in acetic anhydride;[37/65,56/67,215/71,196/73,185/74,128/75] however, the yields are generally rather low. Of course, 4-phenylisoxazole is nitrated exclusively in the benzene ring; the isoxazole nucleus here definitely acts as an activating substituent (*ortho/para* nitration).[129/66,63/67] Table 1.91 presents some examples of nitration on aryl-substituted isoxazoles.

The presence of activating groups, such as acetylamino or succinimido, in the isoxazole 3- or 5-position enhances the reactivity of the 4-position, which can thus be nitrated in good yields.[198/68,159/71,167/73] 3-Anilinoisoxazoles with a free 4-position are nitrated in both the isoxazole and the benzene ring, unless the *para* position of the latter is occupied.[9/37,11/38,16B/39]

Isoxazoles with an electron-withdrawing group substituted behave as deactivating residues: for example, exclusive *meta* nitration is known for methyl 5-methyl-3-phenylisoxazole-4-carboxylate[24/60] or for the corresponding free acid.[54/63] By contrast, ethyl 5-phenylisoxazole-3-carboxylate is nitrated in the phenyl *para* position.[7/39] Clearly, quaternization of the isoxazole ring totally deactivates the benzene ring.[128/75]

### *1.4.9.2 Sulfonation*

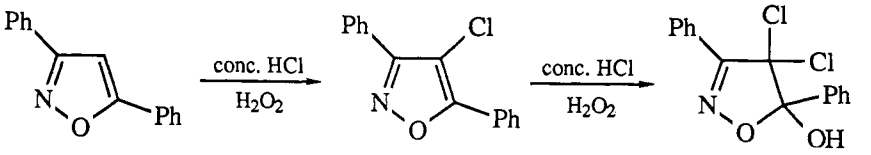
The isoxazole ring is rather resistant to sulfonation and, in this regard, resembles the pyridine nucleus. However, on prolonged heating with excess chlorosulfonic acid, 3-methyl-, 5-methyl-, and 3,5-dimethylisoxazoles are converted to the corresponding 4-sulfonyl chloride, possibly in a mixture with the free acid.[1/40,2/40,129/81] Isoxazole itself could be sulfonated under drastic conditions (20% oleum, 7 h on a steam bath) and in only 17% yield.[69/59] The sulfonation of 5-phenylisoxazole has been investigated in detail:[166/66] only substitution in the phenyl group was observed, in both the *meta* and *para* positions.

### *1.4.9.3 Halogenation*

Halogenation of isoxazoles has been carried out with various reagents and almost invariably led to substitution in the 4-position of the heterocyclic ring, even when other free positions are available. The parent compound, isoxazole itself, is brominated to 4-bromoisoxazole either with bromine in the presence of iron[69/59] or without a catalyst at 100–110°C;[28/60] in the latter case yields up to 42% are attained.

4-Phenylisoxazole is brominated in the phenyl *para* position in excellent yields.[151/77] All other alkyl- and aryl-substituted isoxazoles with a free 4-position are halogenated in the latter position of the heterocyclic ring.[66/58,73/60,214/71] Some methyl derivatives react with halogens to give, first, a molecular complex, which decomposes to 4-haloisoxazole on heating or on exposure to sunlight[1/36] or, better, in the presence of concentrated nitric acid.[76/61] The use of iodine in addition to the latter acid at steam-bath temperature seems the most convenient method for synthesizing 4-iodoisoxazoles.[21/60,76/61,25/76]

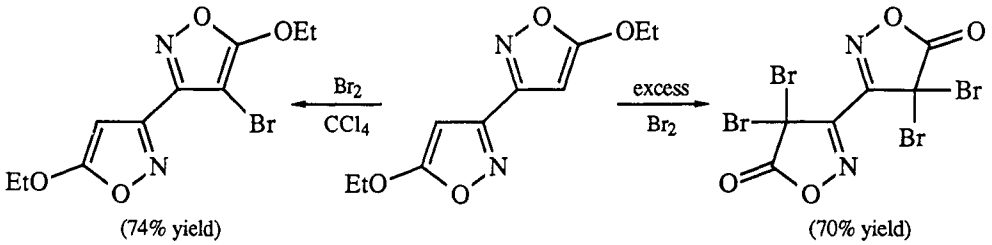
Other halogenating agents that have been used successfully include sulfonyl or thionyl chloride,[72/62,21/77,205/78] *t*-butylhypochloride,[195/73] iodine chloride,[65/64, 87B/67,144/70,127/71] *N*-chloro (or bromo)-succinimide,[72/62,199B/79] and a mixture of hydrogen peroxide and concentrated hydrochloric acid.[39/64,117/67,195/73] The latter reagent can react further with the initially formed 4-chloroisoxazole to give 5-hydroxy-2-isoxazoline derivatives; for example:[39/64,37B/81]




5-Methylisoxazole-3-carboxamide is successfully chlorinated at the 4-position with gaseous chlorine in a biphasic system $H_2O$–$CHCl_3$–20% HCl, whereas N-chlorination occurs if sodium hypochlorite is used.[22/82]

The presence of activating groups such as 3-hydroxy,[12/70] 3- or 5-methoxy[31/59,33/59,177/77,162/80] or 3-arylsulfonylamino[218B/68] raises the yields from moderate to good or excellent. The free amino group seems to be less effective.[76/63,65/64] In some cases (e.g., anilino or *p*-aminophenyl groups) bromination in the phenyl group can compete with heterocyclic ring substitution.[11/38,76/63,156/76]

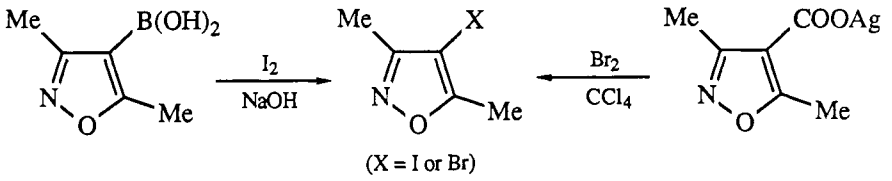
Excess bromine on the 5-alkoxyisoxazoles affords the 4,4-dibromo-5-isoxazolinones;[31/59,33/59] for example:[33/59]



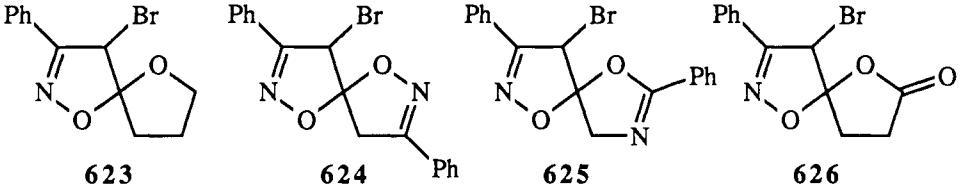

(74% yield) (70% yield)

Both 5-α-furyl-3-phenylisoxazole and its isomer 3-α-furyl-5-phenylisoxazole are brominated by NBS in the furan ring exclusively.[88/68]

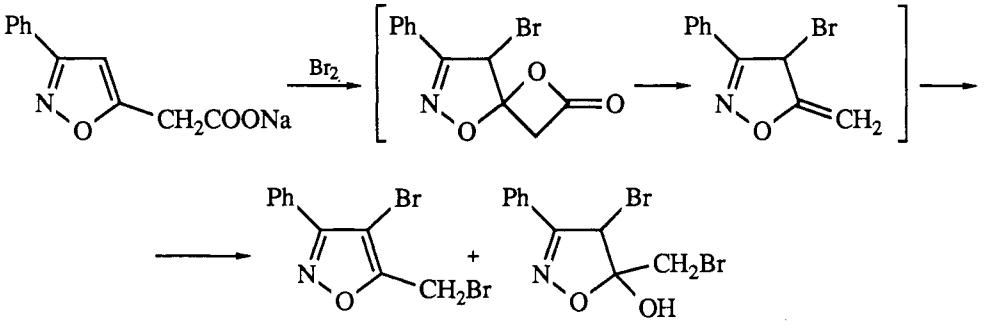
It should also be noted that some groups, present in the isoxazole 4-position, are substituted by halogenation: for example, 3,5-dimethylisoxazole-4-boronic acid reacts with sodium hypoiodide to give 4-iodo-3,5-dimethylisoxazole,[115/67] and silver 3,5-dimethylisoxazole-4-carboxylate undergoes the Hunsdiecker reaction to give the 4-bromo derivative:[189/74]




When the side chain in the isoxazole 5-position contains a nucleophilic oxygen linked to the $\gamma$-atom, the bromination does not furnish the expected 4-bromo derivative, but instead, a 4-bromo-5-spiroisoxazoline derivative. Thus compounds **623–626** (occasionally as a mixture of stereoisomers) have been obtained from 3-phenylisoxazoles with the side chains $CH_2CH_2CH_2OH$,[97/74] $CH_2C(=NOH)Ph$,[143/74] $CH_2NHCOPh$,[156/76] and $CH_2CH_2COONa$,[156/76] respectively, in position 5:




The related sodium 3-phenylisoxazol-5-yl acetate behaves differently: bromination leads, possibly through the intermediacy of a bromoisoxazoline spiro-$\beta$-lactone, to a mixture of dibromo derivatives: 4-bromo-5-bromomethyl-3-phenylisoxazole and the corresponding stereomeric 5-hydroxy-2-isoxazolines:[15/79]



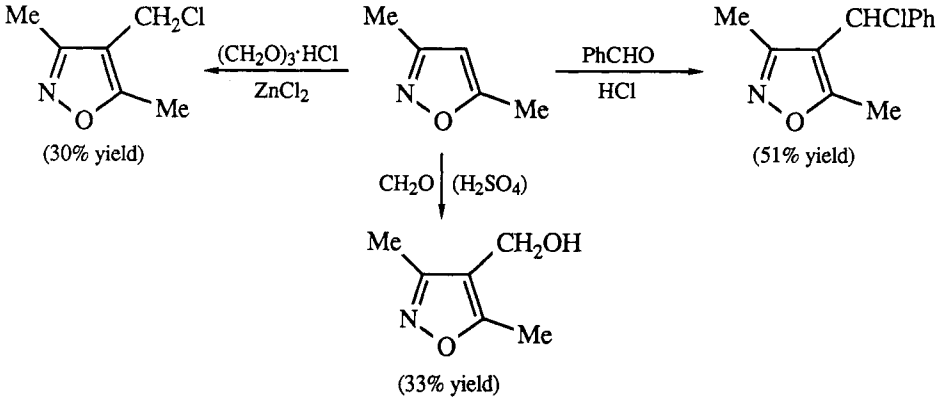

An additional example of neighboring group participation is given by the transformation of sodium 3-phenylisoxazole-5-carboxylate into 4,4-dibromo-3-phenylisoxazolin-5-one by bromination.[156/76] The presence of a double bond in the side chain, as in 3-isopropenyl-5-methylisoxazole, induces both addition to the unsaturation and substitution in the heterocyclic ring.[4/46]

Quaternization deactivates the isoxazole ring toward electrophilic sub-

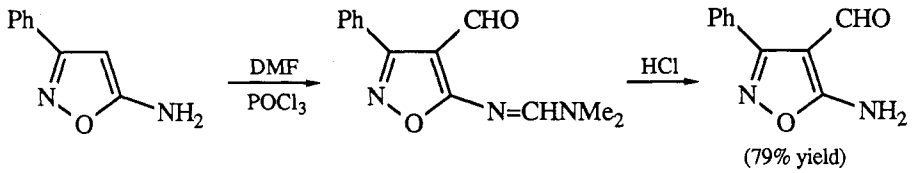
stitution; an attempted bromination of 2-methyl-3,5-diphenylisoxazolium methosulfate resulted in 18% conversion to the 5-*para*-brominated salt together with other products, but without a trace of 4-bromo derivatives.[214/71] For halogenation in the side chains, see § 1.4.11, p. 372.

### *1.4.9.4 Other Substitutions*

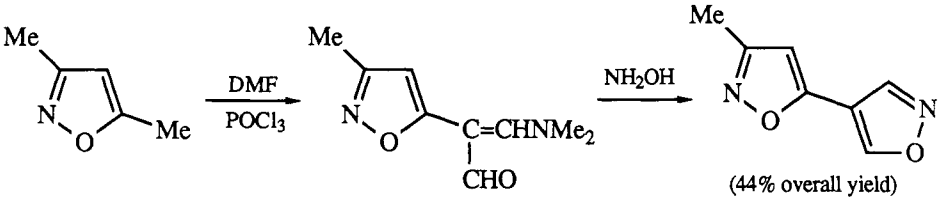
Mercuration of isoxazoles is readily achieved with mercuric acetate. The reaction is faster than in the benzene field, reaches high yields (90–100%), and gives the easily crystallizable 4-isoxazolylmercuric acetate.[66/58,73/60,115/67] The product can be identified by routine conversion (KBr, then bromine) to 4-bromoisoxazole. By contrast to the inertness of pyridine, the isoxazole 4-position can be chloromethylated, the parent isoxazole in very low yield (1.8%) and the methyl derivatives in moderate yields (24–37%). The reaction is carried out by heating with paraformaldehyde/concentrated HCl or with chloromethyl ether, always in the presence of zinc chloride.[40/57,68/58] Use of aromatic aldehydes and dry hydrogen chloride makes it possible to chlorobenzylate 3,5-dimethylisoxazole,[76/60] whereas formaldehyde in concentrated sulfuric acid at 100°C induces hydroxymethylation:[79/61]



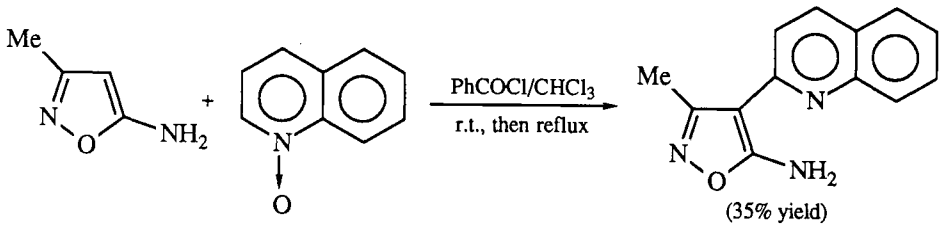

Formylation of an activated isoxazole nucleus is achieved under Vilsmeier–Haack conditions; the 5-aminoisoxazole-4-carboxaldehyde is a useful starting material for the synthesis of condensed heterocyclic rings:[87/77,50/80]



When the isoxazole ring is not activated, as in 3,5-dimethyl- or in 3-methyl-5-phenylisoxazole, formylation occurs with far lower yields on the 5-methyl group or, in its absence, on the 3-methyl group.[166/71] An intermediate is achieved, through which diisoxazoles can be synthesized; for example:




When a heteroaromatic *N*-oxide, such as quinoline, isoquinoline, or pyrimidine *N*-oxide, is treated with a 5-aminoisoxazole in the presence of benzoyl chloride, a 4-heteroaryl isoxazole is formed in low to moderate yields:[67/78,69/78]




The subsequent hydrogenolytic ring cleavage makes it possible to prepare the corresponding heteroaromatics carrying a functionalized side chain in the α-position. Coupling of 5-aminoisoxazole derivatives with aryldiazonium salts is known to yield the corresponding 4-arylazo-substituted isoxazoles.[146/75]

### 1.4.10 Ring Transformations into Other Heterocyclic Systems

Ring transformation of isoxazole derivatives is a well-known method for synthesizing a large variety of other heterocyclic systems, and involves ring opening and subsequent inter- or intramolecular reclosure. As illustrated in the preceding sections, the isoxazole ring can be cleaved mainly through thermal, photochemical, hydrogenolytic, or base-promoted processes. If a suitable functionality is present in the proper position of a side chain, an intramolecular reaction can occur spontaneously or in a two-step sequence, with formation of the new ring. Or a suitable reagent can be added to the open-chain intermediate, either *in situ* or subsequently and an intermolecular cyclization to the new heterocycle takes place. In some cases, especially when the attacking molecule is a nucleophile, the same reagent is responsible for both the ring cleavage and the ring reclosure. Besides the obvious mechanistic interest of these ring trans-

formations, the ready and wide accessibility of isoxazole derivatives supplies synthetic utility to several of these transformations.

In addition to monographs of wider coverage,[257/73,283/74] an excellent comprehensive review[175/75] has been devoted to ring transformation reactions of monocyclic and condensed isoxazole derivatives. These reactions will be here listed according to the increasing complexity of the heterocyclic ring thus obtained.

### *1.4.10.1 Transformations into Three-Membered Heterocycles*

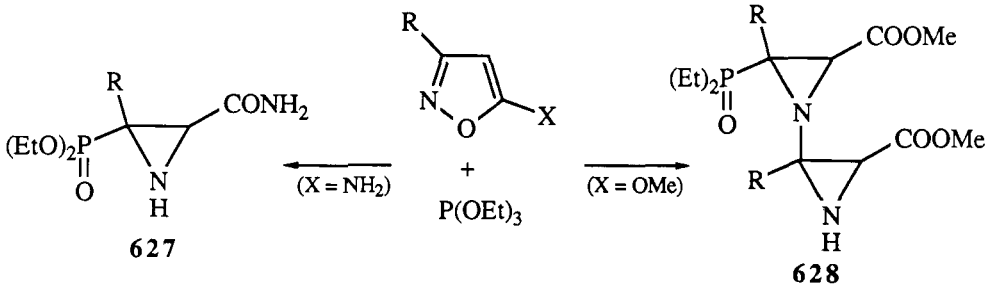
Thermal or photochemical isomerization of isoxazoles into 3-carbonyl-substituted 1-azirines* has been dealt with in § 1.4.5. To acquire synthetic importance and to compete with other preparative methods,[1C/71] the experimental conditions must be chosen carefully. Alkyl- and aryl-substituted isoxazoles are thermally rather stable, and cleave only under severe conditions, so that the 1-azirine derivatives formed initially are further transformed. Thus 2-alkyl (or aryl)-3-acyl-1-azirines are formed only photochemically with moderate yields.[34/66,83/67,92/72,138/74.5/76,138/77]

The presence of a 5-alkoxy group on the isoxazole nucleus greatly facilitates ring cleavage, and 1-azirine-3-carboxylic esters are obtained easily by thermal conversion. The best procedure, which attains almost quantitative yields, utilizes poisoned Lindlar catalyst in dioxane solution warmed at 80°C under a hydrogen pressure of 50 atm for 5–8 min.[143/83] Under different conditions (heating at 200°C in the molten phase or in high-boiling solvents or heating at 60°C in the presence of copper stearate), yields in the range 50–76% are reported.[203/69,202/70,160/75,29/77]

5-Aminoisoxazoles are similarly isomerized to 1-azirine-3-carboxamides, but the substitution pattern is more critical here: photolysis seems preferable with 3-aryl derivatives, and both thermal and photochemical treatments are used for 3-aryl-4-methyl analogues, although the yields reported are only moderate with both types of compounds.[156/70,127/71,129/71] Better results (50–75% yields) have been attained in the thermolysis of 5-amino-3,4-diarylisoxazoles[128/71] and of 3,4-disubstituted-5-methylamino[98/82] and of 5-trimethylhydrazino derivatives,[140/77, 98/82] as well as in the photolysis of 5-amino-3,4-dimethylisoxazole[4/81] and 3-aryl-5-benzylamino derivatives.[137/72]

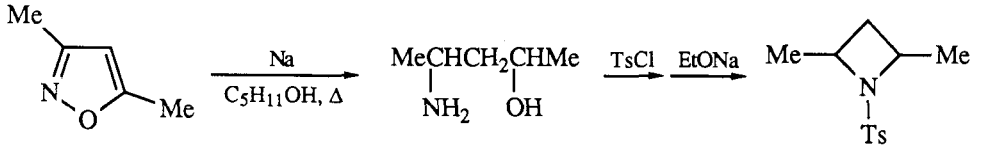
It is well known that 1-azirines can add nucleophilic reagents to give the corresponding aziridine derivatives. It is not surprising, therefore, that heating 5-amino-3-arylisoxazoles in triethyl phosphite directly afforded, albeit in low yields, aziridin-2-ylphosphonates (**627**), arising from the intermediate azirine-carboxamides by addition of the phosphor compound. At variance, 3-aryl-5-alkoxyisoxazoles under the same conditions give a dimeric aziridine phosphonate (**628**):[129/71]

*The IUPAC nomenclature (2*H*-azirines) seems less straightforward here.



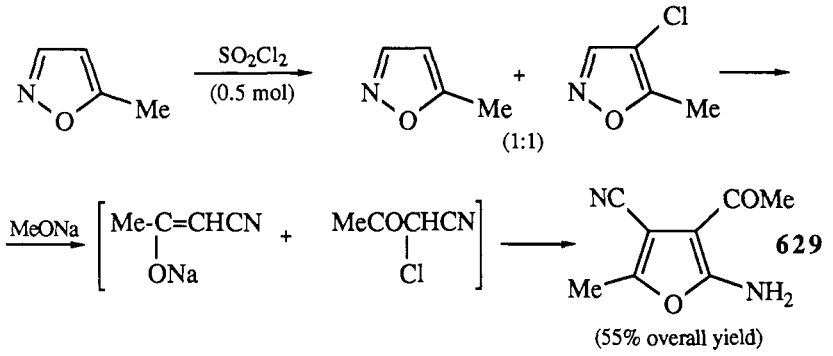

### *1.4.10.2 Transformations into Four-Membered Heterocycles*

Direct rearrangement of isoxazole into four-membered heterocycles is not known at present. An indirect method is based on the reductive ring opening of 3,5-dimethylisoxazole with sodium and 1-pentanol and subsequent tosylation with excess *p*-toluenesulfonyl chloride to give a mixture of diasteromeric ditosylates of 4-aminopentan-2-ol. After isolation of the *threo* isomer and treatment with sodium ethoxide, pure *cis*-2,4-dimethyl-1-tosylazetidine was obtained:[173B/72]

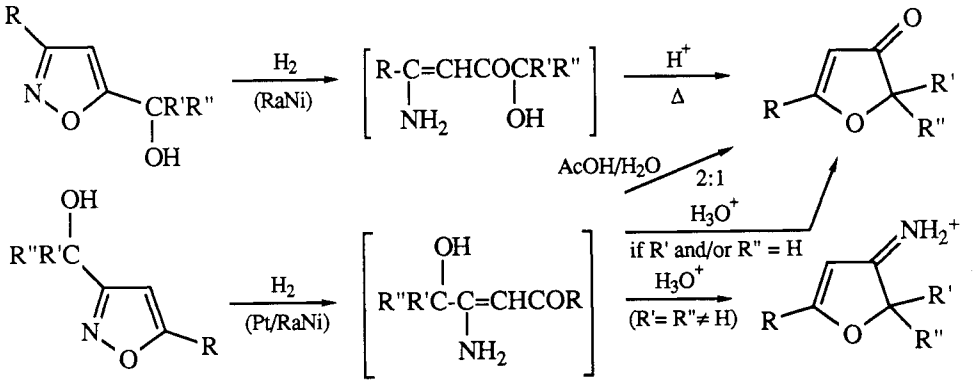



### *1.4.10.3 Transformations into Five-Membered Heterocycles Containing One Heteroatom*

5-Methylisoxazole is a well-known synthon for the unstable cyanoacetone (see also § 1.4.12, p. 393): an ingenious coupling with the chlorination reaction of the same starting material makes it possible to prepare 3-acetyl-2-amino-5-methylfuran-3-carbonitrile (**629**) in two (or three) steps, as outlined in the following scheme:[205/78]

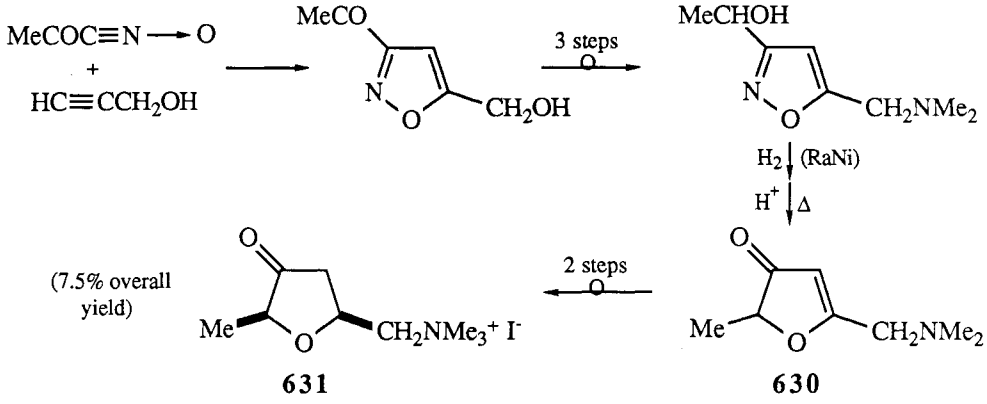


The presence of a hydroxy group in the 5α-position of the isoxazole ring opens a convenient route of general applicability for the synthesis of 3(2*H*)-furanones. Catalytic hydrogenation under mild conditions with subsequent acidic hydrolysis affords the products directly in 40–60% yields:[82/66,168/66,147/67,222/75]



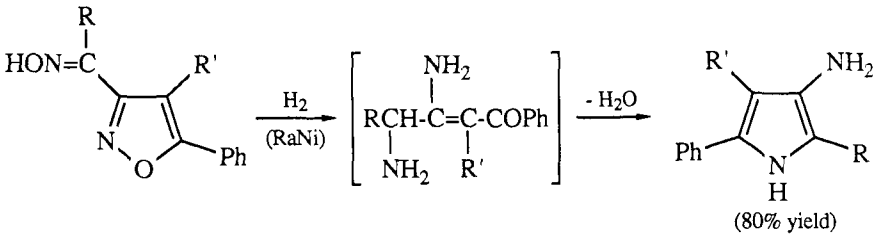

The same products can be achieved by starting from the isomeric 3α-hydroxyisoxazole derivative.[184/84] Moreover, in this case the corresponding 3(2*H*)-iminofurane salts can also be isolated, depending on the substitution pattern.

This type of synthetic strategy has recently been utilized in a convenient procedure for preparing the key intermediate (**630**), a precursor of DL-muscarone (**631**), starting from pyruvonitrile oxide and propargyl alcohol:[34/84]

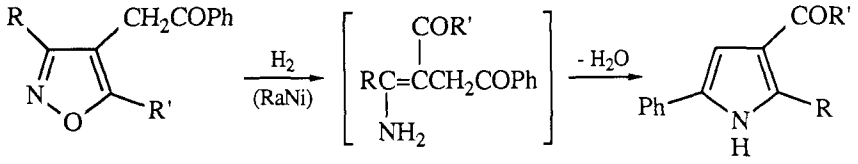



**631** **630**

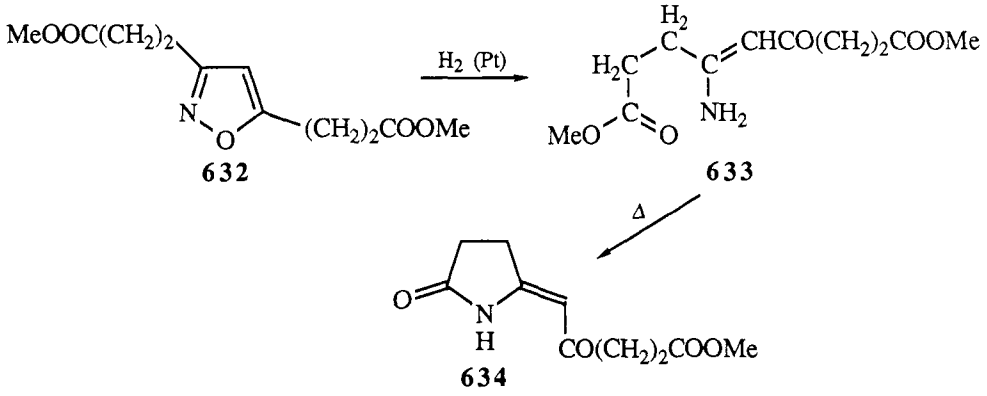
Hydrogenolysis of a suitably substituted isoxazole is also the method of choice for converting it into a pyrrole derivative, whose formation is the result of a condensation between a carbonyl and the γ-amino group. Thus catalytic hydrogenation of the oxime of a 3-acylisoxazole is reported to yield substituted 3-aminopyrroles:[6/66]



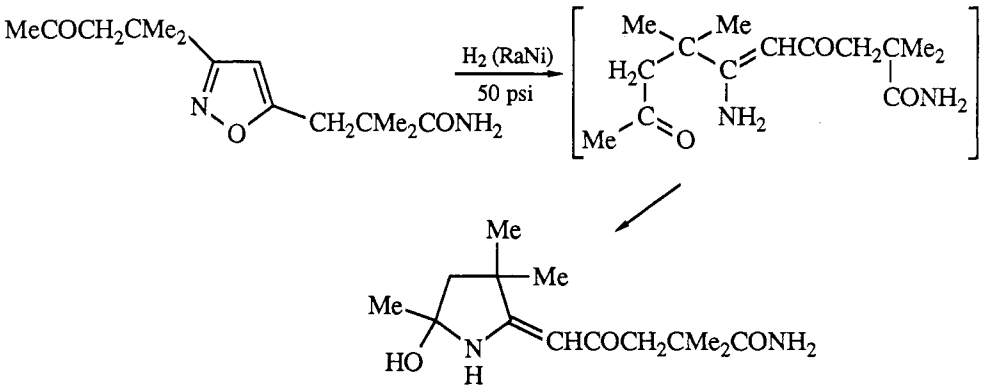

In a similar way, 4-benzoylmethylisoxazoles are hydrogenated to 3-acylpyrroles:[6/66]




Moreover, when the carbonyl group belongs to a carboxylic function, an α-pyrrolidone derivative can arise: if, for example, the isoxazole (**632**) is hydrogenated over a Raney nickel catalyst in the presence of triethylamine, the intermediate enaminoketo diester **633** cyclizes spontaneously to **634** by pyrolysis in 74% yield:[62/69,94/71]

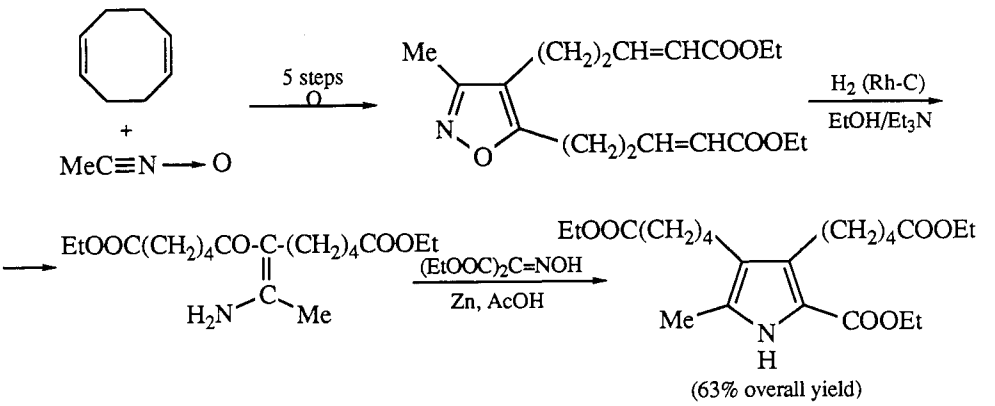



A keto group instead of the ester group causes formation of a substituted 2-hydroxypyrrolidine, as exemplified here:[94/71]



This cyclization process has been developed in a brilliant synthetic approach to corrinoid substances (see § 1.4.12, p. 414).

An interesting approach to tetra-substituted pyrroles, having identical substituents in positions 3 and 4 and therefore potential precursors of symmetrical octa-substituted porphirins, is exemplified here:[41/84]

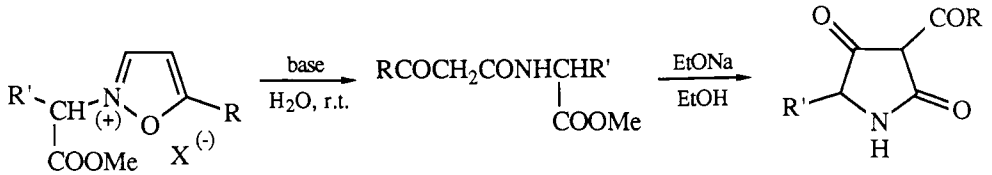


For the synthesis of 2-hydroxypyrrolin-3-ones from 5-acylisoxazoles, see § 1.4.3.1, p. 281.

Pyrrole derivatives have occasionally been obtained by base-promoted ring opening of substituted isoxazolium salts: for example, 2,4-dimethyl-3-phenylisoxazolium perchlorate reacts with various bases to give a mixture of four products in variable amounts.[51/69,52/69] One of them is 1,3,4-trimethyl-2,5-diphenylpyrrole, which is formed in higher, albeit still moderate (20–32%), yields when the sodium salt of cyanoacetamide or ethyl acetoacetate is used as a base.[52/69] Treatment with methanolic ammonia affords 3,4-dimethyl-2,5-diphenylpyrrole.[51/69]

A Woodward–Olofson base-promoted ring opening (see § 1.4.6.1a, p. 310) of

the isoxazolium salt (**635**), having an α-carbethoxy group on the *N*-substituent, make possible easy preparation of a variety of 3-acyltetramic acid:[196/83]




**635**

Conversion of an isoxazole into an indole derivative has sometimes been reported.

As noted in § 1.4.5 (p. 289), pyrolysis of 5-amino-3,4-diarylisoxazoles produces, in addition to the isomeric 1-azirine-3-carboxamide, 2-arylindole-3-carboxamide in low yields. Yield increases up to an overall 40% if the conversion is carried out in two steps, first isolating the azirine carboxamide by heating in boiling decaline and then refluxing the azirine itself in diphenyl ether.[149/74] It may also be worth mentioning that the product mixture produced by flash pyrolysis of 3,5-diphenylisoxazole contains, in addition to 2,5-diphenyloxazole, minor amounts of 2-phenylindole.[147/76]

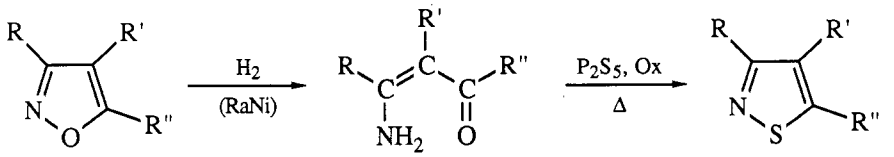
### *1.4.10.4 Transformations into Five-Membered Heterocycles Containing Two Heteroatoms*

Again, isomerization of an isoxazole derivative into the corresponding oxazole is accomplished by thermolysis or photolysis, and the preferred conditions have been illustrated in § 1.4.5. The following examples seem to have some preparative importance (see also Table 1.83, p. 294): irradiation of alkyl 3,5-di- or trisubstituted isoxazoles with 2357-Å wavelength light,[34/66, 83/67,92/72] gas-phase pyrolysis of 3,5-dimethylisoxazole,[5/76] thermal (heating at 230–240°C) or photochemical treatment of 4-acyl (or 4-isopropenyl)-3,5-disubstituted isoxazoles,[176B/74,89/75,99/76] and photoisomerization of ibotenic acid (3-hydroxyisoxazol-5-ylglycine) to muscazone[67/67] (both compounds are natural products isolated from *Amanita muscaria*).

With the exception of the 4,5-tetramethylene compound, which photoisomerizes to the corresponding oxazole in excellent yields,[183/76] 3-unsubstituted isoxazoles do not convert to oxazoles. Rearrangements of 5-alkoxy- or 5-aminoisoxazoles usually stops at the azirine step; at variance, ethyl 5-amino-3-phenylisoxazole-4-carboxylate is reported to isomerize directly to ethyl 5-amino-2-phenyloxazole-4-carboxylate in 20% yield by irradiation in the presence of triphenylene.[17/72] Sometimes the expected oxazole is unstable and rearranges further: thus irradiation of 5-amino-3-phenylisoxazole produces the

azirine and benzoylaminoacetonitrile, possibly arising from ring cleavage of the oxazole.[156/70]

The easy hydrogenolysis of the isoxazole ring to enamino ketones, followed by oxidative thiation, opens a convenient synthetic route to isothiazoles, having the same substitution pattern as the starting isoxazoles:[193/69]

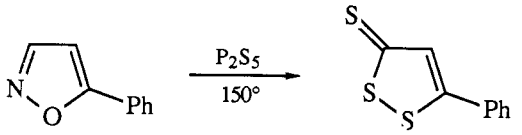



(R,R" = alkyl and/or aryl
R' = H, CN, COOR, $CONH_2$)

The best reagents ratio for the cyclization of the intermediate enamino ketone has proved to be 2 Eq of fresh phosphorus pentasulfide and 1 Eq of chloranil in refluxing toluene; yields in the range 30–50% are currently obtained. The method has been utilized for the synthesis of modified penicillins.[165/67.77/68,78/68]

Thermal treatment of 3-perfluorophenyl-4-nitro-5-phenylisoxazole with phosphorus pentasulfide yields the corresponding isothiazole directly.[257/79]

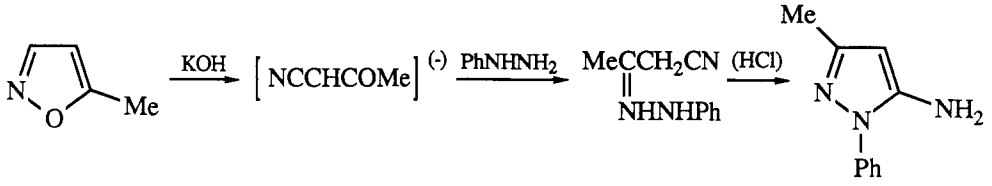
Direct heating of 5-phenylisoxazole with phosphorus pentasulfide at 150°C is claimed to give 5-phenyl-1,2-dithiol-3-thione in unreported yield:[4/58]




An analogous transformation takes place when starting with 3-hydroxy-4,5-dimethylisoxazole.[220/68]

The conversion of isoxazole into pyrazole derivatives has long been known and can be accomplished under the most varied conditions. Instability of the isoxazole nucleus to either thermal treatment or reduction or to basic reagents has been taken advantage of, to realize the transition of the former heterocycle into the latter.

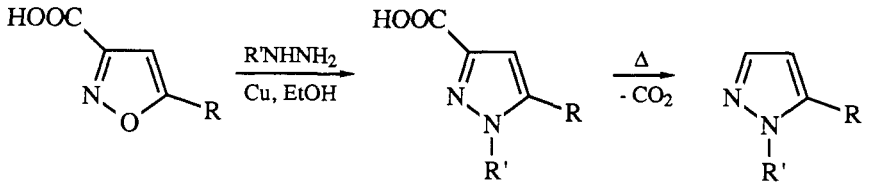
3-Unsubstituted or 3-carboxyisoxazoles are known to open thermally (better in the presence of bases) to the corresponding $\beta$-ketonitriles (in the latter case with decarboxylation). Thus when 5-methylisoxazole is heated with phenylhydrazine, low yields of 5-amino-3-methyl-1-phenylpyrazole are produced.[4/09,10/42] Yields are increased appreciably when potassium hydroxide is added and the intermediate phenylhydrazone is cyclized in an acidic medium:[8/41]



*p*-Nitrophenylhydrazine has been used as well on a base-opened 3-unsubstituted isoxazole.[49/59] The presence of a nitro group in the isoxazole 4-position speeds up ring cleavage, and easy formation of 5-aminopyrazoles is noted both with hydrazine and with phenylhydrazine, even without adding a base.[1/03.10/42.168/71] For example, a 46% yield of 3(5)-amino-5(3)-methyl-4-nitropyrazole is reported in the reaction of 5-methyl-4-nitroisoxazole with 80% hydrazine hydrate in hot alcoholic solution.[168/71]

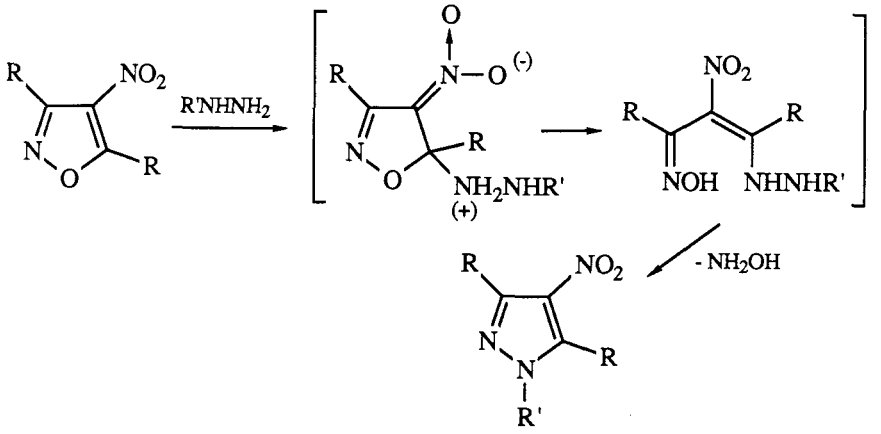
The presence of a carboxylic group in position 3 does not change the course of the reaction substantially. Facilitated by the presence of a base, decarboxylation occurs, giving rise to the anion, which readily converts into the open-chain isomer. 5-Aminopyrazoles are obtained in high yields as final products if the appropriate isoxazole-3-carboxylic acids are heated with excess phenylhydrazine.[14/39,15/39,3/40,34/58,35/58,5/66,62/67]

Interestingly enough, when the reaction is carried out at lower temperature (short boiling in ethanol) under the catalytic influence of copper powder, decarboxylation does not occur, and the corresponding pyrazole-3-carboxylic acid is isolated.[6/40,7/40,8/40] The latter compound can decarboxylate at higher temperatures:

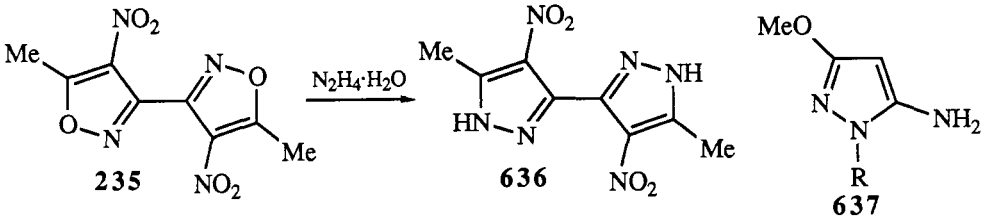



3-Alkyl (or aryl)-substituted isoxazoles usually do not react with hydrazine or its monosubstituted derivatives; individual cases of transformation into pyrazoles have been reported under forcing conditions.[23/60,89/72,60/74] Furthermore, 3-methyl-5-phenylisoxazole has been reported to give 3(5)-methyl-5(3)-phenylpyrazole in low yields when heated with alcoholic ammonia in a sealed tube at 240°C for 14 h.[8/895]

Here, too, an electron-withdrawing substituent such as a nitro group in the 4-position promotes ring cleavage, presumably initiated by a nucleophilic attack on the isoxazole 5-carbon atom. Consequently, 4-nitro-3,5-disubstituted isoxazoles are easily converted into the corresponding pyrazoles by treatment with both hydrazine[10/42.4/43.10/64] and alkyl or aryl hydrazine:[10/42,28/59]



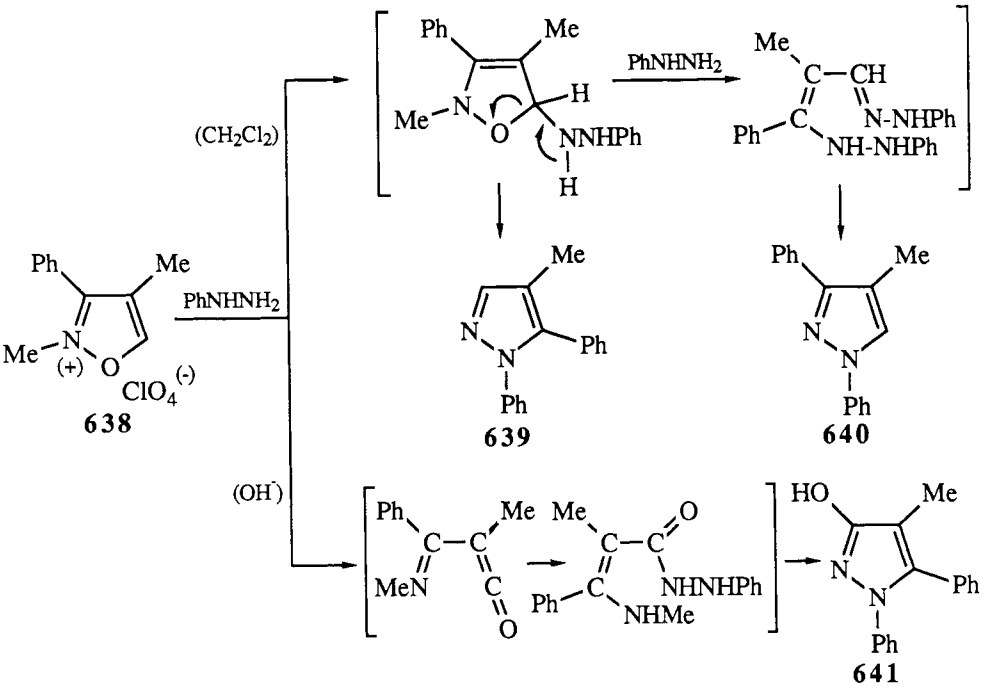
The diisoxazole "dislite" (**235**) is similarly transformed into its pyrazole analogue (**636**):[8/46]



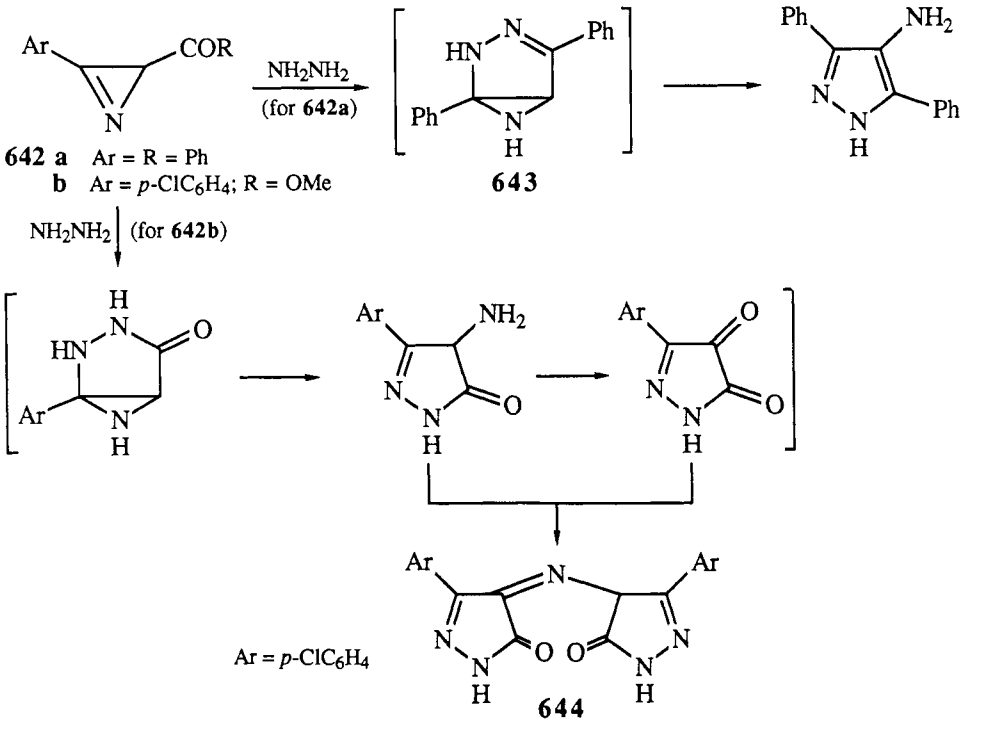
5-Amino-3-methoxyisoxazole has been reported to react with aryl- or tosylhydrazine to yield the pyrazole derivative (**637**).[180/71]

Since, as noted earlier (see § 1.4.6.1e, p. 309), quaternization of isoxazoles enhances their instability toward nucleophiles, it is not surprising that phenylhydrazine reacts with 2,4-dimethyl-3-phenylisoxazolium perchlorate (**638**), giving in neutral media a mixture of methyldiphenylpyrazoles (**639** and **640**) in high yields, and in the presence of potassium hydroxide, of 3-hydroxypyrazole (**641**)(Scheme 1.38).[52/69]

Sometimes pyrazole derivatives can be reached from isoxazoles in two steps through the azirines, formed at first pyrolytically or photolytically. For example, 3-benzoyl-2-phenyl-1-azirine (**642a**), the photochemical rearrangement product from 3,5-diphenylisoxazole, reacts with hydrazine to yield 4-amino-3,5-diphenylpyrazole, presumably via **643**.[83/67] Similarly, methyl 2-*p*-chlorophenyl-1-azirine-3-carboxylate (**642b**), the thermal isomerization product from 3-aryl-5-methoxyisoxazole, gives with hydrazine the rubazonic acid analogue (**644**)(Scheme 1.39).[128/71]

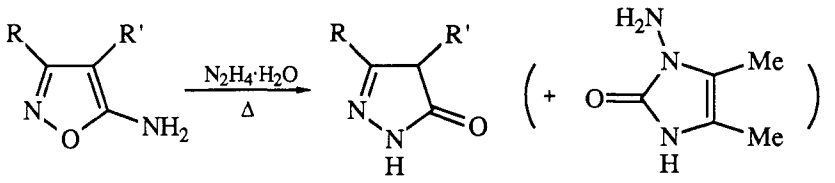



Scheme 1.38.

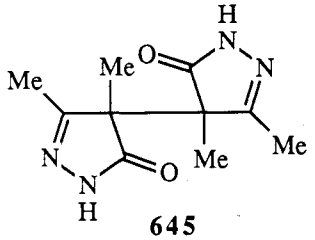



Scheme 1.39.

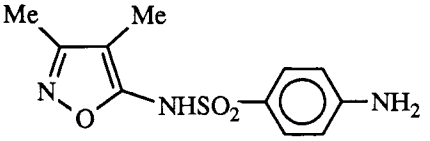
3,4-Dialkyl-5-aminoisoxazoles have been reported to isomerize into the corresponding pyrazolin-5-ones when heated with 50% hydrazine hydrate on a steam bath:[16/53,16B/53]



As a by-product, the 3-aminoimidazol-2-one derivative is sometimes produced.[16B/53] Treatment of 5-amino-3,4-dimethylisoxazole with phenylhydrazine at 100°C afforded the dimeric product **645**,[16/53] whereas reaction of its *p*-aminophenylsulfonyl derivative with hydrazine gives the corresponding pyrazole sulfonamide (**646**).[23/54]



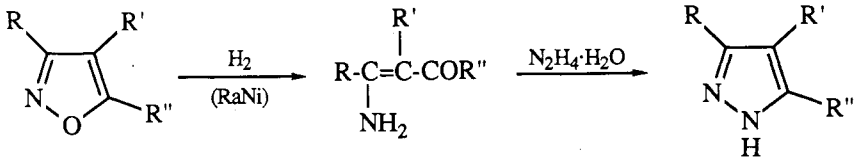
**645**



**646**

As noted earlier (see § 1.4.5, p. 291), when heated alone or in the presence of bases, 5-hydrazinoisoxazoles yield a complex mixture of products containing triazolones and pyrazolinones. Treatment of 3,4-disubstituted 5-hydrazinoisoxazoles (or their precursors, 5-chloro analogues) with hydrazine produces 1-amino-3,4-disubstituted pyrazolin-5-ones as the main products.[157/72]

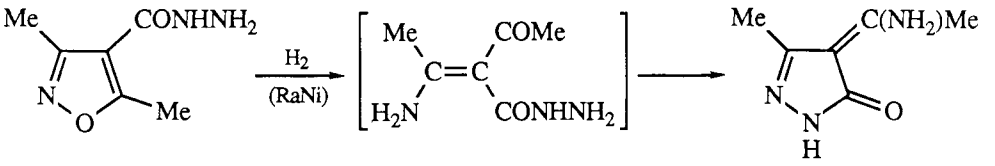
Previous hydrogenolysis to the enamine, which is then treated with hydrazine, makes it possible to transform an isoxazole into a pyrazole having the same substitution pattern:[8/67,8/70,134/71]



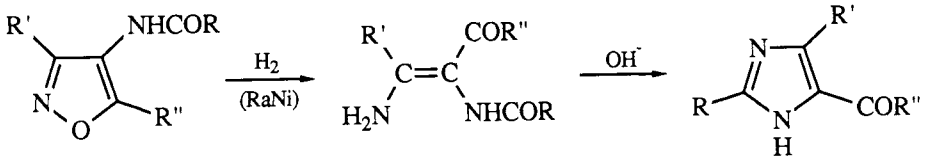
Starting with 5-aminoisoxazoles, the corresponding 5-pyrazolinones are obtained via the same sequence.[18/55]

When the isoxazole has a suitable functional group in the proper position, spontaneous cyclization can occur at the enamine stage: for example, the

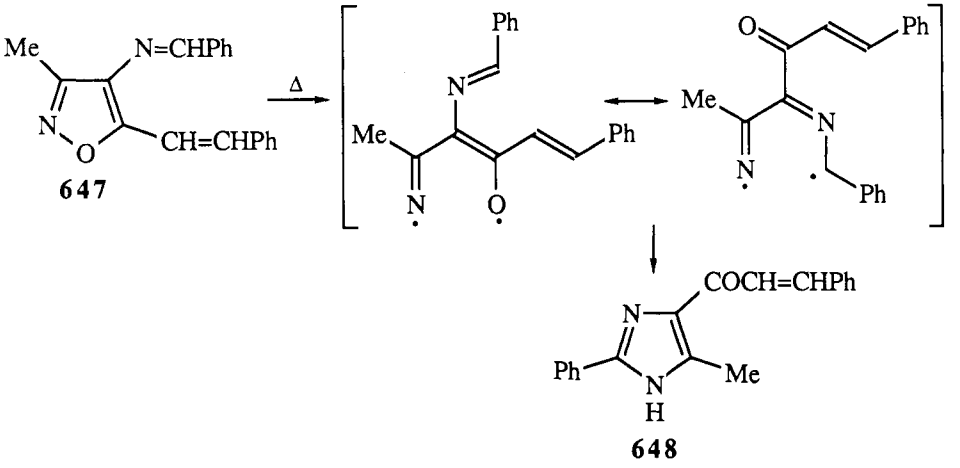
presence of a carbohydrazide group in position 4 causes the formation of 5-pyrazolinone derivatives:[7/66]



When an acylamino group is present in position 4, treatment of the intermediate enamine with alkaline hydroxide causes immediate cyclization to an acylimidazole derivative:[8/70,10/70]



Contrary to results reported previously,[272/83] thermal rearrangement of 4-benzylideneaminoisoxazole (**647**) gives satisfactory yields of the imidazole ketone (**648**):[1/85]



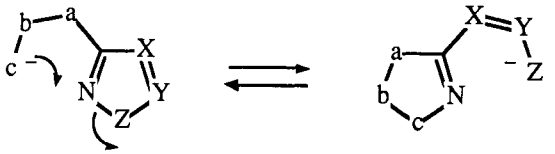
**647**

**648**

Pyrolysis of 3,4-dialkyl-5-aminoisoxazoles at 180–190°C, especially in the presence of urea, results in isomerization to 4,5-dialkyl-4-imidazolin-2-ones in moderate to good yields.[31/52,32/52] With aryl-substituted derivatives, isomerization to 1-azirinecarboxamides is prevalent (see 1.4.5, p. 289).

### *1.4.10.5 Transformations into Five-Membered Heterocycles Containing Three or Four Heteroatoms*

A well-known intramolecular rearrangement[191/74,3B/81] in the heterocyclic field involves a five-membered nitrogen-containing heterocycle having a suitable three-atom substituent in the 3-position and fits the following general scheme:

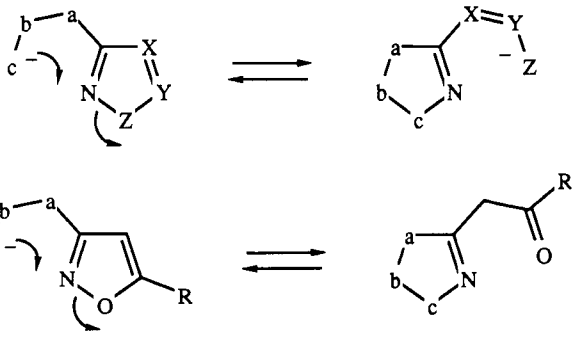


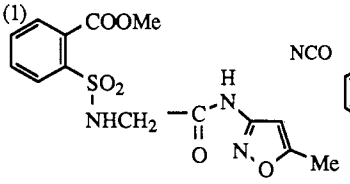
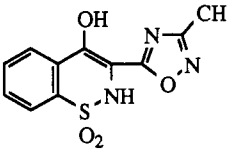
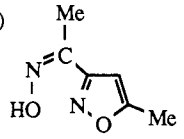
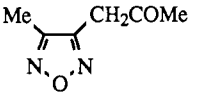
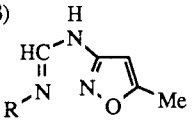
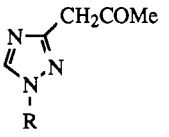
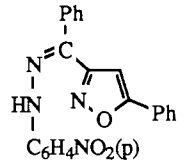
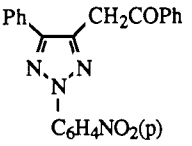
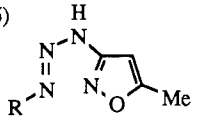
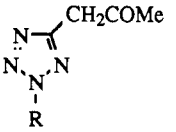
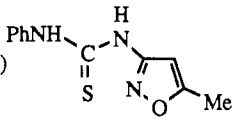
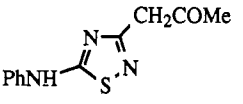

Application of this process to the isoxazole ring (Z = O; X = Y = C) opens an easy route to other polyheteroatomic five-membered heterocycles. A purely thermal procedure (heating the isoxazole to its melting point—better if in the presence of copper powder) and a base-promoted procedure are most frequently used. The reaction probably follows a concerted pathway, although a two-step mechanism cannot be excluded a priori.[191/74] The cleavage of at least one N–O bond in the starting material and the formation of a C–N, N–N, or N–S bond in the product increase the rearrangement rate. The isoxazole ring is prone to this type of transformation, and several other heterocycles can thus be obtained, depending on the nature of the three-atom sequence in the isoxazole 3-position. For a given side chain the following order of rearrangement rate was observed: 1,2,4-oxadiazole > isoxazole > 1,2,5-oxadiazole.[138B/77,142/77]

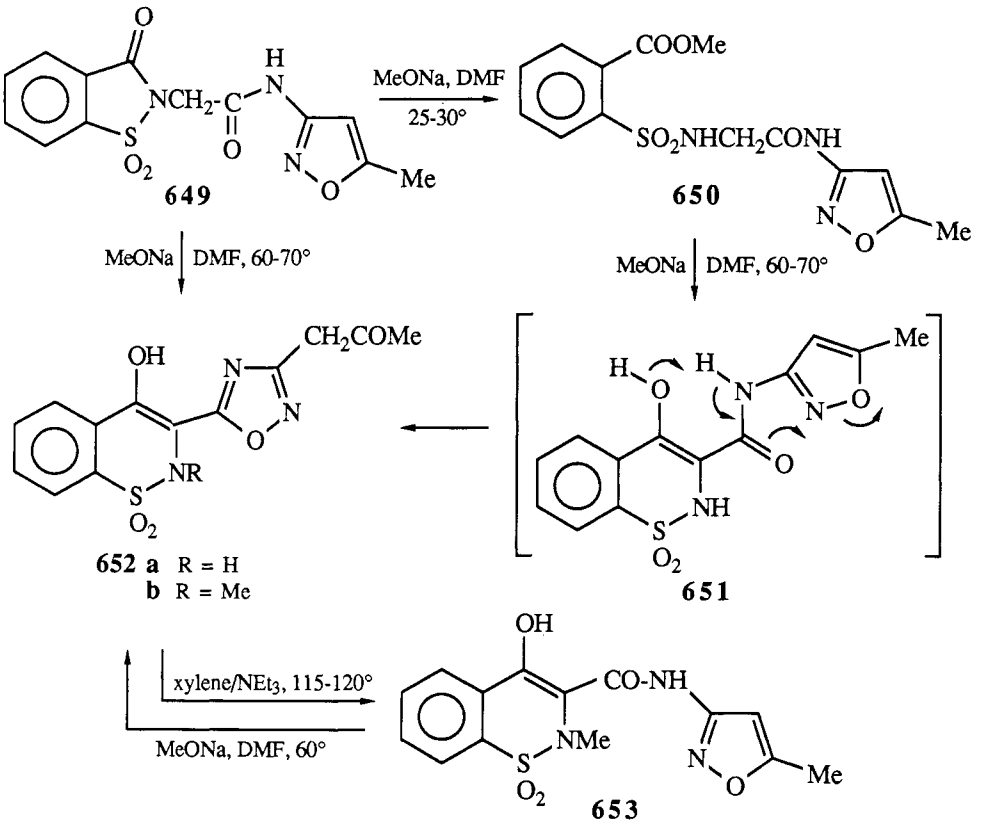
In agreement with the foregoing statements, isoxazoles having the same three-atom sequence in the 4-position cannot rearrange. For example, the oxime or the phenylhydrazone of 4-acetyl-5-methyl-3-phenylisoxazole, apart from *syn/anti* thermal equilibration, failed to rearrange to different heterocyclic systems.[89/75] Some examples of rearrangements involving isoxazole derivatives are collected in Table 1.92. The following ring transformations are exemplified in the table.

(1) *Transformation into 1,2,4-oxadiazoles.* When treated with a strong base, the *N*-substituted saccharin amide (**649**), undergoes both ring enlargement of the thiazole to a 1,2-benzothiazine ring and rearrangement of the isoxazole ring to the 1,2,4-oxadiazole system (**652a**). The route to **652a** has been demonstrated to pass through the open-chain compound **650** and the presumable intermediate (**651**)(Scheme 1.40). The methylated derivative (**652b**) can in turn be rearranged in basic media to *N*-isoxazolyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (**653**).[183/82] This and a series of similar compounds have been synthesized for their anti-inflammatory properties.[255/76,264/76,269/76,256/77,266/77,183/82] As a matter of fact, a simpler derivative, such as 3-acetylamino-5-methylisoxazole, failed to rearrange to 3-acetonyl-5-methyl-1,2,4-oxadiazole.[100/67]

TABLE 1.92



| Starting isoxazole | abc | Product | Conditions | Yield (%) | References |
|---|---|---|---|---|---|
| (1)  | NCO |  | MeONa, DMF, 60-70° | 65 | 183/82 |
| (2)  | CNO |  | Cu, Δ > m.p. | 90 | 100/67 |
| (3)  | NCN |  | EtONa, EtOH, w.b. 20 min, then 10% AcOH | 76-100 | 92/64 |
| (4)  | CNN |  | Cu, Δ > m.p., or $Me_2CO$, $NH_4OH$, Δ | 100 | 18/71 |
| (5)  | NNN |  | aq. $Me_2CO$, 5% $NH_4OH$, Δ w.b. 5 min | 56-94 | 94/64, 69/65 |
| (6)  | NCS |  | EtOH, r.t., 10%aq. KOH, 10 min, or refluxing benzene | 80 | 142/77 |




**Scheme 1.40.**

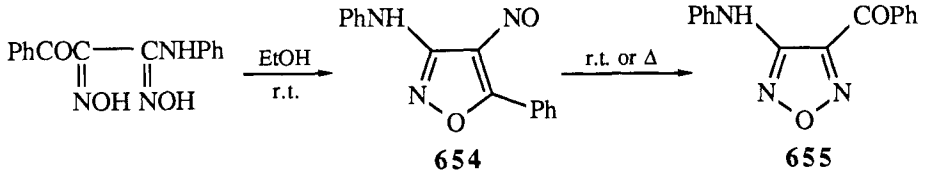
(2) *Transformation into 1,2,5-oxadiazoles.* Oximes of 3-acylisoxazoles are long known to isomerize to 1,2,5-oxadiazole derivatives. The best yields seem to be attained when the oxime is heated with copper powder above its melting point,[100/67] but the reaction also occurs readily in alcoholic potassium hydroxide,[7/37.88/64] at least when 3-aroylisoxazole oximes are chosen as starting materials. The oxadiazole oximated in the side chain is reported to be obtained directly when the 3-acylisoxazole is heated with an excess of hydroxylamine, usually in a slightly basic medium.[3/30,10/38,10/39,1B/46]

Sometimes a strong basic medium can induce further hydrolytic decomposition: for example, treatment of 3-benzoyl-4,5-diphenylisoxazole oxime with ethanolic 30% KOH gives both the expected oxadiazole ketone and 3-benzoyl-4-phenyl-1,2,5-oxadiazole, with spontaneous detachment of benzoic acid.[2/37,160/83]

In addition to correcting erroneous statements of the older literature, a recent reinvestigation[160/83] of the reaction demonstrated that only the isoxazole (*Z*)-

oximes rearrange smoothly into the furazan ketones, the (*E*)-oximes remaining unchanged under the same experimental conditions. This discovery explains why the oximation products of 3-acetylisoxazoles, which have the (*E*)-configuration, do not rearrange in basic media but require heating with copper powder.

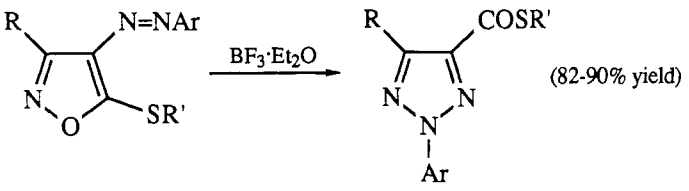
A completely different type of rearrangement to furazan is involved in the conversion of the nitroso derivative **654** to **655**; this rearrangement is slow when storing at room temperature and rapid when heating in solution:[143/69]



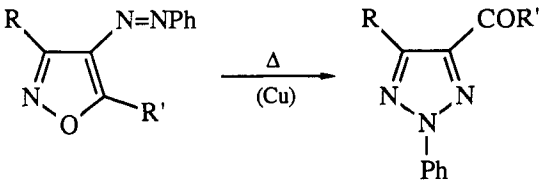

(3) *Transformation into 1,2,4-triazoles.* The necessary starting formamidine derivatives have been prepared either by condensation of 3-amino-5-methylisoxazole with triethyl formate and a heterocyclic amine or by an exchange reaction of the already formed heterocyclic formamidine with an arylamine. Subsequent isomerization occurs either at the melting point or in a basic medium, but always under anhydrous conditions in order to minimize the hydrolytic processes.[92/64]

(4) *Transformation into 1,2,3-triazoles.* The isomerization of 3-acylisoxazole arylhydrazones closely parallels that of the related oximes and shows the same wide applicability. A thermal procedure is usually adopted,[12/40,5/47,100/67,18/71,175/83] but base catalysis is also effective.[18/71,175/83] Depending on the experimental conditions, *N*-methyl- and *N*-phenylhydrazones can also lead to indole derivatives.[175/83]

A completely different approach to 1,2,3-triazoles begins with 4-arylazoisoxazoles. Treatment of their 5-alkylthioderivatives with a Lewis acid gives excellent yields of the isomeric alkyl 2-aryl-1,2,3-triazole-4-thiocarboxylates:[248/79]



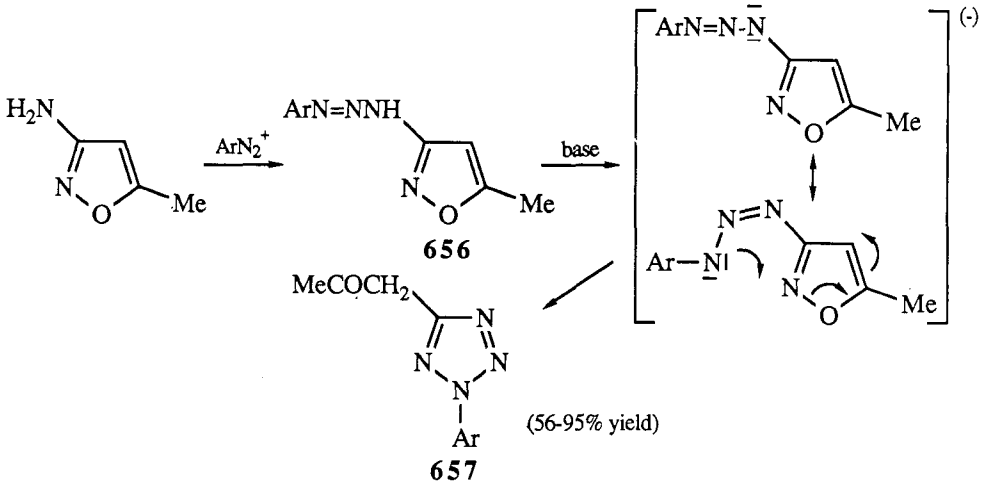

A purely thermal conversion of 3,5-disubstituted-4-phenylazoisoxazoles into 4-acyl-2-phenyl-5-substituted-1,2,3-triazoles has been reported to occur by short heating at 150°C or higher:[3/28,88/66]




A more complicated reaction sequence underlies the conversion of 3,5-dimethyl-4-nitroisoxazole to 5-methyl-2-phenyl-4-phenylazo-1,2,3-triazole upon treatment with 2 mol of phenyldiazonium chloride in dilute alkaline solution, which probably involves a preliminary base-promoted ring cleavage of the activated isoxazole.[7/42]

Treatment of the diazonium salt from 4-amino-3,5-dimethylisoxazole with cupric sulfate can also lead to acetyltriazole derivatives.[4/41,37/62] For the formation of a 4-acyl-1-hydroxy-1,2,3-triazole by diazotization of a 3-unsubstituted 4-aminoisoxazole, see § 1.4.6.2, p. 320.

(5) *Transformation into tetrazoles.* Triazenes (**656**), the condensation products of 3-amino-5-methylisoxazole with aromatic diazonium salts, are isomerized in alkaline media into 2-substituted 5-acetonyltetrazoles (**657**):[16/62,94/64,69/65]




Ammonia in aqueous acetone has been found to give the best results.

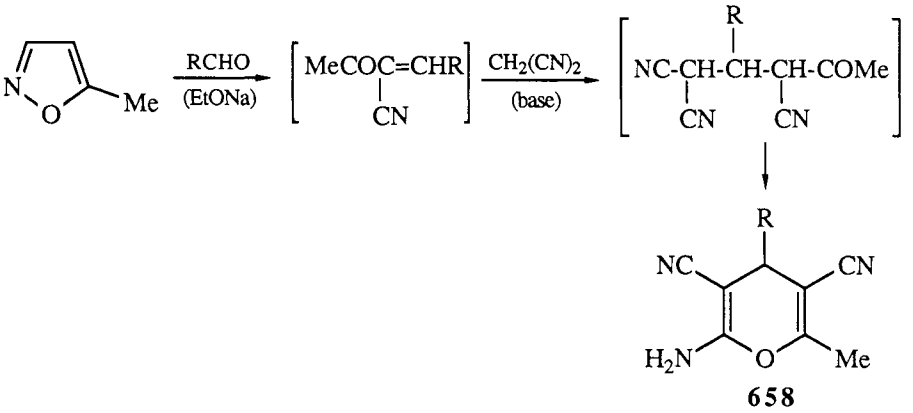
A related rearrangement is the already reported reaction (see § 1.4.6.1e, p. 312) of 2-methyl-5-phenylisoxazolium methosulfate with sodium azide to give an iminoazide, which subsequently cyclizes when refluxed in ethanol.[165/66]

(6) *Transformation into 1,2,4-thiadiazoles.* The intermediate isoxazolylthiourea is isolable only if the reaction of 3-amino-5-methylisoxazole with

phenylisothiocyanate is carried out in solution at room temperature. Careful heating of the two reagents without solvents up to 100°C affords the 1,2,4-thiadiazole derivative directly in 50% yield.[142/77]

### *1.4.10.6 Transformations into Six-Membered Heterocycles Containing One Heteroatom*

Relatively few reports involve transformations of the isoxazole into the *pyran* ring. One of these utilizes the easy *in situ* availability of cyanoacetone (see § 1.4.6.1a, p. 301). Thus, when 5-methylisoxazole is opened by sodium ethoxide in the presence of an aldehyde and a Michael addition of malononitrile to the resulting α,β-unsaturated ketone is carried out, spontaneous cyclization produces 2-amino-3,5-dicyano-4*H*-pyrans (**658**) in variable yields:[39/84]

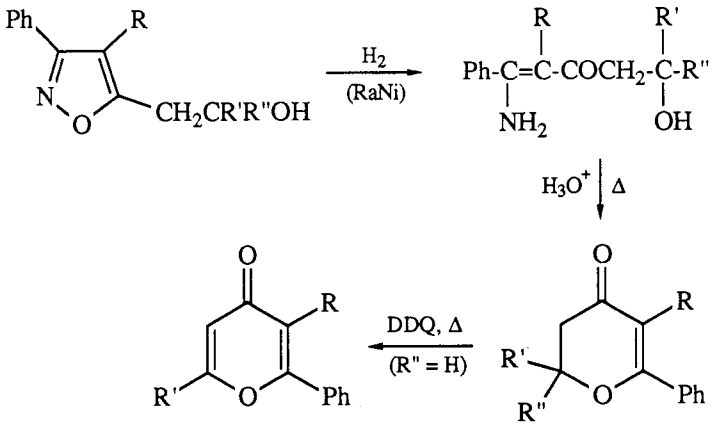



**658**

In fact, 3,5-dicyano-2,6-dimethyl-4-phenyl-4*H*-pyran has also been recognized as a low-yield by-product in the reaction mixture obtained from 5-methylisoxazole and benzaldehyde in the presence of a strong base.[45/84]

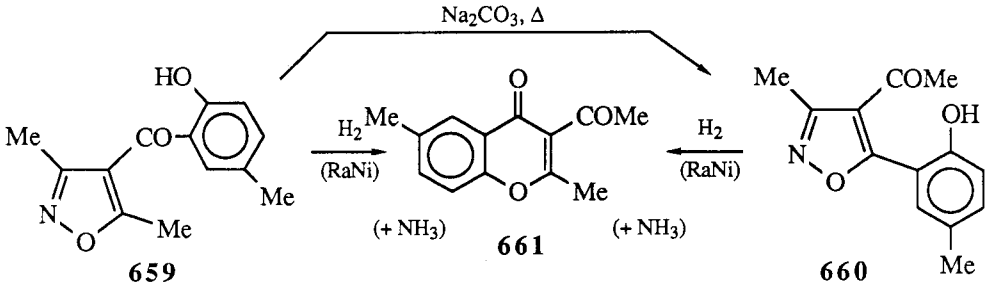
Thermal (or base-promoted) ring opening of 5-(*o*-hydroxyphenyl)isoxazole or its substituted derivatives furnishes 2-aminochromone, presumably by cyclization of the labile intermediate α-cyanoketone.[199/77,227/77,220/78] By contrast, treatment of 5-(*o*-hydroxyphenyl)isoxazole-3-carboxylic acid with acetic anhydride is reported to lead to 3-cyano-2-methylchromone.[227/77] Substituted 3-cyanochromones have also been obtained by alkaline treatment of 4-(2-hydroxybenzoyl)isoxazoles.[15/73,249/78]

Catalytic hydrogenation of suitably substituted isoxazole derivatives also leads to ring opening and reclosure: this occurs, for example, with 5-β-hydroxyalkylisoxazoles, which are transformed in moderate (20–44%) yields into 2,3-dihydro-4-pyrones by acidic treatment of the intermediate (not always isolated) β-hydroxyenamino ketones:[82/66,168/66,276/77]




Oxidation with dichlorodicyanobenzoquinone affords the corresponding 4-pyrones.[276/77]

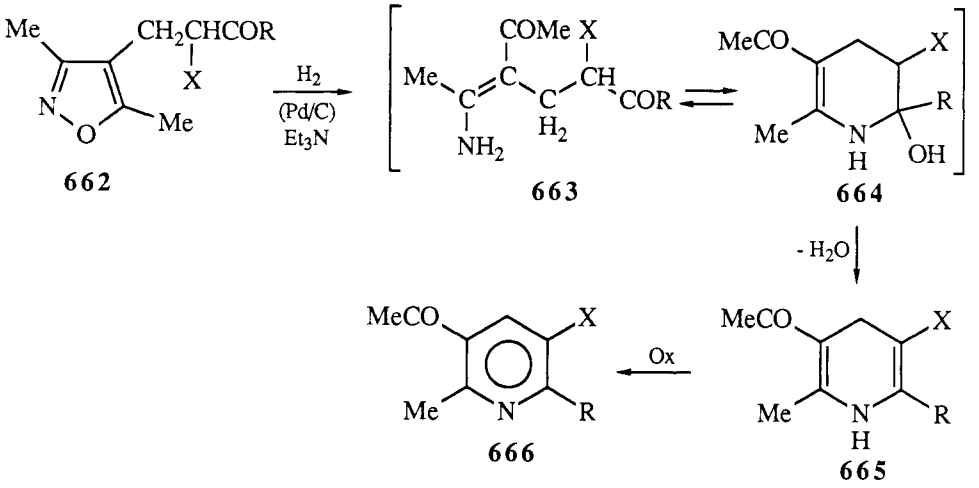
Similarly, 3-acetyl-2,6-dimethylchromone (**661**) is obtained by hydrogenation of both the 4-acetylisoxazole (**659**) and its isomer (**660**). Formation of the enamino ketone, hydrolysis, and intramolecular cyclization with intervention of the phenolic OH situated at the proper distance explains the chromone ring formation:[218/70]




For pyrone derivatives arising from the base-promoted ring opening of isoxazolium salts, see § 1.4.6.1e, p. 311.

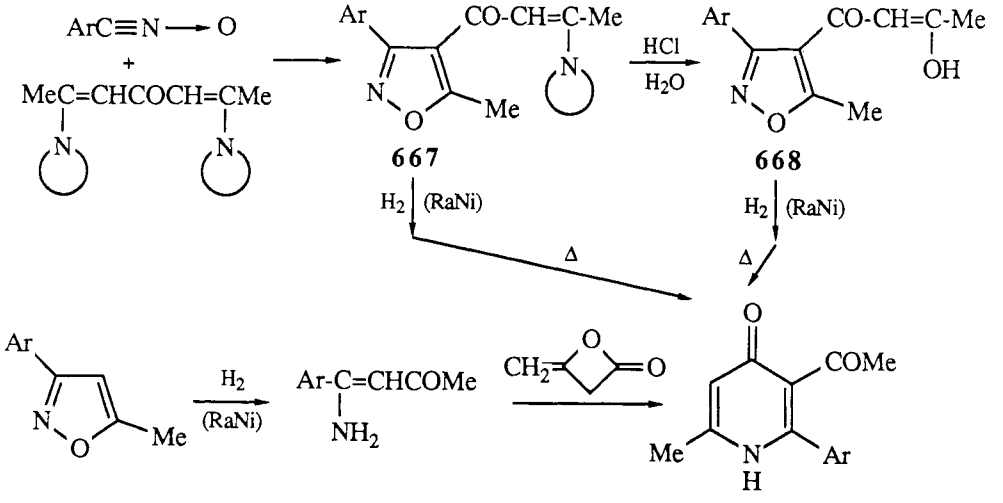
More important are the pathways leading to *pyridine* derivatives. The *in situ* formation of a 1,5-diketone monoimine can be achieved by catalytic hydrogenation of an isoxazole derivative, carrying a carbonyl or a masked carbonyl group in the proper position with respect to the ring nitrogen. Thus 4-(3-oxoalkyl)-isoxazoles (**662**), which can be prepared easily by alkylation of ketones or enamines with the readily available 3,5-disubstituted 4-chloromethylisoxazoles,[68/58] are a convenient source of 3-acylpyridines.[79/67,189/70,148B/71] Catalytic hydrogenation is performed on palladium–charcoal in the presence of triethylamine, and the intermediate hydrogenolyzed product (**663**), which can exist in the

cyclic carbinolamine form (**664**), dehydrates to dihydropyridine (**665**). This in turn is transformed into the final product (**666**) through an oxidation process, which can occur either spontaneously in the air or require treatment with sodium nitrite and hydrochloric acid:



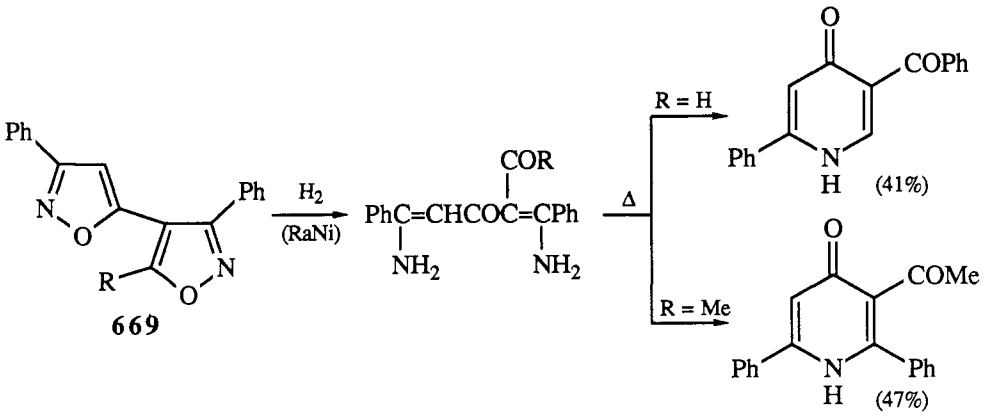

Dehydration of the carbinolamine takes place under the basic conditions of the hydrogenolysis, if the process is activated by the presence of a carbonyl group (**662**: X = COR′), or under the acidic conditions used in the oxidation step.

A $\beta$-diketone side chain in the isoxazole 4-position provides convenient entry into the 3-acyl-4-pyridone system: thus both the enamino ketone (**667**), easily accessible through a nitrile oxide synthesis, and its hydrolysis product (**668**) are hydrogenolyzed to unstable open-chain intermediates, which cyclize on heating:[219/72]

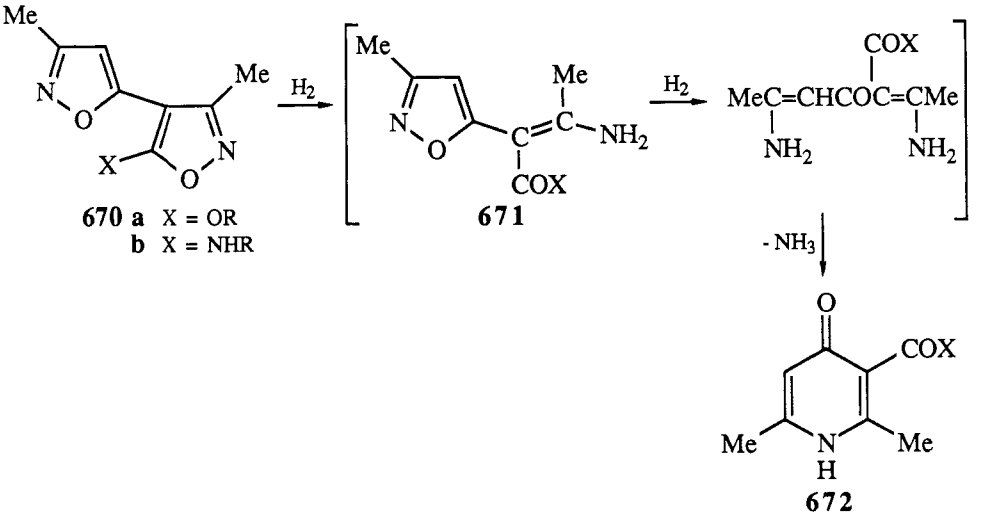


The same compound is formed, following a previously known procedure,[173B/69] by reaction of diketene with the appropriate enaminoketone, most conveniently prepared by hydrogenolysis of 3-aryl-5-methylisoxazole.[219/72]

Since the isoxazole ring is a synthon for β-diketones, the same types of compounds are obtained from 4,5′-diisoxazoles (**669**);[219/72] it is interesting to note that cyclization involves the formyl group (**669**: R = H) with preference to the enamino moiety, which is more reactive when R ≠ H:

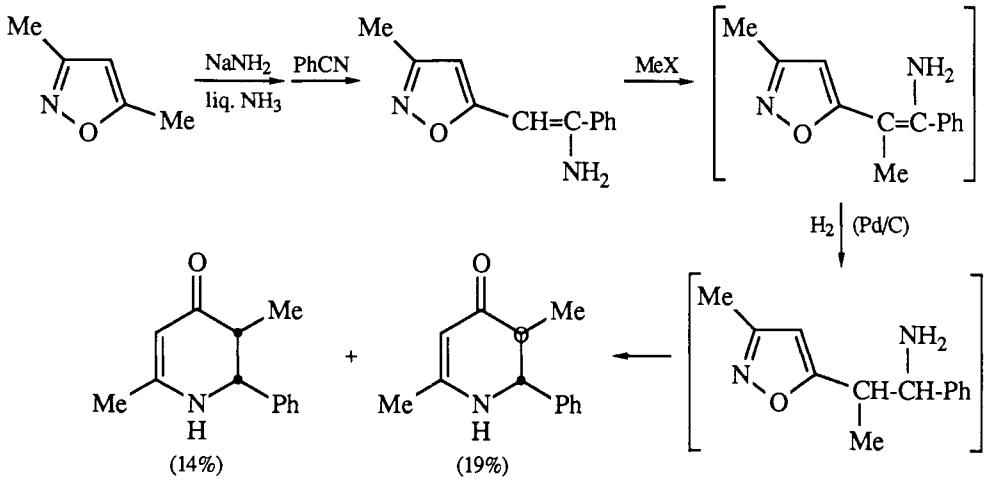



Similarly, γ-lutidone derivatives are prepared by hydrogenolysis of some derivatives of the so-called "dimethyldiisoxazolone," such as **670a** or **670b**. Whereas hydrogenation on Pd/C selectively opens only the activated isoxazole ring to give **671**, catalysis with Raney nickel cleaves both rings and the lutidone carboxylic esters or amides (**672**) are formed (Scheme 1.41).[182/71] Since the

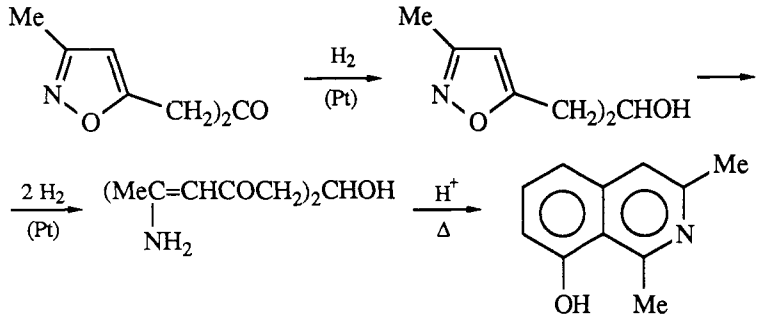



Scheme 1.41.

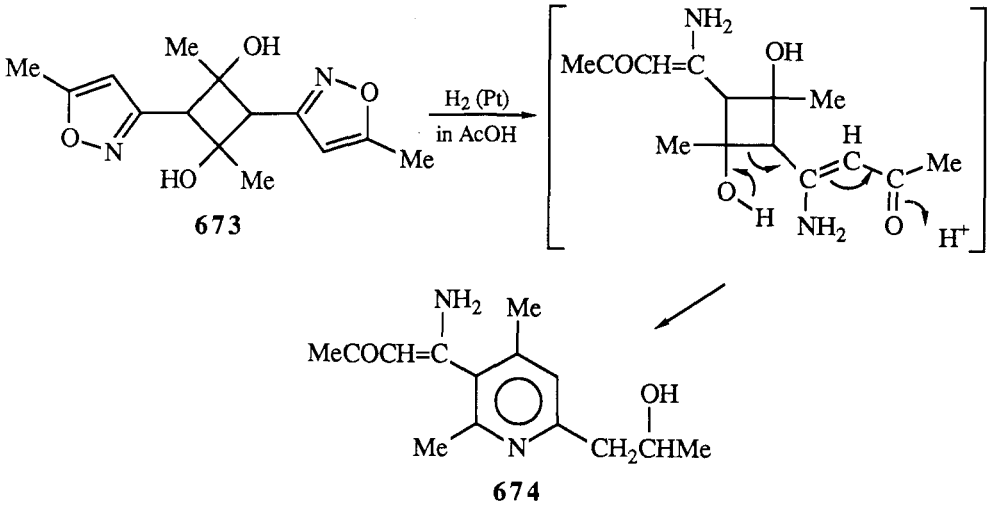
compounds **670** are easily accessible from acetoacetate, the method has an appreciable synthetic significance. Another γ-lutidone derivative has been obtained from a bisisoxazolyl ketone.[94/77] An analogous hydrogenolytic cleavage of 5-β-amino-substituted isoxazoles (easily obtained by treatment of the dimethylisoxazole anion with benzonitrile) leads to 2,3-dihydropyridones, sometimes as a mixture of diastereomers; for example:[42/73]



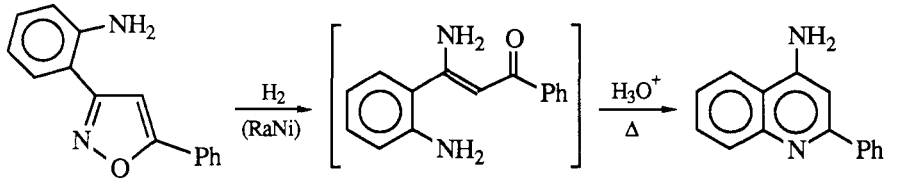

Synthesis of an 8-isoquinolol derivative from a bis(5-isoxazolyl)acetone occurs through acidic treatment of the bis-β-enaminoketo alcohol formed by catalytic hydrogenolysis:[94/77]



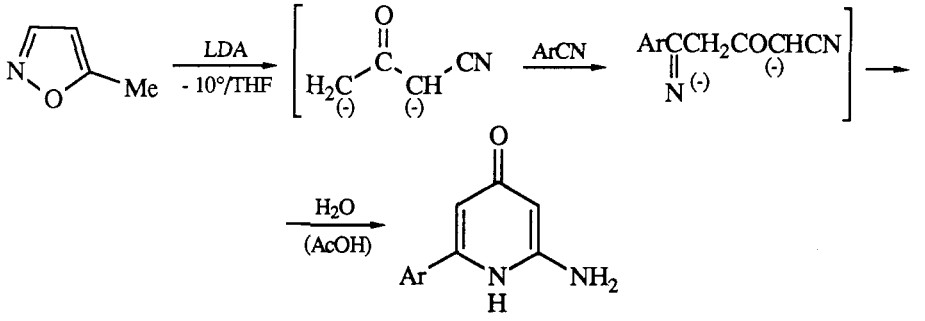

The cyclizing interaction between the ring nitrogen and an appropriately separated functionality is not limited to side chains in position 4 or 5; at least two examples are known, both of which involve a group situated on the 3-substituent. Thus the pyridine derivative **674** is produced when 2,4-bisisoxazolylcyclobutane-1,3-diol (**673**) is hydrogenated on a platinum catalyst:[103/69]




3-*o*-Aminophenyl-5-phenylisoxazole is reported to be catalytically reduced to 4-amino-2-phenylquinoline in 75% yield:[82/66]



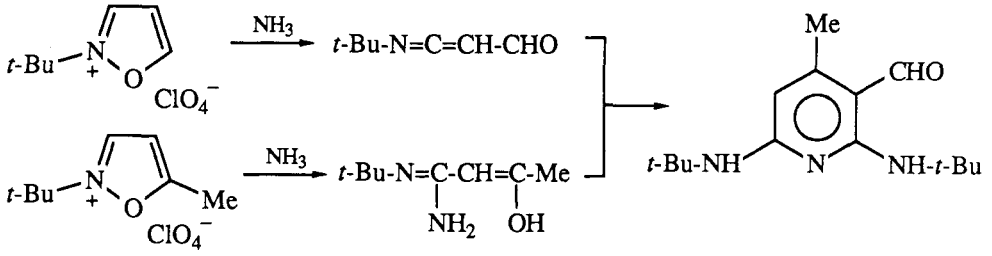

Base-promoted cleavage of suitable isoxazole derivatives has occasionally been utilized for the synthesis of pyridine compounds: 5-methylisoxazole, for example, after formation of the open-chain 1,3-dianion and subsequent treatment with an aromatic nitrile for a long period (18 h) yields a 2-amino-6-aryl-4-pyridone:[264/78]



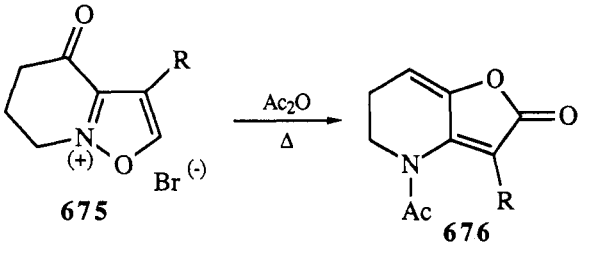
A shorter reaction time makes it possible to isolate the expected open-chain vinylogous amidonitrile.

5-Unsubstituted isoxazolium salts are known to be cleaved by nucleophiles (see § 1.4.6.1e, p. 315). Salts of active methylene compounds, such as alkyl malonates, ethyl acetoacetate, or cyanoacetamide, give minor amounts of 2-pyridone or 4-pyridone compounds. Cyclic enamines give rise to substituted 2,3-trimethylene- or 2,3-tetramethylenepyridinium salts.[52/69]

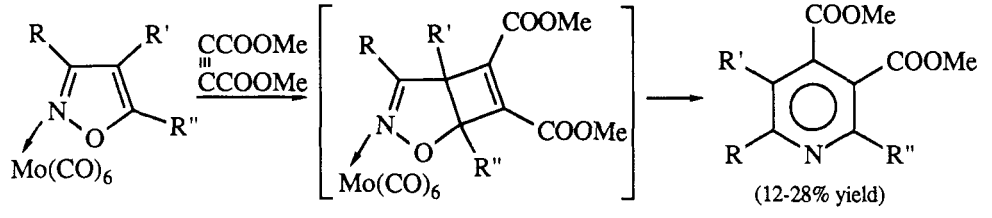
Condensation of the two products, obtained by ammonia-promoted ring cleavage of the unsubstituted and of the 5-methylated isoxazolium salts, respectively, afforded the synthesis of a 3-formylpyridine derivative along the following steps:[274/77]



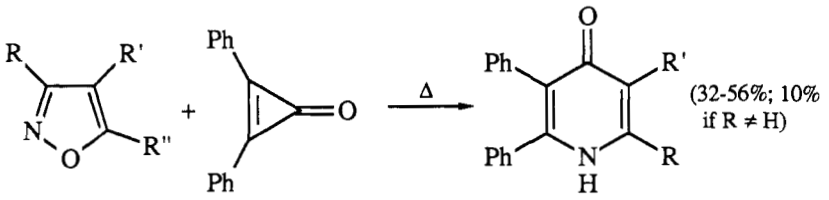

Another interesting transformation concerns the condensed isoxazolium salt **675**, which forms the condensed hydropyridine **676** when treated with acetic anhydride:[141/72]




Complexation with $[Mo(CO)_6]$ induces the reaction of several substituted isoxazoles with dimethyl acetylenedicarboxylate: addition to positions 4 and 5 occurs and moderate yields of pyridine derivatives are obtained:[39/83]



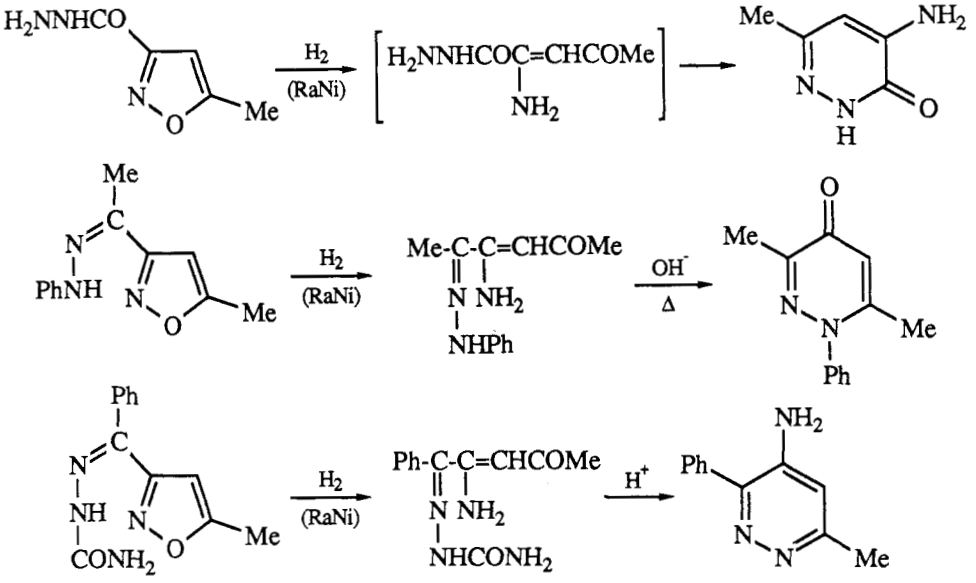
A purely thermal process is the reaction of tri- or 4,5-dialkylisoxazoles with diphenylcyclopropenone in boiling toluene: with loss of a ketene moiety, a polysubstituted 4-pyridone is formed:[48/73]



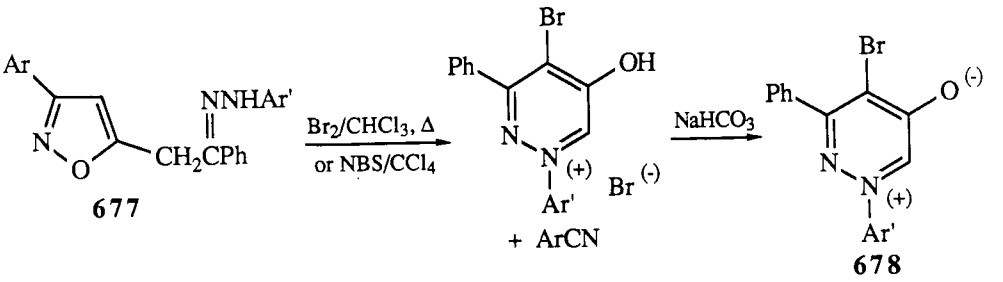

The reaction mechanism is still obscure, but an initial attack on the electrophilic cyclopropenone ring by the ring nitrogen atom seems feasible.

### *1.4.10.7 Transformations into Six-Membered Heterocycles Containing More Than One Heteroatom*

All three types of diazines have been obtained by transformation of isoxazole derivatives, the most frequently used method being catalytic hydrogenation. The 1,2,6-relationship between two nitrogen atoms and the carbonyl group, necessary for the formation of the pyridazine ring, is contained in the following 3-substituted isoxazole derivatives: (1) carboxylic and hydrazides, (2) ketone phenylhydrazones, or (3) semicarbazones. As exemplified below, hydrogenolysis of the foregoing compounds, followed by thermal or base (or acid)-promoted cyclization of the intermediate substituted enamino ketones, furnishes, respectively, (1) 4-amino-2*H*-pyridazin-3-ones,[7/66] (2) 1-phenyl-1*H*-pyridazin-4-one,[7/68] and (3) 4-aminopyridazines:[8/67]



An interesting degradative rearrangement of 3-aryl-5-phenacylisoxazole arylhydrazones (**677**) to pyridazine betaines (**678**) has been reported to occur through bromination (with bromine or with *N*-bromosuccinimide):[293/83]




5-Acylaminoisoxazoles are hydrogenolyzed to pyrimidin-4-ones (**679**), and the process has general applicability, as the examples reported in Table 1.93 show:

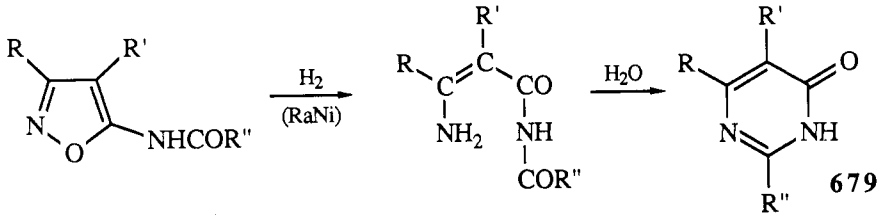


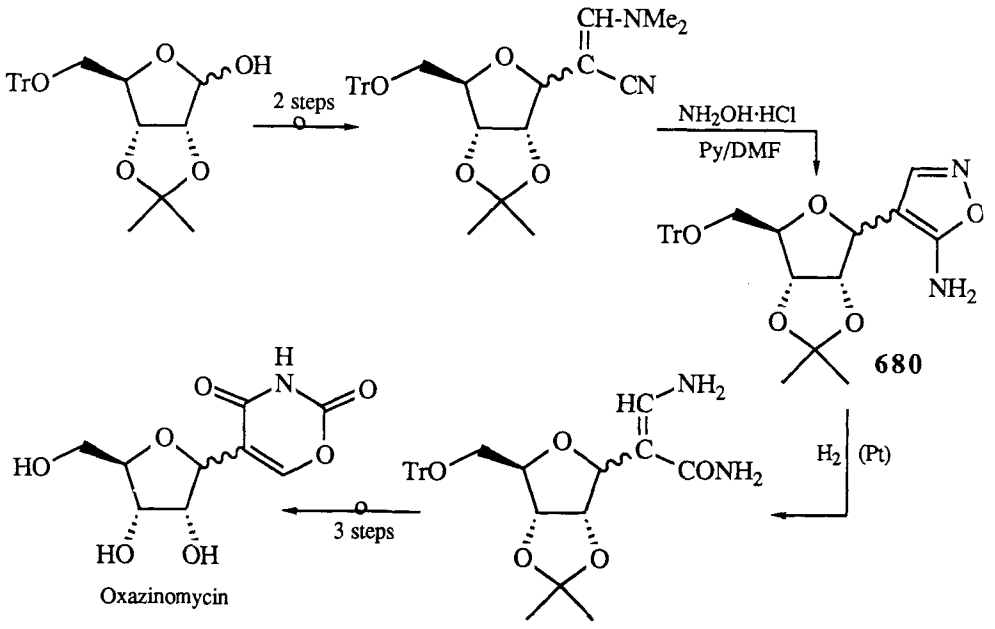

TABLE 1.93. TRANSFORMATIONS OF 5-ACYLAMINOISOXAZOLES INTO PYRIMIDIN-4-ONES (**679**)

| R | R' | R" | Conditions | Yield (%) | References |
|---|---|---|---|---|---|
| $NH_2$ | H | MeCO | $H_2$/Pt | 43 | 89/65 |
| Me | H | MeCO | $H_2$/Ra Ni | (good) | 18/55 |
| Ph | H | CHO | $H_2$/Ra Ni or Adams Pt, then heat | | 17/54 |
| Me | H | 4-$NH_2C_6H_4$[a] | $H_2$/Ra Ni, 3 atm, then reflux in KOH/EtOH | 55 | 162/74 |
| Ph | H | MeCO | $H_2$/Ra Ni or Adams Pt, then heat | 49 | 17/54 |
| Ph | H | EtOOCCO | $H_2$/Pt, EtOH, 50° | 78 | 55/82 |
| Ph | H | 4-$NH_2C_6H_4$[a] | $H_2$/Ra Ni, then reflux in KOH/EtOH | - | 9/70 |
| Ph | H | PhCO | $H_2$/Ra Ni or Adams Pt, then heat | | 17/54 |
| Me | Me | CHO | $H_2$/Ra Ni, 30 atm, 50° | 69.5 | 7/63 |
| Me | Me | MeCO | $H_2$/Ra Ni or Pd-C | 77 | 18/55, 90/63 |
| Et | Me | MeCO | $H_2$/Ra Ni | (good) | 18/55 |
| Me | Me | *n*-BuCO | $H_2$/Ra Ni | 74 | 7/63 |
| Me | Me | 4-$NH_2C_6H_4$[a] | $H_2$/Pd-C, then bases | 32.5 | 90/63 |
| Me | $(CH_2)_2OMe$ | 4-$NH_2C_6H_4$[a] | $H_2$/Pd-C, then reflux in KOH/EtOH | - | 90/63 |
| Ph | Me | 4-$NH_2C_6H_4$[a] | $H_2$/Ra Ni, 3 atm, then reflux in KOH/EtOH | ca. 55 | 162/74 |

[a] Starting material the *p*-nitrophenylaminoisoxazole.

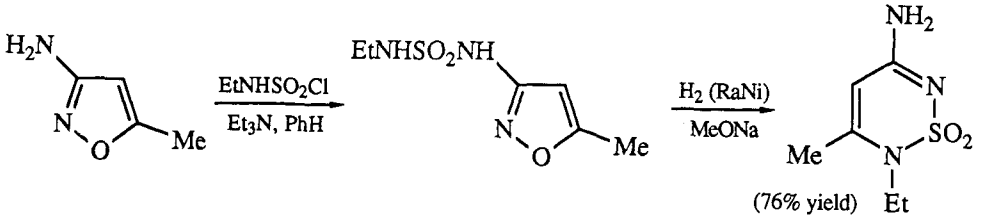
Alternatively, 5-aminoisoxazoles are first transformed by hydrogenolysis into enaminoamides, whose acylation affords the same pyrimidin-4-ones.[3/56] The intermediate open-chain compound has sometimes been isolated but often cyclizes under the reaction conditions. The transformation has also been utilized in the steroid field.[75/66]

Another application of the hydrogenolysis of 5-aminoisoxazoles is illustrated by the synthesis of oxazinomycin, a *C*-nucleoside antibiotic, through the isoxazoles (**680**)(mixture of stereoisomers) in the sequence shown in Scheme 1.42.[180B/77]



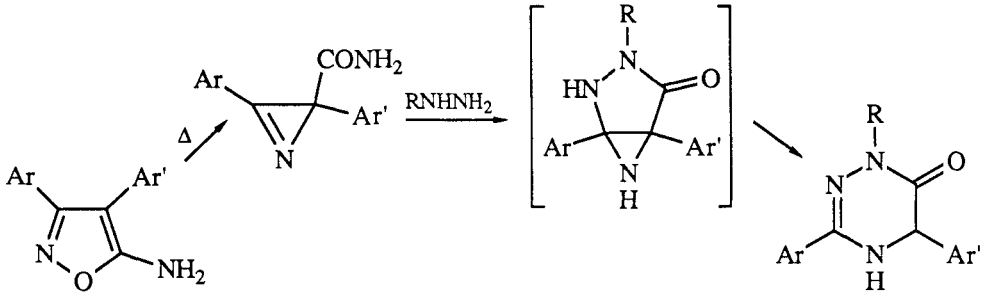

**Scheme 1.42.**

A general synthesis of the otherwise barely accessible 1,2,6-thiadiazine 1,1-dioxides, sulfur analogues of cytosine or thymine, starts from 3- or 5-aminoisoxazoles; for example:[157/79]



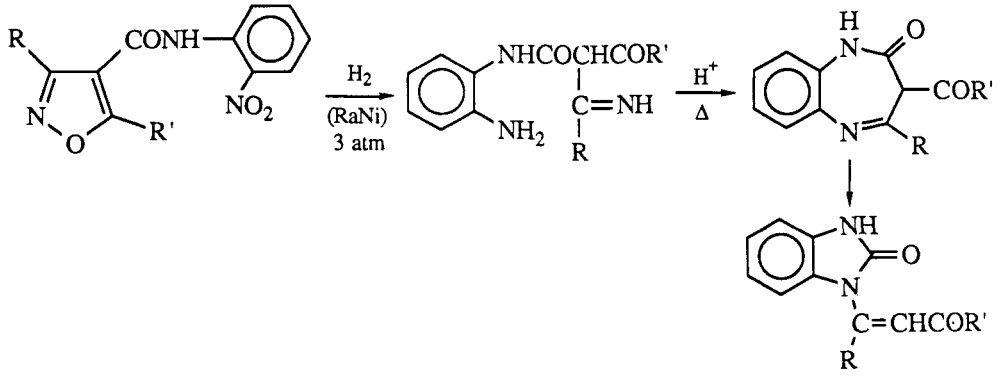
Procedures different from hydrogenolysis have occasionally been employed. Thus the *in situ* formation of α-cyano ketones from 3-unsubstituted isoxazoles and strong bases has been taken advantage of in the preparation of cytosine,[22/58] 2,4-diaminopyrimidines,[272/78] pyrimido[1.2-*a*]azepines,[20/69] and 2-cyanomethylene-3-oxotetrahydroquinoxaline,[25/84] and in ring enlargement from benzofuroxans to quinoxaline-di-*N*-oxides.[63/70] Treatment of 2,4-dimethyl-3-phenylisoxazolium perchlorate with potassium cyanate gives 3,5-dimethyl-4-phenyluracil,[52/69] whereas 2-methyl-3,4,5-triphenylisoxazolium perchlorate is transformed by sodium hydroxide into 4,5,6-triphenyl-2*H*-1,3-oxazine[10/62] (see § 1.4.6.1e, p. 317), and 2-methyl-5-phenylisoxazolium methosulfate reacts with methyl anthranilate to yield a quinazolone derivative[4/12] (see § 1.4.6.1e, p. 314).

Low yields of 3,6-diarylpyrazine-2,5-dicarboxamides are obtained by thermolysis of 5-amino-3-arylisoxazoles or of the isomeric azirinecarboxamides.[156/70] Thermolysis of 5-amino-3,4,-diarylisoxazoles is known (see § 1.4.5, p. 289) to cause isomerization to 2,3-diaryl-1-azirine-3-carboxamides. Treatment of the latter compounds with hydrazine or phenylhydrazine furnishes tetrahydro-1,2,4-triazin-6-ones in moderate yields, possibly through a bicyclic aziridine compound:[128/71]




### *1.4.10.8 Transformations into Seven-Membered Heterocycles*

Hydrogenolysis and subsequent acid-promoted recyclization of 3,5-disubstituted isoxazole-4-carboxylic 2′-nitroanilides yield 2-substituted 3-acyl-1*H*-1,5-benzodiazepin-2(3*H*)-ones, which often isomerize spontaneously into ring-contracted benzimidazol-2(3*H*)-ones:[159/74]

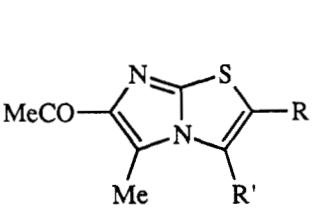


Similarly, 3-acetyl-4-methyl-2,5-dihydro-1,2,5-benzodiazepine 1,1-dioxide has been obtained from 3,5-dimethylisoxazole-4-(*o*-nitro)sulfonanilide.[130/79]

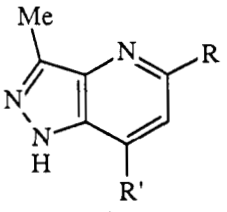
### *1.4.10.9 Transformations into Heterocyclic Condensed Systems*

Several heterocyclic condensed systems have been synthesized by hydrogenolysis of isoxazole compounds, usually containing another heterocyclic ring. The following examples are worth mentioning:

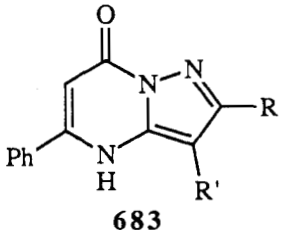
1. Imidazolo[3,1-*b*]thiazoles (**681**) from 4-(2′-thiazolyl)aminoisoxazoles[155/74]
2. Pyrazolo[4,3-*b*]pyridines (**682**),[134/71] pyrazolo[1,5-*a*]pyrimidines (**683**)[154B/72, 164/74] and pyrimido[1,2-*b*]indazoles (**684**)[169/73] from various pyrazolylisoxazoles
3. Pyrrolo[3,2-*b*]pyridines (**685**)[188/78] and pyrrolo[3,4-*b*]pyridines (**686**)[165/77] from pyrroloisoxazoles
4. *s*-Triazolo[4,3-*b*]pyridazines (**687**)[155/72] from 1,3,4-triazolylisoxazoles



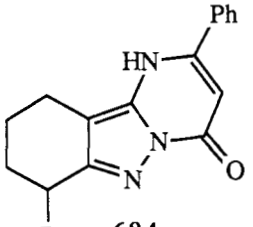

**681**



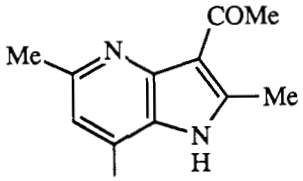

**682**



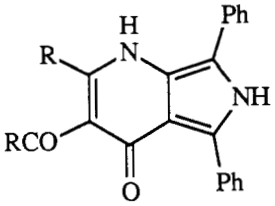

**683**



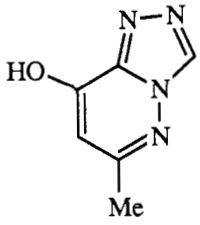

**684**




**685**




**686**

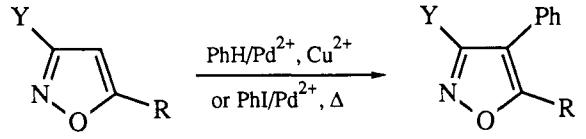



**687**

### 1.4.11 Other Reactions Without Ring Cleavage

Apart from the typical ring-opening reactions (hydrogenolysis, base-promoted cleavage, thermolysis, or photolysis), the isoxazole ring is remarkably stable toward a large variety of more or less common reagents. Two types of reactions, transformations on the ring positions or in the side chains, can be carried out without cleaving the ring. To the first reaction type belong the already illustrated nucleophilic (§ 1.4.6.2) and electrophilic (§ 1.4.9) substitutions, as well as the formation of Grignard reagents (§ 1.4.8).

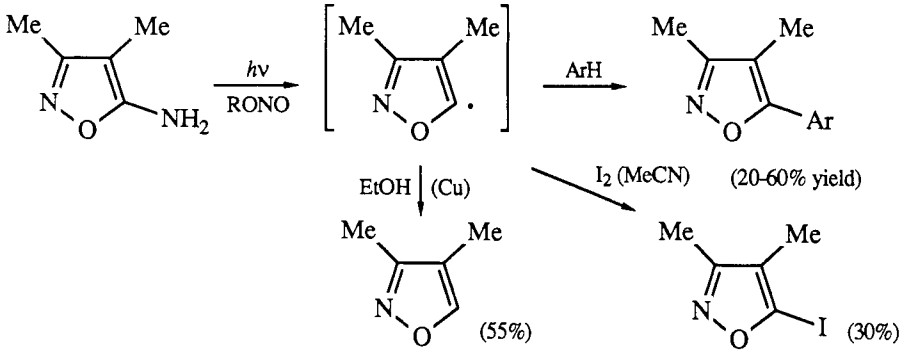
Noteworthy, although little studied, is homolytic substitution, especially *arylation*. Direct phenylation of 4-unsubstituted isoxazoles can be achieved by treating 3-tetrahydropyranyloxymethylisoxazoles or 3-tosyloxy-5-substituted isoxazoles with either benzene and oxygen in the presence of palladium and cupric acetates or with iodobenzene in the presence of palladium acetate or of palladium–charcoal and sodium bicarbonate:[103/82]




| Y | R | Yield(%) |
|---|---|---|
| TsO | Me | 44-66 |
| TsO | Ph | 61 |
| THP-$OCH_2$ | Me | 30 |
| THP-$OCH_2$ | Ph | 43 |

An intramolecular arylation is also feasible.

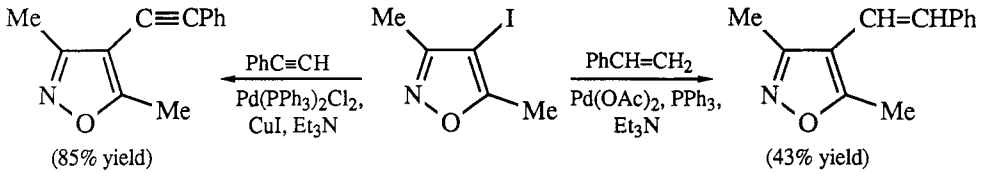
Substitution of the amino group of 5-amino-3,4-dimethylisoxazole by an aryl or a heteroaryl residue is achieved in low to moderate yields by irradiation in the presence of isoamyl or, better, of *t*-butyl nitrite, possibly through a 5-isoxazolyl radical:[148/75.98/76.123/78]



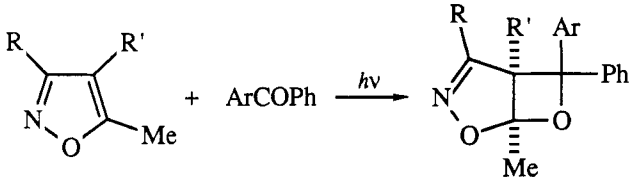

Substitutions of the amino group with iodine or deamination are also feasible.[98/76] The latter transformation can also be effected by treatment with pentyl nitrite in boiling THF.[137/84]

Cross-coupling reactions of 4-iodo- or 5-bromoisoxazole derivatives with

alkynes, catalyzed by a palladium–triphenylphosphine complex and cuprous iodide, is a convenient procedure for preparing *alkynylisoxazoles*. Cross-coupling with alkenes is still effective with 4-iodoisoxazoles, but generally fails with 5-bromoisoxazoles.[31/81] An example follows:

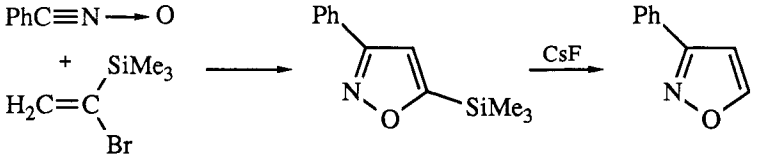



Usually, the aromaticity of the isoxazole nucleus prevents reactivity of the endocyclic C=N and C=C bonds. Nevertheless, the 4,5-double bond can photocycloadd carbonyl compounds to yield condensed oxetane derivatives regioselectively:[188/80]




| R | R' | Ar | Yield(%) |
|---|---|---|---|
| Me | H | Ph | 40 |
| Me | H | 3-pyridyl | 24 |
| H | Me | Ph | 65 |

Trimethylsilylisoxazoles can easily be desilylated with cesium fluoride; for example:[281/82,209/83]

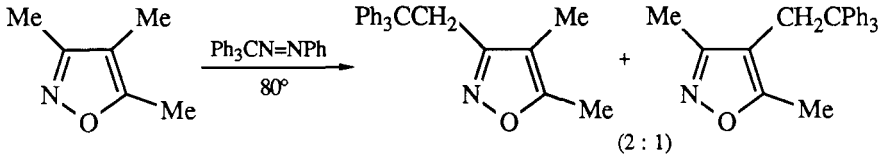



Transformations in the isoxazole side chains will be examined here briefly according to the nature of the side chain. Purely hydrocarbon substituents have most commonly been submitted to the following reactions:

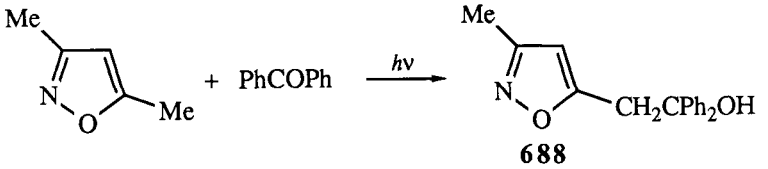
1. *Homolytic halogenation*, especially bromination with *N*-bromosuccinimide, occurs most frequently in a position α to the nucleus. Experiments on various methyl-substituted isoxazoles showed that the reactivity of methyl groups in the different positions decreases in the sequence 4-Me > 5-Me ≫ 3-Me.[72/62,93/63,77/66,186/74] For example, NBS monobromination of 3-methoxy-4,5-dimethylisoxazole gives a 7:3 mixture of the isomers with a 4-bromomethyl and a 5-bromomethyl group, respectively.[1/80] 4-Ethylisoxazole is converted by NBS into 4-α-bromoethylisoxazole.[191/76]

As illustrated in § 1.4.9.3, 4-unsubstituted isoxazoles react with NBS to give halogenation in the 4-position, but this is not a general rule, and the presence of a functional group can change the reaction course. For example, 3-methoxy-5-methylisoxazole,[162/80] 3-substituted 5-isoxazolylacetic esters,[38/66,28/71] or 5-*N*-benzoylaminomethyl-3-phenylisoxazole[26/78] are brominated in the isoxazole 5α-position.

A different course of radical substitution has been illustrated in the treatment of methyl-substituted isoxazoles with triphenylmethyl radicals generated by thermolysis of phenylazotriphenylmethane. Triphenylmethylation occurs in this case in the following order of easiness: 3-Me > 4-Me ≫ 5-Me.[194/77] Thus whereas 3,5-dimethylisoxazole gives 5-methyl-3-β,β,β-triphenylethylisoxazole only, trimethylisoxazole yields a 2:1 mixture of 3α:4α substitution products:



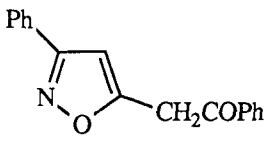

The isoxazole alcohol **688** has been prepared by photochemical addition of benzophenone to excess dimethylisoxazole:[217/74]



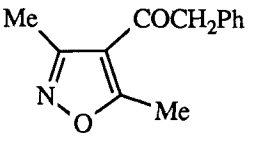

**688**

2. Electrophilic *additions* on double or triple bonds present in side chains occur without special difficulties, and several examples have long been known. Acid-catalyzed hydration of ethynyl isoxazoles gives the acetylisoxazoles expected.[193/75]

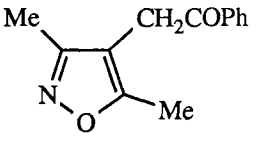
Owing to the different electron availability of the isoxazole 4- and 5-positions (position 5 is electron-poor because of the ring nitrogen electron withdrawal, whereas position 4 is electron-rich due to the ring oxygen electron-donating effect), it is not surprising that hydration of 3-phenyl-5-phenylethynylisoxazole gives the ketone **689** regiospecifically in 75% yield, and 3,5-dimethyl-4-phenylethynylisoxazole produces a 69% yield of ketone **690** along with 7% of the isomer **691**:[32/81]




**689**



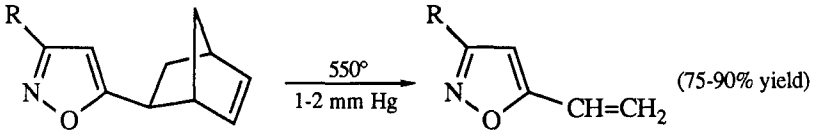

**690**



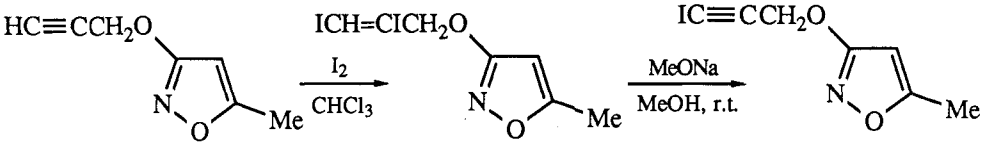

**691**

The polymerization of vinylisoxazoles is easily accomplished by radical initiators and is often spontaneous. As expected, the presence of a 4-nitro group activates the conjugated double bond (e.g., a styryl moiety) in the isoxazole 5-position toward nucleophilic addition. For example, Michael addition of acetylacetone to 3-methyl-4-nitro-5-styrylisoxazole is known,[19/81,81/81,88/81] as well as the retro-Michael reaction in a basic medium.[81/81]

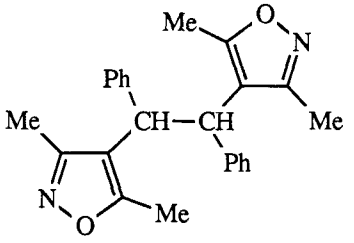
3. 1,3-Dipolar *cycloaddition reactions* to double or triple bonds of side chains have been realized with various 1,3-dipoles in order to prepare bisheterocycles. Reactions with dienes have been less well studied but do not seem to offer special peculiarities. A convenient synthesis of 5-vinylisoxazoles involves the thermal cyclo-reversion of 5-(isoxazol-5-yl)-2-norbornene:[150/75]



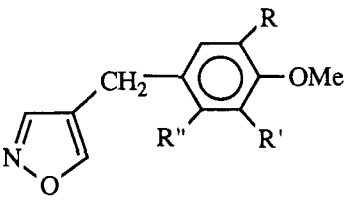

Isoxazole derivatives containing halogen atoms in the side chains can undergo the *substitution* reactions already described (see § 1.4.6.2b, pp. 322–323), as well as base-promoted *elimination* reactions. The latter type of reaction has frequently been adopted for the synthesis of vinylisoxazoles. Despite the strong basic conditions required, dehydro iodination of a diiodoalkene moiety has been reported to occur in good yields in the following example:[166/79]




A Würtz-type *coupling* reaction is known for 4α-chlorobenzyl-3,5-dimethylisoxazole, which is reported to yield the dimeric product **692** in low yields by treatment with sodium dimethylaminoethylate.[76/60]




**692**

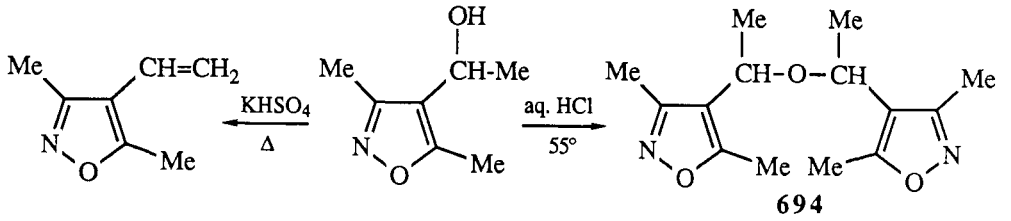



**693**

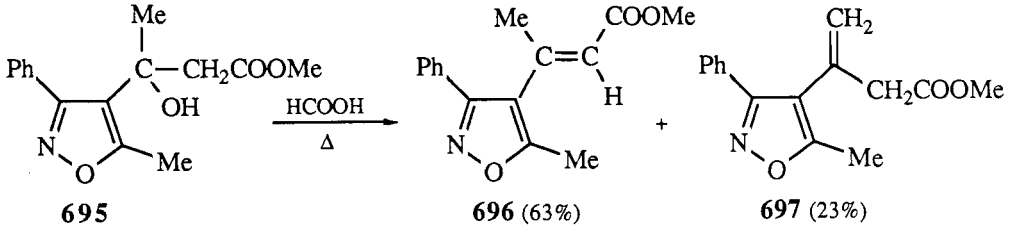
Friedel–Crafts alkylation with 4-chloromethylisoxazole is possible only with activated anisoles: derivatives of structure **693** are thus obtained.[272/78]

*Oxygen-containing functional groups* in the side chains give rise to several reactions, which usually follow the course expected.

1. Alcohols dehydrate under acidic conditions, giving the corresponding double bonds in fairly good yields. The most frequently adopted reaction conditions are distillation over potassium bisulfate,[33/61,3/65.148/76] heating with *p*-toluenesulfonic acid in benzene solution,[33/61.148/76] refluxing with phosphorus pentoxide in benzene solution,[148/76] and heating with polyphosphoric acid.[184/72] Under different conditions, intermolecular dehydration to the ether can occur: for example, heating of 4-α-hydroxyethyl-3,5-dimethylisoxazole at 55°C with 5.43 *N* hydrochloric acid gives the ether **694**:[148/76]




In other cases isomers can arise. For example, the Reformatsky product **695**, when treated with 85% formic acid and sodium acetate, gave a mixture of the two unsaturated esters **696** and **697**:[99/76]

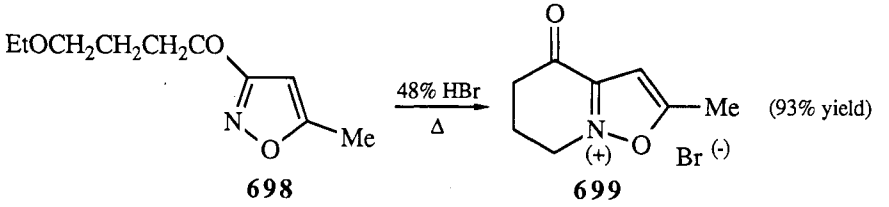



Macrocyclic polyethers containing isoxazole units have been prepared by intramolecular dehydration of isoxazole derivatives, possessing the necessary alcoholic functionalities in the 3- and 5-side chains.[142/83] Transformation of isoxazole alcohols into the corresponding halogen derivatives offers no difficulty with traditional methods. With alcoholic functions in the 3-isoxazole side chains, yields seemingly diminish with increasing distance of the hydroxyl group from the ring.[106/67]

2. Ethers containing the isoxazole nucleus are cleaved only under severe conditions (concentrated hydrochloric acid in a sealed tube), but 2,4-dinitrophenoxymethylisoxazole derivatives are readily cleaved by alkali into the isoxazole alcohol and dinitrophenol.[5/41] 3-Alkoxyisoxazoles, which are easily

obtained from 3-haloisoxazoles, can be transformed into the corresponding 3-hydroxyisoxazoles either in strong acidic conditions (concentrated hydrobromic acid in glacial acetic acid)[125/65,130/68] or, in lower yields, in a mild alkaline medium (stannic chloride in ammonia solution).[162/80] In one case, use of sodium hydroxide has been reported.[68/66]

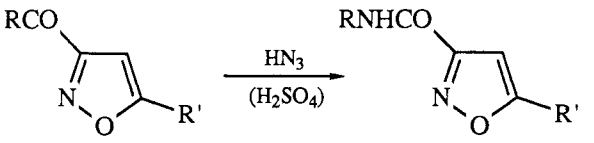
Sometimes the protection of the 3-hydroxy group is made through the *O*-benzyl ether, which can finally be hydrogenolyzed. Treatment of 3-hydroxyisoxazoles with alkyl halides in the presence of alkali produces both *O*- and *N*-alkylation, and the reaction is dealt with in Part 2 of this work. A condensed isoxazolium salt (**699**) results from the acidic hydrolysis of the keto ether (**689**):[141/72]




**698** **699**

3. Isoxazole aldehydes and ketones give normal derivatives with hydroxylamine, arylhydrazines, semicarbazide, and aromatic amines. Even sterically hindered ketones such as 4-benzoyl-5-methyl-3-phenylisoxazole have been derivatized successfully.[90/68] Care must be exerted in reactions with 3-acylisoxazoles, owing to their lability toward nucleophiles (see § 1.4.6.1c, p. 305). A mixture of stereoisomeric oximes is usually obtained, which are barely distinguishable by spectroscopic methods. An indirect identification makes use of the Beckmann rearrangement, using phosphorus pentachloride in ether. The rearrangement takes place in low yields, but the mixture of amides is readily separable and identifiable.[1B/75.32/81] Even an isoxazole carboxaldehyde such as 3-methoxyisoxazole-5-carboxaldehyde gives a 3:2 mixture of stereoisomeric oximes, which, however, is useful as such when the goal is the preparation of the aminomethyl derivative.[2/76]

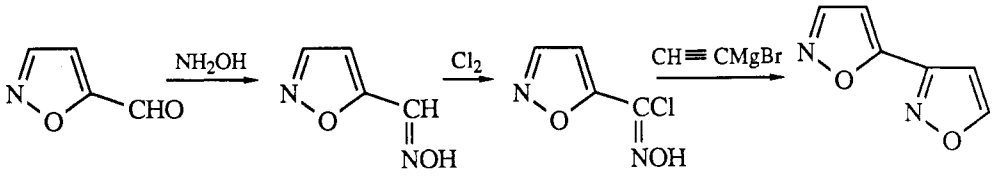
The Schmidt reaction on 3-acylisoxazoles is reported to furnish, although in unstated yields, only the amides of the corresponding isoxazole-3-carboxylic acid:[3/59]



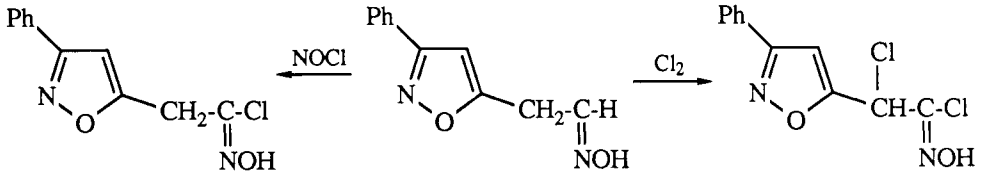

The same reaction carried out on 5-acetyl-3,4-diphenylisoxazole produces the corresponding isoxazole-5-carboxylic *N*-methylamide in 61% yield.[179/74]

Isoxazolecarbaldoximes have been utilized repeatedly, through hydroximoyl

chloride and nitrile oxide syntheses, for the preparation of di- and poly-isoxazoles, as the following synthesis of 3,5′-diisoxazole shows:[49/59]

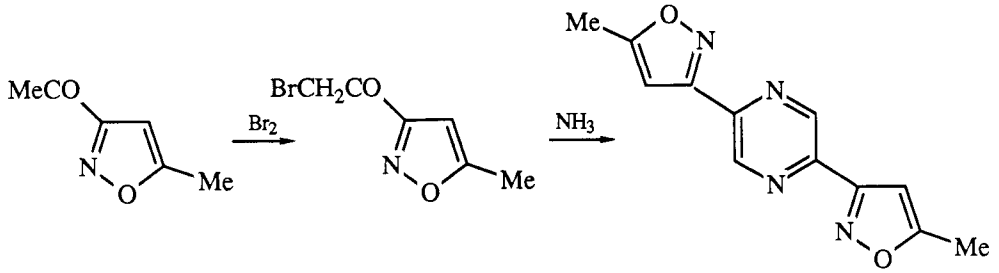



Chlorination of the oximes is not always straightforward: during synthesis of diisoxazolylmethanes, it became necessary to resort to the nitrosyl chloride method since direct treatment with chlorine leads to α-chlorination:[81/66]

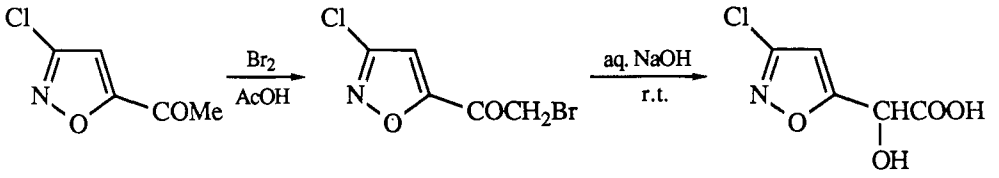



The isomerization of 3-acylisoxazole phenylhydrazones has been studied and an acetic acid–promoted *E*/*Z* equilibration has been found to occur.[175/83] Only the *Z*-isomer is prone to base-induced rearrangement to the triazole ketone (see also § 1.4.10.5, p. 357), whereas thermal rearrangement is also feasible for the *E*-isomer, which equilibrates under these conditions. Thermal (or photochemical) *syn-anti* isomerization of 4-acetyl-5-methyl-3-phenylisoxazole phenylhydrazone and oxime has also been reported.[89/75]

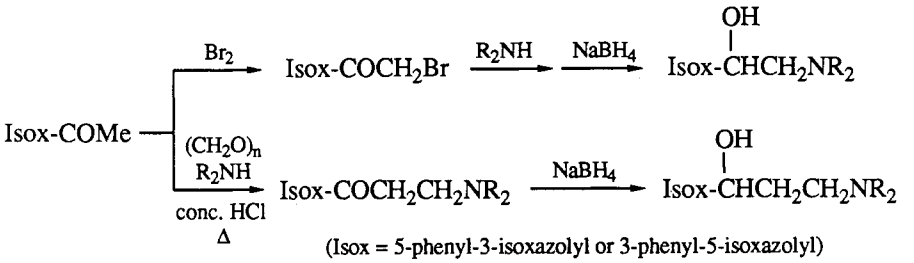
The α-position of acylisoxazoles shows normal reactivity, and bromination,[14/57] deuteration,[99/76] and nitrosation[201/77] are known. 3-Bromoacetylisoxazoles are the starting material for the synthesis of several 3-heterocyclic-substituted isoxazole derivatives; for example, with ammonia a bisisoxazolylpyrazine is obtained.[14/57]




Mono- and dibromination have been reported, the latter process having been utilized for preparing α-hydroxy acids, as illustrated in the following example:[224/81]

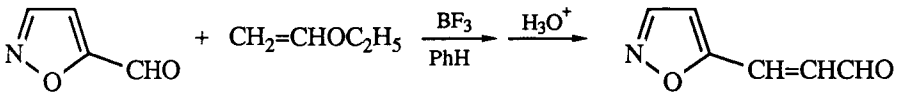



Starting from acetylisoxazoles, both 1,2- and 1,3-amino alcohols can be prepared in two steps through bromination or through Mannich addition:[106/67]



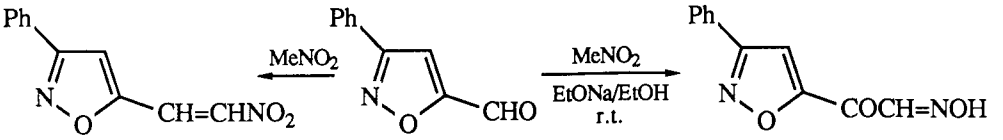

Other standard addition reactions are applicable to isoxazole aldehydes: formation of acetals and aminals; formation of cyanohydrins and the Strecker reaction, which have proved useful in the synthesis of α-hydroxy acids[130/68] and of α-amino acids;[5/57] addition of Grignard reagents to give secondary alcohols; addition of diazomethane to form methyl ketones;[13/39,2/43] and Wittig or analogous reactions to produce the ethylenic double bond. In the latter case the unsaturated compound can, of course, arise conveniently from an isoxazole ylide (or from a phosphonate in the Wittig–Horner version) and the necessary aliphatic or aromatic aldehyde. Isoxazole aldehydes undergo the Cannizzaro reaction.[13/39,2/43]

Several condensations of isoxazole aldehydes with active methylene compounds are known, and the wideness of applicability is limited only by the low stability of the isoxazole ring under the experimental basic conditions. Thus the Knoevenagel condensation furnishes α,β-ethylenic acids in moderate to fair yields, and aldol-type condensation produces α,β-ethylenic carbonyl compounds. It is noteworthy that with alkali-sensitive aldehydes such as isoxazole-5-carbaldehyde, the $BF_3$-promoted process with ethyl vinyl ether has been applied successfully.[145/67]




Condensation with nitromethane in the presence of sodium ethoxide at room temperature has been reported to yield the corresponding isoxazolylglyoxal

oxime.[61/79,172/81] Under different conditions the $\alpha,\beta$-ethylenic nitrocompound is obtained:[13/39]




Derivatives with hydantoin or rhodanine are easily obtained and have proved useful for synthetic purposes, for example, for the synthesis of $\alpha$-amino acids[5/57] or biologically active compounds.[85/64]

4. Carboxylic acid derivatives also show normal behavior, independent of whether the functional group is linked directly to the isoxazole ring or is present in the side chain. Acyl chlorides are usually prepared by conventional methods (thionyl or oxalyl chloride in the presence of bases). They undergo the Friedel–Crafts reaction with arenes, and yields are especially good in the synthesis of 4-aroylisoxazoles.[28/57,124/64] A method for preparing acetylisoxazoles is, for example, the reaction of isoxazole carbonyl chloride with diethyl ethoxymagnesiummalonate followed by decarboxylation of the resulting $\beta$-keto ester.[106/67,3B/74] Homologation of isoxazole carboxylic acids through the Arndt–Eistert procedure is known and has frequently been utilized for syntheses in the pharmaceutical field.[106/67,84/68,117/68,46/75,3/76]

Mixed anhydrides have been prepared by treating isoxazole carboxylic acids with acyl chlorides in the presence of triethylamine.[178/68] Symmetrical isoxazole anhydrides can be prepared from the corresponding carboxylic acids by using, in addition to more conventional reagents, suitable derivatives of phosphoryl chloride.[212/81,215/81]

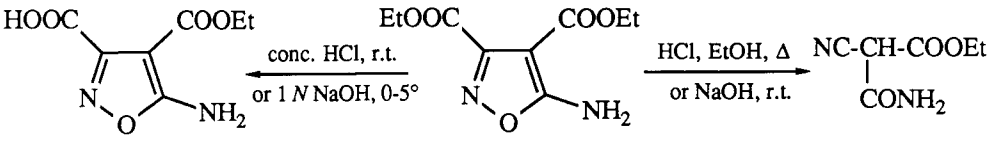
Isoxazole carboxylic chlorides are routinely employed for synthesis of the corresponding esters by reaction with alcohols or phenols, as well as of the corresponding thioesters by reaction with thiols. Conversely, isoxazolyl carbinols or 3-isoxazolols react with acyl, aroyl, sulfonyl, or phosphoryl chlorides or with anhydrides to give the esters expected. No difficulties are encountered in preparing isoxazole carboxylic esters directly from the free acids with diazoalkanes or by acid-promoted esterification. Under such conditions even the 3-unsubstituted ring is perfectly stable.

The esters of 5-methyl-3-isoxazolol have been used as a suitable activated form of the free carboxylic group of *N*-protected amino acids or peptides in order to prepare the triazine derivatives.[51/73] Macrocyclic ester compounds containing isoxazole units have been synthesized from isoxazole-3,5-dicarbonyl chloride and dihydroxy compounds.[134/81]

The *t*-butyl 5-phenylisoxazole-3-peroxycarboxylate, prepared via acid chloride, readily decomposes to 5-phenylisoxazole-3-carboxylic acid by refluxing in toluene in the presence of 1-methylcyclohexa-1,4-diene as hydrogen atom donor.[135/72] Remarkably, no ring opening is observed under these conditions.

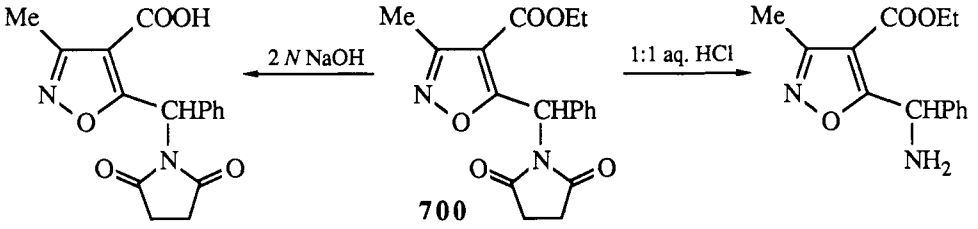
Ester hydrolysis can be carried out in either an acidic or basic medium; in the latter case attention must be paid to the possibility of ring opening. Nevertheless, even alkyl isoxazole-3-carboxylates can be hydrolyzed to the corresponding free acids in good yields under controlled conditions. For example, 4,5-disubstituted isoxazole-3-carboxylates give the free acids either by short heating with concentrated or 1:1 hydrochloric acid or by treatment with cold 2 *N* sodium hydroxide.[91/68] Longer heating or basic treatment at higher temperatures leads to the β-ketonitriles arising from decarboxylation and ring cleavage (see § 1.4.5, p. 288).

Special care must be exerted in preparing unstable isoxazoletricarboxylic acid from the corresponding triethyl ester: a cold aqueous 3% solution of barium hydroxide was found to be most convenient, since alkaline hydroxides induce decomposition to pyruvic acid even in the cold.[5/40] The most generally adopted hydrolysis procedure involves treatment with cold alcoholic solution of potassium hydroxide, followed by cautious acidification. Aqueous solutions of acids or alkalis are also effective. The easiness of hydrolysis depends on the ring position of the ester group if this is linked directly to the ring, and decreases in the sequence 3-COOR > 5-COOR > 4-COOR. The least reactive group (i.e., that in the 4-position), usually requires heat in order to be hydrolyzed. Thus selective hydrolysis is sometimes possible: for example, diethyl 5-aminoisoxazole-3,4-dicarboxylate under mild conditions (acidic or basic) yields 5-amino-4-ethoxycarbonylisoxazole-3-carboxylic acid, whereas more vigorous treatment causes ring opening:[91/68]

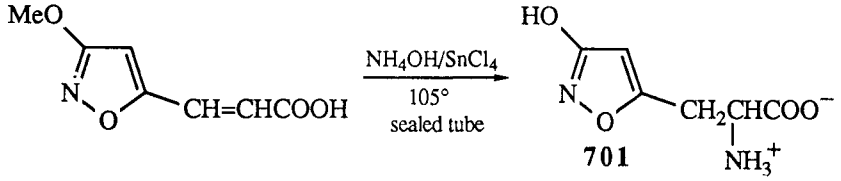



Typical also is the behavior of 5-chloroisoxazole-3- or 5-chloroisoxazole-4-carboxylate.[17/65] Treatment of ethyl 5-chloro-4-methylisoxazole-3-carboxylate with methanolic potassium hydroxide yields the free carboxylic acid; the same treatment of ethyl 5-chloro-3-methylisoxazole-4-carboxylate, owing to increased mobility of the chlorine atom and to decreased reactivity of the carbethoxy group, furnishes a mixture of 4-carbethoxy-3-methylisoxazolin-5-one and ethyl 3-methyl-5-methoxyisoxazole-4-carboxylate. By contrast, acidic hydrolysis influences the sole ester group in both cases, leaving the chlorine atom unchanged.

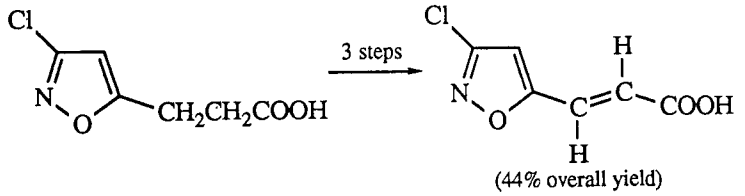
An additional example of selective hydrolysis concerns the α-succinimido derivative **700**: a basic medium promotes hydrolysis of the ester group, and hydrochloric acid hydrolyzes the succinimido function:[12/64]




Nucleophilic addition to electron-poor double bonds is known: Michael-type reactions on α,β-ethylenic carbonyl or carboxyl derivatives have been reported. It is worthwhile noting that in the latter case the 3-methoxyisoxazole nucleus, in the presence of a Lewis acid, is regioselectively dominant with respect to the carboxylic group. For example, only the α-aminocarboxylic acid (**701**) is obtained in 25% yield when 3-(3′-methoxyisoxazol-5′-yl)propenoic acid is treated with ammonia and tin(IV) chloride:[162/80]




An interesting dehydrogenation procedure has been proposed for the transformation of 3-(3′-chloroisoxazol-5′-yl)propanoic acid into *E*-3-(3′-chloro isoxazol-5′-yl)propenoic acid: the suitably protected saturated acid is oxidized with iodosobenzene diacetate (or, less conveniently, with benzoyl peroxide) and subsequently deprotected in an acidic medium:[224/81]



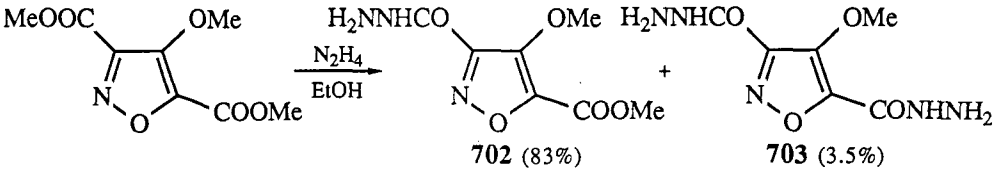

A large variety of isoxazole derivatives having *nitrogen-containing functionalities* in the side chains are known, and usually have been prepared by conventional methods.

Amides, hydrazides, and ureides are easily produced from isoxazole esters or acid chlorides, whichever the ring position may be. *N*-Unsubstituted amides are obtained most conveniently by ammonolysis of isoxazole esters with a large excess of aqueous or methanolic ammonia at room temperature for several

hours. *N*-Mono- and *N,N*-disubstituted amides are more conveniently prepared from the acid chlorides; for example, a quantitative yield of isoxazole-3-carboxamide is achieved when ethyl isoxazole-3-carboxylate in a little methanol is treated with aqueous ammonia ($d$ = 0.88) for 3 days at 0°C.[122/71] Direct amidation from the free acid and the amine in the presence of dicyclohexylcarbodiimide (DCC) or another condensation agent may also be carried out successfully.

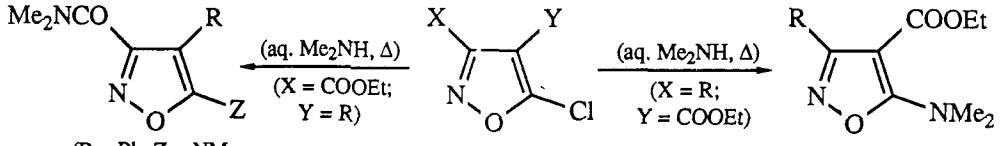
Conversely, amides or hydrazides may proceed from amino- or hydrazino-substituted isoxazoles and acyl or sulfonyl chlorides or anhydrides. With acetic anhydrides or with sulfonyl chlorides both *N*-mono- and *N,N*-diacetyl (or sulfonyl) derivatives have been obtained by standard procedures. Isoxazole ureides have been prepared either by amidation of isoxazolylcarbonylisocyanates, available in turn from the isoxazole amides and oxalyl chloride,[108/72] or by reaction of the isoxazole acid chloride with suitable ureas,[64/71,107/72] or else by direct action of carbodiimide on the isoxazole carboxylic acid.[101/72] Isoxazolyl ureas are available from aminoisoxazoles and carbamoyl chlorides.[132/76,114/78]

3-Amino-5-methylisoxazole reacts with trichloromethanesulfenyl chloride to yield several ring-fused 1,2,4-thiadiazole systems via an isolable isoxazole sulfenamide intermediate.[145/75] Of course, some selectivity can be observed here too. For example, the higher reactivity of the isoxazole-3-carbethoxy group toward the 5-isomeric function is reflected in the reaction of dimethyl 4-methoxy-3,5-dicarboxylate with anhydrous hydrazine, which furnishes a 83% yield of the hydrazide (**702**), along with minor amounts of the dihydrazide (**703**):[77/64]




**702** (83%) **703** (3.5%)

Ethyl 5-chloro-4-methyl (or phenyl)isoxazole-3-carboxylate reacts with dimethylamine to give the 3-dimethylamido derivative, with or without simultaneous substitution of the chlorine atom. By contrast, the same reagent applied on the isomeric ethyl 5-chloro-3-methyl (or phenyl)isoxazole-4-carboxylate gives only a substitution reaction in the 5-position:[17/65]




(R = Ph, Z = $NMe_2$;
R = Me; Z = Cl)

Sometimes the substitution pattern prevents formation of the amide. For example, heating of ethyl 5-methoxy-3-phenylisoxazole-4-carboxylate with

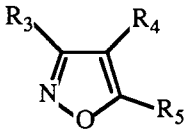
aqueous dimethylamine simply gives 5-methoxy-3-phenylisoxazole,[11/73] whereas more severe hydrolysis directly leads to 3-phenylisoxazolin-5-one.[54/63]

Both alkaline and acidic hydrolysis, usually under heating, is successful with isoxazole amides. Good alkali dilution and moderate temperature are essential when 3-carbamido groups are involved. A kinetic study on the acid-catalyzed hydrolysis of several isoxazole sulfonamides has been undertaken.[187/73,188/73,199/78]

The higher hydrolizability of the 5-carbamido by comparison with the 4-carbamido group is exemplified by easy isolation of 4-carbamido-3-phenyl (or methyl)isoxazole-5-carboxylic acid upon heating of 3-phenyl (or methyl)isoxazole-4,5-dicarboxamide with dilute aqueous potassium hydroxide at 50–70°C.[56/67,159/82]

3- and 5-Benzamidoisoxazoles are slightly acidic and dissolve at room temperature in cold aqueous alkali, precipitating unchanged by acidifica-

TABLE 1.94. SYNTHESIS OF AMINOISOXAZOLES THROUGH HOFMANN OR CURTIUS REACTION

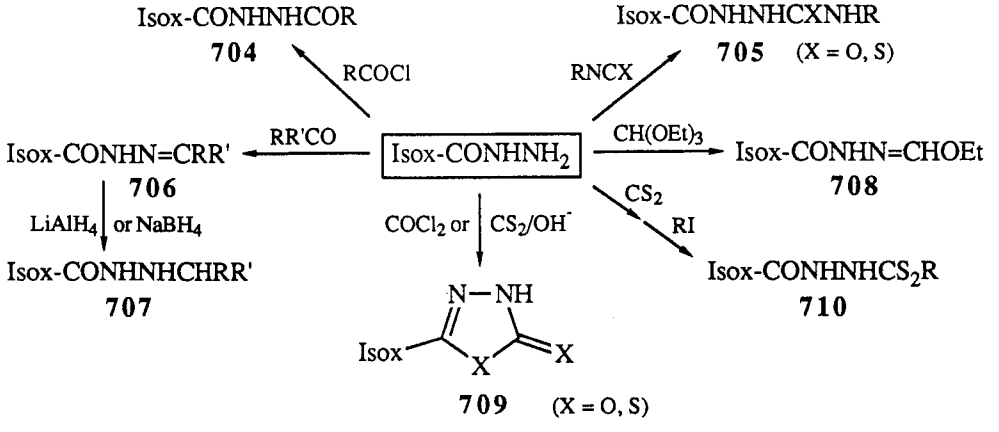


| Aminoisoxazole (starting group) | | | | | |
|---|---|---|---|---|---|
| $R_3$ | $R_4$ | $R_5$ | Reagent | Yield (%) | References |
| NHCOOEt ($CONHNH_2$) | H | H | $NaNO_2$/HCl; EtOH, Δ | 24 | 5/32, 9/46 |
| $NH_2$ ($CONH_2$) | H | Me | NaOX, 50° | > 78 | 33/62, 67/65, 213/76 |
| NHCOOR ($CONHNH_2$) | H | Me | | | 2/57 |
| NHCONHPh (COCl) | H | Me | $NaN_3$/aq. $Me_2CO$; Δ , aniline | 85 | 100/67 |
| $NHCONMe_2$ ($CONH_2$) | H | $CMe_3$ | NaClO/$OH^-$; 40% aq. $Me_2NH$ | 54 | 174/79 |
| MeO | H | $CH_2NHCOOEt$ ($CH_2CONHNH_2$) | *t*-BuONO/HCl, THF; 100°, toluene; EtOH | 68 | 130/68 |
| MeO | H | $(CH_2)_2NHCOOMe$ [$(CH_2)_2COOH$] | $SOCl_2$/DMF; $Me_3SiN_3$; MeOH | 61 | 1/74 |
| Ph | H | $NH_2$ ($CON_3$) | EtOH, Δ | | 249/72 |
| Me | $NH_2$ ($CONH_2$) | COOH | KClO/$OH^-$ | 60 | 159/82 |
| Ph | $NH_2$ ($CONH_2$) | COOH | NaBrO/$OH^-$ | 82 | 56/67 |
| Ph | NHCOOEt ($CONHNH_2$) | Me | $NaNO_2$/HCl; EtOH, Δ | 88 | 161/68 |
| NHCOOR ($CONHNH_2$) | OMe | COOMe | $NaNO_2$/HCl; ROH, Δ | 65-82 | 77/64 |
| $PhCH_2O$ | COOMe | $CH_2NH_2$ ($CH_2COOH$) | $(COCl_2)_2$; $NaN_3$, aq. $Me_2CO$; 90% AcOH, 50-90° | | 151/78 |

tion.[3/31,1/34,8/36] A 5-carbamido derivative has easily been *N*-methylated with methyl iodide in DMF in the presence of potassium carbonate.[91/74] The dehydration of unsubstituted amides to cyanoisoxazoles is currently accomplished either with phosphorus pentoxide or with phosphorus oxychloride/triethylamine, occasionally also with thionyl chloride or aroyl chloride. Conversely, hydrolysis of cyanoisoxazoles may be stopped at the amide stage under suitable conditions (concentrated sulfuric acid).

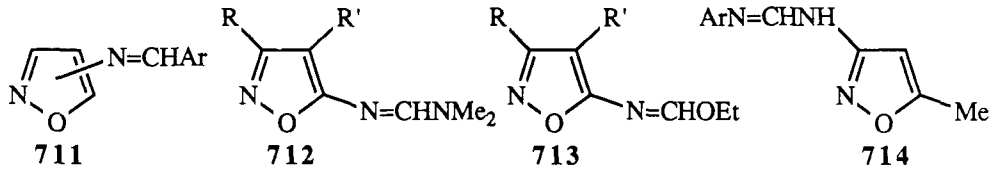
*N*-Phenylimidochlorides are prepared from isoxazoles carbanilides and phosphorus pentachloride; their reduction with stannous chloride can lead either to an isoxazole aldehyde, such as 5-methyl-3-phenylisoxazole-4-carboxaldehyde,[6/38] or to the corresponding *N*-phenylaminomethylisoxazole, as happens starting from 3-cyano-5-methyl- or from 5-cyano-3-methylisoxazole.[9/38] Hofmann and Curtius degradations are favorite methods for preparing aminoisoxazoles or their derivatives (carbamates, ureas) from suitable amides, hydrazides, or acyl azides. Some typical examples of these synthetic procedures are reported in Table 1.94.

A kinetic study of the Hofmann rearrangement of 5-methylisoxazole-3-carboxamide has been carried out.[94/65] Isoxazole hydrazides, apart from their involvement in the Curtius reaction, have been largely employed in synthesis because of their manyfold reactivity. Several classes of compounds, often useful in the pharmaceutical field, are thus accessible. For example, acylation with acyl chlorides leads to diacylhydrazines (**704**),[220/77,212/78] addition to isocyanates or to isothiocyanates yields acylsemicarbazides (**705**),[74/60,160/68] and condensation with aldehydes and ketones is an easy entry to acylhydrazones (**706**),[62/59,34/61,25/62,42/62,5/66,116/67] readily hydrogenated to substituted hydrazines (**707**). Less frequent is condensation with triethyl orthoformate,[212/78] phosgene,[74/60] or carbon disulfide,[74/60,160/68] to give **708**, **709**, and **710**, respectively. Most of these compounds are intermediates, whose ring closure yields isoxazoles linked to another heterocycle, such as 1,3,4-oxadiazole, 1,3,4-thiadiazole, or *sym*-triazole. Sulfonylhydrazides behave analogously.[129/81]



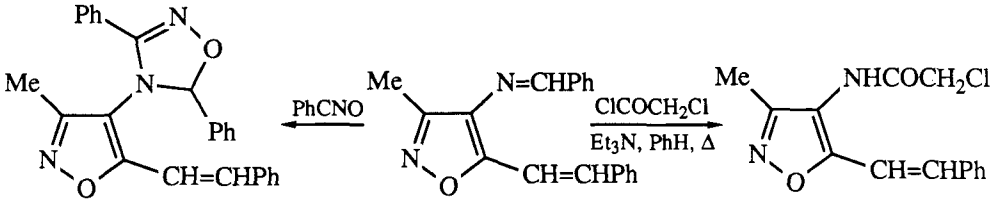
All three possible nuclear aminoisoxazole derivatives have more or less marked aromatic characteristics, and behave consequently. The reactivity toward electrophiles roughly follows the sequence 4-$NH_2$ ≫ 5-$NH_2$ ≥ 3-$NH_2$. Compounds with the aliphatic amino group in the side chain are rather strong bases and react as such without any special influence of the heterocyclic ring.

Aminoisoxazoles react smoothly with aromatic aldehydes to give Schiff bases (**711**), and yields are especially good with 3,5-disubstituted 4-aminoisoxazoles.



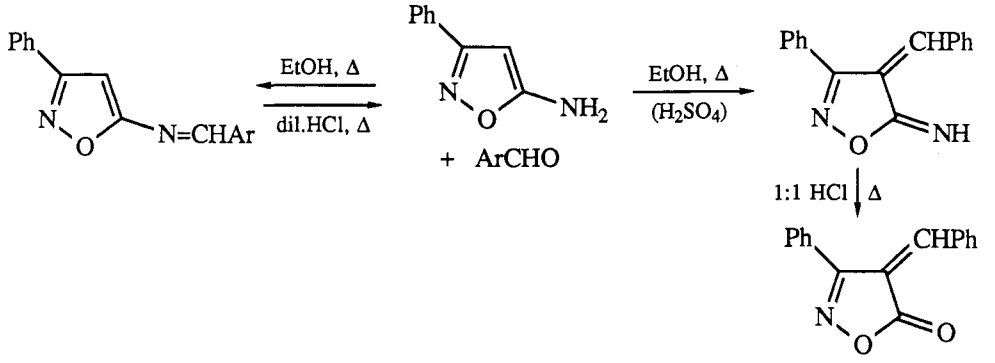

**711** **712** **713** **714**

The N=CH bond of the Schiff bases is an active dipolarophile and reacts with nitrile oxides more readily than does the styryl CH=CH bond, as the following example shows:[86/81]

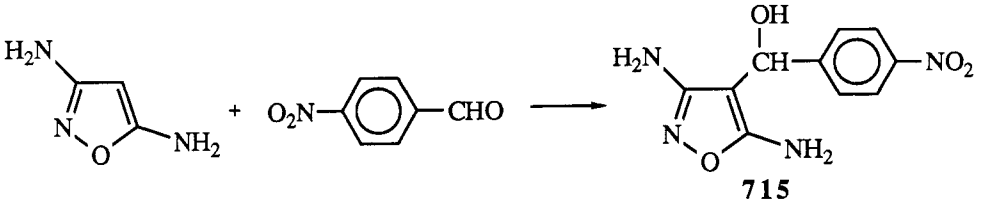



An attempt to obtain a β-lactam through interaction of chloroacetyl chloride on 4-benzalamino-3-methyl-5-styrylisoxazole led to formation of the 4-chloroacetylamino derivative, owing possibly to anchimeric assistance of the styryl group.[120/83] As already mentioned in § 1.4.3.2, p. 281, the imino C=N double bond can afterwards be smoothly reduced with sodium borohydride or lithium aluminum hydride, without touching the ring. *N*-Benzylamino derivatives are thereby produced.

5-Aminoisoxazoles sometimes give diverting results, owing to the double nature of their tautomeric structures. Thus heating an ethanolic solution of 5-amino-3-phenylisoxazole with aromatic aldehydes normally gives moderate to high yields of the Schiff bases,[8/36,24/56,137/72] but if traces of sulfuric acid are present, formation of the iminobenzylidene derivative is reported,[8/53] hydrolyzable to the known benzylideneisoxazolinone:




3,5-Diaminoisoxazole is reported to react with 4-nitrobenzaldehyde in ethanol to yield the addition product **715**:[89/65]



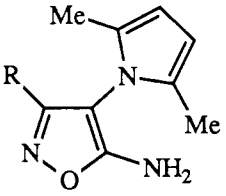

**715**

Dimethylformamide[130/65] or its diethylacetal[91/74] have been used to prepare formamidines (**712**), and triethyl formate in the presence of acetic anhydride has been used to prepare either a methoxymethylene derivative (**713**)(from a 5-amino-4-cyanoisoxazole),[75/64] a valuable intermediate in the synthesis of fused-ring systems, or a formamidine of general structure **714** (from 3-amino-5-methylisoxazole).[92/64] In **714** Ar is 5-methylisoxazol-3-yl if the starting material is the aminoisoxazole alone, or is an aryl (or heteroaryl) residue if a mixture of the aminoisoxazole and the suitable aromatic amine is employed (either with a one-pot or a two-step methodology).

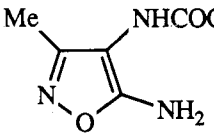
The insertion of a nitro group conceivably decreases the reactivity of the amino group: thus 3-amino-5-methyl-4-nitroisoxazole does not react with *p*-dimethylaminobenzaldehyde,[159/71] while 3-amino-5-phenylisoxazole condenses with *p*-methoxybenzaldehyde, although under heating in the presence of *p*-toluenesulfonic acid.[37C/76]

Some activated keto groups enter the reaction, such as ethyl acetoacetate[295/77] or acetylacetone.[207/70,167/73] Acetonylacetone undergoes a Paal–Knorr reaction, giving rise to a dimethylpyrrole derivative. It is interesting to note that in the case of 4,5-diaminoisoxazole, only the 4-amino group reacts, yielding compound **716**.[207/70,167/73] The large difference in basicity of the two amino groups is also reflected in the stepwise acylation of 4,5-diamino-3-methylisoxazole:[167/73]

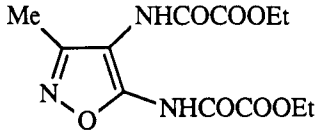
1 mol of oxalyl chloride yields **717**, whereas an excess of reagent yields **718**. Reaction of the same diamine with glyoxal or with α-diketones is an excellent entry into the isoxazolo[4,5-*b*]pyrazine system.[198/68.167/73]




**716**

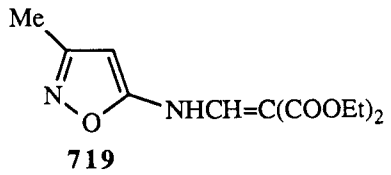



**717**

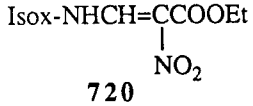



**718**

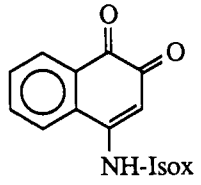
Some nucleophilic attack on suitably substituted α,β-unsaturated carbonyl compounds are known: diethyl ethoxymethylenemalonate reacts with 5-amino-3-methylisoxazole to give **719**, intermediate in the synthesis of the isoxazolo[5,4-*b*]pyridine system;[15/72] similarly, ethyl ethoxymethylenenitroacetate and amino-isoxazoles yield **720**.[28/77]



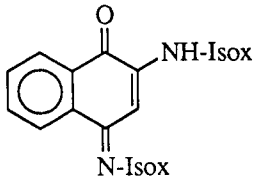

**719**




**720**



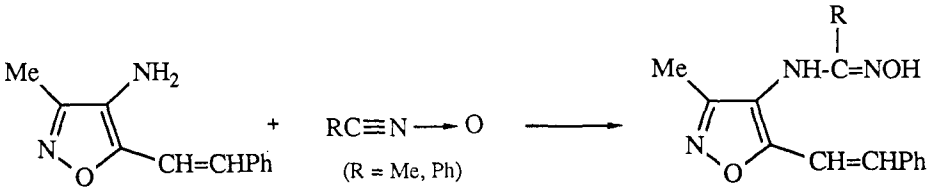

**721**




**722**

Sodium 1,2-naphthoquinone-4-sulfonate is a suitable substrate for nucleophilic attack from various aminomethylisoxazoles, which yield 4-isoxazolylamino-1,2-naphthoquinones (or their tautomers)(**721**), sometimes together with a disubstituted 1,4-naphthoquinoneimine (**722**).[10/82] A Mannich base is easily obtained from 5-amino-3-methyl-4-phenylisoxazole.[144/67]

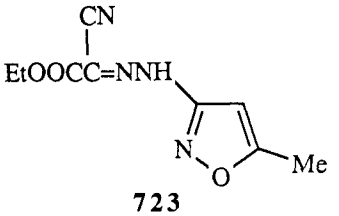
Other electrophiles reactive with aminoisoxazoles are phosgene and isocyanates (or isothiocyanates); in both cases the products are isoxazolylureas, formed through the intermediacy of isoxazolylisocyanates in the former and directly in the latter case. Even nitrile oxides[51/66] or nitrile imines[160/82] are attacked by isoxazole amines to give amidoximes or amidrazones, respectively. It is worth noting that the 4-amino group is more reactive than the double bond of the 5-styryl moiety, as the following example shows:[83/81]



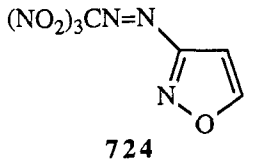

Nitrosobenzene reacts, for example, with 4-amino-3,5-dimethylisoxazole to furnish a 50% yield of 3,5-dimethyl-4-phenylazoisoxazole.[100/67] This method competes with direct synthesis from phenylazopentane-2,4-dione and hydroxylamine. *N*-Alkylation occurs under standard conditions with 4-aminoisoxazoles. Alkylation of some 5-aminoisoxazoles requires the formation of the sodium salt by treatment with sodium hydride. The salt reacts with alkyl halides or sulfates if the 4-position is occupied by an electron-withdrawing (cyano or alkoxycarbonyl) group. In the latter case both *N*-mono- and dialkylation can be achieved under selected conditions.[140/71] The behavior of aminoisoxazoles toward nitrous acid has long been under study and is slightly different according to the ring position of the amino group and to the substitution pattern.

When 4-amino-3,5-dimethylisoxazole is diazotized in an aqueous acidic medium, stable diazonium salts such as chloroaurate can be isolated.[7/21] In the presence of sodium acetate or dimethylamine, a diazoaminoisoxazole is formed.[8/21,73/62] 3-Methyl-, 3-phenyl-, and 5-methyl-4-aminoisoxazoles give extremely unstable diazo compounds, which are immediately decomposed even at low temperatures with loss of nitrogen.[3/03,4/41]

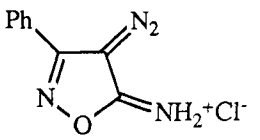
3-Aminoisoxazoles can be diazotized only in strong hydrochloric acid solution, and the diazonium salts are rather unstable and must be transformed immediately. Both 4- and 3-diazonium salts thus obtained couple in the normal way with resorcinol or β-naphthol[7/21,5/31,7/42,5/63] and with *N*,*N*-dimethylaniline[73/62] or β-naphthylamine.[7/21] Condensation of the diazo compounds with acetylacetone[8/21] and other active methylene compounds[16/83] or with trinitromethane[6/32] in alkaline solution yields hydrazones such as **723**, or an azoderivative such as **724**, respectively. The latter compound, a yellow explosive crystalline solid, is present in the complex mixture of isoxazole derivatives formed by interaction of fuming nitric acid and acetylene.[3/31,9/46]



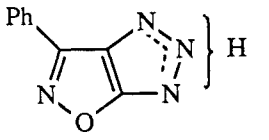

**723**




**724**



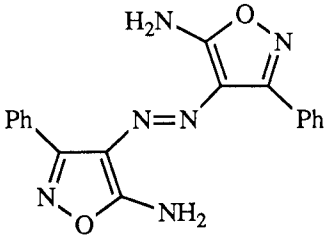

**725**



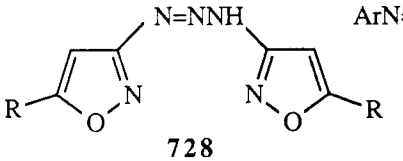

**726**

Diazotization of 4,5-diamino-3-phenylisoxazole with isoamyl nitrite leads to the interesting diazoaminoisoxazole hydrochloride (**725**), which can be cyclized under mild basic conditions to 3-phenylisoxazolo[4,5-*d*][1,2,3]triazole (**726**).[207/70] The same bicyclic ring system was built by diazo-transfer reaction with azidinium salts from 5-amino-3-phenylisoxazole.[119/78] This ring closure occurs in 2.3 *N* alcoholic hydrochloric acid; with more dilute solutions, the azocompound **727** is obtained.

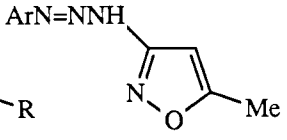
Under suitable conditions diazoamino derivatives can derive from the reaction of 3- or 4-aminoisoxazoles with aqueous nitrous acid or with arenediazonium salts. For example, bisisoxazolyltriazenes of general structure **728** proceed from 3-aminoisoxazoles alone,[5/31.5/63.94/64] whereas asymmetrical triazenes (**729**) are obtained by treatment of 3-amino-5-methylisoxazole with arenediazonium chlorides.[16/62.94/64]



**727**

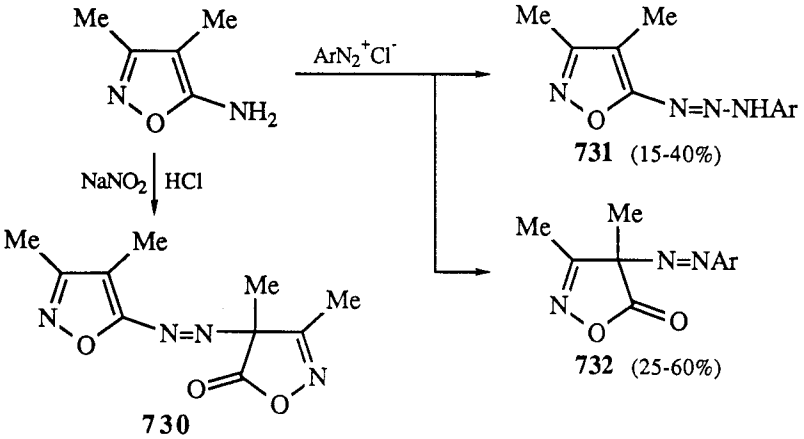


**728**



**729**

The behavior of 5-aminoisoxazoles is not as straightforward. 5-Amino-3,4-dimethylisoxazole is diazotized to the yellow explosive compound **730**; its reaction with arenediazonium chlorides yields either the isoxazolylaryltriazenes (**731**) or the arenediazoisoxazolinones (**732**), depending on the substitution on the aryl group:[78/65.71/79]



**730**

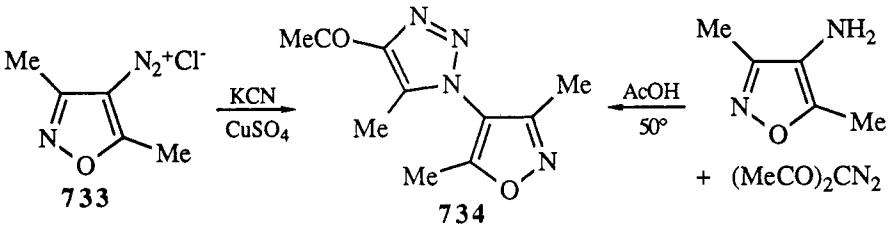
**731** (15-40%)

**732** (25-60%)

The formation of a 5,5′-azoxyisoxazole in a similar reaction has been claimed,[10/891] but a reexamination seems worthwhile. 5-Amino-3-phenylisoxazole with nitrous vapors is reported to yield mainly 3-phenyl-4-isonitrosoisoxazolinone or, by ring cleavage, α-nitro-β-isonitroso-β-phenylpropionamide.[4B/43] Other efforts to trap the diazonium salt were unsuccessful.[16/83]

Sandmayer-type substitutions of isoxazole diazonium salts are known, although the yields are often low to moderate. 4-Halogenoisoxazole derivatives have commonly been prepared from the 4-amino compounds,[8/21,4/41,7/42,2/46,4/46,177/77] and in one case the formation of an open-chain by-product was reported.[4/41] Heating of the diazonium salt aqueous solution from 4-amino-5-methyl-3-phenylisoxazole affords the 4-hydroxy derivative.[4/46]

Ethyl 5-halo-3-methylisoxazole-4-carboxylates have been described as the result of the diazotization in hypohalous acid of the corresponding 5-amino compounds.[245/70] 3- and 4-Azidoisoxazoles[168/77,229/79] have been prepared under standard conditions, but an attempt to prepare 4-cyano-3,5-dimethylisoxazole from the diazonium salt **733** led to the triazolylisoxazole **734**, possibly produced through the diazoamino compound, and available more conveniently by reaction of 4-amino-3,5-dimethylisoxazole with diacetyldiazomethane:[37/62]

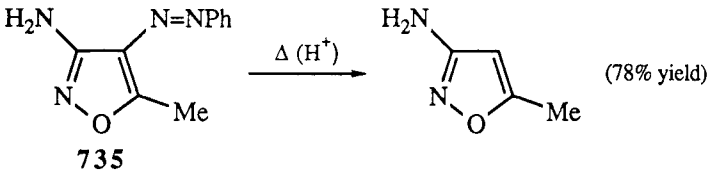



It was already known that the diazonium salt **733** decomposes by heating with cupric sulfate and sulfuric acid into 4-acetyl-5-methyl-1,2,3-triazole and diacetyl.[4/41]

3-Azido-5-methylisoxazole and its equilibrium with the tautomeric form of isoxazolo[2,3-*d*]tetrazole have been studied by physical and theoretical methods, and a large shift toward the azidoimine form in whatsoever solvent has been deduced, with a preference in favor of the *Z* conformation.[39/77]

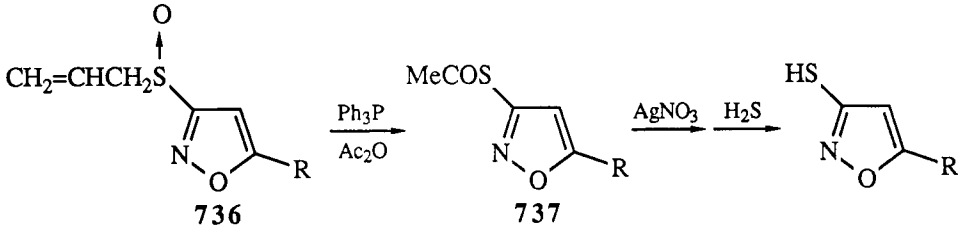
Reduction of isoxazole diazonium salts with stannous chloride furnishes isoxazolylhydrazines. These condense in the normal way with aldehydes and ketones, giving isoxazolylhydrazones. Some hydrazines have been obtained by reduction of the diazoaminoisoxazoles, together with the aminoisoxazoles. Substitution of the 5-hydrazino group with a hydrogen atom can be achieved, as expected, through the tosyl derivative, and represents the key step in the transformation 5-isoxazolinone → isoxazole.[144/69]

Removal of the phenylazo group from the 4-position has been achieved by treatment of **735** with an acetic–hydrochloric acid mixture:[295/77]




The cyano group present in an isoxazole side chain behaves normally: partial or complete hydrolysis to carboxylic amide or acid can easily be effected in both acidic and alkaline media. Isoxazolyl enamines can be obtained by reaction of 3- or 5-cyanoisoxazoles with ketones.[86/77]

The rearrangement of the sulfoxide **736** with triphenylphosphine and concurrent acetylation yields the 3-acetylthioisoxazoles (**737**), a good intermediate for the synthesis of 3-mercaptoisoxazoles.[47/80]

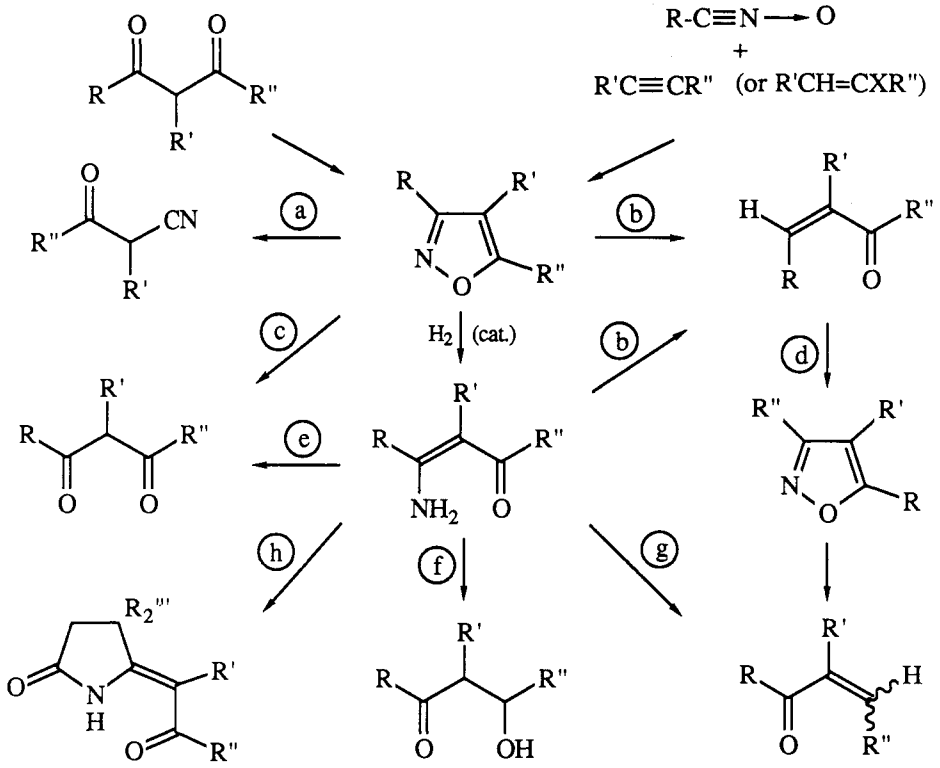



### 1.4.12 Use of Isoxazoles as Key Intermediates in Synthetic Design

Until about 20 years ago, syntheses and reactivity of isoxazole derivatives had been investigated chiefly to reach a comprehensive illustration of the properties of this five-membered heterocyclic ring. More recently, isoxazoles (and their dihydro- and tetrahydro counterparts) have acquired more and more importance as *intermediates* in multistep syntheses of various classes of more or less complex molecules. Use of 2-isoxazolines and of isoxazolidines to achieve this goal will be discussed in §§ 2.2.3.3 and 3.4.10, respectively.

The still increasing popularity of isoxazoles as key intermediates in synthetic design is due on the one hand to the relatively high stability of this heteroaromatic ring toward most reagents (electrophiles, oxidants, most nucleophiles), so that several manipulations in the side chains can safely be performed without opening the ring, and on the other hand, to the relative easiness by which the same ring can specifically be cleaved under mild conditions (chiefly hydrogenolysis, less frequently some suitable nucleophiles) at the stage required. Moreover, isoxazoles derive from easily available materials, such as $\beta$-diketones when the oximation method is used for preparing symmetrically 3,5-disubstituted derivatives, or aldehydes or nitroalkanes when the nitrile oxide synthesis, involving an economical formation of a C–C bond under mild conditions, is adopted.

The synthesis of various heterocyclic compounds through the intermediacy of isoxazoles was illustrated in § 1.4.10. Later, the transformation of the isoxazole nucleus into aliphatic, alicyclic, or aromatic derivatives will be summarized. Finally, special mention will be made of the formation of $\gamma$-butyrolactones, which includes spectacular achievements in the synthesis of macrocyclic ligands such as corrin or corphin. Although not entirely specific, some recent reviews[129B/78.87B/79.187B/79,187/81] contain more or less comprehensive treatments of the subject. Scheme 1.43 provides a summarizing selection of the general structures attainable through the intermediacy of an isoxazole derivative:

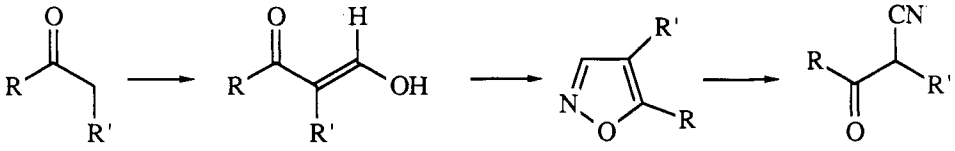



**Scheme 1.43.**

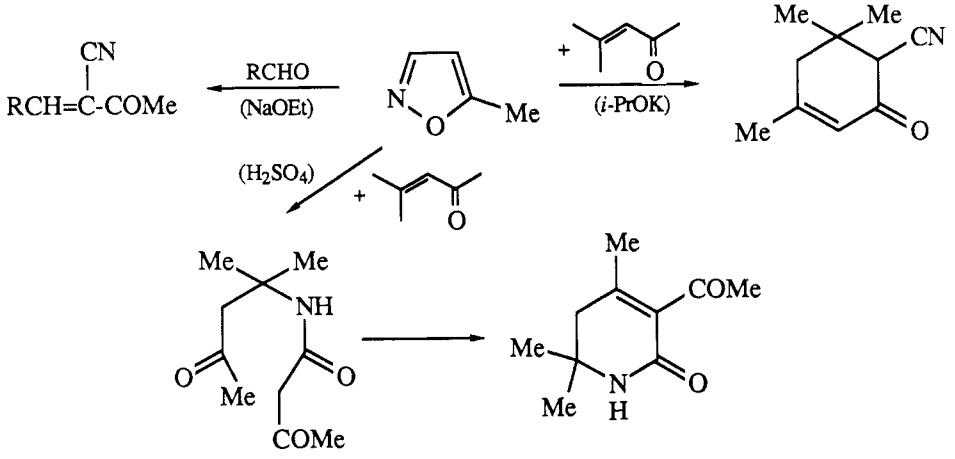
(a) Bases, when R = H
(b) Na, *t*-BuOH, liquid $NH_3$; TosOH, heat
(c) MeI; MeONa; dilute HCl
(d) $NH_2OH$; $I_2$, KI, heat
(e) $H_3O^+$, heat
(f) PhCOCl, Py; $NaBH_4$; AcOH
(g) PhCOCl, Py; $NaBH_4$; HCl
(h) when R = $MeOOCCH_2CMe_2$ (R‴ = Me): spontaneous at room temperature; when R = $HOOCCH_2CH_2$ (R‴ = H): ClCOOEt,$Et_3N$,THF

### *1.4.12.1 Syntheses of Aliphatic Compounds*

The easy base-promoted ring opening of 3-unsubstituted isoxazoles is a well-known general method for transforming ketones into α-cyanoketones in the sequence[7/45.8/47]

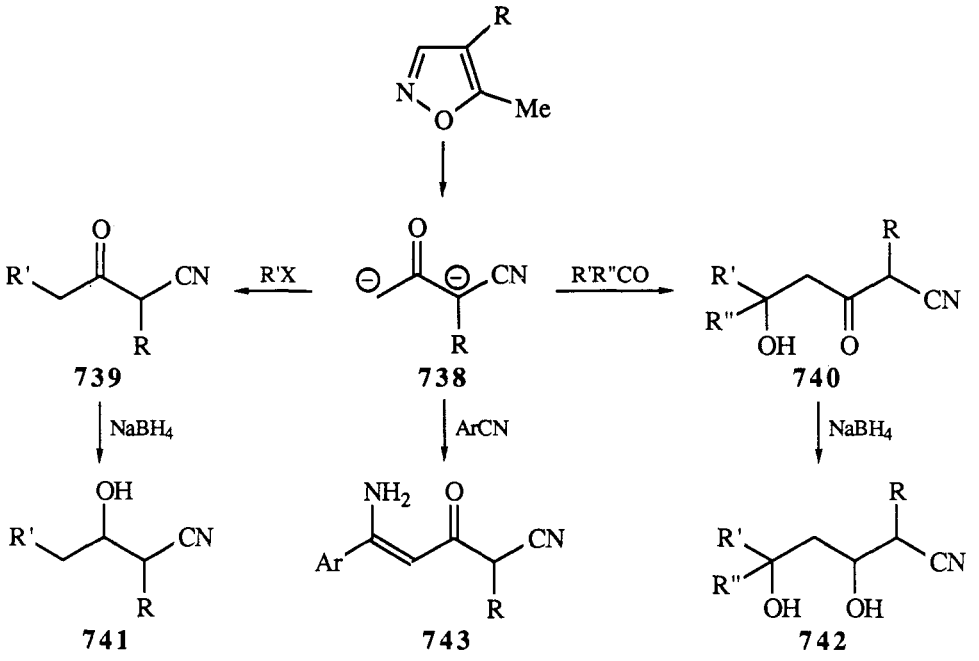


Coupling this sequence with the oxidative scission of α-cyano ketones led to the proposal of a variant to the direct oxidation of cyclanones to dicarboxylic acids (e.g., adipic acid from cyclohexanone).[73/61] As a particular case, 5-methylisoxazole, easily available from acetoacetaldehyde diethylacetal, has been proposed as a suitable synthon for the unstable cyanoacetone, generated *in situ* with strong bases:[40/63] thus aldol condensation with aliphatic or aromatic aldehydes yields substituted methylenecyanoacetones; Michael addition to mesityl oxide or Mannich bases is followed by cyclization to a cyanocyclohexenone. Moreover, a Ritter-like reaction occurs when the same 5-methyl (or phenyl)-isoxazole is treated with mesityl oxide in a strong acetic acid medium: an initial *N*-alkylation by the protonated α,β-unsaturated ketone to the isoxazole system is followed by ring opening with the formation of an intermediate acylacetamide derivative, which usually recloses to a 3-acyl-5,6-dihydro-2-pyridone:



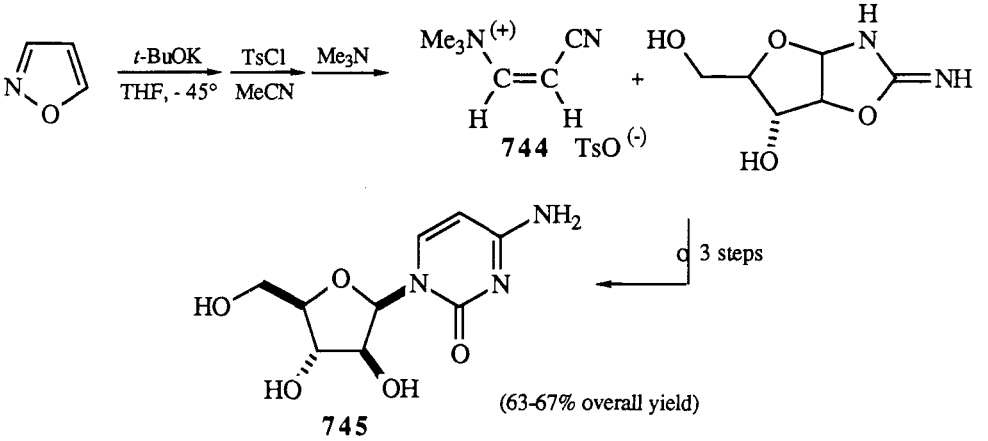
Ring opening of 3-unsubstituted isoxazoles with an excess of lithium diisopropylamide at low temperatures generates the cyanoacetone dianion **738**, whose reactions with electrophiles open a route to several compounds, such as

the $\gamma$-substituted cyanoacetones **739** or **740**, or the corresponding more stable products of their $NaBH_4$ reduction: hydroxy or dihydroxy nitrile (**741** or **742**), or the enamino ketones (**743**)(Scheme 1.44).[264/78]

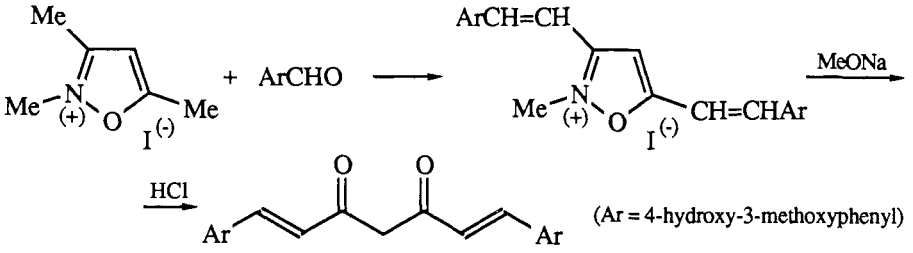



**Scheme 1.44.**

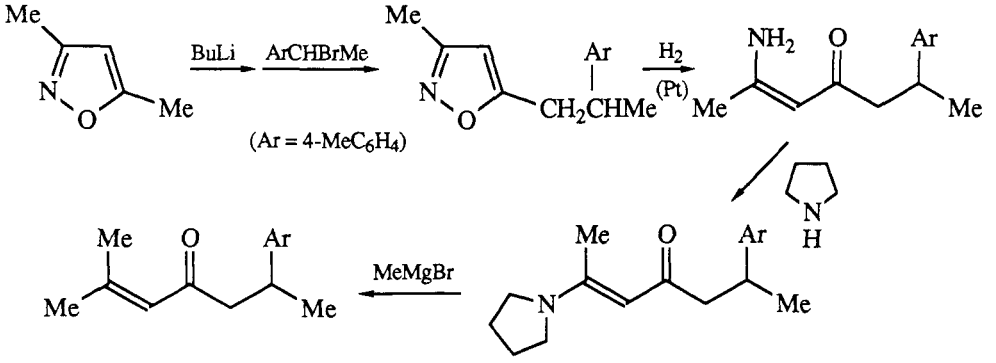
Base-promoted ring opening of the unsubstituted isoxazole (now commercially available) makes it possible to prepare in 85–95% yields *cis*-$\beta$-trimethylammoniumacrylonitrile tosylate (**744**), a key reagent in the efficient synthesis of the antileukemia agent cytarabine (1-$\beta$-D-arabinofuranosylcytosine, **745**) in the sequence[187/76]



Di- and trisubstituted isoxazoles are more resistant to base-promoted ring cleavage, but the higher lability of the isoxazolium salts toward bases has been taken advantage of for a convenient synthesis of curcumin, a naturally occurring unsaturated β-diketone:[23/58.89/77]

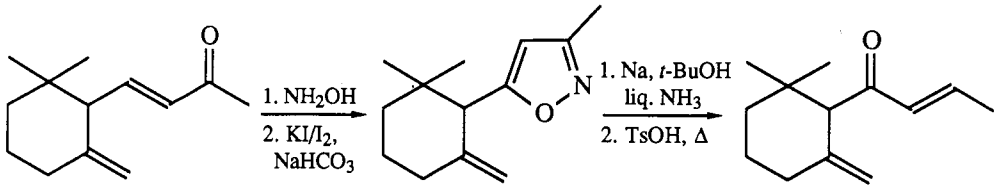



Reductive cleavage of the isoxazole ring can be performed (see § 1.4.3.1) either by metal and alcohols or by catalytic hydrogenation. In both cases the unstable enamino ketone is formed primarily, and then further transformed. Combination in subsequent steps of base-promoted 5α-alkylation, catalytic hydrogenolysis, stereoselective amino exchange, and substitution with Grignard compounds has led to syntheses of terpene derivatives such as tergetone and *ar*-turmerone.[26B/79] As an example of this type of application, synthesis of the latter compound in a 7.7% overall yield from 3,5-dimethylisoxazole, is illustrated here:

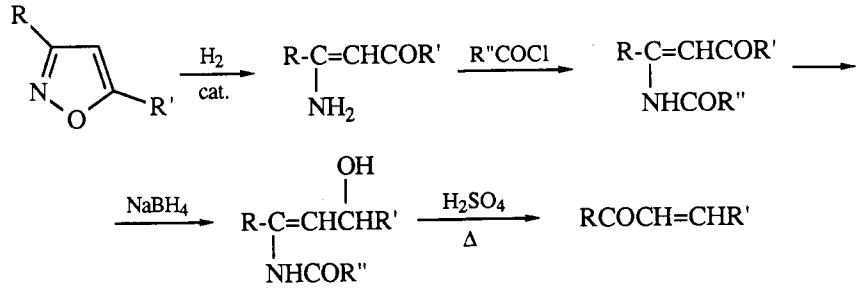



When either the isoxazole or the corresponding enaminone is treated with sodium and *t*-butyl alcohol in liquid ammonia, the reduction proceeds to the saturated β-amino ketone. Acid-promoted or thermal deamination finally gives the α,β-unsaturated ketone, where the carbonyl group proceeds from the 5-carbon atom of the isoxazole ring. Since the oxime of an α,β-unsaturated ketone can be transformed into the isoxazole by oxidative cyclization with iodine–potassium iodide, carrying the formerly carbonyl carbon atom in the 3-position,

an easy interchange of functionalities in α,β-unsaturated ketones can be effected through the isoxazole intermediacy.[96/72] An example of the application of this sequence to the transformation β-ionone → β-damascone was noted earlier (p. 275); an additional example is the transformation γ-ionone → γ-damascone, which has been performed in 25% overall yield:[100/73]



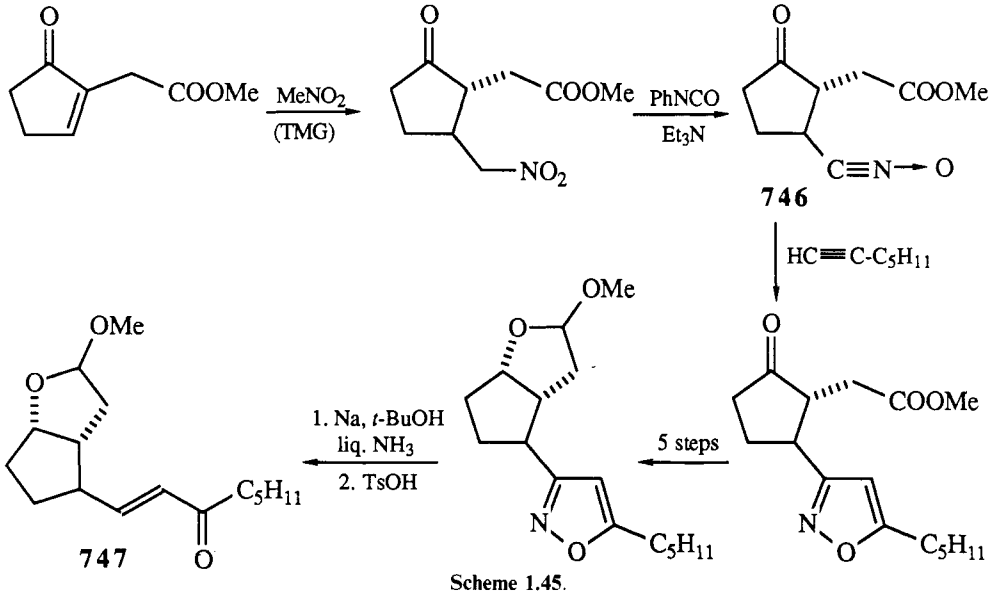

An alternative method for reducing the isoxazole compound to an α,β-unsaturated ketone, this time deriving its carbonyl group from the 3-carbon atom, passes through the β-aminoenone, obtained by catalytic hydrogenation, which, after protection through *N*-acylation, is reduced with sodium borohydride and hydrolyzed. The reaction sequence has general applicability:[139/75]



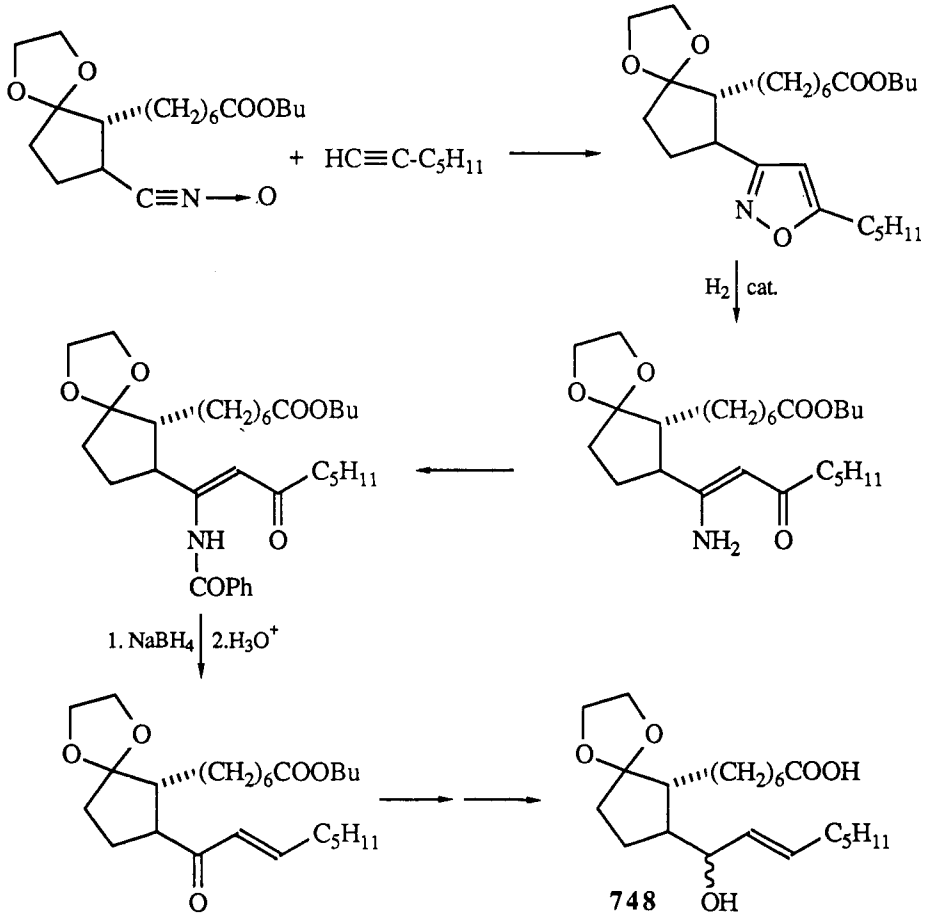

This method has been applied with slight variations for construction of the α,β-enone moieties present in the macrocyclic antibiotics pyrenophorin and vermiculine.[197/83]

An interesting application of both methods for synthesizing isomeric α,β-enones through an isoxazole key step involves construction of the ω-chain of prostanoids:[201/80,159/81] for example, the classical 11-deoxy $PGF_2$ intermediate **747** has been prepared through the nitrile oxide **746** and 1-heptyne in 66% overall yield from methyl 2-oxocyclopent-5-enyl-1-acetate (Scheme 1.45).[201/81] An alternative route to α,β-enones has been utilized in the synthesis of 13-hydroxy-9-oxo-$\Delta^{14,15}$-prostanoic acid (**748**)(Scheme 1.46).[159/81]

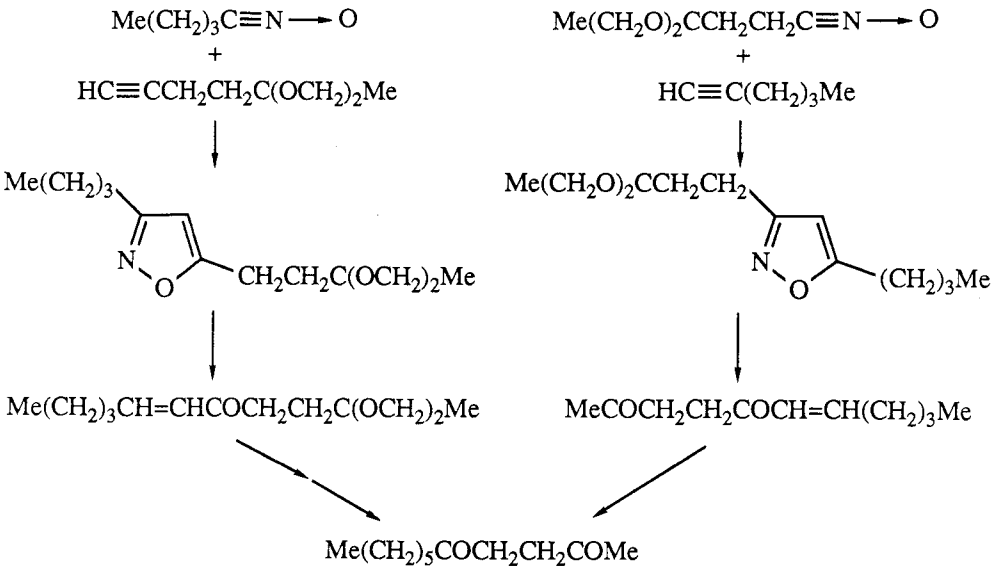
A further instance of the potentiality of these α,β-enones syntheses is the smooth preparation of undecane-2,5-dione, exemplifying a general entry into the class of 1,4-diketones. The starting materials are either the couple 1-nitropentane/hex-5-yn-2-one cyclic ketal or the couple 5-nitropentan-2-one cyclic ketal/1-hexyne (Scheme 1.47).[142/79]




Scheme 1.45.

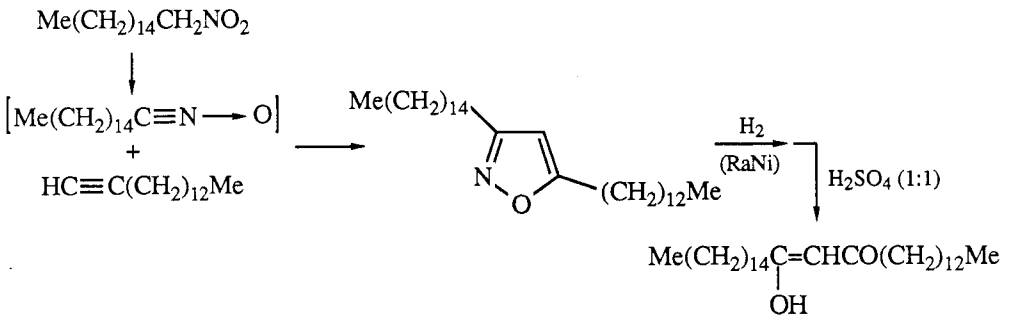



Scheme 1.46.

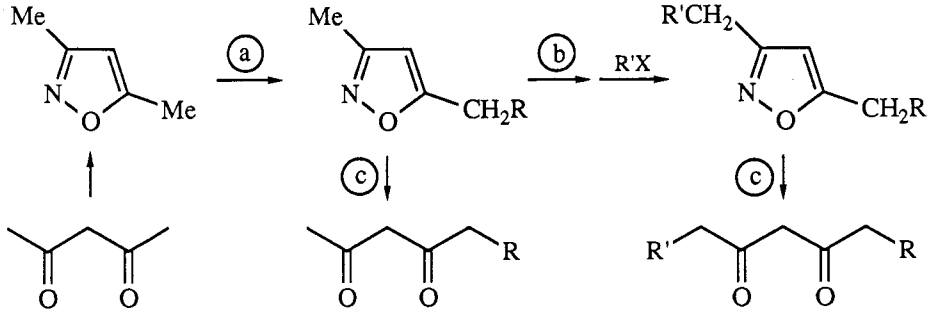


**Scheme 1.47.**

The capability of 3,5-disubstituted isoxazoles to act as masked $\beta$-diketones has been known for a long time: the synthesis of hentriacontane-14,16-dione, a $\beta$-diketone found in plant waxes, from 1-nitrohexadecane and 1-pentadecyne is an example:[183/78]



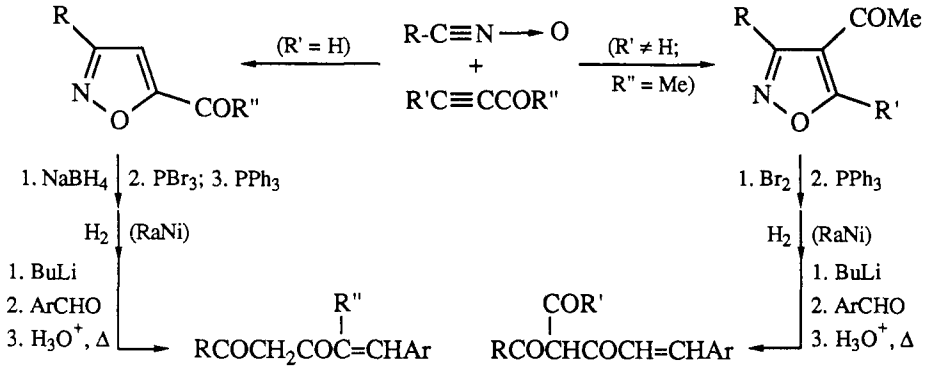
Coupling of this ability with the base-promoted alkylation of 3,5-dimethylisoxazole results in a convenient method of general applicability for mono-[40/73] and dialkylating[237/81] acetylacetone, as the following scheme shows:



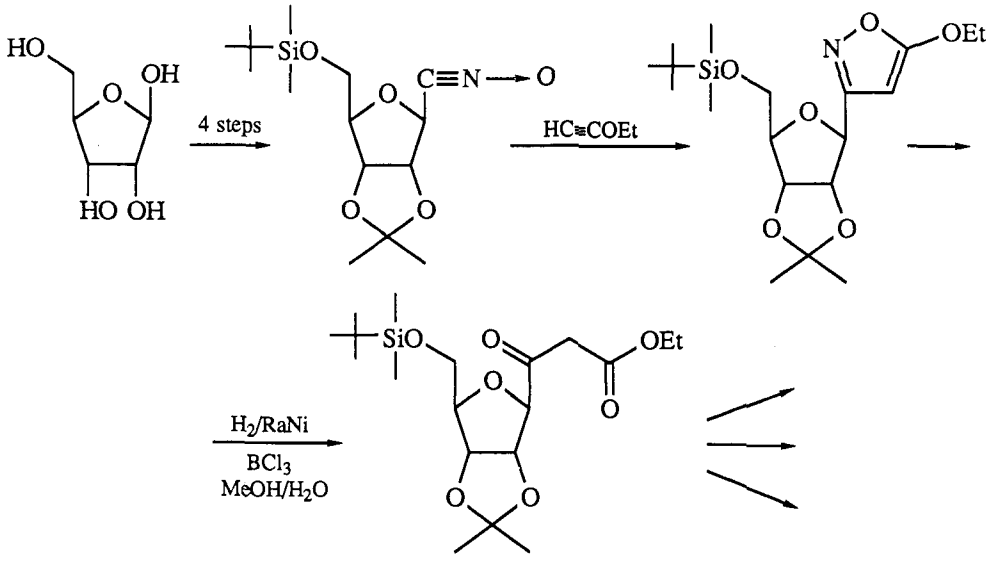
where the conditions of pathway are (a) *n*-BuLi or $LiN(i\text{-}Pr)_2$ or $NaNH_2/NH_3$, then RX; (b), *s*-BuLi or *t*-BuLi, THF, $-75°C$; and (c), $H_2$/RaNi or Pt; $H_3O^+$.

Analogously, a simple synthetic route to the diethyl ester of 2-carboxy-3,5-dioxohexanoic acid, a supposed intermediate in biosynthesis, from 3,5-dimethylisoxazole has been realized.[52/73]

Furthermore, use of the ylids derived from 5- or 4-isoxazolyl ketones allows easy entry into olefinic $\beta$-diketones or $\beta,\beta'$-triketones, respectively, through the following sequence:[29B/75,66/76]



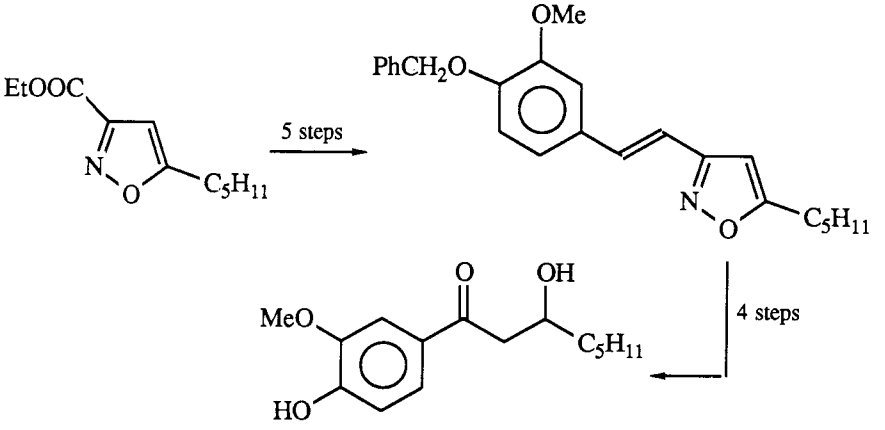

Taking advantage of the easy hydrogenolysis of 5-ethoxyisoxazole to $\beta$-keto esters, an efficient and potentially versatile synthesis of *C*-nucleoside derivatives has been developed through the sequence shown in Scheme 1.48, which profits by practically no epimerization.[195/83]




Scheme 1.48.

A fascinating goal of this 1,3-dicarbonyl masked functionality is represented by the synthesis of β-polyketones from the appropriate isoxazole derivatives, containing two or more rings linked by methylene bridges. As a matter of fact, no free β-polyketone has yet been isolated by the isoxazole synthon route, since the primary products of the catalytic hydrogenolysis (i.e., the polyfunctional enamino ketones) cyclize *prior* to hydrolysis, regardless of what mild conditions may be chosen. Therefore, despite an alleged isolation of 1,7-diphenylheptane-1,3,5,7-tetraone,[36/65] which resulted instead in 5-benzoylacetonyl-3-phenyl-isoxazole,[211/84] only transformations into benzenoid compounds, following the well-known polyketide cyclization pattern, have been observed so far (see below).

If the enamino alcohol arising from the $NaBH_4$ reduction of the acylated β-aminoenone is hydrolyzed under mild conditions, the sensitive β-hydroxy ketone carrying the hydroxy group bound to the carbon atom formerly in the isoxazole 5-position can be isolated. An interesting application of this principle involves the synthesis of (±)[6]-gingerol, starting from ethyl 5-*n*-pentyl-isoxazole-3-carboxylate, in the following sequence:[108/81,162/82]

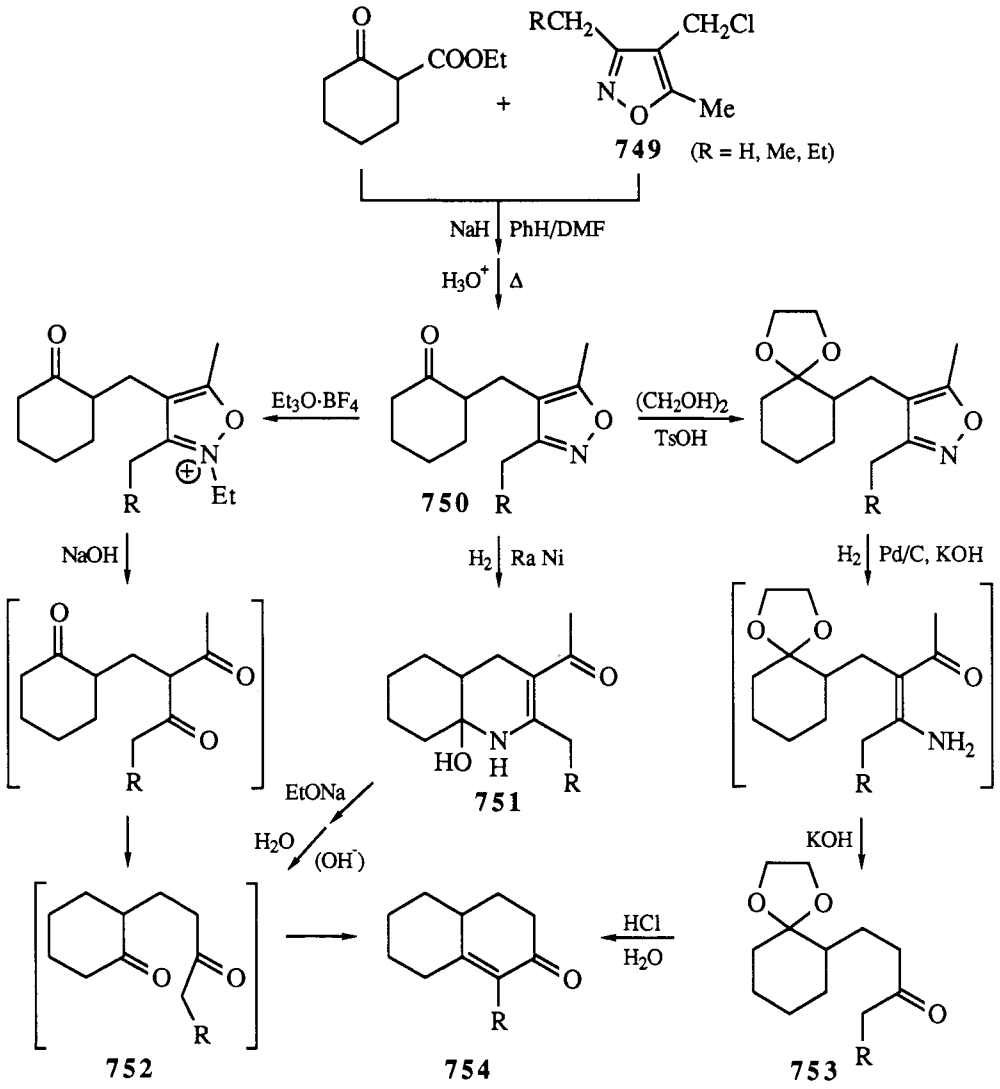



The optically active natural (+)-gingerol was obtained by a similar procedure with a rather modest optical purity of 30–40%.[162/82]

### *1.4.12.2 Synthesis of Alicyclic Compounds*

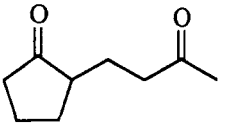
The preparation of α-cyanoketones through 3-unsubstituted isoxazole derivatives noted earlier (p. 299) has frequently been utilized in building up polycyclic structures. A remarkable example of this use of the isoxazole ring is the classical Johnson's synthesis of *d*-equilenin, which was achieved from 7-methoxy-1-keto-1,2,3,4-tetrahydrophenantrene in eight steps and 24% overall yield.[8/47]

The isoxazole annelation reaction discovered by Stork[83/64] utilizes the 3-alkyl-4-chloromethyl-5-methylisoxazole as an alkylating agent of cyclanones, thus introducing in their α-position a masked 3-ketoalkyl moiety. Release of this functionality through quaternization or hydrogenolysis opens the route to the subsequent base-promoted aldol-like cyclization. This sequence parallels the classical Robinson annelation method and is exemplified in Scheme 1.49 by the synthesis of 2-octalones of general structure **754**.

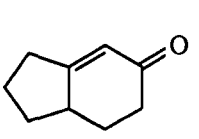



Scheme 1.49.

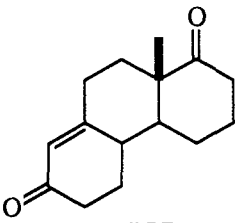
The isoxazole reagent **749** is easily available from ethyl 3-alkyl-5-methylisoxazole-4-carboxylate, in turn synthesizable by nitrile oxide cycloaddition to the suitable enamino ester[80/67] or directly by chloromethylation of the 3,5-disubstituted isoxazole.[68/58] Alkylation is best accomplished on the 2-cyclohexanonecarboxylate,[204B/73] but can also be performed on the cyclanone enamine,[79/67] on the magnesium enolate,[180/72] or on an enone enolate, with subsequent selective hydrogenation of the α-substituted enone double bond.[78/67] The 4-(3-oxoalkyl)isoxazole derivative **750** was originally cleaved by treatment of the quaternary salt with bases,[78/67] but more satisfactory results are obtained by direct hydrogenolysis in the presence of Raney nickel, which gives the carbinolamine **751**. Deacetylation and dehydration are then promoted by sodium ethoxide; addition of water to the mixture gives rise to hydrolytic ring opening to the diketone **752**, which in the basic medium recyclizes to **754**.[81/67,204B/73] Overall yields from the isoxazolyl ketone **750** are in the range 50–60%. Slightly better yields are reported when **750** is first ketalized, then hydrogenolyzed and deacetylated in a basic medium; here, deketalization and cyclization are performed in methanolic hydrochloric acid.[173/72] By the latter procedure, starting with the cyclopentanone analogue of **750** (R = H), 2-(3-oxobutyl)cyclopentanone (**755**) is obtained, which cyclizes only in an alkaline medium to give the tetrahydroindanone **756**.[173/72]



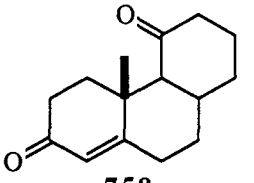
**755**



**756**



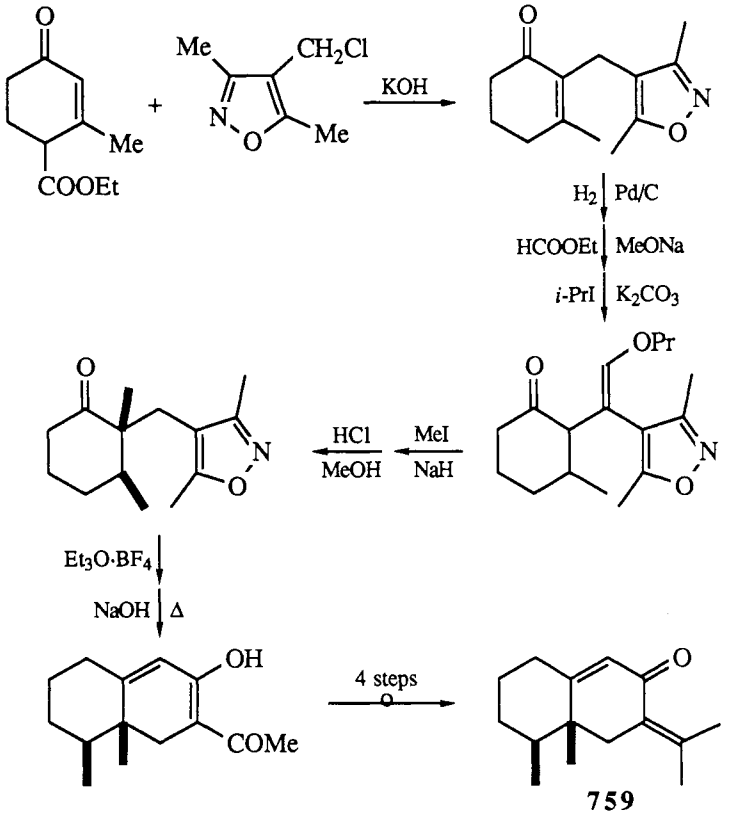
**757**



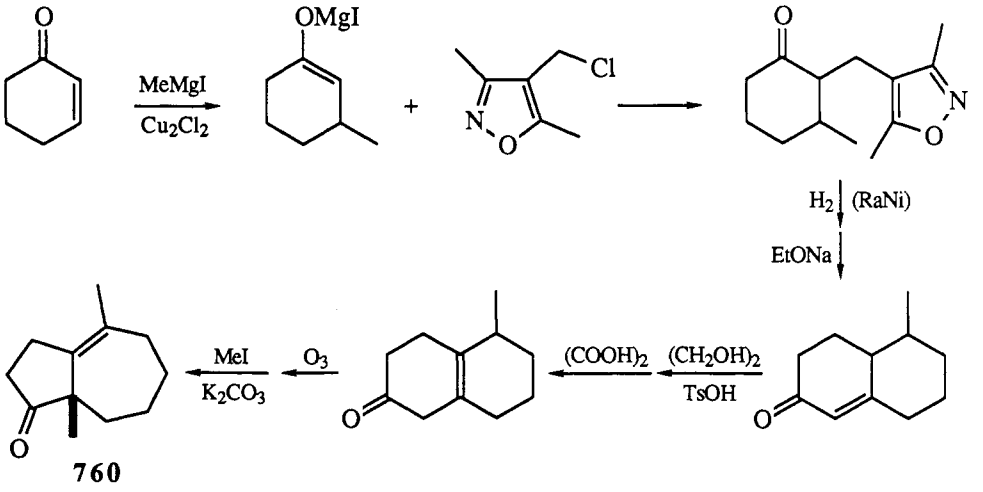
**758**

By analogous sequences the interesting tricyclic enediones **757**[78/67] and **758**[137/80] have been prepared with relative ease, starting with the suitable bicyclic diones and the isoxazole reagent. At this point it should be noted that slight variations in the experimental conditions can lead, starting from the same substrates, to aromatic compounds (see below) or to pyridine derivatives (see § 1.4.10.5, p. 360).[189/70] The isoxazole annelation reaction has been applied to the synthesis of the eremophilonoid sesquiterpene dehydrofukinone (**759**) through the sequence illustrated in Scheme 1.50,[39/69] and to the preparation of substituted hydroazulenes, as exemplified in Scheme 1.51 for compound **760**.[177/73]

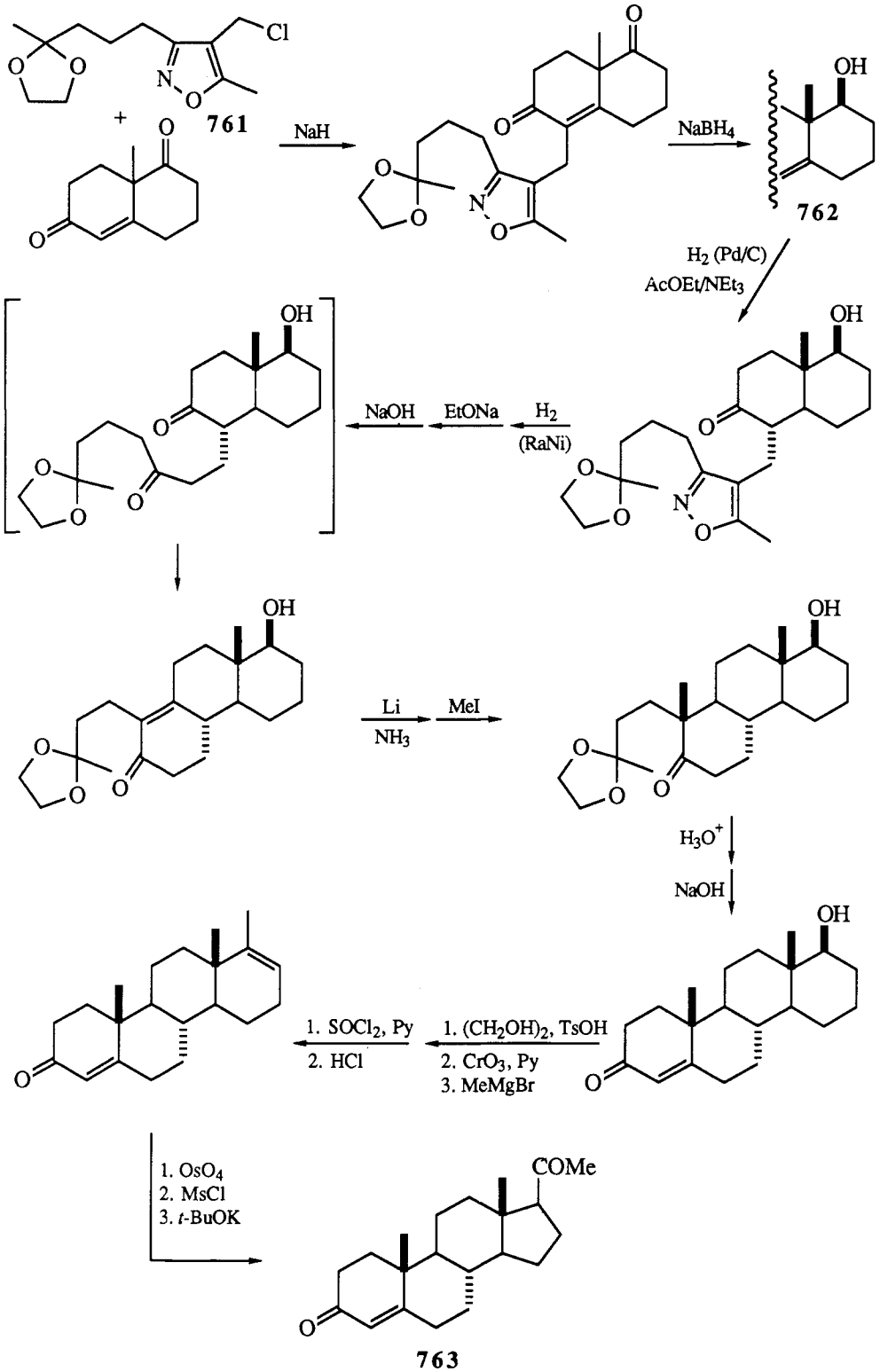
Nevertheless, the greatest achievements based on the isoxazole annelation reaction concern the stereospecific total synthesis of steroids, where the heterocyclic derivative is responsible for the construction of rings A and/or B of the steroidal skeleton. The classical Stork's synthesis of progesterone (**763**)[82/67] is outlined in Scheme 1.52: the 1,5-dicarbonyl moiety essential for forming ring




Scheme 1.50.

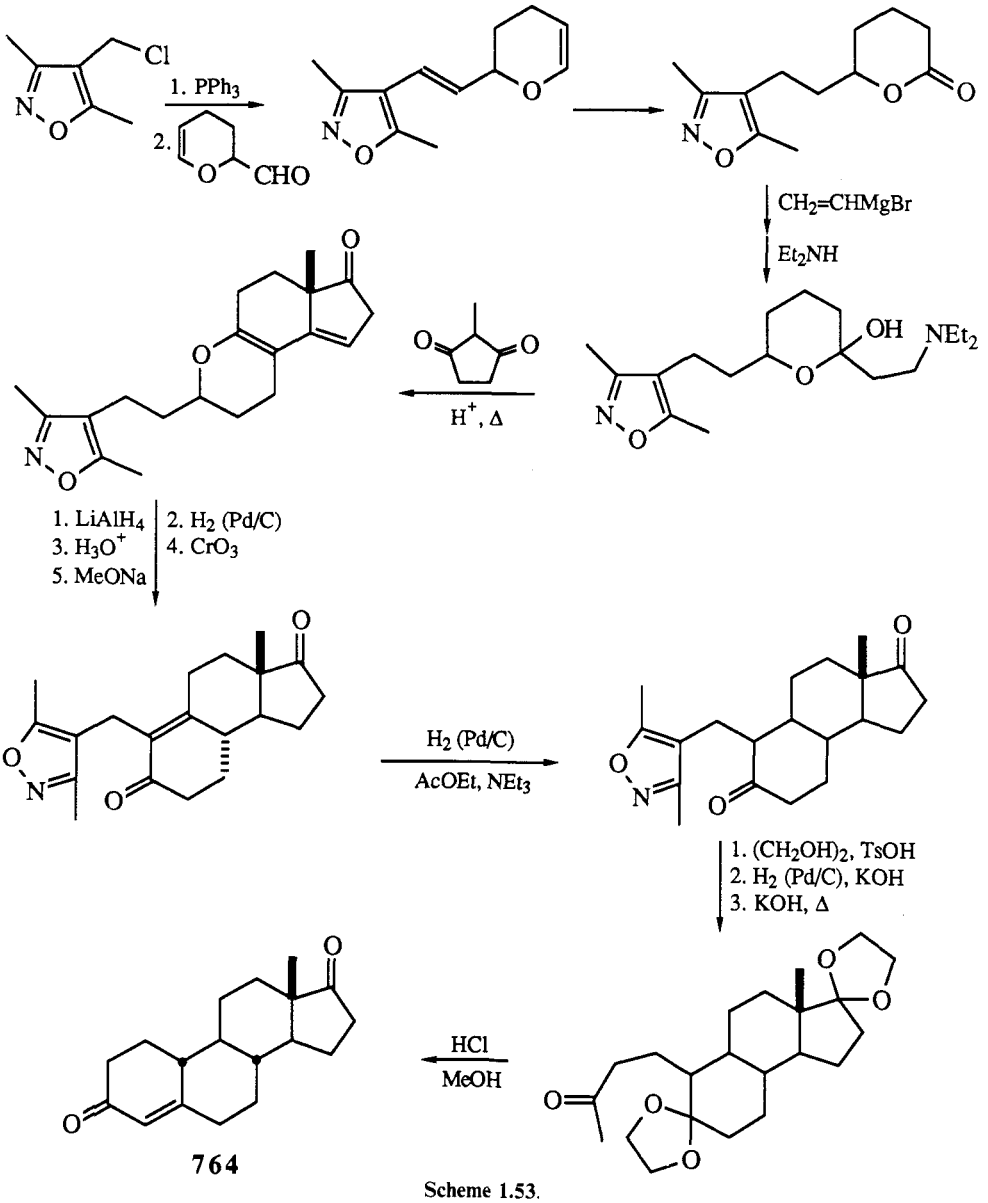



Scheme 1.51.


761
NaH
NaBH4
762
H2 (Pd/C)
AcOEt/NEt3
H2
(RaNi)
EtONa
NaOH
Li
NH3
MeI
H3O+
NaOH
1. (CH2OH)2, TsOH
2. CrO3, Py
3. MeMgBr
1. SOCl2, Py
2. HCl
1. OsO4
2. MsCl
3. t-BuOK
COMe
763

Scheme 1.52.

A is already masked in the functionalized 3-side chain of the isoxazole reagent **761**, whose nucleus is designed to form the steroidal ring B. Another relevant feature of the synthetic engineering is the selective hydrogenation of the conjugated double bond of the alkylated ketone **762**: as already noted in model studies,[78/67] use of palladium–charcoal in a mixture of 3:1 ethyl acetate–triethylamine makes it possible to leave the isoxazole ring unaffected and to grant the required *trans* stereochemistry. The same stereoselectivity is also




**764**

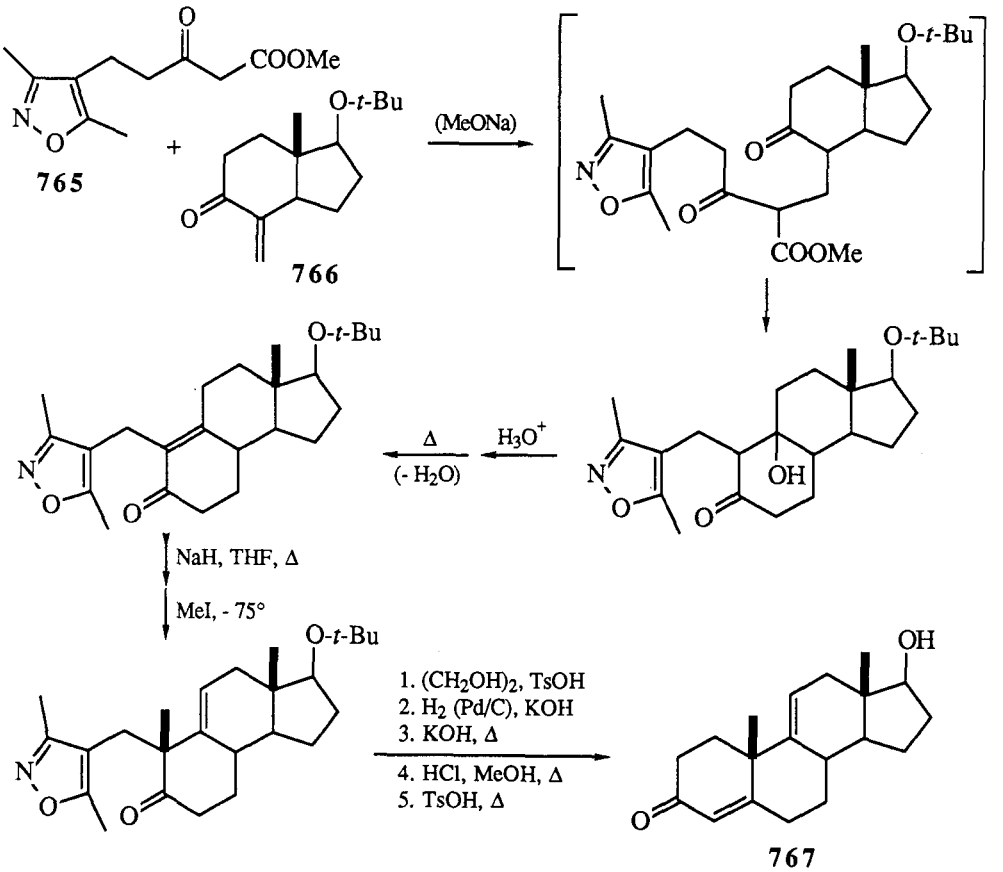
Scheme 1.53.

observed in hydroindanone systems by using palladium–charcoal in acidic methanol.[174/74]

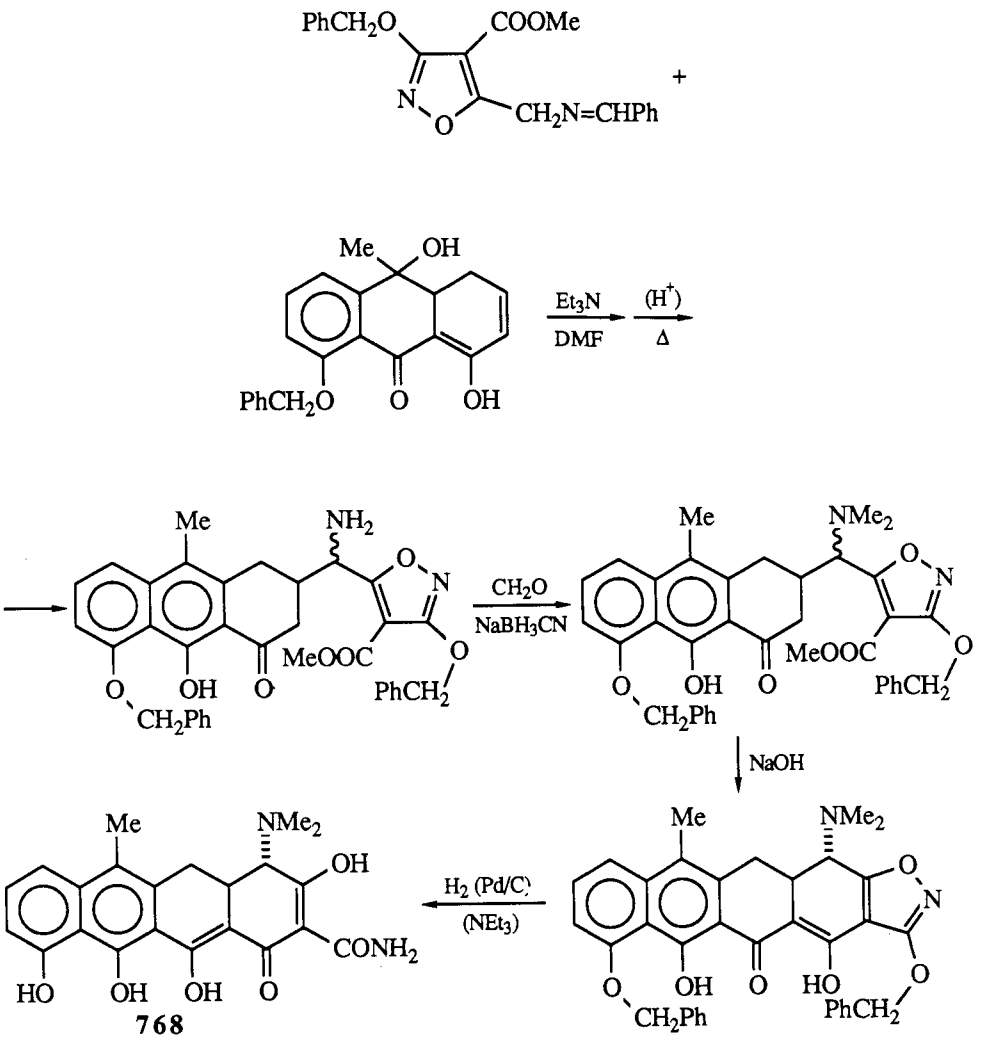
Another remarkable success in the use of isoxazole annelation is the total synthesis of 19-nor-steroids, and in particular Scheme 1.53 illustrates the route followed for the preparation of (±)-estr-4-ene-3,17-dione (**764**).[86/70,87/70,171/72] The foregoing procedure could be suitably modified to produce the optically active (+)-compound.[172/72]

With appropriate variations in the selective hydrogenation step the isomeric 19-nor-9β,10α-steroids have been similarly constructed.[63/72,177B/72,267/76,267/77] The isoxazole **765**, suitably functionalized in the 4-side chain so that its Michael addition to the enone **766** might generate the steroidal ring B, has been the starting material for the synthesis of $\Delta^{9(11)}$-dehydrotestosterone (**767**) in the sequence outlined in Scheme 1.54.[89/74]

3-Benzyloxyisoxazoles are synthons of the β-ketoamide moiety, and this feature has conveniently been utilized for building up the tetracycline ring A, as

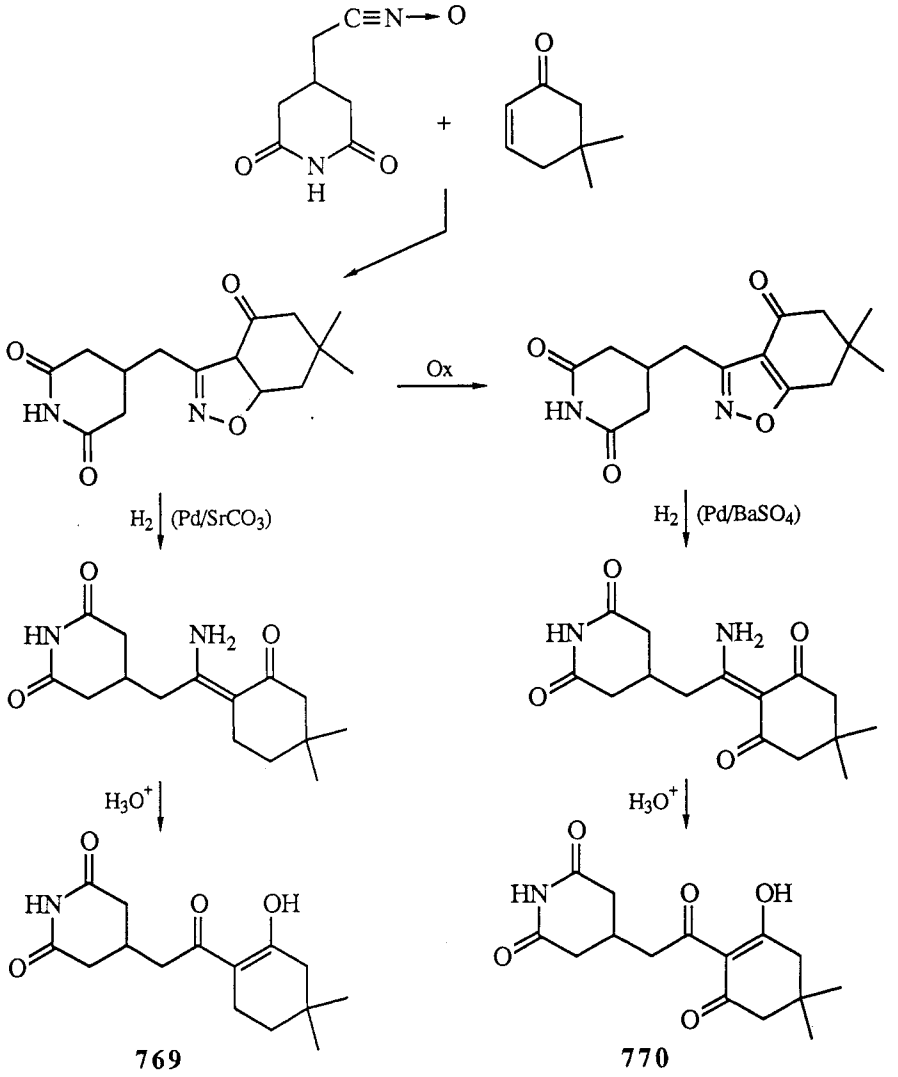



Scheme 1.54.




**Scheme 1.55.**

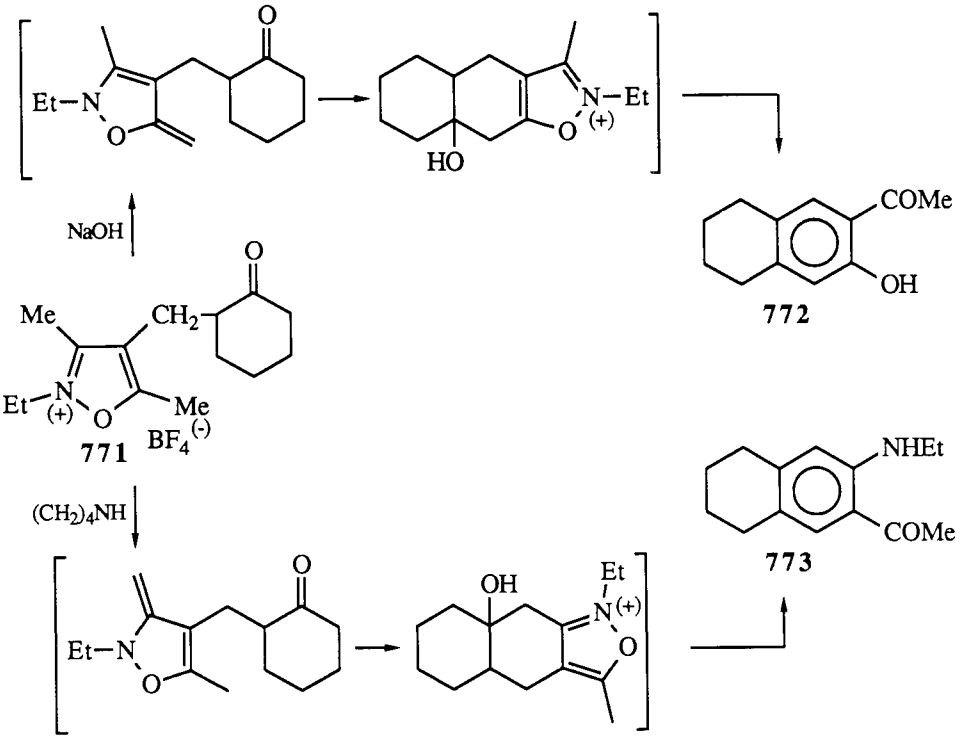
outlined in Scheme 1.55, for 12-deoxyanhydrotetracycline (**768**).[151/78] A different isoxazole synthon approach to ring A of tetracyclines has also been reported.[215/68] The polycarbonyl derivatives **769** and **770**, key intermediates in the synthesis of glutarimide antibiotics, have been achieved by the nitrile oxide route shown in Scheme 1.56.[240/76,188/79]




**Scheme 1.56.**

### *1.4.12.3 Syntheses of Aromatic Compounds*

Under appropriate conditions the isoxazole annelation reaction can be made to diverge toward the synthesis of aromatic compounds.[78/67] Thus, when the quaternary salt (**771**) is treated with either sodium hydroxide or pyrrolidine, the tetrahydronaphthalene derivatives **772** and **773** are obtained, respectively (Scheme 1.57).[205/68]

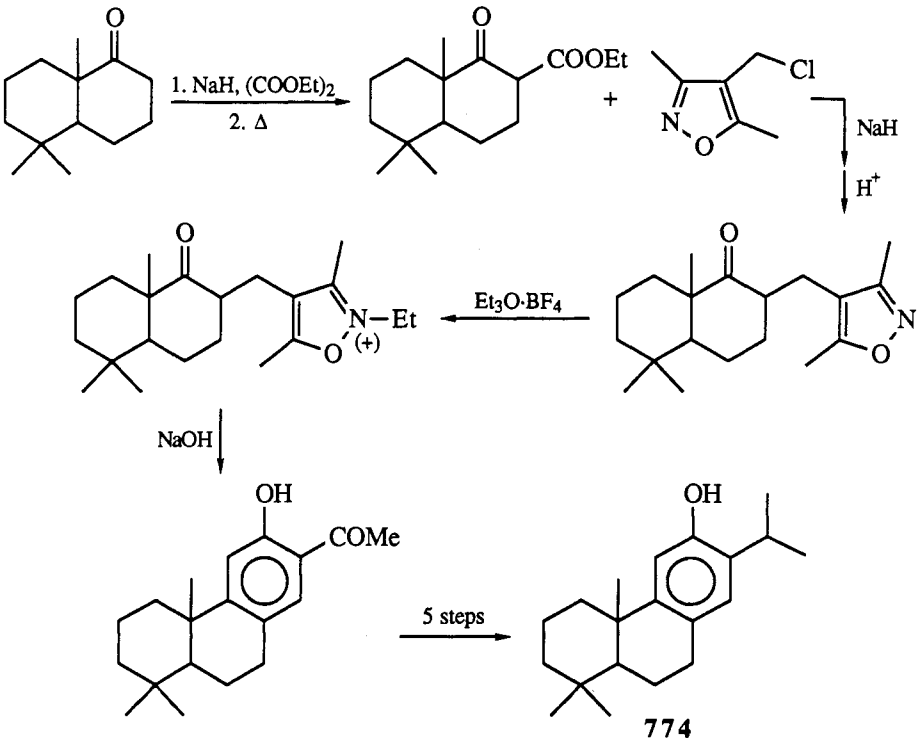



**Scheme 1.57.**

The formation of the phenol or of the alkylaniline derivative (or of a mixture of both) has been attributed to the loss of a proton present in the methyl group in either the 3- or the 5-position. This aromatization reaction has been utilized for the synthesis of ferruginol (**774**), a diterpenoid phenol, in the sequence outlined in Scheme 1.58.[205/68]

The hydrogenolysis of di- and polyisoxazole derivatives, masking $\beta$-polyketone systems, has led to unstable open-chain intermediates, which under hydrolytic conditions cyclize to benzenoid compounds, thus mimicking the biosynthetic polyketide pathway. The starting materials are usually diisoxazolylmethanes[81/66,46/73,69/73,154/77,13/79] or polyisoxazoles, having their rings linked by methylene bridges between positions 3 and 5.[46/73,161/77] These compounds are synthetic equivalents of $\beta$-tetraketones or of higher $\beta$-polyketones having an even number of carbonyl groups, and are most conveniently prepared through repetitive nitrile oxides condensations or through acylation of isoxazole 5$\alpha$-carbanions. The latter method is the only one suitable for synthesizing diisoxazolylacetones,[46/73,67/76,94/77] possible precursors of $\beta$-penta ketones.

The structure of the aromatic compound obtained by hydrogenolysis depends on the nature of the starting material, and Scheme 1.59 illustrates the behavior of the three isomeric diisoxazolymethanes.[69/73,249/74,45/76] This synthesis

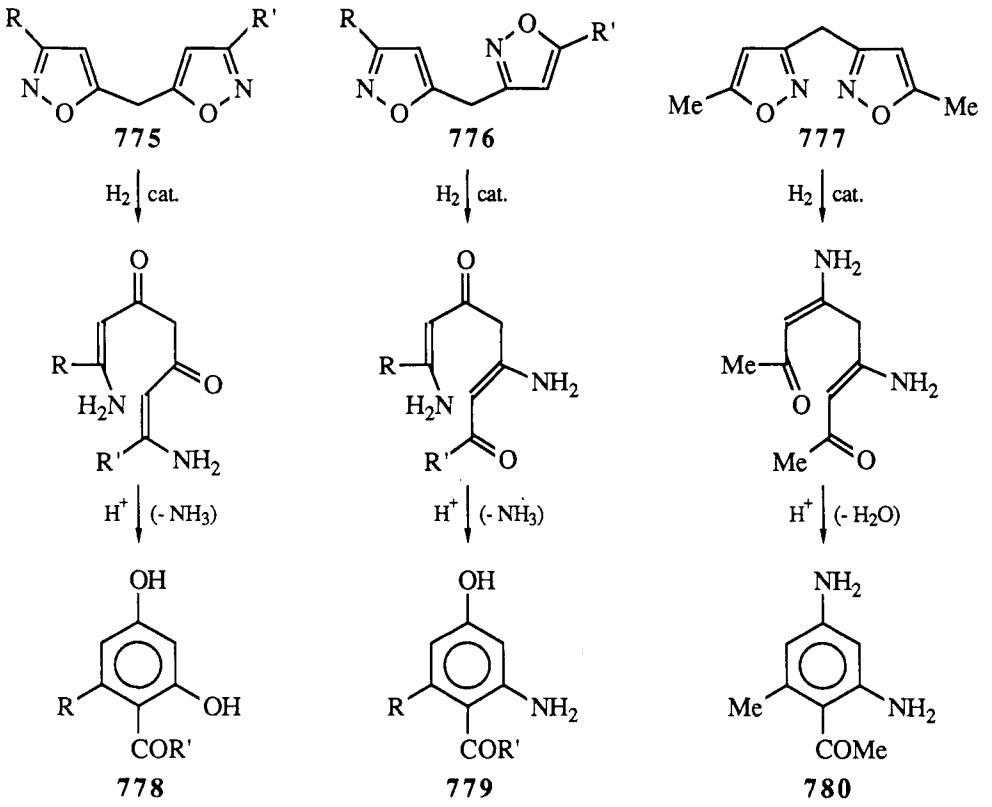



**Scheme 1.58.**

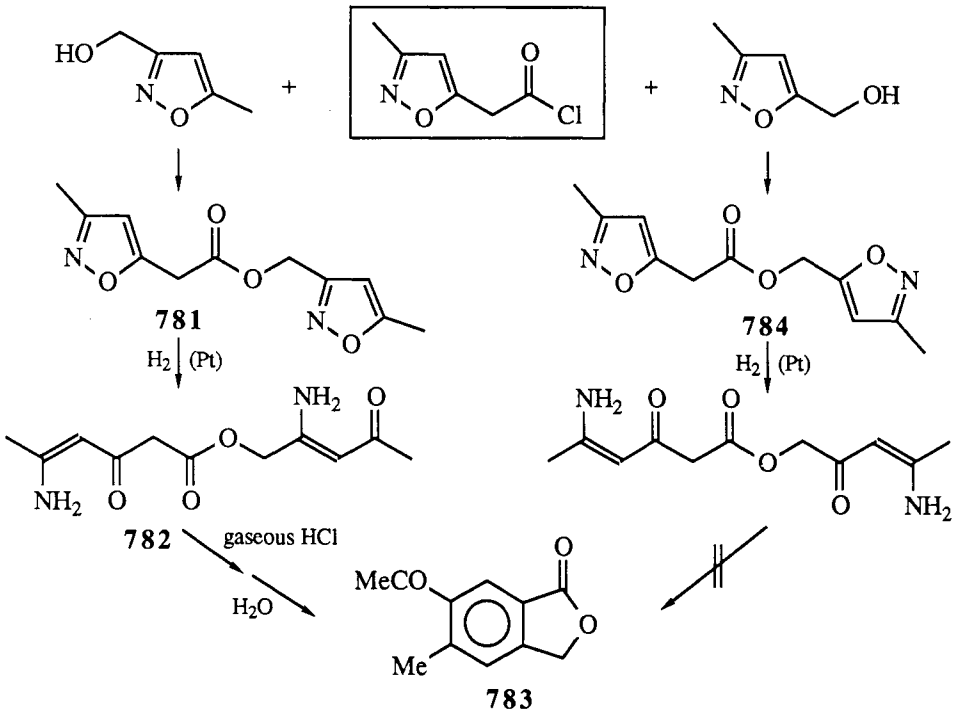
of acetylated resorcinols (**778**), *m*-aminophenols (**779**), and *m*-phenylenediamines (**780**) appears to have preparative relevance and general applicability. The cyclization has been demonstrated to occur at the enamino ketone stage, and the elimination of $NH_3$ is preferred over that of water. Thus when the asymmetrically substituted **776** (R = Ph, R′ = Me, or vice versa) is used as a starting material, aminophenol (**779**) is obtained almost entirely, the other possible isomer (the positions of $OH/NH_2$ and of R/R′ reversed) being present only in trace amounts.[249/74]

A useful application of the polyketide synthetic pathway is the preparation of suitably constructed β-enaminoketo esters, which may condense intramolecularly to give hydroxyphthalides.[88/80,264/80] The success of this operation is strongly bound to the relative positions of the "masked" functionalities in the isoxazole derivative. Thus the diisoxazolyl ester **781** is hydrogenolyzed to the enaminoketo ester **782**, which cyclized in acidic media to the hydroxyphthalide **783** in 26% overall yield (Scheme 1.60). By contrast, the isomeric ester **784** undergoing the same treatment furnishes only traces of **783**.

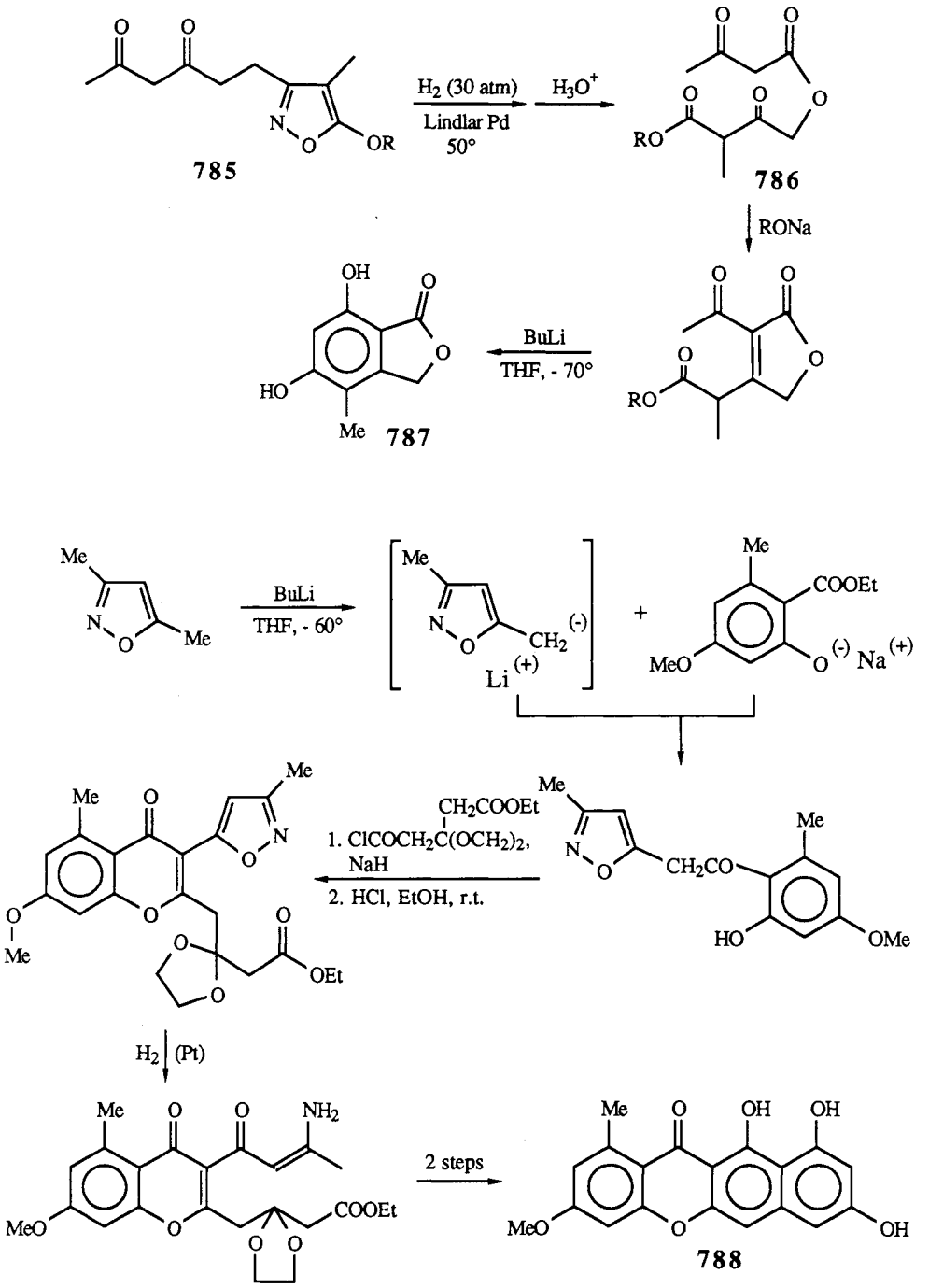
The same synthetic design underlies the preparation of 5,7-dihydroxy-4-




Scheme 1.59.




Scheme 1.60.


785
H2 (30 atm)
Lindlar Pd
50°
H3O+
786
RONa
787
BuLi
THF, - 70°
BuLi
THF, - 60°
1. ClCOCH2C(OCH2)2,
NaH
2. HCl, EtOH, r.t.
H2 (Pt)
2 steps
788

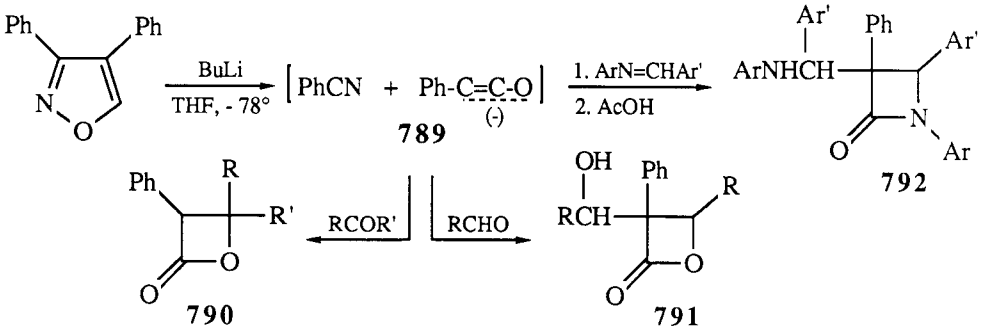
Scheme 1.61.

phthalide (**787**),[193/83] a key intermediate in the synthesis of micophenolic acid, in the sequence outlined at p. 412. It should be remarked that the hydrogenolysis of the isoxazolylketo ester **785** requires well-defined and selective conditions (see § 1.4.3.1), and that the cyclization of the intermediate triketo ester (**786**) is best effected in basic media.

Ring D of the tetracyclic xanthone derivative **788**, as an intermediate in the synthesis of the fungal metabolite bikaverin, has also been constructed using the isoxazole route, as illustrated in Scheme 1.61.[121/79]

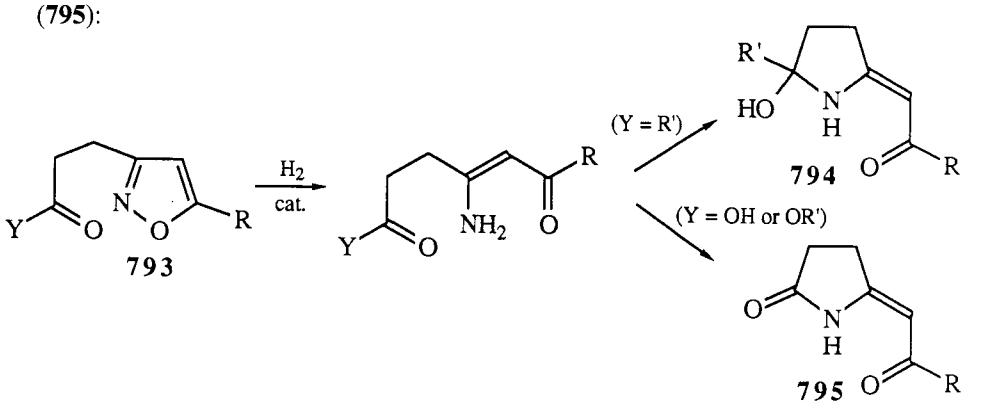
### *1.4.12.4 Syntheses of β-Lactones and β-Lactams*

As noted in § 1.4.6.1a, p. 304, 3,4-diphenylisoxazole is a convenient source of the blue-colored phenylethynolate anion **789**, which can react with ketones or aldehydes to give β-lactones **790** and **791**, respectively,[6B/75.12/79] or with electron-poor diarylimines to give the β-lactam derivatives **792**:[158/82]



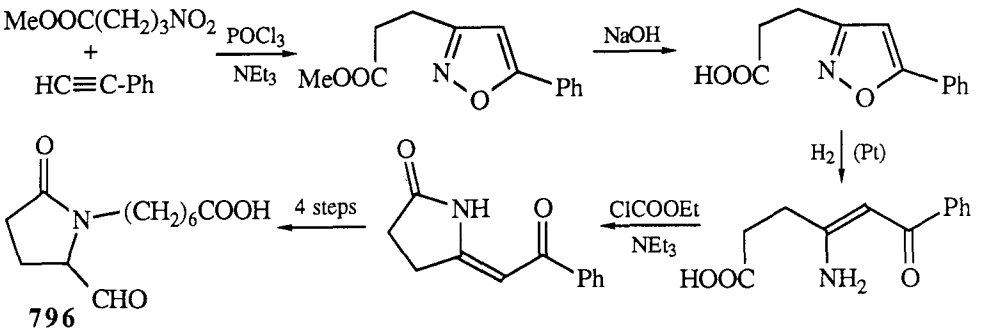

### *1.4.12.5 Syntheses of γ-Butyrolactams*

The presence of a carbonyl or of a carboxylic acid or ester group in the γ-position of the isoxazole 3-side chain, as exemplified in the general structure **793**, provides the opportunity to obtain, by hydrogenolysis followed by cyclization, a large variety of substituted carbinolamides (**794**) or γ-butyrolactams (**795**):



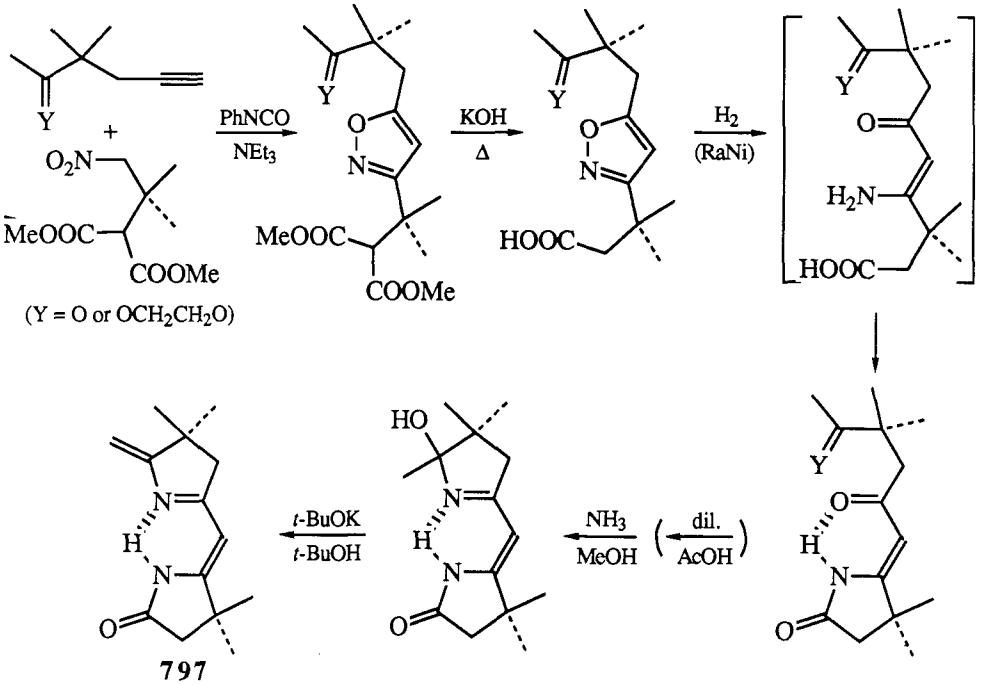
Indeed, an interesting approach to 8-azaprostaglandin analogues takes advantage of the latter possibility, and some 14-hydroxy-8-azaprostanoic acid methyl esters have thus been prepared.[245/78]

As a further example, the following scheme outlines the synthesis of the aldehyde **796**, a key intermediate for 11-deoxy-8-azaprostaglandin $E_1$:[148/79]

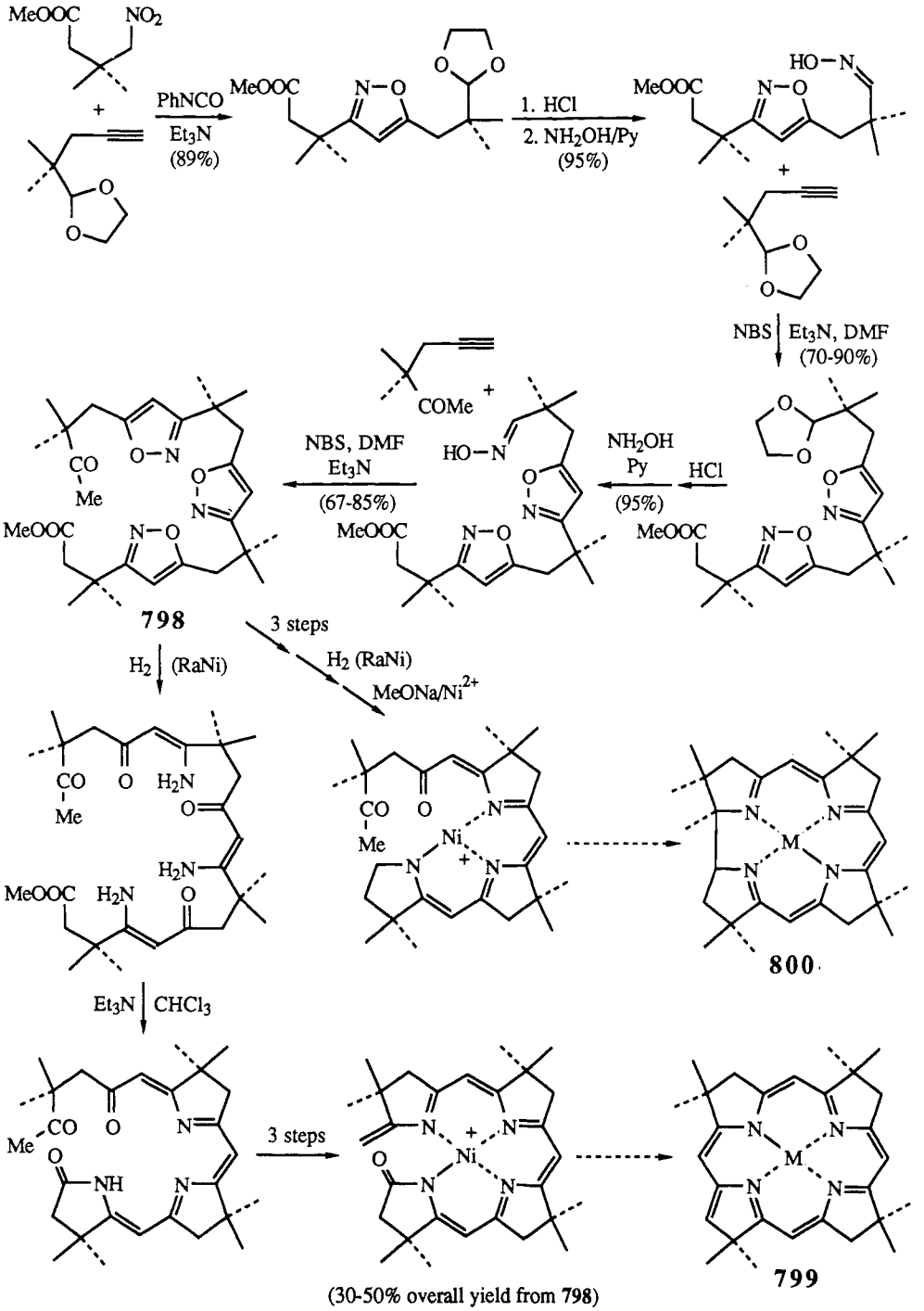



However, the most fascinating achievement, based on the use of isoxazoles as synthetic key intermediates, is undoubtedly Stevens synthesis of macrocyclic ligands such as corphin and corrin.[230/76]

The employment of isoxazole nuclei in the synthesis of vitamin $B_{12}$ was




Scheme 1.62.




(30-50% overall yield from **798**)

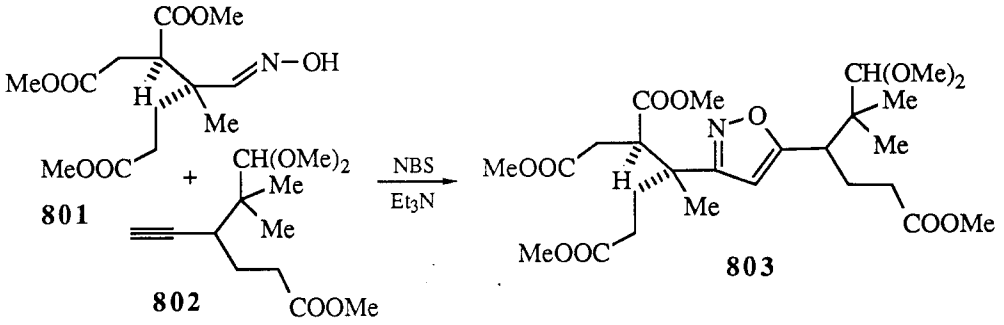
**Scheme 1.63.**

suggested originally by Cornforth[258/73] in various lectures and first dealt with on simple models almost simultaneously by two independent groups of researchers.[62/69,47/70,61/70] With slight variations, the synthesis of semicorrin (**797**) has been achieved by both groups in the sequence summarized in Scheme 1.62.[47/70,26/71,93/71,94/71,49/72] An alternative synthesis of the same semicorrin, which uses a different isoxazole intermediate, was reported later.[193/75]

Subsequently, the Stevens group succeeded in synthesizing the metal complexes of both the octamethylcorphin **799** and the *trans*-octamethylcorrin **800** through a spectacular multistep preparation of a common key intermediate triisoxazole (**798**), as illustrated in Scheme 1.63.[88/75,230/76]

This masterpiece in the synthesis of natural products is based on the following primary features: (1) the three isoxazole nuclei are built consecutively in a "counterclockwise" sequence, utilizing *in situ* preparation of the appropriate nitrile oxide either by NBS dehydrogenation of the aldoxime or by dehydration of the nitroalkane; (2) the 1,3-dipolar cycloaddition steps are rigorously regiospecific and usually enjoy high yields; and (3) the presence of functional groups such as carbonyl, cyano, or ester does not interfere with the cycloaddition, and the groups are ready to enter into the reaction following the hydrogenolysis step.

In a further effort toward total synthesis of vitamin $B_{12}$, the isoxazole **803**, a latent form of the "southern" half of cobyric acid, has been synthesized using the same type of approach.[121/76,122/76] The final step of the synthesis is the reaction between the nitrile oxide precursor (**801**) and the complex alkyne (**802**):



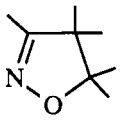
*Chemistry of Heterocyclic Compounds, Volume 49*
Paolo Grünanger, Paola Vita-Finzi
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CHAPTER 2

# Isoxazolines (Dihydroisoxazoles)

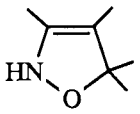
## 2.1 INTRODUCTION

The isoxazole ring can be partially saturated, formally giving rise to three isomeric derivatives containing only one double bond (i.e., **1**, **2**, and **3**). The



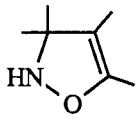

**1**

$\Delta^2$-Isoxazoline
2-Isoxazoline
4,5-Dihydroisoxazole




**2**

$\Delta^3$-Isoxazoline
3-Isoxazoline
2,5-Dihydroisoxazole



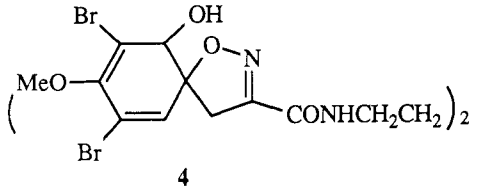

**3**

$\Delta^4$-Isoxazoline
4-Isoxazoline
2,3-Dihydroisoxazole

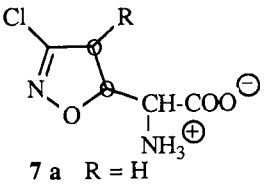
name *isoxazoline* is still the most popular for these compounds, and was retained until recently by IUPAC nomenclature.[197E/79] The old literature advocated the prefix Δ followed by a superscript locant denoting the position of the double bond. From the 1950s on, a simple Arabic numeral was almost always used as the locant. The recent IUPAC revision of the Hantsch–Widman system of heterocyclic nomenclature[261B/83] has discarded the termination *oline* for partially saturated nitrogen-containing rings, leaving the prefix *dihydro* as the only acknowledged nomenclature. Dihydroisoxazole is also the name adopted by *Chemical Abstracts*. Nevertheless, for the sake of simplicity, in this book the "isoxazoline" nomenclature has been used.

Of the three classes of dihydroderivatives, the 2-isoxazolines are by far the most easily prepared and widely studied. Their importance has steadily grown in the last few decades, to such an extent that by now they compete favorably with the isoxazoles. In contrast, the chemistry of 4-isoxazolines and, especially, of 3-isoxazolines has been discovered more recently, undoubtedly because of their more difficult preparation and higher lability. The three classes of compounds are treated separately here.

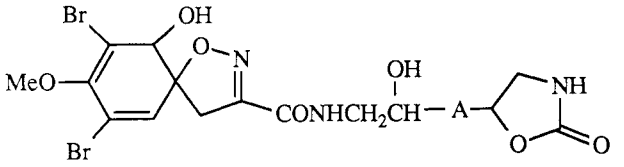
Some natural products have recently been demonstrated to contain the 2-isoxazoline nucleus: the bromotyrosine-related sponge metabolites aerothionin (**4**) and homoaerothionin from *Aplysina* (= *Verongia*) *thiona*,[131/72] *A. aerophoba*,[131/72] *A. fistularis*,[227C/81] and *Denrilla praetensa*;[276/83] fistularin-1 (**5a**), fistularin-2 (**5b**), and fistularin-3 (**6**) from *Aplysina fistularis*;[223/79] and the mold antibiotics AT-125 (= U-42,126)(**7a**)[229/73] and U-43,795 (**7b**),[91/75] isolated from *Streptomyces sviceus*.

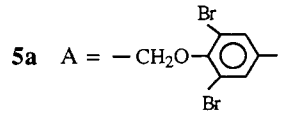


**4**

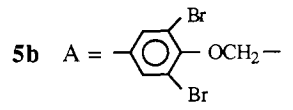


**7 a** R = H
**b** R = OH

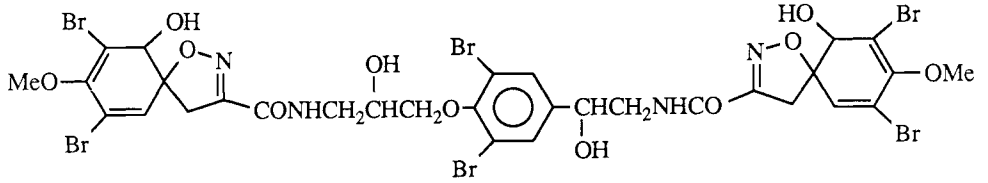




**5a** A = $-CH_2O-$



**5b** A =



**6**

## 2.2 2-ISOXAZOLINES

### 2.2.1 Physicochemical Properties

#### *2.1.1.1 Infrared Spectra*

The infrared spectra are frequently reported as physicochemical data to characterize the isoxazoline compounds mainly by the bands of substituents. Comparison of the infrared spectra of five isoxazoline derivatives obtained by 1,3-dipolar cycloaddition and their open-chain analogues (as styrene, acetophenone oxime, etc.) led to assign them the structure of 2-isoxazolines.[20/57] The band at 1570–1580 $cm^{-1}$ is ascribed to an "aromatic" carbon–carbon stretching vibration enhanced by an external centre of unsaturation.[20/57] However, bands in the range 1560–1640 $cm^{-1}$ [27/67.171/70.84/72.28C/73.34/73.44/73.209/73.223B/74.82/75.29/76.171/78.202/78.

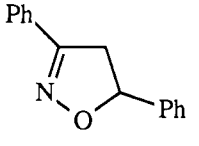
200/79.8/80.24/80.121/80.203/80.310/80.24/81.248/82.249/82.3/83.4/83.5/83.158/83.265/83 and 1670–1690 $cm^{-1}$ 171/82, 25/79 have often been attributed to the C=N or C=N–O double bond, respectively. In the case of 3-phenyl-5-nitroamino-2-isoxazolines the absorption bands at 1455–1470 $cm^{-1}$ have been assigned to the stretching vibrations of the C=N bond of the ring.[336/83] In other cases the same C=N absorption has been reported to be absent or covered by aromatic bands. The N–O stretching absorptions of 5-perfluoroalkylisoxazolines have been attributed to bands at 1350–1358 $cm^{-1}$.[171/78.3/83.4/83.5/83.158/83]

Furthermore, by analogy with the data reported for the isoxazole ring the band at 841–936 $cm^{-1}$ has tentatively been assigned to the N–O bond.[28C/73.3/83.4/83.5/83.265/83] The assignments of the infrared absorptions of seven 2′-cyclohexan-spiro-5-[3-aryl-4-alkyl (or aryl)]-2-isoxazolines have been reported.[201/79] Tautomerism, protonation, and quaternization of 3-amino-2-isoxazolines have been studied and the infrared data reported and discussed.[34/73.35/73.23/74] The ring-chain tautomerism of 5-hydroxy-2-isoxazolines has been investigated and structures discussed on the basis of infrared absorptions together with PMR data.[40/69.161/69.20/74.229/76]

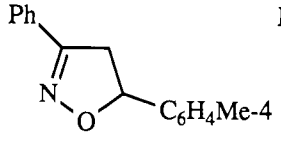
### *2.2.1.2 Ultraviolet and Fluorescence Spectra*

The UV absorptions of 2-isoxazolines are not very characteristic and depend mainly on the ring substituents. However, the UV spectra of some 3,5-diarylisoxazolines have been studied to establish the double-bond position in the ring.[20/57] The UV absorptions of open-chain analogues for 2-, 3-, 4-isoxazolines have been recorded for comparison. It has been stated that the isoxazoline absorptions for **8**–**10**, as well as those of fused isoxazolines, at $\lambda$ 265 ± 3 nm (log $\varepsilon$ ca. 4.2) correspond to the K-band of the acetophenone oxime ($\lambda$ 249 ± 4 nm, log $\varepsilon$ 4.1) but bathochromically displaced.[20/57]

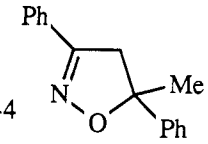
Similar results have been obtained by oximation of 2′-hydroxychalcones, which affords the corresponding flavanone oximes and 2-isoxazolines. The two products can be differentiated by the UV absorptions, the 2-isoxazoline absorbing at higher wavelengths than the oxime relatively to the second peak.[200/79.113/82] Generally, 3-phenyl-2-isoxazolines present the typical absorption band at 261–264 nm, except 3-phenyl-5-cyano-2-isoxazoline ($\lambda_{max}$ 257 nm, log $\varepsilon$ 4.14).[118C/65] Some 3-phenyl-5-aryloxymethyl-2-isoxazolines have been studied. They show two maxima in the UV spectrum: the former at 215 ± 6 nm for the anisole




**8**



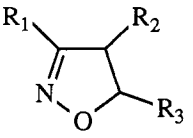

**9**




**10**

moiety and the latter at 260 ± 5 nm for the isoxazoline ring.[86/72] In Table 2.1 selected examples of UV absorptions of 2-isoxazolines are reported.

TABLE 2.1. UV DATA OF 2-ISOXAZOLINES



| $R_1$ | $R_2$ | $R_3$ | Solvent | $\lambda_{max}$ (nm) (log ε) | References |
|---|---|---|---|---|---|
| Ph | H | Ph | EtOH | 263(4.17) | 20/57 |
| Ph | H | 4-$MeC_6H_4$ | EtOH | 262(4.25) | 20/57 |
| Ph | H | Me, Ph | EtOH | 264(4.24) | 20/57 |
| H | H | Ph | EtOH | <220( - ) | 118C/65 |
| Me | H | $n$-$C_8H_{17}$ | EtOH | <220( - ) | 118C/65 |
| Ph | H | $n$-$C_4H_9$ | EtOH | 264(4.11) | 118C/65 |
| Ph | H | $n$-$C_8H_{17}$ | EtOH | 265(4.12) | 118C/65 |
| Ph | H | α-naphthyl | EtOH | 223(4.91), 271(4.21), 281(4.17) | 118C/65 |
| Ph | H | β-naphthyl | EtOH | 266(4.33) | 118C/65 |
| Ph | H | CN | EtOH | 257(4.14) | 118C/65 |
| 4-$MeC_6H_4$ | H | Ph | MeOH | 266 | 175/68 |
| 4-$MeC_6H_4$ | H | 4-$MeC_6H_4$ | MeOH | 266 | 175/68 |
| Ph | H | 4-$MeOC_6H_4$ | MeOH | 265 | 175/68 |
| 4-$MeOC_6H_4$ | H | Ph | MeOH | 274 | 175/68 |
| 4-$MeOC_6H_4$ | H | 4-$MeOC_6H_4$ | MeOH | 274 | 175/68 |
| Ph | H | 4-$BrC_6H_4$ | MeOH | 260 | 175/68 |
| 4-$BrC_6H_4$ | H | Ph | MeOH | 270 | 175/68 |
| 4-$BrC_6H_4$ | H | 4-$BrC_6H_4$ | MeOH | 269 | 175/68 |
| Ph | H | 4-$NO_2C_6H_4$ | EtOH | 310(4.21) | 159/73 |
| 2-$HOC_6H_4$ | H | 4-$HOC_6H_4$ | EtOH | 220(4.27), 265(4.11), 275(3.98), 308(3.77) | 121/80 |
| 2-$HOC_6H_4$ | H | 4-$MeOC_6H_4$ | EtOH | 222(4.30), 264(4.11), 274(4.00), 308(3.76) | 121/80 |
| 2-$HOC_6H_4$ | H | 4-$EtOC_6H_4$ | EtOH | 225(4.32), 265(4.05), 275(3.96), 306(3.77) | 121/80 |
| 2-$HOC_6H_4$ | H | 3,4-$(MeO)_2C_6H_3$ | EtOH | 217(4.32), 265(4.10), 274(4.03), 308(3.80) | 121/80 |
| 2-$HOC_6H_4$ | H | 3,4,5-$(MeO)_3C_6H_2$ | EtOH | 220(4.26), 264(4.12), 273(3.99), 307(3.75) | 121/80 |
| 2-$HOC_6H_4$ | H | 3,4-$(CH_2O_2)C_6H_3$ | EtOH | 218(4.20), 265(4.15), 274(4.05) 288(4.09), 308(3.87) | 121/80 |
| 2-$HOC_6H_4$ | H | NHOH | EtOH | 219(4.19), 259(3.94), 308(3.58) | 200/79 |
| 4-$NO_2C_6H_4$ | H | H | EtOH | 220(4.3) | 87/68 |
| $Me_3C$ | H | H | EtOH | 213(3.5) | 87/68 |
| Ph | PhCO | Ph | EtOH | 253(4.41) | 158/73 |
| Ph | Ph | PhCO | EtOH | 255(4.29), 333(3.27) | 158/73 |
| Ph | 2-Furoyl | Ph | EtOH | 280(4.41) | 158/73 |
| Ph | Ph | 2-Furoyl | EtOH | 276(4.36) | 158/73 |

The isoxazolinium salts, that is, 2-methyl-3-alkyl (or aryl) 2-isoxazolinium salts, show a bathochromic shift relatively to the corresponding isoxazolines. In the case of 3-alkyl derivatives the shift is about 5 nm, with absorption at ca. 235 nm. By contrast, the 3-aryl- and 3,5-diarylisoxazolinium salts show a shift of 15 and 40 nm, absorbing at about 270–275 and 300 nm, respectively.[35/73]

The alkylation products of 3-amino-2-isoxazolines show a bathochromic shift of 10 nm with respect to the free base. However, the protonation causes only a slight hypsochromic shift in the region 250 nm,[23/74] corresponding to a $p \rightarrow \pi$ conjugation; the site of protonation is discussed.

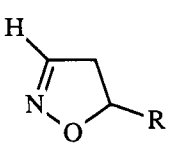
The UV spectra of 2-isoxazolines have been used to determine their $pK_a$ values[202/66] (see § 2.2.1.9). 3,5-Diphenyl-2-isoxazoline and 5-phenyl-3-(2-styryl)-2-isoxazoline, together with 3-phenylhexahydro[1,7*a*]anthranil and two pyrazolines, have been investigated as fluorescent reagents, mainly for the kinetic-fluorimetric determination of vanadium (V) and other metal ions.[10/83]

### *2.2.1.3 Nuclear Magnetic Resonance Spectra*

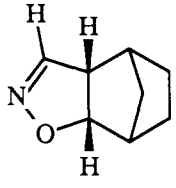
From 1964 on, most papers related to the 2-isoxazolines report the NMR data of the new products. This technique was used mainly to determine the structure of regio and stereoisomers obtained by 1,3-dipolar cycloaddition. Both chemical shifts and coupling constants give important information for structure elucidation. More recently, $^{13}$C-NMR, $^{15}$N-NMR, and other nuclear spectra have sometimes also been reported.

#### a. PMR Spectra

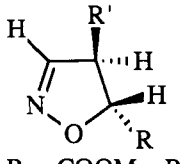
In the PMR spectrum the unsubstituted 2-isoxazoline shows three well-separated signals at $\delta$ 2.9 (m, 2H) for $H_4$, $\delta$ 4.1 (m, 2H) for $H_5$, and $\delta$ 7.1 (m, 1H) for $H_3$.[139/72] Obviously, the complexity of the PMR spectra depends on the ring substitution. Most of the 2-isoxazolines are 3-substituted, but some examples of 2-isoxazolines with the 3-free position could be prepared either by 1,3-dipolar cycloaddition of fulminic acid[3/67,28/73,28C/73] and nitromethane[286/83] or by opening of arylcyclopropanes under nitrosation conditions,[241/83,131/84] affording 5-substituted, 5,5′-disubstituted, and 4,5-disubstituted isoxazolines.[3/67,28/73,28C/73,241/83,131/84] The PMR data of compounds **11–16** are reported in Table 2.2 as examples.



**11** R = COOMe
**12** R = Ph



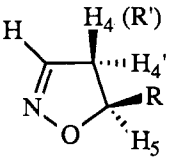
**13**



**14** R = COOMe, R′ = Me
**15** R = Me, R′ = COOMe
**16** R = R′ = COOMe

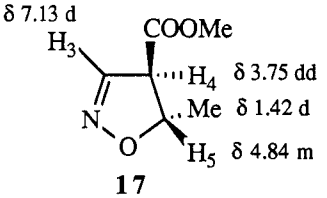
The examples reported show that $H_3$ absorbs at a low field ($\delta$ 6.90–7.30) with a small coupling value (1.5–2.0 Hz) with $H_4$ and a long-range coupling constant (ca. 0.6 Hz) with $H_5$. The latter absorbs at a lower field ($\delta$ 4.5–5.0) than $H_4$ ($\delta$ 2.80–3.75) and shows larger coupling with the *cis* than with the *trans* proton. 2-Isoxazolin-5-yl acetaldehyde oxime was obtained by oximation of the glutacondialdehyde anion as a mixture of *syn* and *anti* products, as indicated in the NMR spectrum mainly by the chemical shifts of the chain protons.[1/77]

TABLE 2.2. PMR DATA OF 3-UNSUBSTITUTED 2-ISOXAZOLINES



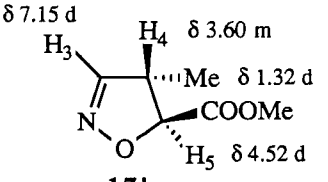

| | $H_3$ | $H_4$ | $H_{4'}$ | $H_5$ | $J_{3-4}$ | $J_{4-4'}$ | $J_{5-4}$ | $J_{5-4'}$ | $J_{3-5}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **11** | 7.28 t | 3.30 t | 3.27 dd | 5.00 t | 1.7 | -18.2 | 10.9 | 7.8 | 0.65 | $CDCl_3$ | 3/67 |
| **12** | 7.09 t | 3.28 m | 2.82 m | 5.41 t | 1.8 | -17.6 | 10.9 | 8.2 | 0.6 | $CDCl_3$ | 3/67 |
| | - | - | - | - | 1.9 | -18.10 | 11.15 | 8.28 | - | $CCl_4$ | 45/66 |
| **13** | 6.92 d | 3.15 d | - | 4.39 d | 1.5 | - | 8.3 | - | - | $CDCl_3$ | 3/67 |
| **14** | 7.15 d | _ | 3.60 m | 4.55 d | 1.8 | - | - | 6.2 | - | $CDCl_3$ | 28C/73 |
| **15** | 7.15 d | _ | 3.75 dd | 4.84 m | 1.9 | - | - | 8.4 | - | $CDCl_3$ | 28C/73 |
| **16** | 7.30 d | - | 4.57 dd | 5.30 d | 2.0 | - | - | 6.5 | | $CDCl_3$ | 28C/73 |

In the case of **13** the absence of coupling of $H_4$ and $H_5$ with the bridgehead protons indicates the *exo* addition.[3/67] As examples, the PMR data of two couples of regioisomeric 3-unsubstituted 2-isoxazolines (**17** and **18**) are reported here.[28C/73]



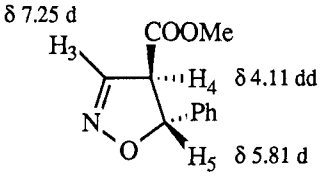

**17**

$J_{3-4}$ = 1.9 Hz
$J_{4-5}$ = 8.4 Hz



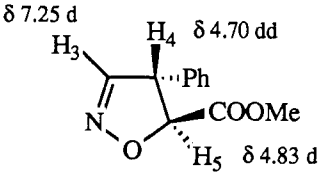

**17'**

$J_{3-4}$ = 1.8 Hz
$J_{4-5}$ = 6.2 Hz




**18**

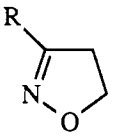
$J_{3-4}$ = 1.8 Hz
$J_{4-5}$ = 8.3 Hz



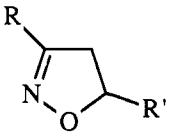

**18'**

$J_{3-4}$ = 1.9 Hz
$J_{4-5}$ = 5.8 Hz

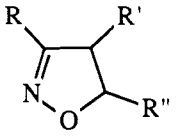
The PMR spectra of some 3- (**19**), 3,5- (**20**), and 3,4,5-substituted 2-isoxazolines (**21**) have been studied according to the $A_2B_2$, ABX, and AB systems, respectively, and by comparison with the theoretical calculations.[45/66.80/66.13/67]



**19**



**20**

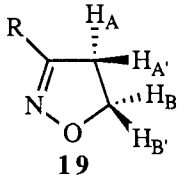


**21**

R' = 2-$NO_2C_6H_4$ R = Ph R = R' = R"= Ph
R' = 3-$NO_2C_6H_4$ R = Ph R = R' = Ph R" = COMe
R' = 4-$NO_2C_6H_4$ R = Ph R = R' = Ph R"= COOEt
R' = COEt R = Ph

For the monosubstituted 2-isoxazolines (**19**) it has been demonstrated that the PMR spectra show the pattern of the $A_2B_2$ system having identical $J_{AB}$.[80/66] The energies of the permitted transitions have been calculated and reported as $\nu \cdot \delta$. The PMR data of some 3-substituted 2-isoxazolines (**19**) are reported in Table 2.3.

TABLE 2.3. PMR DATA OF 3-SUBSTITUTED 2-ISOXAZOLINES (**19**)



**19**

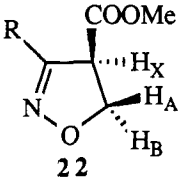
| R | $H_4$ | $H_5$ | R | Solvent | $J_{AA'}$ | $J_{AB'}$ | $J_{A'B'}$ | $J_{BB'}$ | References |
|---|---|---|---|---|---|---|---|---|---|
| Ph | 3.32 | 4.47 | 7.30-7.85 | $CDCl_3$ | - | 10.22 | 10.22 | - | 80/66 |
| | 3.14 m | 4.28 m | | $CDCl_3$ | -16.0 | 8.2 | 10.2 | -10.0 | 13/67 |
| 3-$NO_2C_6H_4$ | 3.42 | 4.61 | 7.33-8.58 | $CDCl_3$ | - | 10.33 | 10.33 | - | 80/66 |
| 4-$NO_2C_6H_4$ | 3.41 | 4.62 | 7.78-8.41 | $CDCl_3$ | - | 10.41 | 10.41 | - | 80/66 |
| Et | 2.95 | 4.22 | 1.12 , 2.37 $J$ = 7.37 | $CDCl_3$ | - | 10.21 | 10.21 | - | 80/66 |
| Mesityl | 3.1 | 4.5 | - | $CDCl_3$ | - | - | - | - | 87/68 |
| | 3.04 | 4.33 | - | $CCl_4$ | - | - | - | - | 125B/73 |
| Me | 2.9 | 4.3 | - | $CDCl_3$ | - | - | - | - | 87/68 |
| $Me_3C$ | 2.9 | 4.3 | - | $CDCl_3$ | - | - | - | - | 87/68 |
| MeO | 2.85 | 4.2 | 3.74 | $CCl_4$ | - | 8.7 | 8.7 | - | 193/73 |
| $PhSO_2$ | 3.30 | 4.55 | 7.5-8.2 | $CDCl_3$ | - | 11.0 | 11.0 | - | 202/78 |
| $N_3$ | 2.95 | 4.50 | - | $CDCl_3$ | - | 10.0 | 10.0 | - | 202/78 |
| CN | 3.23 | 4.63 | - | $CDCl_3$ | - | 10.0 | 10.0 | - | 202/78 |

The chemical shifts of the protons at $C_4$ and $C_5$ are also well differentiated in these cases, the first absorbing at $\delta$ 2.9–3.4 and the latter at a lower field (at $\delta$ 4.3–4.6) because of the deshielding effect of the ring oxygen atom. It is noteworthy that the substituent at $C_3$ influences the chemical shifts of both $H_4$ and

$H_5$. For 3-phenyl-2-isoxazoline the coupling constants could be differentiated[13/67] (see Table 2.3), although the values are very similar: $J_{trans}$ 8.2 Hz and $J_{cis}$ 10.2 Hz.

It has been noted that only the $H_4$ protons of $^{15}N$-3-mesityl-2-isoxazoline show a spin-spin coupling to $^{15}N$ of 2.2 Hz.[125B/73] Few examples of PMR spectra of 3,4-disubstituted 2-isoxazolines showing an ABX system have been reported[27/73,28C/73] (see Table 2.4).

TABLE 2.4. PMR DATA OF 3-SUBSTITUTED-4-METHOXYCARBONYL-2-ISOXAZOLINES (22)




**22**

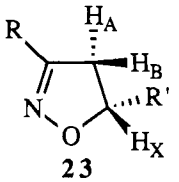
| R | $H_X$ | $H_A$ | $H_B$ | $J_{AB}$ | $J_{AX}$ | $J_{BX}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|
| Ph | 4.49 | 4.74 | 4.54 | -8.57 | 5.92 | 10.87 | $CDCl_3$ | 28C/73 |
| Me | 4.15 | 4.64 | 4.50 | -8.52 | 7.78 | 11.03 | $CDCl_3$ | 28C/73 |
| 2,4,6-$(MeO)_3C_6H_2$ | 4.52 | 4.75 | 4.57 | -8.54 | 8.42 | 11.15 | $CDCl_3$ | 28C/73 |
| Mesityl | 4.43 | 4.80 | 4.63 | -8.55 | 8.45 | 11.27 | $CDCl_3$ | 28C/73 |

However, in 3-(4-chlorophenyl)-4-hydroxy-2-isoxazoline the two protons at $C_5$ absorb at $\delta$ 4.4 (d, $J$ = 6.0 Hz) and the proton at $C_4$ at $\delta$ 5.6 (t, $J$ = 6.0 Hz). By acetylation the latter signal shifts at $\delta$ 6.6.[11/70] In 3-(3,5-dichloro-2,4,6-trimethylphenyl)-4-diphenylmethylene the chemical shift of the two $C_5$ protons is around $\delta$ 5.22–5.46, depending on the solvent.[146/72] In Table 2.5 selected examples of PMR data of variously 3,5-disubstituted 2-isoxazolines are listed.

The ABX system of the 3,5-disubstituted 2-isoxazolines (**23**) usually shows very well separated signals: $H_A$, *trans* to $H_X$, absorbs at a higher field than $H_B$, both in the range of $\delta$ 2.85–3.80, depending on the substituents. $H_X$ absorbs at a lower field for the deshielding effect of the ring oxygen atom ($\delta$ 4.5–6.3). It is interesting to note the strong deshielding effect exerted by the *o*-nitrophenyl substituent at $C_5$ on $H_X$ ($\delta$ 6.35) and $H_B$ ($\delta$ 4.15)(but not on $H_A$); the effect is not as strong in the case of *m*-nitro- and *p*-nitrophenyl groups[80/66] by comparison with the chemical shifts of 3,5-diphenyl-2-isoxazoline[16/64,13/67,187/70] (see Table 2.5). As expected, the presence of a nitromethyl[246/80] or a nitro[249/82] group at $C_5$ also strongly deshielded the ABX system, while no effect has been noticed by introduction of a nitro group on the 3-phenyl substituent.

The PMR data of the cycloadduct obtained by reaction of benzonitrile oxide and *N*-nitroenamines have been considered diagnostic for the 3-phenyl-5-nitroamine-2-isoxazolines and not for their regioisomers (3-phenyl-4-nitroamine-2-isoxazolines) because of the presence of a very low-field triplet ($\delta$ 6.49–6.91 for 1 H), which can be assigned only to a $H_5$ proton showing the O–CH–$N(NO_2)$R

TABLE 2.5. PMR DATA OF 3,5-DISUBSTITUTED 2-ISOXAZOLINES (**23**)



**23**

| R | R' | $H_A$ | $H_B$ | $H_X$ | $J_{AB}$ | $J_{AX}$ *trans* | $J_{BX}$ *cis* | $J_{4\text{-}R}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Me | Ph | 2.7-3.05 m | 3.15-3.55 m | 5.56 | 18 | 8.5 | 10.5-11 | - | $CDCl_3$ | 8/80 |
| Ph | Me | 2.88 dd | 3.38 dd | 4.84 dd | -16.5 | 8.2 | 10.2 | - | $CDCl_3$ | 13/67 |
| Ph | $C_4H_9$ | 2.93 dd | 3.35 dd | 4.72 m | -16.6 | 8.6 | 10.4 | - | $CDCl_3$ | 13/67 |
| Ph | Ph | 3.30 dd | 3.80 dd | 5.78 dd | 17.0 | 8.7 | 10.9 | - | $CDCl_3$ | 187/70 |
| | | 3.31 dd | 3.74 dd | 5.72 dd | -16.8 | 8.2 | 11.0 | - | $CDCl_3$ | 13/67 |
| | | 3.07 | 3.51 | 5.46 | | 8.8 | 10.3 | - | $CDCl_3$ | 16/64 |
| Ph | 2-$NO_2C_6H_4$ | 3.27 | 4.15 | 6.35 | 17.31 | 6.83 | 11.04 | - | $CDCl_3$ | 80/66 |
| Ph | 3-$NO_2C_6H_4$ | 3.37 | 3.91 | 5.87 | 16.81 | 7.89 | 10.36 | - | $CDCl_3$ | 80/66 |
| Ph | 4-$NO_2C_6H_4$ | 3.34 | 3.91 | 5.88 | 16.94 | 7.89 | 11.11 | - | $CDCl_3$ | 80/66 |
| Ph | COEt | 3.53 | 3.63 | 5.10 | 16.91 | 3.09 | 15.16 | - | $CDCl_3$ | 80/66 |
| MeC=NOH | Ph | 3.16 | 3.56 | 5.71 | 17.5 | 9.0 | 11.0 | - | $CDCl_3$ | 246B/74 |
| Ph | COOMe | 3.61 | 3.65 | 5.15 | -17.1 | 6.6 | 12.0 | - | $CDCl_3$ | 28C/73 |
| *t*-Bu | COOMe | 3.28 | 3.28 | 5.00 | -17.4 | 6.9 | 10.8 | - | $CDCl_3$ | 28C/73 |
| CN | COOMe | 3.55 | 3.55 | 5.00 | -18.1 | 7.3 | 12.3 | - | $CDCl_3$ | 28C/73 |
| Me | COOMe | 3.25 | 3.25 | 5.00 | -17.6 | 7.4 | 10.9 | - | $CDCl_3$ | 28C/73 |
| 2,4,6-$(MeO)_3C_6H_2$ | COOMe | 3.55 | 3.55 | 5.13 | - | - | - | - | $CDCl_3$ | 28C/73 |
| Mesityl | COOMe | 3.42 | 3.42 | 5.15 | - | - | - | - | $CDCl_3$ | 28C/73 |
| Ph | CN | 3.70 d | | 5.15 t | | | | | $CDCl_3$ | 13/67 |
| Ph | $CONH_2$ | 3.58 t | | 5.13 q | - | 9.0 | 9.0 | - | DMSO-$d_6$ | 28/67 |
| PhCH=CH | $CONH_2$ | 3.47 d | | 5.04 t | - | 9.0 | 9.0 | - | DMSO-$d_6$ | 28/67 |
| PhCH=CH | Ph | 3.14 dd | 3.63dd | 5.69 dd | 17.0 | 9.0 | 9.0 | - | $CDCl_3$ | 28/67 |
| 4-$MeOC_6H_4$ | Ph | 3.28 | 3.71 | 5.68 | -16.5 | 8.7 | 10.7 | - | $CDCl_3$ | 16/67 |
| 4-$MeC_6H_4$ | Ph | 3.29 | 3.72 | 5.69 | -16.7 | 8.3 | 10.8 | - | $CDCl_3$ | 16/67 |
| 4-$ClCC_6H_4$ | Ph | 3.28 | 3.71 | 5.73 | -17.1 | 8.5 | 11.1 | - | $CDCl_3$ | 16/67 |
| 3-$ClC_6H_4$ | Ph | 3.29 | 3.71 | 5.74 | -17.2 | 8.3 | 11.1 | - | $CDCl_3$ | 16/67 |
| Mesityl | 4-$MeOC_6H_4$ | 3.09 | 3.53 | 5.69 | -17.8 | 8.8 | 10.8 | - | $CDCl_3$ | 16/67 |
| Mesityl | 4-$MeC_6H_4$ | 3.09 | 3.54 | 5.72 | -17.4 | 8.3 | 10.6 | - | $CDCl_3$ | 16/67 |
| Mesityl | 4-$ClC_6H_4$ | 3.05 | 3.60 | 5.73 | -17.4 | 7.9 | 10.9 | - | $CDCl_3$ | 16/67 |
| Mesityl | 3-$ClC_6H_4$ | 3.06 | 3.61 | 5.72 | -17.4 | 7.4 | 11.0 | - | $CDCl_3$ | 16/67 |
| Mesityl | Ph | 3.10 | 3.58 | 5.76 | -17.4 | 8.0 | 10.9 | - | $CDCl_3$ | 16/67 |
| Mesityl | 4-$NO_2C_6H_4$ | 3.09 | 3.72 | 5.88 | -17.5 | 7.2 | 10.9 | - | $CDCl_3$ | 16/67 |
| 2-$HOC_6H_4$ | 4-$HOC_6H_4$ | 3.16 dd | 3.63 dd | 5.46 t | 17 | 8.5 | 11 | - | $CDCl_3$ | 121/80 |
| 2-$HOC_6H_4$ | 4-$MeOC_6H_4$ | 3.21 dd | 3.73 dd | 5.33 t | 17 | 8 | 11 | - | $CDCl_3$ | 121/80 |
| 2-$HOC_6H_4$ | 4-$EtOC_6H_4$ | 3.26 dd | 3.73 dd | 5.4 t | 17 | 8 | 12 | - | $CDCl_3$ | 121/80 |
| 2-$HOC_6H_4$ | 3,4-$(MeO)_2C_6H_3$ | 3.10 dd | 3.76 dd | 5.4 t | 17 | 8 | 11 | - | $CDCl_3$ | 121/80 |
| 2-$HOC_6H_4$ | 3,4,5-$(MeO)_3C_6H_2$ | 3.10 dd | 3.7 dd | 5.4 t | 17 | 8 | 12 | - | $CDCl_3$ | 121/80 |
| 2-$HOC_6H_4$ | 3,4-$(CH_2O_2)C_6H_3$ | 3.10 dd | 3.56 dd | 5.4 t | 17 | 9 | 12 | - | $CDCl_3$ | 121/80 |
| $C_6Br_5$ | Ph | 3.6 m | | 5.95 dd | - | 9.0 | 10.0 | - | $CCl_4$ | 104/81 |
| Ph | 2-MeOOC-$C_6H_4$ | 3.92 dd | 4.08 dd | 6.43 dd | 18 | 6.7 | 11.3 | - | $CDCl_3$ | 172/82 |
| 2-MeOOC-$C_6H_4$ | Ph | 3.26 dd | 3.74 dd | 5.78 dd | 17 | 9.4 | 10.6 | - | $CDCl_3$ | 104/81 |
| PhS | COOMe | 3.24 d | | 5.03 t | | 8.5 | | - | $CDCl_3$ | 193/81 |
| 5-$NO_2$-2-furyl | OEt | 3.27 dd | 3.42 dd | 5.78 dd | 17.9 | 1.6 | 7.0 | - | $CDCl_3$ | 33/67 |
| 5-NO2-2-furyl | COMe | 3.52 dd | 3.73 dd | 5.16 dd | 17.5 | 5.4 | 12.6 | - | $CDCl_3$ | 33/67 |
| 5-$NO_2$-2-furyl | Ph | 3.39 dd | 3.81 dd | 5.85 dd | 17.2 | 9.4 | 10.3 | - | $CDCl_3$ | 33/67 |
| 5-$NO_2$-2-furyl | 4-pyridyl | 3.39 dd | 3.75 dd | 5.85 dd | 17.0 | 7.6 | 11.3 | - | $CDCl_3$ | 33/67 |

TABLE 2.5. *(Continued)*

| R | R' | $H_A$ | $H_B$ | $H_X$ | $J_{AB}$ | $J_{AX}$ *trans* | $J_{BX}$ *cis* | $J_{4\text{-}R}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|
| 5-$NO_2$-2-furyl | 2-Me-5-pyridyl | 3.40 dd | 3.87dd | 5.85 dd | 17.4 | 8.8 | 10.7 | - | $CDCl_3$ | 33/67 |
| Me | 1-Me-2-pyrrolyl | 3.15 dq | | 5.53 t | - | 10.0 | 10.0 | 1.0 | $CDCl_3$ | 115B/80 |
| Me | 1-Ph-2-pyrrolyl | 2.88 dq | | 5.14 t | - | 10.0 | 10.0 | 0.5 | $CDCl_3$ | 115B/80 |
| Me | 1-*t*-Bu-3-pyrrolyl | 3.10 m | | 5.50 t | 6 | 10.0 | 10.0 | 1.0 | $CDCl_3$ | 115B/80 |
| Ph | $CH_2NO_2$ | 3.29 dd | 3.72 dd | 5.42 m | 17.4 | 6.7 | 10.5 | - | $CD_3NO_2$ | 246/80 |
| 4-$NO_2C_6H_4$ | $CH_2NO_2$ | 3.29 dd | 3.73 dd | 5.44 m | 17.3 | 7.0 | 10.6 | - | $CD_3NO_2$ | 246/80 |
| 3-$NO_2C_6H_4$ | $CH_2NO_2$ | 3.31 dd | 3.74 dd | 5.44 m | 17.5 | 7.0 | 10.4 | - | $CD_3NO_2$ | 246/80 |
| Ph | $C(NO_2)_2Me$ | 3.57 dd | 3.96 dd | 5.69 q | 18.4 | 7.2 | 10.7 | | $CD_3NO_2$ | 246/80 |
| 4-$NO_2C_6H_4$ | $C(NO_2)_2Me$ | 3.65 dd | 4.04 dd | 5.79 q | 18.5 | 7.5 | 10.9 | - | $CD_3NO_2$ | 246/80 |
| 3-$NO_2C_6H_4$ | $C(NO_2)_2Me$ | 3.64 dd | 4.04 dd | 5.80 q | 18.5 | 7.5 | 11.0 | - | $CD_3NO_2$ | 246/80 |
| Ph | $NO_2$ | 3.93 dd | 4.19 dd | 6.35 q | 18.9 | 3.7 | 7.1 | - | $CD_3NO_2$ | 249/82 |
| 4-$ClC_6H_4$ | $NO_2$ | 3.93 dd | 4.19 dd | 6.37 q | 19.0 | 3.9 | 7.1 | - | $CD_3NO_2$ | 249/82 |
| 3-$ClC_6H_4$ | $NO_2$ | 3.93 d | 4.20 dd | 6.39q | 19.1 | 3.6 | 7.0 | - | $CD_3NO_2$ | 249/82 |
| 3-$NO_2C_6H_4$ | $NO_2$ | 4.04 dd | 4.30 dd | 6.44 q | 19.1 | 3.9 | 7.1 | - | $CD_3NO_2$ | 249/82 |
| 4-$FC_6H_4$ | $NO_2$ | 4.06 dd | 4.20 dd | 6.44 q | 18.9 | 3.7 | 7.3 | - | $CD_3NO_2$ | 249/82 |
| 2-$NO_2C_6H_4$ | OMe | 3.05 dd | 3.65 dd | 5.7 dd | 18 | 4 | 8 | - | $CCl_4$ | 197/84 |
| 3,5-$Cl_2$-2,4,6-$Me_3C_6$ | $SO_2Ph$ | 3.60 dd | 3.84 dd | 5.57 dd | 19.0 | 6.0 | 10.8 | - | $CDCl_3$ | 211/83 |

feature.[336/83] By contrast, the $C_5$ proton of 3-(4-nitrophenyl)-5-isopropylazo-2-isoxazoline absorbs at $\delta$ 5.94.[321/82]

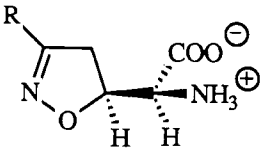
Some examples of 3-ferrocenyl-5-substituted-2-isoxazoline have been reported. The regioisomeric structure has been assigned on the basis of a chemical shift of the ABX system. It is noteworthy that a trimethylsilyl group at $C_5$ caused an upfield shift of $H_5$ at $\delta$ 3.85 close to that of $H_4$ ($\delta$ 2.26–3.2).[71/80]

Particularly diagnostic is the value of $J_{AX}$ to distinguish the 3-(2-hydroxyphenyl)-5-aryl-2-isoxazolines and the corresponding flavanone oximes formed by oximation of appropriate chalcones. In fact, the value of $J_{AX}$ of flavanone oximes (3.2 Hz) is smaller than that of 3,5-diaryl-2-isoxazolines (8 Hz).[121/80,113/82] Furthermore, the signals of a chelated phenolic OH group for 2-isoxazolines appears at $\delta$ 9.6–9.8, while those of oximes absorb at $\delta$ 10.36–10.44.[113/82]

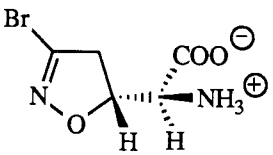
The coupling constants usually are larger for *cis* coupling ($J_{BX}$) than for *trans* coupling ($J_{AX}$); however, in the case of 5-carboxamide isoxazolines the value is identical ($J_{AX} = J_{BX} = 9.0$ Hz)[28/67] (see Table 2.5). Studies of the PMR spectra of 3,5-diaryl-, 3-aryl-, 5-phenyl-, and 3-mesityl-5-aryl-2-isoxazolines and some corresponding deuterated compounds led to evidence that, by comparison with 3-phenyl-2-isoxazoline, the protons $H_X$ and $H_B$ shift downfield for the presence of an aryl at $C_5$, while $H_A$ shifts slightly upfield. Therefore, the influence of the 5-phenyl is stronger on $H_B$, which must be in the same plane of the aromatic ring. By contrast, the chemical shift of $H_A$ is influenced by the 3-phenyl group more than that of $H_B$, as demonstrated by a Hammett correlation. A shielding effect of the $H_4$ protons is observed for the presence of a mesityl group at $C_3$.[16/67] Data are reported in Table 2.5.

In the case of 3-methyl-5-(1-substituted)pyrrolyl-2-isoxazolines (Table 2.5) the simple $A_2X$ system is shown by the 4,5-protons with an additional long-range coupling constant between the 3-methyl group and the 4-methylene group.[115B/80]

PMR data of the antitumor antibiotic AT-125 (**24a**) and its derivatives, obtained during the synthesis from tricholomic acid, have been reported,[96/79] as well as those of the corresponding *erithro* (**24b**) and *threo* (**25**) 3-bromo analogues.[263/80] The two epimers could be individuated quantitatively by the signals



**24 a** R = Cl
**b** R = Br



**25**

of the α proton: for the *erithro* a doublet ($J$ = 3.5 Hz) at δ 3.94 and for the *threo* a doublet ($J$ = 7.4 Hz) at δ 3.79 in $D_2O$ solution. The PMR data have been used to determine the ratio of stereoisomeric (*erithro* and *threo*) 2-isoxazolines obtained mainly by cycloaddition reactions either in the synthesis of acivicin and its derivatives[161/84] or as intermediates in the synthesis of amino sugars.[112/84,167/84] In the case of 5-epimeric 3-glycosyl-5-phenyl-2-isoxazolines from the coupling constants it has been assumed that the isoxazoline ring is almost in the envelope conformation with the $C_5$ out of the plane.[44/73] Regio and stereoisomers of glycosyl-2-isoxazolines have been studied by PMR technique.[98/70,103/73,29/76]

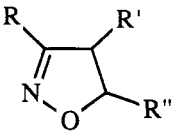
Tautomerism of 3-amino-2-isoxazolines has also been established by the PMR data of the compounds and their methyl and acyl derivatives.[34/73]

PMR spectra have been a useful tool for studying the quaternarization and protonation of 3-aminoisoxazolines. The latter reaction has been followed at different temperatures and pH values.[23/74] Perchlorates of 2-methylisoxazolinium show complicated spectra because of long-range coupling constants between the protons of the *N*-methyl and the others on the ring. Spectra have been analyzed by deuteration and double resonance experiments.[35/73]

Many papers dealing with the regio- and stereoselectivity of 1,3-dipolar cycloaddition of nitrile oxides to 1,2-disubstituted olefins discuss and report the PMR data of 3,4,5-trisubstituted 2-isoxazolines (**21**).[16/64,10/65,157/66,13/67,86/68,28C/73,176/74,246B/74,83/79,52/80,180/80,181/80,52D/81,82/81,193/81,15/82,158/82,248/82,211/83,79/84,79B/84,158/84,160/84] Some examples are reported in Table 2.6.

The value of the chemical shifts depends on the substituents; however, $H_4$ and $H_5$ are always well differentiated. It is noteworthy that in many cases the *trans* isomer shows an upfield shift, by comparison with the *cis* isomer because of the closeness of the protons to the vicinal substituent.[10/65] However, some exceptions can be noted.

TABLE 2.6. PMR DATA OF 3,4,5-TRISUBSTITUTED 2-ISOXAZOLINES (21)



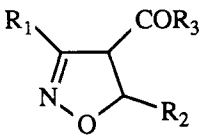
**21**

| R | R' | R'' | Configuration | $H_4$ | $H_5$ | $J_{trans}$ | $J_{cis}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|
| Ph | Me | Me | *cis* | 3.44 m | 4.64 m | - | 8.0 | $CDCl_3$ | 13/67 |
| Ph | Me | Me | *trans* | 3.26 m | 4.43 m | 5.0 | - | $CDCl_3$ | 13/67 |
| Ph | Ph | Ph | *cis* | 4.85 d | 5.93 d | - | 9.7 | $CDCl_3$ | 13/67 |
| Ph | Ph | Ph | *trans* | 4.68 d | 5.52 d | 5.6 | - | $CDCl_3$ | 13/67 |
| Ph | Me | 4-$MeOC_6H_4$ | *trans* | - | 5.18 d | 5.8 | - | $CDCl_3$ | 13/67 |
| Ph | 4-$MeC_6H_4$ | Me | *trans* | 4.25 d | - | 5.5 | - | $CDCl_3$ | 13/67 |
| CH=NOH | Me | COOMe | *trans* | 3.80 m | 4.75 d | 5.0 | - | $CDCl_3$ | 28C/73 |
| CH=NOH | COOMe | Me | *trans* | 3.95 d | 4.97 m | 7.2 | - | $CDCl_3$ | 28C/73 |
| CN | Me | COOMe | *trans* | 3.82 qi | 4.91 d | 7.1 | - | $CDCl_3$ | 28C/73 |
| CN | COOMe | Me | *trans* | 4.06 d | 5.03 dq | 7.8 | - | $CDCl_3$ | 28C/73 |
| Me | Me | COOMe | *trans* | 3.42 m | 4.56 d | 7.0 | - | $CDCl_3$ | 28C/73 |
| Me | COOMe | Me | *trans* | 3.61 dq | 4.90 m | 8.2 | - | $CDCl_3$ | 28C/73 |
| Ph | Me | COOMe | *trans* | 4.01 dq | 4.77 d | 4.2 | - | $CDCl_3$ | 28C/73 |
| Ph | COOMe | Me | *trans* | 4.14 d | 5.04 qi | 6.3 | - | $CDCl_3$ | 28C/73 |
| Mesityl | Me | COOMe | *trans* | 3.9 | 4.7 2 d | 6.3 | - | $CDCl_3$ | 28C/73 |
| Mesityl | COOMe | Me | *trans* | 4.0 3 d | 5.17 dq | 8.6 | - | $CDCl_3$ | 28C/73 |
| $Me_3C$ | Me | COOMe | *trans* | 3.5 | 4.55 d | 4.2 | - | $CDCl_3$ | 28C/73 |
| $Me_3C$ | COOMe | Me | *trans* | 3.68 d | 4.85 qi | 6.2 | - | $CDCl_3$ | 28C/73 |
| Ph | COOMe | COOMe | *cis* | 4.81 d | 5.39 d | - | 11.5 | $CDCl_3$ | 13/67 |
| Ph | COOMe | COOMe | *trans* | 4.95 d | 5.53 d | 4.9 | - | $CDCl_3$ | 13/67 |
| Ph | Ph | COOMe | *cis* | 5.04 d | 5.38 d | - | 10.5 | $CDCl_3$ | 157/66 |
| Ph | Ph | COOMe | *trans* | 4.92 d | 5.09 d | 4.1 | - | $CDCl_3$ | 13/67 |
| Ph | COOMe | Ph | *trans* | 4.46 d | 5.96 d | 6.3 | - | $CDCl_3$ | 157/66 |
| Ph | COOEt | Ph | *cis* | 4.64 d | 5.95 d | - | 11.0 | $CDCl_3$ | 157/66 |
| Ph | COOEt | Ph | *trans* | 4.48 d | 6.00 d | 6.5 | - | $CDCl_3$ | 13/67 |
| CN | Ph | COOMe | *trans* | 4.88 d | 5.19 d | 6.2 | - | $CDCl_3$ | 28C/73 |
| CN | COOMe | Ph | *trans* | 4.27 d | 6.16 d | 8.4 | - | $CDCl_3$ | 28C/73 |
| Me | Ph | COOMe | *trans* | 4.52 dq | 4.87 d | 5.8 | - | $CDCl_3$ | 28C/73 |
| Me | COOMe | Ph | *trans* | 3.98 dq | 5.87 d | 8.3 | - | $CDCl_3$ | 28C/73 |
| Mesityl | Ph | COOMe | *trans* | 4.87 d | 5.35 d | 3.9 | - | $CDCl_3$ | 28C/73 |
| Mesityl | COOMe | Ph | *trans* | 4.39 d | 6.16 d | 9.0 | - | $CDCl_3$ | 28C/73 |
| $Me_3C$ | Ph | COOMe | *trans* | 4.60 d | 4.79 d | 3.0 | - | $CDCl_3$ | 28C/73 |
| $Me_3C$ | COOMe | Ph | *trans* | 4.00 d | 5.78 d | 6.5 | - | $CDCl_3$ | 28C/73 |
| Ph | $COOCH_2Ph$ | $COOCH_2Ph$ | *cis* | 4.55 d | 5.18 d | - | 11.25 | $CDCl_3$ | 86/68 |
| Ph | $COOCH_2Ph$ | $COOCH_2Ph$ | *trans* | 4.89 d | 5.53 d | 5.03 | - | $CDCl_3$ | 86/68 |
| Ph | $COOCMe_3$ | Ph | *trans* | 5.17 d | 5.22 d | 5.12 | - | $CDCl_3$ | 86/68 |
| Ph | COMe | Ph | *trans* | 4.45 d | 5.87 d | 5.08 | - | $CDCl_3$ | 86/68 |
| Ph | COMe | 4-$NO_2C_6H_4$ | *trans* | 4.44 d | 6.00 d | 4.42 | - | $CDCl_3$ | 86/68 |
| Ph | 4-$NO_2C_6H_4$ | COMe | *trans* | 4.82 d | 5.24 d | 3.87 | - | $CDCl_3$ | 86/68 |
| Ph | COPh | 2-$NO_2C_6H_4$ | *trans* | 5.79 d | 6.08 d | 3.75 | - | $CDCl_3$ | 86/68 |
| Ph | COPh | 4-$C_6H_4$ | *trans* | 5.67 d | 5.67 d | 4.75 | - | $C_6D_6$ | 86/68 |
| Ph | 4-$NO_2C_6H_4$ | COPh | *trans* | 5.38 d | 5.87 | 6.50 | - | $CDCl_3$ | 86/68 |
| Ph | $C_6H_4CH_2$- | | *cis* | 4.45 d | 6.13 | - | 9.43 | $CDCl_3$ | 86/68 |
| Ph | 3,4$(MeO)_2C_6H_3$ | 1-pyrrolidinyl | *trans* | 4.1 d | 5.12 d | 2.5 | - | $CDCl_3$ | 158/82 |
| 4-$NO_2C_6H_4$ | 1-morpholinyl-methyl | 1-morpholinyl | *trans* | 3.65 | 5.33 | 2.3 | - | $CDCl_3$ | 180/80 |

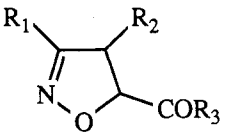
TABLE 2.6. *(Continued)*

| R | R' | R" | Configuration | $H_4$ | $H_5$ | $J_{trans}$ | $J_{cis}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|
| 2,6-$Cl_2C_6H_3$ | 1-morpholinyl-methyl | 1-morpholinyl | *trans* | 3.75 | 5.07 | 4.5 | - | $CDCl_3$ | 180/80 |
| 4-Cl-$C_6H_4$ | 1-morpholinyl-methyl | 1-morpholinyl | *trans* | 3.60 | 5.38 | 3.0 | - | $CDCl_3$ | 180/80 |
| 4-$NO_2C_6H_4$ | 1-piperidinyl-methyl | 1-piperidinyl | *trans* | 3.69 | 5.04 | 4.4 | - | $CDCl_3$ | 180/80 |
| 4-$NO_2C_6H_4$ | 1-pyrrolidinyl-methyl | 1-pyrrolidinyl | *trans* | 3.57 | 5.78 | 2.7 | - | $CDCl_3$ | 180/80 |
| 4-$NO_2C_6H_4$ | $CH_2OMe$ | 1-morpholinyl | *trans* | 3.60 | 5.20 | 2.0 | - | $CDCl_3$ | 181/80 |
| 4-$NO_2C_6H_4$ | 1-pyrrolidinyl-methyl | 1-morpholinyl | *cis* | 3.80 | 5.49 | - | 10.0 | $CDCl_3$ | 181/80 |
| 4-$ClC_6H_4$ | 1-pyrrolidinyl-methyl | 1-morpholinyl | *cis* | 3.70 | 5.35 | - | 9.5 | $CDCl_3$ | 181/80 |
| 2,6-$Cl_2C_6H_3$ | Me | PhS | *trans* | 3.64 | 5.58 | 7.0 | - | $CDCl_3$ | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | Me | PhS | *cis* | 4.05 | 6.10 | - | 9.0 | $CDCl_3$ | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | Ph | PhS | *trans* | 4.91 | 6.09 | 6.0 | - | $CDCl_3$ | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | Ph | PhS | *cis* | 5.26 | 6.33 | - | 10.0 | $CDCl_3$ | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | $PhSO_2$ | Ph | *trans* | 6.21 | 6.35 | 6.5 | - | $CDCl_3$ | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | $PhSO_2$ | Ph | *cis* | 5.98 | 5.59 | - | 10.0 | $CDCl_3$ | 52D/81 |
| PhS | COOMe | COOMe | *trans* | 4.40 | 5.40 | 6.0 | - | $CDCl_3$ | 193/81 |
| Ph | 3-Me,4-$NO_2$-5-isoxazolyl | Ph | *trans* | 5.0 | 6.0 | 4.0 | - | $CDCl_3$ | 82/81 |

Comparison of the PMR data of a large number of isomeric 3,5-disubstituted 4-acyl-2-isoxazolines (**A**) and 3,4-disubstituted 5-acyl-2-isoxazolines (**B**) pointed out that the differences between the chemical shifts of the two isoxazoline protons [$\Delta\delta_{5,4} = \Delta\delta_5 - \Delta\delta_4$] show remarkable regularities within the same group of compounds.[158/73]




**A**




**B**

In the case of diarylacetyl-2-isoxazolines, $\Delta\delta_{5,4}$ is always notably larger for the 4-acetyl- than for the 5-acetylisoxazolines: the values range between 1.05 and 1.85 for the former and between 0.10 and 0.63 for the latter. With diarylaroylisoxazolines or hetero analogues, the same pattern has been observed, although the differences are smaller but still diagnostic. The only exceptions have been found for arylmethylbenzoylisoxazolines and for phenyl-*p*-methoxyphenylbenzoylisoxazolines, where the rule seems to be reversed.[158/73] Some examples are reported in Table 2.7. These regularities in the chemical shifts of 4- and 5-acylisoxazolines can be attributed to the deshielding effects of the groups involved

TABLE 2.7

| | $R_1$ | $R_2$ | $R_3$ | $H_4$ (d) | $H_5$ (d) | $J_{4\text{-}5}$ | $\Delta\delta_{5,4}$ |
|---|---|---|---|---|---|---|---|
| A | Me | Ph | Me | 4.05 | 5.72 | 7.5 | 1.67 |
| B | | | | 4.43 | 4.70 | 4.7 | 0.27 |
| A | Ph | Ph | Me | 4.45 | 5.87 | 5.1 | 1.42 |
| B | | | | 4.69 | 4.95 | 3.7 | 0.26 |
| A | 4-$ClC_6H_4$ | Ph | Me | 4.22 | 5.77 | 4.8 | 1.55 |
| B | | | | 4.66 | 4.96 | 4.0 | 0.30 |
| A | 4-$BrC_6H_4$ | Ph | Me | 4.43 | 5.68 | 5.0 | 1.25 |
| B | | | | 4.83 | 5.08 | 4.2 | 0.25 |
| A | 3-$NO_2C_6H_4$ | Ph | Me | 4.58 | 5.93 | 5.3 | 1.35 |
| B | | | | 4.90 | 5.13 | 4.3 | 0.23 |
| A | 4-$NO_2C_6H_4$ | Ph | Me | 4.56 | 5.94 | 5.6 | 1.38 |
| B | | | | 4.87 | 5.12 | 4.5 | 0.25 |
| A | Mesityl | Ph | Me | 4.52 | 5.57 | 8.6 | 1.05 |
| B | | | | 4.88 | 5.16 | 3.6 | 0.28 |
| A | Ph | Ph | Ph | 5.35 | 5.75 | 7.0 | 0.4 |
| B | | | | 5.41 | 5.65 | 4.5 | 0.24 |
| A | Mesityl | Ph | Ph | 5.30 | 6.40 | 8.0 | 1.1 |
| B | | | | 5.27 | 6.02 | 4.5 | 0.75 |
| A | Ph | 4-$BrC_6H_4$ | Ph | 5.41 | 5.80 | 6.5 | 0.39 |
| B | | | | 5.51 | 5.70 | 4.5 | 0.19 |
| A | Ph | 4-$MeC_6H_4$ | Ph | 5.48 | 5.78 | 6.5 | 0.30 |
| B | | | | 5.44 | 5.70 | 4.5 | 0.26 |
| A | Ph | 4-$MeOC_6H_4$ | Ph | 5.48 | 5.72 | 7.0 | 0.24 |
| B | | | | 5.38 | 5.70 | 4.5 | 0.32 |
| A | Ph | Ph | 2-furyl | 5.18 | 5.85 | 6.5 | 0.67 |
| B | | | | 5.29 | 5.39 | 3.0 | 0.1 |
| A | Ph | Ph | 2-thienyl | 5.15 | 5.85 | 7.0 | 0.7 |
| B | | | | 5.37 | 5.47 | 4.0 | 0.1 |
| A | Ph | Me | Ph | | 4.95 | - | - |
| B | | | | 4.40 | 5.48 | 4.8 | 1.08 |
| A | 2,6-$Cl_2C_6H_3$ | Me | Ph | 5.16 | 5.61 | 6.9 | 0.45 |
| B | | | | 4.43 | 5.50 | 8.0 | 1.07 |
| A | Mesityl | Me | Ph | 4.83 | 5.24 | 8.0 | 0.41 |
| B | | | | 4.18 | 5.24 | 6.8 | 1.06 |

if a rough additivity of the substituent parameters is taken into account.[158/73] It is noteworthy that the value of $J_{4,5}$ is usually larger for isomer **A** than for isomer **B**. Similar behavior has been found in the case of 3,5-diaryl-4-cyano- and 3,4-diaryl-5-cyano-2-isoxazolines.[79B/84]

Cycloadditions of nitrile oxides to *E*- and *Z*-styrylsulfides, sulfoxides, and sulfones led to mixtures of regioisomers with *trans* and *cis* configuration.[278/83] The structures of regioisomers have also been elucidated by PMR data. The stereochemistry has been established from the value of the coupling constants of the isoxazoline protons ($J_{cis} > J_{trans}$) and the regiochemistry followed from the spacing between the same isoxazoline protons. In fact, in this case, because of the higher deshielding effect of a phenyl relative to a thiomethyl substituent, the spacing of a 5-phenyl-substituted isoxazoline is larger than that of the 4-phenyl regioisomer. This trend becomes more evident in the spectra of sulfoxide and sulfones. Noteworthy is the solvent dependence of the chemical shifts of these isoxazolines: in DMSO-$d_6$ the isoxazoline protons of sulfides and

sulfoxides are deshielded (0.2–0.5 ppm) and the effect is larger (1 ppm) in sulfones.[278/83]

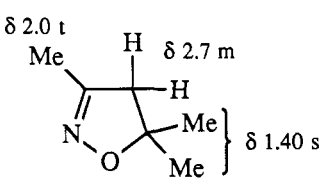
Coupling constants are also valuable in structural assignments, since the $J_{4,5}$ values are always larger for the *cis* configuration (8–12 Hz) than for the *trans* configuration (2–8 Hz).[157/66,13/67,86/68,50/72,176/72,226/72,26/73,28C/73,257/79,52/80,177/83,211/83]

The relationship between coupling constants and the electronegativity of substituents has been reported.[86/68] Regioisomers could be assigned by comparison of the chemical shifts with those of similar known compounds as for 3,5-diphenyl-4-acetyl-2-isoxazoline relative to ethyl 3,5-diphenyl-2-isoxazolin-4-carboxylate.[80/66] PMR chemical shifts have been essential for attributing the structures of stereoisomers obtained by cycloaddition of benzonitrile oxide with *p*-nitrobenzalacetone, *p*-nitrobenzalacetophenone, and indene[86/68] and to 3-methyl-4-nitro-5-styrylisoxazole[82/81] (see the data in Table 2.6).

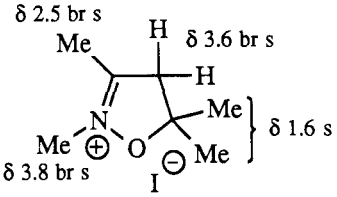
The structure, stereochemistry, and conformation of cycloadducts formed by reaction of nitrile oxides generated from strained 1,2,5-oxadiazoles and 1,2-disubstituted olefins could be solved on the PMR data: the value of coupling constants showed the *cis* ($J_{4,5}$ = 11.0–11.5 Hz) or *trans* ($J_{4,5}$ = 6.5–8.0 Hz) relationship, while the chemical shift of $H_4$ indicated the relative configuration of the proton with the phenyl group contained in the large substituent at $C_3$. The anisotropy effect of the phenyl affects the value of $H_4$ from $\delta$ 4.68–5.01 to $\delta$ 3.86–4.35.[117/80]

3,5,5-Trisubstituted isoxazolines (**26**) show an AB system ($J_{AB}$ = 16–18 Hz) when the substituents at $C_5$ are different or present different electronic effects. Some examples of PMR data are reported in Table 2.8. However, in many cases the two $H_4$ protons appear as a singlet at $\delta$ 3.10–3.40.[25/79,209/83] Equilibrium[40/69] and ring closure[205/70] of $\alpha,\beta$-unsaturated oximes leading to trisubstituted isoxazolines have been studied on the basis of PMR data.

Nitrile oxides react with polyunsaturated monoterpenes (as myrcene,[31B/69] dipentene, and carvone[188/76]), yielding mixtures of isoxazoline monoadducts and/or diadducts. Composition of the reaction mixture could be determined by spectroscopic methods. The PMR data of four diastereoisomeric diadducts from myrcene have been discussed.[31B/69] Both 3,5,5-trimethylisoxazoline (**27a**) and its *N*-methyliodide (**27b**) show only one signal for the methylene group at position 4.[171/82]



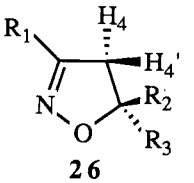

**27a** ($CDCl_3$)




**27b** ($DMSO\text{-}d_6$)

The determination of the absolute configuration of the two diastereomeric 5-substituted 5-methyl-3-(2′,6′-dichlorophenyl)-2-isoxazolines (**28**) obtained by

TABLE 2.8. PMR DATA OF 3,5,5-TRISUBSTITUTED 2-ISOXAZOLINES (**26**)



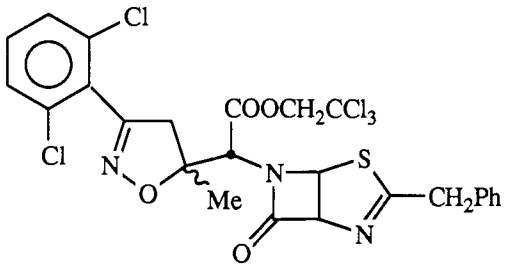
**26**

| $R_1$ | $R_2$ | $R_3$ | $H_4$ | $H_{4'}$ | $J_{4-4'}$ | Solvent | References |
|---|---|---|---|---|---|---|---|
| Ph | Ph | Ph | 3.91 | 3.91 | - | $CDCl_3$ | 13/67 |
| Ph | Me | COOMe | 3.83 | 3.21 | -17.5 | $CDCl_3$ | 13/67 |
| Ph | Ph-C≡C | OH | 3.80 | 3.68 | 17.6 | $CDCl_3$ | 3/68 |
| Me | Ph | OH | 3.05 | 3.05 | - | $CCl_4$ | 40/69 |
| Ph | Ph | $PhCOCH_2$ | 4.09 | 3.68 | 17.5 | $CDCl_3$ | 205/70 |
| Ph | Me | $CH_2NO_2$ | 3.66 | 3.27 | 17.5 | $CD_3NO_2$ | 246/80 |
| | | | 2.93 | 2.51 | 17.2 | $CDCl_3$ | 247/80 |
| 4-$NO_2C_6H_4$ | Me | $CH_2NO_2$ | 3.74 | 3.35 | 17.6 | $CD_3NO_2$ | 246/80 |
| | | | 3.84 | 3.44 | 17.4 | $(CD_3)_2CO$ | 247/80 |
| 3-$NO_2C_6H_4$ | Me | $CH_2NO_2$ | 3.76 | 3.36 | 17.6 | $CD_3NO_2$ | 246/80 |
| Ph | $CH_2CH(SiMe_3)COOMe$ | COOMe | 3.10 | 3.10 | - | $C_6D_6$ | 281/82 |
| Ph | Ph | $OSiMe_3$ | 3.50 | 3.30 | 17.0 | $CCl_4$ | 73/78 |
| 2,6-$Cl_2C_6H_3$ | Ph | $OSiMe_3$ | 3.43 | 3.33 | 17.5 | $CCl_4$ | 73/78 |
| 4-$ClC_6H_4$ | Ph | Ph | 3.93 | 3.93 | - | $CDCl_3$ | 203/80 |
| Mesityl | Me | $COCHMe_2$ | 3.57 | 2.85 | 18.0 | $CDCl_3$ | 161/83 |
| Ph | COOEt | NHCOMe | 3.77 | 3.77 | - | DMSO-$d_6$ | 297/83 |
| Ph | Me | N=N-*iso*Pr | 3.45 | 3.00 | 18.0 | $CDCl_3$ | 321/82 |
| 4-$NO_2C_6H_4$ | Me | N=N-*iso*Pr | 3.40 | 3.15 | 18.0 | $CDCl_3$ | 321/82 |
| 4-$NO_2C_6H_4$ | Me | N=N-*iso*Pr | 3.19 | 2.80 | 16.0 | $CDCl_3$ | 321/82 |
| 4-$FC_6H_4$ | Me | N=N-*iso*Pr | 3.44 | 2.93 | 17.0 | $CDCl_3$ | 321/82 |
| *n*-$C_{14}H_{29}$ | OH | COOEt | 3.57 | 3.00 | 18.0 | $CDCl_3$ | 171/70 |

cycloaddition of nitrile oxides to penicillin derivatives has been discussed on the basis of the chemical shifts of the $C_5$ methyl and $C_4$ protons and the most favored conformations.[27/82]

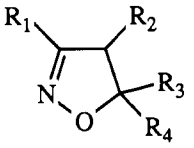
Halogenation with NBS of 3,5,5-trisubstituted isoxazolines led to the corresponding 4-halogenoderivatives.[173/80] The PMR data of these products, along with other compounds, are reported in Table 2.9 to show examples of the chemical shifts of the $C_4$ protons and of the methyl groups in differently substituted 2-isoxazolines.

The $H_4$ protons of 5,5-spiroisoxazolines,[84/72,143/74,82/75,124/75,125/75,226B/76,22/77,19/78,201/79,306/83] exemplified by structures **29–31**, appear either as a singlet at $\delta$ 3.04–3.41 (depending on the substituents)[82/75,226B/76,22/77,215/79] or as an AB system, one doublet at $\delta$ 2.80–3.85 and the other at $\delta$ 3.41–4.48 with $J_{AB}$ = 17–18 Hz.[165/69,19/78,116/79,306/83] Similarly, the $H_{4'}$ protons of 4,5′-spirodiisoxazoline **32** appeared as

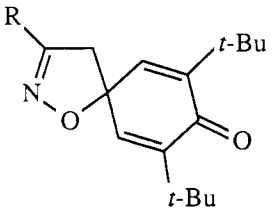


**28**

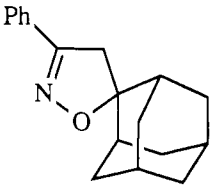
TABLE 2.9. PMR DATA OF 3,4,5,5-TETRASUBSTITUTED-2-ISOXAZOLINES



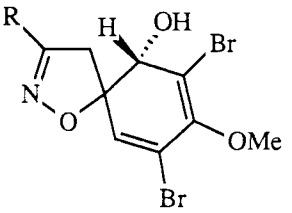
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $H_4$ | H-$R_1$ | H-$R_3$ | H-$R_4$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|
| Ph | COOMe | Me | Me | 4.07 | - | 1.30 | 1.50 | $CDCl_3$ | 13/67 |
| Me | COOMe | Me | Me | 3.70 | 2.02 | 1.30 | 1.50 | $CDCl_3$ | 28C/73 |
| $Me_3C$ | COOMe | Me | Me | 3.57 | 1.21 | 1.34 | 1.42 | $CDCl_3$ | 28C/73 |
| Mesityl | COOMe | Me | Me | 4.13 | - | 1.43 | 1.60 | $CDCl_3$ | 28C/73 |
| Me | Br | Me | Me | 4.72 | 2.13 | 1.59 | 1.34 | $CDCl_3$ | 173/80 |
| Ph | Br | Me | Me | 5.14 | - | 1.70 | 1.38 | $CDCl_3$ | 173/80 |
| Ph | Br | Me | Ph | 5.51 | - | 1.97 | - | $CDCl_3$ | 173/80 |
| Me | Br | Ph | Ph | 5.53 | 2.03 | - | - | $CDCl_3$ | 173/80 |
| Ph | Br | Ph | Ph | 6.07 | - | - | - | $CDCl_3$ | 173/80 |
| Ph | Cl | Me | Ph | 5.42 | - | 1.91 | - | $CDCl_3$ | 173/80 |
| Ph | Cl | Ph | Ph | 5.98 | - | - | - | $CDCl_3$ | 173/80 |
| Ph | I | Me | Ph | 5.67 | - | 2.03 | - | $CDCl_3$ | 173/80 |
| Ph | I | Ph | Ph | 6.26 | - | - | - | $CDCl_3$ | 173/80 |
| $NO_2$ | $NO_2$ | Me | Me | 5.64 | - | 1.60 | 1.60 | $CDCl_3$ | 108/66 |



**29 a** R = COOEt $H_4$ δ 3.30
**b** R = Ph $H_4$ δ 3.41

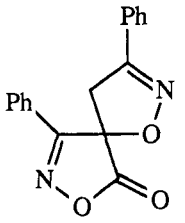


**30**
$H_4$ δ 3.14

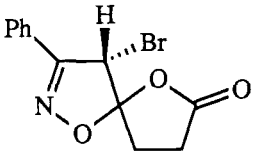


**31**

a singlet ($\delta$ 4.23) in acetone-$d_6$. However, in $C_6D_6$ these protons give rise to an AB system ($\delta_A$ 3.59, $\delta_B$ 3.72, $J_{AB}$ = 18.5 Hz).[51/65]



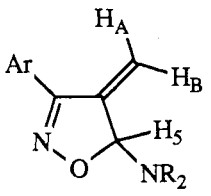
**32**



**33**

A LIS computer simulation technique was used to determine the preferred conformation in solution of the spiroisoxazoline (**33**). The result suggested an envelope conformation for the lactone ring.[27/78] PMR spectra were very useful for following the steps in the synthesis of aerothionin and its stereoisomers[131/72, 19/78.306/83] as well as for the structure determination of fistularins,[223/79] dispiroisoxazolines isolated from different kinds of marine sponges. Recently, by tertiary amine elimination, 5-amino-3-aryl-4-methylene-2-isoxazolines have been obtained as a new class of compounds (**34**)[180/80] (Table 2.10).

TABLE 2.10. PMR DATA OF 5-AMINO-3-ARYL-4-METHYLENE-2-ISOXAZOLINES (**34 a-h**)



**34**

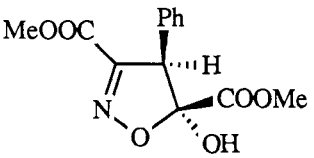
| | Ar | $NR_2$ | $H_A$ | $H_B$ | $H_5$ | $J_{5\text{-}A}$ | $J_{5\text{-}B}$ | Solvent |
|---|---|---|---|---|---|---|---|---|
| a | 4-$NO_2C_6H_4$ | morpholino | 5.13 | 5.21 | 5.42 | 2.8 | 2.5 | $C_6D_6$ |
| | | | 5.59 | 5.59 | 5.45 | - | - | $CDCl_3$ |
| b | 2,6-$Cl_2C_6H_3$ | morpholino | 5.36 | 5.59 | 6.09 | 3.2 | 2.8 | $(CD_3)_2CO$ |
| | | | 5.14 | 5.36 | 5.78 | 3.1 | 2.7 | $CDCl_3$ |
| c | 4-$ClC_6H_4$ | morpholino | 5.94 | 5.94 | 5.62 | - | - | $CDCl_3$ |
| d | 4-$BrC_6H_4$ | morpholino | 5.79 | 5.79 | 5.62 | - | - | $CDCl_3$ |
| | | | 5.13 | 5.26 | 5.38 | - | - | $C_6D_6$ |
| e | 2,6-$Cl_2C_6H_3$ | piperidino | 5.20 | 5.45 | 5.93 | 3.1 | 2.8 | $CDCl_3$ |
| f | 2,6-$Cl_2C_6H_3$ | pyrrolidino | 5.07 | 5.36 | 6.10 | 3.4 | 2.8 | $CDCl_3$ |
| g | 2,4,6-$Me_3C_6H_2$ | pyrrolidino | 5.02 | 5.31 | 6.01 | 3.1 | 2.8 | $CDCl_3$ |
| h | 4-$NO_2C_6H_4$ | pyrrolidino | 5.70 | 5.81 | 6.22 | 2.8 | 2.5 | $CDCl_3$ |

The data of (**34b**, **e–g**) were associated with an ABX system with $J_{AB} \sim 0$ Hz. The lower-field signal was attributed to $H_5$ since it is linked to two electronegative substituents. The higher-field signal was attributed to $H_A$, which must be more affected by the bulky aromatic substituent, which is in a conformation perpendicular to the heterocyclic ring. For (**34c**, **d**, **h**) the signals of $H_A$ and $H_B$ are shifted downfield and almost show identical values, probably owing to the conjugative effect caused by the coplanarity of the aryl and isoxazoline rings. The lanthanide-induced shifts with $Eu(fod)_3$ were in agreement with these assumptions.

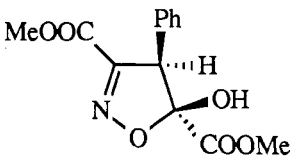
The configuration of the *exo* double bond of 3-aryl-4-phenoxymethylene-2-isoxazoline and analogues could be assigned on the basis of the shielding effect exerted by the $C_3$ aryl group on the chemical shifts of the exocyclic *Z* substituents.[150/79] The percentages of a diastereoisomeric mixture of 5-acetoxy-4-bromo-5-bromomethyl-3-phenyl-2-isoxazolines could be evaluated by the ratio of the signals of the $H_4$ protons (singlets at $\delta$ 5.53 and $\delta$ 5.60) and the AB system for the $CH_2Br$ group.[19B/80] Pyrolysis of these compounds has been followed by proton magnetic resonance.[19B/80]

By contrast, the solvent shift, from $CDCl_3$ to $C_6D_6$ or pyridine-$d_5$, has usefully been employed in identification of the two diastereomeric 4-bromo- and 5-bromomethyl-5-hydroxy-3-phenyl-2-isoxazolines in the reaction mixture. The evaluation of their relative ratio was based on the intensity of the $H_4$ and $CH_2Br$ signals in $C_6D_6$.[15/79] By the same technique the chemical shifts have been assigned to the substituents in tetrasubstituted 5-hydroxy-2-isoxazolines.[37/73]

The composition of the diastereoisomeric mixture of 3,5-dimethoxycarbonyl-5-hydroxy-4-phenyl-2-isoxazolines obtained as a by-product in the reaction of benzaldehyde with methyl nitroacetate has been studied by PMR data. The stereochemical assignments were based on the large diamagnetic shielding by the 4-phenyl group of the eclipsed 5-methoxycarbonyl ($\delta$ 3.25) for the *cis* isomer **35**, while in the *trans* isomer **36** the methoxy group absorbs at $\delta$ 3.80.[45/80]




**35**




**36**

The ring-chain tautomeric equilibrium between $\beta$-oximinoketones and the two diastereomeric 5-hydroxy-2-isoxazolines has been evidenced by PMR data.[40/69.20/74.246/74.229/76.24/80] For example, in the case of 3,4,4,5-tetramethyl-5-hydroxy-2-isoxazoline the methyl groups showed the following chemical shifts: $C_3Me$ $\delta$ 1.91, $C_4Me$ (*cis* to OH) $\delta$ 1.15, $C_4Me$ $\delta$ 1.01, and $C_5Me$ $\delta$ 1.49, the methyl *cis* to the hydroxyl being deshielded relatively to the one *cis* to a methyl. The presence of a phenyl group at $C_5$ (i.e., 3,4,4-trimethyl-5-hydroxy-5-phenyl-

2-isoxazoline) causes an upfield shift of the *cis* methyl at $C_4$ ($\delta$ 0.58). Variation in the ratio of the two diastereomeric 3,4-dimethyl-4-ethyl-5-phenyl-5-hydroxy-isoxazoline in different solvents has been studied.[246/74]

### b. $^{13}$C-NMR Spectra

$^{13}$C-NMR data of 2-isoxazolines are not very widely reported with assignments. However, the literature data show clearly that the three ring carbon atoms absorb in the order $C_4$, $C_5$, $C_3$ from higher to lower fields. Usually, this order is maintained notwithstanding the eventual shift caused by the substituents. The chemical shifts of $C_3$ can be found around 141–146 ppm for 3-unsubstituted-2-isoxazoline[241/83,131/84] and around 150–163 ppm for 3-substituted isoxazolines.[125B/73,104/79,24/81,37B/81,161/83,241/83,131/84,197/84] However, 3-bromo-5-phenyl-2-isoxazoline shows the $C_3$ signal at 139.8 ppm.[131/84] $C_4$ absorbs at about 40–52 ppm[125B/73,104/79,161/83,241/83,131/84,197/84] but shifts downfield (at 90–92 ppm) for the presence of electronegative substituents.[24/81,37B/81] Similarly, the chemical shifts of $C_5$, usually at 74–84 ppm,[125B/73,104/79,161/83,241/83,131/84,197/84] are moved downfield at 104–111 ppm by the presence of an additional directly linked heteroatom.[24/81,37B/81]

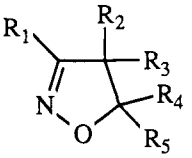
Some selected examples of $^{13}$C-NMR data of the carbon atoms of the 2-isoxazoline ring reported in Table 2.10 are relative to 3- and 5-aryl-2-isoxazolines,[131/84,241/83] 4,5-[131/84,241/83] and 3,5-disubstituted 2-isoxazolines[104/79,197/84] and tri-[104/79,37B/81,109/83,161/83] and tetrasubstituted 2-isoxazolines.[24/81,37B/81] The revised structures of the products obtained by reaction of isoxazoles and hypochlorous acid have been indicated as 4,4-dichloro-5-hydroxy (or alkoxy)-3,5-disubstituted-2-isoxazolines also for the strong downfield shift of the $C_4$ signal (90–92 ppm) by comparison with those of 5-hydroxy-3,5-disubstituted-2-isoxazoline (52.4 ppm)[37B/81] (see Table 2.11).

A $^{13}$C-NMR spectrum of $^{15}N$-3-mesityl-2-isoxazoline has been recorded for comparison with those of mesitonitrile, mesitonitriloxide, and 3-mesitylisoxazole.[125B/73] $^{13}$C-NMR data have often been used for the identification of the possible regioisomers.[104/79,108/79,161/83,131/84,197/84] The stereochemistry of the products of cycloaddition of nitrile oxides to 4-vinyldioxolane has been determined by $^{13}$C-NMR;[310B/83,167/84] full data of the *erithro* and *threo* isoxazolines have been reported.[167/84]

The diastereomeric isoxazolines **37** could also be identified by $^{13}$C-NMR spectra, which exhibit characteristic differences in the values of chemical shifts of carbon atoms of the Me and $CH_2$ groups.[27/82] The 5-*S* isomer shows an upfield shift for $C_4$ and a downfield shift for the 5-Me by comparison with the 5-*R* isomer. Conformational analysis of these molecules on the basis of $^{13}$C-NMR and PMR data has been discussed.

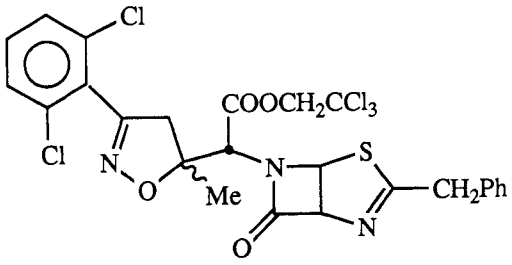
Cycloaddition of acetonitrile oxide to dipentene occurs on the side-chain double bond leading to two diastereoisomers, as was clearly shown by double peaks in the $^{13}$C-NMR spectrum.[188/76] Moreover, it has been evidenced that cycloaddition occurs in only one direction, giving **38**, as indicated by the singlets at 88.5 and 88.1 ppm attributed to $C_5$ and the triplets at 47.4 and 46.4 ppm for $C_{4'}$.

TABLE 2.11. $^{13}$C-NMR CHEMICAL SHIFTS (IN PPM) OF 2-ISOXAZOLINE CARBON ATOMS



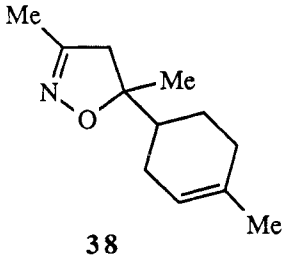
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $C_3$ | $C_4$ | $C_5$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | Ph | 144.2 d | 43.4 t | 79.2 d | $CCl_4$ | 241/83 |
| H | H | H | H | 4-$NO_2C_6H_4$ | 145.2 d | 43.9 t | 78.5 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 2-$NO_2C_6H_4$ | 145.7 d | 44.6 t | 78.6 t | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 4-$IC_6H_4$ | 144.5 d | 43.8 t | 79.0 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 2-$IC_6H_4$ | 143.9 d | 43.8 t | 82.6 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 4-$ClC_6H_4$ | 145.3 d | 43.5 t | 79.0 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 2-$ClC_6H_4$ | 145.7 d | 43.4 t | 74.6 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 4-$BrC_6H_4$ | 145.3 d | 43.6 t | 75.3 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 2-$BrC_6H_4$ | 145.3 d | 43.4 t | 78.5 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 4-$MeC_6H_4$ | 145.2 d | 43.6 t | 79.7 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| H | H | H | H | 4-cyclopropyl$C_6H_4$ | 143.4 d | 41.3 t | 75.3 d | $CCl_4$ or $CDCl_3$ | 131/84 |
| Mesityl | H | H | H | H | 156.3 s | 39.9 t | 124.3 t | dioxane | 125B/73 |
| Me | H | H | H | Ph | 150.2 s | 41.8 t | 76.5 d | $CDCl_3$ | 241/83 |
| Me | H | H | H | 2-$IC_6H_4$ | 152.5 s | 46.6 t | 83.9 | $CDCl_3$ | 131/84 |
| Ph | H | H | H | Ph | 155.9 s | 42.96 t | 82.4 d | $CDCl_3$ | 241/83 |
| Br | H | H | H | Ph | 139.8 s | 49.3 t | 82.9 d | $CDCl_3$ | 131/84 |
| H | H | H | Me | Ph | 141.46 d | 44.7 t | 81.0 s | $CDCl_3$ | 241/83 |
| H | H | H | Me | 4-$NO_2C_6H_4$ | 145.8 d | 49.0 t | 84.9 d | $CDCl_3$ | 131/84 |
| H | H | Me | H | Ph | 146.3 d | 47.5 d | 83.25 d | $CDCl_3$ | 241/83 |
| H | H | Me | H | 2-$IC_6H_4$ | 149.8 d | 51.9 d | 76.9 | $CDCl_3$ | 131/84 |
| H | H | Me | H | 4-$NO_2C_6H_4$ | 145.3 d | 43.8 d | 77.0 d | $CDCl_3$ | 131/84 |
| 2-$NO_2C_6H_4$ | H | H | H | OMe | 154.6 s | 42.6 t | 104.0 d | $CDCl_3$ | 197/84 |
| Ph | H | H | H | $CH_2Br$ | 155.8 s | 39.4 t | 79.5 d | $CDCl_3$ | 104/79 |
| Ph | H | H | H | $CH_2Cl$ | 156.1 s | 38.6 t | 79.9 d | $CDCl_3$ | 104/79 |
| Ph | H | H | Me | $CH_2Cl$ | 156.2 s | 43.7 t | 86.4 s | $CDCl_3$ | 104/79 |
| Mesityl | H | H | Me | $COCHMe_2$ | 158.2 s | 47.4 t | 90.7 s | $CDCl_3$ | 161/83 |
| Ph | Ph | OH | Me | OH | 163.1 s | 90.5 s | 106.4 s | $CDCl_3$ | 24/81 |
| Ph | Cl | Cl | Ph | OH | 159.8 s | 90.6 s | 109.0 s | $CDCl_3$ | 37B/81 |
| Ph | Cl | Cl | Ph | OMe | 160.1 s | 90.9 s | 111.2 s | $CDCl_3$ | 37B/81 |
| Me | Cl | Cl | Me | OH | 158.4 s | 91.8 s | 107.5 s | $CDCl_3$ | 37B/81 |
| Ph | Cl | Cl | Me | OH | 158.8 s | 90.2 s | 109.2 s | $CDCl_3$ | 37B/81 |
| Me | Cl | Cl | Ph | OH | 158.5 s | 92.4 s | 107.4 s | $CDCl_3$ | 37B/81 |
| Me | H | H | Ph | OH | 156.7 s | 52.4 t | 106.9 s | $CDCl_3$ | 37B/81 |
| $Me_3Si$ | H | H | H | Ph | 159.65 s | 49.1 t | 78.3 d | $CDCl_3$ | 109/83 |

The presence of *syn* and *anti* isomers in the ratio 1:1 in the crude 2-isoxazolin-5-yl acetaldehyde oxime has been reported from $^{13}$C-NMR data.[1/77] Also, diastereoisomeric 4-(1,4,2-dioxazol-5-yl)-2-isoxazolines, which showed identical PMR data, could be distinguished by $^{13}$C-NMR spectroscopy.[177/83] Some 5-spi-



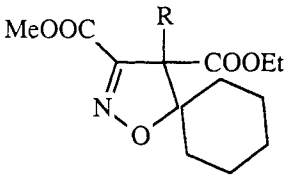
37

| | $C_4$ | $C_5$ | 5Me |
|---|---|---|---|
| 5S | 45.80 | 88.02 | 24.78 |
| 5R | 47.17 | 88.23 | 22.33 |



38

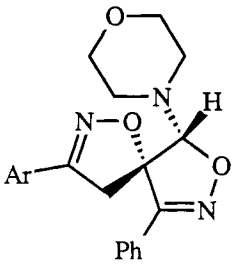
ro-2-isoxazolines have been studied by $^{13}$C-NMR.[25/75,22/77,234B/81,144/83,276/83] Because of the substituents, the rearrangement products (**39**) of ethyl α-hydroxyamino-aconate with bases show downfield shifts of the $C_4$ signal that in some cases is similar to the chemical shifts of $C_5$.[25/75]



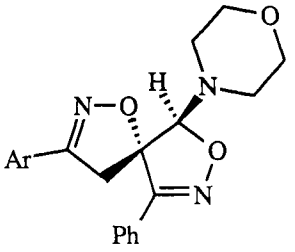
39

| | R | $C_3$ | $C_4$ | $C_5$ |
|---|---|---|---|---|
| **39 a** | H | 149.5 s | 60.5 or 61.6 | 93.1 s |
| **b** | OH | 151.7 s | 87.1 s | 93.9 s |
| **c** | OAc | 150.5 s | 92.1 s | 93.4 s |

The total $^{13}$C-NMR line assignment of acetyl aerothionin, natural spiroisoxazoline and of psammaplysins A and B, natural spirooxazolines, has been afforded by PND, GATED, off-resonance, and SFORD spectra and discussed.[276/83] The assignment of stereochemistry of diastereoisomers 4,5′-spirodiisoxazolines has been based on the C–H coupling constants $^3J_{CH}$ and the values of the Karplus curves connected with the dihedral angles. It has been pointed out that a detectable $^3J_{CH}$ would signify a small angle, showing that $C_{4'}$ and $H_5$ are *cis*, as for **40**. On the contrary, a $^3J_{CH}$ close to zero indicates an angle

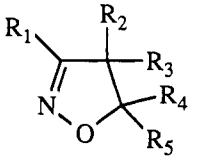



**40**




**41**

TABLE 2.12. $^{13}$C-NMR CHEMICAL SHIFTS OF METHYL GROUPS ON 2-ISOXAZOLINE RING



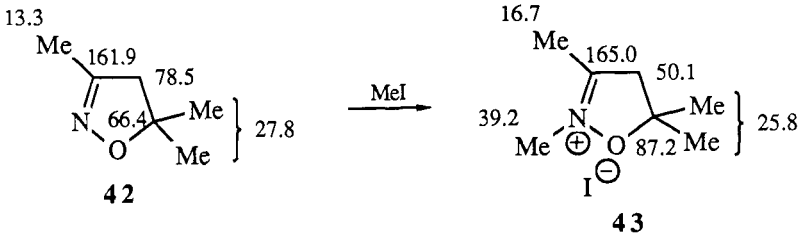

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | 3Me | 4Me | 5Me | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|
| Me | H | H | Ph | H | 8.13 | - | - | $CDCl_3$ | 241/83 |
| Me | H | H | 2-$IC_6H_4$ | H | 12.8 | - | - | $CDCl_3$ | 131/84 |
| H | Me | H | Ph | H | - | 12.23 | - | $CDCl_3$ | 241/83 |
| H | Me | H | 2-$IC_6H_4$ | H | - | 17.5 | - | $CDCl_3$ | 131/84 |
| H | Me | H | 4-$NO_2C_6H_4$ | H | - | 29.3 | - | $CDCl_3$ | 131/84 |
| H | H | H | Me | Ph | - | - | 23.41 | $CDCl_3$ | 241/83 |
| H | H | H | Me | 4-$NO_2C_6H_4$ | - | - | 27.5 | $CDCl_3$ | 131/84 |
| Ph | H | H | Me | $CH_2Cl$ | - | - | 23.7 | $CDCl_3$ | 104/79 |
| Ph | Ph | OH | Me | OH | - | - | 20.63 | $CDCl_3$ | 24/81 |
| Me | Cl | Cl | Me | OH | 9.9 | - | 20.7 | $CDCl_3$ | 37B/81 |
| Ph | Cl | Cl | Me | OH | - | - | 20.7 | $CDCl_3$ | 37B/81 |
| Me | Cl | Cl | Ph | OH | 9.8 | - | - | $CDCl_3$ | 37B/81 |
| Me | H | H | Ph | OH | 13.2 | - | - | $CDCl_3$ | 37B/81 |

close to 90°, corresponding to $C_{4'}$ *trans* to $H_5$, as for **41**.[144/83] This rule seems to be general for spiro compounds of this kind.

Intermediate isoxazolines, in the synthesis of isoxazoles from β-substituted enones and hydroxylamine, have been detected by $^{13}$C-NMR.[105/83] *meso*-5,5′-Di(3,3′-dimethyl-2,2′-isoxazolinyl) shows the following signals identical for the two rings: ppm 13.03 (Me), 41.67 ($CH_2$, $C_4$), 79.97 (CH, $C_5$), and 115.51 (C=N, $C_3$).[286/83]

Table 2.12 reports some examples of chemical shifts of methyl groups on the isoxazoline ring. Methyl groups at $C_3$ usually absorb at 12–13 ppm. However, in 3-methyl-5-phenyl-2-isoxazoline the methyl signal is at 8.13 ppm.[241/83] The $C_4$ methyls absorb in a large range (17–30 ppm) depending on the 5-substituent and $C_5$ methyls between 20 and 28 ppm.

3,5,5-Trimethyl-2-isoxazoline (**42**), obtained by a peculiar heterocyclization of acetone oxime with pyridinium chloride, shows the chemical shifts (ppm) of the carbon atoms as reported on the formula. From the reported attributions the $C_4$ chemical shifts are at lower field than that of $C_5$. However, in the 2-methylated salt (**43**) the chemical shifts follow the usual order:[171/82]




**42** **43**

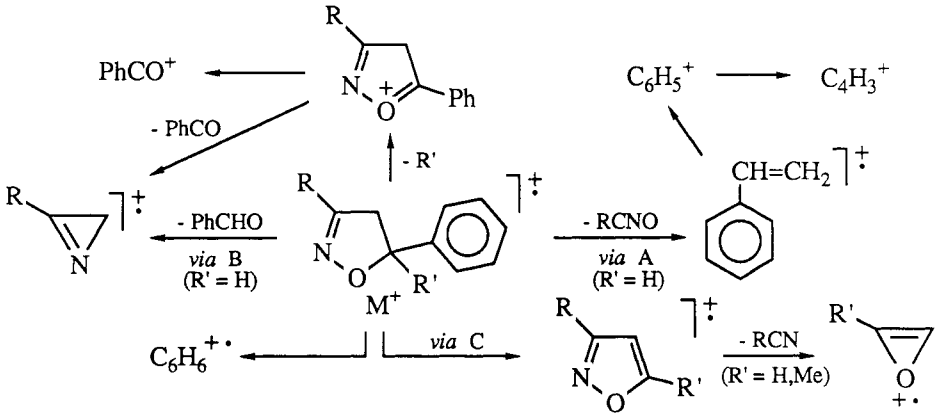
Methyl groups of **38** have tentatively been attributed to the signals at 13.5 ppm ($C_3$ Me) and at 24.1 and 23.0 ppm (diastereoisomeric $C_5$ Me).[188/76]

### c. Other Nuclei NMR Spectra

The value of $\delta_N$ 326.7 ppm has been reported for the nitrogen chemical shifts of $^{15}$*N*-3-mesityl-2-isoxazoline relative to tetramethylammonium chloride.[125B/73] $^{19}$F-NMR data of 3-pentafluorophenyl-4-nitro-5-substituted isoxazolines and of 3-phenyl-4-nitro-5-pentafluorophenylisoxazoline have been reported. It has been noted that the fluorine atoms of the polyfluorinated phenyl at position 3 of the isoxazoline ring are downfield compared with the corresponding signal for the polyfluorinated phenyl at position 5. This fact suggested that the isoxazoline ring is a stronger acceptor for the $C_6F_5$ group at $C_3$ than for that at $C_5$.[257/79] Full $^{19}$F-NMR data of perfluoroalkyl 2-isoxazolines obtained by cycloaddition have been reported.[171/78,310/80] The value of −6.3 ppm has been reported for $^{29}$Si-NMR in the case of 3-trimethylsilyl-5-phenyl-2-isoxazoline.[109/83]

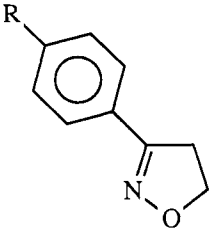
### *2.2.1.4 Mass Spectrometry*

Mass spectra of 2-isoxazolines have been less extensively studied than those of isoxazoles. However, the mass spectra are very often used for determination of the molecular weight of the products. In several papers the fragmentation of variously substituted 2-isoxazolines have been reported, and those are reviewed here. The fragmentation depends mainly on the ring substituents, particularly on those at $C_5$. The mass spectra of 5-substituted-,[322/82,241/83] and 3,5-,[6/82,241/83,322/83] 4,5-[241/83] and 5,5-disubstituted-2-isoxazolines[241/83] have been studied and the fragmentation shown in Scheme 2.1 reported and discussed.[241/83] Following




**Scheme 2.1**

pathway A the cleavage of the C–O and $C_3$–$C_4$ bonds leads to the styrene radical ion. On the contrary, through pathway B the elimination of PhCHO (when R′ = H), which can explain the formation of the azirinium ion, involves N–O and $C_4$–$C_5$ bond cleavages. Moreover, through the loss of a $C_6H_6$ radical ion and N–O and $C_3$–$C_4$ bond cleavages, the oxirene fragment is formed. The mass spectra of six 3-aryl-2-isoxazolines (**44**) have been recorded at different voltages.[200/74]

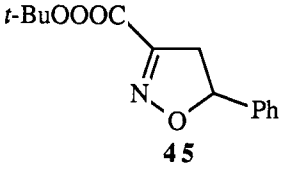


**44** **a** R = H
**b** R = Me
**c** R = MeO
**d** R = $Me_2N$
**e** R = Cl
**f** R = $NO_2$

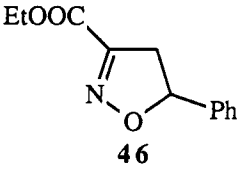
Along with the molecular ion, which almost always is the base peak, the ions originated by three main fragmentation pathways could be observed:

1. $[M - C_2H_4]^{+\cdot}$, due to a retro-1,3-dipolar cycloaddition giving rise to a nitrile oxide, which isomerizes to the corresponding isocyanate. This last rearrangement has been demonstrated by $^{13}C$-labeled compounds.
2. $[M - CH_2O]^{+\cdot}$, which can be formed either by a diradical opening of the ring at the level of the two heteroatoms, as for the isoxazole ring, or as a second competitive process of retro-1,3-cycloaddition.
3. $[M - NO]^{+\cdot}$, which is stabilized by resonance and by loss of hydrogen.

Moreover, ions due to the fragmentation of the substituents on the aryl group could be detected. The first ionization energy of the isoxazolines has been evaluated by photoelectron spectroscopy and correlated with Brown constants. These data and the fragmentation pathways at different voltages have been discussed.[200/74] 3-Phenylisoxazoline (**44a**) showed by electron impact at 70 eV a fragment at *m/z* 91 which could be assigned in part to a PhN ion by high-resolution measurements.[6/74] This ion can be originated by a 1,2-phenyl shift or by isomerization of the benzonitrile oxide to isocianate and subsequent loss of CO. Chemical ionization of **44a,c,f** with methane gave rise to ions at M + 1, M + 2, M + 29, and M + 41 by addition to the molecular ion of hydrogen, ethyl, and propenyl radicals.[6/74]




**45**

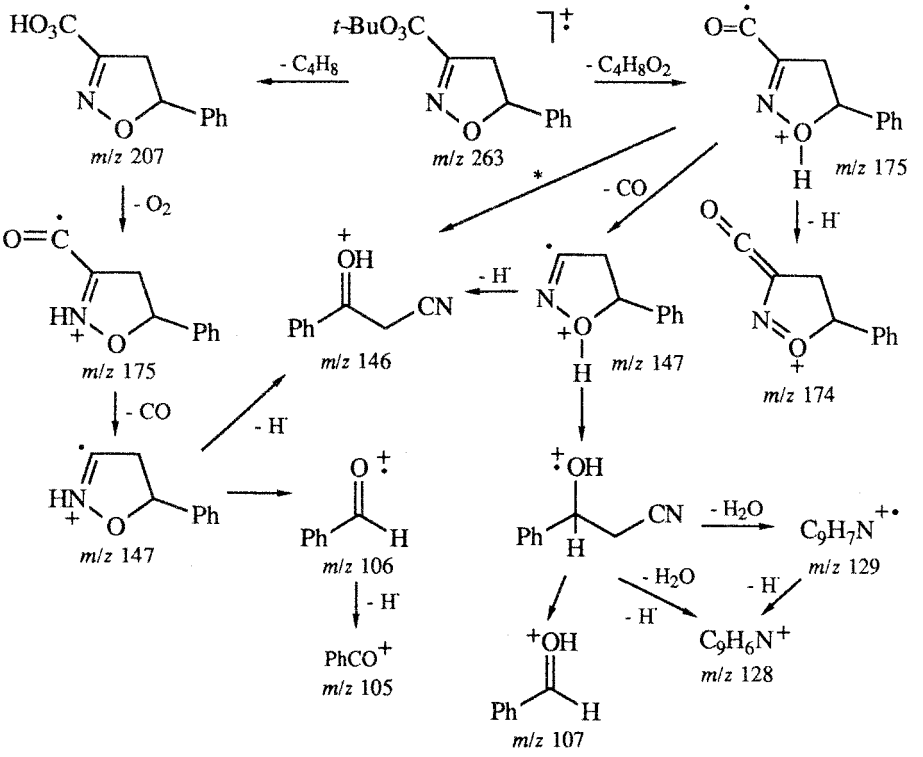



**46**

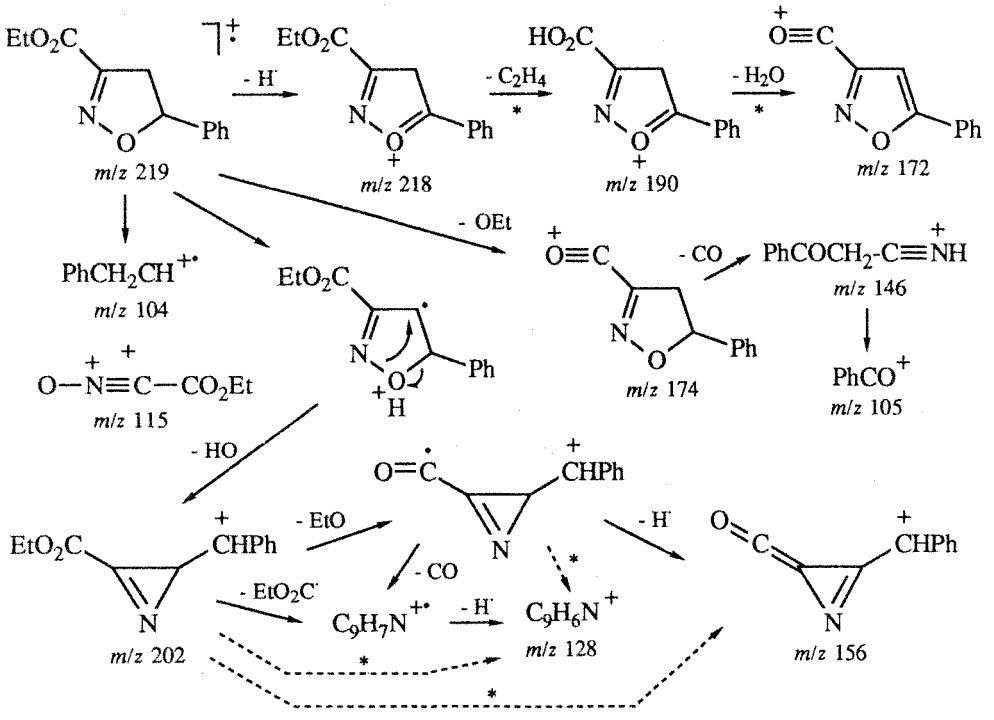
The mass spectra of the *t*-butylperoxy and ethyl ester of 5-phenyl-3-isoxazolinecarboxylic acids (**45** and **46**) have been studied by comparison with thermally oxidative fragmentation.[135/72] Especially in the case of **45**, the two process are comparable, both giving rise to benzaldehyde.

Schemes 2.2 and 2.3 of fragmentations have been proposed. Comparison of the fragmentation of the two products shows that the presence of the *t*-butoxy group seems to direct the fragmentation along two similar pathways. No retro-cycloaddition processes are detected, and many of the peaks characteristic of the ethyl ester fragmentation giving azirines are not present in the spectrum of **45**.

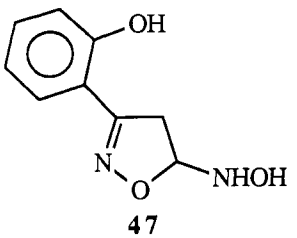
By oximation of chromone, along with isoxazoles and oximes, two isoxazolines (**47** and **48**) have been obtained. Their mass spectral data are reported. The base peaks correspond to cleavage of the $C_5$–N bond.[200/79]



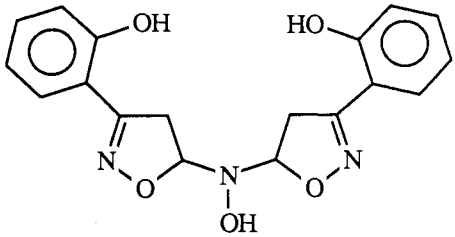

**Scheme 2.2**




**Scheme 2.3**

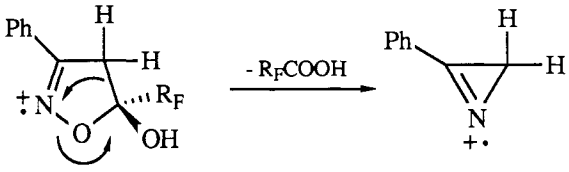


47



48

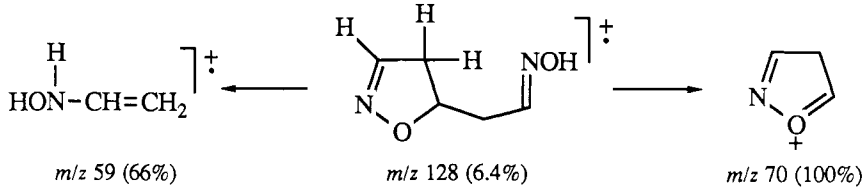
The structure of 5-hydroxy-3,5-disubstituted-2-isoxazoline as an intermediate in the oximation of $\beta$-diketones has been demonstrated in the case of 3-phenyl-5-hydroxy-5-perfluoroalkyl-2-isoxazolines by the loss of perfluoroalkylcarboxylic acid and formation of the phenylazirinium ion:[129/75]



The reported fragmentation[171/78] of 3-phenyl-5-perfluorobutyl-2-isoxazoline shows that the most intense ions correspond to subsequent losses from the ring of the perfluorobutyl radical ($M-C_4F_9$, 68%) and of CO. The last process involves a hydrogen shift from the $C_5$ to the nitrogen, giving rise to protonate phenyl azirinium ion (*m/z* 118, 100%).

Very often the regioisomeric isoxazolines have been identified by formation of an acyl ion $[RCO]^+$ containing the $C_5$ substituent as a radical. For example, 3-aryl-4-cyano-5-phenyl- and 3-aryl-5-cyano-4-phenyl-2-isoxazolines could be differentiated by the presence of ions $[M-PhCO]^{+\cdot}$ and $[PhCO]^-$ only in the mass spectrum of the first isomer.[79B/84]

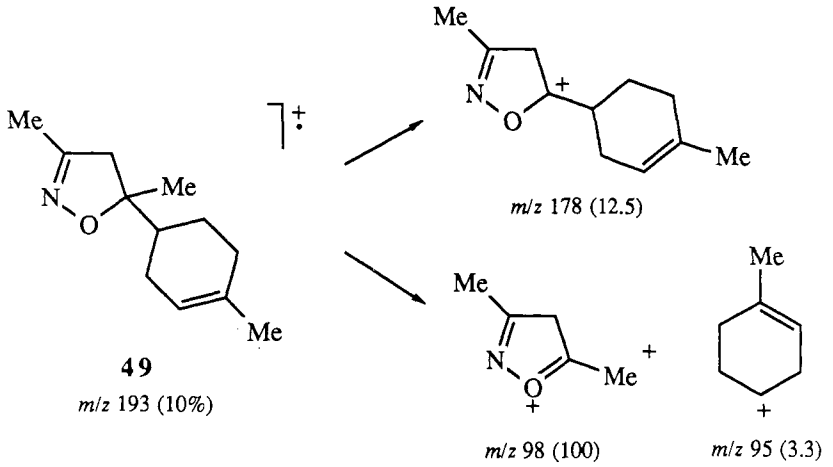
The fragmentation pattern of two regioisomeric 3-phenyl-4-cyano- and 3-phenyl-5-cyano-2-isoxazolines has also been reported.[248/82] First, the formation of azirine has been assumed by cleavage of the N–O bond and formation of the $N-C_4$ bond, followed by losses of H, CO, and CN. Small differences between the spectra of the two regioisomers have been accounted.[248/82] However, in the case of 5-isoxazolinyl acetaldehyde oxime, cleavage of the $C_5$ substituent has been assumed[1/77] as depicted here:



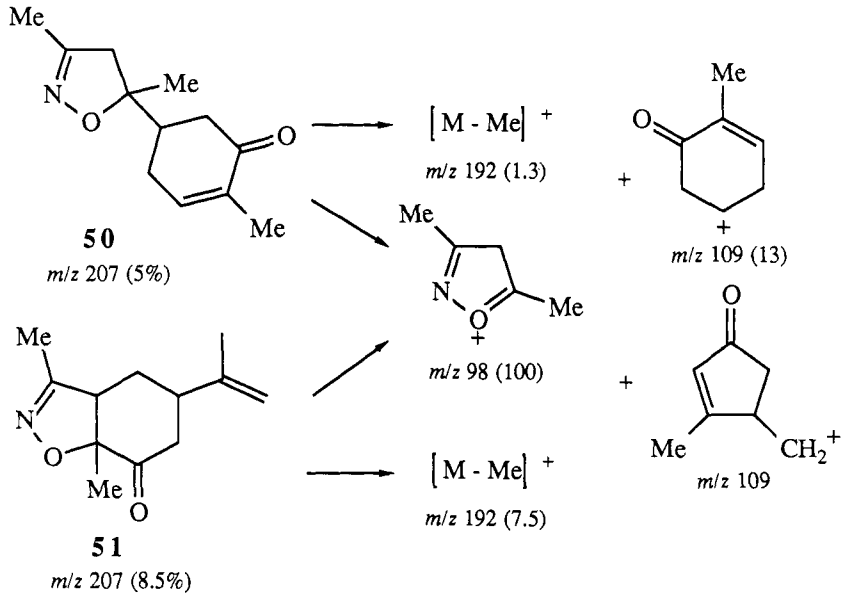
*m/z* 59 (66%) *m/z* 128 (6.4%) *m/z* 70 (100%)

Structures of cycloadducts of acetonitrile oxide to monoterpenes could also be demonstrated from their fragmentation pattern.[188/76]

In the case of dipentene, only one cycloadduct **49** has been obtained by reaction of the $C_8$–$C_9$ double bond. The mass spectrum showed the molecular ion, the loss of a methyl, and two ions arising from the cleavage of the bond between the two rings:

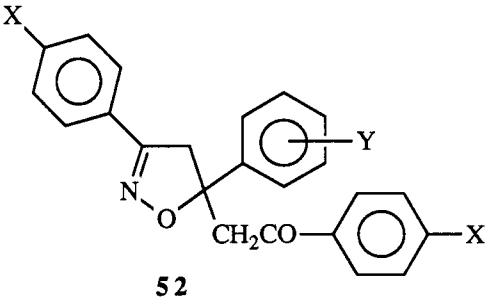



Furthermore, the two cycloadducts obtained by reaction with carvone (**50** and **51**) show a similar fragmentation pattern (Scheme 2.4).



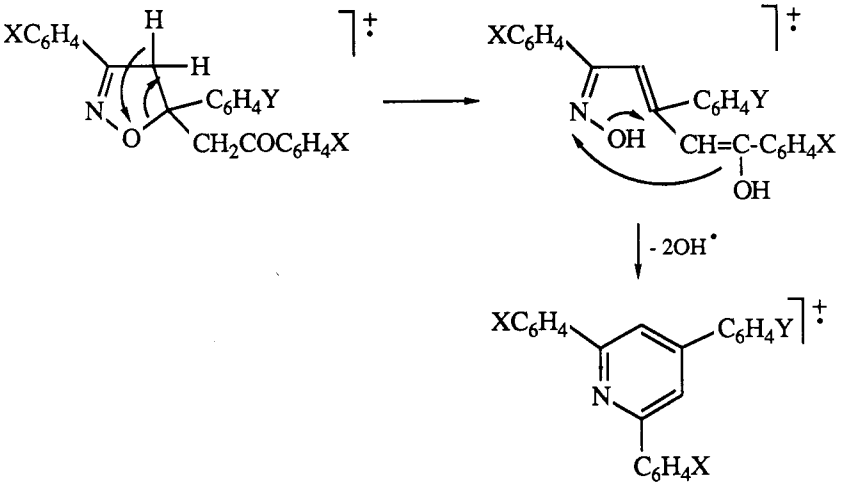

**Scheme 2.4**

The mass spectra of some 5-isoxazolinylacetophenones (**52**) have been reported and discussed.[191/70] The molecular ion was not detectable, but a weak [M − 1] ion was always present. All these products showed a characteristic low-intensity peak at *m/z* [M − 34] corresponding to the loss of $H_2O_2$ which can be explained by rearrangement to a 2,4,6-triarylpyridine radical ion shown in the following scheme:



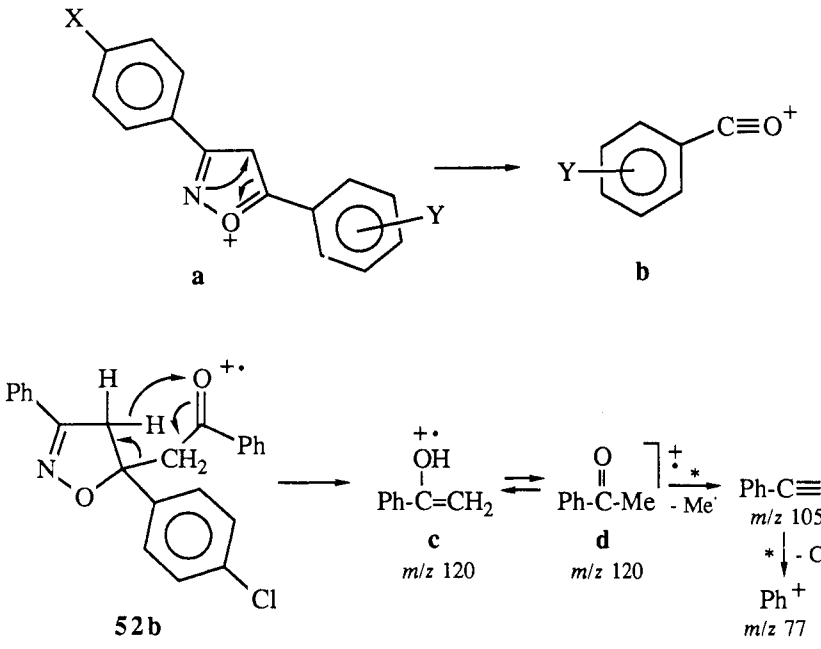
**52**

| | | |
|---|---|---|
| **a** | X = H | Y = 3-$NO_2$ |
| **b** | X = H | Y = 4-Cl |
| **c** | X = H | Y = 4-Br |
| **d** | X = Me | Y = 4-OMe |
| **e** | X = Br | Y = H |

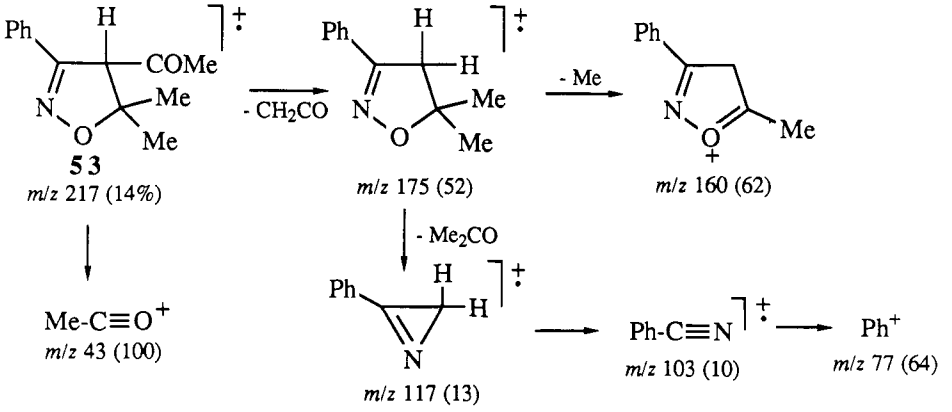


The base peaks correspond to the elimination of X–$C_6H_4$–$COCH_2$ from the molecular ion, giving the ion **a**, which in most cases loses the substituent of the aryl ring as NO and $NO_2$ from **52a** and Br from **52c**:

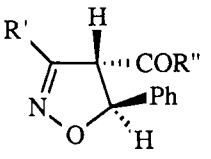
These compounds also show a McLafferty rearrangement, as depicted in the following scheme for **52b**:



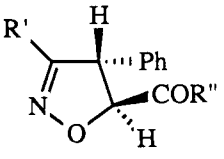

Fragmentation has been studied by metastable ions and at different voltages. Also, the spectrum of 5-methyl-5-(2-methylpropanoyl)-3-(2,4,6-trimethylphenyl)-2-isoxazoline has been reported with the attribution of fragment ions.[161/83] The mass spectrum of the cycloadduct of benzonitrile oxide and mesityl oxide[158/73] clearly indicated that the regioisomer had structure **53**, owing to the presence of the radical ion at *m/z* 117, formed by subsequent loss of ketene and acetone as indicated in the following scheme:




The usefulness of mass spectrometry for identification of the regioisomers formed by cycloaddition has also been demonstrated by analysis of the spectra of seven pairs of regioisomeric 2-isoxazolines (**54a–g**):



**A**

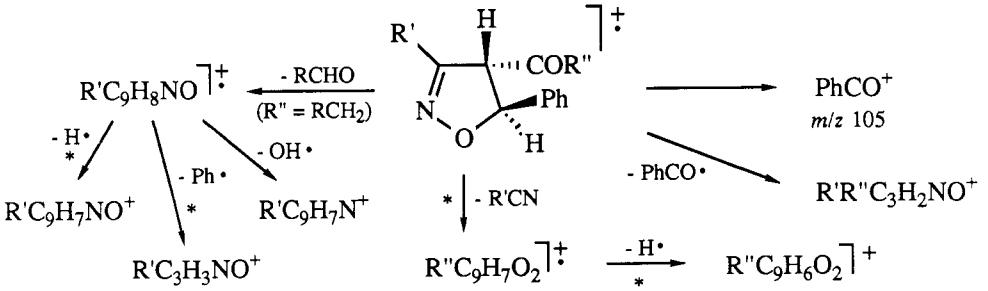


**B**

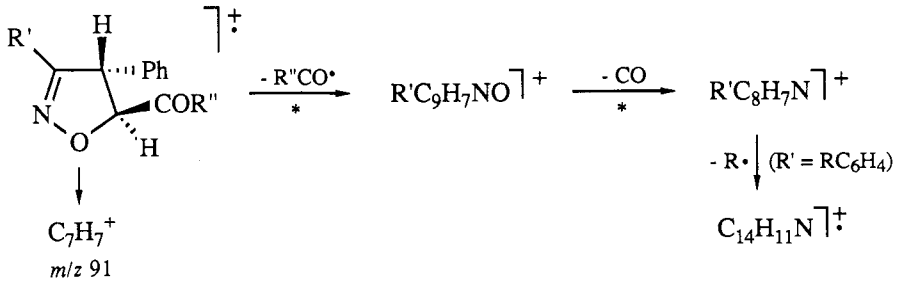
**54**

| R' | R" | |
|---|---|---|
| **a** | 4-$NO_2C_6H_4$ | Me |
| **b** | 4-$BrC_6H_4$ | Me |
| **c** | Ph | Me |
| **d** | Ph | Et |
| **e** | 4-$MeOC_6H_4$ | Me |
| **f** | Ph | Ph |
| **g** | Ph | α-Furyl |

The fragmentation pattern was established by high-resolution mass measurements and metastable ion transition detected by a defocusing technique.[72B/73] The isomers **A** gave rise to the following ions:



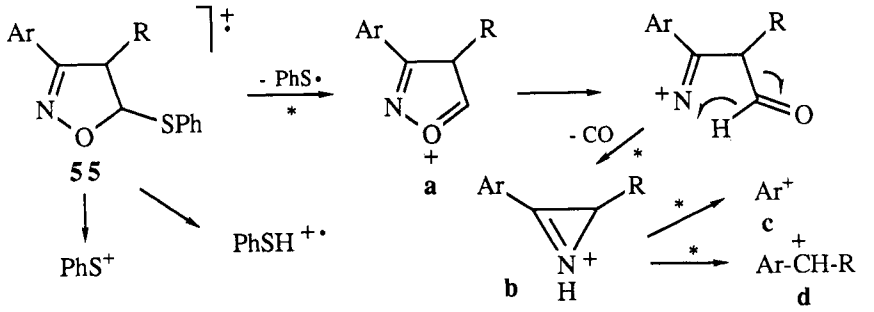

The most characteristic ions are [PhCO], [M–PhCO], [M–R′CN], and [R′$C_3H_3NO$], which is often the base peak. By contrast, the fragmentation of the regioisomers **B**, as depicted in the following scheme, gives rise to the tropilium ion (*m/z* 91), which is often the base peak, and to the [M–R″CO] ion:



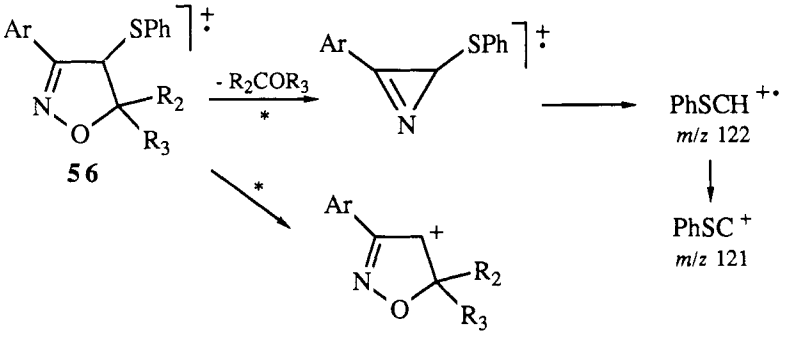
The electronic effect of the 3-phenyl group substituent on the molecular ion and acyl ion relative intensity has also been discussed.[72B/73]

Also, in the case of 5- (**55**) or 4-phenylthio-2-isoxazolines (**56**), the mass spectra can be used to recognize the regioisomer.[52D/81] The fragmentation processes have been determined by metastable peaks.

The 5-phenylthioderivatives show a very low $M^+$, since an easy loss of the PhS occurs from the molecular ion (ion **a**), which then loses CO, giving rise to an azirine ion (ion **b**):



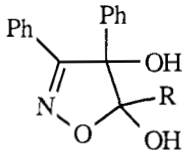

From ion **b** the formation of ions **c** and **d** can easily be explained. However, they are not present in the case of R = Ph; instead, the tropilium ion is formed by a hydrogen shift from the nitrogen to the benzylic carbon. In the case of 4-phenylthio-2-isoxazolines (**56**), the most significant fragmentation is loss of $R_2COR_3$ with formation of the azirine ring:




The ions at *m/z* 122 and 121 are characteristic of these compounds. Comparison of the spectra of *cis* and *trans* isomers for **55** and **56** (one couple for each regioisomer) seems to indicate that the *cis* isomer shows a molecular ion and [M–PhSH] ion of higher intensity than the *trans* isomer. Similar fragmentations have been observed in the case of the corresponding sulfones and sulfoxides. Mass spectra of 18 isoxazolines are reported and particular examples are discussed.[52D/81]

When in position 5 of the isoxazoline ring a group is present that can easily be eliminated, giving rise to the isoxazole derivative, this is shown in the mass spectrum by the corresponding ion. This fact is shown, for example, by 3,5-diphenyl-5-trimethylsilyloxy-2-isoxazoline ($M^+$ 21%), which easily loses $Me_3SiOH$, giving the ion $m/z$ 221 (92%),[73/78] and by 3-phenyl-4-(3,4-dimethoxyphenyl)-5-pyrrolidin-1-yl-2-isoxazoline, which easily loses pyrrolidine.[158/82]

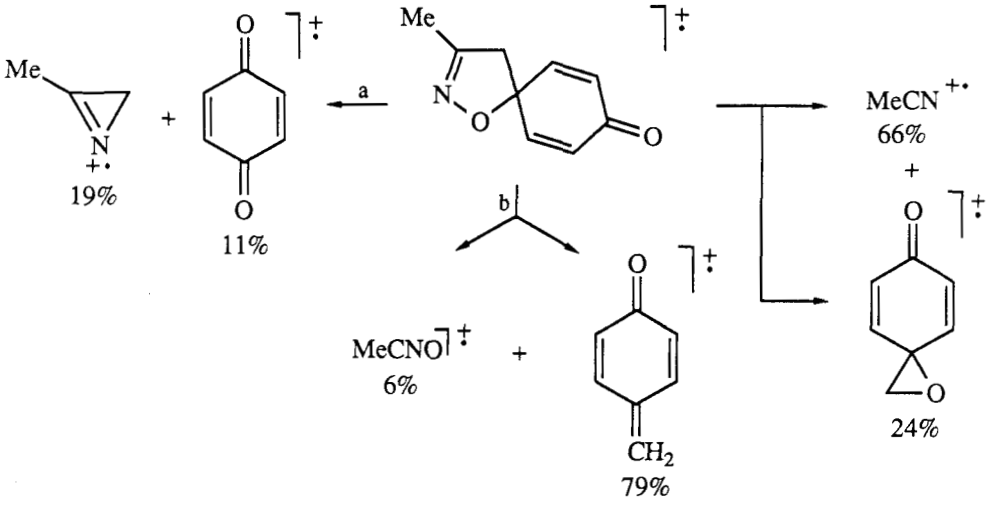
5-Substituted 4,5-dihydroxy-3,5-diphenyl-2-isoxazolines (**57**) do not show the molecular ion at either 70 or 10 eV. The main fragments correspond to the loss of two hydroxyls and then (for **57a** and **b**) of the alkyl radical. After these



**57** **a** R = Me
**b** R = Et
**c** R = Ph

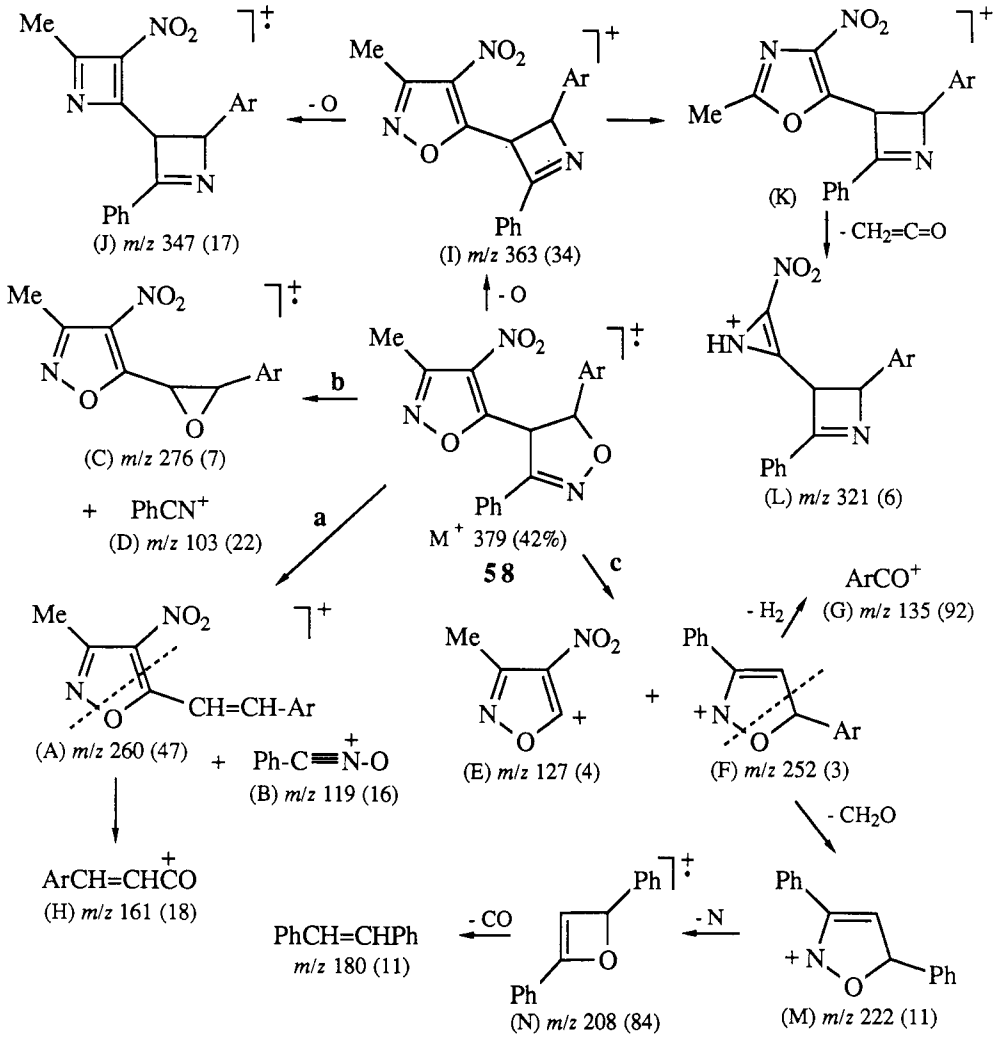
peaks, the principal peaks of diphenylisoxazoles are observed.[24/81] Full spectra with fragmentations of variously substituted 4,4-dichloro-2-isoxazolines have been reported.[37B/81]

The base peak ($m/z$ 80) of the spiro compound, 3-phenyl-2-aza-1-oxaspiro-[4,4]nona-2,6-diene ($M^+$ 199), corresponds to a retro-cycloaddition process.[116/79] Some spiroisoxazolines connected with the sponge metabolite aerothionine have been prepared and their fragmentation explained following the pathways indicated in Scheme 2.5.[124/75.125/75]




**Scheme 2.5**

The mass spectral behavior of 5-aryl-3-phenyl-4-(3-methyl-4-nitro-5-isoxazolyl)-2-isoxazolines has been discussed,[82/81] especially for Ar = 4-$MeOC_6H_4$ (**58**). Fragmentation is reported in Scheme 2.6. It is noteworthy that




**Scheme 2.6**

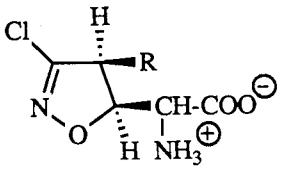
the molecular ion of **58** breaks down through three pathways, resulting in two ions (A + B, C + D, and E + F) which add up exactly to the molecular ion. Pathway **a** is a retro-cycloaddition fragmentation, giving rise to styrylisoxazole (A) and benzonitrile oxide (B) fragments. Presumably, (A) then forms the *p*-methoxycinnamoyl cation (H). The peak at *m/z* 135 is due to the *p*-anisoyl

cation (G) formed from (F)(pathway **c**) by cleavage of the N–O bond, the weakest link in the isoxazole and isoxazoline ring. The molecular ion also shows the loss of two ring oxygens, accounting for the (I) and (J) ions. The loss of ketene can be explained by rearrangement of (I) into (L), containing a 2-methyl-oxazole ring which can lose a 42-mass unit. A curious mass spectral reaction of (M) to explain the formation of a peak at *m/z* 180 attributed to the stilbene cation is described. This transformation involves the loss of nitrogen from (M), formation of the oxete ion (N), and then expulsion of CO.

To determine the structure of some prostaglandin endoperoxide ($PGH_2$) analogues, containing an isoxazoline ring, the mass spectra were carried out after trimethylsilylation.[194/83] In this way a weak molecular ion could be detected. The molecular weight, as $[MH]^+$, of peptidylacivicin could be obtained by the field-desorption technique.[184/83]

### *2.2.1.5 Other Spectra: Circular Dichroism*

Two antitumor isoxazolines (**59a** and **b**) have been isolated from *Streptomyces sviceus*, **59a** (U-42,126) being the main product. A sensitive method for quantitating **59b**(U-43,795) in mixtures is based on the substantially different circular dichroism (CD) spectra of the two products:




**59**

| | | | |
|---|---|---|---|
| **a** | R=H | CD | $[\theta]_{217}$ + 12,600 |
| **b** | R=OH | CD | $[\theta]_{222}$ + 59,000 |
| | | CD | $[\theta]_{202}$ - 46,000 |

For analytical purposes absorptions at 222 and 205 nm were used, leading to detect as little as 1% of **59b** in **59a**.[91/75]

The absolute configuration of aerothionin, a natural metabolite of the sponge *Aplysina fistularis*, has been determined by circular dichroism $[\theta]^{max}_{284} = +70{,}500$; $[\theta]^{max}_{245} = +78{,}200$ and discussed by comparison with other compounds.[227C/81]

### *2.2.1.6 Crystal and Molecular Structure*

Several structures and stereochemistry of 2-isoxazolines have been analyzed by x-ray diffraction. However, in many cases the geometrical parameters are not

reported. The stereochemistry and absolute configuration of (αS,5S) **59a** and (αS,4S,5R) **59b** were established by means of x-ray analysis using the anomalous dispersion techniques.[229/73,91/75] Structure **59a** crystallizes from water in the monoclinic system (space group $C_2$) and **59b** as monohydrate in the orthorombic system (space group $P2_12_12_1$). In both molecules the common chiral centres have the same configuration and the isoxazoline ring is as an envelope with $C_5$ out of the plane of the other atoms. However, the direction of deviation is different and is more pronounced in **59b** because of the presence of a hydroxyl group in 4. In fact, the amino acid moieties are oriented differently relative to the isoxazoline ring. In the case of **59b**, the distance between the ammonium nitrogen and the hydroxyl oxygen (2.867 Å) could allow an intramolecular hydrogen bond, but the ammonium hydrogens are too far away from the hydroxyl oxygen (2.47 Å) to permit the making of hydrogen bonds.

The nonplanarity of the isoxazoline ring in these compounds is not common to all isoxazoline derivatives; for example, the molecule of 3,3′-di-2-isoxazoline is essentially planar.[1/66] Its structure has been determined from three-dimensional scintillation counter Cu Kα diffraction data. Four molecules are contained per

| Bond lengths (Å) | | Dihedral angles (°) | |
|---|---|---|---|
| O-N | 1.41 | O-N-$C_3$ | 110.0 |
| N-$C_3$ | 1.26 | N-$C_3$-$C_4$ | 114.1 |
| $C_3$-$C_4$ | 1.52 | $C_3$-$C_4$-$C_5$ | 100.4 |
| $C_4$-$C_5$ | 1.49 | $C_4$-$C_5$-O | 106.9 |
| $C_5$-O | 1.46 | $C_5$-O-N | 108.6 |

unit cell. Bond distances and angles are reported, and most of them are indicated here. In the solid state the more stable transoid form has been found. The conjugated bridging C–C bond is found to be 1.42 ± 0.02 Å.[1/66]

Other two diisoxazolines have been studied by x-ray analysis: 5,5′-di(3,3′-dimethyl-2,2′-isoxazolinyl)[286/83] and 4(*RS*), 5′(*SR*)-*trans*-3-(*p*-bromophenyl)- 4-(3′-*p*-bromophenyl-2′-isoxazolin-5′-yl)-5-(1-pyrrolidinyl)-2-isoxazoline.[59D/73]

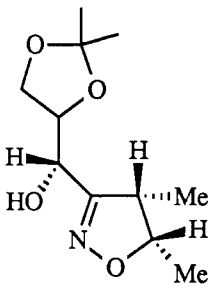
The first, whose molecules possess a center of symmetry, is in a *meso* form. The latter shows two crystallographically independent molecules in the asymmetric unit but both with the same conformation and almost identical. Each molecule can be considered to contain three planes: two formed by the bromine atom, the phenyl, and the isoxazoline ring, and the third by the puckered pyrrolidine ring. The isoxazoline rings are not planar; those linked to the pyrrolidine with a mean deviation of 0.08 Å (A) are greater than the others (B)(0.04 Å). The bond lengths and the dihedral angles of the two isoxazoline rings are reported here; however, full data are published. The length of the $C_4$–$C_5'$ bond is 1.55 Å.[59D/73]

| | Bond lengths (Å) | | | Dihedral angles (°) | |
|---|---|---|---|---|---|
| | ring A | ring B | | ring A | ring B |
| N-O | 1.42 | 1.42 | $O\text{-}N\text{-}C_3$ | 110.0 | 107.5 |
| $N\text{-}C_3$ | 1.29 | 1.28 | $N\text{-}C_3\text{-}C_4$ | 112.7 | 117.7 |
| $C_3\text{-}C_4$ | 1.53 | 1.46 | $C_3\text{-}C_4\text{-}C_5$ | 102.3 | 100.2 |
| $C_4\text{-}C_5$ | 1.52 | 1.55 | $C_4\text{-}C_5\text{-}O$ | 103.0 | 104.2 |
| $C_5\text{-}O$ | 1.50 | 1.48 | $C_5\text{-}O\text{-}N$ | 109.3 | 109.5 |

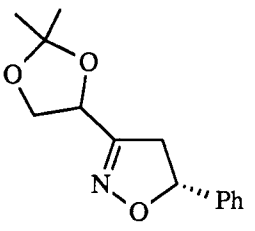
The molecular structure of 3,5-diphenyl-4,4-dichloro-5-methoxy-2-isoxazoline has been reported with values for all bond lengths and dihedral angles:[37B/81]

| Bond lengths (Å) | | Dihedral angles (°) | |
|---|---|---|---|
| O-N | 1.427 | $O\text{-}N\text{-}C_3$ | 109,3 |
| $N\text{-}C_3$ | 1.267 | $N\text{-}C_3\text{-}C_4$ | 112.0 |
| $C_3\text{-}C_4$ | 1.515 | $C_3\text{-}C_4\text{-}C_5$ | 99.5 |
| $C_4\text{-}C_5$ | 1.558 | $C_4\text{-}C_5\text{-}O$ | 100.6 |
| $C_5\text{-}O$ | 1.438 | $C_5\text{-}O\text{-}N$ | 108.5 |

The stereochemistry of 2-isoxazolines containing a 1,3-dioxolane ring, such as **60–61**, has been elucidated by x-ray analysis.[155/83,310B/83,158/84]



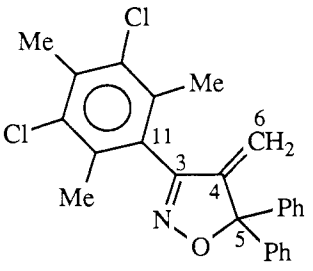

**60**



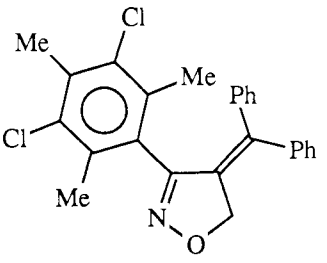

**61**

In the first compound the ketal ring has a half-chair conformation, while the isoxazoline ring has an envelope conformation. In the latter compound both rings have an envelope conformation, but the dioxolane ring is the most puckered.

The real structure of the two cycloadducts **62** and **63** from the reaction of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide with 1,1-diphenylallene has been elucidated by x-ray diffraction analysis.[49/76,50/76,51/76] Crystals of two different forms have been obtained from **62** (form I hexagonal prism[49/76] and form II needles[50/76]). In form I of **62**, the atoms $C_3$, $C_4$, $C_5$, $C_6$, and $C_{11}$ are coplanar, while N and O are out of this plane as the isoxazoline ring was folded along the line $C_3$–$C_5$. The substituted ring is almost perpendicular to that plane (85°) and




**62**

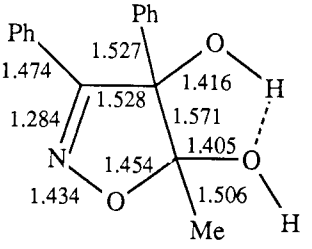



**63**

the two unsubstituted phenyls show angles of 66° and 75°, respectively. These two phenyls are planar and the angle between the planes is 78°. The molecules of form II (**62**) differ appreciably in their conformation; the folding of the isoxazoline ring along the $C_3$–$C_5$ line is more marked than in form I: 14° (against 5° of form I) is the value of the dihedral angle between the two planes $C_3$–$C_4$–$C_5$–$C_6$–$C_{11}$ and O–N–$C_3$–$C_5$–$C_{11}$. In form II the angle between the two unsubstituted phenyl planes is 88°, against 78° of form I. However, bond distances and angles do not show very significant differences in the two forms.

Notwithstanding its high instability, the data of **63** could be recorded. The most significant feature of the molecule conformation is that the substituted phenyl faces the nearest unsubstituted phenyl ring, presenting a dihedral angle of only 13° and a distance in the range 3.1–3.4 Å.[152,74,51,76] For all molecules full data from x-ray analysis have been reported.

Since the usual spectroscopic techniques did not permit assignment of the structure of the product obtained by electrolytic reduction of 1-nitro-1,2-



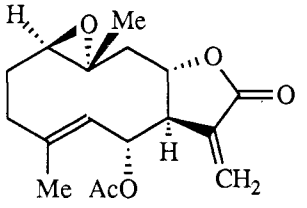

**64**

| Angles (°) | |
|---|---|
| O-N-$C_3$ | 108.8 |
| N-$C_3$-$C_4$ | 113.6 |
| $C_3$-$C_4$-$C_5$ | 98.6 |
| $C_4$-$C_5$-O | 102.3 |
| $C_5$-O-N | 108.5 |

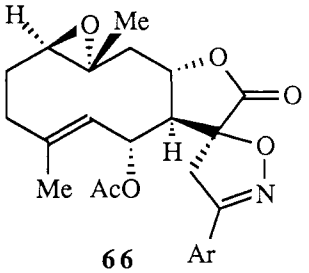
diphenyl-1-buten-3-one, an x-ray diffraction has been carried out.[185,80,24,81] The structure of *cis*-4,5-dihydroxy-3,4-diphenyl-5-methyl-2-isoxazoline has been de-

monstrated, showing parameters for the isoxazoline ring as reported in formula **64**.

The structure of the sesquiterpene pyrethrosin (**65**) has been determined accurately by x-ray analysis of its isoxazoline derivative (**66**), obtained by



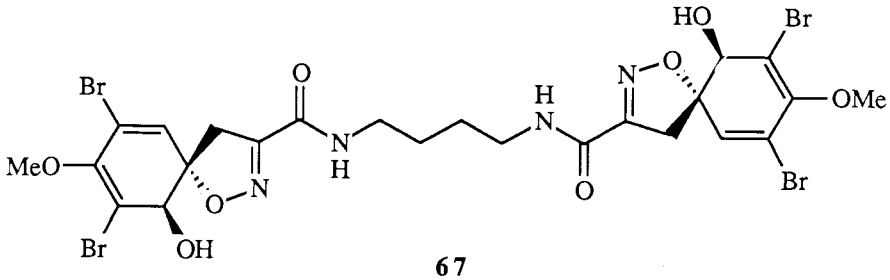
**65**



**66** (Ar = 2-ClC$_6$H$_4$)

cycloaddition of *o*-chlorobenzonitrile oxide to the *exo*-methylene group of pyrethrosin.[24B/71] The addition of the nitrile oxide has occurred *trans* to both the bridgehead hydrogen and the acetoxy group. The $\beta$ approach probably has been dictated by the stereochemistry of the acetoxy group.

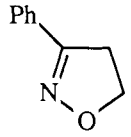
The absolute configuration of the sponge metabolite aerothionin (**67**), a tyrosine-derivative compound containing a spiroisoxazoline ring, has been established by x-ray data. Since the colorless crystals were unstable to x-rays, data from crystals were combined, using the intensities of three standard reflections for scaling and correcting for decay.[227C/81]



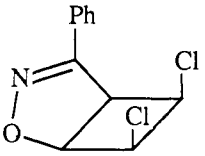
**67**

### *2.2.1.7 Dipole Moments*

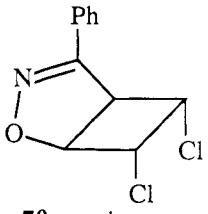
The dipole moments ($\mu$ in debye units) of 3-phenyl-2-isoxazoline (**68**) and of some cycloadducts of nitrile oxides to cyclobutene derivatives (**69–73**) have been measured in benzene solution at 20°C by the dilute solution method.[261/79] This method could not be carried out for **71** because of the low solubility of the product in benzene, and the empirical Srivastava and Charandas equation was used.



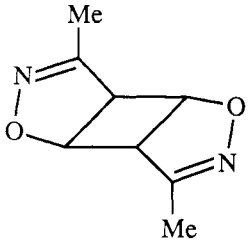
**68**
μ 3.40 D



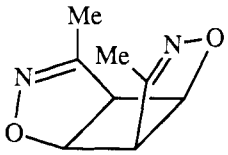
**69** *syn*
μ 4.71 D



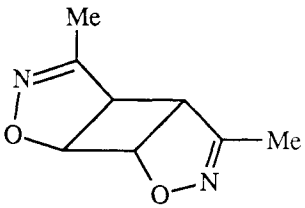
**70** *anti*
μ 2.94 D



**71** *anti trans*
μ ca. 0.8 D



**72** *syn trans*
μ 2.89 D



**73** *anti cis*
μ 4.98 D

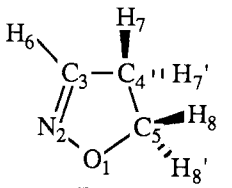
These experimental dipole moments have been compared with those calculated by vector addition for each steric configuration. A good agreement of the observed and calculated values could be obtained for the bicyclic cycloadducts **69** and **70**, thus supporting the assigned configuration: $\mu_{total}$ 4.99–5.35 D for the *syn* and $\mu_{total}$ 1.65–2.20 D for the *anti* configuration. To explain the small moment observed for **71**, the nonplanarity of the cyclobutane ring has been invoked. The calculated dipole moment is in agreement with the observed value in the case of **72** but not in that of **73**. For the latter compound no conclusive results could be obtained.

The difference in dipole moment values of the *syn* isomer (**69**) and the *anti* isomer (**70**) has been invoked in a discussion of the cycloaddition mechanism,[139/74] suggesting that in a concerted process, the transition state leading to the *syn* isomer should be more polar than the one leading to the *anti* isomer. For similar mechanistic reasons, the dipole moments of 3-(3,5-dichloro-2,4,6-trimethylphenyl)-4-methylene-5,5-diphenyl-2-isoxazoline (3.47 D)[146/72,152/74] and 3-(3,5-dichloro-2,4,6-trimethylphenyl)-4-diphenylmethylene-2-isoxazoline (3.77 D) have been determined by measurement of dielectric constant and of refractive index in benzene.[146/72]

### *2.2.1.8 Theoretical Calculations*

In a study on *ab initio* molecular orbital calculations for the 1,3-dipolar cycloaddition of fulminic acid to ethylene, optimized geometries of 2-is-

oxazoline have been reported[12/76] (see Table 2.13) and favorably compared with the experimental data of 3,3′-di-2-isoxazoline.[1/66]




**74**

TABLE 2.13. OPTIMUM GEOMETRIES (STO-3G) FOR 2-ISOXAZOLINE [BOND LENGTHS IN PM (1 PM = $10^{-12}$ M) AND BOND ANGLES IN DEGREES]

| Bond lengths (Å) | | | Bond angles (°) | | |
|---|---|---|---|---|---|
| 1-2 | 140.8 | (141)[a] | 1-2-3 | 110.5 | (110)[a] |
| 2-3 | 128.4 | (126) | 2-3-4 | 114.8 | (114) |
| 3-4 | 152.1 | (152) | 3-4-5 | 99.1 | (101) |
| 4-5 | 154.7 | (149) | 4-5-1 | 106.8 | (107) |
| 5-1 | 146.2 | (146) | 2-3-6 | 120.9 | |
| 3-6 | 108.3 | | 4-3-6 | 103.4 | |
| 4-7 | 108.8 | | 3-4-7 | 97.9 | |
| 5-8 | 109.4 | | 5-4-7 | 112.5 | |
| | | | 5-4-7' | 112.5 | |
| | | | 7-4-7' | 108.5 | |
| | | | 4-5-8 | 112.3 | |
| | | | 1-5-8 | 108.5 | |
| | | | 4-5-8' | 112.3 | |
| | | | 8-5-8' | 108.4 | |

[a]The numbers in parentheses report the values measured by x-ray analysis of 3-3'-bi-2-isoxazoline.[1/66]

A $C_s$ symmetry constraint was imposed on the molecule of 2-isoxazoline during the geometry optimization. These calculations were carried out with a minimal basis set of Gaussian-fitted Slater-type orbitals (STO-3G) and of the split-valence 4-31G level. The total energy of 2-isoxazoline calculated by both methods gave the following results:

STO-3G $-242{,}67787$ Hartree

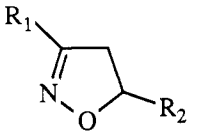
4-31G $-245{,}36937$ Hartree

In relationship to the analysis of the PMR spectra of variously substituted 2-isoxazolines, theoretical spectra have been calculated[80/66,13/67] according to $A_2B_2$, ABX, and AB systems. The transition energies values have been reported as $\mu \cdot \delta$.[80/66]

### *2.2.1.9 Miscellaneous Data*

#### a. Basicity

The $pK_a$ values of three 2-isoxazolines (**75**) have been determined by a



**75**

| | $R_1$ | $R_2$ | $pK_a$ |
|---|---|---|---|
| **a** | Me | H | 0.55 ± 0.10 |
| **b** | Ph | Ph | -3.28 ± 0.03 |
| **c** | Ph | OCOMe | -3.67 ± 0.07 |

spectrophotometric method[202/66] together with those of some isoxazoles. The basicity of **75a** is higher than that of 3-methylisoxazole ($pK_a = -1.76$ to $-1.92$). This fact can be explained as the result of interaction of the lone pair of $\pi$ electrons of the nitrogen atom with the aromatic sextet in the case of isoxazole and its derivatives. Structures **75b** and **75c** show a lower basicity than **75a** due to conjugation of the C=N bond of the isoxazoline ring with the benzene ring at $C_3$. It has been suggested that the influence of the $C_5$ substituent (as for **75b** and **75c**) on the basicity can be due to the formation of conjugated acids of the oxonium type involving the oxygen atom.[202/66]

b. Thermal Properties

The enthalpy of combustion of 3-nitro-2-isoxazoline and 3-nitro-2-isoxazolin-2-oxide has been measured ($\Delta H_C^{298.15} = -414 \pm 0.3$ kcal/mol and $\Delta H_C^{298.15} = -406 \pm 0.5$ kcal/mol, respectively) in order to calculate the bond energy of N → O in the latter compound.[170/69] Thermodynamic properties (activity coefficients, chemical potential, free energy of mixing) of binary mixtures of eight isoxazolines have been studied by means of the analysis of their phase diagrams at solid-liquid equilibrium. The results indicated regular behavior of the systems and the absence of addition compound formation in either the solid or liquid phase.[35/77]

### *2.2.1.10 Chromatographic Analysis*

TLC analysis on silica gel plates has largely been used for detection of 2-isoxazolines in the synthesis and mainly for regioisomers in the cycloaddition reaction mixtures. A variety of solvent combinations have been used, depending on the type of substituent: benzene–ethyl acetate (3:1)[11B/66.175/68.121/80] for 3,5-diaryl-2-isoxazolines, cyclohexane–ethyl acetate, methylene chloride–methanol and benzene–chloroform for variously substituted 4- or 5-acyl-2-isoxazolines.[158/73] Similar solvent mixtures have been used to separate the regioisomers by column chromatography. The $R_f$ values of 3-(2′-hydroxyphenyl)-5-aryl-2-isoxazolines have been reported.[121/80]

2-Isoxazolines can be detected on TLC plates either by visualization with a 254-nm UV lamp or by spraying with a 3% solution of chromic oxide in sulfuric acid (50%) followed by heating at 120°C in an air bath[139/74] or by phosphomolibdic reagent (glycosyl isoxazolines).[44/73,103/73] In the case of 3-aryl-5-nitro-2-isoxazolines the chromatograms were visualized by iodine vapor.[249/82] The intermediary oxime in the reaction of 1-cyclopropyl-3-aryl-3-(1,2,4-triazol-1-yl)-propanone with $NH_2OH \cdot HCl$ to give 3-cyclopropyl-5-aryl-2-isoxazoline could be detected in the course of the reaction by TLC (chloroform/acetone 9:1).[8/81]

The two antitumor agents (**59a** and **b**) could be separated on TLC and paper chromatography with solvent systems based on methyl ethyl ketone, acetone, and water. Chromatograms were visualized with ninhydrin spray.[25C/74,91/75] Both compounds could be isolated from the culture broth by ion-exchange (Amberlite IR 45) and silica gel column chromatography.[25C/74,73B/75] Acivicin (**59a**) has been purified via derivatization, purification of the derivative, and regeneration of the purified product. The most feasible derivatives[101/81,279/80,297/80] were found to be carbo-*p*-nitrobenzoyloxy-, phtalimido-, fluorenyl-, methoxycarbonyl-, and *t*-butyloxycarbonyl derivatives.

Silica gel *column chromatography* has been used to separate the stereoisomeric cycloadducts of nitrile oxides with *cis*-3,4-dichlorocyclobutene with cyclohexane–ethyl acetate.[139/74] The same solvent mixture has been employed on a silica gel column to purify the synthetic analogues of acivicin.[279/83] By flash chromatography stereoisomeric 2-isoxazolines have been separated and purified.[112/84, 121/84,158/84]

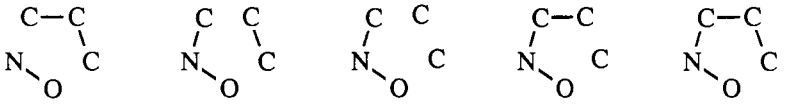
Analytical and preparative gas chromatography have been carried out to evaluate the ratio of regioisomers obtained by cycloaddition of acetonitrile oxide and methyl acrylate and to separate them. E-60 silicone oil on a Kieselguhr column has been used for both purposes: 4.5 m of column length, a temperature of 208°C for analytical GC, and 6 m, 180°C for preparative GC.[28C/73] Purity of 3-nitro-2-isoxazoline has been evaluated on a 3-m 1.5% OV-101 column.[202/78] The ratio of regioisomeric 3-ethoxycarbonyl-5-(4-methoxyphenyl)-4-methylisoxazoline and 3-ethoxycarbonyl-4-(4-methoxyphenyl)-5-methylisoxazoline has been determined by GC on a 25-m SE-30 glass capillary column[13/80] and that of the cycloadducts of nitrile oxides and cinnamonitrile on a glass column packed with 3.8% U.C.W.[79B/84] Separation and purification of the acetyl derivatives of fistularins[223/79] and of variously substituted 2-isoxazolines[121/84] have been carried out by high-performance liquid chromatography (HPLC).

### 2.2.2 Syntheses

The chemistry of 2-isoxazolines attracted moderate interest up to the 1950s, their methods of preparation being confined to the oximation reaction of carbonyl compounds having an $\alpha,\beta$-double bond or a suitable leaving group in $\beta$, favoring the cyclization process. Discovery of the 1,3-dipolar cycloaddition

reaction between nitrile oxides and double-bond compounds[16/50] started a period of steady-rate increasing research in this area which is still in lively development. Both the theoretical and synthetic and preparative aspects of 2-isoxazolines chemistry have been investigated in great detail. Owing to the large variety of preparative methods and the relatively high stability of the ring under controlled conditions, combined with the facility of ring opening under different, well-established conditions, 2-isoxazolines are more and more frequently utilized as synthons in the synthetic design of complex molecules.

Taking into account the starting materials only, the syntheses of the isoxazoline ring known up to now can be included in a few patterns: two (3 + 2), one (3 + 1 + 1), one (4 + 1) and one (5 + 0):

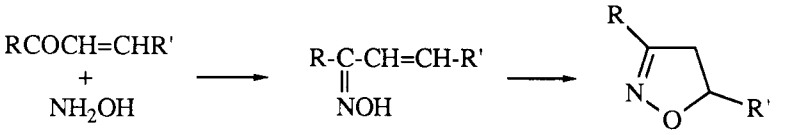


Several methods that start from a pre-formed 1,2-oxazole derivative or from another heterocyclic system are known as well.

### *2.2.2.1 [CCC + NO] Processes*

#### a. Oximation of $\alpha,\beta$-Ethylenic Carbonyl Compounds

The oximation reaction of $\alpha,\beta$-unsaturated ketones is one of the oldest explored methods for the synthesis of 2-isoxazolines. Before the end of the nineteenth century 3,5-diphenyl-2-isoxazoline was isolated among the reaction

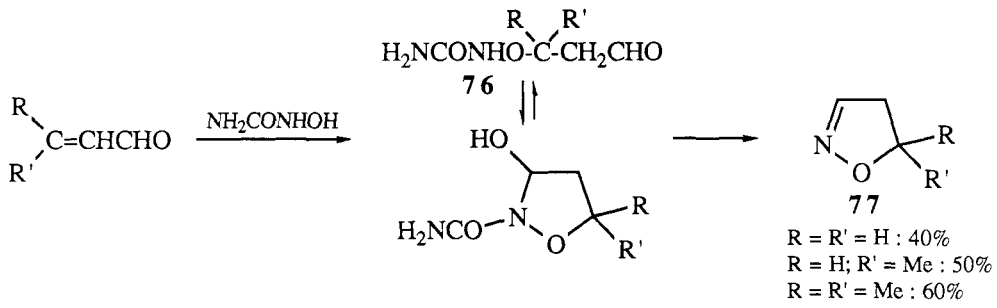


products of hydroxylamine with benzalacetophenone.[2/896] Nevertheless, the reaction is far more complex than the simple equation would indicate.

As a matter of fact, a mixture of products is usually obtained, which varies in dependence on the pH, the reagent ratio, and the substitution pattern. Moreover, under the usual experimental conditions the unsaturated oxime does not seem to be the intermediate in formation of the heterocyclic product, although it can be cyclized under different conditions (e.g., with strong mineral acids or by thermolysis). Finally, it should be noted that the yields in 2-isoxazolines seldom exceed 50–60%, so that the preparative value of this seemingly very simple synthesis is not as high as it would appear at first sight, especially after discovery of the nitrile oxide route (see § 2.2.2.2).

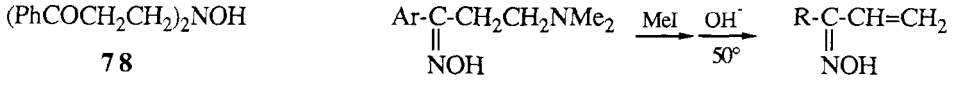
Nevertheless, the method is particularly valuable for the synthesis of 3-

unsubstituted 2-isoxazolines, including the simple unsubstituted 2-isoxazoline itself. In this case the $\alpha,\beta$-ethylenic aldehydes are condensed with *N*-hydroxyurea in a methanol–water mixture at room temperature; subsequent treatment with aqueous hydrochloric acid gives 40–60% yields of 2-isoxazolines **77**.[187/75.24/79]



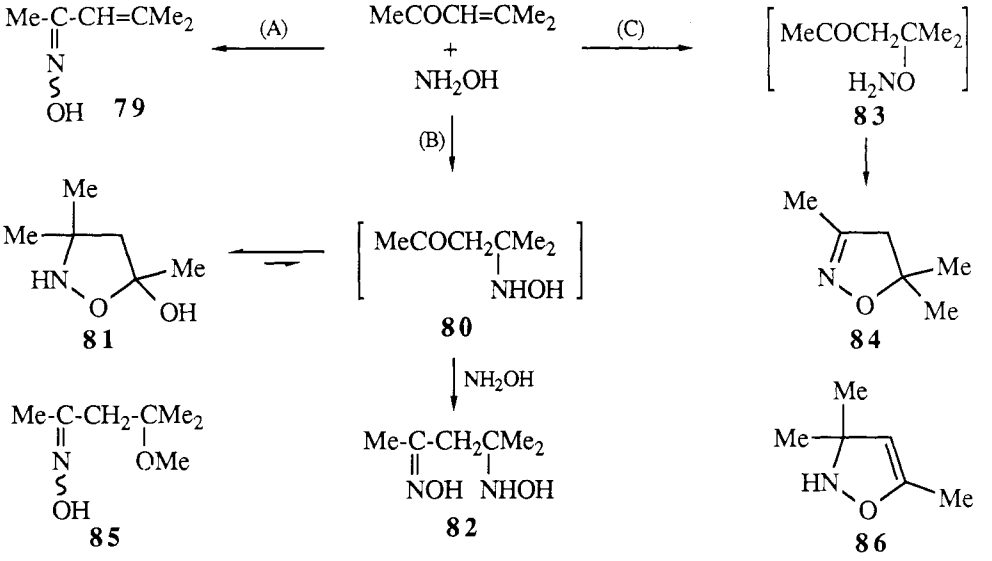

The intermediate $\beta$-ureidoaldehyde (**76**) can be intercepted and reveals a chain-ring tautomerism.

Although in one instance the formation of a 3-monosubstituted 2-isoxazoline is reported,[6/67] oximation of vinyl ketones usually leads to products arising from the attack of hydroxylamine on the double bond. Thus treatment of phenyl vinyl ketone with hydroxylamine gives bis($\beta$-benzoylethyl)hydroxylamine (**78**); use of hydroxylamine in strong excess leads to its dioxime.[44B/59] True aryl vinyl ketoximes have been prepared by an indirect route:[13/53.82/63.75D/65.100C/67]




A strong scientific effort has been devoted to elucidation of the mechanism of the oximation reaction of mesityl oxide,[2/898.2B/899.3B/24.39B/59.17B/61.23/65.193/71.21/72.36/73.85/75] which usually forms a complex mixture of several compounds. The nature of the main product depends strongly on the pH, the nature of the solvent, and the reagent ratio. Thus, under suitable conditions (stoichiometric free hydroxylamine in ethanol[17B/61] or in pyridine/alcohol[39B/59]) a mixture of stereoisomeric oximes (**79**) is mainly formed, the *syn*-methyl isomer being prevalent[21/72] (route A in Scheme 2.7). Under basic conditions not even the *anti*-methyl oxime can be cyclized to 3,5,5-trimethyl-2-isoxazoline (**84**).[21/72] Cyclization can, however, be achieved in strong acidic conditions.[23/65]

With stoichiometric ratios of the reagents at pH 9 in methanolic potassium hydroxide, attack from the nucleophilic hydroxylamine nitrogen occurs mainly on the ethylenic double bond, and the cyclic hemiacetal (**81**) or its *O*-methyl derivative is the prevalent product.[21/72] In the presence of an excess of potassium hydroxide, the reaction diverges toward a mixture of the oximes **85**,[21/72] whereas



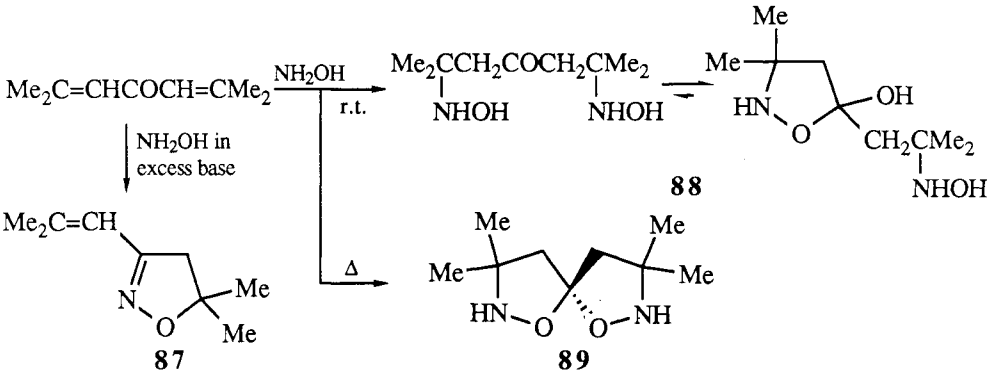

**Scheme 2.7**

an excess of hydroxylamine in aqueous base leads to the hydroxylaminooxime (**82**) as the main product (route B in Scheme 2.7).[36/73]

Use of basic more or less anhydrous conditions (better with an excess of hydroxylamine) enhances the nucleophilicity of the hydroxylamine oxygen toward the double bond (route C in Scheme 2.7), and thus the 2-isoxazoline **84** can be isolated in 50–60% yield;[23/65,21/72] the intermediacy of **83** could be demonstrated with low-temperature experiments.[36/73] The reaction is even simpler and more straightforward if *N*-hydroxyurea is used instead of hydroxylamine; in this case the *β*-ureidoxy ketone is stable and can be isolated. Cyclization to isoxazoline is carried out subsequently by acidic treatment.[187/75]

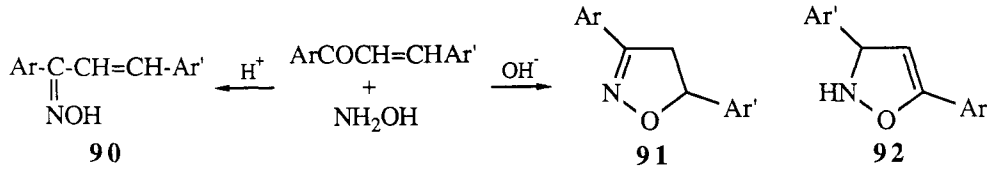
The presence of the isomeric 3,3,5-trimethyl-4-isoxazoline (**86**), originally proposed[2/898] and subsequently rejected on spectroscopic grounds,[21/72] has more recently been claimed as a by-product beside the prevalent 2-isoxazoline (**84**).[85/75] As could be expected from its behavior toward acidic conditions, 3,5,5-trimethyl-2-isoxazoline (**84**) is one of the products formed under Beckmann rearrangement conditions from the mesityl oxide oximes,[23/65,24/67] but the reaction has no preparative value, although other 2-isoxazoline derivatives have thus been isolated.[32/70,53/70,9/71]

The oximation of phorone follows the same mechanism: in strong basic medium (excess of sodium ethoxide or of potassium *t*-butoxide) excellent yields of the isoxazoline **87** are obtained, whereas under neutral conditions two molecules of hydroxylamine are added to give, depending on temperature, either **88** or the spiroheterocycle **89**:[52B/81]



Under strictly controlled conditions, 3,5-dimethyl-2-isoxazoline can be obtained by oximation of 3-penten-2-one;[35/73] under slightly different conditions unsaturated oximes are mainly formed.[193/71] Phenyl ketones such as ethylidene- or isopropylideneacetophenone, give the corresponding 3-phenyl-2-isoxazolines more easily.[8/33.193/71.35/73] On the contrary, increased substitution at the double bond favors the formation of unsaturated oximes.[85/75] Under neutral conditions, prevalent formation of the 4-isoxazoline derivatives has been claimed.[98/74] A kinetic investigation on the oximation reaction of arylideneacetones is also known.[208/72]

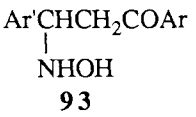
The oximation of chalcones is a long-studied reaction about which controversy has developed concerning both the mechanism of formation and the structure of the products obtained. As a general rule, oximation of chalcones in an acidic or neutral medium (i.e., with hydroxylamine hydrochloride in hot anhydrous alcohol and some drops of concentrated hydrochloric acid[1/07] or in the presence of barium carbonate[11B/66] or of pyridine[11B/66]) furnishes an unsaturated oxime (**90**) having the *syn*-styryl configuration exclusively or prevailingly. On the contrary, an excess of hydroxylamine in an alkaline solution (better on heating) leads to the 2-isoxazoline derivative **91**, where the residue originally linked to the carbonyl always occupies the 3-position:[1/30.6/31.7/31.175/68]



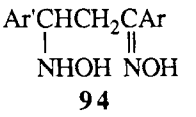
The last general rule has been questioned in a long series of papers by Barnes and co-workers,[3/45.4/45.5/45.9/47.10/47.11/47] who assigned the isomeric structure **92** to the isoxazolines obtained by oximation of several differently substituted chalcones. This assumption was based on an alleged 1,4-addition of the hydroxylamine to the unsaturated ketone. Nevertheless, the structures of some of these

isoxazolines have definitively been demonstrated to be **91** on both spectroscopic and chemical evidence.[8/49,2/54,15/54] Therefore, some of the structures of 3,5-disubstituted unsymmetrical isoxazolines and isoxazoles reported in the papers cited above must be modified by exchanging the position of Ar and Ar' groups.

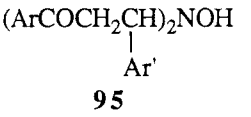
The oximation reaction of chalcones is, however, by far not as straightforward as it would be expected. First, yields seldom reach 50–60% in the synthesis of both oximes and isoxazolines. Furthermore, especially in neutral and alkaline media, the following by-products are present, which can occasionally (according to experimental conditions) become the main or even the sole products of the reaction:[2/896,6/33,7/33,8/33,15/54,284/77] hydroxylamino ketones (**93**),



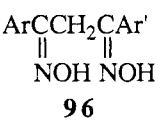
**93**



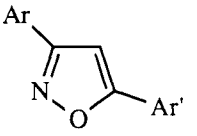
**94**



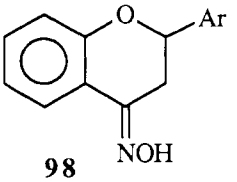
**95**



**96**



**97**



**98**

hydroxylamino oximes (**94**), diketohydroxylamines (**95**), dioximes (**96**), and isoxazoles (**97**)(for these last compounds, see also § 1.3.1.5, pp. 171–172).

When 2'-hydroxychalcones (2-$HOC_6H_4COCH=CHAr'$) are employed as starting materials in ethanol or pyridine solution, flavanone oximes (**98**) are also formed, along with 3,5-diarylisoxazolines, hydroxylamino oximes (**94**), and chalcone oximes (**90**). The nature of the products obtained depends markedly on time of reaction, reaction medium, and Ar' substituent.[95/64,8/68,140B/69,106/76,200/81,6/82]

It should be remarked that the unsaturated oximes, in either the *syn* or the *anti* form, do not cyclize to isoxazolines in alkaline media.[1/30,6/31,7/31,9/32,8/33] Therefore, formation of a heterocyclic compound would result from a complicated process, eventually through the intermediacy of **93** and **95**.[7/31,6/33,15/54] By contrast, $\alpha,\beta$-unsaturated oximes of both conformations do cyclize to the corresponding 2-isoxazolines when dissolved in concentrated sulfuric acid.[7/899,7/31,1/32,9/32,7/33,8/33] Mention should also be made of the route through *N*-methylthiomethyl nitrone and subsequent 1,5-cyclization.[153/80]

The aforementioned general trends are not without exceptions, and in this connection the following facts are worthwhile recording:

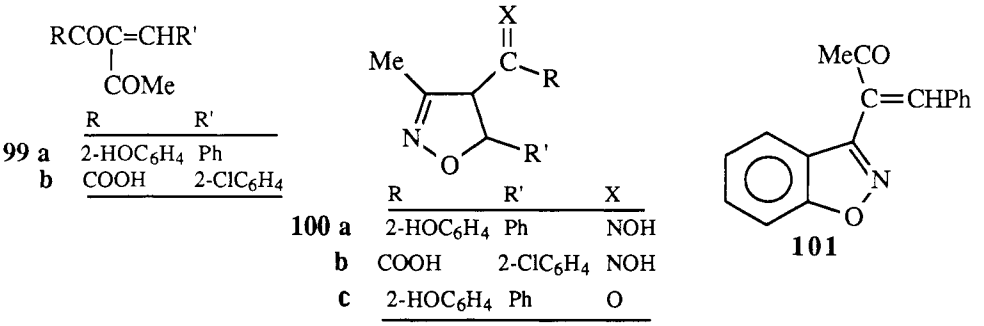
1. Some sterically encumbered chalcones, such as benzal-2,4- (or 2,5-) dimethylacetophenone[1/33] or 4-methoxybenzalacetomesitylene,[10/47] do not react at all with hydroxylamine.
2. With some chalcones (e.g., 3-methoxybenzalacetophenone[1/32]) only the

oximes (and no isoxazolines) could be obtained in both alkaline and acidic media.

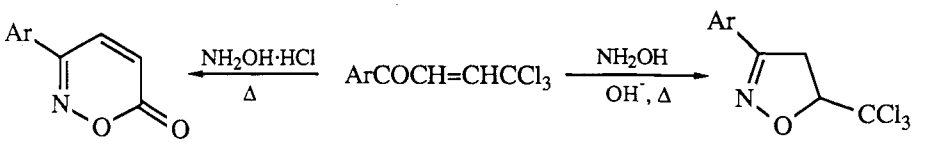
3. With some chalcones, such as benzal-3,4-dimethylacetophenone[1/33] or others,[8/68,204/81] the 2-isoxazoline has also been prepared under acidic conditions.
4. Some unsaturated oximes (e.g., benzaldesoxybenzoin oxime[7/31] or benzal-3-methoxyacetophenone oxime[1/32]) do not cyclize by treatment with concentrated sulfuric acid.
5. An alkali-promoted desulfurization would explain the formation of 3,5-diphenyl-2-isoxazoline when α-mercaptobenzalacetophenone is oximated under strongly basic conditions. An acidic medium makes it possible to isolate the presumed intermediate monooxime, whereas oximation under neutral conditions furnishes 3,5-diphenylisoxazole.[14/58]

Heterochalcones follow essentially the same general oximation trends as do chalcones.

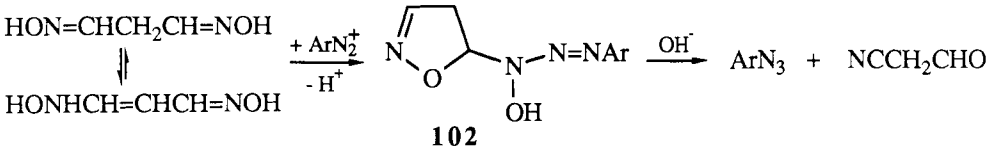
Some special cases deserve some further remarks. Glutacondialdehyde reacts with 2 mol of hydroxylamine in alkaline media, giving 2-isoxazolin-5-yl acetaldehyde oxime.[1/77] α,β-Ethylenic β-diketones of general structure **99** give different results according to the experimental conditions applied.[210/73,233/76,239/76,159/77] Thus the 2-isoxazoline oximes **100a** and **b** or the ketone **100c** are obtained as main products in pyridine (or acetic acid) or in sodium acetate solution, respectively. In acidic conditions, **99a** cyclized to the benzisoxazole derivative (**101**):




Different behavior in terms of pH dependence is also shown by aryl trichloropropenyl ketones; whereas an acidic medium causes cyclization to the six-membered 1,2-oxazin-6-ones, oximation in the presence of excess potassium hydroxide furnishes the expected 3-aryl-5-trichloromethyl-2-isoxazolines in good yields:[304/80]



An uncommon cyclization has been recorded for malondialdehyde dioxime, which gave with aryldiazonium salts the 2-isoxazolin-5-yl-triazene derivatives **102**,[7/69] whose structure is assured by the facile base-promoted decomposition to arylazides and cyanoacetaldehyde:

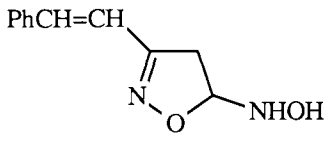



**102**

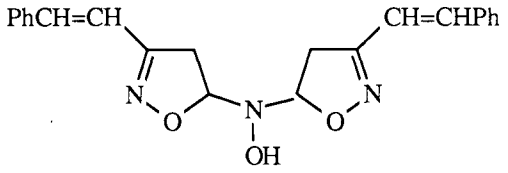
Cinnamoylacetaldehyde can be oximated to give one of the three products **103–105**, depending on experimental conditions. In many cases, heating in an acidic medium provokes aromatization to isoxazoles.[40/62] Analogous results are known in the oximation of 2-hydroxybenzoylacetaldehyde.[226/77]




**103**




**104**



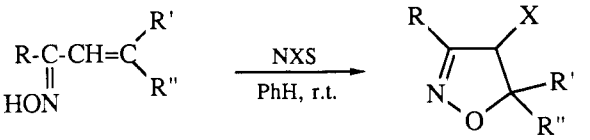

**105**

Doubly unsaturated ketones such as cinnamylideneacetophenone[10/09,7/12] react with hydroxylamine to give the isoxazolines expected. When both an ethylenic and an acetylenic bond are conjugated with a carbonyl group, as in cinnamoylphenylacetylene, 2 mol of hydroxylamine is added, but a preferred cyclization to an isoxazole derivative, carrying a hydroxylamino residue in the side chain, is observed.[6/45,3/68] It is worth noting that ethyl α-arylideneacetacetates, whose oximation could in principle give rise to either a 5-aryl-3-methyl-2-isoxazoline-4-carboxylate or a 3-methyl-4-arylidene-5-isoxazolinone, are reported to yield only the former type of compounds.[74/80]

It is important to stress here that α,β-ethylenic oximes can cyclize to 2-isoxazoline derivatives, in addition to the aforementioned treatment with sulfuric acid, also under different conditions. Thus a widely applicable method is thermolysis at 190–200°C;[183/75] care should be exerted here, since in turn the isoxazolines themselves decompose at higher temperatures (280–320°C)(see § 2.2.3.2, pp. 557–559).

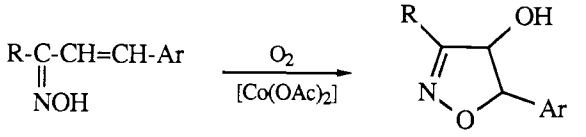
Action of iodine and potassium iodide on unsaturated oximes is known to yield isoxazoles directly (see § 1.3.6.4, p. 226). Sometimes, however, formation of an isoxazoline has been reported: for example, when *N*-bromo (or *N*-chloro)-

succinimide is employed as a cyclizing agent. Thus fair yields of 4-halo-2-isoxazolines are obtained by cyclization of $\beta,\beta$-disubstituted vinyl ketoximes:[167/77,173/80]




Cyclization occurs with chalcone oxime itself, but is particularly easy with di- or triaryl-substituted oximes. By contrast, $\alpha$-substituted chalcones yield isoxazoles directly.

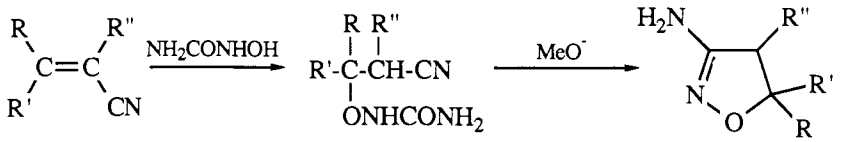
Very interesting is the oxidative cyclization of $\alpha,\beta$-ethylenic ketoximes under the catalytic effect of cobalt(II), copper(II), or manganese(II) acetate (or acetacetonate). The reaction takes place in methanol under an atmosphere of oxygen at room temperature or slightly above, and results in moderate-to-fair yields of 4-hydroxy-2-isoxazolines:[130/78]




Starting from dibenzalacetone oxime, cinnamonitrile and benzaldehyde are present as by-products in variable amounts. The oximation reaction of $\alpha,\beta$-ethylenic carboxylic esters, which could in principle lead to 3-hydroxy-2-isoxazolines, is examined in Part 2 of this work under the heading "isoxazolidin-3-ones," the stable form of 3-hydroxy-2-isoxazolines.

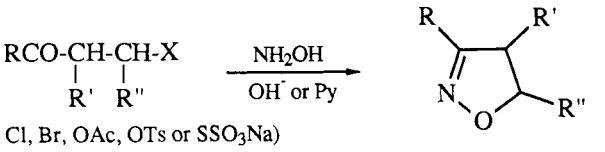
### b. Oximation of $\alpha,\beta$-Ethylenic Nitriles

The reaction of hydroxylamine with $\alpha,\beta$-ethylenic nitriles takes a different course from the analogous reaction on $\alpha,\beta$-unsaturated ketones: 2-isoxazolines are never isolated, except in the case of crotononitrile (and of allyl cyanide), where very low yields (5–10%) of 3-amino-5-methyl-2-isoxazoline could be evidenced if the oximation is carried out in the presence of an excess of sodium methoxide.[188/70,32/73] On the contrary, when crotononitrile (or allyl cyanide) is reacted with *N*-hydroxyurea in basic medium, 50–75% yields of 3-amino-5-methyl-2-isoxazoline are obtained.[188/70,32/73] The reaction has been generalized according to the following sequence, and the intermediacy of the 3-ureidoxynitrile has been assured by its isolation when the reaction is carried out in a neutral medium:[33/73]



### c. Oximation of β-Haloethylketones and Related Compounds

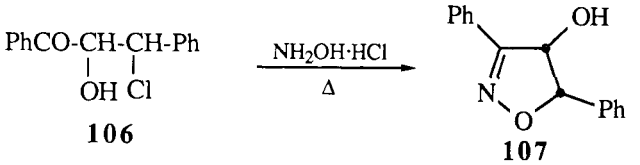
3,5-Diphenyl-2-isoxazoline, the first isoxazoline ever isolated, was obtained from β-chloro-β-phenylpropiophenone and hydroxylamine by heating in alkaline medium.[2/895] The reaction has been extended to other aromatic[1/32,8/33,24/54,42/58,304/80] and aliphatic[5/06,3B/08,118/65] β-chloro (or β-bromo)-ethyl ketones, according to the following general scheme:




(X = Cl, Br, OAc, OTs or $SSO_3Na$)

This oximation process seems to offer only a modest preparative horizon, in particular for the synthesis of 3-monosubstituted 2-isoxazolines.

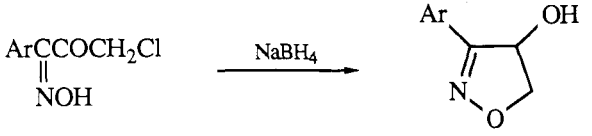
The reaction is usually carried out by heating in the presence of potassium hydroxide in excess, but pyridine has been preferred in some instances. As a by-product the bisoximinohydroxylamine of the type $[RC(=NOH)CH_2CH_2]NOH$ is often produced. Interestingly enough, cyclizing oximation of 3-chloro-1,2,3-triphenyl-propan-1-one has been demonstrated to give *cis*-3,4,5-triphenyl-2-isoxazoline stereoselectively,[154/69] although with unstated yields. A similar stereospecificity has been reported for the oximation of *erythro*-chlorohydrin (**106**), which gave a 59% yield of the *cis* derivative **107**:[250/78]



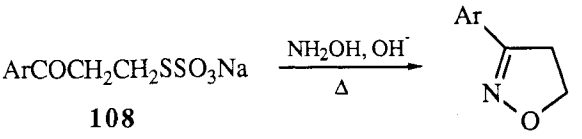

**106** **107**

The oximation of chalcone dibromides is a widely used synthetic approach to isoxazoles (see § 1.3.1.3, pp. 155–156), but use of pyridine as a reaction medium may sometimes lead to the formation of an isoxazoline as the main product.[102/70]

Treatment of 1-aryl-1-hydroxyimino-3-chloro-2-propanone with $NaBH_4$ afforded both reduction and base-promoted cyclization to 3-aryl-4-hydroxy-2-isoxazoline:[11/70]



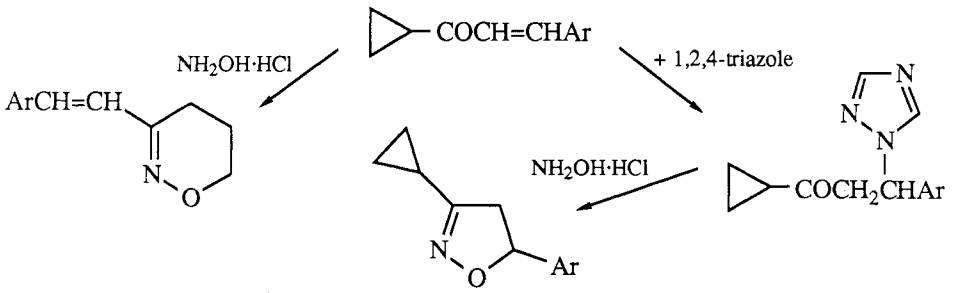
The β-acetoxy[8/33,1/54,24/54] or β-tosyloxy[99/66] derivative can also be used conveniently instead of the halogen compound. Oximation of thiosulfates **108** seems less straightforward and gives lower yields of 2-isoxazolines:[38/74]




**108**

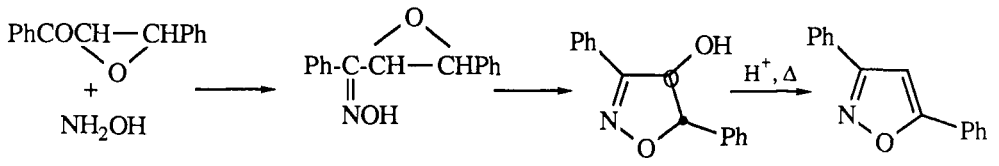
As expected from the low disposability of the ethoxy ion as a leaving group, β-ethoxypropiophenone oxime does not cyclize at all;[119/71] however, acetacetaldehyde dimethylacetal is claimed to react with hydroxylamine under proper acidic conditions to give the cyclized product (i.e., 3-methyl-5-methoxy-2-isoxazoline).[58/71] The cyclization of a β-hydroxyketoxime with trifluoroacetic acid has also been reported.[153/83]

Other leaving groups in the β-position can propitiate the ring closure during oximation of ketones. Interesting in this connection is the behavior of cyclopropyl styryl ketones: whereas direct oximation furnishes 5,6-dihydro-4*H*-1,2-oxazines,[6C/80] resort to the β-triazolyl derivative makes it possible to prepare 3-cyclopropyl-5-aryl-2-isoxazolines with a 46–50% yield.[8/81]

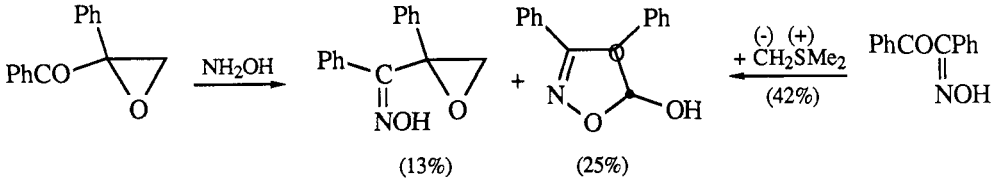



d. Oximation of Chalcone Epoxides and Related Compounds

The oximation reaction of chalcone epoxides is a known source of 3,5-diarylisoxazoles (see § 1.3.1.6, p. 173). In some instances, however, the intermediate chalcone oximes and/or the hydroxy-2-isoxazolines can be isolated.[7/16,11/61,119/64,250/78] The ease of their separation depends on the stability of the epoxide ring and on the propensity of the latter compounds t undergo dehydration (see also § 1.3.7.1c, pp. 231–232). For example, the relatively stable *trans*-3,5-diphenyl-4-hydroxy-2-isoxazoline[250/78] is prepared by treatment of chalcone epoxide with hydroxylamine hydrochloride in aqueous dioxane at 70°C. Dehydration to 3,5-diphenylisoxazole occurs only by heating in a mixture of glacial acetic acid and concentrated sulfuric acid:[11/61]

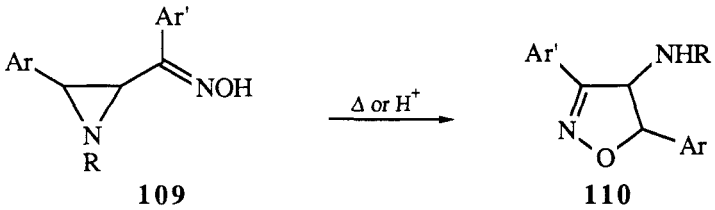


The regioisomer of chalcone epoxide (i.e., 1-phenyl-1-benzoylethylene oxide) reacts with hydroxylamine hydrochloride in boiling methanol–pyridine to give *trans*-3,4-diphenyl-5-hydroxy-2-isoxazoline, together with minor amounts of the oxime, easily cyclizable under mild basic conditions:[222/70,50/72]



The same 5-hydroxyisoxazoline has been achieved by treatment of benzil monoxime with dimethylsulfonium or triphenylarsonium ylide: the chalcone epoxide oximate anion is suggested as intermediate here, too. The condensation, which can be considered a [CCNO + C] process, has been extended to other α-nitroso ketones and to substituted ylides; the 2-isoxazolines are sometimes accompanied by the corresponding isoxazoles or methylisoxazolium salts.[50/72]

The aza analogues of chalcone epoxide oximes (i.e., the oximes of 2-aroyl-3-arylaziridines of general structure **109**) are claimed to cyclize thermally or by treatment with acids to 3,5-diaryl-4-amino-2-isoxazolines **110**:[130/74]



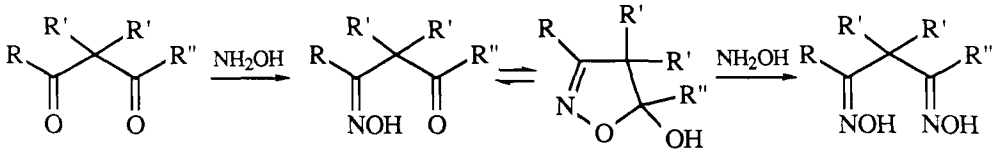
**109** **110**

## e. Oximation of β-Diketones

Oximation of α-unsubstituted or α-monosubstituted β-diketones is one of the most popular isoxazole syntheses. The presumed intermediates, diketone monoximes and 5-hydroxy-2-isoxazolines (i.e., 2-isoxazolin-5-ols), are usually too unstable under the normally adopted reaction parameters. Only a suitable substitution pattern or carefully controlled experimental conditions (room temperature, neutral or slightly alkaline medium) make it possible to isolate 5-

hydroxy-2-isoxazolines with moderate to good yields.[40/69,20/74,215/83] Ketoaldehydes behave similarly.

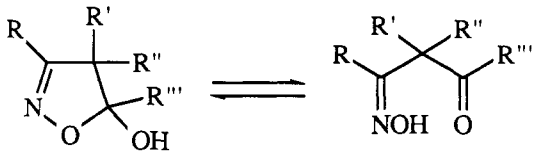
α,α-Disubstituted β-diketones cannot furnish isoxazoles, and the 4,4-disubstituted 2-isoxazolin-5-ols are the final products of the oximation reaction with an equimolar ratio of the reactants.[161/69,20/74,37B/81] Of course, the reaction here can be carried out without special precautions. The most common conditions involve use of hydroxylamine hydrochloride and sodium acetate or potassium carbonate in aqueous ethanol at room temperature or at reflux. When treated with an excess of hydroxylamine, both the β-diketone and the isoxazolinol can give the diketone dioxime,[19/66,161/69,24/80] possibly through the open-chain tautomer of the latter compound:




The cyclic tautomer can be stabilized by alkylation with acidic methanol or ethanol, which produces the corresponding 5-alkoxy-2-isoxazolines.[246/74,24/80] The ring-chain tautomerism of 2-isoxazolin-5-ols has been thoroughly studied by IR and NMR spectroscopies.[229/76] As far as the equilibrium between the two stereoisomeric monoximes is concerned, the monoxime carrying the hydroxyl *syn* to the carbonyl is largely predominant, owing possibly to intramolecular hydrogen bonding.

As shown in Table 2.14,[229/76] the cyclic tautomer is stabilized by increasing

TABLE 2.14



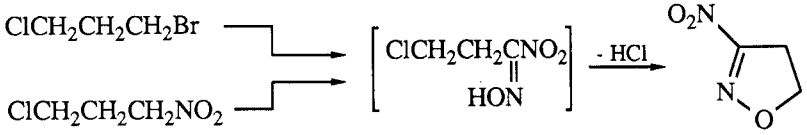

**A** **B**

| R | R' | R" | R"' | Ratio A: B |
|---|---|---|---|---|
| H | H | H | $CMe_3$ | 97:3 |
| H | H | H | Ph | 63:37 |
| H | H | H | *p*-$Me_2NC_6H_4$ | 0:100 |
| H | H | H | *p*-$MeOC_6H_4$ | 25:75 |
| H | H | H | *p*-$O_2NC_6H_4$ | 97:3 |
| Me | H | H | Ph | 92:8 |
| H | Me | H | Ph | 89:11 |
| H | Me | Me | Ph | 100:0 |
| Me | Me | Me | Ph | 100:0 |

substitution in positions 3, 4, and/or 5, and the effect of disubstitution in position 4 (the "gem" effect) appears particularly striking. The presence of a 5-aryl group decreases the reactivity of the neighboring carbonyl function and shifts the equilibrium toward the open-chain tautomer, especially when the aromatic ring carries an electron-releasing substituent.

### f. Nitrosation of Halopropane Derivatives

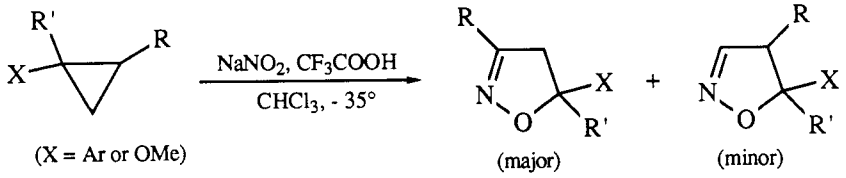
A simple and convenient procedure for synthesis of the highly reactive 3-nitro-2-isoxazoline involves treatment of 1-bromo-3-chloropropane or of 1-chloro-3-nitropropane with sodium nitrite in DMF[133/65] or, better, with a mixture of sodium and *n*-propyl nitrites in $Me_2SO$:[202/78]



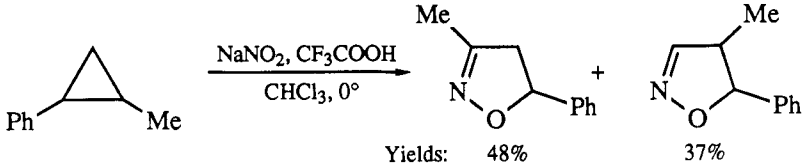

The reasonable intermediacy of the β-chlorosubstituted nitrolic acid leads this process back to the aforementioned cyclization of a β-haloethyl ketoxime.

### g. Nitrosation of Cyclopropane or Cyclopropene Derivatives

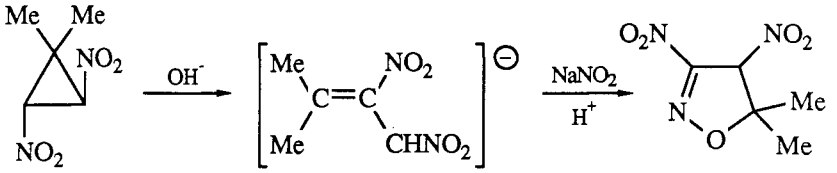
The nitrosation of suitably substituted cyclopropanes, best accomplished with sodium nitrite and trifluoroacetic acid, furnishes the 2-isoxazolines with moderate to good yields:[290/77,322/82,241/83,131/84,197/84]




The reaction is particularly easy when a carbocation-stabilizing group such as phenyl, *p*-tolyl, or methoxy becomes attached to the isoxazoline 5-position. This fact points toward a possible attack by the nitrosyl cation to give an intermediate open-chain carbocationoid species, which then recloses to the five-membered ring by loss of a proton. 1,2-Di- and 1,1,2-trisubstituted cyclopropanes usually yield a mixture of the two regioisomers, as exemplified here:[241/83]

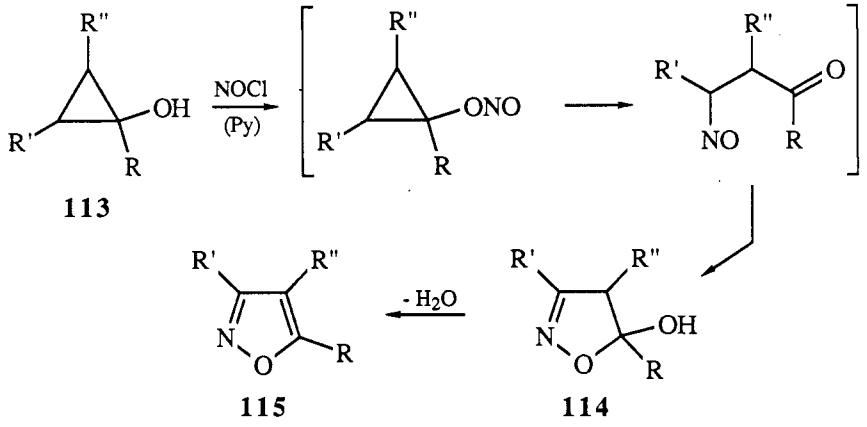


A synthesis of limited applicability seems to be transformation of the 1,2-dinitrocyclopropane derivative **111** into 3,4-dinitro-5,5-dimethyl-2-isoxazoline through the base-promoted ring cleavage to the dinitroanion **112** and subsequent nitrosation in an acidic medium:[108/66]



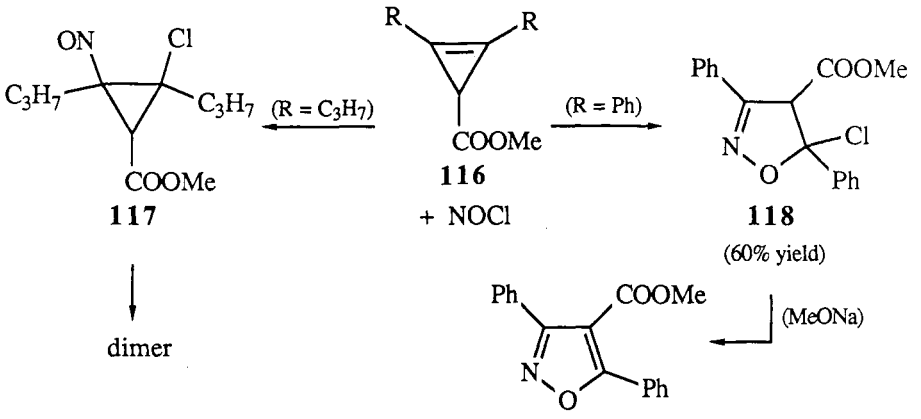

**111** **112**

Gaseous nitrosyl chloride easily reacts with cyclopropanols in the presence of pyridine to give the corresponding cyclopropyl nitrites. Contrary to their aliphatic or cycloalkyl counterparts of higher ring size, these nitrites are unstable and rearrange, even at low temperatures, to keto-nitroso compounds, eventually stabilized as dimers. Especially with 2-unsubstituted or 2-monosubstituted derivatives (**113**), further ring closure affords 5-hydroxy-2-isoxazoline (**114**), or if these, in turn, are not stable under the reaction conditions (e.g., when R″ = Me), the corresponding isoxazoles (**115**):[93/72]



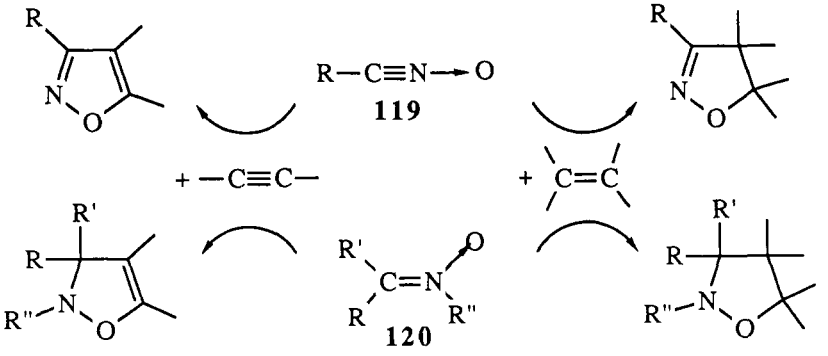

**113** **115** **114**

The products from the chloronitrosation of methyl 2,3-disubstituted cyclopropene-1-carboxylates (**116**) depend on the nature of the substituents. With alkyl substitution a chloronitroso derivative (**117**), stabilized as its dimer, is formed; on the contrary, when two phenyl groups are present, the chloronitrosocyclopropane is not stable, and gives rise to a presumably heterolytic cleavage of the C–C bond with subsequent reclosure to a 5-chloro-2-isoxazoline derivative **118**,[256/72,215B/73,252/73] identified through its base-promoted aromatization to isoxazole:




### 2.2.2.2 *[CNO + CC] Process: Cycloaddition of Nitrile Oxides and Their Precursors to Ethylenic Compounds*

The [3 + 2] cycloaddition pattern has grown in the last two decades into the most popular method for constructing five-membered heterocyclic rings of isoxazole and of its dihydro and tetrahydro derivatives. In its most general version, summarized in the following scheme, the CNO moiety is represented by the nitrile oxides **119** or by the nitrones **120**, and the CC moiety is a triple- or a double-bond compound. Isoxazoles, 2- or 4-isoxazolines, and isoxazolidines with the most different substitution pattern can thus be obtained:




These cycloaddition types fall into the wide and now well-documented field of the 1,3-dipolar cycloadditions, a class of reactions that has now gained for heterocyclic chemistry at least the same importance as diene synthesis long ago acquired in the homocyclic series.

Although some 1,3-dipoles (e.g., diazoalkanes and azides) have been known and used extensively since the end of the nineteenth century, it was not until the

1940s that Quilico[11/39,7/49,16/50] discovered the cycloaddition of nitrile oxides to triple- and double-bond compounds, giving start to a lively synthetic effort in the isoxazole and 2-isoxazoline field, as also testified by the first edition of the present volume.[77/62]

Soon afterward the cycloaddition was extended to nitrones by several groups of researchers,[43/59,48/60,49/60,56/60] thus opening the wide field of isoxazolidine chemistry. Nevertheless, it was only after Huisgen's extensive and thorough investigations that the 1,3-dipolar cycloaddition, whose first definition and illustration date back to 1960,[25/60,59/61] acquired the wide significance and generality that justifies its explosive development in the following period. The Woodward–Hoffmann rules[64B/65,227D/70] provide a brilliant theoretical background and insert the cycloadditions in the wider framework of pericyclic reactions. The frontier orbital theory[109B/68,35B/69,61B/70,1/71,26B/71,188B/71,7B/72,35B/72,36C/73,38C/74,207C/74,195B/75,195C/75,62B/76] allowed an easy understanding of the various reactivity and selectivity phenomena involved in this kind of reaction. Of particular relevance to the field of 1,3-dipolar cycloadditions is the work of Houk,[128B/73,128C/73,1/75,209B/77] who proposed a broad and convincing rationalization of the factors governing the reactivity and the different kinds of selectivity (peri, site, regio, and stereo selectivity). The steadily increasing importance of 1,3-dipolar cycloadditions from both synthetic and mechanistic viewpoints can be followed through Huisgen's masterful series of reviews[4B/63,4C/63,103B/64,150/68,184B/76,205/84] and some others.[227E/70,36B/73,240B/77,248B/77,265E/78]

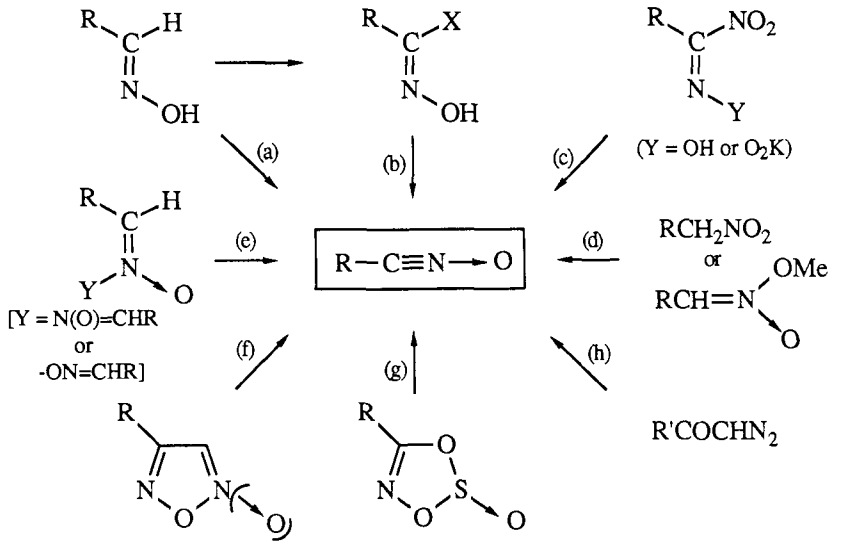
The present status of the research in this field is thoroughly illustrated in a recent comprehensive volume,[204/84] where two chapters are devoted to nitrile oxides[206/84] and nitrones,[207/84] respectively. In this chapter only the cycloaddition reaction of nitrile oxides with carbon–carbon double-bond compounds, leading to 2-isoxazolines, will be examined in detail. However, since nitrile oxides are usually not isolated because of their instability, but prepared *in situ* in the presence of the dipolarophile, the generation methods and the properties of this 1,3-dipole will be briefly discussed before examining more closely the mechanism and the synthetic potentiality of the cycloaddition itself. Nitrile oxides have been the objects of several reviews[60/65,67/66,60/70,199/70,227C/70,53/73,267/74,313/83] and of a comprehensive monograph.[193B/71]

### a. Generation of Nitrile Oxides

Although its mercury salt is by far the oldest known derivative of nitrile oxides, having been described as early as 1800,[1/800] the structure of fulminic acid gave rise to a controversy lasted more than 100 years and involving many of the most famous names in the history of organic chemistry, including Liebig, Wöhler, Kekulè, Griess, Nef, and Wieland. For a historical summary, see ref. 193B/71, pp. 3–7 and 33–43; see also refs. 8/73 and 8B/75. Fulminic acid was recognized as the parent term of the nitrile oxides series (i.e., as formonitrile oxide HCNO), far early in the twentieth century, both on a theoretical[7B/26] and an experimental[5/46] basis. The most intensely studied member of the series, benzonitrile oxide ($C_6H_5CNO$), was firstly generated by Gabriel in 1886[1/886] and

subsequently identified by Werner[4/894] and isolated in pure form by Wieland.[6/07] At present, about 60 aliphatic, cycloaliphatic, aromatic, and heterocyclic nitrile oxides have been isolated and characterized, having shown a more or less distinct stability, whereas a large number of other terms have only been generated *in situ* and intercepted with the reactant without isolation, owing to their instability.

With the exception of fulminic acid, whose chemistry presents specific peculiarities due to its acidic properties, the methods of generating nitrile oxides, summarized in Scheme 2.8, can be divided into two main groups: elimination reaction of substrates containing the moiety $>C=NOH$ (pathways a–d) and thermal decomposition of more complex molecules (pathways e–g).




**Scheme 2.8**

More precisely, nitrile oxides can be prepared by one of the following pathways:

(a) Direct dehydrogenation of aldoximes is usually achieved by treatment with potassium ferric cyanide or sodium hypobromite[88/65,113/67] or, preferably, with *N*-bromosuccinimide in the presence of a base.[150B/68,158/69] The latter procedure is particularly valuable in the preparation of stable nitrile oxides, which can thus be isolated in satisfactory to very good yields. *syn*-Aldoximes have also been dehydrogenated by action of lead tetracetate at $-78°C$,[171/66,200/68] but the method has limited synthetic value. A biphasic system, utilizing aqueous sodium hypochlorite as an oxidant in the presence of small amounts of triethylamine at room temperature, is reported to grant good yields of cycloadducts.[52B/79,266/82] In some special cases the use of nitrogen dioxide at 0°C has been alleged to be superior to other methods.[33/75,144/75] Silver carbonate on celite has also been utilized, but yields of cycloadducts are rather low.[177C/75]

(b) Dehydrohalogenation of hydroximoyl halides (usually chlorides), which are in turn most conveniently prepared from the corresponding aldoximes either by direct halogenation (the oldest method),[166B/68] or by treatment with aqueous sodium hypochlorite[34B/84] or with *N*-chlorosuccinimide.[202B/80,171/84] Sometimes, especially with unsaturated or aromatic aldoximes, polychlorination can occur, leading to mixtures or to undesirable products. In these cases the use of nitrosyl chloride as a chlorinating agent may be useful.[4/27,4B/33,36/68] Preferably, aliphatic hydroximoyl chlorides are prepared in ether at $-60°C$, through the intermediate chloronitrosoderivative and its dimer.[147/67] Aromatic hydroximoyl chlorides are fairly stable and can be stored for long periods of time (*Caution*: Some of them are very irritating and vesicant compounds!). When necessary, nitrile oxides are generated from them by the action of aqueous bases[4/894,6/07, 97/79,279/83] or of triethylamine in an inert solvent.[68B/61] This last method is by far the most popular when the nitrile oxide is generated *in situ* in the presence of the reactant. To avoid the easy dimerization of most members of the series [i.e., formation of furazan-*N*-oxides (furoxans)], slow addition of triethylamine to the solution of hydroximoyl chloride and of dipolarophile in stoichiometric amounts is recommended.[68B/61] The mechanism of the elimination reaction has been investigated thoroughly.[186B/78,44B/67,39B/68,151B/77,198/78]

The slow evolution of hydrogen chloride can also be carried out by thermal dissociation in boiling toluene;[40B/63,86/64,116/65,27/67] a radical mechanism has been put forward for this kind of reaction.[213B/72,253/74] This method of nitrile oxide formation is enjoying increasing favor and may well be the method of choice with less reactive dipolarophiles, provided that these can withstand the presence of hydrogen chloride.[3/85]

When the nitrile oxide is base sensitive, such as chloroformonitrile oxide (ClCNO) or benzenesulfonylcarbonitrile oxide ($PhSO_2CNO$), dehydrohalogenation is best effected by silver nitrate in THF solution, thus generating nitrile oxide *in situ* in the presence of excess dipolarophile.[163/81,285/82] In turn, BrCNO can profitably be generated by using solid sodium carbonate.

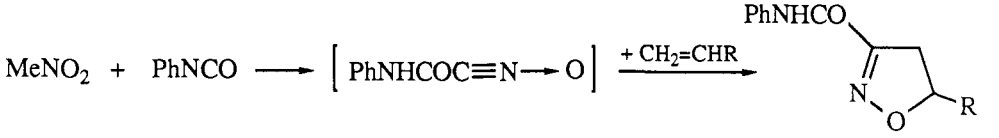
When hydroximoyl chloride is only weakly stable (e.g., in the case of acetonitrile oxide), it may be convenient to store it as its trimethylsilyl ether: the pertinent nitrile oxide can be generated whenever necessary under mild conditions (potassium fluoride in acetonitrile at room temperature).[206/83]

(c) The thermal elimination of nitrous acid from nitrolic acids occurs at room temperature or under gentle heating.[1/06,4/07] However, since nitrolic acids are usually obtained by nitrosation of primary nitroalkanes, which can yield nitrile oxides by simple dehydration, this method has been abandoned in favor of the following more direct route (pathway d).

Perhaps a higher preparative value should be attributed to the thermal dissociation of the potassium salts of *gem*-dinitroalkanes, which generate nitrile oxides *in situ* by heating in dimethylformamide at 80°C in the presence of the dipolarophile.[164C/75,184/76]

(d) The dehydration of nitroalkanes can be effected with the aid of several dehydrating agents, the most largely used being phenylisocyanate in the

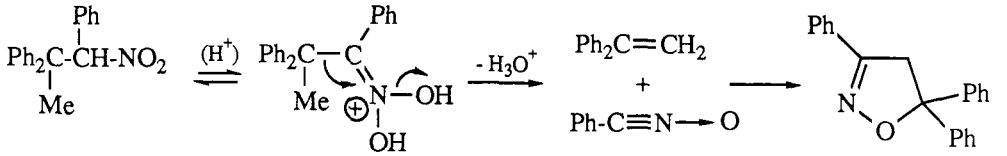
presence of catalytic amounts of triethylamine.[38B/59,37/60] All primary nitro derivatives, including arylnitromethanes, can be utilized in this general method, which is particularly popular for the generation of aliphatic nitrile oxides. Nevertheless, it should be noted that nitromethane leads to slightly anomalous results, giving rise to a preliminary addition to isocyanate, as the following equation shows:[16/63,28/73]




Other dehydrating agents used, preferably on the sodium salts, are phosphorus oxychloride,[64/63,204/73,148/79] diketene,[127B/68,114/69,125/69] acetyl chloride,[68/78,52/80,193/81] and acetic anhydride.[236/74,227/78,158/83] The former reagent should have the advantage that the inorganic by-products are easily removed by washing with water. Sometimes the dehydrating agent contemporarily acts as dipolarophile and the isoxazole ring derivative is obtained directly: this is the case with butoxyacetylene[16/60] or with isopropenyl acetate or α-acetoxystyrene (ketene-generating compounds).[174B/72]

The dehydration of nitro compounds and nitronate salts appears to involve the *aci*-nitro tautomer. Because of the known difficulty of generating the *aci* form under acidic conditions, conversion of nitro compounds to nitrile oxides by heating with *p*-toluenesulfonic acid in the presence of the dipolarophile, is limited to α-nitro ketones and to ethyl nitroacetate.[124/84] α-Nitrosulfones require more drastic conditions, and phenylnitromethane does not react at all as such, although moderate yields of cycloadducts are obtained by starting from its lithium salt. Nevertheless, isolated *aci*-phenylnitromethane cycloadds phenylacetylene in the presence of borontrifluoride etherate to give a 61% yield of 3,5-diphenylisoxazole;[3/58] for its simplicity, the reaction would deserve further attention.

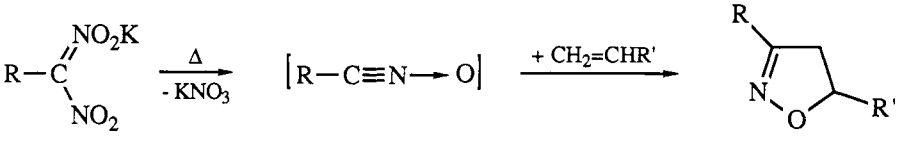
Nitrile oxides are also considered to be intermediates in the decomposition of nitro compounds into carboxylic acids and hydroxylamine by the action of hot concentrated mineral acids[145B/68,22B/71,17/75] and have been trapped in some instances by a dipolarophile. Even a suitably substituted secondary nitro compound, such as 1,2,2-triphenyl-1-nitropropane (and its sodium salts), decomposes into benzonitrile oxide and 1,1-diphenylethylene, as documented by the fact that besides 37% of the olefin, a 39% yield of 3,5,5-triphenyl-2-isoxazoline is formed:[17/75]

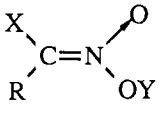


An intermediate nitrile oxide step is involved in the conversion of primary nitro compounds into nitriles by trimethylamine–sulfur dioxide complexes[205B/79] or by triphenylphosphine, without or in the presence of triethylamine.[38B/60,248/83,265/83,178/84]

Of preparative value seems the generation of nitrile oxides from methyl nitronates, which easily occurs under acidic conditions when the nitronic ester is substituted with electron-attracting groups. Thus the crude products obtained by O-methylation of α-nitro ketones, esters, or sulfones, produce the corresponding nitrile oxides by treatment with *p*-toluenesulfonic acid in refluxing methylene chloride.[124/84] Boron trifluoride catalysis is also effective with this type of compound.[229/74,124/84] Furthermore, thermal decomposition of the nitronic ester, derived from phenylsulfonylnitromethane and diazomethane, seems to be a convenient source of benzenesulfonylcarbonitrile oxide.[163/81,46/84]

Base-promoted decomposition of methyl nitronic esters, derived from the O-methylation of the nitroalkanes with diazomethane, has occasionally been dealt with as a nitrile oxide source.[30B/66] The known instability of nitronic esters has prevented a larger utilization of this method. Thermal decomposition of potassium salts of 1,1-dinitroalkanes at 80°C in aprotic polar solvents in the presence of olefins results in moderate to good yields of 2-isoxazolines;[184/76] the intermediacy of the nitrile oxides has been deduced:





**121 a** X = Br; Y = Na
**b** X = H; Y = COMe

By contrast, thermolysis of aryldinitromethane silver salts at 100°C in the presence of electron-rich olefins mainly gives 2-isoxazoline-*N*-oxides, along with minor amounts of 2-isoxazolines, whereas only isoxazoles or 2-isoxazolines in low yields were obtained when the reaction is carried out in the presence of alkynes or of electron-poor alkenes, respectively.[203/80]

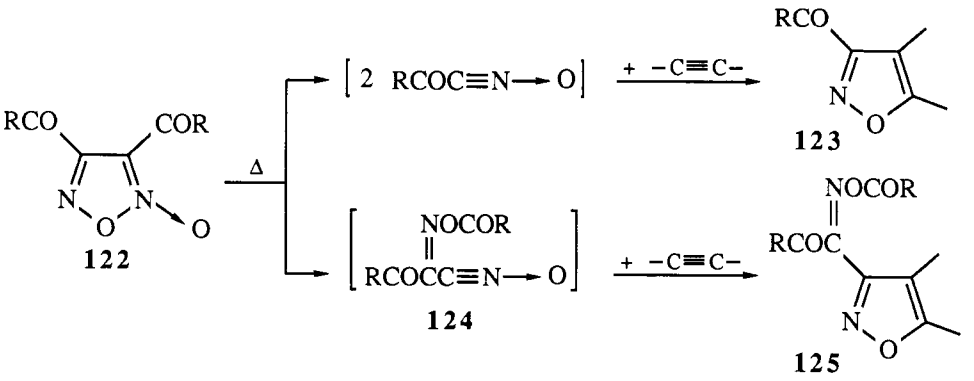
Finally, it is interesting to note that the thermal decomposition of arylbromonitromethane salts (**121a**), carried out in the presence of unsaturated systems, gives 15–35% yields of isoxazoles (or 2-isoxazolines).[186/75] However, because of the absence of furoxans, the intermediacy of a nitrile oxide has been questioned, and a direct cycloaddition of the nitrone-like structure **121a** to the dipolarophile with subsequent elimination of sodium hypobromite has been alleged. A similar proposal has been put forward for the reaction of nitroalkanes with acetic anhydride, which should initially form **121b**.

(e)–(g) The thermal methods of generating nitrile oxides are far less utilized than the ones reported above, chiefly because of the less easily available starting materials. Moreover, nitrile oxides are thermally unstable and isomerize more or less rapidly to isocyanate (see further below) upon heating. Thus generation *in situ* in the presence of an active dipolarophile (usually in large excess) is unavoidable. Nevertheless, in special cases these methods may become convenient, especially when a neutral medium is essential for the cycloaddition step, for example, if the dipolarophile is acid or base sensitive.

The thermal decomposition of 3,4-disubstituted furazan-*N*-oxides (furoxans), although previously known to occur through the nitrile oxides,[1/886.249/73] has assumed synthetic significance only recently. Use of the dipolarophile as a solvent and heating to 200–260°C were found to assure high yields in cycloadducts,[145/76.108/79] and flash-vacuum pyrolysis has made it possible to isolate even the unstable aliphatic nitrile oxides in a pure state and to use low-boiling partners in the subsequent cycloaddition.[221/79]

The use of boiling *o*-dichlorobenzene as a solvent during the generation of nitrile oxides from furoxans seems to furnish lower yields.[311/82.312/82] Lower temperatures are required for the ring opening of strained condensed furoxans.[138/72.181B/78]

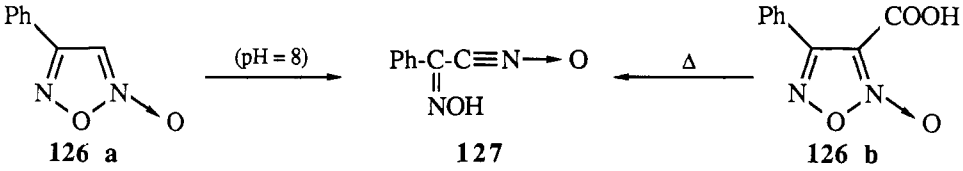
The highly reactive acyl-[149/81] and benzenesulfonyl-[235/81] carbonitrile oxides have been prepared *in situ* by heating the corresponding 3,4-disubstituted furazan-*N*-oxides in refluxing toluene or xylene, respectively. As also shown by mass spectrometry, cycloreversion of diacylfuroxans is particularly easy. An interesting duality of behavior is here shown by the 3,4-diacylfuroxans **122**:[149/81]




When R is a sterically very large group, the expected bisection of the molecule occurs at last to give the 3-acylisoxazole **123**, whereas with the 3,4-dibenzoyl derivative or other less encumbering terms, the N–O scission is accompanied by an acyl transfer to give an isomeric nitrile oxide (**124**) which cycloadds to yield an unexpected isoxazole derivative (**125**). The formation of the latter type of compound had previously been observed by other authors,[235/72] who gave a different mechanistic interpretation however.

Recently, the thermal dissociation of bis[(trimethylsilyloxy)prop-2-yl] furoxan has been found convenient to force the *in situ*-generated nitrile oxide to react even with poor dipolarophiles, such as 1,2-di- or tri-substituted olefins.[4/85]

The functionalized nitrile oxide **127** can be prepared *in situ* either by slight alkaline treatment of the monosubstituted furazan-*N*-oxide **126a**[168B/72] or by thermolysis of the furazan-monocarboxylic acid **126b**:[246B/74]



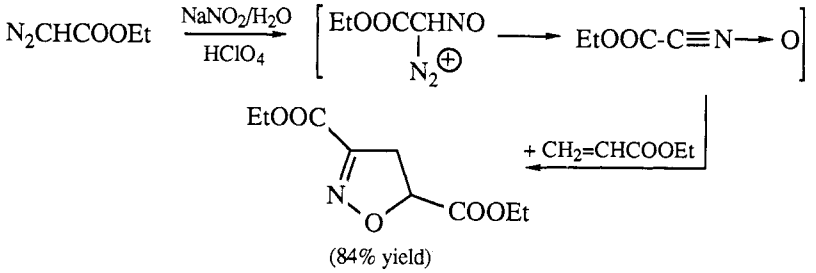

**126 a** **127** **126 b**

3,4-Disubstituted 1,2,5-oxadiazoles (i.e., furazans) have long been known to decompose either thermally[1B/888,1/890] or photolytically[49/68,31C/69] into nitrile and nitrile oxide. The fragmentation has acquired some synthetic value either with benzofurazan[147/75] or with strained polycondensed 1,2,5-oxadiazoles of the thianorbornane,[33B/79] or thieno[41/80,117/80] series, where it occurs under fairly mild conditions.

The thermolysis of the cyclic sulfite esters (1,3,2,4-dioxathiazole-2-oxides, pathway g) has also been shown to proceed at 100–110°C through a nitrile oxide intermediate, since moderate yields of cycloadducts are obtained if a dipolarophile is present.[186/76] In this case as well as with furoxans, in the absence of the dipolarophile, excellent yields of isocyanates from isomerization of the nitrile oxides are obtained.[159B/70,145/76,186/76,11B/77,37B/80]

The so-called "aldoxime dihydromers," having the structure ArCH=N–O–N)=CHAr and/or ArCH=N(O)–N(O)=CHAr, decompose under relatively mild conditions (refluxing chloroform for 3 h) in 1 mol of nitrile oxide and 1 mol of aldoxime; in the presence of a triple- or a double-bond compound, an isoxazole or a 2-isoxazoline is obtained, respectively, although with lower yields than with the normal elimination methods.[216/73]

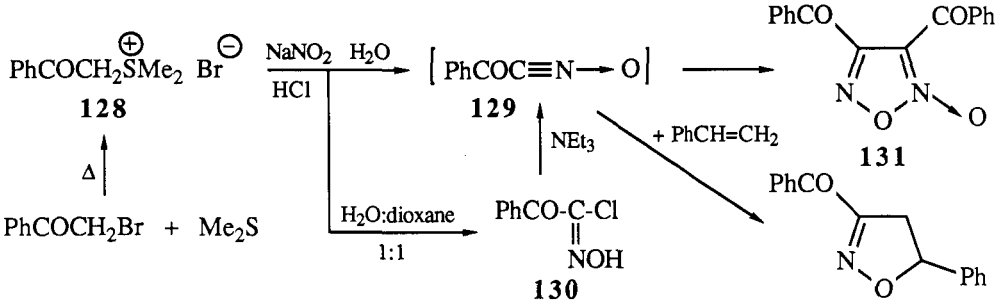
(h) The nitrosation of α-diazocarbonyl derivatives in the presence of perchloric acid is a promising method for generation *in situ* of α-carbonylnitrile oxides, starting from readily available materials; for example:[101/73]




(84% yield)

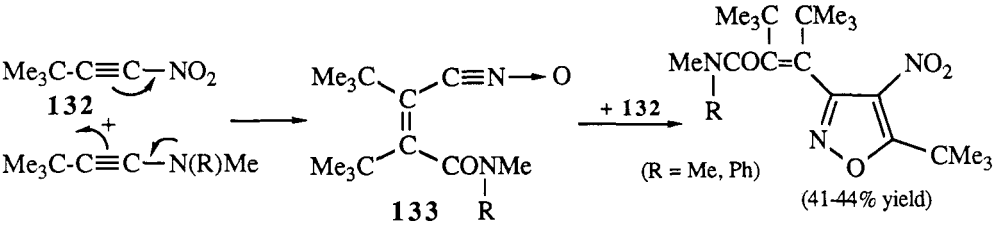
The reaction of α-diazosulfones with nitrosyl chloride seems less satisfactory for preparative purposes, since hydroximoyl chlorides are first obtained in admixture with furoxans (from dimerization of the intermediate nitrile oxide) and with α-chlorosulfones.[227/74]

A related method of generating acylformonitrile oxides (acyl fulmides) relies on the nitrosation of dimethyl phenacylsulfonium bromide (**128**) in aqueous media: the formation of benzoylformonitrile oxide (**129**) is testified by the formation of 3,4-dibenzoylfuroxan (**131**) in 76% yield. Nevertheless, it seems more convenient to isolate benzoylformohydroximoyl chloride (**130**) and then to dehydrohalogenate it in the usual manner to give the nitrile oxide **129**, which can be trapped *in situ* by the dipolarophile:[19/71]




The method would deserve a generalization, since the sulfonium salts are easily available from the α-bromoketones, whereas aroyl (and the simpler acyl)-formonitrile oxides are not accessible, as already mentioned above, through thermolysis of 3,4-diacylfuroxans.

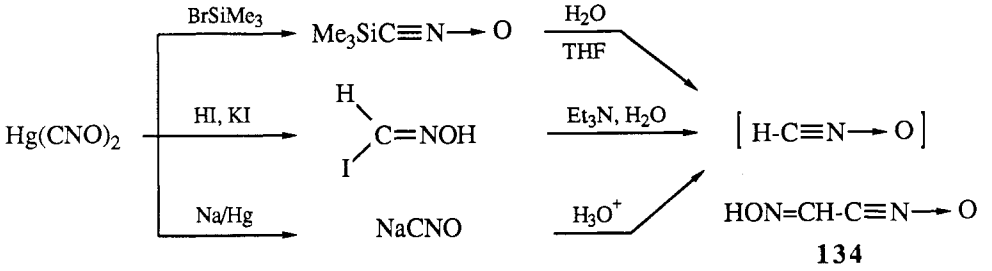
Other miscellaneous methods of generating nitrile oxides: the rather peculiar nitrile oxide **133** has been obtained by reaction of the nitroacetylene **132** with an ynamine;[4/70] reaction with cyclic enamines is on the contrary completely different and leads to nitrocycloalkadiene derivatives:




Nitrile oxides have been trapped in low yields during the photochemical degradation of some β-substituted β-nitrostyrenes.[189/75,9/84]

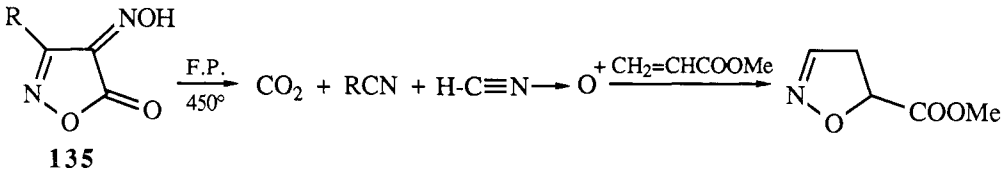
The preparation of the parent term of the series (i.e., fulminic acid or formonitrile oxide) deserves a special mention. The most convenient method of generating it *in situ* seems at present to be the mild neutral hydrolysis of the

relatively stable trimethylsilanecarbonitrile oxide,[295/83] which in turn arises from mercuric fulminate and bromotrimethylsilane.[268/82] The dehydrohalogenation of formohydroximoyl iodide, easily prepared from the same fulminate by treatment with hydroiodic acid and potassium iodide, has also been used.[3/67,28/73] The latter method had replaced the older formation of fulminic acid in aqueous solution through the sodium salt;[11/39] in this case, formation of the dimer **134** usually cannot be avoided:[5/49,7/49]




**134**

Furthermore, formonitrile oxide has successfully been isolated in pure form by trapping in liquid nitrogen the dissociation products of the flash pyrolysis of isonitrosophenylisoxazolinone (**135**).[9/79] Excellent yields of 3-unsubstituted 2-isoxazolines or isoxazoles can thus be achieved; for example:



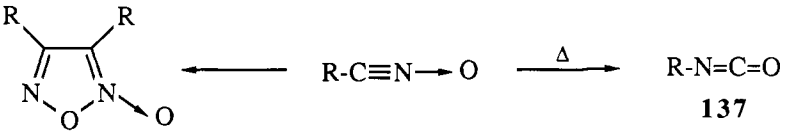

**135**

### b. General Properties of Nitrile Oxides

Nitrile oxides are thermally more or less unstable and highly reactive compounds. Therefore, the 1,3-dipolar cycloaddition reaction often enters in competition with other reactions: dimerization (and polymerization), isomerization, and 1,3-addition. For a complete analysis of this kind of reactivity, reference is made to the specialized literature.[193B/71,313/83,206/84] Only a few factors to be kept in mind before undertaking an isoxazole or a 2-isoxazoline synthesis are summarized here.

In a neutral medium nitrile oxides dimerize to 3,4-disubstituted furazan-*N*-oxides (**136**) (furoxans); the process is very rapid even at room temperature for aliphatic or acyl nitrile oxides, whereas aromatic terms are moderately stable at room temperature, becoming more resistant in the presence of electron-donating or sterically encumbering substituents. Heating or base catalysis increase the process rate. *o,o'*-Disubstituted benzonitrile oxides do not dimerize at all or only

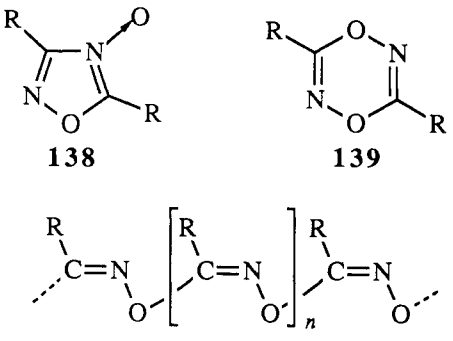
very slowly on heating at 80–90°C; quick heating at 110–140°C causes isomerization to isocyanates (**137**). With other aromatic nitrile oxides the isomerization is always in competition with the dimerization:



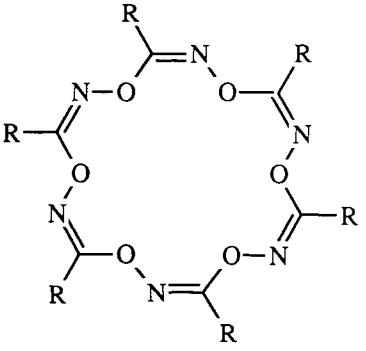

**136** **137**

Luckily enough, when the nitrile oxide is prepared *in situ* at temperatures higher than that of isomerization but in the presence of the dipolarophile, the rate of the 1,3-dipolar cycloaddition is always faster than that of the isomerization to isocyanates.[145/76] Similarly, the dimerization reaction is usually suppressed in the presence of an effective dipolarophile; only when weak dipolarophiles are employed, it can enter in competition or even become the unique fate of the nitrile oxide.

In the presence of some organic bases, different processes may prevail, and other products can be obtained, such as 1,2,4-oxadiazole-4-oxides (**138**), 1,4,2,5-dioxadiazines (**139**), cyclic oligomers such as the hexamer **140**, or polymeric material of general structure **141**.



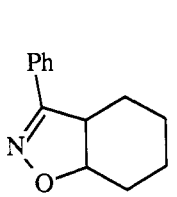

**138** **139** **141**



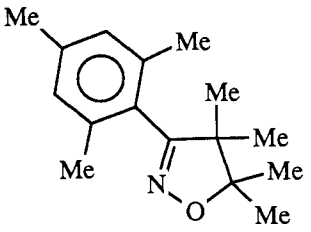

**140**

Active dipolarophiles compete successfully with the dimerization process, but when dipolarophiles of low reactivity have to be employed in the cycloaddition step, the formation of furoxan can either be suppressed by turning to a stable nitrile oxide or minimized by using the "high dilution technique," that is, by dropping triethylamine, for example, very slowly into a dilute solution of hydroximoyl chloride and dipolarophile (possibly present in large excess). Thus benzonitrile oxide in ethereal solution does not react with equimolecular quantities of cyclohexene,[68/61] whereas the cycloadduct **142** is regularly obtained if the

nitrile oxide is generated *in situ*.[11/65] Even this last method fails with the highly unreactive dipolarophile tetramethylethylene; nevertheless, a 18% yield of 3-mesityl-4,4,5,5-tetramethyl-2-isoxazoline **143** is obtained when the alkene is refluxed for several days with the stable 2,4,6-trimethylbenzonitrile oxide.[148/68]

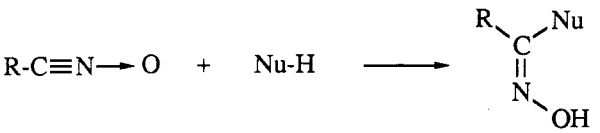



**142**




**143**

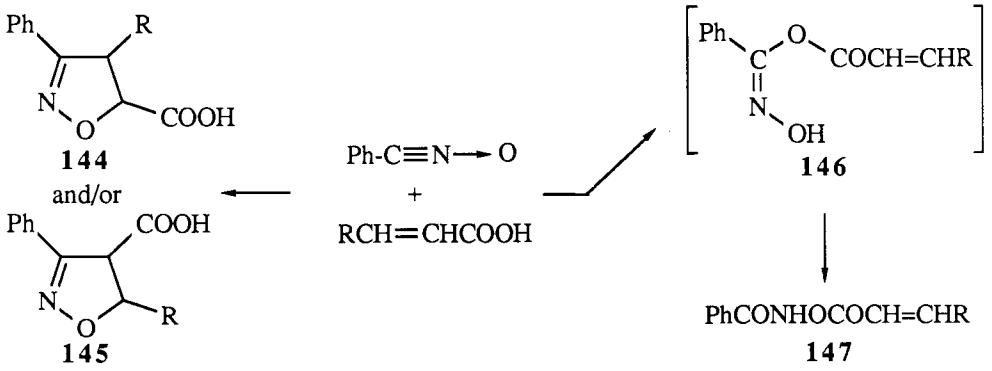
Nitrile oxides are known to react with a large variety of nucleophiles as well as with several acidic compounds to yield open-chain 1,3-addition products, where the nucleophilic atom of the reactant is bonded to the carbon atom of the 1,3-dipole and the electrophilic end (usually a proton) to the oxygen:




In all cases hitherto studied from this point of view, the addition has proved to be kinetically controlled and 100% stereoselective, yielding only the *Z*-isomer of the adduct.

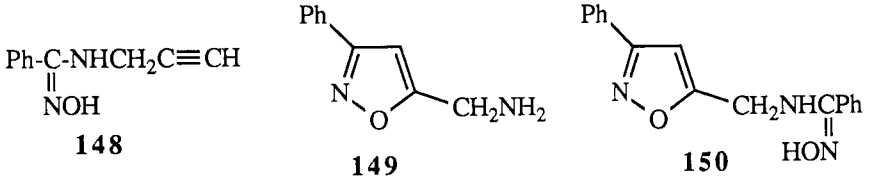
Among the commonest reactive molecules it is worthwhile to mention water and alcohols (only under acidic or basic catalysis), phenols (or better phenoxides), carboxylic acids, sulfides, ammonia and amines, azides, cyanides and thiocyanates, carbanions, and nucleophilic radicals. The reactivity of triethylamine, especially when used in excess, on nitrile oxides explains the frequent formation of 1,2,4-oxadiazole derivatives as by-products of the cycloaddition reaction with less active dipolarophiles.[309/83]

When the addition partner's molecule includes a double or a triple bond, competition between the 1,3-addition and 1,3-dipolar cycloaddition can arise, and one or the other functionality may prevail, depending on the nature of the substituents. Thus the reaction of $\alpha,\beta$-unsaturated carboxylic acids with benzonitrile oxide follows two distinct pathways:[50/59]




Acrylic acid,[50/59.27/73] maleic acid,[12/55] and the nitrocinnamic acids,[9/53] which possess a highly dipolarophilic double bond, give only the 2-isoxazoline carboxylic acids **144** and **145**, respectively. Crotonic acid,[50/59] *cis*-cinnamic acid,[51/59] and some β-heteroarylacrylic acids, where the dipolarophilic activity is greatly reduced, react only with their free carboxylic group to give, after an acyl transfer in the primary adduct **146**, the aroyl benzhydroxamate **147**. *Trans*-cinnamic acid[27/73.51/59] and its *p*-chloro derivative[50/59] give rise to a mixture of the two adducts.

Reaction of propargylamine with benzonitrile oxide yields a mixture of all three possible products, the two monoadducts **148** and **149** and the bis adduct **150**. The nucleophilic reactivity of the amino group is higher than the dipolarophilic activity of the triple bond.[51/66]

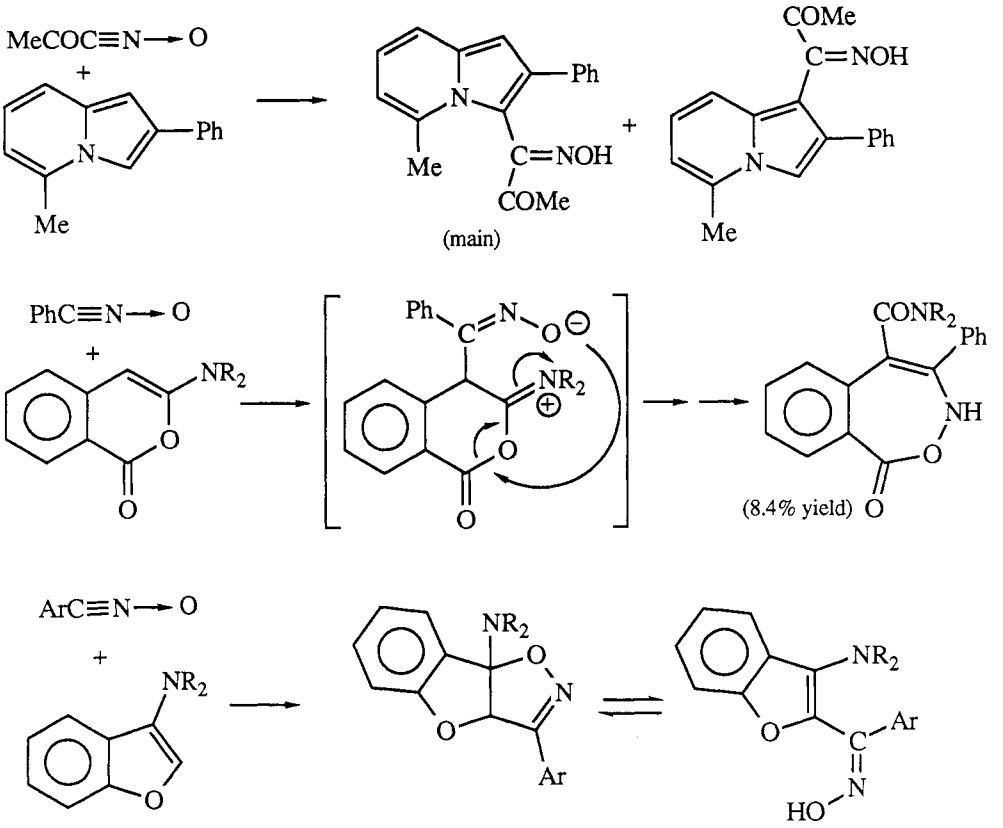



4-Amino-3-methyl-5-styrylisoxazole adds nitrile oxides to the amino group only, yielding the corresponding amidoxime.[83/81] In other cases the unsaturated bond itself can act as a nucleophile. It is well known that arylacetylenes react in neutral medium with nitrile oxides to give isoxazoles along with variable amounts of acetylenic oximes, arising from an independent and concurrent 1,3-addition process (see § 1.3.2.1, pp. 183–184).

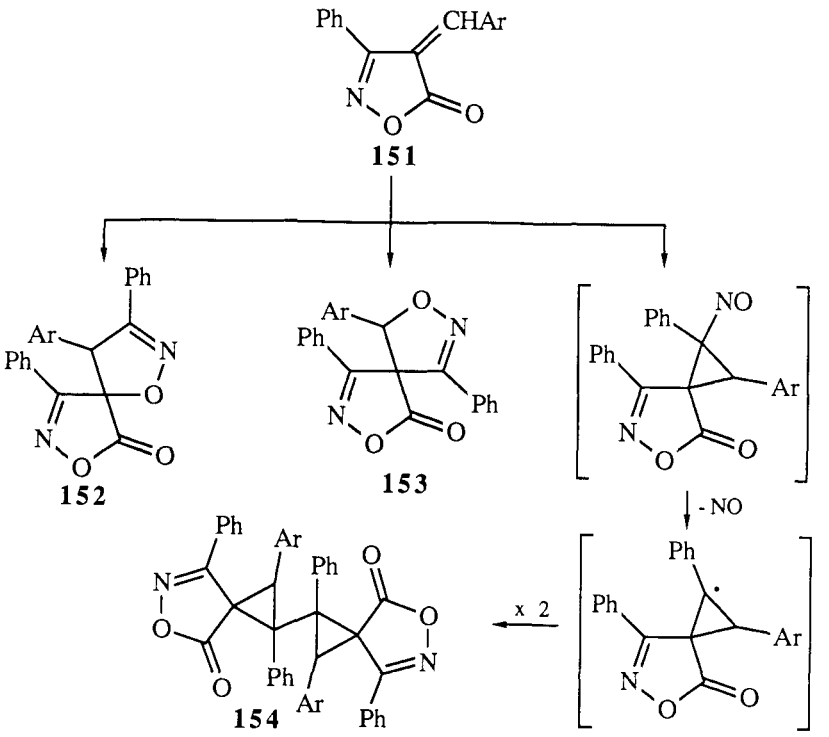
Ethylenic bonds have a higher dipolarophilic activity and do not give 1,3-addition products unless special favorable conditions are present. Thus the presence of 1% phenylfurylketoxime besides the two regioisomeric cycloadducts in the reaction of benzonitrile oxide with furan has been attributed to the tendency of the heteroaromatic ring to retain its resonance energy.[189/76] Analo-

gous results are known for pyrrole derivatives,[212/84] whereas thiophene and its benzo derivative react, although very slowly, only as dipolarophiles (see Part 2 of this work). Benzimidazole reacts on the contrary with its nucleophilic nitrogen atom to give the oxime.[98B/77]

Enamines are a borderline case: they usually behave as active dipolarophiles, yielding the expected 5-amino-2-isoxazolines as result of a normal 1,3-dipolar cycloaddition (see below). However, in some instances different products are obtained, arising either from an zwitterionic intermediate or from an easy ring open-chain tautomerism of the primarily formed cycloadduct, as the following examples show[213B/74,157B/80] (see also ref. 193B/71, p. 168):




A further variation of standard 1,3-dipolar cycloaddition occurs in the reaction of benzonitrile oxide with the sterically encumbered benzalisoxazolinones of structure **151**: besides the expected spiroisoxazolines **152** and **153**, a dimeric cyclopropane derivative **154** is obtained[231/73] whose percentage increases with increasing temperature and even becomes the main product when the 2,4,6-trimethylbenzalisoxazolinone is used as starting material (Scheme 2.9).[8B/74]




**Scheme 2.9**

Possibly because of the low dipolarophilic activity of **151**, either a two-step process through a zwitterionic or a diradical intermediate or a concerted 1,1-cycloaddition through the carbene form Ph–C–N=O of the nitrile oxide (see below) enters in competition with the usual [3 + 2] pattern of the 1,3-dipolar cycloaddition.

It should also be emphasized that CC unsaturated bonds are not the only dipolarophilic bonds: several other unsaturations (e.g., C=N, C≡N, C=O, C=S, and other X=Y bonds) are also reactive. When two or more different kinds of unsaturations are present in the molecule, competition may arise and other types of heterocyclic rings can be formed instead of an isoxazole or a 2-isoxazoline derivative. This type of competition is discussed below in examining site selectivity.

c. Mechanism of Cycloaddition Reaction: Reactivity and Selectivity

1,3-Dipolar cycloadditions are considered, according to Woodward–Hoffmann terminology, as [$\pi$4s + $\pi$2s] "symmetry-allowed," one-step concerted reactions; that is, the two new $\sigma$-bonds C–C and O–C between the nitrile oxide and the double (or triple) bond are formed simultaneously, also not

necessarily in a synchronous manner, at the expense of two π-bonds of the reagents.

The concertedness of the cycloaddition is supported mainly by the following factors:[184B/76,205/84] (1) the strict *cis* stereospecificity observed in all cycloadditions with *cis-trans* isomeric dipolarophiles; (2) the feeble influence of solvent polarity on the reaction rate; (3) the small $\rho$ value in Hammett kinetic studies; and (4) the activation parameters, which show moderate activation enthalpies and strongly negative entropies.

The original two-plane parallel approach proposed by Huisgen is not supported by theoretical calculations on the simplest cycloadditions of fulminic acid to acetylene[90C/75,12/76,153/78,140/80,57B/84] or to ethylene,[90C/75,12/76] which rather suggest a coplanarity of the atoms involved in the transition state. As far as the concertedness of the reaction is concerned, it has been pointed out[115B/77] that *ab initio* methods (STO-3G and 4-31G) as well as semiempirical methods, including overlap (EH), tend to favor a more symmetrical two-bond transition state, whereas semiempirical calculations, neglecting overlap (CNDO/2, MINDO/2, MINDO/3, MNDDO), lead to a more or less highly unsymmetrical one-bond geometry for the transition state.

A two-step diradical mechanism has been proposed for 1,3-dipolar cycloadditions[240B/77] and has also found support in recent *ab initio* calculations.[132/83] However, qualitative valence-bond theory considerations seem to point toward a concerted diradical mechanism.[253B/78,57/84] Moreover, independent synthesis of some 1,5-diradicals[98C/74] showed that their intermediacy in 1,3-dipolar cycloadditions should lead to loss of stereospecificity and to formation of 1,1-cycloaddition products.

Application of the simplest perturbation theory, which only takes into account the interactions between the frontier orbitals (HOMO–LUMO interactions) of the two reagents, has made it possible to interpret most phenomena of reactivity and of selectivities encountered in the cycloadditions of nitrile oxides to double or triple CC bond compounds. In Sustmann's simplified scheme (see Fig. 2.1),[188B/71,7B/72,207C/74] 1,3-dipoles are classified in three types, according to the prevailing HOMO–LUMO interaction (i.e., the one with the smallest HO–LU distance). Nitrile oxides, being relatively electron-poor dipoles, are usually

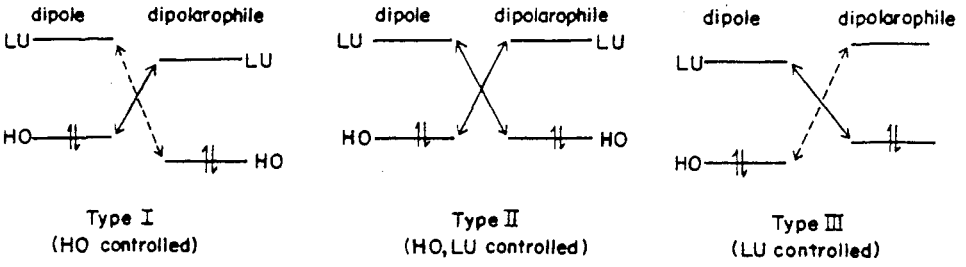



**Figure 2.1.** Sustmann's classification of 1,3-dipolar cycloadditions.[188B/71,7B/72,207C/74]

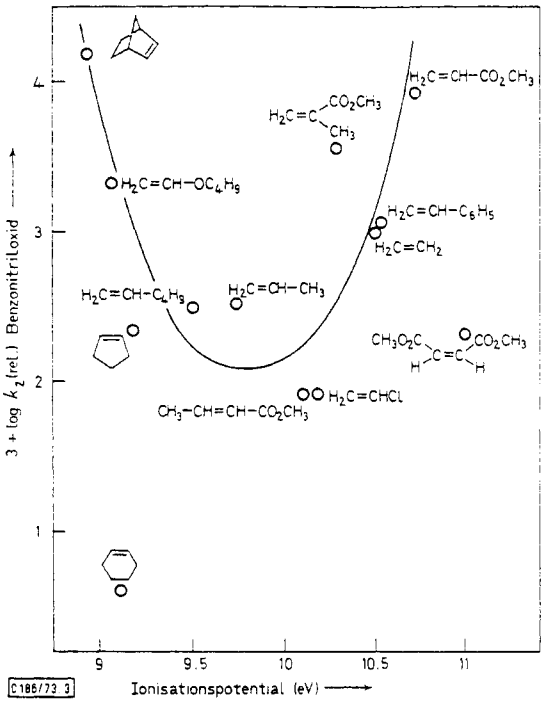



**Figure 2.2**. Reaction rate constants versus dipolarophiles ionization potentials (IPs) in cycloaddition with benzonitrile oxide.[28B/73]

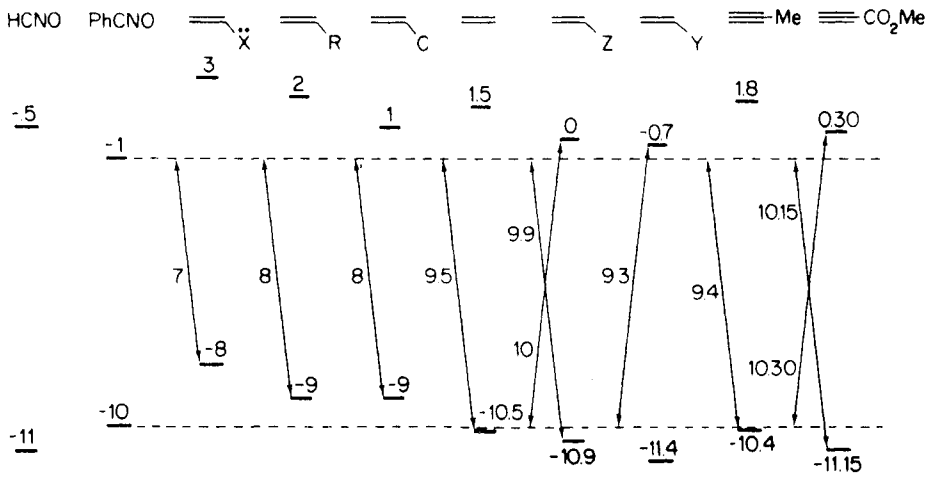



**Figure 2.3**. Frontier orbital energies for nitrile oxides and dipolarophiles:[313/83] X = OR, $NR_2$; R = alkyl; C = C=C, Ph; Z = COR, $CO_2R$, X, CN; Y = $NO_2$, $SO_2R$.

TABLE 2.15 [28B/73]

| | $K_{rel}$ ($K_{ethylene}$ = 1.00) | | $K_{rel}$ |
|---|---|---|---|
| β-Pyrrolidinostyrene | 25.2 | 1,1-Diphenylenethylene | 0.40 |
| Norbornene | 15.3 | Acetylene | 0.40 |
| Methyl acrylate | 8.3 | Propylene | 0.32 |
| Dimethyl fumarate | 6.1 | Cyclopentene | 0.21 |
| Methyl methacrylate | 3.6 | Dimethyl maleate | 0.21 |
| Dimethyl acetylenedicarboxylate | 3.1 | Phenylacetylene | 0.112 |
| Butyl vinyl ether | 2.1 | Methyl *trans*-crotonate | 0.082 |
| Methyl 3-pyrrolidinoacrylate | 1.88 | Methyl *trans*-cinnamate | 0.071 |
| Methyl propiolate | 1.24 | 1-Hexyne | 0.066 |
| Styrene | 1.15 | Methyl tetrolate | 0.030 |
| Ethylene | 1.00 | *trans*-Stilbene | 0.023 |
| Cyclopentadiene | 0.44 | Methyl 3,3-dimethylacrylate | 0.0062 |
| | | Cyclohexene | 0.0025 |

considered to fall into type II and to undergo dipole HO,LU control. Accordingly, both electron-withdrawing and electron-releasing substituents on the dipolarophile increase the reaction rate. A rather ill-defined U-shaped curve (see Fig. 2.2)[28B/73] is obtained by plotting log $k_2$ versus the ionization potentials of various dipolarophiles (which in a simplified approach can be taken as a measure of the HOMO energies). Of course, other effects not accounted for in the simple FMO treatment (e.g., steric effects and bond deformations) are responsible for the scattering of points.

Figure 2.3 shows the approximated frontier orbital (FMO) energies for benzonitrile oxide and several classes of dipolarophiles.[128B/73] It is evident from this estimation that with electron-rich and conjugated dipolarophiles (which have the HOMO energy raised) and in a highest degree, with more electron-poor nitrile oxides, such as benzenesulfonylcarbonitrile oxide and benzoyl formonitrile oxide, where LUMO (dipole) energy is strongly decreased, the cycloaddition will tend to fall in type III [i.e., under LU(dipole) control]. This will have consequences on both the reactivity and the selectivities of the reaction.

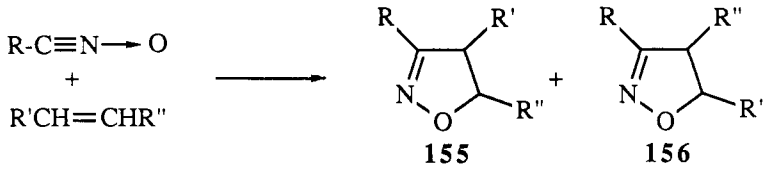
Table 2.15 summarizes the relative reactivities of some typical dipolarophiles toward benzonitrile oxide.[28B/73] The following general trends must be pointed out:

1. The *n*- and π-conjugating substituents on the double- or triple-bonded dipolarophile increase the rate of the cycloaddition: β-pyrrolidinostyrene reacts 22 times faster than styrene, butyl vinyl ether 6.6 times faster than propylene, styrene 3.6 times faster than propylene, and cyclopentadiene twice than cyclopentene.
2. A sharp increase in reactivity is also observed for conjugative electron-withdrawing groups, such as COOR and COR: the rate increase is 8.3 for methyl acrylate versus ethylene and 11.2 for methyl methacrylate, respectively, relative to propylene. In other cases (e.g., with 1,1-diphenylethylene), a decrease in reactivity can be ascribed to steric hindrance to conjugation.

3. A general rate retardation is observed for 1,2-disubstitution that is somewhat more remarkable than for 1,1-disubstitution: methyl crotonate is 43.9 times less reactive than methyl methacrylate and 101 times less reactive than methyl acrylate; stilbene is 17.4 times less reactive than 1,1-diphenylethylene and 50 times less reactive than styrene. The relatively low reactivity of methyl $\beta$-pyrrolidino acrylate is also noteworthy: two activating groups of opposite sign tend to cancel each other. This fact is nicely accounted for by perturbation molecular orbital (PMO) theory, since raising frontier orbital (FO) energy levels due to the donor substituent is counterbalanced by the lowering effect of the acceptor substituent. Heavier substitution decreases the reactivity further: 3,3-dimethyl acrylate is more than 1300 times less reactive than methyl acrylate. Polysubstitution with alkyl groups practically cancels out reactivity: tetramethylethylene does not react with benzonitrile oxide even when the latter is generated *in situ*.[4B/63] Nevertheless, a reaction occurs with highly electron-poor nitrile oxides, such as benzenesulfonyl carbonitrile oxide[97/79.163/81] or with a stable nitrile oxide such as mesitonitrile oxide under forcing conditions.[148/68]
4. *Trans*-alkenes cycloadd to nitrile oxides much faster than do the corresponding *cis* isomers: the rate decrease is 29 for the couple fumarate/maleate. This loss of reactivity has been ascribed to a steric hindrance of resonance in the *cis* isomer, which strongly diminishes the activating effect of the substituent (see ref. 205/84, p. 126).
5. Alkenes react slower than do the corresponding alkynes, indicating that the gain in aromaticity is not meaningful in the early stages of the reaction, when the transition state is reached. A decreased FO interaction owing to the higher IPs of alkenes offers an easy explanation (see Fig. 2.3).
6. Cyclic alkenes are somewhat anomalous, since their reactivity with nitrile oxides are spread over a very large range of values, despite the similarities of their IPs. Thus norbornene reacts with benzonitrile oxide 73 times faster than cyclopentene and 6120 times faster than cyclohexene.

A more detailed discussion of these effects is postponed to Part 2 of the present work.

The cycloaddition reaction of unsymmetrical dipolarophiles to 1,3-dipoles makes it possible to observe regioselectivity. In the case of nitrile oxides and CC double-bond compounds, the two regioisomeric 2-isoxazolines **155** and **156** can arise:




**155** **156**

In the light of perturbational theory, the formation of one or the other regioisomer depends on the coefficients of the frontier orbitals involved (or, more precisely, from the squares of the products of the coefficients $c$ with the bond integrals $\gamma$ of the forming bonds) and on steric factors. According to the principle of greatest energy gain, the atoms having the largest orbital coefficients combine preferentially, thus governing the direction of addition.

Some cycloadditions to mono- and disubstituted dipolarophiles, where the isomer ratios of the products have been accurately measured, are reported in Table 2.16. Figure 2.4 briefly illustrates the effects of the substituents on the shapes of the frontier orbitals. As far as regiochemistry is concerned, comparison of Table 2.16 with Figs. 2.3 and 2.4 leads to the following main trends:

TABLE 2.16. REGIOISOMER RATIOS (**155/156**) FOR THE CYCLOADDITION OF NITRILE OXIDES TO CC DOUBLE-BOND COMPOUNDS

| R | R' | R'' | Ratio **155:156** | (Total yield) | References |
|---|---|---|---|---|---|
| H | H | COOMe | 100:0 | (94) | 28C/73, 28/73 |
| CN | H | COOMe | 99:1 | (72) | 28C/73 |
| Me | H | COOMe | 95:5 | (86) | 28C/73 |
| $Me_3C$ | H | COOMe | 100:0 | (95) | 28C/73 |
| Ph | H | COOMe | 96:4 | (98) | 27/73 |
| 2,4,6-$Me_3C_6H_2$ | H | COOMe | 93:7 | (99) | 28C/73 |
| H | H | Ph | 100:0 | (70) | 28/73 |
| Ph | H | Ph | 99.5:0.5 | (~100) | 212/84 |
| Ph | H | C(Ph)=NOH | 98.5:1.5 | (96.5) | 44/67 |
| 2,4,6-$Me_3C_6H_2$ | H | Ph | 98:2 | (~100) | 212/84 |
| 2,4,6-$Me_3C_6H_2$ | H | $NO_2$ | 100:0 | | 91/77 |
| 2,4,6-$Me_3C_6H_2$ | H | CN | 98:2 | | 91/77 |
| 2,4,6-$Me_3C_6H_2$ | H | $SO_2Ph$ | 96:4 | | 91/77 |
| 2,4,6-$Me_3C_6H_2$ | H | $CF_3$ | 97:3 | (96) | 213/84 |
| 2,4,6-$Me_3C_6H_2$ | H | $SO_2Me$ | 94:6 | | 91/77 |
| H | Me | COOMe | 62:38 | (36) | 28/73 |
| Ph | Me | COOMe | 34:66 | (84) | 28C/73 |
| 2,4,6-$Me_3C_6H_2$ | Me | COOMe | 27:73 | (97) | 28C/73 |
| $PhSO_2$ | Me | COOMe | 62:38 | | 219/79 |
| H | Ph | COOMe | 24:76 | (23) | 28/73 |
| Ph | Ph | COOMe | 30:70 | (89) | 28C/73 |
| 2,4,6-$Me_3C_6H_2$ | Ph | COOMe | 36:64 | (93) | 28C/73 |
| $PhSO_2$ | Ph | COOMe | 12:88 | | 219/79 |
| $(MeO)_2CH$ | Me | COO*t*-Bu | 19:81 | (72) | 116/80 |
| Ph | Me | COMe | 50:50 | | 212/84 |
| Ph | Me | COPh | 68:38 | (n.d.) | 158/73 |
| Ph | Ph | COMe | 41:59 | (92) | 158/73 |
| 2,4,6-$Me_3C_6H_2$ | Ph | COMe | 80:20 | (90) | 158/73 |
| Ph | Ph | COPh | 71:29 | (80) | 158/73 |
| 2,4,6-$Me_3C_6H_2$ | Ph | COPh | 75:25 | (92) | 158/73 |
| Ph | Ph | Br | 25:75 | (85) | 26/73 |
| Ph | Ph | Me | 34:66 | (43.5) | 155/76 |
| Ph | Ph | OMe | 100:0 | | 212/84 |
| Ph | Ph | $N(CH_2)_4$ | 100:0 | (69) | 26/73 |
| Ph | Ph | $NO_2$ | 33:67 | (75) | 26/73 |

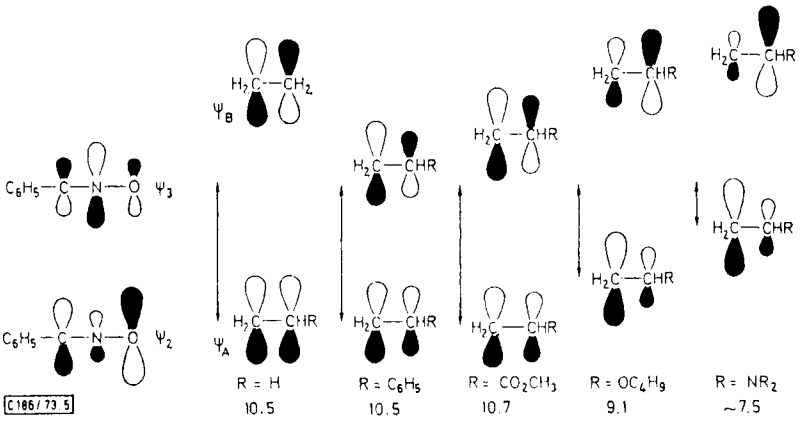



**Figure 2.4**. Shapes of the frontier orbitals of benzonitrile oxide and of ethylenic dipolarophiles.[28B/73]

1. Monosubstituted alkenes show an almost complete regioselectivity, always yielding 5-substituted 2-isoxazolines. With electron-rich dipolarophiles (e.g., vinyl ethers, enamines, 1-alkenes) LUMO-dipole control is dominant and yields the 5-substituted isomer; in this case the other interaction [i.e., HOMO (dipole)–LUMO (dipolarophile)], albeit with far less pronounced effect (see below), would also lead to the same regioisomer.

With dipolarophiles having conjugating (e.g., 1,3-butadiene or styrene) or electron-withdrawing substituents (e.g., methyl acrylate or vinyl ketones or sulfones), the two frontier interactions give rise to opposite regiochemical results. The former class of compounds is still subjected to a dominant LUMO–dipole control, thus leading to the 5-substituted isoxazoline exclusively or almost exclusively. It is easily conceivable that the more nucleophilic mesitonitrile oxide reacts with styrene to give, besides the 5-substituted cycloadduct, a small amount of isomeric 4-substituted isoxazoline, arising from the HOMO (dipole)–LUMO (dipolarophile) interaction.

With electron-deficient olefins, as can be inferred from the reactivity data (see above), the HOMO (dipole)–LUMO (dipolarophile) interaction should prevail; and the more nucleophilic oxygen atom of the nitrile oxide should combine with the more electrophilic unsubstituted carbon atom of the alkene, thus producing the 4-substituted isoxazoline. Nevertheless, this "reversal" of regiochemistry is far less pronounced than was expected, even with the electron-rich mesitonitrile oxide: the 4-substituted regioisomer never exceeds 5–7% of the isomeric products mixture (see Table 2.16).[91/77] This fact has been ascribed to both steric and electronic factors. An energy partitioning analysis[214/84] (see ref. 206/84, pp. 337–345) has confirmed that exchange repulsion (a steric effect) definitively destabilizes all transition states, leading to the 4-substituted isomer. Furthermore, in the transition-state geometry the nitrile oxide moiety is already bent,

thus notably diminishing polarization of the HOMO (dipole) and consequently, the directing power of its controlled interaction; the regiochemistry of the cycloaddition here, too, would be governed primarily by the LUMO (dipole)–HOMO (dipolarophile) interaction, leading to a 5-substituted regioisomer. Other calculations would indicate in the carbon atom both the most nucleophilic and the most electrophilic terminus of the nitrile oxide.[36D/73] Despite the great achievements of FMO theory in the field of 1,3-dipole cycloadditions, the problem of regioselectivity, especially with electron-poor dipolarophiles, has not yet been settled definitively. The necessity of including other interactions has recently been stressed, and for a deeper insight into the mechanism of the reaction, reference is made to more recent specialized reviews.[205/84,208/84]

2. Monosubstituted alkynes with the same substituent always give larger amounts of the 4-substituted cycloadducts than the corresponding alkenes (see § 1.3.2.1, pp. 184–185);

3. 1,2-Disubstituted alkenes usually give rise to a mixture of the two possible regioisomers, whose ratio is the result of a subtle interplay of steric and electronic factors. The cycloaddition reactions of methyl crotonate with different nitrile oxides change from a 5:3 balance in favor of the 5-methoxycarbonyl isomer in the case of benzenesulfonylcarbonitrile oxide to a balance of 8:3 in favor of the 4-methoxycarbonyl isomer in the case of mesitonitrile oxide. Cinnamate behaves in a reversed manner toward the same nitrile oxide series.[28B/73]

Noteworthy is the high directive power of amino substituents, which invariably tend to occupy the 5-isoxazoline position. Even with the highly encumbered 2-methyl-1-morpholinylpropene, benzonitrile oxide reacts to furnish, in addition to a large amount of furoxane, a 17% yield of 3-phenyl-4,4-dimethyl-5-morpholinyl-2-isoxazoline.[26/73]

4. Although no extensive study on the influence of the solvent polarity on the regiochemistry of 1,3-dipolar cycloadditions is known, the nature of the solvent usually does not seem to affect the isomer ratios notably. An exception to this rule is represented by the reaction of mesitonitrile oxide to benzylidene acetone. A remarkable shift toward the 4-acyl regioisomer is produced by increasing the solvent polarity: an 83:17 ratio in favor of the 5-acyl isomer is obtained in cyclohexane, but the ratio shifts to 55:45 in favor of the 4-acyl isomer when the reaction is run in acetonitrile.[158/73]

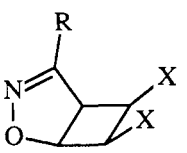
As mentioned above, in all cases where stereoisomeric dipolarophiles are used, the configuration of the starting olefin is retained in the final cycloadduct. This complete *cis* stereospecificity has been observed in the cycloaddition of nitrile oxides to fumaric and maleic esters,[5/50,12/52,12/55] mesaconic and citraconic esters,[12/52] *cis*- and *trans*-cinnamates,[51/59] *cis*- and *trans*-1,2-dideuteroethylene,[2/85] *cis*- and *trans*-butene,[26/73] *cis*- and *trans*-cyclooctene,[160/76] and *cis*- and *trans*-stilbene.[51/59,26/73] Absence of the diastereoisomeric adduct in the mother liquors has been verified, although the analytical limits of the detection have rarely been specified. Only in the cycloaddition of benzonitrile oxide to *cis*-stilbene has the degree of stereospecificity been found to be greater than 97% by NMR.[26/73]

Equilibration of the stereoisomeric dicarboxylic esters can occur successively either thermally or by action of bases.[10/55,12/55,27/73]

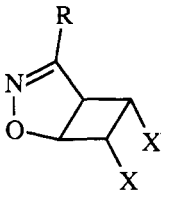
Far more interesting is the stereoselectivity encountered when the double-bond dipolarophile shows two diastereotopic faces. In this case two cycloadducts can form, depending on whether the nitrile oxide attacks from the same side or from the opposite side of the perturbing substituent. The terms *syn-anti*[248B/77] or π-facial[147B/80] stereoselectivity have been proposed to describe this difference of attack, although the *endo-exo* nomenclature is still widely used in the field of bridged cyclic olefins, such as norbornene and its derivatives.

Deferring to Part 2 of this work for a more detailed discussion of the cycloaddition of nitrile oxides to cyclic olefins, the following main features must be briefly outlined here:

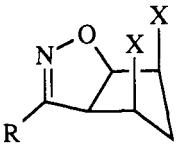
1. Nitrile oxides react with *cis*-3,4-disubstituted cyclobutenes to yield mixtures of *syn* and *anti* cycloadducts **157** and **158**. An abnormal high proportion of *syn* attack is noted with cyclobutenes carrying electron withdrawing groups having a lone pair (e.g., chlorine or acetoxy) and with sterically less encumbered nitrile oxides.[139/74,145B/76]



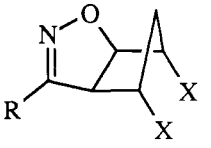

**157**




**158**




**159**



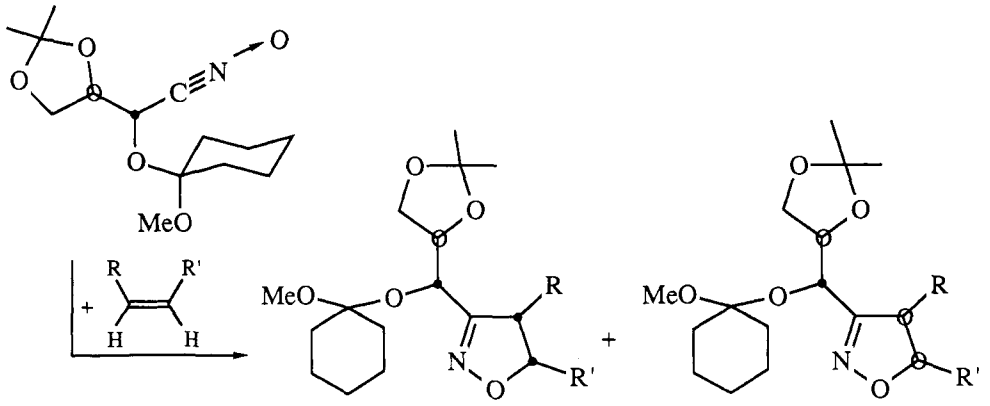

**160**

2. By contrast, *cis*-3,5-disubstituted cyclopentenes react with nitrile oxides to give *anti* cycloadducts **160** as main products, besides small amounts of *syn* adducts **159**.[177/84]
3. High stereoselectivity is a general rule in [4 + 2] cycloaddition reactions of bicyclic alkenes, such as norbornenes and norbornadienes. More or less exclusive *syn*-methylene (= *exo*) attack has been recorded in the reaction of nitrile oxides with the former compounds,[28/73,10/73] even with the sterically encumbered 7,7-dimethylnorbornene.[10/73] Analogous behavior has been verified for similar bridged systems.[142/72,34B/77,155B/77,49B/78,51/78,196/80,96B/81,228/81]

Mixtures of *syn*/*anti* stereoisomers are normally obtained in the cycloaddition of nitrile oxides to norbornadiene and its substituted derivatives.[177/68,181B/69,34/76,51/78,198/80,228/81] The preferred stereochemistry depends on the substitution pattern of the dipolarophile, on the nature of the nitrile oxide, and even on the solvent and the temperature.[34C/77,52/78] Less spectacular, but by no means less interesting,

especially for its implication in the synthesis of complex natural molecules (see § 2.2.2.3), is the face selectivity that can arise in intermolecular reactions involving open-chain compounds.

Diastereoselection can be sought by cycloadding either chiral nitrile oxides to achiral alkenes or achiral nitrile oxides to chiral alkenes. In both cases mixtures of diastereoisomeric isoxazolines are obtained, which usually can be separated by chromatographic methods. Chiral nitrile oxides, derived either from sugars[44/73,195/83] or from substituted 1,3-dioxolane derivatives,[155/83,158/84] show practically no stereoselection in the cycloaddition with monosubstituted alkenes, such as styrene[44/73,155/83,195/83,158/84] or allylbenzene,[175/84] owing possibly to the far too large distance between the chiral center and the developing new asymmetric center. By contrast, a modest diastereoselectivity has been ascertained with 1,2-disubstituted alkenes, especially *cis*-conformed, such as cyclopentene,[155/83.158/84] *cis*-2-butene,[155/83] or dimethyl maleate.[158/84] For example, the mixtures of diastereoisomers **161** and **162**, separable through column chromatography, shown in Scheme 2.10 have been obtained.[155/83]



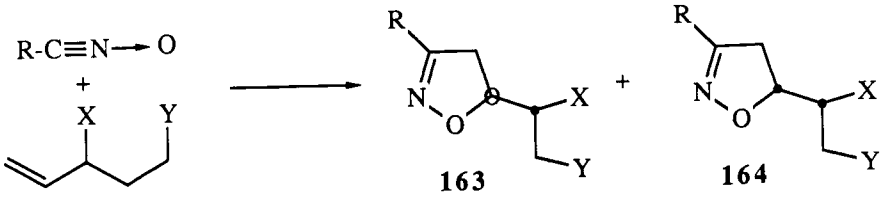
**161** **162**

| R | R' | Ratio **161** : **162** |
|---|---|---|
| H | Ph | 50 : 50 |
| Me | Me | 75 : 25 |
| -$(CH_2)_3$- | | 70 : 30 |

**Scheme 2.10**

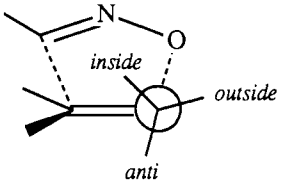
A remarkably higher stereocontrol can be achieved by using chiral alkenes possessing an allylic asymmetric center. The presence of an allylic oxygen seems most effective, especially when cyclic derivatives of 3-butene-1,2-diol are employed as dipolarophiles. Some relevant selected data are collected in Table 2.17.

TABLE 2.17. CYCLOADDITION OF NITRILE OXIDES TO CHIRAL ALLYLIC ETHERS AND ALCOHOLS




| R | X | Y | Ratio **163**:**164** (*Erythro*:*threo*) | Total yield (%) | References |
|---|---|---|---|---|---|
| Ph | OAc | H | 50:50 | | 112/84 |
| Ph | $OSiMe_3$ | H | 71:29 | | 61/84 |
| THP-$OCH_2$ | $OSi(t\text{-}Bu)Me_2$ | H | 81:19 | 84 | 112/84 |
| Ph | OH | H | 40:60 | | 61/84 |
| Ph | OH | OH | 61:39 | 67 | 310B/83 |
| 4-$NO_2C_6H_4$ | OH | Me | 36:64 | | 61/84 |
| Ph | OAc | OAc | 53:47 | 67 | 310B/83 |
| Ph | $OSiMe_3$ | $OSiMe_3$ | 75:25 | 65 | 310B/83 |
| Et | -$OCMe_2O$- | | 90:10 | 83 | 112/84 |
| MeOOC | -$OCMe_2O$- | | 80:20 | 71 | 112/84, 61/84 |
| Ph | -$OCMe_2O$- | | 85:15 | 88 | 142/82, 190/83 112/84, 167/84 |
| THP-$OCH_2$ | -$OCMe_2O$- | | >94:<6 | | 112/84 |
| Ph | -$OC(CH_2)_5O$- | | 81:19 | 100 | 167/84 |
| (*S*)-$PhCH_2OCH_2CH(Me)$ | -$OCMe_2O$- | | 80:20 | | 112/84 |

The prevalence of the *erythro* isomer **163** is more or less neat for allylic ethers, whereas allylic alcohols show a slight preference for the *threo* cycloadduct **164**. These selectivities have been attributed to a staggered transition state, where the nitrile oxide attacks preferentially *anti* to one of the allylic bonds (the anti-periplanar effect).[97C/81] Theoretical computations would favor an "inside" position of the alkoxy group and an "outside" position of the hydroxy group in the transition states.[61/84] This last fact should be attributed to the tendency to maximalize hydrogen bonding between the allylic hydroxy group and the oxygen atom of the incoming nitrile oxide. The following values for the relative energies (in kcal/mol) of the three different positions in the transition state have been calculated:[61/84]



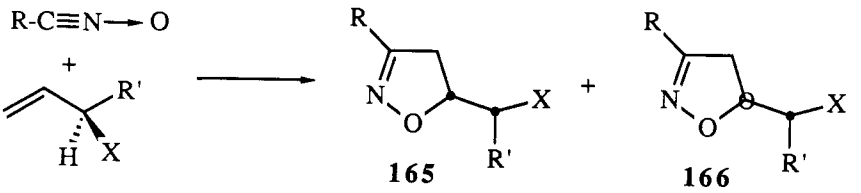

| | Me | OH | OR |
|---|---|---|---|
| Anti | 0.0 | 4.9 | 0.7 |
| Inside | 1.1 | 0.8 | 0.0 |
| Outside | 0.6 | 0.0 | 2.9 |

The presence of an α-chiral center in the nitrile oxide does not change the observed stereoselectivity.[112/84]

A moderate degree of diastereoselectivity has been also reported in the reaction of 5-vinyl-2-isoxazolines[286/83] and of (−)-menthyl crotonate[120/81] with nitrile oxides, whereas no stereo selection was observed in the cycloaddition with 3-chloro-1-butene.[24/77]

Some face selectivity, not surpassing a 3:1 ratio between the two epimers, has been evidenced with chiral alkenes having an allylic nitrogen substituent, such as several vinyl glycine derivatives.[263/80.285/82.161/84.174/84] Starting from (*S*)-vinylglycine, preferred formation of the 5*R*,α*S*-isomer has been noticed; some relevant data are reported in Table 2.18.

TABLE 2.18. CYCLOADDITION OF NITRILE OXIDES TO VINYLGLYCINE DERIVATIVES



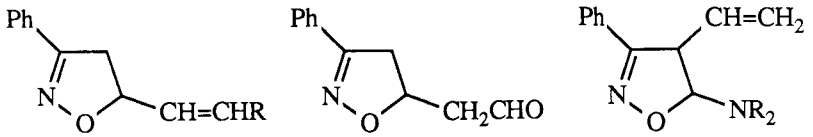

| R | R' | X | Ratio **165:166** | Total yield (%) | References |
|---|---|---|---|---|---|
| Cl | COOH | NPht | 71:29 | 52 | 285/82, 161/84 |
| Br | $COO^-$ | $NH_3^+$ | 75:25 | 70-80 | 263/80 |
| Br | $CH_2OH$ | $NHCOCCl_3$ | 60:40 | | 174/84 |
| $PhSO_2$ | COOH | NPht | 62:38 | 80 | 161/84 |
| $PhSO_2$ | COOH | NHCOO-*t*-Bu | 70:30 | 24 | 161/84 |
| $PhSO_2$ | COOMe | $NHCOOCH_2Ph$ | 55:45 | 83 | 161/84 |
| $PhSO_2$ | $CH_2OAc$ | $NHCOOCH_2Ph$ | 50:50 | 77 | 161/84 |

For a discussion on stereocontrol in intramolecular cycloadditions, see Part 2 of this work.

Site selectivity can intervene when the dipolarophile possesses two or more different double bonds suitable for undergoing a [4 + 2] cycloaddition reaction with nitrile oxides. The following main trends are worth mentioning:

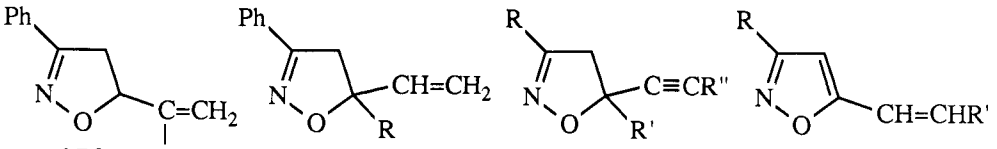
1. Unsymmetrically substituted 1,3-dienes show a different dipolarophilic activity for the two bonds, steric factors usually being predominant. For example, 1-alkyl- or 1-aryl-1,3-butadienes react with benzonitrile oxide only on their unsubstituted double bond, yielding regiospecifically 5-alkenyl- or 5-styryl-2-isoxazolines **167**.[16/52.42/63] On the contrary, owing to the strong activating effect of the amino group on the adjacent double bond, 1-amino-substituted buta-

dienes give rise both to aldehyde **168** (deriving from the cyclodduct **167**, R = $NR_2'$) as minor product and to the 4-vinylisoxazolines **169** (or thereby derived bis adducts) as main product.[210/70]




**167** **168** **169**

Cycloaddition with 2-substituted 1,3-butadienes is only site-selective and regiospecific; usually, a mixture of the two possible isomers **170** and **171** is obtained (together possibly with the bis adduct).[42/63.123/64]

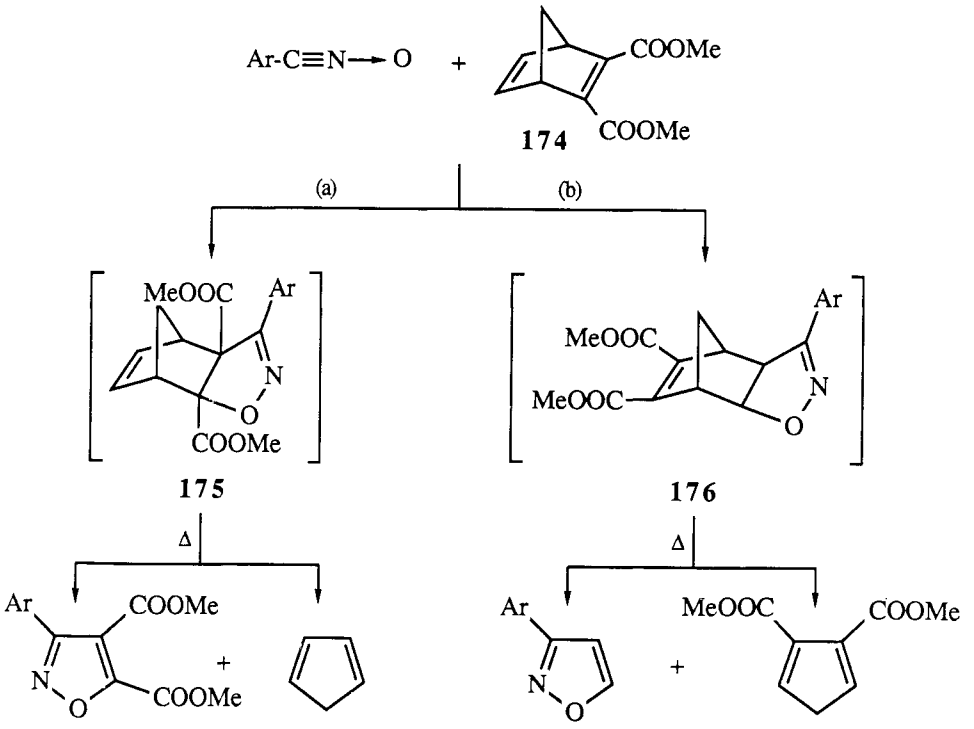



**170** **171** **172** **173**

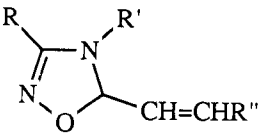
2. The double bond of conjugated enynes is more reactive than the triple bond and 5-ethynylisoxazolines of general formula **172** are produced mainly by cycloaddition to nitrile oxides.[20/55.22/60.97/63.123/64.135/65.226/68] Nevertheless, 1-monosubstituted enynes react on their triple bond to yield 5-alkenylisoxazoles **173**.[20/55.91/63.123/64.81/66]

3. The disubstituted norbornadiene system **174** allows us to evaluate the competition between the two double bonds. As illustrated in more detail in Part 2 of this work, a mixture of the two site isomers **175** (minor product) and **176** (main product) is formed, which, however, are not isolated as such because of their instability, but measured as their thermal decomposition products (Scheme 2.11).[220/81]

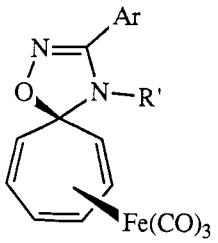
4. In some cases the cycloaddition to a CC double bond can enter in competition with a hetero-dipolarophilic double or triple bond, such as C=N, C=O, C=S, or C≡N. The C=N double bond shows a dipolarophilic activity highly comparable to that of a C=C double bond. In cinnamylideneanilines the former bond is even more reactive, and only the 1,2,4-oxadiazoline derivatives **177** are formed.[207B/68,100B/77] An analogous site-specific preference in favor of the C=N bond has been observed with 1,2-diazepines,[238/77] 8-substituted 8-azaheptafulvenes,[213/84] and 4-benzalamino-5-styrylisoxazoles.[86/81] An interesting instance of solvent-promoted change of site selectivity is worth recording in the case of 8-*p*-tolyl-8-azaheptafulvene irontricarbonyl: whereas the cycloaddition



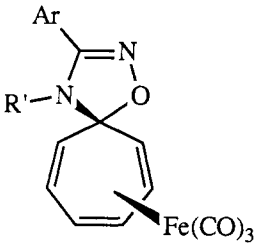
Scheme 2.11



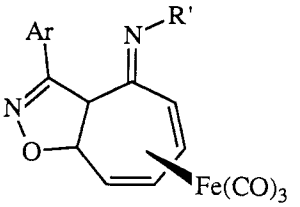
177



178



179



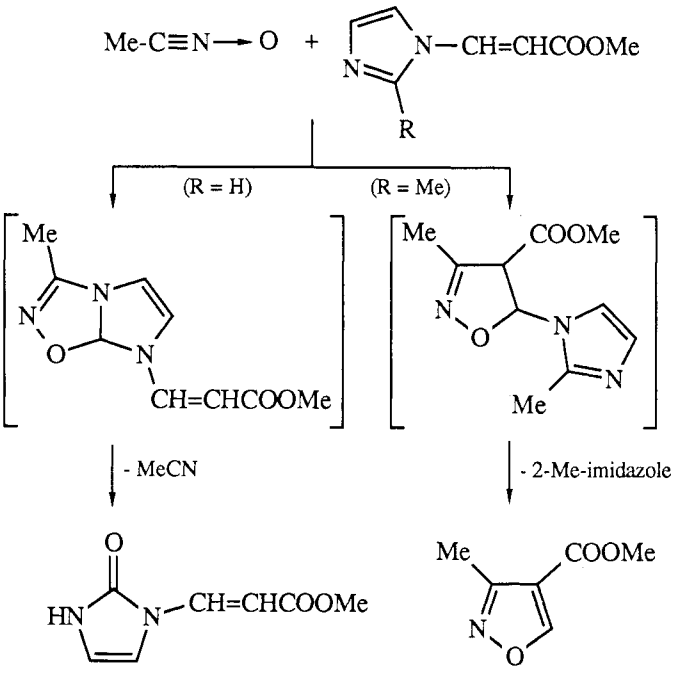
180

TABLE 2.19

| Ar | 178 | : | 179 | : | 180 | Solvent |
|---|---|---|---|---|---|---|
| Ph | 10 | : | 90 | : | 0 | |
| 2,6-$Cl_2C_6H_3$ | 3 | : | 20.5 | : | 76.5 | cyclohexane |
| 2,6-$Cl_2C_6H_3$ | 27 | : | 69 | : | 4 | methanol |

to benzonitrile oxide is site specific on the exocyclic C=N bond to yield a mixture of stereoisomers **178** and **179** irrespective of the solvent used, cycloaddition to 2,6-dichlorobenzonitrile oxide still results in site-selective attack to the C=N bond when carried out in methanol, but shifts to a prevailing attack to the endocyclic C=C bond to give **180** when the reaction is performed in cyclohexane (Table 2.19).[213/84]

Steric effects may also affect the competition between C=N and C=C bonds. Thus, in the cycloaddition between methyl β-imidazolylacrylate (or β-imidazolylcrotonate or β-imadazolylcinnamate) and acetonitrile oxide, only the imidazole C=N bond is reactive. By contrast, substitution with a 2-methyl group in the imidazolyl residue shifts the dipolarophilic activity toward the activated C=C bond. In both cases the primary cycloadduct is not stable, as Scheme 2.12 shows.[83/84]




**Scheme 2.12**

Other examples of competition between C=N and C=C bonds are to be found in the cycloadditions of the nitrile oxides to tautomerizable Schiff bases[153/72] or β-diketone monoimines.[36/67] On the contrary in acrolein dimethylhydrazone[11/84] as well as in *p*-benzoquinone-*N*-sulfonylmonoimine[248/73] only the C=C double bonds are reactive. For the reaction of the C=N double bond of 2-isoxazolines themselves, see § 2.2.3.1d, p. 552.

The triple bond C≡N is less reactive than the C=N bond and is therefore

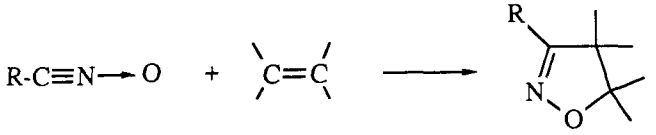
a poorer dipolarophile than the C=C bond. Acrylonitrile always yields the corresponding 2-isoxazoline-5-carbonitrile. Nevertheless, when the C=C bond is heavily substituted, the C≡N bond may become the most reactive, leading to the formation of 1,2,4-oxadiazole derivative. This is the case of tetracyanoethylene,[184C/76] cyanomethylene adamantane,[215/79] and α,β-unsaturated steroidal nitriles.[224B/72] Site selectivity has been observed in the cycloaddition of nitrile oxides to cinnamonitrile and some of its derivatives.[143/77,159/80,79B/84]

The carbonyl double bond is a very poor dipolarophile, and ethylenic aldehydes and ketones always cycloadd to give isoxazoline derivatives. Nevertheless, here too some examples of site selectivity are known, particularly in the field of quinones (see Part 2 of this work). Another substrate where nitrile oxides attack primarily the strained C=O groups is represented by disubstituted cyclobutenediones; as by-products tris adducts are obtained, thus testifying a minor reactivity of the C=C bond.[231B/76] Only the C=O bond of diphenylcyclopropenone is reported to be reactive in the cycloaddition with nitrile oxides.[136B/74]

Some polyunsaturated cyclic systems offer the possibility of undergoing different thermally allowed pericyclic reactions, and at least two cases of this periselectivity have been observed in cycloaddition with nitrile oxides. As illustrated in greater detail in Part 2 of this work, competition between a [4 + 2] and a [6 + 4] cycloaddition process has been observed in the reactions of nitrile oxides with tropone[240/74] and with 6-dialkylaminofulvenes.[190/71]

### d. Synthetic Potentiality: Synthesis of 2-Isoxazolines

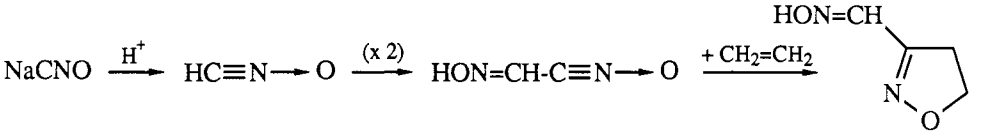
The cycloaddition reaction of nitrile oxides to alkenes has an astonishingly large versatility and has, in fact, been widely utilized for different purposes. A comprehensive treatment published in 1971[193B/71] lists over 800 2-isoxazolines prepared by this method; at the present this number surely exceeds 2000.




Because of this high degree of reactivity, the cycloaddition reaction has often been adopted as a "trapping" device for the isolation of more or less unstable ethylenic derivatives or, conversely, for demonstrating the presence of a nitrile oxide as a reactive intermediate in a reaction sequence. In the former case the reagent of choice may be benzonitrile oxide or, still better, the *p*-chloro- or *p*-nitro derivative, both of which are more stable than the unsubstituted compound, although still highly reactive as dipoles. In the latter case a highly active dipolarophile must be chosen, such as methyl acrylate, acenaphthylene,

or norbornene. The 2-isoxazolines thus obtained are usually separable crystalline compounds.

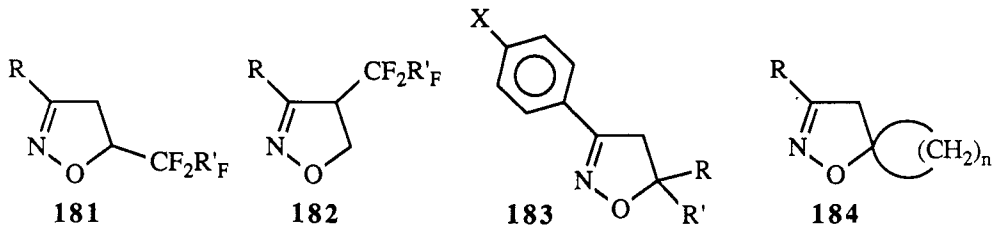
Ethylene and its higher homologues with a terminal double-bond cycloadd nitrile oxides to give 5-unsubstituted or 5-alkyl-2-isoxazolines regiospecifically.[17/52.14/64.108/64.118C/65.80/66.179/67.87/68.26/73.221/79.225/81] The synthesis of 3-unsubstituted derivatives requires the *in situ* formation of fulminic acid, usually accomplished from mercuric fulminate through formohydroximoyl iodide.[28/73] The generation of fulminic acid *in situ* by cautious acidification of aqueous solutions of its sodium salt usually affords cycloadducts derived from the dimer, as in the following example:[154/74]




It should also be remembered that the attempted formation of fulminic acid *in situ* by dehydration of nitromethane with phenylisocyanate and triethylamine in the presence of a 1-alkene leads to the formation of a 5-alkyl-2-isoxazoline-3-carboxanilide, owing to the preliminary reaction of nitromethane with phenylisocyanate.[16/63/28/73]

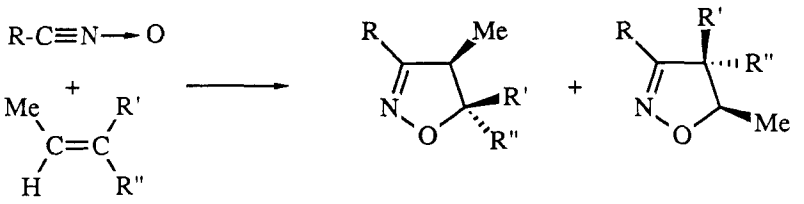
Perfluoroalkylethenes normally cycloadd nitrile oxides to give 5-perfluoroalkylisoxazolines **181**, but in this case minor amounts (3–5%) of the regioisomers **182** can sometimes be detected.[171/78.213/84] The same slight loss of regioselectivity has been observed in the cycloaddition of chloroformonitrile oxide to 1-octene.[285/82]

A kinetic study of the cycloaddition reactions of *p*-nitro- or *p*-methoxybenzonitrile oxides with 1-alkenes or with isobutene to give isoxazolines **183** has been performed. Owing to the dominant HOMO (alkene)–LUMO (dipole) interaction, the *p*-nitrosubstituted nitrile oxide reacts 10 times faster than the *p*-methoxy derivative. Moreover, a relatively slight decrease in reaction rate is observed with increasing alkylation of the 1-alkene, this fact being ascribed primarily to a steric effect.[151/79]



1,1-Disubstituted ethylenes invariably yield 5,5-disubstituted isoxazolines.[17/52.8/54.26/73] The exocyclic double bond of methylene–cycloalkenes is very reactive, and 5-spiro-2-isoxazolines of general formula **184** are obtained with good yields.[31/61.216/74.226B/76.215/79] 1,2-Disubstituted ethylenes react with greater difficulty; nevertheless, both *trans*- and *cis*-2-butene cycloadd benzonitrile oxide, stereospecifically affording the corresponding 3-phenyl-4,5-dimethyl-2-isoxazoline, along with more or less diphenylfuroxan.[17/52,26/73,10/80] As evidenced by the reported regioisomeric ratios, *cis*-1,2-dialkylethylenes show a greater regioselectivity toward nitrile oxides than do their *trans* counterparts (Table 2.20). This remarkable trend has been ascribed to steric effects in the transition states.[294/83]

TABLE 2.20

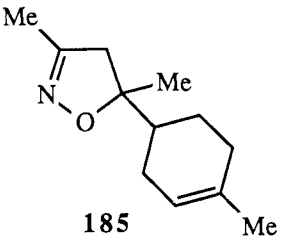


| R | R' | R" | Total yield (%) | Isomers ratio |
|---|---|---|---|---|
| $CMe_3$ | $CHMe_2$ | H | 26 | 100 : 0 |
| $CMe_3$ | H | $CHMe_2$ | 50 | 70 : 30 |
| $CPh_3$ | $CHMe_2$ | H | 96 | 100 : 0 |
| $CPh_3$ | H | $CHMe_2$ | 99 | 68 : 32 |
| Ph | $CMe_3$ | H | 27 | 100 : 0 |
| Ph | H | $CMe_3$ | 56 | 100 : 0 |
| $Me_3C_6H_2$ | $CHMe_2$ | H | 92 | 100 : 0 |
| $Me_3C_6H_2$ | H | $CHMe_2$ | 94 | 62 : 38 |

Tetramethylethylene no longer reacts with benzonitrile oxide,[4B/63] but can still be forced to cycloadd mesitonitrile oxide by heating for several days[148/68] or the highly reactive benzenesulfonyl carbonitrile oxide prepared *in situ*.[97/79] Even so, yields no higher than 18% and 17%, respectively, could be obtained. Trimethylethylene has also been reported to react with mesitonitrile oxide at room temperature to yield the unstable 3-mesityl-4,5,5-trimethyl-2-isoxazoline.[75/79]

When compounds containing two (or more) different nonconjugated double bonds are employed as dipolarophiles, only the more reactive double bond (usually the less substituted) enters cycloaddition. For example, only the terminal double bond of (±)-limonene reacts with acetonitrile oxide to give the monoadduct **185** with 49% yield.[188/76]

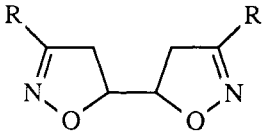
With more symmetrically substituted double bonds the bis adducts are usually obtained, but sometimes the monoadducts can be isolated (alone or in



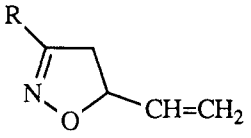

**185**

mixture), either because of their reduced reactivity or because the reaction is carried out in the presence of a large excess of diene. For example, 1,10-undecadiene,[17/52] 1,6-heptadiene,[8/80] and divinylbenzenes[60/62] react with nitrile oxides to give bis adducts exclusively.

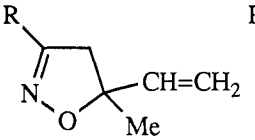
Diallyl furnishes the corresponding bis(3-phenyl-5-isoxazolinyl)ethane when the reactants are present in stoichiometric amounts, but a mixture of bis and mono adduct is obtained by using an excess of diallyl.[16/52] Similar results are obtained with 1,4-pentadiene.[32/72] Further examples will be considered in Part 2 of this work, when dealing with cycloadditions of nitrile oxides to cyclic and polycyclic dienes or polyenes. Depending on experimental conditions and reactants ratio, conjugated dienes can cycloadd nitrile oxide to yield either monoadducts or bis adducts. For example, 1,3-butadiene yields with benzonitrile oxide both the 5,5′-diisoxazoline **186** (R = Ph), which is easily separ-



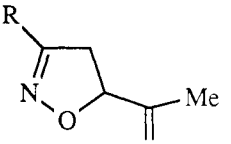

**186**




**187**




**188**



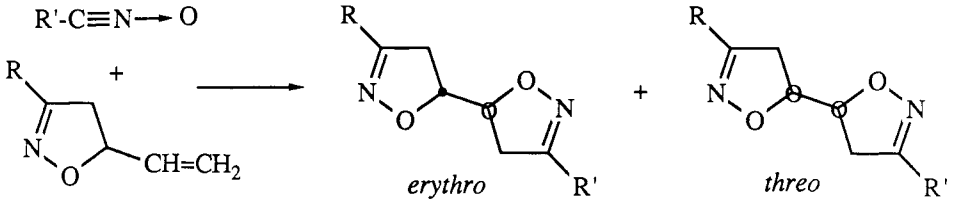

**189**

able because of its low solubility in ether, and the 5-vinyl-2-isoxazoline **187** (R = Ph).[16/52] With other nitrile oxides, formation of monoadducts of type **187**[67/63,2/65.118/66.177/67] and/or of bis adducts of type **186**[1/64.209/70] has been reported.

The stereochemistry of the bis adducts **186** has been studied: usually, a mixture of the two possible stereoisomers (*erythro*/*meso* and *threo*/D,L) is isolated, whose composition depends on the substitution pattern, as shown by Table 2.21. Analogously, hepta-1,6-diene cycloadds benzonitrile oxide to give a 1:1 diastereoisomeric mixture of the two 5,5′-diisoxazolinyl-1,3-propanes with a 81% yield.[8/80] Conversely, oxalobisnitrile oxide reacts with styrene or with stilbene to yield a mixture of the two possible stereoisomers.[2/65.116/65]

Isoprene gives with benzonitrile oxide or with heptanonitrile oxide a mixture of the two possible monoadducts **188** and **189** and of the bisadduct;[123/64.286/83]

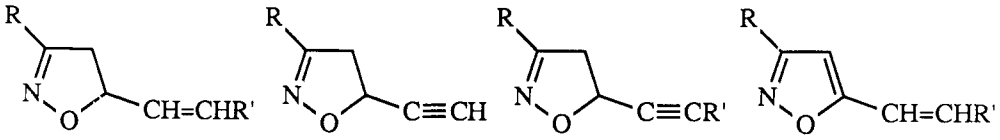
TABLE 2.21




| R | R' | Total yield (%) | Ratio *erythro* : *threo* | References |
|---|---|---|---|---|
| Me | Me | 20 | 97 : 3 | 286/83 |
| *n*-$C_6H_{13}$ | *n*-$C_6H_{13}$ | 81 | 77 : 23 | 286/83 |
| *n*-$C_7H_{15}$ | *n*-$C_7H_{15}$ | ca. 15 | 79 : 21 | 286/83 |
| Me | *n*-$C_6H_{13}$ | 79 | 69 : 31 | 286/83 |
| *n*-$C_6H_{13}$ | COOEt | 54 | 62 : 38 | 286/83 |
| Ph | Ph | | 65 : 35 | 212/84 |
| H | *n*-$C_6H_{13}$ | 85 | 69 : 31 | 286/83 |
| 2,4,6-$Me_3C_6H_2$ | 2,4,6-$Me_3C_6H_2$ | | 81 : 19 | 212/84 |

mircene furnishes, although with low yield, only the bis adducts, presumably on the conjugated diene moiety.[31B/69] Similarly, bis adducts have usually been isolated by cycloaddition of benzonitrile oxide to 2,3-disubstituted 1,3-butadiene. 1-Substituted 1,3-butadienes react only with the more reactive terminal double bond, leading to compounds of type **190**.[16/52,9/58,42/63,177/67]

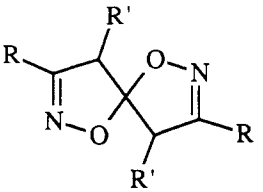
Due to the different dipolarophilic activity of the double versus the triple bond, vinylacetylene cycloadds nitrile oxide to yield 5-ethynyl-2-isoxazolines **191**[20/55,22/60,67/63,200/66] exclusively or preferentially; in the presence of an excess of nitrile oxide, bis adducts can be obtained. Analogous results have been reported for 1-penten-4-yne[69/73] and for 1-hexen-3,5-diyne.[228/75] In other enynes (such as isopropenylacetylene) both unsaturations compete in the cycloaddition and variable amounts of isoxazolines and isoxazole derivatives are formed.[33/61,123/64,200/66]



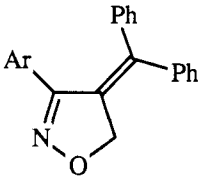

Monosubstitution at the terminal carbon atom of either the triple or the double bond lowers the reactivity, so that only a monoadduct is obtained, that is, a substituted 5-ethynyl-2-isoxazoline (**192**) or a 5-vinylisoxazole (**193**), res-

pectively.[22/60,91/63,97/63,200/66,73/73,196/76,282/77] Cyclic conjugated dienes follow more or less the same reactivity pattern of acyclic dienes toward nitrile oxides and will be examined in Part 2 of this work.

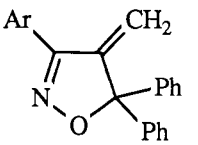
Allene reacts with two molecules of nitrile oxides to give the 5,5′-spirodiisoxazolines **194** (R′ = H);[29/60,88B/68] the same derivatives are achieved by treatment of nitrile oxide with diketene.[127/67,127/67,31/69] Two stereoisomers (**194**): R′ = Ph or Me) are isolated when methyl- or phenylallene is used.[29/60] 1,1-Diphenylallene behaves differently: cycloaddition of a threefold excess of the cumulated




**194**




**195**




**196**

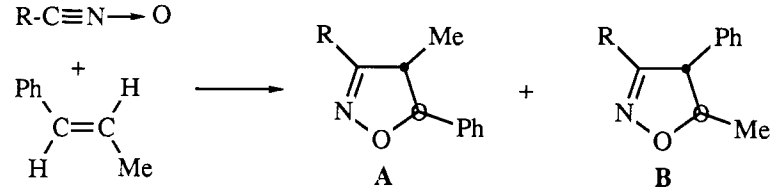
diene with 3,5-dichloromesitonitrile oxide affords a nearly 1:1 mixture of the two site-isomeric monoadducts **195** and **196**, where only the latter is able to react with an additional molecule of nitrile oxide to yield the spiro compound.[146/72,152/74,53/75,49/76,51/76]

As already mentioned, conjugation with a phenyl group enhances the dipolarophilic activity of the double bond: styrene[9/50,37/60,43/60,116/65,118/66,16/67,27/67,154/70,26/73,97/79,235/81] and its ring-substituted derivatives[8/54,15/66,16/66,16/67] are very active and largely employed dipolarophiles. 3,5-Diaryl- or 3-alkyl-5-aryl-2-isoxazolines are thus easily available with excellent yields; up to now, only the cycloaddition of benzonitrile oxide to styrene itself has made it possible to isolate a very small amount (0.5:99.5 ratio) of the regioisomeric 3,4-diphenyl-2-isoxazoline besides the "normal" 3,5-diphenyl-2-isoxazoline.[212/84] Of course, use of fulminic acid makes it possible to prepare 3-unsubstituted 5-aryl-2-isoxazolines with good yields.[28/73]

Kinetic studies have revealed V-shaped Hammett plots; that is, the cycloaddition rate is increased both by electron-donating or electron-accepting *p*-substituents on the styrene.[165/73] Other vinylaromatic compounds, such as α- and β-vinylnaphthalene,[34/65,118C/65] or vinylheteroaromatic compounds, such as vinylfuran,[11/55] vinylthiophene,[11/55] vinylpyrroles,[115B/80] vinylpyridines,[33/67] or vinyltetrazoles,[110/67] react easily as dipolarophiles, giving the corresponding 3,5-disubstituted 2-isoxazolines.

Whereas the substitution in position α to styrene does not notably change the course of the cycloaddition, β-substitution with a methyl group remarkably reduces both the reaction rate and the regioselectivity: indeed, cycloaddition of several nitrile oxides with *trans*-β-methylstyrene gives rise to a mixture of the two regioisomers, as shown in Table 2.22.

TABLE 2.22




| R | Ratio[a] A : B | Total yield (%) | References |
|---|---|---|---|
| Cl | 66 : 34 | 40 | 285/82 |
| Ph | 66 : 34 | 43.5 | 155/76 |
| 4-$MeC_6H_4$ | 72 : 28 | 78 | 155/76 |
| 4-$MeOC_6H_4$ | 58 : 42 | 55 | 155/76 |
| 4-$NO_2C_6H_4$ | 75 : 25 | 72 | 155/76 |
| 2,4,6-$Me_3C_6H_2$ | 20 : 80 | 72.5 | 155/76 |
| 2,4,6-$(MeO)_3C_6H_2$ | 61.5 : 38.5[b] | 82 | 155/76 |

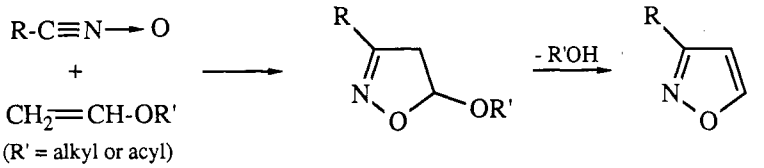
[a]In benzene.

[b]In ethyl acetate 70:30; in ethylene chloride 77:23.

A higher regioselectivity (93:7 in favor of the 4-methylisoxazoline) has been observed with carbethoxyformonitrile oxide as 1,3-dipole;[13/80] by contrast, a nearly 1:1 regioisomeric mixture is obtained from benzonitrile oxide and β-isopropylstyrene.[26/73] The cycloaddition with *trans*-[9/50,27/67,203/70,26/73,143/76,124/84] or *cis*-stilbene[51/59,26/73] is somewhat slower than that with styrene, especially the latter, but the corresponding 4,5-diphenylisoxazoline derivatives are always obtained stereospecifically with yields ranging from 32 to 75%. The intramolecular version of the 1,3-dipolar cycloaddition between nitrile oxides and double-bond compounds has been utilized extensively for the regio- and stereo-specific synthesis of complex polycyclic molecules (see § 2.2.3.3).

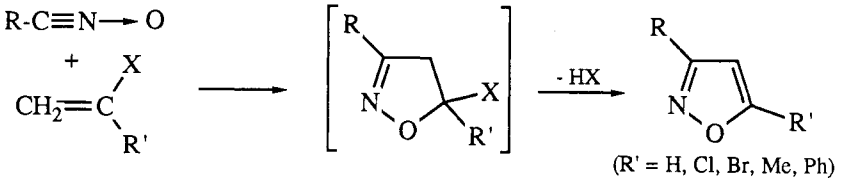
Turning to double-bond compounds with an oxygen-containing functionality, allyl alcohol[8/50,36/68] and ethers,[8/50,86/72,184/76,197/76] vinyl ethers,[9/62,16/63,33/67,82/71,26/73,184/76,10/80,152/80] and esters[8/50,9/62,16/63,120/66,38/70,26/73,33/75,184/76,10/80] react promptly with nitrile oxides to yield 3,5-disubstituted-2-isoxazolines. In the case of 2-methoxypropene the normally used *in situ* generation of benzonitrile oxide from benzohydroximoyl chloride fails, since O-alkylation occurs predominantly; pregeneration of the free nitrile oxide at 0°C is necessary here, followed by olefin addition.[296/83]

It should also be mentioned here that 5-alkoxy or, even easier, 5-acetoxyisoxazolines, can lose, either thermally or by action of acids or bases, one molecule of alcohol or of acetic acid to give the corresponding isoxazole (see §1.3.7.1, pp. 233–234):

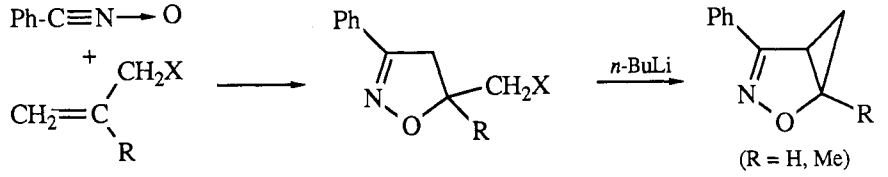



For example, the intermediate isoxazoline, expected from benzonitrile oxide and 2-acetoxypropene, loses acetic acid spontaneously, and 5-methyl-3-phenylisoxazole is the sole product isolated.[56/67,38/70] Similarly, the isoxazoline obtained by cycloaddition of 2,6-dichlorobenzonitrile oxide to α-trimethylsilyloxystyrene decomposes rapidly to 3-(2′,6′-dichlorophenyl)-5-phenylisoxazole on a TLC plate.[73/78]

The elimination reaction is particularly easy when vinyl halides are used as dipolarophiles: cycloaddition of nitrile oxides to vinyl chloride[26/73] or bromide,[38/70] 2-halopropenes,[118C/65,42/70] α-halogenostyrenes,[8/54] or 1,1-dichloroethylene[42/70] yields the corresponding isoxazoles:

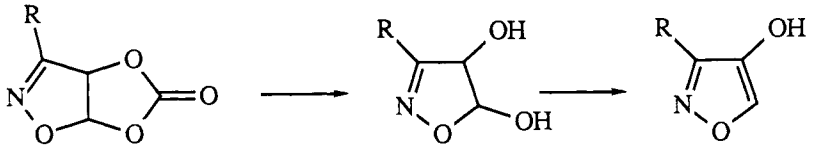



Allyl halides cycloadd nitrile oxides normally to give 5-halogenomethyl-2-isoxazolines,[8/50,14/64,13B/76,8/79] which can be cyclized to the oxazabicylo[3.1.0]-hex-3-ene system under appropriate treatment with bases:[24/77,8/79,104/79]




Practically no regioselectivity has been observed in the cycloaddition of benzonitrile oxide to *E*-1-chloro-2-butene.[65/76]

Vinylenecarbonate leads to the interesting bicyclic 2-isoxazolines **197**, which can easily be hydrolyzed to 4,5-dihydroxy-2-isoxazolines and subsequently dehydrated to 4-hydroxyisoxazoles:[12/68]

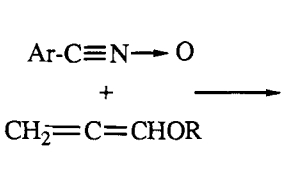


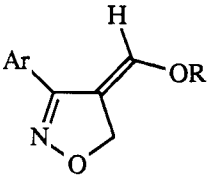

**197**

Ketene acetals are active dipolarophiles and their reaction with nitrile oxides yields 5,5-dialkoxy-2-isoxazolines,[26/59,31/59] which are useful starting material for preparing 5-alkoxyisoxazoles and 5-isoxazolinones. It is worthy pointing out that ketene mercaptals and aminals behave differently, yielding 5-alkylthio- or 5-aminoisoxazole derivatives, respectively (see § 1.3.2.2, pp. 200–201).

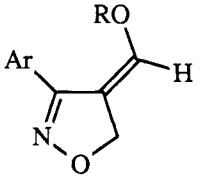
Somewhat peculiar is the behavior of allenic ethers of general structure $ROCH=C=CH_2$:[44/78,150/79] both double bonds are reactive toward nitrile oxides, the *sp*-hybridized carbon becoming prevailingly or exclusively bonded to the carbon atom of the 1,3-dipole (Table 2.23).

TABLE 2.23

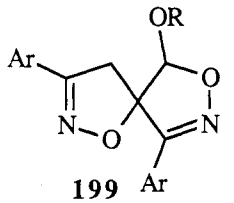


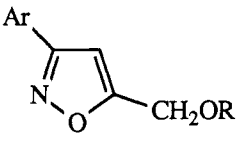

**198a**



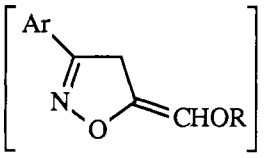

**198b**




**199**




**200**



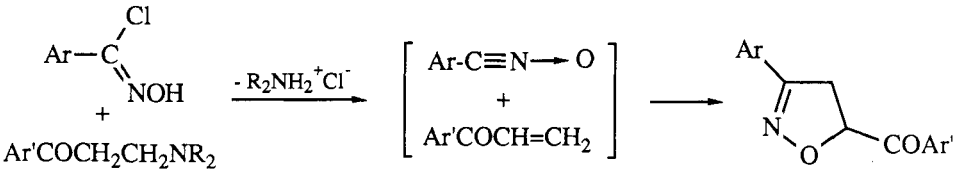

**201**

| Ar | R | Ratio 198a | : | 198b | : | 199 | : | 200 | Total yield (%) | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Ph | Me | 22.5 | : | 5.5 | : | 72 | : | 0 | 77 | 44/78 |
| Ph | Ph | 28.5 | : | 5.5 | : | 35 | : | 31 | 80 | 44/78 |
| $4\text{-}ClC_6H_4$ | Ph | 61 | : | 16.5 | : | 22.5 | : | 0 | 72 | 44/78 |
| $2,4,6\text{-}(Me)_3\text{-}3,5\text{-}Cl_2C_6$ | Ph | 51.5 | : | 21.5 | : | 27 | : | 0 | 70 | 150/79 |

The 4-methylene isoxazoline derivative has not been isolated but gives rise to the bis adducts **199**, in line with the high reactivity of the *exo*-methylene group. Sometimes a competitive regiochemical pathway is revealed by the presence of the isoxazole **200**, clearly arising from the ready aromatization of the intermediate **201**. When 3-phenoxy-1,2-butadiene is used as dipolarophile, the intermediate 4-methylene isoxazoline derivative prefers to isomerize through a Claisen rearrangement to an isoxazole compound[150/79] instead of cycloadding a second molecule of nitrile oxide. The prevalent regiochemistry is reversed with bromoallene:[143/74] besides a 10% yield of the bis adduct, the isomerized 3-phenyl-5-bromomethylisoxazole has been obtained in 41% yield. Allenic thioethers

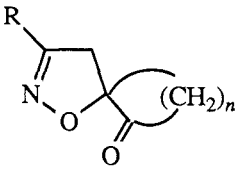
such as 1-phenylthiopropa-1,2-diene react with 2,6-dichlorobenzonitrile oxide with low site selectivity but regiospecifically, the central allenic carbon atom always becoming attached to the nitrile oxide carbon site.[145/83]

As mentioned earlier, the conjugation with a carbonyl group greatly enhances the reactivity of the double bond. Vinyl carbonyl compounds, such as acrolein[7/59] (and its diethylacetal) and alkyl (or aryl) vinyl ketones,[20/55.80/66.33/67.138/68.148/74] react regiospecifically to give 5-acyl-2-isoxazolines with excellent yields. A convenient synthetic method for preparing the latter compounds is the direct treatment of Mannich bases with hydroximoyl chlorides;[35/64.89/68.148/74] this variant seems particularly valuable for the synthesis of 5-aroyl derivatives:

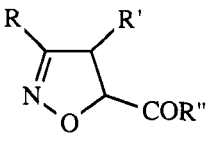



The only reported instance of noncomplete regio selectivity concerns the cycloaddition of benzonitrile oxide to *anti* phenyl vinyl ketoxime, which produces a 1.5% yield of the 4-regioisomer besides a 95% yield of the expected 3-phenyl-5-benzoyl-2-isoxazoline oxime.[44/67]

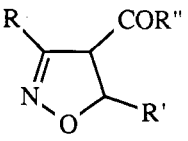
The cycloaddition of methylene-cycloalkanones[165/69] or of their heterocyclic counterparts (e.g., 4-methyleneisoxazolinones,[102/64.51/65]) is also straightforward and unidirectional, leading to spiro compounds of general structure **202**. The facile formation of the isoxazoline spiro derivative can be diagnostic for the presence of the *exo*-methylene group (even unconjugated) in complex molecules, such as methyl gibberellate,[34/63] pyrethrosine,[24B/71] or methylene steroids.[143/76.144/76.53/77]




**202**

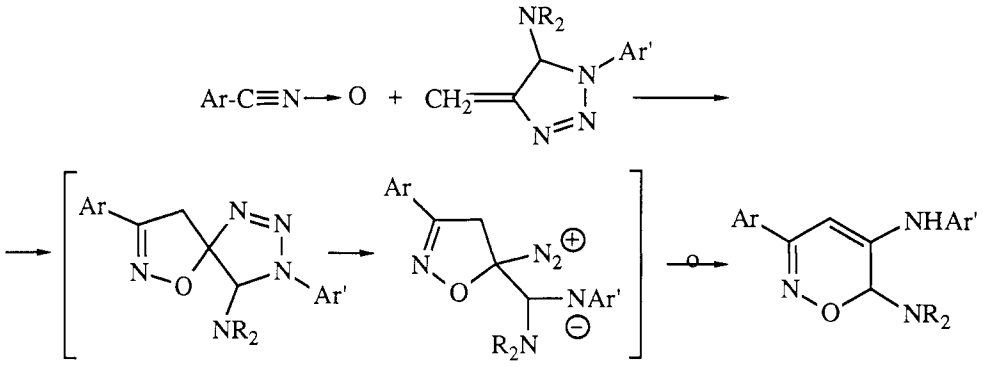



**203**



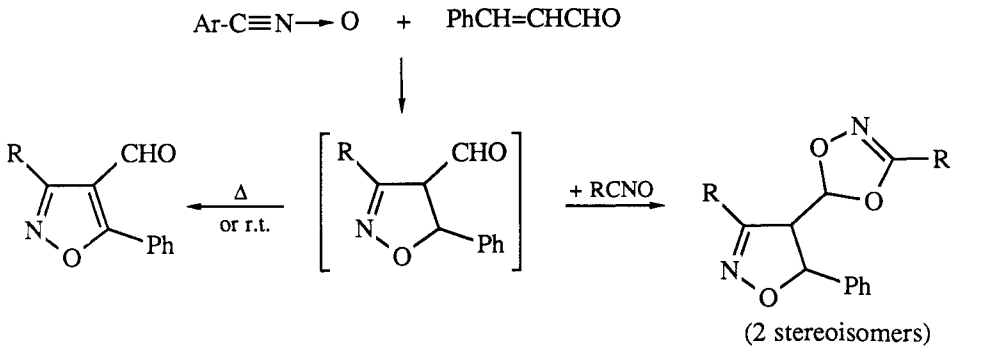

**204**

With some 4-methylene heterocycle the isoxazoline spiro compounds are too unstable to be separable, and transposition products can arise. This is the case of 5-amino-1-aryl-4-methylene-4,5-dihydro-1,2,3-triazoles, which cycloadd aromatic nitrile oxides to furnish oxadiazine derivatives:[151/80]



In other instances (e.g., 3-phenyl-4-methylene-5-morpholino-2-isoxazoline) the spirocompound is stable and eventually equilibrates with the diastereoisomer.[14/83]

Cinnamaldehyde reacts sluggishly with nitrile oxides to yield the unstable isoxazoline 4-carboxaldehyde regiospecifically, which, however, dehydrogenates spontaneously to the isoxazole aldehyde. Moreover, the carbonyl group reacts further with a second molecule of nitrile oxide to give the stable bis adduct:[177/83]

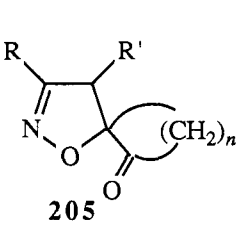


Apart from the symmetrical *trans*-1,2-dibenzoylethylene, which cycloadds benzonitrile oxide to give *trans*-3-phenyl-4,5-dibenzoyl-2-isoxazoline with 89% yield,[138/68] the asymmetrically substituted $\alpha,\beta$-ethylenic ketones, such as arylidene acetones, chalcones, or their hetero analogues, furnish a mixture of the two possible regioisomeric ketones **203** and **204**.[1/53,11/55,158/73,148/74] The two isomers can easily be separated by column chromatography or fractional crystallization and characterized by their spectroscopic and chemical properties.

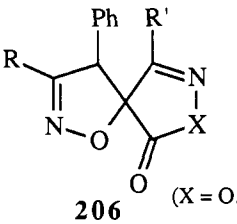
As a general rule, with chalcones the 5-acyl isomer **203** is largely prevalent or happens to be the only isolated cycloadduct; benzylidene acetones are less

regioselective and the composition of the isomer mixture depends on the nature of both the nitrile oxide and the arylidene group. For example, the cycloaddition of benzylideneacetone to acetonitrile oxide yields a 55:45 ratio of **203**/**204** (5-acyl to 4-acyl), whereas the same dipolarophile reacts with mesitonitrile oxide or with 2,4,6-trimethoxybenzonitrile oxide to give an 80:20 ratio or an exactly reverted 20:80 ratio, respectively.[158/73] The presence of a heteroaromatic five-membered residue (such as 2-furyl or 2-thienyl) on the double bond favors the prevalence of the 4-aroyl isomer **204**.[158/73] Only a 35–40% yield of 4-acetyl-5,5-dimethyl-3-phenyl-2-isoxazoline, along with diphenylfuroxan, has been obtained from the cycloaddition of benzonitrile oxide to a large excess of mesityl oxide.[158/73]

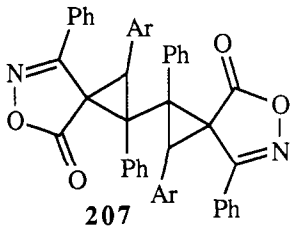
*β*-Chlorovinyl ketones usually furnish the 5-acylisoxazoles with nitrile oxides directly (see § 1.3.2.2, p. 197); the intermediate 3-aryl-4-chloro-5-aroyl-2-isoxazolines could be isolated only with some aroyl derivatives and operating under controlled conditions.[11/64] The exocyclic bond of alkylidene or arylidene cycloalkanones is an active dipolarophile and its reaction with nitrile oxide easily furnishes a large variety of spiro compounds having the general formula **205**.[29/61.2/63.8/64.80/65.84/66.201/79]




**205**



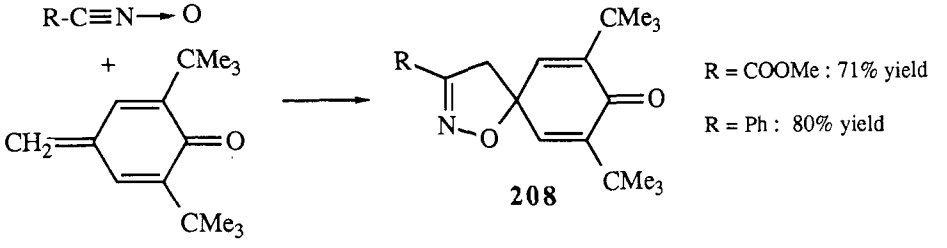

**206** (X = O, NPh)




**207**

Using benzylidene isoxazolones or benzylidene pyrazolones, spiro heterocycles of general structure **206** are obtained; sometimes a mixture of stereoisomers and/or minor amounts of the regioisomer are formed.[102/64.50/65.51/65.14C/68.15B/68.74/69.16/72.16B/72] When the cycloaddition is carried out at higher temperature, the nitrile oxide seems to enter a reaction in its carbene form, leading to higher-melting compounds of general formula **207**.[231/73.8B/74] The cycloaddition of nitrile oxides to quinone derivatives gives rise to bicyclic or polycyclic compounds and will be dealt with in Part 2 of this work.

The only quinone methide tested up to now, 2,6-di-*tert*-butyl-4-methylenecyclohexa-2,5-dienone, reacts with its exocyclic methylene double bond, conceivably more active than the endocyclic double bonds, yielding the spiro-2-isoxazolines **208**.[22/77]

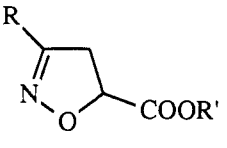



**208**

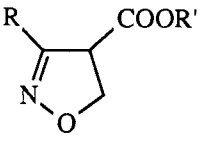
R = COOMe : 71% yield

R = Ph : 80% yield

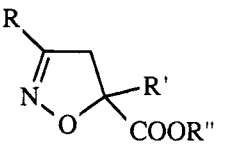
Excellent yields of 2-isoxazoline-5-carboxylic esters (**209**) are obtained by the cycloaddition of a large variety of nitrile oxides (fulminic acid included) to acrylic esters;[5/50,12/55,36/68,39/70,82/71,27/73,28/73,28C/73,101/73,184/76,49/78,9/79] in most cases the product is accompanied by small amounts of the regioisomeric 4-carboxylic ester **210**.[28C/73]




**209**



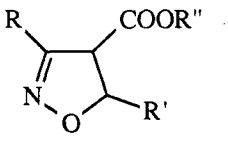

**210**



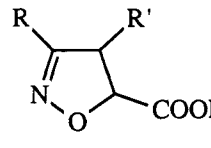

**211**

(R' = Me, COOR")

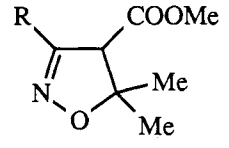
α-Substitution (with both electron-releasing and electron-attracting groups) definitively shifts the regioselectivity toward the 5-substituted ester: with alkyl methacrylate[5/50,36/68,89/68,28C/73,219/79] and dialkyl methylenemalonate[28C/73] only cycloadducts **211** are produced. β-Monosubstitution strongly diminishes the regioselectivity of the reaction: both alkyl crotonates and alkyl cinnamates deliver a mixture of the two possible isomers **212** and **213**.[27/73,28/73,28C/73,219/79] Table 2.16 (p. 494) furnishes some typical examples. A general trend toward a more or less large predominance of the 4-carboxylic ester **212** has been observed, usually more pronounced with cinnamates. With fulminic acid[28/73] or benzenesulfonylcarbonitrile oxide,[219/79] methyl crotonate affords a 38:62 mixture in favor of the 5-carboxylate ester **213**. The two regioisomers can easily be separated by chromatographic methods.




**212**




**213**




**214**

*trans*-Crotonates or cinnamates have been employed, and the stereochemistry has been maintained in the isoxazoline esters. Albeit in far lower yield, a mixture of the two *cis* isomers could be produced from benzonitrile oxide and alkyl *cis*-cinnamates.[51/59] Hetero analogues of cinnamates behave analogously.

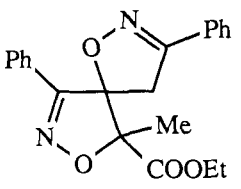
β,β-Disubstitution shifts the regiochemical control to completeness: only the isoxazoline 4-carboxylic esters **214** are formed from nitrile oxides and β,β-dimethylacrylate.[28C/73] Furthermore, methyl α-methylcrotonate reacts regiospecifically with propionitrile oxide to yield the isoxazoline 5-carboxylate.[112/84]

Strict stereochemical control has also been verified in the cycloaddition of nitrile oxides to stereoisomeric α,β-unsaturated dicarboxylic esters, such as

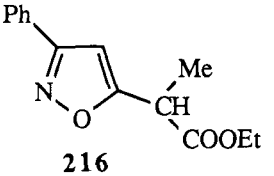
dialkyl fumarates and maleates,[5/50,12/52,10/55,12/55,37/60,138/68,27/73,28/73] and dialkyl mesaconates and citraconates.[12/52] With maleates or citraconates the 1,3-dipole is conveniently used as such in an inert solvent, since the *cis*-isoxazoline esters readily equilibrate into the *trans* isomers under the influence of traces of triethylamine at room temperature or by heating at 80°C.[27/73,184/76]

Maleic anhydride[5/50,12/55,86/64] and maleic *N*-arylimides[33/67,101/67,36/68,250/79] are widely used dipolarophilic partners, since the corresponding isoxazolines are usually insoluble and nicely purifiable products. On the reaction of nitrile oxides with free α,β-ethylenic carboxylic acid, where competition between the cycloaddition on the double bond and the 1,3-addition of the carboxylic group has been proved, see § 2.2.2.2b, p. 487.

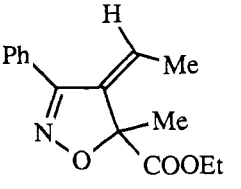
Allenic carboxylates show different reactivity toward benzonitrile oxide in dependence on the substitution pattern: starting from alkyl butadienoate and its 2-methyl derivative, both double bonds are reactive, but in the former case the four possible isomeric monoadducts isomerize immediately to the corresponding isoxazoles, whereas in the latter case the addition is unidirectional, and from the nonisomerizable 4-methylene compound the two stereoisomeric spiro-bis adducts of structure **215** are formed, along with the isoxazole **216**, which arose from the 5-exocyclic doubly bonded isoxazoline.[44/78]




**215**




**216**




**217**

With ethyl 2-methyl-2,3-pentadienoate only the double bond conjugated with the carboxylic group is reactive, and the unsaturated isoxazoline **217**, along with minor amounts of its stereoisomer,[44/78] are obtained. Sulfur-containing double-bond compounds behave in 1,3-dipolar cycloaddition to nitrile oxide roughly like their oxygenated counterparts, albeit with less pronounced regioselectivity. For example, α,β-unsaturated thioethers, such as propenyl- or styrylsulfides or 2,3-dihydrothiophene, furnish 5-thio-substituted-2-isoxazolines, usually contaminated with a minor amount of the 4-thio-substituted regioisomer.[52C/81,52D/81,278/83,160/84]

1-Phenylthio-1,3-butadiene adds nitrile oxides only on its terminal vinylic double bond, thus leading to 3-substituted 5-(2′-phenylthio)vinyl-2-isoxazolines:[155/82]

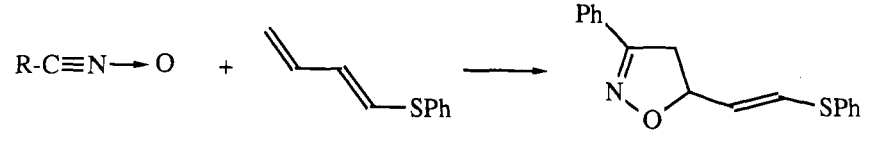
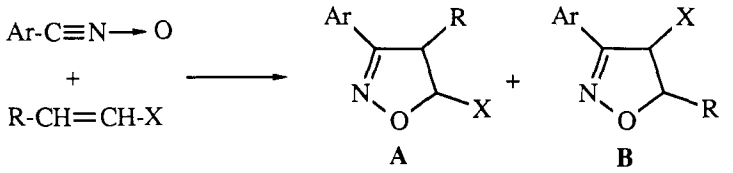


TABLE 2.24. CYCLOADDITION OF NITRILE OXIDES TO ACYCLIC SULFUR-CONTAINING OLEFINS




**A** **B**

| Ar | R | X | Total yield (%)[a] | Ratio A | : | B[b] | References |
|---|---|---|---|---|---|---|---|
| Ph | Me | (*E*)SMe | ~64 | 96 | : | 4 | 160/84 |
| Ph | Me | (*E*)SPh | ~60 | 84 | : | 16 | 160/84 |
| Ph | Ph | (*E*)SMe | 24 | 97 | : | 3 | 278/83 |
| Ph | Ph | (*Z*)SMe | 10 | 100 | : | 0 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Me | (*E*)SMe | ca. 54 (part.) | 96 | : | 4 | 160/84 |
| 2,4,6-$Me_3C_6H_2$ | Me | (*E*)SPh | ca. 48 (part.) | 83 | : | 17 | 160/84 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*E*)SMe | 90 | 100 | : | 0 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*Z*)SMe | 16 | 100 | : | 0 | 278/83 |
| 2,6-$Cl_2C_6H_3$ | H | SPh | 82 | | | | 52D/81 |
| 4-$NO_2C_6H_4$ | H | SPh | 63 | | | | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | Me | (*E*+*Z*)SPh | 78 | ca. 100 | : | traces | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | Ph | (*E*)SPh | 68 | 80-90 | : | 10 | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | Ph | (*Z*)SPh | 50 | 80-90 | : | 10 | 52D/81 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*E*)SPh | 59 | 100 | : | 0 | 52D/81 |
| 3,5-$Cl_2$-2,4,6-$Me_3C_6$ | Ph | (*E*)SPh | 75 | 100 | : | 0 | 52D/81 |
| 2,6-$Cl_2C_6H_3$ | $CH_2Cl$ | (*E*)SPh | 45 | 100 | : | 0 | 52C/81 |
| 2,4,6-$Me_3C_6H_2$ | $CH_2Cl$ | (*E*)SPh | 50 | 100 | : | 0 | 52C/81 |
| 4-$NO_2C_6H_4$ | $CH_2Cl$ | (*E*)SPh | 10-15 | 100 | : | 0 | 52C/81 |
| 2,6-$Cl_2C_6H_3$ | $CH_2NH_2$ | (*E*)SPh | 40 | 100 | : | 0 | 52C/81 |
| 2,4,6-$Me_3C_6H_2$ | $CH_2NMe_2$ | (*E*)SPh | 40 | 100 | : | 0 | 52C/81 |
| Ph | Ph | (*E*)SOMe | | 45 | : | 55 | 278/83 |
| Ph | Ph | (*Z*)SOMe | ca. 33 | 90 | : | 10 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*E*)SOMe | | 79 | : | 21 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*Z*)SOMe | 48 | 70 | : | 30 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | H | $SO_2Me$ | | 94 | : | 6 | 91/77 |
| 3,5-$Cl_2$-2,4,6-$Me_3C_6$ | H | $SO_2Ph$ | 80 | 91 | : | 9 | 211/83 |
| Ph | Me | (*E*)$SO_2Ph$ | 78 | 0 | : | 100 | 163/82 |
| Ph | Ph | (*E*)$SO_2Me$ | 51 | 29 | : | 71 | 278/83 |
| Ph | Ph | (*Z*)$SO_2Me$ | 72 | 22 | : | 78 | 278/83 |
| Ph | Ph | (*Z*)$SO_2C_4H_9$-*n* | 45 | 21 | : | 79 | 278/83 |
| Ph | Ph | (*E*)$SO_2Ph$ | 56 | 16 | : | 84 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*E*)$SO_2Me$ | 34.5 | 57 | : | 43 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*Z*)$SO_2Me$ | 54 | 2 | : | 98 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*Z*)$SO_2C_4H_9$-*n* | 74 | 5 | : | 95 | 278/83 |
| 2,4,6-$Me_3C_6H_2$ | Ph | (*E*)$SO_2Ph$ | 82 | 38 | : | 62 | 278/83 |
| 3,5-$Cl_2$-2,4,6-$Me_3C_6$ | Me | (*E*)$SO_2Ph$ | 60 | 10 | : | 90 | 211/83 |
| 3,5-$Cl_2$-2,4,6-$Me_3C_6$ | Ph | (*E*)$SO_2Ph$ | 75 | 40 | : | 60 | 211/83 |
| 3,5-$Cl_2$-2,4,6-$Me_3C_6$ | COPh | (*E*)$SO_2Ph$ | 88 | 25 | : | 75 | 211/83 |

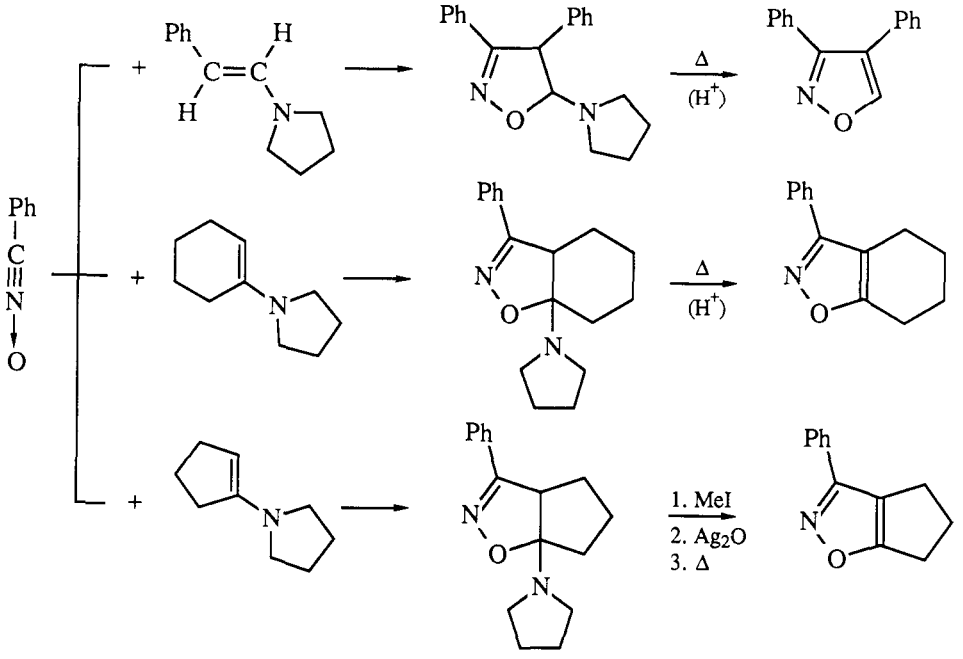
[a]Of purified products.

[b]Measured by NMR integration on cycloaddition mixture.

The sulfonyl group, although far less activating, mimics the carbonyl group, and thus both acyclic[154/66,91/77,52C/81,52D/81,163/82,211/83,278/83] and cyclic[121/67,195/74,232/79,155/81,163/82,197/82,276/82,278/83] unsaturated sulfones or sulfoxides are active dipolarophiles, leading to regiospecific monoadducts or to a mixture of regioisomers, depending on the nature of the substituents on the double bond and on the nitrile oxide. Typical examples are reported in Table 2.24. Whereas the sulfonylisoxazolines are well-isolable, stable compounds, sulfinylisoxazolines are markedly unstable and undergo RSOH elimination, furnishing isoxazole derivatives.[211/83,278/83]

Turning now to double-bond compounds with nitrogen-containing functional groups, enamines of both acyclic aldehydes or ketones[37/63,73/64,13/65,28/67,33/67,57/63,35/68,27/69,68/70,26/73,180/80] and cyclic ketones[38/63,32/64,73/64,79/66,96/67,27/69,6/71,235B/72,74/78] are very active dipolarophiles: by reaction with nitrile oxides, without exception, only 2-isoxazolines substituted in the 5-position with the basic residue are regiospecifically produced. Even the sterically encumbered 2-methyl-1-morpholinyl-1-propene does not escape this rule, although the cycloaddition reaction takes place with lowered (17%) yields.[27/69,82/71,26/73]

3-Phenyl-5-diethylamino-2-isoxazoline can be generated directly, albeit in low yield (12%), by treatment of benzonitrile oxide with an excess of triethylamine; the intermediacy of *N*,*N*-diethylvinylamine has been inferred.[309/83] These 5-amino-substituted 2-isoxazolines owe their interest to the easy elimination (thermal- or acid-promoted) of the amino residue to give the corresponding

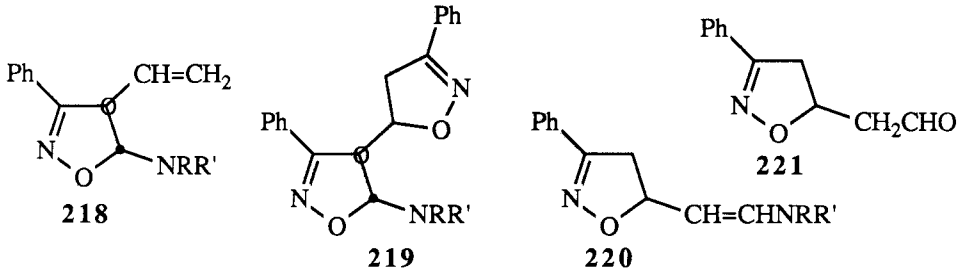



**Scheme 2.13**

isoxazoles. This elimination even occurs spontaneously at room temperature when an electron-attracting group (such as COR, COOR, or CN) is linked to the double bond, thus representing a convenient synthesis of 4-acyl-, 4-alkoxycarbonyl-, or 4-cyanoisoxazoles (see § 1.3.2.2, pp. 199–200). Some typical examples of 1,3-dipolar cycloaddition with enamines are shown in Scheme 2.13.[38/63,32/64,26/73]

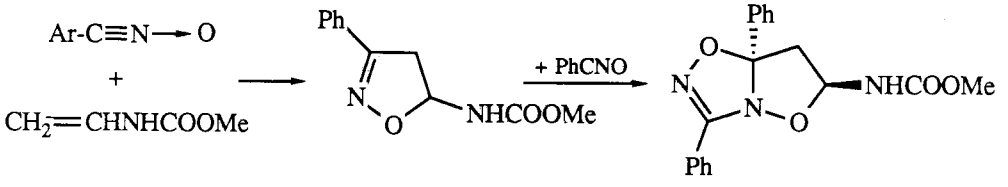
The condensation can conveniently be carried out directly with the precursors of the nitrile oxides (i.e., hydroximoyl chlorides), using as a dehydrohalogenating agent either one molecule of triethylamine or a second molecule of the enamine. The only exception known to this general behavior of enamines is the peculiar result reported for the reaction of diphenylacetohydroximoyl chloride with 2 mol of 1-morpholinylcyclohexene. Instead of the cycloadduct expected, the corresponding morpholinooxime has been isolated.[201D/81]

Both double bonds of 1-amino-substituted 1,3-butadienes are reactive toward benzonitrile oxide: indeed, the monoadduct **218**, formed from the attack to the enaminic double bond, as well as two stereoisomeric bis adducts (**219**),




could be isolated. The other monoadduct (**220**) was not isolated, but instead, the aldehyde (**221**), along with the crotonic condensation product thereof, was separated.[210/70] The [6 + 4] periselective cycloaddition of 6-dimethylaminofulvene should be remembered here[190/71] (see p. 504).

Methyl *N*-vinylcarbamate gives the expected 5-substituted 2-isoxazoline monoadduct only if an excess of dipolarophile is used; otherwise, a *syn* attack of a second molecule of nitrile oxide occurs on the activated C=N double bond, resulting in a 100% stereoselective bis adduct:[152/80]




The directive power of the amino group seems to vanish when the nitrogen atom is not bonded directly to the unsaturation: for example, cinnamyl-

arylamines are reported to give 3,5-diphenyl-4-arylaminomethyl-2-isoxazolines regiospecifically with benzonitrile oxide.[136/71]

5-Isoxazolinyl amino acid derivatives have been prepared by 1,3-dipolar cycloaddition reaction of various vinylglycine derivatives.[14/63,263/80,235/81,285/82,161/84,174/84] Some difficulties have been reported with chloronitrile oxide, which can be circumvented either by generating the nitrile oxide from dichloroformaldoxime with silver nitrate,[285/82] or by reacting the dipole with a vinyl nitronate and subsequently reducing the nitro-substituted cycloadduct.[146/76]

The azido group also has a powerful directing effect, and the cycloaddition reaction of azidostyrenes or azidovinyl ketones with nitrile oxides always delivers 5-azido-2-isoxazolines. However, these compounds are not always sufficiently stable, and often the isoxazole, derived from elimination of hydrazoic acid, is produced directly.[176/74] For example, *trans*-β-azidostyrene gives a 64% yield of the relatively stable 3,4-diphenyl-5-azido-2-isoxazoline, whereas α-azidostyrene furnishes the same yield of 3,5-diphenylisoxazole. Analogously, α-azidovinyl ketones give isolable, although barely stable, 5-azido-5-acyl-2-isoxazolines, but *E*-β-azidovinyl ketones afford 4-acylisoxazoles directly.

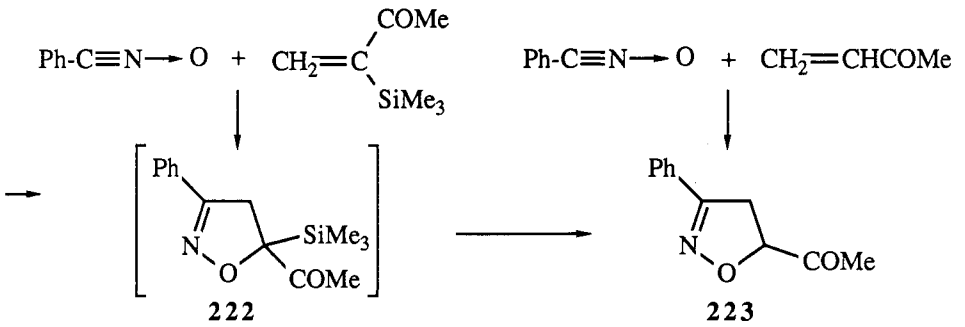
The behavior of azidostyrenes is similar to that of halogeno- and nitrostyrenes: α-bromostyrene and benzonitrile oxide afford 3,5-diphenylisoxazole,[9/50] and *E*-β-bromostyrene yields mainly 4-bromo-3,5-diphenyl-2-isoxazoline[9/50] accompanied by substantial amounts of the regioisomer.[26/73] Analogously, *E*-β-nitrostyrene furnishes with benzonitrile oxide a 67:33 mixture of 4-nitro- and 5-nitro-2-isoxazoline, thermally unstable;[26/73] the former isomer could be isolated.[8/54] Other β-nitrostyrenes behave similarly.[2/56]

Nitroethylene[225/76,91/77,249/82] and other 2-nitro[151/71,225/76] or 3-nitro olefins[160/71,209/73,246/80,247/80] invariably give 5-nitro (or 5-α-nitroalkyl)-2-isoxazoline derivatives regioselectively; some of them are unstable and furnish isoxazoles directly. 1-Nitropropene (or its 3,3,3-trichloroderivative) reverses the cycloaddition direction, and 3-aryl-5-methyl (or 5-trichloromethyl)-4-nitro-2-isoxazolines are obtained by reaction with aromatic nitrile oxides.[225/76,248/82] α-Nitrostilbene is a poor dipolarophile, and low yields of triphenylisoxazole are formed in cycloaddition with benzonitrile oxide.[8/54] Acrylonitrile[8/50,37/60,118/66,18/71,26/73,101/73,91/77,198/78] and acrylamide[27/67,28/67,121/67,36/68,27/69] are very active dipolarophiles, and consequently, 5-cyano- or 5-carboxamido-2-isoxazolines are easily available compounds.

Substitution at the CC double bond lowers its dipolarophilicity, and the CN triple bond can enter in competition with the former bond, leading to mixtures of 2-isoxazolines and 1,2,4-oxadiazoles, or to the latter derivatives only (see § 2.2.2.2c, p. 501). For example, in the cycloaddition of cinnamonitrile with nitrile oxides, the CC double bond reacts about three times faster than the CN triple bond;[79B/84] nevertheless, β-amino substitution shifts the 1,3-dipolar reactivity toward the CN bond, this leading to exclusive or prevalent formation of 1,2,4-oxadiazole derivatives.[143/77,159/80] On the other hand, *N*,*N*-disubstituted β-aminocinnamonitriles react with their CC double bond only.[159/80] The site selectivity is also affected remarkably by the nature of the substituents on the aryl group.

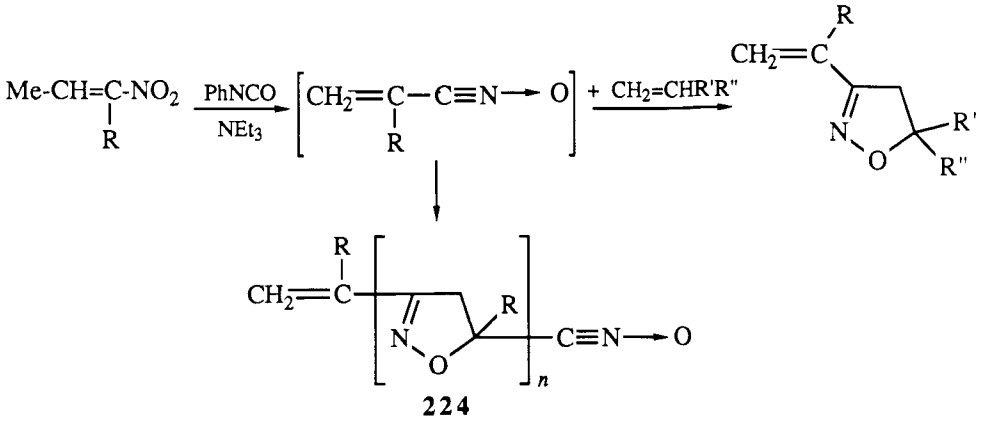
Special precautions are necessary to isolate the unstable 4-cyanoisoxazoline phosphonium salt from 4-nitrobenzonitrile oxide and β-cyanoallylic phosphonium ylide; base-promoted elimination of triphenyl phosphonium methyl ylide is very easy and the 4-cyanoisoxazole can be obtained with good yields.[149/76] Nonconjugated unsaturated nitriles, such as allylcyanide[3/65,27/69] and 5-hexenonitrile,[119/66] furnish the expected 5-substituted 2-isoxazolines.

Several elemento-organic unsaturated compounds have been employed as dipolarophiles in the 1,3-dipolar cycloaddition to nitrile oxides (e.g., vinyl boronates,[152/66] vinyl and allyl phosphoranes[225/68,224/75] or cyclic phosphoranes,[50/67] alkenyl silanes[44/64,47/65,252/70,71/80,147/81,281/82,209/83]). A kinetic study of the latter type of compound revealed a higher rate of cycloaddition in comparison with standard unsaturated hydrocarbons.[226/68,253/70] On the contrary, some substituted vinylsilanes are reported to be slightly less reactive than the corresponding nonsilylated ethylenes.[281/82,209/83] Moreover, α-acetylvinyltrimethylsilane cycloadds benzonitrile oxide to give unexpectedly 5-acetyl-3-phenyl-2-isoxazoline (**223**),[281/82,209/83] possibly through the intermediacy of the cycloadduct **222**:




It should also be pointed out that, by contrast, 3-phenyl-5,5-bis(trimethylsilyl)-2-isoxazoline does not desilylate either spontaneously or in the presence of cesium fluoride.[209/83]

Unsaturated nitrile oxides, such as acrylo- or methacrylonitrile oxide, have been prepared by treatment of nitropropenes with phenyl isocyanate and triethylamine (Mukaiyama's method): they are unstable and polymerize to give oligomers of structure **224**. However, when the nitrile oxide is generated in the presence of a four- to five-fold excess of an active dipolarophile, 3-vinyl (or 3-isopropenyl)-2-isoxazolines can be obtained with moderate to good yields:[201C/81]



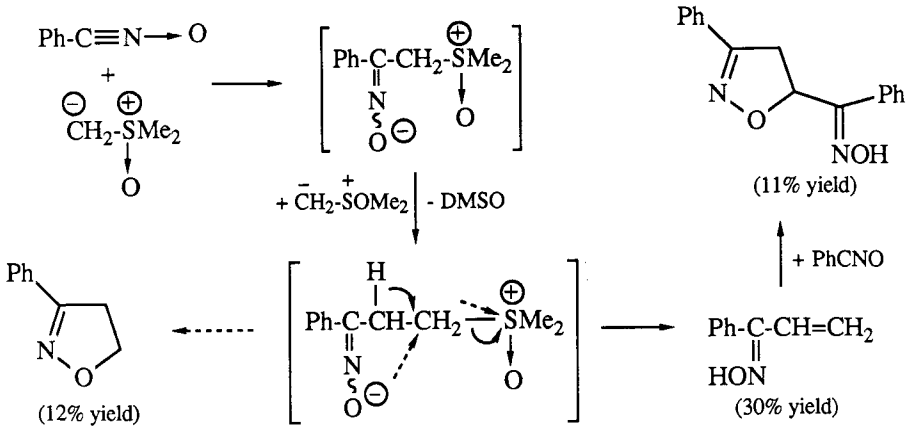
224

The aforementioned examples of 1,3-dipolar cycloaddition reactions of nitrile oxides (or of their precursors) with ethylenic compounds do not exhaust the synthetic possibilities of this type of reaction, and reference is made to Part 2 of this work for further examples. The number of active dipolarophiles seems almost endless. To summarize the spectrum of activity, it can be safely asserted that monosubstituted and 1,1-disubstituted olefins are always reactive, yielding with ease the corresponding 5-mono- or 5,5-disubstituted 2-isoxazoline derivatives (with minor amounts of the 4-regioisomer, when highly electron-deficient olefins are used). 1,2-Disubstituted olefins react more sluggishly unless some activating groups are present (e.g., conjugated carbonyl or alkoxycarbonyl, cyano, aryl, CC double bond, etc.), and problems of regio- and stereoselectivity can arise, leading to mixtures of products. Tri- and tetra-substituted olefins are usually unreactive and the dimerization (or isomerization) reaction of the nitrile oxides occurs overwhelmingly. Only few examples (with low yields) of successful reaction between polysubstituted double-bond compounds and activated nitrile oxides are known.

### *2.2.2.3 [CNO + C + C] Process: Reaction of Nitrile Oxides with Ylides*

The 1,3-dipolar cycloaddition, although by far the most important for synthetic purposes, is not the only reaction of nitrile oxides leading to 2-isoxazoline derivatives. Phosphor ylides react with nitrile oxides to give a true cycloadduct, which can either be stable enough to be isolated or instead, evolve to decomposition or fragmentation products. On the contrary, sulfur ylides usually act as nucleophiles, and the primarily formed adduct can transform into an acyclic product or cyclize to isoxazoline or isoxazole derivative.

For example, the reaction between benzonitrile oxide and dimethyloxosulfonium methylide in excess yields a mixture of *syn*-acrylophenone oxime and of 3-phenyl-2-isoxazoline presumably through the following mechanism:[174/66.64/67]

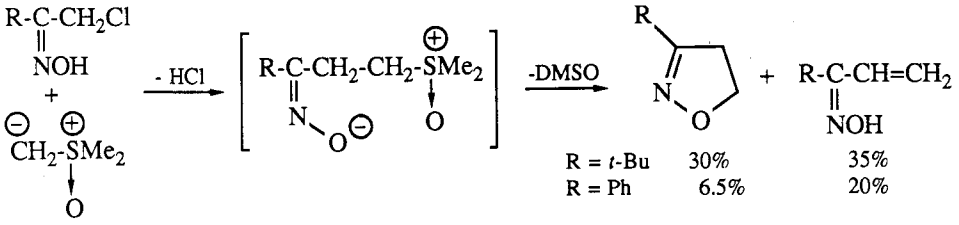



Analogous results have been obtained with dimethylsulfonium methylide.[38/67] Use of the more stable dimethylsulfonium phenacylide[213/70] and dimethyloxosulfonium 4-nitrobenzylide[141/77] made it possible to isolate 3-phenyl-4,5-dibenzoyl-2-isoxazoline with 15% and 3-phenyl-4,5-di(*p*-nitrophenyl)-2-isoxazoline with 31% yield, respectively. Triphenylarsonium methylide behaves somewhat differently, since with benzonitrile oxides it gave a total 20% yield of the two stereoisomeric 3-phenyl-4-benzoyl-2-isoxazoline oximes, together with 11% of 3,5-diphenylisoxazole.[44/67]

### *2.2.2.4 [CCNO + C] Processes*

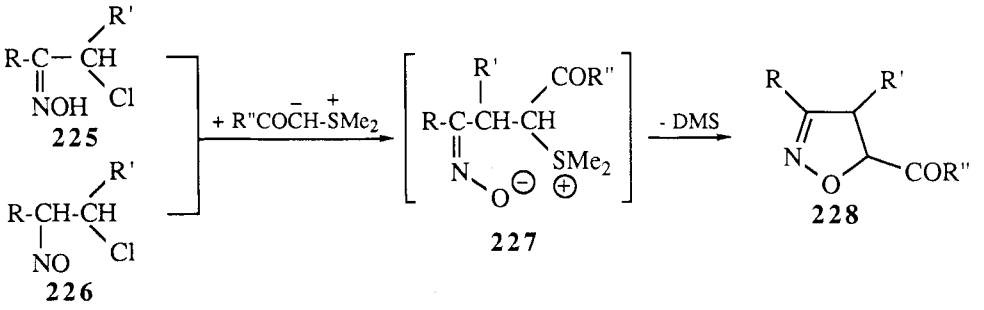
#### a. Condensation of α-Chlorooximes with Sulfur Ylides

α-Methylene oximes are usually the principal products obtainable when the α-chlorooximes **225** (from oximation of α-chloroketones) or the α-nitrosochlorides **226** (from addition of NOCl to olefins) are treated with dimethylsulfoxonium methylide. Only in individual cases (e.g., when R = *t*-Bu or Ph) is a mixture of vinyl oxime and 3-monosubstituted 2-isoxazoline formed in comparable amount:[64/67,50/68,75/69]




For an approach involving the same intermediate, compare the reaction between sulfur ylides and nitrile oxides (§ 2.2.2.3, pp. 523–524). By contrast,

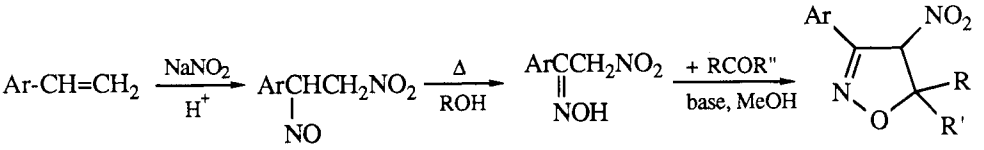
excellent yields of 5-acyl-2-isoxazolines (**228**) are obtained from α-chlorooximes or α-nitrosochlorides and the less basic keto-stabilized sulfonium (or arsonium) ylides:[226/72]



4,5-Disubstituted compounds all have the *trans* structure. When R′ = OEt, the isoxazoline cannot be isolated, because it spontaneously eliminates ethanol to give the corresponding isoxazole.

b. Condensation of α-Nitrooximes with Carbonyl Compounds

A simple and convenient synthesis of 4-nitro-2-isoxazolines is based on the condensation of more or less substituted α-nitroacetophenone oximes with aldehydes or ketones:[281/76,287/77,253/79,257/79]

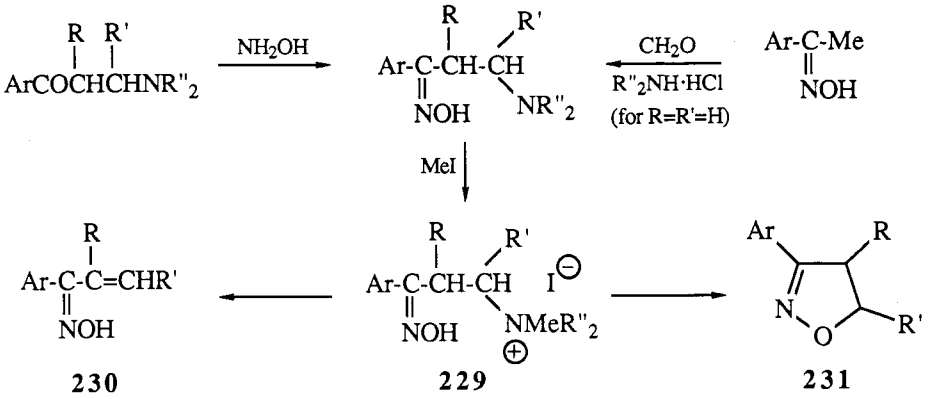


The starting nitrooxime (which may not be isolated) is available from the corresponding styrene by diazotization to the pseudo-nitrosate and subsequent heating in alcohol. The condensation itself is catalyzed by organic bases, goes faster with aldehydes than with ketones, and is favored by electron-attracting groups in the aryl ring.

### *2.2.2.5 [CCCNO] Processes*

a. Cyclization of Oximes of Mannich Bases Quarternary Salts

Mannich bases are known to react easily with hydroxylamine to yield fairly stable oximes. After quaternization of the latter compounds to **229**, treatment with bases furnishes vinyl oximes (**230**) and/or 2-isoxazolines (**231**):[13/53,82/63,203/70,35/73]




Considering the easy availability of the starting materials, this method seems especially valuable for the synthesis of 3-aryl-monosubstituted 2-isoxazolines; however, to reach convenient yields, several factors must be taken into account. A thorough investigation of the reaction[153/67,220/70,119/71,231/72,232/72] led to the following conclusions:

1. The two reactions are competitive, and cyclization to isoxazoline does not proceed through an intermediate vinyl oxime but involves direct intramolecular displacement by the oximate anion. Even at pH 8 the oximate anion is still the nucleophilic species.
2. Competition between elimination and cyclization processes depends strongly on variations in oxime configuration, base–solvent system, side-chain substitution, and the nature of the leaving group. Substitution in the aryl group does not notably affect the balance between the two processes.
3. Only *anti*-aryl oximes are susceptible of cyclization, this configuration is the usual one for salts derived from acetophenones (**229**: R = H; R′ = H or aryl or alkyl). With 2-substituted methiodides (**229**: R ≠ H) mixtures of stereoisomers are involved, whose ratio usually is solvent dependent (e.g., pyridine favors formation of the *anti* form). A steric factor should not be excluded, since the 2-methyl derivative (*anti* form) cyclizes completely, while in the case of the 2-phenyl derivative, elimination predominates.
4. Aqueous bases favor elimination, whereas alkoxides in absolute alcohol shift the balance toward a more or less exclusive cyclization.
5. Cyclization is greatly favored by a decrease in the $pK_a$ value of the leaving group: thus excellent yields of 2-isoxazolines are reached by use of morpholino or, even better, of *N*-methylanilino Mannich bases (the latter even in aqueous media).

Some characteristic data are given in Table 2.25. Unsaturated quaternary salts,

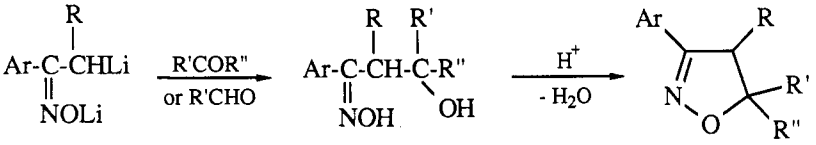
TABLE 2.25. COMPETITION BETWEEN CYCLIZATION AND ELIMINATION IN BASE TREATMENT OF QUATERNARY SALTS [ArC(=NOH)CHRCHR'$NR_2$"(Me)]$^+$ 231/72

| Ar | R | R' | Base/solvent | $NR_2$" | Yield (%) in: 2-Isoxazoline | Vinyloxime |
|---|---|---|---|---|---|---|
| Ph | H | H | $OH^-/H_2O$ | $NMe_2$ | 1.5 | 98 |
| 4-$NO_2C_6H_4$ | H | H | $OH^-/H_2O$ | $NMe_2$ | 18 | 61 |
| Ph | H | H | $EtO^-/EtOH$ | $NMe_2$ | 71 | 26 |
| Ph | H | H | $t$-$BuO^-/t$-BuOH | $NMe_2$ | 97 | 2.7 |
| Ph | H | H | $OH^-/H_2O$ | $N(CH_2)_5$ | 0.5 | 98 |
| Ph | H | H | $OH^-/H_2O$ | $NMeCH_2Ph$ | 8 | 85 |
| Ph | H | H | $OH^-/H_2O$ | $N(CH_2CH_2)_2O$ | 33 | 60 |
| Ph | H | H | $OH^-/H_2O$ | NMePh | 97 | 1 |
| Ph | Me | H | $OH^-/H_2O$ | $NMe_2$ | 51 | 25 |
| Ph | Ph | H | $OH^-/H_2O$ | $NMe_2$ | 16 | 76 |
| Ph | H | Me | $OH^-/H_2O$ | $NMe_2$ | 10 | 78 |
| Ph | H | Me | $EtO^-/EtOH$ | $NMe_2$ | 74 | 9 |
| Ph | H | Ph | $OH^-/H_2O$ | $NMe_2$ | ≥98 | ≤2 |

such as those originated from benzylidene acetone or its heteroaryl analogues, behave similarly: the *anti*-styryl oxime cyclizes by base treatment to 3-styryl-2-isoxazoline (or its heteroaryl analogues).[31/58.33/58.29/59.6/63]

### b. Cyclization of β-Hydroxy Ketoximes

β-Hydroxy ketoximes of general structure **232** form 2-isoxazoline derivatives (**233**) easily by treatment with concentrated sulfuric acid.[162/76] The β-hydroxyoximes are in turn readily available by condensation of $C(\alpha)',O$-dilithiooximes with aldehydes or ketones:

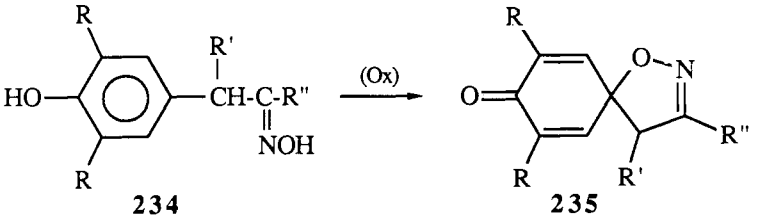



**232** **233**

This interesting approach, which employs simple starting materials and leads to one specific regioisomer, seems particularly attractive for the synthesis of multisubstituted isoxazolines, where the nitrile oxide route (see above) furnishes mixtures of regioisomers. In some cases (e.g., when condensation with *p*-anisaldehyde is involved) the β-hydroxyoxime may not be isolated and the 2-isoxazolines are obtained directly after treatment of the crude reaction mixture with 3 *N* hydrochloric acid. Thus a substantial [CCNO + C] process can be realized here.

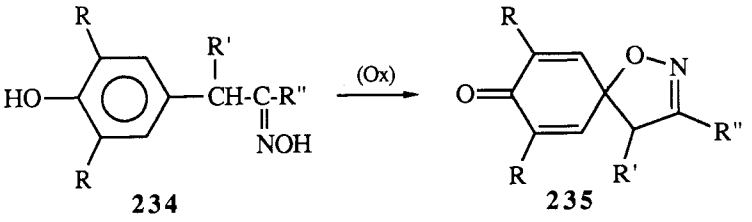
### c. Oxidative Cyclization of Phenolic Oximes

After the discovery that some brominated metabolites for *Aplysina* (= *Verongia*) sponges have spirocyclohexadienylisoxazoline entities[131/72,223/79] (see, e.g., aerothionin on p. 418), some efforts were addressed toward the synthesis of this moiety. In this sense the action of several oxidizing agents on phenolic oximes of structure **234** has been studied.[124/75,125/75,232/83] In fact, whereas silver oxide, alkaline ferricyanide, sodium periodate, and Fremy's salt failed to effect cyclization, this goal was achieved with lead tetraacetate, or better, with manganese(III) tris(acetylacetonate)(MTA) or with *N*-bromosuccinimide, according to the following equation:




**234** **235**

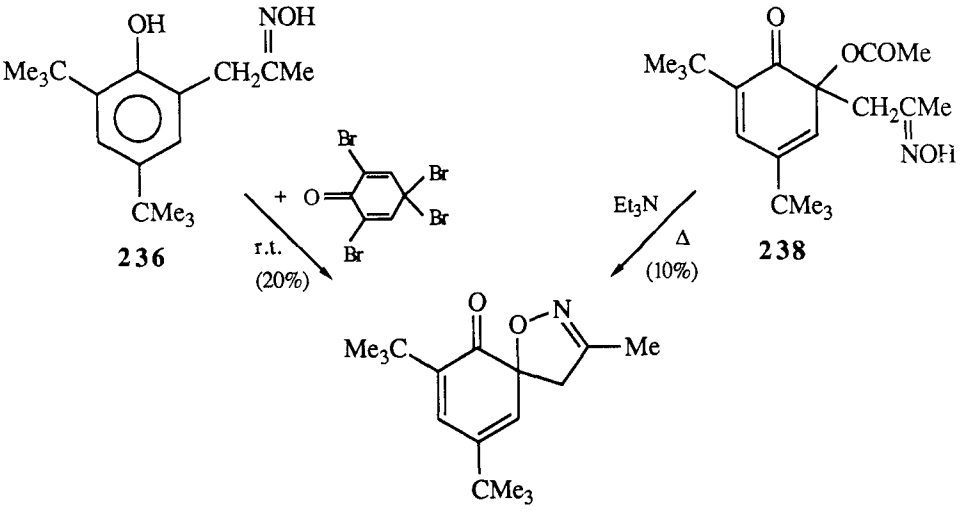
TABLE 2.26. OXIDATIVE CYCLIZATION OF PHENOLIC OXIMES TO SPIROISOXAZOLINES




**234** **235**

| R | R' | R" | Cyclizing agent | R | R' | R" | Yield (%) | References |
|---|---|---|---|---|---|---|---|---|
| H | H | H | MTA, reflux MeCN | H | H | H | 19 | 124/75 |
| H | H | Me | MTA, reflux MeCN | H | H | Me | 50 | 124/75 |
| *t*-Bu | H | Me | MTA in MeCN | *t*-Bu | H | Me | 40 | 124/75 |
| *t*-Bu | H | Me | MTA in EtOH | *t*-Bu | H | Me | 62 | 124/75 |
| *t*-Bu | H | Me | NBS | *t*-Bu | H | Me | 72 | 125/75 |
| *t*-Bu | Me | Me | MTA in MeCN | *t*-Bu | Me | Me | 31 | 124/75 |
| *t*-Bu | Me | Me | $Pb(OAc)_4$, r.t. in PhH | *t*-Bu | Me | Me | 10 | 124/75 |
| H | H | COOMe | MTA, refluxing MeCN | H | H | COOMe | 42 | 124/75 |
| | | | $Br_2/H_2O$ in AcOMe | Br | H | COOMe | 65 | 125/75 |
| Br | H | COOMe | MTA, refluxing MeCN | Br | H | COOMe | 21 | 124/75 |
| | | | anodic oxidation | Br | H | COOMe | ca. 100 | 234B/81 |

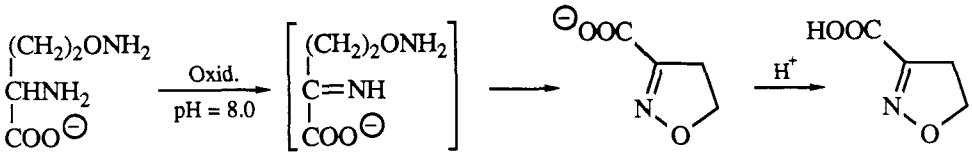
An almost quantitative yield of **235** (R = Br, R′ = H, R″ = COOMe or CONHR) has been reached by means of anodic oxidation.[234B/81.233/83] Use of bromine water accomplished both cyclization and bromination of the *ortho* positions to the starting phenolic group. *Ortho*-phenolic oximes do not cyclize with the foregoing reagents, but instead, gave benzofuran derivatives and the parent ketone. Nevertheless, a low yield of cyclized product was finally achieved on oxime (**236**) with tetrabromocyclohexa-2,5-dienone in acetonitrile at room temperature (Table 2.26). The same spiro compound (**237**) was prepared by base-promoted cyclizing elimination of acetic acid from the β-acetoxyoxime **238** (Scheme 2.14).[125/75] A further example of the use of tetrabromocyclohexadienone concerns a dimeric phenolic oxime.[19/78] In another case of *ortho*-phenolic oxime, bromine and tetrabromocyclodienone proved unsuccessful but cyclization could be achieved, although in low yield, by using thallium(III) trifluoroacetate.[306/83]



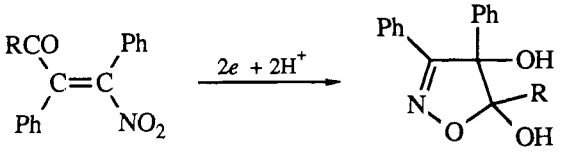

**Scheme 2.14**

d. Other Cyclizations

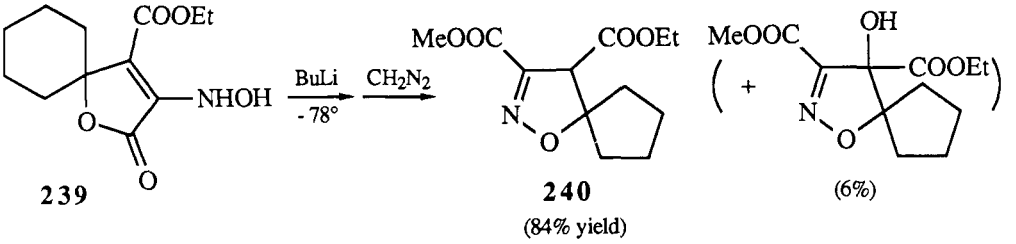
Although of low preparative interest, it is worth mentioning that the enzymatic oxidation (with L-amino acid oxidase) of L-canaline (i.e., γ-aminooxy-α-aminobutyric acid) or its derivatives involves a cyclization step, leading to isoxazoline-3-carboxylic acid:[5/84]



A [5 + 0] process is examplified by the electrochemical reduction of β-nitrostyryl ketones, which give 4,5-dihydroxy-2-isoxazoline derivatives with excellent yields:[185/80,24/81]




Another [5 + 0] process of limited applicability is the base-catalyzed rearrangement of hydroxyamino lactone (**239**) to the 5-spiro-2-isoxazoline-3,4-dicarboxylic ester **240**:[25/75]




**239**

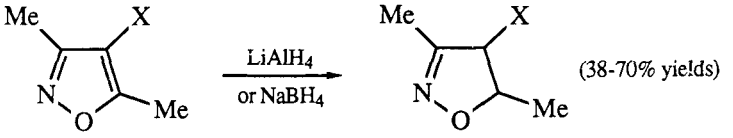
**240**
(84% yield)

(6%)

### *2.2.2.6 Syntheses from Heterocyclic Compounds*

#### a. From Isoxazoles

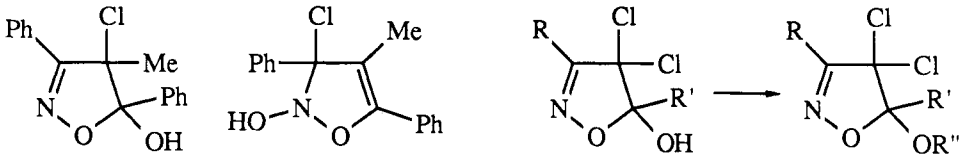
As a rule, the isoxazole ring is remarkably stable toward reduction with complex metal hydrides (see § 1.4.3.2, pp. 281–282) unless preceded by quaternarization. Nevertheless, the presence of a strong electron-withdrawing group in the 4-position, such as $NO_2$, CN, or $SO_2OR$, promotes the reduction of the substituted 3,5-dialkylisoxazole to the corresponding 2-isoxazoline in reasonable yields:[270/83]




When nitro or cyano groups are involved, a mixture of the two diastereoisomers is obtained, which can easily be converted into the pure *trans* isomer by basic treatment. This isomer is formed only when a sulfonyl group is present. An analogous nucleophilic addition to the ring C=C bond has been reported when 3,5-dimethyl-4-nitroisoxazole is treated with *n*-butyllithium: instead of giving the expected side-chain lithiation in the 5α-position (see § 1.4.7.1, pp.

324–325), 5-butyl-3,5-dimethyl-4-nitro-2-isoxazoline is obtained in 50% yield.[212/82]

Selective addition to the C=C bond of isoxazoles is also known with hypochlorous acid. For example, treatment of 3,5-diphenyl-4-methylisoxazole with hydrochloric acid and hydrogen peroxide resulted in a 65% yield of the 4-chloro-5-hydroxy-2-isoxazoline **241**, to which originally the isomeric 4-isoxazoline structure **242** was allotted.[39/64,97/69,37B/81] The same reaction, extended to 4-unsubstituted isoxazoles and carried out with an excess of chlorinating agent, afforded analogous products (**243**) chlorinated in the 4-position.




**241** **242** **243** **244**

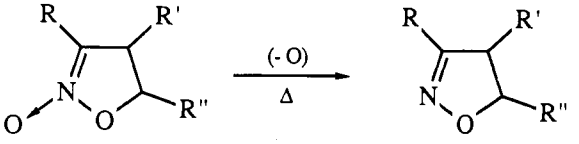
These compounds can be stabilized by alkylation or acylation to **244**, and their structure has been assured definitively by independent synthesis from the 2,2-dichloro-1,3-diketone and hydroxylamine.[37B/81] When the chlorinating mixture is added to 3,5-diarylisoxazoles in stoichiometric amounts, the intermediate 3,5-diaryl-4-chloroisoxazoles can be isolated smoothly[195/73] (see also § 1.4.9.3, p. 338).

### b. Alkylation of 2-Isoxazolines

As will be illustrated further in § 2.2.3.1, p. 550, metallation at low temperatures with subsequent reaction of the carbanion with an alkyl halide is an excellent method of alkylating 2-isoxazoline derivatives in position 4 or 3α. Table 2.27 collects some typical examples and illustrates the generality of the method.

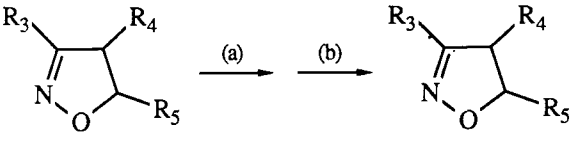
### c. From 2-Isoxazoline *N*-Oxides or Condensed 2-Isoxazolines

Like most *N*-oxides, 2-isoxazoline *N*-oxides (see § 2.3.3.1, p. 615) are easily deoxygenated by treatment with phosphorus pentachloride,[10/24,8/26,154/69,16/79] triethyl phosphite,[27/79,203/80] or triphenylphosphine:[133/77]




The reaction is usually carried out at 75–80°C, without or in solvents, and care must be taken to avoid higher temperatures, since dehydration to is-

TABLE 2.27

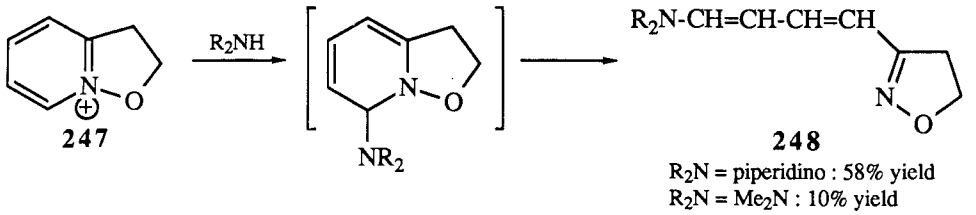



**245** **246**

| 245 | | | | | 246 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $R_3$ | $R_4$ | $R_5$ | (a) | (b) | $R_3$ | $R_4$ | $R_5$ | Yield (%) | References |
| Me | H | H | *n*-BuLi, -65° THF/HMPA | MeI | Me | Me | H | 73 | 14/83 |
| Me | H | H | *n*-BuLi, -65°, THF/HMPA | $PhCH_2Br$ | Me | $CH_2Ph$ | H | 68 | 14/83 |
| Me | H | H | *n*-BuLi, -65°, THF/$n$-$C_6H_{14}$ | $PhCH_2Br$ | $PhCH_2CH_2$ | H | H | 65 | 14/83 |
| Ph | H | H | LDA, -78°, THF/HMPA | EtI | Ph | Et | H | 91 | 260/78 |
| Ph | H | Me | LDA, -78° THF/HMPA | MeI | Ph | Me | Me | 73 | 260/78 |
| Ph | H | H | LDA, -78°, THF/HMPA | *i*-PrI | Ph | *i*-Pr | H | 49 | 260/78 |
| Ph | Me | H | LDA, 78°, THF/HMPA | MeI | Ph | $Me_2$ | H | 76 | 260/78 |
| Ph | H | Me | LDA, -78°, THF/HMPA | $(RO)_3B$,-78°; $H_2O_2$, $NR_3$ | Ph | OH | Me | 78 | 7/81 |
| Me | $-(CH_2)_3-$ | | LDA, -78°, THF | MeI | Et | $-(CH_2)_3-$ | | 80 | 8/80 6/76 |
| Ph | H | $(CH_2)_2OCH_2OMe$ | LDA, -78°, THF, HMPA | ClCOOMe; then MeI | Ph | Me COOMe | $(CH_2)_2OCH_2OMe$ | 58 | 162/84 |

oxazoles can enter in competition. Sodium or potassium nitrite failed to accomplish the same deoxygenation.[184/76,16/79]

When treated with piperidine, the bicyclic isoxazolinopyridinium cation **247** is a convenient source of the dienamino 2-isoxazoline **248**:[140/67]

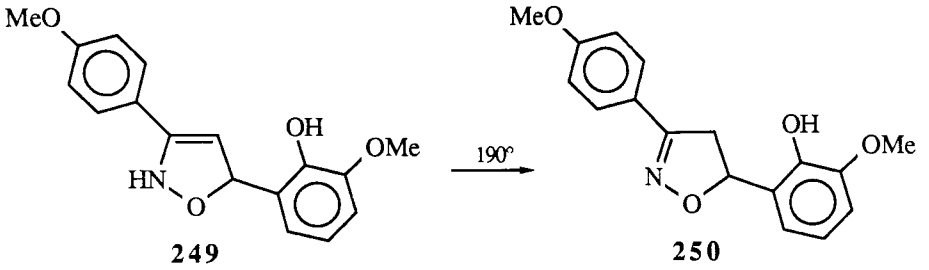



**247** **248**

$R_2N$ = piperidino : 58% yield
$R_2N$ = $Me_2N$ : 10% yield

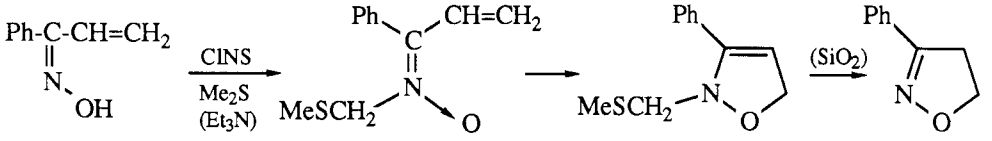
d. From 3-Isoxazolines

2*H*-3-Isoxazoline derivatives (see § 2.4) are rather unstable compounds, and only a few representatives of the class are known. Upon heating above its melting point, the 3-isoxazoline **249** rearranges to the corresponding 2-isoxazoline (**250**):[49/70]



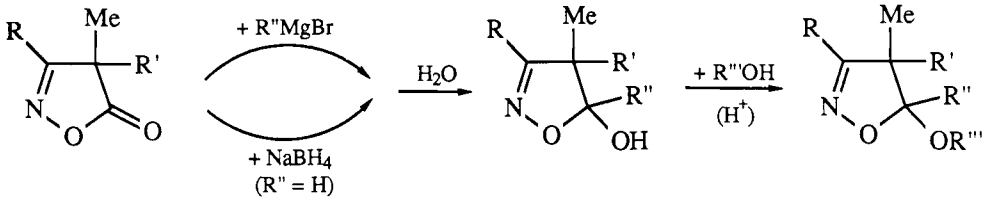

**249** **250**

The 2-methylthiomethyl-3-phenyl-3-isoxazoline, obtained from phenyl vinyl ketone *E*-oxime through oxidative alkylation and subsequent 1,5-cyclization, is unstable and transforms into 3-phenyl-2-isoxazoline by simple chromatography on silica gel (hydrolysis and tautomerization):[153/80]




e. From 5-Isoxazolinones

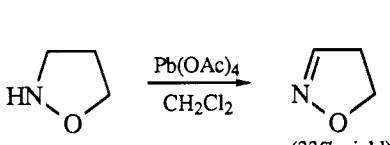
4,4-Disubstituted 5-hydroxy-2-isoxazolines are relatively stable compounds and can be achieved by action of Grignard reagents or of sodium borohydride on the corresponding 5-isoxazolinones:[37/73,20/74,246/74]



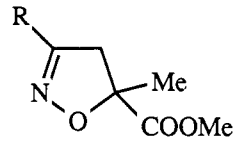

When R′ ≠ $CH_3$ and R″ ≠ H, an equilibrium between two interconvertible diastereoisomers can be reached through a ring-chain tautomerism.[246/74] 3,4,4-Trimethylated derivatives are promptly alkylated to 5-alkoxy compounds,[246/74] possibly by acetalization of the open-chain tautomer.

### f. From Isoxazolidine Derivatives

Dehydrogenation of N-unsubstituted isoxazolidines is known for a limited number of derivatives. Lead tetraacetate in dichloromethane has been utilized to prepare the simple 2-isoxazoline from the easily available isoxazolidine:[139/72]




(33% yield)

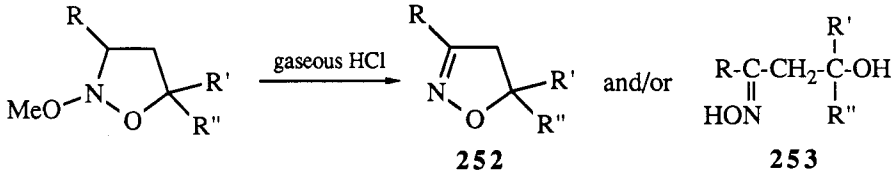



**251** (R = H,Me)

In other instances *N*-chlorosuccinimide gave higher yields (60–80%);[81/77,70/84] optically active methyl 2-isoxazoline-5-carboxylates (**251**) could thus be produced. A remarkably larger number of examples refer to the elimination reaction of *N*-methoxy- or *N*-silyloxyisoxazolidines, easily accessible through the 1,3-dipolar cycloaddition of alkyl or silyl nitronates to olefins (see § 3.3.1).

*N*-Methoxy-3-monosubstituted isoxazolidines lose methanol by treatment with gaseous hydrogen chloride in benzene solution. Nevertheless, some substituents favor a competitive ring-opening isomerization to methoxyiminohydroxy compounds (**253**). The data shown in Table 2.28 illustrate the substituent

TABLE 2.28




**252** **253**

| R | R' | R" | 252 | 253 | References |
|---|---|---|---|---|---|
| $NO_2$ | H | COOMe | 48 | - | 91/66 |
| COOMe | H | COOMe | - | 100 | 205/66 |
| COOEt | H | $CH_2Cl$ | 100 | - | 205/66 |
| COOEt | H | Ph | 98 | - | 205/66 |
| Ph | H | COOMe | 39 | 50 | 228/68 |
| 4-$NO_2C_6H_4$ | H | COMe | 84.5 | - | 228/68 |
| Ph | COOMe | COOMe | - | 80 | 228/68 |
| 4-$NO_2C_6H_4$ | COOMe | COOMe | - | 100 | 228/68 |

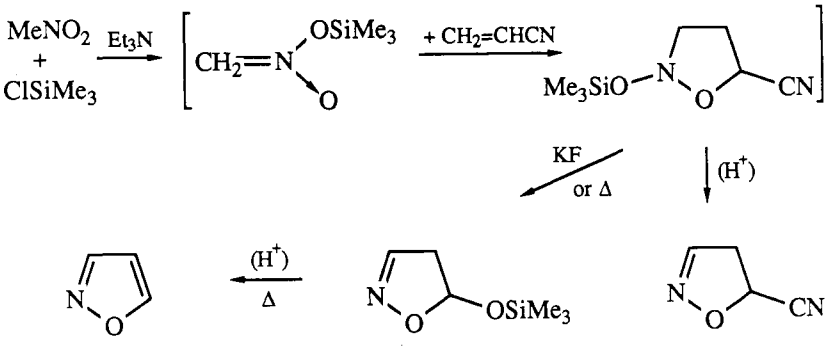
effect on this competition between elimination and ring-opening isomerization.

The presence of the nitro group at the 3-position activates the elimination so much that the 2-isoxazoline is sometimes obtained directly as an exclusive product of the cycloaddition reaction.[91/66,210/72] The elimination of methanol

from 2-methoxyisoxazolidines can also be accomplished by other acidic promoters, such as boron trifluoride etherate[205/66,177/67] or zinc chloride,[205/66] as well as by bases.[61/65,205/66] It is worth noting that sulfuric acid, either concentrated or diluted, enables ring-opening processes.[61/65,91/66,205/66]

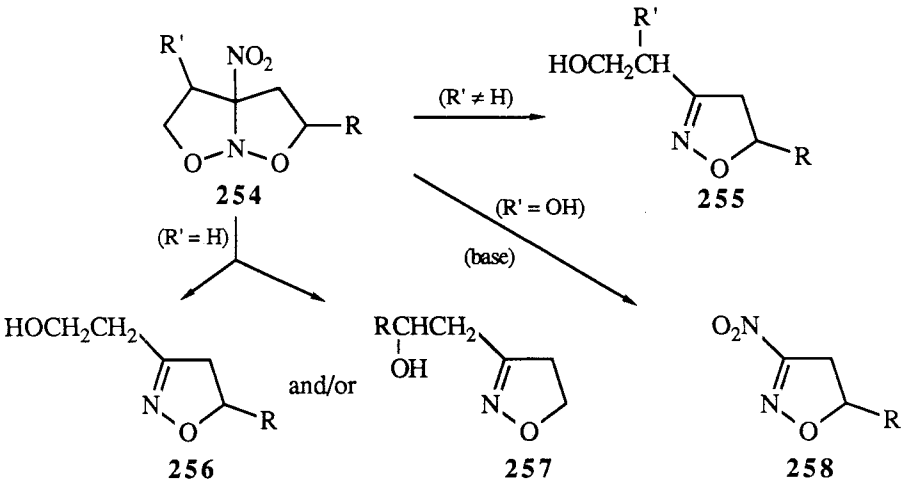
3,3-Diethoxycarbonylisoxazolidines can be transformed in 3-carboxy-2-isoxazoline derivatives upon previous decarboxylation.[229/68,212/79] 2-Isoxazoline-3-carboxylic *N*-methylamide is obtained in 97% yield by acidic treatment of 2-methoxyisoxazolidine-3,3-dicarboxylic acid bis-*N*-methylamide.[94/81]

Elimination of trimethylsilanol from the relatively unstable 2-silyloxy-isoxazolidines proceeds more smoothly and the corresponding 2-isoxazolines are obtained with good to excellent yields either by heating or by treatment with hydrogen chloride or (better) with *p*-toluenesulfonic acid in benzene.[250/73,3/78,4/79,1/82] It should be noted that silyl nitronates enter cycloaddition only with electron-poor olefins.[3/78] In turn, since silyl nitronates are prepared by silylation of primary nitroalkanes, this approach usually has no real advantage over the direct dehydration of nitroalkanes to nitrile oxides, which cycloadd *in situ* a greater variety of both electron-poor and electron-rich olefins (see § 2.2.2.2). However, the silyl nitronates method seems particularly attractive for the synthesis of 3-unsubstituted 2-isoxazolines, since direct dehydration of nitromethane leads to different products (see p. 479). The "one-pot" procedure may be applied successfully here: for example, 5-cyano-2-isoxazoline has thus been prepared from nitromethane and acrylonitrile with a 40% overall yield:[4/79]



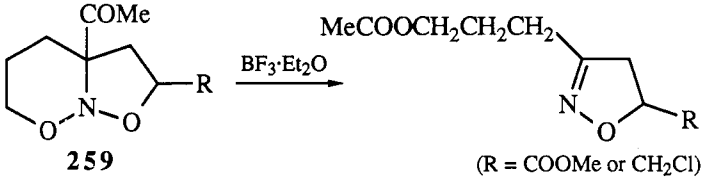

Surprisingly, heating or treatment at room temperature of the intermediate 2-silyloxy-5-cyanoisoxazolidine (which can be eventually isolated) with fluoride ion provokes loss of hydrogen cyanide and rearrangement to 5-trimethylsilyloxy-2-isoxazoline. This compound, in turn, eliminates trimethylsilanol by acidic treatment, giving isoxazole with a 59% overall yield from nitromethane.[4/79] Base catalysis is far less straightforward and frequently gives rise to open-chain decomposition products.[90/72,250/73,253/73,48/74]

2-Isoxazoline carbinols of general structures **255–257** can be obtained in variable yields by acid-promoted (anhydrous HCl in benzene or $BF_3$-etherate) cleavage of the bicyclic ring systems of 8-nitroisoxazolizidines **254**.[173/67,178/67,209/72]

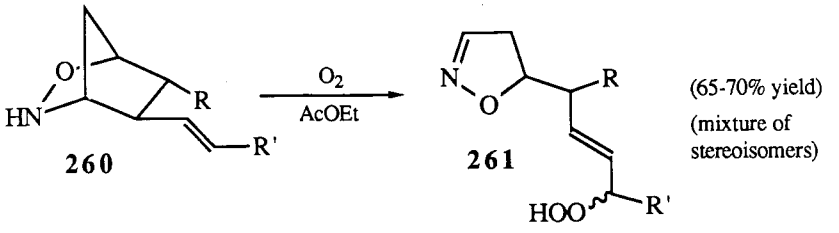



The formation of one or the other type of carbinol (or possibly of a mixture of the two isomers) depends on the nature of the substituents R and R′.

Nucleophiles usually react on the same system to give substitution products. Nevertheless, when a hydroxy group is present in the 4-position of one ring, fragmentation of the same ring occurs, and the 3-nitroisoxazolines **258** are obtained in fair to good yields.[63/66,188/66] The higher homologue of isoxazolizidine, the bicyclic system **259**, cleaves to an isoxazoline derivative only when substituted at the bridge carbon atom by an acetyl group and only with some R′s.[115/76,144/78]




The strained bicyclic isoxazolidine system **260** has been reported to be oxidized to the 2-isoxazoline derivative **261**, limited to some PGF-type compounds:[254/81,194/83]



3-Chloro-2-isoxazoline derivatives **263** have recently received considerable attention because the antibiotic AT-125 belongs to this class of compounds. They can conveniently be synthesized by treatment of the corresponding 2H- (or 2-benzyl)-isoxazolin-3-ones **262** (see also Part 2 of this work) with phosphorus oxychloride and bases[249/81.258C/81] or phosphorus pentachloride[97/81] or, better, with $(Me_2N)_3PCl_2$ in THF:[96/79.100/81.258C/81]

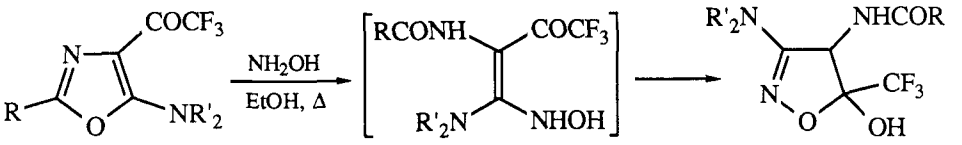


**262** **263**

The same isoxazolidinones can give 3-alkoxyisoxazolines by alkylation with appropriate reagents (see Part 2 of this work).

g. From 5-Aminooxazoles

A convenient synthesis of 3-amino-5-hydroxy-2-isoxazolines **265** stabilized by the presence of a trifluoromethyl group in position 5, is based on the oximation reaction of 5-aminooxazoles **264**, as illustrated by the following scheme:[166/76]

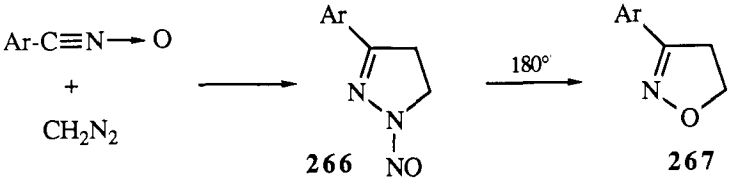


**264** **265**

(86-95% yield)

h. From *N*-Nitrosopyrazolines

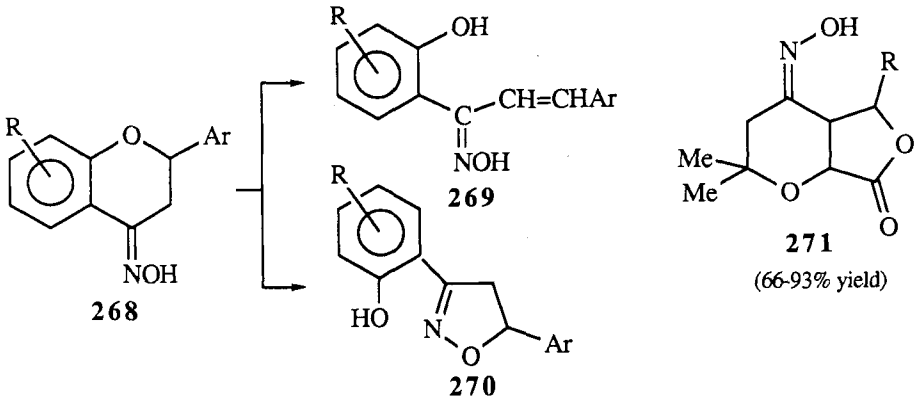
Reaction of aromatic nitrile oxides with diazomethane is known to lead to *N*-nitrosopyrazolines **266**;[169B/66] thermolysis of these compounds gives moderate yields of 3-aryl-2-isoxazolines **267**:[179/66]



**266** **267**

### i. From Six-Membered Heterocycles

The oximation of 2-aryl-2,3-dihydro-4*H*-benzopyran-4-ones has been the object of several controversial studies. Summing up briefly, the primary products of the reaction (i.e., the *E*-oximes of general structure **268**) can rearrange under different conditions either to the open-chain 1-(2-hydroxyaryl)-3-aryl-2-propen-1-one *E*-oximes **269**[8/68,200B/79] or to the isomeric (3-(2-hydroxy-




aryl)-5-aryl-2-isoxazolines **270**.[121/80,113/82,5/83] The latter transformation usually occurs only when a group having a strong -M effect, such as a 4-hydroxy or a 4-alkoxy group, is present in the 2-phenyl substituent.

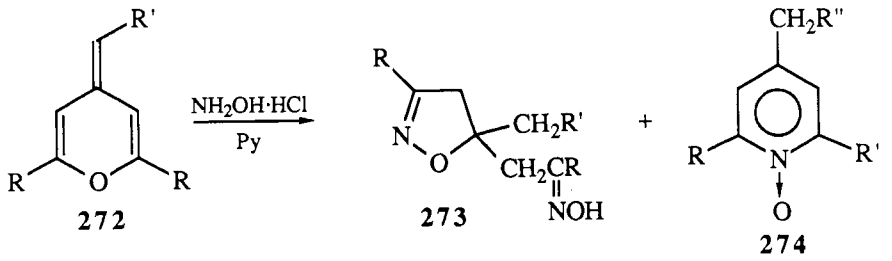
The formation of regioisomeric compounds has been claimed in the acidic oximation of some 3-aroylflavonones.[3/83] With lower yield an analogous rearrangement promoted by $BF_3$/AcOH treatment is known for dihydropyrone oximes (**271**).[25/79]

For the reaction of chromone and its open-chain precursor with hydroxylamine, which yields, among other isoxazole derivatives, some 5-hydroxylamino- or 5-hydroxy-2-isoxazolines, see § 1.3.7.2f, pp. 255–256.

Oximation of substituted 4-methylenepyrans (**272**) leads to 5,5-disubstituted 2-isoxazolines (**273**) and/or trisubstituted pyridine-*N*-oxides (**274**).[156/72,120/75] Hydroxylamine is supposed to attack position 2 of the pyran ring, causing cleavage of the carbon–oxygen bond. Recyclization can then occur at either position 4 (leading to isoxazolines) or at position 6 or 2′ (affording a six-membered ring). The competition between the two processes depends on the pH and on the nature of the substituents. As the yields listed in Table 2.29 for the pyridine–ethanol solution indicate, formation of isoxazolines is favored by a 2,6-diphenyl substitution, whereas a 2′-keto group shifts the reaction toward pyridine-*N*-oxides.

A similar mixture of 2-isoxazolinylacetophenone oximes (**277a**) and pyridine-*N*-oxides is produced by oximation of 3,5-unsubstituted 2,4,6-triarylpyrylium

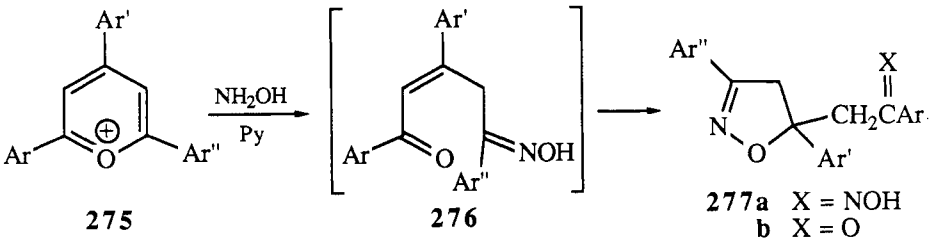
TABLE 2.29




272 273 274

| R | R' | R | R' | Yield (%) | R | R' | R" | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| Me | COMe | Me | C(=NOH)Me | 13 | Me | Me | C(=NOH)Me | 78 |
| Me | COOMe | Me | COOMe | 34 | Me | Me | COOMe | 45 |
| Ph | Ph | Ph | Ph | 73 | | | | - |
| Ph | COMe | Ph | C(=NOH)Me | 52 | Me | Ph | C(=NOH)Ph | 38 |
| Ph | COOMe | Ph | COOMe | 94 | | | | - |

salts (**275**) in acidic media;[1/70] in this case, however, good yield of the ketones of general structure **277b** are obtained as sole products when the oximation is carried out under basic conditions.[1/68,199/68]

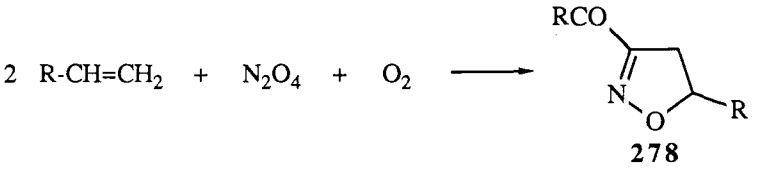



275 276

The intermediacy of the open-chain oxime **276** could be demonstrated by its isolation under carefully controlled mild conditions.[199/68] A related synthesis of a compound having a **277**-like structure is known in the pyridinium salts series, operating with a large excess of hydroxylamine in pyridine; equimolecular amounts of hydroxylamine, on the contrary, furnish the pyridine-*N*-oxide.[12/81]

### *2.2.2.7 Miscellaneous Methods*

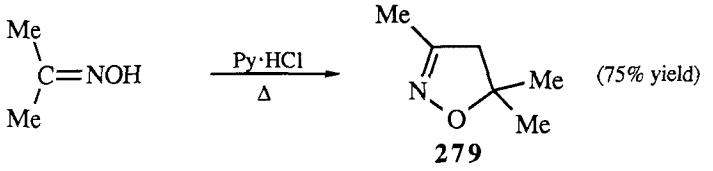
The oxidative nitration of alkenes in the presence of calcium oxide and *N*-methylpyrrolidone as the denitrating agent is claimed to yield 3-acyl-2-isoxazolines **278**:[270/78]




**278**

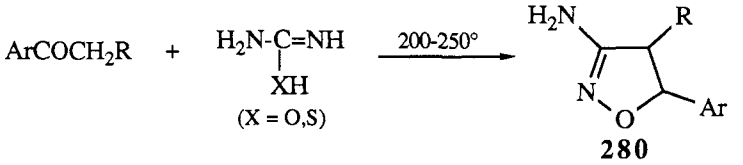
The reaction deserves further study.

3,3′-Diisoxazoline has been prepared by direct treatment of ethylene under pressure with aqueous nitric acid at 80°C in the presence of traces of metal salts.[76B/68,69/69] Despite the fact that the reaction cannot be extended to other homologues or phenologues, it is important to report the simple preparation of 3,5,5-trimethyl-2-isoxazoline (**279**) by heating an equimolecular mixture of acetone oxime and pyridinium chloride:[171/82]




**279**

Condensation of acetophenones or steroidal ketones with urea or thiourea under severe conditions is reported to yield 3-amino-2-isoxazolines **280**; the reaction seems to have a wide applicability:[301/78]




**280**

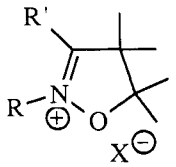
### 2.2.3 Reactions

The 2-isoxazolines can formally be considered as cyclic ethers of the oximes, and their chemical behavior corresponds fairly well to expectations based on this structure. The heterocyclic ring is remarkably stable toward heating, acids or alkali, or even oxidizing agents, unless destabilizing substituents of particular kind are present in the molecule. However, the ring is easily cleaved either by hydrogenolysis or by some nucleophiles or photochemically. The various reactions of the 2-isoxazolines will be here divided into two classes, depending on whether or not they provoke ring cleavage.

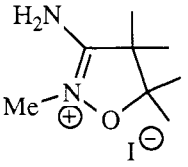
### *2.2.3.1 Reactions without Ring Cleavage*

#### a. Quaternization

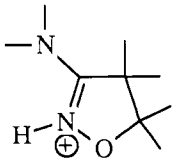
2-Isoxazolines are endowed with weakly basic character, not very different (only slightly higher) from that of the corresponding isoxazoles. Quaternarization at the 2-nitrogen atom is conveniently accomplished by treatment with excess trimethyl (or triethyl)-oxonium tetrafluoroborate in nitromethane or dichloromethane at room temperature[232/74.14/83] or with dimethyl sulfate in methanol solution;[35/73] in the latter case, subsequent treatment with sodium perchlorate made it possible to separate the crystalline 2-methylisoxazolinium perchlorates. Chloroferrates[16/55.50/63] are also known and have been prepared analogously.



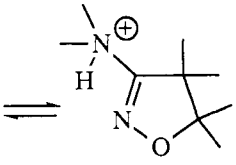
**281**



**282**



**283a**



**283b**

3-Phenyl-2-methyl-2-isoxazolinium perchlorate has also been obtained by reduction of the corresponding isoxazolium salt with sodium borohydride in methanol, but the reaction has a low preparative value, showing severe limitations as far as substitution pattern, solvent, and yields are concerned.[36/74]

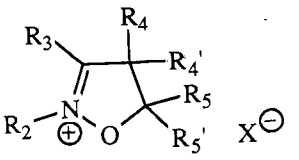
The 2-isoxazolinium salts (**281**) are attractive starting materials for stereocontrolled synthesis of isoxazolidines through reaction with sodium borohydride or Grignard reagents.[232/74.220/81] The spectroscopic properties and the substituent-depending propensity of the 2-isoxazolinium salts to undergo hydrolysis to $\beta$-aminoxyketone salts have been evaluated and discussed.[35/73]

Interestingly enough, 3-aminoisoxazolines are methylated by methyl iodide at the ring nitrogen to give isoxazolinium salts (**282**), whose structure has been assured through chemical and spectroscopic evidence. The protonation leads to a monoprotonated chloride or perchlorate, where the proton is rapidly exchanged between the ring (**283a**) and the *exo* (**283b**) nitrogen atom.[23/74] The 3-amino-2-methylisoxazolium salts are hydrolyzed by aqueous sodium hydroxide to 2-methyl-3-isoxazolinones.

As expected by the higher basicity of the amino residues, a 5-pyrrolidinyl-2-isoxazoline methylates at the pyrrolidino nitrogen atom,[32/64] and a 5-amino-4-aminomethyl derivative at the 4-aminomethyl residue.[180/80] The known 2-isoxazolinium salts are displayed in Table 2.30.

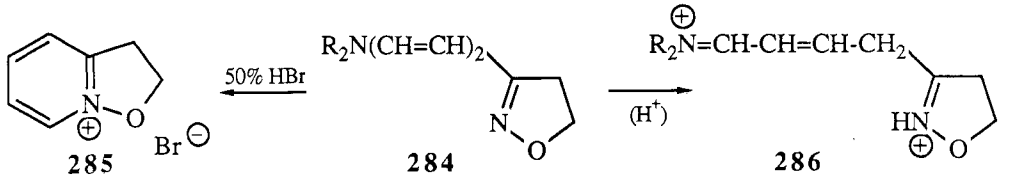
An interesting intramolecular quaternarization is provoked by the action of aqueous mineral acids on the isoxazolinyl dienamine **284**, which cyclized to the

TABLE 2.30. MONOCYCLIC 2-ISOXAZOLINIUM SALTS



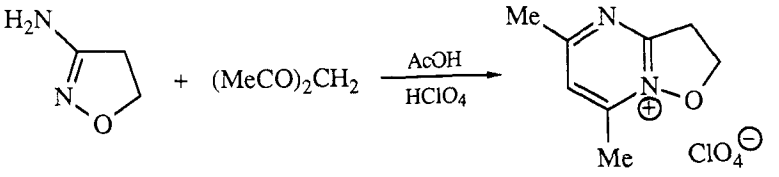
| $R_2$ | $R_3$ | $R_4$ | $R'_4$ | $R_5$ | $R'_5$ | X | M.p. (° C) | Yield (%) | References |
|---|---|---|---|---|---|---|---|---|---|
| Me | $NH_2$ | H | H | H | H | I | 153-155 | 95 | 23/74 |
| Me | $NH_2$ | H | H | Me | H | I | 113 | 80 | 23/74 |
| Me | $NH_2$ | Me | H | H | H | I | 119-120 | 60 | 23/74 |
| Me | Me | H | H | H | H | $ClO_4$ | 149-150 | 50 | 35/73 |
| Me | $NH_2$ | H | H | Me | Me | I | 169-171 | 95 | 23/74 |
| Me | Me | H | H | Me | H | $ClO_4$ | 92-94 | 70 | 35/73 |
| Et | Me | H | H | H | H | $BF_4$ | 52-56 | 91 | 14/83 |
| Me | $NMe_2$ | H | H | H | H | $ClO_4$ | 115 | 50 | 23/74 |
| Me | Me | H | H | Me | Me | $ClO_4$ | 154-156 | 65 | 35/73 |
| Me | Me | H | H | Me | Me | I | 170 | 67 | 171/82 |
| Et | Me | Me | H | H | H | $BF_4$ | 56-59 | 95 | 14/83 |
| Me | $NMe_2$ | H | H | Me | Me | $ClO_4$ | 141 | 50 | 23/74 |
| Me | Ph | H | H | H | H | $ClO_4$ | 143-144 | 55 | 35/73 |
| | | | | | | | 149-150 | 31 | 36/74 |
| Me | H | H | H | Ph | H | $ClO_4$ | 100 | 40 | 35/73 |
| Me | 4-$ClC_6H_4$ | H | H | H | H | $ClO_4$ | 148-150 | 75 | 35/73 |
| Me | 4-$BrC_6H_4$ | H | H | H | H | $ClO_4$ | 168-170 | 70 | 35/73 |
| Me | $NH_2$ | H | H | Ph | H | I | 143 | 70 | 23/74 |
| Me | Ph | Me | H | H | H | $ClO_4$ | 152-154 | 70 | 35/73 |
| Me | Ph | H | H | Me | H | $ClO_4$ | 132-133 | 65 | 35/73 |
| Me | Me | H | H | Ph | H | $ClO_4$ | 108-109 | 65 | 35/73 |
| Me | Ph | H | H | Me | Me | $ClO_4$ | 174-176 | 50 | 35/73 |
| Et | Me | $CH_2Ph$ | H | H | H | $BF_4$ | 93-98 dec. | 89 | 14/83 |
| Et | $CH_2CH_2Ph$ | H | H | H | H | $BF_4$ | 132-135 | 92 | 14/83 |
| Me | Ph | H | H | 4-$BrC_6H_4$ | H | $FeCl_4$ | 138 | | 50/63 |
| Me | 4-$BrC_6H_4$ | H | H | Ph | H | $FeCl_4$ | 115-116 | | 16/55, 50/63 |
| cyclo$C_6H_{11}$ | Me | H | H | Ph | H | $BF_4$ | 90-92 | 74 | 14/83 |

isoxazolopyridinium cation **285**. Protonation in a weak acidic medium occurs at positions $\beta$ and $\delta$ of the amino side chain; dissolution in concentrated sulfuric acid produces the diprotonated species **286**.[140/67]




**285** **284** **286**

Another intramolecular quaternarization starts from the condensation of 3-aminoisoxazolines with β-diketones and is induced by strong acids;[244B/76] for example:




b. Aromatization to Isoxazoles

The conversion 2-isoxazoline → isoxazole is moderately favored by the higher stability of the heteroaromatic ring, and can be accomplished by an elimination reaction of either two hydrogen atoms (dehydrogenation) by use of several types of oxidizing agents or an easily leaving molecule under suitable conditions (usually, weak bases or acids or heat).

DEHYDROGENATION. Owing to the much higher availability and variety of 2-isoxazoline derivatives known at present in comparison to isoxazoles, this method has acquired some preparative significance, and a large number of oxidizing agents for this purpose have been proposed.

Although reference is made to § 1.3.7.1, pp. 227–230, for a deeper insight into the subject, it should be remembered that the following reagents, primarily, have been utilized:

1. Simple air oxidation is limited at present to some 4-formyl-2-isoxazolines[177/83] and, with base promotion, to 4-acyl-2-isoxazolines.[148/74]
2. Chromic acid,[2/896] whose applicability is confined to 3,5-diaryl-2-isoxazolines.
3. *N*-bromosuccinimide,[118C/65] possibly combined with a weak base treatment if the intermediate bromo derivative is sufficiently stable to be isolated, as in fused di- or polycyclic isoxazolines.
4. Chloranil,[240/74,240/76] especially useful for fused 4-acylisoxazolines.
5. 2,3-Dichloro-5,6-dicyanobenzoquinone,[107/79] which seems highly convenient for alkyl-substituted isoxazolines.
6. γ-Active manganese dioxide,[234/77,245/78] which shows a broad compatibility with several critical functional groups.
7. Potassium permanganate in acidic medium has been reported to be successful in one case;[43/60] under mild conditions it usually does not affect the isoxazoline ring. The presence of a 4-nitro group has been reported to activate the isoxazoline ring toward oxidation with potassium permanganate: under basic conditions 5-monosubstituted compounds are oxidized to 3,5-disubstituted-4-nitroisoxazole,[260/79,264/81] and 5,5-disub-

stituted derivatives are transformed into trisubstituted 2-isoxazolin-4-ones.[263/81] The latter transformation has also been performed with peracetic acid.[259/79]

ELIMINATION REACTIONS. Several classes of suitably 4- or 5-substituted 2-isoxazolines more or less easily undergo elimination of one molecule of HX, where X can be a halogen, OH, $OCOCH_3$, OR, SR, $NR_2$, NCO, $N_3$, $NO_2$, or another leaving group. Although reference is made to § 1.3.7.1, pp. 230–239, for a more exhaustive treatment, several elimination reactions will be summarized briefly.

1. *Dehydrohalogenation.* This can be effected either thermally or (better) in the presence of a base such as triethylamine, sodium hydroxide, or methoxide. Often the chloro- or bromoisoxazoline is unstable under the reaction conditions chosen for its synthesis, and isoxazole is the only product isolated, hydrohalogenidric acid being evolved spontaneously. This is true especially for 5-haloisoxazolines. The higher mobility of the halogen in the 5-position is also illustrated by the exclusive formation of 3-aryl-4-chloroisoxazole from the corresponding 3-aryl-4,5-dichloro-2-isoxazoline.[42/70] Moreover, the *cis* isomer dehydrochlorinates more rapidly that does the *trans* isomer, as expected for an *anti* elimination. The 4-halo-2-isoxazolines are relatively more stable unless an acyl group is present in the 5-position.[32/58] Even 4-bromo-3,5,5-triphenyl-2-isoxazoline has been dehydrobrominated with ethanolic silver nitrate, producing 3,4,5-triphenylisoxazole through a phenyl rearrangement.[167/77]

2. *Dehydration.* 4- or 5-Hydroxy-2-isoxazolines dehydrate spontaneously or by short heating, more readily under acidic catalysis. Here, too, the 4-hydroxy isomer dehydrates much more slowly than does the 5-hydroxy derivative:[250/78] accordingly, 3-phenyl-*cis*-4,5-dihydroxy-2-isoxazoline furnishes 3-phenyl-4-hydroxyisoxazole by treatment with sulfuric acid.[12/68] Moreover, *cis*-3,5-diphenyl-4-hydroxy-2-isoxazoline eliminates water more readily than does the *trans* isomer.[250/78] 5-Hydroxy-5-trifluoromethyl-2-isoxazoline derivatives are particularly stable and require a mixture of trifluoroacetic anhydride and acid to be dehydrated.[166/76]

3. *Elimination of acetic acid.* This proceeds from the easily available 5-acetoxy-2-isoxazolines either thermally by heating at 160–200°C[37/60.38/70] or by heating under acidic conditions.[8/50.9/62] The 5-acetoxyisoxazolines decompose more readily than does the corresponding 4-acetoxy regioisomer; moreover, *cis*-3-phenyl-4-methyl-5-acetoxy-2-isoxazoline eliminates acetic acid thermally more rapidly than does the *trans* isomer, thus suggesting an $E_i$ mechanism.[199/72]

4. *Elimination of other oxygen-containing molecules.* Elimination of one molecule of methanol or ethanol from 5-alkoxy-2-isoxazolines is utilized far less for the synthesis of isoxazoles and takes place by heating in an acidic medium.[9/62] Milder conditions are required for the elimination of ethanol from 5,5-diethoxyisoxazolines.[26/59] Decomposition of 5-trimethylsilyloxyisoxazolines with elimination of trimethylsilanol is also easy.[73/78.4/79]

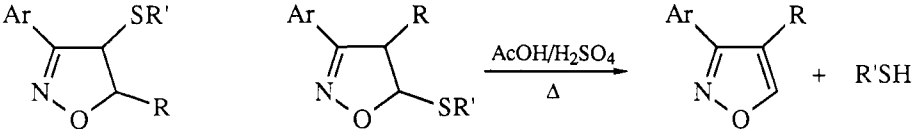
5. *Deamination.* 2-Isoxazoline derivatives carrying a tertiary amino residue in positions 5 are deaminated easily by treatment with mineral acids.[37/63,38/63] Since the above-mentioned 5-aminoisoxazolines are accessible easily and regiospecifically through the nitrile oxide route (see § 2.2.2.2, p. 519), this elimination reaction represents the most important and popular synthesis of 4-substituted isoxazole derivatives (see also § 1.3.7.1f, p. 235). It is worth mentioning that whereas 5-aminosubstituted 4,5-tetramethylene-2-isoxazolines deaminate normally, the corresponding 4,5-trimethylene derivatives require a Hofmann degradation procedure in order to aromatize to the cyclopentaisoxazoles.[32/64,73/64]

Sometimes, especially when an electron-attracting group is present in the 4-position, the isoxazoline is unstable even at room temperature, and cycloaddition of nitrile oxides to the substituted enamine furnishes the isoxazoles directly. This represents a particularly attractive synthesis of 4-acyl-,[37/63,178/71] 4-alkoxycarbonyl-,[80/67] 4-cyano-,[35/68] or 4-nitroisoxazoles.[149/81] In one special case, base-promoted deamination seems to be more convenient than acidic deamination.[180/80] An unstable 5-acylamino-2-isoxazoline as a presumable intermediate explains the formation of isoxazoles either by a Schmidt reaction on 5-acyl-2-isoxazolines or by Beckmann rearrangement of their oximes of appropriate stereochemistry.[89/68]

6. *Elimination of other nitrogen-containing molecules.* 5-Isocyanato-2-isoxazolines eliminate isocyanic acid by thermolysis,[249/72] 5-azido derivatives aromatize with evolution of $HN_3$ when treated with triethylamine,[176/74] and methyl 3-phenyl-2-isoxazolin-5-ylcarbamate aromatizes to 3-phenylisoxazole by heating in an acidic medium.[152/80]

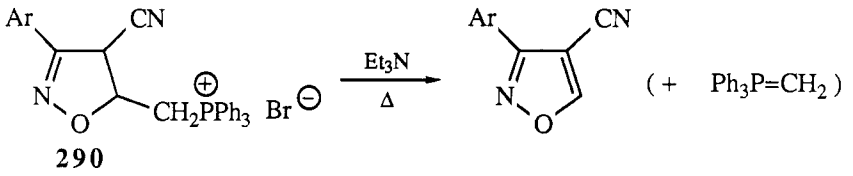
Both 4-nitro- and 5-nitro-2-isoxazolines evolve $HNO_2$ (*syn* elimination) by heating above the melting point or in inert solvents, the latter isomer aromatizing more readily.[8/54,26/73,225/76,52/80,248/82] The thermal stability of 3-aryl-5-nitro-2-isoxazolines increases with increasing Hammett $\sigma$ values.[249/82] 3,5-Diphenyl-4-arylisoxazoles are obtained by attack of aryldiazonium cations on 3,5-diphenyl-4-nitro-2-isoxazoline.[258/79]

7. *Miscellaneous elimination reactions.* 4-Alkyl (or aryl)thio-2-isoxazolines (**287**) behave differently toward acid-promoted desulfonation than do their 5-regioisomers (**288**). Whereas the former compounds are stable in a boiling mixture of acetic–sulfuric acids, the latter, owing to their S,O-acetalic structure, promptly suffer a loss of thiol, giving the corresponding 3,4-disubstituted isoxazoles **289**:[278/83,160/84]



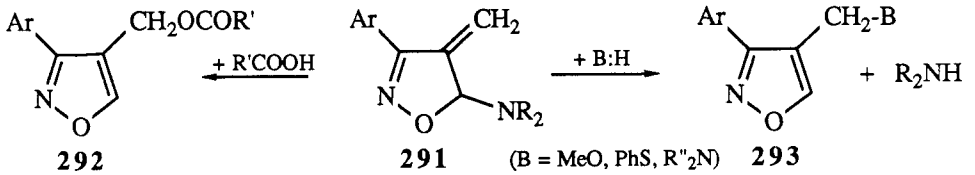
Both 4- and 5-isoxazolinyl *trans*-sulfoxides are unstable even at ambient temperature, and decompose spontaneously to isoxazoles; on the contrary, the *cis* stereoisomers are moderately stable under controlled conditions.[52D/81,278/83] The behavior of sulfonyl derivatives also depends markedly on their regio- and stereochemistry: *cis*-5-sulfonylisoxazolines readily aromatize with triethylamine, whereas *cis*-4-sulfonyl compounds epimerize to the *trans* isomers.[278/83] The latter, in turn, desulfonate to isoxazole under stronger basic conditions (alcoholic alkaline hydroxides).[154/66,278/83]

The molecule of an acetophenone is eliminated from some 3,5-diaryl-5-acetonyl-2-isoxazolines by acidic or basic treatment or photolytically;[1/68,199/68] however, it should be mentioned that the formation of a 2,4,6-trisubstituted pyridine-*N*-oxide has been demonstrated under different acidic conditions.[106/79] Analogously, one molecule of triphenylphosphonium methylide can be eliminated from the unstable salt **290**:[149/76]



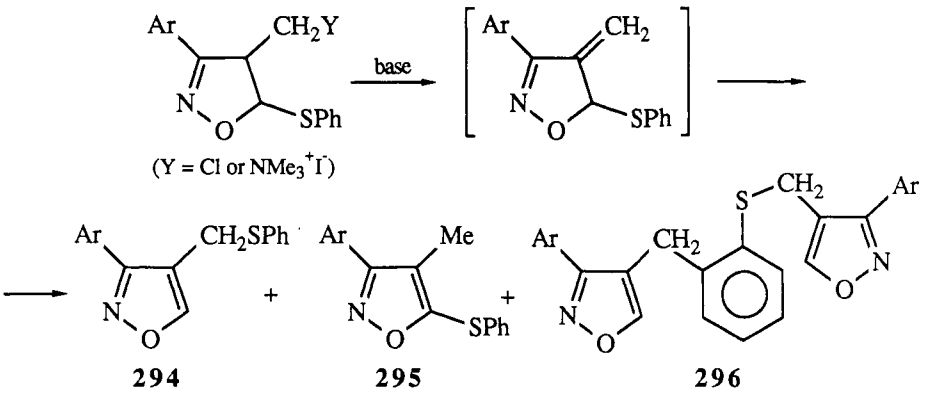

**290**

OTHER REACTIONS. 4-Methylene-2-isoxazolines of general formula **291** react both with carboxylic acids and with bases to give isoxazoles **292** or **293**, respectively, through an addition–elimination sequence; in basic media the pure addition reaction sometimes competes with the isoxazole formation:[181/80]

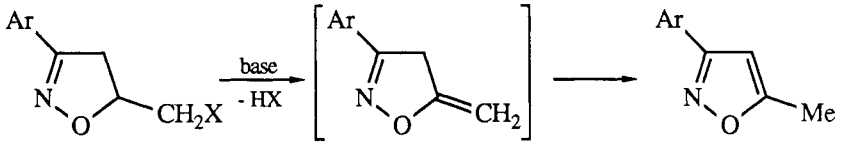



**292** **291** (B = MeO, PhS, R"$_2$N) **293**

The analogous 3-aryl-4-methylene-5-phenylthio-2-isoxazolines, on the contrary, are too unstable to be isolated under strong basic conditions, and promptly rearrange to the addition–elimination products **294**, sometimes accompanied by minor amounts of the isomers **295** and of the bisisoxazolyl thioether compounds **296**, derived through a Claisen rearrangement:[52C/81]

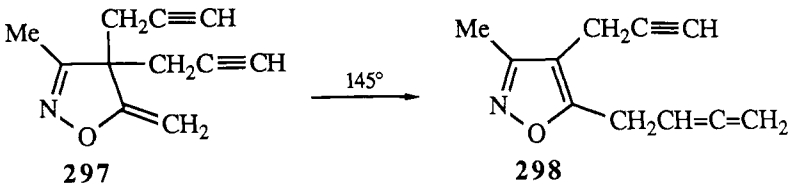



The base-promoted rearrangement of 3-aryl-4-diphenylmethylene-2-isoxazolines to 3-aryl-4-diphenylmethylisoxazole has also been reported.[146/72] Instead of the 5-methylene-2-isoxazolines, usually not isolable, the corresponding 5-methylisoxazoles are obtained.[31/69,212/84] For example, attempts to isolate the elusive 3-aryl-5-methylene-2-isoxazoline by dehydrohalogenation of the easily available 3-aryl-5-halomethyl-2-isoxazolines led to 3-aryl-5-methylisoxazoles:[212/84]

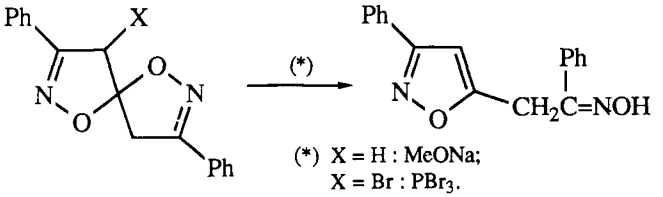



Dehydration of 3-phenyl-5-(α-hydroxy)benzhydryl-2-isoxazoline yields 3-phenyl-5-benzhydrylisoxazole.[89/68]

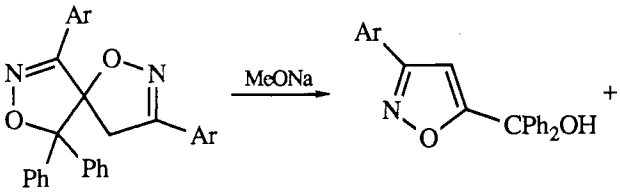
A 4,4-dipropargyl-5-methylene derivative (**297**) can, however, be prepared by dehydration of 3,5-dimethyl-4,4-dipropargyl-5-hydroxy-2-isoxazoline; thermal rearrangement of **297** furnishes the isomeric isoxazole **298**:[161/69]




One ring of 4,4′- or 4,5′-spirodiisoxazolines is frequently cleaved by bases, the other ring being aromatized to isoxazole. Two examples are reported:




Refs. 29/60, 88B/68, 16B/75

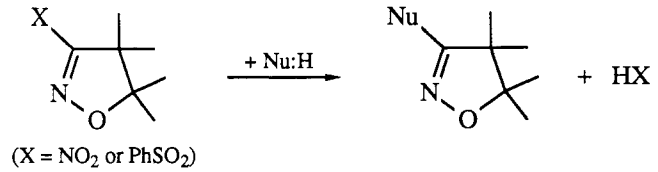



Ref. 146/72

For the aromatizing fragmentation of condensed polycyclic 2-isoxazolines to isoxazole derivatives, see § 1.3.7.1j, pp. 243–245.

### c. Substitution at the Ring Atoms

SUBSTITUTION AT POSITION 3. The presence of a strong electron-withdrawing group such as nitro or sulfonyl at position 3 of the 2-isoxazoline ring allows nucleophilic substitution to occur at the same position, according to the following general scheme:[91/66,210/72,202/78,97/79,201/83]



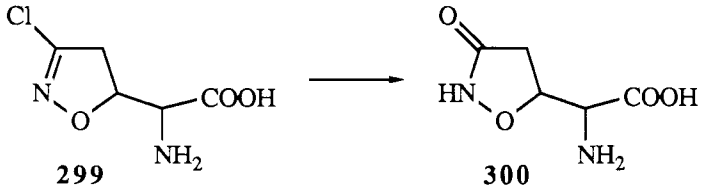

The reaction is suitably carried out in protic solvents and represents a convenient entry into 2-isoxazolines, having groups such as H, RO, CN, ArS, and $N_3$ in position 3. These compounds are difficult, if not impossible, to prepare by direct cycloaddition of nitrile oxides to alkenes. Table 2.31 exemplifies reagents and entering groups.

Substitution of a chlorine by a bromine atom in isoxazoline position 3 and the reverse process are known to occur by treatment with hydrobromic or hydrochloric acid, respectively, under appropriate conditions.[96/79.174/84] Another important substitution reaction links the antitumor antibiotic AT-125, a 3-chloroisoxazoline derivative (**299**), to tricholomic acid (**300**), obtained by simple hydrolysis of the former compound with 2 *N* NaOH:[96/79.249/81.258C/81]

TABLE 2.31. NUCLEOPHILIC SUBSTITUTION AT POSITION 3 OF 2-ISOXAZOLINES



| X | R | R' | Nucleophile | y | Yield (%) | References |
|---|---|---|---|---|---|---|
| $NO_2$ | H | H | $NaN_3$ | $N_3$ | 69 | 202/78 |
| $NO_2$ | H | H | NaCN | CN | 85 | 202/78 |
| $NO_2$ | H | H | *n*-$Bu_2Cd$ | *n*-Bu | 51 | 202/78 |
| $NO_2$ | H | H | PhSNa | PhS | 91 | 202/78 |
| $NO_2$ | H | H | $PhSO_2Na$ | $PhSO_2$ | 28 | 202/78 |
| $NO_2$ | H | $SiMe_3$ | EtOH/KOH | EtO | 75 | 210/72 |
| $NO_2$ | H | $CH_2SiMe_3$ | EtOH/KOH | EtO | 70 | 210/72 |
| $NO_2$ | H | $CH_2CH_2SiMe_3$ | EtOH/KOH | EtO | 72 | 210/72 |
| $NO_2$ | H | Ph | EtOH/KOH | EtO | 75 | 91/66 |
| $PhSO_2$ | -$(CH_2)_3$- | | LiOMe | MeO | 82 | 97/79 |
| $PhSO_2$ | -$(CH_2)_3$- | | KCN | CN | 87 | 97/79 |
| $PhSO_2$ | -$(CH_2)_3$- | | $NaBH_4$ | H | 51 | 97/79 |
| $PhSO_2$ | -$(CH_2)_4$- | | LiOMe | MeO | 88 | 97/79 |
| $PhSO_2$ | H | Ph | $CH_2$=CHMgBr | $CH_2$=CH | 72 | 124/84 |
| $PhSO_2$ | H | CHNHCOOC$H_2$Ph $CMe_2OH$ | MeLi | Me | 39-57 | 161/84 |
| $PhSO_2$ | H | CH(NPht)COOH | NaCN | NC | 86 | 201/83 |
| $PhSO_2$ | Ph(*cis*) | Ph | PhLi | Ph | 78 | 201/83 |
| $PhSO_2$ | Ph(*trans*) | Ph | PhLi | Ph | 88 | 201/83 |



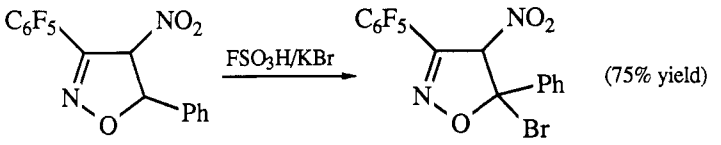
**299** (αS, 5S)

**300** (αS, 5S)

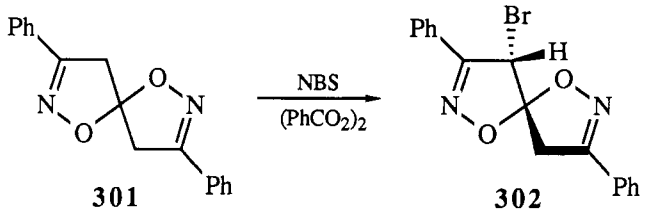
SUBSTITUTION AT POSITION 4 AND/OR 5. Although radical bromination with *N*-bromosuccinimide usually yields the isoxazole directly (see above), the intermediate substitution product can sometimes be isolated. This is particularly easy when the isoxazoline is fused with a five-membered ring in positions 4 and 5[100/64,149/66,96/67] (see Part 2 of this work). The reactivity of the nonfused ring is, however, lower than that of, for example, the furan ring, since treatment of

3-phenyl-5-*a*-furyl-2-isoxazoline with 1 mol of *N*-bromosuccinimide brominates the furan ring only.[88/68]

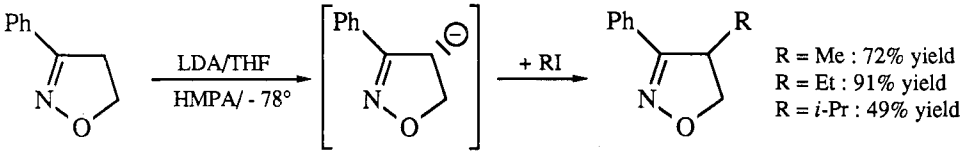
The presence of a 4-nitro-group allows easy bromination in position 4 under basic conditions. It is interesting to note that in this case bromination in position 5 can be achieved under strong acidic treatment:[257/79]




When dehydrobromination is impossible because of disubstitution in position 5, the 4-bromo derivative is obtained without difficulty. This is the case, for example, with the spiroisoxazoline **301**, where compound **302** is the only configurational isomer obtained:[143/74]

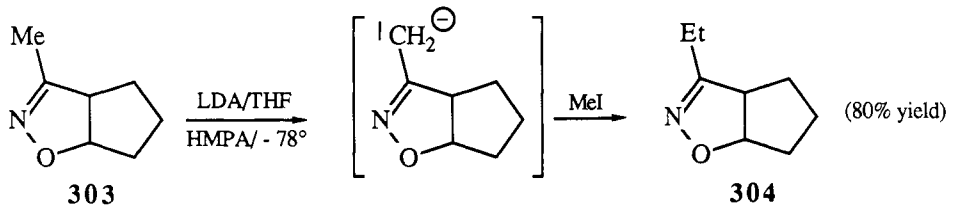



An important method of general applicability for introducing an alkyl substituent in position 4 of 3-aryl-2-isoxazolines is based on formation of the 4-anion by use of lithium diisopropylamide at low temperature, followed by reaction with alkyl iodide;[260/78] for example:




The substitution can be repeated, 3-phenyl-4,4-dimethyl-2-isoxazoline thus being prepared with 76% yield. Different substituents in position 4 have also been introduced.[162/84]

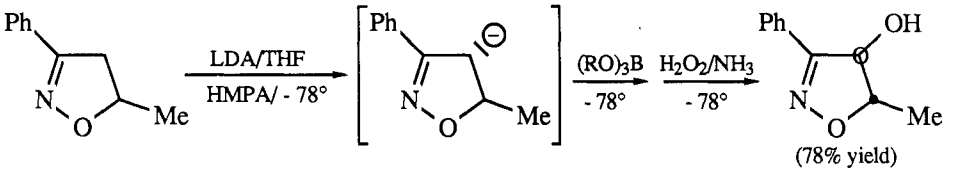
Starting from 3-phenyl-5-methyl-2-isoxazoline, this procedure furnishes *trans*-3-phenyl-4,5-dimethylisoxazoline with high stereoselectivity (93:7 ratio *trans*:*cis*).[260/78] With 3-methyl-2-isoxazoline the competitive formation of the 3α anion must be taken into account: for example, the bicyclic isoxazoline **303** delivers the 3-ethyl derivative **304**:[6/76,8/80]




303 304

The nature of the solvent may also influence the regiochemistry of the alkylation reaction: metallation of 3-methyl-2-isoxazoline in the polar mixture THF/HMPTA furnishes, after treatment with benzyl bromide, 3-methyl-4-benzyl-2-isoxazoline, whereas metallation in the less polar mixture THF/*n*-hexane leads, under the same conditions, to 3-phenethyl-2-isoxazoline.[14/83]

The formation of the 4-carbanion has also been utilized to prepare 4-hydroxyisoxazolines.[7/81] Treatment of the carbanion with borates, followed by oxidation with hydrogen peroxide or *t*-butyl hydroperoxide in the presence of ammonia or amine, makes it possible to insert the hydroxy group with good yields, mainly in the *trans* position to the 5-substituent; for example:

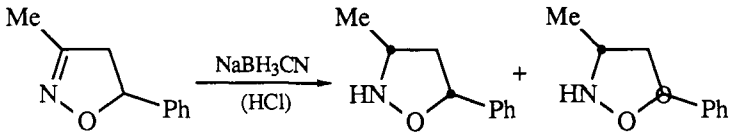



For the behavior of 5-halomethyl-2-isoxazolines toward strong bases, see Part 2 of this work and this §, p. 547. A substitution reaction in position 5 is exemplified by the synthesis of 3-phenyl-5-hydroxy-2-isoxazoline from the corresponding 5-boronic acid and hydrogen peroxide.[152/66]

### d. Addition Reaction at the C=N Bond

The most common way of transformation from 2-isoxazolines to isoxazolidine derivatives through addition to the C=N double bond utilizes the isoxazoline quaternary salts (see § 2.2.3.1a, p. 541). Some particular cases are worthy of mention here.

A neat hydrogenation of the C=N double bond, albeit with low yields, could be achieved through the use of sodium cyanoborohydride in methanol in the presence of concentrated hydrochloric acid. Thus a 2:1 mixture of the two epimers **305** and **306** is obtained starting with 3-methyl-5-phenyl-2-isoxazoline:[9/80]

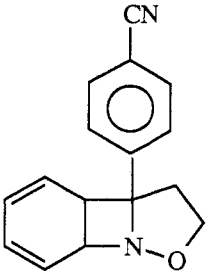



305 306

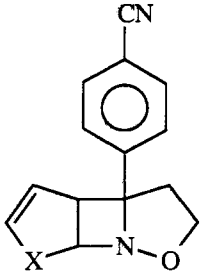
A 30% yield of the isoxazolidine carboxylic acid is reported by hydrogenation of sodium 5-phenylisoxazoline-3-carboxylate with sodium borohydride in ethanol.[135/72]

The isoxazoline C=N bond can be considered as a strained double bond of a cyclic oxime ether. Unlike its acyclic counterpart, the 2-isoxazoline ring sometimes shows dipolarophilic activity, especially toward the nitrile oxides, known to be a very active class of 1,3-dipoles. Thus a cycloaddition reaction can occur with 2-isoxazolines fused in positions 4 and 5 with a carbo- or a heterocyclic ring[69/70,190/71,140/72,70/73,189/76,254/78] (see Part 2 of this work); reactive monocyclic isoxazolines contain a 3-amino-[24/79] or a 5-hydroxy (or 5-carbethoxyamino) group.[152/80]

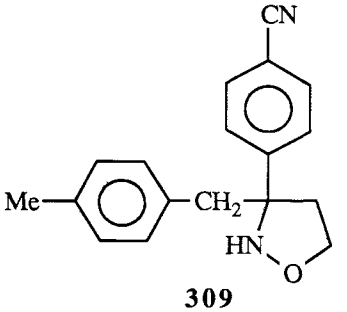
The presence of a suitable group, such as cyano or methoxy carbonyl, in the *para* position of 3-arylisoxazolines promotes a [2 + 2] photocycloaddition of some aromatic compounds on the C=N bond. Thus irradiation of 3-(4-cyanophenyl)-2-isoxazoline in benzene gives a mixture of products, where, in addition



**307**
(4% yield)



**308**
X = O: 42% yield
X = S: 54% yield

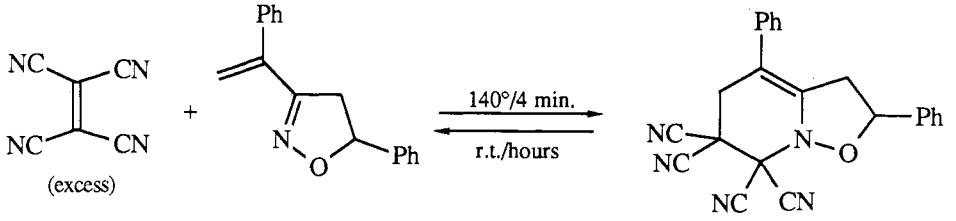


**309**
(58% yield)

to the expected photoproducts derived from scission of the N–O bond (see § 2.2.3.2a, pp. 259–261), a low yield of the cycloadduct **307** was isolated.[225/81]

Better yields of [2 + 2] photocycloadducts **308** are obtained by irradiation with furan or thiophene, and even higher with indene, which reacts to furnish a mixture of *exo-endo* stereoisomeric adducts.[163B/81,40/83] By contrast, with methylated benzenes such as *p*-xylene, hydrogen abstraction occurs, and monocyclic isoxazolidines such as **309** are formed.[301/83]

Conjugation of the isoxazoline C=N bond with a double bond in position 3 creates a 1-aza-1,3-diene system, which under drastic conditions can be forced to enter Diels–Alder cycloaddition with tetracyanoethylene, as the following example shows:[124/84]



### e. Transformations in the Side Chain

The 2-isoxazoline ring is fairly stable toward a large variety of reagents, so that a relatively high amount of chemical transformations in the chain (or in position 4 or 5) can be accomplished without cleavage of the heterocyclic ring.

As already mentioned in § 2.2.3.1b, pp. 543–544, a large variety of oxidizing agents bring about dehydrogenation of 2-isoxazolines to isoxazoles. Nevertheless, the 2-isoxazoline moiety is stable toward several other oxidants, so that oxidations in side chains do not present many difficulties provided that a suitable reagent is chosen. Thus oxidations of double or triple bonds can be afforded by cautious treatment with potassium permanganate in acetone or with ozone; for example, 3-phenyl-5-vinyl-2-isoxazoline or 3-phenyl-5-β-styryl-2-isoxazoline is oxidized to 3-phenyl-2-isoxazoline-5-carboxylic acid.[16/52.9/58] A furyl substituent is oxidized to a carboxylic group by the same reagents.[29/61.88/68]

Oxidations of aldehydes to acids with potassium bichromate,[7/59] of primary or secondary alcohols to aldehydes or ketones with Jones reagent,[29/61.86/65.229/72] and of sulfides to sulfoxides or sulfones with sodium periodide or with peracids[52D/81.278/83.160/84] are additional examples of routine transformations in the side chains. In the latter case it should be noted that sometimes, owing to the high instability of some sulfoxides, the elimination reaction to isoxazoles competes with the oxidation process (see § 2.2.3.1b, p. 546).

Catalytic hydrogenation of 2-isoxazolines usually provokes cleavage of the ring N–O bond (see later), but sometimes a CC double bond in the side chain can be selectively hydrogenated without affecting the ring.[209/70.240/74.160/84] Pd/C is the catalyst of choice. Reduction of a nitro to an amino group has been accomplished by using zinc and acetic acid or zinc or aluminum amalgam.[188/70.146/76] More or less stereoselective transformation of a keto into a secondary alcoholic group has been achieved with sodium borohydride[229/72.265/81] or under Meerwein–Ponndorf conditions.[29/61] It is interesting to note that the isoxazoline nucleus activates a carboxylic ester group in position 3, which is smoothly reduced to the carbinol with sodium borohydride at room temperature. For example, ethyl 5-phenyl-2-isoxazoline-3-carboxylate furnishes 3-hydroxymethyl-5-phenyl-2-isoxazoline in 78% yield.[124/84] By contrast, lithium aluminum hydride is known to cleave the heterocyclic ring.

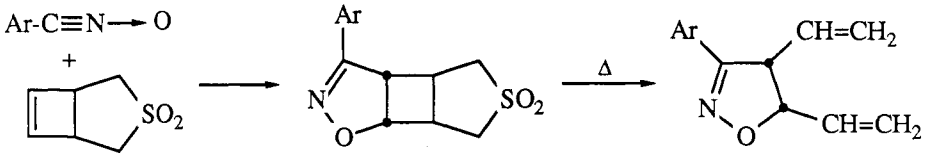
Electrophilic addition reactions to side-chain double bonds are known: as reagents bromine,[31/58] hydrobromic acid[6/60] or *m*-chloroperbenzoic acid[286/82.286/83] can be cited. Contrary to what happens with 2-pyrazolines, bromine does not convert the isoxazoline ring to isoxazole. Another example of addition reaction is the hydration of a triple bond; thus 3-phenyl-5-ethynyl-2-isoxazoline is transformed into 3-phenyl-5-acetyl-2-isoxazoline by treatment with mercuric salts in hydroalcoholic solution.[20/55]

1,3-Dipolar cycloadditions on side-chain unsaturations[16/52.20/55.200/66.177/83] or [4 + 2] cycloadditions on dienic systems[209/70] have also been reported.

As mentioned earlier, 2-isoxazolines are thermally rather stable; however, 4-carboxyderivatives smoothly decarboxylate by heating above their melting

points. This is probably due to the presence of a β-keto-acid-like structure. For example, 3-phenyl-2-isoxazoline-4,5-dicarboxylic acid (both *cis* and *trans*) decarboxylates to 3-phenyl-2-isoxazoline-5-carboxylic acid,[5/50] and 3,5-diphenyl-2-isoxazoline-4-carboxylic acid gives 3,5-diphenyl-2-isoxazoline.[11/52]

4,5-Divinyl-2-isoxazolines cannot be obtained directly by nitrile oxide cycloaddition to *cis*-1,3,5-hexatriene, because of the lack of dipolarophilicity of its central double bond. Nevertheless, the same product has been conveniently produced by an indirect route: by pyrolytic extrusion of $SO_2$ from the cycloadduct **310**:[157/82]




**310**

The isoxazoline ring is stable toward most acidic media. Thus nitration of 3-phenyl-2-isoxazoline with mixed acids furnishes a mixture of 3-nitrophenyl derivatives with excellent yield, where the chief component results in the *para*-nitro isomer.[179/67]

Additional examples of routine reactions carried out in an acidic medium may be cited:

1. Diazotization of primary amines to give primary alcohols.[61/65]
2. O-alkylation of 5-hydroxy-2-isoxazolines.[161/69,246/74]
3. Acidic cleavage of the epoxide ring.[209/70]
4. Ketalization of the carbonyl group.[1D/65,109/67]
5. Oximation of 5-acyl-2-isoxazolines, leading to *syn* and/or *anti* oximes.[89/68] (alkaline oximation provokes ring cleavage; see later).
6. Beckmann and Schmidt reactions on the oximes or on the ketones, respectively.[89/68]
7. Several transformations of carboxylic acid derivatives, such as acid-promoted esterification,[8/59.6/60.209/70] hydrolysis of amides[89/68.176/72] or nitriles,[8/50.18/71] Curtius degradation of acyl azides,[43/60.249/72] and cyclizations of 4,5-bifunctional derivatives.[176/72]

Other manipulations in the field of carboxylic acid derivatives are:

1. The easy hydrolysis[5/50] or ammonolysis[5/50,176/72] of isoxazoline-4,5-dicarboxylic anhydrides, as well as their transformation into the corresponding *N*-hydroxyimides.[176/72]

2. The esterification of free carboxylic acids with diazoalkanes.[5/50,43/60]
3. The synthesis of amides or hydrazides from the corresponding acyl chlorides[89/68] or esters.[43/60,14/64,176/72]
4. The alkaline hydrolysis of carboxylic esters, to be performed with caution to prevent decarboxylation or ring cleavage. Methanolic potassium hydroxide in the cold[5/50] or by refluxing[1D/65] has frequently been used for this purpose, but aqueous bases[43/60] can also be successful. 5-Hydroxy-2-isoxazolines can be obtained by cautious saponification of the acetates with methanolic sodium hydroxide and intermediate isolation of the sodium salt,[38/70] but also by reduction with methyl lithium in diethyl ester.[93/72]
5. The alkaline hydrolysis of nitriles.[118/66]

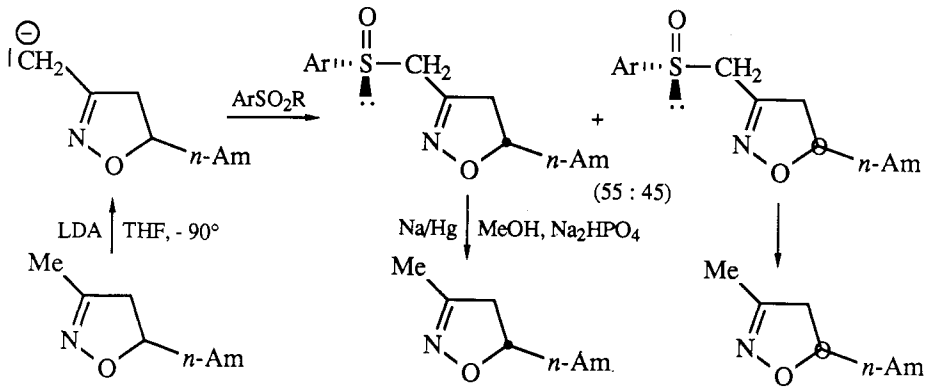
The isoxazoline ring is also normally stable under basic conditions, at least if the conditions remain relatively mild. Some examples of successful reactions in the side chains involve the following:

1. Nucleophilic substitutions on halo compounds or on sulfonates.[8/50,6/60, 117/74,257/79]
2. Ammonolysis of the epoxide ring.[117/74]
3. Addition reactions of Grignard reagents[43/60,89/68] or methyllithium[124/84] to carbonyl or ester groups.
4. Hofmann elimination for the synthesis of some 4-methylene isoxazoline derivatives.[180/80]

3-Amino-2-isoxazolines can easily be acylated with acetic acid or anhydride[43/60,34/73] or methylated by treatment first with potassium *t*-butoxide and subsequently with methyl iodide.[34/73] It must also be remembered that 3-methyl-2-isoxazolines can be alkylated in the 3α-position by metallation at low temperature with lithium diisopropylamide in THF and subsequent treatment with alkyl halide.[6/76,8/80] An interesting application of this is the resolution of racemic isoxazolines into pure enantiomers. Reaction of the metallated isoxazoline with (*S*)-menthyl toluene-*p*-sulfinate affords a mixture of the two diastereomeric isoxazolines, which can be separated chromatographically in excellent yields. Desulfurization of the individual stereoisomers is easily accomplished with sodium amalgam, giving enantiomerically pure isoxazolines, as shown by the example on p. 556.[69/84]

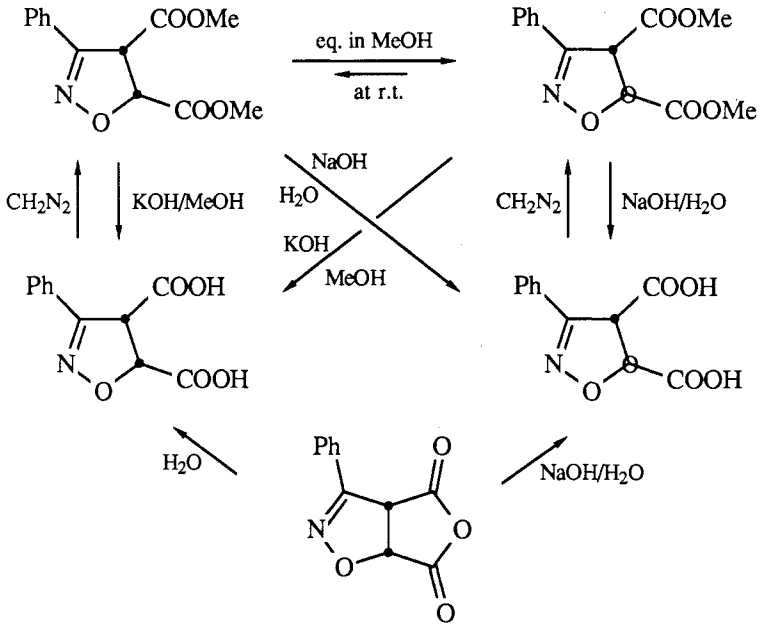
4,5-Disubstituted 2-isoxazolines show geometrical isomerism. Especially when the substituents are electron-withdrawing groups, bases or heat or solvent can promote epimerization.

A detailed study of the stereoisomerism has been carried out with 3-arylisoxazoline-4,5-carboxylic acids.[5/50,12/52,10/55,12/55] The esters of these acids are stereospecifically synthesized from maleic and fumaric esters with aromatic nitrile oxides. In most cases the *cis* form melts at a higher temperature than the




*trans* isomer and is less soluble in organic solvents. Both epimeric esters on hydrolysis at room temperature with methanolic potassium hydroxide give the same dicarboxylic acid, whose *cis* configuration is assured by its formation also from the anhydride and cold water. Methanolic solutions of the pure stereoisomeric esters, when kept at room temperature for several days, furnish an equilibrium mixture of the two forms. The equilibration is accelerated by heat or a mild basic medium.[176/72.164C/75]

On treatment with cold aqueous sodium hydroxide, *trans*-dicarboxylic acid has been obtained from the *cis* isomer or from both diastereomeric esters. The relationships linking pairs of acids and esters, exemplified on the 3-phenyl derivative and the methyl esters, are summarized in Scheme 2.15.

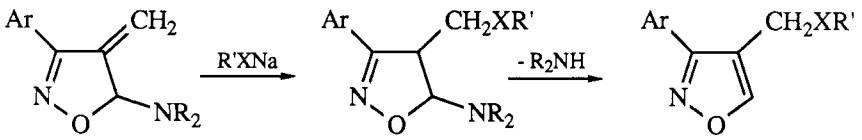



**Scheme 2.15**

The easy interconversion of diastereoisomers is reasonably connected with the possibility of enolization of the carboxy or carbomethoxy group in the 4-position.[10/55] The formation of *cis* acid in methanolic potassium hydroxide is undoubtedly due to the low solubility of the dipotassium salt, which separates out under those conditions.

3-Phenyl-5-methylisoxazoline-4,5-dicarboxylic acid esters, which have been synthesized from benzonitrile oxide and citraconic or mesaconic esters, also exist in two diastereomeric forms.[12/52] The two diastereomeric esters obtained from benzonitrile oxide and *cis*- or *trans*- cinnamic esters, also equilibrate in methanolic solutions, but only the *trans* acid is isolated by alkaline hydrolysis from both isomers.[51/59] Epimerization of isoxazoline-4-sulfones by heating or by treatment with triethylamine is also known.[278/83] Under the same conditions the regioisomeric 5-sulfones do not epimerize, but with triethylamine aromatize to isoxazoles.

Isomerism has also been observed with 3,4,5-triphenyl-2-isoxazolines: in this case isomerization from the *cis* to the *trans* form is completed by dissolution in concentrated sulfuric acid.[51/59] 5-Amino-3-aryl-4-methylene-2-isoxazolines **311**, prepared through base-catalyzed deamination of the ammonium salts, add nucleophiles, such as sodium methoxide or benzenethiolate, to yield isoxazolines **312**, easily transformable into 3,4-disubstituted isoxazoles by elimination:[181/80]




**311** **312**

Sometimes the presence of the 4-methylene functionality can be evidenced by 1,3-dipolar cycloaddition with nitrile oxides or other dipoles to give 4,5′-spirodiisoxazolines or other spiro heterocycles, respectively.[52C/81,144/83]

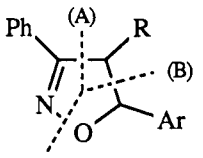
### *2.2.3.2 Reactions with Ring Cleavage*

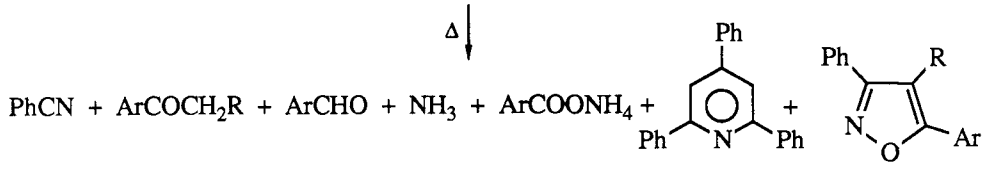
#### a. Thermolysis and Photolysis

3-Aryl-2-isoxazolines are usually stable to heat until 280–300°C. Above this temperature 3,4- or 3,5-disubstituted or 3,4,5-trisubstituted 2-isoxazolines, either separated or prepared *in situ* from α,β-ethylenic ketoximes, pyrolyze to give several fragmentation products.[183/75] Some example are presented in Table 2.32.

Thermolysis of 3-aryl-2-isoxazoline-4,5-dicarboxylic esters has been noted in boiling *o*-dichlorobenzene.[312/82] Most of the fragments obtained by the ther-

TABLE 2.32



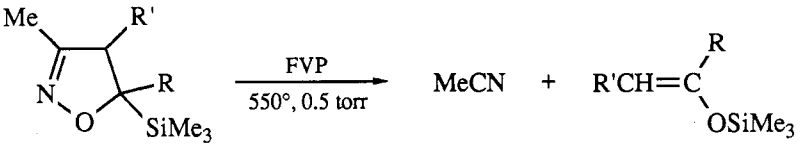




| R | Ar | T(°C) | % | % | % | [a] | % | % | % |
|---|---|---|---|---|---|---|---|---|---|
| H | Ph | 280 | 36 | 30 | 4 | + | 6 | 7 | - |
| | | 290[b] | 28 | 27 | 6 | + | - | 23 | - |
| Me | Ph | 330 | 50 | 56 | - | - | - | - | 22 |
| H | *p*-$MeOC_6H_4$ | 310 | 15 | 10+23[c] | 4 | + | traces | - | - |
| Me | α-$C_4H_3S$ | 310 | 25 | 17+7[c] | 10 | + | 4 | - | - |

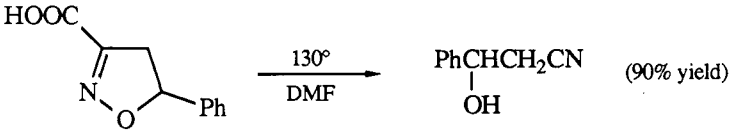
[a]Presence (+) or absence (-). [b]From separated 2-isoxazoline. [c]Yield in $PhCOCH_2R$.

molysis of 2-isoxazolines can be rationalized by assuming two different modes of ring cleavage: (1) a 1,3-cyclo-reversion, and (2) a reductive 1,4-cleavage.

A clear-cut example of 1,3-cyclo-reversion accompanied by a rearrangement is the pyrolysis of 5-trimethylsilyl-2-isoxazolines, which furnishes silyl enol ethers in almost quantitative yield:[147/81]




3-Carboxy-2-isoxazolines undergo thermal decarboxylation and ring opening to β-hydroxynitriles; for example:[143/76]

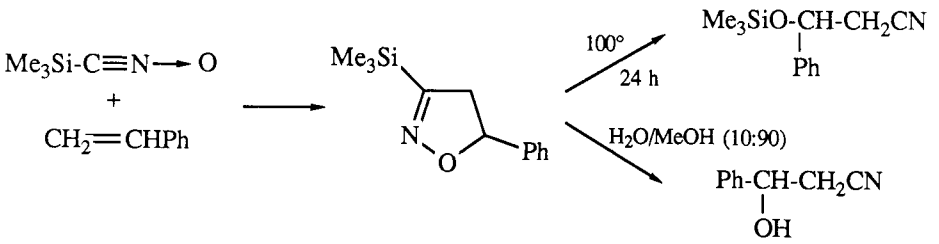



The decomposition temperature seems to depend markedly on the structure of 2-isoxazoline and on the experimental conditions (solvent or not). Under the

same conditions as above, *trans*-4,5-diphenyl-2-isoxazoline-3-carboxylic acid furnishes a 1:1 mixture of benzaldehyde and benzyl cyanide.[143/76,144/76,190/83] The ring opening to β-hydroxynitriles has general applicability, and has been utilized primarily in the steroid field.[1D/65,86/65,109/67,57B/69,143/76]

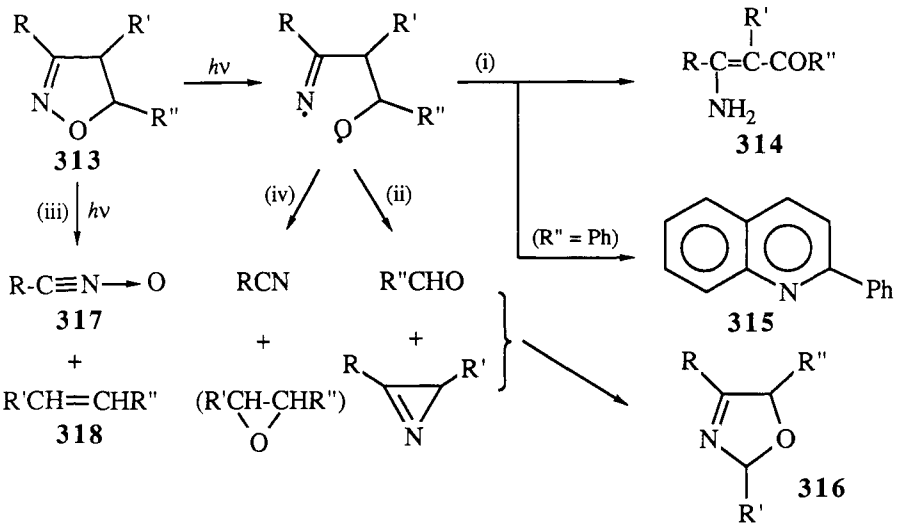
Thermal decomposition of the *t*-butyl peroxy ester has also been investigated, a mixture of products being thus obtained, along with the β-hydroxynitrile.[135/72] More straightforward seems to be decarboxylation of the trimethylsilyl ester, which furnishes trimethylsilyloxynitrile as a first step, easily hydrolyzed to β-hydroxynitrile.[95/81]

3-Unsubstituted 2-isoxazolines can also open to give β-hydroxynitriles, but usually this scission requires base promotion; only strained isoxazoline systems cleave thermally.[233B/74] Easier is the thermal ring opening of 3-trimethylsilyl-2-isoxazolines, which rearrange by heating to the trimethylsilyl ethers of the corresponding β-hydroxynitriles. The latter compounds can also be obtained directly by mild hydrolytic cleavage of the isoxazoline derivatives, as illustrated by the following example:[268/82,109/83]




It is interesting to note that up to now, in marked contrast to what happens with isoxazolidines (see § 3.4.4.1, pp. 738–740), no report of a thermal 1,3-dipolar cyclo-reversion, leading to nitrile oxides and alkenes, is known for 2-isoxazolines.

The photochemical behavior of 2-isoxazolines has been investigated extensively by several groups of researchers. Usually, a complex mixture of products is produced, which depends mainly on the nature of the substituents on the heterocyclic ring.[80B/72,105/73,228/73,24/74,180/75,85/77,214/77,225/81] When monocyclic isoxazolines are involved, the following pathways are the most relevant: (i) fission of the N–O bond, with subsequent rearrangement to either enamino carbonyl compounds or an isoquinoline; (ii) fission of the N–O and $C_4$–$C_5$ bonds with formation of an azirine and an aldehyde, which eventually recombine to give a 3-oxazoline; and (iii) 1,3-dipolar cyclo-reversion to nitrile oxide and olefin. A minor pathway (iv) to a nitrile (fission of the N–O and $C_3$–$C_4$ bonds) has also been observed. These mechanistic possibilities are summarized in Scheme 2.16, and Table 2.33 presents the yields of the various products obtained from selected 2-isoxazolines.




Scheme 2.16

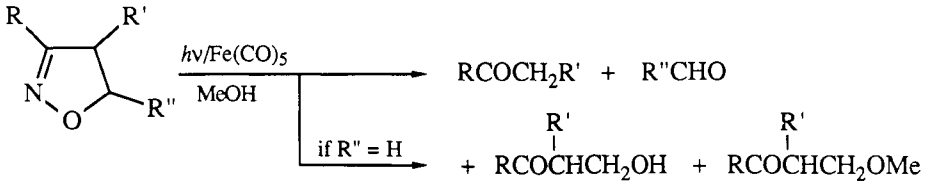
TABLE 2.33. PHOTOLYSIS PRODUCTS FROM MONOCYCLIC 2-ISOXAZOLINES 313

| | | | Yield (%) of products obtained[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Pathway: | i | | ii | | iii | | iv | |
| R | R' | R" | 314 | 315 | 316 | R"CHO | 317 | 318 | RCN | Solvent | References |
| Ph | H | H | 62 | - | 5 | - | - | - | 24 | $C_6H_6$ | 214/77, 225/81 |
| 4-ClPh | H | H | 53 | - | 5 | - | - | - | 23 | $C_6H_6$ | 225/81 |
| Ph | Ph | H | 86 | - | 6 | - | - | - | - | MeCN | 228/73, 180/75 |
| Ph | H | Ph | 3 | 15 | 19 | 1.1 | - | 1.6 | 2.0 | MeCN | 228/73, 180/75 |
| | | | 5 | - | 6.5 | 34 | - | - | - | $C_6H_6$ | 105/73 |
| 4-MePh | H | Ph | 4.5 | - | 5 | 10 | - | - | - | $C_6H_6$ | 105/73 |
| Ph | H | α-$C_{10}H_7$ | - | - | - | 12 | - | 16 | - | MeCN | 228/73, 180/75 |
| Me | Ph | Ph | - | - | - | 1.0 | 29 | 66 | - | MeCN | 228/73, 180/75 |
| Ph | Ph | Ph | - | - | 28 | 0.7 | - | 39 | 0.6 | MeCN | 228/73, 180/75 |

[a]Calculated on the 2-isoxazoline reacted.

On the whole, 5-unsubstituted isoxazolines prefer to follow pathway (i) to β-enaminoaldehydes, whereas 3,5-di- or 3,4,5-trisubstituted isoxazolines favor pathway (ii) to the isomeric 3-oxazolines and pathway (iii) to the $C_4$–$C_5$ olefins. A somewhat modified mechanism has been put forward to explain the mixture of products formed by photolysis of some 5,5′-bis-2-isoxazolines.[85/77]

Ultraviolet irradiation of a methanolic solution of a 3,5-disubstituted 2-isoxazoline in the presence of iron pentacarbonyl has recently been demonstrated to cause ring fragmentation to an aldehyde and a ketone. Analogous treatment of 5-unsubstituted 2-isoxazolines leads, in addition to the fragments above, to products derived from the sole N–O bond fission:[37/83]

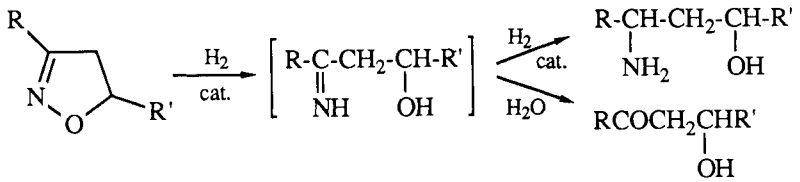



The proposed mechanism involves a N-donor complexation with the photochemically generated iron tetracarbonyl previous to N–O and $C_3$–$C_4$ bond fissions. Similarly, thermolysis of 3,5-diphenyl-2-isoxazoline with diiron enneacarbonyl provokes scission to acetophenone and benzaldehyde.[37/83]

b. Hydrogenolysis of the N–O Bond

The weak N–O bond of the 2-isoxazoline ring can be cleaved hydrogenolytically by two principal methods: catalytic hydrogenation or treatment with lithium aluminum hydride. Since this ring opening is a key step in the construction of complex molecules by use of 2-isoxazoline intermediacy (see § 2.2.3.3), the experimental conditions of the two reactions have been investigated thoroughly, especially more recently.

Catalytic hydrogenation usually opens the N–O bond of the heterocyclic ring to give, through the intermediacy of a β-hydroxy ketimine, the γ-amino alcohol as a final product. Nevertheless, if the proper conditions are adopted, the labile iminoalcohol can be hydrolyzed to the β-hydroxy ketone:



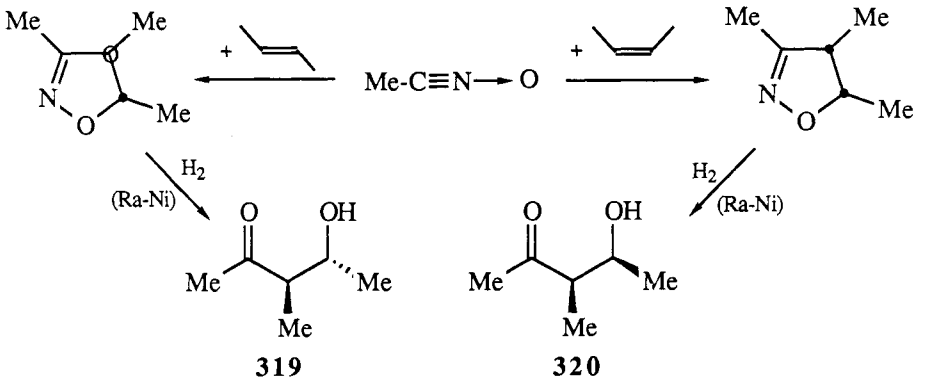

Use of platinum as a catalyst, whatever the solvent may be (alcohol, glacial or aqueous acetic acid, presence or absence of hydrochloric acid), always gives the amino alcohol.[141/82.135/83] For example, dialkyl 2-isoxazolines-3,5-dicarboxylates furnish a mixture of *threo* and *erithro* γ-hydroxyglutamic diesters;[49/78] isoxazoline-4-carboxylates afford diastereomeric hydroxylated β-amino esters, highly useful for the synthesis of α′-hydroxy β-lactams.[83/79.142/80.218/81] It is worthwhile noting that 3-amino-5-methyl-2-isoxazoline hydrogenolyses under platinum catalysis to 3-hydroxybutyramide.[188/70]

Palladium on carbon has also been utilized in preparing amino alcohols: for example, γ-hydroxy-α-amino acids have been obtained in 80–87% yield starting from 2-isoxazoline-3-carboxylic acids.[14/64.56/65] Especially if carried out in hydroxylic solvent in the presence of acetic acid, the hydrogenation can sometimes be stopped after the absorption of one equivalent, thus leading to the β-hydroxy ketone.[3/78.229B/81] For example, methyl 2-hydroxy-4-ketocaproate has been

obtained under these conditions from methyl 3-ethyl-2-isoxazoline-5-carboxylate.[3/78]

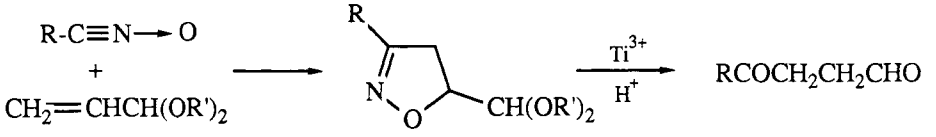
The presence of a phenyl group in the 5-position facilitates dehydration and further hydrogenation: from 3-ethyl-5-phenyl-2-isoxazoline a 21% yield of 1-phenyl-3-pentanone is obtained by hydrogenation over Pd/C in ethanol–acetic acid.[3/78] A retro-aldol scission follows the reductive cleavage of some spiroisoxazoline pyrazolones.[74/69]

The cleanest method for isolating β-hydroxy ketones is based on the use of Raney nickel as a catalyst in an aqueous methanolic or acetic medium.[259/80,141/82,280/82,135/83,294/83,112/84] Two recent accurate studies have demonstrated that with 4,5-disubstituted 2-isoxazolines the hydrogenolysis–hydrolysis sequence occurs without any noticeable epimerization if 4 Eq of aluminum chloride[280/82] or 2 Eq of trimethyl borate or (better) boric acid[135/83] is added to the aqueous methanolic solution. This diastereospecificity is exemplified on isomeric 3,4,5-trimethyl-2-isoxazolines:[141/82,135/83] the *threo* aldol **319** is obtained from the *trans* isomer and the *erythro* aldol **320** from the *cis* isomer:




**319** **320**

A suitable chemical reduction procedure is based on the use of titanous chloride in methanol. The reaction is rather slow and lasts 3–4 days in relatively moderate acidic conditions (pH = 3–4). Good yields of β-hydroxy ketones are thus obtained.[1/82] Whereas 5-acylisoxazolines regularly give the expected 2-hydroxy-1,4-diketones with this method, it is interesting to note that 2-isoxazoline-5-acetals, obtained by cycloaddition of nitrile oxides to acrolein acetal, furnish moderate yields of γ-ketoaldehydes by the same methodology:[283/83]

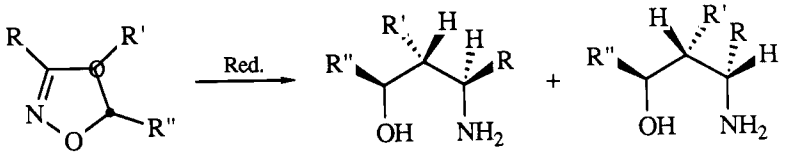


Although sodium amalgam,[1B/51,2B/53,14/64,13/80] zinc and acetic acid,[135/72,15/82] and diborane[48/74] have occasionally been utilized, the reductive cleavage of 2-isoxazolines to γ-amino alcohols has been carried out predominantly with lithium aluminum hydride in ether solution. Frequently, this ring opening has been used for structural determinations,[21/57,23B/57,29/61,31/61,9/62,2/63,44/64,88/68,165/69,216/74] particularly with the aim of fixing the regiochemistry of the 1,3-dipolar cycloaddition of nitrile oxides to unsymmetrical olefins leading to isoxazoline derivatives.

The stereoselectivity of the reductive cleavage by several reducing agents

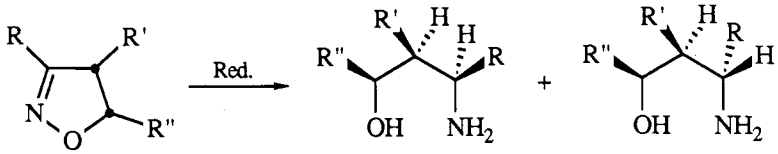
TABLE 2.34. γ-AMINO ALCOHOLS FROM REDUCTION OF HYDROCARBYL-SUBSTITUTED 2-ISOXAZOLINES

*trans*- Series




| R | R' | R" | Reductive agent | Isomer ratio |
|---|---|---|---|---|
| Me | H | Me | $LiAlH_4$ | 85 : 15 |
| | | | Na/EtOH | 55 : 45 |
| Me | H | Ph | $LiAlH_4$ | 95 : 5 |
| | | | $Me_2S/BH_3$ | 58 : 42 |
| Ph | H | Me | $LiAlH_4$ | 87 : 13 |
| | | | Na/Hg | 39 : 61 |
| | | | $Me_2S/BH_3$ | 58 : 42 |
| Ph | H | Ph | $LiAlH_4$ | 95 : 5 |
| | | | Na/Hg | 42 : 58 |
| Ph | Me | H | $LiAlH_4$ | 69 : 31 |
| Ph | Me | Me | $LiAlH_4$ | 72 : 28 |
| | | | Na/EtOH | 40 : 60 |
| Me | H | $n$-$C_{14}H_{29}$ | $LiAlH_4$ | 88 : 12 |

*cis*- Series



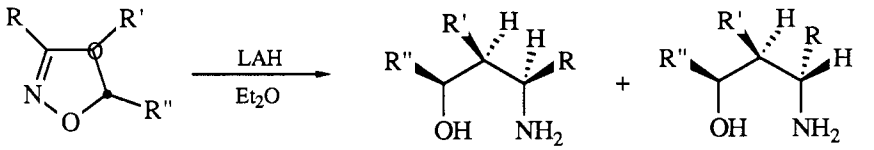

| | | | | |
|---|---|---|---|---|
| Ph | Me | Me | $LiAlH_4$ | 90 : 10 |
| Me | -$(CH_2)_3$- | | $LiAlH_4$ | 97 : 3 |
| | | | Na/EtOH | 42 : 58 |
| Et | -$(CH_2)_3$- | | $LiAlH_4$ | 97 : 3 |
| Ph | -$(CH_2)_3$- | | $LiAlH_4$ | >95 : <5 |

($LiAlH_4$, Na/Hg, Na/EtOH, $Me_2S \cdot BH_3$) has been studied systematically,[261/78.9/80.10/80] and lithium aluminum hydride has been found to be the most selective agent. One stereoisomer is formed prevailingly, which is expected from steric control during hydride attack: for example, the *erythro*-1,3-diphenyl-3-aminopropanol from 3,5-diphenyl-2-isoxazoline. Furthermore, the substituent in position 5 displays a higher steric hindrance than that in position 4. Table 2.34 presents some typical examples.[261/78.9/80.10/80.6/81]

Remarkably, sodium amalgam does not reduce 3-methyl-2-isoxazolines;[261/78.10/80] moreover, reduction with sodium and ethanol can provoke some C–O hydrogenolysis with 5-phenyl-substituted isoxazolines (e.g., 3-methyl-5-phenyl- or 3,5-diphenylisoxazoline), leading partially or totally to amines (e.g., 4-phenyl-2-butylamine or 1,3-diphenyl-1-propylamine, respectively).[1/07.261/78] The stereoselectivity observed indicates that the reductive cleavage can follow two different mechanistic pathways: (1) an addition to the C=N bond, followed by N–O fission, for hydride reduction; and (2) an N–O bond fission, followed by C=N hydrogenation, with sodium amalgam or sodium in ethanol.[9/80]

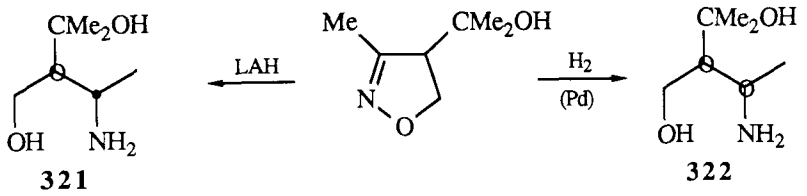
Admitting a lithium ion-ring oxygen coordination linkage in the transition state of the LAH reduction, the presence of an oxygenated function in one of the isoxazoline ring positions should markedly alter the diastereoselectivity. Indeed, as Table 2.35 shows, the *syn*-directly power is particularly strong with free OH groups in the 4-position, whereas ether and acetal groups have a weaker, although not insignificant influence on the diastereoisomer ratio.[6/81.5/85]

TABLE 2.35. γ-AMINO ALCOHOLS FROM REDUCTION OF OXYGENATED 2-ISOXAZOLINES



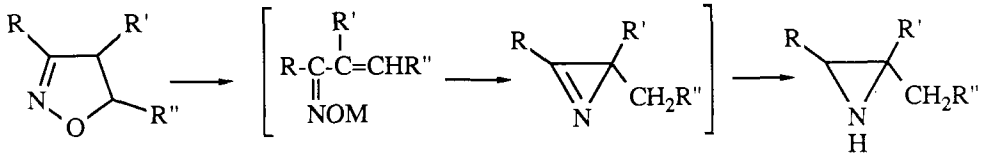

| R | R' | R" | Isomer ratio |
|---|---|---|---|
| $CH_2OH$ | H | $n$-$C_{14}H_{29}$ | 58 : 42 |
| $CH_2OTHP$ | H | $n$-$C_{14}H_{29}$ | 78 : 22 |
| Me | H | $CH_2OH$ | 37 : 63 |
| Me | H | $CH_2OTPH$ | 72 : 28 |
| Me | H | $CH_2OTrt$ | 92 : 8 |
| Me | H | $CH(OEt)_2$ | 81 : 19 |
| Me | H | $CH(OCH_2)_2CMe_2$ | 54 : 48 |
| Ph | OH | H | >90 : <10 |
| Me | $CMe_2OH$ | H | 95 : 5 |

Remarkable is the stereocontrol observed in the ring opening of 3-methyl-4α-hydroxyisopropyl-2-isoxazoline; whereas LAH reduction furnishes a 95:5 prevalence of the stereoisomer **321**, catalytic reduction reverses the stereoselection, leading to a 3:97 ratio in favor of its diastereoisomer **322**:[5/85]



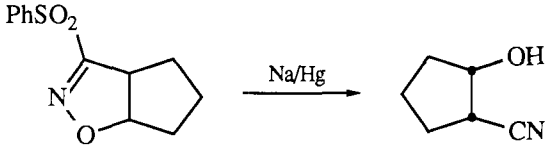

321 322

Analogous high stereoselectivities have been observed in the reductions with *i*-$Bu_2AlH$ in tetrahydrofuran at 55°C[153D/78] or with Red-Al in THF at −78°C.[153/83] By contrast, use of tetrahydrofuran as a solvent in lithium aluminum hydride reduction has been reported to afford, in addition to the γ-amino alcohol, variable yields of the corresponding aziridines:[209/68,203/70]




The presence of a 4-phenyl group clearly enhances the formation of the latter compounds, thus supporting an initial attack of the hydride on the benzylic 4-proton.

In one case resistance of the isoxazoline nucleus to LAH action has been signaled.[61/65] An interesting variation is the reductive cleavage of 3-phenylsulfonyl-2-isoxazolines with 2% sodium amalgam: excellent yields of vicinal cyanohydrins are thus reached. When stereoisomerism is expected, only the *cis* isomer is obtained.[97/79,163/81] For example, the 4,5-trimethylene derivative **323** gives a 91% yield of *cis*-2-cyanocyclopentanol:




**323**

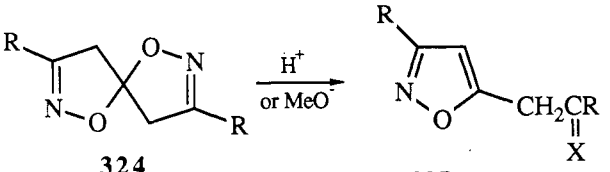
Finally, polarographic reduction of 3-phenyl-2-isoxazoline to 3-amino-3-phenyl-1-propanol has been reported.[85/71]

### c. Cleavage of the C–O Bond

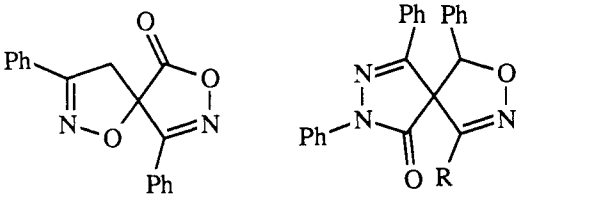
Although less common than the N–O bond, the $C_5$–O bond of the 2-isoxazoline ring can also be cleaved, usually under strong acidic or basic conditions. A long-known reaction is reductive cleavage with boiling hydroiodic acid, which leads to the saturated ketone. Thus 3,5-diphenyl-2-isoxazoline is cleaved to β-phenylpropiophenone and, with lower yields, to 4-phenyl-3,4-

dihydrocarbostyryl,[21/57] which possibly arose from a Beckmann rearrangement of the intermediate iodooxime.

5,5′-Spirodiisoxazoline derivatives (**324**) are easily opened by hydroiodic acid to isoxazole ketones (**325a**); the corresponding oximes (**325b**) are obtained if the ring cleavage is provoked by sodium methoxide:[29/60.88B/68]



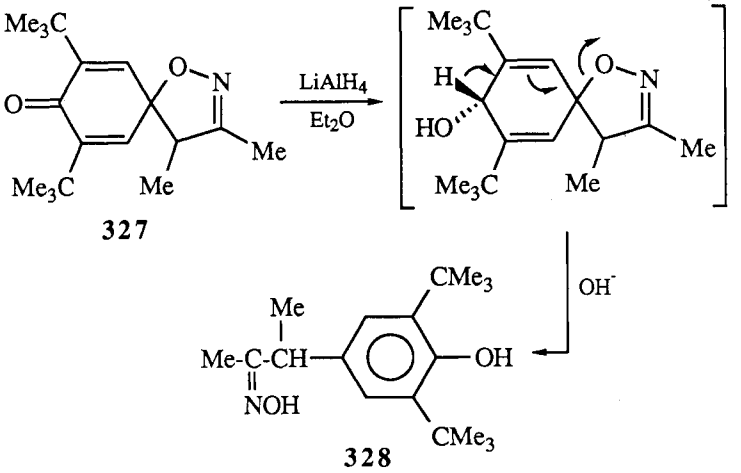
**324** **325 a** X = O
**b** X = NOH



**326A** **326B** (R = Me, Ph)

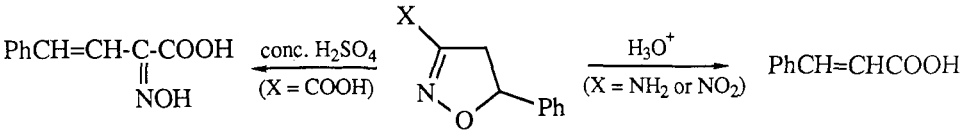
An analogous ring opening occurs with 4,5′-spirodiisoxazolines;[51/65] on the other hand, acidic treatment of the 4,5′-spiroisoxazolinone isoxazoline **326A** cleaves the isoxazoline ring more easily, giving 3-phenyl-5-benzoylisoxazole.[51/65] The 4,4′-spiropyrazolone isoxazoline **326B**, which possesses a stable pyrazolone ring, fragments the isoxazoline ring by treatment with concentrated sulfuric acid, yielding benzaldehyde and 1,3-diphenyl-4-acyl-5-pyrazolone oxime.[14C/68]

A special case of $LiAlH_4$ reduction concerns the quinone-like spiroisoxazoline **327**, which after reduction of the CO group rearranges in basic media to the phenolic oxime **328**:[19/78]



**327** **328**

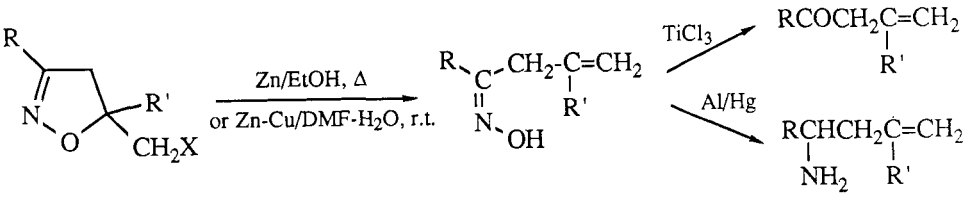
5-Phenyl-2-isoxazoline-3-carboxylic acid is opened by concentrated sulfuric acid to benzylidene–pyruvic acid oxime.[43/60] Moreover, 5-phenyl-3-amino (or 3-nitro)-isoxazoline is decomposed by heating with dilute mineral acids down to cinnamic acid:[43/60,91/66]




Interesting behavior is shown by 3,5-diphenyl-5-acetonyl-2-isoxazoline, which rearranges with good yields to 2-methyl-4,6-diphenylpyridine-*N*-oxide by refluxing in concentrated hydrochloric acid.[106/79]

As cyclic oximes, 2-isoxazolines would be expected to undergo Beckmann rearrangement. Indeed, whereas most classical reagents fail to provoke the desired rearrangement, ring cleavage and subsequent rearrangement are accomplished by acetic anhydride–boron trifluoride. Different unsaturated amides are obtained depending on the substitution pattern.[84/63,53/65] The presence of at least one phenyl group in the 5-position is essential for the reaction to occur, thus offering convincing evidence for the intermediacy of an open-chain carbocation.

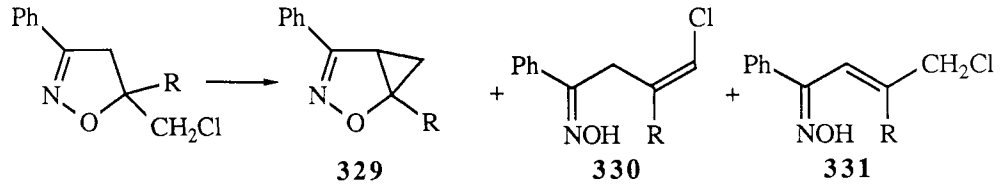
A ring-opening reaction of large applicability is the reductive dehalogenation of the easily accessible 5-bromo (or iodo)-methyl-2-isoxazolines: on treatment with zinc or zinc–copper, $\beta,\gamma$-enoximes are obtained in good to excellent yields without perceptible isomerization:[8/79]




The enoximes can be transformed by routine methods into $\beta,\gamma$-enones or into $\gamma,\delta$-unsaturated amines.

A similar transformation has been achieved by treating 3-phenyl-5-bromomethyl-2-isoxazoline with a strong base such as *n*-butyllithium: a 94% yield of 1-phenyl-3-buten-1-one oxime, contaminated (6:1) by the isomeric $\alpha,\beta$-unsaturated oxime, is achieved.[104/79] Different results are obtained from 5-chloromethyl derivatives and metallorganic bases: either intramolecular dehydrochlorination to the bicyclic 2-isoxazoline **329** or ring opening to isomeric chlorinated $\beta,\gamma$- or $\alpha,\beta$-enoximes. The formation of one or the other product depends on the substitution pattern and on the nature of the base and the reaction medium, as shown in Table 2.36.[24/77,104/79]

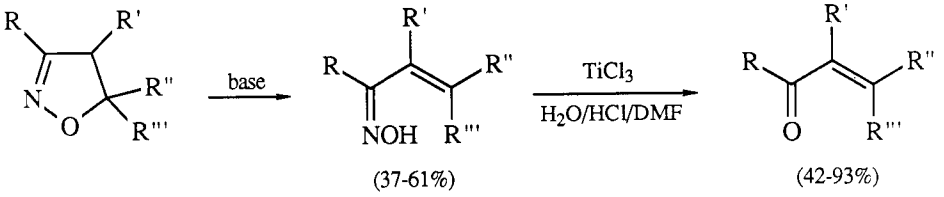
TABLE 2.36




329 330 331

| R | Reaction conditions | Total yield (%) | 329 | : | 330 | : | 331 |
|---|---|---|---|---|---|---|---|
| H | *t*-BuOK, DMSO, r.t. | 82 | 100 | : | 0 | : | 0 |
| H | *n*-BuLi, THF, -78° | 74 | 100 | : | 0 | : | 0 |
| Me | *n*-BuLi, THF, -78° | 78 | 12 | : | 68 | : | 20 |
| Me | *i*-$Pr_2NLi$, HMPT, -78° | 65 | 51 | : | 20 | : | 29 |
| Me | *i*-$Pr_2NLi$, HMPT, -78° | 100 | 100 | : | 0 | : | 0 |
| Me | *n*-BuLi, HMPT, -78° | 82 | 100 | : | 0 | : | 0 |

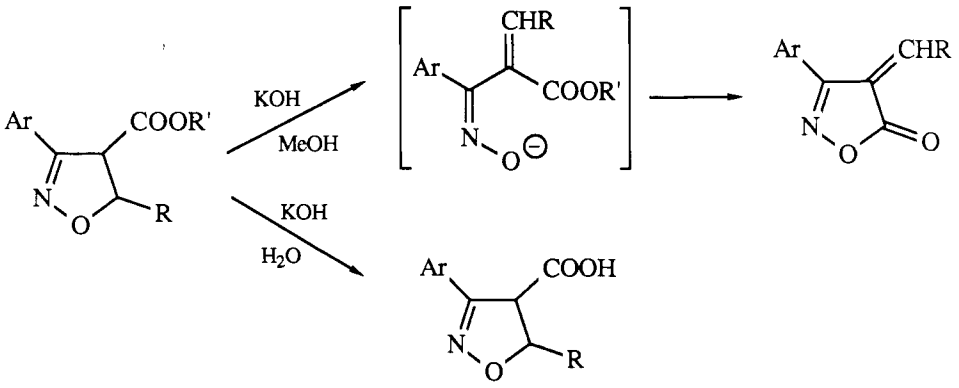
Formation of **329** and **331** is thought to occur through an intermediate carbanion in position 4. The reaction has been generalized with variously substituted 2-isoxazolines to give α,β-ethylenic oximes and subsequently α,β-enones.[6/76.97/79.8/80.11/84]




(37-61%) (42-93%)

The best suited base has proved to be lithium diisopropylamide, but *n*-butyllithium, phenyllithium, potassium *t*-butoxide, and ethyl magnesium bromide have also been used. The (*E*)-oxime is obtained exclusively or almost exclusively. The reaction path through the 4-carbanion has been substantiated by deuteration studies. When R′ = Me, sometimes (e.g., with the 4,5-trimethylene derivative) metallation in position 3′ competes favorably with position 4, and 3′-alkylation can be achieved without ring opening.[6/76.8/80]

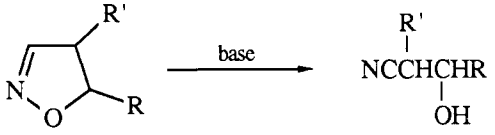
The presence of an alkoxycarbonyl group in position 4 favors base-promoted ring opening, which in this case is followed immediately by ring reclosure to 4-arylidene-5-isoxazolinones. This rearrangement is carried out with methanolic potassium hydroxide and is accompanied by variable amounts of the simple hydrolysis product, the isoxazoline 4-carboxylic acid.[30/59.51/59] This compound is the only product obtained with aqueous bases.



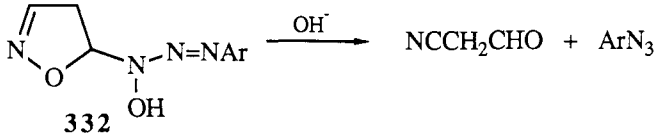

Finally, it should be noted that the formation of aziridines by treatment with lithium aluminum hydride has been thought to involve ring opening and intermediacy of an $\alpha,\beta$-unsaturated oxime metal salt.[203/70] It must also be remembered that 5-hydroxy-2-isoxazolines show a ring-chain tautomerism (see § 1.3.1.1h, p. 141). Therefore, some of their reactions, such as oximation,[161/69] acetylation,[40/69] or the Beckmann rearrangement,[37B/81] can be envisaged to occur through their open-chain tautomers.

d. Other Reactions with Nucleophiles

3-Unsubstituted 2-isoxazolines are easily opened by base treatment. Thus heating with triethylamine gives cyanohydrins, and the reaction has very broad applicability:[3/67,28/73]



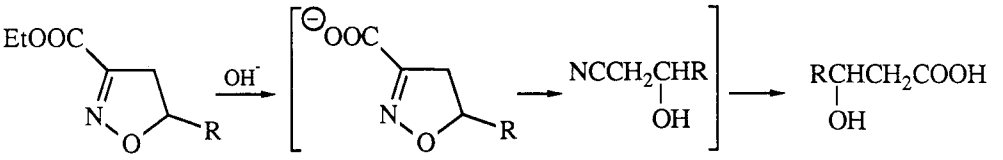

When methyl magnesium iodide is used as a nucleophile, the corresponding $\beta$-hydroxyalkyl methyl ketone is obtained.[208/69,233B/74] If isoxazoline position 5 possesses a suitable leaving group, a $\beta$-carbonyl nitrile can arise. Thus 5-hydroxyisoxazolines give $\alpha$-cyanoketones when treated with sodium methoxide,[53/67] and the isoxazolinyltriazene **332** fragments under basic conditions into cyanacetaldehyde and phenylazide:[7/69,76/70]



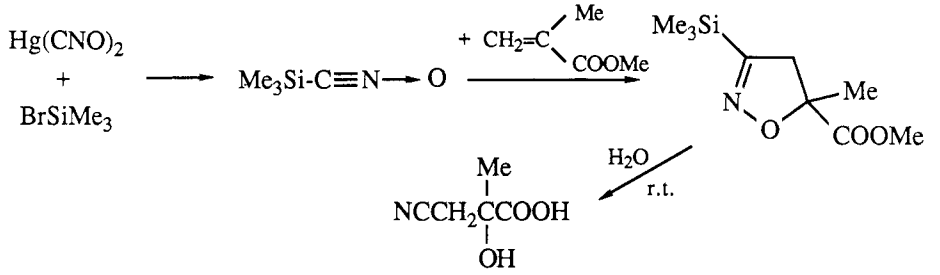

**332**

Instead of the 3-unsubstituted isoxazoline, a 3-alkoxycarbonyl (or a 3-carboxy) derivative functions as well, provided that a strong base is used to

perform ester hydrolysis and/or decarboxylation. With hot aqueous sodium hydroxide the reaction can proceed beyond the β-hydroxy nitrile step and finally, produce a β-hydroxycarboxylic acid:[142/82]



A trimethylsilyl group in the 3-position is even better, because ring cleavage occurs under very mild conditions, which leave unaltered other base-sensitive substituents, as the following example shows:[268/82,109/83]

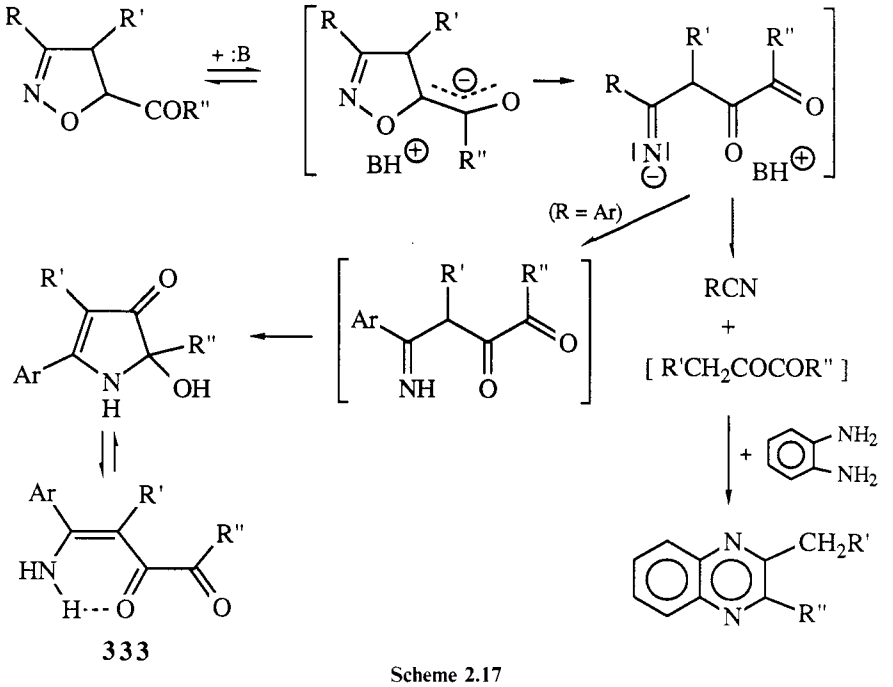


The presence of an electron-withdrawing group such as a carbonyl or alkoxycarbonyl enhances the acidity of the isoxazoline 5-proton. Bases, then, both inorganic (sodium hydroxide) and organic (triethylamine), provoke fragmentation of the molecule to nitriles and α-diketones (usually intercepted as quinoxaline derivatives).[138/68] As by-products, whose amount is solvent dependent, 5-hydroxy-2-pyrrolin-4-ones (**333**) are formed from 3-aryl-2-isoxazoline derivatives.[148/74] Their presence can again be explained through N–O fission subsequent to 5-carbanion formation; the resulting anion can either fragment further to nitrile and α-diketones or recyclize to pyrrolines (Scheme 2.17).

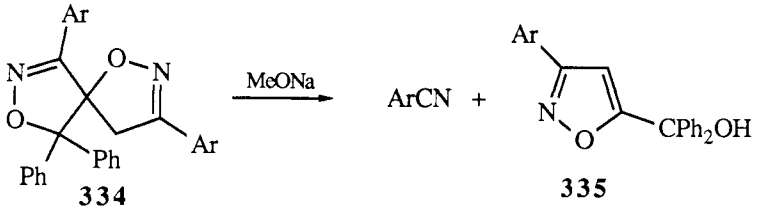
In view of the aforementioned instability, it is not surprising that 3-phenyl-5-acetyl-2-isoxazoline gives the corresponding oxime in acidic medium only, whereas hydroxylamine in basic solution furnishes a 37% yield of dimethylglyoxime, together with benzonitrile.[89/68]

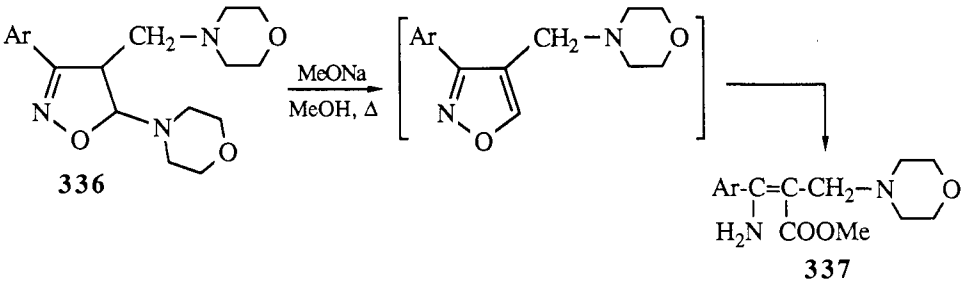
A ring fragmentation takes place when the 4,5′-spirodiisoxazoline **334** is treated with sodium methoxide, yielding an aromatic nitrile and the isoxazole compound **335**[152/74] (see p. 571).

An enamino ester (**337**) is the product of a vigorous basic treatment (prolonged heating with alcoholic sodium methoxide) of the dimorpholinyl isoxazoline **336**;[180/80] ring opening possibly occurs on the intermediate isoxazole compound (see p. 571).


+ :B
(R = Ar)
RCN
+
[ R'CH2COCOR" ]
333

Scheme 2.17

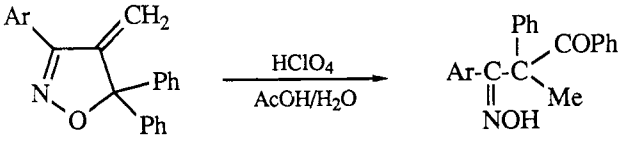

MeONa
ArCN +
334
335


MeONa
MeOH, Δ
336
337

### e. Other Ring-Opening Reactions

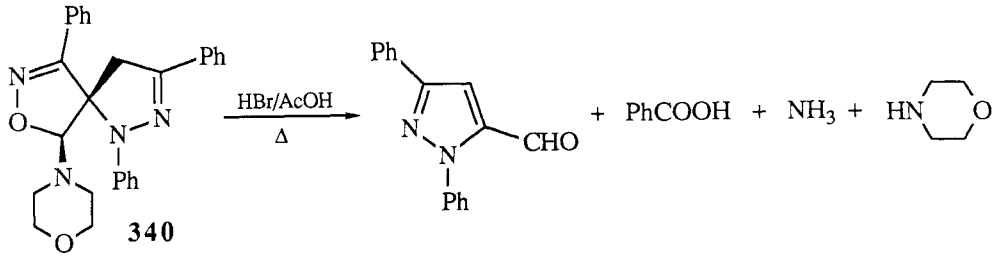
Ozonolysis of 2-isoxazolines at low temperature proceeds smoothly, and pure β-hydroxy ketones are isolated in 61–74% yields. Complete stereospecificity is achieved here, no epimerization being observed with 4,5-disubstituted compounds.[280/82,308/83] This procedure, however, involves lower yields than those in the normally applied hydrogenolytic cleavage process (see § 2.2.3.2, pp. 561–562) and is convenient only when the molecule contains other reducible groups.

The 4-methylene isoxazoline **338** rearranges to the diketone monoxime **339** when treated with strong acid:[152/74]




**338** **339**

5-Morpholino-2-isoxazolines are known to deaminate smoothly to isoxazoles under strong acidic treatment (see § 1.3.7.1f, pp. 235–237). When the 4-position is disubstituted, the reaction can take a different course. For example, spiro(isoxazoline-4,5-pyrazoline)(**340**) is fragmented with complete destruction of the isoxazoline ring:[144/83]

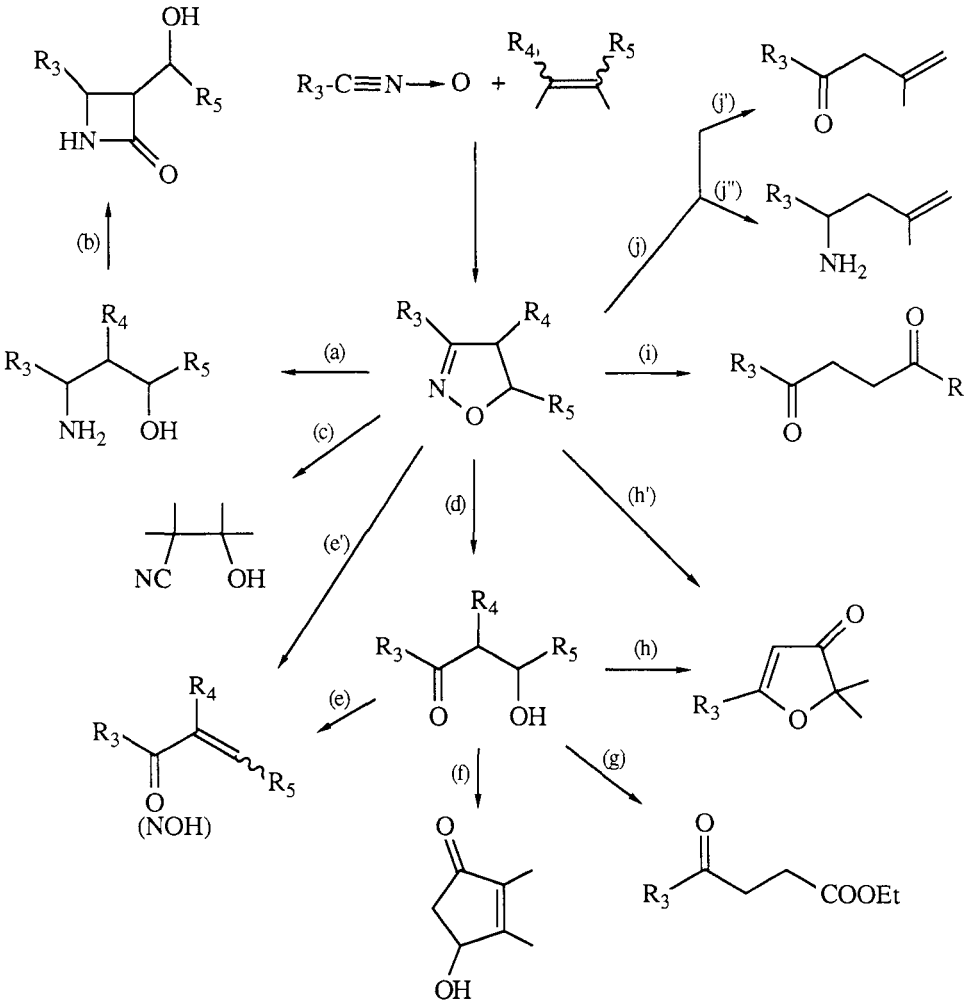



**340**

## *2.2.3.3 Use of 2-Isoxazolines as Key Intermediates in Synthetic Design*

Although the importance of isoxazoles and isoxazolidines as key intermediates in the syntheses of more or less complex molecules has been recognized since long, utilization of 2-isoxazolines remained rare until a few years ago. Nonetheless, this gap has recently been filled, and applications of the isoxazoline route in the synthetic strategy are about to exceed those using the other two approaches.

Indeed, the isoxazoline route can at least compete advantageously with the two aforementioned related systems. An isoxazoline ring is formed under mild conditions and is remarkably stable under various conditions. This fact allows extensive manipulations to be performed on the side-chain functionalities. The 1,3-dipolar cycloaddition (nitrile oxides/alkenes), which originates the isoxazoline ring, is 100% stereoselective and can exploit diastereofacial selection. Unfortunately, the cycloaddition is not always regiospecific, and mixtures of regioisomers often arise. Appropriate choice of the substituents of the dipolarophile can diminish or suppress this drawback. For a discussion of the factors controlling the cycloaddition reactions, see § 2.2.2.2c.




**Scheme 2.18**

Appropriate control of experimental conditions can insert a higher or lower degree of stereo control during the ring cleavage step. For a discussion of the various types of ring scissions and of the factors controlling stereoselectivity, see § 2.2.3.2. If suitable functionalities are present in the isoxazoline side chains, the primary product of the ring cleavage can be further converted into other types of acyclic or cyclic compounds.

Scheme 2.18 (where the substituents are only indicative) summarizes the principal transformations of 2-isoxazolines utilized in synthetic strategy, along with indicating the conditions most commonly encountered for each reaction. Brief notes on the individual pathways follow:

(a) $LiAlH_4$ or Dibal; Na/Hg; Zn/AcOH, $H_2$/Pt, or Pd/C

(b) $R_4$ = COOR: (i) TMSCl, $Et_3N$; (ii) EtMgBr; (iii) aqueous $NH_4Cl$

(c) $R_3$ = $PhSO_2$(c′), EtOOC (c″), or $Me_3SiOOC$ (c‴): (c′) Na/Hg, $H_2O$; (c″) aqueous NaOH, then heat; (c‴) heat, then NaOH

(d) $H_2$/Raney Ni/$AlCl_3$ or $B(OMe)_3$ or $H_3BO_3$; $Ti^{3+}$, $H^+$; $O_3/O_2$, −78°C, then $Me_2S$

(e) $MsCl/Et_3N$ or $Ac_2O$, heat

(e′) (i) LDA, THF, −78°C; (ii) $TiCl_3$, $H_2O$, HCl, DMF

(f) $R_5$ = COR: aqueous NaOH

(g) $R_5$ = $CH(OEt)_2$: EtOH, dry HCl

(h) AcOH, AcONa, heat

(h′) $H_2$ (Raney Ni), then $H_3O^+$

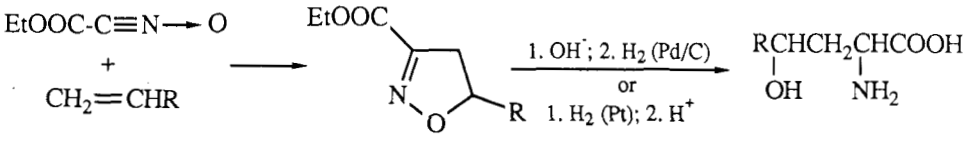
(i) $R_5$ = COR: (R = H) aqueous $Ti^{3+}$; (R = alkyl) Zn/HCl, $Ti^{3+}$

(j) $R_5$ = $CH_2Br$: (i) Zn or Zn/Cu, ROH; (ii) $TiCl_3$, buffer (j′), or Al/Hg, $H_2O$ (jj′)

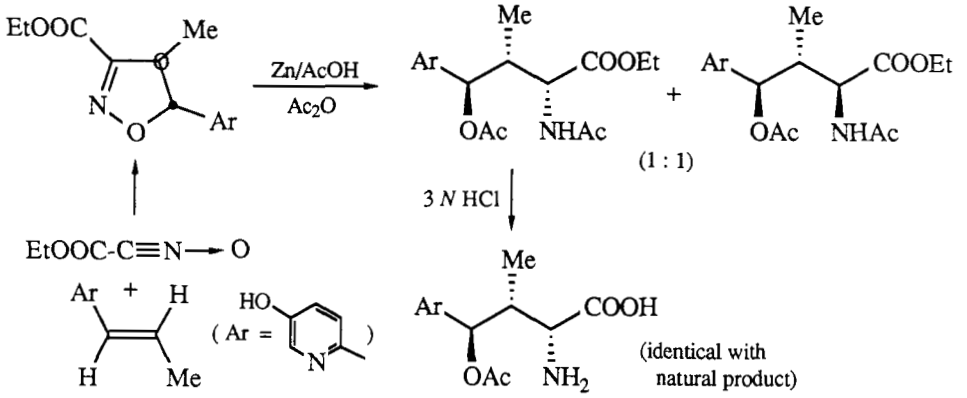
More details may be found in recently published authoritative reviews, which cover broader or narrower parts of the subject.[104/82,33/83,1/84,5/85]

(a) The longest known ring cleavage of 2-isoxazolines derives from reduction of both the C=N double bond and the N–O bond to give γ-amino alcohols under various hydrogenolytic conditions (see § 2.2.3.2b, pp. 561–565). The entire sequence, starting with the cycloaddition step, corresponds to an α-aminoalkylation–hydroxylation of the olefinic double bond, and can be carried out with some high degree of stereo selectivity. With metal complex hydrides, the *erythro* isomer is usually predominant. The possibility of controlling the stereoselection, of using either inter- or intramolecular cycloadditions, and of inserting appropriate functionalities in the isoxazoline side chains for further transformations opens a wide field of applications.

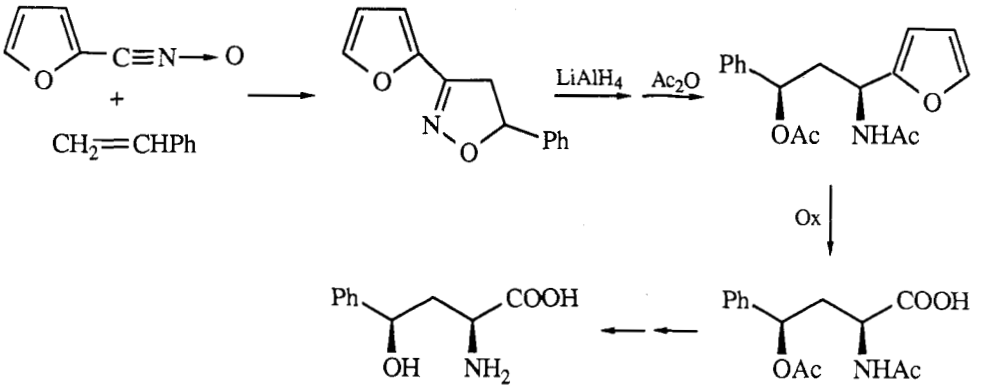
The simplest reaction concerns the synthesis of γ-hydroxy-α-amino acids, which employs carbethoxyformonitrile oxide as the 1,3-dipole partner:[14/64,56/65,137/72,49/78]




Unfortunately, catalytic hydrogenation leads to a nonevaluated mixture of *threo* and *erythro* isomers. Chemical reduction was utilized in the synthesis of the N-terminal γ-hydroxyamino acid residue of the nucleoside antibiotic nikkomycins.[13/80,15/82] The reduction step here is too unselective, but in one case the two diastereomers could easily be separated by column chromatography, as reported in the following example:

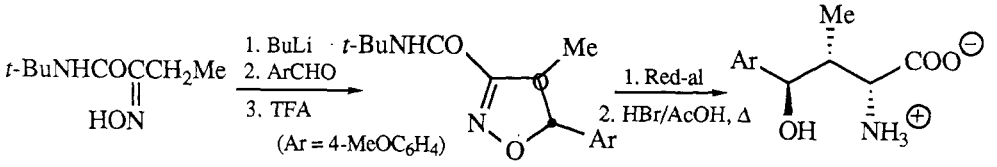



A different approach is based on the use of masked carboxylic groups in the nitrile oxide unit, such as easily oxidable aromatic rings (anisyl or furyl), to allow a stereoselective $LiAlH_4$ reduction.[33/83] For example, racemic γ-phenylhomoserine could be synthesized from furonitrile oxide in the following sequence:



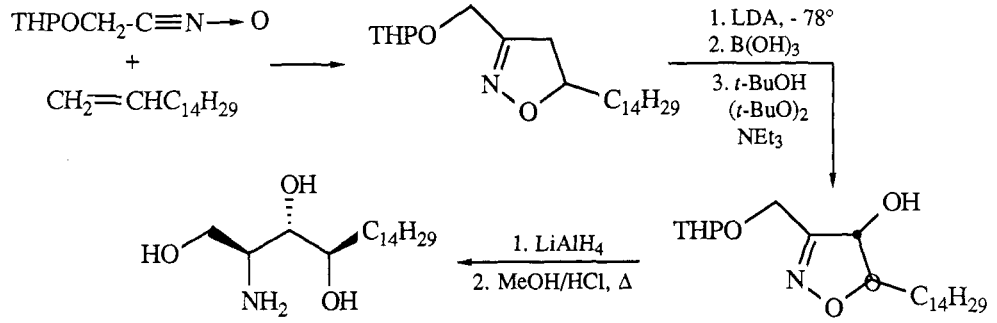
Unfortunately, although the stereoselectivity of the reduction step is good, during the acidic N,O-deprotection, considerable epimerization occurs. Therefore, it seemed more convenient to reduce the isoxazoline ring nonstereoselectively and to equilibrate at the lactone stage in solution or in suspension (as hydrochloride), thus obtaining with satisfactory yield pure *threo* or *erythro* amino acid, respectively. Analogously, the N-terminal amino acid methyl ether from nikkomycin B has been constructed in 36% overall yield from carbethoxyformonitrile oxide and 1-*p*-methoxyphenylpropene.

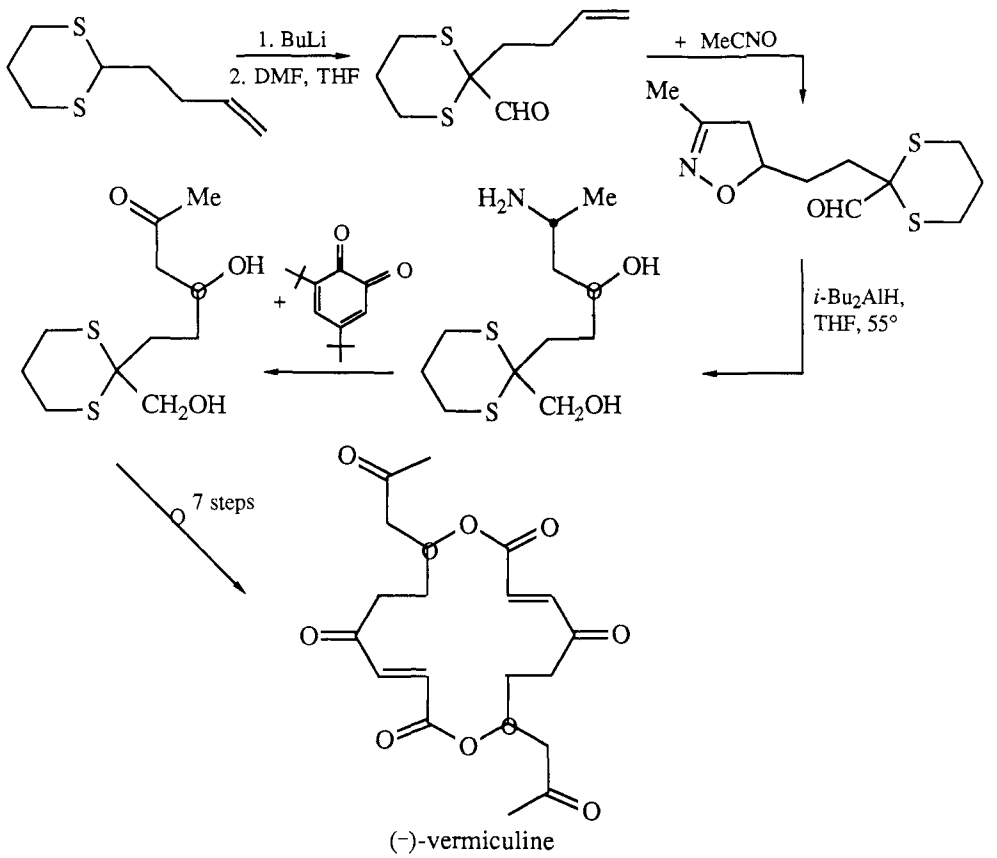
Far higher diastereoselectivity in the reduction step was achieved by using Red-Al as the reductant of the isoxazoline ring; fairly good yields of pure N-terminal amino acid of nikkomycin B have been obtained through the following route:[153/83]




A more sophisticated application of the 2-isoxazoline cleavage to γ-amino alcohols is represented by the stereospecific total synthesis of the macrolide antibiotic (−)vermiculine,[153D/78] outlined in Scheme 2.19. Not only is the Dibal reduction of the heterocyclic ring stereospecific, but optical resolution at the stage of the amino diol thus obtained makes it possible to build a macrolide with the desired configuration. A further utilization of 2-isoxazoline synthons in the field of macrolides has been found in the building of the northern hemisphere intermediate of milbemycin and avermectin.[254/83]

Coupling the cycloaddition–hydrogenolysis strategy with the stereoselective anion hydroxylation in position 4 led to an advantageous synthesis of racemic $C_{18}$-phytosphingosine, obtained in 30% overall yield from 2-nitroethanol as illustrated in the following sequence.[7/81] Both the bulkiness of the 5-substituent



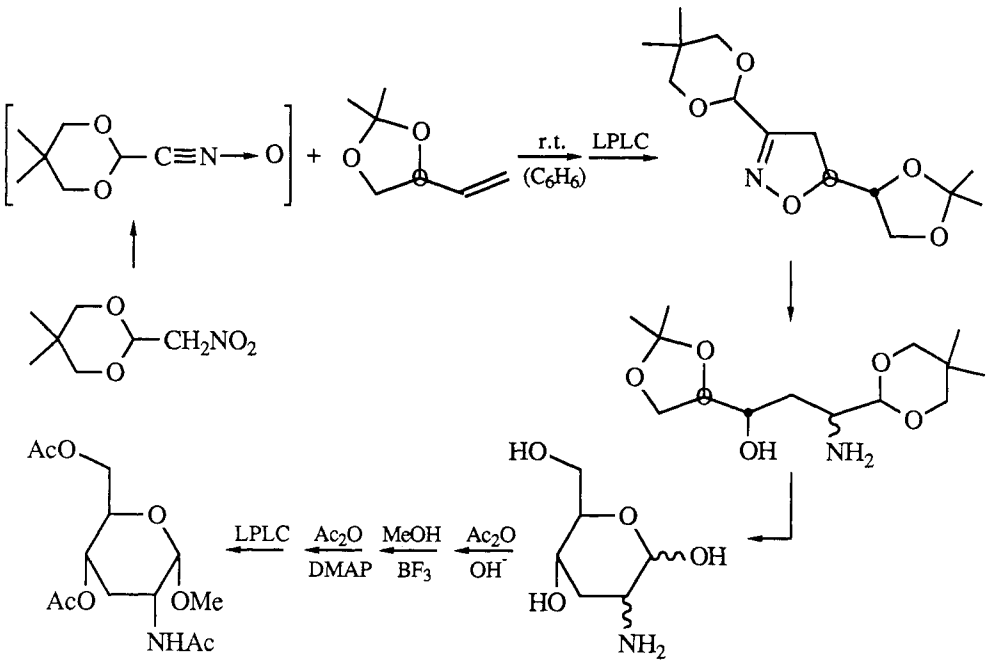



**Scheme 2.19**

and the coordinating power of the 4-hydroxyl conspire in granting practically complete stereoselectivity to the ring-opening step.

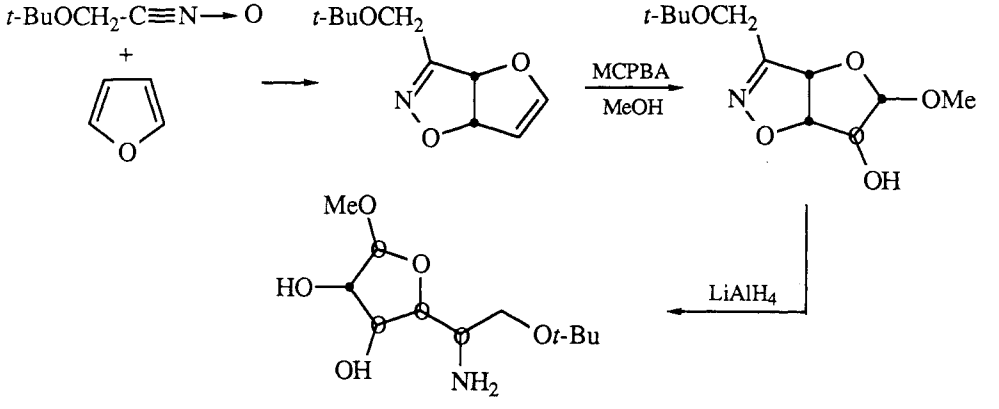
The insertion of other oxygenated stereo-controlled functionalities in either the dipolarophile and/or the 1,3-dipole opens an elegant entry into the wide field of amino sugars.[33/83,5/85] To this end two principal strategies have been envisaged, illustrated here by two examples.

The optically active (*S*)-2-vinyl-1,3-dioxolane, an appropriate synthon for 3-buten-1,2-diol, and ketalized nitroacetaldehyde, a convenient synthon for glyoxylonitrile oxide, are the starting materials. From the cycloaddition reaction a mixture of diastereoisomers was obtained, and the major product, the *erythro* isomer, was isolated through LPLC. $LiAlH_4$ reduction furnished a 78:22 mixture of nonseparable isomeric amino alcohols in high yields, which was then hydrolyzed, acetylated, and methylated. The final target was a protected D-lividosamine, *ribo*-configurationally homogeneous, synthesized from the starting materials with a 9% overall yield (Scheme 2.20).[167/84]



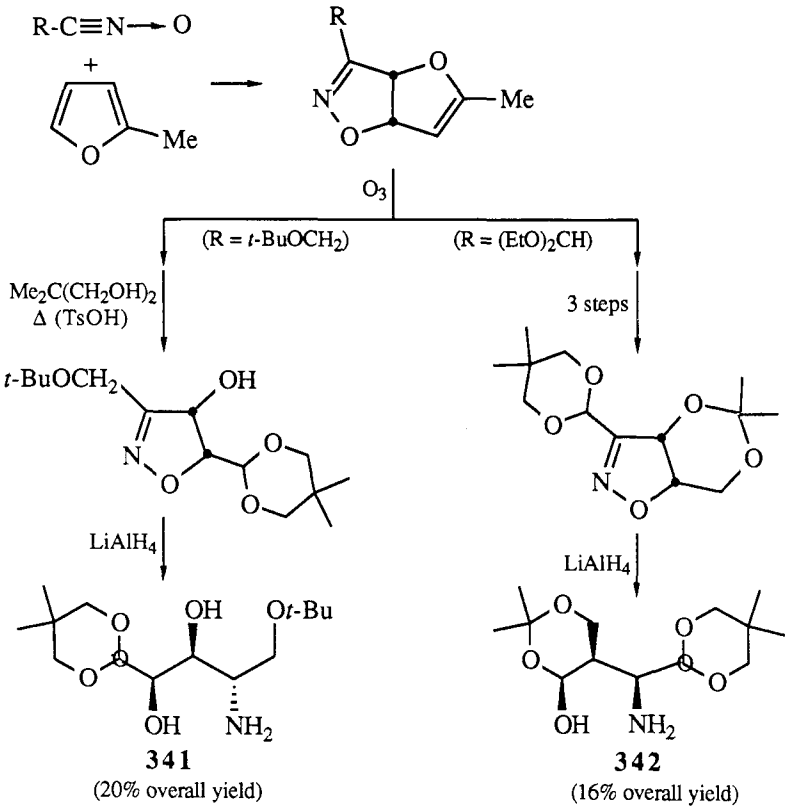

**Scheme 2.20**

A different useful starting point is the highly regioselective cycloaddition of nitrile oxides and furans. Albeit the moderate yields of the cycloaddition step, the possibility of stereoselectively functionalizing the dihydrofuran double bond offers an attractive opportunity of creating several adjacent oxygenated chiral centers. This approach is exemplified here by the following short synthesis of a protected 5-amino-5-deoxyidose (= 5-*epi*-nojirimycin):[167/84]




(26% overall yield)

Two additional examples of this method are reported below.[6/85] Ozonization of the furoisoxazolines is utilized here for creating the appropriate polyoxygenated functionalities, fostering the necessary diastereoselectivity in the reduction step. Only the protected DL-4-amino-4-deoxyarabinose (**341**) and DL-2-amino-2-deoxyxylose (**342**), respectively, were thus obtained (Scheme 2.21). Owing to the possibility of manifoldly varying the substituents in both the nitrile oxide and the dipolarophile unit, this "isoxazoline" approach seems very promising for further developments in the stereo-controlled synthesis of amino polyols and amino sugars.[5/85]

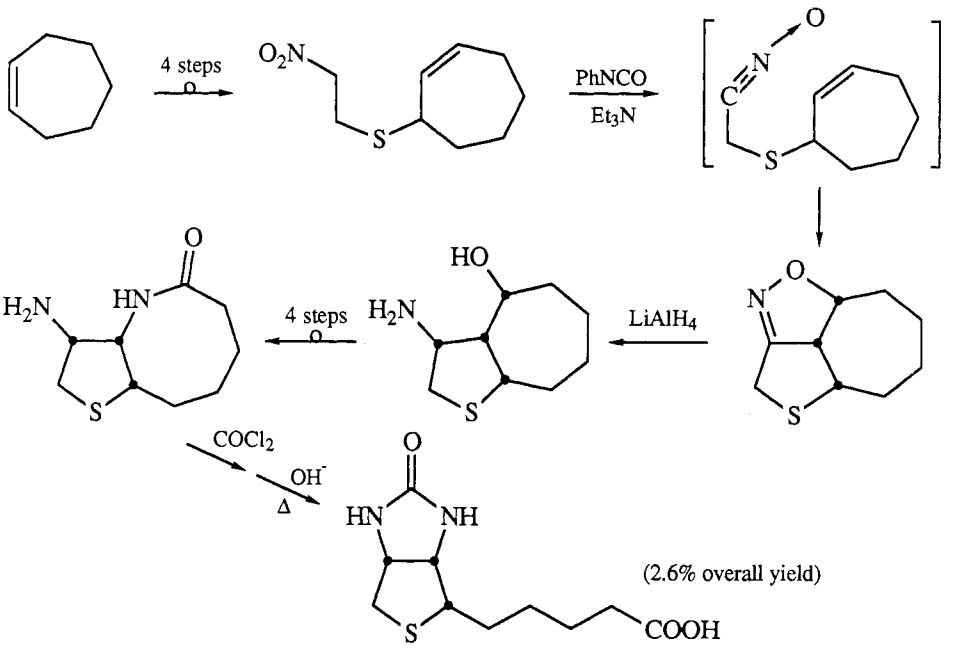



**341**
(20% overall yield)

**342**
(16% overall yield)

**Scheme 2.21**

The intramolecular version of the 1,3-dipolar cycloaddition is also prone to involve remarkable stereoselection. Thus an interesting synthesis of (+)-biotin builds the three chiral centers through an isoxazoline step followed by a highly stereoselective hydrogenolysis, as illustrated in Scheme 2.22.[153C/78] A variation on this synthetic design starts from L-cystine and involves a double isoxazoline/isoxazolidine step, also stereoselective.[243/81] The possibility of alkylating the

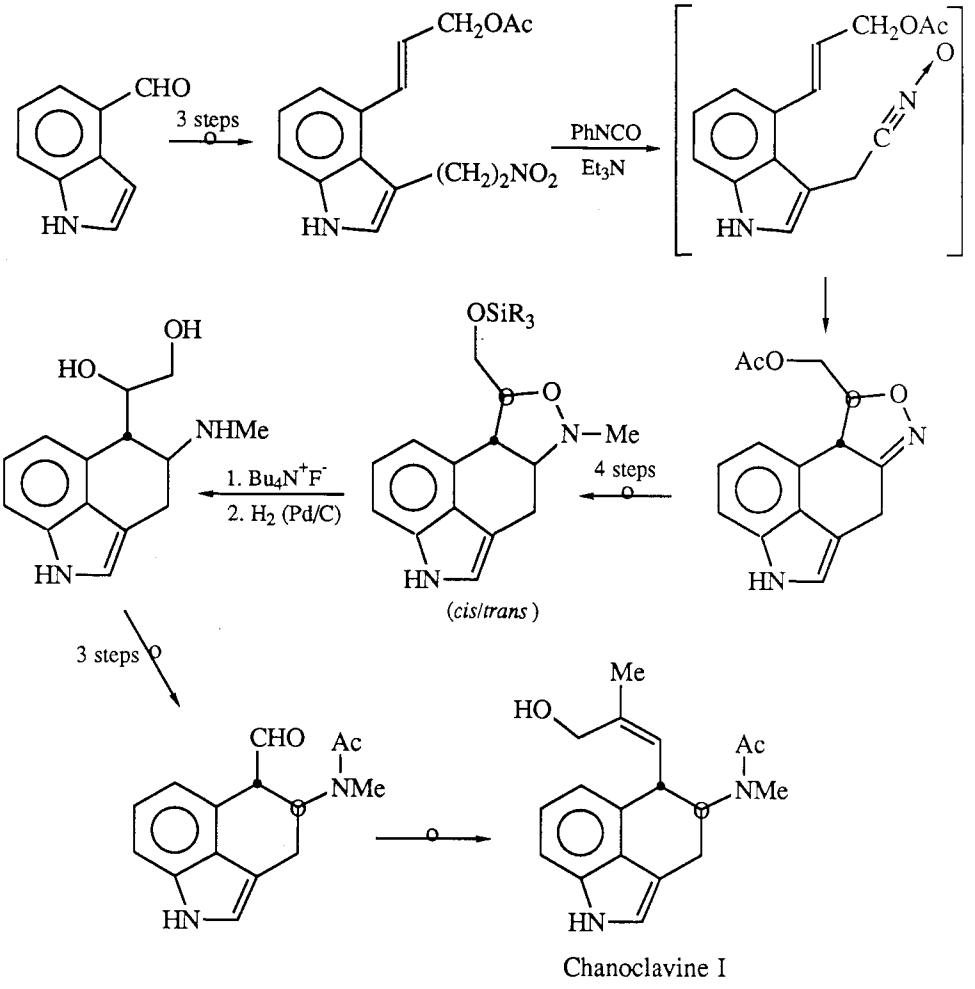



**Scheme 2.22**

isoxazoline ring nitrogen *prior* to reduction further expands the applicability of the intramolecular nitrile oxide cycloaddition approach and furnishes a valuable entry into the alkaloid field.

The total synthesis of chanoclavine I is summarized in Scheme 2.23[146/80] and represents an alternative route to the nitrone-mediated approach (see § 3.4.10.2c, pp. 764–765). Reduction of the isoxazoline to the isoxazolidine ring through N-methylation followed by $NaBH_4$ treatment is stereo-unselective, and a 1:1 mixture of *cis*/*trans* isomers is formed. Nevertheless, this is unimportant in the overall assemblage, since at a later stage complete epimerization at $C_{10}$ occurs, leading to the natural *trans* configuration.

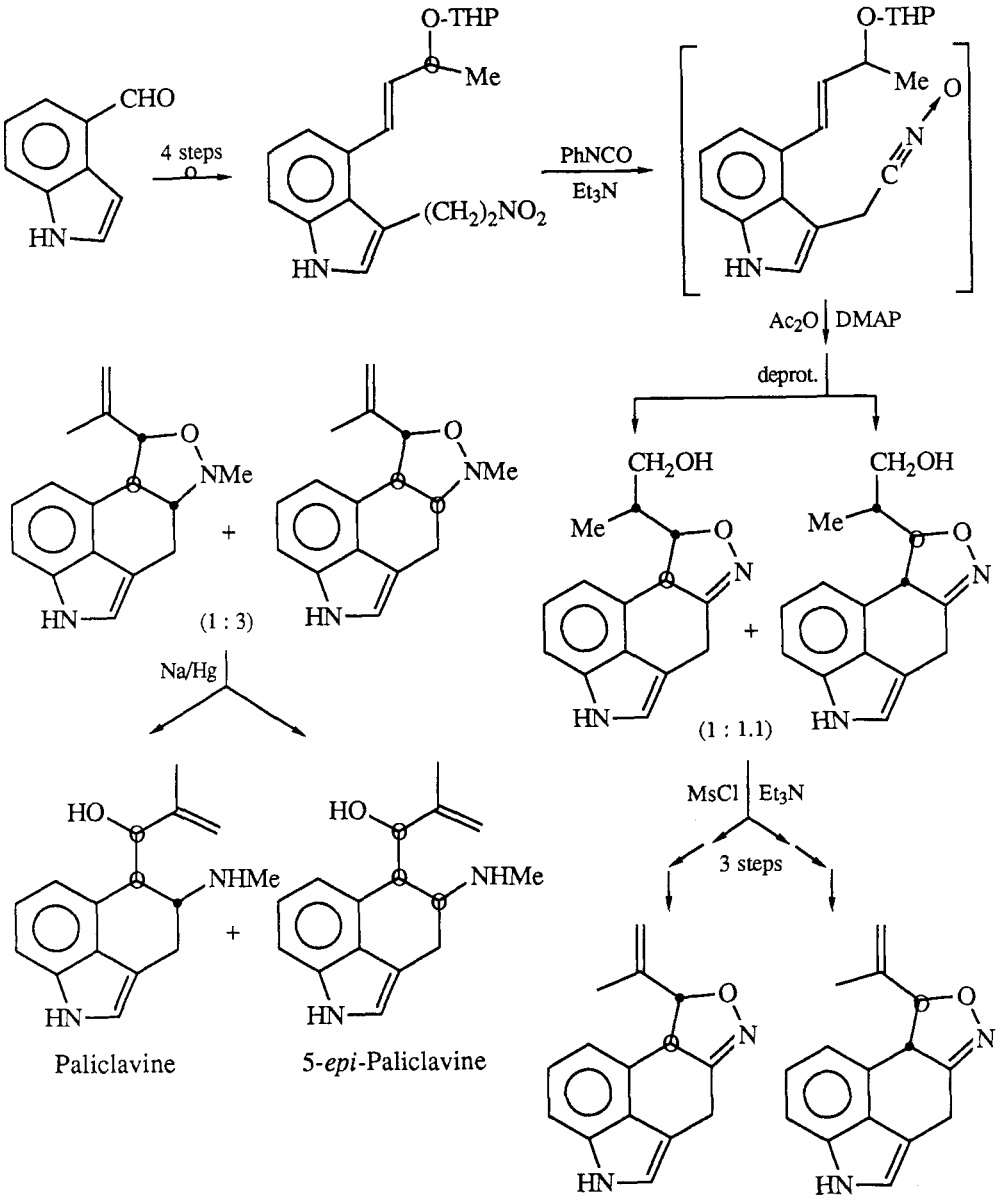
Slight variations on the theme results in a total synthesis of (+)-paliclavine, outlined in Scheme 2.24.[162/81,169/84] The lack of stereoselectivity in the cycloaddition step could be overcome by separation of the two diastereomeric isoxazoline alcohols, which, after destruction of the outside chiral center by dehydration, furnished the pure antipodes. Again N-methylation/$LiAlH_4$ reduction of the proper enantiomer, followed by ring opening, gave a 1:3 mixture of the *trans* fused (+)-paliclavine and of the *cis* fused 5-*epi*-paliclavine, easily separated by column chromatography.




**Scheme 2.23**

An interesting synthetic variation of the 1,3-amino alcohol general procedure has been realized by starting with 1-phenylthio-1,3-butadiene as dipolarophile. Regiospecific cycloaddition to nitrile oxides is followed by reductive cleavage, amine group protection, and mild hydrolysis, giving $\delta$-amino-$\alpha,\beta$-unsaturated aldehydes as final products[155/82] (see p. 583).

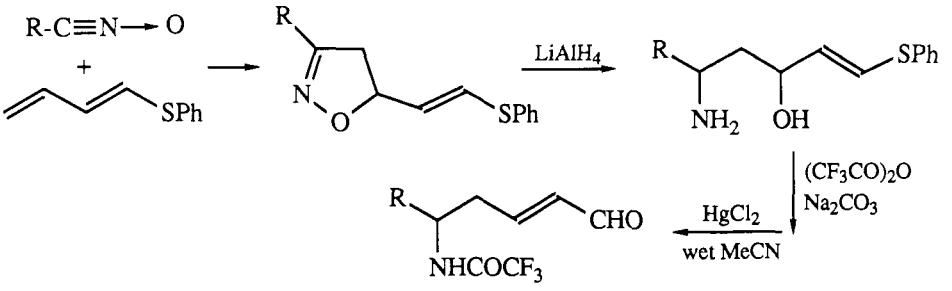
(b) The presence of a carboxylic ester group in the isoxazoline 4-position opens a facile route to $\beta$-lactams, since the amino group, liberated in the catalytic hydrogenation of the heterocyclic ring, can more or less easily cyclize on the carboxylic group to yield the azetidinone ring. This approach has been



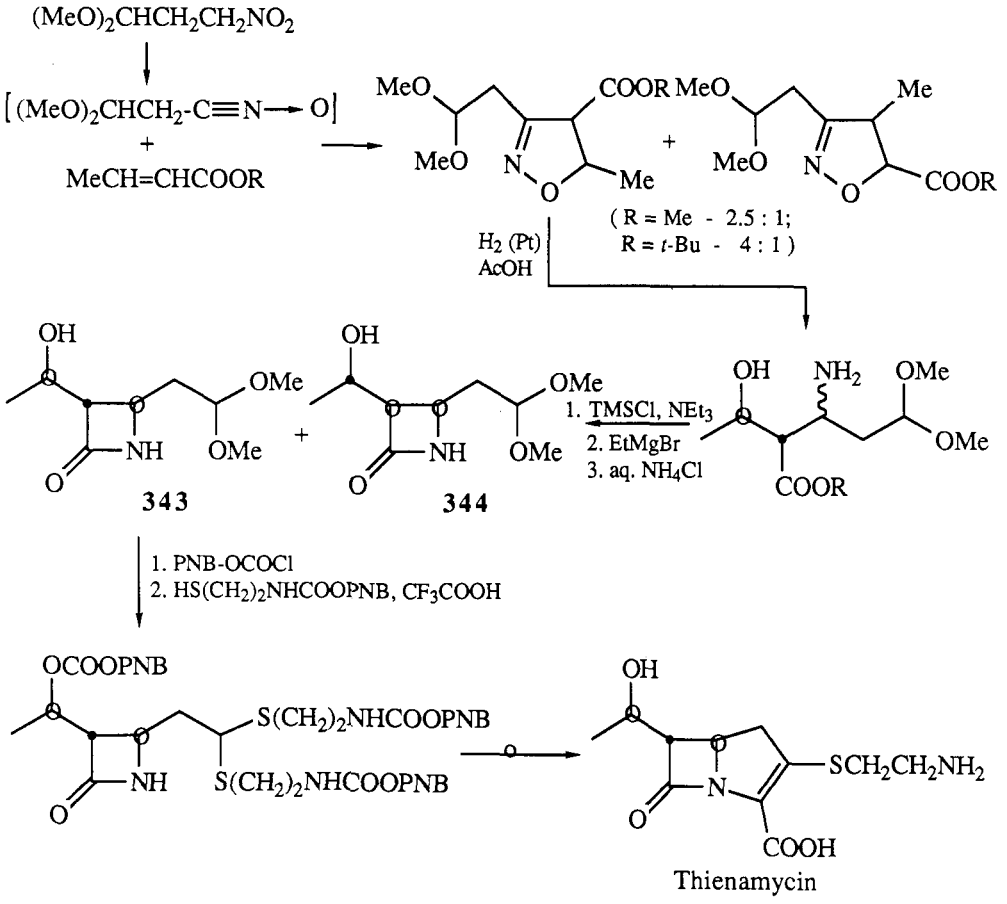

**Scheme 2.24**

utilized in the stereoselective construction of carbapenem antibiotics,[104/82] and is illustrated in Scheme 2.25 by the formal total synthesis of (±)-thienamycin.[83/79,84/79,86/79,142/80,114/81]

The 1,3-dipolar cycloaddition of *trans*-crotonic esters is 100% stereoselective




but only 2.5–4:1 regioselective: the desired regioisomer (isoxazoline-4-carboxylic ester) is the major product, easily separated. The low stereoselectivity of the isoxazoline catalytic hydrogenolysis is the critical step and mixtures of the stereoisomeric amino esters are obtained as a rule. Moreover, cyclization of the

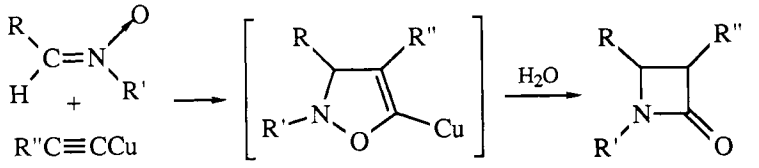



Scheme 2.25

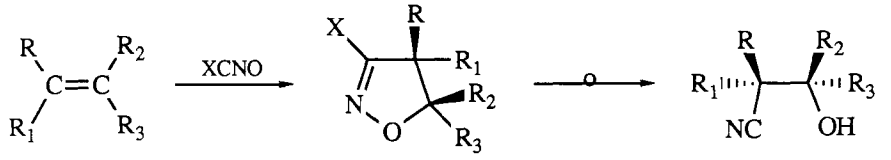
amino esters to azetidinones (e.g., with DDC) often suffers extended epimerization. Use of the bulky isoxazoline *t*-butyl ester and cyclization on the protected (trimethylsilylated) hydroxyamino ester gave, after deprotection, only the desired *trans*-azetidinone (**343**) in 41% overall yield from the isoxazoline.[116/80,218/81] By contrast, starting from the isoxazoline methyl ester, a 38% overall yield of *cis*-azetidinone (**344**) was produced, intermediate for the synthesis of (±)-*epi*-thienamycin.[68/81,118/81] Furthermore, transformation of *cis*- to *trans*-azetidinone is known.[69B/81]

The synthetic approach outlined here has general applicability, and other carbapenem derivatives[67/81] (carpetimycin A) can be constructed.[67/81,117/83] An asymmetric synthesis of the two azetidinones was achieved starting from optically active crotonic esters.[70/81,120/81]

A rather odd formation of β-lactam derivatives (*cis*/*trans* mixtures) starts from the reaction of some nitrones with cuprous acetylides and involves the alleged intermediacy of an unstable 4-isoxazoline, as shown in the following scheme:[158B/76]




(c) Use of the easily generated benzenesulfonyl-, alkoxycarbonylformo-, or trimethylsilanecarbonitrile oxides allows a *cis*-cyanohydroxylation of olefinic double bonds along the following sequence of general applicability:[143/76,97/79,95/81,163/81,109/83,190/83]

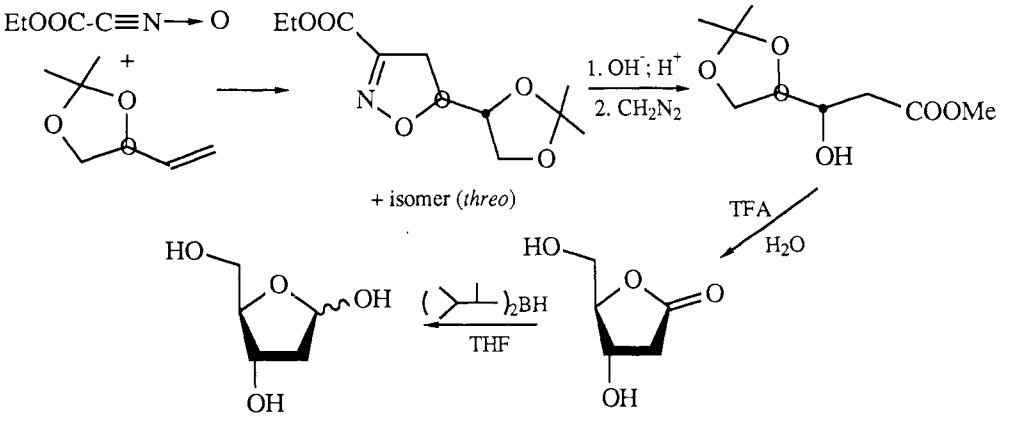



(X = $PhSO_2$, EtOOC, $Me_3SiOOC$, $Me_3Si$)

In all cases the 100% stereoselectivity of the cycloaddition step and the lack of epimerization in the ring-opening step (either under reductive or decarboxylative conditions) warrant complete stereospecificity in the overall addition. Enlightening is the case of *cis*- and *trans*-2-butene, which by the ethoxycarbonylformonitrile oxide route furnish stereoisomerically pure *erythro*- and *threo*-2-methyl-3-hydroxybutanonitrile in 62% and 64% overall yield, respectively.[190/83] Cyanogen-*N*-oxide can also be used, although less conveniently, in the same sequence.[190/83]

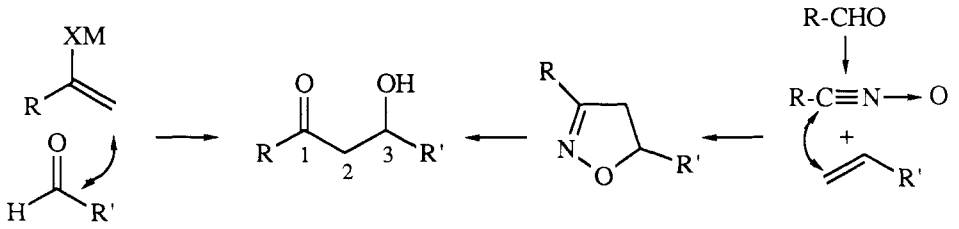
Under appropriate hydrolytic conditions the cyano group can be further

transformed into a carboxylic group, thus realizing an overall *cis*-carboxyhydroxylation of the double bond. On this variant is based a short synthesis of 2-deoxy-D-ribose, outlined in the following scheme:[142/82]



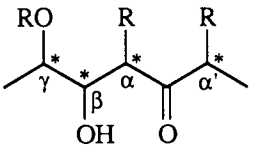

The starting material is optically active (+)-*S*-isopropilidene-3-butene-1,2-diol, which induces a remarkable diastereoface selectivity in the cycloaddition reaction. A 80:20 mixture of diastereomers, separable through gravity chromatography, is formed, the required *erythro* adduct being the major product.

(d) The transformation of 2-isoxazolines into β-hydroxy ketones by catalytic hydrogenation or by chemical means (see § 2.2.3.2b, pp. 561–562) has general applicability and, coupled with the preceding cycloaddition reaction, represents a valuable alternative to the classical aldol-type reaction:[141/82,135/83,112/84]



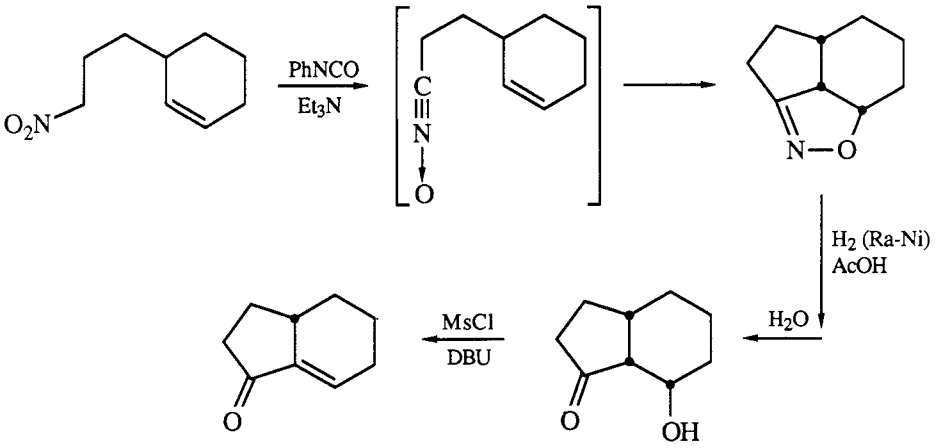

The main advantages of this cycloadditon–reduction sequence are the following: (1) the relative mildness of the reaction conditions; (2) a large tolerance toward a wide variety of functional groups in the side chains; (3) the absence of retroaldol complications; (4) complementarity with regard to carbon–carbon bond formation ($C_1$–$C_2$ instead of $C_2$–$C_3$); and (5) the possibility (under controlled conditions) of stereospecific control as far as centers 2 and 3 (α and β) are concerned. Since the use of nitrile oxide bearing an α-asymmetric center and of alkenes provided with an allylic oxygen substituent can produce a remarkable

stereoselection in the cycloaddition step, the route is opened to the stereo-controlled synthesis of β-hydroxy ketones having up to four chiral centers (α′, α, β, and γ):




Of course, the substituent in the α-position can either be present in the starting alkene or be introduced stereoselectively at the isoxazoline stage by a metallation–alkylation sequence.

The stereo control is even higher in intramolecular 1,3-dipolar cycloaddition. Thus a general ring annulation procedure starts from 3-ω-nitroalkylcycloalkenes; for example:[259/80]

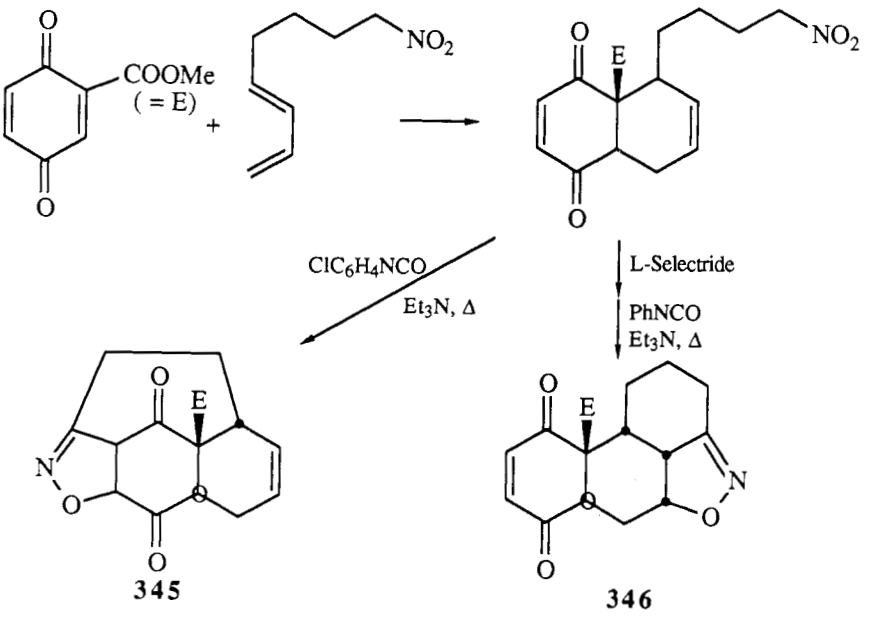



An analogous approach to hydroazulenone derivatives is known.[308/83]

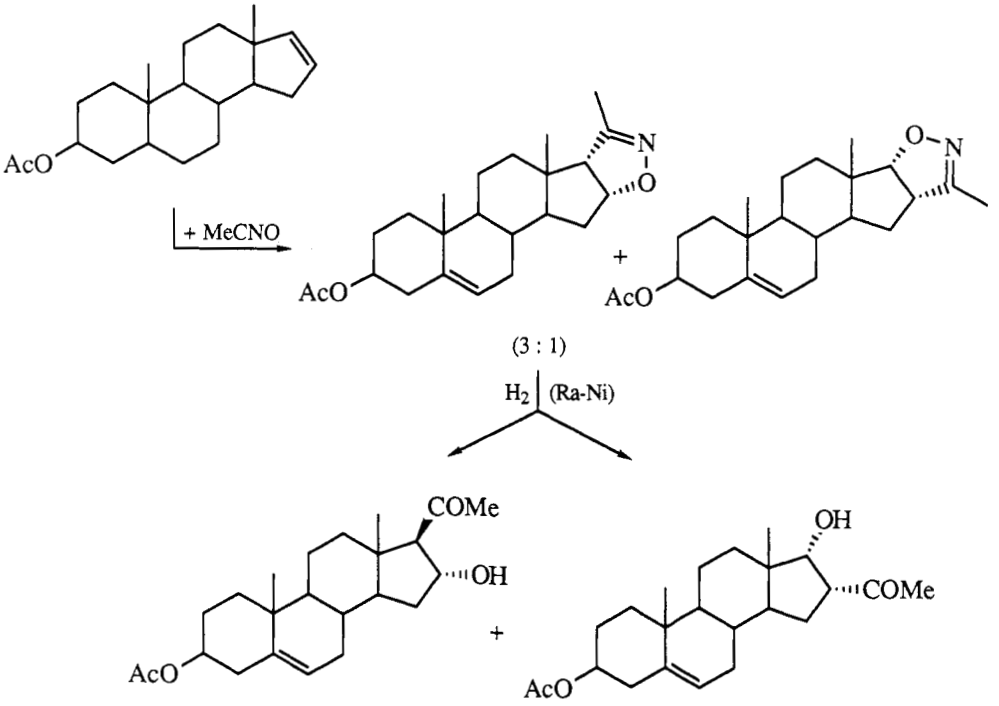
A more sophisticated stereo-controlled approach to polycyclic systems involves two consecutive [4 + 2] and [3 + 2] cycloadditions: an example is shown in Scheme 2.26.[60/84]

It is worth noting that the Diels–Alder adduct possesses two dipolarophilic double bonds, and that the *in situ* prepared nitrile oxide reacts with the more reactive carbonyl-conjugated double bond, giving the more strained isoxazoline **345**. Only if the activated double bond has been hydrogenated previously can the nitrile oxide cycloadd the isolated double bond to yield the six-membered ring compounds **346**.

The intermolecular cycloaddition–reduction sequence allows a simple conversion of dehydro-*epi*-androsterone into 16α-hydroxypregnenolone 3-



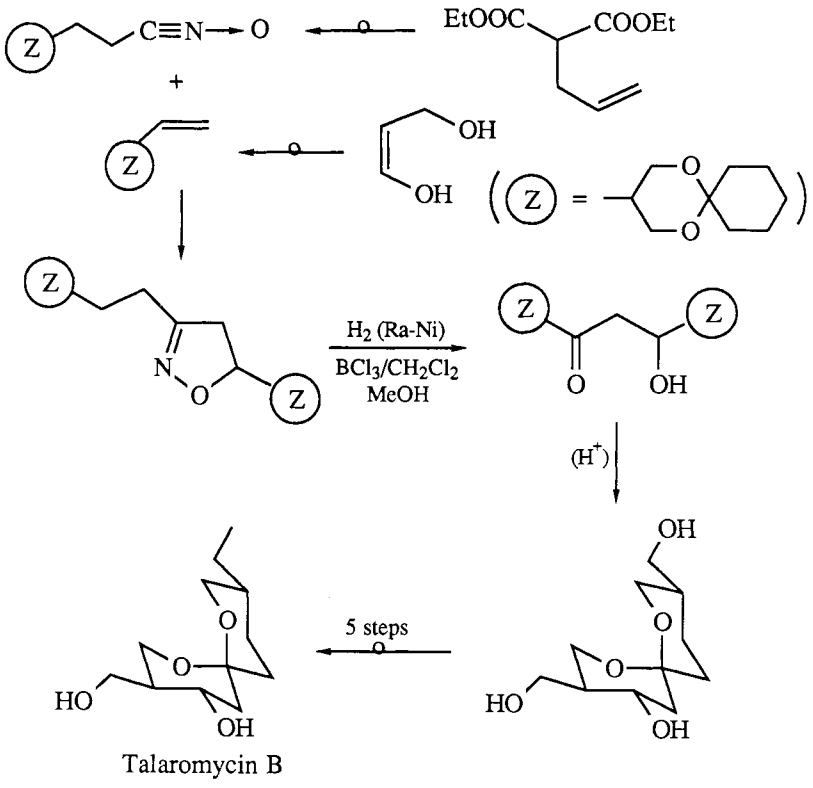

Scheme 2.26




Scheme 2.27

acetate,[109/82] produced in admixture with a regioisomer. Noteworthy is the epimerization occurring during the reduction step (Scheme 2.27).

An interesting application of the isoxazoline route to β-ketols is the total synthesis of the naturally occurring toxin talaromycin B.[58/84] The isoxazoline/β-hydroxyketone two-steps sequence is followed by acidic deprotection, spiroketalization and final routine conversion of one $CH_2OH$ into an ethyl group (Scheme 2.28):

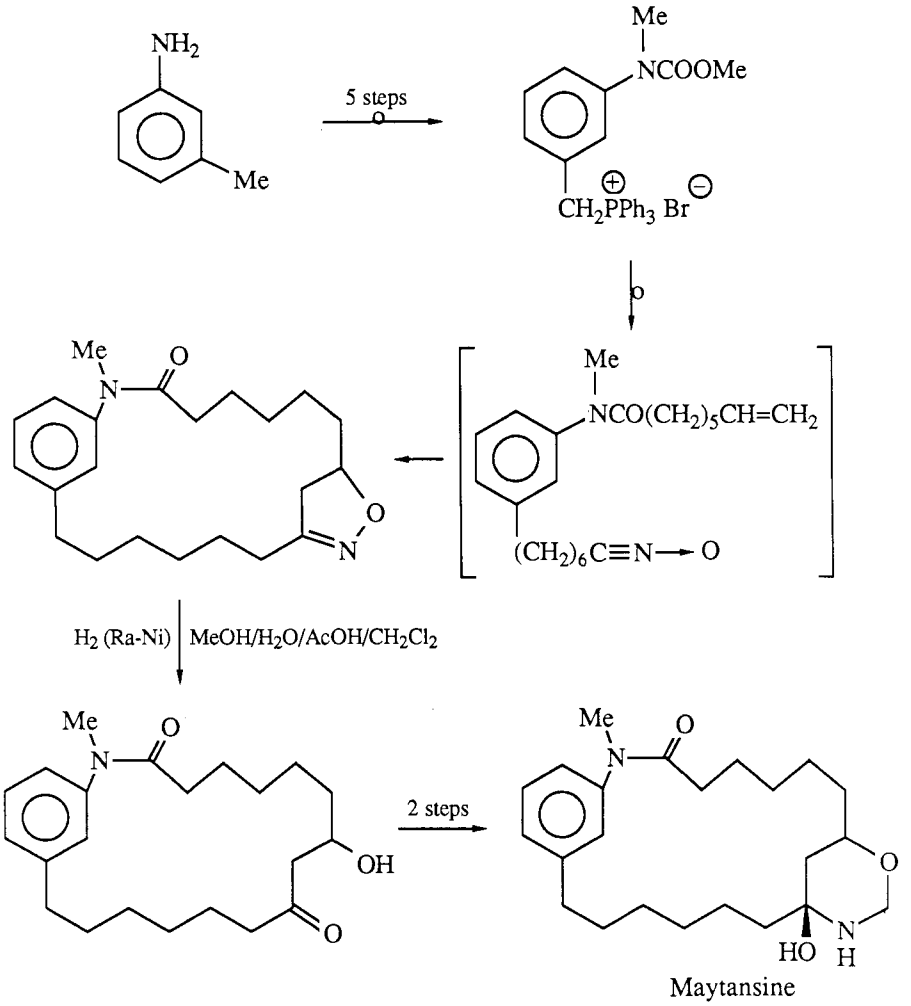



**Scheme 2.28**

Another interesting application of the hydrogenolytic ring cleavage of isoxazolines is the construction of a simplified macrolide skeleton of the antitumor agent maytansine through an intramolecular nitrile oxide 1,3-cycloaddition, as summarized in Scheme 2.29.[175/84]

A β,δ-dihydroxyketone moiety is present in the toxin produced by *Helminthosporium maydis* race T and has been synthesized through a 2-isoxazoline derivative[56/84] although without any stereochemical indication.

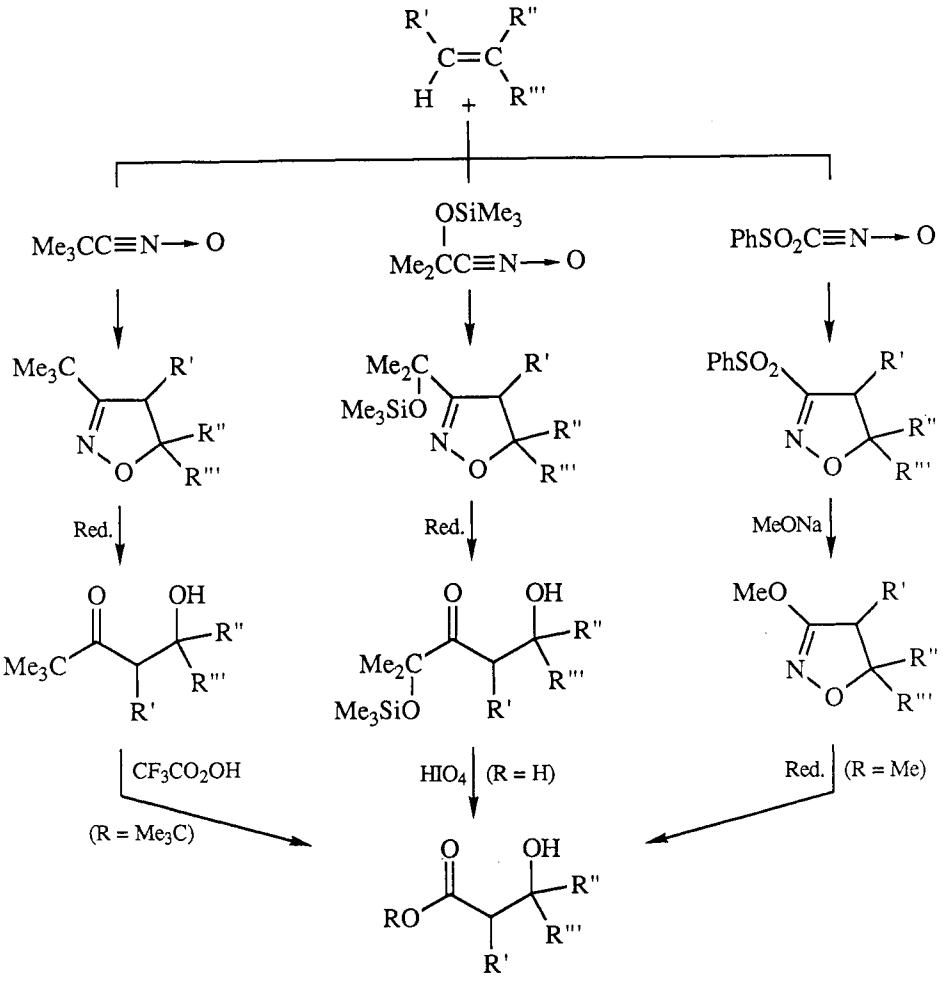
The aldol synthesis can be modified into a general route to β-hydroxy acids and derivatives, either oxidizing an appropriately substituted ketone function or hydrogenolyzing a 3-methoxyisoxazoline, as illustrated in Scheme 2.30.[121/84]




**Scheme 2.29**

Taking advantage of the moderate diastereoselectivity presented by the cycloaddition reaction of a chiral nitrile oxide (e.g., **347**) with a 1,2-disubstituted alkene, a route to optically active $\beta$-hydroxy acids has been developed. An example is shown in Scheme 2.31.[155/83]

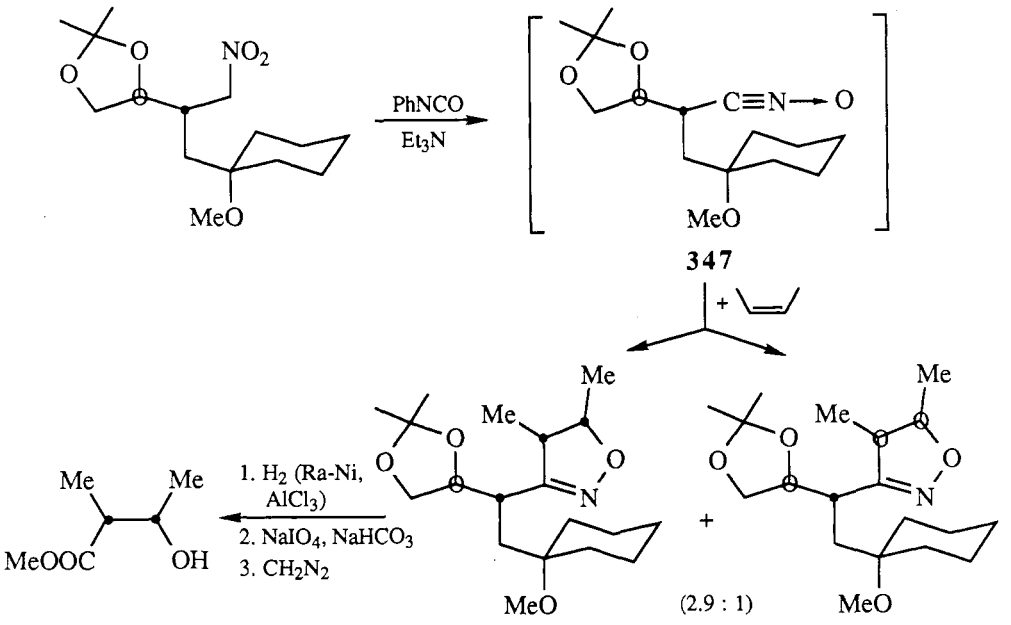
The nitrile oxide prepared *in situ* from the tetrahydropyranyl ether of 2-nitroethanol and protected 3-buten-2-ol is the starting material for an elegant synthesis of (±)-blastmycinone, a degradation product of the antibiotic antimycin $A_3$ (Scheme 2.32). Diastereoselectivity here is profitable in the cycloaddition and alkylation of the isoxazoline 4-position and in the subsequent hyd-




**Scheme 2.30**

rogenolytic ring cleavage. Oxidation of the α-ketol moiety then produces the carboxylic group,[190/83] which after deprotection cyclizes to the epimeric lactol. Base-promoted epimerization and esterification lead to the final target.[112/84]

A convenient synthesis of the optically pure (+)-(*S*)-gingerol has been performed by taking advantage of the resolution of isoxazolines through the 3β-sulfoxide derivatives (see § 2.2.3.1e, pp. 555–556). After metallation and 3α-sulfoxidation of 3-methyl-5-*n*-amyl-2-isoxazoline, the 3α position is again alkylated with the properly substituted benzyl bromide. Raney-nickel catalyzed reduction simultaneously accomplished both desulfuration and ring scission to the β-ketol (Scheme 2.33).[69/84] The sequence has been generalized into a highly

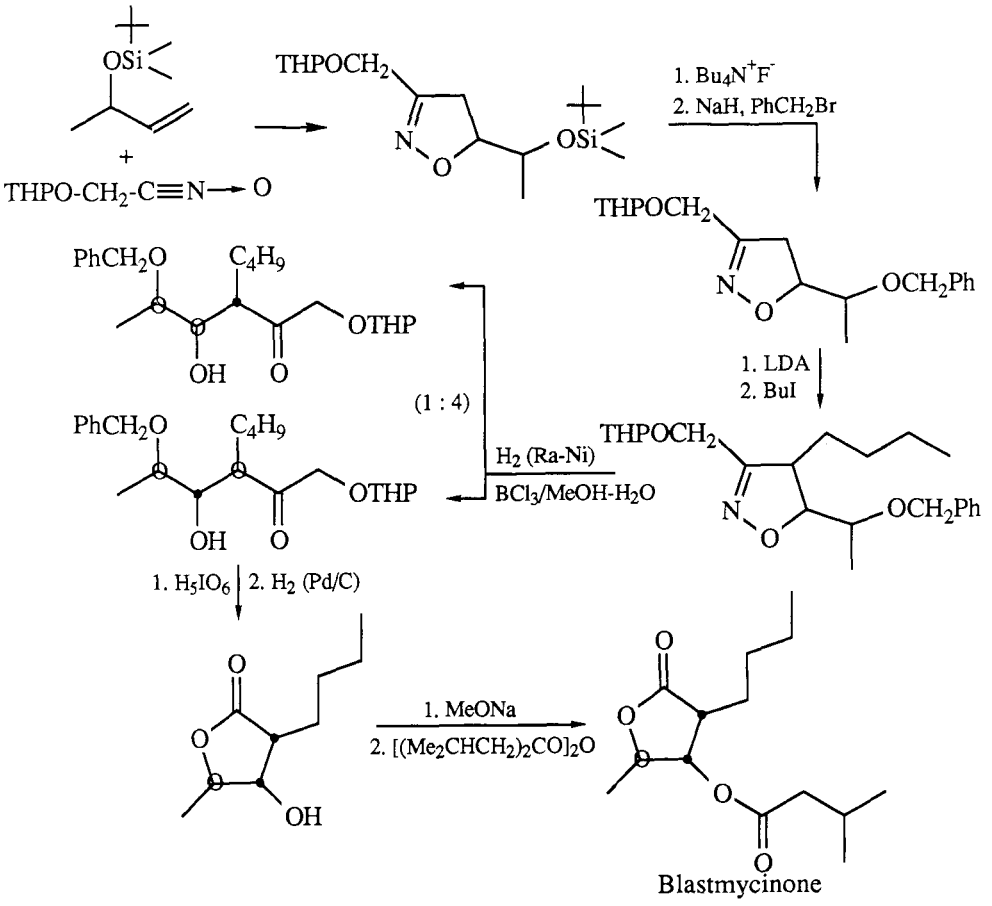



**Scheme 2.31**

stereoselective synthesis of $\beta,\beta'$-dihydroxy ketones.[71/84] For example, the enantiomerically pure isoxazoline **348**, alkylated with hexenal, yielded a mixture of diastereomeric isoxazolines, which was reduced to a mixture of separable 8-oxo-6,10-pentadecanediols, containing the *R,R*-isomer as major and the *meso* isomer as minor component.

(e) Dehydration of the $\beta$-ketol easily furnishes the $\alpha,\beta$-unsaturated ketones, which are also obtainable directly from the 2-isoxazoline derivatives through base-promoted ring cleavage to the oximes and subsequent hydrolysis (see § 2.2.3.2c, p. 568)(Scheme 2.18, pathway e'). In its simplest version the sequence cycloaddition–ring opening to $\alpha,\beta$-unsaturated ketones corresponds to a general method for acylating alkenes with respect to the original stereochemistry around the double bond. Analogously, acylation of dienes can be accomplished through their monocycloaddition to nitrile oxides. Diaddition of the nitrile oxides to the same compounds opens a general route to furan derivatives.[286/83] Use of a 1,5-diene leads, on the contrary, to a diacylated tetrahydropyran (Scheme 2.34).[8/80]

The ability of the isoxazoline ring to operate as a masked 2-enone has been taken advantage of in several syntheses of naturally occurring substances. A simple application of this strategy is exemplified in Scheme 2.35 by the total synthesis of the antitumor agent sarkomycin (in the form of its ethyl ester),

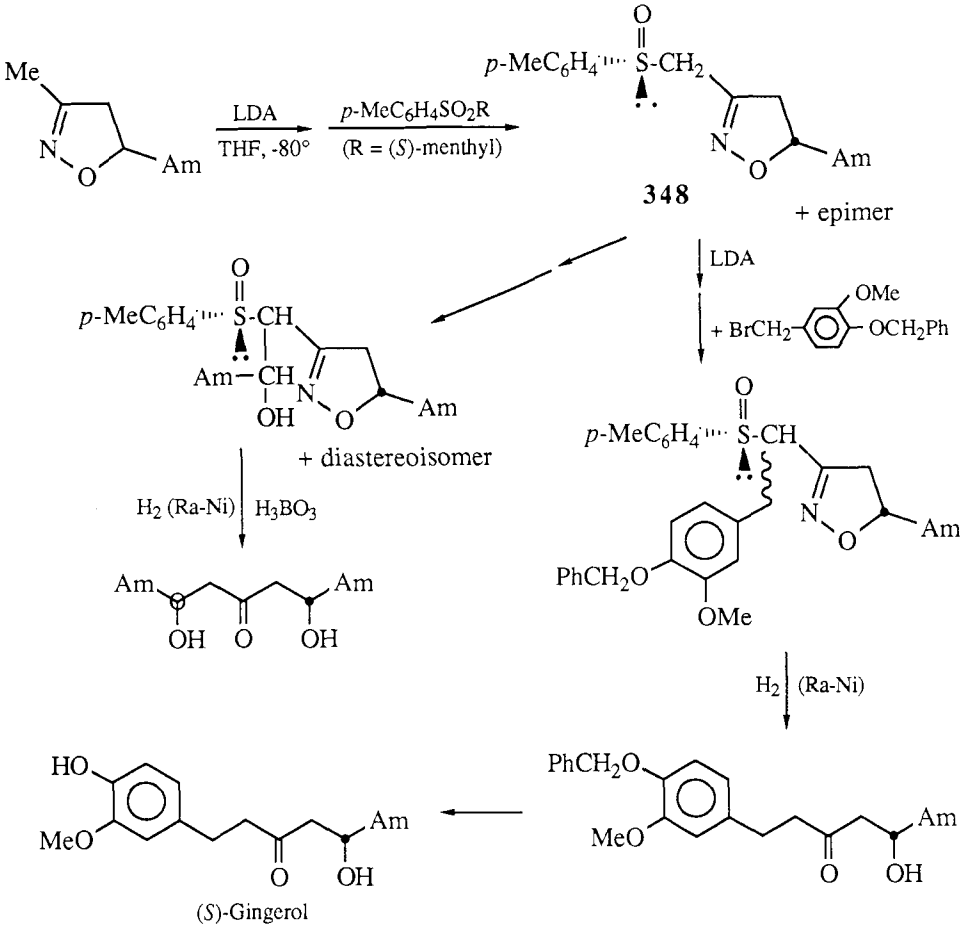



**Scheme 2.32**

accomplished in six steps from the anion of ethyl crotonate and 1,3-dibromopropane with an overall 40% yield.[140/82]

The same 2-methylenecyclopentanone moiety is present in compound **349**, a precursor of the prostaglandin $PGF_{2\alpha}$ and has been stereoselectively synthesized in the sequence outlined in Scheme 2.36.[107/84] Here it is interesting to emphasize the elaborated construction of the cyclopentane side chain, accomplished without affecting the isoxazoline ring. Also noteworthy is the hydrogenolytic cleavage of this ring at the appropriate stage without affecting the benzylic protecting groups. This result could be achieved by using a deactivated Raney nickel catalyst.

Hydrogenolysis and dehydration can be effected in a single step by using Raney nickel in the presence of strong acids; this has been exploited for the

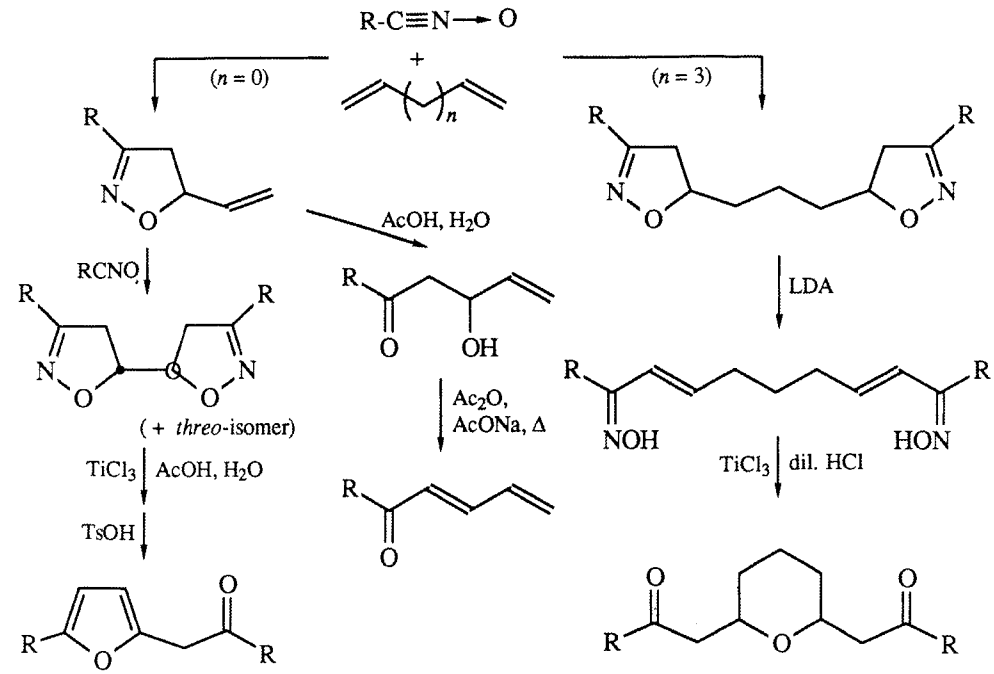



**Scheme 2.33**

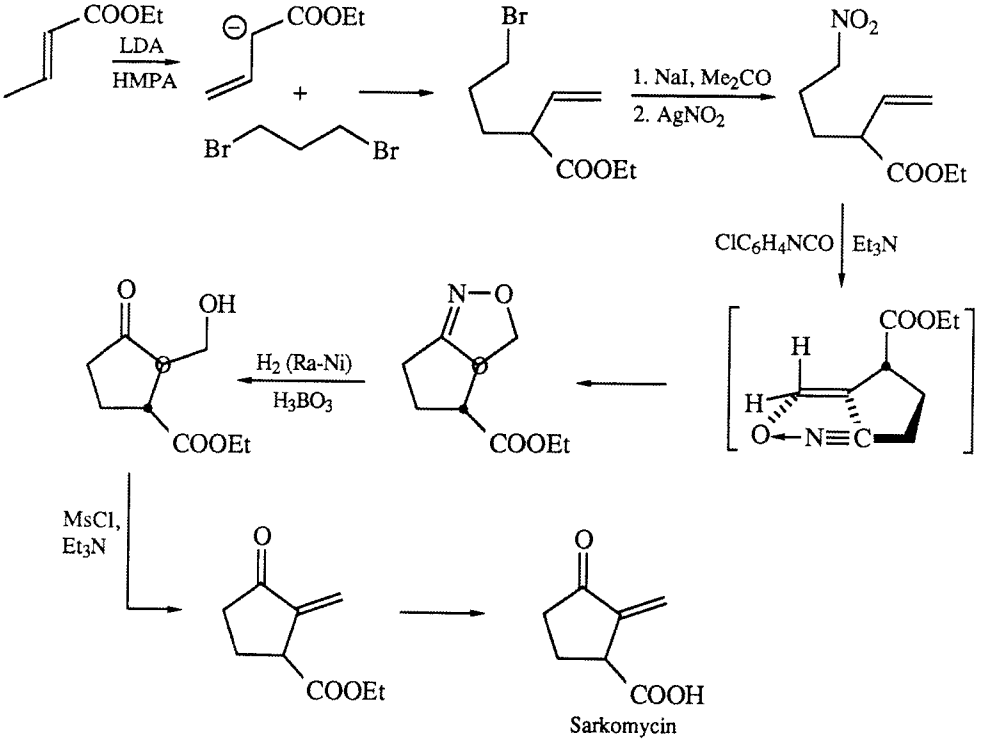
preparation of 2-acylcycloalken-3-ols, possible intermediates in the synthesis of prostaglandins and steroids.[265C/78]

Two different syntheses to the macrocyclic bislactone antibiotic pyrenophorin utilize the 2-isoxazoline route and are illustrated in Scheme 2.37. In one approach the macrocyclic ring is constructed during the cycloaddition step;[229B/81] in the other the cycloaddition is only an intermediate passage for assembling the unsaturated hydroxyketo acid that is apt to dimerize to the macrocyclic bislactone.[197/83]

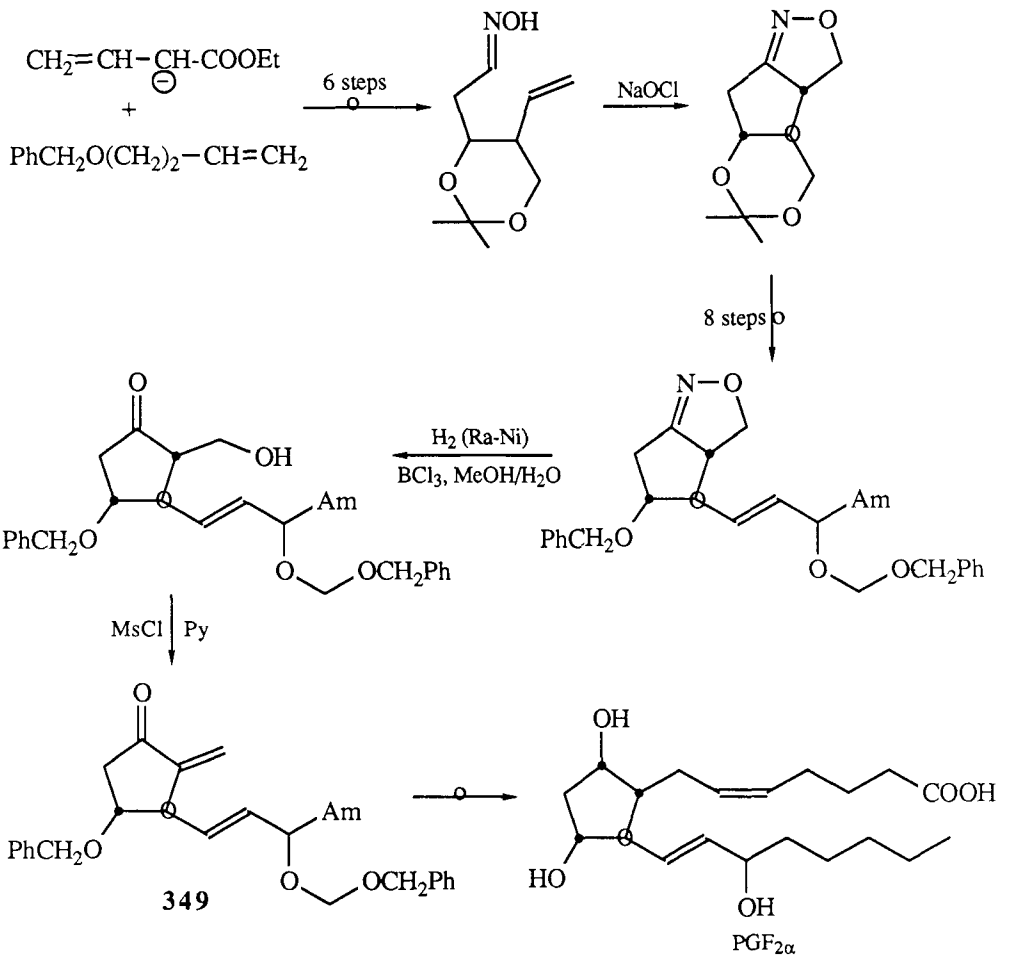
A formal total synthesis of (±)-vermiculine, another macrocyclic antibiotic bislactone, involves both an isoxazoline and an isoxazole nucleus: the former masks the exocyclic carbonyl groups, and the latter the unsaturated ketocarboxylic moieties. Noteworthy also is the selectivity in the hydrogenolytic




Scheme 2.34




Scheme 2.35



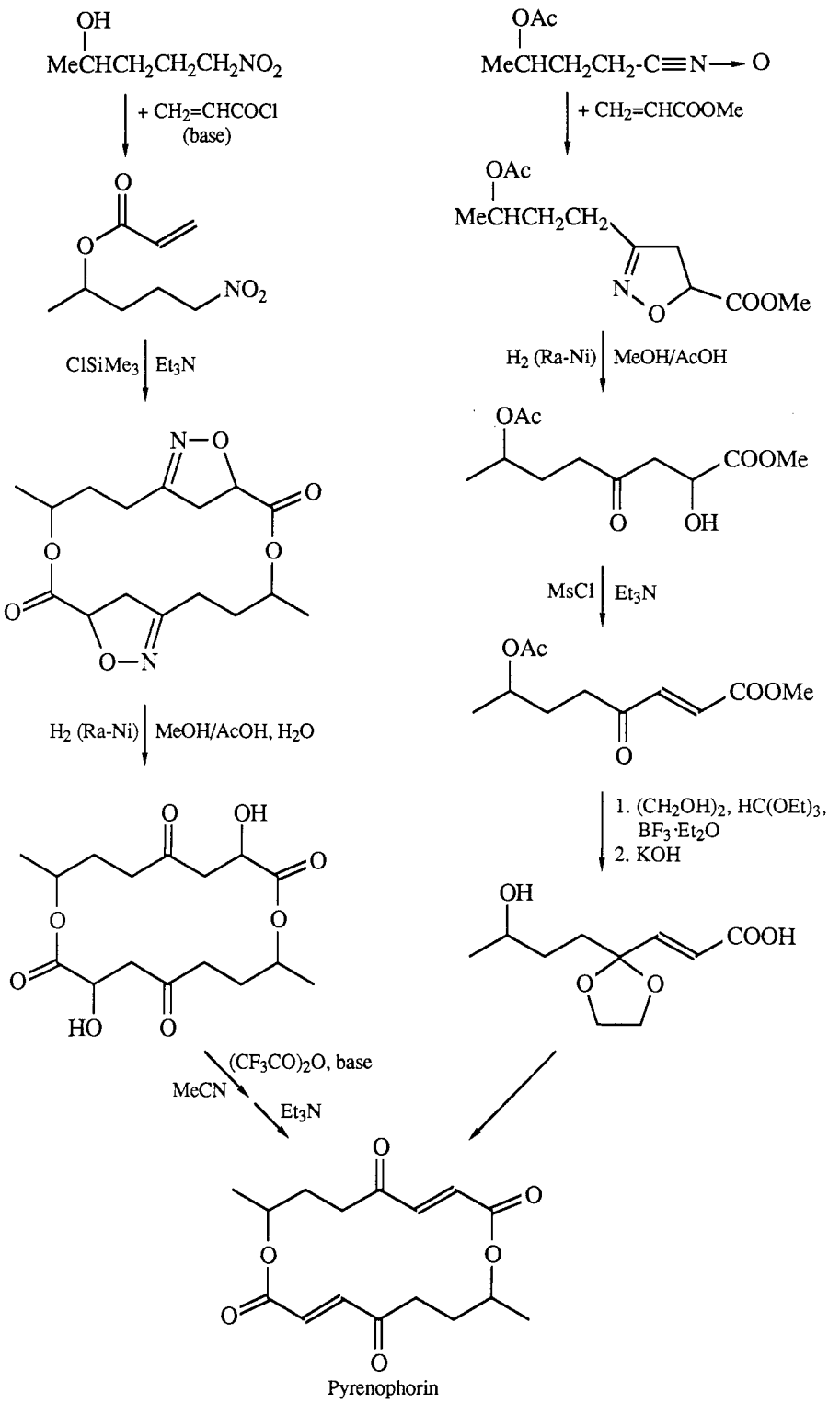

**Scheme 2.36**

cleavage of the two rings, which makes it possible to eliminate the regioisomeric isoxazole-3-carboxylate (not reducible)(Scheme 2.38).[197/83]

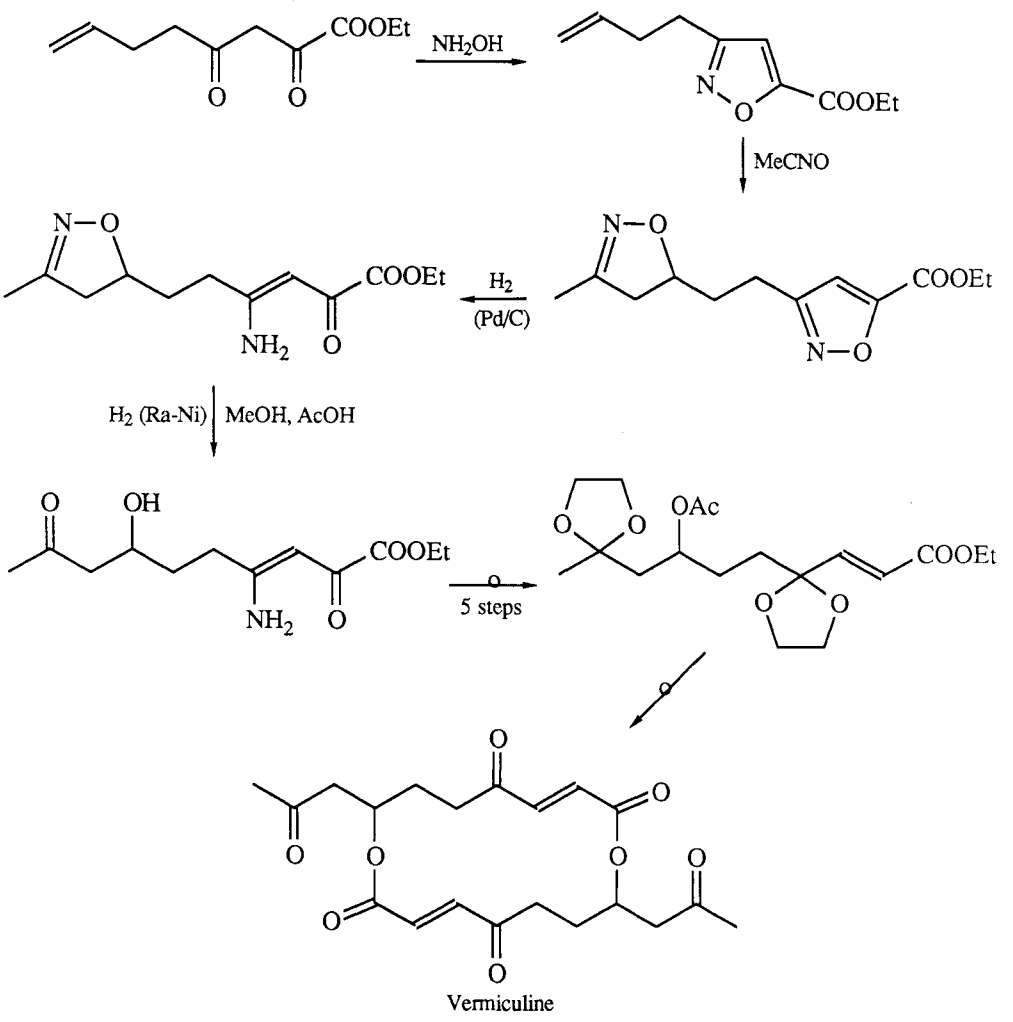
Another macrocyclic lactone is the antibiotic (±)-A26771B, which has been synthesized along the route shown in Scheme 2.39.[39/82]

(f) Appropriate substitution pattern at the isoxazoline ring sponsors further transformation of the β-hydroxy ketones into useful secondary products.

When an acyl group is present in the isoxazoline 5-position, the 2-hydroxy-1,4-diketone resulting from the reductive cleavage can reclose in a basic medium to 2,3-disubstituted α-hydroxycyclopentenones (**350**) along the sequence of general applicability shown in Scheme 2.40.[1/82,282/83,283/83,307/83] This structural subunit is present in several important natural substances, such as rethrolones


OH
MeCHCH2CH2CH2NO2
+ CH2=CHCOCl
(base)
NO2
ClSiMe3
Et3N
H2 (Ra-Ni)
MeOH/AcOH, H2O
OAc
MeCHCH2CH2-C≡N→O
+ CH2=CHCOOMe
MeCHCH2CH2
COOMe
H2 (Ra-Ni)
MeOH/AcOH
COOMe
OH
MsCl
Et3N
COOMe
1. (CH2OH)2, HC(OEt)3,
BF3·Et2O
2. KOH
COOH
HO
(CF3CO)2O, base
MeCN
Et3N
Pyrenophorin

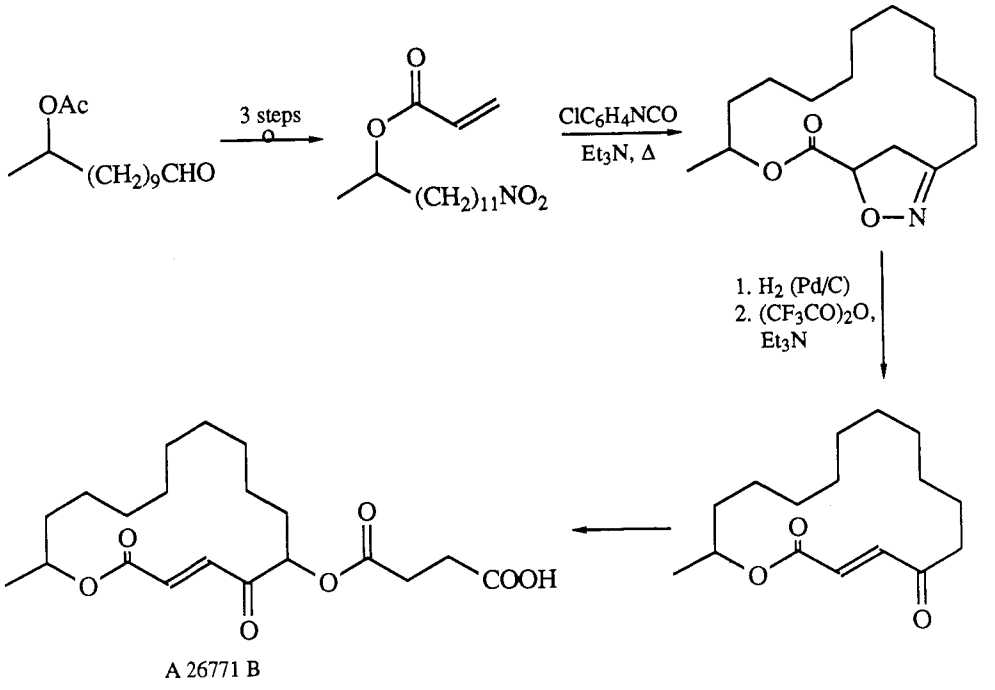
**Scheme 2.37**




**Scheme 2.38**

and prostaglandins. Thus the syntheses of allethrone,[1/82] (±)-dihydrocinerolone,[307/83] calythrone,[1/82] and several precursors of $PGE_1$ [282/83,307/83] are known along this approach.

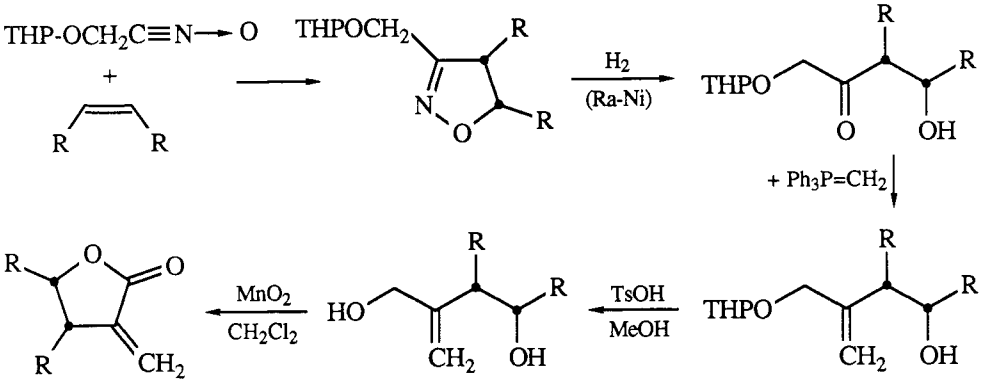
Monosubstituted α-hydroxycyclopentenones (**350**: R′ = H) can be obtained from isoxazolines having an acetal group in the 5-position by selective hydrogenolysis and subsequent ring reclosure under carefully controlled acidic conditions.[164/84] With a β-carbethoxyethyl substituent in the isoxazoline 3-position, the 2-hydroxy-1,4-dione cyclized under acidic catalysis to a furan derivative.[1/82] When an acetamido group is present in the isoxazoline 5-position,

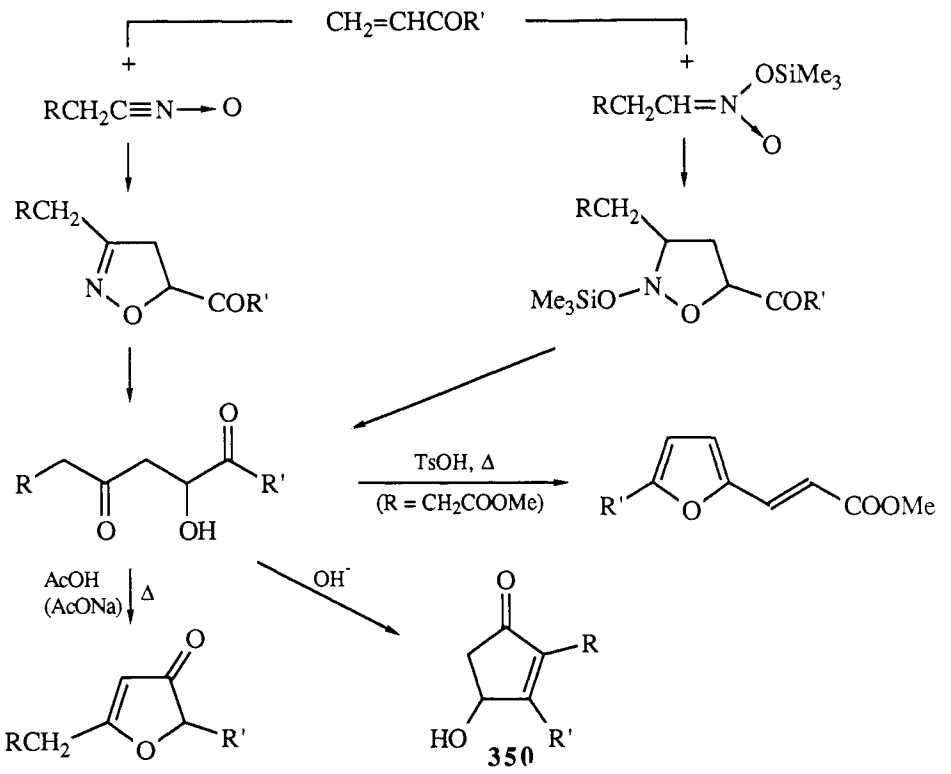



**Scheme 2.39**

the $\beta$-hydroxy ketone can reclose to an *N*-acetylpyrrole derivative by acidic treatment.[283/83]

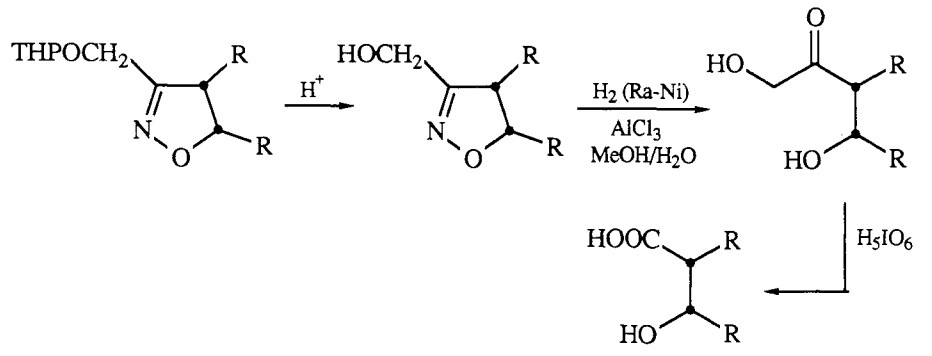
A protected primary carbinol group can easily be placed in the isoxazoline 3-position starting from the tetrahydropyranyl ether of 2-nitroethanol. This feature results in the general route to $\alpha$-methylene-$\gamma$-lactones outlined in the following scheme:[302/83]





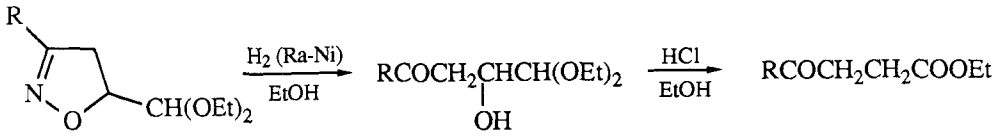

**Scheme 2.40**

The same intermediate 2-isoxazoline can be utilized, through deprotection, stereospecific reductive cleavage, and oxidation, for another general process of *cis* carboxyhydroxylation:[190/83]

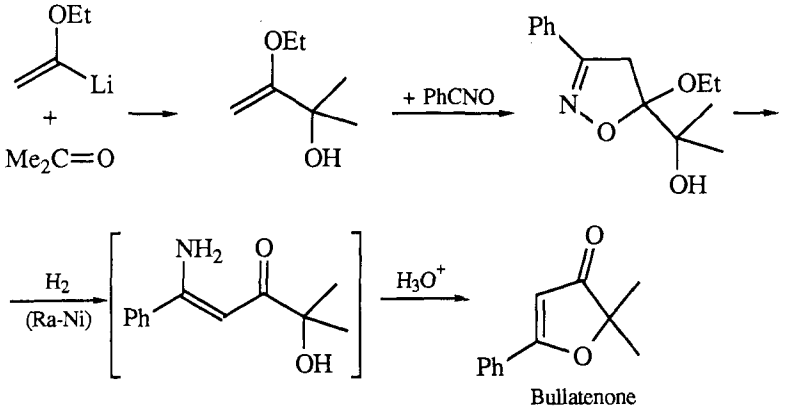



(g) When the isoxazoline arises from cycloaddition of a nitrile oxide to acrolein diethylacetal (i.e., a masked aldehyde function is present in the 5-

position), treatment of the product from its selective reduction with dry hydrogen chloride in ethanol affords an easy entry to γ-ketocarboxylic esters:[164/84]

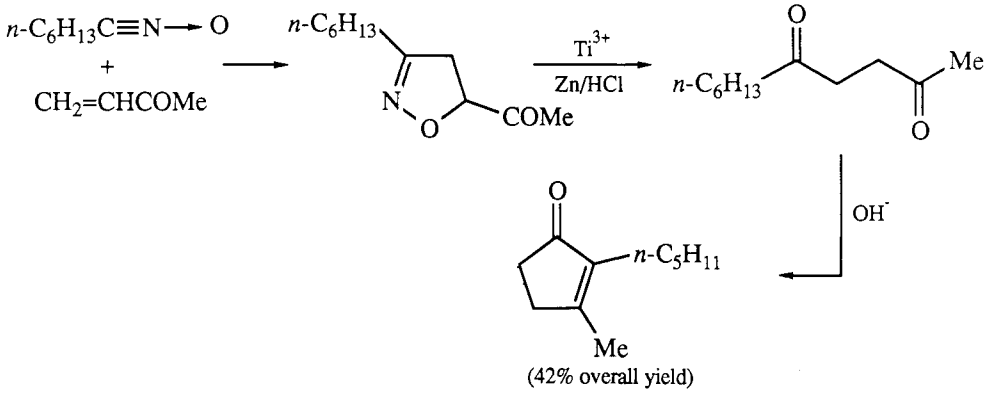



(h) The 2-hydroxy-1,4-diketones, obtainable from 5-acyl-2-isoxazolines, can also cyclize by heating with acetic acid to 3(2*H*)-furanones.[1/82,283/83,285/83] A different approach to 3(2*H*)-furanones (Scheme 2.18, pathway h′) involves the initial cycloaddition of nitrile oxides to α′-hydroxylated enol ethers. The intermediate 5-ethoxy-2-isoxazoline-5-carbinol is then catalytically hydrogenolyzed and the unstable reduction product cyclodehydrated directly in an acidic medium. The sequence is exemplified in the following scheme by the synthesis of the plant metabolite bullatenone:[296/83]

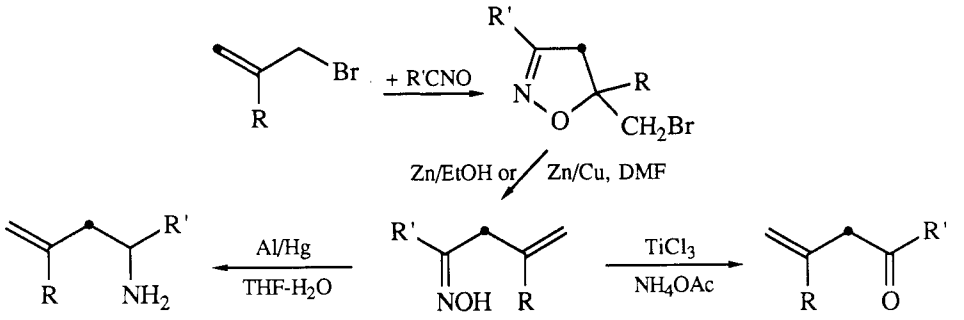



Both approaches to 3(2*H*)-furanones are valid alternative methods to the previously known hydrogenolysis of 5-isoxazolylcarbinols (see § 1.4.10.3, p. 344).

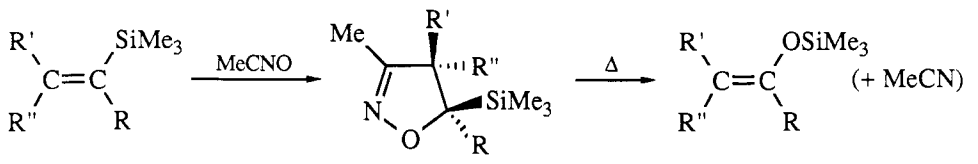
(i) As already mentioned (see § 2.2.3.2b, p. 562), γ-ketoaldehydes are obtained by $Ti^{3+}$ reduction of isoxazoline-5-acetals; however, as shown previously, the same reduction of 5-acylisoxazolines furnishes the corresponding 2-hydroxyalka-1,4-diones. Nevertheless, the addition of zinc and hydrochloric acid to the reductive agent provokes fission of the isoxazoline C–O bond, thus leading to 1,4-diketones. A facile synthesis of dihydrojasmone is based on this finding:[283/83]



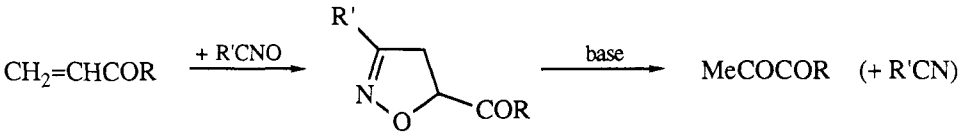

(j) Employment of allyl bromides in the nitrile oxide cycloaddition, with subsequent reductive elimination and routine elaboration along the following scheme, constitutes a convenient method of general applicability for acylation (Scheme 2.18, pathway j′) and α-aminoalkylation (pathway j″) of allyl bromides.[8/79] As the fate of the marked carbon atom shows, a transposition of the double bond is also involved.



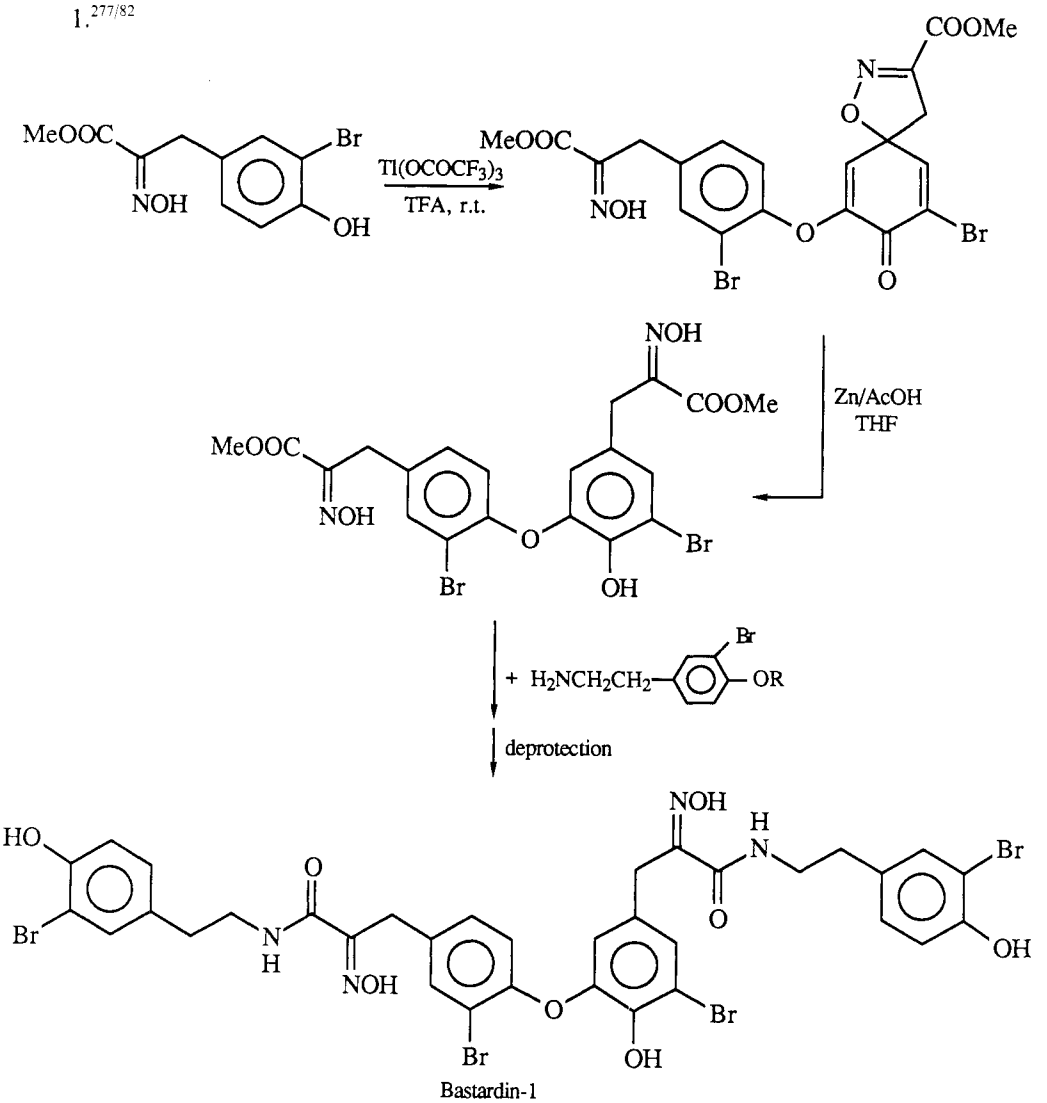

Among the applications of 2-isoxazolines not illustrated in Scheme 2.18, two reaction sequences should be mentioned, where intervention by the nitrile oxides results substantially in the transfer of an oxygen atom. The former example is the thermolytic rearrangement–fragmentation of 5-trimethylsilylisoxazolines. It makes it possible to transform alkenyltrimethylsilanes into silyl enol ethers of retained configuration along the following general route:[147/81]




A further general sequence, involving base-promoted fragmentation of 5-acyl-2-isoxazolines, is the conversion of vinyl ketones into α-diketones:[138/68,148/74]



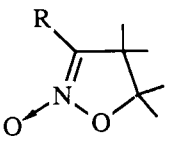

The oxidative cyclization of some phenolic oximes (see § 2.2.2.5c, pp. 528–529), followed by hydrogenolitic ring opening of the dimeric spiroisoxazoline derivative thus obtained, makes it possible to build the appropriate central diphenyl oxide moiety of the bromotyrosine-derived group of the algal metabolites bastardins, as illustrated in Scheme 2.41 for the synthesis of bastardin-1.[277/82]



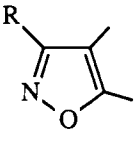

Scheme 2.41

## 2.3 2-ISOXAZOLINE *N*-OXIDES

The 2-isoxazoline *N*-oxides, first described in 1924,[10/24] have the general structure **351** and cannot be prepared easily by direct oxidation of 2-isoxazolines.



**351**



**352**

Moreover, until recently, only 3-substituted compounds (**351**: R ≠ H) were known as moderately stable compounds. In planning a synthesis of **351**, it must always be kept in mind that these compounds dehydrate easily (if two hydrogens are present in the 4 and 5 positions) to isoxazoles (**352**) under the influence of bases or of acids or even thermally, and therefore experimental conditions must be optimized carefully. As cyclic nitronic esters, isoxazoline *N*-oxides have been included in a review of the chemistry of nitronic esters.[212B/69]

### 2.3.1 Physical Properties

Almost all known 2-isoxazoline *N*-oxides are crystalline solids, which exhibit a neutral character. Spectroscopic analysis has frequently been adopted for structural assignments and corroboration. The absorption data can easily be interpreted by taking into account the resemblance to both nitronic esters and 2-isoxazolines.

Electronic spectra of 3-unsubstituted compounds are not known. Conjugation of the nitronic ester moiety with a phenyl, a cyano, a methoxycarbonyl, or a nitro group in position 3 gives rise to a strong $\pi$-$\pi^*$ absorption band in the region 260–320 nm. More precisely, 3,4,5-triphenyl-2-isoxazoline *N*-oxide has a $\lambda_{max}^{95\%/EtOH}$ at 285 nm (log $\varepsilon$ 4.25),[154/69] 3-cyano-5-arylisoxazoline *N*-oxides absorb in $CCl_4$ solution at 268 nm (log $\varepsilon$ ca. 4.01),[290/76] and some 3-ethoxycarbonyl-4-aryl-5-nitro-2-isoxazoline *N*-oxides absorb at 259–263 nm (EtOH log $\varepsilon$ 4.0–4.3).[268/74] In the spectra of some 4-glycosyl-3,5-diethoxycarbonylisoxazoline *N*-oxides, besides the 270-nm absorption band, a second stronger band at 230 nm (MeOH, log $\varepsilon$ 4.6) has been recorded.[27/79] Moreover, in the latter examples the negative sign of the CD curve centered at 270 nm could aid in assigning the stereochemistry of these compounds.[27/79,203/79]

A larger number of 3-nitro derivatives have been examined. The simple 3-nitroisoxazoline *N*-oxides show $\lambda_{max}^{H_2O}$ = 320 nm (log $\varepsilon$ 3.92),[62/65] other 4- or 5-monosubstituted or 5,5-diarylsubstituted derivatives absorb at 315–

TABLE 2.37. IR AND PMR DATA OF 2-ISOXAZOLINE *N*-OXIDES

| -2-Isoxazoline *N*-oxide | IR data[a] $\nu_{C=N}$ | $\nu_{NO_2}$ | Other absorption bands | Solvent | References |
|---|---|---|---|---|---|
| 3-Nitro- | 1640 | 1510, 1310 | 1292, 830 (O-N->O) | $CH_2Cl_2$ | 63/65, 121/66 62/65 |
| 4-Phenyl- | 1660 | - | | $CHCl_3$ | 192/76 |
| 3-Methyl-4-(α-nitro)isopropyl- | 1653 | 1563, 1361 | 851 ($\delta_{C-N}$) | $(CHCl_2)_2$ | 16/54 |
| 3-Methyl-4-phenyl- | 1640 | - | | $CCl_4$ | 192/76 |
| 3-Nitro-5,5-diphenyl- | 1640 | 1532, 1310 | | | 261/72 |
| 5-Methyl-3,5-di(*p*-nitro)phenyl- | 1605 | 1510, 1350 | 1575, 840 | nujol | 16/79 |
| 3,4,5-Triphenyl- | 1613 | - | 1220 ($\nu_{-O-}$) | KBr | 154/69, 247/78 |
| 3,5,5-Triphenyl- | 1615 | - | 1222, 1235 ($\nu_{N->O}$) | *nujol* | 203/80 |
| 3-Cyano-4-ethyl-5-nitro- | 1665 | 1582, 1365 | 2228 ($\nu_{CN}$) | liquid | 268/74 |
| 3-Cyano-4-phenyl-5-nitro- | 1668 | 1582, 362 | 2235 ($\nu_{CN}$) | $CHCl_3$ | 268/74 |
| 3-Ethoxycarbonyl-4-*p*-methoxyphenyl-5-nitro- | 1682 | 1582, 1370 | 1755 ($\nu_{CO}$) | $CHCl_3$ | 268/74 |
| 4-Methyl-3,5-bis-methoxycarbonyl- | 1615 | - | 1760, 1735 ($\nu_{CO}$) | KBr | 37/74 |
| 4-Acetonyl-3,5-bis-methoxycarbonyl- | 1630 | - | 1740, 1710 ($\nu_{CO}$) | KBr | 94/74 |
| 4-Phenyl-3,5-bis-methoxycarbonyl- | 1610 | - | 1340 ($\nu_{N->O}$) | KBr | 21/71 |

| 2-Isoxazoline *N*-oxide | PMR data[b] $H_4$ | $H_5$ | $J_{4,5}$ | Aromatics | Other signals | Solvent | References |
|---|---|---|---|---|---|---|---|
| 4-Phenyl- | 2.92 (3H) | | - | 7.12-7.61 m | 8.08 bs ($H_3$) | $CDCl_3$ | 192/76 |
| 3-Methyl-4-phenyl- | 4.12-4.93 m (3H) | | - | 7.40 | 1.82 d ($CH_3$) | $CCl_4$ | 192/76 |
| 5-Methyl-3,5-di-(*p*-nitro)phenyl- | 3.89, 3.97[c] | - | - | 7.81, 8.10, 8.27[d] | 1.93 s ($CH_3$) | DMSO-$d_6$ $CDCl_3$ | 16/79 |
| 3,4,5-Triphenyl- | 4.89 d | 5.45 d | 4.4 | ~7.6 | | $CDCl_3$ | 154/69, 247/78 |
| | 5.41 d | 5.59 d | n.r. | 7.41-8.20 | | DMSO-$d_6$ | |
| 3,5,5-Triphenyl- | 4.12 s | - | - | 7.40-7.95 | | $CDCl_3$ | 203/80 |
| 3-Cyano-4-ethyl-5-nitro- | 3.95 m | 6.32 d | 1.0 | - | 1.80 ($CH_2$) 0.90 ($CH_3$) | $CD_3COCD_2H$ | 268/74 |
| 3-Cyano-4-phenyl-5-nitro- | 5.30 d | 6.60 d | 2.5 | n.r. | | $CD_3COCD_2H$ | 268/74 |
| 3-Ethoxycarbonyl-4-*p*-methoxyphenyl-5-nitro- | 5.04 d | 6.23 d | 1.0 | n.r. | 3.91 q ($CH_2$) 3.52 s ($OCH_3$)-0.83 t ($CH_3$) | $CD_3COCD_2H$ | 268/74 |
| 4-Methyl-3,5-bis-methoxycarbonyl- | 3.67 m | 4.68 d | 3.0 | - | 3.83-3.87 ($2OCH_3$) | $CDCl_3$ | 37/74 |
| 4-Acetonyl-3,5-bis-methoxycarbonyl- | 4.05 dt | 4.69 d | 3.5 | - | 2.98 ($COCH_2$) 2.15 ($CH_3CO$) | $CDCl_3$ | 94/74 |
| 4-Phenyl-3,5-bis-methoxycarbonyl- | 4.88 d | 4.98 d | n.r. | 7.39 | 3.94-3.76 ($2OCH_3$) | $CDCl_3$ | 21/71 |

[a]Values in $cm^{-1}$.

[b]Values in δ (ppm); *J* in Hz; n.r.=not reported.

[c]AB system; $J_{AB}$ = 16.6 Hz.

[d]AA'XX' system.

320 nm,[62/65,211/71,261/72] whereas 4-succinimidyl-5-carboxylates show absorption bands at 305–308 nm (log $\varepsilon$ ca. 4.02).[184/74] A larger bathochromic (as well as hyperchromic) shift is observed for the 5-methyl-3,5-bis(*p*-nitrophenyl) derivative, which exhibits two strong bands at 256 and 341 nm (MeOH, log $\varepsilon$ 4.22 and log $\varepsilon$ 4.21, respectively).[16/79]

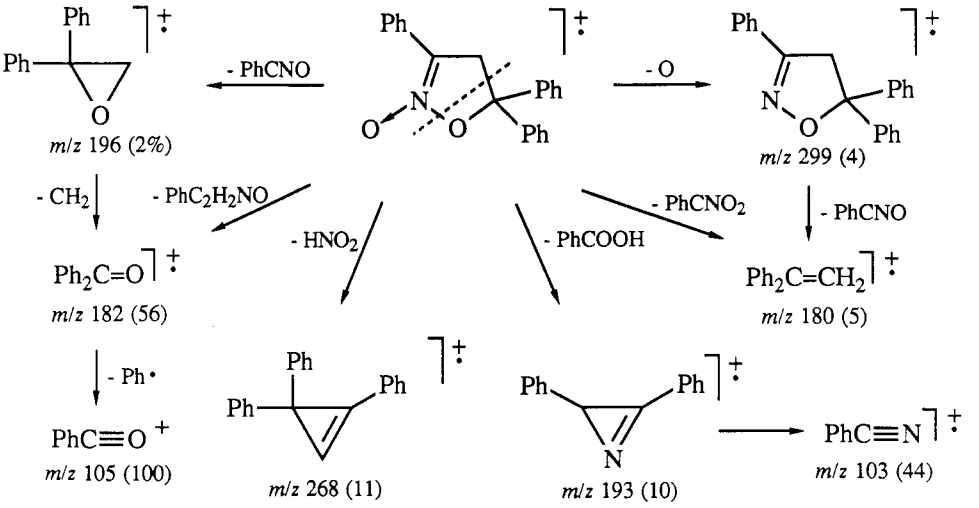
The infrared spectra of 2-isoxazoline *N*-oxides are characterized by an intense absorption band in the region 1600–1660 $cm^{-1}$, attributable to the stretching vibration of the $C=N^{(+)}$ bond. This is perfectly in line with the absorption pattern of acyclic nitronic esters and 2-isoxazolines. Other relevant absorption bands have been attributed to specific bonds: worth mentioning are the two absorption bands at 830–880 $cm^{-1}$ and at 1270–1300 $cm^{-1}$, allotted to the $N \rightarrow O$ bond in 3-nitro derivatives;[62/65,63/65,121/66] these compounds also show the usual bands at 1310 and 1510 $cm^{-1}$, typical for conjugated nitro groups, and the $C=N$ stretching vibration centered at 1630–1640 $cm^{-1}$. A band at 1200–1220 $cm^{-1}$, present in 3,4,5-triaryl-2-isoxazoline *N*-oxides, has been assigned to the stretching vibration of the cyclic oxime ether oxygen bonds,[247/78] whereas the bands in the region 1220–1235 $cm^{-1}$, present in 3,5,5-triaryl derivatives, have been attributed to the $N \rightarrow O$ bond.[203/80] Some significant features of the IR and PMR spectra of selected 2-isoxazoline *N*-oxides are presented in Table 2.37.

Several PMR spectra of 2-isoxazoline *N*-oxides are known, whereas only a limited number of $^{13}C$-NMR spectra has been reported up to now.[192/76,249/83] The only 3-unsubstituted derivative known, 4-phenyl-2-isoxazoline *N*-oxide, shows a broad singlet at $\delta$ 8.08 for the proton in position 3,[192/76] a value in line with the vinyl proton of aldoxime ethers.

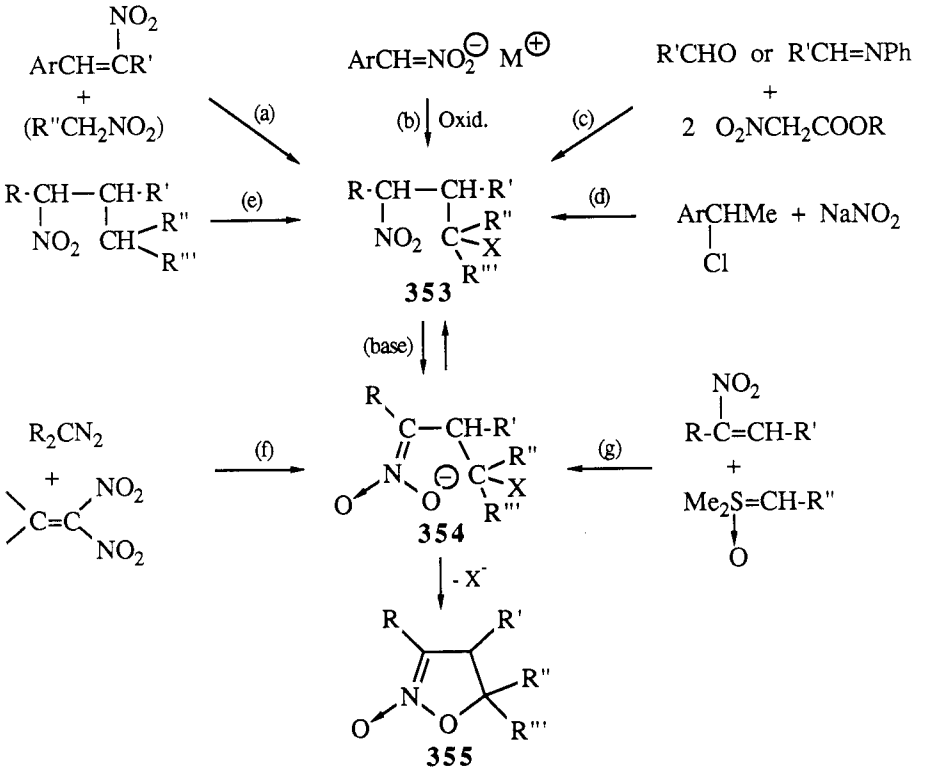
The chemical shift of the unconjugated 4-proton falls within the region $\delta$ 3.7–4.3,[37/74,94/74,268/74,16/79,203/79,203/80] whereas the presence of an aryl group shifts the signal into the region $\delta$ 4.9–5.8,[154/69,21/71,268/74,247/78] and that of a nitro group even into the aromatic region, as happens for 3,5,5-triaryl-4-nitro derivatives.[213/78]

As a general rule, the 5-proton is more deshielded than the 4-proton. For example, a 5-unsubstituted 3,4-condensed isoxazoline *N*-oxide shows two NMR signals at $\delta$ 4.02 and 4.74 ($J_{gem}$ 8.0 Hz) attributed to 5-protons.[165C/71] When an ester group is bonded in the 5-position, the 5-proton absorbs around $\delta$ 5;[21/71,37/74,94/74,27/79,203/79] with a 5-aryl substituent a shift toward $\delta$ 5.5–6.1 is observed;[247/78] and with a 5-nitro group the deshielding effect shifts the signal into the region $\delta$ 6.2–6.7.[268/74]

As a matter of fact, however, the most important utilization of the NMR data concerns the stereochemistry of the two substituents in positions 4 and 5 of the heterocyclic ring. In all 2-isoxazoline *N*-oxides carrying one hydrogen atom each in positions 4 and 5 whose NMR data are known up to now, the coupling constant $J_{4,5}$ falls between 1.0 and 4.5 Hz, the most frequently encountered range being 2.5–3.0 Hz.[154/69,37/74,94/74,268/74,27/79,203/79,249/83] This allows us to conclude that whatever the preparation method may be (from 1,3-dinitroalkanes, from 1-halo-3-nitroalkanes, from *S*-ylids or diazoalkanes), a *trans*-4,5-disubstituted derivative is always formed. A *cis* relationship would require a considerably higher




**Scheme 2.42**




**Scheme 2.43**

value of the coupling constant; for example, $J_{4,5}$ for *cis*-3,4,5-triphenyl-2-isoxazoline is 9.50 Hz.[86/68]

A few mass spectra of 2-isoxazoline *N*-oxides have been reported, although usually without interpretation of the fragmentation pattern;[192/76,16/79] however, dehydration seems to represent an important process at least in the case of the 3-methyl-4-phenyl derivative, where the molecular peak is not noticeable even at 10 eV.[192/76] The fragmentation pattern of 3,5,5-triphenyl-2-isoxazoline *N*-oxide is reproduced in Scheme 2.42, where the prevailing ring-opening process is pointed out by a dashed line.[203/80] The energy of the exocyclic N → O bond in 3-nitro-2-isoxazoline *N*-oxide has been calculated to be 64 ± 3 kcal/mol.[170/69]

## 2.3.2 Methods of Preparation

Several different starting materials have been proposed for preparing 2-isoxazoline *N*-oxides, but most methods in their last step involve a nitroalkane, carrying a suitable leaving group in position 3. This type of structure is prone to a base-promoted intramolecular O-alkylation of the nitro group, which leads to ring closure. Often this key intermediate is not isolated, although it can conceivably be supposed to be transient under the reaction conditions. Scheme 2.43 summarizes the hitherto explored synthetic routes starting from nitro derivatives, and the various pathways are then briefly illustrated.

### *2.3.2.1 From 1,3-Dinitroalkanes (**353**: X = $NO_2$) or Their Precursors*

3,4,5-Triaryl-2-isoxazoline *N*-oxides have been isolated by different methods, using essentially arylnitromethanes as starting materials. The intermediate substituted 1,3-dinitroalkanes are usually not easy to be isolated, but a mechanistic study has used preformed 1,3-dinitro-1,2,3-triphenylpropane, which on heating with sodium methoxide is converted with 79% yield to 3,4,5-triphenyl-2-isoxazoline *N*-oxide, accompanied by an 88% yield of nitrite ion. Contrary to previous work,[6/11,10/24,4/35,16/39,14/50] which invoked the intermediacy of a nitroolefin, it could be demonstrated that in this case ring closure involves direct internal displacement of nitrite ion by the mononitronate oxygen atom.[206/68,154/69]

1,3-Dinitroalkanes (**353**: X = $NO_2$) are conveniently prepared and cyclized *in situ* under basic conditions from one of the following starting materials:

Nitroolefins and Primary or Secondary Nitrocompounds (Pathway *a*)

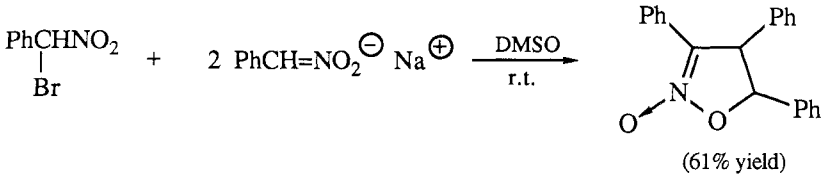
The condensation between α-nitrostilbenes and arylnitromethane represents the oldest method of preparation of isoxazoline *N*-oxides, but requires carefully controlled experimental conditions in order to avoid formation of the triarylisoxazole, easily formed in the presence of but a slight excess of base and separable only with great difficulty. Very short treatment with sodium meth-

oxide in hot anhydrous methanol can furnish up to a 67% yield of 3,4,5-triphenyl-2-isoxazoline *N*-oxide;[10/24,7/30] attempts to carry out the condensation in one step from benzaldehyde and phenylnitromethane were unsuccessful.[10/24] Use of an arylnitromethane having an aryl group different from those of the α-nitrostilbenes gives rise to nonisolable mixtures of isomeric isoxazoline *N*-oxides.[10/28] Use of gaseous ammonia in ethanol[4/35,17/40,27/54] seems to offer some advantages. Sometimes α-nitrostilbenes have been used alone in the presence of ammonia, piperidine, or methylamine.[4/35,3/52]

Aliphatic 1,3-dinitro derivatives or the corresponding mixtures of alkanenitronates and nitroolefins do not cyclize in alkaline medium, owing to the stability of their bis anions; upon acidification 3,5-dialkylisoxazoles can be isolated directly,[72/64] possibly without intermediacy of an isoxazoline *N*-oxide.[72/64,154/69] For this and analogous isoxazole synthesis and for the direct synthesis of triarylisoxazoles from α-nitrostilbenes and/or arylnitromethanes, see § 1.3.3, pp. 209–211.

### Alkali Metal Arylmethanenitronates (Pathway *b*)

The direct oxidation of salts of primary or secondary nitro compounds is known to be a general method for preparing vicinal dinitro compounds. Under particularly controlled experimental conditions, however, treatment of sodium or potassium arylmethanenitronates, either previously isolated or prepared *in situ*, with silver nitrate or potassium persulfate in DMSO can give 3,4,5-triaryl-2-isoxazoline *N*-oxides in 40–65% yield without concomitant formation of the corresponding vicinal dinitrocompounds.[247/78,26/79] Because of easy availability of starting materials and simplicity of procedure, this method seems at the moment the most convenient for preparing aryl-substituted isoxazoline *N*-oxides. A variation of the method employs α-bromophenylnitromethane together with the sodium salt of phenylnitromethane:[247/78]




(61% yield)

The proposed mechanism invokes $S_{RN}$ and $E_{RC}$ processes to reach the 1,3-dinitro intermediate.[26/79,235/82]

Under different experimental conditions (ammonium persulfate in water or water–chloroform) the oxidation of sodium phenylmethanenitronate gives a complex mixture of compounds, where the main product is α-nitrostilbene in homogeneous medium and 1,2-dinitro-1,2-diphenylethane in heterogeneous medium, the isoxazoline *N*-oxide and the triphenylisoxazole being present only in very low (0.4–2.4%) yields.[170/70]

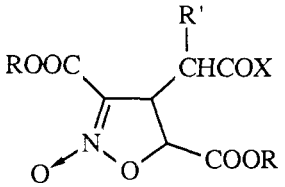
### Alkyl Nitroacetates and Aldehydes or Their Derivatives (Pathway *c*)

Aromatic aldehydes or their Schiff's bases easily add two molecules of methyl nitroacetate under the catalytic influence of methylamine or diethylamine to give the *N*-oxides of 4-aryl-2-isoxazoline-3,5-dicarboxylates or of their monodiethylamides.[5/52,6/52,1B/53,249/83] The intermediate 2,4-dinitroglutaric esters can almost always be isolated, and the overall yields are usually in the range 50–90%. Heterocyclic aldehydes such as 2-pyridyl,[249/83] 3-indolyl,[185/70,222/78] or aldehydo sugars[138/76,27/79,203/79] can be employed to prepare the dicarboxylic esters of 4-heteroaryl- or 4-glycosylisoxazoline *N*-oxides, respectively.

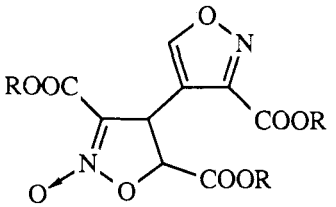
In the aliphatic series, alkyl halides in the presence of sodium methoxide are used instead of the aldehyde.[37/74] Besides minor amounts (6–29%) of the C-alkylation product, O-alkylation of the nitroacetate with subsequent decomposition of the alkylnitronate should possibly furnish *in situ* the necessary aldehyde, which condenses with an excess of nitroacetate. Moderate yields (32–43%) are obtained.

Better yields are achieved by using the aldehyde in a dipolar aprotic solvent such as DMA: yields of 67–95% are common with aliphatic aldehydes; the yields with aromatic aldehydes are somewhat lower.[45/80,249/83]

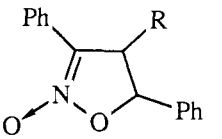
As a matter of fact, the reaction between aldehydes and nitroacetate seems more interesting if used as a direct method of synthesis of 4-substituted isoxazole-3,5-dicarboxylic acids and their amides (see § 1.3.3; pp. 211–212). β-Dialkylaminovinyl ketones or esters condense in a fashion similar to that of nitroacetate, and isoxazoline *N*-oxides of general structure **356** are thus obtained.[94/74,262/74]




**356**
(X = R" or OR")




**357**




**358 a** R = 4-$NO_2C_6H_4$
**b** R = *n*-Pr

The reaction with β-dialkylaminoacrolein is slightly different: besides normal condensation with the aldehydo group, a third molecule of methyl nitroacetate acts as a 1,3-dipole (possibly as a nitrile oxide precursor; see § 2.2.2.2a) on the activated double bond to give an isoxazolyl moiety as in **357**.[94/74]

Occasionally, the alkyl nitroacetate is substituted by phenylnitromethane: thus a mixture of the latter compound and of 4-nitrobenzaldehyde in the presence of *n*-butylamine gives a 16% yield of 4-*p*-nitrophenyl-3,5-diphenyl-2-isoxazoline *N*-oxide **358a**;[9/84] under somewhat different conditions, phenylnitromethane reacts with propylidenebutylamine to furnish a 68% yield of the 3,5-diphenyl-4-propyl derivative **358b**.[52/80]

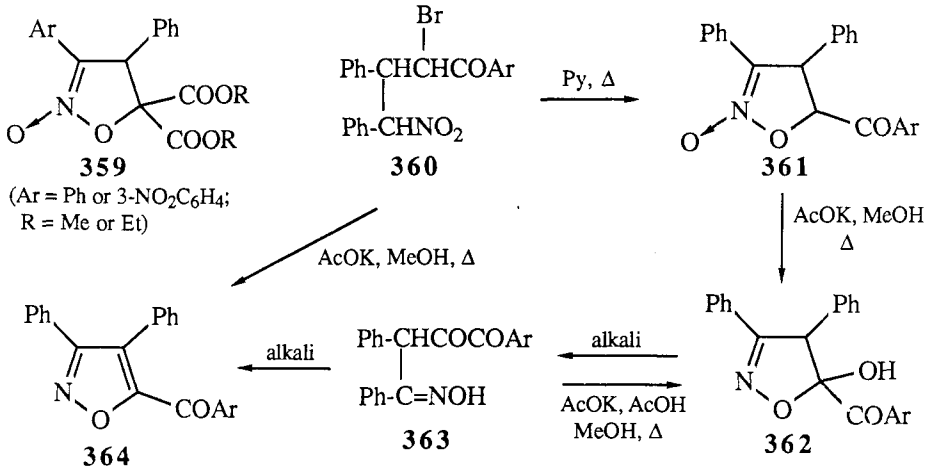
### α-Haloethylarenes (Pathway *d*)

The nitrosation of α-methyl-*p*-nitrobenzyl chloride with sodium nitrite in DMSO is reported to give a complex mixture of products, from which 5-methyl-3,5-di(*p*-nitrophenyl)-2-isoxazoline *N*-oxide could be isolated in 20% yield.[16/79] The proposed mechanism for this rather peculiar synthesis involves the α-mononitro- and the α,α-dinitroethylarene; indeed, the latter compound reacts with the lithium salt of the former, giving the isoxazoline *N*-oxide in 81% yield.

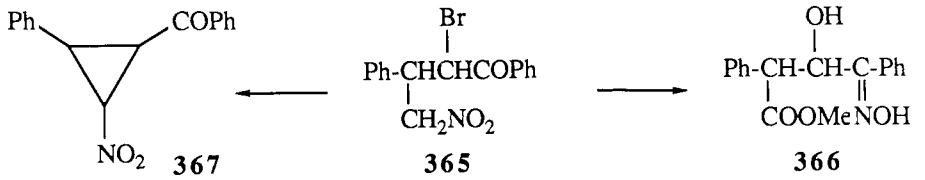
## *2.3.2.2 From 3-Halo-1-Nitroalkanes (353: X = Br)* (Pathway *e*)

Michael addition of arylnitromethane to α,β-ethylenic ketones or arylidenemalonic esters or of malonic esters to α-nitrostilbenes easily furnishes γ-nitro ketones or γ-nitrocarboxylic esters. Bromination of these compounds with bromine in chloroform privileges attack of bromine atom to the position *alpha* to the carbonyl group, thus leading to a 3-bromo-1-nitro compound of general structure **353** (X = Br). Cyclization to the corresponding isoxazoline *N*-oxide is usually effected by heating with fused potassium acetate in absolute methanol: by this method, for example, a 90% yield of the 5,5-dicarboxylic ester **359** was reached.[8/26,6/30]

The reaction is not always so straightforward. Heating the mixture of stereoisomeric bromoderivatives **360** with potassium acetate in dry methanol gave the isoxazole ketone **364** directly, whereas the isoxazoline *N*-oxide **361** could be obtained in 92% yield by short heating with pyridine. By further treatment with potassium acetate, the *N*-oxide **361** isomerized to the 5-hydroxyisoxazoline **362**, which in alkaline medium was rapidly transformed into the isoxazole ketone **364** through the intermediate monooxime **363**.[8/24,10/25,9/27,8/30]



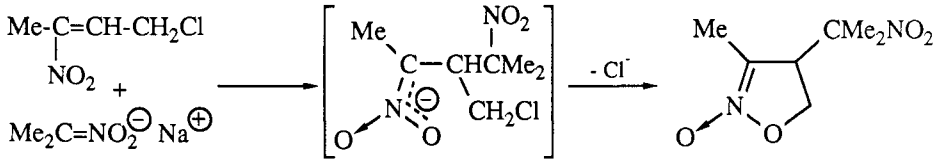
All efforts directed to prepare a 3-unsubstituted isoxazoline *N*-oxide by dehydrohalogenation of a 3-bromo-1-nitroderivative were fruitless: thus base treatment of 3-phenyl-2-bromo-4-nitrobutyrophenone (**365**) yields, according to experimental conditions, either the oximinoester **366** or the cyclopropane ketone **367**.[7/24.9/26.5/28]




**367** **365** **366**

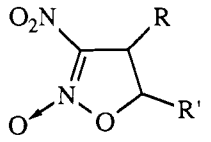
Nitrocyclopropane compounds, derived from a carbanionic intramolecular attack, are also the main products when bromination is carried out on the sodium salt of the starting nitro ketone or ester.[6B/28.6/30.14/56.20/56]

The 5-unsubstituted isoxazoline *N*-oxide **369** is the product of cyclization obtained from 1-chloro-3-nitro-2-butene and sodium propane-2-nitronate.[16/54] As could have been expected, in the presumable intermediate *β*-nitro-*β*′-chloronitronate (**368**) the internal displacement reaction concerns the chlorine ion and not the nitrite anion:

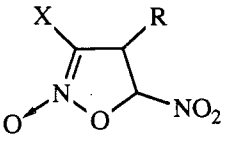



**368** **369**

The simple 3-nitro-2-isoxazoline *N*-oxide has been synthesized in 84% yield by treatment of 3,3-dinitro-1-bromopropane with sodium acetate.[63/65] Similarly, several other 2-isoxazoline *N*-oxides of general structure **370**, where R or R′ can also be a hydrogen atom, have thus been prepared.[63/65.210/66.178/67.209/72.184/74.197/75] They are excellent starting material for preparing isoxazolizidines (see Part 2 of this work). Condensation of the potassium salt of dinitromethane with chloroacetaldehyde furnishes a 74% yield of 3-nitro-4-hydroxy-2-isoxazoline *N*-oxide, a starting material for the synthesis of 3-nitroisoxazolines.[63/66] Also worth mentioning is the synthesis of 5-nitroisoxazoline *N*-oxides of general structure **371** from *gem*-bromonitroethylenes and activated nitro compounds, such as nitroacetonitrile or ethyl nitroacetate in the presence of sodium methoxide.[268/74] Here, too, the bromine ion neatly prevails upon the nitrite anion as the leaving group.

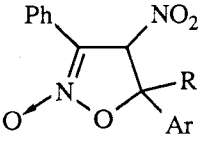


**370**



**371**

(R = CN or COOEt)



**372**

Finally, it should be mentioned that intermediates of structure **353** (X = Cl; R″ = R‴ = H) can be prepared *in situ* most simply by nitrosation of 1-bromo-3-chloroderivatives with sodium nitrite in dimethylformamide: for example, 3-phenyl- and 3-methoxycarbonyl-2-isoxazoline *N*-oxide have been synthesized from 1-bromo-1-phenyl-3-chloropropane and from methyl 2-bromo-4-chlorobutyrate in 43 and 36% yield, respectively.[99/69]

### 2.3.2.3 *From Diazoalkanes (**353**: X = $N_2^+$)* (Pathway *f*)

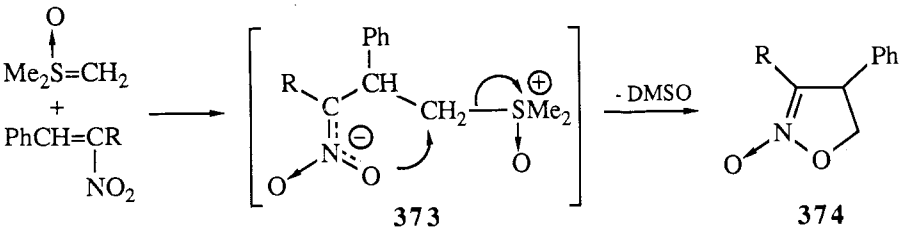
Whereas mononitroalkenes react with diazoalkanes to give the expected nitropyrazolines (or the corresponding pyrazoles) or nitrocyclopropanes, *gem*-dinitroalkenes undergo nucleophilic attack by diazoalkanes, giving excellent yields of 3-nitro-2-isoxazoline *N*-oxides, possibly through the intermediacy of the mononitronate **353** (X = $N_2^+$), which cyclizes immediately with splitting out of nitrogen.[211/71.246/72.261/72.198/73] For example, 3-nitro-5-biphenylene-2-isoxazoline *N*-oxide was obtained in 85% yield from 9-diazofluorene and 1,1-dinitroethylene (produced *in situ* from 2,2-dinitroethanol), and vice versa, the reaction of diazomethane with 2-biphenylene-1,1-dinitroethylene furnished a 76% yield of 4-biphenylene-3-nitro-2-isoxazoline *N*-oxide.[261/72] Analogously, the addition of disubstituted diazomethanes to α,β-dinitrostyrene leads to 4-nitro-isoxazoline *N*-oxides of general structure **372**.[213/78]

Of lesser preparative importance seems to be the production, under controlled conditions, of the unsubstituted 3-nitroisoxazoline *N*-oxide in 20–25% yield from halonitroforms[217/68.232/68] or even simple nitroform[86/71] and diazomethane. The mechanism proposed involves, here too, the intermediacy of 1,1-dinitroethylene.[261/72] The reaction has been extended to the preparation of 3-cyano-2-isoxazoline *N*-oxide from halodinitroacetonitrile.[199/84] However, C- and O-methylation are concurrent reactions, and the method has perhaps more significance for the synthesis of isoxazolidine derivatives than for isoxazoline *N*-oxides. Moreover, the reaction could not be extended to diaryldiazomethanes, which react with iodonitroform to give diaryldinitroethylenes.[233B/69]

### 2.3.2.4 *From Ylides [**353**: X = $R_2S(O)^+$]* (Pathway *g*)

Nucleophilic attack of sulfonium or sulfoxonium methylide on electron-poor

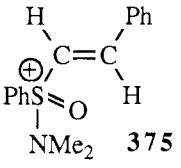
olefins is a well-known synthetic route to cyclopropane derivatives. Nevertheless, when nitroolefins are employed, sometimes cyclization of the conceivable initial adduct, having a zwitterionic structure **373** of sulfonium-nitronate salt, can lead to the formation of isoxazoline *N*-oxides. For example, treatment of the dimethyl sulfoxonium ylide–copper (I) complex with β-nitro- or with β-nitro-β-methylstyrene resulted in a 64–71% yield of the corresponding 4-phenyl-2-isoxazoline *N*-oxide **374**:[192/76]



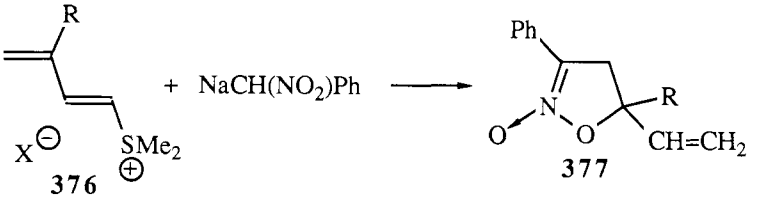

**373** **374**

Some sugar-condensed isoxazoline *N*-oxides were analogously prepared from a nitro sugar and *S*-ylides.[133/77,48/78]

Conversely, a vinylsulfoxonium salt such as **365** can react with a sodium nitronate to give, presumably through a **373**-type intermediate, 3,4-disubstituted isoxazoline *N*-oxides (**374**); nitrocyclopropanes are sometimes obtained as by-products. By using an optically active **375**, an isoxazoline oxide (**374**: R = COOMe) with 33% enantiomeric excess was obtained.[195/80]




**375**



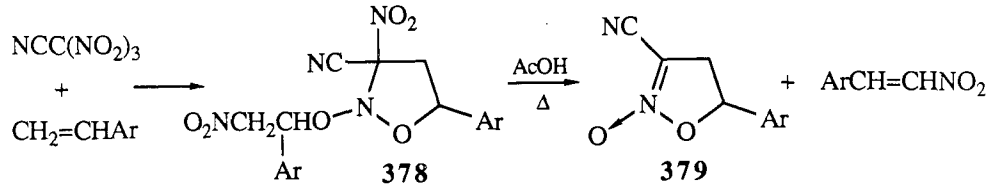

**376** **377**

Analogously, good yields of 5-vinyl-2-isoxazoline *N*-oxide (**377**) were reached by reacting *trans*-(1,3-butadienyl)dimethylsulfonium halides (**376**) with the sodium salt of phenylnitromethane.[234/76]

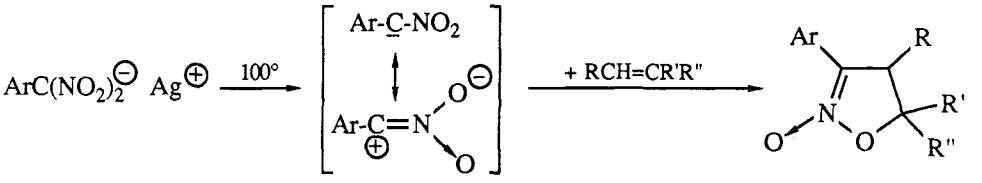
### *2.3.2.5 Miscellaneous Methods*

3-Cyano-5-aryl-2-isoxazoline *N*-oxides **379** have been obtained by mild

acidic treatment (refluxing acetic acid) of the suitably substituted *N*-alkoxyisoxazolidines **378**; stronger conditions caused ring decomposition.[290/76]




Thermolysis of the silver salts of aryldinitromethanes at 100°C in the presence of electron-rich olefins, such as 1,1-diarylethylenes, gives low to moderate yields of 2-isoxazoline *N*-oxides, along with minor amounts of 2-isoxazolines:[203/80]



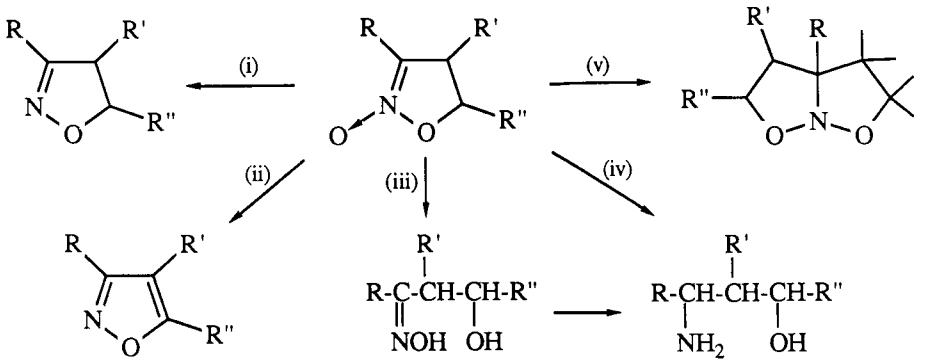

Use of electron-poor olefins or of potassium salts of dinitroalkanes[184/76] or of sodium salts of arylbromonitromethanes[186/75] leads to exclusive production of 2-isoxazolines. The formation of the *N*-oxides is presumed to arise through an intermediate nitrocarbene.[203/80]

As already mentioned, direct oxidation of 2-isoxazolines normally does not yield the corresponding *N*-oxides; nevertheless, in one case (i.e., dimethyl-3,4-diphenyl-2-isoxazoline-5,5-dicarboxylate) treatment with peracetic acid is claimed to achieve this goal, although with limited preparative value (only 19% yield).[8/26] Finally, the somehow peculiar oxidative cyclization of 3-amino-1,2,3-triphenylpropan-1-ol with nitrous acid to give 3,4,5-triphenylisoxazoline *N*-oxide in 38% yield has been reported.[7/30]

### 2.3.3 Chemical Properties

As mentioned earlier, 2-isoxazoline *N*-oxides share the structural characteristics of both the heterocyclic isoxazoline ring and a cyclic nitronic ester. Thus, as representatives of the latter group of compounds, they can undergo a 1,3-dipolar cycloaddition with more or less activated olefinic compounds, giving bicyclic nitrogen-bridged heterocycles, the so-called *isoxazolizidines*. This cycloaddition reaction will be treated in Part 2 of this work and will not be considered here.

The main reactions of the isoxazoline *N*-oxides are summarized in the following scheme:




where the pathways are characterized as follows:

(i) $PCl_5$ or $PPh_3$ or $P(OEt)_3$;
(ii) heat or base or acid;
(iii) $PhCH_2MgBr$ or $H_2/Pt$;
(iv) Zn/AcOH; and
(v) $>C=X<$, heat.

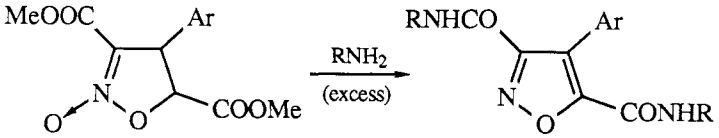
### *2.3.3.1 Deoxygenation*

This reaction has frequently been used to establish the structure of the isoxazoline *N*-oxides and is commonly carried out by heating an intimate mixture of the *N*-oxide with phosphorus pentachloride at 75°C.[10/24.8/26.16/79] If the temperature is too high, variable amounts of the dehydration product (i.e., the isoxazole) are formed as by-products (see below). Evolution of chlorine has been assumed diagnostic for the presence of the *N*-oxide moiety.[10/25.8/30] The use of triethyl phosphite in refluxing toluene[27/79] or of triphenylphosphine in boiling benzene[133/77] seems to be more advantageous.

### *2.3.3.2 Dehydration*

2-Isoxazoline *N*-oxides are rather unstable compounds, since either thermally or by action of bases or, more seldom, of acids, they easily lose water to yield the corresponding isoxazoles. Frequently, dehydration takes place spontaneously under the conditions employed for preparing the oxides, and isoxazoles are obtained directly (see, e.g., § 1.3.3, pp. 209–215).

When 3,4,5-triphenyl-2-isoxazoline *N*-oxide is heated slowly over its melting point under vacuum, 3,4,5-triphenylisoxazole is formed in high yields, together with some benzonitrile.[10/24] Nevertheless, strong bases seem to promote dehydration more smoothly: the same above-mentioned transformation can be effected by refluxing an ethanolic solution of the *N*-oxide containing sodium ethoxide for 5 min.[154/69] Sodium methoxide,[10/28] alcoholic potassium hydroxyde,[4/35] and 1% aqueous sodium hydroxide[195/80] have also been employed successfully. If suitable side chains are present, other transformations can sometimes accompany the dehydration. Thus, when concentrated aqueous ammonia[5/52,185/70] or ethanolic *n*-butylamine[21/71] is reacted with esters such as **380**, isoxazole diamide (**381**) is formed in good yields:



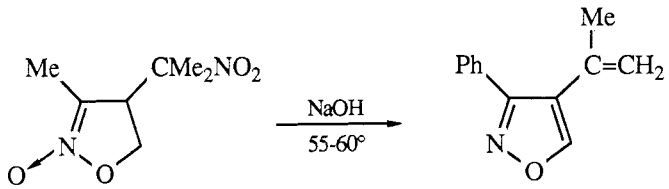

**380** **381**

Furthermore, the extremely unstable dicarboxylic acid **382** is converted quantitatively to 3,4-diphenylisoxazole-5-carboxylic acid (**383**) by simple boiling in water:[8/26]



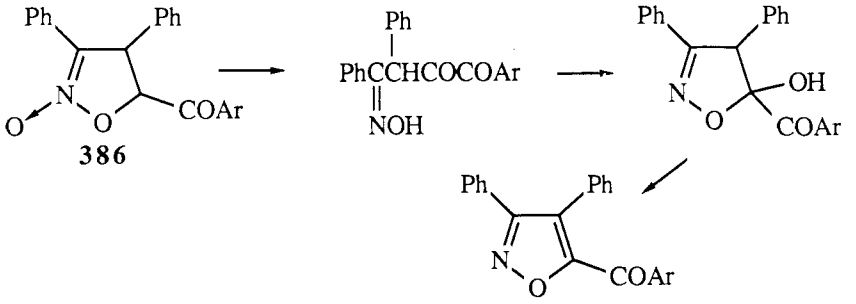

**382** **383**

Although with lower yields, basic treatment transforms 3,4-disubstituted isoxazoline *N*-oxide (**384**) into unsaturated isoxazole (**385**):[16/54]



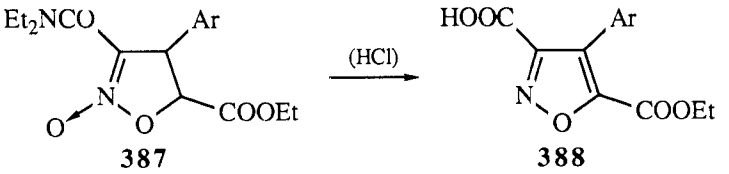

**384** **385**

The mechanism of the dehydration possibly involves a ring opening to a β-ketone monooxime, which then readily cyclizes to isoxazole, eventually through the intermediate 5-hydroxyisoxazoline. Both these intermediates could be isolated in the case of a 5-acylisoxazoline *N*-oxide; for example:[8/24,10/25,8/30]



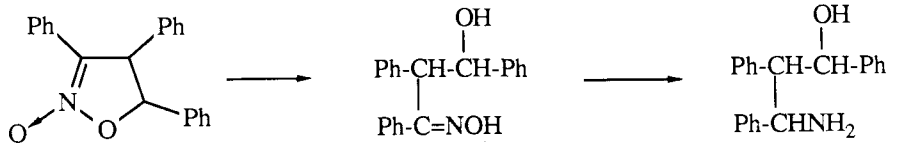

More drastic treatment of the ketone **386** with ethanolic potassium hydroxide affords further decomposition, and an 88% yield of 3,4-diphenylisoxazole is obtained.[8/30]

In some instances the same dehydration process can occur in an acidic medium; thus bubbling gaseous HCl in a wet ether solution of **387** at 0°C resulted in 83–92% conversion to the isoxazole derivative **388**:[5/52,6/52]




### *2.3.3.3 Reduction*

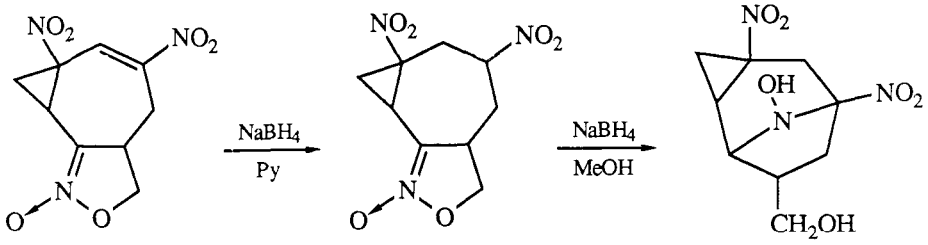
The ring of the isoxazoline *N*-oxides is relatively resistant toward reducing agents. For example, selective hydrogenolysis of a benzyl ester to a carboxylic group[185/70] or catalytic reduction of a keto group to secondary alcohol[8/30] can be performed without affecting the isoxazoline *N*-oxide moiety. By contrast, reduction of 3,4,5-triphenylisoxazoline *N*-oxide with zinc and acetic acid opens the ring, giving either a hydroxyoxime[10/24,8/26,7/30] or, after a prolonged treatment, the 1,3-amino alcohol.[7/30]




The hydroxyoxime can also be obtained by treatment with benzylmagnesium bromide[7/30] or by catalytic hydrogenation.[6/52] The ultimate product of the catalytic (Pt or Ni Raney) hydrogenation seems, however, to be the 1,3-amino alcohol.[8/30,133/77]

Reduction of the N → O bond and hydrogenolytic ring opening are also the results of polarographic reduction of 3-monosubstituted isoxazoline *N*-oxides; a hydroxylamino or an amino alcohol are the final products, depending on the acidity of the solution.[85/71]

Sodium borohydride in the presence of pyridine at 0°C does not open the ring; on the contrary, the same reagent in methanolic solution hydrogenolyzes the ring, as the following example shows:[202/72]

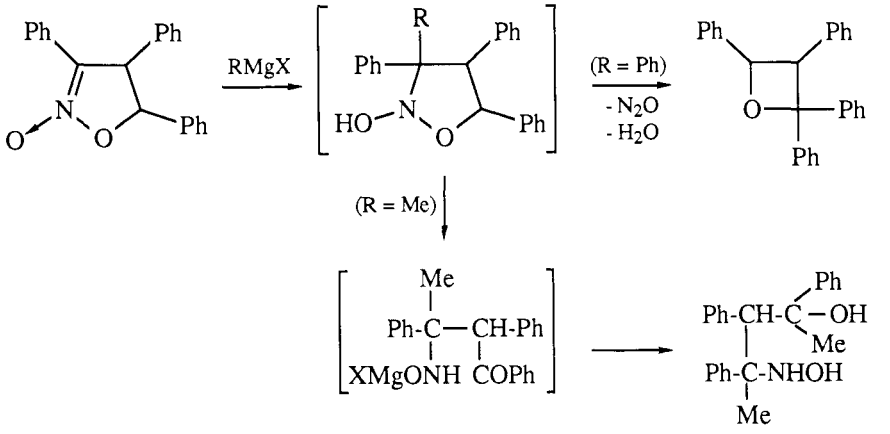



### *2.3.3.4 Oxidation*

2-Isoxazoline *N*-oxides are remarkably stable toward oxidizing reagents: for example, 3,4,5-triphenylisoxazoline *N*-oxide remains unaltered by treatment with nitrous acid in acetic acid or with permanganate in acetone. Small amounts of 1,2,3-triphenylpropane-1,3-dione are formed by heating with chromic acid in acetic acid.[10/24] 3,4-Diphenyl-5-anisoylisoxazoline *N*-oxide is stable toward sodium dichromate in boiling glacial acetic acid, so that it can be prepared by oxidation of the corresponding secondary alcohol.[8/30] Obtaining 3,4-diphenyl-5-isoxazolinone by treatment of 3,4-diphenyl-5-aroyl-2-isoxazoline *N*-oxide with sodium peroxide[8/24] may possibly be ascribed to an initial isomerization to the 5-hydroxy-2-isoxazoline derivative, which is known to decompose oxidatively under these conditions.[8/30]

### *2.3.3.5 Reaction with Grignard Reagents*

Grignard reagents react with triphenylisoxazoline *N*-oxide to give different types of products, depending on the nature of the Grignard reagent used.[7/30] Apart from benzyl- and ethylmagnesium bromides, which yield only a reduction product (see above), phenylmagnesium bromide adds to the C=N double bond to give a highly unstable adduct, which decomposes both in solution and in solid form. In glacial acetic acid it is readily converted into tetraphenyloxetane. Methylmagnesium iodide behaves differently: 3 mol of reagent is consumed, and a hydroxylamino alcohol is the final product:[7/30]




### *2.3.3.6 Rearrangement Reactions*

Treatment of a 4-aryl-2-isoxazoline-3,5-dicarboxylate *N*-oxide (**380**) with Lewis acids gives rise to ring opening followed by an electrophilic attack to the aromatic ring. The structure of the final product depends on the substitution pattern on the aryl ring. The presence of a halogen atom in the *para* position favors an attack by the oxygen atom with formation of a tricyclic spiro-isoxazoline derivative (**389**). By contrast, the unsubstituted or *meta*-substituted aryl ring promotes an attack of the nitrogen atom on the *ortho* position with formation of a 3*H*-indole-1-oxide **390**.[87/79,42/83,136/84,153/84,7/85]
The results are summarized in Table 2.38.

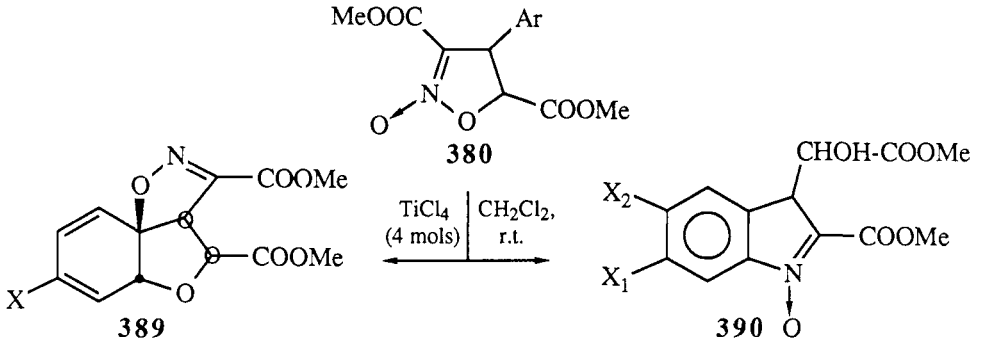


TABLE 2.38

| Ar | X | $X_1$ | $X_2$ | Yield (%) in: 389 | Yield (%) in: 390 | References |
|---|---|---|---|---|---|---|
| Ph | | H | H | - | 85 | 87/79, 7/85 |
| 4-$FC_6H_4$ | F | F | H | 77 | 12 | 153/84, 7/85 |
| 4-$ClC_6H_4$ | Cl | Cl | H | 81 | 8 | 42/83, 153/84, 7/85 |
| 4-$BrC_6H_4$ | Br | Br | H | 73 | 11 | 153/84, 7/85 |
| 3-$FC_6H_4$ | | H | F | - | 76 | 7/85 |
| 3-$ClC_6H_4$ | | H | Cl | - | 69 | 7/85 |
| α-Naphthyl | [a] | | | 55 | - | 136/84 |
| 4-$MeC_6H_4$ | Me | Me | H | 44 | 15 | 7/85 |
| 3-$MeC_6H_4$ | | H | Me | - | 69 | 7/85 |
| 2-$MeC_6H_4$ | | H | H[b] | - | 18 | 7/85 |

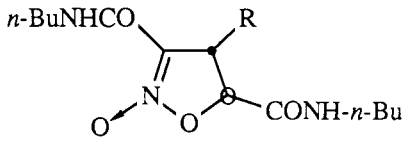
[a] 8,9-Benzo derivative.
[b] 4-Me substituted.

### 2.3.3.7 *Miscellaneous Reactions*

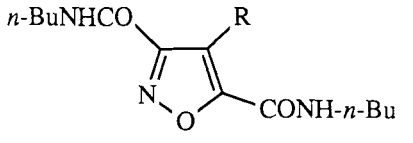
As a rule, 2-isoxazoline *N*-oxides are neutral compounds which decompose under the action of bases or strong acids. Nevertheless, 4-nitro derivatives form potassium salts with ethanolic potassium hydroxide, which revert to the starting material by acidification.[213/78] 3-Nitroisoxazoline *N*-oxide is reported to give a crystalline 1:1 complex with bis(trinitromethyl)mercury.[108/68,88/71] Heating 3-cyano-5-aryl-2-isoxazoline *N*-oxides with 1:1 aqueous hydrochloric acid provokes decomposition of the ring with formation of the corresponding cinnamic acid.[290/76]

Some other group transformations in the side chains without affecting the *N*-oxide moiety are also possible, provided that the conditions are held mild enough; this is the case, for example, of the hydrolysis[8/26,6/30] or ammonolysis[37/74,27/79,45/80] of carboxylic esters and of the esterification of carboxylic acids.[6/30]

It has already been mentioned that heating with *n*-butylamine usually transforms the dimethyl 4-alkyisoxazoline-3,5-dicarboxylate *N*-oxide into the corresponding isoxazole diamide. The isoxazoline *N*-oxide diamide is often isolated as a by-product, which can become the main product if the refluxing time is maintained appropriately short:[45/80]




**391 a** R = *n*-Bu
**b** R = *i*-Pr

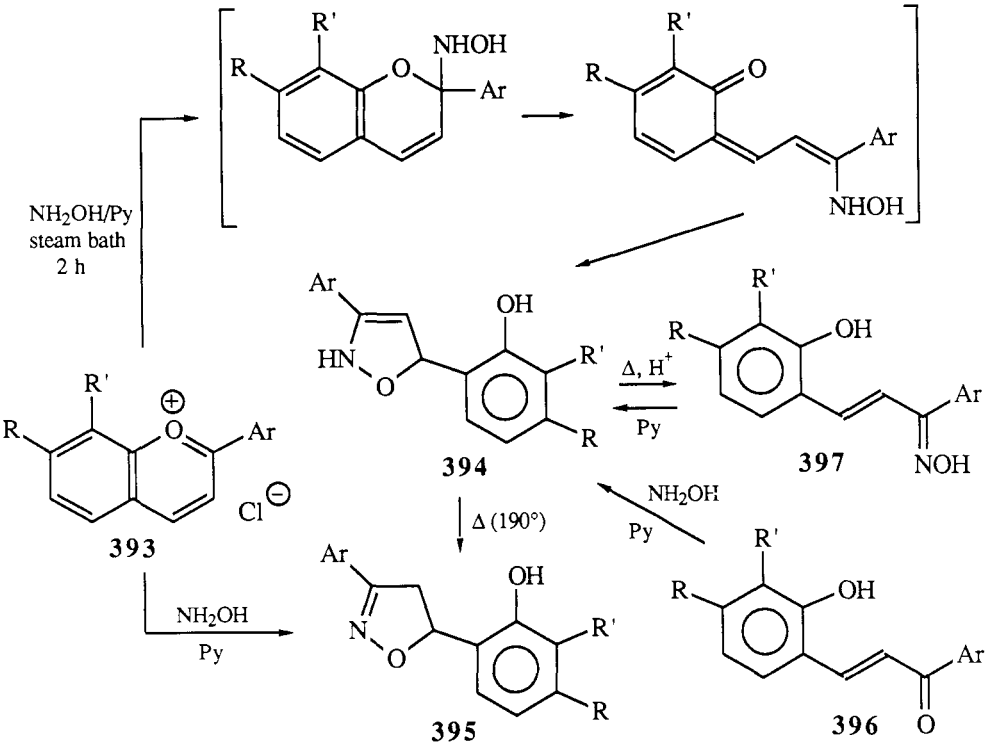



**392 a** R = *n*-Bu
**b** R = *i*-Pr

For example, refluxing for 2 h gives 55% **391a** and 11% **392a**, and refluxing for 10 h gives 10% **391a** and 53% **392a**. Furthermore, steric dependence of the dehydration step has also been noted, since the 4-isopropylisoxazoline *N*-oxide diester yields only **391b** and no isoxazole (**392b**), even after 10 h of refluxing.

## 2.4 3-ISOXAZOLINES

Practically unknown until the late 1960s, 3-isoxazolines have received little attention and have not yet been studied systematically. A limited number of polysubstituted derivatives have been obtained through one of the three methods of preparation having general applicability explored up to now, all of them starting from quaternary salts: oximation of flavylium salts, nucleophilic addition to isoxazolium salts, and basic treatment of 2-isoxazolinium salts.



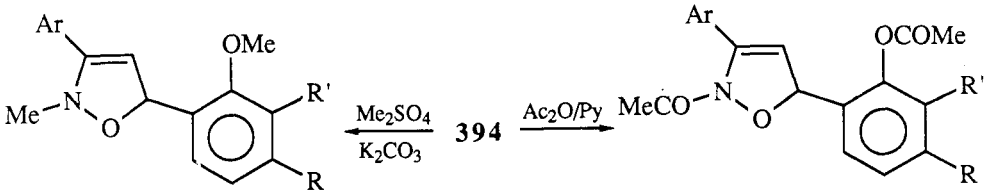

Scheme 2.44

The former method[49/70,182/75] leads to N-unsubstituted 3,5-diaryl-3-isoxazolines, presumably through an initial nucleophilic attack by hydroxylamine on position 2 of the pyrylium ring (Scheme 2.44).[182/75]

Analogous products are obtained from 3-methylflavylium salts. N-unsubstituted 3-isoxazolines (**394**) are thermally unstable and rearrange to stable isomeric 2-isoxazolines (**395**) by heating briefly above their melting point.[49/70,182/75] The latter compounds were previously reported[13B/50] to be produced by prolonged heating of **393** with hydroxylamine in pyridine.

The N-unsubstituted 3-isoxazolines, which can also be prepared in good yield by oximating 2-hydroxychalcone (**396**) in pyridine, rearrange in acidic media to the chalcone oxime (**397**), which in turn recyclizes to 3-isoxazoline (**394**) on treatment with pyridine. It is worth remembering that alkaline oximation of chalcones usually yields the 2-isoxazoline derivative (see § 2.2.2.1a, pp. 464–466).

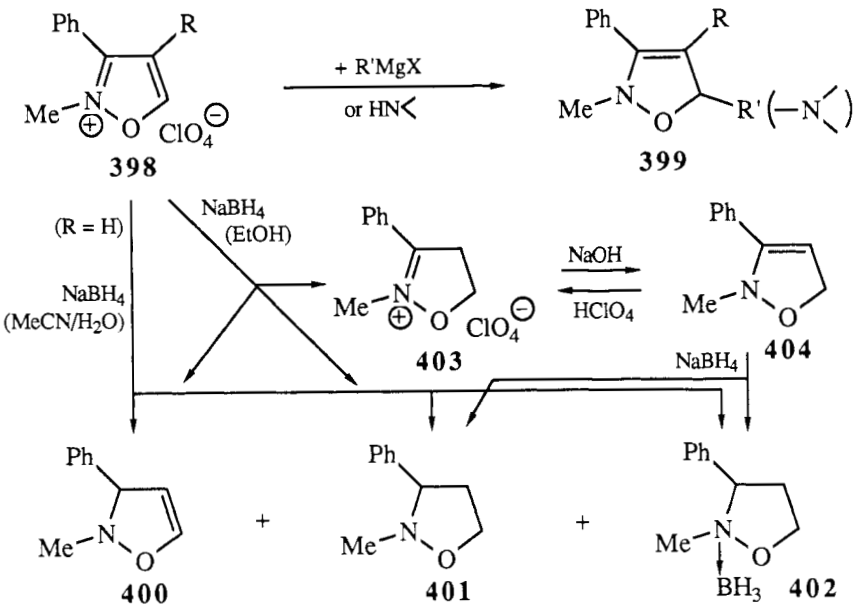
According to their structure, 3-isoxazolines of type **394** give an intense blue color with Gibbs reagent and can easily be methylated or acylated to give *N*-methyl- or *N*-acetyl derivatives, respectively:[182/75]




2-Methyl-3-phenyl-3-isoxazolines (**399**) have been synthesized by treatment of the suitable 5-unsubstituted *N*-methylisoxazolium perchlorates (**398**) with Grignard reagents or with cyclic amines such as piperidine or morpholine (Scheme 2.45).[51/69]

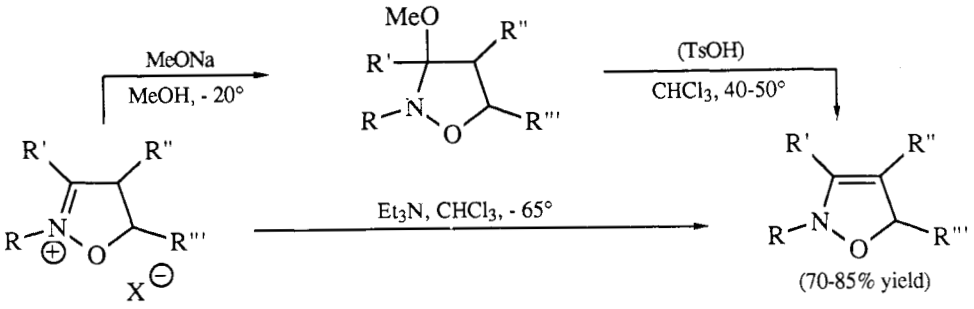
The reaction of 2-methyl-3-phenylisoxazolium perchlorate (**398**: R = H) with sodium borohydride gives different results depending on experimental conditions: in aqueous acetonitrile a mixture of 2-methyl-3-phenyl-4-isoxazoline (**400**) and of the isoxazolidines **401** and **402** is formed. When the reaction is carried out in ethanol and subsequently acidified with acetic acid, a mixture of **400**, **401**, and 2-methyl-3-phenyl-2-isoxazolinium perchlorate (**403**) is formed. This last salt is deprotonated by treatment with sodium hydroxide, yielding 2-methyl-3-phenyl-3-isoxazoline (**404**), which in turn can be hydrogenated to a mixture of **401** and **402** by treatment with sodium borohydride.[36/74] Apparently, the latter nucleophile attacks both the 3- and the 5-positions of the isoxazolium salt; in the former case the 4-isoxazoline produced is stable under the reaction conditions, whereas the 3-isoxazoline formed in the latter case reacts further.

2,3,5-Trialkylisoxazolium salts, carrying an electron-withdrawing substituent such as CN, COOR, or COR in the 4-position, are dihydrogenated by complex metal hydrides to give mixtures of 3- and 4-isoxazolines.[157/84] Far more



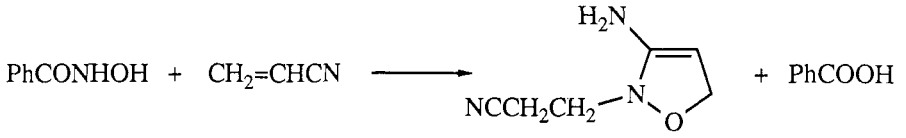

Scheme 2.45

straightforward is the synthesis of 3-isoxazolines by treatment of 2-isoxazolinium salts with bases. The most convenient procedures are (1) treatment with sodium methoxide and subsequent acid-promoted methanol elimination from the unstable intermediate 3-methoxyisoxazolidine derivative;[21/74] and (2) treatment with triethylamine at low temperature:[14/83]

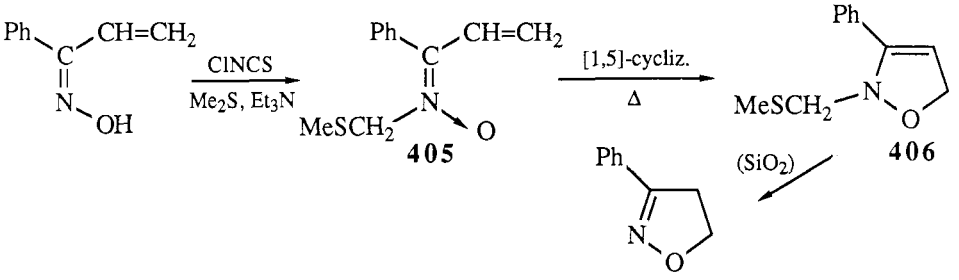



The use of aqueous sodium hydroxide gives lower yields.[21/74]

In a rather unusual synthesis of a 3-isoxazoline derivative, low yields of 2-cyanoethyl-3-amino-3-isoxazoline are obtained by treatment of benzohydroxamic acid with acrylonitrile:[33/73]

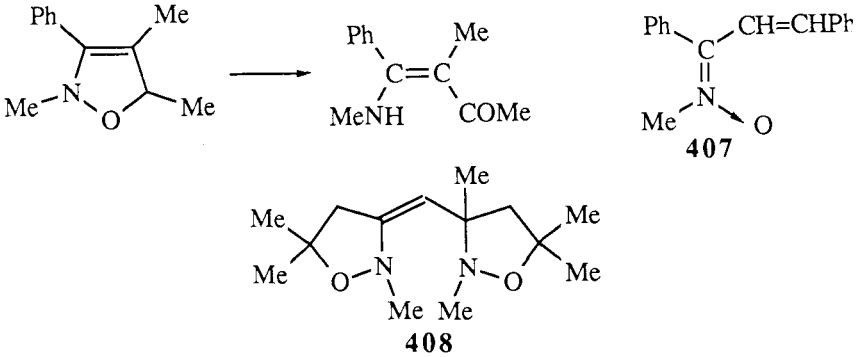


3,5-Dimethyl-4-nitro-3-isoxazoline has been isolated as a by-product during the preparation of the isomeric 2-isoxazoline by reduction of the corresponding isoxazole.[270/83] Sometimes the 3-isoxazoline structure has been invoked as a presumable intermediate: for example, in reactions of 5-unsubstituted isoxazolium salts with sodium hydroxide,[51/69] phenylhydrazine,[52/69] or carbanions.[52/69] Furthermore, the presence of the unstable 3-isoxazoline (**406**) has been shown in the crude reaction mixture from the thermolysis of the unsaturated nitrone **405**; simple chromatography on silica gel causes hydrolysis and tautomerization to 3-phenyl-2-isoxazoline:[153/80]



The 3-isoxazolines are colorless oils or crystals, which give perchlorates on treatment with perchloric acid. If the 5-position is amino-substituted, 5-unsubstituted isoxazolium perchlorates are formed upon deamination under the same conditions. Quarternarization occurs at the ring nitrogen atom when 3-isoxazolines are treated with methyl iodide.[14/83]

N-Substituted 3-isoxazolines are rather unstable, especially under basic conditions. For example, sodium hydroxide opens the ring with formation of an enamino ketone:[51/69]



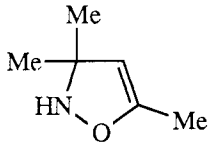
Attempts to isolate 2-methyl-3,5-diphenyl-3-isoxazoline or 2,3,5,5-tetramethyl-3-isoxazoline led to the isomeric nitrone **407** or to the dimeric product **408**, respectively.[21/74] Hydrogenolytic ring opening can also be accompanied by deamination: thus catalytic hydrogenation of 2-methyl-3-phenyl-3-isoxazoline yields β-hydroxypropiophenone.[36/74]

Spectroscopic data are known for some derivatives: C=C stretching absorption appears at 1610–1630 $cm^{-1}$ in 4-functionalized 2,3,5-trialkyl-3-isoxazolines,[157/84] and at 1641 $cm^{-1}$ in 2-methyl-3-phenyl-3-isoxazoline;[36/74] this and other 3-aryl derivatives show two UV absorption bands at 223–225 and 285–290 nm, whereas a second phenyl group in position 4 shifts the absorption to 315 nm.[51/69]

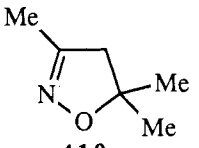
PMR spectra are also helpful in structural determination: the 5-proton absorbs at δ 5.1–5.2 when the 5-substituent is methyl or benzyl,[51/69] at δ 5.6–5.9 when the neighboring substituent is a piperidino or a morpholino group,[51/69] and is shifted into the aromatic region when a methoxyphenyl group is present in the 5-position.[182/75] The olefinic proton in the 4-position absorbs at δ 5.33 in 2-methyl-3-phenyl-3-isoxazoline[36/74] and shifts toward δ 7.0 in 3-*p*-methoxyphenyl-5-aryl derivatives.[182/75]

## 2.5 4-ISOXAZOLINES

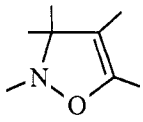
Although a 4-isoxazoline structure [i.e., 3,3,5-trimethyl-4-isoxazoline (**409**)] was claimed in the literature as early as 1898[2/898] as a result of the oximation of mesityl oxide, the compound has subsequently been assigned the isomeric 2-isoxazoline structure **410**.[21/72] Attempts to prepare 4-isoxazolines through partial hydrogenation of isoxazoles failed, leading to hydrogenolytic ring opening (see § 1.4.3.1). Thus 4-isoxazolines (**411**) were practically unknown until



**409**



**410**



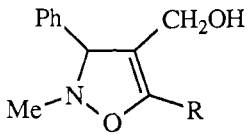
**411**

the 1960s, when the discovery of the 1,3-dipolar cycloaddition of nitrones to triple-bond compounds opened an easy route to these compounds.[85/63,33/66] Several representatives are now known, but their number is limited, because of the more or less pronounced instability of this class of derivatives, which often cannot be isolated, and in some cases not even spectroscopically revealed as intermediates. An exhaustive review on 4-isoxazolines has recently appeared.[48/83]

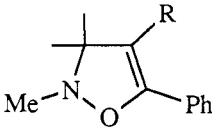
### 2.5.1 Physical Properties

4-Isoxazoline derivatives with less than two substituents are still unknown, and the large majority of the derivatives described in the literature are tri- or tetrasubstituted. Alkyl-substituted 4-isoxazolines are colorless oils, which often cannot be distilled even under high vacuum because of their thermal instability (see § 2.5.3.1). Phenyl- or polymethoxycarbonyl-substituted 4-isoxazolines are usually crystalline compounds.

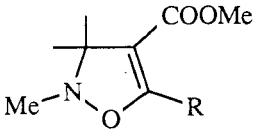
UV spectra are not very characteristic for 4-isoxazolines and are of little diagnostic value. 5-Phenyl-4-isoxazolines show two absorption bands at $\lambda_{max}$ = 222–229 and 274–282 nm in ethanol (or methanol).[211/69.81/72.35/74.36/74.86/75] A single absorption band in the region 260–290 nm appears in the electronic spectra of 4-methoxycarbonyl- or 4,5-bis(methoxycarbonyl)-4-isoxazolines.[113/68.18/69.19/69.19/70.119/82]



**412 a** R = Me
**b** R = Ph



**413 a** R = Me
**b** R = Ph



**414**

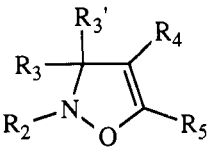
IR spectroscopy of 4-isoxazolines reflects their nature of cyclic enolethers. Thus the double bond of compound **412a** absorbs at a frequency as high as 1710 $cm^{-1}$.[175B/75] Conjugation with a 5-phenyl group decreases the frequency, and thus **412b** shows a $\nu_{C=C}$ at 1680 $cm^{-1}$;[175B/75] consistently, absorptions in the range 1670–1681 $cm^{-1}$ are commonly presented by 4-isoxazolines of general structure **413a**.[211/69.35/74]

4-Unsubstituted 5-phenyl-4-isoxazolines (**413b**) usually absorb around 1640–1650 $cm^{-1}$.[81/72.35/74.36/74.41B/75.11/76.269/82] The presence of one methoxycarbonyl group in position 4 or 5 or of two 4,5-bismethoxycarbonyl groups causes the C=C stretching vibration to give rise to bands around 1640 or 1660 $cm^{-1}$, respectively.[19/69.127/73.66/84]

These absorptions do not help make it possible to choose between the 4- and the 5-methoxycarbonyl regioisomer; a better diagnostic value is offered in this case by the ester C=O absorption band, which always appears at lower frequency in the 4-substituted regioisomer.[15/69.127/73.66/84] Analogous frequency values are reported for other 4-isoxazoline carboxylates of general structure **414**.[15/69.41B/75.175B/75]

More useful for determining structure and regiochemistry of 4-isoxazolines are the PMR spectra. Ring protons, if not heavily influenced by other substituents, absorb in the following sequence from the higher to the lower field: $H_3$,

TABLE 2.39. PMR DATA OF 4-ISOXAZOLINES



| | | | | | Chemical shifts (δ) | | | | | Coupling | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | $R_3'$ | $R_4$ | $R_5$ | $R_2$ | $R_3$ | $R_3'$ | $R_4$ | $R_5$ | constants (Hz) | Reference |
| Me | Me | H | H | Me | 2.60 s | 3.55 dq | | 4.30 d | - | $J_{3,4}$ = 2 | 269/82 |
| | | | | | 1.10 d (3-Me); 1.70 s (5-Me) | | | | | $J_{3,3a}$ = 6 | |
| $CMe_3$ | H | H | H | $CMe_2OH$ | 1.12 s | 3.97 d | | 4.68 t | | $J_{3,4}$ = 2.0 | 113/68 |
| | | | | | | 1.42 s (2 Me) | | | | | |
| Me | H | H | H | Ph | 2.81 s | 4.15 m | | 5.12 t | 7.44 m | $J_{3,4}$ = 2.5 | 36/74 |
| $CMe_3$ | H | H | H | Ph | 1.18 s | 4.12 d | | 5.15 t | 7.38 m | $J_{3,4}$ = 2.5 | 36/74 |
| Me | Ph | H | H | H | 2.83 s | 7.28 m | 4.93 t | 4.64 t | 4.97 d | $J_{3,4}$ = 2.5; | 36/74 |
| | | | | | | | | | | $J_{4,5}$ = 2.0 | |
| $CMe_3$ | H | H | H | COOEt | | 4.00 d | | 5.60 t | - | $J_{3,4}$ = 2.5 | 127/73 |
| $CMe_3$ | H | H | COOEt | H | | 4.00 d | | - | 7.11 t | $J_{3,5}$ = 2.0 | 127/73 |
| $CMe_3$ | H | H | H | CN | | 4.05 d | | 5.62 t | - | $J_{3,4}$ = 3.0 | 127/73 |
| $CMe_3$ | H | H | CN | H | | 4.05 d | | - | 7.10 t | $J_{3,5}$ = 2.0 | 127/73 |
| $CMe_3$ | H | H | COOMe | COOMe | 1.12 s | 4.18 s | | - | - | | 113/68 |
| | | | | | | 3.67; 3.82 (OMe) | | | | | |
| Me | Me | H | H | Ph | 2.78 s | - | 3.83 qd | 5.19 d | - | $J_{3,4}$ = 2.4; | 35/74 |
| | | | | | | | | | | $J_{3,3a}$ = 6.2 | |
| | | | | | 2.70 s | | 3.75 qd | 5.05 d | | $J_{3,4}$ = 2.5; | 269/82 |
| | | | | | 1.20 d (3-Me); 7.2 m (5-Ph) | | | | | $J_{3,3a}$ = 6 | |
| Me | Ph | H | H | Ph | 2.95 s | - | 4.82 d | 5.32 d | - | $J_{3,4}$ = 2.4 | 35/74 |
| | | | | | 2.85 s | - | 4.65 d | 5.10 d | - | $J_{3,4}$ = 3 | 269/82 |
| | | | | | 7.1 m (3-Ph); 7.1 m (5-Ph) | | | | | | |
| $CMe_3$ | Me | H | H | Ph | 1.16 s | 1.29 d | 4.32 qd | 5.12 d | 7.1-7.6 m | $J_{3,3a}$ = 7.0 | 86/75 |
| | | | | | | | | | | $J_{3,4}$ = 3.0 | |
| Me | $CH_2Ph$ | H | H | Ph | 2.71 s | - | 3.93 td | 5.13 d | - | $J_{3,3a}$ = 7.0; | 211/69 |
| | | | | | | | | | | $J_{3,4}$ = 2.4 | |
| Me | Ph | H | H | COOMe | 2.80 s | - | 4.75 d | 5.75 d | - | $J_{3,4}$ = 3.0 | 15/69 |
| | | | | | | | | | | | 99/84 |
| Me | Ph | H | COOMe | H | 2.80 s | - | 4.75 d | - | under | $J_{3,5}$ = 3.0 | 15/69 |
| | | | | | | | | aromatics (7.1-7.4 m) | | | 99/84 |
| Me | Ph | H | CN | H | 2.91 s | - | 4.85 d | - | 7.20 d | $J_{3,5}$ = 1.8 | 127/73 |
| | | | | | | | | | | | 99/84 |
| Me | Ph | H | H | CN | 2.7 s | - | 4.70 d | 5.65 d | - | $J_{3,4}$ = 4.0 | 99/84 |

TABLE 2.39. *(Continued)*

| | | | | | Chemical shifts (δ) | | | | | Coupling | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | $R_{3'}$ | $R_4$ | $R_5$ | $R_2$ | $R_3$ | $R_{3'}$ | $R_4$ | $R_5$ | constants (Hz) | References |
| Me | COOMe | H | COOMe | H | 2.89 s | - | 4.33 q | - | 7.32 | | 19/69 |
| | | | | | | 3.69; 3.73 (OMe) | | | | | |
| Me | Me | H | Me | Ph | 2.77 s | | 3.66 qq | 1.86 d | | $J_{3,3a}$ = 6.2 | 35/74 |
| | | | | | | | | | | $J_{3,4a}$ = 1.1 | |
| Me | Ph | H | COOMe | Me | 2.89 s | 7.32 s | 4.89 | - | 2.29 d | | 175B/75 |
| | | | | | | | 3.60 (OMe) | | | | |
| Me | Me | Me | H | Ph | 2.73 s | 1.30 s | | 5.17 s | | | 35/74 |
| Me | Ph | Me | H | Ph | 2.58 s | - | 1.68 s | 5.48 s | - | | 11/76 |
| | | | | | | | 7.38 (2 Ph) | | | | |
| Et | Me | H | CN | Me | | 1.25 d | 3.95 q | - | 2.05 s | $J_{3,3'}$ = 6 | 157/84 |
| Et | Me | H | COOEt | Me | | 1.35 d | 4.10 q | - | 2.15 s | $J_{3,3'}$ = 7 | 157/84 |
| Me | Me | H | COMe | Me | | 1.20 d | 3.90 q | - | 2.20 s | $J_{3,3'}$ = 7 | 157/84 |
| Me | Me | H | COPh | Me | | 1.20 d | 4.10 q | - | 1.65 s | $J_{3,3'}$ = 6 | 157/84 |
| Et | Me | H | Cl | Me | | 1.25 d | 3.75 q | - | 1.85 s | $J_{3,3'}$ = 6 | 157/84 |
| Et | Me | H | Br | Me | | 1.25 d | 3.80 q | - | 1.90 s | $J_{3,3'}$ = 6 | 157/84 |
| $CMe_3$ | Ph | H | H | COOMe | 1.1 s | - | 5.22 d | 5.60 d | - | $J_{3,4}$ = 3.0 | 99/84 |
| | | | | | 7.1-7.4 (3-Ph); 3.75 s (OMe) | | | | | | |
| $CMe_3$ | Ph | H | COOMe | H | 1.1 s | - | 5.20 d | - | under | $J_{3,5}$ = 1.5 | 99/84 |
| | | | | | 3.50 s (OMe) | | | | aromatics (7.2-7.4) | | |
| $CMe_3$ | Ph | H | H | CN | 1.15 s | - | 5.30 d | 5.6 d | - | $J_{3,4}$ = 3.0 | 99/84 |
| | | | | | | | 7.4 m (3-Ph) | | | | |

$H_4$, $H_5$. The PMR absorption of the methyl group in position 2 usually appears in the range $\delta$ 2.6–2.9.

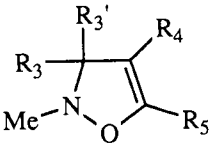
PMR data of some representative 4-isoxazoline derivatives have been collected in Table 2.39. As can be deduced from an inspection of the table, other things being equal, the 3-proton absorbs at about $\delta$ 3.7–4.1, the 4-proton at $\delta$ 4.65, and the 5-proton at about $\delta$ 5.0. Of course, the presence of other substituents alters these values more or less heavily. Thus a methoxycarbonyl or a phenyl group in the 3-position shifts the 3-proton to $\delta$ 4.5 or 4.7–4.9, respectively.

The shift caused by conjugation on the olefinic protons is of course far larger. Thus the presence of a phenyl or a methoxycarbonyl group in position 5 shifts the 4-proton to $\delta$ 5.1–5.3 or to $\delta$ 5.6–5.8, respectively. Even more dramatic is the change caused by a 4-methoxycarbonyl or a 4-cyano group on the 5-proton, which in these cases is shifted into the aromatic region ($\delta$ 6.9–7.6).

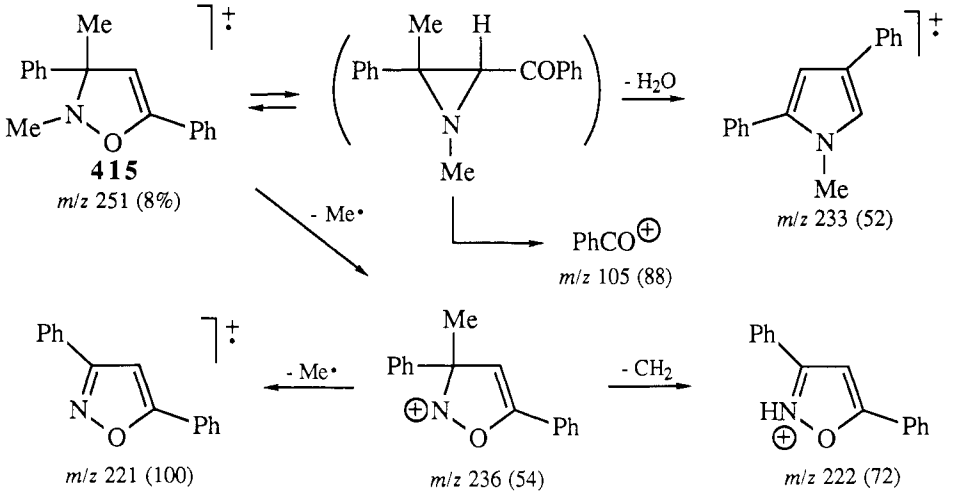
From the chemical shift values above and splitting of the corresponding signals, it is easy to assess regiochemical assignments. For example, 2-*t*-butyl-4-cyano- and its regioisomer 2-*t*-butyl-5-cyano-4-isoxazoline can promptly be distinguished and identified by examining their PMR spectra (see Table 2.37). It is worth noting that in this and other cases an allylic coupling between the 3- and 5-protons is always present with a constant of about 2.0 Hz. The coupling constant between the $CH_2$ in position 3 and the 4-proton is around 2.5–3.0 Hz, consistent with the dihedral angle calculated for a nearly planar molecule.

A limited number of *$^{13}$C-NMR spectra* of 4-isoxazoline derivatives are also known;[157B/82,194/82,66/84] the relevant data are reported in Table 2.40.

TABLE 2.40. $^{13}$C NMR DATA OF 4-ISOXAZOLINES

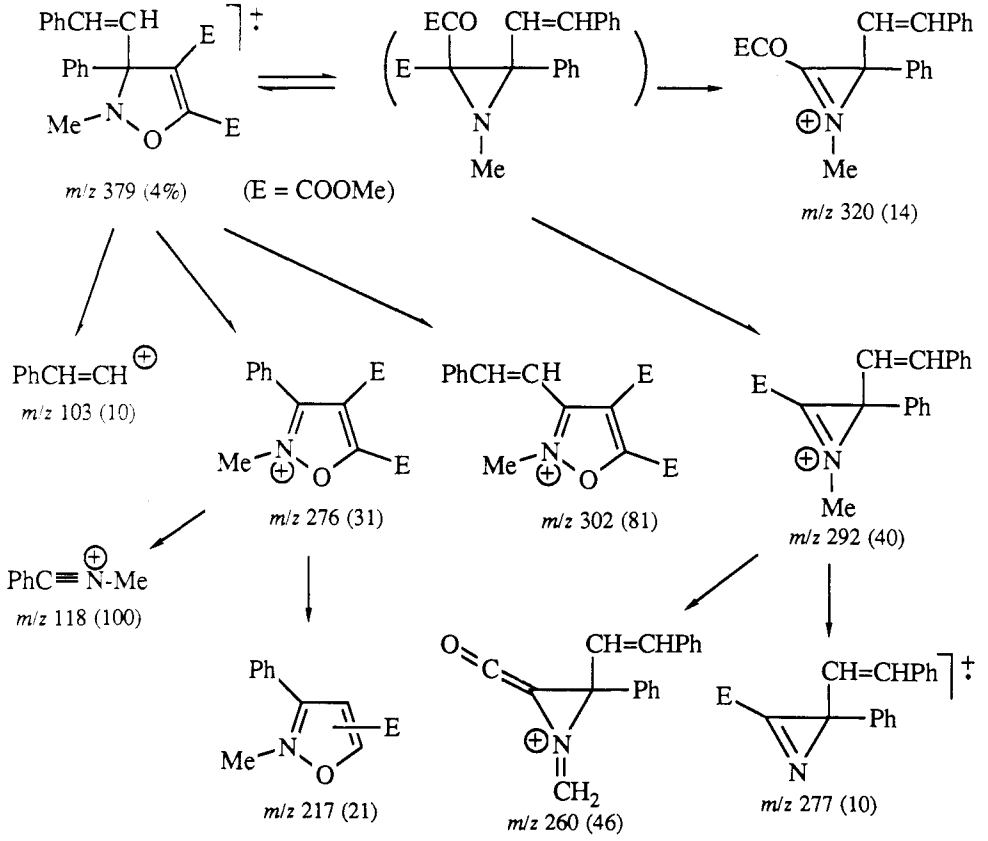


| $R_3$ | $R_3$' | $R_4$ | $R_5$ | $C_3$ | $C_4$ | $C_5$ | NMe | References |
|---|---|---|---|---|---|---|---|---|
| H | -CHPh-)$_2$ | COOMe | COOMe | 75.65 | 109.85 | 149.7 | 46.9 | 157B/82 |
| Ph | CH=CHC$_6$H$_4$OMe | COOMe | COOMe | 78.4 | 112.7 | 151.9 | 41.1 | 66/84 |
| 4-MeOC$_6$H$_4$ | CH=CHPh | COOMe | COOMe | 77.9 | 112.7 | 152.0 | 41.1 | 66/84 |
| Ph | CH=CHPh | COOMe | COOMe | 78.3 | 112.7 | 152.2 | 41.6 | 66/84 |
| Ph | CH=CHC$_6$H$_4$NO$_2$ | COOMe | COOMe | 78.4 | 111.7 | 152.6 | 41.6 | 66/84 |
| 4-NO$_2$C$_6$H$_4$ | CH=CHPh | COOMe | COOMe | 77.7 | 111.4 | 153.2 | 40.8 | 66/84 |




**Scheme 2.46**

The *mass spectra* of 4-isoxazolines have sometimes been reported in order to corroborate the structural assignments. Usually, in monocyclic 4-isoxazolines the molecular ion has a very low relative intensity (1–8%), thus reflecting the general instability of this class of compounds (Scheme 2.46). The tendency to aromatize is a striking feature in the mass spectrum of compounds **415**, whose base peak corresponds to the molecular ion of 3,5-diphenylisoxazole, formed as indicated in Scheme 2.46.[11/76] In addition to aromatization, a cyclo-reversion process is sometimes important, as in Scheme 2.47.[66/84]



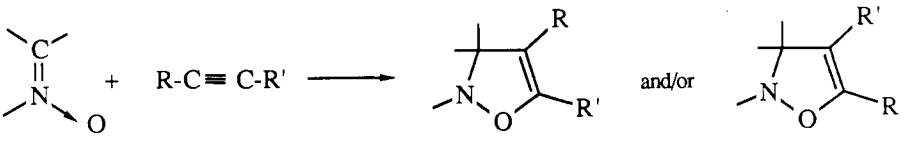

**Scheme 2.47**

## 2.5.2 Methods of Preparation

### *2.5.2.1 [CNO + CC] Cycloaddition Reaction*

The 1,3-dipolar cycloaddition of nitrones to CC triple-bond compounds is by

far the most important method for preparing 4-isoxazole derivatives and obeys the following general equation:




Of course, with asymmetrically substituted alkynes, regioisomerism can arise. The reaction falls within the wide framework of 1,3-dipolar cycloadditions, and reference is made to the general discussion outlined in § 2.2.2.2, particularly to the remarks relating to the cycloaddition of nitrones to alkenes in § 3.3.1.1a.

Some specific reviews on the 1,3-dipolar cycloadditions of CC triple-bond compounds should also be mentioned.[36B/73.265E/78] Some special features belonging to the cycloaddition of nitrones to triple-bond derivatives are emphasized here.

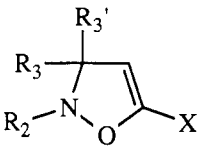
The limited solvent effect (slight acceleration by decreasing solvent polarity) measured for the reaction between *C*-phenyl-*N*-methylnitrone and cyanoacetylene[194/75] parallels similar behavior in the case of ethyl acrylate,[15C/69] thus supporting the concerted nature of the cycloaddition reaction.

Alkynes are usually better dipolarophiles than the corresponding alkenes, although quantitative kinetic data are scarce, undoubtedly owing to the instability of the 4-isoxazolines themselves. Nevertheless, it has been reported,[15C/69] for example, that methyl propiolate reacts with *C*-phenyl-*N*-methylnitrone 4 times faster than methyl acrylate, and that acetylenedicarboxylate reacts even 44 times faster than fumarate.

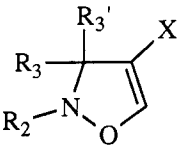
The reason for this increased reactivity relies prevalently on the easier distortion of the HCC angle in alkynes than in alkenes, which causes a drastic drop in alkyne LUMO energy on going toward the transition state. Since nitrones are relatively electron-rich 1,3-dipoles, and therefore HOMO (nitrone)–LUMO (dipolarophile) interaction controls reactivity, lowering LUMO (dipolarophile) energy increases the rate of the reaction.[90B/77.91/77.97B/79]

Interestingly enough, vinylacetylene cycloadds to nitrones to yield only 5-ethynylisoxazolidines:[76/62.136/65] the triple bond is totally unreactive here. Also remarkable is the activation promoted by a second ester group: acetylene dicarboxylate reacts 28 times faster than propiolate.[15C/69] This is a high value compared with other 1,3-dipoles.

As far as the regiochemistry of the cycloaddition is concerned, monosubstituted alkynes such as *n*-butyl- or phenylacetylene, react regiospecifically to give only the 5-monosubstituted 4-isoxazoline derivatives **416**. By contrast, highly electron-deficient alkynes, such as methyl propiolate or cyanoacetylene, yield either a mixture of the two possible regioisomers or the 4-monosubstituted derivative **417** exclusively. The results obtained with different nitrones are reported in Table 2.41 and have been nicely rationalized using FMO theory.



**416**



**417**

TABLE 2.41. CYCLOADDITION OF NITRONES TO METHYL PROPIOLATE AND CYANOACETYLENE

| Nitrone | (πIP)[a] | Ratio **416:417** in the cycloaddition with: CH≡CCOOMe | CH≡CCN | References |
|---|---|---|---|---|
| $CH_2$=N(*t*-Bu)-->O | (8.64) | 70 : 30 | 50 : 50 | 127/73 |
| PhCH=N(Me)-->0 | (8.58) | 42 : 58 | 0 : 100 | 15/69, 194/75, 127/73 |
| Dihydroisoquinoline *N*-oxide | (8.46) | 0 : 100 | 0 : 100 | 15/69, 90B/77 |
| MesitylCH=N(Me)-->O | (8.39) | 0 : 100 | 0 : 100 | 90B/77 |
| CyclopropylCH=N(Me)-->0 | (8.30) | 20 : 80 | | 289/83 |
| $(Cyclopropyl)_2$C=N(Me)-->O | (7.89) | 0 : 100 | | 289/83 |

[a]In eV; for C-conjugated nitrones the value $0.71IP_1 + 0.31IP_2$ is reported.

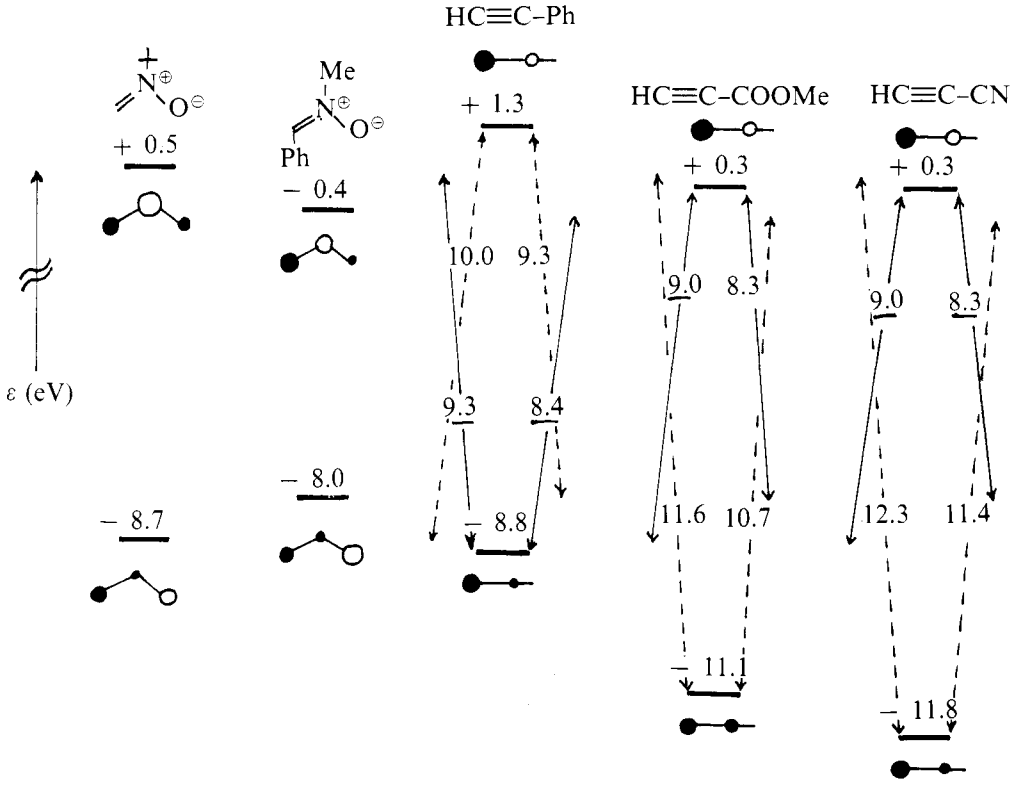


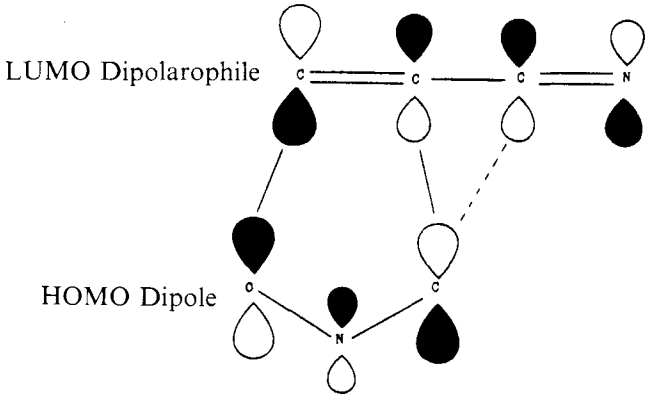

**Figure 2.5**. HOMO and LUMO energies of nitrones and alkynes.

As shown by Fig. 2.5, which represents the frontier orbital energies, as evaluated by photoelectron spectroscopy and $\pi \rightarrow \pi^*$ transition energies,[128B/73,128C/73,265E/78] with electron-rich alkynes the LUMO (nitrone)–HOMO (alkyne) interaction is dominant and leads to the 5-monosubstituted isoxazolines because of the larger coefficients on the nitrone carbon atom and on the $\beta$-carbon of the dipolarophile.

A "reversed" regiochemistry, leading to the 4-monosubstituted isomer, is required by the other FMO interactions [i.e., HOMO (nitrone)–LUMO (alkyne)]. As can be deduced from Table 2.41, the amount of the 4-regioisomer increases with decreasing values of nitrone $\pi$ ionization potentials, which correspond to raising the HOMO (nitrone) energy, and with increasing polarization of the HOMO toward the oxygen atom, effected by increasing the donor properties of the substituent at a nitrone carbon atom.[90B/77,289/83]

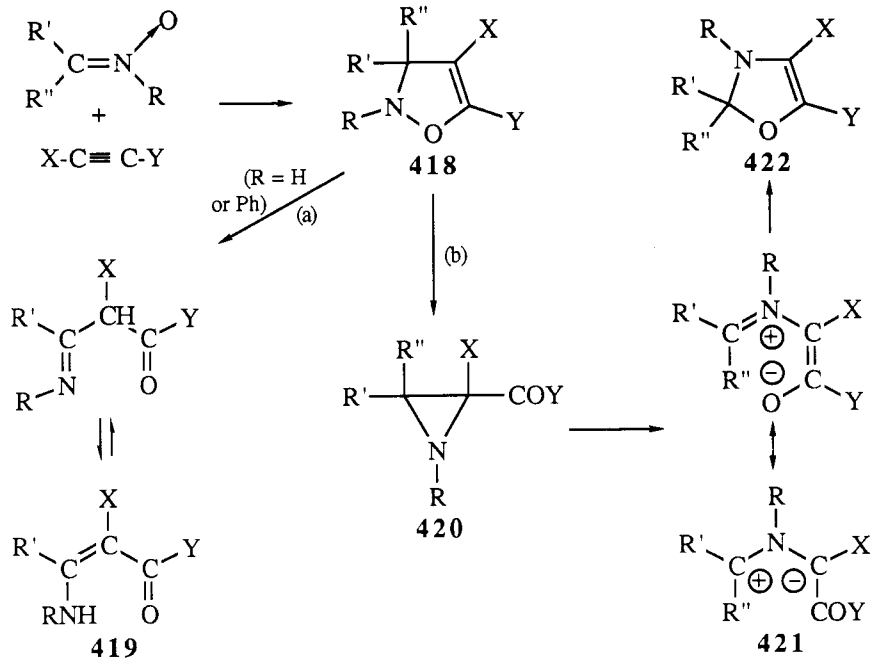
The higher "reversal" of regioselectivity in the cycloadditions of nitrones to electron-poor dipolarophiles compared with the corresponding cycloadditions of nitrile oxides (see § 1.3.2.1, pp. 184–185) derives from the higher HOMO (nitrone) energy and from the lower easiness of the nitrone HCN angle bending, which in the case of nitrile oxides causes a strong diminution of the dipole oxygen nucleophilicity.[91/77]

The higher "reversal" of regiochemistry in cycloadditions to alkynes than to alkenes has also been attributed to the intervention of a long-range attractive interaction between primary and secondary centers.[36/73,153B/78] For example, when cyanoacetylene reacts with *t*-butylnitrone (whose HOMO is practically unpolarized), a primary–secondary interaction between an end atom of the nitrone and the cyano carbon atom can arise. Because of the greater overlap granted at long distances by a carbon atom in comparison with an oxygen, this interaction would favor the 4-regioisomer:[153B/78]




As a result, acrylonitrile, whose bent structure prevents this interaction, gives only the 5-regioisomer, whereas cyanoacetylene yields a 1:1 mixture of the two regioisomers.[127/73]

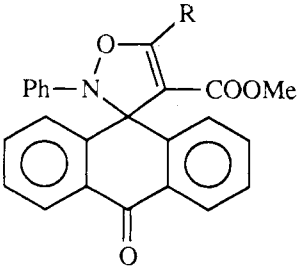
The cycloadducts from nitrones and alkynes are thermally more or less unstable (see also § 2.5.3.1). Therefore, it is advisable to perform the reaction under experimental conditions that are as mild as possible. Inert solvents such as benzene, diethyl ether, or dimethylformamide, and reaction temperatures from 0 to 80–90°C, have been employed. Even under mild conditions, the 4-isoxazolines often could not be isolated and their decomposition products have been obtained directly. The main products derived from further transformation of the 4-isoxazolines (**418**) are summarized in Scheme 2.48.



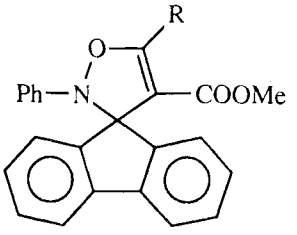

**Scheme 2.48**

The stability of the 4-isoxazolines depends on the substitution pattern, and some general trends can be recognized, although no systematic study has been performed up to now. *N*-Alkyl-substituted nitrones, such as *t*-butylnitrone or *C*-phenyl-*N*-methylnitrone, and monosubstituted alkynes, such as phenylacetylene, 3-methylbutyn-3-ol, methyl propiolate, and cyanoacetylene, give rise to stable 4-isoxazolines.[113/68,15/69,19/69,19/70,127/73,86/75,194/75,90B/77,206/78] Some carbohydrate nitrones have been used.[81/72,11/74] Disubstituted triple-bond compounds such as methyl tetrolate,[41B/75] phenylpropiolate,[41B/75,30/79] or dimethyl acetylenedicarboxylate[113/68,19/69,18/79] also undergo facile cycloaddition to the same nitrones, the former two esters yielding regiospecifically the 4-isoxazoline **418** carrying the ester group in the 4-position.

Anthraquinone or fluorenone imine-*N*-oxides normally cycloadd acetylenic esters, forming spiro-4-isoxazoline **423** or **424**, respectively.[113/81] Benzoquinone imine *N*-oxides yield completely different products.

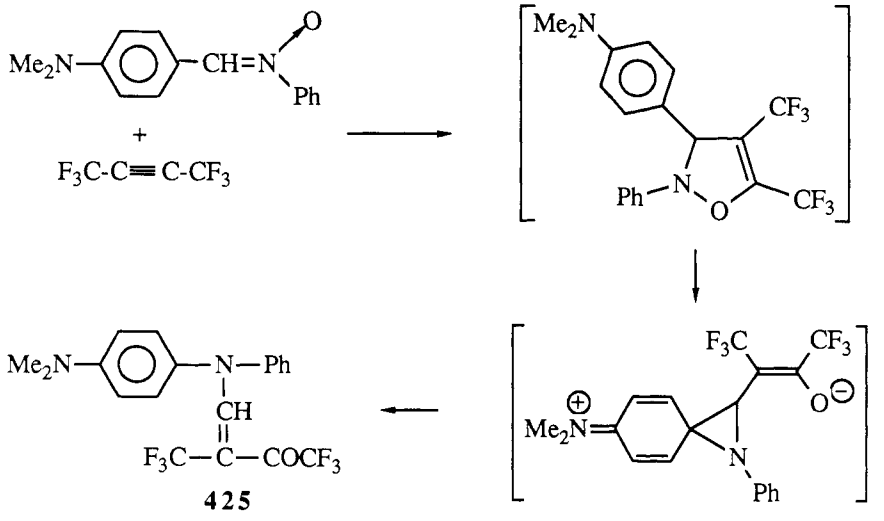



**423**




**424**

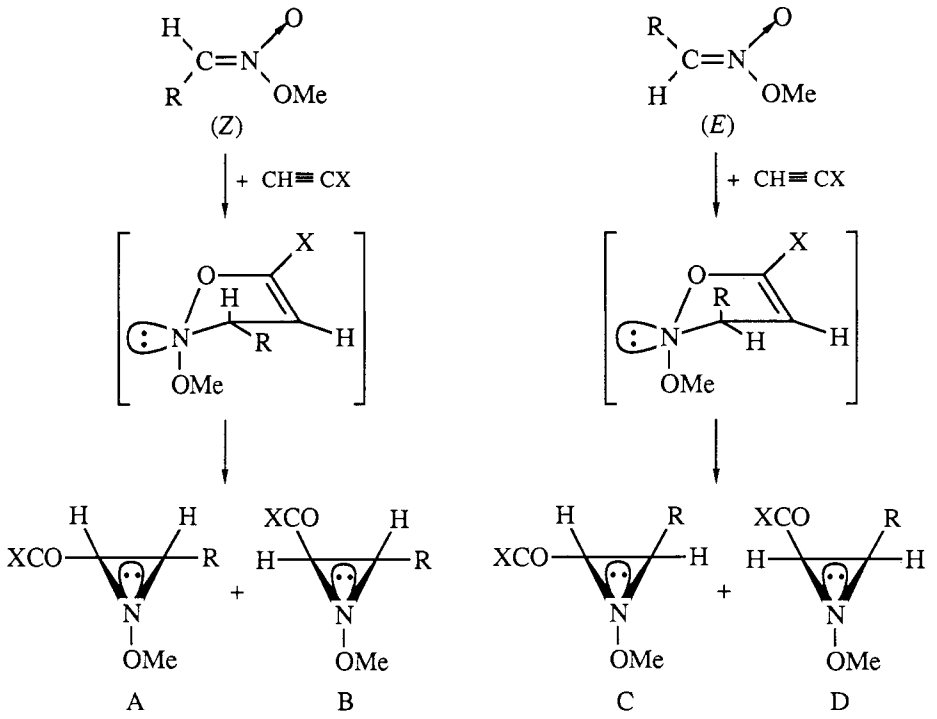
*C*,*N*-Diarylnitrones seem to furnish stable 4-isoxazolines only in cycloaddition with dialkylamino-substituted triple-bond compounds; structure of 5-dialkylamino regioisomers have been assigned.[2/66,196/69] With other acetylenic dipolarophiles (methyl propiolate or phenylpropiolate,[41B/75] perfluoro-2-butyne,[95/77] diacetylacetylene[237/83]) almost invariably the corresponding 4-oxazolines of type **422** are obtained (through decomposition pathway b of the scheme). Cycloaddition of *C*-benzoyl-*N*-phenylnitrone to *n*-butyl- or phenylacetylene led instead to 2-acylaziridines of type **420**.[41B/75] A different rearrangement pattern (i.e., a 1,2-shift of the 3-substituent to the ring nitrogen) is presumably involved in the reaction of *C*-*p*-dimethylaminophenyl-*N*-phenylnitrone with perfluoro-2-butyne, which yields the enamine **425** (Scheme 2.49).[95/77]




**425**

**Scheme 2.49**

*N*-Mesitylnitrone reacts with dimethyl acetylenedicarboxylate to give the corresponding acylaziridine **420**;[113/68] by contrast, when the dipole is a five-membered cyclic nitrone,[33/66,268B/80] pathway a of the scheme is privileged, even when R″ is a phenyl. The behavior of cyclic nitrones with alkynes to give condensed 4-isoxazoline compounds or their transformation products is examined in Part 2 of this work. Particularly striking is the possibility, in that case, of sometimes isolating the betaines **421**, owing to the stabilization induced by suitable cyclic moieties.




| R | X | A : B | C : D |
|---|---|---|---|
| CN | COPh | 96 : 4 | 19 : 81 |
| CN | COMe | 96 : 4 | 20 : 80 |
| COOMe | COPh | 94 : 4 | 36 : 64 |
| COOMe | COMe | 88 : 12 | 38 : 62 |
| COOMe | COOMe | 75 : 25 | 45 : 55 |

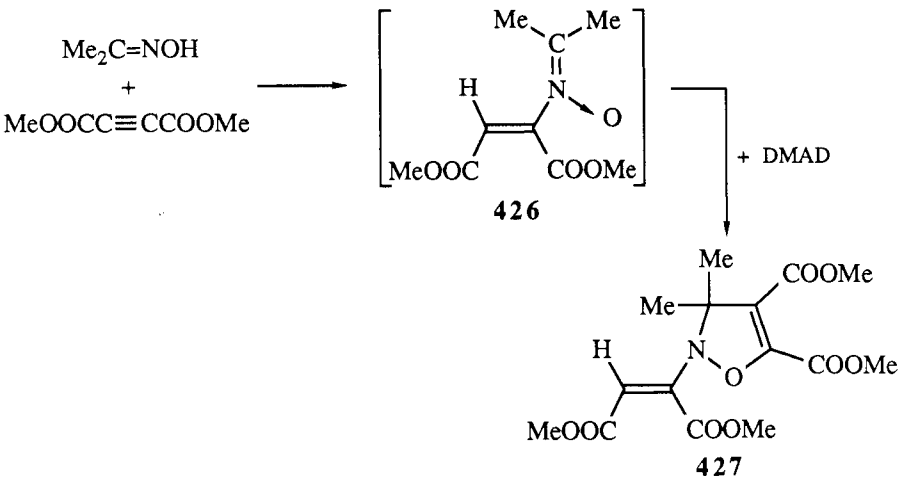
D (R = CN; X = COPh) —110°, refluxing toluene, for 5 h→ B + C + D (49%) (16%) (35%)

**Scheme 2.50**

Nitronic esters promptly react at low temperature with alkynes to give the corresponding *N*-methoxyacylaziridines (**420**: R = $OCH_3$) in good yields.[94/66,70/68] The intermediate 2-methoxy-4-isoxazoline could never be evidenced. The reaction is reported to be regiospecific with monosubstituted

alkynes, the oxygen atom of the nitronic ester always becoming linked to the substituted carbon of the alkyne. The stereochemistry has been studied utilizing pairs of *Z*/*E* isomeric methyl nitronates, and the cycloaddition has been found to be fully stereospecific, each starting isomer leading to different invertomers of the acylaziridines under kinetic control (Scheme 2.50).[118B/75,116/77] Finally, it should be mentioned that at least one example of intramolecular cycloaddition of a ketonitrone to a triple bond is known:[114/70] however, the presumed bicyclic 4-isoxazoline readily adds *in situ* one molecule of ethanol used as solvent, giving an isoxazolidine derivative.

A further variation of the nitrone 1,3-dipolar cycloaddition is represented by the reaction of some ketoximes (e.g., acetone oxime) with dimethyl acetylenedicarboxylate: at room temperature in DMSO a 1:2 cycloadduct is produced in 63% yield. Its structure (**427**) implies an initial nucleophilic attack of the oxime to the triple bond with the formation of an intermediate nitrone (**426**) and subsequent cycloaddition to a second molecule of the acetylenic ester:[4/67,18/69]




For a synthesis of β-lactams presumably involving an intermediate formation of 4-isoxazoline cuprous derivatives, see § 2.2.3.3, p. 584.

### *2.5.2.2 [CCC + NO] Process*

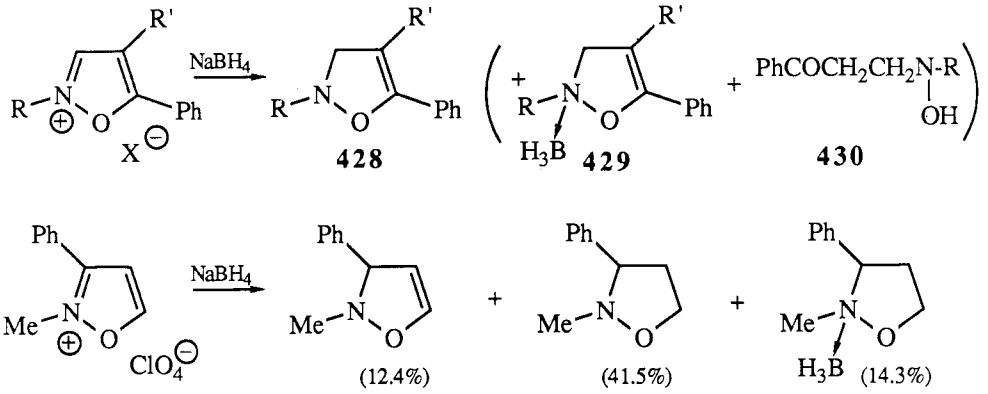
The oximation reaction of α,β-ethylenic ketones is far more complicated than the oximation of α-acetylenic ketones and aldehydes, and reference is made to § 2.2.2.1, for a complete treatment. 2-Isoxazoline derivatives are the most commonly isolated cyclized products, together with oximes and hydroxylamines. The pH of the reaction and the ratio of the reactants greatly influence the nature and composition of the reaction mixture.

Nevertheless, some claims on the formation of 4-isoxazolines have appeared in the literature from time to time. The oximation of mesityl oxide has been studied in some detail.[2/898,2B/899,39B/59,23/65,193/71,21/72,26/73] The structure of one of the compound obtained by oximation in the presence of sodium methoxide, originally[2/898] proposed as 3,3,5-trimethyl-4-isoxazoline, has subsequently been verified as being 3,5,5-trimethyl-2-isoxazoline.[21/72] More recently, the presence of the former compound and of other bi- and trisubstituted 4-isoxazolines in the reaction mixture obtained by oximation of mesityl oxide[85/75] and other α,β-ethylenic ketones[98/74] under neutral conditions has been claimed. In an alkaline medium the yields are reported to be far lower. However, no spectroscopic proof of the alleged structure is available.

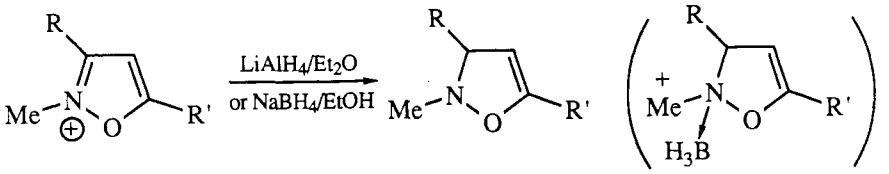
### *2.5.2.3 Syntheses from Isoxazole or Isoxazolidine Derivatives*

As already mentioned, selective reduction of the isoxazole C=N bond is always preceded by hydrogenolysis of the weak N–O bond (see § 1.4.3.1), but formation of the isoxazolium salts offers an interesting way to circumvent this difficulty. As described in § 1.4.6.1, pp. 309–318, isoxazolium salts usually undergo facile ring cleavage with nucleophiles, especially when the 3-position is unsubstituted. Nevertheless, under suitable circumstances, addition occurs and the nature of the product obtained depends strongly on the substitution pattern of the starting material.

Treatment of 4-methyl-2,5-diphenylisoxazolium perchlorate with sodium borohydride is reported to give 4-methyl-2,5-diphenyl-4-isoxazoline (**428**:R = Ph; R′ = Me) with excellent yield; 4-unsubstituted 2-alkylisoxazolium salts furnish a mixture of the expected 4-isoxazolines (**428**) and of their borane complexes (**429**), together with variable amounts of β-hydroxyaminopropiophenones (**430**), produced by ring cleavage.[36/74] The reduction of 5-unsubstituted isoxazolium salts is not as straightforward, and besides minor amounts of 4-isoxazoline derivative, 3-isoxazolines and isoxazolidines (i.e., the products of their further reduction), can be obtained, as shown here:[36/74]

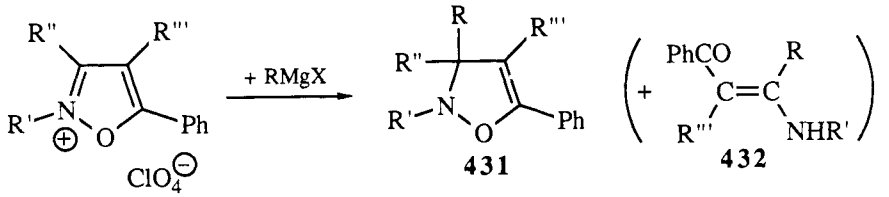


Fair to good yields of 2-methyl-3,5-disubstituted 4-isoxazolines are regularly attained by reduction of the corresponding isoxazolium salts with lithium aluminum hydride or sodium borohydride; occasionally, accompanying borane complexes are easily converted into 4-isoxazolines by treatment with triethylamine or ether. The method has fairly general applicability.[269/82]



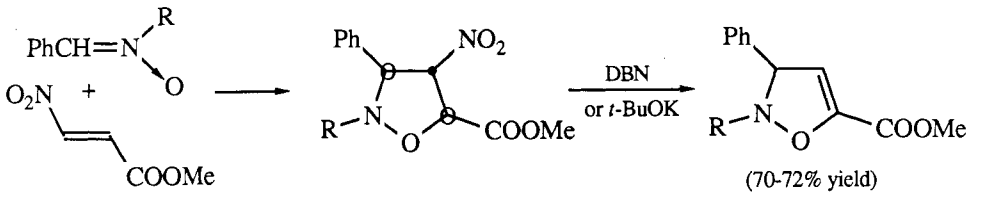

When the isoxazolium salt carries an electron-withdrawing substituent in the 4-position, reduction with complex metal hydrides is far from being so straightforward. The reaction acquires preparative usefulness only with the 4-halogen derivatives, since yields up to 45–55% of 4-isoxazolines are attained when sodium borohydride is used. With cyano, ethoxycarbonyl, or acyl groups, mixtures of 3- and 4-isoxazolines are obtained, whereas the presence of a 4-nitro group or the use of lithium aluminum hydride with 4-acyl-substituted derivatives drives the reduction toward the corresponding isoxazolidines.[157/84]

An improved synthetic procedure involves the reaction of 5-phenyl- or 3-methyl-5-phenylisoxazolium perchlorates with Grignard reagents.[211/69.35/74] Especially with benzyl (or allyl)-magnesium chloride, exclusive formation and high yields of the corresponding 4-isoxazoline (**431**) are obtained; in other cases more or less remarkable amounts of ring-cleaved enamino ketones (**432**) are also produced:[35/74]

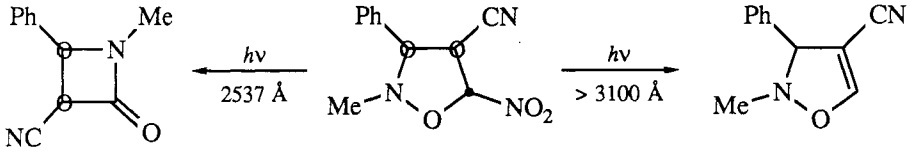



It should be noted that 5-unsubstituted isoxazolium salts react with Grignard reagents, giving 3-isoxazolines (see § 2.4, pp. 622–623).

Elimination reactions of isoxazolidines, suitably substituted in the 4- or 5-position, are still inadequately studied. Base-promoted elimination of nitrous acids from 4-nitro-3-phenylisoxazolidine-5-carboxylates, easily attainable through 1,3-dipolar cycloaddition, smoothly yields the expected 4-isoxazoline-5-carboxylates:[99/84]




On the contrary, analogous treatment of the isomeric 5-nitro-4-carboxylates or of the 4,5- or 5,4-cyanonitroisoxazolidines furnishes open-chain products and/or β-lactam derivatives. As better illustrated in § 3.4.10.3, pp. 765–767, thermolysis or photolysis of the same compounds resulted mainly in the formation of β-lactams. However, it is remarkable that irradiation of *trans*-4-cyano-5-nitro-*cis*-3-phenyl-2-methylisoxazolidine with light of wavelength > 3100 Å gives rise to high yields of 4-cyano-2-methyl-3-phenyl-4-isoxazoline:[99/84]

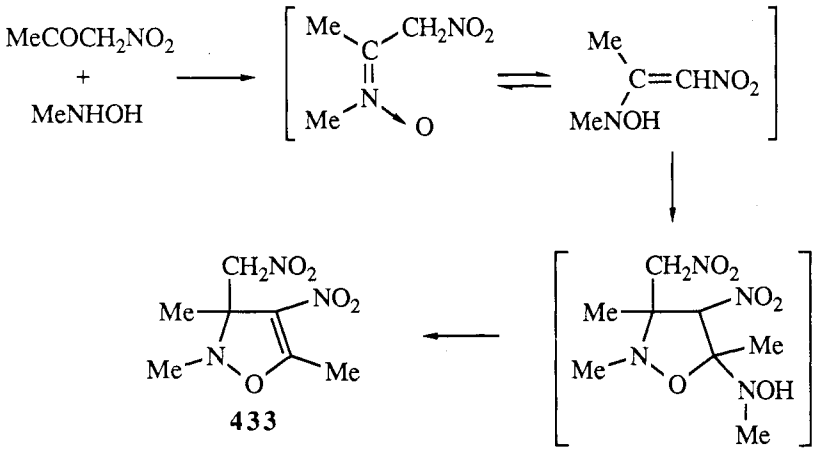



2,3-Dimethyl-3,5-diphenyl-4-isoxazoline has been isolated as a by-product during the study of the Reformatzky reaction on *C*-phenyl-*C*,*N*-dimethylnitrone; elimination of *N*-methylhydroxylamine from the nitrone dimer has been invoked.[11/76] Of little preparative value is the smooth elimination of ethanol from some 5-ethoxyisoxazolidine derivatives by treatment with concentrated sulfuric acid to give the same 4-isoxazolines from which they had been originated.[41B/75]

### *2.5.2.4 Miscellaneous Methods*

By contrast with the easy cycloaddition reaction observed with free alkynes, nitrones react with phenylethynylmagnesium bromide to yield the open-chain acetylenic substituted hydroxylamine. Treatment of the latter compounds with sodium methoxide is reported in one case to promote cyclization to the corresponding 4-isoxazoline.[81/72]

Reaction of nitroacetone with *N*-methylhydroxylamine furnishes, instead of the expected ketonitrone, the 4-isoxazoline **433** in moderate yields. Cycloaddition of the ketonitrone with its tautomer enehydroxylamine, and subsequent elimination of *N*-methylhydroxylamine, would explain the formation of **433**:[41/83]




**433**

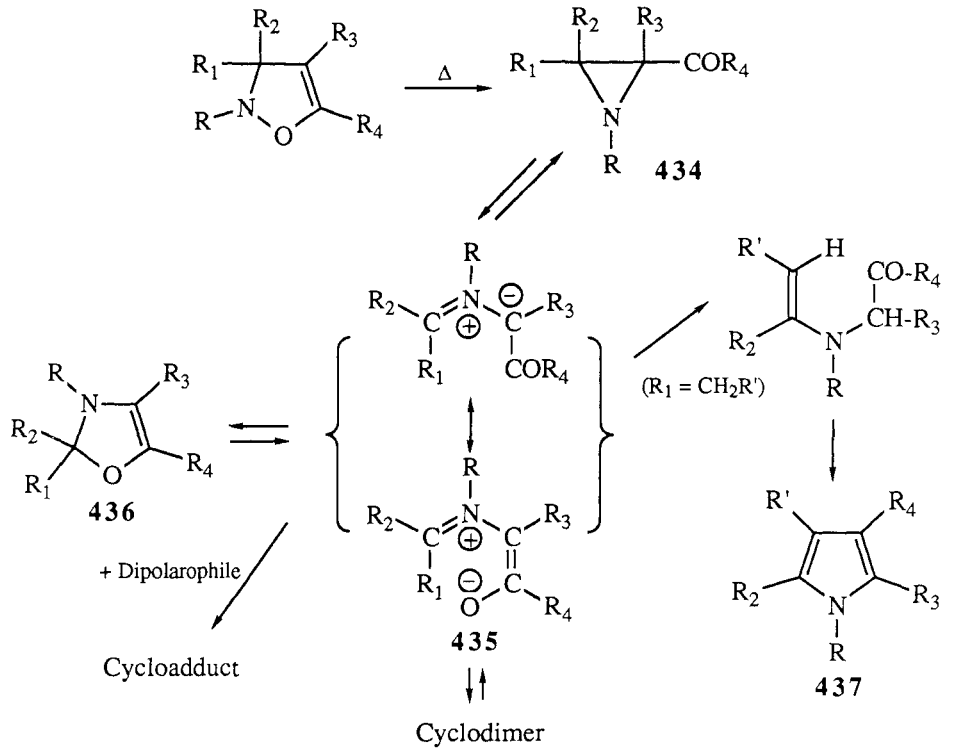
The reaction could not be extended by analogy to other compounds: for example, reaction of β-keto esters with N-substituted hydroxylamines gave pyrrole and pyrroline derivatives.

## 2.5.3 Chemical Properties

### *2.5.3.1 Thermolysis*

As already mentioned (see § 2.5.2.1, pp. 634–637), 4-isoxazolines are thermally more or less unstable, and several examples of cycloaddition reactions between nitrones and triple bond compounds have been illustrated, where the decomposition products are obtained directly. The steps involved have been thoroughly studied by investigating the behavior of stable 4-isoxazolines on heating in inert solvents. The most commonly encountered final products of the thermolytic process are 2-acylaziridines (**434**), azomethine-ylids (**435**), 4-oxazolines (**436**), and pyrrole derivatives (**437**). Scheme 2.51 summarizes the conceivable sequence of their formation and the mechanistic rationalization.

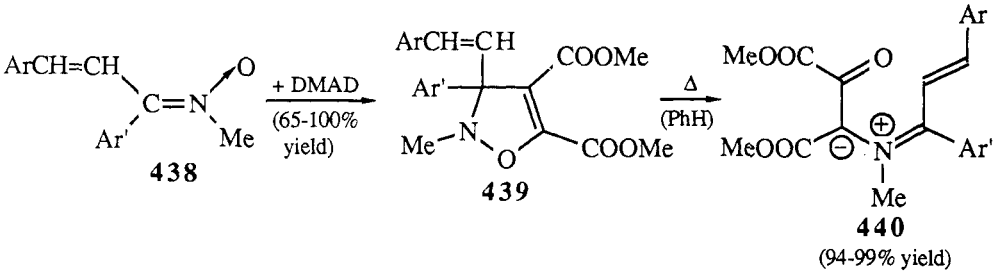
The first step of the thermolysis is a valence rearrangement of the 4-isoxazoline to the thermodinamically more stable 2-acylaziridine. This rearrangement can be visualized either as a concerted sigmatropic process or (less likely) as a two-step sequence involving a diradical intermediate.[211/69,41B/75] Acylaziridines can be isolated only when the starting 4-isoxazolines are little substituted on the ring carbon atoms. For example, 3-unsubstituted 5-phenyl-4-isoxazolines furnish substantial yields of 2-benzoylaziridines.[36/74] The temperature can be very critical: cycloaddition of *N*-*t*-butylnitrone with 3-methylbutyn-3-ol at 74°C produces the 4-isoxazoline, which rearranges to the corresponding acylaziridine at 78°C.[113/68]




**Scheme 2.51**

Acylaziridines are usually not isolable when the starting 4-isoxazoline is more heavily substituted. 4-Isoxazolines, derived from *C*-aryl-*N*-alkyl- or from *C*,*N*-diarylnitrones, directly isomerize to 4-oxazolines (**436**) under heating at variable temperatures (from 60 to 165°C, according to the substitution pattern).[113/68,41B/75,24/76,30/79] The mechanistic pathway involves a conrotatory ring opening of the 2-acylaziridine to the azomethine-ylid (**435**), followed by a 1,5-dipolar cyclization to the stabilized oxazoline ring.

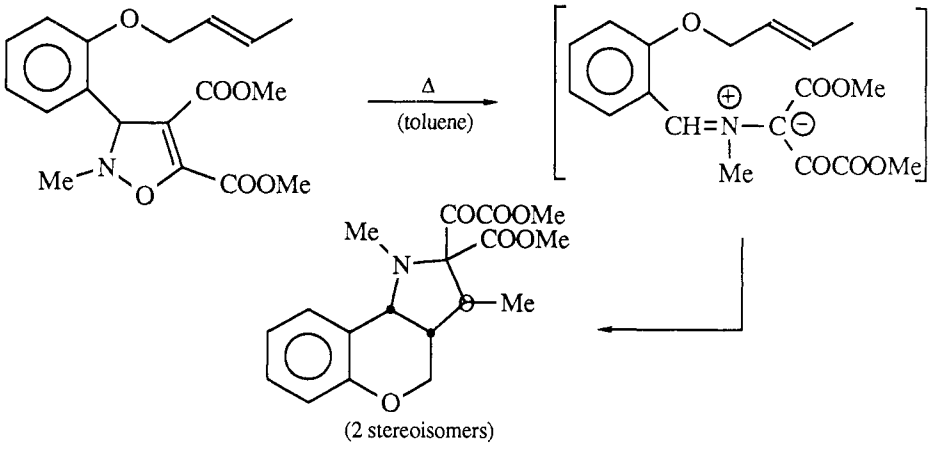
In the presence of suitably stabilizing substituents, the azomethine ylids **435** can be isolated as reasonably stable orange-red compounds. For example, the α,β-unsaturated nitrones **438** cycloadd dimethyl acetylenedicarboxylate to yield the heavily substituted 4-isoxazolines **439**, which thermolyze to the stable solids **440**:[66/84]



However, stable azomethine ylids are more frequently isolated from bicyclic or polycyclic 4-isoxazolines (see Part 2 of this work). Sometimes their intermediacy can be demonstrated either by the formation of cyclodimers, having a piperazine structure, or by trapping experiments with ethylenic or acetylenic dipolarophiles.

Following a well-known process,[168B/66,73B/67] cycloadducts having a pyrrolidine or a pyrroline structure (or their further transformation products) can be achieved in the latter case. Obtaining the same cycloadducts by heating either the corresponding 2-acylaziridines or the 4-oxazolines or the piperazine cyclodimers demonstrates that all these products are in equilibrium with the azomethine ylid.[41B/75,40/84]

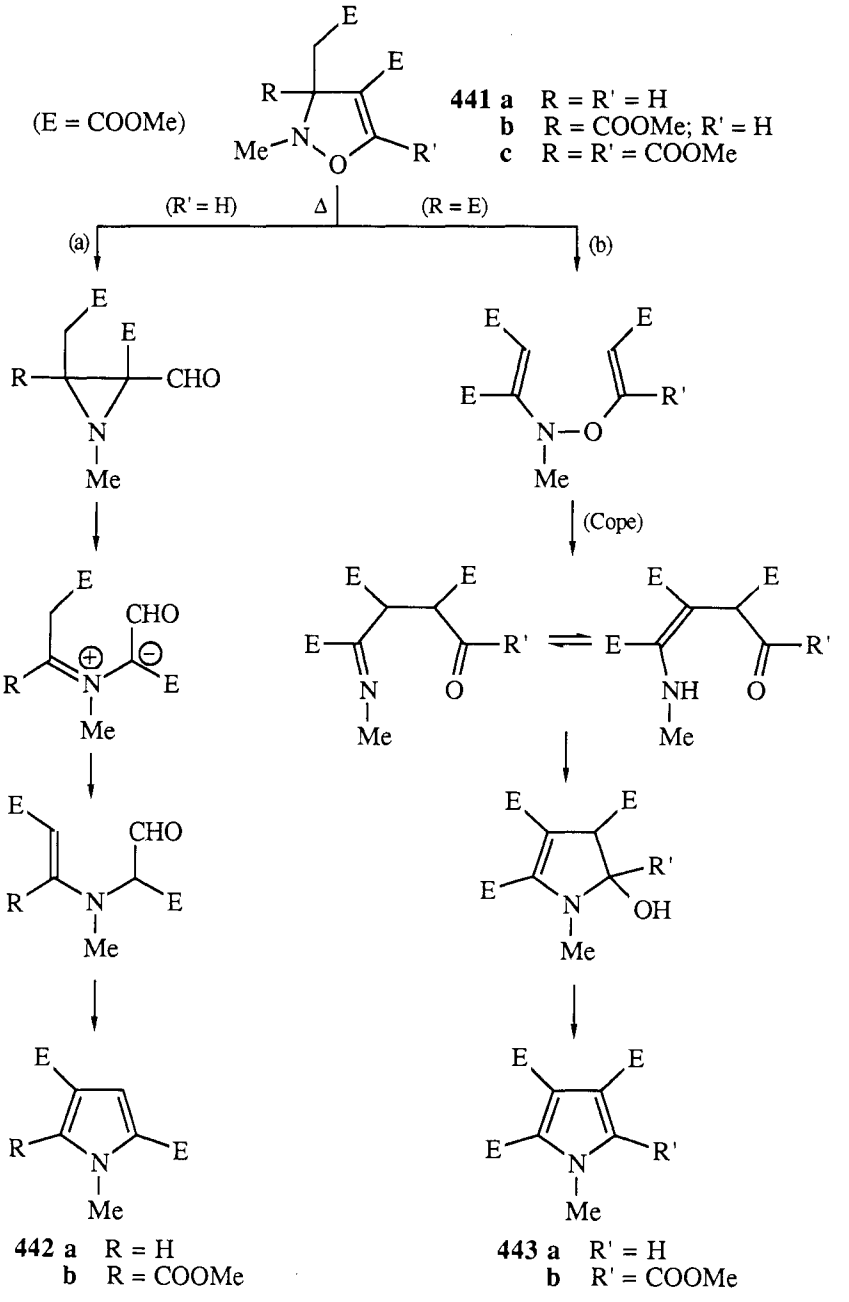
An intramolecular trapping process can be observed with 4-isoxazoline derivatives having a double bond in a suitable position of the side chain, as shown by the following example:[17/84]




It should be noted that a 4-isoxazoline 3,4,5-triester and 3,4-diester are thermally unstable and furnish dimers of unidentified structure.[19/69]

When the 4-isoxazoline bears a methylene group in position 3$\alpha$, the intermediate azomethine ylid usually evolves toward a pyrrole derivative of structure **437** through tautomerization to an amino ketone and subsequent cyclizing dehydration.[211/69,35/74,86/75] For example, heating a methanolic solution of 2-*t*-butyl-3-methyl-5-phenyl-4-isoxazoline in a sealed tube at 120°C resulted in a 45% yield of *N*-*t*-butyl-3-phenylpyrrole.[86/75] Analogously, heating in refluxing xylene transforms 2-methyl-3-benzyl-5-phenyl-4-isoxazoline into 1-methyl-3,4-diphenylpyrrole in 59% yield.[35/74]

A competitive different mechanism of ring opening must be taken into account with some 4-isoxazolines of general formula **441**, carrying three or four methoxycarbonyl groups as substituents in positions 3 to 5, as Scheme 2.52 illustrates.

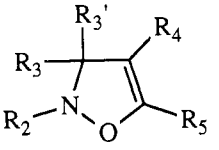

(E = COOMe)
441 a R = R' = H
b R = COOMe; R' = H
c R = R' = COOMe
(R' = H)
Δ
(R = E)
(a)
(b)
(Cope)
442 a R = H
b R = COOMe
443 a R' = H
b R' = COOMe

**Scheme 2.52**

Whereas **441a** thermolyzes at 80°C to the expected dimethyl 1-methylpyrrole-2,4-dicarboxylate **442a**, heating of the little stable triester **441b** in refluxing toluene yields a mixture of the two isomeric pyrroltricarboxylates **442b** and **443a**. The latter compound cannot arise from the usual acylaziridine–azomethine ylid rearrangement route, but must derive from a $C_3$–$C_4$ bond scission, followed by a hetero-Cope rearrangement, imine–enamine tautomerism, ring closure, and dehydration. In the case of **441c**, this mechanism has been substantiated by isolation of the intermediate enamino ketone, which easily cyclizes to the pyrroletetracarboxylic ester **443b**.[19/69,19/70,206/78]

The ease of thermal rearrangement depends sharply on the substitution pattern. As a general rule, 4-substituted 5-unsubstituted isoxazolines rearrange more easily than do 4-unsubstituted 5-substituted isomers, and this fact has

TABLE 2.42. THERMOLYSIS OF MONOCYCLIC 4-ISOXAZOLINES

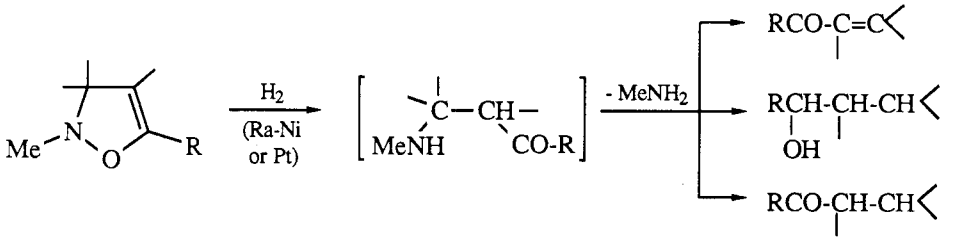



| $R_2$ | $R_3$ | $R_{3'}$ | $R_4$ | $R_5$ | Exper. conditions | Product | Yield (%) | References |
|---|---|---|---|---|---|---|---|---|
| $CMe_3$ | H | H | H | $CMe_2OH$ | 78° (2 h) | 2-acylaziridine | | 113/68 |
| Me | H | H | H | Ph | xylene, 110° (2 h) | 2-acylaziridine | 65.4 | 36/74 |
| Ph | H | H | Me | Ph | ether, r.t. (overnight) | 2-acylaziridine | 93 | 36/74 |
| 2,4,6-$Me_3C_6H_2$ | H | H | COOMe | COOMe | r.t. | 2-acylaziridine | | 113/68 |
| Me | Ph | H | COOMe | Ph | *o*-$Cl_2C_6H_4$,reflux or 135-140° | 4-oxazoline | 94 | 41B/75, 30/79 |
| $CMe_3$ | H | H | COOMe | COOMe | 80°, dark | 4-oxazoline | | 113/68 |
| $CMe_3$ | Me | H | H | Ph | methanol, 120° (1 h) | pyrrole der. | 45 | 86/75 |
| Me | $CH_2Ph$ | H | H | Ph | xylene, reflux (2.5 h) | pyrrole der. | 59 | 35/74 |
| Me | Me | Me | H | Ph | xylene, reflux | pyrrole der. | 51 | 35/74 |
| Ph | $CH_2Ph$ | Me | Me | Ph | xylene, reflux | pyrrole der. | 61 | 35/74 |
| Me | $CH_2COOMe$ | H | COOMe | H | benzene, reflux (12 h) | pyrrole der. | 88; 58 | 206/78, 19/70 |
| Me | $CH_2COOMe$ | COOMe | COOMe | H | toluene, 110° (4 h) | pyrrole der. | 50 | 19/69, 19/70 |
| Me | $CH_2COOMe$ | COOMe | COOMe | COOMe | benzene, reflux (1 h) | enaminoketone | 100 | 19/69 |

helped in assessing the regiochemistry of the cycloaddition reaction.[127/73] A certain degree of stability seems to be introduced by a 5-dialkylamino group[2/66,196/69] or by a 4,5-diphenyl substitution pattern.[175B/75] As a summary, Table 2.42 presents some significant examples of the several different products obtained by thermolysis of monocyclic 4-isoxazolines.

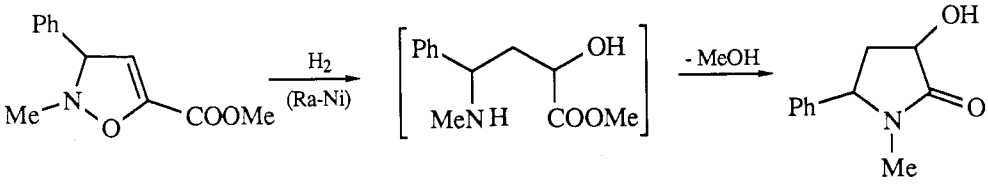
### *2.5.3.2 Other Ring-Opening Reactions*

Catalytic hydrogenation of 4-isoxazolines always induces primary hydrogenolysis of the weak N–O bond to give a β-amino ketone, which is promptly transformed into the final product, usually by elimination of one molecule of amine.[18/69,19/70,35/74,36/74,41B/75] From *N*-methyl-substituted 4-isoxazolines, the following products can be obtained:




For example, 2-methyl-3-phenyl-4-isoxazoline hydrogenolyzes to cinnamaldehyde,[36/74] 2,3,4-trimethyl-5-phenyl-4-isoxazoline to a mixture of α-ethylidenepropiophenone and α-methylbutyrophenone,[35/74] and methyl 2-methyl-3,5-diphenyl-4-isoxazoline-4-carboxylate to methyl 2-benzyl-3-hydroxy-3-phenylpropionate.[41B/75]

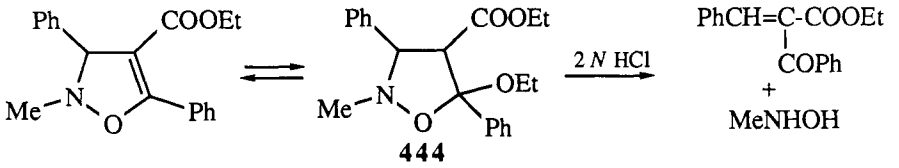
When a carboxylic ester group is present in position 5, a lactamization can occur prior to elimination, as in the following example:[15/69]




Monocyclic 4-isoxazolines are fairly stable toward metal hydride attack: from 2,5-dimethyl-3-phenyl (or 2-methyl-3,5-diphenyl)-4-isoxazoline-4-carboxylate, 51% and 72% yields of the corresponding 4-isoxazoline carbinols are obtained by treatment with $LiAlH_4$.[41B/75]

### *2.5.3.3 Addition Reactions to the CC Double Bond*

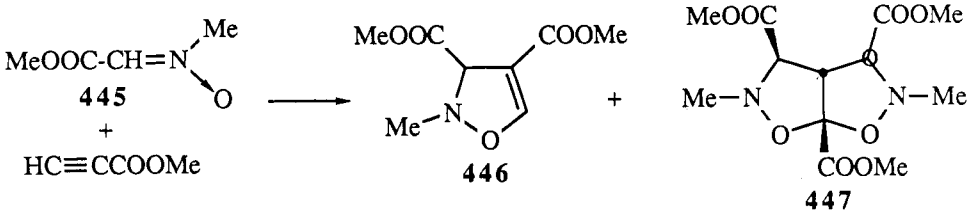
Additions of water or alcohols to the 4-isoxazoline double bond are known in some cases. Addition obviously is regiospecific, 5-hydroxy- or 5-alkoxy-isoxazolidines always being obtained.[41B/75] Under certain circumstances these compounds are unstable, and the products of their further conversion are directly isolated:




**444**

For example, the ethanol adduct **444** has been obtained,[41B/75] which converts back to the starting 4-isoxazoline in concentrated sulfuric acid. By contrast, heating in 2 *N* hydrochloric acid provokes ring cleavage.

The 1,3-dipolarophilicity of the 4-isoxazoline double bond has been evidenced in one instance. Cycloaddition of nitrone **445** to methyl propiolate in ether at room temperature yielded a mixture of an unstable 1:1 cycloadduct **446**, having the methoxycarbonyl group in the 4-position, and of a stable 2:1 cycloadduct, for which structure **447**, arising from the cycloaddition of a second molecule of nitrone to the 5-methoxycarbonyl regioisomer, was asserted:[19/69]



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Paolo Grünanger, Paola Vita-Finzi
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CHAPTER 3

# Isoxazolidines (Tetrahydroisoxazoles)

## 3.1 INTRODUCTION

The parent isoxazolidine (this is the nomenclature used in *Chemical Abstracts*) can also be named 1,2-oxazolidine or tetrahydroisoxazole. Substitution follows the normal numbering of the isoxazole (or 1,2-oxazole) ring. Condensed systems will be considered in an appropriate chapter of Part 2 of this work. The monocyclic isoxazolidines, containing the completely hydrogenated isoxazole ring, cannot normally be prepared by reduction or hydrogenation of the corresponding isoxazoles or isoxazolines, because cleavage of the N–O linkage usually occurs first, leading to acyclic compounds.

Although the first isoxazolidine derivatives were known in 1918,[1/18] and the parent compound (i.e., isoxazolidine itself) was first prepared in 1942,[10B/42] it was not until the 1960s that this nucleus became easily available through discoveries of the cycloaddition of nitrones to olefins by Brown,[48/60] Delpierre,[49/60] and Huisgen[56/60] and of the intramolecular cyclization of unsaturated nitrones by Le Bel.[43/59] This synthetic pathway follows the general pattern of 1,3-dipolar cycloaddition,[59/61.4B/63.4C/63] already illustrated for the synthesis of isoxazoles and isoxazolines, respectively (see §§ 1.3.2 and 2.2.2.2). Since then more than 300 papers have appeared on the synthesis and chemical behavior of isoxazolidines. An excellent review, covering the literature up to May 1974, has been devoted to the chemistry of isoxazolidines,[9/77] whereas specific aspects have been covered in detail by other reviews: the cycloaddition of nitrones to olefins,[28/64.175B/75] the cycloaddition of nitronic esters to olefins,[212B/69.93B/79] and the synthesis of alkaloids through isoxazolidines.[1/79]

## 3.2 PHYSICOCHEMICAL PROPERTIES

Sections on physicochemical properties are included in the review of the chemistry of isoxazolines.[9/77]

### 3.2.1 Infrared Spectra

The infrared spectra are not very useful for characterization of the isoxazolidine ring; therefore, usually, only the absorption bands of the substituents are reported. However, in the case of 5-cyanoisoxazolidine the absorption band at 1035 $cm^{-1}$ has been attributed to a C–O bond.[139/67] It has also been pointed out that isoxazolidines often present absorptions at about 950 and 1070 $cm^{-1}$. The former band was assigned to the N–O bond frequency.[59/64]

2-Hydroxyethyl-5-phenyl-3-*n*-propylisoxazolidine[229/69] and other 2,3,5-trisubstituted isoxazolidines[258/72] show absorptions at 918–940 and 1180–1185 $cm^{-1}$ for the N–O and C–N bond, respectively. In the case of the isomeric 4-*trans*, 5-*cis*- and 4-*cis*, 5-*trans*-bismethoxycarbonyl-3(2′,5′-dimethoxyphenyl)-2-phenylisoxazolidine and similar compounds, absorptions in the infrared spectra for a N–O bond are reported at 1270–1275 $cm^{-1}$.[103/76]

By analogy with the IR absorptions assigned for 8-nitroisoxazolizidines, bands in the range 1000–1065 $cm^{-1}$ have been attributed to O–N–O bonds in the spectra of many 2-alkoxy- and 2-silyloxyisoxazolidines.[121/66,171/67,106/68,107/68,228/68,210/72,212/72,253/73,291/76,292/77] Many 3,3-dinitro-2-O-substituted isoxazolidines are known to present, along with the O–N–O band, absorptions for the geminal dinitro groups at 1510–1597 and 1310–1380 $cm^{-1}$.[121/66,171/67,180/67,106/68,107/68,228/68,254/70,212B/71,210/72,212/72,255/72,257/72,251/73,292/77]

2-Unsubstituted isoxazolidines show sharp N–H absorptions at 3210 $cm^{-1}$.[230/81] By contrast, the infrared spectrum of 2,2-diethyl-5-iodomethylisoxazolidinium iodide[204/76] presents bands between 2500 and 3000 $cm^{-1}$ for the quaternary nitrogen.

### 3.2.2 Ultraviolet Spectra

Ultraviolet spectra are not very characteristic for isoxazolidines, since the ring is saturated, but in some cases the UV absorptions due to the ring substituents have been reported.[26/67,34/70,103/76] It is worth noting that the two N-invertomers of *N*-methoxy-3,3-dimethoxycarbonyl-5-cyanoisoxazolidine show the same $\lambda_{max}$ (220 nm in ethanol) but different absorption intensity ($\varepsilon$ about 250 for the $\beta$-isomer and $\varepsilon$ about 350 for the $\alpha$-isomer).[87/69] It has been noted that the 2-aryl-3-arylamminocarbonyl-5-cyanoisoxazolidines show absorptions in the ultraviolet region at shorter wavelengths than those of the corresponding nitrones.[260/72]

### 3.2.3 Nuclear Magnetic Resonance Spectra

NMR spectra are quite useful for determination of the structure and stereochemistry of isoxazolidines. In fact, the ring protons usually give well separated

signals, and the mutual positions of the protons are clearly indicated by the coupling constants. In some cases the attribution of the PMR signals to the single protons is based on the $^{13}C$-NMR signal multiplicity and on $^{1}H$–$^{13}C$ couplings. Therefore, in the last 20 years almost all the papers concerning the synthesis or the stereochemistry of isoxazolidines report or discuss NMR data.

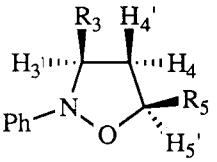
### *3.2.3.1 PMR Spectra*

In this section only the most important examples of PMR studies in the isoxazolidines field will be illustrated.

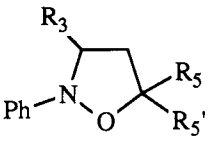
The protons of simple isoxazolidine[16/68,139/72] absorb from the high to the low fields in the following order: $H_4$ ($\delta$ 2.14), $H_3$ ($\delta$ 3.11), $H_5$ ($\delta$ 3.81), $H_2$ ($\delta$ 4.87). By irradiation at the NH frequency, appearing at about $\delta$ 5.0 as a broad singlet, no change of the other signals has been detected.

A downfield shift of all the signals occurs in the PMR spectrum of isoxazolidine hydrobromide recorded in $D_2O$: $\delta$ 2.5 (q, $J$ = 7 Hz, 2H, $H_4$), 3.7 (t, $J$ = 7 Hz, 2H, $H_3$), 4.3 (t, $J$ = 7 Hz, 2H, $H_5$), 4.8 (s, 2H, HOD).[139/80] Similar PMR data for 2-isopropylidenisoxazolidinium perchlorate have also been reported, although the spectra have been recorded in DMSO-$d_6$ and $CD_3CN$.[139/80] Generally, the presence of a withdrawing group on the ring nitrogen causes a downfield shift on the $H_3$ signal, as in 2-benzoylisoxazolidine (see Table 3.1).[142/71]

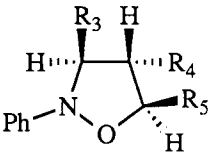
Analysis of the PMR spectra of several variously substituted isoxazolidines and comparison with their theoretically calculated spectra showed that the signals were in agreement with the following spin systems: ABXY for 2,3,5-trisubstitution (**1**), ABX for 2,3,5,5-tetrasubstitution (**2**), and BXY for 2,3,4,5-tetrasubstitution (**3**) of the ring.[93/68]




**1**




**2**

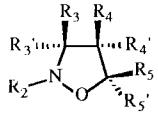



**3**

From the values of the coupling constants and additional stereochemical criteria the configurations reported in the formula were assigned. To explain differences in the coupling constants (e.g., $J_{4,5'}$ in the case of 5-acetoxy-isoxazolidines), the stereochemistry of the electronegative substituent has been invoked.[93/68]

PMR data have largely been used in studies on the mechanism and regio-isomerism of the 1,3-dipolar cycloaddition (see § 3.3.1), leading to the synthesis of simple isoxazolidines.[135/65,76/66,139/67,156/67,20/68,21/68,22/68,38/68,39/68,16/69,198/72,258/72,115/73,218/73,103/76,134/77,173/78,146/79,224/79,195/82,196/82,172/83,72/84] In Table 3.1 the PMR data of some selected isoxazolidines are reported as examples.

TABLE 3.1. PMR DATA OF SIMPLE ISOXAZOLIDINES[a] (d, $J$ in Hz)




| $R_2$ | $R_3$ | $R_{3'}$ | $R_4$ | $R_{4'}$ | $R_5$ | $R_{5'}$ | $H_2$[b] | $H_3$[b] | $H_{3'}$[b] | $H_4$[b] | $H_{4'}$[b] | $H_5$[b] | $H_{5'}$[b] | $J_{3-4}$ | $J_{3-4'}$ | $J_{3'-4}$ | $J_{3'-4'}$ | $J_{4-4'}$ | $J_{4-5}$ | $J_{4-5'}$ | $J_{4'-5}$ | $J_{4'-5'}$ | $J_{5-5'}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| COPh | H | H | H | H | H | H | - | 3.82 | 3.82 | 2.17 | 2.17 | 3.77 | 3.77 | - | - | 7.0 | 7.0 | - | 7.0 | 7.0 | 7.0 | 7.0 | - | $CDCl_3$ | 142/71 |
| Cyclohex-2-en-1-yl | H | H | H | H | H | H | - | 3.0 | - | - | - | 3.92 | - | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 165/80 |
| Cyclohex-1-en-1-yl | H | H | H | H | H | H | - | 3.15 | - | - | - | 3.87 | - | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 165/80 |
| Me | Ph | H | H | H | H | H | (2.59) | - | 3.54 | 2.52 | - | 4.05 | - | - | - | 8.0 | 8.0 | - | - | - | 8.0 | 8.0 | - | $CDCl_3$ | 36/74 |
| H | Me | H | Me | Me | H | H | 4.6 | (1.03) | 3.02 | (1.11) | (0.97) | 3.70 | 3.58 | - | - | - | - | - | - | - | - | - | 7.3 | $CDCl_3$ | 291/83 |
| Me | Ph | H | H | H | Ph | H | - | - | 3.76 | 2.36 | 3.05 | - | 5.22 | - | - | 6.8 | 9.1 | 11.4 | - | 7.4 | - | 7.5 | - | $CDCl_3$ | 20/68 |
| Me | Ph | H | H | H | H | Ph | - | - | 3.68 | 2.4 | 2.8 | 5.22 | - | - | - | 8.4 | 8.4 | - | 7.5 | - | 7.5 | - | - | $CDCl_3$ | 20/68 |
| Ph | Ph | H | H | H | Ph | H | - | - | 4.79 | 2.46 | 2.98 | - | 5.04 | - | - | 7.7 | 7.5 | 11.6 | - | 9.6 | - | 5.5 | - | $CDCl_3$ | 20/68 |
| Ph | Ph | H | H | H | H | Ph | - | - | 4.60 | 2.52 | 2.68 | 5.27 | - | - | - | 5.7 | 5.5 | 12.0 | 7.4 | - | 7.4 | - | - | $CDCl_3$ | 20/68 |
| Ph | 2-$NO_2C_6H_4$ | H | H | H | Ph | H | - | - | 5.71 | 2.26 | 3.49 | - | 5.23 | - | - | 6.33 | 8.32 | 12.54 | - | 9.81 | - | 6.43 | - | $CDCl_3$ | 93/68 |
| Ph | 3-$NO_2C_6H_4$ | H | H | H | Ph | H | - | - | 5.08 | 2.44 | 3.28 | - | 5.25 | - | - | 7.56 | 8.18 | 12.27 | - | 9.92 | - | 6.12 | - | $CDCl_3$ | 93/68 |
| Ph | 4-$NO_2C_6H_4$ | H | H | H | Ph | H | - | - | 5.06 | 2.41 | 3.25 | - | 5.21 | - | - | 7.07 | 8.36 | 12.17 | - | 9.83 | - | 5.96 | - | $CDCl_3$ | 93/68 |
| Ph | 5-$NO_2$-2-furyl | H | H | H | Ph | H | - | - | 5.10 | 2.68 | 3.05 | - | 5.24 | - | - | 6.0 | 9.0 | 13.0 | - | 7.0 | - | 9.0 | - | $CDCl_3$ | 38/68 |
| Ph | Ph | H | H | H | OAc | H | - | - | 4.38 | 2.49 | 3.13 | - | 6.55 | - | - | 6.75 | 9.31 | 13.67 | - | 1.95 | - | 6.13 | - | $CDCl_3$ | 93/68 |
| 4-$ClC_6H_4$ | 2-$NO_2C_6H_4CH{=}CH$ | H | H | H | Ph | H | - | - | 4.82 | 2.92 | 2.42 | - | 5.08 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 95/74 |
| 4-$ClC_6H_4$ | 2-$NO_2C_6H_4CH{=}CH$ | H | H | H | 4-$BrC_6H_4$ | H | - | - | 4.48 | 2.96 | 2.30 | - | 5.08 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 95/74 |
| OMe | Me | Me | H | H | H | H | (3.43) | (0.88) | (1.44) | 1.24 | 2.18 | 3.55 | 4.02 | - | - | - | - | - | - | - | - | - | - | $C_6D_6$ | 132/80 |
| OMe | COOR | H | H | H | COOMe | H | (3.60) | - | 4.25 | 2.87 | 2.87 | - | 4.73 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 205/66 |
| OMe | COOR | H | H | H | CN | H | (3.60) | - | 4.22 | 2.89 | 2.89 | - | 4.96 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 205/66 |
| OMe | COOR | H | H | H | COMe | H | (3.60) | - | 4.17 | 2.72 | 2.72 | - | 4.70 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 205/66 |
| OMe | COOR | H | H | H | Ph | H | (3.56) | - | 4.12 | 2.85 | 2.85 | - | 5.18 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 205/66 |
| OMe | COOR | H | H | H | $CH_2Cl$ | H | (3.30) | - | 4.23 | 3.00 | 3.00 | - | 5.00 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 205/66 |
| Me | H | H | 2-thienyl | H | $SO_2C_6F_{13}$ | H | (2.87) | 3.48 | 3.48 | - | 4.31 | - | 5.86 | - | - | - | - | - | - | - | - | 5.3 | - | $CDCl_3$ | 81/84 |

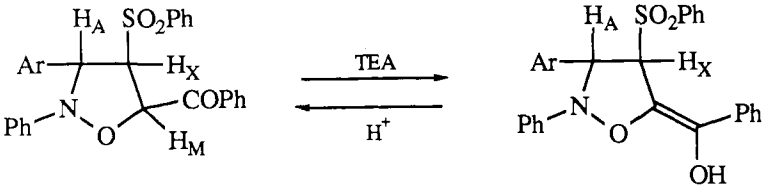
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | | | | | | | | | 5.6 | - | $CDCl_3$ | 81/84 |
| Me | H | H | 4-$MeOC_6H_4$ | H | $SO_2C_6F_{13}$ | H | (2.77) | 3.40 | 3.40 | - | 4.9 | - | 5.37 | - | - | - | - | - | - | - | - | 5.6 | - | $CDCl_3$ | 81/84 |
| Ph | Ph | H | $SO_2Ph$ | H | H | H | - | - | 4.95 | - | 4.16 | 4.50 | 4.35 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 172/83 |
| Me | Me | H | $NO_2$ | H | Me | H | - | (1.05) | 3.10 | - | 4.70 | (1.30) | 4.45 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 157/84 |
| Et | Me | H | $NO_2$ | H | Me | H | - | (1.05) | 3.25 | - | 4.55 | (1.15) | 4.00 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 157/84 |
| Me | Me | H | COMe | H | Me | H | - | (1.15) | 2.90 | - | - | (1.25) | 4.60 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 157/84 |
| Me | Me | H | COPh | H | Me | H | - | (1.10) | 3.75 | - | - | (1.35) | 4.65 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 157/84 |
| Et | Me | H | Cl | H | Me | H | - | (1.20) | 3.20 | - | 4.55 | (1.30) | 4.40 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 157/84 |
| Et | Me | H | Br | H | Me | H | - | (1.25) | 3.15 | - | 4.70 | (1.30) | 4.45 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 157/84 |
| OMe | $NO_2$ | $NO_2$ | H | H | COOMe | H | (3.81) | - | - | 3.8 | 3.8 | - | 5.2 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 41/65 |
| OMe | $NO_2$ | $NO_2$ | H | H | Ph | H | - | - | - | 3.8 | 3.8 | - | 5.2 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 41/65 |
| Ph | Ph | H | H | Ph | Ph | H | - | - | 4.94 | 3.73 | - | - | 5.25 | - | - | 8.00 | - | - | - | 9.75 | - | - | - | $CDCl_3$ | 93/68 |
| Ph | H | Ph | $NO_2$ | H | H | Ph | - | 5.57 | - | - | 5.23 | 5.72 | - | - | 4.0 | - | - | - | - | - | 5.6 | - | - | $CDCl_3$ | 218/73 |
| Ph | Ph | H | $NO_2$ | H | H | Ph | - | - | 4.92 | - | 5.35 | 6.05 | - | - | - | - | 9.6 | - | - | - | 7.2 | - | - | $CDCl_3$ | 218/73 |
| Ph | H | COPh | $NO_2$ | H | H | Ph | - | 6.22 | - | - | 6.33 | 5.57 | - | - | 1.6 | - | - | - | - | - | 6.2 | - | - | $CDCl_3$ | 218/73 |
| Ph | Ph | H | H | COOEt | Me | H | - | - | 5.16 | 3.13 | - | - | 4.41 | - | - | 6.83 | - | - | - | 9.02 | - | - | - | $CCl_4$ | 93/68 |
| Ph | H | Ph | COOMe | H | H | Ph | - | 5.25 | - | (3.52) | 3.61 | 5.41 | - | - | 6.7 | - | - | - | - | - | 8.7 | - | - | $CDCl_3$ | 218/73 |
| Ph | H | Ph | H | COOMe | H | Ph | - | 5.20 | - | 4.15 | (3.03) | 5.45 | - | 7.6 | - | - | - | - | 5.0 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | Ph | H | H | COOMe | H | Ph | - | - | 4.98 | 3.79 | (3.11) | 5.67 | - | - | - | 6.8 | - | - | 8.1 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | H | Ph | CN | H | H | Ph | - | 5.13 | - | - | 3.48 | 5.33 | - | - | 7.5 | - | - | - | - | - | 8.8 | - | - | $CDCl_3$ | 218/73 |
| Ph | H | Ph | H | CN | H | Ph | - | 5.06 | - | 3.99 | - | 5.27 | - | 7.4 | - | - | - | - | 5.4 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | Ph | H | H | CN | H | Ph | - | - | 4.66 | 3.68 | - | 5.50 | - | - | - | 5.0 | - | - | 6.8 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | COPh | H | H | CN | H | Ph | - | - | 5.41 | 4.09 | - | 5.56 | - | - | - | 4.5 | - | - | 6.5 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | H | Ph | CN | H | H | CN | - | 4.78 | - | - | 4.38 | 5.95 | - | - | 6.4 | - | - | - | - | - | 2.9 | - | - | $CDCl_3$ | 218/73 |
| Ph | 2-$MeC_6H_4$ | H | H | CN | CN | H | - | - | 4.82 | 3.80 | - | - | 5.25 | - | - | 7.0 | - | - | - | 3.0 | - | - | - | $CDCl_3$ | 237/83 |
| Ph | Ph | H | SBu-*t* | CN | H | H | - | - | 4.97 | - | - | 4.82 | 4.40 | - | - | - | - | - | - | - | - | - | 8.8 | $CDCl_3$ | 24/82 |
| Ph | COPh | H | H | H | N=N-Pr-*i* | Me | - | - | 4.55 | 2.85 | 2.50 | - | (1.45) | - | - | 6.80 | 8.0 | 14 | - | - | - | - | - | $CDCl_3$ | 198/84 |
| Ph | H | COPh | H | H | COOH | Me | - | 5.45 | - | 2.56 | 3.28 | - | (1.61) | 6.0 | 8.0 | - | - | 10 | - | - | - | - | - | $CD_3OD$/150/82 $(CD_3)_2CO$ | |

TABLE 3.1. *(Continued)*

| $R_2$ | $R_3$ | $R_{3'}$ | $R_4$ | $R_{4'}$ | $R_5$ | $R_{5'}$ | $H_2$[b] | $H_3$[b] | $H_{3'}$[b] | $H_4$[b] | $H_{4'}$[b] | $H_5$[b] | $H_{5'}$[b] | $J_{3-4}$ | $J_{3-4'}$ | $J_{3'-4}$ | $J_{3'-4'}$ | $J_{4-4'}$ | $J_{4-5}$ | $J_{4-5'}$ | $J_{4'-5}$ | $J_{4'-5'}$ | $J_{5-5'}$ | Solvent | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ph | H | COPh | COOMe | H | H | Ph | - | 5.87 | - | (3.50) | 4.47 | 5.28 | - | - | 3.2 | - | - | - | - | - | 7.7 | - | - | $CDCl_3$ | 218/73 |
| Ph | H | COPh | CN | H | H | Ph | - | 5.82 | - | - | 4.56 | 5.20 | - | - | 2.8 | - | - | - | - | - | 7.8 | - | - | $CDCl_3$ | 218/73 |
| Ph | H | COPh | COOMe | H | H | COOMe | - | 5.75 | - | (3.50) | 4.60 | 5.22 | (3.82) | - | 2.4 | - | - | - | - | - | 5.2 | - | - | $CDCl_3$ | 218/73 |
| Ph | COPh | H | H | COOMe | H | COOMe | - | - | 5.68 | 4.30 | (3.49) | 5.05 | (3.55) | - | - | 6.0 | - | - | 8.0 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | H | COPh | CN | H | H | CN | - | 6.52 | - | - | 5.05 | 5.53 | - | - | 1.4 | - | - | - | - | - | 5.1 | - | - | $CDCl_3$ | 218/73 |
| Ph | COPh | H | H | COOMe | H | Ph | - | - | 5.60 | 3.85 | (3.02) | 5.66 | - | - | - | 3.5 | - | - | 5.6 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | H | Ph | COOMe | H | H | COOMe | - | 4.77 | - | (3.65) | 4.00 | 5.10 | (3.78) | - | 6.4 | - | - | - | - | - | 4.8 | - | - | $CDCl_3$ | 218/73 |
| Ph | Ph | H | H | COOMe | H | COOMe | - | - | 4.99 | 3.79 | (3.60) | 5.04 | (3.63) | - | - | 8.1 | - | - | 7.8 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | H | Ph | H | COOMe | H | COOMe | - | 5.05 | - | 4.05 | (3.06) | 4.80 | (3.69) | 8.7 | - | - | - | - | 7.1 | - | - | - | - | $CDCl_3$ | 218/73 |
| Ph | Ph | H | COOMe | H | H | COOMe | - | - | 5.07 | (3.47) | 4.05 | 5.25 | (3.71) | - | - | - | 8.6 | - | - | - | 7.8 | - | - | $CDCl_3$ | 218/73 |
| Ph | H | Ph | H | COOMe | H | COOMe | - | 4.80 | - | 4.05 | - | 5.05 | - | 8.7 | - | - | - | - | 7.1 | - | - | - | - | $CDCl_3$ | 39/71 |
| Ph | Ph | H | H | COOMe | H | COOMe | - | - | 4.99 | 3.79 | - | 5.04 | - | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 39/71 |
| Ph | Ph | H | COOMe | H | H | COOMe | - | - | 5.23 | - | 4.07 | 5.05 | - | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 39/71 |
| Ph | H | Ph | COOMe | H | H | COOMe | - | 5.10 | - | - | 4.00 | 4.77 | - | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 39/71 |
| Ph | COPh | H | H | COOMe | H | COOMe | - | - | 4.60 | 3.91 | - | 5.07 | - | - | - | 6.0 | - | - | 8.0 | - | - | - | - | $CDCl_3$ | 39/71 |
| Ph | H | COPh | COOMe | H | H | COOMe | - | 5.75 | - | - | 4.60 | 5.22 | - | - | 2.4 | - | - | - | - | - | 5.2 | - | - | $CDCl_3$ | 39/71 |
| OMe | H | $SO_2Ph$ | COOMe | H | COOMe | H | (3.45) | 5.3 | - | - | 4.2 | - | 5.1 | - | 6.0 | - | - | - | - | - | - | 11.0 | - | $CDCl_3$ | 46/84 |
| $CH_2SMe$ | Ph | Ph | H | H | COOMe | H | - | - | - | 3.14 | 2.96 | - | 4.31 | - | - | - | - | 12.2 | - | 8.6 | - | 7.6 | - | $C_6D_6$ | 155/70 |
| 4-$ClC_6H_4$ | 2-$NO_2C_6H_4CH$=CH | H | COPh | H | COPh | H | - | - | 4.56 | - | 5.20 | - | 5.62 | - | - | - | - | - | - | - | - | - | - | $CDCl_3$ | 95/74 |
| Ph | H | Ph | $P(O)(OEt)_2$ | H | H | COOMe | - | 4.77 | - | - | 3.38 | 4.61 | - | - | 5.9 | - | - | - | - | - | 6.6 | - | - | $CDCl_3$ | 130B/80 |
| Ph | H | 4-$NO_2C_6H_4$ | $P(O)(OEt)_2$ | H | H | COOMe | - | 4.93 | - | - | 3.33 | 4.77 | - | - | 5.1 | - | - | - | - | - | 6.0 | - | - | $CDCl_3$ | 130B/80 |
| Ph | H | 4-$ClC_6H_4$ | $P(O)(OEt)_2$ | H | H | COOMe | - | 4.70 | - | - | 3.30 | 4.59 | - | - | 5.5 | - | - | - | - | - | 6.2 | - | - | $CDCl_3$ | 130B/80 |
| Ph | H | 4-$MeC_6H_4$ | $P(O)(OEt)_2$ | H | H | COOMe | - | 4.93 | - | - | 3.54 | 4.64 | - | - | 5.4 | - | - | - | - | - | 7.3 | - | - | $CDCl_3$ | 130B/80 |
| Ph | Ph | H | H | H | OEt | OEt | - | - | 4.63 | 2.39 | 2.67 | - | - | - | - | 9.5 | 8.0 | 12.0 | - | - | - | - | - | $CDCl_3$ | 21/68 |
| H | $CONEt_2$ | Me | Ph | H | OH | H | - | - | (1.86) | - | 3.61 | - | 5.50 | - | - | - | - | - | - | - | - | 1.0 | - | $CDCl_3$ | 230/81 |
| H | $CONEt_2$ | Me | Ph | H | H | OH | - | - | (1.70) | - | 3.50 | 5.70 | - | - | - | - | - | - | - | - | 6.0 | - | - | $CDCl_3$ | 230/81 |

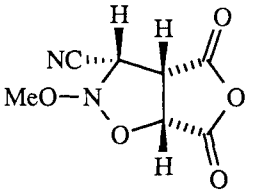
[a]Stereochemistry of the reported isoxazolidines is relative. [b]The chemical shifts of substituents are reported in parentheses.

Regio-isomeric structure of 3-aryl-4-benzenesulfonyl-5-benzoyl-2-phenyl-isoxazolidine has been assigned on the basis of the PMR spectrum recorded in both $CDCl_3$ and basic media by adding triethylamine to the solution. In the former solution the AMX system associated with the $H_3$, $H_4$, and $H_5$ protons ($J_{AX}$ = 6.5 Hz, $J_{MX}$ = 3.0 Hz, and $J_{AM}$ = 0 Hz) was evidentiated. In the basic solution this system evolved to a simpler AX system ($J_{AX}$ = 6.5 Hz) because of the complete enolization of the carbonyl group at $C_5$:[172/83]

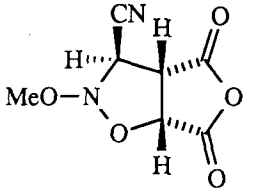



The *coupling constants* of the vicinal protons gave in many cases a clear indication of the stereochemistry of substituents. Generally speaking, one can say that the value of the *cis* is always larger than that of the *trans* coupling constants. As examples, the coupling constants of some couples of isomers (**4–7**) are reported.[192/71,55/73,218/73]

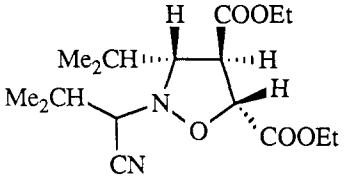
From the data reported above it is possible to assert that the $J_{3-4}$ are in the range 8.1–9.0 Hz for the *cis* and 0.6–8.1 Hz for the *trans* coupling; by contrast, the $J_{4-5}$ are in the range 7.0–11.0 Hz for the *cis* and 6.0–8.0 Hz for the *trans* coupling. Other data on the coupling constants are reported in the literature.[139/67,21/68,39/71,23/75,103/76,134/77,173/78,28/79,146/79,190/79,9/80,230/81,163/82,207/82,191/83,237/83,46/84]



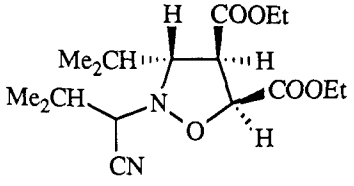

**4a** $J_{3-4}$ 8.9 Hz *cis*
$J_{4-5}$ 8.8 Hz *cis*



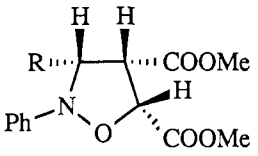

**4b** $J_{3-4}$ 0.8 Hz *trans*
$J_{4-5}$ 8.1 Hz *cis*



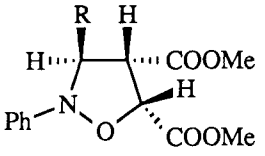

**5a** $J_{3-4}$ 3.5 Hz *trans*
$J_{4-5}$ 6.0 Hz *trans*



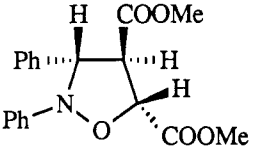

**5b** $J_{3-4}$ 3.0 Hz *trans*
$J_{4-5}$ 10.5 Hz *cis*



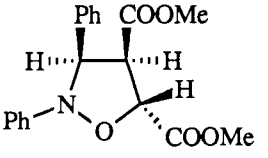
**6a** $J_{3\text{-}4}$ 8.7 Hz *cis*
$J_{4\text{-}5}$ 7.1 Hz *cis*



**6b** $J_{3\text{-}4}$ 8.1 Hz *trans*
$J_{4\text{-}5}$ 7.8 Hz *cis*



**7a** $J_{3\text{-}4}$ 6.4 Hz *trans*
$J_{4\text{-}5}$ 4.8 Hz *trans*

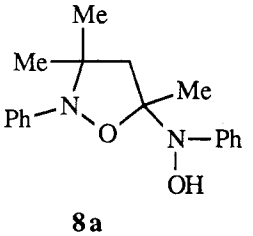


**7b** $J_{3\text{-}4}$ 8.6 Hz *cis*
$J_{4\text{-}5}$ 7.8 Hz *trans*

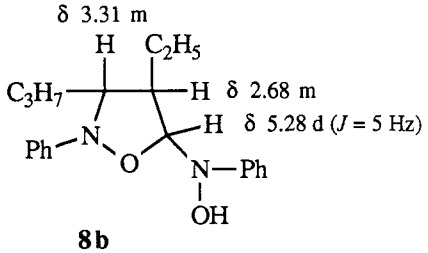
The *structure determination* of the reaction product between *N*-phenylhydroxylamine and acetone could be accomplished through the PMR data. The structure of 5-hydroxy[(phenyl)amino]-3,3,5-trimethyl-2-phenylisoxazolidine (**8a**)[151/74] could then be confirmed by means of x-ray analysis.

As a matter of fact, the AB system ($\delta$ 3.14 and $\delta$ 2.16, 1H each, doublets, $J$ = 13.0 Hz) and the nonequivalence of the two geminal methyl groups in the PMR spectrum were more in agreement with a cyclic structure than with an open-chain compound. Compound **8a** can be considered as the dimerization product of a *N*-phenylnitrone.

The structures of some other similar dimers have been solved by means of PMR data.[206/69,159/76,272/80,214/81] One example is here shown for **8b**:[206/69]



**8a**

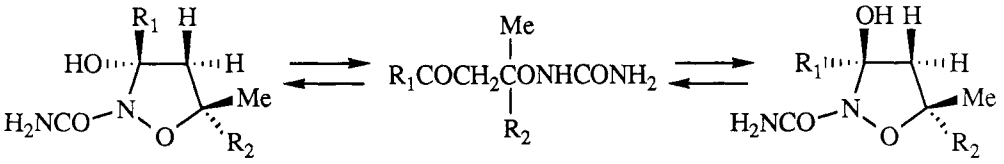


**8b**

Sometimes mixtures of stereoisomers have been obtained; however, PMR data of each single isomer have been reported.[159/76]

The contemporary presence of the open-chain and cyclic compounds have

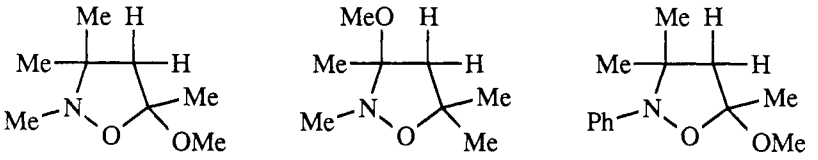
been shown in the case of **9** ($R_1$ = Me, $R_2$ = H or Me), while with other substituents only cyclic products ($R_1$ = $R_2$ = H) or open-chain products ($R_1$ = Ph, $R_2$ = H) are formed.[187/75] The different chemical shifts of the signals of the three following products permitted the demonstration that the solvent effect does not affect the equilibrium. Instead, it is shifted toward the open-chain derivatives by increase in temperature.



**9a** **9b**

Many studies on structure elucidation of the isoxazolidines based on the substituent chemical shifts have been reported. For example, from the chemical shifts of the methyl groups it is possible to distinguish the isomeric 2,3,3,5-tetramethylisoxazolidine (**10**) and 2,3,5,5-tetramethylisoxazolidine (**11**)(Table

TABLE 3.2



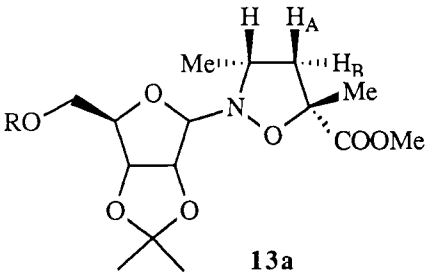
**10** **11** **12**

| Compound | $Me_2C(\delta)$ | | $CH_2(\delta)$ ($J_{A\text{-}B}$, Hz) | Me($\delta$) | N-Me($\delta$) | O-Me($\delta$) | N-Ph($\delta$) |
|---|---|---|---|---|---|---|---|
| **10** | 1.03 | 1.16 | 2.11 (13.0) | 1.40 | 2.60 | 3.33 | - |
| **11** | 1.30 | 1.33 | 2.16 (13.0) | 1.30 | 2.60 | 3.33 | - |
| **12** | 0.90 | 1.53 | 2.33 (13.0) | 1.40 | - | 3.33 | 7.20 |

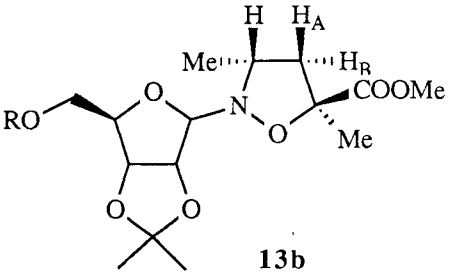
3.2). It is interesting to note the nonequivalence of the geminal methyl groups, which increases by the presence of a phenyl group in position 2 (as in **12**) and that the $CH_2$ in position 4, shows an AB system.[24/72] Also, in the case of 3-(4-chlorophenyl)-5-hydroxy-2,4,4,5-tetramethylisoxazolidine the geminal methyl groups (*cis* and *trans*) show different absorptions ($\delta$ 0.73 and $\delta$ 1.11, respectively) well separated from the $C_5$–Me ($\delta$ 1.40) and N-Me ($\delta$ 2.81).[7/84]

In the case of isoxazolidine ribosides it has been shown that the difference in

chemical shifts of the two $C_4$ protons in the AB system can be used to establish the relative stereochemistry of the $C_3$ and $C_5$ substituents.[80/77] When the $\Delta\delta_{HA\text{-}HB}$ is around 0.3, the $C_3$ and $C_5$ methyls are *trans* and when $\Delta\delta_{HA\text{-}HB}$ is about 1, the two methyls are *cis*. We report here the NMR data of (**13**) for R = H:




**13a**



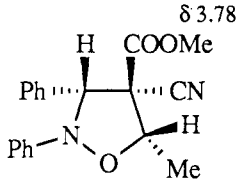

**13b**

| Compound | $C_4$-$H_A$ ($J_{AB}$, $J_{3\text{-}4}$, Hz) | $C_4$-$H_B$ ($J_{3\text{-}4}$, Hz) | $\Delta\delta_{HA\text{-}HB}$ | $C_3$-Me | $C_5$-Me |
|---|---|---|---|---|---|
| **13** a *trans* | 2.24 (12.0, 8.0) | 2.50 (8.0) | 0.36 | 1.17 | 1.50 |
| b *cis* | 1.93 (13.0, 6.0) | 3.03 (7.0) | 1.08 | 1.33 | 1.52 |

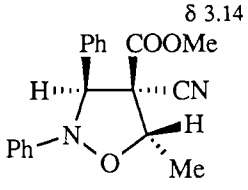
Sometimes the stereochemistry of glycosyl isoxazolidines has been determined by NMR data.[81/77,106/81]

It is interesting to note that in the case of **8a**, where, by the presence of a geminal dimethyl group in position 3, the $C_5$ methyl is in any case *cis* the difference of $\delta_{HA\text{-}HB}$ is 0.98, in agreement with this rule. Furthermore, the influence of the *cis* substituents on the chemical shifts has usefully been taken into account to establish the structure of two isomeric products from the cycloaddition of nitrones to olefins.[38/73,31/78]

In fact, the methyl of the ester function is highly upfield shielded when it is *cis* to a vicinal phenyl group as in **14b** ($\delta$ 3.14), while in the *trans* derivative **14a**

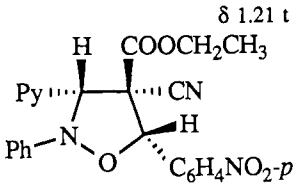



**14a**

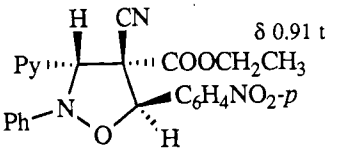



**14b**

the methyl absorbs at a lower field ($\delta$ 3.78).[38/73] Similarly, the structure for the isoxazolidines **15a** and **15b** have been assigned from the PMR spectrum of the reaction mixture.[31/78] In both papers[38/73,31/78] other examples are reported.

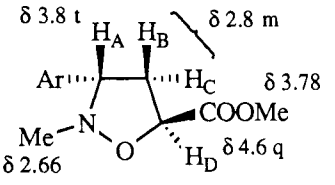



**15a** (Py = 2-pyridyl)

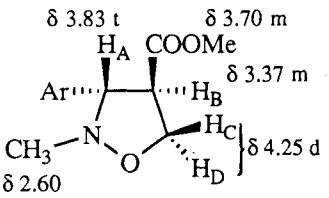



**15b**

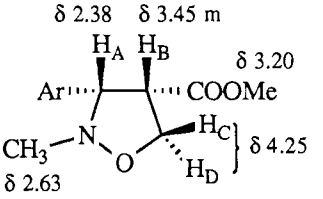
Cycloaddition of α-3-pyridyl-*N*-methylnitrone with methyl acrylate yielded a mixture of three products as indicated by the presence of three *N*-methyl signals in the ratio 8:1:1 in the PMR spectrum. To the major product the structure of 2-methyl-3-α-(3′-pyridyl)-5-β-methoxycarbonylisoxazolidine (**16**) has been assigned.




**16**

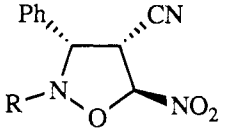



**17a**



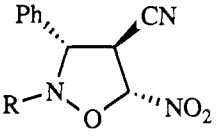

**17b**

By contrast to the two minor products, the *trans* (**17a**) and *cis* (**17b**) regioisomeric structures with the COOMe group in position 4 have been assigned. The NMR data are reported on the formula. Also in these cases the methyl group of the *cis* isomer resonates at a higher field than that of the *trans* isomer.[161/72] The number and the structures of the isomers obtained by cycloaddition of *trans*-1-cyano-2-nitroethylene to nitrones[99/81] could be revealed by NMR data: phenyl-*N*-methylnitrone led to the three isomers **18–20** and phenyl-*N*-*tert*-butylnitrone only to the two regioisomers **19** and **20**.



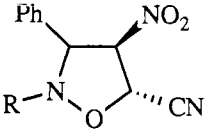

**18**

R = Me




**19**

R = Me
R = *t*-Bu (60%)

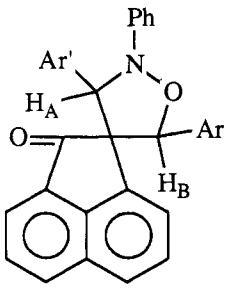



**20**

R = Me
R = *t*-Bu (40%)

The regiochemistry of the spiroisoxazolidines **21**, obtained by 1,3-dipolar cycloaddition of *C,N*-diarylnitrones to some benzylideneacenaphthenones, was promptly identified from the lacking of coupling between the two isoxazolidine protons, which show well-differentiated chemical shifts (Table 3.3).[223/70]

TABLE 3.3



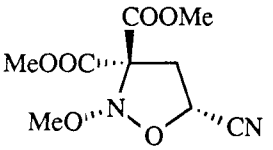

**21**

| Ar | Ar' | $\delta_{HA}$ (s) | $\delta_{HB}$ (s) |
|---|---|---|---|
| Ph | Ph | 5.79 | 5.94 |
| Ph | 4-$ClC_6H_4$ | 5.69 | 5.87 |
| 4-$ClC_6H_4$ | Ph | 5.75 | 5.89 |
| 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 5.71 | 5.88 |

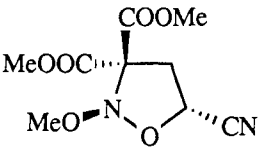
The PMR data also gave useful informations for structure elucidation for 3-[113/77] or 5-spiroisoxazolidines.[226B/76,52B/81,231/82] The symmetry of 3,3,3′,3′-tetramethyl-5-5′-isoxazolidine is shown by one single signal ($\delta$ 1.25, 12H) for the methyls, and one for the methylenes ($\delta$ 2.25, 4H) and the NH groups ($\delta$ 5.75, 2H).[52B/81] 2,3-Disubstituted-5,5-spiroisoxazolidines and 2,5-disubstituted-3,3-spiroisoxazolidines show the characteristic ABX pattern for the ring hydrogens.[226B/76,113/77,231/82]

The chemical shifts of the methyl groups of an epimeric mixture of isoxazolidinium salts, obtained by iodomethylation of isoxazolidines, have been indicated.[176/83,277/83] The PMR data of nitrones bearing a butadiene iron tricarbonyl moiety and of the corresponding isoxazolidines, obtained by 1,3-dipolar cycloaddition, have been reported.[146/81]

Conformational analysis of the isoxazolidine ring (see § 3.2.8) relies primarily on PMR evidence. Many authors have shown that the conformations assumed by an isoxazolidine derivative are promoted by inversion of the piramidally bonded ring nitrogen atom. For the *N*-alkyl or *N*-aryl derivatives the presence of invertomers could be demonstrated by recording the PMR spectra at a low temperature.[51/68,53/68,172/70,148/77] By contrast, the *N*-alkoxyisoxazolidines, which show a higher energy barrier for the nitrogen inversion, could easily be studied at room temperature, and in many cases the invertomers could be isolated. The



**22a**

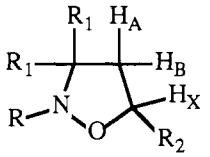


**22b**

first instance of successful isolation concerns the two *N*-methoxy-3,3-dimethoxycarbonyl-5-cyanoisoxazolidines **22a** and **22b**.[87/69] The two invertomers show PMR spectra being dissimilar primarily for the quite different coupling constants.

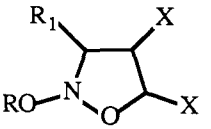
In Tables 3.4 to 3.6 the PMR data of variously substituted isoxazolidine invertomers are reported.[87/69.90/72.234/72.223/73.250/73.253/73.227/76.228/76.164/77] In most of the cycloadditions leading to isoxazolidines that were studied, only one invertomer has been obtained.[90/72.234/72.223/73.227/76.228/76] Heating this invertomer in a suitable solvent at a temperature usually higher than 100°C causes nitrogen inversion. Once equilibrium is reached the relative amounts of the two invertomers depend on the heating temperature and can be estimated from an integration curve. In the case of 2-methoxy-3,3-dinitro-5-substituted isoxazolidines,[260/70.81C/75] the

TABLE 3.4. PMR DATA OF 2,3,3,5-TETRASUBSTITUTED ISOXAZOLIDINE INVERTOMERS (CHEMICAL SHIFTS in δ, *J* in Hz)

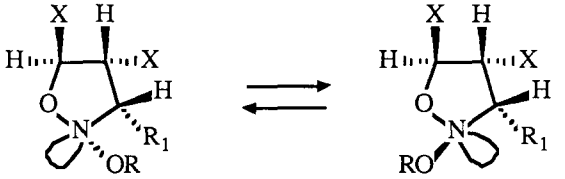


| | | R | $R_1$ | $R_2$ | $Me_3Si$ | Ph | MeO | $H_A$ | $H_B$ | $H_X$ | $J_{AB}$ | $J_{AX}$ | $J_{BX}$ | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **22** | **a** | MeO | COOMe | CN | - | - | 3.77 3.84 3.86 | 3.29 | 3.38 | 5.03 | 13.2 | 9.7 | 6.0 | 87/69 |
| | **b** | | | | - | - | 3.72 3.88 3.93 | 3.02 | 3.37 | 5.08 | 13.5 | 4.3 | 10.5 | 87/69 |
| **23** | **a** | $Me_3SiO$ | COOMe | COOMe | 0.20 | - | 3.51 3.55 3.60 | 3.00 | 3.34 | 4.68 | -13.0 | 9.2 | 6.2 | 90/72 |
| | **b** | | | | 0.24 | - | 3.54 3.57 | 2.88 | 3.46 | 4.91 | -13.0 | 4.3 | 10.1 | 90/72 |
| **24** | **a** | $Me_3SiO$ | COOMe | Ph | 0.12 | 7.33 | 3.80 | 2.96 | 3.06 | 5.05 | -12.5 | 7.6 | 10.0 | 90/72 |
| | **b** | | | | 0.15 | 7.33 | 3.79 3.80 | 2.46 | 3.69 | 5.62 | -13.0 | 6.4 | 9.0 | 90/72 |
| **25** | **a** | $Me_3SiO$ | $NO_2$ | Ph | | | | 3.75 | 4.00 | 5.55 | -14.5 | 7.3 | 9.3 | 253/73 |
| | **b** | | | | | | | 3.10 | 4.39 | 6.09 | -15 | 7.0 | 8.0 | 253/73 |
| **26** | **a** | MeO | $NO_2$ | Ph | | | | 3.50 | 3.50 | 5.23 | - | - | - | 260/70 |
| | **b** | | | | | | | 2.84 | 4.04 | 5.65 | 15.6 | 7.0 | 8.1 | 260/70 |
| **27** | **a** | MeO | COOMe | Ph | | | | - | - | 5.13 | - | - | - | 254/72 |
| | **b** | | | | | | | 2.38 | 3.52 | 5.38 | -13.0 | 6.0 | 9.0 | 254/72 |

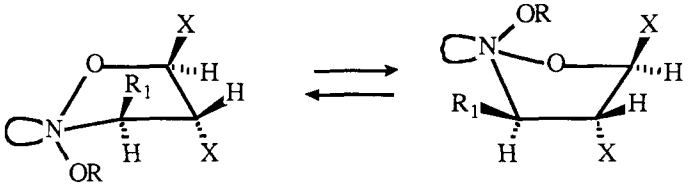
TABLE 3.5. PMR DATA OF 2,3,4,5-TETRASUBSTITUTED ISOXAZOLIDINE INVERTOMERS (CHEMICAL SHIFTS in δ, *J* in Hz)



| | | R | $R_1$ | X | $H_3$ | $H_4$ | $H_5$ | $J_{3-4}$ | $J_{4-5}$ | Equil.(%) | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **28** | **a** | Me | COOMe | COOMe | 4.34 | 4.36 | 5.34 | 8.9 | 5.1 | 10 | 234/72, 228/76 |
| | **b** | | | | 4.59 | 4.36 | 5.24 | 7.8 | 6.2 | 90 | 234/72, 228/76 |
| **29** | **a** | Me | COOMe | CN | 4.47 | 4.11 | 5.32 | 8.5 | 4.0 | 15 | 234/72, 228/76 |
| | **b** | | | | 4.82 | 4.52 | 5.39 | 7.0 | 6.5 | 85 | 234/72, 228/76 |
| **30** | **a** | Me | CN | COOMe | 4.50 | 4.35 | 5.42 | 9.2 | 4.8 | 16 | 228/76 |
| | **b** | | | | 4.73 | 4.51 | 5.31 | 8.2 | 5.8 | 84 | 228/76 |
| **31** | **a** | Me | COOMe | COOMe | 4.74 | 4.18 | 5.25 | 2.2 | 5.4 | 45 | 234/72, 228/76 |
| | **b** | | | | 4.56 | 4.39 | 4.97 | 9.5 | 5.0 | 55 | 234/72, 228/76 |
| **32** | **a** | Me | COOMe | CN | 4.48 | 4.40 | 5.16 | 2.0 | 5.4 | 45 | 228/76 |
| | **b** | | | | 4.86 | 4.64 | 5.75 | 9.8 | 5.9 | 55 | 228/76 |

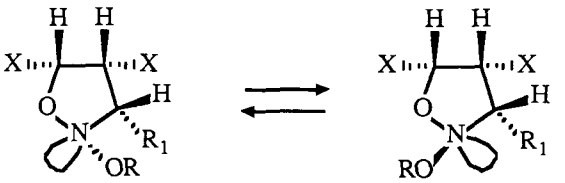


**a** **28-30** **b**



**a** **31-32** **b**

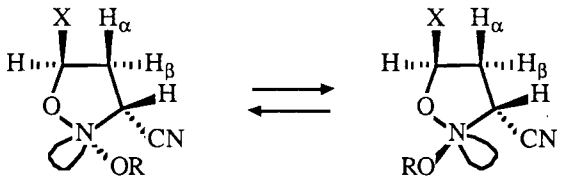
| | | R | $R_1$ | XX | $H_3$ | $H_4$ | $H_5$ | $J_{3-4}$ | $J_{4-5}$ | Equil.(%) | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **33** | **a** | Me | COOMe | CON(Me)CO | 4.51 | 4.09 | 5.13 | 8.3 | 7.3 | 30 | 234/72 |
| | **b** | | | | 4.61 | 4.27 | 5.20 | 8.9 | 7.5 | 70 | 234/72 |
| **34** | **a** | Me | COOMe | COOMe | 4.60 | 4.31 | 5.10 | 10.3 | 10.1 | 75 | 228/76 |
| | **b** | | | | 4.79 | 4.13 | 4.99 | 4.8 | 8.6 | 25 | 228/76 |
| **35** | **a** | Me | CN | COOMe | 4.55 | 4.22 | 5.07 | 10.5 | 10.0 | 89 | 228/76 |
| | **b** | | | | 4.92 | 4.07 | 5.12 | 5.1 | 8.6 | 11 | 228/76 |



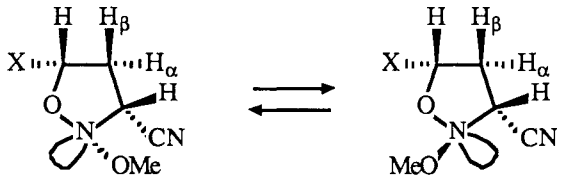
**a** **33-35** **b**

TABLE 3.6. PMR DATA OF 2,3,5-TRISUBSTITUTED ISOXAZOLIDINES

| | | R | X | $H_5$ | $H_3$ | $H_{4\alpha}$ | $H_{4\beta}$ | OMe | $J_{3\text{-}4\alpha}$ | $J_{3\text{-}4\beta}$ | $J_{5\text{-}4\alpha}$ | $J_{5\text{-}4\beta}$ | $J_{4\alpha\text{-}4\beta}$ | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **36** | **a** | Me | CN | 5.08 | 4.32 | ca.3.0 | ca.3.0 | 3.70 | 10.3 | 9.0 | 4.6 | 9.5 | - | 223/73, 227/76 |
| | **b** | | | 5.10 | 4.59 | 3.10 | 3.0 | 3.74 | 7.7 | 2.1 | 6.3 | 8.8 | 13.5 | 223/73, 227/76 |
| **37** | **a** | Me | 4-$BrC_6H_4$ | 5.40 | 4.20 | 2.40 | 3.04 | 3.72 | 9.0 | 9.8 | 5.0 | 9.2 | 12.0 | 227/76 |
| **38** | **a** | Me | 4-$MeC_6H_4$ | 5.44 | 4.25 | 2.40 | 3.10 | 3.73 | 9.5 | 10.0 | 5.1 | 9.4 | 11.9 | 223/73, 227/76 |
| **39** | **a** | Me | COOMe | 4.89 | 4.18 | 2.82 | 2.99 | 3.70/3.78 | 10.7 | 9.0 | 4.1 | 9.2 | 12.5 | 223/73, 227/76 |
| | **b** | | | 4.94 | 4.49 | 3.22 | 2.80 | 3.60/3.76 | 8.0 | 1.6 | 6.1 | 9.2 | 13.2 | 223/73, 227/76 |
| **40** | **a** | Me | CN | 5.16 | 4.23 | ca.3.2 | ca.3.2 | 3.77 | 10.7 | 8.2 | 6.4 | 9.0 | - | 227/76 |
| | **b** | | | 4.96 | 4.53 | 2.84 | 3.22 | 3.66 | 2.0 | 8.0 | 5.0 | 9.5 | 13.2 | 227/76 |
| **41** | **a** | Me | 4-$BrC_6H_4$ | 5.20 | 4.14 | 2.32 | 2.88 | 3.72 | 6.8 | 11.4 | 7.2 | 9.0 | 12.1 | 227/76 |
| | **b** | | | 5.30 | 4.46 | 2.32 | 3.14 | 3.67 | 3.0 | 8.8 | 6.8 | 8.8 | 13.0 | 227/76 |
| **42** | **b** | Me | 4-$MeC_6H_4$ | 5.44 | 4.56 | 2.20 | 2.98 | 3.72 | 3.2 | 9.0 | 6.8 | 8.8 | 12.8 | 227/76 |
| **43** | **a** | Me | COOMe | 4.80 | 4.02 | ca.2.8 | ca.2.8 | 3.63/3.76 | 10.5 | 9.2 | 6.5 | 8.4 | - | 227/76 |
| | **b** | | | 4.87 | 4.48 | 2.77 | 3.10 | 3.66/3.84 | 2.3 | 8.3 | 5.2 | 9.2 | 13.1 | 227/76 |




**a** **36-39** **b**




**a** **40-43** **b**

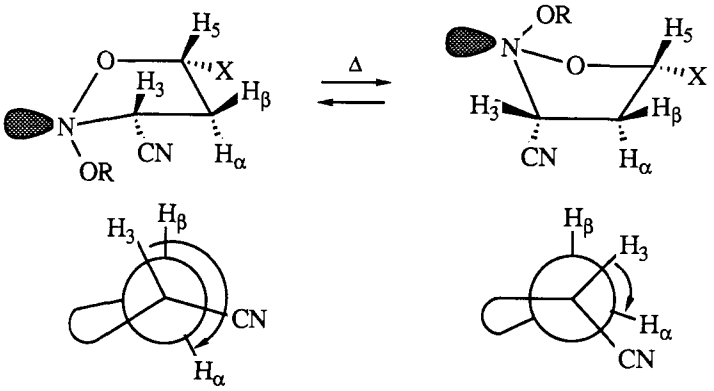
spectra recorded at different temperatures make it possible to calculate the inversion rate and barrier and relative concentration of the conformations at a given temperature. For the first time it has been postulated that nitrogen inversion should also cause reorientation of the substituents, particularly those in position 3. It has been also pointed out[90/72] that the cycloaddition invertomers are always most abundant at equilibrium and that the value of $\delta_A - \delta_B$ and the ratio $J_{AX}/J_{BX}$ are greater for invertomer **a** than for **b**. In the case of 5-substituted

2-methoxy-3,3-dinitroisoxazolidines, the substantial difference in chemical shifts $\delta_{HA}-\delta_{HB}$ can be explained by the different anisotropic effects of "pseudo-axial" or "pseudo-equatorial" $NO_2$ groups.[260/70]

X-ray analysis of two invertomers[88/69,42/74] (**22b** and **41b**) confirmed the exact interpretation of the PMR data for both the stereochemistry of the cycloaddition and for conformational analysis of the isoxazolidine ring (see § 3.2.6). Since the two invertomers often could be isolated, the following remarks are in order:[227/76]

1. The $H_3$ proton is always more shielded in the invertomer in which $H_3$ is *cis* to the free doublet of the nitrogen.
2. The coupling constants $J_{5\text{-}4\alpha}$ (*trans*) are larger when $H_5$ is *cis* to the free doublet of the nitrogen.
3. The values of the $J_{5\text{-}4\alpha}$ (*trans*) are lower (4.6–6.4 Hz) than the $J_{5\text{-}4\beta}$ (*cis*)(8.8–9.5 Hz) in the case of 2,3,5-trisubstituted isoxazolidines.
4. Low values of $J_{3\text{-}4}$ (ca. 2 Hz) correspond to a *trans* configuration.

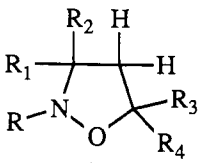
By these data it is possible to determine the relative stereochemistry of the substituted isoxazolidine. Comparison of the *trans* $J_{3\text{-}4}$ values in the two invertomers, which change from a low value (2 Hz, see note 4) to a value of 9–11 Hz, affirmed that the nitrogen inversion also causes a conformational variation in the ring. In both invertomers the most similar conformation is that of an envelope with the nitrogen atom out of plane, the free doublet being in a pseudo-equatorial configuration and the substituent in a pseudo-axial configuration, as represented in the following examples:




From molecular models it is possible to verify (as reported in the Newman projections) that the dihedral angles $H_3-C_3-C_4-H_{4\alpha}$ are quite different in the two invertomers, and therefore for the Karplus rule, the coupling constants are different. It has also been stated[228/76] that the preferred conformations assumed

by both invertomers are unique in always keeping the three free doublets and the three doublets of the polar bands (N–OR, C–N, O–C) in a *gauche* position.

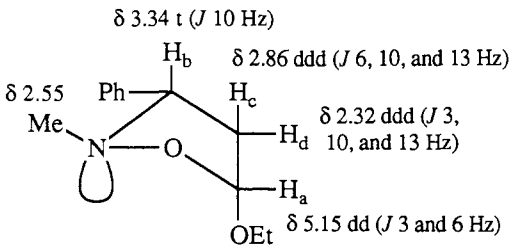
The conformation of the isoxazolidine ring for some other 2,3,3-trisubstituted-5-phenylisoxazolidines (see Tables 3.4 and 3.6, and **36** and **25–27**) has been studied in comparison with those of substituted isoxazolidines.[254/72] As one can check from the PMR data reported in Table 3.4, in these cases in going from one isomer to the other (**b** → **a**), only nitrogen inversion occurs. In fact, the mutual position of the protons is the same in both invertomers, as shown by the coupling constants ($J_{BX} > J_{AX}$ in all cases). In the work cited, the PMR data are discussed in relation to the substituent effect. In all cases the cycloaddition of nitronic esters to styrene yielded the **b** isomer with the phenyl group *cis* to the free pair of the nitrogen. For some 2,3,5-tri- and 2,3,5,5-tetrasubstituted isoxazolidines, the configuration and conformation have been determined by means of nuclear Overhauser effect difference spectroscopy[204/82] (NOEDS) and the coupling-constant values:[204/82]



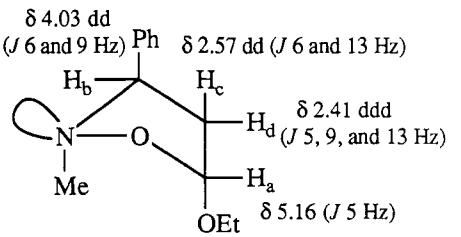

**44**

| Compound | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|---|
| **44a** | Me | Ph | H | OEt | H |
| **44b** | Me | Ph | H | OEt | H |

For example, the conformation of the two 5-ethoxy-2-methyl-3-phenylisoxazolidines (**45**) and other simple isoxazolidines could be determined only by NOEDS, since in all cases the measured coupling constants could be interpreted in different ways. Data using the NOEDS technique have been reported in detail and discussed.[204/82]



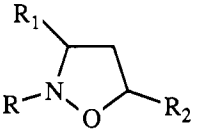

**45a**




**45b**

The *cis* and *trans* 2-$^{15}N$-methyl-3,3,4,5-tetra(methoxycarbonyl)isoxazolidines have been studied largely by means of different techniques. The conformation in solution of the *trans* isomer detected by NMR spectroscopy was the same as that in the crystalline state as determined by x-ray analysis.[136/82] Full NMR data recorded in five different solvents were reported and discussed. An envelope conformation with a pseudo-equatorial *N*-methyl group was found.[136/82]

Lanthanide shift reagents have been utilized successfully in the isoxazolidine field either to study the molecular geometry or to estimate the relative quantity of two isomers. The first papers concerned mainly compounds with the isoxazolidine ring fused to other heterocyclic systems,[141/74,179B/74,193/76,30/78,28/79,20/81] which often contain more than one coordination center. However, the NMR-LIS (Lanthanide induced shift) technique has been well utilized for evaluation of epimeric mixtures of 5-regioisomeric isoxazolidines[139/84] as, for example:



**46 a** $R = R_1 = R_2 = Ph$
**b** $R = Me$, $R_1 = R_2 = Ph$
**c** $R = R_1 = Ph$, $R_2 = COOMe$

**46a** and **46b** have been used as reference compounds.

The equilibrium constant for the reaction

$$\text{Lanthanide} + \text{Substrate} \rightleftharpoons \text{Lanthanide - Substrate}$$

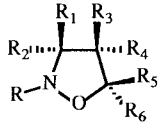
is negligible for **46a**. The complex is more stable for **46b**, but a strong increase in the line width, due probably to the dipolar relaxation of the paramagnetic center, enables the signals to be identified. Better results were obtained for **46c**. Chemical and limiting shifts have been reported and discussed.

The LISCA computer program made it possible to assign the stereochemistry of the various isomers.[139/84] The optical purity of (+)-2-methoxyisoxazolidine-3,3-dicarboxylic acid bismethylamide has been determined by the NMR spectrum in the presence of the optically active shift reagent tris[3-trifluoromethyloxymethylene-D-camphorate]europium III.[212/79]

### *3.2.3.2 $^{13}C$-NMR Spectra*

$^{13}C$-NMR has also been used to elucidate the structure and stereochemistry of some isoxazolidine cycloadducts. The first $^{13}C$-NMR data were reported for cycloadducts obtained from *C*-(2′,5′-dimethoxyphenyl)-*N*-phenylnitrone and dimethyl fumarate or methyl metacrylate[103/76] (see Table 3.7). In the latter case it was possible to assign the relative configuration of the methyl group at the 5-position by the presence of a long-range $^3J$ value ($^{13}C$–C–C–$^1H$)(3.90 Hz), beyond the usual one-bond $^{13}C$–$^1H$ coupling. This small coupling constant has

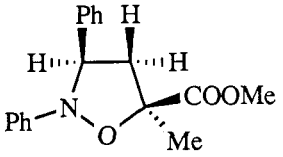
TABLE 3.7. $^{13}$C-NMR CHEMICAL SHIFTS (ppm) OF ISOXAZOLIDINES



| R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Solvent | $C_3$ | $C_4$ | $C_5$ | Others | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1-cyclohexen-3-yl | H | H | H | H | H | H | neat | 51.6 t | not indicated | 65.0 t | - | 165/80 |
| H | H | COOBu-*t* | H | H | H | H | $CDCl_3$ | 61.1 d | 34.9 t | 69.4 t | 27.9 q (Me), 82.1 s (C), 171.1 s (C=O) | 103/83 |
| H | Me | H | Me | Me | H | H | $CDCl_3$ | 64.3 d | 44.6 s | 82.6 t | - | 213/83 |
| H | $CONEt_2$ | Me | Ph | H | H | OH | $CDCl_3$ | 71.3 s | 65.6 d | 106.4 d | 27.1 q (Me) | 230/81 |
| H | $CONEt_2$ | Me | Ph | H | OH | H | $CDCl_3$ | 70.7 s | 64.6 d | 100.5 d | 27.1 q (Me) | 230/81 |
| H | $CONEt_2$ | Me | Ph | H | OH | Me | $CDCl_3$ | 71.1 s | 69.2 d | 107.1 s | - | 191/83 |
| H | $CONEt_2$ | Me | Ph | H | Me | OH | $CDCl_3$ | 72.3 s | 67.3 d | 108.5 s | - | 191/83 |
| t-Bu | Ph | H | H | CN | $NO_2$ | H | $CDCl_3$ | 69.2 d | 50.2 d | 102.5 d | 20.6 q (Me), 59.9 s (C), 116.1 s (CN) | 99/81 |
| t-Bu | Ph | H | H | $NO_2$ | CN | H | $CDCl_3$ | 68.3 d | 66.7 d | 98.8 d | 26.1 q (Me), 59.6 s (C), 115.8 s (CN) | 99/81 |
| Ph | Ph | H | H | H | COOMe | Me | $CDCl_3$ | 69.7 d | 50.0 t | 83.2 s | 22.42 q (Me) | 103/76, 88/77 |
| Ph | $2,5(MeO)_2C_6H_3$ | H | H | H | COOMe | Me | $CDCl_3$ | 63.9 d | 55.8 t | 83.4 s | - | 103/76 |
| Ph | $2,5(MeO)_2C_6H_3$ | H | H | COOMe | COOMe | H | $CDCl_3$ | 67.7 d | 59.9 d | 78.6 d | - | 103/76 |
| Ph | $CH_2COOEt$ | H | COOEt | H | N(Ph)OH | H | DMSO-$d_6$ | 66.3 d [a] | 52.1 d [a] | 95.7 d [a] | 38.6 t ($CH_2$) | 272/80 |
| Ph | Et | H | Me | H | N(Ph)OH | H | DMSO-$d_6$ | 76.4 d | 43.4 d | 99.5 d | 26.4 t ($CH_2$) | 272/80 |
| CO(2-$C_6H_4$COOMe) | H | H | OH | H | H | H | $CDCl_3$ | 53.2 t | 72.7 d | 77.0 t | - | 190/82 |
| Ph | Ph | H | H | $SO_2Ph$ | H | H | $CDCl_3$ | 70.0 d | 77.0 d | 66.6 t | - | 172/83 |
| Ph | Ph | H | H | $SO_2Ph$ | Ph | H | $CDCl_3$ | 71.0 d | 80.7 d | 83.7 d | - | 172/83 |
| Ph | 4-$NO_2C_6H_4$ | H | H | $SO_2Ph$ | Me | H | $CDCl_3$ | 70.1 d | 83.0 d | 76.3 d | 17.9 q (Me) | 172/83 |
| Ph | Ph | H | H | $SO_2Ph$ | COPh | H | $CDCl_3$ | 71.1 d | 75.5 d | 79.5 d | - | 172/83 |

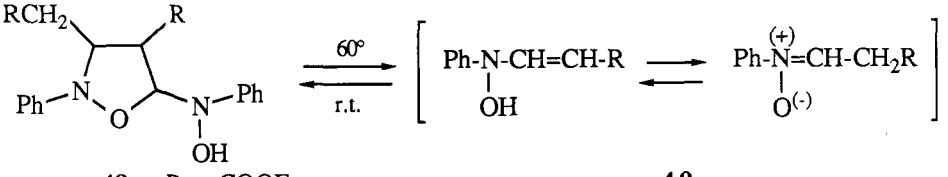
[a] $J_{H\text{-}C\text{-}3}$ = 145 Hz; $J_{H\text{-}C\text{-}4}$ = 136 Hz; $J_{H\text{-}C\text{-}5}$ 161 Hz.

been attributed to interaction between the methyl group and the 4-*cis* proton.[88/77] In fact, this proton, as shown by molecular models, has a dihedral angle of about 0° with the methyl. Since this proton is also *cis* to the proton at $C_3$, the relative configuration of the cycloadduct is as depicted in formula **47** (see the data in Table 3.7).




**47**

Thermal equilibrium in DMSO between isoxazolidines (**48a** and **b**) and *N*-hydroxyenamines (**49**) has been studied by $^1$H and $^{13}$C-NMR[272/80] (see Table 3.7):



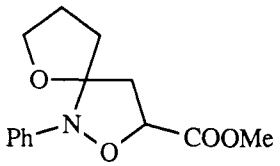

**48 a** R = COOEt
**b** R = Me

**49**

The cycloaddition of phenyl-*N*-*tert*-butylnitrones to *trans* 1-cyano-2-nitroethylene led to two isomeric isoxazolidines, useful intermediates in the synthesis of β-lactams,[99/81] whose structures were determined by PMR and $^{13}$C-NMR data. The latter are reported in Table 3.7 together with the $^{13}$C-NMR data of simple isoxazolidines.[165/80,230/81,190/82,172/83,191/83,213/83] Signals showing similar chemical shifts also have been assigned on the basis of long-range coupling constants.[172/83] The structure of the epimer 2-glycosylisoxazolidine carboxylates has also been determined by means of $^{13}$C-NMR data.[103/83]

The $^{13}$C-NMR data for some *cis* and *trans* stereoisomeric isoxazolidines have been reported and discussed. The $^{13}$C-NMR spectrum of the *cis*/*trans* 3-methyl-5-phenylisoxazolidine mixture (2:1) has been recorded at different temperatures (−30 and +60°C). At the lower temperature the equilibrium between the invertomers is blocked and the presence of four isomeric species could be detected. The coalescence point is at about 30°C.[9/80]

For *cis*/*trans* 2-methyl-3,3,4,5-tetra(methoxycarbonyl)isoxazolidines the $^{13}$C-NMR data in different solvents are reported.[136/82] $^{13}$C-NMR chemical shifts of two isomeric spiro(isoxazolidin-3,2′-tetrahydrofuran) compounds (**50**), together with other spectroscopic data, made it possible to determine the structure.[113/77]

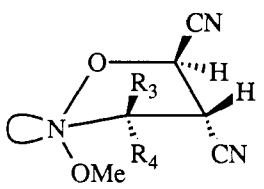


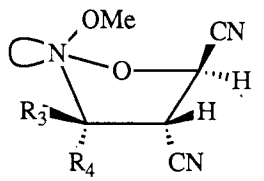
**50**

### *3.2.3.3 $^{15}N$-NMR Spectra*

Configurations of 2-methoxy-4,5-dicyano-3-methoxycarbonylisoxazolidine invertomers have been studied on the basis of the $^{2}J_{^{15}N\text{-}H}$ and $^{3}J_{^{15}N\text{-}H}$ coupling constants (Table 3.8).[83/75] In studies of the stereochemistry of 2-methyl-3,3,4,5-

TABLE 3.8





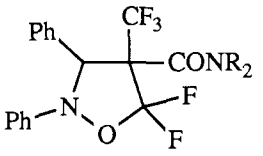
**51 a** $R_3 = H$ $R_4 = COOMe$ **51 b**
**52 a** $R_3 = COOMe$ $R_4 = H$ **52 b**

| Compound | $^{2}J(^{15}N\text{-}H_3)$ | $^{3}J(^{15}N\text{-}H_4)$ | $^{3}J(^{15}N\text{-}H_5)$ | $J(^{15}N\text{-}OMe)$ |
|---|---|---|---|---|
| **51 a** | 4.1 | 1.4 | < 0.1 | 4.1 |
| **b** | 1.1 | < 0.1 | 1.9 | 4.1 |
| **52 a** | < 0.1 | 0.8 | < 0.1 | 4.0 |
| **b** | 4.1 | < 0.1 | 1.9 | 4.0 |

tetramethoxycarbonylisoxazolidine, the $^{15}N$ derivative has been prepared and analyzed. For the *trans* isomer the following $^{15}N$-NMR data have been recorded in benzene solution: $\delta\ ^{15}N = 200.8$; $J_{H_5\text{-}^{15}N} = 3.0$ Hz, $J_{H_4\text{-}^{15}N} = 2.5$ Hz, $J_{Me\text{-}^{15}N} = 2.1$ Hz, and $J_{^{15}N\text{-}^{13}C_5} = 3.66$, $J_{^{15}N\text{-}^{13}C_3} = 3.66$ Hz. Some data are also reported for the *cis* isomer.[136/82]

### *3.2.3.4 $^{19}F$- and $^{31}P$-NMR Spectra*

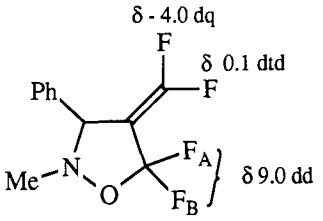
$^{19}F$-NMR and PMR data for 4-dialkylaminocarbonyl-5,5-difluoro-2,3-diphenyl-4-trifluoromethylisoxazolidines (**53**),[145/78] 5-alkoxy-3,3-bis(trifluoromethyl)-2-nitrosoisoxazolidines ($CF_3$ groups absorbing in the range $-21.02$ to



**53 a** R = Et
**b** R = Me

$-21.02$ to $-25.43$ from trifluoroacetic acid with $J = 10.5$ Hz),[337/83] and 2-methyl-4-aryl-5-(perfluorohexylsulfonyl)isoxazolidines[81/84] have been reported.

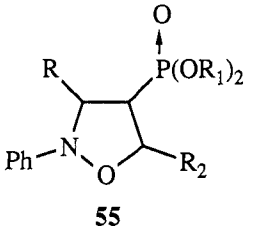
The following data for 4-difluoromethylene-5,5-difluoro-2-methyl-3-phenylisoxazolidine (**54**) are reported using $CF_3COOH$ as the internal standard:[159/83]



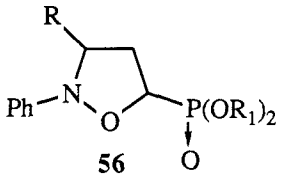
$^2J_{FF} = 27$ Hz $J_t = 9$ Hz
$J_q = 4$ Hz $J_{AB} = 168$ Hz

**54**

$^{31}$P-NMR and PMR studies were very useful in establishing structures and conformations of several variously substituted *N*-phenyl-4-(or 5-)phosphonoisoxazolidines (**55** and **56**).[81/75,84/75,117/76,147/78,129/80,130B/80] Spectra are reported in these studies, and detailed discussions of the coupling constants of both NMR spectra illustrate how the data can be used to elucidate configurations in this field.



**55**

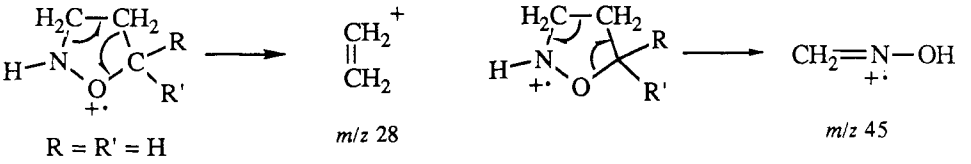


**56**

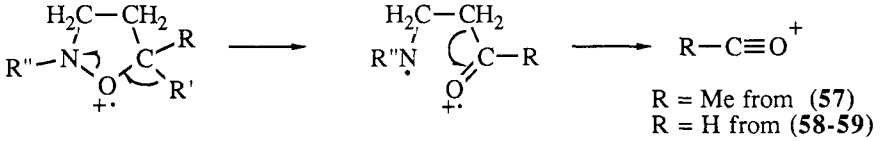
### 3.2.4 Mass Spectra

Mass spectra of isoxazolidines show peaks due to many different ring cleavages which are more or less important depending on the substituents on the ring. Usually, the molecular ion is detectable.

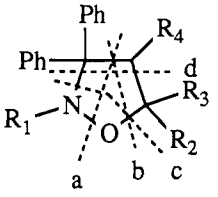
In addition to the molecular ion ($M^+$ = 73, 67%), isoxazolidine itself shows two strong peaks at *m/z* 45 (100%) and *m/z* 28 (67%) due to the formaldoxime and ethylene ions, respectively.[139/67] They arise as indicated in the following scheme:




Comparison of the mass spectra of isoxazolidine and 2-D-isoxazolidine, recorded at 30 eV, with those of pyrrolidine and other amines showed that the intensities of the amine-type fragments $[M - 1]^+$ for isoxazolidine and its deuterated derivative are lower than for amines.[141/84] In the case of 5-methyl-5-methoxycarbonylisoxazolidine (**57**), 2-ethoxycarbonylisoxazolidine (**58**), and 2-ethoxycarbonyl-5-methoxycarbonylisoxazolidine (**59**),[139/67] the first loss of the COOMe and COOEt ions is followed by cleavage of the ring as reported above. Moreover, peaks at *m/z* 43 for **57** and at *m/z* 29 for **58** and **59** are assigned to $MeC{\equiv}O^+$ and $HC{\equiv}O^+$ ions, respectively. These are formed by cleavage of the N–O and $C_4$–$C_5$ bonds:

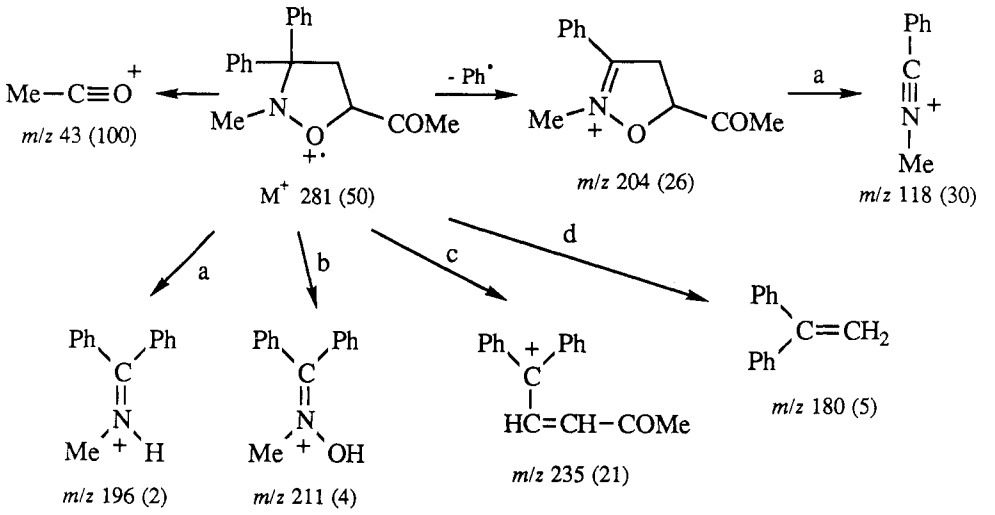



The presence of two phenyl groups in position 3 gives rise to many fragments, due to the competing simultaneous cleavage of two bonds of the isoxazolidine ring as indicated by the letters *a* (N–O and $C_3$–$C_4$ bonds), *b* (C–O and $C_3$–$C_4$ bonds), *c* (C–N and C–O bonds), and *d* (C–N and $C_4$–$C_5$ bonds)[156/67] in **60**. For



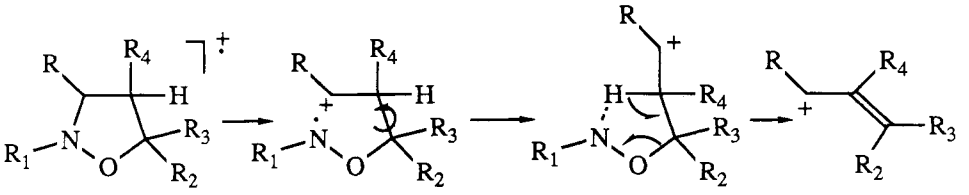
**60**

example, the mass spectrum of 5-acetyl-3,3-diphenyl-2-methylisoxazolidine shows the ions arising from the loss of the substituents and from the ring cleavages (Scheme 3.1).




**Scheme 3.1.**

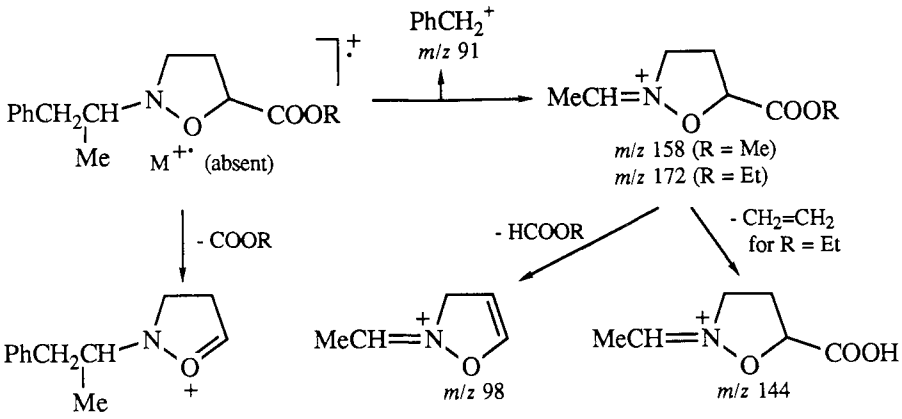
In *N*-alkyl and *N*-arylisoxazolidines, rearrangement with loss of the $R^1NHO$ radical and *c* ring cleavage occurs, which can be explained as in the following scheme:[189/71]




When hydrogens are not present at $C_4$, the rearrangement is not observed. The proposed mechanism has been proved by deuterium labeling at $C_4$ in the case of 2,3,5,5-tetraphenylisoxazolidine and of 2-methyl-3,5,5-triphenylisoxazolidine, which lose from the molecular ion the fragments *m/z* 109 (PhNDO) and *m/z* 47 ($CH_3NDO$), respectively. Cleavages of the isoxazolidine ring described above represent a useful tool to establish the position of substituents on the isoxazolidine nucleus. For example, in two regioisomeric compounds, 2,4-dimethyl-5-ethylisoxazolidine and 2,5-dimethyl-4-ethylisoxazolidine, the most characteristic peaks at *m/z* 57 ($C_2H_5C{\equiv}O^+$) for the former and at *m/z* 43 ($CH_3C{\equiv}O^+$) for the latter made it possible to establish the nature of the 5-substituent beyond any doubt.[125/73]

Similar results have been obtained for the cycloaddition products of alkyl acrylates and α-methyl-(*N*-methylene)benzeneethanamine *N*-oxide: only the

diastereoisomeric 2,5-disubstituted isoxazolidines could be detected.[40/78] Diastereoisomers show identical mass spectra which have readily been interpreted as follows:




It is worth noting that the mass spectra of cycloadducts are much more diagnostic than the spectrum of nitrones. Therefore, this method can be used for nitrone structure determination.[40/78] Some other structures of regioisomeric isoxazolidines have been determined by mass spectrometry on the basis of retro-cycloaddition and of preferential ring cleavages.[78/75,103/76,30/78,31/78,40/79]

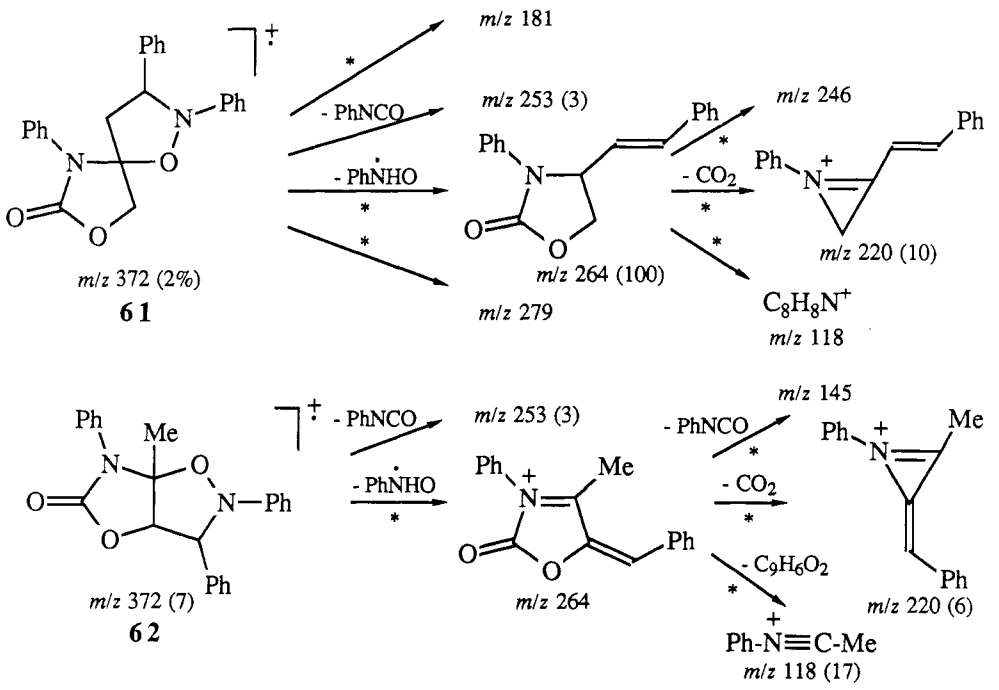
The mass spectrum of isoxazolidines obtained by nitrone dimerization shows, in addition to the molecular ion, a strong peak corresponding to the protonated nitrone, thus indicating that the retro-dimerization process occurs with the transfer of one hydrogen.[40/79] Epimeric isoxazolidines show quite similar mass spectra.[87/69] Mass spectral data of epimeric 2-methyl-3-phenyl-5-ethoxyisoxazolidines have been reported.[204/82]

From the reaction between 4-methylene-1,3-isoxazolidin-2-ones and nitrones, two structural isomers containing either a spiro or a condensed isoxazolidine ring have been obtained. Structures have been elucidated by spectroscopic methods, particularly by mass spectroscopy.[141/74] Fragmentations have been studied by DADI (direct analysis of daughter ions) and IKE (ion kinetic energy) techniques. Results are reported in Scheme 3.2 for compounds **61** and **62**.

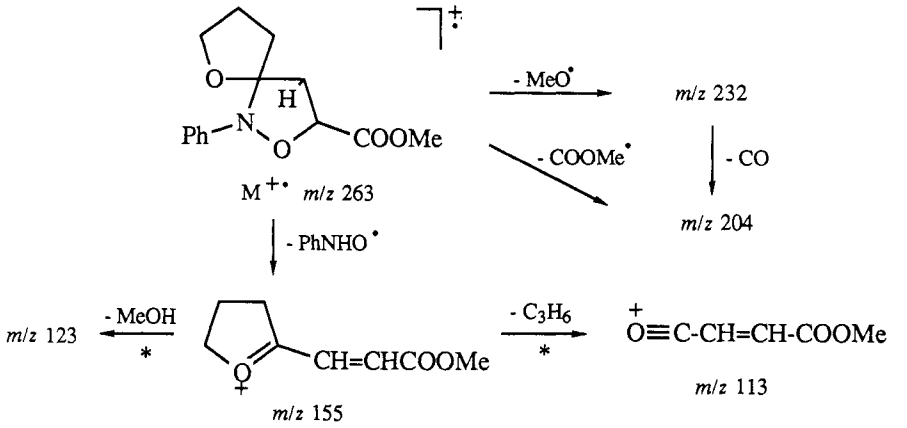
The mass spectrum of spiro(2-phenyl-5-ethoxycarbonyl-isoxazolidin-3,2′-tetrahydrofurane) has been discussed as shown in the scheme on p. 674, the first ring opening being due to the isoxazolidine cleavage.[113/77]

It is interesting to note that the most characteristic fragment ions derive from cleavage of the isoxazolidine ring.

Field desorption ionization has been used to study a mixture of synthetic isoxazolidines[60B/82] and chemical ionization, with isobutane as the carrier gas, to detect the molecular ion.[204/82,217/83] The most characteristic ions identified from



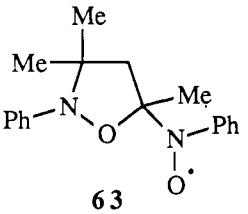

Scheme 3.2.




some 4-difluoromethylene-5,5-difluoro-3-phenyl-2-substituted isoxazolidines have been reported without discussion.[159/83]

### 3.2.5 Other Spectra

The oxidation product of 5-[hydroxy(phenyl)amino]-3,3,5-trimethyl-2-phenylisoxazolidine, known as nitroxide of Banfield and Kenyon, is the red



**63**

crystalline free radical **63**. Its electron spin resonance (ESR) spectrum and those of related nitroxides have been analyzed and all proton coupling constants measured and discussed.[159/76] ESR spectra of some other 5-isoxazolidineamino oxides have been studied together with those of other types of amino oxides.[19/79]

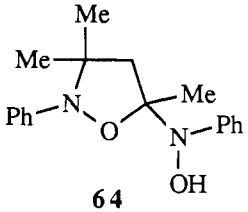
Conformational analysis studies by photoelectron spectroscopy (PES)[256/78] on isoxazolidine, 2-methylisoxazolidine, and *tert*-butylisoxazolidine indicated the presence of two conformers, depending on the equatorial or axial configuration of the substituents. The two conformers are present in the following ratio:

| | *ax* | *eq* |
|---|---|---|
| Isoxazolidine | 3 | 1 |
| 2-Methylisoxazolidine | 1 | 4 |
| 2-*tert*-Butylisoxazolidine | 1 | 10 |

The formation of isoxazolidines from tetranitromethane and olefins has been studied by means of electron paramagnetic resonance (EPR) spectroscopy.[243/70]

### 3.2.6 Crystal and Molecular Structure

X-ray analysis has occasionally been used as a tool to establish the structure of isoxazolidines. In this way the actual structure of the reaction products from acetone and *N*-phenylhydroxylamine has been determined as 5-[hydroxy-(phenyl)amino]-3,3,5-trimethyl-2-phenylisoxazolidine (**64**).[52/68,151/74]

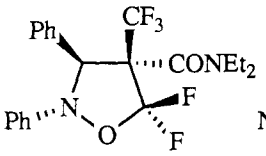


**64**

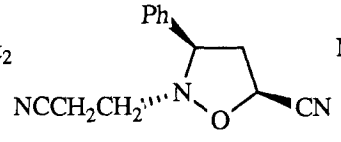
From a detailed x-ray analysis[145/78] of the structure of 4-(diethylaminocarbonyl)5,5-difluoro-2,3-diphenyl-4-(trifluoromethyl)isoxazolidine (**65**) it has been shown that the heterocyclic ring is in an "envelope-like" conformation

with the N–O–$C_4$–$C_5$ atoms in one plane (with a torsional angle of 95°) and the $C_3$ out of plane. Both phenyl groups are in an axial *trans* configuration.[145/78]

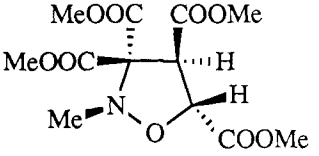
ORTEP diagrams and full data have also been reported for the *cis*-2-(2′-cyanoethyl)-3-phenyl-5-cyanoisoxazolidine (**66**)[72/84] and for the *trans*-2-methyl-3,3,4,5-tetramethoxycarbonylisoxazolidine (**67**).[136/82] In the former compound (**66**) the isoxazolidine ring has an envelope conformation (flop angle of 49.9°) like that of most isoxazolidines. The stereochemical arrangement found shows




**65**



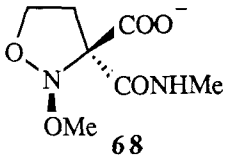

**66**



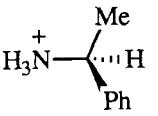

**67**

that the phenyl and cyano substituents are *cis* with respect to each other and with respect to the nitrogen of the heterocyclic ring.[72/84] The latter compound (**67**) also shows an envelope conformation with a pseudo-equatorial N-Me group, both in the crystalline state and in solution.[136/82] Some examples of bond lengths and angles of isoxazolidine rings are given in Table 3.9.

The absolute configuration of *S*-α-phenylethylammonium salt of 2-methoxyisoxazolidine-3,3-dicarboxylic acid *trans*-methylamide (**68**) has also been established by means of x-ray analysis.[212/79] All the bond lengths and bond




**68**

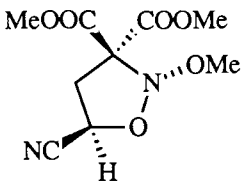



angles have been tabulated. The heterocyclic anion in this case is also in the "envelope-like" conformation, but with the nitrogen out of plane and the MeO–N group axial. Some hydrogen bonding, evidenced by the shortening of the N(ring)···H(NH) length, stabilizes the *trans* orientation of the amide group with respect to the nitrogen substituent. Comparison of the structural parameters of the isoxazolidine ring studied previously is also reported.

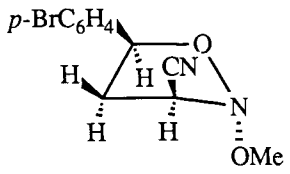
1,3-Dipolar cycloaddition of nitronic esters to activated olefins can lead under kinetic control to only one invertomer (see § 3.2.8, p. 681). Some *N*-methoxy invertomers have been isolated and their structures determined by x-ray analysis. For example, to the most stable invertomer of the reaction of α,α-diethoxycarbonyl-*N*-methylnitrone with acrylonitrile, structure **69**[88/69] has been assigned with the *N*-methoxy group *trans* to the cyano group.

TABLE 3.9. BOND LENGTHS (Å) AND ANGLES (DEGREES) OF SOME ISOXAZOLIDINES

| | **64** Form I 151/74 | Form II 151/74 | **65** 145/78 | **66** 72/84 | **67** 136/82 | **68** 212/79 | **70** 42/74 | **71** 143/78 |
|---|---|---|---|---|---|---|---|---|
| Bond lengths | | | | | | | | |
| N-O | 1.460 | 1.470 | 1.484 | 1.466 | 1.466 | 1.418 | 1.412 | 1.430 |
| N-$C_3$ | 1.507 | 1.504 | 1.467 | 1.467 | 1.494 | 1.488 | 1.498 | 1.477 |
| $C_3$-$C_4$ | 1.514 | 1.507 | 1.570 | 1.534 | 1.545 | 1.522 | 1.512 | 1.523 |
| $C_4$-$C_5$ | 1.519 | 1.551 | 1.547 | 1.533 | 1.547 | 1.501 | 1.533 | 1.524 |
| $C_5$-O | 1.411 | 1.384 | 1.334 | 1.436 | 1.421 | 1.460 | 1.455 | 1.450 |
| N-R | 1.425 | 1.394 | 1.437 | 1.470 | 1.472 | 1.434 | 1.455 | 1.435 |
| $C_3$-R | 1.514 | 1.499 | 1.515 | 1.515 | 1.533 | 1.535 | 1.480 | 1.545 |
| $C_3$-R' | 1.525 | 1.504 | - | - | 1.535 | 1.555 | - | 1.539 |
| $C_4$-R | - | - | 1.573 | - | 1.512 | - | - | - |
| $C_4$-R' | - | - | 1.535 | - | - | - | - | - |
| $C_5$-R | 1.505 | 1.503 | 1.349 | 1.475 | 1.521 | - | 1.518 | 1.537 |
| $C_5$-R' | 1.543 | 1.495 | 1.345 | - | - | - | - | 1.562 |
| Bond angles | | | | | | | | |
| O-N-$C_3$ | 100.9 | 101.5 | 102.4 | 101.6 | 103.3 | 103.1 | 102.1 | 101.4 |
| N-$C_3$-$C_4$ | 98.2 | 100.1 | 101.6 | 101.3 | 100.2 | 105.2 | 105.9 | 104.2 |
| $C_3$-$C_4$-$C_5$ | 104.0 | 103.9 | 98.3 | 103.3 | 103.9 | 102.8 | 103.5 | 100.9 |
| $C_4$-$C_5$-O | 106.5 | 106.2 | 110.7 | 105.0 | 106.3 | 106.8 | 105.0 | 106.2 |
| $C_5$-O-N | 103.2 | 104.2 | 108.2 | 101.4 | 104.4 | 109.5 | 109.1 | 109.2 |
| N-$C_3$-R | 113.4 | 114.4 | 108.9 | - | 106.5 | 107.8 (β) | 106.1 | 108.7 |
| N-$C_3$-R' | 108.3 | 106.3 | - | 111.0 | 114.7 | 111.2 (α) | - | 111.4 |
| $C_4$-$C_3$-R | 112.8 | 111.4 | 122.4 | 115.8 | 113.8/113.9 | 111.4 | 112.8 | 110.2 |
| $C_4$-$C_3$-R' | 112.4 | 111.7 | - | - | - | 115.2 | - | 114.9 |
| $C_4$-$C_5$-R | 112.9 | 115.2 | - | 112.6 | 110.8 | 109 | - | 114.1 |
| $C_4$-$C_5$-R' | 108.6 | 108.4 | - | - | - | 116 | - | 111.5 |
| O-$C_5$-R | 107.4 | 106.1 | - | 109.6 | 113.6 | 107 | 108.1 | 108.9 |
| O-$C_5$-R' | 107.6 | 106.9 | - | - | - | 111 | - | 109.0 |
| $C_3$-N-R | 115.9 | 116.6 | 118.1 | 112.4 | 115.1 | 104.5 | 101.5 | 103.1 |
| O-N-R | 106.8 | 107.0 | 104.5 | 104.7 | 103.7 | 107.2 | 107.5 | 107.4 |
| $C_3$-$C_4$-R | - | - | 108.4 | - | - | 114 | - | - |
| $C_3$-$C_4$-R' | - | - | - | - | - | 115 | - | - |

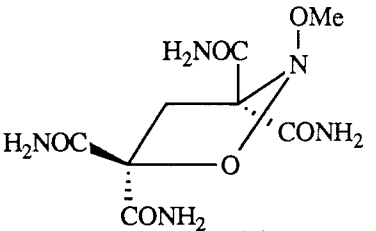



**69**




**70**

In the case of 3-cyano-5-*p*-bromophenyl-*N*-methoxyisoxazolidine (**70**), the *N*-methoxy group is *trans* to both other substituents.[42/74] In all cases the envelope conformation of the heterocyclic ring shows the nitrogen atom out of the plane of $O-C_3-C_4-C_5$ with the substituent in the axial configuration. A similar structure was determined in the case of 2-methoxyisoxazolidine-3,3,5,5-tetracarboxamide (**71**).[143/78]

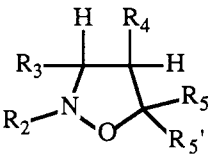



**71**

### 3.2.7 Dipole Moments

The dipole moments of some isoxazolidines have been measured[55/69] (see Table 3.10). Isoxazolidine itself shows a dipole moment of 2.88 D in $C_6H_6$ at

TABLE 3.10

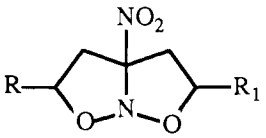



| | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_5'$ | $\mu_{benzene}$ (D) | $\mu_{dioxane}$ (D) | References |
|---|---|---|---|---|---|---|---|---|
| a | H | H | H | H | H | 2.88 | 3.10 | 55/69 |
| b | Ph | Ph | H | Ph | H | 2.47 | - | 55/69 |
| c | Ph | Ph | H | Ph | Ph | 2.19 | - | 55/69 |
| d | Ph | Ph | Ph | Ph | H | 2.54 | - | 55/69 |
| e | Ph | *p*-$NO_2C_6H_4$ | H | Ph | H | - | 5.15 | 55/69 |
| f | Ph | *p*-$NO_2C_6H_4$ | H | Ph | Ph | - | 4.35 | 55/69 |
| g | Ph | H | H | OCOMe | H | 2.95 | - | 55/69 |
| h | COOEt | Ph | H | H | H | 2.97 | - | 55/69 |
| i | Me | Ph | H | COOEt | H | 2.48 | - | 15C/69 |

25°C and 3.10 D in dioxane at 25°C which can be explained by a half-chair conformation of the ring.

Two isomeric 8-nitro-2,6-diphenylisoxazolizidines (**1**, **m**, Table 3.11) could be obtained by reaction of 3-nitro-5-phenylisoxazoline *N*-oxide with styrene and isolated by PLC.[254/72] The spatial configuration of these two isomers has been

TABLE 3.11

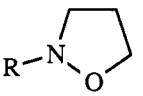


| | R | $R_1$ | $\mu_{benzene}$ (D) | References |
|---|---|---|---|---|
| l | H | H | 5.03 | 254/72 |
| m | β Ph | β Ph | 5.21 | 254/72 |
| n | α Ph | β Ph | 4.92 | 254/72 |

determined, along with a study of the PMR spectra, by comparison of their dipole moments with that of 8-nitroisoxazolizidine (**1**, Table 3.11). Since the vector of the dipole moment of **1** must be directed, according to x-ray structural analysis, out of the "book" formed by the two isoxazolidine rings in the $C^8$–$N^4$–$NO_2$ plane and the vector of the C–Ph bond is directed toward the phenyl group, the increase of 0.18 D in the dipole moment of **m** could be explained by a symmetrical structure with both phenyl groups in the *exo* configuration. By contrast, the decrease of 0.11 D for **n** indicated the nonequivalence of the phenyl groups in the second compound.

### 3.2.8 Invertomers

As mentioned briefly in § 3.2.3.1, p. 660, PMR studies pointed out for the first time that the isoxazolidine ring can assume different conformations due to the inversion of the ring nitrogen atom. Some simple N-substituted isoxazolidines (**72**) have been studied[51/68,53/68] to measure the coalescence temperature ($T_c$) and the activation free energy ($\Delta G_c^+$).



**72 a** R = Me
**b** R = $Me_2CH$
**c** R = $CH_2OMe$

In the case of **72a**, the signal of the N–$CH_2$ ring protons has been recorded at different temperatures: at high temperatures it appeared in a $CDCl_3$ solution as a triplet, but at low temperatures the two protons were no longer equivalent. $T_c$ was at about 42°C, with $\Delta G_c^{\ddagger} = 15.6 \pm 0.5$ kcal/mol. In strongly hydrogen-bonding solvents, $T_c$ increases about 20°C, corresponding to a rise of the barrier by about 1.3 kcal/mol. This fact indicated that ring inversion is dissimilar but that nitrogen inversion can occur through a hydrogen-bond cleavage.

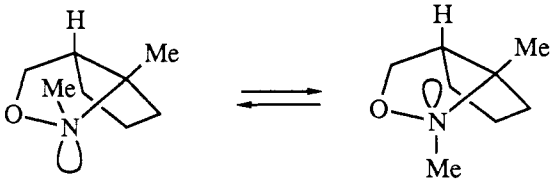
Similar results have been obtained from the PMR signals of the N-side chain protons of **72b** and **c**[53/68] recorded at different temperatures: at room tempera-

TABLE 3.12

| Compound | Solvent | Protons studied | $T_c$ | $K_c$ (sec$^{-1}$) | $\Delta G_c^{\neq}$ (kcal/mol) | References |
|---|---|---|---|---|---|---|
| 72 a | $CDCl_3$ | $CH_2$ at 3 | +42° | - | 15.6 | 51/68 |
| b | $CH_2Cl_2$ | $(\underline{CH_3})_2$-CH | +5° | 15 | 14.8 | 53/68 |
| c | $CH_2Cl_2$ | -O-$CH_2$-N | -74° | 34 | 10.3 | 53/68 |
| 73 | $CH_2Cl_2$ | $CH_3$-C | -25° | 5.8 | 13.7 | 172/70 |
| 74 | $CDCl_3$ | $CH_2$ at 3 | -32° | - | 11.6 | 148/77 |

ture, **72b** showed a doublet for the two methyls and **72c** a singlet for the O–$CH_2$–N protons, while at lower temperatures they showed a pair of doublets and an AB quartet, respectively. $T_c$, $\Delta G_c^{\ddagger}$ and the measured rate exchange ($K_c$) are reported in Table 3.12. These data are in agreement with those reported for the cyclic amines, which show an inversion too rapid to be detectable in the NMR spectra. Inversion slows down when a heteroatom is linked to the nitrogen, and this is the case for the isoxazolidine nucleus.

The presence of two invertomers could also be observed in the case of the bicyclic isoxazolidine **73** in the low-temperature PMR spectrum, which showed two singlets (at $\delta$ 0.90 and 1.00) for the *C*-methyl group:[172/70]

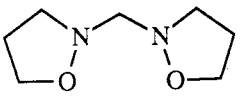



*exo*-**73** *endo*-**73**

Rates and free energies of activation have been calculated from the PMR spectra of **73** recorded in solvents of different polarity from both the equation $K_c = \pi \Delta\nu/\sqrt{2}$ and by use of a complete line shape analysis. On the basis of electronic influence (a methyl group in the less congested *exo* side), and of the effect of the hydrogen-bonding solvents on the equilibrium constants, the most intense high-field *C*-methyl singlet was assigned to *exo*-**73**. The data reported in Table 3.12 in relation to the compound structures indicated that the increase in steric bulk on the nitrogen results in a decrease of $T_c$ and $\Delta G_c^{\ddagger}$ due to the destabilization of the ground state (CNC angles of about 109°) with respect to the transition state (CNC angles of about 120°).

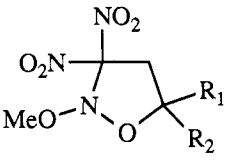
In the case of **72c**, the presence of the oxygen atom is probably responsible for the very low barrier. The same effect of a $\beta$-heteroatom has been assumed to explain the low barrier in the nitrogen inversion process for compound **74**[148/77] (see Table 3.12). By $^1$H- and $^{13}$C-NMR data for a mixture of *cis*- and *trans*-3-methyl-5-phenylisoxazolidines recorded at different temperatures, a cohalescent temperature of 30°C has been found.[9/80] An accurate conformational analysis of

2-methyl-3,3,4,5-tetramethoxycarbonyl isoxazolidines has been reported. Activation free energy of $^{14}N$ and $^{15}N$ invertomers has been evaluated.[136/82]



**74**

An accurate study of the PMR spectra of eight *N*-methoxy-3,3-dinitroisoxazolidines (**75**) at different temperatures based on the chemical shifts and coupling constants of the $C_4$ and $C_5$ protons, or in the case of **75b**, of the $C_5$ methyl groups, showed clearly the presence at low temperatures of two conformations.[260/70]



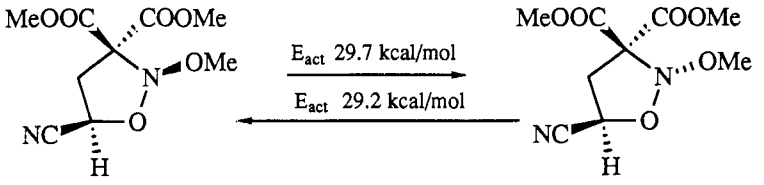
**75**

**a** $R_1 = R_2 = H$
**b** $R_1 = R_2 = Me$
**c** $R_1 = OMe$ $R_2 = H$
**d** $R_1 = OAc$ $R_2 = H$
**e** $R_1 = CN$ $R_2 = H$
**f** $R_1 = Me$ $R_2 = H$
**g** $R_1 = Ac$ $R_2 = H$
**h** $R_1 = Ph$ $R_2 = H$

The relative concentrations of the two conformers at a given temperature and the free energies of the conformations are reported. The calculated activation energy of 14.6 kcal/mol for **75b** has been attributed by the author not only to the nitrogen inversion but also to ring inversion with reorientation of the nitro groups.

Subsequently, from an analysis of the multispin *ABNQ* system of 2-methoxy-3,3-dinitroisoxazolidine invertomers (**75a**),[81C/75] the energy barrier for the inversion process has been calculated as 16 kcal/mol. Comparison of this value with those measured for some couples of substituted 2-methoxyisoxazolidines[234/72, 223/73,227/76,228/76] led the authors to assert that the introduction of a geminal dinitro group in position 3 results in decreasing the inversion barrier by 8–10 kcal/mol.

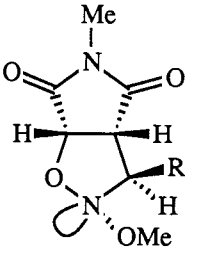
The conformations of hydroxylamine derivatives have been reviewed.[219/81] In a section on five-membered ring analogues, the literature data for isoxazolidines are reported.[219/81] In fact, as pointed in the NMR section, in some cases the 2-methoxy diastereoisomers could be isolated, because they do not invert at room temperature. For example, both invertomeric *N*-methoxy-3,3-dimethoxycarbonyl-5-cyanoisoxazolidines (**22a** and **b**) have been obtained and the Arrhenius activation energy for the epimerization calculated as reported on the arrows:[87/69]




**22 a** **22 b**

A study of the rotation process around the N–O single bond in terms of a semiempirical MO method has been reported.[97/70] The presence of two heteroatoms linked to the nitrogen can explain the increase in the energy barrier of **22** with respect to the isoxazolidines described previously (**72–74**).[208B/70]

The energy barrier has been measured for some other couples of *N*-methoxyisoxazolidine invertomers showing a different stereochemistry: $\Delta G^{\ddagger}_{110°} = 27.7$ kcal/mol for isoxazolidines with 3,4-*trans* and 4,5-*cis* substituents,[234/72] $\Delta G^{\ddagger}_{110°} = 29.3$ kcal/mol for those with all *trans* 3,4,5-substituents,[228/76] and $\Delta G^{\ddagger}_{110°} = 28.7$ kcal/mol for *cis*-3,5-dicyano-*N*-methoxyisoxazolidine.[227/76] These isoxazolidines have been obtained by cycloaddition under kinetic control of nitronic esters to mono- or diactivated olefins. Usually, only one invertomer for each regioisomer has been formed, but when the reaction products are heated in toluene, an equilibrium is reached between the invertomers.[234/72.223/73] Only the reaction product (**76**) from *trans*-nitronic ester and *N*-methylmaleimide does not isomerize in boiling toluene for 3 days.




**76**

The structure determination of the invertomers rested on the values of the coupling constants of the protons of the isoxazolidine ring deduced from PMR spectra (see § 3.2.3.1 and Table 3.1) and on the x-ray analysis of invertomers (see § 3.2.6), which showed an envelope-like structure with an axial N-substituent. However, both invertomers show a preferential conformation with the nitrogen lone pair in a pseudo-equatorial configuration and all three lone pairs and the three electron pairs of the polar bonds in the *gauche* conformation.

Regarding the nucleophilic reactivity of isoxazolidine toward 4-nitrophenylacetate, it has been reported that the interaction of lone pairs on the vicinal nitrogen and oxygen atoms may cause a small increase in the reaction rate (e.g.,

nine times greater than for tetrahydro-1,2-oxazine). In this study it was established that isoxazolidines undergo nitrogen inversion slowly with energy barriers of 14–17 kcal/mol. These values are higher than those of cyclic amines because of the strong $p_\pi$–$p_\pi$ repulsions of the lone pairs in the transition state where the nitrogen is in a trigonal configuration.[3/73]

In a study of the substituent constants for pyramidal inversion, a Hammet $\rho$ value of 1.2 has been reported for the isoxazolidine nucleus.[232/73] Configurations of 2-methoxy-4,5-dicyano-3-methoxycarbonylisoxazolidine[83/75] invertomers and of 2-methyl-3,3,4,5-tetramethoxycarbonylisoxazolidine[136/82] have also been discussed for $^{15}$N-NMR data (see § 3.2.3.3). NMR conformational studies on some *N*-trimethylsilyloxyisoxazolidines have also been reported.[112/77] In a study of the asymmetric reactions of nitrogen invertomers at equilibrium, the reaction between methyl (–)-lactate and 2-methoxyisoxazolidine-3,3-dicarboxyamide is reported and discussed.[110B/77]

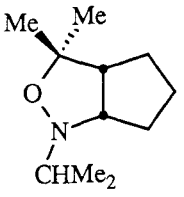
### 3.2.9 Theoretical Calculations

In the field of isoxazolidines the theoretical calculations concern primarily the nitrogen-inversion process and the stability of invertomers. For 5-cyano-2-methoxy-3,3-dimethoxycarbonylisoxazolidines, the slow N-inversion and rotation around the N–O single bond are discussed in terms of a semiempirical molecular orbital method.[97/70]

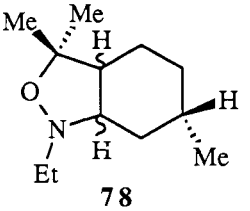
The inversion angle and energetic barriers for different dihedral angles of the envelope conformation of the isoxazolidine ring have been calculated (STO-3G method) for a theoretical study of concerted 1,3-dipolar cycloadditions.[252/78] The influence of the vicinal $n \rightarrow \sigma^*$ interaction on the structural peculiarities of *N*-alkoxyisoxazolidines, and in general of *N*,*N*-dialkoxyamines, has been taken into account.[274/82] The calculated barrier value is lower (6.4 kcal/mol) than the average experimental value ($\Delta G^{\ddagger}$ = 27.9 kcal/mol). This difference has been explained with the gain in energy due to the ground-state stabilization by $n \rightarrow \sigma^*$ hyperconjugation. The results are discussed by comparison with the data in the literature.[274/82]

### 3.2.10 Basicity

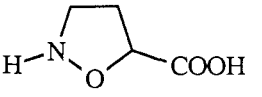
Isoxazolidine is a strong base[10B/42] with a p$K_A$ value of 5.05,[144/72] while substituted isoxazolidines show the properties of weak bases. They react with acids to give crystalline derivatives such as picrate and hydrogen oxalate salts.[20/61] They can also form methiodide salts.[20/61] Determinations of p$K_A$ carried out for **77**[59/64] and **78** in the *cis* and *trans* configurations[128/65] gave the values 5.82, 5.90, and 5.65, respectively. The amphoteric properties of isoxazolidine-5-carboxylic acid (**79**) were proved by the p$K_A$ values, measured by electrometrical titration: p$K_{AI}$ = 2.18 ± 0.05 and p$K_{AII}$ = 4.77 ± 0.05 at 22°C.[39/72]



77



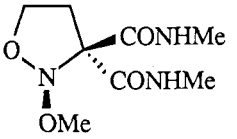
78



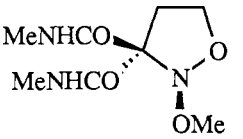
79

### 3.2.11 Miscellaneous Data

2-Methoxyisoxazolidine-3,3-dicarboxylic acid *trans*-methylamide potassium salt by transformation in the diastereoisomeric *R*(+)- and *S*(−)-phenylethylammonium salts could be separated in the two enantiomers. Esterification and amidation of these compounds yielded two pure enantiomeric 2*S*(+) and



**80 a**
2*S* (+)



**80 b**
2*R* (+)

2*R*(−) 2-methoxyisoxazolidine-3,3-carboxylic acid bismethylamides (**80a** and **b**). The spectra of circular dichroism[212/79] of the two enantiomers have been reported: **80a** showed a positive Cotton effect [$\theta^{20}_{max}$ = 54.1 ($\lambda$ 243) and 379.9 ($\lambda$ 196)] and **80b** a negative Cotton effect [$\theta^{20}_{max}$ = 50.9 ($\lambda$ 243) and 357.1 ($\lambda$ 196)].

### 3.2.12 Analysis

The TLC spots in the analysis of isoxazolidines are usually evidentiated under a UV lamp using fluorescent TLC plates. However, in some cases they are detected by iodine vapors or by spraying the plate with sulfuric acid. The Dragendorff reagent has been used to visualize diastereoisomeric alkyl 2-(1-benzyl)ethylisoxazolidine-5-carboxylate.[40/78]

Gas-liquid chromatographic analysis of isoxazolidine derivatives has been carried out primarily on various kinds of silicon grease columns: SE-30 and OV-101 for *cis* and *trans* isomers[63/63,195/82,204/82] and capillary GROB OV-61 for *N*-glycosylisoxazolidines.[103/83] By means of GLC methods, the percentages of *cis* and *trans* isomeric methyl 2-ethyl-3,4-dimethylisoxazolidine-5-carboxylate[63/63] and 5-ethoxy-2-methyl-3-phenyl- and 5-ethoxy-2-ethyl-3-methyl-isoxazolidines [195/82,204/82] have been evaluated.

In most papers dealing with the synthesis of isoxazolidines, column chromatography or preparative thin-layer chromatography for separation and purification of the products is described. In most cases chromatographic methods are carried out on silica gel. In recent years flash chromatography has been used increasingly. As usual, eluants change depending on the polarity of the molecules.

For CC separations of 2-benzoyloxycarbonyl-5-hydroxyaminocarbonylisoxazolidines mixtures of ethyl acetate and formic acid (99:1) or methylene chloride/MeOH/HCOOH (95:5:0.5) have been used.[4/78] Purification from the 1,3-dipolar cycloaddition mixture of *N*-butoxy-3,3-dinitro-5-hydroxymethylisoxazoline and similar compounds has been afforded by PLC with acidic aluminum oxide (pH 4) of grade III activity as adsorbent and a hexane/benzene (2:1) mixture as eluant.[106/68]

The percentages of *cis*- and *trans*-2,3-bis(*p*-substituted phenyl)-4,5-bis(*p*-substituted benzoyl)isoxazolidines obtained by 1,3-dipolar cycloaddition have been determined by HPLC.[296/78] The diastereoisomeric 5(*R*)-hydroxymethyl- and 5(*S*)-hydroxymethyl-2(*R*)(α-methylbenzyl)isoxazolidine have been separated by means of preparative HPLC on a Water Prep/LC-500 column using 9:1 ethyl acetate/hexane as eluant.[217/83]

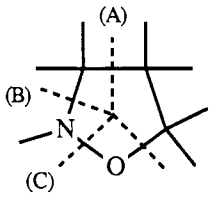
Regio- and stereo-isomer ratios of isoxazolidines obtained from cycloaddition of aldehyde oxime to acrylonitrile and methyl acrylate have been determined by analytical HPLC or by separation of the isomers by HPLC or PLC. Spherisorb silica S5W or Partisil columns have been used.[72/84]

A quantitative method for the simultaneous determination in blood of methyl methacrylate and methacrylic acid takes advantage of their reactivity toward *N*-phenyl-*C*-benzoylnitrone. Labeled compounds are used and separated by HPLC on a μ-Bondapack $C_{18}$ column to evaluate their radioactivity.[150/82]

Total separation into antipodes of 2-methoxyisoxazolidine-3,3-dicarboxylic acid bis(methylamide)[110/77] and of alkyl 2-methoxyisoxazolidine-3,3,5,5-tetracarboxylate and derivatives[116/76] could be afforded using the optical isomers of α-phenylethylamine, methyl lactate, and ephedrine. A polarographical electroreduction on hydroxylamine derivatives includes some isoxazolidine derivatives; results are discussed.[21/78]

## 3.3 SYNTHESIS

As anticipated (§ 3.1, p. 649), by far the most important method of isoxazoli-




(A) CNO + CC
(B) CCC + NO
(C) CCCN + O

dine synthesis employs nitrones or nitronic esters, which undergo 1,3-dipolar cycloadditions to olefinic compounds. This is a 3 + 2 or, more accurately, a [CNO + CC] process for ring formation:

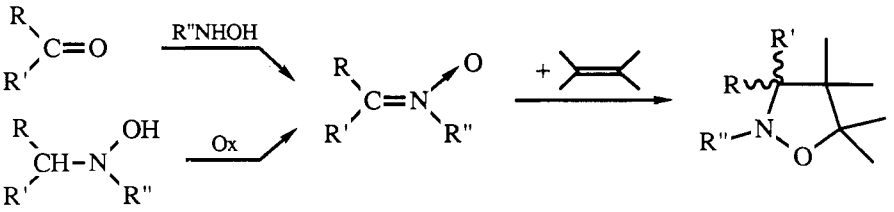
Two processes of minor preparative importance can be assigned to the same pattern: simple dimerization of some nitrones, and the reaction involving oximes instead of nitrones. Two other addition ring formation patterns [CCC + NO] and [CCCN + O], have been known up to now, and the former still accounts for the most convenient preparation of the parent compound, isoxazolidine itself. Furthermore, isoxazolidines can be built up by cyclization reactions or by transformation of other heterocycles.

## 3.3.1 [CNO + CC] Processes

### *3.3.1.1 Cycloaddition of Nitrones to Ethylenic Compounds*

#### a. General Aspects of the Reaction

Nitrones (or azomethine *N*-oxides) are perhaps the most extensively studied allyl-type[207C/74.184B/76] (or class II[4B/63]) 1,3-dipoles, and can be prepared by two main procedures: condensation of aldehydes or ketones with N-monosubstituted hydroxylamines, and oxidation of N,N-disubstituted hydroxylamines with yellow mercuric oxide or other oxidants:




Several reviews[1B/38.28/64.111B/65.211/66.166C/68.235B/73.163/75.210B/77.227B/78] are concerned with their preparations and chemical properties. 1,3-Dipolar cycloaddition reaction with olefins represents the main method of isoxazolidine synthesis and has recently been reviewed in detail.[207/84] All the important aspects of the reaction (i.e., its regio-, site, and stereoselectivity), as well as its synthetic potentiality, have been investigated thoroughly in the past two decades.

A concerted one-step mechanism, falling within the general concept of 1,3-dipolar cycloaddition, has been formulated by Huisgen[4B/63.4C/63.150/68.184B/76.205/84] and is now generally accepted, although a two-step diradical mechanism has been put forward by Firestone,[149/68.154B/70.173C/72] who based his view on the high degree of regioselectivity of the cycloaddition.[240B/77]

A theoretical study on the concerted reaction of the simple unsubstituted nitrone with ethylene has been carried out by an *ab initio* method.[252/78] The results seem to indicate that the reagents approach each other on two parallel

planes until the very early transition state is reached at a distance of 2.25 Å, a slight asynchronism in the formation of the two new bonds being observed, the C–O bond going ahead over C–C bond. By contrast, a semiempirical method, applied on the cycloaddition of nitronic esters to olefins, indicated a reversed asynchronism.[24/75]

The result of the cycloaddition reaction between higher nitrones and substituted alkenes depends on both electronic and steric effects. If concerted, the reaction may be classified as a thermally allowed $[\pi^4 s + \pi^2 s]$ process, and its electronic nature has been investigated advantageously using the frontier molecular orbital theory of Fukui.[61B/70.1/71] This approach involves both the energy levels and the coefficients associated with the reacting atoms of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reactants as most important in determining reactivity and regioselectivity of the reaction.

The estimated orbital energies of the parent and of *C*-phenyl-*N*-methyl nitrone, together with the levels evaluated for the most common classes of ethylenic dipolarophiles, are reported in Fig. 3.1.[128B/73] Some selected kinetic data are presented in Table 3.13.[15C/69]

Referring to the frontier orbital model, nitrones (except nitronic esters) belong to type II dipoles in Sustmann's classification,[188B/71] that is, both frontier orbital interactions are important in controlling reactivity and regio- or stereoselectivity. The following principal points should be noted:

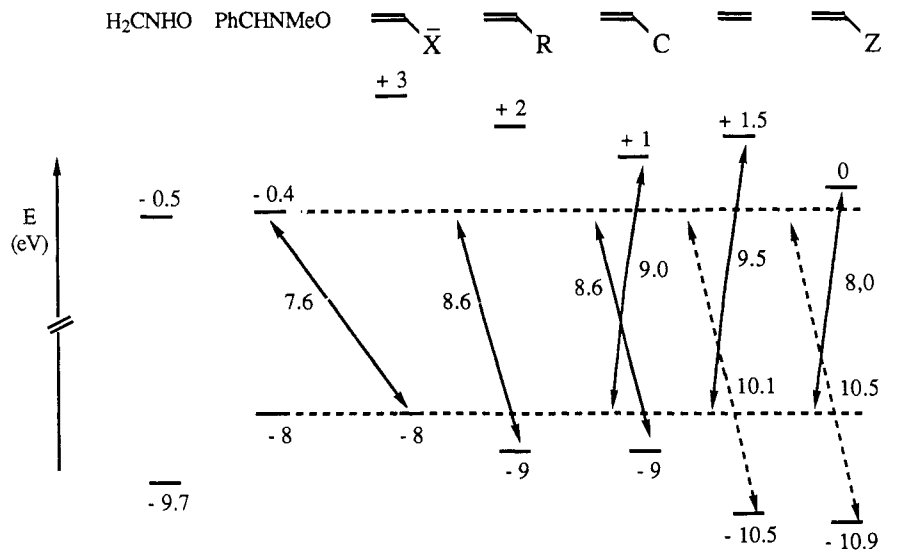



**Figure 3.1.** Frontier orbital energies of nitrones and dipolarophiles.[128B/73]

TABLE 3.13. RELATIVE RATE CONSTANTS FOR THE CYCLOADDITION OF NITRONES TO ETHYLENIC DIPOLAROPHILES[15C/69]

| | ($k_{rel}$) | | |
|---|---|---|---|
| *N-Methyl-C-phenylnitrone* + | (Toluene, 120°) | Dimethyl fumarate | 229 |
| 1-Heptene | 1.00 | Dimethyl maleate | 86 |
| Styrene | 4.4 | Maleic anhydride | 2523 |
| *p*-Nitrostyrene | 19 | *trans*-Dibenzoylethylene | 902 |
| α-Methylstyrene | 0.40 | *cis*-Dibenzoylethylene | 210 |
| Indene | 0.72 | | |
| Acenaphthylene | 2.2 | | ($k_{rel}$) |
| 1,1-Diphenylethylene | 0.37 | *Methyl crotonate* + | (Toluene, 100°) |
| Cyclopentene | 0.31 | *C*-Phenyl-*N*-methylnitrone | 1.1 |
| Norbornadiene | 3.3 | *C*-Propyl-*N*-cyclohexylnitrone | 1.0 |
| Methyl vinyl ether | 2.8 | *C,N*-Diphenylnitrone | 5.7 |
| Acrylonitrile | 106 | Triphenylnitrone | 1.1 |
| Methyl acrylate | 145 | *C*-Benzoyl-*N*-phenylnitrone | 642 |
| Methyl methacrylate | 49 | 1-Pyrroline-*N*-oxide | 166 |
| Ethyl crotonate | 12 | 2-Phenyl-1-pyrroline-*N*-oxide | 2.1 |
| Ethyl β,β-dimethylacrylate | 1.0 | 3,4-Dihydroisoquinoline-*N*-oxide | 248 |
| Ethyl trimethylacrylate | 0.04 | Isoquinoline-*N*-oxide | 0.007 |

1. Reactivity depends on the nature of the substituents on both the nitrone and the dipolarophilic double bond. Rate constants of the cycloadditions of ethyl crotonate to a large number of nitrones[15C/69] range over five powers of 10. Both electron-releasing and electron-withdrawing substituents on the nitrone enhance the rate of the reaction, as does an electronic-withdrawing substituent on the double bond (e.g., the Hammett $\rho$ value for the cycloaddition of *C*-phenyl-*N*-methylnitrone to *p*-substituted styrenes is $+0.77$).

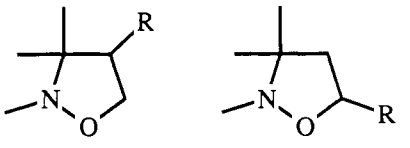
Particularly striking is rate acceleration when the dipolarophilic double bond is conjugated with a carbonyl or cyano group (compare, for example, the relative rate constants measured for the cycloadditions of *C*-phenyl-*N*-methylnitrone with methyl acrylate, dimethyl fumarate, and maleic anhydride).[15C/69] The *trans* isomer of a 1,2-disubstituted alkene is usually more reactive than the *cis* isomer (see, for example, the pairs dimethyl fumarate/maleate or *trans*/*cis*-dibenzoylethylene), and this fact has been ascribed to the sterically justified diminution of resonance in the *cis* dipolarophile, which partially prevents the accelerating effect on the 1,3-dipolar cycloaddition.[205/84] As expected from both electronic and steric considerations, insertion of one or more methyl substituents on methyl acrylate markedly slows the reaction rate, as easily seen by comparison of the rates of alkyl acrylate, methacrylate, crotonate, dimethylacrylate, and trimethylacrylate.

As a rule, *E*-nitrones are more reactive than their *Z* counterparts, particularly reactive result some cyclic nitrones, having an *E* configuration imposed. By contrast, the reactivity of the aromatic nitrone isoquinoline-*N*-oxide is very low, due to the loss of aromaticity during the cycloaddition process. Solvent effects are very moderate, polar solvents slightly decreasing the rate.[15C/69] For example, a 5.6-fold decrease in the rate constant, passing from toluene to ethanol, has

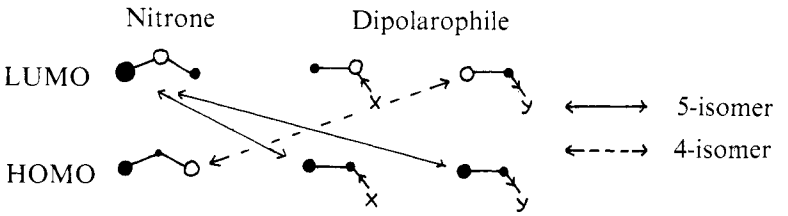
been observed for the cycloaddition of *C*-phenyl-*N*-methylnitrone to ethyl acrylate.

A primary kinetic isotope effect (smallest value: $k/k^* = 1.012 \pm 0.002$) has been observed in the cycloaddition of $^{14}$C-labeled *C,N*-diphenylnitrone to styrene, in turn $^{14}$C-labeled at either the $\alpha$- or the $\beta$-carbon atom.[127B/73] This fact is considered to be inconsistent with a diradical (two-step) mechanism, thus strengthening the evidence in favor of the concerted process.

2. The cycloaddition of nitrones to monosubstituted alkenes (and generally to unsymmetrically substituted dipolarophiles) can a priori furnish two possible regioisomers, the 4-substituted isoxazolidine (**81**) or the 5-substituted isoxazolidine (**82**):




**81** **82**



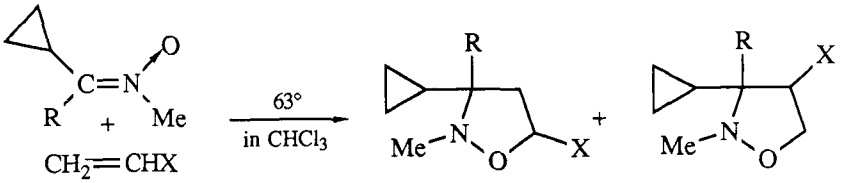

As shown schematically in the diagram, isomer **82** is favored by LUMO (nitrone)–HOMO (dipolarophile) interaction both when the alkene substituent is electron-releasing and when it is electron withdrawing. Isomer **81**, by contrast, is formed only when the dominant interaction is HOMO (nitrone)–LUMO (dipolarophile).

Regioselectivity is fairly high with both electron-rich and with moderately electron-poor dipolarophiles; usually, only 5-substituted isoxazolidines are obtained with C-unsubstituted nitrones. This fact depends on the low polarization of the HOMO (the terminal coefficients on C and O are nearly identical), so that although the HOMO (dipole)–LUMO (dipolarophile) interaction should predominate with electron-poor dipolarophiles, the dipole LUMO (where the carbon has a much larger coefficient) controls regioselectivity.[128B/73] Nevertheless, substitution at the nitrone carbon atom with a donor group will increase both the energy and the polarization of dipole HOMO toward the oxygen atom. A tendency to "reversal" of the regioselectivity toward 4-substituted isoxazolidine is thus observed and is even more pronounced with strongly deficient dipolarophiles.[127/73,224/79] Accordingly, a nice proportionality between this reversal of regioselectivity and nitrone or dipolarophile ionization

potentials has been found.[90B/77] With strongly electron-poor dipolarophiles, coulombic or dipole–dipole interactions also favor predominant or exclusive formation of the 4-substituted regioisomer.

A nice example of the aforementioned tendencies involves electron-rich *C*-cyclopropyl and *C*,*C*-dicyclopropyl nitrones. As the data in Table 3.14 show,

TABLE 3.14



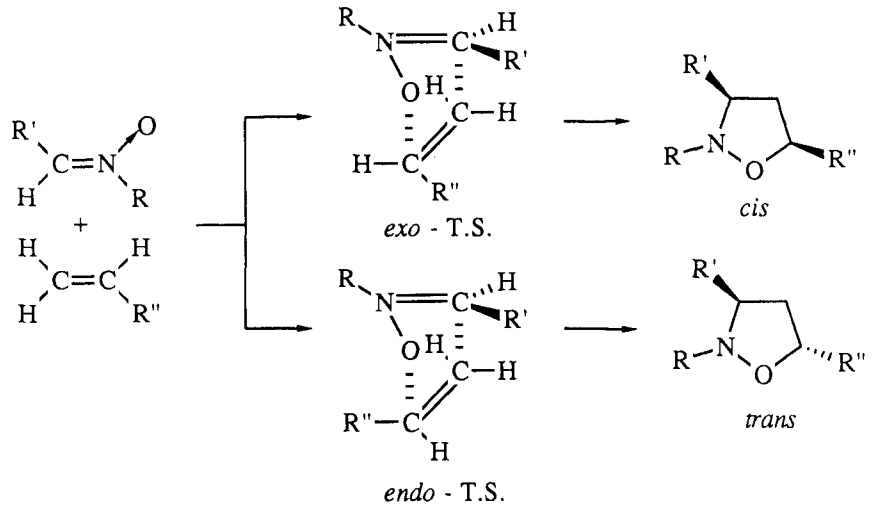

| R | X | Isomer ratio |
|---|---|---|
| H | Ph | a : 0 |
| H | COOMe | 4 : 1 |
| H | CN | 2 : 1 |
| H | $SO_2Ph$ | 1 : 1.6 |
| cyclopropyl | Ph | a : 0 |
| cyclopropyl | COOMe | 1 : 1 |
| cyclopropyl | CN | 1 : 3 |
| cyclopropyl | $SO_2Ph$ | 0 : a |

a = Only isomer detected.

a neat reversal of regiochemistry is observed with electron-poor dipolarophiles, thus supporting the change toward the HOMO (dipole)–LUMO (dipolarophile) interaction.[289/83] Since *C*,*C*-dicyclopropyl nitrone in all cases reacts more slowly than does its monosubstituted analogue, it may be deduced that steric factors control reactivity and electronic factors control regioselectivity.

3. Intramolecular *N*-alkenylnitrone cycloadditions reveal that in the transition state, ring strain must also be taken into account and that the CC bond is more developed than the CO bond.[227/79]

4. As with other 1,3-dipolar cycloadditions, the reaction of nitrones with alkenes is strictly stereospecific with regards to the dipolarophile: its starting configuration is always retained in the final isoxazolidine. The stereochemical course of the cycloaddition is complicated by the fact that nitrones show geometrical isomerism. Several pairs of *E*/*Z* (i.e., *cis*/*trans*) isomers have been separated and characterized, examples being known in the fields of aldonitrones, ketonitrones, and nitronic esters. Interconversions between the two forms are known, and in a few cases the energy barrier of the process has been measured and found to be comparable to that of the activation parameters of the cycloaddition reaction. *cis*-Nitrones show a higher 1,3-dipolar reactivity than those of the thermodynamically more stable *trans* isomers.[192/71]




**Scheme 3.3.**

Since the two reagents can approach each other through an *endo* or *exo* transition state,* mixture of diastereoisomers are very often obtained, as Scheme 3.3 for aldonitrones (having a *trans* or *Z* configuration) and monosubstituted olefins shows. Conversely, the reaction of cyclic nitrones, having a fixed *cis* or E configuration, with monosubstituted alkenes yields a mixture of the *trans*-isoxazolidine through an *exo* addition and of the *cis* isomer through an *endo* addition (for further details on cyclic nitrones, see Part 2 of this work).

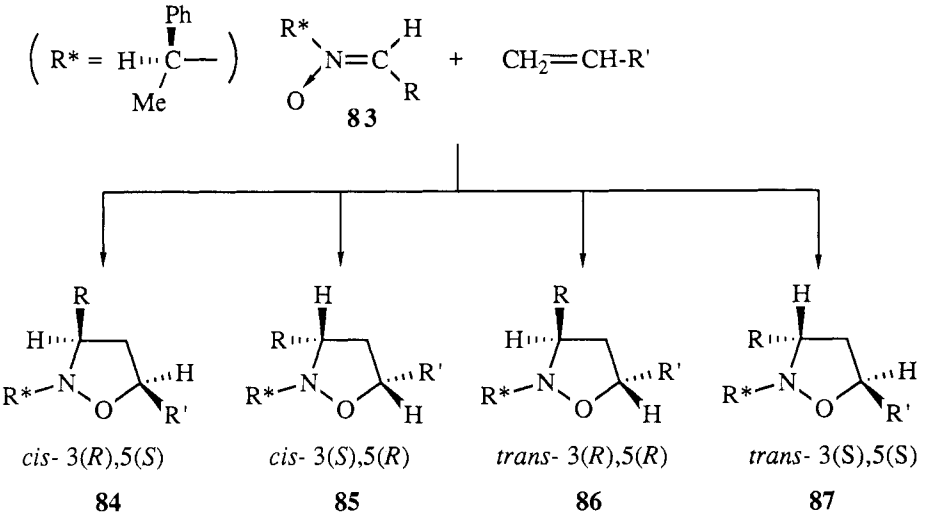
The predominance of one or another diastereoisomer depends on a subtle interplay of several steric and electronic factors. The composition of the mixture of cycloadducts is usually variable, according to the substitution pattern of both the nitrone and the dipolarophile, as the examples presented later substantiate.

When low-reactive or sterically hindered dipolarophiles are involved, a previous *E–Z* interconversion of the nitrone seems most probable and strongly influences the stereoisomeric composition of the products mixture.[113/71,120/79] Indeed, this possibility should always be kept in mind when dealing with acyclic nitrones.

5. With dipolarophiles having diastereotopic faces *syn-anti* isomerism arises, and its study has been cultivated particularly for some typical cyclic structures, such as substituted cyclobutenes[187B/75,145B/76,80/79] or norbornadienes.[34B/77,120/79,220/81] Diastereofacial selection, often considerable, is also observed when the cycloaddition involves either chiral nitrones and substituted alkenes or nitrones and chiral dipolarophiles. This type of selectivity has proved invaluable for controlling stereospecific syntheses of complex molecules (see below and § 3.4.10).

*For *exo-endo* as well as *syn-anti* nomenclature, see ref. 248B/77, pp. 403–404.

An asymmetric synthesis of isoxazolidines is achieved by use of chiral nitrones, prepared by condensation of aldehydes with chiral monosubstituted hydroxylamines.[134/77,146/79] For example, the (*S*),(*Z*)-nitrone **83** was subjected to cycloaddition with styrene, methyl acrylate, and other prochiral alkenes. In each




**Scheme 3.4.**

TABLE 3.15

| R | R' | Total yield (%) | Ratio **84 : 85 : 86 : 87** | Ratio *cis* : *trans* | *cis* d.e.(%) | *trans* d.e.(%) |
|---|---|---|---|---|---|---|
| Ph | Ph | 90 | 76 : 11 : 8 : 5 | 87 : 13 | 75 | 23 |
| Ph | COOMe | 60 | 40 : 24 : 29 : 7 | 64 : 36 | 25 | 61 |
| *t*-Bu | Ph | 85 | 42 : 24 : 22 : 12 | 66 : 34 | 27 | 29 |
| COOMe | Ph | 95 | 56 : 13 : 31 : 0 | 69 : 31 | 62 | 100 |
| COOBu-*t* | Ph | 95 | 62 : 6 : 32 : 0 | 68 : 32 | 82 | 100 |

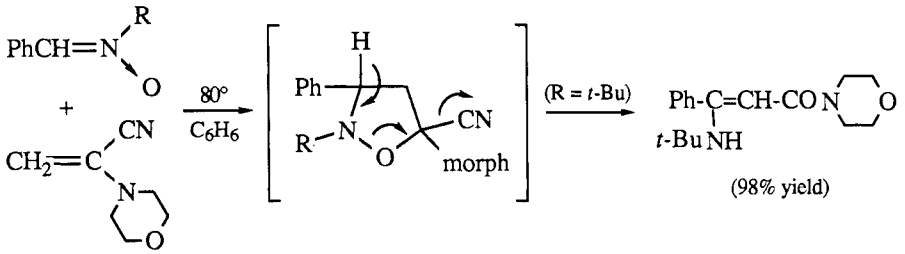
case the four (or at least three) possible diastereoisomers are obtained and isolated: as shown in Scheme 3.4 and in Table 3.15, a more or less large excess of the *cis* pair is formed and within each pair one of the two diastereoisomers clearly dominates. The *cis*/*trans* ratio reflects the stereoselectivity of the reaction, and the diastereoisomeric excess (d.e.) in each pair is a measure of its asymmetrical induction. No asymmetric induction was achieved in the cycloaddition of the nitrone **83** (R = H) to allyl alcohol: a 1:1 mixture of the two 5-substituted stereoisomeric isoxazolidines was obtained.[217/83]

When the chiral center is more distant from the reaction center, very low or no selectivity at all is observed: this is the case when an optically active carbomethoxy substituent is attached either at the C-atom of the nitrone or at the dipolarophilic double bond.[201B/81] High chiral induction can also be provoked by the use of a chiral dipolarophile, such as (*R*)-(+)-*p*-tolylvinyl sulfone, in the

cycloaddition to *C*-phenyl-*N*-methyl (or phenyl) nitrones: a diastereomeric excess of 80–90% has been observed.[200/82]

6. Most isoxazolidines are only moderately thermally stable and 1,3-dipolar cycloreversion[10/79,209/84] is easier than for other 1,3-dipolar cycloadducts. Therefore, the possibility of an altered composition of the product mixture depending on the low stability of the products themselves should always be kept in mind when dealing with nitrone cycloadditions.

Furthermore, suitable substituents can induce different instability patterns in the isoxazolidine ring. For example, the captodative olefin 2-(morpholin-1-yl)acrylonitrile reacts with aldonitrones to yield nonisolable isoxazolidines, which promptly lose hydrogen cyanide, yielding enamino morpholides:[112/83]




7. Site selectivity has also been a subject of study with dipolarophiles containing two or more different double bonds, such as some norbornadiene derivatives.[224/72,214/76,220/81] As a general trend, nitrones are more sensitive to steric factors and relatively more electron-rich than are other 1,3-dipoles of allenyl anion type, such as azides, nitrile oxides, or nitrile imines.

8. With low-reactive olefins, such as ethyl vinyl ether, the cycloaddition to nitrones can conveniently be improved by high-pressure conditions; better yields and slight variations in stereoselectivity have been observed.[195/82] A high-pressure kinetic study of the reaction between *C*-benzoyl-*N*-methylnitrone and some activated dipolarophiles has also been reported.[134/83]

The preparative applications of the cycloaddition nitrones/double-bond compounds will be examined in the following pages according to the nature of the nitrone and its substitution pattern.

### b. Cycloaddition of *N*-Alkylnitrones

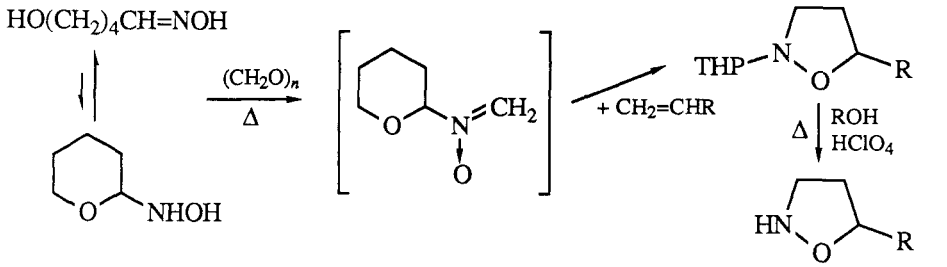
The simplest nitrone, *N*-methylnitrone, is rather unstable and is usually prepared *in situ*, most conveniently by slow addition of *N*-methylhydroxylamine hydrochloride to a mixture of aqueous formaldehyde, sodium acetate, and the appropriate dipolarophile.[144/79] Paraformaldehyde in dry benzene in the presence of anhydrous potassium carbonate as a base has also been used.[10B/60,29/74] Another method of preparation of *N*-methylnitrone *in situ* is based on the oxidizing property at a high temperature (100°C) of a tertiary amine oxide on dimethylhydroxylamine;[125/73] consequently, in particular con-

ditions the Cope elimination can produce the isoxazolidine as an important side product.

*N*-Ethyl-,[10B/60,48/60] *N*-*n*-butyl-,[181/73] and *N*-*t*-butylnitrones[127/73] have also been prepared *in situ* from paraformaldehyde, whereas the stable *N*-(1-ethylcyclohexyl)nitrone[45/68,138/69,113/71] is available by reaction of diazomethane on monomeric 1-ethyl-1-nitrosocyclohexane. All *N*-alkylnitrones react regiospecifically both with monosubstituted ethylenes such as 1-dodecene,[125/73] styrene,[45/68,138/69,181/73,144/79] acrylonitrile,[153B/78,144/79] vinylnaphthalenes,[144/79] and ethyl acrylate,[144/79] and with several 1,1-disubstituted ethylenes[144/79] to yield only 5-mono- or 5,5-di-substituted isoxazolidines, respectively. Even the highly electron-deficient nitroethylene[127/73] and diethyl methylenemalonate[224/79] gave the "normal" cycloadducts. The only exception known[127/73] up to now is phenyl vinyl sulfone, which reacts with *N*-*tert*-butylnitrone to give a 70:30 mixture of the two possible regioisomers, the "normal" product being prevalent.

A "reversed" regiochemistry is reported in the cycloaddition of *N*-methylnitrone to α,β-unsaturated fluoroalkylsulfones: 2-methyl-4-aryl (or heteroaryl)-5-perfluoroalkylsulfonylisoxazolidines are produced.[81/84] A series of isoxazolidine *N*-ribosides[80/77,81/77] have been prepared; they are interesting among other reasons because a relatively mild acidic treatment gives the corresponding N-unsubstituted compounds.

Nevertheless, a more convenient synthesis of N-unsubstituted isoxazolidines uses the *N*-tetrahydropyran-2-yl nitrone, generated *in situ* from the 5-hydroxypentanal oxime: acidic alcoholysis of the intermediate THP–isoxazolidine affords good yields of the target compounds:[70/84]




(55-76% overall yield)

The structure of an in vitro metabolite of *N*-methylamphetamine was shown to be *N*-α-methylphenethylnitrone by trapping it with alkyl acrylate to give the corresponding isoxazolidine.[40/78]

### c. Cycloadditions of *C*,*N*-Dialkylnitrones

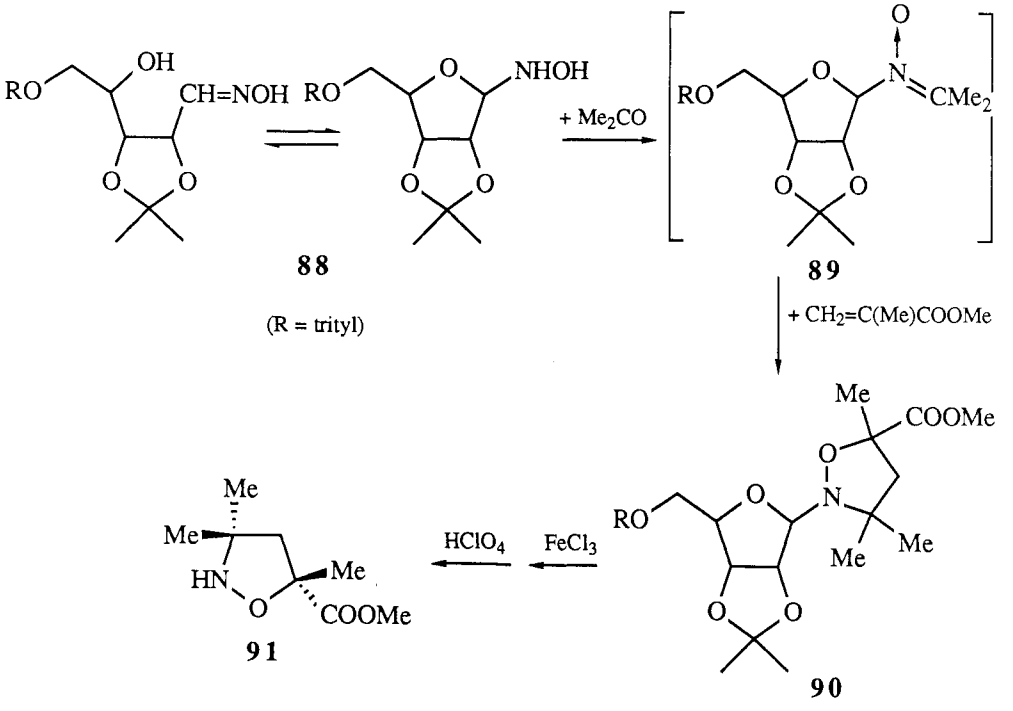
Relatively few *C*,*N*-dialkylnitrones, usually prepared *in situ* from aldehydes and hydroxylamines, have been used as 1,3-dipoles in the cycloaddition to olefins. Monosubstituted olefins such as ethyl acrylate, acrylonitrile, and styrene

yield the corresponding 5-substituted isoxazolidines.[20/68,229/69,258/72] Regiochemistry has usually been ascertained by NMR spectroscopy, but stereochemistry was usually not determined.

Symmetrically 1,2-disubstituted olefins such as dialkyl maleate or fumarate[55/73] give the expected adducts; similarly, alkyl crotonates or crotononitrile obey electronic control, reacting regiospecifically with *C*,*N*-dialkylnitrones to yield the 5-methyl-4-alkoxycarbonyl (or cyano) isoxazolidine derivative.[55/73,222/83] In the case of crotononitrile a 2:1 mixture of the *cis*/*trans* and *trans*/*cis* stereoisomers was determined.[55/73]

Cycloaddition with alkyl methacrylate is not as straightforward and literature data are contradictory: whereas *C*-isopropyl-*N*-(1-cyanoisobutyl)-[55/73] and *C*-propyl-*N*-cyclohexylnitrones[22/68] as well as some *N*-glycosylnitrones[80/77,81/77] are reported to yield 5,5′-disubstituted isoxazolidines, in analogy to the results obtained with other nitrones, *C*-methyl-*N*-ethylnitrone, prepared *in situ* by oxidation of diethylhydroxylamine, is claimed to enter the cycloaddition with "reversed" regiochemistry, yielding the 4,4′-disbustituted isoxazolidine derivatives.[63/63,43/69] Reverse-oriented cycloadducts are also obtained with perfluoropropene and with perfluoroisobutene.[262/72]

Chiral *N*-(alkoxyalkyl)nitrones show an enhanced reactivity and a remarkable stereoselectivity in cycloaddition with both unactivated and activated

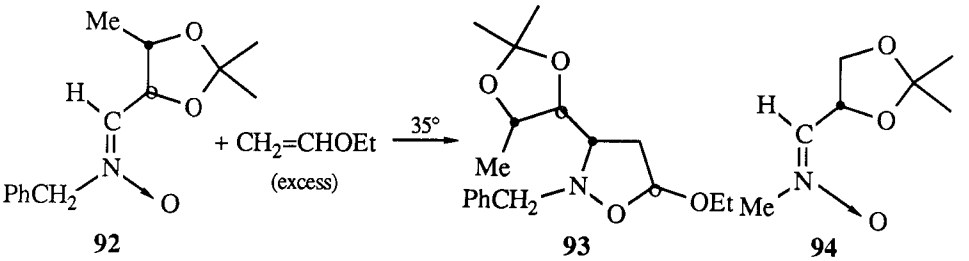



Scheme 3.5.

olefins.[80/77,81/77] For example, reaction of the hydroxyoxime (**88**) with an excess of acetone and of methyl methacrylate leads, through the *in situ* produced nitrone **89**, to the cycloadduct **90**, which, upon detritylation and cleavage of the glycoside moiety, gives an overall 46% yield of pure (−)-*R*-5-methoxycarbonyl-3,3,5-trimethylisoxazolidine (**91**) (Scheme 3.5).

The stereoselectivity is still remarkable, although not absolute, and ranges between 67 and 95% with less substituted nitrones of type **89**, prepared *in situ* from acetaldehyde or formaldehyde. This stereoselectivity has been explained by a stereo-electronic (kinetic anomeric) effect in the transition state of the cycloaddition.

The nitrone **92**, which bears a chiral center α to the carbon atom in addition to a marked preference for the *endo* transition state, also displays diastereofacial selection in the cycloaddition reaction to monosubstituted alkenes. For example, with ethyl vinyl ether a single cycloadduct (**93**) is formed, presumably through a Felkin–Anh model transition state in which the nitrone is attached by the alkene *anti* to the more bulky substituent of the chiral center:[133/83,62/84]




**92** **93** **94**

Reaction of the same nitrone with vinyl acetate proceeds with a diminished preference for the *endo* transition state, a 4:1 mixture of the possible *anti*/*syn* cycloadducts being obtained. By contrast, cycloaddition of the nitrone **92** to vinylene carbonate results in an exclusive formation of the *anti* cycloadducts, with high (80% d.e.) diastereo-facial selectivity. When the less bulky nitrone **94** was used as a 1,3-dipole, the preference for *anti* cycloadducts is still exclusive but diastereo-facial selectivity was not observed.[62/84]

An unusual synthesis of 2-ethyl-5-hydroxy-methyl-3,5-dimethylisoxazolidine from 2-methyl-2-propen-1-ol and diethylhydroxylamine or its molybdenum(VI) complex $Mo_2(ONEt_2)_2$ is known, but has low preparative value;[241/80] the intermediacy (oxidatively achieved) of *C*-methyl-*N*-ethylnitrone has been proposed.

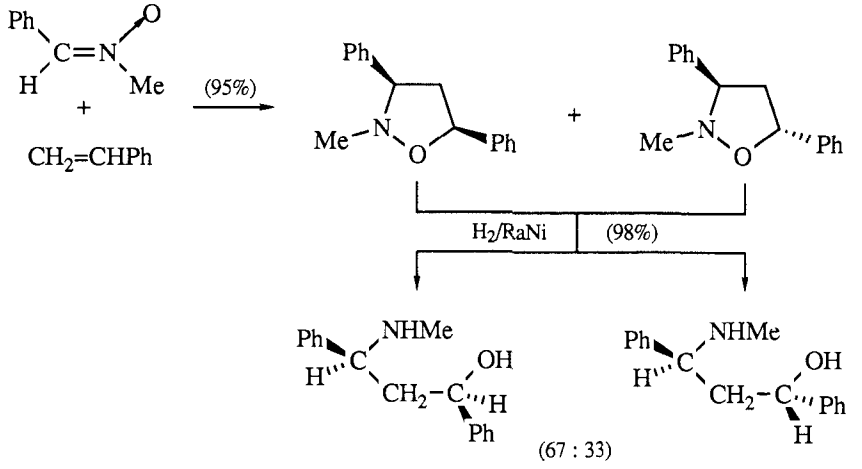
### d. Cycloaddition of *C*-Alkyl-*N*-arylnitrones

Although a phenyl group on the N-atom stabilizes the nitrone, little work has been done on *N*-aryl nitrones C-substituted with an alkyl group, easily available *in situ* (to avoid dimerization of the nitrone; see § 3.3.1.3, p. 721) by reaction of an aliphatic aldehyde with an arylhydroxylamine. For example, *C*-methyl-*N*-phenylnitrone[20/68] or, more frequently, *C*-*n*-propyl-*N*-phenylnitrone condenses

with monosubstituted olefins such as styrene[20/68] or ethyl acrylate[22/68] to give regiospecifically, the expected 2-phenyl-3-alkyl-5-substituted isoxazolidine, whose stereochemistry has not been determined. Some *C*-silyl-substituted-*N*-phenylnitrones are known and react regularly with acrylonitrile to give the corresponding 5-cyanoisoxazolidines.[313/82]

### e. Cycloaddition of *C*-Aryl-*N*-alkylnitrones

*C*-Phenyl-*N*-methylnitrone, easily obtainable from benzaldehyde and methylhydroxylamine, is one of the most thoroughly investigated open-chain nitrones. The cycloaddition reactions with monosubstituted olefins such as aliphatic 1-alkenes,[19/68,157/71] styrene,[20/68] vinyl alkyl ethers,[21/68] allyl alcohol,[19/68] and allyl amines[116/68] are regiospecific and stereoselective, yielding the 2,3,5-trisubstituted isoxazolidines or, more precisely, a mixture of the two possible diastereoisomers, with the *cis* isomer predominating over the *trans* isomer; for example, with styrene a 67:33 ratio of *cis*- and *trans*-2-methyl-3,5-diphenylisoxazolidine has been determined[20/68] from NMR analysis and from the ratio of *erythro*- to *threo*-3-methylamino-1,3-diphenylpropanol obtained by hydrogenolysis of the reaction mixture:



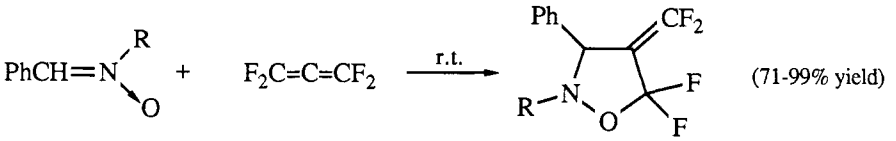

The cycloaddition of the same *Z*-nitrone with ethyl vinyl ether is reported to be completely stereo-unselective.[195/82,204/82] In this case high-pressure reaction conditions speed up the cycloaddition and introduce a very slight stereoselectivity in favor of the *cis* isomer.[195/82]

According to predictions based on the frontier orbital treatment (see p. 687), electron-deficient monosubstituted double-bond compounds no longer react regiospecifically. For example, ethyl acrylate[22/68] and acrylonitrile[22/68,127/73,98/84] are reported to give the 5-substituted isoxazolidine compound only when reacted with *C*-phenyl-*N*-methylnitrone.

By contrast, cycloaddition of the same nitrone (or *C*-pyridyl-*N*-methylnitrone[161/72]) to an excess of methyl acrylate leads to a mixture of cycloadducts, containing the 5-substituted isomer as the major component, together with minor amounts of the 4-substituted compound.[161/72.98/84] Moreover, the highly electron-deficient dipolarophiles phenyl vinyl sulfone and nitroethylene react with *C*-phenyl-*N*-methylnitrone, yielding a 68:32 mixture of 4- or 5-substituted isoxazolidines, respectively, in the former case, and only 2-methyl-3-phenyl-4-isoxazolidine in the latter case.[127/73,98/84]

As far as the stereochemistry of the single regioisomer is concerned, mixtures of stereoisomers are often obtained. Somewhat contradictory results are reported in the literature,[161/72.98/84] since the configurational attribution on a PMR spectroscopy basis only is difficult, owing to conformational equilibration and substituent effects (see § 3.2.3.1). All four possible regio- and stereoisomeric isoxazolidines have been obtained by cycloaddition of *C*-phenyl-*N*-alkylnitrones to methyl *E*-3-nitroacrylate.[98/84]

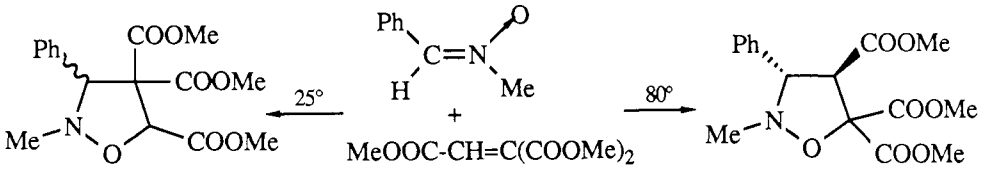
Accordingly to expectations, based on frontier orbital considerations, perfluoropropadiene condenses quite easily with *C*-phenyl-*N*-alkylnitrones to give only one regioisomer, 2-alkyl-4-difluoromethylene-5,5-difluoroisoxazolidine:[159/83]




5,5-Disubstituted isoxazolidines (generally a mixture of diastereoisomers if the substituents are different) are produced by reaction of the same nitrone with 1,1-disubstituted ethylene such as α-methylstyrene,[21/68] 1,1-diphenylethylene,[21/68] or methyl methacrylate.[22/68] *cis*-1,2-Disubstituted activated olefins such as dimethyl maleate and *cis*-dibenzoylethylene require heating to cycloadd stereospecifically to all-*cis*-tetrasubstituted isoxazolidines;[13/69] by contrast, with dimethyl fumarate and *trans*-1,2-dibenzoylethylene, a mixture of *cis-trans* and *trans-trans* isomers is obtained.[13/69]

Cycloadditions to alkyl crotonates,[22/68] cinnamates,[198/72] β,β′-dimethylacrylate,[22/68] *trans*-chalcones,[198/72] or *trans*-propenyl phenyl sulfone[163/82] are always regiospecific, yielding isoxazolidines having the ester or keto or sulfone group, respectively, in the 4-position. Epimeric mixtures are often obtained. Dimethyl citraconate and mesaconate behave analogously, giving the isomeric 5-methyl-4,5-dicarbomethoxyisoxazolidine derivatives.[13/69]

The behavior of tricarbomethoxyethylene (**95**) toward *C*-phenyl-*N*-methylnitrone is interesting. The cycloaddition reaction is temperature dependent: at room temperature a kinetically determined mixture of the two epimers of (**96**) is obtained, whereas in refluxing benzene only the most stable isomer (**97**) is formed:



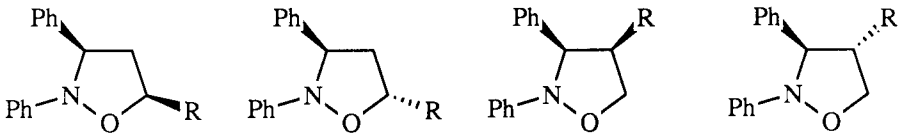

**96** **95** **97**

These results have been interpreted as invoking secondary orbital interactions in the transition states.[173/78] In addition, these results confirm that in some cases of nitrone cycloadditions, cyclo-reversion takes place, more or less readily.

The reaction of a heteroaromatic nitrone, *C*-(5-nitro-2-imidazolyl)-*N*-methylnitrone, with olefins has been investigated and yields the cycloadducts expected.[68/71,252/77] For the reaction of *C*-phenyl-*N*-alkylnitrones with allene and derivatives, see p. 702.

### f. Cycloaddition of *C*,*N*-Diarylnitrones

The cycloaddition of *C*,*N*-diphenylnitrone, one of the most readily available 1,3-dipoles, with monosubstituted olefins has been studied thoroughly. Usually, the reaction has been reported to be regiospecific: for example, styrene[56/60,143/66,20/68,93/68,109/71] or vinyl ethyl ether[25/67] react to give the 5-substituted isoxazolidine (**98**) only. Sometimes a mixture of diastereoisomers is obtained, where the *cis* isomer **98a** predominates[25/67,20/68] (in the case of styrene, a 90:10 ratio of *cis*/*trans* isomers has been calculated under kinetically controlled conditions).[20/68]



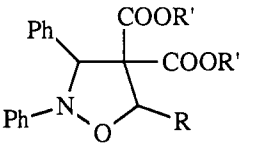

**98a** **98b** **99a** **99b**

Analogous results have been reported with other monosubstituted olefins, such as 1-hexene,[19/68] 1-hexadecene,[34/71] allyl alcohol,[19/68] vinyl acetate,[93/68] 9-vinyl acridine,[24/76] and 1-vinylimidazole,[83/84] or with other *C*,*N*-diarylnitrones[25/67] or *C*-heterocyclic-*N*-aryl nitrones.[25/67,37/68,38/68,39/68,35/69,137/70,109/71,24/76,65/77,234/79,29/80] A contradictory result is known in the case of *C*-furyl-*N*-phenyl nitrone, which has been claimed to condense with styrene to yield 2,4-diphenyl-3-α-furyl-isoxazolidine,[78/75] and with acrylonitrile to yield the corresponding 5-cyano compound. Nevertheless, recent investigations have revealed that the cycloaddition reaction is far from being regiospecific, especially if the ethylenic double bond is substituted for by electron-attracting groups. For example, the cycloaddition of *C*,*N*-diphenylnitrone with methyl acrylate[173/78] or even with propylene[224/79] leads to a mixture of all four possible regio- and stereoisomers (**98a**

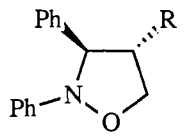
and **b** and **99a** and **b**) in the following proportions, evaluated by NMR spectroscopy:

| | **98a** | **98b** | **99a** | **99b** |
|---|---|---|---|---|
| $R = COOCH_3$ | 28 % | 38 % | 14 % | 20 % |
| $R = CH_3$ | 90.4 % | 7.9 % | 0.4 % | 1.3 % |

Similar mixtures of isomers have been obtained with acrylonitrile, acrolein, and vinyl methyl ketone.[224/79] Increased substitution by electron-attracting groups causes a sharp shift toward the formation of isoxazolidine substituted more highly in the 4-position: reaction with diethyl ethylidenemalonate[224/79] or with triethyl ethylenetricarboxylate[173/78] under kinetically controlled conditions yields only isomer **100a** or the epimeric mixture **100b**, respectively.




**100 a** R = H; R' = Et
**b** R = COOMe; R' = Me



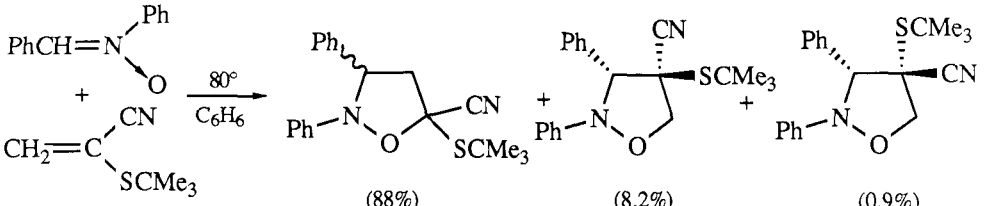

**101 a** $R = PO(OMe)_2$
**b** $R = SO_2Ph$

The regiochemical control described above has been incorporated into the general pattern of the frontier molecular orbital treatment,[173/78.224/79] and the tendency toward increasing amounts of 4-substituted regioisomer with increasing substitution by alkoxycarbonyl groups has been attributed to secondary orbital interactions between the carbonyl group and either the nitrone *C*-phenyl or its central nitrogen atom.[173/78] A slight predominance of the latter interaction is reflected by the higher proportion of 3,4-*trans* stereoisomer (**99b**) than of the corresponding *cis* isomer (**99a**). Another example may be that of obtaining *trans*-2,3-diphenyl-4-dimethoxyphosphonoisoxazolidine (**101a**),[81/75] described previously as the 5-isomer,[225/68] in the reaction between *C*,*N*-diphenyl nitrone and dimethyl vinyl phosphonate. Other *C*-aryl-*N*-phenyl nitrones behave analogously.[129/80] The same regiospecificity has been observed when phenyl vinyl sulfone is used as dipolarophile: only the isoxazolidine (**101b**) is obtained by reaction with *C*-aryl-*N*-phenylnitrone.[172/83]

By contrast, 1,1-diphenylethylene,[21/68.93/68] α-methylstyrene,[21/68] methyleneadamantane,[226B/76] methyl methacrylate,[22/68.103/76] and α-acetylamino acrylate[297/83] condense with *C*,*N*-diphenyl nitrone to yield, as expected, the "normal" 5,5-disubstituted isoxazolidines. In the latter cases the cycloaddition is stereoselective and the preferred product results from the transition state where the interaction between the *N*-phenyl group and the dipolarophile substituents is minimized. Thus a 4:1 or a 96:4 mixture of the two epimers is

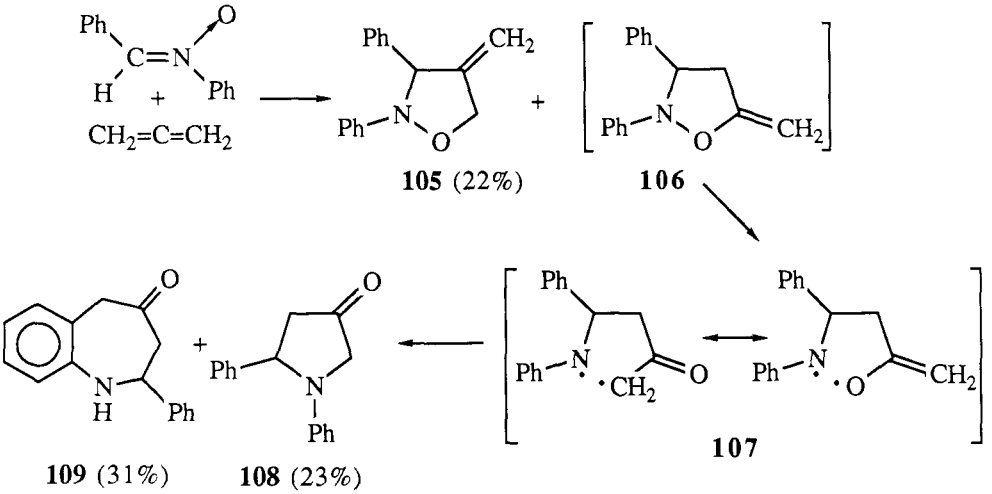
obtained, respectively, where the major components possess the structure 3,5-*trans*-diphenyl[21/68] or 3,5-*trans*-phenylmethyl,[103/76] respectively. Epimeric mixtures are also obtained in reactions with α-pyrrolidinylstyrene and other open-chain enamines.[161/71]

Some degree of regiochemical distribution has been observed in the cycloaddition of *C*,*N*-diphenylnitrone with the captodative 1,1-disubstituted olefin **102**, which furnishes up to a 9% yield of the "abnormal" regioisomers **104**:[24/82]




**102** **103** **104**

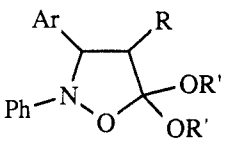
A mixture of three isomeric monoadducts is obtained by treatment of *C*,*N*-diphenylnitrone with excess allene in a sealed tube at 72°C for 60 h. Structure **105** has been assured for one of the products, whereas the expected regioisomer **106** is apparently unstable and undergoes ring opening spontaneously, possibly to the diradical **107** (or the dipolar species[23/71]), which further rearranges to the 3-pyrrolidone (**108**) and to the benzazepinone (**109**).[158/79]



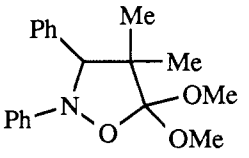

1,1-Dimethylallene affords 2,2-dimethyl-1,5-diphenyl-3-pyrrolidinone as the sole product,[23/71,149B/76] thus revealing that only the unsubstituted double bond reacts regiospecifically with the nitrone. Other nitrones do not seem to behave

uniformly: thus *C*-benzoyl-*N*-phenylnitrone reacts with allene to yield only a 3-pyrrolidinone,[23/71] whereas *C*-phenyl-*N*-methylnitrone affords a 3:2 mixture of 2-methyl-3-phenyl-4-methyleneisoxazolidine and 1-methyl-5-phenyl-3-pyrrolidinone.[158/79] Reaction of dimethylallene with *C*-phenyl-*N*-alkylnitrones is reported to give 3-pyrrolidinone and in some cases 4-piperidinone derivatives also[149B/76] by electrophilic addition of a second molecule of nitrone on the exocyclic double bond of the dimethyl derivative of **106**.

Ketene dialkylacetal and its alkyl derivative together with *C*,*N*-diarylnitrones afford good yields of 5,5-dialkoxyisoxazolidine derivatives (**110**);[76/66,21/68] far lower yields of **111** have been obtained with dimethylketene dimethylacetal,[21/68] thus confirming here, too, the high susceptibility of nitrone 1,3-dipolar cycloadditions to the steric encumbrance of dipolarophiles.




**110**



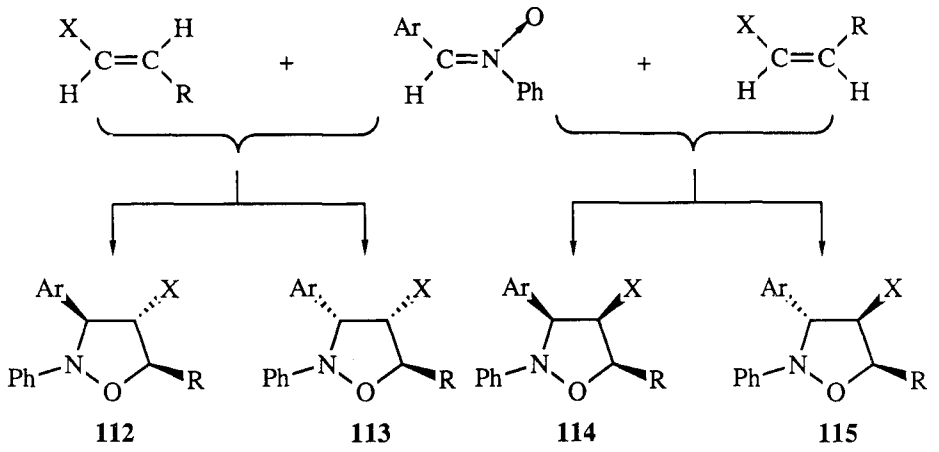

**111**

Both symmetrically 1,2-disubstituted electron-deficient olefins such as dialkyl maleate or fumarate,[39/71,218/73,103/76] fumarodinitrile,[218/73] or dibenzoylethylene,[13/69,296/78] and asymmetrically 1,2-disubstituted compounds such as alkyl crotonate,[22/68,218/73] cinnamate,[39/71,198/72,218/73] cinnamonitrile[39/71,218/73] chalcones,[198/72] ω-nitrostyrene,[218/73] or phenyl styryl or propenyl sulfone[135/71,163/82,172/83] react easily with *C*,*N*-diarylnitrones. The cycloaddition reaction proceeds with a strict dipolarophilic stereospecificity and, in the latter cases, with regiospecificity, the electron-attracting group (alkoxycarbonyl, cyano, benzoyl, nitro, or sulfonyl) always occupying the 4-position in the resulting isoxazolidine. Usually, a mixture of the two possible epimers at the 3-position is obtained. As shown in Table 3.16, which provides some examples, where the epimer ratio could be evaluated spectroscopically, the *trans*-1,2-disubstituted olefins yield, predominantly or exclusively, the 3,4-*trans* isomer (**112**) arising from an *endo* transition state with respect to the substituent bound to occupy the isoxazolidine 4-position. The results are more variable with the *cis* series, where the 3,4-*trans*-isoxazolidine derivative (**115**) sometimes predominates, but in other cases a large amount of the all-*cis* isomer **114**, possibly arising from an *exo* transition state, is also formed.

Trisubstituted olefins such as arylidene malonates or cyano acetates give analogous results, the reaction being regiospecific and stereoselective. With arylidene cyanoacetates of known stereochemistry (aryl and cyano groups *cis* to each other), only 4,4-disubstituted isoxazolidines are obtained, the epimer possessing a 3-aryl and 4-cyano group *cis* to each other being prevalent in the mixture.[38/73,31/78]

Nonactivated olefins react only under extreme conditions. For example,

TABLE 3.16

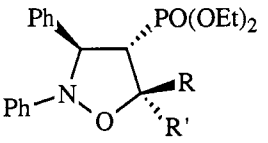



| Ar | X | R | 112:113 | References | 114:115 | References |
|---|---|---|---|---|---|---|
| Ph | COOMe | COOMe | 65:35<br>80:20 | 39/71<br>218/73 | 10:90<br>20:80 | 39/71, 218/73<br>103/76 |
| 2,3(MeO)$_2$C$_6$H$_3$ | COOMe | COOMe | 92:8 | 103/76 | 0:100 | 103/76 |
| 2,3(MeO)$_2$C$_6$H$_3$ | COOMe | COOMe | 94:6 | 103/76 | - | |
| Ph | CN | CN | 100:0 | 218/73 | - | |
| 2-MeC$_6$H$_4$ | CN | CN | 100:0 | 237/83 | | |
| Ph | -CO-O-CO- | | - | | 55:45 | 39/71, 218/73 |
| Ph | -CO-NPh-CO- | | - | | 37:63 | 25/72 |
| Ph | COOMe | Me | 85:15<br>90:10 | 22/68<br>218/73 | - | |
| Ph | COOMe | Ph | 95:5 | 218/73 | 50:50 | 218/73 |
| Ph | CN | Ph | 95:5 | 218/73 | 63:37 | 218/73 |
| Ph | $NO_2$ | Ph | 70:30 | 218/73 | - | |
| Ph | COPh | COPh | 81:19 | 296/78 | | |
| 4-NO$_2$C$_6$H$_4$ | COC$_6$H$_4$OMe-4 | COC$_6$H$_4$OMe-4 | 86:14 | 296/78 | | |
| 4-NO$_2$C$_6$H$_4$ | PO(OEt)$_2$ | COOMe | 100:0 | 130B/80 | | |
| C$_6$H$_5$(Ar) | $SO_2$Ph | Ph(Me) | 100:0 | 172/83 | | |
| C$_6$H$_5$(Ar) | $SO_2$Ph | COPh | 100:0 | 172/83 | | |

when 2-methyl-2-butene is heated in a sealed tube at 110°C with *C,N*-diphenylnitrone, an 11% yield of 4,5,5-trimethyl-2,3-diphenylisoxazoline was achieved.[279/82] These results were rationalized on the basis of a HOMO (nitrone)–LUMO (olefin) relationship, with secondary orbital interactions between the central nitrogen atom or the *C*-phenyl group of the nitrone and the electron-attracting substituent group of the olefin. The former interaction is favorable to the *endo* transition state and the latter one to the *exo* transition state.[172/78]

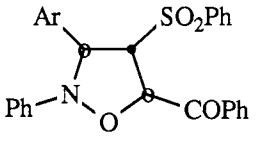
It should be added here that the diethoxyphosphono group also controls the cycloaddition reaction regio-specifically, always leading to 4-diethylphosphonoisoxazolidine derivatives (**116**), even if the 5-position is occupied by

another (or two other) electron-attracting group, such as a cyano, acetyl, or methoxycarbonyl group.[84/75.147/78.130B/80] The same regiospecific control is exerted by the phenylsulfonyl in comparison with the carbonyl group: reaction of the *trans*-2-benzoylvinyl phenyl sulfone with *C*,*N*-diarylnitrones gives the regioisomer **117** only (one epimer).[172/83]



**116**

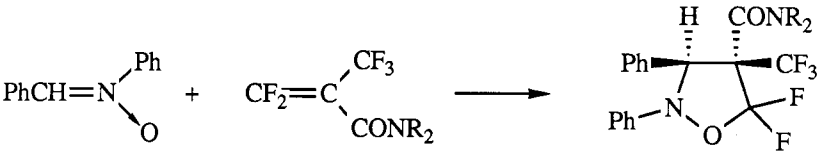
| R | R' |
|---|---|
| CN | H |
| COOMe | H |
| COMe | COMe |



**117**

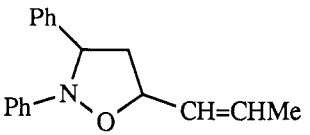
(Ar = Ph, *p*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$)

Only one product is obtained in the cycloaddition reaction between *C*,*N*-diphenylnitrone and pentafluoromethacrylic dialkylamide, whose structure (**118**) has been assured through x-ray analysis:[145/78]

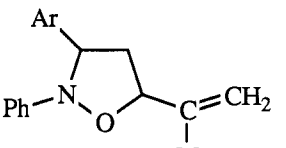


**118**

The cycloaddition of nitrones with conjugated dienes has been studied very little. 1,3-Pentadiene shows reactivity, as expected, at the terminal double bond only, thus yielding, with *C*,*N*-diphenyl nitrone, the 5-propenyl derivative (**119**).[136/65] By contrast, isoprene is reactive at both its double bonds and cycloaddition with *N*-phenyl-*C*-(5-nitro-2-furyl)nitrone affords a mixture of the two monoadducts **120** and **121**.[38/68]

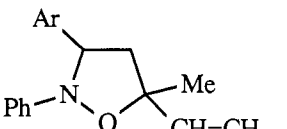


**119**



**120**

(Ar = 5-$NO_2$-2-furyl)



**121**

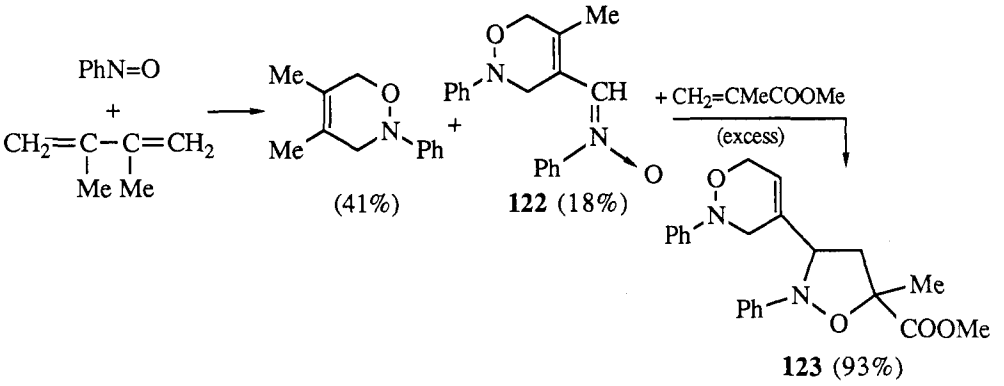
In vinylacetylenes only the double bond is reactive toward nitrones, whereas the triple bond, either unsubstituted[76/62.136/65] or substituted with alkyl,[136/65]

alkylthio, alkylseleno, alkyltelluro,[135/65] or trialkylsilyl groups,[226/68] is unreactive and invariably occupies the 5-position in the resulting isoxazolidine derivative, as demonstrated by the products of the hydrogenolysis. 4-Spiroisoxazolidine derivatives are obtained by cycloaddition of diarylnitrones to benzylideneacenaphthenones, and the regiochemistry depends on the directing power of the conjugated carbonyl group.[223/70]

### g. Cycloaddition of *C*-Conjugated-*N*-arylnitrones

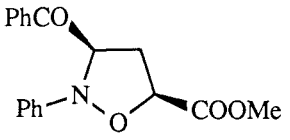
Nitrones, obtained from cinnamaldehyde or its substituted derivatives or heterocyclic analogues and arylhydroxylamine, are stable and react readily with several types of ethylenic double-bond compounds to yield the expected isoxazolidine derivatives.[47/68,111/73,95/74] Nitrones conjugated with a butadieneiron tricarbonyl moiety are easily prepared and react with dimethyl fumarate or with methyl crotonate in quantitative yields.[146/81] Their regio- and stereoselectivity are very similar to those already illustrated for *C*,*N*-diarylnitrones.

One of the reaction products of nitrosobenzene and 2,3-dimethylbutadiene was determined to be a nitrone (**122**) through its cycloadduct **123** with methyl α-methacrylate:[41/73]

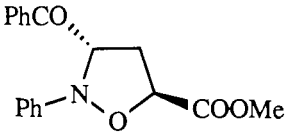



*C*-Benzoyl-*N*-phenylnitrone, easily available through condensation of phenacylpyridinium salts with nitrosobenzene, is a very active dipole, far more reactive than *C*,*N*-diarylnitrones. For example, it reacts smoothly with ethylene at room temperature to give a 79% yield of 2-phenyl-3-benzoylisoxazolidine,[16/69] whereas neither *C*-phenyl-*N*-methyl- nor *C*,*N*-diphenylnitrone react with the same olefin even at 100°C.[19/68] Furthermore, *C*-benzoyl-*N*-phenylnitrone undergoes cycloaddition with methyl crotonate 110 times faster than does the last-mentioned nitrone.[15C/69] This high reactivity led to the use of *C*-benzoyl-*N*-phenylnitrone as a trapping reagent for developing olefins such as styrene,[18B/72] methacrylic acid (and its ester),[150/82] and ethyl vinyl ether.[159/73] In the latter case 3-benzoyl-5-ethoxy-2-phenylisoxazolidine is formed (incorrectly denoted as 4-ethoxy isomer in the original literature).

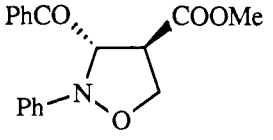
The *C*-aroylnitrones also seem to be more regio- and stereoselective than do their *C*-aryl counterparts, at least with mono- or disubstituted double-bond compounds. For example, *C*-benzoyl-*N*-phenylnitrone reacts quantitatively with methyl acrylate, yielding 90% of a mixture of the two possible 3,5-disubstituted epimers **124** and **125** in equal amounts and 10% of the *trans*-3,4-disubstituted regioisomer **126**.[173/78]



**124**

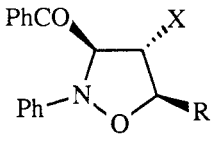


**125**



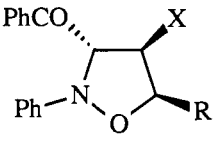
**126**

Cycloaddition with double bonds activated by one or more electron-withdrawing groups is very often strictly regio- and stereospecific: for example, reactions with methyl *trans*-crotonate or cinnamate, cinnamonitrile, *β*-nitrostyrene, methyl fumarate, and fumaronitrile are reported to yield the all-*trans* isoxazolidine derivative **127** as the sole cycloadduct. *cis*-Olefins such as methyl maleate, maleic anhydride, *cis*-cinnamate, and cinnamonitrile invariably afford the *trans-cis* stereoisomer of general structure **128**.[39/71,218/73]



**127**

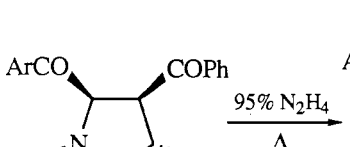
| R | X |
|---|---|
| Me | COOMe |
| Ph | COOMe |
| Ph | CN |
| Ph | $NO_2$ |
| COOMe | COOMe |
| CN | CN |



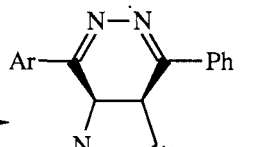
**128**

| R | X |
|---|---|
| COOMe | COOMe |
| CO-O-CO | |
| Ph | COOMe |
| Ph | CN |

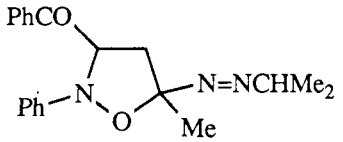
*trans*-1,2-Dibenzoylethylene seems to react anomalously with *C*-*p*-chlorobenzoyl-*N*-*p*-dimethylaminophenyl nitrone to give the 3,4-*cis* derivative **129**, whose structure could be confirmed by conversion to the bicyclic product **130**:[27/74]



**129**



**130**

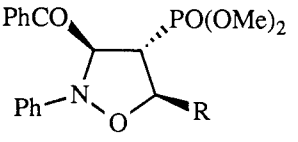


**131**

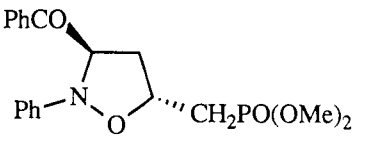
The 5-alkylazoisoxazolidine **131** is the only product obtained from *C*-benzoyl-*N*-phenylnitrone and 1-methyl-1-isopropylazoethylene; no indication of stereochemistry is reported.[198/84]

Cycloaddition with trisubstituted olefins is also remarkably regio- and stereoselective,[38/73.173/78] and a rational explanation based on secondary orbital interactions in the transition state has been offered.[172/78] $\beta,\beta$-Dimethyl acrylate and ethylenetetracarboxylate do not react at all.[16/69]

Several other olefins have been tested and the "normal" cycloadducts have been obtained. It should be noted that in this case, too, dimethyl vinyl- and $\beta$-cyanovinylphosphonates yield the 4-diethylphosphono compounds **132**, whereas the allylphosphonate gives the expected 3,5-*trans*-disubstituted isoxazolidine (**133**).[117/76]

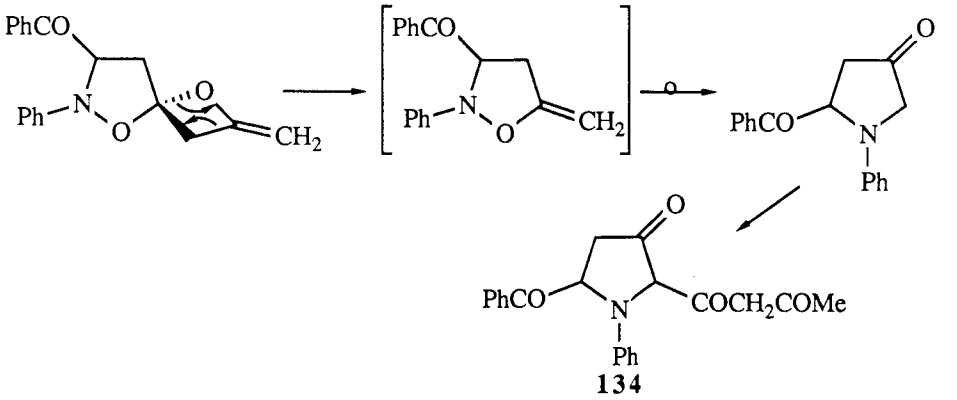



**132**
(R = H or CN)




**133**

Sometimes the primarily formed isoxazolidine cannot be isolated and rearranges spontaneously to a different heterocyclic ring: for example, when *C*-benzoyl-*N*-phenylnitrone was allowed to react with a large excess of diketene in anhydrous benzene, a 58% yield of the 3-pyrrolidine derivative **134** was obtained through the decarboxylation of the isoxazolidine formed initially, followed by ring opening, reclosure, and acetacetylation;[134/72] diketene behaves here as a "masked" allene:

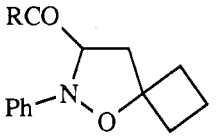


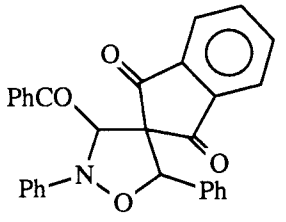

**134**

Indeed, allene itself yields the same pyrrolidinone derivatives.[23/71]

Other spiroisoxazolidine structures are stable: thus the following 5- or 4-spiroisoxazolidines are easily obtained by cycloaddition of the corresponding

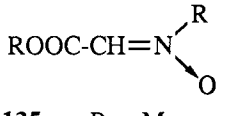
nitrones to methylenecyclobutane[231/82] or benzylideneindandione, respectively:[201/84]



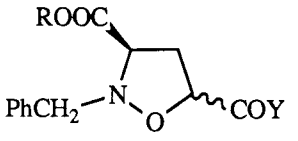




The condensation of several *C*-arylcarbamoyl-*N*-arylnitrones with acrylonitrile,[259/72,260/72,208B/76] styrene,[269/74,270/74] cyclopropylalkenes,[230/82] or alkenylsilanes[305/80] to give the corresponding 5-substituted isoxazolidine derivatives has been reported and its kinetics studied.[208/76] It is worth noting that even low-reactive olefins such as 1-methylcyclobutene or bicyclobutylidene give good yields of the expected cycloadducts with *C*-phenylcarbamoyl-*N*-phenylnitrone.[231/82]

Alkoxycarbonylnitrones such as **135** (usually, a mixture of *E*/*Z* isomers) behave similarly and show remarkable regio- and stereoselectivity. For example, cycloaddition of **135b** to isobutylene furnishes excellent yields of ethyl 2-benzyl-5,5-dimethylisoxazolidine-3-carboxylate,[28/79] whereas cycloaddition of **135a** to acrolein[20/81] or of **135b** to methyl acrylate[28/79] gives a mixture of the two possible

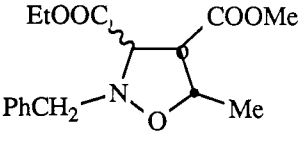



**135 a** R = Me
**b** R = Et




**136**

R = Me, Y = H : *trans*/*cis* = 1.87
R = Et, Y = OMe : *trans*/*cis* = 4.0

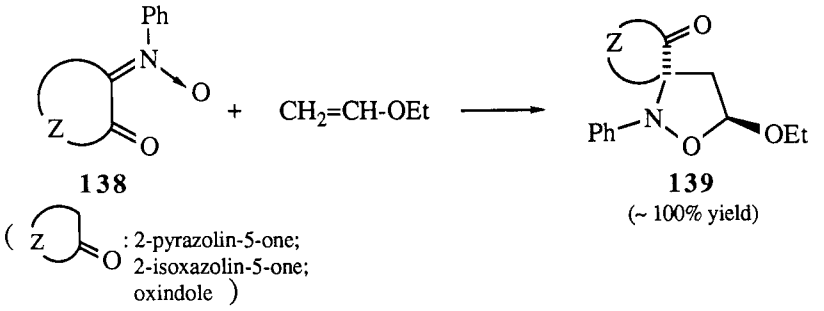



**137**

$C_3/C_4$ : *trans*/*cis* = 19/81

epimers of structure **136**, where the *trans* isomer is clearly prevalent. Furthermore, cycloaddition of **135b** to methyl crotonate is reported to give a mixture of the two epimers (**137**), heavily shifted toward the $C_3/C_4$ *cis* isomer.[28/79] Most unusually, the *E*/*Z*-isomeric mixture of *C*-ethoxycarbonyl-*N*-methylnitrone regio- and stereospecifically cycloadds ethyl vinyl ether to give the corresponding *trans*-3,5-disubstituted isoxazolidine in 92% yield.[204/82]

A special kind of carbonyl-activated nitrone is represented by the heterocyclic system **138**, which also possesses an $\alpha,\beta$-unsaturated carbonyl group, a priori suitable to act as a heterodiene moiety. Reaction with an electron-rich ethylenic compound such as ethyl vinyl ether affords the 3,3-spiroisoxazolidine (**139**) as the only product:[220/80]

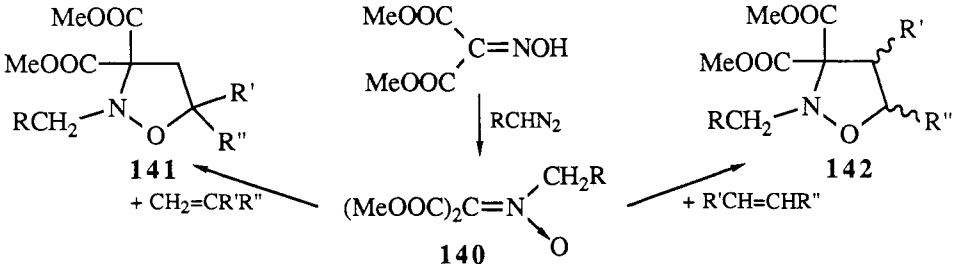



h. Cycloaddition of Trisubstituted Nitrones and Bisnitrones

*C,C,N*-Triphenylnitrone, despite its steric encumbrance, reacts slowly with styrene to yield 2,3,3,5-tetraphenylisoxazolidine.[20/68] Analogous cycloadditions are known with ethyl crotonate[22/68] and with dimethyl maleate (by contrast, dimethyl fumarate is unreactive).[13/69] The regiochemistry of the cycloaddition with activated alkenes is temperature dependent, as illustrated in § 3.4.4.1.

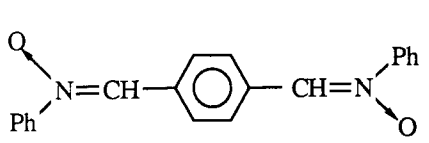
The corresponding *C,C*-diphenyl-*N*-alkylnitrones seem less reactive and are reported to be indifferent to styrene;[155/70] nevertheless, the expected cycloadducts are formed with methyl vinyl ketone[156/67,202/68] or methyl acrylate.[155/70] Antraquinone or fluorenone imine-*N*-oxides normally react with activated double-bond compounds to give 3-spiroisoxazolidine derivatives.[113/81]

Excellent yields of 2-alkylisoxazolidine-3,3-dicarboxylates (**141** and **142**) are obtained in the cycloaddition reactions of the nitrones (**140**) available through alkylation of isonitrosomalonic esters with diazoalkanes:[109/77.92/79.190/79]

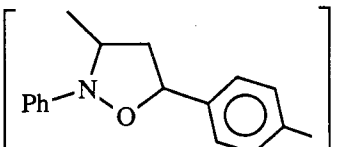



Both dialkyl maleate and fumarate react readily.[190/79]

The use of the bisnitrone **143**, prepared from terephthalaldehyde and phenylhydroxylamine, in cycloaddition to methyl methacrylate or styrene makes it possible to obtain the corresponding bisisoxazolidine derivatives.[25/65.120/67.28/68]



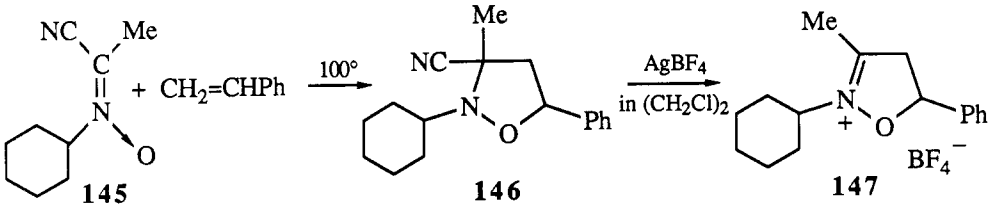
143



144

The 2,5-thiophene analogue of **143** is also reactive with several ethylenic compounds.[95/71] *C*-4-Vinylphenyl-*N*-phenylnitrone is the starting material for polimerization either in the melt or in DMF solution to give a low-molecular-weight polymer of structure **144**.[120/67]

The cycloaddition of a cyano-substituted nitrone (**145**) to styrene seems interesting, since the cycloadduct **146** can easily be transformed into the 2-isoxazolinium salt **147**:[14/833]



145 146 147

### *3.3.1.2 Cycloaddition of Nitronic Esters to Double-Bond Compounds*

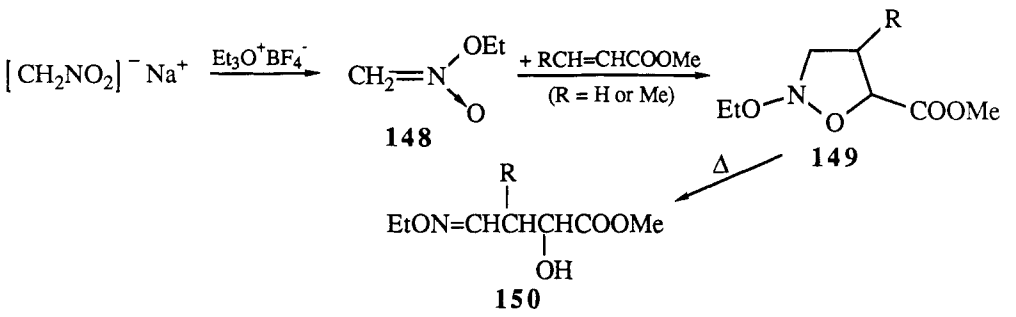
Nitronic esters (or alkyl nitronates) are easily prepared by the reaction of diazoalkanes on aliphatic nitro derivatives, or by reaction of the salts of nitroalkanes with alkyl halides. They can be regarded as *N*-alkoxynitrones and, consistent with this formulation, cycloadd to olefins to yield a large variety of *N*-alkoxyisoxazolidines.

The wide applicability of the reaction has been explored thoroughly since 1964 by Tartakovskii and his school,[113/64] whereas the stereoselectivity of the cycloaddition has been studied in detail more recently by Carrié and co-workers. Because they tend to decompose into oximes and carbonyl compounds, nitronic esters are usually used for cycloadditions immediately after preparation and without purification.

Besides alkyl nitronates, the more stable trialkylsilyl nitronates have been employed successfully in the same cycloaddition reaction. Both types of resulting isoxazolidines, having an oxygenated ring nitrogen, are easily transformed in 2-isoxazolines or into open-chain compounds.

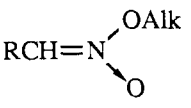
Nitronic esters derived from nitromethane are little known: the ethyl nitronate (**148**), obtained by treatment at $-5°C$ of the sodium salt of nitromethane

with triethyloxonium fluoroborate, was reacted with methyl acrylate or crotonate without further purification. Low yields of the isoxazolidine 5-carboxylates (**149**) are obtained; they are thermally unstable, being quantitatively isomerized by heating at 100–200°C to the corresponding methyl-4-ethoxyimino-2-hydroxybutanoate:[30/75.25B/76]

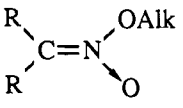



The regiochemistry of the cycloaddition to methyl crotonate is here opposite to the one observed when other nitrones are involved, but the very low yields do not permit any mechanistic significance to be attached to this result. By the way, reduction and hydrolysis of compound **150** open a simple route of some preparative prominence to 4-amino-2-hydroxybutanoic acid and its *erythro*-3-methyl derivative.

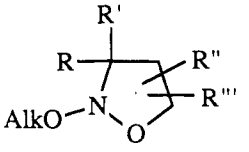
*O*-Alkyl ethers (especially the methyl term) of homologous nitroalkanes have been studied widely. Alkylation of nitro compounds, such as phenylnitromethane, nitroacetic ester, nitroacetonitrile, nitroacetone, or benzenesulfonylnitromethane, with diazomethane or diazoethane gives the *O*-alkylnitrones (**151**), whose cycloadditions to olefins lead to 3-monosubstituted *N*-alkoxyisoxazolidines (**153a**). Analogously, *O*-alkoxynitrones (**152**), obtained from nitro compounds such as nitromalonic esters or trinitromethane, yield 3,3-disubstituted*N*-alkoxyisoxazolidines (**153b**):




**151**




**152**

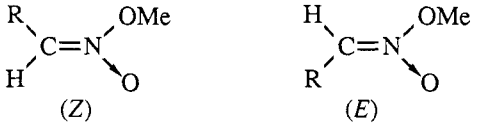



**153 a** R' = H; R ≠ H
**b** R' = R ≠ H

Cycloaddition to monosubstituted or 1,1-disubstituted ethylenes is regiospecific and invariably affords the 5-substituted isoxazolidine. The structure of the adduct is usually assured by ring-opening or NMR spectroscopy. The *O*-methyl derivatives from arylnitromethanes are not very reactive and cycloadd only to the activated double bonds of acrylonitrile,[53/64.61/65.228/68] methyl

acrylate,[61/65,228/68] or vinyl methyl ketone[228/68] to give moderate (24–45%) yields of 2-methoxy-3-aryl-5-substituted isoxazolidines. Similarly, dimethyl methylenemalonate affords dimethyl 2-methoxy-3-arylisoxazolidine-5,5-dicarboxylate.[228/68]

Nitronic esters bearing an activating group (e.g., the cyano or alkoxycarbonyl group) on the carbon atom of the nitrone moiety are more reactive and the cycloaddition reaction usually proceeds with excellent yields. Particularly interesting are the results obtained with the cyano- (**154a**) and methoxycarbonylnitronate (**154**). Here the two geometrical isomers *E* and *Z* could be identified and characterized through dipole moment measurements ($\mu_E > \mu_Z$) and NMR spectroscopical values.[192/71]



(*Z*) (*E*)

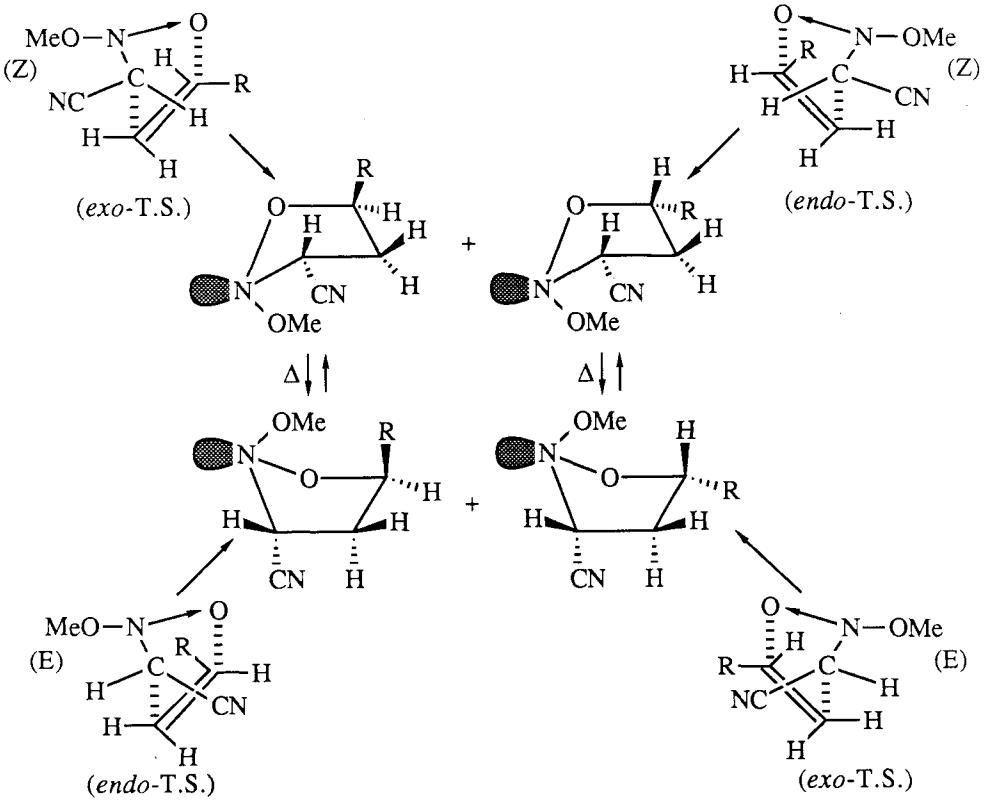
**154 a** R = CN
**b** R = COOMe

Since the two geometrical isomers do not interconvert under experimental conditions, the following general conclusions could be drawn from the results of the cycloaddition reaction with activated olefins.

1. The stereoisomers *Z* are always more reactive than the isomers *E*, although the latter are more stable. For example, reaction of a mixture of isomers *Z* and *E* with an insufficient amount of methyl acrylate at 0°C gave, after separation of the cycloadduct from *Z*, the unreacted pure isomers *E*.[192/71] Moreover, whereas isomers *Z* of nitronic esters **154a** and **154b** are always reactive, isomers *E* do not react at all with dimethyl maleate;[228/76] isomer *E*-(**154a**) is reported to be unreactive with both dimethyl fumarate and fumaronitrile,[23/75] and isomer *E*-(**154b**) is reported to be unreactive with methyl crotonate.[164/77]

2. With monosubstituted olefins such as methyl acrylate, acrylonitrile, or substituted styrenes, the cycloaddition is always regiospecific to give the 5-substituted isoxazolidine.

From the stereochemical point of view, Scheme 3.6 and Table 3.17 summarize the results obtained with the nitronates **154a**.[223/73,227/76] Similar results are known for the nitronates **154b**.[164/77] Both the *endo* and *exo* approaches are effective with acrylonitrile, and mixtures of the two possible epimers are obtained from both geometrical isomers; with styrene or *p*-bromostyrene, by contrast, only the isomers arising from the *exo* transition states are formed. Methyl acrylate reacts normally with nitronates **154b**, the *exo*-derived products being formed exclusively, but with **154a** it behaves anomalously, reacting stereospecifically through an *exo* approach with the *Z* nitronic ester and yielding the epimeric mixture with the *E*-isomer.




Scheme 3.6.

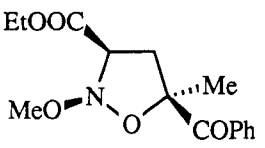
TABLE 3.17

| R | Nitrone isomers | Total yield (%) | Epimers ratio |
|---|---|---|---|
| CN | *Z* | 41 | 50 : 50 |
| | *E* | 36 | 50 : 50 |
| COOMe | *Z* | 48 | 100 : 0 |
| | *E* | 100 | 50 : 50 |
| 4-$BrC_6H_4$ | *Z* | | 100 : 0 |
| | *E* | 67 | 0 : 100 |

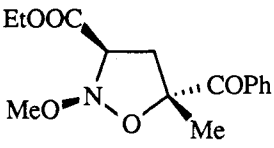
It is interesting to note that under kinetic control only one invertomer is always formed: during the rehybridization accompanying the concerted cycloaddition process, the nitrogen lone pair develops on one side only (i.e., on the side opposite to the reacting olefin).[227/76] Thermodynamic equilibration of the two invertomers is effected in boiling benzene or toluene, and is accompanied by a change in the "envelope"-type conformation of the isoxazolidine ring, so

that the methoxy group is always situated in a pseudo-axial position. The tendency of the isoxazolidine ring to assume these preferred conformations had been confirmed by an x-ray determination[42/74] and $^{15}$N-NMR measurements,[83/75] and has been ascribed, similarly to what is known for the anomeric effect, to the stabilizing interaction between the antibonding orbital of the pseudo-axial N–OMe bond and the $p_y$ lone pair of the ring oxygen.[228/76] According to the same authors, this interaction arises at the beginning of the reaction, and the reacting complex evolves by always keeping it at a maximum, thus leading to the kinetic formation of only one invertomer.

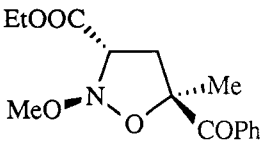
3. Similar results have been obtained with a 1,1-disubstituted olefin such as 1-phenyl-2-methyl-2-propen-1-one [$PhCOC(CH_3)=CH_2$]. This activated double-bond compound cycloadds a 40:60 mixture of *E*/*Z* methyl ethoxycarbonylnitronate $EtOOCCH=N(OCH_3)\rightarrow O$, yielding a 50:15:35 mixture of the three stereoisomeric isoxazolidines **155**, **156**, and **157**, configurationally stable at the nitrogen atom even at room temperature:[204/82]




**155**




**156**



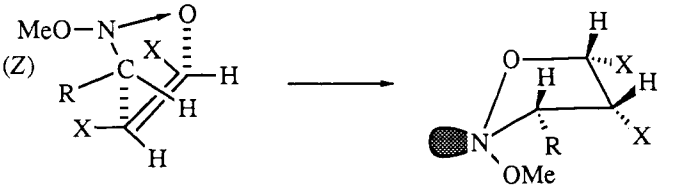

**157**

The higher dipolarophilic reactivity of the nitrone *Z*-isomer and the preferential formation of the *endo* transition states, possibly due to a secondary orbital effect, explain the isomer ratio observed.

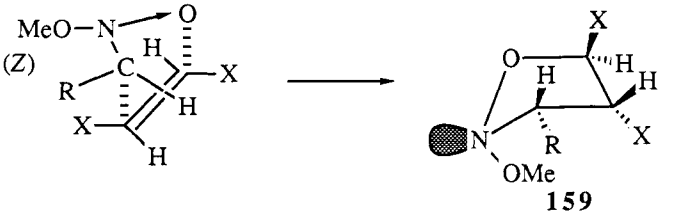
4. With 1,2-disubstituted olefins such as dimethyl maleate or fumarate, furmaronitrile, maleic anhydride, or maleimides, cycloaddition to nitronic esters is strictly stereospecific not only with regard to the original stereochemistry of the activated olefin, but also at the nitrogen atom and in position 3 of the isoxazolidine ring. Only one invertomer is obtained and the epimer arising from an exclusive *endo* approach is formed in each case. Highly remarkable is the fact that in the case of the *Z*-nitrone, changing from methyl acrylate to dimethyl maleate completely reverses the stereoselectivity of the reaction (from 100% *exo* to 100% *endo*).

Thus isomers *Z* of **154a** or of **154b** react with *Z*-olefins to yield **158** and with *E*-olefins to yield **159**; isomers *E* react more slowly to yield **160** and **161**, respectively.[192/71,234/72,23/75] Here, too, equilibration of the invertomers can subsequently be reached by heating.

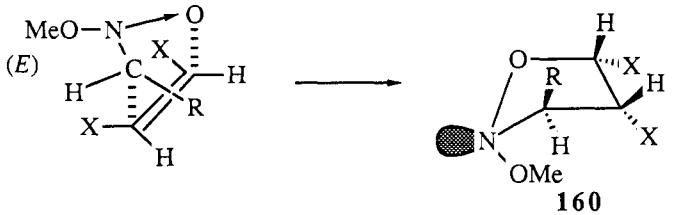
Methyl crotonate cycloadds *Z*-(**154b**) to give regio- and stereospecifically the isoxazolidine derivative **162**, which involves an *endo* position of the methyl group in the transition state.[164/77] Equilibration to its invertomer can be achieved by heating. Regio- and stereospecificity is also observed in the cycloaddition of



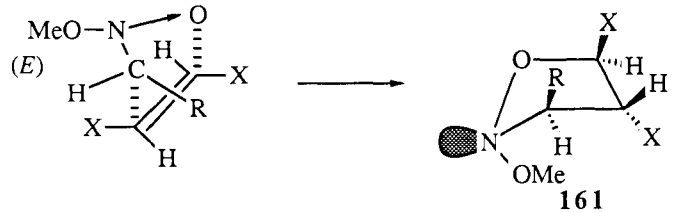
158



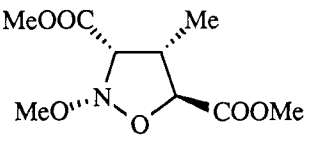
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160



161

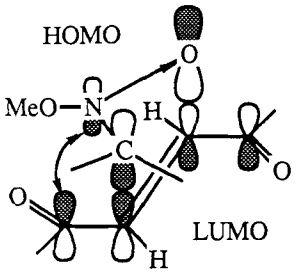


162

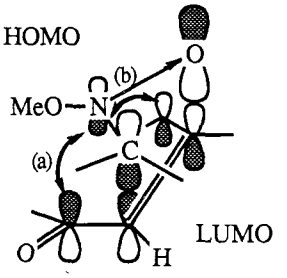
**154a** with activated trisubstituted olefins such as methyl ethylidenecyanoacetate and the triester $MeOOCCH=C(COOMe)_2$.[164/77] Heating of the cycloadducts can sometimes provoke cyclo-reversion to the starting olefin and to the decomposition products of the nitronic ester.

5. Perturbation theory allows the rationalization of these stereochemical results: INDO calculations on the frontier orbitals of nitronic esters and of 1,2-disubstituted olefins reveal that the HOMO (dipoles)–LUMO (olefin) is the dominant interaction. The exclusive *endo* approach observed in this case has been attributed to stabilizing secondary orbital interactions between the lobes

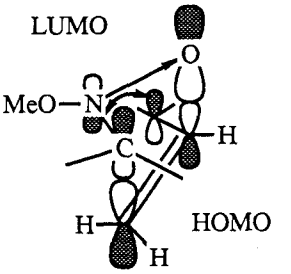
of the nitrogen atom and the carbon atom of the olefin *endo* substituent, as depicted in **163** for *E*-olefins. In the transition state (**164**) from *Z*-olefins a prevalence for the favorable interaction (a) over the antibonding (b) must be involved.[243B/74,24/75]




**163**




**164**

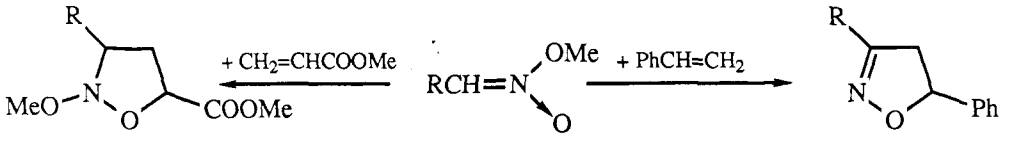



**165**

Cycloaddition with monosubstituted olefins is less straightforward, and both HOMO (dipole)–LUMO (olefin) and HOMO (olefin)–LUMO (dipole) interactions should be considered. In the latter case the stabilizing interaction depicted in **165** counterbalances the unfavorable interaction (b) of **164** as far as the *endo* transition states are concerned; an *exo* approach do not present secondary orbital interactions.[227/76]

6. The use of high pressure seems to be useful in some cases, for example in the cycloaddition of nitronic esters to $\Delta^{16}$-pregnen-20-one derivatives.[265D/78]

The nitronic esters, obtained by methylation of dinitromethane or phenylsulfonylnitromethane with diazomethane, are very reactive and the strong electron-withdrawing group on the nitrone carbon atom promotes the easy elimination of one molecule of methanol; for example, they react with methyl acrylate to yield the expected 2-methoxyisoxazolidine cycloadducts. By contrast, a 34–50% yield of 3-nitro- or 3-benzenesulfonyl-5-phenyl-2-isoxazoline, respectively, is obtained directly by cycloaddition with styrene:[91/66,46/84]

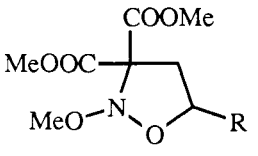



(R = $NO_2$ or $PhSO_2$)

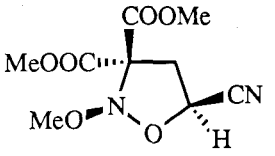
Analogous results have been reported with vinylsilanes.[210/72] Bisnitronic esters act as the starting material in the synthesis of bisisoxazolidines alkoxylated at the nitrogen atom.[291/76]

*O*-Methyl esters of dimethyl nitromalonate and trinitromethane are highly

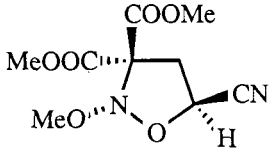
reactive 1,3-dipoles; the former cycloadds even to ethylene in an autoclave at 20–25 atm, yielding dimethyl 2-methoxyisoxazolidine-3,3-dicarboxylate (**166**: R = H).[229/68] Several other monosubstituted olefins, included nitroethylene, give regiospecific cycloaddition to isoxazolidines of general formula **166**.[229/68,210/72] 1,1-Disubstituted activated olefins react as well.[143/78]



**166**



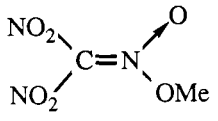
**166 a**



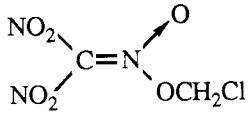
**166 b**

Cycloaddition with an excess of acrylonitrile gave the two invertomers (**166a** and **166b**) in yields of 41% and 45%, respectively.[87/69] The *trans* relationship of 2- and 5-substituents in **166b** was proved by x-ray analysis.[88/69] PMR spectroscopy was applied to prove the structures of the invertomers obtained by cycloaddition of nitronic esters to styrene, for example, **166** (R = Ph): here, too, the predominant product has a *trans* relationship between the substituents in the 2- and 5-positions.[254/72]

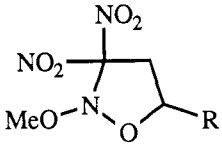
The O-methylation of trinitromethane with diazomethane proceeds well in benzene, but in dioxane the reaction switches over to give the C-methylation product (i.e., 1,1,1-trinitroethane) primarily; the intermediacy of an oxonium complex has been demonstrated.[103/70] *C*,*C*-dinitro-*N*-methoxynitrone (**167**) can also be prepared, although in lower yields, by treatment of diazomethane with iodo- or bromotrinitromethane; in the case of chlorotrinitromethane, the chlorinated nitronic ester **168** is said to be formed instead.[86/71]



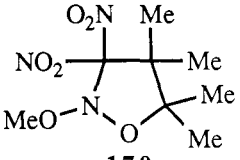
**167**



**168**



**169**

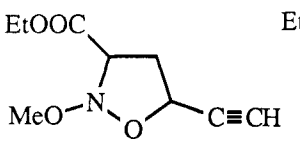


**170**

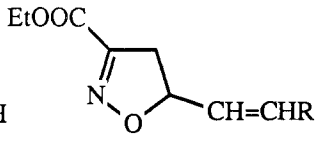
Usually, the dinitronitronic ester **167** is prepared *in situ* and trapped directly with the dipolarophile; a large variety of isoxazolidines of general formula **169** have thus been prepared.[53/64,41/65] Ethylene reacts to give a 73% yield of the cycloadduct **169** (R = H); even the usually unreactive tetramethylethylene can be forced to react, affording a 20% yield of the highly encumbered isoxazolidine **170**.[41/65]

Reactions of nitronic esters with dienes or enynes are also known: as expected for 1,3-dipolar cycloadditions, the double bond is more reactive than the triple

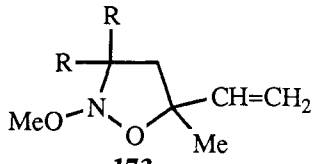
bond, and the less substituted bond usually reacts preferentially. For example, vinylacetylene reacts with *C*-ethoxycarbonyl-*N*-methoxynitrone to yield ethyl 2-methoxy-5-ethynylisoxazolidine-3-carboxylate (**171**); treatment of the same nitrone with butadiene or 1,3-pentadiene affords the methyl 5-vinylisoxazoline-3-carboxylate (**172**) directly.[177/67]



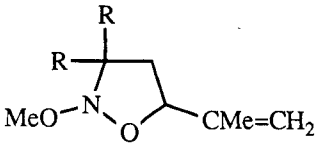

**171**



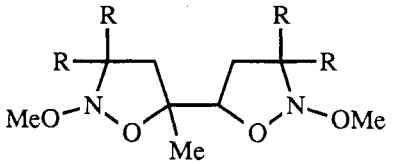

**172**




**173**




**174**




**175**

The disubstituted *C,C*-dinitro- or *C,C*-diethoxycarbonyl-*N*-methoxynitrones are also known to react with dienes: isoprene yields a mixture of monoadducts **173** and **174**.[177/67,227/68] Use of an excess nitrone led to isolation of the bis adduct (**175**).

Tetranitromethane reacts with olefins directly, and the product formed depends on the structure of the unsaturated substrate. Nucleophilic olefins (alkyl-, aryl-, or alkoxy-substituted) attack the tetranitro compound to form, possibly through an initial $\pi$-complex, an ion pair: the nitrocarbocation **176** and the ambident trinitromethane anion **177**.

This system can evolve in various directions, both steric and electronic factors being at work:

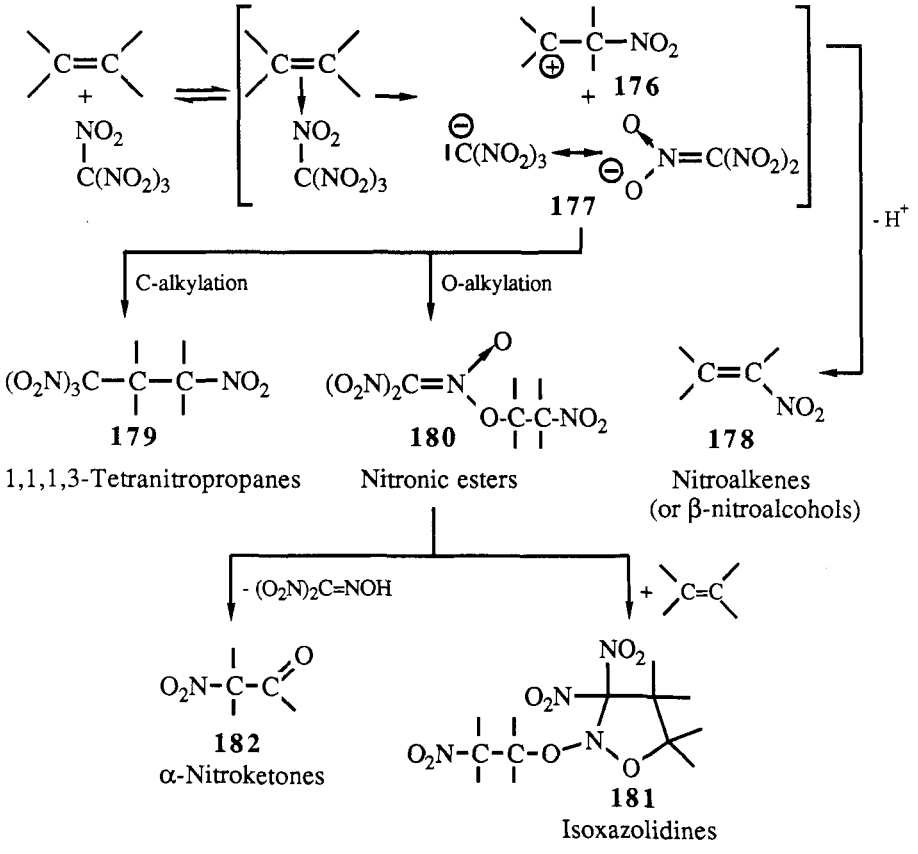
1. The nitrocarbocations arising from 1,1-diarylethylenes or from triphenylethylene are too heavily encumbered to be attacked by the anion and therefore lose a proton to give $\alpha$-nitroalkenes (**178**).[255/70,256B/70,253/72]
2. In all other cases the ion pair collapses, giving rise to either C- or O-alkylation of the ambident anion. Attack on the carbon atom is favored when the positive charge of the nitrocarbocation is delocalized by an electron-releasing group such as methoxy or methyl in the *para* position of the starting styrene derivative. Stable 1,1,1,3-tetra-nitropropane compounds (**179**) are thus formed,[233C/69,253/72,257/72] but the C-alkylation is very sensitive both to electronic and steric effects. For example, *p*-methylstyrene undergoes O-alkylation, whereas $\alpha$,*p*-dimethylstyrene undergoes only C-alkylation.[257/72] Moreover, 1-*p*-methoxyphenyl-2-methylpropene is too encumbered for attack by the anionic carbon atom and undergoes O-alkylation.[253/72]

3. O-alkylation is prevalent when the localized positive charge attracts the more negative end of the ambident anion. This happens with styrene and most of its derivatives, mono- and polyalkylated olefins, and mixed aryl-alkyl ethylenes. Nevertheless, few of the resulting nitronic esters (**180**) are stable,[255/70] and in most cases the system evolves spontaneously toward one of the two following pathways:

   a. The most general development is cycloaddition with a second molecule of olefin to give moderate to excellent yields of the corresponding 2-alkoxyisoxazolidine (**181**).[207/66,71/67,180/67,227/69,255/70,212/72,257/72]

   b. When the olefin is sterically burdened (e.g., with 1-phenylpropene or β,β-dimethylstyrenes), cycloaddition cannot take place and the nitronic ester decomposes to the corresponding α-nitro ketone or its derivatives.[255/70,253/72]

The several reaction patterns are summarized in Scheme 3.7. Electron-withdrawing substituents greatly decrease the nucleophilicity of the double bond,

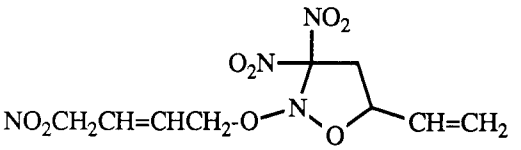



Scheme 3.7.

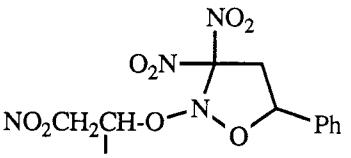
and therefore ethylenic derivatives such as vinyl chloride, acrylonitrile, and β-nitrostyrene do not react at all with tetranitromethane.[257/72]

Dienes also react directly with tetranitromethane, and the product obtained depends on the substitution pattern. 1,3-Butadiene[232/69] and its monomethylated homologues isoprene and piperylene[255/72] react with tetranitromethane in the ratio 2:1 to give the 2-alkoxylated isoxazolidines, generally arising from an initial 1,4-addition (e.g., from butadiene the cycloadduct **183** is formed). With higher-substituted dienes, C-alkylation predominates, yielding only 1:1 products of 1,2- and 1,4-addition.[255/72]

An analogous dual reactivity is shown by cyanotrinitromethane, a compound very close to tetranitromethane in its structure and chemical properties. Thus reaction with styrene affords the expected isoxazolidine **184**, whereas with *p*-methoxystyrene C-alkylation occurs.[271/74]



**183**



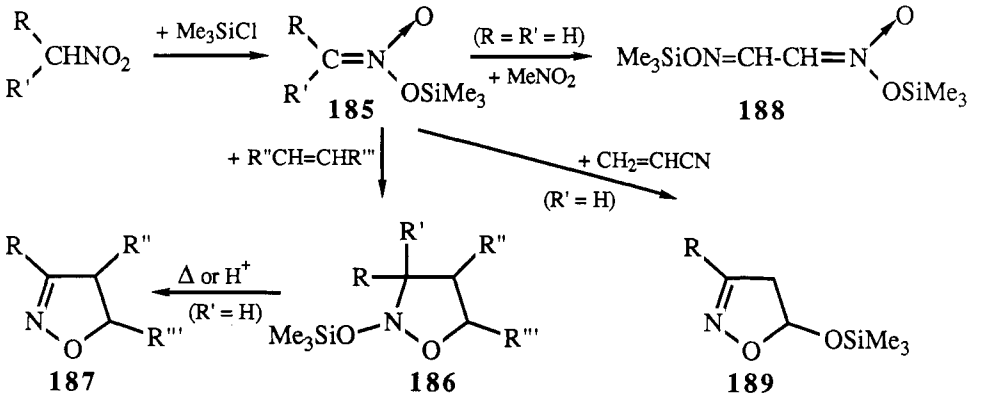
**184**

A mixture of isoxazolidine derivative and of α-nitro-*p*-methylacetophenone in comparable amounts results from the reaction of *p*-methylstyrene and cyanotrinitromethane.[290/76] Similar results are known when a halogentrinitromethane reacts with an olefin. Substantial yields of *O*-β-halogenalkoxyisoxazolidines are obtained with mono- and disubstituted olefins,[92/66.171/67.105/68.211/72.251/73] whereas with α-methylstyrene and *p*-methoxystyrene, C-alkylation is dominant.[251/73] As may be expected, fluorotrinitromethane shows a lower reactivity and cycloadds only to *p*-methoxystyrene, giving a 3-fluoro-3-nitroisoxazolidine derivative with a **181**-like structure.[292/77]

The anion of trinitromethane is present also in the corresponding salts, for example in the silver salt, and reaction with primary halides affords both C- and O-alkylation. The nitronic ester formed in the latter case can be trapped with a suitable dipolarophile (e.g., allyl alcohol) to yield the corresponding 2-alkoxy-3,3-dinitro-5-hydroxymethylisoxazolidine.[104/68.106/68] Reaction with secondary or tertiary halides affords, besides O-alkylation, the alkene, which in turn cycloadds to the intermediate nitronate to give low yields of the isoxazolidine derivative.[104/68.107/68]

Silyl nitronates (**185**) are also known, being prepared by directly silylation of nitroalkanes with trimethyl (or triphenyl) chlorosilane and triethylamine or their silver salts in an inert solvent at low temperature. *N,N*-Bis(trimethylsilyl)acetamide[48/74.263/74] or *N,N'*-diphenyl-*N*-trimethylsilylurea[253/73] have also been proposed as silylating agents. The silyl nitronates are usually unstable and must be trapped *in situ* with an olefin to give the corresponding isoxazolidines

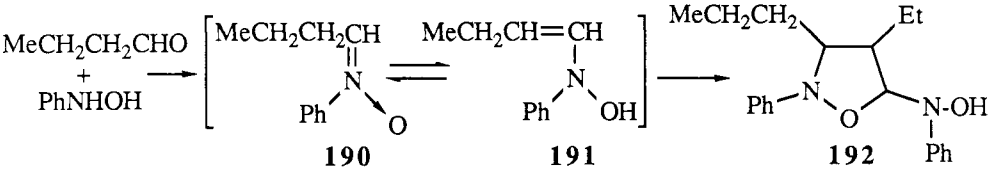
(**186**).[90/72,115/73,250/73,253/73,254/73,48/74,263/74,3/78,4/79,2/81] The latter compounds in turn can suffer trimethylsilanol elimination by acidic or basic catalysis, or spontaneously to afford the 2-isoxazolines (**187**):[90/72,250/73,253/73,254/73,48/74,3/78,4/79]




Mixtures of stereoisomers are obtained when the silyl nitronates bear different substituents at the carbon atom, and the mixture composition indicates that the *exo* approach of the dipolarophile predominates.[112/77] When the dipolarophile is absent, trimethylsilylation of nitromethane yields the open-chain nitronate **188**.[57C/64] Acrylonitrile provokes formation of 5-trimethylsilyloxy-2-isoxazoline (**189**)[3/78,4/79] when the silyl nitronate is derived from a primary nitroalkane; silylnitronates derived from secondary nitroalkane cycloadd regularly.[2/81]

### *3.3.1.3 Dimerization of Nitrones*

Nitrones derived from aliphatic aldehydes are often unstable even at room temperature and promptly dimerize to isoxazolidine derivatives. For example, so-called "*C*-propyl-*N*-phenylnitrone," obtained by reaction of butyraldehyde with *N*-phenylhydroxylamine,[8C/54,6B/56,90C/63] has long[38/69,206/69] been recognized by spectroscopic evidence to possess the dimeric structure **192** instead of the monomeric structure **190**:



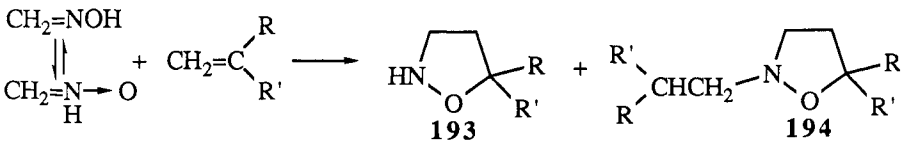
The formation of **192** has been envisaged as a cycloaddition of the nitrone **190** to its tautomeric form, the *N*-hydroxyenamine **191**,[206/69] although a somewhat different mechanism through a vinylaminyloxide radical has also been proposed.[19/79] Evidence of the existence of a thermal equilibrium between 5-hydroxylaminoisoxazolidines and the *N*-hydroxyenamines in some special cases has recently been provided.[272/80]

Similar dimeric structures have been assigned to the products obtained starting from phenylhydroxylamine and propionaldehyde or the sodium salt of ethyl formylacetate,[272/80] phenylacetaldehyde and some N-substituted hydroxylamines,[214/81] phenylhydroxylamine and activated alkynes such as dimethyl acetylenedicarboxylate[19/69,18/79] or phenyl sulfonyl acetylene,[18/79] and even from ketonitrones such as those prepared from acetone and *N*-phenylhydroxylamine[52/68,151/74] or from α-phenyldiazoethane and nitrosobenzene.[159/76]

Whereas *C*-alkyl-*N*-arylnitrones are easily stabilized as dimers, and consequently have usually been prepared *in situ* if an intramolecular cycloaddition is to be performed (see Part 2 of this work), *C*,*N*-dialkylnitrones seem to be more stable as monomers. Slow dimerization is observed by long storage, and the process is accelerated by basic catalysis.[40/79] On the whole, dimerization of nitrones is not very useful as a preparative procedure for isoxazolidine derivatives, but may be important as an intermediate step for other synthetic purposes, such as the formation of stable free radicals[9B/26,151/74,159/76,19/79] or the synthesis of 3,4-disubstituted pyrroles.[214/81]

### *3.3.1.4 Cycloaddition of Oximes to Ethylenic Compounds*

Under appropriate circumstances oximes can be brought to act as their tautomeric counterparts (i.e., nitrones) and to enter into 1,3-dipolar cycloaddition to activated double bonds, giving rise to isoxazolidine derivatives. For example, formaldoxime cycloadds to acrylonitrile, methyl acrylate, or methacrylate, to yield regiospecifically a mixture of 5-substituted isoxazolidines (**193**) and of the corresponding N-alkylated derivatives (**194**):[139/67,127/70]

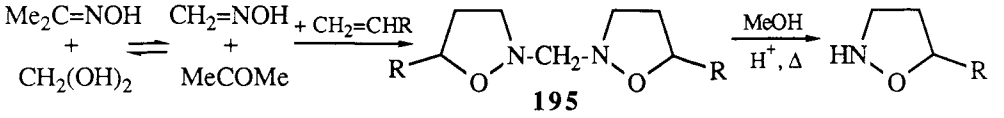


**193** **194**

| R | R' | Ratio | Total yield (%) |
|---|---|---|---|
| H | CN | 24 : 76 | 42.2 |
| H | COOMe | 13 : 87 | 21.4 |
| Me | COOMe | **193** only | 22.6 |

The reaction occurs with strict retention of the stereochemistry of the olefinic reagent in the final isoxazolidine, as demonstrated by the results obtained with dimethyl fumarate and maleate.[139/67]

The N-unsubstituted isoxazolidines have been prepared more conveniently in two steps: treatment of formaldoxime in excess, generated *in situ* from acetone oxime and formalin, with styrene (or other double-bond compounds) yields the intermediate bisisoxazolidinylmethane (**195**), whose acid-promoted methanolysis furnishes a 5-substituted isoxazolidine:[2/84]

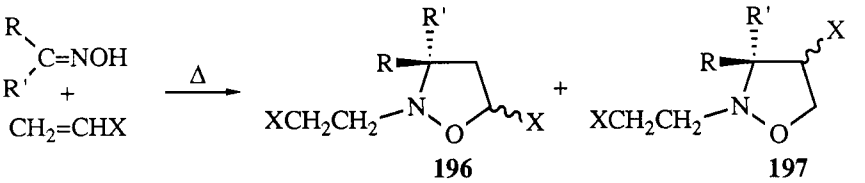



**195**

Benzophenone oxime was analogously found to react with methyl vinyl ketone to yield a mixture of 1:1 and 2:1 adducts having isoxazolidine structure.[156/67,202/68]

The reaction has been generalized with both aldoximes and ketoximes, which normally yield 2:1 adducts as prevalent or exclusive products.[215/80,2/84,72/84] Their formation has been attributed to an initial Michael addition of the oxime nitrogen to the electron-poor olefin, followed by 1,3-dipolar cycloaddition of

TABLE 3.18



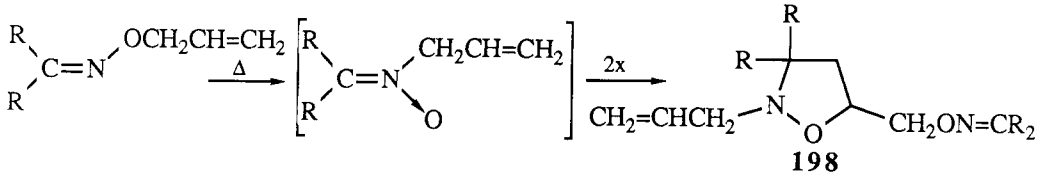

**196** **197**

| R | R' | X | Temp. (°C) | Ratio (**196**):(**197**) | Total yield (%) | References |
|---|---|---|---|---|---|---|
| Me | Me | CN | 80-85 (in pyridine) | 7 : 9 | 75 | 72/84 |
| | | | 80 (neat) | 2 : 1 | 100 | 2/84 |
| Me | Me | COOMe | 80-85 (Py) | 5 : 2 | 81 | 72/84 |
| | | | 90 | 7.7 : 2.3 | 77 | 2/84 |
| Et | Et | CN | 80-85 (Py) | 3 : 4 | 74 | 72/84 |
| Et | Et | COOMe | 80-85 (Py) | 5 : 1 | 81 | 72/84 |
| -$(CH_2)_5$- | | CN | 80 | 7 : 3 | 61 | 2/84 |
| Me | H | COOMe | 80 | 9 : 1 | 72 | 2/84 |
| Ph | H | COOMe | 75 | 2 : 1 | 84 | 2/84 |
| | | | | Ratio (**196**)*cis*:(**196**)*trans*:(**197**)*cis*:(**197**)*trans* | | |
| 2-Furyl | H | CN | 80-85 (Py) | 10 : 3 : 7 : 2 | 78.5 | 72/84 |
| Ph | H | CN | 80-85 (Py) | 9 : 5 : 4.2 : 2.8 | 81 | 72/84 |
| Ph | H | COOMe | 80-85 (Py) | 4 : 3 : 2.3 : 2.7 | 83 | 72/84 |
| 4-$MeOC_6H_4$ | H | CN | 80-85 (Py) | 4 : 2 : 3.5 : 5.6 | 82 | 72/84 |
| 4-$F_3CC_6H_4$ | H | CN | 80-85 (Py) | 9 : 7 : 0 : 5 | 79 | 72/84 |

the N-substituted nitrone to the double-bond compound.[72/84] The alternative process (cycloaddition involving the nitrone tautomeric form of the oxime, followed by Michael addition of a second molecule of alkene)[156/67] is also possible, but requires higher energy.[72/84]

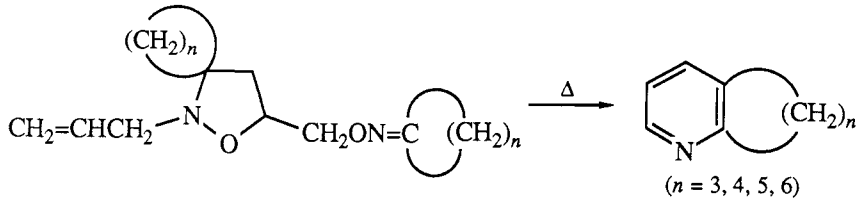
To perform the reaction in good yields, the two reagents (oxime and electron-deficient olefin) are heated together at 80–90°C, with[72/84] or without[2/84] pyridine. A mixture of the possible regioisomers is obtained from symmetrical ketone oximes, whereas from asymmetrically substituted ketoximes or from aldoximes all four possible regio and stereo isomers arise in variable proportions. A selection of the available data is presented in Table 3.18. Here, too, the various ratios obtained under different experimental conditions are probably due to solvent effects and/or partial equilibration of the kinetic mixture bound to cyclo-reversion processes.

In agreement with the proposed mechanism, the *O*-methyl ethers of the oximes do not react.[202/68] By contrast, the *O*-allyl ether of some ketoximes, heated in benzene at 200°C, afforded a low yield of the dimeric isoxazolidine **198**, presumably arising through previous isomerization to *N*-allyl-nitrone:[247B/74,207/79]




**198**

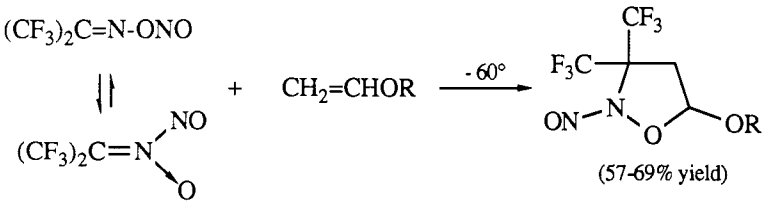
The reaction has some preparative importance, since by longer heating, compounds **198**, obtained from cyclanone oximes, are easily converted into cycloalkenopyridines:[207/79]




(*n* = 3, 4, 5, 6)

Treatment of oximes with butadiene in the presence of palladium nitrate and triphenylphosphine generally provokes O-alkylation of the oxime. However, aliphatic aldoximes undergo N-alkylation to give nitrones, which immediately react with excess butadiene to afford moderate to low yields of 3-alkyl-*N*-(2′,7′-octadienyl)-5-vinylisoxazolidines.[245/77]

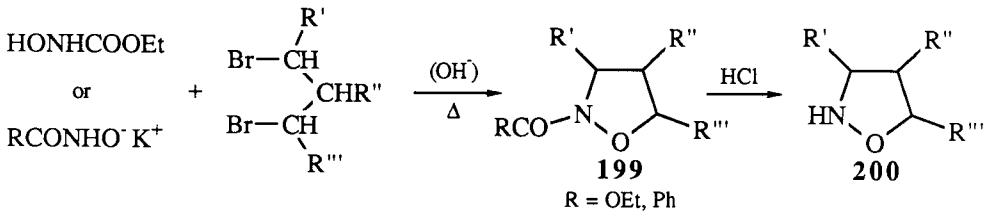
Hexafluoroacetone oxime nitrite has been reported to interact at low temperatures with electron-rich olefins such as vinyl ethers to yield the corresponding *N*-nitrosoisoxazolidine derivatives:[337/83]




### 3.3.2 [CCC + NO] Processes

#### *3.3.2.1 Synthesis from 1,3-Dihalo Compounds*

The oldest synthesis of fairly general applicability still convenient for the formation of N-unsubstituted isoxazolidines involves the reaction of *N*-hydroxyurethanes or of hydroxamic acids and their salts with 1,3-dihalo compounds in an alkaline medium. *N*-Alkoxycarbonyl or *N*-acylisoxazolidine derivatives (**199**) are obtained in moderate yields, whose acidic hydrolysis leads to the corresponding N-unsaturated compounds (**200**):

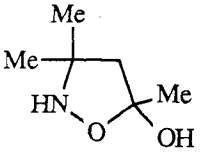



Using this method, in 1942 King[10B/42] prepared the parent isoxazolidine, starting from 1,3-dibromopropane and *N*-hydroxyurethane. The reaction has been extended to several other homologues and is especially valuable for the synthesis of 3- or 5-mono- and 3,5-disubstituted isoxazolidines.[142/71.39/72.235/73.70/74.4/78] The parent compound may also be prepared directly from 1,3-dibromopropane and hydroxylamine in a warm alkaline solution; the base is usually isolated as hydrochloride or (better) hydrobromide.[139/80]

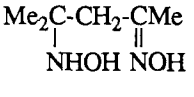
#### *3.3.2.2 Oximation of α,β-Ethylenic Carbonyl Compounds*

It is well known that the reaction between α,β-ethylenic carbonyl compounds and hydroxylamine often leads to a mixture of products, and that which product is obtained depends on the experimental parameters, such as pH, solvent, temperature, substituent, and reagent ratio (see also § 2.2.1). In some cases, especially with aliphatic ketones, the 5-hydroxyisoxazolidine derivative can be isolated in good yields; for example, treatment of mesityl oxide with an equi-

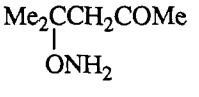
molar amount of hydroxylamine in the presence of a slight excess of potassium hydroxide (pH 8–9) in ethanol at room temperature gives a 70% yield of 3,3,5-trimethyl-5-hydroxyisoxazolidine (**201**);[21/72,36/73] treatment of the latter compound with a second molecule of hydroxylamine gives the hydroxylamino-oxime **202**, probably through the open-chain tautomer of **201**.[36/73] At lower temperatures in the presence of sodium methoxide attack by the hydroxylamine oxygen atom is favored and the formation of **203** has been detected, which easily cyclizes to the 2-isoxazoline **204**.[36/73] In a neutral or slightly acidic medium the formation of (**202**) is prevalent.[193/71,36/73]



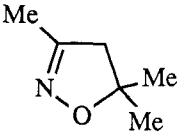
**201**



**202**

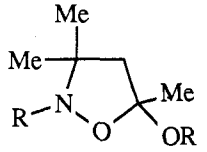


**203**

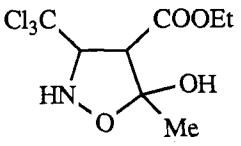


**204**

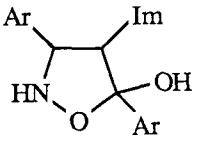
The same 3,3,5-trimethyl-5-hydroxyisoxazolidine (**201**), mixed with about an equal amount of the hydroxylaminooxime (**202**), is obtained by oximation of the condensation product of 4-methylpent-3-en-2-one and benzaldehyde.[120/73] Other N-substituted hydroxylamines react with 4-methylpent-3-en-2-one, affording 5-hydroxyisoxazolidines (**205**) in basic media and 5-alkoxy derivatives (**206**)



**205** R = H
**206** R = Me, Et



**207**



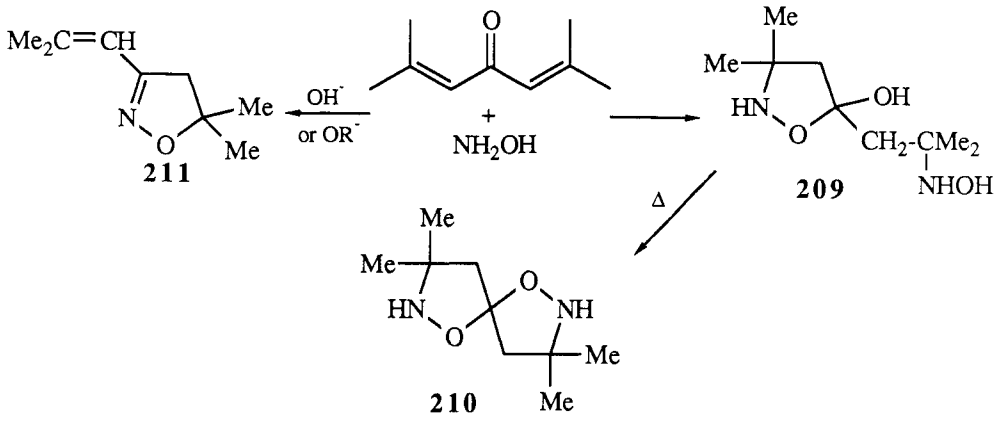
**208**
(Ar = 2,4-$Cl_2C_6H_3$; Im = 1-imidazolyl)

under alcoholic neutral conditions.[24/72] Analogously, by treatment of acrolein or crotonaldehyde with *t*-butylhydroxylamine, a 1,4-addition occurs and cyclization affords 2-*t*-butyl- and 2-*t*-butyl-3-methyl-5-hydroxyisoxazolidine, respectively.[3/78] It is worth noting that under the same conditions, cinnamaldehyde yields the normally expected nitrone.

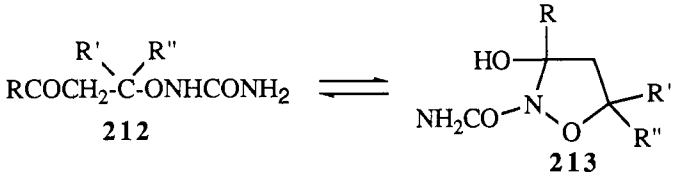
Considering the results above, it seems reasonable to confirm the proposed structure (**207**) for the product formed by base-catalyzed oximation of ethyl trichloroethylidene acetacetate.[27/57] Another 1,4-addition pattern has been claimed in the formation of **208** by oximation of the corresponding $\alpha,\beta$-ethylenic ketones.[182B/79]

The ambident behavior of hydroxylamine has also been evidenced in the reaction with phorone, where again the prevalence of Michael-type addition, from either the nitrogen or the oxygen atom of hydroxylamine, is observed.

Thus in neutral conditions a slow reaction to **209** at low temperature occurs, which evolves to **210** at higher temperatures, whereas under basic conditions the isoxazoline **211** is mainly produced:[52B/81]

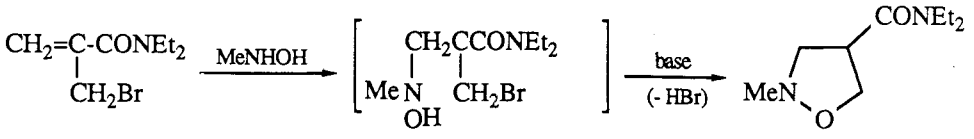



On the other hand, *N*-hydroxyurea attacks α,β-unsaturated aldehydes or ketones with its saturated oxygen atom to yield either the open-chain tautomer **212** or the 3-hydroxyisoxazolidine compound **213** or a mixture thereof, depending on the substituent pattern and the temperature.[187/75] In any case, acidic treatment causes dehydration to 2-isoxazoline.




### *3.3.2.3 Other Processes*

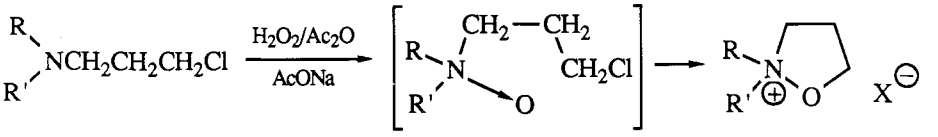
A 2-methylisoxazolidine-4-carboxamide has been said to form by treatment of α-bromomethylacrylamide with *N*-methylhydroxylamine, presumably through a Michael-type addition to the activated double bond and subsequent base-promoted cyclization:[73/72]



This reaction deserves further confirmation.

### 3.3.3 [CCCN + O] Process

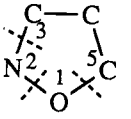
Isoxazolidinium salts can be achieved by oxidative cyclization of tertiary amines, containing one 3-chloropropyl group, with peracetic acid.[17/57,19/60,20/61,30C/62,30D/62] The nonisolated intermediate *N*-oxides immediately cyclize to isoxazolidinium salts, usually isolated as picrates or iodides:



An analogous result has been achieved by iodo cyclization of the preformed 3-butenyldiethylamine-*N*-oxide.[204/76] 2-Methyl-5-decylisoxazolidine has been reported as a secondary product in the ruthenium chloride–catalyzed oxidation of dodecyldimethylamine.[156/83]

### 3.3.4 Cyclization Processes

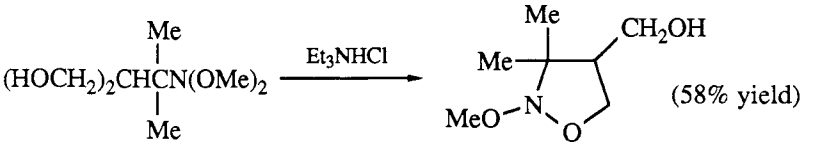
Cyclization methods have been used only occasionally for building up the isoxazolidine nucleus. They can be distinguished on the basis of the bond closed in the ring formation:



All three processes known up to now involve at least one (or both) heteroatom. Thus ring closure is carried out through formation of the O–N (1–2), or N–C (2–3), or C–O (5–1) bond, respectively.

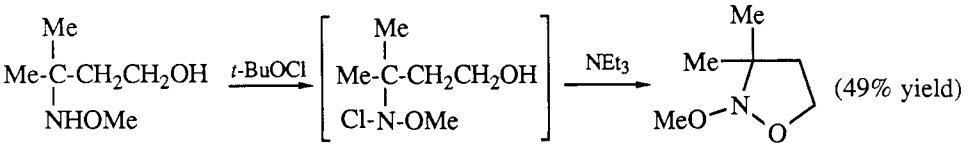
#### *3.3.4.1 [OCCCN] Process*

γ-Hydroxylated *N*,*N*-dialkoxyamines have been cyclized to 2-methoxy-isoxazolidines in a weakly acidic medium; for example:[93/81]



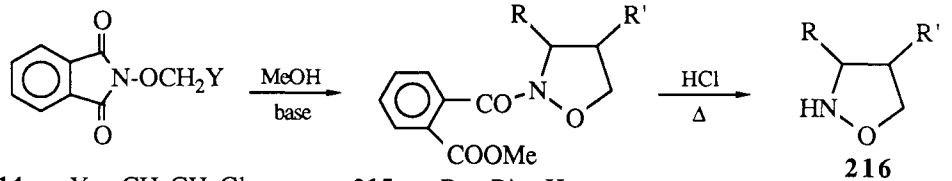

(58% yield)

The same type of 2-methoxy-3,3-dimethylisoxazolidines can be prepared by base-promoted cyclization of $\gamma$-hydroxylated-*N*-chloro, *N*-methoxyamines, as in the following example:[132/80,227B/81]




### *3.3.4.2 [NOCCC] Process*

The presence of a $\gamma$-haloatom[181/84] or a $\beta,\gamma$- or $\gamma,\delta$-epoxy group[190/82,264/82] on the alkyl residue of *N*-hydroxyphtalimide ethers (**214**) promotes a base-catalyzed methanol addition with intramolecular ring closure to a 2-(2-methoxycarbonylbenzoyl)isoxazolidine (**215**):



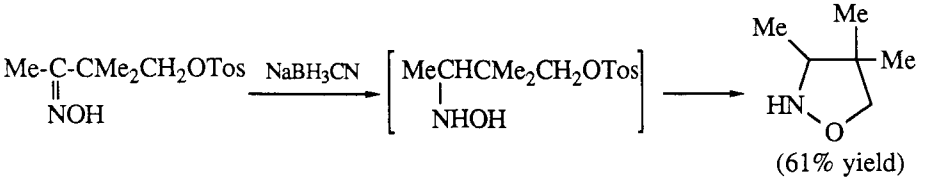

**214 a** Y = $CH_2CH_2Cl$
**b** Y = $CH{-}CH_2$ (O)
**c** Y = $CH_2CH{-}CH_2$ (O)

**215 a** R = R' = H
**b** R = H; R' = OH
**c** R = $CH_2OH$; R' = H

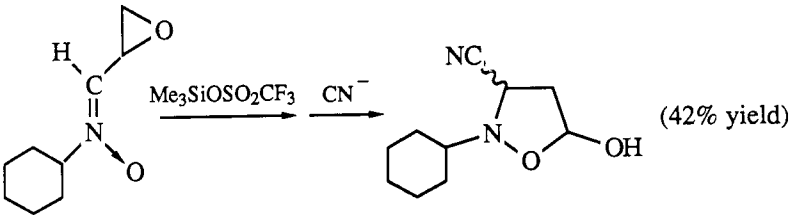
Hydrolysis of this compound affords excellent yields of N-unsubstituted isoxazolidines (**216**).[264/82] The parent (**216a**) (isolated as hydrochloride) can be obtained directly by treatment of **215a** with hydrazine hydrate.[181/84]

### *3.3.4.3 [CCCNO] Processes*

Hydroxylamino derivatives, carrying a good leaving group in the $\gamma$-position, can be brought to cyclyzation under favorable circumstances. For example, reduction of the 3,3-dimethyl-4-tosyloxy-2-butanone oxime represents a convenient synthesis of 3,4,4-trimethylisoxazolidine:[213/83,291/83]



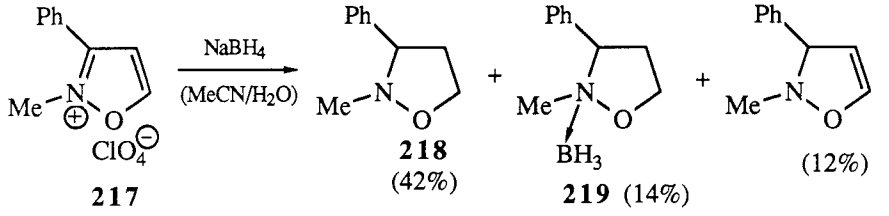
A rather unusual synthesis of 2-cyclohexyl-3-cyano-5-hydroxyisoxazolidine (mixture of two diastereoisomers) starts from *N*-cyclohexyl-*C*-epoxyethylene nitrone by successive treatment with trimethylsilyl trifluoromethanesulfonate and potassium cyanide:[64/79]




### 3.3.5 From Heterocyclic Compounds

#### *3.3.5.1 From Other 1,2-Oxazole Derivatives*

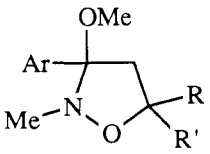
Although the hydrogenation of isoxazoles or isoxazolines (both 2- and 4-) usually does not lead to isoxazolidine derivatives since the N–O bond is preferentially broken with formation of open-chain compounds, some special cases are known. Whereas reduction of 5-phenyl-substituted isoxazolium salts with sodium borohydride generally stops at the stage of 4-isoxazoline compounds (see § 2.5.2.3, p. 638), 5-unsubstituted isoxazolium salts behave differently. Thus 2-methyl-3-phenylisoxazolium perchlorate (**217**), when treated with sodium borohydride in aqueous acetonitrile, afforded a mixture of three products in which 2-methyl-3-phenylisoxazolidine (**218**) and its borane complex (**219**) are dominant:[36/74]



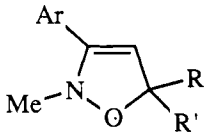

The reaction is solvent dependent: in ethanol the major products are **218** and 2-methyl-3-phenyl-2-isoxazolinium perchlorate. The formation of 3- or 4-isoxazolines or of isoxazolidines seems to depend strongly on the isoxazolium salt substituents, especially those in the 4-position, and on the nature of the complex metal hydride to be used. For example, isoxazolidines are obtained by reduction of 3,5-dimethyl-4-nitroisoxazolium salts with $NaBH_4$ or $LiAlH(OBu)_3$ or of 3,5-dimethyl-4-acetylisoxazolium salt with $LiAlH_4$.[157/84]

Nucleophilic attack of sodium methoxide on 2-isoxazolinium salts makes it possible to obtain 3-methoxyisoxazolidines (**220**); usually, these compounds are

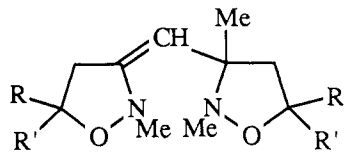
not interesting as such but rather as intermediates in the synthesis of 3-isoxazolines (**221**)(see § 2.4, p. 623). Moreover, 3-aryl-3-methoxyisoxazolidines are sufficiently stable as sometimes to be isolated, whereas the 3-methyl-3-methoxy derivative decomposed slowly at room temperature to the corresponding 3-isoxazoline, which in turn dimerizes to compound **222**.[24/72,21/74]




**220**

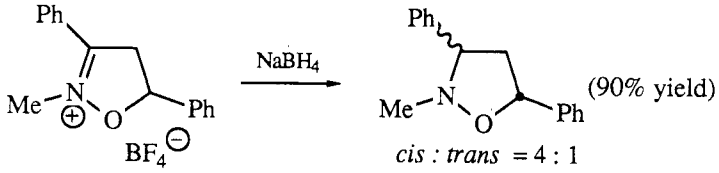



**221**

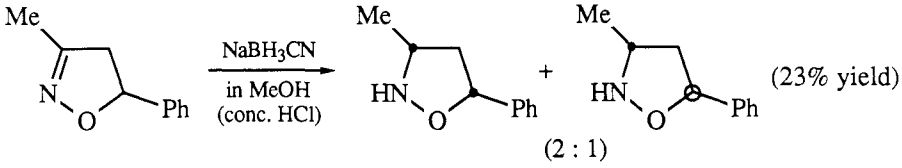



**222**

Of general applicability is the sodium borohydride reduction of 2-isoxazolinium tetrafluoroborates to give the corresponding isoxazolidines: the reaction is particularly useful in the case of 4,5-ring-condensed isoxazolines, where the hydride attack is 100% stereoselective[232/74] (see Part 2 of this work). In the only monocyclic isoxazolium salt checked so far, the attack of the reducing agent still occurs preferentially from the less hindered side, but the reaction here is partially stereoselective:



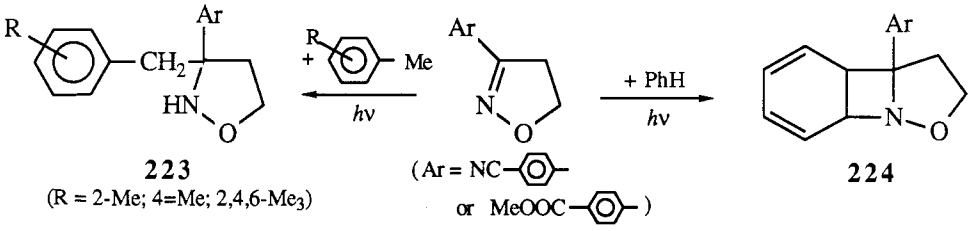

An attractive synthesis of N-unsubstituted isoxazolidines, which would deserve further study despite its reported low yield, is exemplified by the formation of a mixture of the two epimeric 3-methyl-5-phenylisoxazolidines from 3-methyl-5-phenyl-2-isoxazoline and sodium cyanoborohydride in methanol and concentrated HCl:[9/80]



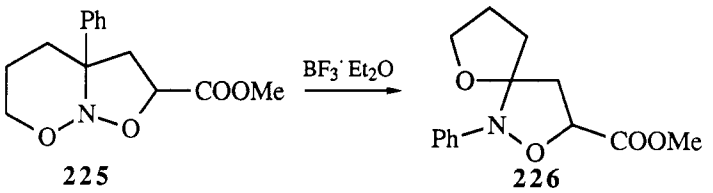

Moreover, 5-phenylisoxazolidine-3-carboxylic acid has been prepared in 30% yield by treatment of the corresponding sodium 2-isoxazoline-3-carboxylate with sodium borohydride in ethanol.[135/72]

A photochemical addition of methyl-substituted benzenes to the C=N

double bond of 3-*p*-cyano (or *p*-methoxycarbonyl)-phenylisoxazolines is known to occur, the isoxazolidines (**223**) being formed in 58% yield.[163B/81,301/83] The reaction has a limited applicability, since other arenes, such as benzene, indene, and some heteroaromatics, give [2 + 2] photocycloadditions on the same substrate, leading to condensed polycyclic isoxazolidines such as **224** (see § 2.2.3.1, p. 552):



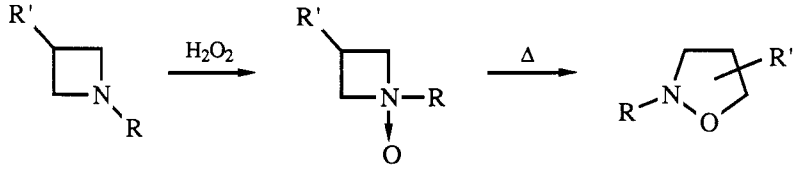

Of even more limited synthetic value is the $BF_3$-etherate-catalyzed rearrangement of the bicyclic compound **225** to the spiroisoxazolidine **226**:[114/76,113/77]



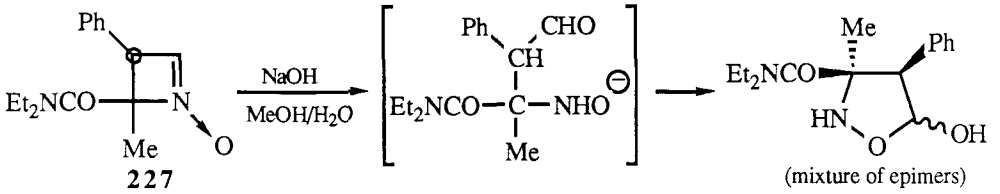

Some 5-alkoxyisoxazolidine derivatives have been prepared by acid-catalyzed addition of methanol or ethanol to 4-isoxazolines; mixtures of diastereoisomers are thus formed.[41B/75] A 3-aryl-5-hydroxy-2,4,4,5-tetramethylisoxazolidine has been reported to arise by reaction of the corresponding isoxazolidin-5-one with methylmagnesium iodide.[7/84]

### *3.3.5.2 From Other Heterocycles*

Of course, isoxazolidines have also been obtained from other heterocyclic sources. For example, azetidine *N*-oxides, easily attainable by treatment of azetidines with hydrogen peroxide, can isomerize with ring enlargement on heating to 120–160°C without solvent or in an inert solvent:[97/73,79/74]



Some substituted 1-azetine-1-oxides (i.e., four-membered cyclic nitrones) such as **227** undergo a base-promoted hydrolytic ring expansion to 5-hydroxy-isoxazolidines, the ring tautomers of β-hydroxyaminoaldehydes:[230/81,207/82,191/83]



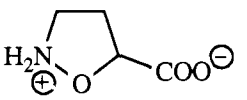

**227**

(mixture of epimers)

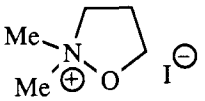
## 3.4 CHEMICAL PROPERTIES

### 3.4.1 Formation of Salts and Quaternization

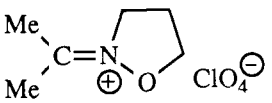
As already mentioned (§ 3.2.10), isoxazolidines are relatively strong bases and readily form crystalline salts with acids. Hydrochlorides, picrates, hydrogen oxalates, and maleates are frequently used to characterize the isoxazolidine compound, especially when the free base is liquid or unstable.[43/59,30/62,59/64,181/73,144/79] The different solubilities of the picrates have permitted the separation of the two diastereomeric 2-methyl-3,5-diphenylisoxazolidines.[20/68] An internal salt such as **228** could be isolated when the hydrochloride was cautiously treated with ethanolic pyridine. The amphoteric character of **228** was deduced from the IR spectrum, and $pK_a$ values of 2.18 and 4.77 at 22°C were determined.[39/72]




**228**




**229**

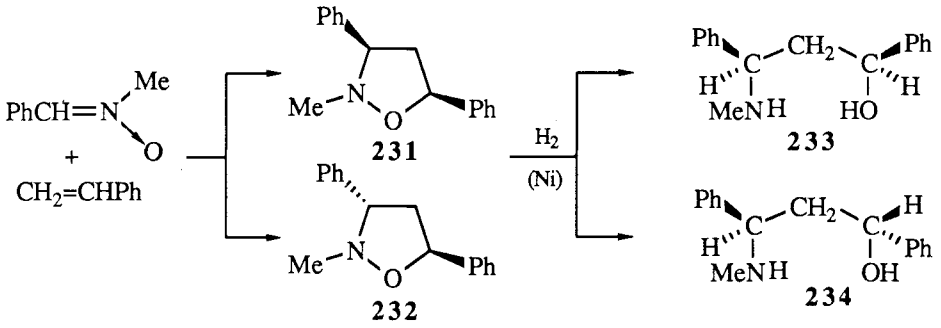



**230**

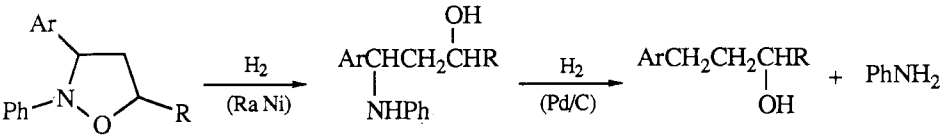
Quaternary salts are also currently prepared by quaternization, and methiodides are easily obtained with an excess of methyl iodide in a solvent such as ether or diglyme at room temperature or by heating without solvent. Even the unsubstituted 2,2-dimethylisoxazolidinium iodide (**229**) is known.[10B/42] The iminium salt **230** is known to form in moderate yield by treatment of the unsubstituted isoxazolidine perchlorate with acetone.[139/80] Isoxazolidinium salts can also be obtained directly from acyclic precursors (see § 3.3.3, p. 728). Quaternary salts of isoxazolidines are easily crystallizable compounds and are suitable derivatives for characterization purposes, but they are also useful as activated compounds for ring-opening reactions; see especially hydrogenation (§ 3.4.2) or reaction toward nucleophiles (§ 3.4.7).

### 3.4.2 Hydrogenolysis

Cleavage of the N–O bond is easily promoted by a large variety of reducing agents on both the free base and the quaternary salts. 3-Amino and 3-dialkylamino alcohols, respectively, are usually obtained, and their formation has frequently been put forward as structural proof for the starting isoxazolidines. Since the hydrogenolysis reaction is stereospecific, conclusions concerning the stereochemistry of the isoxazolidine derivative can be drawn.[20/68,146/79] For example, cycloaddition of styrene to *C*-phenyl-*N*-methyl nitrone gives a mixture of the two diastereomeric isoxazolidines **231** and **232**; hydrogenation in the presence of Raney nickel gave a 63:37 mixture of *erythro*- and *threo*-3-methylamino-1,3-diphenylpropanols (**233**) and (**234**):[20/68]




With 2,3-diphenyl-substituted isoxazolidine derivatives, hydrogenation can be stopped at the amino alcohol stage only with less active catalysts such as Raney nickel,[19/68,20/68,21/68] used Pd/C,[78/66,19/68] or Pd/C supported on $CaCO_3$;[76/62,136/65] use of fresh Pd/C provokes loss of aniline and formation of 1-phenyl-3-alkanols:[56/60,19/68,21/68]

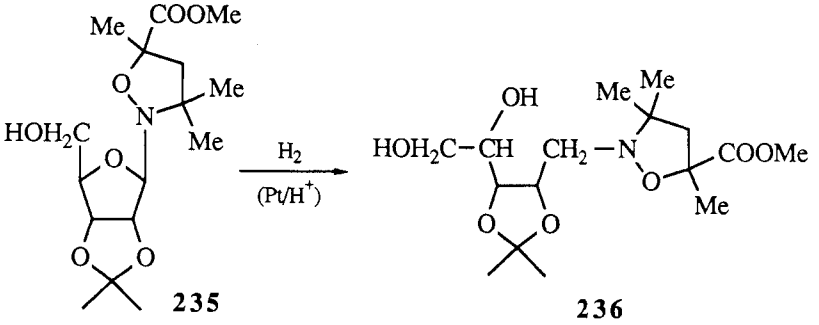



Analogous deamination has been reported for 2-methyl-3,3-diphenylisoxazolidines.[202/68]

The catalytic hydrogenation is quite general both with monocyclic and bicyclic or polycyclic isoxazolidines, and excellent yields of 3-amino alcohols are usually achieved with Raney nickel,[59/64,128/65,19/68,20/68,21/68,158/71,29/74] platinum oxide,[59/64,127/66] Pd/C,[59/64,21/68,102/69,223/70,21/72,219/73,141/74,188/77,77/79] or Rh/C.[182/84] In special cases (5-alkoxysubstituted isoxazolidines) the hydrogenation proved difficult and required a special Pd-catalyst under pressure in methanolic HCl.[133/83]

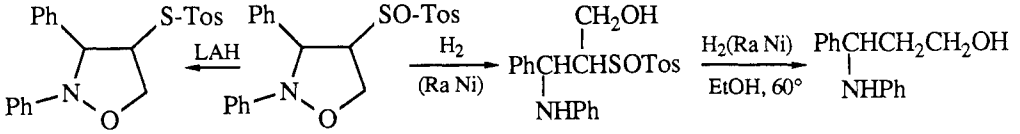
Aluminum amalgam in $THF/H_2O$,[20/68,204/79] diborane,[48/74] titanium trichloride in refluxing ethanol,[17/81] or more frequently, zinc and acetic acid[43/59,59/64,128/65,20/68,219/73,259/78] have also been reported to carry out the hydrogenolytic ring cleavage both on the free base and on the quaternary salt.[200/82] Nevertheless, some degree of selectivity has sometimes been evidenced. Thus hydrogenation over Pd/C or $PtO_2$ can be limited to double bonds present in the side chain.[48/60,170/66,133B/69]

Hydrogenolysis of the isoxazolidine N–O bond seems to be slowed by steric encumbrance: for example, acid-promoted hydrogenation of the *N*-glycoside (**235**) on Pt catalyst opens the furanoside ring only, giving the isoxazolidine derivative **236** in 51% yield; by contrast, hydrogenation on Raney nickel causes the isoxazolidine ring to open slowly.[80/77]



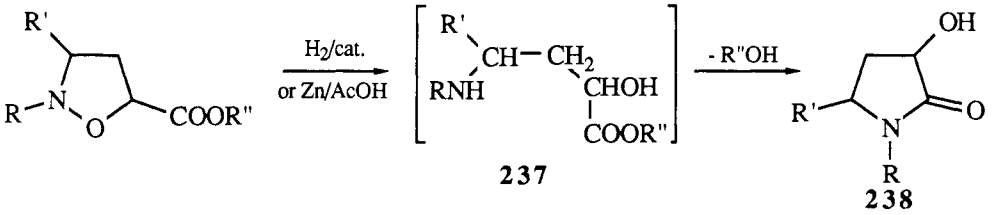

**235** **236**

Reduction with lithium aluminum hydride is far less straightforward. 2,3,5-Triphenylisoxazolidine does not react at all;[20/68] several instances are known where reduction occurs in the side chain (e.g., on carbonyl, ester, or sulfoxide groups) without affecting the heterocyclic ring.[22/68,202/68,146/79,201B/81] It is interesting to note that the sulfoxide group is selectively reduced by $LiAlH_4$ without affecting the ring; by contrast, catalytic hydrogenation first cleaves the ring and subsequently, removes the sulfinyl group:[200/82]



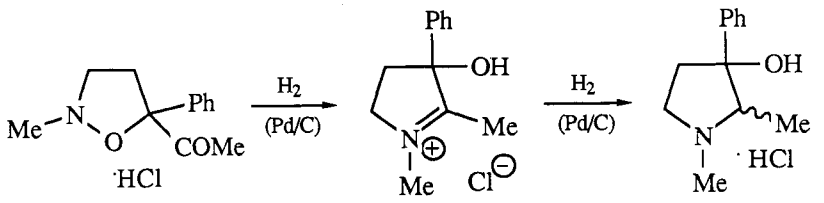

With *N*-alkoxyisoxazolidine, hydride attack at $H_3$ promotes alcohol elimination with formation of the C=N double bond. For example, treatment of 2-methoxy-3-phenyl-5-cyanoisoxazolidine with $LiAlH_4$ gives (3-phenyl-2-isoxazolin-5-yl)methylamine in good yields.[61/65] In several other cases, ring opening has been observed with formation of the 1,3-amino alcohol; in any case, reduction of the ester group is obviously much faster than N–O hydrogenolysis.[49/60,52/63,59/64,128/65,25/67]

When the isoxazolidine is appropriately substituted, the hydrogenolytic ring opening can be followed, more or less spontaneously, by subsequent recyclization to other heterocyclic systems. The most common of these secondary reactions is the formation of 3-hydroxy-2-pyrrolidinones (**238**) by hydrogenation of isoxazolidines, carrying an alkoxycarbonyl group or an equivalent group in the 5-position. The reaction is quite a general one, and catalysts such as Raney nickel,[22/68,13/69,161/72,80/77,3/78,2/81,2/84] 10% Pd/C,[139/67,39/72,103/76,4/78,144/79,146/79] or Rh[81/77] have been used successfully as well as reduction with zinc and acetic acid.[178/74] The intermediate 3-amino alcohol (**237**) can sometimes be isolated,[103/76,4/78] especially if hydrogenation is undertaken on the hydrochloride.[2/79,144/79] Nevertheless it usually undergoes loss of alcohol immediately to give the hydroxy-γ-lactam directly:

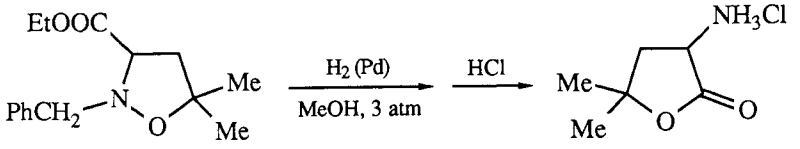



**237** **238**

Starting from 5-acylisoxazolidines, 3-hydroxypyrrolidine derivatives can be achieved according to the following example:[144/79]



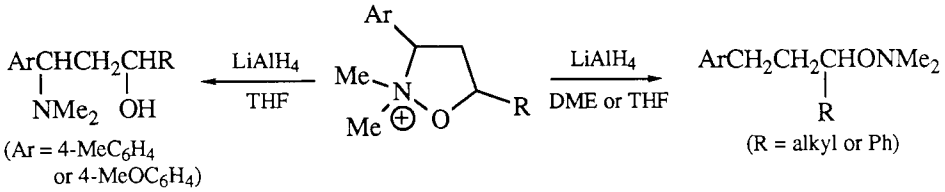

The presence of a 3-alkoxycarbonyl group leads to a γ-hydroxy-α-amino acid, which is usually isolated as the corresponding lactone, as shown in the following example:[28/79]




In some cases hydrogenation of an N-phenyl group can occur over platinum.[22/68,103/76] When the alkoxycarbonyl group is in the 4-position, no cyclization to lactam is observed, even under heating with oxalic acid, and only the corresponding 3-amino alcohol is obtained.[22/68]

Of course, the quaternary salts derived from N-substituted isoxazolidines are also prone to be hydrogenolyzed, either catalytically[20/61,127/66,175/72,96/73,216/75,144/79] or by treatment with zinc and acetic acid[40/68,200/82] or even polarographically.[21/78] In all the cases above the expected 3-dialkylamino alcohol is obtained easily. The methosulfates are reported to be more reactive than methiodides.[144/79]

Ring opening with lithium aluminum hydride seems somewhat diverging. Whereas some 3,5-diaryl or 3,5,5-triaryl derivatives yield the "normal" amino alcohol derivatives,[176/83,165/84] other 3,5-diaryl- and 3-aryl-5-alkylisoxazolidines are opened to N,N,O-trisubstituted hydroxylamines, owing possibly to a hydride attack at position 3:[176/83,277/83]

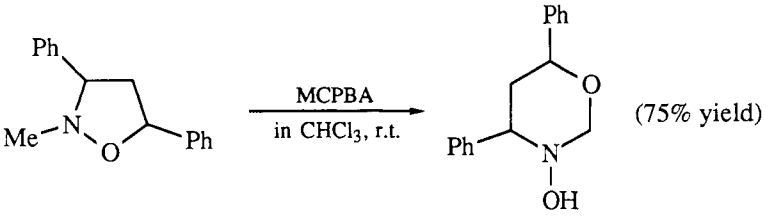



Hydrogenolysis of isoxazolidine derivatives is very often the key step in the synthesis of complex molecules, usually from natural sources (e.g., alkaloids). This type of utilization of the isoxazolidine ring will be illustrated in greater depth in § 3.4.10.

### 3.4.3 Oxidation

N-Unsubstituted isoxazolidines are oxidizable with relative ease to 2-isoxazolines (see § 2.2.2.6f) either with lead tetraacetate[139/72] or better with *N*-chlorosuccinimide in methylene chloride at room temperature.[81/77] The resistance of the isoxazolidine ring to stronger oxidants, such as potassium permanganate or chromic acid, depends strongly on the nature of the substituent: N-alkoxy or N-acyl derivatives are fairly stable, and cautious oxidation of a double bond[227/68] or a secondary alcoholic group[219/73] can be carried out safely. Pyridinium dichromate has been used successfully for oxidizing a 4-hydroxy to a 4-carbonyl group or a 3-hydroxymethyl to a 3-carboxy group in some *N*-aroylisoxazolidines.[190/82,264/82]

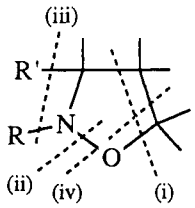
Of definite synthetic usefulness is the oxidative cleavage of *N*-methylisoxazolidines by *m*-chloroperbenzoic acid to yield *N*-hydroxy-1,3-tetrahydrooxazines; for example:[128/65,149/79,226/81]



In another case the same reagent oxidizes the sulfide to the sulfoxide group, leaving the ring unaltered.[200/82]

### 3.4.4 Thermolysis

The isoxazolidine ring is relatively unstable upon heating, and different decomposition patterns, as depicted in formula **239**, are known:




**239**

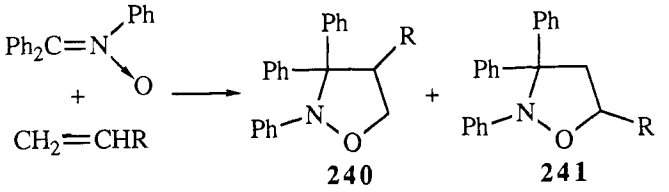
(i) 1,3-Dipolar cycloreversion to the starting addends (nitrones and alkenes).
(ii) Cleavage of the N–O bond, followed by several rearrangement paths.
(iii) Elimination reaction, leading to the formation of the 2-isoxazoline ring.
(iv) Separation of a C=O moiety from positions 1 to 5.

#### *3.4.4.1 1,3-Dipolar Cycloreversion*

As already mentioned elsewhere (§ 3.3.1.1a, p. 693), 1,3-dipolar cycloaddition of nitrones to alkenes can be reversed at more or less high temperatures. Owing to the noteworthy stability of nitrones, 1,3-cycloreversion (for recent reviews, see refs. 10/79 and 209/84) seems to occur here under particularly mild conditions. Thus, when the kinetically controlled reaction leads to the least stable cycloadduct, carrying out the reaction at higher temperatures or heating the cycloadduct at the same temperature results in an isomerization process toward the thermodynamically more stable regio- or stereoisomeric cycloadduct. The reversibility of the cycloaddition has been observed since the discovery of the reaction,[48/60.49/60.22/68] although a systematic study of the various factors involved is still lacking.

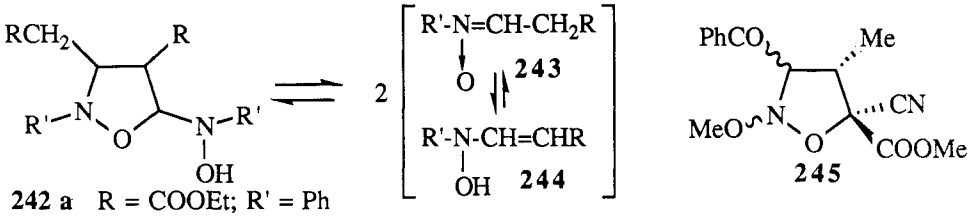
Very close regiochemical control has been ascertained in the cycloaddition of triphenylnitrone with several activated alkenes, as shown in the following table (see ref. 209/84, p. 512).

In this case, electronic and steric factors appear to exert strong control over the regiochemistry of the reaction, operating in opposite directions. It is therefore easy to isolate one or the other regioisomeric cycloadducts in turn, according to the experimental conditions adopted. Where cycloaddition with




| | | | | |
|---|---|---|---|---|
| R = CHO | 20° : | ≥ 97 : | 3 |
| | 120° : | ≤ 5 : | 95 |
| R = COMe | 20° : | 90 : | 10 |
| | 120° : | ≤ 2 : | 98 |
| R = COOMe | 20° : | 87 : | 13 |
| | 120° : | ≤ 2 : | 98 |
| R = $NO_2$ | 20° : | 100 : | 0 |

nitroethylene, by far the most active dipolarophile of the series, is concerned, although suitable experimental conditions for the synthesis of **241** (R = $NO_2$) are not easily conceivable, the existence of a cycloreversion at 30°C has been evidenced by treating a solution of **240** with isobenzofuran as a trapping agent for nitroethylene and isolating triphenylnitrone on the other side.




**242 a** R = COOEt; R' = Ph
**b** R = Ph; R' = Me
**c** R = Me; R' = Ph
**d** R = R' = Ph

Sometimes cycloreversion does not lead to the nitrone itself but to an isomer thereof: thermolysis of the *C*-ethoxycarbonylmethyl-*N*-phenylnitrone "dimer" (**242a**) in DMSO at 60°C completely decomposes the isoxazolidine ring, but the product present in solution was shown to be the enamine **244a** instead of the expected nitrone **243a**.[272/80] Possibly the equilibrium **243** ⇌ **244** is shifted to the right here because of the conjugating substituent R. When R = Ph, the isoxazolidine **242b** equilibrates at room temperature with the nitrone **243b**;[214/81] the *N*-phenyl-substituted isoxazolidines **242c** and **242d** are stable and do not dissociate, at least under relatively mild conditions. Thus it appears that both the dissociation equilibrium **242** ⇌ **243** + **244** and the isomerization equilibrium **243** ⇌ **244** depend strongly on the nature of the substituents R and R′.

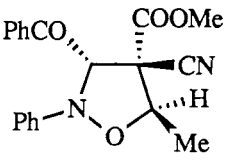
The two "kinetic" diastereomeric (at position 3) isoxazolidines (**245**) undergo a quantitative cycloreversion on mild heating (3 h in refluxing benzene). This is the only reported example of easy cycloreversion of *N*-methoxyisoxazolidines,

which otherwise withstand more drastic conditions (e.g., 4 h in refluxing toluene).[164/77]

Several other examples of regio- and stereoisomerization attributable to a cycloreversion process are known.[132/68,13/69,55/73,134/77,146/79] The easy reversibility of the cycloaddition nitrones and acrylate has been cleverly utilized to "protect" a nitrone moiety in a multistep process involving a nitrone intramolecular cycloaddition as the key step.[152/78,99/79]

Of course, simple epimerization of a 5-methoxycarbonylisoxazolidine by heating does not necessarily involve a cycloreversion/cycloaddition process, but might be more reasonably attributed to a base-catalyzed pathway (the isoxazolidine itself has basic properties).[178/74] In a more recent paper the cycloreversion has been studied by trapping the restored nitrone with an excess of the highly dipolarophilic norbornene, which gives a cycloadduct stable under the reaction conditions.[78/79] Thermal instability has been reported for the monocycloadduct from *C*-benzoyl-*N*-phenylnitrone and 2-methylfuran.[81/79]

Sometimes the cycloreversion is attainable even at room temperature. This is the case, for example, with the isoxazolidine derivative **246**.[38/73]

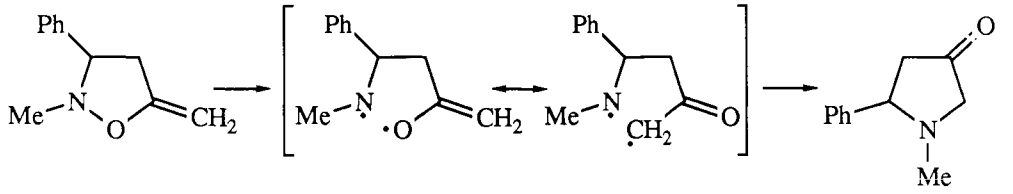



**246**

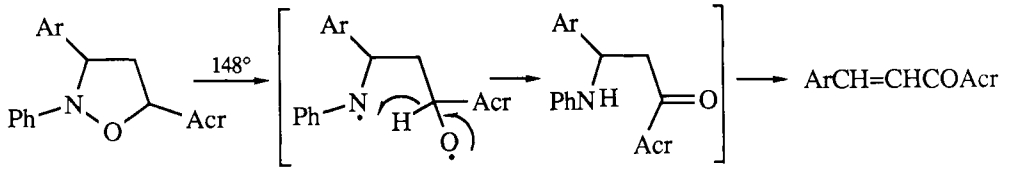
It is worth mentioning that in some cases the lack of reactivity of some otherwise highly efficient dipolarophiles has been ascribed to an equilibrium addends $\rightleftharpoons$ adducts far shifted toward the addends. This could explain why triphenylnitrone cycloadds methyl maleate but not methyl fumarate.[13/69]

### *3.4.4.2 N–O Bond Cleavage*

The N–O bond is known to be relatively weak, and its cleavage can prevail upon the cycloreversion pathway if a suitably favorable environment is present. Thus the different behavior of 4-methyleneisoxazolidine derivatives and their 5-methylene counterparts is remarkable:[23/71,134/72,149B/76,158/79] as already mentioned (§ 3.3.1.1f, p. 701), the former regioisomers are thermally stable, whereas the latter compounds are cleaved under the same experimental conditions (sealed tube, 70–80°C) to give, after recyclization, the isomeric 3-pyrrolidinones. For example, 1-methyl-5-phenyl-3-pyrrolidinone is obtained from the nonisolable 2-methyl-3-phenyl-5-methyleneisoxazolidine:[158/79]

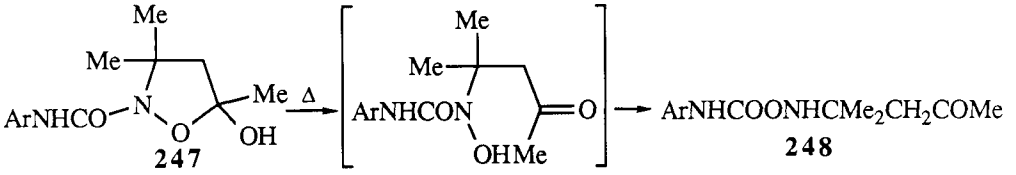


An initial N–O cleavage and subsequent H-shift has been proposed to explain the thermal breakdown of some 5-(9-acridinyl)isoxazolidines to 9-acridinyl styryl ketones:[24/76]

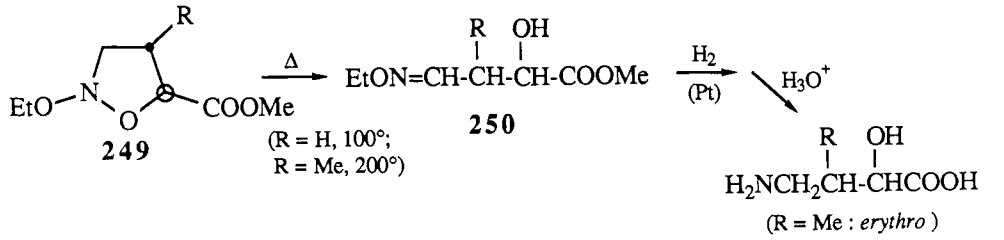


The presence of a nitro group in the 5-position of the isoxazolidine ring facilitates N–O bond fission with subsequent reclosure to a $\beta$-lactam derivative; photolysis causes a similar reorganization[99/81,99/84] (see also § 3.4.10.3, p. 767).

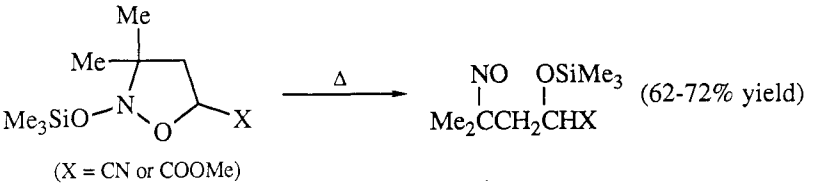
Facile ring-chain tautomerism is known for 5-hydroxyisoxazolidines, and this, followed by an acyl migration, explains the formation of a carbamoyl-hydroxylamine derivative (**248**) by the heating of compound (**247**):[191/79]



3-Unsubstituted 2-ethoxyisoxazolidines (**249**), which are remarkably stable toward catalytic hydrogenation, thermolyze very smoothly to the isomeric oxime ethers **250** (a mixture of *syn* and *anti* isomers); the latter compounds can now be hydrogenated and hydrolyzed to 4-amino-2-hydroxybutanoic acids:[30/75,25B/76]

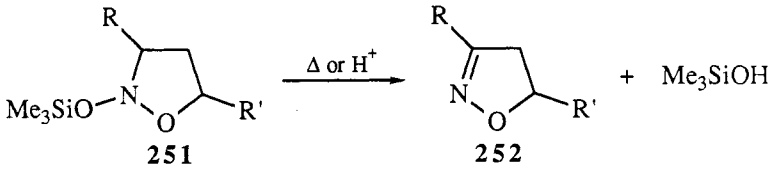


3,3-Dimethyl-2-trimethylsilyloxyisoxazolidine, having an electron-deficient group in the 5-position, heated either alone or in the presence of potassium fluoride, rearranges to a γ-nitroso-α-trimethylsilyloxy open-chain derivative:[2/81]




### *3.4.4.3 Elimination Reactions*

2-Trimethylsilyloxyisoxazolidines (**251**) are thermally unstable and eliminate trimethylsilanol by heating, or even spontaneously, to give the corresponding 2-isoxazolines (**252**):[250/73.3/78]



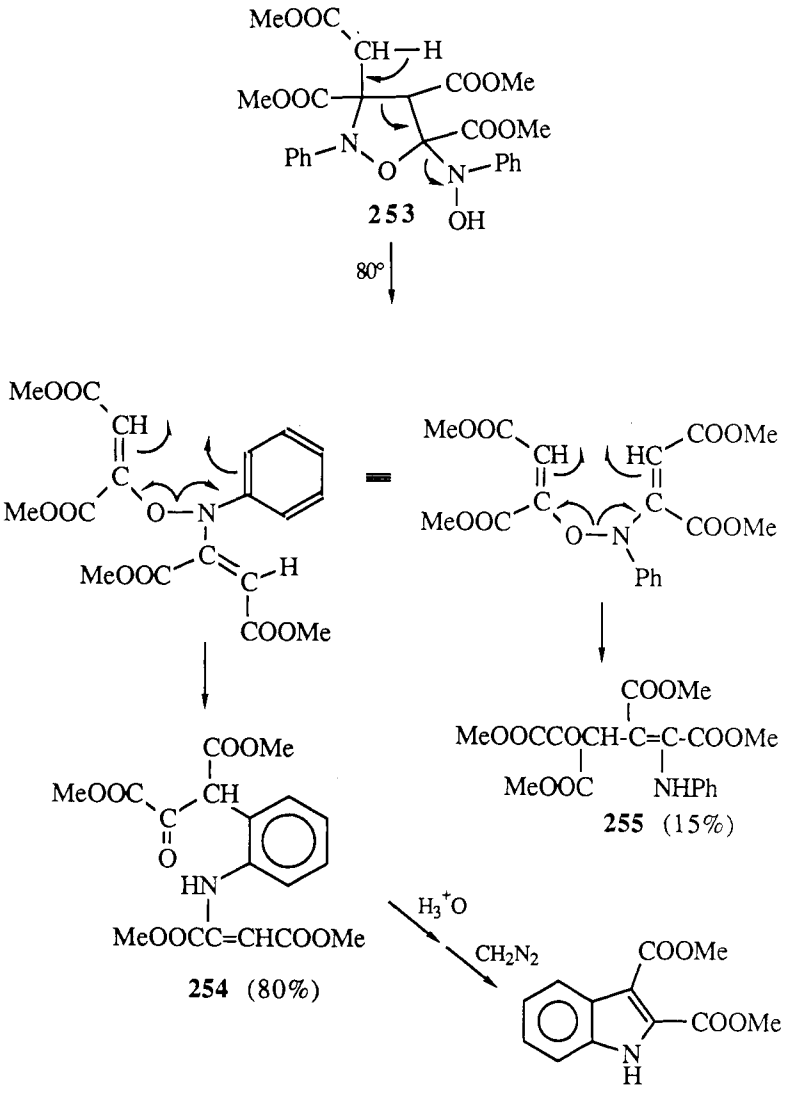

**251** **252**

Nevertheless, the best way to effect this elimination is by acidic catalysis (see § 3.4.6, p. 745).

Heating the so-called "dimer" (**253**) of the nitrone, prepared from *N*-phenylhydroxylamine and dimethyl acetylenedicarboxylate, in refluxing benzene causes the elimination of *N*-phenylhydroxylamine with simultaneous opening of the ring and formation of the two tetraesters **254** and **255**, possibly arising from two competitive hetero-Cope rearrangements, as depicted in Scheme 3.8.[19/69] The major product can easily be transformed in the dimethyl indole-2,3-dicarboxylate.

### *3.4.4.4 Decomposition to Carbonyl Compounds*

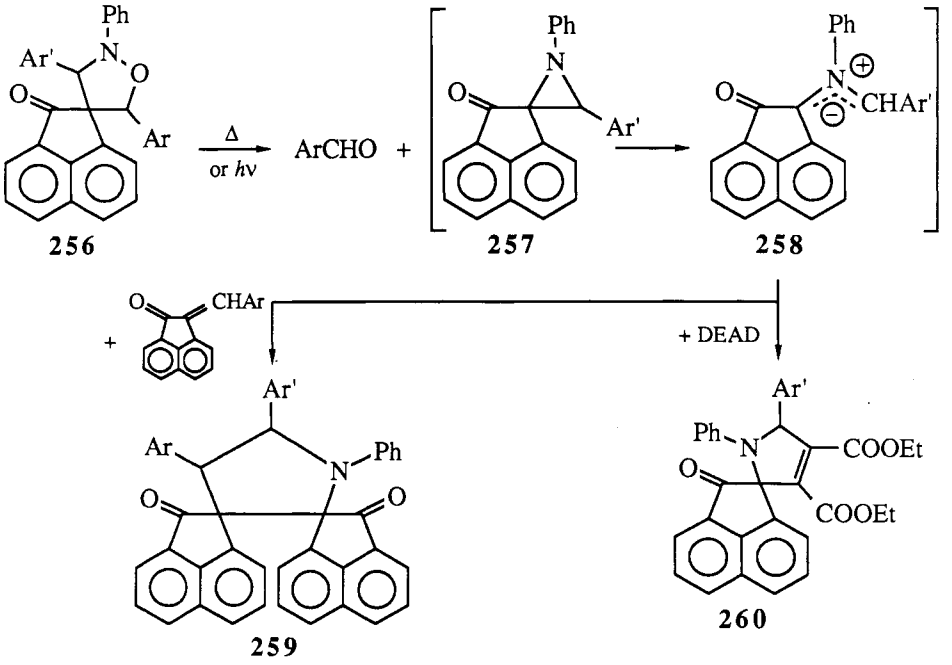
When the spiroisoxazolidines **256** are thermolyzed in refluxing xylene (or photolyzed in benzene solution at room temperature), decomposition to a benzaldehyde and an azomethine ylid (**258**) is observed.[223/70] The latter very reactive intermediate, probably arising by cleavage of the initially formed spiroaziridine (**257**), must be trapped with a suitable dipolarophile to give, for example, **259** or **260** (Scheme 3.9).



Scheme 3.8.

### 3.4.5 Photolysis

Little is known about the photochemical behavior of the isoxazolidine ring. An epimerization of a 3-benzoylisoxazolidine derivative occurs under UV irradiation, whereas the corresponding 3-phenyl derivative is stable under the same conditions.[38/73] Depending on the experimental conditions, photolysis of 5-nitroisoxazolidine derivatives causes either elimination of nitrous acid to give 4-isoxazolines (see § 2.5.2.3) or ring opening followed by reclosure to yield $\beta$-lactam derivatives[99/84] (see also § 3.4.10.3).

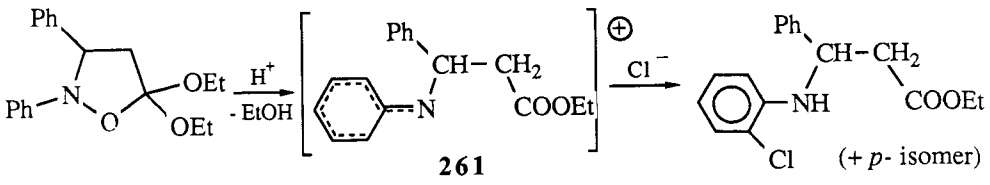



Scheme 3.9.

### 3.4.6 Decomposition by Acids

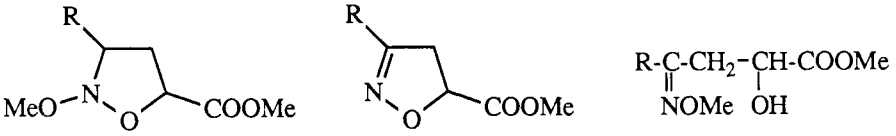
The behavior of isoxazolidines toward acids depends strongly on the nature of the substituents. The ring of N-unsubstituted and N-alkyl- or N-aryl-substituted compounds is stable under mild conditions, only reversible formation of salts being observed (see §§ 3.4.1, p. 733, and 3.2.10, p. 683). Under strong conditions, N–O cleavage may occur and open-chain compounds are formed; when hydroxy or alkoxy groups are present on the heterocyclic ring, elimination of water or of alkanol can compete with or prevail over their N–O cleavage, leading to isoxazolines.

It has already been mentioned that optically active N-unsubstituted isoxazolidines can be prepared most conveniently by hydrolysis of N-glycosyl derivatives with acetic acid, or hydrochloric or perchloric acid, at room temperature or by heating at 60–70°C (see § 3.3.1.1c, p. 695).[80/77,81/77] Treatment of 2,3-diphenyl-5,5-diethoxyisoxazolidine with concentrated HCl in dioxane at 80°C furnishes a mixture of ethyl 3-(*o*- and *p*-chloroanilino)-3-phenylpropionate, probably arising through an intermediate delocalized cation (**261**):[76/66]



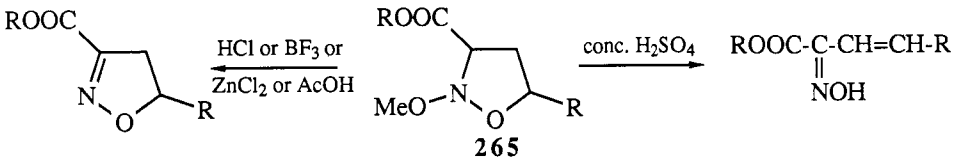
A similar mechanism can be envisaged in the cleavage of 2,3,5-triarylisoxazolines by 20% aqueous hydrochloric acid to yield 1,3-diaryl-3-(*p*-chloroanilino)-1-propanol.[161/71,24/76]

Under acidic treatment N-methoxy (and other N-alkoxy) isoxazolidines may either cleave the N–O bond to yield β-hydroxyoxime methyl ethers or other open-chain products derived by further hydrolytic processes, or eliminate (if there is a hydrogen atom in the 3-position) one molecule of methanol (or similar alcohol) to yield a 2-isoxazoline. Sometimes the two processes occur simultaneously: for example, treatment of a benzene solution of **262a** with gaseous hydrogen chloride leads to a mixture of 39% **263a** and 50% **264a**;[228/68] with the derivatives **262b** and **262c** only elimination to **263b** or, respectively, exclusive isomerization to **264c** are observed under the same conditions,[91/66,205/66] whereas hydrolysis of **262b** with 20% aqueous $H_2SO_4$ at 80°C furnishes good yields of malic acid.[91/66]

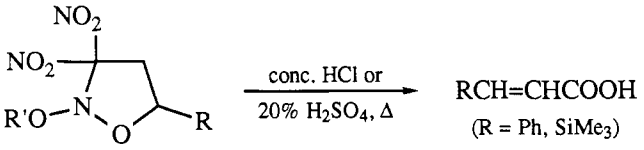



**a** R = Ph **b** R = $NO_2$ **c** R = COOMe

Isoxazolidines of type **265** can give one or the other product according to the acidic medium used, as shown by the following scheme:[205/66]



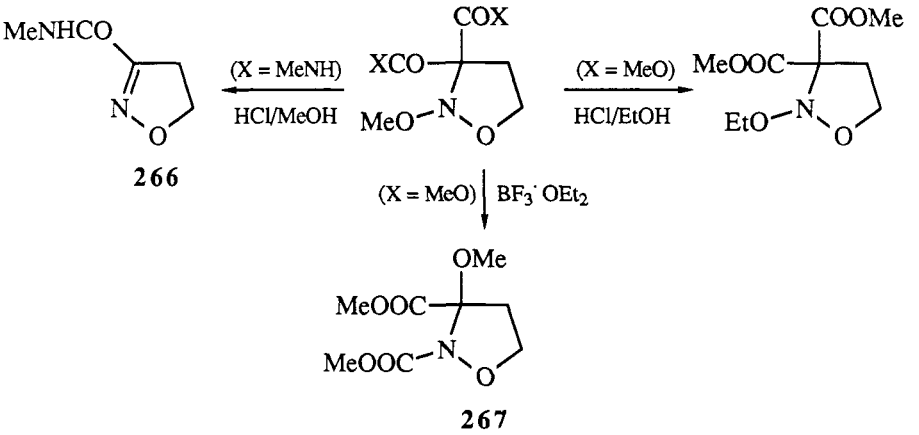

If two nitro groups are present in the 3-position of the isoxazolidine ring, acidic treatment furnishes α,β-unsaturated carboxylic acid:[71/67,107/68,210/72,290/76]




Good yields of 2-isoxazolines are also obtained by elimination of methanol from 2-methoxyisoxazolidines by action of $BF_3$-etherate,[189/66,177/67] by elimination of trimethylsilanol from the corresponding 2-trimethylsilyloxy derivatives,[250/73,3/78,4/79,1/82] or by elimination of a carbamic acid unit from the adducts hydroxyurea–α,β-unsaturated ketones.[187/75] In suitable cases (e.g., from 3,3-

dicarboxyisoxazolidines) elimination is accompanied by decarboxylation.[229/68,212/79]

Even the bismethylamide of 2-methoxyisoxazolidine-3,3-dicarboxylic acid converts to 3-*N*-methylcarbamoyl-2-isoxazoline (**266**) upon acidic anhydrous treatment.[94/81] By contrast, the corresponding dimethyl ester gives only *trans* alkoxylation under the same conditions; the same compound, when treated with borontrifluoride etherate, isomerizes to dimethyl 3-methoxyisoxazolidine-2,3-dicarboxylate (**267**):[94/81]

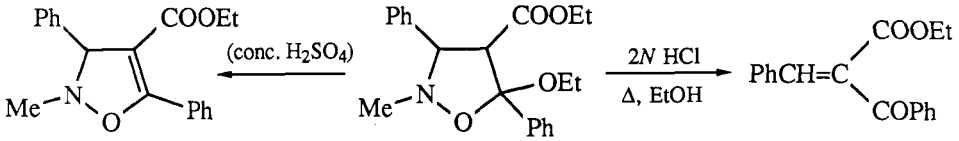



**266**

**267**

As mentioned elsewhere (see § 2.4, p. 623), 3-aryl-3-methoxyisoxazolidines easily eliminate methanol to yield 3-isoxazolines.[21/74]

5-Alkoxyisoxazolidine derivatives, which can also be prepared by acid-catalyzed addition of methanol or ethanol to 4-isoxazolines, can either revert to the latter compounds or suffer ring cleavage, as illustrated by the following example:[41B/75]



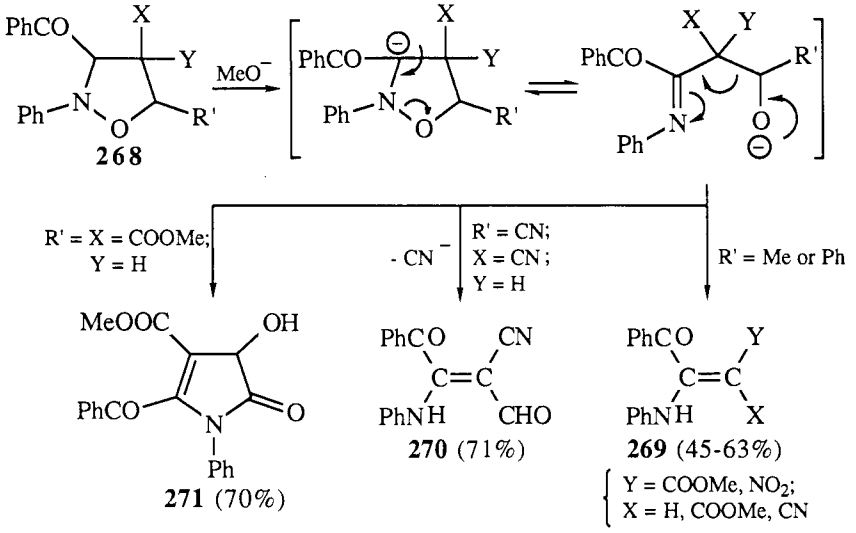

(64% yield) (81% yield)

For the action of hydrofluoric acid on 5-trimethylsilylisoxazolines, which results in ring opening to α,β-unsaturated aldehydes, see § 3.4.10.4, p. 774.

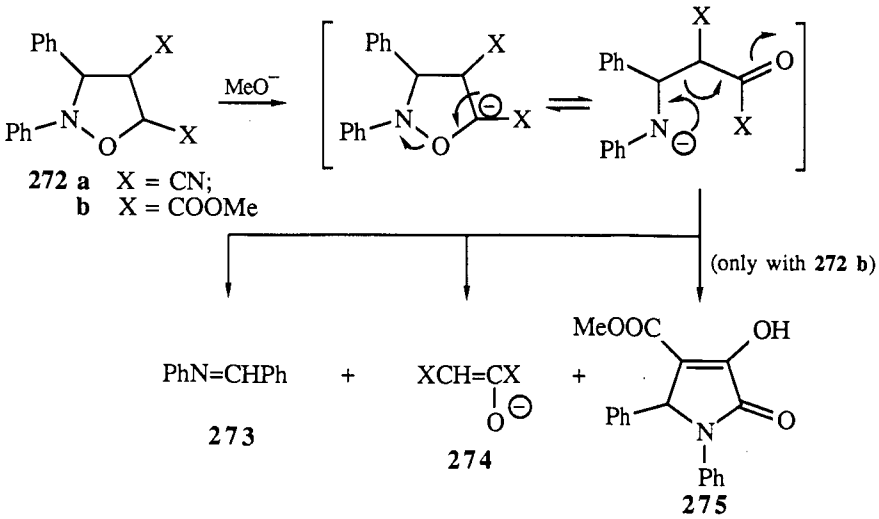
Finally, it should be recalled that mild acidic treatment transforms several N-substituted isoxazolidines to N-unsubstituted isoxazolidines: this is the case with N-acyl (see § 3.3.2, p. 725), *N*-tetrahydropyran-2-yl (see § 3.3.1.1b, p. 694) isoxazolidines, bisisoxazolidinylmethanes (see § 3.3.1.4, p. 723), and *N*-methylthiomethylisoxazolidines.[2/84]

### 3.4.7 Decomposition by Bases

Both N-unsubstituted and N-alkyl or N-aryl isoxazolidines are fairly stable to bases under mild conditions. Thus methanolic potassium hydroxide hydrolyzes an acetoxy group without affecting the isoxazolidine ring.[219/73] However, ring cleavage can occur with anhydrous strong bases and usually involves fission




Scheme 3.10.



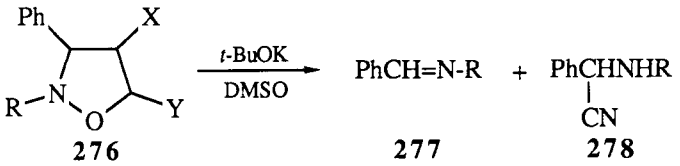

Scheme 3.11.

of the N–O bond as the result of an attack on the activated protons in the 3- or 5-position or to the proton in the α-position of the N-alkyl residue. Activation of the ring toward bases can easily be effected by quaternarization, and the type of decomposition pattern depends on the nature of the substituents.

The behavior toward sodium methoxide of 2-phenylisoxazolidines activated in the 3- or 5-position by an electron-withdrawing group (such as carbonyl or cyano) has been investigated thoroughly and can be summarized as follows (see Schemes 3.10 and 3.11).[235/74]

1. With 3-benzoylisoxazolidines (**268**) the carbanion in the 3-position is primarily formed, which evolves according to the nature of the substituent present in the 5-position: methyl or phenyl provokes cleavage to an aldehyde and to the enamine **269**; a cyano group is prone to act as a leaving group, yielding the enamine **270**, whereas the presence of methoxycarbonyl groups in positions 4 and 5 favors a recyclization to the hydroxy lactam **271**. Sometimes fragmentation to enamines is promoted by the basic nitrone formed through cycloreversion.[38/73,218/73]
2. 2,3-Diphenylisoxazolidines (**272**) carrying a cyano or a methoxycarbonyl group in the 5-position afford ring fragmentation to benzalaniline (**273**) and to the sodium salt **274**, together with the enol lactam **275** in the latter case.

With 2,3,5-triphenylisoxazolidine, carrying an activating group in the 4-position, only epimerization through carbanion in position 4 has been noted. With isoxazolidines (**276**) having both a nitro and a cyano substituent alkoxide-promoted fragmentation gives, along with the imines **277**, the corresponding α-cyanobenzylamines (**278**):[99/84]

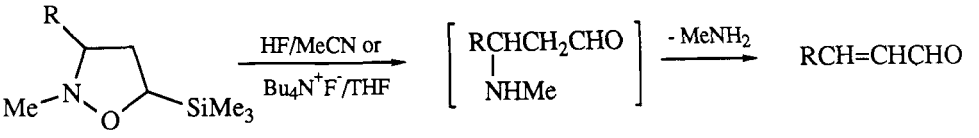



**276** **277** **278**

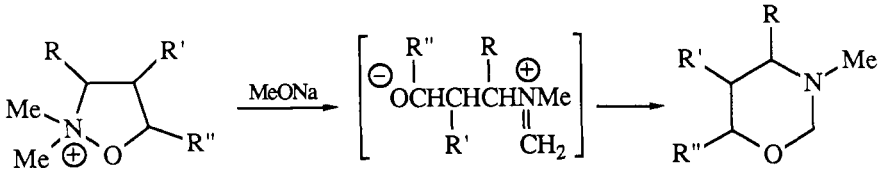
| R | X | Y | Yield (%) | Yield (%) |
|---|---|---|---|---|
| *t*-Bu | CN | $NO_2$ | 43 | 57 |
| *t*-Bu | $NO_2$ | CN | 42 | 58 |
| Me | CN | $NO_2$ | - | 20 |
| Me | $NO_2$ | CN | - | 79 |

With different bases (e.g., DBN) and/or with different substituents (e.g., COOMe), the reaction can follow different courses, giving rise either to β-lactams (see § 3.4.10.3, p. 767) and/or to 4-isoxazolines (§ 2.5.2.3, p. 640).

A completely different ring fission type is promoted by the presence of a silyl residue in the isoxazolidine 5-position. Nucleophilic attack of a fluoride anion at silicon (treatment with either 50% aqueous HF in acetonitrile or tetrabutylammonium fluoride in THF) produces an $\alpha,\beta$-unsaturated aldehyde, possibly formed through the intermediacy of a transient $\beta$-aminoaldehyde:[186/84]

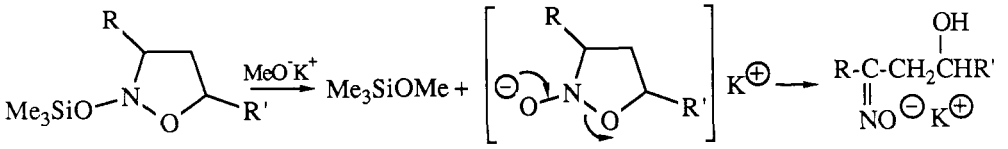



Sometimes ring expansion can possibly occur through ring opening to imino alcohols and subsequent ring reclosure: thus treatment of *N,N*-dialkylisoxazolidinium salts with an equimolar amount of sodium methoxide in refluxing THF affords a high yield (60–90%) of the corresponding tetrahydro-1,3-oxazines:

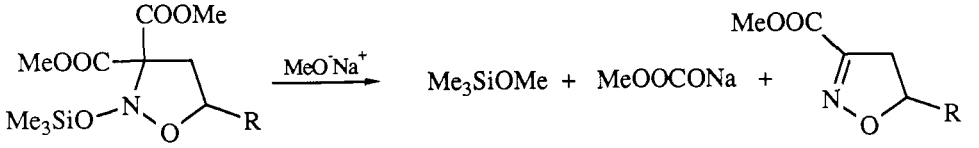



The reaction is rather general, being effective even with isoxazolidinium salts, unsubstituted in the 5-position, but has some structural limitations.[128/65.215/84]

3-Monosubstituted *N*-trimethylsilyloxyisoxazolidines suffer attack by the methoxide anion on the silicon atom and a $\beta$-hydroxyoxime salt is obtained, which upon acidification undergoes different fates depending on the nature of R:[250/73.48/74.3/78]

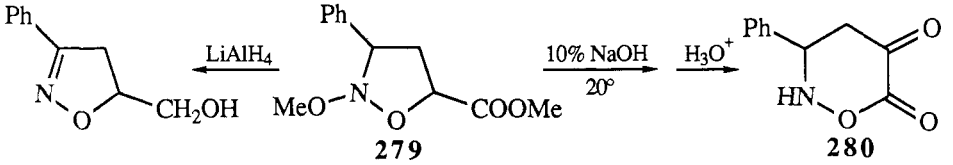



When two methoxycarbonyl groups are present in the 3-position, one of the two gets lost and a 2-isoxazoline derivative is the final product:[90/72]



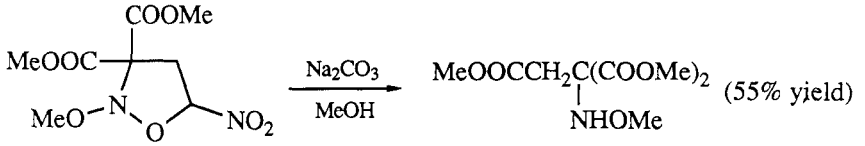
Simple elimination of methanol has been reported to occur with methyl 2-methoxy-5-phenylisoxazolidine-3-carboxylate, which on treatment with aqueous sodium hydroxide furnishes the 5-phenyl-2-isoxazoline-3-carboxylic acid.[205/66]

An interesting ring expansion has been observed when the isoxazolidine (**279**) is treated with aqueous NaOH: the 1,2-oxazinedione **280** is isolated:[228/68]

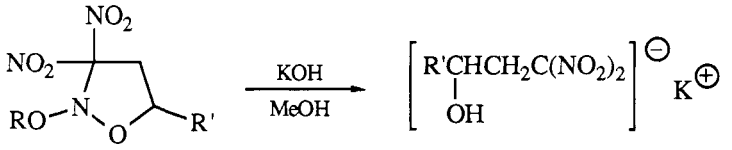



By contrast, treatment with $LiAlH_4$ results in the elimination of methanol, in addition to reduction of the ester group.[61/65]

The presence of a nitro group in the 5-position can activate the 5-proton and orients the N–O fission differently so as to leave unaltered the N-methoxy moiety:[229/68]




When two nitro groups are present in the 3-position, the base-promoted decomposition takes still another course, and fission of the $C_3$–N bond is favored over that of N–O bond, owing to the great stability of the dinitrocarbanion. Alcoholic potassium hydroxide is usually utilized as the base, and the potassium salt of a $\beta,\beta$-dinitrocarbinol results from the reaction: [207/66.1/67,71/67,180/67,254/70,211/72,212/72,253/73]

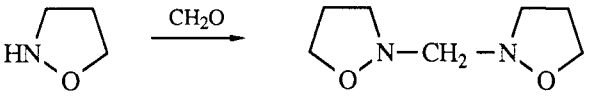



### 3.4.8 Nucleophilic Reactivity

Consistent with their cyclic hydroxylamine structure, isoxazolidines behave as nucleophiles and can be more or less easily alkylated or acylated. Kinetic studies of the displacement reactions of the parent isoxazolidine with ethyl *p*-nitrophenylacetate[3/73] or with *p*-nitrophenyl methylphosphonate[144/72] have

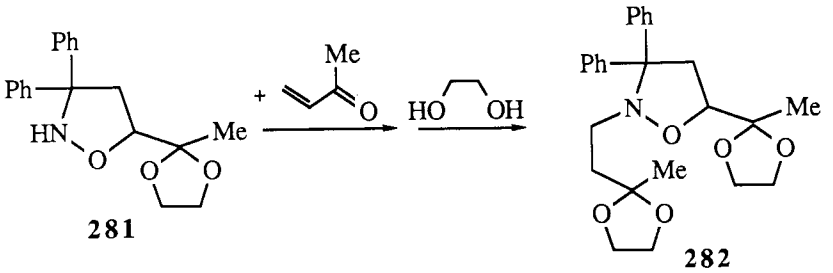
shown that as far as the latter reaction is concerned, this compound is 73 times more reactive than *N,O*-dimethylhydroxylamine and about 26 times more reactive than tetrahydro-1,2-oxazine, the six-membered analogue, but 14 times less reactive than the simple hydroxylamine. The higher relative reactivity of isoxazolidine and tetrahydro-1,2-oxazine toward the former reagent, where steric hindrance differences should be negligible, is attributed to weak interaction between the lone pairs on adjacent nitrogen and oxygen atoms (the α-effect). Methylation on the nitrogen atom can be effected by using methyl iodide[10B/42,202/68] or, better, methyl tosylate.[219/73]

Condensation with aqueous formaldehyde or with paraformaldehyde in benzene solution or with a mixture of formaldehyde and formic acid (the Eschweiler–Clark reagent) forms 2,2′-bisisoxazolidinylmethane; for example:[148/77,74/79]

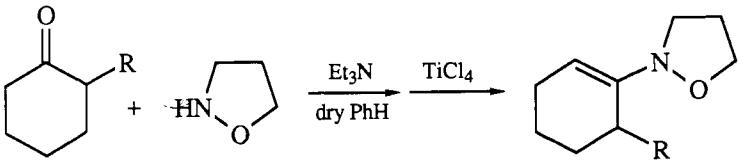



An N-trityl derivative has been obtained by reaction with tritylchloride.[8/63] Substitution of the mobile bromine atom in 2-bromo-5-nitrothiazole has also been carried out in good yields.[72/74] Only moderate yields are obtained in the substitution reaction of isoxazolidine on 3-bromocyclohexene.[165/80] *N*-amidinoisoxazolidine has been reported to form when free isoxazolidine is reacted with 5-methylisothiourea.[70/77,37/80]

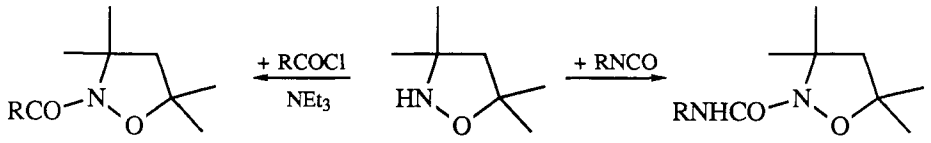
Nucleophilic addition of isoxazolidine (**281**) to methyl vinyl ketone gives the 2-(3′-oxobutyl) derivative **282**:[202/68]




Enamine formation does not occur under normal conditions but requires application of the titanium chloride procedure; crude enamines are thus obtained by reaction with cyclic ketones, which decompose thermally on attempted purification:[165/80]




Acylation with acetic anhydride[202/68] or with an acyl chloride in the presence of triethylamine[10B/42.68/69.93/70.163/72.242/72.68/73.70/74] has led to a variety of 2-acylisoxazolidines, whereas treatment with isocyanates affords 2-carbamoylisoxazolidines.[65/69.35B/78.109/78.191/79] The latter compounds may also be prepared through 2-chlorocarbonyl derivatives.[72/71]

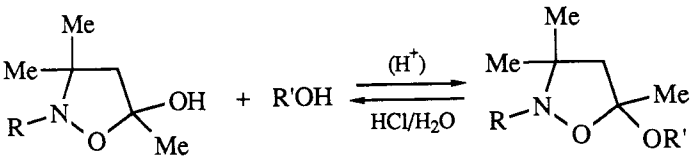



An analogous reaction with sulfonyl chlorides gives the corresponding 2-sulfonyl derivatives.[189/73] Thiocarbonyl compounds are also known.[60/72]

### 3.4.9 Other Reactions in Side Chains

Several reactions are known which modify the side chains without affecting the heterocyclic ring of isoxazolidines. Some of those caused by the action of reducing or oxidizing agents have already been illustrated (see §§ 3.4.2.1 and 3.4.3). Ketalization of a side-chain carbonyl group occurs under normal conditions[202/68] such as esterification, hydrolysis, and ammonolysis reactions. Selective use of this type of reaction makes it possible to separate the antipodes of 2-methoxyisoxazolidine-3,3-dicarboxamide.[110/77]

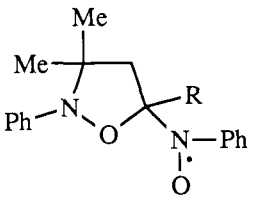
As expected from their hemiacetal-type structure, 5-hydroxyisoxazolidines are promptly alkylated by methanol or ethanol, and yields are higher when the reaction is catalyzed by traces of acid (e.g., *p*-toluenesulfonic acid):[24/72.191/79]



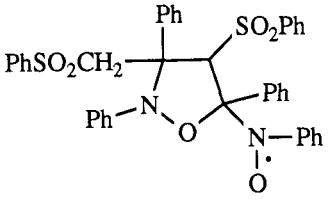

Conversely, the hydroxy compound is easily re-formed by acidic hydrolysis.

A mutual transformation of 2-alkoxy- versus 2-chloroisoxazolidine derivatives is known.[92/81] Conversion of 2-aroyl- to 2-thioaroylisoxazolidines occurs under normal conditions (phosphorus pentasulfide in dioxane or pyridine).[46B/79]

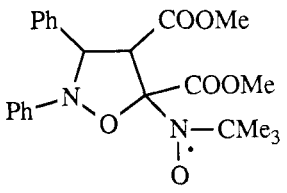
The so-called "nitrone dimers" or their analogues [i.e., the 5-hydroxy-(phenyl)aminoisoxazolidine derivatives] easily oxidize to relatively stable nitroxide radicals[9B/26.151/74.159/76.19/79] when treated with a suitable oxide (lead dioxide or nickel peroxide or silver oxide). Some of them are even isolable as relatively stable orange or red crystalline compounds, such as the so-called Banfield and Kenyon radical (**283a**)[159/76] or the radical **283b**.[159/76]



**283 a** R = Me (m.p: 88-90°)
**b** R = Ph (m.p. 89-90°)



**284**



**285**

In some other examples, such as **284**, the nitroxide radical is formed only by directly oxidizing the nitrone, which by itself does not dimerize.[19/79] In some other cases, such as **285**, the nitroxide radical is produced by cycloaddition of a nitrone with a preformed vinylaminyloxide.[19/79]

When a bisnitrone is heated with a diolefin (e.g., *p*- or *m*-phenylenebis-*N*-phenylnitrone and *p*-phenylenebismaleimide or ethylene dimethacrylate) or when a vinyl-containing nitrone such as *C*-(*p*-vinylphenyl)-*N*-phenylnitrone (prepared from *p*-vinyl benzaldehyde and *N*-phenylhydroxylamine) is heated in the melt or in DMF solution, a polymerization can take place by condensation of several molecules of the initial cycloadduct, an isoxazolidine derivative containing, at the opposite chain ends, nitrone and olefinic moieties.[25/65.120/67.28/68]

Polybutadiene modified with isoxazolidine rings is obtained when polybutadiene rubber is reacted with nitrones.[109/71] This modified rubber presents a large improvement in tensile strength at the break point, attributed mainly to the interaction between the carbon black particles and electron-donating heterocyclic rings.

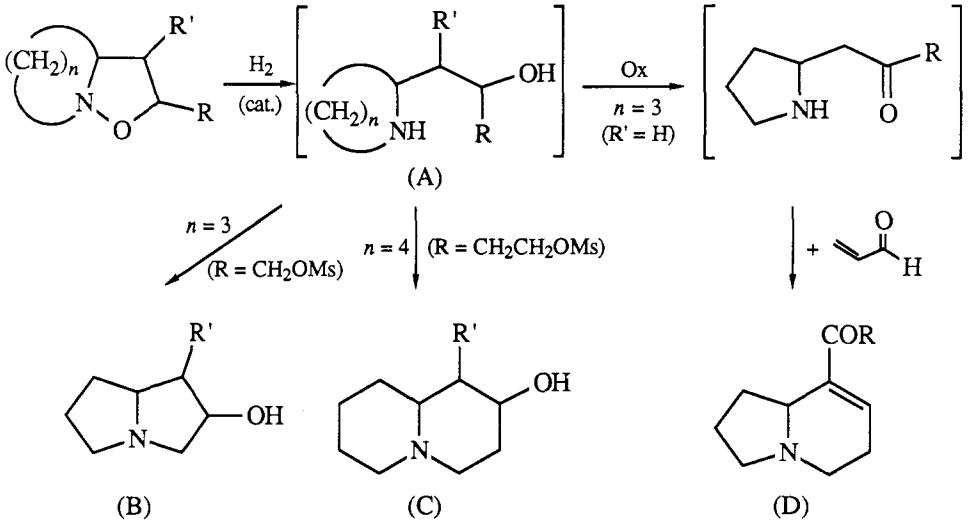
### 3.4.10 Use of Isoxazolidines as Key Intermediates in Synthetic Design

The ever-increasing use of isoxazolidine derivatives as important intermediates in multistep synthesis of complex natural products is based on some unquestionable advantages of this heterocyclic ring: (1) the remarkable regio- and stereoselectivities of both inter- and intramolecular cycloadditions of nitrones to olefinic compounds; (2) the ease of ring opening either by hydrogenolysis of the N–O bond or by thermolytic or oxidative processes; and (3) the numerous possibilities for recyclization, usually arising from the nitrogen atom nucleophilicity and from a suitable substitution pattern in either position 5 or

4 of the isoxazolidine ring. Up to now the synthetic utility of isoxazolidine intermediates has been evidenced mainly in the alkaloid field (for a recent review, see ref. 1/79), but some applications in other areas of natural products chemistry will also be mentioned here.

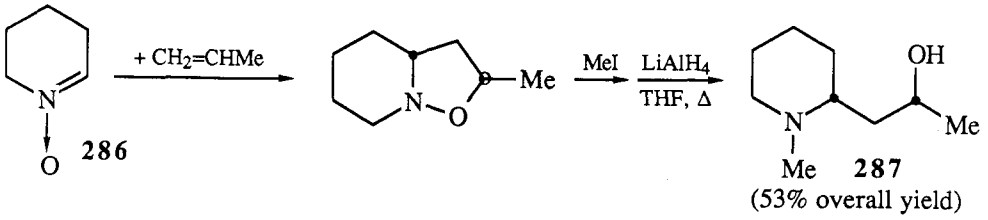
### *3.4.10.1 Alkaloids via Intermolecular Nitrone Cycloadditions*

Isoxazolidines derived from alicyclic nitrones provide easy entry into three classes of alkaloids, as shown in Scheme 3.12. After cycloaddition of the nitrone with a suitable olefin derivative, catalytic hydrogenation affords an amino alcohol which can be transformed, depending on whether the starting nitrone had a five- or a six-membered ring, into the following alkaloid classes:



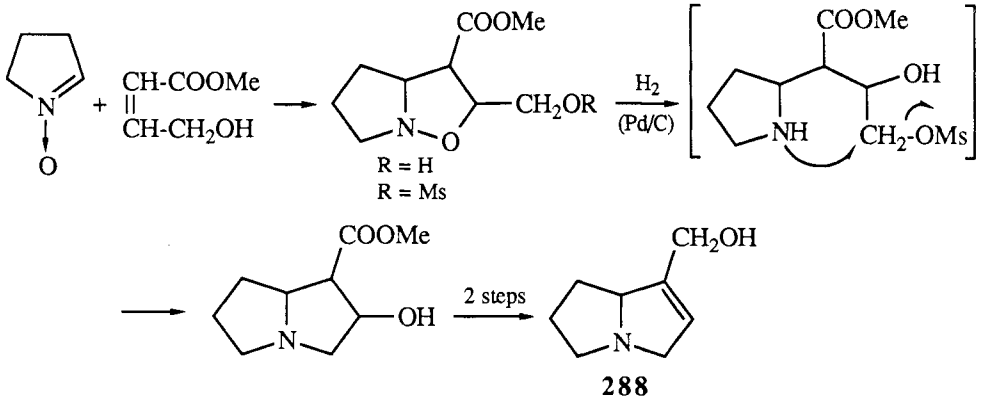

**Scheme 3.12.**

(A) *Piperidine alkaloids.* A short synthesis of *dl*-sedridine (**287**), based on the regio- and stereospecific cycloaddition of the cyclic nitrone (**286**) to propylene, followed by stereo-controlled ring opening, is outlined as follows:[265B/78]



The cycloaddition to styrene is less stereoselective, and the same elaboration yielded a 78:22 mixture of *dl*-allosedamine and *dl*-sedamine.

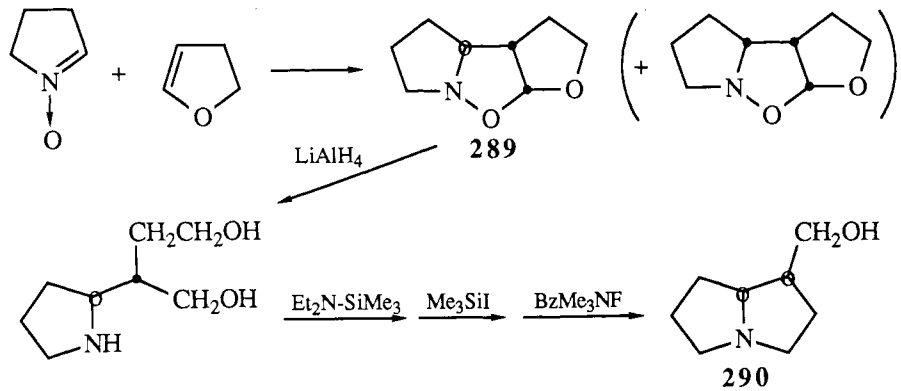
(B) *Pyrrolizidine alkaloids.* Starting from 1-pyrroline 1-oxide, regioselective cycloaddition to methyl 4-hydroxycrotonate, functionalization of the resulting isoxazolidine, and subsequent hydrogenolysis afford easy entry to the pyrrolizidine nucleus; (±)-supinidine (**288**), the necine base obtained from supinine, heleurine, and related alkaloids, has thus been synthetized in five steps:[24/71.149/75]




**288**

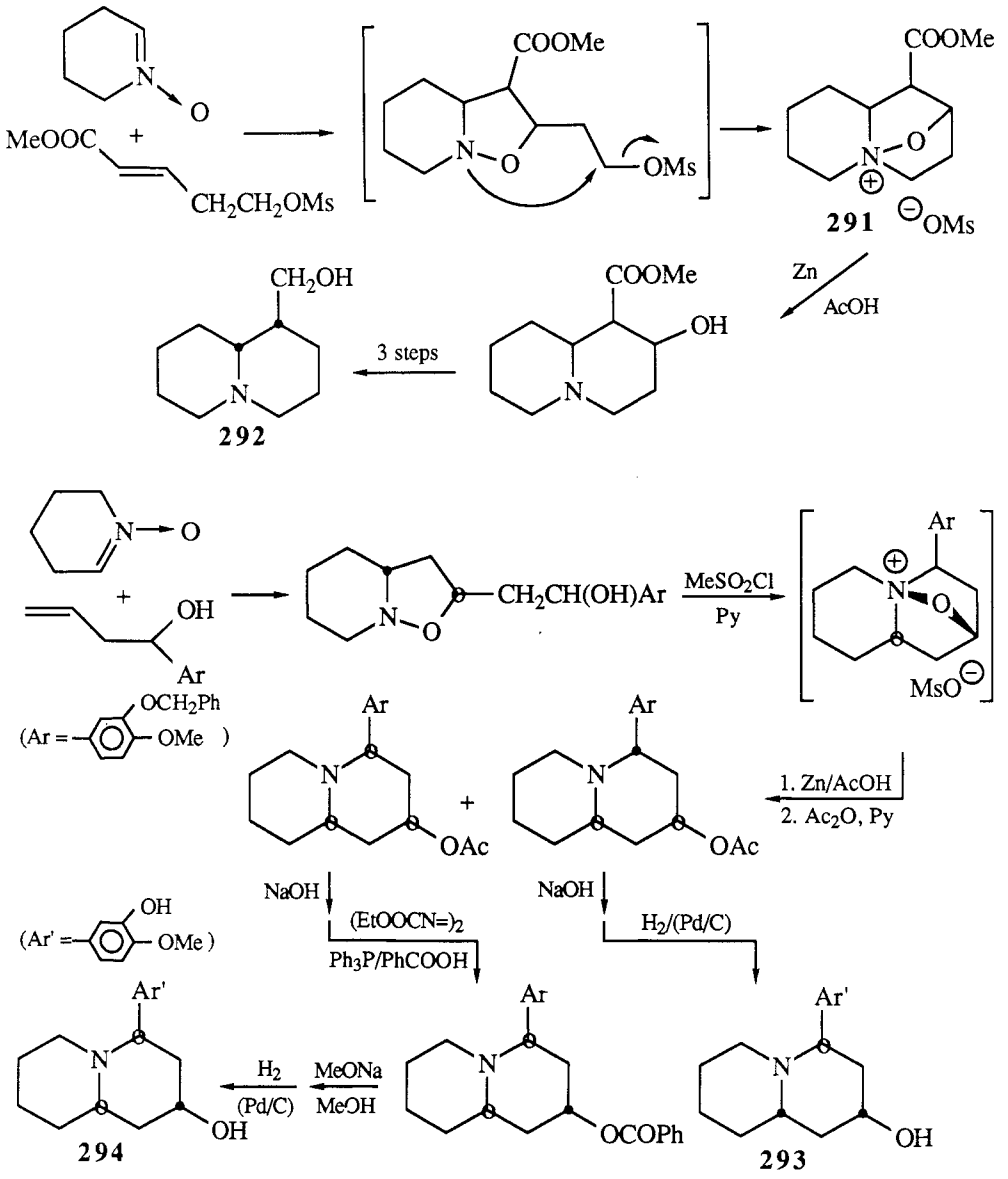
The sequence has general applicability: see, for example, the syntheses of *dl*-retronecine[136/80] and *dl*-croalbinecine (unpublished results cited in ref. 207/84, p. 137).

An interesting variation is represented by the total synthesis of *dl*-isoretronecanol (**290**), outlined in the following scheme. The cycloaddition of 1-pyrroline-1-oxide to 2,3-dihydrofuran is regiospecific and highly stereoselective, and produces predominantly (92% yield) the cycloadduct **289**, arising from an *exo* transition state.[33C/79.189/82]




**289** **290**

(C) *Quinolizidine alkaloids.* When the starting nitrone is 3,4,5,6-tetrahydropyridine 1-oxide and a mesylated $\beta$-hydroxyethyl group is present in the isoxazoline 5-position, an internal nucleophilic substitution occurs spontaneously immediately after the cycloaddition step, and a mesylate (**291**) can be isolated. Its ring-opening reduction with zinc and acetic acid has afforded a convenient synthesis of (±)-lupinine (**292**):[241/76]



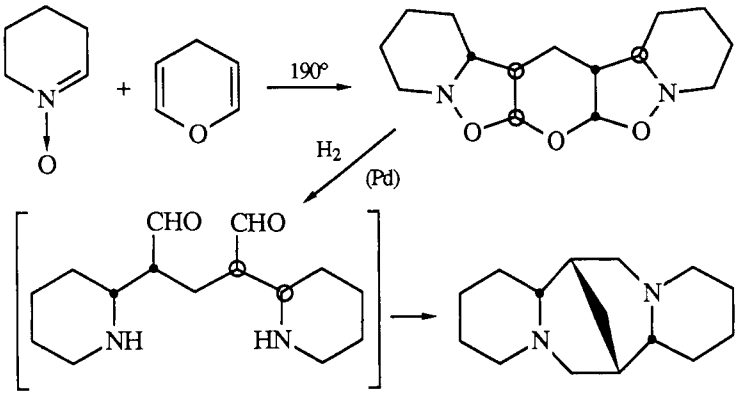

Scheme 3.13.

Mesylation can be carried out after the cycloaddition step, as the general route to naturally occurring *cis*- and *trans*-arylquinolizidinols (**293** and **294**) shown in Scheme 3.13 illustrates.[109B/81.116/82.303/83]

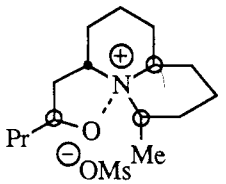
The mixture of diastereoisomeric isoxazolidines is not separable, but separation can be achieved after the reduction step on the amino alcohol acetates. In order to obtain the *trans*-quinolizidinols (**294**), inversion at the $C_2$ center must be accomplished. A slight modified procedure, employing 1-arylbuta-1,3-diene as dipolarophile in the crucial cycloaddition step, allowed a total synthesis of lasubine I and II [**293** and **294**, respectively; Ar = 3,4-$(MeO)_2C_6H_3$] and of subcosine I.[154/83.105/84]

A second synthesis of *dl*-lupinine utilizes as a starting reaction the cycloaddition of tetrahydropyridine 1-oxide with dihydropyran, which, although regiospecific, has only moderate yield. The subsequent elaboration closely follows the route outlined in the synthesis of *dl*-isoretronecanol (see p. 755).[189/82]

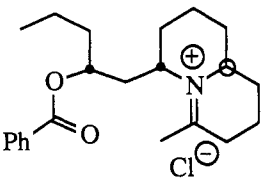
A simple three-step synthesis of α-isosparteine starts from the same cyclic nitrone, which cycloadds 4*H*-pyran at 190°C with high regio- and stereoselectivity:[151/83]



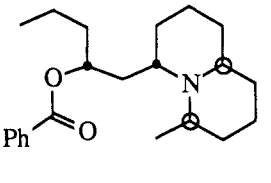

If a 4,6-diallylquinolizidine is needed, the synthetic scheme starts from a suitably 6-substituted tetrahydropyridine 1-oxide. Thus, intermediacy of the mesylate **295** or, better, of the iminiun salt **296** allowed efficient stereoselective synthesis of (±)-porantherilidine (**297**) and (±)-porantheridine (**298**).[237/80.238/80.269/80]



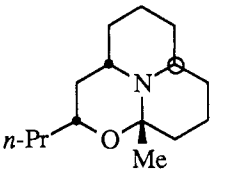

**295**




**296**

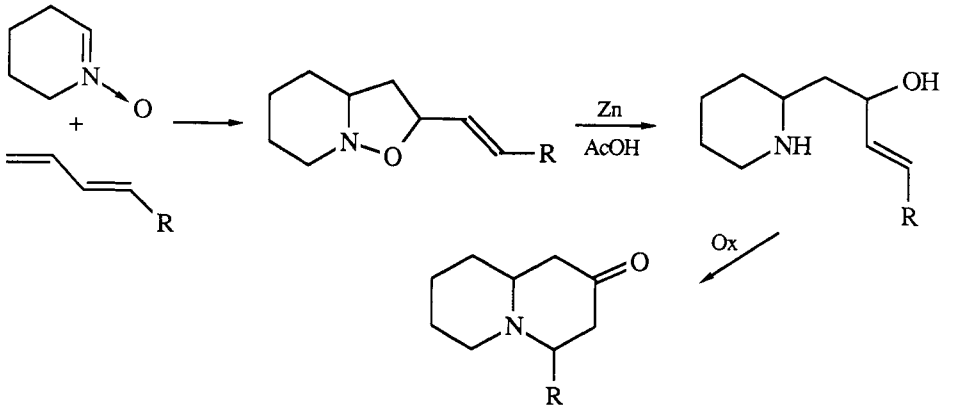



**297**

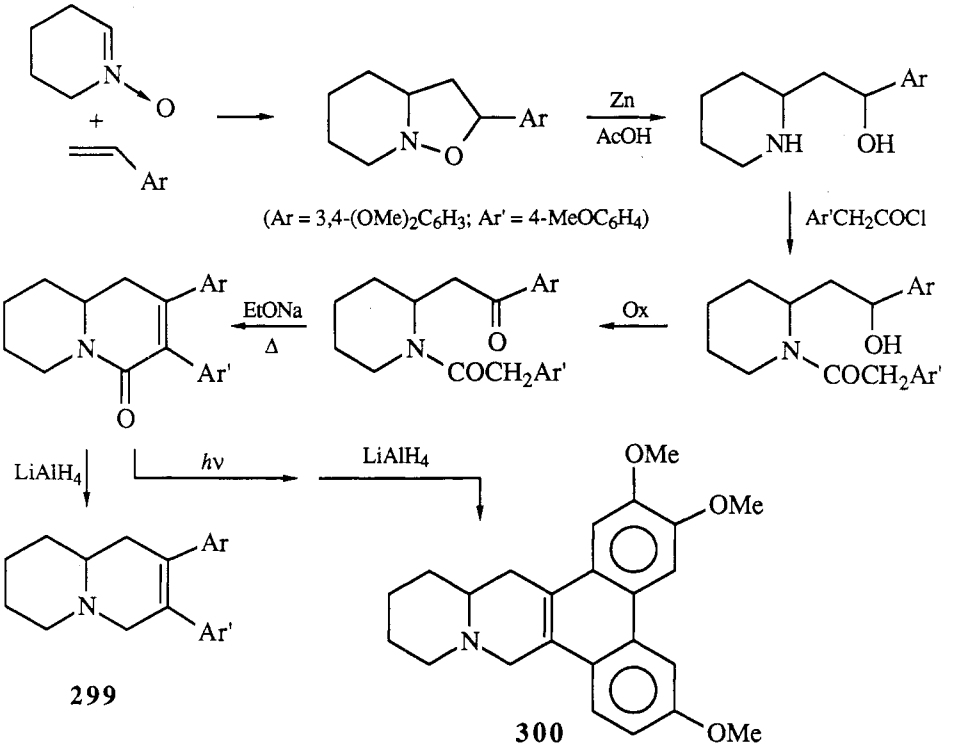



**298**

Another efficient entry to 4-substituted quinolizidines takes advantage of the highly regioselective cycloaddition of 1-monosubstituted dienes and of a subsequent Michael-type recyclization:[259/78]

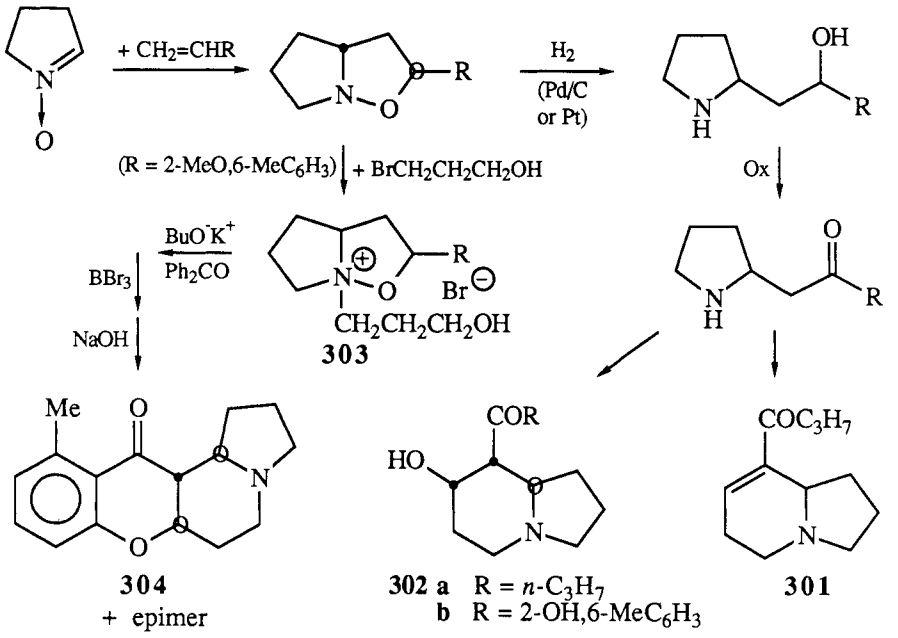



A further variation, used in the synthesis of (±)-julandine (**299**) and (±)-cryptopleurine (**300**), involves the acylation of the amino alcohol with subsequent aldol-type recyclization (Scheme 3.14).[233/81]




**Scheme 3.14.**

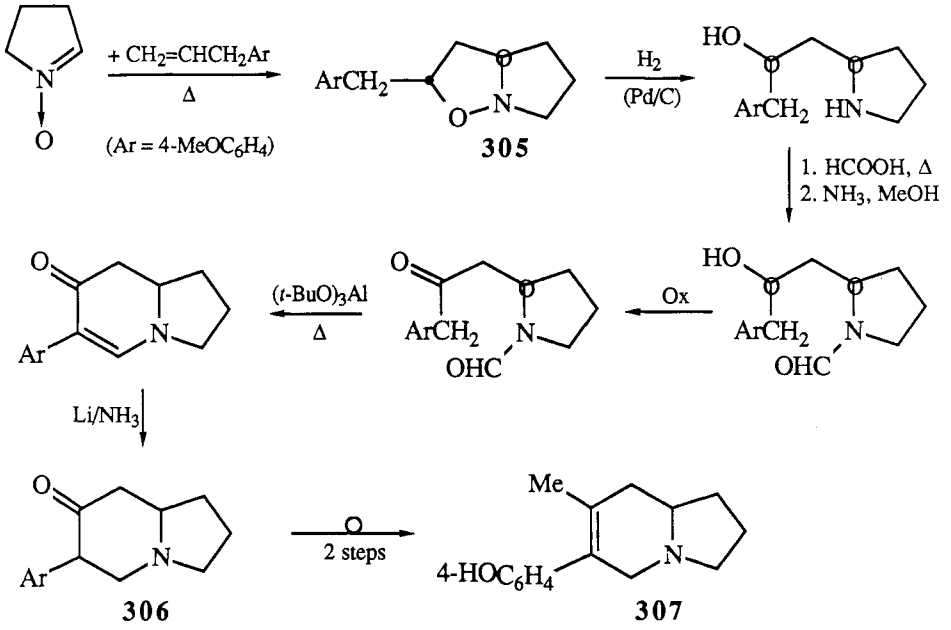
(D) *Indolizidine alkaloids.* If the β-amino alcohol, derived from the isoxazolidine obtained by the regio- and stereoselective cycloaddition of 1-pyrroline 1-oxide and a monosubstituted olefin, is oxidized to the corresponding ketone, a Michael-aldol annulation sequence provides an easy way to produce the condensed six-membered ring necessary for construction of the indolizidine system. Stereoselective syntheses of *dl*-elaeokanine-A (**301**) or *dl*-elaeokanine-C (**302a**)[228/79] and *dl*-isoelaeocarpicine (**302b**)[102/79] have thus been achieved (Scheme 3.15).




**Scheme 3.15.**

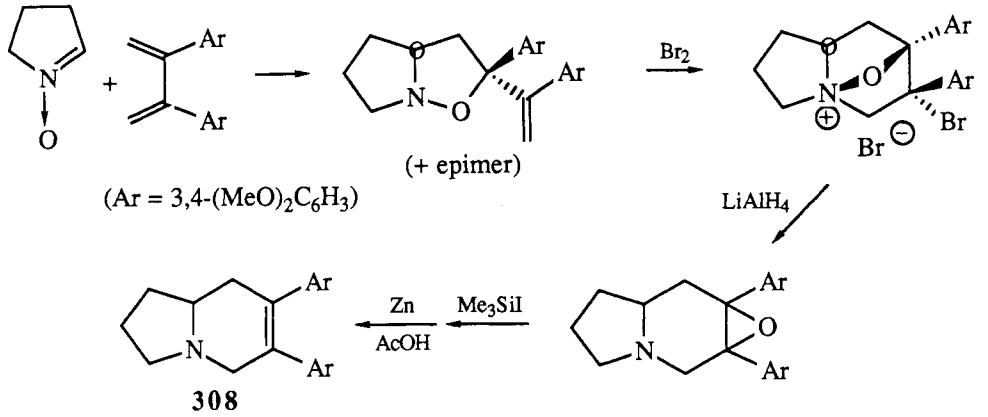
A variation of the method, involving quaternization of the isoxazolidine intermediate to the salt **303**, followed by its base-promoted opening, Oppenhauer oxidation and aldol reclosure in one step, and subsequent hydrolysis of the methoxy group and base-induced cyclization, yielded a mixture of *dl*-elaeocarpine (**304**) and its epimer *dl*-isoelaeocarpine.[102/79] A convenient synthesis of ipalbidine (**307**) through the key intermediate ketone **306** relied on the regio- and stereospecific cycloaddition of 1-pyrroline 1-oxide to *p*-allylanisole to give the bicyclic isoxazolidine **305**, followed by routine elaboration (Scheme 3.16).[38/83]

Two different syntheses of the indolizidine alkaloid (±)-septicine (**308**) via isoxazolidines have recently been reported. 1-Pyrroline 1-oxide is initially reacted either with 3,4-dimethoxystyrene[150/83] or with 2,3-bis(3,4-dimethoxyphenyl)butadiene.[38/80] In both cases a diastereomeric mixture of isoxazolidines




**Scheme 3.16.**

is regiospecifically produced. Further routine elaborations lead to the target molecule with 44% or 18% overall yields, respectively. The former synthetic approach closely follows the route illustrated for the synthesis of the homologous alkaloid (±)-julandine (see p. 758); the second approach is outlined in the following scheme:

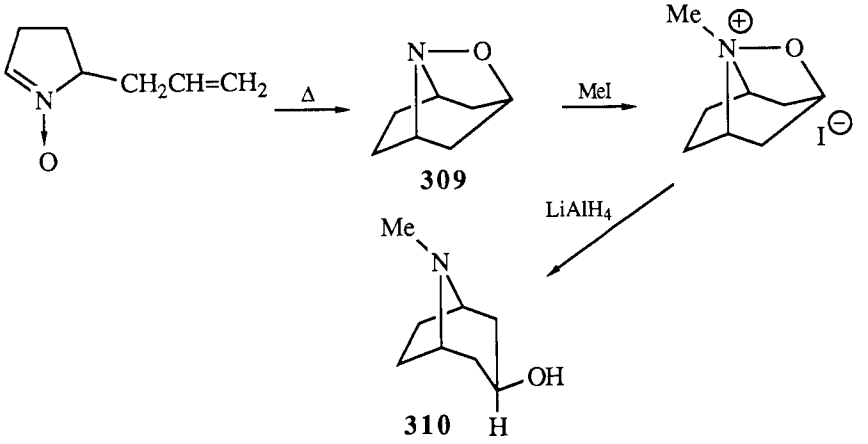


### *3.4.10.2 Alkaloids via Intramolecular Nitrone Cycloadditions*

Several bridged polycyclic alkaloidal ring systems have been built up through the intramolecular formation of an intermediate isoxazolidine nucleus. Both *C*-alkenyl- and *N*-alkenylnitrones have been utilized as starting materials for the cycloaddition step, leading to elegant entries into the tropane and *Lycopodium* classes on the one hand and the ergot class on the other.

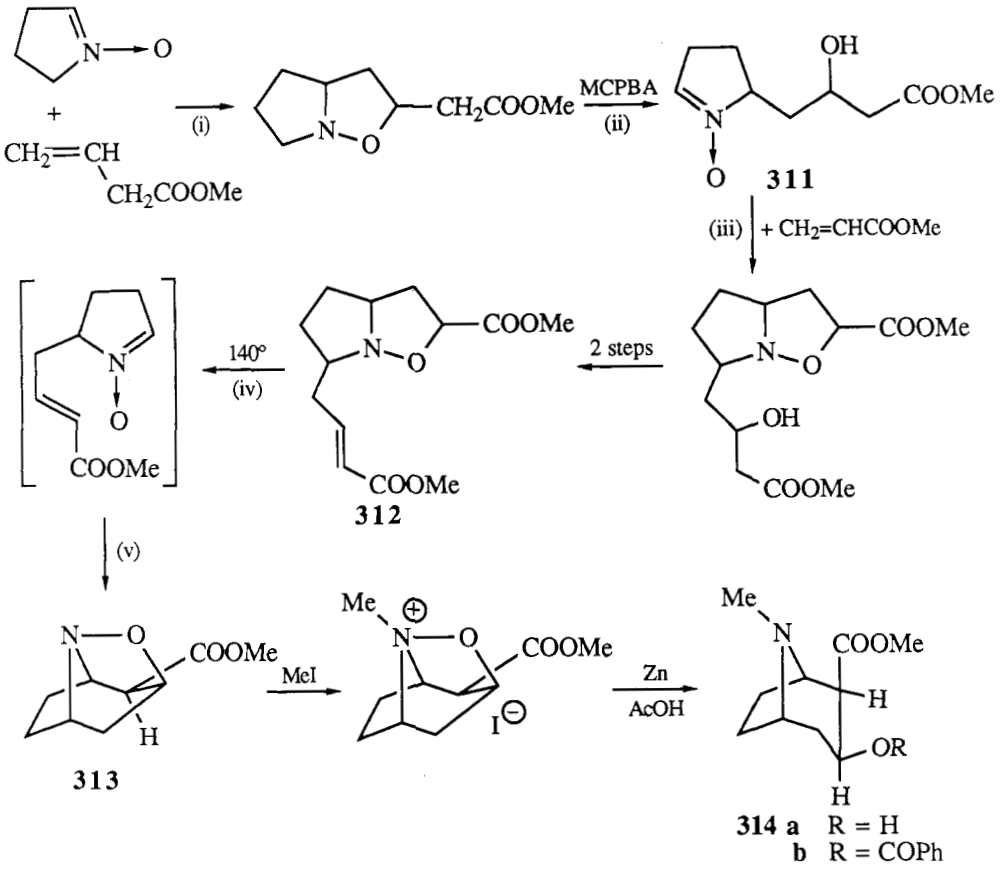
a. Tropane Class of Alkaloids

That the easily available 5-allyl-3,3,5-trimethyl-1-pyrroline 1-oxide can be transformed in a tropane derivative has been known for several years.[16C/72] Application of this scheme to the unsubstituted 5-allyl-1-pyrroline 1-oxide led to an easy three-step synthesis of pseudotropine (**310**) through the key compound 9-oxa-8-azatricylo[3.2.1.$1^{8,3}$]nonane (**309**)[49C/73] and with a 22% overall yield from 4-nitro-6-heptenal dimethyl acetal:[99/79]




A superb example of how almost the entire isoxazolidine chemistry can be utilized in the construction of complex molecules is the stereospecific synthesis of *dl*-cocaine (**314b**),[152/78.256C/78.99/79] illustrated in Scheme 3.17.

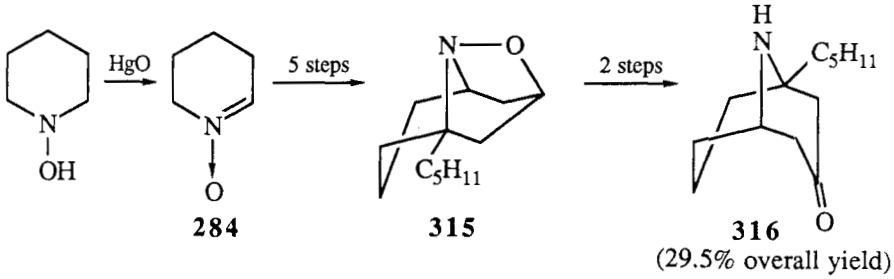
The following principal features should be noted: (i) the regiospecific intermolecular cycloaddition of 1-pyrroline 1-oxide to methyl 3-butenoate; (ii) the ability to obtain nitrone **311** by oxidative ring cleavage (see Part 2 of this work); (iii) the successful protection of this nitrone functionality through a second intermolecular cycloaddition to methyl acrylate in order to achieve dehydration in the side chain to give **312**; (iv) thermal cycloreversion (see § 3.4.4.1, p. 738); and (v) spontaneous regio- and stereospecific intramolecular cycloaddition to the tricyclic crucial compound **313** (see Part 2 of this work), and quaternization and hydrogenolysis of the quaternary salt to yield ecgonine methyl ester



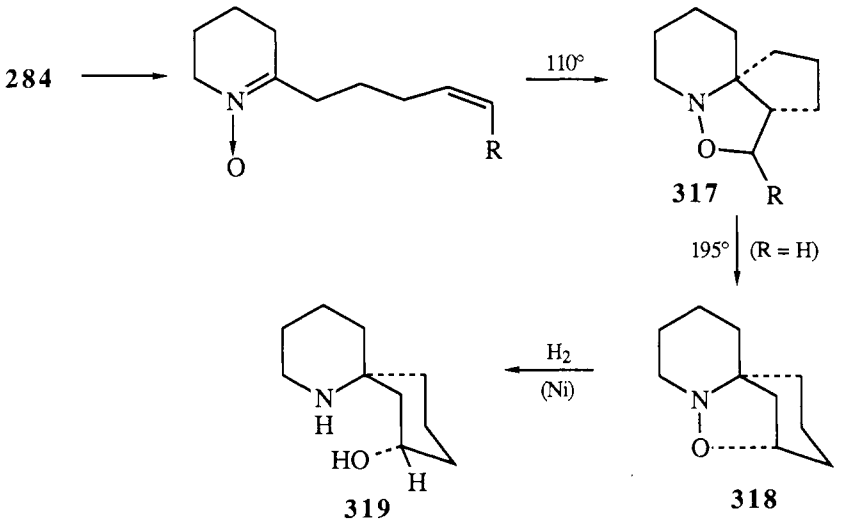

**Scheme 3.17.**

(**314a**)(§§ 3.4.1, p. 733, and 3.4.2, p. 735), the already known precursor of *dl*-cocaine (**314b**). The overall yield through the nine steps is reported to be about 4%. A second method of preparing **313**, starting from methyl 5-nitro-8,8-dimethoxy-2-octanoate, afforded lower yields.[256C/78]

The synthesis of (±)-adaline (**316**), the higher homologue derivative of the tropone class of alkaloids, involves as a key intermediate the tricyclic isoxazolidine (**315**):[239/80]



Starting from the cyclic nitrone **284**, some efforts have been made toward the synthesis of histrionicotoxin, an interesting alkaloidal system possessing a spiro structure.[105/82] The 2-(4′-pentenyl) derivative of **284** was cyclized to the tricyclic 4-alkylated isoxazolidine (**317**), which under thermal treatment furnished the 5-alkylated isomer (**318**). Hydrogenolysis led to the spiro base (**319**), a model compound for perhydrohistrionicotoxin (Scheme 3.18).[74/75]

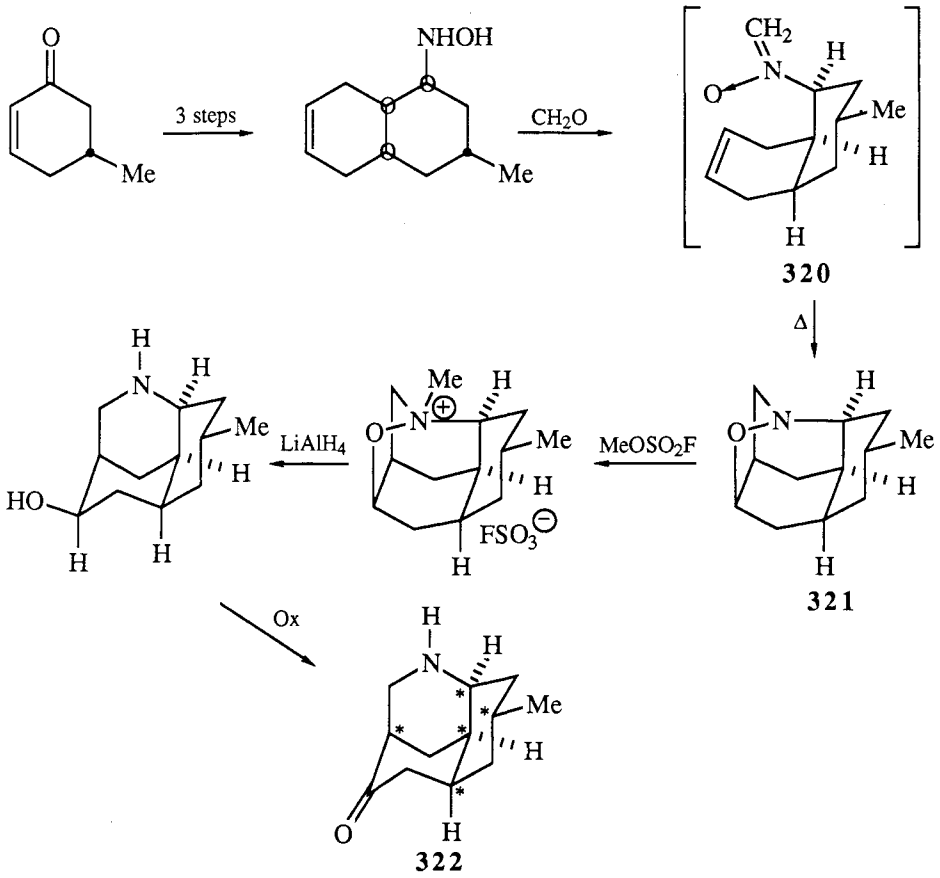



**Scheme 3.18.**

An attempted application of this intramolecular cycloaddition pattern to a derivative carrying a carbomethoxy group at the end of the side chain (R = COOMe) gave the derivative (**317**)(R = COOMe), which thermally epimerizes but does not isomerize to the compound corresponding to **318**.[178/74]

### b. Lycopodium Alkaloids

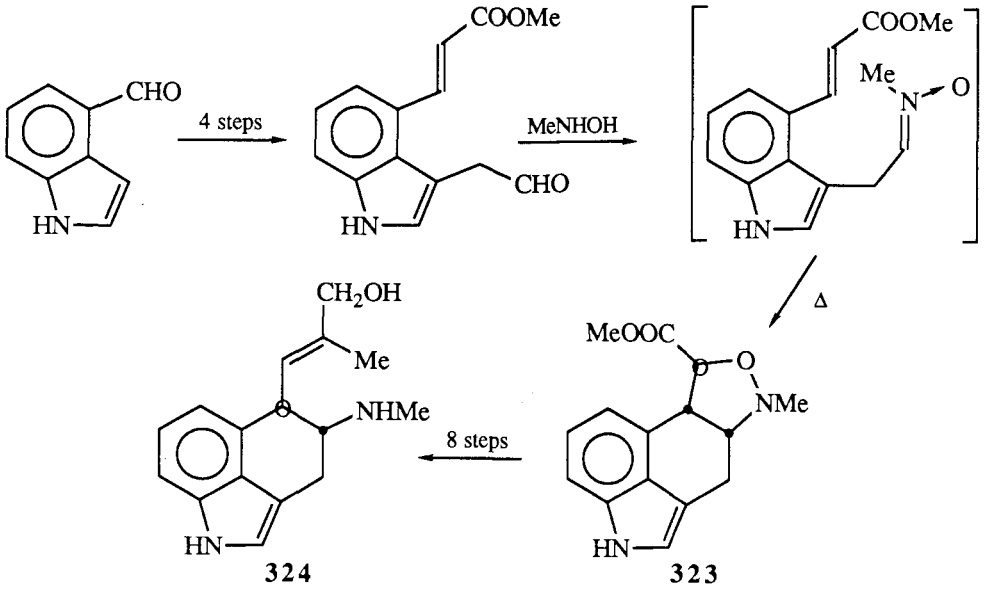
Another outstanding piece of work in the field of natural products is the total synthesis of *dl*-luciduline (**322**)[122B/76] and of the naturally occurring pure (+)-enantiomer[121/78] along the following pathway shown in Scheme 3.19. The key step is the formation of the bridged polycyclic isoxazolidine **321** through the highly regioselective intramolecular cycloaddition of the transient *N*-alkenylnitrone **320** (see Part 2 of this work). Methylation, hydrogenolysis, and oxidation of the alcoholic function in succession affords luciduline in seven steps from 5-methyl-2-cyclohexenone with a 33% overall yield.




**Scheme 3.19.**

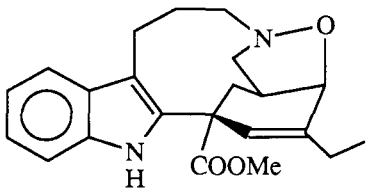
## c. Indole Class of Alkaloids

The key step of an elegant synthesis of the ergot alkaloid (±)-chanoclavine I (**324**) involves the intramolecular formation of the isoxazolidine derivative **323** (Scheme 3.20).[112/80] Here the nitrone function, prepared *in situ* in position 3 of the indole, cycloadds regio- and stereoselectively to the 1,2-disubstituted double bond present in position 4 of the same nucleus. A 14% overall yield from the indole-4-carbaldehyde has thus been achieved. A second synthetic design,[146/80] starting from 4-indolealdehyde, follows a longer sequence, involving the intramolecular cycloaddition of an unsaturated nitrile oxide to give an isoxazoline, which is then transformed into an isoxazolidine derivative (see § 2.2.3.3, p. 580). It is interesting to note that in both synthetic schemes the indole nucleus remains unaltered through the entire sequence.

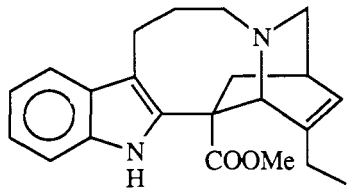



Scheme 3.20.

Another polycyclic isoxazolidine containing the indole moiety (i.e., **325**[228B/76]), potentially available by regioselective intramolecular cycloaddition, was successfully transformed in five steps (40% overall yield) into catharanthine (**326**),[122/80] an important intermediate on the way toward the vinblastine group of alkaloids.




**325**



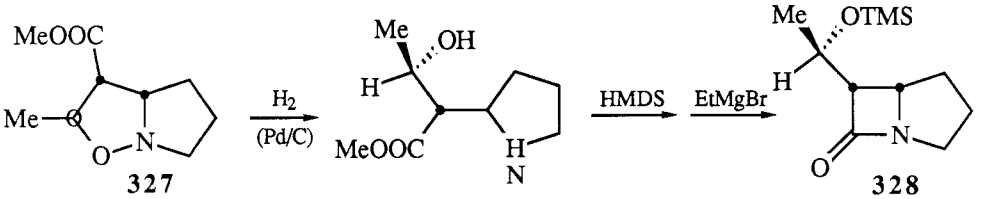

**326**

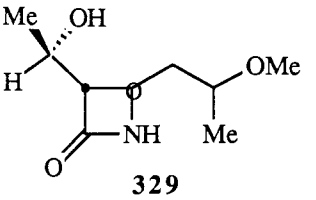
For the total synthesis of (+)-paliclavine, achieved through the intramolecular formation of a 2-isoxazoline derivative, followed by methylation, reduction to an isoxazolidine compound, and hydrogenolytic scission of the latter, see § 2.2.3.3, p. 580.

### *3.4.10.3 Other Nitrogen-Containing Products*

Two different approaches to the synthesis of β-lactam antibiotics are known,

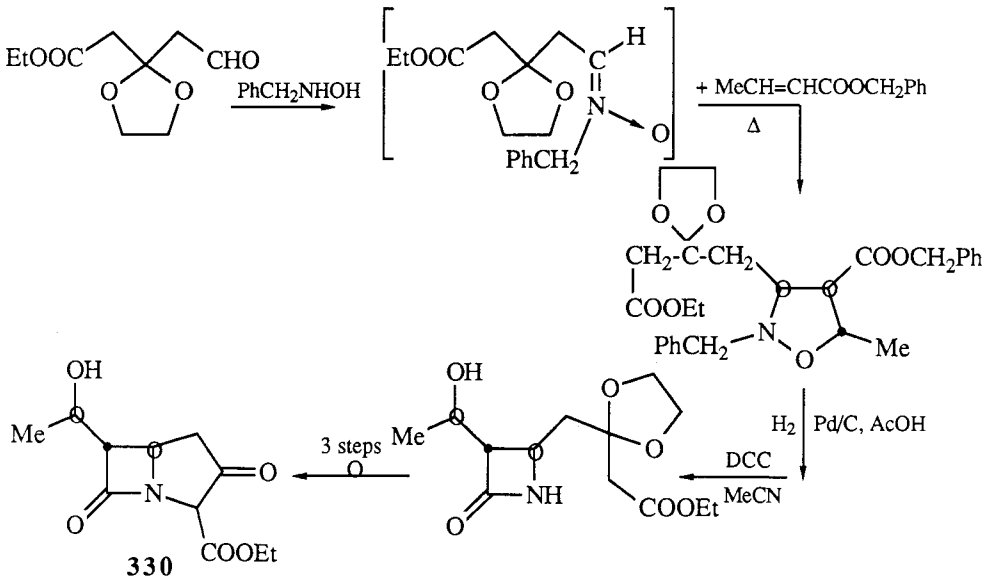
which utilize the intermediacy of isoxazolidine derivatives. The first is based on the regio- and stereoselective cycloaddition of a cyclic nitrone to methyl *trans*-crotonate. Hydrogenolysis of the isoxazolidine (**327**) thus obtained, protection of the hydroxy group, and lactonization with ethylmagnesium bromide led to the stereoisomerically pure **328**, where the three chiral centers show the same stereochemistry as in thienamycin:[226/79]




Along a similar synthetic approach the analogous thienamycin intermediate (**329**) has been prepared from an open-chain nitrone and benzyl crotonate with good regio- and stereoselectivities.[153/82]

A different approach to carbapenem antibiotics utilizes an isoxazolidine-4-carboxylate, obtained by regio- and stereoselective cycloaddition of an appro-

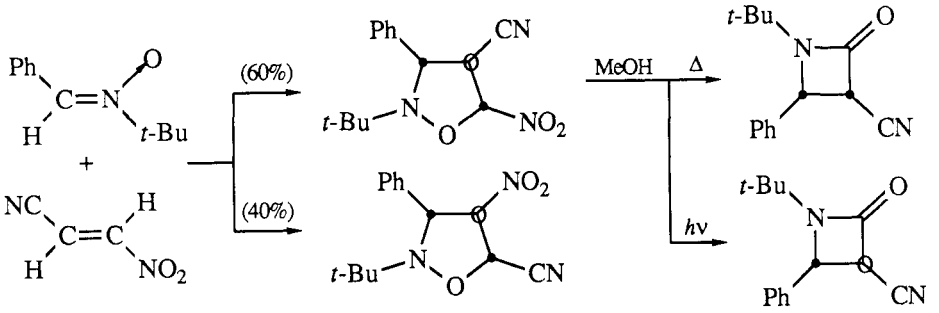



330

**Scheme 3.21.**

priately substituted nitrone to benzyl crotonate. Hydrogenolytic ring opening in acetic acid, followed by DCC-promoted closure to the β-lactam ring, opens an easy route to the bicyclic keto ester (**330**), a precursor in the total synthesis of thienamycin. The entire process,[196/82] illustrated in Scheme 3.21, is an interesting alternative to the 2-isoxazoline route (see § 2.2.3.3, p. 582).

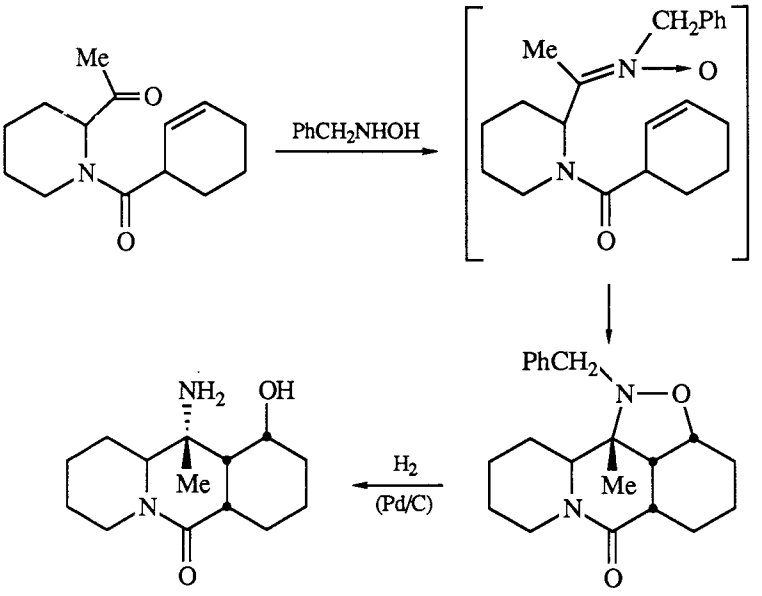
Another method utilizes as starting point the cycloaddition of a nitrone to *trans*-1-cyano-2-nitroethylene: of the two regioisomers thus obtained, the 5-nitro derivative easily undergoes ring contraction to a β-lactam; for example:[99/81,99/84]



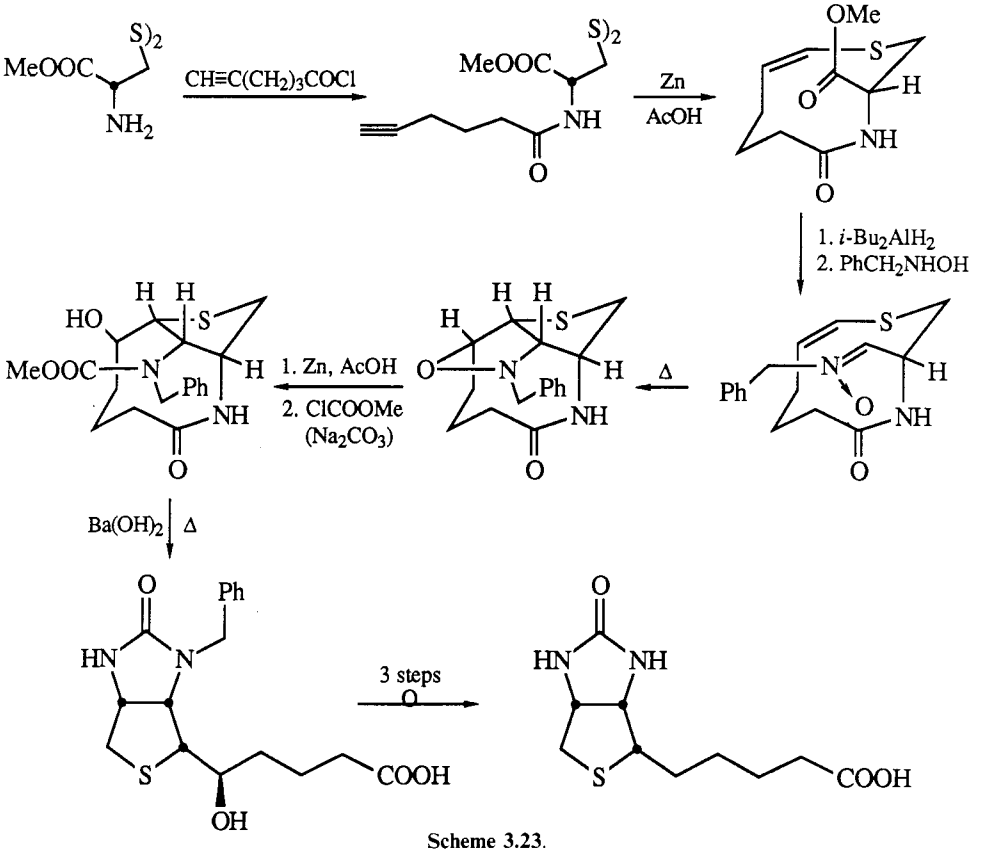

The conversion above is favored by protic and polar aprotic solvents, and is possibly originated by removal of the acidic 5-proton coupled with N–O bond cleavage, followed by reclosure to the four-membered ring. The process can also be induced by some bases (e.g., DBN), which affords a mixture of *cis* and *trans* β-lactams.[99/84] By contrast, *t*-BuOK in DMSO provokes ring cleavage with the formation of open-chain compounds (see § 3.4.7, p. 748). With 5-substituents different from a nitro group (e.g., cyano or ester groups), other products are obtained (see §§ 2.5.2.3, p. 640, and 3.4.7, p. 748).

A γ-lactam analogue of carbapenicillanic acid has been synthesized in seven steps, starting from a 1,3-dipolar cycloaddition of 5-methoxycarbonyl-1-pyrroline-1-oxide to methyl acrylate.[149/83] A regiospecific and stereoselective synthesis of δ-lactams, possessing general applicability, also involves an intramolecular cycloaddition of an unsaturated nitrone with an amide function in a suitable position; an example is shown in Scheme 3.22.[226/81]

(±)-Biotin has been synthesized stereospecifically through a 2-isoxazoline derivative. A variation of the method goes through a condensed isoxazolidine, but the overall yields are far lower.[141/80] A similar method, also starting from cycloheptene and using the same intramolecular nitrone cycloaddition as a key step, does not reach notably higher yields.[6B/80] Better results have been obtained in a stereocontrolled synthesis of *d*-biotin, which involves an intramolecular nitrone cycloaddition as the key step. The nine-step synthesis, outlined in Scheme 3.23, has been achieved with a 9% overall yield from L-cystein dimethyl ester.[32/82,143/82]

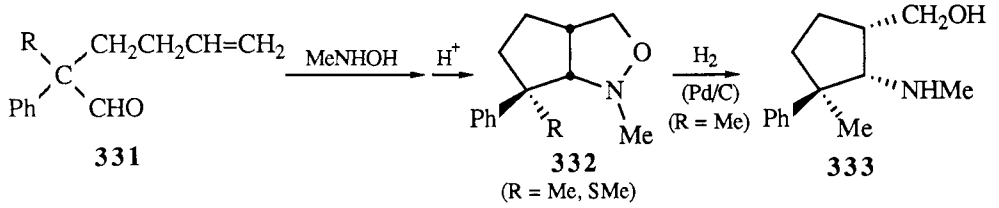


Scheme 3.22.



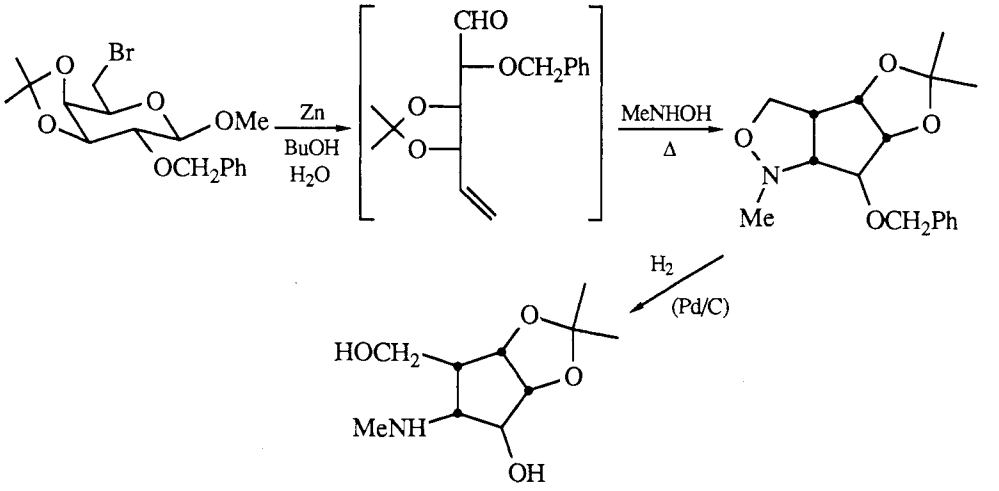
Scheme 3.23.

An approach to the stereoselective synthesis of a key section of the macrocyclic antibiotic lankacidin molecule utilizes 2-isoxazolines and the related isoxazolidines as convenient intermediates.[162/84] From bicyclic isoxazolidines, easily attainable by intramolecular cycloaddition of unsaturated nitrones (see Part 2 of this work), a large variety of cyclopentane derivatives, containing three or more contiguous asymmetric centers, can be constructed stereospecifically starting from acyclic precursors with a limited number of steps. For example, the bicyclic isoxazolinocyclopentane **322** is stereospecifically produced by cyclization of the nonisolated nitrone of the unsaturated aldehyde **331**. Subsequent hydrogenolysis leads to the isomerically pure tetrasubstituted cyclopentane amino alcohol **333**:[188/77]



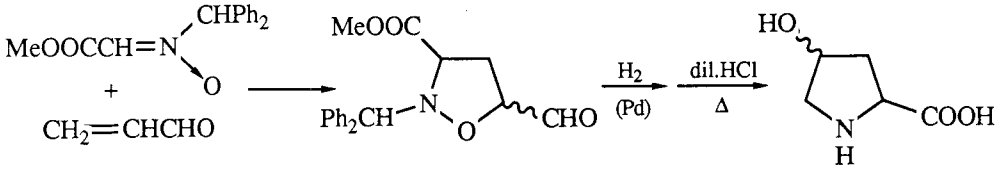

**331** **332** (R = Me, SMe) **333**

An interesting extension of this sequence in the field of monosaccharides makes it possible to prepare stereoisomerically pure polyhydroxylated aminocyclopentane derivatives,[74/79,76/79,77/79,110/81] as the following typical example[77/79] shows:



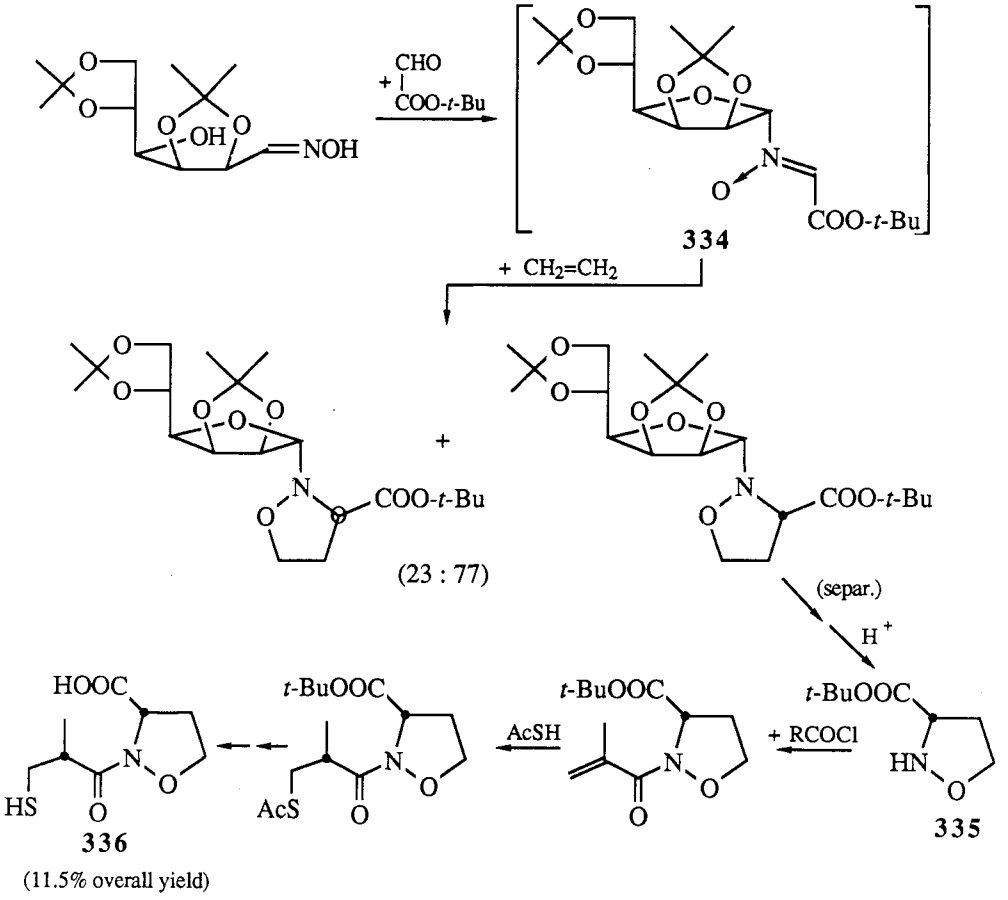

If suitably substituted, intermolecular formation of *N*-glycosylisoxazolidines [80/77,81/77] can produce the enatiomerically pure 5-oxaprolines, which can easily be incorporated in synthetic peptides and can readily be hydrogenolyzed to homoserine derivatives.[106/81]

A short, efficient synthesis of 4-hydroxyproline (as a mixture of *cis*/*trans* isomers) has been realized by starting with a nitrone cycloaddition:[42/80.20/81]

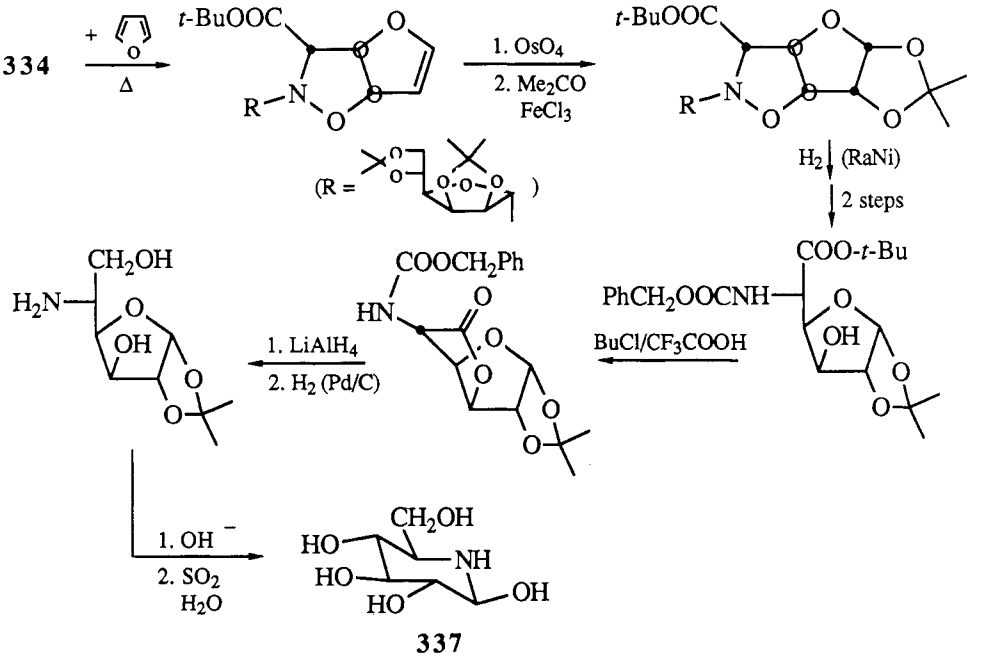



The best selectivity (a *cis*/*trans* ratio of about 6:1) was reached by adding acrolein to an equilibrium mixture of *E*/*Z*-nitrones in benzene.

The asymmetric synthesis of the oxa analogue (**336**) of captopril, a biologically active proline derivative, is based on the stereoselective cycloaddition of the *N*-glycosyl-*C*-*t*-butoxycarbonylnitrone (**334**) to ethylene. Separation of the major cycloadduct, followed by hydrolysis, yields the pure enantiomer 5-oxaproline ester **335**, which has the desired (3*S*)-configuration. The target molecule is then built as shown in Scheme 3.24.[103/83]




**Scheme 3.24.**



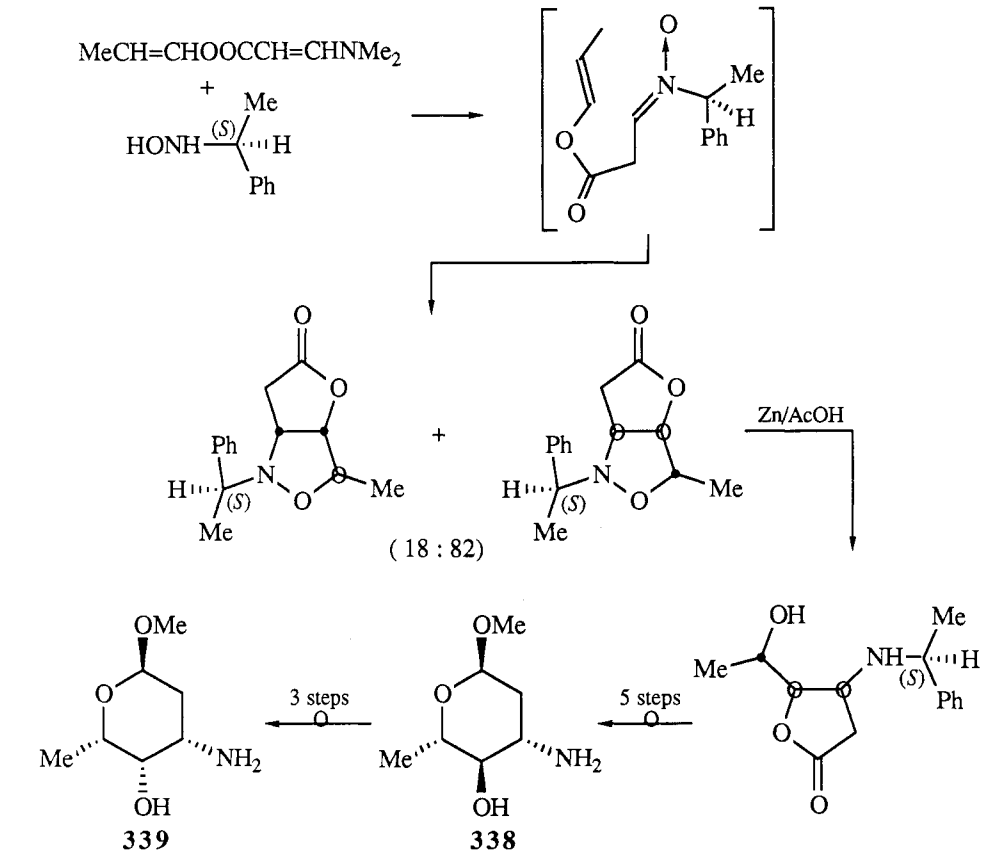

**Scheme 3.25.**

Starting from the same glycosyloxime, a total synthesis of the naturally occurring heteroside nojirimycin (**337**) has been achieved with a 19.5% overall yield along the route shown in Scheme 3.25.[101/82] The formation of the five contiguous chiral centers relies on the stereoselectivities encountered in both the nitrone cycloaddition to furan and the hydroxylation of the cyclic enol ether double bond. The stereoselectivity induced by a chiral nitrone in the 1,3-dipolar cycloaddition has been utilized in the synthesis of L-α-methyl acosaminide (**338**) and daunosaminide (**339**) along the route outlined in Scheme 3.26.[98/81]

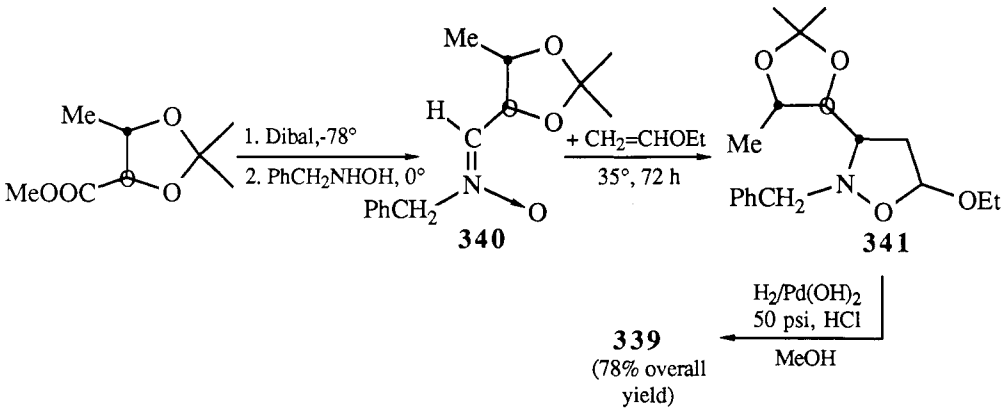
A different, short synthesis of the same methyl glycoside of daunosamine (**339**) utilizes the chiral nitrone **340**, which reacts stereospecifically with ethyl vinyl ether. The isoxazolidine (**341**) thus formed is transformed directly into **339** upon catalytic hydrogenation (see scheme on p. 772).[113/83,62/84]

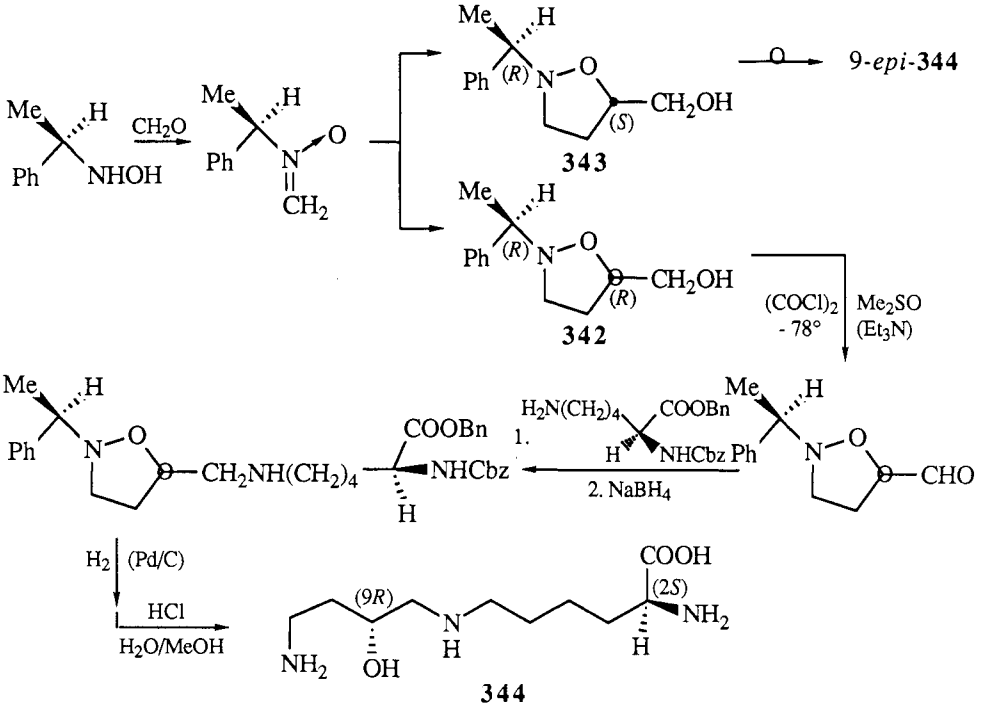
Use of vinylene carbonate as a dipolarophile in the cycloaddition step opens an analogous, simple route to 3-amino-3-deoxypyranoses, such as 3-*epi*-gentosamine.[62/84]

The total synthesis of the rare naturally occurring polyamino acid (+)-hypusine (**344**) and its 9-epimer is achieved by using the optically active *N*-(α-methylbenzyl)hydroxylamine as a starting material. 1,3-Dipolar cycloaddition of the corresponding nitrone to allyl alcohol produces an equimolar mixture of the two diastereomeric isoxazolidines **342** and **343**, easily separated by HPLC, which are then transformed into the natural and unnatural products, respectively, as illustrated in Scheme 3.27.[217/83]

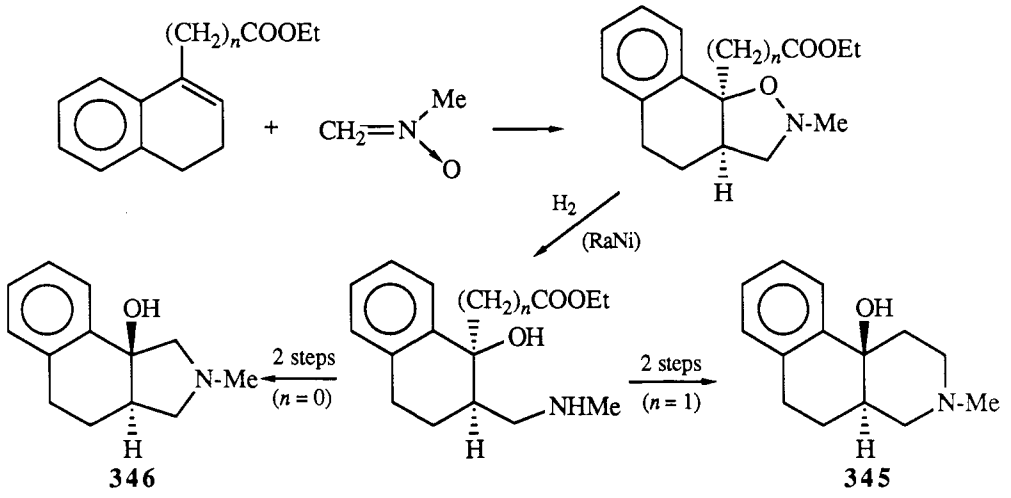

MeCH=CHOOCCH=CHNMe2
HONH
Me
(S)
H
Ph
Zn/AcOH
( 18 : 82)
3 steps
5 steps
339
338

Scheme 3.26.


1. Dibal,-78°
2. PhCH2NHOH, 0°
+ CH2=CHOEt
35°, 72 h
340
341
H2/Pd(OH)2
50 psi, HCl
MeOH
339
(78% overall
yield)




Scheme 3.27.

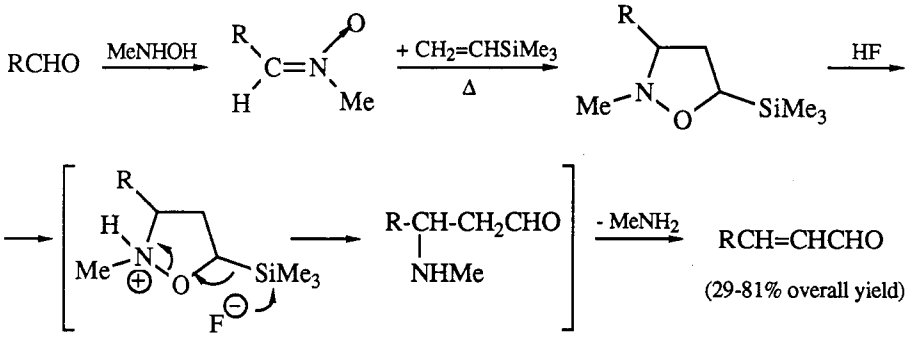



Scheme 3.28.

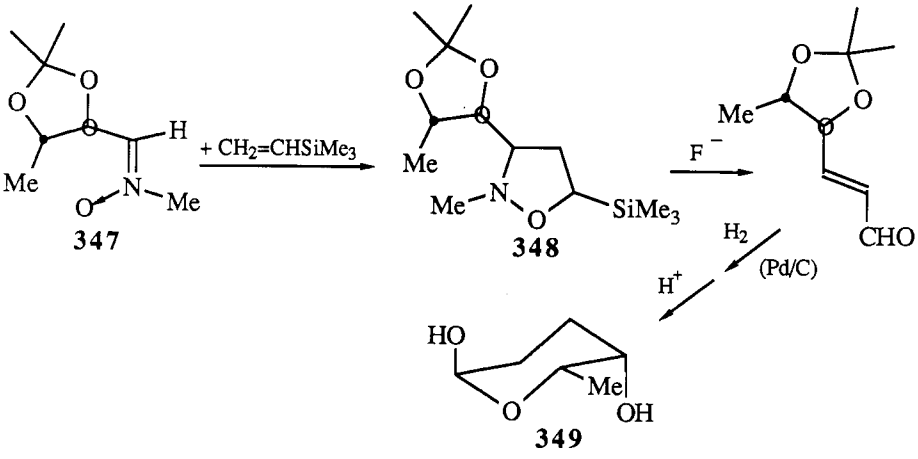
It is known that hydrogenolysis of isoxazolidine-5-carboxylates yields 3-hydroxy-2-pyrrolidinones (see § 3.4.2, p. 736): application of this reaction to the *trans*-2-methyl-3-(3′-pyridyl) derivative permits definitive confirmation of the stereochemical structure of hydroxycotinine, a mammalian metabolite of nicotine found in the urine of smokers.[161/72] Extension of this hydrogenolytic pattern to isoxazolidine-5-acetic esters offers an easy synthetic entry to the octahydrobenz[*f*]isoquinoline system (**345**) or to its lower homologue (**346**), as shown in Scheme 3.28.[29/74]

### *3.4.10.4 Nitrogen-Free Systems*

A convenient alternative to the Wittig procedure for homologating aldehydes RCHO to α,β-unsaturated aldehydes RCH=CHCHO, particularly useful with base-sensitive aldehydes, is illustrated by the following sequence, which has general applicability:[119/84]

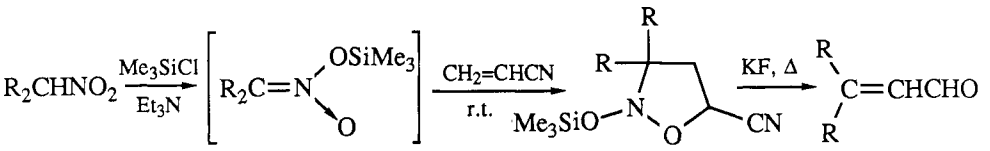



The procedure described above has been applied successfully to the total synthesis of deoxy sugars, as exemplified by the following preparation of (±)-rhodinose (**349**), the trideoxyhexose component of streptolydigin:[186/84]



Cycloaddition of nitrone **347** to vinyl trimethylsilane to furnish a mixture of two diastereomeric isoxazolidines (**348**), followed by fluorine-induced ring fission, hydrogenation of the double bond, and deprotection gives a 37% overall yield of the target molecule. A similar sequence allows to synthesize a model system of the glycosidic part of the antibiotic nogalomycin.[186/84]

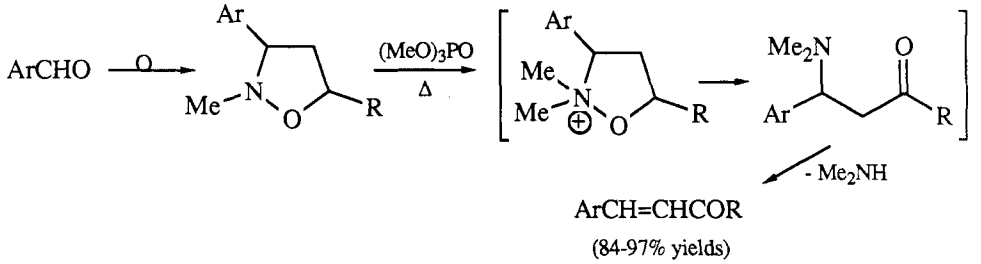
A far less general procedure for preparing α,β-unsaturated aldehydes starts from secondary nitro compounds and involves the *N*-trimethylsilyloxyisoxazolidines, as illustrated here:[2/81]




(R = Me or $R_2$ = $(CH_2)_4$)

With other substituents (e.g., 5-COOMe) rearrangement to γ-nitroso-α-silyloxy derivatives is preferred (see § 3.4.4, p. 742).

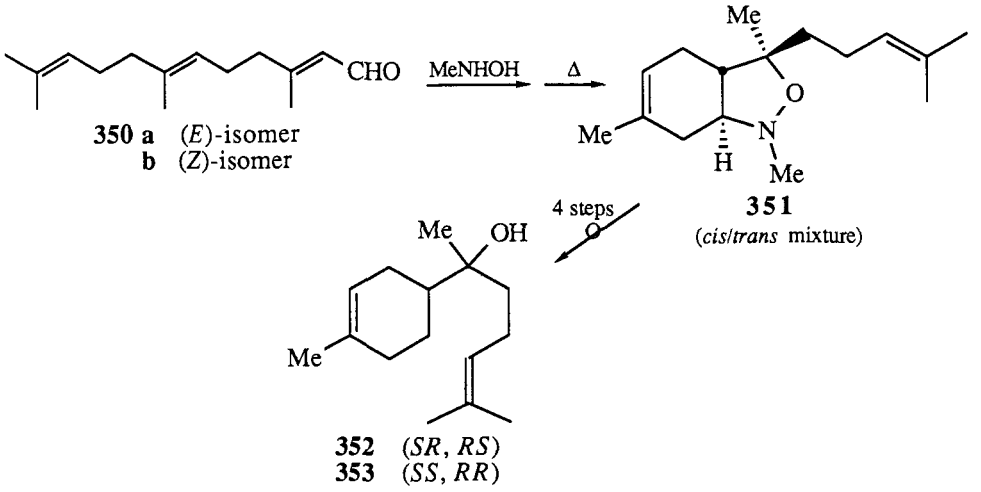
A general method for transforming an aromatic aldehyde ArCHO into an α,β-enone ArCH=CHCOR involves the formation of the nonisolated isoxazolidinium salt, which suffers thermal ring opening and elimination to the final target. The reaction is best carried out by heating the appropriate isoxazolidine with trimethyl phosphate at 150°C without or in the presence of diglyme:[165/84]




(84-97% yields)

Other synthetic procedures take advantage of the hydrogenolytic N–O bond cleavage of the isoxazolidine ring (see § 3.4.2).

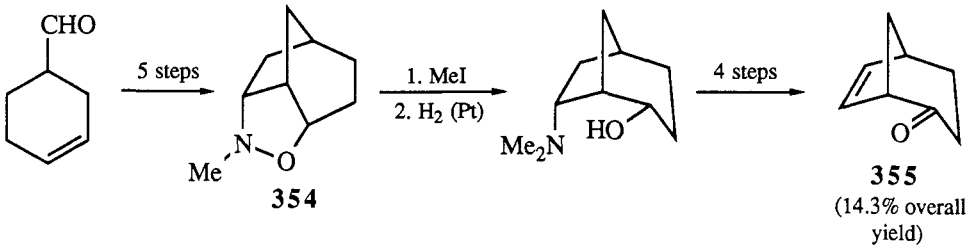
Thus the two racemic α-bisabolols **352** and **353** have been prepared independently by two groups of researchers.[33/79,145B/79] Starting from (6*E*)-farnesal (**350a**), the synthetic sequence successively involves thermal intramolecular cycloaddition of the corresponding nitrone to give a mixture of stereoisomeric isoxazolidines (**351**), $LiAlH_4$-promoted ring opening of their methiodides to an amino alcohol[33/79] or base-promoted rearrangement to a bicyclic 1,3-oxazine,[145B/79] quaternarization, and reductive deamination to racemic **352** (Scheme 3.29).




**Scheme 3.29.**

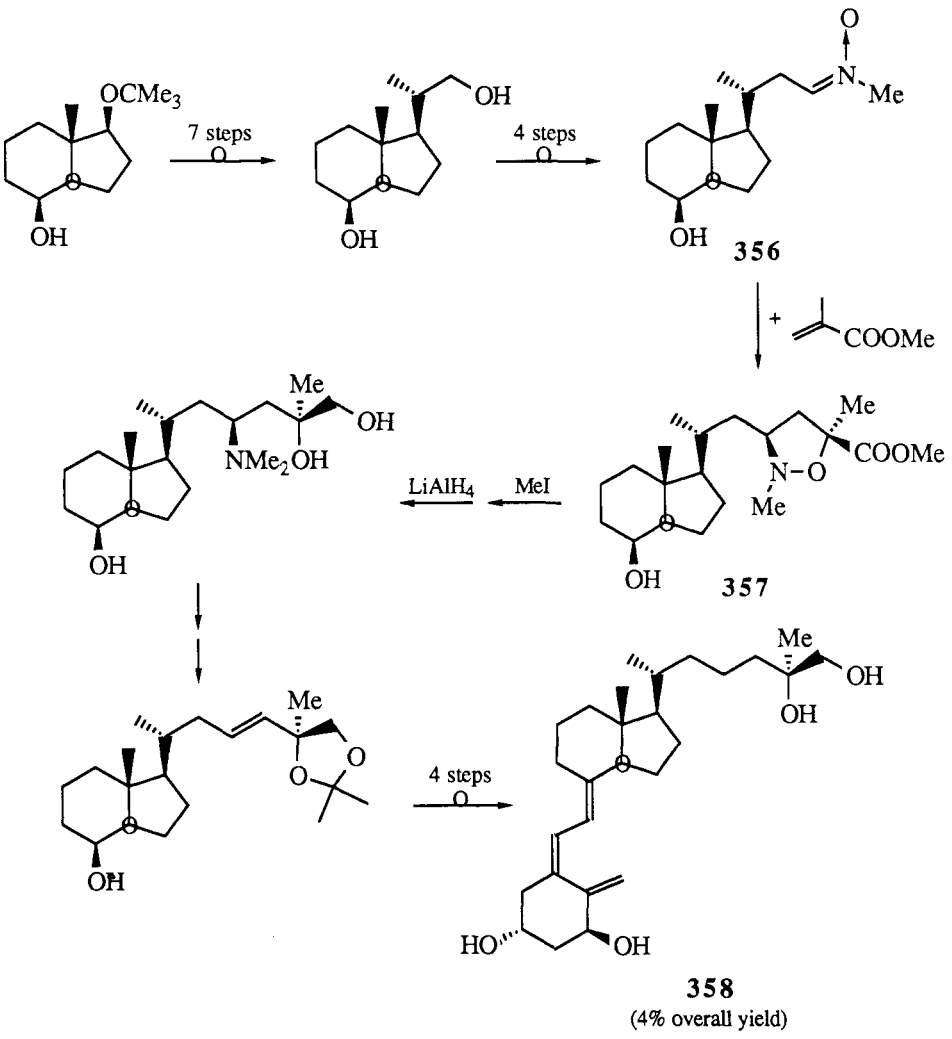
Analogously from (6*Z*)-farnesal (**350b**), the stereoisomer **353** could be obtained, and comparison of this compound with the naturally occurring (−)-α-bisabolol allowed to assign the configuration 6*S*,7*S* to the natural product. Some $\Delta^1$ double-bond isomer is sometimes present as by-product.[145B/79] A similar sequence, starting from citral, led to α-terpineol.[145B/79]

An efficient synthesis of polycyclic homoconjugated ketones, such as **355**, starting from 3-cyclohexene-1-carbaldehyde, involves the tricyclic isoxazolidine (**354**) as a key intermediate and should possess wide applicability:[175/72]




A further application of isoxazolidines as intermediates is the synthesis of benzylamine analgesics.[96/73,216/75]

An interesting application of the nitrone cycloaddition tendency to reversibility is illustrated by the stereoselective total synthesis of 1α,25*S*,26-trihydroxycholecalciferol (**358**), a metabolite of vitamin $D_3$. The 1,3-dipolar cycloaddition of the nitrone **356** to methyl methacrylate shows regiospecificity but a low stereoselectivity, giving a mixture of four diastereoisomeric isoxazolidines, the two isomers arising from the possible *exo* transition states being predominant.




**Scheme 3.30.**

After separation (29% yield) of the desired 23*S*,25*S*-isomeric cycloadduct (**357**), the other three isomers were thermally equilibrated (140°C in xylene) back to the four-component mixture. Repetition of this separation–equilibration sequence made it possible to raise the yield of isolated **357** to 71%. The isoxazolidine ring was subsequently quaternarized, hydrogenolyzed, deaminated after diol protection, and routinely transformed into the target molecule (Scheme 3.30).[254/82,168/84]

The examples reported here surely do not exhaust the potential utility of the isoxazolidine ring in synthetic design, and the field is now being explored with increasing intensity. This powerful tool relies essentially on the peculiar property of the 1,3-dipolar cycloaddition of nitrones to an olefin, followed by the hydrogenolytic cleavage of the isoxazolidine ring: stereo- and regioselective formation of a new C–C bond with contemporary oxidation of the $\beta$-carbon atom of the double bond.

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# Index

A26771B, 595
Acetacetaldehyde dimethylacetal, *oximation*, 470
Acetonedicarboxylic esters, 182
β-Acetoxyethylketones, oximation, 470
Acetoxy-2-isoxazolines, 233
5-Acetoxy-2-isoxazolines, 544
Acetylacetone, alkylation, 398
Acetylene, 179
α,β-Acetylenic carbonyl compounds, oximation, 149
Acetylenic Grignard reagents, 208
α,β-Acetylenic nitriles, oximation, 154
α,β-Acetylenic oximes, 152, 183, 487
Acetylenic salts, 208
Acetylsulfisoxazole, 41, 120, 124
Acivicin, 427, 453, 460
Acrylamide, 521
Acrylic esters, 516
Acrylonitrile, 521
Active methylene compounds, sodium salts, 203
2-Acylaziridines, 641
Acyl-2*H*-azirines, 263
3-Acyl-1-azirines, 342
3-Acyl-1*H*-1,5-benzodiazepin-2(3*H*)-ones, 369
2-Acylbenzofurans, 248
2-Acylcycloalken-3-ols, 593
3-Acyl-5,6-dihydro-2-pyridone, 393
Acyl fulmides, 483
Acylimidazoles, 353
3-Acylisoxazoles, 305
  arylhydrazones, 357
  oximes, 356
5-Acylisoxazolidines, 736
*N*-Acylisoxazolidines, 737, 744
Acyl-2-isoxazolines, mass spectra, 447
  PMR spectra, 429
3-Acyl-2-isoxazolines, 539
5-Acyl-2-isoxazolines, 513, 525, 554, 601
4-Acylisoxazolin-5-ones, 246
2-Acyl-3-keto esters, oximation, 136
Acylphosphoranes, 207
Acyl-*N*-(1-pyridinio)vinylaminides, 218
3-Acylpyrroles, 345
Acylvinylsulfinimines, 218
Adaline, 762
Aerothionin, 418, 434, 450, 452, 456
Aldol synthesis, 585
Aldoxime dihydromers, 482
Aldoximes, dehydrogenation, 477
Alka-1,4-dion-2-ols, 599
Alkaloids, 754
Alkenes, acylation, 591
  *cis*-carboxyhydroxylation, 598
  *cis*-cyanohydroxylation, 584
1-Alkenes, 505
3-Alkoxy-5-amino-4-cyanoisoxazoles, 169
5-Alkoxy-3-aminoisoxazoles, 169
β-Alkoxy-α,β-ethylenic carbonyl compounds, oximation, 161
β-Alkoxy-α,β-ethylenic nitriles, oximation, 169
Alkoxyisoxazoles, 21, 84
5-Alkoxyisoxazoles, 342
  thermolysis, 288
5-Alkoxyisoxazolidines, 732, 734, 746
*N*-Alkoxyisoxazolidines, 614, 660, 710, 735, 737, 745
5-Alkoxy-2-isoxazolines, 233, 472, 544
*C*-Alkyl-*N*-arylnitrones, 696
Alkylarylisoxazoles, 17, 29, 65
Alkylidene-2-isoxazolines, rearrangements, 239
Alkylisoxazoles, 8, 26, 61, 283
4-Alkylisoxazoles, 166
2-Alkylisoxazolidine-3,3-dicarboxylates, 709
Alkylisoxazolines, 543
Alkyl nitronates, *see* Nitronic esters
*N*-Alkylnitrones, 693
Allene, 202
Allenes, 202, 509
Allenic carboxylates, 517
Allethrone, 597
*dl*-Allosedamine, 755
Allyl alcohols, 510
Allyl bromides, acylation, 599
  α-aminoalkylation, 599
Allyl ethers, 510
Allyl halides, 511
α-Aminoacids, 379
1,3-Amino alcohols, 278, 561, 563, 574
3-Amino alcohols, 734
5-Amino-3-aryl-4-methylene-2-isoxazolines, 434

2-Aminochromone, 359
4-Amino-4-deoxyarabinose, 579
5-Amino-5-deoxyidose, 578
3-Amino-3-deoxypyranoses, 771
2-Amino-2-deoxyxylose, 579
δ-Amino-α,β-ethylenic aldehydes, 581
3-Aminoisoxazole, 220
Aminoisoxazoles, 21, 36, 39, 200, 385
  tautomerism, 6, 23,101
3-Aminoisoxazoles, 146, 148, 154, 164, 388
4-Aminoisoxazoles, 81, 269, 385
5-Aminoisoxazoles, 145, 146, 171, 224, 277, 280, 283, 308, 342, 352, 388
  photolysis, 296
  thermolysis, 289
3-Amino-2-isoxazolines, 427, 468, 540, 541
  tautomerism, 427
4-Amino-2-isoxazolines, 471
5-Amino-2-isoxazolines, 488, 519, 545
  deamination, 235
5-Aminooxazoles, oximation, 537
*m*-Aminophenols, 410
3-Aminopropionitrile, oxidation, 218
3-Aminopyrroles, 344
Aminosugars, 427, 576
Antibiotic A26771B, 595
Antibiotic AT-125, 418, 537, 548
  PMR spectra, 427
Antibiotic U-42, 126, 452, 460
Antibiotic U-43, 418, 452, 460, 795
Antimycin $A_3$, 589
Arndt-Eistert reaction, 379
5-Aroylisoxazoles, 280
*C*-Aroyl-*N*-arylnitrones, 705
Arylacetylenes, 183
Arylacetylides, sodium salts, 207
*C*-Aryl-*N*-alkylnitrones, 697
Arylheteroarylisoxazoles, 27
3-Aryl-4-hydroxy-2-isoxazolines, 469
Arylideneacetones, oximation, 464
Arylisoxazoles, 10, 27, 62, 68
4-Arylisoxazoles, 166
5-Arylisoxazoles, 127, 515
*N*-Arylisoxazolium salts, 220
Arylquinolizidinols, 757
Arylthio-2-isoxazolines, 449
AT-125, 418, 537, 548
  PMR spectra, 427
Avermectin, 576
8-Azaprostaglandins, 414
Azetidine *N*-oxides, 732
1-Azetine-1-oxides, 733
Azidoisoxazoles, 390
5-Azido-2-isoxazolines, 238
Azidostyrenes, 521
α-Azidovinyl ketones, 220
β-Azidovinyl ketones, 218
Aziridines, 569
1-Azirine-3-carboxamides, 342
1-Azirine-3-carboxylic esters, 342
1,2-Azole, 2
Azomethine-ylids, 641

Banfield and Kenyon radical, 753
Bastardin-1, 602
Beckmann rearrangement, 236, 376, 463, 554, 566, 567, 569
Benzensolfonylcarbonitrile oxide, 516
Benzonitrile oxide, 476, 492
Benzylamine analgesics, 776
Bicyclo[3.2.1]oct-6-en-2-ones, 776
Bikaverin, 413
Biotin, 579, 767
α-Bisabolols, 775
Bis-(β-benzoylethyl)-hydroxylamine, 462
Bisnitrones, 709
Blastmycinone, 589
Bullatenone, 599
1,3-Butadiynes, oximation, 174
γ-Butyrolactams, 413

Calythrone, 597
L-Canaline, 529
Cannizzaro reaction, 378
Captopril, 770
Carbapenem antibiotics, 582, 766
Carpetimycin A, 584
Catharanthine, 765
Chalcone dibromides, oximation, 469
Chalcone epoxides, oximation, 173, 470
Chalcones, 514
  oximation, 172, 464
Chanoclavine I, 580, 764
3-Chloro-2-isoxazolines, 537
5-Chloro-2-isoxazolines, 474
α-Chloroketoximes, 218
α-Chlorooximes, 524
β-Chlorovinyl ketones, 515
  oximation, 159
Chromone, oximation, 538
Chromones, 255, 359
Cinnamaldehyde, 514
Cinnamic esters, 516
Cinnamonitrile, 521
Cinnamoylacetaldehyde, oximation, 467
Cinnamylideneacetophenone, oximation, 467

Citraconic esters, 517
Claisen condensation, 332
Claisen rearrangement, 240, 241, 512, 546
Cloxacillin, 97, 98, 204
Cloxacillinsulfoxide, 97
Cobyric acid, 416
*dl*-Cocaine, 761
*dl*-Croalbinecine, 755
Crotonic esters, 516
(±)Cryptopleurine, 758
Curcumin, 395
Curtius reaction, 237, 384, 554
Cyanoacetone, 343
α-Cyanocarbonyl compounds, 299
α-Cyanoesters, 203
Cyanohydrins, 565, 569
Cyanoisoxazoles, 391
4-Cyanoisoxazoles, 277
α-Cyanoketones, 393, 569
1,5-Cyclization, 533
Cyclopropanes, nitrosation, 473
Cyclopropenes, chloronitrosation, 474
Cycloreversion, 243, 761
Cytarabine, 394
Cytosine, 369

β-Damascone, 275, 396
γ-Damascone, 396
Daunosaminide, 771
Dehydrofukinone, 402
$\Delta^{9(11)}$Dehydrotestosterone, 406
12-Deoxyanhydrotetracycline, 407
2-Deoxy-D-ribose, 585
Deoxysugars, 774
β-Dialdehydes, oximation, 126
5,5-Dialkoxy-2-isoxazolines, 512
β-Dialkylamino-α,β-ethylenic carbonyl compounds, oximation, 165
*C,N*-Dialkylnitrones, 694
3,5-Diaminoisoxazole, 148
2,4-Diaminopyrimidines, 369
Diaroylfuroxans, 251
Diarylisoxazoles, 27
3,5-Diarylisoxazoles, 183
3,5-Diaryl-2-isoxazolines, 465, 543
*C,N*-Diarylnitrones, 635, 699
Diastereofacial selection, 691
Diazines, 366
Diazomethane, 537
*trans*-1,2-Dibenzoylethylene, 514
γ-Dicarbonyl compounds, 176
Dicloxacillin, 7, 97, 98, 123, 204
Dicyanoketene acetals, oximation, 169
Diels–Alder cycloaddition, 552, 553
Dienes, 506, 717
  acylation, 591
3,3-Diethoxycarbonylisoxazolidines, decarboxylation, 535
α,β-Dihalocarbonyl compounds, oximation, 155
2,3-Dihydro-4*H*-benzopyran-4-ones, oximation, 538
Dihydrocinerolone, 597
Dihydroisoxazole, 417
5,6-Dihydro-4*H*-1,2-oxazines, 470
2,3-Dihydro-4-pyrones, 359
3,5-Dihydroxyisoxazole, 117
  tautomerism, 35, 102
4,5-Dihydroxy-2-isoxazolines, 450, 511, 530
Dihydrojasmone, 599
β,β′Dihydroxyketones, 591
3,3′-Diisoxazole, 6, 25, 181, 194, 304
5,5′-Diisoxazole, 6, 25
Diisoxazoles, 6, 14, 70, 93, 96, 139, 208, 336
4,5′-Diisoxazoles, 279, 362
5,5′-Diisoxazoles, 301
3,3′-Diisoxazoline, 453, 540
5,5′-Diisoxazoline, 507, 560
Diisoxazolines, 453
Diisoxazolylalkanes, 195
Diketene, 707
2,4-Diketo esters, oximation, 137
Diketohydroxylamines, 465
α-Diketones, 570, 601
β-Diketone dioximes, 142, 465
β-Diketone monoimines, 143
β-Diketone monoximes, 140
β-Diketones, 142, 203, 362
  oximation, 129, 471
1,4-Diketones, 396, 599
1,4-Dilithium salts oximes, 215
Dimethyldiisoxazolone, 362
Dimethylglyoxime, 570
3,5-Dimethylisoxazole, 324
Dimethyl phenacylsulfonium bromide, nitrosation, 483
1,3-Dinitroalkanes, 607
2,4-Dinitroglutaric esters, 609
1,4,2,5-Dioxadiazines, 485
1,3,2,4-Dioxathiazole-2-oxides, thermolysis, 482
3,5-Diphenyl-2-isoxazoline, 461
1,5-Dipolar cyclization, 642
1,3-Dipolar cycloaddition, 183, 475, 553, 630, 686, 722
  mechanism, 489
1,3-Dipolar cycloreversion, 693, 738

1,3-Dipoles, 475
Disic acid, 102, 117
Dislite, 1, 178, 350
3,3-Disubstituted *N*-alkoxyisoxazolidines, 711
Disubstituted isoxazoles, 33, 188
3,4-Disubstituted isoxazoles, 216, 233, 245
3,5-Disubstituted isoxazoles, 130, 155, 173, 216, 233, 246, 286, 306
4,5-Disubstituted isoxazoles, 159, 302
4,4-Disubstituted isoxazolidines, 702
5,5-Disubstituted isoxazolidines, 694, 698, 700
3,5-Disubstituted 2-isoxazolines, 425, 441, 509, 510, 560
4,5-Disubstituted 2-isoxazolines, 441
5,5-Disubstituted 2-isoxazolines, 441, 538

*dl*-Elaeocarpine, 759
*dl*-Elaeokanine A, 759
*dl*-Elaeokanine C, 759
Elasnin, 139, 254
Enamines, 200, 488, 519
β-Enaminoaldehydes, 560
β-Enaminoketones, 273, 278
α,β-Enones, 275, 568, 775
β,γ-Enoximes, 567
Enynes, 501, 508, 717
*d*-Equilenin, 400
Estr-4-ene-3,17-dione, 406
Ethylene, 505
Ethylenes:
  1,1-disubstituted, 506
  1,2-disubstituted, 506
α,β-Ethylenic aldehydes, 177, 774
  oximation, 462
α,β-Ethylenic carbonyl compounds, oximation, 157, 171, 461, 725
α,β-Ethylenic ketones, 177, 461, 514
  oximation, 461, 637
α,β-Ethylenic ketoximes, oxypalladation, 225
α,β-Ethylenic nitriles, oximation, 468
α,β-Ethylenic oximes, 568
  cyclization, 467
  oxidative cyclization, 226
  thermolysis, 467
α,β-Ethylenic sulfones, 518
α,β-Ethylenic sulfoxides, 518
α,β-Ethylenic thioethers, 517
Ethynyl-2-isoxazolines, 508
Ethynyl ketones, 219
Eulite 1, 178

Face selectivity, 498
Ferruginol, 409
Fistularin-1, 418
Fistularin-2, 418
Fistularin-3, 418
Fistularins, 434, 460
Flucloxacillin, 97
Formonitrile oxide, *see* Fulminic acid
Friedel–Crafts acylation, 379
Friedel–Crafts alkylation, 375
Frontier orbital theory, 476, 490, 631, 687
Fulminic acid, 180, 186, 476, 505, 516
  generation, 483
Fumaric esters, 517
3(2*H*)-Furanones, 344, 598
Furazan-*N*-oxides, 478, 481, 484
Furazans, 482
Furoxans, 478, 481, 484

3-*epi*-Gentosamine, 771
(+)-Gingerol, 400, 590
Glutacondialdehyde, oximation, 466
Glutarimide antibiotics, 407
Glycosylisoxazoles, 31, 40, 191
Glycosylisoxazolidines, 658
Grignard reagents, 333, 378, 555, 622

β-Halo-α,β-ethylenic aldehydes, oximation, 159
β-Halo-α,β-ethylenic nitriles, oximation, 168
β-Haloethylketones, oximation, 469
3-Haloisoxazole, 221
Haloisoxazoles, 75, 280, 319, 337
Halo-2-isoxazolines, dehydrohalogenation, 230, 544
Halopropanes, nitrosation, 473
Hammett correlations, 30, 188, 426, 490, 509, 545, 683, 688
Hentriacontane-14,16-dione, 398
Hetero-Cope rearrangement, 645, 742
Hexaisoxazole, 6
Histrionicotoxin, 763
Hofmann elimination, 241, 555
Hofmann rearrangement, 384
Homoaerothionin, 418
Hunsdiecker reaction, 338
5-Hydrazinoisoxazoles:
  photolysis, 296
  thermolysis, 291
Hydroximoyl chlorides, 203, 207
  dehydrohalogenation, 478
β-Hydroxy acids, 588

γ-Hydroxy-α-aminoacid lactone, 736
γ-Hydroxy-α-aminoacids, 561, 574
β-Hydroxycarboxylic acids, 570
2′-Hydroxychalcones, oximation, 465
Hydroxycotinine, 774
β-Hydroxycyclopentenones, 595, 597
2-Hydroxy-1,4-diketones, 562, 595
*N*-Hydroxyenamines, ring-chain equilibrium, 722
γ-Hydroxyglutamic diesters, 561
Hydroxyisoxazoles, 21, 35, 78, 338
4-Hydroxyisoxazole, 3
3-Hydroxyisoxazoles, 145, 153, 280, 319
  tautomerism, 6, 23, 101
4-Hydroxyisoxazoles, 511
  tautomerism, 6, 23
5-Hydroxyisoxazolidines, 725
  tautomerism, 741
Hydroxy-2-isoxazolines, dehydration, 231, 544
3-Hydroxy-2-isoxazolines, 468
4-Hydroxy-2-isoxazolines, 231, 468, 470, 550
5-Hydroxy-2-isoxazolines, 141, 231, 419, 471, 533, 554
  mass spectra, 444
  PMR spectra, 435
  tautomerism, 471
β-Hydroxyketones, 561, 562, 585
β-Hydroxyketoxime, cyclization, 470, 527
α′-Hydroxy-β-lactams, 561
5-Hydroxylaminoisoxazolidines, ring-chain equilibrium, 722
Hydroxylamino ketones, 465
Hydroxylamino oximes, 465
Hydroxyphthalides, 410
4-Hydroxyproline, 770
2-Hydroxypyrrolidine, 345
3-Hydroxypyrrolidine, 736
3-Hydroxypyrrolidin-2-ones, 736
5-Hydroxy-2-pyrrolin-4-ones, 570
*N*-Hydroxyurea, 154, 157, 171, 462, 468, 727
Hymexazole, 153
(+)Hypusin, 771

Ibotenic acid, 2, 6, 39, 85, 123, 153, 287, 347
4-Imidazolin-2-ones, 353
Imidazolo[3,1-*b*]thiazoles, 370
β-Iminonitriles, oximation, 147
Indole alkaloids, 764
Indolizidine alkaloids, 759
Invertomers, 661, 676, 679, 713, 717
2-Iodo-3-azido ketones, 220
β-Ionone, 275, 396
γ-Ionone, 396
Ipalbidine, 759
Isocarboxazide, 23, 87, 92, 124
Isocyanates, 485
Isocyanato-2-isoxazolines, 237
*dl*-Isoelaeocarpicine, 759
*dl*-Isoelaeocarpine, 759
Isonitrosophenylisoxazolinone, pyrolysis, 484
8-Isoquinolol, 363
*dl*-Isoretronecanol, 755
α-Isosparteine, 757
Isothiazoles, 348
Isouron, 24, 124
Isoxazole, 2, 3, 6, 8, 24, 45, 55, 59, 62, 90, 103, 106, 107, 109, 110, 111, 114, 118, 119, 150, 159, 164, 186, 199, 245, 294, 298, 335, 337
Isoxazole carbonyl compounds, 18, 79
Isoxazole carboxaldehydes, 340
Isoxazole carboxamides, 383
Isoxazole carboxylic acids, 18, 77, 137, 143, 284
Isoxazole carboxylic esters, 77, 190
Isoxazole 4-carboxylic esters, 203
Isoxazole complexes, 24, 44, 90, 98, 118, 120, 268
  metallic complexes, 121, 268
  molecular complexes, 273
Isoxazole diazonium salts, 390
Isoxazole nitriles, 18
Isoxazoles:
  acylation, 329
  alkylation, 327
  analytical methods, 121
  arylation, 371
  basicity, 5, 107, 114
  carboxylation, 328
  chemical properties, 264
  $^{13}$C-NMR spectra, 45
    chemical shifts, 46, 49, 50
    coupling constants, 48, 54
  dipole moments, 98, 107
  electrophilic additions, 373
  electrophilic substitutions, 334
  elimination reactions, 374
  EPR spectra, 90
  ESR spectra, 90
  $^{19}$F-NMR spectra, 58
  fluorescence spectra, 92

Isoxazoles (*Continued*)
formylation, 340
GLC analysis, 122
halogenation, 337
homolytic, 372
hydrogenolysis, 273
IR spectra, 3
isomerization, 299
as key intermediates, 391
magnetic susceptibility, 119, 121
mass spectra, 59
mercuriation, 340
metallation, 324
microwave spectra, 88
nitration, 335
$^{14}$N-NMR spectra, 55
$^{15}$N-NMR spectra, 55
nomenclature, 2
NQR spectra, 91
$^{17}$O-NMR spectra, 58
oxidation, 284
ozonolysis, 284
PES, 88
photolysis, 293
physicochemical properties, 3
PMR spectra, 24
coupling constants, 44
substituents chemical shifts, 37
protonation, 265
quaternization, 265
Raman spectra, 3
reactions, with nucleophiles, 298
reactivity, 264
reduction, 281
ring transformations, 341
substitution reactions, 374
sulfonation, 337
syntheses, cyclization processes, 218
from acetylenes, 179
from γ-dicarbonyl compounds, 176
from 1,3-dicarbonyl compounds, 126
from α,β-ethylenic carbonyl compounds, 177
from heterocyclic compounds, 227
from 2-isoxazolines, 543
from nitrile oxides, 183, 196, 203, 207
from nitro derivatives, 209
from oxime dilithium salts, 215
theoretical calculations, 103, 110
ionization potentials, 109
molecular geometries, 106
thermolysis, 285
TLC analysis, 122
UV spectra, 7, 15
x-ray analysis, 92
Isoxazolidine, 649, 651, 671, 683, 729, 750
hydrobromide, 651
Isoxazolidine 5-carboxylates, 711
Isoxazolidine 3-carboxylic acids, 731
Isoxazolidine invertomers, 661, 676, 679
Isoxazolidine *N*-ribosides, 694
Isoxazolidines, acylation, 752
alkylation, 750
basicity, 683
circular dichroism, 684
$^{13}$C-NMR spectra, 666, 680
conformational analysis, 660, 679, 713
decomposition by acids, 744
decomposition by bases, 747
decomposition to carbonyl compounds, 744
dehydrogenation, 534
dipole moments, 678
elimination, 742
ESR spectra, 675
$^{19}$F-NMR spectra, 669
GLC analysis, 684
hydrogenolysis, 734
IR spectra, 650
invertomers, 661, 676, 679, 713, 717
as key intermediates, 753
mass spectra, 670
NMR spectra, 650
$^{15}$N-NMR spectra, 669, 683
nomenclature, 649
nucleophilic reactivity, 750
oxidation, 737
PES spectra, 675
photolysis, 744
physicochemical properties, 649
PMR spectra, 651, 680
coupling constants, 651
lanthanide shift , 666
$^{31}$P-NMR spectra, 670
reactions, 733, 742, 744
rearrangement, 247
syntheses, 685
from *C*-alkyl-*N*-arylnitrones, 696
from *N*-alkylnitrones, 693
from *C*-aroyl-*N*-arylnitrones, 705
from *C*-aryl-*N*-alkylnitrones, 697
by cyclization methods, 728
from *C,N*-dialkylnitrones, 694
from *C,N*-diarylnitrones, 699, 704
from 1,3-dihalo compounds, 725
from α,β-ethylenic compounds, 725

from heterocyclic compounds, 730
from nitrones, 686
from nitronic esters, 710
from oximes, 722
from trisubstituted nitrones, 709
theoretical calculations, 683
thermolysis, 738
decomposition to carbonyl compounds, 744
elimination, 742
TLC analysis, 684
UV spectra, 650
x-ray analysis, 675
Isoxazolidinium salts, 660, 728, 733
2-Isoxazoline, 421, 457, 462
2-Isoxazoline carbinols, 535
2-Isoxazoline 4-carboxylates, 516
2-Isoxazoline carboxylic acids, 487
decarboxylation, 553
Isoxazolines, nomenclature, 417
2-Isoxazolines, addition reactions, 551
alkylation, 531, 550
basicity, 458
$^{13}$C-NMR spectra, 436
methyl chemical shifts, 439
cycloaddition reactions, 552
dehydrogenation, 227, 543
dipole moments, 456
elimination reactions, 544
$^{19}$F-NMR spectra, 440
hydrogenation, 553
hydrogenolysis, 561
IR spectra, 418
as key intermediates, 572
mass spectra, 441
metallation, 531
ozonolysis, 572
photocycloaddition, 552
photolysis, 559
physicochemical properties, 418
PMR spectra, 421, 458
coupling constants, 431
polymers, 522
quaternization, 541
reactions, in the side chain, 553
with nucleophiles, 569
with ring cleavage, 557
without ring cleavage, 540
resolution, 555
stereoisomerism, 555
substitution at the ring atoms, 548
syntheses, 460
from 5-aminooxazoles, 537
from chalcone epoxides, 470
from α-chlorooximes, 524
by cyclization processes, 525
from cyclopropanes or cyclopropenes, 473
from β-diketones, 471
from α,β-ethylenic carbonyl compounds, 461
from α,β-ethylenic nitriles, 468
from β-haloethylketones, 469
from halopropanes, 473
from isoxazoles, 530
from isoxazolidines, 534
from 3-isoxazolines, 533
from isoxazolin-5-ones, 533
from nitrile oxides, 475, 504
from α-nitrooximes, 525
from *N*-nitrosopyrazolines, 537
from six-membered heterocycles, 538
thermodynamic properties, 459
thermolysis, 557
TLC analysis, 459
UV spectra, 419
x-ray analysis, 452
2-Isoxazolines condensed, cycloreversion, 243
3-Isoxazolines, 621
spectroscopic data, 625
2*H*-3-Isoxazolines, 533
4-Isoxazolines, 464, 625
addition reactions, 647
$^{13}$C-NMR spectra, 629
hydrogenation, 646
IR spectra, 626
mass spectra, 630
physicochemical properties, 626
PMR spectra, 626
reactions, 641
stability, 634
syntheses, from α,β-ethylenic ketones, 637
from isoxazolidines, 639
from isoxazolium salts, 638
from nitrones, 630
thermolysis, 641
UV spectra, 626
2-Isoxazoline *N*-oxides, 603
dehydration, 247, 615
deoxygenation, 531, 615
IR spectra, 605
mass spectra, 607
oxidation, 618
physicochemical properties, 603

2-Isoxazoline *N*-oxides (*Continued*)
PMR spectra, 605
reactions, 614
with Grignard reagents, 618
rearrangements, 619
reduction, 617
syntheses, 607
from diazoalkanes, 612
from 1,3-dinitroalkanes, 607
from 3-halo-1-nitroalkanes, 610
from ylides, 612
UV spectra, 603
2-Isoxazolinium salts, 541, 621, 730, 733
reduction, 731
UV spectra, 420
2-Isoxazolin-5-ols, *see* 5-Hydroxy-2-isoxazolines
Isoxazolin-3-ones, 541
Isoxazolin-5-ones, 144, 533
tautomerism, 6, 23, 51, *101*
Isoxazolinyl sulfones, 239
Isoxazolinyl sulfoxides, 239
2-Isoxazolin-5-yl-triazenes, 467
Isoxazolium salts, 42, 128, 265, 638
decomposition, 293
reaction with nucleophiles, 309
reduction, 283, 541, 730
Isoxazolizidines, 614, 650
Isoxazolo[4,5-*b*]pyrazines, 387
Isoxazolyl-2-isoxazolines, 451
Isoxazolylpenicillins, 7, 40, 53, 97, 123, 193, 204
Isoxicam, 87, 124

Johnson's synthesis, 400
(±)Julandine, 758

Ketene aminals, 200
Ketene dialkylacetals, 702
β-Ketoaldehydes, oximation, 127
γ-Ketoaldehydes, 562, 599
γ-Ketocarboxylic esters, 598
β-Keto esters, 203, 279
oximation, 143
β-Ketonitriles, 203
oximation, 145
Knoevenagel condensation, 378

β-Lactam antibiotics, 765
β-Lactams, 413, 581, 637, 640, 767
γ-Lactams, 767
δ-Lactams, 767
β-Lactones, 413
Lankacidin, 769
Lasubine, 757
Lividosamine, 577
*dl*-Luciduline, 763
Lupinine, 756, 757
γ-Lutidones, 362
Lycopodium alkaloids, 763

Maleic anhydride, 517
Maleic *N*-arylimides, 517
Maleic esters, 517
Malononitrile, oximation, 148
Mannich bases, 393, 513
oximes, 525
Mannich reaction, 332, 378
Maytansine, 588
Meerwein–Ponndorf reaction, 553
3-Mercaptoisoxazoles, 391
tautomerism, 6, 23
Mesaconic esters, 517
Mesityl oxide, oximation, 462
1-Methoxybutenyne, oximation, 175
Methoxyisoxazoles, 35
Methoxyisoxazolidines, 682
α-Methyl acosaminide, 771
4-Methyleneisoxazolidines, 740
4-Methylene-2-isoxazolines, 512
5-Methylene-2-isoxazolines, 547
α-Methylene-γ-lactones, 598
4-Methylenepyrans, oximation, 538
Methylisoxazoles, 5, 62
Methylisoxazolidines, 657
Methyl-2-isoxazolines, 564
Michael addition, 167, 168, 329, 332, 374, 381, 393, 406, 610, 726, 727, 758
Micophenolic acid, 413
Milbemycin, 576
Monoalkylacetylenes, 184
Monoarylacetylenes, 184
Monocyanoketene acetals, oximation, 169
Monosaccarides, 769
Monosubstituted isoxazoles, 32
3-Monosubstituted isoxazoles, 179, 208, 216, 301
4-Monosubstituted isoxazoles, *126*
5-Monosubstituted isoxazolidines, 694
3-Monosubstituted 2-isoxazolines, 462, 469, 524
Musca-aurin, 3, 23, 92
Muscarone, 344, 347
Muscimol, 2, 6, 34, 39, 47, 85, 95, 116, 123, 154, 287

Nikkomycin B, 576
Nikkomycins, 575

Nitrile oxides, 183, 203, 475, 490
1,3-addition, 486
dimerization, 484
generation, 476
isomerization, 484
Nitroalkanes, dehydration, 478
Nitroalkenes, 521
Nitroisoxazoles, 20, 82, 335
4-Nitroisoxazoles, 238
Nitroisoxazolidines, 681
Nitro-2-isoxazolines, 237
3-Nitro-2-isoxazoline, 459, 460, 473
3-Nitro-2-isoxazolines, 536
4-Nitro-2-isoxazolines, 521
3-Nitro-2-isoxazoline-*N*-oxide, 459, 603, 620
8-Nitroisoxazolizidines, 535, 678
β-Nitroketones, 221
Nitroolefins, 521
Nitrolic acids, thermolysis, 478
Nitronate salts, dehydration, 479
Nitrone-dimers, 673, 753
Nitrones, 475, 630, 686
dimerization, 721
Nitronic esters, 636, 710
decomposition, 480
α-Nitrooximes, 525
*N*-Nitrosopyrazolines, thermolysis, 537
3-Nitrosopyrroles, 249
α-Nitrosulfones, dehydration, 479
Nogalomycin, 775
Nojirimycin, 771
5-*epi*-Nojirimycin, 578
19-Nor-steroids, 406
*C*-Nucleosides, 399

Octahydrobenz[*f*]isoquinolines, 774
Octaisoxazoles, 6
2-Octalones, 401
Octamethylcorphin, 416
Octamethylcorrin, 416
Oxacillin, 97, 204
Oxacillin penicilloic methyl diester, 97
1,2,4-Oxadiazole-4-oxides, 485
1,2,4-Oxadiazoles, 252, 354
1,2,5-Oxadiazoles, 354
decomposition, 482
5-Oxaprolines, 769
2*H*-1,3-Oxazines, 369
Oxazinomycin, 368
1,2-Oxazin-4-ones, 262
1,2-Oxazin-6-ones, 466
1,3-Oxazin-4-ones, 261
Oxazoles, 250, 347
1,2-Oxazolidines, *see* Isoxazolidines
3-Oxazolines, 560
4-Oxazolines, 641

Paal–Knorr reaction, 386
Paliclavine, 580
(+)-Paliclavine, 765
5-*epi*-Paliclavine, 580
Peptide synthesis, 312
Perfluoroalkyl-2-isoxazolines, 440
Pericyclic reactions, 476
Periselectivity, 504
Perisoxal, 124
$PGE_1$ precursors, 597
Phenolic oximes, cyclization, 528
*m*-Phenylenediamines, 410
γ-Phenylhomoserine, 575
*N*-Phenylnitrone dimer, 656
Phorone, oximation, 463, 726
Phosphonoisoxazolidines, 703
Phosphor ylides, 523
$C_{18}$-Phytosphingosine, 576
Piperidine alkaloids, 754
Polybutadiene, 753
Polyisoxazoles, 14, 175, 194, 208
Polyketones, oximation, 138
β-Polyketones, 400, 409
(±)Porantheridine, 757
(±)Porantherilidine, 757
Porphirins, 346
Progesterone, 402
Propargylamine, 487
Prostaglandin $PGF_{2\alpha}$, 592
Prostaglandins, 597
Prostanoids, 396
Pseudotropine, 761
Pyrazoles, 348
Pyrazolin-5-ones, 352
Pyrazolo[4,3-*b*]pyridines, 370
Pyrazolo[1,5-*a*]pyrimidines, 370
Pyrenophorin, 396, 593
Pyrethrosin, 456
Pyridines, 360
Pyridinium salts, oximation, 261
4-Pyridones, 364
Pyrimidin-4-ones, 368
Pyrimidine *N*-oxides, 258, 260
Pyrimidines, 258
2(1*H*)Pyrimidinones, 259
Pyrimido[1,2-*b*]indazoles, 370
4-Pyrones, 253, 360
Pyrroles, 344, 346, 641
α-Pyrrolidones, 345
Pyrrolizidine alkaloids, 755

Pyrrolo[3,2-*b*]pyridines, 370
Pyrrolo[3,4-*b*]pyridines, 370

Quilico reaction, 475
Quinolizidine alkaloids, 756
Quinoxaline-di-*N*-oxides, 369

Reformatsky reaction, 375, 640
Regiochemistry, 633, 694, 695
Regioisomers, 444, 447, 495, 519, 527, 651, 673, 698
Regioselectivity, 197, 493, 511, 633, 689
Resorcinols, 410
Rethrolones, 595
Retro-Mannich reaction, 237
Retro-Michael reaction, 374
*dl*-Retronecine, 755
(±)Rhodinose, 774
Ritter reaction, 393
Robinson annelation reaction, 401

Sarkomycin, 591
Schiff bases, 385
Schmidt reaction, 236, 376, 554
*dl*-Sedamine, 755
*dl*-Sedridine, 754
Semicorrins, 416
(±)Septicine, 759
Sesquioximes, 128
Silyl nitronates, 720
Site selectivity, 132, 140, 191, 325, 500, 504, 693
Spirocyclohexadienylisoxazoline, 528
Spirodiisoxazolines, 202, 242
4,4′-Spirodiisoxazolines, 547
4,5′-Spirodiisoxazolines, 432, 439, 517, 547, 557, 570
5,5′-Spirodiisoxazolines, 509, 566
Spiroisoxazolidines, 660, 668, 673, 707, 708, 732
Spiroisoxazolines, 232, 339, 431, 513, 528, 550, 562
5-Spiro-2-isoxazolines, 506, 515, 530
Stereoselectivity, 497, 564, 690
Stereospecificity, 496
Steroids, 402
Stevens synthesis, 414
Stilbene, 510
Stork annelation reaction, 401, 402
Styrenes, 509
Subcosine, 757
3-Substituted isoxazoles, 199
4-Substituted isoxazoles, 200
5-Substituted isoxazoles, 150
4-Substituted isoxazolidines, 689
5-Substituted isoxazolidines, 689
3-Substituted 2-isoxazolines, 423, 523
  4-carboxylates, 424
5-Substituted 2-isoxazolines, 441, 494
*N*-Substituted 3-isoxazolines, 624
Sulfamethoxazole, 23, 41, 98, 117, 120, 124, 273
Sulfisomezole, 7, 87
Sulfisoxazole, 23, 40, 98, 117, 120, 124
Sulfisoxazole diolamine, 41
Sulfur ylides, 523, 524
(±)Supinidine, 755
Sustmann's classification, 687
Sustmann's scheme, 490

Talaromycin B, 588
Tergetone, 395
α-Terpineol, 776
Tetracyclines, 407
Tetrahydro-1,2,4-triazin-6-ones, 369
Tetrahydroisoxazoles, *see* Isoxazolidines
Tetraisoxazole, 6
Tetramethylethylene, 506
Tetranitromethane, 718
2,3,4,5-Tetrasubstituted isoxazolidines, 662
2,3,5,5-Tetrasubstituted isoxazolidines, 661
3,4,5,5-Tetrasubstituted 2-isoxazolines, 433, 506
Tetrasubstituted isoxazolium salts, 317
Tetrazoles, 358
1,2,6-Thiadiazine 1,1-dioxides, 368
1,2,4-Thiadiazoles, 358
Thienamycin, 582, 766
*epi*-Thienamycin, 584
Thymine, 368
β-Tosyloxyethylketones, oximation, 470
Trialkylisoxazolium salts, 622
Triarylisoxazoles, 213
1,2,3-Triazoles, 357
1,2,4-Triazoles, 357
*s*-Triazolo[4,3-*b*]pyridazines, 370
Tricholomic acid, 427, 548
1α,25*S*, 26-Trihydroxycholecalciferol, 776
Triisoxazole, 6
Trimethyl-2-isoxazoline, 462
Trimethyl-4-isoxazoline, 463
2-Trimethylsilyloxyisoxazolidines, 742, 749
*C,C,N*-Triphenylnitrone, 709
Trisubstituted isoxazoles, 192, 306
3,4,5-Trisubstituted isoxazoles, 130, 216

2,3,5-Trisubstituted isoxazolidines, 663
3,4,5-Trisubstituted 2-isoxazolines, 428, 506
3,5,5-Trisubstituted 2-isoxazolines, 432, 540
2,3,5-Trisubstituted isoxazolium salts, 317
Triumferol, 3, 34, 47, 85, 116
Tropane alkaloids, 761
*ar*-Turmerone, 395

U-42, 126, 452, 460
U-43, 418, 452, 460, 795
3-Unsubstituted arylisoxazoles, 284
3-Unsubstituted 2-ethoxyisoxazolidines, 741
3-Unsubstituted isoxazoles, 298
5-Unsubstituted isoxazoles, 304
2-Unsubstituted isoxazolidines, 650, 723, 729, 731, 737, 744
3-Unsubstituted 2-isoxazolines, 422, 462, 559, 560, 569
*N*-Unsubstituted 3-isoxazolines, 622
5-Unsubstituted 2-isoxazoline *N*-oxides, 611
3-Unsubstituted isoxazolium salts, 310
5-Unsubstituted isoxazolium salts, 315

Vermiculine, 396, 576, 593
Vilsmeier reaction, 166
Vilsmeier–Haack reaction, 340
Vinyl acetate, 199
Vinylacetylenes, 631, 704
Vinyl esters, 510
Vinyl ethers, 510
Vinyl halides, 511
Vinyl ketones, oximation, 462
Vinylisoxazoles, polymerization, 374
5-Vinylisoxazoles, 508
Vitamin $B_{12}$, 414

Wittig reaction, 378
Woodward–Hoffmann rules, 476
Woodward reagent, 125, 313
Wurtz-type coupling reaction, 374

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