

OXAZOLES

This is the forty-fifth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER AND EDWARD C. TAYLOR

Editors



OXAZOLES

Edited by

I. J. Turchi

FMC CORPORATION
AGRICULTURAL CHEMICALS GROUP
PRINCETON, NEW JERSEY

AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS
NEW YORK · CHICHESTER · BRISBANE · TORONTO · SINGAPORE

An Interscience® Publication

Copyright © 1986 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

Main entry under title:

Oxazoles.

(The Chemistry of heterocyclic compounds,
ISSN 0069-3154; v. 45)

Includes indexes.

1. Oxazoles. I. Turchi, I. J. (Ignatius J.)

II. Series.

QD401.095 1986 547'.592 85-12478

ISBN 0-471-86958-9

Contributors

JONATHAN S. BAUM
FMC Corporation
Agricultural Chemicals Group
Princeton, New Jersey

ROBERT FILLER
Lewis College of Sciences and Letters
Illinois Institute of Technology
Chicago, Illinois

HENRY L. GINGRICH
FMC Corporation
Agricultural Chemicals Group
Princeton, New Jersey

BRUCE E. MARYANOFF
Chemical Research Department
McNeil Pharmaceutical
Spring House, Pennsylvania

CYNTHIA A. MARYANOFF
Chemical Development Department
McNeil Pharmaceutical
Spring House, Pennsylvania

Y. S. RAO
Department of Chemistry
Kennedy-King College
Chicago, Illinois

IGNATIUS J. TURCHI
FMC Corporation
Agricultural Chemicals Group
Princeton, New Jersey

Present address:
Ayerst Laboratories Research
Princeton, New Jersey

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry "as readily accessible as possible," new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

ARNOLD WEISSBERGER

*Research Laboratories
Eastman Kodak Company
Rochester, New York*

EDWARD C. TAYLOR

*Princeton University
Princeton, New Jersey*

Preface

The first synthesis of an oxazole, 2,4,5-triphenyloxazole, was reported over 140 years ago. For 100 years thereafter most of the research on this heterocyclic system revolved around alkyl- and aryloxazoles. In the 1940s, research on the synthesis and structure of penicillin also led to work that shed light on other heterocycles, including oxazoles and oxazolones. During this period, Cornforth and others developed several new syntheses that provided access to a variety of oxazoles bearing carboxylic acid and aldehyde functionalities and heteroatom substituents. With these substances in hand it was possible for these researchers to define the scope of various functional group transformations leading to new oxazole derivatives.

The discovery by Kondrat'eva in the late 1950s that pyridines arise in the Diels–Alder reaction of oxazoles as azadienes with olefins and the application of this process by Firestone to a vitamin B₆ synthesis prompted a great deal of research into the synthesis of oxazoles for use as substrates in this reaction. At about the same time, the monumental work of Huisgen and his collaborators on 1,3-dipolar cycloaddition chemistry led to the synthesis of the first mesoionic oxazoles and the observation that these unusual systems react as masked azomethine ylides in their reactions with acetylenes and olefins, leading to pyrroles and pyrrolines, respectively. These results, as well as an imidazole synthesis from the reaction of oxazoles with ammonia or amines, reported by Gompper and co-workers, demonstrated the relative ease with which oxazoles undergo ring transformations. Thus, oxazoles provide a vehicle for the synthesis of novel, difficultly accessible, and biologically interesting heterocycles and heterocyclic ring-containing natural products. Consequently, over the last 20 years a great deal of effort has been expended in developing new methodology and improving existing processes leading to this important class of heterocyclic compounds. A fascinating, recent advance in oxazole chemistry involves the study of the metalation of the oxazole ring and alkyl substituents and the reactions of these organometallic species with electrophiles. This development should prove useful in the synthesis of various complex oxazole ring-containing macrocyclic antibiotics.

This volume represents a survey of the published work on the synthesis, reactions, and spectroscopy of mononuclear oxazoles, oxazolones, and mesoionic oxazoles. A short chapter on the use of oxazoles and oxazolines in synthesis has been included. Otherwise, a discussion of reduced oxazoles is outside the scope of this volume.

My thanks go to the series editors Edward C. Taylor and Arnold Weissberger and to Stanley Kudzin and the staff of John Wiley & Sons for their help. Thanks are

due also to Nancy Pepper for typing the major portion of the manuscript. I am indebted to my coauthors for their dedication and cooperation. Finally, I dedicate this book with love to my daughter Christiana.

I. J. TURCHI

Princeton, New Jersey
September 1985

Contents

1. OXAZOLES	1
<i>I. J. Turchi</i>	
2. SPECTROSCOPIC PROPERTIES OF OXAZOLES	343
<i>C. A. Maryanoff</i>	
3. OXAZOLONES	361
<i>Y. S. Rao and R. Filler</i>	
4. MESOIONIC OXAZOLES	731
<i>H. L. Gingrich and J. S. Baum</i>	
5. OXAZOLES AND OXAZOLINES IN ORGANIC SYNTHESIS	963
<i>B. E. Maryanoff</i>	
Author Index	1019
Subject Index	1053

OXAZOLES

This is the forty-fifth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

CHAPTER 1

Oxazoles

IGNATIUS J. TURCHI

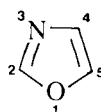
FMC Corporation, Agricultural Chemicals Group, Princeton, New Jersey

1.1.	Introduction	2
1.2.	Synthesis and Reactions of Alkyl-, Aryl-, and Aralkyloxazoles	3
1.2.1.	From 2-Acylaminoketones	3
1.2.2.	From 2-Ketonitriles	6
1.2.3.	From Isonitriles	7
1.2.4.	From Aldehydes and Cyanohydrins	10
1.2.5.	From 2-Hydroxyketones and Formamide	10
1.2.6.	From 2-Acyloxyketones and Ammonium Acetate	10
1.2.7.	From 2-Haloketones and Amides or Ammonium Salts	11
1.2.8.	From 2-Hydroxyketones or 2-Haloketones and Nitriles	13
1.2.9.	From Propargyl Amides	14
1.2.10.	From Nitriles and Propargyl Alcohols and from <i>O</i> -Propargyl Imidates	15
1.2.11.	From Ketoximes and Acyl Halides	16
1.2.12.	From 2-Azidoketones, Acyl Halides, and Triphenylphosphine	17
1.2.13.	From Carbonyl Carbenes and Nitriles	18
1.2.14.	From Isoxazoles and from Azirines	18
1.2.15.	Oxidation of Oxazolines	21
1.2.16.	From Oxazolinones	22
1.2.17.	Deoxygenation of Oxazole <i>N</i> -oxides	24
1.2.18.	Ring and Side-Chain Metalation	24
1.2.19.	Functionalization of Phenyl Substituents	28
1.2.20.	Miscellaneous	33
1.3.	Synthesis and Reactions of Functionalized Oxazoles	36
1.3.1.	Halooxazoles	36
1.3.2.	Oxazole Esters and Their Derivatives	43
1.3.3.	Halooxazole Esters	55
1.3.4.	Alkoxyoxazoles and Acyloxyoxazoles	56
1.3.5.	Alkyl- and Arylthiooxazoles	66
1.3.6.	Formyloxazoles and Their Derivatives	74
1.3.7.	Ketooxazoles and Their Derivatives	78
1.3.8.	Aminooxazoles and Their Derivatives	82
1.3.9.	Nitrooxazoles	103
1.3.10.	Phosphorus-substituted Oxazoles	104
1.3.11.	Miscellaneous Oxazole Derivatives	105
1.3.12.	Oxazole <i>N</i> -Oxides	106
1.3.13.	Oxazolium Salts	106
1.4.	Naturally Occurring Oxazoles	109
1.5.	Reaction of Oxazoles with Singlet Oxygen	111
1.6.	Ring Transformations of Oxazoles	113

1.6.1.	Oxetanes	113
1.6.2.	Furans and Tetrones	114
1.6.3.	Pyrroles and Pyrrolidines.	117
1.6.4.	Imidazoles and Thiazoles.	119
1.6.5.	Pyrazoles and Isoxazoles	123
1.6.6.	Triazoles and Dioxazoles.	125
1.6.7.	Pyrones and Coumarins	126
1.6.8.	Pyridines and Isoquinolines	127
1.6.9.	Pyrimidines, Quinazolones, and Oxazinones.	134
1.6.10.	1,2,4-Triazines.	135
1.6.11.	Cyclopentadienes	136
1.7.	Systematic Survey of Oxazole Derivatives	137
1.7.1.	Scope of the Survey	137
1.7.2.	Abbreviations	137
1.8.	Addendum.	319

1.1. INTRODUCTION

The chemistry of oxazole (1) and its derivatives has been the subject of several



1

reviews.¹⁻⁶ Wiley's review (1945)¹ gives a historical account of oxazole chemistry, while Cornforth's review (1957)² includes much of his and his collaborators' work on alkoxy- and aminooxazoles and derivatives of oxazole carboxylic acids and aldehydes. This work with experimental details appeared in *The Chemistry of Penicillin*.³ The last three reviews published in 1974,⁴ 1975,⁵ and 1980⁶ provide coverage of modern oxazole chemistry including new syntheses, reactions, spectroscopy, and commercial applications.

This chapter is designed to provide a detailed, comprehensive description of the synthetic methods leading to monocyclic oxazoles and reactions of these species reported up to 1982. Oxazolinones and mesoionic oxazoles are discussed in Chapters 3 and 4, respectively. The second and third sections of this chapter are organized according to the types of functional groups present on the oxazole ring. Both the synthesis of these systems and reactions where the oxazole ring remains intact as well as where acyclic products arise are treated here.

A section involving naturally occurring oxazoles has been included. Only a few oxazoles have been derived from natural sources. The simplest of these have been prepared, while considerable effort is being expended in developing the technology required for the total synthesis of complex oxazole-containing antibiotics such as griseoviridin and virginiamycin.

The reaction of oxazoles with singlet oxygen has been applied to the total synthesis of several macrocyclic lactone natural products and dipeptide derivatives.

This fascinating and useful aspect of oxazole chemistry is discussed in Section 1.5.

The conversion of oxazole derivatives to other heterocyclic systems is another intriguing facet of oxazole chemistry. Not only have these ring transformations received a great deal of attention in heterocyclic synthesis but they have also been utilized in the total synthesis of several heterocyclic natural products. Thus these interconversions are outlined in Section 1.6 in detail both from a synthetic and mechanistic standpoint.

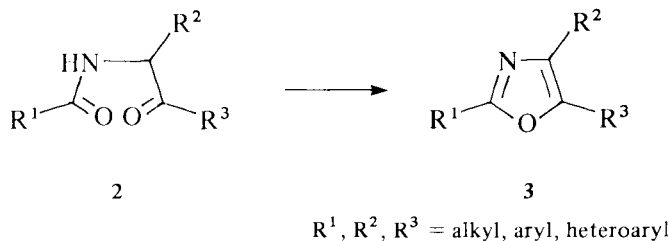
Finally, an extensive list of oxazole derivatives has been tabulated along with literature references to their preparation. An addendum covering novel chemistry and new applications of oxazoles reported in 1983 is included.

Only monocyclic oxazoles are treated in this volume.

1.2. SYNTHESIS AND REACTIONS OF ALKYL-, ARYL-, AND ARALKYLOXAZOLES

1.2.1. From 2-Acylaminoketones

The cyclodehydration of 2-acylaminoketones **2**, that is, the Robinson–Gabriel synthesis, is one of the oldest yet most versatile syntheses of 2,5-di- and 2,4,5-trialkyl, aryl-, heteroaryl-, and aralkyloxazoles **3** (Tables 1.2 and 1.3).^{*} Cyclo-



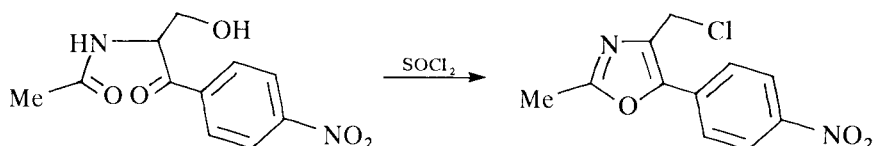
dehydration reagents which allow this transformation include concentrated sulfuric acid, phosphorus pentachloride, phosphorus pentoxide, phosphoryl chloride, thionyl chloride, phosphoric acid–acetic anhydride, polyphosphoric acid, and anhydrous hydrogen fluoride.^{5,6} The yields of oxazoles are generally fair to very good. A variety of functional groups present on the alkyl or aryl substituents R^1 – R^3 survive the reaction conditions unscathed provided the proper dehydrating agent is employed. Several examples are listed in Table 1.1.

When a free hydroxyalkyl functionality is present on the 2-acylaminoketone and thionyl chloride or phosphoryl chloride is the dehydrating agent, the chloroalkyloxazole is produced in low yield.⁷

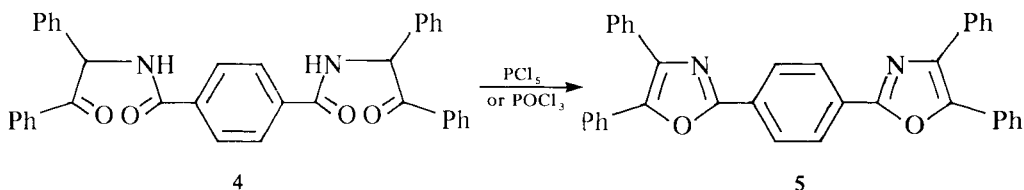
^{*}Tables 1.2 through 1.63 can be found in Section 1.7.1.

TABLE 1.1. SIDE-CHAIN-SUBSTITUTED OXAZOLES PREPARED BY THE ROBINSON-GABRIEL SYNTHESIS

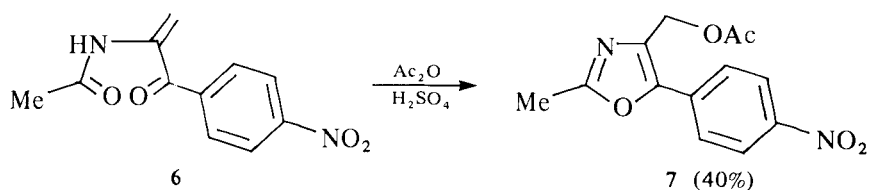
R ¹	R ²	R ³	Conditions	Reference
Me	CH ₂ OH	4-NO ₂ Ph	H ₂ SO ₄	7
CH ₂ Cl	H	Ph	H ₂ SO ₄	8
CH ₂ Br	Ph	Ph	POCl ₃	9
Ph	PhCH ₂	(CH ₂) ₂ CO ₂ Me	POCl ₃	10
Ph	CH ₂ CO ₂ H	Ph	H ₂ SO ₄	11
(CH ₂) ₂ CO ₂ H	H	XPh	H ₂ SO ₄	12
RC=CH ₂ 	H, Alkyl	Me	PPA	13



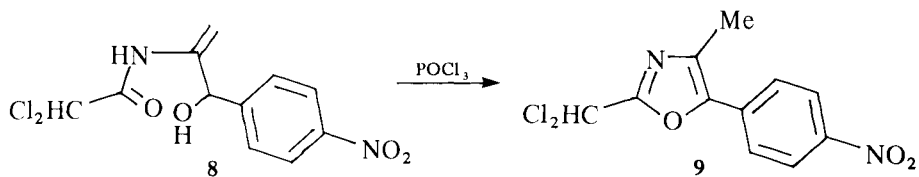
Bioxazoles or bisoxazolylbenzenes (e.g., **5**) have been prepared by this method.¹⁴
4-Acetoxy-methyloxazoles such as **7** are formed when unsaturated 2-acylamino-



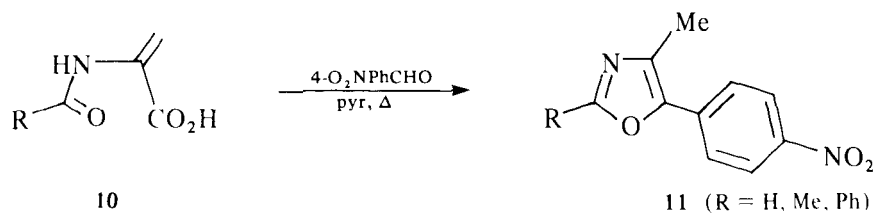
ketones (e.g., **6**) are allowed to react with sulfuric acid in the presence of acetic anhydride.⁷



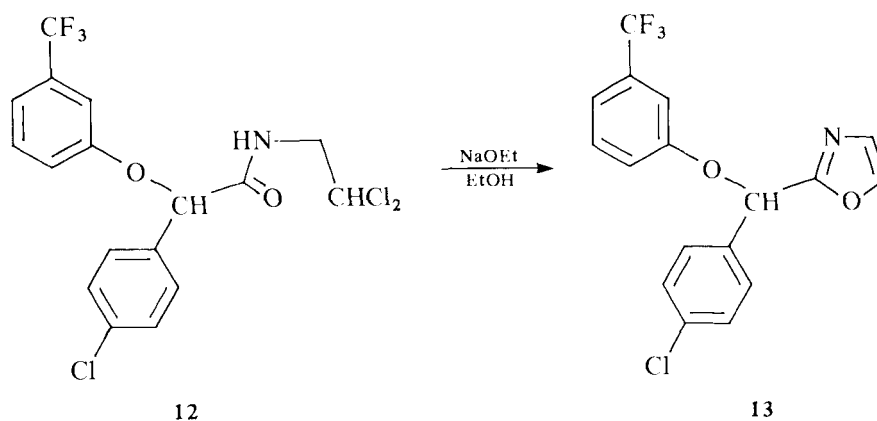
An interesting variation of this type of cyclization occurs upon treatment of 2-dichloroacetyl-amino-3-hydroxy-(4-nitrophenyl)propene (**8**) with phosphoryl chloride. In this case 2-chloroacetyl-4-methyl-5-(4-nitrophenyl)oxazole (**9**) is obtained in 85% yield.⁸



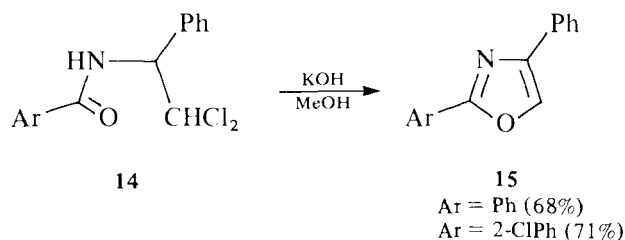
An unusual transformation which yields 4-methyl-5-(4-nitrophenyl)oxazoles **11** (66–89%) is the thermal decarboxylation of the 2-acylaminoacrylic acids **10** in the presence of 4-nitrobenzaldehyde in pyridine.¹⁵



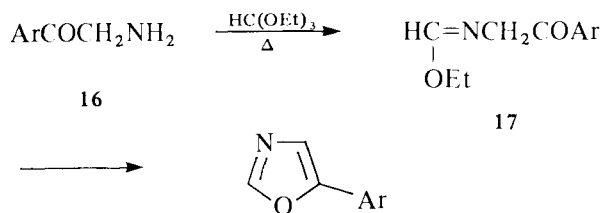
Monosubstituted oxazoles are generally inaccessible by this method, however, the preparation of 2-(4-hydroxyphenyl)-oxazole from 4-hydroxybenzoylaminoacetaldehyde dialkyl acetals by treatment with acid was recently described although no experimental details were given.¹⁶ Although not mechanistically related, the cyclization of *N*-(2,2-dichloroethyl)-3-(trifluoromethylphenoxy)-4-chlorophenylacetamide (**12**) with sodium ethoxide gives 2-[α-(3-trifluoromethylphenoxy)-4-chloro-



benzyl] oxazole (**13**) in 52% yield.¹⁷ Similarly the 2-aryl-4-phenyloxazoles **15** have been obtained from the 1-arylamino-1-phenyl-2,2-dichloroethanes **14**.¹⁸



Heating a mixture of triethylorthoformate and arylaminomethylketones **16** results in the formation of 5-aryloxazoles **18** presumably via cyclization of the intermediate formimidate **17**.¹⁹

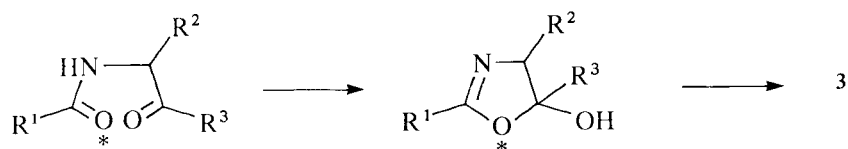


18 Ar = Ph, 1-C₁₀H₇,
4-biphenyl

The yield of **18**, Ar = Ph, was reported to be 61%; however, attempts to reproduce this result lead to this compound in only 33% yield.²⁰ The reaction of other arylaminomethyl ketones with orthoformate and orthoacetate esters provides 5-aryl- and 2-alkyl-5-aryloxazoles, respectively, in 41–79% yield.²⁰

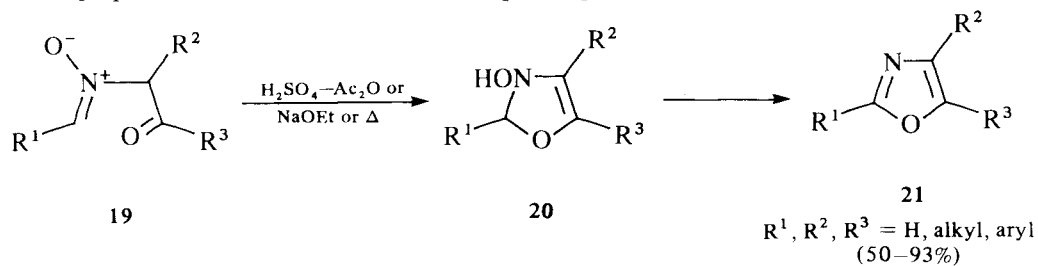
2,5-Dimethyl-4-substituted oxazoles are obtained from the cyclodehydration of 2-acetamidoketones which are derived in turn by the reaction of α -amino acids with acetic anhydride in the presence of sodium acetate or pyridine.^{4,5} The overall transformation, known as the Wrede synthesis^{21,22} is unsatisfactory as a synthetic method because of low overall yields of oxazoles.

¹⁸O labeling studies of the Robinson–Gabriel synthesis demonstrate that the amide carbonyl oxygen is incorporated into the oxazole ring upon cyclization of ¹⁸O-labeled 2-benzamidopropiophenone consistent with the mechanism shown in the scheme.²³

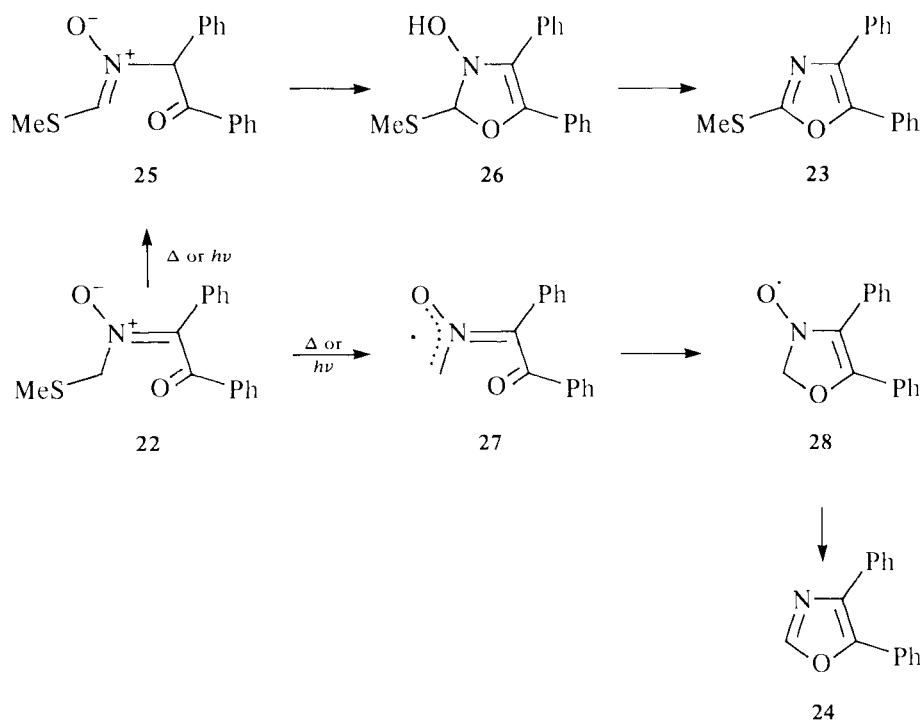


1.2.2. From 2-Ketonitriles

A class of compounds isomeric to the 2-acylaminoketones are the 2-ketonitriles **19**. These dipolar species undergo cyclization to afford aryl- or aralkyloxazoles **21** in fair to good yields under acidic, basic, or thermal conditions presumably via 3-hydroxy-4-oxazolines **20**.²⁴ Several examples for bisoxazolybenzenes have been prepared in like manner from the corresponding bisketonitriles (Table 1.4).²⁴

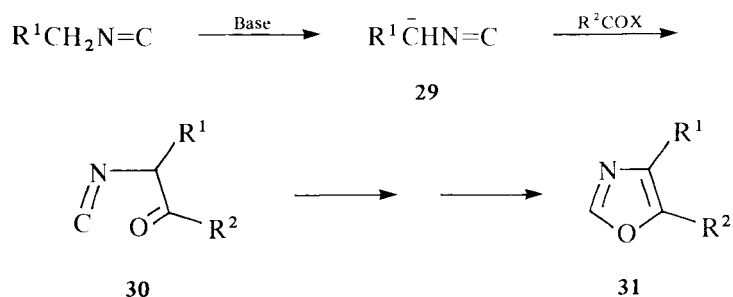


C-Benzoyl-*C*-phenyl-*N*-methylthiomethyl nitron (22) affords several products upon thermolysis or photolysis. Two of these are 2-methylthio-4,5-diphenyloxazole (23) and 4,5-diphenyloxazole (24) along with benzil and dimethyl disulfides.²⁵ The 2-methylthiooxazole 23 is believed to arise via a prototropic shift in 22 resulting in the formation of the isomeric ketonitron 25. Cyclization of 25 and elimination of water from the intermediate 2-methylthio-3-hydroxy-4,5-diphenyl-4-oxazoline 26 leads to the product 23. 4,5-Diphenyloxazole (24) is postulated to arise by way of a radical dissociation of 22 to give the azaallyl radical 27 followed by cyclization to the *N*-oxo radical 28 which leads to 24.

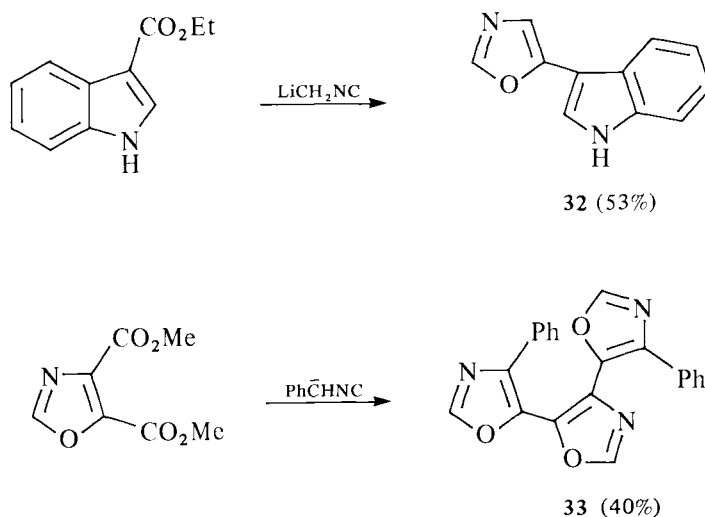


1.2.3. From Isonitriles

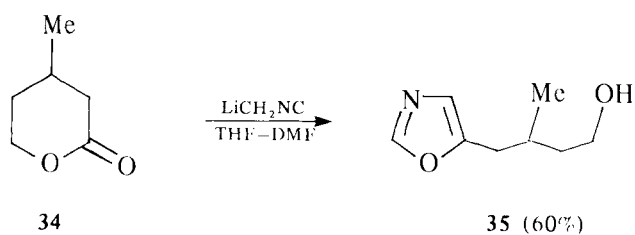
α -Metalated isonitriles 29 are valuable intermediates in synthesis and especially in heterocyclic synthesis.²⁶⁻²⁸ The reaction of these species (generated from the isonitrile with various bases) with acyl halides, imidazolides, esters, and dimethyl amides is a versatile method for the preparation of 2-unsubstituted oxazoles 31 in modest to excellent yields (Table 1.5).^{5,6} R^1 and R^2 can be H, alkyl, aryl, or heteroaryl. The intermediate ketoisonitrile 30 is in general not isolable but cyclizes rapidly under the reaction conditions to the oxazole 31. Some recent examples of



this technique include the synthesis of 3-(5-oxazolyl)indole (**32**)²⁹ and the teroxazole **33**.³⁰ The reaction of **29** with lactones yields hydroxyalkyl oxazoles. The

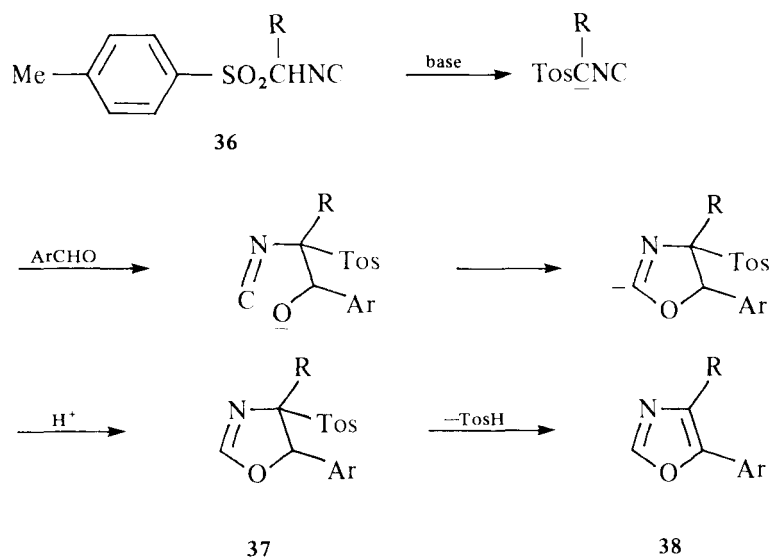


reaction of lithiomethyl isocyanide with the δ -lactone **34** gives 3-methyl-4-(5-oxazolyl)butan-1-ol (**35**).³¹



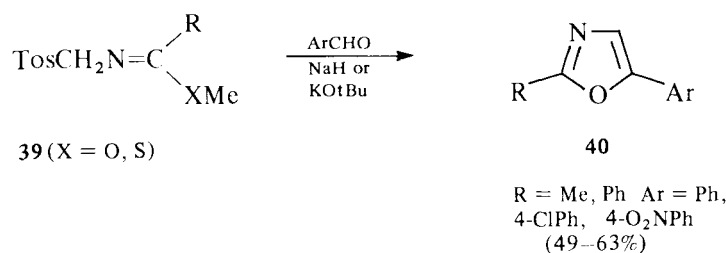
Toluenesulfonyl isonitrile **36**, R = H, is a related synthon for many heterocyclic systems including pyrroles, imidazoles, and oxazoles.²⁸ In the oxazole series, 5-aryl- or 5-heteroaryloxazoles **38**, R = H, are formed in good yield in the reaction of **36**, R = H, with aromatic or heteroaromatic aldehydes, respectively, under basic

conditions such as potassium *t*-butoxide or potassium carbonate in refluxing methanol.^{9,32,33} The isonitrile **36**, R = H, can be alkylated to afford **36**, R = alkyl, and subjected to the above reaction conditions to give 4-alkyl-5-aryloxazoles **38**, R = alkyl.³⁴ The presumed reaction pathway is shown below. In most cases the intermediate 4-tosyl-2-oxazolines can be isolated by combining the reactants at room temperature.^{32,34}



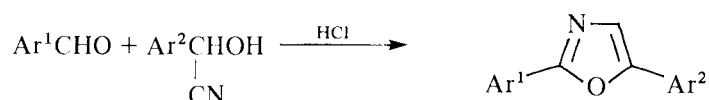
R = H, alkyl; Ar = Ph, XPh,
 2-C₄H₃O, 2-C₄H₃S,
 2-(1-Me)C₄H₃N,
 2-, 3- and 4-C₅H₄N (47–91%)

Employment of the tosylmethylimino ethers **39** rather than tosylmethyl isonitrile (**36**) in the reaction with aryl aldehydes in the presence of base results in the formation of 2-alkyl or -aryl-5-aryloxazoles **40** thereby broadening the scope of this oxazole synthesis.³⁵ Alkoxy-, alkylthio-, amino-, and carbalkoxyoxazoles have been derived from α -metalated isonitriles. These are discussed below in the appropriate sections.



1.2.4. From Aldehydes and Cyanohydrins

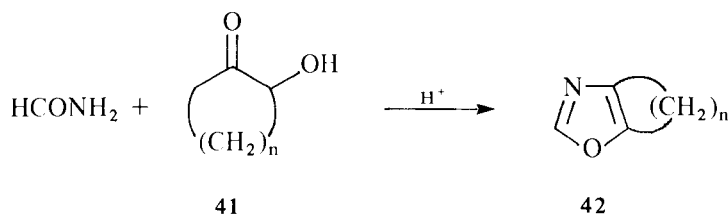
2,5-Diaryloxazoles result when aldehydes and cyanohydrins are treated with dry hydrogen chloride in ether (Fischer synthesis, Table 1.6).³⁶ This synthesis is plagued, however, by severe limitations. Very often, 2,5-diaryloxazolidin-4-ones



are formed as side products and are the major products when aliphatic aldehydes are employed as substrates.^{5,6} In the case of aromatic aldehydes it was found that the addition of thionyl chloride to the reaction mixture eliminates the oxazolidinone by-products.³⁷ A second potential limitation is that mixtures of regioisomers may arise when the cyanohydrin is derived from a different aromatic aldehyde. Finally, oxazole ring chlorination occurs to give 2,5-di(4-bromophenyl)-4-chloro-oxazole along with 2,5-di(4-bromophenyl)oxazolidin-4-one when 4-bromobenzaldehyde and its cyanohydrin are combined in the presence of hydrogen chloride.³⁸ Despite its unpredictable nature, the Fischer oxazole synthesis has some important applications such as in the preparation of halfordinol, (2-(3-pyridyl)-5-(4-hydroxyphenyl)oxazole), an oxazole alkaloid.³⁹

1.2.5. From 2-Hydroxyketones and Formamide

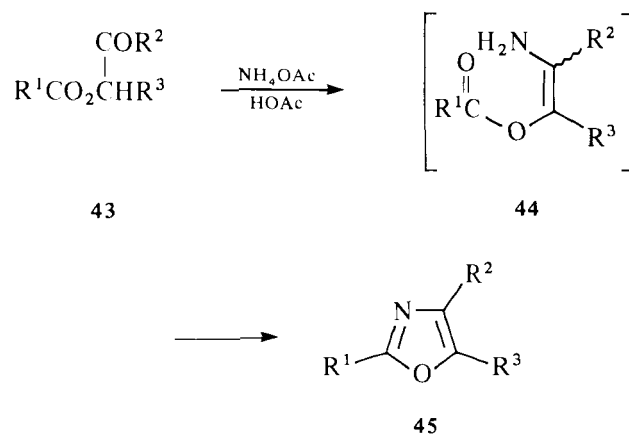
The 2-unsubstituted oxazoles are readily available from 2-hydroxyketones, formamide, and sulfuric acid.^{5,6} With cyclic 2-hydroxyketones **41** under these conditions, 4,5-cycloalkaoxazoles **42** are obtained in fair yields.^{40,41} This method, along with



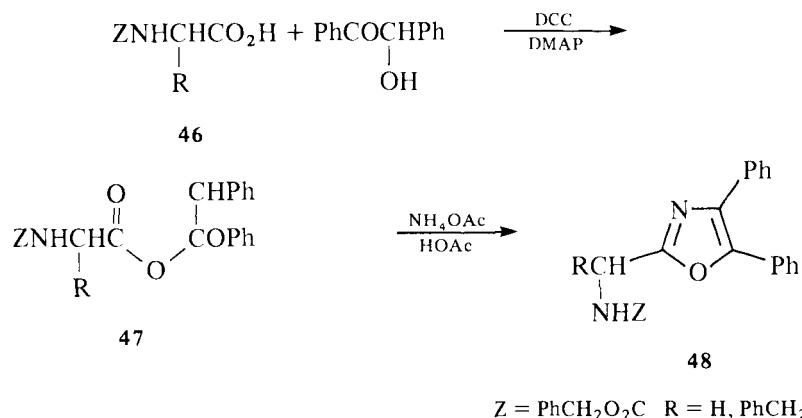
the reaction of amides with cyclic 2-haloketones, is particularly advantageous for the preparation of such systems (Table 1.7).

1.2.6. From 2-Acyloxyketones and Ammonium Acetate

The oxazole synthesis due to Davidson, that is, the reaction of 2-acyloxyketones **43** with ammonium acetate (or urea) in acetic acid, is another highly versatile procedure for the construction of the oxazole ring (Table 1.8).⁴² The acyloxyen-



amine **44** is a probable intermediate in the reaction. A host of 2-unsubstituted or substituted-4,5-diaryl (most commonly) -4,5-dialkyl- and -4,5-aralkyloxazoles are available via this method. The substituent in the 2-position can be hydrogen,⁴³ alkyl,⁴⁴ aryl,^{45,46} carboxyalkyl,⁴⁷ and vinyl.^{47,48} Recently Wasserman and Lu prepared the carbobenzyloxy- (Z-) protected aminomethyloxazoles **48** in 80–85% yield by the reaction of the benzoin ester **47** with ammonium acetate in acetic acid.⁴⁹ The ester **47** is conveniently obtained by coupling of the Z-amino acids **46** with benzoin in the presence of dicyclohexylcarbodiimide and dimethylamino-pyridine. The oxazole **48** was further converted to dipeptide derivatives.



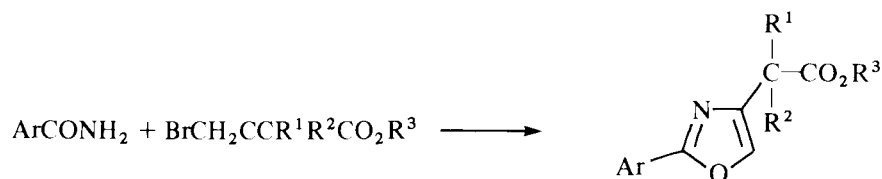
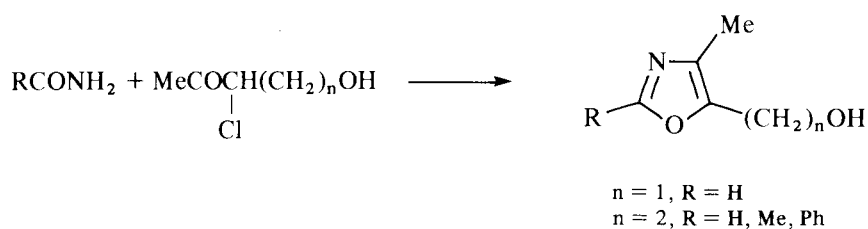
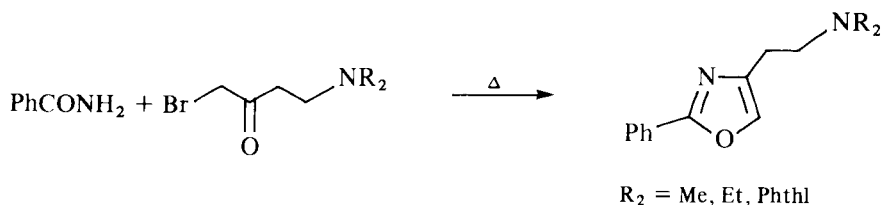
1.2.7. From 2-Haloketones and Amides or Ammonium Salts

The reaction of amides or ammonium salts with 2-haloketones at elevated temperatures affords mono-, di-, and trisubstituted alkyl, aryl, and aralkyloxazoles in widely but generally acceptable yields (Table 1.9). The ready availability of the

starting materials makes this procedure the method of choice in many oxazole syntheses.⁴⁻⁶ 4-Phenyloxazole, an important substrate for the Diels–Alder reaction with acetylenes leading to furans, has been obtained in kilogram quantities in about 40% yield by the reaction of α -bromoacetophenone with ammonium formate.⁵⁰

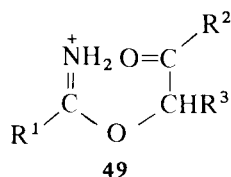
An important feature of this process is the ability to control the regiochemistry of the products by employing the appropriately substituted haloketones. This is exemplified in the synthesis of 4-phenyl-5-benzyloxazole (67%) or 4-benzyl-5-phenyloxazole (62%) from ammonium formate and 2-bromo-1,3-diphenyl-1-propanone or 1-bromo-1,3-diphenyl-2-propanone, respectively.⁵¹

Aminoalkyl,⁵² hydroxyalkyl,^{53,54} and alkoxy carbonylalkyloxazoles⁵⁵ have been prepared from the amides and the corresponding haloketones. Some examples are outlined.



2-Aminooxazoles as well as 4- or 5-oxazolecarboxylic esters may be obtained by modifications of this procedure (Sections 1.3.8 and 1.3.2, respectively).

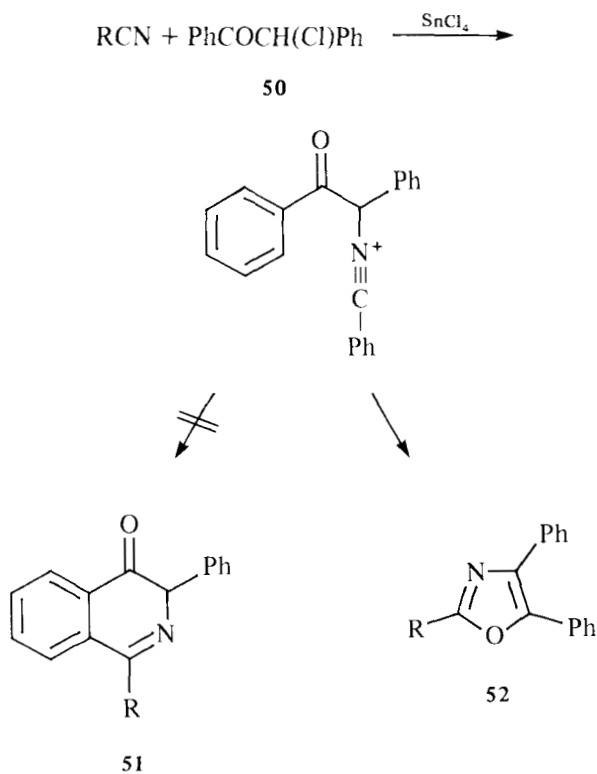
The mechanisms of this reaction is not known with certainty but presumably involves the intermediacy of the ketoimidates **49**. A more detailed discussion of this mechanism is found in previous reviews.⁴⁻⁶



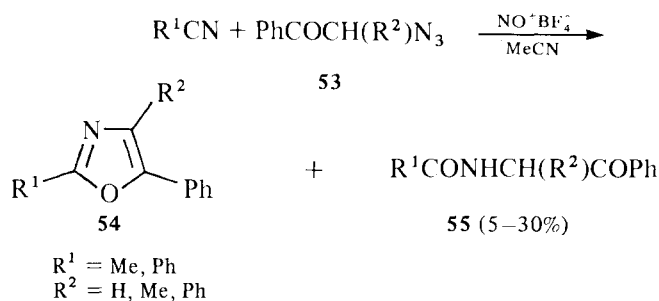
1.2.8. From 2-Hydroxyketones or 2-Haloketones and Nitriles

2-Hydroxyketones (especially benzoin)s combine with nitriles in the presence of sulfuric acid to provide oxazoles in moderate to good yields (Table 1.10). This reaction was first observed by Japp and Murray over 80 years ago and is still used for the preparation of 2-substituted 4,5-diaryloxazoles.⁵⁶ The 2-substituent on the resulting oxazole is derived from the nitrile substrate and can be hydrogen,⁵⁷ alkyl,⁵⁶⁻⁵⁸ aryl,^{56,57} and vinyl.^{48,57}

Lora-Tamayo et al. studied the reaction of nitriles with desyl chloride **50** in the presence of stannic chloride.⁵⁹ None of the expected dihydroisoquinolones **51** were isolated, rather the 4,5-diphenyloxazoles **52** were obtained. Beside 2-alkyl- and

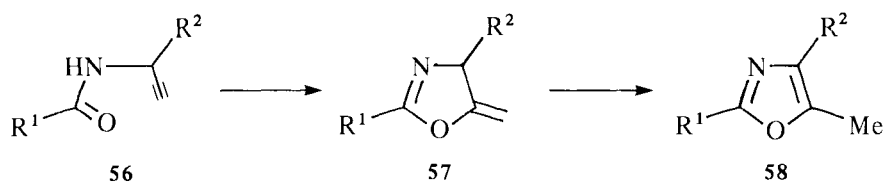


-2-aryl-4,5-diphenyloxazoles, these investigators prepared the 2-methoxymethyl-, 2-chloromethyl-, and 2-(2-chloroethyl) derivatives by this procedure, although it was impossible to obtain the halogenated compounds in a pure state. A variation of this procedure, the reaction of phenacyl azide **53** with nitriles in the presence of nitrosonium tetrafluoroborate provides 5-phenyloxazoles **54** in 49–75% yield along with the acylaminoketones **55**.⁶⁰

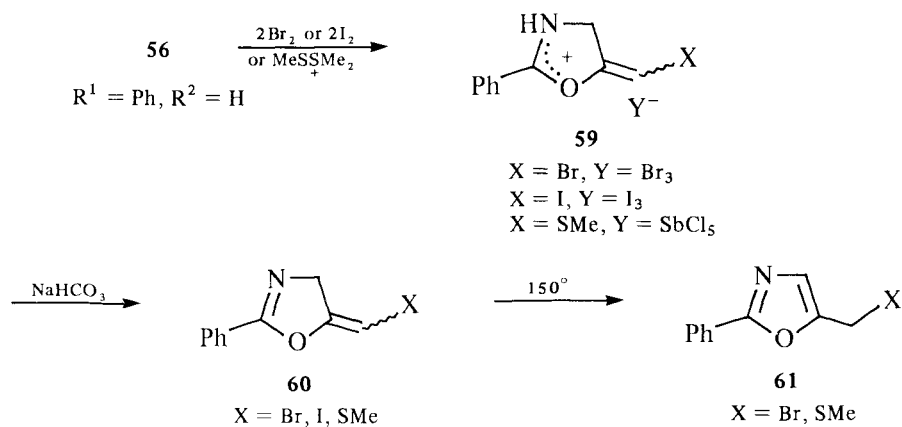


1.2.9. From Propargyl Amides

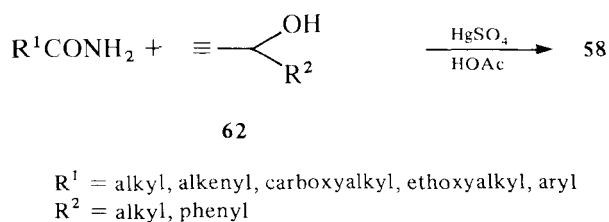
Propargyl amides **56** are useful intermediates in the synthesis of 5-methyloxazoles **58** as is evidenced by their cyclization under acidic conditions⁶¹⁻⁶³ (with or without added mercury salts) or basic conditions (sodium hydride).⁶³ The yields of oxazoles



are generally between 50 and 70% (Table 1.11). Putative intermediates in this process are the 5-methylene-2-oxazolines **57**. Evidence for the intermediacy of **57** is derived from the recently reported work of Caristi et al. who isolated the 5-methyleneoxazolinium salts **59** (X = Br, I, SMe) when *N*-propargylbenzamide (**56**, R¹ = Ph, R² = H) is allowed to react with electrophiles such as bromine, iodine, or (MeS-S⁺Me₂)SbCl₅⁻.⁶⁴ Treatment of **59** with aqueous sodium bicarbonate provides the 5-methyleneoxazolines **60** (X = Br, I, SMe), which when thermolyzed give the 2-phenyloxazoles **61** (X = Br, SMe; no yields given).

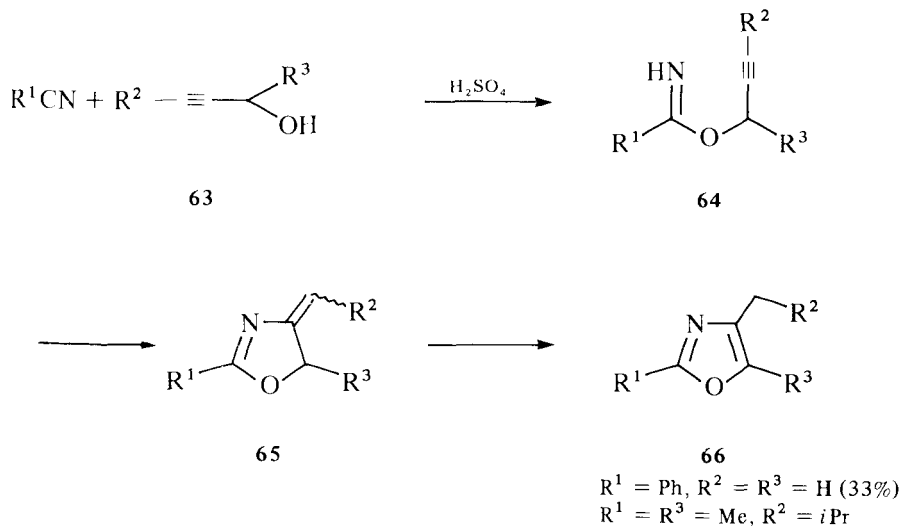


A variation of the above-described procedure was reported in the patent literature and involves the preparation of 5-methyloxazoles of the type **58** by the reaction of amides with propargyl alcohols **62** and mercuric sulfate in acetic acid.⁶⁵ The formation of oxazoles **58** may involve the intermediacy of the propargyl amides **56**.

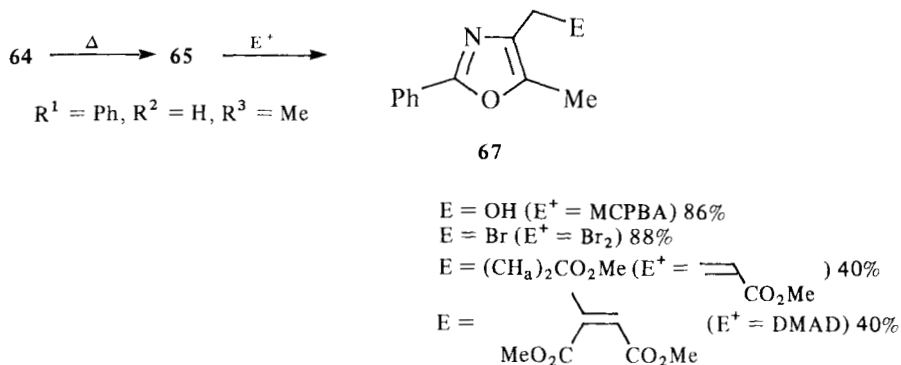


1.2.10. From Nitriles and Propargyl Alcohols and from *O*-Propargyl Imidates

4-Alkyloxazoles **66** are accessible from the reaction of nitriles with propargyl alcohols **63** in the presence of sulfuric acid (Table 1.12).⁶⁶ The *O*-propargyl imidates **64** are possible intermediates in this transformation since these species undergo cyclization to oxazoles **66** in 45–60% yields under the same conditions.⁶² Under neutral, thermal conditions the propargyl imidate **64**, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, and

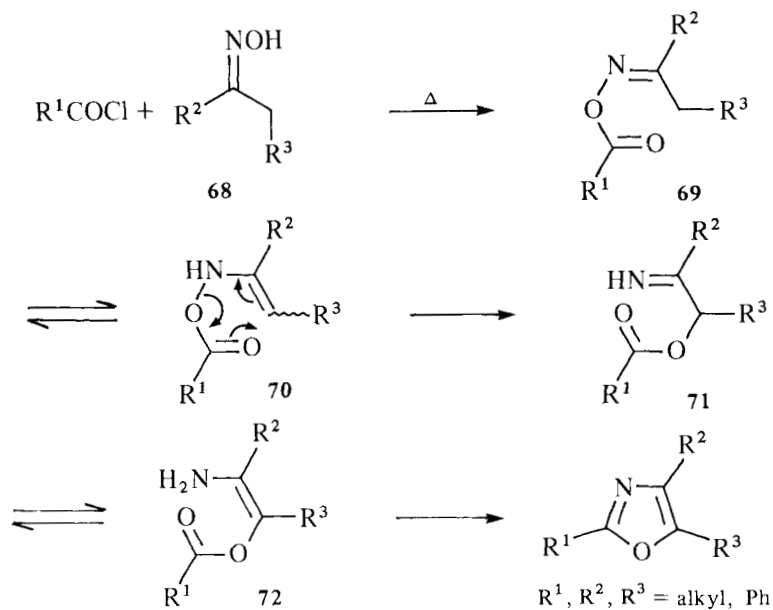


$\text{R}^3 = \text{Me}$, affords 2-phenyl-4-methylene-5-methyl-2-oxazoline (**65**, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$).⁶⁷ Combination of the latter with electrophilic species provides oxazoles **67**. This result suggests that the 4-methylenoxazolines **65** are intermediates in the reaction of nitriles with propargyl alcohols **63** and in the cyclization of propargyl imidates **64** under acidic conditions.



1.2.11. From Ketoximes and Acyl Halides

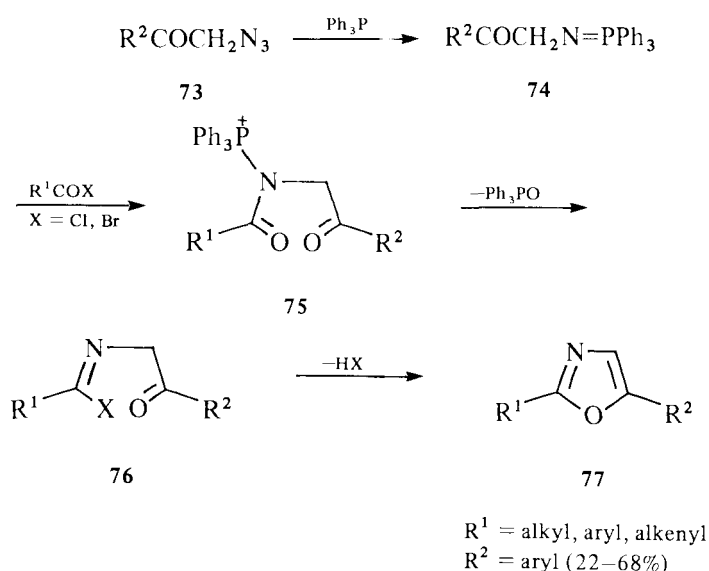
A recent patent described the preparation of 2-chloromethyl-4-methyl-5-phenyl-oxazole in high yield by the reaction of 3-phenyl-2-propanone oxime with chloroacetyl chloride.⁶⁸ The formation of 2-chloromethyl-4-alkyl-5-phenoxy- and -5-alkylthioxazoles (Sections 1.3.4 and 1.3.5, respectively) from the corresponding ketoximes and chloroacetyl chloride or bromide was also described. Subsequently the scope of this process was expanded to include a number of 2,4,5-trisubstituted aryl-, alkyl-, and aralkyloxazoles (68–85%, Table 1.13).^{69,70} The proposed mechanism is outlined below. Acylation of the oxime **68** followed by tautomerization of the resulting acyloxyamine **69** provides the enacyloxyamine **70**. A [3,3] sigmatropic shift of **70** leads to the intermediate acyloxyenamine **72** via the imine **71**.



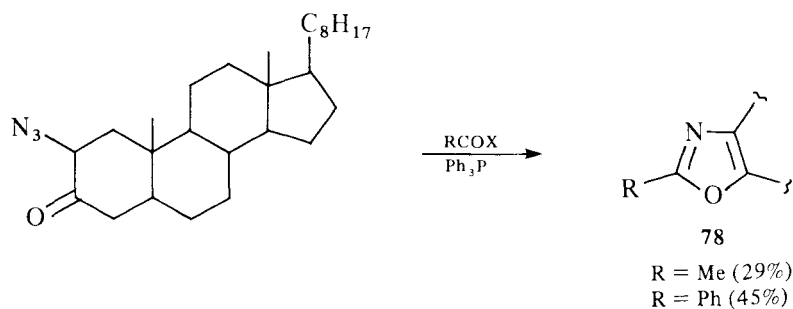
Cyclization of **72** gives the oxazoles. Acyloxyenamines of this type are probably intermediates in the synthesis of oxazoles from 2-acyloxyketones and ammonium salts (Section 1.2.6). Compounds of this type have been prepared independently and cyclize to oxazoles under acidic conditions (Section 1.3.2 and 1.3.7).

1.2.12. From 2-Azidoketones, Acyl Halides, and Triphenylphosphine

A useful and novel approach to 2,5-disubstituted oxazoles **77** was reported by Zbiral et al. and involves the reaction of 2-azidoketones **73** and triphenylphosphine in the presence of acyl halides (Table 1.14).⁷¹ The reaction proceeds via the imino-phosphoranes **74**. Elimination of triphenylphosphine oxide from the phosphonium salt **75**, derived in turn by attack of the acyl halide on **74**, leads to the imidoyl halide **76** which cyclizes with elimination of the hydrogen halide to afford **77**.

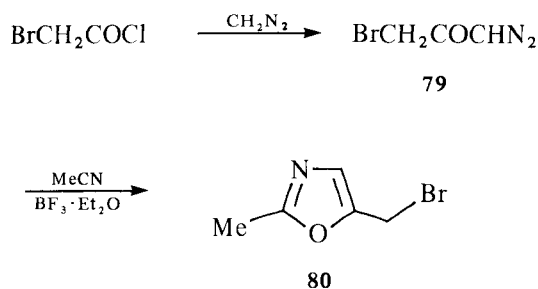


A number of steroidal oxazoles **78** have been obtained by this method.⁷²



1.2.13. From Carbonyl Carbenes and Nitriles

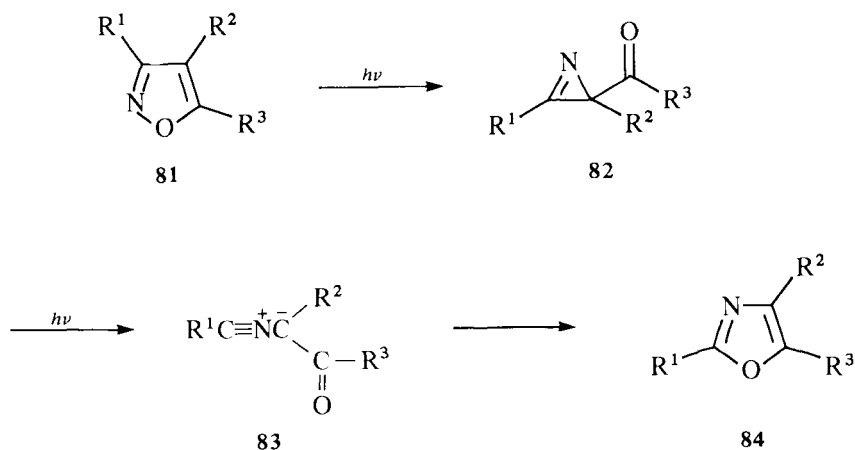
Carbonyl carbenes (or carbenoids) generated by the thermal or catalyzed decomposition of diazoketones undergo 1,3-dipolar cycloadditions to nitriles to give oxazoles in fair to good yields (Table 1.15).^{5,6} This oxazole synthesis has recently become a viable one largely because of the efforts of Dyole and his co-workers⁷³ and Ibata and Sato⁷⁴ who studied the scope and mechanism of the Lewis-acid-catalyzed decomposition of α -diazoketones and α -diazoesters in the presence of nitriles. These workers reported the results of a thorough study leading to optimum conditions for the formation of a variety of 2,5-disubstituted oxazoles. An application of this process provides easy access to a relatively simple system, 2-methyl-5-bromomethyloxazole **80** from bromomethyl diazomethyl ketone **79**, which is an intermediate in the preparation of oxazolophanes.⁷⁵ Despite its simple structure, **80** would be difficult to obtain by other means.



1.2.14. From Isoxazoles and from Azirines

The photochemical interconversion of isoxazoles, acylazirines, and oxazoles is a well-studied process and has been described in detail in a number of reviews.^{5,6,76-78} The isoxazole **81** suffers a photochemically induced ring contraction to the acylazirine **82**. Further irradiation of the azirine **82** results in cleavage of the carbon-carbon bond leading to the carbonylnitrile ylide **83** which cyclizes via a thermal electrocyclic reaction to oxazoles **84** (Tables 1.16 and 1.17).

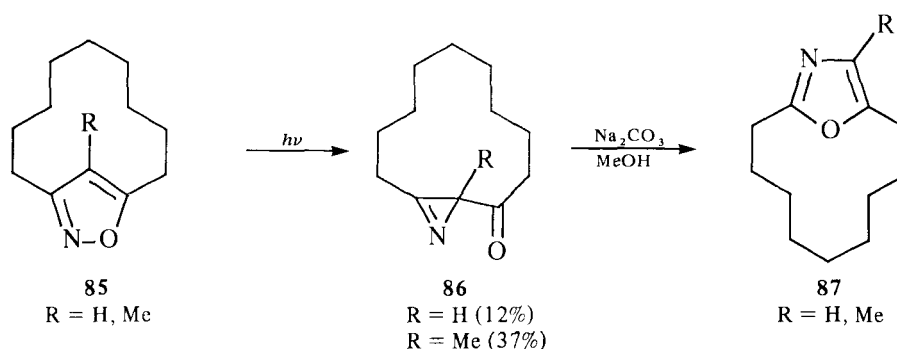
Isoxazoles have been transformed into acyl azirines and oxazoles among other products via gas phase thermolysis.⁶ The course of this complex reaction is highly substituent and condition dependent. Perez et al. recently reported the findings of a kinetic study of the gas phase pyrolysis of 3,5-dimethylisoxazole (**81**, $R^1 = R^3 = \text{Me}$, $R^2 = \text{H}$), 3-amino-5-methylisoxazole (**81**, $R^1 = \text{NH}_2$, $R^2 = \text{H}$, $R^3 = \text{Me}$) and 5-amino-3,4-dimethylisoxazole (**81**, $R^1 = R^2 = \text{Me}$, $R^3 = \text{NH}_2$).^{79,80} The former two isoxazoles provide only the corresponding oxazoles **84**, $R^1 = R^3 = \text{Me}$, $R^2 = \text{H}$, and **84**, $R^1 = \text{NH}_2$, $R^2 = \text{H}$, $R^3 = \text{Me}$ while the latter compound produces only the azirine **82**, $R^1 = R^2 = \text{Me}$, $R^3 = \text{NH}_2$. The results obtained by these investigators suggest that the ring contraction of the isoxazoles to the azirines is rate limiting and that this reaction is a concerted [1,3]-sigmatropic shift. The mode



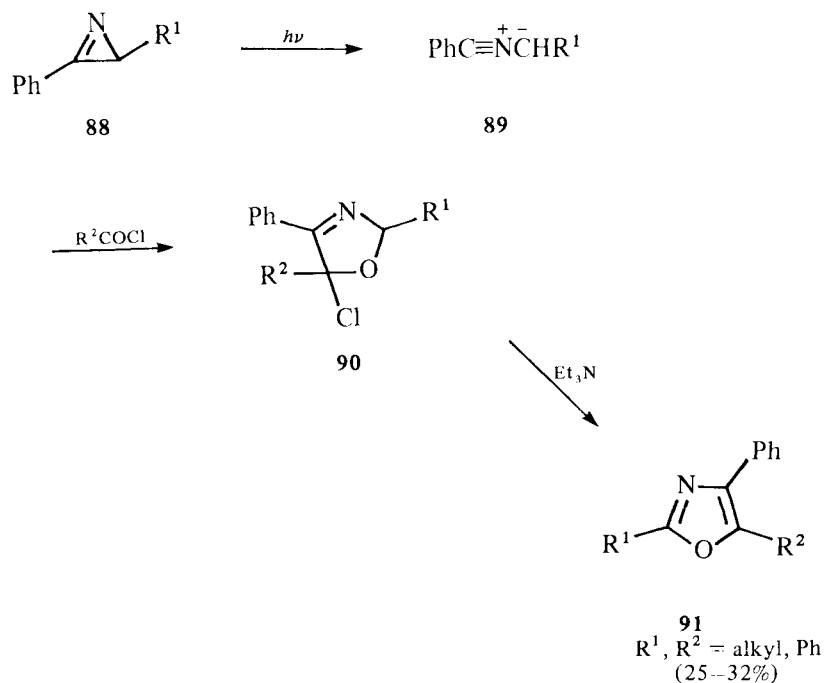
of this rearrangement is believed to be a forbidden supra (migrating group)–supra (migrating framework) migration.

Thermolysis of 3-acylazirines **82** at lower temperatures in solution generally yields isoxazoles **81** rather than oxazoles **84**.⁸¹ In the presence of catalytic quantities of acids such as benzoic acid or boron trifluoride etherate, oxazoles **84** are formed along with isoxazoles **81**.⁸² When the acylazirines **82** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$ and $R^1 = R^3 = \text{Ph}$, $R^2 = \text{Me}$) are heated with the Lewis acid, boron trifluoride etherate, only the corresponding oxazoles **84** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$ and $R^1 = R^3 = \text{Ph}$, $R^2 = \text{Me}$) are isolated to the exclusion of the isoxazoles **81**.

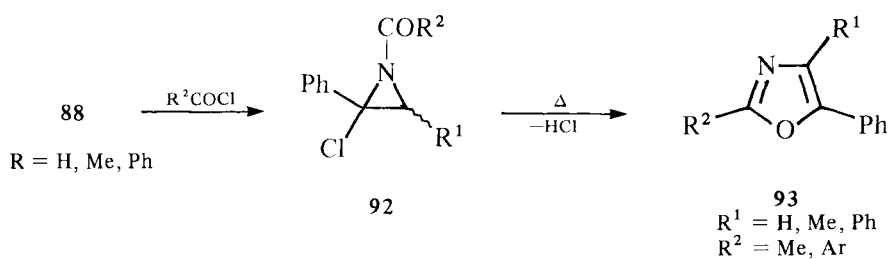
When heated in methanol with a catalytic amount of sodium carbonate, 3-acylazirines **82** give oxazoles in good yields.⁸³ This procedure was applied to a synthesis of (2,5)[9]oxazolophanes **87**.⁸⁴ Irradiation of (3,5)[9]isoxazolophanes **85** gives the 3-acylazirines **86** which rearrange nearly quantitatively to **87**.



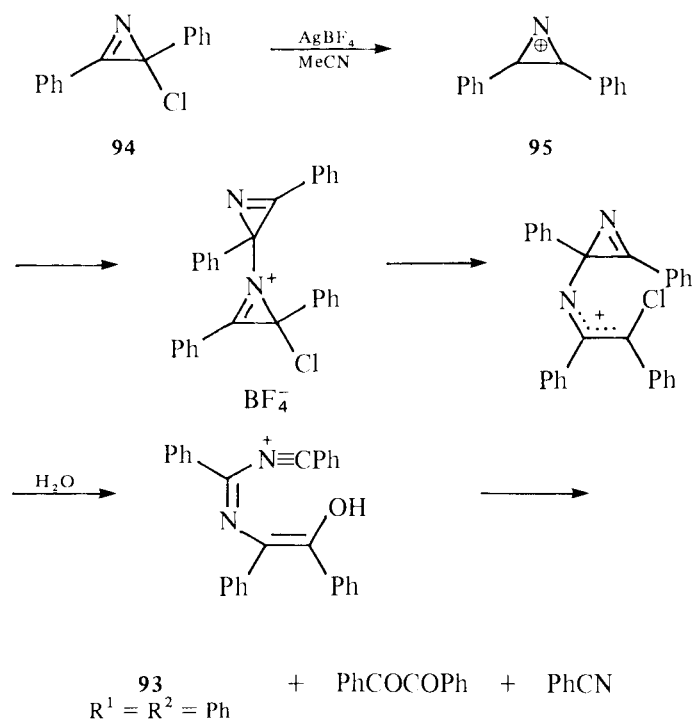
Photolysis of the 2-phenylazirines **88** promotes carbon–carbon bond cleavage of these species leading to the nitrile ylides **89**. When the irradiation is performed in the presence of acyl chlorides and triethylamine, 1,3-dipolar addition of **89** to the acyl chloride results in the formation of the 4-phenyl-5-chloro-3-oxazolines **90**, which are not isolated but suffer base-induced elimination of hydrogen chloride to



give 4-phenyloxazoles **91** in modest yields.⁸⁵ Under thermal conditions in the absence of light and base, 2-phenylazirines **88** react with acid chlorides (or anhydrides) to yield 5-phenyloxazoles **93**.⁸⁶⁻⁸⁸ In this case addition of the acyl chloride to **88** occurs to afford the intermediate 1-acyl-2-chloro-2-phenylaziridine **92**, which undergoes thermal ring expansion to **93**.

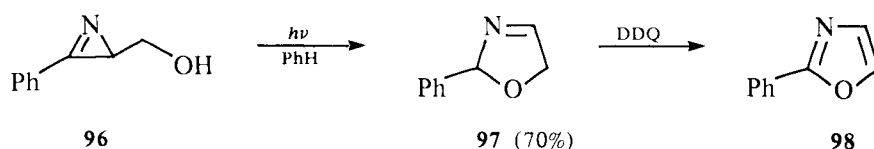


In an attempt to generate azacyclopropenium cations **95**, Gallagher and Storr treated 2,3-diphenyl-3-chloro-1-azirine (**94**) with silver tetrafluoroborate in acetonitrile.⁸⁹ Along with silver chloride, 2,4,5-triphenyloxazole (**93**, $\text{R}^1 = \text{R}^2 = \text{Ph}$), benzil and benzonitrile are formed. The proportions of the organic compounds that arise are highly dependent on reactant concentrations and mixing rate. The oxazole is thought to arise via the scheme

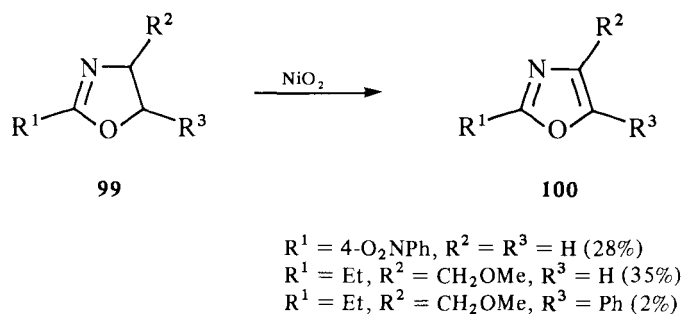


1.2.15. Oxidation of Oxazolines

The oxidation of oxazolines is an attractive yet little explored synthetic approach to oxazoles. This is mainly because of the ready availability of a variety of substituted oxazolines. 2-Phenyloxazole (**98**) has been obtained in 65% yield from the oxidation of 2-phenyl-3-oxazoline (**97**) with 2,3-dichloro-5,6-dicyanobenzoquinone.⁹⁰ In this case the oxazoline **97** was formed upon irradiation of 2-phenyl-3-hydroxymethyl-1-azirine (**96**) in benzene.

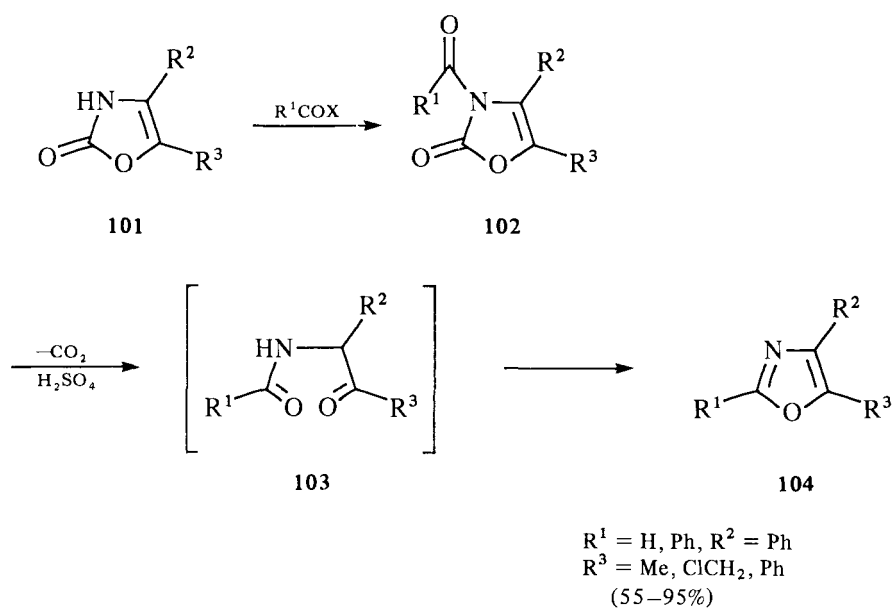


The use of nickel peroxide as an oxidizing agent for the introduction of a double bond into a partially saturated nitrogen-containing heterocycle has been investigated.⁹¹ The yields of oxazoles **100** from the 2-oxazolines **99** using this reagent were modest. Other oxidizing agents such as manganese dioxide and 2,3-dichloro-5,6-dicyanobenzoquinone give disappointing results (Table 1.18).



1.2.16. From Oxazolinones

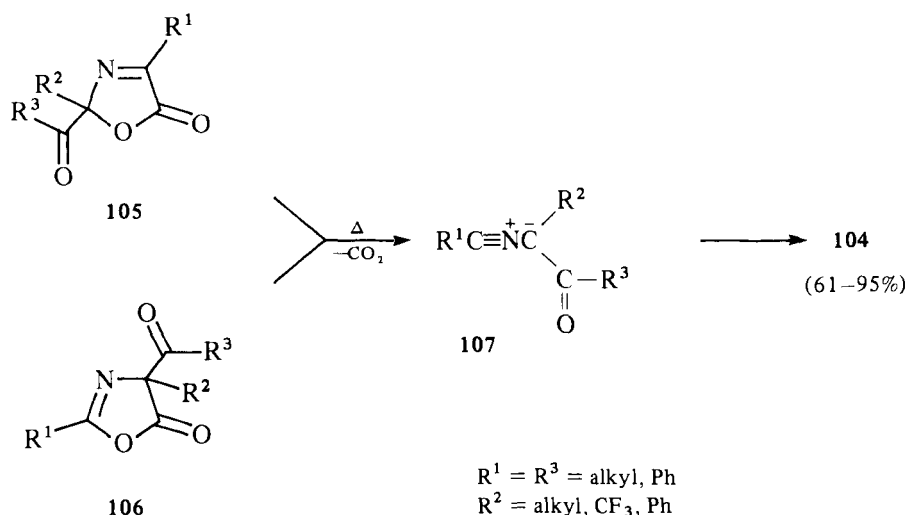
Oxazolinones are useful precursors to a variety of oxazole derivatives (Table 1.19). Lautenschlager has prepared 3-acyl-4-oxazolin-2-ones **102** by acylation of 4-oxazolin-2-ones **101**.⁹² Treatment of **102** with sulfuric acid leads to oxazoles **104**.



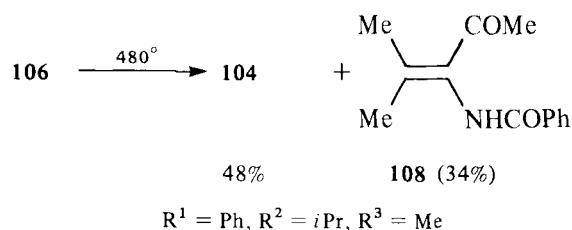
A likely intermediate is the acylaminoketone **103**, and thus this procedure is simply a variant of the Robinson–Gabriel synthesis. For **102** ($\text{R}^1 = \text{OEt}, \text{R}^2 = \text{H; Ph}, \text{R}^3 = \text{Ph}$) only the carbamoylketones **103** ($\text{R}^1 = \text{OEt}, \text{R}^2 = \text{H; Ph}, \text{R}^3 = \text{Ph}$) could be isolated.

Oxazolin-5-ones have also been converted into oxazoles. The thermal decomposition of 2,4-diphenyl-2-oxazolin-5-one in the presence of aryl anhydrides in 2-picoline leading to 2,4-diphenyl-5-aryloxazoles was first described by Lawson.⁹³ This reaction probably proceeds via the 4-aroxy-2-oxazolin-5-ones. Höfle and

Steglich reported the results of a study of the scope and mechanism of this unusual and preparatively useful interconversion.⁹⁴ When 4-acyl-2- and 2-acyl-3-oxalin-5-ones **105** and **106** respectively, are heated, oxazoles are formed in good yields.



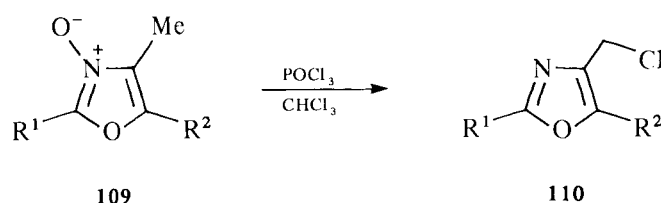
The mechanism of this reaction involves the formation of the carbonylnitrile ylides **107**, which undergo a 1,5-dipolar electrocyclization⁷⁸ to give **104**. A recent study of the gas phase pyrolysis of 2-oxazolin-5-ones reveals that these heterocycles undergo elimination of carbon monoxide at temperatures of 550°C to yield *N*-acylimines and enamides.⁹⁵ Thermolysis of 2-phenyl-4-isopropyl-4-acetyl-2-oxazolin-5-one (**106**, $R^1 = \text{Ph}$, $R^2 = i\text{-Pr}$, $R^3 = \text{Me}$), however, affords oxazole **104**, $R^1 = \text{Ph}$, $R^2 = i\text{-Pr}$, $R^3 = \text{Me}$, along with 3-(benzoylamino)-2-methyl-2-penten-4-one (**108**) when subjected to vacuum pyrolysis at 480°C. On the other hand, only the oxazole arises in 91% yield upon thermolysis of the same oxazoline in the condensed phase at 230°C. The enamidoketone **108** presumably arises from elimi-



nation of carbon monoxide from **106** while the oxazole results from carbon dioxide elimination and cyclization of the ensuing carbonylnitrile ylide intermediates as described above.

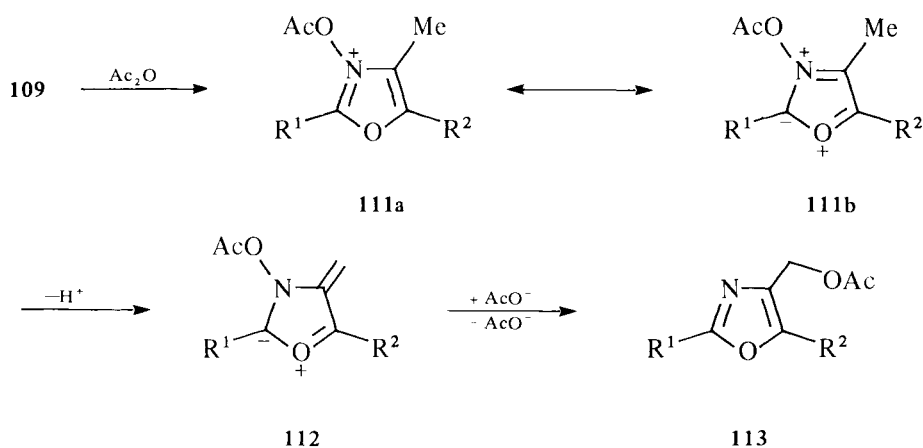
1.2.17. Deoxygenation of Oxazole *N*-oxides

Oxazole *N*-oxides (prepared from α -diketone monoximes and aldehydes, Section 1.3.12) have been deoxygenated to oxazoles in good yield with reagents such as zinc–acetic acid,⁹⁶ Raney-nickel,⁹⁷ phosphoryl chloride,⁹⁷ or phosphorus pentachloride⁹⁸ (Table 1.20). When 4-methyloxazole *N*-oxides **109** are subjected to deoxygenation with phosphoryl chloride, 4-chloromethyloxazoles **110** result.⁹⁷



$\text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me}$ (77%)
 $\text{R}^1 = 4\text{-MeOPh}, \text{R}^2 = \text{Me}$ (84%)
 $\text{R}^1 = \text{R}^2 = \text{Ph}$ (59%)

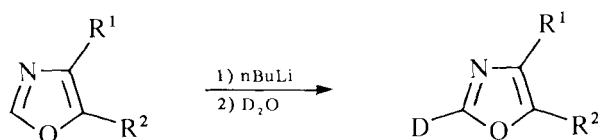
Similarly **109** treated with acetic anhydride lead to 4-acetoxymethyloxazoles **113** along with α -diketones and amides.⁹⁷ The mechanism of this transformation can be envisioned as involving acylation at the *N*-oxide oxygen to provide the oxazolium salt **111**, which undergoes proton elimination to give the carbonyl ylide **112**. The latter suffers attack by acetate at the exocyclic methylene with elimination of acetate leading to **113**. Exact analogies of these processes are found in pyridine *N*-oxide chemistry.⁹⁹



1.2.18. Ring and Side-Chain Metalation (Tables 1.21 and 1.22)

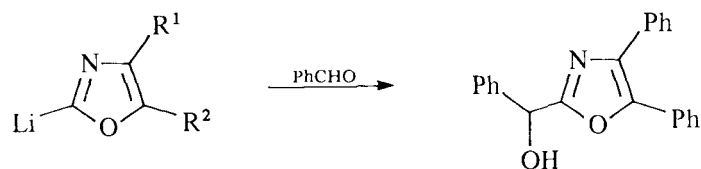
In their studies of oxazole mass spectrometry, Bowie et al. prepared various ring and side-chain deuterated oxazoles. Treatment of 2-unsubstituted oxazoles with

n-butyllithium followed by quenching with deuterium oxide yields 2-deuterio-oxazoles **114**.^{100,101} These results were later confirmed by Schollkopf and co-workers for **114**, $R^1 = H$, Ph , $R^2 = Ph$.¹⁰² 2-Lithio-4,5-diphenyloxazole (**115**,


114

$R^1 = H$, $R^2 = Ph$ (96%)
 $R^1 = Ph$, $R^2 = H$
 $R^1 = Me$, $R^2 = Ph$
 $R^1 = R^2 = Ph$ (95%)

$R^1 = R^2 = Ph$) reacts with benzaldehyde to give 2-(2-hydroxybenzyl)-4,5-diphenyloxazole (**116**) in 67% yield. Alternatively **115**, $R^1 = R^2 = Ph$, when combined with chlorotrimethylsilane leads to *E*- and *Z*-1,2-diphenyl-2-(trimethylsiloxy)vinyl isonitrile (**118**) in 85% overall yield.¹⁰² The latter presumably arises via the open-chain isocyanovinyl lithium alkoxide **117**. A surprising result is obtained when


115

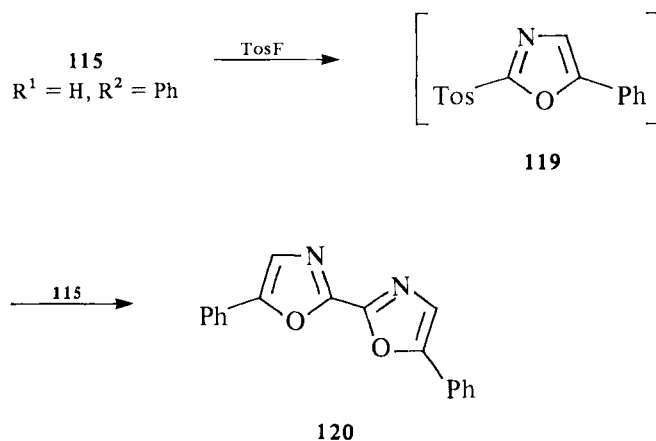
($R^1 = R^2 = Ph$)

116

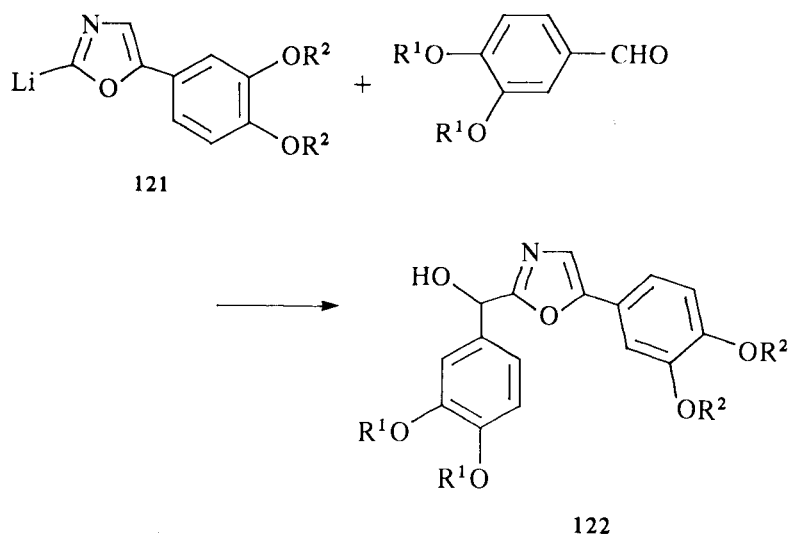
117
118

Z : *E* = 3 : 1

115, $R^1 = H$, $R^2 = Ph$, is allowed to react with 4-toluenesulfonyl fluoride. In this case the 2,2'-bioxazole **120** is produced in 25% yield.¹⁰² The bioxazole **120** could be formed by displacement of the tosyl group of **119** by the lithio compound **115**.

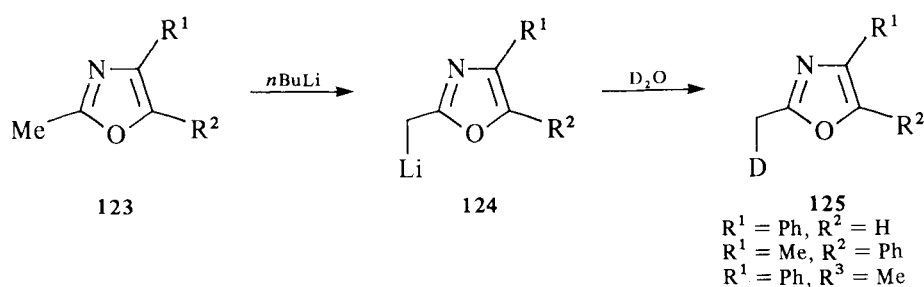


Some 4- or 5-lithiooxazoles can be formed by lithium-halogen exchange of 4- or 5-bromooxazoles (Section 1.3.1).^{100,101} In a synthesis of benzyloisoquinoline alkaloids, Kozikowski and Ames prepared the 2-(2-hydroxybenzyl)5-aryloxazoles **122** in 50–90% yields via the 2-lithio-5-aryloxazoles **121** generated from the corresponding oxazole and either *n*-butyllithium or lithium diisopropylamide in hexamethylphosphoric triamide.¹⁰³

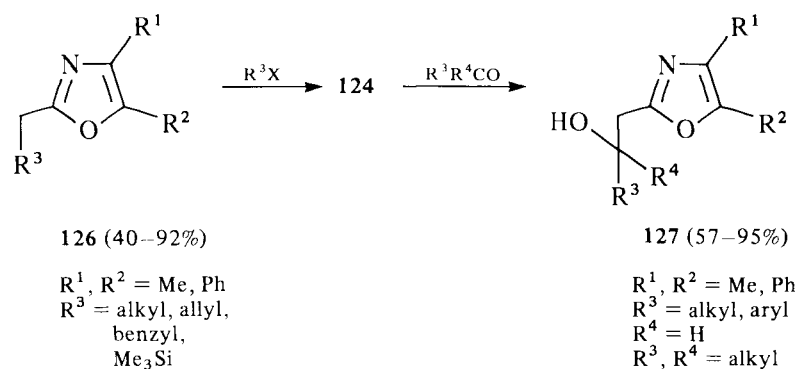


Upon treatment with *n*-butyllithium, 2-methyloxazoles **123** lead to the 2-lithiomethyloxazoles **124**. Elaboration of the 2-methyl substituent is thus possible and has been accomplished by reaction of **124** with a variety of electrophiles. Methyl groups at the 4- or 5-position of the oxazole nucleus in contrast are not deprotonated under these conditions. The relatively higher acidity of the 2-methyl substituent is presumably due to delocalization of the partial negative charge onto

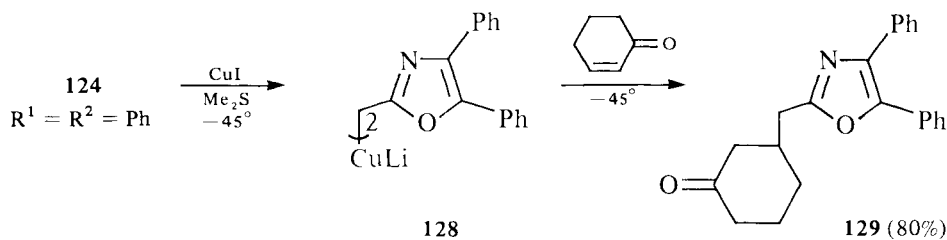
the ring nitrogen. Deuterium oxide and the 2-lithiomethyloxazoles **124** give rise to the 2-deuteriomethyloxazoles **125**.¹⁰⁰ Alkyl, allyl, and benzyl halides provide the



corresponding 2-alkylated derivatives **126** with **124** while aldehydes or ketones afford the 2-(2-hydroxyethyl)oxazoles **127**.^{104,106} When the aldehyde or ketone is α,β -unsaturated, only 1,2-addition ensues with **124**.¹⁰⁴ If **124**, $\text{R}^1 = \text{R}^2 = \text{Ph}$, is



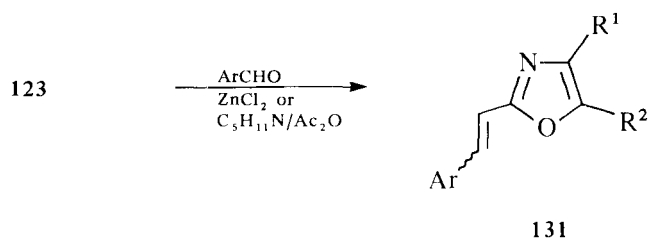
allowed to react with cuprous iodide–dimethyl sulfide to form the cuprate **128**, 1,4-addition to cyclohexenone occurs leading to the ketone **129**.¹⁰⁴



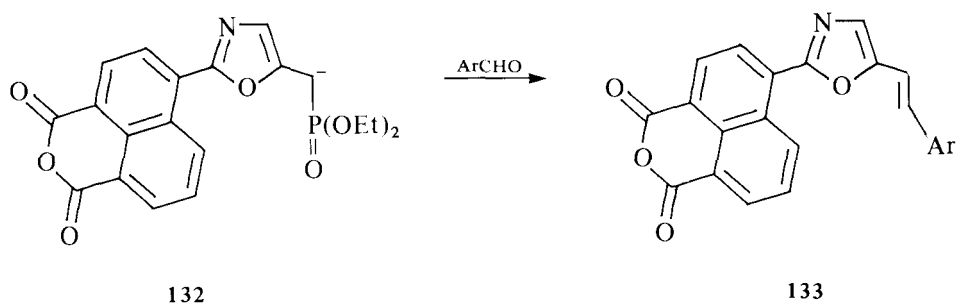
Reaction of **126**, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{PhCH}_2$, with lithium diisopropylamide followed by quenching of the resulting anion with cinnamaldehyde provides the alcohol **130** in 60% yield as a 1:1 mixture of diastereomers demonstrating that deprotonation occurs at the α -oxazole methylene function rather than at the benzylic methylene.¹⁰⁴



2-Methyloxazoles **123** undergo Claisen-type condensations with aromatic aldehydes in the presence of zinc chloride¹⁰⁷ or piperidine^{108,109} to yield 1-(2-oxazolyl)-2-arylethylenes **131**. The oxazolylethylene **131**, $\text{R}^1 = \text{Ar} = \text{Ph}$, $\text{R}^2 = \text{Me}$, is derived from a Peterson olefination of **126** $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Me}_3\text{Si}$, with benzaldehyde.¹⁰⁴



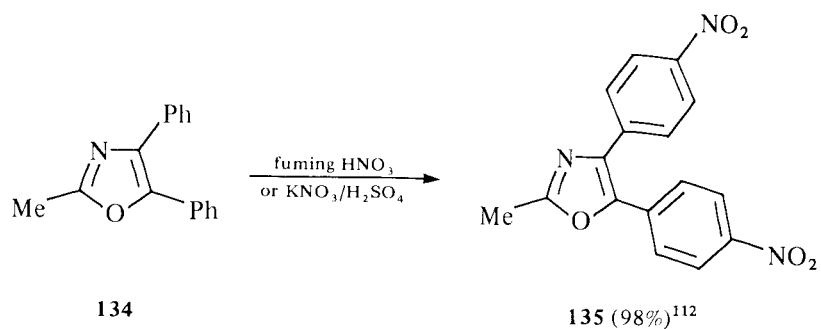
1-(5-Oxazolyl)-2-arylethylenes **133** can be obtained via a Horner–Emmons reactions of the phosphonate ylide **132** with aromatic aldehydes.¹¹¹



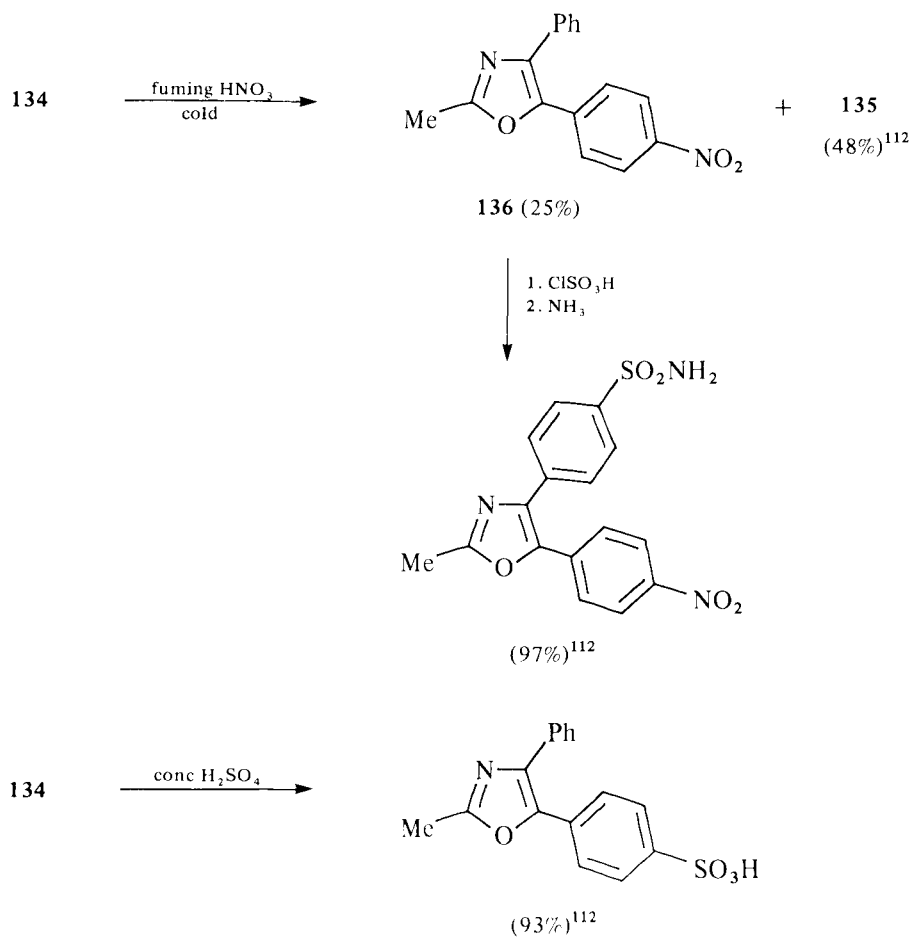
1.2.19. Functionalization of Phenyl Substituents (Table 1.23)

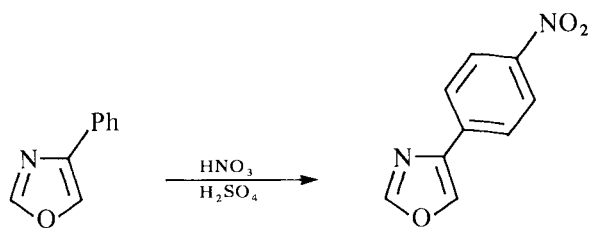
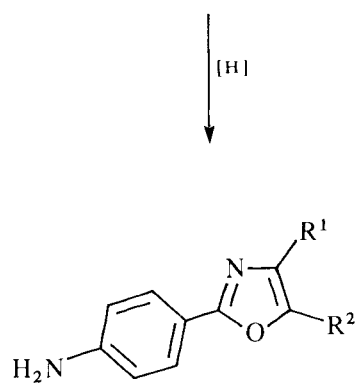
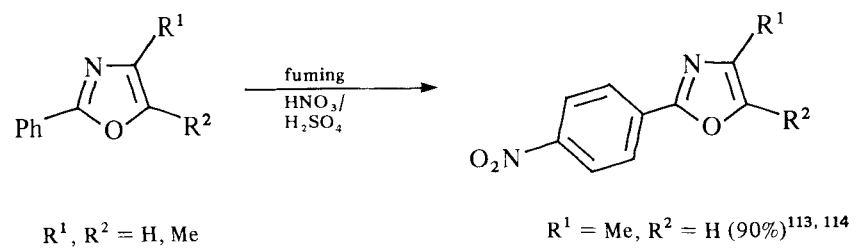
The reaction of phenyloxazoles with electrophiles in general leads to the formation of substituted phenyloxazoles because of the low reactivity of the oxazole nucleus toward these species. Substitution occurs in the 4-position of the phenyl moiety with the order of reactivity being dependent on the position it occupies on the oxazole ring, that is, $5\text{-Ph} > 4\text{-Ph} \gg 2\text{-Ph}$. The phenyl substituents thus introduced

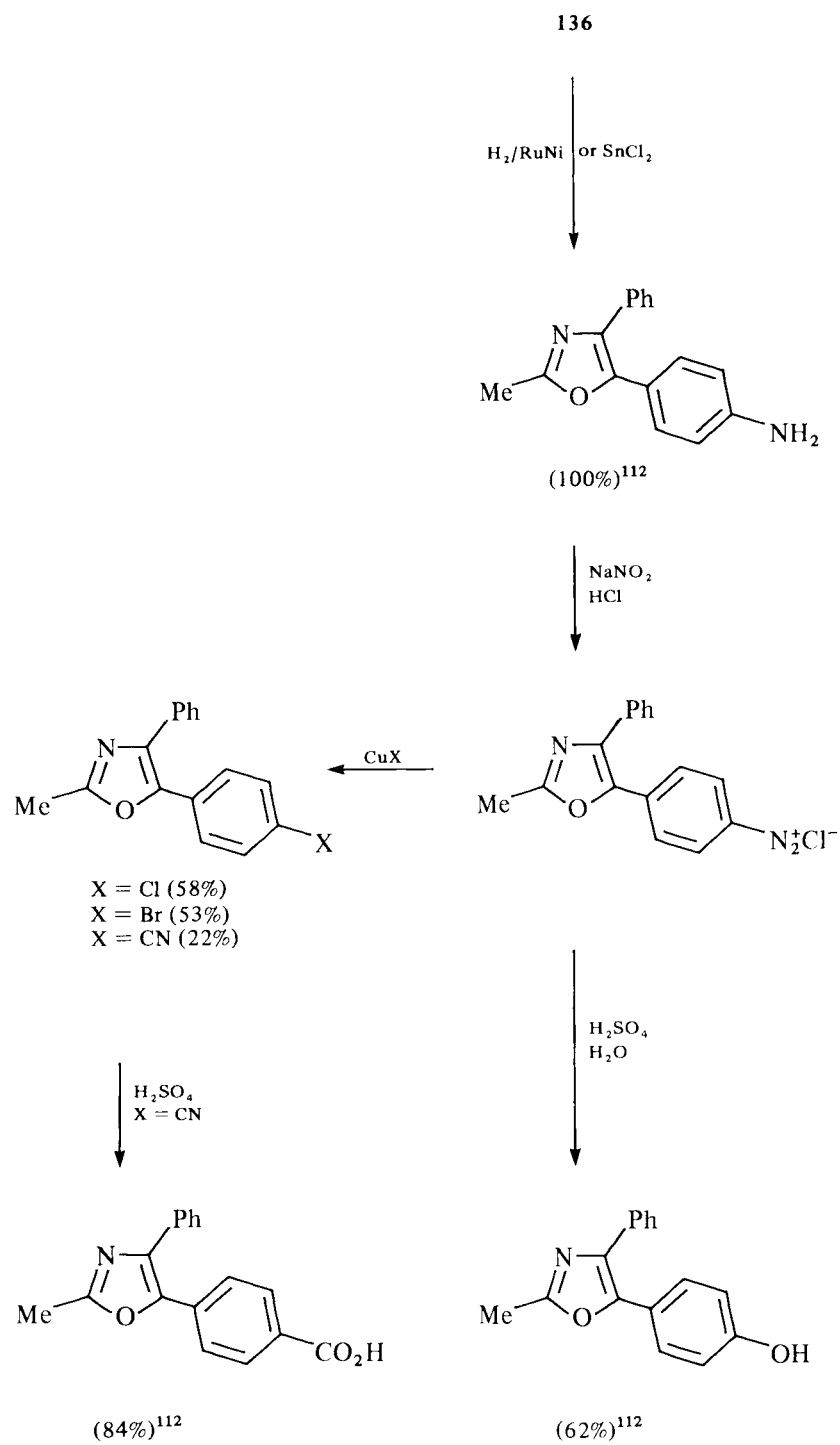
undergo the normal types of reactions expected of these functional groups. The above statements are best illustrated by

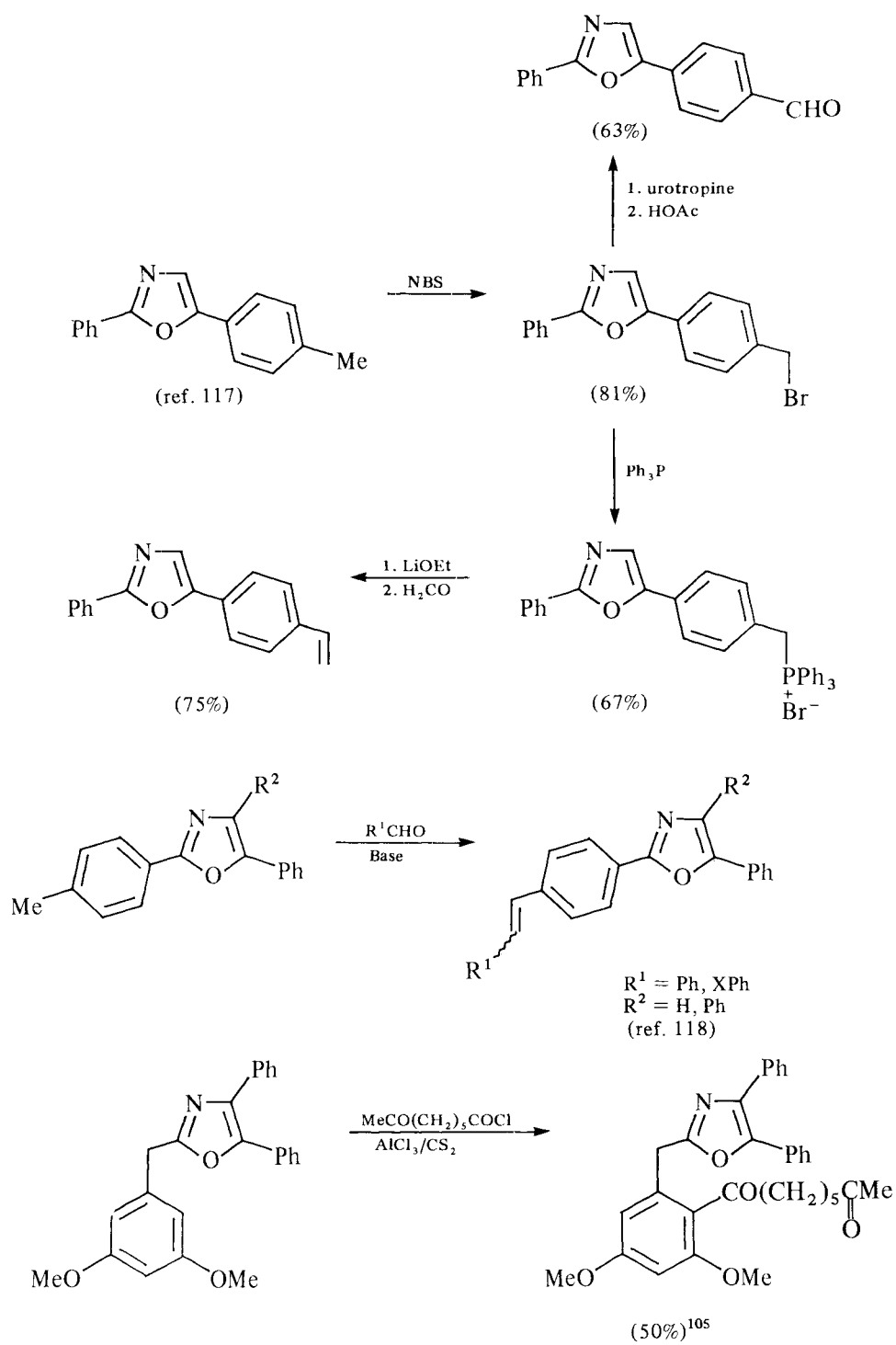


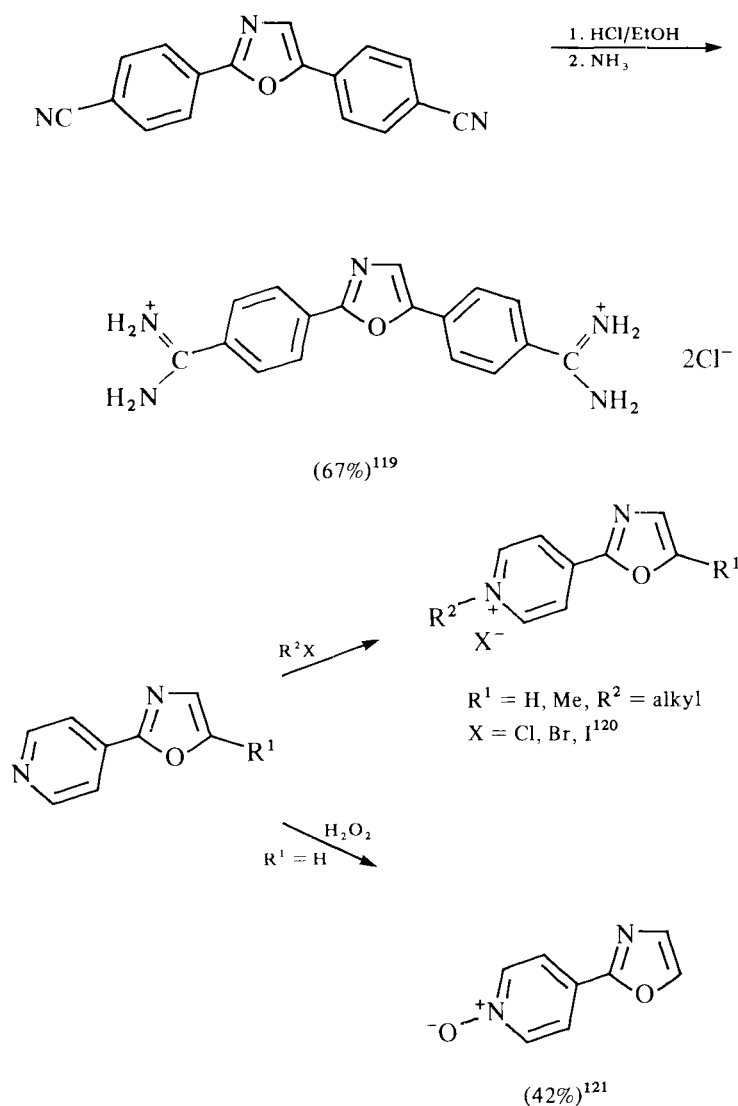
Pyridyl-substituted oxazoles undergo quarternization and *N*-oxidation at the more basic pyridyl nitrogen.¹²⁰⁻¹²²







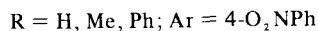
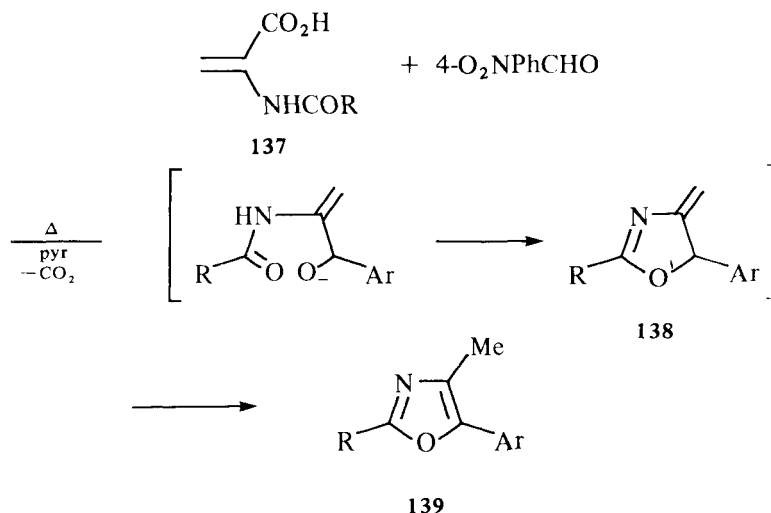




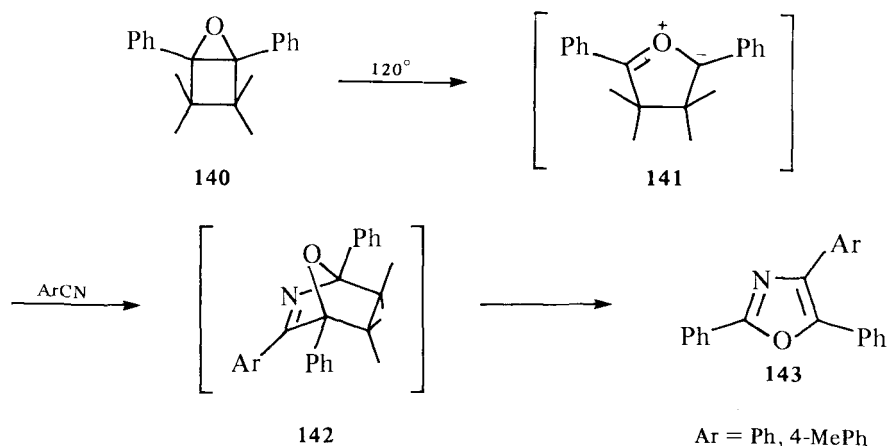
1.2.20. Miscellaneous (Table 1.24)

The parent oxazole has been isolated from the reaction of propylene, oxygen, and ammonia in the vapor phase in the presence of tin and antimony oxides. Water, benzene, methanol, acetone, acrylonitrile, acrolein, and hydrogen cyanide are also formed.¹²³ Despite the low yield of oxazole (5%) obtained in this process, it is probably the most cost-effective method for producing oxazole in an industrial scale because of the inexpensive reactants and the ease of separation of the heterocycle from the other products.

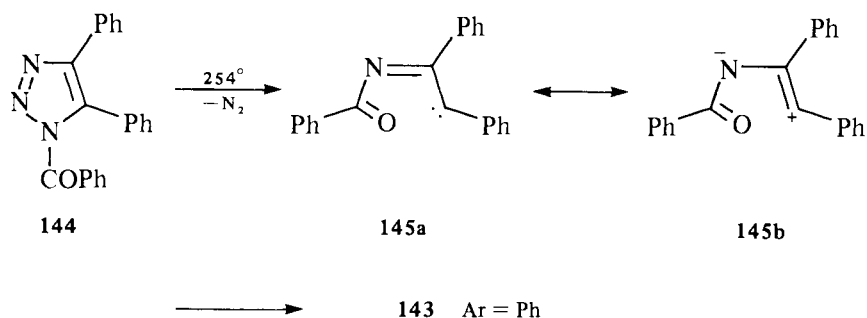
2-Acylaminoacrylic acids **137** react with 4-nitrobenzaldehyde when heated in pyridine to provide 4-methyl-5-(4-nitrophenyl)oxazoles **139**.¹²⁴ The mechanism of this transformation is uncertain but could involve the 4-methylene-2-oxazoline **138** (Section 1.2.10) produced as outlined above.



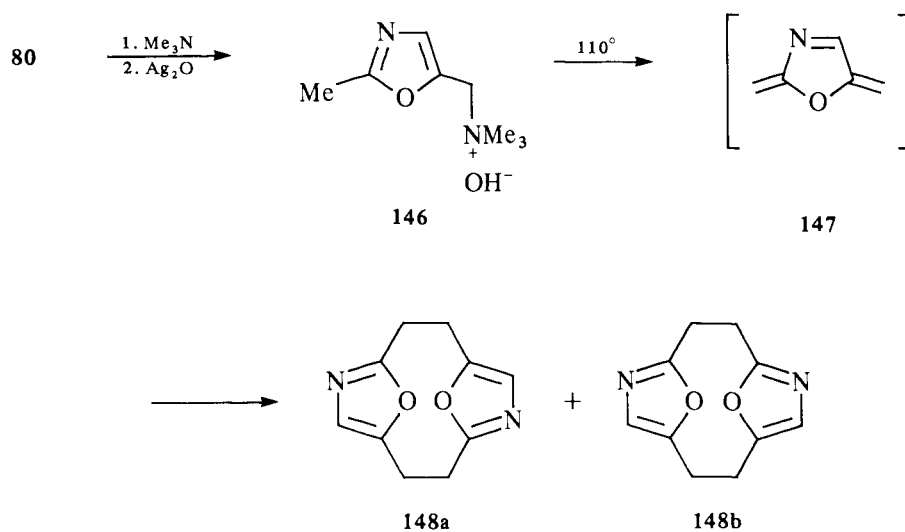
The 1,3-dipolar cycloaddition of carbonyl ylides to various dipolarophiles provides oxygen-containing heterocycles.¹²⁵ Consequently these dipolar species have the potential to act as intermediates leading to oxazoles or oxazolines if allowed to combine with nitriles. The cyclic carbonyl ylide **141** generated in the thermolysis (120°C) of the 5-oxabicyclo[2.1.0]pentane **140** is trapped by aryl nitriles to afford the nonisolable bicyclic intermediate **142**. The latter can be viewed as a Diels–Alder adduct of a 2,5-diphenyl-4-aryloxazole with tetramethylethylene and as such suffers a $[4 + 2]$ cycloreversion to provide the oxazole **143**.¹²⁶



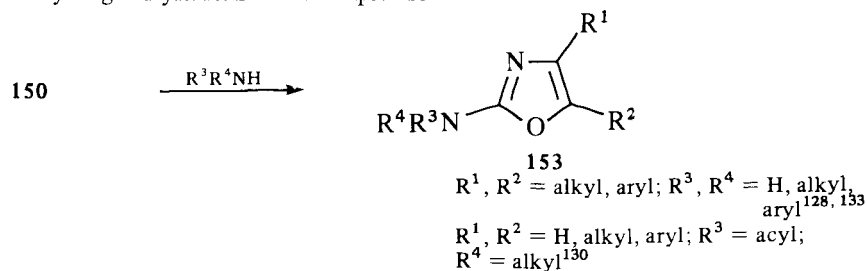
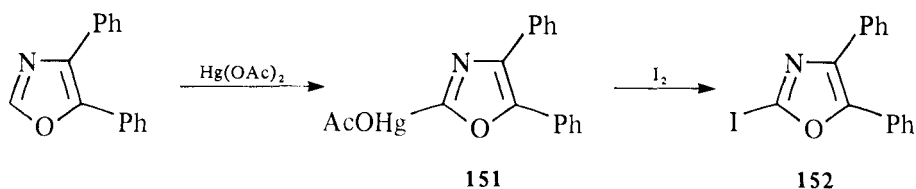
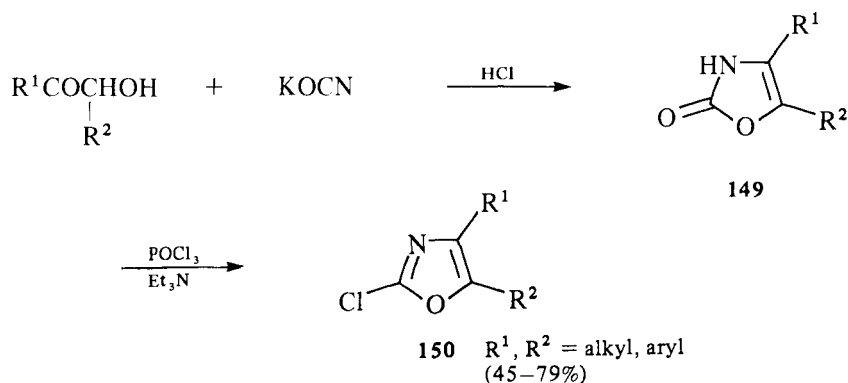
Another type of 1,3-dipole, the *N*-benzoylamino carbene **145** is the proposed intermediate in the pyrolytic decomposition of 1-benzoyl-4,5-diphenyl-1,2,3-triazole (**144**). 1,5-Dipolar electrocyclicization of **145** provides 2,4,5-triphenyloxazole (**143**, Ar = Ph) in 30% yield.¹²⁷

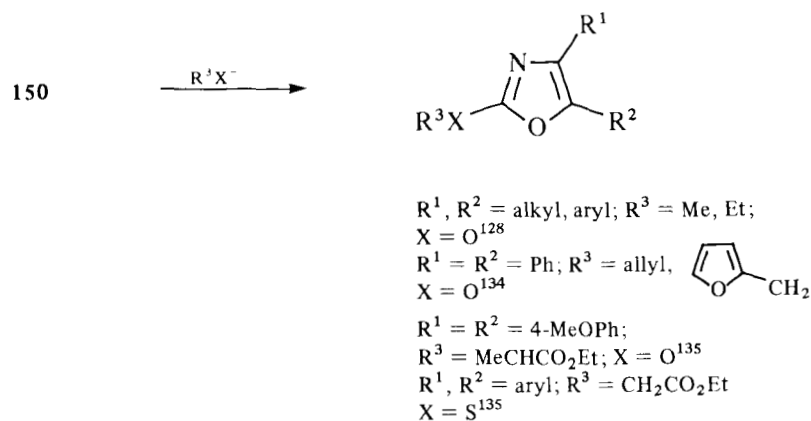


The synthesis of oxazolophanes **87** from acylazirines **86** has been discussed in Section 1.2.14. A second type of oxazolophane, [2.2](2,5)oxazolophane (**148**) (and the corresponding thiazolophane) has recently been reported.⁷⁵ 2-Methyl-5-bromomethyloxazole (**80**) prepared by the reaction of the ketocarbene derived from bromomethyl diazoketone with acetonitrile (Section 1.2.13.) is converted to the quarternary ammonium hydroxide **146** by the reaction of **80** with trimethylamine followed by treatment of the resulting bromide with silver oxide. The isomeric *anti-anti* and *anti-syn* oxazolophanes **148a** and **148b** are obtained in 10.3% overall yield upon thermolysis of **146** in refluxing toluene. The 2,5-bismethylene-3-oxazoline **147** is the presumed intermediate in this reaction by analogy to similar pyrolytic routes to other heterophanes. The structures of **148a** and **148b** were determined primarily by ¹H NMR. None of the isomeric *syn-anti* or *syn-syn* isomers could be detected by this technique.

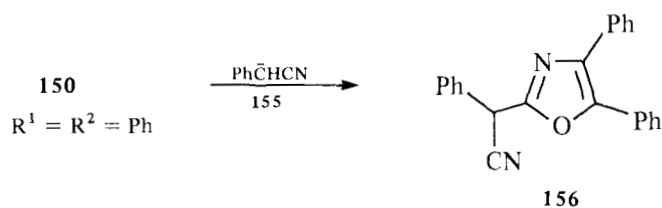


1.3.1. Halooxazoles (Table 1.25)

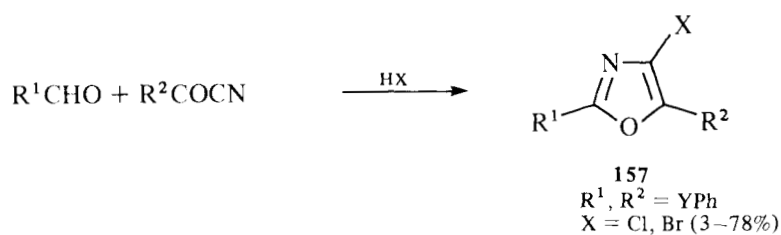




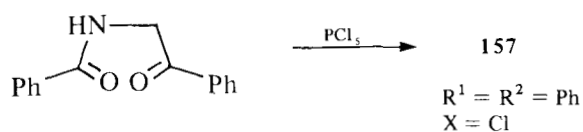
With the carbon nucleophile **155**, **150** gives 2-(cyanobenzyl)-4,5-diphenyloxazole (**156**) in 50% yield.¹²⁸



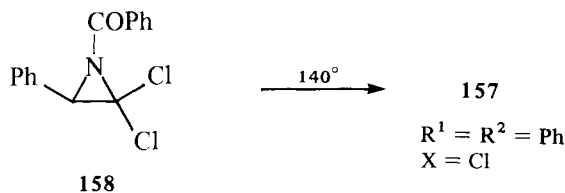
4-Halooxazoles are available by several methods. A variation of the Fisher oxazole synthesis wherein aryl cyanides are used in place of cyanohydrins in their reaction with aryl aldehydes in the presence of hydrogen chloride or bromide provides 2,5-diaryl-4-chloro- or -bromooxazoles **157**.¹³⁷⁻¹³⁹



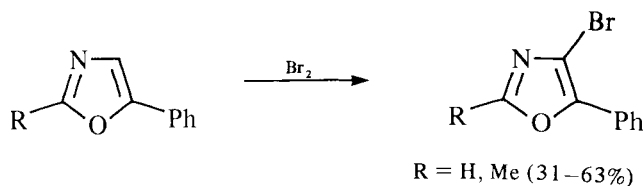
One of the first reports of the synthesis of a 4-chlorooxazole was described by Gabriel and involves the reaction of 2-benzoylaminoacetophenone with phosphorus pentachloride to give **157**, $R^1 = R^2 = \text{Ph}$, $X = \text{Cl}$.¹⁴⁰



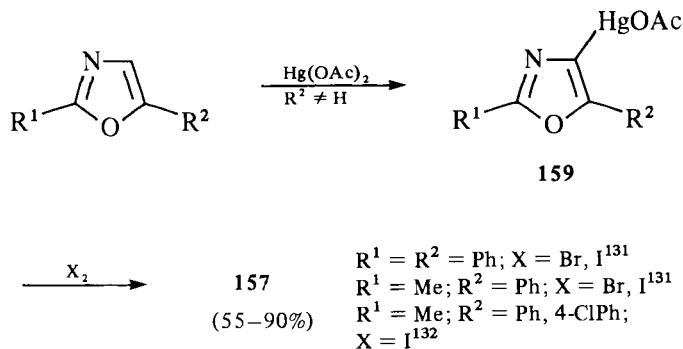
2,5-Diphenyl-4-chlorooxazole (**157**, $R^1 = R^2 = \text{Ph}$, $X = \text{Cl}$) is formed in 81% yield upon thermal ring expansion of 1-benzoyl-2,2-dichloro-3-phenylaziridine (**158**).^{141,142} The corresponding 3-methylaziridine is unreactive under these conditions.



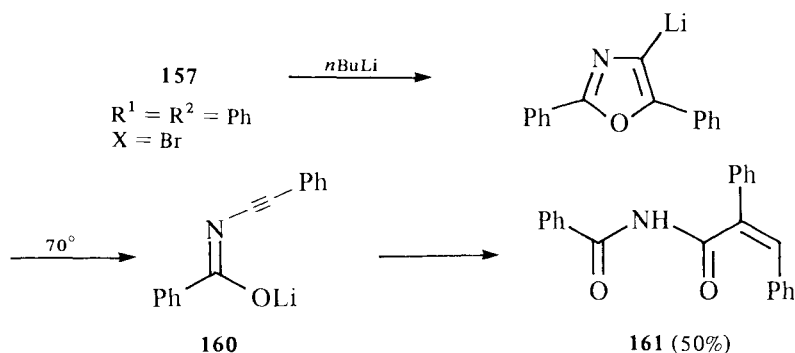
Since the 5-position of the oxazole ring is most susceptible to attack by electrophiles, this position must be blocked in order to successfully brominate the 4-position under electrophilic conditions. This has been accomplished in the case of 2-methyl-5-phenyl- and 2,5-diphenyloxazoles¹⁴³ *N*-bromosuccinimide with bromine/*N*-bromosuccinimide, in carbon tetrachloride in the presence of a trace of hydrogen bromide,¹⁴⁴ or with bromine in acetic acid.⁴⁵



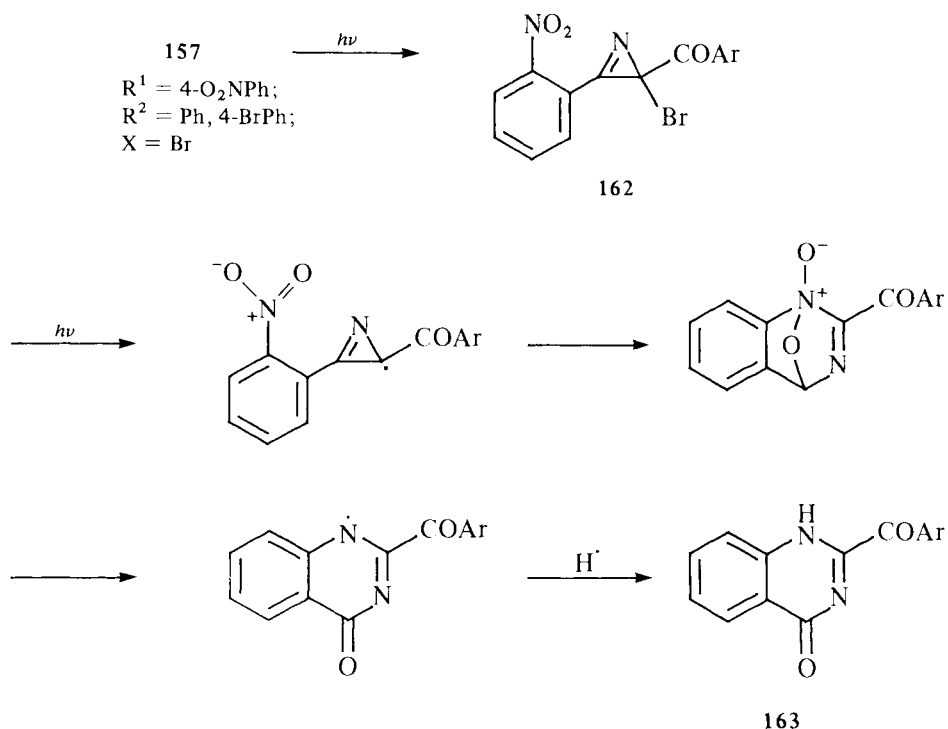
The reaction of bromine or iodine with the 4-acetoxymercurioxazoles **159** affords 4-bromo- or 4-iodooxazoles **157**.^{131,132}



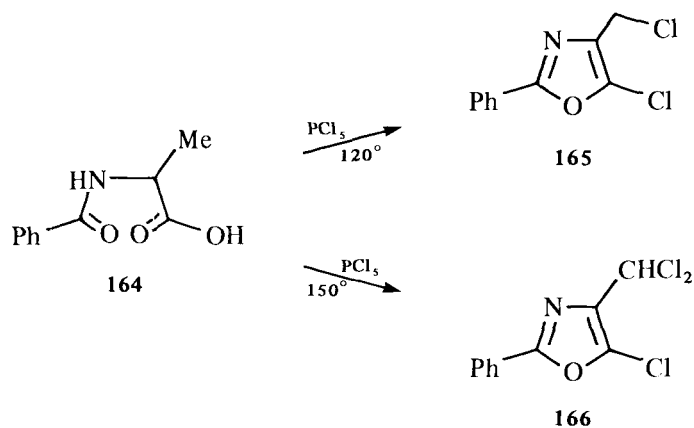
2,5-Diphenyl-4-chlorooxazole is smoothly hydrogenolyzed with 5% palladium on charcoal to 2,5-diphenyloxazole in 83% yield.¹⁴¹ 2,5-Diphenyl-4-deuteriooxazole (**157**, $R^1 = R^2 = \text{Ph}$, $X = \text{D}$) is obtained when the 4-bromo derivative is subjected to bromine-lithium exchange with *n*-butyllithium at -65°C followed by quenching of the resulting 4-lithiooxazole with deuterium oxide.⁴⁵ Heating the same 4-lithiooxazole to 70°C affords the open-chain species **160**, which reacts with benzaldehyde to provide the imide **161**.¹⁴⁴



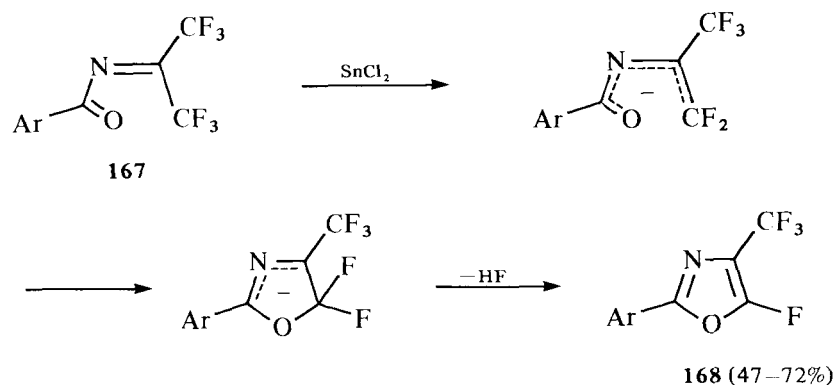
An unusual rearrangement occurs upon photolysis of 2-(2-nitrophenyl)-4-bromo-5-aryloxazoles **157** ($\text{R}^1 = 2\text{-O}_2\text{NPh}$, $\text{R}^2 = \text{Ph}$, 4-BrPh , $\text{X} = \text{Br}$).¹⁴⁵ The products isolated are the 2-arylquinazolones **163** ($\text{R} = \text{H}$, Br). Similar products are not formed upon irradiation of the corresponding 2-(3- and 4-nitrophenyl)-4-bromo-5-aryloxazoles. A mechanism involving the acylazirine **162** was invoked to rationalize the formation of **163**.



The cyclization of *N*-benzoylalanine (**164**) with phosphorus pentachloride at 120°C affords 2-phenyl-4-chloromethyl-5-chlorooxazole (**165**) in 20% yield.¹⁴⁶ 2-Phenyl-4-dichloromethyl-5-chlorooxazole (**166**) is obtained from **164** in 20–25% yield at 150°C with the same reagent. Burger et al. have recently reported the

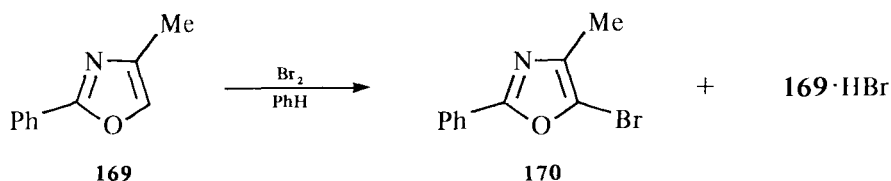


synthesis of 2-aryl-4-trifluoromethyl-5-fluorooxazole (**168**) by the reaction of the *N*-arylimines of hexafluoroacetone **167** with stannous chloride.¹⁴⁷ The proposed mechanism is

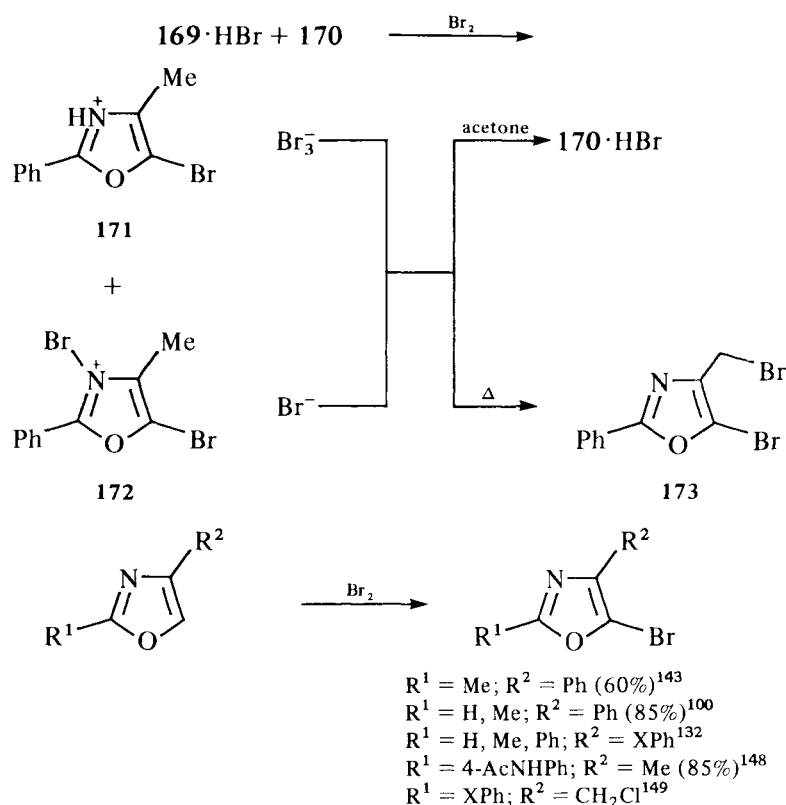


This is the first reported example of a fluorooxazole. The corresponding 5-fluorothiazoles and 5-fluoroimidazoles were prepared in an analogous fashion.

The bromination of alkyl- and aryloxazoles was first investigated by Gompper and Ruhle.¹⁴³ The 5-position of the oxazole ring appears to be the most reactive toward electrophiles, followed by the 4-position which is much more reaction than the 2-position. Phenyl substituents are completely unreactive toward electrophilic bromination even in the presence of catalysts. The reaction of 2-phenyl-4-methyloxazole (**169**) with bromine is of interest. Addition of one equivalent of bromine to a benzene solution of **169** provides 2-phenyl-4-methyl-5-bromooxazole (**170**) in

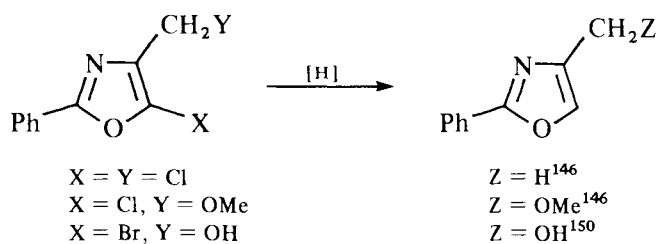


90% yield along with the hydrobromide salt of **169**. Addition of a second equivalent of bromine yields a perbromide and an *N*-bromo derivative whose structures are represented by **171** and **172**, respectively. Treatment of this mixture with acetone gives **170**·HBr, while heating of the mixture in benzene leads to 2-phenyl-4-bromomethyl-5-bromooxazole (**173**) in 61% yield.¹⁴³ Further examples of this process are

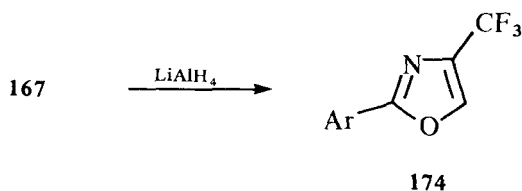


5-Acetoxymercurioxazoles are easily transformed into the corresponding 5-bromo- or 5-iodooxazoles in good yields with bromine or iodine as is the case for the 2- and 4-acetoxymercurioxazoles **151** and **159**, respectively,^{131,132}

The reduction of 5-halooxazoles with hydrogen/palladium on charcoal or zinc in acetic acid leads to 5-unsubstituted oxazoles. This is illustrated by



The 4-trifluoromethyl moiety of the 2-aryl-4-trifluoromethyl-5-fluorooxazoles **167** is presumably responsible for the propensity with which they undergo displacement of fluoride by nucleophiles.¹⁴⁷ Thus the reaction of **167** (Ar = 4-tolyl) with lithium aluminium hydride affords 2-(4-tolyl)-4-trifluoromethyloxazole (**174**) in 60% yield.

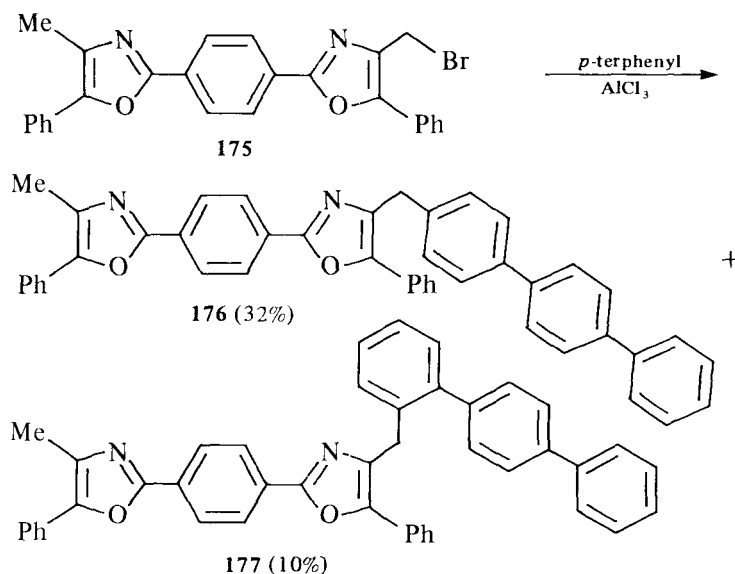


2-Methyl-4-phenyl-5-deuteriooxazole is derived from the reaction of *n*-butyllithium with 2-methyl-4-phenyl-5-bromooxazole followed by quenching of the resulting 5-lithiooxazole with deuterium oxide.¹⁰⁰

Some methods of preparing haloalkyloxazoles are described above (Sections 1.2.1, 1.2.8–1.2.10, 1.2.13, and 1.2.16). Bromomethyloxazoles are readily available by the reaction of *N*-bromosuccinimide (NBS) with methyloxazoles (see Table 1.24).^{46,64,143,151} Although the relative reactivity of methyl groups in the 2-, 4-, and 5-positions of the oxazole ring toward NBS is not known, these substituents all give bromomethyl derivatives when treated with this reagent. The NBS bromination of alkyl substituents other than methyl has not been reported.

Chlorination or bromination of hydroxyalkyloxazoles with thionyl chloride or phosphorus pentabromide provides a useful entry into haloalkyloxazoles (see Table 1.24).

Haloalkyloxazoles demonstrate the normal reactivity patterns expected for these types of species. The halogens are readily displaced by nucleophiles such as amines,^{146,152,153} alkoxides,^{146,151–154} and mercaptides^{151–154} to yield the corre-

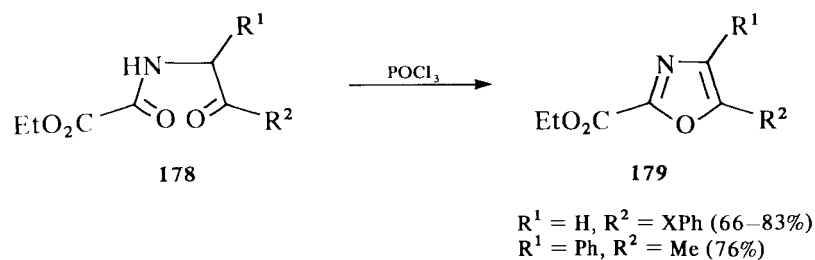


spending aminoalkyloxazoles, oxazolealkyl ethers, and thioethers. Aqueous silver nitrate converts 2-bromomethyl-4,5-diphenyloxazole into 2-hydroxymethyl-4,5-diphenyloxazole.⁴⁶

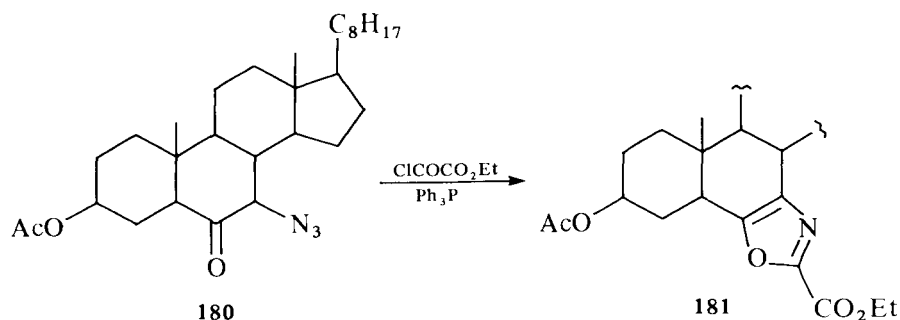
The 4-bromomethylbisoxazolyl benzene **175** undergoes Friedel–Crafts alkylation with *p*-terphenyl to afford the isomeric bisoxazolylbenzenes **176** and **177**.¹⁵¹

1.3.2. Oxazole Esters and Their Derivatives (Tables 1.26–1.38)

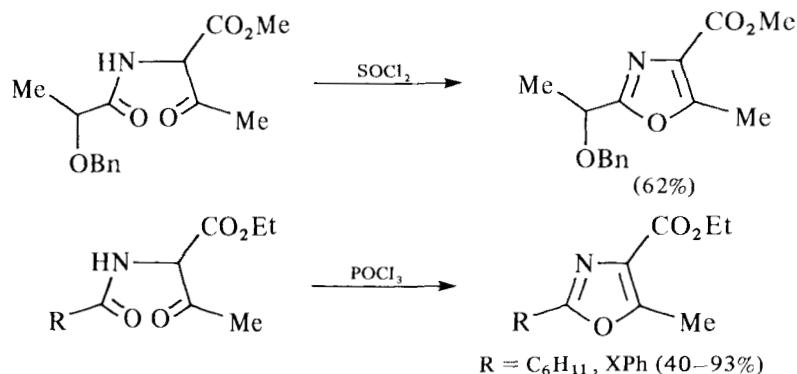
The Robinson–Gabriel cyclization of the 2-acylaminoketones **178** with phosphoryl chloride provides a useful and general synthesis of the ethyl oxazole-2-carboxylates **179**.^{155,156}



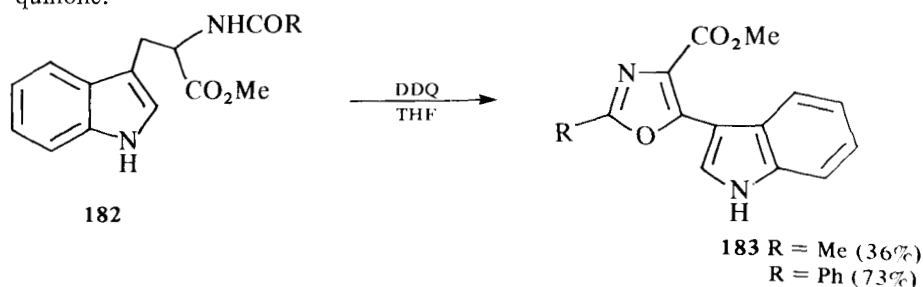
The steroidal azido ketone **180** is converted to the oxazole-2-carboxylic ester **181** (42%) by the reaction with ethyl oxalyl chloride in the presence of triphenylphosphine (Section 1.2.12).⁷²



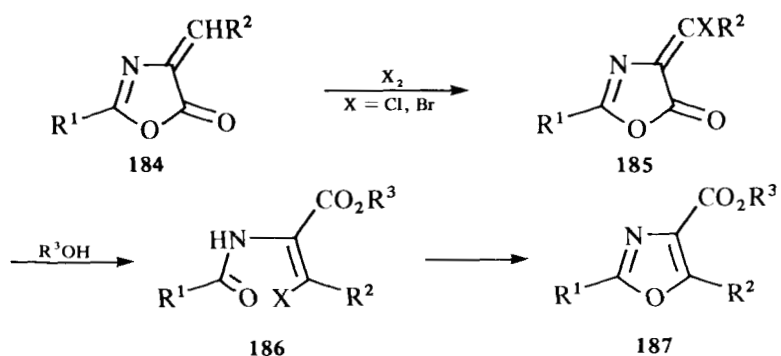
A variety of methods have been developed for the preparation of oxazole-4-carboxylic esters. Alkyl 2,5-disubstituted oxazole-4-carboxylates are available in modest to good yields via the Robinson–Gabriel cyclization of β -acylamino- β -ketoesters. Two recently reported examples are^{157,158}



N-Acyl derivatives of tryptophan **182** have been converted to methyl 5-(3-indolyl)oxazole-4-carboxylates **183** by reaction with dichlorodicyano-*p*-benzoquinone.¹⁵⁹

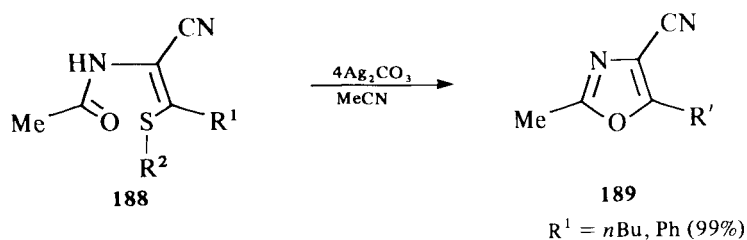


2-Acylamino-3-haloacrylic esters **186** are converted to the oxazole-4-carboxylic esters **187** by treatment with silver fluoride,¹⁶⁰ sodium acetate (175°C)¹⁶¹ or triethylamine.¹⁶² The acrylic esters **186** are prepared by halogenation of the 4-alkylidene oxazolones **184** followed by ring opening of the resulting haloalkylidene oxazolone **185** with alcohols.¹⁶⁰ The best yields of oxazoles **187** are obtained from the bromoacrylic esters **186** $\text{X} = \text{Br}$.

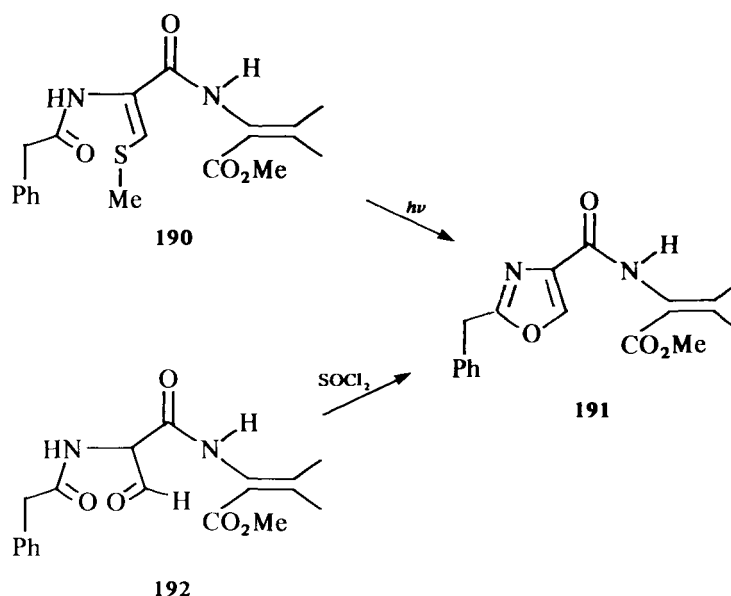


$\text{R}^1 = \text{Ph}; \text{R}^2 = \text{Me}, \text{Ph}; \text{R}^3 = \text{Me}, \text{Et}$ (53–62%)¹⁶⁰
 $\text{R}^1 = \text{Me}; \text{R}^2 = \text{Ph}; \text{R}^3 = \text{Et}$ (56%)¹⁶¹
 $\text{R}^1 = \text{Me}; \text{R}^2 = \text{Me}, \text{Et}; \text{R}^3 = \text{Et}, t\text{Bu}$ (25–58%)¹⁶²

2-Acylamino-3-alkylmercaptoacrylonitriles **188** undergo a similar cyclization in the presence of silver carbonate to afford the 4-cyanooxazoles **189** in high yields.¹⁶³

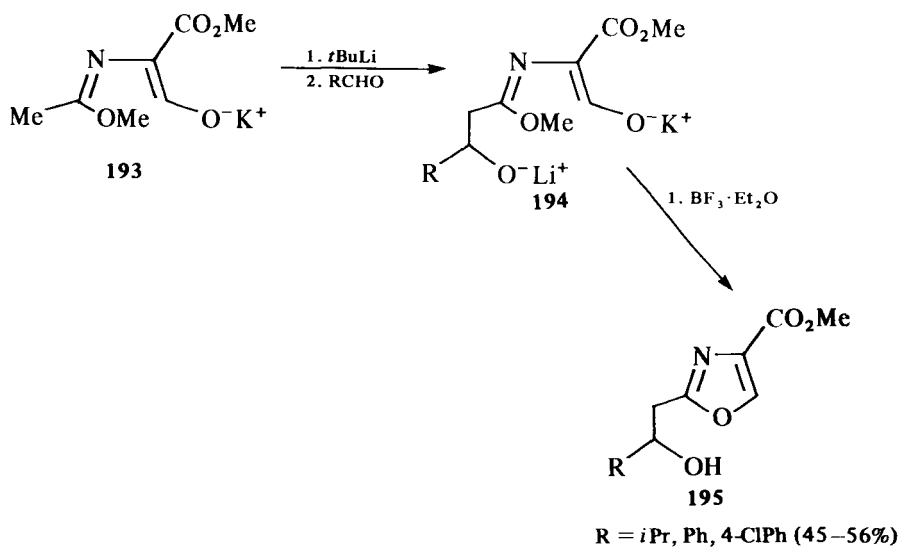


Under photochemical conditions, methyl (*Z*)-*N*-phenylacetyl-*S*-methyldehydrocysteinyldihydrovalinate (**190**) cyclizes to form the oxazole-4-carboxamide **191** in 13% yield along with unchanged starting material and the corresponding (*E*)-isomer of **190**.¹⁶⁴ Thionyl chloride promotes the cyclization of methyl benzylpenaldyldehydrovalinate (**192**) to the same oxazole-4-carboxamide in 8.5% yield.¹⁶⁴

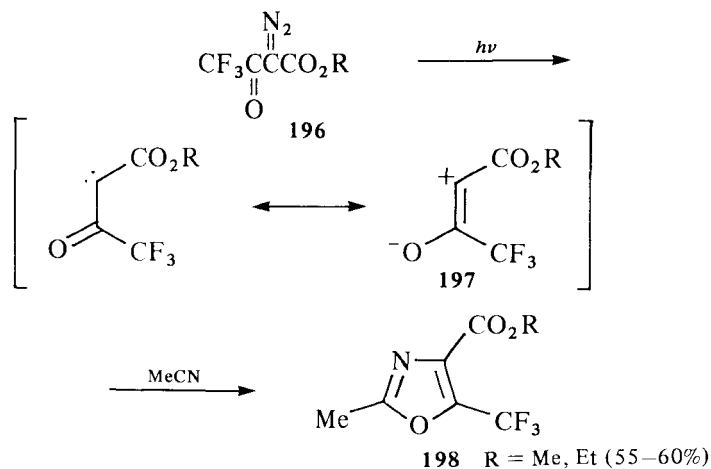


Nearly 40 years ago, Conforth et al. developed a versatile multistep synthesis of oxazole-4-carboxylic esters via cyclization of the potassium salt of alkyl 1-(1-ethoxyethylideneamino)-2-hydroxyacrylates with hot acetic acid.³ The same reaction of the corresponding acrylonitrile provides 4-cyanooxazoles.¹⁶⁵ The total synthesis of Griseoviridin, a naturally occurring oxazole-containing macrocycle, requires methodology for constructing 2-hydroxyethyloxazole-4-carboxylic esters.¹⁶⁶ Attempted metalation of methyl 2-methyloxazole-4-carboxylate or the corresponding carboxylic acid with *n*-butyllithium provided only the 5-lithio-

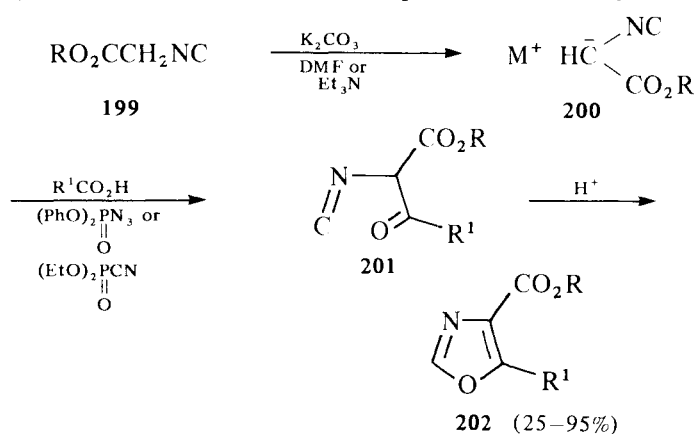
oxazole. No evidence for the formation of the desired 2-lithiomethyloxazole was found (D_2O quench). Elaboration of the methyl moiety of the potassium salt of methyl (1-methoxyethylidene)-2-hydroxyacrylate (**193**) was achieved by deprotonation with *t*-butyllithium following by reaction of the resulting carbanion with aldehydes to yield the products **194**. Cyclization of **194** with $BF_3 \cdot Et_2O$ at room temperature gives the methyl 2-hydroxyethyloxazole-4-carboxylates **195** in moderate yields.¹⁶⁶



Photolysis of alkyl 2-diaza-4,4,4-trifluoroacetoacetates (**196**) leads to the carbonyl carbenes **197**. When the latter is generated in acetonitrile, a 1,3-dipolar addition occurs to provide alkyl 2-methyl-5-trifluoromethyloxazole-4-carboxylates **198** (Section 1.2.13).^{167,168} Similarly, the boron trifluoride etherate catalyzed decomposition of methyl 2-diazoacetoacetate in acetonitrile produces methyl 2,5-dimethyloxazole-4-carboxylate in 32% yield.⁷⁴

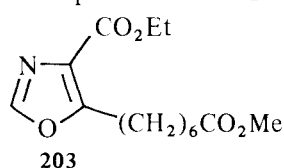


Alkyl isocyanoacetates **199** are easily deprotonated with bases such as *n*-butyllithium or potassium *t*-butoxide to give the 2-metallated isocyanoesters **200**. These species react with acyl halides or anhydrides to provide alkyl 5-substituted oxazole-4-carboxylates **202**.⁶ This reaction proceeds via the acylated isocyanoesters **201** and is a versatile procedure for the preparation of a variety of oxazole derivatives (see Section 1.2.3). To avoid the use of acyl halides in this process, Shioiri et al. utilized diphenyl phosphorazidate^{169,170} or diethyl phosphorocyanidate¹⁷¹ as coupling reagents in the reaction of **200** (R = Me) with carboxylic acids to give **202** (R = Me). The reaction conditions are compatible with a variety of functional

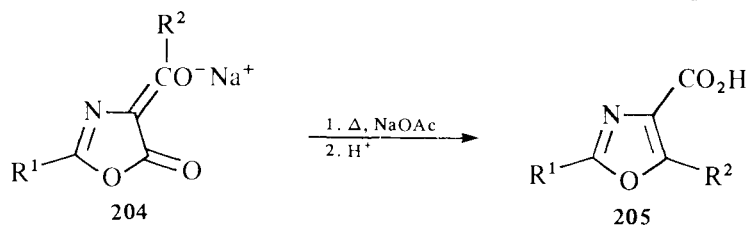


groups present on the carboxylic acid. For example, *N*-protected α -amino acids may be used as substrates in this process leading to methyl 5-aminomethyloxazole-4-carboxylates.^{169,170}

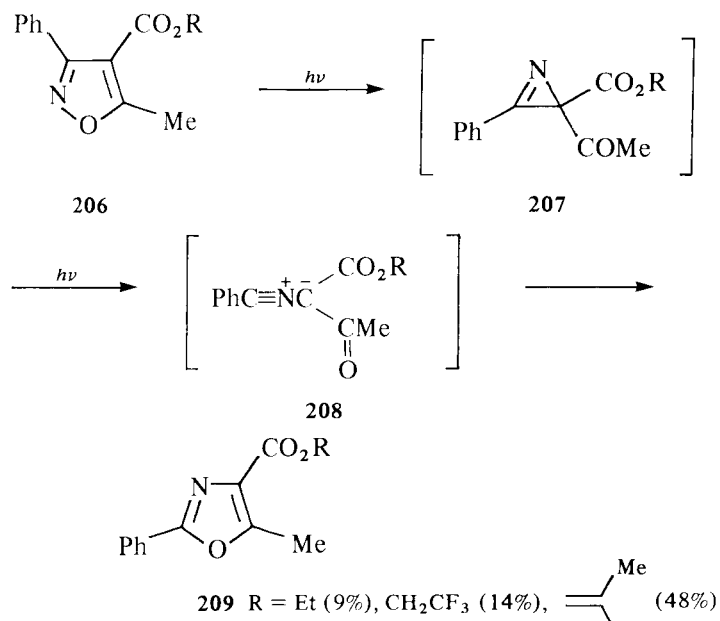
Treatment of ethyl isocyanoacetate (**199**, R = Et) with base followed by reaction of the resulting carbanion **200**, R = Et, with methyl suberyl chloride yields the oxazole ester **203**, which is a precursor to oxazole analogs of prostaglandins.¹⁷²



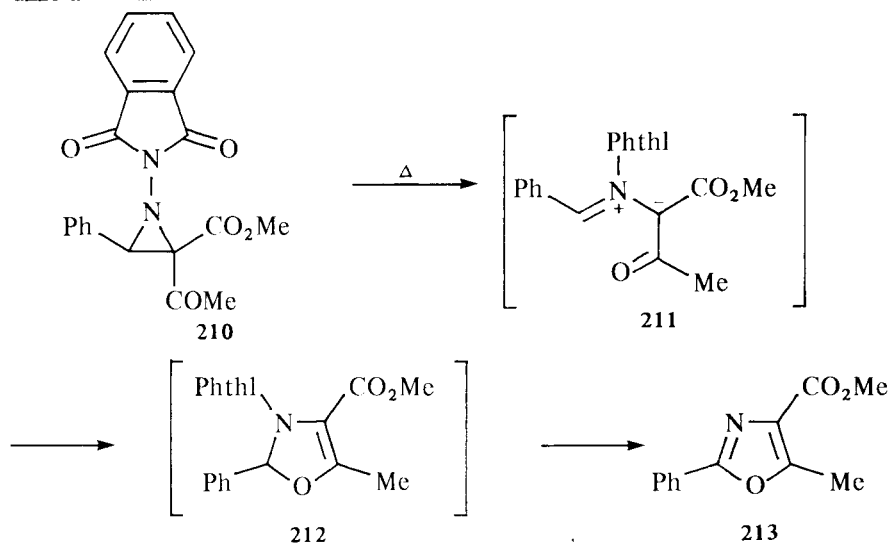
Upon heating in the presence of sodium acetate, the sodium or potassium salts of 2-vinyl- or -aryl-4-hydroxyalkylidene-5-oxazolones **204** rearrange to produce 2-vinyl- or -aryloxazole-4-carboxylic acids **205** in moderate yields.^{3,173,174} The mechanism of this transformation was studied using ¹⁴C labeling techniques.¹⁷⁵



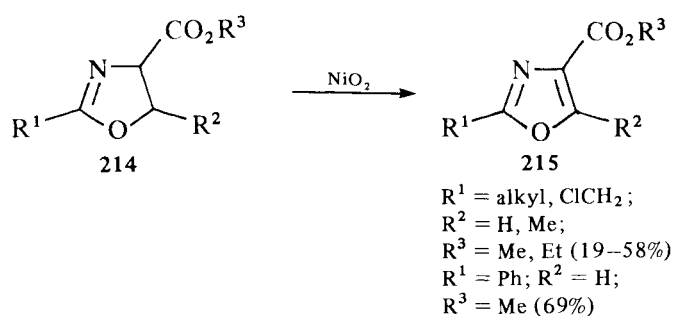
Irradiation of the 3-phenyl-5-methylisoxazole-4-carboxylic esters **206** leads to the formation of the 2-phenyl-5-methyloxazole 4-carboxylic esters **209**, presumably via the azirines **207** and nitrile ylides **208** (Section 1.2.14).¹⁷⁶



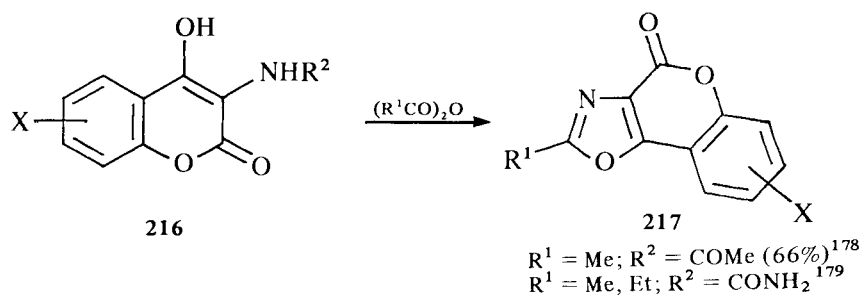
Methyl 2-phenyl-5-methyloxazole-4-carboxylate **213** is obtained in 98% yield when the *N*-phthalimidoaziridine **210** is thermolyzed.¹⁷⁷ A mechanism involving a 1,5-dipolar cyclization of the initially formed azomethine ylide **211** to the oxazoline **212** followed by elimination of phthalimide was postulated in order to rationalize the formation of **213**.



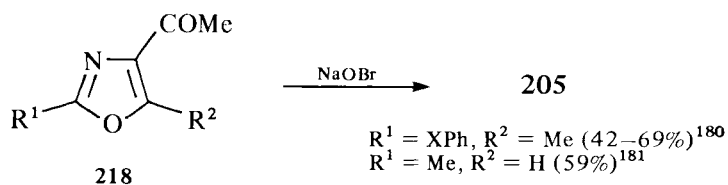
The oxidation of the alkyl 2-oxazoline-4-carboxylates **214** with nickel peroxide affords the alkyl oxazole-4-carboxylates **215** (Section 1.2.15).⁹¹



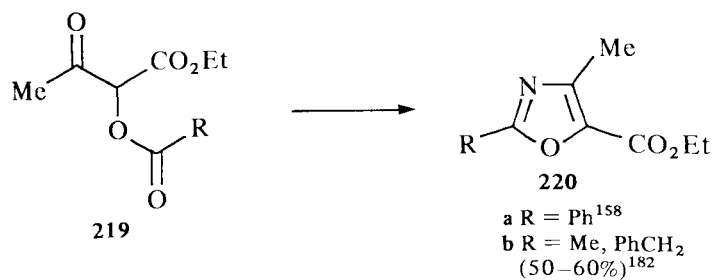
The oxazolocoumarins **217** have been prepared by the reaction of the coumarins **216** with carboxylic acid anhydrides.^{178,179}



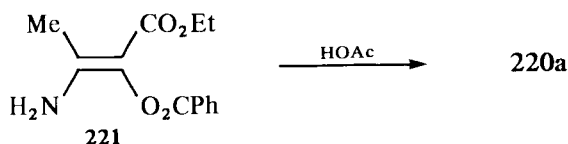
The 4-acetyloxazoles **218** are converted to the oxazole-4-carboxylic acids **205** by oxidation with sodium hypobromite.^{180,181}



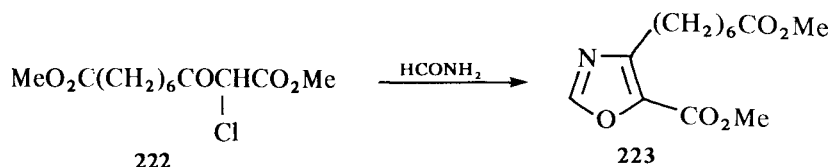
Two classical oxazole syntheses have been applied to the preparation of oxazole-5-carboxylic esters **220**. The first employs the Davidson synthesis, that is, the reaction of α -acyloxy- β -ketoesters **219** with formamide or ammonium acetate (Section 1.2.6).^{158,182}



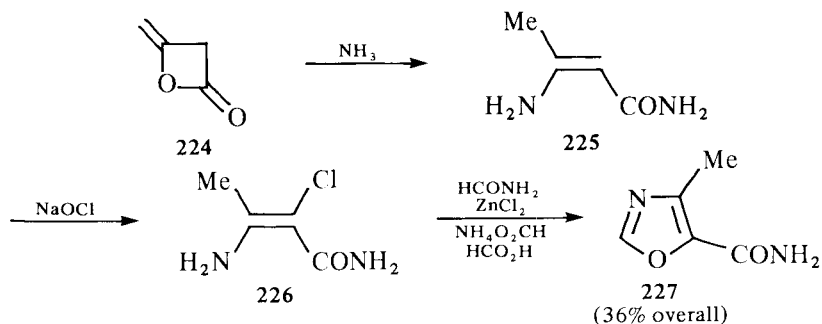
A variation of this procedure involves the cyclization of the enaminoester **221** to **220a** in 82% yield with acetic acid.¹⁸³



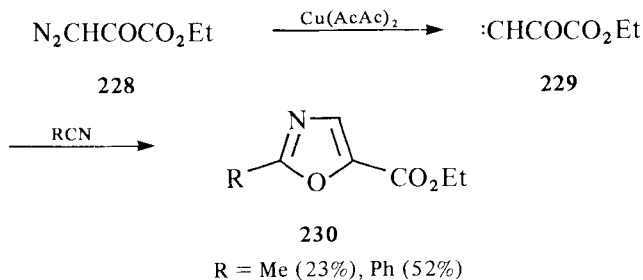
The second method, due to Blumlein and Lewy, is the reaction of α -chloro- β -ketoesters with amides or ammonium formate (Section 1.2.7). A recently reported application of this process is the synthesis of the methyl oxazole-5-carboxylate **223** from **222** and formamide.¹⁸⁴



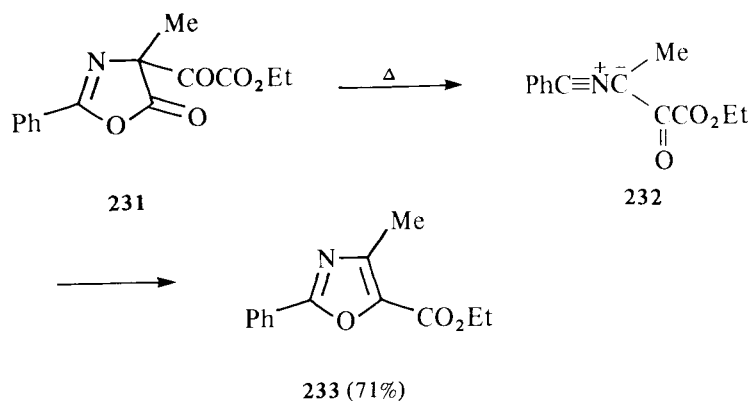
Diketene (**224**) reacts with ammonium to give β -aminocrotonamide (**225**). Treatment of **225** with sodium hypochlorite affords *trans*- α -chloro- β -aminocrotonamide (**226**). Cyclization of **226** with formamide, zinc chloride, and ammonium formate in formic acid solution provides 4-methyloxazole-5-carboxamide (**227**).¹⁸⁵



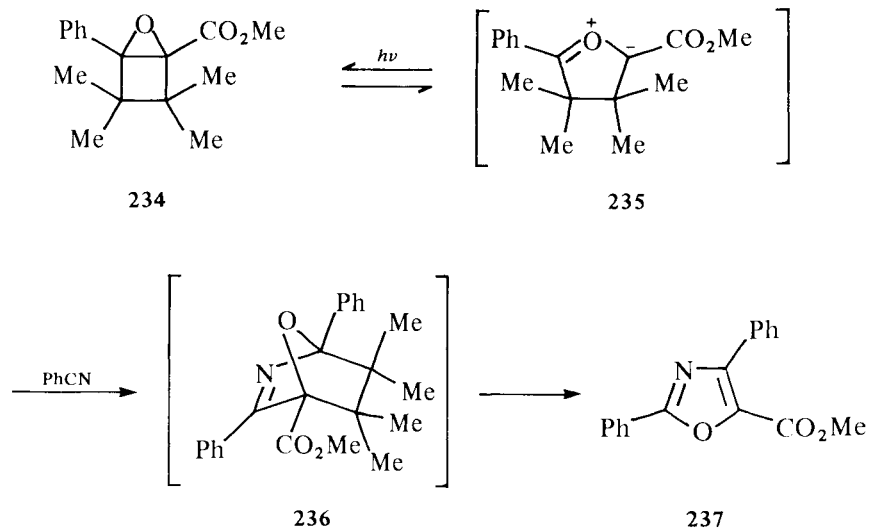
Ethyl diazopyruvate (**228**) suffers elimination of nitrogen upon treatment with copper acetylacetonate. When this reaction is performed in the presence of nitriles, the ethyl 5-oxazolecarboxylates **230** are formed presumably via the carbonyl carbene **229**.¹⁸⁶



Elimination of carbon dioxide occurs when 2-phenyl-4-methyl-4-ethoxyallyl-2-oxazolin-5-one (**231**) is pyrolyzed leading to the carbonylnitrile ylide **232**. 1,5-Dipolar cyclization of **232** yields 2-phenyl-4-methyloxazole-5-carboxylate (**233**).⁹⁴



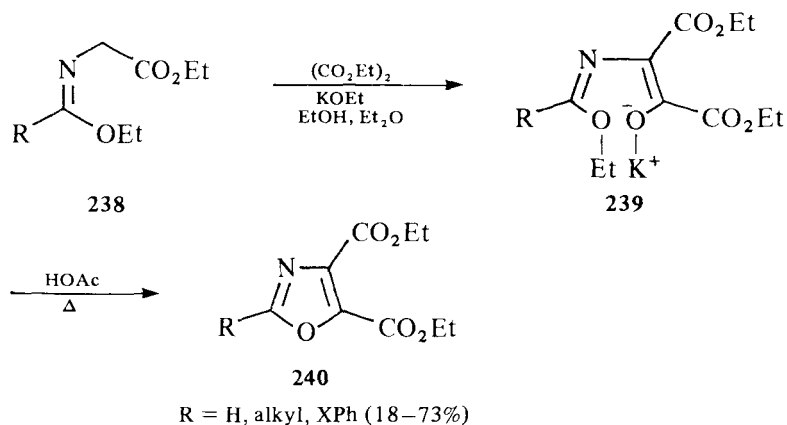
The photochemical electrocyclic ring opening of the bicyclic epoxide **234** gives the carbonyl ylide **235**, which is trapped by nitriles, leading to the formation of the bicyclic intermediate **236**. Elimination of tetramethylethylene from **236** in a retro Diels–Alder reaction provides methyl 2,4-diphenyloxazole-5-carboxylate (**237**).¹⁸⁷



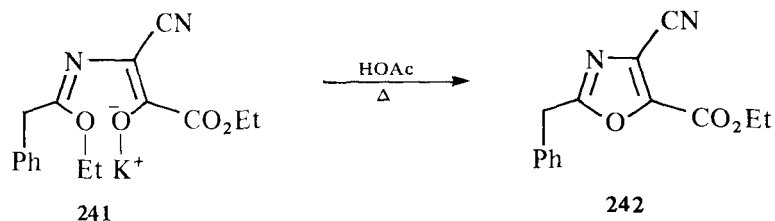
It is of interest to note that the dipolar addition of benzonitrile to the ylide **235** is regiospecific since the isomeric methyl 4,5-diphenyloxazole-2-carboxylate was not detected.

Several procedures have been developed which provide access to oxazole-4,5-dicarboxylic esters **240**. The first of these involves the Cornforth oxazole ester synthesis, that is, the cyclization of the imidates **239** with hot acetic acid. Com-

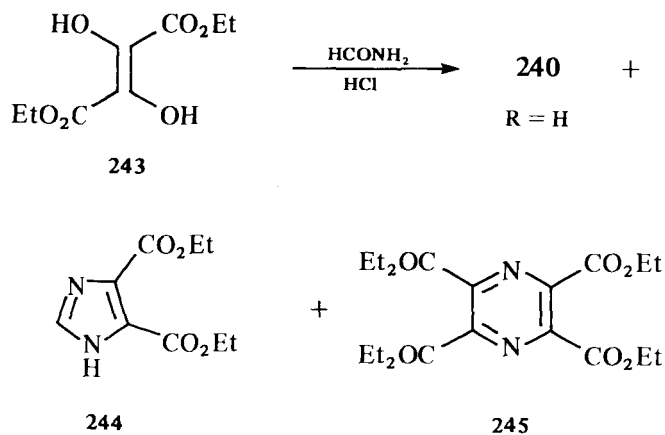
pound **239** is in turn derived from the reaction of the imidate **238** with ethyl oxalate and potassium ethoxide.^{158,182} Diamides prepared from **240** were tested as



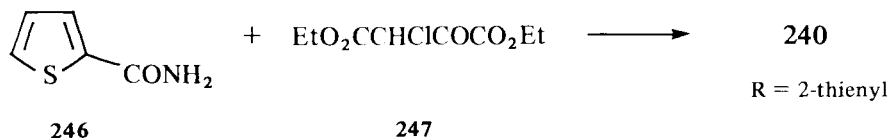
antiinflammatory agents.¹⁵⁸ Similarly, ethyl 2-benzyl-4-cyanooxazole-5-carboxylate (**242**) was prepared from the imidate **241**.¹⁸²



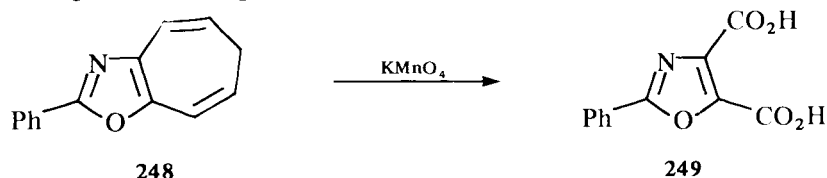
Dimethyl and diethyl dihydroxyfumarates (**243**) combine with formamide in the presence of anhydrous hydrogen chloride to afford dimethyl or diethyl oxazole-4,5-dicarboxylates (**240**, R¹ = H, R² = Me, Et) along with small amounts of the corresponding imidazole-4,5-dicarboxylates **244** and the pyrazine tetracarboxylates **245**.¹⁸⁸



Diethyl 2-(2-thienyl)oxazole-4,5-dicarboxylate (**240**, $R^1 = 2\text{-thienyl}$, $R^2 = \text{Et}$) has been prepared by the reaction of thiophene-2-carboxamide (**246**) with the chloroketone **247**.¹⁸⁹ The corresponding thiazole and selenazole diesters were obtained analogously.



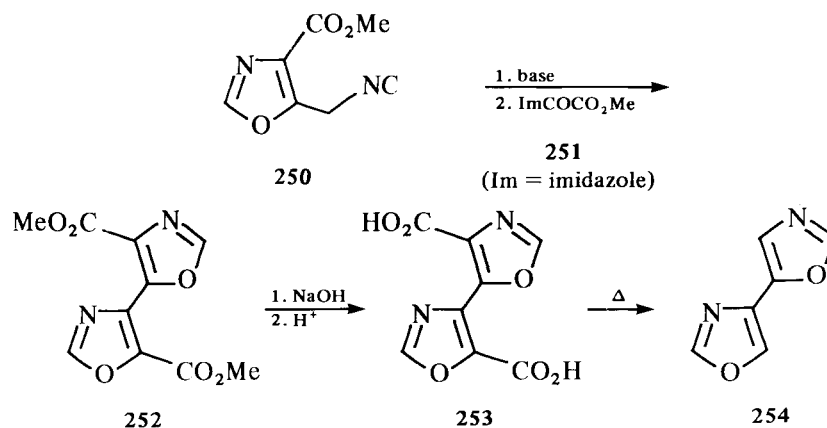
Treatment of the oxazolocycloheptatriene **248** with potassium permanganate produces 2-phenyloxazole-4,5-dicarboxylic acid (**249**).¹⁹⁰ It is surprising that any oxazole-containing product could be isolated in view of the lability of the ring toward vigorous oxidizing conditions.²⁻⁵



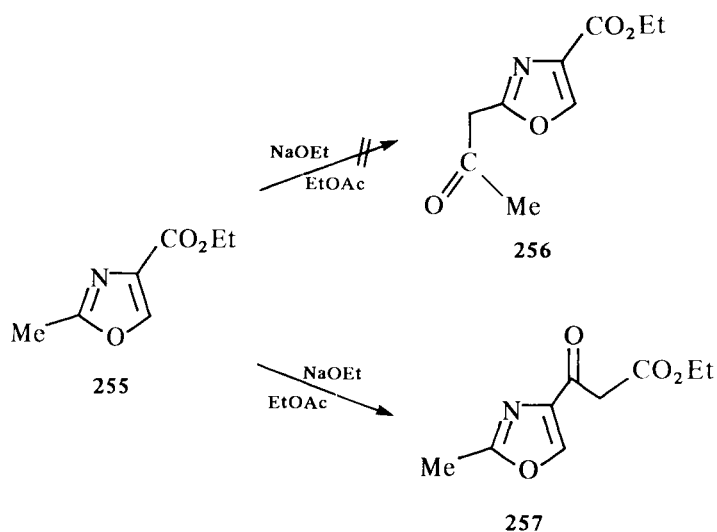
Oxazole carboxylic esters undergo many of the standard transformations of other aromatic esters. Most of the references given for the synthesis of oxazole esters also describe these ester group modifications. Hydrolysis of oxazole carboxylic esters with alkali provides the acids.^{3,156,158,167,182} Reactions with ammonia or amines give amides^{3,156,158,188} and with hydrazines afford hydrazides.³ The acids are easily converted to the corresponding acid chlorides with thionyl chloride or phosphorus pentachloride^{3,191} and from these intermediates, amides,^{3,158,191,192} hydrazides,^{191,192} esters,¹⁹³ and thioesters¹⁹⁴ have been obtained. Under dehydration conditions, for example, phosphorus pentoxide, primary oxazole carboxamides yield cyanooxazoles.^{3,156,195,197} The cyanooxazoles are converted into oxazole thioamides with hydrogen sulfide under basic conditions^{182,195} while *N*-substituted thioamides are obtained from *N*-substituted amides with phosphorus pentasulfide.^{196,197} The primary thioamides react with 2-bromoketones to give thiazolyloxazoles.¹⁹⁵ Oxazole carboxylic acids and their derivatives are useful intermediates in the synthesis of aminooxazoles (via the Curtius rearrangement) and oxazole aldehydes and ketones. These transformations are discussed below in the appropriate sections.

Thermolysis of oxazole-2-,¹⁵⁵ 4-,^{51,175,198} and 5-¹⁸² carboxylic acids and oxazole-4,5-dicarboxylic acids^{188,189} usually in the presence of copper or cuprous oxide leads to decarboxylation affording the oxazole derivatives in moderate to high yields. This procedure when applied to oxazole-4-carboxylic acid¹⁸⁸ or oxazole-4,5-dicarboxylic acid¹⁸⁸ remains the only method for the preparation of the parent heterocycle on a laboratory scale. A second interesting application of the thermal decarboxylation of oxazole carboxylic acids is the synthesis of 4,5'-bioxazole (**254**).³⁰ Treatment of methyl 5-isocyanomethyloxazole-4-carboxylate (**250**) with base followed by reaction of the resulting carbanion with the imidazolidine **251**

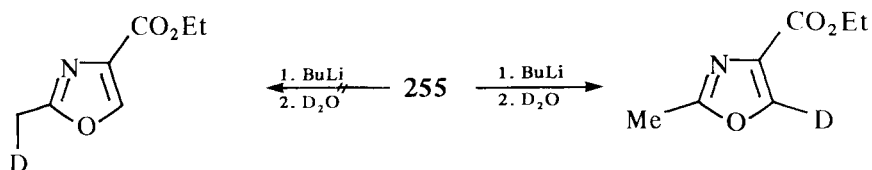
yields 5,4'-bioxazole-4,5-dicarboxylate (**252**). Hydrolysis of **251** and decarboxylation of the diacid **253** provides **254** in 20% overall yield.



The reaction of ethyl 2-methyloxazole-4-carboxylate (**255**) with ethyl acetate and sodium ethoxide was reported to give the 2-acetyl derivative **256**.¹⁹⁹ This claim has been refuted by Meyers and Walker who showed that the product of this reaction is the ketoester **257**.¹⁸¹ Deprotonation of **255** with the stronger base,

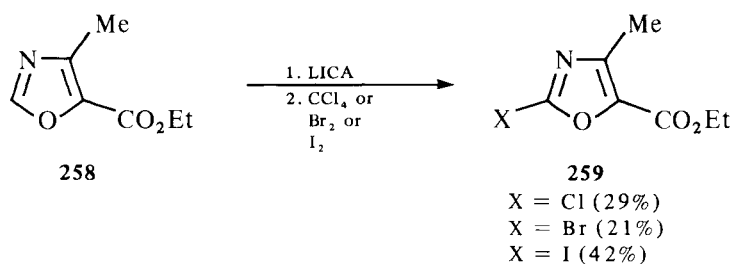


n-butyllithium, leads to the 5-lithiooxazole rather than the 2-lithiomethyl derivative as shown by quenching of the reaction mixture with deuterium oxide.¹⁸¹

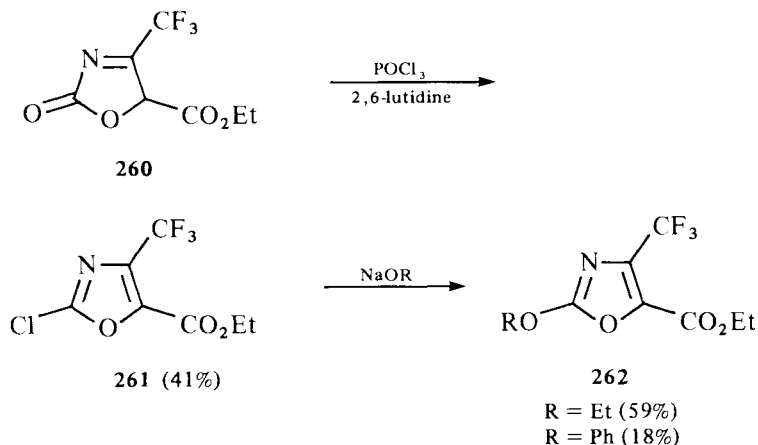


1.3.3. Halooxazole Esters (Table 1.51)

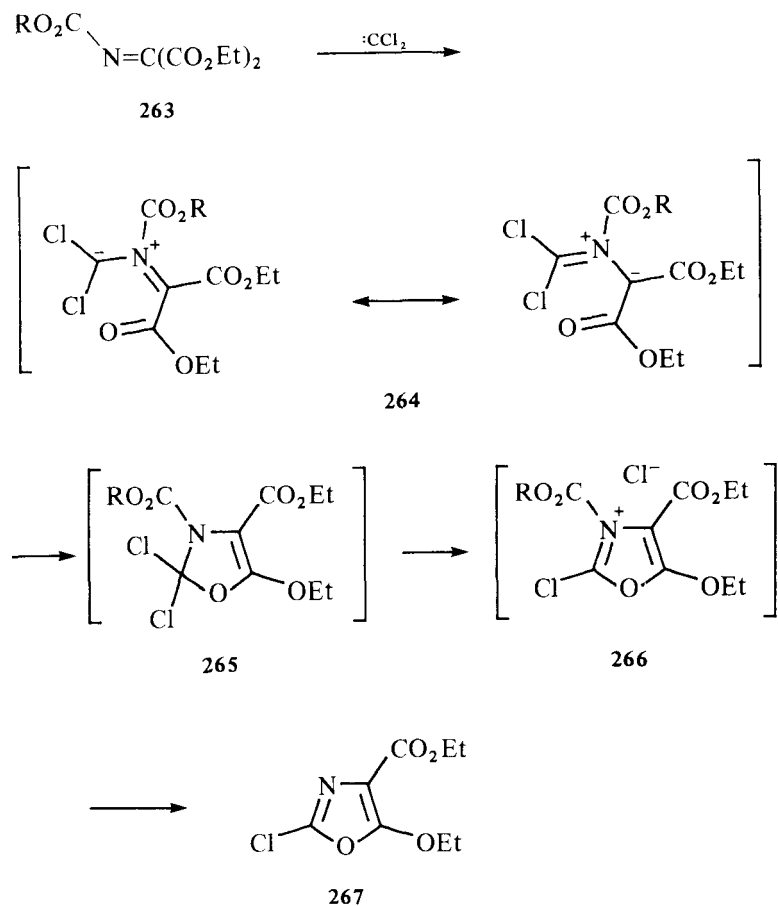
A recent report in the patent literature discloses a novel method for the preparation of ethyl 2-halo-4-methyloxazole-5-carboxylates **259**.²⁰⁰ Deprotonation of ethyl 4-methyloxazole-5-carboxylate (**258**) with lithium isopropylcyclohexyl amide followed by reaction of the anion with a halogenating agent affords **259** in modest yields. Ethyl 2-chloro-4-trifluoromethyloxazole-5-carboxylate (**261**) was prepared



by a different approach, that is, the reaction of ethyl 4-trifluoromethyl-3-oxazolin-2-one-5-carboxylate (**260**) with phosphoryl chloride.²⁰⁰ Displacement of the 2-chloro substituent from **261** with ethoxide or phenoxide leads to the ethyl 2-ethoxy- or 2-phenoxy-4-trifluoromethyloxazole-5-carboxylates **262**.²⁰⁰ These compounds are effective in reducing injury to plants caused by certain herbicides.



Studies on the 1,4-addition of dichlorocarbene to heterodienes lead to the observation that the carbene adds to the *N*-alkoxycarbonyl imine **263** to produce ethyl 2-chloro-5-ethoxyoxazole-4-carboxylate **267** in 20–35% yield.²⁰¹ The proposed mechanism for this transformation involves attack of dichlorocarbene (generated by the thermolysis of phenyl trichloromethylmercury) on the imine nitrogen leading to the azomethine ylide **264**, which undergoes a 1,5-dipolar cyclization to give the 4-oxazoline **265**. This intermediate collapses to the observed product **267** via the oxazolium cation **266**.

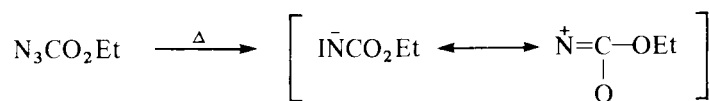


Ethyl 5-chlorooxazole-4-carboxylates are accessible via the Cornforth rearrangement of 5-alkoxyoxazole-4-carboxylic acid chlorides. This reaction is discussed in greater detail in Section 1.3.4.

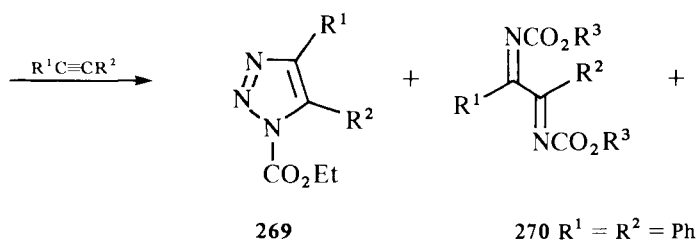
1.3.4. Alkoxyoxazoles and Acyloxyoxazoles (Tables 1.42, 1.43, 1.53, and 1.54)

One of the best methods for preparing 2-alkoxyoxazoles involves displacement of chloride from 2-chlorooxazoles by alkoxide as described in Section 1.3.1.

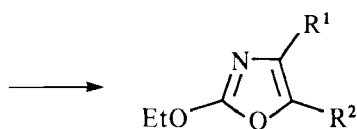
An intriguing process that provides 2-ethoxyoxazoles **271** is the 1,3-dipolar cycloaddition of ethoxycarbonyl nitrene **268** (generated via thermolysis of ethyl azidoformate) to acetylenes.^{202,203} In some cases, the triazoles **269** derived from a dipolar addition of ethyl azidoformate to the acetylene were isolated as the major products while for diphenylacetylene as the dipolarophile, the bis adduct **270** was also produced.²⁰² The reaction is thus of limited synthetic utility.



268



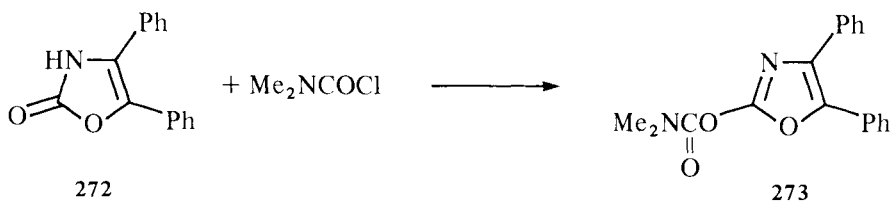
269

270 $\text{R}^1 = \text{R}^2 = \text{Ph}$ 

271

$\text{R}^1 = \text{R}^2 = \text{Ph}$ (33%); $\text{R}^1 = \text{CO}_2\text{Et}$, $\text{R}^2 = \text{Ph}$ (27%);
 $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$ +/or $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$ (16%)
 $\text{R}^1 = \text{R}^2 = \text{CO}_2\text{Me}$ (3%); $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{H}$ (3%)

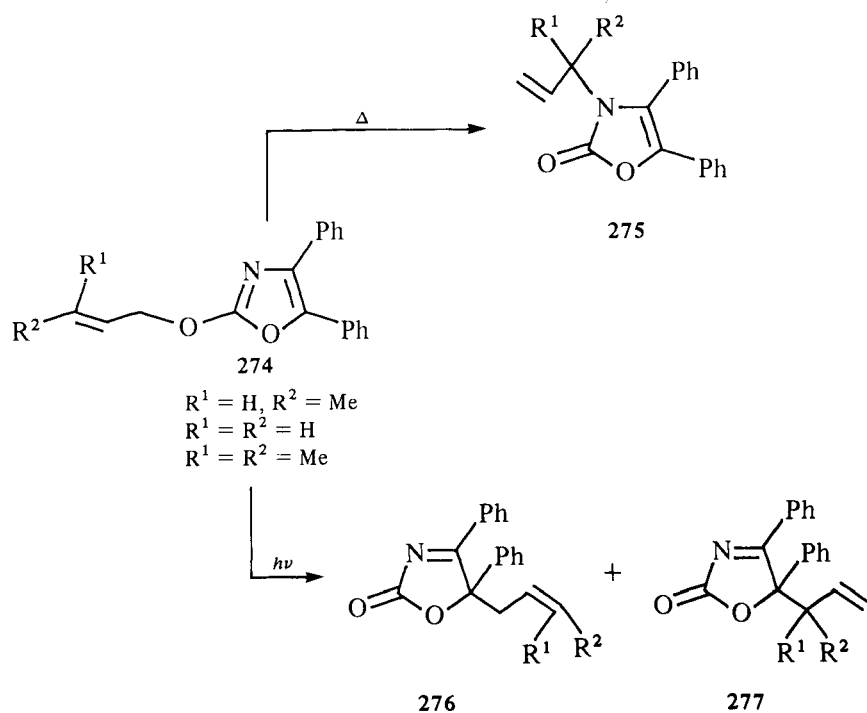
The reaction of 4,5-diphenyl-4-oxazolin-2-one (272) with dimethylcarbamoyl chloride leads to *O*-acylation to provide the oxazole 273.⁹²



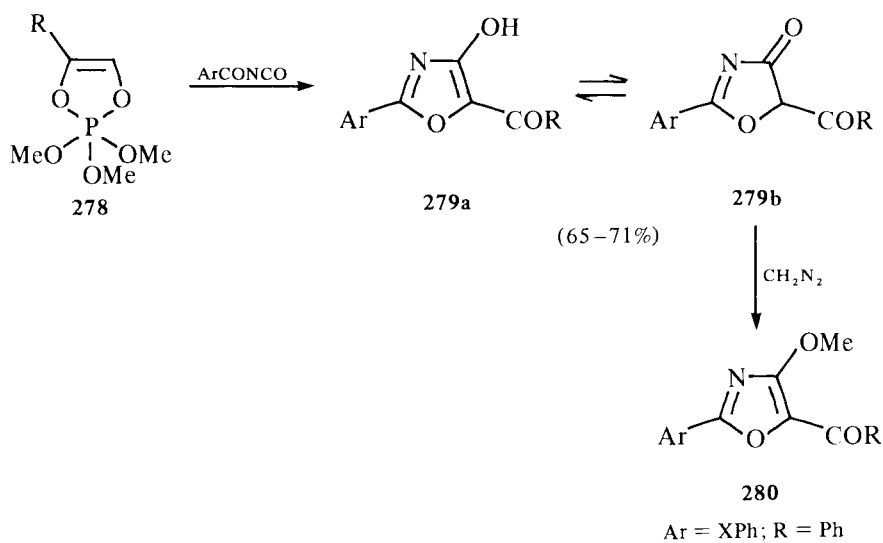
272

273

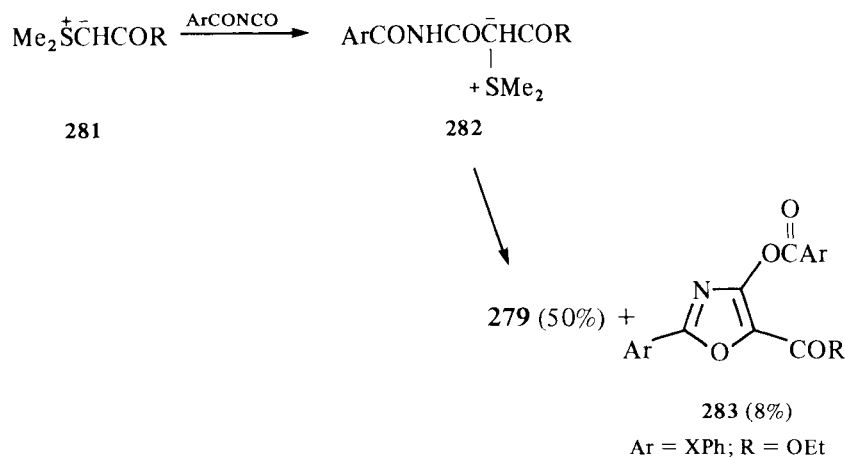
2-Allyloxy-4,5-diphenyloxazoles 274, prepared by treating 2-chloro-4,5-diphenyloxazole with allyl alkoxides, undergo a thermal Claisen rearrangement to give the 3-allyl-4-oxazolin-2-ones 275 in high yields. In contrast, upon photolysis, 274 provides the 5-allyl-3-oxazolin-2-ones 276 and 277.¹³⁴ The proposed mechanism for the photochemical process which is consistent with the experimental results involves carbon-oxygen bond scission to give a pair of radicals which undergo a subsequent recombination to afford the observed products 276 and 277.



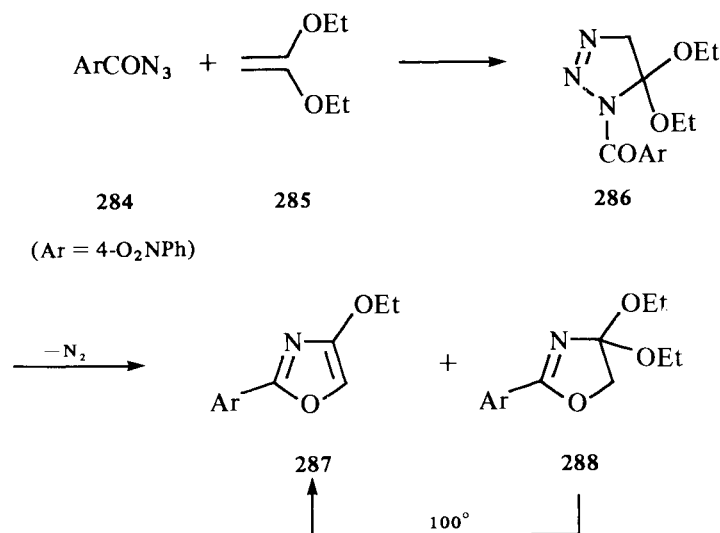
Only a few reports of the preparation of 4-alkoxyoxazoles have appeared in the literature thus far. The reaction of the 4-hydroxyoxazoles (or 2-oxazolin-4-ones) **279** with diazomethane provides the 4-methoxyoxazoles **280**.²⁰⁴ The 4-hydroxyoxazoles **279** were prepared by the reaction of the phospholene **278** with aryl isocyanates.



Aroyl isocyanates combine with the carbonyl-stabilized sulfonium ylides **281** to provide the ylides **282** which, upon thermolysis, produce **279** (Ar = XPh, R = OEt) as the major products along with the 4-aroxyoxazoles **283**.²⁰⁵

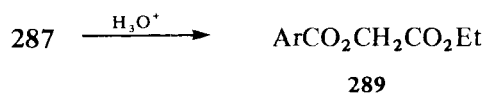


Scarpati et al. have reported the results of their studies of the reaction of azides with ketene acetals. These workers have shown that 4-nitrobenzoyl azide (**284**) and ketene diethylacetal (**285**) combine to yield 2-(4-nitrophenyl)-4-ethoxyoxazole (**287**) and the diethoxyoxazoline **288**.²⁰⁶ At 100°C **288** suffers elimination of ethanol to give the oxazole **287**.

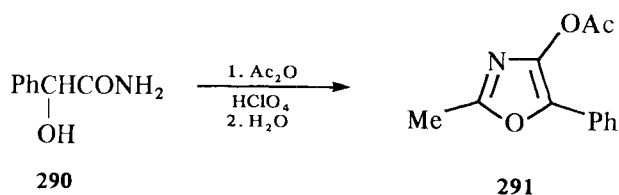


The ester **289** is formed upon acid hydrolysis of the oxazole **287**. Oxazoline formation presumably occurs via the thermal decomposition of the initially formed cycloadduct, 1-(4-nitrobenzoyl)-5,5-diethoxy-2-triazoline (**286**). A similar process

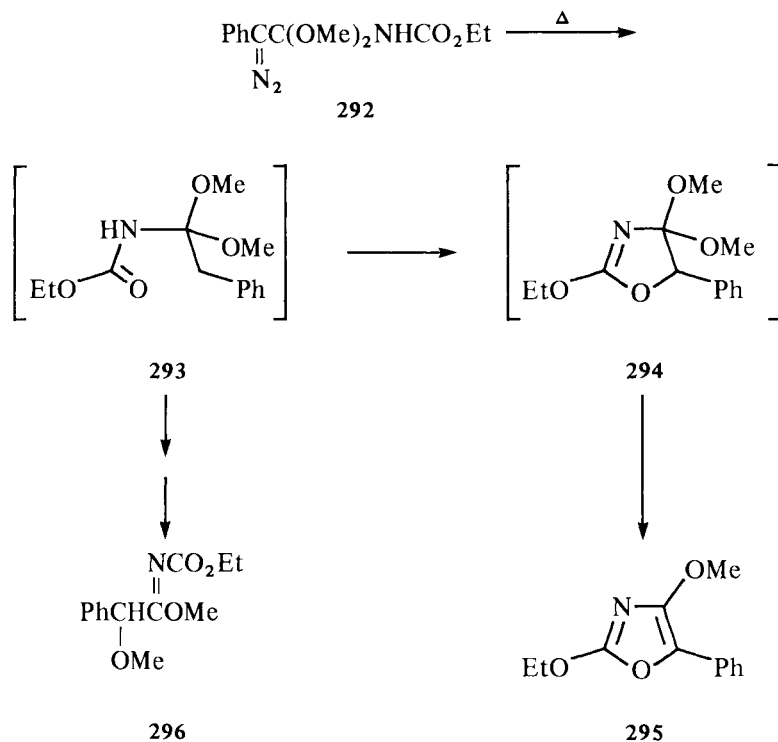
affording 2-ethoxy-4-methoxyoxazole occurs with ketene dimethylacetal and ethyl azidoformate.²⁰⁷



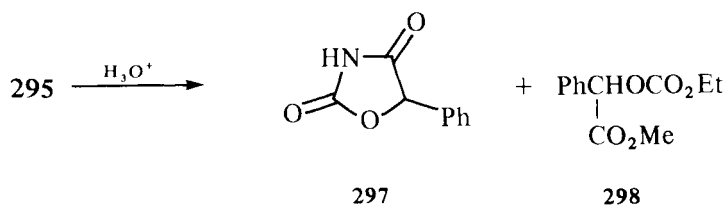
A potentially useful procedure for the synthesis of 4-acetoxoxazoles (e.g., **291**) involves the cyclodehydration of α -hydroxyphenylacetamide (**290**) with acetic anhydride in the presence of perchloric acid.²⁰⁸



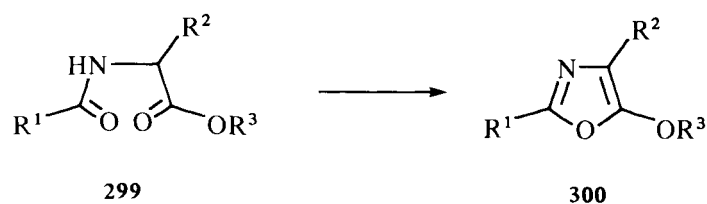
A novel approach to the synthesis of 4,4-dialkoxyoxazolines and thus to the synthesis of 4-alkoxyoxazoles is derived from the thermolysis of 1-phenyl-2,2-dimethoxy-2-(*N*-ethoxycarbonyl)-diazooethane (**292**). When this reaction is carried out at 220°C, 2-ethoxy-4-methoxy-5-phenyloxazole (**295**) and the imide **296** are isolated as the major products.²⁰⁹ The mechanism put forth to rationalize oxazole



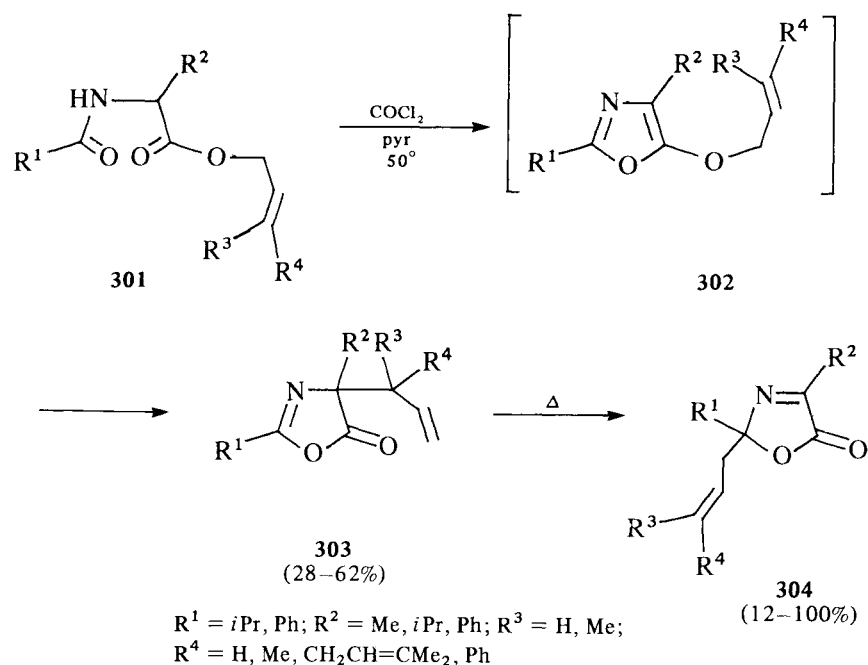
formation involves cyclization of the initially formed carbene **293** to the oxazoline **294**. The oxazoline, which can be isolated when the reaction is carried out at lower temperatures, affords the 2,4-dialkoxyoxazole **295** at 220°C as shown in an independent experiment. Hydrolysis of **295** under acidic conditions provides the oxazolidinedione **297** and the carbonate **298**.²⁰⁹



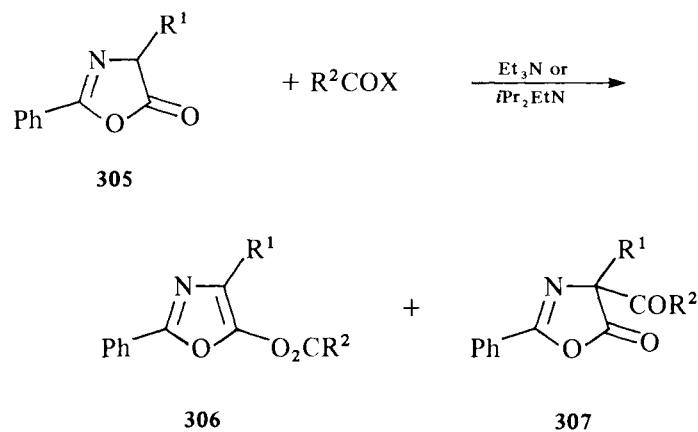
5-Alkoxyoxazoles are important intermediates in the synthesis of 3-hydroxypyridines, including pyridoxal via the Diels–Alder reaction with olefins (Section 1.6.8). Thus a variety of methods have been developed to prepare these useful oxazole derivatives. The most versatile of these methods, which is probably the oldest, is the Robinson–Gabriel cyclization of the α -acylamino esters **299**.^{2–6} The generality of this approach is evidenced by the wide variety of substituted 5-alkoxyoxazoles **300** which have been prepared in this manner. For example, R^1 and R^2 may be H, alkyl, alkoxy-carbonylalkyl, alkenyl, aryl, heteroaryl, and alkoxy-carbonyl while R^3 may be alkyl, aryl, acyl, alkoxy-carbonyl, and trimethylsilyl (Table 1.42).^{5,6} The cyclodehydrating agents employed in this process are phosphorus pentoxide, phosphorus pentachloride, phosphoryl chloride, thionyl chloride, and phosgene in the presence of triethylamine. The yields of **300** in most cases are modest to good.



The Robinson–Gabriel cyclization of the allyl α -acylamino esters **301** affords the 2-allyl-2-oxazolin-5-ones **303**, presumably via Claisen rearrangement of the initially formed 5-allyloxyoxazoles **302** which were not isolated.²¹⁰ Prolonged heating of **303** yields the 2-allyl-3-oxazolin-5-ones **304** via further Claisen rearrangement of **303**.



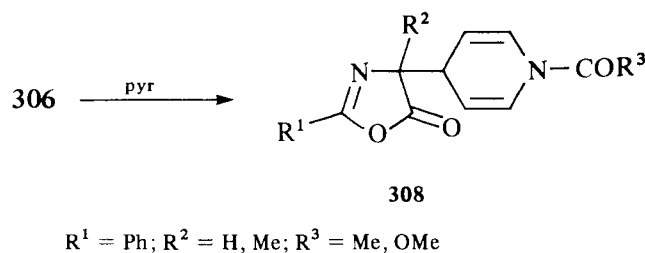
Steglich and Höfle have extensively studied the acylation of oxazolin-5-ones **305**.^{211,212} The products of this reaction are the 5-acyloxyoxazoles **306** and the 3-acyloxazolin-5-ones **307**. The relative amounts of **306** and **307** formed in this



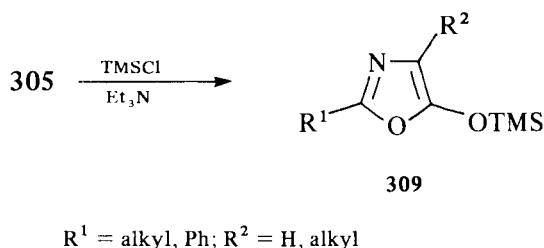
$R^1 = H, alkyl$; $R^2 = YPh$; $X = Cl, Br$

process are dependent on the nature of the acylating agent, the substituent, R^1 , on the oxazolin-5-one ring, and the solvent polarity. The *O*-acylated materials **306** generally predominate under the reaction conditions employed.

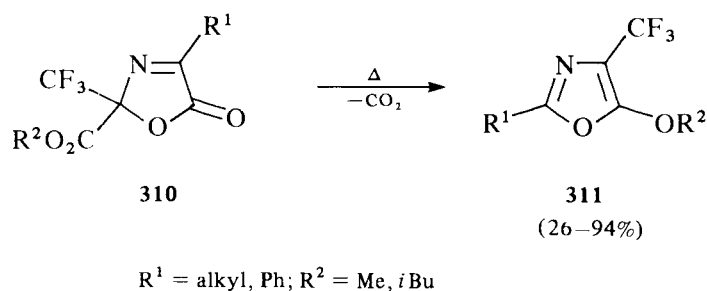
When 2-phenyl-5-acyloxyoxazole (**306**, $R^1 = \text{Ph}$, $R^2 = \text{H, Me}$; $R^3 = \text{OMe, Me}$) are treated with pyridine, the 2-phenyl-4-[1-acyl-1,4-dihydropyridyl(4)]-5-oxazolones **308** are isolated.²¹³



2-Oxazolin-5-ones **305** ($R^1 = \text{alkyl, Ph}$; $R^2 = \text{H, alkyl}$) have been transformed into the 5-trimethylsilyloxyoxazoles **309** ($R^1 = \text{alkyl, Ph}$; $R^2 = \text{H, alkyl}$) with chlorotrimethylsilane in the presence of base.²¹⁴⁻²¹⁶

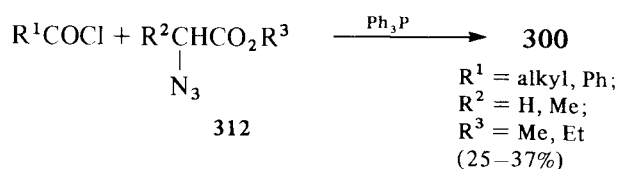


A series of 4-trifluoromethyl-5-alkoxyoxazoles **311** have been prepared by the thermal elimination of carbon dioxide from the 2-alkoxycarbonyl-3-oxazolin-5-ones **310** (Section 1.3.2).⁹⁴

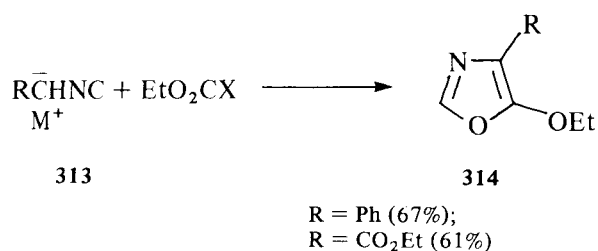


The reaction of α -azidoesters **312** with acid chlorides in the presence of triphenylphosphine yields the 5-alkoxyoxazoles **300** ($R^1 = \text{alkyl, Ph}$; $R^2 = \text{H, Me}$; $R^3 = \text{Me, Et}$).⁷¹

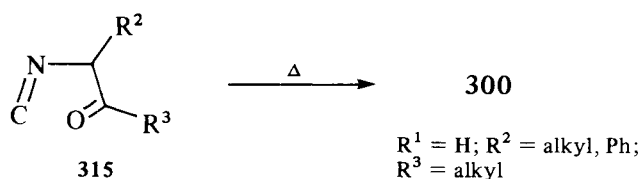
The metal or Lewis-acid-catalyzed decomposition of α -diazesters provides 5-alkoxyoxazoles **300** ($R^1 = \text{H, alkyl, XPh, alkenyl}$; $R^2 = \text{H, Me, CO}_2\text{Et, CONHPh}$; $R^3 = \text{Me, Et}$) in 20–30% yields when this reaction is performed in the presence of nitriles (Section 1.2.13).^{73,74,217-219}



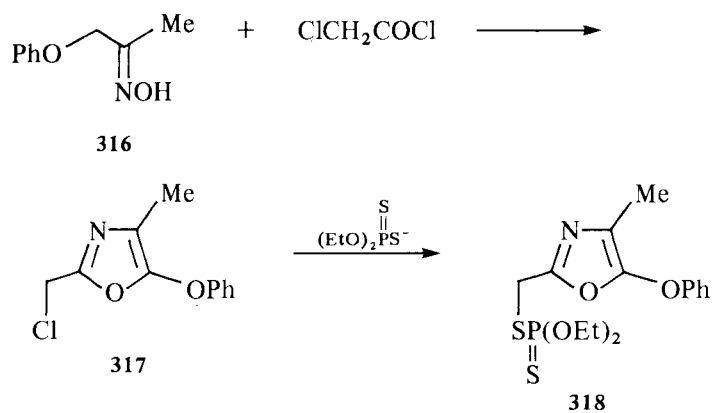
α -Metalated isocyanides **313** combine with diethyl carbonate or ethyl chloroformate to afford the 5-ethoxyoxazoles **314** (R = Ph, CO₂Et).²²⁰



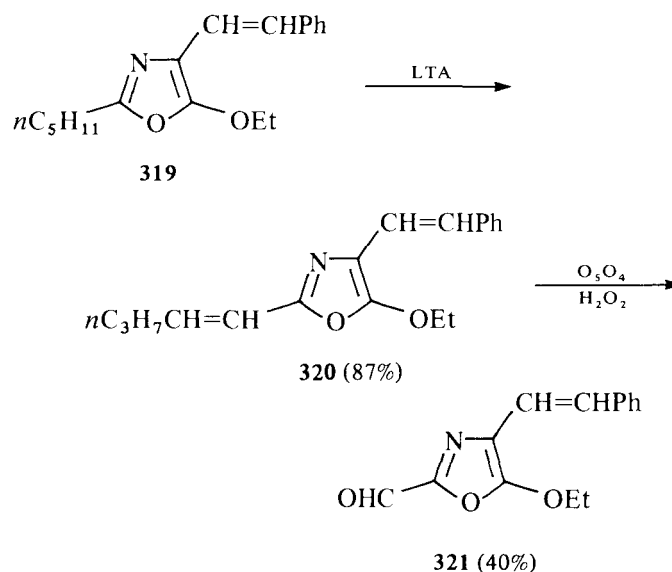
The thermal cyclization of alkyl isocyanoacetates **315** produce 5-alkoxyoxazoles **300** (R¹ = H; R² = alkyl, Ph; R³ = alkyl).²²¹⁻²²³



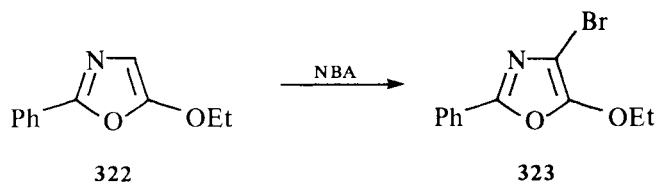
2-Chloromethyl-4-methyl-5-phenoxyoxazole (**317**) was prepared by the reaction of phenoxyacetone oxime (**316**) with chloroacetyl chloride.⁶⁸ This compound was converted into the insecticidal phosphorodithioate **318**



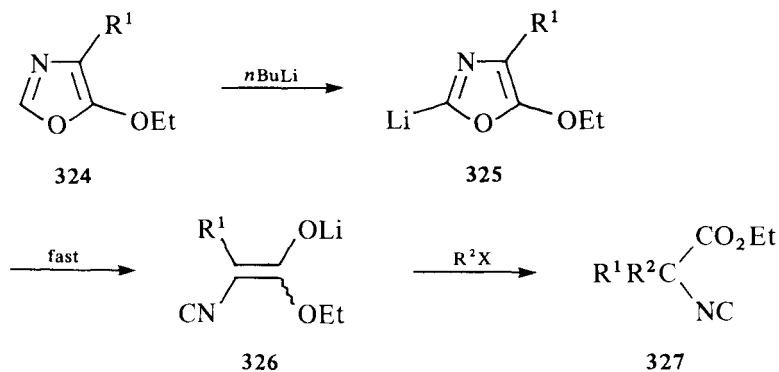
Oxidation of 2-*n*-pentyl-4-styryl-5-ethoxyoxazole (**319**) with lead tetraacetate provides 2-(1-pentenyl)-4-styryl-5-ethoxyoxazole (**320**), which is further transformed into 2-formyl-4-styryl-5-ethoxyoxazole (**321**) with osmium tetroxide in the presence of hydrogen peroxide.³ The reaction of 5-alkoxyoxazoles with other oxidizing agents such as selenium dioxide, chromic anhydride, or ozone leads to the formation of ring fragmentation products.³



2-Phenyl-5-ethoxyoxazole (**322**) can be brominated with *N*-bromoacetamide to afford 2-phenyl-4-bromo-5-ethoxyoxazole (**323**) in 35% yield.³ Hydrolysis of **323** with hydrochloric acid yields glyoxylic acid and benzoic acid. Exposure of **323** to air causes rapid decomposition leading to a white solid, the structure of which was not elucidated.



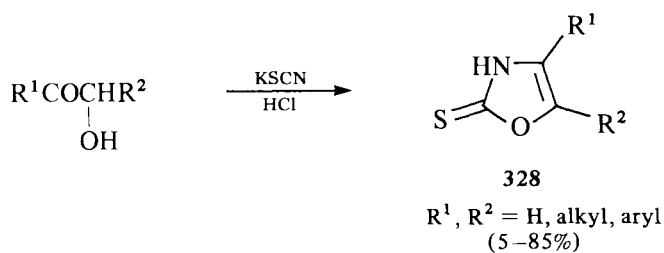
The 2-lithio-5-ethoxyoxazoles **325** generated by treating the 2-unsubstituted 5-ethoxyoxazoles **324** with *n*-butyllithium, suffer rapid, irreversible ring opening leading to the formation of the isocyanoester enolates **326** which are intercepted with electrophiles to provide the *C*-alkylated species **327**.²²⁴ This result is in contrast to the reaction of 4,5-diphenyloxazole (and other alkyl- or aryloxazoles) with *n*-butyllithium (Section 1.2.18). In this case the initially formed 2-lithiooxazole is believed to be in *equilibrium* with the open-chain isocyanoketone enolate. Upon quenching with electrophiles, the product isolated (either the oxazole or the



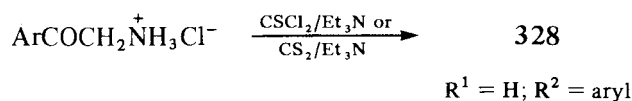
open-chain isocyano derivative) is dependent upon the nature of the electrophilic species.²²⁰

1.3.5. Alkyl- and Arylthiooxazoles (Table 1.44, 1.45, and 1.55)

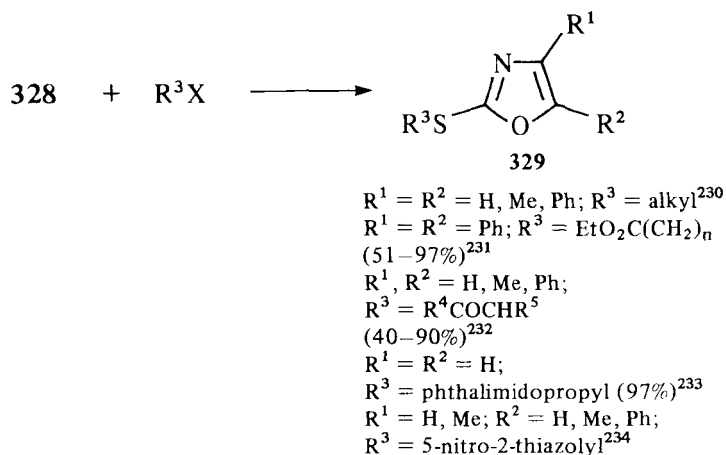
The best method for the preparation of 2-alkylthiooxazoles is via the alkylation of 4-oxazolin-2-thiones (2-mercaptooxazoles) **328**. Thus a discussion of the syntheses of **328** is included here. The first synthesis of 4-oxazolin-2-thiones, due to Gompper, involves the reaction of 4-oxazolin-2-ones with phosphorus pentasulfide.²²⁵ The reaction of thiocyanic acid with α -hydroxyketones represents an improved method for the preparation of **328**.²²⁶ This process has been applied to the synthesis of 4-oxazolin-2-thione (**328**, $\text{R}^1 = \text{R}^2 = \text{H}$) from glycoaldehyde and hydrocyanic acid.²²⁷



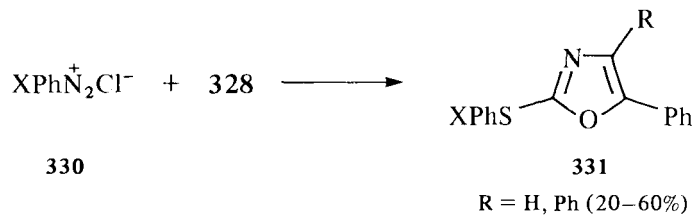
A third procedure useful in the preparation of 5-aryl-4-oxazolin-2-thiones **328**, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ar}$, involves the reaction of aminoacetophenones with either thiophosgene or carbon disulfide in the presence of triethylamine.^{228,229}



A variety of 2-alkylthioxazoles **329** have been prepared from **328** by the reaction with alkyl halides. Several examples are

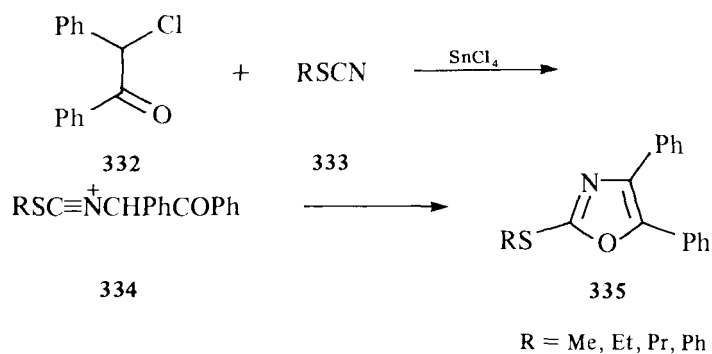


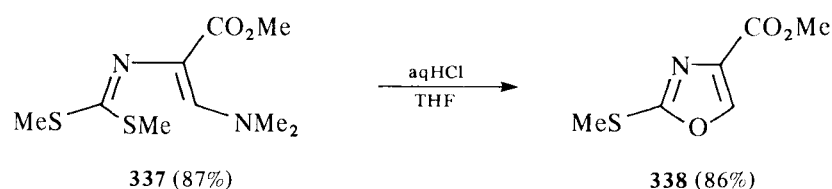
The benzenediazonium salts **330** serve as alkylating agents in the preparation of the 2-arylthioxazoles **331** from **328**.²³⁵



A potentially general, but little exploited, method for the synthesis of 2-alkylthioxazoles is the displacement of chloride from 2-chlorooxazoles with mercaptans as discussed in Section 1.3.1.

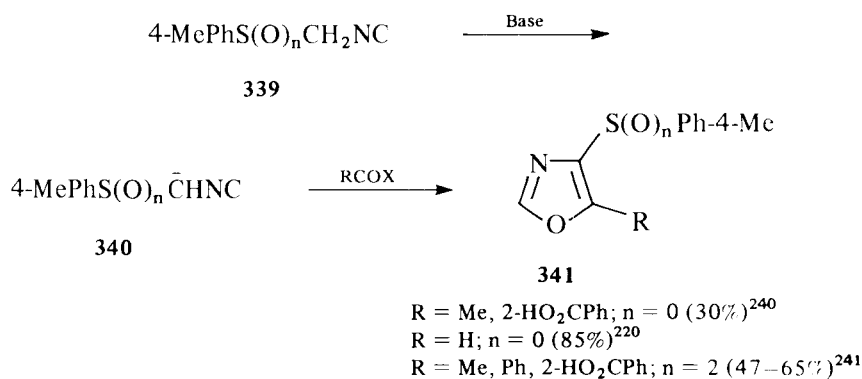
The nitrilium salts **334**, formed upon reaction of desyl chloride (**332**) with alkyl or phenyl thiocyanates **333** in the presence of stannic chloride, spontaneously cyclize to give the 2-alkylthio- or 2-phenylthio-4,5-diphenyloxazoles **335** in 40–85% yield.²³⁶



CSCC(=NCCOC(=O)C)SC.CCOC(=O)CC>>CSCC(=NCCOC(=O)C)SC

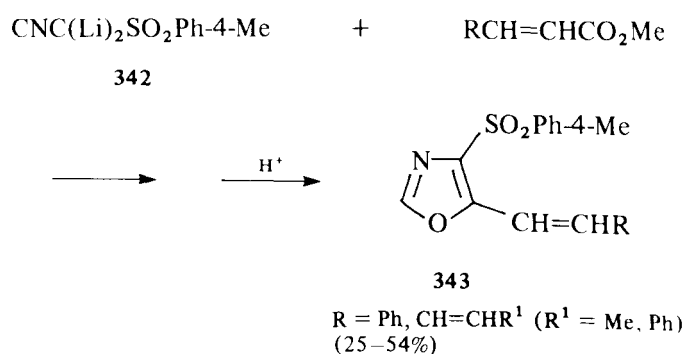
Oxidation of 4-methyl-4-oxazolin-2-thione **328**, $R^1 = \text{Me}$, $R^2 = \text{H}$, with nitric acid results in desulfurization to produce 4-methyloxazole in 75% yield.²³⁹

4-(4-Tolylthio)-5-alkyl- or aryloxazoles **341**, $n = 0$, and the corresponding sulfones **341**, $n = 2$, are most conveniently obtained by the reaction of the anions **340**, $n = 0, 2$, derived from 4-tolylthiomethyl isocyanide (**340**, $n = 0$) and 4-tolylsulfonylmethyl isocyanide (**340**, $n = 2$, TOSMIC), respectively, with acyl halides or anhydrides.^{220,240,241}

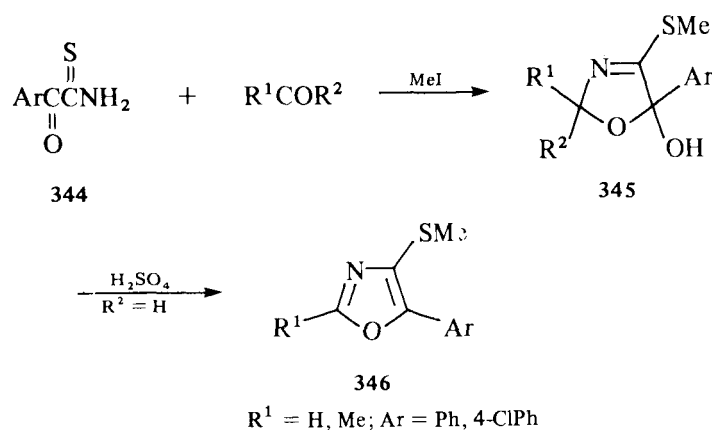


TOSMIC (**340**, $n = 2$) is a versatile intermediate in heterocyclic synthesis.²⁸ Recently van Leusen et al., who developed this reagent, extended its utility by the discovery that the dilithio species **342** provides 4-(4-toluenesulfonyl)-5-alkenyl-

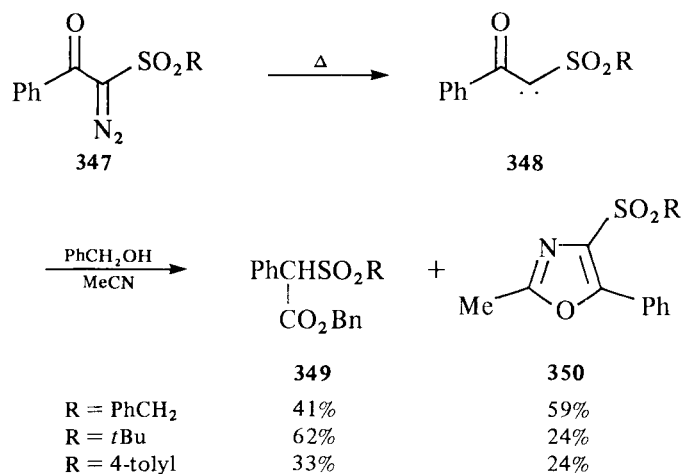
oxazoles **343** when allowed to react with α,β -unsaturated esters.²⁴² Oxazole formation most likely occurs by a 1,2-addition of **342** to the ester carbonyl followed by cyclization of the intermediate alkoxide. In contrast, the reaction of the monolithiosylmethyl isocyanide **340** ($n = 2$, $M = \text{Li}$) with α,β -unsaturated esters yields pyrrole carboxylic esters via a Michael addition–cyclization sequence.²⁴²



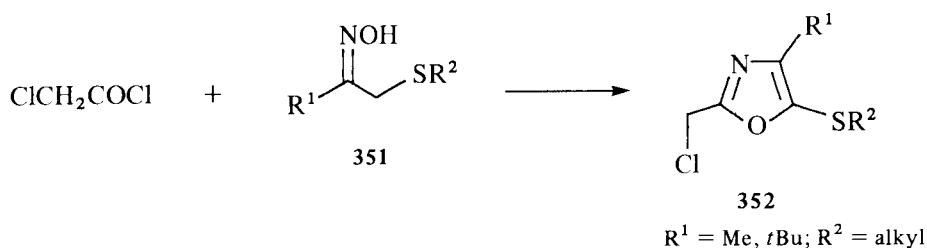
A novel approach to the synthesis of 4-methylthio-5-aryl-5-hydroxy-3-oxazolines **345** and 4-methylthio-5-aryloxazoles **346** utilizes the phenyl 1-thioglyoxylic acid carboxamides **344** as intermediates.²⁴³ When **344** are allowed to react with iodo-methane in the presence of aldehydes or ketones, the 3-oxazolines **345** are obtained. Dehydration of **345**, $\text{R}^2 = \text{H}$, with sulfuric acid affords the 4-methylthiooxazoles **346** in 80–90% yields.



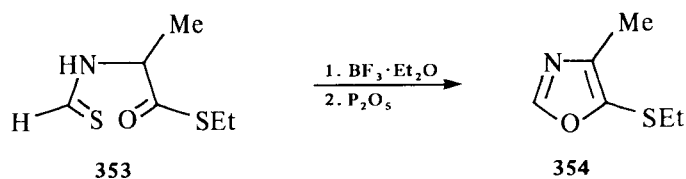
Thermolysis of 2-acylsulfonyldiazomethanes **347** in benzyl alcohol produces the 2-sulfonylacetates **349** via a Wolff rearrangement of the intermediate ketocarbenes **348**. When this reaction is performed in the presence of acetonitrile, the 4-sulfonyloxazoles **350** are isolated along with **349** (Section 1.2.13).²⁴⁴



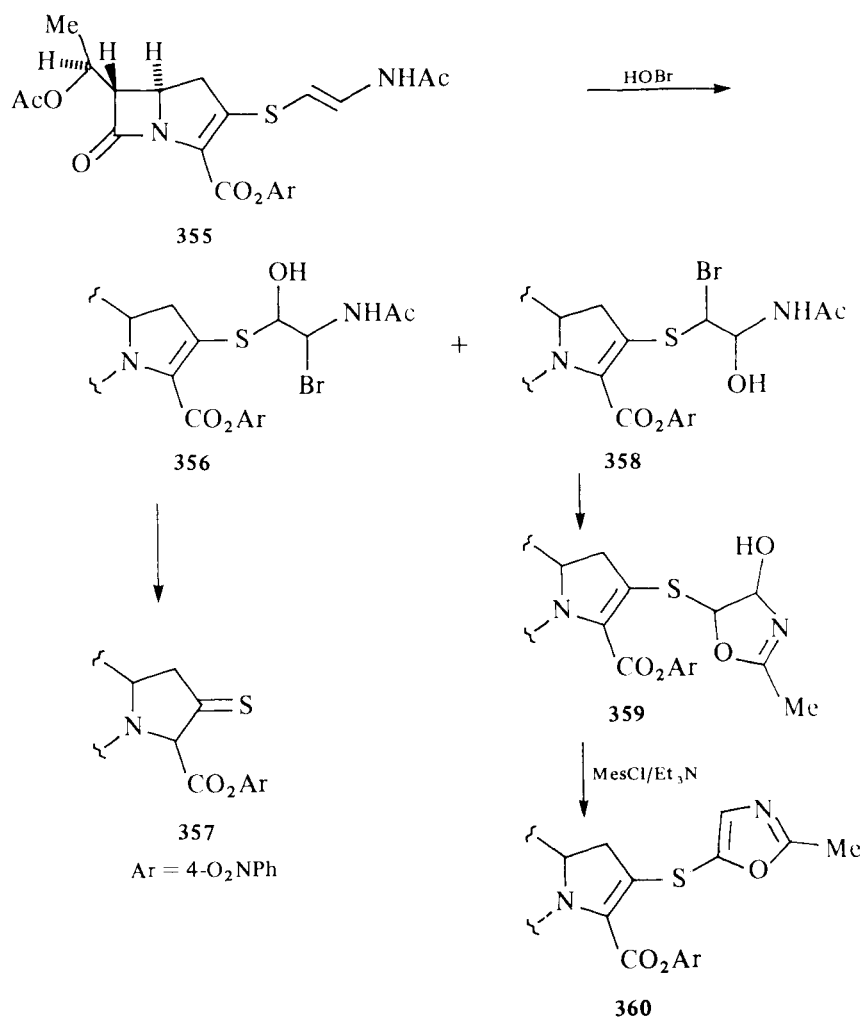
Several potentially general methods for the preparation of 5-alkylthio and 5-arylthiooxazoles have been reported. A procedure which appears quite versatile provides 2-chloromethyl-4-alkyl-5-alkylthiooxazoles **352** in 65–90% yields via the reaction of alkylthiomethyl ketoximes **351** with chloroacetyl chloride as described in Section 1.2.11.⁶⁸



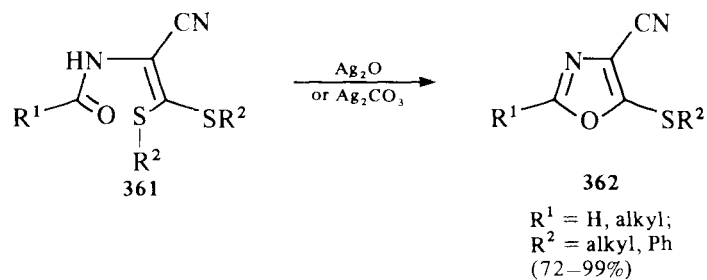
A report in the patent literature describes the synthesis of 4-methyl-5-thioethyl-oxazole (**354**) from the 2-thioformylaminothiolester **353** via a Robinson–Gabriel-type cyclization.



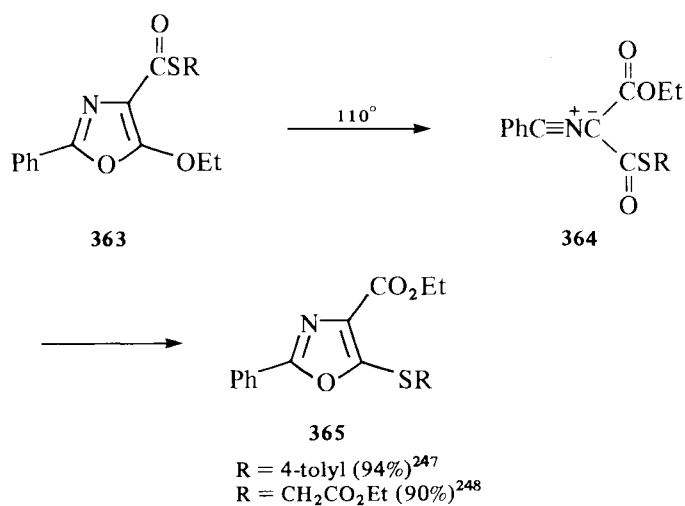
The reaction of hypobromous acid with the olivanic acid derivative **355** leads to the formation of two products. The first is the expected thione **357** arising from decomposition of the adduct **356**. The second and major product, the 4-hydroxy-oxazoline **359** is derived from the intermediate **358** as outlined.²⁴⁶ The structure assignment of **359** was based on its conversion to the oxazole **360** with methane-sulfonyl chloride.



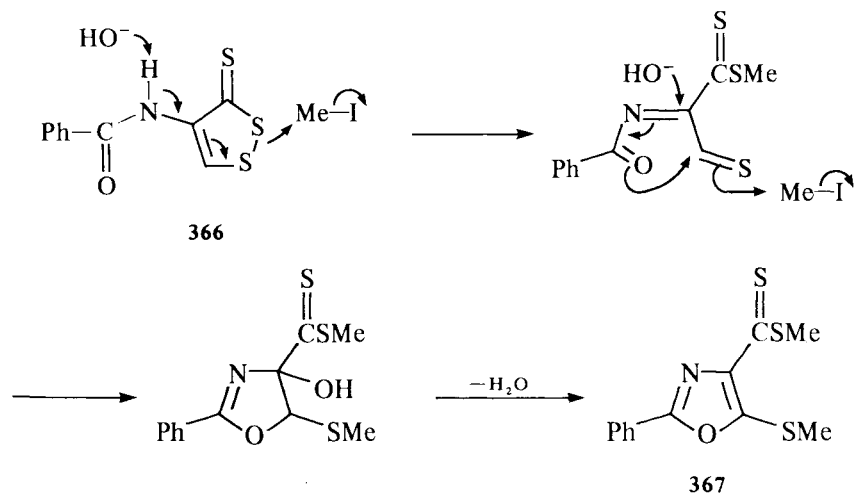
Attempts to prepare fluorinated amino acids by the reaction of 2-acetamido-3,3-bis(methylthio)acrylonitrile (**361**, $\text{R}^1 = \text{R}^2 = \text{Me}$) with silver oxide—anhydrous hydrogen fluoride leads instead to 2-methyl-4-cyano-5-methylthiooxazole (**362**, $\text{R}^1 = \text{R}^2 = \text{Me}$).¹⁶³ A number of derivatives of **362** have been obtained in high



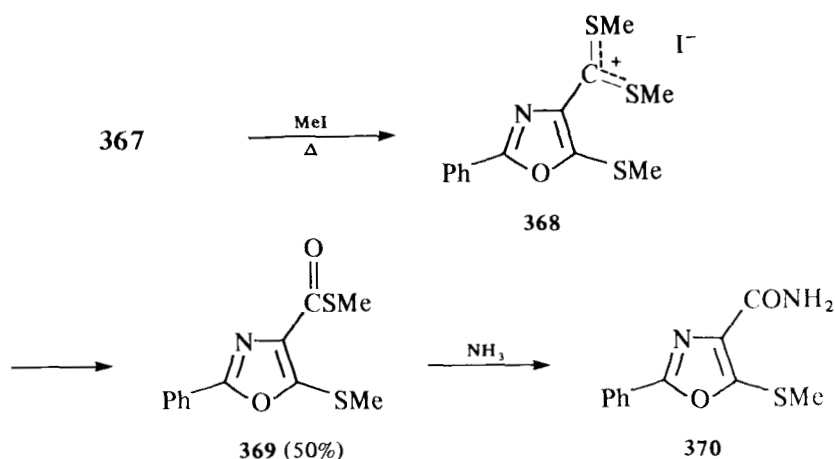
yields by this procedure. The Cornforth rearrangement of the alkyl or aryl 5-ethoxyoxazole-4-thiolcarboxylates **363** furnishes the ethyl 5-alkylthio or 5-arylthiooxazole-4-carboxylates **365** in excellent yields.^{247,248} This reaction, which most likely proceeds via the nitrile ylide intermediates **364**, represents a general method for the preparation of compounds of this type.



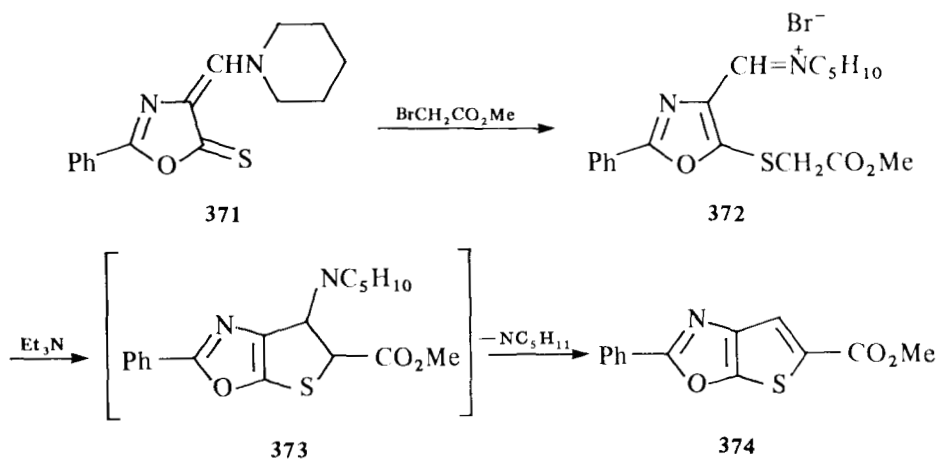
An unusual rearrangement of 4-benzamido-1,2-dithiole-3-thione (**366**) occurs upon reaction with iodomethane in the presence of hydroxide. The product isolated is methyl 2-phenyl-5-methylthio-4-carbodithioate (**367**) formed



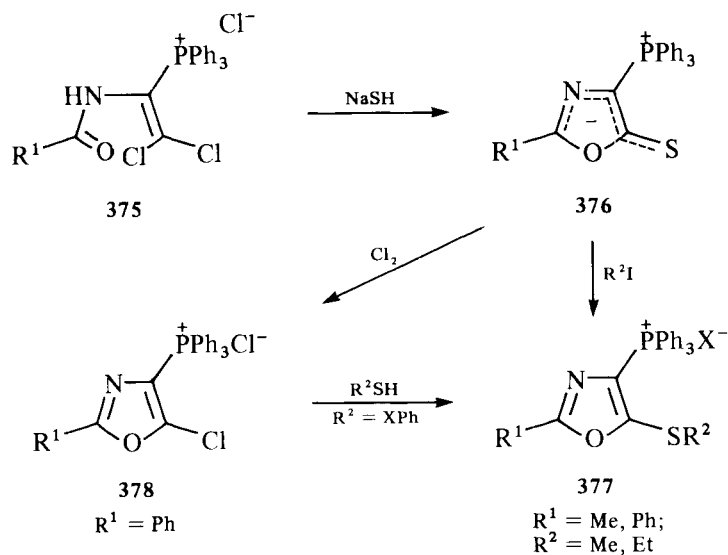
Desulfurization of **367** with Raney-nickel gives 2-phenyl-4-methyloxazole, while the reaction of **367** with iodomethane at 100°C provides methyl 2-phenyl-5-methylthiooxazole-4-thiolcarboxylate **369** via hydrolysis of the salt **368**.²⁴⁹ The conversion of **369** to the amide **370** is effected with ammonia.



Whereas alkylation of 4-oxazolin-2-thiones is a widely used method for the preparation of 2-alkylthiooxazoles, alkylation of 2-oxazolin-5-thiones has not been exploited to a great extent in this regard. This process has been utilized, however, in the synthesis of the oxazolothiophene **374**.²⁵⁰ Alkylation of the oxazolin-5-thione **371** with methylbromoacetate provides the 5-methoxycarbonylmethylthiooxazole **372**. Base-induced cyclization of **372** with triethylamine followed by elimination of piperidine from the intermediate **373** yields **374**.

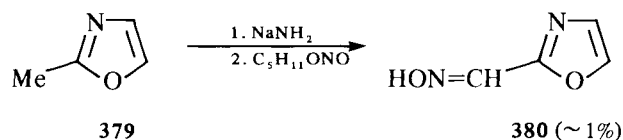


Treatment of the 1-acylamino-2,2-dichlorovinyl triphenylphosphonium chlorides **375** with sodium hydrosulfide affords the novel phosphorus ylides **376**.²⁵¹ The conversion of **376** to the (5-alkylthiooxazol-4-yl) triphenylphosphonium iodides **377** is readily effected by treatment of **376** with iodoalkanes.²⁵¹ The corresponding 5-arylthiooxazoles **377**, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{XPh}$, are obtained via the reaction of the 5-chlorooxazole **378** with thiophenols.²⁵² The 5-chlorooxazole **378** is obtained by allowing **376** to react with chlorine.²⁵²

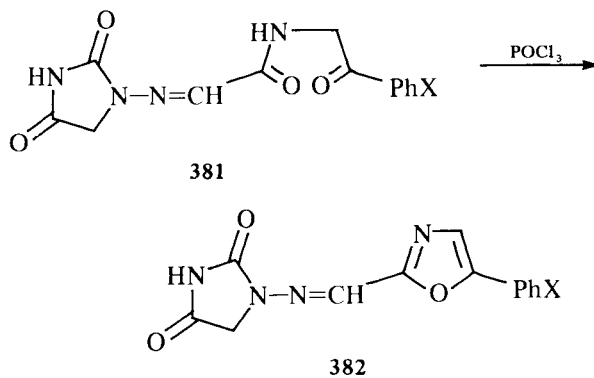


1.3.6. Formyloxazoles and Their Derivatives (Tables 1.39, 1.41, and 1.52)

2-Formyloxazoles are a poorly investigated class of compounds, and only a few derivatives have been reported to date. 2-Methyloxazole (**379**) has been converted to oxazole-2-carboxaldehyde oxime (**380**) in poor yield:¹⁵⁶



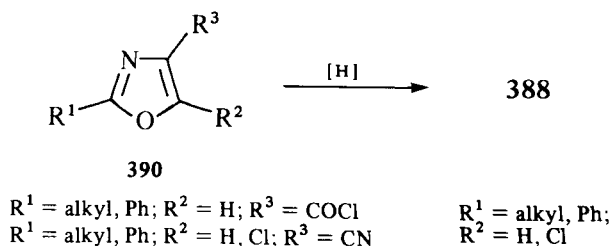
The Robinson–Gabriel cyclization of the acylaminoketones **381** has been applied to the synthesis of the 1-[[5-aryl-2-oxazolyl)methylene]amino]-2,4-imidazolidinediones (**382**).²⁵³ These compounds are useful as muscle relaxants.



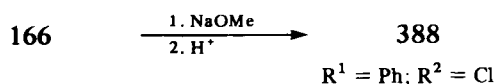
387 $\xrightarrow[2. \text{HOAc, H}_2\text{O}]{1. \text{C}_6\text{H}_{12}\text{N}_4}$ 388
 $\text{R}^1 = \text{XPh}; \text{R}^2 = \text{H, Br}$

The reduction of oxazole-4-carboxylic acid derivatives represents an entry into formyloxazoles. For example, the Rosenmund reduction of the oxazole-4-carboxylic acid chlorides **390** ($R^1 = \text{alkyl, Ph}$; $R^2 = \text{H}$; $R^3 = \text{COCl}$) gives **388** ($R^1 =$

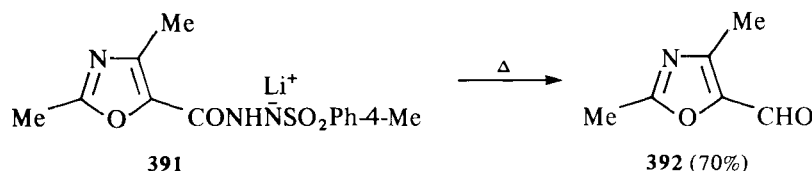
alkyl, Ph; $R^2 = H$)^{165,255} while **388** ($R^1 = \text{alkyl, Ph}$; $R^2 = H$) are produced when the 4-cyanooxazoles **390** ($R^1 = \text{alkyl, Ph}$; $R^2 = H, Cl$; $R^3 = CN$) are treated with anhydrous stannous chloride in the presence of anhydrous hydrogen chloride.^{3,165}



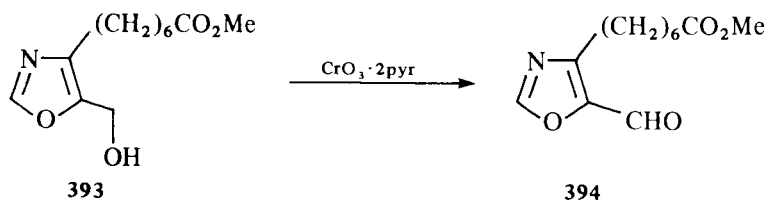
2-Phenyl-4-dichloromethyl-5-chlorooxazole **166** (prepared by the reaction of benzoylalanine with phosphorus pentachloride at 150°C) affords 2-phenyl-4-formyl-5-chlorooxazole (**388**, $R^1 = Ph$, $R^2 = Cl$) when treated with sodium methoxide followed by acid hydrolysis of the intermediate dimethyl acetal.¹⁴⁶



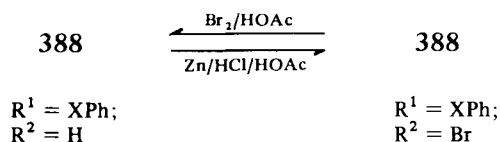
Only two examples of 5-formyloxazoles have been reported thus far. The vacuum pyrolysis of the lithium salt of 2,4-dimethyloxazole-5-carboxylic acid toluenesulfonyl hydrazide (**391**) leads to the formation of 2,4-dimethyl-5-formyloxazole (**392**).²⁵⁶



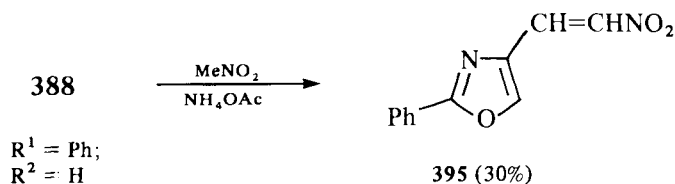
The 5-formyloxazole **394** is derived from the oxidation of the 5-hydroxymethyl-oxazole **393** with chromic anhydride–pyridine.¹⁸⁴



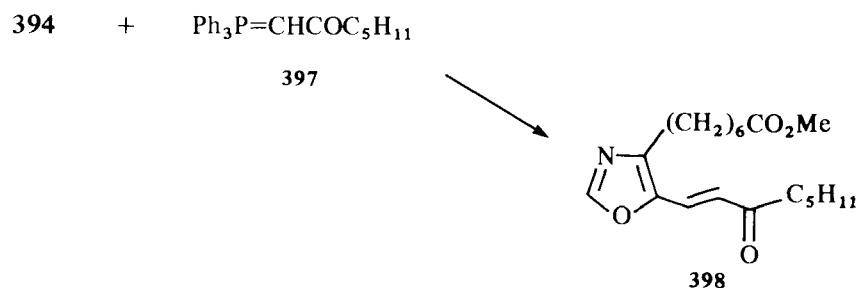
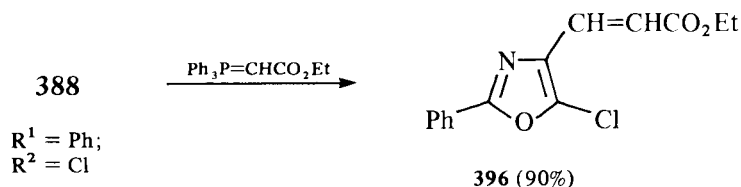
The reaction of 2-aryl-4-formyloxazoles **388** ($R^1 = XPh$, $R^2 = H$) with bromine in acetic acid results in substitution of bromine at the 5-position of the oxazole ring to provide the 4-formyl-5-bromooxazoles **388** ($R^1 = XPh$, $R^2 = Br$).¹⁵⁰ Reduction of the latter with zinc–hydrochloric acid effects dehalogenation.



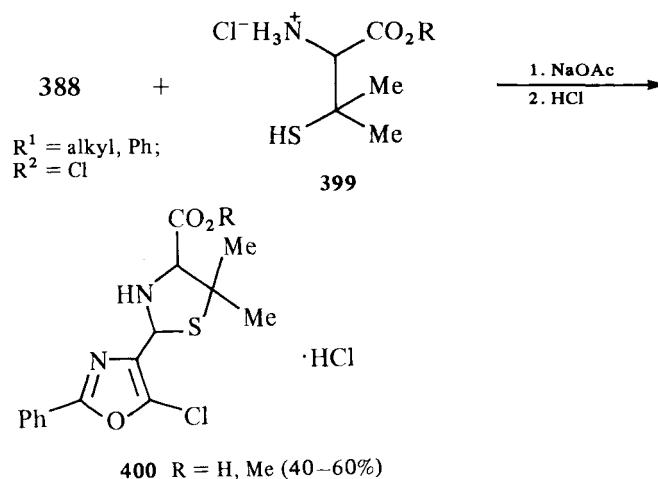
Formyloxazoles react normally with active methylene compounds or Wittig reagents to produce olefins. 2-Phenyl-4-formyloxazole reacts with nitromethane in the presence of ammonium acetate to give 2-phenyl-4,2'-nitrovinyloxazole (**395**).¹⁹¹



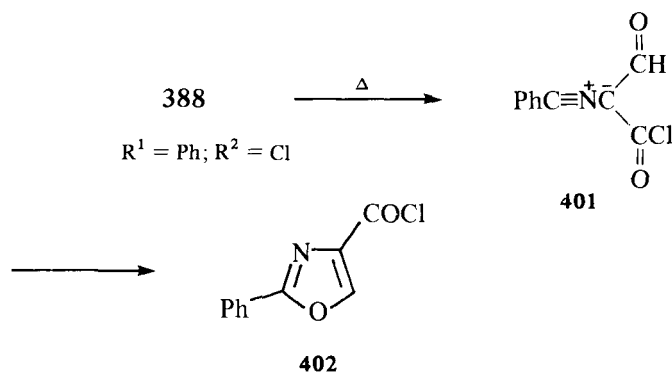
2-Phenyl-4-formyl-5-chlorooxazole (**388**, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Cl}$) is converted to ethyl 3-(2-phenyl-5-chlorooxazolyl)acrylate **396** with carboethoxymethylene triphenylphosphorane.²⁴⁷ The 5-formyloxazole **394** reacts similarly with the ylide **397** to yield the oxazolyvinyl ketone **398**.¹⁸⁴



4-Formyl-5-chlorooxazole (**388**, $\text{R}^1 = \text{alkyl}$, Ph ; $\text{R}^2 = \text{Cl}$) form the oxazolythiazolidines **400** when allowed to react with *dl*-penicillamine or its methyl ester (**399**, $\text{R} = \text{H}$ or Me).³



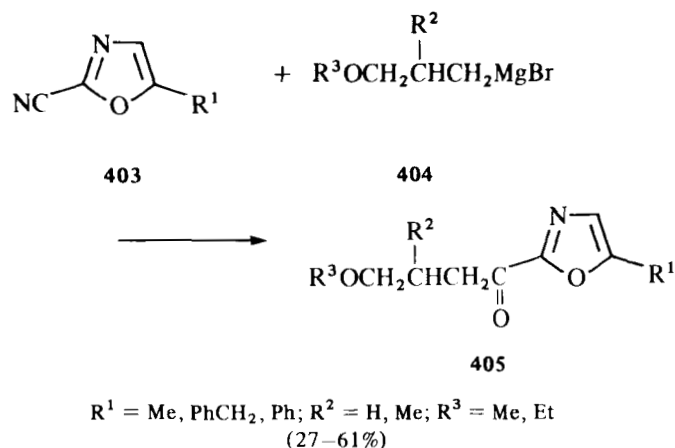
One of the most intriguing reactions of oxazoles is the Cornforth rearrangement.^{5,6,247} Thermal electrocyclic ring opening of 4-carbonyl-substituted oxazoles leads to biscarbonylnitrile ylides which undergo a 1,5-dipolar electrocyclization leading to a rearranged oxazole. An example of this process arises when 2-phenyl-4-formyl-5-chlorooxazole (388, R¹ = Ph, R² = Cl) is heated. The resulting product, 2-phenyloxazole-4-carboxylic acid chloride (402), is formed via the nitrile ylide 401 in good yield.³



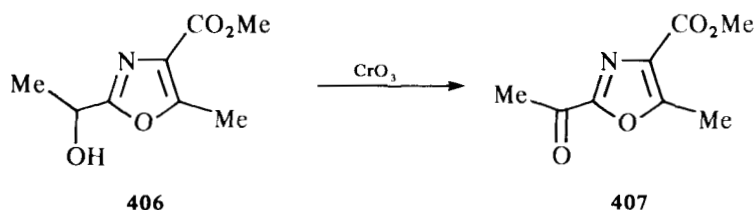
2-*n*-Pentyl-4-formyl-5-chlorooxazole (388, R¹ = *n*-C₅H₁₁, R² = Cl) rearranges to 2-*n*-pentyloxazole-4-carboxylic acid chloride after three days at room temperature. Further examples of the Cornforth rearrangement are described below.

1.3.7. Ketooxazoles and Their Derivatives (Tables 1.40 and 1.41)

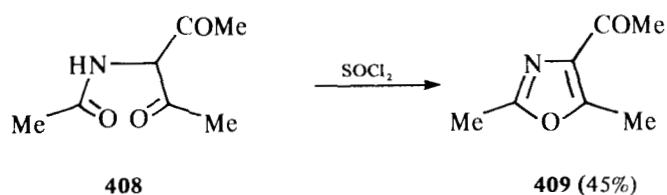
The synthesis of oxazolo[3,2-*a*]pyridinium salts requires the preparation of the 2-ketooxazoles 405. These intermediates were obtained by the reaction of the 2-cyanooxazoles 403 with the Grignard reagents 404.¹⁵⁶



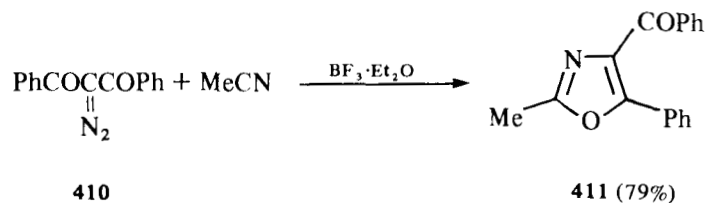
In their studies on the structure of berninamycin, Rinehart et al. prepared methyl 2-acetyl-5-methyloxazole-4-carboxylate (**407**) in 33% yield by the Jones oxidation of the alcohol **406** in order to determine the position of the substituents on the oxazole ring of a degradation product of berninamycin A.¹⁵⁷



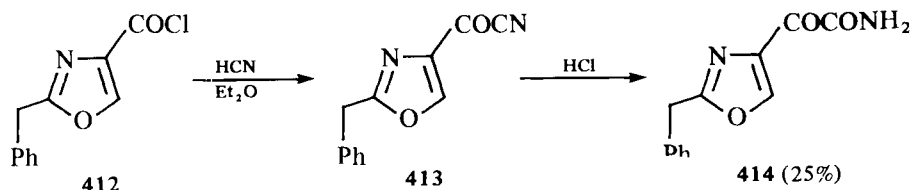
The Robinson–Gabriel cyclization of 3-acylaminoacetylacetone (**408**) gives 2,5-dimethyl-5-acetyloxazole (**409**).²⁵⁷



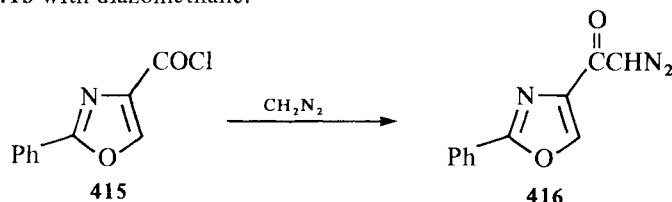
Dibenzoyldiazomethane (**410**) and acetonitrile yield 2-methyl-4-benzoyl-5-phenyloxazole (**411**) when combined in the presence of boron trifluoride etherate as described in Section 1.2.13.⁷⁴



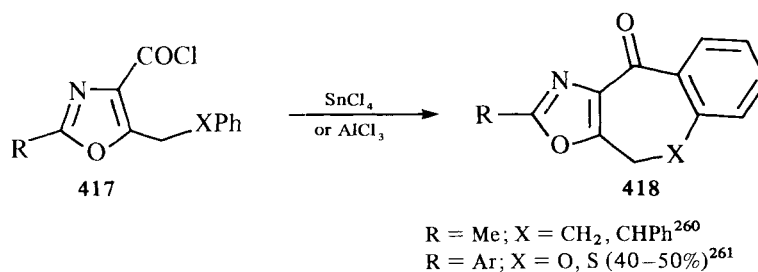
Various methods have been developed to convert oxazole-4-carboxylic acid derivatives to 4-ketooxazoles. The reaction of hydrogen cyanide with 2-benzyl-oxazole-4-carboxylic acid chloride (**412**) gives the unstable acyl cyanide **413**, which is hydrolyzed with acid to the ketoamide **414**.²⁵⁸



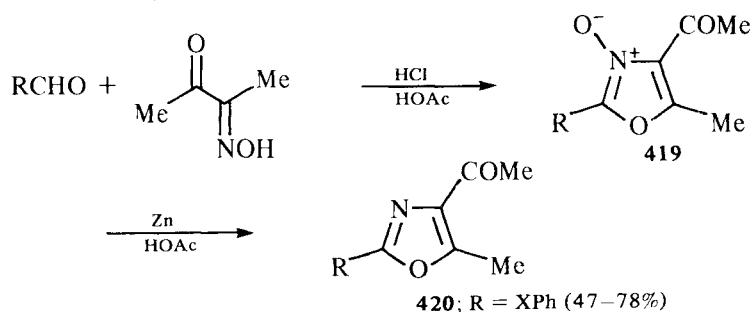
The diazoketone **416** is obtained in good yield by the reaction of the acid chloride **415** with diazomethane.¹⁹¹



2-Phenyl-5-methyloxazole-4-carboxylic acid chloride affords 2-phenyl-4-benzoyl-5-methyloxazole when treated with diphenylcadmium.²⁵⁹ An intramolecular Friedel-Crafts reaction of the oxazole-4-carboxylic acid chloride **417** has been utilized in the synthesis of the tricyclic 4-ketooxazoles **418**.^{260,261}

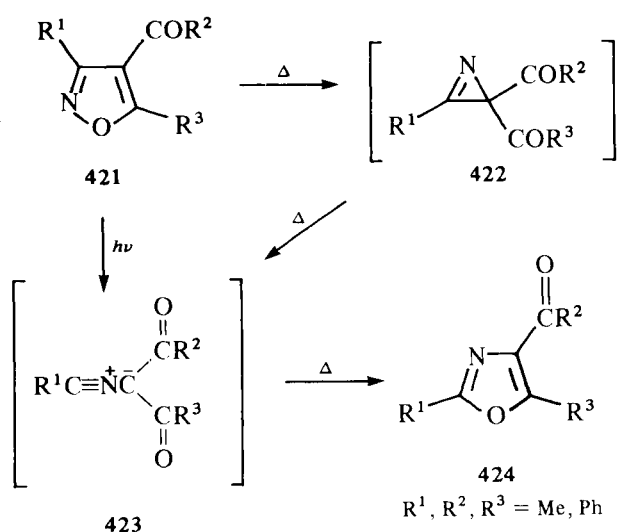


The unstable 4-acetyloxazole *N*-oxides **419**, prepared by the condensation of hydroximino acetylacetone with aromatic aldehydes, are converted to the 4-acetyloxazoles **420** by reduction with zinc in acetic acid.¹⁸⁰ A similar procedure,

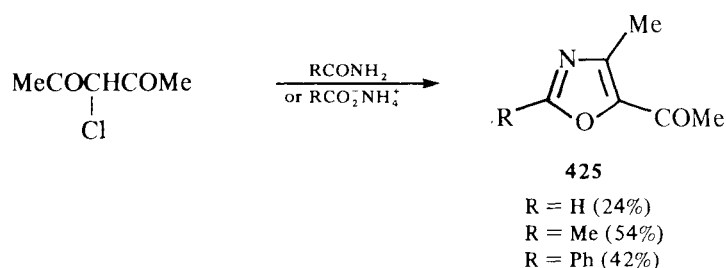


which gives **420**, R = Me, in 45% yield, directly involves the reaction of hydrox-imino acetylacetone with acetic anhydride in the presence of zinc and mercuric chloride.²⁵⁹

The 4-ketooxazoles **421** undergo a thermal or photochemical isomerization to provide the 4-ketooxazoles **424** in good yields.²⁵⁹ The mechanism of this inter-conversion is believed to involve a 1,5-dipolar cyclization of the nitrile ylides **423**.⁷⁸ The results of this investigation are consistent with the formation of the azirine intermediates **422** in the thermal process but not in the photochemical reaction.

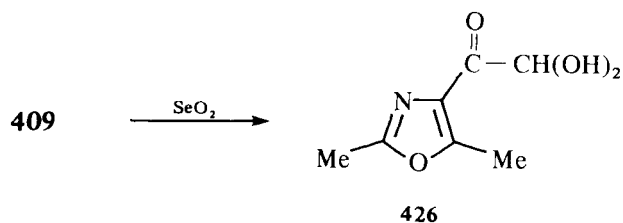


The reaction of amides or ammonium carboxylates with 3-chloroacetylacetone provides 5-acetyloxazoles **425**.^{183,263,264}

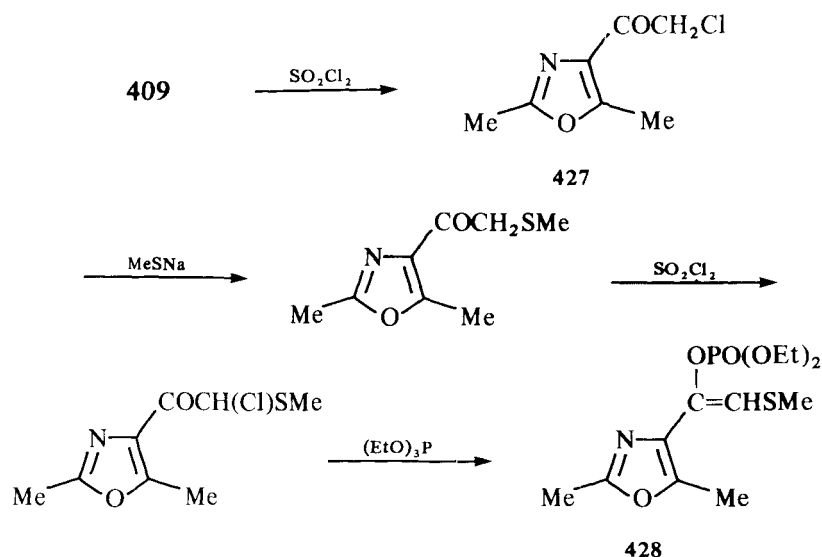


The Friedel-Crafts reaction of 2,4-dimethyloxazole-5-carboxylic acid chloride with benzene and aluminum chloride as the Lewis acid yields 2,4-dimethyl-5-benzoyloxazole.²⁶⁴

Ketooxazoles react with Grignard reagents to afford the corresponding alcohols.^{257,259} The hydrated α-ketoaldehyde **426** is formed when 2,5-dimethyl-4-acetyloxazole (**409**) is subjected to oxidation with selenium dioxide.²⁶⁵



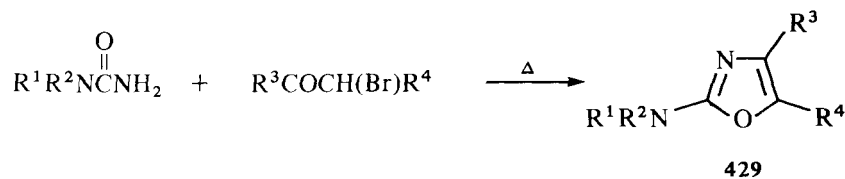
Sulfuryl chloride effects α -chlorination of the 4-ketooxazole **409** to afford the 2-chloroketone **427**, which is converted in a series of steps to the insecticidal enol phosphate **428**:²⁶⁶



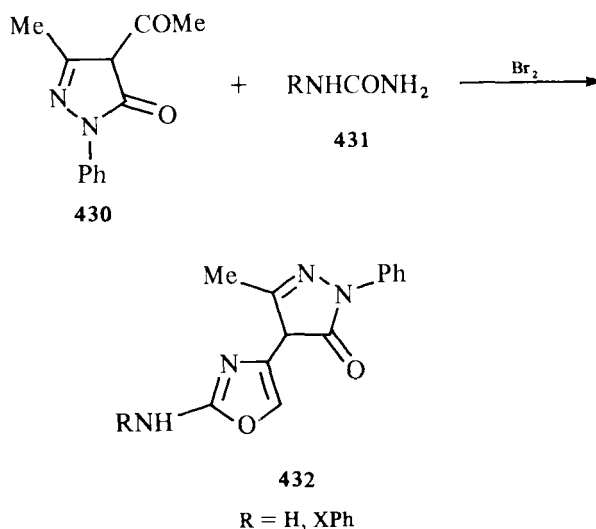
1.3.8. Aminooxazoles and Their Derivatives (Tables 1.46–1.49 and 1.56–1.59)

A review of the literature of 2-aminooxazoles has appeared.²⁶⁷

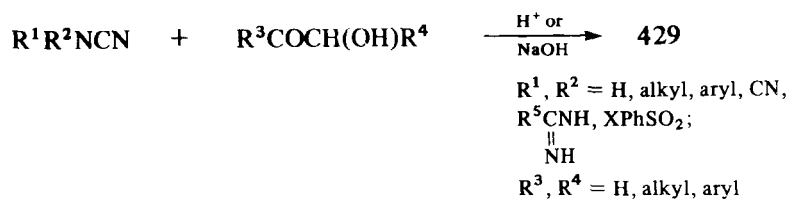
Two widely applicable methods have been developed to prepare 2-aminooxazoles.^{4–6} The first, the reaction of urea or urea derivatives with 2-bromoketones, is a general and convenient method for obtaining 2-aminooxazoles **429**. The groups R^1 and R^2 may be H, alkyl, or aryl while R^3 and R^4 may be H, alkyl, aryl, hetero-aryl, alkoxy-carbonylalkyl, or alkoxy-carbonyl (Table 1.46).



Recently it has been found that when 2-bromoketones are generated *in situ* (by the reaction of bromine with the corresponding ketone) in the presence of urea derivatives, 2-aminooxazoles are formed.^{268,269} One example of this process leading to the 2-aminooxazoles **432** involves the reaction of the pyrazolyl methyl ketones **430** with bromine followed by the ureas **431**.²⁷⁰ The 2-aminooxazoles **432** are claimed to possess fungicidal and bacteriocidal activity.

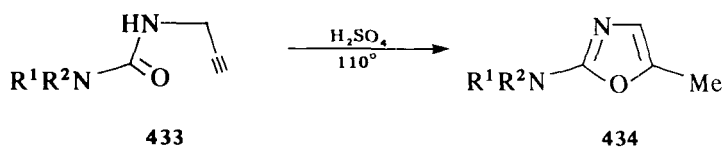


The second major approach to 2-aminooxazoles involves the reaction of 2-hydroxyketones with cyanamide derivatives (Table 1.46).⁴⁻⁶ It appears that this procedure is most successful when the reaction is run in aqueous sodium hydroxide rather than under acidic conditions.²⁷¹

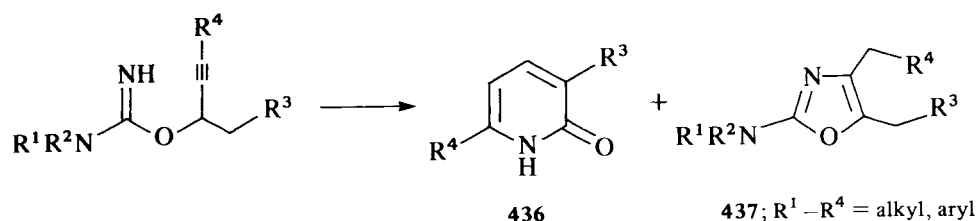


A third method for preparing 2-aminooxazoles is the reaction of 2-chlorooxazoles with amines or amide anions as discussed in Section 1.3.1.

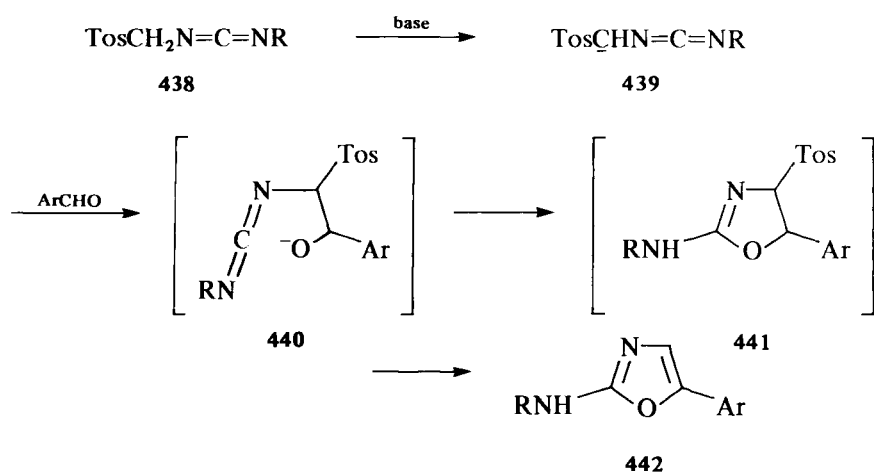
The 2-amino-5-methyloxazoles **434** have been isolated in good yields by the cyclization of the *N*-propargylureas **433** with hot sulfuric acid.²⁷²



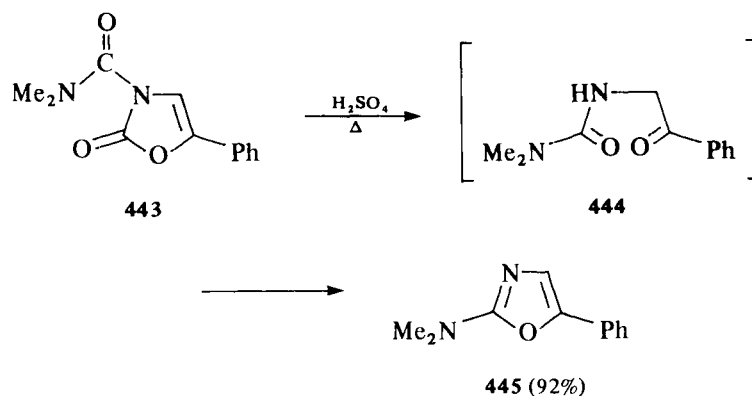
A recently reported synthesis of 2-pyridines **436** via the thermolysis of *O*-propargylisoureas **435** in some cases produces the 2-aminooxazoles **437** as side products.^{273,274} The intermediates **435** are derived from the reaction of *N,N*-disubstituted cyanamides with propargyl alcohols. The products **436** and **437** are formed in good yields in roughly equal amounts and are easily separated by silica gel chromatography.



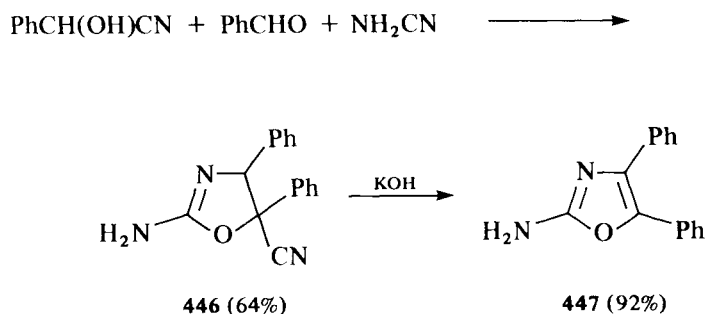
Recently, a novel and preparatively useful procedure leading to the 2-amino-oxazoles **442** has been reported by van Leusen et al.²⁷⁵ The *N*-tosylmethylcarbodiimides **438** combine with aromatic aldehydes in the presence of base to furnish 2-*t*-butyl- or 2-triphenylmethylamino-5-aryloxazoles **442** in good yields. The mechanism of this transformation involves deprotonation of **438** to give the anion **439**. Attack of **439** on the aldehyde followed by cyclization of the intermediate adduct **440** affords the 2-amino-4-toluenesulfonyl-5-aryl-2-oxazolines **441**, which suffer elimination of the toluenesulfinic acid, to produce the oxazoles **442**. Removal of the trityl group from **442**, $R = \text{Ph}_3\text{C}$, leads to the primary aminooxazoles **442**, $R = \text{H}$.



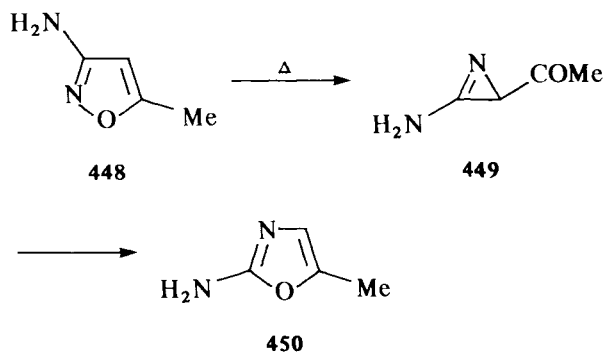
The 2-ureidoketone **444** (not isolated) generated by the reaction of the 4-oxazolin-2-one **443** with sulfuric acid yields 2-(*N,N*-dimethylamino)-5-phenyl-oxazole (**445**).⁹²



Benzaldehyde, benzaldehyde cyanohydrin, and cyanamide combine to provide 2-amino-4,5-diphenyl-5-cyano-2-oxazoline (**446**).²⁷⁶ Dehydrocyanation of **446** with base gives 2-amino-4,5-diphenyloxazole (**447**).



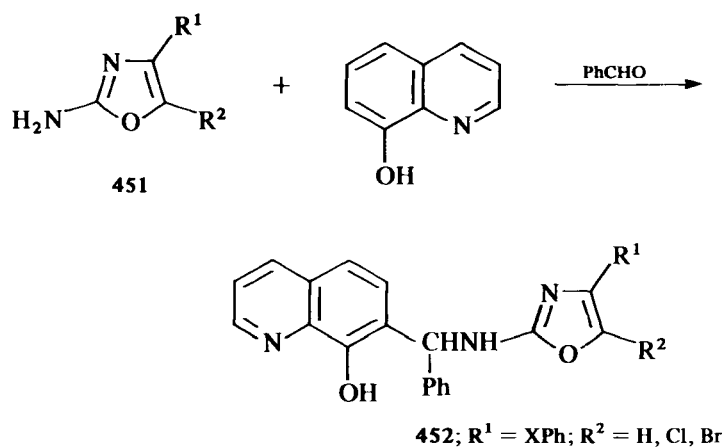
The gas phase thermolysis of 3-amino-5-methylisoxazole (**448**) produces 2-amino-5-methyloxazole (**450**) as the only isolable product.²⁷⁷ The yield of **450** was not reported and the mechanism of this interconversion has not been ascertained, however, 2-amino-3-acetyl-1-azirine (**449**) may be an intermediate.



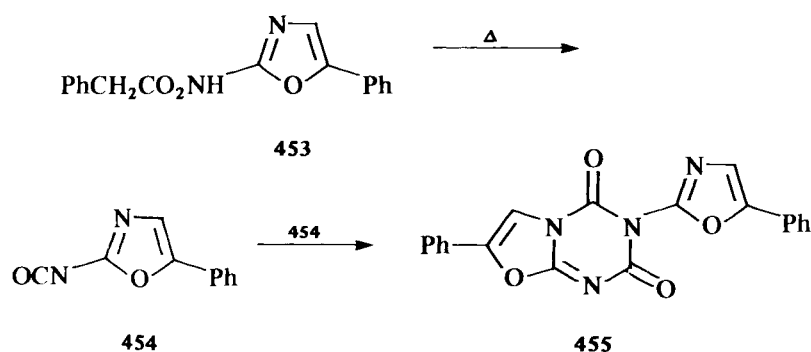
In general, 2-aminooxazoles react as normal aromatic amines. They may be acylated with anhydrides,²⁷⁸⁻²⁸² sulfonylated with sulfonyl chlorides,²⁸³ and the

amides may be alkylated with alkyl bromides.²⁸² Unsuccessful attempts to diazotize 2-aminooxazoles have been reported.²⁸⁴

The 2-aminooxazoles **451** undergo a Mannich reaction to yield the (2'-oxazolyl-amino)(8-hydroxy-7-quinolino)phenylmethanes **452** when allowed to condense with 8-hydroxyquinone and benzaldehyde.²⁸⁵ These compounds exhibit fungicidal activity.

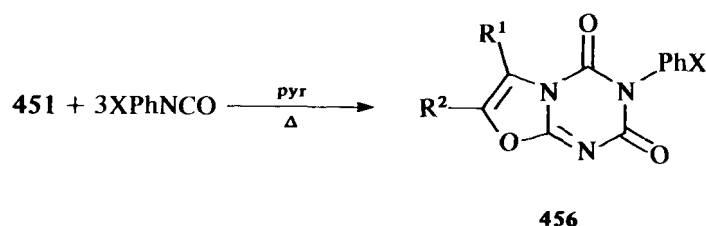


The product isolated when benzyl 5-phenyl-2-oxazolecabamate (**453**) is thermolyzed was formulated as a dimer of 2-isocyanato-5-phenyloxazole. The structure of this dimer was determined by X-ray analysis to be 2-phenyl-6-(5-phenyl-2-oxazolyl)oxazolo[3,2-*a*]-1,3,5-triazine-5,7-dione (**455**).²⁸⁶ The dimer **455** is formally derived by [4 + 2] cycloaddition of two molecules of the isocyanate **454**:

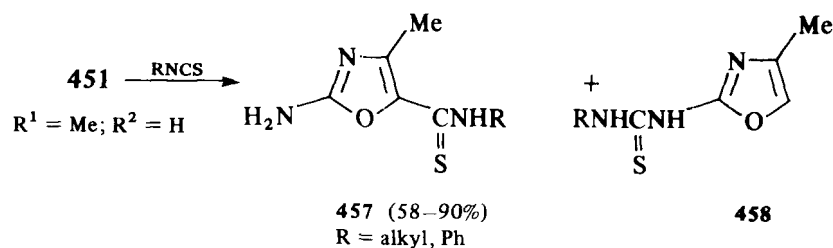


The 2-(*N*-cyanoamino)oxazoles afford 2-guanidinooxazoles when combined with amines.²⁸⁷ The 2-ureidooxazoles are formed from the cyanamides upon hydrolysis with hydrochloric acid while complete decyanation of the cyanamides to the corresponding 2-aminooxazoles results with sulfuric acid.²⁸⁷

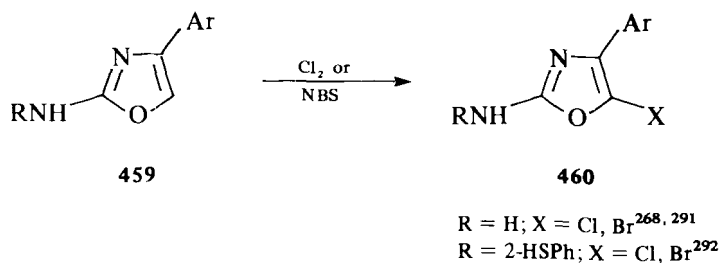
The 2-ureidooxazoles have been prepared by the reaction of 2-aminooxazoles with isocyanates.²⁸⁸ Several of these compounds possess antiinflammatory activity. When the primary 2-aminooxazoles **451** are allowed to react with three equivalents of aryl isocyanates in refluxing pyridine, the oxazolo[3,2-*a*]-*s*-triazine-5,7-diones **456** result.²⁸⁸



The reaction of 2-aminooxazoles with isothiocyanates in general gives the expected 2-thioureidooxazoles, many of which exhibit fungicidal properties.²⁸⁹ An exception to this is the reaction of 2-amino-4-methyloxazole (**451**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) with isothiocyanates. In this case the major products are the thioamides **457**, with the expected thioureas **458** being produced in trace quantities.²⁹⁰

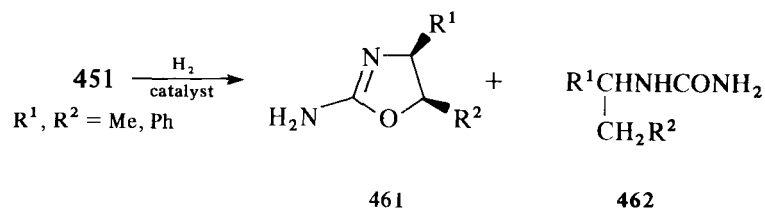


The first and only example of the direct electrophilic nitration of an oxazole was reported by Gompper and Christmann who isolated 2-dimethylamino-4-(4-nitrophenyl)-5-nitrooxazole (**429**, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = 4\text{NO}_2\text{Ph}$, $\text{R}^4 = \text{NO}_2$) from the reaction of 2-dimethylamino-4-phenyloxazole (**429**, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Ph}$, $\text{R}^4 = \text{H}$) with potassium nitrate in sulfuric acid.²⁸⁴ Halogenation of the 2-amino-4-aryloxazoles **459** with chlorine or *N*-bromosuccinimide affords the 2-amino-5-chloro- or -5-bromooxazoles **460**.^{268,291,292}

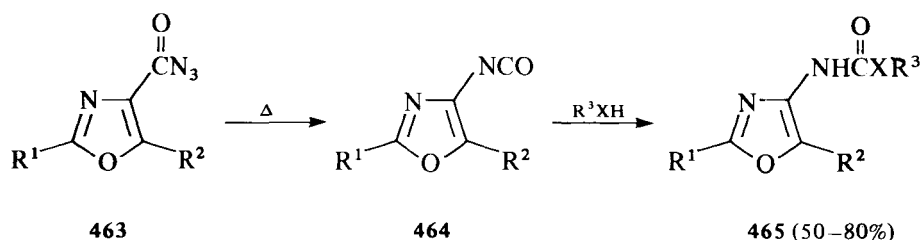


Tanaka and his co-workers have extensively studied the hydrogenolysis of 2-aminooxazoles and their derivatives. In general when these species are treated

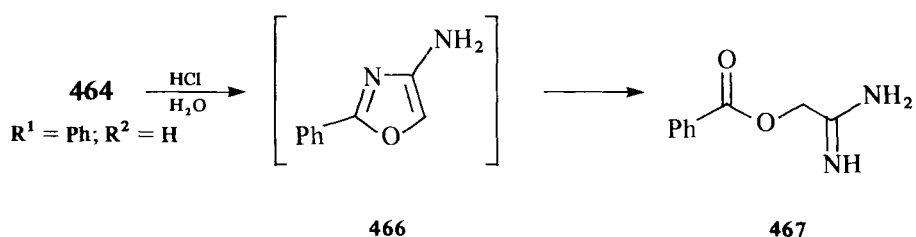
with hydrogen in the presence of palladium or platinum catalysts, the 2-amino-2-oxazolines **461** and the ureas **462** are obtained.²⁹³ The relative proportions of the oxazolines **461** and the ring-opened products **462** are dependent on the reaction time and the nature of the catalysts.



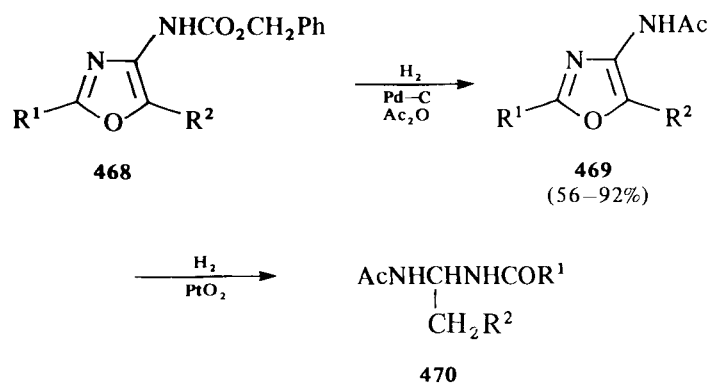
The 4-aminooxazoles are unknown; only acylated derivatives are stable enough to be isolated. The best method for preparing these compounds is via the Curtius rearrangement of the 4-azidocarbonyloxazoles **463**.^{173,191,294} The resulting isocyanates **464** can be trapped by alcohols or amines to furnish the corresponding urethanes **465**, X = O, or ureas **465**, X = NR⁴.



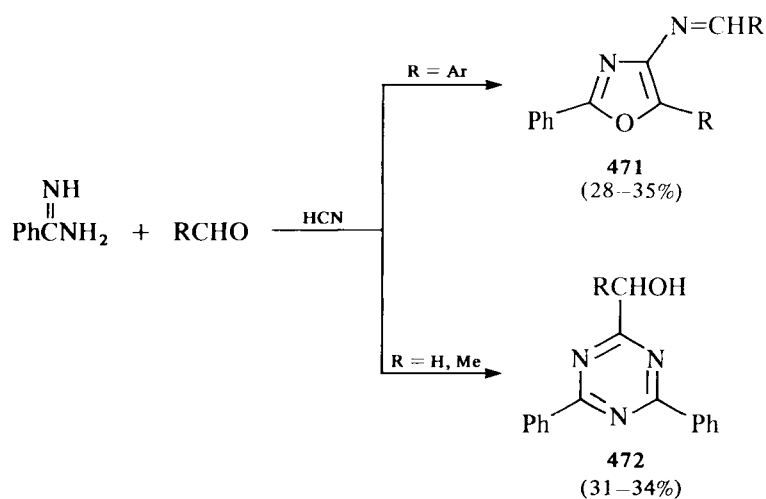
Attempts to isolate 2-phenyl-4-aminooxazole (**466**) by the acidic hydrolysis of the isocyanate **464**, R¹ = Ph, R² = H, provides only the ring-opened product, *O*-benzoylglycollamidine (**467**) presumably via **466**.¹⁷³



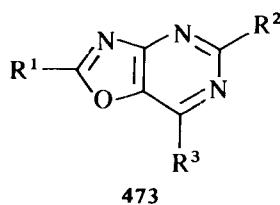
Hydrogenolysis of the *O*-benzyl carbamates **468** (R¹, R² = Me, Ph) with palladium on charcoal in ethanol leads to the formation of intractable materials, while under the same conditions in the presence of acetic anhydride, the acetamides **469**, (R¹, R² = Me, Ph) were obtained. Hydrogenation of **469** with platinum oxide as catalyst in acetic acid affords the ring-opened products **470**.



The reaction of benzamidine with aromatic aldehydes in the presence of hydrogen cyanide yields 2-phenyl-4-arylmethylideneamino-5-aryloxazoles **471**.²⁹⁵ With aliphatic aldehydes on the other hand, the 1,3,5-triazines **472** are formed under these conditions. A mechanism attempting to rationalize these results was offered.

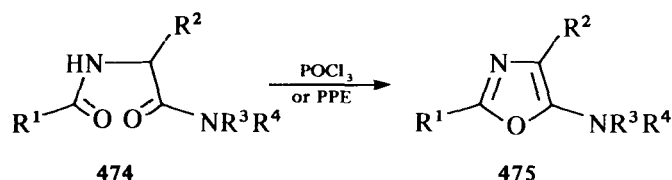


A few examples of the synthesis of oxazolo[4,5-*d*]pyrimidines **473**, derivatives of 4-aminooxazoles, have been reported.²⁹⁶⁻²⁹⁸



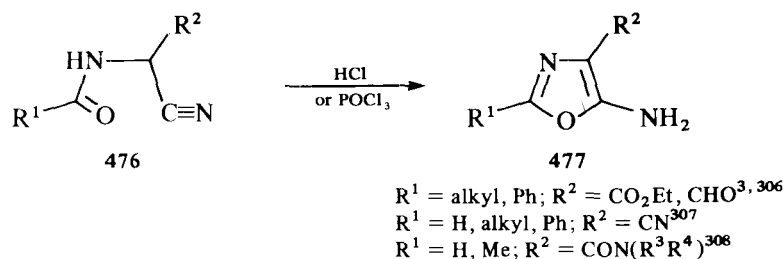
2-Acylamino amides **474** are, in some cases, useful precursors to 5-aminooxazoles **475** via the Robinson-Gabriel cyclization.²⁹⁹⁻³⁰¹ When trifluoroacetic anhydride

is used as the cyclodehydrating agent with **474**, $R^2 = H$, the initially formed 5-aminooxazole **475**, $R^2 = H$, is not isolated; rather **475**, $R^2 = COCF_3$ is produced.³⁰²⁻³⁰⁵ It was reported that the trifluoroacetyl group of **475**, $R^2 = COCF_3$,

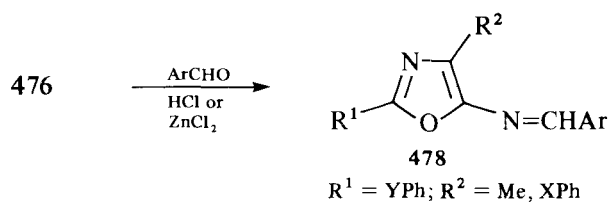


could be hydrolyzed to the corresponding acid, **475**, $R^2 = CO_2H$, and decarboxylated to give **475**, $R^2 = H$.³⁰³ This result could not be obtained in the case of **475**, $R^1 = Me$, $R^2 = COCF_3$, $NR^3R^4 = \text{morpholino}$.²⁹⁹ In this case only the corresponding open-chain product **474** could be isolated.

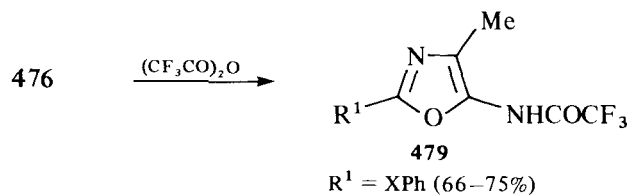
The 5-primary aminooxazoles unsubstituted in the 4-position are unstable relative to their ring-opened tautomers, 2-acylaminoacetonitriles.^{5,6} Other types of 2-acylaminoacetonitriles **476**, however, serve as intermediates in the synthesis of 5-primary aminooxazoles **477** if the nitrile **476** bears electron-withdrawing substituents at the 2-position.^{3,306-308}



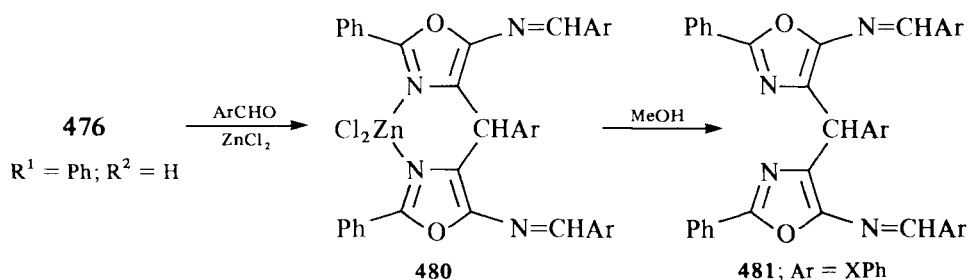
When the 2-acylamino nitriles **476**, $R^2 = Me$, XPh , are treated with hydrogen chloride or zinc chloride in the presence of aromatic aldehydes, the 5-aminooxazole derivatives **478** are obtained.³⁰⁹⁻³¹¹



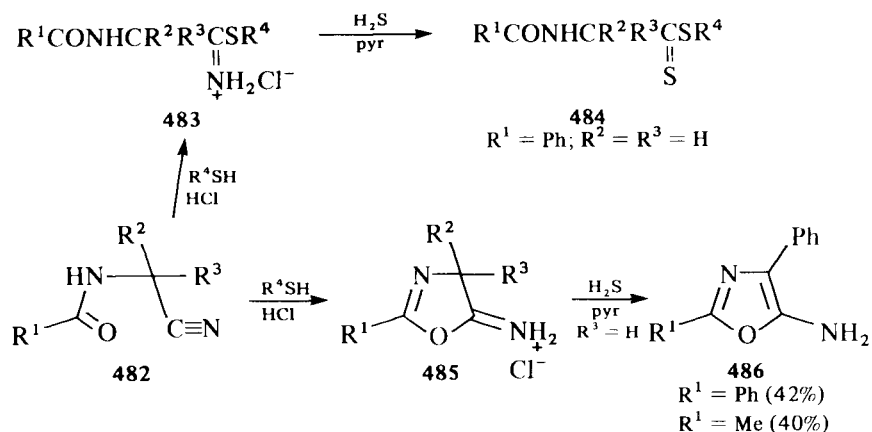
Trifluoroacetic anhydride effects the cyclization of the nitriles **476**, $R^1 = XPh$, $R^2 = Me$, to yield the 5-trifluoroacetamidooxazoles **479**.³¹¹



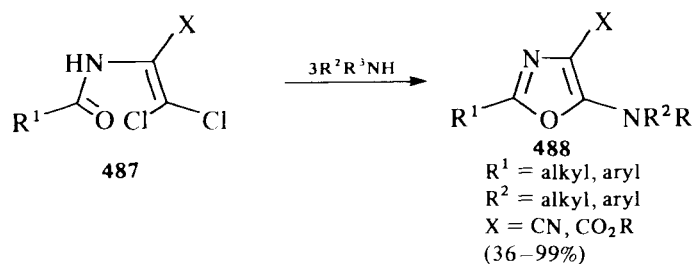
Benzoylaminoacetonitrile **476**, $R^1 = \text{Ph}$, $R^2 = \text{H}$, provides the bisoxazolyaryl-methanes **481** via the zinc complex **480** when treated with zinc chloride and aromatic aldehydes at 110°C .³¹²



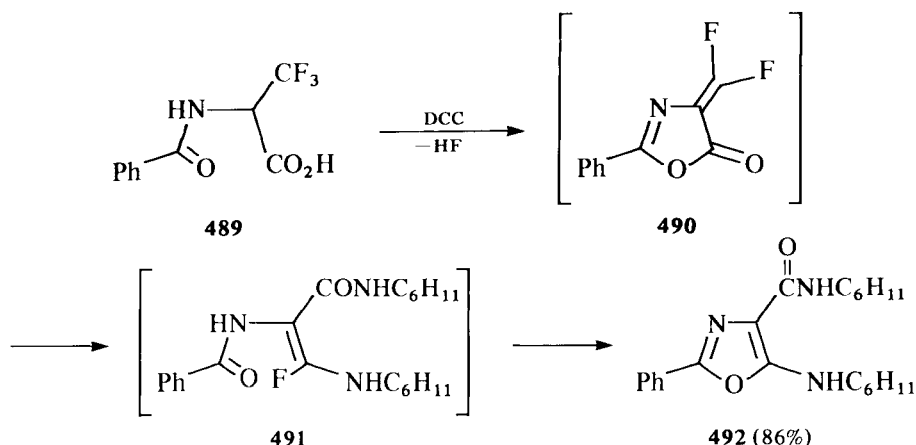
The Pinner reaction of the 2-acylamino nitriles **482** with thiols in the presence of anhydrous hydrogen chloride affords, in only one case, the expected thioimidates **483**, which lead to the dithioester **484** when treated with hydrogen sulfide in pyridine.³¹³ However, the same sequence when applied to **482**, $R^1 = \text{Me}$, $R^2 = \text{Me}$, Ph , $R^3 = \text{H}$ furnished the 5-aminoxazoles **486** in moderate yields via the 5-imino-2-oxazolines **485**.³¹³



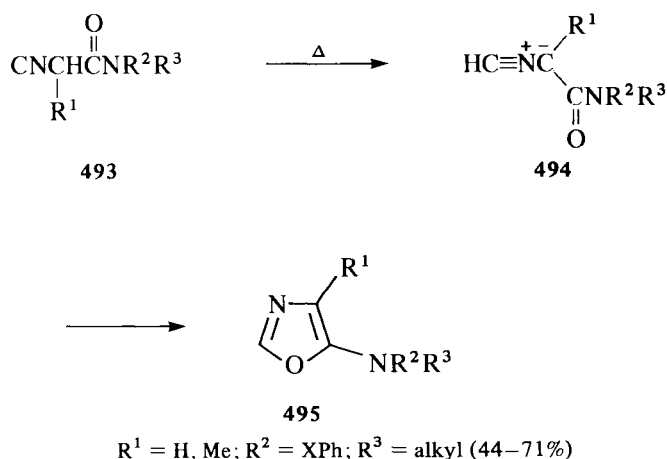
A useful method for the preparation of 5-amino-4-cyano- or -4-alkoxycarbonyloxazoles **488**, $\text{X} = \text{CN}$, CO_2R , involves the reaction of amines with the 1-acylamino-1-cyano- or -1-alkoxycarbonyl-2,2-dichloroethylenes **487**.³¹⁴⁻³¹⁷ Under the same conditions the phosphonium salts **487**, $\text{X} = -\text{P}^+\text{Ph}_3$, provide the 5-aminoxazoles **488**, $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{Me}$, XPh , $\text{X} = -\text{P}^+\text{Ph}_3$, in 71–89% yields.²⁵¹ In a



related process when 3,3,3-trifluoro-*N*-benzoylalanine (**489**) is allowed to react with dicyclohexylcarbodiimide and two equivalents of cyclohexylamine, the 5-aminoxazole-4-carboxamide **492** is formed. Cyclization of **489** affords 2-phenyl-4-difluoromethylene-2-oxazolin-5-one (**490**), which suffers ring opening and displacement of fluoride by the amine to give the intermediate **491**. Cyclization of **491** yields the observed product **492**.³¹⁸



Isonitriles are valuable intermediates in oxazole synthesis as described above. Chupp and co-workers reported their results on the chemistry of 2-isocyanoacetamides. These species serve as precursors to a variety of 5-aminoxazoles that were previously unavailable by known methods. Thermolysis of 2-isocyanoacetamides **493** produces the 5-aminoxazoles **495** in fair to good yields.³¹⁹ The postulated intermediates, the carbonylnitrile ylides, **494** undergo a 1,5-dipolar electrocyclozation leading to the observed products.



The isonitrile carbon of 2-isocyanoacetanilides **493** appears to act as a nucleophile when combined with reactive electrophiles such as isocyanates. When **493**

[illegible]

$493 + R^4NCO \quad \nrightarrow \quad \begin{array}{c} \text{O} \\ \parallel \\ \text{CNH} \\ | \\ \text{CNHR}^4 \\ \parallel \\ \text{O} \\ 499 \end{array} \quad \begin{array}{c} \text{O} \\ \parallel \\ \text{CNR}^2\text{R}^3 \end{array}$

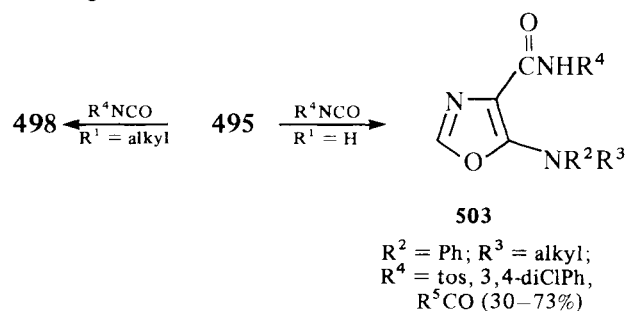
$R^1 = H$

500

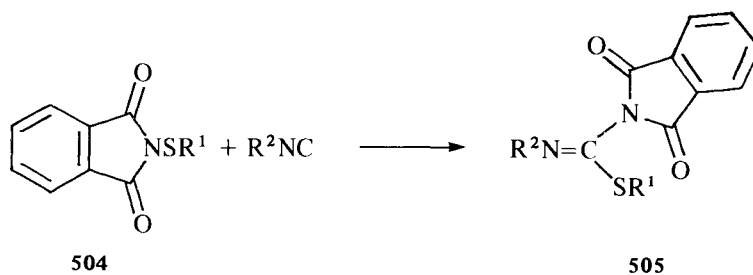
501

502

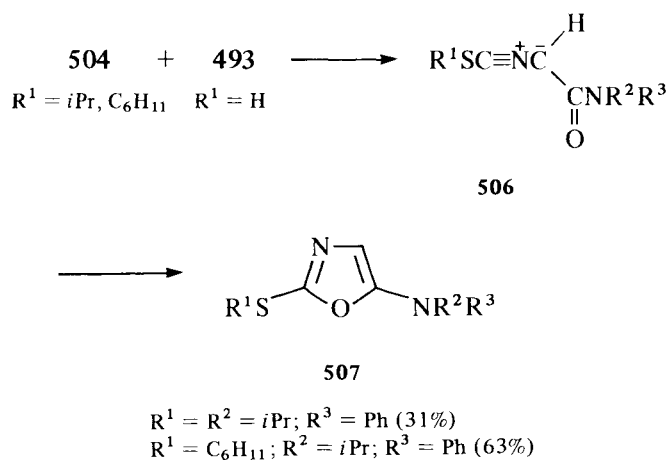
ylide **494** followed by electrophilic addition of the isocyanate to the 2-position of the oxazole) was discounted since for **495**, $R^1 = H$, attack by isocyanates occurs at the 4-position, yielding the 5-aminoxazole-4-carboxamides **503**, and only when this position is blocked by an alkyl substituent does attack occur (sluggishly) at the 2-position to give **498**.



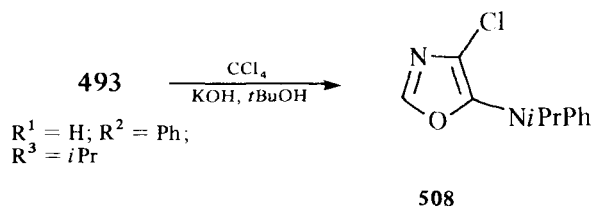
The isonitrile carbon is subject to attack by electrophilic sulfur species. Thus isonitriles combine with *N*-substituted (thio)phthalimides **504** to yield the 1,1-adducts **505**.³²¹ The reaction of **504** ($R^1 = i\text{-Pr}, C_6H_{11}$) with 2-isocyanoacetanilides



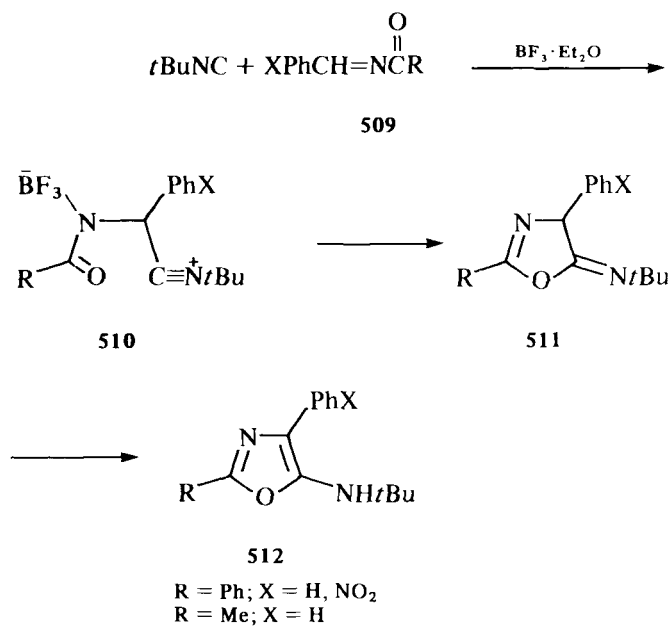
takes a different course. In this case the 2-alkylthio-5-aminoxazoles **507** are formed.³²¹ It is thought that this transformation proceeds via the carbonylnitrile ylide **506**.



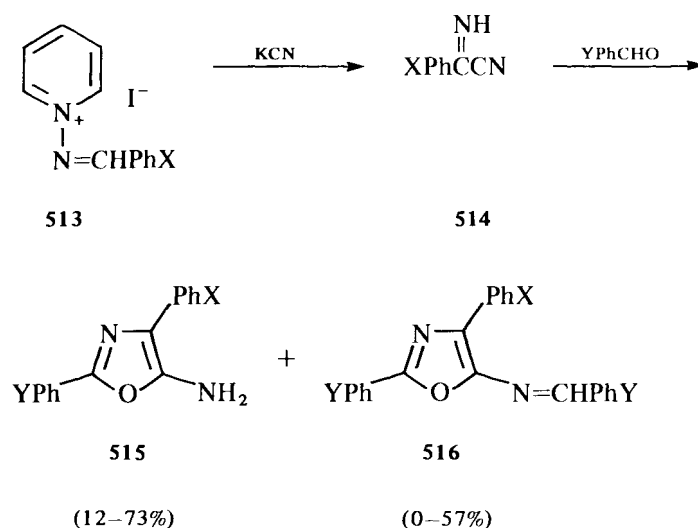
Attempted chlorination of 2-isocyano-*N*-*i*-propylacetanilide (**493**, $R^1 = H$, $R^2 = Ph$, $R^3 = i\text{-}Pr$) with carbon tetrachloride in the presence of base leads to the novel 4-chloro-5-aminoxazole (**508**) in 45% yield.³¹⁹



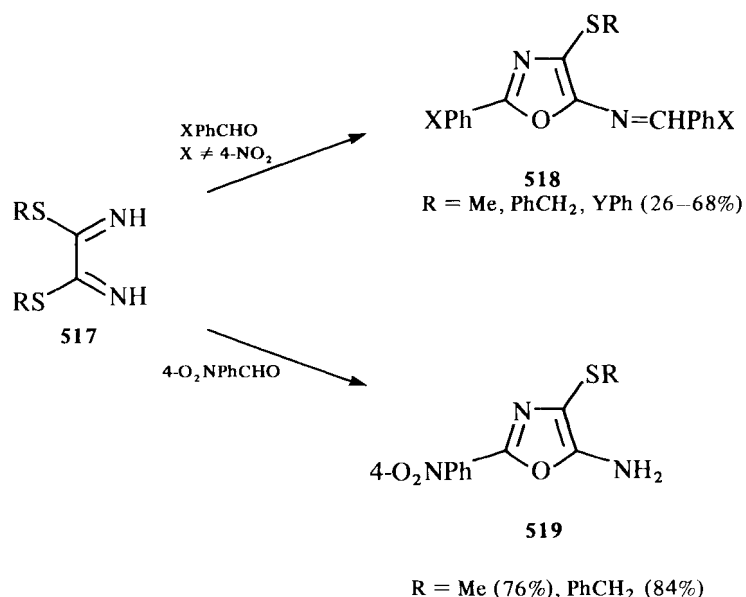
Under catalysis by boron trifluoride etherate *t*-butyl isonitrile and the *N*-acylimines **509** combine to furnish the 5-*t*-butylaminooxazoles **512**.³²² The interconversion is believed to involve nucleophilic attack by the isonitrile carbon on the imine carbon of **509**, leading to the nitrilium ions **510**. Cyclization of **510** to the iminoxazolines **511** and subsequent tautomerization yields the observed products **512**.



The iminonitriles **514** produced upon reaction of the *N*-benzylideneamino-pyridinium salts **513** with potassium cyanide, combine with aromatic aldehydes to afford the 2,4-diaryl-5-aminoxazoles **515** along with the corresponding Schiff's bases **516**.³²³ If $Y = 4\text{-NO}_2$, however, none of the latter is formed. This reaction appears to be related to the Fischer oxazole synthesis (Section 1.2.4).

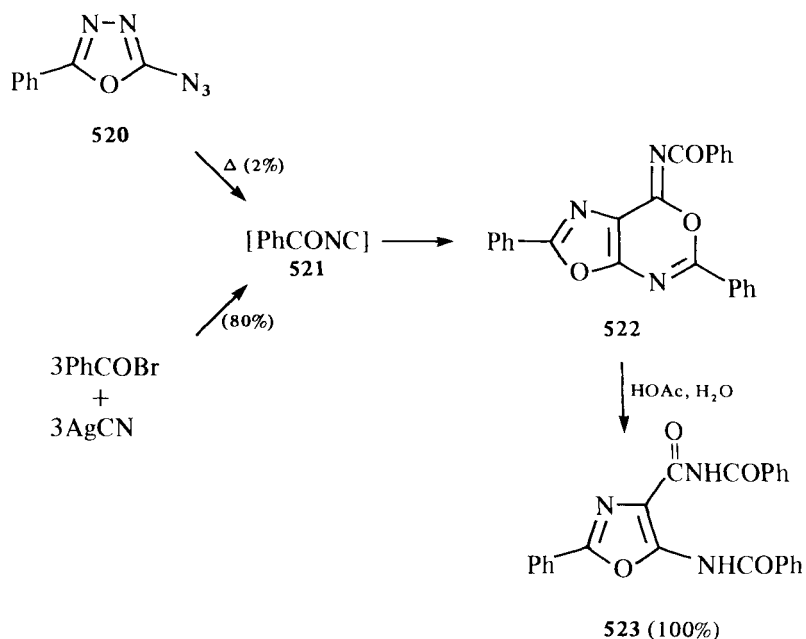


S,S'-Dialkyl- or dialkyl dithiooraldiimides **517** yield 2-aryl-5-benzylideneamino-4-aryl- or -alkylmercaptooxazoles **518** when allowed to react with aromatic aldehydes.^{324,325} When 4-nitrobenzaldehyde is employed, only the 5-aminooxazoles **519**, $\text{R} = \text{Me}$, PhCH_2 , are isolated. These compounds exhibit sedative and weak antitumor activity.³²⁵

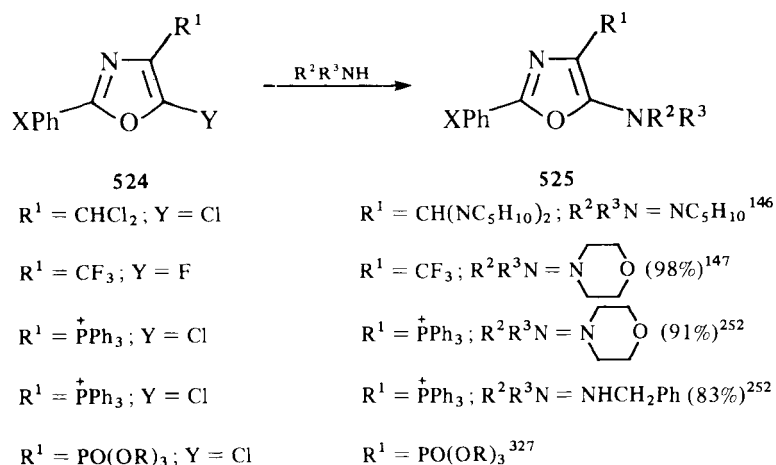


Thermolysis of 2-phenyl-5-azido-1,3,4-thiadiazole (**520**) or treatment of benzoyl bromide with silver cyanide provides the oxazolooxazine **522**.³²⁶ Both reactions

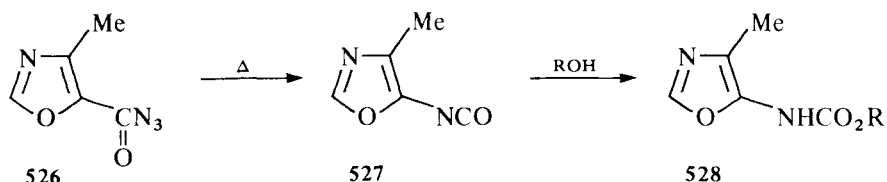
are believed to proceed via benzoyl isocyanide (**521**). Hydrolysis of **522** with acetic acid gives the 5-benzoylaminoxazole-4-carboxamide **523**.



5-Halooxazoles bearing an electron-withdrawing substituent at the 4-position, for example, **524**, are susceptible to nucleophilic attack by amines leading to 5-aminoxazoles **525**.^{146,147,252,327}

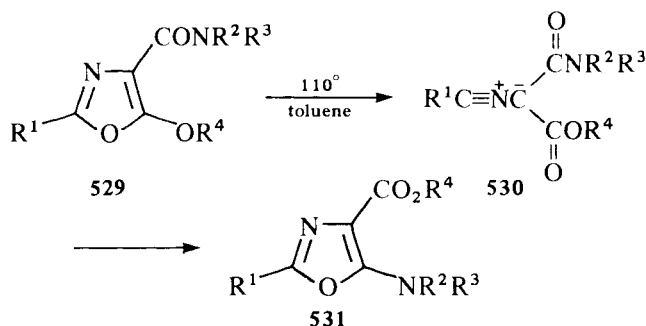


The 4-methyl-5-oxazolecarbamate esters **528** are readily available via the reaction of 4-methyl-5-isocyanatooxazole (**527**) with alcohols. The isocyanate **527** is derived from the Curtius rearrangement of 4-methyl-5-azidocarbonyloxazole (**526**).³²⁸



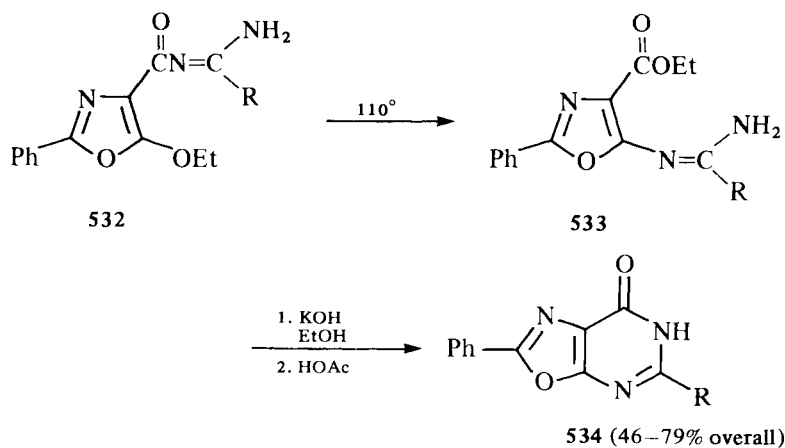
R = alkyl, XPh, 2-naphthyl, 2-furylmethyl

Thermolysis of 5-alkoxyoxazole-4-carboxamides **529** furnishes alkyl 5-amino-oxazole-4-carboxylates **531** in excellent yields, uncomplicated by side reactions.^{3,247,329} This reaction, known as the Cornforth rearrangement, is a general



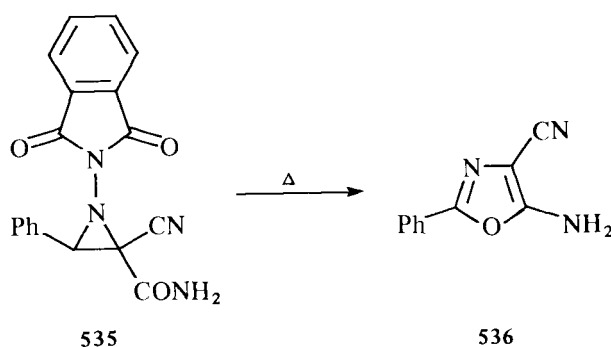
R¹ = alkyl, XPh; R², R³ = H, alkyl, aryl; R⁴ = Me, Et

method for the preparation of **531**. Studies of the mechanism of the Cornforth rearrangement by kinetic and molecular orbital methods suggest that this transformation occurs via electrocyclic ring opening of **529**, leading to the carbonyl-nitrile ylide **530** followed by electrocyclic ring closure of **530** to afford the observed products.^{329,330} A useful application of this rearrangement involves the synthesis of the oxazolo[5,4-*d*]pyrimidones **534** via the 5-aminomethyleneaminooxazoles **533** derived from **532**:³³¹

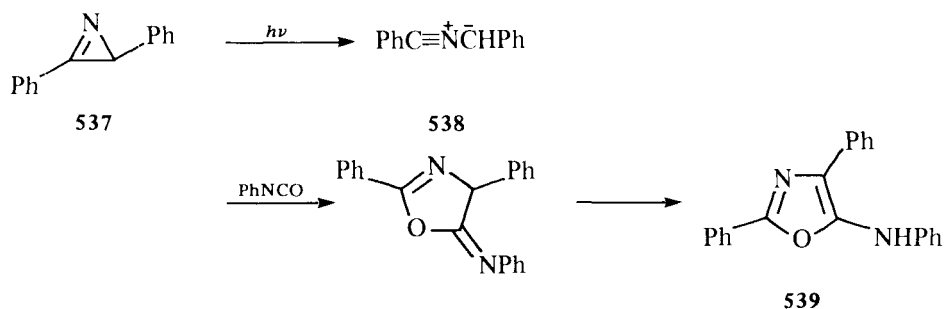


R = H, Me, Ph, 2-pyr, NMe₂, OMe

A related transformation leading to 2-phenyl-4-cyano-5-aminooxazole (**536**) occurs upon thermolysis of 1-(*N*-phthalimido)-2-cyano-3-phenylaziridine-2-carboxamide (**535**) (Section 1.3.2).¹⁷⁷

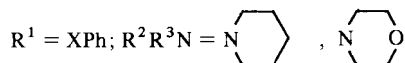


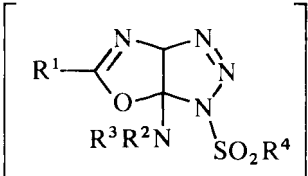
Diphenylnitrile ylide (**538**) generated via photolysis of 2,3-diphenyl-1-azirine (**537**) undergoes a 1,3-dipolar addition to phenyl isocyanate to produce 2,4-diphenyl-5-anilinoxazole (**539**).³³²



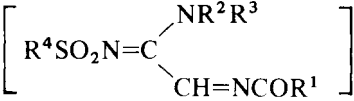
The 5-aminooxazoles may be acylated with anhydrides^{294,302,333} and converted to *N*-oxazolylimidates with orthoesters.^{334,335} 5-Carbamoyloxazoles are *N*-alkylated with alkyl halides.³²⁸

As discussed above, 5-*t*-aminooxazoles undergo electrophilic substitution primarily at the 4-position. Phenyl isocyanate and phenyl isothiocyanate furnish the corresponding 4-carboxamides and 4-thioamides in good yields with 2-aryl-5-*t*-aminooxazoles.³³⁶ With aryl diazonium salts, the 5-*t*-aminooxazoles **540** give the salts **541**, which when treated with base provide the azo derivatives **542**.³³⁶ Treatment of 2-aryl-4-methyl-5-aminooxazoles with aryl diazonium salts provide ring

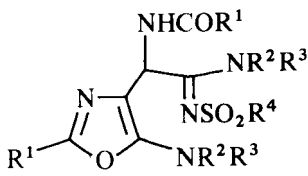


540 $\xrightarrow{R^4SO_2N_3}$ 

543

$\xrightarrow{-N_2}$ 

544

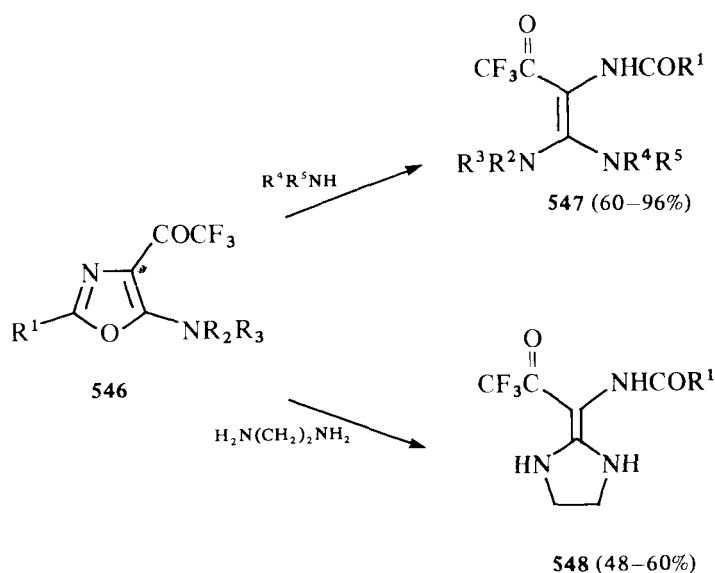


545 (83–93%)

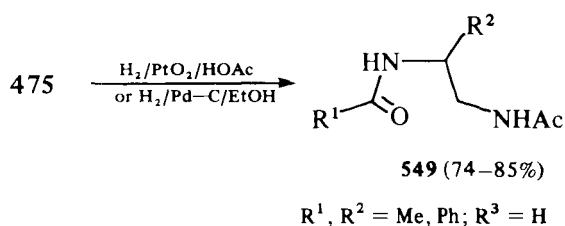
$R^1 = XPh; R^2R^3N = \text{N} \text{ (cyclohexyl) }, \text{N} \text{ (morpholinyl) } \quad R^4 = \text{Me}, 4\text{-MePh}$

Like 5-alkoxyoxazoles, 5-aminooxazoles **475** suffer facile ring opening when treated with aqueous acid, leading to 2-acylamino amides **474**.^{304,319,336} Primary 5-aminooxazoles or 5-benzylideneaminooxazoles in general give 2-acylamino nitriles or primary 2-acylamino amides under these conditions, depending on the substituents present on the oxazole ring.^{311,312,324,325,337}

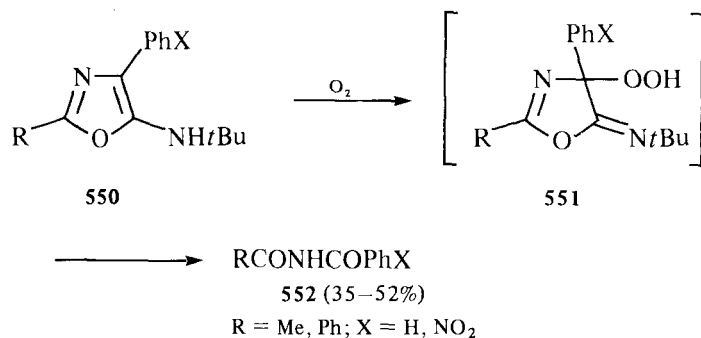
The 1-trifluoroacetyl-1-acylamino-2,2-diaminoethylenes **547** result when the 4-trifluoroacetyl-5-*t*-aminooxazoles **546** ($R^1 = CF_3$, XPh) are allowed to react with primary or secondary amines.³⁰⁵ With ethylenediamine, **546** furnishes the methyleneimidazolidines **548**.



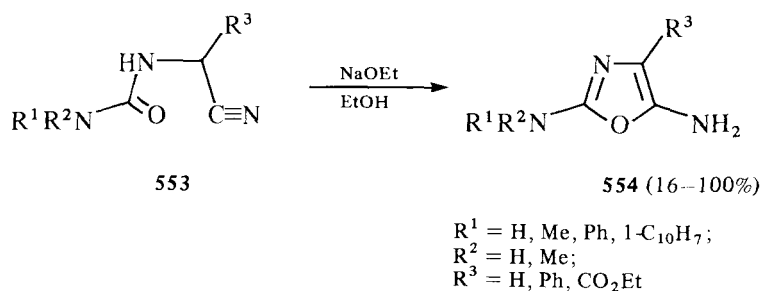
The 1,2-diacylaminoethanes **549** have been isolated when the 5-acetylamino-oxazoles **475** are subjected to hydrogenolysis conditions.²⁹⁴



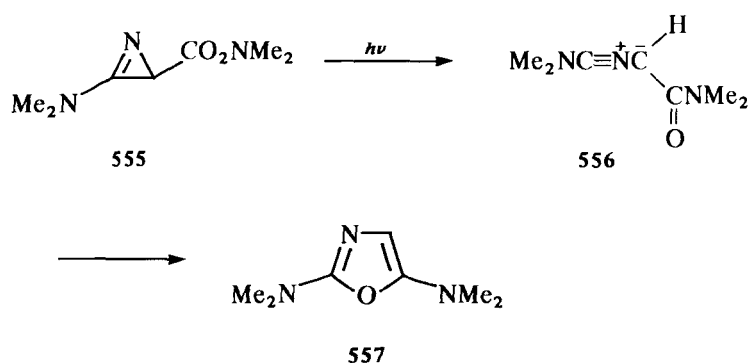
A novel and little explored reaction of 5-aminooxazoles is their autooxidation. When the 5-*t*-butylaminooxazoles **550**, $R^1 = Me, Ph$, are allowed to react with atmospheric oxygen in benzene, the imides **552** are isolated in moderate yields.³²² The proposed intermediate in this reaction is the 4-hydroperoxy-5-*t*-butylimino-2-oxazoline **551**.



To date there exists a paucity of synthetic methods leading to diaminooxazoles. The first example of the preparation of 2,5-diaminooxazoles **554** was reported by Cook and Hunter more than 30 years ago.³³⁸ When the *N*-cyanoalkylureas **553** are treated with sodium ethoxide in ethanol, cyclization occurs to afford **554**.

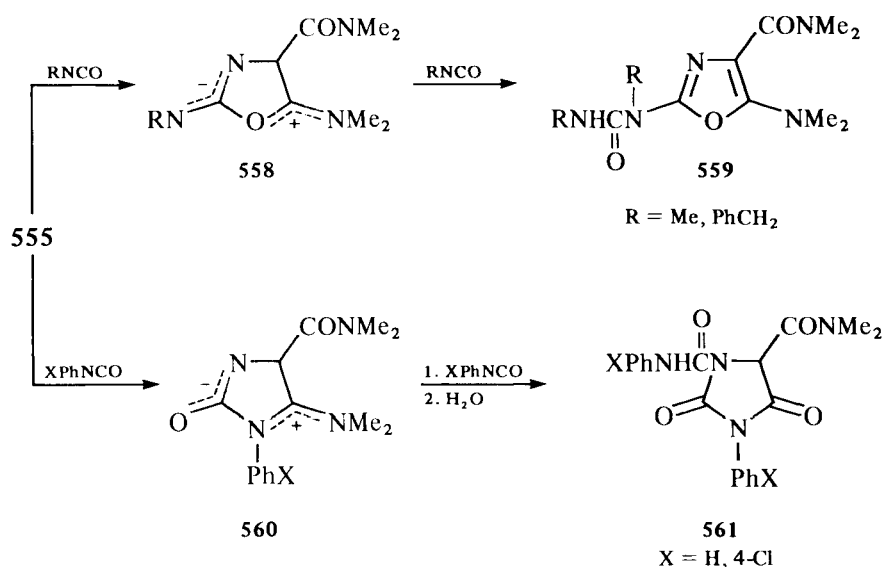


The availability of 2-amino-1-azirines makes these species potentially attractive intermediates in the synthesis of larger ring amino heterocycles. For example, photolysis of 2-(*N,N*-dimethylamino)-3-(*N,N*-dimethyl)-1-azirine carboxamide (**555**) effects carbon-carbon bond cleavage leading to the carbonylnitrile ylide **556**. Electrocyclization of **556** affords 2,5-bis(dimethylamino)oxazole (**557**) in 60% yield.³³⁹

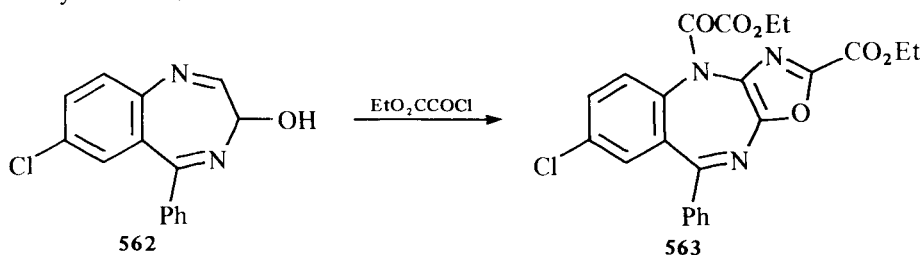


Multiple-reaction pathways are observed when the same azirine **555** is allowed to react with isocyanates. When **555** is treated with two equivalents of methyl-

or benzyl isocyanates, 1,3-dimethyl- or 1,3-dibenzyl(5-dimethylamino-4-dimethyl carbamoyloxazol-2-yl)ureas (**559**, $R = \text{Me}, \text{PhCH}_2$), respectively, are obtained. With two equivalents of aryl isocyanates, **555** yields the imidazolidine diones **561** ($X = \text{H}, 4\text{-Cl}$).³⁴⁰ The zwitterionic species **558** and **560** were implicated as intermediates in this transformation.



No simple 2,4- or 4,5-diaminoxazoles are known; however, some examples of 4,5-diaminoxazoles have been reported where the nitrogen substituents are part of a fused heterocyclic ring. For example, in their studies on tricyclic benzodiazepines, Fryer et al. prepared 7-chloro-2-ethoxycarbonyl-9-phenyl-4*H*-oxazolo-[4,5-*b*] [1,4] benzodiazepine-4-glyoxylic acid ethyl ester (**563**) by the reaction of 2-amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (**562**) with ethyl-oxalyl chloride.³⁴¹



1.3.9. Nitrooxazoles (Table 1.50)

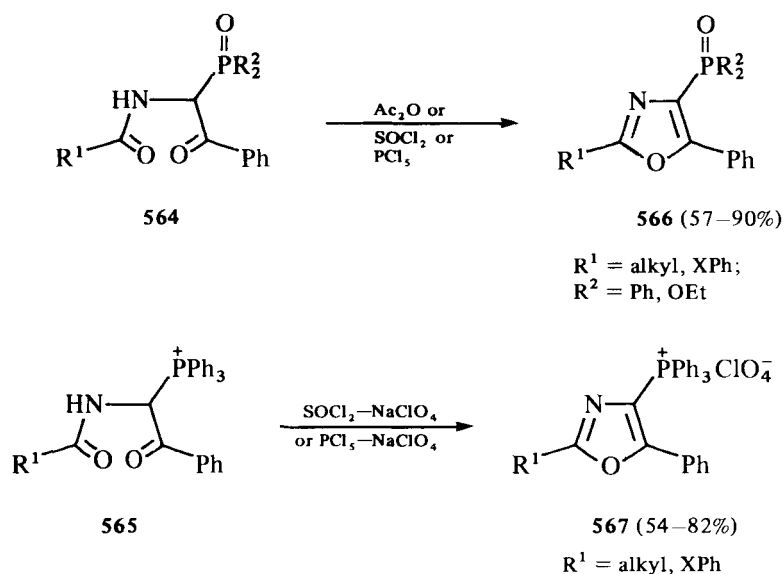
In general the oxazole ring is resistant to direct nitration. The only example of this is the nitration of 2-dimethylamino-4-phenyloxazole to provide 2-dimethylamino-4-(4-nitrophenyl)5-nitrooxazole as described in Section 1.3.8.

Recently the conversion of 2-, 4- and 5-halo-oxazoles to 2-, 4-, and 5-nitro-oxazoles, respectively, with dinitrogen tetroxide has been reported.¹³² The halo-oxazoles were obtained by the reaction of the corresponding oxazolymercuri-acetates with halogenating agents (Section 1.3.1). The best yields (19–52%) of products are obtained for the 5-halo-oxazole to 5-nitrooxazole conversion. The 2- and 4-iodooxazoles furnish 2- and 4-nitrooxazoles with N_2O_4 in 4–12% yields. The low yields obtained for these nitrooxazoles are more than offset by the fact that these oxazole derivatives were unknown prior to this work. This method has been applied to the preparation of 2-methyl-4-(4-bromophenyl)-5-nitrooxazole, a potent antithrombotic agent.³⁴²

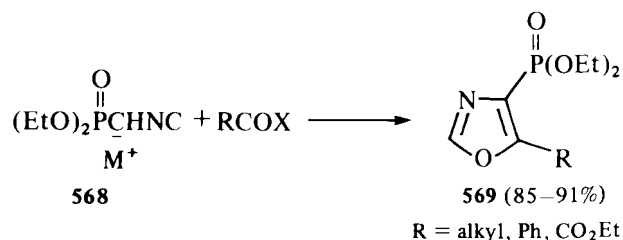
1.3.10. Phosphorus-substituted Oxazoles (Table 1.60)

The synthesis and reactions of several 5-halo-, 5-thio-, and 5-amino-oxazoles bearing phosphorus substituents at the 4-position have been described in Sections 1.3.1, 1.3.5, and 1.3.8.

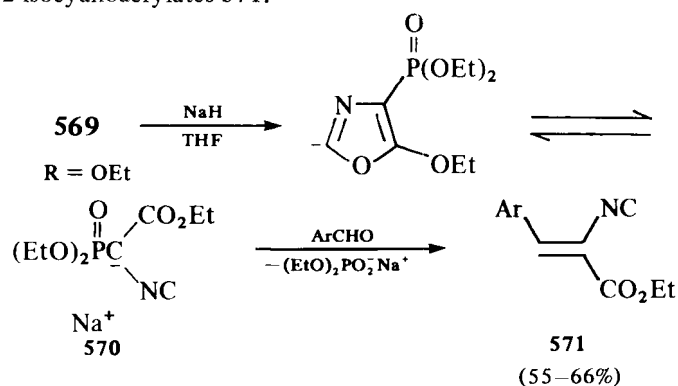
The Robinson–Gabriel cyclization of the 2-acylaminoketones **564** and **565** has been applied to the preparation of the oxazole-4-phosphinic- and -phosphonic esters **566** and the oxazol-4-yltriphenylphosphonium salts **567**.³⁴³



The condensation of acyl halides or imidazolides with the 2-metalated diethyl isocyanomethylphosphonate (**568**) provides the diethyl oxazol-4-ylphosphonates **569** in good yields.³⁴⁴ If the carbonyl compound is a chloroformate or an isocyanate, the corresponding 5-alkoxyl- or 5-amino-oxazol-4-ylphosphonates **569**, $\text{R} = \text{OR}^1, \text{NR}^1\text{R}^2$ are isolated in 77–82% yields.³⁴⁵

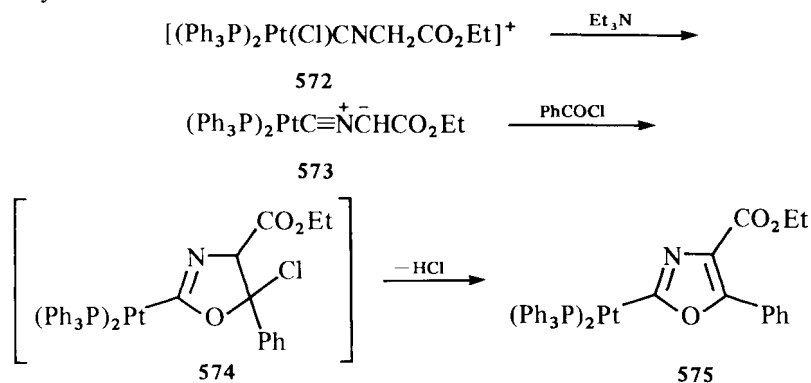


An interesting and useful transformation occurs when diethyl 5-ethoxyoxazol-4-ylphosphonate (**569**, R = OEt) is allowed to react with sodium hydride. Under these conditions reversible ring opening is affected leading to the Wittig–Horner intermediate **570**, which when intercepted by aromatic aldehydes provide the (*Z*)-ethyl 2-isocyanoacrylates **571**.

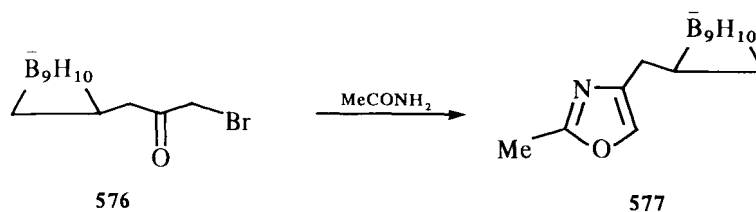


1.3.11. Miscellaneous Oxazole Derivatives (Table 1.61)

The platinum-substituted nitrile ylide **573** is formed when the platinum species **572** is treated with triethylamine.³⁴⁶ When **573** is generated in the presence of benzoyl chloride, a 1,3-dipolar cycloaddition occurs to give the oxazoline **574**, which suffers elimination of hydrogen chloride leading to the 2-platinum-substituted oxazole-4-carboxylate **575**.

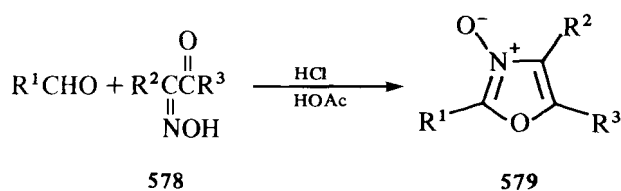


The 4-carboranylmethyloxazole **577** was prepared by the reaction of 1-carboranyl-3-bromo-2-propanone (**576**) with acetamide.³⁴⁷



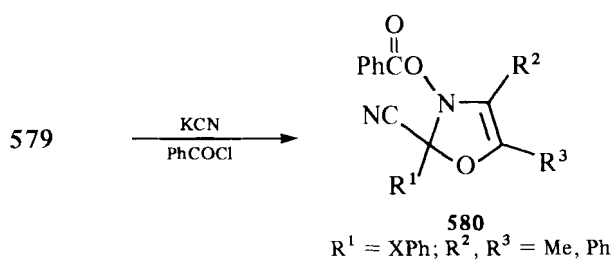
1.3.12. Oxazole *N*-Oxides (Table 1.62)

The only method that exists for the preparation of oxazole *N*-oxides **579** is the reaction of α -diketone monoximes **578** with aldehydes in acetic acid in presence of anhydrous hydrogen chloride.^{96,180,348} A number of derivatives of **579** were tested as antibacterial agents but were ineffective.³⁴⁸



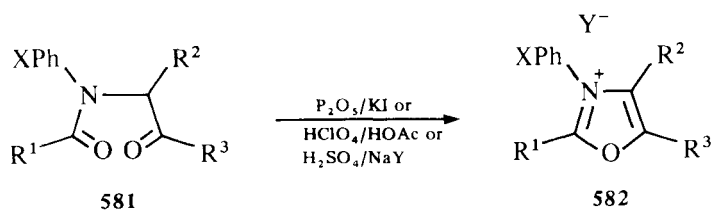
The deoxygenation of oxazole *N*-oxides **579** to give alkyl-, aryl-, or ketooxazoles has been discussed (Sections 1.2.17 and 1.3.7).

The reaction of aralkyloxazole *N*-oxides **579** with potassium cyanide and benzoyl chloride furnishes the Reissert-like compounds, the 2-cyano-3-benzoyloxy-4-oxazolines **580**.³⁴⁹

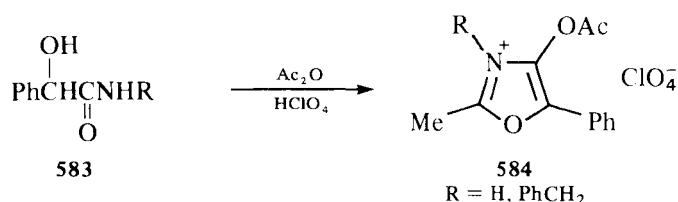


1.3.13. Oxazolium Salts (Table 1.63)

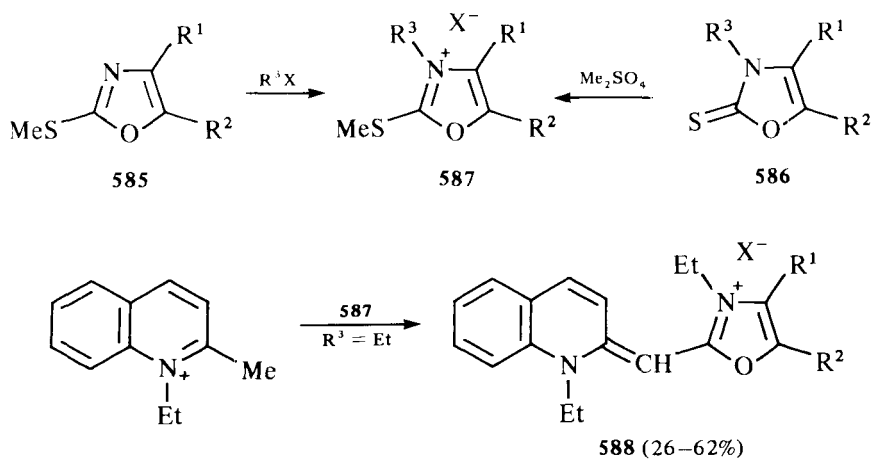
The alkylation of oxazoles with alkyl halides,³⁵⁰ sulfonates,^{351,352} and oxonium salts³⁵³ represents a general method for the preparation of 3-alkyloxazolium salts. The 3-aryloxazolium salts **582** are obtained by the cyclization of 2-(*N*-acyl-*N*-aryl)-aminoketones **581**.³⁵⁴⁻³⁵⁶



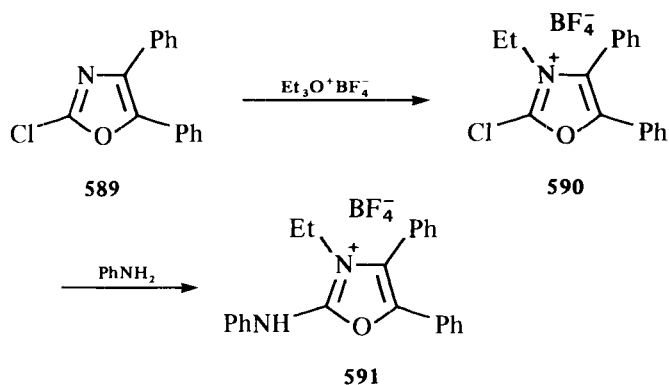
The 2-hydroxy-2-phenylacetamides **583** have been converted to the 4-acetoxy-oxazolium salts **584** with acetic anhydride–perchloric acid.³⁵⁷



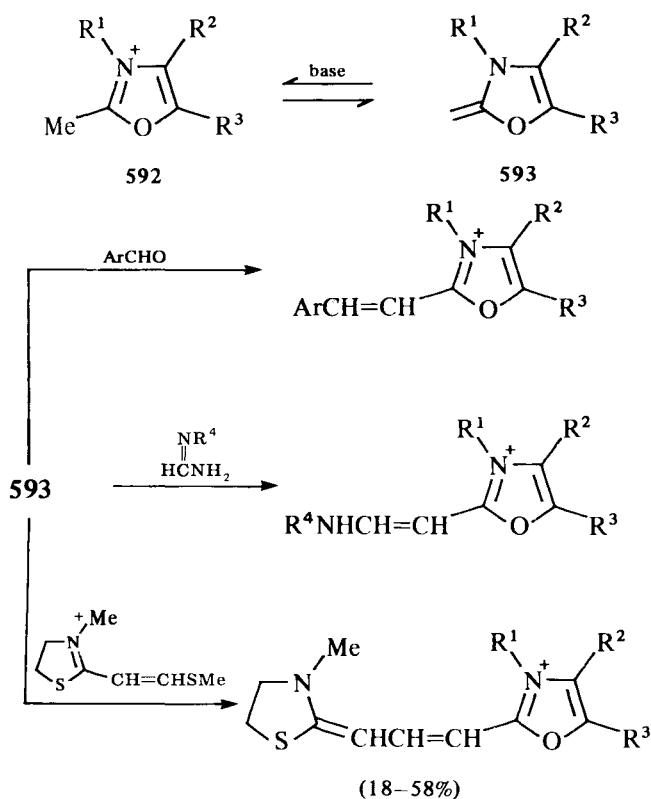
The 2-methylthio-3-alkyloxazolium salts **587** are prepared by *N*-alkylation of 2-methylthiooxazoles **585** with alkyl halides³⁵⁸ or dialkyl sulfates²²⁵ or by *S*-alkylation of 4-oxazolin-2-thiones **586** with dimethyl sulfate.^{128,359} These salts are intermediates in the synthesis of cyanine dyes such as **588**.³⁵⁸



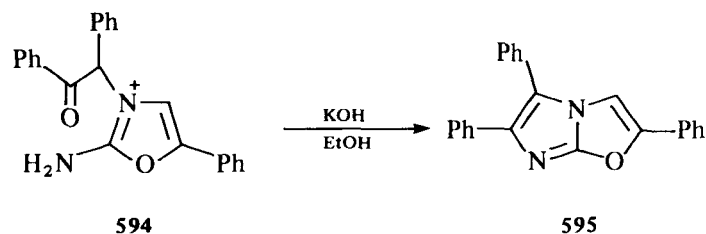
2-Chloro-4,5-diphenyloxazole (**589**) yields 2-chloro-3-ethyl-4,5-diphenyloxazolium tetrafluoroborate (**590**) when treated with triethyloxonium tetrafluoroborate.¹²⁸ When **590** is caused to react with aniline, 2-anilino-3-ethyl-4,5-diphenyloxazolium tetrafluoroborate (**591**) results.



The anhydro bases **593** are formed when 2-methyl-3-alkyloxazolium salts **592** are treated with base (usually tertiary amines). When these species are generated in the presence of electrophiles such as aldehydes or Michael acceptors, coupling occurs to give 2-vinyl-3-alkyloxazolium salts.^{351,360,361} Some examples are

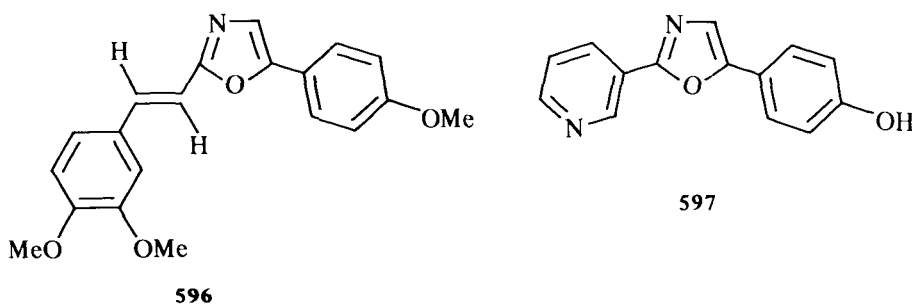


The 2-aminoxazolium bromide **594**, prepared by the reaction of 2-amino-5-phenyloxazole with 2-phenyl-2-bromoacetophenone, affords the imidazo[2,1-*b*]-oxazole **595** when heated in ethanolic potassium hydroxide.³⁶²

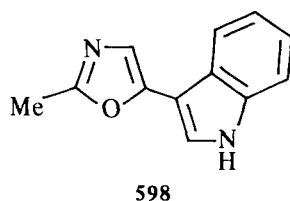


1.4. NATURALLY OCCURRING OXAZOLES

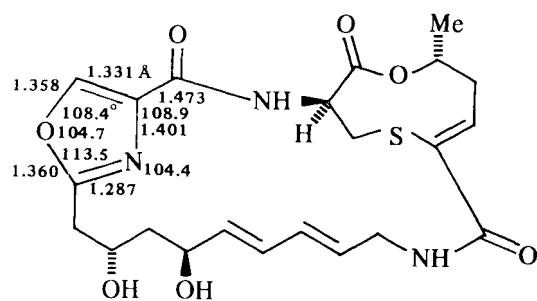
Oxazole derivatives occur only rarely in nature. Two 2,5-diaryloxazoles (and related compounds), annuloline (**596**, from *Lolium multiflorum*),^{363–365} and halfordinol (**597**, from *Halfordia scleroxyla*)^{110,366–369} have been isolated from plant sources and have been prepared by standard procedures.



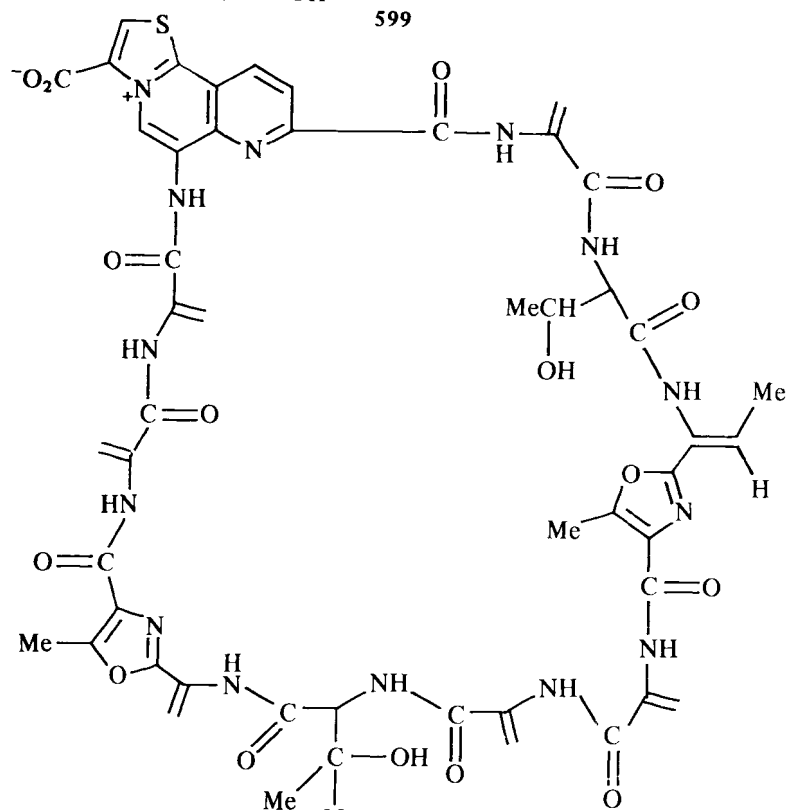
A number of oxazole ring-containing antibiotics have been isolated and characterized. These include pimprinine (**598**, a mould metabolite from *Streptomyces pimprina*) for which several syntheses have been reported,^{159,370,371} griseoviridin



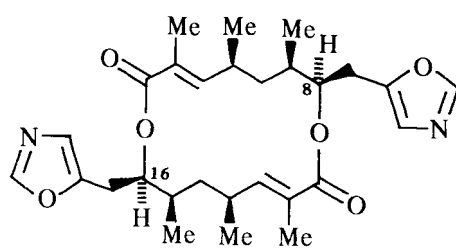
(**599**, from *S. graminofaciens*),^{372,373} the peptidic compound berninamycin A (**600**),^{157,374} and conglobatin (**601**, from *S. conglobatus* ATCC 31005).³⁷⁵



599

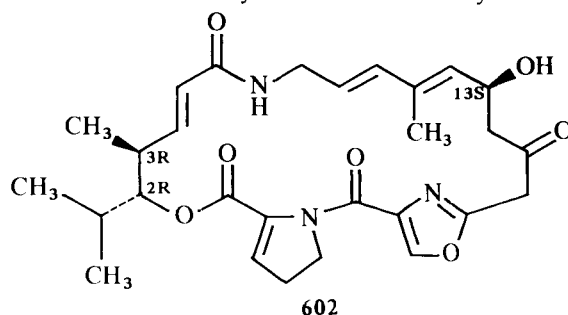


600



601

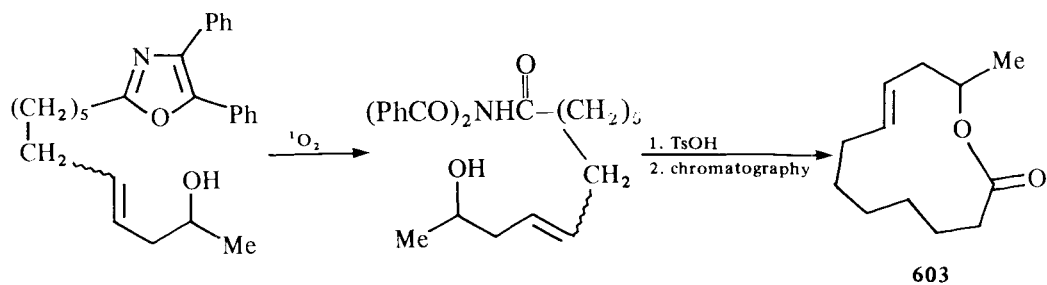
Recently, there has been considerable interest in the structure^{199,376} stereochemistry,^{377,378} biosynthesis,³⁷⁹ and synthesis³⁷⁸ of virginiamycin M (**602**, from *S. virginiae* and several other microorganisms, also known as ostreogrycin A,^{199,376} mikamycin A, staphylomycin M, streptogramin A, and pristnamycin IIA). Crystal structure data³⁷⁷ and degradation studies³⁷⁸ revealed that **602** possesses the 2R; 3R, 13S configuration. When the 13-hydroxyl function of **602** (in this case isolated from *S. pristinaspiralis* and called pristnamycin) is oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone loss of antibiotic activity is observed while reduction of the 15-keto function with sodium borohydride does not modify its activity.³⁸⁰



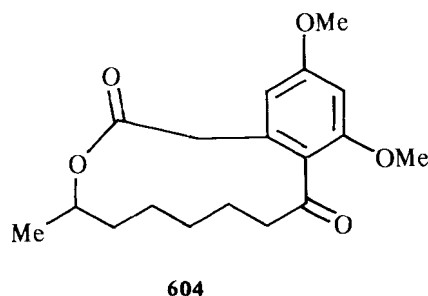
1.5. REACTION OF OXAZOLES WITH SINGLET OXYGEN

Oxazoles are remarkably reactive toward singlet oxygen. The dye-sensitized photo-oxygenation of alkyl- or aryloxazoles produces triacylamines.⁵ The mechanism of this reaction involves a [4 + 2] cycloaddition of singlet oxygen to the oxazole to afford a bicyclic endoperoxide, some of which are stable at 0°C in chloroform solution. Warming of the solution to room temperature causes the collapse of the endoperoxide, producing an iminoanhydride which undergoes an *N*- to *O*-acyl migration to yield the observed triacylamines.³⁸¹ The 2-aryloxazolocycloalkanes lead to isolable cyclic iminoanhydrides³⁸² while 2-unsubstituted oxazolocycloalkanes furnish ω -cyanoalkyl carboxylic acids⁵ under photooxidation conditions.

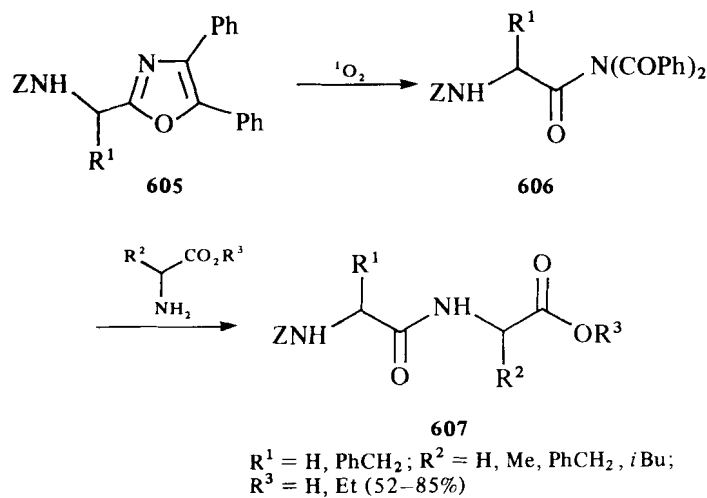
The triacylamines derived from the reaction of 2-hydroxyalkyl-4,5-diphenyl-oxazoles with singlet oxygen are intermediates in a general synthesis of macrocides.¹⁰⁵ This procedure, developed by Wasserman et al., was applied to a total synthesis of ($\pm$)-recifeiolide (**603**):



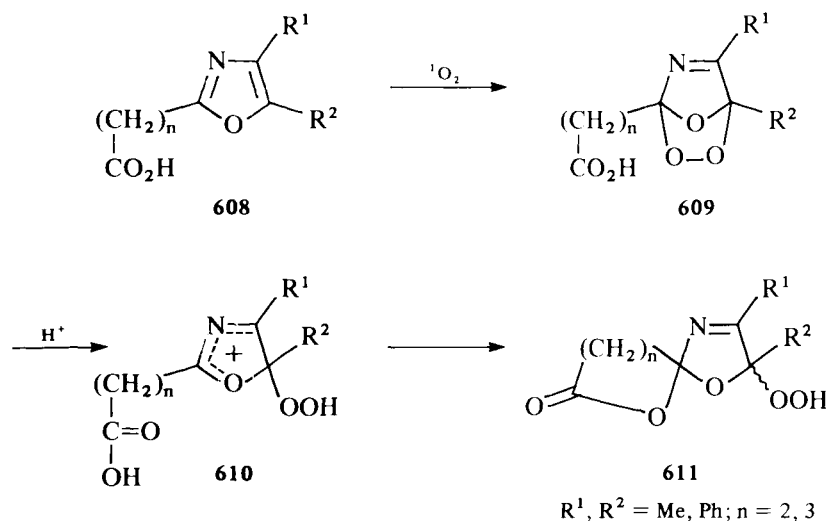
(±)-Di-*O*-methylcurvularin **604** was obtained in a similar manner. Thus the oxazole ring acts as a masked activated carboxyl group. A second application of this principle involves the synthesis of some dipeptide derivatives.³⁸³ When the



N-protected 2-(2-aminoalkyl)-4,5-diphenyloxazoles **605** are subjected to photo-oxygenation, the triacylamines **606** are formed. These intermediates couple with amino acids or esters to provide the dipeptides **607**.



The reaction of singlet oxygen with oxazoles bearing a 2-carboxyalkyl substituent, that is, **608**, provides the spirolactones **611** after treatment of the reaction mixture with methanol. It is thought that the initially formed endoperoxide **609** suffers carbon-oxygen bond cleavage to afford the cation **610**, which undergoes intramolecular attack by the carboxyl oxygen to form the observed products **611**.³⁸⁴ In addition, solvent effects on the reaction rate and Hammett data suggest that the addition of singlet oxygen to oxazoles is a concerted process.³⁸⁴



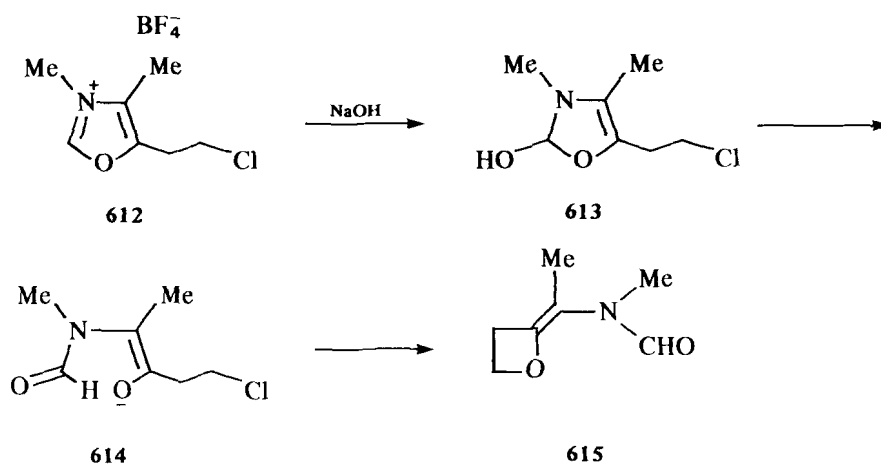
1.6. RING TRANSFORMATIONS OF OXAZOLES

One of the most intriguing aspects of heterocyclic chemistry is the conversion of one heterocyclic system to another. Most of these processes occur via ring opening of the heterocycle under acidic, basic, thermal, or photochemical conditions followed by recyclization of an acyclic intermediate. Cycloadditions provide a second mode for heterocyclic ring transformations. The reactivity of oxazoles toward acids, bases, heat, and dienophiles make them a particularly attractive and useful starting point for a variety of ring transformations as can be seen in the ensuing discussion. This section is organized by the type of heterocycles that have been derived from oxazoles rather than reaction type.

1,3-Dipolar cycloadditions of various dipolarophiles to mesoionic oxazoles produce new heterocyclic systems. These reactions are discussed in detail in Chapter 4 of this volume.

1.6.1. Oxetanes

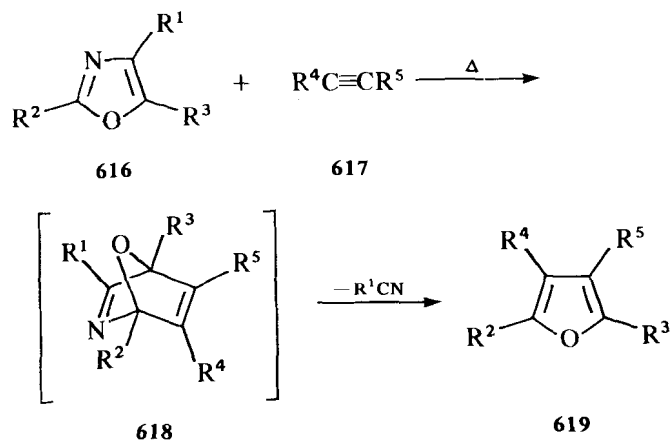
Upon treatment with aqueous sodium hydroxide, 3,4-dimethyl-5-(2-chloroethyl)-oxazolium tetrafluoroborate (**612**) rearranges to the ethylidene oxetane **615** in low yield.³⁵³ The mechanism most likely involves nucleophilic attack by hydroxide at the 2-position of **612** to give the 2-hydroxy-4-oxazoline **613**. Ring opening of **613** leads to the enolate **614**. Displacement of chloride by the enolate oxygen leads to the observed ring-contracted product **615**. The corresponding thiazolium salts are converted to ethylidene thietanes in much higher yields under these conditions. This is probably due to the higher nucleophilicity of the sulfur of the



thioenolate (corresponding to 614) and the lower strain energy of the thietane ring relative to the oxetane.

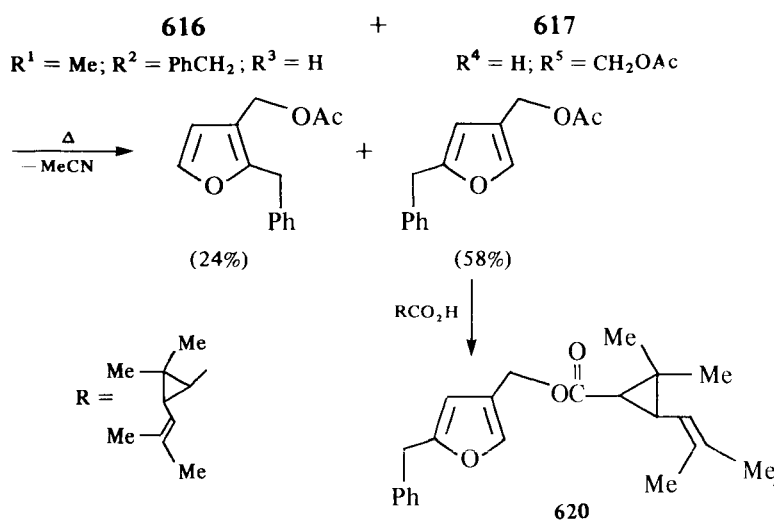
1.6.2. Furans and Tetrones

Oxazoles 616 serve as dienic components in Diels–Alder reactions with acetylenes and olefins.^{5,6} With acetylenes 617, furans 619 are formed via elimination of a nitrile fragment in a retro Diels–Alder reaction of the bicyclic adduct 618

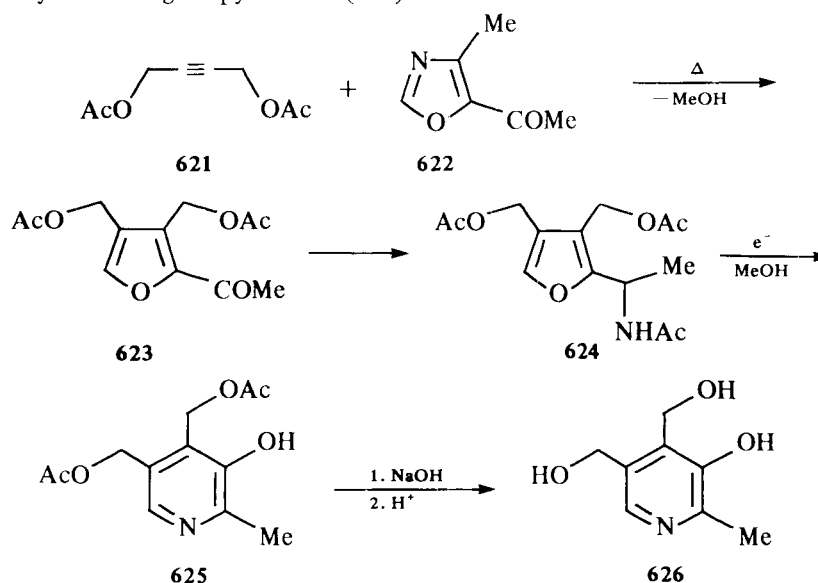


Recently, König et al. reported the results of further studies of the scope of this reaction.³⁸⁵ The groups R^2 and R^3 on the oxazole may be H, 2- or 5-alkyl, 2-alkenyl, 5-cyano, 5-acetyl and 5-alkoxy. The alkyne substituents R^4 and R^5 may be H, alkyl, phenyl, carboethoxy, and dimethoxymethyl. When R^2 = benzyl and the dienophile is a terminal alkyne, the major product is the 2,4-disubstituted furan while the minor product is the 2,3-disubstituted furan. The

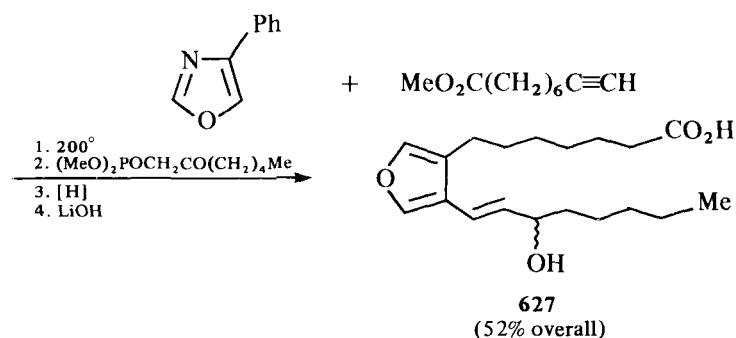
regiochemistry is reversed when the oxazole bears a 2-alkenyl substituent. In this case electronic factors presumably override steric effects since the 2-alkenyl moiety is sterically less demanding than the 2-benzyl substituent.³⁸⁵ This process has been applied to a synthesis of the pyrethroid insecticide, resmethrin **620**.³⁸⁵



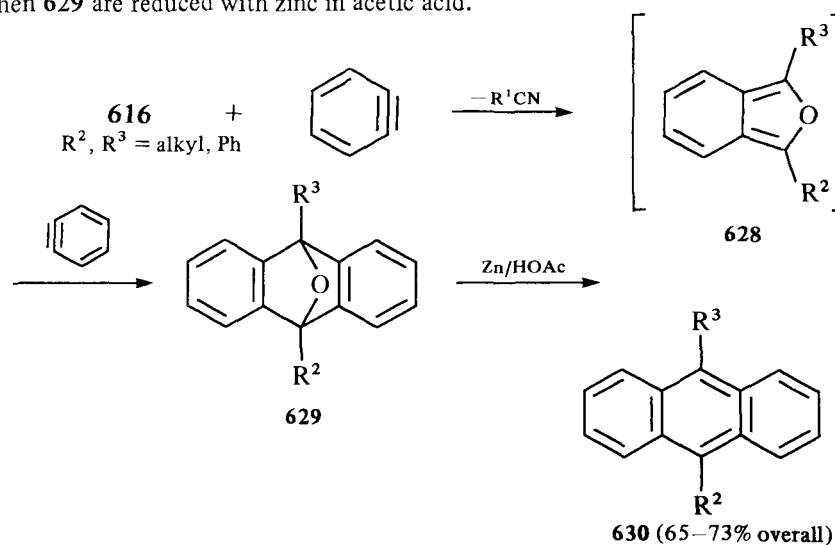
The 2-acetylfuran **623**, prepared by the Diels–Alder reaction of the acetylene **621** with 4-methyl-5-acetyloxazole (**622**), has been utilized as an intermediate in a synthesis of pyridoxine (**626**).³⁸⁵ Reductive amination of **623** gives the 2-(*N*-acetylaminoethyl)furan **624**, which upon electrolysis in methanol undergoes a ring expansion to afford 2-methyl-3-hydroxy-4,5-diacetoxymethylpyridine (**625**). Base hydrolysis of **625** gives pyridoxine (**626**).



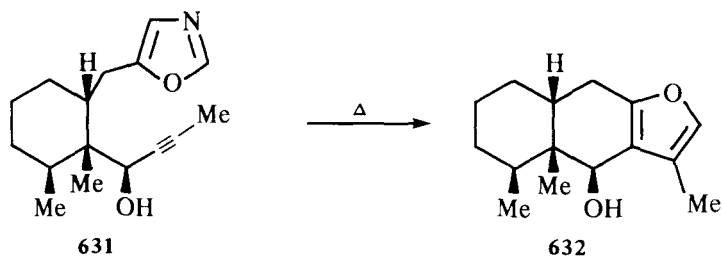
Another application of this process to the synthesis of biologically interesting substances is in the preparation of the furan prostanoïd **627**.³⁸⁶



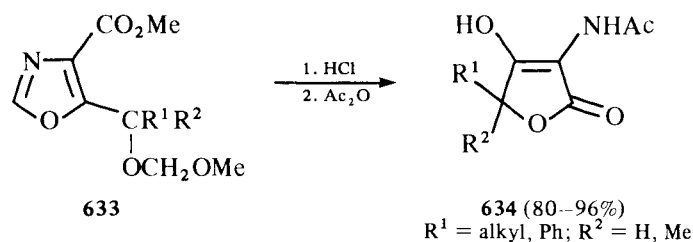
The reaction of the oxazoles **616** (R^1, R^2, R^3 = alkyl, phenyl) with benzyne produces the ethers **629**.³⁸⁷ It is believed that the isobenzofurans **628** derived from the Diels–Alder/retro Diels–Alder sequence reacts with a second molecule of benzyne to give the observed products **629**. The anthracene derivatives **630** arise when **629** are reduced with zinc in acetic acid.



The intramolecular version of this reaction has been applied to a synthesis of the furanosesquiterpene, evodone,³¹ and the furanoeremophilanes, ligularone and petasalbine.³⁸⁸ The synthesis of petasalbine (**632**) from the oxazole **631** is

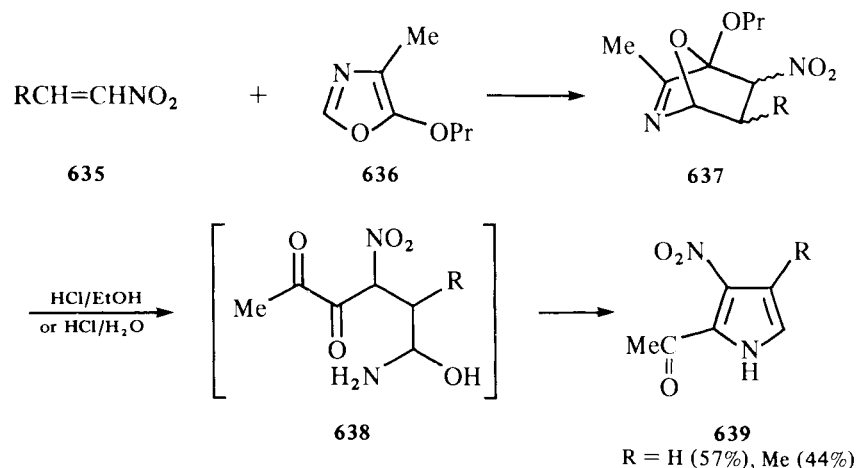


A recently reported synthesis of the 3-amino-4-hydroxytetrones **634** takes advantage of the lability of 2-unsubstituted oxazole-4-carboxylates **633** toward ring opening.¹⁷¹ The latter are prepared via coupling of methyl isocynoacetate with carboxylic acids (Section 1.3.2).



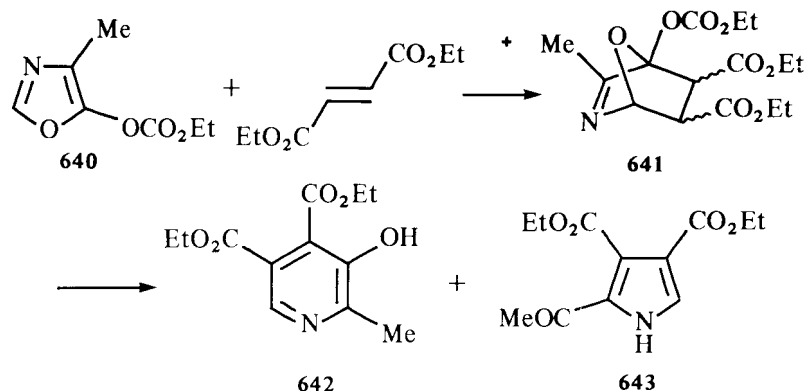
1.6.3. Pyrroles and Pyrrolidines

The Diels–Alder reaction of 5-alkoxyoxazoles with olefins normally leads to 3-hydroxypyridines by carbon–oxygen bond cleavage of the initial adduct (Section 1.6.8). However, when nitroethylene (**635**, $R = \text{H}$) and 1-nitropropene (**635**, $R = \text{Me}$) react with 2-methyl-5-propoxyoxazole (**636**), 2-acetyl-3-nitropyrrole (**639**, $R = \text{H}$) and 2-acetyl-3-nitro-4-methylpyrrole (**639**, $R = \text{Me}$), respectively, arise.^{389,390} The pyrroles **639** are presumably formed via carbon–nitrogen double bond cleavage when the cycloadducts **637** are treated with acids. Cyclization of the resulting aminoketones **638** afford the pyrroles. The formation of pyrroles rather

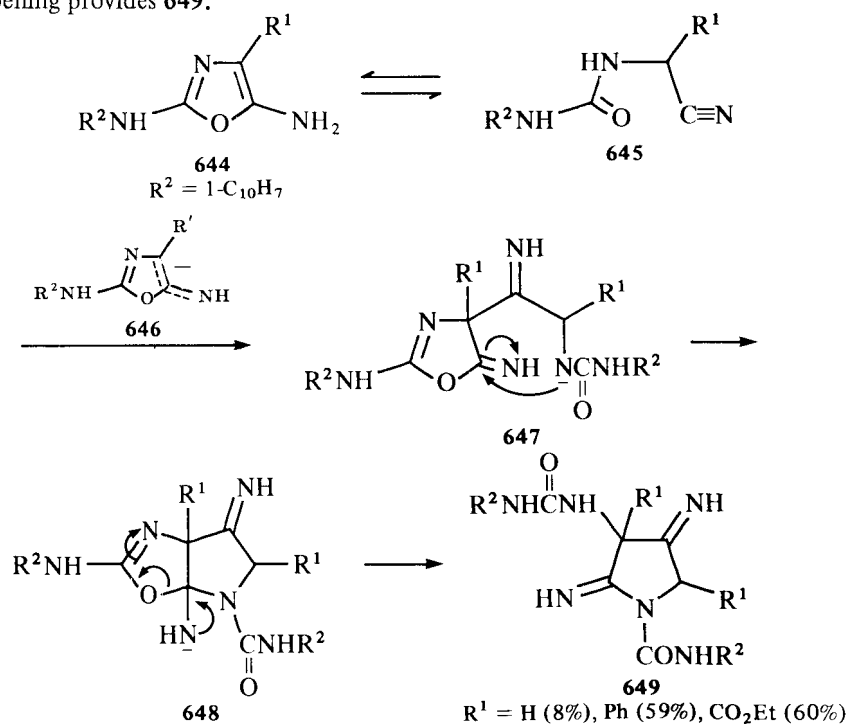


than pyridines as the major products may be a function of the method used for the decomposition of the cycloadducts in some cases. Murakami et al. obtained the 3-hydroxypyridine **642** in 50% yield along with the 2-acetylpyrrole **643** in 5% yield when the adduct **641** derived from 4-methyl-5-ethoxycarbonyloxyoxazole (**640**) and diethyl fumarate is treated with anhydrous hydrogen chloride in ethanol.

When **641** is allowed to react with aqueous HCl, only a trace of the pyridine **642** is isolated. In this case the major product, the pyrrole, **643** is obtained in 54% yield.³⁹¹ In contrast the nitropyrroles **639** were formed from **637** both under aqueous or anhydrous acidic conditions.^{389,390}

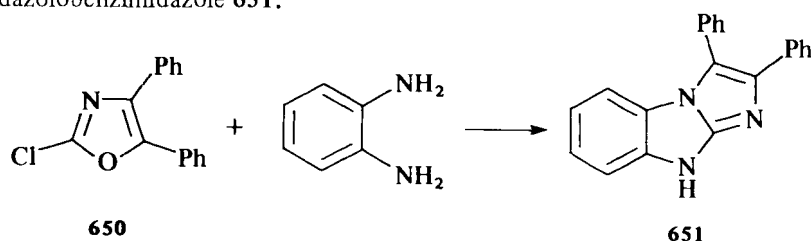


The 2,5-diaminooxazoles **644** are transformed into the 2,4-diiminopyrrolidines **649** when treated with aqueous sodium hydroxide.³³⁸ A plausible mechanistic pathway rationalizing the formation of **649** involves attack of the anion **646** on the chain tautomer of **644**, the cyanoalkyl urea **645**, leading to the intermediate **647**. Cyclization of **647** to the pyrrolidinooxazoline **648** followed by oxazoline ring opening provides **649**.

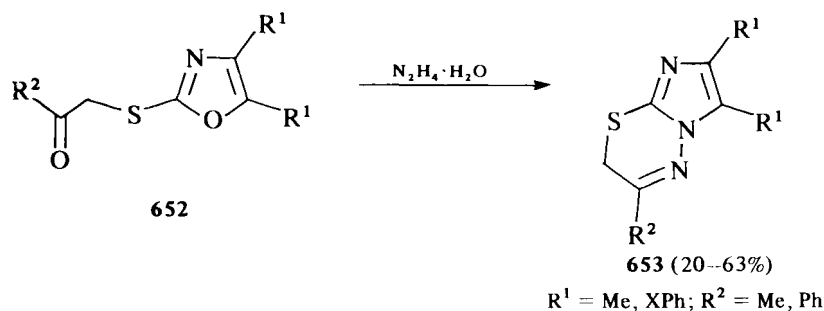


1.6.4. Imidazoles and Thiazoles

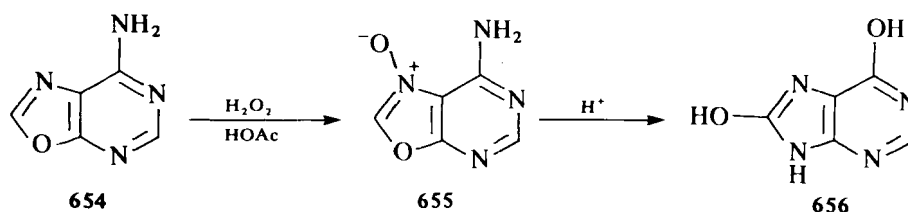
The conversion of oxazoles to imidazoles with ammonia, amines, or formamide has been discussed in previous reviews.^{5,6} Imidazoles fused to other heterocyclic system are accessible by intramolecular variants of this process. Gompper and Effenberger reported the first example of this in the reaction of 2-chloro-4,5-diphenyloxazole (**650**) with *o*-phenylenediamine.¹²⁸ The product isolated is the imidazolobenzimidazole **651**.



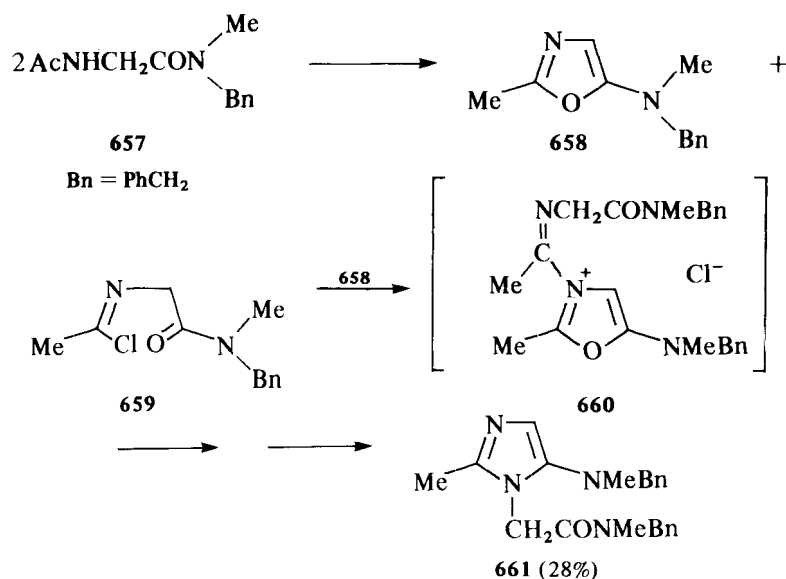
When treated with hydrazine, the 2-acylmethylthioxazoles **652** produce the 2*H*-imidazo[2,1-*b*](1,3,4)thiadiazines **653** in moderate yields.³⁹²



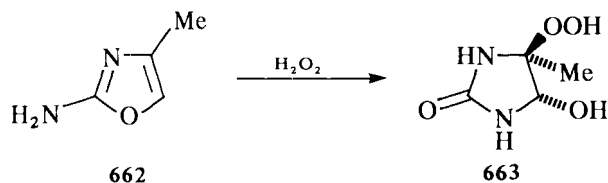
Ohtsuka has published his results on the conversion of oxazolopyrimidines to xanthines and hypoxanthines with amines or formamide.^{393,394} Upon treatment of 7-aminooxazo[5,4-*d*]pyrimidine (**654**) with hydrogen peroxide in acetic acid, 6,8-dihydroxypurine (**656**) is obtained in 48% yield.³⁹⁵ The proposed intermediate, the oxazole *N*-oxide **655**, is believed to undergo a ring transformation under the acidic reaction conditions, giving rise to the observed product **656**. This mechanistic scheme seems unlikely since monocyclic oxazoles are not oxidized to the *N*-oxides under these conditions. A more plausible mechanism is the acid-induced ring opening of **654** followed by oxidation of the intermediate monocyclic pyrimidine thus formed and ring closure to give the purine **656**.



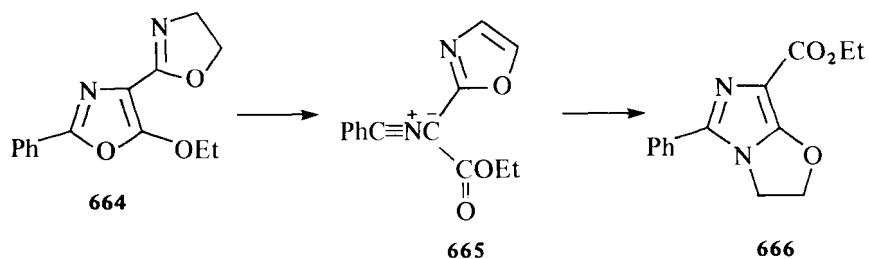
When the 2-acylamino amide **657** is allowed to react with phosphoryl chloride for 16 h at room temperature, the 5-aminoimidazole **661** is formed.²⁹⁹ A mechanism rationalizing the formation of the imidazole **661** involves *N*-acylation of the oxazole **658** by the imidoyl chloride **659** to give the oxazolium salt **660** which undergoes ring opening and ring closure. When the reaction was quenched after 4 hr, the isolation of the 5-aminooxazole **658** in 20% yield was possible.



An unusual transformation of 2-amino-4-methyloxazole (**662**) to 4-methyl-4-hydroperoxy-5-hydroxyimidazolidin-2-one (**663**) occurs when **662** is combined with aqueous hydrogen peroxide.³⁹⁶

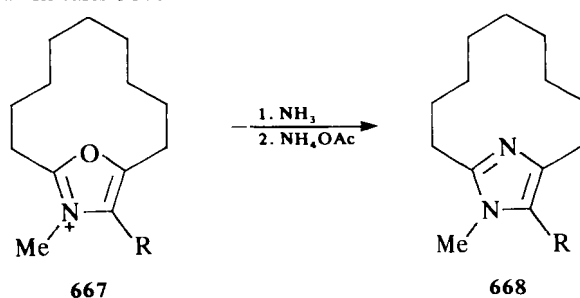


The Cornforth rearrangement (Section 1.3.8) of the oxazolyloxazoline **664** furnishes the imidazolooxazolidine **666** in 95% yield via the iminotrile ylide **665**.²⁴⁷

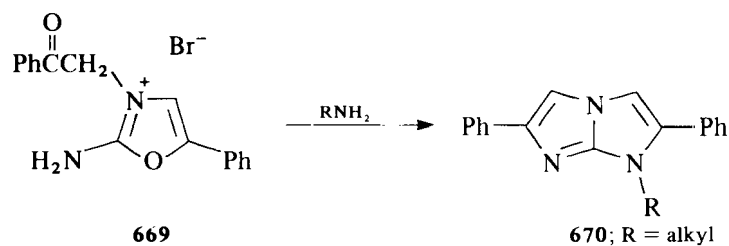


Oxazolium salts have been converted to imidazoles and imidazolium salts with amines under much milder conditions than oxazoles.^{397,398} An intriguing appli-

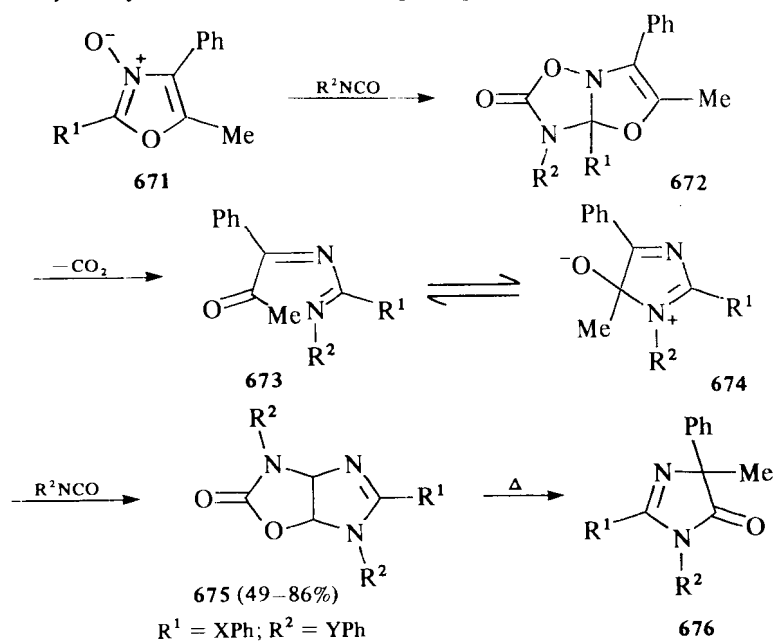
cation of this transformation involves the synthesis of the imidazolophanes **668** from the oxazolium salts **667**.⁸⁴



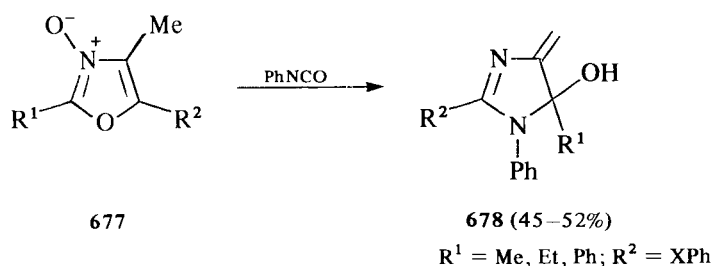
A synthesis of the imidazoloimidazoles **670** from the reaction of 2-amino-5-phenyl-3-phenacyloxazolium bromide (**669**) with primary amines has been reported.³⁹⁹



Goto et al. reported an unusual transformation of oxazole *N*-oxides to imidazole derivatives when the oxazoles are allowed to react with aryl isocyanates.⁴⁰⁰ Thus when the 4-phenyl-5-methyloxazole *N*-oxides **671** are combined with two equivalents of aryl isocyanates, the imidazolino[4,5-*d*]oxazolid-2-ones **675** are produced.

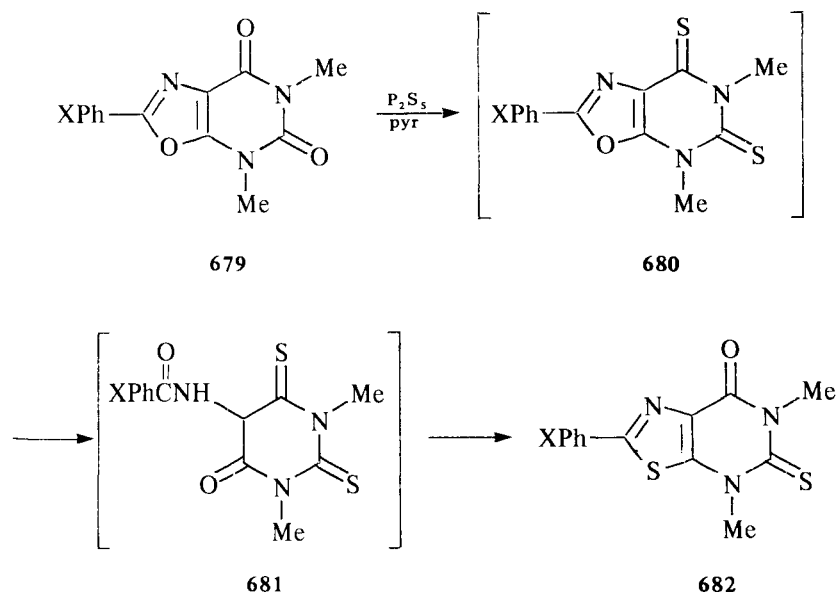


The 1,3-dipolar addition of the isocyanates to the *N*-oxides **671** gives the unstable adducts **672**, which suffer elimination of carbon dioxide leading to the acyclic species **673** which undergoes a subsequent cyclization to the zwitterionic intermediate **674**. Addition of a second molecule of isocyanate to **674** furnishes the observed product **675**. Thermolysis of **675** results in elimination of the aryl isocyanate and methyl group migration leading to the imidazolin-5-ones **676**. The 4-Methyloxazole *N*-oxides **677** suffer a different fate when treated with phenyl isocyanate. In this case the 4-methylene-5-hydroxyimidazolines **678** arise.⁴⁰¹

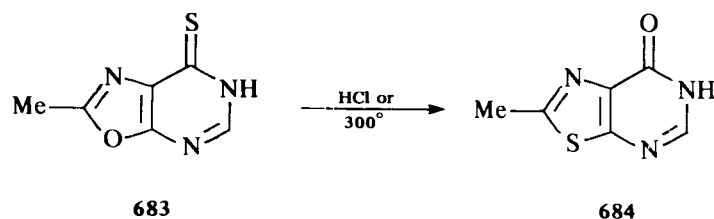


The analogous conversion of oxazoles to thiazoles has received relatively little attention. The first example of such a conversion is the formation of 2-methyl-5-phenylthiazole (85%) from 2-methyl-5-phenyloxazole and phosphorus pentasulfide.⁴⁰² Alkyl oxazoles are converted into alkyl thiazoles in 10–13% yields by passage of the oxazole over hot alumina in a current of hydrogen sulfide.⁴⁰³

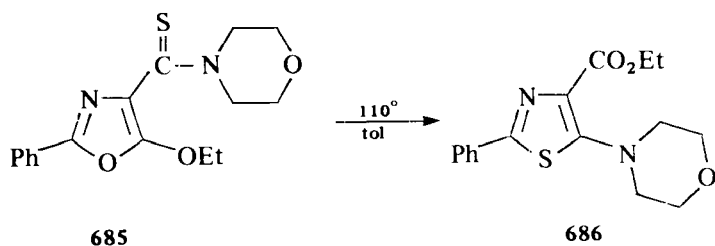
Heating the oxazolopyrimidine diones **679** with phosphorus pentasulfide in pyridine gives the thiazolopyrimidines **682** in 71–98% yields.⁴⁰⁴ Conversion of the pyrimidine diones **679** to the dithiones **680** followed by oxazole ring opening and subsequent ring closure of the resulting intermediates **681** gives **682**.



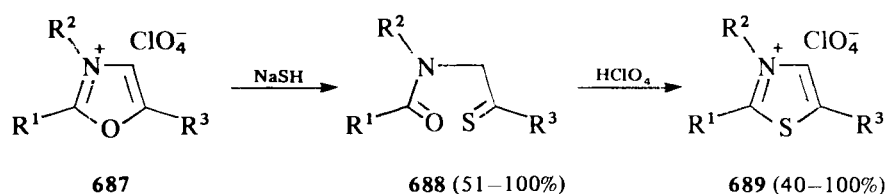
A related transformation involves the rearrangement of 2-methyloxazolo[5,4-*d*]-pyrimid-7-thione (**683**) to 2-methylthiazolo[5,4-*d*]pyrimid-7-one (**684**) by treatment of **683** with hydrochloric acid or by thermolysis of **683**.⁴⁰⁵



The Cornforth rearrangement of the oxazole-4-thioamide **685** affords ethyl 2-phenyl-5-morpholinothiazole-4-carboxylate **686** in good yield.²⁴⁸

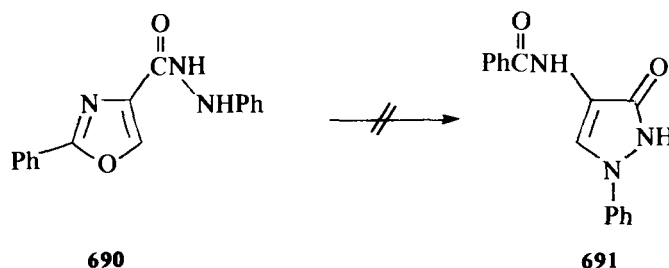


Sodium hydrosulfide effects the conversion of the oxazolium salts **687** to the acylaminothioketones **688**. Treatment of these species with perchloric acid gives the thiazolium salts **689**.⁴⁰⁶

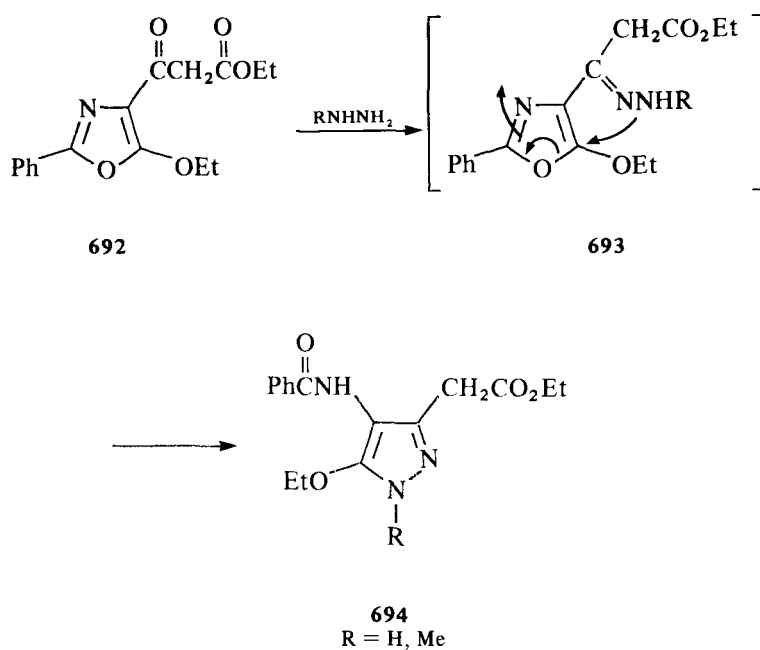


1.6.5. Pyrazoles and Isoxazoles

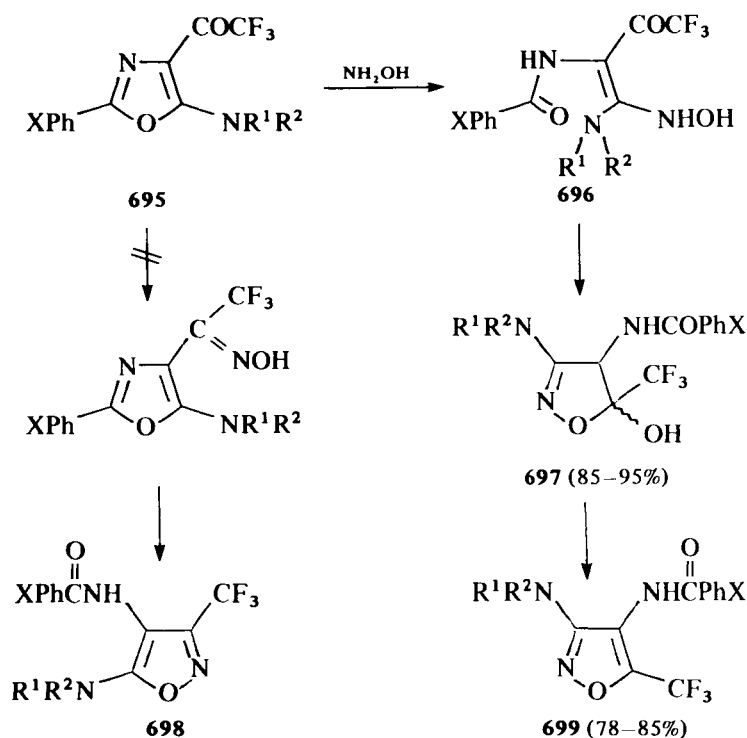
The ring opening of a heterocyclic ring by a nucleophile attached to a side chain to form a new heterocyclic ring with destruction of the original heterocycle was recognized as a general type of ring transformation by Katritzky et al.⁴⁰⁷ This is a seldom-observed process in oxazole chemistry. Attempts to apply this rearrangement to the conversion of 2-phenyl-4-phenylcarbazyloxazole (**690**) to 1-phenyl-4-benzoylamino-pyrazol-3-one (**691**) under a variety of conditions failed to give the desired product.¹⁹²



A 5-ethoxy substituent on the oxazole ring appears to promote this process, however. The unique oxazole to pyrazole rearrangement occurs when ethyl 4-(2-phenyl-5-ethoxyoxazolyl)acetoacetate (**692**) is heated under reflux with hydrazines in ethanol.⁴⁰⁸ The products, the 3-carboethoxymethyl-4-benzoylamino-5-ethoxy-pyrazoles **694** are formed in 60–65% yields possibly via the hydrazones **693**.

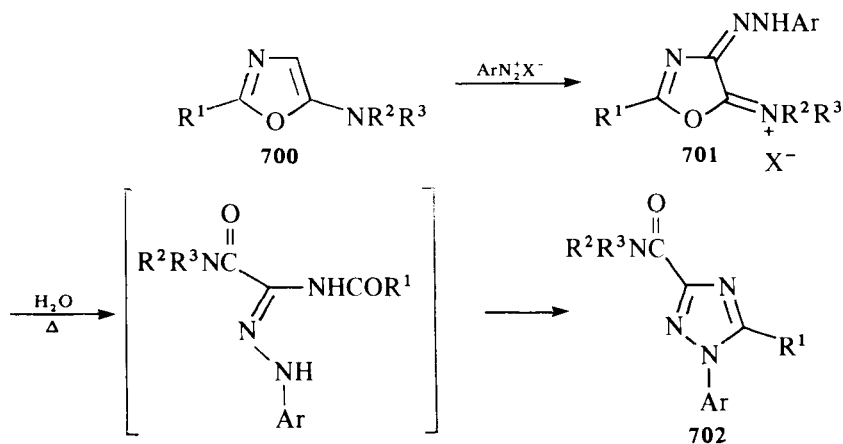


The only example of an oxazole to isoxazole rearrangement was reported by Fleury et al.⁴⁰⁹ Hydroxylamine effects the ring opening of 4-trifluoroacetyl-5-*t*-aminooxazoles **695** by nucleophilic attack at the 5-position to give the acyclic species **696**. These intermediates recyclize under the reaction conditions to furnish the 3-amino-4-arylamino-5-hydroxy-5-trifluoroacetyl-3-isoxazolines **697** in good yields. The isoxazoles **698**, which could be obtained via a rearrangement of the Katrizky type, were not isolated. Treatment of **697** with acetic anhydride causes elimination of trifluoroacetic acid to furnish the isoxazoles **699**.

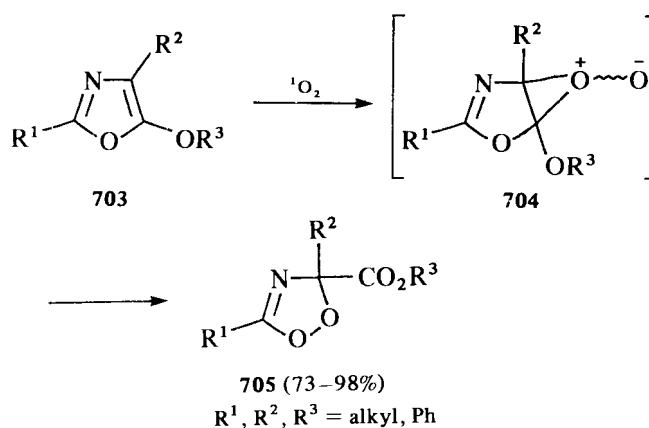


1.6.6. Triazoles and Dioxazoles

When 4-unsubstituted 5-(*N,N*-dialkylamino)oxazoles **700** are allowed to react with aryl diazonium salts, electrophilic substitution occurs at the 4-position of the oxazole ring to produce the salts **701** (Section 1.3.8).³³⁶ The 1-aryl-1,2,4-triazole-3-carboxamides **702** are isolated when the salts **701** are heated in water. These products are formed via a ring opening–recyclization sequence:

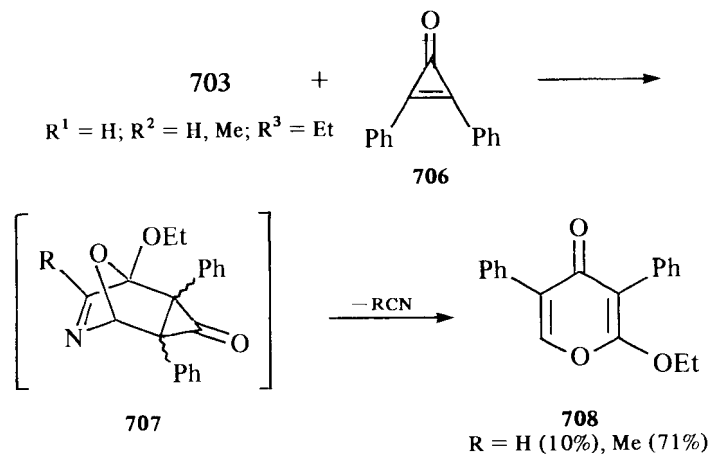


The 1,2,4-dioxazoles are novel heterocyclic systems formed upon reaction of 5-alkoxyoxazoles with singlet oxygen.⁴¹⁰⁻⁴¹² As described above (Section 1.5) singlet oxygen yields open-chain products with alkyl- or aryloxazoles via a 1,4-addition. With 5-alkoxyoxazoles **703**, however, it is thought that the major reaction pathway is 1,2-addition of singlet oxygen to the 4,5-position of the oxazole ring leading to the peroxirane intermediates **704**. Collapse of **704** produces the dioxazoles **705**. Addition of 0.1 molar equivalent of 1,4-diazabicyclo[2.2.2]octane to the reaction mixture completely inhibits the 1,4-addition of singlet oxygen to the 5-alkoxyoxazoles **703** and increases the yields of dioxazoles **705** markedly.⁴¹²

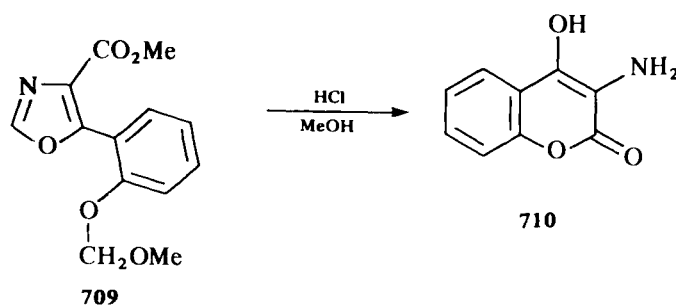


1.6.7. Pyrones and Coumarins

The strained, cyclic dienophile, diphenylcyclopropenone (**706**) undergoes a 1,4-cycloaddition to 5-ethoxyoxazoles **703** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H, Me}$, $\text{R}^3 = \text{Et}$) to give 2-ethoxy-3,5-diphenyl-4-pyrone (**708**) after elimination of R^2CN from the adducts **707**.⁴¹³



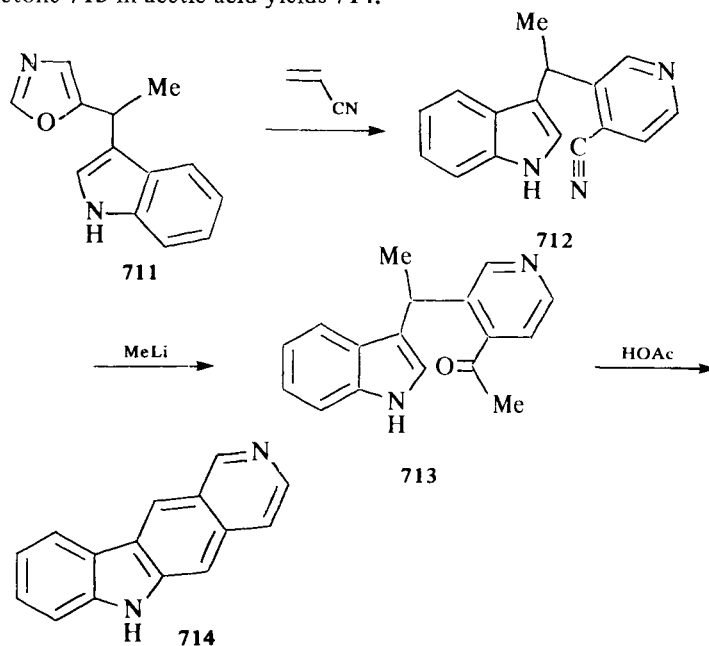
The oxazole-4-carboxylic ester **709** has been converted to the 3-amino-4-hydroxycoumarin **710** in 81% yield by treatment with acid.¹⁷¹



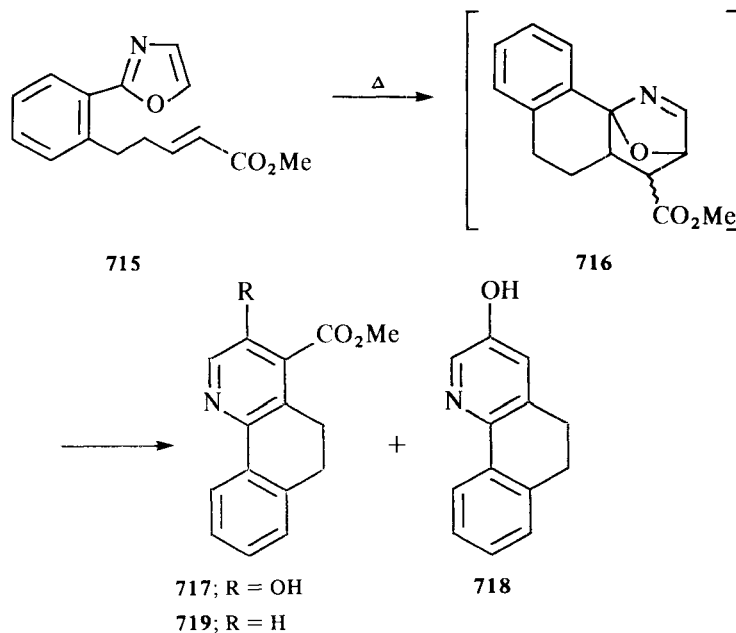
1.6.8. Pyridines and Isoquinolines.

One of the most important methods for the construction of the pyridine nucleus is the Diels–Alder reaction of oxazoles with olefinic dienophiles. Because of the length of this topic, the reader is referred to previous reviews.^{5,6,414}

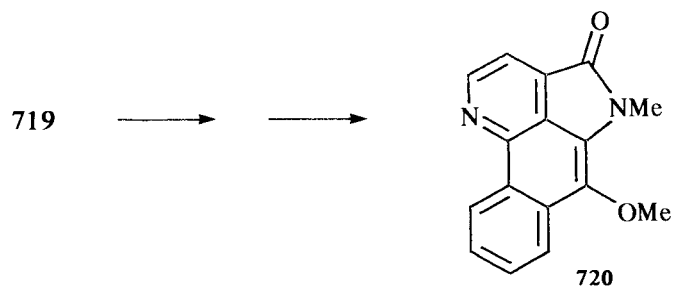
Alkyl- and arylpyridines are obtained from the reaction of alkyl- and aryloxazoles with olefins.^{5,6,414} This procedure has found utility in the total synthesis of two alkaloids. The first, ellipticine **714** was prepared in four steps from the oxazole **711**.⁴¹⁵ Diels–Alder reaction of **711** with acrylonitrile affords the 4-cyanopyridine **712**. Treatment of **712** with methyllithium followed by cyclization of the resulting methylketone **713** in acetic acid yields **714**.



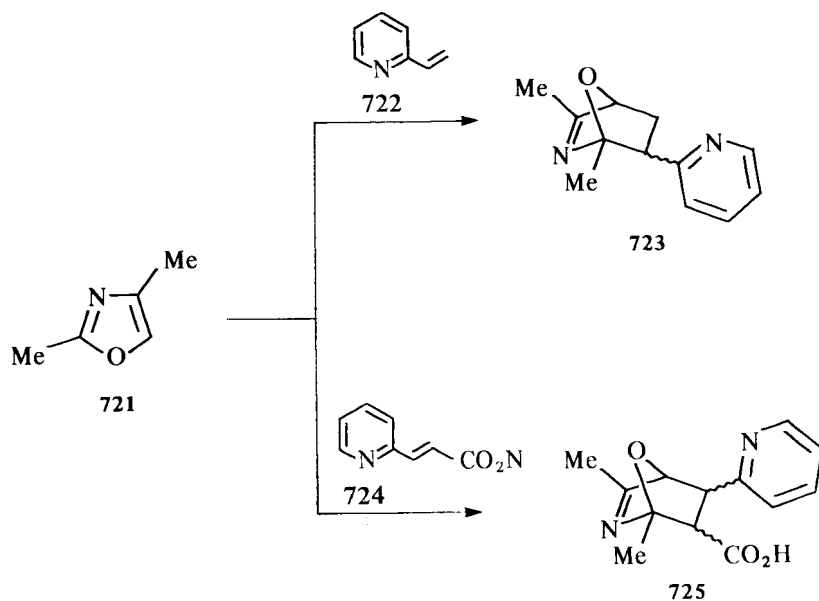
The key step in a total synthesis of eupolauramine (**720**), an azaphenanthrene alkaloid produced in *Eupomatia laurina*, involves the first reported example of an intramolecular Diels–Alder reaction of an oxazole with an olefinic dienophile.⁴¹⁶ Thus, when the oxazole **715** is heated under reflux in *o*-dichlorobenzene, the two pyridine derivatives **717** and **718** are obtained as a 1:1.7 mixture. It was suggested that the initial adduct **716** undergoes oxidative fragmentation to give **717** and **718**. Neither of these intermediates is useful in the eupolauramine synthesis, however. Addition of 0.75 molar equivalents of 1,5-diazabicyclo[3.4.0]nonene-5 gives only the desired pyridine **719** in 76% yield, which was converted in a series of steps to the natural product **720**. Several features of this reaction are noteworthy. While



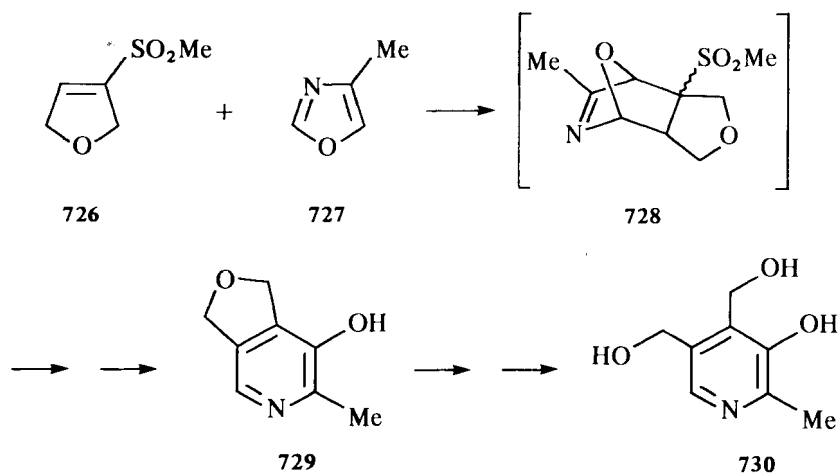
the presence of DBN in the reaction mixture promotes the elimination of water from the adduct **716**, it significantly retards the cycloaddition process. Second, it is the first example of a Diels–Alder reaction between an olefin and a 2-aryloxazole. Finally, the oxidative cleavage of adducts of the type **716** to give 3-hydroxy-pyridines is unusual although preceded.⁴¹⁴



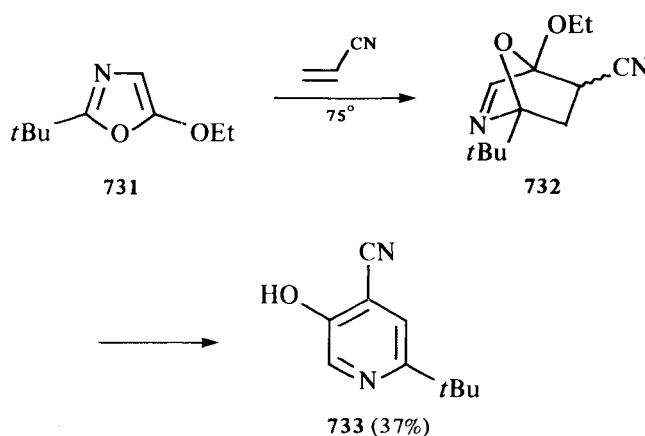
Recently, a study of the regiochemistry of the addition of 2,4-dimethyloxazole (721) to vinylpyridines was reported.⁴¹⁷ 2-Vinylpyridine (722) provides the adduct 723 with 721. Alternatively, when 721 is combined with acrylic acid 724, the adduct 725 is isolated. A rationalization of these results was derived from frontier orbital theory and product stabilization energies. The adducts 723 and 725 were converted to the corresponding 2,3'-bipyridyl and the 2,4'-bipyridyl, respectively.



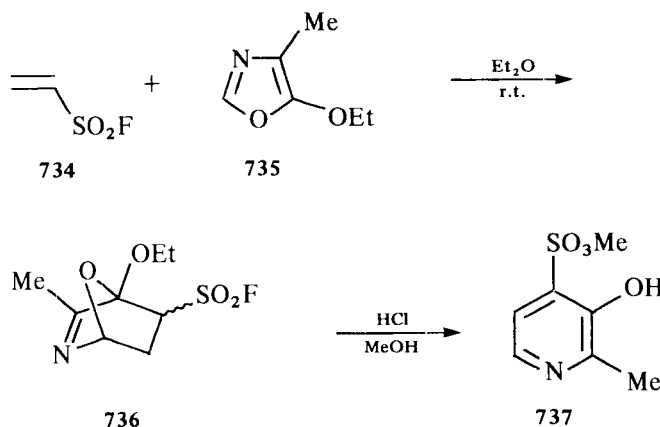
3-Methylsulfonyl-2,5-dihydrofuran (726) serves as a reactive dienophile with 4-methyloxazole (727) to provide the furopyridine 729 via the adduct 728.⁴¹⁸ The presence of the methylsulfonyl moiety on the adduct 728 allows the formation of the 3-hydroxypyridine via elimination of methanesulfinic acid. The 3-hydroxypyridine 729 was converted in several steps to pyridoxine (730).



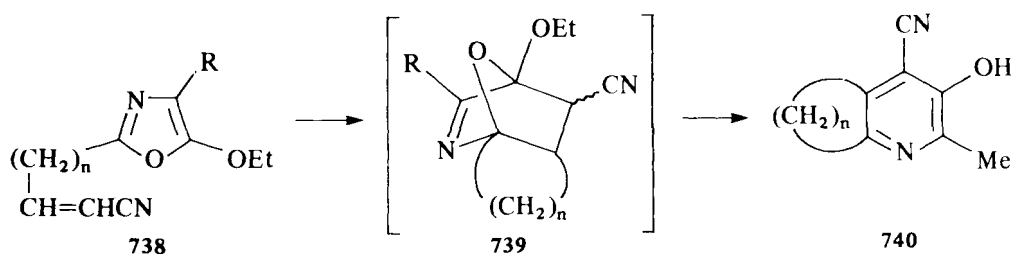
5-Ethoxyoxazoles are unusually reactive azadienes in the Diels–Alder reaction with olefins. In general these oxazoles lead to 3-hydroxypyridines in fair to good overall yields. Several syntheses of pyridoxine take advantage of this reactivity.^{5,6,414} With terminal olefins bearing electron-withdrawing substituents, 4-substituted 3-hydroxypyridines arise.^{5,6} For example, 2-*t*-butyl-5-ethoxyoxazole (**731**) gives 2-*t*-butyl-4-cyano-5-hydroxypyridine (**733**) via the adduct **732** when allowed to react with acrylonitrile.⁴¹⁹ The product of this reaction was converted to 2-*t*-butyl-4-aminomethyl-5-hydroxy-6-iodopyridine, which exhibits diuretic and saluretic activity in rats.



Ethenesulfonyl fluoride (**734**) reacts with 4-methyl-5-ethoxyoxazole (**735**) to give the adduct **736**. Treatment of **736** with methanolic hydrogen chloride furnishes methyl-3-hydroxy-4-pyridinesulfonate (**737**).²⁴⁸



The intramolecular Diels–Alder reaction of the 5-ethoxyoxazoles **738** provides the 3-hydroxy-4-cyano-5,6-cycloalkapyridines **740** without isolation of the intermediate adducts **739**.⁴⁰⁸

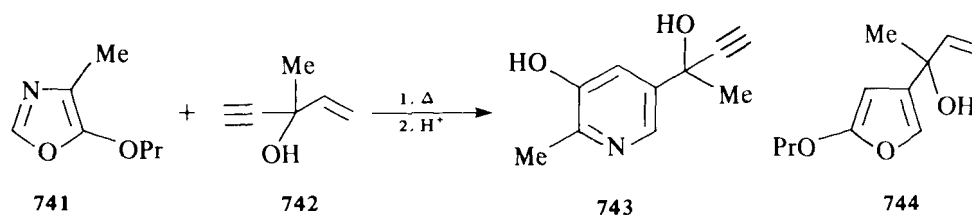


R	<i>n</i>	Yield (%)	Time (hr)	Temperature (°C)
H	3	0	—	—
Me	3	53	48	110
H	4	32	8	83
Me	4	75	96	25
<i>i</i> Pr	4	80	96	25
Ph	4	0	—	—
Me	5	19	336	110
Me	9	0	—	—

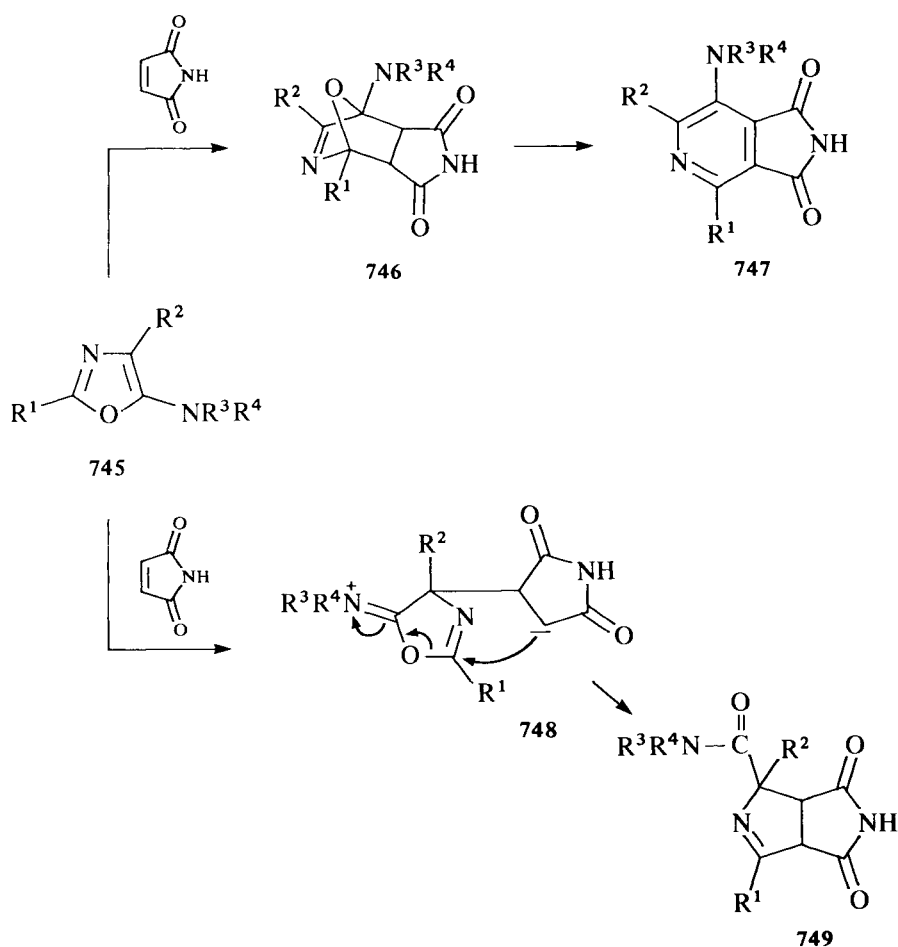
The relative rates and product yields are dependent on the alkyl chain length, *n*, and the nature of the substituent, R, as shown.

Terminal olefins possessing electron-releasing substituents take the opposite regiochemical course. Thus, the major products formed when 4-methyl-5-ethoxyoxazole is allowed to react with allyl alkyl ethers are 3-hydroxy-5-alkoxymethylpyridines.⁴²⁰ The regioisomeric 4-alkoxymethylpyridines are also produced in this reaction as minor components.

A study of the site selectivity of the Diels–Alder reaction of 4-methyl-5-propoxyoxazole (**741**) with the enyne **742** reveals the preference for the cycloaddition to occur only at the carbon–carbon double bond to afford the 3-hydroxy-5-propargylpyridine **743** to the exclusion of the furan **744**.^{421,422} The latter would arise via addition of the oxazole **741** to the triple bond of **742**, followed by elimination of acetonitrile from the resulting adduct. In contrast, replacement of the terminal acetylenic hydrogen of **742** with a phosphinic ester functionality leads to cycloaddition at the carbon–carbon triple bond to give the corresponding furan.



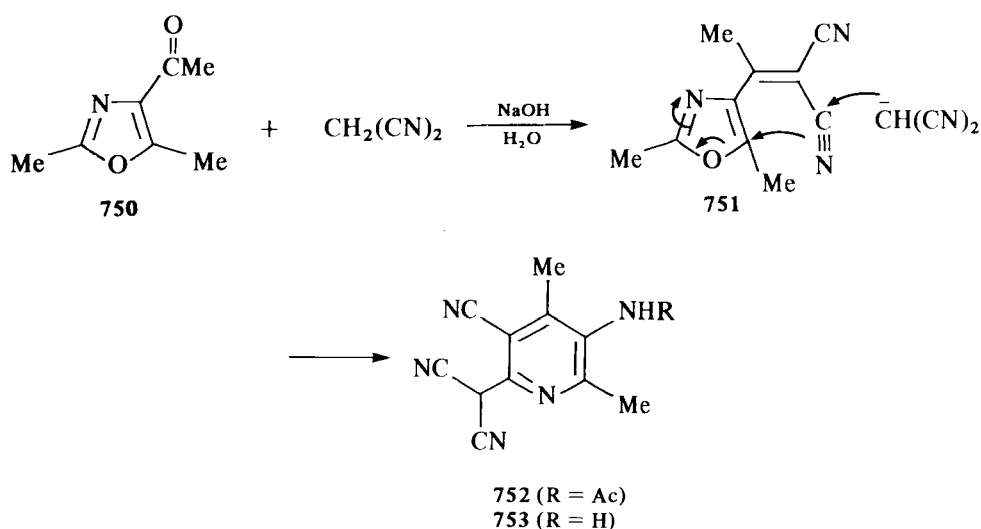
Kondrat'eva et al. investigated the reaction of the 5-(*N,N*-dialkyl)-, 5-(*N,N*-diaryl)-, and 5-(*N,N*-aralkylamino)oxazoles **745** with maleimide.⁴²³ The products isolated are the 3-aminopyridines **747**, the pyrrolines **749**, and in some cases the adducts **746**. No 3-hydroxypyridines were obtained. The 1-pyrrolines **749** may be formed by collapse of the Michael adduct **748**. Oxazoles **745**, $R^2 = H$, give predominately if not exclusively the 1-pyrrolines **749** while the pyridines **747** are the major products when the oxazoles **745**, $R^1, R^2 = \text{alkyl}$, $R^3 = \text{Me}$, $R^4 = \text{Ph}$, are treated with maleimide. The 5-diphenylaminooxazoles **745**, $R^3 = R^4 = \text{Ph}$, provide



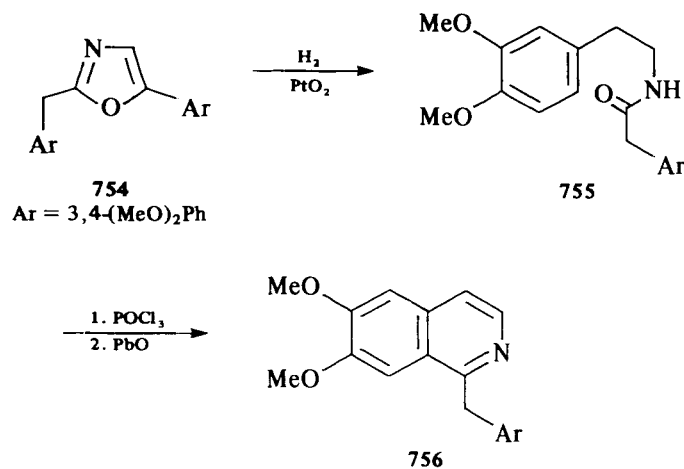
only the pyridines **747** presumably because of the decreased nucleophilicity of the oxazole in these compounds. When these reactions are carried out in acetic acid, protonation of the 5-amino substituent occurs, resulting in the formation of the Diels–Alder products exclusively.

A second type of oxazole to pyridine interconversion involves the reaction of 2,5-dimethyl-4-acetyloxazole (**750**) with two equivalents of malonitrile in the

presence of aqueous sodium hydroxide.⁴²⁴ The product of this reaction, 2,4-dimethyl-3-amino-5-cyano-6-(dicyanomethyl)pyridine (**753**), is presumably derived by attack of malononitrile anion on the intermediate dicyanovinylloxazole **751** followed by hydrolysis of the pyridine acetamide **752**. This transformation is the first reported example of a rearrangement of an oxazole which appears to follow the Katritzky scheme. The intermediate **751** can be isolated when **750** is combined with one equivalent of malononitrile in refluxing benzene in the presence of potassium acetate.

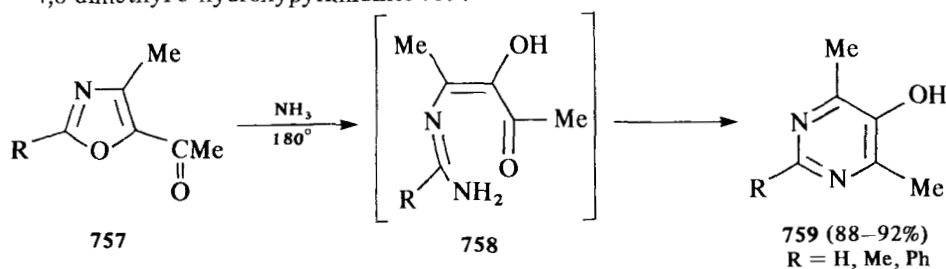


A key step in the synthesis of papaverine (**756**) is the reductive ring opening of the oxazole **754** with hydrogen— PtO_2 to yield the amide **755**.⁴²⁵ Cyclization of **755** with phosphoryl chloride followed by lead oxide oxidation of the resulting dihydroisoquinoline gives the natural product **756**.

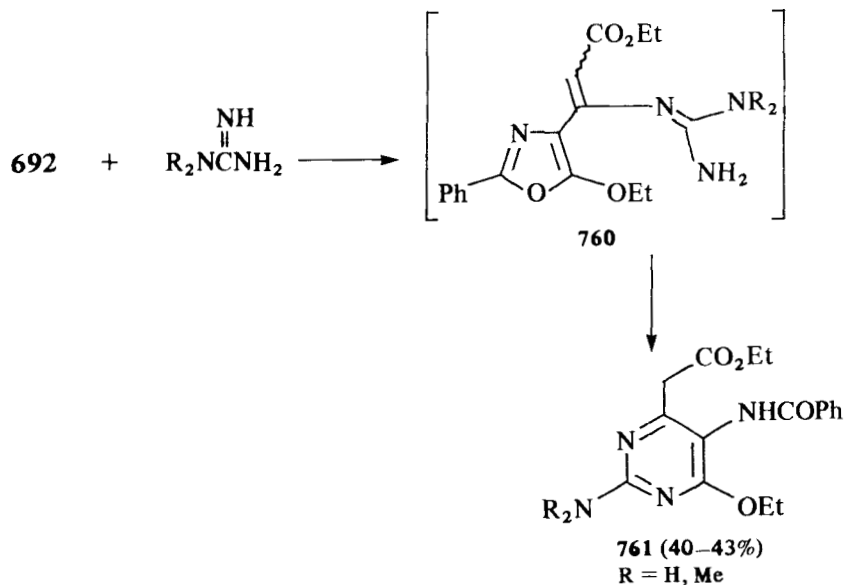


1.6.9. Pyrimidines, Quinazolones, and Oxazinones

As described above, the reaction of oxazoles with ammonia at elevated temperatures provides imidazoles. With the 4-methyl-5-acetyloxazoles **757**, however, the intermediates **758**, derived from **757** and ammonia, undergo cyclization to provide the 4,6-dimethyl-5-hydroxypyrimidines **759**.²⁶²



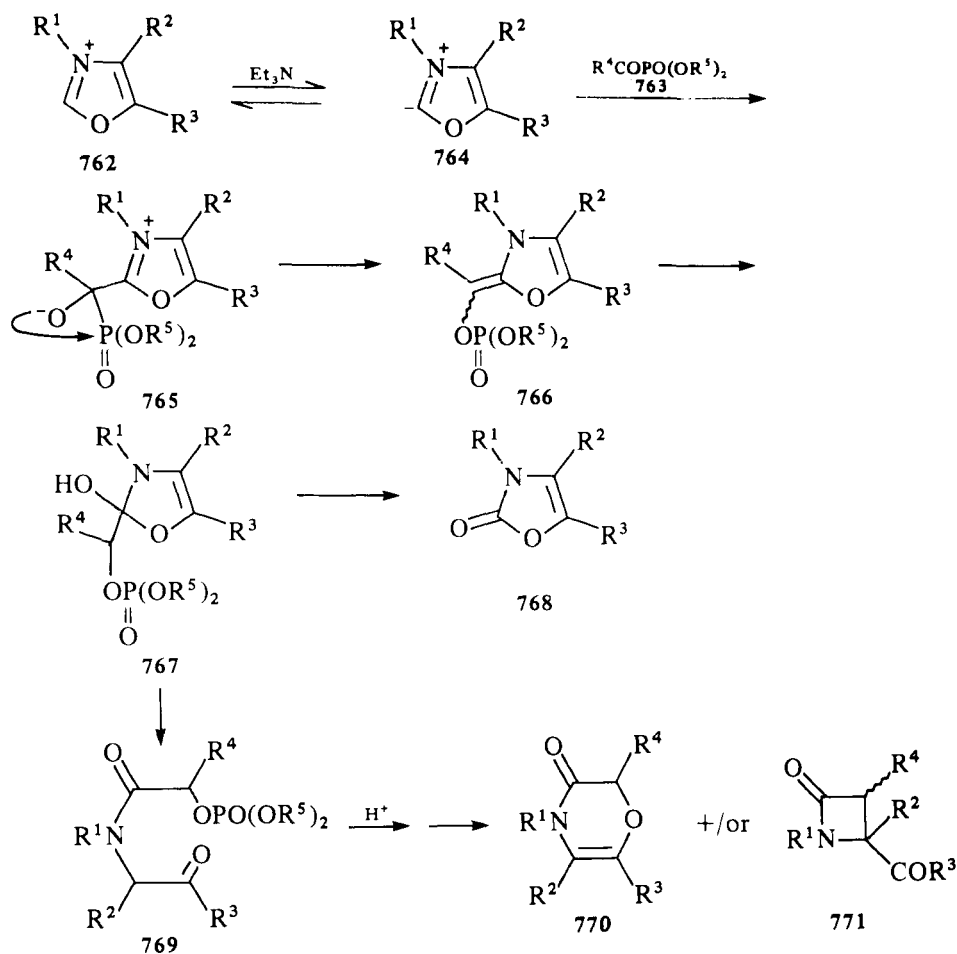
A second example of an oxazole to pyrimidine interconversion results when the keto ester **692** is allowed to react with guanidines.⁴⁰⁸ The 2-aminopyrimidines **761** formed in this process may arise via a Katritzky-type rearrangement of the intermediates **760**.



The photochemically induced rearrangement of the 2-(2-nitrophenyl)-4-bromo-5-aryloxazoles **157** to the 2-arylquinazolin-4-ones **163** is discussed in Section 1.3.1.¹⁴⁵

The reaction of oxazolium salts **762** with dialkyl acylphosphonates **763** in the presence of triethylamine is quite complex. The products obtained in this process are the 1,4-oxazin-3-ones **770** and/or the azetidin-2-ones **771**.³⁵⁰ Deprotonation of the oxazolium salts **762** by the amine produces the ylides **764**. Attack on the ylides **764** by the phosphonates **763** and rearrangement of the resulting zwitterionic

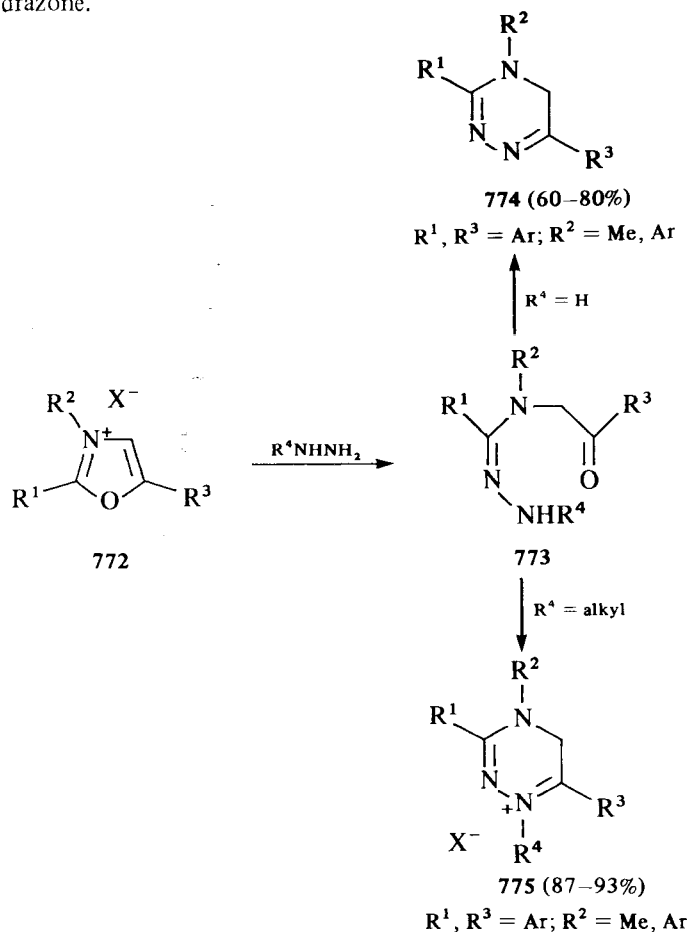
species **765** leads to the formation of the methylenioxazolines **766**. Addition of water to the exocyclic double bond of **766** gives **767**. These intermediates collapse to yield the oxazolones **768** which are formed in trace amounts or to give the acyclic phosphate **769**. Deprotonation of **769** and closure of the resulting enolates give the 1,4-oxazin-3-ones and/or the azetidinones **771**. The relative amounts of **770** and **771** formed along with the stereochemistry of **771** is dependent on the substituents on the oxazolium salts **762** and on R^4 of the phosphonate **763**.



1.6.10. 1,2,4-Triazines

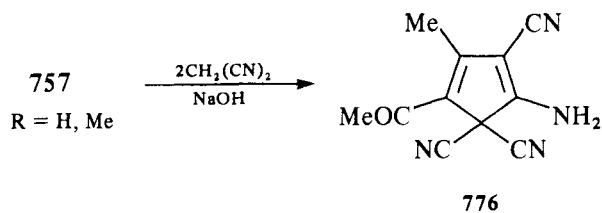
As described above, oxazolium salts may be converted to imidazoles by treatment with ammonia or amines. A related transformation occurs when the oxazolium salts **772** are allowed to react with hydrazine or alkylhydrazines.³⁵⁵ Attack of the hydrazine on the 2-position of **772** followed by ring opening leads to the amino-amidines **773**, which cyclize to furnish the 4,5-dihydro-1,2,4-triazines **774** or the

1-alkyl-4,5-dihydro-1,2,4-triazinium salts **775**. With arylhydrazines the intermediates **773** do not undergo cyclization to the corresponding triazanium salts **775**, $R^4 = \text{aryl}$, but are intercepted by a second equivalent of the hydrazine to afford an acyclic hydrazone.



1.6.11. Cyclopentadienes

The only conversion of an oxazole to a carbocyclic system reported to date involves the reaction of the 5-acetyloxazoles **757** with malonitrile and base.⁴²⁴ This process provides 1,1,4-tricyano-2-acetyl-3-methyl-5-aminocyclopentadiene (**776**) in 60% yield.



1.7. SYSTEMATIC SURVEY OF OXAZOLE DERIVATIVES

1.7.1. Scope of the Survey

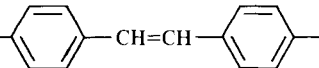
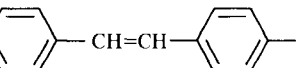
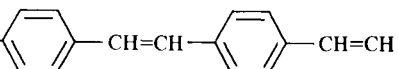
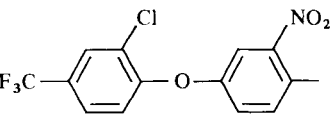
This section contains a tabular survey of oxazole derivatives reported through 1982 (Tables 1.2–1.63). The physicochemical data such as melting point have been omitted as have been yields of products. In most cases, however, the oxazoles are obtained in preparatively useful yields.

Several oxazoles are available from Aldrich Chemical Company. These are oxazole, 4-methyloxazole, 2,4,5-trimethyloxazole, 2,5-diphenyloxazole, 2-(4-biphenyl)-5-phenyloxazole, 2,5-bis(4-biphenyl)oxazole, 2-methyl-4,5-diphenyloxazole, *N'*-(4,5-dimethyloxazol-2-yl)sulfanilamide, 2-(4-pyridyl)-5-phenyloxazole, 1-methyl-4-(5-phenyl-2-oxazolyl)pyridinium 4-toluenesulfonate, 1,4-bis(4-methyl-5-phenyloxazol-2-yl)benzene, 1,4-bis(5-phenyloxazol-2-yl)benzene, and ethyl 4-methyloxazole-5-carboxylate.

1.7.2. Abbreviations

R	Alkyl (unless otherwise stated)
Me	Methyl
Et	Ethyl
Pr	Propyl
Bu	Butyl
Ph	Phenyl
Ar	Aryl
Ac	Acetyl
Mes	Methanesulfonyl
Tos	<i>p</i> -Toluenesulfonyl
THP	Tetrahydropyranyl
Phthl	Phthaloyl
TMS	Trimethylsilyl
PPA	Polyphosphoric acid
DDQ	2,3-Dichloro-5,6-dicyano- <i>p</i> -benzoquinone
LDA	Lithium diisopropylamide
LICA	Lithium isopropyl cyclohexylamide
DABCO	1,4-Diazabicyclo[2.2.2]octane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DIBAH	Diisobutylaluminum hydride
LTA	Lead tetraacetate
TosMIC	<i>p</i> -Toluenesulfonylmethyl isocyanide
PTC	Phase transfer catalysis

TABLE 1.2. ALKYL-, ARYL-, AND ARALKYLOXAZOLES PREPARED BY CYCLO-

R ²	R ⁴
Ph	H
Me	H
Me	XPhCH ₂ (X = H, 2-Cl, 4-Cl)
Me	H
H	H
Me	H
Ph	H
Me	H
Et	<i>i</i> -Bu
Me(CH ₂) ₄	<i>i</i> -Bu
Me(CH ₂) ₁₄	<i>i</i> -Bu
Me(CH ₂) ₁₆	<i>i</i> -Bu
Me	H
Me	H
Me ₂ NCO- 	Me
X- 	H, Alkyl, aryl
(X = H, Me, COR, OMe, NHAc, NHBz)	
X- 	H, Alkyl, aryl
(X = H, Me, COR, OMe, NHAc, NHBz)	
Me	Me
Me	H
Me	Me
	H
Me	Me
Me	<i>i</i> -Bu
Me	Ph
Et	H
Et	Me
Et	Et
Et	<i>n</i> -C ₃ H ₇
Et	<i>n</i> -C ₄ H ₉
Me	H
Me	Me
Me	Et

DEHYDRATION OF 2-ACYLAMINOKETONES (ROBINSON–GABRIEL SYNTHESIS)

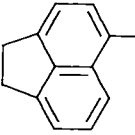
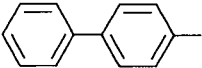
R ⁵	Reagents	Reference
Me	H ₂ SO ₄	263
Ph	H ₂ SO ₄	263
Ph	POCl ₃	116
4-O ₂ NPh	H ₂ SO ₄	7
Ph	PCl ₅	426
Ph	PCl ₅	427
Me	PCl ₅	427
Me	PCl ₅	427
Et	H ₂ SO ₄	428
Me(CH ₂) ₄	H ₂ SO ₄	428
Me(CH ₂) ₁₄	H ₂ SO ₄	428
Me(CH ₂) ₁₆	H ₂ SO ₄	428
4-O ₂ NPh	H ₂ SO ₄ , Ac ₂ O	429
Me	PCl ₅	430
Me	H ₂ SO ₄	431
H, Alkyl, aryl	H ₂ SO ₄	431
H, Alkyl, aryl	H ₂ SO ₄	431
4-O ₂ NPh	HCl/dioxane	432
	—	433
4-Me(CH ₂) ₇ Ph	—	434
Me	—	435
Me	H ₂ SO ₄	436, 437
Ph	H ₂ SO ₄	436, 437
Me	H ₂ SO ₄	436, 437
Et	PPA	438
Et	PPA	438
Et	PPA	438
Et	PPA	438
Et	PPA	438
Et	PPA	438
Me	PPA	439
Me	PPA	439
Me	PPA	439

TABLE 1.2. (Continued)

R ²	R ⁴
Me	<i>n</i> -C ₃ H ₇
Me	<i>n</i> -C ₄ H ₉
Me	Me
Me	Me
Me	Me
Me	<i>i</i> -Bu
Ph	H
XPh	H
(X = 3-CN, 4-Br)	
4Br-PhCH ₂	H
Me	H
4-Me ₂ NPh	H
4-Me ₂ NPh	Me
3,4-DiMeOPhCH ₂	H
4-ClPh(CH ₂) ₂	H
4-ClPhCH=CH—	H
3-Pyridyl	H
3-Pyridyl	H
Me	H
Ph	H
Ph	H
	H
Ph	H
Ph	H
PhCH ₂	H
Ph	H
PhCH ₂	H
2,3,4-TriMePh	H
XPh	H
(X = 2-Cl, 4-MeO)	
Ph	H
2,3,4-TriO ₂ NPh	H
PhCH=CH—	H
1-C ₁₀ H ₇	H
XPh	H
(X = H, Me, C ₁ –C ₆ alkoxy)	
4-XPh	H
(X = H, Me, MeO, Me ₂ N)	
4-Me ₂ NPh	H
1-C ₁₀ H ₇	H

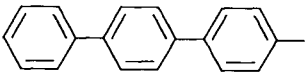
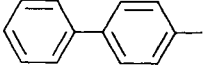
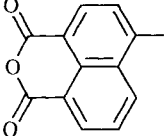
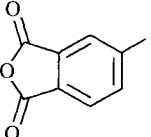
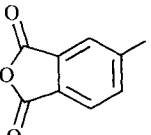
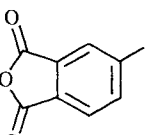
R ⁵	Reagents	Reference
Me	PPA	439
Me	PPA	439
PhCH ₂	COCl ₂ /Et ₃ N	440
Me	COCl ₂ /Et ₃ N	440
Me	H ₂ SO ₄ or PCl ₅	440
Me	H ₂ SO ₄ or PCl ₅	441
3,4-DiMeOPh	—	369
4-BrPh	H ₂ SO ₄ or POCl ₃	119
4-BrPh	H ₂ SO ₄ or POCl ₃	119
4-XPh (X = H, NO ₂)	H ₂ SO ₄	8
4-XPh (X = H, Cl)	H ₂ SO ₄	57
Ph	H ₂ SO ₄	57
4-MeOPh	POCl ₃	110
4-MeOPh	POCl ₃	110
4-MeOPh	POCl ₃	110
4-MeOPh	POCl ₃	110
4-PhCH ₂ OPh	POCl ₃	110
4-XPh (X = H, MeO)	—	58
4-XPh (X = H, Me, Ph)	POCl ₃	442, 443
1-C ₁₀ H ₇	POCl ₃ or H ₂ SO ₄	442, 443, 446
4-XPh (X = H, Me, Ph)	POCl ₃	443
	POCl ₃	444
Ph	H ₂ SO ₄	445
Ph	H ₂ SO ₄	445
3,4-DiMeOPh	H ₂ SO ₄	445
3,4-DiMeOPh	H ₂ SO ₄	445
Ph	H ₂ SO ₄	446
Ph	H ₂ SO ₄	446
4-MeOPh	H ₂ SO ₄	446
Ph	H ₂ SO ₄	446
4-XPh (X = H, MeO)	H ₂ SO ₄	446
Ph	H ₂ SO ₄	446
4-O ₂ NPh	SOCl ₂	447
4-Me ₂ NPh	98% H ₃ PO ₄ /Ac ₂ O	448
Ph	98% H ₃ PO ₄ /Ac ₂ O	448
4-Me ₂ NPh	98% H ₃ PO ₄ /Ac ₂ O	448

TABLE 1.2. (Continued)

R ²	R ⁴
3-Pyridyl	H
Ph	H
Tridecyl	H
Ph	H
Ph	Me
XPh (X = 2-Br, 4-Br, 4-NO ₂ , 3-NO ₂ , 3-I)	H
	H
	H
	H
	H
	H
4-F ₂ CHSO ₂ Ph	H
4-F ₂ CHSO ₂ Ph	H
4-F ₂ CHSO ₂ Ph	H
MeCH=CH—	H
RCH=CH— (R = H, Me)	Me
RCH=CH— (R = H, Me)	<i>i</i> -Bu
RCH=CH— (R = H, Me)	PhCH ₂

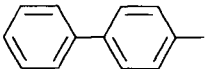
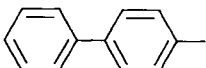
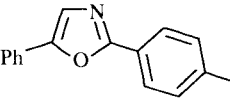
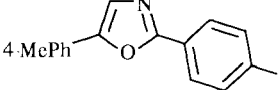
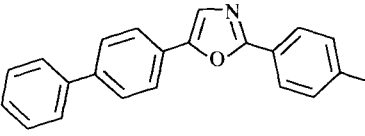
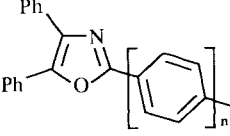
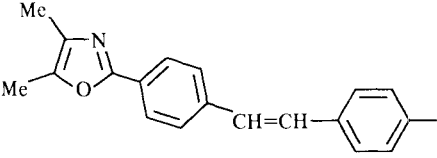
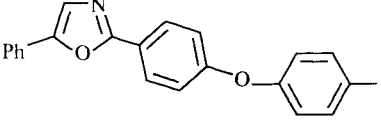
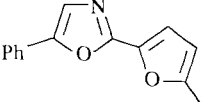
R^5	Reagents	Reference
4-Me ₂ NPh	98% H ₃ PO ₄ /Ac ₂ O	448
	H ₂ SO ₄ or PCl ₅	449
2-C ₁₀ H ₇	H ₂ SO ₄ or PCl ₅	449
2-C ₁₀ H ₇	H ₂ SO ₄ or PCl ₅	449
Ph	H ₂ SO ₄	450, 451
	HF	
Ph	HF	451
	HF	451
4-XPh (X = H, Cl, Br, NO ₂ MeO, Me ₂ N)	POCl ₃	452
4-XPh (X = H, Ph, Cl, NO ₂ , MeO, Me ₂ N)	POCl ₃	453
1- and 2-C ₁₀ H ₇	POCl ₃	453
2,4,5-TriMePh	POCl ₃	453
4-XPh (X = H, Ph, Me, MeO, H ₂ N, Me ₂ N, AcNH, Cl, Br)	—	454
1- and 2-C ₁₀ H ₇	—	454
2,4,5-TriMePh	—	454
Me	PPA	13
Me	PPA	13
Me	PPA	13
Me	PPA	13

TABLE 1.2. (Continued)

R ²	R ⁴
3,4-DiMeOPhCH=CH—	H
3,4-DiMeOPhCH=CH—	H
4-XPhCH=CH— (X = H, Cl, CO ₂ Me)	H
4-XPh (X = H, NO ₂)	Ph
Me	H
4-Pyridyl	H
4-Pyridyl	H
4-Me ₂ NPh	H
Me, Et, PhCH ₂	H
<i>i</i> -Pr, Ph, 4-MeOPh	H
	H
	H
	H
 $n = 0, 1, 2, 3$	Ph
	Me
	H
	H

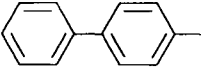
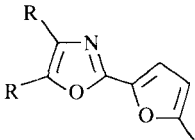
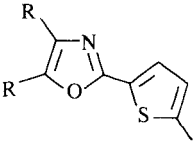
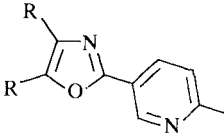
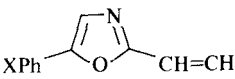
R ⁵	Reagents	Reference
4-MeOPh	POCl ₃	363, 364
3,4-DiMeOPh	POCl ₃	363, 364
Ph	H ₂ SO ₄	455
Ph	H ₂ SO ₄ , PCl ₅ , or PCl ₃	14, 456
4-Pyridyl	H ₃ PO ₄ /Ac ₂ O	120
Me	H ₃ PO ₄ /Ac ₂ O	120
Ph	H ₃ PO ₄	352
4-Me ₂ NPh	POCl ₃	457
3-Indolyl	POCl ₃	159, 371
3-Indolyl	POCl ₃	159
Ph	Bisamide and POCl ₃ or H ₂ SO ₄	443, 457–459
4-McPh	Bisamide	443
	Bisamide	443
Ph	Bisamide and PCl ₅ or POCl ₃	14
Me	Bisamide and H ₂ SO ₄	431
Ph	Bisamide and H ₂ SO ₄	460
Ph	Bisamide and H ₂ SO ₄	461

TABLE 1.2. (Continued)

R ²	R ⁴
	H, Me, Et, Ph
	H, Me, Et, Ph
	H, Me, Et, Ph
	H
PhCHOH	H
4-NCPhOCH ₂	H
Me	CH ₂ OAc
Me	CH ₂ OH
Me	CH ₂ OSO ₃ H
Me	CH ₂ OAc
ClCH ₂	H
XCH ₂ (X = Cl, Br)	Ph
RCHBr (R = H, Me)	H
Cl ₂ CH	H
Cl(CH ₂) ₂	H
Me	CH ₂ Cl
Me	CH ₂ X (X = Cl, Br)
ClCH ₂	ClCH ₂

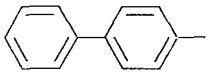
R ⁵	Reagents	Reference
Me, XPh, 1-C ₁₀ H ₇	Bisamide and H ₂ SO ₄	462
Me, XPh, 1-C ₁₀ H ₇	Bisamide and H ₂ SO ₄	462
Me, XPh, 1-C ₁₀ H ₇	Bisamide and H ₂ SO ₄	462
XPh	Bisamide and H ₂ SO ₄	455, 463
4-O ₂ NPh	—	465
4-NCPh	POCl ₃	464
Ph	AcNHCH(CH ₂ OH)COPh/ H ₂ SO ₄ /Ac ₂ O	429
4-O ₂ NPh	H ₂ SO ₄	7
4-O ₂ NPh	AcNHCH(CH ₂ OH)COPhNO ₂ 4/ H ₂ SO ₄ ; then NaHCO ₃	8
4-O ₂ NPh	AcNHCHCOPhNO ₂ 4 CH ₂ OAc	432
4-XPh (X = H, NO ₂)	SOCl ₂ H ₂ SO ₄	8
Ph	POCl ₃	9
Ph	H ₂ SO ₄	131
4-XPh (X = H, NO ₂)	H ₂ SO ₄ or POCl ₃	8
4-XPh (X = H, Cl)	H ₂ SO ₄	466
4-O ₂ NPh	AcNHCHCOPhNO ₂ 4/SOCl ₂ CH ₂ OH	7, 432
4-O ₂ NPh	AcNHCHCOPhNO ₂ 4/POX ₃ CH ₂ OH	8
4-XPh	ClCH ₂ CONHCHCOPhX CH ₂ OH POCl ₃	8

TABLE 1.2. (Continued)

R^2	R^4
$\text{MeO}_2\text{C}(\text{CH}_2)_2$	H
$\text{HO}_2\text{C}(\text{CH}_2)_2$	H
$\text{HO}_2\text{C}(\text{CH}_2)_2$	H
$\text{RO}_2\text{C}(\text{CH}_2)_n$ (R = Me, Et; $n = 0, 1, 2$)	Ph
Ph	$\text{CH}_2\text{CO}_2\text{H}$
Ph	PhCH_2

R ⁵	Reagents	Reference
4-XPh (X = H, Br, Cl)	—	467
4-XPh (X = H, F, Cl, Br, MeO)	H ₂ SO ₄	12
3-HO ₃ S-4-MeOPh	H ₂ SO ₄	12
Ph	—	468
Ph	—	11
(CH ₂) ₂ CO ₂ Me	POCl ₃	10

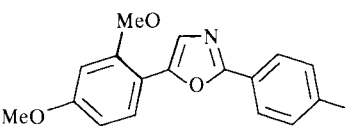
TABLE 1.3. ALKYL-, ARYL-, AND ARALKYLOXAZOLES PREPARED BY MODIFI-

R ²	R ⁴	R ⁵
H	H	Ph, 1-C ₁₀ H ₇ , 
H, Me, Et	H	4-Pyridyl
H, Me, Et	H	Ph
H	H	4-BrPh
Et	H	4-O ₂ NPh
4-HOPh	H	H
3-O ₂ NPh	H	H
2- and 4-O ₂ NPh	H	H
2-, 3-, 4-Pyridyl,	H	H
6-Me-2-Pyridyl,		
2-Quinoliny-		
2-Pyridyl, 2-Quinoliny-	Me	H
3-F ₃ CPhOCH-	H	H
4-ClPh		
2-XPh	Ph	H
(X = H, Cl)		
PhCH ₂	H	Ph
Me	H, Me, <i>i</i> -Pr	Me
	<i>i</i> -Bu, PhCH ₂ ,	
	4-HOPhCH ₂ ,	
Me	(CH ₂) ₂ CO ₂ Me	Me
Me	Ph	Me
4-O ₂ NPh	H	4-MeOPh
4-O ₂ NPh	H	2,4-DiMeOPh
Ph	H	2,4-DiXPh
		(X = MeO, EtO)
Ph	H	4-MeOPh
4-MeOPh	H, Ph	2,4-DiMeOPh
Ph	Me, <i>i</i> -Bu,	2,4-DiMeOPh
	Ph	
Ph	H	2-MeO-4-HOPh
Ph	Me, <i>i</i> -Bu,	2,4-DiMeOPh
	Ph	
Ph	H	2-MeO-4-HOPh
Ph	H	2-MeO, 4-MeO-,
		2,6-DiMeO-1-C ₁₀ H ₇

CATIONS OF THE ROBINSON–GABRIEL SYNTHESIS

Reagents	Reference
$\text{HC(OEt)}_3/\text{R}^5\text{COCH}_2\text{NH}_2$	19
$\text{R}^2\text{C(OEt)}_3/\text{R}^5\text{COCH}_2\text{NH}_2/\text{TsOH}$	20
$\text{R}^2\text{C(OEt)}_3/\text{PhCOCH}_2\text{NH}_2/\text{TsOH}$	20
$\text{HC(OEt)}_3/4\text{BrPhCOCH}_2\text{NH}_2/\text{TsOH}$	20
$\text{EtC(OEt)}_3/4\text{O}_2\text{NPhCH}_2\text{NH}_2/\text{TsOH}$	20
$\text{R}^2\text{CONCH(OR)}_2/\text{H}^+$	16
$\text{R}^2\text{CH}=\text{NCH}_2\text{CH(OMe)}_2/\text{P}_2\text{O}_5/\text{H}_2\text{SO}_4$	114, 469, 470
$\text{R}^2\text{CH}=\text{NCH}_2\text{CH(OMe)}_2/\text{P}_2\text{O}_5/\text{H}_2\text{SO}_4$	469, 470
$\text{R}^2\text{CH}=\text{NCH}_2\text{CH(OMe)}_2/\text{P}_2\text{O}_5/\text{H}_2\text{SO}_4$	471
$\text{R}^2\text{CH}=\text{NCHR}^4\text{CH(OEt)}_2/\text{P}_2\text{O}_5/\text{H}_2\text{SO}_4$	471
$\text{R}^2\text{CONHCH}_2\text{CHCl}_2/\text{NaOEt}/\text{EtOH}$	17
$\text{R}^2\text{CONHCHR}^4\text{CHCl}_2/\text{KOH}/\text{MeOH}$	18
$\begin{array}{c} \text{MeO}_2\text{C} \quad \text{Ph} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{PhCONH} \quad \text{Br} \end{array}$	161
$\text{NaOAc}/\text{HOAc}/170^\circ$	
$\text{R}^4\text{CH(NH}_2\text{)CO}_2\text{H}/\text{Ac}_2\text{O}/\text{NaOAc}/\text{PCl}_5$; then NaOH	21
$\text{MeO}_2\text{C(CH}_2\text{)}_2\text{CHCO}_2\text{H}/\text{Ac}_2\text{O}/\text{NaOAc}/\text{PCl}_5$; NH_2 then NaOH	21
$\text{PhCH(NH}_2\text{)CO}_2\text{H}/\text{Ac}_2\text{O}$	472
$4\text{-O}_2\text{NPhCONHCH}_2\text{CO}_2\text{H}/$ MeOPh/PPA	57
$4\text{-O}_2\text{NPhCONHCH}_2\text{CO}_2\text{H}/$ $1,3\text{-DiMeOPh}/\text{PPA}$	57, 473
$\text{PhCONHCH}_2\text{CO}_2\text{H}/$ $1,3\text{-diXPh}/\text{PPA}$	473
$\text{PhCONHCH}_2\text{CO}_2\text{H}/\text{MeOPh}/\text{PPA}$	473
$\text{R}^2\text{CONHCHR}^4\text{CO}_2\text{H}/$ $1,3\text{-DiMeOPh}/\text{PPA}$	473
$\text{R}^2\text{CONHCHR}^4\text{CO}_2\text{H}/$ $1,3\text{-DiMeOPh}/\text{PPA}$	473
$\text{R}^2\text{CONHCH}_2\text{CO}_2\text{H}/$ $1\text{-HO-3-MeOPh}/\text{PPA}$	473
$\text{R}^2\text{CONHCHR}^4\text{CO}_2\text{H}/$ $1,3\text{-DiMeOPh}/\text{PPA}$	473
$\text{R}^2\text{CONHCH}_2\text{CO}_2\text{H}/$ $1\text{-HO-3-MeOPh}/\text{PPA}$	473
$\text{R}^2\text{CONHCH}_2\text{CO}_2\text{H}/\text{MeO-C}_{10}\text{H}_7/$ PPA	473

TABLE 1.3. (Continued)

R ²	R ⁴	R ⁵
	H	2,4-DiMeOPh
Me	CH ₂ OCOR (R = Me, Et)	4-O ₂ NPh
Me	PhCHOAc 	4-O ₂ NPh
ClCH ₂	Me	4-O ₂ NPh
Cl ₂ CH	Me	4-O ₂ NPh
Cl ₃ C	Me	4-O ₂ NPh

Reagents	Reference
$\text{Ph}(\text{CONHCH}_2\text{CO}_2\text{H})_2 / 1,3\text{-DiMeOPh/PPA}$	473
$\text{AcNH}-\text{C}(\text{CH}_3)=\text{C}(\text{O})-\text{Ph-4-NO}_2 / \text{H}_2\text{SO}_4 / (\text{RCO})_2\text{O}$	7
$\text{AcNH}-\text{C}(\text{CHPh})=\text{C}(\text{O})-\text{Ph-4-NO}_2 / \text{H}_2\text{SO}_4 / \text{Ac}_2\text{O}$	7
$\text{ClCH}_2\text{CONH}-\text{C}(\text{CH}_3)=\text{C}(\text{O})-\text{Ph-4-NO}_2 / \text{POCl}_3$	8
$\text{Cl}_2\text{CHCONH}-\text{C}(\text{CH}_3)=\text{C}(\text{O})-\text{Ph-4-NO}_2 / \text{POCl}_3 \text{ or } \text{H}_2\text{SO}_4$	8
$\text{Cl}_3\text{CCONH}-\text{C}(\text{CH}_3)=\text{C}(\text{O})-\text{Ph-4-NO}_2 / \text{POCl}_3$	8

TABLE 1.4. ARYL- AND ARALKYLOXAZOLES FROM 2-KETONITRONES

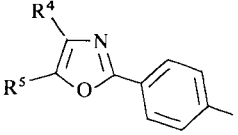
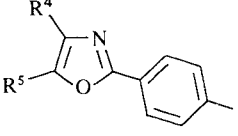
R ²	R ⁴	R ⁵	Reference
Me	Me	Ph	24
Ph	H	Ph	24
Ph	Me	Ph	24
	H	4-XPh (X = H, Me)	24
	Me	Ph	24

TABLE 1.5. ALKYL-, ARYL-, AND ARALKYLOXAZOLES FROM ISONITRILES

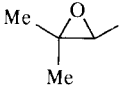
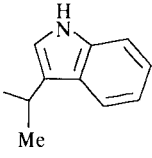
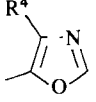
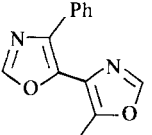
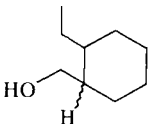
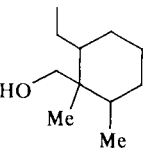
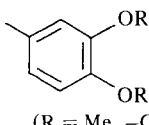
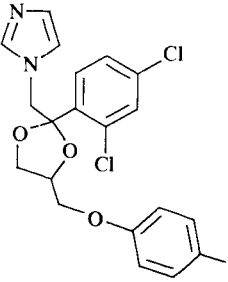
R ²	R ⁴	R ⁵	Method ^a	Reference
H	H	Et, <i>i</i> -Pr, PhCH ₂ , Ph, 4-MePh	A	102
H	Ph	H, <i>i</i> -Pr, Ph	A	102
H	Me ₂ C=CH		A	102
H	H	3-Indolyl	A	29
H	H		A	415
H	H, Ph		A	30
H	Ph		A	30
H	H	CH ₂ CH(CH ₂) ₂ OH Me	A	31

TABLE 1.5. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
H	H		A	31
H	H		A	31
H	H	4-XPh (X = H, Cl, NO ₂)	B	32
H	H	 (R = Me, -CH ₂ -)	B	425
H	H	5-X-2-Furyl (X = H, NO ₂ , CO ₂ Me)	B	33
H	H	5-X-2-Thienyl (X = H, NO ₂)	B	33
H	H	1-Me-2-pyrrolyl	B	33
H	H	2-, 3-, 4-Pyridyl	B	33
H	Me	4-XPh (X = H, Cl)	B	34
H	Me	2-Furyl	B	34
H	Et	4-XPh (X = H, Cl)	B	34
H	PhCH ₂	4-ClPh	B	34
H	PhCH ₂	2-Furyl, 2-thienyl	B	34
H	H		B	16
Me	H	4-XPh (X = H, Cl)	C	35
Ph	H	4-O ₂ NPh	C	35

^aA = R⁴-CHNC + R⁵COXB = TosMIC + R⁵CHO + baseC = TosCH₂N=C(X)R² + R⁵CHO + base

TABLE 1.6. ARYLOXAZOLES FROM ALDEHYDES AND CYANOHYDRINS (FISCHER SYNTHESIS)

R ²	R ⁴	R ⁵	Reference
Ph	H	Ph	36, 474
XPh	H	XPh	475
(X = 4-MeO, 3- and 4-NO ₂)	H	(X = 4-MeO, 3- and 4-NO ₂)	
4-BrPh	H	Ph	38
Ph, 1-C ₁₀ H ₇	H	Ph	457
4-XPh	H	Ph	57
(X = NH ₂ , NEt ₂)			
3-Pyridyl	H	4-HOPh	39

TABLE 1.7. ALKYL- AND ARYLOXAZOLES FROM 2-HYDROXYKETONES AND FORMAMIDE

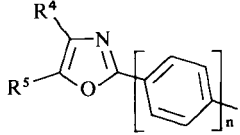
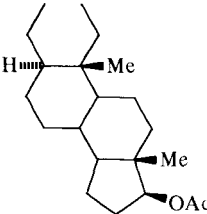
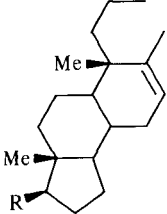
R ²	R ⁴	R ⁵	Reference
H	Me	H	476 ^a
H	Et	Et	43
H	<i>n</i> -Pr	<i>n</i> -Pr	43
H	<i>i</i> -Pr	<i>i</i> -Pr	43
H	<i>i</i> -Bu	<i>i</i> -Bu	43
H	Ph	Ph	43, 477
H	—(CH ₂) ₄ —		43
H	—(CH ₂) ₁₀ —		41
H	1-C ₁₀ H ₇	1-C ₁₀ H ₇	478
H	Me ₂ CCH ₂ -S-CH ₂ CMe ₂		40

^aFrom HC=NH and acetol.
OR

TABLE 1.8. ALKYL-, ARYL-, AND ARALKYLOXAZOLES FROM 2-ACYLOXYKETONES AND AMMONIUM ACETATE

R ²	R ⁴	R ⁵	Reference
XPh (X = H, 2-Cl, 3-NO ₂)	H	H	479 ^a
2-Pyridyl	H	H	479 ^a
H	<i>n</i> -Pr	<i>n</i> -Pr	43
H	<i>n</i> -Bu	<i>n</i> -Bu	43
H	Ph	Ph	43
H	Me	H	480
Et	Et	Et	44 ^b
<i>n</i> -Pr	<i>n</i> -Pr	<i>n</i> -Pr	44 ^b
<i>i</i> -Bu	<i>i</i> -Bu	<i>i</i> -Bu	44 ^b
Me	Ph	Et	44
Me	4-MePh	<i>i</i> -Pr	44
Me	Me, Ph	H	44
<i>n</i> -C ₆ H ₁₃	Me	Me	100
Me	<i>n</i> -C ₆ H ₁₃	Me	100
Me	Me	<i>n</i> -C ₆ H ₁₃	100
<i>n</i> -C ₅ H ₁₁	Ph	Ph	100, 481
Me	4-XPh (X = H, MeO)	Ph	351
Me	2-C ₁₀ H ₇	2-C ₁₀ H ₇	351
Me	2-Furyl	2-Furyl	351
Me	2-Thienyl	2-Thienyl	351
Et, <i>i</i> -Pr, <i>i</i> -Bu, <i>t</i> -Bu, <i>n</i> -C ₆ H ₁₃ , C ₃ H ₅	4-MeOPh	4-MeOPh	482
<i>i</i> -Pr, <i>t</i> -Bu, C ₃ H ₅	4-MeOPh	Ph	482
<i>t</i> -Bu	4-MeOPh	4-MePh	482
<i>t</i> -Bu	4-MeSO ₂ Ph	Ph	482
<i>t</i> -Bu	4-HOPh	Ph	482
<i>t</i> -Bu	4-MeOPh	4-ClPh	482
Me, Et	Et	Et	44
Me	<i>n</i> -Pr	<i>n</i> -Pr	44
Me	<i>i</i> -Pr	<i>i</i> -Pr	44
<i>n</i> -Pr, <i>i</i> -Bu, <i>n</i> -C ₆ H ₁₃	Ph	Ph	44
3,5-DiMeOPhCH ₂	Ph	Ph	105
Me	Ph	4-O ₂ NPh	112
4-O ₂ NPh	Ph	Ph	112
Ph	Ph	Ph	46
X-Ph (X = H, 4-Cl, 4-O ₂ N, 4-Me, 2,4-diCl)	4-MeOPh	Me	483
Ph	4-MeOPh	Ph	483
4-ClPh	4-MeOPh	4-ClPh	483
Ph	Me	Ph	484
6-Quinoliny	Ph	Me	484
2,4,6-TriDPh	Ph	Ph	45

TABLE 1.8. (Continued)

R ²	R ⁴	R ⁵	Reference
 (R = H, alkyl, alkoxy; n = 0, . . . , 4) Ph 4-MePh 4-MeOPh PhCH₂OCNHCH— $\begin{array}{c} \parallel \\ \text{O} \end{array}$ $\begin{array}{c} \\ \text{R} \end{array}$ (R = H, PhCH₂) HO₂C(CH₂)₂ HO₂C(CH₂)₂ HO₂C(CH₂)₂ HO₂C(CH₂)₂ HO₂C(CH₂)₂ HO₂C(CH₂)₂ HO₂C(CH₂)_n (n = 3, 4) HO₂CCH=CH Me	XPh Ph 4-MePh 4-MeOPh Ph Ph H XPh (X = H, Me, CF₃, F, Cl, Br, NO₂, OMe) Ph Ph Ph 2-Furyl 2-Thienyl Ph Ph	YPh Ph 4-MePh 4-MeOPh Ph H, Me Ph YPh (Y = H, Me, F, Cl, Br, NO₂, OMe) 1- and 2-C₁₀H₇ 2-Furyl 2-Thienyl Ph Ph Ph Ph	485 486^c 486^c 486^c 49 47 47 47 47 47 47 47 47 47 47 487 487, 488
Me			
	 (R = COMe, C₈H₁₇, OAc)		

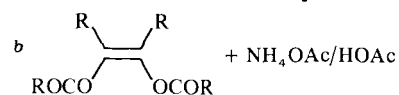
^aVinylene carbonate/R²CONH₂/PPA^cRCOCOR/NH₃/H₂O/120°C

TABLE 1.9. ALKYL-, ARYL-, AND ARALKYLOXAZOLES FROM 2-HALOKETONES AND AMIDES OR AMMONIUM SALTS

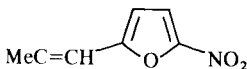
R ²	R ⁴	R ⁵	Reference
H	Me	H	498
H	<i>t</i> -Bu	H	263, 489
H	<i>n</i> -Bu, <i>n</i> -C ₇ H ₁₅	H	490
H	Me	Me	44
H	Me	<i>n</i> -Pr	263, 489, 490
H	Me	<i>i</i> -Pr	489
H	Me	<i>n</i> -Bu, <i>n</i> -C ₆ H ₁₃	489, 490
H	Et	Et	490
H	Pr	Me	490
H	Et	Pr	490
H	Pr	Et	490
H	Bu	Me	490
H	Et	<i>n</i> -Bu, <i>n</i> -C ₅ H ₁₁	490
H	<i>n</i> -C ₅ H ₁₁	Me	490
H	Bu	Pr	490
H	<i>n</i> -C ₆ H ₁₃	Me	490
H	<i>n</i> -Pr	<i>n</i> -Pr	498
H	Me	PhCH ₂	51, 430
H	—————(CH ₂) ₄ —————		491
Me	Me	H	108
Me	<i>t</i> -Bu	H	489
<i>n</i> -Pr, <i>n</i> -C ₅ H ₁₁	Me	H	489
Me		H	492
Me, <i>n</i> -Pr	Me	Me	44
<i>i</i> -Pr	Me	Me	44, 493, 494
<i>n</i> -Pr	<i>n</i> -Pr	Et	44
Me	Me	PhCH ₂	494b
Me	—————(CH ₂) ₄ —————		495
Ph	H	H	496
H	2-Cl-4-O ₂ NPh	H	115
H	Ph	PhCH ₂	51
H	PhCH ₂	Ph	51
H	Ph	Ph	44, 497, 498
H	4-MeOPh	Ph	496
H	Ph	Me	263, 478, 498, 499
H	4-PhCH ₂ OPh	Me	499
H	Ph	H	50, 498, 500, 501
H	4-BrPh	H	498
H	Ph	Et, <i>n</i> -Bu, <i>n</i> -C ₆ H ₁₃ , <i>n</i> -C ₇ H ₁₅ , <i>n</i> -C ₈ H ₁₇	498
Me	Ph	H	58, 263, 478, 500, 501
Me	4-MeOPh	H	58
<i>n</i> -Pr	Ph	H	44
4-McPh	Me	H	147

TABLE 1.9. (Continued)

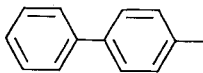
R ²	R ⁴	R ⁵	Reference
3-XPh (X = H, NO ₂)	Me	H	113
Ph	Me	Me	113
Ph	<i>t</i> -Bu	H	497
<i>t</i> -Bu	Ph	H	497
Ph	—————(CH ₂) ₅ —————		41, 113
H	Me, Et, <i>i</i> -Pr	Ph	498
H	Ph	Et, <i>i</i> -Pr	498, 499
H	Ph	<i>n</i> -Pr	430
H	Ph	<i>n</i> -Bu, <i>n</i> -C ₆ H ₁₃	499
Me	XPh (X = 2- and 4-Cl, 4-F, 2-Br, 4-Me, 4-MeO, 4-NO ₂)	H	132
Et	4-ClPh	H	132
Me		H	121
Me	Me	Ph	494b
Me	Ph	Me, Et, <i>i</i> -Bu	44, 494b
Me	Ph	<i>n</i> -Pr	494b
Et	Ph	Me, Et	44
Ph	Ph	H	497, 500, 501
Ph	4-O ₂ NPh	H	57
Ph	4-ClPh	H	132
Ph	4-MeOPh	H	496
4-MeOPh	Ph	H	496
4-BrPh	H	Ph	131
Me	XPh (X = 4-MeO, 2,4-diMeOPh)	Ph	58
Ph	Ph	Ph	497
2- and 3-thienyl	CH ₂ Cl	H	189
2- and 3-selenyl	CH ₂ Cl	H	189
Ph	(CH ₂) ₂ NR ₂ (R = Me, Et)	H	52
Ph	(CH ₂) ₂ NPhthl	H	52
H	Me	CH ₂ OH	53, 54
H, Me, Ph	Me	(CH ₂) ₂ OH	53, 54
XPh (X = H, halogen)	R ₂ CCOR ⁶ (R = H, alkyl; R ⁶ = <i>O</i> -alkyl, <i>O</i> -dialkylaminoalkyl)	H	55

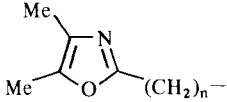
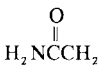
TABLE 1.10. ALKYL-, ARYL-, AND ARALKYLOXAZOLES FROM 2-HYDROXY-KETONES AND NITRILES

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	<i>n</i> -Pr	<i>n</i> -Pr	A	58
H	4-Me ₂ NPh	2-ClPh	A	57
Me	Ph	Ph	A	58
H, Me, Et, Ph	Ph	Ph	A	56
Me	4-Me ₂ NPh	Ph	A	58
Me, Et, <i>n</i> -Pr	4-Me ₂ NPh	4-ClPh	A	57
CH ₂ =CH-	Ph	Ph	A	48
CH ₂ =CH-	4-R ₂ NPh	2-ClPh	A	57
	(R = Me, Et, <i>n</i> -Pr, <i>n</i> -Bu)			
XPh	YPh	ZPh	A	57
(X = H, Cl, NH ₂ , NR ₂)	(Y = H, 4-R ₂ NPh)	(Z = H, Cl)		
4-Pyridyl	4-Me ₂ NPh	4-ClPh	A	57
Me, Et, <i>n</i> -Pr, <i>i</i> -Pr, PhCH ₂ , 4-ClPhCH ₂	Ph	Ph	B	59
XPh	Ph	Ph	B	59
(X = H, 4-OMe, 3-NO ₂)				
Ph	Me	Ph	B	59
MeOCH ₂	Ph	Ph	B	59
Cl(CH ₂) _n	Ph	Ph	B	59
(<i>n</i> = 1, 2)				

^aA = R²CN + R⁴COCH(OH)R⁵ + H₂SO₄

B = R²CN + R⁵COCH(Cl)R⁴ + SnCl₄

TABLE 1.11. ALKYL- AND ARALKYLOXAZOLES FROM PROPARGYL AND RELATED AMIDES

R ²	R ⁴	R ⁵	Method ^a	Reference
H	Me	Me	A	62
Ph	H	Me	A	61, 63
2-XPh	H	Me	A	63
(X = 2- and 4-NO ₂ , 2-NH ₂)				
2,4-DiClPh	H	Me	A	63
3-Pyridyl	H	Me	A	63
Ph	Me, Et	Me	A	62
Ph	H	CH ₂ Br	B	64
Ph	H	CH ₂ SMe	B	64
Me, Et, <i>n</i> -Pr, C ₆ H ₁₁ , PhCH ₂	Me	Me	C	65
MeCH=CH	Me	Me	C	65
2-XPh	Me	Me	C	65
3-Pyridyl	Me	Me	C	65
Me	Et, <i>i</i> -Pr	Me	C	65
Me	Ph	Me	C	65
 (<i>n</i> = 4, 8)	Me	Me	C	65
EtO(CH ₂) ₂	Me	Me	C	65
HO ₂ C(CH ₂) _{<i>n</i>} (<i>n</i> = 4, 8)	Me	Me	C	65
 H ₂ NCCH ₂	Me	Me	C	65
H	Me	H	D	502
H	Me	Me, Et, <i>n</i> -Pr	D	502
Me, Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, <i>t</i> -Bu	Me	H	D	502
Me	Me	Et, <i>n</i> -Pr	D	502
Me, Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, <i>t</i> -Bu	Me	Me	D	502
Ph	Me	H	D	502
Me	Me	Ph	D	502
2-XPh	Me	Me	D	502
(X = H, OH)				

^aA = R²CONHCH(R⁴)C≡CH/H₂SO₄ or Hg(OAc)₂

B = 1. R²CONHCH₂C≡CH/E⁺ [E = Br₂ or (MeS)₂⁺SMe]

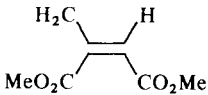
2. NaHCO₃

3. Δ

C = R²CONH₂/CH≡CCH(OH)R⁴/HgSO₄

D = R²CONH₂/CH≡CH(OH)R⁵/PPA/HgSO₄/Cl₃CCO₂H

TABLE 1.12. ALKYL- AND ARALKYLOXAZOLES FROM NITRILES AND PROPARGYL ALCOHOLS OR FROM PROPARGYL IMIDATES

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	<i>i</i> -Bu	Me	A	66
Ph	Me	H	A	66
Me	Me	Me	B	503
Ph	Me	H	B	503
Me	Et	Ph	B	503
Ph	CH ₂ OH	Me	C	67
Ph	CH ₂ Br	Me	C	67
Ph	(CH ₂) ₃ CO ₂ Me	Me	C	67
Ph		Me	C	67

^aA = R²CN/Propargyl alcohol/H₂SO₄

B = R²C(=NH)-OCHC≡CR/H₂SO₄

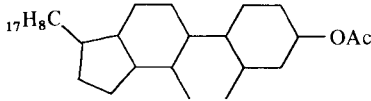
C = 1. R²C(=NH)-OCHC≡CH/Δ (base or neutral)

2. E⁺ (E = Br₂, CH₂=CHCO₂Me, MeO₂CC≡CCO₂Me)

TABLE 1.13. ALKYL- AND ARALKYLOXAZOLES FROM KETOXIMES AND ACYL HALIDES

R ²	R ⁴	R ⁵	Reference
Me, Et	Me	Me	69
Ph	Me	Me, <i>i</i> -Pr	69
Ph	—————(CH ₂) ₄ —————		69
Et	Me	Ph	69
Ph	Me	Ph	69
ClCH ₂	Me	Ph	68

TABLE 1.14. ALKYL-, ARYL-, AND ARALKYLOXAZOLES FROM 2-AZIDOKETONES

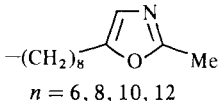
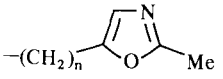
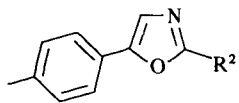
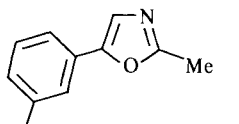
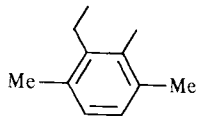
R ²	R ⁴	R ⁵	Method ^a	Reference
<i>i</i> -Pr, C ₃ H ₅	H	4-MeOPh	A	71
<i>i</i> -Pr, C ₃ H ₅	H	4-O ₂ NPh	A	71
PhCH ₂ , MeCH=CH-CH=CH	H	Ph	A	71
Me, MeCH=CH-CH=CH	H	4-O ₂ NPh	A	71
Ph	H	Ph	A	71
ClCH ₂	H	Ph	A	71
Me, PhCH ₂ , Ph			A	72
Me	H, Me	Ph	B	60
Ph	H	Ph	B	60
Me	Ph	Ph	B	60

^aA = R²COX/N₃CH(R⁴)COR⁵/Ph₃PB = R²CN/R⁴CH(N₃)COR⁵/NO⁺BF₄⁻/SnCl₄

TABLE 1.15. ALKYL-, ARYL-, AND ARALKYLOXAZOLES FROM 2-DIAZOKETONES AND NITRILES

R ²	R ⁴	R ⁵	Reference
Me	H	<i>t</i> -Bu, <i>n</i> -C ₆ H ₁₃	73
<i>t</i> -Bu	H	<i>t</i> -Bu	73
Me	H	Ph	73, 74, 504
Me	H	XPh	74
		(X = 3- and 4-MeO, 3- and 4-Me, 3- and 4-Cl, 3- and 4-Br, 3- and 4-CN, 3- and 4-O ₂ N)	
Et, <i>i</i> -Pr	H	Ph	74
Et	H	4-MeOPh	74
<i>t</i> -Bu	H	Ph	73
PhCH ₂	H	Ph	73, 74
CH ₂ =CH	H	4-XPh	73
		(X = H, MeO)	

TABLE 1.15. (Continued)

R ²	R ⁴	R ⁵	Reference
CH ₂ =C(Me) 	H	4-XPh (X = H, MeO)	73
PhCH=CH	H	Ph	74
PhCH=CH	H	Ph	73
3,4-DiMeOPhCH=CH	H	4-MeOPh	73
Ph	H	Ph	73, 74, 505
4-XPh (X = MeO, NO ₂)	H	Ph	74
Ph	H	4-XPh (X = Cl, NO ₂)	505
Me	Ph	Ph	74, 504
Et	Ph	Ph	504
CH ₂ =CH	Ph	Ph	504
Ph	Ph	Ph	504
Me	H	 $n = 6, 8, 10, 12$	74 ^a
Me	H	 $n = 6, 8, 10, 12$	73 ^a
Me, Ph	H		74 ^b
Me	H		74 ^b
Ph			505
Me	H	CH ₂ Br	75
ClCH ₂	H	Ph	74
PhSCH ₂	H	Ph	74
MeO ₂ CCH ₂	H	Ph	74
NC(CH ₂) ₆	H	Ph	73
Me	H	(CH ₂) ₁₀ CN	74

^aMeCN/N₂CHCO(CH₂)_nCOCHN₂/BF₃ · Et₂O or AlCl₃.^bBisdiazoketone/nitrile/BF₃ · Et₂O.

TABLE 1.16. ARYL-, AND ARALKYLOXAZOLES FROM AZIRINES

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	H	Ph	A	86
	H	Ph	A	86
4-XPh (X = H, NO ₂)	H	Ph	A	86
Ph	Me	Ph	A	87, 88
Ph	Ph	Ph	A	87, 88
Me	Ph	Ph	B	85
Ph	Ph	<i>t</i> -Bu	B	85
Ph	Ph	Ph	B	85
Ph	H	H	C	82
Ph	Me	Ph	C	82
Ph	H	H	D	81

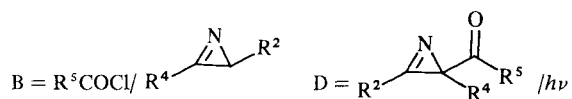
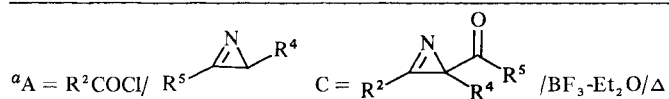


TABLE 1.17. ALKYL- AND ARALKYLOXAZOLES FROM ISOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	H	Me	A	79, 80
Me	————(CH ₂) ₄ ————	Me	B	506
Ph	MeC=CHCO ₂ R (R = Me, CH ₂ CF ₃)	Me	B	176

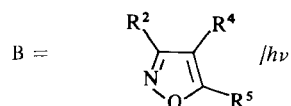
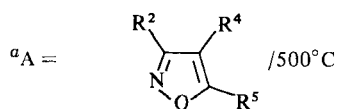


TABLE 1.18. ALKYL-, ARYL-, AND ARALKYLOXAZOLES BY OXIDATION OF OXAZOLINES

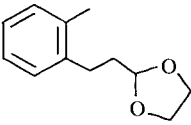
R ²	R ⁴	R ⁵	Reagent	Reference
Ph	H	H	DDQ	90
4-O ₂ NPh	H	H	NiO ₂	91
	H	H	NiO ₂	416
Ph	H	Ph	DDQ	90
Et	CH ₂ OMe	H	NiO ₂	91
Et	CH ₂ OMe	Ph	NiO ₂	91

TABLE 1.19. ARYL- AND ARALKYLOXAZOLES FROM OXAZOLINONES

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	H	Ph	A	92
Me	Ph	Ph	A	92
Ph	Ph	Ph	A	92
Ph	H	Me	B	474
Ph	Ph	Ph	C	93
Ph	Ph	3- and 4-pyridyl	C	93
Me	Me	Ph	D	94
Ph	Me, <i>i</i> -Pr	Me	D	94
Ph	Me	Ph	D	94
<i>i</i> -Pr	Ph	Me	E	94
Me	Ph	Ph	E	94
CH ₂ Cl	H	Ph	A	92
CH ₂ Cl	Ph	Ph	A	92
Me	CF ₃	4-XPh	E	94

(X = H, NO₂)

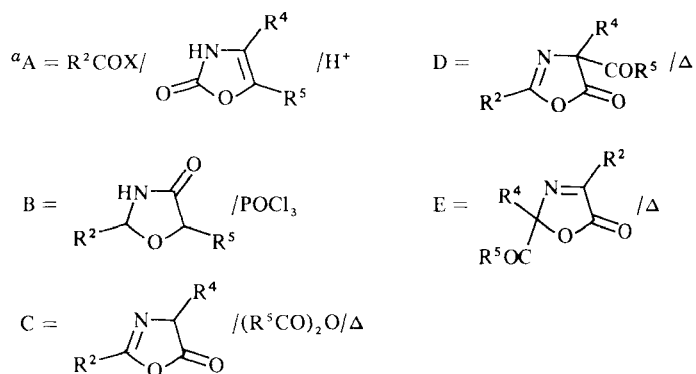


TABLE 1.20. ARYL- AND ARALKYLOXAZOLES FROM OXAZOLE-N-OXIDES

R ²	R ⁴	R ⁵	Method ^a	Reference
Ph	Me	Me	A	97
XPh (X = 2-, 3-, and 4-Cl, 2-, 3-, and 4-NO ₂)	H	Ph	B	98
Ph	Me	Ph	A	97
4-MeOPh	Me	Ph	B	96
Ph	Ph	Ph	B	96
4-XPh (X = H, OMe)	CH ₂ OAc	Me	C	97
Ph	CH ₂ OAc	Ph	C	97
Ph	Me	CH ₂ OAc	B	97
4-XPh (X = H, MeO)	CH ₂ Cl	Me	D	97
Ph	CH ₂ Cl	Ph	D	97

^aA = PCl₃/4-methyloxazole-*N*-oxide (the chloromethyloxazoles are formed as by-products); B = deoxygenation of the oxazole-*N*-oxide with either Zn or H₂/Ra-Ni; C = Ac₂O/4-methyloxazole-*N*-oxide; D = POCl₃/4-methyloxazole-*N*-oxide.

TABLE 1.21. ALKYL-, ARYL-, AND ARALKYLOXAZOLES FROM OXAZOLYL LITHIUMS OR 2-LITHIOALKYLOXAZOLES AND ELECTROPHILES

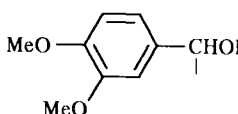
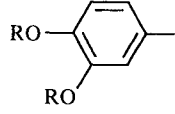
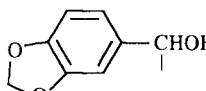
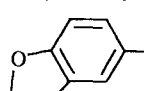
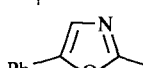
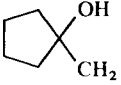
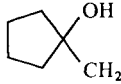
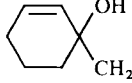
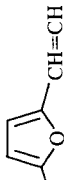
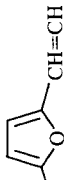
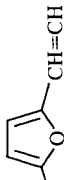
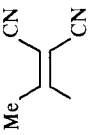
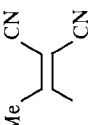
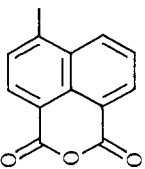
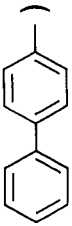
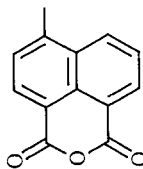
R ²	R ⁴	R ⁵	Method ^a	Reference
D	Ph	H	A	100
D	H	Ph	A	102
D	Me	Ph	A	100
Me	Ph	D	B	100
D	Ph	Ph	A	101, 102
Ph	D	Ph	B	101
	H	 (R = Me, -CH ₂ -)	C	103
	H		C	103
PhCHOH	Ph	Ph	C	102
	H	Ph	D	102

TABLE 1.21. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Ph(CH ₂) ₂	Me	Me	E	104
2-C ₁₀ H ₇ (CH ₂) ₂	Me	Me	E	104
DCH ₂	Ph	H	F	100
DCH ₂	Me	Ph	F	100
DCH ₂	Ph	Me	F	100
CH ₂ =CHCH ₂	Ph	Me	E	104
Me ₃ SiCH ₂	Ph	Me	E	104
<i>i</i> -Bu	Me	Ph	E	104
Et	Ph	Ph	E	104, 105
<i>n</i> -Bu	Ph	Ph	E	105
THPO(CH ₂) _n CH ₂ (<i>n</i> = 11, 12)	Ph	Ph	E	105
THPOCH(Me)(CH ₂) ₁₂	Ph	Ph	E	105
MeCHOTHP	Ph	Ph	E	105
$\begin{array}{c} \text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_6 \\ \\ \text{ArCHOH} \end{array}$	Me	Me	G	104
(Ar = Ph, 2-furyl, ferrocenyl)				
$\begin{array}{c} \text{PhCH}_2\text{CH}- \\ \\ \text{HOCH} \\ \\ \text{PhHC}=\text{CH} \end{array}$	Me	Me	G	104
	Me	Me	G	104
$\begin{array}{c} \text{PhCH}(\text{CH}_2)_2 \\ \\ \text{OH} \end{array}$	Me	Me	H	104
$\begin{array}{c} n\text{-C}_6\text{H}_{13}\text{CHCH}_2- \\ \\ \text{OH} \end{array}$	Me	Ph	G	104
PhCHOH	Ph	Ph	G	106
Ph ₂ COH	Ph	Ph	G	106
	Ph	Ph	G	104, 106
	Ph	Ph	G	104

^aA = (1) 2-Unsubstituted oxazole/*n*-BuLi, (2) D₂O; B = (1) halooxazole/*n*-BuLi, (2), D₂O; C = (1) 2-unsubstituted oxazole/*n*-BuLi, (2) ArCHO; D = (1) 5-phenyloxazole/*n*-BuLi, (2) TosF; E = (1) 2-methyloxazoles/*n*-BuLi or LDA; (2) RX; F = (1) 2-methyloxazoles/*n*-BuLi, (2) D₂O G = (1) 2-alkyloxazoles/*n*-BuLi, LDA or LiNH₂, (2) RR'CO; H = (1) 2,4,5-trimethyloxazole/LDA, (2) styrene oxide.

TABLE 1.22. ALKENYLOXAZOLES VIA CARBONYL CONDENSATION REACTIONS

R ²	R ⁴	R ⁵	Method	Reference
PhCH=CH 	Me	H	2-Methyloxazole/PhCHO	108
O ₂ N- 	H	Me	2-Methyloxazole/ O ₂ N-  /BuNH ₂	109
PhCH ₂	CH=C(Me)NO ₂	H	4-Formyloxazole/EtNO ₂ /BuNH ₂	507, 508
Me		Me	4-Ketooxazole/CH ₂ (CN) ₂ /KOAc	424
Me	Me		5-Ketooxazole/CH ₂ (CN) ₂ /KOAc	424
Ph	CH=CHCO ₂ H	H	4-Formyloxazole/CH ₂ (CO ₂ H) ₂	191
Ph	CH=C(CN)CO ₂ Et	Me	4-Formyloxazole/CH ₂ (CN)CO ₂ Et/ C ₂ H ₅ N	254
PhCH=CH 	H	Ph	Wittig reaction of oxazol-2-yl-methylene triphenylphosphorane + PhCHO	71
	H	4-XPhCH=CH (X = MeO, Me, Me ₂ N, Cl, Br, NO ₂ , Ph, )	Horner-Emmons reaction of diethyl oxazol-5-ylmethyl phosphonate + 4-XPhCHO	111
	H	RCH=CH (R = 1- and 2-C ₁₀ H ₇ , 9-anthryl)	Horner-Emmons reaction of diethyl oxazol-5-ylmethyl phosphonate + RCHO	111

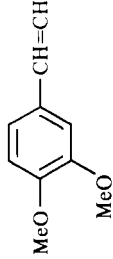
PhCH=CH	Ph	Me	Oxazol-2-ylmethyl trimethylsilane/ <i>n</i> -BuLi; then PhCHO	104
	H	Ph	2-Methyloxazole/3,4-diMeOPhCHO/ Ac ₂ O/C ₅ H ₁₁ N	110
XPhCH=CH (X = H, 4-MeO, 2-HO, 3,4-O- CH ₂ -O)	Ph	Ph	2-Methyloxazole/XPhCHO/ZnCl ₂	107
	Ph	Ph	Oxazole aldehyde/Wittig reagent	105

TABLE 1.23. ARYL- AND ARALKYLOXAZOLES VIA THE INTRODUCTION AND

R ²	R ⁴
4-O ₂ NPh	Me
H	4-O ₂ NPh
H	H
Me	H
H, Me	Me
XPh	H
(X = H, 2-, 3-, and 4-NO ₂)	
H, Me	4-O ₂ NPh
2-O ₂ N-4-XPh	CH ₂ Cl
(X = H, Me, Cl, Br, NO ₂)	
Me	4-HO ₃ S-2-XPhCH ₂
Me	Ph
H, Me	4-H ₂ NO ₂ SPh
Me	4-H ₂ NO ₂ SPh
Me	4-H ₂ NO ₂ SPh
2-, 3- and 4-H ₂ NPh	H
4-H ₂ NPh	Me
4-H ₂ NPh	Me
3-H ₂ NPh	Me
H	H
Et	H
Me	Me
2-, 3-, and 4-H ₂ NPh	H
4-H ₂ NPh	H
4-H ₂ NPh	H
Ph	4-H ₂ NPh
Me	4-H ₂ NPh
4-XPh	H
(X = H, Me, C ₁ -C ₆ alkoxy)	
Me	Ph
Me	4-O ₂ NPh
Me	4-H ₂ NPh
Me	CH ₂ OAc
4-AcNHPh	Me
Me	4-AcNHPh
H	H
Me	Ph
Me	4-O ₂ NPh
Me	4-AcNHPh
Me	4-PhCONHPh
4-XPh	H
(X = H, Me, C ₁ -C ₆ alkoxy)	

MODIFICATION OF ARYL SUBSTITUENTS ON THE OXAZOLE RING

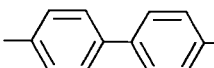
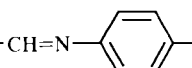
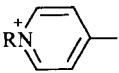
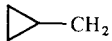
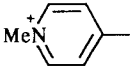
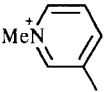
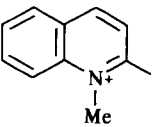
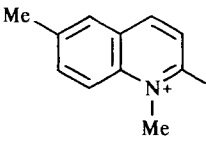
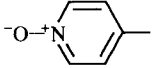
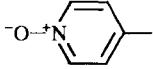
R ⁵	Method ^a	Reference
H, Me	A	113
H	A	115
4-O ₂ NPh	A	155
4-O ₂ NPh	A	429
4-O ₂ NPh	A	509
4-O ₂ NPh	A	510
4-O ₂ NPh	A	112
H	A	149
Ph	B	116
4-HO ₃ SPh	B	112
4-O ₂ NPh	C	112
4-H ₂ NO ₂ SPh	C	112
4-AcNHPh	C	112
H	D	114
H	D	148
H, Me	D	113
H	D	113
4-H ₂ NPh	D	155
4-H ₂ NPh	D	20
4-H ₂ NPh	D	511
Ph	D	446
4-MeOPh	D	57
2,4-DiMeOPh	D	57
H	D	57
4-XPh	D	112
(X = Cl, Br, OH)		
4-H ₂ NPh	D	447
4-H ₂ NPh	D	112
4-H ₂ NPh	D	112
4-H ₂ NPh	D	112
4-AcNHPh	D	7
H	E	148
4-XPh	E	112
(X = Cl, Br)		
4-AcNHPh	E	155
4-RCONHPh	E	112
(R = Me, Ph)		
4-RCONHPh	E	112
(R = Me, Cl ₂ CH)		
4-AcNHPh	E	112
4-PhCONHPh	E	112
 -CH=N- 	Anilinooxazole/4-formylbiphenyl	447

TABLE 1.23. (Continued)

R ²	R ⁴
Ph	4-Et ₂ NPh
4-Me ₃ N ⁺ Ph	H
4-Et ₂ MeN ⁺ Ph	H
4-Me ₃ N ⁺ Ph	H
 (R = Me, Et, CH ₂ =CHCH ₂ ,  -CH ₂ PhCH=CHCH ₂)	H
	H
	H
	H
Me	H
	H
	H
	H
	H
	H
2-, 3-, and 4-ClPh	H
4-HOPh	H

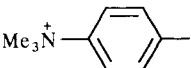
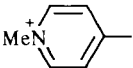
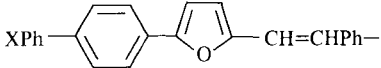
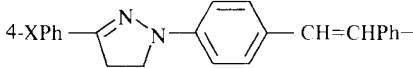
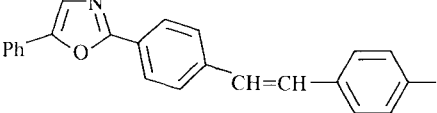
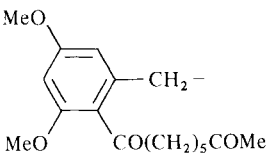
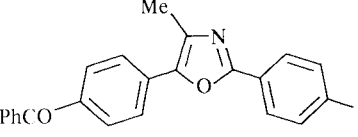
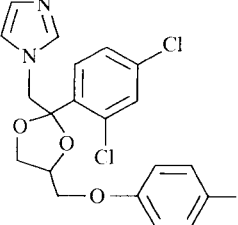
R ⁵	Method ^a	Reference
H	Anilinoxazole/diethylphosphate	57
Ph	Dimethylanilinoxazole/MeOTs	121
Ph	Diethylanilinoxazole/MeOTs	121
4-Me ₃ N ⁺ Ph	Bisdimethylanilinoxazole/ MeOTs	121
H	F	120
Me	F	120
Ph	F	352
	F	121
	F	120
Ph	F	121
Ph	F	121
H	Oxidation of pyridyloxazole	122
Ph	Oxidation of pyridyloxazole	122
4-Me ₂ C(OH)CH ₂ OPh	Thermal dealkylation of methylpyridinium salt	366
H	G	114
Ph	H	446

TABLE 1.23. (Continued)

R ²	R ⁴
	H
Me	4-BrPh
Me	4-ClPh
Me	Me
Me	4-XPh
	(X = H, NO ₂ , SO ₂ NH ₂)
Me	4-XPh
	(X = H, NO ₂ , SO ₂ NH ₂)
Me	4-XPh
	(X = H, NO ₂ , SO ₂ NH ₂)
Me	4-H ₂ NO ₂ SPh
Me	4-XPh
	(X = H, NO ₂ , SO ₂ NH ₂)
Me	Ph
Me	4-ClPh
Me	4-HOPh
Me	4-BrPh
Me	4-IPh
4-NCPhCH ₂	H
3- and 4-NCPh	H
4-XPh	H
(X = H, Ph)	
4-Ph ₃ P ⁺ CH ₂ Ph	H
(EtO) ₂ POCH ₂ Ph-	H
4-XPh	H
(X = H, Ph)	
4-XPh	H
(X = H, Ph)	
4-XPhCH=CHPh-	H
(X = H, Cl, <i>i</i> -Pr, OMe, Ph)	
4-RCH=CHPh-	H
(R = 1- and 2-C ₁₀ H ₇)	
4-XPhCH=CHPh-	Ph
(X = H, OMe, Et ₂ N, Ph)	
2,4-DiClPhCH=CHPh-	Ph
RCH=CHPh-	Ph
(R = 1- and 2-C ₁₀ H ₇ , 2-thienyl)	
Ph	PhCH=CHPh-
Ph	4-Ph--CH=CHPh-
Ph	
4-CH ₂ =CHPh	1-C ₁₀ H ₇ CH=CHPh-
4-PhCH=CHPh-	4-CH ₂ =CHPh-
	4-PhCH=CHPh-

R ⁵	Method ^a	Reference
Ph	I	446
4-ClPh	J	112
4-BrPh	G	112
Ph	K	511
4-ClPh	G	112
4-BrPh	J	112
4-HOPh	H	112
Ph	K	112
4-NCPH	L	112
4-H ₂ NO ₂ SPh	M	112
4-ClPh	G	112
4-HOPh	H	112
4-BrPh	J	112
4-IPh	N	112
4-NCPH	O	119
4-NCPH	O	119
CH ₂ Br	Tolyloxazole/NBS	117
Ph, 1-biphenyl, 1-C ₁₀ H ₇	Bromomethylphenyloxazole/Ph ₃ P	512
Ph	Bromomethylphenyloxazole/(EtO) ₃ P	513, 514, 515
4-Ph ₃ P ⁺ CH ₂ Ph	Bromomethylphenyloxazole/Ph ₃ P	117
4-OHCPh	Bromomethylphenyloxazole/hexamethylenetetramine; then HOAc	117
Ph	P	118
Ph	P	118
Ph	p	118
Ph	P	118
Ph	P	118
PhCH=CHPh-	P	118
4-Ph-  -CH=CHPh-	P	118
1-C ₁₀ H ₇ CH=CHPh-	P	118
4-CH ₂ =CHPh-	P	118
4-PhCH=CHPh-	P	118

TABLE 1.23. (Continued)

R ²	R ⁴
4-CH ₂ =CHPh-	H
 (X = H, 2- and 4-Cl, 2- and 4-Br, 4-I, 2-, 3-, and 4-NO ₂ , 4-Me, 4-Ph, 2,4-diCl)	H
 (X = H, Me, OMe, Cl, NMe ₂ , CH=CHPh, Ph)	H
4-XPh (X = H, Ph)	H
4-XPh (X = H, Ph)	H
	H
	Ph
	Me
	H

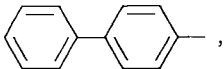
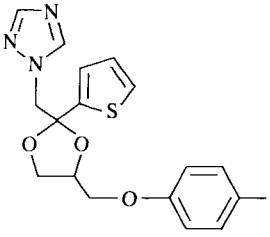
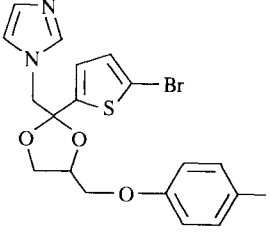
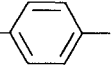
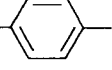
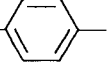
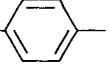
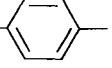
R ⁵	Method ^a	Reference
Ph,  , 1-C ₁₀ H ₇	Q	512
Ph	R	514, 515
Ph	R	513
CH ₂ =CHPh–	Q	117
CH ₂ =CH–  –CH=CHPh–	Q	117
Ph	2-(4-Dibromomethylphenyl)-5-phenyloxazole/base	516
Ph	Friedel–Crafts	105
Ph	Friedel–Crafts	151
H	S	16

TABLE 1.23. (Continued)

R ²	R ⁴
	H
PhCH ₂	
Et	H
3-Pyridyl	H
XPh (X = H, 4-Cl, 4-NO ₂ , 4-Me, 2,4-diCl)	EtO ₂ CCH ₂ O- 
4-XPh (X = H, Cl)	EtO ₂ CCH(Me)O- 
4-ClPh	EtO ₂ CCH(Et)O- 
XPh (X = H, 4-Cl, 4-NO ₂ , 4-Me, 2,4-diCl)	EtO ₂ C(Me) ₂ O- 
Ph	EtO ₂ CCH ₂ O- 

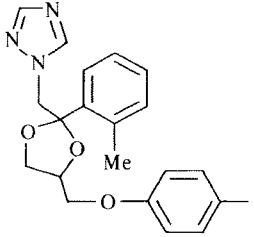
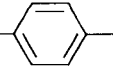
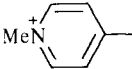
R ^s	Method ^a	Reference
H	S	16
H	S	16
	S	16
4-MeOPh	S	366
Me	S	483
Me	S	483
Me	S	483
Me	S	483
Ph	S	483
	181	

TABLE 1.23. (Continued)

R ²	R ⁴
Ph	EtO ₂ CCH(Me)O- 
Ph	EtO ₂ C(Me) ₂ O- 
4-ClPh	EtO ₂ CCH ₂ O- 
XPh (X = H, 4-Cl, 4-NO ₂ , 4-Me, 2,4-diCl)	4-HOPh
Ph	4-HOPh
4-ClPh	4-HOPh
3-Pyridyl	H
	H
3,4-(HO ₂ C) ₂ Ph	H
Me	H
Me	H
Me	4-XPh (X = H, NO ₂ , SO ₂ NH ₂)
Me	4-HO ₂ CPh
Me	4-XPh (X = H, NO ₂ , SO ₂ NH ₂)
Me	4-MeO ₂ CPh
Me	4-H ₂ NOCPh
4-H ₂ NCCH ₂ Ph-	H
	
3- and 4-H ₂ NCPh-	H
	
XPh (X = H, 4-Cl, 4-NO ₂ , 4-Me, 2,4-DiCl)	4-HO ₂ CCH ₂ OPh

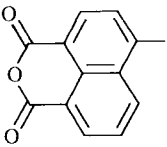
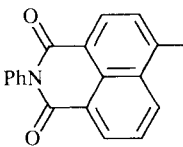
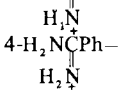
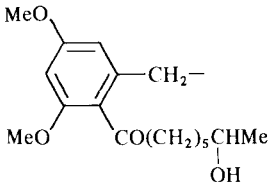
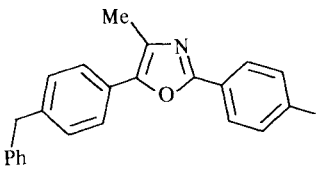
R ⁵	Method ^a	Reference
Ph	S	483
Ph	S	483
4-ClPh	S	483
Me	Demethylation of MeOPhoxazole/HBr	483
Ph	Demethylation of MeOPhoxazole/HBr	483
4-ClPh	Demethylation of MeOPhoxazole/HBr	483
4-HOPh	Dealkylation of ether/H ⁺	366, 483
4-HOPh	Dealkylation of ether/H ⁺	366
4-XPh (X = H, Cl, Me, Ph)	From the phthalic anhydride	453
	Oxidation of the acenaphthene	433
	Anhydride/PhNH ₂	433
4-HO ₂ CPh	Hydrolysis of nitrile	112
4-HO ₂ CPh	Hydrolysis of dinitrile	112
4-MeO ₂ CPh	Esterification of acid	112
4-MeO ₂ CPh	Esterification of diacid	112
4-H ₂ NOCPh	Dinitrile/PPA	112
4-H ₂ N-CPh-	Dinitrile/HCl/EtOH; then NH ₃	119
	Dinitrile/HCl/EtOH; then NH ₃	119
Me	Hydrolysis of ester	483

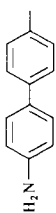
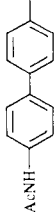
TABLE 1.23. (Continued)

R ²	R ⁴
4-ClPh XPh (X-H, 4-Cl, 4-NO ₂ , 4-Me, 2,4-diCl)	4-HO ₂ CCH(Et)Ph- 4-HO ₂ CC(Me) ₂ Ph-
Ph	4-HO ₂ CC(R) ₂ Ph- (R = H, Me)
	Ph
	Me

^aA = nitration of phenyloxazole; B = sulfonation of phenyloxazole; C = chlorosulfonation of phenyloxazole then NH₃; D = reduction of nitrophenyloxazole; E = acylation of anilino-oxazole; F = alkylation of pyridyloxazole; G = diazonium salt/CuCl; H = diazonium salt/H₃O⁺; I = diazonium salt/Et₃NPh; J = diazonium salt/CuBr; K = diazonium salt/H₃PO₂; L = diazonium salt/CuCN; M = diazonium salt/CuCl₂/SO₂/HOAc then NH₃; N = diazonium salt/CuI; O = bromophenyloxazole/CuCN; P = tolyloxazole/RCHO/base; Q = Wittig reaction; R = Horner-Emmons reaction; S = alkylation of the phenol.

R ^s	Method ^a	Reference
Me	Hydrolysis of ester	483
Me	Hydrolysis of ester	483
Ph	Hydrolysis of ester	483
Ph	Ketone/ NaBH_4	105
Ph	Ketone/ LAH/AlCl_3	151

TABLE 1.24. ALKYL-, ARYL-, AND ARALKYLOXAZOLES BY MISCELLANEOUS METHODS

R ²	R ⁴	R ⁵	Method ^a	Reference
H	H	H	Decarboxylation of oxazole-4-carboxylic acid	198
H	H	H	Decarboxylation of oxazole-4,5-dicarboxylic acid	188
Me	H	H	Decarboxylation of oxazole-4-carboxylic acid	198
H	Me	H	Decarboxylation of oxazole-5-carboxylic acid	182
Me	Me	H	Decarboxylation of oxazole-5-carboxylic acid	182
PhCH ₂	Me	H	Decarboxylation of oxazole-5-carboxylic acid	182
H	H	PhCH ₃	Decarboxylation of oxazole-4-carboxylic acid	51
H	Me	H	Oxazol-2-thione/NaNO ₂ /HNO ₃	239
H	<i>t</i> -Bu	<i>t</i> -Bu	Oxazolotetrahydrothiepin/Ra-Ni	40
Ph	H	H	Decarboxylation of oxazole-4-carboxylic acid	175
Ph	Me	H	4-Chloromethyl-5-chlorooxazole/H ₂ /Pd-C	146
	H	H	Hydrolysis of acetal	416
	H	H	Horner-Emmons reaction	416
	Ph	Me	oxazolocycloheptatriene/H ₂	517
H	H	4-XPh (X = H, OMe, SMe, OH, Ph, 4'-O ₂ NPh) 4-MeO ₂ SPh	Decarboxylation of oxazole-2-carboxylic acid	155
H	H	H	Decarboxylation of oxazole-2-carboxylic acid	155
H	H	H	Oxidation of 4-methylthiophenylloxazole	155
H	H	H ₂ N- 	Reduction of nitrobiphenylloxazole	155
H	H	AcNH- 	Acetylation of aminobiphenylloxazole	155

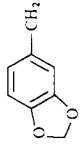
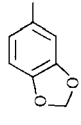
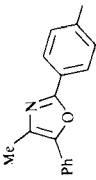
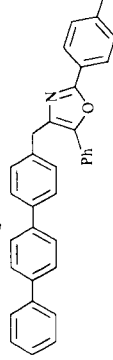
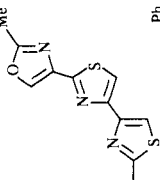
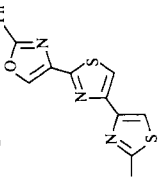
H	Me	Ph	Decarboxylation of oxazole-2-carboxylic acid	155
Me	H	4-O ₂ NPh	Decarboxylation of oxazole-4-carboxylic acid	7
3,4-DiMeOPhCH ₂	H	3,4-DiMeOPh	2-Hydroxybenzylloxazole/ H ₂ /Pd-C	103
	H		2-Hydroxybenzylloxazole/ H ₂ /Pd-C	103
3,4-DiMeOPhCH ₂	H		2-Hydroxybenzylloxazole/ H ₂ /Pd-C	103
H, Me	Me	4-O ₂ NPh	4-O ₂ NPhCHO/1- aminoacrylic acid/pyr/Δ	15
Ph ₃ P'CH ₂ 2- and 3-thienyl	H H	Ph H	2-Chloromethylloxazole/Ph ₃ P Decarboxylation of oxazole-4,5-dicarboxylic acid	71 189
H	H		Decarboxylation of 4,4'- bioxazole dicarboxylic acid	30
Ph Ph	H Me	Ph 4-O ₂ NPh	4-Chloromethylloxazole/H ₂ /Pd-C 4-O ₂ NPhCHO/ 1-benzoylaminoacrylic acid/pyr/Δ	141 15
		Ph	4-bromomethylloxazole/ p-terphenyl/AlCl ₃	151
		Ph	Bis(4-bromomethylloxazole/ p-terphenyl/AlCl ₃	151
PhCH=CH- Ph, C≡CH - 	Ph Ph Ph	Ph Ph Ph	2-hydroxyethylloxazole/-H ₂ O 2-Hydroxyethylloxazole/-H ₂ O	106
Ph	Ph	Ph	2-Hydroxyethylloxazole/-H ₂ O	106
Ph	Ph	Ph	1-Benzoyl-4,5-diphenyl-1,2,3- triazole/Δ	127
Ph	4-XPh (X = H, Me)	Ph	1,2-Diphenyl-3,4,4- tetramethylcyclobutene oxide/XPhCN/Δ	126

TABLE 1.24. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
H	 (R = H, Me, Ph)	H	Oxazole-4-thioamide/ RCOCH ₂ Br	195
Me	 (R = H, Me, Ph, 4-MeOPh, 4-BrPh, 4-ClPh)	H	Oxazole-4-thioamide/ RCOCH ₂ Br	195
H	Me	 (R = H, Me, Ph)	Oxazole-5-thioamide/ RCOCH ₂ Br	195
Ph		H	Oxazole-4-thioamide/ RCOCH ₂ Br	195
Me		H	2-Oxazole-4-thioamide/ BrCH ₂ COCOCH ₂ Br	195
Ph		H	2-Oxazole-4-thioamide/ BrCH ₂ COCOCH ₂ Br	195
H, Me	CH ₂ OH	Me	A	233, 518–520
H	CH ₂ OH	PhCH ₂	A	152, 233, 518–520
C ₆ H ₁₁	CH ₂ OH	H	Acid/LAH	521
H	Me	CH ₂ OH	A	233, 518– 520, 522

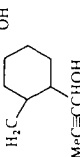
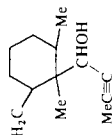
H	CH ₂ OH	CH ₂ OH	Diester/LAH or diacid/B ₂ H ₆	233, 518–520, 152
H	CH ₂ OH	(CH ₂) ₆ CO ₂ Me	B	172
H	Me	CH ₂ OH	B	184
Me	Me	PhCHOH	Ketone/LAH	264
Me	PhC(Me)OH	Me	Methyl ketone/PhMgBr	257
Me	Ph ₂ COH	Me	Ester/2-PhMgBr	257
H	Me	(CH ₂) ₂ OH	A or amine/HNO ₂	233, 518–520, 522
H	CF ₃	(CH ₂) ₂ OH	A	233, 518–520
H	CH=CH–CH(OH)–CH(CH ₃) ₄ Me	(CH ₂) ₆ CO ₂ Me	Ketone/NaBH ₄	172
H	CH=CH–CH(OH)–CH(CH ₃) ₄ Me	(CH ₂) ₆ CO ₂ H	C	172
H	(CH ₂) ₆ CO ₂ me	CH=CH–CH(OH)–CH(CH ₃) ₄ Me	Ketone/NaBH ₄	184
H	(CH ₂) ₆ CO ₂ Me	CH=CH–CH(OH)–CH(CH ₃) ₄ Me	C	184
H	H	–CH ₂ CH(Me)CH ₂ CHC–CMe OH	Aldehyde/MeC≡CMgBr	31
H	H		Aldehyde/MeC≡CLi	31
H	H		Aldehyde/MeC≡CLi	388
Ph	CH ₂ OH	H	A or B	191
4-XPh (X = H, Me, Br, Cl, NO ₂)	CH ₂ OH	H	4-Hydroxymethyl-5-bromoxazole/Zn/HOAc	150
Me	CH ₂ OH	4-O ₂ NPh	Hydrolysis of acetate or sulfate or chloromethylloxazole	7, 429, 8, 432
Me	CH ₂ OH	Ph	Hydrolysis of acetate	429
MeCHOH	H	4-O ₂ NPh	Hydrolysis of acetate	465
Ph	PhC(Me)OH	Me	Methyl ketone/PhMgBr	259
CH ₂ OH	Ph	Ph	Bromomethylloxazole/AgNO ₃ /H ₂ O	46
Ph	PhC(Me)OH	Ph	Phenyl ketone/MeMgI or methyl ketone/PhMgBr	259
(CH ₂) _n OH (n = 12, 13)	Ph	Ph	Hydrolysis of THP ether	105
(CH ₂) ₂ CH(Me)OH	Ph	Ph	Hydrolysis of THP ether	105

TABLE 1.24. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
	$(\text{CH}_2)_n\text{CH}=\text{CHCH}_2\text{CHMe}$ OH	Ph	Hydrolysis of THP ether	105
H	(CH ₂) ₃ OH	Ph	A	151
H	Me	CH ₂ OR	D	54
H	CH ₂ O(CH ₂) ₃ OH	Me	D	152
H	CH ₂ O(CH ₂) ₃ Cl	Me	E	152
H	CH ₂ O(CH ₂) ₃ N ₃	Me	Chloroalkyloxazole/NaN ₃	152
H	CH ₂ O(CH ₂) ₃ NH ₂	Me	Azide/H ₂ /PtO ₂	152
H	CH ₂ O(CH ₂) ₃ NHCNHMe	Me	F	152
H	CH ₂ O(CH ₂) ₃ OH	Me	D	518–520
H	CH ₂ O(CH ₂) ₃ Cl	Me	E	518–520
H	CH ₂ O(CH ₂) ₃ N ₃	Me	Chloroalkyloxazole/NaN ₃	518–520
H	CH ₂ O(CH ₂) ₃ NH ₂	Me	Azide/H ₂ /PtO ₂	518–520
H	CH ₂ O(CH ₂) ₃ NHCNMe	Me	G	518–520
H	CH ₂ O(CH ₂) ₃ NHCNHMe	Me	H	518–520
Me	Me	PhCHO(CH ₂) ₂ NEt ₃	Alcohol/Cl(CH ₂) ₂ NEt ₃	264
Ph	CH ₂ OMe	H	5-Chlorooxazole/H ₂ /Pd-C	146
	Ph	Ph	D	151
	Ph	Ph	D	151
H	Me	CH ₂ O ₂ CNHPh	Alcohol/PhNCO	522
	Me	Me	Alcohol/acid chloride	523
Ph	CH ₂ OAc	Me	Chloromethylloxazole/ KOAc/HOAc	97

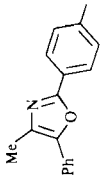
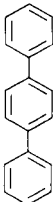
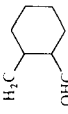
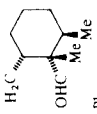
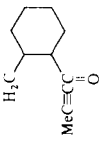
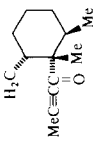
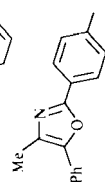
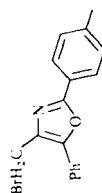
Me	CH ₂ OAc	4-O ₂ NPh	Alcohol/Ac ₂ O/pyr	432
Me	CH ₂ O ₂ CNHPH	4-O ₂ NPh	Alcohol/PhNCO	7
Me	CH ₂ OCO ₂ Et	4-O ₂ NPh	Alcohol/EtO ₂ CCl	7
PhCHOAc	H	4-O ₂ NPh	Alcohol/AcCl	465
Ph	CH ₂ OAc	Ph	Chloromethylloxazole/ KOAc/HOAc	97
H	Me	(CH ₂) ₂ OAc	Chloromethylloxazole/AcO ⁻	54
H	Me	(CH ₂) ₂ O ₂ CNHPH	Alcohol/PhNCO	522
	-(CH ₂) _n O ₂ CCH ₂ -		Bromoalkylloxazole/acid/Et ₃ N	151
H	H	CH ₃ CHCH ₂ CHO Me	Alcohol/(COCl) ₂ /DMSO; then Et ₃ N	31
H	H		Alcohol/(COCl) ₂ /DMSO; then Et ₃ N	31
H	H		Alcohol/(COCl) ₂ /DMSO; then Et ₃ N	388
H	Ph	Ph	2-Methylloxazole/LDA/RI	105
Ph	Ph	CH ₃ CHCH ₂ CC≡CMe O	Acetal/H ⁺	105
H	H	Ph	Alcohol/(COCl) ₂ /DMSO; then Et ₃ N	31
H	H		Alcohol/(COCl) ₂ /DMSO; then Et ₃ N	31
H	H		Alcohol/(COCl) ₂ /DMSO; then Et ₃ N	388
H	(CH ₂) ₆ CO ₂ Me	CH=CHC- <i>rr</i> -C ₅ H ₁₁ O	Aldehyde/Ph ₃ P ⁺ C ⁻ HCOC ₄ H ₉	184
H	CH=CHC- <i>rr</i> -C ₅ H ₁₁ O	(CH ₂) ₆ CO ₂ Me	Aldehyde/Ph ₃ P ⁺ C ⁻ HCOC ₄ H ₉	172

TABLE 1.24. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
	Ph	Ph	2-Methyloxazole/BuLi; then CuI/Me ₂ S; then cyclohexenone	104
H	CH ₂ Cl	Me, PhCH ₂	E	233, 518–520
Me	CH ₂ Cl	Me	E	152, 233
C ₆ H ₁₁	CH ₂ Cl	H	E	518–520
H	Me	CH ₂ Cl	E	521
				53, 54, 233, 518–520, 522
H	CH ₂ Cl	CH ₂ Cl	E	152, 233, 518–520
H	Me	(CH ₂) ₂ Cl	E	233, 518–520, 524, 525
H	CF ₃	(CH ₂) ₂ Cl	E	233, 518–520, 525
H	Me	(CH ₂) ₂ Br	E	53, 525
Me	Me	(CH ₂) ₂ Cl	E	53, 525
CF ₃	CF ₃	(CH ₂) ₂ Cl	E	525
CF ₃	CF ₃	(CH ₂) ₂ Cl	E	525
Ph	Me	(CH ₂) ₂ Cl	E	525
	CH ₂ X (X = Cl, Br)	H	E	191
Ph	CH ₂ Br	Me	I	143
Ph	H	CH ₂ Br	I	64
	H	CH ₂ Br	I	111
4-MePh	CF ₃	H	5-Fluorooxazole/LAH	147
Ph	Me	(CH ₂) ₂ Cl	E	53
BrCH ₂	Ph	Ph	I	46
Ph	CH ₂ Br	Ph	I	143
	CH ₂ Br	Ph	I	151



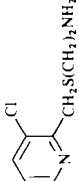
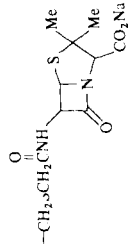
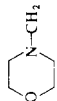
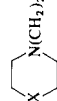
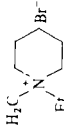
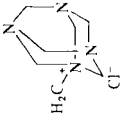
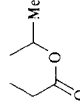
BrH ₂ C	Ph	CH ₂ Br	Ph	I	151
		(CH ₂) ₂ Cl	Ph	E	151
H	H	CH ₂ S(CH ₂) ₂ NHCNHCH ₂ CH=CHPh	H	N-Cyano-S-methylisothiourea/ ArCH=CHCH ₂ NH ₂	526
H	H	CH ₂ S(CH ₂) ₂ NHCNHCH ₂ CH=CHPhOH-4	H	N-Cyano-S-methylisothiourea/ ArCH=CHCH ₂ NH ₂	526
H	H	CH ₂ S(CH ₂) ₂ NHCNHCH ₂ CH=CHPhMe-4	H	N-Cyano-S-methylisothiourea/ ArCH=CHCH ₂ NH ₂	526
H	H	CH ₂ S(CH ₂) ₂ NPhthl	PhCH ₂	J	152, 518-520
H	H	CH ₂ S(CH ₂) ₂ NH ₂	PhCH ₂	K	152, 518-520
H	H	CH ₂ S(CH ₂) ₂ NHCNHMe	PhCH ₂	F	152
H	H	CH ₂ S(CH ₂) ₂ NHCSCMe	PhCH ₂	G	518-520
H	H	CH ₂ S(CH ₂) ₂ NHCNHMe	PhCH ₂	H	518-520
H	H	Me	CH ₂ S(CH ₂) ₂ Phthl	J	152, 233
H	H	Me	CH ₂ S(CH ₂) ₂ NH ₂	K	152, 233
H	H	Me	CH ₂ S(CH ₂) ₂ NHCNHMe	Amine/MeNCO	152
H	H	Me	CH ₂ S(CH ₂) ₂ NHCNHMe	F	152
H	H	Me	CH ₂ S(CH ₂) ₂ NHCNHCOPh	F	152
H	H	Me	CH ₂ S(CH ₂) ₂ NHCNH ₂	Benzoylthiourea/K ₂ CO ₃	152
H	H	Me	CH ₂ S(CH ₂) ₂ NHCNH(CH ₂) ₂ NMe ₂	F	152
H	H	Me	CH ₂ S(CH ₂) ₂ NHCSCMe	L	233
H	H	Me	-CH ₂ S(CH ₂) ₂ NHCNH(CH ₂) ₂ SCH ₂ -	Aminothiomethyl nitroethylene/ 	233

TABLE 1.24. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	CH ₂ S(CH ₂) ₂ NPhthl	Me	J	152, 518–520
Me	CH ₂ S(CH ₂) ₂ NH ₂	Me	K	152, 518–520
Me	CH ₂ S(CH ₂) ₂ NHCNHMe	Me	F	152
Me	CH ₂ S(CH ₂) ₂ NHCNHMe	Me	G; then H	518–520
Me	CH ₂ S(CH ₂) ₂ NHCNHMe	Me	Chloromethylloxazole/ NH ₂ (CH ₂) ₂ SH	518–520
Me	CH ₂ S(CH ₂) ₂ NH ₂	Me	G; then H	518–520
Me	CH ₂ S(CH ₂) ₂ NHCNHMe	Me		
H	CH ₂ S(CH ₂) ₂ NPhthl	CH ₂ S(CH ₂) ₂ NPhthl	J	152
H	CH ₂ S(CH ₂) ₂ NH ₂	CH ₂ S(CH ₂) ₂ NH ₂	K	152
H	CH ₂ S(CH ₂) ₂ NHCNHMe	CH ₂ S(CH ₂) ₂ NHCNHMe	F	152
H	CH ₂ S(CH ₂) ₂ NHCNHMe	CH ₂ S(CH ₂) ₂ NHCNHMe	G; then H	518–520
H	Me, CF ₃	(CH ₂) ₂ S(CH ₂) ₂ NPhthl	J	152
H	Me, CF ₃	(CH ₂) ₂ S(CH ₂) ₂ NH ₂	K	152
H	Me, CF ₃	(CH ₂) ₂ S(CH ₂) ₂ NHCNHMe	F	152
H	Me	(CH ₂) _n S(CH ₂) ₂ NHCNHMe	L	233
		(n = 1, 2)		
H	Me	(CH ₂) _n S(CH ₂) ₂ NHCNH(CH ₂) ₂ SCH ₂ - 	Animomethylthioethyl- nitroethylene/ 	233
		(n = 1, 2)		
H	Me, CF ₃	(CH ₂) ₂ S(CH ₂) ₂ NHCNHMe	Thiourea/Pb(NCN) ₂	518–520
4-XPh (X = H, Cl)		H	Amine/acid/DCC	527
(RO) ₂ PSCH ₃ (R = Me, Et)	Me	Ph	Halomethylloxazole/ (RO) ₂ PSH	154

$\begin{array}{c} \text{S} \\ \\ \text{EtPSCH}_2\text{-OEt} \end{array}$	H	Ph	Me	Halomethylloxazole/ $\begin{array}{c} \text{S} \\ \\ \text{EtPSH-OEt} \end{array}$	154
	H	H	-CH ₂ SCH ₂ -	Bromomethylloxazole/thiol Me	151
Me	OPO(OEt) ₂ -C=CHSMc	Me		Methylthiochloromethyl oxazoly ketone/(EtO) ₃ P	266
H	CH ₂ NH(CH ₂) ₂ NH ₂	PhCH ₂		M	152
H	CH ₂ NH(CH ₂) ₂ NHCNHMc	PhCH ₂		F	157
Me	CH ₂ NH(CH ₂) ₂ NH ₂	Me		M	152
Me	CH ₂ NH(CH ₂) ₂ NHCNHMc	Me		F	152
H	CH ₂ NH(CH ₂) ₂ NH ₂	CH ₂ NH(CH ₂) ₂ NH ₂		M	528
H	CH ₂ NH(CH ₂) ₂ NHCNHMc	CH ₂ NH(CH ₂) ₂ NHCNHMc		F	528
CH ₂ CHCO ₂ H NH ₂	$\begin{array}{c} \text{R} \\ \\ -\text{CH}- (\text{CH}_2)_2-\text{CH}- \\ \qquad \qquad \qquad \\ \text{R} \qquad \qquad \qquad \text{R} \end{array}$	(R = H, Cl)		N	528
CH ₂ CHCO ₂ H NH ₂	$\begin{array}{c} \text{Me} \\ \\ -\text{CH}- (\text{CH}_2)_2-\text{CH}_2 \\ \\ \text{Me} \end{array}$			N	528
CH ₂ CHCO ₂ H NH ₂	$\begin{array}{c} \text{Me} \\ \\ -\text{CH}- (\text{CH}_2)_2-\text{CH}- \\ \\ \text{Cl} \end{array}$			N	528
CH ₂ CHCO ₂ H NH ₂	$\begin{array}{c} \text{Cl} \\ \\ -\text{CH}- (\text{CH}_2)_2-\text{CH}- \\ \\ \text{Cl} \end{array}$			N	528
CH ₂ CHCO ₂ H NH ₂		X = Me, Et		N	528
CH ₂ CHCO ₂ H NH ₂		X = Me, Et		N	528
H	(X = H, Me, Cl)			Nitrile/LAH	522
H	Me, CF ₃	(CH ₂) ₂ NH ₂		M	152
H	Me, CF ₃	(CH ₂) ₂ NH(CH ₂) ₂ NH ₂		F	152
Ph	[R = Me, Et, (CH ₂) _n , NMe ₂]				191

TABLE 1.24. (Continued)

R ²	R ⁴	R ³	Method ^a	Reference
Ph	CH ₂ N[(CH ₂) ₂ OH] ₂	H	M	191
Ph	CH ₂ NR ₂ [R = Me, Et, -(CH ₂) ₅ -]	H	Amide/LAH	191
Ph	(CH ₂) ₂ NPhthl	H	M	52
Ph	(CH ₂) ₂ NH ₂	H	K	52
Ph			4-Aminoethyloxazole/HCHO/ HCO ₂ H	52
R ₂ NCH ₂ [R = Me, Et, (CH ₂) ₂ OH]	Ph	Ph	M	9
	Ph	Ph	M	9
R ₂ N(CH ₂) ₂ [R = Me, <i>i</i> -Pr, (CH ₂) ₂ OH]	Ph	Ph	M	529
	Ph	Ph	M	529
(X = CHMe, O)				
Me	H	CH ₂ N ⁺ Me ₃ Br ⁻	M	75
Ph	CH ₂ N ⁺ EtBr ⁻	H	M	191
Ph		H	M	191
4-XPh		H	M	150
MeCOCH=C(NH ₂)	H	Me	2-Cyanoethoxazole/acetone/ NaNH ₂	530
H	Me	CH ₂ CO ₂ H	Hydrolysis of nitrile	522
H	M ⁺	CH ₂ CO ₂ Me	O	522
H	Me	CH ₂ CN	Chloromethyloxazole/NaCN	522
C ₆ H ₁₁	CH ₂ CO ₂ H	H	Hydrolysis of nitrile	521
C ₆ H ₁₁	CH ₂ CN	H	Chloromethyloxazole/KCN	521
Ph	CH ₂ CN	H	Bromomethyloxazole/KCN	191
Ph			5-Acetyloxazol-4-ylacetic acid/NaBH ₄	531

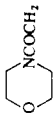
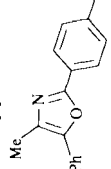
Ph	(CH ₃) ₂ CO ₂ H	H	Acrylic acid/H ₂ /Pd-C	191
Ph	PhCH ₂	(CH ₃) ₂ CO ₂ H	C	10
HO ₂ C(CH ₂) ₂	H	4-XPh (X = H, Br, Cl)	C	467
NC(CH ₂) ₂	Ph	H	P	532
NC(CH ₂) ₂	H	Ph	P	532
Ph	CH ₂ CH(CN)CO ₂ Et	Me	Olefin/Na(Hg)	254
Ph	CH ₂ CH(CN)CON ₃	Me	Ester/NaN ₃	254
Ph	CH ₂ CH(NH ₂)CN	Me	Azide/Δ	254
Ph	CH ₂ CH(NH ₂)CO ₂ H	Me	Hydrolysis of nitrile	254
2-HO ₂ CPh	Ph	CH(OMe)CO ₂ Et	PhCH ₂ COCH(Ac)CO ₂ Et/ NPhthl	533
2-HO ₂ CPh	Ph	CH ₂ CO ₂ H	NaOEt/EtOH	533
HO ₂ CCH ₂	Ph	Ph	Acetoacetate/NaOH	468
EtO ₂ CCH ₂	Ph	Ph	C	47
PhCHCN	Ph	Ph	O	128
H ₂ NOCCH ₂	Ph	Ph	2-Chlorooxazole/ PhCH ₂ CN/NaNH ₂	47
MeNHOCCH ₂	Ph	Ph	Acid/ <i>i</i> -BuOCOC/NH ₃	529
	Ph	Ph	Ester/MeNH ₂	529
H ₂ NCNHOCCH ₂	Ph	Ph	Ester/morpholine	529
HO ₂ C(CH ₂) ₂	Ph	Ph	Ester/guanidine	468
RO ₂ C(CH ₂) ₂	Ph	Ph	C	468
(R = Me, Et)	Ph	Ph	O	47
H ₂ NOC(CH ₂) ₂	Ph	Ph	Acid/ <i>i</i> -BuOCOC; then NH ₃	47
H ₂ NOC(CH ₂) ₂	4-ClPh	4-ClPh	Acid/EtOCOC; then NH ₃	534
H ₂ NOC(CH ₂) ₂	4-FPh	4-FPh	Acid/EtOCOC; then NH ₃	534
H ₂ NHOC(CH ₂) ₂	Ph	Ph	Ester/N ₂ H ₄	529
H ₂ N ⁺ HNOC(CH ₂) ₂	Ph	Ph	Ester/guanidine	468
NC(CH ₂) ₂	Ph	4-XPh (X = H, Cl)	P	532
NC(CH ₂) ₂	4-MeOPh	4-XPh (X = H, Cl)	P	532
NC(CH ₂) ₂	4-XPh (X = Me, Cl)	4-MeOPh (X = H, Cl)	P	532
NC(CH ₂) ₂	4-ClPh	4-ClPh	P	532
	Ph	Ph	Bromomethylloxazole/ethyl terphenylacetate/NaOH/PTC	151

TABLE 1.24. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
	CH ₂ CH(CO ₂ Et) ₂	Ph	Bromomethylloxazole/ diethylmalonate/NaOEt	151
	(CH ₂) ₂ CO ₂ H	Ph	Malonate/KOH; then H ⁺	151
	(CH ₂) ₂ CO ₂ Et	Ph	O	151
		Ph	Bromomethylloxazole/ terphenylacetonitrile/PTC	151
EtO ₂ CCH=CH	Ph	Ph	O	47
EtO ₂ C(CH ₂) ₃	Ph	Ph	O	47
H ₂ NOC(CH ₂) ₃	Ph	Ph	Acid/ <i>i</i> -BuOCOCl; then NH ₃	47
Ph			Q	532
C ₆ H ₁₁		H	Q	532
4-ClPh		H	Q	532
Ph		Ph	Q	532
Ph		H	Q	532

	Ph	H	Q	532
	H	Ph	Q	532
	Ph	4-XPh (X = H, Cl)	Q	532
	4-MeOPh	4-XPh (X = H, Cl, OMe)	Q	532
	4-ClPh	4-XPh (X = Cl, OMe)	Q	532

^aA = ester/LAH; B = acid chloride/NaBH₄; C = hydrolysis of ester; D = halomethylloxazole/alkoxide; E = alcohol/SOX₂ (X = Cl, Br); F = amine/isothiocyanate; G = amine/(MeS)₂C=NCN; H = N-cyano-S-methylisothiourea/MeNH₂; I = methylloxazole/N-bromosuccinimide; J = haloalkyloxazole/PhthN(CH₂)₂SH; K = phthalimide/H⁺; L = amine/(MeS)₂C=CHNO₂; M = haloalkyloxazole/amine; N = benzoxazole/H₂/PO₂; O = esterification of acid; P = amide/SOCl₂; Q = nitrile/NaN₃.

TABLE 1.25. HALOOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
Cl	<i>n</i> -Pr	<i>n</i> -Pr	A	128, 535
Cl	<i>i</i> -Pr	<i>i</i> -Pr	A	129
Cl	H	Ph	A	130
Cl	Ph	Et	A	128, 535
Cl	Alkyl ¹ , aryl ¹	Alkyl ¹ , aryl ¹	A	135
Cl	Ph	Ph	A	128, 535
I	Ph	Ph	B	131, 132
Cl	Me	(CH ₃) ₂ Cl	Alcohol/SOCl ₂	525
Me	Br	Ph	B	131
			C	143
Me	I	Ph	B	131, 132
Me	I	4-ClPh	B	132
Ph	Cl	Ph	D	140
			E	141, 142
			F	137
4-XPh (X = OMe, Me, Et, NO ₂ , OH)	Cl	Ph	F	137
Ph	Cl	4-O ₂ NPh	F	137
Ph	Cl	4-Cl ₃ CPh	F	138
4-Cl ₃ CPh	Cl	4-MeOPh	F	139
4-BrPh	Cl	4-BrPh	G	38
Ph	Br	Ph	B	131
			C	45, 143, 144
4-XPh (X = OMe, NO ₂)	Br	Ph	F	137
Ph	Br		F	137
Ph	I	4-O ₂ NPh	F	137
		Ph	B	131, 132

Me	<i>t</i> -Bu	Br	C	132
<i>n</i> -C ₅ H ₁₁	Me	I	B	132
4-XPh	CF ₃	F	(CF ₃) ₂ C=NCOR ² /SnCl ₂	147
(X = H, Me, F, Cl)				
H	Ph	Br	C	100, 132
Me	Ph	Br	C	100, 132, 143
Me	XPh	Br	C	132
	(X = 2- and 4-Cl, 2- and 4-Br, 4-F, 4-Me, 4-MeO, 4-NO ₂)			
Et	4-ClPh	Br	C	132
4-XPh	Me	Br	C	143
(X = H, 4-NO ₂)				
4-AcNHPh	Me	Br	C	148, 536
4-H ₂ NPh	Me	Br	Hydrolysis of amide	536
H	Ph	I	B	132
Me	XPh	I	B	132
	(X = H, 2- and 4-Cl, 2- and 4-Br, 4-F, 4-MeO, 4-Me, 4-NO ₂)			
Ph	Me	I	B	132
Ph	Ph	Br	B	131, 132
Ph	4-ClPh	Br	B	132
Ph	Ph	I	B	131, 132
Me	CH ₂ OH	Cl	Acid/B ₂ H ₆	152
Me	CH ₂ Cl	Cl	Alcohol/SOCl ₂	152
Me	CH ₂ S(CH ₂) ₂ NPhthl	Cl	Chloromethylloxazole/PhthlN(CH ₂) ₂ SH	152
Me	CH ₂ S(CH ₂) ₂ NH ₂	Cl	Phthalimide/HBr	152
Me	CH ₂ S(CH ₂) ₂ C(=S)NHMe	Cl	Amine/MeNCS	152

TABLE 1.25. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	CH ₂ S(CH ₂) ₂ CNHNHMe 	Cl	Amine/(MeS) ₂ C=NCN; then MeNH ₂	518-520
Me	CH ₂ S(CH ₂) ₂ CNHNHMe 	Cl	Amine/(MeS) ₂ C=CHNO ₂	233
Me	-CH ₂ S(CH ₂) ₂ NHCNH(CH ₂) ₂ SCH ₂ - 	Cl	Aminomethylthionitroethylene/ 	233
Me	CH ₂ S(CH ₂) ₃ NPhthl	Cl	Chloromethylloxazole/ PhthlN(CH ₂) ₃ SH	152
Me	CH ₂ S(CH ₂) ₃ NH ₂	Cl	Phthalimide/HBr	152
Me	CH ₂ S(CH ₂) ₃ NHCNHMe 	Cl	Amine/MeNCS	152
Me	CH ₂ NH(CH ₂) ₂ NH ₂	Cl	Chloromethylloxazole/ H ₂ N(CH ₂) ₂ NH ₂	152
Me	CH ₂ NH(CH ₂) ₂ NHCNHMe 	Cl	Amine/MeNCS	152
Ph	CH ₂ Cl	Cl	N-Benzoylalanine/PCl ₅ /120° C	146
Ph	CHCl ₂	Cl	N-Benzoylalanine/PCl ₅ /150° C	146
Ph	CH ₂ OMe	Cl	4-Chloromethyl- 5-chloroioxazole/NaOMe	146
Ph	CH ₂ N 	Cl	4-chloromethyl- 5-chloroioxazole/piperidine	146
Ph	CH ₂ Br	Br	4-Methylloxazole/Br ₂ /NBS	143
Ph	CH ₂ OEt	Br	4-Bromomethyl- 5-bromooxazole/NaOEt	153

4-XPh (X = H, Me, Br, Cl, NO ₂)	CH ₂ Cl	Br	4-Chloromethyloxazole/Br ₂	149]
Ph	CH ₂ SC(=NH ₂) NH ₂	Br	4-Bromomethyl- 5-bromooxazole/thiourea	153
Ph	CH ₂ NHPh	Br	4-bromomethyl- 5-bromooxazole/PhNH ₂	153

^aA = oxazolin-2-one/POCl₃; B = oxazoly1 mercuriacetate/X₂ (X = Br, I); C = oxazole/Br₂/NBS or Br₂/HOAc; D = N-benzoylaminoacetophenone/PCl₅; E = 1-benzoyl-2,2-dichloroaziridine/Δ; F = R²CHO/R⁵COCN/HX (X = Cl, Br); G = R²CHO/R³CH(OH)CN/HCl.

TABLE 1.26. OXAZOLE CARBOXYLIC ACIDS

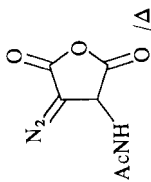
R ²	R ⁴	R ⁵	Method ^a	Reference
CO ₂ H	H	4-XPh (X = H, OMe, OH, Cl, NO ₂ , NH ₂ , SMe, SO ₂ Me, Ph, 4'-O ₂ NPh, 4'-H ₃ NPh)	A	155
CO ₂ H	H	Ph	A	155
CO ₂ H	Ph	Me	A	155
CO ₂ H	Ph	Ph	A	155
H	CO ₂ H	H	A	198
H	CO ₂ H	D	Acid/2-BuLi; then MeOD	166
Me	CO ₂ H	H	A	197, 198
Me	CO ₂ H	H	B	181
Me	CO ₂ H	H		203
Me	CO ₂ H	D	Acid/2-BuLi; then MeOD	166
<i>n</i> -C ₃ H ₁₁	CO ₂ H	H	A	3
C ₆ H ₁₁	CO ₂ H	H	A	521
PhCH ₂	CO ₂ H	H	A	165, 197, 198
PhCH ₂	CO ₂ H	H		255
PhCH ₂	CO ₂ H	H	C	3
<i>n</i> -C ₃ H ₇ , CH=CH	CO ₂ H	H	C	3
H	CO ₂ H	PhCH ₂	A	51
H	CO ₂ H	(CH ₂) ₆ CO ₂ H	A	172
H	CO ₂ H	(CH ₂) ₆ CO ₂ Me	D	172

TABLE 1.26. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	CO ₂ H	4-O ₂ NPh	$\begin{array}{c} \text{AcNH} \\ \\ \text{CH} \\ \\ \text{C}=\text{C} \\ \quad \\ \text{4-O}_2\text{NPh} \quad \text{Br} \\ \parallel \\ \text{O} \end{array}$ /base	7
Ph	CO ₂ H	Ph	A	160, 174
			B	180
Ph	CO ₂ H	2-HO ₂ -CPh	A	174
H	Me	CO ₂ H	A	182, 522
H	(CH ₂) ₆ CO ₂ H	CO ₂ H	A	184
H	(CH ₂) ₆ CO ₂ Me	CO ₂ H	D	184
Me	Me	CO ₂ H	A	182, 264
PhCH ₂	Me	CO ₂ H	A	182
Ph	Ph	CO ₂ H	A	484
H	$\begin{array}{c} \text{CO}_2\text{H} \\ \\ \text{N} \\ \\ \text{C} \\ \\ \text{O} \end{array}$	CO ₂ H	A	30

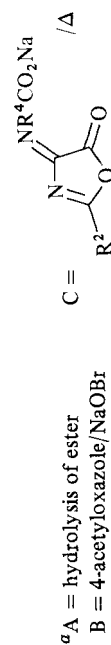


TABLE 1.27. OXAZOLE DICARBOXYLIC ACIDS

R ²	R ⁴	R ⁵	Method ^a	Reference
H	CO ₂ H	CO ₂ H	A	188
Me	CO ₂ H	CO ₂ H	A	182
PhCH ₂	CO ₂ H	CO ₂ H	A	182
Ph	CO ₂ H	CO ₂ H	B	190
2- and 3-thienyl	CO ₂ H	CO ₂ H	A	189

^aA = hydrolysis of diester; B = oxazolocycloheptatriene/KMnO₄.

TABLE 1.28. OXAZOLE CARBOXYLIC ESTERS

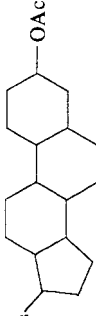
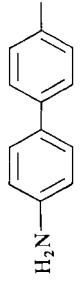
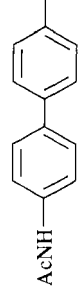
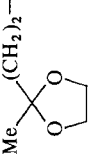
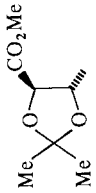
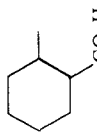
R ²	R ⁴	R ⁵	Method ^a	Reference
CO ₂ Et	H	Me	A	156, 537
CO ₂ Et	H	PhCH ₂	A	156, 537
CO ₂ Et	H ₁₈ C ₈		2-Azidoketone/ EtO ₂ CCl/Ph ₃ P	72
CO ₂ Et	H	Ph	A	537
CO ₂ Et	H	4-XPh (X = OMe, OH, PhCH ₂ O, Cl, NO ₂ , SMe, Ph, 4'-O ₂ NPh)	A	155
CO ₂ Et	H	4-H ₂ NPh	Reduction of nitrophenyloxazole	155
CO ₂ Et	H		Reduction of nitro biphenylyloxazole	155
CO ₂ Et	H	4-AcNHPh	Acetylation of anilinoxazole	155
CO ₂ Et	H		Acetylation of aminobiphenylyloxazole	155
CO ₂ Et	H	4-MeO ₂ SPh	Oxidation of methylthiophenyloxazole	155
CO ₂ Et	Me	Ph	A	155
CO ₂ Et	Ph	Me	A	155
CO ₂ R	Ph	Ph	A	468
(R = Me, Et)				
H	CO ₂ Et	H	B	195, 198
			C	30

TABLE 1.28. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
H	CO ₂ Me	RCHOCH ₂ OMe (R = Me, Et, Ph)	C	171
H	CO ₂ Et	Me ₂ COCH ₂ OMe	C	171
H	CO ₂ Et	$ \begin{array}{c} \text{OR}^6 \quad \text{OR}^8 \\ \quad \\ \text{R}^6\text{OCH}_2\text{CHCHCH}- \\ \quad \\ \text{OR}^7 \quad \text{OR}^9 \end{array} $	C	545
		(R ⁶ -R ⁹ = alkyl, acetyl)		
H	CO ₂ Et		C	544
H	CO ₂ Me	HO ₂ C(CH ₂) _n (n = 2, 3)	C	543
H	CO ₂ Me		C	169
H	CO ₂ Me		C	546
H	CO ₂ Et	MeO ₂ C(CH ₂) ₂	C	171
H	CO ₂ Me	BocNHCHR	C	169, 171
		(R = H, Me, <i>i</i> -Pr, <i>t</i> -Bu, PhCH ₂ , Boc = CO ₂ - <i>t</i> -Bu)		

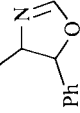
H	CO ₂ Me	BocNHCHR [R = 4-(PhCH ₂ O)PhCH ₂ , 3-indolylmethyl, MeS(CH ₂) ₂ , Boc = CO ₂ - <i>t</i> -Bu] PhCH ₂ CO ₂ NHCHCH ₂ Ph PhCH ₂ O ₂ CNHCH- <i>t</i> -BuOH ₂ C PhCH ₂ O ₂ CNHCH HOH ₂ C PhCH ₂ O ₂ CNHCH <i>t</i> -BuCOH ₂ C C≡NCH ₂ - C≡NCHR (R = Me, Et, <i>i</i> -Pr, <i>n</i> -C ₆ H ₁₃ , CH ₂ =CHCH ₃ , MeCH=CHCH ₃ , PhCH ₂) 	C	169
H	CO ₂ Me		C	171
H	CO ₂ Me		C	170
H	CO ₂ Me		<i>t</i> -Butyl ether/TFA	170
H	CO ₂ Me		Alcohol/ <i>t</i> -BuCOCl	170
H	CO ₂ R (R = Me, Et) CO ₂ Me		C	30
H			5-Isocyanomethylloxazole/ base; then RX	30
H	CO ₂ Me		5-Isocyanomethylloxazole/ base; then RX	30
Me	CO ₂ Et	Me	A	174, 257, 263
Me	CO ₂ Me	Me	D	91
			F	74

TABLE 1.28. (Continued)

R ²	R ⁴	R ⁵	Method ^d	Reference
Me	CO ₂ R (R = Et, <i>t</i> -Bu)	Me	$\begin{array}{c} \text{AcNH} \\ \\ \text{C} = \text{C} \\ \quad \\ \text{RO}_2\text{C} \quad \text{Me} \\ \\ \text{Br} \end{array}$	162
Me	CO ₂ <i>t</i> -Bu	Et	$\begin{array}{c} \text{Et}_3\text{N} \\ \\ \text{AcNH} \\ \\ \text{C} = \text{C} \\ \quad \\ \text{Et} \quad \text{Br} \\ \\ \text{t-BuO}_2\text{C} \end{array}$	162
C ₆ H ₁₁	CO ₂ Et	Me	Et ₃ N	158
PhCH ₂	CO ₂ Et	Me	A	174
PhCH=CH ₂	CO ₂ Et	Me	A	174
Me	CO ₂ Et	Ph(CH ₂) ₂ CHCH ₂ Ph	A or G	260, 542
Me	CO ₂ Et	2-XPh(CH ₂) ₂ (X = H, Cl)	G	260, 542
Me	CO ₂ Et	Ph ₂ CHCH ₂	G	260, 542
MeCH— OCH ₂ Ph MeCHOH	CO ₂ Me	Me	A	157
Me	CO ₂ R (R = Me, Et)	Me	Benzyl ether/H ₂ /Pd-C	157
Me	CO ₂ Et	CF ₃	F	167
Ph	CO ₂ Et	CF ₃ , C ₂ F ₅ , C ₃ F ₇	F	168
Ph	CO ₂ Et	H	A	174
Ph	CO ₂ Me	H	B	3, 195
H	CO ₂ Me	H	D	91
	CO ₂ Me	Ph	C	169, 543, 547

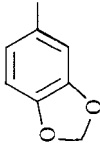
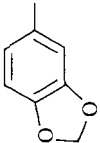
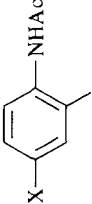
H	CO ₂ Et	Ph	C	102, 544
H	CO ₂ CH ₂ Ph	Ph	C	547
H	CO ₂ Me	XPh (X = 4-NO ₂ , 3,5-diNO ₂)	C	30
H	CO ₂ Me	XPh (X = 3,4-diCl, 3,4,5-triOMe)	C	543, 547
H	CO ₂ Me		C	543, 547
H	CO ₂ Me	2-Naphthyl	C	543, 547
H	CO ₂ Et	XPh (X = 4-NO ₂ , 3,5-diNO ₂)	C	30
H	CO ₂ CH ₂ Ph	XPh (X = 3,4-diCl, 3,4,5-triOMe)	C	547
H	CO ₂ CH ₂ Ph		C	547
H	CO ₂ CH ₂ Ph	2-Naphthyl	C	547
H	CO ₂ Me	2-HO ₂ CPh	C	546, 548
H	CO ₂ Me		C	549
H	CO ₂ Me	(X = H, OMe, Me, Cl)	C	549
H	CO ₂ Me	2-EtCONHPh	C	171
H	CO ₂ Me	2-MeOCH ₂ OPh	C	30
H	CO ₂ Me	PhCH=CH	C	30

TABLE 1.28. (Continued)

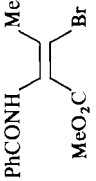
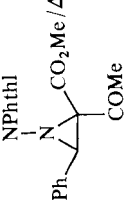
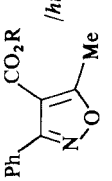
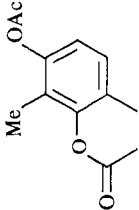
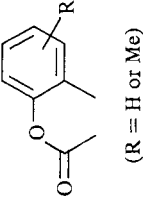
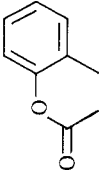
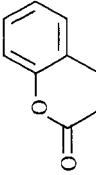
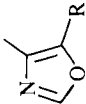
R ²	R ⁴	R ⁵	Method ^a	References
Ph	CO ₂ Me	Me	 Δ or Ag F	160
Ph	CO ₂ Me	Me	 Δ	177
Ph	CO ₂ Et	Me	A	3, 158, 174
Ph	CO ₂ R (R = Et, CF ₃ CH ₂ , )	Me	 $h\nu$	176
XPh (X = 2-, 3-, and 4-F, 4-Cl) 4-XPh	CO ₂ Et	Me	A	158
XPh (X = H, Cl, Br) 4-XPh (X = H, Cl, Br) Me	CO ₂ Et CO ₂ Et CO ₂ Et CO ₂ Et	CH ₂ Br PhOCH ₂ PhSCH ₂ Ph	Ethyl 5-methyloxazole-4-carboxylate/NBS Ethyl 5-bromomethyloxazole-4-carboxylate/PhONa Ethyl 5-bromomethyloxazole-4-carboxylate/PhSNa A	261 261 261 174

TABLE 1.28. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Me			J	553
Me, Et		 (R = H or Me)	J	179
XPh (X = H, 4-OMe, 4-OH, 3-NO ₂ , 2,4-diCl, 4-NMe ₂ , 3-OMe-4-OH)			K	179
2-Ethoxy-1-naphthyl, 9-anthryl			K	554
H	CO ₂ Me	 (R = Me, Ph)	C	30

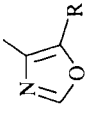
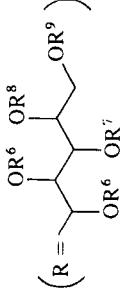
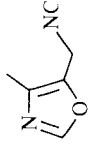
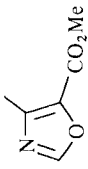
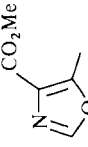
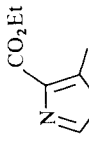
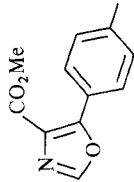
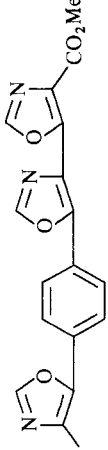
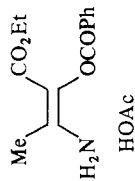
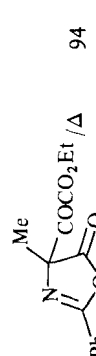
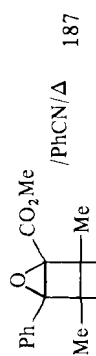
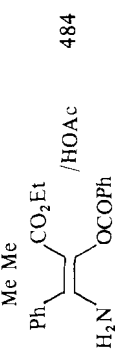
H	CO ₂ Et		C	545
				
H	CO ₂ Et		C	30
H	CO ₂ Me		C	30
H	CO ₂ Me		C	30
H	CO ₂ Et		C	30
H	CO ₂ Et		C	30

TABLE 1.28. (Continued)

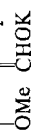
R ²	R ⁴	R ⁵	Method ^a	Reference
H	CO ₂ Me		C	30
H	CO ₂ Me		C	30
Me	H	CO ₂ Et	L	186
H	Me	CO ₂ Me	M	509
H	Me	CO ₂ Me	M	182, 200, 263, 522, 555, 556
H	Me	CO ₂ - <i>n</i> -Bu	M	556
H	MeO ₂ C(CH ₂) ₆	CO ₂ Me	M	184
Me	Me	CO ₂ Et	M	182
Me	Me	CO ₂ (CH ₂) _n NMe ₂ (<i>n</i> = 2, 3, 4)	Acid chloride/alcohol	557
Me	Me	CO ₂ (CH ₂) _n N ⁺ Me ₃ I ⁻	Amine/Mel	557
PhCH ₂	Me	CO ₂ Et	M	182
Ph	H	CO ₂ Et	L	186
Ph	Me	CO ₂ Me	M	497
Ph	Me	CO ₂ Et	M	158
Ph	Me	CO ₂ Et		183

Ph	Me	CO ₂ Et		94
Ph	Ph	CO ₂ Me		187
Ph	Ph	CO ₂ Et		484

^aA = R²CONHCH(R⁴)COR⁵/SOCl₂ or POCl₃
 B = R²C=NCCO₂R⁶/HOAc/ Δ



C = C=NCH₂CO₂R/R⁵COX or anhydride/base or C=NCH₂CO₂R/R⁵CO₂H/(EtO)₂POCN
 D = 2-oxazoline/NiO₂
 E = MeC=NCCO₂Me/*t*-BuLi; then E⁺; then HOAc/ Δ



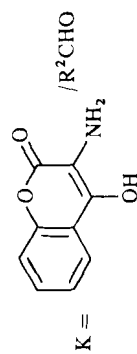
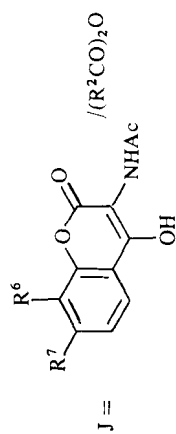
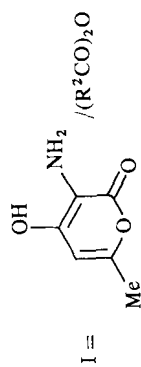
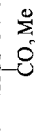
F = R²CN/R⁵COCCO₂R/Lewis acid or *h* ν



G = R⁵COCCO₂Et/Ac₂O/HgCl₂/NaOAc/Zn/HOAc



H = R²CONHCHCO-3-indolyl/DDQ/THF



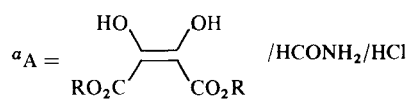
L = R²CN/N₂CHCOCO₂Et/CuAcAc

M = NH₂O₂CR or R²CONH₂/

R⁴COCH(X)CO₂R (X = Cl, O₂CR²)

TABLE 1.29. OXAZOLE DICARBOXYLIC ESTERS

R ²	R ⁴	R ⁵	Method ^a	Reference
H	CO ₂ Me	CO ₂ Me	A	188
			B	30
H	CO ₂ Et	CO ₂ Et	A	188
Me	CO ₂ Et	CO ₂ Et	C	158, 182
C ₆ H ₁₁	CO ₂ Et	CO ₂ Et	C	158
PhCH ₂	CO ₂ Et	CO ₂ Et	C	182
XPh	CO ₂ Et	CO ₂ Et	C	158
(X = H, 4-OMe, 3- and 4-Me, 4- <i>t</i> -Bu, 4-Cl, 2-, 3- and 4-F, 3-CF ₃)				
2- and 3-thienyl	CO ₂ Et	CO ₂ Et	D	189



B = C=NCH₂CO₂Me/ClCO₂Me/base

C = R²C=NCCO₂R/HOAc/Δ

OR' C(OK)CO₂R

D = R²CONH₂/EtO₂CCOCH(Cl)CO₂Et/Δ

TABLE 1.30. OXAZOLE CARBOXYLIC ACID CHLORIDES^a

R ²	R ⁴	R ⁵	Reference
H	COCl	H	193
<i>n</i> -C ₅ H ₁₁	COCl	H	3
PhCH ₂	COCl	H	3, 165, 255
H	COCl	MeO ₂ C(CH ₂) ₆	172
C ₆ H ₁₁	COCl	Me	158
Me	COCl	2-XPh(CH ₂) ₂ (X = H, Cl)	260, 542
Me	COCl	Ph ₂ CHCH ₂	260, 542
Ph	COCl	Me	158, 259
XPh (X = 2-, 3-, and 4-F, 4-Cl)	COCl	Me	158
4-XPh (X = H, Cl, Br)	COCl	PhOCH ₂	261
4-XPh (X = H, Cl, Br)	COCl	PhSCH ₂	261
H	Me	COCl	328
H	MeO ₂ C(CH ₂) ₆	COCl	184
Me	Me	COCl	264, 557

^aPrepared from the acid and a chlorinating agent, for example, SOCl₂, (COCl)₂, or PhSO₂Cl.

TABLE 1.31. OXAZOLE CARBOXAMIDES

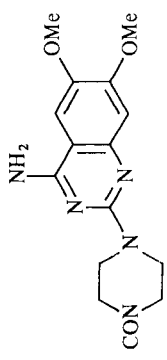
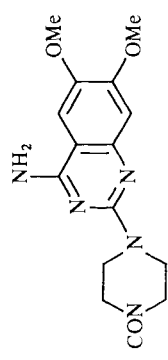
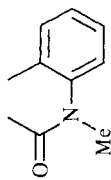
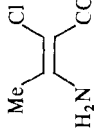
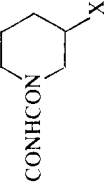
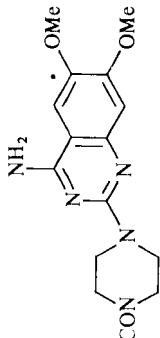
R ²	R ⁴	R ⁵	Method ^d	Reference
CONH ₂	H	Me	A	156
CONH ₂	H	PhCH ₂	A	156
CONH ₂	H	Ph	A	156, 196
CONH ₂	H	4-O ₂ NPh	Nitration of phenyloxazole carboxamide	196
CONH ₂	H	4-H ₂ NPh	Reduction of nitrophenyloxazole	196
CONHPh	H	Ph	B	196
CONHC(=NH) ₂	Ph	Ph	A	468
CONEt ₃	Ph	Ph	A	529
H	CONH ₂	H	A	195
H		H	C	558
Me	CONH ₂	H	A	195
Me	CONHPh	H	B	197
Me		H	C	558
PhCH ₂	CONHCH ₂ Ph	H	A	3
PhCH ₂	CONHPh-4-X	H	B	197

TABLE 1.31. (Continued)

R ²	R ⁴	R ⁵	Method ^c	Reference
Ph	CONHCNH ₂ 	H	C	191
Ph	CONEt ₂	H	C	191
Ph	CON(CH ₂ CH ₂ OH) ₂	H	C	191
Ph	CON 	H	C	191
XPh (X = H, 4-Cl, 2-, 3-, 4-F)	(X = CH ₂ , O) CONH ₂	Me	C	158
2-FPh	CONHEt	Me	C	158
H			<i>N</i> -Methylisatoic anhydride/ CNCH ₂ CO ₂ Et/NaH	562
H	Me	CONH ₂	A	195
H	Me	CONH ₂		185
H	Me	CONH- <i>t</i> -Bu	HCONH ₂ /NH ₄ O ₂ CH/ ZnCl ₂ /HCO ₂ H/Δ MeCOCHClCONH- <i>t</i> -Bu/ HCONH ₂ /NH ₄ O ₂ CH/ HCO ₂ H/Δ	185
H	Me	CONHCONHR (R = H, <i>n</i> -Pr, C ₈ H ₁₁ , 1-naphthyl)	G	563

H	Me	CONHCONMe ₂	G	563
H	Me	CONHCON(Me) C ₅ H ₉	G	563
H	Me	CONHCON(CH ₂ Ph)- <i>n</i> -Bu	G	563
H	Me	CONHCON(Ph)Et	G	
H	Me	CONHCON 	G	563
		(X = H, Cl)		
H	Me	CONHCON-(CH ₂) ₃ Ph	G	563
H	Me	CONHCON 	G	543
H	Me	CONHCON 	G	563
H	Me	CON-Cl Na ⁺	Amide/NaOCl/NaOH	328
H	Me	CON 	C	558
Ph	Me	CONH ₂	A	158
Ph	Ph	CONH(CH ₂) ₃ NMe ₂	Acid/(COCl) ₂ ; then Me ₂ N(CH ₂) ₃ ·H ₂	46

^aA = ester/R⁶R⁷NH

B = acid/POCl₃; then R⁶R⁷NH

C = acid chloride/R⁶R⁷NH

D = acyl azide/R⁶R⁷NH

E = PhCH₂CONHCH(CHO)CONHR/SOCl₂

F = PhCH₂CONHCCONHR/*hν*

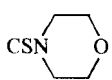
G = amide/(COCl)₂; then R⁶R⁷NH

TABLE 1.32. OXAZOLE DICARBOXAMIDES

R ²	R ⁴	R ⁵	Method ^a	Reference
H	CONH ₂	CONH ₂	A	188
H	CONHMe	CONHMe	A	188
H	CONH <i>i</i> -Pr	CONH <i>i</i> -Pr	A	188
H	CONHCH ₂ Ph	CONHCH ₂ Ph	A	188
H	CONHPh	CONHPh	A	188
Me	CONH ₂	CONH ₂	A	158
C ₆ H ₁₁	CONH ₂	CONH ₂	A	158
XPh	CONH ₂	CONH ₂	A	158
(X = H, 3- and 4-OMe, 4-Me, 4- <i>t</i> -Bu, 4-Cl, 2-, 3-, and 4-F, 3-CF ₃)				
Ph	CONHMe	CONHMe	A	158
Ph	CONHEt	CONHEt	A	158
Ph	CONH <i>i</i> -Pr	CONH <i>i</i> -Pr	A	158
Ph	CONMe ₂	CONMe ₂	A	158
Ph	CONEt ₂	CONEt ₂	A	158
Ph	CON- <i>n</i> -Pr ₂	CON- <i>n</i> -Pr ₂	A	158

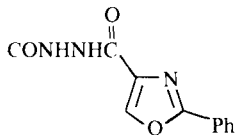
^aA = diester/R⁶R⁷NH.

TABLE 1.33. OXAZOLE THIOAMIDES

R ²	R ⁴	R ⁵	Method ^a	Reference
CSNH ₂	H	Ph	A	196
CSNH ₂	H	4-H ₂ NPh	B	196
CSNH ₂	H	4-AcHNPh	Acetylation of anilinoxazole	196
CSNHPh	H	Ph	C	196
H	CSNH ₂	H	A	195
Me	CSNH ₂	H	A	195
Me	CSNHPh	H	C	197
PhCH ₂	CSNHPh-4-X (X = H, Me)	H	C	197
PhCH ₂	CSN 	H	C	197
Ph	CSNH ₂	H	A	195
Ph	CSNHPh	H	C	197
H	Me	CSNH ₂	A	195

^aA = nitrile/H₂S; B = amide/H₂S/Et₃N; C = amide/P₂S₅.

TABLE 1.34. OXAZOLE CARBOXYLIC ACID HYDRAZIDES AND OXAZOLOYL AZIDES

R ²	R ⁴	R ⁵	Method ^a	Reference
CONHNH ₂	H	H	A	538
CONHNH ₂	H	4-XPh (X = H, OMe, OH, OCH ₂ Ph, Cl, NO ₂ , SO ₂ Me)	A	539, 540
CONHNMe ₂	Ph	Ph	A	529
CONHN=CCO ₂ H Me	H	H	Hydrazide/ levulinic acid	538
PhCH ₂	CONHNH ₂	H	A	3, 560
Ph	CONHNHPh	H	B	192
Ph	CONHNHPh-2,4-diNO ₂	H	B	192
Ph	CONHNCOPh	H	B	192
Ph		H	B	192
Ph	CONHN=CHPh	H	Acid chloride/ hydrazine/ PhCHO	192
H	Me	CONHNH ₂	A	328
Me	Me	CONHNHSO ₂ Ph- 4-Me	B or hydrazide/ ArSO ₂ Cl	256
H	CONHNH ₂	CONHNH ₂	A	188
PhCH ₂	CON ₃	H	C	3, 559, 560
H	Me	CON ₃	C	328

^aA = ester/R₂NNH₂ (R = H, Me); B = acid chloride/RNHNH₂ (R = XPh, PhCO, XPhSO₂); C = hydrazide/NaNO₂/HCl.

TABLE 1.35. CYANOOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
CN	H	Me	A	156
CN	H	PhCH ₂	A	156
CN	H	Ph	A	156, 196
CN	H	4-O ₂ NPh	Nitration of phenyloxazole	196
CN	H	4-XPh (X = H, Cl, NO ₂)	Oxime/Ac ₂ O/NaOAc (X = H, Cl, NO ₂)	541
H	CN	H	A	195
Me	CN	H	A	195
PhCH ₂	CN	H	B	165
Me	CN	<i>n</i> -Bu	C	163
Ph	CN	H	A	195
Me	CN	Ph	C	163
Ph	CN	Ph	D	177
H	Me	CN	A	185, 195, 555, 564–567

^aA = amide/P₂O₅B = $\text{R}^2\text{C}=\text{N}\overset{\text{OMeCHO}^-\text{K}^+}{\underset{\text{K}^+}{\text{C}}}\text{CN}/\text{HOAc}/\Delta$ C = AcNHCCN/Ag₂CO₃/MeCN $\text{C}(\text{SR})\text{R}^5$

NPhthl

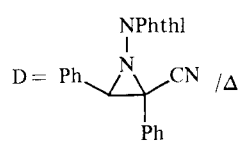
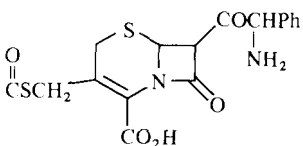
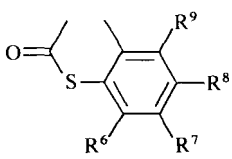
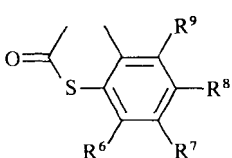


TABLE 1.36. OXAZOLE THIOESTERS

R ²	R ⁴	R ⁵	Method ^a	Reference
Me		H	A	194
Me	 (R⁶ = R⁷ = R⁸ = R⁹ = H, R⁶ = R⁷ = R⁹ = H, R⁸ = Me R⁶ = Me, R⁷ = R⁸ = R⁹ = H)		B	179
Et	 (R⁶ = R⁷ = R⁸ = R⁹ = H, R⁶ = R⁷ = R⁹ = H, R⁸ = Me, R⁶ = Me, R⁷ = R⁸ = R⁹ = H)		B	179

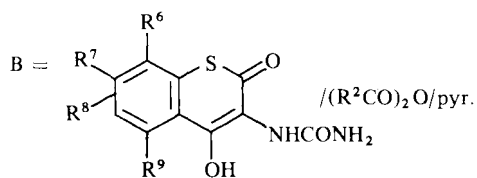
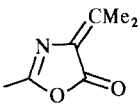
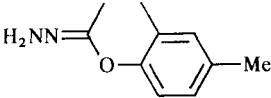
^aacid chloride/thiol

TABLE 1.37. OXAZOLE CARBOXIMIDATES AND CARBOXAMIDINES

R ²	R ⁴	R ⁵	Method ^a	Reference
$\begin{array}{c} \text{NH} \\ \parallel \\ \text{C}=\text{OMe} \end{array}$	H	4-XPh (X = H, Cl, NO ₂)	Nitrile/NaOMe	541
PhCH ₂		H	A	164
3- and 4-MePh			Lactone/N ₂ H ₄	568
$\begin{array}{c} \text{NH} \\ \parallel \\ \text{C}-\text{NH}_2 \end{array}$	H	4-XPh (X = H, Cl, NO ₂)	Imidate/NH ₃	541

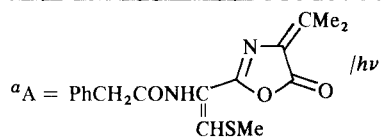


TABLE 1.38. MIXED DIFUNCTIONAL OXAZOLE CARBOXYLIC ACID DERIVATIVES

R ²	R ⁴	R ⁵	Method ^a	Reference
PhCH ₂	CN	CO ₂ Et	A	182
PhCH ₂	CN	CO ₂ H	Ester/KOH/MeOH; then H ⁺	182
PhCH ₂	CONH ₂	CO ₂ H	Cyanooxazole carboxylate/ NaOH/H ₂ O/Δ; then H ⁺	182
PhCH ₂	CSNH ₂	CO ₂ Et	Nitrile/H ₂ S	182
PhCH ₂	CSNH ₂	CO ₂ H	Ester/NaOH/EtOH; then H ⁺	182

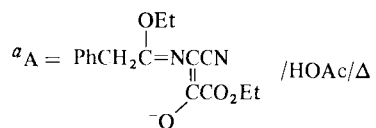


TABLE 1.39. FORMYLOXAZOLES

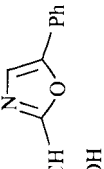
R ²	R ⁴	R ⁵	Method ^a	Reference
<i>n</i> -C ₅ H ₁₁	CHO	H	A	3, 507
PhCH ₂	CHO	H	A or B	165, 255
H	CHO	(CH ₂) ₆ CO ₂ Me	C	172
Ph	CHO	H	A	165
4-XPh (X = H, Me, Br, Cl, NO ₂)	CHO	H	C, D, E	150
3-Thienyl	CHO	H	F	189
Ph	CHO	Me	G	254
Me	CH(OAc) ₂	4-O ₂ NPh	H	7
H	(CH ₂) ₆ CO ₂ Me	CHO	C	172
Me	Me	CHO	I	256

^aA = acid chloride/H₂/Pd-BaSO₄/thioureaB = nitrile/SnCl₂/HCl; then H₂OC = alcohol/Na₂Cr₂O₇/H⁺ or CrO₃ · PyrD = chloromethyloxazole/hexamethylenetetramine;
then HOAC

E = 4-formyl-5-bromooxazole/Zn/HCl

F = chloromethyloxazole/*i*-PrNO₂/
NaOEt/DMSO/EtOHG = 2-phenyl-5-methyloxazole/
HCON(Ph)Me/POCl₃H = AcNHCCOPh-4-NO₂/Ac₂O/H₂SO₄
||
CHBrI = *p*-toluenesulfonylhydrazide Li⁺
salt/Δ

TABLE 1.40. KETOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
CO(CH ₂) ₃ OEt	H	Me, PhCH ₂	A	156
CO(CH ₂) ₃ OEt	H	Ph	A	156
COCH ₂ CHCH ₂ OMe Me	H	Ph	A	156
COC(CH ₂ Ph) ₂ (CH ₂) ₂ OEt	H	Ph	Ketone/NaH; then 2 PhCH ₂ Br	156
COCH(Br)(CH ₂) ₂ OEt	H	Ph	Ketone/PhN ⁺ Me ₃ Br ⁻	156
COCH OH 	H	Ph	2-(4-Ethoxybutyryl)-5-phenyloxazole/NaH	156
Me	COMe	H	Ketoester/DABCO	181
Me	COCH ₂ CO ₂ Et	H	Ester/NaH/EtOAc	181
PhCH ₂	COCONH ₂	H	Acid chloride/HCN; then HCl	258
Me	COMe	Me	B	257
Me	COMe	Me	C	259
Me	COMe	Me	D	259
Me	COCH ₂ Cl	Me	Methyl ketone/SOCl ₂	266
Me	COCH ₂ SMe	Me	Chloroketone/NaSMe	266
Me	COCH(Cl)SMe	Me	Methylthio ketone/SO ₂ Cl ₂	266
Me	COCH(OH) ₂	Me	Methyl ketone/SeO ₂	265
Me	COCH=NPh-4-X (X = CO ₂ H, SO ₂ NH ₂)	Me	E	265
Me	COCH=NOH	Me	E	265
Me	COCH=NNHCNH ₂ 	Me	E	265

(X = O, S)

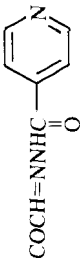
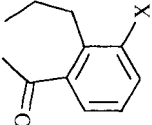
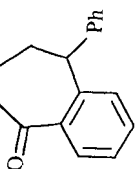
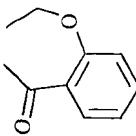
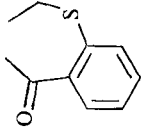
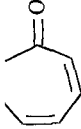
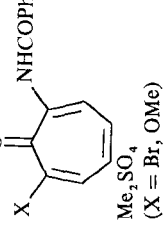
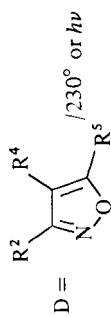
Me		Me	E	265
Me			F	260, 542
Me			F	260, 542
Ph	COMe	Me	D	176, 259
Ph	COMe	Me	G	177
4-XPh (X = H, Cl, OMe, NO ₂)	COMe	Me	H	180
Ph	COPh	Me	Acid chloride/Ph ₃ Cd	259
PhCH=CH	COMe	Me	H	180
Me	COPh	Ph	(PhCO) ₂ C=N ₂ / MeCN/BF ₃ ·Et ₂ O	74
Me	COPh-4-NO ₂	4-XPh (X = H, OMe)	I	7
4-XPh (X = H, Cl, Br)			F	261

TABLE 1.40. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
4-XPh (X = H, Cl, Br)			F	261
Ph	COMe	Ph	H	180
Ph	COMe	Ph	D	259
Ph	COMe	Ph	G	177
Ph	COPh	Ph	G	177
H	Me	COMe	J	262, 263
Me	Me	COMe	J	262
Me	Me	COPh	Acid chloride/PhH/AlCl ₃	264
Ph	Me	COMe	J	262
Ph	Me	COMe	K	183
Ph	CH ₂ Br	COMe	4-Me-5-Ac-oxazole/NBS	531
Ph	CH ₂ CN	COMe	4-Bromomethyl- 5-oxazole/HCN/KCN	531
Ph	CH ₂ CO ₂ Me	COMe	4-Cyanomethyl- 5-oxazole/HCl/MeOH	531
Ph	CH ₂ CO ₂ H	COMe	Ester/HCl/HOAc	531
Ph				190

^aA = nitrile/Grignard
 B = AcNHCH(COMe)₂/SOCl₂
 C = MeC(COMe)/Ac₂O/NaOAc/HgCl₂/Zn/HOAc



E = hydrated ketoaldehyde/RNH₂
 F = acid chloride/AlCl₃

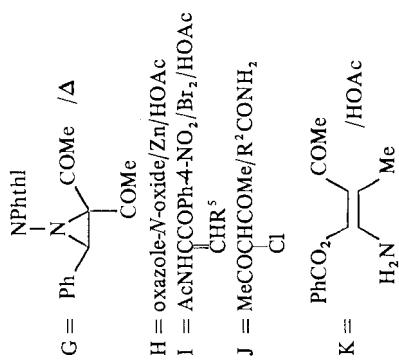
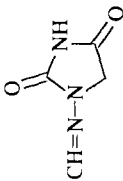
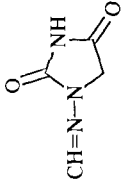
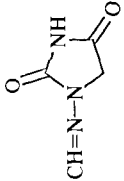


TABLE 1.41. OXAZOLE ALDIMINES AND KETIMINES

R ²	R ⁴	R ⁵	Method ^a	Reference
CH=NOH 	H	H	2-Methylloxazole/ NaNH ₂ ; then <i>n</i> -C ₈ H ₁₁ ONO	156
CH=N-N-N 	H	4-XPh (X = H, OMe, Me, F, Cl, Br, NO ₂)	A	253
CH=N-N-N 	H	XPh (X = 3-CF ₃ , 3,4-diCl)	A	253
Ph	CH=NOH	Me	B	254
Ph	CH=NNHPh-2,4-diNO ₂	Me	B	254
Me	C=NNHCO-4-pyridyl	Me	B	265
Me	CH=NNHCO-4-pyridyl	Me	B	265
Me	C=NNHCONH ₂	Me	B	265
H	CH=NNHCONH ₂	MeC=NOH	B	262
Me	Me	MeC=NOH	B	262
Me	Me	MeC=NNHPhX	B	262
Me	Me	(X = H, 2,4-diNO ₂) MeC=NNHC(=S)NH ₂	B	262
Me	Me	MeC=NNHSO ₂ -4-Tol	B	509
Ph	Me	MeC=NOH	B	262

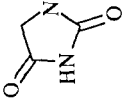
^aA =  NN=CHCONHCH₂COR⁵/POCl₃ B = formyl- or keto-oxazole/RNH₂

TABLE 1.42. ALKOXY- AND ARYLOXYOXAZOLES

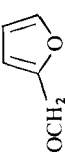
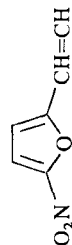
R ²	R ⁴	R ⁵	Method ^a	Reference
OEt	Me	H	A	569
OMe	Me	Me	B	570
OEt	Et	Et	B	570
OMe	<i>n</i> -Pr	<i>n</i> -Pr	A	128
OEt	Ph	H	B	202
OMe	Ph	Et	A	128
OCH ₂ CO ₂ Et	H	4-ClPh	A	135
OCH ₂ CO ₂ Et	H	4-ClPh	C	135
OCH ₂ CO ₂ Et	Me	4-ClPh	A	135
OCH ₂ CO ₂ H	Me	4-ClPh	C	135
OMe	Ph	Ph	A	128
OMe	Ph	Ph	B	202
OEt	Ph	Ph	A	128
OEt	Ph	Ph	B	202
<i>O</i> - <i>n</i> -Pr	Ph	Ph	B	202
OCH ₂ CH=CH ₂	Ph	Ph	A	134
OCH ₂ CH=CHMe	Ph	Ph	A	134
OCH ₂ CH=CMe ₂	Ph	Ph	A	134
	Ph	Ph	A	134
OCH ₂ CO ₂ Et	Ph	Ph	A	135
OCH ₂ CO ₂ H	Ph	Ph	C	135
OCH ₂ CO ₂ Et	4-ClPh	4-ClPh	A	135
OCH ₂ CO ₂ H	4-ClPh	4-ClPh	C	135
OCH(R)CO ₂ Et (R = H, Me)	4-MeOPh	4-MeOPh	A	135
OCH(R)CO ₂ H (R = H, Me)	4-MeOPh	4-MeOPh	C	135

TABLE 1.42. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Ph	OR	H	D	206
4-O ₂ NPh	OR	(R = Me, Et)		
H	H	H	D	206
H	H	OEt	E	571
	H	OEt	5-Ethoxyoxazole-2-carboxylic acid/100°C	572
H	H	OEt	F	221
Me	H	OEt	E	263, 571
Me	H	OEt	G	73, 74, 573
Et	H	OEt	E	263
<i>n</i> -Pr	H	OEt	E	263
<i>i</i> -Pr	H	OEt	H	71
<i>n</i> -Bu	H	OEt	E	263
<i>t</i> -Bu	H	OEt	E	419
<i>n</i> -C ₃ H ₁₁	H	OR	E	3
		(R = Me, Et)		
<i>n</i> -C ₃ H ₁₁	H	OEt	E	263
<i>n</i> -C ₃ H ₁₁	H	OMe	G	217
PhCH ₂	H	OEt	G	73, 217, 573
PhCH ₂	H	OR	E	3
		(R = Me, Et)		
PhCH ₂	H	OSiMe ₃	I	214
CH ₂ =CH	H	OEt	G	218
MeCH=CH	H	OEt	G	218
<i>n</i> -C ₃ H ₇ CH=CH	H	OR	E	3
		(R = Me, Et)		
PhCH=CH	H	OEt	E	3, 263
PhCH=CH	H	OCH ₂ Ph	E	3
	H	OEt	E	574

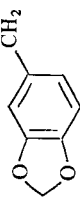


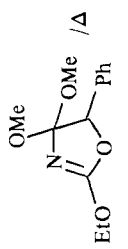
CH ₃ OH	H	OE _t	J	572
(CH ₂) _n CO ₂ Me (<i>n</i> = 3, 4)	H	OE _t	E	408
(CH ₂) _n OH (<i>n</i> = 4, 5)	H	OE _t	J	408
(CH ₂) _n CHO (<i>n</i> = 3, 4)	H	OE _t	K	408
(CH ₂) _n CH=CHCN (<i>n</i> = 3, 4)	H	OE _t	L	408
H	Me	OMe	F	221
H	Me	OMe	E	575, 576
H	Me	OE _t	E	571, 575, 576
H	Me	OE _t	F	221, 577
H	Me	OE _t	G	578
H	Me	O- <i>n</i> -Pr	F	222, 577
H	Me	O- <i>i</i> -Pr	E	575
H	Me	O- <i>i</i> -Pr	F	221
H	Me	O- <i>n</i> -Bu	F	221, 577
H	Me	O- <i>i</i> -Bu	F	577
H	<i>i</i> -Pr	OE _t	E	571
H	<i>n</i> -Bu	OE _t	E	571
H	Me	OSiMe ₃	M	215
H	<i>i</i> -Bu	OE _t	F	221
H	CH ₃ CO ₂ Et	OE _t	E	571, 579, 580
H	CH ₂ CO ₂ H	OE _t	C	579
Me	Me	OMe	E	263
Me	Me	OE _t	E	571, 575
Me	Me	OSiMe ₃	M	215

TABLE 1.42. (Continued)

R ²	R ⁴	K ^c	Method ^a	Reference
Et	Me	OMe	E	263
<i>n</i> -C ₅ H ₁₁	Me	OMe	E	263
<i>n</i> -C ₅ H ₁₁	Me	OMe	E	3, 263
Me	Et	OMe	E	263
Me	<i>i</i> -Pr	OSiMe ₃	M	215
PhCH ₂	Me	OMe	E	3
Me	PhCH ₂	OSiMe ₃	M	215
PhCH ₂	PhCH ₂	OMe	E	3
<i>n</i> -C ₅ H ₁₁	PhCH=CH	OMe	E	3
<i>n</i> -C ₃ H ₇ CH=CH	PhCH=CH	OMe	2- <i>n</i> -Pentylloxazole/LTA	3
Me	CF ₃	OMe	N	94
<i>i</i> -Bu	CF ₃	OR	N	94
		(R = Me, <i>i</i> -Bu)		
CH ₂ Cl	Me	OPh	O	154
CH ₂ SP(OEt) ₂	Me	OPh	2-Chloromethylloxazole/ (EtO) ₂ PS ⁻ K ⁺	154
Me	(CH ₂) ₂ CO ₂ Et	OMe	E	581
(CH ₂) ₂ Ph	CH ₂ CO ₂ Et	OMe	E	581
CH ₂ NPhthl	CH ₂ CO ₂ Et	OMe	E	581
(CH ₂) ₂ CO ₂ Et	(CH ₂) ₂ CO ₂ Et	OMe	E	581
(CH ₂) ₃ CO ₂ Me	Me	OMe	E	408, 582
(CH ₂) _n CO ₂ Me (<i>n</i> = 4, 5)	Me	OMe	E	408
(CH ₂) ₇ CO ₂ Et	Me	OMe	E	583
(CH ₂) _n OH (<i>n</i> = 4, 5, 6, 8)	Me	OMe	J	408
(CH ₂) ₃ CHO	Me	OMe	Ester/DIBAH	582
(CH ₂) _n CHO (<i>n</i> = 3, 4, 5, 7)	Me	OMe	K	408
(CH ₂) _n CH=CHCN	Me	OMe	L	408

$(\text{CH}_2)_3\text{CHC}\equiv\text{CCH}_2\text{OMe}$ OH	Me	OEt	Aldehyde/MeOCH ₂ C≡CLi	582
$(\text{CH}_2)_3\text{CHC}\equiv\text{CCH}_2\text{OMe}$ OH	Me	OEt	Alcohol/NaH; then MeI	582
Ph	H	OMe	E	3,440, 584
XPh	H	OMe	G	217
(X = H, 4-OMe, 3- and 4-Me, 3- and 4-Cl, 4-Br, 4-NO ₂)				
4-EtOPh	H	OMe	E	585
Ph	H	OEt	E	3,263
Ph	H	OEt	G	573
Ph	H	OEt	H	71
4-NCCH ₂ Ph	H	OEt	E	586
4-HO ₂ CCH ₂ Ph	H	OEt	Nitrile/NaOH	586
4-MeO ₂ CCH ₂ Ph	H	OEt	Acid/CH ₂ N ₂	586
Ph	H	OCH ₂ Ph	E	3
Ph	H	OSiMe ₃	I	215, 216
H	Ph	OR	F	223
		(R = Me, Et)		
H	Ph	OEt	G	220
Ph	Me	OMe	H	71
Ph	Me	OMe	P	94
Ph	Me	OEt	E	3
4-NCCH ₂ Ph	Me	OEt	E	586
4-HO ₂ CCH ₂ Ph	Me	OEt	Nitrile/NaOH	586
4-MeO ₂ CCH ₂ Ph	Me	OEt	Acid/CH ₂ N ₂	586
Ph	<i>i</i> -Pr	OMe	E	412
4-NCCH ₂ Ph	<i>i</i> -Pr	OEt	E	586
4-HO ₂ CCH ₂ Ph	<i>i</i> -Pr	OEt	Nitrile/NaOH	586
4-MeO ₂ CCH ₂ Ph	<i>i</i> -Pr	OEt	Acid/CH ₂ N ₂	586

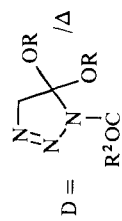
TABLE 1.42. (Continued)		XPh	O		
R ²		R ⁴	R ⁵	Method ^a	Reference
Ph		Me	OCH ₂ Ph	E	3
Ph		PhCH ₂	OMe	E	412
3,4,5-TriMeOPh			OMe	E	587
Ph		PhCH ₂	OEt	E	3
Ph		PhCH ₂	OCH ₂ Ph	E	3
Ph		CF ₃	OMe	N	94
XPh	(X = 3-CF ₃ , 4-ClPhO, 4-ClPh, 2,4-diCl, 3,4-diCl)	CH ₂ CO ₂ Et	OEt	E	588, 589
XPh	(X = 3-CF ₃ , 4-ClPhO, 4-ClPh, 2,4-diCl, 3,4-diCl)	CH ₂ CO ₂ H	OEt	C	588, 589
XPh		CH ₂ CO ₂ Et	OPh-Y	E	590
XPh		CH(R)CONR ⁶ R ⁷	OEt	Ester/R ⁶ R ⁷ NH	591
<i>t</i> -Bu		Ph	OMe	N	94
(CH ₂) _n CO ₂ Et (<i>n</i> = 1, 2)		XPh	OEt	E	592
(CH ₂) _n CO ₂ H (<i>n</i> = 1, 2)		XPh	OEt	C	592
(CH ₂) ₄ CO ₂ Me		Ph	OEt	E	408
(CH ₂) ₅ OH		Ph	OEt	J	408
(CH ₂) ₄ CHO		Ph	OEt	K	408
(CH ₂) ₄ CH=CHCN		Ph	OEt	L	408
Ph		Ph	OMe	E	412
Ph		Ph	OEt	E	3

4-NCCH ₂ Ph	4-XPh (X = H, Cl)	OMe	E	586
4-NCCH ₂ Ph	XPh (X = H, 4-OMe, 4-Cl, 3,4-diOMe, 2,4-diCl)	OEt	E	586
4-HO ₂ CCH ₂ Ph	4-XPh (X = H, Cl)	OMe	Nitrile/NaOH	586
4-HO ₂ CCH ₂ Ph	XPh (X = H, 4-OMe, 4-Cl, 3,4-diOMe, 2,4-diCl)	OEt	Nitrile/NaOH	586
4-MeO ₂ CCH ₂ Ph	4-XPh (X = H, Cl)	OMe	Acid/CH ₂ N ₂	586
4-MeO ₂ CCH ₂ Ph	XPh (X = H, 4-OMe, 4-Cl, 3,4-diOMe, 2,4-diCl)	OEt	Acid/CH ₂ N ₂	586
4-ClPh	4-ROPh [R = CH ₂ CO ₂ Et, C(Me) ₂ CO ₂ Et]	OEt	E	483
Ph	Br	OEt	2-Phenyl-5- ethoxyoxazole/NBA	3
OEt	OMe	H	D	207
OEt	OMe	Ph		209
OAc	2-Pyridyl	OMe	Oxazolin-2-one/Ac ₂ O	593

^aA = 2-chlorooxazole/ RO^-

B = $\text{N}_3\text{CO}_2\text{R}/\text{R}^4\text{C}\equiv\text{CR}^5$

C = hydrolysis of ester



E = $\text{R}^2\text{CONHCH}(\text{R}^4)\text{CO}_2\text{R}/\text{cyclodehydrating agent}$

F = $\text{R}^4\text{CHCO}_2\text{Et}/\Delta$



H = $\text{R}^2\text{COCl}/\text{N}_3\text{CH}(\text{R}^4)\text{CO}_2\text{R}/\text{Ph}_3\text{P}$

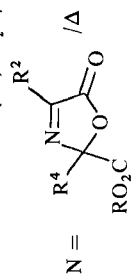
I = oxazolin-5-one/ $\text{Me}_3\text{SiCl}/\text{Et}_3\text{N}$

J = ester/ LAH

K = alcohol/ $(\text{COCl})_2/\text{DMSO}$; then Et_3N

L = aldehyde/ $\text{Ph}_3\text{P}=\text{CHCN}$

M = $\text{R}^2\text{CONHCH}(\text{R}^4)\text{CO}_2\text{H}/\text{Et}_3\text{N}$; then ClCO_2Et ; then Me_3SiCl



O = $\text{PhOCH}_2\text{C}(\text{Me})=\text{NOH}/\text{ClCH}_2\text{COCl}$

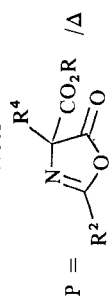
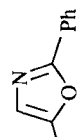


TABLE 1.43. ACYLOXYOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
OCOMe ₂	Ph	Ph	A	92
Me	OAc	Ph	PhCHCONH ₂ /Ac ₂ O/HClO ₄ OH	208
H	Me	OCOMe	A	211, 213
H	Me	OCO ₂ Et	B	594
H	<i>i</i> -Bu	OCOPh	A	595, 596
Me	Me	OCOPh	A	211, 213
Me	PhCH ₂	OCO ₂ Et	A	594
CF ₃	Me	OCOR	A	212, 213
		(R = Me, Ph, 4-O ₂ NPh, OMe)		
CF ₃	Me	OCOPh-3,4-diOCH ₂ Ph	A	595, 596
CF ₃	Me	OCO ₂ CH ₂ Ph	A	597
CF ₃	<i>i</i> -Bu	OCOR	A	597
		(R = Me, <i>i</i> -Bu)		
CH ₂ NPhthl	PhCH ₂	OCOMe	A	211, 213
Ph	H	OCOR	A	211, 213
		(R = Me, Ph, OMe)		
Ph	Me	OCOR	A	211, 213
		(R = Me, Et, <i>t</i> -Bu, Ph, 4-MeOPh, OMe)		
4-BrPh	Me	OCOMe	A	211, 213
Ph	Me	OCOR	A	595, 596
		(R = Ph, 4-ClPh, 3-MeOPh, 3,4-diPh-CH ₂ OPh)		
4-O ₂ NPh	Me	OCOPh	A	595, 596
				
Ph	Me	OC(CH ₂) ₄ C(=O)O	A	211, 213
Ph	<i>i</i> -Pr	OCOMe	A	211, 213
Ph	<i>t</i> -Bu	OCOMe	A	211, 213
CF ₃	Ph	OCO ₂ Me	A	597
Ph	CH(CF ₃) ₂	OCOPh	A	598

^aA = oxazolinone/RCOCl; B = R²CONHCH(R⁴)CO₂H/RCOCl.

TABLE 1.44. ALKYL- AND ARYLTHIOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
S(CH ₂) ₃ NPhthl	H	H	A	233
S(CH ₂) ₃ NH ₂	H	H	B	233
S(CH ₂) ₃ NHCNHMe	H	H	Amine/MeNCS	518-520
S(CH ₂) ₃ NHCNHMe	H	H	Thiourea/Pb(NCN) ₂	518-520
S(CH ₂) ₃ NHCNHMe	H	H	Amine/MeSC(=NH) NH ₂	518-520
S(CH ₂) ₃ NHCNHMe	H	N	Amine/(MeS) ₂ C=NCN	518-520
S(CH ₂) ₃ NHCNHR	H	H	MeSCNH(CH ₂) ₃ SR'/RNH ₂ NCN	518-520
(R = H, Et) S(CH ₂) ₃ NHCNHR	H	H	Amine/MeSCHNR NNO ₂	518-520
(R = H, Me) S(CH ₂) ₃ NHCNMe	H	H	Amine/(MeS) ₂ C=CHNO ₂	233
S(CH ₂) ₃ NHCNH(CH ₂) ₂ SCH ₂ CHNO ₂	H	H	C	233
S(CH ₂) ₃ NHCNH(CH ₂) ₂ SCH ₂ CHNO ₂	H	H	A	599

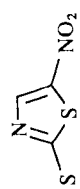
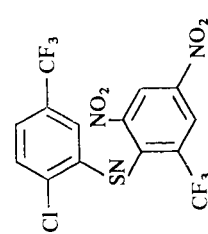
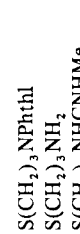
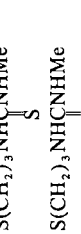
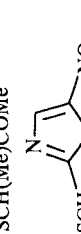
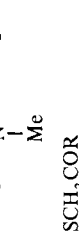
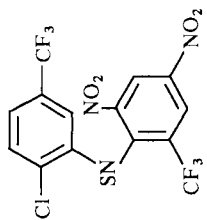
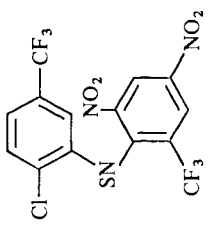
	H	H	A	234
	H	H	Sulfonyl chloride/ R ⁶ R ⁷ NH	600
	Me	H	A	233
	Me	H	B	233
	Me	H	Amine/MeNCS	518–520
	Me	H	Thiourea/Pb(NCN) ₂	518–520
	Me	H	Amine/(MeS) ₂ CH=CHNO ₂	518–520
	Me	H	C	518–520
	Me	H	A	232
	Me	H	A	232
	H	Me	A	601
	Me	Me	A	232

TABLE 1.44. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
(R = Me, Ph) SCH(Me)COMe	Me	Me	A	232
	Et	Et	Sulfonyl chloride/ R ⁶ R ⁷ NH	600
SMe	Ph	H	A	226, 230 238, 358 238 358
SEt	Ph	H	A	238
SMe	1- and 2-naphthyl	H	A	358
SCH ₂ CO ₂ Et	4-ClPh	H	D	135
SCH ₂ CO ₂ H	4-ClPh	H	E	135
SCH ₂ COR	Ph	H	A	232
(R = Me, Ph)				
SMe	Ph	Me	A	230, 238
SEt	Ph	Me	A	238
SMe	H	Ph	A	228, 230, 238
SEt	H	Ph	A	238
SPh-4-X	H	Ph	F	235
(X = H, OMe, OEt, Me, Cl, Br, NO ₂ , CO ₂ Et)				
SPh-4-NO ₂	H	Ph	F	235
SCH ₂ CO ₂ Et	H	4-ClPh	D	135
SCH ₂ CO ₂ H	H	4-ClPh	E	135

SR (R = Me, Et) SCH ₂ CO ₂ Et SCH ₂ CO ₂ H SMe	Me Me Me Ph	Ph 4-ClPh 4-ClPh Ph	A D E A	238 135 135 225, 226, 230 230, 238
SR (R = Et, <i>n</i> -Bu) SCH ₂ Ph	Ph	Ph	A	225
SR (R = Me, Et, <i>n</i> -Pr, Ph)	Ph	Ph	G	236
SPh-4-X (X = H, MeO, EtO, Me, Cl, Br, NO ₂ , CO ₂ Et)	Ph	Ph	F	235
SPh-2-NO ₂ SCH ₂ CO ₂ Et SCH ₂ CO ₂ Et SCH ₂ CO ₂ H SCH ₂ CO ₂ Et SCH ₂ CO ₂ H SCH ₂ CO ₂ Et SCH ₂ CO ₂ H SCH ₂ CO ₂ H S(CH ₂) _n CO(CH ₂) ₂ NMe ₂	Ph Ph Ph Ph 4-MeOPh 4-MeOPh 4-ClPh 4-ClPh Ph	Ph Ph Ph Ph 4-MeOPh 4-MeOPh 4-ClPh 4-ClPh Ph	F A D E D E D E H	235 231 135 135, 231 135 135 135 135 231
(<i>n</i> = 1, 2) S(CH ₂) _n CO(CH ₂) ₂ N 	Ph	Ph	H	231
(<i>n</i> = 1, 2) SCH ₂ CN(R ⁶)R ⁷ [R ⁶ = R ⁷ = H, R ⁶ = R ⁷ = Et, R ⁶ = H, R ⁷ = <i>n</i> -Pr, R ⁶ = H, R ⁷ = (CH ₂) ₂ NMe ₂]	Ph	Ph	I	231

TABLE 1.44. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
$\text{SCH}_2\text{CN} \begin{array}{c} \diagup \text{X} \\ \diagdown \end{array} \text{C}=\text{O}$ (X = CH ₂ , O, NMe) S(CH ₂) ₂ CO ₂ Et S(CH ₂) ₂ CO ₂ H S(CH ₂) ₂ CNR ⁶ R ⁷	Ph	Ph	I	231
[R ⁶ = R ⁷ = H, R ⁶ = R ⁷ = Et, R ⁶ = H, R ⁷ = <i>n</i> -Pr, R ⁶ = H, R ⁷ = (CH ₂) ₂ NMe ₂]	Ph	Ph	A	231
	Ph	Ph	E	231
	Ph	Ph	I	231
$\text{S(CH}_2)_2\text{CN} \begin{array}{c} \diagup \text{X} \\ \diagdown \end{array} \text{C}=\text{O}$	Ph	Ph	I	231
(X = CH ₂ , O, NMe) SCH ₂ COR (R = Me, Ph) SCOPh	Ph	Ph	A	232
	Ph	Ph	A	225
	Cl	H	Sulfonyl chloride/ R ⁶ R ⁷ NH	600
H	SMe-4-Me	H	J	220

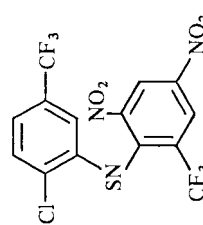
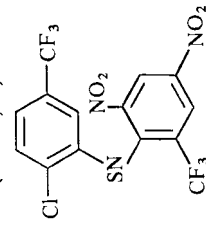
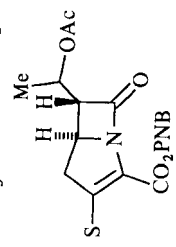
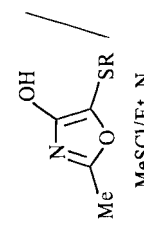
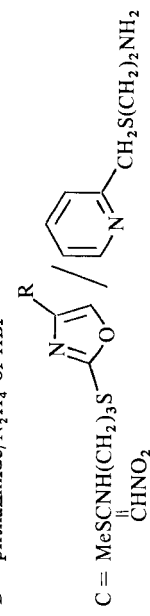
H		H	Sulfonyl chloride/ R ⁶ R ⁷ NH	600
H	SPh-4-Me SMe	Me 4-XPh (X = H, Cl)	J	240
H		2-HO ₂ CPh	K	243
H	SPH-4-Me SMe	4-XPh (X = H, Cl)	J	240
Me			K	243
H			Sulfonyl chloride/ R ⁶ R ⁷ NH	600
Me	H		 MeSCl/Et ₃ N	246
H	Me	SEt	L	245
CH ₂ Cl	Me	SR (R = Me, Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, <i>t</i> -Bu, Ph)	M	154
CH ₂ Cl	<i>t</i> -Bu	SMe	M	154

TABLE 1.44. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
CH ₂ SP(OEt)OEt	Me	SR (R = Me, Et, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, <i>t</i> -bu)	N	154
CH ₂ SP(OMe) ₂	Me	SR (R = Me, Et, <i>i</i> -Pr, <i>t</i> -Bu)	N	154
CH ₂ SP(OEt) ₂	Me	SR (R = Me, Et, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, <i>t</i> -Bu, Ph)	N	154
CH ₂ SP(OEt) ₂	Me	SEt	N	154
CH ₂ SP(OMe) ₂	<i>t</i> -Bu	SR (R = Me, Et)	N	154
CH ₂ SP(OEt) ₂	<i>t</i> -Bu	SR (R = Me, Et)	N	154

^aA = oxazolin-2-thione/base; then RXB = phthalimide/N₂H₄ or HBrD = 2-chlorooxazole/RS⁻

E = hydrolysis of ester

F = oxazolin-2-thione/XPhN⁺G = PhCOCH(Cl)Ph/RSCN/SnCl₄

H = acid chloride/alcohol

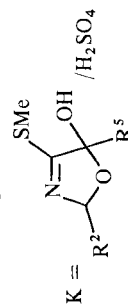
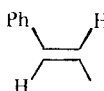
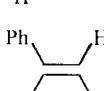
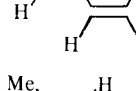
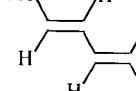
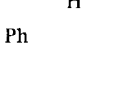
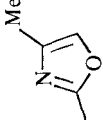
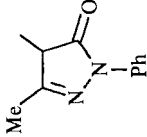
I = ester/R⁶R⁷NHJ = RSCN₂N=C/BuLi; then R⁵COXL = HCSNHCH(Me)CSEt/BF₃Et₂O; then P₂O₅M = ClCH₂COCl/R⁵CH₂CR⁴
NOHN = 2-chloromethyloxazole/R¹R²PS⁻K⁺
X

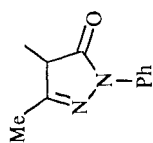
TABLE 1.45. SULFINYL- AND SULFONYLOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
S(O)Me	Ph	H	A	230, 238
S(O)Et	Ph	H	A	238
S(O)Me	Ph	Me	A	230, 238
S(O)Et	Ph	Me	A	238
S(O)Me	H	Ph	A	230, 238
S(O)Et	H	Ph	A	238
S(O)Me	Me	Ph	A	238
S(O)R	Ph	Ph	A	230, 238
(R = Me, Et, Bu)				
S(O) ₂ Me	Ph	H	A	230
S(O) ₂ Me	Ph	Me	A	230
S(O) ₂ Me	H	Ph	A	230
S(O) ₂ R	Ph	Ph	A	230
(R = Me, Et, Bu)				
H	S(O) ₂ Ph-4-Me	Me	B	241
H	S(O) ₂ Ph-4-Me	<i>n</i> -C ₆ H ₁₃	B	544
H	S(O) ₂ Ph-4-Me	2-XPh	B	241
(X = H, CO ₂ H)				
H	S(O) ₂ Ph-4-Me	Ph	C	242
H	S(O) ₂ Ph-4-Me		C	242
				
				
				
Me	S(O) ₂ R		D	244
				
(R = <i>t</i> -Bu, PhCH ₂ , 4-MeOPh, 4-MePh)				

^aA = alkylthioxazole/peracidB = TOSMIC/base; then R⁵COXC = TOSMIC/2-*n*-BuLi; then R⁵CO₂EtD = PhCO₂SO₂R/MeCN/Δ

TABLE 1.46. AMINOOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
NH ₂	H	H	A	271
NH ₂	H	H	B	602, 603
NHR	H	H	B	603
[R = Me, Et, PhCH ₂ , Ph(CH ₂) ₂ , PhCH ₂ CHMe, Ph ₂ CH, ph, 2-MePh, 1-naphthyl]				
NH ₂	Me	H	A	271
NHR	Me	H	A	271
[R = Me, <i>i</i> -Pr, <i>n</i> -Bu, <i>sec</i> -Bu, <i>n</i> -C ₆ H ₁₃ , CH ₂ =CHCH ₂ , PhCH ₂ , 4-ClPhCH ₂ , Ph(CH ₂) ₂ , MeO(CH ₂) ₂]				
NH- <i>n</i> -Bu	Et, <i>i</i> -Pr, C ₆ H ₁₁ , CH ₂ OH	H	A	271
NEt ₂	Me	H	B	108
				
NH(CH ₂) ₆ NH	Me	H	A	282
NH ₂	CF ₃	H	B	288
NH ₂	CH ₂ CO ₂ H	H	B or oxazole-5-carboxylic acid/Δ	280
NHPh	CH ₂ CO ₂ H	H	B or oxazole-5-carboxylic acid/Δ	280
				
NH ₂		H	B	270



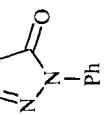
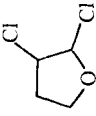
	NHPhX (X = H, 2-OMe, 4-OEt, 2-, 3-, and 4-Me, 2-, 3-, and 4-Cl)	H	H	H	B	270
	NH ₂	H	H	Me, Et	B	604
	NH ₂	H	H	Me	3-Amino-5-methyl- isoxazole/ Δ	79, 80
	NR ₂	H	H	Me	C	272
	(R = Et, <i>n</i> -Pr)	H	H	Me	C	272
	N(Ph)Et	H	H	CH ₃ OH	A	271
	NH- <i>n</i> -Bu	H	H	(CH ₂) ₂ OH	 /urea/ Δ	605, 606
	NH ₂	H	H	(CH ₂) ₂ Cl	Alcohol/SOCl ₂	233
	NH ₂	H	H	(CH ₂) ₂ S(CH ₂) ₂ NPhthl	5-Chloroethylloxazole/RS ⁻	152, 233
	NH ₂	H	H	(CH ₂) ₂ S(CH ₂) ₂ NH ₂	Phthalimide/N ₂ H ₄	152, 233
NH ₂	H	H	(CH ₂) ₂ NH(CH ₂) ₂ NH ₂	5-Chloroethylloxazole/ H ₂ N(CH ₂) ₂ NH ₂	152	
NH ₂	H	H	(CH ₂) ₂ S(CH ₂) ₂ NHCNHMe	Amine/McNCS	152	
NH ₂	H	H	(CH ₂) ₂ S(CH ₂) ₂ NHCNHMe	Amine/McNCS	152	
NH ₂	H	H	(CH ₂) ₂ S(CH ₂) ₂ NHCNHMe	Thiourea/Pb(NCN) ₂	152	
NH ₂	H	H	(CH ₂) ₂ S(CH ₂) ₂ NHCNHMe	Amine/(MeS) ₂ C=CHNO ₂	233	

TABLE 1.46. (Continued)

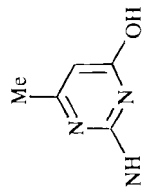
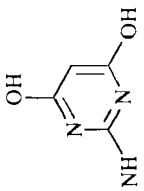
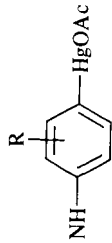
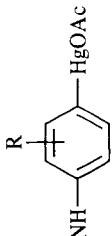
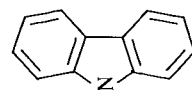
	Me	Me	Guanidinooxazole/ MeCOCH ₂ CO ₂ Et	287
	Me	Me	Guanidinooxazole/ CH ₂ (CO ₂ Et) ₂	287
NEt ₂	Me	Me	A	287
NH ₂	Me	Et, <i>n</i> -Pr, <i>n</i> -Bu	A	609
NH ₃	Et	Me	A	609
NHPhX	Me	Et	B	269
(X = H, 2-, 3-, and 4-OMe, 2-, 3-, and 4-Me, 2-, 3-, and 4-Cl)				
NHPh-4-Br	Me	Et	Mercuriacetate/KBr ₃	269
	Me	Et	G	269
(R = H, 2- and 3-OMe, 2- and 3-Me, 2- and 3-Cl)				
NHPhX	Me	<i>i</i> -Pr	B	269
(X = H, 2-, 3-, and 4-OMe, 2-, 3-, and 4-Me, 2-, 3-, and 4-Cl)				

TABLE 1.46. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
 (R = H, 2- and 3-OMe, 2- and 3-Me, 2- and 3-Cl)	Me	<i>i</i> -Pr	G	269
N(Ph)Me	<i>n</i> -Pr	<i>n</i> -Pr	H	128
	Me	<i>n</i> -Pr	I	273
	PhCH ₂	<i>n</i> -Pr, PhCH ₂	I	273
N(Ph)Me	Me, 2,5-diMeOPhCH ₂	<i>n</i> -Pr	I	274
	2,5-DiMeOPhCH ₂	<i>n</i> -Pr	I	274
NH ₂	(CH ₂) ₄		A	610, 611
NH ₂	(CH ₂) ₅		A	611
NH ₂	(CH ₂) _{<i>n</i>}		B	610, 611
NMe ₂	(<i>n</i> = 4, 5)			
	(CH ₂) ₄		B	610

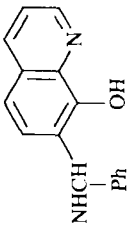
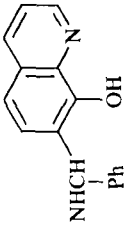
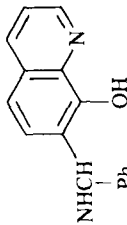
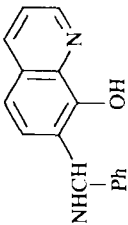
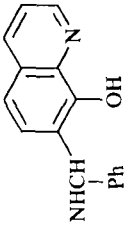
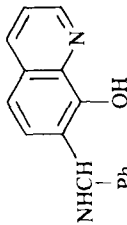
NH ₂		$\text{---}(\text{CH}_2)_2\text{N}(\text{CH}_2)_2\text{---}$ R	B	612
NH ₂		(R = Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, CH ₂ =CHCH ₂ , PhCH ₂ , 4-MePhCH ₂)	B	268, 284
NH ₂		Ph	B	268
		XPh		
NH ₂		(X = 4-OMe, 2- and 4-OH, 4-Me, 4-Cl, 4-NO ₂)	B	268
NH ₂		1- and 2-naphthyl	B	268
NH- <i>n</i> -Bu		2-Thienyl	A	271
		4-XPh (X = H, Cl)		
		4-XPh (X = H, OMe, OH, Me, Cl, Br, NO ₂)	J	285
		3-O ₂ NPh	J	285
		1- and 2-naphthyl	J	285
NMe ₂		Ph	B	284
NH ₂		H	K	275
		4-XPh (X = H, OMe, Cl, NO ₂)		
NH ₂		4-O ₂ NPh	F	608
NH ₂		4-XPh (X = OMe, Me, Br)	F	613

TABLE 1.46. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
NH- <i>i</i> -Bu	H	4-XPh (X = H, OMe, Cl, NO ₂)	L	275
NMe ₂	H	Ph	M	92
NH ₂	Ph	Me, Et, <i>n</i> -Pr, <i>n</i> -Bu	B	284
NMe ₂	Ph	Me	B	284
NEt ₂	Ph	Et	B	614
N(Me)CH ₂ Ph	Ph	Et	H	128
NH ₂	Me	Ph	A	607
NH ₂	Me	Ph	F	608
NH ₂	Ph	Ph	A	615
NH ₂	Ph	Ph	B	284
NH ₂	Ph	Ph	F	608
NH ₂	Ph	Ph	N	276
NH ₂	4-MeOPh	4-MeOPh	A	615
NH ₂	2-Furyl	2-Furyl	A	615
NHR	Ph	Ph	H	133
[R = Me, Et, <i>i</i> -Pr, <i>n</i> -Bu, C ₆ H ₁₁ , (CH ₂) ₂ OH, (CH ₂) ₃ OH, (CH ₂)CH(OH)Me, (CH ₂) ₂ NMe ₂ , (CH ₂) ₂ NEt ₂ , (CH ₂) ₃ NEt ₂]				
NHCH ₂ Ph	Ph	Ph	H	128
NHPh	Ph	Ph	B	284
NHPh	Ph	Ph	H	128
NMe ₂	Ph	Ph	B	284
NEt ₂	Ph	Ph	B	616
NR ₂	Ph	Ph	H	133
[R = Me, Et, (CH ₂) ₂ OH, CH ₂ CH(OH)Me, (CH ₂) ₃ NMe ₂]				

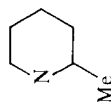
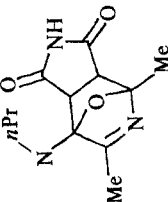
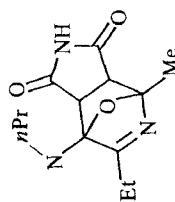
N(Me)CH ₂ Ph N(CH ₂) ₂ OH R	Ph Ph	H H	128 133
(R = Me, Et, <i>n</i> -Bu, <i>t</i> -Bu)			
	Ph	H	133
	Ph	H	133
[X = CH ₂ , O, NH, NMe, NCO ₂ Et, N(CH ₂) ₂ OH] N(Ph)R (R = Me, CH ₂ Ph)	Ph	H	128
H		O	319
H	N(Ph)R (R = Et, <i>i</i> -Pr)	O	319
H	N(Ph-4-Cl)Me	O	319
H	N(Ph-2,4-diCl)Me	O	319
Me	N(Me)CH ₂ Ph	P	299
Me	N(Ph)Me	P	301
H	N(Ph)- <i>i</i> -Pr	O	319
Me	NR ₂ (R = Et, <i>n</i> -Bu, Ph)	P	301
Me	N(Ph)Me	P	301

TABLE 1.46. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	Me		Q	617
Me	Et	N(Ph)Me	P	301
Me	Et	NPh ₂	P	301
Me	Et		Q	617
Me	N=NPh-4-Me		5-Aminooxazole/XPhN ⁺ ₃ ; then OH ⁻	336
4-O ₂ NPh	H	NHMe	5-Trifluoroacetylamino- oxazole/NH ₃ /MeOH	302
Ph	H	NHR (R = 2-pyridyl, 5-chloro-2-pyridyl, 2-pyrimidinyl, 2-quinolyl, 2-thiazolyl, 5-tetrazolyl, 2-indolyl, 1-methyl-2- indolyl, 2-benzimidazolyl, 2-benzothiazolyl)	P	300

4-O ₂ NPh	H	NMe ₂ 	R	303
4-O ₂ NPh	H		R	303
4-O ₂ NPh	H		R	303
4-XPh (X = H, OMe, Me, NO ₂)	H		R	303
Ph	H	N(Ph)Me	P	301
Ph	Me	NH ₂	S	311
4-O ₂ NPh	Me	NHCH ₂ Ph	5-Trifluoroacetyl- aminoxazole/ NH ₃ /MeOH	302
4-XPh (X = H, NO ₂)	Me		P	303
4-O ₂ NPh	Me		P	303
Ph	Me	N(Ph)Me	P	301
4-MePh	CF ₃	NEt ₂	5-Fluorooxazole/R ⁶ R ⁷ NH	147
4-ClPh	CF ₃		5-Fluorooxazole/R ⁶ R ⁷ NH	
Ph	CF ₃ CHOH	 (X = CH ₂ , O)	4-Trifluoroacetyl- 5-aminoxazole/LAH	303

TABLE 1.46. (Continued)

R^2	R^4	R^5	Method ^a	Reference
Ph	$\begin{array}{c} \text{C}(\text{OH})\text{CF}_3 \\ \\ \text{R} \end{array}$ (R = Me, Ph)		4-Trifluoroacetyl- 5-aminoxazole/RMgX	303
Ph	$\begin{array}{c} \text{C}(\text{OH})\text{CF}_3 \\ \\ \text{R} \end{array}$ (R = Me, Et)		4-Trifluoroacetyl- 5-aminoxazole/RMgX	303
Ph	$\text{CH} \left(\text{N} \begin{array}{c} \diagup \diagdown \\ \text{---} \text{---} \end{array} \right)_2$		4-Dichloromethyl- 5-chlorooxazole/piperidine	146
Ph	$\begin{array}{c} \text{NHCOPh} \\ \\ \text{CH} \\ \\ \text{C}=\text{N} \\ \\ \text{MeO}_2\text{SN} \end{array}$ 		T	336
Ph	$\begin{array}{c} \text{NHCOPh} \\ \\ \text{CH} \\ \\ \text{C}=\text{N} \\ \\ \text{4-TolO}_2\text{SN} \end{array}$ 		T	336
4-MePh	$\begin{array}{c} \text{NHCOPh} \\ \\ \text{CH} \\ \\ \text{C}=\text{N} \\ \\ \text{4-TolO}_2\text{SN} \end{array}$ 		T	336
4-O ₂ NPh	$\begin{array}{c} \text{NHCOPh} \\ \\ \text{CH} \\ \\ \text{C}=\text{N} \\ \\ \text{4-TolO}_2\text{SN} \end{array}$ 		T	336

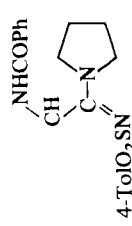
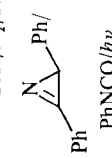
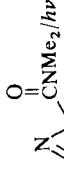
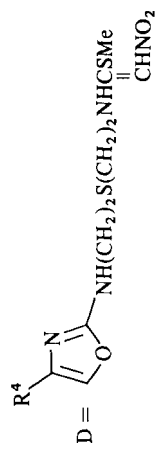
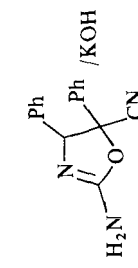
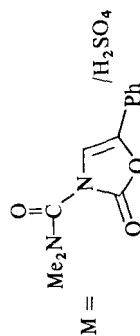
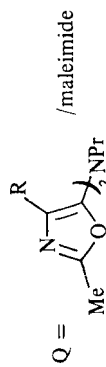
4-O ₂ NPh		T	336
Ph	N=NPh-4-X (X = H, Me)	5-Aminooxazole/ XPhN ⁺ ₂ ; then OH ⁻	336
4-O ₂ NPh	N=NPh-4-X (X = H, Me)	5-Aminooxazole/ XPhN ⁺ ₂ ; then OH ⁻	336
Me	Ph	U	313
Me	Ph	R ² CON=CHR ⁴ / <i>t</i> -BuN=C/BF ₃ • Et ₂ O	322
Me	Ph	P	301
Ph	Ph	U	313
Ph	4-XPh	V	323
4-ClPh	(X = H, Cl, NO ₂) 4-XPh	V	323
4-MeOPh	(X = OMe, Cl, NO ₂) 4-XPh	V	323
4-O ₂ NPh	(X = OMe, Cl) 4-XPh	V	323
Ph	(X = Cl, NO ₂) 4-XPh	R ² CON=CHR ⁴ / <i>t</i> -BuNC/ BF ₃ • Et ₂ O	322
Ph	(X = H, NO ₂) Ph	5-Benzylideneamino- oxazole/H ₂ /Ra-Ni/HOAc	309
Ph	Ph		332

TABLE 1.46. (Continued)

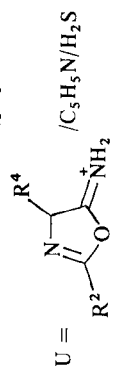
R ²	R ⁴	R ⁵	Method ^a	Reference
NH-1-C ₁₀ H ₇	H	NH ₂	W	338
N(Me)-1-C ₁₀ H ₇	H	NH ₂	W	338
NMe ₂	H	N(Me) ₂		339
NH ₂	Ph	NH ₂	W	338
NHR	Ph	NH ₂	W	338
(R = Me, 1-C ₁₀ H ₇)				

^aA = R⁴COCH(OH)R⁶R⁷NCN/acid or OH⁻B = R⁴COCH(Br)R⁵/R⁶R⁷CONH₂C = R⁶R⁷NCNHC≡CH/H₂SO₄/ΔE = 2-cyanamidooxazole/H₂SO₄F = NH₂CONHCN/R⁴CHBrCOR⁵/NaOAcG = aminooxazole/Hg(OAc)₂H = 2-chlorooxazole/R⁶R⁷NHI = RCH₂CHC≡CR/140°CO = CNCH(R⁴)CONR⁶R⁷/ΔP = R²CONHCH(R⁴)CONR⁶R⁷/POCl₃

/maleimide

J = 2-aminoxazole/PhCHO/8-hydroxyquinoline
 K = 2-tritylaminoxazole/HCl
 L = R⁶N=C=NCH₃ Tos/R⁵CHO/base

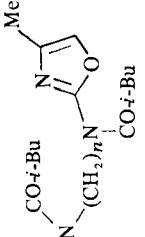
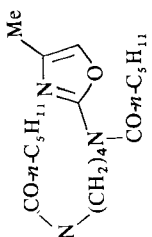
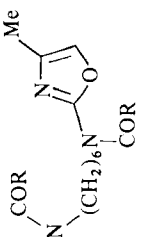
R = oxazole-4-carboxylic acid/ Δ
 S = R²CONHCH(R³)CN/(CF₃CO)₂O
 T = 5-aminoxazole/RSO₂N₃



V = R²CCN/R⁴CHO (5-benzylideneaminoxazoles isolated as
 minor products in some cases)

W = R⁶R⁷NCONHCH(R⁴)CN/NaOEt/EtOH

TABLE 1.47. ACYL-, AROYL-, AND ACYLOXYCARBONYLAMINOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
NHAc	Me	H	A	279
NHAc	CF ₃	H	A	279, 288
NHAc	H	Me	A	278, 293
 $(n = 3, 4, 5)$	Me	H	B	282
 $(n = 3, 4, 5)$	Me	H	B	282
 $(R = i\text{-Bu}, n\text{-C}_5\text{H}_{11})$	Me	H	C	282
NHAc	Me	Me	A	279
NHAc	CF ₃	Me	A	279
N(R ⁶)COR ⁷	H, alkyl, Ph	H, alkyl, acetoxymethyl, Ph	D	130
(R ⁶ , R ⁷ = alkyl, cycloalkyl, allyl, benzyl)				
NHAc	Ph	H	A	279, 288
NHAc	H	Ph	A	278, 293

NHAc	Ph	Me	A	278, 279, 293
NHAc	Me	Ph	A	278, 293
NHCHO	Ph	Ph	Amine/HCONH ₂ /Δ	284
NHAc	Ph	Ph	A	288
NAC ₂	Ph	Ph	A/Δ	288
NHCO ₂ R	Me	H	A	281
(R = Et, <i>n</i> -Bu, PhCH ₂)	Me	H	A	281
N(<i>n</i> -Bu)CO ₂ R	Me	H	A	281
(R = Et, <i>n</i> -Bu, PhCH ₂)	Me	H	A	281
N(CH ₂ Ph)CO ₂ R	H	Me, <i>i</i> -Pr, <i>t</i> -Bu	E	278, 293, 294, 539, 540
(R = Et, <i>n</i> -Bu, PhCH ₂)	H	Me, <i>i</i> -Pr, <i>t</i> -Bu	E	281
NHCO ₂ CH ₂ Ph	Me	Me	A	281
NHCO ₂ R	Me	Me	A	281
(R = Et, <i>n</i> -Bu, PhCH ₂)	H	Ph	E	278, 293, 294, 539, 540
N(CH ₂ Ph)CO ₂ R	Me, <i>i</i> -Pr	Ph	E	278, 293, 294, 539, 540
(R = Et, <i>n</i> -Bu, PhCH ₂)	Me, <i>i</i> -Pr	Ph	E	278, 293, 294, 539, 540
NHCO ₂ CH ₂ Ph	NHAc	Me	F	294
Me	NHAc	H	F	294
Ph	NHAc	Me	F	294
Ph	NHAc	Ph	F	294
Me	NHAc	Ph	F	294
Ph	NHCO ₂ CH ₂ Ph	Me	F	294
Me	NHCO ₂ Et	H	E	294
Ph	NHCO ₂ CH ₂ Ph	H	E	173
Ph	NHCO ₂ CH ₂ Ph	H	E	191, 294

TABLE 1.47. (Continued)

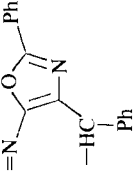
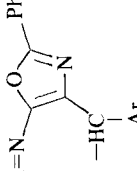
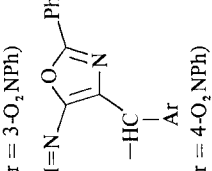
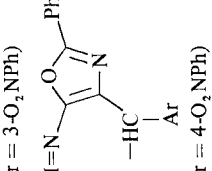
R ²	R ⁴	R ⁵	Method ^a	Reference
Ph	NHCO ₂ R [R = C ₆ H ₁₁ , (CH ₂) ₂ Cl] NHCOCH ₂ Ph NHCO ₂ CH ₂ Ph NHCO ₂ CH ₂ Ph Me H	H	E	191
Ph		Me	E	294
Me		Ph	E	294
Ph		Ph	E	294
Me		NHAc	F	294
4-O ₂ NPh		N(R)Ac (R = PhCH ₂ , 4-MePh)	A	303
4-O ₂ NPh	H	NHCOCF ₃	G	312
Ph	Me	NHAc	F	294
4-XPh (X = H, NO ₂)	Me	NHCOCF ₃	G	311
Ph	Me	N(CH ₂ Ph)COCF ₃	H	302
4-O ₂ NPh	Me	N(R)COCF ₃	H	302
		(R = Me, PhCH ₂)		
4-O ₂ NPh	Me	N(CH ₂ Ph)COCF ₃	A	302
Me	Ph	NHAc	F	294
Ph	Ph	NHAc	F	294
XPh (X = H, 4-OMe, 4-Cl, 3- and 4-NO ₂)	Ph	NAc ₂	A/Δ	333
H	Me	NHCO ₂ R [R = Me, Et, <i>n</i> -Bu, <i>i</i> -Bu, PhCH ₂ , 2-furylmethyl, (CH ₂) ₂ Cl, Ph, 4-MeOPh, 4-ClPh, 4-Cl-3,5-diMePh, 2-C ₁₀ H ₇] NHCO ₂ R (R = Me, Et)	E	328
H	Me		<i>N</i> -Chloroamide/Δ/ROH	328

H	Me	N(R)CO ₂ Et (R = Me, <i>n</i> -Pr, CH ₂ =CHCH ₂ , PhCH ₂ , 4-ClPhCH ₂)	I	328
H	Me	N(CH ₂ CH=CH ₂)CO ₂ R (R = <i>t</i> -Bu, PhCH ₂)	I	328
Me	Me	NHCO ₂ CH ₂ Ph	E	294
Ph	Me	NHCO ₂ CH ₂ Ph	E	294
Me	Ph	NHCO ₂ CH ₂ Ph	E	294
Ph	Ph	NHCO ₂ CH ₂ Ph	E	294

^aA = amine/RCOX
 B = acylaminooxazole/Br(CH₂)_{*n*}Br/(CH₂)_{*n*}Br/K₂CO₃/DMF
 C = diamine/(RCO)₂O
 D = 2-chlorooxazole/R⁶N⁺COR⁷
 E = acylazide/Δ/ROH

F = 4-benzoyloxycarbonylaminooxazole/H₂/Pd-C/Ac₂O
 G = R²CONHCH(R⁴)CN/(CF₃CO)₂O
 H = R²CONHCH(R⁴)CONHR/(CF₃CO)₂O
 I = 5-alkoxycarbonylaminooxazole/base/RX

TABLE 1.48. MISCELLANEOUS NITROGEN-CONTAINING GROUPS: ANILS, UREAS, THIUREAS, CYANAMIDES, AMIDINES, GUANIDINES, AND SULFONAMIDES

R ²	R ⁴	R ⁵	Method ^a	Reference
Ph	N=CHPh	Ph	A	295
Ph	N=CHPh-4-Cl	4-ClPh	A	295
Ph	N=CH- 	2-furyl	A	295
Ph	Me	N=CHPh	B	311
Ph	PhCH=N- 	N=CHPh	C	312
Ph	ArCH=N- 	N=CHAr	C	312
Ph	ArCH=N-  (Ar = 3-O ₂ NPh)	N=CHAr	C	312
Ph	ArCH=N-  (Ar = 4-O ₂ NPh)	N=CHAr	C	312

Me	Ph	N=CHPhX (X = H, 2-, 3-, and 4-OH, 4-NMe ₂ , 4-Me, 2- and 4-Cl, 2-, 3-, and 4-NO ₂)	B	310
Me	Ph	N=CH-CH=CHPh	B	310
PhCH=CH	Ph	N=CHPhX (X = H, 2-, 3-, and 4-OH, 4-NMe ₂ , 4-Me, 2- and 4-Cl, 2-, 3-, and 4-NO ₂)	B	310
PhCH=CH	Ph	N=CH-CH=CHPh	B	310
	Ph	N=CHPhX (X = H, 2-, 3-, and 4-OH, 4-NMe ₂ , 4-Me, 2- and 4-Cl, 2-, 3-, and 4-NO ₂)	B	310
4-MePh	Ph	N=CHPhX (X = H, 2-, 3-, and 4-OH, 4-NMe ₂ , 4-Me, 2- and 4-Cl, 2-, 3-, and 4-NO ₂)	B	310
	Ph	N=CHPhX (X = H, 2-, 3-, and 4-OH, 4-NMe ₂ , 4-Me, 2- and 4-Cl, 2-, 3-, and 4-NO ₂)	B	310
3-I ⁻³ CPh	Ph	N=CHPhX (X = H, 2-, 3- and 4-OH, 4-NMe ₂ , 4-Me, 2- and 4-Cl, 2-, 3-, and 4-NO ₂)	B	310
4-O ₂ NPh	Ph	N=CHPhX (X = H, 2-, 3-, and 4-OH, 4-NMe ₂ , 4-Me, 2- and 4-Cl, 2-, 3-, and 4-NO ₂)	B	310
XPh	Ph	N=CH-CH=CHPh (X = H, 4-Me, 3-CF ₃ , 4-NO ₂)	B	310

TABLE 1.48. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
NHCONHR (R = Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu, Ph, 2-MePh, 2-ClPh, 3-ClPh, 4-ClPh, 4-O ₂ NPh, 1-C ₁₀ H ₇)	H	H	D	288
NHCSNHR [R = Me, Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, <i>n</i> -C ₅ H ₁₁ , C ₆ H ₁₁ , <i>n</i> -C ₈ H ₁₇ , CH ₂ =CHCH ₂ , PhCH ₂ , Ph(CH ₂) ₂ , Ph]	H	H	D	289
NHCONHR (R = Et, <i>n</i> -Bu, Ph)	Me	H	D	281
N(<i>n</i> -Bu)CONHR	Me	H	D	281
(R = Et, <i>n</i> -Bu, Ph)				
N(CH ₂ Ph)CONHR	Me	H	D	281
(R = Et, <i>n</i> -Bu, Ph)				
NHCSNHMe	Me	H	D	289
NHCSNHEt	CF ₃	H	D	289
NHCONH ₂	Me	Me	2-Cyanamidooxazole/HCl	287
NHCONHR	Me	Me	D	287
(R = Et, <i>n</i> -Bu, Ph)				
NHCONHPhX (X = 2-, 3-, and 4-Cl)	Me	Me	D	288
N(<i>n</i> -Bu)CONHR	Me	Me	D	281
(R = Et, <i>n</i> -Bu, Ph)				
N(CH ₂ Ph)CONHR	Me	Me	D	281
(R = Et, <i>n</i> -Bu, Ph)				
NHCSNHR (R = Me, <i>n</i> -Pr, <i>n</i> -Bu, CH ₂ =CHCH ₂)	Me	Me	D	289

NHCONHR (R = Et, Ph, 3-ClPh)	Ph	Ph	D	288
NHCSNHR (R = Me, Et)	Ph	Ph	D	289
Ph	NHCONHR [R = CH ₂ =CHCH ₂ , C ₆ H ₁₁ , CH ₂ CO ₂ H, (CH ₂) ₃ NMe ₂]	H	E	191
Ph	NHCON 	H	E	191
NHCN	Me	Me	F	287
NHCN	(CH ₂) ₄	Me	F	287
NHCN	Ph	Ph	F	287
NHCR	Me	Me	G	287
NH (R = Me, Ph)				
NHCNH ₂	Me	Me	G	287
NH (R = Et, PhCH ₃)	Me	Me	G	287
NHCNH ₂	Me	Me	G	287
NH (R = Et, PhCH ₃)	Me	Me	2-Cyanamidooxazole/ EtNH ₂ /160°C	287
NHCNH ₂	(CH ₂) ₄		G	287
NH (R = Et, PhCH ₃)	(CH ₂) ₄		H	618
NHCNH ₂	H	Me, Et	G	619
NH (R = Et, PhCH ₃)	Ph	Ph	G	287

TABLE 1.48. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
NHSO ₂ Ph-4-NHCO ₂ Me	H	Me, Et	I	604
NHSO ₂ Ph-4-NH ₂	H	Me, Et	Urethane/Na ₂ S ₂ O ₅ /NaOH	604
N(SO ₂ Ph-4-NHCO ₂ Me) ₂	H	Me, Et	J	604
NHSO ₂ Ph-4-NHAc	Me	Me	G	604, 607
NHSO ₂ Ph-4-NH ₂	Me	Me	G or acetamide/NaOH or urethane/Na ₂ S ₂ O ₅ /NaOH	604, 607
NHSO ₂ Ph-4-NHCO ₂ Me	Me	Me	I	604
N(SO ₂ Ph-4-NHCO ₂ Me) ₂	Me	Me	J	604
NHSO ₂ Ph-4-NHAc	Et	Me	G	607
NHSO ₂ Ph-4-NHAc	Me, PhCH ₂	Ph	G	607
NHSO ₂ Ph-4-NHAc	Ph	Ph	G	607

$P^2A = R^2\overset{\text{NH}}{\underset{\text{NH}}{\text{C}}}\text{NH}_2/R^5\text{CH}(\text{OH})\text{CN}$
 $F = \text{RCOCH}(\text{OH})\text{R}/\text{NaN}(\text{CN})_2$
 $G = \text{RCNHCN}/\text{MeCOCH}(\text{OH})\text{Me}$
 $H = \text{H}_2\text{NCNHCNCH}_2/2\text{-bromocyclohexanone}$
 $I = \text{bissulfonamidooxazole}/\text{Pyr}/\text{H}_2\text{O}/\Delta$
 $J = \text{aminooxazole}/\text{RSO}_2\text{Cl}$

TABLE 1.49. HYDRAZINO- AND HYDRAZONOOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
NHNH ₂	Ph	Ph	A	136
NHNHCOPh	Ph	Ph	A or B	136
NHN(COPh) ₂	Ph	Ph	C	136
N(COPh)N(COPh) ₂	Ph	Ph	D	136
NHNHCONHR (R = H, Ph)	Ph	Ph	E	136
NHNHCSNHR (R = Me, Et, Ph)	Ph	Ph	E	136
NHN=CHPh-4-X (X = H, NO ₂)	Ph	Ph	F	136
NHN=C(R)Me (R = Me, Ph)	Ph	Ph	F	136

^aA = 2-chlorooxazole/RNHNH₂; B = 2-hydrazinooxazole/PhCOCl/Pyr; C = 2-hydrazinooxazole/3PhCOCl/Pyr; D = 2-dibenzoylhydrazinooxazole/PhCOCl/Pyr/Δ; E = 2-hydrazinooxazole/RNCX (X = O, S); F = 2-hydrazinooxazole/RR'CO.

TABLE 1.50. NITROOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
NO ₂	Ph	Ph	A	132
Me	NO ₂	4-XPh (X = H, Cl)	A	132
Me	<i>t</i> -Bu	NO ₂	A	132
<i>n</i> -C ₅ H ₁₁	Me	NO ₂	A	132
H	Ph	NO ₂	A	132
Ph	Me	NO ₂	A	132
Me	XPh (X = H, 4-OMe, 4-Me, 4-F 2- and 4-Cl, 2- and 4-Br, 4-NO ₂)	NO ₂	A	132
Et	4-ClPh	NO ₂	A	132
Ph	4-XPh (X = H, Cl)	NO ₂	A	132
NMe ₂	4-O ₂ NPh	NO ₂	B	284

^aA = bromo- or iodooxazole/N₂O₄; B = 2-(*N,N*-dimethylamino)-4-phenyloxazole/HNO₃/H₂SO₄.

TABLE 1.51. HALOOXAZOLE CARBOXYLIC ESTERS, ACIDS, ACID CHLORIDES, AMIDES, AND NITRILES

R ²	R ⁴	R ⁵	Method ^a	Reference
Cl	CO ₂ Et	OEt	A	201
Cl, Br, I	Me	CO ₂ Et	B	200
Cl	CF ₃	CO ₂ Et	C	200
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	CO ₂ Et	Cl	D	3
Ph	CO ₂ Et	Cl	D	3
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	CO ₂ H	Cl	E	3
Ph	CO ₂ H	Cl	E	3
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	COCl	Cl	F	3
Ph	COCl	Cl	F	3
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	CONH ₂	Cl	G	3
Ph	CONH ₂	Cl	G	3
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	CN	Cl	H	3
Ph	CN	Cl	H	3

^aA = (EtO₂C)₂C=NCO₂R/PhHgCCl₂Br/PhH/Δ
 B = ethyl 4-methyloxazole-5-carboxylate/LICA;
 then CCl₄ or X₂

E = ester/OH⁻ then H⁺

F = acid/SOCl₂

G = acid chloride/NH₃

H = amide/POCl₃

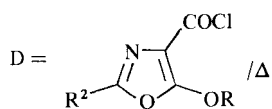
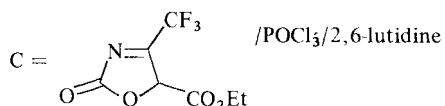
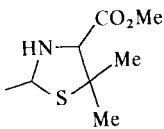
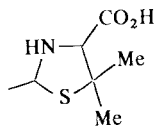
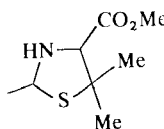
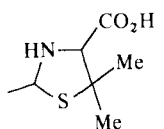


TABLE 1.52. HALOOXAZOLE CARBOXYALDEHYDES AND -THIAZOLIDINES

R ²	R ⁴	R ⁵	Method ^a	Reference
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	CHO	Cl	A	3
Ph	CHO	Cl	A	3
Ph	CHO	Cl	B	146
4-XPh (X = H, Me, Br, Cl, NO ₂)	CHO	Br	C or D or E	150
<i>n</i> -C ₅ H ₁₁ , PhCH ₂		Cl	F	3
<i>n</i> -C ₅ H ₁₁ , PhCH ₂		Cl	G	3
Ph		Cl	F	3
Ph		Cl	G	3

^aA = nitrile/SnCl₂/HCl/Et₂O, then H⁺; B = 4-dichloromethyl-5-chlorooxazole/NaOMe, then H⁺; C = 4-formyloxazole/Br/HOAc; D = 4-chloromethyl-5-bromooxazole/urotropine/HOAc; E = 4-hydroxymethyl-5-bromooxazole/Na₂Cr₂O₇/HOAc; F = 4-formyl-5-chlorooxazole/penicillamine/NaOAc/Et₂O/EtOH; G = ester/OH⁻, then H⁺.

TABLE 1.53. ALKOXYOXAZOLE CARBOXYLIC ESTERS, ACIDS, ACID HALIDES, AMIDES, THIOAMIDES, THIOLESTERS, NITRILES, AND KETOXAZOLE CARBOXYLIC ESTERS

R ²	R ⁴	R ⁵	Method ^a	Reference
CO ₂ Et	H	OEt	A	572, 620
CO ₂ Me	Me	OMe, O- <i>n</i> -Bu	A	620
CO ₂ Et	Me	OMe, OEt	A	620
CO ₂ Me	CH ₂ CO ₂ Me	OMe	A	620
CO ₂ Et	CH ₂ CO ₂ Et	OEt	A	440, 620
CO ₂ Et	(CH ₂) ₂ CO ₂ Et	OEt	A	584
CO ₂ H	H	OEt	B	572, 620
CO ₂ H	Me	OR	B	620
		(R = Me, Et, <i>n</i> -Bu)		
CO ₂ H	CH ₂ CO ₂ H	OEt	B	620
H	CO ₂ Et	OEt	A	621
H	CO ₂ Et	OEt	C	102
Me	CO ₂ Me	OMe	A	412
Me	CO ₂ Me	OMe	D	74
Me	CO ₂ Et	OEt	A	584
<i>n</i> -C ₃ H ₁₁ , PhCH ₂	CO ₂ Et	OEt	A	3
<i>n</i> -PrCH=CH	CO ₂ Et	OEt	A	3
Ph	CO ₂ Me	OMe	A	3, 329
4-XPh	CO ₂ Me	OMe	A	329
		(X = OMe, Me, <i>t</i> -Bu, F, Br, CF ₃)		
3-BrPh	CO ₂ Me	OMe	A	329
Ph	CO ₂ Et	OMe	E	3
Ph	CO ₂ Et	OEt	A	3
Me	CO ₂ H	OEt	B	248
<i>n</i> -C ₃ H ₁₁ , PhCH ₂	CO ₂ H	OEt	B	3
<i>n</i> -C ₃ H ₁₁	CO ₂ H	OEt	F	3
<i>n</i> -PrCH=CH	CO ₂ H	OEt	B	3

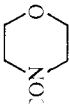
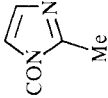
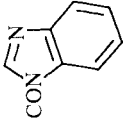
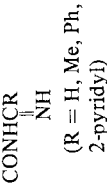
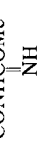
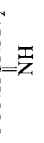
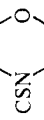
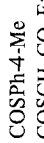
4-XPh (X = H, OMe, Me, <i>t</i> -Bu, F, Br, CF ₃)	CO ₂ H	OMe	B	329
3-BrPh	CO ₂ H	OMe	B	329
Ph	CO ₂ H	OEt	B	3
Me	COCl	OEt	G	248
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	COCl	OEt	G	3
4-XPh (X = H, OMe, Me, <i>t</i> -Bu, F, Br, CF ₃)	COCl	OMe	G	329
3-BrPh	COCl	OMe	G	329
Ph	COCl	OEt	G	3
Ph	COF	OEt	Acid/cyanuric fluoride/Pyr	247
H	CONMe ₂	OEt	C	102
Me	CONHPh	OEt	D	219
<i>n</i> -C ₅ H ₁₁ , PhCH ₂	CONH ₂	OEt	H	3
Ph	CONH ₂	OEt	H	3
Ph	CONHR (R = Me, <i>t</i> -Bu)	OMe	H	329
Ph	CONHPhX (X = H, 4-OMe, 4-Me, 3-Cl, 3- and 4-CF ₃)	OMe	H	329
Ph	CONMe ₂	OMe	H	329
4-XPh (X = H, OMe, Me, <i>t</i> -Bu, F, Br, CF ₃)	CON(Me)Ph	OMe	H	329
3-BrPh	CON(Me)Ph	OMe	H	329
Ph	CON 	OEt	H	247
Ph	CON 	OEt	H	247

TABLE 1.53. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Ph		OEt	H	247
Ph		OEt	H	247
Ph		OEt	H	247
Ph	 (R = H, Me, Ph, 2-pyridyl)	OEt	H	331
Ph		OEt	H	331
Ph		OEt	H	331
Ph		OEt	Amide/P ₂ S ₅ /THF/ultrasound	248
Ph		OMe	Acid chloride/RSH	247
Ph		OEt	Acid chloride/RSH	248
<i>n</i> -C ₅ H ₁₁		OEt	I	3
Ph		OEt	I	3

Ph		OEt	Oxazoloylaziridine/ Na/acetone	247
OEt	CO ₂ Me	H	J	202
OEt	Me	CO ₂ Et	K	200
OPh	Me	CO ₂ Et	K	200
OEt	Ph	CO ₂ Et	J	202
4-ClPh	OMe	CO ₂ Et	Ethyl 2-oxazolin-4-one-5-carboxylate/Me ₂ S ⁺ C ⁻ HCO ₂ Et	205
4-XPh (X = Cl, NO ₂)	O ₂ CPh-4-X	CO ₂ Et	4-XPhCONCO/ Me ₂ S ⁺ C ⁻ HCO ₂ Et	205
OEt	CO ₂ Me	CO ₂ Me	J	202
COMe	CO ₂ Me	Me	Alcohol/CrO ₃	157

^aA = R²CONHCH(R⁴)CO₂R/cyclodehydrating agent; B = ester/OH⁻, then H⁺; C = C=NCH₂CO₂Et/base, then R⁵COX; D = N₂C(COR)CO₂R'/MeCN/BF₃·Et₂O or *hν*; E = 2-oxazolin-5-one/CH₂N₂; F = 5-chlorooxazole-4-carboxylic acid/NaOEt; G = acid/(COCl)₂/Et₂O/DMF or SOCl₂; H = acid chloride/R³R¹NH; I = amide/POCl₃ or P₂O₅; J = EtO₂CN₃/RC≡CCO₂R'/Δ or *hν*; K = 2-chlorooxazole/NaOR.

TABLE 1.54. ALKOXYOXAZOLE CARBOXALDEHYDES AND KETONES

R ²	R ⁴	R ⁵	Method ^a	Reference
CHO	CH=CHPh	OEt	A	3
Ph	COCH ₂ CO ₂ Et	OEt	B	408
4-XPh	OMe	COPh	C	204
(X = H, OMe, F)				
4-ClPh	OMe	COPh	D	205
4-ClPh	OCH ₂ COPh	COPh	E	205

^aA = 2-pentenyl-4-styryl-5-ethoxyoxazole/OsO₄/H₂O₂; B = CH₂(CO₂Et)CO₂TMS/*n*-BuLi, then acid chloride, then H₂O; C = 5-benzoyl-2-oxazolin-4-one/CH₂N₂; D = 5-benzoyl-2-oxazolin-4-one/Me₂S⁺C⁻HCO₂Et; E = 4-ClPhCONCO/Me₂S⁺C⁻HCOPh.

TABLE 1.55. ALKYL- AND ARYLTHIOOXAZOLE CARBOXYLIC ESTERS, ACIDS, AMIDES, THIOLESTERS, DITHIOESTERS, AND NITRILES

R ²	R ⁴	R ⁵	Method ^a	Reference
SMe	CO ₂ Me	H	A	237
Me	CO ₂ Me	SPh	B	163
Ph	CO ₂ Et	SPh-4-Me	C	247
Ph	CO ₂ Et	SCH ₂ CO ₂ Et	C	248
Me	CO ₂ H	SPh	B	163
Me	CONH ₂	SR	B	163
		(R = Me, Ph)		
Me	CONH- <i>t</i> -Bu	SPh	B	163
Me	CONHAc	SR	B	163
		(R = Me, Et, Ph)		
Me	CONHCOEt	SR	B	163
Me	CONHCOEt	SMe	B	163
Ph	CONH ₂	SMe	Thiolester/NH ₃	249
Ph	COSMe	SMe	Dithiolester/Mel; then H ⁺	249
Ph	CS ₂ Me	SMe	D	249
H	CN	SR	B	163
		(R = Me, Et, Ph)		
Et	CN	SR	B	163
		(R = Me, Ph)		
<i>n</i> -Pr	CN	SR	B	163
		(R = Me, Ph)		
CF ₃	CN	SPh	B	163

^aA = Me₂NCH=CN=C(SMe)₂/HCl/H₂O/THF/Δ
 CO_2Me

B = R²CONH(R⁴)C=C(SR)₂/Ag₂CO₃/MeCN/Δ

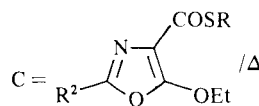
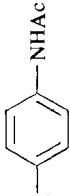


TABLE 1.56. AMINOXAZOLE CARBOXYLIC ESTERS, ACIDS, AMIDES, HYDRAZIDES, THIOAMIDES, AND NITRILES

R ²	R ⁴	R ⁵	Method ^a	Reference
NH ₂	CO ₂ Et	H	A	288
NH ₂	CO ₂ Et	CH ₂ CO ₂ Et	A	283
NHAc	CO ₂ Et	H	B	279, 288
NHAc	CO ₂ Et	CH ₂ CO ₂ Et	B	283
NHSO ₂ - 	CO ₂ Et	CH ₂ CO ₂ Et	C	283
NH ₂	CH ₂ CO ₂ Me	CO ₂ Me	A	280
NHPh	CH ₂ CO ₂ Me	CO ₂ Me	A	280
NHAc	CH ₂ CO ₂ Me	CO ₂ Me	B	280
<i>n</i> -C ₅ H ₁₁	CO ₂ R (R = Et, PhCH ₂)	NH ₂	D	3
<i>n</i> -PrCH=CH	CO ₂ Et	NH ₂	D	306
Ph	CO ₂ R (R = Et, PhCH ₂)	NH ₂	D	306
Ph	CO ₂ Et	NH ₂	E	3
Ph	CO ₂ Et	NH ₂	F	622
Ph	CO ₂ Me	NHR	E	329
Ph	CO ₂ Me	(R = Me, <i>t</i> -Bu)	E	329
		NHPhX (X = H, 4-OMe, 4-Me, 3-Cl, 3- and 4-CF ₃)	E	329
Ph	CO ₂ Me	NMe ₂	E	329
Ph	CO ₂ Et		E	247
Ph	CO ₂ Et		E	247

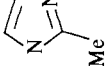
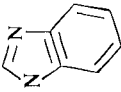
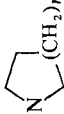
Ph	CO ₂ R (R = Me, Et)	NMe ₂	G	316
Ph	CO ₂ Me		G	316
Ph	CO ₂ R (R = Me, Et, <i>i</i> -Pr)		G	316
4-XPh (X = H, OMe, Me, <i>i</i> -Bu, F, Br, CF ₃)	CO ₂ Me	N(Me)Ph	E	329
3-BrPh	CO ₂ Me	N(Me)Ph	E	329
Ph	CO ₂ Et		E	247
Ph	CO ₂ Et		E	247
Ph	CO ₂ Et		E	247
Ph	CO ₂ Et	NHCR NH (R = H, Me, Ph, 2-pyridyl)	E	331
Ph	CO ₂ Et	NHCOMe NH	E	331

TABLE 1.56. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Ph	CO ₂ Et	NHCNMe ₂ 	E	331
NHR	CO ₂ Et	NH ₂	H	338
(R = Ph, 1-C ₁₀ H ₇)				
NH-1-C ₁₀ H ₇	CO ₂ Et	NHAc	B	338
NH ₂	CO ₂ H	CH ₂ CO ₂ H	I	283
NHPh	CH ₂ CO ₂ H	CO ₂ H	I	280
4-O ₂ NPh	CO ₂ H	NMe ₂	J	303
4-O ₂ NPh	CO ₂ H	 (n = 1, 2)	J	303
4-XPh	CO ₂ H		J	303
(X = H, OMe, Me, NO ₂)				
NH ₂	CONH ₂	H	K	288
NHAc	CONH ₂	H	K	288
NHAc	CH ₂ CONH ₂	CONH ₂	K	280
H	CONHR	N(<i>i</i> -Pr)Ph	L	320
	(R = <i>t</i> -BuCO, ClCH ₂ CO, Cl ₃ CO, PhCO, SO ₂ Ph-4-Me)			
H	CONHR		L	320
	(R = 3,4-diClPh, SO ₂ Ph-4-Me)			
H	CONH ₂	NHCOR (R = H, Me)	M	308

H	CONHMe	NHCOR (R = H, Me)	M	308
H	CONHAc	NHAc	M	308
H	CON(Me)Ac	NHAc	M	308
H	CONMe ₂	NHCOR (R = H, Me)	M	308
Me	CONH ₂	NH ₂	G	314
Me	CONH ₂	NHR (R = Me, <i>n</i> -Pr, C ₆ H ₁₁ , allyl, PhCH ₂)	G	314
Me	CONH ₂		G	314
Me	CONHAc	NR ₂ (X = CH ₂ , O)	G	315
Me	CONHAc	(R = Et, <i>n</i> -Pr)	G	315
Me	CONHAc	 (<i>n</i> = 1, 2)	G	315
Me	CONHAc		G	315
Me	CONHCOR (R = Et, <i>n</i> -Pr)		G	315
Me	CONH ₂	NHCOR (R = H, Me)	M	308
Me	CONHMe	NHCOR (R = H, Me)	M	308
Me	CONHMe	NAc ₂	M	308
Me	CONHAc	NHAc	M	308

TABLE 1.56. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	CONHAc	NAc ₂	M	308
Me	CONMe ₂	NHCOR (R = H, Me)	M	308
Et	CONCOEt		M	315
<i>n</i> -Pr	CONHCO- <i>n</i> -Pr		M	315
<i>i</i> -Pr	CONHCO- <i>i</i> -Pr		G	315
<i>n</i> -C ₃ H ₁₁	CONHCO- <i>n</i> -C ₃ H ₁₁		G	315
<i>n</i> -C ₉ H ₁₉	CONHCO- <i>n</i> -C ₉ H ₁₉		G	315
Ph	CONH ₂	NH ₂	4-Cyano-5-amino-oxazole/H ₂ SO ₄	191
Ph	CONHC ₆ H ₁₁	NHC ₆ H ₁₁	N	318
4-O ₂ NPh	CONHPh	 (n = 1, 2)	L	336
Ph	CONH ₂	NHCOPh	O	326
Ph	CONHCOPh	NHCOPh	P	326

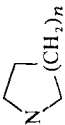
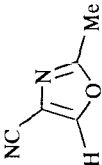
CONHPh-3,4-diCl	H	N(Me)Ph-4-Cl	Q	320
CONHCO- <i>t</i> -Bu	H	N(<i>i</i> -Pr)Ph	Q	320
CONHSO ₂ Ph-4-Me	H	NHCH ₂ Ph	Q	320
CONHSO ₂ Ph-4-Me	H	N(<i>i</i> -Pr)PhX	Q	320
		(X = H, 4-Cl, 3,4-diCl)		
CONHSO ₂ Ph-4-Me	Me	N(<i>i</i> -Pr)Ph	Q	320
N(R)CONHR	CONMe ₂	NMe ₂	R	340
		(R = Me, PhCH ₂)		
Ph	CONHNH ₂	NH ₂	K	191
Ph	CON ₃	NH ₂	Hydrazide/NaNO ₂ /H ⁺	
NH ₂	Me	CSNHR	L	191
		(R = Me, Et, CH ₂ =CHCH ₂ , Ph)		
NHCNHMe	Me	CSNHMe	L	290
Ph	CSNHPh		L	336
4-O ₂ NPh	CSNHPh		L	336
		(n = 1, 2)		
H	CN	NH ₂	S	307
H	CN		G	315
H	CN	N=C(OEt)R	T	334
		(R = H, Me, Et)		
Me	CN	NH ₂	S	307
Me	CN	NH ₂	G	315
Me	CN	NHR	G	315
		[R = Me, Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu, <i>i</i> -Bu, <i>sec</i> -Bu, <i>t</i> -Bu, <i>n</i> -C ₅ H ₁₁ ,		

TABLE 1.56. (Continued)

R ²	R ⁴	R ⁵	Method ^a	Reference
Me	CN	C ₆ H ₁₁ , (CH ₂) ₂ Cl, (CH ₂) ₂ CN, CH ₂ CH(OEt) ₂ , CH ₂ =CHCH ₂ , PhCH ₂ ,] NHR (R = Me, Et, <i>i</i> -Bu, PhCH ₂)	G	623
Me	CN	NMe ₂	G	337
Me	CN	NEt ₂	G	315, 337
Me	CN		G	315, 337
		(X = CH ₂ , O)		
Me	CN		G	315
Me	CN	NH(CH ₂) ₃ NH N=C(OEt)R (R = H, Me)	T	334, 335
Et	CN	NH ₂	S	307
Et	CN	NHEt	G	623
Et	CN	NEt ₂	G	337
Et	CN		G	315, 337
Et	CN	N=CHOEt	T	335
<i>n</i> -Pr	CN		G	315
<i>n</i> -C ₅ H ₁₁	CN	NH ₂	U	3

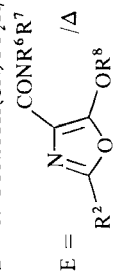
CF ₃	CN		G	315
Ph	CN	NH ₂	T	307
Ph	CN	NH ₂	U	3
Ph	CN	NH ₂	V	177
Ph	CN	NHR	G	623
Ph	CN	[R = Me, Et, Ph(CH ₂) ₂]		
4-ClPh	CN	NHCH ₂ Ph	G	317
	CN	NHR	G	623
Ph	CN	[R = Et, Ph(CH ₂) ₂]		
	CN	NHPhX-4	G	317
	CN	(X = H, Me)		
Ph	CN	NMe ₂	G	317
Ph	CN	NHCOPh	Amide/POCl ₃	326
Ph	CN	N=CHOEt	T	335
OMe	CN	NMe ₂	G	337
OR	CN		G	337
		(R = Me, Et)		
OR	CN		G	337
		(R = Me, Et)		

^aA = R⁶R⁷NCONH₂/R⁴COCH(Br)R⁵

B = amine/(RCO)₂O

C = amine/RSO₂Cl

D = R²CONHCH(CN)CO₂R/Δ, or HCl/EtOH, or POCl₃

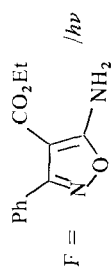


L = 5-aminooxazole/R⁶NCX

M = R²CONHCH(CN)CONR⁶R⁷/(RCO)₂O/HClO₄

N = R²CONHCH(CF₃)CO₂H/DCC/R⁶R⁷NH





$\text{G} = \text{R}^2\text{CONH}(\text{R}^4)\text{C}=\text{CCl}_2/\text{R}^6\text{R}^7\text{NH}$
 $\text{H} = \text{RNHCONHCH}(\text{CN})\text{CO}_2\text{Et}/\text{NaOEt}/\text{EtOH}$
 $\text{I} = \text{ester}/\text{OH}^-$; then H^+
 $\text{J} = 4\text{-trifluoroacetyl-5-aminooxazole}/\text{OH}^-$; then H^+
 $\text{K} = \text{ester}/\text{NH}_3$

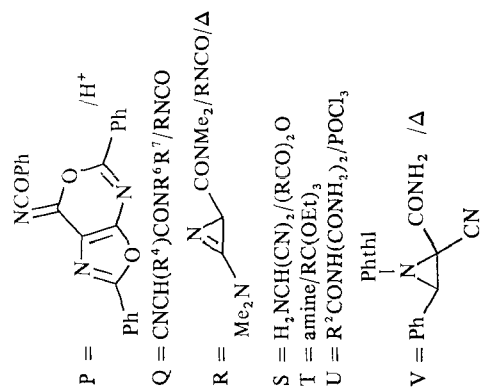
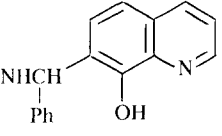
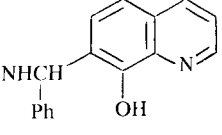
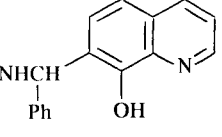
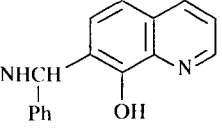


TABLE 1.57. AMINOXAZOLE CARBOXALDEHYDES AND KETONES

R ²	R ⁴	R ⁵	Method ^a	Reference
Ph	CHO	NH ₂	A	3, 191
Me	COCF ₃	NHPh-4-NO ₂	B	302
Me	COCF ₃		B	303, 305
PhCH ₂	COCF ₃	NHPh-4-X (X = H, Me, CN, NO ₂)	B	302
CH ₂ CO ₂ Et	COCF ₃	NHPh-4-NO ₂	B	302
CF ₃	COCF ₃	NMe ₂	B	305
CF ₃	COCF ₃	 (X = CH ₂ , O)	B	305
4-XPh (X = H, Me)	COCF ₃	NHPh-4-NO ₂	B	302
4-XPh (X = Me, NO ₂)	COCF ₃	NHPh	B	302
4-XPh (X = H, NO ₂)	COCF ₃	NMe ₂	B	303
4-O ₂ NPh	COCF ₃		B	303
4-XPh (X = H, OMe, CN, NO ₂)	COCF ₃		B	303
4-XPh	COCF ₃		B	303, 304

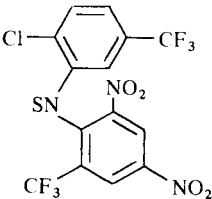
^aA = R²CONHCH(CHO)CN/H₂SO₄/pH4; B = R²CONHCH₂CONR⁶R⁷/TFAA.

TABLE 1.58. AMINOHALOOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
NH ₂	XPh (X = H, 4-OMe, 2- and 4-OH, 4-Me, 4-Cl, 4-NO ₂)	Cl	A	268, 291
NH ₂	1- and 2-naphthyl	Cl	A	268, 291
NH ₂	2-Thienyl	Cl	A	268, 291
NH ₂	XPh (X = H, 4-OMe, 2- and 4-OH, 4-Me, 4-Cl, 4-NO ₂)	Br	A	268, 291
NH ₂	1- and 2-naphthyl	Br	A	268, 291
NH ₂	2-Thienyl	Br	A	268, 291
NHPh-2-SH	Me	Cl, Br	A	292
NHPh-2-SH	XPh (X = H, 4-OMe, 4-OEt, 4-OH, 4-Me, 4-Cl, 3- and 4-NO ₂)	Cl	A	292
NHPh-2-SH	1- and 2-naphthyl	Cl	A	292
NHPh-2-SH	2-Thienyl	Cl	A	292
NHPh-2-SH	XPh (X = H, 4-OMe, 4-OEt, 4-OH, 4-Me, 4-Cl, 3- and 4-NO ₂)	Br	A	292
NHPh-2-SH	1- and 2-naphthyl	Br	A	292
NHPh-2-SH	2-Thienyl	Br	A	292
	XPh (X = H, 4-OMe, 4-OH, 4-Me, 4-Cl, 4-Br, 3- and 4-NO ₂)	Cl	B	285
	1- and 2-naphthyl	Cl	B	285
	XPh (X = H, 4-OMe, 4-OH, 4-Me, 4-Cl, 4-Br, 3- and 4-NO ₂)	Br	B	285
	1- and 2-naphthyl	Br	B	285
H	Cl	N(<i>i</i> -Pr)Ph	C	319

^aA = 2-amino-4-aryloxazoles/NCS or NBS or X₂ (X = Cl, Br); B = 2-aminoxazole/PhCHO/8-hydroxyquinoline; C = CNCH₂CONR⁶R⁷/KOH/CCl₄.

TABLE 1.59. ALKYL- AND ARYLTHIOAMINOXAZOLES

R ²	R ⁴	R ⁵	Method ^a	Reference
N- <i>n</i> -Pr ₂	H		R ⁶ R ⁷ NH/NaH; then sulfenyl chloride	600
SR (R = <i>i</i> -Pr, Ph)	H	N(<i>i</i> -Pr)Ph	A	321
4-O ₂ NPh	SR (R = Me, PhCH ₂)	NH ₂	B	324, 325
Ph	SR (R = Me, PhCH ₂ , Ph)	N=CHPh	B	324, 325
4-MeOPh	SMe	N=CHPh-4-OMe	B	324, 325
4-O ₂ NPh	SPh	N=CHPh-4-NO ₂	B	324, 325

^aA = CNCH₂CONR⁶R⁷/RSNPhthl
$$B = \begin{array}{c} \text{NH} \\ \parallel \\ \text{RSCCSR/R}^2\text{CHO} \\ \parallel \\ \text{NH} \end{array}$$

TABLE 1.60. PHOSPHORUS DERIVATIVES

R ²	R ⁴	R ⁵	Method ^a	Reference
H	PO(OEt) ₂	Me, <i>t</i> -Bu	A	344
H	PO(OEt) ₂	Ph	A	344
Me	P(O)R ₂ (R = Ph, OEt)	Ph	B	343
Et	P(O)Ph ₂	Ph	B	343
4-XPh (X = H, Cl)	P(O)Ph ₂	Ph	B	343
Me	P ⁺ Ph ₃ Cl ⁻	Ph	B	343
<i>n</i> -Pr	P ⁺ Ph ₃ Cl ⁻	Ph	B	343
4-XPh (X = H, Cl)	P ⁺ Ph ₃ Cl ⁻	Ph	B	343
H	PO(OEt) ₂	CO ₂ Et	A	344
H	PO(OEt) ₂	OR (R = Me, Et)	A	345
Ph	P ⁺ Ph ₂ Cl ⁻	Cl	C	251, 252
Me	P ⁺ Ph ₃ I ⁻	SR (R = Me, Et)	D	251
Ph	P ⁺ Ph ₃ I ⁻	SR (R = Me, Et)	D	251
Ph	P ⁺ Ph ₃ Cl ⁻	SPh	E	252
H	PO(OEt) ₂	NHMe	A	345
H	PO(OEt) ₂	NMe ₂	A	345
Ph	P ⁺ Ph ₃ Cl ⁻	NHMe	F	251
Ph	P ⁺ Ph ₃ Cl ⁻	NHCH ₂ Ph	G	252
Ph	P ⁺ Ph ₃ Cl ⁻	NHPh-4-X (X = H, OMe, Me)	F	251
Ph	P ⁺ Ph ₃ Cl ⁻	NMe ₂	H	251
Ph	P ⁺ Ph ₃ Cl ⁻		G	252
Ph	P ⁺ Ph ₃ Cl ⁻	N(Me)Ph-4-X (X = H, OMe, Me)	H	251

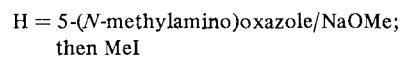
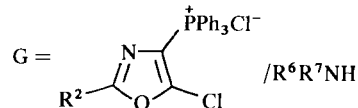
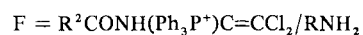
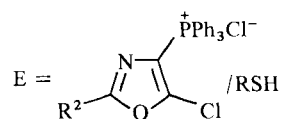
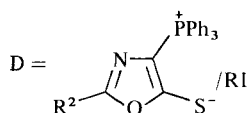
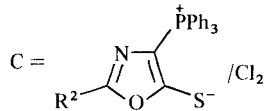
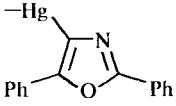
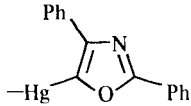
^aA = CNCH₂PO(OEt)₂/KO-*t*-Bu; then R⁵COXB = R²COCH(R⁴)COR⁵/SOCl₂, or PCl₅, or Ac₂O

TABLE 1.61. MERCURY AND PLATINUM DERIVATIVES

R ²	R ⁴	R ⁵	Method ^a	Reference
HgOAc	Ph	Ph	A	131, 132
Me	HgOAc	4-XPh (X = H, Cl)	A	131, 132
<i>n</i> -C ₅ H ₁₁	Me	HgOAc	A	132
H	Ph	HgOAc	A	132
Me	XPh (X = H, 4-OMe, 4-Me, 2- and 4-Cl, 2- and 4-Br, 4-F, 4-NO ₂)	HgOAc	A	132
Ph	Me	HgOAc	A	132
Ph	Ph	HgOAc	A	132
Ph		Ph	B	624
Ph	Ph		B	624
Pt(PPh ₃) ₂	CO ₂ Et	Ph	C	346

^aA = oxazole/Hg(OAc)₂

B = oxazolylmercuriacetate/sodium stannite

C = [(Ph₃P)₂Pt(Cl)CNCH₂CO₂Et] ⁺BF₄⁻/PhCOCl/Et₃N

TABLE 1.62. OXAZOLE *N*-OXIDES^a

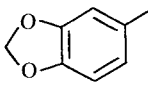
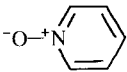
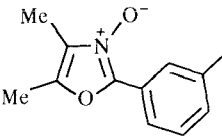
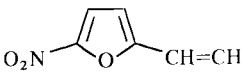
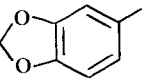
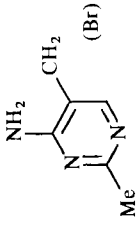
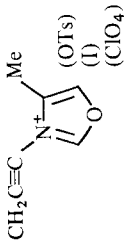
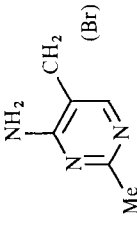
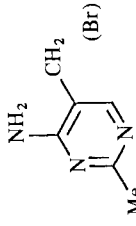
R ²	R ⁴	R ⁵	Reference
Ph	Me	Me	96, 97, 348
4-MeOPh	Me	Me	96, 97
3-O ₂ NPh	Me	Me	96, 348
XPh (X = 2-OH, 4-NO ₂ , 2,4-diOH)	Me	Me	96
4-Me ₂ NPh	Me	Me	348
	Me	Me	96
2-Thienyl	Me	Me	348
5-Nitro-2-furyl	Me	Me	348
	Me	Me	348
	Me	Me	348
PhCH=CH	Me	Me	96
	Me	Me	348
Ph	Me	Et	97
Ph	Me	CH ₂ OAc	97
Et	PhCH ₂	Ph	348
XPh (X = H, 3- and 4-NO ₂)	H	Ph	348
XPh (X = 2-, 3-, and 4-Cl, 2-, 3-, and 4-NO ₂)	H	Ph	98
H	Ph	Ph	348
Ph	Me	Ph	97
XPh (X = H, 4-OMe, 2-OH, 2-, 3-, and 4-NO ₂)	Me	Me	96
	Me	Ph	96
4-Biphenyl	Me	Ph	348
4-XPh (X = H, OMe)	Ph	Me	348
PhCH ₂	Ph	Ph	348
XPh (X = H, 4-OMe, 3-NO ₂)	Ph	Ph	96

TABLE 1.62. (Continued)

R ²	R ⁴	R ⁵	Reference
Ph	CO ₂ Et	Me	348
4-XPh (X = H, OMe, Cl, NO ₂)	COMe	Me	180
PhCH=CH	COMe	Me	180
Ph	COMe	Ph	180

^aMethod = R²CHO/R⁴ $\overset{\text{NOH}}{\underset{|}{\text{C}}}$ COR⁵/HCl/HOAc

TABLE I.63. OXAZOLIUM SALTS

R ²	R ³ (X)	R ⁴	R ⁵	Method ^a	Reference
Me	Et(OTs)	H	H	A	351
H	Me(I)	Me	H	A	625, 626
H	Me(OTs)	Me	H	A	627
H		Me	H	A	628
H		Me	H	A	629
Me	Me, Et, (I)	H	Me	A	361
H	Me(I)	<i>n</i> -Pr	<i>n</i> -Pr	A	630
H		Et	Et	A	350
H		Me	(CH ₂) ₂ OH	A	522, 628
H	Me(BF ₄)	Me	(CH ₂) ₂ Cl	A	353

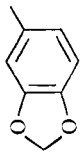
Me	Me(l)	Me, <i>i</i> -Bu	Me	441
Me	Et(OTs)	<i>n</i> -Pr	<i>n</i> -Pr	351
1-C ₁₀ H ₇	Me(OTs)	H	Me	352
H	Me(l)	H	Ph	350
H	PhCH ₂ (Cl)	H	Ph	350
H	Me(CF ₃ SO ₃)	Ph	Me	397
H	Me(l)	Ph	Me	350
H	Me(CF ₃ SO ₃)	Me	Ph	397
H	Me(l)	Me	Ph	350
H	PhCH ₂ (PhSO ₃)	Me	Ph	397
Me	Me(OTs)	H	Ph	121
Me	Et(OTs)	4-XPh	H	351
Me	Et(OTs)	(X = H, OMe)	4-XPh	351
Me	Me(CF ₃ SO ₃)	H	(X = H, OMe)	
Me	Me(OTs)	Ph	Me	397
Et	Me(CF ₃ SO ₃)	4-Biphenyl	H	121
C ₆ H ₁₁	Me(OTs)	Ph	Et	397
Ph	Me(OTs)	H	Ph	352
XPh	Me(OTs)	H	Ph	355
(X = H, 3- and 4-OMe, 4-Me, 2-Cl, 3,4-diCl)			Ph	352
XPh	Me(OTs)	H	Ph	121
(X = 4-NO ₂ , 2,5-diMe)				
	Me(OTs)	H	Ph	352
4-XPh	Me(OTs)	H	4-Me ₃ N ⁺ Ph	121
(X = H, OMe, Me)				
Ph	Me(OTs)	H	4-Biphenyl	352
4-Biphenyl	Me(OTs)	H	Ph	352, 355
4-Biphenyl	Me(OTs)	H	4-Biphenyl	352

TABLE 1.63. (Continued)

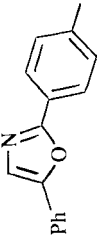
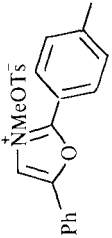
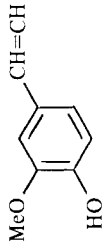
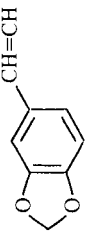
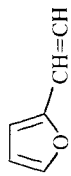
R ²	R ³ (X)	R ⁴	R ⁵	Method ^a	Reference
1- and 2-C ₁₀ H ₇	Me(OTs)	H	Ph	A	352
1-C ₁₀ H ₇	Me(CIO ₄) (I)	H	Ph	B	352
1-C ₁₀ H ₇	(Cl)	H	4-Me ₃ N ⁺ Ph	A	121
Ph	Me(OTs)	H	1-C ₁₀ H ₇	A	121
1-C ₁₀ H ₇	Me(OTs)	H	1-C ₁₀ H ₇	A	352
PhCH=CH	Me(OTs)	H	Ph	A	352
2-Furyl, 2-thienyl	Me(OTs)	H	Ph	A	352
	Me(OTs)	H	Ph	A	121
	Me(OTs)	H	Ph	A	352
H	Me(I)	Ph	Ph	A	350, 630
Me	Me, Et, <i>n</i> -C ₁₂ H ₂₅ , <i>n</i> -C ₁₈ H ₃₇ (ClO ₄)	Ph	Ph	C	359
Me	<i>n</i> -Bu, <i>n</i> -C ₈ H ₁₇ (I)	Ph	Ph	C	379
Me	<i>n</i> -Bu, <i>n</i> -C ₁₂ H ₂₅ (ClO ₄)	4-MeOPh	4-MeOPh	C	359
Me	Et(OTs)	4-XPh (X = H, OMe, NMe ₂ , N ⁺ Me ₃)	Ph	A	351
Me	Et(OTs)	3,4-DiMeOPh	Ph	A	351
Me	Et(OTs)	2-C ₁₀ H ₇	2-C ₁₀ H ₇	A	351
Me	Et(OTs)	2-Furyl	2-Furyl	A	351

TABLE 1.63. (Continued)

R ²	R ³ (X)	R ⁴	R ⁵	Method ^d	Reference
SMe	Et(I)	Ph	Ph	A	358
SMe	Et(MeSO ₄)	XPh	Ph	G	359
SMe	Et(MeSO ₄)	(X = H, OMe)	4-MeOPh	G	359
SMe	<i>n</i> -Bu, <i>n</i> -C ₈ H ₁₈ , (MeSO ₄)	Ph	Ph	G	359
SMe	PhCH ₂ (MeSO ₄)	Ph	Ph	G	128
SMe	Ph(MeSO ₄)	Ph	Ph	G	359
NH ₂	PhCOCH ₂ (Br)	Me	Me	A	399, 634
NH ₂	PhCOCH ₂ (Br)	H	Ph	A	399, 634
NHPh	Et(BF ₄)	Ph	Ph	H	128
XPhCH=CH	Me(I)	H	Me	I	360
(X = H, 2- and 4-OMe, 2- and 4-OH, 4-NMe ₂ , 4-NHAc, 4-Cl, 3- and 4-NO ₂)					
	Me(I)	H	Me	I	360
	Me(I)	H	Me	I	360
PhCH=CHCH=CH	Me(I)	H	Me	I	360
1-C ₁₀ H ₇ CH=CH	Me(I)	H	Me	I	360
	Me(I)	H	Me	I	360

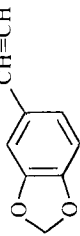
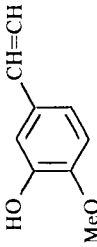
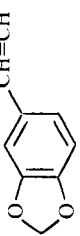
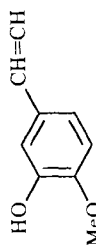
4-XPhCH=CH (X = 4-OH, 4-NMe ₂ , 4-NO ₂)	Et(I)	H	Me	I	360
	Et(I)	H	Me	I	360
	Et(I)	H	Me	I	360
XPhCH=CH (X = 2- and 4-OH, 4-NMe ₂ , 4-NHAc, 4-NO ₂)	Me(I)	Me	Me	J	441
	Me(I)	Me	Me	J	441
	Me(I)	Me	Me	J	441
PhCH=CHCH=CH XPhCH=CH (X = 4-OH, 4-NMe ₂ , 4-NHAc, 3- and 4-NO ₂)	Me(I) Me(I)	Me <i>i</i> -Bu	Me Me	J J	441 441
4-Me ₂ NPhCH=CH 4-Me ₂ NPhCH=CH 4-Me ₂ NPhCH=CH 4-Me ₂ NPhCH=CH PhNHCH=CH PhN(Ac)CH=CH	Et(I) Et(I) Et(ClO ₄) Et(ClO ₄) Et(OTs) Et(OTs)	Ph H Ph 4-Me ₂ NPh H H	H Ph Ph Ph H H	J J J J K L	635 635 351, 635 351 351 351

TABLE 1.63. (Continued)

R ²	R ³ (X)	R ⁴	R ⁵	Method ^a	Reference
XPhNHCH=CH (X = 4-OMe, 4-OEt, 4-NMe ₂ , 2-, 3-, and 4-Me, 4-CO ₂ Et, 3-CO ₂ H) 1- and 2-C ₁₀ H ₇ NHCH=CH	Me(I)	H	Me	K	361
	Me(I)	H	Me	K	361
	Me(I)	H	Me	K	361
X  (X = Cl, Br, I) 4-XPhNHCH=CH (X = CO ₂ Et)	Me(I)	H	Me	K	361
Br 	Et(I)	H	Me	K	361
4-XPhN(R)CH=CH (X = CO ₂ R', R = alkyl)	Alkyl(I)	Me	H	M	636

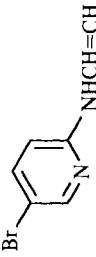
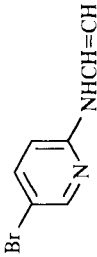
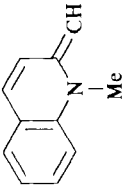
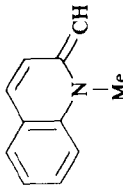
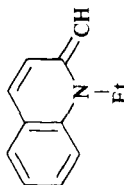
4-XPhNHCH=CH (X = OMe, OEt, NMe ₂ , NEt ₂ , Me, CO ₂ Et) 2-C ₁₀ H ₇ NHCH=CH	Me(l)	Me	Me	K	441
	Me(l)	Me	Me	K	441
XPhNHCH=CH (X = 4-OMe, 4-OEt, 4-NMe ₂ , 4-NEt ₂ , 2-, 3-, and 4-Me, 4-CO ₂ Et) 1- and 2-C ₁₀ H ₇ NHCH=CH	Me(l)	<i>i</i> -Bu	Me	K	441
	Me(l)	<i>i</i> -Bu	Me	K	441
PhNHCH=CH PhN(Ac)CH=CH PhNHCH=CH	Et(OTs) Et(OTs) Et(OTs)	<i>n</i> -Pr <i>n</i> -Pr 4-XPh (X = H, OMe) Ph	<i>n</i> -Pr <i>n</i> -Pr Ph 4-XPh (X = H, OMe) Ph	K L K K	351 351 351 351
PhNHCH=CH	Et(OTs)	4-XPh (X = H, OMe)	4-XPh (X = H, OMe) Ph	K L	351 351
PhN(Ac)CH=CH	Et(OTs)	4-XPh (X = H, OMe)	4-XPh (X = H, OMe) Ph	L K	351 351
PhN(Ac)CH=CH	Et(OTs)	4-XPh (X = H, OMe)	4-XPh (X = H, OMe) Ph	L K	351 351
PhNHCH=CH PhNHCH=CH	Et(OTs) Et(OTs)	3,4-DiMeOPh 2-C ₁₀ H ₇	Ph 2-C ₁₀ H ₇	K K	351 351

TABLE 1.63. (Continued)

R ²	R ³ (X)	R ⁴	R ⁵	Method ^a	Reference
PhNHCH=CH	Et(OTs)	2-Furyl	2-Furyl	K	351
PhNHCH=CH	Et(OTs)	2-Thienyl	2-Thienyl	K	351
PhN(Ac)CH=CH	Et(OTs)	4-XPh (X = H, OMe, NMe ₂ , N ⁺ Me ₃)	Ph	L	351
PhN(Ac)CH=CH	Et(OTs)	3,4-DiMeOPh	Ph	L	351
PhN(Ac)CH=CH	Et(OTs)	2-C ₁₀ H ₇	2-C ₁₀ H ₇	L	351
PhN(Ac)CH=CH	Et(OTs)	2-Furyl	2-Furyl	L	351
PhNHCH=CH	Et(OTs)	2-Thienyl	2-Thienyl	L	351
PhNHCH=CH	<i>n</i> -C ₈ H ₁₇ (l)	Ph	Ph	K	359
PhNHCH=CH	<i>n</i> -C ₁₂ H ₂₅ , <i>n</i> -C ₁₈ H ₃₇ (ClO ₄)	Ph	Ph	K	359
PhNHCH=CH	<i>n</i> -Bu	4-MeOPh	4-MeOPh	K	359
PhNHCH=CH	<i>n</i> -C ₁₂ H ₂₅ (ClO ₄)	Ph	Ph	K	359
PhNHCH=CH	Ph(l)	Ph	Ph	K	359
	Et(ClO ₄)	H	H	N	351
	Et(ClO ₄)	<i>n</i> -Pr	<i>n</i> -Pr	N	351
	Et(OTs)	Ph	H	O	358

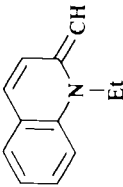
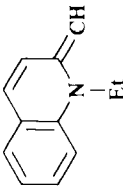
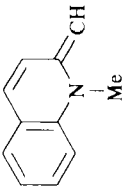
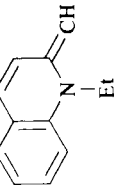
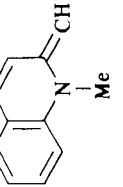
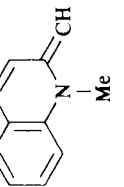
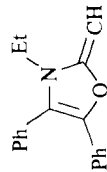
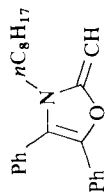
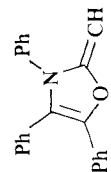
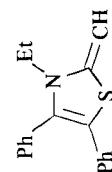
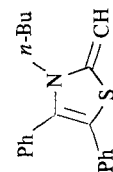
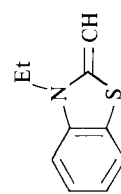
	Et(I)	1- and 2-C ₁₀ H ₇	H	O	358
	Et(I)	H	Ph, 1-C ₁₀ H ₇	O	358
	Et(I)	Ph	Ph	N	351
	Et(I)	Ph	Ph	O	358
	Et(ClO ₄)	4-MeOPh	Ph	N	351
	Et(I)	4-XPh (X = NMe ₂ , N ⁺ Me ₃)	Ph	N	351

TABLE 1.63. (Continued)

R ²	R ³ (X)	R ⁴	R ⁵	Method ^a	Reference
	Et(ClO ₄)	Ph	Ph	P	359
	<i>n</i> -C ₈ H ₁₇ (ClO ₄)	Ph	Ph	P	359
	Ph(I)	Ph	Ph	P	359
	Et(I)	Ph	Ph	P	359
	Et(ClO ₄)	Ph	Ph	P	359
	Et(I)	Ph	H	Q	358

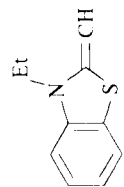
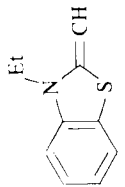
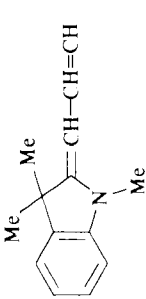
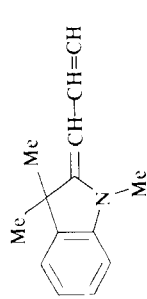
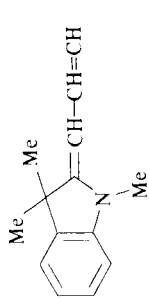
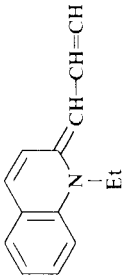
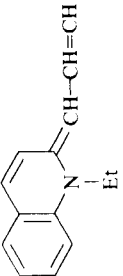
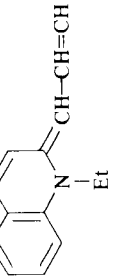
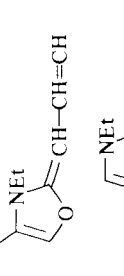
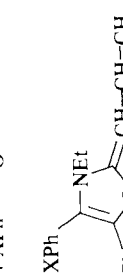
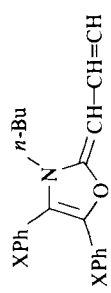
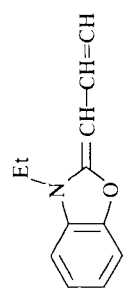
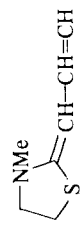
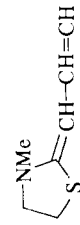
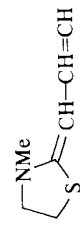
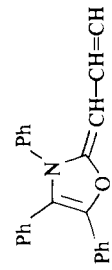
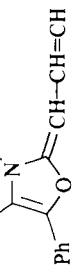
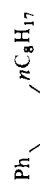
	Et(I)	H	Ph	Q	358
	Et(I)	Ph	Ph, 1-C ₁₀ H ₇ ,	Q	358
	Et(ClO ₄)	Ph	H	R	635
	Et(ClO ₄)	H	Ph	R	635
	Et(ClO ₄)	Ph	Ph	R	635

TABLE 1.63. (Continued)

R ²	R ³ (X)	R ⁴	R ⁵	Method ^a	Reference
	Et(I)	Ph	H	R	635
	Et(ClO ₄)	H	Ph	R	635
	Et(I)	Ph	Ph	R	635
	Et(ClO ₄)	Ph	H	S	351
	Et(ClO ₄)	H	4-XPh (X = H, OMe)	S	351
	Et(ClO ₄)	XPh (X = H, 4-OMe, 3,4-diOMe)	Ph	S	351



(X = OMe)



n-Bu(ClO₄)

n-C₈H₁₇(I)

Ph(I)

Et(I)

Et(ClO₄)

Et(I)

Et(ClO₄)

4-MeOPh

Ph

Ph

Ph

4-XPh
(X = OMe, NMe₂)

2-Furyl

H

4-MeOPh

Ph

Ph

Ph

Ph

2-Furyl

H

S

S

S

T

T

T

R

359

359

359

351

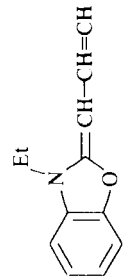
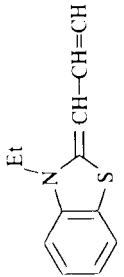
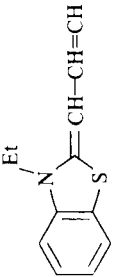
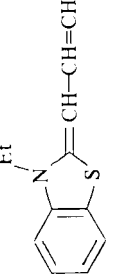
351

351

351

TABLE 1.63. (Continued)

R ²	R ³ (X)	R ⁴	R ⁵	Method ^a	Reference
	Et(ClO ₄)	4-XPh (X = H, OMe)	H	R	351
	Et(ClO ₄)	H	Ph	R	351
	Et(I)	H	4-MeOPh	R	351
	Et(I)	Ph	Ph	R	351
	Et(ClO ₄)	XPh (X = 4-OMe, 4-NMe ₂ , 4-N ⁺ Me ₃ , 3,4-diOMe)	Ph	R	351

	Et(I)	2-Furyl	R	351
	Et(I)	Ph	H	635
	Et(I)	H	Ph	635
	Et(I)	Ph	Ph	635

317

^aA = oxazole/RX

B = oxazolium tosylate/MX (M = H, metal)

C = (R²CO)₂/R⁵COCH(R⁴)NHR³; then MX

D = R²CON(R³)CH(R⁴)COR⁵/P₂O₅ or H₂SO₄; then MX

E = MeCN/R³COCH=N₂/HX/CF₃SO₃H

F = R⁵CH(OH)CONHR³/Ac₂O/HClO₄

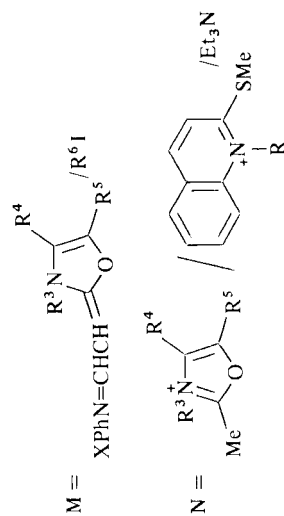
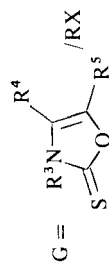
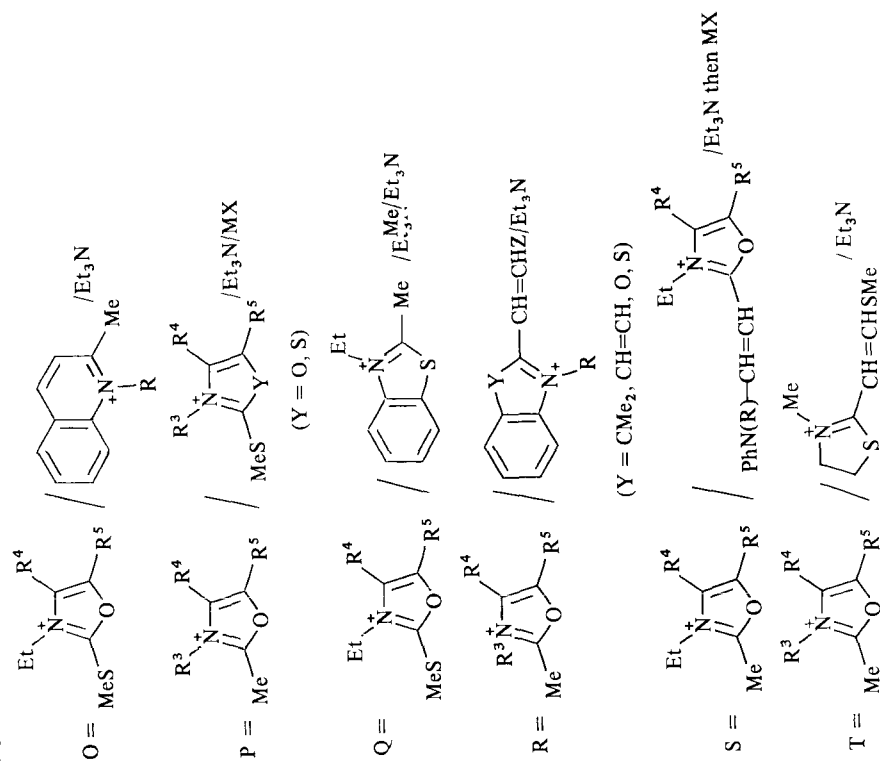


TABLE 1.63. (Continued)

H = 2-chloro-3-ethyl-4,5-diphenyloxazolium tetrafluoroborate/PhNH₂

I = 2-methyloxazole/RX/ArCHO

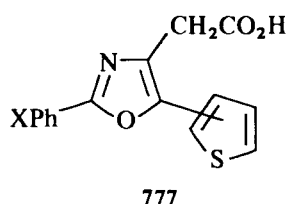
J = oxazolium salt/ArCHO/piperidine

K = oxazolium salt/H₂C=NR (X = OEt, NH₂)L = enamine/Ac₂O

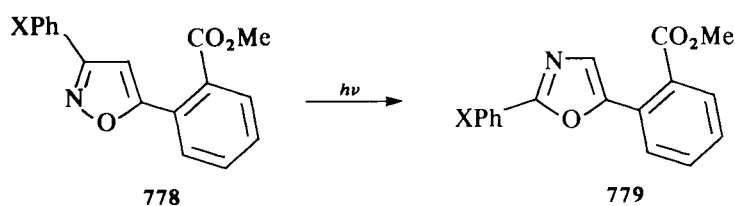
1.8. ADDENDUM

This section includes selected publications and patents that have appeared in 1982 and 1983. These are reports of new processes or extensions of the scope of established processes in oxazole chemistry or new applications of oxazoles.

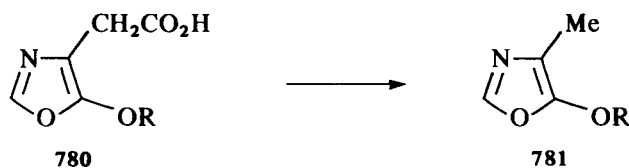
The 5-thienyloxazolylacetic acids **777**, prepared by the Robinson–Gabriel method, are claimed to possess hypolipemic and platelet aggregation inhibitory activity.⁶³⁷



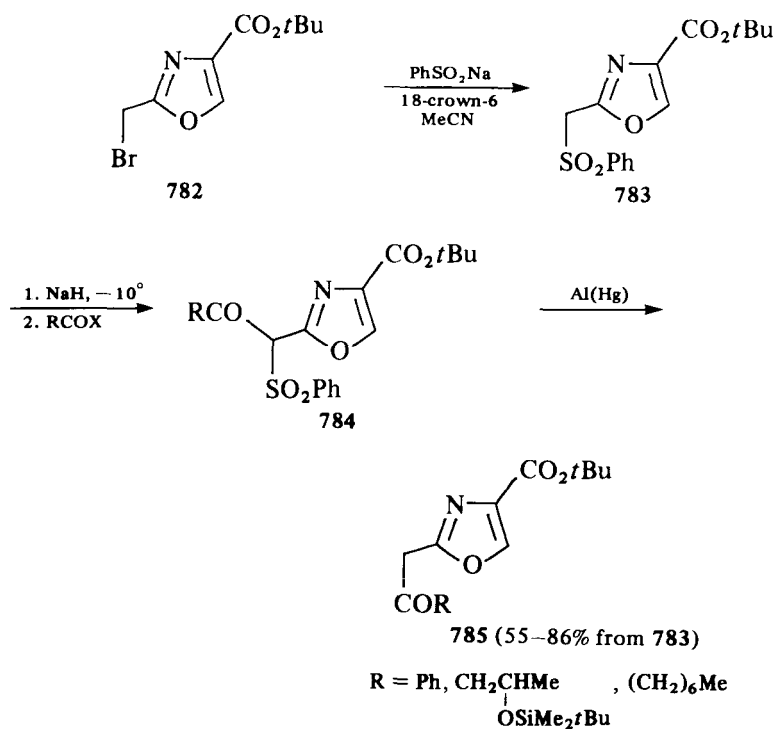
Irradiation of the 2-(3-phenyl-5-isoxazolyl)benzoates **778** gives the 2-(2-phenyl-5-oxazolyl)benzoates **779**.⁶³⁸ These oxazoles are potentially useful as plant growth regulants and herbicides.



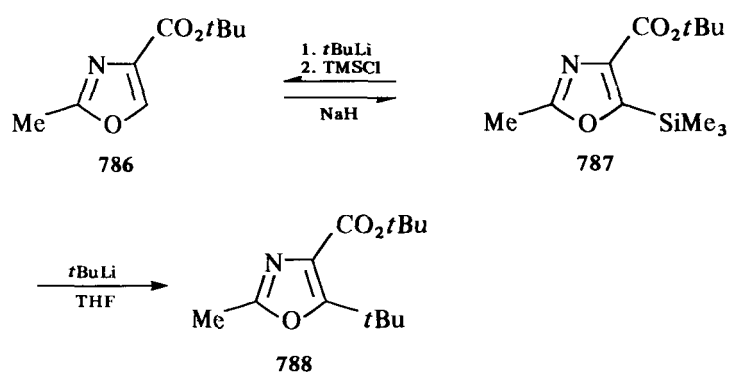
Decarboxylation of the 5-alkoxyoxazolylacetic acids **780** in the presence of maleic anhydride gives the 4-methyl-5-alkoxyoxazoles **781**.⁶³⁹



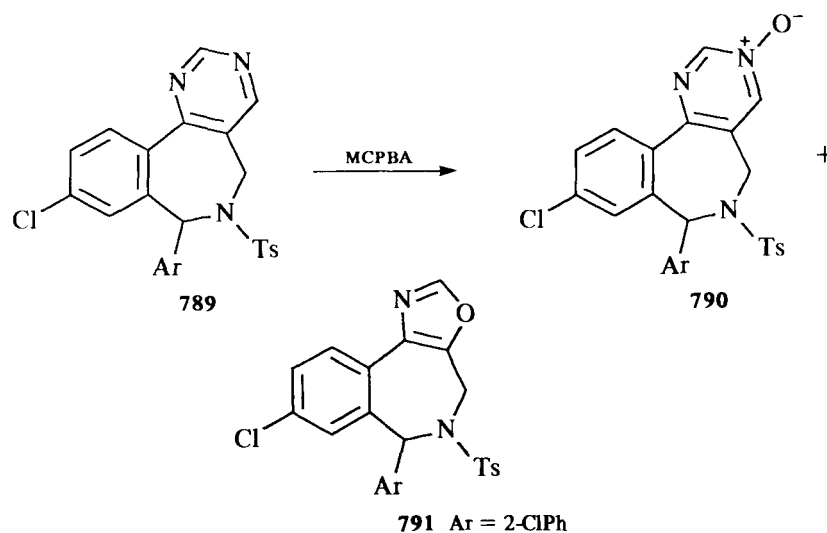
In their studies on the synthesis of the oxazole antibiotic, virginiamycin M2 (**602**), Fijita et al. prepared *t*-butyl 2-benzenesulfonylmethyloxazole-4-carboxylate **783** from the 2-bromomethyl derivative **782** and sodium benzenesulfonate.⁶⁴⁰ Compound **783** is acylated to give **784**, which are reduced with aluminum amalgam to give the 2-acylmethyloxazole esters **785**. Attempts to silylate *t*-butyl 2-methyloxazole-4-carboxylate **786** at the 2-methyl group by treatment of **786** with *t*-butyllithium followed by quenching with chlorotrimethylsilane instead affords the 5-trimethylsilyloxazole **787** (cf. Section 1.3.2).⁶⁴⁰ The oxazole **787** is the



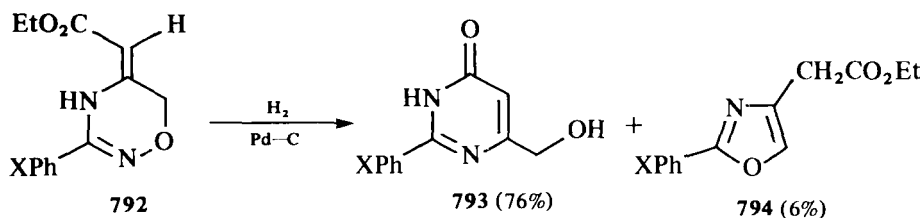
first example of a silicon-substituted oxazole. The reaction of 787 with sodium hydride produces 786 while 787 gives *t*-butyl 2-methyl-5-*t*-butyloxazole-4-carboxylate (788) when treated with *t*-butyllithium.



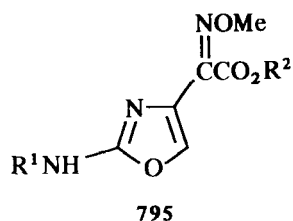
Oxidation of the tricyclic pyrimidine 789 with *m*-chloroperbenzoic acid gives the pyrimidine-3-oxide 790 in 26% yield along with the oxazolo[5,4-*d*] [2] benzazepine 791 in 2% yield.⁶⁴¹ The oxazole was identified by a crystal structure determination.



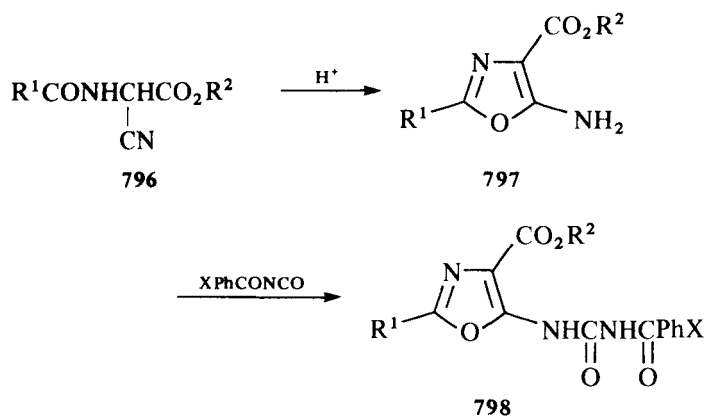
An unusual process that yields the hydroxymethylpyrimidones **793** involves the hydrogenolysis of the 1,2,4-oxadiazines **792**. The oxazolyacetates **794** are isolated as by-products.⁶⁴²



The 2-aminooxazoles **795**, $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{H}$, alkyl, have been prepared by the reaction of urea with the corresponding bromoketones.⁶⁴³ These compounds have been converted to cephalosporin derivatives by the reaction of **795**, $\text{R}^1 = \text{CO}_2 t\text{-Bu}$; $\text{R}^2 = \text{H}$, with benzhydryl 7-aminocephalosporanate.

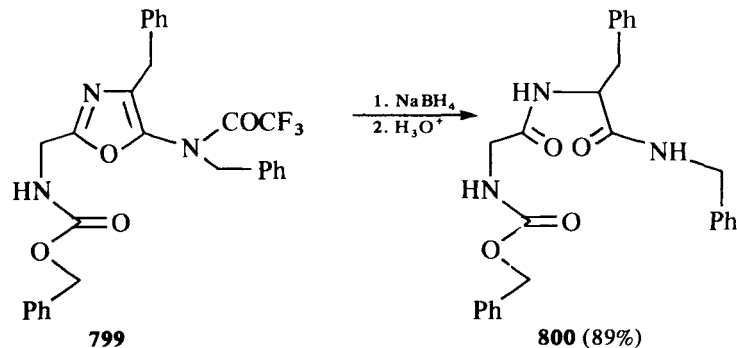


The insecticidal oxazoly ureas **798** were obtained by cyclization of **796** to the 5-aminooxazole-4-carboxylic esters **797** followed by the reaction of **797** with benzoyl isocyanates.⁶⁴⁴



Simple alkylacetylenes when heated with 4-phenyloxazole give 3-alkylfurans (Section 1.6.2).⁶⁴⁵

In their studies directed toward the synthesis of cyclopeptide alkaloids, Lipshutz et al. effected the conversion of the 5-acylaminoxazole **799** to the dipeptide derivative **800**.⁶⁴⁶ The propensity with which 5-heteroatom-substituted oxazoles suffer acid-induced ring opening makes this process a viable one for obtaining compounds such as **800**. In order to prepare suitable oxazole precursors, these



workers have made significant improvements in the established methodology for the synthesis of 5-acylaminoxazoles via cyclization of 2-acylamino nitriles and -amides as well as the development of new procedures for the *N*-alkylation of these species. Successful functionalization of the 2-methyl substituent of 2-methyl-4-alkyl-5-acylaminoxazoles by a lithiation-alkylation sequence was also described for the first time.

REFERENCES

1. R. H. Wiley, *Chem. Rev.*, **37**, 401 (1945).
2. J. W. Cornforth, in *Heterocyclic Compounds*, Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, New York, 1956.

3. J. W. Cornforth, in *The Chemistry of Penicillin*, Princeton University Press, Princeton, N.J., 1949.
4. R. Lakham and B. Ternai, *Adv. Heterocycl. Chem.*, **17**, 99 (1974).
5. I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
6. I. J. Turchi, *Ind. Eng. Chem., Product R/D*, **20**, 32 (1981).
7. V. Petrow, O. Stephenson, and B. Sturgeon, *J. Chem. Soc.*, 4066 (1953).
8. L. Cima, A. Iliceto, M. Mando, and E. Scoffone, *Il Farmaco (Pavia) Ed. Sci.*, **13**, 177 (1958); *Chem. Abstr.*, **53**, 2205i (1959).
9. G. Mattalia and E. Marchetti, *Il Farmaco, Ed. Sci.*, **26**, 512 (1971); *Chem. Abstr.* **75**, 76658q (1971).
10. R. F. Meyer, A. D. Essenburg, R. D. Smith, and H. R. Kaplan, *J. Med. Chem.*, **25**, 996 (1982).
11. S. Ceriani and G. Tarzia, *Ann. Chim. (Rome)*, **63**, 457 (1973); *Chem. Abstr.*, **82**, 43710s (1975).
12. F. W. Short and L. M. Long, *J. Heterocycl. Chem.*, **6**, 707 (1969).
13. Y. Iwakura, F. Toda, H. Suzuki, N. Kusakawa, and K. Yagi, *J. Polymer Sci., A-1*, **10**, 1133 (1972).
14. J. Heinze and H. Baumgärtel, *Chem. Ber.*, **103**, 1572 (1970).
15. S. Emoto and M. Ando, *Nippon Nogei Kagaku Kaishi*, **35**, 1030 (1961); *Chem. Abstr.*, **60**, 8121a (1964).
16. J. Heeres and J. H. Mostmans, U.S. Patent 4,313,953 (1982).
17. W. A. Bolhofer, U.S. Patent 3,953,465 (1976); *Chem. Abstr.* **85**, 21384y (1976).
18. Ya. G. Bal'on and V. A. Smirnov, *J. Org. Chem. USSR*, **17**, 333 (1981).
19. N. P. Demchenko and A. P. Grekov, *Zh. Obshch. Khim.*, **32**, 1219 (1962); *Chem. Abstr.*, **58**, 14431 (1963).
20. J. L. LaMattina, *J. Org. Chem.*, **45**, 2261 (1980).
21. F. Wrede and G. Feuerriegel, *Z. Physiol. Chem.*, **218**, 129 (1933).
22. R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, **70**, 2005 (1948).
23. H. H. Wasserman and F. J. Vinick, *J. Org. Chem.*, **38**, 2407 (1973).
24. T. K. Sevast'yanova and L. B. Volodarskii, *J. Org. Chem. USSR*, **7**, 2046 (1971).
25. N. S. Ooi and D. A. Wilson, *J. Chem. Res. (S)*, 366 (1980).
26. D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, **13**, 789 (1974).
27. U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.*, **16**, 339 (1977).
28. A. M. van Leusen, *Lectures in Heterocyclic Chemistry*, V, S-111 (1980).
29. Y. Koyama, K. Yokose, and L. J. Dolby, *Agric. Biol. Chem.*, **45**, 1285 (1981).
30. K. Henneke, U. Schöllkopf, and T. Neudecker, *Liebigs Ann. Chem.*, **1370** (1979).
31. P. A. Jacobi, D. G. Walker, and I. M. A. Odeh, *J. Org. Chem.*, **46**, 2065 (1981).
32. A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972).
33. H. Saikachi, T. Kitagawa, H. Sasaki, and A. M. van Leusen, *Chem. Pharm. Bull.*, **27**, 793 (1979).
34. O. Possel and A. M. van Leusen, *Heterocycl.*, **7**, 77 (1977).
35. H. A. Houwing, J. Wildeman and A. M. van Leusen, *Tetrahedron Lett.*, 143 (1976).
36. E. Fisher, *Ber.*, **29**, 205 (1896).
37. A. T. Balaban and P. Frangopol, *Acad. Rep. Pop. Rom., Stud. Cercet. Chim.*, **6**, 427 (1958); *Chem. Abstr.*, **53**, 16112 (1969).
38. M. Ionescu, R. Macarovici, and L. Beu, *Stud. Univ. Babes-Bolyai, Ser. Chem.*, **20**, 59 (1975); *Chem. Abstr.*, **84**, 74152g (1976).

39. T. Onaka, *Tetrahedron Lett.*, 4393 (1971).
40. A. DeGroot and H. Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).
41. H. H. Wasserman, J. R. Scheffer, and J. L. Cooper, *J. Am. Chem. Soc.*, **94**, 4991 (1972).
42. D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 328 (1937).
43. H. Bredereck and R. Gompper, *Chem. Ber.*, **87**, 726 (1954).
44. G. Theilig, *Chem. Ber.*, **86**, 96 (1953).
45. J. H. Bowie, P. F. Donaghue, H. J. Rodda, and B. K. Simons, *Tetrahedron*, **24**, 3965 (1968).
46. D. L. Aldous, J. L. Riebsomer, and R. N. Castle, *J. Org. Chem.*, **25**, 1151 (1960).
47. K. Brown, U.S. Patent 3,578,671 (1971); *Chem. Abstr.*, **75**, 36005 (1971).
48. K. Kurusu, H. Nishiyama, and M. Okawara, *Kogyo Kagaku Zasshi*, **71**, 1741 (1968); *Chem. Abstr.*, **70**, 47942u (1969).
49. H. H. Wasserman and T.-J. Lu, *Tetrahedron Lett.*, **23**, 3831 (1982).
50. J. Hutton, B. Potts, and P. F. Southern, *Syn. Commun.*, **9**, 789 (1979).
51. J. J. K. Novák, *Coll. Czech. Chem. Commun.*, **40**, 2855 (1975).
52. M. Tavella, *Ann. Chem. (Rome)*, **53**, 488 (1963), *Chem. Abstr.*, **59**, 7507g (1963).
53. U. H. Lindberg, J. Pedersen, and B. Ulff, *Acta Pharm. Suecica*, **4**, 269 (1967), *Chem. Abstr.*, **68**, 105069m (1968).
54. U. H. Lindberg, *Acta Pharm. Suecica*, **8**, 39 (1971); *Chem. Abstr.*, **74**, 141617w (1971).
55. D. M. O'Mant, Brit. Amended 1,139,940 (1966); *Chem. Abstr.*, **75**, 140825w (1971).
56. F. R. Japp and T. S. Murray, *J. Chem. Soc.*, **63**, 474 (1893).
57. O. Süss, W. Neugebauer, E. Lind, and K. W. Klüpfel, U.S. Patent 3,257,203 (1966); *Chem. Abstr.*, **65**, 16973h (1966).
58. R. A. Jeffreys, *J. Chem. Soc.*, 4823 (1952).
59. M. Lora-Tamayo, R. Madroñero, and H. Leipprand, *Chem. Ber.*, **97**, 2230 (1964).
60. M. P. Doyle, G. D. Spoelhof, and M. A. Zaleta, *J. Heterocycl. Chem.*, **12**, 263 (1975).
61. K. E. Schulte, J. Reisch, and M. Sommer, *Arch. Pharm.*, **299**, 107 (1966).
62. Y. Yura, Japan. Patent 10,129 (1964); *Chem. Abstr.*, **61**, 12006f (1964).
63. F. Eloy and A. Deryckere, *Chem. Thérap.*, **8**, 437 (1973); *Chem. Abstr.*, **81**, 13439x (1974).
64. G. Cappozzi, C. Caristi, M. Gattuso, and G. S. d'Alcontres, *Tetrahedron Lett.*, **22**, 3325 (1981).
65. W. Reppe and A. Magin, Fr. Patent 1,340,996 (1963); *Chem. Abstr.*, **60**, 5506g (1964).
66. Y. Yura, Japan. Patent 29,849 (1964); *Chem. Abstr.*, **62**, 11818d (1965).
67. L. E. Overman, S. Tsuboi, and S. Angle, *J. Org. Chem.*, **44**, 2323 (1979).
68. A. D. Gutman, U.S. Patent 4,137,308 (1979); *Chem. Abstr.*, **90**, 198577a (1979).
69. G. S. Reddy and M. V. Bhatt, *Ind. J. Chem.*, **20B**, 322 (1981).
70. M. V. Bhatt and G. S. Reddy, *Tetrahedron Lett.*, **21**, 2359 (1980).
71. E. Zbiral, E. Bauer, and J. Stroh, *Monatsh Chem.*, **102**, 168 (1971).
72. A. Wolloch and E. Zbiral, *Tetrahedron*, **32**, 1289 (1976).
73. M. P. Doyle, W. E. Buhro, J. G. Davidson, R. C. Elliot, J. W. Hoekstra, and M. Oppenhuizen, *J. Org. Chem.*, **45**, 3657 (1980).
74. T. Ibata and R. Sato, *Bull. Chem. Soc. Japan*, **52**, 3597 (1979).
75. S. H. Mashraqui and P. M. Keehn, *J. Am. Chem. Soc.*, **104**, 4461 (1982).
76. A. Padwa, *Acc. Chem. Res.*, **9**, 371 (1976).
77. P. Gilgen, H. Heimgartner, and H. Schmid, *Heterocycl.*, **6**, 143 (1977).

78. E. C. Taylor and I. J. Turchi, *Chem. Rev.*, **79**, 181 (1979).
79. J. D. Pérez, R. G. deDiaz, and G. I. Yranzo, *J. Org. Chem.*, **46**, 3505 (1981).
80. J. D. Pérez, G. I. Yranzo, and D. A. Wunderlin, *J. Org. Chem.*, **47**, 982 (1982).
81. A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.*, **97**, 4682 (1975).
82. K. Isomura, Y. Hirose, H. Shuyama, S. Abe, G. Ayabe, and H. Taniguchi, *Heterocycl.*, **9**, 1207 (1978).
83. B. Singh and E. F. Ullman, *J. Am. Chem. Soc.*, **89**, 6911 (1967).
84. E. M. Beccalli, L. Majori, A. Marchesini, and C. Torricelli, *Chem. Lett.*, **1980**, 659.
85. U. Schmid, P. Gilgen, H. Heimgartner, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **57**, 1393 (1974).
86. S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Japan*, **40**, 2938 (1967).
87. F. W. Fowler and A. Hassner, *J. Am. Chem. Soc.*, **90**, 2875 (1968).
88. A. Hassner, S. S. Burke, and J. Cheng-fan, *J. Am. Chem. Soc.*, **97**, 4692 (1975).
89. T. C. Gallagher and R. C. Storr, *Tetrahedron Lett.*, **22**, 2905 (1981).
90. A. Padwa, J. K. Rasmussen, and A. Tremper, *J. Am. Chem. Soc.*, **98**, 2605 (1976).
91. D. L. Evans, D. K. Minster, U. Jordis, S. M. Hecht, A. L. Mazzu, Jr., and A. I. Meyers, *J. Org. Chem.*, **44**, 497 (1979).
92. H. Lautenschläger, *Liebigs Ann. Chem.*, 566 (1978).
93. A. Lawson, *J. Chem. Soc.*, 2910 (1956).
94. G. Höfle and W. Steglich, *Chem. Ber.*, **104**, 1408 (1971).
95. S. Jendrzewski and W. Steglich, *Chem. Ber.*, **114**, 1337 (1981).
96. W. Diltthey and J. Friedrichson, *J. Prakt. Chem.*, **127**, 292 (1930).
97. Y. Goto, M. Yamazaki, and M. Hamana, *Chem. Pharm. Bull.*, **19**, 2050 (1971).
98. C. Makkay, L. Hidisan-Tautean, and M. Ionescu, *Rev. Roum. Chim.*, **20**, 643 (1975); *Chem. Abstr.*, **83**, 178889y (1975).
99. A. R. Katritzky and J. M. Lagowski, *Chemistry of the Heterocyclic N-oxides*, Academic Press, New York, 1971.
100. J. H. Bowie, P. F. Donaghue, H. J. Rodda, R. G. Cooks, and D. H. Williams, *Org. Mass. Spectrom.*, **1**, 13 (1968).
101. J. H. Bowie, P. F. Donaghue, H. J. Rodda, and B. K. Simons, *Tetrahedron*, **24**, 3965 (1968).
102. R. Schröder, V. Schöllkopf, E. Blume, and I. Hoppe, *Liebigs Ann. Chem.*, 533 (1975).
103. A. P. Kozikowski and A. Ames, *J. Org. Chem.*, **45**, 2548 (1980).
104. B. H. Lipshutz and R. W. Hungate, *J. Org. Chem.*, **46**, 1410 (1981).
105. H. H. Wasserman, R. J. Gambale, and M. J. Pulwer, *Tetrahedron*, **37**, 4059 (1981).
106. V. Dryanska and K. Ivanov, *God. Sofi. Univ. Khim. Fak.*, **63**, 105 (1968–1969); *Chem. Abstr.*, **76**, 126844r (1972).
107. D. L. Aldous, J. L. Riebsomer, and R. N. Castle, *J. Org. Chem.*, **25**, 1151 (1960).
108. J. Haginiwa, *J. Pharm. Soc. Japan*, **73**, 1310 (1953).
109. H. Takamatsu, S. Minami, J. Aritomi, K. Fujimoto, M. Shimizu, and Y. Takase, Japan. Patent 3284 (1964); *Chem. Abstr.* **61**, 663c (1964).
110. A. Brossi and E. Wenis, *J. Heterocycl. Chem.*, **2**, 310 (1965).
111. B. M. Krasovitskii and V. M. Shershukov, *Khim. Geterotsikl Soedin*, 1977, 611; *Chem. Abstr.*, **87**, 84875w (1977).
112. T. vanEs and O. C. Backelberg, *J. Chem. Soc.*, 1363 (1963).
113. B. S. Friedman, M. Sparks, and R. Adams, *J. Am. Chem. Soc.*, **59**, 2262 (1937).
114. E. V. Brown, *J. Org. Chem.*, **42**, 3208 (1977).

115. Merck and Co., Inc., Netherland Appl. 6,515,006 (1966); *Chem. Abstr.* 65, 13721d (1966).
116. T. N. Ghosh, B. Bhattacharya, and S. Datta, *J. Ind. Chem. Soc.*, **34**, 417 (1957).
117. G. Drefahl and K. Winnefeld, *J. Prakt. Chem.*, **29**, 72 (1965).
118. A. E. Siegrist, *Helv. Chim. Acta*, **50**, 906 (1967).
119. O. Dann, H. Fick, B. Pietzner, E. Walkenhorst, R. Fernbach, and D. Zeh, *Liebigs Ann. Chem.*, 160 (1975).
120. G. E. Wiegand, V. J. Bauer, S. R. Safir, D. . Blickens, and S. J. Riggi, *J. Med. Chem.*, **12**, 943 (1969).
121. V. N. Kerr, D. G. Ott, and F. N. Hayes, *J. Am. Chem. Soc.*, **82**, 186 (1960).
122. V. J. Bauer, W. J. Fanshawe, G. E. Wiegand, and S. R. Safir, *J. Med. Chem.*, **12**, 945 (1969).
123. C. J. Brown, British Patent 1,130,846 (1968); *Chem. Abstr.*, **70**, 28909x (1969).
124. S. Emoto and M. Ando, *Nippon Nogei Kagaku Kaishi*, **35**, 1030 (1961); *Chem. Abstr.*, **60**, 8121a (1964).
125. R. Huisgen and S. Sustmann, *Heterocycl.* **5**, 141 (1976).
126. D. R. Arnold and L. A. Karnischky, *J. Am. Chem. Soc.*, **92**, 1404 (1970).
127. R. Huisgen and M. Seidel, *Chem. Ber.*, **94**, 2509 (1961).
128. R. Gompper and F. Effenberger, *Chem. Ber.*, **92**, 1928 (1959).
129. V. M. Dziomko and A. V. Ivashchenko, *J. Org. Chem.*, *USSR*, **9**, 2206 (1973).
130. R. G. Harrison, German Patent 2,625,229 (1976); *Chem. Abstr.*, **86**, 121320p (1977).
131. O. P. Shvaika and G. P. Klimisha, *Khim. Geterotsikl. Soedin*, **677** (1966); *Chem. Abstr.*, **66**, 46356m (1967).
132. W. J. Hammar and M. A. Rustad, *J. Heterocycl. Chem.*, **18**, 885 (1981).
133. E. Marchetti, G. Mattalia, and V. Rosnati, *J. Med. Chem.*, **11**, 1092 (1968).
134. A. Padwa and L. A. Cohen, *Tetrahedron Lett.*, **23**, 915 (1982).
135. P. H. Derible and L. Taliani, French Patent 2,156,486 (1973); *Chem. Abstr.*, **79**, 126485m (1973).
136. H. Beyer, E. Bulka, and K. Dittrich, *J. Prakt. Chem.*, **30**, 280 (1965).
137. M. Davis, R. Lakhan, and B. Ternai, *J. Heterocycl. Chem.*, **14**, 317 (1977).
138. R. Doenges, German Patent DE 3,021,590 (1981); *Chem. Abstr.*, **96**, 105237t (1982).
139. R. Doenges, German Patent DE 3,021,599 (1981); *Chem. Abstr.*, **96**, 85546n (1982).
140. S. Gabriel, *Ber.*, **43**, 134 (1910).
141. H. E. Zaugg and R. W. De Net, *J. Org. Chem.*, **36**, 1937 (1971).
142. H. E. Zaugg, U.S. Patent 3,819,356 (1974); *Chem. Abstr.*, **82**, 12276a (1975).
143. R. Gompper and H. Rühle, *Liebigs Ann. Chem.*, **626**, 83 (1959).
144. T. L. Gilchrist and D. P. J. Pearson, *J. Chem. Soc., Perkin I*, 989 (1976).
145. I. A. Silberg, R. Macarovici, and N. Palibroda, *Tetrahedron Lett.*, 1321 (1976).
146. T. Wieland, B. Hennig, and W. Löw, *Chem. Ber.*, **95**, 2232 (1962).
147. K. Burger, R. Ottlinger, H. Goth, and J. Firl, *Chem. Ber.*, **115**, 2494 (1982).
148. N. Saito, T. Kurihara, K. Yamanaka, S. Tsuruta, and S. Yasuda, *Yakugaku Zasshi*, **88**, 1289 (1968); *Chem. Abstr.*, **70**, 37686z (1969).
149. I. Simiti and E. Chindris, *Arch. Pharm. (Weinheim)*, **305**, 509 (1972).
150. I. Simiti and E. Chindris, *Arch. Pharm. (Weinheim)*, **308**, 688 (1975).
151. B. Liphardt and W. Lüttke, *Liebigs Ann. Chem.*, **1981**, 1118.
152. G. J. Durant, J. C. Emmett, and C. R. Ganellin, U.S. Patent 3,950,353 (1976); *Chem. Abstr.*, **85**, 21373 (1976).

153. R. Gompper and H. Rühle, *Liebigs Ann. Chem.*, **626**, 92 (1959).
154. A. D. Gutman, U.S. Patent 4,137,308 (1979); *Chem. Abstr.*, **90**, 168577a (1979).
155. C. Tanaka, *Yakugaku Zasshi*, **85**, 186 (1965); *Chem. Abstr.*, **62**, 16222 (1965).
156. R. H. Good and G. Jones, *J. Chem. Soc. (C)*, 1938 (1970).
157. J. M. Liesch, D. S. Millington, R. C. Pandey, and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **98**, 8237 (1976).
158. G. Tarzia, P. Schiatti, D. Selva, D. Favara, and S. Ceriani, *Eur. J. Med. Chem. – Chim. Therap.*, **11**, 263 (1976).
159. Y. Oikawa, T. Yoshioka, K. Mohri, and O. Yonemitsu, *Heterocycl.*, **12**, 1457 (1979).
160. R. Pflieger and M. von Strandtmann, *Chem. Ber.*, **90**, 1455 (1957).
161. R. Pflieger and H. Vogt, *Chem. Ber.*, **90**, 1467 (1957).
162. C. Shin, Y. Sato, H. Sugiyama, K. Nanjo, and J. Yoshimura, *Bull. Chem. Soc. Japan*, **50**, 1788 (1977).
163. K. Matsumura, O. Miyashita, H. Shimadzu, and N. Hashimoto, *Chem. Pharm. Bull.*, **24**, 948 (1976).
164. P. K. Sen, C. J. Veal, and D. W. Young, *J. Chem. Soc., Perkin I*, 3053 (1981).
165. J. W. Cornforth, E. Fawaz, L. J. Goldsworthy, and Sir Robert Robinson, *J. Chem. Soc.*, 1549 (1949).
166. A. I. Meyers and J. P. Lawson, *Tetrahedron Lett.*, **22**, 3163 (1981).
167. H. Dworschak and F. Weygand, *Chem. Ber.*, **101**, 302 (1968).
168. W. Steglich, H.-U. Heininger, H. Dworschak, and F. Weygand, *Angew. Chem., Internat. Edit. Engl.*, **6**, 807 (1967).
169. Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, **23**, 235 (1982).
170. Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, **23**, 1193 (1982).
171. Y. Hamada, S. Morita, and T. Shioiri, *Heterocycl.*, **17**, 321 (1982).
172. G. Ambrus, I. Barta, G. Horvath, M. Soti, and P. Sohar, *Acta Chim. Acad. Sci. Hung.* **99**, 421 (1979); *Chem. Abstr.*, **91**, 192869p (1979).
173. J. W. Cornforth and E. Cookson, *J. Chem. Soc.*, 1085 (1952).
174. F. Korte and K. Störiko, *Chem. Ber.*, **93**, 1033 (1960).
175. C. G. Stuckwisch and D. D. Powers, *J. Org. Chem.*, **25**, 1819 (1960).
176. K. Dietliker, P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **59**, 2074 (1976).
177. H. Person, K. Luanglath, M. Baudru, and A. Foucaud, *Bull. Soc. Chim. Fr.*, 1989 (1976).
178. C. H. Stammer, *J. Org. Chem.*, **25**, 460 (1960).
179. J. R. Merchant, M. S. Venkatesh, and G. Martyres, *Ind. J. Chem.*, **20B**, 712 (1981).
180. A. W. Allan and B. H. Walter, *J. Chem. Soc. (C)*, 1397 (1968).
181. A. I. Meyers and D. G. Walker, *J. Org. Chem.*, **47**, 2999 (1982).
182. J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 93 (1953).
183. H. J. Jakobsen, E. H. Larsen, P. Madsen, and S.-O. Lawesson, *Ark. Kemi*, **24**, 519 (1965); *Chem. Abstr.*, **64**, 3404c (1966).
184. G. Ambrus and I. Barta, *Prostaglandins*, **10**, 661 (1975).
185. D. L. Coffen, U.S. Patent 4,093,654 (1978); *Chem. Abstr.*, **89**, 179982j (1978).
186. M. E. Alonso and P. Jano, *J. Heterocycl. Chem.*, **17**, 721 (1980).
187. D. R. Arnold and Y. C. Chang, *J. Heterocycl. Chem.*, **8**, 1097 (1971).
188. H. Bredereck and R. Bangert, *Chem. Ber.*, **97**, 1414 (1964).
189. P. Chauvin, J. Morel, P. Pastour, and J. Martinez, *Bull. Soc. Chim. Fr.*, 2079 (1974).

190. N. Soma, J. Nakazawa, T. Watanabe, Y. Sato, and G. Sunagawa, *Chem. Pharm. Bull.*, **15**, 619 (1967).
191. A. B. A. Jansen and M. Szelke, *J. Chem. Soc.*, 405 (1961).
192. A. S. Afridi, A. R. Katritzky, and C. A. Ramsden, *J. Chem. Soc., Perkin I*, 315 (1976).
193. A. Furlenmeier, P. Quitt, K. Vogler, and P. Lanz, U.S. Patent 3,957,758 (1976); *Chem. Abstr.*, **85**, 123909 (1976).
194. J. M. Essery, U. Corbin, V. Sprancmanis, L. B. Crast, R. Graham, P. F. Misco, D. Willner, D. N. McGregor, and L. C. Cheney, *J. Antibiotics*, **27**, 573 (1974).
195. Th. Rinderspacher and B. Prijs, *Helv. Chim. Acta*, **43**, 1522 (1960).
196. T. P. Sycheva, T. Kh. Trupp, and M. N. Shchukina, *Zh. Obshch. Khim.*, **32**, 3666 (1962); *Chem. Abstr.*, **58**, 12527h (1963).
197. T. P. Sycheva, T. Kh. Trupp, and M. N. Shchukina, *Z. Obshch. Khim.*, **32**, 2839 (1962).
198. J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 96 (1947).
199. G. R. Delpierre, F. W. Eastwood, G. E. Gream, D. G. I. Kingston, P. S. Sarin, Lord Todd, and D. H. Williams, *J. Chem. Soc. C*, 1653 (1966).
200. R. K. Howe and L. F. Lee, U.S. Patent 4,360,678 (1982).
201. D. Seyferth and H. Shih, *J. Am. Chem. Soc.*, **95**, 8464 (1973).
202. R. Huisgen and H. Blaschke, *Chem. Ber.*, **98**, 2985 (1965).
203. D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Perkin I*, 550 (1973).
204. F. Ramirez, S. B. Bhatia, C. D. Telefus, and C. P. Smith, *Tetrahedron*, **25**, 771 (1969).
205. O. Tsuge, K. Sakai, and M. Tashiro, *Tetrahedron*, **29**, 1983 (1973).
206. R. Scarpati, M. L. Graziano, and R. A. Nicolaus, *Gazz. Chim. Ital.*, **98**, 681 (1968).
207. R. Scarpati, M. L. Graziano, and R. A. Nicolaus, *Gazz. Chim. Ital.*, **99**, 1339 (1969).
208. Yu. I. Ryabukhin, V. D. Karpenko, and G. N. Dorofeenko, *J. Org. Chem. USSR*, **18**, 206 (1982).
209. M. L. Graziano, R. Scarpati, and E. Fattorusso, *J. Heterocycl. Chem.*, **11**, 529 (1974).
210. B. Kübel, G. Höfle, and W. Steglich, *Angew. Chem., Intl. Ed. Engl.* **14**, 58 (1975).
211. W. Steglich and G. Höfle, *Chem. Ber.*, **102**, 883 (1969).
212. W. Steglich and G. Höfle, *Chem. Ber.*, **102**, 899 (1969).
213. W. Steglich and G. Höfle, *Chem. Ber.*, **102**, 1129 (1969).
214. D. Hoppe, *Ann. Chem.*, 2185 (1976).
215. H. Takagaki, N. Yasuda, M. Asaoka, and H. Takci, *Chem. Lett.*, 183 (1979).
216. H. Takagaki, S. Tanabe, S. Asaoka, and H. Takei, *Chem. Lett.*, 347 (1979).
217. M. I. Komendantov, R. R. Bektukhametov, and R. R. Kostikov, *J. Org. Chem. USSR*, **14**, 1448 (1978).
218. R. Paulissen, Ph. Moniotte, A. J. Hubert, and Ph. Teyssié, *Tetrahedron Lett.*, 3311 (1974).
219. N. T. Buu and J. T. Edward, *Can. J. Chem.*, **50**, 3730 (1972).
220. R. Schröder, U. Schöllkopf, E. Blume, and I. Hoppe, *Liebigs Ann. Chem.*, 533 (1975).
221. I. Maeda, K. Togo, and R. Yoshida, *Bull. Chem. Soc. Jap.*, **44**, 1407 (1971).
222. Z. I. Itov, S. D. L'vova, and V. I. Gunar, *Khim. Farm. Zh.*, **12**, 102 (1978); *Chem. Abstr.*, **90**, 168489y (1979).
223. A. Kakehi, S. Ito, T. Funahashi, and Y. Ota, *J. Org. Chem.*, **41**, 1570 (1976).
224. P. A. Jacobi, S. Ueng, and D. Carr, *J. Org. Chem.*, **44**, 2042 (1979).
225. R. Gompper, *Chem. Ber.*, **89**, 1762 (1956).

226. J. F. Willems and A. Vandenberghe, *Bull. Soc. Chim. Belg.*, **70** 745 (1961).
227. G. Lacasse and J. M. Muchowski, *Can. J. Chem.*, **50**, 3082 (1972).
228. G. Kjellin and J. Sandström, *Acta Chem. Scand.*, **23**, 2879 (1969).
229. Institute of Organic Chemistry, Academy of Sciences, Ukrainian S.S.R., Fr. Patent 1,450,443 (1966); *Chem. Abstr.*, **67**, 43806t (1967).
230. T. E. Jackson, U.S. Patent 4,022,607 (1977); *Chem. Abstr.*, **87**, 5284 (1977).
231. G. Mattalia, C. Serafini, and U. Bucciarelli, *Farmaco Ed. Sci.*, **31**, 457 (1976); *Chem. Abstr.*, **85**, 94267x (1976).
232. C. K. Bradsher and W. J. Jones, Jr., *J. Org. Chem.*, **32**, 2079 (1967).
233. G. J. Durant, J. C. Emmett, C. R. Ganellin, and H. D. Prain, U.S. Patent 4,013,769 (1977); *Chem. Abstr.*, **87**, 23063 (1977).
234. P. G. Hughes and J. P. Verge, German Patent 2,213,569 (1972); *Chem. Abstr.*, **78**, 4240 (1973).
235. E. P. Nesynov, M. M. Besprozvannaya, and Zh. N. Belaya, *Khim. Geterotsikl. Soedin.*, 753 (1975).
236. M. Lora-Tamayo, R. Madroñero, D. Gracián, and V. Gómez-Parra, *Tetrahedron Suppl.*, **8**, (1) 305 (1966).
237. R. Gompper and U. Heinemann, *Angew. Chem. Int. Ed. Engl.*, **20**, 296 (1981).
238. T. E. Jackson, U.S. Patent 3,888,870 (1975); *Chem. Abstr.*, **83**, 114383w (1975).
239. S. Shimada, Japan. Patent 79 32, 465 (1979); *Chem. Abstr.*, **91**, 107970x (1979).
240. A. M. van Leusen and H. E. van Gennep, *Tetrahedron Lett.*, **1973**, 627.
241. A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972).
242. S. P. J. M. van Nispen, C. Mensink, and A. M. van Leusen, *Tetrahedron Lett.*, **21**, 3723 (1980).
243. P. Girault and J. Perronnet, *J. Heterocycl. Chem.* **18**, 419 (1981).
244. Y-C. Kuo, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, **30**, 526 (1982).
245. T. Naito, K. Veno, and T. Miki, Japan. Patent 23,088 (1969); *Chem. Abstr.*, **71**, 124405 (1969).
246. D. F. Corbett, *Chem. Commun.*, 803 (1981).
247. M. J. S. Dewar and I. J. Turchi, *J. Org. Chem.* **40**, 1521 (1975).
248. I. J. Turchi, unpublished result.
249. R. F. C. Brown, I. D. Rae, J. S. Shannon, S. Sternhell, and J. M. Swan, *Aust. J. Chem.*, **19**, 503 (1966).
250. N. Ya. Kvitko, R. V. Khozeva, N. S. Fedorova, V. A. Smirnova, and A. V. El'tsov, *Khim. Geterotsikl. Soedin.*, 474 (1979); *Chem. Abstr.*, **91**, 74517z (1979).
251. O. P. Lobanov, A. P. Martynyuk, and B. S. Drach, *Zh. Obshch. Khim.*, **50**, 2248 (1980); *Chem. Abstr.*, **94**, 84229h (1981).
252. V. S. Brovarets, O. P. Lobanov, and B. S. Drach, *Zh. Obshch. Khim.*, **52**, 1438 (1982); *Chem. Abstr.*, **97**, 182536n (1982).
253. R. L. White, U.S. Patent 4,049,650 (1977); *Chem. Abstr.* **88**, 6887h (1978).
254. C. Makkay and I. Literati-Kiraly, *Stud. Univ. Babes-Bolyai, Ser. Chem.*, **23**, 52 (1978); *Chem. Abstr.*, **90**, 203923j (1979).
255. A. F. Vompe, N. V. Monich, and N. S. Spasokukotskii, *J. Org. Chem. USSR*, **10**, 1988 (1974).
256. M. Nair and H. Shechter *Chem. Commun.*, 793 (1978).
257. A. Treibs and W. Sutter, *Chem. Ber.*, **84**, 96 (1951).
258. J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 158 (1957).

259. A. Padwa, E. Chen, and A. Ku, *J. Am. Chem. Soc.*, **97**, 6484 (1975).
260. W. G. Salmond, U.S. Patent 3,994,915 (1976); *Chem. Abstr.*, **86**, 106564 (1977).
261. A. Shafice and G. Kiacay, *J. Heterocycl. Chem.*, **18**, 899 (1981).
262. A. Dornow and H. Hell, *Chem. Ber.*, **93**, 1998 (1960).
263. G. Ya Kondrat'eva and K. Chzhi-Khen, *Z. Obshch. Khim.*, **32**, 2348 (1962).
264. P. N. Craig and M. P. Olmsted, *J. Org. Chem.*, **22**, 559 (1957).
265. M. Giannella and F. Gualtieri, *Boll. Chem. Farm.*, **105**, 708 (1966); *Chem. Abstr.*, **66**, 104945 (1967).
266. H-J. Riebel, I. Hammann, and G. Unterstenhoefer, German Patent 2,144,393 (1973); *Chem. Abstr.* **78**, 147975 (1973).
267. L. Peshakova, V. Kalcheva and D. Simov, *Khim. Geterotsikl. Soedin.*, 1011 (1981); *Chem. Abstr.*, **95**, 187106r (1981).
268. B. K. Pattanayak, D. N. Rout, and G. N. Mahapatra, *Ind. J. Chem.*, **16B**, 1030 (1978).
269. J. P. Nath, B. L. Nayak, and G. N. Mahapatra, *Ind. J. Chem.*, **20B**, 827 (1981).
270. S. Rao and A. S. Mittra, *J. Ind. Chem. Soc.*, **58**, 925 (1981).
271. A. F. Cockerill, A. Deacon, R. G. Harrison, D. J. Osborne, D. M. Prime, W. J. Ross, A. Todd, and J. P. Verge, *Synthesis*, 591 (1976).
272. F. Eloy and A. Deryckere, *Chim. Theráp.*, **8**, 437 (1973).
273. L. E. Overman, S. Tsuboi, J. P. Roos, and G. F. Taylor, *J. Am. Chem. Soc.*, **102**, 747 (1980).
274. L. E. Overman and J. P. Roos, *J. Org. Chem.*, **46**, 811 (1981).
275. A. M. van Leusen, H. J. Jeuring, J. Wildeman, and S. P. J. M. van Nispen, *J. Org. Chem.*, **46**, 2069 (1981).
276. K. Gewald, H. Schäfer and B. Plumbohm, *J. Prakt. Chem.*, **315**, 44 (1973).
277. J. D. Pérez, R. G. de Díaz, and G. I. Yranzo, *J. Org. Chem.*, **46**, 3505 (1981).
278. C. Tanaka and M. Nishida, *Yakugaku Zasshi*, **98**, 605 (1978); *Chem. Abstr.*, **89**, 197378w (1978).
279. G. Crank, British Patent 1,264,258 (1972); *Chem. Abstr.*, **76**, 126963d (1972).
280. I. Ito, S. Murakami, and K. Tanabe, *Yakugaku Zasshi*, **86**, 300 (1966); *Chem. Abstr.*, **65**, 3852d (1966).
281. W. J. Ross, A. Todd, and J. P. Verge, German Patent 2,618,547 (1976); *Chem. Abstr.*, **86**, 89797m (1977).
282. W. J. Ross and A. Todd, U.S. Patent 4,216,219 (1980); *Chem. Abstr.*, **94**, 65663d (1981).
283. I. Kumashiro, *Nippon Kagaku Zasshi*, **82**, 928 (1961); *Chem. Abstr.*, **57**, 11183d (1962).
284. R. Gompper and O. Christmann, *Chem. Ber.*, **92**, 1944 (1959).
285. J. P. Nath, M. Dash, S. C. Satrusallya, and G. N. Mahapatra, *Ind. J. Chem.*, **20B**, 606 (1981).
286. M. Shibata, C. Tanaka, M. Inoue, and T. Ishida, *Chem. Pharm. Bull.*, **30**, 412 (1982).
287. W. Loop, H-J. May, and H. Baganz, *Chem. Ber.*, **102**, 230 (1969).
288. G. Crank and M. J. Foulis, *J. Med. Chem.*, **14**, 1075 (1971).
289. G. Crank, M. Neville, and R. Ryden, *J. Med. Chem.*, **16**, 1402 (1973).
290. G. Crank, *Tetrahedron Lett.*, 4537 (1974).
291. B. K. Pattanayak, D. N. Rout, and G. N. Mahapatra, *J. Ind. Chem. Soc.*, **55**, 264 (1978).
292. J. P. Nath, M. Dash, D. N. Rout, and G. N. Mahapatra, *Ind. J. Chem.*, **18B**, 384 (1979).

293. C. Tanaka and S. Kuriyama, *Yakugaku Zasshi*, **99**, 78 (1979); *Chem. Abstr.*, **90**, 203922h (1979).
294. C. Tanaka and H. Asai, *Yakugaku Zasshi*, **91**, 425, 436 (1971); *Chem. Abstr.*, **75**, 48962r, 35847g (1971).
295. E. Haruki, H. Imanaka, and E. Imoto, *Bull. Chem. Soc. Japan*, **41**, 1368 (1968).
296. K. Ikeda, T. Sumi, K. Yokoi, and Y. Mizuno, *Chem. Pharm. Bull.*, **21**, 1327 (1973).
297. T. Kato, N. Oda, and I. Ito, *Chem. Pharm. Bull.*, **25**, 491 (1977).
298. S. Nishigaki, Y. Kanamori, and K. Senga, *Chem. Pharm. Bull.*, **26**, 2497 (1978).
299. R. G. Harrison, M. R. J. Jolley, and J. C. Saunders, *Tetrahedron Lett.*, 293 (1976).
300. R. A. Glennon and M. von Strandtmann, *J. Heterocycl. Chem.*, **12**, 135 (1975).
301. G. Ya. Kondrat'eva, M. A. Aitzhanova, V. S. Bogdanov, and Z. N. Ivanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 894 (1978); *Chem. Abstr.*, **89**, 24203g (1978).
302. D. Clerin and J-P. Fleury, *Bull. Soc. Chim. Fr.*, 3127 (1973).
303. D. Clerin and J-P. Fleury, *Bull. Soc. Chim. Fr.*, 3134 (1973).
304. D. Clerin, G. Kille, and J-P. Fleury, *Tetrahedron*, **30**, 469 (1974).
305. D. Clerin, B. Meyer, and J-P. Fleury, *Bull. Soc. Chim. Fr.*, 2053 (1976).
306. W. G. M. Jones and G. R. Ramage, British Patent 596,537 (1948); *Chem. Abstr.*, **42**, 7342e (1948).
307. J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.*, **88**, 3829 (1966).
308. M. Sekiya, J. Suzuki, and Y. Kakiya, *Chem. Pharm. Bull.*, **18**, 1233 (1970).
309. J. Lichtenberger and J-P. Fleury, *Bull. Soc. Chim. Fr.*, 1320 (1955).
310. J. Lichtenberger and J-P. Fleury, *Bull. Soc. Chim. Fr.*, 1184 (1956).
311. J-P. Fleury, A. Baysang, and D. Clerin, *Bull. Soc. Chim. Fr.*, 4108 (1969).
312. J-P. Fleury, A. Baysang, *Bull. Soc. Chim. Fr.*, 4102 (1969).
313. J. Poupaert, A. Bruylants, and P. Crooy, *Synthesis*, 622 (1972).
314. K. Matsumura, H. Shimadzu, O. Miyashita, and N. Hashimoto, *Chem. Pharm. Bull.*, **24**, 491 (1976).
315. K. Matsumura, T. Saraie, and N. Hashimoto, *Chem. Pharm. Bull.*, **24**, 924 (1976).
316. B. S. Drach and G. N. Mis'kevich, *J. Org. Chem. USSR*, **10**, 2329 (1974).
317. B. S. Drach and G. N. Mis'kevich, *J. Org. Chem. USSR*, **13**, 1283 (1977).
318. F. Weygand, W. Steglich, and W. Oettmeier, *Chem. Ber.*, **103**, 1655 (1970).
319. J. P. Chupp and K. L. Leschinsky, *J. Heterocycl. Chem.*, **17**, 705 (1980).
320. J. P. Chupp and K. L. Leschinsky, *J. Heterocycl. Chem.*, **17**, 711 (1980).
321. J. P. Chupp, J. J. D'Amico, and K. L. Leschinsky, *J. Org. Chem.*, **43**, 3553 (1978).
322. J. A. Deyrup and K. K. Killion, *J. Heterocycl. Chem.*, **9**, 1045 (1972).
323. M. Hirobe, R. Sato, and T. Okamoto, *Yakugaku Zasshi*, **91**, 834 (1971); *Chem. Abstr.*, **75**, 129699n (1971).
324. A. R. Martin and R. Ketcham, *J. Org. Chem.*, **31**, 3612 (1966).
325. V. P. Shah, G. Lam, and R. Ketcham, *J. Med. Chem.*, **14**, 456 (1971).
326. H. Dounchis, *J. Org. Chem.*, **37**, 2583 (1972).
327. G. V. Protopopova, A. D. Dzyuban, N. I. Nesterenko, L. I. Reidalova, B. S. Drach, E. P. Sviridov, and Ya. P. Shaturskii, *Otkrytiya Izobret. Prom. Obrabztsy, Tovarnye Znaki*, 254 (1979); *Chem. Abstr.*, **91**, 205664 (1979).
328. M. Hoffer, U.S. Patent 3,290,326 (1966); *Chem. Abstr.*, **66**, 65455j (1967).
329. M. J. S. Dewar and I. J. Turchi, *J. Am. Chem. Soc.*, **96**, 6148 (1974).
330. M. J. S. Dewar and I. J. Turchi, *J. Chem. Soc. Perkin 2*, 724 (1977).
331. I. J. Turchi and C. A. Maryanoff, *Synthesis*, 837 (1983).

332. B. Jackson, N. Gakis, M. Märky, H-J. Hansen, W. von Phillipsborn, and H. Schmid, *Helv. Chim. Acta*, **55**, 916 (1972).
333. G. Kille and J-P. Fleury, *Bull. Soc. Chim. Fr.*, 4631 (1968).
334. Y. Ohtsuka, *Bull. Chem. Soc. Jap.*, **43**, 187 (1970).
335. V. D. Patil and L. B. Townsend, *J. Heterocycl. Chem.*, **8**, 503 (1971).
336. D. Clerin and J-P. Fleury, *Bull. Soc. Chim. Fr.*, 211 (1974).
337. B. S. Drach, E. P. Sviridov, A. A. Kisilenko, and A. V. Kirsanov, *J. Org. Chem. USSR*, **9**, 1842 (1973).
338. A. H. Cook and G. D. Hunter, *J. Chem. Soc.*, 3789 (1952).
339. K. Dietliker, W. Stegmann, and H. Heimgartner, *Heterocycl.*, **14**, 929 (1980).
340. E. Schaumann, S. Grabley, and G. Adiwidjaja, *Leibigs Ann. Chem.*, 264 (1981).
341. R. I. Fryer, J. V. Earley, and J. F. Blount, *J. Org. Chem.*, **42**, 2212 (1977).
342. R. L. Vigdahl, R. H. Ferber, and S. L. Parrish, *Thrombosis Res.*, **21**, 547 (1981).
343. B. S. Drach, I. Ya. Dolgushina, and A. D. Sinitsa, *Zh. Obshch. Khim.*, **45**, 1251 (1975); *Chem. Abstr.*, **83**, 131688s (1975).
344. J. Rachón and U. Schöllkopf, *Liebigs Ann. Chem.*, 1186 (1981).
345. J. Rachón and U. Schöllkopf, *Liebigs Ann. Chem.*, 1693 (1981).
346. W. P. Fehlhammer, K. Bartel, and W. Petri, *J. Organometal. Chem.*, **87**, C34 (1975).
347. L. I. Zakharkin, A. V. Grebennikov, and A. I. L'vov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 106 (1970).
348. P. M. Weintraub, *J. Med. Chem.*, **15**, 419 (1972).
349. Y. Goto and M. Yamazaki, *Chem. Pharm. Bull.*, **18**, 756 (1970).
350. A. Takamizawa and H. Sato, *Chem. Pharm. Bull.*, **22**, 1526 (1974).
351. R. A. Jeffreys, *J. Chem. Soc.*, 4823 (1952).
352. D. G. Ott, F. N. Hayes, and V. V. Kerr, *J. Am. Chem. Soc.*, **78**, 1941 (1956).
353. H-J. Federsel and J. Bergman, *Heterocycl.*, **14**, 33 (1980).
354. E. D. Sych and O. V. Moreiko, *Khim. Geterotsikl. Soedin.*, 1034 (1970); *Chem. Abstr.*, **74**, 143297r (1971).
355. O. P. Shvaika and V. I. Fomenko, *J. Org. Chem. USSR*, **10**, 2441 (1974).
356. A. R. Katritzky and A. Zia, *J. Chem. Soc.*, 131 (1982).
357. Yu. I. Ryabukhin, V. D. Karpenko, and G. N. Dorofeenko, *J. Org. Chem. (USSR)*, **18**, 206 (1982).
358. E. D. Sych and Zh. N. Belaya, *Zh. Obshch. Khim.*, 1507 (1963); *Chem. Abstr.*, **60**, 695f (1964).
359. R. A. Jeffreys, *J. Chem. Soc.*, 3396 (1957).
360. T. Takahashi and M. Hayami, *Yakugaku Zasshi*, **80**, 651 (1960); *Chem. Abstr.*, **54**, 22569a (1960).
361. T. Takahashi and M. Hayami, *Yakugaku Zasshi*, **80**, 646 (1960); *Chem. Abstr.*, **54**, 22568h (1960).
362. A. Hetzheim and H. Pusch, *Z. Chem.*, **15**, 267 (1975).
363. R. S. Karimoto, B. Axelrod, J. Wolinsky, and E. D. Schall, *Tetrahedron Lett.*, 83 (1962).
364. R. S. Karimoto, B. Axelrod, J. Wolinsky, and E. D. Schall, *Phytochemistry*, **3**, 349 (1964).
365. D. G. O'Donovan and H. Horan, *J. Chem. Soc., (C)*, 331 (1971).
366. W. D. Crow and J. H. Hodgkin, *Aust. J. Chem.*, **17**, 119 (1964).
367. D. L. Dreyer, *J. Org. Chem.*, **33**, 3658 (1968).

368. T. Onaka, *Tetrahedron Lett.*, 4393 (1971).
369. B. Burke, H. Parkins, and A. M. Talbot, *Heterocycl.*, **12**, 349 (1979).
370. B. S. Joshi, W. I. Taylor, D. S. Bhate, and S. S. Karmarkar, *Tetrahedron*, **19**, 1437 (1963).
371. Y. Koyama, K. Yokose, and L. J. Dolby, *Agric. Biol. Chem.*, **45**, 1285 (1981).
372. G. I. Birnbaum and S. R. Hall, *J. Am. Chem. Soc.*, **98**, 1926 (1976).
373. A. I. Meyers and R. A. Amos, *J. Am. Chem. Soc.*, **102**, 870 (1980).
374. J. M. Liesch and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **99**, 1645 (1977).
375. J. W. Westley, C-M. Liu, R. H. Evans, and J. F. Blount, *J. Antibiotics*, **32**, 874 (1979).
376. D. G. I. Kingston, Lord Todd, and D. H. Williams, *J. Chem. Soc., (C)*, 1669 (1966).
377. F. Durant, G. Evrard, J. P. Declercq, and G. Germain, *Cryst. Struct. Comm.*, **3**, 503 (1974).
378. R. D. Wood and B. Ganem, *Tetrahedron Lett.*, 707 (1982).
379. D. G. I. Kingston and M. X. Kolpak, *J. Am. Chem. Soc.*, **102**, 5966 (1980).
380. F. Le Goffic, M-L. Capmau, J. Abbe', L. Charles, and J. Montastier, *Eur. J. Med. Chem., Chim. Therap.*, **16**, 69 (1981).
381. H. H. Wasserman, F. J. Vinick, and Y. C. Chang, *J. Am. Chem. Soc.*, **94**, 7180 (1972).
382. H. H. Wasserman and G. R. Lenz, *Heterocycl.*, **5**, 409 (1976).
383. H. H. Wasserman and T.-J. Lu, *Tetrahedron Lett.*, **23**, 3831 (1982).
384. H. H. Wasserman, J. E. Pickett, and F. S. Vinnick, *Heterocycl.*, **15**, 1069 (1981).
385. H. König, F. Graf, and V. Weberndörfer, *Liebigs Ann. Chem.*, 668 (1981).
386. M. F. Ansell, M. P. L. Caton, and P. C. North, *Tetrahedron Lett.*, **22**, 1727 (1981).
387. G. S. Reddy and M. V. Bhatt, *Tetrahedron Lett.*, **21**, 3627 (1980).
388. P. A. Jacobi and D. G. Walker, *J. Am. Chem. Soc.*, **103**, 4611 (1981).
389. S. V. Stepanova, S. D. L'vova, A. B. Belikov, and V. I. Gunar, *J. Org. Chem. USSR*, **13**, 812 (1977).
390. S. V. Stepanova, S. D. L'vova, B. S. El'yanov, and V. I. Gunar, *Khim.-Farm. Zh.*, **11**, 92 (1977); *Chem. Abstr.*, **87**, 117803b (1977).
391. M. Murakami, Annual Meeting of the Pharmacological Society of Japan, 1966.
392. T. Sasaki, E. Ito, and I. Shimizu, *Heterocycl.*, **19**, 2119 (1982).
393. Y. Ohtsuka, *Bull. Chem. Soc. Jap.*, **46**, 506 (1973).
394. Y. Ohtsuka, *Bull. Chem. Soc. Jap.*, **43**, 3909 (1970).
395. Y. Ohtsuka and K. Sugimoto, *Bull. Chem. Soc. Jap.*, **43**, 2281 (1970).
396. G. Rapi, M. Chelli, M. Ginanneschi, D. Donati, and A. Selva, *J. Chem. Soc., Chem. Commun.*, 1339 (1982).
397. Y. Kikugawa and L. A. Cohen, *Chem. Pharm. Bull.*, **24**, 3205 (1976).
398. A. R. Katritzky and A. Zia, *J. Chem. Soc., Perkin I*, 131 (1982).
399. A. Hetzheim and H. Pusch, *Z. Chem.*, **10**, 385 (1970).
400. Y. Goto and N. Honjo, *Chem. Pharm. Bull.*, **26**, 3798 (1978).
401. Y. Goto, N. Honjo, and M. Yamazaki, *Chem. Pharm. Bull.*, **18**, 2000 (1970).
402. G. H. Keyes and L. G. S. Brooker, U.S. Patent 2,652,396 (1953); *Chem. Abstr.*, **48**, 486b (1954).
403. Iu. K. Iur'ev and I. G. Zhukova, *Zh. Obshch. Khim.*, **28**, 7 (1958); *Chem. Abstr.*, **52**, 11821c (1958).
404. K. Senga, J. Sato, and S. Nishigaki, *Chem. Pharm. Bull.*, **26**, 765 (1978).
405. M. Ishidate and H. Yuki, *Chem. Pharm. Bull.*, **8**, 137 (1960).

406. O. P. Shvaika and V. I. Fomenko, *Khim. Geterotsikl. Soedin.*, 635 (1976); *Chem. Abstr.*, 85, 123879f (1976).
407. A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, *J. Chem. Soc. (C)*, 2005 (1967).
408. I. J. Turchi and T. G. Cullen, *Heterocycl.*, 22, 2463 (1984).
409. D. Clerin, J-P. Fleury, and H. Fritz, *J. Heterocycl. Chem.*, 13, 825 (1976).
410. M. L. Graziano, M. R. Iesce, and R. Scarpati, *J. Heterocycl. Chem.*, 15, 1205 (1978).
411. M. L. Graziano, M. R. Iesce, and R. Scarpati, *J. Heterocycl. Chem.*, 16, 129 (1979).
412. M. L. Graziano, M. R. Iesce, A. Carotenuto, and R. Scarpati, *Synthesis*, 572 (1977).
413. R. Grigg and J. L. Jackson, *J. Chem. Soc. (C)*, 552 (1970).
414. M. Ya. Karpeiskii and V. L. Florent'ev, *Russian Chem. Rev.*, 38, 540 (1969).
415. A. P. Kozikowski and N. M. Hasan, *J. Org. Chem.*, 42, 2039 (1977).
416. J. I. Levin and S. M. Weinreb, *J. Am. Chem. Soc.*, 105, 1397 (1983).
417. P. B. Terent'ev, N. P. Lomakina, M. I. Rahimi, D. K. Riad, Ya. B. Zelikhover, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 1255 (1980); *Chem. Abstr.*, 94, 30072h (1981).
418. W. Böll and H. König, *Liebigs Ann. Chem.*, 1657 (1979).
419. G. E. Stokker, R. L. Smith, E. J. Cragoe, Jr., C. T. Ludden, H. F. Russo, C. S. Sweet, and L. S. Watson, *J. Med. Chem.*, 24, 115 (1981).
420. Y. Morisawa, M. Kataoka, and T. Watanabe, *Chem. Pharm. Bull.*, 24, 1089 (1976).
421. S. D. L'vova, S. V. Stepanova, I. S. Cherkasova, and V. I. Gunar, *J. Org. Chem. USSR*, 11, 1514 (1975).
422. S. V. Stepanova, S. D. L'vova, T. M. Filippova, and V. I. Gunar, *J. Org. Chem. USSR*, 12, 1544 (1976).
423. G. Ya. Kondrat'eva, M. A. Aitzhanova, V. S. Bogdanov, and O. S. Chizhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1313 (1979); *Chem. Abstr.*, 91, 140753b (1979).
424. P. B. Ghosh and B. Ternai, *J. Org. Chem.*, 37, 1047 (1972).
425. A. P. Kozikowski and A. J. Ames, *J. Org. Chem.*, 45, 2548 (1980).
426. M. Bachstez, *Ber.*, 47, 3163 (1914).
427. S. Gabriel, *Ber.*, 43, 1283 (1910).
428. A. Castek and M. Prostenik, *Bull. Sci. Conceil. Acad. RSF Yugoslavie*, 11, 100 (1966).
429. E. Gustak, *Arkiv. Kem.*, 24, 15 (1952); *Chem. Abstr.*, 49, 296e (1955).
430. H. Bredereck, R. Gompper, and F. Reich, *Chem. Ber.*, 93, 723 (1960).
431. M. Matsuo, T. Sakaguchi, and T. Akamatsu, German Patent 2,050,711 (1971); *Chem. Abstr.*, 75, 50423j (1971).
432. C. G. Alberti, L. Bernardi, B. Camerino, S. Redaelli, and A. Vercellone, *Gazz. Chim. Ital.*, 83, 922 (1953).
433. V. M. Shershukov and B. M. Krasovitskii, *Khim. Geterotsikl. Soedin.*, 1613 (1977); *Chem. Abstr.*, 88, 89566b (1978).
434. T. Ueda, S. Kato, S. Toyoshima, R. Takahashi, and A. Shimizu, Japan. Patent 9229 (1957); *Chem. Abstr.*, 52, 15592e (1958).
435. D. Dürr, U.S. Patent 4,350,519 (1982).
436. R. H. Wiley, *J. Org. Chem.*, 12, 43 (1947).
437. R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, 70, 2005 (1948).
438. E. E. Wiegand and D. W. Rathburn, *J. Chem. Eng. Data*, 18, 237 (1973).
439. E. E. Wiegand and D. W. Rathburn, *Synthesis*, 1970, 648.
440. R. Maeda, M. Takehara and Y. Yoshida, Japan. Patent 71 34,422 (1971); *Chem. Abstr.*, 76, 3838j (1972).

441. T. Takahashi and M. Hayami, *Yakugaku Zasshi*, **80**, 895 (1960); *Chem. Abstr.*, **54**, 24656i (1960).
442. S. D. Paul and D. L. Dhane, *J. Ind. Chem. Soc.*, **49**, 279 (1972).
443. S. D. Paul, D. L. Dhane, K. A. Noras, and A. U. Mushrif, *J. Ind. Chem. Soc.*, **49**, 579 (1972).
444. D. L. Dhane and G. M. Gaiki, *India, A.E.C., Bhabha At. Res. Cent. [Rep.]*, B.A.R.C-1030 (1979); *Chem. Abstr.*, **94**, 103218x (1981).
445. R. Robinson, *J. Chem. Soc.*, **95**, 2167 (1909).
446. J. Lister and R. Robinson, *J. Chem. Soc.*, **101**, 1297 (1912).
447. T-S. Li and C-K. Tai, *K'o Hsueh T'ung Pao*, **25**, 593 (1980); *Chem. Abstr.*, **94**, 30609p (1981).
448. V. N. Kerr, F. N. Hayes, D. G. Ott, R. Lier, and E. Hansbury, *J. Org. Chem.*, **24**, 1864 (1959).
449. F. N. Hayes, L. C. King, and D. E. Peterson, *J. Am. Chem. Soc.*, **74**, 1106 (1952).
450. G. H. Cleland and C. Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).
451. G. H. Daub, M. E. Ackerman, and F. N. Hayes, *J. Org. Chem.*, **38**, 828 (1973).
452. B. M. Krastovitskii, S. E. Kovelev, and V. M. Shershukov, *Khim. Geterotsikl. Soedin.*, 1049 (1974); *Chem. Abstr.*, **81**, 136031r (1974).
453. B. M. Krasovitskii and V. M. Shershukov, *Khim. Geterotsikl. Soedin.*, 35 (1979); *Chem. Abstr.*, **90**, 152057v (1979).
454. B. M. Krasovitskii, V. M. Shershukov, and L. M. Yagupol'skii, *Khim. Geterotsikl. Soedin.*, 1042 (1982); *Chem. Abstr.*, **97**, 216061w (1982).
455. O. Manabe, T. Nagakoshi, and H. Hiyama, *Yuki Gosei Kagaku Kyokai Shi*, **26**, 355 (1968); *Chem. Abstr.*, **69**, 67291p (1968).
456. K. Bunge, R. Huisgen, R. Raab, and H. Stangl, *Chem. Ber.*, **105**, 1279 (1972).
457. Gevaert Photo-Producten N.V., Belgian Patent 585,555 (1960); *Chem. Abstr.*, **58**, 2530f (1963).
458. Cassella Farbwerke Mainkur Akt.-Ges., British Patent 722, 543 (1955); *Chem. Abstr.*, **49**, 9286i (1955).
459. O. Trösken, German Patent 926,249 (1955); *Chem. Abstr.*, **52**, 3867 (1958).
460. T. Shono, M. Hachihama, and K. Shinra, *Polymer Lett.*, **5**, 1001 (1967).
461. CIBA Ltd., Belgian Patent 619,755 (1963); *Chem. Abstr.*, **58**, 12713c (1963).
462. M. Matsuo, T. Sakaguchi, Y. Muroyama, and N. Akamatsu, Japan. Patent 74 14,849 (1974); *Chem. Abstr.*, **82**, 45070g (1975).
463. Cassella Farbwerke Mainkur Akt.-Ges., British Patent 734,981 (1955); *Chem. Abstr.*, **50**, 580d (1956).
464. O. Dann, H. Fick, B. Pietzner, E. Walkenhorst, R. Fernbach, and D. Zeh, *Liebigs Ann. Chem.*, 160 (1975).
465. S. Tricerri, A. Pedrazzoli, and T. Treu, *Gazz. Chim. Ital.*, **84**, 701 (1954).
466. S. Inoue, K. Ohata, T. Tsutsui, and T. Normura, Japan. Patent 79 30,168 (1979); *Chem. Abstr.*, **91**, 39462f (1979).
467. K. Brown, S. African Patent 68 01,726 (1969); *Chem. Abstr.*, **73**, 14833t (1970).
468. E. Marchetti, Canadian Patent 956963 (1974); *Chem. Abstr.*, **83**, 58789u (1975).
469. W. E. Cass, *J. Am. Chem. Soc.*, **64**, 785 (1942).
470. J. J. Rosenbaum and W. E. Cass, *J. Am. Chem. Soc.*, **64**, 2466 (1942).
471. M. Dadkhah and B. Prijs, *Helv. Chim. Acta*, **45**, 375 (1962).
472. J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **77**, 2814 (1955).

473. P. Schlack and W. Koller, German Patent 1,109,690 (1958); *Chem. Abstr.*, **56**, 8719d (1962).
474. J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 1028 (1949).
475. B. H. Ingham, *J. Chem. Soc.*, 692 (1927).
476. H. Koenig and W. Böll, German Patent 2,451,725 (1976); *Chem. Abstr.*, **85**, 78108r (1976).
477. H. Bredereck, R. Gompper, F. Reich, and U. Gotsmann, *Chem. Ber.*, **93**, 2010 (1960).
478. H. Schubert and L. Selisko, *J. prakt. Chem.*, **16**, 1 (1962).
479. P. G. Ferrini and A. Marxer, *Angew. Chem., Int. Ed. Engl.*, **2**, 99 (1963).
480. T. Yoshikawa, S. Omura, and T. Naito, Japan. Patent 68 18,900 (1968); *Chem. Abstr.*, **70**, 57810p (1969).
481. H. Bredereck, R. Gompper, and H. Wild, *Chem. Ber.*, **88**, 1351 (1955).
482. K. Fitzl and R. Pfister, U.S. Patent 3,901,908 (1975); *Chem. Abstr.*, **83**, 206272 (1975).
483. D. R. Shridhar, B. Ram, C. R. Sarma, N. K. Saxena, G. S. Thaper, and A. Krishnamurthy, *Ind. J. Chem.*, **21B**, 860 (1982).
484. P. P. E. Strzybny, T. van Es, and O. G. Backeberg, *J. Org. Chem.*, **28**, 3381 (1963).
485. J. Heinze, German Patent 2,731,457 (1979); *Chem. Abstr.*, **90**, 152164c (1979).
486. A. Schönberg, *Ber.*, **54**, 242 (1921).
487. B. Fürer, S. Julia, and C. P. Papantoniou, *Bull. Soc. Chim. Fr.*, 3407 (1966).
488. G. Ohta, K. Koshi, and K. Obata, *Chem. Pharm. Bull.*, **16**, 1487 (1968).
489. P. B. Terent'ev, A. N. Kost, N. P. Lomakina, and V. G. Kartev, *Org. Prep. Proceed. Int.*, **6**, 145 (1974).
490. C. T. Ho and R. M. Tuorto, *J. Agr. Food Chem.*, **29**, 1306 (1981).
491. J. J. K. Novak, *Coll. Czech. Chem. Commun.*, **42**, 1170 (1977).
492. I. Saikawa and S. Takano, Japan. Patent 71 21,866 (1971); *Chem. Abstr.*, **75**, 76773y (1971).
493. T. J. van Bergen and R. M. Kellogg, *J. Am. Chem. Soc.*, **94**, 8451 (1972).
494. a. A. B. Issatschenko, *J. prakt. Chem.*, **88**, 655 (1913), b. H. Bredereck, R. Gompper, and F. Reich, *Chem. Ber.*, **93**, 1389 (1960).
495. G. Ya. Kondrat'eva, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 484 (1959); *Chem. Abstr.*, **53**, 21940 (1959).
496. M. Maeda and M. Kojima, *J. Chem. Soc. Perkin I*, 239 (1977).
497. G. Vernin, S. Treppendahl, and J. Metzger, *Helv. Chim. Acta*, **60**, 284 (1977).
498. H. Bredereck and R. Gompper, *Chem. Ber.*, **87**, 700 (1954).
499. K. Omura, N. Tada, M. Tomimoto, Y. Usui, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.*, **24**, 6699 (1976).
500. F. O. Blümlein, *Ber.*, **17**, 2578 (1884).
501. M. Lewy, *Ber.*, **20**, 2576 (1887).
502. B. Tramier and A. Bonzom, German Patent 1,915,232 (1969); *Chem. Abstr.*, **72**, 21679e (1970).
503. Y. Yura, Japan. Patent 10,130 (1964); *Chem. Abstr.*, **61**, 12006g (1964).
504. K. Kitatani, T. Hiyama, and H. Nazaki, *Bull. Chem. Soc. Jap.*, **50**, 1647 (1977).
505. R. Huisgen, G. Binsch, and L. Ghosez, *Chem. Ber.*, **97**, 2628 (1964).
506. J. P. Ferris and R. W. Trimmer, *J. Org. Chem.*, **41**, 13 (1976).
507. G. Sunagawa and H. Nakao, Japan. Patent 21,723 (1963); *Chem. Abstr.*, **60**, 4153c (1964).

508. M. Koremura, H. Oku, T. Shono, and T. Nakanishi, *Takamine Kenkyusho Nempo*, **13**, 216 (1961); *Chem. Abstr.*, **57**, 16451d (1962).
509. D. J. Brown and P. B. Ghosh, *J. Chem. Soc. (B)*, 270 (1969).
510. C. Makkay, M. Nagy, and M. Ionescu, *Stud. Univ. Babes-Bolyai, Ser Chem.*, **19**, 14 (1974); *Chem. Abstr.*, **82**, 43231m (1975).
511. A. Hajós and J. Kollonitsch, *Acta Chim. Acad. Sci. Hung.*, **16**, 461 (1958); *Chem. Abstr.*, **53**, 6206c (1959).
512. V. I. Grigor'eva, B. M. Krasovitskii, and R. S. Mil'ner, *Khim. Geterotsikl. Soedin*, 633 (1966); *Chem. Abstr.*, **66**, 2951u (1967).
513. B. M. Krasovitskii, L. A. Kutulya, A. E. Shevchenko, L. Sh. Afanasiadi, N. P. Egorova, and A. L. Shvorina, *Khim. Geterotsikl. Soedin*, 656 (1977); *Chem. Abstr.*, **87**, 84887b (1977).
514. B. M. Krasovitskii, S. V. Tsukerman, L. Sh. Afanasiadi, V. K. Polyakov, N. P. Egorova, and E. M. Shaulova, *Khim. Geterotsikl. Soedin*, 1616 (1977); *Chem. Abstr.*, **88**, 105200k (1978).
515. B. M. Krasovitskii, N. P. Egorova, L. Sh. Afanasiadi, I. V. Lysova, V. K. Polyakov, and S. V. Tsukerman, *Khim. Geterotsikl. Soedin*, 617 (1982); *Chem. Abstr.*, **97**, 92212z (1982).
516. E. M. Vernigor, V. K. Shalaev, and E. A. Lukyanets, *Khim. Geterotsikl. Soedin*, 463 (1981); *Chem. Abstr.*, **95**, 97645m (1981).
517. N. Soma, J. Nakazawa, T. Watanabe, Y. Sato, and G. Sunagawa, *Chem. Pharm. Bull.*, **15**, 627 (1967).
518. G. J. Durant, J. C. Emmett, and C. R. Ganellin, U.S. Patent 3,950,333 (1976); *Chem. Abstr.*, **85**, 33015 (1976).
519. G. J. Durant, J. C. Emmett, and C. R. Ganellin, U.S. Patent 4,024,271 (1977); *Chem. Abstr.*, **87**, 85007 (1977).
520. G. J. Durant, J. C. Emmett, and C. R. Ganellin, U.S. Patent 4,022,797 (1977); *Chem. Abstr.*, **87**, 85001 (1977).
521. K. Brown and J. F. Cavella, German Patent 1,804,306 (1969); *Chem. Abstr.*, **71**, 81351f (1969).
522. A. Dornow and H. Hell, *Chem. Ber.*, **94**, 1248 (1961).
523. K. Ogawa, T. Muramoto, and Y. Takei, Japan. Patent 74 40,934 (1974); *Chem. Abstr.*, **82**, 165910c (1975).
524. P. E. Saeter and H. A. Lindberg, U.S. Patent 3,401,172 (1968); *Chem. Abstr.*, **69**, 106694 (1968).
525. H. A. Lindberg and P. E. Saeter, Fr. M3008 (1965); *Chem. Abstr.*, **62**, 11818f (1965).
526. G. W. Adelstein, U.S. Patent 4,239,908 (1980); *Chem. Abstr.*, **94**, 139485w (1981).
527. I. Cojocariu, Z. Cojocariu, V. Zvoristeanu, and N. Stavri, Romanian Patent 64,909 (1979); *Chem. Abstr.*, **93**, 220734e (1980).
528. J. J. Nestor, G. H. Jones, and B. H. Vickery, U.S. Patent 4,318,905 (1982).
529. E. Marchetti, German Patent 2,108,437 (1971); *Chem. Abstr.*, **76**, 46188 (1972).
530. T. Honma and Y. Tada, Japan. Patent 75 49,271 (1975); *Chem. Abstr.*, **83**, 206088g (1975).
531. C. M. Wong, T-L. Ho, and W. P. Niemczura, *Can. J. Chem.*, **53**, 3144 (1975).
532. J. Hollowood and J. F. Cavalla, Brit. Patent 1,381,860 (1975); *Chem. Abstr.*, **82**, 170971c (1975).
533. M. Viscontini, *Helv. Chim. Acta*, **44**, 631 (1961).
534. K. Brown and R. A. Newberry, Brit. Patent 1,373,352 (1974); *Chem. Abstr.*, **82**, 112056 (1975).

535. V. M. Dziomko and A. V. Ivashchenko, *J. Org. Chem. USSR*, **9**, 2191 (1973).
536. T. Saito, Japan. Patent 20538 (1967); *Chem. Abstr.*, **69**, 10427h (1968).
537. N. Saito and C. Tanaka, *J. Pharm. Soc. Japan*, **76**, 305 (1956); *Chem. Abstr.*, **50**, 13,873 (1956).
538. G. Carrara, F. M. Chiancone, V. D'Amato, E. Ginoulhiac, C. Martinuzzi, U. M. Teotino, and N. Visconti, *Gazz. Chim. Ital.*, **82**, 652 (1952).
539. C. Tanaka, *Yakugaku Zasshi*, **87**, 10 (1967); *Chem. Abstr.*, **66**, 94929x (1967).
540. C. Tanaka and H. Nishiki, *Yakugaku Zasshi*, **87**, 14 (1967); *Chem. Abstr.*, **66**, 94930r (1967).
541. R. L. White, U.S. Patent 4,151,168 (1979); *Chem. Abstr.*, **91**, 20486v (1979).
542. W. G. Salmond, U.S. Patent 4,042,596 (1977); *Chem. Abstr.*, **87**, 184484m (1977).
543. M. Suzuki, T. Iwasaki, M. Miyoshi, K. Okumura, and K. Matsumoto, *J. Org. Chem.*, **38**, 3571 (1973).
544. A. P. Kozikowski and A. Ames, *J. Am. Chem. Soc.*, **102**, 860 (1980).
545. R. H. Hall, K. Bischofberger, S. J. Eitelman, and A. Jordan, *J. Chem. Soc. Perkin I*, 2236 (1977).
546. K. Nunami, M. Suzuki, K. Matsumoto, M. Miyoshi, and N. Yoneda, *Chem. Pharm. Bull.*, **27**, 1373 (1979).
547. K. Okumura, Japan. Patent 73 19,533 (1973); *Chem. Abstr.*, **79**, 42,474u (1973).
548. M. Suzuki, K. Nunami, K. Matsumoto, N. Yoneda, and M. Miyoshi, *Synthesis*, 461 (1978).
549. K. Matsumoto, M. Suzuki, N. Yoneda, and M. Miyoshi, *Synthesis*, 805 (1976).
550. Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **42**, 1213 (1977).
551. T. Nishiwaki, T. Kitamura, and A. Nakano, *Tetrahedron*, **26**, 453 (1970).
552. F. Dallacker, P. Kratzer, and M. Lipp, *Liebigs Ann. Chem.*, **643**, 97 (1961).
553. J. W. Hinman, H. Hoeksema, E. L. Caron, and W. G. Jackson, *J. Am. Chem. Soc.*, **78**, 1072 (1956).
554. K. S. R. Rao Mohan Krishna and N. V. Subba Rao, *Ind. J. Chem.*, **3**, 522 (1965).
555. T. Jaworski and T. Mizerski, *Rocz. Chem.*, **50**, 359 (1976); *Chem. Abstr.*, **85**, 32735q (1976).
556. Badische-Anilin and Soda-Fabrik A.-G. Fr. Patent 1,543,853 (1970); *Chem. Abstr.*, **72**, 21678d (1970).
557. T. M. Timofeeva and L. M. Bykova, *Deposited Doc.*, VINITI 543-77, 51 (1977); *Chem. Abstr.*, **90**, 137718 (1979).
558. R. A. Partyka and R. R. Crenshaw, U.S. Patent 4,001,237 (1977); *Chem. Abstr.*, **86**, 140028 (1977).
559. H. Adkins, R. M. Ross, D. C. Schroeder, C. L. Mahoney, and W. W. Gilbert, *J. Am. Chem. Soc.*, **76**, 147 (1954).
560. H. Adkins, R. M. Ross, and D. C. Schroeder, *J. Am. Chem. Soc.*, **72**, 5401 (1950).
561. N. M. Vikhrova, I. T. Strukov, and G. A. Garkusha, *Antibiotiki*, **9**, 867 (1964); *Chem. Abstr.*, **62**, 4020d (1965).
562. G. M. Coppolla, G. E. Hardtmann, and O. R. Pfister, *J. Org. Chem.*, **41**, 825 (1976).
563. G. F. Holland, U.S. Patent 4,163,784 (1979); *Chem. Abstr.*, **91**, 211277n (1979).
564. G. O. Chase, U.S. Patent 3,222,374 (1965); *Chem. Abstr.*, **64**, 6657 (1966).
565. Netherland Appl. 6,404,750 (1964); *Chem. Abstr.*, **62**, 11818h (1965).
566. H. Hoffmann-Poquette, German Patent 2,847,625 (1980); *Chem. Abstr.*, **94**, 15705y (1981).
567. S. V. Stepanova, S. D. L'vova, and V. I. Gunar, *Khim.-Farm. Zh.*, **10**, 102 (1976); *Chem. Abstr.*, **85**, 143020 (1976).

568. K. M. Bakre and J. P. Merchant, *Ind. J. Chem.*, **20B**, 614 (1981).
569. A. Gorgues and A. LeCoq, *Tetrahedron Lett.*, 4829 (1979).
570. J. Meinwald and D. H. Aue, *J. Am. Chem. Soc.*, **88**, 2849 (1966).
571. R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron*, **23**, 943 (1967).
572. A. P. Kozikowski and K. Isobe, *Heterocycl.*, **9**, 1271 (1978).
573. R. Huisgen, H. J. Sturm, and G. Binsch, *Chem. Ber.*, **97**, 2864 (1964).
574. H. Nakano, A. Sugihara, and M. Ito, Japan. Patent, 67 23,585 (1967); *Chem. Abstr.*, **69**, 36109f (1968).
575. Hoffmann-LaRoche and Co. A-G., Netherlands Appl. 6,508,673 (1966); *Chem. Abstr.*, **64**, 14193e (1966).
576. S. Shimada and K. Nagato, Japan. Patent 74 55,663 (1974); *Chem. Abstr.*, **82**, 43393r (1975).
577. S. Shimada, M. Nonaka, S. Ohnishi, and Y. Morita, Japan. Patent 79 20,493 (1979); *Chem. Abstr.*, **91**, 157722p (1979).
578. J. M. Chemerda and E. E. Harris, French Patent 1,497,391 (1967); *Chem. Abstr.*, **69**, 59219f (1968).
579. N. D. Doktorova, L. V. Ionova, M. Ya. Karpeiskii, N. Sh. Pakyukova, K. F. Turchin, and V. L. Florent'ev, *Tetrahedron*, **25**, 3527 (1969).
580. T. Matsuo and T. Miki, *Chem. Pharm. Bull.*, **20**, 806 (1972).
581. M. Kawazu, M. Seto, M. Watanabe, I. Wada, and E. Kaneko, Japan. Patent 71 43,383 (1971); *Chem. Abstr.*, **76**, 59598y (1972).
582. P. A. Jacobi and T. Craig, *J. Am. Chem. Soc.*, **100**, 7748 (1978).
583. L. B. Medvedskaya and G. Ya. Kontrat'eva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2164 (1980); *Chem. Abstr.*, **94**, 103127s (1981).
584. M. Takehara and Y. Yoshida, Japan. Patent 71 34,422 (1971); *Chem. Abstr.*, **76**, 3838j (1972).
585. T. Nishiwaki, K. Azechi, and F. Fujiyama, *J. Chem. Soc., Perkin I*, 1867 (1974).
586. D. R. Shridhar, B. Ram, C. R. Sarma, R. R. Krishna, P. P. Singh, and C. Seshagiri Rao, *Ind. J. Chem.*, **20B**, 891 (1981).
587. W. Reeve and P. J. Pare', *J. Am. Chem. Soc.*, **79**, 675 (1957).
588. T. Yamanaka, K. Ikeda, M. Konishi, and A. Kohayakawa, Japan. Patent 77 95,662 (1977); *Chem. Abstr.*, **88**, 89653c (1978).
589. T. Yamanaka, T. Kohayakawa, M. Konishi, and K. Ikeda, Japan. Patent 76 91259 (1959); *Chem. Abstr.*, **86**, 89792f (1977).
590. T. Yamanaka, H. Yasuda, and K. Osuga, German Patent 2,812,353 (1978); *Chem. Abstr.*, **90**, 6388n (1979).
591. T. Yamanaka and K. Osuga, Japan. Patent 78 07,667 (1978); *Chem. Abstr.*, **89**, 43386k (1978).
592. T. Yamanaka, K. Ikeda, A. Kohayakawa, and K. Osuga, Japan. Patent 77 95,663 (1977); *Chem. Abstr.*, **88**, 190802a (1978).
593. M. Viscontini and H. Raschig, *Helv. Chim. Acta*, **42**, 570 (1959).
594. M. Murakami and M. Iwanami, *Bull. Chem. Soc. Jap.*, **41**, 726 (1968).
595. S. H. Pines and M. Sletzinger, U.S. Patent 3,676,453 (1972); *Chem. Abstr.*, **77**, 101565 (1972).
596. S. H. Pines and M. Sletzinger, *Tetrahedron Lett.*, 727 (1969).
597. W. Steglich and G. Höfle, *Tetrahedron Lett.*, 4727 (1970).
598. I. L. Knunyants, N. P. Gambaryan, and E. M. Rokhlin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 924 (1962); *Chem. Abstr.*, **57**, 1243c (1962).
599. J. A. Webber, U.S. Patent 4,261,991 (1979); *Chem. Abstr.*, **95**, 43149j (1981).

600. G. E. Lepone, U.S. Patent 4,298,613 (1981); *Chem. Abstr.*, **96**, 68832k (1982).
601. E. Winkelmann and H. Kroha, German Patent 2,455,582 (1976); *Chem. Abstr.*, **85**, 108669u (1976).
602. G. W. Anderson, U.S. Patent 2,362,337 (1944); *Chem. Abstr.*, **39**, 2516 (1945).
603. H. Najer, R. Guidicelli, and J. Menin, *Bull. Soc. Chim. Fr.*, 2052 (1960).
604. V. Wolf, P. Hauschildt, and W. Loop, *Chem. Ber.*, **95**, 2419 (1962).
605. H. Pasedach and M. Seefelder, German Patent 936,686 (1955); *Chem. Abstr.*, **52**, 20197 (1958).
606. W. Reppe, *Liebigs Ann. Chem.*, **596**, 80 (1955).
607. V. Wolf and W. Loop, German Patent 1,121,052 (1962); *Chem. Abstr.*, **57**, 833h (1962).
608. H. Beyer and H. Schilling, *Z. Chem.*, **5**, 182 (1965).
609. Nordmark Werke G.m.b.H., French M.2736 (1964); *Chem. Abstr.*, **61**, 16069d (1964).
610. H. Najer, R. Guidicelli, and J. Menin, *Bull. Soc. Chim. Fr.*, 2040 (1967).
611. Laboratories Dausee, S. A., British Patent 1,106,679 (1968); *Chem. Abstr.*, **69**, 59220z (1968).
612. G. Griss, M. Kleemann, W. Grell, and H. Ballhause, German Patent 2,127,267 (1972); *Chem. Abstr.*, **79**, 78777j (1973).
613. H. Beyer and H. Schilling, *Chem. Ber.*, **99**, 2110 (1966).
614. U. H. Lindberg, G. Bexell, and B. Ulf, *Acta Pharm. Suecica*, **8**, 49 (1971); *Chem. Abstr.*, **74**, 141618x (1971).
615. Yu. A. Sharanin, *J. Org. Chem. USSR*, **16**, 1864 (1980).
616. Instituto Farmacologico Serrono S. p. A., French M. 7043 (1969); *Chem. Abstr.*, **74**, 100024g (1971).
617. V. S. Bogdanov, G. Ya. Kondrat'eva, and M. A. Aitzhanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1017 (1980); *Chem. Abstr.*, **93**, 185242s (1980).
618. H. Ulbricht and I. M. Rodin, German (East) Patent 135,906 (1979); *Chem. Abstr.*, **91**, 193295k (1979).
619. W. Loop, H. Baganz, F. W. Kohlmann, and H. Schultze, Canadian Patent 950,903 (1974); *Chem. Abstr.*, **83**, 58790n (1975).
620. I. Maeda, M. Takehara, K. Togo, S. Asai, and M. Yoshida, *Bull. Chem. Soc. Jap.*, **42**, 1435 (1969).
621. M. Grafantini, M. L. Stein, and A. Temperilli, *Ann. Chim. (Rome)*, **56**, 946 (1966); *Chem. Abstr.*, **66**, 37805e (1967).
622. H. Wamhoff, *Chem. Ber.*, **105**, 748 (1972).
623. B. S. Drach, E. P. Sviridov, and T. Ya. Lavrenyuk, *J. Org. Chem. USSR*, **10**, 1278 (1974).
624. O. P. Shvaika and G. P. Klimisha, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR*, **19** (1966); *Chem. Abstr.*, **64**, 19670a (1966).
625. P. Haake, L. P. Bausher, and W. B. Miller, *J. Am. Chem. Soc.*, **91**, 1113 (1969).
626. W. Hafferl, R. Lundin, and L. L. Ingraham, *Biochem.*, **2**, 1298 (1963).
627. J. M. Duclos and P. Haake, *Biochem.*, **13**, 5258 (1974).
628. R. G. Yount and D. E. Metzler, *J. Biol. Chem.*, **234**, 738 (1959).
629. T. Jaworski, J. Prejzner, and J. Terpinski, *Rocz. Chem.*, **48**, 1093 (1974); *Chem. Abstr.*, **82**, 4158y (1975).
630. H. A. Staab, H. Irngartinger, A. Mannschreck, and M.-Th. Wu, *Liebigs Ann. Chem.*, **695**, 55 (1966).
631. G. N. Dorofeenko, L. V. Mezheritskaya, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*,

- Sb. 2: *Kislorodsoderzhashchie Geterotsikly*, 287 (1970); *Chem. Abstr.*, **76**, 140618b (1972).
632. P. Haake, L. P. Bausher, and J. P. McNeal, *J. Am. Chem. Soc.*, **93**, 7045 (1971).
633. W. T. Flowers, G. Holt, and P. P. McCleery, *J. Chem. Soc. Perkin I*, 1485 (1979).
634. A. Hetzheim, G. Köhler, and H. Beyer, *Z. Chem.*, **7**, 186 (1967).
635. E. D. Sych, Zh. N. Belaya, and G. G. Dyadyusha, *Ukr. Khim. Zh.*, **30**, 1065 (1964); *Chem. Abstr.*, **62**, 9268d (1965).
636. Japan Research Institute for Photosensitizing Co., Ltd., Japan. Patent 80 147 269 (1980); *Chem. Abstr.*, **94**, 139786v (1981).
637. Tanabe Seiyaku Co., Ltd., Jpn. Kokai Tokkyo Koho JP 57, 188, 587 (1982); *Chem. Abstr.*, **98**, 198197j (1983).
638. K-C. Liu and R. K. Howe, *Org. Prep. Proced. Int.*, **15**, 265 (1983).
639. Takeda Chemical Industries, Ltd., Jpn. Kokai Tokkyo Koho JP 58 10,571 (1983); *Chem. Abstr.*, **98**, 179361s (1983).
640. Y. Nagao, S. Yamada, and E. Fujita, *Tetrahedron Lett.*, **24**, 2287 (1983).
641. E. J. Trybulski, R. I. Fryer, E. Reeder, A. Walser, and J. Blount, *J. Med. Chem.*, **26**, 1596 (1983).
642. K. Tabei, E. Kawashima, and T. Takada, *Heterocycl.*, **19**, 2061 (1982).
643. R. Scartazzini, Eur. Pat. Appl. EP 76,452 (1983); *Chem. Abstr.*, **99**, 53480g (1983).
644. E. J. Canada, U.S. Patent 4,380,641 (1983); *Chem. Abstr.*, **99**, 22452v (1983).
645. D. Liotta, M. Saindane, and W. Ott, *Tetrahedron Lett.*, **24**, 2473 (1983).
646. B. H. Lipschultz, R. W. Hungate, and K. E. McCarthy, *J. Am. Chem. Soc.*, **105**, 7703 (1983).

CHAPTER 2

Spectroscopic Properties of Oxazoles

CYNTHIA A. MARYANOFF

*Chemical Development Department, McNeil Pharmaceutical, Spring House, Pennsylvania
19477-0776 USA*

2.1.	Introduction	343
2.2.	Nuclear Magnetic Resonance	343
2.2.1.	Proton NMR	343
2.2.2.	¹³ C NMR	348
2.2.3.	¹⁴ N NMR	353
2.3.	Mass Spectrometry	353
2.4.	Ultraviolet Spectroscopy	357
2.5.	Infrared Spectroscopy	358
2.6.	Conclusion	359
	References	359

2.1. INTRODUCTION

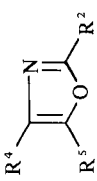
The physical organic properties of oxazoles have been briefly reviewed elsewhere.^{1,2} The aim of this chapter is to give the practicing chemist an overview of spectroscopic properties rather than to serve as a repository of all published data. Nuclear magnetic resonance (NMR) is covered first, followed by mass spectrometry, ultraviolet (UV) spectroscopy, and infrared (IR) spectroscopy.

2.2. NUCLEAR MAGNETIC RESONANCE

2.2.1. Proton NMR

Proton (¹H) chemical shifts are reported for mono-, di-, and trisubstituted oxazoles, as well as the parent compound¹⁻⁹ (see Table 2.1). These shifts are deshielded in the order H₄ < H₅ < H₂. Assignments have been made by deuterium labeling, ¹⁴N quadrupole effect, and spin-spin coupling.³ Substitution by electron-donating groups at C₅ increases the shielding of H₂ and H₄, while similar substitution at C₂

TABLE 2.1. ¹H NMR CHEMICAL SHIFTS

Compound Number	R ²	R ⁴	R ⁵			δ R ⁴	δ R ⁵	Solvent ^b	Reference
				δ ^a R ²	δ R ³				
1	H	H	H	7.95 7.84 7.84 8.25 9.89 9.66 8.05	7.09 7.10 7.12 7.25 8.01 7.94 7.10	7.69 7.65 7.66 7.97 8.54 8.37 7.72	A A A B C D M	3 4 5 3 3 3 5	
2	H	H	Ph	7.90	7.34	—	E	3	
3	H	H	<i>p</i> -ClPh	7.94	7.36	—	E	3	
4	H	H	<i>p</i> -CH ₃ Ph	7.87	7.25	—	E	3	
5	H	H	<i>p</i> -NO ₂ Ph	8.36	8.10	—	H	3	
6	H	CH ₃	H	7.77 7.70 8.10 9.75 8.54 8.20 8.66 9.75 8.29	(2.11) (2.17) (2.17) (2.40) — — — — —	7.27 7.32 7.59 8.22 8.27 7.91 8.40 9.02 7.87	A A B C B E B F A	3 4, 5 3 3 3 3 3 3 3	
7	H	CO ₂ H	H	8.29	—	—	E	3	
8	H	CO ₂ Et	H	8.47	—	—	B	3	
9	H	CONH ₂	H	7.91	—	—	A	3	
10	H	Ph	H	7.81 7.29	— —	7.80 7.29	E A L	3 4 4	

11	H	<i>p</i> -NO ₂ Ph	H	8.92	—	8.60	G	3
12	CH ₃	H	H	(2.40)	6.86	7.43	A	4
				(2.37)	6.82	7.41	A	3
				(2.44)	7.17	7.78	B	3
				(2.91)	7.79	8.28	C	3
13	Ph	H	H	—	7.26	7.74	E	3
14	H	CH ₃	COCH ₃	7.95	(2.49)	—	A	3
				8.52	(2.52)	—	B	3
15	H	CH ₃	COOH	8.25	(2.43)	—	B	3
16	H	CH ₃	CN	8.41	(2.40)	—	J	3
17	H	CH ₃	CONH ₂	7.82	(2.51)	—	E	3
18	H	CH ₃	CO ₂ Et	7.96	(2.47)	—	A	3
				7.99	(2.48)	—	K	3
19	H	CH ₃	CO ₂ CH ₃	7.99	(2.46)	—	A	3
				8.42	(2.55)	—	K	3
20	H	CH ₃	Ph	7.86	(2.45)	—	A	3
				7.71	(2.43)	—	A	4
				7.27	(2.22)	—	L	4
21	H	CH ₃	<i>p</i> -NO ₂ Ph	8.38	(2.55)	—	H	3
22	H	CH ₃	CH ₃	7.69	(2.08)	(2.24)	A	3
23	H	CH ₃	OC ₃ H ₇	~ 7.1	—	—	A	5
24	H	Tos	CH ₃	7.70	—	—	Z	7
25	H	Ph	CH ₃	7.66	—	(2.57)	A	5
				7.24	—	(1.99)	E	5
26	H	Ph	Ph	7.83	—	—	A	4
				7.31	—	—	L	4
27	CH ₃	H	CH ₃	(2.29)	6.42	(2.22)	A	3
				(2.39)	6.64	(2.26)	B	3
				(2.82)	7.39	2.46	C	3
				—	~ 6.5	—	M	5
28	CH ₃	H	NCH ₃ Ph	—	~ 6.4	—	A	5
29	CH ₃	H	O- <i>π</i> -Bu	—	~ 5.9	—	M	5
30	CH ₃ CH ₂	H	CH ₃	(1.31)	6.59	(2.75)	A	8

TABLE 2.1. (Continued)

Compound Number	R ²	R ⁴	R ⁵	δ^a R ²	δ R ⁴	δ R ⁵	Solvent ^b	Reference
31	Ph	H	Ph	[7.1–8]	7.61	[7.1–8]	I	8
32	Ph	H	<i>p</i> -NO ₂ Ph	—	7.35	—	A	4
33	Ph	H	CH ₃	—	7.27	—	L	4
				—	8.10	—	I	3
				—	—	(2.36)	A	4
				—	—	(1.80)	E	5
34	COOH	H	Ph	—	7.68	—	H	3
35	COOH	H	<i>p</i> -ClPh	—	7.55	—	H	3
36	COOH	H	<i>p</i> -CH ₃ OPh	—	7.68	—	H	3
37	COOH	H	<i>p</i> -NO ₂ Ph	—	8.15	—	H	3
38	CO ₂ Et	H	Ph	—	7.50	—	E	3
39	CO ₂ Et	H	<i>p</i> -ClPh	—	7.54	—	E	3
40	CO ₂ Et	H	<i>p</i> -CH ₃ OPh	—	7.41	—	E	3
41	CO ₂ Et	H	<i>p</i> -NO ₂ Ph	—	8.10	—	I	3
42	CH ₃	CH ₃	H	(2.22)	(2.06)	7.14	A	5
				(2.40)	(2.09)	7.43	B	3
				(2.85)	(2.35)	7.85	C	3
43	CH ₃	CO ₂ Et	H	(2.55)	—	8.17	B	3
				(2.50)	—	8.42	E	3
44	CH ₃	Ph	H	(2.49)	—	7.72	A	5
				(2.10)	—	7.32	L	4
45	CH ₂ D	CH ₃	CH ₃	(2.28)	(1.95)	(2.14)	A	4
46	CH ₃	CH ₃	CH ₃	(2.32)	(1.96)	(2.15)	A	3
				(2.77)	(1.99)	(2.15)	B	3
				(2.27)	(2.24)	(2.37)	C	3
				(2.03)	(1.95)	(2.14)	A	4
				(2.46)	(1.93)	(1.82)	L	4
47	CH ₃	CH ₃	COOH	—	(2.35)	—	B	3
48	CH ₃	CH ₃	CO ₂ Et	(2.55)	(2.40)	—	B	3

49	CH ₃	CH ₃	Ph	(2.45)	(2.36)	—	A	3
50	CH ₃	CH ₃	<i>p</i> -NO ₂ Ph	(2.54)	(2.45)	—	G	3
51	CH ₃	CH ₃ CO	CH ₃	(2.40)	—	(2.35) ^c	A	3
52	CH ₃	CH ₃	<i>t</i> -Bu	(2.28)	(1.95)	(0.90) ^c	A	4
53	CH ₃	CH ₃	<i>t</i> -Bu	(2.05)	(2.01)	(0.79) ^c	L	4
54	CH ₃	CH ₃	<i>n</i> -C ₆ H ₁₃	(2.37)	(2.27)	(0.92) ^c	A	4
55	CH ₃	COOH	CH ₃	(2.00)	(2.32)	(0.95) ^c	L	4
56	CH ₃	CO ₂ Et	CH ₃	(2.38)	(2.05)	(0.92) ^c	A	4
57	CH ₃	<i>i</i> -Bu	CH ₃	(2.18)	(2.13)	(0.85) ^c	L	4
58	CH ₃	<i>t</i> -Bu	CH ₃	(2.53)	—	(2.41)	B	3
59	CH ₃	Ph	Ph	(2.55)	—	(2.40)	B	3
60	<i>i</i> -Bu	CH ₃	CH ₃	(2.29)	(0.88) ^c	(2.14)	A	4
61	<i>t</i> -Bu	CH ₃	CH ₃	(2.07)	(0.94) ^c	(1.92)	L	4
62	<i>n</i> -C ₆ H ₁₃	CH ₃	CH ₃	(2.27)	(1.21) ^c	(2.27)	A	4
63	Ph	CH ₃	CH ₃	(2.06)	(1.33) ^c	(2.01)	L	4
64	Et	Ph	Ph	(2.60)	—	—	A	4
65	<i>n</i> -C ₃ H ₇	Ph	Ph	(2.16)	—	—	L	4
66	<i>n</i> -C ₅ H ₁₁	Ph	Ph	(0.95) ^c	(1.97)	(2.13)	A	4
				(0.88) ^c	(1.95)	(1.85)	L	4
				(1.29) ^c	(1.98)	(2.17)	A	4
				(1.35) ^c	(1.83)	(1.95)	L	4
				(0.87) ^c	(2.05)	(2.23)	A	4
				(0.73) ^c	(2.07)	(1.96)	L	4
				—	(2.08)	(2.28)	A	4
				—	(1.97)	(1.82)	L	4
				(1.42) ^c			A	4
				(1.15) ^c			L	4
				(1.07) ^c			A	4
				(0.85) ^c			L	4
				(0.95) ^c			A	4
				(0.79) ^c			L	4

^aFrom TMS or TSS.

^bA = CCl₄, B = D₂O, C = 5 *N* DCl–D₂O, D = CH₃COOH, E = CDCl₃, F = 10 *N* DCl–D₂O, G = (CD₃)₂SO, H = (CD₃)₂CO, I = (CH₃)₂SO, J = CH₃OD,

K = CD₃OD, L = C₆D₆, M = neat, Z = no solvent listed.

^cChemical shifts for terminal methyl groups.

TABLE 2.2. ^1H -NMR COUPLING CONSTANTS (Hz)

Compound	$J(\text{R}^2\text{R}^5)$	$J(\text{R}^4\text{R}^5)$	$J(\text{R}^2\text{R}^4)$	Solvent	Reference
1	0.8	0.8	—	D_2O	3
	0.95	0.85	0.34	CCl_4	5
6	0.8	1.1	—	D_2O	3
	2.4	1.3	0.45	CCl_4	4
	1.01	1.28	0.45	Neat	6
	—	1.15	—	CF_3COOH	6
8	0.9	—	—	D_2O	3
12	—	0.9	—	D_2O	3
	0	0.8	0	CCl_4	4
13	—	0.9	—	CDCl_3	3
27	—	1.2	—	D_2O	3
20	0.4	1.26	br ^a	CCl_4	8
42	—	1.2	—	D_2O	3

^aBroadening due to coupling noted.

increases the shielding of H_5 .⁵ Electron-withdrawing groups exhibit the expected opposite effect.^{3,5} Protonation deshields the ring protons (Table 2.1: compounds **1**, **6**, **8**, **12**, **27**, **42**) in the order $\text{H}_2 > \text{H}_3 \geq \text{H}_5$ and the substituent methyl protons in the positional order $2 > 4 > 5$.³ For the same compounds a change of solvent from carbon tetrachloride to deuterium oxide causes a deshielding of H_2 and H_5 (0.3 ppm) $> \text{H}_4$ (0.2 ppm), while methyl substituents are deshielded only about 0.1 ppm.³ Change of solvent from carbon tetrachloride to benzene leads to a greater magnitude of shift for aryloxazoles than for alkylloxazoles, as would be expected from aromatic ring stacking in the former case. Substituents at C_4 consistently shift the least, or are deshielded, while those at C_2 and C_5 are shielded⁴ (Table 2.1). Substitution of a methyl by a *t*-butyl group at the 2- or 5-position produces consistent methyl shifts, while a *t*-butyl substituent at the 4-position has little effect. The alkyl shift for methyl resonances in 2-alkyl-4,5-diphenyloxazoles is increasingly deshielded in the order 2-methyl $>$ 2-ethyl $>$ 2-*n*-propyl $>$ 2-*n*-pentyl.⁴

Spin-spin coupling constants are reported in Table 2.2. Long-range coupling is observed for protons on C_2 and C_5 . Decoupling of ^{14}N revealed the four-bond proton-proton coupling ($^4J_{2,4}$) in oxazole itself, which is 0.34 Hz.⁵

2.2.2. ^{13}C NMR

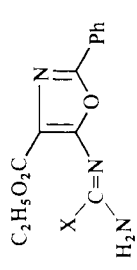
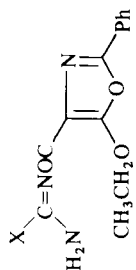
Carbon chemical shifts are reported for mono-, di-, and trisubstituted oxazoles, as well as the parent molecule in Table 2.3. Analogous to proton chemical shifts, deshielding is observed to increase in the order $\text{C}_2 > \text{C}_5 > \text{C}_4$. In all cases C_2 (between the heteroatoms) resonates at the lowest field. Additivity, parameters for seven types of substituents were compared by regression analysis to ^{13}C chemical shift data for the ring carbon nuclei of compounds **1**, **6**, **22**, **23**, **25**, **28**, **29**, **42**, **44**, **46**, **73**, **74**, **75**, **81**, **88**, **89**, and **91**. Results indicated a good correlation between

TABLE 2.3. ¹³C-NMR CHEMICAL SHIFTS

Compound Number	R ²	R ⁴	R ⁵	δ^a R ²	δ R ⁴	δ R ⁵	Solvent ^b	Reference
1	H	H	H	150.6	125.4	138.1	A	9
3	H		<i>p</i> -ClPh	151.9	126.4	139.3	B	10
13	Ph	H		152.5	127.2	139.9	C	5
14	H	H	H	150.1	121.3	149.8	A	9
17	H	CH ₃	COCH ₃	160.9	127.6	137.7	A	9
20	H	CH ₃	CONH ₂	152.3	144.0	145.5	C	5
22	H	CH ₃	Ph	152.7	140.5	143.0	C	5
23	H	CH ₃	CH ₃	149.2	131.7	145.4	C	5
25	H	CH ₃	O- <i>n</i> -C ₃ H ₇	149.5	130.7	143.5	C	5
27	CH ₃	Ph	CH ₃	142.7	112.2	155.1	C	5
28	CH ₃	H	CH ₃	149.5	134.2	144.2	C	5
29	CH ₃	H	CH ₃	160.2	123.3	148.6	C	5
42	CH ₃	H	NCH ₃ Ph	156.8	115.9	152.8	D	5
44	CH ₃	CH ₃	O- <i>n</i> -C ₄ H ₉	151.6	99.3	160.5	C	5
46	CH ₃	CH ₃	H	161.3	137.2	134.5	C	5
48	CH ₃	Ph	H	161.3	140.9	133.1	C	5
67	H	CH ₃	CH ₃	161.0	140.1	132.8	A	9
68	H	CH ₃	CH ₃	158.4	130.9	142.5	C	5
69	H	Tos	CO ₂ C ₂ H ₅	166.2	146.0	137.4	C	5
70	H	<i>t</i> -C ₄ H ₉	H	152.1	142.1	141.8	A	9
71	CH ₃	CH ₃	<i>p</i> -ClPh	151.4	150.5	132.1	C	5
	H	CO ₂ C ₁ H ₅	CO ₂ C ₂ H ₅	148.5	131.0	143.8	A	9
	CH ₃	H	<i>p</i> -ClPh	153.8	136.5	143.0	C	5
				160.3	121.7	149.3	A	9

TABLE 2.3. (CONTINUED)

Compound Number	R ²	R ⁴	R ⁵	δ^a R ²	δ R ⁴	δ R ⁵	Solvent ^b	Reference
72	CH ₃ O	H	<i>p</i> -ClPh	162.1	121.1	145.3	A	9
73	Ph	H	NCH ₃ Ph	156.9	114.2	152.9	D	9
74	Ph	CH ₃	H	161.5	138.2	134.8	C	5
75	N(CH ₃) ₂	CH ₃	H	162.4	137.0	128.2	C	5
76	N(C ₂ H ₅) ₂	CH ₃	H	161.3	136.5	127.7	C	5
77	<i>p</i> -CH ₃ Ph	CF ₃	H	163.7	133.7	137.8	E	11
78	<i>p</i> -CH ₃ Ph	CF ₃	F	152.8	105.1	154.5	E	11
79	<i>p</i> -CH ₃ Ph	CF ₃	N(C ₂ H ₅) ₂	152.9	109.2	153.9	E	11
80	NH ₂	CH ₃	CH ₃	159.2	128.8	135.9	A	5
81	N(CH ₃) ₂	CH ₃	CH ₃	160.6	130.3	136.1	C	5
82	N(CH ₂ H ₅) ₂	CH ₃	CH ₃	159.4	130.1	135.3	C	5
83	NHCOCH ₃	CH ₃	CH ₃	151.9	129.0	139.6	C	5
84	NCH ₃ Ph	CH ₃	CH ₃	157.6	130.2	136.6	C	5
85	N(CH ₃) ₂	Ph	CH ₃	160.4	134.4	137.2	F	5
86	CH ₃	CH ₃	N(C ₂ H ₅) ₂	156.4	127.6	149.1	C	5
87	CH ₃	CH ₃	OC ₂ H ₅	152.0	112.9	154.3	C	5
88	CH ₃	CH ₃	CH ₃ NPh	157.2	127.6	147.0	C	5
89	CH ₃	CH ₃	NPh ₂	156.9	128.3	144.7	D	5
90	CH ₃	Ph	CH ₃ NPh	158.3	129.9	146.0	A	5
91	Ph	CH ₃	CH ₃ NPh	157.6	128.7	147.2	A	5
92	Ph	Ph	Ph	160.4	137.1	145.7	C	12
93	H	Benzo		153.7	140.0	149.6	B	10
		Benzo		152.6	140.1	150.0	A	9
94	CH ₃			164.1	142.1	151.5	C	12

Compound Number	X		δ^a C ₂	δ C ₄	δ C ₅	Solvent ^b	Reference
95	OCH ₃		161.6	114.0	152.6	A	13
96	N(CH ₃) ₂		162.2	110.2	150.4	A	13
97	Pyridyl		161.5	115.7	150.1	A	13
98	Ph		161.6	115.0	153.1	A	13
							
99	Ph		161.1	108.0	150.3	A	13
100	OCH ₃		160.2	114.0	150.6	A	13
101	Pyridyl		161.0	115.0	149.8	A	13

^aAll shifts in ppm relative to TMS.

^bA = CDCl₃, B = DMSO, C = neat, D = CCl₄, E = none listed, F = melt.

TABLE 2.4. REPRESENTATIVE ^{13}C – ^1H COUPLING CONSTANTS (Hz)

Compound	$^1J_{\text{CH}}$			Reference	$^2J_{\text{CH}}$	
	C_2H_2	C_4H_4	C_5H_5		C_4H_5	C_5H_4
1	231.1	195.2	209.0	10	16.4	18.8
	231.1	195.3	209.1	9	16.5	18.9
	229.0	194.0	207.0	5	16.5	19.0
3	230.9	194.3	—	9	—	17.4
6	231.0	—	209.0	14	—	—
13	—	193.8	207.8	9	16.2	18.6
23	231.6	—	—	5	—	—
42	—	—	205.5	5	15.5	—
44	—	—	205.1	5	13.7	—
67	236.2	—	217.2	9	13.7	—
68	227.0	—	204.0	5	15.0	—
74	—	—	205.5	5	15.0	—
75	—	—	206.5	5	14.5	—
93	233.1	—	—	10	—	—

theoretical and experimental chemical shifts, with $r = 0.996$ (C_2), $r = 0.995$ (C_4), and $r = 0.999$ (C_5).⁵

Substitution by electron-withdrawing or electron-donating groups on C_2 or C_5 deshields both nuclei. Electron-donating substituents on C_2 shield C_5 , and electron-withdrawing substituents deshield C_5 . Whereas C_4 is sensitive to the effect of substituents on C_5 , it is little affected by substituents on C_2 . Alkyl substitution at C_4 deshields C_4 in the order methyl (11 ppm) < ethyl (17 ppm) < *t*-butyl (23 ppm), and shields C_5 in the order *t*-butyl (7.8 ppm) > ethyl (6.0 ppm) > methyl (5.6 ppm), relative to the parent oxazole; little effect is seen at C_2 . This effect of C_4 substitution on C_4 and C_5 chemical shifts is similar to the effect across a carbon–carbon double bond or in an ortho-substituted benzene.

A linear relationship is observed for C_2 and C_4 , C_4 and C_5 , C_2 and H_2 , and C_4 and H_4 chemical shifts, the electronegativity of the substituent on C_5 and C_5 chemical shifts, and the chemical shifts of 4,5-disubstituted oxazoles with ortho-disubstituted benzenes.⁵

The ^{13}C chemical shifts of oxazoles exhibit relatively small solvent dependence. The chemical shift of C_2 is most subject to solvent and concentration effects.⁵ Addition of benzene has almost no influence on ^{13}C chemical shifts of oxazoles.⁵

Table 2.4 lists representative carbon–proton coupling constants.^{5,9,10,14} Generally, $^1J > ^2J > ^3J$. Values of 1J (CH) range from 194 to 240 Hz with $^1J(\text{C}_2\text{H}_2) > ^1J(\text{C}_5\text{H}_5) > ^1J(\text{C}_4\text{H}_4)$. Values of 2J (CH) range from 14–20 Hz with $^2J(\text{C}_5\text{H}_4) > ^2J(\text{C}_4\text{H}_5)$. The smallest coupling observed is 3J (CH) with $^3J(\text{C}_2\text{H}_4) > ^3J(\text{C}_4\text{H}_2) \approx ^3J(\text{C}_2\text{H}_5) > ^3J(\text{C}_5\text{H}_2)$. For 4-methyloxazole the one-bond coupling constants increased about 15 Hz on protonation (comparison of spectra of a neat sample to one in trifluoroacetic acid).¹⁴

Compound	$^3J_{CH}$				Reference
	C_2H_4	C_4H_2	C_2H_5	C_5H_2	
1	10.6	8.8	8.1	3.9	10
	10.7	8.9	7.9	4.1	9
	11.0	9.0	8.5	4.0	5
3	11.3	8.4	—	4.2	9
23	—	7.3	—	4.5	5
42	—	—	7.5	—	5
44	—	—	8.3	—	5
67	—	9.3	9.0	4.0	9
68	—	8.0	8.0	3.6	5
74	—	—	8.0	—	5
75	—	—	9.0	—	5
93	—	5.2	—	—	10

2.2.3. ^{14}N NMR

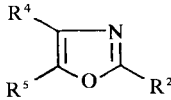
Background information on nitrogen NMR is available in ref. 15. Generally, ^{14}N NMR chemical shifts show a linear relationship with SCF-PPP-MO π charge densities. Nitrogen resonance moves to higher field as the π charge density at the nitrogen atom increases.¹⁶ This can be seen by inspection of Table 2.5, which lists some exemplary chemical shift data. The nitrogen chemical shift varies from 100 to 177 ppm (referenced against nitromethane). The 2-dialkylamino group exhibits the strongest shielding effect listed (compounds **76** and **81**).

2.3. MASS SPECTROMETRY

A review of the mass spectrometry of oxazoles has appeared.¹⁸ The majority of reports to date involve the use of electron impact ionization (all references listed in this section used same).

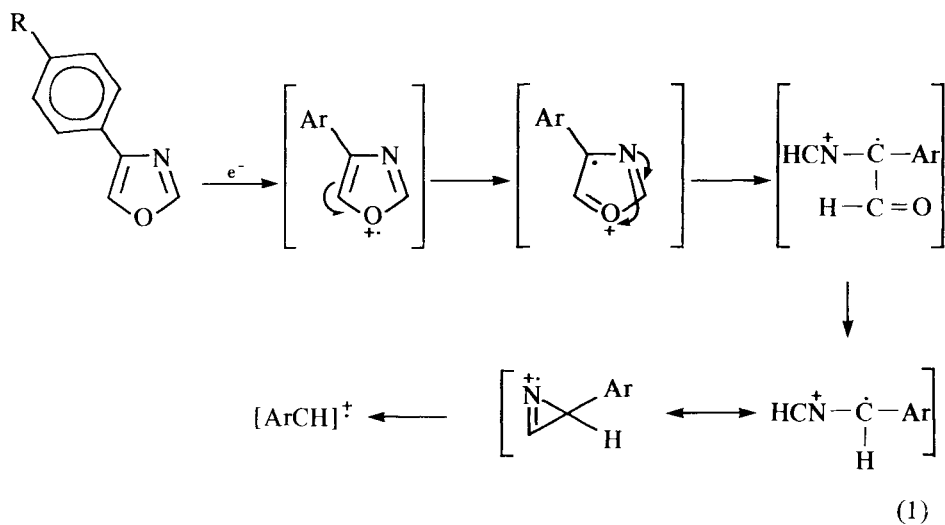
A mechanistic study of the fragmentation of oxazole was carried out; deuterium labeling, metastable-ion studies, appearance potential measurements, and molecular orbital calculations were used to support proposed mechanisms.¹⁹ Oxazole itself, like unsubstituted aromatic compounds, has the molecular ion as the most abundant ion (base peak). The molecular ion (M) decomposes to four peaks: 68 $[M-H]^+$ (loss of 5H); 42 $[M-HCN]^+$ (loss of C and H at position 2, and N); 41 $[M-CO]^+$, $[M-CH_2N]^+$, and $[M-HCO]^+$ (loss of C and H at position 5, and O). Ring cleavage, even in the presence of substituents, is often the primary mode of fragmentation for oxazoles. Generally, the oxygen atom is more easily eliminated than

TABLE 2.5. ^{14}N NMR CHEMICAL SHIFT DATA

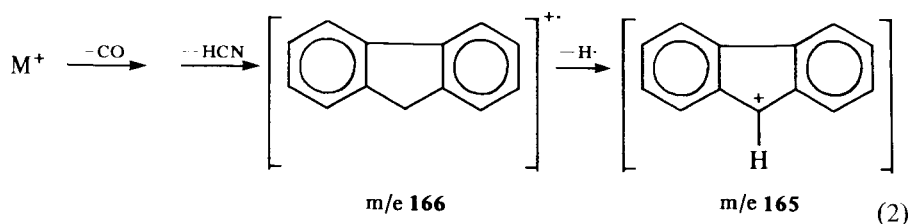
						
Compound Number	R ²	R ⁴	R ⁵	δ ^a N	Line Width	Reference
1	H	H	H	124 ± 1	106 ± 4 ^b	16
				123 ± 1.5	150 ± 5	5
14	H	CH ₃	COCH ₃	100 ± 10	500 ± 20	5
22	H	CH ₃	OC ₃ H ₇	117 ± 5	220 ± 5	5
31	Ph	H	Ph	125 ± 10 ^c	—	17
42	CH ₃	CH ₃	H	117 ± 1.5	120 ± 5	5
48	CH ₃	CH ₃	CO ₂ Et	100 ± 10	600 ± 20	5
74	Ph	CH ₃	H	128 ± 5	650 ± 25	5
76	N(C ₂ H ₅) ₂	CH ₃	H	177 ± 5	400 ± 20	5
81	N(CH ₃) ₂	CH ₃	CH ₃	175 ± 5	300 ± 20	5
86	CH ₃	CH ₃	N(CH ₂ H ₅)	122 ± 1.5	240 ± 5	5
87	CH ₃	CH ₃	OC ₂ H ₅	117 ± 5	350 ± 20	5

^aIn CCl_4 using CH_3NO_2 as standard.^bWidth at half height.^cIn Et_2O .

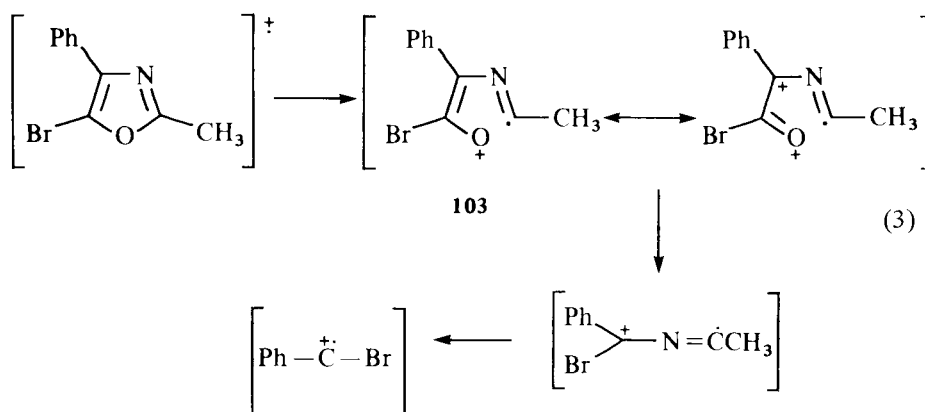
the nitrogen. Thus, the pattern of oxazole ring cleavage noted for phenyl-substituted oxazoles (compounds **10**, **13**, **26**, **31**, **93**, and **102**) is similar to that seen for oxazole itself in which consecutive losses of CO, HCN, and $\text{H}\cdot$ occurred.^{20–22} Deuterium labeling showed that 2-phenyloxazole (**13**) and 4-phenyloxazole (**10**) lost CO and HCN (C and H from position 2), and that no randomization of deuterium occurred.²¹ Similar mechanisms were claimed for electron impact patterns for compounds **102** (R = methyl, ethyl, bromo, methoxy, and nitro), as in Eq. 1.²²



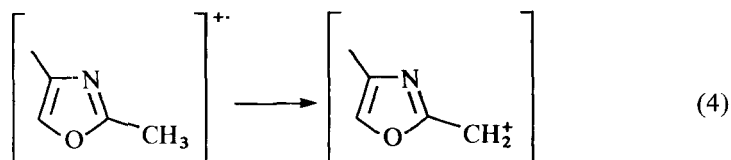
For compound series **102**, if the para substituent could be cleaved to generate a 4-tropylium ion, such a process occurs first, followed by loss of CO, then HCN.²² For diphenyl-substituted oxazoles, cleavage with rearrangement leads to ions *m/e* **165** and **166** (Eq. 2); the mechanism of rearrangement varies with substitution pattern.^{20,21}



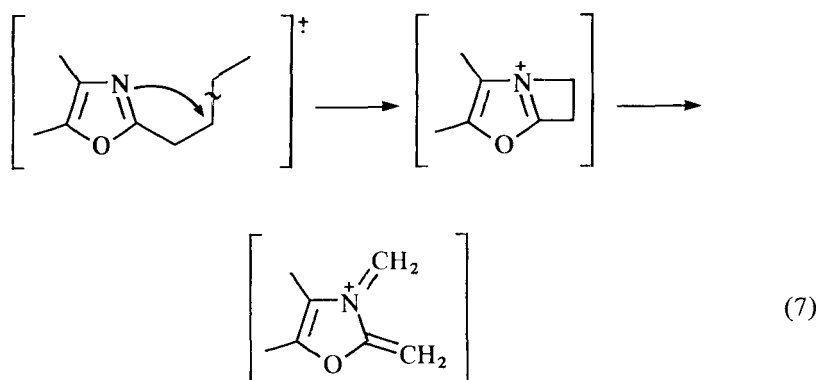
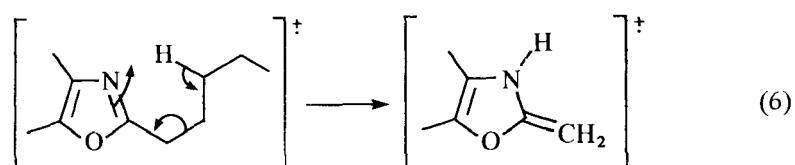
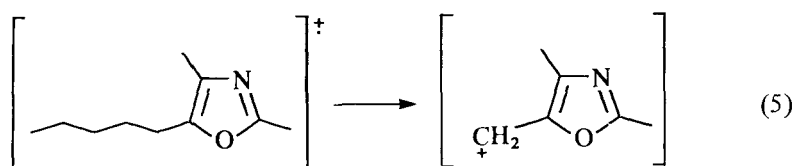
Phenyl-, methyl-, and/or bromo-substituted oxazoles exhibit consecutive losses of CO and H $\cdot$ from M $^+$. Deuterium labeling established CO loss as a process involving the 5-position carbon, probably by ring opening to an ion analogous to **103**, followed by or concomitant with migration of the original substituent at C₅ to C₄ (Eq. 3). Ions corresponding to M - CO are abundant when substituents at the 5-position are H, Ph, and Br but are reduced or absent when substituents are methyl or alkyl.²⁰



Detailed investigations of alkyl-substituted oxazoles using deuterium labeling techniques and high-resolution mass spectrometry have been reported.^{21,23,24} Fragmentation of methyl-substituted oxazoles reveals some interesting points. Whereas 4,5-dimethyloxazole (**22**) gives M - H, M - methyl, M - HCN, and M - HCO peaks, 2,5-dimethyloxazole (**42**) gives mainly M - CH₃CN, M - CO, and M - HCO. The absence of M - H in **42** was interpreted as an indication of the instability of an ion such as **104** (Eq. 4). The major fragmentation patterns observed for alkyl-substituted oxazoles are simple $\alpha\beta$ cleavage (benzylic-type cleavage, Eq. 5), $\alpha\beta$ cleavage with H shift (McLafferty rearrangement to nitrogen, Eq. 6), or $\beta\gamma$ cleavage of the alkyl chain (Eq. 7).

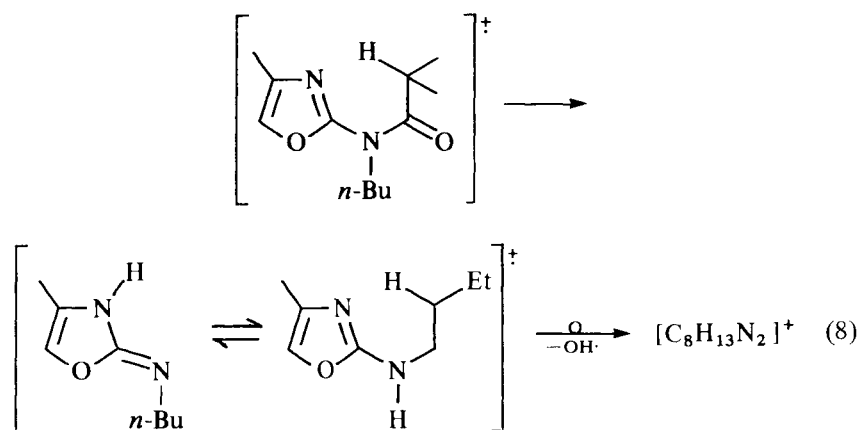


104

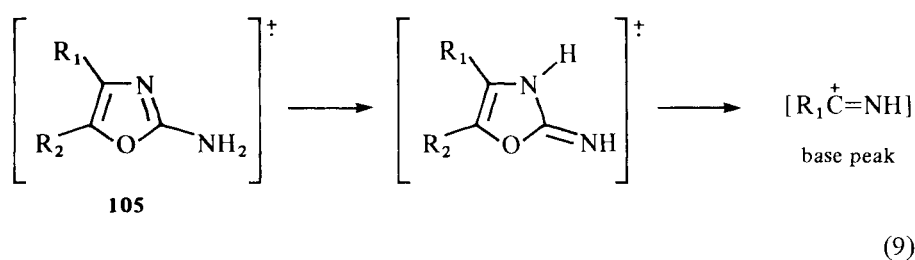


A study of 50 alkyl-substituted oxazoles indicated that the major fragmentations are α,β cleavage and α,β cleavage with hydrogen rearrangement.²³ For 5-pentyloxazole the rearrangement process predominates, but for 5-pentyloxazoles with methyl or ethyl groups in the 2- or 4-position, the α,β cleavage predominates. However, when both the 2- and 4-positions are substituted by methyl or ethyl groups, only benzylic cleavage occurs.

Primary fragmentation of the molecular ion of 2-[acyl(alkyl)amino] oxazoles involves McLafferty rearrangement with loss of the acyl substituent²⁴ (Eq. 8). The most significant base ion fragmentation reported was elimination of a hydroxy radical by ring opening.^{2,24}



The 2-aminoxazoles (**105**) often give a base peak arising from rearrangement¹⁸ (Eq. 9).



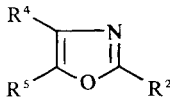
Thus, the nature of the substituents on the oxazole nucleus plays a pivotal role in determining the mode of electron impact–mass spectrometry fragmentation.

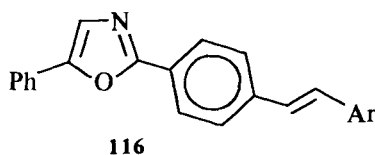
2.4. ULTRAVIOLET SPECTROSCOPY

UV maxima for selected oxazoles are listed in Table 2.6. Mono phenyl-substituted oxazoles (**2**, **10**, and **13**) exhibit one major band of strong intensity between 243 and 267 nm.^{3,25} Substitution on the aromatic ring (**11** and **106–108**) gives the expected shifts. Alkyl substitution on the oxazole ring has little effect: compare compounds **2**, **10**, and **13** to **20**, **25**, **49**, and **109**. The spectrum of 2,4-diphenyloxazole (**115**) is similar to a superimposition of the spectra of **10** and **13**. However, 2,5-diphenyloxazole (**31**) has an intense absorption at 314 nm, probably due to extended conjugation. Spectra of 2,5-diaryloxazoles generally have maxima between 315 and 350 nm ($\log \epsilon > 3$), 260 and 300 nm ($\log \epsilon < 3$), and 220 and 240 nm ($\log \epsilon > 3$).²⁶ Alkyl substitution on the phenyl group of 2,5-diphenyloxazoles results in little change in spectral properties.^{26,27}

UV spectra of heterocycle-substituted styryloxazoles (**116**, Ar = heterocycle) exhibit bands between 363 and 385 nm with a $\log \epsilon$ of 4.79–4.94.^{30–32}

TABLE 2.6. UV MAXIMA FOR SELECTED OXAZOLES

Compound Number				$\lambda_{\max}$, nm (log ϵ)	Solvent ^b	Reference
	R ² ^a	R ⁴	R ⁵ ^a			
1	H	H	H	205 (3.59)	A	25
13	Ph	H	H	263 (4.21)	A	3
10	H	Ph	H	245 (4.25)	A	25
				243 (4.24)	A	3
2	H	H	Ph	267 (4.29), 261 (4.30)	A	3
106	H	<i>p</i> -CH ₃ Ph	H	250 (4.27), 274 (2.96)	B	22
107	H	<i>p</i> -BrPh	H	254 (4.47), 283 (3.21)	B	22
108	H	<i>p</i> -CH ₃ OPh	H	256 (4.23), 286 (3.30)	B	22
11	H	<i>p</i> -NO ₂ Ph	H	218 (4.14), 3.12 (4.15), 354 (3.47)	B	22
20	H	CH ₃	Ph	265 (4.23)	A	25
25	H	Ph	CH ₃	247 (4.18)	A	25
49	CH ₃	CH ₃	Ph	264 (4.29)	A	25
109	CH ₃	Ph	CH ₃	247 (4.06)	A	25
115	Ph	Ph	H	276 (4.23), 232 (4.24)	A	3
31	Ph	H	Ph	224 (2.05), 302 (2.81) 244 (4.08), 314 (4.34)	C A	26 3
110	Ph	COOH	Ph	303 (4.66)	A	28
111	Ph	H	1Np	229 (4.12), 279 (1.44), 323 (2.33)	C	26
112	1Np	H	1Np	234 (5.31), 339 (2.30)	C	26
113	CH ₃ S	H	Ph	248 (3.85), 289 (4.33)	D	29
114	Ph	COOH	CH ₃	270 (4.34)	A	28

^a 1Np = 1-naphthyl.^b A = methanol, B = ethanol, C = cyclohexane, D = H₂O.

Overall, UV spectra of oxazoles suggest their consideration as conjugated dienes.

2.5. INFRARED SPECTROSCOPY

IR spectra of substituted phenyloxazoles were reported as early as 1953 (ref. 33). Solid-state spectra of a number of compounds suggested two characteristic bands for the oxazole ring: a weak to medium absorption around 1656 cm⁻¹ and a strong

absorption between 1555 and 1587 cm^{-1} (ref. 34). The spectrum of oxazole was first reported in 1964 (ref. 35); subsequently, several groups have recorded and interpreted the IR and Raman spectra of oxazole and its alkyl derivatives.³⁴⁻³⁹ All reports are in agreement that the strong band between 1555 and 1587 cm^{-1} is a $-\text{N}=\text{C}-\text{O}-$ ring stretching frequency. More recently, the effect of solvent on the IR absorptions of oxazole was disclosed.⁴⁰

2.6. CONCLUSION

This presentation of spectroscopic information is intended to be an aid to organic synthetic chemists in the interpretation of their data. The interested reader should consult the cited literature for further details and theoretical discussions.

ACKNOWLEDGMENTS

The author strongly thanks Dr. Ruth R. Inners for invaluable discussions on the NMR spectroscopic data. She also thanks Cathy Braun for typing the tables.

REFERENCES

1. I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
2. I. J. Turchi, *Ind. Eng. Chem. Prod. Res. Dev.*, **20**, 32 (1981).
3. D. J. Brown and P. B. Ghosh, *J. Chem. Soc. (B)*, 270 (1969).
4. J. H. Bowie, P. F. Donaghue, and H. J. Rodda, *J. Chem. Soc. (B)*, 1122 (1969).
5. V. S. Bogdanov, M. A. Aitzhavona, I. A. Abronin, and L. B. Medvedskaaya, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 305 (1980); *Chem. Abstr.*, **92**, 214449b (1980).
6. P. Haake and W. B. Miller, *J. Am. Chem. Soc.*, **85**, 4044 (1963).
7. A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972).
8. D. L. Deavenport, C. H. Harrison, and R. W. Rathburn, *Org. Magn. Reson.*, **5**, 285 (1973).
9. H. Hiemstra, H. A. Houwing, O. Possel, and A. M. van Leusen, *Can. J. Chem.*, **57**, 3168 (1979).
10. J. Llinares, J.-P. Galey, R. Faure, E.-J. Vincent, and J. Elguero, *Can. J. Chem.*, **57**, 937 (1979).
11. R. Ottlinger, K. Burger, and H. Goth, *Tetrahedron Lett.*, 5003 (1978).
12. I. Yavari, S. Esfandiar, A. J. Mostashari, and P. W. W. Hunter, *J. Org. Chem.*, **40**, 2880 (1975).
13. I. J. Turchi and C. A. Maryanoff, *Synthesis*, 837 (1983).
14. P. Haake, L. P. Bausher, and W. B. Miller, *J. Am. Chem. Soc.*, **91**, 1113 (1969).
15. M. Witanowski and G. A. Webb, Eds., *Nitrogen NMR*, Plenum Press, London, 1973.
16. M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron*, **28**, 637 (1972).

17. D. Herbison-Evans and R. E. Richards, *J. Mol. Phys.*, **8**, 19 (1964).
18. P. Traldi and U. Vettori, *Heterocycl.*, **14**, 847 (1980).
19. H. E. Audier, M. Fetizon, Y. Henry, and T. Prange, *Org. Mass. Spectrom.*, **11**, 1047 (1976).
20. J. H. Bowie, P. F. Donaghue, H. J. Rodda, and B. K. Simons, *Tetrahedron*, **24**, 3965 (1968).
21. J. H. Bowie, P. F. Donaghue, H. J. Rodda, R. G. Cooks, and D. H. Williams, *Org. Mass Spectrom.*, **1**, 13 (1968).
22. P. B. Terent'ev and N. P. Lomakina, *Chem. Abstr.*, **82**, 57021e; *Khim. Geterot. Soedin.*, 1472 (1974); Engl. translation: *Chem. Het. Compds.*, **10**, 1294 (1976).
23. C. T. Ho and Q. Z. Jin, *J. Agric. Food Chem.*, **31**, 180 (1983).
24. D. N. B. Mallen, L. A. Cort, and A. F. Cockerill, *Org. Mass Spectrom.*, **14**, 167 (1979).
25. H. Brederick, R. Gompfer, and F. Reich, *Chem. Ber.*, **93**, 1383 (1960).
26. A. T. Balaban, I. Bally, P. T. Frangopol, M. Bacescu, E. Cioranescu, and L. Birladeanu, *Tetrahedron*, **19**, 169 (1963).
27. A. T. Balaban, L. Birladeanu, I. Bally, P. T. Frangopol, M. Mocanu, and Z. Simon, *Chem. Abstr.*, **60**, 7570 (1964); *Acad. Repub. Pop. Rom., Inst. Fiz. At.*, IFA/CO-25 (1963).
28. F. Korte and K. Storiko, *Chem. Ber.*, **93**, 1033 (1960).
29. G. Kjellin and J. Sandstrom, *Acta Chem. Scand.*, **23**, 2888 (1969).
30. A. deBuman and A. E. Siegrist, *Helv. Chim. Acta*, **57**, 1352 (1974).
31. J. Garmatter and A. E. Siegrist, *Helv. Chim. Acta*, **57**, 945 (1974).
32. A. E. Siegrist, G. Kormany, and G. Kabas, *Helv. Chem. Acta*, **59**, 2469 (1976).
33. V. L. Koenig, F. N. Hayes, B. S. Rogers, and J. D. Perrings, *Chem. Abstr.*, **49**, 6713e (1955); U.S.A.E.C. No. AECU-2778 (1953).
34. P. Bassignana, C. Cogrossi, and M. Gandino, *Spectrochim. Acta*, **19**, 1885 (1963).
35. H. Brederick and R. Bangert, *Chem. Ber.*, **97**, 1414 (1964).
36. E. Borello, A. Zecchina, and A. Appiano, *Spectrochim. Acta, Part A*, **23**, 1335 (1967).
37. G. Sbrana, E. Castellucci, and M. Ginanneschi, *Spectrochim. Acta, Part A*, **23**, 751 (1967).
38. E. Bormello, A. Zecchina, and A. Appiano, *Spectrochim. Acta, Part A*, **23**, 751 (1967).
39. A. R. Katritzky and P. J. Taylor in *Physical Methods in Heterocyclic Chemistry*, Vol. 4, A. R. Katritzky, Ed., Academic Press, New York, 1971, pp. 324-334.
40. G. Mille, C. Pouchan, H. Sauvatre, and J. Chouteau, *Chem. Abstr.*, **82**, 138741s (1975); *J. Chim. Phys.-Chim. Biol.*, **72**, 37 (1975).

CHAPTER 3

Oxazolones

Y. SHYAMSUNDER RAO

Department of Chemistry, Kennedy-King College, Chicago, Illinois

ROBERT FILLER

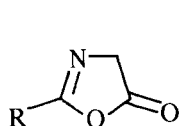
*Department of Chemistry, Lewis College of Sciences and Letters, Institute of Technology,
Chicago, Illinois*

3.1.	Introduction	362
3.2.	5-[4 <i>H</i>] Oxazolones	363
3.2.1.	Preparation of Saturated Azlactones	363
3.2.1.1.	Azlactonization of α -Acylamino Acids	363
3.2.1.2.	From Unsaturated Azlactones	366
3.2.1.3.	Alkylation Reactions	368
3.2.1.4.	Dakin–West Reaction	368
3.2.1.5.	Optically Active Azlactones	370
3.2.2.	Preparation of Unsaturated Azlactones	370
3.2.2.1.	Erlenmeyer Reaction	370
3.2.2.2.	Dehydration of β -Hydroxy- α -Acylamino Acids	374
3.2.2.3.	α -Hydroxy-Alkylidene Azlactones	375
3.2.2.4.	Bergmann Synthesis	376
3.2.2.5.	Miscellaneous Methods	384
3.2.3.	Properties and Reaction Chemistry of Azlactones	391
3.2.3.1.	α -Amino Acids	392
3.2.3.2.	α -Ketoacids	394
3.2.3.3.	Arylacetonitriles	395
3.2.3.4.	Arylacetic Acids	395
3.2.3.5.	Conversion to Other Heterocycles	396
3.2.3.6.	Heterocycles from Mesoionic Oxazolones	409
3.2.3.7.	Spectral Data on Oxazolones	412
3.2.3.8.	Reaction Toward Enzymes	416
3.2.3.9.	Tests for Azlactones	416
3.2.4.	Tables	417
3.3.	5-[2 <i>H</i>] Oxazolones	616
3.3.1.	Methods of Preparation	617
3.3.1.1.	Geometric Isomers of 2-Alkylidene(arylidene)-4-Alkyl-(aryl)-5-[2 <i>H</i>] Oxazolones	618
3.3.1.2.	Saturated Pseudoxazolones	618
3.3.1.3.	Pseudoxazolones as Intermediates in Other Syntheses	619

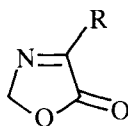
3.3.2.	Reactions of Pseudoxazolones.	622
3.3.2.1.	Unsaturated 5-[2 <i>H</i>] Oxazolones.	622
3.3.2.2.	Saturated 5-[2 <i>H</i>] Oxazolones	623
3.4.	4-[5 <i>H</i>] Oxazolones	644
3.4.1.	Methods of Preparation	645
3.4.1.1.	From Benzoylisocyanate.	645
3.4.1.2.	From <i>N</i> -Acylsulfilimines.	646
3.4.1.3.	From α -Haloamides.	646
3.4.1.4.	Salts of 4-[5 <i>H</i>] Oxazolones	647
3.4.1.5.	From 5-Arylidene-2-Thiooxazolidin-4-Ones	648
3.4.1.6.	Alkylation With Ethylbromoacetate	648
3.4.2.	Reactions	649
3.5.	2-[3 <i>H</i>] Oxazolones	660
3.5.1.	Methods of Preparation	660
3.5.1.1.	From Benzoin and Isocyanates	661
3.5.1.2.	From Isoxazole Derivatives	663
3.5.1.3.	Miscellaneous Methods	664
3.5.2.	Reactions	666
3.5.2.1.	Conversion to Phenanthrene Derivatives	666
3.5.2.2.	Conversion to 4-Aroylbenzils	667
3.5.2.3.	Conversion to Oxazole Thiones	667
3.5.2.4.	Reaction With Amines	667
3.5.2.5.	Conversion to Oxazoles	669
3.5.2.6.	Reaction With Grignard Reagents.	670
3.5.2.7.	Diels–Alder Reaction	670
3.5.2.8.	Formation of Telomers	673
3.6.	2-[5 <i>H</i>] Oxazolones	684
3.6.1.	Methods of Preparation	684
3.6.1.1.	From Cyanohydrins	684
3.6.1.2.	From Tertiary α -Hydroxyketones.	684
3.6.1.3.	From Urethanes.	687
3.6.1.4.	From α -Bromoamidines	688
3.6.1.5.	From Ynamine Amidines	688
3.6.1.6.	From Epoxyacyl Azides	689
3.6.1.7.	Oxidation of 2-Exocyclic-oxazolidines.	690
3.6.2.	Reactions	690

3.1. INTRODUCTION

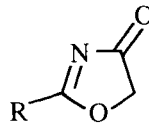
Oxazolones can exist in five isomeric forms, all of which are known.



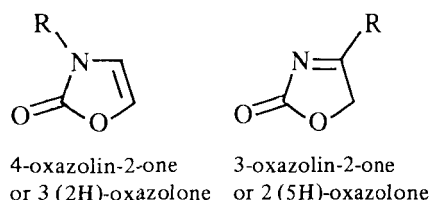
2-oxazolin-5-one
or 5 (4*H*)-oxazolone
or Azlactone



3-oxazolin-5-one
or 5 (2*H*)-oxazolone
or Pseudoxazolone



2-oxazolin-4-one
or 4 (5*H*)-oxazolone



Of all these isomers, azlactones or 2-oxazolin-5-ones (oxazolones) may be regarded as cyclic esters of α -acylamino acids. Their chemistry has been investigated very thoroughly. This interest may be attributed in large measure to the structural studies on penicillin and the fact that oxazolones are starting materials for the synthesis of α -amino acids, peptides, α -keto and arylacetic acids, and a host of other heterocyclic compounds.

Since the original chapter on azlactones,¹ a host of other reviews have been published,²⁻¹⁴ including a classic chapter dealing with the chemistry of penicillin.² Most of these articles deal with the chemistry of all the oxazolone isomers. The chemistry of the geometric isomers of 4-arylidene (alkylidene) azlactones has recently been surveyed.¹²

This chapter summarizes some of the important advances in this chemistry of azlactones, pseudoxazolones, and the 4-[5*H*]-, 3-[2*H*]-, and 2-[5*H*] oxazolones. Methods of synthesis, mechanism, and stereochemistry are discussed. The chapter is divided into five sections, one for each of the isomers. Literature up to the end of June 1983 has been surveyed.

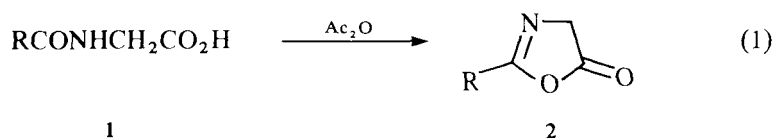
3.2. 5-[4*H*]-OXAZOLONES

These compounds are classified as saturated azlactones (no exocyclic bond) and unsaturated azlactones (those with an exocyclic double bond at the 4-position of the oxazolone ring).

3.2.1. Preparation of Saturated Azlactones

3.2.1.1. Azlactonization of α -Acylamino Acids

Several methods for converting α -acylamino acids **1** to saturated azlactones **2** are known. Cyclodehydration is usually effected in the same way as for unsaturated azlactones by heating with acetic anhydride.^{2,15}

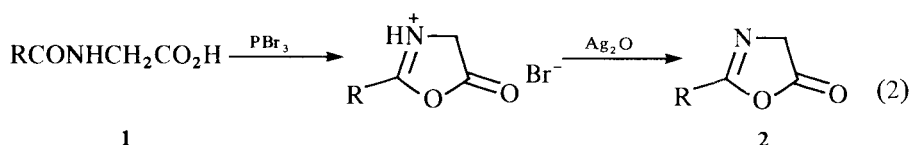


Several 2-aryl-2-oxazolin-5-ones have been prepared from substituted hippuric acids by the acetic anhydride method¹⁵⁻²⁰ and their solvolytic behavior studied. However, it has been observed that 2-nitrohippuric acid and acetic anhydride give a mixed anhydride **3**. 3,5-Dinitrohippuric acid also gives the mixed anhydride.¹⁹ A detailed description of the preparation of 2-phenyl-2-oxazolin-5-one is given in "Organic Syntheses."²¹ Saturated azlactones containing alkyl and aralkyl groups in the 2-position of the azlactone ring are also obtained by this method.²³⁻²⁶

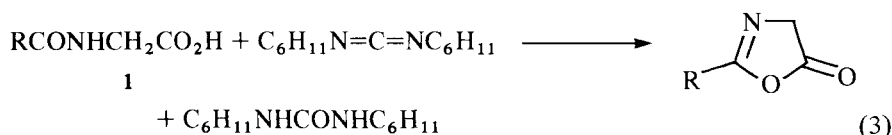


3

α -Acylamino acids, **1**, may be azlactonized by treatment with phosphorus tribromide in dioxane. The hydrobromide of the saturated azlactone **2** formed initially is dehydrobrominated with silver oxide, aqueous sodium acetate, or diazomethane. Phosphorus tribromide in pyridine, on the other hand, gives the saturated azlactone directly. The acids are also converted to azlactones by tosyl chloride in pyridine.¹⁵⁻¹⁶

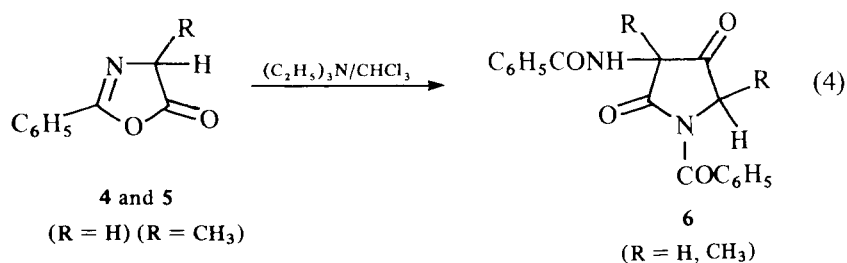


Dehydration of α -acylamino acids can also be effected with dicyclohexylcarbodiimide (DCC)²⁷⁻³¹ in chloroform and other solvents. Several optically active azlactones have been prepared by the DCC method.³²⁻³⁹

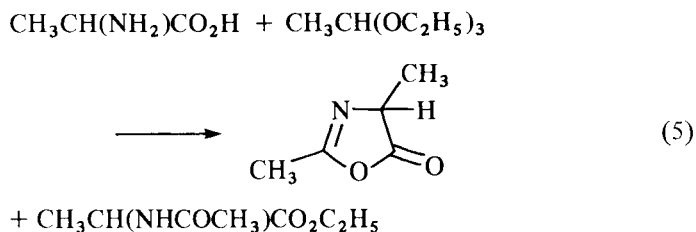


A new water-soluble carbodiimide for cyclization of α -acylamino acids, *N*-cyclohexyl-*N*- α -[(4-methylmorpholinium)ethyl]carbodiimide] α -*p*-toluenesulfonate has been reported.⁴⁰ Cyclization of hippuric acid in dichloromethane with *N*-*t*-butyl-5-methylisoxazolium perchlorate has been described⁴¹ and benzoyl-L-leucine has been converted to 4-isobutyl-2-phenyl-2-oxazolin-5-one by reaction with silicon tetrachloride in acetonitrile containing sodium hydride.⁴²

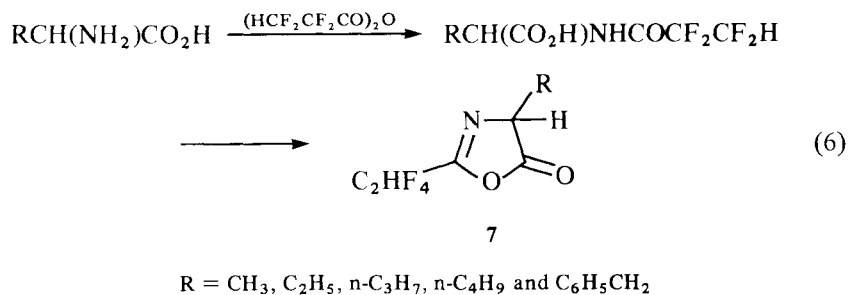
Treatment of α -acylamino acids with ethyl chloroformate and triethylamine is reported to give saturated azlactones in 40–71% yields,⁴³⁻⁴⁸ including 2-isopropenyl-2-oxazolin-5-one, 2-vinyl-4,4-dimethyl-2-oxazolin-5-one, and 2-phenyl-2-oxazolin-5-one **4** (R = H).⁴⁹⁻⁵² On treatment with triethylamine and ethyl chloroformate in chloroform, hippuric acid, and *N*-benzoyl alanine initially form compounds **4** and **5**, respectively, which dimerize to **6**.



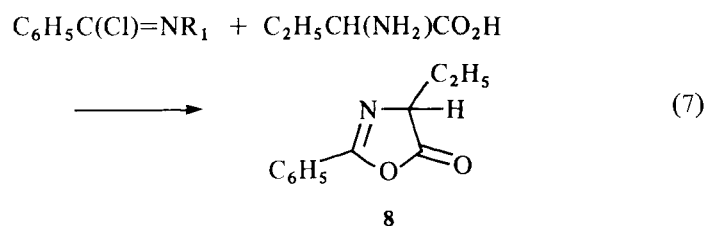
Amino acids, such as alanine, valine, isovaline, and methionine, react with triethyl orthoacetate in dimethylacetamide to give mixtures of *N*-acetamido acid esters along with saturated azlactones.⁵³



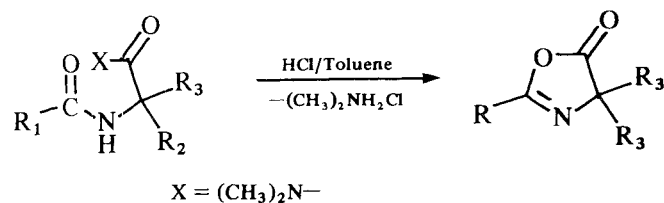
Tetrafluoropropionic anhydride converts amino acids directly to saturated azlactones **7**, containing the tetrafluoroethyl group.⁵⁴



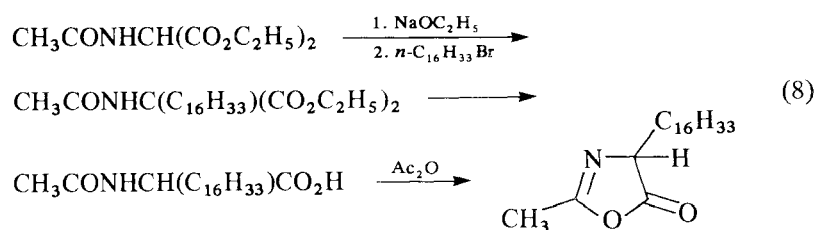
DL-Amino acids reportedly react with *N*-phenylbenzimidio chloride in benzene containing triethylamine to give saturated azlactones such as **8**.^{55,56}



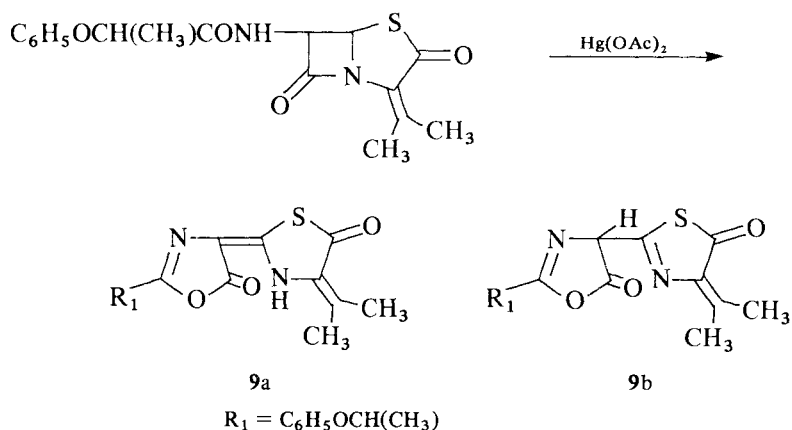
Acid-catalyzed cyclization of diamides, which may be regarded as activated *N*-acyl- α -amino acids, also leads to the formation of saturated azlactones.⁵⁷



Saturated azlactones have also been obtained from acetamidomalonic ester by alkylation, hydrolysis, and cyclization with acetic anhydride.⁵⁸

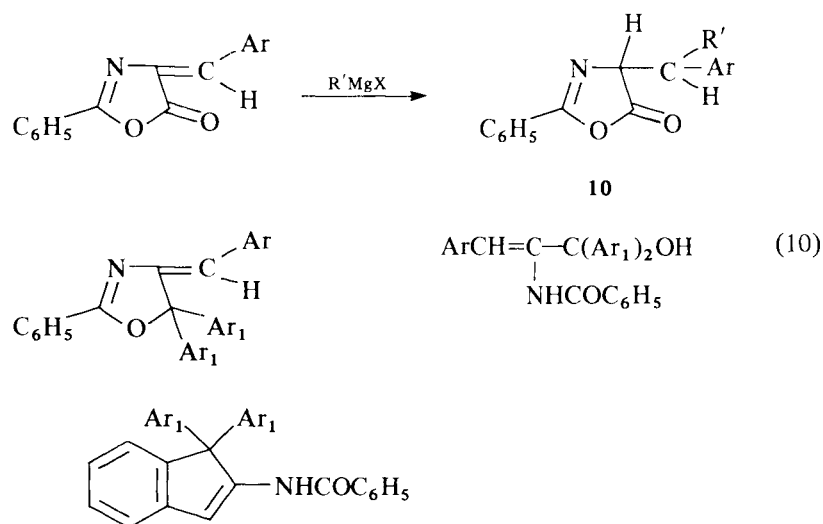


The penicillenic acids **9a** and **9b** are obtained by mercuric acetate oxidation of anhydro- α -phenoxyethylpenicillin.^{59,60}

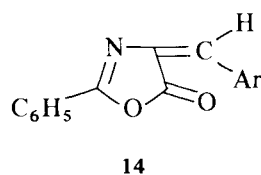


3.2.1.2. From Unsaturated Azlactones

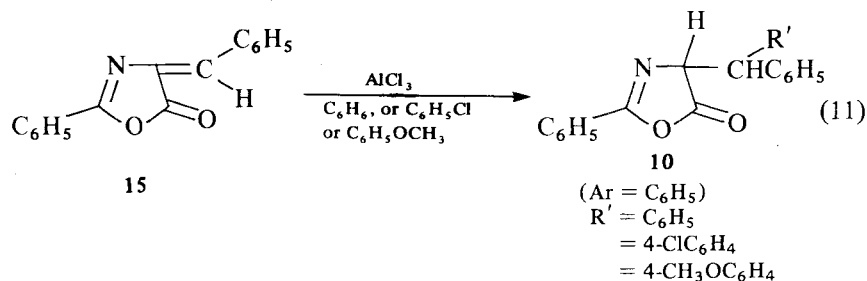
The behavior of unsaturated azlactones with organometallic reagents has been studied extensively.^{62,65} Alkyl Grignard reagents react with unsaturated oxazolones to give saturated compounds **10**, the products of 1,4-addition.⁷²⁻⁷⁷ However, with aryl magnesium halides and aryl lithium derivatives, the products (**11**, **12**, and **13**) derived by 1,2-addition to the lactone carbonyl group are obtained.^{63,64,74-76}



An exception to the latter behavior illustrates the effect on the reaction of the stereochemistry around the exocyclic double bond. Whereas aryl Grignard reagents react with the *Z*-isomers of 2-phenyl-4-arylidene-2-oxazolin-5-ones to give the 1,2-addition products, the *E*-isomers **14** preferentially yield the product of conjugate addition **10** ($R' = \text{aryl}$). However, 1,4-addition of aryl Grignard reagents to the *Z*-isomers of 4-arylidene oxazolones is also observed when cuprous chloride is added to the Grignard reagent in a 2:3 mole ratio. Some analogs of **12** are also obtained in this reaction, with their yields being determined by the nature of the Grignard reagent. The participation of phenyl copper is suggested in these conjugate additions.⁶⁷ Saturated azlactones, thus formed, react further with excess aryl-magnesium halides to give 2-benzamido-1,1-diaryl-1-propanols.^{2,70,80-83} The open-chain compounds **12** may be cyclized to **11** by treatment with acetic anhydride or to substituted indenes, **13**, by cyclization with hydrochloric acid-acetic acid.



While the reaction of the *Z*-isomer of 4-benzylidene-2-phenyl-2-oxazolin-5-one **15** ($\text{Ar} = \text{C}_6\text{H}_5$) with aromatic hydrocarbons in the presence of anhydrous aluminum chloride is quite complex, the method may be used under controlled conditions to give saturated azlactones.^{70,71,77,84-89} In contrast, with aged aluminum chloride containing moisture, acylation of the aromatic substrate leads to the formation of α -benzamidoacetophenone.⁸⁸

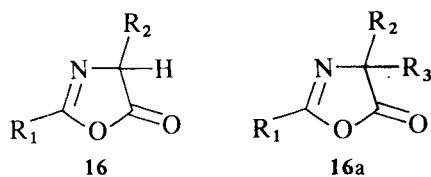


Hydrogenation of 2-phenyl-4-benzylidene-2-oxazolin-5-one in anhydrous dioxane in the presence of 5% Pd-charcoal catalyst for 18 h gives 2-phenyl-4-benzyl-2-oxazolin-5-one.² In general, unsaturated azlactones undergo reduction much more slowly than the α -acylaminoacrylic acids derived from them.

Asymmetric synthesis of amino acids is achieved by the catalytic reduction of unsaturated azlactones in the presence of various catalysts.⁹⁰⁻¹⁰⁵

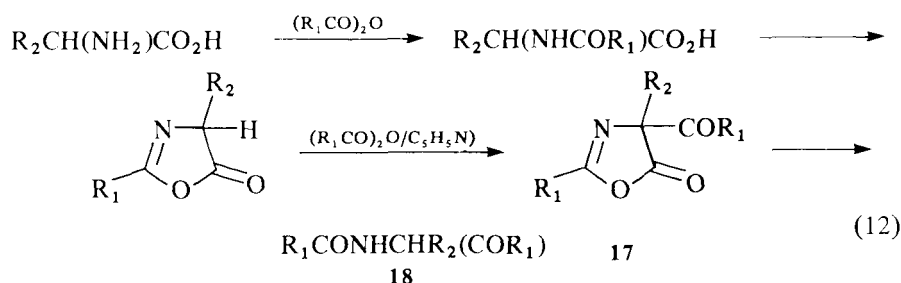
3.2.1.3. Alkylation Reactions

Saturated azlactones, such as **16**, have been alkylated in aprotic solvents, for example, anhydrous dimethylformamide, to yield 4,4-disubstituted azlactones, such as **16a**. Diisopropylethylamine, triethylamine, or α -picoline act as catalysts. The alkylation is quite facile with primary alkyl halides, benzyl and substituted benzyl halides, allyl and propargyl bromides, tropylium perchlorate, and triphenylmethyl chloride. Ethyl chloroacetate has also been employed successfully. The 4,4-disubstituted azlactones thus prepared are converted into α -amino acids on hydrolysis.¹⁰⁶⁻¹¹⁴ Benzylation of 2-phenyl-2-oxazolin-5-one in dimethylformamide in the presence of 50% potassium hydroxide at 170°C fails to give the saturated azlactone, but, instead, α -benzylhippuric acid is obtained.¹¹⁵



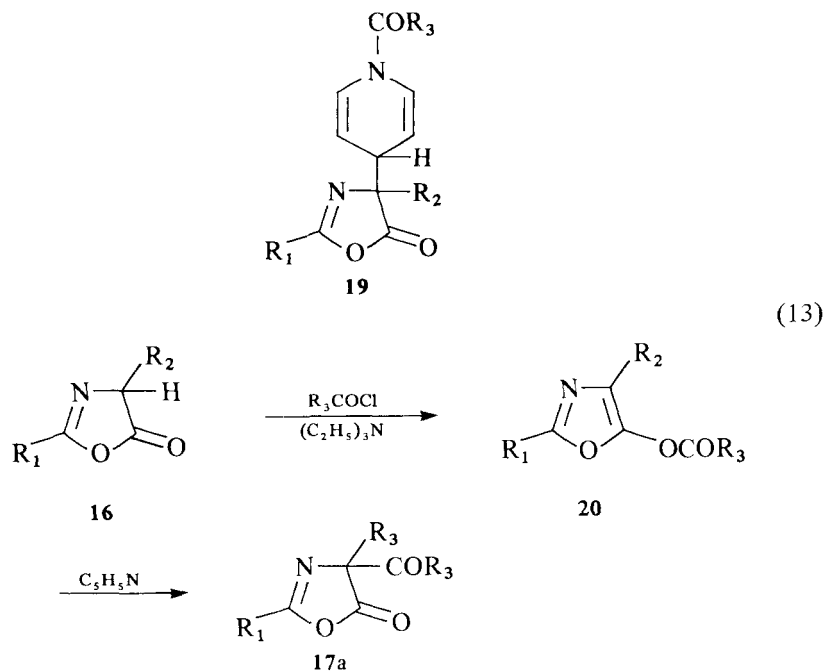
3.2.1.4. Dakin-West Reaction

The Dakin-West reaction for converting α -amino acids to α -acylamino ketones **18** consists of three steps: (1) acylation of the amino acid followed by cyclodehydration to 2-oxazolin-5-ones **16**, (2) the acylation of the oxazolone to its 4-acyl analog **17**, and (3) oxazolone ring opening followed by decarboxylation to give **18**¹¹⁶ (Eq. 12).



The reaction may be interrupted at the 4-acyl azlactone stage (vide infra), thereby providing a method for the synthesis of selected saturated azlactones.

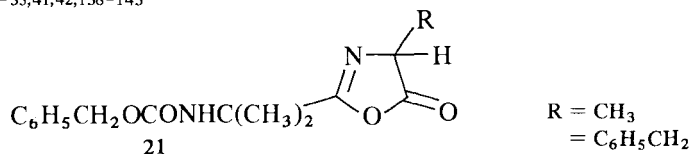
Although this method is suitable for the preparation of 4-acyl azlactones,¹¹⁶ the reaction is considerably more complex, as evidenced by the isolation of intermediates such as 4-(1-acyl-1,4-dihydro-4-pyridyl)-2-oxazolin-5-ones **19**,¹¹⁷⁻¹²² oxazoles **20**¹²³⁻¹²⁶ (Eq. 13), and 5-acetoxyoaxazolium salts (when mesionic 3-alkyl-2-oxazolium-5-ones are the starting materials instead of α -amino acids).¹²⁷⁻¹³⁰



In general, aliphatic carboxylic acid derivatives form substituted oxazole intermediates, which are products of *O*-acylation, while aromatic acid chlorides give the *C*-acylation product. The intermediate oxazole **20** can be isomerized to the 4-acyl azlactone on heating with bases such as pyridine^{82,125,126} and γ -picoline, but not with α - or β -picoline.^{121,122} The conversion of **20** to **17a** can also be brought about in the presence of boron trifluoride etherate.^{130,131}

3.2.1.5. Optically Active Azlactones

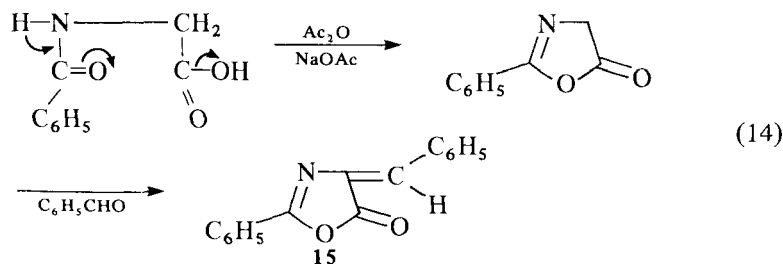
In studies involving racemization during peptide synthesis, several optically active azlactones have been prepared.^{132,133} The *l*-isomer of 2-phenyl-4-benzyl-2-oxazolin-5-one has been synthesized and its rate of racemization in the presence of various nucleophiles determined. It has been conclusively shown that oxazolones are intermediates in the racemization of peptides. Optically active tripeptides are prepared from optically active azlactones such as **21** and the rates of racemization of **21** have been studied.^{134,135} Analogs of **21** are made in dioxane containing acetic anhydride. The dicyclohexylcarbodiimide method has been employed as well.^{32,136,137} Several other optically active oxazolones have been reported.^{33-35,41,42,138-143}



3.2.2. Preparation of Unsaturated Azlactones

3.2.2.1. Erlenmeyer Reaction

The Erlenmeyer azlactone synthesis (Eq. 14) consists of the condensation of an aldehyde (or ketone) with an α -acylamino acid (e.g., hippuric acid) in the presence of acetic anhydride and anhydrous sodium acetate as catalyst. The reaction may be considered a special case of the Perkin condensation but takes place under much milder conditions. The original mechanism proposed by Erlenmeyer, which involves the intermediacy of a β -aryl- β -hydroxy- α -acylamino acid, has given way to one that postulates the formation of a reactive saturated azlactone **2** that condenses with the aromatic aldehyde to give the unsaturated azlactone (Eq. 14). The use of the saturated azlactone **2** instead of the free α -acylamino acid in the Erlenmeyer reaction has markedly improved the yields.¹⁹ Aliphatic aldehydes and ketones also condense with saturated azlactones when heated for 3 h at 50°C. The yields increase markedly when lead acetate is added to the reaction mixture, with shorter



reaction times. In support of the proposed mechanism, benzoyl sarcosine and benzenesulfonyl glycine, which cannot form saturated azlactones, fail to condense with aromatic aldehydes.¹

The azlactonization reaction has been studied with hippuric acid as the model compound. Hippuric acid dissolved in pyridine is treated with phosphorus oxychloride in dioxane at -5° , followed by addition of benzaldehyde. The progress of the reaction is observed by the color change to deep orange. The reaction proceeds equally well with *p*-toluenesulfonyl chloride and triethylamine. The initial formation of 2-phenyloxazolone is indicated by this study.¹⁴⁴ The suggestion that the anhydride of α -benzamidocinnamic acid is initially formed has also been advanced.¹⁴⁵

3.2.2.1.1. SCOPE AND LIMITATIONS

CARBONYL COMPONENTS.¹⁴⁶⁻¹⁵⁰ All aromatic aldehydes, without exception, can be used in the Erlenmeyer reaction. Most heterocyclic aldehydes also react with α -acylamino acids to give unsaturated azlactones, which are used as derivatives to identify the parent aldehydes.¹⁵¹ In the case of certain reactive aldehydes it is beneficial to use the acetals rather than the aldehydes themselves.⁷⁵ The lower aliphatic aldehydes (C_2 – C_4) have been employed in the azlactone synthesis. Higher aliphatic aldehydes (C_5 – C_9) condense with hippuric acid in polyphosphoric acid. Among the ketones, acetone, methyl ethyl ketone, cyclopentanone, cyclohexanone, 2-methyl- and 4-methylcyclohexanones, and 5-nitro-2-acetylfuran react under normal Erlenmeyer conditions. Acetophenone and its ring-substituted analogs and propiophenone react both in polyphosphoric acid¹⁵¹ and in the presence of lead (IV) acetate in tetrahydrofuran.¹⁵² Although benzophenone fails to react, 9-flourenone (with its less hindered carbonyl group) and ring-substituted 9-fluorones condense with hippuric acid.³ Phthalic and substituted phthalic anhydrides give phthalylidene azlactones.¹⁵³⁻¹⁵⁷

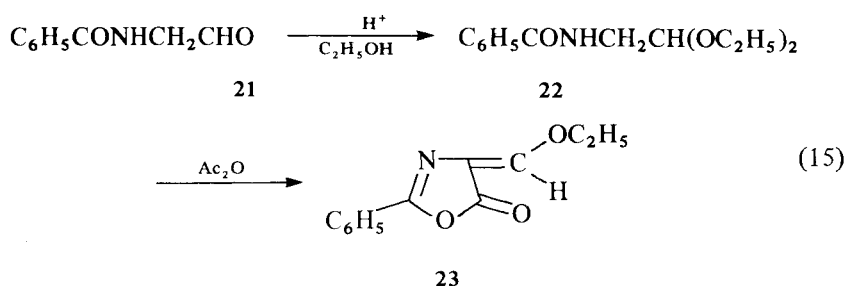
The substituents on the ring of aromatic aldehydes include alkyl, fluoro, chloro, bromo, iodo, nitro, acetamido, dimethylamino, diethylamino, alkoxy, acyloxy, carboethoxy, di-, tri- and tetramethoxy, and combinations of these groups. Aldehydes of furan, thiophene, pyrrole, selenophene, thiazole, benzofuran, ajmaline, phenothiazines, indole, thiochromans, ferrocene, and coumarin have all been employed successfully.

In most of the reported azlactone preparations, neither the yields nor the details of preparation are given. It is, therefore, not possible to correlate the yields of azlactones with the structure of the aldehydes. Generally, the yields are in the range of 60 to 85%. The yields of azlactones derived from ortho-substituted benzaldehydes vary widely, from 30 to 80% (Table 3.2A). The effect of catalysts on the yields will be discussed later.

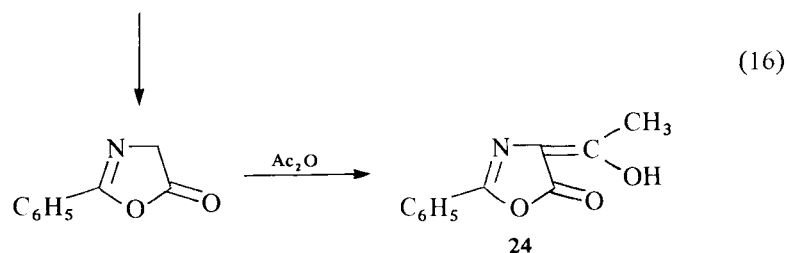
Azlactones derived from hydroxybenzaldehydes can be prepared from their acetoxy analogs by hydrolysis with concentrated sulfuric acid at 0°C .¹⁵⁸ Examples are the azlactones from salicylaldehyde and vanillin. The claims^{159,160} that azlactones containing the free phenolic group can be prepared directly from the hydroxybenzaldehyde in the presence of acetic anhydride–sodium acetate are

quite surprising and merit further investigation. Studies with gentisaldehyde azlactone revealed that the intermediate acetoxy azlactone is rapidly converted to a coumarin derivative under the reaction conditions and that with shorter times, greater yields of the acetoxy azlactone are obtained.¹⁶¹ Several dihydroxybenzaldehydes have been converted to the corresponding diacetoxyazlactones. In all of these reactions, coumarin formation is a side reaction.¹⁵²⁻¹⁵⁶ In contrast to these results in acetic anhydride-sodium acetate, azlactones containing the free phenolic function can, in some cases, be prepared directly from the hydroxy benzaldehyde in acidic medium, for example, dimethylformamide-sulfur trioxide or polyphosphoric acid (vide infra).

ACYLGLYCINES. Hippuric acid is the most commonly employed α -acylamino acid in Erlenmeyer syntheses. Substituted hippuric acids with either electron-donating or electron-withdrawing substituents at various ring positions are also suitable for the reaction.¹⁶⁷⁻¹⁹⁷ Cinnamoyl and substituted cinnamoylglycines have been used.^{172,173,182} Aceturic and substituted aceturic acids as well as acryloylglycines have also been employed. 2-Furoylglycine and 5-nitro-2-furoylglycine react normally,^{179,197} but formylglycine does not react. Hippuraldehyde diethyl acetal **22** prepared from hippuraldehyde **21** gives 2-phenyl-4-ethoxymethylene-2-oxazolin-5-one **23** on heating with acetic anhydride.^{201,202}



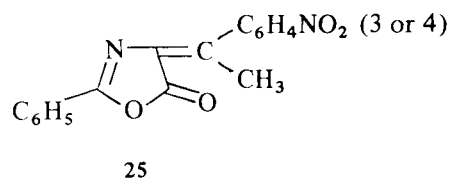
CATALYSTS. Erlenmeyer azlactone syntheses are usually catalyzed by anhydrous sodium acetate; sometimes, however, no catalyst is necessary.² A systematic study of the effect of various catalysts in the preparation of the azlactone of acetaldehyde and hippuric acid²⁰³ reveals that lithium acetate is not very effective, giving only a 30% yield of the azlactone, while potassium acetate causes an exothermic reaction to give a gummy product from which the azlactone can be isolated in low yield. Sodium acetate is intermediate in reactivity. Cupric and mercuric acetates fail to catalyze the reaction, while the acetates of ammonium, thallium, barium, and calcium lead to low yields of azlactone. Lead (II) acetate, either anhydrous or as the trihydrate, affords 50–60% yields of the azlactone. Studies on the effects of temperature show that the reaction, when catalyzed by sodium acetate, is complete after 36 h at 20°. The same yields are obtained in 10–20 min at 100°. In the absence of catalyst, sodium hippurate and acetic anhydride react directly to give 2-phenyl-4-(1-hydroxyethylidene)-2-oxazolin-5-one **24**. Acetic acid inhibits the catalytic activity of sodium acetate.²⁰⁴



Anhydrous potassium acetate seems to be an excellent catalyst for the Erlenmeyer reaction involving aromatic aldehydes. The yield of 2-phenyl-4-benzylidene-2-oxazolin-5-one in the presence of potassium acetate is 95%,²⁰⁵ while the corresponding yield with sodium acetate catalysis is 52–64%.^{206–209} 2-Nitrohippuric acid does not yield an azlactone with acetic anhydride–sodium acetate¹⁷ but forms instead a mixed anhydride. By contrast, with potassium acetate catalysis, a 30% yield of azlactone is obtained.¹⁸¹ These differences between sodium acetate and potassium acetate merit further study.

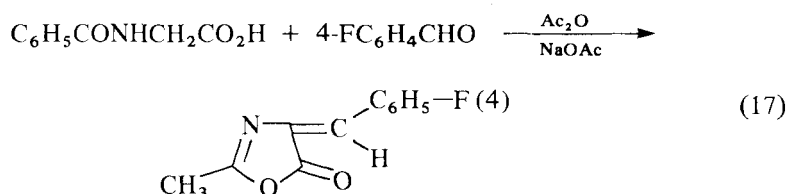
Lead (II) acetate in tetrahydrofuran has been used in the synthesis of azlactones derived from hippuric acid and aliphatic aldehydes, for example, propionaldehyde and isobutyraldehyde, and ketones.^{146,210a} Condensation of 2-phenyl-2-oxazolin-5-one with aromatic and aliphatic aldehydes proceeds much better in the presence of lead (II) acetate than with sodium acetate.¹⁹ The use of lead (IV) acetate in tetrahydrofuran leads to mixtures of *Z*- and *E*-isomers of azlactones derived from acetophenone and substituted acetophenones.¹⁵²

The use of potassium bicarbonate as a catalyst appears to increase the yield of azlactones.^{210b} Piperonal reacts with hippuric acid and potassium bicarbonate to give the azlactone in 82% yield (67% yield in the presence of sodium acetate).^{1,211,212} The reaction is exothermic and requires no external heating. Veratraldehyde gives 84–85% of desired product, while with sodium acetate the yield is only 70%.^{213,214} A 92% yield of azlactone is obtained from pyridine-3-carboxaldehyde and hippuric acid in the presence of potassium bicarbonate,²¹⁵ while no product is isolated with sodium acetate. Potassium carbonate is also found to improve the yields of azlactones derived from both aldehydes and ketones. Ketones such as 3-nitro- and 4-nitroacetophenones also condense with hippuric acid to give the oxazolones **25**.^{216–218} Sodium bicarbonate works equally well. Anhydrous zinc chloride has also been found to be an effective catalyst.^{219,220}

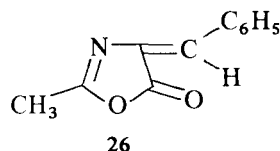


Bases such as pyridine and β - and γ -picolines²²¹ have also been employed as catalysts. Triethylamine, acetamide, morpholine, piperidine, and the *N*-acetyl derivatives of the latter two bases also catalyze the reaction, but the yields are low.²⁰³

ANHYDRIDE. While acetic anhydride is usually the reagent of choice in the Erlenmeyer synthesis, acyl interchange (Eq. 17) has been reported in the preparation of the azlactone from 4-fluorobenzaldehyde.²²² No such exchange has been observed in the formation of azlactones from other aromatic aldehydes or thiophene aldehydes,²²³ although phenaceturic acid and caproylglycine, with benzaldehyde, acetic anhydride, and sodium acetate at 100°C, give the product of acyl interchange, 2-methyl-4-benzylidene-2-oxazolin-5-one **26**,² instead of the expected 2-benzyl or 2-*n*-pentyl analog of **26**. The subject of acyl interchange in these reactions clearly needs further investigation.



Instead of acetic anhydride, phosphorus oxychloride in dioxane, thionyl chloride, phosphorus pentachloride in ether, or phosphorus tribromide can be used for cyclodehydration.^{144,224}

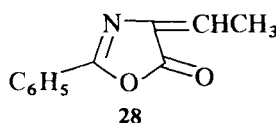
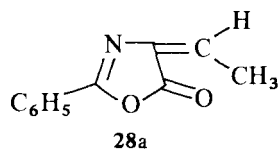


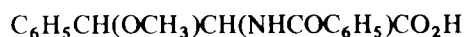
3.2.2.2. Dehydration of β -Hydroxy- α -Acylamino Acids

The *N*-benzoyl derivatives of *dl*-threonine or allothreonine **27** yield 2-phenyl-4-ethylidene-2-oxazolin-5-one **28** on heating with benzoyl chloride in pyridine or acetic anhydride in pyridine. The labile geometric isomer **28a** is obtained when *N*-benzoyl-*O*-methyl-*dl*-allothreonine is heated with acetic anhydride.^{225,226} When

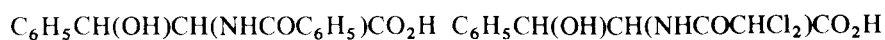
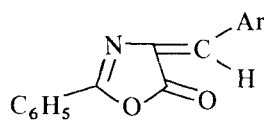


27

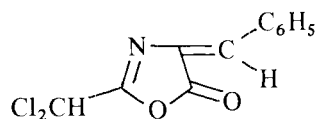


**29**

dl-*O*-methyl-*N*-benzoylphenyl serine **29** is heated with acetic anhydride, a mixture of the geometric isomers of 2-phenyl-4-benzylidene-2-oxazolin-5-one is obtained.²²⁷⁻²²⁹ When the phenylserine derivative **29** is heated with acetic anhydride or benzoyl chloride in pyridine, only the more stable *Z*-isomer **15** (Ar = C₆H₅) is formed.²³⁰

**30a, b***(Erythro, Threo)***31****15**(Ar = C₆H₅)

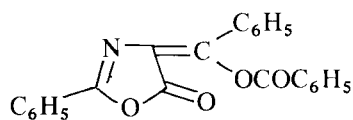
Erythro-*N*-benzoylphenyl serine **30a**, on cyclization with acetic anhydride, gives a mixture of the *Z*- and *E*-isomers, while the *threo* compound **30b** yields only the *Z*-isomer.^{231,232} Heating *N*-dichloroacetylphenyl serine **31** with acetic anhydride gives **32**, while heating DL-*threo*-phenyl serine leads to the formation of the 2-methyl analog of **32**.^{233,234} Threonine derivatives have also been converted to 2-aryl-4-ethylidene-2-oxazolin-5-ones.^{196,197,234}

**32**

Thionyl chloride in pyridine reportedly converts *dl*-*O*-acetyl-*N*-benzoylphenyl serine to 2-methyl-4-benzylidene-2-oxazolin-5-one.²³⁵ Treatment of β-(2-furyl)serine with benzoyl chloride and sodium hydroxide yields the α-furylidene azlactone.²³⁶

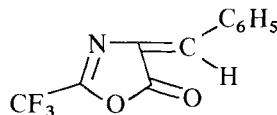
3.2.2.3. α-Hydroxy-Alkylidene Azlactones

Acylation of 2-phenyl-2-oxazolin-5-one with acid chlorides in the presence of β-picoline affords 2-phenyl-4-(1-hydroxyarylidene or alkylidene) oxazolones.^{204,237,238} 2-Phenyl-4-(1-hydroxypalmitylidene)-2-oxazolin-5-one is similarly formed from palmitoyl chloride.²³⁹ Sodium hippurate and benzoic anhydride react in the presence of β-picoline to give 2-phenyl-4-(α-benzoyloxybenzylidene)-2-oxazolin-5-one **33**.²⁴⁰ With *p*-nitrobenzoyl chloride, the *p*-nitrobenzoate analog of **33** is



33

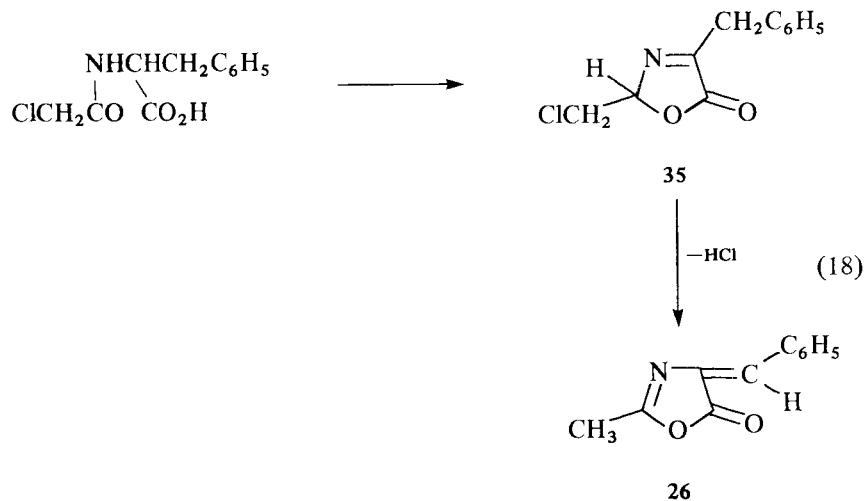
obtained.²⁴¹ Hippuric and substituted hippuric acids react with trifluoroacetic anhydride to give 2-aryl-4-(α -hydroxy-2',2',2'-trifluoroethylidene)-2-oxazolin-5-ones.²⁴² When glycine is treated with trifluoroacetic anhydride in the presence of sodium alkoxide and benzaldehyde, compound **34** is obtained.²⁴³



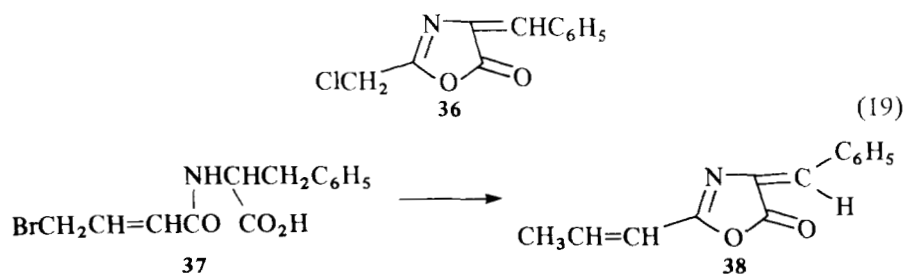
34

3.2.2.4. Bergmann Synthesis

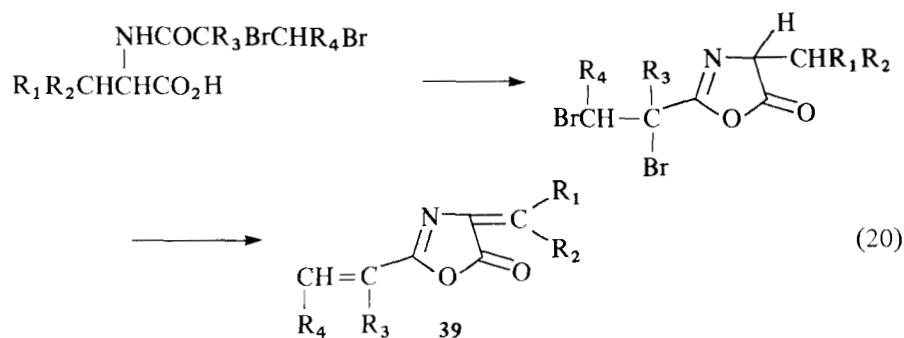
Acetic anhydride converts *N*-chloroacetylphenylalanine to 2-methyl-4-benzylidene-2-oxazolin-5-one **26**. A pseudoxazolone, **35**, initially formed, rearranges to **26**.²⁴⁴



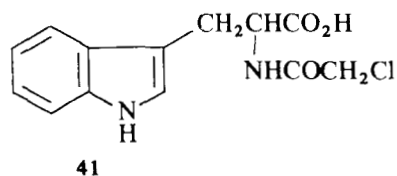
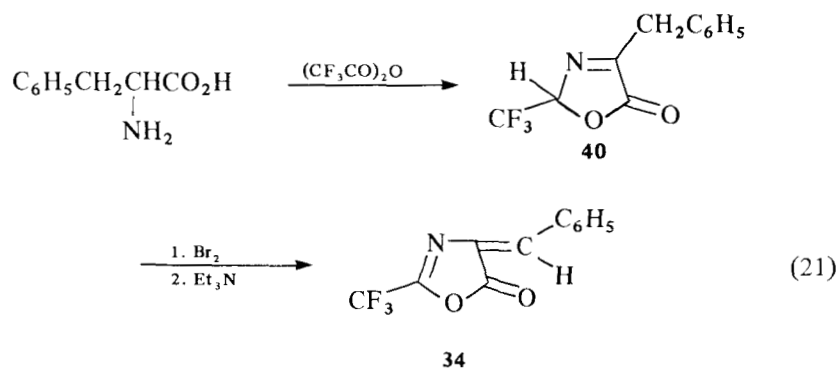
2-Chloromethyl-4-benzylidene-2-oxazolin-5-one **36** is obtained when trichloroacetyl phenylserine is heated with acetic anhydride and 2,5-lutidine.²⁴⁴ γ -Bromocrotonyl phenylalanine **37** is similarly converted to **38**.²⁴⁵ Amino acids such as phenylalanine, tyrosine, valine, leucine, and isoleucine have been converted to *N*-(α -methylcinnamoyl)amino acids and thence to the dibromide addition product.



Az lactonization in acetic anhydride–pyridine followed by oxidation with pyridine hydrobromide perbromide gives analogs of **39**.^{29,246} Compound **39** has the *Z* configuration around the newly formed double bond in the 2-position.

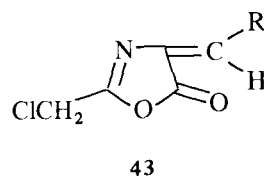
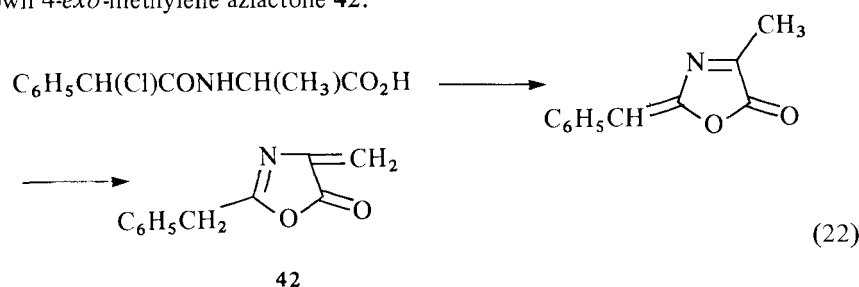


Phenylalanine is converted to the pseudoxazolone **40**, which on addition of bromine and dehydrobromination gives 2-trifluoromethyl-4-benzylidene-2-oxazolin-5-one **34**.^{247,248}

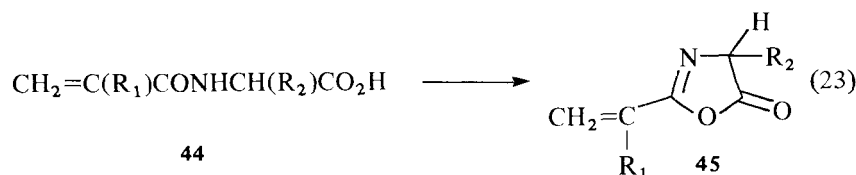


A study of conditions for conversion of *N*-chloroacetyl-DL-tryptophan **41** to 2-methyl-4-(3'-indolylidene)-2-oxazolin-5-one has led to an optimal procedure: 8 mol of acetic anhydride, 3 mol of pyridine, and 1 mol of **41** are allowed to react for 20 min. The amount of pyridine is especially critical, with larger quantities giving decreased yields. Longer reaction periods are not beneficial.²⁴⁹

Heating *N*-(α -chlorophenylacetyl)alanine with acetic anhydride gives the only known 4-*exo*-methylene azlactone **42**.²⁵⁰

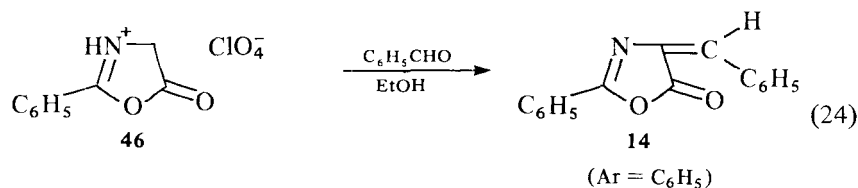


A series of 2-chloromethyl oxazolones **43** has also been prepared by Bergmann's method²⁵¹ as are 2-methyl-4-(2'-thenylidene) and 2-benzyl-4-methylene-2-oxazolin-5-ones.²⁵⁰⁻²⁵² 2-Alkenyl oxazolones **45** are obtained by heating unsaturated acids **44** with acetic anhydride.^{123,253,254}



3.2.2.4.1. OXAZOLINONIUM PERCHLORATES

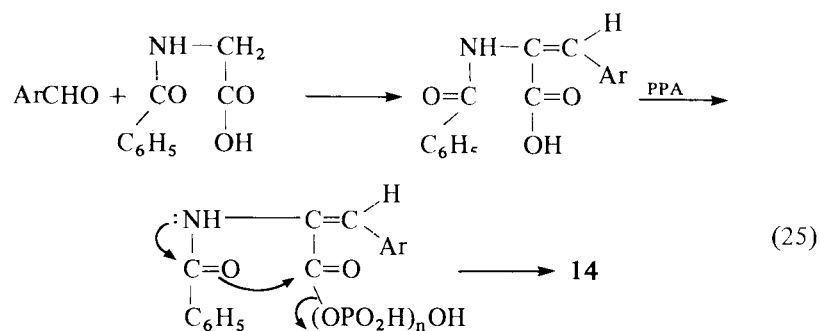
Perchloric acid converts hippuric acid into 2-phenyl-2-oxazolinonium perchlorate **46**.²⁵⁷ Compound **46** condenses with benzaldehyde to give the *E*-isomer of 2-phenyl-4-benzylidene-2-oxazolin-5-one.^{144,255}



3.2.2.4.2. SYNTHESIS OF 2-PHENYL-4-ARYLIDENE-2-OXAZOLIN-5-ONES IN POLYPHOSPHORIC ACID

Indole reacts with 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one in polyphosphoric acid (PPA) to give the 3-indolylidene derivative.²⁵⁹ Unsaturated 2-oxazolin-5-ones derived from 2-, 3-, and 4-methylcyclohexanones and hippuric acid, which are not otherwise accessible, are readily prepared in PPA.¹⁴⁷ Aromatic aldehydes condense with hippuric acid in PPA to give the lower-melting geometric isomers.²¹⁷ The method has been employed for the hitherto inaccessible *E*-isomers derived from *p*-methyl, *p*-chloro, *p*-nitro, and *p*-methoxybenzaldehydes. The *o*-, and *p*-hydroxybenzaldehydes yield the corresponding hydroxybenzylidene azlactones. Acetophenone and its ring-substituted analogs also react in PPA to give α -arylethylidene azlactones and phenylacetaldehyde. Hydrocinnamaldehyde and 2-methylcyclohexanone also form the corresponding azlactones. The higher-melting isomeric azlactones with the *Z* configuration can be transformed to the lower-melting *E*-isomers by heating with PPA.

This is the best method currently available for the preparation of these less accessible geometric isomers. Lower aliphatic aldehydes such as acetaldehyde give tars, while higher aldehydes provide low yields of the alkylidene azlactones.¹⁵¹ The following mechanism is suggested for the cyclodehydration–condensation reaction.



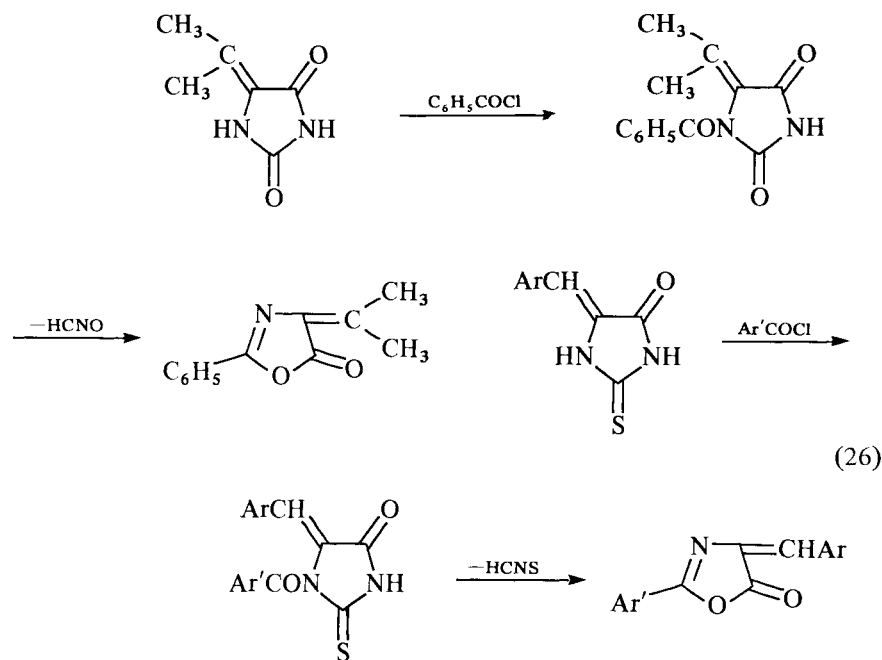
It has been reported that the PPA method leads to the formation of a mixture of *E*- and *Z*-isomers when benzaldehyde reacts with hippuric acid,²⁶⁰ although the method appears to be effective in other cases.²⁶¹

3.2.2.4.3. CYCLODEHYDRATION WITH SULFUR TRIOXIDE IN DIMETHYLFORMAMIDE

A complex of sulfur trioxide in anhydrous dimethylformamide containing 30% sulfur trioxide is useful in the synthesis of unsaturated azlactones.²⁶² The procedure, which is quite simple, consists of heating equimolar quantities of the aromatic aldehyde and hippuric acid in a threefold molar excess of the DMF–SO₃ reagent. High yields of azlactone are usually obtained. While salicylaldehyde presumably gives 2-phenyl-4-(*o*-hydroxybenzylidene)-2-oxazolin-5-one, it has been claimed²⁶³ recently that the product is not an azlactone but a coumarin derivative.

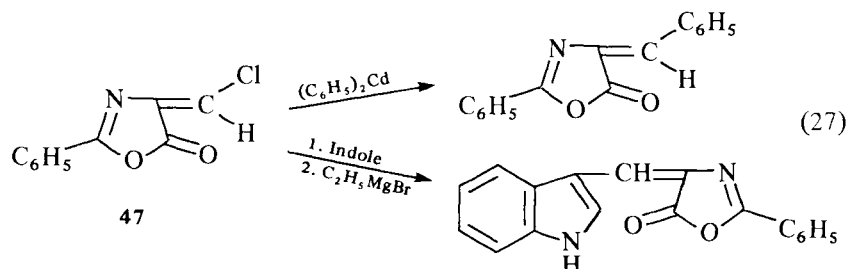
When this method is applied to the synthesis of azlactones derived from pyridine-3 and 4-carboxyaldehyde, sulfur trioxide adducts are formed from which the free oxazolones can be isolated by shaking with aqueous sodium acetate.^{74,75}

FROM HYDANTOINS AND THIOHYDANTOINS. Reaction of 5-isopropylidene hydantoin with benzoyl chloride in acetic anhydride has been reported to give 2-phenyl-4-isopropylidene-2-oxazolin-5-one with elimination of hydrogen cyanate.²²² Heating 5-arylidene-2-thiohydantoin with two- to fourfold excess of benzoyl or substituted benzoyl chlorides in pyridine gives 80–95% yields of 4-arylidene azlactones. This method provides a convenient route to azlactones with substituted aryl groups in the 2-position, thereby avoiding the need of preparing ring-substituted hippuric acids for the Erlenmeyer synthesis.^{264,265}

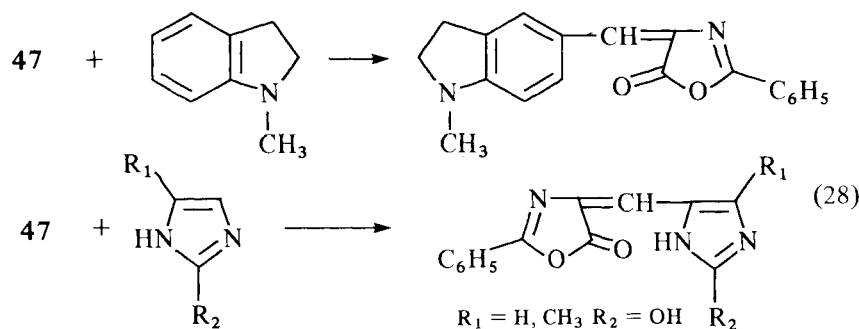


FROM 4-CHLOROMETHYLENE-2-PHENYL-OXAZOLONE. A versatile synthesis of unsaturated azlactones that is very useful if the aldehyde is not readily available consists of the nucleophilic displacement of chlorine in 4-chloromethylene-2-phenyl-2-oxazolin-5-one **47**,[†] by an organocadmium reagent. The lability of the chloro group is due to its vinylogous acid halide structure. The organomagnesium compound is employed in the synthesis of heterocyclic methylene oxazolones.²⁶⁶ *N*-Methylindoline reacts directly with **47** to give the corresponding oxazolone, while imidazole and 4-methylimidazole react with **47** in nitromethane to afford

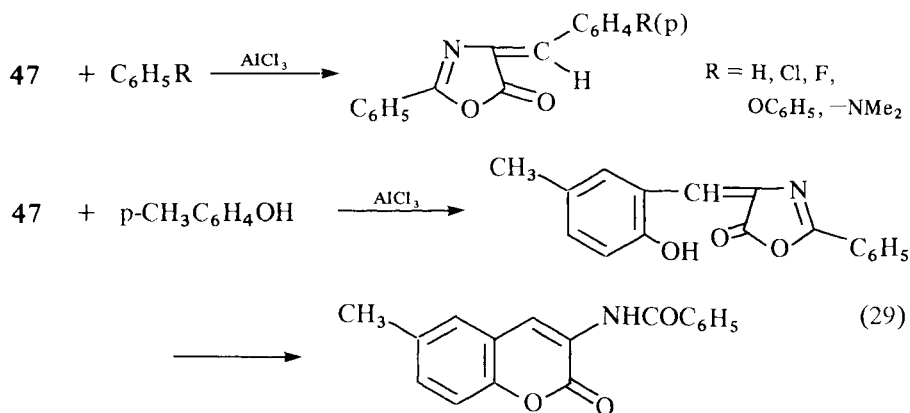
[†]The structure of **47** was recently determined. See J. M. Bland, C. H. Stammer, and K. I. Varughese, *J. Org. Chem.*, **49**, 1634 (1984).

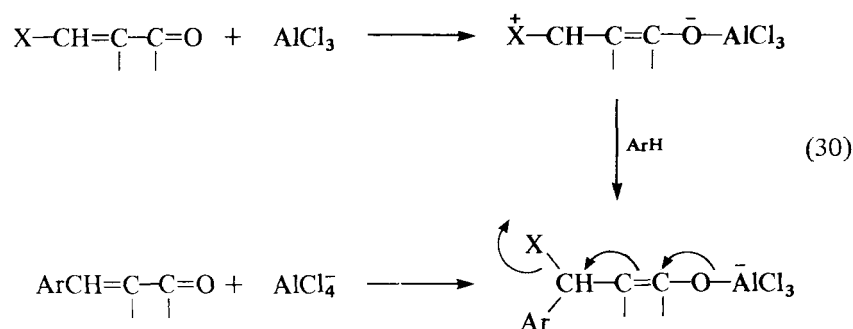


the azlactones.^{267,268} These compounds may then be converted to DL- and substituted histidines. The yields of the oxazolones exceed 75%. With pentafluorophenylmagnesium bromide, the reaction with **47** gives only 2% of 2-phenyl-4-pentafluorobenzylidene-2-oxazolin-5-one.²⁶⁹ This poor result is probably due to the relatively facile decomposition of C_6F_5MgBr to tetrafluorobenzene.

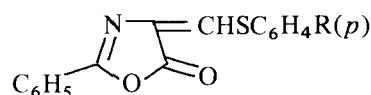


Reaction of **47** with benzene, chlorobenzene, fluorobenzene, diphenyl ether, dimethylaniline, or *p*-cresol in the presence of anhydrous aluminum chloride affords *p*-substituted arylidene azlactones in 93–97% yields.²⁷⁰ The product derived from *p*-cresol **48** isomerizes to the coumarin derivative **49**, when treated with triethylamine.²⁷⁰ The electrophilic character of the α,β -unsaturated carbonyl system is enhanced by anhydrous aluminum chloride and permits attack on the aromatic nucleus.



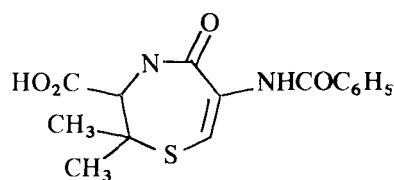


When the Friedel-Crafts reaction of **47** with thiophenol and substituted thiophenols is conducted in CH_2Cl_2 , 4-phenylthiomethylene oxazolones **50** are obtained.²⁷¹



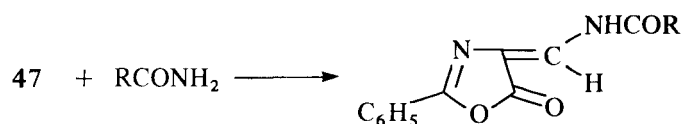
50 R = H, CH_3 , Br, Cl

Reaction of **47** with penicillamine hydrobromide gives 1-thia-3-benzamido-4-oxo-5-aza-7,7-dimethyl-2-cycloheptane-6-carboxylic acid **51**.²⁷² Amides also react with **47** to yield acylamide derivatives **52**.²⁷³



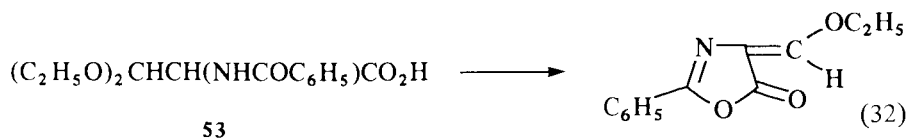
51

(31)

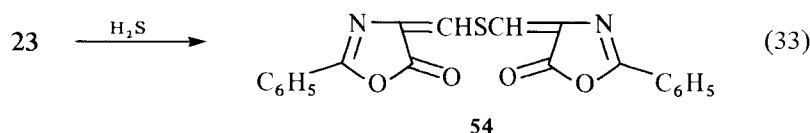


52

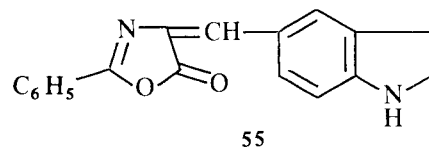
FROM 4-ETHOXYMETHYLENE-2-OXAZOLIN-5-ONES. Condensation of hippuric acid with ethyl orthoformate and acetic anhydride gives 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one, **23**.²⁷⁴⁻²⁸⁰ Compound **23** is also prepared by cyclization of penaldic acid **53**.^{202,282} These alkoxyethylene compounds react with ammonia and primary or secondary amines to yield 4-aminomethylene azlactones.^{2,283,284}



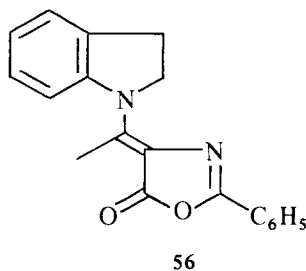
Substitution occurs at the 4-position without affecting the oxazolone ring. The aminomethylene oxazolones are feebly basic. A survey of the substitution reactions that **23** undergoes with various substrates has been tabulated.² The amino compounds used in the substitution reaction include aniline, hydrazine, guanidine, and acetamide. Disubstitution occurs with hydrogen sulfide to give the bisoxazolone **54**.



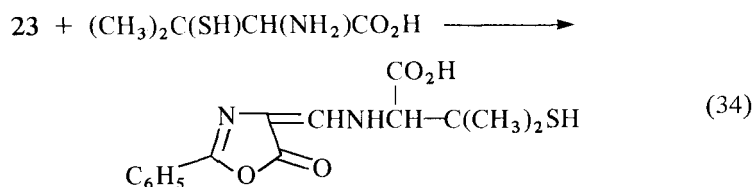
Compound **23** reacts with indole in the presence of polyphosphoric acid to yield the 3-indolylidene oxazolone.²⁵⁷



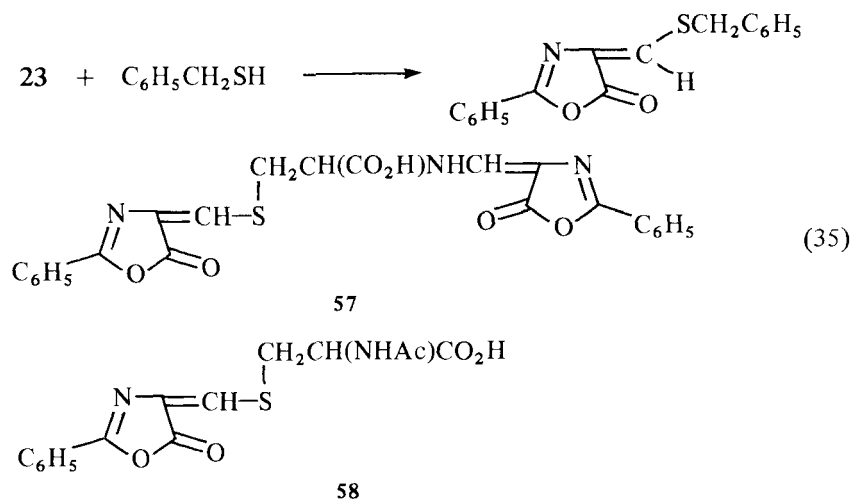
With indoline, **23** gives 2-phenyl-4-(*N*-indolyl(methylene))-5-[4*H*] oxazolone **56** rather than the previously reported²⁶⁷ **55**. Compound **56** is brominated to give the 5-bromo compound that is also obtained by reaction of 5-bromoindoline with **23**.²⁸⁵ Several merocyanines have been prepared from the appropriate heterocyclic compounds and **23** in the presence of a tertiary amine catalyst.^{154,286-305} These merocyanines are useful dyes.



4-Ethoxymethylene-2-aryl-2-oxazolin-5-ones react with cysteine, valine, DL- β -methylcysteine, β,β -diethylcysteine, β -ethyl- β -methylcysteine, penicillamine, β,β -dimethylcysteine, and proteins to give products in which the point of attachment is at the amino function of the amino acids, as shown below.³⁰⁶⁻³¹⁰ This result is in contrast to the behavior of compound **47**, which reacts with penicillamine to give **51** (vide supra).



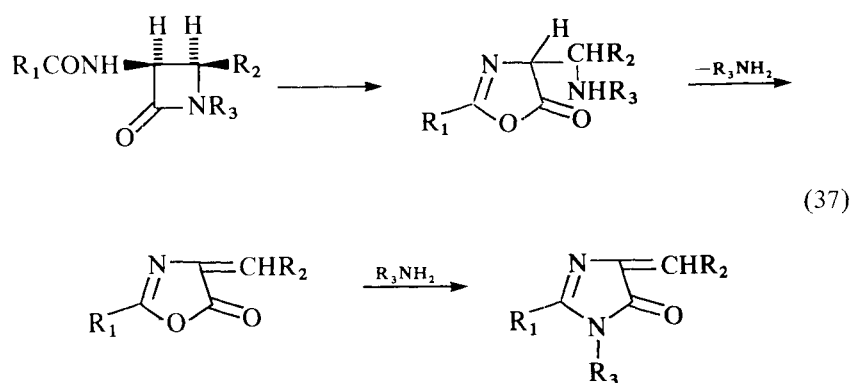
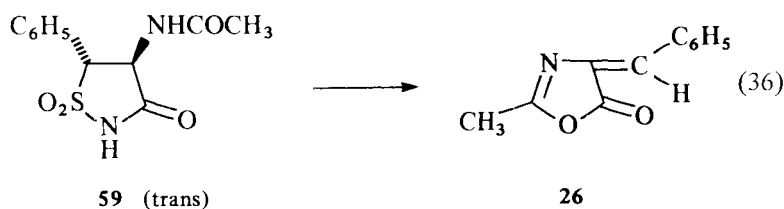
With mercaptans and sulfur compounds, the corresponding sulfide analogs are obtained. Reaction of aminoalcohols with **23** yields the corresponding aminomethylene derivatives,³¹⁵ while cysteine and 2 mol of **23** reportedly give the dilactone **57**.³¹⁶ *N*-Acetylcysteine, on the other hand, forms only compound **58**.³¹⁷



3.2.2.5. Miscellaneous Methods

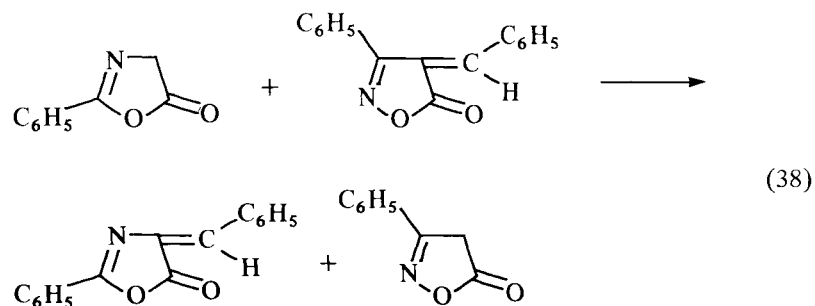
Some of the following methods have been used for specific syntheses, while others are instrumental in converting products derived from oxazolones back to the parent compounds. *cis*- or *trans*-4-Acetamido-5-phenylisothiazoline-3-one-1,1-dioxide **59** is converted to 2-methyl-4-benzylidene-2-oxazolin-5-one on heating with acetic anhydride–pyridine.³¹⁸ Rearrangement of 3-benzamido-1,4-diphenylazetidin-2-one **60** affords unsaturated azlactones, among other products.¹⁸⁶

Open-chain hydrazides, obtained from 2-aryl-4-arylidene-2-oxazolin-5-ones **15** and hydrazine hydrate are reported to form 1,2,4-triazines on heating with a mixture of acetic acid–acetic anhydride.³¹⁹ The hydrazides, in turn, are reconverted to the oxazolones when heated with a mixture of acetic acid–acetic anhydride.³²⁰ Hydroxyamides obtained from the oxazolone **15** (Ar = C₆H₅) and its analogs with ethanolamine revert to the azlactones when heated with acetic anhydride, thionyl chloride, or an acid chloride.³²¹



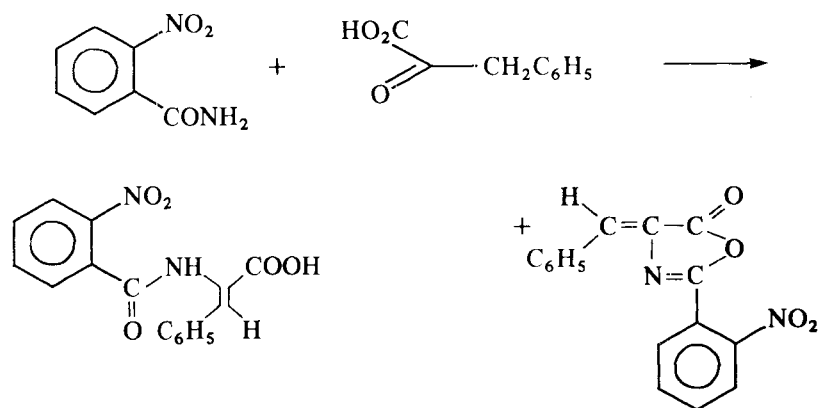
An isoxazolone–oxazolone exchange reaction has also been reported.³²²

Nitration of 2-phenyl-4-alkoxybenzylidene-2-oxazolin-5-one derivatives gives the corresponding mono-nitro derivatives. However, with 2-methyl analogs, hydrolysis occurs with the formation of α -acetamidocinnamic acids.^{32,3} Bromination and chlorination of 2-phenyl-4-benzylidene-2-oxazolin-5-ones provide the corresponding α -bromo and α -chloro analogs.³²⁴⁻³³¹

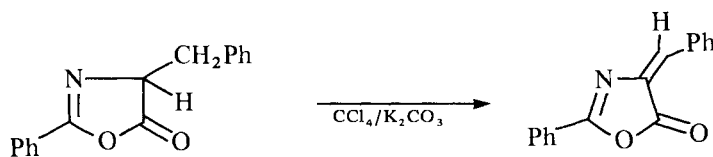


Isomerization of the *Z*-isomer of 2-phenyl-4-benzylidene-2-oxazolin-5-one **15** (Ar = C₆H₅) to its *E*-isomer^{332–337} occurs on photolysis in isopropyl alcohol. Under similar conditions, 4-(2'-acetoxy arylidene)-azlactones isomerize to coumarins.^{338,339}

Reaction of *o*-nitrobenzamide with phenylpyruvic acid in toluene in the presence of *p*-toluenesulfonic acid gives *trans*-2-benzylidene-*o*-nitrohippuric acid along with 4-benzylidene-2-(*o*-nitrophenyl)-5-[4*H*] oxazolone.^{339a}

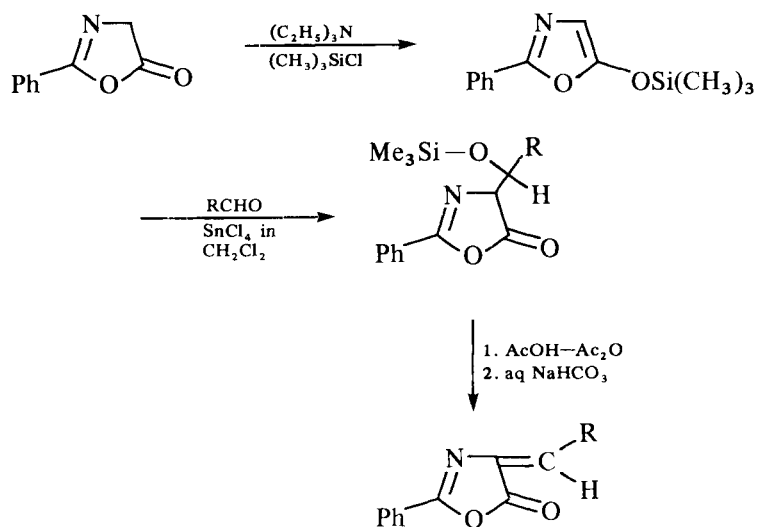


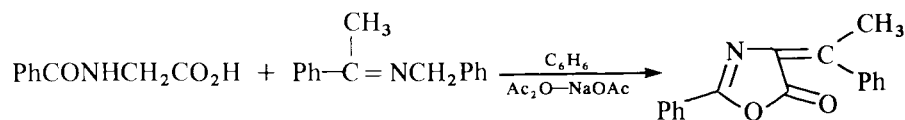
An interesting method for the synthesis of 2-phenyl-4-benzylidene-5-[4H]-oxazolone consists of treating 2-phenyl-4-benzyl-5-[4H]-oxazolone with reagents such as Br₂, SO₂Cl₂, *N*-bromosuccinimide, and dibromantin in CCl₄ containing potassium carbonate.^{339b}



Ion exchange resins, which are mildly alkaline macroporous, have also been used in the synthesis of oxazolones. The authors claim the isolation of *E*-isomers when, in fact, their melting point data correspond to those of the *Z*-isomers.³⁴⁰

2-Phenyl-5-trimethylsilyloxyoxazole reacts with aldehydes and acetals of ketones to give oxazolones in high yields.³⁴¹

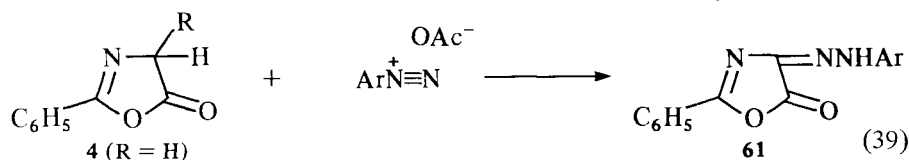




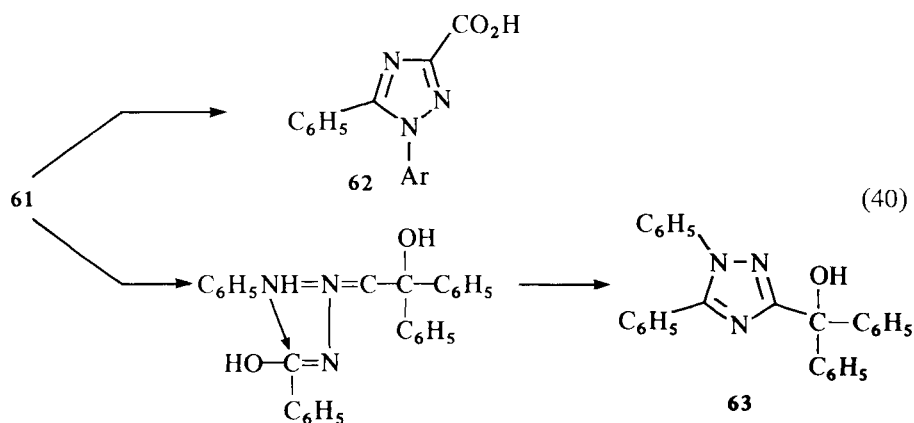
A novel approach to oxazolones derived from ketones is the reaction of hippuric acid with ketimines^{342,343} in the presence of sodium acetate and acetic anhydride. Enamines¹⁴⁷ of methylcyclohexanones had been employed earlier in the condensation reaction. Aldimines have also been used.^{344,345} 2-Acetyl-5-nitrofurans is reported to condense with hippuric acid under Erlenmeyer conditions.³⁴⁶

3.2.2.5.1. 4-ARYLAZO OXAZOLONES

Aryldiazo compounds react with 2-phenyl-2-oxazolin-5-one to yield 4-aryazo derivatives **61**.^{73,347-352} In general procedure, isoamyl nitrite is added to a cold solution of arylamine in acetic acid and concentrated hydrochloric acid.

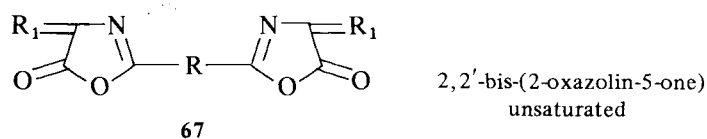
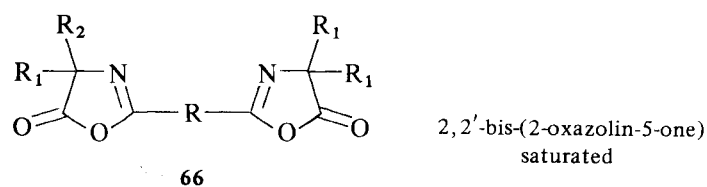
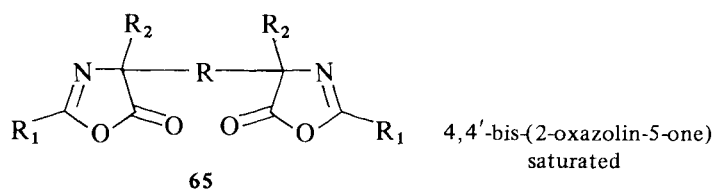
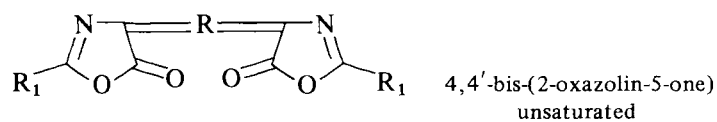


The resulting diazonium salt is treated with sodium acetate and hippuric acid in acetic anhydride. The yields of **61** vary from 18 to 85%. These compounds are converted to a triazole carboxylic acid **62** on treatment with alcoholic potassium hydroxide.³⁴⁸ Reaction of the aryl azo compounds with Grignard reagents also yields 1,2,4-triazole derivatives.⁷³ Similarly, **61**, on heating with a primary amine in an acetic acid–sodium acetate mixture, gives 1,2,4-triazole carboxamides.³⁵²

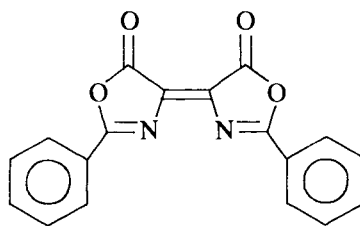


3.2.2.5.2. BISOXAZOLONES

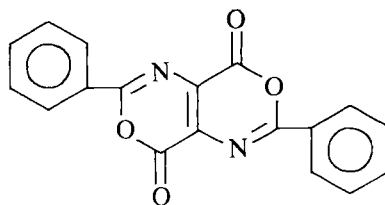
Bisoxazolones may be divided into four types depending on the position of coupling (2 or 4) and the presence or absence of an exocyclic double bond at the 4-position.³⁵³



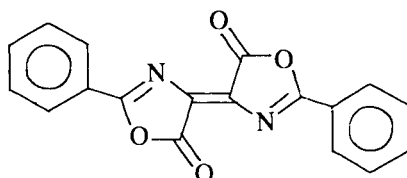
Hippuroflavin obtained by the action of the phosphorus pentachloride on ethylhippurate³⁵⁴ was assigned the bisoxazolone structure.³⁵⁵



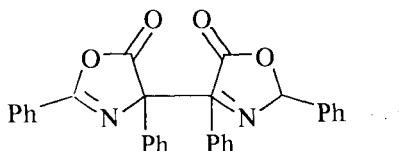
This compound has subsequently been shown to possess the following structure on the basis of X-ray crystallography.³⁵⁶ Hippurorubrin, a red-colored dye isomeric with the yellow-colored hippuroflavin, is obtained by reaction of thionyl chloride



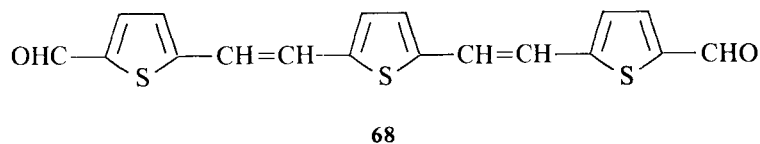
and diethyl 2,3-dibenzamidosuccinate. Based on X-ray crystallographic data, this compound has been assigned the following structure.³⁵⁶



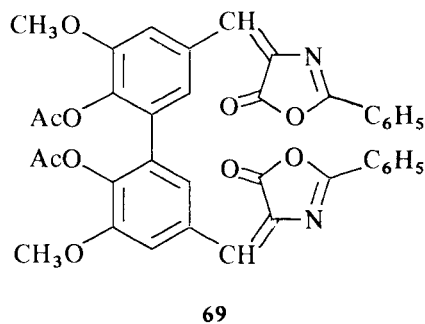
Compound **65** with the oxazolone rings connected at the 4,4'-positions is prepared by photooxygenation for 15 min of 2,4-diphenyl-5-[4*H*]oxazolone in a mixture of benzene and methanol or by nickel peroxide oxidation.³⁵⁷

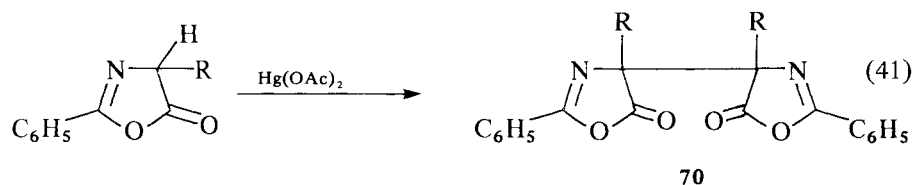


Compounds of type **64** may be prepared by the Erlenmeyer reaction of dialdehydes with hippuric acid. Thus, the three phthalaldehydes³⁵⁸⁻³⁶³ 4,4'-diformyl-diphenylether,³⁶⁴⁻³⁶⁸ naphthalene-2,6-dialdehyde,³⁶⁹ and 4,4'-diformylstilbene,³⁷⁰ the dialdehyde **68**,³⁷¹ the C-24 and C-30 apocarotenals,³⁷² 4,5-dimethoxyisophthalaldehyde,³⁷³ and thiophene-2,5-dialdehyde³⁷⁴ have been employed. For



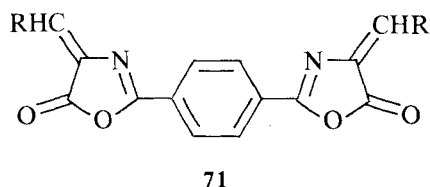
the synthesis of DOPA dimer, the intermediate bisoxazolone **69** is prepared.^{375,376} A cysteine dilactone has also been reported.²⁴⁰ Other bisoxazolones have been reported.³⁷⁷⁻³⁸⁶



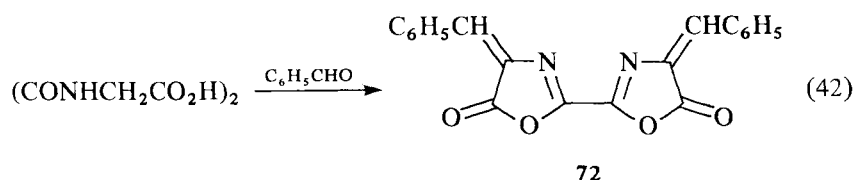


Compounds of type **70** have been obtained from 4-alkyl oxazolones² (Eq. 41).

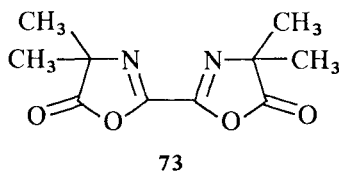
Bisoxazolones connected at the 2-position, **66**, have also been characterized. These compounds react with ethyl esters of amino acids to give dipeptides.³⁸⁷⁻³⁹³ Terephthaloyldiglycine is employed in the synthesis of oxazolone dyes of the type **71**,³⁹⁴ which are examples of unsaturated 2,2'-bisoxazolones **67**.



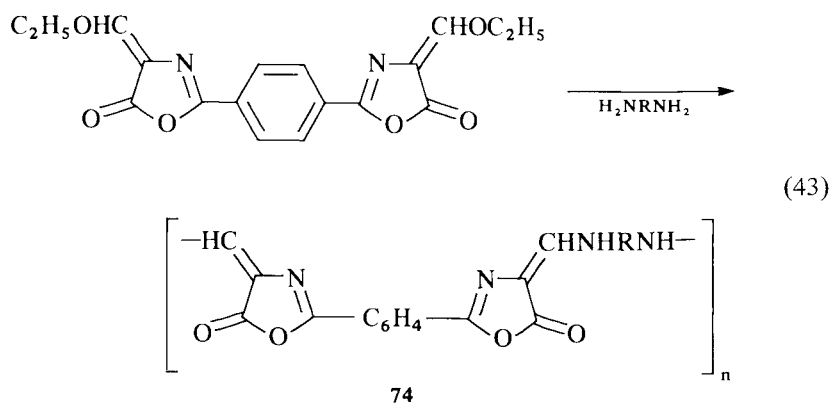
Oxalyl chloride reacts with glycine to form oxalyldiglycine, which condenses with benzaldehyde to yield **72**.³⁹⁰



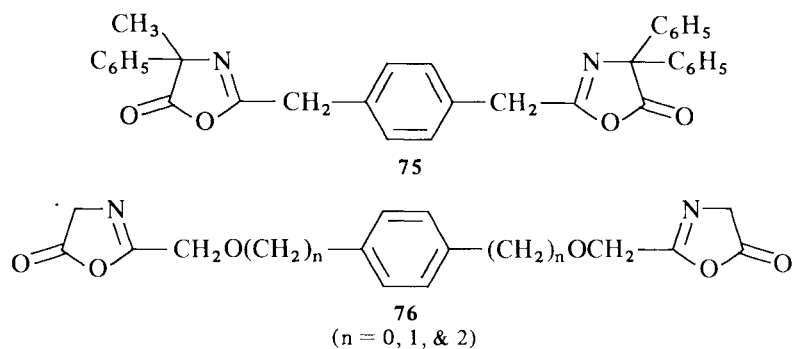
Compound **73**, 2,2'-bis(4,4'-dimethyl-2-oxazolin-5-one), which could not be prepared earlier, was obtained in 10% yield from oxalylbis(α -aminoisobutyric acid) and acetic anhydride or acetyl chloride.^{353,395,396} The same compound has since been prepared in 55% yield by employing the mixed-anhydride synthesis.⁵²



2,2'-Disubstituted bis(4-ethoxymethylene)-5-oxazolones react with diamines to give products of nucleophilic substitution at the 4-position (e.g., **74**), rather than polyamides, which would be formed by ring opening.^{353,397}



Bisoxazolones of types **75** and **76** have also been reported and their reactions with hexamethylene diamine studied.³⁹⁸



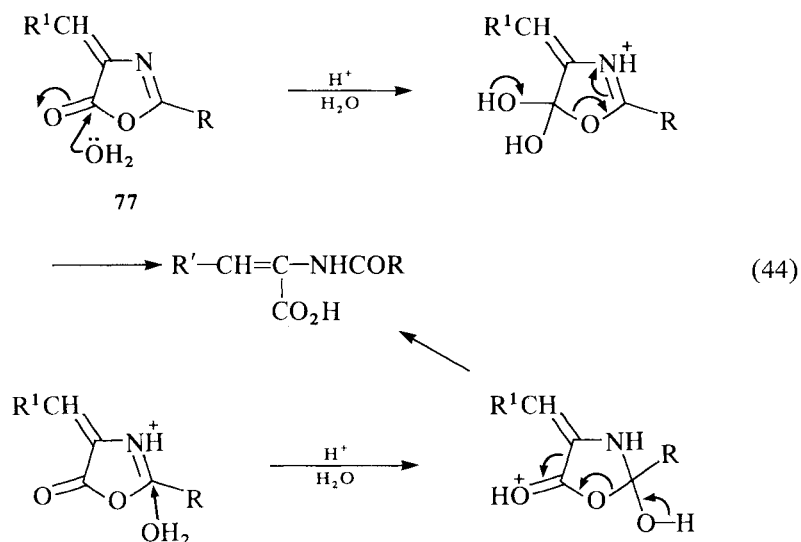
3.2.3. Properties and Reaction Chemistry of Azlactones

Unsaturated azlactones are usually high-melting solids, with colors ranging from yellow to dark red, owing to the high order of conjugation. The labile geometric isomers of 2-aryl-4-arylidene-2-oxazolin-5-ones are darker in color than the corresponding stable isomers. Saturated azlactones are liquids or low-melting solids and are usually colorless.

The reactions of azlactones with amines and amine derivatives will be discussed under compounds that can be prepared from oxazolones. Alcohols react with azlactones less readily, but in the presence of alkoxides, reaction proceeds with the quantitative conversion to the alkyl esters.^{2,399}

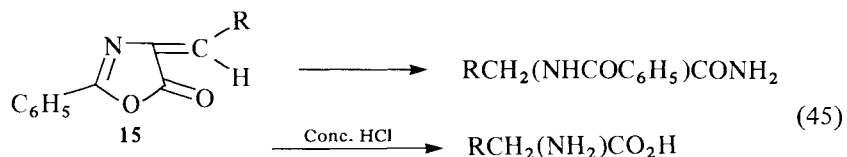
While acidic (aqueous HCl) hydrolysis of azlactones, such as **77**, could in theory proceed by addition of water at either the C–O or C–N double-bond linkages (Eq. 44), attack actually occurs at the C–N double bond, as demonstrated by a series of experiments involving use of H₂O¹⁸ and mass spectrometry.⁴⁰⁰

The acetic-acid-catalyzed ring opening reaction of oxazolones has also been investigated.^{401,402}

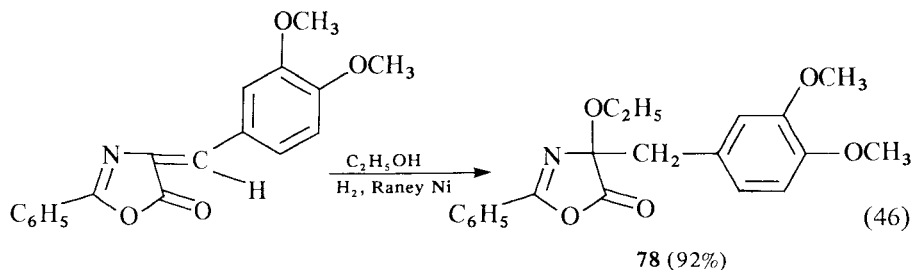


3.2.3.1. α -Amino Acids

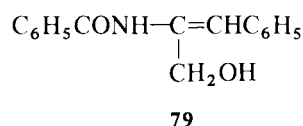
In the synthesis of α -amino acids from unsaturated azlactones, the latter compounds are hydrolyzed prior to hydrogenation. Other methods of converting azlactones to amino acids consist of reduction with sodium or sodium amalgam in water or ethanol, hydroiodic acid and red phosphorus in acetic acid or acetic anhydride, or catalytic hydrogenation over platinum, palladium, or Raney nickel.^{403-406,206} A single-step reduction of azlactones to *N*-acylamino acids has been reported.^{407,408}



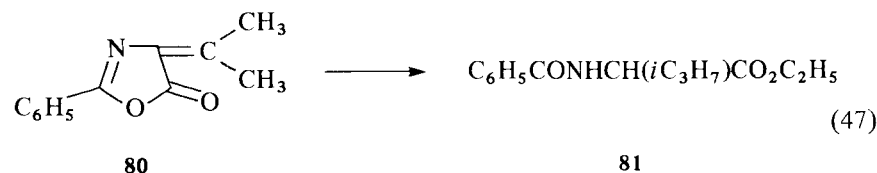
In an example of anomalous behavior, a saturated azlactone **78** formed by addition of the elements of solvent ethanol to the exocyclic double bond is obtained instead of the expected ring-opened product.⁴⁰⁹



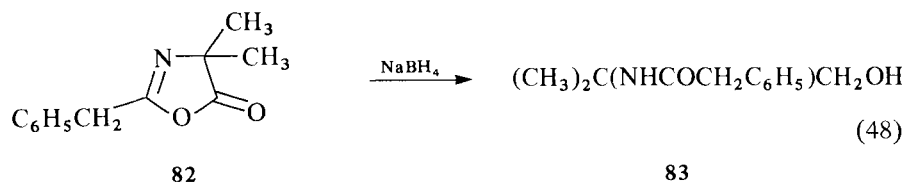
Reduction of **15** ($R = C_6H_5$) with lithium aluminum hydride or calcium borohydride gives α -benzamidocinnamyl alcohol **79**.^{410,411}



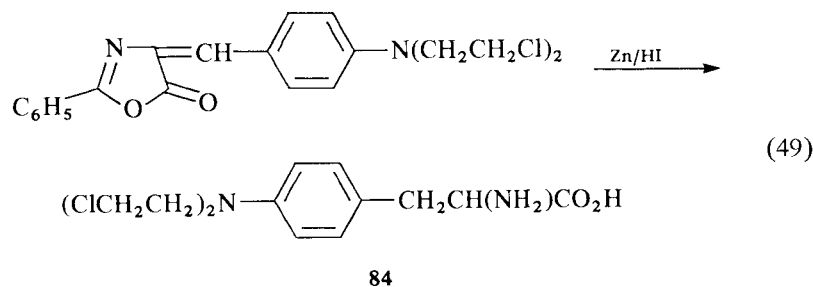
Reduction of 2-phenyl-4-isopropylidene-2-oxazolin-5-one **80** with lithium aluminum hydride affords the saturated azlactone, which reacts further with ethanol solvent to give **81**, which may also be obtained directly from **80** by reduction with potassium borohydrate at room temperature.⁴¹²



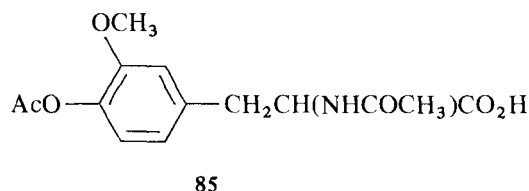
Reduction of saturated azlactones **82** with sodium borohydride yields amido alcohols **83**.⁴¹³



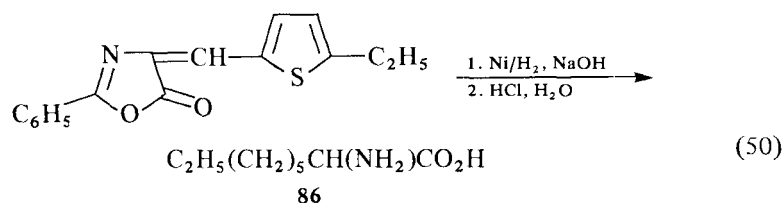
Electrochemical reduction of 2-phenyl-4-arylidene-2-oxazolin-5-ones, such as **15**, in alkaline medium gives *N*-benzoylphenylalanine.⁴¹⁴ Reduction of an azlactone with zinc in hydroiodic acid is employed in the synthesis of sarcosine **84**.⁴¹⁵



Asymmetric hydrogenation over 1,5-cyclohexadienerrhodium chloride of the azlactone derived from 4-hydroxy-3-methoxybenzaldehyde (vanillin) and acetic acid gives an 80–90% yield of the L-isomer of **85**.⁴¹⁶ Reductive hydrolysis of 2-methyl-4-benzylidene-2-oxazolin-5-one dissolved in optically active α -phenylalanine and palladium provides optically pure α -phenylalanine.^{90–103,417} Reduction



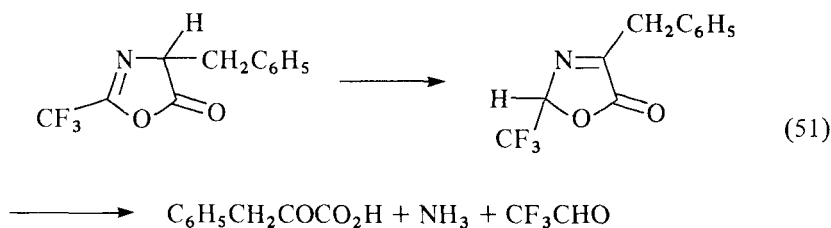
of unsaturated oxazolones may also be carried out in the presence of bisdimethylglyoximato cobalt (II).⁴¹⁸ Higher aliphatic amino acids such as α -aminopelargonic acid **86** are prepared by reducing 2-phenyl-4-(5'-ethyl-2'-thenylidene)-2-oxazolin-5-one over Raney nickel catalyst, which desulfurizes the thiophene nucleus.⁴¹⁹⁻⁴²¹



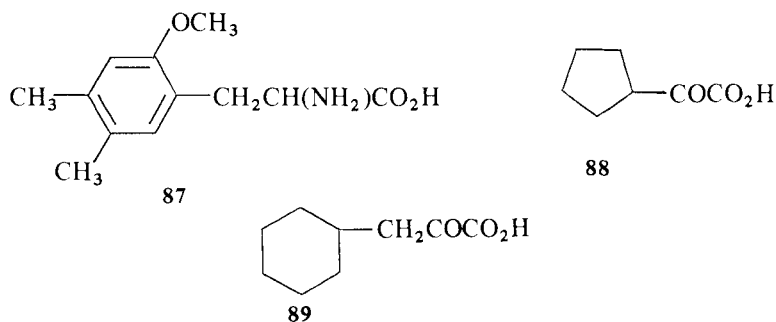
3.2.3.2. α -Ketoacids

Hydrolysis of unsaturated azlactones and α -acylaminoacrylic acids by strong mineral acid or alkali converts them to arylpyruvic acids. The reaction consists of heating the azlactone with strong alkali, such as sodium, potassium, or barium hydroxide, or with hydrochloric acid. Alkali is usually preferred and heating is continued until the evolution of ammonia ceases. This mode of hydrolysis has been used extensively.⁴²²⁻⁴⁴⁷

An anomalous conversion of 2-trifluoromethyl azlactones to α -oxoacids has been reported.⁴⁴⁸ The saturated azlactone isomerizes to a pseudoxazolone, which then undergoes hydrolytic cleavage to form phenylpyruvic acid.

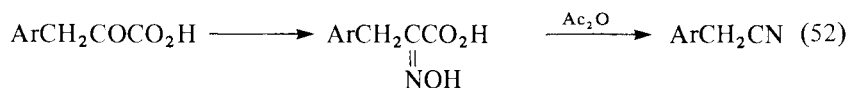


In the synthesis of 2,5-dimethoxy-4-methylphenylalanine **87** from the corresponding azlactone, the pyruvic acid is prepared and its oxime, on reduction, gives the desired amino acid **87**.^{449a} Cycloalkyl pyruvic acids **88** and **89** are similarly prepared,^{148,195} as well as the arylpyruvic acids derived from vanillin^{449b} and its 5-chloro and 5-bromo analogs.⁴²¹ α -(3-indolyl)Pyruvic acid has also been obtained by alkaline hydrolysis.²⁴⁹



3.2.3.3. Arylacetonitriles

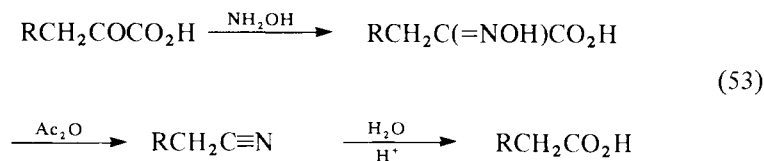
The arylpyruvic acids obtained from azlactones are converted to arylacetonitriles via the intermediate oximes. This method has been used extensively for the synthesis of substituted acetonitriles.⁴²³⁻⁴³²



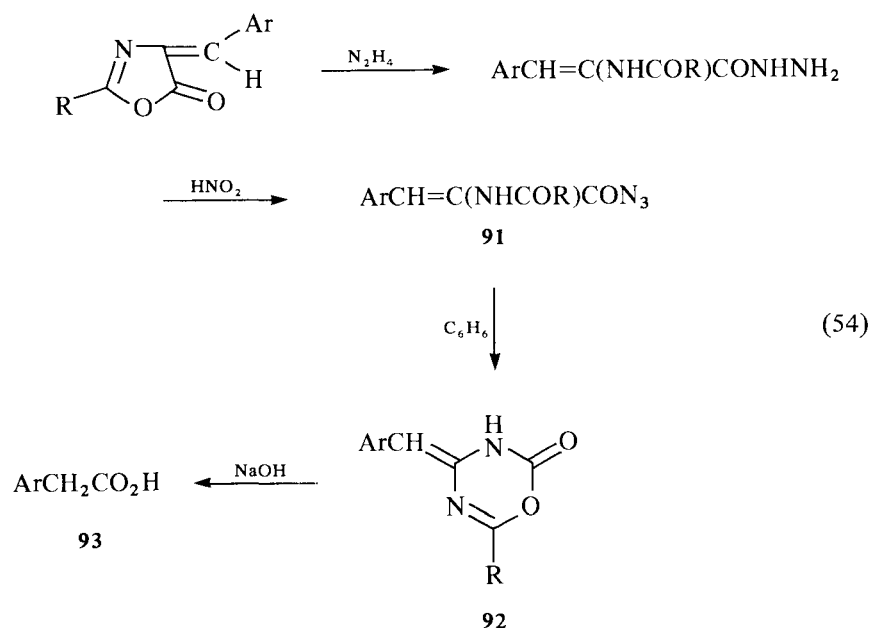
3.2.3.4. Arylacetic Acids

Arylacetic acids are conveniently prepared by alkaline hydrolysis of 4-arylidene azlactones. The 2-methyl derivatives are preferred to the 2-phenyl derivatives, thus obviating the tedious removal of benzoic acid, the by-product of alkaline hydrolysis of the azlactone. Usually, the benzoic acid is removed after conversion to its methyl ester. The initially formed α -keto acids are directly oxidized with hydrogen peroxide.

Preparations of 3,4-dimethoxyphenyl and 4-chlorophenyl acetic acids are described in "Organic Syntheses"⁴⁵⁰ and "Organic Reactions."¹ Saturation with sulfur dioxide of the reaction mixture from the alkaline hydrolysis of 2-phenyl-4-arylidene-2-oxazolin-5-ones helps to precipitate the benzoic acid while the pyruvic acid remains in solution.^{425,441} The organic syntheses method has been employed in the preparation of many arylacetic acids.^{200,259,324,366,449,451-475} In a recent modification, the α -keto acid is converted to its oxime, which is dehydrated to the arylacetonitrile by heating with acetic anhydride. The nitrile can then be hydrolysed to the arylacetic acid.^{359,426,434,476-479}



Another procedure for the conversion of unsaturated azlactones to arylacetic acids consists of the following steps (Eq. 54):⁴⁸⁰



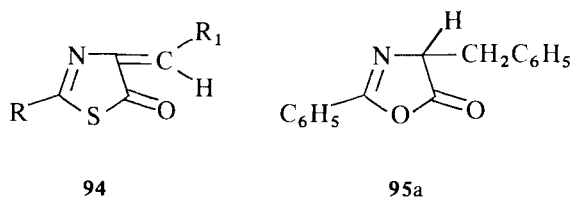
The overall yield from *m*-nitrobenzaldehyde is only about 4%.²⁷⁴ This method has been used extensively in the synthesis of substituted benzofurylacetic acids.⁴⁵⁶

3.2.3.5. Conversion to Other Heterocycles

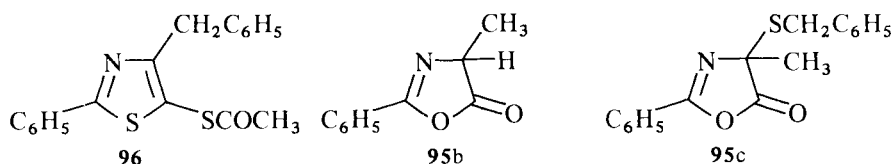
3.2.3.5.1. THIAZOLONES

Unsaturated azlactones (e.g., **15**) react with thioacetic acid at 100° for 18 h in the presence of triethylamine to give unsaturated thiazolones **94**. However, compound **15** fails to react with thioacetic acid if benzyl mercaptan is present, since the latter normally adds to the exocyclic double bond.² The conversion to thiazolones may also be carried out in the presence of thiopropionic or thiobutyric acids. This reaction has been extensively used in thiazolone preparations.^{66,286,489-495} However, triethylamine need not be added.⁴⁹²

The saturated azlactone 2-phenyl-4-benzyl-5-oxazolin-2-one **95a** gives a compound originally assumed to be a thiazolone on treatment with thioacetic acid.

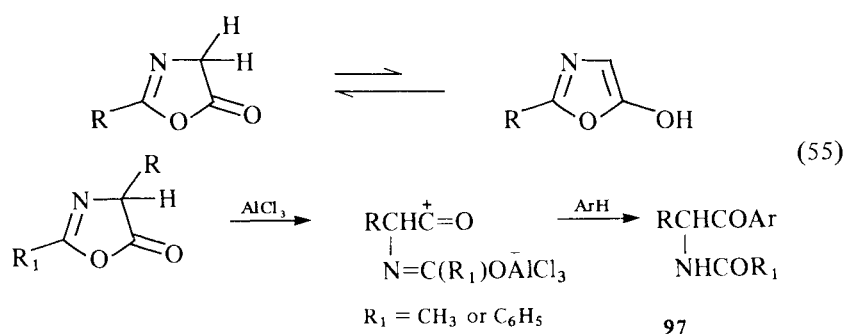


However, the product has since been shown to be the thiazole **96**.⁴⁹⁶ The anion derived from **95b** reacts with *S*-benzyl-*p*-toluenethiosulfonate to give 4-benzylthio-4-methyl-2-phenyl-2-oxazolin-5-one **95c**.^{497,498}

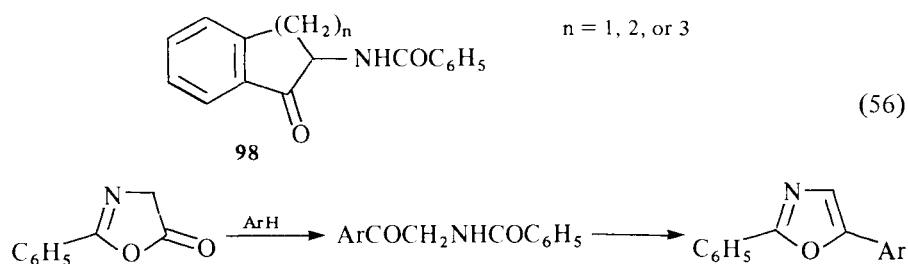


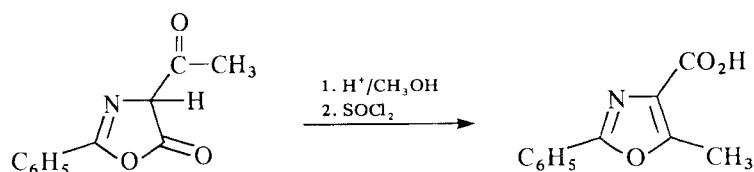
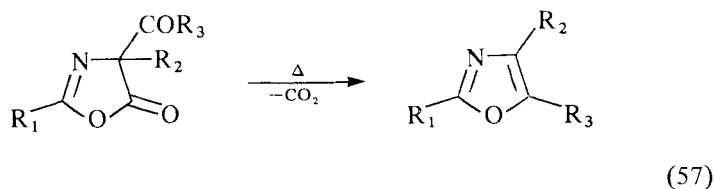
3.2.3.5.2. OXAZOLES

Theoretically, saturated azlactones may exist as the tautomeric 5-hydroxyoxazoles. However, they behave as acylating agents and react with aromatic hydrocarbons under Friedel–Crafts conditions to give open-chain acylamino ketones **97** in high yields. The hydrocarbons employed are benzene, toluene, and anisole.⁴⁹⁹ When R is benzyl-, 2-phenethyl-, or 3-phenylpropyl, intramolecular acylation occurs to give cyclic acylamino ketones **98**.⁵⁰⁰ Phosphorus oxychloride converts the acylamino ketones **97** to 2,5-diaryloxazoles in high yields.^{501–503}



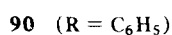
Introduction of an acyl or aroyl group in the 4-position decreases the thermal stability of oxazolones. Thermolysis of 2,4-dialkyl-4-aroil-2-oxazolin-5-ones at 180° leads to decarboxylation and the formation of trisubstituted oxazoles.⁵⁰⁴ 4-Acyloxazolones rearrange to oxazole derivatives when treated with thionyl chloride.^{238,505,507}



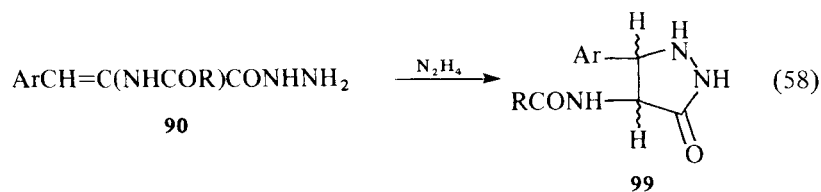


3.2.3.5.3. PYRAZOLONES

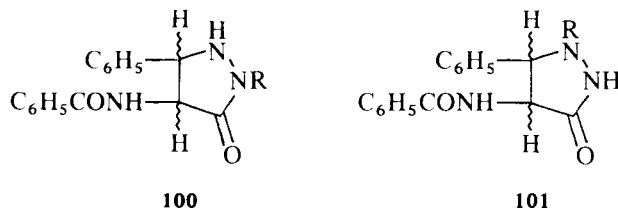
The reactions of unsaturated azlactones with hydrazine hydrate, substituted hydrazines, or amines have been extensively studied.⁵⁰⁸⁻⁵²⁴

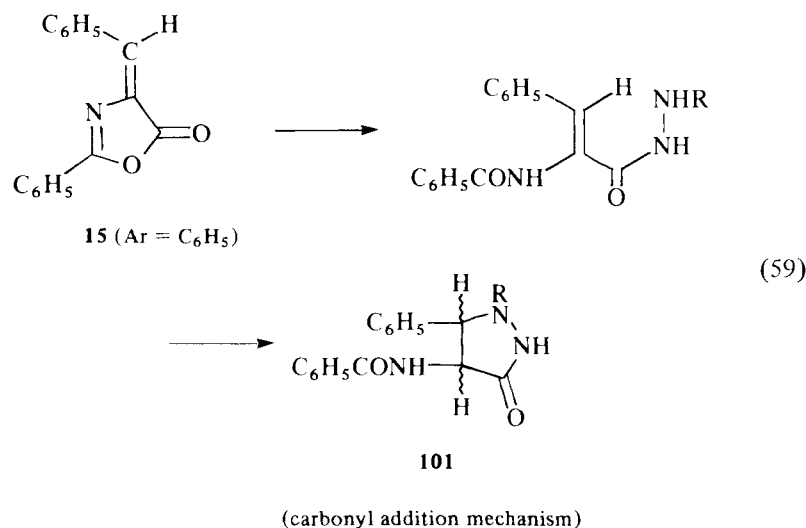


Two isomeric products are obtained in the reaction with hydrazine, depending on the reaction temperature⁵⁰⁸: the normal hydrazide **90** obtained at room temperature on reaction with 99.9% hydrazine hydrate and the alleged hydrazine adduct on reaction with 50% hydrazine in ethanol.⁵¹⁷ A reinvestigation of the latter reaction showed that the product is, in fact, a pyrazolidinone derivative **99**.⁵²⁷ The

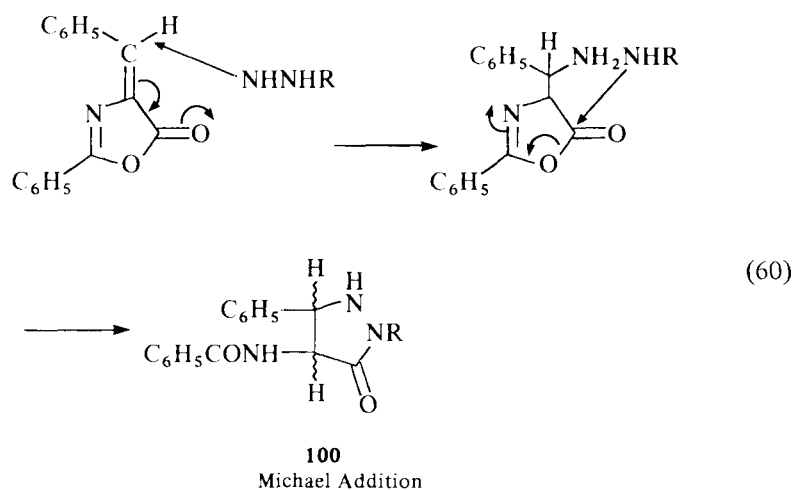


conversion of **90** to **99** may be effected by heating with alcoholic hydrazine. In alcoholic solutions, substituted hydrazines react with the oxazolone **15** ($\text{Ar} = \text{C}_6\text{H}_5$) to give not only hydrazides but also isomeric pyrazolidinones **100** and **101**. These



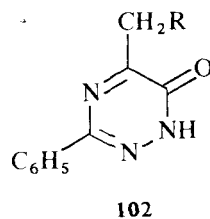


products are obtained in higher yields when the hydrazines are 2-pyridyl or 2-quinolyl hydrazine.⁵²⁷ In benzene, however, the hydrazides **90** are obtained exclusively. Two mechanisms have been suggested to account for the products observed.

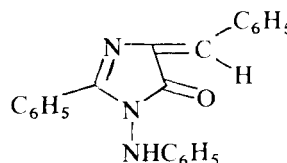
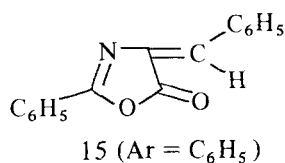


It is noteworthy that in Eq. 59, involving a 5-endo-trig system, ring closure is disfavored according to Baldwin's rules.⁵²⁸

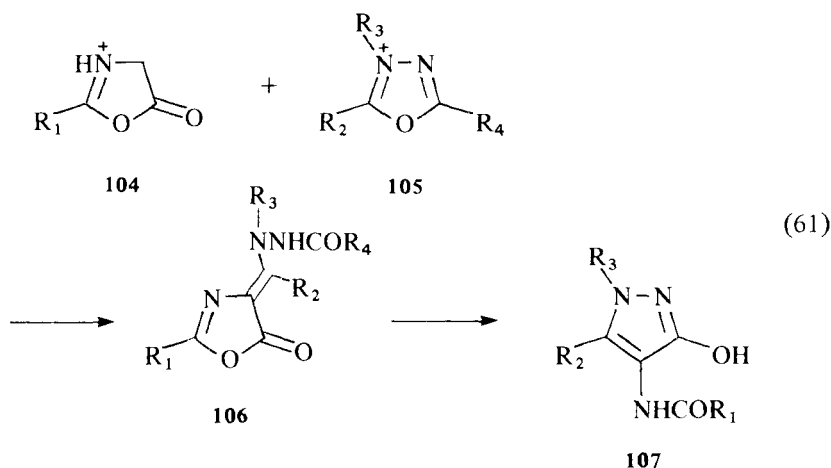
Treatment of the hydrazides **90** with hot alkali gives 1,2,4-triazine derivatives **102**,^{169,524,525} which are also obtained by treatment of hydrazides **90** with acetic anhydride–acetic acid.⁴⁷⁹ However, the products of acid treatment of hydrazides **90** are the parent oxazolones.³²⁰ Reactions with diphenylsulfonylhydrazine,



cyanacetylhydrazine, phenylsemicarbazide, isoniazid, isonicotinylhydrazine, phenylacetylhydrazine, diphenylacetylhydrazine, and diphenoxycetylhydrazine have been studied.⁵⁰⁸⁻⁵²² Phenylhydrazine in glacial acetic acid reacts with **15** to yield the imidazole **103**.⁵²⁹

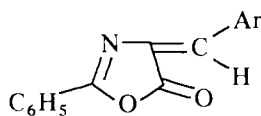
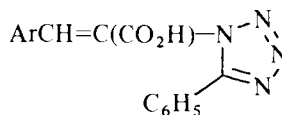
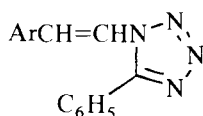


Pyrazole derivatives **107** are isolated by alkali treatment of the oxazolones **106**, obtained from 1,3,4-oxadiazolium salts **105** and the salt of 2-methyl (or phenyl) 2-oxazolin-5-one **104**.⁵³⁰



3.2.3.5.4. TETRAZOLES

Oxazolones such as **15** react with a sodium azide–anhydrous aluminum chloride mixture in tetrahydrofuran to give tetrazolyl acrylic acids **108**.⁵³¹ The reaction can also be carried out by heating **15** in glacial acetic acid with a solution of sodium azide in water.⁵³² The tetrazolyl acrylic acids readily undergo decarboxylation

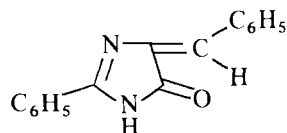
**15****108****109**

to give 1,5-disubstituted tetrazoles **109**.⁵³³ The claim that an open-chain azide of the type **91** is obtained by treating **15** with sodium azide in acetic acid was challenged and the product subsequently shown to be tetrazolyl cinnamic acid.^{485,534} However, **91** may be obtained by treating the hydrazide with nitrous acid.

**91** (R = C₆H₅)

3.2.3.5.5. IMIDAZOLONES

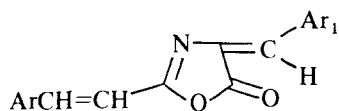
Az lactones react with alcoholic ammonia in the presence of potassium carbonate to give imidazolones (e.g., **110**).²⁰⁵ Compound **110** is identical with the product obtained from benzamidine, glyoxal, and benzaldehyde.⁵³⁵ With ammonia and primary amines, attack occurs readily at the carbonyl carbon atom.^{536,537} The

**110**

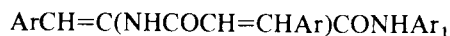
resulting amides can, in turn, be cyclized to imidazolones. With aniline, the anilide **111** is obtained.⁵³⁸ With secondary amines such as dimethylamine, diethylamine, and methylaniline, saturated oxazolones yield the corresponding α -benzamido-*N,N*-disubstituted hydrocinnamides, while with unsaturated azlactones, the corresponding substituted cinnamamides are obtained.⁵³⁹ 2-Styryl-4-arylidene-2-oxazo-

**111**

line-5-ones **112** behave analogously to give anilides **113**.^{89,540} Recently, a host of these imidazolones have been prepared.⁵⁴⁰⁻⁵⁵⁴ Similar results have been reported with 2,4-disubstituted 2-oxazolin 5-ones and pyrazolylmethylenoxa-

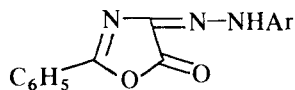


112

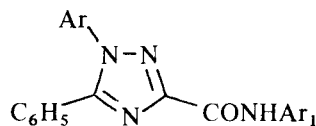


113

zolones.^{529,68,540} In the presence of acetic acid and sodium acetate, 2-aryl-4-arylidene-2-oxazoline-5-ones react with aromatic amines to give imidazolin-5-ones.^{185,190} Under similar conditions, 2-aryl-4-aryldio oxazolones **61** yield triazole carboxamides **114**.^{352a}



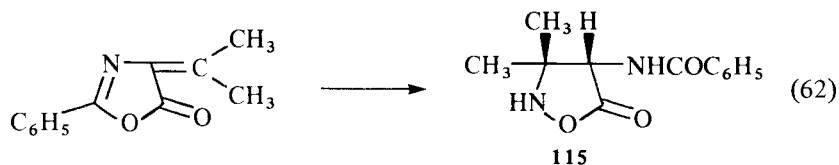
61



114

3.2.3.5.6. ISOXAZOLIDONES

Alkylidene azlactones react with methanolic solutions of hydroxylamine acetate to yield substituted isoxazolidones **115**.⁵⁵⁵ Reaction with arylidene azlactones, however, afford α -benzamido- α -arylacryloylhydroxamic acids **116**.^{230,556} The two geometric isomers of **116** (Ar = Ph) are obtained, depending on the conditions.



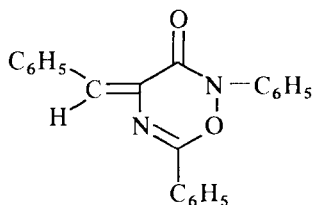
115

The reaction has been used in the structure determination of the geometric isomers of 2-phenyl-4-benzylidene-2-oxazolin-5-one **15** (Ar = C₆H₅).



116

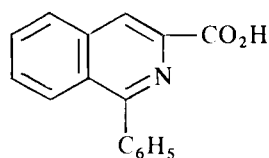
Heating oxazolone **15** or its substituted analogs with *N*-phenyl hydroxylamine in acetic acid–acetic anhydride leads to the 1,2,5-oxadiazinone derivative **117**.⁵²⁹



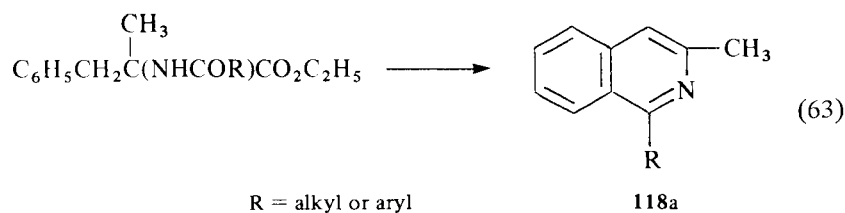
117

3.2.3.5.7. ISOQUINOLINE DERIVATIVES

When 2-phenyl-4-benzylidene-2-oxazolin-5-one is treated with anhydrous aluminum chloride in tetrachloroethane, intramolecular imidoylation occurs with the formation of 1-phenylisoquinoline carboxylic acid **118**.^{85,86} Ethyl- α -methyl- α -acyl-

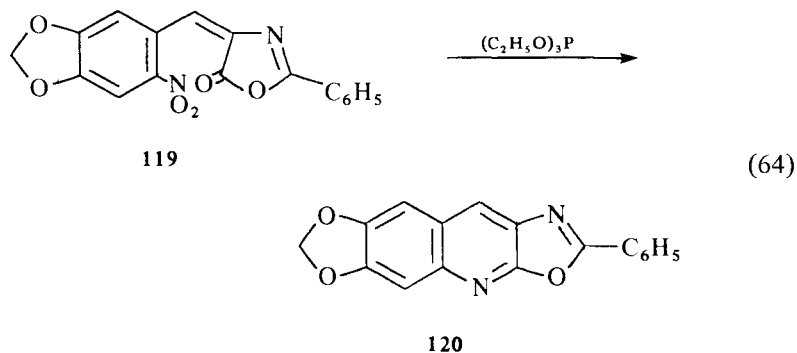
**118**

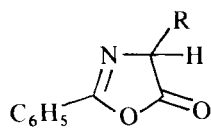
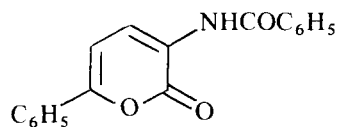
amido- β -phenyl-propionates obtained from oxazolones are converted to isoquinoline derivatives **118a** when heated with nitrobenzene at 180° with phosphorus oxychloride or polyphosphoric acid at 130–140°. ^{557,558} The azlactones derived from veratroylglycine and veratraldehyde or benzaldehyde are converted to 3,4-dihydroisoquinoline derivatives via the propionate derivative. ^{559–561}



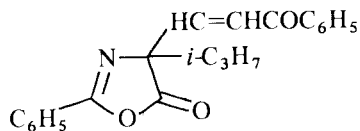
3.2.3.5.8. MISCELLANEOUS

Several reactions have been reported in which unsaturated azlactones are transformed into other heterocycles. In the following section some of these special reactions are briefly reviewed. The azlactone **119** obtained from 6-nitropiperonal and hippuric acid is converted to oxazolo-(5,4*b*)quinoline **120** by heating with triethylphosphite. ^{562,563}

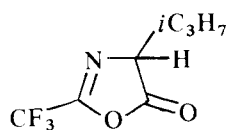
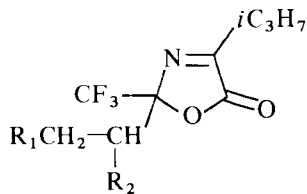
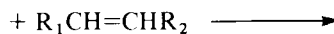


**4** (R = H)**121**

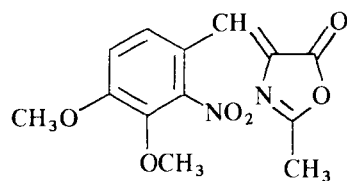
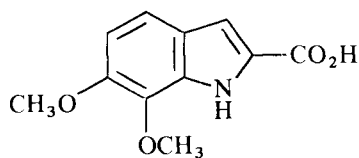
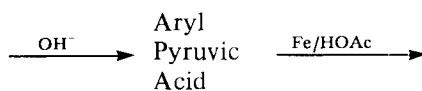
Reaction of benzoylacetylene with 2-phenyl-2-oxazolin-5-one **4** is reported to give 3-benzamido-6-phenyl-2H-pyran-2-one **121**.^{564,565} With a substituent (isopropyl or *tert*-butyl) in the 4-position of **4**, benzoylacetylene, in the presence of

**122**

triethylamine, adds to the 4-position to give **122**.⁵⁶⁶ Compound **123**, with a CF₃ group in the 2-position of the azlactone ring, reacts with olefins to give the pseudo-oxazolone **124**. (An indole derivative **126** is reportedly obtained from **125**.⁵⁶⁷)

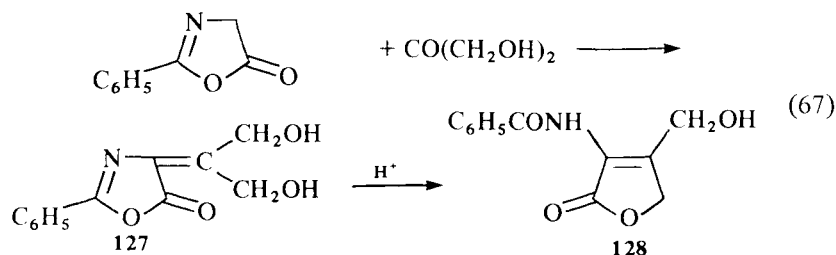
**123****124**

(65)

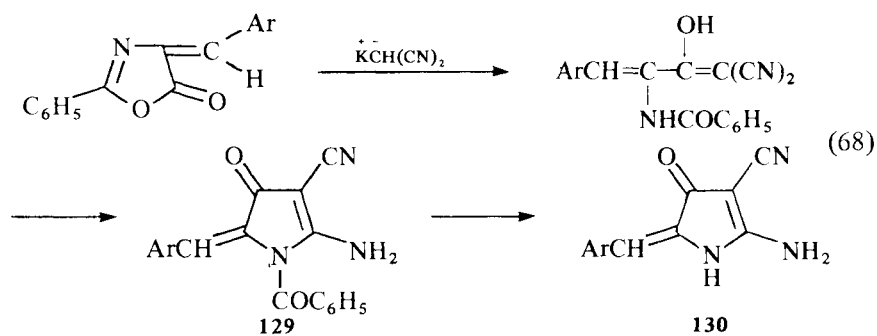
**125****126**

(66)

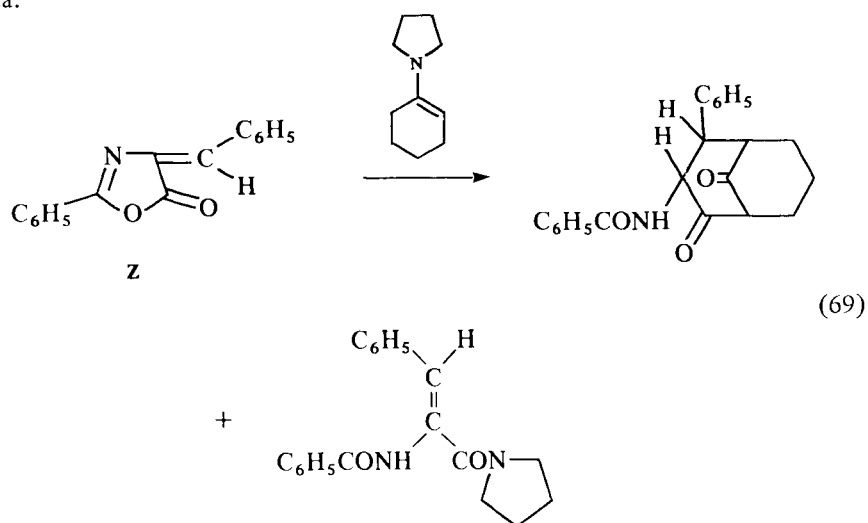
Condensation of **4** with dihydroxyacetone in tetrahydrofuran and lead acetate yields **127**. On treatment with acid, **127** undergoes rearrangement to a furanone (butenolide) derivative **128**.^{568,175}

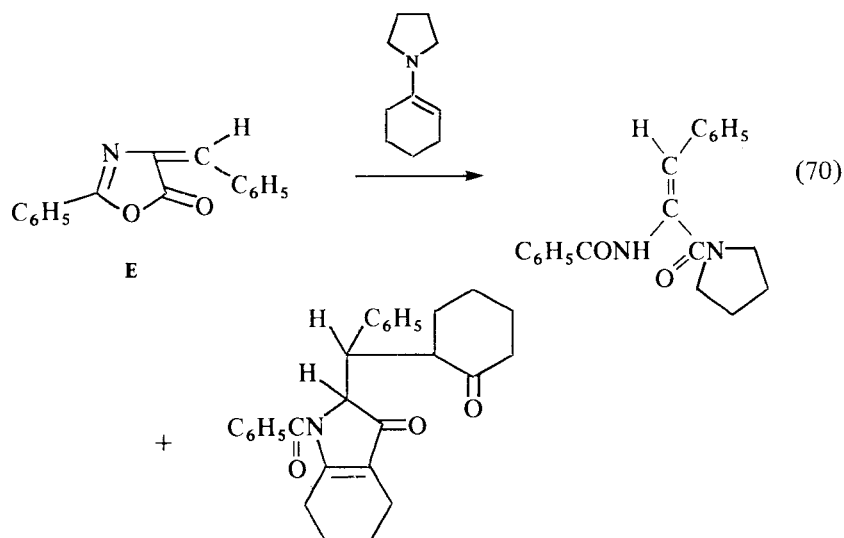


Pyrrolinone derivatives **129** and **130** are obtained when arylidene azlactones react with potassium malononitrile.^{569,570}

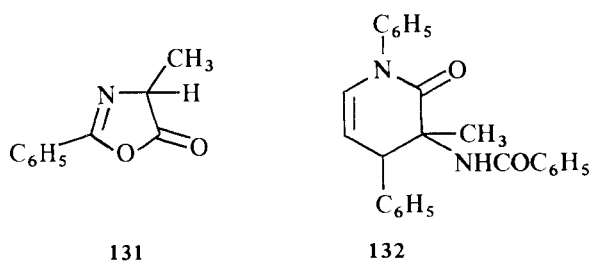


Reactions of the *Z*- and *E*-isomers of 2-phenyl-4-benzylidene-2-oxazolin-5-one with 1-*N*-pyrrolidinocyclohexene afford the expected ring-opened amides, as well as unusual products whose structures have been assigned solely on the basis of NMR data.⁵⁷¹

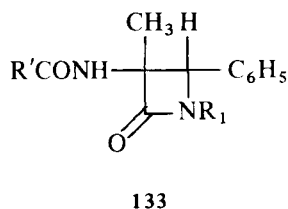




A pyridone derivative **132** is obtained when *N*-cinnamylidenaniline is treated with 2-phenyl-4-methyl-2-oxazolin-5-one **131**.^{572,573}

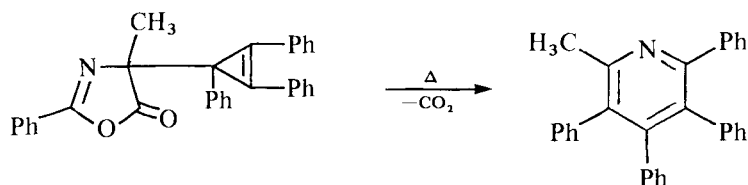


Azetidinones **133** are the products when saturated azlactones react with benzylidenaniline in boiling toluene.⁵⁷⁴ Compound **4** and benzylidenaniline, on heating in pyridine, give the 4-benzylidene azlactone **15** (Ar = C₆H₅).⁵⁷⁵ Because azetidinones rearrange to give oxazolones, it is possible that the azetidinone initially formed rearranges to the oxazolone.¹⁸⁶

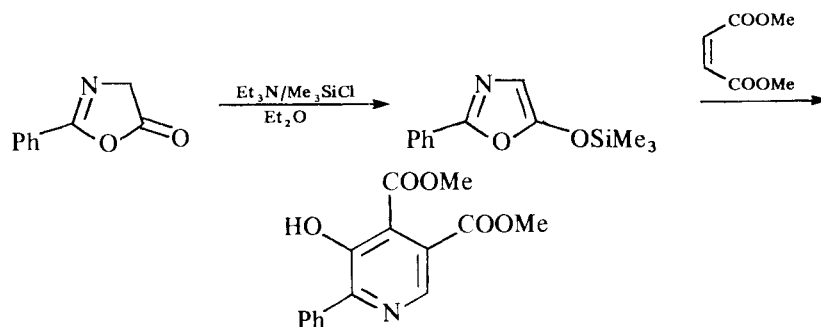


Azlactones prepared from pyridine-2, 3-, and 4-carboxaldehyde and hippuric acid have been converted to 5-[*H*] -, 7-[*H*] -, and 6-[*H*] pyridenes **134a-c**.⁷⁴⁻⁷⁶

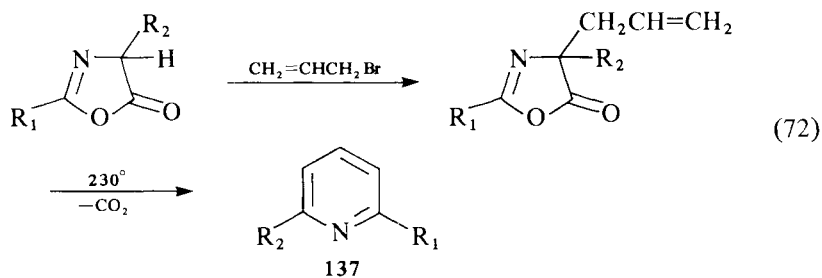
Thermolysis of 2-phenyl-4-methyl 4-(1,2,3-triphenylcyclopropyl)-2-oxazolin-5-one gives a pentasubstituted pyridine derivative.⁵⁸²



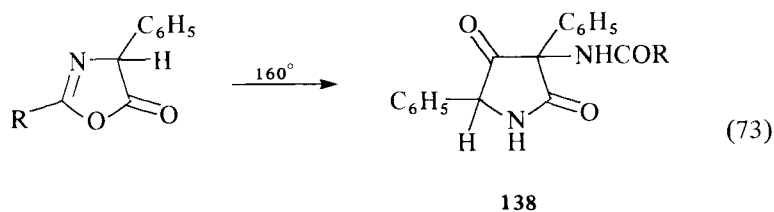
Pyridine derivatives are also obtained by the Diels–Alder reaction of dimethylmaleate with 5-trimethylsilyloxyoxazoles, which are obtained by treating 2-oxazolin-5-ones with chlorotrimethylsilane in ether.⁵⁸³



2,6-Disubstituted pyridines **137** are obtained by heating 4-allyl-2-oxazolin-5-ones.⁵⁸⁴



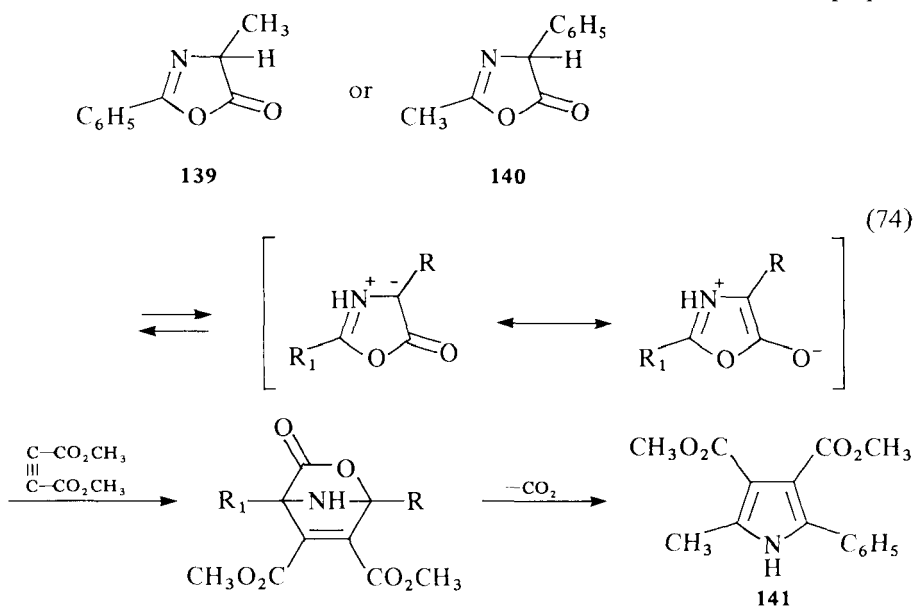
Pyrrolidindiones **138** are the products of pyrolysis of 4-phenyl-2-alkyl-2-oxazolin-5-ones.⁵⁸⁵



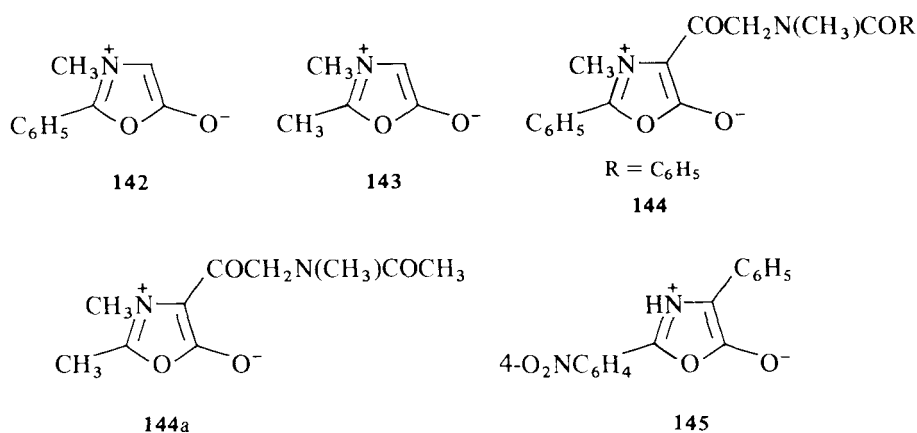
R = *i*-C₃H₇, *n*-C₄H₉, *i*-C₄H₉, Benzyl, *t*-C₄H₉

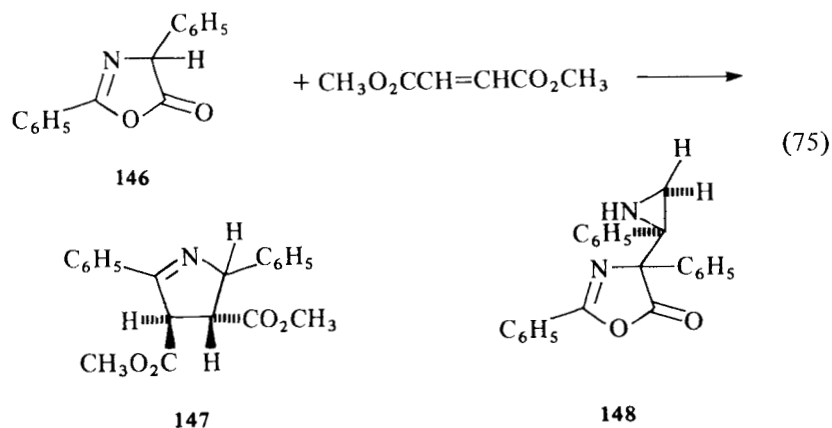
3.2.3.6. Heterocycles from Mesionic Oxazolones

The saturated azlactones **139** and **140** react with dimethyl acetylenedicarboxylate in xylene to give dimethyl-2-phenyl-5-methyl-pyrrole-3,4-dicarboxylate **141** via a 1,3-dipolar cycloaddition reaction.⁵⁸⁶⁻⁵⁹⁵ A whole series of oxazolonium compounds have been prepared by treating *N*-benzoyl- or *N*-acetylsarcosine with trifluoroacetic anhydride. When dicyclohexylcarbodiimide is used to prepare

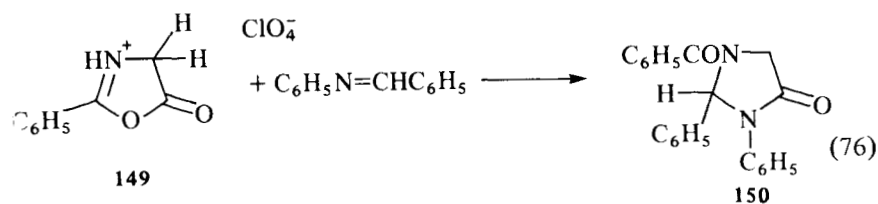


mesoionic oxazolones **142** and **143**, only dimeric compounds **144** and **144a** are formed.⁵⁹⁶ Cyclization of α -phenyl- α -*p*-nitrobenzamidoacetic acid gives the mesoionic azlactone **145**.^{597,598} Reaction of 2,4-diphenyl-2-oxazolin-5-one **146** with dimethylfumarate yields the pyrrole derivative **147**. Compound **146** and alkyl

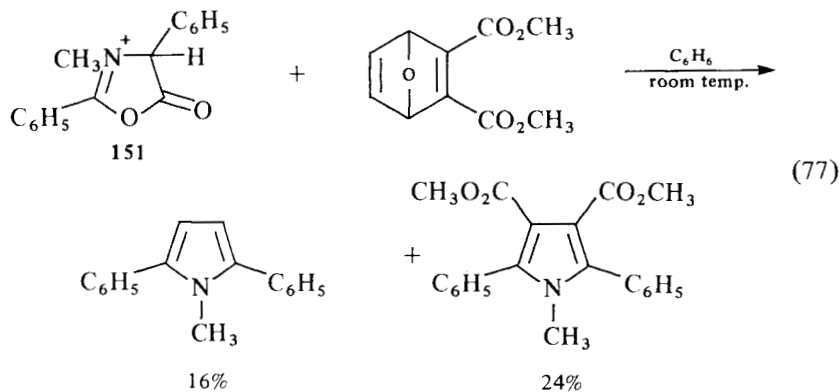


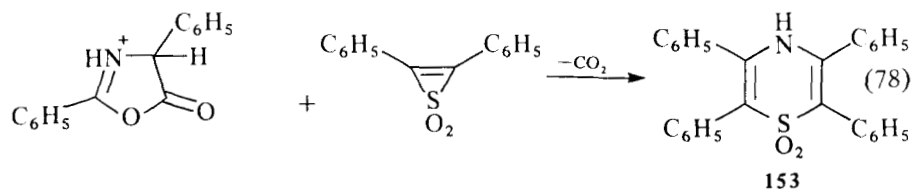


acrylates also yield pyrroline derivatives.⁵⁹⁷⁻⁶⁰¹ The hope that 3-phenyl-2*H*-azirine would behave as a dipolarophile did not materialize. Instead, **146** undergoes alkylation with this reagent to yield **148**.⁶⁰²



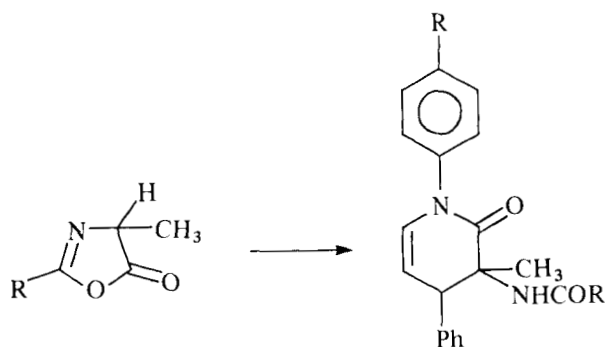
The chemistry of mesoionic oxazolones such as 2-phenyl-2-oxazolin-5-one perchlorate **149** has been extensively studied.^{147,174,255,258,530,603,604} Reaction of **149** with benzylideneaniline affords the imidazolone derivative **150**. Pyrroles are obtained when the mesoionic oxazolone **151** reacts with dimethyl-7-oxabicyclo-[2,2,1]hepta-2,5-diene-2,3-dicarboxylate.⁶⁰⁵ Similarly, **152** and 2,3-diphenylthiirene dioxide yield 2,3,5,6-tetraphenyl-4*H*-1,4-thiazine-1,1-dioxide **153**.⁶⁰⁶



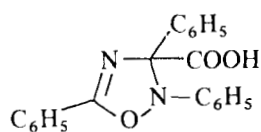


1-Methyl-3-phenyl-4-trifluoromethylsulfonyl pyrrole is prepared via a mesoionic oxazolone intermediate.⁶⁰⁷

Oxazolones substituted in the 4-position that are capable of mesoionic behavior react with cinnamaldehyde anils to give α -pyridones.⁶⁰⁸

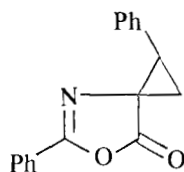


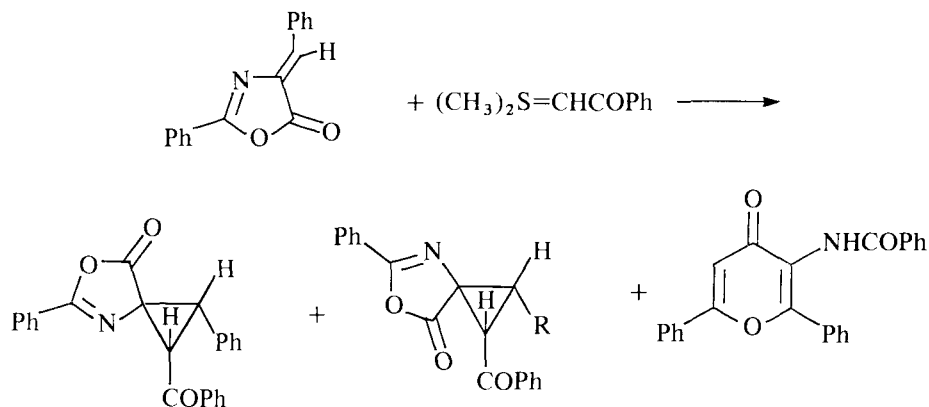
Nitrosobenzene reacts with 2,4-diphenyl-2-oxazolin-5-one at 80–110°C to yield benzamidine, while at room temperature, 2,3,5-triphenyl- Δ^4 -1,2,4-oxadiazolin-3-carboxylic acid is formed.^{609,610}



Reaction of 2-phenyl-4-benzylidene-5-[4*H*] oxazolone and its analogs with diazomethane gives cyclopropyl compounds.^{248,260,611–615}

Cyclopropane derivatives are also obtained by the reaction of unsaturated azlactones with sulfur ylids.^{616,617}





3.2.3.7. Spectral Data on Oxazolones

Although a systematic study of the spectral properties of saturated and unsaturated azlactones has not been undertaken, the literature contains sufficient information to permit some generalizations. The ultraviolet spectra of unsaturated oxazolones have been studied most extensively, while infrared spectral data have been used as a means of distinguishing between saturated and unsaturated azlactones.⁶¹⁸⁻⁶²³ Nuclear magnetic resonance data have been used mainly in structural assignments of the geometric isomers⁶²⁴⁻⁶³⁰ of unsaturated azlactones. The Raman spectra of geometric isomers **14** and **15** ($\text{Ar} = \text{C}_6\text{H}_5$) show no substantial differences.⁶⁴⁶ Although spectral data have not been reported, the color differences for several geometric isomers have been reported.⁶³¹⁻⁶⁴⁵

3.2.3.7.1. ULTRAVIOLET SPECTRA

The UV spectra of 2-aryl(alkyl)-4-arylidene-2-oxazolin-5-ones have been studied in detail.^{179,180,198,72,227,647-662} Two absorption maxima appear near 260 and 360 nm. The geometric isomers of 2-phenyl-4-benzylidene-2-oxazolin-5-one exhibit spectra in which differences exist in the intensities of the fine structure maxima in the short-wavelength band and in the fine structure content of the long-wavelength band.⁶⁵³ The UV absorption spectra of phthalylidene azlactones have been published.¹⁵⁴ Systematic studies of 2-aryl-4-(α -furfurylidene)oxazolones have been made.¹⁷⁹ Similar spectral studies of azlactones derived from α -furoylglycine and substituted hippuric acids and 5-nitrofurfural are available.¹⁹⁸ A host of azlactones¹⁸⁰ have been prepared from nitrohippuric acids and their spectra examined. The UV spectral data of several arylidene oxazolones, thiophene-based oxazolones, and 4-pyranylidene oxazolones have been reported.^{168,615,649,650,652,655,664} All these UV spectra exhibit the two maxima, one at 240–260 nm and the other at 300–360 nm. However, in the case of the highly colored 4-pyranylidene azlactones, the absorption maximum at 360 nm shifts bathochromically to 440–570 nm.¹⁶⁸ Saturated azlactones show only end absorption.

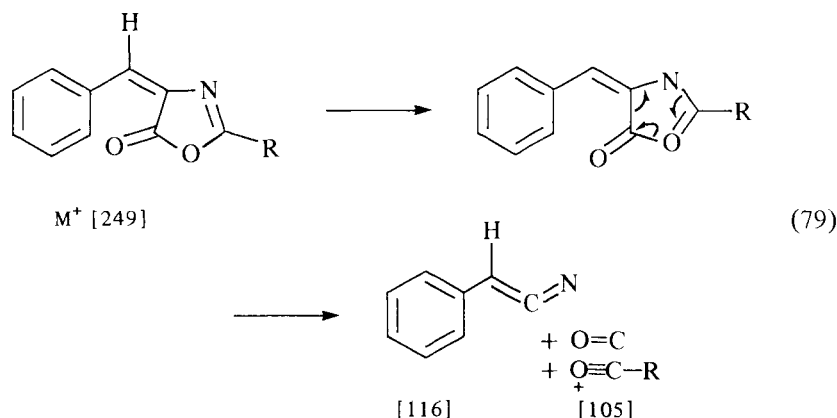
3.2.3.7.2. INFRARED SPECTRA

Saturated oxazolones show lactone C=O absorption in the region of 1810–1825 cm^{-1} and C=N absorption near 1690 cm^{-1} .^{84,665,666} The IR spectra of 2-phenyl-4-arylidene oxazolones and their 2-methyl analogs have also been studied.^{667,668} In general, unsaturated azlactones show carbonyl absorption in the 1760–1795 cm^{-1} region. Other bands are observed at 1675–1690 (C=N), 1630, and 1600 cm^{-1} , all characteristic of oxazolones. The spectra of the oxazolones derived from 3,4,5-trimethoxybenzoylglycine are found to show carbonyl absorption in the region of 1730–1770 cm^{-1} .¹⁷⁷ Similar studies of 4-arylidene-2-(*p*-acetamidophenyl)oxazolones have been reported.¹⁶⁷ The spectra of several arylidene oxazolones and those derived from substituted acetophenones have been recorded. The C–O band appears in the region of 1150–1250 cm^{-1} .

The spectra of 4-pyranylidene, benzopyranylidene, and pyridinyldene oxazolones show weak bands at 1600, 1625, and 1700 cm^{-1} , in addition to lactone carbonyl absorption in the 1780–1800 cm^{-1} region.¹⁶⁸ Spectra of phenothiazine-based oxazolones have also been reported.⁶⁶⁹ A detailed study of the spectra of the geometric isomers of 2-phenyl-4-benzylidene-2-oxazolin-5-ones has also been made. Raman spectra of several azlactones were also determined.^{670,671,646} Fluorescence spectra of oxazolones derived from 3-methoxy-4-ethoxy- and 3-ethoxy-4-methoxy-benzaldehydes and benzaldehyde have been determined.^{337,621}

3.2.3.7.3. MASS SPECTRA

Studies of the mass spectra of 4-arylidene oxazolones show no evidence of isomerization induced by electron impact. The fragmentation pattern follows the accompanying pathway.^{672,668} The mass spectra of saturated azlactones have also been reported.^{37,38}



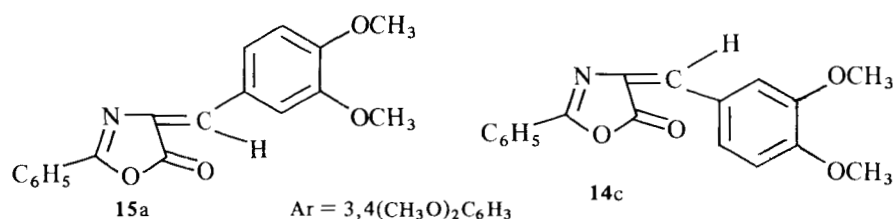
3.2.3.7.4. ORD MEASUREMENTS

The shape of the ORD curves of the saturated azlactones derived from *N*-acetyl- and *N*-formyl-L-leucine depend on two bands resulting from $n \rightarrow \pi^*$ excitation of the C=N group (240 nm) and the carbonyl group (215 nm). The band at 240 nm

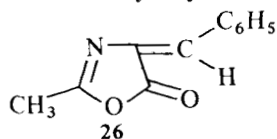
disappears on addition of trifluoroacetic acid, with the simultaneous appearance of a positive Cotton effect at 213 nm.⁶⁷³ It has been shown on the basis of ORD and NMR studies that for azlactones derived from aromatic amino acids, a conformation in which the aryl group faces the azlactone ring is favored.⁶⁷⁴

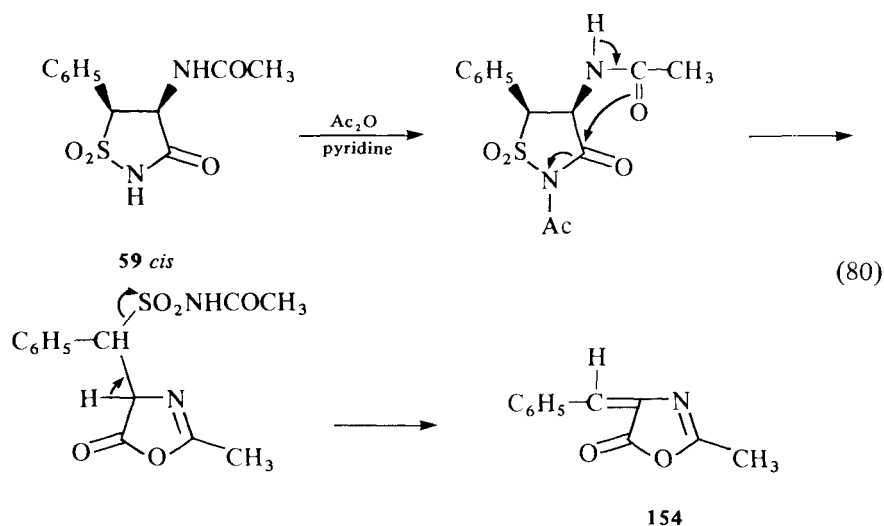
3.2.3.7.5. NMR STUDIES

Nuclear magnetic resonance data on several oxazolones have been published.^{217,218,332,333,335,336,615,629,653,654,675-682} In general, the data have been used in assigning structures to geometric isomers of unsaturated azlactones. The NMR spectra of the geometric isomers of 2-phenyl-4-veratrylidene-2-oxazolin-5-one **15** and **14a**, ethyl- α -benzamido-3,4-dimethoxycinnamates derived from **15a** have been determined. Substituent effects due to the benzamido group in *cis* and *trans* positions have been calculated by using data for methyl- α -benzamidoacrylate and methyl acrylate. These values are in agreement with those observed. By comparing calculated values with data for ethyl- α -benzamido-3,4-dimethoxycinnamates, the higher-melting isomer is assigned the *trans* configuration and the lower-melting isomer the *cis*, thus fixing the structures for the parent azlactones. The NMR spectra of oxazolones show the deshielding influence of *cis* N=C-Ph on the olefinic hydrogen, which shifts further downfield than when the olefinic hydrogen is *cis* to the carbonyl group.^{676,679}

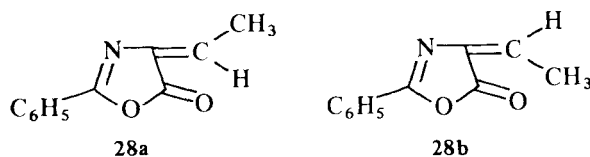


Similar structural assignments for the stable isomers of 2-methyl-4-arylidene-2-oxazolin-5-ones have been made.⁶⁸¹ 2-Methyl-4-benzylidene-2-oxazolin-5-one is represented by **26**. The geometry depicted is in disagreement with the previous assignment.³¹⁸ The same oxazolone is reportedly obtained by heating either *cis*- or *trans*-4-acetamido-5-phenyl-3-isothiazolidinone-1,1-dioxide **59** in acetic anhydride and pyridine. It is well established that the labile isomers of oxazolones are converted to the stable isomers in the presence of pyridine.^{226,229} It is conceivable, therefore, that the unstable isomer **154** formed from **59b** is converted to the stable configuration **26**. The assignment of *E* geometry (via NMR) to the stable isomer of 2-phenyl-4-ethylidene-2-oxazolin-5-one **28b**, in which the methyl group is *cis* to the azlactone carbonyl was questioned and the compound subsequently assigned the *Z* configuration **28a**.^{629,678} From these data, it would appear that all the stable isomers prepared by the Erlenmeyer synthesis possess the *Z* configuration.





In the NMR spectra of the stable isomers of 4-arylidene oxazolones, the ethylenic proton appears as a singlet at δ 7.2–7.3, while in the labile isomers the singlet is masked by aromatic protons.^{31,217,218,246,615,653,654,676,682b,c} The ^{13}C NMR of several oxazolones have been reported.^{261,682 d–g}

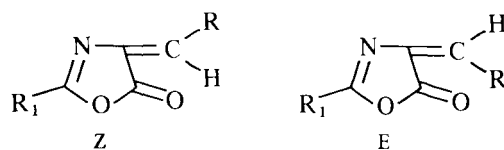


3.2.3.7.6. GAS CHROMATOGRAPHY OF OXAZOLONES

Separation and identification of saturated azlactones have been accomplished by gas chromatography.³⁹

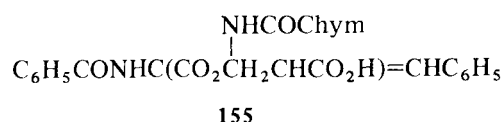
3.2.3.7.7. GEOMETRIC ISOMERISM

The chemistry of geometric isomers of 2-aryl (aralkyl)-4-aryl(alkyl)methylene-2-oxazolin-5-ones has been reviewed recently.¹² Methods of isomerization, spectral properties, and chemical reactions are discussed. By drawing on data from a host of studies.^{161,171,202,409,522,533,539,618–645} we conclude that the azlactones obtained by the Erlenmeyer reaction are the *Z*-isomers and that the labile, lower-melting isomers possess the *E* configuration.



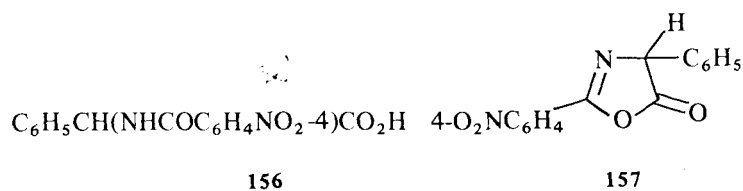
3.2.3.8. Reaction Toward Enzymes

The 2-oxazolin-5-ones are excellent acylating agents for a variety of enzymes. Thus, 2-phenyloxazolin-5-one and 4,4-dimethyl-2-phenyl-2-oxazolin-5-one react with α -chymotrypsin, trypsin, and papain to form acyl enzymes.⁶⁸⁶⁻⁶⁸⁹ When the azlactone from *p*-nitrobenzoylvaline reacts with α -chymotrypsin, the enzymatic activity decreases with increasing number of amino acid residues.⁶⁹⁰ The reaction of α -chymotrypsin with 2-phenyl-4-benzylidene-2-oxazolin-5-one **15** (Ar = C₆H₅) has been studied extensively.⁶⁹⁰⁻⁶⁹⁵ In this reaction the oxazolone disappears, with the formation of two new species: at pH 5 a species involving an acylated histidine-containing enzyme and at pH 8 an acylated serine-containing enzyme. The second species has been identified as **155**.^{692,693} The reaction of either of the isomers **14** or **15** (Ar = C₆H₅) gives an acyl enzyme, possibly α -benzamidocinnamoyl- α -chymotrypsin.

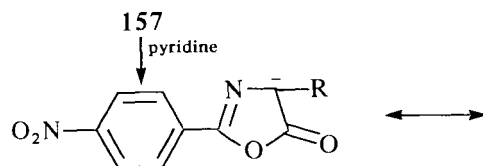


3.2.3.9. Tests for Azlactones

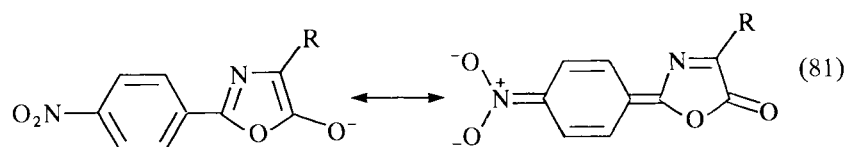
The Altman test consists of converting hippuric acid to the azlactone of *p*-dimethylaminobenzaldehyde in the presence of acetic anhydride and the aldehyde.⁶²² The formation of a deep orange-colored azlactone is indicative of the presence of hippuric acid. This test has been employed in detecting the presence of substituted hippuric acids in human urine.¹⁷² Acid anhydrides, on the other hand, can be detected by the conversion of *N-p*-nitrobenzoylphenylglycine **156** to its azlactone **157**, which forms a blue anion with pyridine.⁶⁹⁶



The blue color has been ascribed to the formation of a resonance-stabilized anion of the azlactone **157**.⁶⁹⁷



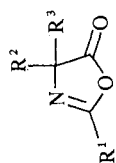
Many 4-(*p*-dimethylaminobenzylidene)oxazolones have been prepared in connection with the Altman test.^{171,620}



3.2.4. Tables

In the following section, eight tables are given. The format of tables changes from one table to the next. For example, Table 3.1 deals with saturated azlactones, for which the number of carbon atoms in the azlactone ring is given. For Tables 3.2A–3.2C, the number of carbon atoms in the carbonyl compound is indicated. Table 3.2A deals with aromatic aldehydes, while Table 3.2B includes both aliphatic aldehydes and ketones. Table 3.2C includes heterocyclic aldehydes while Table 3.2D deals with aminomethylene- and arylazoazlactones. In Table 3.2D the total number of carbon atoms in the oxazolone is used. Table 3.3 deals with bisoxazolones, Table 3.4 deals with azlactone-based merocyanines, and Table 3.5 includes mesoionic azlactones.

The authors have taken great pains to refer to most of the original papers and the yields reported in the tables are taken out of the original papers and not from *Chemical Abstracts*. Any discrepancy in the spelling and the names of the authors is due to the fact that the names as reported here are taken out of the source material.

TABLE 3.1. SATURATED AZLACTONES^a

Total Carbon Atoms in Azlactone	R ¹	R ²	R ³	Yield Percent	Reference
3	H	H	H	—	40
4	H	CH ₃	H	—	40
	CH ₃	H	H	—	40
5	H	CH ₃	CH ₃	—	698
	CH ₃	CH ₃	H	—	40
	CF ₃	H	CH ₃	65	698, 699
	CF ₃	Br	CH ₂ Br	—	699
	CH ₂ =CH	H	H	—	50
	CH ₂ NHCOH	H	H	—	40
6	H	(CH ₃) ₂ CH	H	—	40
	CF ₃	CH ₃	CH ₃	50	448a, 700
	CH ₂ NHCOH	CH ₃	H	—	40
	C ₂ HF ₄	CH ₃	H	80	54
	CH ₃ C(=CH ₂)	H	H	—	49
	H	(CH ₃) ₂ CHCH ₂	H	—	39, 139, 683
	CH ₃	(CH ₃) ₂ CH	H	39	32
	CH ₃	CH ₃	CO ₂ CH ₃	—	40
	CF ₃	CH ₃	C ₂ H ₅	—	83
7	CF ₃	H	(CH ₃) ₂ CH	—	698
	CF ₃	H	CH ₂ CO ₂ CH ₃	77	448a
	CF ₃	H	H	78	448a
	CH ₂ NHCOCH ₂ NHCHO	H	H	—	40
	C ₂ HF ₄	C ₂ H ₅	H	59	54
	(CH ₃) ₂ CNH ₂	H	CH ₃	—	135

8	CH ₃	(CH ₃) ₂ CHCH ₂	-(CH ₂) ₄ -	H	39, 139, 683
	CH ₃			-	701
	CH ₃	CH ₃		CH ₃ OCH ₂ CH ₂	702
	CH ₃	CH ₃		CH ₃ SCH ₂ CH ₂	702
	CF ₃	H		(CH ₃) ₂ CHCH ₂	76-85
	CF ₃	H		CH ₃ CH ₂ CHCH ₃	448a, 683, 39
	CF ₃	H		CH ₃ CH ₂ CHCH ₃	87
	CF ₃	H		CH ₂ CO ₂ C ₂ H ₅	448a
	CH ₂ NHCHO	(CH ₃) ₂ CH		H	40
	CH ₂ NHCOCH ₂ NHCHO	CH ₃		H	40
	C ₂ HF ₄	CH ₃ CH ₂ CH ₂		H	54
	(CH ₃) ₂ CNH ₂	CH ₃		CH ₃	705
	CH ₃ C(=CH ₂)	CH ₃		CH ₃	-
					50, 253,
					703, 704
9	(CH ₃) ₃ C	CH ₃		H	572
	CF ₃	H		CH ₂ CH ₂ CO ₂ C ₂ H ₅	78
	C ₂ H ₅	(CH ₃) ₂ CHCH ₂		H	448a
					38, 417
					54
	C ₂ HF ₄	CH ₃ CH ₂ CH ₂ CH ₂		H	65
	CH ₃ C(=CH ₂)	CH ₃		CH ₃ CO ^b	54
					123, 253,
					254
	C ₆ H ₅	H		H	80
					21, 28, 51,
					564,
					706-711
	C ₆ H ₅	H		Br	20, 22, 572,
					712
10	2-ClC ₆ H ₄	H		H	17
	4-ClC ₆ H ₄	H		H	17
	2-O ₂ NC ₆ H ₄	H		H	17, 181
	4-O ₂ NC ₆ H ₄	H		H	17, 18, 713
	CF ₃	H		C ₆ H ₅	94
	CH ₂ NHCOCH ₂ NHCHO	(CH ₃) ₂ CH		H	448a
	CH ₃ CH ₂ CH ₂	(CH ₃) ₂ CHCH ₂		H	40
	(CH ₃) ₂ CH	(CH ₃) ₂ CHCH ₂		H	37, 38
				H	37, 38
					-
					-
					-
					-
					-
					-

TABLE 3.1. (Continued)

Total Carbon Atoms in Azlactone	R ¹	R ²	R ³	Yield Percent	Reference
	CH ₃ C(=CH ₂)	(CH ₃) ₂ CHCH ₂	H	—	37, 38
	CH ₃ C(=CH ₂)	CH ₃ CH ₂ CH ₂	CH ₃	—	714, 715
	CH ₃ CH ₂ C(NH ₂)CH ₃	CH ₃	C ₂ H ₅	—	698
	C ₆ H ₅	CH ₃	H	80	20, 22, 572, 716
				90	52
	C ₆ H ₅	CH ₃	Cl	—	497, 498
	2-CH ₃ C ₆ H ₄	H	H	—	17
	4-CH ₃ C ₆ H ₄	H	H	—	17, 19
	4-CH ₃ OC ₆ H ₄	H	H	—	17
	4-BrC ₆ H ₄	CH ₃	H	—	20
	4-O ₂ NC ₆ H ₄	CH ₃	H	—	20
	CH ₃	CH ₃	C ₆ H ₅	—	701
	CH ₃	CH ₃	4-ClC ₆ H ₄	—	701
	CH ₃	H	C ₆ H ₅ CH ₂	—	116
	CH ₃	CH ₃	<i>n</i> -C ₄ H ₉ OCH ₂ CH ₂	—	702
	CF ₃	CH ₃	C ₆ H ₅	92	698, 448a
	CF ₃	H	4-CH ₃ OC ₆ H ₄	90	448a
	CF ₃	H	C ₆ H ₅ CH ₂	85	448a, 685
	CF ₃	H	4-ClC ₆ H ₄ CH ₂	89	448a
	CHCl ₂	4-O ₂ NC ₆ H ₄ CO	H ^b	—	237, 238
	CHCl ₂	4-O ₂ N-3-BrC ₆ H ₃ CO	H ^b	—	237, 238
	(CH ₃) ₃ C	(CH ₃) ₂ CHCH ₂	H	—	37, 38
	CH ₃ CHC ₆ H ₅	(CH ₃) ₂ CHCH ₂	H	—	37, 38
	(CH ₃) ₂ CHCH ₂	(CH ₃) ₂ CHCH ₂	H	—	37, 38
	C ₆ H ₅	C ₂ H ₅	H	90	20, 22, 572, 716, 717
	C ₆ H ₅	H	CH ₃ CO ^b	—	506
	C ₆ H ₅	H	CF ₃ CO ^b	—	242

11

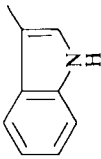
4-O ₂ NC ₆ H ₄	CH ₃	C ₆ H ₅ CH ₂	696
C ₆ H ₅ CH ₂	CH ₃	H	50, 715
C ₆ H ₅ CH ₂	ClCH ₂	Cl	714
2-CH ₃ CONHC ₆ H ₄	H	H	17
4-CH ₃ CONHC ₆ H ₄	H	H	17
CH ₃	ClCH ₂	C ₆ H ₅ CONH	55 718
CH ₃	BrCH ₂	C ₆ H ₅ CONH	55 718
CH ₃	C ₂ H ₅	C ₆ H ₅	712
CH ₃	C ₂ H ₅	4-ClC ₆ H ₄	712
CH ₃	H		719
CH ₃	4-CH ₃ O-3-BrC ₆ H ₃ CO	H	237, 238
Cl ₂ CH	4-CH ₃ C ₆ H ₄ CO	H	237, 238
CH ₂ =CH	CH ₃	C ₆ H ₅	714, 715
C ₂ H ₅	CH ₃	C ₆ H ₅	701
C ₂ HF ⁴	C ₆ H ₅ CH ₂	H	54
(CH ₃) ₂ CNHCOC(CH ₃) ₂ -NH ₂	CH ₃	CH ₃	705
CH ₃	(CH ₃) ₂ CHCH ₂	CH ₃ CO ^b	76 123, 253, 254
<i>n</i> -C ₄ H ₉ C(=CH ₂)	(CH ₃) ₂ CH	H	253
<i>N</i> -Methylphthalimide	H	H	720
C ₆ H ₅	(CH ₃) ₂ CH	H	80 20, 22, 572, 716, 717
C ₆ H ₅	(CH ₃) ₂ CH	Cl	75 20, 22, 572, 710, 717
C ₆ H ₅	C ₂ H ₅	CH ₃	536
C ₆ H ₅	CH ₃	CO ₂ CH ₃	72 504
C ₆ H ₅	CH ₃	CH ₃ COS	497, 498
C ₆ H ₅	H	CH ₃ CHClCH(Cl)	326
C ₆ H ₅	CH ₃	CH ₃ CONH	90 128

TABLE 3.1. (Continued)

Total Carbon Atoms in Azlactone	R ¹	R ²	R ³	Yield Percent	Reference
13	C ₆ H ₅	H	CH ₃ CH ₂ CO ^b	75	153
	4-ClC ₆ H ₄	H	CH ₂ CH ₂ SCH ₃	—	586
	4-CH ₃ OC ₆ H ₄	H	CF ₃ CO	—	242
	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	H	72	55, 56
	C ₆ H ₅ CH ₂	CH ₃	CH ₃	—	413, 536
	CH ₃	H	3,5-(CH ₃) ₂ C ₆ H ₃ CO ^b	—	237, 238
	CF ₃	(CH ₃) ₂ CH	C ₆ H ₅ S	69	721
	CCl ₃	Cl	C ₆ H ₅ C(OAc)Cl	—	328
	CH ₂ =CH	CH ₃	C ₆ H ₅ CH ₂	—	714, 715
	C ₂ H ₅	C ₂ H ₅	C ₆ H ₅	—	722
	(CH ₃) ₂ C(NH ₂)	H	C ₆ H ₅ CH ₂	—	135
	C ₆ H ₅	<i>n</i> -C ₄ H ₉	H	92	20, 22, 572, 716, 717
	C ₆ H ₅	(CH ₃) ₂ CHCH ₂	H	—	20, 33, 37–39, 42, 139
14	C ₆ H ₅	H	CH ₂ CO ₂ C ₂ H ₅ ^b	—	114
	C ₆ H ₅	H	(CH ₃) ₂ CHCO ^b	—	722
	C ₆ H ₅	H	<i>n</i> -C ₄ H ₉ CO ^b	10	153
	C ₆ H ₅	H	(CH ₃) ₂ C(OCH ₃)	—	723
	C ₆ H ₅ CH=CH	H	CH ₃ CO	—	506
	C ₆ H ₅ CH ₂	CH ₂ Cl	CH ₃ CO ₂	—	724
		CH ₂ Br	CH ₃ CO ₂	—	724
	CF ₃	(CH ₃) ₂ CH	4-CH ₃ C ₆ H ₄ S	90	721
	CF ₃	(CH ₃) ₂ CH	4-O ₂ NC ₆ H ₄ S	90	721
	C ₆ H ₅	H	CH=C(COCH ₃)CONH ₂	58	725
	C ₆ H ₅	CH ₃	COCO ₂ C ₂ H ₅	71	504
	C ₆ H ₅ CH ₂	(CH ₃) ₂ CHCH ₂	H	—	37, 38

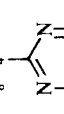
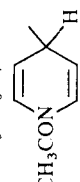
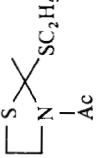
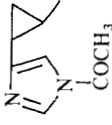
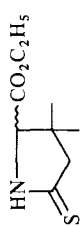
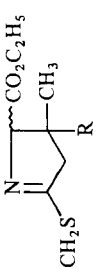
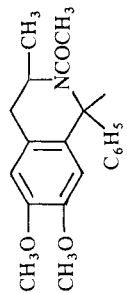
15	$C(CH_3)_2NHCO_2CH_2C_6H_5$	CH_3	H	134
	$CH_2=CHCOCH_2CH_2$	CH_3	C_6H_{11}	714, 715
	$CH_3C=CH_2$	$C_6H_5CH_2$	CH_3CO	123, 253, 254
	C_6H_5	$(CH_3)_2CH$	$CH_2=CHCH_2^c$	114
	C_6H_5	$(CH_3)_2CH$	$HC\equiv CCH_2^c$	114
	C_6H_5	C_6H_5	H	20, 536, 588, 591, 602
	C_6H_5	$2-O_2NC_6H_4$	H	586, 587
	C_6H_5	$4-O_2NC_6H_4$	H	586, 587
	C_6H_5	$4-ClC_6H_4$	H	386
	$4-O_2NC_6H_4$	C_6H_5	H	586, 587, 588, 696
	$2-AcC_6H_4$	$(CH_3)_2CHCH_2$	H	726
	$3-O_2NC_6H_4$	$3-O_2NC_6H_4$	H	386
		H	H	727
	$C_6H_5-N-OC_4H_9$	H	H	193, 194, 586, 587, 696
	$4-ClC_6H_4$	C_6H_5	H	19, 501, 728, 729
16	$4-C_6H_4C_6H_5$	H	C_6H_5	725
	CH_3	C_6H_5	$CH=C(COCH_3)COC_2H_5$	114
	C_6H_5	H	$CH_2CO_2C_2H_5$	116, 730, 731
	C_6H_5	$(CH_3)_2CH$	$C_6H_5CH_2$	387
	C_6H_5	H	$4-CH_3C_6H_4$	586, 587
	C_6H_5	H	$4-CH_3OC_6H_4$	224, 128
	C_6H_5	H		

TABLE 3.1. (Continued)

Total Carbon Atoms in Azlactone	R ¹	R ²	R ³	Yield Percent	Reference
17	C ₆ H ₅	H	C ₆ H ₅ CO ^b	—	237, 238, 732, 733
	C ₆ H ₅ 4-CH ₃ OC ₆ H ₄	4-O ₂ NC ₆ H ₄ CO	H	—	246
	2-C ₆ H ₅ CONHC ₆ H ₄	H	C ₆ H ₅	—	586, 587
	4-C ₆ H ₅ CONHC ₆ H ₄	H	H	—	17
	2-Amino-1-cyclohexyl	H	H	—	17
	CH ₃	2-ClC ₆ H ₄	1-Methyl(1-cyclohexyl) 4-CH ₃ OC ₆ H ₄	—	734
	C ₆ H ₅	CH ₃		34	114
	C ₆ H ₅	C ₆ H ₅ CH ₂	CH ₃	—	735
	C ₆ H ₅	CH ₃	C ₆ H ₅ CONH	—	718
	C ₆ H ₅	CH ₂ Cl	C ₆ H ₅ CONH	—	718
	C ₆ H ₅	CH ₂ Br	C ₆ H ₅ CONH	—	224
	C ₆ H ₅	H	4-CH ₃ OC ₆ H ₄ CO	—	—
	C ₆ H ₅		H ^d	—	613, 614
	C ₆ H ₅	C ₆ H ₅ CH ₂ S	CH ₃	—	497, 498
	4-O ₂ NC ₆ H ₄	CH ₃	C ₆ H ₅ CH ₂ ^c	—	696
	4-O ₂ NC ₆ H ₄	CH ₃	C ₆ H ₅ CH ₂ O	—	557, 558
	2-ClC ₆ H ₄	CH ₃	C ₆ H ₅ CH ₂ O	—	557, 558

18	4-ClC ₆ H ₄	CH ₃	C ₆ H ₅ CH ₂ O	—	557, 558
	C ₆ H ₅ CH ₂	CH ₃	C ₆ H ₅ CH ₂ ^c	—	536
	C ₆ H ₅ CH ₂ O	H	C ₆ H ₅ CH ₂	—	736
	CH ₂ Cl		C ₆ H ₅ CH ₂	—	34
	C ₆ H ₅	C ₆ H ₅ CH ₂	2,4(O ₂ N) ₂ C ₆ H ₃	—	737
	C ₆ H ₅	(CH ₃) ₂ CH	C ₂ H ₅	32	114
	C ₆ H ₅	C ₆ H ₅ CH ₂	CH ₃	—	735
	C ₆ H ₅	C ₆ H ₅ CH ₂ CONH			
	C ₆ H ₅		H ^d	—	493, 615, 611 ^d
	C ₆ H ₅	4-ClC ₆ H ₄ 	H	—	615, 611 ^d
	C ₆ H ₅	4-O ₂ NC ₆ H ₄ 	H	—	615 ^d
	4-CH ₃ OC ₆ H ₄	CH ₃	C ₆ H ₅ CH ₂ O	—	557, 558
	4-O ₂ NC ₆ H ₄	C ₆ H ₅ 	H	—	615 ^d
19	4-ClC ₆ H ₄	(CH ₃) ₂ CHCH ₂	(CH ₃) ₂ C=CHCH ₂	95	738
	C ₆ H ₅	4-ClC ₆ H ₄ CH ₂	(CH ₃) ₂ CH	85	730
	C ₆ H ₅	C ₆ H ₅ CH ₂	CH ₂ =CHCH ₂	93	114
	C ₆ H ₅	(CH ₃) ₂ CH	C ₆ H ₅ CH ₂	85	114
	C ₆ H ₅	(CH ₃) ₂ CH	2-O ₂ NC ₆ H ₄ CH ₂	66	114
	C ₆ H ₅	(CH ₃) ₂ CH	4-O ₂ NC ₆ H ₄ CH ₂	—	114
	C ₆ H ₅	(CH ₃) ₂ CH	Cycloheptatrienyl	90	114
	C ₆ H ₅	C ₆ H ₅ CH ₂	HC≡CCH ₂	43	114
	C ₆ H ₅	CH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	—	114
	C ₆ H ₅	4-CH ₃ OC ₆ H ₄ 	H	—	611, 615, 58, 741 ^d

TABLE 3.1. (Continued)

Total Carbon Atoms in Azlactone	R ¹	R ²	R ³	Yield Percent	Reference
C ₆ H ₅		3,4-OCH ₂ OC ₆ H ₃ - 	H	—	611 ^d
C ₆ H ₅		4-CH ₃ C ₆ H ₄ - 	H	—	615 ^d
1-C ₁₀ H ₇		H	C ₆ H ₅	—	586, 587
C ₆ H ₅ CH ₂			H	—	741
C ₆ H ₅ CH ₂		EtO ₂ CCH ₂ -N=C=S C(CH ₃) ₂	CH ₃	—	741
20 CH ₃ C ₆ H ₅		H (CH ₃) ₂ CH	C ₁₆ H ₃₁ C ₆ H ₅ COCH ₂	— 67	742 114
C ₆ H ₅ CH ₂			H	—	741
C ₆ H ₅		3-AcOC ₆ H ₄ - 	H	—	615 ^d
C ₆ H ₅		4-AcOC ₆ H ₄ - 	H	—	615 ^d
C ₆ H ₅			H	—	743

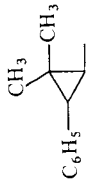
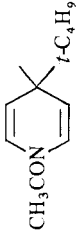
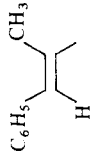
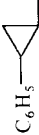
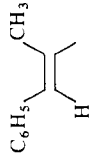
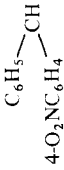
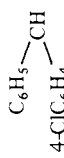
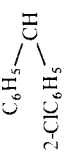
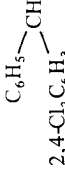
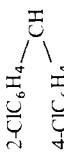
21	C_6H_5	$C_6H_5CH_2$	$CH_2CO_2C_2H_5^c$	45	114
	C_6H_5		H	—	492, 615 611 ^d
	$(CH_3)_2CNHCO_2CH_2-$ C_6H_5 C_6H_5	$C_6H_5CH_2$ $C_6H_5CH_2$ $(CH_3)_2CH$	H $(CH_3)_2CH=CH_2$ $3,4-(CH_3O)_2C_6H_3CH_2$	— 87 —	135 738 114 ^c
	C_6H_5	CH_3		—	80, 128
	C_6H_5	C_6H_5	C_6H_5	—	744–746
	C_6H_5	$3-CH_3O-4-AcOC_6H_3-$ 	H	—	615 ^d
	C_6H_5	$3-AcO-4CH_3OC_6H_3-$ 	H	—	615 ^d
	C_6H_5NH	C_6H_5	C_6H_5	—	555, 597–601
			H	—	248 ^d
		$3,4-(HO)_2C_6H_3-$ 	H	—	248 ^d

TABLE 3.1. (Continued)

Total Carbon Atoms in Azlactone	R ¹	R ²		R ³	Yield Percent	Reference
22	C ₆ H ₅	3,4-(AcO) ₂ C ₆ H ₃ - 		H	—	615 ^d
	C ₆ H ₅	H		(C ₆ H ₅) ₂ CH	74	70, 71, 84, ^{e,f} 85, 499, 717
	C ₆ H ₅	H			90	85 ^e
	C ₆ H ₅	H			10	67, 84, 85 ^e
	C ₆ H ₅	H			80	85 ^e
	C ₆ H ₅	H			65	77, 84, 85, 747 ^{e,f}
	C ₆ H ₅	H			60	67, 85, 747 ^e
	C ₆ H ₅	H			60	67 ^f

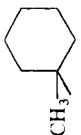
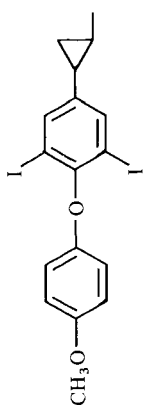
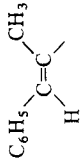
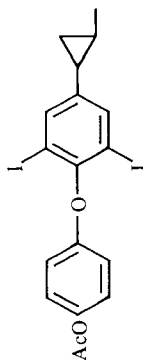
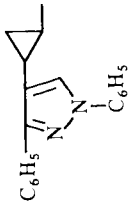
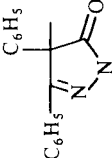
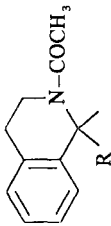
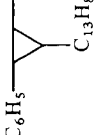
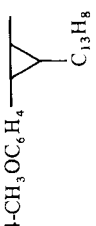
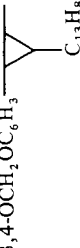
23	C_6H_5	H	$1-C_{10}H_7-$ 	—	493 ^d
	C_6H_5	Cycloheptatrienyl	Cycloheptatrienyl	33	114
	C_6H_5	H	$4-CH_3OC_6H_4-$ 	40	67, 85 ^f
	C_6H_5	H	$4-CH_3OC_6H_4-$ 	60	67 ^f
	C_6H_5	H	$4-CH_3OC_6H_4-$ 	14	67, 85 ^{e,f}
	C_6H_5	H	$3-CH_3C_6H_4-$ 	63	67 ^f
	C_6H_5	H	$2-CH_3C_6H_4-$ 	40	67, 85 ^f
	C_6H_5	H	$2-CH_3OC_6H_4-$ 	40	67, 85 ^f
	$(CH_3)_2CHCH$	$(CH_3)_2CH$	Cycloheptatrienyl	—	114 ^c
	$NHCOC_6H_5$		H	—	734
	$C_6H_5CH_2O_2CNH$		$4-CH_3OC_6H_4-$ 	40	67 ^f
	C_6H_5	H	$4-CH_3OC_6H_4-$ 	40	67 ^f

TABLE 3.1. (Continued)

Total Carbon Atoms in Azlactone	R ¹	R ²		R ³	Yield Percent	Reference
25	C ₆ H ₅	H		Palmitoyl	—	239
	C ₆ H ₅	H		4-(CH ₃) ₂ CHC ₆ H ₄ CH(C ₆ H ₅)	20	85 ^e
	C ₆ H ₅			H	—	741, 742, 749 ^d
		3,4-(AcO) ₂ C ₆ H ₃ — 		H	—	248
26	<i>t</i> -C ₄ H ₉ C ₆ H ₅ CH ₂ O ₂ CNHCH ₂	(C ₆ H ₅) ₃ C C ₆ H ₅ CH ₂		H	—	748
	C ₆ H ₅	H		C ₆ H ₅	—	34
	C ₆ H ₅			1-C ₁₀ H ₇ CH(C ₆ H ₅)	60	66, 67 ^f
	C ₆ H ₅	H		2-C ₁₀ H ₇ CH(C ₆ H ₅)	62	67 ^f
	C ₆ H ₅			H	—	749 ^d

27	C_6H_5		H	—	69 ^d
28	$t-C_4H_9$ C_6H_5	CH_3S $(C_6H_5)_3C$	$(C_6H_5)_3C$ H	— 50	845 114
30	C_6H_5		H	—	322
	C_6H_5		H	—	743
31	C_6H_5	$R = C_6H_5, C_6H_{13}$ 	H	—	492 ^g
32	C_6H_5	$4-CH_3OC_6H_4$ 	H	—	492 ^g
	C_6H_5	$3,4-OCH_2OC_6H_3$ 	H	—	492 ^g

^aPrepared by cyclodehydration of acylamino acids with acetic anhydride.

^bPrepared by acylation of corresponding saturated azlactone with R^2 (or R^3) $COCl$ in pyridine.

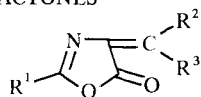
^cAlkylation of corresponding saturated azlactone ($R^3 = H$) with alkyl halide.

^dPrepared by treating corresponding unsaturated azlactone with diazoalkane.

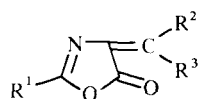
^ePrepared by reacting corresponding unsaturated azlactone with benzene in presence of anhydrous $AlCl_3$.

^fPrepared by reacting unsaturated azlactone with $ArMgX$ in presence of Cu_2Cl_2 .

^gPrepared by reacting corresponding unsaturated azlactone with diazofluorene.

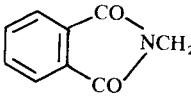
TABLE 3.2A. UNSATURATED AZLACTONES^a

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
7	C ₆ H ₅ CHO	Aceturic acid	CH ₃
		Diethylaceturic acid	(C ₂ H ₅) ₂ CH
		Phenaceturic acid	C ₆ H ₅ CH ₂
		α-Ethylphenaceturic acid	C ₆ H ₅ CHC ₂ H ₅
		Trifluoroaceturic acid	CF ₃
		Chloroaceturic acid	ClCH ₂
		Dichloroaceturic acid	Cl ₂ CH
		Dibromoaceturic acid	Br ₂ CH
		Isopropenoylglycine	CH ₃ C(=CH ₂)
		3-Butenoylglycine	CH ₂ CH=CH ₂
		N-Tigloylglycine	CH ₃ CH=C(CH ₃)
		Hippuric acid	C ₆ H ₅
			C ₆ H ₅
		2-Chlorohippuric acid	2-ClC ₆ H ₄
		4-Chlorohippuric acid	4-ClC ₆ H ₄
		2-Bromohippuric acid	2-BrC ₆ H ₄
		2-Iodohippuric acid	2-IC ₆ H ₄
		2,4-Dichlorohippuric acid	2,4-Cl ₂ C ₆ H ₃
		2-Methoxyhippuric acid	2-CH ₃ OC ₆ H ₄
		4-Methoxyhippuric acid	4-CH ₃ OC ₆ H ₄
		3,4-Dimethoxyhippuric acid	3,4-(CH ₃ O) ₂ C ₆ H ₃
		3,4,5-Trimethoxyhippuric acid	3,4,5-(CH ₃ O) ₃ C ₆ H ₂
		3-Methylhippuric acid	3-CH ₃ C ₆ H ₄



R^2d	R^3d	Yield Percent	Reference
C_6H_5	H	70	422
		—	325, 537, 750
			752
C_6H_5	H	—	756
C_6H_5	H	—	78, 751
C_6H_5	H	—	756
C_6H_5	H	—	243
		77	247
C_6H_5	H	61	251, 304 ^e
C_6H_5	H	36	304, 757
		—	329
		63	757
C_6H_5	H	40	329 ^f
C_6H_5	H	—	49
		69	11 ^a
C_6H_5	H	50	304
C_6H_5	H	26	31
C_6H_5	H	—	213
		97	266 ^g
		84	266 ^h
		77	169
		77	262 ⁱ
		58	19 ^j
		88	265, 266 ^k
H	C_6H_5	90	217 ^l
		100	217 ^m
		97	266 ⁿ
		—	23 ⁿ
C_6H_5	H	89	190
C_6H_5	H	80	19 ^j , 186
		83	190
		—	758
C_6H_5	H	89	190
C_6H_5	H	80	492
C_6H_5	H	—	759, 760
C_6H_5	H	—	169
C_6H_5	H	—	186
		—	758, 803
C_6H_5	H	—	560
C_6H_5	H	—	177
C_6H_5	H	87	185

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ H	R ¹
		4-Methylhippuric acid	4-CH ₃ C ₆ H ₄
		2-Acetoxyhippuric acid	2-CH ₃ CO ₂ C ₆ H ₄
		2-Acetoxy-3-methyl- hippuric acid	2-CH ₃ CO ₂ -3MeC ₆ H ₃
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		3,5-Dinitrohippuric acid	3,5-(O ₂ N) ₂ C ₆ H ₃
		4-Acetamidohippuric acid	4-CH ₃ CONHC ₆ H ₄
		4-Phenylhippuric acid	4-C ₆ H ₅ C ₆ H ₄
		2-Furoylglycine	2-C ₄ H ₃ O
		γ-Phthaloylamino- propylglycine	
		α-(p-Xenyl)ethylaceturic acid	CH ₃ CHC ₁₂ H ₉
		2-Methacrylamido- isopropionylglycine	CH ₃ C(=CH ₂)CO— —NHC(CH ₃) ₂
		α-Benzamidocinna- moylglycine	C ₆ H ₅ CONHC(=CHC
		Acetyldehydroleucyl- glycine	CH ₃ CONHC— [=CHCH(CH ₃) ₂]
		Acetyldehydrophenyl- alanylglycine	AcNHC(=CHC ₆ H ₅)
		Cinnamoylglycine	C ₆ H ₅ CH=CH
		α-Methylcinnamoyl- glycine	C ₆ H ₅ CH=C(CH ₃)
		N-Tigloylphenylalanine	
		$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{CHCO}_2\text{H} \\ \\ \text{NHCOCCH}_3 \\ \\ \text{CHCH}_3 \end{array}$	

R^{2d}	R^{3d}	Yield Percent	Reference
C_6H_5	H	56	19
		82	328
		—	759
C_6H_5	H	—	759
C_6H_5	H	—	195
C_6H_5	H	—	18
		30	181
		43	180
C_6H_5	H	80	180
C_6H_5	H	86	264, 265 ^k
		—	169
		83	264, 265
C_6H_5	H	62	180
		15	18 ^o
		—	167, 169
C_6H_5	H	64	19 ^j
C_6H_5	H	40	198
		—	761
C_6H_5	H	—	762
		50	763
C_6H_5	H	—	764
C_6H_5	H	41	11 ^a
C_6H_5	H	—	765
C_6H_5	H	—	766
C_6H_5	H	—	766
C_6H_5	H	54	31 ^p
		70	767–769
		78	304
		44	327
C_6H_5	H	63	31 ^p
C_6H_5	H	50	31 ^p

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ H	R ¹
		2,3-Dibromo-2-methyl- <i>N</i> - tigloylphenylalanine $ \begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{CHCO}_2\text{H} \\ \\ \text{NHCOC}(\text{CH}_3)-\text{CH} \\ \quad \\ \text{Br} \quad \text{Br} \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array} $	
		Aceturic acid	CH ₃
		Trichloroaceturic acid	CCl ₃
		Aceturic acid	C ₆ H ₅
		Dibromoaceturic acid	CHBr ₂
		4-Methylhippuric acid	C ₆ H ₅
			4CH ₃ C ₆ H ₄
			4-BrCH ₂ C ₆ H ₄
			4-Br ₂ CHC ₆ H ₄
			4-Br ₃ CC ₆ H ₄
	C ₆ H ₅ CDO	Aceturic acid	CH ₃
			C ₆ H ₅
	C ₆ D ₅ CHO	Aceturic acid	C ₆ H ₅
			CH ₃
	2-FC ₆ H ₄ CHO		C ₆ H ₅
			C ₆ H ₅
	3-FC ₆ H ₄ CHO	Aceturic acid	C ₆ H ₅
			CH ₃
			C ₆ H ₅
	4-FC ₆ H ₄ CHO	Aceturic acid	C ₆ H ₅
			CH ₃
			C ₆ H ₅
	2-ClC ₆ H ₄ CHO	Aceturic acid	C ₆ H ₅
			CH ₃
			C ₆ H ₅
		2,4-Dichlorohippuric acid	C ₆ H ₅
			2,4-Cl ₂ C ₆ H ₃
		2-Acetoxyhippuric acid	2-CH ₃ CO ₂ C ₆ H ₄
		2-Acetoxy-3-methyl- hippuric acid	2-CH ₃ CO ₂ -3-CH ₃ -C ₆ H ₄
		4-Methylhippuric acid	4-CH ₃ C ₆ H ₄
		4-Acetamidohippuric acid	4-CH ₃ CONHC ₆ H ₄
		2-Furoylglycine	2-C ₄ H ₃ O

R^2d	R^3d	Yield Percent	Reference
C_6H_5	H	93	31 ^p
C_6H_5	Cl	77	328 ^e
C_6H_5	Cl	72	328 ^e
C_6H_5	Cl	25	326 ^e
C_6H_5	Br	70	327 ^f
C_6H_5	Br	61	327 ^f
C_6H_5	Br	36	326 ^f
C_6H_5	Br	92	329 ^f
C_6H_5	Br	15	329 ^f
C_6H_5	Br	9	329 ^f
C_6H_5	Br	5	329 ^f
C_6H_5	D	—	769
C_6H_5	D	—	770
D	C_6H_5	—	771
C_6D_5	H	—	772 ^q
C_6D_5	H	—	772
2-FC ₆ H ₄	H	35	773
		34	774
H	2-FC ₆ H ₄	52	151
3-FC ₆ H ₄	H	—	222
3-FC ₆ H ₄	H	70	773
		32	774
H	3-FC ₆ H ₄	65	151
4-FC ₆ H ₄	H	—	222
		—	774 ^r
4-FC ₆ H ₄	H	37	773
		32	774
		—	775
		96	226 ^k
H	4-FC ₆ H ₄	50	151 ⁱ
2-ClC ₆ H ₄	H	—	414, 652, 672
2-ClC ₆ H ₄	H	—	187
		61	266 ^k
H	2-ClC ₆ H ₄	55	151 ⁱ
2-ClC ₆ H ₄	H	—	759
2-ClC ₆ H ₄	H	—	759
2-ClC ₆ H ₄	H	—	759
2-ClC ₆ H ₄	H	65	167
2-ClC ₆ H ₄	H	60	198

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino acid ^c R ¹ CONHCH ₂ H	R ¹
	3-ClC ₆ H ₄ CHO	5-Nitro-2-furoylglycine Aceturic acid	5-O ₂ N-2-C ₄ H ₂ O CH ₃
		4-Chlorohippuric acid 2-Furoylglycine	C ₆ H ₅ 4-ClC ₆ H ₄ 2-C ₄ H ₃ O
	4-ClC ₆ H ₄ CHO	Aceturic acid	CH ₃
	3,4-Cl ₂ C ₆ H ₃ CHO		C ₆ H ₅
	2,6-Cl ₂ C ₆ H ₃ CHO		C ₆ H ₅
	2-BrC ₆ H ₄ CHO	2-Furoylglycine	2-C ₄ H ₃ O
		5-Nitro-2-furoylglycine	5-O ₂ NC ₄ H ₂ O
	3-BrC ₆ H ₄ CHO	2-Furoylglycine	2-C ₄ H ₃ O
		5-Nitro-2-furoylglycine	5-O ₂ NC ₄ H ₂ O
	4-BrC ₆ H ₄ CHO		C ₆ H ₅
			C ₆ H ₅
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		2-Furoylglycine	2-C ₄ H ₃ O
		5-Nitro-2-furoylglycine	5-O ₂ NC ₄ H ₂ O
	C ₆ F ₅ CHO		C ₆ H ₅
	2-HOC ₆ H ₄ CHO	4-Nitrohippuric acid Aceturic acid	4-O ₂ NC ₆ H ₄ CH ₃
			C ₆ H ₅
			C ₆ H ₅
		4-Acetamidohippuric acid	4-CH ₃ CONHC ₆ H ₄
		α[<i>p</i> -Xenyl] ethyl- aceturic acid	C ₂ H ₅ CH(C ₁₂ H ₉)
	3-HOC ₆ H ₄ CHO	Aceturic acid	CH ₃ C ₆ H ₅
		4-Chlorohippuric acid	C ₆ H ₅
		3,5-Dichlorohippuric acid	4-ClC ₆ H ₄
		2-Nitrohippuric acid	3,4-Cl ₂ C ₆ H ₃
		3-Nitrohippuric acid	2-O ₂ NC ₆ H ₄ 3-O ₂ NC ₆ H ₄
		2-Furoylglycine	2-C ₄ H ₃ O
	2,4-Cl ₂ C ₆ H ₃ CHO		C ₆ H ₅
		4-Chlorohippuric acid	C ₆ H ₅ 4-ClC ₆ H ₄

R^{2d}	R^{3d}	Yield Percent	Reference
2-ClC ₆ H ₄	H	40	198
3-ClC ₆ H ₄	H	69	777, 778
		—	414
3-ClC ₆ H ₄	H	—	779
3-ClC ₆ H ₄	H	—	758
3-ClC ₆ H ₄	H	60	198
		62	776
4-ClC ₆ H ₄	H	—	652, 766
3,4-Cl ₂ C ₆ H ₃	H	98	262 ⁱ
2,6-Cl ₂ C ₆ H ₃	H	86	649
2-BrC ₆ H ₄	H	90	198
2-BrC ₆ H ₄	H	40	198
3-BrC ₆ H ₄	H	40	198
3-BrC ₆ H ₄	H	55	198
4-BrC ₆ H ₄	H	79	164, 165 ^k
H	4-BrC ₆ H ₄	76	151 ^l
4-BrC ₆ H ₄	H	—	264, 265 ^k
4-BrC ₆ H ₄	H	60	198
4-BrC ₆ H ₄	H	70	198
C ₆ F ₅	H	—	183
		—	269
		73	781
C ₆ F ₅	H	—	183
2-CH ₃ CO ₂ ^{-s,t}	H	—	667, 783
C ₆ H ₄			
2-CH ₃ CO ₂ ^{-t,q}	H	—	262, 667, 784
C ₆ H ₄			
H	2-HOC ₆ H ₄	70	217 ^l
2-CH ₃ CO ₂ C ₆ H ₄	H	—	167
2-CH ₃ CO ₂ C ₆ H ₄	H	—	764
3-CH ₃ CO ₂ C ₆ H ₄	H	—	667, 783, 784 ^t
4-ClC ₆ H ₄	H	—	187, 414, 492,
			75, 776
		93	264, 265
		95	266 ^h
H	4-ClC ₆ H ₄	—	217 ^{a,l}
4-ClC ₆ H ₄	H	—	758, 780, 781
4-ClC ₆ H ₄	H	—	780, 781, 782
4-ClC ₆ H ₄	H	—	352a
4-ClC ₆ H ₄	H	—	264, 265 ^k
		—	352a
4-ClC ₆ H ₄	H	60	198
2,4-Cl ₂ C ₆ H ₃	H	90	262 ⁱ
		—	758
H	2,4-Cl ₂ C ₆ H ₃	100	217 ^{a,m}
2,4-Cl ₂ C ₆ H ₃	H	—	758

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
			C ₆ H ₅
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		4-Acetamidohippuric acid	4-CH ₃ CONHC ₆ H ₄
		α-[<i>p</i> -Xenyl] ethyl- aceturic acid	C ₂ H ₅ CH(C ₁₂ H ₉)
	4-HOC ₆ H ₄	Aceturic acid	CH ₃
		Chloroaceturic acid	ClCH ₂
		Diethylaceturic acid	(C ₂ H ₅) ₂ CH C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		4-Acetamidohippuric acid	4-CH ₃ CONHC ₆ H ₄
		α-[<i>p</i> -Xenyl] ethylaceturic acid	C ₂ H ₅ CH(C ₁₂ H ₉)
	2,4-(HO) ₂ C ₆ H ₃ CHO	Cinnamoylglycine	C ₆ H ₅ CH=CH
		Aceturic acid	CH ₃
			C ₆ H ₅
	2, 5-(HO) ₂ C ₆ H ₃ CHO	Cinnamoylglycine	C ₆ H ₅ CH=CH
		Aceturic acid	CH ₃
			C ₆ H ₅
	3,4-(HO) ₂ C ₆ H ₃ CHO		C ₆ H ₅
			C ₆ H ₅
	2,3,4-(HO) ₃ C ₆ H ₂ CHO	Cinnamoylglycine	C ₆ H ₅ CH=CH ^v
	4-HO-3-ClC ₆ H ₃ CHO		C ₆ H ₅
	4-HO-3-IC ₆ H ₃ CHO		C ₆ H ₅
			C ₆ H ₅
	4-HO-3,4-Br ₂ C ₆ H ₂ CHO	Aceturic acid	CH ₃
			C ₆ H ₅
	4-HO-3,5-I ₂ C ₆ H ₂ CHO	Aceturic acid	CH ₃
	4-HO-2,5-I ₂ C ₆ H ₂ CHO	Aceturic acid	C ₆ H ₅
	2-O ₂ NC ₆ H ₄ CHO	Aceturic acid	CH ₃
		<i>n</i> -Propionoylglycine	CH ₃ C ₂ H ₅ C ₆ H ₅
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		2-Chlorohippuric acid	2-ClC ₆ H ₄
		4-Chlorohippuric acid	4-ClC ₆ H ₄

R ^{2d}	R ^{3d}	Yield Percent	Reference
3-CH ₃ CO ₂ C ₆ H ₄	H	—	409, 455
		65	615a
3-CH ₃ CO ₂ C ₆ H ₄	H	50	180
3-CH ₃ CO ₂ C ₆ H ₄	H	75	180
3-CH ₃ CO ₂ C ₆ H ₄	H	57	262 ⁱ
3-CH ₃ CO ₂ C ₆ H ₄	H	—	764
4-CH ₃ CO ₂ C ₆ H ₄	H	—	188, 667, 785
4-CH ₃ CO ₂ C ₆ H ₄	H	78	251 ^b
4-CH ₃ CO ₂ C ₆ H ₄	H	—	756
4-CH ₃ CO ₂ C ₆ H ₄	H	—	160, 667, 786,
			788
4-HOC ₆ H ₄	H	—	262 ⁱ
H	4-HO	80	217 ⁱ
4-CH ₃ CO ₂ C ₆ H ₄	H	36	180
4-CH ₃ CO ₂ C ₆ H ₄	H	70	180
4-CH ₃ CO ₂ C ₆ H ₄	H	84	180
4-CH ₃ CO ₂ C ₆ H ₄	H	72	167
4-CH ₃ CO ₂ C ₆ H ₄	H	—	764
4-CH ₃ CO ₂ C ₆ H ₄	H	59	31
2,4(AcO) ₂ C ₆ H ₃	H	—	667
2,4(AcO) ₂ C ₆ H ₃	H	—	667
2,4(AcO) ₂ C ₆ H ₃	H	—	31
2,5-AcO ₂ C ₆ H ₃	H	—	161 ^u
		21	162
2,5-AcO ₂ C ₆ H ₃	H	29	164
3,4-AcO ₂ C ₆ H ₃	H	50	615a
3,4-AcO ₂ C ₆ H ₃	H	—	789
2,3,4-AcO ₃ C ₆ H ₂	H	87	267
4-AcO-3-ClC ₆ H ₃	H	—	796
4-AcO-3-IC ₆ H ₃	H	—	436
		—	790 ^u
4-AcO-3,5-Br ₂ C ₆ H ₂	H	—	437 ^u
4-AcO-3,5-Br ₂ C ₆ H ₂	H	—	791 ^u
4-AcO-3,5-I ₂ C ₆ H ₂	H	—	792 ^u
		—	652
		86	437 ^u
4-AcO-3,5-I ₂ C ₆ H ₂	H	80	793
4-AcO-2,5-I ₂ C ₆ H ₂	H	46	794 ^u
2-O ₂ NC ₆ H ₄	H	—	777, 761
2-O ₂ NC ₆ H ₄	H	—	780
2-O ₂ NC ₆ H ₄	H	—	169
		82	215
2-O ₂ NC ₆ H ₄	H	57	180
2-O ₂ NC ₆ H ₄	H	36	180
2-O ₂ NC ₆ H ₄	H	71	180
2-O ₂ NC ₆ H ₄	H	85	190
2-O ₂ NC ₆ H ₄	H	84	190

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
3-O ₂ NC ₆ H ₄ CHO		3-Methylhippuric acid	3-CH ₃ C ₆ H ₄
		2-Furoylglycine	2-C ₄ H ₃ O
		5-Nitro-2-furoylglycine	5-O ₂ N-2-C ₄ H ₂ O
		Aceturic acid	CH ₃ C ₆ H ₅
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		4-Acetamidohippuric acid	4-CH ₃ CONHC ₆ H ₄
		2-Chlorohippuric acid	2-ClC ₆ H ₄
		4-Chlorohippuric acid	4-ClC ₆ H ₄
		2,4-Dichlorohippuric acid	2,4-Cl ₂ C ₆ H ₃
		3-Methylhippuric acid	3-CH ₃ C ₆ H ₄
		4-Methylhippuric acid	4-CH ₃ C ₆ H ₄
		2-Acetoxyhippuric acid	2-CH ₃ CO ₂ C ₆ H ₄
		2-Acetoxy-3-methyl-hippuric acid	2-AcO-3-CH ₃ C ₆ H ₃
4-O ₂ NC ₆ H ₄ CHO		2-Furoylglycine	2-C ₄ H ₃ O
		5-Nitro-2-furoylglycine	5-O ₂ N-2-C ₄ H ₂ O
		Aceturic acid	CH ₃
		α-Acetamidopropionyl-glycine	CH ₃ CH(NHAc)
		α-Acetamidocinnamoyl-glycine	C ₆ H ₅ CH(NHAc)
			C ₆ H ₅
		2-Nitrohippuric acid	C ₆ H ₅ 2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		4-Acetamidohippuric acid	4-AcNHC ₆ H ₄
		2-Furoylglycine	2-C ₄ H ₃ O
		5-Nitro-2-furoylglycine	5-O ₂ N-2-C ₄ H ₂ O
		Aceturic acid	CH ₃ C ₆ H ₅
		Aceturic acid	CH ₃ C ₆ H ₅
		Aceturic acid	CH ₃ C ₆ H ₅
2,4(O ₂ N) ₂ C ₆ H ₃ CHO		Aceturic acid	CH ₃ C ₆ H ₅
2-HO-4-O ₂ NC ₆ H ₃ CHO		Aceturic acid	CH ₃ C ₆ H ₅
4-HO-3-O ₂ NC ₆ H ₃ CHO		Aceturic acid	CH ₃ C ₆ H ₅
5-HO-2-O ₂ NC ₆ H ₃ CHO		Aceturic acid	CH ₃ C ₆ H ₅
6-HO-2-O ₂ NC ₆ H ₃ CHO		Aceturic acid	CH ₃ C ₆ H ₅
4-H ₂ NC ₆ H ₄ CHO		Aceturic acid	CH ₃ C ₆ H ₅

R ^{2d}	R ^{3d}	Yield Percent	Reference
2-O ₂ NC ₆ H ₄	H	89	185
2-O ₂ NC ₆ H ₄	H	65	198
		—	199
2-O ₂ NC ₆ H ₄	H	30	198
3-O ₂ NC ₆ H ₄	H	—	310, 780
3-O ₂ NC ₆ H ₄	H	—	320, 780, 97, 264, 265 ^k
3-O ₂ NC ₆ H ₄	H	60	180
3-O ₂ NC ₆ H ₄	H	83	180
3-O ₂ NC ₆ H ₄	H	85	180
3-O ₂ NC ₆ H ₄	H	69	567
3-O ₂ NC ₆ H ₄	H	90	190
3-O ₂ NC ₆ H ₄	H	78	190
3-O ₂ NC ₆ H ₄	H	—	759
3-O ₂ NC ₆ H ₄	H	83	190
3-O ₂ NC ₆ H ₄	H	—	759
3-O ₂ NC ₆ H ₄	H	—	759
3-O ₂ NC ₆ H ₄	H	—	195
3-O ₂ NC ₆ H ₄	H	85	198
3-O ₂ NC ₆ H ₄	H	80	198
4-O ₂ NC ₆ H ₄	H	86	777, 794
		—	795
4-O ₂ NC ₆ H ₄	H	97	777
4-O ₂ NC ₆ H ₄	H	—	796a
4-O ₂ NC ₆ H ₄	H	—	169, 426
		80	261 ^l
		81	264, 265 ^k
H	4-O ₂ NC ₆ H ₄ ^m	100	217
4-O ₂ NC ₆ H ₄	H	50	180
		—	662, 796b
4-O ₂ NC ₆ H ₄	H	72	780
4-O ₂ NC ₆ H ₄	H	—	263, 264 ^k
		60	180
4-O ₂ NC ₆ H ₄	H	58	167
4-O ₂ NC ₆ H ₄	H	85	198
4-O ₂ NC ₆ H ₄	H	90	198
2,4(O ₂ N) ₂ C ₆ H ₃	H	—	777
2,4(O ₂ N) ₂ C ₆ H ₃	H	—	795, 798
2-AcO-4-O ₂ NC ₆ H ₃	H	—	777
4-AcO-3-O ₂ NC ₆ H ₃	—	—	799
5-AcO-2-O ₂ NC ₆ H ₃	H	—	800
6-AcO-2-O ₂ NC ₆ H ₃	H	—	800
4,5AcO ₂ -2-O ₂ NC ₆ H ₂	H	—	801
4-CH ₃ CONHC ₆ H ₄	H	—	801
4-CH ₃ CONHC ₆ H ₄	H	—	662, 787, 797

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
8	2-NCC ₆ H ₄ CHO 2-CH ₃ C ₆ H ₄ CHO 3-CH ₃ C ₆ H ₄ CHO 4-CH ₃ C ₆ H ₄ CHO	4-Acetamidohippuric acid 2-Benzamidoheptanoic acid	4-AcNHC ₆ H ₄ <i>n</i> -C ₅ H ₁₁ CH NHCOC ₆ H ₅
		2-Furaylglycine 5-Nitrofuroylglycine Aceturic acid	C ₆ H ₅ C ₆ H ₅ 2-C ₄ H ₃ O 5-O ₂ NC ₄ H ₃ O CH ₃ C ₆ H ₅
		2-Furoylglycine 5-Nitro-2-furoylglycine Aceturic acid	2-C ₄ H ₃ O 5-O ₂ NC ₄ H ₃ O CH ₃ C ₆ H ₅
		3-Nitrohippuric acid 2-Furoylglycine 5-Nitro-2-furoylglycine	C ₆ H ₅ 3-O ₂ NC ₆ H ₄ 2-C ₄ H ₃ O 5-O ₂ NC ₄ H ₂ O C ₆ H ₅ C ₆ H ₅
	4-Me-2-HOC ₆ H ₃ CHO 5-Me-2-HOC ₆ H ₃ CHO		
	4-CHF ₂ SO ₂ C ₆ H ₄ CHO 2-F ₃ CC ₆ H ₄ CHO	Aceturic acid	C ₆ H ₅ CH ₃ C ₆ H ₅
	3-F ₃ CC ₆ H ₄ CHO	Aceturic acid	CH ₃ C ₆ H ₅
	4-F ₃ CC ₆ H ₄ CHO 2-CH ₃ OC ₆ H ₄ CHO	Aceturic acid Diethylaceturic acid α (<i>p</i> -Xenyl)ethylaceturic acid	CH ₃ (C ₂ H ₅) ₂ CH C ₂ H ₅ CHC ₁₂ H ₉ C ₆ H ₅
	3-CH ₃ OC ₆ H ₄ CHO		C ₆ H ₅
		2-Nitrohippuric acid 3-Nitrohippuric acid 4-Nitrohippuric acid Aceturic acid Phenaceturic acid Diethylaceturic acid	2-O ₂ NC ₆ H ₄ 3-O ₂ NC ₆ H ₄ 4-O ₂ NC ₆ H ₄ CH ₃ C ₆ H ₅ CH ₂ (C ₂ H ₅) ₂ CH C ₆ H ₅
		2-Nitrohippuric acid 3-Nitrohippuric acid 4-Nitrohippuric acid Aceturic acid Phenaceturic acid Diethylaceturic acid	2-O ₂ NC ₆ H ₄ 3-O ₂ NC ₆ H ₄ 4-O ₂ NC ₆ H ₄ CH ₃ C ₆ H ₅ CH ₂ (C ₂ H ₅) ₂ CH
	4-CH ₃ OC ₆ H ₄ CHO		

$R^2{}^d$	$R^3{}^d$	Yield Percent	Reference
4-AcNHC ₆ H ₄	H	70	167
4-AcNHC ₆ H ₄	H	—	787
2-NCC ₆ H ₄	H	—	780
2-CH ₃ C ₆ H ₄	H	70	151, 680
2-CH ₃ C ₆ H ₄	H	30	198
2-CH ₃ C ₆ H ₄	H	90	198
3-CH ₃ C ₆ H ₄	H	—	414, 151
3-CH ₃ C ₆ H ₄	H	—	414, 67, 151
3-CH ₃ C ₆ H ₄	H	30	198
3-CH ₃ C ₆ H ₄	H	90	198
4-CH ₃ C ₆ H ₄	H	—	776
4-CH ₃ C ₆ H ₄	H	—	802
		85	198, 529, 262
H	4-CH ₃ C ₆ H ₃	80	217 ⁱ
4-CH ₃ C ₆ H ₄	H	—	352a
4-CH ₃ C ₆ H ₄	H	20	198
4-CH ₃ C ₆ H ₄	H	90	198
4-CH ₃ -2-AcOC ₆ H ₃	H	—	664
5-CH ₃ -2-AcOC ₆ H ₃	H	60	271
		—	270
4-CHF ₂ SO ₂ C ₆ H ₄	H	—	740, 830
2-F ₃ CC ₆ H ₄	H	—	780
		30	804
3-F ₃ CC ₆ H ₄	H	33	805
3-F ₃ CC ₆ H ₄	H	84	804
4-F ₃ CC ₆ H ₄	H	70	805
2-CH ₃ OC ₆ H ₄	H	80	804 ^q
2-CH ₃ OC ₆ H ₄	H	—	764
2-CH ₃ OC ₆ H ₄	H	—	569, 759
		95	441 ^w
		—	465 ^w
H	2-CH ₃ OC ₆ H ₄	—	12, 66
		100	151 ^m
2-CH ₃ OC ₆ H ₄	H	38	180
2-CH ₃ OC ₆ H ₄	H	72	180
2-CH ₃ OC ₆ H ₄	H	87	180
3-CH ₃ OC ₆ H ₄	H	—	44
3-CH ₃ OC ₆ H ₄	H	—	806 ^q
3-CH ₃ OC ₆ H ₄	H	—	756
3-CH ₃ OC ₆ H ₄	H	—	776
3-CH ₃ OC ₆ H ₄	H	64	180
3-CH ₃ OC ₆ H ₄	H	78	180
3-CH ₃ OC ₆ H ₄	H	87	180
4-CH ₃ OC ₆ H ₄	H	—	169, 524, 806
4-CH ₃ OC ₆ H ₄	H	70	529
4-CH ₃ OC ₆ H ₄	H	—	752

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
		α -(<i>p</i> -Xenyl)ethylaceturic acid	C ₂ H ₅ CHC ₁₂ H ₉ C ₆ H ₅
		4-Methylhippuric acid	C ₆ H ₅
		4-Methoxyhippuric acid	4-CH ₃ C ₆ H ₄
		4-Chlorohippuric acid	4-CH ₃ OC ₆ H ₄
		4-Acetamidohippuric acid	4-ClC ₆ H ₄
		2-Acetoxylhippuric acid	4-CH ₃ CONHC ₆ H ₄
		2-Nitrohippuric acid	2-CH ₃ CO ₂ C ₆ H ₄
		3-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		2-Acetoxyl-3-methyl-hippuric acid	4-O ₂ NC ₆ H ₄
		2,4-Dichlorohippuric acid	2-AcO-3-MeC ₆ H ₃
		2-Furoylglycine	2,4-Cl ₂ C ₆ H ₃
		Cinnamoylglycine	2-C ₄ H ₃ C
		Aceturic acid	C ₆ H ₅ CH=CH
	4-CH ₃ OC ₆ H ₄ CDO		CH ₃
	2-CH ₃ O-5-BrC ₆ H ₃ CHO		C ₆ H ₅
	4-CH ₃ O-3-FC ₆ H ₃ CHO		C ₆ H ₅
	4-CH ₃ O-3-ClC ₆ H ₃ CHO		C ₆ H ₅
	4-CH ₃ O-3,5-I ₂ C ₆ H ₂ CHO		C ₆ H ₅
	2-CH ₃ O-5-O ₂ NC ₆ H ₃ CHO		C ₆ H ₅
	4-CH ₃ O-2-O ₂ NC ₆ H ₃ CHO		C ₆ H ₅
	3-CH ₃ O-4-HOC ₆ H ₃ CHO (vanillin)	Aceturic acid	CH ₃
		Dibromoaceturic acid	BR ₂ CH
		Diethylaceturic acid	(C ₂ H ₅) ₂ CH
		α -(<i>p</i> -Xenyl)ethylaceturic acid	C ₂ H ₅ CHC ₁₂ H ₉ C ₆ H ₅
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		4-Bromohippuric acid	4-BrC ₆ H ₄
		4-Acetamidohippuric acid	4-CH ₃ CONHC ₆ H ₄
		Cinnamoylglycine	C ₆ H ₅ CH=CH
		3,4,5-Trimethoxycinnamoylglycine	3,4,5(MeO)C ₆ H ₂ CH=

R^{2d}	R^{3d}	Yield Percent	Reference
4-CH ₃ OC ₆ H ₄	H	—	764
4-CH ₃ OC ₆ H ₄	H	—	186, 529
		55	19, 466 ^w , 802
		74	466
		70	475
H	4-CH ₃ OC ₆ H ₄	90	217 ^l
4-CH ₃ OC ₆ H ₄	H	—	759
4-CH ₃ OC ₆ H ₄	H	—	187, 758
4-CH ₃ OC ₆ H ₄	H	—	758
4-CH ₃ OC ₆ H ₄	H	—	169
4-CH ₃ OC ₆ H ₄	H	—	759
4-CH ₃ OC ₆ H ₄	H	—	180
4-CH ₃ OC ₆ H ₄	H	—	180
4-CH ₃ OC ₆ H ₄	H	72	180
4-CH ₃ OC ₆ H ₄	H	86	169, 180
4-CH ₃ OC ₆ H ₄	H	—	195
4-CH ₃ OC ₆ H ₄	H	—	199
4-CH ₃ OC ₆ H ₄	H	—	89
4-CH ₃ OC ₆ H ₄	D	—	806
2-CH ₃ O-5-BrC ₆ H ₃	H	75	807 ^{t,u}
4-CH ₃ O-3-FC ₆ H ₃	H	—	808
4-CH ₃ O-3-ClC ₆ H ₃	H	—	809
4-CH ₃ O-3,5-I ₂ C ₆ H ₂	H	—	792 ^u
2-CH ₃ O-5-O ₂ NC ₆ H ₃	H	59	810
4-CH ₃ O-5-O ₂ NC ₆ H ₃	H	93	323
3-CH ₃ O-4-AcOC ₆ H ₃	H	—	91, 414, 421, 667, 750
3-CH ₃ O-4-AcOC ₆ H ₃	Br	—	811
		52	327 ^b
3-CH ₃ O-4-AcOC ₆ H ₃	H	—	756
3-CH ₃ O-4-AcOC ₆ H ₃	H	—	764
3-CH ₃ O-4-AcOC ₆ H ₃	H	80	615a, 72, 422
		—	158, 160, 414, 790, 621, 667, 668, 329, 262 ⁱ
3-CH ₃ O-4-AcOC ₆ H ₃	H	51	180
3-CH ₃ O-4-AcOC ₆ H ₃	H	58	180
3-CH ₃ O-4-AcOC ₆ H ₃	H	71	180
3-CH ₃ O-4-AcOC ₆ H ₃	H	61	422
3-CH ₃ O-4-AcOC ₆ H ₃	H	—	167
3-CH ₃ O-4-AcOC ₆ H ₃	H	—	789
3-CH ₃ O-4-AcOC ₆ H ₃	H	—	789

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	4-CH ₃ O-3-HOC ₆ H ₃ CHO (isovanillin)	2-Nitrohippuric acid 3-Nitrohippuric acid 4-Nitrohippuric acid	C ₆ H ₅ 2-O ₂ NC ₆ H ₄ 3-O ₂ NC ₆ H ₄ 4-O ₂ NC ₆ H ₄
	4-CH ₃ O-2-HOC ₆ H ₃ CHO		C ₆ H ₅
	3-CH ₃ O-2-HOC ₆ H ₃ CHO		C ₆ H ₅
	5-CH ₃ O-2-HOC ₆ H ₃ CHO		C ₆ H ₅
	2-O ₂ N-3-HO-4-CH ₃ OC ₆ H ₂ CHO 2-O ₂ N-3-CH ₃ O-4-HOC ₆ H ₂ CHO	Aceturic acid Aceturic acid	CH ₃ CH ₃
			C ₆ H ₅
	3-CH ₃ O-4-HO-5-ClC ₆ H ₂ CHO	Aceturic acid	CH ₃
	3-CH ₃ O-4,5(HO) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	3-CH ₃ O-4-HO-6-ClC ₆ H ₂ CHO		C ₆ H ₅
	3-CH ₃ O-4-HO-2,6-Cl ₂ C ₆ HCHO		C ₆ H ₅
	4-CH ₃ O-3-HO-2-BrC ₆ H ₂ CHO		C ₆ H ₅
	4-CH ₃ O-5-HO-3-BrC ₆ H ₂ CHO		C ₆ H ₅
	3-CH ₃ O-4-HO-5-BrC ₆ H ₂ CHO	Aceturic acid	CH ₃ C ₆ H ₅
	3-CH ₃ O-4-HO-6-BrC ₆ H ₂ CHO	4-Bromohippuric acid Aceturic acid	4-BrC ₆ H ₄ CH ₃
			C ₆ H ₅
	3-CH ₃ O-4-HO-2,6-Br ₂ C ₆ HCHO	4-Bromohippuric acid	4-BrC ₆ H ₄
	3-CH ₃ O-4-HO-5,6-Br ₂ C ₆ HCHO		C ₆ H ₅
	3-CH ₃ O-4-HO-2,5,6-Br ₃ C ₆ CHO	4-Bromohippuric acid	4-BrC ₆ H ₄
			C ₆ H ₅
	3-CH ₃ O-4-HO-5-IC ₆ H ₂ CHO	4-Bromohippuric acid Aceturic acid	4-BrC ₆ H ₄ CH ₃
			C ₆ H ₅
	3-CH ₃ O-4-HO-6-IC ₆ H ₂	4-Benzyloxyhippuric acid	4-C ₆ H ₅ -CH ₂ OC ₆ H ₄
	3,4-OCH ₂ OC ₆ H ₃ CHO	Aceturic acid Aceturic acid	CH ₃ CH ₃
		Diethylaceturic acid	(C ₂ H ₅) ₂ CH
		α-(p-Xenyl)ethylaceturic acid	C ₂ H ₅ CHC ₁₂ H ₉
		Phenaceturic acid	C ₆ H ₅ CH ₂

R^2 ^d	R^3 ^d	Yield Percent	Reference
4-CH ₃ O-3-AcOC ₆ H ₃	H	65	615a
4-CH ₃ O-3-AcOC ₆ H ₃	H	21	180
4-CH ₃ O-3-AcOC ₆ H ₃	H	57	180
4-CH ₃ O-3-AcOC ₆ H ₃	H	67	180
4-CH ₃ O-2-AcOC ₆ H ₃	H	93	812 ^t
		—	489
3-CH ₃ O-2-AcOC ₆ H ₃	H	23, 47	164
		25, 51	440
		—	813
5-CH ₃ O-2-AcOC ₆ H ₃	H	51	814
		—	815
2-O ₂ N-3-AcO-4-CH ₃ OC ₆ H ₂	H	61	200 ^t
2-O ₂ N-3-CH ₃ O-4-AcOC ₆ H ₂	H	62	200 ^u
		—	816 ^u
2-O ₂ N-3-CH ₃ O-4-AcOC ₆ H ₂	H	—	816, 817 ^u
		61	200
3-CH ₃ O-4-AcO-5-ClC ₆ H ₂	H	55	422
3-CH ₃ O-4-AcO-5-ClC ₆ H ₂	H	80	422 ^u
3-CH ₃ O-4,5-(AcO) ₂ C ₆ H ₂	H	—	818
3-CH ₃ O-4-AcO-6-ClC ₆ H ₂	H	68	422
3-CH ₃ O-4-AcO-2,6-Cl ₂ C ₆ H	H	62	422
4-CH ₃ O-3-AcO-2-BrC ₆ H ₂	H	67	819 ^q
4-CH ₃ O-5-AcO-3-BrC ₆ H ₂	H	63	820 ^{q,u}
3-CH ₃ O-4-AcO-5-BrC ₆ H ₂	H	72	422
3-CH ₃ O-4-AcO-5-BrC ₆ H ₂	H	62	422 ^u
		71	821 ^t
3-CH ₃ O-4-AcO-5-BrC ₆ H ₂	H	65	422
3-CH ₃ O-4-AcO-6-BrC ₆ H ₃	H	—	422
3-CH ₃ O-4-AcO-6-BrC ₆ H ₂	H	73	821 ^t
3-CH ₃ O-4-AcO-6-BrC ₆ H ₂	H	62	422
3-CH ₃ O-4-AcO-2,6-Br ₂ C ₆ H ₅	H	51	422
3-CH ₃ O-4-AcO-5,6-Br ₂ C ₆ H	H	62	422
3-CH ₃ O-4-AcO-2,5-6C ₆	H	28	422
3-CH ₃ O-4-AcO-2,5-6C ₆ l	H	62	422
3-CH ₃ O-4-AcO-5-IC ₆ H ₂	H	86	437
3-CH ₃ O-4-AcO-5-IC ₆ H ₂	H	71	422
3-CH ₃ O-4-AcO-5-IC ₆ H ₂	H	—	822 ^x
3-CH ₃ O-4-AcO-6-IC ₆ H ₂	H	27	422
3,4-OCH ₂ OC ₆ H ₃	H	—	823, 824, 825, 826, 414, 323, 621
3,4-OCH ₂ OC ₆ H ₃	H	—	414, 756, 826
		75	562
3,4-OCH ₂ OC ₆ H ₃	H	—	764
3,4-OCH ₂ OC ₆ H ₃	H	—	827 ^q

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
			C ₆ H ₅ C ₆ H ₅
		4-Methylhippuric acid	4-CH ₃ C ₆ H ₄
		2-Acetoxyhippuric acid	2-AcOC ₆ H ₄
		2-Acetoxy-3-methyl- hippuric acid	2-AcO-3-MeC ₆ H ₃
	3,4-OCH ₂ OC ₆ H ₃ CHO	2,4-Dichlorohippuric acid	2,4-Cl ₂ C ₆ H ₃
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		4-Acetamidohippuric acid	4-AcNHC ₆ H ₄
		3,4,5-Trimethoxyhippuric acid	3,4,5-(CH ₃ O)C ₆ H ₂
	3,4-OCH ₂ O-6-NO ₂ C ₆ H ₂ CHO	Cinnamoylglycine	C ₆ H ₅ CH=CH C ₆ H ₅
	3-CH ₂ OH-4-HOC ₆ H ₃ CHO	Aceturic acid	CH ₃ C ₆ H ₅
	2,4-(HO ₂ -6-CH ₃ C ₆ H ₂ CHO)		C ₆ H ₅
	4-CH ₃ SO ₂ C ₆ H ₄ CHO		C ₆ H ₅
	4-CH ₃ SO ₂ C ₆ H ₄ CHO		C ₆ H ₅
	2-CO ₂ HC ₆ H ₄ CHO		C ₆ H ₅
	2-CH ₃ CONHSO ₂ C ₆ H ₄ CHO		C ₆ H ₅
9	3,4-OCH ₂ CH ₂ OC ₆ H ₃ CHO		C ₆ H ₅
	3,4-OCH ₂ CH ₂ O-6-BrC ₆ H ₂ CHO		C ₆ H ₅
	2-CH ₃ OCH ₂ OC ₆ H ₄ CHO		C ₆ H ₅
	4-CH ₃ OCH ₂ OC ₆ H ₄ CHO		C ₆ H ₅
	5-CH ₃ O-3,4-OCH ₂ OC ₆ H ₂ CHO		C ₆ H ₅
	2-CH ₃ O-4,5-OCH ₂ OC ₆ H ₂ CHO		C ₆ H ₅
	2-CH ₃ O-3,4-OCH ₂ OC ₆ H ₂ CHO		C ₆ H ₅
	3,5-(CH ₃) ₂ -4-HOC ₆ H ₂ CHO		C ₆ H ₅
	3,5-(CH ₃) ₂ -4-O ₂ NC ₆ H ₂ CHO		C ₆ H ₅
	3,5-(CH ₃) ₂ -4-IC ₆ H ₂ CHO		C ₆ H ₅
	2-CH ₃ -3-CH ₃ O-4-HOC ₆ H ₂ CHO		C ₆ H ₅
	5-CH ₃ -3-CH ₃ O-2-HOC ₆ H ₂ CHO		C ₆ H ₅
	5-CH ₃ -3-CH ₃ O-4-HOC ₆ H ₂ CHO		C ₆ H ₅
	2-CH ₃ O-3-CH ₃ C ₆ H ₃ CHO		C ₆ H ₅
	2-CH ₃ O-4-CH ₃ C ₆ H ₃ CHO		C ₆ H ₅
	2-CH ₃ O-5-CH ₃ C ₆ H ₃ CHO		C ₆ H ₅
	2-CH ₃ O-6-CH ₃ C ₆ H ₃ CHO		C ₆ H ₅
	4-CH ₃ O-2-CH ₃ C ₆ H ₃ CHO		C ₆ H ₅
	2-HO-4,6-(CH ₃ O) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	2-HO-3,4-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	2-HO-3,5-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	2-HO-3,6-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅

R^{2d}	R^{3d}	Yield Percent	Reference
3,4-OCH ₂ OC ₆ H ₃	H	—	211
3,4-OCH ₂ OC ₆ H ₃	Br	68	430
		21	326 ^b
3,4-OCH ₂ OC ₆ H ₃	H	—	759
3,4-OCH ₂ OC ₆ H ₃	H	—	759
3,4-OCH ₂ OC ₆ H ₃	H	—	195
3,4-OCH ₂ OC ₆ H ₃	H	—	759
3,4-OCH ₂ OC ₆ H ₃	H	35	180
3,4-OCH ₂ OC ₆ H ₃	H	69	180
3,4-OCH ₂ OC ₆ H ₃	H	71	180
3,4-OCH ₂ OC ₆ H ₃	H	—	167
3,4-OCH ₂ OC ₆ H ₃	H	—	176, 561, 750
3,4-OCH ₂ OC ₆ H ₃	H	—	789
3,4-OCH ₂ O-6-O ₂ NC ₆ H ₂	H	75	562
		97	323
3-CH ₂ OAc-4-AcOC ₆ H ₃	H	81	828 ^q
3-CH ₂ OAc-4-AcOC ₆ H ₃	H	74	828 ^q
2,4-(AcO) ₂ -6-CH ₃ C ₆ H ₂	H	45	829 ^q
4-CH ₃ SO ₃ C ₆ H ₄	H	—	830 ^q
4-CH ₃ SO ₂ C ₆ H ₄	H	—	831 ^q
2-HO ₂ CC ₆ H ₄	H	77	832, 833 ^u
2-AcNHSO ₂ C ₆ H ₄	H	62	830 ^q
3,4-OCH ₂ CH ₂ OC ₆ H ₃	H	67	463 ^{t,u}
3,4-OCH ₂ CH ₂ O-6-BrC ₆ H ₂	H	66	464 ^{t,u}
2-CH ₃ OCH ₂ OC ₆ H ₄	H	—	787
4-CH ₃ OCH ₂ OC ₆ H ₄	H	—	787
5-CH ₃ O-3,4-OCH ₂ OC ₆ H ₂	H	—	489
2-CH ₃ O-4,5-OCH ₂ OC ₆ H ₂	H	—	834 ^{t,u}
2-CH ₃ O-3,4-OCH ₂ OC ₆ H ₂	H	—	471 ^w
3,5-(CH ₃) ₂ -4-AcOC ₆ H ₂	H	—	835 ^q
3,5-(CH ₃) ₂ -4-O ₂ NC ₆ H ₂	H	—	835 ^q
3,5-(CH ₃) ₂ -4-IC ₆ H ₂	H	—	835 ^q
2-CH ₃ -3CH ₃ O-4-AcOC ₆ H ₂	H	—	836
5-CH ₃ -3CH ₃ O-2-AcOC ₆ H ₂	H	—	836 ^q
3-CH ₃ O-4-AcO-5-CH ₃ C ₆ H ₂	H	—	837 ^q
2-CH ₃ O-3-CH ₃ -C ₆ H ₃	H	61	166 ^q
2-CH ₃ O-4-CH ₃ C ₆ H ₃	H	51	166 ^q
		—	559
2-CH ₃ O-5-CH ₃ C ₆ H ₃	H	45	166 ^q
2-CH ₃ O-6-CH ₃ C ₆ H ₃	H	49	166 ^q
4-CH ₃ O-2-CH ₃ C ₆ H ₃	H	—	457 ^t
		—	812
2-AcO-4,6-(CH ₃ O) ₂ C ₆ H ₂	H	—	461
2-AcO-3,4-(CH ₃) ₂ C ₆ H ₂	H	—	664 ^t
2-AcO-3,5-(CH ₃) ₂ C ₆ H ₂	H	—	664
2-AcO-3,6-(CH ₃) ₂ C ₆ H ₂	H	—	664 ^t

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	3-HO-2,4-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	3-HO-4,6-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	4-HO-3-CH ₃ COC ₆ H ₃ CHO		C ₆ H ₅
	4-HO-2,3-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	4-HO-2,5-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	4-HO-2,6-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	4-HO-3,5-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	2,3-(CH ₃ O) ₂ C ₆ H ₃ CHO		C ₆ H ₅
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
	2,4-(CH ₃ O) ₂ C ₆ H ₃ CHO		C ₆ H ₅
		α-(p-Xenyl)ethylaceturic acid	C ₂ H ₅ CHC ₁₂ H ₉
	2,5-(CH ₃ O) ₂ C ₆ H ₃ CHO	Aceturic acid	CH ₃
	2,6-(CH ₃ O) ₂ C ₆ H ₃ CHO		C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅
	3,4-(CH ₃ O) ₂ C ₆ H ₃ CHO	Aceturic acid	CH ₃
		Diethylaceturic acid	(C ₂ H ₅) ₂ CH
		α-Ethylphenaceturic acid	C ₆ H ₅ CHC ₆ H ₅
		3,4-Dimethoxyphenaceturic acid	3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂
			C ₆ H ₅
			C ₆ H ₅
		2-Acetoxyhippuric acid	2-AcOC ₆ H ₄
		4-Methylhippuric acid	4-CH ₃ C ₆ H ₄
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		2,4-Dichlorohippuric acid	2,4-Cl ₂ C ₆ H ₃
		2-Acetoxy-3-methylhippuric acid	2-AcO-3-CH ₃ C ₆ H ₃
		3,4-Dimethoxyhippuric acid	3,4-(CH ₃ O) ₂ C ₆ H ₃
	3,4-(CH ₃ O) ₂ -2-ClC ₆ H ₂ CHO		C ₆ H ₅
	3,4-(CH ₃ O) ₂ -5-ClC ₆ H ₂ CHO	Aceturic acid	CH ₃

R ^{2d}	R ^{3d}	Yield Percent	Reference
3-AcO-2,4-(CH ₃) ₂ C ₆ H ₂	H	—	664
H	3-AcO-2,4-(CH ₃) ₂ C ₆ H ₂	—	664 ^y
3-AcO-4,6-(CH ₃) ₂ C ₆ H ₂	H	—	664
4-HO-3-CH ₃ COC ₆ H ₃	H	—	838
4-AcO-2,3-(CH ₃) ₂ C ₆ H ₂	H	—	664
H	4-AcO-2,3-(CH ₃) ₂ C ₆ H ₂	—	664 ^y
4-AcO-2,5-(CH ₃) ₂ C ₆ H ₂	H	—	664 ^t
H	4-AcO-2,5-(CH ₃) ₂ C ₆ H ₂	—	664 ^y
4-AcO-2,6-(CH ₃) ₂ C ₆ H ₂	H	—	664
4-AcO-3,5-(CH ₃) ₂ C ₆ H ₂	H	—	664, 838
H	4-AcO-3,5-(CH ₃) ₂ C ₆ H ₂	—	664 ^y
2,3-(CH ₃ O) ₂ C ₆ H ₃	H	68	164 ^q
		—	664, 180
2,3-(CH ₃ O) ₂ C ₆ H ₃	H	19	180
2,3-(CH ₃ O) ₂ C ₆ H ₃	H	68	180
2,3-(CH ₃ O) ₂ C ₆ H ₃	H	72	180
2,4-(CH ₃ O) ₂ C ₆ H ₃	H	77	164 ^q
2,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	764
2,5-(CH ₃ O) ₂ C ₆ H ₃	H	—	839
2,5-(CH ₃ O) ₂ C ₆ H ₃	H	75	161, 814
2,6-(CH ₃ O) ₂ C ₆ H ₃	H	31	164 ^q
H	2,6-(CH ₃ O) ₂ C ₆ H ₃	10	164
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	414
		—	824, 825
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	756
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	756
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	840
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	65	343
		—	61, 621, 841, 211, 758
		67	262 ^t
		94	842
H	3,4-(CH ₃ O) ₂ C ₆ H ₃	—	676 ⁿ
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	759
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	759
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	34	180
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	63	180
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	63	180, 843
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	759
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	195
3,4-(CH ₃ O) ₂ C ₆ H ₃	H	—	560
		73	840
3,4-(CH ₃ O) ₂ -2-ClC ₆ H ₂	H	99	454 ^t
3,4-(CH ₃ O) ₂ -5-ClC ₆ H ₂	H	70	422

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
			C ₆ H ₅
	3,4-(CH ₃ O) ₂ -6-ClC ₆ H ₂ CHO		C ₆ H ₅
	3,4-(CH ₃ O) ₂ -5-BrC ₆ H ₂ CHO	Aceturic acid	CH ₃
	3,4-(CH ₃ O) ₂ -2-O ₂ NC ₆ H ₂ CHO	Aceturic acid	CH ₃
			C ₆ H ₅
	3,4-(CH ₃ O) ₂ -6-O ₂ NC ₆ H ₂ CHO	Aceturic acid	CH ₃
			C ₆ H ₅
	3,5-(CH ₃ O) ₂ C ₆ H ₃ CHO	Aceturic acid	CH ₃
			C ₆ H ₅
	2-C ₂ H ₅ OC ₆ H ₄ CHO		C ₆ H ₅
	3-F-4-C ₂ H ₅ OC ₆ H ₃ CHO	4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
	4-(CH ₃) ₂ NC ₆ H ₄ CHO		C ₆ H ₅
		2-Acetoxyhippuric acid	C ₆ H ₅
		2-Hydroxyhippuric acid	2-AcOC ₆ H ₄
		3-Hydroxyhippuric acid	2-AcOC ₆ H ₄
		4-Hydroxyhippuric acid	3-AcOC ₆ H ₄
		4-Methylhippuric acid	4-AcOC ₆ H ₄
		3-Methoxyhippuric acid	4-CH ₃ C ₆ H ₄
		4-Methoxyhippuric acid	3-CH ₃ OC ₆ H ₄
		4-Acetamidohippuric acid	4-CH ₃ OC ₆ H ₄
		3,4-Dimethoxyhippuric acid	4-AcNHC ₆ H ₄
		3,4-Methylenedioxyhippuric acid	3,4-(CH ₃ O) ₂ C ₆ H ₃
		3-Methoxy-4-hydroxyhippuric acid	3,4-OCH ₂ OC ₆ H ₃
		2,4-Dichlorohippuric acid	3-CH ₃ O-4-AcOC ₆ H ₃
		3,4,5-Trimethoxyhippuric acid	acid
		Cinnamoylglycine	2,4-Cl ₂ C ₆ H ₃
		4-Methoxycinnamoylglycine	3,4,5-(CH ₃ O) ₃ C ₆ H ₂
		3,4-Dimethoxycinnamoylglycine	acid
		3,4-Methylenedioxy-cinnamoylglycine	C ₆ H ₅ CH=CH
		2-Acetoxy-3-methyl-cinnamoylglycine	4-CH ₃ OC ₆ H ₄ CH=CH
		5-Phenyl-2,4-pentadienoylglycine	3,4-(CH ₃ O) ₂
			C ₆ H ₃ CH=CH
			3,4-OCH ₂ O
			C ₆ H ₃ CH=CH
			2-AcO-3-CH ₃ -
			C ₆ H ₃ CH=CH
			C ₆ H ₅ CH=CH-
			CH=CH
			C ₆ H ₅
			CH ₃
	4-(CH ₃) ₂ N-3-O ₂ NC ₆ H ₃ CHO		
	C ₆ H ₅ CH=CHCHO	Aceturic acid	

R^{2d}	R^{3d}	Yield Percent	Reference
3,4-(CH ₃ O) ₂ -5-ClC ₆ H ₂	H	79	447 ^t
		94	454 ^t
3,4-(CH ₃ O) ₂ -6-ClC ₆ H ₂	H	91	821
3,4-(CH ₃ O) ₂ -5-BrC ₆ H ₂	H	70	416
3,4-(CH ₃ O) ₂ -2-O ₂ NC ₆ H ₂	H	—	300
3,4-(CH ₃ O) ₂ -2-O ₂ NC ₆ H ₂	H	37	819
		100	323 ^z
3,4-(CH ₃ O) ₂ -6-O ₂ NC ₆ H ₂ CHO	H	—	843
3,4-(CH ₃ O) ₂ -6-O ₂ NC ₆ H ₂ CHO	H	—	562, 563 ^w
		—	843
3,5-(CH ₃ O) ₂ C ₆ H ₃	H	—	164 ^a , 829
3,5-(CH ₃ O) ₂ C ₆ H ₃	H	—	479 ^a
		—	829 ^w
2-C ₂ H ₅ OC ₆ H ₄	H	—	843
3-F-4-C ₂ H ₅ OC ₆ H ₃	H	—	844
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171, 220, 845, 620, 621, 569
		65	649
		86	266, 955, 615 ^q
H	4-(CH ₃) ₂ NC ₆ H ₄	—	620
4-(CH ₃) ₂ NC ₆ H ₄	H	—	759
4-(CH ₃) ₂ NC ₆ H ₄	H	—	172
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171, 172
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171, 172
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171, 172
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	167, 321
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171, 172
4-(CH ₃) ₂ NC ₆ H ₄	H	—	759
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171, 172, 177, 178
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄	H	—	195
4-(CH ₃) ₂ NC ₆ H ₄	H	—	171
4-(CH ₃) ₂ N-3-O ₂ NC ₆ H ₃	H	—	847
C ₆ H ₅ CH=CH	H	—	77

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
10	4-O ₂ NC ₆ H ₄ CH=CHCHO 2-O ₂ NC ₆ H ₄ CH=CHCHO	Phenaceturic acid	C ₆ H ₅ CH ₂ C ₆ H ₅
		2-Acetoxyhippuric acid	2-AcOC ₆ H ₄
		4-Methylhippuric acid	4-CH ₃ C ₆ H ₄
		4-Acetamidohippuric acid	4-AcNHC ₆ H ₄
		2,4-Dichlorohippuric acid	2,4-Cl ₂ C ₆ H ₄
		2-Acetoxy-3-methylhippuric acid	2-AcO-3-CH ₃ C ₆ H ₃
	2,3,4-(CH ₃ O) ₃ C ₆ H ₂ CHO 2,4,5-(CH ₃ O) ₃ C ₆ H ₂ CHO 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ CHO	Phenaceturic acid	C ₆ H ₅ C ₆ H ₅ CH ₂ C ₆ H ₅
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		2-Chlorohippuric acid	2-ClC ₆ H ₄
		4-Chlorohippuric acid	4-ClC ₆ H ₄
		4-Methoxyhippuric acid	4-CH ₃ OC ₆ H ₄
		3,4-Methylenedioxy-hippuric acid	3,4OCH ₂ OC ₆ H ₃
		3,5-Dinitrohippuric acid	3,5(O ₂ N) ₂ C ₆ H ₃
		Cinnamoylglycine	C ₆ H ₅ CH=CH
	2,4,6-(CH ₃ O) ₃ -3-ClC ₆ H ₂ CHO 2,4-(CH ₃ O) ₂ -3-CH ₃ C ₆ H ₂ CHO 2,4-(CH ₃ O)-5-CH ₃ C ₆ H ₂ CHO 2,4-(CH ₃ O) ₂ -6-CH ₃ C ₆ H ₂ CHO 2,5-(CH ₃ O) ₂ -4-CH ₃ C ₆ H ₂ CHO	Aceturic acid	CH ₃ C ₆ H ₅ CH ₃ C ₆ H ₅ 3,4,5-(CH ₃ O) ₃ C ₆ H ₂
		Aceturic acid	CH ₃
		3,4,5-Trimethoxy-hippuric acid	
		Aceturic acid	CH ₃
	3,4-(CH ₃ O) ₂ -2-CH ₃ C ₆ H ₂ CHO 3,5-(CH ₃ O) ₂ -4-CH ₃ C ₆ H ₂ CHO 4,5-(CH ₃ O) ₂ -2-CH ₃ C ₆ H ₂ CHO 2-CH ₃ O-4-C ₂ H ₅ OC ₆ H ₃ CHO 3-CH ₃ O-4-C ₂ H ₅ OC ₆ H ₃ CHO	2-Nitrohippuric acid	C ₆ H ₅ 2-O ₂ NC ₆ H ₄ 3-O ₂ NC ₆ H ₄ 4-O ₂ NC ₆ H ₄ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ CH ₃
		3-Nitrohippuric acid	
		4-Nitrohippuric acid	
		Aceturic acid	

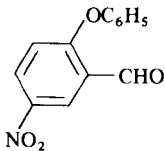
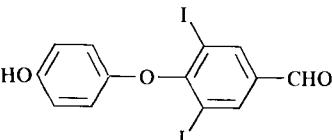
R ^{2d}	R ^{3d}	Yield Percent	Reference
C ₆ H ₅ CH=CH	H	25	848
C ₆ H ₅ CH=CH	H	34	169
C ₆ H ₅ CH=CH	H	—	262
C ₆ H ₅ CH=CH	H	—	759
C ₆ H ₅ CH=CH	H	—	167
C ₆ H ₅ CH=CH	H	—	759
C ₆ H ₅ CH=CH	H	—	195
4-O ₂ NC ₆ H ₄ CH=CH	H	—	740
2-O ₂ NC ₆ H ₄ CH=CH	H	35	849
2-O ₂ NC ₆ H ₄ CH=CH	H	—	849
2-O ₂ NC ₆ H ₄ CH=CH	H	22	849
2-O ₂ NC ₆ H ₄ CH=CH	H	67	849
2-O ₂ NC ₆ H ₄ CH=CH	H	80	849
2-O ₂ NC ₆ H ₄ CH=CH	H	18	849
2-O ₂ NC ₆ H ₄ CH=CH	H	79	849
2-O ₂ NC ₆ H ₄ CH=CH	H	76	849
2-O ₂ NC ₆ H ₄ CH=CH	H	55	849
2-O ₂ NC ₆ H ₄ CH=CH	H	38	849
2-O ₂ NC ₆ H ₄ CH=CH	H	60	849
2,3,4-(CH ₃ O) ₃ C ₆ H ₂	H	—	177, 178
2,3,4-(CH ₃ O) ₃ C ₆ H ₂	H	—	850 ^t
2,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	—	177, 178, 444
2,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	—	444
2,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	—	177, 178
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	71	462
		—	851, 852
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	—	180, 432 ^t , 853
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	28	180
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	50	180
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	H	54	180
2,4,6-(CH ₃ O) ₃ -3-ClC ₆ H	H	—	467 ^{t,u}
2,4-(CH ₃ O) ₂ -3-CH ₃ C ₆ H ₂	H	59	824 ^q
2,4-(CH ₃ O) ₂ -5-CH ₃ C ₆ H ₂	H	80	824 ^q
2,4-(CH ₃ O) ₂ -6-CH ₃ C ₆ H ₂	H	74	824 ^q
2,5-(CH ₃ O) ₂ -4-CH ₃ C ₆ H ₂	H	32	448b
		—	839
2,5-(CH ₃ O) ₂ -4-CH ₃ C ₆ H ₂	H	55	448b
3,4-(CH ₃ O) ₂ -2-CH ₃ C ₆ H ₂	H	—	837, 839
3,5-(CH ₃ O) ₂ -4-CH ₃ C ₆ H ₂	H	—	479
3,5-(CH ₃ O) ₂ -4-CH ₃ C ₆ H ₂	H	—	479
4,5-(CH ₃ O) ₂ -2-CH ₃ C ₆ H ₂	H	72	675, 677 ^q
2-CH ₃ O-4-C ₂ H ₅ OC ₆ H ₃	H	75	453 ^t
		—	664 ^t
3-CH ₃ O-4-C ₂ H ₅ OC ₆ H ₃	H	75	453 ^t
		—	664 ^t

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
	4-CH ₃ O-2-C ₂ H ₅ OC ₆ H ₃ CHO		C ₆ H ₅
	4-CH ₃ -2-C ₂ H ₅ OC ₆ H ₃ CHO		C ₆ H ₅
	3-CH ₂ =CH-CH ₂ -4-HOC ₆ H ₃ CHO		C ₆ H ₅
	4-C ₂ H ₅ CO ₂ C ₆ H ₄ CHO		C ₆ H ₅
	3,4-(CH ₃ O) ₂ -2-CO ₂ HC ₆ H ₂ CHO		C ₆ H ₅
	3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃ CHO		C ₆ H ₅
	4-NCCH ₂ N(CH ₃)C ₆ H ₄ CHO		C ₆ H ₅
		4-Methoxyhippuric acid	4-CH ₃ OC ₆ H ₄
		2-Chlorohippuric acid	2-ClC ₆ H ₄
		4-Chlorohippuric acid	4-ClC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		Cinnamoylglycine	C ₆ H ₅ CH=CH C ₆ H ₅
	4-(CH ₃) ₂ CHC ₆ H ₄ CHO		
11	1-C ₁₀ H ₇ CHO	4-Methoxyhippuric acid	4-CH ₃ OC ₆ H ₄
		Aceturic acid	CH ₃
		Diethylaceturic acid	(C ₂ H ₅) ₂ CH C ₆ H ₅
			C ₆ H ₅
	2-C ₁₀ H ₇ CHO	Aceturic acid	CH ₃ C ₆ H ₅
	3-Cl-2-C ₁₀ H ₇ CHO	Aceturic acid	C ₆ H ₅ CH ₃
			C ₆ H ₅
	2,4-(CH ₃ O) ₂ -5-C ₂ H ₅ C ₆ H ₂ CHO		C ₆ H ₅
	3,4-(CH ₃ O) ₂ -2-C ₂ H ₅ C ₆ H ₂ CHO		C ₆ H ₅
	4,5-(CH ₃ O) ₂ -2-C ₆ H ₅ C ₆ H ₂ CHO		C ₆ H ₅
	2,4-(C ₂ H ₅ O) ₂ C ₆ H ₃ CHO		C ₆ H ₅
	3,4-(C ₂ H ₅ O) ₂ C ₆ H ₃ CHO	2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
	3,4-(C ₂ H ₅ O) ₂ -2-O ₂ NC ₆ H ₂ CHO		C ₆ H ₅
	2-C ₂ H ₅ O-3,5-(CH ₃) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	2-C ₂ H ₅ O-5-C ₂ H ₅ C ₆ H ₃ CHO		C ₆ H ₅
	3-CH ₃ O-4-HO-5-CH ₂ CH=CH ₂ C ₆ H ₂ CHO		C ₆ H ₅
	3,4-OCH ₂ O-6-CH ₂ CH=CH ₂ C ₆ H ₂ CHO		C ₆ H ₅
	3-(CH ₃) ₂ CH-4-CH ₃ OC ₆ H ₃ CHO		C ₆ H ₅

R ^{2d}	R ^{3d}	Yield Percent	Reference
3-CH ₃ O-4-C ₂ H ₅ O	H	33	180
3-CH ₃ O-4-C ₂ H ₅ O	H	69	180
3-CH ₃ O-4-C ₂ H ₅ OC ₆ H ₃	H	73	180
4-CH ₃ O-2-C ₂ H ₅ OC ₆ H ₃	H	75	453 ^t
4-CH ₃ -2-C ₂ H ₅ OC ₆ H ₃	H	—	664 ^t
3-CH ₂ =CH-CH ₂ -4-AcOC ₆ H ₃	H	—	790
4-C ₂ H ₅ CO ₂ C ₆ H ₄	H	—	790
3,4-(CH ₃ O) ₂ -2-CO ₂ HC ₆ H ₂	H	—	854, 188
3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃	H	43	832, ^u 833
4-NCCH ₂ N(CH ₃)C ₆ H ₄	H	42	173
3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃	H	67	173
3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃	H	35	173
3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃	H	44	173
3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃	H	52	173
3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃	H	58	173
3-CH ₃ -4-(CH ₃) ₂ NC ₆ H ₃	H	32	173
4-(CH ₃) ₂ CHC ₆ H ₄	H	—	782
		60	776
4-(CH ₃) ₂ CHC ₆ H ₄	H	—	782
1-C ₁₀ H ₇	H	—	761
1-C ₁₀ H ₇	H	—	756
1-C ₁₀ H ₇	H	57	776
		—	474, ^u 761
H	1-C ₁₀ H ₇	—	66 ⁿ
		100	217 ^m
2-C ₁₀ H ₇	H	—	780
2-C ₁₀ H ₇	H	50	776
		—	740
H	2-C ₁₀ H ₇	75	151 ^m
3-Cl-2-C ₁₀ H ₇	H	—	856
		68	853 ^q
3-Cl-2-C ₁₀ H ₇	H	—	415, 857, 858, ^u
		63	859, 860
2,4-(CH ₃ O) ₂ -5-C ₂ H ₅ C ₆ H ₂	H	—	478 ^b
3,4-(CH ₃ O) ₂ -2-C ₂ H ₅ C ₆ H ₂	H	—	819 ^q
4,5-(CH ₃ O) ₂ -2-C ₂ H ₅ C ₆ H ₂	H	57	675, 677 ^q
2,4-(C ₂ H ₅ O) ₂ C ₆ H ₃	H	65	453 ^t
		51	821
3,4-(C ₂ H ₅ O) ₂ C ₆ H ₃	H	34	180
3,4-(C ₂ H ₅ O) ₂ C ₆ H ₃	H	69	180
3,4-(C ₂ H ₅ O) ₂ C ₆ H ₃	H	71	180
3,4-(C ₂ H ₅ O) ₂ -2-O ₂ NC ₆ H ₂	H	90	323
2-C ₂ H ₅ O-3,5-(CH ₃) ₂ C ₆ H ₂	H	—	664 ^t
2-C ₂ H ₅ O-5-C ₂ H ₅ C ₆ H ₃	H	—	425
3-CH ₃ O-4-AcO-5-CH ₂ -CH=CH ₂ C ₆ H ₂	H	—	836
3,4-OCH ₂ O-6-CH ₂ =CH-CH ₂ C ₆ H ₂	H	—	861
3-(CH ₃) ₂ CH-4-CH ₃ OC ₆ H ₃	H	—	862

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
12	5-CH ₃ CH ₂ CH ₂ -2-HO ₃ CH ₃ OC ₆ H ₂ CHO 4-(C ₂ H ₅) ₂ NC ₆ H ₄ CHO	4-Acetamidohippuric acid	C ₆ H ₅ C ₆ H ₅ 4-AcNHC ₆ H ₄
	4(CH ₃) ₂ NC ₆ H ₄ CH=CHCHO		C ₆ H ₅ 3-CH ₃ OC ₆ H ₄
			C ₆ H ₅ 4-CH ₃ OC ₆ H ₄
			C ₆ H ₅ CH=CH
			C ₆ H ₅ CH=CH— CH=CH—
			C ₆ H ₅
	4-(<i>N</i> -Methyl- <i>N</i> -allyl)C ₆ H ₄ CHO	Diethylaceturic acid	C ₆ H ₅
	2-(1'-Pyrrolidyl)C ₆ H ₄ CHO		C ₆ H ₅
	2-(1'-Pyrrolidyl)5-O ₂ NC ₆ H ₃ CHO		C ₆ H ₅
	2-(4'-Morpholinyl)C ₆ H ₄ CHO		C ₆ H ₅
	2-(4'-Morpholinyl)5-O ₂ NC ₆ H ₃ CHO		C ₆ H ₅
	Ferrocenealdehyde		C ₆ H ₅
	3-CH ₃ O-4- <i>n</i> -C ₄ H ₉ OC ₆ H ₃ CHO		C ₆ H ₅
	2-CH ₃ O-1-C ₁₀ H ₆ CHO		(C ₂ H ₅) ₂ CH
	2,3-(CH ₃ O) ₂ -5-CH ₃ CH ₂ CH ₂ C ₆ H ₂ CHO		C ₆ H ₅
	4,5-(CH ₃ O) ₂ -5- <i>i</i> -C ₃ H ₇ C ₆ H ₂ CHO		C ₆ H ₅
	2-(1'-Piperidyl)C ₆ H ₄ CHO		C ₆ H ₅
	4-(1'-Piperidyl)C ₆ H ₄ CHO		C ₆ H ₅
	2-(1'-Piperidyl)-5-O ₂ NC ₆ H ₃ CHO		C ₆ H ₅
	4-(1'-Piperidyl)-3-ClC ₆ H ₃ CHO		C ₆ H ₅
	2-MeO-4-(ClCH ₂ CH ₂) ₂ NC ₆ H ₃ CHO		C ₆ H ₅
	4-HO-3,5-(<i>i</i> -Pr) ₂ C ₆ H ₂ CHO		C ₆ H ₅
	4,5-(CH ₃ O) ₂ -2- <i>t</i> -BuC ₆ H ₂ CHO		C ₆ H ₅
	2-PhCO ₂ C ₆ H ₄ CHO		C ₆ H ₅
	4-C ₆ H ₅ SO ₂ C ₆ H ₄ CHO		C ₆ H ₅
	4-ClC ₆ H ₄ SO ₂ C ₆ H ₄ CHO		C ₆ H ₅
	4-C ₆ H ₅ OC ₆ H ₄ CHO		C ₆ H ₅
		Aceturic acid	CH ₃
			C ₆ H ₅

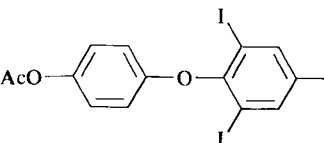
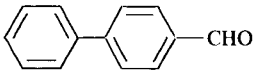
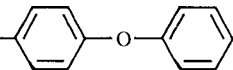
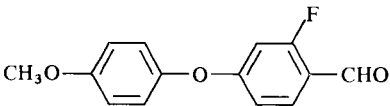
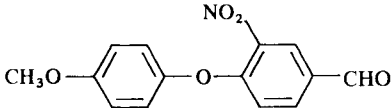
R ^{2d}	R ^{3d}	Yield Percent	Reference
5-CH ₃ CH ₂ CH ₂ -2-AcO-3-CH ₃ OC ₆ H ₃	H	—	836
4-(C ₂ H ₅) ₂ NC ₆ H ₄	H	31	649
4-(C ₂ H ₅) ₂ NC ₆ H ₄	H	75	167
4-(CH ₃) ₂ NC ₆ H ₄ CH=CH	H	—	740
4-(CH ₃) ₂ NC ₆ H ₄ CH=CH	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄ CH=CH	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄ CH=CH	H	—	171
4-(CH ₃) ₂ NC ₆ H ₄ CH=CH	H	—	171
$\begin{array}{c} \text{H}_3\text{C} \\ \diagup \\ \text{CH}_2=\text{CH}-\text{CH}_2-\text{NC}_6\text{H}_4 \end{array}$	H	—	863
2-(1'-C ₄ H ₈ N)C ₆ H ₄	H	82	864
2-(1'-C ₄ H ₈ N)-5-O ₂ NC ₆ H ₃	H	70	864 ^x
2-(4'-C ₄ H ₈ NO)C ₆ H ₄	H	78	864 ^x
2-(4'-C ₄ H ₈ NO)-5-O ₂ NC ₆ H ₃	H	68	864 ^x
1-Ferrocenyl	H	—	865, 866 ^t
3-CH ₃ O-4- <i>n</i> -C ₄ H ₉ OC ₆ H ₃	H	—	867 ^q
2-CH ₃ O-1-C ₁₀ H ₆	H	—	756
2,3-(CH ₃ O) ₂ -5- <i>n</i> -C ₃ H ₇ C ₆ H ₂	H	57	469 ^t
		—	458
4,5-(CH ₃ O) ₂ -5- <i>i</i> -C ₃ H ₇ C ₆ H ₂	H	53	675, 677 ^q
2-(1'-Piperidyl)C ₆ H ₄	H	85	864 ^x
4-(1'-Piperidyl)C ₆ H ₄	H	—	868
2-(1'-Piperidyl)-5-O ₂ NC ₆ H ₃	H	69	864 ^y
4-(1'-Piperidyl)-3-ClC ₆ H ₃	H	—	868
2-MeO-4-(ClCH ₂ CH ₂) ₂ NC ₆ H ₃	H	—	869
4-AcO-3,5-(<i>i</i> -Pr) ₂ C ₆ H ₂	H	49	871
4,5-(CH ₃ O) ₂ -2- <i>t</i> -BuC ₆ H ₂	H	10	675, 677
2-C ₆ H ₅ CO ₂ C ₆ H ₄	H	97	264, 265
4-C ₆ H ₅ SOC ₆ H ₄	H	73	830 ^q
4-ClC ₆ H ₄ SO ₂ C ₆ H ₄	H	60	64 ^q
4-C ₆ H ₅ OC ₆ H ₄	H	—	470 ^t
		56	872
		96	266
2-C ₆ H ₅ O-4-O ₂ NC ₆ H ₃	H	75	455 ^{t,u}
	H	44	793

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
13	2-C ₆ H ₅ C ₆ H ₄ CHO		
			C ₆ H ₅ C ₆ H ₅
	2-(1-Azacycloheptyl)C ₆ H ₄ CHO		C ₆ H ₅
	5-O ₂ N-2(1-Azacyclo-heptyl)C ₆ H ₃ CHO		C ₆ H ₅
	4-(Hexamethyleneimino)C ₆ H ₄ CHO		C ₆ H ₅
	3-Chloro-4-(hexamethyleneimino)C ₆ H ₃ CHO		C ₆ H ₅
	Acenaphthene-5-carboxaldehyde		C ₆ H ₅
	4- <i>N</i> -bis-2'-Chloropropyl)C ₆ H ₄ CHO		C ₆ H ₅
	3-Cl-4-Cyclohexyl-C ₆ H ₃ CHO		C ₆ H ₅
	4-(2',5'-Dichloromethyl-1-pyrroilyl)C ₆ H ₄		C ₆ H ₅
14	3-F ₃ C-4-(1-piperidyl)C ₆ H ₃ CHO		C ₆ H ₅
	CH ₃ O- 		C ₆ H ₅
	CH ₃ O- 		C ₆ H ₅
	CH ₃ O- 	Aceturic acid	CH ₃
			C ₆ H ₅

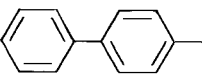
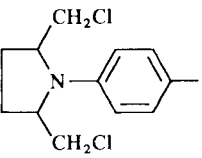
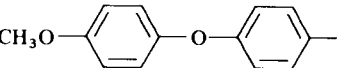
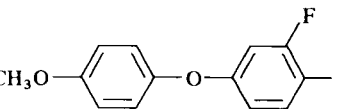
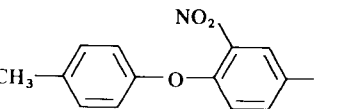
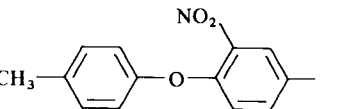
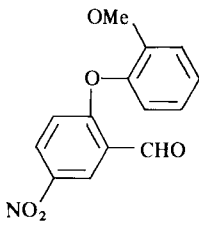
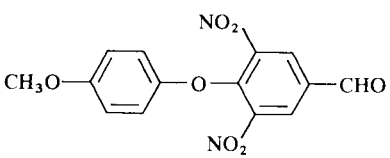
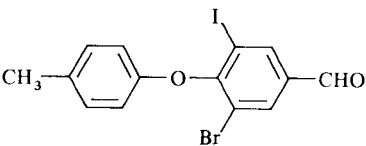
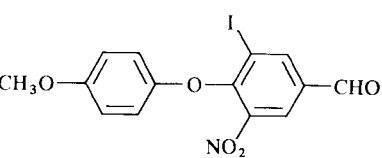
$R^2{}^d$	$R^3{}^d$	Yield Percent	Reference
2-C ₆ H ₅ C ₆ H ₄ 	H	50	593
	H	—	873 ^u
		92	874 ^t
2-(1-Azacycloheptyl)C ₆ H ₄	H	92	864 ^x
5-O ₂ N-2-(1-azacycloheptyl)C ₆ H ₃	H	75	864 ^x
4-(Hexamethyleneimino)C ₆ H ₄	H	—	868
3-Cl-4-(hexamethyleneimino)C ₆ H ₃	H	—	868
5-Acenaphthyl	H	—	711
4-N-(CH ₂ CH ₂ CH ₂) ₂ C ₆ H ₄	H	—	875 ^a
3-Cl-4-C ₆ H ₄ C ₆ H ₃	H	—	876
	H	26	877 ^a
3-F ₃ C-4-(1'-C ₃ H ₁₀ N)C ₆ H ₃	H	—	868
	H	90	830 ^a
	H	—	844 ^a
	H	—	878 ^a
	H	—	792 ^{a, t}

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
		Aceturic acid	CH ₃
	4-PhCH ₂ O-2-TC ₆ H ₃ CHO		C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅
		Aceturic acid	CH ₃
			C ₆ H ₅
		Propionylglycine	C ₂ H ₅

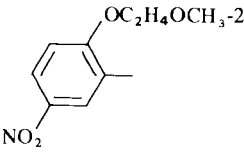
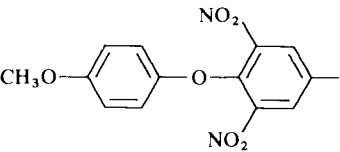
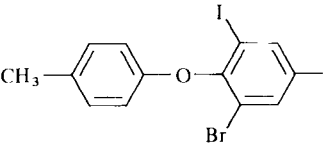
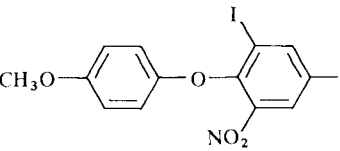
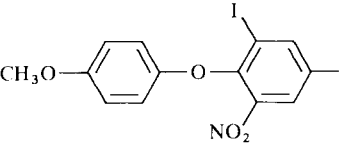
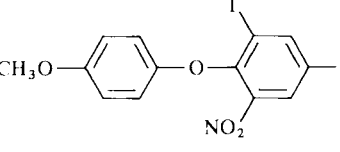
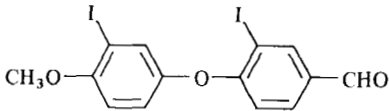
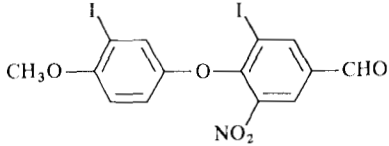
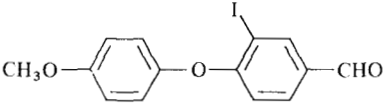
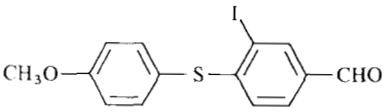
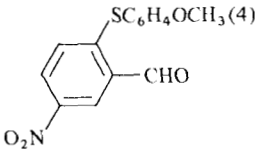
R^{2d}	R^{3d}	Yield Percent	Reference
	H	—	455 ^{t,u}
4-PhCH ₂ O-2-TC ₆ H ₃	H	—	771
	H	45	829
	H	99	879 ^a
	H	—	880, 881 ^a
	H	—	881
	H	—	881

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
		Octadecanoylglycine	<i>n</i> -C ₁₈ H ₃₅
		3-Phenylpropionylglycine	C ₆ H ₅ CH ₂ CH ₂
			C ₆ H ₅
		Aceturic acid	CH ₃
			C ₆ H ₅
			C ₆ H ₅
		Aceturic acid	CH ₃
	2-C ₆ H ₄ CH ₂ OC ₆ H ₄ CHO		C ₆ H ₅

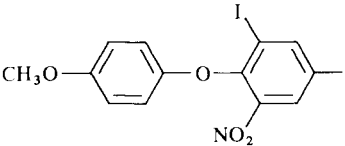
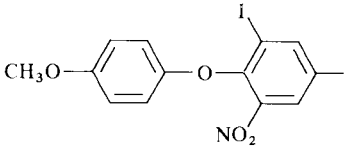
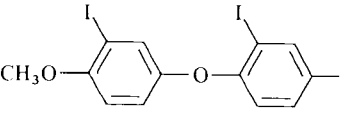
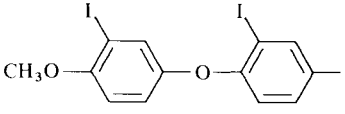
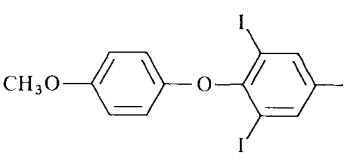
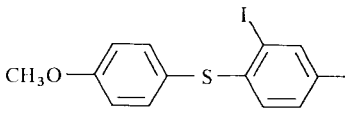
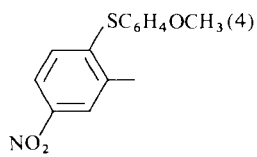
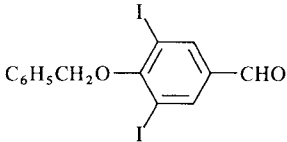
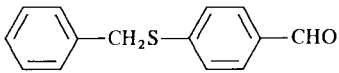
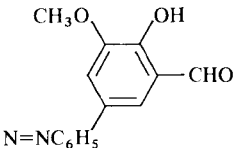
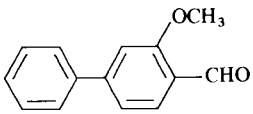
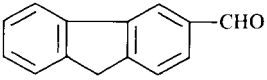
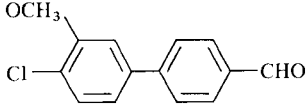
R^{2d}	R^{3d}	Yield Percent	Reference
	H	—	881
	H	—	881
	H	70	879 ^q
	H	—	881
	H	65 — 100	793 882 879 ^q
	H	—	883 ^{aa}
	H	55	434 ^{t,u}
2-C ₆ H ₄ CH ₂ OC ₆ H ₄	H	63	429 ^u

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	4-C ₆ H ₄ CH ₂ OC ₆ H ₄ CHO	Phenaceturic acid	C ₆ H ₅ CH ₂
		2-Nitrophenaceturic acid	2-O ₂ NC ₆ H ₄ CH ₂
	4-C ₆ H ₄ CH ₂ OC ₆ H ₄ CHO		C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅
	3-Trifluoromethyleneimino)C ₆ H ₃ CHO		C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅
	4-C ₆ H ₅ CH ₂ C ₆ H ₄ CHO		C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅

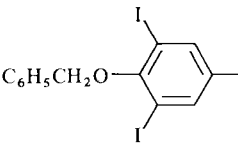
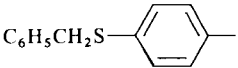
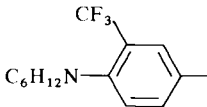
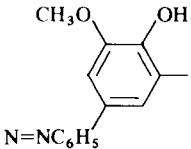
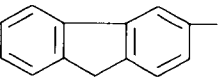
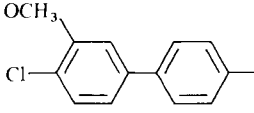
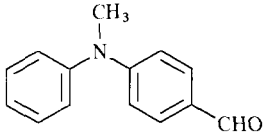
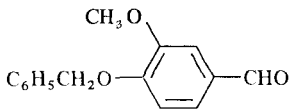
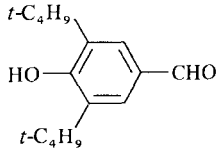
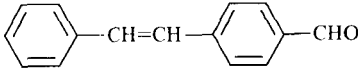
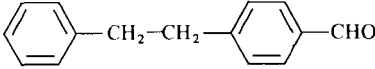
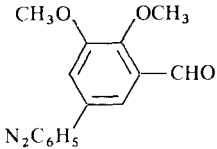
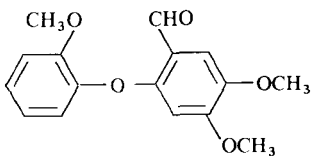
R^{2d}	R^{3d}	Yield Percent	Reference
		—	476 ^q
		—	884 ^u
4-C ₆ H ₄ CH ₂ OC ₆ H ₄	H	—	885
4-C ₆ H ₄ CH ₂ OC ₆ H ₄	H	—	885
4-C ₆ H ₄ CH ₂ OC ₆ H ₄	H	—	785
4-C ₆ H ₄ CH ₂ OC ₆ H ₄	T	70	885
	H	72	793
	H	74	840 ^q
	H	—	868
	H	—	886
4-C ₆ H ₅ -2-CH ₃ OC ₆ H ₃	H	56	872
4-C ₆ H ₅ CH ₂ C ₆ H ₄	H	20	872
	H		
	H	62	872

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
			C ₆ H ₅
			C ₆ H ₅
15		Aceturic acid	CH ₃
			C ₆ H ₅
			C ₆ H ₅
	Anthracene-9-carboxyaldehyde		C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅

R^{2d}	R^{3d}	Yield Percent	Reference
	H	—	522
H		—	522 ^y
	H	—	825 ^a
	H	—	824, 825, ^a 402 ^t
	H	— 60	887, 888 889
9-C ₁₄ H ₉	H	48 —	72 761
	H	—	313
	H	60	872
	H	—	886

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
4-	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C}_6\text{H}_5\text{CH}_2-\text{NC}_6\text{H}_4\text{CHO} \end{array}$		C ₆ H ₅
		2-Chlorohippuric acid	2-ClC ₆ H ₄
		4-Chlorohippuric acid	4-ClC ₆ H ₄
		2-Nitrohippuric acid	2-O ₂ NC ₆ H ₄
		3-Nitrohippuric acid	3-O ₂ NC ₆ H ₄
		3,5-Dinitrohippuric acid	3,5-(O ₂ N) ₂ C ₆ H ₃
		Cinnamoylglycine	C ₆ H ₅ CH=CH
	4-(3-Azabicyclo-[3,3,0] 3',4')- C ₆ H ₄ CHO		C ₆ H ₅
	3-Chloro-4-(3-Azabicyclo-[3,3,0] 3',4')- C ₆ H ₃ CHO		C ₆ H ₅
16			C ₆ H ₅

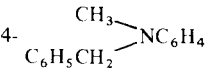
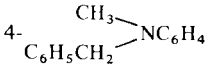
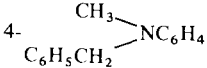
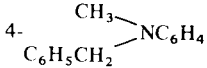
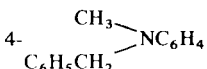
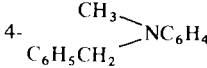
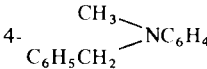
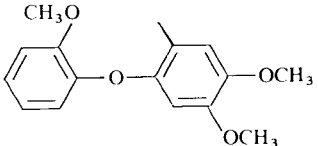
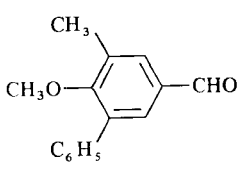
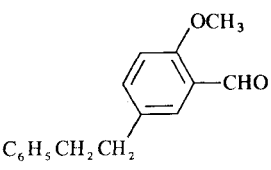
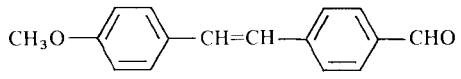
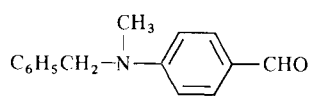
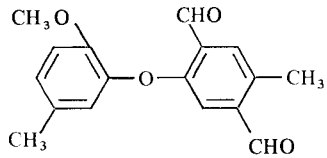
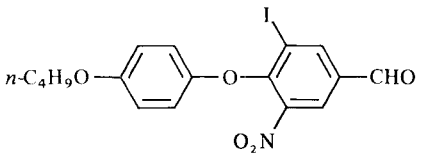
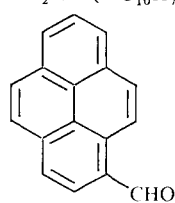
R^{2d}	R^{3d}	Yield Percent	Reference
4- 	H	44	182
4- 	H	42	182
4- 	H	51	182
4- 	H	39	182
4- 	H	57	182
4- 	H	47	182
4- 	H	55	182
4-(3-Azabicyclo-[3,3,0] 3',4')- C ₆ H ₄	H	—	868
3-Cl-4-(3-Azabicyclo-[3,3,0] 3',4')- C ₆ H ₃	H	—	868
	H	—	890

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
			C ₆ H ₅
			C ₆ H ₅
			C ₆ H ₅
	3-F ₃ C-4-[3-Azabicyclo-(3,3,0)-3',4')-C ₆ H ₃ CHO		C ₆ H ₅
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₅
17			C ₆ H ₅
		Aceturic acid	CH ₃
	5-O ₂ N-2-(1'-C ₁₀ H ₇ S)-C ₆ H ₃ CHO	Aceturic acid	CH ₃
	5-O ₂ N-2-(2'-C ₁₀ H ₇ S)-C ₆ H ₃ CHO	Aceturic acid	CH ₃
	 (Pyrene-3-carboxaldehyde)		C ₆ H ₅

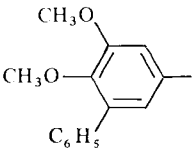
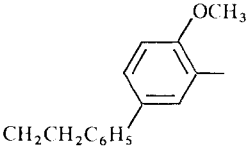
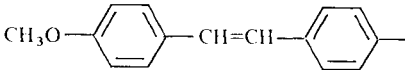
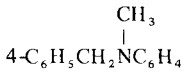
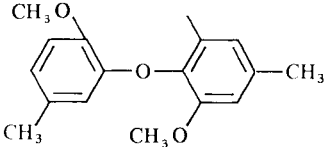
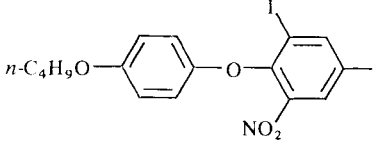
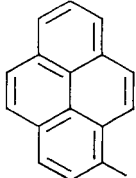
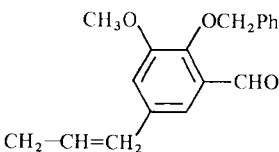
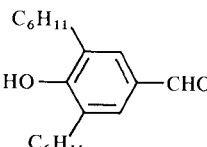
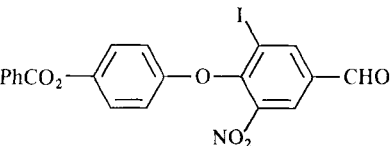
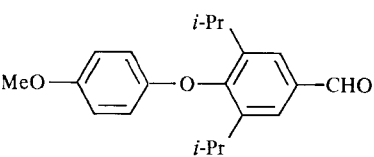
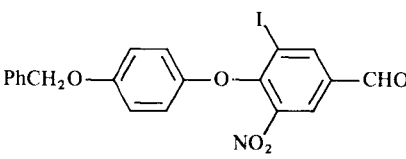
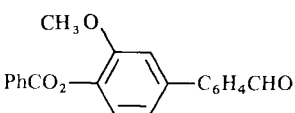
R^{2d}	R^{3d}	Yield Percent	Reference
	H	—	433
	H	—	874
	H	—	872
3-Cl-4-(3-Azabicyclo-[3,3,0]3,4')- C ₆ H ₃	H	—	868
	H	—	855
	H	—	890
	H	—	884
5-O ₂ N-2-(1'-C ₁₀ H ₇ S)-C ₆ H ₃	H	—	434
5-O ₂ N-2-(2'-C ₁₀ H ₇ S)-C ₆ H ₃	H	—	434
	H	—	266

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
18			C ₆ H ₅
19			C ₆ H ₅
		Aceturic acid	CH ₃
	(4-Me ₂ NC ₆ H ₄) ₂ C=CH-CHO		C ₆ H ₅
20			C ₆ H ₅
		Aceturic acid	CH ₃
			C ₆ H ₅
21			C ₆ H ₅

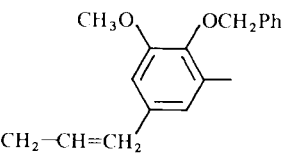
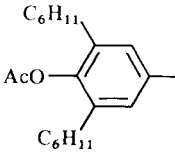
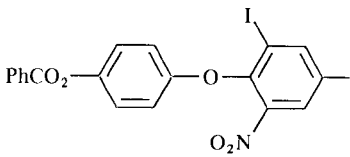
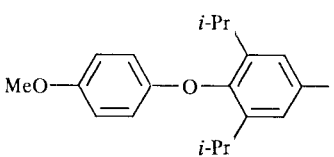
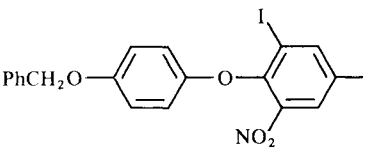
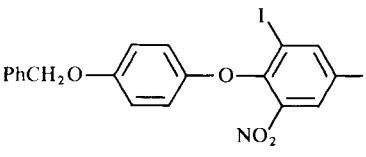
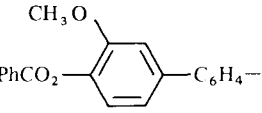
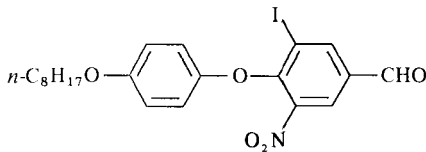
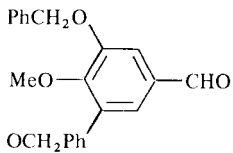
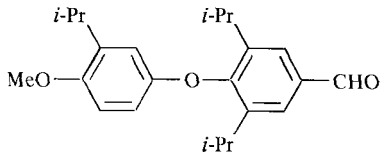
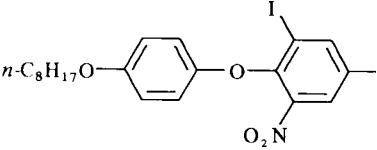
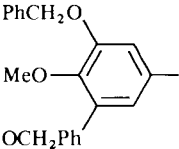
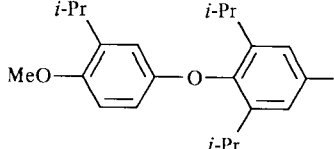
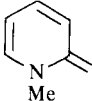
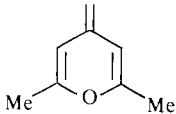
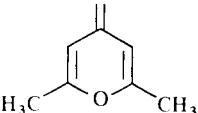
R^{2d}	R^{3d}	Yield Percent	Reference
	H	—	466
	H	—	687
	H	—	892
(4-Me ₂ NC ₆ H ₄) ₂ C=CH—	H	—	270
	H	—	892
	H	—	880
	H	—	881
	H	—	399

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
		Aceturic acid	CH ₃
22			C ₆ H ₅
23			C ₆ H ₅
6	2-Acetofuran ^{b*††} 5-Nitro-2-acetofuran 2-Aceto thiophene <i>N</i> -Methyl-2-pyridone	2-Chlorohippuric acid 4-Chlorohippuric acid 4-Methoxyhippuric acid	C ₆ H ₅ C ₆ H ₅ 2-ClC ₆ H ₄ 4-ClC ₆ H ₄ 4-CH ₃ OC ₆ H ₄ C ₆ H ₅ C ₆ H ₅
7	2,6-Dimethyl-4-pyrone		C ₆ H ₅
		4-Acetamidohippuric acid	4-AcNHC ₆ H ₄

†† Compounds from hereonwards are aromatic ketones.

R^{2d}	R^{3d}	Yield Percent	Reference
	H	—	880
	H	—	893
	H	—	894
2-C ₄ H ₃ O	CH ₃	42	615b
5-O ₂ NC ₄ H ₂ O	CH ₃	—	149
5-O ₂ NC ₄ H ₂ O	CH ₃	—	149
5-O ₂ NC ₄ H ₂ O	CH ₃	—	149
5-O ₂ NC ₄ H ₂ O	CH ₃	—	149
2-C ₄ H ₅ S	CH ₃	34	615b
		—	618
		—	168 ^{ab}
		—	168

‡‡ See page 446 for the footnote.

‡‡ Compounds from hereonwards are aromatic ketones.

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
		4-Phenylhippuric acid	4-C ₆ H ₅ C ₆ H ₄
		Cinnamoylglycine	C ₆ H ₅ CH=CH
		2,6-Dimethylthia-4-pyrone	C ₆ H ₅
8	1,2,6-Trimethyl-4-pyridone		C ₆ H ₅
	C ₆ H ₅ COCH ₃	Aceturic acid	CH ₃
	3-O ₂ NC ₆ H ₄ COCH ₃		C ₆ H ₅
	4-O ₂ NC ₆ H ₄ COCH ₃		C ₆ H ₅
	4-ClC ₆ H ₄ COCH ₃		C ₆ H ₅
	Phthalic anhydride		C ₆ H ₅
		4-Methylhippuric acid	4-H ₃ CC ₆ H ₄

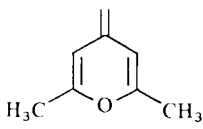
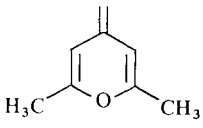
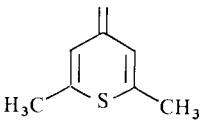
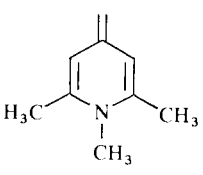
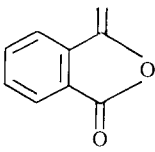
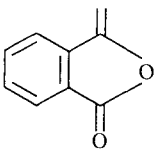
R^{2d}	R^{3d}	Yield Percent	Reference
		—	168
		—	168
		—	168
		—	168 ^{ac}
C ₆ H ₅	CH ₃	—	615a
CH ₃	C ₆ H ₅	—	615a
C ₆ H ₅	CH ₃	80	217
3-O ₂ NC ₆ H ₄	CH ₃	13	216, 658
CH ₃	3-O ₂ NC ₆ H ₄	40	615b
4-O ₂ NC ₆ H ₄	CH ₃	28	216, 658
CH ₃	4-O ₂ NC ₆ H ₄	52	615b
CH ₃	4-ClC ₆ H ₄	52	615b
		82 —	157 123
		84	157

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
		4-Methoxyhippuric acid	4-CH ₃ OC ₆ H ₄
		Phenaceturic acid	C ₆ H ₅ CH ₃
	3-Nitrophthalic anhydride		C ₆ H ₅
	4-Nitrophthalic anhydride		C ₆ H ₅
	4-Chlorophthalic anhydride		C ₆ H ₅
	4-Bromophthalic anhydride		C ₆ H ₅
	5-Chlorophthalic anhydride		C ₆ H ₅

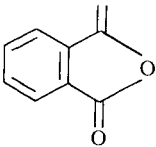
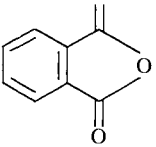
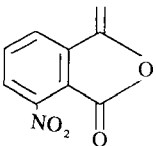
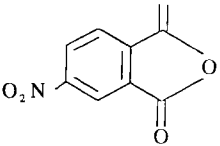
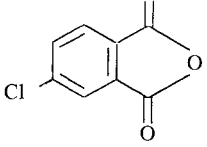
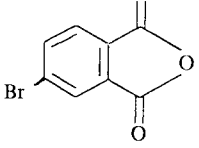
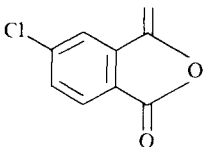
R^{2d}	R^{3d}	Yield Percent	Reference
		85	157
		70	157
		—	154
		61 —	154 156
		50	156
		—	156
		—	156

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	5-Bromophthalic anhydride		C ₆ H ₅
	5-Iodophthalic anhydride		C ₆ H ₅
	5-Nitrophthalic anhydride		C ₆ H ₅
	3,4,5,6-Tetrachlorophthalic anhydride	Aceturic acid	CH ₃
			C ₆ H ₅
	3,4,5,6-Tetrabromophthalic anhydride		C ₆ H ₅
9	C ₆ H ₅ COCH ₂ CH ₃ C ₆ H ₅ CH ₂ COCH ₃ 4-CH ₃ C ₆ H ₄ COCH ₃		C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅

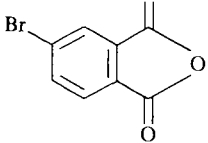
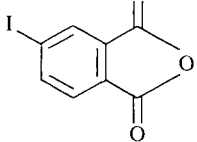
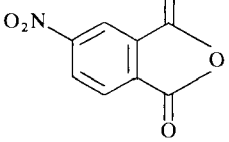
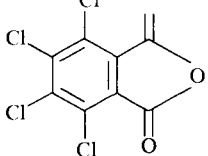
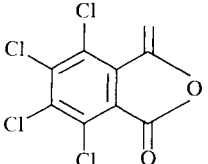
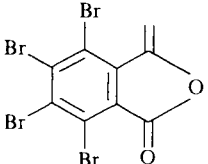
R^{2d}	R^{3d}	Yield Percent	Reference
		—	156
		—	156
		—	156
		—	761
		—	761
		—	895
C_6H_5	C_2H_5	50	151 ^l
$C_6H_5CH_2$	CH_3		
CH_3	$C_6H_5CH_2$	25	151 ^l
$4-CH_3C_6H_4$	CH_3	3	538 ^{ad}
		38	615 ^b
CH_3	$4-CH_3C_6H_4$	70	217 ^l
	485		

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	4-CH ₃ OC ₆ H ₄ COCH ₃		C ₆ H ₅ C ₆ H ₅
	2,6-Dimethyl-1-ethyl(4'-pyridone)		C ₆ H ₅
	3-CH ₃ C ₆ H ₄ COCH ₃		C ₆ H ₅
10	C ₆ H ₅ COCO ₂ CH ₃		C ₆ H ₅
	4(CH ₃) ₂ NC ₆ H ₄ COCH ₃		C ₆ H ₅
	C ₆ H ₅ COCO ₂ C ₂ H ₅		C ₆ H ₅
	.		
	5,6-Dimethoxyphthalic anhydride	Aceturic acid	CH ₃
	2-Methyl-5,6-benzo-4-pyranone		C ₆ H ₅
	2-Methyl-5,6-benzo-1-thia-4-pyranone		C ₆ H ₅
	2,6-Dimethyl-1- <i>n</i> -propyl-4-pyridone		C ₆ H ₅
11	2,6-Dimethyl-1- <i>n</i> -butyl-4-pyridone		C ₆ H ₅
	3-CH ₃ O-4-AcOC ₆ H ₃ COCH ₃		C ₆ H ₅
	3,4-OCH ₂ OC ₆ H ₃ COCO ₂ C ₂ H ₅		C ₆ H ₅

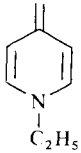
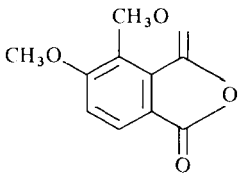
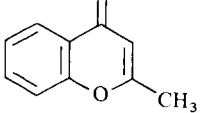
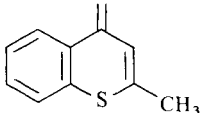
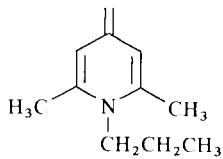
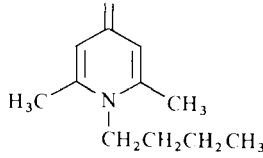
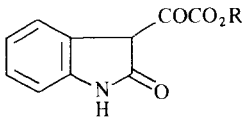
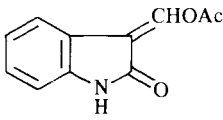
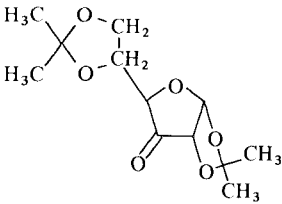
R^{2d}		R^{3d}	Yield Percent	Reference
CH ₃		4-CH ₃ OC ₆ H ₄	50	217 ^l
4-CH ₃ OC ₆ H ₄		CH ₃	16	615b
			—	168 ^{ac}
3-CH ₃ C ₆ H ₄		CH ₃	30	615b
CH ₃		3-CH ₃ C ₆ H ₄	20	151
C ₆ H ₅		CO ₂ CH ₃	33	896
4-(CH ₃) ₂ NC ₆ H ₄		CH ₃	—	615a ^{ad}
C ₆ H ₅		CO ₂ C ₂ H ₅	29	896
			25	897
			—	156
			—	168
			—	168
			—	168 ^{ac}
			—	168 ^{ac}
3-CH ₃ O-4-AcOC ₆ H ₃		CH ₃	—	615a
3,4-OCH ₂ OC ₆ H ₃		CO ₂ C ₂ H ₅	33	896

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
			C ₆ H ₅
			C ₆ H ₅
12			C ₆ H ₅
13	2,6-Dimethyl-1-phenyl-4-pyridone		C ₆ H ₅
	2,6-Dimethyl-1-(2'-diethylaminoethyl)-4-pyridone		C ₆ H ₅
	9-Fluorenone		C ₆ H ₅
	2,4-Dinitro-9-fluorenone		C ₆ H ₅

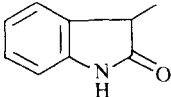
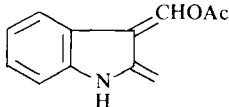
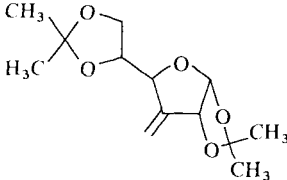
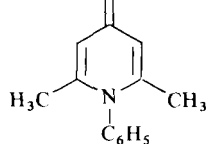
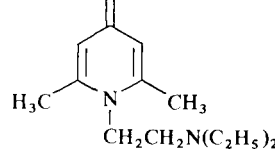
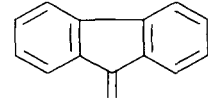
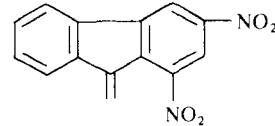
R^{2d}	R^{3d}	Yield Percent	Reference
	CO_2R	—	898
		—	898
		—	624 ^{j,y}
		—	168 ^{a,c}
		—	168 ^{a,c}
		—	210a
		66	262
		83	410
		—	210a

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	2,5-Dinitro-9-fluorenone		C ₆ H ₅
	2,6-Dinitro-9-fluorenone		C ₆ H ₅
	2,7-Dinitro-9-fluorenone		C ₆ H ₅
	3,6-Dinitro-9-fluorenone		C ₆ H ₅
	2,4,7-Trinitro-9-fluorenone		C ₆ H ₅
	2,4,5,7-Tetranitro-9-fluorenone		C ₆ H ₅
	2,4-Dichloro-9-fluorenone		C ₆ H ₅
	2,4,7-Trichloro-9-fluorenone		C ₆ H ₅

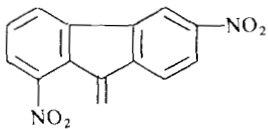
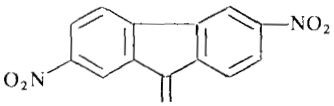
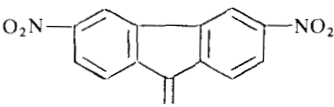
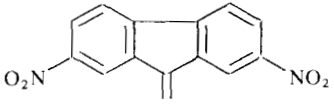
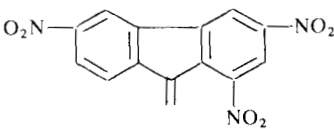
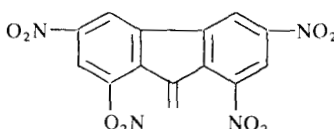
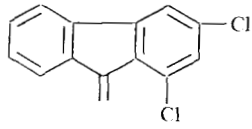
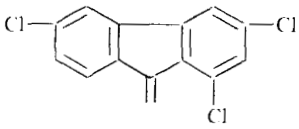
R^{2d}	R^{3d}	Yield Percent	Reference
		—	210a
		—	210a
		—	210a
		—	210a
		—	210a
		—	210a
		—	210a
		—	210a

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	2,4,5,7-Tetrachloro-9-fluorenone		C ₆ H ₅
14	2,6-Dimethyl-1-benzyl-4-pyridone		C ₆ H ₅
	2,4-Dicyano-9-fluorenone		C ₆ H ₅
	2,4-Bistrifluoromethyl-9-fluorenone		C ₆ H ₅
	2,3-Diphenyl-2-cyclopropenone		C ₆ H ₅
	2-Phenylbenzopyran-4-one		C ₆ H ₅
	2,3,5,6-Dibenzopyran-4-one		C ₆ H ₅
	2-Phenylbenzo-1-thiapyran-4-one		C ₆ H ₅

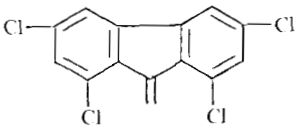
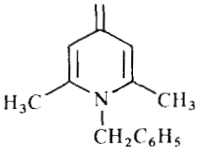
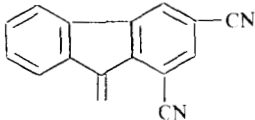
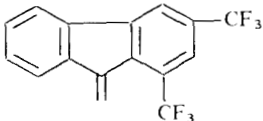
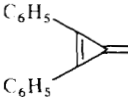
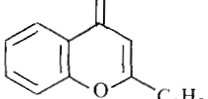
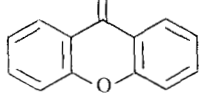
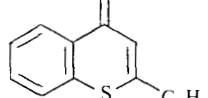
R^{2d}	R^{3d}	Yield Percent	Reference
		—	210a
		—	168 ^{a,c}
		—	210a
		—	210a
		80	899
		80 —	899 168
		80	899
		—	168

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
	2,6-Dimethyl-1-(2'-phenethyl)-4-pyridone		C ₆ H ₅
16	2,4,7-Tricyano-9-fluorenone		C ₆ H ₅
17	2,4,5,7-Tetracyano-9-fluorenone		C ₆ H ₅
	2,6-Diphenyl-4-pyranone	Aceturic acid	C ₆ H ₅
			C ₆ H ₅
		4-Phenylhippuric acid	4-C ₆ H ₅ C ₆ H ₄
	2,6-Diphenylthiapyran-4-one		C ₆ H ₅
	2,6-Diphenyl-1-selenapyran-4-one		C ₆ H ₅

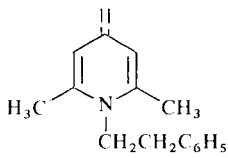
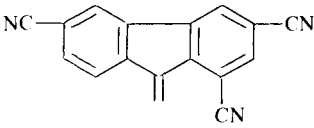
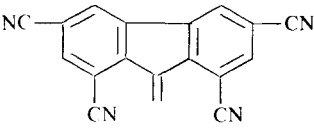
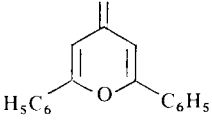
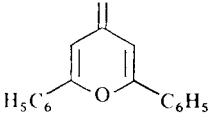
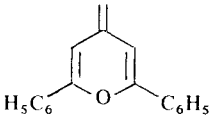
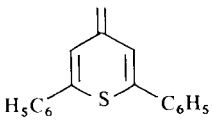
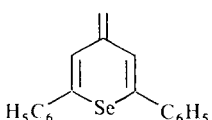
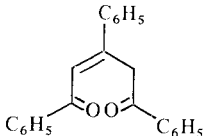
R^{2d}	R^{3d}	Yield Percent	Reference
		—	168 ^{a,c}
		—	210a
		—	210a
		—	900, 901
		— 20 80	168 603 899, 900, 901
		—	168
		80 —	899, 900, 901 168
		59	901

TABLE 3.2A. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^b R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	R ¹
21	2,6-Biscinnamyl-4-pyranone		C ₆ H ₅
		4-Nitrohippuric acid	4-O ₂ NC ₆ H ₄
		Cinnamoylglycine	C ₆ H ₅ CH=CH
23			C ₆ H ₅

Note: The complete list of footnotes is given at the end of Table 3.2D.

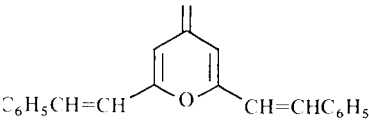
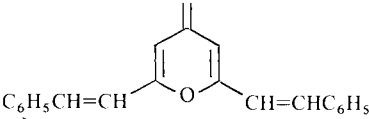
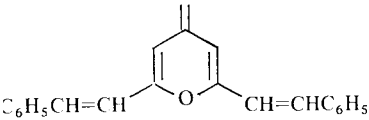
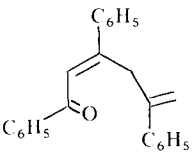
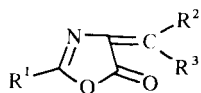
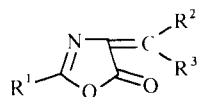
R^{2d}	R^{3d}	Yield Percent	Reference
 <chem>C=C1C=C(C=Cc2ccccc2)OC(C=Cc3ccccc3)=C1C</chem>		—	168
 <chem>C=C1C=C(C=Cc2ccccc2)OC(C=Cc3ccccc3)=C1C</chem>		—	168
 <chem>C=C1C=C(C=Cc2ccccc2)OC(C=Cc3ccccc3)=C1C</chem>		—	168
 <chem>C=C1C=C(C=Cc2ccccc2)OC(C=Cc3ccccc3)=C1C</chem>		21	603

TABLE 3.2B. UNSATURATED AZLACTONES^a

No. of Carbon Atoms	Carbonyl Component ^{ae} R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H
	HCHO ^{af}	Caproylglycine Phenaceturic acid
		Cinnamoylglycine
		Phenaceturic acid
		4-Methylhippuric acid 4-Methoxyhippuric acid 4-Chlorohippuric acid Phenoxyaceturic acid Phenaceturic acid
		Caproylglycine
		Cinnamoylglycine Phenoxyaceturic acid Caproylglycine
		4-Nitrohippuric acid 2,6-Dimethoxyhippuric acid Cinnamoylglycine



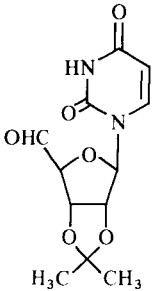
R ¹	R ^{2d}	R ^{3d}	Yield Percent	Reference
<i>n</i> -C ₅ H ₁₁	ONa	H	—	283
C ₆ H ₅ CH ₂	OH	H	—	281
			—	892
C ₆ H ₅	H	H	—	893
C ₆ H ₅	OH	H	—	892
C ₆ H ₅ CH=CH	OH	H	—	894, 178, 281, 283, 892
C ₆ H ₅	SNa	H		
C ₆ H ₅	H	SNa	—	870
C ₆ H ₅	SH	H	—	314, 892— 895
C ₆ H ₅	H	SH		
			—	895
C ₆ H ₅	F	H	—	314, 892
C ₆ H ₅	Cl	H	85	27
			—	273, 274, 308, 896
C ₆ H ₅ CH ₂	Cl	H	58	714
C ₆ H ₅	Cl	Cl	—	897, 898
4-CH ₃ C ₆ H ₄	Cl	Cl	70	899
4-CH ₃ OC ₆ H ₄	Cl	Cl	90	899
4-ClC ₆ H ₄	Cl	Cl	62	899
C ₆ H ₅ OCH ₂	CH ₃ O	H	—	306, 307
C ₆ H ₅ CH ₂	CH ₃ O	H	68	278 ^{ag}
			—	892, 900
<i>n</i> -C ₅ H ₁₁	CH ₃ O	H	—	311 ^{ag}
C ₆ H ₅	CH ₃ O	H	—	308, 892 901 ^{ag}
C ₆ H ₅ CH=CH	CH ₃ O	H	—	281 ^{ag}
C ₆ H ₅ OCH ₂	C ₂ H ₅ O	H	—	301 ^{ag}
<i>n</i> -C ₅ H ₁₁	C ₂ H ₅ O	H	—	283 ^{ag}
C ₆ H ₅	C ₂ H ₅ O	H	56	27 ^{ag}
			78	275, 276, 308, 309, 202, 564, 707, 894
4-O ₂ NC ₆ H ₄	C ₂ H ₅ O	H	70	306 ^{ag}
2,6-(CH ₃ O) ₂ C ₆ H ₃	C ₂ H ₅ O	H	—	306 ^{ag}
C ₆ H ₅ CH=CH	C ₂ H ₅ O	H	—	281, 283, ^{ag} 306, 892 750, 902

TABLE 3.2B. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^{ae} R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H
2	CH ₃ CHO	2-Nitrocinnamoylglycine
		2-Hydroxyhippuric acid
		Cinnamoylglycine
		4-Nitrocinnamoylglycine
		2-(4-Phenoxybenzyloxy)- 3-nitrohippuric acid
		2-Methoxy-3-nitrohippuric acid
		2-Methoxy-4-nitrohippuric acid
		2-Methoxy-5-nitrohippuric acid
		2-Methoxy-3-acetamido- hippuric acid
		2-Methoxy-4-acetamido- hippuric acid
		2-Methoxy-5-acetamido- hippuric acid
		2-Hydroxy-3-acetamido- hippuric acid
3	CH ₃ CH ₂ CHO	
4	CH ₃ CH ₂ CH ₂ CHO	4-Methylhippuric acid
		4-Chlorohippuric acid
		4-Phenylhippuric acid
		Chloroaceturic acid

R ¹	R ^{2d}	R ^{3d}	Yield Percent	Reference
2-O ₂ NC ₆ H ₄ CH=CH C ₆ H ₅	C ₂ H ₅ O C ₂ H ₅ O	H CH ₃	87 62 —	847 184 648, 894 303
C ₆ H ₅ 2-AcOC ₆ H ₄ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ CH=CH 4-O ₂ NC ₆ H ₄ CH=CH C ₆ H ₅	CH ₃ C ₂ H ₅ O C ₂ H ₅ O C ₂ H ₅ S CH ₃ COS CH ₃ CH ₂ CH ₂ O CH ₃ CH ₂ CH ₂ O CH ₃	C ₂ H ₅ O CH ₃ C ₂ H ₅ H H H H H	— — — — — — — —	648, 66 507 299 308 314 283 184 555, 326, 903, 904 702, 225 12, 629, 668 226
	H	CH ₃	—	234
2-C ₆ H ₅ OC ₆ H ₄ - CH ₂ O-3-O ₂ N- C ₆ H ₃ 2-CH ₃ O-3-O ₂ N- C ₆ H ₃ 2-CH ₃ O-4-O ₂ N- C ₆ H ₃ 2-CH ₃ O-5-O ₂ N- C ₆ H ₃ 2-CH ₃ O-3-AcNH- C ₆ H ₃ 2-CH ₃ O-4-AcNH- C ₆ H ₃ 2-CH ₃ O-5-AcNH- C ₆ H ₃ 2-HO-3-AcNHC ₆ H ₃	CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃	H H H H H H H H	85 75 81 84 46 56 —	196, 197 196, 197 196, 197 196, 197 196, 197 195, 196 234
C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅	CH ₃ CH ₃ C ₂ H ₅	Cl HO H	21 — 55	326 894 412, 903, 904
			35	19
C ₆ H ₅ 4-CH ₃ C ₆ H ₄ 4-ClC ₆ H ₄ 4-C ₆ H ₅ C ₆ H ₄ C ₆ H ₅	C ₂ H ₅ S C ₂ H ₅ C ₂ H ₅ C ₂ H ₅ CH ₃ CH ₂ CH ₂	H H H H H	— 48 65 64 7	915 19 19 19 913
			20	19
C ₆ H ₅ C ₆ H ₅ ClCH ₂	H <i>n</i> -C ₃ H ₇ S (CH ₃) ₂ CH	CH ₃ CH ₂ CH ₂ H H	18 — 67	151 905 251

TABLE 3.2B. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^{ae} R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H
	(CH ₃) ₂ CHCHO	
	Cl ₂ CHCCl=CHCHO CH ₃ OCH=CHCHO	4-Nitrohippuric acid
5	CH ₃ (CH ₂) ₃ CHO	
6	HO ₂ C(AcNH)-CH ₂ SCHO ^{ah} CH ₃ (CH ₂) ₄ CHO C ₂ H ₅ CH(CH ₃)CHO	Aceturic acid
7	C ₆ H ₁₁ CHO	Diethylaceturic acid
8	CH ₃ (CH ₂) ₅ CHO 4-ClC ₆ H ₄ SCHO ^{ah} 4-BrC ₆ H ₄ SCHO ^{ah} CH ₃ (CH ₂) ₆ CHO C ₆ H ₅ CH ₂ CHO 4-CH ₃ C ₆ H ₄ SCHO ^{ah} C ₆ H ₅ CH ₂ SCHO ^{ah}	
9	C ₆ H ₅ CH ₂ SCHO ^{ah} 4-ClC ₆ H ₄ CH ₂ SCHO ^{ah} 4-CH ₃ C ₆ H ₄ SCHO ^{ah} C ₂ H ₅ O ₂ C(CH ₂) ₅ CHO C ₆ H ₅ CH ₂ CH ₂ CHO	Caprolylglycine
12		

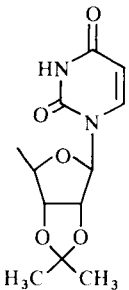
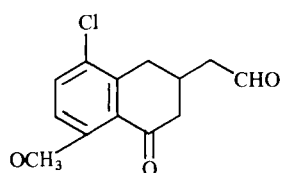
R ¹	R ^{2d}	R ^{3d}	Yield Percent	Reference
C ₆ H ₅	(CH ₃) ₂ CH	H	—	19
			31	903
			61	410
			—	906, 218,
C ₆ H ₅	H	(CH ₃) ₂ CH	10	151
C ₆ H ₅	Cl ₂ CHCCl=CH	H	93	266
C ₆ H ₅	CH ₃ OCH=CH	H	70	184
4-O ₂ NC ₆ H ₄	CH ₃ OCH=CH	H	50	184
C ₆ H ₅	H	<i>n</i> -C ₄ H ₉	15	151
C ₆ H ₅	SCH ₂ (NHAc)CO ₂ H	H	—	317 ^{ah}
C ₆ H ₅	H	<i>n</i> -C ₅ H ₁₁	12	151
CH ₃	C ₂ H ₅ CH(CH ₃)	H	—	531
C ₆ H ₅	C ₂ H ₅ CH(CH ₃)	H	—	907
(C ₂ H ₅) ₂ CH		H	—	746
C ₆ H ₅	H	CH ₃ (CH ₂) ₅	12	151
C ₆ H ₅	4-ClC ₆ H ₄ S	H	68	339
C ₆ H ₅	4-BrC ₆ H ₄ S	H	78	339
C ₆ H ₅	H	CH ₃ (CH ₂) ₅	10	151
C ₆ H ₅	H	C ₆ H ₅ CH ₂	18	151
C ₆ H ₅	4-CH ₃ C ₆ H ₄ S	H	75	339
C ₆ H ₅	C ₆ H ₅ CH ₂ S	H	—	283, 312,
				908, 879
				892
<i>n</i> -C ₅ H ₁₁	C ₆ H ₅ CH ₂ S	H	—	311
C ₆ H ₅	4-ClC ₆ H ₄ CH ₂ S	H	83	339
C ₆ H ₅	H	4-CH ₃ C ₆ H ₄ S	—	905
C ₆ H ₅	C ₂ H ₅ O ₂ C(CH ₂) ₄	H	—	909, 910
C ₆ H ₅	H	C ₆ H ₅ CH ₂ CH ₂	15	151
C ₆ H ₅		H	—	624

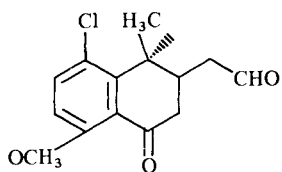
TABLE 3.2B. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^{ae} R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H
---------------------------	--	---

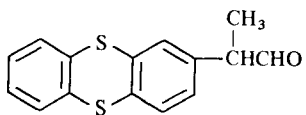
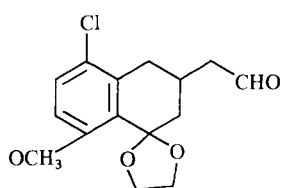
13



14



15



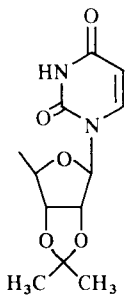
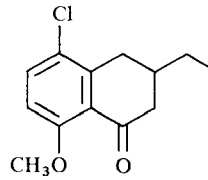
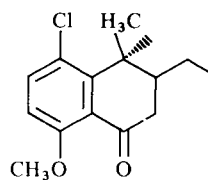
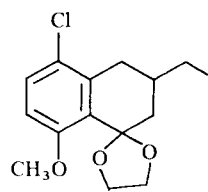
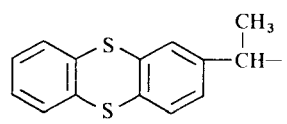
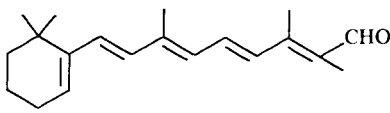
R^1	R^{2d}	R^{3d}	Yield Percent	Reference
C_6H_5	H		—	624
C_6H_5		H	—	911, 912 913, 914
C_6H_5		H	—	915
C_6H_5		H	—	912, 913 914
C_6H_5		H	—	916

TABLE 3.2B. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^{ae} R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H
20		
23	(C ₆ H ₅) ₃ P=C(CO ₂ C ₂ H ₅)CHO	
25	β -Apo-6'-carotenal	
27	β -Apo-10'-carotenal	
29	β -Apo-12'-carotenal	
30	β -Citraurin	
3	Thiazolidin-2-one †††	
	Acetone	Formylglycine Aceturic acid Chloroaceturic acid 2-Methylpropenoylglycine 3-Butenoylglycine Phenaceturic acid 3-Phenylpropanoylglycine γ -Phthaloylamino propanoylglycine 2-Chlorohippuric acid 4-Bromohippuric acid 4-Methoxyhippuric acid Cinnamoylglycine α -Methylcinnamoylglycine CONHCH ₂ CO ₂ H C(=CHSH)NHCOCH ₂ OC ₆ H ₅ CONHCH ₂ CO ₂ H C(=CHSAc)NHCOCH ₂ OC ₆ H ₅ CONHCH ₂ CO ₂ H C(=CHSCH ₃)NHCOCH ₂ C ₆ H ₅
4	CF ₃ COCF ₃ Methyl ethyl ketone	Aceturic acid Chloroaceturic acid

††† The carbonyl compounds from hereon are aliphatic ketones.

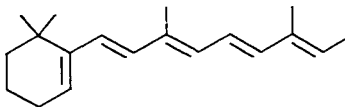
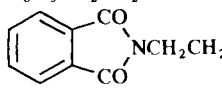
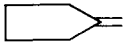
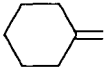
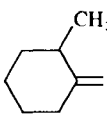
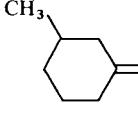
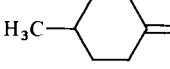
R ¹	R ^{2d}	R ^{3d}	Yield Percent	Reference
C ₆ H ₅		H	—	917
C ₆ H ₅	(C ₆ H ₅) ₃ P=C(CO ₂ C ₂ H ₅)	H	77	270
C ₆ H ₅	β-Apo-8'-carotenyl	H	75	372
C ₆ H ₅	β-Apo-10'-carotenyl	H	70	372
C ₆ H ₅	β-Apo-12'-carotenyl	H	65	372
C ₆ H ₅	β-Citrauriny	H	60	372
C ₆ H ₅			—	190
H	CH ₃	CH ₃	—	699
CH ₃	CH ₃	CH ₃	—	904, 696— 704
ClCH ₂	CH ₃	CH ₃	78	251 ^b
CH ₃ C(=CH ₂)	CH ₃	CH ₃	25	11
CH ₂ =CHCH ₂	CH ₃	CH ₃	—	50
C ₆ H ₅ CH ₂	CH ₃	CH ₃	—	704
C ₆ H ₅ CH ₂ CH ₂	CH ₃	CH ₃	—	30
	CH ₃	CH ₃	—	918
C ₆ H ₅	CH ₃	CH ₃	65	175, 47, 263, 410, 455, 660, 661, 904, 689— 695
2-ClC ₆ H ₄	CH ₃	CH ₃	44	175
4-BrC ₆ H ₄	CH ₃	CH ₃	59	175
4-CH ₃ OC ₆ H ₄	CH ₃	CH ₃	39	175
C ₆ H ₅ CH=CH	CH ₃	CH ₃	24	31 ^p
			—	30
			68	175
C ₆ H ₅ CH=C(CH ₃)	CH ₃	CH ₃	63	31 ^p
C=CHSH	CH ₃	CH ₃	—	625
NHCOCH ₂ OC ₆ H ₅				
C=CHSAc	CH ₃	CH ₃	—	59, 919, 920
NHCOCH ₂ OC ₆ H ₅				
C=CHSCH ₃	CH ₃	CH ₃	—	913, 921
NHCOCH ₂ C ₆ H ₅				
C ₆ H ₅	CF ₃	CF ₃	—	922
CH ₃	C ₂ H ₅	CH ₃	54	309
ClCH ₂	C ₂ H ₅	CH ₃	67	251 ^b

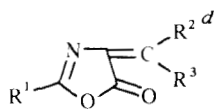
TABLE 3.2B. (CONTINUED)

No. of Carbon Atoms	Carbonyl Component ^{ae} R ² COR ³	Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H
		α -Methylcinnamoylglycine
5	CH ₃ COCOCH ₃ Diethyl ketone	Aceturic acid
6	Cyclopentanone Cyclohexanone	
	C ₂ H ₅ SCH ₂ CH ₂ COCH ₃ CF ₃ CHOHCOCH ₃	Trifluoroaceturic acid
7	2-Methylcyclohexanone	
	3-Methylcyclohexanone	
	4-Methylcyclohexanone	
	(CH ₃ COSCH ₂) ₂ C=O	Aceturic acid
8	C ₂ H ₅ SCH(CH ₃)CH ₂ COCH ₃	
9	<i>n</i> -C ₄ H ₉ SCH ₂ CH ₂ CH ₂ COCH ₃	
10	<i>n</i> -C ₄ H ₉ SCH(CH ₃)CH ₂ COCH ₃	
12	Benzalacetone	
12	C ₂ H ₅ SCH(C ₆ H ₅)CH ₂ COCH ₃	
14	<i>n</i> -C ₄ H ₉ SCH(C ₆ H ₅)CH ₂ COCH ₃	

Note: The complete list of footnotes is given at the end of Table 3.2D.

R ¹	R ^{2d}	R ^{3d}	Yield Percent	Reference
C ₆ H ₅	C ₂ H ₅	CH ₃	—	649, 650
C ₆ H ₅	CH ₃	C ₂ H ₅	—	649, 650
C ₆ H ₅ CH=C(CH ₃)	CH ₃	CH ₃	47	31 ^P
C ₆ H ₅	CH ₃	CH ₃ CO	33	923
C ₆ H ₅	CH ₃ CO	CH ₃	4	923
CH ₃	C ₂ H ₅	C ₂ H ₅	79	923
C ₆ H ₅			—	147, 148
C ₆ H ₅			—	147, 148, 312, 529, 555
			70	151
			94	410
C ₆ H ₅	C ₂ H ₅ SCH ₂ CH ₂	CH ₃	—	924
CF ₃	CF ₃ CHOAcC(CH ₃)=		—	630
C ₆ H ₅			—	145, 312
			5	410
			56	151
C ₆ H ₅			—	147
C ₆ H ₅			—	147
CH ₃	CH ₃ COSCH ₂	CH ₃ COSCH ₂	—	925
C ₆ H ₅	C ₂ H ₅ SCH(CH ₃)CH ₂	CH ₃	—	924
C ₆ H ₅	<i>n</i> -C ₄ H ₉ SCH ₂ CH ₂	CH ₃	—	924
C ₆ H ₅	<i>n</i> -C ₄ H ₉ CH(CH ₃)CH ₂	CH ₃	—	924
C ₆ H ₅	C ₆ H ₅ CH=CH	CH ₃	—	887
C ₆ H ₅	C ₂ H ₅ SCH(C ₆ H ₅)CH ₂	CH ₃	—	924
C ₆ H ₅	<i>n</i> -C ₄ H ₉ SCH(C ₆ H ₅)CH ₂	CH ₃	—	924

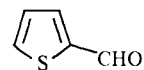
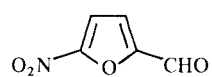
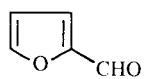
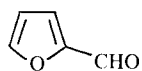
COMPOUNDS^a



Acylamino Acid ^c R¹CONHCH₂CO₂H	Yield Percent	Reference
	52	926
	—	927
	90	715 ^{ai}
	—	928
	—	928
	—	285 ^q
	—	929 ^q
	—	930 ^q
	—	928 ^q
	—	931 ^{q, y}
	98	166 ^g

TABLE 3.2C. (CONTINUED)

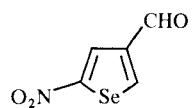
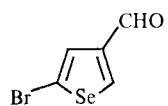
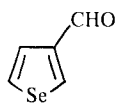
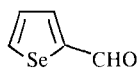
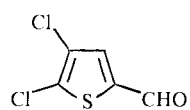
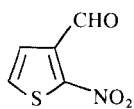
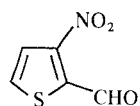
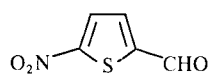
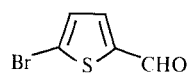
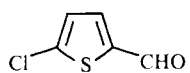
No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---



Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
Aceturic acid	82 79 43 30 —	19 ^j 264, 265 ^k 533 ^a 179 45, 169, 236, 510, 511, 461
2-Methylhippuric acid	60	179
3-Methylhippuric acid	75	179
4-Methylhippuric acid	80	179, 749
2-Acetoxyhippuric acid	—	749, 176
2-Chlorohippuric acid	65	179
3-Chlorohippuric acid	70	179
4-Chlorohippuric acid	90	179
2-Bromohippuric acid	75	179
3-Bromohippuric acid	65	179
4-Bromohippuric acid	55	179
2-Nitrohippuric acid	30	179
3-Nitrohippuric acid	90	179
4-Nitrohippuric acid	60	179
4-Acetamidohippuric acid	—	167
2,4-Dichlorohippuric acid	—	176, 749
Furoylglycine	—	751
Aceturic acid	—	446, ^u 932
	68	645
Aceturic acid	—	297, 223, 419
2-Nitrohippuric acid	14	933
3-Nitrohippuric acid	60	933
4-Nitrohippuric acid	66	933
2-Chlorohippuric acid	35	933
4-Chlorohippuric acid	42	933
2-Methylhippuric acid	40	933
4-Methoxyhippuric acid	43	933
3,4-Methylenedioxyhippuric acid	54	

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---

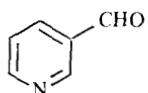
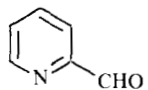
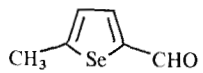
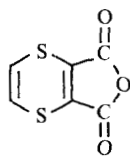
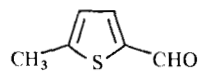
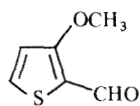
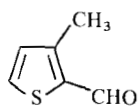
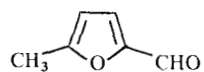
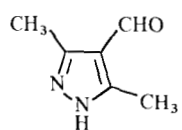
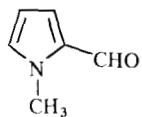


Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
3,5-Dinitrohippuric acid	35	933
Cinnamoylglycine	—	933
	64	645
	64	645
Aceturic acid	—	533
	81	934, 935
	82	936
	84	934
Aceturic acid	65	435 ^w
Aceturic acid	56	435 ^w
	59	619
	80	937
	—	938
	87	939
	77	765

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---

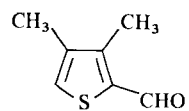
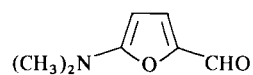
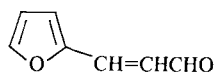
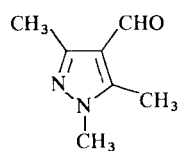
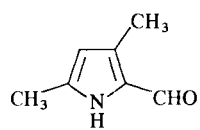
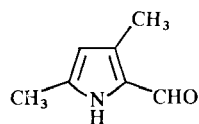
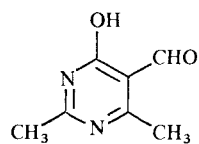
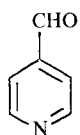
6



Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	—	931
	—	940 ^q
	—	941
Aceturic acid	60	645
	43	421
Aceturic acid	58	645
	60	642
	83	885
	62	75 ^{k,t,x}
	72	74 ^{i,t} 75 ^x

TABLE 3.2C. (CONTINUED)

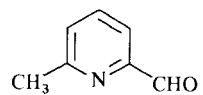
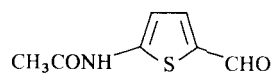
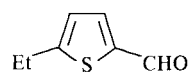
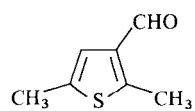
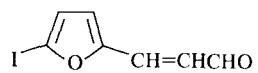
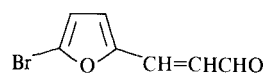
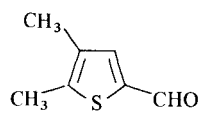
No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---



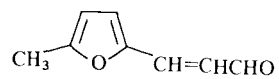
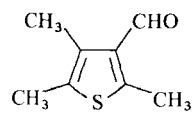
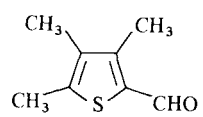
Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	— 65	932 ^{q,i} 74 ^{i,q} 945 ^{t,x}
	88	715 ^{q,ai}
	91	166 ^g
	91	266 ^g
	45	940 ^q
	— 61	611, 943 639
	82 62	19 ^j 944
	54	945

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---



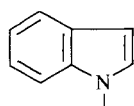
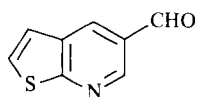
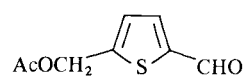
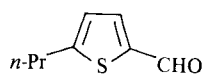
8



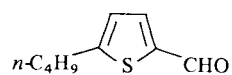
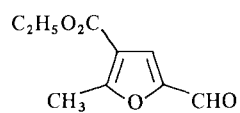
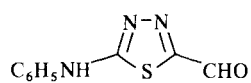
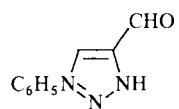
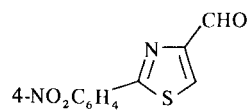
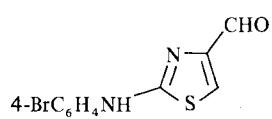
Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	75	945
	—	943
	—	943
	79	945
	— 73	419, 645 420 ^q
Aceturic acid	15 44 66	934 936 420
	—	76 ⁱ
	64	945
	18	945
	—	943

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---



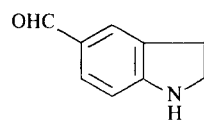
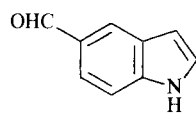
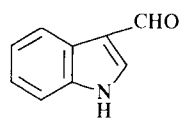
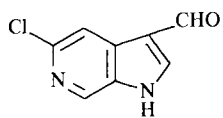
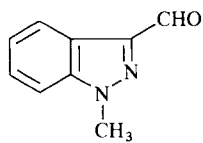
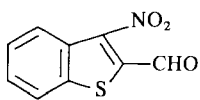
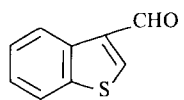
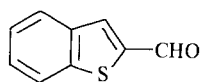
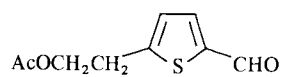
9



Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	60	640
	42	421
	49	946
	59	285
	—	947
Aceturic acid	—	71 ^a
	—	928 ^a
	—	947
Aceturic acid	—	446
	—	419
	68	417 ^a

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---



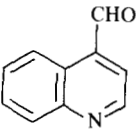
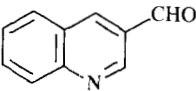
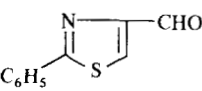
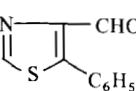
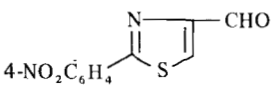
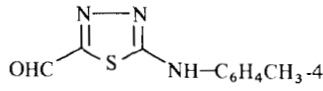
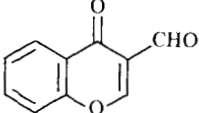
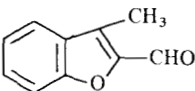
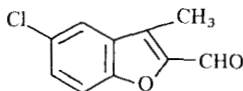
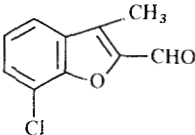
Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	70	421 ^q
Sodium hippurate	95	948 ^q
Sodium hippurate	57 69	915 ^q 945
Aceturic acid	—	949
	79	54
	—	950
	—	259 ^{aj}
	—	267 ^{g, q}
	40	285

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
10	

Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	93	266
	63	940
	71	903
	—	951
	—	285 ^{q,x}
	—	706
	85	266 ^g
	90	266 ^g

TABLE 3.2C. (CONTINUED)

No. of Carbon	Heterocyclic Carbonyl Compound ^b
Atoms in	R ² CHO
Carbonyl	R ² CHO
Component	R ² CHO
	
	
	
	
	
	
	
	
	
	

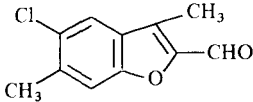
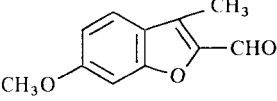
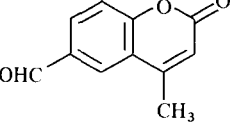
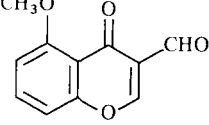
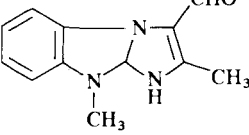
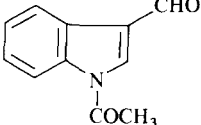
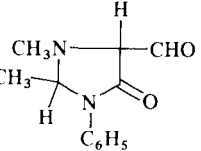
Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	—	953
	—	953
	—	508, 438
Aceturic acid	—	954
Aceturic acid	—	957 ^{q,u}
	—	947
	41	848
Aceturic acid	—	956 ^q , 488
	94	534, 956 ^t 957 ^q
	—	482, 483 ^t
	84	957 ^q

TABLE 3.2C. (CONTINUED)

No. of Carbon	Heterocyclic Carbonyl Compound ^b
Atoms in	R ² CHO
Carbonyl	R ² CHO
Component	R ² CHO
11	<chem>CCOC(=O)CCc1cc(C=O)sc1</chem> <chem>Cc1nc(C=O)c(Cl)n(Cc2ccccc2)c1</chem> <chem>Cc1cc(C=O)sc1N=Cc2ccccc2</chem> <chem>Cc1cc(C=O)sc1N=Cc2ccccc2</chem> <chem>Cc1cc(C=O)sc1N=Cc2ccccc2</chem> <chem>Cc1cc(C=O)sc1N=Cc2ccccc2</chem> <chem>Cc1cc(C=O)sc1c2ccccc2</chem> <chem>Cc1cc(C=O)sc1c2ccccc2</chem> <chem>Cc1cc(C=O)sc1c2ccccc2</chem> <chem>Cc1cc(C=O)sc1c2ccccc2</chem>

Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	57	707 ^a
	73	940 ^a
Aceturic acid	—	964, 438
Aceturic acid	—	954, 438
	—	947
	—	947
	— 90	477 957
	—	486
	—	958 ^{a, t, u} 486
	91	957 ^a

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
	
	
	
	
	
	
	

Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	—	482, 483
	—	452 ^{t,u}
Aceturic acid	— —	959 ^q 959 ^q
	40	838
	62	960
Aceturic acid	—	249, ^q 961
Phenaceturic acid	93 —	166 962, ^q 406, 951, 953 ^q
	—	964

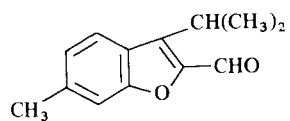
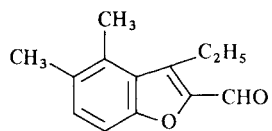
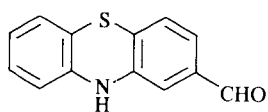
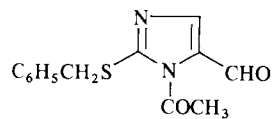
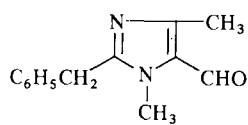
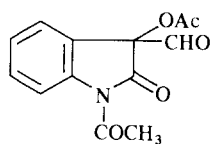
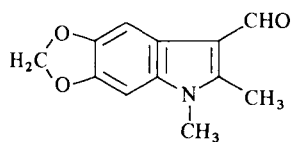
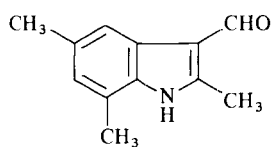
TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
12	

Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	52	838
	—	460 ^{t,u}
	—	484, 485 ^{t,u}
	—	452 ^{t,u}
	—	459 ^{t,u}
	—	442
	—	487
	—	947

TABLE 3.2C. (CONTINUED)

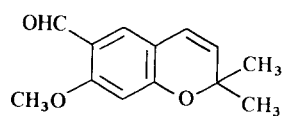
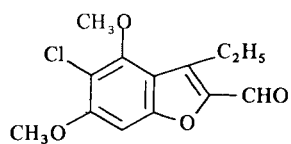
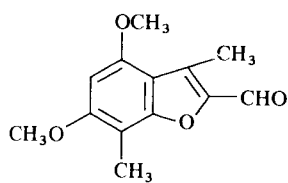
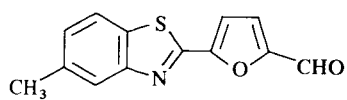
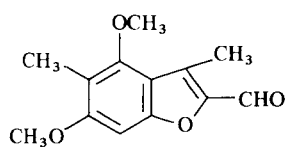
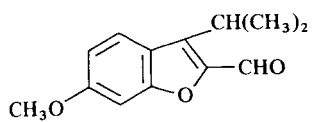
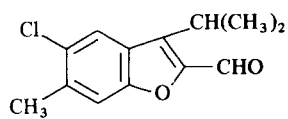
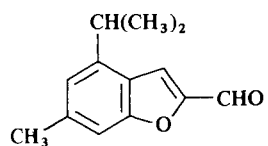
No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---



Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	—	706 ^a
	—	946
	77	266
	—	965
	23	940 ^a
	—	966
	—	456, ^t 460, ^{t,u} 485
	—	456, 485

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---

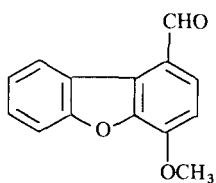
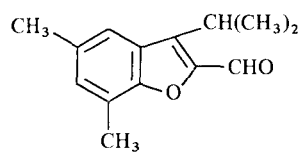
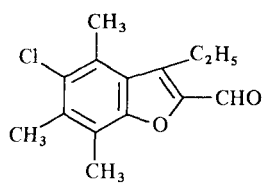
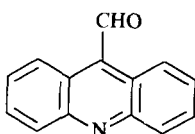
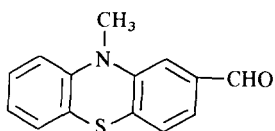
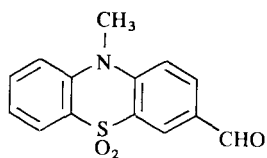
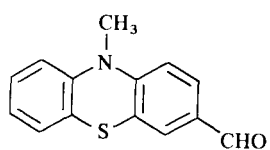


Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	72	481 ^t
	—	485
	—	485
	—	485, 456 ^t
	—	459 ^{t,u}
	—	487
	—	967
	—	456 ^t
	—	427

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---

14



Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	60	521
	73	521
	—	966
	71	968
	—	485
	—	697
	—	893

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
--	---

15	
16	
17	

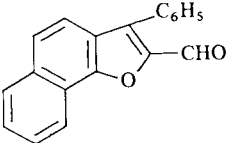
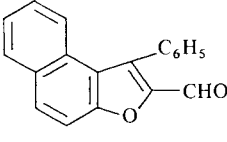
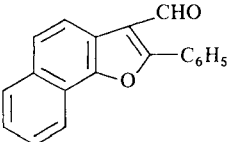
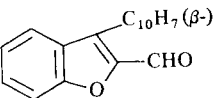
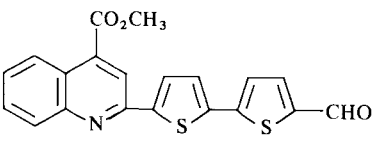
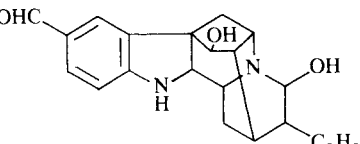
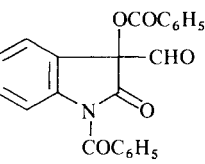
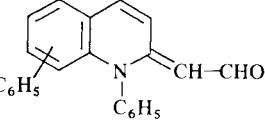
Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	54	969
	—	423
	70	68 ^a
	—	970
	—	971
Aceturic acid	—	972 ^a
	—	973
	24	960

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
18	
19	

Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	—	451 ^u
	—	428
	—	473 ^{t,u}
	—	473 ^{t,u}
	—	974
	—	473 ^{t,u}
	—	975
	—	425

TABLE 3.2C. (CONTINUED)

No. of Carbon Atoms in Carbonyl Component	Heterocyclic Carbonyl Compound ^b R ² CHO
	
	
	
	
20	
	
22	
23	

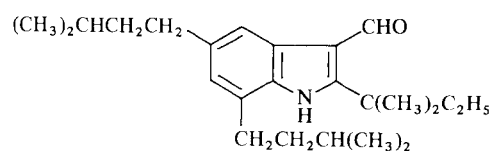
Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	—	425 ^u
	—	426
	—	426
	—	424
	—	974
	49	976 ^{ak}
	—	266
	—	441

TABLE 3.2C. (CONTINUED)

No. of Carbon
Atoms in
Carbonyl
Component

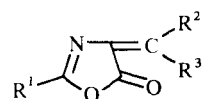
Heterocyclic Carbonyl Compound^b
R²CHO

24

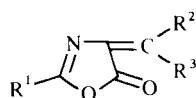


Note: The complete list of footnotes is given at the end of Table 3.2D.

Acylamino Acid ^c R ¹ CONHCH ₂ CO ₂ H	Yield Percent	Reference
	—	733 ^q

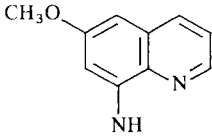
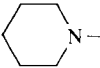
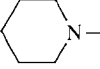
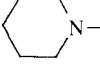
TABLE 3.2D. AMINOMETHYLENE AZLACTONES^{al}

No. of Carbon Atoms in the azlactone ring	R ¹	R ²
10	C ₆ H ₅	NH ₂
	C ₆ H ₅	H
	C ₆ H ₅	H ₂ NNH
	C ₆ H ₅	H
11	C ₆ H ₅	CH ₃ NH
	C ₆ H ₅	H ₂ NC(=NH)NH
	C ₆ H ₅	H
12	C ₆ H ₅	NH ₂
	C ₆ H ₅	(CH ₃) ₂ N
	C ₆ H ₅	HOCH ₂ CH ₂ NH
	C ₆ H ₅	CH ₃ CONH
	C ₆ H ₅	CH ₃ C(=NH)NH
	C ₆ H ₅	H
	C ₆ H ₅	NH ₂
12	C ₆ H ₅ CH=CH	NH ₂
13	C ₆ H ₅	CH ₃ N(CH ₂ CH ₂ OH)
	4-CH ₃ OC ₆ H ₄ CHCH ₃	NH ₂
14	C ₆ H ₅	
	C ₆ H ₅	1-Morpholinyl
15	CH ₃ CH ₂ CH=CH	C ₆ H ₅ NH
	C ₆ H ₅	<i>n</i> -C ₄ H ₉ NH
	C ₆ H ₅ CH ₂	(CH ₃) ₂ C=CHNH
16	C ₆ H ₅ OCH ₂	(CH ₃) ₂ C(SH)CHNH
	C ₆ H ₅ OCH ₂	
	C ₆ H ₅	C ₆ H ₅ NH
	C ₆ H ₅	H
	C ₆ H ₅	CH ₃ CONCH ₂ CH ₂ OCOCH ₃
	C ₆ H ₅	
17	C ₆ H ₅	C ₆ H ₅ CONH
	C ₆ H ₅	C ₆ H ₅ NCH ₃
	C ₆ H ₅	C ₆ H ₅ CH ₂ NH



R ³	Yield Percent	Reference
H	—	273, 283, 314, 894, 977, 978
NH ₂	—	2
H	—	2
H ₂ NNH	—	2
H	—	894
H	—	2 ^{am}
H ₂ NC(=NH)NH	—	2 ^{am}
CH ₃	—	894
H	—	892, 979
H	—	315
H	—	2 ^{am}
H	—	2 ^{am}
CH ₃ C(=NH)NH	—	2 ^{am}
CH ₃	—	894
H	—	283, 729, 79, 315
H	—	
H	—	277
H	—	283
	94	530
Cl	88	899
H	—	631
H	93	530
H	—	626
H	—	306
H	—	306
H	—	202, 892, 894 908, 980
C ₆ H ₅ NH	—	2 ^{am}
H	—	315
H	—	981
H	—	273
H	—	894
H	—	631, 894

TABLE 3.2D. (CONTINUED)

No. of Carbon Atoms in the azlactone ring	R ¹	R ²
18	C ₆ H ₅	C ₆ H ₅ NH
	C ₆ H ₅	C ₆ H ₅ CH ₂ NH
	C ₆ H ₅	CH ₃
	C ₆ H ₅	C ₆ H ₅ CH ₂ NCH ₃
	C ₆ H ₅	C ₆ H ₅ NCOCH ₃
	C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂ NH
	C ₆ H ₅	1-Morpholinyl
	C ₆ H ₅ CH=CH	C ₆ H ₅ NH
	2,6(CH ₃ O) ₂ C ₆ H ₃	(CH ₃) ₂ C(SH)CHNH
	2,6(CH ₃ O) ₂ C ₆ H ₃	$\begin{array}{c} \text{CO}_2\text{H} \\ \\ (\text{CH}_3)_2\text{CHCHNH} \end{array}$
19	C ₆ H ₅	$\begin{array}{c} \text{CO}_2\text{H} \\ \\ \text{C}_6\text{H}_5\text{CH}_2\text{NCOCH}_3 \end{array}$
	C ₆ H ₅	C ₆ H ₅ CH ₂ NCH ₃
20	C ₆ H ₅	C ₆ H ₅ CONHNCH ₃
	C ₆ H ₅	CH ₃ CONCH ₂ CH(OH)C ₆ H ₅
	C ₆ H ₅ CH ₂	CH ₃ CONCH ₂ C ₆ H ₅
21	C ₆ H ₅	
22	C ₆ H ₅	C ₆ H ₅ NH
	4-CH ₃ C ₆ H ₄	
	4-CH ₃ OC ₆ H ₄	
	4-ClC ₆ H ₄	
24	C ₆ H ₅	4-CH ₃ C ₆ H ₄ NH
25 15 ^{an}	C ₆ H ₅	C ₆ H ₅ NNHCOC ₆ H ₅
	C ₆ H ₅	C ₆ H ₅ NNHCOCH ₃
	C ₆ H ₅	C ₆ H ₅ NNHCOC ₆ H ₅
	C ₆ H ₅	C ₆ H ₅
	C ₆ H ₅	4-ClC ₆ H ₄
	C ₆ H ₅	4-BrC ₆ H ₄
	C ₆ H ₅	4-O ₂ NC ₆ H ₄

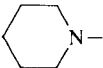
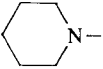
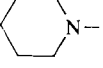
R ³	Yield Percent	Reference
CH ₃	—	894
CH ₃	—	322, 894
	82	530
C ₆ H ₅ CH ₂ NH	—	322
H	—	894
H	—	631
H	—	631
1-Morpholinyl	—	899
H	—	631
H	—	306
H	—	306
H	—	631, 894
CH ₃	—	894
CH ₃	—	530
H	—	315
H	—	631
H	—	283
C ₆ H ₅ NH	—	897
	—	899
	—	899
	—	899
4-CH ₃ C ₆ H ₄ NH	—	897
CH ₃	53	530
C ₆ H ₅	30	530
C ₂ H ₅	48	530
H	70	73, 347, 349
H	—	352 ^a
H	40	350, 351
H	30	347

TABLE 3.2D. (CONTINUED)

No. of Carbon Atoms	R ¹	R ²
16	4-ClC ₆ H ₄	C ₆ H ₅
	4-ClC ₆ H ₄	4-ClC ₆ H ₄
	4-ClC ₆ H ₄	4-O ₂ NC ₆ H ₄
	C ₆ H ₅	2-CH ₃ C ₆ H ₄
	C ₆ H ₅	3-CH ₃ C ₆ H ₄
	C ₆ H ₅	4-CH ₃ C ₆ H ₄
	C ₆ H ₅	4-CH ₃ OC ₆ H ₄
	C ₆ H ₅	3-CO ₂ HC ₆ H ₄
	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄
19	C ₆ H ₅	1-C ₁₀ H ₇
	C ₆ H ₅	2-C ₁₀ H ₇
27	C ₆ H ₅	4- <i>n</i> -C ₁₂ H ₂₅ O-3-SO ₃ HC ₆ H ₃

^aErlenmeyer method of heating the aldehyde with acylamino acid acetic anhydride and anhydrous sodium acetate was employed, unless otherwise stated.

^bCarbonyl components are aromatic aldehydes or ketones. Substituents on the benzene ring of the aldehyde are given in R² (or R³).

^cAcetylamino acid is hippuric acid (R¹ = Ph) unless otherwise stated.

^dConfiguration at the exocyclic double bond is presumed.

^eCompound prepared by chlorination of the azlactone (R¹ = Me, R² = Ph, R³ = H).

^fCompound prepared by the bromination of the azlactone (R¹ = Me, R² = Ph, R³ = H).

^gReactions of the azlactone (R¹ = Ph, R² = Cl, R³ = H) with benzene and anhydrous AlCl₃.

^hReaction of the azlactone (R¹ = Ph, R² = Cl, R³ = H) with PhMgBr and CdCl₂.

ⁱReaction of benzaldehyde with hippuric acid in DMF-SO₃.

^jReaction of ArCHO with 2-phenyl-2-oxazolin-5-one.

^kTreatment of 5-benzylidenehydantoin with ArCOCl in C₅H₅N.

^lThe *E*-isomer prepared by heating the aldehyde with hippuric acid in PPA.

^mThe *Z*-isomer converted to *E*-isomer by heating with PPA.

ⁿThe *Z*-isomer converted to *E*-isomer in saturated hydrobromic acid.

^oMixed anhydride of acetic and 3,5-dinitrohippuric acids used instead of free acylamino acid.

^pBergmann synthesis has been used. Prepared by heating *N*-dichloroacetyl-L-tyrosine with acetic anhydride.

^qConverted to the corresponding amino acid.

^rFormed by acyl interchange.

^sCoumarin derivative also formed.

^tConverted to the corresponding acrylacetic acid.

^uConverted to the corresponding arylpyruvic acid.

^vThe azlactone is converted to a coumarin derivative by photolysis.

^wConverted to the nitrile.

^xConverted to the benzamido cinnamic acid.

^yThe isomeric azlactone isolated from the mother liquor of the Erlenmeyer reaction of the aldehyde with hippuric acid.

^zCompound prepared by nitration of the azlactone. R¹ = C₆H₅, R² = 3,4-MeO₂C₆H₃, R³ = H.

^{aa}Only the *N*-benzylalanine was prepared.

^{*}Carbonyl components from here on are aromatic ketones.

^{ab}Prepared by heating the 4-pyrone derivative with hippuric acid and acetic anhydride.

^{ac}Prepared by heating the corresponding 4-pyranylidene-2-oxazolin-5-one with the appropriate amine.

R ³	Yield Percent	Reference
H	—	352
H	—	352
H	—	352
H	30	73, 350, 351
H	18	350, 351
H	68	73, 347
H	45	73, 350, 351
H	—	348
H	—	352 ^a
H	—	350
H	35	73, 351
H	—	348

^{ad} Prepared as a by-product by reacting the azlactone. R¹ = C₆H₅, R² = 4-CH₃C₆H₄, R³ = H with CH₂N₂.

^{ae} Carbonyl compounds are aliphatic or alicyclic aldehydes unless otherwise stated.

^{af} Formaldehyde itself does not react but derivatives of the 4-methylene analog are known.

^{ag} Prepared by heating the appropriate acylamino acid with trialkylortho ester in the presence of acetic anhydride and sodium acetate.

^{ah} These compounds (hypothetical) do not exist; prepared by reacting the azlactone R¹ = C₆H₅, R² = Cl and R³ = H with ArSH in the presence of AlCl₃.

^{ai} Carbonyl components from here on are aliphatic (or alicyclic ketones).

^{aj} The R² group contains acetoxy groups instead of the —OH and —NH₂ groups.

^{ak} Condensation of indole with the azlactone R¹ = C₆H₅, R² = C₂H₅O, and R³ = H carried out in PPA. E isomer obtained.

^{al} Diacetoxy derivative of ajmaline carboxaldehyde azlactone is obtained.

^{am} Compounds in this table of 10–24 atoms are prepared by the action of ammonia or the appropriate amine on the azlactones R¹ = aryl or aralkyl, R² = Cl or C₂H₅O, and R³ = H. Compounds of 24–27 carbon atoms are prepared by diazonium salt solutions to 2-phenyl-2-oxazolin-5-one; or by adding amyl nitrite diazotized arylamine to a solution of hippuric acid in acetic anhydride.

^{an} Isomer is obtained as a red-colored compound in the reaction.

^{ao} Compounds from here on are 4-arylaazo azlactones:

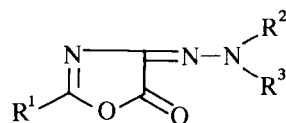
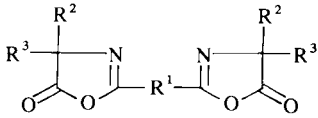
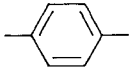
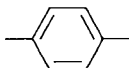
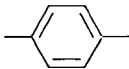
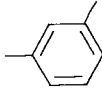
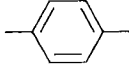
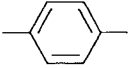
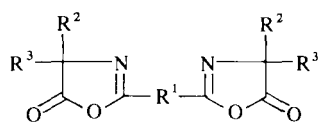


TABLE 3.3A. SATURATED BISAZLACTONES^a

		
No. of Carbon Atoms in Bisazlactone	R ¹	R ²
10	—	CH ₃
12		H
14	—(CH ₂) ₄ —	CH ₃
	—(CH ₂) ₈ —	H
		CH ₃
16		CH ₃
		CH ₃
		C ₂ H ₅
	—CH ₂ OCH ₂ —  —CH ₂ OCH ₂ —	H
18	—(CH ₂) ₄ —	(CH ₃) ₂ CHCH ₂
20		(CH ₃) ₂ CHCH ₂
22	—(CH ₂) ₄ —	Cyclohexyl



R ³	Yield Percent	Reference
CH ₃	55 10	52 396
H	100	353, 395, 393
CH ₃	82 —	353, 395 383
H	—	393
H	80	353, 390, 391, 392, 395, 384
CH ₃	72	353, 390, 395
CH ₃	—	384
H	—	387, 388
H	—	397
H	—	353, 395
H	65	353, 395, 393
H	60	353, 393

TABLE 3.3A. (CONTINUED)

No. of Carbon Atoms in Bisazlactone	R ¹	R ²
38		C ₆ H ₅
		C ₆ H ₅
42		C ₆ H ₅
19 ^b	C ₆ H ₅	H
26	C ₆ H ₄ ^c (1,4)	H
30	C ₆ H ₄ (1,4)	CH ₃
36	C ₆ H ₄ (1,4)	C ₆ H ₅
	C ₆ H ₄ (1,4)	C ₆ H ₅
<i>Saturated Bisazlactones (4,4')</i>		
20	R ¹ C ₆ H ₅	R ² CH ₃
22	4-O ₂ NC ₆ H ₄ 4-CH ₃ C ₆ H ₄	CH ₃ CH ₃

Note: The complete list of footnotes is given at the end of Table 3.3B.

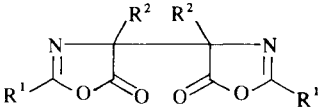
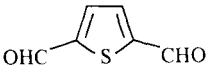
R ³	Yield Percent	Reference
C ₆ H ₅	—	397
C ₆ H ₅	—	397
C ₆ H ₅	—	397
$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{H} \end{array}$	—	294
	—	982
$\begin{array}{c} \text{O} \qquad \text{O} \\ \parallel \qquad \parallel \\ -\text{C}(\text{CH}_2)_4-\text{C}- \end{array}$	60	353, 395
—	—	588
C ₆ H ₅	—	385
		
—	—	386
—	—	386
—	—	386

TABLE 3.3B. UNSATURATED BISAZLACTONE^d

No. of Carbon Atoms in Dialdehyde	Dialdehyde $R^2(CHO)_2$
6	
8	1,2-C ₆ H ₄ (CHO) ₂ 1,3-C ₆ H ₄ (CHO) ₂ 1,4-C ₆ H ₄ (CHO) ₂

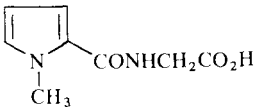
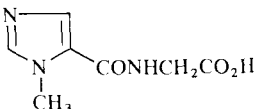
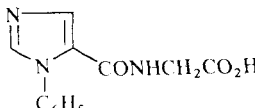
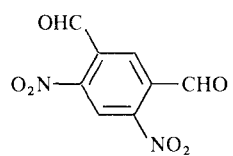
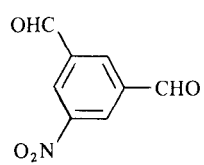
Acylamino Acid R ¹ CONH—CH ₂ CO ₂ H	Yield Percent	Reference
Hippuric acid	—	374
Hippuric acid	15	362
	36	359 ^e
Hippuric acid	56	359 ^e
Hippuric acid	85	359 ^e
4-Bromohippuric acid	—	850
3-Furoylglycine	—	851, 377
5-Methyl-2-furoylglycine	—	377
5-Chloro-2-furoylglycine	—	377
5-Nitro-2-furoylglycine	—	377
3,4-Dichloro-2-furoylglycine	—	377
3,5-Dimethyl-2-furoylglycine	—	377
2-Thenoylglycine	—	377
3-Thenoylglycine	—	377
3-Methyl-2-thenoylglycine	—	377
5-Methyl-2-thenoylglycine	—	377
3,5-Dimethyl-2-thenoylglycine	—	377
2,5-Dimethyl-3-thenoylglycine	—	377
3-Methyl-5-ethyl-2-thenoylglycine	—	377
5- <i>t</i> -Butyl-2-thenoylglycine	—	377
3-Chloro-2-thenoylglycine	—	377
5-Chloro-2-thenoylglycine	—	377
5-Bromo-2-thenoylglycine	—	377
4-Bromo-3-thenoylglycine	—	377
5-Nitro-2-thenoylglycine	—	377
4,5-Dichloro-2-thenoylglycine	—	377
	—	377
	—	377
	—	377

TABLE 3.3B. (CONTINUED)

No. of Carbon Atoms in Dialdehyde	Dialdehyde $R^2(CHO)_2$
--	----------------------------



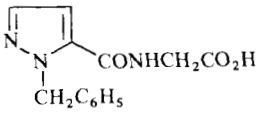
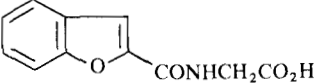
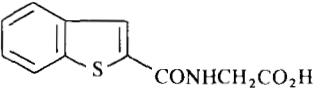
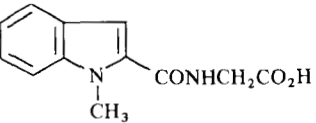
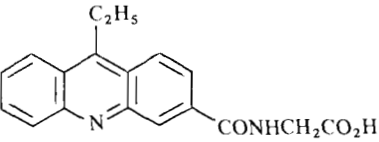
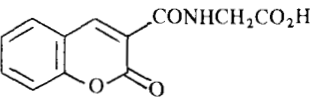
Acylamino Acid $R' \text{CONH}-\text{CH}_2\text{CO}_2\text{H}$	Yield Percent	Reference
 <chem>Nc1ccncc1C(=O)NCC(=O)O</chem>	—	377
 <chem>c1ccc2c(c1)oc(c2)C(=O)NCC(=O)O</chem>	—	377
 <chem>c1ccc2c(c1)sc(c2)C(=O)NCC(=O)O</chem>	—	377
 <chem>CN1C=Cc2ccccc21C(=O)NCC(=O)O</chem>	—	377
 <chem>CCc1c2ccccc2n(c1)C(=O)NCC(=O)O</chem>	—	377
 <chem>CCc1c2ccccc2c(c1)C(=O)NCC(=O)O</chem>	—	377
Mixture of 2-Thenoyl and ^f 2-furoylglycines	—	377 ^f
Aceturic acid	—	363
Hippuric acid	—	363

TABLE 3.3B. (CONTINUED)

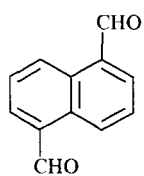
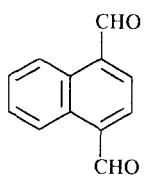
No. of Carbon Atoms in Dialdehyde	Dialdehyde $R^2(CHO)_2$		
10	Mixture of 1,4-$C_6H_4(CHO)_2$ and 2,5-$Cl_2C_6H_4(CHO)_2$-1,4 Mixture of 1,4-$C_6H_4(CHO)_2$ and 3,5-$(CH_3O)_2C_6H_2(CHO)_2$-1,4 <td data-bbox="341 1666 368 1688">12</td> <td> </td>	12	

Acylamino Acid $R^1\text{CONH}-\text{CH}_2\text{CO}_2\text{H}$	Yield Percent	Reference
Hippuric acid	—	354
2-Thenoylglycine	—	377
2-Thenoylglycine	—	377
2-Thenoylglycine ^g	—	377
2-Furoylglycine	—	377
2-Thenoylglycine	—	377
2-Thenoylglycine ^g	—	377
Hippuric acid	—	373
2-Thenoylglycine	—	377
2-Chlorohippuric acid	—	373
3-Chlorohippuric acid	—	373
4-Chlorohippuric acid	—	373
4-Bromohippuric acid	—	373
3-Methylhippuric acid	—	373

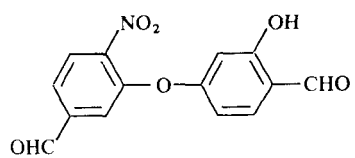
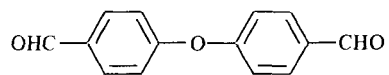
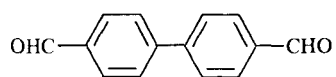
TABLE 3.3B. (CONTINUED)

No. of
Carbon
Atoms in
Dialdehyde

Dialdehyde
 $R^1(CHO)_2$



14



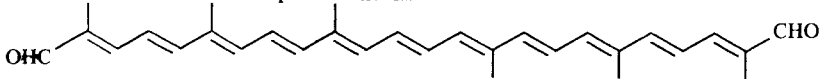
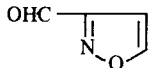
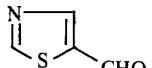
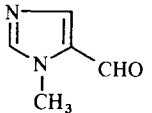
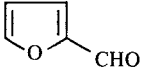
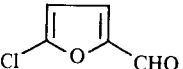
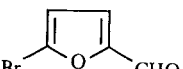
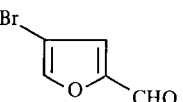
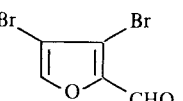
Acylamino Acid R ¹ CONH—CH ₂ CO ₂ H	Yield Percent	Reference
4-Methylhippuric acid	—	373
3-Methoxyhippuric acid	—	373
4-Methoxyhippuric acid	—	373
2,4-Dichlorohippuric acid	—	373
2,5-Dichlorohippuric acid	—	373
2-Thenoylglycine	—	373
<i>h</i>	—	373
Hippuric acid	—	373
2-Chlorohippuric acid	—	373
3-Chlorohippuric acid	—	373
4-Chlorohippuric acid	—	373
2-Methylhippuric acid	—	373
3-Methylhippuric acid	—	373
4-Methylhippuric acid	—	373
3-Methoxyhippuric acid	—	373
4-Methoxyhippuric acid	—	373
Hippuric acid	—	373
2-Thenoylglycine	—	377
Hippuric acid	60	367 ^e
Hippuric acid	—	361

TABLE 3.3B. (CONTINUED)

No. of Carbon Atoms in Dialdehyde	Dialdehyde $R^2(CHO)_2$
15	
16	
16	
16	
16	
18	
18	
	C-24 Diapocarotenedial

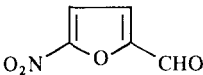
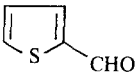
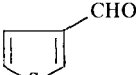
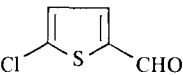
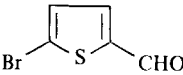
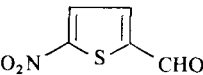
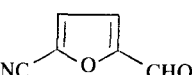
Acylamino Acid $R^1\text{CONH}-\text{CH}_2\text{CO}_2\text{H}$	Yield Percent	Reference
Hippuric acid	57	366
Hippuric acid	—	364
Hippuric acid	—	364
Hippuric acid	—	365
Hippuric acid	—	370
Hippuric acid	—	375, 376 ^e
Hippuric acid	—	371
Hippuric acid	—	372

TABLE 3.3B. (CONTINUED)

No. of Carbon Atoms in Aldehyde	Aldehyde R^2CHO
30	C-30-Diapocarotenedial 
4	
5	      

Bisacylamino Acid	Yield Percent	Reference
Hippuric acid	—	372
Terephthaloyl-bisglycine	—	378
	—	378
	—	378
2,5-Cl ² —1,4-C ₆ H ₂ (CONHCH ₂ CO ₂ H) ₂ 2,6-C ₁₀ H ₆ (CONHCH ₂ CO ₂ H ₂)	—	378
HO ₂ CH ₂ CHNOC—  —CONHCH ₂ CO ₂ H ⁱ	—	378
	—	378
	—	378
	—	378
	—	378

TABLE 3.3B. (CONTINUED)

No. of Carbon Atoms in Aldehyde	Aldehyde R^2CHO
5	
	
	Mixture of 2-thienaldehyde and furfural
	
	
6	
	
	

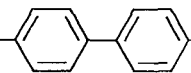
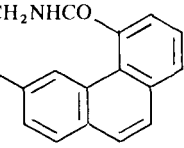
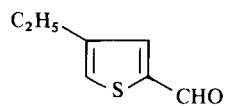
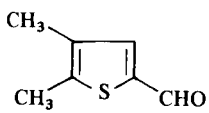
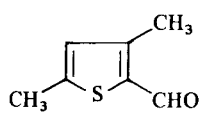
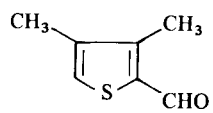
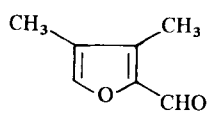
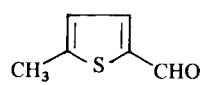
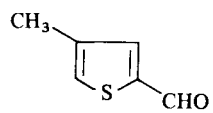
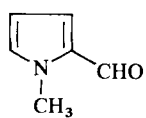
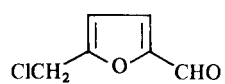
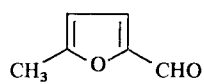
Bisacylamino Acid ⁱ	Yield Percent	Reference
	—	378
$C_6H_4(CNHCH_2COOH)_2$	—	378
$2,5(CH_3)_2 1,4C_6H_2(CONHCH_2CO_2H)_2$	—	378
$2,5(CH_3O)_2 1,4C_6H_2(CONHCH_2CO_2H)_2$	—	378
$2,5Br_2 1,4C_6H_2(CONHCH_2CO_2H)_2$	—	378
HO_2CCH_2NHCO —  — $CONHCH_2CO_2H$	—	378
$2,6C_{10}H_6(CONHCH_2CO_2H)_2$	—	378
HO_2CCH_2NHCO —  — $CONHCH_2CO_2H$	—	378
<i>h</i>	—	378
	—	378 ^g
	—	378
	—	378
	—	378
	—	378
	—	378

TABLE 3.3B. (CONTINUED)

No. of
Carbon
Atoms in
Aldehyde

Aldehyde
 R^2CHO



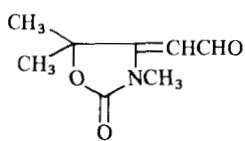
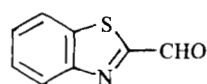
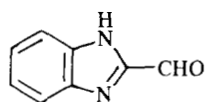
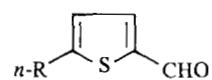
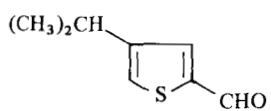
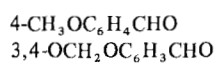
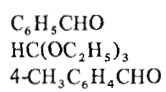
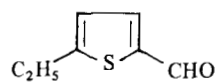
Bisacylamino Acid ⁱ	Yield Percent	Reference
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378

TABLE 3.3B. (CONTINUED)

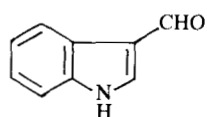
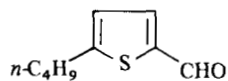
No. of
Carbon
Atoms in
Aldehyde

Aldehyde
 R^2CHO

8

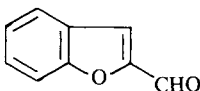
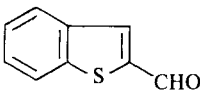
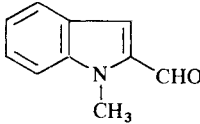
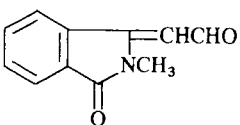
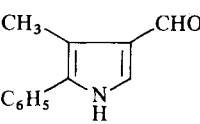
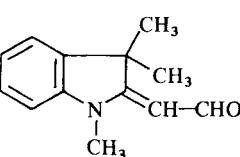
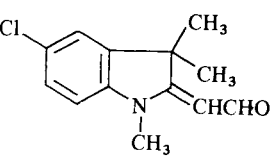
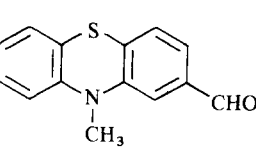


9



Bisacylamino Acid ⁱ	Yield Percent	Reference
	—	378
(CONHCH ₂ CO ₂ H) ₂	—	383
	—	394, 379, 380
	—	381, 382
	—	394
	—	394
	—	394
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378

TABLE 3.3B. (CONTINUED)

No. of Carbon Atoms in Aldehyde	Aldehyde R^2CHO
	
	
10	
11	
12	
13	
	
14	

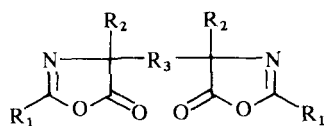
Bisacylamino Acid ⁱ	Yield Percent	Reference
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378

TABLE 3.3B. (CONTINUED)

No. of Carbon Atoms in Aldehyde	Aldehyde R^2CHO
15	
16	
17	
21	

^aThese compounds are prepared by the mixed-anhydride method – heating the bisacylamino acid with ethyl chloroformate and triethylamine.

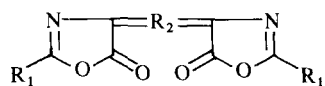
^bThe bisazlactones from here on are connected in the 4-position of the azlactone, e.g.,



^cThis compound is actually a bimeso-oxazolone and bears a CH_3 group on the nitrogen atom.

Bisacylamino Acid ⁱ	Yield Percent	Reference
	—	378
	—	378
	—	378
	—	378
	—	378
	—	378

^dBisazlactones are of the type



^eConverted to the corresponding amino acid.

^fA mixture of 3 bisazlactones is obtained.

^gA mixture of bisazlactones and azlactones is obtained.

^hMixtures of hippuric and substituted hippuric acids were employed to give mixtures of bisazlactones. No yields were reported. See ref. 378 for details.

ⁱThe bisazlactones from here on have the following structure unless otherwise stated: the bisacylamino acid is terephthaloyl-bisglycine, 1,4-C₆H₄(CONHCH₂CO₂H)₂.

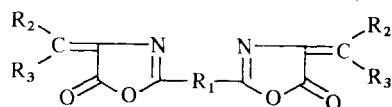
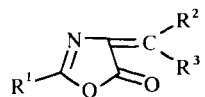
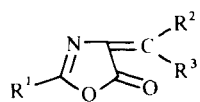


TABLE 3.4. AZLACTONE-BASED MEROCYANINES



No. of Carbon Atoms in Merocyanine	R¹	R²
6	C₆H₅	
	C₆H₅	
	C₆H₅	
	C₆H₅	
	C₆H₅	
	C₆H₅	
	C₆H₅	
	C₆H₅	



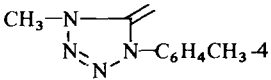
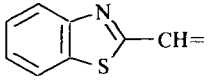
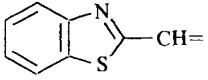
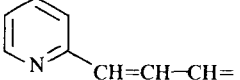
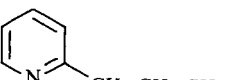
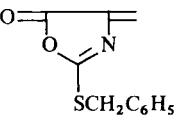
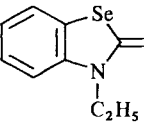
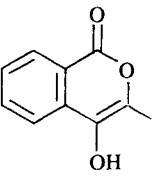
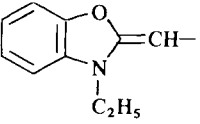
R ³	Yield Percent	Reference
H	—	297 ^a
H	—	297
H	—	297
CH ₃	—	297
H	—	983
—	—	302
H	—	302
—	—	984

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
7	C ₆ H ₅	
	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
8	C ₆ H ₅	
9	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	

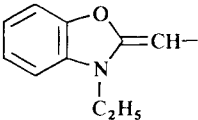
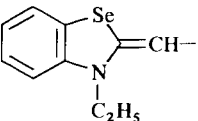
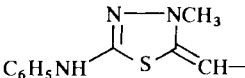
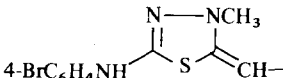
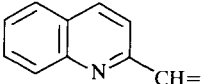
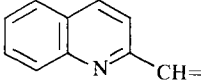
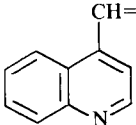
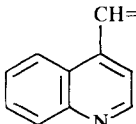
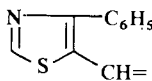
R ³	Yield Percent	Reference
H	—	289
H	—	184
H	—	184
H	—	290
H	—	984
	—	985
H	—	290
H	—	290

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
	C ₆ H ₅	
	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
10	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
11	C ₆ H ₅	

R ³	Yield Percent	Reference
H	—	986
H	—	184
H	—	184
H	—	184
H	—	184
OH	—	294
H	—	302
H	—	292
H	—	297

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	4-CH ₃ C ₆ H ₄	
	C ₆ H ₅	
	4-CH ₃ C ₆ H ₄	
	C ₆ H ₅	

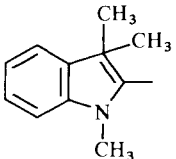
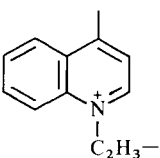
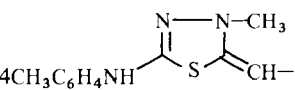
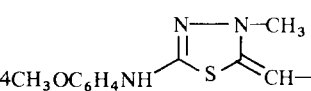
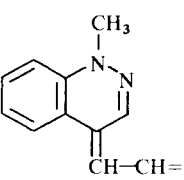
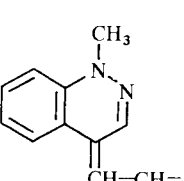
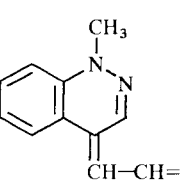
R ³	Yield Percent	Reference
H	—	297
H	—	297
H	—	304
H	—	305
H	—	184
H	—	184
H	—	184
H	—	184
H	—	184

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
12	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	C ₆ H ₅	
	4-CH ₃ C ₆ H ₄	
	C ₆ H ₅	
	C ₆ H ₅ CH=CH-	
	C ₆ H ₅	

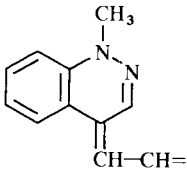
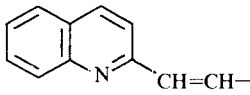
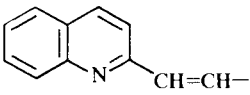
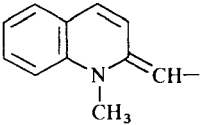
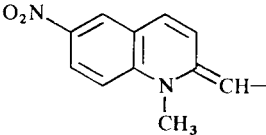
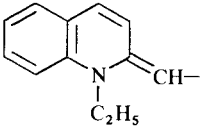
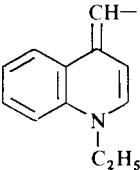
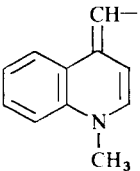
R ³	Yield Percent	Reference
H	—	184
H	—	184
H	—	184
CH ₃	—	297
CH ₃	—	297
H	—	287
H	—	300
H	—	300
H	—	293

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	4-CH ₃ C ₆ H ₄	
	4-CH ₃ OC ₆ H ₄	

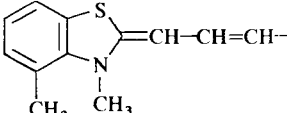
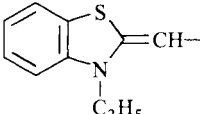
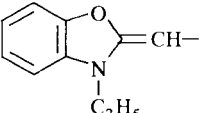
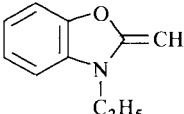
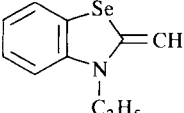
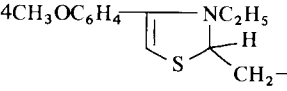
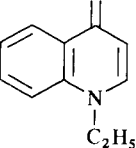
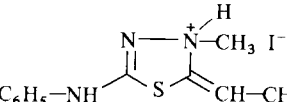
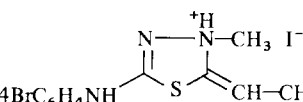
R ³	Yield Percent	Reference
H	—	302
H	—	302
H	—	305
H	—	305
H	—	288, 390, 296
H	—	288, 290, 296
H	—	288, 290, 296

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
13	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
C ₆ H ₅		
C ₆ H ₅		

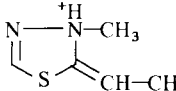
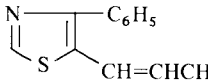
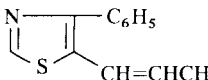
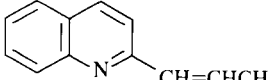
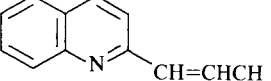
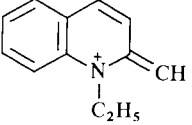
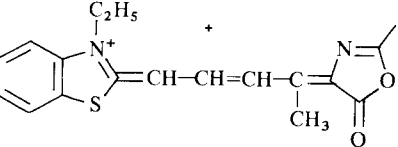
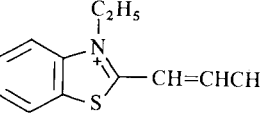
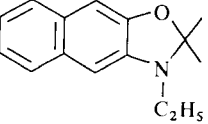
R ³	Yield Percent	Reference
H	—	288, 290, 296
H	—	297
H	—	297
H	—	297
H	—	297
H	—	297, 759
H	—	297
CH ₃	—	297

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	

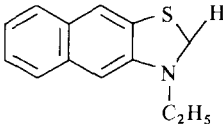
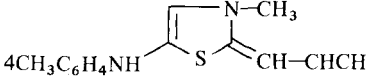
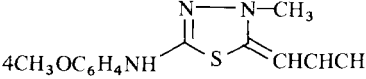
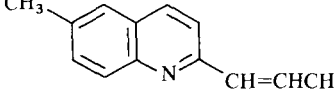
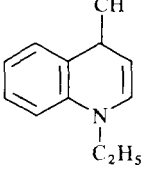
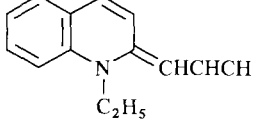
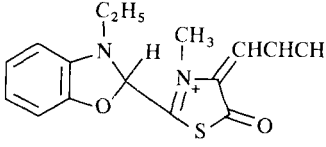
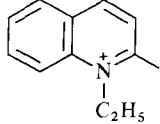
R ³	Yield Percent	Reference
C ₂ H ₅	—	302
C ₂ H ₅	—	297
C ₂ H ₅	—	297
H	—	302
H	—	302
H	—	302
H	—	302
H	—	306
H	—	306

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
14	C ₆ H ₅	
	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅ CH=CH	
	C ₆ H ₅	

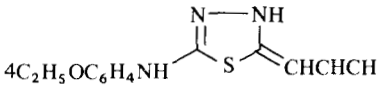
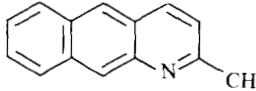
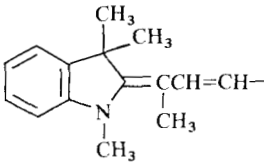
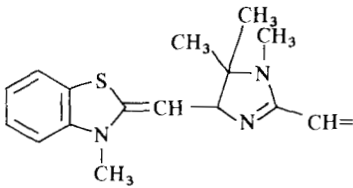
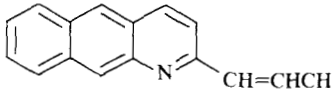
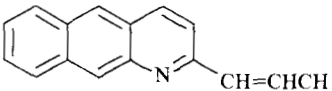
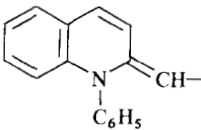
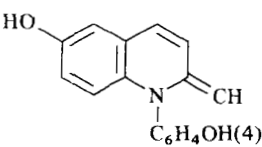
R ³	Yield Percent	Reference
H	—	306
H	—	184
H	—	184
H	—	184
H	—	184
CH ₃	—	297
CH ₃	—	300
CH ₃	—	300
H	—	302

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
15	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	

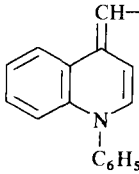
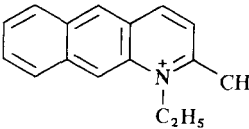
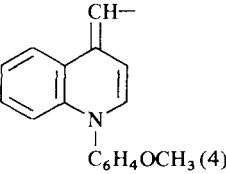
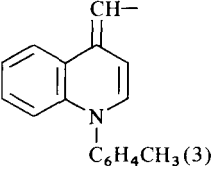
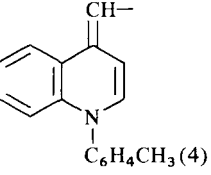
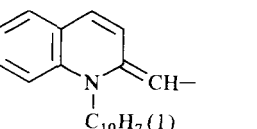
R ³	Yield Percent	Reference
H	—	302
H	—	308
H	—	308
H	—	184
C ₂ H ₅	—	297
C ₂ H ₅	—	297
H	—	301
H	—	302

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
16	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
	C ₆ H ₅	
17	C ₆ H ₅	
	4-O ₂ NC ₆ H ₄	
	C ₆ H ₅	
	C ₆ H ₅	

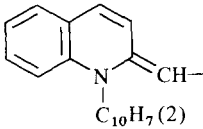
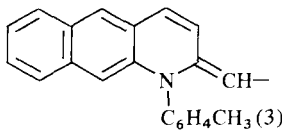
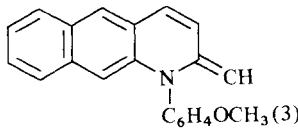
R ³	Yield Percent	Reference
H	—	295
H	—	184
H	—	300
H	—	299
H	—	184
H	—	184
H	—	983
H	—	983

TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R^1	R^2
19	C_6H_5	
	C_6H_5	
	C_6H_5	
	C_6H_5	
21	C_6H_5	
	C_6H_5	

R ³	Yield Percent	Reference
H	—	923
H	—	302
H	—	441
H	—	983
H	—	983
H	—	983
H	—	983

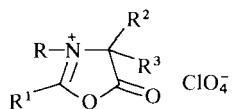
TABLE 3.4. (CONTINUED)

No. of Carbon Atoms in Merocyanine	R ¹	R ²
22	C ₆ H ₅	 C ₁₀ H ₇ (2)
	C ₆ H ₅	 C ₆ H ₄ CH ₃ (3)
	C ₆ H ₅	 C ₆ H ₄ OCH ₃ (3)

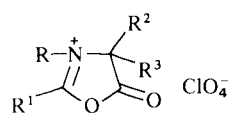
^aThese compounds are prepared by reacting the merocyanine salt with 2-aryl-4-ethoxymethylene-2-oxazotin-5-one.

R ³	Yield Percent	Reference
H	—	983
H	—	983
H	—	983

TABLE 3.5. MESOIONIC AZLACTONES



No. of Carbon Atoms in Mesionic Azlactone	R	R ¹	R ²	R ³	Reactant
9	H	C ₆ H ₅	H	H	C ₆ H ₅ CHO C ₆ H ₅ CH=NC ₆ H ₅
10	CH ₃	C ₆ H ₅	H	H	Intermolecular reaction with itself
	CH ₃	4-ClC ₆ H ₄	H	H	—
	CH ₃	4-O ₂ NC ₆ H ₄	H	H	Intermolecular reaction with itself
	C ₆ H ₅	CH ₃	H	H	Intermolecular reaction with itself
	—	C ₆ H ₅	CH ₃	H	C ₆ H ₅ N=CH—CH=CHC ₆ H ₅
	—	CH ₃	C ₆ H ₅	H	Dimethylacetylene- dicarboxylate



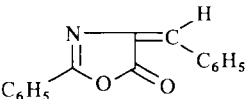
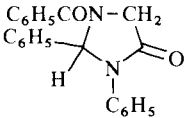
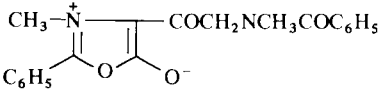
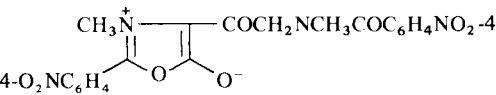
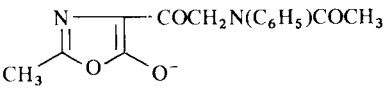
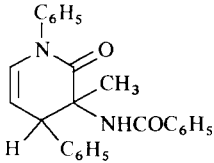
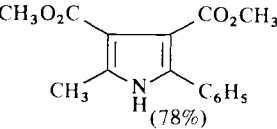
Product	Yield Percent	Reference
	94	174
	—	604, 147
	96	174
—	—	174, 258
—	94	174
	—	174
	85	174
	—	572
	—	587

TABLE 3.5. (CONTINUED)

No. of Carbon Atoms in Mesionic Azlactone	R	R ¹	R ²	R ³	Reactant
	—	C ₆ H ₅	CH ₃	H	Dimethylacetylene- dicarboxylate
11	CH ₃	CH ₃	C ₆ H ₅	H	Dimethyl fumarate
	H	CH ₃	C ₆ H ₅ CH ₂	H	—
12	CH ₃	C ₆ H ₅	CF ₃ CO	H	—
	C ₆ H ₅	CH ₃	CF ₃ CO	H	—
13	—		C ₆ H ₅	H	Dimethyl fumarate
15	C ₆ H ₅	C ₆ H ₅	H	H	Intermolecular reaction with itself
	C ₆ H ₅	4-O ₂ NC ₆ H ₄	H	H	Intermolecular reaction with itself
	C ₆ H ₅	4-ClC ₆ H ₄	H	H	Intermolecular reaction with itself
	H	C ₆ H ₅	C ₆ H ₅	H	—
	—	C ₆ H ₅	C ₆ H ₅	H	CH ₂ =CHX (X = CN; —CO ₂ CH ₃)

Product	Yield Percent	Reference
$ \begin{array}{c} \text{CH}_3\text{O}_2\text{C} \quad \text{CO}_2\text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{CH}_3 \quad \text{C}_6\text{H}_5 \\ \text{N} \\ \text{H} \\ (78\%) \end{array} $	—	587
(Liquid) 83	—	588
—	—	174
—	22	596
—	84	596
$ \begin{array}{c} \text{H} \quad \text{CO}_2\text{CH}_3 \\ \quad \\ \text{CH}_3\text{O}_2\text{C} \quad \text{H} \\ \quad \\ \text{C}_6\text{H}_5 \quad \text{NH} \quad \text{C}_6\text{H}_5 \\ \quad \\ \text{H} \quad \text{CO}_2\text{CH}_3 \\ \quad \\ \text{CH}_3\text{O}_2\text{C} \quad \text{H} \end{array} $	33	591
$ \begin{array}{c} \text{C}_6\text{H}_5-\text{N}^+ \quad \text{COCH}_2\text{N}(\text{C}_6\text{H}_5)\text{COC}_6\text{H}_5 \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5 \quad \text{O} \quad \text{O}^- \end{array} $	74	174
$ \begin{array}{c} \text{C}_6\text{H}_5-\text{N}^+ \quad \text{COCH}_2\text{N}(\text{C}_6\text{H}_5)\text{COC}_6\text{H}_4\text{NO}_2-4 \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ 4-\text{O}_2\text{NC}_6\text{H}_4 \quad \text{O} \quad \text{O}^- \end{array} $	90	174
$ \begin{array}{c} \text{C}_6\text{H}_5-\text{N}^+ \quad \text{COCH}_2\text{N}(\text{C}_6\text{H}_5)\text{COC}_6\text{H}_4\text{Cl}-4 \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ 4-\text{ClC}_6\text{H}_4 \quad \text{O} \quad \text{O}^- \end{array} $	—	174
—	—	174
$ \begin{array}{c} \text{X} \\ \\ \text{C} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5 \quad \text{N} \quad \text{C}_6\text{H}_5 \\ \diagup \quad \diagdown \\ \text{H} \end{array} $ (X = CN; -CO ₂ CH ₃)	—	594, 598, 599–601

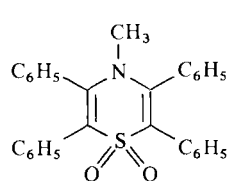
TABLE 3.5. (CONTINUED)

No. of Carbon Atoms in Mesionic Azlactone	R	R ¹	R ²	R ³	Reactant
					$\text{CH}_3\text{O}_2\text{CC}\equiv\text{CCO}_2\text{CH}_3$
15	—	C_6H_5	$2\text{-O}_2\text{NC}_6\text{H}_4$	H	$\text{CH}_3\text{O}_2\text{CC}\equiv\text{CCO}_2\text{CH}_3$
	—	C_6H_5	$4\text{-O}_2\text{NC}_6\text{H}_4$	H	$\text{CH}_3\text{O}_2\text{CC}\equiv\text{CCO}_2\text{CH}_3$
16	C_6H_5	$4\text{CH}_3\text{OC}_6\text{H}_4$	H	H	Intermolecular reaction with itself
	—	$4\text{-CH}_3\text{OC}_6\text{H}_4$	C_6H_5	H	$\text{CH}_3\text{O}_2\text{CC}\equiv\text{CCO}_2\text{CH}_3$
	CH_3	$(\text{C}_6\text{H}_5)_2\text{N}$	H	H	—
	CH_3	C_6H_5	C_6H_5	H	—
					Dimethyl maleate Ethyl cinnamate $\text{C}_6\text{H}_5\text{C}\equiv\text{CC}_6\text{H}_5$
					Dimethyl fumarate
					Dibenzoyl ethylene Styrene $(\text{C}_6\text{H}_5)_2\text{C}=\text{CH}_2$ Stilbene

Product	Yield Percent	Reference
$ \begin{array}{c} \text{CH}_3\text{O}_2\text{C} \quad \text{CO}_2\text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5 \quad \text{N} \quad \text{C}_6\text{H}_5 \\ \diagup \quad \diagdown \\ \text{H} \end{array} $	—	586, 587 589, 591, 593
$ \begin{array}{c} \text{CH}_3\text{O}_2\text{C} \quad \text{CO}_2\text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5 \quad \text{N} \quad \text{C}_6\text{H}_4\text{NO}_2-2 \\ \diagup \quad \diagdown \\ \text{H} \end{array} $	—	586, 587, 593
$ \begin{array}{c} \text{CH}_3\text{O}_2\text{C} \quad \text{CO}_2\text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5 \quad \text{N} \quad \text{C}_6\text{H}_4\text{NO}_2-4 \\ \diagup \quad \diagdown \\ \text{H} \end{array} $	—	586, 587, 593
$ \begin{array}{c} \text{C}_6\text{H}_5-\text{N}^+ \quad \text{COCH}_2\text{N}(\text{C}_6\text{H}_5)\text{COC}_6\text{H}_4\text{OCH}_3-4 \\ \diagdown \quad \diagup \\ 4\text{CH}_3\text{OC}_6\text{H}_4 \quad \text{O} \quad \text{O}^- \end{array} $	83	174
$ \begin{array}{c} \text{CH}_3\text{O}_2\text{C} \quad \text{CO}_2\text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C}_6\text{H}_5 \quad \text{N} \quad \text{C}_6\text{H}_4\text{OCH}_3-4 \\ \diagup \quad \diagdown \\ \text{H} \end{array} $	—	586, 587, 593
—	92	174
—	83	596
$ \begin{array}{c} \text{X} \quad \text{Y} \quad \text{Z} \\ \diagdown \quad \diagup \quad \diagdown \\ \text{H} \quad \text{N} \quad \text{C}_6\text{H}_5 \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5 \quad \text{CH}_3 \end{array} $	— —	589 592, 593, 594
X = Z = CO ₂ CH ₃ ; Y = H		
X = C ₆ H ₅ ; Z = CO ₂ CH ₃		
X = Z = C ₆ H ₅ , Y = H	—	589, 591, 594
X = Z = CO ₂ CH ₃ , Y = H		
X = Z = C ₆ H ₅ CO, Y = H	—	589, 591, 594
Y = X = H; Z = C ₆ H ₅		
Z = H; X = Y = C ₆ H ₅	—	589, 591, 594
X = Z = C ₆ H ₅ ; Y = H	—	589, 591, 594

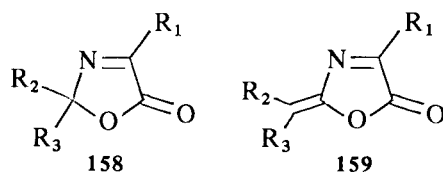
TABLE 3.5. (CONTINUED)

No. of Carbon Atoms in Mesoionic Azlactone	R	R ¹	R ²	R ³	Reactant
16	CH ₃	C ₆ H ₅	C ₆ H ₅	H	$\begin{array}{c} \text{C}_6\text{H}_5\text{C}=\text{CC}_6\text{H}_5 \\ \diagdown \quad \diagup \\ \text{S} \\ \text{O}_2 \end{array}$
17	CH ₃	C ₆ H ₅	C ₆ H ₅ CH=	—	
22	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅ CH=	—	
24	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅ CH=CHCH	—	
	CH ₃	C ₆ H ₅	$\begin{array}{c} \text{O} \quad \text{O} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{C}_6\text{H}_5 \\ \\ \text{N}^+ \\ \\ \text{CH}_3 \end{array}$	H	4-IIC≡COC ₆ H ₄ COC≡CH

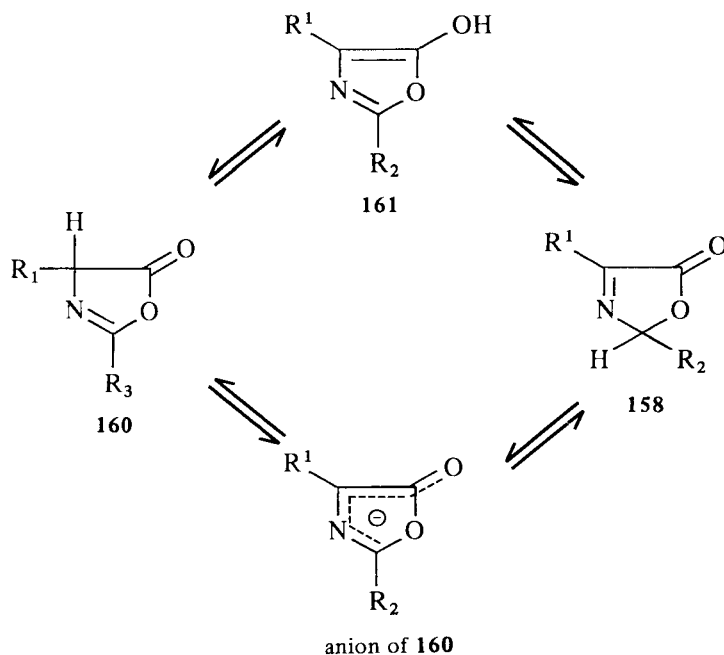
Product	Yield Percent	Reference
	—	605
—	81	704
—	72	174
—	49	174
Pyrrole derivative	—	605

3.3. 5-[2H] OXAZOLONES (3-OXAZOLIN-5-ONES)

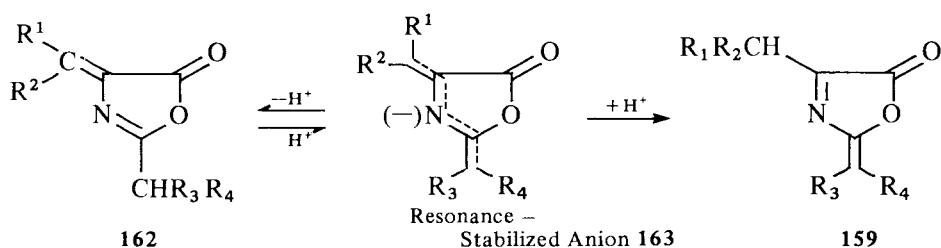
3-Oxazolin-5-ones (**158** and **159**) are commonly known as 'pseudoxazolones.' Their chemistry has been extensively reviewed.⁹⁸⁷⁻⁹⁹⁴



These compounds may be considered to be a special class of oxazolones formed by a 1,3-prototropic shift in the azlactones.

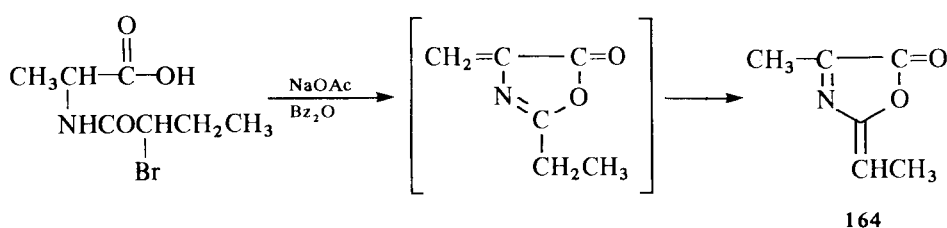


For pseudoxazolones with an exocyclic double bond, the equilibrium may be depicted as



Steglich⁹⁹⁰ pointed out that **159** will be the product when R¹R² are (H, H; Br, H; CH₃, CH₃ and C₆H₅, H) and R³ and R⁴ are (CH₃, CH₃ or C₆H₅, H; C₆H₅, H; Cl, and Cl, Cl).

Pseudoxazolones may be classified as saturated 5-[2H] oxazolones with no exocyclic double bond **158** and unsaturated 5-[2H] oxazolones with an exocyclic double bond in the 2-position of the ring **159**. The first example of type **159** was 4-methyl-2-ethylidene-5-[2H] oxazolone **164** formed by cyclization of a haloacyl-amino acid, such as α-bromopropionyl glycine.



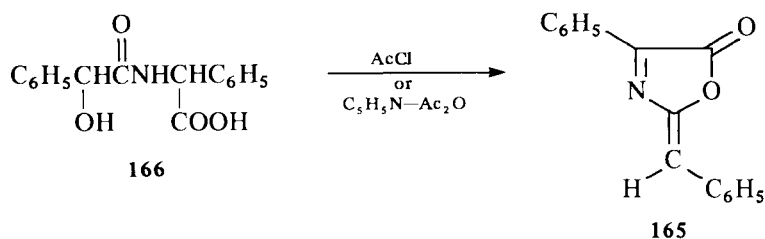
The use of acetic anhydride instead of benzoic anhydride led to the formation of pyruvic acid (CH₃COCO₂H).⁹⁹⁵ 4-Methyl-2-benzylidene-5-[2H] oxazolone was prepared similarly by cyclization of 2-phenyl acetamido-3-bromopropionic acid⁹⁹⁶ or *N*-α-chlorophenyl acetylalanine.⁹⁹⁷

This first saturated pseudoxazolone reported was 2-trifluoromethyl-4-methyl oxazolone.⁹⁹⁸ This compound was originally thought to be a 2-oxazolin-5-one. Subsequently, NMR studies established the pseudoxazolone structure.⁹⁹⁹

3.3.1. Methods of Preparation

The unsaturated pseudoxazolones have been prepared by application of the Bergmann–Stern reaction (see 5-[4H] oxazolone section for a detailed discussion). α-Haloacylamino acids may be cyclized by heating in an acetic anhydride–pyridine mixture.^{995, 997, 1000–1003}

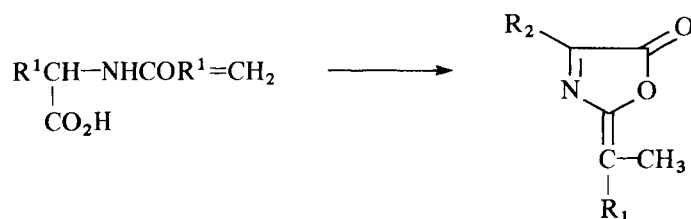
For the preparation of 4-phenyl-2-benzylidene 5-[2H] oxazolone **165**, *dl*-*N*-mandeloyl phenylglycine **166** was heated with acetyl chloride.¹⁰⁰² Both diastereomers of **166** were converted to **165**.¹⁰⁰⁴



The *trans* geometry of **165** was established by NMR.

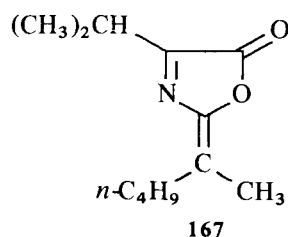
Steglich and co-workers applied the Bergmann–Stern reaction to the synthesis of 2-alkylidene and 2-dichloromethylene-4-alkyl-pseudooxazolones.^{1005,1006}

Cyclodehydration of *N*-acryloyl- α -amino acids in an acetic anhydride–pyridine mixture gives pseudooxazolones, whereas in the absence of pyridine, only 2-oxazolin-5-ones are obtained.^{1007–1010}



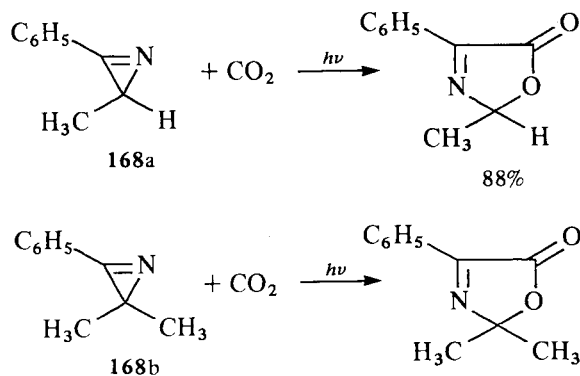
3.3.1.1. Geometric Isomers of 2-Alkylidene-(arylidene)-4-Alkyl-(aryl)-5-[2*H*]Oxazolones

The existence of isomers of 4-alkyl-2-alkylidene-5-[2*H*] oxazolones and of **167** has been identified by NMR.^{1005,1007} However, the less stable isomers have not been isolated.

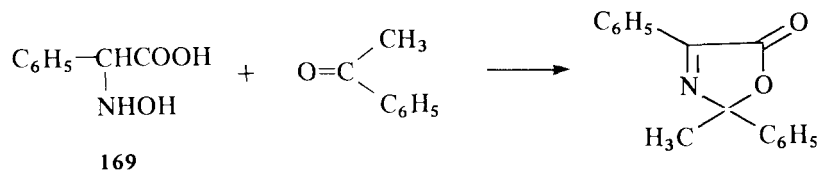


3.3.1.2. Saturated Pseudooxazolones

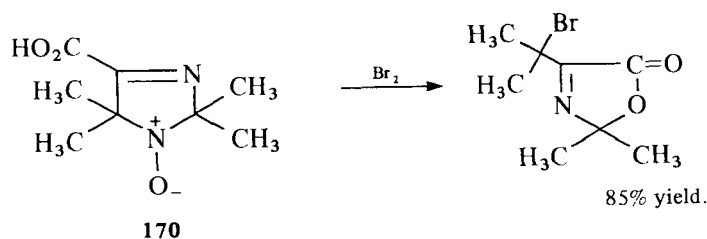
Arylazirines **168** undergo smooth photocycloaddition to carbon dioxide in an inert solvent.¹⁰¹¹ 2-Phenylazirine similarly gives 2,4-diphenyl-5-[2*H*] oxazolone.^{1012–1018}



α -Hydroxyamino acids **169** react with carbonyl compounds (which also serve as the solvent) in the presence of triethylamine to give 3-oxazolin-5-ones.¹⁰¹⁹ *N*-Formylamino acids work equally well.¹⁰²⁰

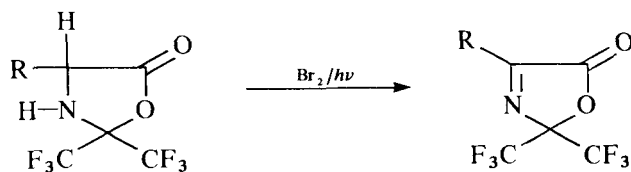


An interesting conversion of an imidazoline **170** to a pseudooxazolone has been reported.¹⁰²¹



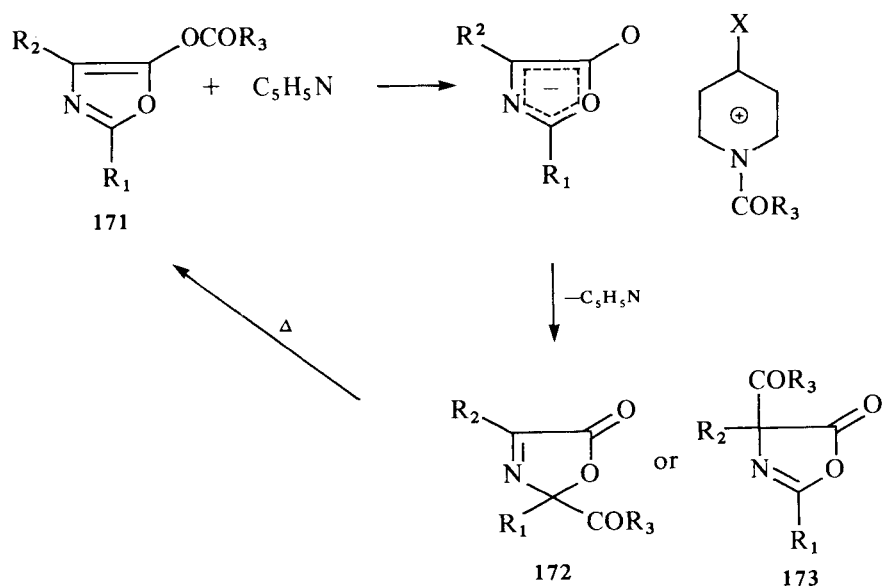
Reaction of methyl [4*S*, 6*S*]-5,5,9,9-tetramethyl-7-oxo-8-oxa-4-thial-azabicyclo-[4.3.0] non-2-ene-3-carboxylate-4-oxide with acetyl chloride followed by a series of transformations leads to the formation of 3-oxazolin-5-ones.^{1022, 1023}

Photolysis in the presence of bromine or heating with sulfur chloride converts 2,2 bis(trifluoromethyl) 1,3-oxazolidin-5-ones to 2,2-bis(trifluoromethyl) 5-[2*H*]-oxazolones.¹⁰²⁴

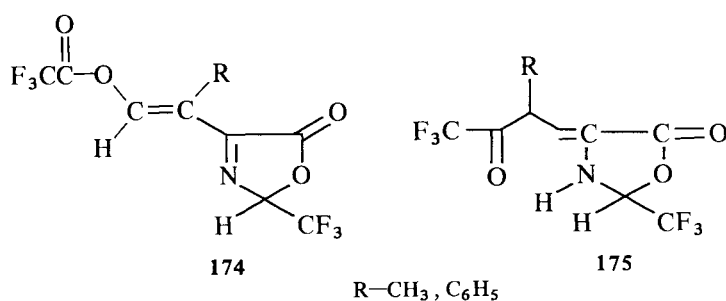


3.3.1.3. Pseudoxazolones as Intermediates in Other Syntheses

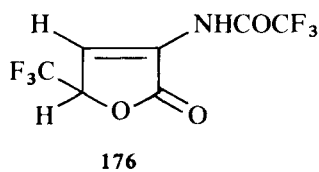
Much work has been done by Steglich and co-workers in this field. In the Dakin-West reaction (see section on 2-oxazolin-5-ones), pseudoxazolones were isolated as intermediates.^{1025, 1026} It is noteworthy that the original trisubstituted oxazole **171** may be recovered by heating either **172** or **173**.¹⁰²⁵⁻¹⁰²⁷

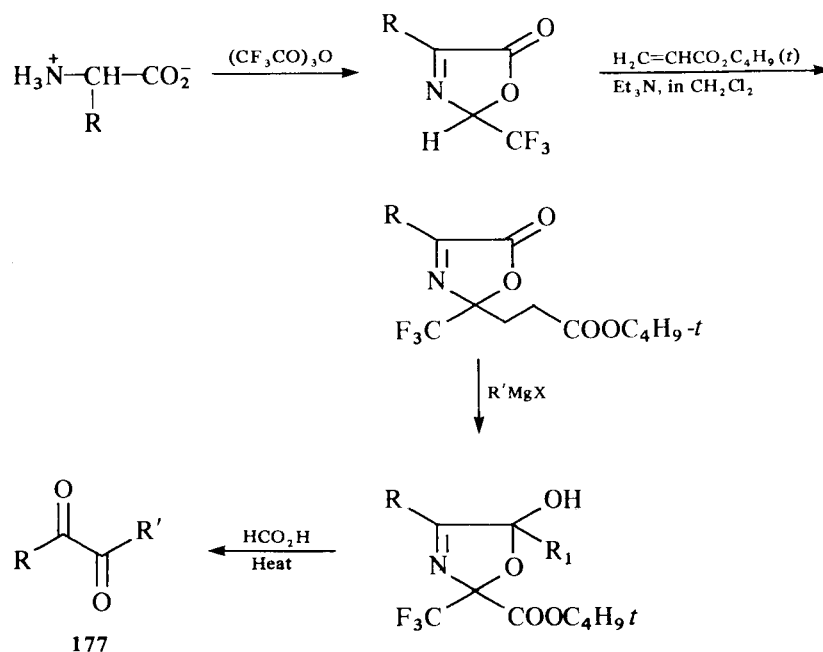


Treatment of α -amino acids with an excess of trifluoroacetic anhydride yields pseudoxazolone enol trifluoroacetates **174** and oxazolidinones **175**.¹⁰²⁸⁻¹⁰³¹

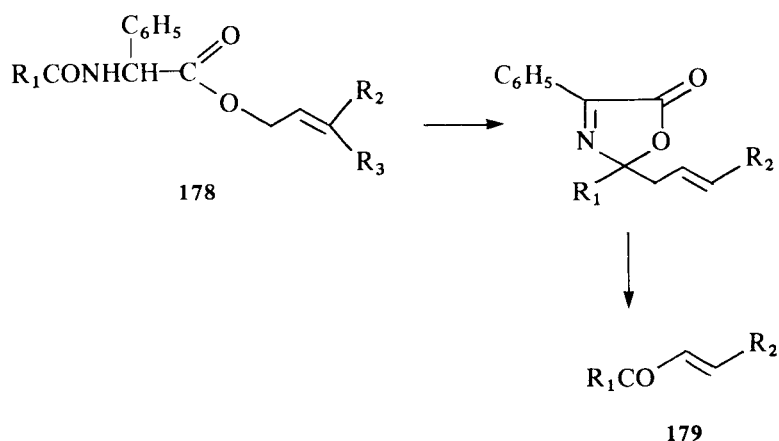


Further reaction of **174** with excess trifluoroacetic anhydride converts it to a dihydrofuranone derivative **176**.¹⁰³² The conversion of α -amino acids to 5-[2*H*]-oxazolones provides a useful method for the asymmetric synthesis of optically pure dipeptides.¹⁰⁴³ α -Diketones may be prepared from α -amino acids through the intermediacy of pseudoxazolones.¹⁰³⁴

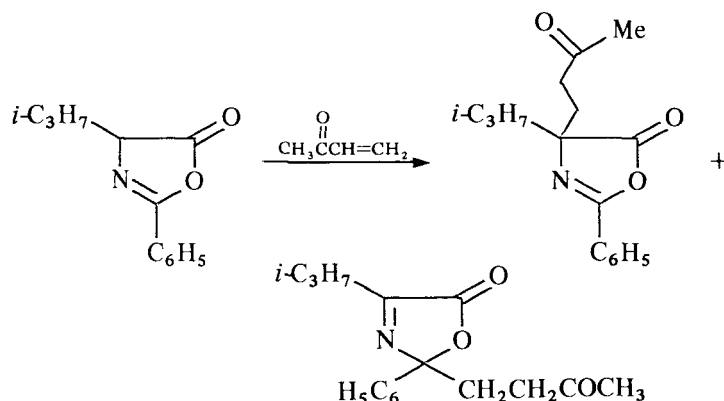




The allyl esters of phenylglycine 178 have been converted to pseudoxazolones by treatment with phosgene or triphenylphosphine carbon tetrachloride in a triethylamine–acetonitrile mixture.^{1035, 1036} These compounds can be hydrolyzed to β,γ -unsaturated ketones 179.



5-Allyloxyoxazoles, prepared from allyl and propargyl esters of N-acylamino acids, undergo rearrangement to 2-[5H]- and 5-[2H] oxazolones on treatment with phosgene in toluene.¹⁰³⁷ 5-[2H] Oxazolones are also obtained as by-products in the acylation of 5-[4H] oxazolones.^{1038, 1039}



The most obvious method for preparing saturated pseudoxazolones is to start from the corresponding 5-[4*H*] oxazolones¹⁰⁴⁰ by alkylation and thermolysis or by acylation.¹⁰³⁹

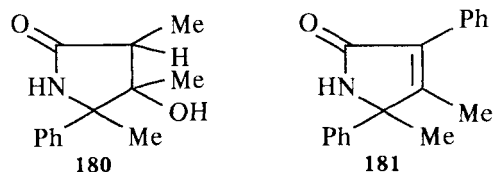
3.3.2. Reactions of Pseudoxazolones

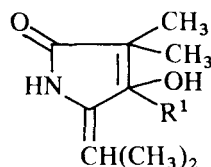
3.3.2.1. Unsaturated 5-[2*H*] Oxazolones

The reactions of this class have been extensively reviewed previously⁹⁸⁹⁻⁹⁹¹ Aminolysis and treatment with hydrazine yield ring-opened products.¹⁰⁴¹⁻¹⁰⁴⁴ Reaction with hydrazoic acid provides ureas via the intermediate isocyanate.¹⁰⁴⁵ Under Friedel-Crafts conditions, 2-benzylidene-4-phenyl-5-[2*H*] oxazolone is converted to 2-benzhydryl-4-phenyl-5[4*H*] oxazolone, which hydrolyzes to *N*-(2,2-diphenylacetyl)phenylglycine.¹⁰⁴⁶ Similar results have been obtained with 2-isopropylidene pseudoxazolones.^{1047,1048}

3.3.2.1.1. REACTION WITH GRIGNARD REAGENTS

Adembri¹⁰⁴⁹⁻¹⁰⁵¹ reinvestigated the reaction of 4-phenyl-2-benzylidene-5-[2*H*]-oxazolone with methyl magnesium iodide. Instead of the open-chain product claimed by Mustafa,¹⁰⁴⁶ two of the four possible pairs of enantiomers of 4-hydroxy-4,5-dimethyl-3,5-diphenylpyrrolidin-2-one **180** were obtained, which on elimination of water gave 4-5-dimethyl-3,5-diphenylpyrroline-2-one **181**. Compound **180** arises from both 2,4-addition and nucleophilic attack of the Grignard reagent at the lactone carbonyl carbon. Phenylmagnesium bromide yielded the 2,3,4,5-tetra-phenyl analog of **180** and the 2,3,5,5-tetraphenyl analog of **181**.



**182**

3,3,5,5-Tetrasubstituted pyrrolidin-2,4-diones were reportedly the end products of the reaction of 2-alkylidene pseudoxazolones with Grignard reagents.¹⁰⁵²

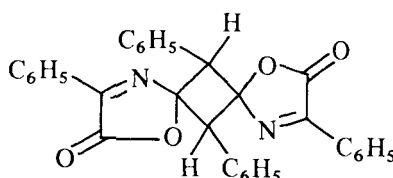
Reaction with methyl- or phenyllithium¹⁰⁵³ yielded 3,5-dimethyl-4-hydroxy-4-alkyl (aryl)-5-alkylidene-2-pyrrolidin-2-ones **182**.

3.3.2.1.2. POLYMERIZATION REACTIONS OF 2-ISOPROPYLIDENE PSEUDOXAZOLONES

2-Isopropylidene-5-[2*H*] oxazolone **183** polymerizes spontaneously at room temperature.¹⁰⁵⁴ Also, γ -rays convert the 4-methyl derivative **183** of **180** to a polymer.¹⁰⁵⁵ Compound **181** was block copolymerized with styrene,¹⁰⁵⁶ 1,6-hexamethylene diamine,¹⁰⁵⁷ and other monomers.¹⁰⁵⁸⁻¹⁰⁶⁰ 4-Methyl-2-ethylidene-5-[2*H*] oxazolone was also polymerized.^{1054, 1061}

3.3.2.1.3. PHOTODIMERIZATION

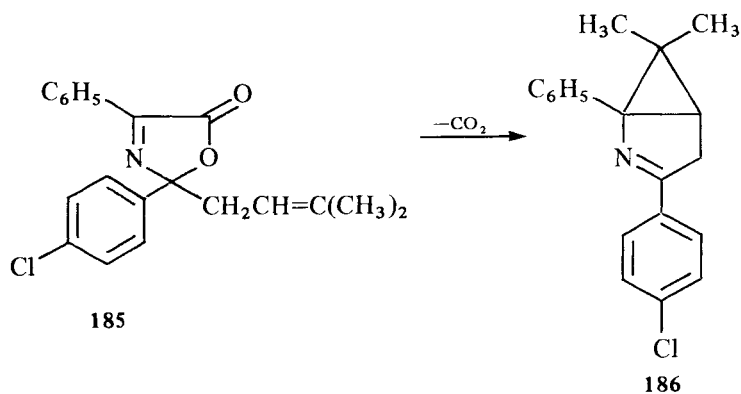
2-Methyl (and phenyl)-4-benzylidene-5-[2*H*]-oxazolones dimerize either in the solid state or in a solution of benzene to give a cyclobutane centrosymmetric structure, for example, **184**.^{1000, 1062, 1063}

**184**

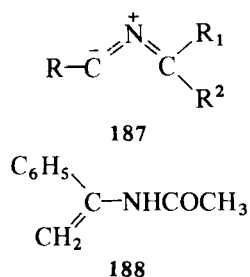
3.3.2.2. Saturated 5-[2*H*] Oxazolones

Some of the applications of the 5-[2*H*] oxazolone moiety in organic synthesis have been discussed earlier. Quinoxaline and pterines were obtained on reaction with *o*-phenylenediamine¹⁰⁶⁴ and 2,4,5-triamino 6-isopropoxyxypyrimidine.¹⁰⁶⁵

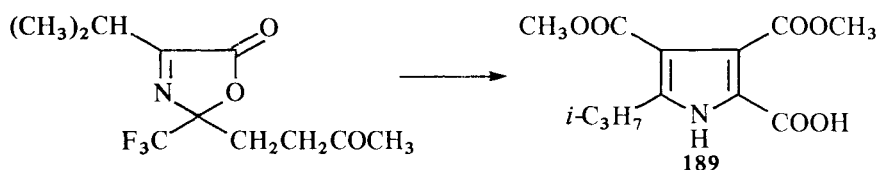
Benzothiazines¹⁰⁶⁶ and 1-acyloxyindazolones¹⁰⁶⁷ are obtained by heating pseudoxazolones containing thiophenyl or 2,4-dinitrophenyl substituents in the 2-position of the oxazolone ring. When **185**, a 2-allyl-substituted pseudoxazolone is heated, an azabicyclohexane 3,1,0 derivative¹⁰⁶⁸ **186** is obtained.



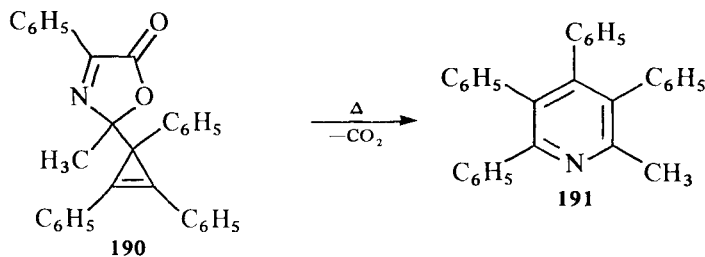
It has been reported that pseudoxazolones are converted to nitrile ylids by loss of CO_2 on heating.^{1069,1070} By contrast, decarbonylation of pseudoxazolones gives actimides 188.¹⁰¹⁶



Compound 187 ($\text{R} = i\text{-C}_3\text{H}_7$; $\text{R}^1 = \text{CF}_3$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{COCH}_3$) reacts with dimethylacetylene dicarboxylate, and after hydrolysis, a pyrrole derivative 189 is obtained.¹⁰⁷¹ Imidazolines have been isolated from nitrile ylids.¹⁰⁷²



Pyrolysis of the pseudoxazolone 190 converts it into a pyridine derivative 191.¹⁰⁷³

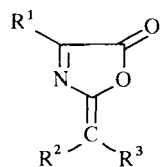


Stereospecific synthesis of *E*-3-alkoxy and 3-alkylthio-2-butenols has been achieved via the intermediate pseudoxazolone.¹⁰⁷⁴ Finally, pseudoxazolones are valuable for the synthesis of Δ -aminolevulinic acid.¹⁰⁷⁵

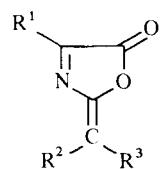
The gas chromatographic and mass spectrometric character of 2-trifluoromethyl 3-oxazolin-5-ones was determined.¹⁰⁷⁶

Several reported unsaturated and saturated pseudoxazolones are tabulated in Tables 3.6A and 3.6B.

TABLE 3.6A. UNSATURATED 3-OXAZOLIN-5-ONES



No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
4	H	Cl
5	CH ₃	Cl
6	CH ₃	H
	CH ₃	H
	C ₂ H ₅	Cl
	C ₂ H ₅	H
	C ₂ H ₅ S	H
7	CH ₃	H
	<i>n</i> -C ₃ H ₇	Cl
	<i>i</i> -C ₃ H ₇	Cl
	<i>i</i> -C ₃ H ₇	H
	CH ₃	CH ₃
8	<i>i</i> -C ₃ H ₇	H
	C ₂ H ₅	CH ₃
	<i>n</i> -C ₄ H ₉	Cl
	(CH ₃) ₂ CHCH ₂	H
	(CH ₃) ₂ CHCH ₂	Cl
	<i>s</i> -C ₄ H ₉	Cl
	C ₂ H ₅	CH ₃
	CH ₃	CH ₃
9	(CH ₃) ₂ CH	CH ₃
	(CH ₃) ₂ CHCH ₂	CH ₃
	<i>i</i> -C ₃ H ₇	CH ₃
10	<i>i</i> -C ₄ H ₉	CH ₃
11	(CH ₃) ₂ CHCH ₂	CH ₃
	(CH ₃) ₃ C	CH ₃
	C ₆ H ₅	Cl
	CH ₃	H
12	C ₆ H ₅	CH ₃
	<i>i</i> -C ₃ H ₇	CH ₃
	C ₆ H ₅ CH ₂ OCH ₂	Cl
14	CH ₃ O ₂ CCH ₂ CH ₂	C ₆ H ₅
15	C ₆ H ₅	H



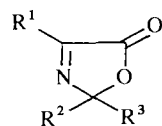
R ³	Yield Percent	Reference
Cl	70	1006
Cl	89	1006
	81	1006
H	100	1005
H	92	1005
Cl	81, 86	1006
H	18, 85	1005
Cl	69	1006
CH ₃	—	1021
Cl	85	1006
Cl	86	1006
H	100	1005
CH ₃	41	1007, 1008
Br	90	1005
H	85, 80	1005
Cl	82	1006
H	100	1005
Cl	81	1006
Cl	74	1006
CH ₃	90	1005
CH ₃	100	1005
CH ₃	100	1005
H	100	1005
CH ₃	64	1007, 1008
CH ₃	41	1009
	78	1009
	100	1005
CH ₃	78	1007
		1008
CH ₃	69	1007
		1008
Cl	81	1006
C ₆ H ₅	84	1000
		1040
	—	1009
	91	1002
CH ₃	14	1007
<i>n</i> -C ₄ H ₉	58	1007
Cl	49	1006
H	—	1003
C ₆ H ₅	53	1004
	—	1002

TABLE 3.6A. (CONTINUED)

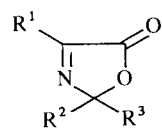
No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
16	CH ₃	C ₆ H ₅
18	Dimethylbenzyl	H
19	CH ₃	4CH ₃ C ₆ H ₄
20	<i>i</i> -C ₄ H ₉	C ₆ H ₅
21	<i>i</i> -C ₃ H ₇	4CH ₃ C ₆ H ₄
22	C ₆ H ₅	C ₆ H ₅ S
	<i>i</i> -C ₄ H ₉	4CH ₃ C ₆ H ₄

R ³	Yield Percent	Reference
C ₆ H ₅	59	1077
C ₆ H ₅	—	1003
4CH ₃ C ₆ H ₄	53	1077
C ₆ H ₅	58	1077
4CH ₃ C ₆ H ₄	84	1077
C ₆ H ₅ S	50	1006
4-CH ₃ C ₆ H ₄	54	1077

TABLE 3.6B. SATURATED-3-OXAZOLIN-5-ONES



No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
5	CH ₃	H
	H	CF ₃
6	CH ₃	CH ₃
	C ₂ H ₅	H
	CH ₃	CF ₃
	CH ₃	H
	CH ₃	CF ₃
	CH ₃	CF ₃
7	(CH ₃) ₂ CH	H
	C ₂ H ₅	CF ₃
	CH ₃ O ₂ CCH ₂ —	H
	CH ₃ SCH ₂ CH ₂	H
	CH ₃	H
	CH ₃	CF ₃
8	C ₂ H ₅ C—CH ₃ Br	H
	(CH ₃)CH ₂ CHBr	H
	(CH ₃) ₂ CHCH ₂ CH ₂	H
	CH ₃ —C— i-C ₃ H ₇	CH ₃
	Br CH ₃ C	CF ₃
	CH ₃ C ₂ H ₅ O ₂ CCH ₂ — CH ₃	H
	C ₂ H ₅ C	H
	(CH ₃) ₃ C	H
	C ₆ H ₅	H
	CF ₃ CO ₂ C(CF ₃) CH—	H
	CH ₃ CH ₂ CBrCH ₃ 	CH ₃
	CF ₃ CONHCH ₂ CH ₂ CH ₂ —	H
	C ₆ H ₅ CH ₂	H
	C ₆ H ₅	H



R ³	Yield Percent	Reference
CF ₃	—	1078
CF ₃	72	1024, 1084
CH ₃	3	1019
CF ₃	66	1079
CF ₃	71	1024
C ₂ H ₅	—	990
COCH ₃	60	1026
COOCH ₃	66	1026
CF ₃	—	1035, 1078
CF ₃	62	1024
CF ₃	—	1031
CF ₃	—	1034
<i>n</i> -C ₃ F ₇	41	1032
COOCH ₃	—	1025
CF ₃	78	1079
CF ₃	86	1079
CF ₃	—	1078
CH ₃	66	1022, 1023
CF ₃	62	1024
CF ₃	60	1024
CF ₃	—	1031
CF ₃	—	1034
CF ₃	83	1033
H	30	1013
	92	1015
CF ₃	70	1029, 1031
		1081
CH ₃	85	1079
CF ₃	—	1034
H	40	1003
	—	1077
CH ₃	63–72	1015, 1016

TABLE 3.6B. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R^1	R^2
11	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_2\text{H}_5\text{C}- \\ \\ \text{Br} \end{array}$	
	C_6H_5 $\text{CF}_3\text{CONHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ $i\text{-C}_4\text{H}_9$	H H CF_3
	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CF}_3\text{CO}_2\text{C}=\text{C}- \\ \\ \text{CH}_3 \end{array}$	H
	C_6H_5	CH_3
	$\text{C}_6\text{H}_5\text{CH}_2$ $\text{C}_6\text{H}_5\text{CHBr}$ CH_3	H H
	CH_3	H
	CH_3 $(\text{CH}_3)_2\text{C}-\text{CH}(\text{Cl})\text{COOMe}$ $(\text{CH}_3)_2\text{C}-\text{SCH}_2\text{COOMe}$	H CH_3 CH_3
	$\begin{array}{c} \text{O} \\ \uparrow \\ (\text{CH}_3)_2\text{C}-\text{SCH}_2\text{COOMe} \end{array}$	CH_3
	C_6H_5 $(\text{CH}_3)_2\text{CH}$ $\text{CO}_2\text{C}(\text{CF}_3)=\text{C}-$ $\quad\quad\quad $ $\quad\quad\quad \text{CH}_3$	CF_3 CF_3 CF_3
	C_6H_5 C_6H_5	H CH_3
	$\begin{array}{c} \text{CHO} \\ \\ (\text{CH}_3)_2\text{C}-\text{SC}-\text{CO}_2\text{CH}_3 \\ \\ \text{Cl} \end{array}$	CH_3

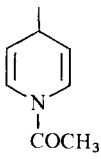
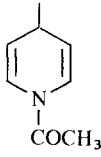
R ³	Yield Percent	Reference
	70	1021
CF ₃	—	1034
CF ₃	—	1034
—COOCH ₃	—	1025
CF ₃	46	1029, 1081 1082
CH ₃	70	1015
	80	1071
	94	1079
CF ₃	50	1079
CF ₃	62	1079, 1080
	—	1020
	—	1020
	—	1020
CH ₃	16	1022, 1023
CH ₃	—	1022
CF ₃	—	1022
CF ₃	87	1024
—CH ₂ CH ₂ COH ₃	84	1071
H	—	1082
<i>i</i> -C ₃ H ₇	33	1018
C ₂ H ₅	70	1019
C ₂ H ₅	—	1022, 1023

TABLE 3.6B. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
	C ₆ H ₅ CH ₂	CF ₃
	C ₆ H ₅ CH— Br	CF ₃
	(CH ₃) ₂ CH—	—CH ₂ CH ₂ CN
	CH ₃	CF ₃
	CH ₃	CF ₃
	C ₆ H ₅	CF ₃
	CH ₃	CF ₃
	CH ₃	CF ₃
	CH ₃	CF ₃
	CH ₃	CF ₃
	CH ₃	CF ₃
13	$\begin{array}{c} \text{C}_6\text{H}_5 \\ \\ (\text{CH}_3)_2\text{C} - \text{S} - \text{C} - \text{COOCH}_3 \\ \quad \quad \\ \text{CHOCH}_3 \end{array}$	H CH ₃
	$\begin{array}{c} \text{SCHCOOCH}_3 \\ \\ (\text{CH}_3)_2\text{C} - \text{C} - \text{OCOCH}_3 \end{array}$	CH ₃
	(CH ₃) ₂ CH—	2-Furyl
	(CH ₃) ₂ CH	CF ₃
	(CH ₃) ₂ CH	CF ₃
	<i>i</i> -C ₄ H ₉	CF ₃
	CH ₃	CF ₃
14	C ₆ H ₅	CH ₃
	(CH ₃) ₂ CH	<i>n</i> -C ₅ H ₁₁
	(CH ₃) ₂ CH	—CH ₂ CH ₂ CO ₂ C ₂ H ₅
	(CH ₃) ₂ CH	CF ₃
	(CH ₃) ₂ CH	C ₆ H ₅

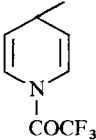
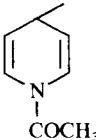
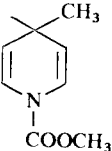
R ³	Yield Percent	Reference
CF ₃	69	1024
CF ₃	54	1024
—CH ₂ NHCOCH ₃	89	1072
C ₆ H ₅ CO	—	1025
4NO ₂ C ₆ H ₄ CO	—	1025
—COOCH ₃	—	1025
	89	1027
	68	1027
<i>n</i> -C ₄ H ₉	20	1019
CH ₃	63	1022, 1023
CH ₃	55	1023
—CH ₂ CH ₂ CN	—	1040
C ₆ H ₅ S—	62	1086
2,4(NO ₂) ₂ C ₆ H ₃	80	1085
CO ₂ CH ₂ CH(CH ₃) ₂	—	1025
	100	1027
<i>i</i> -C ₄ H ₉	43	1015
—CH ₂ CH ₂ CN	85	1039, 1040
—CH ₂ NHCOCH ₃	90	1072
4CH ₃ C ₆ H ₄ S—	65	1086
COCH ₃	—	1025

TABLE 3.6B. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
15	C ₆ H ₅	H
	C ₆ H ₅	CH ₃
	CF ₃ CO ₂ C(CF ₃)=C(C ₆ H ₅)	H
	(CH ₃) ₂ CH	C ₆ H ₅
	(CH ₃) ₂ CH	3-ClC ₆ H ₄
	(CH ₃) ₂ CH	4-NO ₂ C ₆ H ₄
	(CH ₃) ₃ C	CF ₃
	(CH ₃) ₂ CH	CH ₂ CH ₂ CN
	<i>t</i> -C ₄ H ₉	C ₆ H ₅
	C ₆ H ₅	CH ₃
16	(CH ₃) ₂ CH	C ₆ H ₅
	(CH ₃) ₂ CH	C ₆ H ₅ CH ₂
	C ₆ H ₅	H
	(CH ₃) ₂ CH	C ₆ H ₅
	CH ₃	CF ₃
	C ₆ H ₅	
	(CH ₃) ₂ CH	
	CH ₃	
	C ₆ H ₅	
	(CH ₃) ₂ CH	
17	C ₆ H ₅	$\begin{array}{c} \text{H}_3\text{C} \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \\ \text{CH}-\text{CH}_2- \end{array}$
	(CH ₃) ₂ CH	C ₆ H ₅
	(CH ₃) ₂ CH	4CH ₃ OC ₆ H ₄
18	CH ₃	C ₆ H ₅
	(CH ₃) ₂ CH	C ₆ H ₅
	(CH ₃) ₂ CH	2-Br-3,4,5-(CH ₃ O) ₃
		C ₆ H—

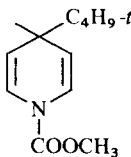
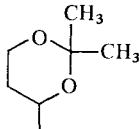
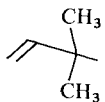
R ³	Yield Percent	Reference
C ₆ H ₅	60	1013
	49	1015
$-\text{CH}_2\text{C}=\text{C}\begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$	—	1015
CF ₃	33, 58	1029, 1081
CH ₂ CH ₂ CN	97	1071
	98	1039, 1040
CH ₂ CH ₂ CN	—	1040
CH ₂ CH ₂ CN	—	1040
$-\text{C}=\text{CHCH}_3$	—	1084
$\begin{matrix} \\ \text{N}(\text{C}_2\text{H}_5)_2 \end{matrix}$		
2,4-(NO ₂) ₂ C ₆ H ₃ —	46	1038
COOCH ₃	—	1025
C ₆ H ₅	15	1019
$-\text{CHCH}_2\text{CN}$	92	1039
$\begin{matrix} \\ \text{CN} \end{matrix}$		
CH ₂ CH ₂ CN	—	1040
CF ₃	—	1040
$-\text{CH}_2\text{CH}_2\text{COCH}_3$	—	1038
	100	1027
$-\text{CH}_2-\text{CH}=\text{CH}_2$	—	1036
$\begin{matrix} \text{H} & & \text{CH}_3 \\ & \diagdown & / \\ & \text{C}=\text{C} \\ & / & \diagdown \\ -\text{CH}_2 & & \text{CH}_3 \end{matrix}$	41	1037
$-\text{CH}_2\text{CH}_2\text{COCH}_3$	—	1038
C ₆ H ₅ CO	—	1025
$-\text{CHCH}_2\text{CO}_2\text{CH}_3$	91	1071
$\begin{matrix} \\ \text{CO}_2\text{CH}_3 \end{matrix}$	92	1039
$-\text{CH}_2\text{CH}_2\text{CN}$	—	1040

TABLE 3.6B. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
	(CH ₃) ₂ CH (CH ₃) ₂ CH (CH ₃) ₂ CH	—CH ₂ CH ₂ CN C ₆ H ₅ 4NO ₂ C ₆ H ₄
19	C ₆ H ₅	4ClC ₆ H ₄
	C ₆ H ₅	
	C ₆ H ₅	4ClC ₆ H ₄
	C ₆ H ₅ (CH ₃) ₂ CH	3-Pyridyl —CH ₂ CH ₂ CN
	C ₆ H ₅	
20	C ₆ H ₅	C ₆ H ₅
	C ₆ H ₅	4ClC ₆ H ₄
	C ₆ H ₅ (CH ₃) ₂ CH	4ClC ₆ H ₄ —CH ₂ CH ₂ CO ₂ C ₂ H ₅
	C ₆ H ₅	4ClC ₆ H ₄

R ³	Yield Percent	Reference
—CH ₂ NHCO ₂ CH ₂ C ₆ H ₅	86	1072
2,4-(NO ₂) ₂ C ₆ H ₃	28	1038
2,4-(NO ₂) ₂ C ₆ H ₃	60	1038
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{CH}_2 \quad \quad \text{H} \end{array}$	92	1035
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{CH}_2 \quad \quad \text{CH}_3 \end{array}$	77	1035
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{CH}_2 \quad \quad \text{Cl} \end{array}$	89	1035
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{CH}_2 \quad \quad \text{CH}_3 \end{array}$	92	1035
$\begin{array}{c} -\text{CHCH}_3 \\ \\ \text{NHCO}_2\text{CH}_2\text{C}_6\text{H}_5 \end{array}$	85	1072, 1075
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{CH}_2 \quad \quad \text{CH}_3 \end{array}$	—	1036
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{CH}_2 \quad \quad \text{CH}_3 \end{array}$	93	1035
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{H}_2\text{C} \quad \quad \text{CH}_3 \end{array}$	86, 95, 92	1035
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ -\text{CH}_2 \quad \quad \text{CD}_3 \end{array}$	—	1068
—CH ₂ NHCO ₂ CH ₂ C ₆ H ₅	88	1072, 1075
$\begin{array}{c} \text{CH}=\text{C}-\text{CH}_3 \\ \quad \quad \\ \text{CH}_2 \quad \quad \text{CH}_3 \end{array}$	—	1075

TABLE 3.6B. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
21	(CH ₃) ₃ C	C ₆ H ₅
	CH ₃	C ₆ H ₅
	C ₆ H ₅	C ₆ H ₅
	(CH ₃) ₂ CH	C ₆ H ₅
	C ₆ H ₅	4ClC ₆ H ₄
	(CH ₃) ₂ CH	—CH ₂ CH ₂ CN
	(CH ₃) ₂ CH	—CH ₂ CH ₂ CO ₂ C ₂ H ₅
	C ₆ H ₅	C ₆ H ₅
	(CH ₃) ₂ CH	C ₆ H ₅
	C ₆ H ₅	C ₆ H ₅ CH=CH
22	C ₆ H ₅	(CH ₃) ₂ CH
	(CH ₃) ₂ CH	C ₆ H ₅
	C ₆ H ₅	2-CH ₂ =CH—CH ₂ OC ₆ H ₄
23	C ₆ H ₅	

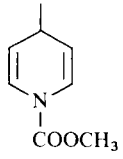
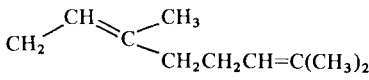
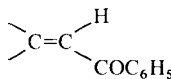
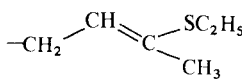
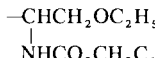
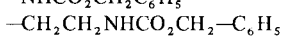
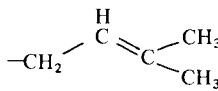
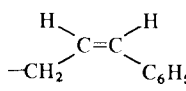
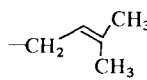
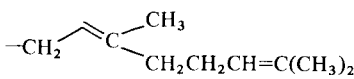
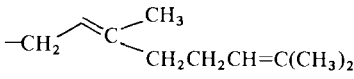
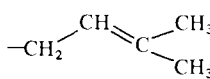
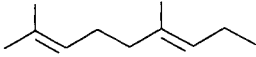
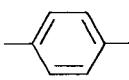
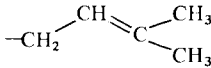
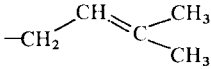
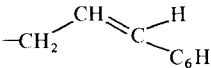
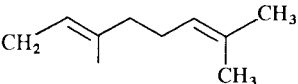
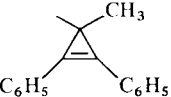
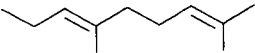
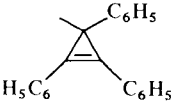
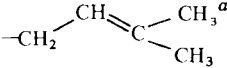
R ³	Yield Percent	Reference
	100	1027
	100	1037
C ₆ H ₅	31	1014
	65	1071
	92	1074
	83	1072
	72	1072, 1075
	—	1036
	12	1037
	82	1035
	67	1037
	100	1037
	86	1035

TABLE 3.6B. (CONTINUED)

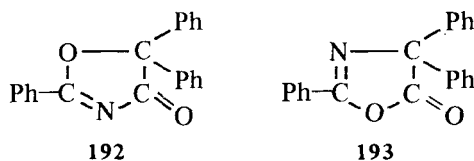
No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
	C ₆ H ₅	1-Methyl-3-indolyl
	C ₆ H ₅	3,4,5-(CH ₃ O) ₃ C ₆ H ₂
24	C ₆ H ₅	4-ClC ₆ H ₄
25	C ₆ H ₅	4-ClC ₆ H ₄
	C ₆ H ₅	4-ClC ₆ H ₄
26	C ₆ H ₅	CH ₃
27	C ₆ H ₅ (CH ₃) ₂ CH	1-Cyclopropyl —CH ₂ CH ₂ CN
28	C ₆ H ₅	
31	C ₆ H ₅	CH ₃
32	C ₆ H ₅	1-Geranyl
34	C ₆ H ₅ ^a	

^aThis is a bispseudooxazolone.

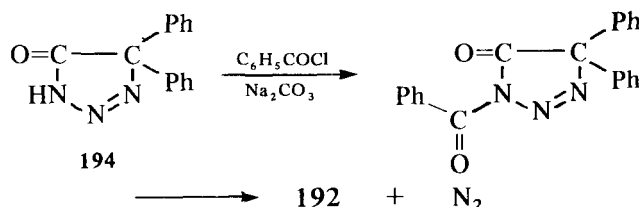
R ³	Yield Percent	Reference
	70	1035
	90	1035
	87, 89	1035
1-Geranyl	93	1035
	—	1036
(1-Geranyl)	—	1036
	—	1016
1-(Farnesyl)	63	1035
10-(Benzyl-oxycarbonylamino)decyl-	—	1075
	—	1036
	—	1016
1-Farnesyl	85	1035
	86	1035

3.4. 4-[5H] OXAZOLONES (2-OXAZOLIN-4-ONES)

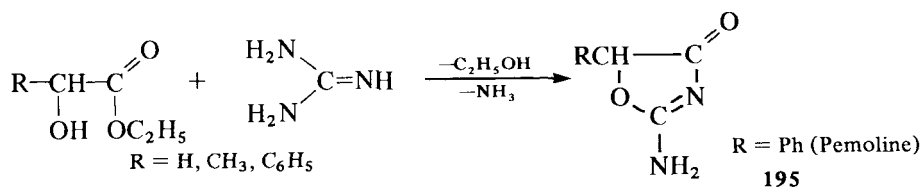
Japp and Findlay's proposed structure **192** obtained by the reaction of benzoic acid and benzonitrile in concentrated sulfuric acid, has been shown¹⁰⁸⁸ to be the 5-[4H]-oxazolone **193**.¹⁰⁸⁷



An authentic sample of **192** has been prepared from a suitably substituted 2-triazolin-5-one **194**.¹⁰⁸⁹



The reaction of ethyl mandelate with guanidine in the presence of a base is reported to give the 2-iminooxazolidone structure.¹⁰⁹⁰ Ethyl glycolate and ethyl lactate react similarly.

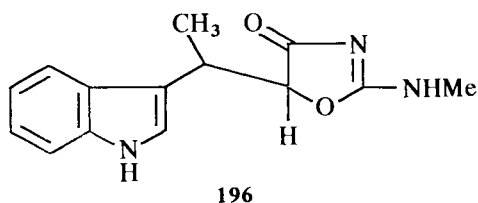


Many compounds possessing the 2-amino-4-[5H]oxazolone structure have been prepared since they are therapeutically active as tranquilizers, antidepressants, memory aids, and hunger suppressants. Patent literature abounds with examples. These compounds may be prepared by the following methods or with slight variations thereof:¹⁰⁹¹⁻¹¹¹⁰

1. Traube and Asher's method,¹⁰⁸⁹
2. reaction of **195** with secondary amines,
3. reaction α -hydroxy carboxylic acid esters and dimethylcyanamide,
4. alkylation reaction of **195**, and
5. aminolysis of 5-aryl-4-oxo-2-oxazolin-2-thione.

The above cited references deal with methods of preparations, transformations, spectral properties, and physiological action of derivatives of 2-amino 5-phenyl-4-[5H] oxazolone. The sources cited are not exhaustive and do not contain patent references.

The antibiotic indolymycin **196** contains the 4-[5H] oxazolone ring.¹¹¹¹⁻¹¹¹³

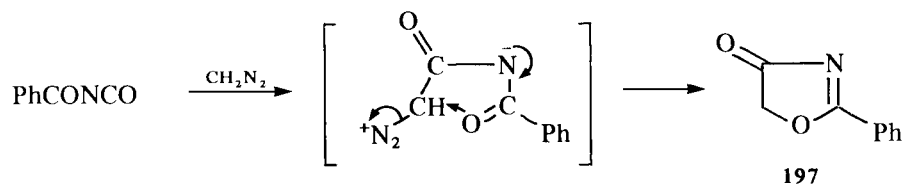


In the following section, methods of preparation and properties of 4-[5H]-oxazolones other than the 2-amino compounds are discussed.

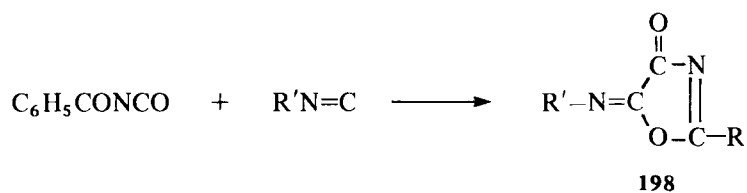
3.4.1. Methods of Preparation

3.4.1.1. From Benzoylisocyanate

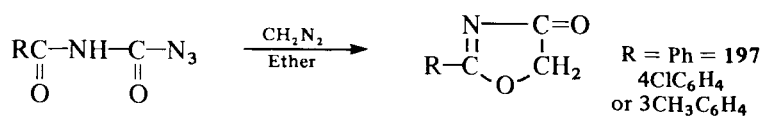
Benzoylisocyanate, obtained from benzamide and oxalylchloride, reacts with diazomethane to give 2-phenyl-4-[5H] oxazolone **197**.¹¹¹⁴



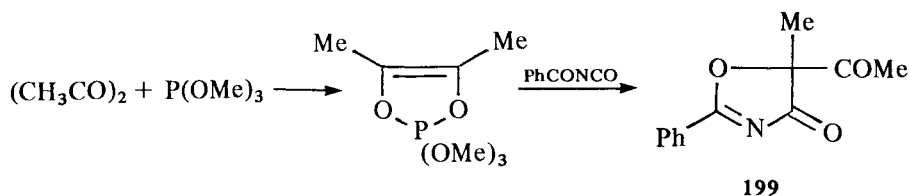
This method was applied to substituted isocyanates and diazomethanes¹¹¹⁵⁻¹¹¹⁸ as well as acylisocyanates.^{1119,1120} Benzoylisocyanate reacts with isonitriles to give 5-imino-2-substituted 4-[5H] oxazolones **198**.¹¹²¹⁻¹¹²⁸



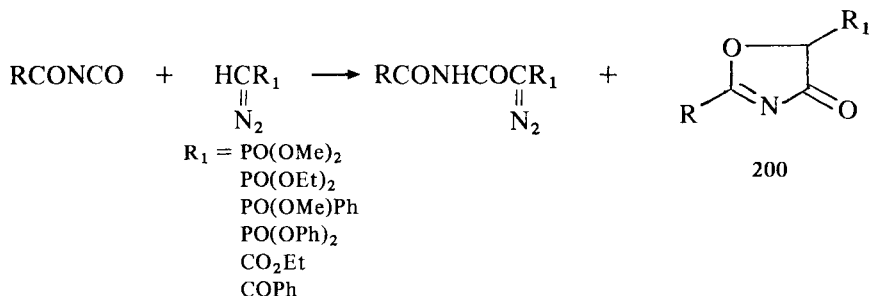
Reaction of *N*-benzoylcarbamic acid azide with diazomethane yields 4-[5H]-oxazolones.¹¹²⁴



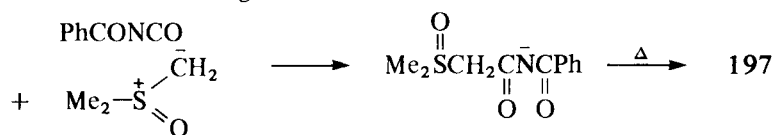
Benzoylisocyanate and 2,2,2-trialkoxo 2,2-dihydro-1,3,5-dioxaphosphenes from 5-acyl-2-oxazolin-4-ones **199**.¹¹²⁵⁻¹¹²⁸



Aroylisocyanates also react with diazomethylphosphoryl compounds to give diazoacetamides as well as 4-[5H] oxazolones containing the phosphorus atom at the 5-position of the ring, **200**.¹¹²⁹

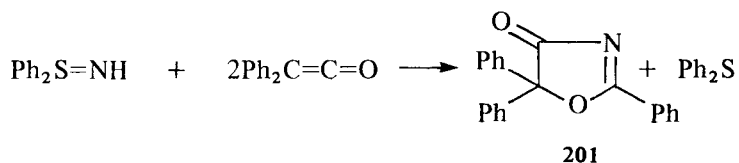


Finally, benzoylisocyanate and dimethyloxosulfonium methylide form products that when heated at 140°C give **197**.¹¹³⁰



3.4.1.2. From *N*-Acylsulfilimines

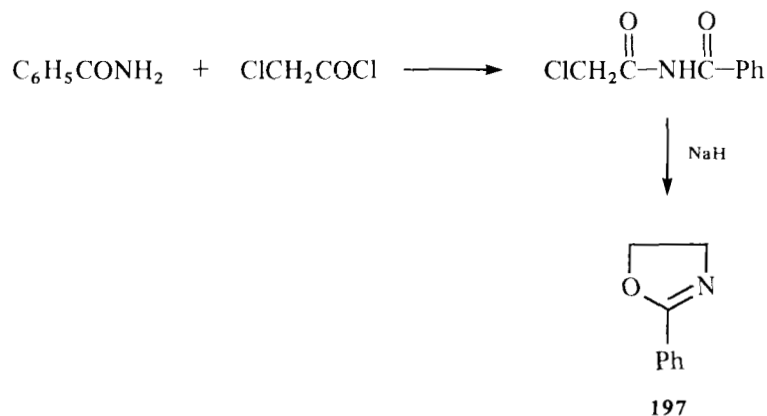
Two moles of phenylketene react with *N*-acylsulfilimines to give 2-oxazolin-4-ones **201**.¹¹³¹



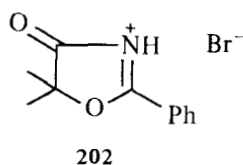
Originally, the structure of the compound was thought to be a sulfilimines.¹¹³²

3.4.1.3. From α -Haloamides

Bisamides¹¹³³ prepared by the reaction of benzamide (or substituted benzamides) with chloroacetylchloride react with sodium hydride in benzene¹¹¹⁵ or glyme^{1134–1136} to give 4-[5H] oxazolones.

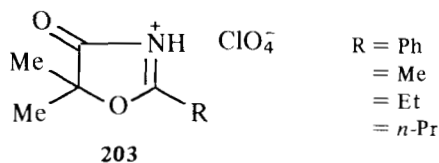


Staninets and co-workers¹¹³⁷⁻¹¹⁴² employed bromoacetyl bromide and always isolated the hydrobromides of 4-[5*H*] oxazolones as the end products **202**.

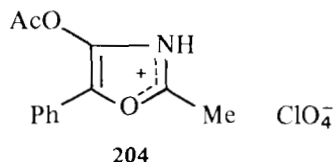


3.4.1.4. Salts of 4-[5*H*] Oxazolones

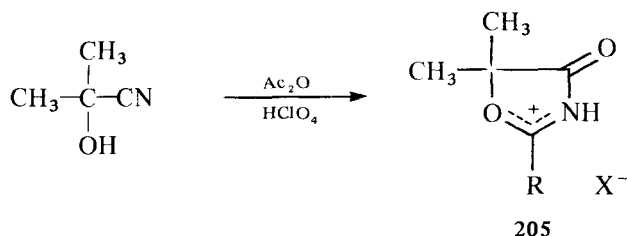
Perchlorate salts of 5,5-dimethyl-4-[5*H*] oxazolone **203** have been reported.¹¹⁴³ These salts are the end products in cases where the precursor for the 4-[5*H*] oxazolone is cyclized in acetic anhydride and a strong acid with a pH of less than 1.¹¹⁴⁴



4-Acetoxyoxazolium salts **204** also may result in such a reaction.^{1148, 1149} Tri-fluoroacetate salts are similarly obtained.¹¹⁴⁸

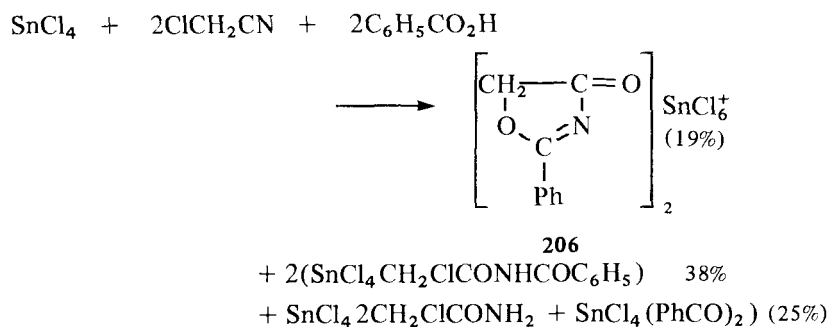


Treatment of acetone cyanohydrin with acetic anhydride followed by addition of perchloric acid leads to the formation of perchlorates **205**, which are decomposed to the parent oxazolones by triethylamine.¹¹⁴⁸



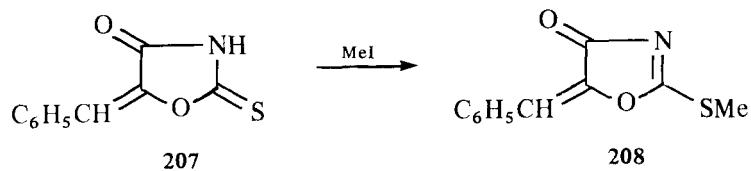
The perchlorate salts **205** may be condensed^{1149,1150} with aldehydes (when R = Me) to give 2-styryl derivatives.

An interesting reaction leading to the synthesis of 2-phenyl-4-[5H]oxazolone **197** consists of heating a 1:2:2 mixture of stannic chloride, chloroacetonitrile, and benzoic acid. The oxazolone complex **206** is not formed from chloroacetylbenzamide but by the direct reaction between the Sn⁴⁺ coordinated ligands of chloroacetonitrile and benzoic acid.¹¹⁵¹



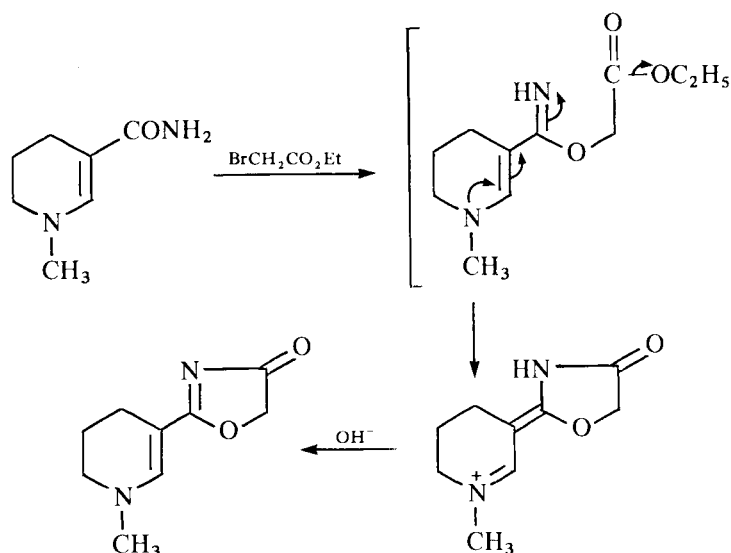
3.4.1.5. From 5-Arylidene-2-Thioxazolidin-4-Ones

Alkylation of **207** with methyl iodide gives 2-thiomethyl-5-arylidene-4-[5H]-oxazolone **208** — the first exocyclic double-bonded compound of this class to be reported.¹¹⁵²



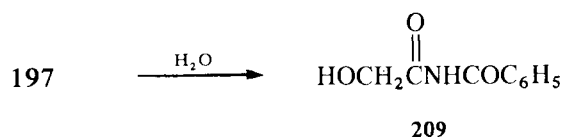
3.4.1.6. Alkylation with Ethyl Bromoacetate

The product obtained by alkylating a nicotinamide derivative with ethyl bromoacetate has been designated as a 4-[5H]oxazolone.¹¹⁵³

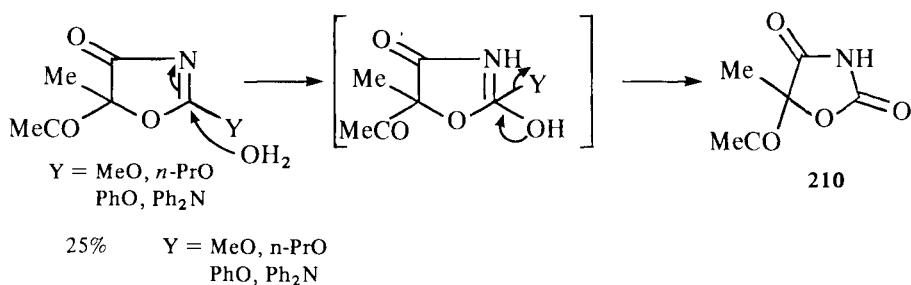


3.4.2. Reactions

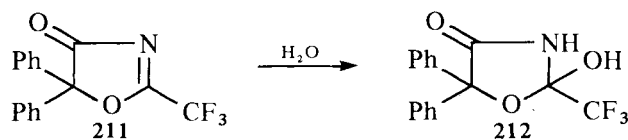
The 2-oxazolin-4-one ring is readily opened on heating with water^{1114,1115} to give benzoyl glycolic acid amide **209**.



If alkoxy or phenoxy groups are present in the 2-position, the compound is cleaved rapidly by water in organic solvents.¹¹²⁷ Oxazolidinediones **210** are the end products.



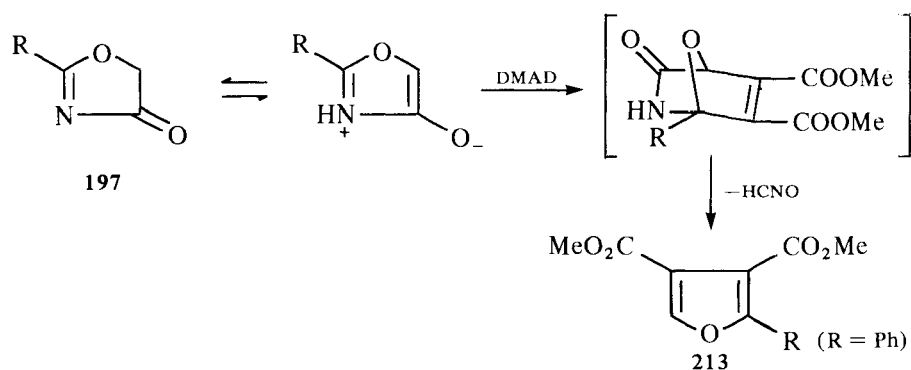
2-Trifluoromethyl-5,5-diphenyl-4-[5H] oxazolone **211** reacts with water to give the oxazolidone **212**. The corresponding 2-ethoxy derivative is obtained when the reaction is carried out in ethanol.¹¹³¹



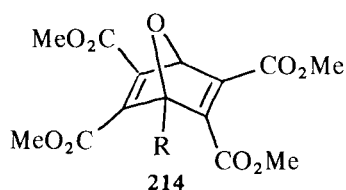
Reduction of 2-oxazolin-4-ones with LAH or sodium borohydride converts them to the corresponding oxazolidones.¹¹³¹



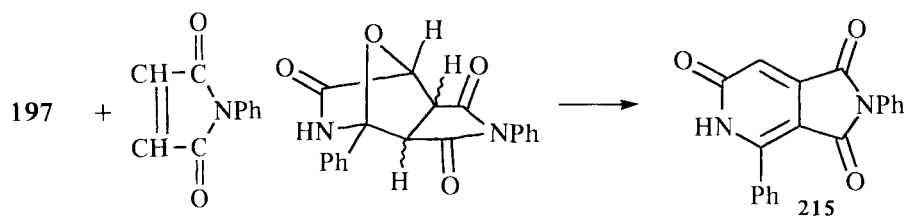
Compound **197** is capable of reacting like a mesoionic system^{1117,1118} and undergoes cycloaddition reactions with dipolarophiles such as dimethyl acetylenedicarboxylate to give a furan derivative **213**.



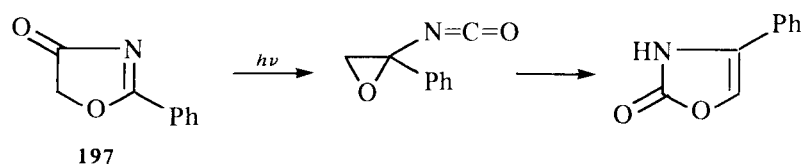
When R is 4ClC₆H₄, the end product is **214**.



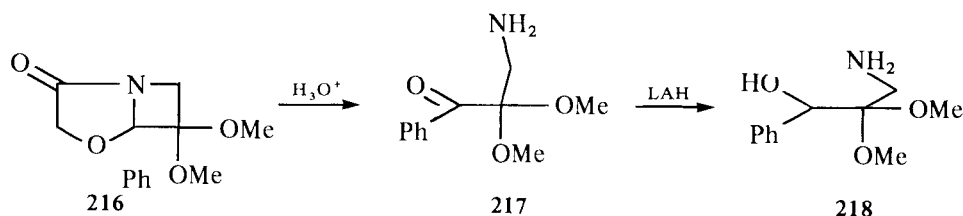
When *N*-phenylmaleimide is the dipolarophile, the product is a fused pyridone derivative **215**.



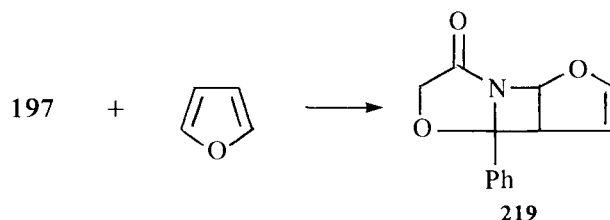
Photolysis of **197** in benzene produces an epoxyisocyanate that isomerizes to 4-oxazolin-2-one:



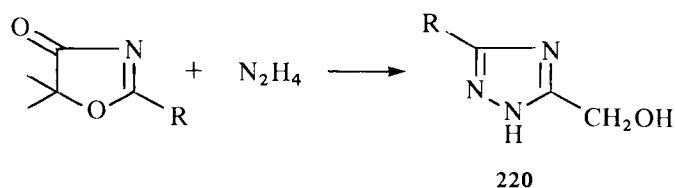
Compound **197** also reacts with 2,3-dimethoxyethene¹¹³¹ to give **216**, which may be hydrolyzed to 2-benzoyl-2,2-dimethoxyethylamine **217**. Compound **217** gives the amino alcohol **218** on reduction.



The photolytic reaction of **197** with furan yields a (2 + 2)photocycloadduct **219**.¹¹³⁵



Reaction of 2-oxazolin-4-ones with hydrazine converts then to triazoles **220**.¹¹¹⁶



Finally, reaction of 3,5,5-triphenyl-2-oxazolin-4-one **192** with phosphorus pentasulfide in THF gives *N*-(3-phenyl-2-benzo[6]thienyl)thiobenzamide **221**.^{1133b} These compounds are tabulated in Tables 3.7A and 3.7B.

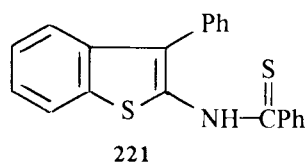
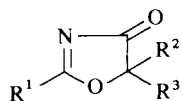
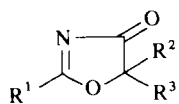


TABLE 3.7A. 4-[5H] OXAZOLONES or 2-OXAZOLIN-4-ONES

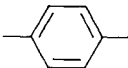


No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
4	CH ₃	H
5	C ₂ H ₅ O	H
6	CH ₃	H
	CH ₃	CH ₃
7	CH ₃ O	CH ₃
	CCl ₃	CH ₃
	C ₂ H ₅	CH ₃
8	CH ₃ } CH ₃ }	—
	<i>n</i> -C ₃ H ₇	CH ₃
9	C ₆ H ₅	H
	4ClC ₆ H ₄	H
		H
10	C ₃ H ₇ O	CH ₃
	CH ₃	—(CH ₂) ₅
	3-MeOC ₆ H ₄	H
	4-MeOC ₆ H ₄	H
	3-CF ₃ C ₆ H ₄	H
	Cl ₂ CH	C ₆ H ₅ N=
	3-MeC ₆ H ₄	H
	NH ₂	C ₆ H ₅ CHBr
	(CH ₃) ₃ C	CH ₃
11		H



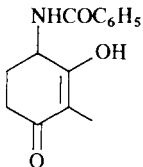
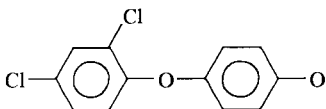
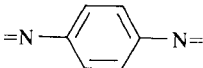
R ³	Yield Percent	Reference
H	25	1137 (HBr)
H	68	1135
CH ₃	95	1148
CH ₃	92	1143, 1148 (HClO ₄)
	—	1147
CH ₃ CO	—	1127
CH ₃ CO	60	1125
CH ₃	79	1143, 1148 (HClO ₄)
H	—	1138 ^a
H		
CH ₃	80	1143, 1148 (HClO ₄)
H	70	1115
	80	1135
	93	1124
	—	1151
H	66	1118
	—	1116
	78	1124
H	—	1153
CH ₃ CO	97	1127
	75	1148 (HClO ₄)
H	77	1135
H	77	1135
H	48	1135
	96	1121 ^b
H	88	1124
H	—	1139
O OCCH ₃	—	1144
H	73	1120

TABLE 3.7A. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
	CH ₃ CONH 2-C ₂ H ₅ OC ₆ H ₄ C ₆ H ₅ CH ₃	C ₆ H ₅ H PO(OCH ₃) ₂ C ₆ H ₅ CHBr HO ₂ CCHBr CH ₃
	o C ₆ H ₅ C ₆ H ₅	
	SCH ₃ SCH ₃ SCH ₃ 4BrC ₆ H ₄	C ₆ H ₅ CH= 4-BrC ₆ H ₄ CH= 4-NO ₂ C ₆ H ₄ CH= CH ₃
12		H
	(1,4) C ₆ H ₅ O C ₆ H ₅ 4FC ₆ H ₄ 4CH ₃ OC ₆ H ₄	H CH ₃ CH ₃ CH ₃ PO(OC ₂ H ₅) ₂
		H
13	(1,2) C ₆ H ₅ NH 4(F ₃ C) ₂ CHC ₆ H ₄ NH SCH ₃ SCH ₃ 4CH ₃ C ₆ H ₄ 4CH ₃ OC ₆ H ₄ CH ₃ 4-CH ₃ OC ₆ H ₄ C ₆ H ₅ 4-NO ₂ C ₆ H ₄ SCH ₃ 4-CH ₃ OC ₆ H ₄	H HO ₂ CCHBr-- H 4-CH ₃ C ₆ H ₄ CH= 4-CH ₃ OC ₆ H ₄ CH= CH ₃ CH ₃ Ph CH ₃ PO(OC ₂ H ₅) ₂ PO(OC ₂ H ₅) ₂ 4-(CH ₃) ₂ NC ₆ H ₄ CH= PO(OC ₂ H ₅) ₂
14	C ₆ H ₅	C ₆ H ₅
15	C ₆ H ₅ C ₆ H ₅ C ₆ H ₅	C ₆ H ₅ N= 4-NO ₂ C ₆ H ₄ N= C ₆ H ₁₁ N=

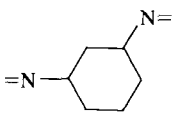
R ³	Yield Percent	Reference
H	55	1109
H	67	1116
H	—	1129
H	—	1139
H	—	1139
CH ₃	70	1143
	90	1148
	58	1132
	58	1152
	62	1152
CH ₃	75	1148
H } H } CH ₃ CO CH ₃ CO CH ₃ CO H	61 65 92 78 48	1119 (bis-oxazolone) 1127 1125 1125 1129
H	—	1138 ^c
H		
H	—	1139
H	—	1155
	—	1152
	65	1152
CH ₃	60	1148
CH ₃	100	1148
H	—	1145 ^d
CH ₃ CO	87	1125
H	41	1129
H	45	1129
	60	1152
H	31	1129
H	50	1115
	—	1116
	93	1121 ^b
	57	1121 ^b
	83	1121 ^b

TABLE 3.7A. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
16	 CH_3 CF_3 C_6H_5 C_6H_5 $4\text{-NO}_2\text{C}_6\text{H}_5$ C_6H_5	 H C_6H_5 C_6H_5 $\text{C}_6\text{H}_5\text{CO}$ $\text{PO}(\text{CH}_3\text{OC}_6\text{H}_4)$ $\text{PO}(\text{CH}_3\text{OC}_6\text{H}_4)$ $\text{C}_6\text{H}_5\text{CHBr}$
17	 $4\text{-(2',4'-Cl}_2\text{C}_6\text{H}_3\text{O)-C}_6\text{H}_4\text{O-}$	 CH_3
18	$4\text{-BrC}_6\text{H}_5\text{CH=CH-}$	H
20	$(\text{C}_6\text{H}_5)_2\text{N}$	CH_3
21	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{CH=CH}$	H
	C_6H_5	H
	C_6H_5	$\text{-(CH}_2)_2\text{-}$
	C_6H_5	C_6H_5
22	C_6H_5 $4\text{NO}_2\text{C}_6\text{H}_4$ C_6H_5 $4\text{-CH}_3\text{OC}_6\text{H}_4$	$\text{PO}(\text{C}_6\text{H}_5)_2$ $\text{PO}(\text{C}_6\text{H}_5)_2$ C_6H_5 $\text{PO}(\text{C}_6\text{H}_5)_2$
24	C_6H_5 C_6H_5	 

R ³	Yield Percent	Reference
H	48	1120
C ₆ H ₅	56	1131 ^e
C ₆ H ₅	44	1131 ^f
H	53	1128
H	60	1129
H	50	1129
H	—	1139
CH ₃	—	1154
CH ₃ CO ₂ CH ₂ C(CH ₃) ₂ —	52	1149
CH ₃ CO	95	1127
CH ₃ CO ₂ CH ₂ C(CH ₃) ₂ —	92	1149
H	—	1140 ^a
C ₆ H ₅	52	1115
	—	1089
	80	1131
	24	1133
H	54	1129
H	56	1129
C ₆ H ₅ CO	56	1128
H	54	1129
	74	1123 ^a
	91	1123 ^a

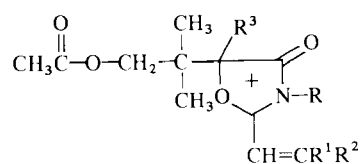
TABLE 3.7A. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
	C ₆ H ₅ C ₆ H ₅	
28	-CH(C ₆ H ₅) ₂	C ₆ H ₅

^aThis compound is a 5,5'-bisoxazolone.^bAn exocyclic double-bonded compound.^cThis compound is a 2,2'-bisoxazolone.^dIsolated as the 4-acetoxy perchlorate.^eIsolated yield of the oxazolidone after reduction.^fIsolated as the 2-hydroxy oxazolidone structure.

R ³	Yield Percent	Reference
	87	1123 ^a
C ₆ H ₅	73	1131

TABLE 3.7B. 4-[5*H*] OXAZOLONIUM PERCHLORATES

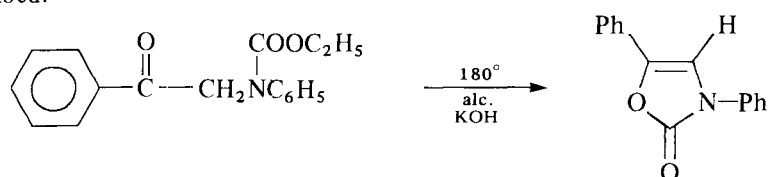


No. of Carbon Atoms in Oxazolone Ring	R	R ¹	R ²	R ³	Yield Percent	Reference
14	CH ₃	CH ₃	CH ₃	H	44	1150
16	H	H	5-Methyl-2-furyl	H	40	1150
	CH ₃	H	2-furyl	H	40	1150
	CH ₃	H	5-Bromo-2-furyl	H	62	1150
	CH ₃	H	5-Iodo-2-furyl	H	68	1150
	CH ₃	H	5-Nitro-2-furyl	H	15	1150
17	CH ₃	H	5-Methyl-2-furyl	H	68	1150
	H	H	C ₆ H ₅	H	66	1150
	H	H	4-BrC ₆ H ₄	H	81	1150
	H	H	4-NO ₂ -C ₆ H ₄	H	10	1150
18	H	H	4CH ₃ O-C ₆ H ₄	H	92	1150
	CH ₃	H	C ₆ H ₅	H	80	1150
	CH ₃	H	4-BrC ₆ H ₄	H	65	1150
	CH ₃	H	4-NO ₂ -C ₆ H ₄	H	42	1150
	CH ₃	H	3-NO ₂ -C ₆ H ₄	H	30	1150
	CH ₃	H	2-NO ₂ -C ₆ H ₄	H	37	1150
	CH ₃	H	Vinyl-2-furyl	H	70	1150
	CH ₃	CH ₃	5-Methyl-2-furyl	H	27	1150
19	H	H	C ₆ H ₅ CH=CH	H	72	1150
	CH ₃	H	4CH ₃ OC ₆ H ₄	H	98	1150
	CH ₃	CH ₃	C ₆ H ₅	H	37	1150
	CH ₃	CH	C ₆ H ₅ CH=CH	H	72	1150

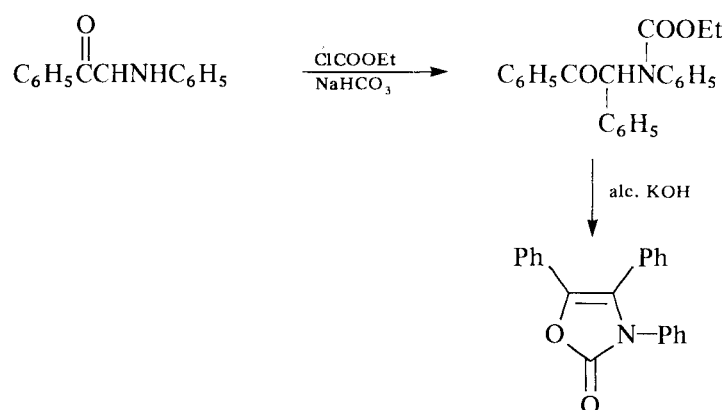
3.5. 2-[3*H*] OXAZOLONES (4-OXAZOLIN-2-ONES)

3.5.1. Methods of Preparation

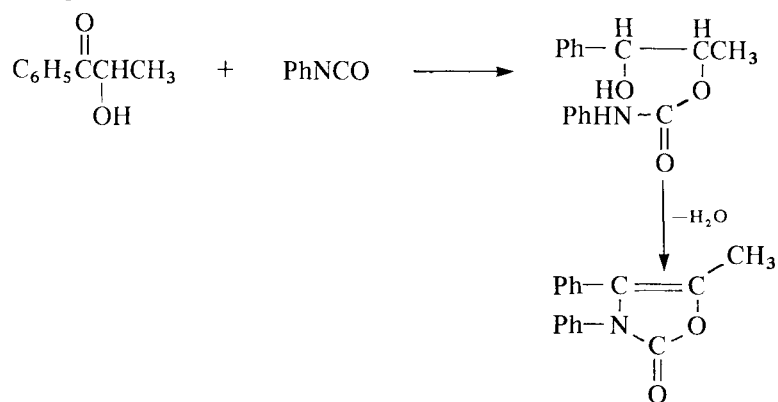
This class of compounds has been known since 1905, when the first example was described.¹¹⁵⁶



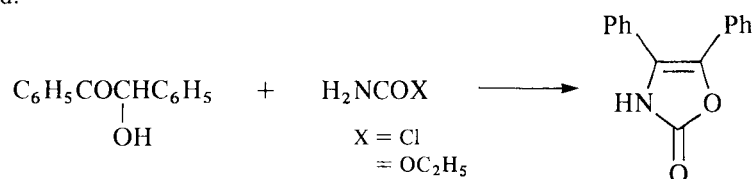
A modification of this method was used to synthesize 3,4,5-triphenyl-4-oxazoline-2-one.^{1157, 1158}



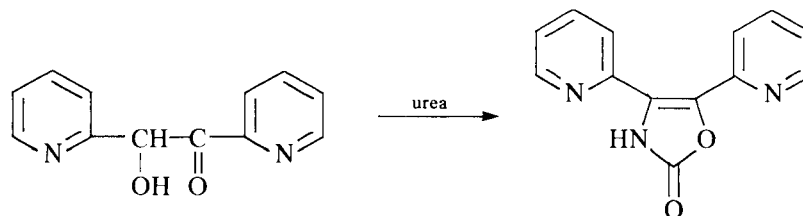
Phosgene was employed instead of ethyl chloroformate in the synthesis of 3,5-diphenyl- and 3-aryl-5-phenyl-2-[3*H*] oxazolones.¹¹⁵⁹ Isocyanates and acylins react to give compounds of this class.¹¹⁶⁰



Benzoin and other α -hydroxyketones react with ethyl carbamate or carbamoyl chloride to yield a substituted carbamate, which undergoes cyclodehydration to give a 2-[3*H*] oxazolone.¹¹⁶¹⁻¹¹⁶³ Both 3-unsubstituted and 3-substituted oxazolones were thus prepared. The UV and IR spectra of these oxazolones were studied.^{1164, 1165}

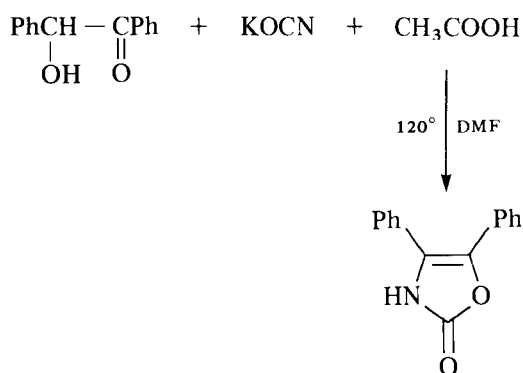


The reaction of 2-pyridoin with urea proceeds with elimination of ammonia to afford the 2-[3*H*] oxazolone¹¹⁷⁶ instead of the expected imidazolone derivative.



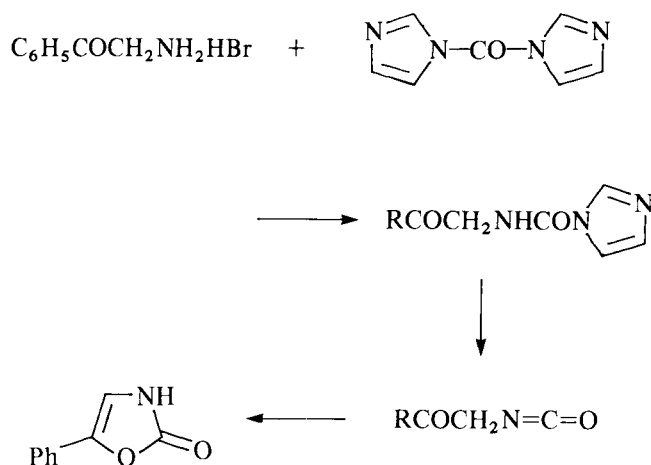
3.5.1.1. From Benzoin and Isocyanates

Reaction of benzoin with potassium isocyanate in DMSO or pyridine yields carbamates that undergo cyclodehydration to give 2-[3*H*] oxazolones.¹¹⁶⁷⁻¹¹⁶⁹

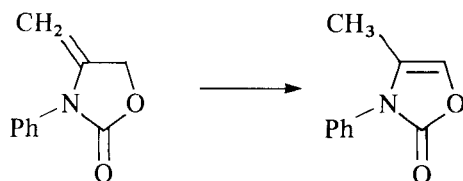


Instead of benzoin, α -bromocarbonyl compounds may also be used.¹¹⁷⁰⁻¹¹⁷³ Instead of KOCN, other alkali metal isocyanates have been employed.^{1174, 1175}

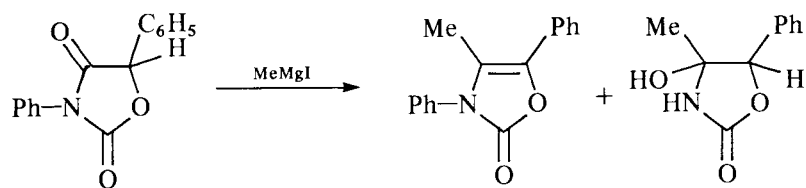
Isocyanates are presumed to be intermediates in the formation of 2-[3*H*]-oxazolones.^{1176, 1177}



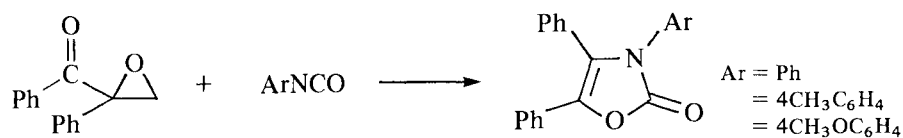
Reaction of propargyl alcohol with phenyl isocyanate in the presence of sodium acetate gives 3-phenyl-4-methylene-oxazolidone, which undergoes acid-catalyzed isomerization to yield 3-phenyl-4-methyl-2-[3*H*] oxazolone.¹¹⁷⁸⁻¹¹⁸⁰



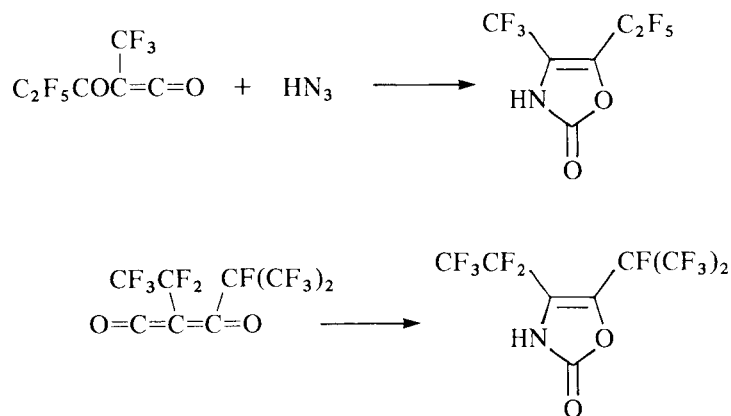
Grignard reagents react with 3,5-diphenyl-2,4-oxazolidinedione to form a 2-[3*H*] oxazolone derivative.¹¹⁸¹



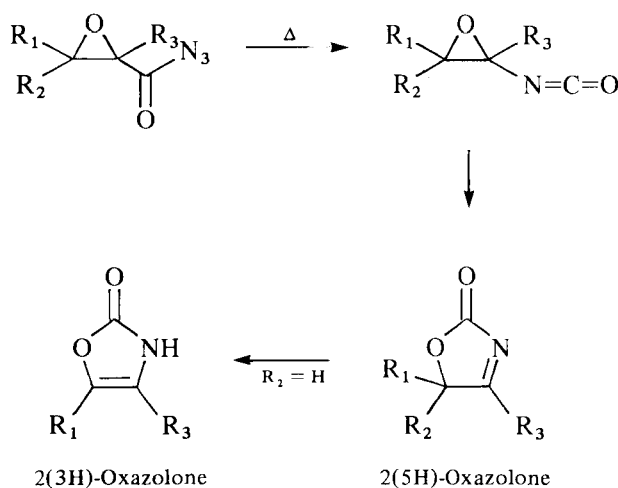
2-Benzoyl-2-phenyloxirane reacts with aryl isocyanates to give 2-[3*H*] -oxazolones.¹¹⁸²



Finally, azides, which can undergo Curtius–Lossen rearrangement to form isocyanates, also give 2-[3*H*] oxazolones on reaction with perfluoroacylketene.^{1183, 1184}



α -Epoxyacyl azides rearrange to epoxyisocyanates and subsequently to 4-oxazolin-2-ones.¹¹⁸⁵

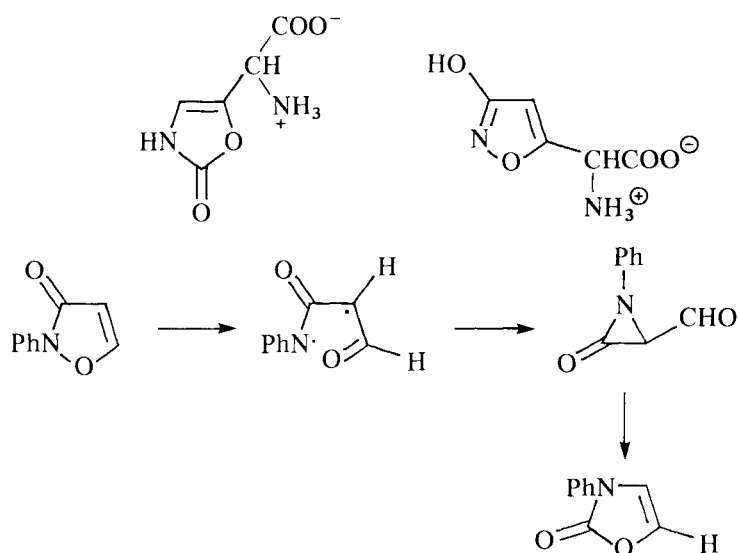


Isocyanates also react with dimethylformamide dialkyl acetal to yield 3,5-diphenyl-4-dimethylamino-2-[3H]oxazolone.¹¹⁸⁶

3.5.1.2. From Isooxazole Derivatives

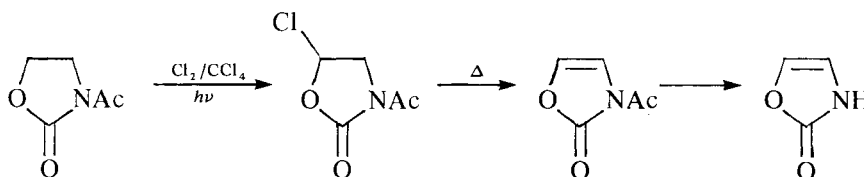
Most of the studies on the isooxazolone-2-[3H]oxazolone conversion stems from work on muscazone and ibotenic acid.¹¹⁸⁷⁻¹¹⁸⁹ Both these naturally occurring compounds are transformed photochemically.¹¹⁹⁰⁻¹¹⁹²

Similarly, 3-hydroxyisooxazoles isomerize thermally and photochemically to 2-[3H]oxazolones.¹¹⁹⁰⁻¹¹⁹²

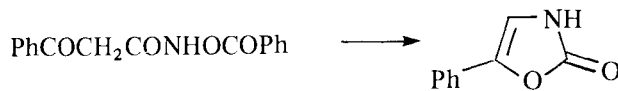


3.5.1.3. Miscellaneous Methods

N-Acetyl-2-[3*H*] oxazolone was prepared as follows^{1193, 1194}

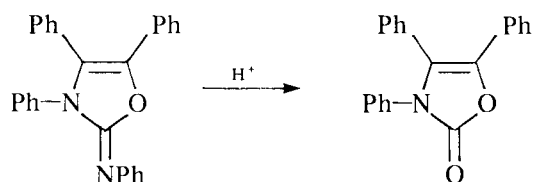


A number of other approaches include hydrolysis of 2-amino 4,5-diphenyl-5-cyanooxazole,¹¹⁹⁵ by acid treatment of *O*-benzoyl benzoylacetoxyhydroxamate,¹¹⁹⁶ and by 1,3-dipolar cycloaddition of diphenylacetylene to ethylazidoformate followed by hydrolysis.¹¹⁹⁷

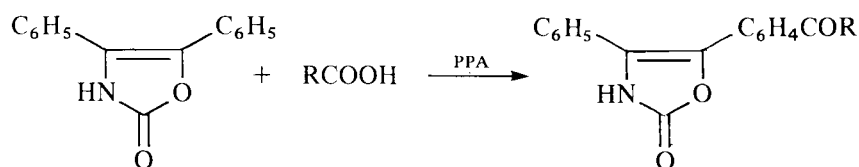


3.5.1.3.1. FROM 2-IMINO COMPOUNDS

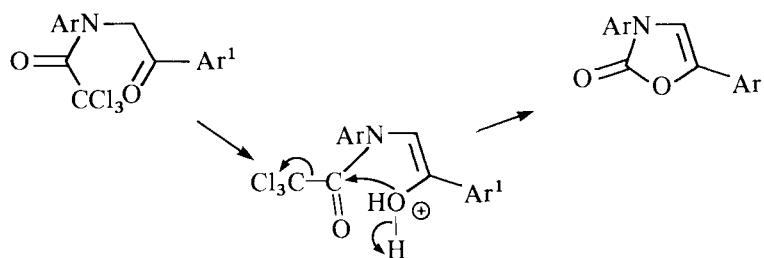
2-Phenylimino-3,4,5-triphenyloxazoline obtained by reaction of benzoyl phenylacetaldehyde and phenylhydroxylamine gives 3,4,5-triphenyl-2-[3*H*] oxazolone on acid hydrolysis.¹¹⁹⁸⁻¹²⁰⁰ Benzil-mono-*N*-isopropylimine, when treated with Na in ether followed by ethyl chloroformate, affords *N*-isopropyl-4,5-diphenyl-2-[3*H*] oxazolone.¹²⁰¹

3.5.1.3.2. FROM 2-[3*H*] OXAZOLONES

4,5-Diphenyl-2-[3*H*] oxazolone may be acylated with aromatic carboxylic acids on the phenyl ring attached to the 5-position.¹²⁰²

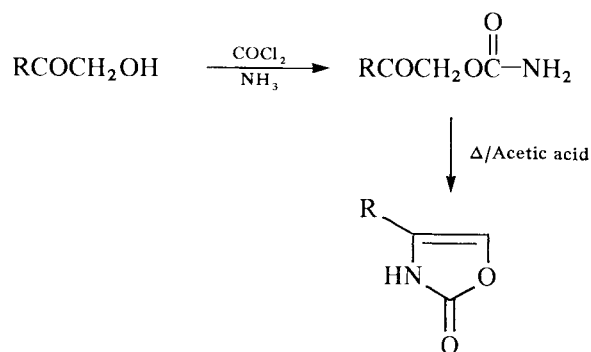


N-Trichloroacetyl phenacylanilines undergo ring closure on treatment with bases such as triethylamine, alcoholic KOH, and sodium methoxide in methanol.¹²⁰³



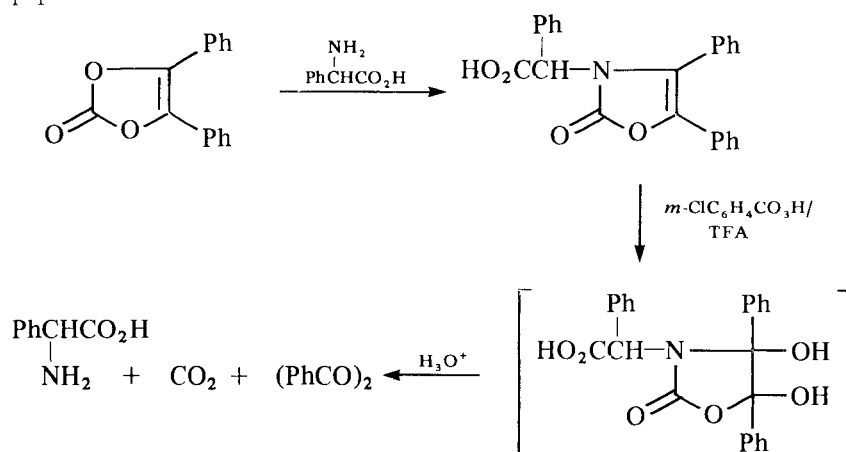
3.5.1.3.3. FROM AMMONIA AND AROYLCARBINOLS

4-Substituted-2-[3*H*] oxazolones have been prepared according to the following scheme.¹²⁰⁴⁻¹²⁰⁶



3.5.1.3.4. 4,5-DIPHENYL-2-[3H] OXAZOLONES AS INTERMEDIATES AND AS AMINO ACID PROTECTIVE AGENTS

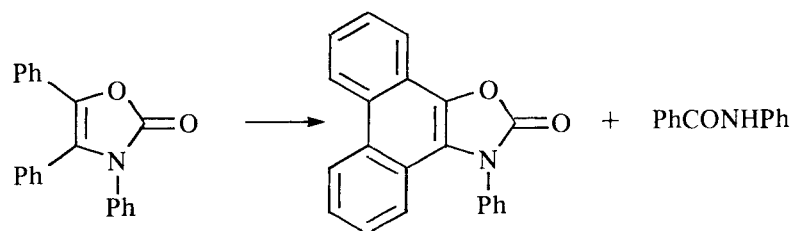
Dioxolanones react with amines to form the corresponding oxazolones. Oxidation with *m*-chloroperbenzoic acid in $\text{CF}_3\text{CO}_2\text{H}$ gives the *vic*-diol, which undergoes ring cleavage to regenerate the amino acid. This method has been used for the synthesis of peptides.¹²⁰⁷⁻¹²¹¹



3.5.2. Reaction

3.5.2.1. Conversion to Phenanthrene Derivatives

3,4,5-Triphenyl-2-[3H] oxazolone on photolysis in benzene in the presence of oxidizing agents such as oxygen and iodine yields a phenanthrene derivative and a trace of benzanilide. In the absence of iodine, the products are benzanilide, benzoic acid, 2- and 4-benzamidobenzophenones.¹²¹²

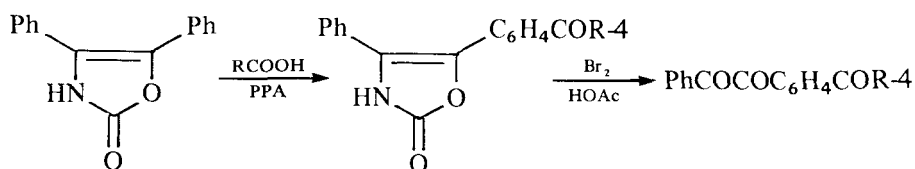


When photolysis is carried out in the presence of cuprous chloride in methanol, 3-benzyl-4,5-diphenyl-2-[3H] oxazolone gives the corresponding phenanthrene derivative in 70% yield. High yields of phenanthrene derivatives are also reported with oxazolones bearing the 4- and 5-phenyl groups.¹²¹³ A mixture of cuprous chloride and iodine has also been used as catalyst in the photolysis reaction.^{1214, 1219}

Ultraviolet irradiation in air of 3-carboxymethyl-4,5-diphenyl-2-[3H]-oxazolone in methanol yields methyl benzoate and hippuric acid.¹²¹⁶

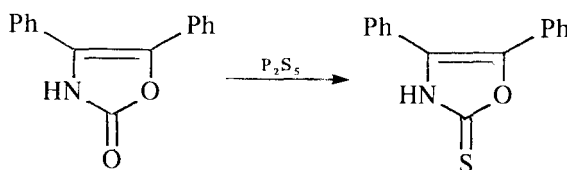
3.5.2.2. Conversion to 4-Aroylbenzils

4,5-Diphenyl-2-[3H] oxazolone is acylated in polyphosphoric acid at 100° with the appropriate benzoic acid. The product may be converted to the corresponding 4-aroylbenzils.¹²⁰²



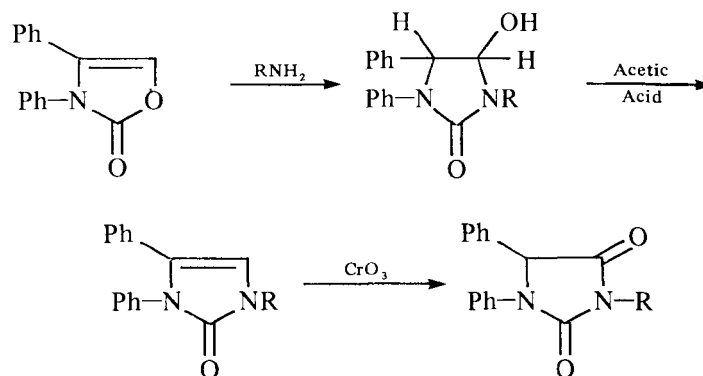
3.5.2.3. Conversion to Oxazole Thiones

Reaction of 2-[3H] oxazolones with P_2S_5 in toluene gives 2-oxazole thiones.¹²¹⁷⁻¹²¹⁹

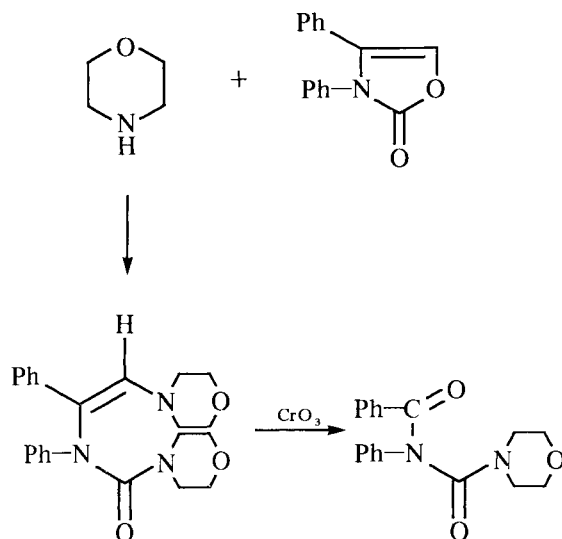


3.5.2.4. Reaction with Amines¹²²⁰⁻¹²²⁴

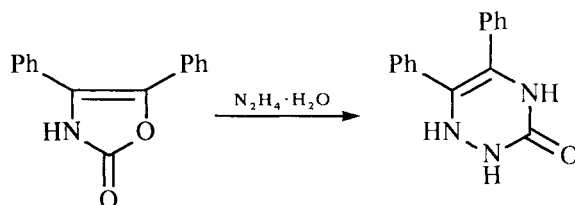
2-[3H] Oxazolones react with primary amines to give imidazolone derivatives after heating with acetic acid. Chromium trioxide oxidation of the latter leads to the formation of a hydantoin derivative.



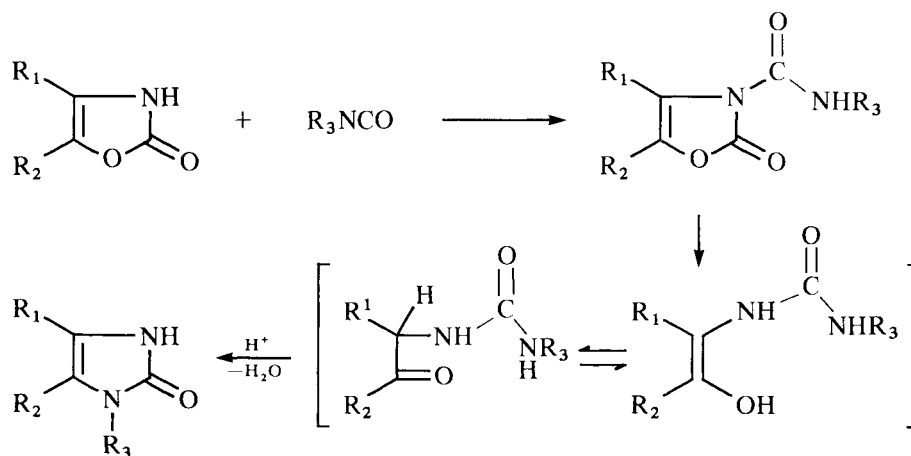
Secondary amines, by contrast, yield β -acylaminoenamines with 2-[3*H*]-oxazolones.¹²²⁵



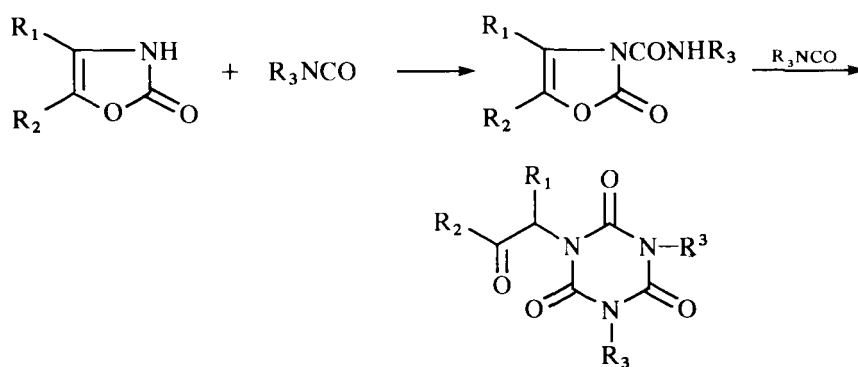
Hydrazine hydrate reacts with 4,5-diphenyl-2-[3*H*] oxazolone to give triazinones.¹²²⁶



Reaction of 2-[3*H*] oxazolones with isocyanates affords 2-oxo-4-oxazoline-3-carboxamides, which when heated with acids lead to 4-imidazolin-2-one.¹²²⁷⁻¹²²⁹

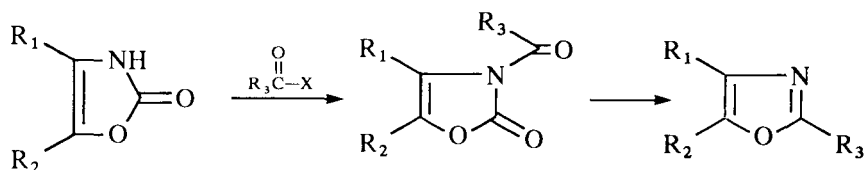


With 2 mol of phenyl isocyanate, the products from 2-[3H] oxazolones are 1,3,5-triazine-2,4,6-triones.¹²³⁰

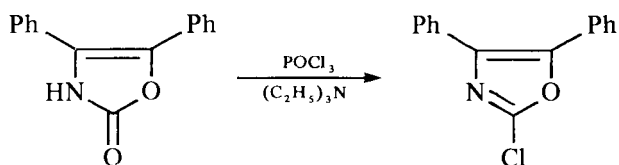


3.5.2.5. Conversion to Oxazoles

Reaction of 2-[3H] oxazolones with acid anhydrides or acid chlorides gives the *N*-acyl-2-[3H] oxazolones, which undergoes acyl-lactone rearrangement to oxazoles.

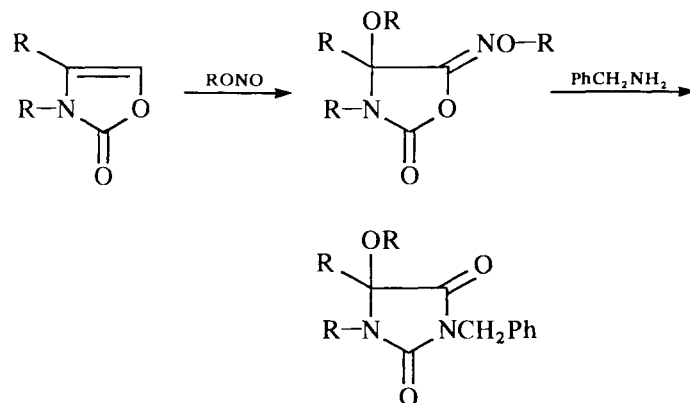


Direct conversion to oxazoles is achieved by treatment with POCl_3 in the presence of triethylamine. The chlorine in the 2-position may be replaced by ammonia and amines to give 2-amino- and 2-substituted aminooxazoles and by alkoxy groups to yield 2-alkoxyoxazoles.



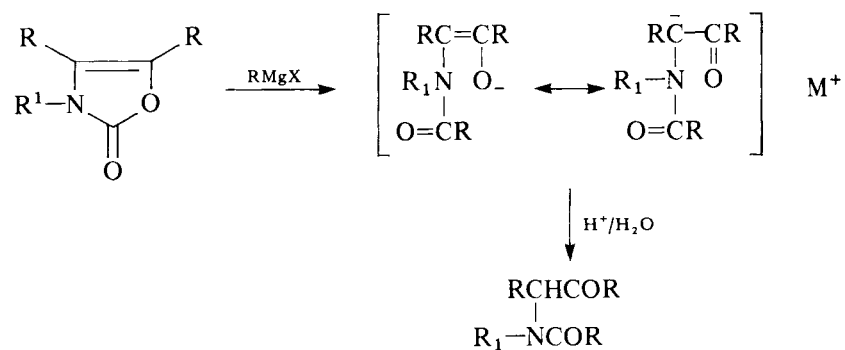
2-Chloro-4,5-diphenyloxazole reverts to the parent 2-[3H] oxazolone on heating in formamide to 185° .¹²³²

Organic nitrites react with 2-[3H] oxazolones under acidic conditions to form 4-alkoxy-3,4-disubstituted-4-oximinooxazolidin-2-ones, which rearrange to hydantions.¹²³³



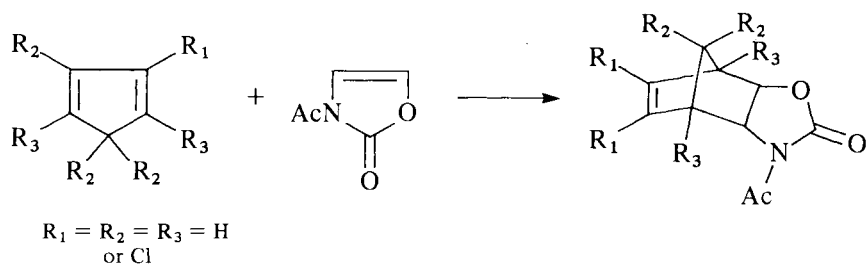
3.5.2.6. Reaction with Grignard Reagents

Organometallic reagents (RMgX and RLi) react with 3,4,5-triphenyl-2-[3H]-oxazolone to give α -acylamino ketones.¹²³⁴

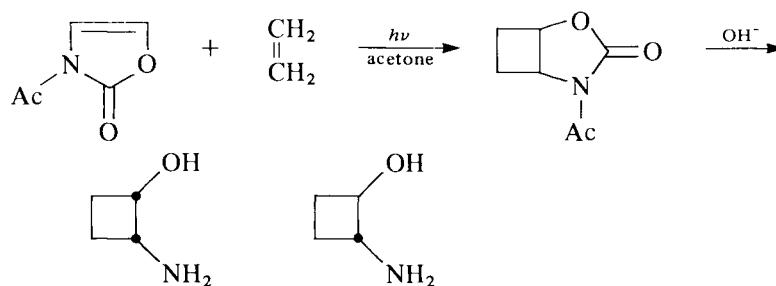


3.5.2.7. Diels-Alder Reaction

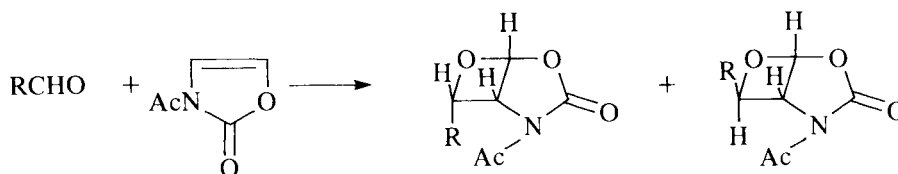
3-Acetyl-2-[3H]oxazolone reacts selectively with cyclic 2,3-dienes to give *endo*-isomers.^{1235,1236}



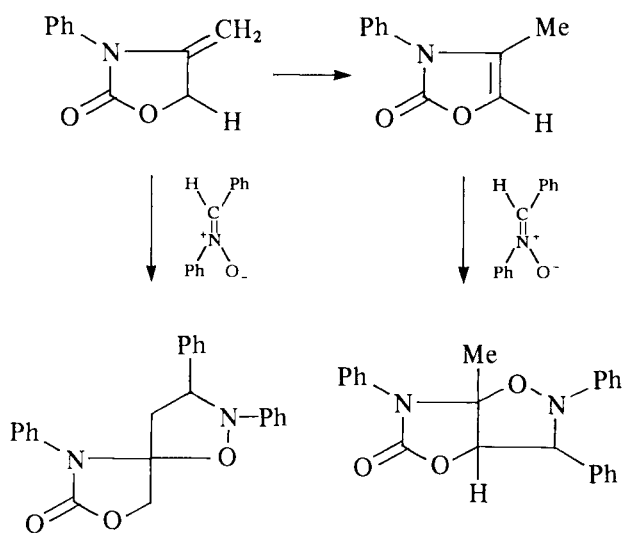
The photosensitized cycloaddition of alkenes with 3-acetyl-2-[3H] oxazolone has been utilized in the synthesis of diastereomeric 2-aminocyclobutanols.¹²³⁷⁻¹²³⁹



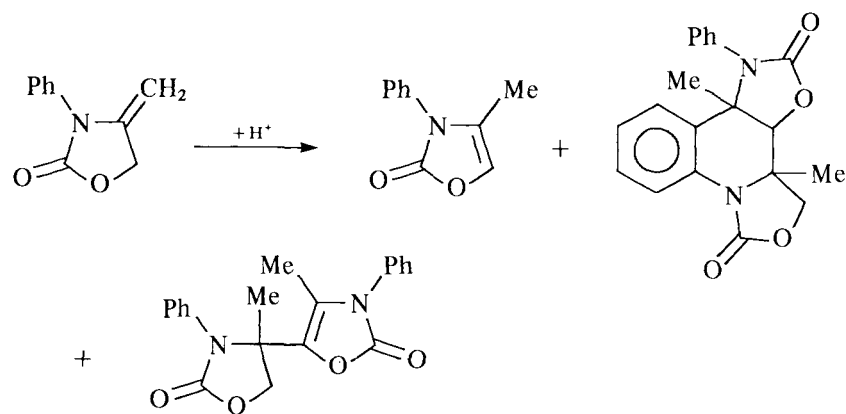
3-Acetyl-2-[3H] oxazolone reportedly adds to aldehydes (and ketones) photochemically to give oxetane derivatives.¹²⁴⁰



3-Phenyl-4-methylene-1,3-oxazolidin-2-one, which is isomeric with 3-phenyl-4-methyl-1,3-oxazolin-2-one, reacts with various nitrones to yield two structural isomers.¹²⁴¹

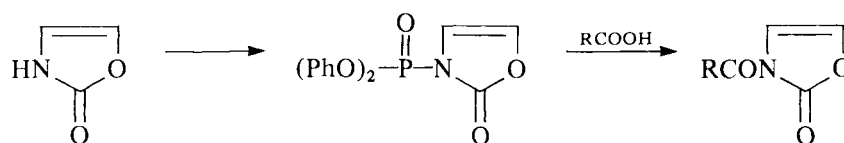


The acid-catalyzed isomerization of a methylene oxazolone to a 4-oxazolin-2-one is accompanied by the formation of a dimer and a tetrahydroisoquinoline derivative.¹²⁴²⁻¹²⁴⁴



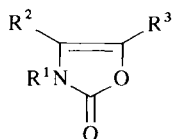
3.5.2.8. *Formation of Telomers*

Free-radical-initiated reaction of 3-acyl-2-oxazolones proceeds smoothly in carbon tetrachloride, which functions as a telogen to give telomers of important synthetic utility with high regio- and stereoselectivity.^{1245, 1246} These compounds are useful in highly selective acylation of alcohols and amines¹²⁴⁷ and as amino-acid-protecting agents.^{1248, 1249} They may also be used in the synthesis of amino sugars.¹²⁵⁰

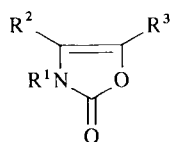


Reaction of 3-acyl-2-oxazolone with diphenyl phosphorochloridate provides diphenyl-2-oxo-3-oxazolonylphosphonate [DDPOx], which functions as a carboxyl activating agent.¹²⁵¹

The [DPPOx] may be transformed to RCONR^1R^2 , esters, thiolesters, or ketones and the acyloxazolone may be converted to primary alcohols and aldehydes (see Table 3.8).^{1252, 1253}

TABLE 3.8. 2-[3*H*] OXAZOLONES OR 4-OXAZOLIN-2-ONES

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
3	H	H
4	H	H
	H	H
	CH ₃ CO	H
5	H	CH ₃
	H	H
	H	H
6	H	CF ₃
	CH ₃ CO	CH ₃
7	H	C ₂ H ₅
	CH ₃ CO	CH ₃
	CH ₃ NHCO	CH ₃
	(CH ₃) ₂ CHCO	H
	COOC ₄ H ₉ - <i>t</i>	H
8	H	CF ₃ CFS
	C ₂ H ₅ NHCO	CH ₃
9	H	CH ₃ CH ₂ CH ₂ O
	H	<i>i</i> -C ₃ H ₇
	H	H
	H	H
	H	H
	C ₆ H ₅	H
	H	C ₆ H ₅
	H	2-ClC ₆ H ₄
	H	4-ClC ₆ H ₄
	H	4-BrC ₆ H ₄
	H	4-FC ₆ H ₄
	CH ₃ NHCO	C ₂ H ₅
10	CH ₃	<i>n</i> -C ₃ H ₇
	(CH ₃) ₂ NCH ₂ CH ₂ CH ₂	CH ₃
	H	CH ₃
	H	C ₆ H ₅
	CH ₃	H
	CH ₃	H
	C ₆ H ₅	CH ₃
	COC ₆ H ₅	H
	4-Methylcyclohexyl	H



R ³	Yield Percent	Reference
H	100	1194
CH ₃	—	1191, 1196
CH ₂ NH ₂	—	1192
H	—	1193, 1194
CH ₃	75	1163
CH(COOH) NH ₂	—	1187
CH ₃ CO	—	1193, 1194
C ₂ F ₅	31	1183
H	—	1240
C ₂ H ₅	37	1161
CH ₃	—	1163
CH ₃	85	1227
H	—	1245
H	—	1245
CF(CF ₃) ₂	5	1184
CH ₃	79	1227
CH ₃ CH ₂ CH ₂	41	1161
<i>i</i> -C ₃ H ₇	46	1161
	58	1170
C ₆ H ₅	80	1174, 1185
	40	1176
4-ClC ₆ H ₄	66	1176
4-NO ₂ C ₆ H ₄	82	1185
	—	1196
H	50	1190
H	80	1204
H	10	1204
H	60	1204
H	90	1204
H	55	1204
C ₂ H ₅	90	1227
<i>n</i> -C ₃ H ₇	51	1161
CH ₃	—	1163
C ₆ H ₅	98	1176
CH ₃	25	1176
	66	1185
C ₆ H ₅	34, 82	1176
4-ClC ₆ H ₄	55	1176
H	—	1178–1180
H	—	1193
H	—	1211

TABLE 3.8. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
11	C ₂ H ₅ -NHCO	C ₂ H ₅
	H	<i>n</i> -C ₄ H ₉
	H	<i>i</i> -C ₄ H ₉
	H	C ₆ H ₅
	CH ₃ CO	<i>n</i> -C ₃ H ₇
	H	H
	CH ₃	CH ₃
	H	CH ₃ C ₆ H ₄ OCH ₂
	H	2,5-(CH ₃ O) ₂ C ₆ H ₃
	H	4-FC ₆ H ₄
	CH ₃ NHCO	H
	CH ₃ CO	H
	ClCH ₂ CO	H
	CH ₃ CO	C ₆ H ₅
12	H	C ₆ H ₅
	C ₆ H ₅ CH ₂	CH ₃
	2-Piperidinoethyl	CH ₃
	CH ₃	H
	C ₆ H ₅ NHCO	CH ₃
	C ₆ H ₅ NHCO	H
	(CH ₃) ₂ NCO	H
	-COOC ₂ H ₅	H
	H	<i>n</i> -C ₅ H ₁₁
	H	C ₆ H ₅
13	H	2-Pyridyl
	C ₆ H ₅	C ₂ H ₅
	4CH ₃ OC ₆ H ₄ CO	C ₂ H ₅
14	H	1-C ₁₀ H ₇
	H	2-C ₁₀ H ₇
	CH ₃ CO	4-FC ₆ H ₄
	2,6-(CH ₃) ₂ C ₆ H ₃ N—	
	CH ₃ OCH ₂ C(=O)	H
15	C ₆ H ₅	H
	H	2-ClC ₆ H ₄
	C ₆ H ₅	<i>n</i> -C ₃ H ₇
	4-CH ₃ CONHC ₆ H ₄ OC ₂ H ₄	CH ₃
	H	C ₆ H ₅
	H	C ₆ H ₅
	4-ClC ₆ H ₄	H
	4-BrC ₆ H ₄	H
	C ₆ H ₅	H
	C ₆ H ₅	H
	H	4C ₆ H ₅ C ₆ H ₄
	<i>n</i> -C ₄ H ₉	4-FC ₆ H ₄
	C ₆ H ₅	C ₆ H ₅

R ³	Yield Percent	Reference
C ₂ H ₅	85	1227
<i>n</i> -C ₄ H ₉	42	1161
<i>i</i> -C ₄ H ₉	64	1161
C ₂ H ₅	49	1161
<i>n</i> -C ₃ H ₇	64	1161
3,4-(CH ₃ O) ₂ C ₆ H ₃	46	1176
C ₆ H ₅	99	1176
H	—	1203
H	50	1204
C ₂ H ₅	—	1257
C ₆ H ₅	95	1227
C ₆ H ₅	87	1231
C ₆ H ₅	90	1231
H	—	1240
<i>n</i> -C ₃ H ₇	94	1161
CH ₃	—	1163
CH ₃	—	1163
(3,4-CH ₃ O) ₂ C ₆ H ₃	57	1176
CH ₃	89	1227
C ₂ H ₅	92	1227
C ₆ H ₅	88	1231
C ₆ H ₅	96	1231
<i>n</i> -C ₅ H ₁₁	17	1161
<i>n</i> -C ₄ H ₉	41	1161
2-Pyridyl	41	1161
	72	1166
C ₂ H ₅	42	1161
H	—	1173
H	60	1204
H	78	1204
C ₂ H ₅	—	1257
H	—	1255
C ₆ H ₅	—	1156, 1159
2-ClC ₆ H ₄	57	1161
<i>n</i> -C ₃ H ₇	84	1161
CH ₃	—	1163
C ₆ H ₅	70	1170, 1185
		1195
	—	1197
4-O ₂ NC ₆ H ₄	84	1185
C ₆ H ₅	84	1203
C ₆ H ₅	80	1203
4-O ₂ NC ₆ H ₄	78	1203
3-O ₂ NC ₆ H ₄	75	1203
H	70	1204
C ₂ H ₅	—	1257
H	—	1240

TABLE 3.8. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
16	(C ₆ H ₅ O) ₂ PO	H
	C ₆ H ₅	C ₆ H ₅
	H	C ₆ H ₅
	C ₆ H ₅ CH ₂	<i>n</i> -C ₃ H ₇
	CH ₃	C ₆ H ₅
	C ₆ H ₅	CH ₃
	H	4-CH ₃ C ₆ H ₄
	H	C ₆ H ₅
	4-CH ₃ C ₆ H ₄	H
	4-CH ₃ OC ₆ H ₄	H
	H	4-CH ₃ OC ₆ H ₄
	C ₆ H ₅ CH ₂	C ₆ H ₅
	H	3,4-OCH ₂ OC ₆ H ₃
	H	3,4-OCH ₂ OC ₆ H ₃
	H	C ₆ H ₅
17	C ₆ H ₅ NHCO	H
	2-CH ₃ C ₆ H ₄	H
	3-CH ₃ C ₆ H ₄	H
	4-CH ₃ C ₆ H ₄	H
	H	<i>n</i> -Heptyl
	H	C ₆ H ₅
	H	4-(CH ₃) ₂ NC ₆ H ₄
	C ₆ H ₅	<i>n</i> -C ₄ H ₉
	C ₆ H ₁₁	<i>n</i> -C ₄ H ₉
	C ₆ H ₅	(CH ₃) ₂ N
	C ₆ H ₅	2-CH ₃ C ₆ H ₄ OCH ₂
	CH ₃ CO	C ₆ H ₅
	H	4-CH ₃ OC ₆ H ₄
	H	3,4-OCH ₂ OC ₆ H ₃
	H	4-CH ₃ C ₆ H ₄
	H	3,4-(CH ₃ O) ₂ C ₆ H ₃
	CH ₃ NHCO	C ₆ H ₅
	ClCH ₂ CO	C ₆ H ₅
	HO ₂ CCH ₂ —	4-ClC ₆ H ₄
18	<i>i</i> -C ₃ H ₇	C ₆ H ₅
	4-C ₂ H ₅ OOCC ₆ H ₄	H
	4-C ₂ H ₅ OOCC ₆ H ₄	H
	4-C ₂ H ₅ OOCC ₆ H ₄	H
	C ₆ H ₅ CO	4-FC ₆ H ₄
	—COOC ₂ H ₅	C ₆ H ₅
	—CH ₂ CH=CH ₂	C ₆ H ₅
	C ₂ H ₅ NHCO	C ₆ H ₅
	—COOC ₂ H ₅	C ₆ H ₅
	HO ₂ CCHCH ₃	4-ClC ₆ H ₄
19	H	4-(C ₂ H ₅ O) ₂ NC ₆ H ₄
	CH ₃ CO	4-(CH ₃ O) ₂ NC ₆ H ₄
	—(CH ₂) ₇ COOC ₂ H ₅	H

R ³	Yield Percent	Reference
H	—	1251, 1253
CH ₃	—	1160
4-CH ₃ OC ₆ H ₄	71	1161
	93	1213
<i>n</i> -C ₃ H ₇	82	1161
C ₆ H ₅	90	1161
C ₆ H ₅	—	1181
C ₆ H ₅	84	1185
4-CH ₃ C ₆ H ₄	57	1185
C ₆ H ₅	83	1203
4-O ₂ NC ₆ H ₄	74	1203
C ₆ H ₅	—	1218
H	95	1220
C ₆ H ₅	88	1213
2-ClC ₆ H ₄	90	1213
4-CH ₃ C ₆ H ₄	87	1213
C ₆ H ₅	92	1227
C ₆ H ₅	—	1159
C ₆ H ₅	—	1159
C ₆ H ₅	—	1159
<i>n</i> -Heptyl	50	1159
<i>n</i> -Octyl	44	1159
C ₆ H ₅	42	1159
<i>n</i> -C ₄ H ₉	40	1159
<i>n</i> -C ₄ H ₉	46	1159
C ₆ H ₅	—	1186
H	—	1203
C ₆ H ₅	—	1212
4-CH ₃ OC ₆ H ₄	84	1213
3,4-OCH ₂ OC ₆ H ₃	95	1213
4-CH ₃ C ₆ H ₄ —	94	1213
C ₆ H ₅	68	1213
C ₆ H ₅	90	1227
C ₆ H ₅	—	1231
4-ClC ₆ H ₄	—	1249
C ₆ H ₅	35	12-1
4-ClC ₆ H ₄	85	1203
4-BrC ₆ H ₄	78	1203
4-O ₂ NC ₆ H ₄	65	1203
C ₂ H ₅	—	1257
C ₆ H ₅	75	1214
C ₆ H ₅	—	1215
C ₆ H ₅	74	1227
C ₆ H ₅	78	1231
4-ClC ₆ H ₄	—	1249
C ₆ H ₅	43	1161
C ₆ H ₅	55	1161
C ₆ H ₅	—	1223

TABLE 3.8. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
20	4-C ₂ H ₅ OOCC ₆ H ₄ -CH ₂ COOC ₂ H ₅ HO ₂ CCHCH ₃ CH ₂ COOC ₂ H ₅ <i>t</i> -C ₄ H ₉ NHCO	H C ₆ H ₅ 4-CH ₃ OC ₆ H ₄ 3,4-OCH ₂ OC ₆ H ₃ C ₆ H ₅
	C ₆ H ₅	CH ₃
21	Me ₂ CHCH ₂ CH— CO ₂ H Me HO ₂ C—CH— C ₆ H ₅	4-ClC ₆ H ₄ 4-CH ₃ OC ₆ H ₄ C ₆ H ₅
22	H H CH ₂ CH(OC ₂ H ₅) ₂ C ₆ H ₅ CH ₂ C ₆ H ₅ CO C ₆ H ₅ C ₆ H ₅ 4-CH ₃ OC ₆ H ₄ 4-CH ₃ C ₆ H ₄	<i>n</i> -C ₉ H ₁₉ 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ 4-CH ₃ OC ₆ H ₄ H C ₆ H ₅ C ₆ H ₅
	H H H H H CH ₃ -CHCONHCH ₂ CO ₂ C ₂ H ₅	C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅
23	H	4-FC ₆ H ₄
	CH ₂ CH(OC ₂ H ₅) ₂ C ₆ H ₅ NHCO C ₆ H ₅ C ₆ H ₅ CHCOOH C ₆ H ₅ CH ₂ CH ₂ —	3,4-OCH ₂ OC ₆ H ₃ C ₆ H ₅ 4-(CH ₃) ₂ NC ₆ H ₄ C ₆ H ₅ C ₆ H ₅

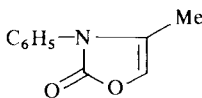
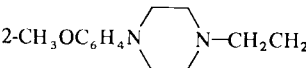
R ³	Yield Percent	Reference
3-NO ₂ -4-CH ₃ C ₆ H ₃	67	1203
C ₆ H ₅	—	1215
4-CH ₃ OC ₆ H ₄	—	1249
C ₆ H ₅	—	1215
C ₆ H ₅	—	1227, 1228
	—	1242, 1244
4-ClC ₆ H ₄	—	1249
4-CH ₃ OC ₆ H ₄	—	1249
C ₆ H ₅	—	1157, 1158
		1198
		1199
	90	1161
	62	1192
<i>n</i> -C ₉ H ₁₉	41	1161
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	75	1161
C ₆ H ₅	—	1215
C ₆ H ₅	83	1161
C ₆ H ₅	67	1161
C ₆ H ₅	85	1161
4-CH ₃ OC ₆ H ₄	—	1212
C ₆ H ₅	26	1182
C ₆ H ₅	72	1182
	—	1199
C ₆ H ₅ COC ₆ H ₅	97	1199
4-BrC ₆ H ₄ COC ₆ H ₅	—	1199
4-ClC ₆ H ₄ COC ₆ H ₅	95	1199
4-O ₂ NC ₆ H ₄ COC ₆ H ₅	—	1199
3,4-Cl ₂ C ₆ H ₃ COC ₆ H ₅	81	1199
C ₆ H ₅	81	1207
	—	1254
C ₆ H ₅	—	1215
C ₆ H ₅	90	1227
C ₆ H ₅	89	1227
C ₆ H ₅	84	1161
C ₆ H ₅	79	1207

TABLE 3.8. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²
	C ₆ H ₅ CH ₂	C ₆ H ₅
	C ₆ H ₅ CH ₂	3,4-OCH ₂ OC ₆ H ₃
	C ₆ H ₄ CH ₂	3,4-OCH ₂ OC ₆ H ₃
	C ₆ H ₅ CH ₂	C ₆ H ₅
	(CH ₃) ₂ CHCH ₂	
	—CHCO ₂ H	4-CH ₃ OC ₆ H ₄
		
24	—(CH ₂) ₇ COOCH ₃	n-C ₃ H ₇
	C ₆ H ₅ CH ₂	n-C ₃ H ₇
	C ₆ H ₅ CH ₂	C ₆ H ₅
	C ₆ H ₄ CH ₂	4-CH ₃ OC ₆ H ₄
	CH ₃ CO	4-CH ₃ C ₆ H ₄
	C ₆ H ₅ CH ₂ CHCO ₂ H	3,4-OCH ₂ OC ₆ H ₃
		C ₆ H ₅
25	2-C ₁₀ H ₇	4-ClC ₆ H ₄
26	C ₆ H ₅ CH ₂ CHCO ₂ H	C ₆ H ₅
29	C ₆ H ₅ CH ₂ OOCNHCHCOOH	4-CH ₃ OC ₆ H ₄
		C ₆ H ₅
	(CH ₂) ₄ —	

R ³	Yield Percent	Reference
4-CH ₃ OC ₆ H ₄	80	1213
2-ClC ₆ H ₄	75	1213
C ₆ H ₅	50	1213
4-CH ₃ C ₆ H ₄	55	1213
4-CH ₃ OC ₆ H ₄	—	1249
<i>n</i> -C ₃ H ₇	81	1161 (bisoxaz- olone)
<i>n</i> -C ₃ H ₇	—	1224
C ₆ H ₅	—	1213
4-CH ₃ OC ₆ H ₄	80	1213
4-CH ₃ C ₆ H ₄	77	1213
3,4-OCH ₂ OC ₆ H ₃	98	1213
4-C ₆ H ₅ COC ₆ H ₄	77	1231
4-ClC ₆ H ₄	—	1249
C ₆ H ₅	52	1161
4-CH ₃ OC ₆ H ₄	—	1249
C ₆ H ₅	—	1210

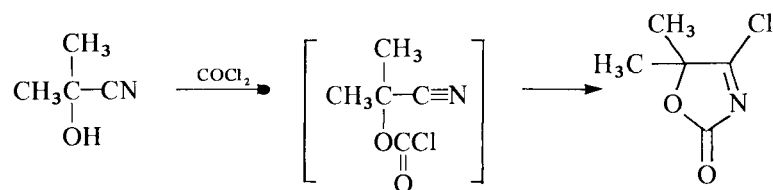
3.6. 2-[5H] OXAZOLONES (3-OXAZOLIN-2-ONES)

A substantial number of compounds of this class have been reported since 1977 (Tables 3.9A and 3.9B). The methods of preparation may be categorized as (1) general methods and (2) structure analyses of other compounds by oxidation or hydrolysis leading to the formation of 2-[5H] oxazolones.

3.6.1. Methods of Preparation

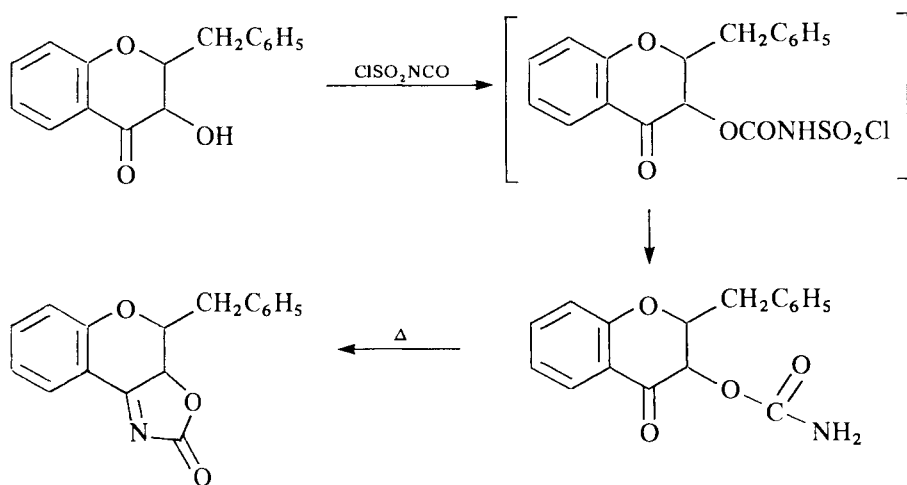
3.6.1.1. From Cyanohydrins

Reaction of acetone cyanohydrin with phosgene leads to the formation of 4-chloro-5,5-dimethyl-3-oxazoline-2-one.¹²⁵⁸ The latter compound reacts with aniline to give the 4-anilino derivative.



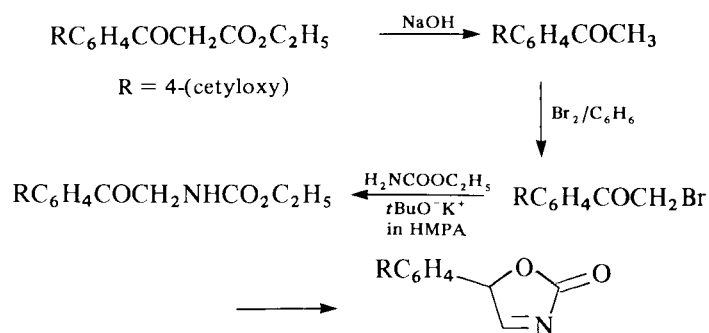
3.6.1.2. From Tertiary α -Hydroxyketones

Reaction of chlorosulfonyl isocyanate with tertiary α -hydroxyketones, followed by hydrolysis, affords carbonates, which on pyrolysis cyclize to 3-oxazoline-2-ones.¹²⁵⁹

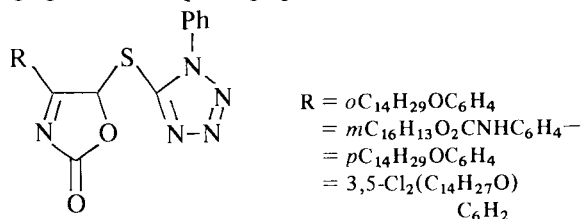


3.6.1.3. From Urethanes

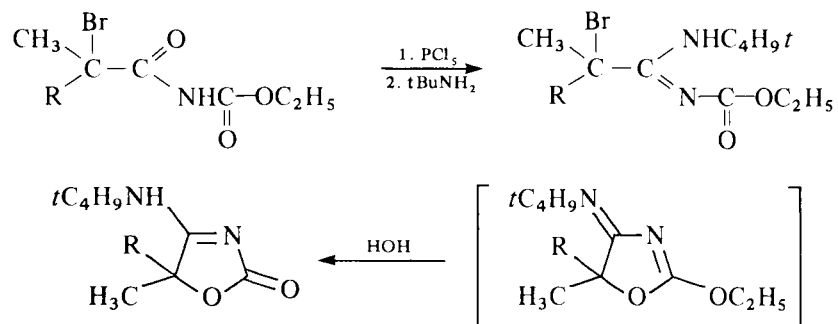
α -Haloketones condense with urethane in HMPA [(Me₂N)₃PO] in the presence of potassium *tert*-butoxide to yield 2-[5H] oxazolones.¹²⁶⁰



Compounds containing mercaptophenyl tetrazole as one of the R groups are useful in making light-sensitive photographic materials.^{1261, 1262}

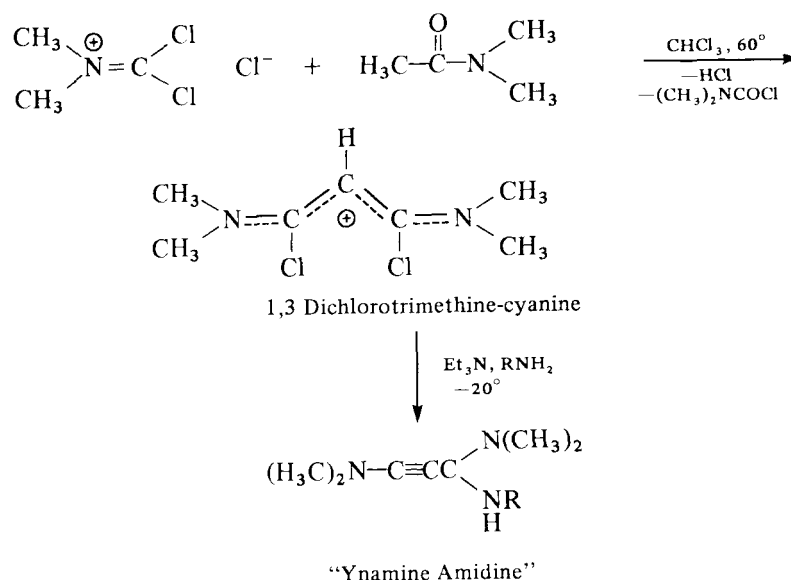
3.6.1.4. From α -Bromoamidines

α -Bromoamidines are also useful as starting materials.¹²⁶³

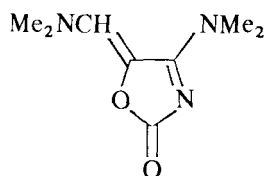


3.6.1.5. From Ynamine Amidines

Ynamine amidines are obtained as follows:

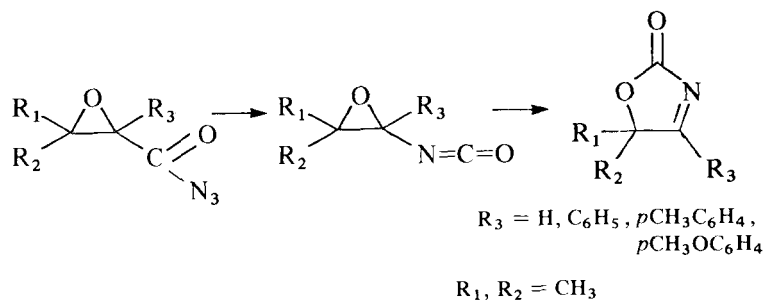


This compound (R = H) reacts with CO₂ at 20°C to give a 2-[5*H*] oxazolone, 4-dimethylamino-5-dimethylaminomethylidene-3-oxazoline-2-one.¹²⁶⁴ The structure of this compound was established by X-ray crystallography.¹²⁶⁴

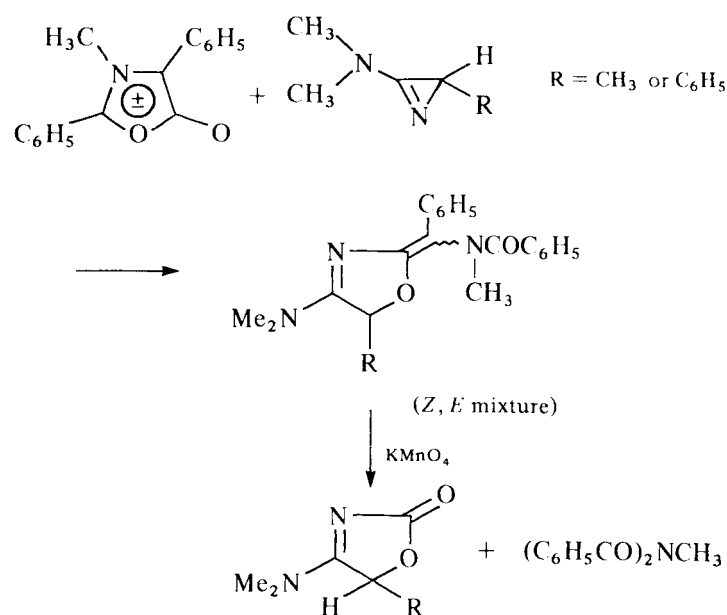


3.6.1.6. From Epoxyacyl Azides

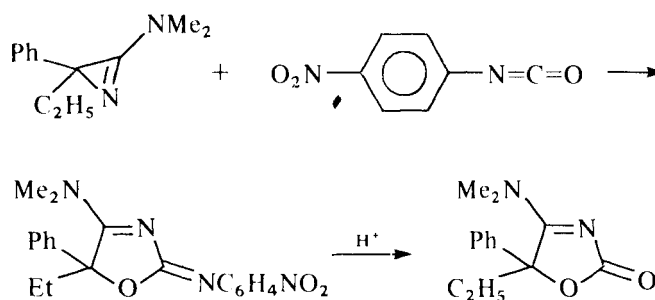
Epoxyacyl azides readily rearrange to epoxy isocyanates, which undergo ring expansion on heating in an inert solvent.¹²⁶⁵



The mesoionic oxazolone 3-methyl-2,4-diphenyloxazolium-5-olate reacts with 3-dimethylamino-2,2-dimethyl-2*H*-azirine in acetonitrile to form a 1:1 adduct.^{1266, 1267}

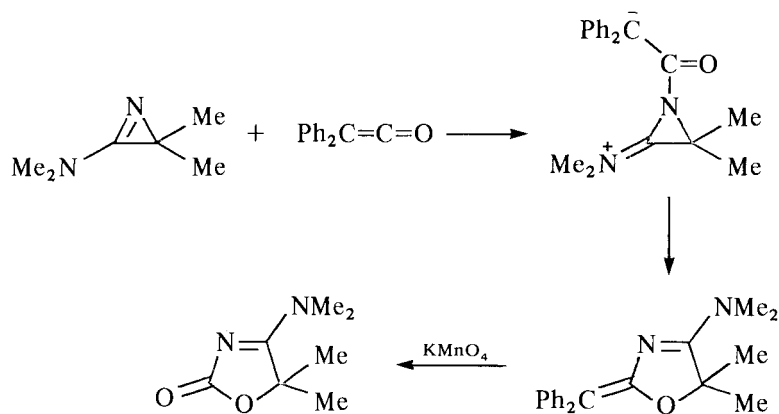


2-Phenyl-3-dimethylamino-2*H*-azirines react with isocyanates to give an adduct,¹²⁶⁸ which on hydrolysis yields a 3-oxazolin-2-one derivative.¹²⁶⁸



3.6.1.7. Oxidation of 2-Exocyclic-Oxazolidines

3-Dimethylamino-2,2-dimethyl-2*H*-azirine reacts with diphenylketene to give an intermediate which on oxidation with KMnO₄ undergoes cleavage to form a 2-[5*H*] oxazolone derivative.¹²⁶⁹



3.6.2. Reactions

3-Oxazolin-2-one compounds form 4-oxazolin-2-one derivatives by a 1,3 proton shift when one of the R groups on the 5-position of the ring is a hydrogen.⁸ The IR and ¹³C NMR spectra have been widely reported. The carbonyl absorption is in the region 1790–1755 cm⁻¹

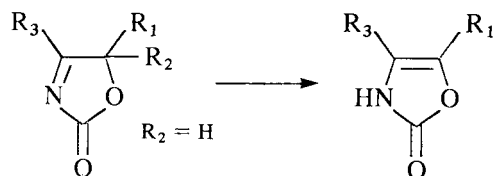
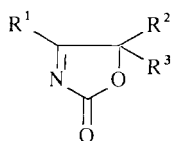


TABLE 3.9A. 3-OXAZOLIN-2-ONE or 2-[5*H*] OXAZOLONE



No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²	R ³	Reference
5	Cl	CH ₃	CH ₃	1258
7	(CH ₂) ₂ N	CH ₃	CH ₃	1266, 1269
	OC ₂ H ₅	CH ₃	CH ₃	1270–1273
9	(CH ₃) ₂ N		(CH ₃)NCH=	1264
	C ₄ H ₉ NH	CH ₃	CH ₃	
	(CH ₃) ₃ C	CH ₃	CH ₃	1263
	C ₄ H ₉ NH	CH ₃	CH ₃	1263

TABLE 3.9A. (CONTINUED)

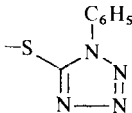
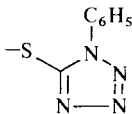
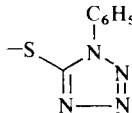
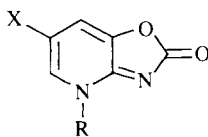
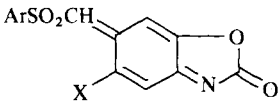
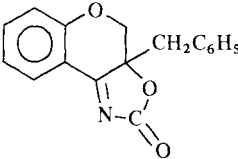
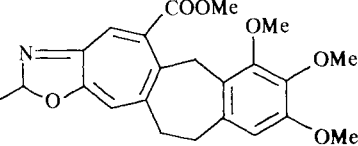
No. of Carbon Atoms in Oxazolone Ring	R ¹	R ²	R ³	Reference
11	C ₆ H ₅	CH ₃	CH ₃	1266
12	C ₆ H ₅ NH	CH ₃	CH ₃	1266
	(CH ₃) ₂ N	CH ₃	C ₆ H ₅	1265
	H		Adamantane	1259
	4CH ₃ C ₆ H ₄	CH ₃	CH ₃	1259
	4CH ₃ OC ₆ H ₄	CH ₃	CH ₃	1259
13	(CH ₃) ₂ N	C ₂ H ₅	C ₆ H ₅	1258
14	C ₆ H ₅		-(CH ₂) ₅ -	1259
15	C ₆ H ₅	C ₆ H ₅	H	1262
	C ₆ H ₅	4FC ₆ H ₄	H	1262
16	C ₆ H ₅	C ₆ H ₅	CH ₃	1259
21	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	1259
25	H	H	4-(C ₁₆ H ₃₃ OC ₆ H ₄)	1260
30	3,5-Cl ₂ -2-C ₁₄ H ₂₉ OC ₆ H ₄	H		1261
	2-C ₁₄ H ₂₉ OC ₆ H ₄	H		1261
	4-C ₁₄ H ₂₉ OC ₆ H ₄	H		1261

TABLE 3.9B. FUSED OXAZOLONES (4-SUBSTITUTED OXAZOLONE [4,5-*b*] PYRIDIN-2-[4*H*]-ONE)

No. of Carbon Atoms in Oxazolone Ring	X	R	Reference
8	H	C ₂ H ₅	1274
9	H	<i>n</i> -C ₃ H ₇	1274
	H	CH ₂ =CH-CH ₂	1274

TABLE 3.9B. (CONTINUED)

No. of Carbon Atoms in Oxazolone Ring	X	R	Reference
10	H	<i>n</i> -C ₄ H ₉	1274
	H	2-Thienyl	1247
	H	C ₂ H ₅ O ₂ CCH ₂	1274
	H	Cyclopropyl methyl	1274
12	H	<i>t</i> -C ₄ H ₉ O ₂ CCH ₂	1274
	H	2-Pyridylmethyl	1274
13	H	C ₆ H ₅ CH ₂	1274
	H	4-ClC ₆ H ₅ CH ₂	1274
	H	2,4-Cl ₂ C ₆ H ₃ CH ₃	1274
	Br	C ₆ H ₅ CH ₂	1274
	NO ₂	C ₆ H ₅ CH ₂	1274
14	H	4-CH ₃ OC ₆ H ₄ CH ₂	1274
	H	3-CH ₃ OC ₆ H ₄ CH ₂	1274
	H	2-CH ₃ C ₆ H ₄ CH ₂	1274
	H	3-CH ₃ C ₆ H ₄ CH ₂	1274
	H	4-CH ₃ C ₆ H ₄ CH ₂	1274
	H	C ₆ H ₅ COCH ₂	1274
	H	C ₆ H ₅ CH=CH	1274
	H	C ₆ H ₅ CH ₂ CH ₂	1274
	H	C ₆ H ₅ CHCH ₂ OH	1274
13			
	Ar = C ₆ H ₅ X = H		
	Ar = C ₆ H ₅ X = Cl		
14	Ar = 4CH ₃ C ₆ H ₄ X = H		
	Ar = 4CH ₃ C ₆ H ₄ X = Cl		
17			
22			

ACKNOWLEDGMENTS

The authors would like to thank Ms. Betty Alston, E. I. duPont de Nemours and Company, Wilmington, Delaware, for the initial literature search; Mrs. Usha V. Murthy for typing the preliminary draft; Mrs. Alice F. Cap for the tables; and Mrs. Janet Meredith-Patla for typing the final manuscript.

REFERENCES

1. H. E. Carter, *Org. Reactions*, **3**, 198–239 (1947).
2. J. W. Cornforth, in *Chemistry of Penicillin*, H. T. Clarke, J. R. Johnson, and R. Robinson, Eds., Princeton, N.J., 1949, pp. 688–848.
3. E. Baltazzi, *Quart. Revs. Chem. Soc.*, **9**, 150 (1955).
4. J. W. Cornforth, *Heterocyclic Compounds*, R. C. Elderfield, Ed., Vol. 5, John Wiley & Sons, New York, 1957, pp. 298–417.
5. R. Filler, *Advances in Heterocyclic Chemistry*, Vol. 4, A. R. Katritzky, Ed., Academic Press, New York, 1965, pp. 75–106.
6. W. Steglich, *Fortschr. Chem. Forsch.*, **12**, 77 (1969); *Chem. Abstr.*, **71**, 101742q (1969).
7. R. Filler and Y. S. Rao, *Advances in Heterocyclic Chemistry*, Vol. 21, A. R. Katritzky, Ed., Academic Press, New York, 1977, pp. 175–206.
- 8a. T. Wieland, R. Müller, E. Nieman, L. Birkofer, A. Schöberl, A. Wagner, and H. Soll, *Methoden Zur Herstellung und Umwandlung von Amino Suaren und Derivaten*, Houben-Weyl, 1962.
- 8b. E. H. Rodd, *Chemistry of Carbon Compounds*, Vol. IVA, Elsevier, New York, 1957, pp. 365–71.
9. A. Neuberger, *Advances in Protein Chemistry*, Vol. 4, Academic Press, New York, 1948, p. 356.
10. S. I. Lurye and E. S. Chaman, *Reatskii I Metody Isseldovan Org. Soedenenii*, **9**, 155–286 (1959); *Moscow, Chem. Abstr.*, **54**, 17368h (1960).
- 11a. K. Huebner, F. Kollinsky, G. Markert, and H. Pennewiss, *Angew. Makromol. Chemie*, **11**, 1109–24 (1970); *Chem. Abstr.*, **73**, 15334k (1970).
- 11b. K. Nalepa, *Acta Univ. Palacki, Olomuc. Fac. Rerum Nat.*, **53** (1977); *Chem. Abstr.*, **90**, 38812n (1977).
- 11c. K. Nalepa, *Chem. Zvesti*, **32**, 565 (1978); *Chem. Abstr.*, **90**, 168507e (1979).
- 11d. A. Antonova and D. Simov, *Khim. Geterosikl. Soeden.*, 1587 (1979); *Chem. Abstr.*, **92**, R110883x (1980).
12. Y. S. Rao and R. Filler, *Synthesis*, 749–64 (1975).
13. A. K. Mukerjee and P. Kumar, *Heterocycl.*, **16**, 1995 (1981).
14. T. Kametani and K. Fukumoto, *Heterocycl.*, **10**, 349 (1978).
- 15a. J. Plochl, *Ber. Dtsch. Chem. Ges.*, **16**, 2815 (1883).
- 15b. F. Erlenmeyer, *Justus Liebigs Ann. Chem.*, **275**, 1 (1893).
- 16a. H. L. Slates and N. L. Wendler, U.S. Patent 3,275,648b (1966); *Chem. Abstr.*, **65**, 18684 (1966).
- 16b. H. L. Slates, D. S. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **29**, 1424 (1964).

17. W. F. Cartwright, Ph.D. thesis, University of Wisconsin, Madison, Wisc. (1968); *Diss. Abs.*, **29B**, 4488B (1968).
18. M. M. Botvinik and S. M. Avaeva, Uchenye Zapiski Moskov Gosudarst. Univ. im. M. V. Lomonosova No. 132, *Org. Khim.*, **7**, 288 (1950); *Chem. Abstr.*, **49**, 3943i (1955).
19. M. Crawford and W. T. Little, *J. Chem. Soc.*, 3525 (1953).
20. Z. T. Kaminski, M. T. Leplawy, and S. Zabrocki, *Synthesis*, 792 (1973).
21. G. E. VandenBerg, J. B. Harrison, H. E. Carter, and B. J. Magerlein, *Org. Synth.*, **5**, 946 (1973).
22. M. M. Shemyakin, E. S. Chaman, L. I. Denisova, G. A. Ravdel, and W. J. Rodionow, *Bull. Soc. Chim. France*, 539 (1958).
23. M. M. Shemyakin, E. S. Chaman, and L. I. Denisova, *J. Gen. Chem. USSR*, **26**, 101 (1956).
24. M. M. Shemyakin, L. I. Denisova, and E. S. Chaman, *J. Gen. Chem. USSR*, **27**, 659 (1957).
25. M. M. Shemyakin, G. A. Ravdel, and E. S. Chaman, *J. Gen. Chem. USSR*, **26**, 195 (1956).
26. E. S. Chaman and M. M. Shemyakin, *J. Gen. Chem. USSR*, **25**, 1309 (1955).
27. I. T. Strukov, *Zh. Obsch. Khim.*, **29**, 2359 (1959).
28. I. Z. Siemion and K. Nowak, *Rocz. Chem.*, **25**, 979 (1961).
29. M. Goodman and C. B. Glaser, *J. Org. Chem.*, **35**, 1954 (1970).
30. D. N. Reinhoudt and P. M. M. Van der Kamp, *Org. Prep. & Procedures*, **2**, 265 (1970).
31. J. M. Riordan and C. H. Stammer, *J. Org. Chem.*, **39**, 654 (1974).
32. E. Schnabel, *Ann.*, **688**, 238 (1965).
33. C. DiBello, F. Filira, and F. D'Angeli, *J. Org. Chem.*, **36**, 1818 (1971).
34. H. L. Maia, B. Ridge, and H. N. Rydan, *J. Chem. Soc. Perkin Trans. I*, 98 (1973).
- 35a. W. J. McGahren, Ph.D. thesis, Brooklyn Polytech. Inst., Brooklyn, NY; *Diss. Abs.*, **27B**, 588 (1966).
- 35b. W. J. McGahren and M. Goodman, *Tetrahedron*, **23**, 2017 (1967).
- 36a. I. Z. Siemion and A. Dzugaj, *Rocz. Chem.*, **40**, 1699 (1966).
- 36b. I. Z. Siemion, *Rocz. Chem.*, **42**, 237 (1968).
37. O. Grahl-Nielsen, *J. Chromat.*, **93**, 229 (1974).
38. O. Grahl-Nielsen and E. Solheim, *J. Chromat.*, **105**, 89 (1975).
39. O. Grahl-Nielsen and E. Solheim, *Chem. Commun.*, 1092 (1972).
40. D. G. Knorre and O. A. Mirgorodskaya, *Izv. Sib. Otd. Akad. Nauk. SSSR Ser. Khim. Nauk.*, **106** (1968); *Chem. Abstr.*, **71**, 61756p (1969).
41. R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **34**, 2742 (1969).
42. T. H. Chan and L. T. Wong, *J. Org. Chem.*, **36**, 850 (1971).
43. K. Nowak, I. Z. Siemion, and H. Siemieniewsky, *Rocz. Chem.*, **36**, 557 (1962).
44. G. A. Swan, *J. Chem. Soc.*, 1534 (1950).
- 45a. J. M. Swan, *Aust. J. Sci. Res.* **A5**, 728 (1952); *Chem. Abstr.*, **47**, 9274e (1953).
- 45b. J. M. Swan, *Aust. J. Sci. Res.*, **5**, 711 (1952); *Chem. Abstr.*, **47**, 9273i (1952).
46. M. Brenner and K. Rufenacht, *Helv. Chim. Acta*, **37**, 203 (1954).
47. M. Brenner and K. Rufenacht, *Helv. Chim. Acta*, **37**, 209 (1953).
48. M. Brenner and K. Rufenacht, *Helv. Chim. Acta*, **36**, 1832 (1953).
49. L. D. Taylor and T. E. Platt, *J. Polym. Sci. B*, **7**, 597 (1969).
50. L. D. Taylor, C. E. Chiklis, and T. E. Platt, *J. Polym. Sci. B*, **8**, 537 (1970).
51. L. D. Taylor and T. E. Platt, *Org. Prep. Proced.*, **1**, 217 (1969).

52. L. D. Taylor, T. E. Platt, and M. H. Mach, *J. Polym. Sci. B*, **8**, 537 (1970).
53. S. V. Rogozhin, Y. A. Davidovich, and V. V. Korshak, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1593 (1971).
54. H. Kayahara and I. Tomida, *Shinshu Daigaku Nogakubu Kiyo*, **11**, 87 (1974); *Chem. Abstr.*, **81**, 169793u (1974).
55. E. I. Boksiner, *Zh. Org. Khim.*, **8**, 604 (1972).
56. E. I. Boksiner and B. V. Passeg, USSR Patent 368,263 (1973); *Chem. Abstr.*, **79**, 32033k (1973).
57. D. Obrecht and H. Heimgartner, *Chimia*, **36**, 78 (1983).
58. K. J. Morgan, A. Thomson, P. Forton, and R. K. Whitham, *Ger. Offen.* 2,307,512 (1973); *Chem. Abstr.*, 801676X (1974).
59. S. Wolfe, C. Ferrari, and W. S. Lee, *Tet. Lett.*, 3385 (1969).
60. S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *Can. J. Chem.*, **46**, 2549 (1968).
61. H. Pourrat, *Bull. Soc. Chim. France*, 823 (1956).
62. A. Mustafa and A. H. E. Harhash, *J. Org. Chem.*, **21**, 575 (1956).
63. R. Filler and J. D. Wismar, *J. Org. Chem.*, **22**, 853 (1957).
64. W. I. Awad and M. S. Hafez, *J. Org. Chem.*, **25**, 1180 (1960).
65. W. I. Awad and M. S. Hafez, *J. Org. Chem.*, **25**, 1183 (1960).
66. R. Filler, K. B. Rao, and Y. S. Rao, *J. Org. Chem.*, **27**, 1110 (1962).
67. R. Filler and Y. S. Rao, *J. Org. Chem.*, **27**, 3348 (1962).
68. M. A. El-Kaschef, F. M. E. Abdel-Megeid, and S. M. Yassin, *Liebigs. Ann. Chem.*, 37 (1974).
69. M. A. F. El-Kaschef, F. M. E. Abdel-Megeid, and S. M. A. Yassin, *J. Prakt. Chem.*, **316**, 363 (1974).
70. A. Mustafa and M. N. N. Sallam, *J. Org. Chem.*, **24**, 2406 (1962).
71. R. Filler and Y. S. Rao, *J. Het. Chem.*, **1**, 153 (1964).
72. L. Horner and H. Schwann, *Ann.*, **591**, 99 (1955).
73. W. Asker and Z. E. Elargoudi, *J. Org. Chem.*, **26**, 140 (1961).
74. G. L. Slater and A. W. Somerville, *Tetrahedron*, **22**, 35 (1966).
75. G. L. Slater and A. W. Somerville, *Tetrahedron*, **23**, 2823 (1967).
76. A. W. Somerville and S. G. Davis, *Tetrahedron*, **25**, 1105 (1969).
77. A. H. Harhash, A. I. Kashab, and Z. Al-Saigh, *Ind. J. Chem.*, **10**, 41 (1972).
78. A. H. Harhash, N. A. L. Kassab, and A. A. A. Elbanani, *Ind. J. Chem.*, **9**, 789 (1971).
79. A. Mustafa, W. Asker, A. H. Harhash, T. M. S. Abdin, and E. M. Zayed, *Justus Liebigs. Ann.*, **714**, 146 (1968).
80. W. I. Awad, M. S. Hafez, and A. E. A. Gadallah, *J. Org. Chem.*, **27**, 1050 (1962).
81. W. I. Awad and A. E. A. Gadallah, *J. Org. Chem.*, **26**, 598 (1961).
82. S. H. Pines and M. Sletzinger, *Ger Offen.* 1,954,727 (1970); *Chem. Abstr.*, **73**, 35759p (1970).
83. S. H. Pines, S. Karady, and M. Sletzinger, *J. Org. Chem.*, **33**, 1758 (1968).
84. R. Filler and L. M. Hebron, *J. Org. Chem.*, **23**, 1815 (1958).
85. R. Filler and Y. S. Rao, *J. Org. Chem.*, **27**, 2403 (1962).
86. W. I. Awad and M. S. Hafez, *J. Org. Chem.*, **26**, 2055 (1961).
87. W. J. Awad and M. A. Abdul-Monem, *J. Iraqi. Chem. Soc.*, **1**, 63 (1976); *Chem. Abstr.*, **87**, 68205 (1977).

88. E. Cioranescu, L. Birladeanu, A. T. Balaban, and C. D. Nenitzescu, *Tet. Lett.*, **349** (1962).
89. A. F. M. Fahmy and M. O. A. Orabi, *Ind. J. Chem.*, **10**, 961 (1972).
90. E. I. Karpeiskaya, L. F. Godunova, E. S. Neupokoeva, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1104 (1978); *Chem. Abstr.*, **90**, 39214f (1979).
91. L. F. Godunova, E. S. Neupokoeva, E. I. Karpeiskaya, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1363 (1978); *Chem. Abstr.*, **90**, 23636j (1979).
92. E. I. Karpeiskaya, E. S. Neupokoeva, L. F. Godunova, I. P. Murina, A. P. Kharchevnikov, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **90**, 23635h (1979).
93. E. S. Neupokoeva, E. I. Karpeiskaya, L. F. Godunova, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 139 (1979); *Chem. Abstr.*, **91**, 21019g (1979).
94. G. Chel'tsova, E. I. Karpeiskaya, E. I. Klabunovskii, and E. D. Lubuzh, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 59 (1982); *Chem. Abstr.*, **98**, 198680m (1983).
95. G. V. Chel'tsova, E. I. Karpeiskaya, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2350 (1981); *Chem. Abstr.*, **96**, 104708k (1983).
96. I. E. Khatskevich, I. K. Kalnin, E. I. Karpeiskaya, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 366 (1983); *Chem. Abstr.*, **98**, 215947y (1983).
97. I. E. Khatskevich, I. K. Kalnin, E. I. Karpeiskaya, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 359 (1983); *Chem. Abstr.*, **99**, 22874j (1983).
98. L. F. Godunova, E. S. Levitina, E. I. Karpeiskaya, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 815 (1981); *Chem. Abstr.*, **95**, 187613d (1981).
99. E. I. Karpeiskaya, G. V. Chel'tsova, E. I. Klabunovskii, and A. P. Kharchevnikov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1082 (1980); *Chem. Abstr.*, **93**, 105614n (1980).
100. L. F. Godunova, E. I. Karpeiskaya, E. S. Neupokoeva, and E. I. Klabunovskii, *Katal. Reakts. Zhidk. Faze, Mater Vses. Konf.*, 4th, 121 (1974); *Chem. Abstr.*, **86**, 170690t (1977).
101. E. I. Klabunovskii, A. A. Vendenypin, E. I. Karpeiskaya, and V. A. Pavlov, *Stud. Surf. Sci. Catal.*, **390** (1981); *Chem. Abstr.*, **95**, 226360r (1981).
102. E. S. Neupokoeva, E. I. Karpeiskaya, L. F. Godunova, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 146 (1979); *Chem. Abstr.*, **91**, 21020a (1979).
103. V. A. Pavlov, E. N. Rasadkina, E. I. Karpeiskaya, G. V. Chel'tsova, L. N. Kaigorodova, and E. I. Klabunovskii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1087 (1980); *Chem. Abstr.*, **93**, 238017f (1980).
104. K. Onuma, T. Ito, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, **53**, 2016 (1980).
105. R. Glaser and S. Geresh, *Tetrahedron*, **35**, 2381 (1979).
106. W. Steglich and H. Wegmann, *Synthesis*, 481 (1980).
107. H. Wegmann, G. Schulz, and W. Steglich, *Liebigs Ann. Chem.*, 1736 (1980).
108. G. Schulz, P. Gruber, and W. Steglich, *Chem. Ber.*, **112**, 322 (1979).
109. H. Wegmann and W. Steglich, *Chem. Ber.*, **114**, 2580 (1981).
110. R. Lohmar and W. Steglich, *Chem. Ber.*, **113**, 3706 (1980).
111. R. Lohmar and W. Steglich, *Angew. Chem.*, **90**, 493 (1978).
112. G. Schulz and W. Steglich, *Chem. Ber.*, **113**, 770 (1980).
113. B. Kubel, P. Gruber, R. Hurnaus, and W. Steglich, *Chem. Ber.*, **112**, 128 (1979).
114. W. Steglich, R. Hurnaus, P. Gruber, and B. Kuebel, *Ger. Offen.* 2,336,718 (1975); *Chem. Abstr.*, **82**, 156263s (1975).
115. H. Akashi, *Yuki Goeikagaku Kyokai Shi*, **32**, 200 (1973); *Chem. Abstr.*, **81**, 91400s (1974).

116. N. L. Allinger, G. L. Wang, and B. D. Dewhurst, *J. Org. Chem.*, **39**, 1730 (1974).
117. W. Steglich, and G. Höfle, *Angew. Chem. Internat. Ed.*, **6**, 61 (1967).
118. S. Umio, K. Kariyone, K. Tanaka, and H. Noguchi, *Jap. Pat.* 67,25657 (1967); *Chem. Abstr.*, **69**, 52121j (1968).
119. S. H. Pines, U.S. Patent 3,716,573 (1973); *Chem. Abstr.*, **78**, 124884h (1973).
120. S. H. Pines and M. Sletzing, U.S. Patent 3,676,453 (1972); *Chem. Abstr.*, **77**, 101565h (1972).
121. N. I. Aronova, N. N. Makhova, and S. I. Zavyalov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 401 (1972).
122. N. I. Aronova, N. N. Makhova, and S. I. Zavyalov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 724 (1970).
123. Y. Iwakura, F. Toda, and H. Suzuki, *J. Org. Chem.*, **32**, 440 (1967).
124. G. Höfle, A. Prox, and W. Steglich, *Chem. Ber.*, **105**, 1718 (1972).
125. W. Steglich and G. Höfle, *Tet. Lett.*, 1619 (1968).
126. W. Steglich and G. Höfle, *Chem. Ber.*, **104**, 3644 (1971).
127. W. Steglich and G. Höfle, *Chem. Ber.*, **102**, 883 (1969).
128. W. Steglich and G. Höfle, *Chem. Ber.*, **102**, 1129 (1969).
129. R. Knorr and R. Huisgen, *Chem. Ber.*, **103**, 2598 (1978).
130. R. Knorr and G. K. Staudinger, *Chem. Ber.*, **104**, 3621 (1971).
131. R. Knorr, *Angew. Chem. Internat. Edit.*, **4**, 705 (1965).
132. M. Goodman and L. Levine, *J. Org. Chem.*, **29**, 2918 (1964).
133. M. Goodman and K. C. Steuben, *J. Org. Chem.*, **27**, 3409 (1962).
134. M. Goodman and W. J. McGahren, *J. Am. Chem. Soc.*, **87**, 3028 (1965).
135. M. Goodman and W. J. McGahren, *J. Am. Chem. Soc.*, **88**, 3887 (1966).
136. M. Goodman and C. B. Glaser, *Tet. Lett.*, 3473 (1968).
137. M. Goodman and C. B. Glaser, *Tetrahedron*, **23**, 2017 (1967).
138. I. Z. Siemion, and L. Wilschowitz, *Z. Naturforsch. B*, **26**, 762 (1971).
139. O. Grahl-Nielsen, *Chem. Commun.*, 1588 (1971).
140. J. Kovacs, L. Kisfaludi, and M. Q. Ceprini, *Peptides Proc. Eur. Pep. Symp. 8th*, Noordwijk, Neth., 23 (1960).
141. D. S. Kemp and J. Rebek, Jr., *J. Am. Chem. Soc.*, **92**, 5792 (1970).
142. D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.*, **89**, 2745 (1967).
143. R. G. Jones, Q. F. Soper, O. K. Behrens, and J. W. Corse, *J. Am. Chem. Soc.*, **70**, 2843 (1948).
144. I. Z. Siemion, K. Nowak, and Z. Kaczorowski, *Rocz. Chem.*, **36**, 1191 (1962).
145. H. Singh, *Agra Univ. J. of Research*, **11**, 213 (1962); *Chem. Abstr.*, **58**, 5651 (1965).
146. E. Baltazzi and R. Robinson, *Chem. & Industry* (London), 541 (1953).
147. A. M. Knowles, A. Lawson, G. V. Boyd, and R. A. Newberry, *J. Chem. Soc. C*, 598 (1971).
148. J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, **81**, 2715 (1959).
149. G. Jommi, F. Mawri, and G. Riva, British Patent 1,250,973 (1971); *Chem. Abstr.*, **76**, 3836g (1972).
150. A. M. Simonov, V. A. Anisimova, and L. E. Grushina, *Khim. Geterosikl. Soedin.*, 838 (1970); *Chem. Abstr.*, **73**, 109739f (1970).
151. Y. S. Rao, unpublished results.
152. C. Cativela and E. Melendez, *Synthesis*, 837 (1978).

153. R. A. F. Bullerwell and A. Lawson, *J. Chem. Soc.*, 1350 (1952).
154. C. Hanna and W. T. Smith, Jr., *Proc. Iowa Acad. Sci.*, **58**, 251 (1951); *Chem. Abstr.*, **47**, 6765e (1953).
155. W. T. Smith, Jr., and C. Hanna, *J. Am. Chem. Soc.*, **73**, 2387 (1951).
156. J. Rotbergs, S. Rotberga, and V. Oskaja, *Uch. Zap. Latv. Univ.*, **117**, 186 (1970); *Chem. Abstr.*, **76**, 126842p (1972).
157. A. M. Islam, A. M. Khalil, and A. I. I. Abdel-Gawad, *Chem. Zvesti.*, **18**, 666 (1974).
158. V. N. Gupta, *J. Sci. & Ind. Res. (India)*, **19B**, 117 (1960).
159. J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Org. Chem.*, **24**, 1722 (1959).
160. S. P. Gupta, S. N. Rastogi, and R. K. Arora, *J. Ind. Chem. Soc.*, **43**, 650 (1966).
161. A. Neuberger, *Biochem. J.*, **43**, 599 (1948).
162. J. P. Lambooy, *J. Am. Chem. Soc.*, **71**, 3758 (1949).
163. J. P. Lambooy, *J. Am. Chem. Soc.*, **77**, 1288 (1955).
164. J. P. Lambooy, *J. Am. Chem. Soc.*, **76**, 133 (1954).
165. J. P. Lambooy, *J. Am. Chem. Soc.*, **78**, 771 (1956).
166. B. H. Bower and J. P. Lambooy, *J. Med. Chem.*, **12**, 1028 (1969).
167. C. Demetrescu, C. Chirita, and V. Ion, *Rev. Roum. Chim.*, **12**, 1039 (1965).
168. F. Eiden and A. Engelhardt, *Arch. Pharm.*, **300**, 211 (1967).
169. K. Nalepa, V. Bekarek, and J. Slouka, *J. Prakt. Chem.*, **314**, 851 (1972).
170. M. Vanghelovici, I. Lupsa, C. Bilegan, and A. Muste, *Acad. Rep. Populare Rom., Baza Cercetari Stiint Timisoara Studii Cercet. i Stiint Ser. Chem.*, **7**, 295 (1960); *Chem. Abstr.*, **55**, 23491i (1961).
171. R. M. Acheson, D. A. Booth, R. Brettle, and A. M. Harris, *J. Chem. Soc.*, 3457 (1960).
172. M. D. Armstrong, K. N. Shaw, and P. E. Wall, *J. Biol. Chem.*, **218**, 293 (1956).
173. B. P. Asthana and P. I. Ittyerah, *J. Ind. Chem. Soc.*, **46**, 137 (1969).
174. G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin I*, 909 (1972).
175. H. S. Tan, D. N. Reinhoudt, and H. C. Beyerman, *Rec. Trav. Chim.*, **88**, 209 (1969).
176. L. Dubrakova, I. Jezo, P. Sefcovic, and Z. Voticky, *Chem. Zvesti.*, **11**, 536 (1957).
177. P. K. Sharma and S. S. Dave, *J. Pharm. Sci.*, **56**, 1178 (1967).
178. P. K. Sharma, M. K. Menon, and P. C. Dandiya, *J. Pharm. Sci.*, **53**, 1055 (1964).
179. R. Andrisano and S. Agnello, *Gazz. Chim. Ital.*, **85**, 374 (1955).
180. D. A. Bassi, V. Delofeu, and F. A. Ortega, *J. Am. Chem. Soc.*, **75**, 171 (1953).
181. J. D. White, W. E. Haefliger, and M. J. Dimsdale, *Tetrahedron*, **26**, 234 (1970).
182. I. M. Hora, V. Gupta, and P. I. Ittyerah, *J. Ind. Chem. Soc.*, **49**, 901 (1972).
183. T. D. Petrova, V. P. Mamaev, G. G. Yakobson, and N. N. Vorozhtsov, Jr., *Khim. Geterosikl. Seodin.*, **5**, 771 (1968); *Chem. Abstr.*, **71**, 13104c (1969).
184. P. B. Tripathy and M. K. Rout, *J. Ind. Chem. Soc.*, **36**, 625 (1959).
185. A. M. Islam, A. M. Khalil, and M. S. El-Houseni, *Aust. J. Chem.*, **26**, 1701 (1973).
186. C. W. Bird and J. D. Twibell, *J. Chem. Soc. C*, 3155 (1971).
187. I. Lupsa, *Rev. Chem. (Bucharest)*, **26**, 6 (1975).
188. M. H. Hubacher and S. Boernberg, *J. Pharm. Soc.*, **53**, 1067 (1964).
189. I. Lupsa, *Rev. Chim. (Bucharest)*, **25**, 525 (1974).
190. A. M. Islam, A. M. Khalil, and I. I. Abd-El-Gawad, *Aust. J. Chem.*, **26**, 827 (1973).
191. J. Grimshaw and J. T. Grimshaw, *Tet. Lett.*, **30**, 2601 (1975).
192. H. J. Petersen, *Acta Chem. Scand.*, **25**, 1542 (1971).

193. H. J. Petersen, *Acta Chem. Scand.*, **25**, 1502 (1971).
194. H. J. Petersen, *Tet. Lett.*, 1559 (1969).
195. C. S. Pande and S. K. Gandhi, *Naturwissenschaften*, **51**, 510 (1964).
196. S. Okumura, M. Masumura, T. Horie, and F. M. Strong, *Bull. Chem. Soc. Japan*, **31**, 1002 (1959).
197. F. S. Okumura, M. Masumura, T. Horie, and F. M. Strong, *J. Am. Chem. Soc.*, **81**, 3753 (1959).
198. G. Pappalardo, *Gazz. Chim. Ital.*, **90**, 52 (1960).
199. A. F. M. Fahmy, A. A. Afifi, and I. G. Shenouda, *Pak. J. Sci. Ind. Res.*, **20**, 150 (1977); *Chem. Abstr.*, **90**, 127737y (1979).
200. S. F. MacDonald, *J. Chem. Soc.*, 376 (1948).
201. S. Tatsuoka, A. Minato, A. Miyake, M. Miyamoto, J. Veyanagi, J. Shimada, and H. Miyazaki, *J. Pharm. Soc. Japan*, **71**, 776 (1951).
202. A. S. Elina and O. Y. Magidson, *Zh. Obshch. Khim.*, **22**, 874 (1952).
203. I. L. Finar and D. D. Libman, *J. Chem. Soc.*, 2726 (1949).
204. J. Attenburrow, D. F. Elliott, and G. F. Penny, *J. Chem. Soc.*, 310 (1948).
205. D. L. Williams and A. R. Ronzio, *J. Am. Chem. Soc.*, **68**, 647 (1946).
206. H. B. Gillespie and H. R. Snyder, *Org. Synth.*, **2**, 489 (1943).
207. R. J. Thibert and C. Patel, *Can. J. Chem.*, **48**, 2000 (1970).
208. A. O. Fitton and R. K. Smaley, *Practical Heterocyclic Chemistry*, Vol. 30, Academic Press, New York, 1968.
209. C. Wentrup and W. Reichen, *Helv. Chim. Acta*, **59**, 2616 (1976).
- 210a. E. Baltazzi, French DeMande No. 2,002,460 (1969); *Chem. Abstr.*, **73**, 104336n (1974).
- 210b. E. S. Nicholas and D. J. Phelps, *J. Chem. Eng. Data*, **25**, 89 (1980).
211. A. Galat, *J. Am. Chem. Soc.*, **72**, 4436 (1950).
212. R. J. Spangler, B. G. Beckman, and J. H. Kim, *J. Org. Chem.*, **42**, 2989 (1977).
213. J. S. Buck and W. S. Ide, *Org. Synth.*, **2**, 55 (1943).
214. D. M. Herbst and D. Shemin, *Org. Synth.*, **2**, 1 (1943).
215. R. K. Griffith and H. J. Harwood, *J. Org. Chem.*, **29**, 2658 (1964).
216. S. I. Lure, E. S. Chaman, and G. A. Ravdel, *J. Gen. Chem. USSR*, **23**, 1458 (1953).
217. Y. S. Rao, *J. Org. Chem.*, **42**, 722 (1976).
218. R. Bisson, R. B. Yeats, and E. W. Warnhoff, *Can. J. Chem.*, **50**, 2851 (1972).
219. V. K. Matveev, USSR Patent 112,670 (1958); *Chem. Abstr.*, **53**, 4302f (1959); *Metod. Lyumines. Sente Anali*, **8b**, 78 (1960); *Chem. Abstr.*, **57**, 8555d (1962).
220. J. P. Fleury and A. Baysang, *Compt. Rend.*, **254**, 4310 (1962).
221. Y. A. Zhdanov, A. N. Kiryanov, and G. A. Korol'chenko, *Zh. Obshch. Khim.*, **49**, 2618 (1979); *Chem. Abstr.*, **92**, 129220a (1979).
222. E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **72**, 1803 (1950).
223. S. N. Timasheff and F. F. Nord, *J. Am. Chem. Soc.*, **73**, 2390 (1951).
224. H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, **178**, 403 (1949).
225. H. E. Carter, P. Handler, and D. B. Melville, *J. Biol. Chem.*, **129**, 359 (1939).
226. H. E. Carter and W. C. Risser, *J. Biol. Chem.*, **139**, 255 (1941).
227. R. E. Buckles, R. Filler, and L. Hilfman, *J. Org. Chem.*, **17**, 233 (1952).
228. E. J. Vanloon and H. E. Carter, *J. Am. Chem. Soc.*, **59**, 2555 (1937).
229. H. E. Carter and C. M. Stevens, *J. Biol. Chem.*, **133**, 117 (1940).

230. N. K. Kochetkov, E. I. Budovski, R. M. Khomutov, M. Y. Karpeiski, and E. S. Severin, *J. Gen. Chem. USSR*, **30**, 2573 (1960).
231. I. Elphimoff-Felkin, H. Felkin, B. Tchoubar, and Z. Welvart, *Bull. Soc. Chim. France*, 252 (1952).
232. T. A. Girard and R. J. Mosby, *J. Org. Chem.*, **23**, 1942 (1958).
233. G. Weitnauer, *Gazz. Chim. Ital.*, **81**, 156 (1961).
234. F. S. Okumura, M. Masamura, and T. Horie, *J. Am. Chem. Soc.*, **81**, 5215 (1959).
235. E. Takagi and H. Ichikawa, *J. Pharm. Soc. Japan*, **71**, 952 (1951); *Chem. Abstr.*, **46**, 4482 (1952).
236. K. Hayes and G. Gever, *J. Org. Chem.*, **16**, 269 (1951).
237. Lepetit S.P.A. British Patent 720,649 (1954); *Chem. Abstr.*, **50**, 1922g (1956).
238. Lepetit S.P.A. British Patent 723,714 (1955); *Chem. Abstr.*, **50**, 5747d (1956).
239. H. E. Carter, J. B. Harrison, and D. Shapiro, *J. Am. Chem. Soc.*, **75**, 4705 (1953).
240. S. Tatsuoka, K. Osugi, A. Miyaki, M. Honjo, and R. N. Akamori, *J. Pharm. Soc. Japan*, **71**, 778 (1951); *Chem. Abstr.*, **46**, 8050d (1952).
241. S. Tatsuoka, K. Osugi, A. Morimoto, A. Miyaki, J. Ueyanagi, M. Hiyamoto, M. Honjo, H. Miyazri, T. Shimada, and R. Nakamori, *J. Pharm. Soc. Japan*, **71**, 604 (1951); *Chem. Abstr.*, **46**, 464r (1952).
242. E. Bourne, J. Burdon, V. C. R. McLoughlin, and J. C. Tatlow, *J. Chem. Soc.*, 1771 (1961).
243. F. Weygand and F. Leising, *Chem. Ber.*, **87**, 248 (1954).
244. M. Bergmann and F. Stern, *Ann.*, **448**, 20 (1926).
245. J. C. Sheehan and W. E. Duggins, *J. Am. Chem. Soc.*, **72**, 2475 (1950).
246. J. M. Riordan and C. H. Stammer, *Tet. Lett.*, 4969 (1971).
247. E. G. Breitholle and C. H. Stammer, *Tet. Lett.*, 2381 (1975).
248. J. W. Hines, Jr., E. G. Breitholle, M. Sato, and C. H. Stammer, *J. Org. Chem.*, **41**, 1466 (1976).
249. K. N. F. Shaw, A. McMillan, A. G. Fudmundsno, and M. D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).
250. E. W. Cook, E. O. Hook, and S. Kushner, U.S. Patent 2,569,801 (1951); *Chem. Abstr.*, **46**, 5089 (1952).
251. H. Kurita, Y. Chigira, M. Masaki, and M. Ohta, *Bull. Chem. Soc. Japan*, **41**, 2758 (1968).
252. B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 688 (1950).
253. Y. Iwakura, F. Toda, and Y. Torii, *Tet. Lett.*, 4427 (1966).
254. Y. Iwakura, F. Toda, and Y. Torii, Japan Patent 69,25,579 (1969); *Chem. Abstr.*, **72**, 3477h (1970).
255. G. V. Boyd, *JCS Chem. Commun.*, 1410 (1968).
256. G. V. Boyd, *Jerusalem Symposium. Quantum Che. Biochem.*, **3**, 166 (1971); *Chem. Abstr.*, **81**, 91401f (1974).
257. G. V. Boyd and P. H. Wright, *J. Chem. Soc. Perkin I*, 914 (1972).
258. G. V. Boyd and P. H. Wright, *JCS Chem. Commun.*, 182 (1968).
259. T. Kaneko, K. Oizumi, and H. Katsura, *Yakugaku Zasshi*, **79**, 91 (1958); *Chem. Abstr.*, **54**, 5485h (1960).
260. I. Arenal, M. Bernabe, and E. Fernandez-Alvarez, *Anales de Quimica*, **77B**, 56 (1981).
261. E. P. Prokof'ev, E. I. Karpeiskaya, G. V. Cheltsova, and T. B. Dantsig, *Izv. Akad. SSSR. Khim.*, 823 (1980); *Chem. Abstr.*, **93**, 94711c (1980).

262. E. Baltazzi and E. A. Davis, *Chem. & Industry* (London), 929 (1962).
263. P. Kumar and A. K. Mukerjee, *Ind. J. Chem.*, **19B**, 704 (1980).
264. V. G. Zubenko, *Dopov. Akad. Nauk. Ukr. RSR Ser. B*, **30**, 547 (1968); *Chem. Abstr.*, **69**, 106596p (1968).
265. V. G. Zubenko, USSR Patent 188,976 (1966); *Chem. Abstr.*, **67**, 73601g (1967).
266. H. Behringer and H. Taul, *Chem. Ber.*, **90**, 1398 (1957).
267. H. Behringer and P. Duesberg, *Chem. Ber.*, **96**, 377 (1963).
268. H. Behringer and P. Duesberg, *Chem. Ber.*, **96**, 380 (1963).
269. R. Filler, N. R. Ayyangar, W. Gustowski, and H. H. Kang, *J. Org. Chem.*, **34**, 534 (1969).
270. H. Behringer and K. Falkenberg, *Chem. Ber.*, **96**, 1428 (1963).
271. R. Walter, H. Zimmer, and I. L. Schwartz, *J. Het. Chem.*, **3**, 352 (1966).
272. I. T. Strukov, *Zh. Obshch. Khim.*, **27**, 432 (1957).
273. I. T. Strukov and Y. V. Zhdanovich, *Zh. Obshch. Khim.*, 910 (1963).
274. S. I. Lure and G. A. Ravdel, *Doklady Akad. Nauk. SSSR*, **83**, 97 (1952); *Chem. Abstr.*, **47**, 2167 (1953).
275. R. L. Clark, U.S. Patent 2,483,530 (1949); *Chem. Abstr.*, **44**, 5918e (1950).
276. R. L. Clark, U.S. Patent 2,483,529 (1949); *Chem. Abstr.*, **44**, 5918f (1950).
277. W. Baker, *J. Chem. Soc.*, 176 (1949).
278. S. T. Rolfson, J. H. Hunter, and J. W. Hinman, U.S. Patent 2,555,006 (1951); *Chem. Abstr.*, **45**, 9557i (1951).
279. S. Tatsuoka, B. Ota, and J. Ueyanagi, *J. Penicillin*, **1**, 383 (1947); *Chem. Abstr.*, **43**, 2618d (1949).
280. W. Schulz, *Chem. Ber.*, **85**, 249 (1952).
281. J. W. Cornforth and E. Cookson, *J. Chem. Soc.*, 1085 (1952).
282. A. S. Elina and O. Y. Magidson, *Zh. Obshch. Khim.*, **21**, 780 (1951).
283. H. J. Barber, R. Slack, C. E. Stickings, D. F. Elliott, and J. Attenburrow, British Patent 585,089 (1947); *Chem. Abstr.*, **41**, 3822a (1947).
284. I. T. Strukov, *Zh. Obshch. Khim.*, **26**, 3422 (1956).
285. K. Srinivasan, K. Narasimhan, K. V. Narayanan, and S. Swaminathan, *Ind. J. Chem.*, **14B**, 991 (1976).
286. H. Behringer and J. B. Jepson, *Chem. Ber.*, **85**, 138 (1952).
287. A. H. Cook, G. Harris, and G. Shaw, *J. Chem. Soc.*, 1435 (1949).
288. A. K. Misra, A. Nayak, and M. K. Rout, *J. Ind. Chem. Soc.*, **48**, 165 (1971).
289. G. F. Duffin, D. J. Fry, and J. D. Kendall, British Patent 785,939 (1957); *Chem. Abstr.*, **52**, 10777e (1958).
290. G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 3798 (1959); G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *J. Chem. Soc.*, 3799 (1959).
291. E. B. Knott, U.S. Patent 274,273 (1956); *Chem. Abstr.*, **51**, 908a (1957).
292. E. B. Knott, *J. Chem. Soc.*, 402 (1963).
293. E. B. Knott, U.S. Patent 2,691,581 (1954); *Chem. Abstr.*, **49**, 83d (1954).
294. E. B. Knott, *J. Chem. Soc.*, 2399 (1952).
295. J. D. Kendall and G. F. Duffin, British Patent 749,189 (1956); *Chem. Abstr.*, **51**, 904g (1957).
296. J. D. Kendall, G. F. Duffin, and H. R. J. Waddington, British Patent 743,133 (1956); *Chem. Abstr.*, **51**, 899b (1957).

297. J. D. Kendall and G. F. Duffin, British Patent 633,735 (1949); *Chem. Abstr.*, **44**, 9284r (1950).
298. J. D. Kendall and G. F. Duffin, British Patent 633,736 (1949); *Chem. Abstr.*, **44**, 7175d (1950).
299. J. D. Kendall and G. F. Duffin, British Patent 749,193 (1956); *Chem. Abstr.*, **50**, 16492f (1956).
300. S. J. Palling, F. P. Doyle, and H. D. Edwards, British Patent 720,556 (1954); *Chem. Abstr.*, **49**, 10777h (1955).
301. R. A. Jefferys and E. B. Knott, U.S. Patent 2,656,353 (1953); *Chem. Abstr.*, **48**, 3826c (1953).
302. P. Aubert, E. B. Knott, and L. A. Williams, *J. Chem. Soc.*, 2185 (1951).
303. L. G. S. Brooker, G. H. Keyes, R. H. Sprague, R. H. Van Dyke, E. Van Lare, G. Van Zandt, and F. L. White, *J. Am. Chem. Soc.*, **73**, 5326 (1951).
304. P. B. Tripathy and M. K. Rout, *J. Sci. Ind. Res.*, **20B**, 177 (1961).
305. P. Tripathy and M. K. Rout, *J. Ind. Chem. Soc.*, **36**, 625 (1959).
306. F. H. Carpenter, R. A. Turner, and V. du Vigneaud, *J. Biol. Chem.*, **176**, 893 (1948).
307. F. H. Carpenter, G. W. Stacy, D. S. Genghof, A. H. Livermore, and V. du Vigneaud, *J. Biol. Chem.*, **176**, 915 (1948).
308. E. W. Cook and S. Kushner, U.S. Patent 2,494,745 (1950); *Chem. Abstr.*, **44**, P5395f (1950); T. Okutome, Y. Sakurai, M. Kurumi, H. Kawamura, S. Sato, and K. Yamauchi, *Chem. Pharm. Bull.*, **23**, 48 (1975); *Chem. Abstr.*, **83**, 9875k (1975).
309. V. du Vigneaud, G. W. Stacy, and D. Todd, *J. Biol. Chem.*, **176**, 907 (1948).
310. V. du Vigneaud, F. H. Carpenter, R. W. Holley, A. H. Livermore, and J. R. Rachelle, *Science*, **104**, 431,450 (1946).
311. J. W. Cornforth and H. T. Huang, *J. Chem. Soc.*, 1964 (1948).
312. E. A. Baltazzi and J. W. Davis, *Compt. Rend.*, **240**, 208 (1951).
313. G. Cavallini and E. Massarini, *II Farmace (Pavia) Ed. Sci.*, **11**, 167 (1956).
314. I. T. Strukov, *Zh. Obshch. Khim.*, **23**, 690 (1953).
315. G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962).
316. I. T. Strukov, *Doklady Akad. Nauk SSSR*, **88**, 483 (1953).
317. I. T. Strukov, *Zh. Obshch. Khim.*, **22**, 2193 (1952).
318. J. C. Howard, *J. Org. Chem.*, **36**, 1073 (1971).
319. K. F. Jennings, *J. Chem. Soc.*, 1512 (1957).
320. C. Bodea and I. Oprean, *Rev. Roum. Chim.*, **13**, 1647 (1968).
321. I. Lupsa, C. Bilegan, and M. Vanghelovici, *Rev. Chem. (Bucharest)*, **23**, 660 (1972); *Chem. Abstr.*, **79**, 5287q (1973).
322. D. C. Cook and A. Lawson, *J. Chem. Soc., Perkin I*, 1112 (1974).
323. R. Walter and H. Zimmer, *J. Prakt. Chem.*, **26**, 128 (1964).
324. R. Pflieger and H. Kasperek, German Patent 914,973 (1954); *Chem. Abstr.*, **52**, 15585c (1958).
325. R. Pflieger and E. Garthe, German Patent 924,212 (1955); *Chem. Abstr.*, **52**, 3867f (1958).
326. R. Pflieger and M. Von Strandtmann, *Chem. Ber.*, **90**, 1455 (1957).
327. R. Pflieger and H. Vogt, *Chem. Ber.*, **90**, 1467 (1957).
328. R. Pflieger and A. Sauter, *Chem. Ber.*, **90**, 1475 (1957).
329. R. Pflieger and G. Markert, *Chem. Ber.*, **90**, 1482 (1957).
330. R. Pflieger and G. Markert, *Chem. Ber.*, **90**, 1494 (1957).

331. R. Pflieger and J. Pelz, *Chem. Ber.*, **90**, 1489 (1957).
332. E. F. Ullman and N. Baumann, *J. Am. Chem. Soc.*, **92**, 5892 (1970).
- 333a. E. F. Ullman and N. Baumann, *J. Am. Chem. Soc.*, **90**, 4157 (1968).
- 333b. E. F. Ullman, U.S. Patent 3,689,391 (1972); *Chem. Abstr.*, **79**, 3585r (1973).
334. G. W. Kirby, J. Michael, and S. Narayanaswami, *J. Chem. Soc. Perkin I*, 203 (1972).
335. N. Baumann, *Chimia*, **27a** 471 (1973).
336. N. Baumann, M. Suna, and E. F. Ullman, *J. Am. Chem. Soc.*, **90**, 4157 (1968).
337. H. Sakuragi, I. Uno, N. Hata, and K. Tokumaru, *Bull. Chem. Soc. Japan*, **49**, 270 (1976).
338. R. Walter, F. Purcell, and H. Zimmer, *J. Het. Chem.*, **3**, 235 (1966).
- 339a. R. P. Rhee and J. D. White, *J. Org. Chem.*, **42**, 3650 (1977).
- 339b. R. S. Lott, E. G. Breitholle, and C. H. Stammer, *J. Org. Chem.*, **45**, 1151 (1980).
340. A. Gaset and J. P. Gorrichon, *Synth. Commun.*, **12**, 71 (1982).
341. M. Takagaki, S. Tanabe, M. Asaoka, and H. Takei, *Chem. Lett.*, 347 (1979).
342. S. Kumar, M. Rai, K. Krishan, and A. Singh, *J. Ind. Chem. Soc.*, **56**, 432 (1979).
343. M. R. Manrao, R. C. Sharma, B. S. Dhir, and P. S. Kalsi, *J. Ind. Chem. Soc.*, **59**, 901 (1982).
344. P. Kumar, H. D. Mishra, and A. K. Mukerjee, *Synthesis*, 836 (1980).
- 345a. M. Rai, S. Kumar, K. Krishan, and A. Singh, *Chem. Ind. (London)*, 211 (1979).
- 345b. M. Rai, K. Krishan, and A. Singh, *Ind. J. Chem.*, **15B**, 847 (1977).
346. G. Jommi, F. Mauri, and G. Riva, British Patent 1,250,973; *Chem. Abstr.*, **76**, 3836g (1972).
347. V. K. Kuskov, *Zh. Obshch. Khim.*, **21**, 152 (1961).
348. G. W. Sawdey, U.S. Patent 2,852,376 (1959); *Chem. Abstr.*, **53**, 2902g (1959).
349. G. W. Sawdey, *J. Am. Chem. Soc.*, **79**, 1955 (1957).
350. E. J. Browne and J. B. Polya, *Chem. & Ind. (London)*, 1086 (1960).
351. E. J. Browne and J. B. Polya, *J. Chem. Soc.*, 575 (1962).
- 352a. A. M. Khalil, I. I. Abd El-Gawrd, and M. Hammouda, *Aust. J. Chem.*, **27**, 2035 (1974).
- 352b. M. A. E. Khalifa, G. H. Tammam, R. M. Abdel-Motaleb, and M. H. Elnagdi, *Heterocycl.*, 2045 (1983).
- 352c. N. A. Kassab, A. H. Harhash, and S. A. Elbhail, *Z. Naturforsch. B. Anorg. Chem. Org. Chem.*, **33B**, 1145 (1978).
353. C. L. Cleaver and B. C. Pratt, *J. Am. Chem. Soc.*, **77**, 1541 (1955).
354. L. Rugheimer, *Chem. Ber.*, **21**, 3321 (1889).
355. J. W. Cornforth, in *Chemistry of Penicillin*, H. T. Clarke, J. R. Johnson, and R. Robinson, Eds., Princeton, N.J., 1949, p. 688.
356. H. D. Stachel and H. Erhardt, *Arch. Pharm. (Weinheim)*, **312**, 968 (1979).
- 357a. V. M. Dixit, V. Bhat, A. M. Trozzolo, and M. V. George, *J. Org. Chem.*, **44**, 4169 (1979).
- 357b. H. Kato, K. Tani, H. Kurumisawa, and Y. Tamura, *Chem. Lett.*, 717 (1980).
358. P. Ruggli and O. Schetty, *Helv. Chim. Acta*, **23**, 718 (1940).
359. W. Ried and B. Schleimer, *Ann.*, **639**, 68 (1961).
360. N. Zimmerman, E. Daubach, and H. Saukel, Ger. Offen. 2,440,405 (1976); *Chem. Abstr.*, **84**, 166264y (1976).
361. S. A. Vichakanova, V. N. Tokachev, L. V. Markova, and Y. S. Tsizin, *Farmakol Toksikol (Moscow)*, **37**, 711 (1976); *Chem. Abstr.*, **82**, 106878a (1975).

362. P. L. Wineman, G. P. Scott, and F. H. Kingdon, *Proc. S. Dak. Acad. Sci.*, **32**, 32 (1953); *Chem. Abstr.*, **49**, 8184f (1953).
363. K. F. Jennings, *J. Chem. Soc.*, 1172 (1957).
364. S. Sugawara, K. Kobayashi, and H. Kawamura, *J. Pharm. Soc. Jap.*, **65**, 6 (1945).
365. W. J. P. Neish, *Rec. Trav. Chim.*, **66**, 433 (1967).
366. T. Kametani, K. Fukamoto, and M. Ro, *Yakugaku Zasshi*, **84**, 532 (1964).
367. E. Gustak and A. Markovac-Prpic, *Arkiv. Kem.*, **27**, 125 (1955).
368. R. Robinson and S. Sugawara, *J. Chem. Soc.*, 3173 (1931).
369. H. Kast, G. Hansen, and H. R. Mueller, Ger. Offen., 2,031,133 (1971); *Chem. Abstr.*, **76**, 12883g (1972).
370. H. Schuermann, Ger. Offen. 2,059,291 (1972); *Chem. Abstr.*, **77**, 128087r (1972).
371. G. Kossmehl, M. Hartzel, and G. Manecke, *Makromol. Chem.*, **131**, 15 (1970).
372. V. Tamas, V. Ciordaru, and C. Bodea, *Rev. Roum. Chimie*, **18**, 1409 (1973).
373. K. W. Merz, J. Wiedlich and J. Fink, *Arch. Pharm.*, **297**, 392 (1964).
374. V. I. Rogovik and Y. L. Goldfarb, *Izv. Akad. Nauk SSSR Ser. Khim.*, 2178 (1963).
375. Y. Omote, Y. Fujinuma, and N. Sugiyama, *Chem. Commun.*, 190 (1968).
376. Y. Omote, Y. Fujinuma, and N. Sugiyama, *Bull. Chem. Soc. Jap.*, **42**, 1752 (1969).
377. G. Hansen and W. D. Kermer, Ger. Offen. 2,415,819 (1975); *Chem. Abstr.*, **84**, 19194x (1976).
378. H. R. Mueller, G. Hansen, and W. D. Kermer, Ger. Offen. 2,408,486 (1975); *Chem. Abstr.*, **84**, 6488w (1976).
379. M. Ueda, K. Kino, T. Hirono, and Y. Imai, *J. Polym. Sci. Chem. Ed.*, **14**, 931 (1976).
380. M. Ueda, M. Funayama, and Y. Imai, *J. Polym. Sci. Chem. Ed.*, **13**, 2751 (1977).
381. W. Tiege and R. Schickfluss, Ger. Offen. 2,608,482 (1977); *Chem. Abstr.*, **87**, 169171r (1977).
382. N. P. Shimanskaya, I. V. Lysova, L. A. Kotok, and L. S. Afanasiadi, *Zh. Obshch. Khim.*, **48**, 2315 (1978); *Chem. Abstr.*, **90**, 86424 (1979).
383. H. Diefenbach, R. Kroker, and K. L. Platt, Ger. Offen. 2,516,978 (1976); *Chem. Abstr.*, **86**, 31112t (1977).
384. M. Ueda, K. Kino, K. Yamaki, and Y. Imai, *J. Polym. Sci. Chem. Ed.*, **16**, 155 (1978).
385. H. Heiko and D. Pirck, Ger. Offen. 2,522,192 (1976); *Chem. Abstr.*, **87**, 18524 (1977).
386. A. Maquestiau, Y. Van Haverbeke, J. J. Van Denende, and A. G. Crunele, *Bull. Chim. Soc. Belg.*, **86**, 81 (1977).
387. L. Diaz Azan, *An. Fac. Quim. Farm. Univ. Chile*, **20**, 43 (1970); *Chem. Abstr.*, **74**, 142328d (1971).
388. S. Diaz Palominos, *An. Fac. Quim. Farm. Univ. Chile*, **20**, 47 (1970); *Chem. Abstr.*, **74**, 142327h (1971).
389. M. E. Aquilera, *An. Fac. Quim. Farm. Univ. Chile*, **19**, 9 (1967); *Chem. Abstr.*, **71**, 22314y (1969).
390. F. Mella, *An. Fac. Quim. Farm. Univ. Chile*, **20**, 77 (1968); *Chem. Abstr.*, **74**, 125594f (1971).
391. T. Pinto, *An. Fac. Quim. Farm. Univ. Chile*, **21**, 53 (1967); *Chem. Abstr.*, **77**, 19995q (1972).
392. R. Torres-Gaone, *An. Fac. Quim. Farm. Univ. Chile*, **19**, 124 (1967); *Chem. Abstr.*, **70**, 115535m (1969).
393. T. M. Frunze, V. V. Korshak, and L. V. Kozlov, *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk*, 535 (1959).

394. R. Schickfluss and W. Steckelberg, Ger. Offen. 2,225,546 (1973); *Chem. Abstr.*, **80**, 97348g (1974).
395. C. S. Cleaver and B. C. Pratt, *J. Am. Chem. Soc.*, **77**, 2544 (1955).
396. W. R. Hearn and J. Medina-Castro, *J. Org. Chem.*, **33**, 3980 (1946).
397. M. Ueda, K. Kino, T. Kirono, and Y. Imai, *J. Polym. Sci.*, **14**, 931 (1976).
398. L. Stoicescu-Crivat, G. Chirac, G. Caraculacu, and I. Zugravescu, *Rev. Roum. Chim.*, **10**, 917 (1965).
399. E. Baltazzi, *Compt. Rend.*, **254**, 2187 (1962).
400. W. Steglich, V. Austel, and A. Prox, *Angew. Chem. Internat. Ed.*, **7**, 726 (1968).
401. C. Chuaqui, S. Atala, A. Marques, and H. Rodriguez, *Tetrahedron*, **29**, 1197 (1973).
402. H. Rodriguez, C. Chuaqui, S. Atala, and A. Marques, *Tetrahedron*, **27**, 2425 (1971).
403. H. Fischer and W. Zerweck, *Ber.*, **56**, 519 (1923).
404. A. Sonn, E. Muller, W. Bulow, and W. Meyer, *Ber.*, **58**, 1103 (1925).
405. F. Schaaf and A. Labouchere, *Helv. Chim. Acta*, **7**, 357 (1924).
406. L. Horner, H. Reuter, and E. Herrmann, *Ann.*, **660**, 1 (1962).
407. A. Badshah, N. H. Khan, and A. R. Kidwai, *J. Org. Chem.*, **37**, 2916 (1972).
408. M. Ali, N. H. Khan, and A. A. Siddiqui, *Syn. Comm.*, **6**, 227 (1976).
409. J. R. Butterick and A. M. Unrau, *Can. J. Chem.*, **52**, 2873 (1974).
410. E. Baltazzi and R. Robinson, *Chem. & Ind. (London)*, 191 (1954).
411. J. Kollonitsch, O. Fuchs, and V. Gabor, *Nature*, **175**, 346 (1955).
412. E. Baltazzi and R. Robinson, *Chem. & Ind. (London)*, 868 (1953).
413. P. Truitt and J. Chakaravarty, *J. Org. Chem.*, **35**, 864 (1970).
414. P. E. Berentsson, F. Vastra, J. O. Gaarder, and B. B. Lanm, Ger. Offen. 2,243,665 (1973); *Chem. Abstr.*, **79**, 19116v (1973).
415. V. Konyukhov, Z. V. Pushkaraeva, Y. A. Ostrovskaya, A. I. Adamovich, E. T. Kuklina, E. M. Poznauskaya, E. A. Glagoleva, and S. A. Shneur, USSR Patent 152,541 (1969); *Chem. Abstr.*, **69**, 36446p (1968).
416. W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, Ger. Offen. 2,210,938 (1972); *Chem. Abstr.*, **77**, 165073d (1972).
417. E. I. Karpeiskaya, L. F. Godunova, E. S. Neupokoeva, and E. I. Klabunovskii, *Izv. Akad. Nauk SSSR Ser. Khim.*, 1943 (1974).
418. Y. Ohgo, S. Takeuchi, and J. Yoshimura, *Bull. Chem. Soc. Jap.*, **44**, 283 (1971).
419. B. P. Fabrichinyi, E. A. Krasnovskaya, and Y. A. Goldfarb, *Dokl. Akad. Nauk SSSR*, **143**, 1370 (1962).
420. B. F. Fabrichinyi, E. A. Krasnovskaya, I. F. Shalavina, and Y. A. Goldfarb, *Zh. Obshch. Khim.*, **33**, 2697 (1963).
421. Y. L. Goldfarb, B. P. Fabrichinyi, and V. I. Rogovik, *Izv. Akad. Nauk SSSR Ser. Khim.*, 2172 (1963).
422. L. C. Raiford and C. H. Buurman, *J. Org. Chem.*, **8**, 466 (1963).
423. J. N. Chatterjea, *J. Ind. Chem. Soc.*, **33**, 339 (1956).
424. J. N. Chatterjea and S. K. Roy, *J. Ind. Chem. Soc.*, **40**, 144 (1963).
425. J. N. Chatterjea, V. N. Mehrotra, and S. K. Roy, *Chem. Ber.*, **96**, 1156 (1963).
426. J. N. Chatterjea, V. N. Mehrotra, and S. K. Roy, *Chem. Ber.*, **96**, 1167 (1963).
427. J. N. Chatterjea, K. D. Banerji, and N. Prasad, *Chem. Ber.*, **96**, 2356 (1961).
428. J. N. Chatterjea, *J. Ind. Chem. Soc.*, **30**, 103 (1953).
429. M. Miyano, S. Murakami, T. Kusunori, T. Morita, and M. Matsui, *Nippon Nogeikagaku Faishi*, **34**, 638 (1963); *Chem. Abstr.*, **59**, 13929 (1963).

430. L. Farkas and V. Szantho, *Acta Chim., Acad. Sci. Hung.*, **19**, 217 (1959); *Chem. Abstr.*, **54**, 33981 (1960).
431. L. Farkas and J. Varady, *Magyar-Kemfolyoirat*, **67**, 390 (1961); *Chem. Abstr.*, **56**, 13933 (1962).
432. L. Frakas, J. Varady, and A. Gottsegen, *Chem. Ber.*, **96**, 1865, **68**, 9–11 (1962); *Chem. Abstr.*, **57**, 3401h (1962).
433. L. Frakas, J. Varady, and A. Gottsegen, *Magyar-Kemfolyoirat*, **70**, 276 (1964); *Chem. Abstr.*, **61**, 9459b (1964).
434. J. D. Loudon, A. D. B. Sloan, and L. A. Summers, *J. Chem. Soc.*, 3814 (1957).
435. H. R. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, *J. Am. Chem. Soc.*, **79**, 2556 (1957).
436. T. Shiba and H. J. Cahnmann, *J. Org. Chem.*, **29**, 1652 (1964).
437. T. Shiba and H. J. Cahnmann, *J. Org. Chem.*, **27**, 1773 (1962).
438. A. Silberg, I. Smiti, and H. Mantsch, *Acad. Rep. Populare Romaine Studii Cerceturi Chim.*, **12**, 315 (1961); *Chem. Abstr.*, **59**, 591a (1963).
439. A. Silberg, Z. Frenkel, and L. Cormos, *Studia Univ. Babes Bolyai, Ser. Chem.*, **7**, 23 (1962); *Chem. Abstr.*, **62**, 1643b (1965).
440. R. M. Acheson, *J. Chem. Soc.*, 499 (1957).
441. W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1860 (1953).
442. A. W. Dawkins and T. P. Mulholland, *J. Chem. Soc.*, 2211 (1959).
443. M. Nakano, S. Tsuchiya, and G. Unma, *J. Med. Sci.*, **10**, 280 (1961).
444. F. Sanchez-Viesca, *Ciencia (Mexico City)*, **27**, 139 (1972); *Chem. Abstr.*, **77**, 164207 (1972).
445. A. G. Sanchez and J. F. Bolanos, *Anales Real Soc. Espan. Fis. Y. Chim.*, **49B**, 51 (1953); *Chem. Abstr.*, **48**, 3343 (1954).
446. J. F. Bolanos, A. G. Sanchez, and F. G. Gonzalez, *Anales Real Soc. Espan. Fis. Y. Chim.*, **49B**, 57 (1953); *Chem. Abstr.*, **48**, 3344 (1954).
447. A. Buzas, C. Hoffmann, and G. L. Regnier, *Bull. Soc. Chim. France*, 645 (1960).
448. F. Weygand, W. Steglich, and H. Tanner, *Ann.*, **658**, 128 (1962).
- 449a. B. T. Ho, L. W. Tansey, and J. T. Huang, *J. Med. Chem.*, **14**, 1132 (1971).
- 449b. K. F. N. Shaw, A. McMillan, and M. D. Armstrong, *J. Org. Chem.*, **23**, 27 (1958).
450. H. R. Snyder, J. S. Buck, and W. S. Ide, *Org. Synth.*, **2**, 333 (1943).
451. J. N. Chatterjea, *J. Chem. Soc.*, 1167 (1963).
452. R. T. Foster, A. Robertson, and T. V. Healey, *J. Chem. Soc.*, 1594 (1939).
453. J. R. Merchant, A. C. Kaushik, and D. D. Vaghani, *Ind. J. Chem.*, **4**, 27 (1966).
454. T. E. Young and M. F. Mizianty, *J. Med. Chem.*, **9**, 635 (1966).
455. J. D. Loudon and L. A. Summers, *J. Chem. Soc.*, 3809 (1957).
456. F. M. Dean, D. S. Deorha, J. C. Knight, and T. Francis, *J. Chem. Soc.*, 327 (1961).
457. B. J. F. Hudson and E. Walton, *J. Chem. Soc.*, 85 (1946).
458. K. Freudenberg and H. Richtzenham, *Ann.*, **552**, 126 (1942).
459. H. F. Birch and A. Robertson, *J. Chem. Soc.*, 306 (1938).
460. F. M. Dean and A. Robertson, *J. Chem. Soc.*, 1241 (1953).
461. T. Kubota, Y. Naya, and N. Ichikawa, *Nippon Kagaku Zasshi*, **77**, 648 (1956); *Chem. Abstr.*, **52**, 375 (1958).
462. N. I. Kudryashova, L. R. Davidenkov, and N. V. Khromov-Borisov, *Zh. Obshch. Khim.*, **29**, 1885 (1959).
463. M. Sasamoto, *Chem. Pharm. Bull. Jap.*, **8**, 324 (1960).

464. M. Sasamoto, *Chem. Pharm. Bull. Jap.*, **8**, 329 (1960).
465. T. R. Seshadri and S. Varadarajan, *Proc. Ind. Acad. Sci.*, **37A**, 514 (1953).
466. T. R. Seshadri and S. Varadarajan, *Proc. Ind. Acad. Sci.*, **37A**, 145 (1953).
467. G. Lloyd and W. B. Shalley, *H. Chem. Soc.*, 3209 (1956).
468. T. Kametani and J. Serizawa, *J. Pharm. Soc. Jap.*, **72**, 1084 (1952).
469. K. Freudenberg and F. Bittner, *Chem. Ber.*, **85**, 86 (1952).
470. R. F. H. Manske and A. E. Ledingham, *J. Am. Chem. Soc.*, **72**, 4797 (1950).
471. A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1440 (1954).
472. G. A. Swan, *J. Chem. Soc.*, 1534 (1950).
473. P. C. Johnson and A. Robertson, *J. Chem. Soc.*, 2381 (1950).
474. K. A. Jensen and S. A. K. Christensen, *Acta Chem. Scand.*, **4**, 703 (1950).
475. K. Kratzl and G. Billek, *Monat. Chem.*, **82**, 568 (1951).
476. F. Bergel, J. W. Haworth, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, **261**, (1944).
477. B. Sila and K. Seyda, *Rocz. Chem.*, **44**, 1319 (1970).
478. J. P. Brown, N. J. Cartwright, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 859 (1949).
479. A. A. Bell, J. N. Chatterjea, J. S. E. Holker, J. Staunton, and W. B. Whalley, *J. Chem. Soc.*, 4307 (1964).
480. D. S. Deorha and P. Gupta, *J. Ind. Chem. Soc.*, **42**, 739 (1964).
481. D. S. Deorha and P. Gupta, *Bull. Chem. Soc. Jap.*, **39**, 2768 (1966).
482. D. S. Deorha and P. Gupta, *Rec. Trav. Chim.*, **83**, 1056 (1964).
483. D. S. Deorha and P. Gupta, *Ind. J. Chem.*, **2**, 459 (1964); *Chem. Abstr.*, **62**, 7714d (1965).
484. D. S. Deorha and P. Gupta, *J. Ind. Chem. Soc.*, **41**, 371 (1964).
485. D. S. Deorha and P. Gupta, *J. Ind. Chem. Soc.*, **42**, 199 (1965); *Chem. Abstr.*, **63**, 4298f (1965).
486. B. Sila, J. Wotjanis, and I. Lesiak, *Rocz. Chem.*, 491661 (1975); *Chem. Abstr.*, **84**, 90531k (1976).
487. V. Farcasan, F. Paiu, and C. Iasu, *Stud. Univ. Babes Bolya, Ser. Chem.* **22**, 15 (1977); *Chem. Abstr.*, **87**, 53005h (1977).
488. D. S. Deorha and P. Gupta, *Chem. Ber.*, **97**, 3577 (1964).
489. H. Behringer and H. W. Stein, *Chem. Ber.*, **82**, 209 (1949).
490. R. Filler and Y. S. Rao, *J. Org. Chem.*, **27**, 3730 (1962).
491. M. A. F. Elkashef, M. E. Abdel-Megeid, and S. M. A. Yassin, *Acta Chim. Hung.*, **80**, 119 (1974).
492. S. I. Lure and L. G. Gatsenko, *J. Gen. Chem. USSR*, **22**, 262 (1951).
493. A. Mustafa, W. Asker, A. H. Harhash, and A. M. Fleifel, *Tetrahedron*, **21**, 2215 (1965).
494. A. M. Khalil, I. I. Abd. El-Gawad, and H. M. Hassan, *Aust. J. Chem.*, **27**, 2035 (1974).
495. J. Sicher, M. Svoboda, and J. Farkas, *Collect. Czech. Chem. Commun.*, **20**, 1439 (1955).
496. G. C. Barrett, A. R. Khokhar, and J. R. Chapman, *J. Chem. Soc. Chem. Commun.*, 818 (1969).
497. P. M. Pojer and I. D. Rae, *Tet. Lett.*, 3077 (1971).
498. P. M. Pojer and I. D. Rae, *Aust. J. Chem.*, **25**, 1737 (1972).
499. E. I. Cioranescu, L. B. Birladeanu, and R. Shternberg, *Izv. Akad. Nauk SSSR Khim. Nauk.*, 144 (1961).

500. E. I. Cioranescu and L. B. Birladeanu, *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk*, 149 (1961).
501. A. T. Balaban, I. Bally, P. T. Frangopol, M. Bacescu, E. Cioranescu, and L. Birladeanu, *Tetrahedron*, **19**, 169 (1963).
502. P. T. Frangopol, A. T. Balaban, L. B. Birladeanu, and E. Cioranescu, *Tetrahedron*, **16**, 59 (1961).
503. P. T. Frangopol, A. T. Balaban, L. B. Birladeanu, and E. Cioranescu, *Acad. Rep. Populare Romine Fiz. Chem.*, **16** (1961); *Chem. Abstr.*, **57**, 5769 (1962).
504. G. Höfle and W. Steglich, *Chem. Ber.*, **104**, 1408 (1971).
505. F. Korte and K. Storiko, *Chem. Ber.*, **93**, 1033 (1960).
506. C. Ratledge and G. A. Snow, *Biochem. J.*, **139**, 407 (1974).
507. S. I. Zavyalov, N. E. Knyaz'kova, and L. B. Kulikova, *Izv. Akad. Nauk. SSSR. Ser. Khim.*, 2521 (1982); *Chem. Abstr.*, 198082t (1982).
508. M. Vanghelovici and I. Moise, *Soc. Chim. Romania*, **2**, **3A**, 85 (1941); *Chem. Abstr.*, **38**, 5500 (1944).
509. M. Vanghelovici and A. Stefanescu, *Soc. Chim. Romania*, 159 (1944); *Chem. Abstr.*, **38**, 5501 (1944).
510. M. Vanghelovici, I. Lupsa, C. Bilegan, and A. Muste, *Acad. Rep. Populare Romine, Baza Cercetari Stiint Timisoara Studii Cercetari Stiint Ser. Chim.*, **6**, 103 (1959); *Chem. Abstr.*, **55**, 4484 (1961).
511. M. Vanghelovici and C. Demetrescu, *Acad. Rep. Populare Romine, Baza Cercetari Stiint Timisoara Studii Cercetari Stiint Ser. Chim.*, **8**, 79 (1961); *Chem. Abstr.*, **57**, 727 (1962).
512. M. Vanghelovici, I. Lupsa, C. Bilegan, and A. Muste, *Acad. Rep. Populare Romine, Baza Cercetari Stiint Timisoara Studii Cercetari Stiint Ser. Chim.*, **8**, 249 (1961); *Chem. Abstr.*, **57**, 16583 (1962).
513. M. Vanghelovici, C. Demetrescu, and A. Muste, *Acad. Rep. Populare Romine Baza, Cercetari Stiint Timisoara Studii Cercetari, Stiint Chim.*, **8**, 89 (1961); *Chem. Abstr.*, **57**, 16582 (1962).
514. M. Vanghelovici and C. Demetrescu, *Acad. Rep. Populare Romine Baza, Cercetari Stiint Timisoara Studii Cercetari, Stiint Chim.*, **9**, 291 (1962); *Chem. Abstr.*, **59**, 6360 (1963).
515. M. Vanghelovici and C. Demetrescu, *Acad. Rep. Populare Romine Baza, Cercetari Stiint Timisoara Studii Cercetari, Stiint Chim.*, **9**, 299 (1962); *Chem. Abstr.*, **59**, 6308 (1963).
516. C. Demetrescu, C. Chirita, and V. Ion, *Rev. Roum. Chimie*, **12**, 1039 (1967).
517. C. Demetrescu, C. Chirita, and V. Ion, *Chim. Ther.*, **2**, 144 (1967); *Chem. Abstr.*, **67**, 116696 (1967).
518. C. Demetrescu, C. Chirita, and V. Ion, *Pharm. Zent. Deutsch.*, **127** (1968); *Chem. Abstr.*, **69**, 35888 (1968).
519. C. Demetrescu, C. Chirita, and V. Ion, *Arch. Pharm.*, **300**, 1045 (1967); *Chem. Abstr.*, **69**, 35888 (1968).
520. C. Demetrescu, A. Teitel, and A. Popa, *Pharmazie*, **19**, 451 (1964).
521. C. Bodea, V. Farcasan, and I. Oprean, *Rev. Roum. Chim.*, **11**, 1117 (1968); *Chem. Abstr.*, **67**, 64334 (1967).
522. C. Bodea, V. Farcasan, and I. Oprean, *Rev. Roum. Chim.*, **14**, 673 (1969).
523. C. Bodea, V. Farcasan, and I. Oprean, *Studii Cercetari Chim.*, **13**, 1157 (1965); *Chem. Abstr.*, **64**, 11667 (1966).
524. F. H. Stodola, *J. Org. Chem.*, **13**, 757 (1948).

525. K. Nalepa, *Monat. Chem.*, **98**, 1230 (1967).
526. K. Nalepa and J. Slouka, *Monat. Chem.*, **98**, 423 (1967).
527. D. S. Iyengar, K. K. Prasad, and R. V. Venkataratnam, *Aust. J. Chem.*, **27**, 1439 (1974).
528. J. E. Baldwin, *J. Chem. Soc. Chem. Commun.*, 734 (1976).
529. A. Mustafa, W. Asker, A. H. Harhash, M. A. E. Khalifa, and E. M. Zayed, *Justus Liebigs Ann.*, **713**, 151 (1968).
530. G. V. Boyd and S. R. Dando, *J. Chem. Soc. Perkin I*, 1142 (1972).
531. H. Behringer and W. Grimme, *Chem. Ber.*, **92**, 2967 (1959).
532. W. I. Awad, A. F. M. Fahmy, and A. M. A. Sammour, *J. Org. Chem.*, **30**, 2222 (1965).
533. J. Lykkeberg and N. A. Klitgaard, *Acta Chem. Scand.*, **26**, 266 (1972).
534. W. I. Awad and A. F. M. Fahmy, *Can. J. Chem.*, **46**, 2207 (1968).
535. D. L. Williams, F. L. Symonds, J. B. Ekeley, and A. R. Ronzio, *J. Am. Chem. Soc.*, **67**, 1157 (1945).
536. A. Kjaer, *Acta Chem. Scan.*, **7**, 889 (1953).
537. A. Kjaer, *Acta Chem. Scan.*, **7**, 900 (1953).
538. S. I. Lure, S. M. Mamiofe, and K. M. Ravikovich, *J. Gen. Chem. USSR*, **21**, 1431 (1951).
539. D. K. Barnes, E. Campaigne, and R. L. Shriner, *J. Am. Chem. Soc.*, **70**, 1769 (1947).
540. I. Lupsa and C. Bilegan, *Rev. Chim. (Bucharest)*, **25**, 95 (1974); *Chem. Abstr.*, **81**, 49610 (1974).
541. K. Nalepa and L. Matela, *Acta Univ. Palacki. Olomuc. Fac. Rerum Nat.* **69**, 95 (1981); *Chem. Abstr.*, **98**, 53768m (1983).
542. S. S. Tiwari and R. K. Satsangi, *J. Ind. Chem. Soc.*, **56**, 627 (1979).
543. S. S. Tiwari, R. Agarwal, and R. K. Satsangi, *J. Ind. Chem. Soc.*, **57**, 1040 (1980).
544. A. K. Mukerjee and P. Kumar, *Chem. Ind.*, 936 (1980).
545. P. Kumar and A. K. Mukerjee, *Ind. J. Chem.*, **20B**, 416 (1981).
546. A. K. Mukerjee and P. Kumar, *Can. J. Chem.*, **60**, 317 (1982).
547. M. S. Reddy, P. Hanumanthu, and C. V. Ratnam, *Ind. J. Chem.*, **21B**, 646 (1982).
548. M. Z. Badr, H. A. H. El-Sherief, and M. E. Tadros, *Bull. Chem. Soc. Jap.*, **55**, 2267 (1982).
549. V. K. Srivastava, B. R. Pandey, R. C. Gupta, J. P. Barthwal, and K. Kishor, *J. Ind. Chem. Soc.*, **56**, 1024 (1979).
550. N. M. El-Ebrashi, A. M. Nasef, and A. K. M. N. Gohari, *Ind. J. Chem. Soc.*, **21B**, 773 (1982).
551. M. Z. A. Badr, H. A. H. El-Sherief, and M. E. Tadros, *Ind. J. Chem.*, **18B**, 240 (1979).
552. S. T. Zavyalov, N. E. Knyazkova, and L. B. Kulikova, *Izv. Acad. Nauk SSSR, Ser. Khim.*, 2521 (1982).
553. A. K. Sengupta and A. A. Gupta, *J. Ind. Chem. Soc.*, **58**, 297 (1981).
554. J. Grimshaw, R. Hamilton, and J. Trocha-Grimshaw, *J. Chem. Soc. Perkin I*, 229 (1982).
555. N. K. Kochetkov, R. M. Khomutov, E. I. Budovskii, M. Y. Karpeiski, and E. S. Severin, *Zh. Obshch. Khim.*, **29**, 4069 (1959).
556. Rakshinda, M. Ali and N. H. Khan, *Syn. Commun.*, **8**, 497 (1978).
557. T. N. Ghosh, *J. Ind. Chem. Soc.*, **25**, 515 (1948).
558. T. N. Ghosh, B. K. Ghosh, and B. Bhattacharya, *J. Sci. Ind. Res.*, **21B**, 133 (1962).
559. S. Nakajima, Y. Koike, and S. Kato, *Chem. Pharm. Bull.*, **20**, 751 (1972).

560. S. Nakajima, *J. Pharm. Soc. Jap.*, **76**, 1008 (1956).
561. M. Ohara, *J. Pharm. Soc. Jap.*, **72**, 145 (1952); *Chem. Abstr.*, **46**, 11206 (1952).
562. T. Kametani, *Japan Patent* 71, 31550 (1971); *Chem. Abstr.*, **76**, 3834 (1972).
563. T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Chem. Soc. C*, 3851 (1969).
564. T. Hiraoka and Y. Kishida, *Chem. Pharm. Bull.*, **16**, 1576 (1968).
565. Y. Kishida, T. Hiraoka, and M. Yoshimoto, *Japan Patent* 71,31855 (1971); *Chem. Abstr.*, **75**, 140830 (1970).
566. W. Steglich, P. Gruber, G. Hoffle, and W. Konig, *Angew. Chem. Internat. Ed.*, **10**, 653 (1971).
567. A. DeAntoni, G. Allegri, and C. Costa, *Gazz. Chim. Ital.*, **100**, 1056 (1970).
568. D. N. Reinhoudt and P. R. M. Van der Kamp, *Org. Prep & Pro.*, **2**, 165 (1970).
569. H. D. Stachel and K. K. Harigel, *Arch. Pharm.*, **302**, 654 (1969).
570. H. D. Stachel, K. K. Harigel, H. Poschenreider, and H. Burghard, *J. Het. Chem.*, **17**, 1195 (1980).
571. K. K. Prasad, D. S. Iyengar, and R. V. Venkataratnam, *Tet. Lett.*, 2865 (1972).
572. S. Mohan, B. Kumar, and J. S. Sandhu, *Chem. & Ind. (London)*, 671 (1971).
573. B. Sain, G. Thyagarajan and J. S. Sandhu, *Can. J. Chem.*, **58**, 2034 (1980).
574. K. K. Prasad and T. Petrzilka, *Helv. Chim. Acta*, **58**, 2504 (1975).
575. A. B. A. Jensen and R. Robinson, *Monat. Chem.*, **98** (1967).
576. N. F. Ewiess and A. A. Hosni, *J. Univ. Kuwait Sci.*, **8**, 195 (1981); *Chem. Abstr.*, **96**, 217733h (1981).
577. S. Gotze and W. Steglich, *Chem. Ber.*, **109**, 2327 (1976).
578. S. Jendrzewski and W. Steglich, *Chem. Ber.*, **114**, 1337 (1981).
579. H. M. Bestermann, R. Harder, H. W. Winter, and C. Wentrup, *Angew. Chem.* **92**, 555 (1980); *Angew. Chem. Int. Ed.*, **19**, 564 (1980).
580. A. Padwa, M. Akiba, L. A. Cohen, and J. Gavin MacDonald, *J. Org. Chem.*, **48**, 695 (1983).
581. A. Padwa, M. Akiba, L. A. Cohen, and J. Gavin MacDonald, *Tet. Lett.*, 1435 (1981).
582. A. Padwa, M. Akida, L. A. Cohen, H. L. Gingrich, and N. Kamigata, *J. Am. Chem. Soc.*, **104**, 286 (1982).
583. H. Takagaki, N. Yasuda, M. Asaoka, and H. Take, *Chem. Lett.*, 183 (1979).
584. S. Gotze, B. Kubel, and W. Steglich, *Chem. Ber.*, **109**, 2331 (1976).
585. S. Gotze and W. Steglich, *Chem. Ber.*, **109**, 2335 (1976).
586. H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **103**, 125 (1970).
587. H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).
588. H. Gotthardt, R. Huisgen, and F. C. Schaefer, *Tet. Lett.*, 487 (1964).
589. J. L. O'Brien and C. Niemann, *J. Am. Chem. Soc.*, **72**, 5348 (1950).
590. J. L. O'Brien and C. Niemann, *J. Am. Chem. Soc.*, **79**, 80 (1957).
591. R. Huisgen, H. Gotthardt, and H. O. Bayer, *Chem. Ber.*, **103**, 2368 (1970).
592. R. Huisgen, H. Gotthardt, and H. O. Bayer, *Tet. Lett.*, 481 (1961).
593. R. Huisgen, H. Gotthardt, and H. O. Bayer, *Angew. Chem. Int. Edit.*, **3**, 135 (1964).
594. R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem. Int. Edit.*, **3**, 136 (1964).
595. G. Singh and S. Singh, *Tet. Lett.*, 3780 (1964).
596. C. V. Greco, R. P. Gray, and V. G. Grosso, *J. Org. Chem.*, **29**, 2658 (1964).
597. G. Kille and J. P. Fleury, *Bull. Soc. Chim. Fr.*, 4631 (1968).

598. G. Kille and J. P. Fleury, *Bull. Soc. Chim. Fr.*, 4636 (1968).
599. A. Padwa and S. I. Wetmore, *J. Am. Chem. Soc.*, **96**, 2414 (1974).
600. A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore Jr., *J. Am. Chem. Soc.*, **95**, 1945 (1973).
601. A. Padwa and J. Smolanoff, *J. Am. Chem. Soc.*, **93**, 548 (1971).
602. N. S. Narasimhan, H. Heimgartner, H. J. Hausen, and H. Schmid, *Helv. Chim. Acta*, **56**, 1351 (1973).
603. G. V. Boyd and S. R. Dando, *J. Chem. Soc. Perkin I*, 1142 (1972).
604. A. M. Knowles, A. Lawson, G. V. Boyd, and R. A. Newberry, *Tet. Lett.*, 485 (1971).
605. H. Matsukubo, M. Kojima, and H. Kato, *Chem. Lett. (Japan)*, 1153 (1975).
606. H. Matsukubo and H. Kato, *J. Chem. Soc. Chem. Commun.*, 840 (1975).
607. H. C. Berk and J. E. Franz, *Syn. Commun.*, **11**, 267 (1981).
608. B. Sain, J. N. Baruah, and J. S. Sandhu, *J. Heterocyclic Chem.*, **19**, 1511 (1982).
609. H. Rodriguez, H. Pavez, A. Marquez, and P. Navarrete, *Tetrahedron*, **39**, 23 (1983).
610. A. Marquez, P. Navarrete, H. Rodriguez, and H. Pavez, *Bol. Soc. Chil. Quim.*, **27**, 125 (1982); *Chem. Abstr.*, **97**, 38891g (1982).
611. W. I. Awad, A. K. Fateen, and M. A. Zayed, *Tetrahedron*, **20**, 891 (1964).
612. S. W. King, J. M. Riordan, E. M. Holt, and C. H. Stammer, *J. Org. Chem.*, **47**, 3270 (1982).
613. R. A. Pages and A. Burger, *J. Med. Chem.*, **9**, 766 (1966).
614. R. A. Pages and A. Burger, *J. Med. Chem.*, **10**, 435 (1967).
- 615a. M. Bernabe, E. Fernandez-Alvarez, and S. Pullate, *Anales. Quim.*, **68**, 501 (1972); *Anales. Quim.*, **68**, 1005 (1972).
- 615b. I. Arenal, M. Bernabe, and E. Fernandez-Alvarez, *J. Het. Chem.*, **20**, 607 (1983).
616. O. Tsuge, M. Noguchi, and H. Moriyama, *Heterocycl.*, **16**, 209 (1981).
617. O. Tsuge, M. Noguchi, and H. Moriyama, *Heterocycl.*, **19**, 1823 (1982).
618. J. K. Sutherland and D. A. Widdowson, *J. Chem. Soc.*, 4650 (1964).
619. E. Profft and H. E. Petzold, *J. Prakt. Chem.*, **16**, 26 (1962).
620. L. Hellerman, C. C. Porter, H. J. Lowe, and H. F. Koster, *J. Am. Chem. Soc.*, **68**, 1890 (1946).
621. J. Eisenbrand, *Arch. Pharm.*, **286**, 441 (1953).
622. G. W. Gaffney, K. Schreier, N. Diferrante, and K. Altman, *J. Biol. Chem.*, **206**, 695 (1954).
623. C. J. Veal and D. W. Young, *J. Chem. Soc. Perkin I*, 2086 (1975).
624. A. Rosenthal and K. Dooley, *J. Carbohyd. Nucleosides & Nucleotides*, **1**, 61 (1974); *Chem. Abstr.*, **82**, 140418r (1975).
625. H. Bundgaard and H. R. Angelo, *Tet. Lett.*, 3001 (1974).
626. D. F. Corbett and R. J. Stoodley, *J. Chem. Soc. Perkin I*, 185 (1974).
627. J. Hoogmartens, P. J. Claes, and H. Vanderhaege, *J. Org. Chem.*, **39**, 425 (1974).
628. H. Ohle and A. G. Schering, German Patent 824,204 (1951); *Chem. Abstr.*, **49**, 7603 (1954).
629. A. Srinivasan, K. D. Richards, and R. K. Olsen, *Tet. Lett.*, 891 (1976).
630. V. Austel and W. Steglich, *Chem. Ber.*, **108**, 2361 (1975).
631. J. S. H. Davies and W. G. M. Jones, British Patent 583,190 (1946); *Chem. Abstr.*, **41**, 3491e (1947).
632. R. Pschorr and G. Knoffler, *Ann.*, **382**, 55 (1911).
633. V. Deulofeu, *Anal. Soc. Espan. Fis. Quim.*, **32**, 152 (1934).

634. P. C. Mitter and S. S. Maitra, *J. Ind. Chem. Soc.*, **13**, 236 (1936).
635. G. Wittig, *Angew. Chem.*, **53**, 241 (1940).
636. K. Kumar, D. J. Phelps, and P. R. Carey, *Can. J. Chem.*, **56**, 232 (1978).
637. T. Asahina, *Bull. Chem. Soc. Jap.*, **4**, 202 (1928).
638. T. Asahina, *Bull. Chem. Soc. Jap.*, **5**, 354 (1930).
639. F. W. Schueler and S. C. Wang, *J. Am. Chem. Soc.*, **72**, 2220 (1950).
640. F. W. Schueler and C. Hanna, *J. Am. Chem. Soc.*, **73**, 3528 (1951).
641. F. W. Schueler and C. Hanna, *J. Am. Chem. Soc.*, **74**, 5542 (1952).
642. E. L. Bennett and E. Hoerger, *J. Am. Chem. Soc.*, **74**, 5975 (1952).
643. K. Brocklehurst and K. Williamson, *Tetrahedron*, **30**, 351 (1974).
644. K. Brocklehurst, H. S. Price, and K. Williamson, *J. Chem. Soc. Chem. Commun.*, 884 (1968).
645. B. F. Crowe and F. F. Nord., *J. Org. Chem.*, **15**, 81 (1950).
646. R. Filler and R. C. Orlowski, unpublished results.
647. S. I. Lure, E. S. Chaman, and G. A. Ravdel, *Zh. Obshch. Khim.*, **23**, 1392 (1953).
648. S. I. Lure and G. A. Ravdel, *Doklady Akad. Nauk SSSR*, **83**, 97 (1952).
649. S. I. Lure and R. G. Vdovina, *Doklady Akad. Nauk SSSR*, **79**, 81 (1951).
650. S. I. Lure and R. G. Vdovina, *Zh. Obshch. Khim.*, **22**, 1883 (1952).
651. S. I. Lure, G. A. Ravdel, *Sbornik State Obshchei Khim. Akad. Nauk SSSR*, **1**, 498 (1953); *Chem. Abstr.*, **49**, 1009t (1955).
652. A. Pedrazzoli, *Helv. Chem. Acta*, **40**, 80 (1957).
654. M. Bernabe, E. P. Alvarez, and S. P. Ullate, *An. Quim.*, **68**, 501 (1972).
653. J. R. Merchant and S. M. Shetty, *J. Ind. Chem. Soc.*, **45**, 863 (1968).
655. C. W. Smith and R. S. Rasmussen, *J. Am. Chem. Soc.*, **71**, 1080 (1949).
656. C. W. Smith, *J. Am. Chem. Soc.*, **72**, 2387 (1950).
657. F. Micheel and B. Schleppinghoff, *Chem. Ber.*, **88**, 763 (1955).
658. M. Rai, K. Krishan, and A. Singh, *Ind. J. Chem.*, **15B**, 847 (1977).
659. I. Oprean, C. Bodea, and V. Farcasan, *Stud. Univ. Babes-Boyai Ser. Chem.*, **19**, 25 (1974); *Chem. Abstr.*, **82**, 56907 (1975).
660. D. N. Shigorin, Y. K. Syrkin, *Izvest. Akad. Nauk SSSR Otdel. Khim. Nauk*, 59 (1946).
661. D. N. Shigorin and Y. K. Syrkin, *Acta Physiol. Chem. URSS*, **21**, 423 (1946); *Chem. Abstr.*, **40**, 6995 (1946).
662. J. A. Ballantine and R. Fenwick, *Org. Mass. Spectra*, **5**, 615 (1971).
663. I. Z. Siemion, G. Baran, M. Gizler, and S. Jaworski, *Rocz. Chem.*, **47**, 513 (1973).
664. I. Z. Siemion and G. Baran, *Bull. Acad. Polon. Scien. Series Sic. Chim.*, **23**, 317 (1975).
665. A. P. Morgenstern, Ph.D. thesis, Vrije Universitat, Amsterdam (1969).
666. A. P. Morgenstern, C. Schuijt, and W. Th. Nauta, *Chem. Commun.*, 321 (1969).
667. A. P. Morgenstern, C. Schuijt, and W. Th. Nauta, *J. Chem. Soc. C*, 3706 (1971).
668. A. G. Brown and T. C. Smale, *Chem. Commun.*, 1489 (1969).
669. G. S. Sidhu, R. V. Venkataratnam, K. K. Prasad, and D. S. Iyengar, *Ind. J. Chem.*, **10**, 448 (1972).
670. A. Maquestiau, Y. V. Haverbeke, and R. N. Muller, *Bull. Soc. Chim. Belg.*, **83**, 259 (1974).
671. R. Glaser and M. Twaik, *Tet. Lett.*, 1219 (1976).
672a. E. Galantay, A. Szabo, and J. Fried, *J. Org. Chem.*, **28**, 98 (1963).

- 672b. J. Sekacis, I. E. Khatskevich, J. Kalnina, and J. Pumpure, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* 368 (1978); *Chem. Abstr.*, **89**, 162925v (1978).
- 672c. D. J. Phelps, P. V. Godreau, and E. S. Nicholas, *J. Chem. Soc. Perkin II*, 140 (1981).
- 672d. E. P. Prokofiev and E. I. Karpeiskaya, *Tet. Lett.*, 737 (1979).
- 672e. J. M. Brown and P. A. Chaloner, *J. Am. Chem. Soc.*, **102**, 3040 (1980).
- 672f. P. A. Chaloner, *J. Chem. Soc. Perkin II*, 1028 (1980).
- 672g. J. M. Brown, *J. Chem. Soc. Perkin II*, 711 (1982).
673. O. Grahl-Nielsen and E. Solheim, *J. Chromat.*, **69**, 366 (1972).
674. O. Grahl-Nielsen and E. Solheim, *Anal. Chem.*, **47**, 333 (1975); *Chem. Abstr.*, **82**, 927101a (1975).
675. O. Grahl-Nielsen and B. Moevik, *Biochem. Med.*, **12**, 143 (1975); *Chem. Abstr.*, **82**, 166899f (1975).
676. J. deJersey and B. Zerner, *Biochem.*, **8**, 1967 (1969).
677. J. deJersey, P. Willadsen, and B. Zerner, *Biochem.*, **8**, 1959 (1969).
678. J. K. Stoops, D. J. Horgan, M. T. C. Runnegar, J. deJersey, E. C. Webb, and B. Zerner, *Biochem.*, **8**, 2026 (1969).
679. J. deJersey, *Biochem.*, **9**, 1761 (1970).
680. H. Siemieniowski and T. Baranowski, *Acta Biochem. Pol.*, **16**, 243 (1969).
681. K. Brocklehurst and K. Williamson, *Chem. Commun.*, 462 (1966).
682. K. Brocklehurst and K. Williamson, *Chem. Commun.*, 666 (1967).
683. K. Brocklehurst and K. Williamson, *Biochem. Biophys. Res. Commun.*, **26**, 175 (1967).
684. J. deJersey and B. Zerner, *Biochem. Biophys. Res. Commun.*, **28**, 173 (1967).
685. J. deJersey and B. Zerner, *Biochem.*, **8**, 1975 (1969).
686. D. Davidson and L. Auerbach, *J. Am. Chem. Soc.*, **75**, 5984 (1953).
687. P. Karrer and R. Keller, *Helv. Chim. Acta*, **26**, 50 (1943).
688. D. S. Jones, G. W. Kenner, J. Preston, and R. C. Sheppard, *J. Chem. Soc.*, 6227 (1965).
689. V. K. Antonov and A. L. Kurts, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 99 (1964).
690. M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, **11**, 39 (1961).
691. J. P. Branquet, H. Pacheco, and A. Cier, *Bull. Soc. Chim. France*, 1942 (1965).
692. Y. Shimodoi and N. Morita, *Kogyo Kagaku Zasshi*, **65**, 1664 (1962); *Chem. Abstr.*, **59**, 16112 (1963).
693. Y. Iwakura, F. Toda, and Y. Torii, *J. Polym. Sci., A-1*, **4**, 2649 (1966).
694. H. Pennewiss, Ger. Offen. 1,936,155 (1971); *Chem. Abstr.*, **74**, 127705 (1971).
695. D. S. Jones, G. W. Kenner, R. C. Sheppard, *Experientia*, **19**, 126 (1963).
696. E. P. Abraham, E. B. Chain, W. Baker, and R. Robinson, British Patent 588,101 (1947); *Chem. Abstr.*, **42**, 2287 (1948).
697. A. Dzugat, I. Z. Siemion, and J. Ojrzynski, *Rocz. Chem.*, **40**, 1329 (1962).
698. Pfizer, Inc., British Patent 1,314,480 (1973); *Chem. Abstr.*, **79**, 66355 (1973).
699. J. M. Stewart and D. W. Woolley, *J. Am. Chem. Soc.*, **78**, 5336 (1956).
700. G. Barger and R. Silberschmidt, *J. Chem. Soc.*, 2919, (1928).
701. H. Dannenberg, D. Dannenberg, and U. Dressler, *Chem. Ber.*, **89**, 1326 (1956).
702. Y. N. Sheiaker and B. M. Golovner, *Doklady. Akad. Nauk SSSR*, **79**, 269 (1951).
703. A. Williams, *J. Chem. Soc. Perkin II*, 947 (1975).
704. Roehm and Hass, British Patent 1,121,418 (1968); *Chem. Abstr.*, **69**, 68409 (1968).

705. F. Killinsky, K. Hubner, and G. Markert, U.S. Patent 3,591,790 (1971); *Chem. Abstr.*, **75**, 141996 (1971).
706. G. Casnati and A. Ricca, *Gazz. Chim. Ital.*, **93**, 355 (1961).
707. F. C. Copp and S. Wilkinson, British Patent 587,735 (1945); *Chem. Abstr.*, **41**, 6900 (1947).
708. O. V. Kildisheva, V. V. Shokina, and I. L. Knunyants, *Izvest. Akad. Nauk SSSR Otdel. Khim. Nauk*, 1461 (1958).
709. R. Tschesche and T. Jenssen, *Chem. Ber.*, **93**, 271 (1960).
710. F. E. King, J. W. Clark-Lewis, R. Wade, and W. A. Swindin, *J. Chem. Soc.*, 873 (1957).
711. P. Gruber, I. Mueller, and W. Steglich, *Chem. Ber.*, **106**, 1863 (1973).
712. S. Dalby, G. W. Kenner, and R. C. Sheppard, *J. Chem. Soc.*, 968 (1960).
713. Z. Foldi, *Acad. Chim. Acad. Sci. Hung.*, **3**, 371 (1953).
714. O. V. Kildisheva, L. P. Rastelkeve, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 260 (1950).
715. O. E. Schulz and P. Warnecke, *Arzneim. Forsch.*, **17**, 1060 (1967).
716. C. Panetta and A. L. Miller, *Synthesis*, 43 (1977).
717. A. H. Harhash, M. H. El-Nagdi, A. A. A. Albanani, and F. A. Sli, *Ind. J. Chem.*, **14B**, 744 (1976).
718. K. Hohenlohe-Oehringen, *Monat. Chem.*, **93**, 639 (1962).
719. K. Hohenlohe-Oehringen, *Monat. Chem.*, **94**, 645 (1962).
720. C. W. Rigby and B. P. Stark, Ger. Offen. 2,036,405 (1971); *Chem. Abstr.*, **74**, 126514 (1971).
721. E. Bordignon, P. Cinganotto, and A. Scatturin, *Atti Acad. Peloritana Pericolanti Cl. Sci. Fis. Mat. Nature*, **52**, 239 (1972); *Chem. Abstr.*, **81**, 4248 (1974).
722. G. Weitnauer, U.S. Patent 2,782,203 (1957); *Chem. Abstr.*, **52**, 444 (1958).
723. E. A. Bashkir, Y. A. Lapvk, *Metody Polucheniya Khim. Reaktivov i Preparatov*, **13**, 73 (1965); *Chem. Abstr.*, **65**, 5522 (1966).
724. G. W. Kenner, J. Preston, and R. C. Sheppard, *J. Chem. Soc.*, 6239 (1965).
725. I. L. Knunyants and V. V. Shokita, *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk.*, 462 (1955).
726. J. H. Jones and M. J. Witty, *J. Chem. Soc. Chem. Commun.*, 281 (1977).
727. W. Steglich, R. Kubel, and P. Gruber, *Chem. Ber.* **106**, 2870 (1973).
728. R. Lohmar and W. Steglich, *Angew. Chem.*, **90**, 493 (1973).
729. D. Hoppe, *Just. Liebigs Ann. Chem.*, 2185 (1976).
730. N. P. Shimanskaya, I. V. Lysova, L. A. Kotok, and L. S. Afanasiadi, *Zh. Obshch. Khim.*, **48**, 2315 (1978); *Chem. Abstr.*, **90**, 86424 (1979).
731. M. R. Bell, S. D. Clemans, R. Oesterlin, and J. Carlson, *J. Het. Chem.*, **11**, 823 (1974).
732. M. R. Bell, J. A. Carlson, and R. Oesterlin, *J. Org. Chem.*, **37**, 2733 (1972).
733. J. Gardent, *Bull. Soc. Chim. France*, 114 (1960).
734. C. W. Bird, *J. Org. Chem.*, **27**, 4091 (1962).
735. C. Dufraisse, G. Rio, and A. Ranjan, *Compt. Rend.*, **246**, 1337 (1958).
736. G. Rio and A. Ranjan, *Bull. Soc. Chim. France*, 543 (1958).
737. R. Filler and Y. S. Rao, *J. Org. Chem.*, **26**, 1685 (1961).
738. M. Shiozaki and T. Hiraoka, *Agr. Biol. Chem. (Tokyo)*, **41**, 65 (1977); *Chem. Abstr.*, **86**, 189822 (1977).
739. H. J. Waddington, G. D. Duffin, and J. D. Kendall, British Patent 785,334 (1957); *Chem. Abstr.*, **52**, 6031 (1958).

740. H. Poisel and U. Schmidt, *Chem. Ber.*, **106**, 3408 (1973).
741. K. Rufenacht, *Experientia*, **10**, 247 (1954).
742. U. Schmidt, A. Preco, and E. Ohler, *Chem. Ber.*, **107**, 2816 (1974).
743. E. Oehler and U. Schmidt, *Chem. Ber.*, **110**, 921 (1977).
744. L. F. Godunova, E. I. Karpeiskaya, E. S. Neupokoeva, and E. I. Klobunovskii, *Katal. Reakts. Zhidk Faze Mater Vese Konf.*, 4th, 121 (1974); *Chem. Abstr.*, **86**, 170690 (1977).
745. E. I. Karpeiskaya, E. S. Neupokoeva, L. F. Godunova, I. P. Murina, A. P. Kharchevnikov, and E. I. Klabunovskii, *Izv. Akad. Nauk SSSR Ser. Chem.*, 1368 (1978); *Chem. Abstr.*, **90**, 23635 (1979).
746. R. Granger, J. Giroux, J. Lanet, and M. Corbier, *Bull. Soc. Chim. France*, 1160 (1958).
747. D. O. Holland, P. A. Jenkins, and J. H. C. Naylor, *J. Chem. Soc.*, 273 (1953).
748. M. Kuchar, B. Brunova, J. Grimova, J. Holubek, and O. Nemeck, *Cesk. Farm.*, **24**, 287 (1975).
749. S. K. Gandhi, C. S. Pande, and R. K. Raut, *Monat. Chem.*, **97**, 1751 (1966).
750. A. M. Brenner, J. P. Zimmerman, J. Wehrmuller, P. Quitt, A. Hartmann, W. Schneider, and V. Beglinger, *Helv. Chim. Acta*, **40**, 1497 (1957).
751. J. T. Hackmann and P. T. Hackne, British Patent 818,186 (1959); *Chem. Abstr.*, **54**, 9193 (1960).
752. O. Shimomura and S. Eguchi, *Nippon Kagaku Zasshi*, **81**, 1434 (1960).
753. J. M. Riordan, M. Sato, and C. H. Stammer, *J. Org. Chem.*, **42**, 236 (1977).
754. L. Turbanti, G. F. DiPaco, *Farmaco (Pavia) Ed. Sci.*, **15**, 406 (1960); *Chem. Abstr.*, **54**, 24532 (1960).
755. J. E. Tietzman, D. G. Doherty, and M. Bergmann, *J. Biol. Chem.*, **151**, 387 (1943).
756. D. G. Doherty, J. E. Tietzman, and M. Bergmann, *J. Biol. Chem.*, **147**, 617 (1943).
757. K. Rufenacht, *Helv. Chim. Acta*, **37**, 1451 (1954).
758. R. Filler and E. J. Piasek, *J. Org. Chem.*, **29**, 2205 (1964).
759. G. W. Kirby, S. Narayanaswami, and P. S. Rao, *J. Chem. Soc. Perkin Trans. I*, 645 (1975).
760. K. R. Hanson, R. H. Wightman, J. Staunton, and A. R. Battersby, *J. Chem. Soc. Chem. Commun.*, 185 (1971).
761. R. H. Wightman, J. Staunton, and A. R. Battersby, *J. Chem. Soc. Perkin Trans. I*, 2355 (1972).
762. A. T. Blomquist and R. J. Cedergren, *Can. J. Chem.*, **46**, 1053 (1968).
763. G. Schiemann and W. Roselius, *Chem. Ber.*, **65**, 1439 (1932).
764. E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **71**, 1800 (1950).
765. Y. K. Yurev, N. N. Mezentsova, and V. E. Vaskovski, *Zh. Obshch. Khim.*, **27**, 3155 (1957).
766. Y. S. Rao, Ph.D. thesis, Illinois Institute of Technology, Chicago (1963).
767. E. Havinga, and E. L. T. M. Spitzer, *Rec. Trav. Chim.*, **76**, 173 (1957).
768. H. Meyer, F. Bossert, W. Vater, and K. Stopel, Ger. Offen. 2,406,200 (1975); *Chem. Abstr.*, **84**, 30898 (1976).
769. C. Viel, R. Dorme, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1956 (1966).
770. A. P. A. Rossi, L. H. Werner, W. L. Bencze, and G. Destevens, Belgian Patent 641,254 (1964); *Chem. Abstr.*, **63**, 9956 (1965).
771. G. V. Shishkin and V. P. Mamaev, *Zh. Obshch. Khim.*, **36**, 660 (1966).
772. H. Meyer, F. Bossert, W. Vater, and K. Stoepel, Ger. Offen. 2,406,200 (1975); *Chem. Abstr.*, **84**, 30898 (1976).

773. H. A. Offe and H. Jatzkewitz, *Chem. Ber.*, **80**, 496 (1947).
774. S. I. Lure, E. S. Chaman, and G. A. Ravdel, *Zh. Obshch. Khim.*, **25**, 175 (1955).
775. G. Ehrhart and I. Hennig, *Chem. Ber.*, **87**, 892 (1954).
776. A. H. Cook, G. Harris, and I. M. Heilbron, *J. Chem. Soc.*, 1060 (1948).
777. D. H. Marrian, P. B. Russell, and A. R. Todd, *Biochem. J.*, **45**, 533 (1948).
778. T. D. Banfi and L. Otvos, *Acta Chem. Hung.*, **34**, 705 (1962).
779. F. Shimada, S. Sekine, and T. Kono, Japan Kokai 75,32,172 (1975); *Chem. Abstr.*, **83**, 193282 (1975).
780. K. A. Jaeggi, F. Ostermeyer, and H. Schroeter, Ger. Offen. 2,324,584 (1974); *Chem. Abstr.*, **82**, 3575 (1974).
781. G. Habild, *Z. Physiol. Chem.*, **283**, 150 (1950).
782. R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).
783. R. I. Meltzer, U.S. Patent 2,954,399 (1960); *Chem. Abstr.*, **55**, 7308 (1961).
784. A. Hajos and J. Kollonitsch, *Acta Chem. Hung.*, **27**, 449 (1958).
785. D. J. Phelps, R. G. Carriere, K. Kumar, and P. R. Carey, *Can. J. Chem.*, **56**, 240 (1978).
786. E. Estchenberg, W. Opitz, and S. Raddatz, Ger. Offen. 2,659,114 (1978); *Chem. Abstr.*, **90**, 55277j (1979).
787. A. Pedrazzoli, *Chimia*, **10**, 260 (1956).
788. A. W. Hanson, *Acta Crystallogr.*, **33B**, 594 (1977).
789. L. Dall'Asta and P. Ferrario, *Helv. Chim. Acta*, **45**, 1065 (1962).
790. R. J. S. Beer, L. McGrath, A. Robertson, A. B. Woodier, and J. S. E. Halker, *J. Chem. Soc.*, 2061 (1949).
791. R. J. S. Beer, K. Clarke, H. G. Khorana, and A. Robertson, *J. Chem. Soc.*, 1605 (1948).
792. G. Stefanovich and M. Stefanovich, *J. Org. Chem.*, **21**, 161 (1956).
793. B. M. Krasovitskii, I. V. Lysova, and L. F. Afanasiadi, *Khim. Geterosikl. Soedin.*, 158 (1978); *Chem. Abstr.*, **88**, 190656 (1978).
794. R. Filler and H. Novar, *J. Org. Chem.*, **25**, 733 (1960).
795. R. Filler and H. Novar, *J. Org. Chem.*, **25**, 663 (1960).
796. G. W. Kirby and J. Michael, *J. Chem. Soc. Perkin I*, 115 (1973).
797. J. N. Ashley and J. O. Harris, *J. Chem. Soc.*, 567 (1946).
798. A. G. Knoll, *Chem. Fabrik* Ger. 819,696 (1951); *Chem. Abstr.*, **47**, 11250 (1953).
799. C. Salat-Ferrer, M. B. Guitierrez, and P. A. Agnesetti, Spanish Patent 428,272 (1976); *Chem. Abstr.*, **86**, 89415 (1977).
800. H. N. Rydon and S. Siddappa, *J. Chem. Soc.*, 2462 (1951).
801. W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, U.S. Patent 4,005,127 (1977); *Chem. Abstr.*, **86**, 190463z (1977).
802. E. Walton and B. J. F. Hudson, British Patent 600,114 (1947); *Chem. Abstr.*, **42**, 7794 (1948); U.S. Patent 2,496,968 (1950); *Chem. Abstr.*, **44**, 5913 (1950).
803. G. R. Clemo and F. K. Duxbury, *J. Chem. Soc.*, 1795 (1950).
804. V. G. Yakolev, *Zh. Obshch. Khim.*, **20**, 361 (1950); V. G. Yakolev, *Doklady Akad. Nauk SSSR*, **71**, 497 (1950).
805. H. B. Gillespie, *Biochem. Prep.*, **3**, 79 (1953).
806. T. Kametani and K. Fukumoto, *Yakugaku Kenkyu*, **30**, 412 (1958); *Chem. Abstr.*, **53**, 21886 (1959).
807. R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).

808. L. Fennoy, *J. Org. Chem.*, **26**, 6 (1961).
809. C. Kaiser and A. Burger, *J. Am. Chem. Soc.*, **79**, 4365 (1957).
- 810a. M. L. Anhoury, P. C. Rooy, R. Deneys, and J. Eliaers, *Bull. Soc. Chim Belg.*, **83**, 117 (1974).
- 810b. P. Crooij, South African Patent 68,03,083 (1968); *Chem. Abstr.*, **71**, 22327 (1969).
- 810c. Belgian Patent 715,588 (1968); *Chem. Abstr.*, **71**, 81728 (1969).
811. T. Kametani, O. Umezawa, Y. Sato, K. Ogasawara, S. Shiboya, M. Ishiguro, and D. Mizuno, *J. Pharm. Soc. Jap.*, **83**, 838 (1963); *Chem. Abstr.*, **60**, 447 (1964).
812. X. A. Dominguez, B. Gomez, A. Homberg, and J. Slim, *J. Am. Chem. Soc.*, **77**, 1288 (1955).
813. H. Muxfeldt, J. P. Bell, J. H. Baker, and U. Cuntze, *Tet. Lett.*, 4587 (1975).
814. M. S. Matta, J. A. Kelley, J. Tietz, and A. Nishinaga, *J. Med. Chem.*, **11**, 899 (1968).
815. M. S. Matta, J. A. Kelley, M. F. Rohde, U.S. Patent 3,878,043 (1975); *Chem. Abstr.*, **83**, 164578 (1975).
816. J. P. Bell, Ph.D. thesis, University of Wisconsin, Madison, Wisc., 1967; *Diss. Abs. B*, **28**, 830 (1967).
817. P. Bambers, B. O. H. Sjoberg, Ger. Offen. 2,100,445 (1971); *Chem. Abstr.*, **75**, 129517 (1971).
818. T. S. T. Wang and J. A. Vida, *J. Med. Chem.*, **17**, 1120 (1974).
819. G. Schenider, *Biochem. Z.*, **330**, 428 (1958).
820. H. Burton and P. F. Hu, *J. Chem. Soc.*, 178 (1949).
821. H. S. Forest, A. T. Fuller, and J. Walker, *J. Chem. Soc.*, 150 (1948).
822. C. Ribbens, *Sci. Communs. Res. Dept. V. V. Konin. Pharm.*, 209 (1960); *Chem. Abstr.*, **56**, 7378 (1962).
823. C. Ribbens, C. Vender Stelt, and W. T. Nauta, *Rec. Trav. Chim.*, **79**, 78 (1960).
824. M. Brink, W. Nel, G. J. H. Rall, J. C. Weitz, and K. G. R. Pachler, *J. S. Afr. Chem. Inst.*, **19**, 24 (1966).
825. K. U. Steiner and E. Sorkhin, *Helv. Chem. Acta*, **35**, 2486 (1952).
826. G. R. Clemo and F. K. Duxbury, *J. Chem. Soc.*, 3844 (1952).
827. R. I. T. Cromatie and J. Harley-Mason, *J. Chem. Soc.*, 1052 (1952).
828. T. Kametani, H. I. Ida, and C. Kibayashi, *J. Het. Chem.*, **7**, 339 (1970).
829. R. T. Coutts and J. L. Mallicky, *Can. J. Chem.*, **52**, 390 (1974).
830. J. Redel and Bouteville, *Bull. Soc. Chim. France*, 443 (1949).
831. Z. V. Pushkaraeva, F. D. Medovshchikova, A. K. Shtamm, and L. V. Smirnova, *Med. Prom. SSSR*, **25** (1955); *Chem. Abstr.*, **50**, 4959 (1956).
832. Y. Ozawa, K. Izawa, and T. Yamashita, *Japan Kokai*, 78,84,968 (1978); *Chem. Abstr.*, **90**, 23025 (1979).
833. W. B. Whalley, *J. Chem. Soc.*, 3366 (1953).
834. G. Schiemann, W. Winkemuller, and W. Roselius, *Chem. Ber.*, **65**, 1435 (1932).
835. A. E. Porai-Koshits and N. V. Khromov, *J. Gen. Chem. USSR*, **10**, 557 (1947).
836. G. H. Labib, *Compt. Rend.*, **250**, 2904 (1960).
837. P. R. Carey, R. G. Carriere, K. R. Lynn, and H. Schneider, *Biochem.*, **15**, 2387 (1976).
838. A. O. Fitton, J. R. Frost, H. Suschitzky, and P. G. Houghton, *Synthesis*, 138 (1977).
839. O. P. Singhal and P. I. Ittyerah, *Curr. Sci. (Ind.)*, **34**, 455 (1965); *Chem. Abstr.*, **63**, 11534 (1965).
840. T. Kametani and Y. Ohkubo, *J. Pharm. Soc., Jap.*, **87**, 279 (1969).
841. R. M. Acheson, D. P. Dearnaley, A. O. Plunkett, and V. C. Porter, *J. Chem. Soc.*, 2085 (1963).

842. K. Brewster and R. M. Pinder, *J. Med. Chem.*, **14**, 650 (1971).
- 843a. B. L. Moldver and Z. V. Pushakareva, *Zh. Org. Khim.*, **1**, 348 (1965).
- 843b. K. Wasti and M. M. Joullie, *J. Chem. Soc. Perkin Trans. I*, 252 (1976).
- 844a. K. Kigasawa, M. Hiragi, N. Wagatsuma and T. Nakamura, *Japan Kokai*, **77**, 83343 (1977); *Chem. Abstr.*, **88**, 22403c (1978); **77**, 133979 (1977); *Chem. Abstr.*, **88**, 136606b (1978); **77**, 71,438 (1977); *Chem. Abstr.*, **87**, 16774d (1977); **77**, 71,463 (1977); *Chem. Abstr.*, **87**, 168013b (1977); **77**, 133,943 (1977); *Chem. Abstr.*, **88**, 104919q (1978).
845. S. I. Mahori and I. Okada, *Japan Kokai*, **75**,160,580 (1975); *Chem. Abstr.*, **84**, 152218z (1976).
846. E. N. Shkodinskaya, M. N. Vasileva, O. S. Vasina, and A. Y. Berlin, *Zh. Obshch. Khim.*, **29**, 3776 (1959).
847. R. G. Jones, Q. F. Soper, O. K. Behrens, and J. Corse, *J. Am. Chem. Soc.*, **70**, 2843 (1948).
848. F. D. Popp, *J. Org. Chem.*, **26**, 3020 (1961).
849. A. F. Martinez, W. A. Skinner, W. W. Lee, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 6050 (1964).
850. F. Bergel and J. A. Stock, *J. Chem. Soc.*, 4563 (1957).
851. S. Sugawara and N. Yoshida, *Pharm. Bull. (Jap.)*, **1**, 281 (1953); *Chem. Abstr.*, **49**, 8256 (1955).
852. H. V. Hansen, R. I. Meltzer, U.S. Patent 3,544,623 (1970); *Chem. Abstr.*, **74**, 125181 (1971).
853. S. D. Warren and Co., Netherlands Pat. 6,409,096 (1965); *Chem. Abstr.*, **63**, 605 (1965).
854. K. B. Niewiadomsky and H. Suschitzky, *J. Chem. Soc. Perkin I*, 1679 (1975).
855. G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *Chem. & Ind. (London)*, 209 (1957).
856. J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 656 (1958).
857. C. G. Wermuth and J. Chan, *Fr. Demande*, 2170,870 (1973); *Chem. Abstr.*, **80**, 83943 (1974).
858. L. Beregi, P. Hugoh, J. Duhault, and J. C. Poignant, *Ger. Offen.* 2,310,829 (1973); *Chem. Abstr.*, **79**, 146848 (1973).
859. P. C. Pan, T. Li, H. Y. Yao, and I. Kao., *Yao Hsueh Pao*, **B**, 432 (1966); *Chem. Abstr.*, **68**, 50029 (1968).
860. A. Silberg, Z. Frenkel, and L. Cormos, *Studia Univ. Babes-Bolyai, Ser. Chem.*, **7**, 23 (1962); *Chem. Abstr.*, **62**, 1643b (1965).
861. G. A. Nikiforov and K. M. Dyumaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1068 (1964).
862. E. Massarini, D. Nardi, L. Mauri, and G. Cavallini, *Farmacol. (Pavia) Ed. Sci.*, **18**, 582 (1963); *Chem. Abstr.*, **59**, 11465 (1963).
863. Maggini & Co. Italian Patent 611,973 (1960); *Chem. Abstr.*, **55**, 19868 (1961).
864. G. Caballini, E. Massarini, D. Nari, and R. D'Ambrosion, *J. Am. Chem. Soc.*, **79**, 3514 (1957).
865. K. Karpavicius, G. Pramickiene, and O. V. Kildisheva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1887 (1973).
866. J. Diamond, U.S. Patent 3,907,897 (1975); *Chem. Abstr.*, **84**, 4675 (1976).
867. S. S. Okolov and S. N. Bordulina, *Zh. Org. Khim.*, **2**, 1088 (1966).
868. J. Roche, R. Michel, J. Nunez, and C. Jacquemin, *Bull. Soc. Chim France*, 715 (1959).
869. C. L. Gemmili, J. J. Anderson, and A. Burger, *J. Am. Chem. Soc.*, **78**, 2434 (1956).

870. H. Nahm and W. Siedel, *Chem. Ber.*, **96**, 1 (1963).
871. W. Siedel, H. Nahm, and H. Pini, U.S. Patent 2,894,977 (1959); *Chem. Abstr.*, **54**, 18552 (1960).
872. E. T. Burrows, J. C. Clayton, and B. A. Hems, *J. Chem. Soc. Suppl.*, **1**, 185 (1949).
873. D. F. Elliott and C. Harington, *J. Chem. Soc.*, 1377 (1949).
874. T. Kametani, H. I. Ida, and C. Kibayashi, *J. Het. Chem.*, **7**, 339 (1970).
875. P. G. Strange, J. Staunton, H. R. Wiltshire, A. R. Battersby, K. R. Hanson, and E. A. Havir, *J. Chem. Soc. Perkin I*, 2364 (1972).
876. W. Ried and H. G. Gebhardts-Bauer, *Chem. Ber.*, **89**, 2933 (1956).
877. O. N. Karpukhin, K. V. Y. Shlyapurtokh, and N. V. Zoltova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1722 (1963); *Chem. Abstr.*, **60**, 4985 (1964).
878. G. V. Karpukhin, Z. K. Laizus, and L. Matienko, *Nefte-Khimiya*, 603 (1966).
879. L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **84**, 1629 (1962).
880. M. Kulka and R. F. H. Manske, *J. Am. Chem. Soc.*, **75**, 1322 (1953).
881. H. J. Teuber, H. Krause, and V. Beriaru, *Liebigs Ann. Chem.*, 757 (1978).
882. T. Matura, T. Nagamachi, and A. Nishinaga, *J. Med. Chem.*, **11**, 899 (1968).
883. B. Hegedus and P. Zeller, French Patent 1,555,764 (1969); *Chem. Abstr.*, **72**, 121933 (1970).
884. T. Matura, T. Nagamachi, and A. Nishinaga, *Chem. Pharm. Bull. (Tokyo)*, **17**, 2176 (1969).
885. W. I. Awad and A. I. Hashem, *Egypt J. Chem.*, **16**, 287 (1973); *Chem. Abstr.*, **81**, 151877q (1974).
886. H. Muxfeldt and R. S. Schneider, *J. Org. Chem.*, **33**, 1645 (1968); H. Muxfeldt, J. Behling, G. Grethe, and W. Rogalski, *J. Am. Chem. Soc.*, **89**, 4991 (1967).
887. K. H. Boltze, E. Etschenberg, W. Opitz, S. Raddatz, and D. Vollbrecht, *Ger. Offen.* 2,659,543 (1978); *Chem. Abstr.*, **89**, 179979p (1978).
888. L. Horner, *Ann.*, **548**, 117 (1941).
889. S. V. Krivun, USSR Patent 410,016 (1974); *Chem. Abstr.*, **80**, 12090 (1974).
- 890a. S. V. Krivun, *Dopv. Akad. Nauk RSR, Ser. B.*, **36**, 717 (1974); *Chem. Abstr.*, **81**, 169463 (1974).
- 890b. S. V. Krivun, *Khim. Geterosikl. Soedin*, 757 (1976); S. V. Krivun, *Khim. Geterosikl.*, 764 (1976); *Chem. Abstr.*, **85**, 12380s (1976).
891. S. V. Krivun, *Dopv. Akad. Nauk Ukr RSR Ser. B*, **36**, 717 (1974); *Chem. Abstr.*, **81**, 169463 (1974).
892. K. T. Sukita, *J. Pharm. Soc. Jap.*, **69**, 102 (1949).
893. H. Pracejus, F. W. Wilcke, and K. Hanemann, *J. Prakt. Chem.*, **319**, 329 (1977).
894. Y. V. Haverbeke, A. Maquestiau, R. N. Muller, J. J. Vanden Eynde, T. Zeeger-Huyskens, J. B. Rulinda, G. LeRoy, and G. Louterman Le Loup, *Bull. Soc. Chim. Belg.*, **84**, 845 (1975).
895. G. Just, B. Y. Chung, S. Kim, G. Rosebery, and P. Russy, *Can. J. Chem.*, **54**, 2089 (1976).
896. O. V. Kildisheva, M. Linkova, and I. L. Knunyants, *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk*, 282 (1955).
897. B. S. Drach and G. N. Miskevich, *Zh. Org. Chem.*, **10**, 2315 (1974).
898. B. S. Drach, A. P. Martynyuk and G. N. Miskevich, *Zh. Org. Khim.*, **12**, 2238 (1976); *Chem. Abstr.*, **86**, 72500 (1977).
899. B. S. Drach and G. N. Miskevich, *Zh. Org. Khim.*, **14**, 943 (1978); *Chem. Abstr.*, **89**, 146835 (1978).

900. A. H. Livermore, F. H. Carpenter, R. W. Holley, and V. DuVigneaud, *J. Biol. Chem.*, **175**, 721 (1948).
901. G. Maslova and I. T. Strukov, *Zh. Org. Khim.*, **1**, 348 (1965).
902. Merck & Co., Netherlands Patent 6,513,581 (1966); *Chem. Abstr.*, **65**, 15499 (1966).
903. I. L. Finar and K. E. Godfrey, *J. Chem. Soc.*, 2293 (1954).
904. A. A. Evans and W. Bradley, British Patent 584,736 (1947); *Chem. Abstr.*, **42**, 4517 (1947).
905. A. Maquestiau, Y. Van Haverbeke, J. C. VanOvervelt, and R. Postiaux, *Bull. Chim. Soc. Belg.*, **85**, 697 (1976).
- 906a. I. Kalnin, I. E. Khatskevich, USSR Patent 529,154 (1976); *Chem. Abstr.*, **86**, 43418 (1976).
- 906b. I. Kalnin and I. E. Khatskevich, USSR Patent 536,162 (1976); *Chem. Abstr.*, **87**, 22802 (1977).
907. S. Futagawa, M. Nakahara, T. Inui, H. Katsura, and T. Kaneko, *Nippon Kagaku Zasshi*, **92**, 374 (1971).
908. H. J. Barber, R. Slack, and C. E. Stickings, British Patent 585,145 (1947); *Chem. Abstr.*, **41**, 4516 (1947).
909. S. A. Safir, S. Bernstein, B. R. Baker, W. L. McEwen, and Y. Subbarow, *J. Org. Chem.*, **12**, 475 (1947).
910. S. A. Safir, S. Bernstein, and B. R. Baker, U.S. Patent 2,431,967 (1947); *Chem. Abstr.*, **42**, 1962 (1948).
911. H. Urbach, H. Hartung, W. Martin, and W. Durckheimer, *Tet. Lett.*, 4907 (1973).
912. H. Muxfeldt and W. T. Rogalski, *J. Am. Chem. Soc.*, **87**, 933 (1965).
913. H. Muxfeldt, U.S. Patent 3,914,299 (1975); *Chem. Abstr.*, **84**, 3076s (1976).
914. W. Rogalski, Ger. Offen, 2,543,22 (1975); *Chem. Abstr.*, **84**, 89902 (1976).
915. W. Martin, H. Hartung, H. Urbach, and W. Durckheimer, *Tet. Lett.*, 3513 (1973).
916. J. Gante, W. Mehrhof, and A. Wild, Ger. Offen. 2,245,940 (1974); *Chem. Abstr.*, **81**, 25683 (1974).
917. V. Tamas and C. Bodea, *Rev. Roum. Chimie*, **19**, 701 (1974).
918. O. Shimomura and S. Eguchi, *Nippon Kagaku Zasshi*, **81**, 1434 (1960).
919. S. Kukloja, R. D. G. Cooper, and R. B. Morin, *Tet. Lett.*, 3381 (1969).
920. S. P. Kukloja and R. B. Morin, U.S. Patent 3,758,488 (1973); *Chem. Abstr.*, **79**, 126487 (1973).
921. C. J. Veal and D. W. Young, *Tet. Lett.*, 2985 (1976).
922. E. M. Rokhlin, N. P. Gambaryan, and I. L. Knunyants, *Izv. Akad. Nauk SSSR Otdel. Khim.*, 1952 (1963).
923. T. Wieland and V. Georgi, *Ann.*, **700**, 133 (1966).
924. M. A. Rakshinda and N. H. Khan, *Ind. J. Chem.*, **16B**, 634 (1978).
925. M. Miyamoto, H. Ohshio, and T. Matsuo, Japan Patent 74,04,332 (1974); *Chem. Abstr.*, **81**, 63477 (1974).
926. J. C. Sheehan and C. A. Robinson, *J. Am. Chem. Soc.*, **71**, 1436 (1949).
927. F. Hucbenett, F. H. Block, W. Hansel, H. Heinze, and H. Hoffman, *Angew. Chem.*, **75**, 1189 (1963).
928. R. Huttel, T. Schneiderahn, H. Hertwig, A. Leuchs, V. Reincke, and J. Muller, *Ann.*, **585**, 115 (1954).
929. H. Bursock, C. L. Deasy, A. J. Haagen-Smit, G. Keighley, and P. H. Lowy, *J. Biol. Chem.*, **196**, 669 (1952).

931. W. Herz and J. Brasch, *J. Org. Chem.*, **23**, 1513 (1958).
932. T. Sasaki, *Pharm. Bull. (Japan)*, **2**, 123 (1954); *Chem. Abstr.*, **50**, 972 (1956).
933. O. P. Singhal and P. I. Ittyerah, *J. Ind. Chem. Soc.*, **42**, 579 (1965).
934. B. M. DeMalleray, *Helv. Chim. Acta*, **54**, 351 (1971).
935. P. Fournair and J. P. Chane, *Bull. Soc. Chim. France*, 484 (1964).
936. C. Y. Yuan, C. N. Chang, and I. Yeh, *Tao Hsueh Hsueh Pao*, **7**, 237 (1950); *Chem. Abstr.*, **54**, 12096 (1960).
937. Y. K. Yurev, N. N. Magdesieva, and A. T. Monakhova, *Khim. Geterosikl. Soedin.*, **4**, 645 (1968).
938. Y. K. Yurev, N. N. Mezentsova, and A. T. Balashova, *Zh. Obshch. Khim.*, **27**, 2536 (1957).
939. Y. K. Yurev, N. N. Mezentsova, and A. T. Monakhova, *Zh. Obshch. Khim.*, **30**, 1726 (1960).
940. A. N. Kost, L. F. Morozova, and P. T. Grandsberg, *Zh. Org. Khim.*, **1**, 739 (1965).
941. K. Maekawa, *Sci. Reports Matsuyama Agr. College*, **3**, 113 (1950); *Chem. Abstr.*, **46**, 4524 (1952).
942. M. Lacova, and P. Hrnica, *Coll. Czech. Chem. Commun.*, 281 (1977).
943. E. Otazo, L. Cordova, and V. Pustovarov, *Sobre Dev. Ir. Cana Azucar*, **10**, 20 (1976); *Chem. Abstr.*, **87**, 68208a (1977).
944. Z. N. Nazorova, V. N. Novikov, and V. M. Strovakov, *Zh. Org. Khim.*, **2**, 161 (1966).
945. B. F. Crowe and F. F. Nord., *J. Org. Chem.*, **15**, 1177 (1950).
946. L. H. Klemm and R. H. Merrill, *J. Het. Chem.*, **11**, 355 (1974).
947. L. Proinov, *Farmacia (Bucharest)*, **20**, 553 (1972); *Chem. Abstr.*, **78**, 147901 (1973).
948. W. Ried and H. Bender, *Chem. Ber.*, **88**, 34 (1955).
949. O. P. Shkurko and V. P. Mamaev, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, **2**, 112 (1967); *Chem. Abstr.*, **69**, 27209 (1968).
950. V. A. Azimov, M. Y. Uritskaya, and L. N. Yakhontov, *Khim. Farm. Zh.*, **2**, 16 (1968); *Chem. Abstr.*, **70**, 7834 (1969).
951. T. Matura, K. Matsui, and K. I. Chirahara, *Med. J. Osaka Univ.*, **4**, 449 (1954); *Chem. Abstr.*, **49**, 6222 (1955).
952. D. M. Griffin and P. M. Dean, *J. Am. Chem. Soc.*, **67**, 1231 (1945).
953. E. Dyer and W. Yokoyama, *J. Org. Chem.*, **26**, 2124 (1961).
954. I. Smiti and A. Silberg, *Omaigu Raluca Ripon*, 533 (1966); *Chem. Abstr.*, **68**, 12891 (1968).
955. A. Silberg, E. Hamburg, Z. Frankel, and L. Cormos, *Rev. Roum. Chim.*, **9**, 218 (1964).
956. B. Sila, J. Wotjanis, and T. Lesiak, *Rocz. Chem.*, **47**, 128 (1973).
957. B. Sila, *Rocz. Chem.*, **38**, 1387 (1964).
958. R. T. Foster, A. Robertson, H. Bushra, J. B. D. McKenzie, and T. V. Healey, *J. Chem. Soc.*, 2254 (1948).
959. K. M. Jainamma and S. Sethna, *J. Ind. Chem. Soc.*, **50**, 606 (1973).
960. A. M. Simovov, V. A. Anisimova, and L. E. Grushina, *Khim. Geterosikl. Soedin.*, 838 (1970); *Chem. Abstr.*, **73**, 109739 (1970).
961. L. K. Vinograd and N. K. Suvorov, *Khim. Geterosikl. Soedin.*, 1233 (1974); *Chem. Abstr.*, **82**, 43126 (1975).
962. F. H. Johnson, H. D. Stachel, E. C. Taylor, and O. Shimamura, *Biolumin. Progress Proc.*, **67**, (1965); *Chem. Abstr.*, **67**, 53974 (1967).
963. E. K. Stillier, U.S. Patent 2,380,479 (1945); *Chem. Abstr.*, **40**, 367 (1946).

964. I. Ito, *J. Pharm. Soc. Jap.*, **76**, 167 (1956).
965. J. Fernandez-Bolanos, J. R. Cruz, and F. G. Gonzalez, *Anales Real. Soc. Espan. Fis Y Quim.*, **47B**, 737 (1951).
966. V. Farcasan, I. Oprean, and C. Bodea, *Rev. Roum. Chim.*, **13**, 647 (1968).
967. F. M. Dean, C. A. Evans, T. Francis, and R. Robertson, *J. Chem. Soc.*, 1577 (1957).
968. L. B. Radina and Z. V. Pushkaraeva, *Zh. Obshch. Khim.*, **31**, 2362 (1961).
969. L. N. Yakhontov and M. V. Rubtov, *Khim. Geterosikl. Soedin.*, 141 (1967).
970. K. Fitzi and A. Sallmann, Swiss Patent 509,317 (1971); *Chem. Abstr.*, **76**, 14371c (1972).
971. N. V. Mani and S. Sethna, *J. Inst. Chem. (Calcutta)*, **46**, 61 (1974); *Chem. Abstr.*, **82**, 9791 (1975).
972. S. G. Patel and S. Sethna, *J. Ind. Chem. Soc.*, **50**, 295 (1973).
973. A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph, *J. Chem. Soc.*, 3388 (1959).
974. P. L. Trakhtenberg and A. E. Lipkin, *Khim. Geterosikl. Soedin.*, 61 (1974).
975. S. V. Lepikhova and G. T. Pilyugin, *Zh. Obshch. Khim.*, **38**, 2399 (1968).
976. P. Bite and E. Diszler, *Acta Chim. Hung.*, **71**, 121 (1972).
977. G. Casnati, R. Cavalleri, F. Piozzi, and A. Quilico, *Gazz. Chim. Ital.*, **90**, 105 (1962).
978. I. T. Strukov, *Zh. Obshch. Khim.*, **22**, 1869 (1952).
979. E. Yamato and K. Okamura, Jap. Kokai 75,58,063 (1975); *Chem. Abstr.*, **83**, 19307 (1971).
980. J. P. Wibaut, H. P. Wallingford, H. J. Rang, and D. K. Kettenes, *Rec. Trav. Chim.*, **74**, 1049 (1955).
981. R. G. Glushkov and O. Y. Magidson, *Zh. Obshch. Khim.*, **30**, 1855 (1960).
982. G. Manecke and J. Klawitter, *Makromol Chem.*, **175**, 3383 (1973).
983. S. V. Lepikhova and G. T. Pilyugin, *Zh. Obshch. Khim.*, **38**, 2399 (1968).
984. R. Bentley, A. H. Cook, and J. A. E. Elvidge, *J. Chem. Soc.*, 3216 (1949).
985. R. A. Jeffreys, *J. Chem. Soc.*, 1991 (1956).
986. H. J. Waddington, G. D. Duffin, and J. D. Kendall, British Patent 785,334 (1957); *Chem. Abstr.*, **52**, 6031 (1958).
987. H. T. Clarke, J. R. Johnson, and R. Robinson, Eds., *The Chemistry of Penicillin*, Princeton University Press, Princeton, N.J., 1949.
988. J. W. Cornforth, in *Heterocyclic Compounds*, R. C. Elderfield, Ed., Vol. V, Wiley, New York, 1957, pp. 336–377.
989. R. Filler, *Adv. Heter. Chem.*, **4**, 75–106 (1965).
990. W. Steglich, *Fortschr. Chem. Forsch.*, **12**, 77–118 (1969).
991. R. Filler and Y. S. Rao, *Adv. Heter. Chem.*, **21**, 175–206 (1977).
992. Y. Iwakura, F. Toda, and Y. Torri, *Progr. Polym. Sci. Jap.*, **4**, 73 (1972); *Chem. Abstr.*, **78**, 30235h (1973).
993. G. V. Boyd, *Comprehensive Heterocyclic Chemistry*, Vol. 6, A. R. Katritzky, C. W. Rees, and K. T. Potts, Eds. Pergamon Press, N.Y., 1984, p. 177.
994. Y. Iwakura, *Yuki Gosei Kagaku Shi*, **26**, 479 (1968); *Chem. Abstr.*, **69**, 67253 (1968).
995. M. Bergmann and F. Stern, *Ann.*, **488**, 20 (1926).
996. I. L. Knunyants and V. V. Shokina, *Izv. Akad. Nauk. SSSR Otd. Khim. Naul.*, 409 (1955), English trans.
997. J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.*, **72**, 833 (1954).

998. F. Weygand and U. Glocker, *Chem. Ber.*, **89**, 653 (1956).
- 999a. F. Weygand and W. Steglich, *Angew. Chem.*, **73**, 433 (1961).
- 999b. F. Weygand, W. Steglich, D. Mayer, and W. von Philipsborn, *Chem. Ber.*, **97**, 2033 (1964).
1000. R. Filler and E. J. Piasek, *J. Org. Chem.*, **28**, 22 (1963).
1001. R. Filler and E. J. Piasek, *J. Org. Chem.*, **29**, 2205 (1964).
1002. G. Adembri, *Ann. Chimica* (Rome), **50**, 374 (1960); *Chem. Abstr.*, **66**, 38209a (1967).
1003. G. Lucente, C. Gallina, and A. Romeo, *Ann. Chimica* (Rome), **56**, 1192 (1966); *Chem. Abstr.*, **66**, 38209a (1967).
1004. E. G. Breitholle and C. H. Stammer, *J. Org. Chem.*, **39**, 1311 (1974).
1005. W. Steglich and R. Hurnaus, *Tetrahedron Lett.*, 383 (1966).
1006. W. Steglich, H. Tanner, and R. Hurnaus, *Chem. Ber.*, **100**, 1824 (1967).
1007. Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron Lett.*, 4427 (1966).
1008. Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron*, **23**, 3363 (1967).
1009. Y. Iwakura, F. Toda, and Y. Torii, *J. Org. Chem.*, **31**, 2875 (1969).
1010. Y. Iwakura, F. Toda, and Y. Torii, *Bull. Chem. Soc. Jap.*, **40**, 149 (1967).
1011. A. Padwa and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **96**, 2414 (1974).
1012. H. Glezendanner, M. Marky, B. Jackson, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 745 (1972).
1013. A. Orahovats, B. Jackson, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **56**, 2007 (1973).
1014. W. Sieber, P. Gilgen, S. Chaloupka, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 1673 (1973).
1015. N. Gakis, M. Marky, H. J. Hansen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **59**, 2148 (1976).
1016. A. Padwa, M. Akiba, L. A. Cohen, and J. G. MacDonald, *Tetrahedron Lett.*, **22**, 1435 (1981).
1017. A. Padwa, M. Akiba, L. A. Cohen, and J. B. MacDonald, *J. Org. Chem.*, **48**, 695 (1983).
1018. A. Padwa and S. I. Wetmore, Jr., *Org. Photochem. Synth.*, **2**, 87 (1976); *Chem. Abstr.*, **87**, 22932d (1977).
1019. M. Pinza, G. Pifferi, and F. Nasi, *Synthesis*, 55 (1980).
1020. S. Weber, H. L. Slates, and N. J. Wendler, *J. Org. Chem.*, **32**, 1668 (1967).
1021. G. I. Schukin, I. A. Grigorev, and L. B. Volodarski, *Izv. Akad. Nauk. SSSR Ser. Khim.*, 158 (1981); *Chem. Abstr.*, **95**, 1877150a (1981).
1022. R. J. Stoodley and R. B. Wilkins, *J.C.S. Chem. Commun.*, 796 (1974).
1023. R. J. Stoodley and R. B. Wilkins, *J. Chem. Soc. Perkin I*, 746 (1975).
1024. K. Burger and M. Eggersdorfer, *Liebigs Ann. Chem.*, 1547 (1979).
1025. G. Höfle and W. Steglich, *Liebigs Ann. Chem.* **104**, 1408 (1971).
1026. W. Steglich and G. Höfle, *Liebigs Ann. Chem.* **102**, 899 (1969).
1027. W. Steglich and G. Höfle, *Liebigs Ann. Chem.* **102**, 1129 (1969).
1028. W. Steglich and V. Austel, *Angew. Chem. Int. Ed.*, **6**, 184 (1967).
1029. W. Steglich and V. Austel, *Chem. Ber.*, **100**, 547 (1967).
1030. V. Austel and W. Steglich, *Chem. Ber.*, **108**, 2361 (1975).
1031. W. Steglich, V. Austel, and H. Tanner, *Chem. Ber.*, **101**, 916 (1968).
1032. F. Weygand, W. Steglich, and W. Oettmeier, *Chem. Ber.*, **103**, 818 (1970).

1033. W. Steglich, E. Frauendorfer, and F. Weygand, *Chem. Ber.*, **104**, 687 (1971).
1034. J. Leyendecker, U. Niewohner, and W. Steglich, *Tetrahedron Lett.*, **24**, 2375 (1983).
1035. N. Engel, B. Kubel, and W. Steglich, *Angew. Chem. Int. Ed.*, **16**, 394 (1977).
1036. V. Niewohner and W. Steglich, *Angew. Chem.*, **93**, 411 (1981).
1047. B. Kubel, G. Höfle, and W. Steglich, *Angew. Chem. Int. Ed.*, **14**, 58 (1975).
1038. H. Wegmann and W. Steglich, *Chem. Ber.*, **114**, 1580 (1981).
1039. W. Steglich, P. Gruber, G. Höfle, and W. König, *Angew. Chem. Int. Ed.*, **10**, 653 (1971).
1040. W. Steglich and P. Gruber, *Angew. Chem. Int. Ed.*, **10**, 655 (1971).
1041. E. J. Piasek, Ph.D. thesis, Illinois Institute of Technology, Chicago (1962).
1042. Y. Iwakura, F. Toda, Y. Torii, and K. Tomioka, *Tetrahedron Lett.*, 5461 (1966).
1043. Y. Iwakura, F. Toda, Y. Torii, and K. Tomioka, *Tetrahedron*, **24**, 575 (1968).
1044. A. Mustafa, M. K. Hilmy, A. E. Sammour, and M. M. N. El Deen, *Tetrahedron*, **20**, 1063 (1964).
1045. Y. Iwakura, F. Toda, and Y. Torii, *J. Org. Chem.*, **33**, 2541 (1968).
1046. A. Mustafa, A. E. Sammour, M. M. Noureideen, T. Salama, and M. K. Hilmy, *Ann.*, **689**, 189 (1965).
1047. Y. Iwakura, F. Toda, and Y. Torii, Japanese Patent 70,04,489h (1970); *Chem. Abstr.*, **73**, 14509s (1970).
1048. Y. Iwakura, F. Toda, and Y. Torii, *J. Org. Chem.*, **32**, 3202 (1967).
1049. G. Adembri, M. Scotton, and P. Tedeschi, *Chim. Ind. (Rome)*, **48**, 1346 (1966).
1050. G. Adembri, M. Scotton, G. Speroni, and P. Tedeschi, *Gazz. Chim. Ital.*, **103**, 3 (1973).
1051. G. Adembri, M. Scotton, and P. Tedeschi, *Gazz. Chim. Ital.*, **109**, 121 (1979).
1052. Y. Iwakura, F. Toda, and Y. Torii, Japan Patent 71,25,380 (1971); *Chem. Abstr.*, **75**, 140677z (1971).
1053. Y. Iwakura, F. Toda, and Y. Torii, Japan Patent 71,15,382 (1971); *Chem. Abstr.*, **75**, 140680v (1971).
1054. H. Katsuki, F. Toda, S. Matsukawa, and K. Horie, *Polymer. Prepr. ACS Polymer Div.*, **20**, 664 (1979); *Chem. Abstr.*, **94**, 121994b (1981).
1055. Y. Iwakura, F. Toda, and Y. Torii, *J. Polym. Sci. Polym. Lett.*, **16**, 635 (1978).
1056. Y. Iwakura, F. Toda, M. Kosuigi, and Y. Torii, *J. Polym. Sci.*, (Part A-1) **9**, 2423 (1971).
1057. Y. Iwakura, F. Toda, and Y. Torii, Japan Patent 69,29,666 (1969); *Chem. Abstr.*, **72**, 67520z (1970).
1058. Y. Iwakura, F. Toda, and Y. Torii, Japan Patent 70,04,489 (1970); *Chem. Abstr.*, **73**, 14509s (1970).
1059. Y. Iwakura, F. Toda, and Y. Torii, *J. Polym. Sci.*, **6**, 1876 (1968).
1060. Y. Iwakura, F. Toda, and Y. Torii, *J. Polym. Sci.*, **9**, 2423 (1971).
1061. H. Katsuki, K. Shinooka, H. Mori, Y. Kawaguchi, M. Hagesao, and F. Toda, *Proc. IUPAC; Iupac 28th Macromol. Symp.*, 173 (1982); *Chem. Abstr.*, **99**, 12303a (1983).
1062. G. Adembri, F. M. Carlini, P. Sarti-Fantoni, and M. Scotton, *Tetrahedron Lett.*, 3347 (1972).
1063. R. Filler, B. S. Green, and L. Heller, unpublished results.
1064. F. Weygand, W. Steglich, and H. Tanner, *Ann.*, **658**, 128 (1962).
1065. F. Weygand and B. Spiess, *Chem. Ber.* **97**, 3456 (1964).
1066. P. Gruber, L. Müller, and W. Steglich, *Chem. Ber.*, **106**, 1863 (1973).

1067. W. Steglich, B. Kubel, and P. Gruber, *Chem. Ber.*, **106**, 2870 (1973).
1068. N. Engel, J. Fischer, and W. Steglich, *J. Chem. Res. S. (Synopsis)*, 162 (1977); *Chem. Abstr.*, **87**, 151970p (1977).
1069. H. H. Bestermann, K. P. Netsch, and C. Wentrup, *J. Chem. Soc. Chem. Commun.*, 503 (1980).
1070. J. Fischer and W. Steglich, *Angew. Chem. Int. Ed.*, **18**, 167 (1979).
1071. W. Steglich, P. Gruber, H. U. Heininger, and F. Kneidl, *Chem. Ber.*, **104**, 3816 (1971).
1072. G. Schulz and W. Steglich, *Chem. Ber.*, **113**, 770 (1980).
1073. A. Padwa, M. Akiba, L. A. Cohen, and J. G. MacDonald, *J. Am. Chem. Soc.*, **104**, 286 (1982).
1074. R. Moller, N. Engel, and W. Steglich, *Synthesis*, 620 (1978).
1075. G. Schulz and W. Steglich, *Chem. Ber.*, **113**, 787 (1980).
1076. V. Ferrito, R. Borg, J. Eagles, and G. R. Fenwick, *Biomed. Mass Spectrom.*, **6**, 499 (1979); *Chem. Abstr.*, **93**, 8478c (1980).
1077. Y. Iwakura, F. Toda, M. Kosugi, and Y. Torii, *J. Org. Chem.*, **36**, 3990 (1971).
1078. I. Tomida, S. Senda, T. Kuwabara, and K. Katayama, *Agr. Biol. Chem.*, **40**, 2033 (1976); *Chem. Abstr.*, **86**, 121751e (1977).
1079. E. G. Breitholle and C. H. Stammer, *J. Org. Chem.*, **41**, 1344 (1977).
1080. E. G. Breitholle and C. H. Stammer, *Tet. Letters*, 2381 (1975).
1081. W. Steglich and V. Austel, *Angew. Chem. Int. Ed.*, **6**, 184 (1967).
1082. V. Austel and W. Steglich, *Chem. Ber.*, **108**, 2361 (1975).
1083. A. Orahovats, H. Heimgartner, H. Schmid, and W. Heinzelman, *Helv. Chem. Acta*, **57**, 2626 (1974).
1084. W. Steglich, G. Hofle, W. Konig, and F. Weygand, *Chem. Ber.*, **101**, 308 (1968).
1085. F. Weygand, A. Prox, L. Schmidhammer, and W. Konig, *Angew. Chem. Int. Ed.*, **2**, 183 (1963).
1086. S. Gotze and W. Steglich, *Chem. Ber.*, **109**, 2995 (1976).
1087. F. R. Japp and A. Findlay, *J. Chem. Soc.*, **75**, 1028 (1899).
1088. C. W. Bird, *J. Org. Chem.*, **27**, 4091 (1962).
1089. K. Hohenlohe-Oehringen, *Monatsh. Chem.*, **89**, 588 (1958).
1090. W. Traube and R. Asher, *Chem. Ber.*, **46**, 2077 (1913).
1091. C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1679 (1962).
1092. C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1686 (1962).
1093. C. F. Howell, W. Fulmor, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **29**, 370 (1964).
1094. G. Rapi, M. Ginanneschi, E. Belgodere, and M. Chelli, *J. Het. Chem.*, **9**, 285 (1972).
1095. H. Najer, R. Giudicelli, and J. Menin, *Bull. Soc. Chim. France*, 1810 (1963).
1096. H. Najer, R. Giudicelli, J. Menin, and N. Voronine, *Bull. Soc. Chim. France*, 207 (1967).
1097. H. Najer, R. Giudicelli, E. Joannic-Voisinet, and M. Joannic, *Bull. Soc. Chim. France*, 1226 (1961).
1098. H. Najer and R. Giudicelli, *Bull. Soc. Chim. France*, 1231 (1961).
1099. H. Najer, R. Giudicelli, J. Menin, and J. Loiseau, *C. R. Acad. Sci.*, **254**, 2173 (1962); *C. R. Acad. Sci.*, **254**, 2591 (1962).
1100. H. Najer, R. Giudicelli, J. Menin, and J. Loiseau, *Bull. Soc. Chim. France*, 1186 (1962).

1101. H. Najer, R. Giudicelli, J. Menin, and J. Loiseau, *Bull. Soc. Chim. France*, 1186 (1962).
1102. R. Giudicelli, H. Najer, M. Prouteau, and M. Sarret, *C.R. Acad. Sci.*, **254**, 2862 (1962).
1103. J. F. Giudicelli, J. Menin, and H. Najer, *Bull. Soc. Chim. France*, 1099 (1968).
1104. J. F. Giudicelli, J. Menin, and H. Najer, *Bull. Soc. Chim. France*, 874 (1969).
1105. A. T. Dren and R. S. Janicki, *Pharmacol. Biochem. Prep. Drug Subst.*, **1**, 33 (1977); *Chem. Abstr.*, **88**, 163489x (1978).
1106. C. M. Lee, B. W. Horrom, R. J. Michaels, R. M. Rasmussen, and N. P. Plotnikoff, *J. Med. Chem.*, **15**, 1252 (1972).
1107. C. M. Lee and N. P. Plotnikoff, *J. Med. Chem.*, **19**, 731 (1976).
1108. T. R. Herrin, J. M. Pauvlik, E. V. Schuber, and A. O. Geiszcler, *J. Med. Chem.*, **18**, 1216 (1975).
1109. S. M. Ramsh, N. G. Zheltonog, L. P. Shamina, Y. G. Basova, and A. I. Ginak, *Khim. Geterosikl. Soedin*, 601 (1983); *Chem. Abstr.*, **99**, 122373p (1983).
1110. U. H. Lindberg and J. Pedersen, *Acta Pharm. Suecia* **5**, 15 (1968); *Chem. Abstr.*, **84**, 52050k (1968).
1111. U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *J. Am. Chem. Soc.*, **93**, 3028 (1971).
1112. T. H. Chan and R. K. Hill, *J. Org. Chem.*, **35**, 3519 (1970).
1113. M. N. Preobrazhenskaya, E. G. Balashova, K. F. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, *Tetrahedron*, **24**, 6131 (1968).
1114. J. C. Sheehan and P. T. Izzo, *J. Am. Chem. Soc.*, **71**, 4059 (1949).
1115. Y. S. Rao and R. Filler, *Chem. Commun.*, 1622 (1970).
1116. E. J. Brown, E. E. Nunn, and J. B. Polya, *J. Chem. Soc. (C)*, 1515 (1970).
1117. K. T. Potts and J. Marshall, *J. Chem. Soc. Chem. Commun.*, 1000 (1972).
1118. K. T. Potts and J. Marshall, *J. Org. Chem.*, **44**, 626 (1979).
1119. R. Neidlein and R. Bottler, *Chem. Ber.*, **100**, 698 (1967).
1120. R. E. Mosalyk, A. L. C. Mak, L. G. Chatten, and R. A. Locock, *J. Pharm. Sci.*, **70**, 496 (1981).
1121. R. Neidlein, *Chem. Ber.*, **97**, 3476 (1964).
1122. R. Neidlein, *Angew. Chem. Int. Ed.*, **3**, 652 (1964).
1123. R. Neidlein, *Arch. Pharm.*, **298**, 125 (1965).
1124. R. Neidlein and H. Krull, *Arch. Pharm.*, **304**, 749 (1971).
1125. F. Ramirez and C. D. Telefus, *J. Org. Chem.*, **34**, 376 (1969).
1126. F. Ramirez, *Synthesis*, 103 (1974).
1127. F. Ramirez, C. D. Telefus, and V. A. V. Prasad, *Tetrahedron*, **31**, 2007 (1975).
1128. R. Neidlein and R. Mosebach, *Arch. Pharm.*, **309**, 707 (1976).
1129. M. Regitz, B. Weber, and A. Heydt, *Liebig's Ann. Chem.*, 305 (1980).
1130. O. Tsuge, K. Sakai, and M. Tashiro, *Tetrahedron*, **29**, 1984 (1973).
1131. D. M. Ketcha, M. Abou-Gharbia, F. X. Smith, and D. Swern, *Tet. Lett.*, **24**, 2811 (1983).
1132. Y. Tomimatsu, K. Satoh, and M. Sakamoto, *Heterocycl.*, **8**, 109 (1977).
- 1133a. J. B. Polya and T. M. Spotswood, *Rec. Trav. Chim. Pays. Bas.*, **67**, 927 (1948).
- 1133b. E. Koltai and K. Lempert, *Tetrahedron*, **29**, 1795 (1973).
1134. T. H. Koch, and R. M. Rodehorst, *Tet. Lett.*, 4039 (1972).
1135. R. M. Rodehorst and T. H. Koch, *J. Am. Chem. Soc.*, **97**, 7298 (1975).

1136. A. J. Gordon and R. Lavalley, Abstracts of Papers 106th National Meeting of ACS, Chicago, Illinois, Sept. 1970.
1137. I. V. Smolanka, S. M. Khripak, and V. I. Staninets, *Ukr. Khim. Zh.*, **30**, 265 (1964); *Chem. Abstr.*, **60**, 15590h (1964).
1138. S. M. Khripak, I. V. Smolanka, and V. I. Staninets, *Ukr. Khim. Zh.*, **30**, 618 (1964); *Chem. Abstr.*, **61**, 9485g (1964).
1139. I. V. Smolanka, S. M. Khripak, and V. I. Staninets, *Ukr. Khim. Zh.*, **30**, 950 (1964); *Chem. Abstr.*, **62**, 2770d (1965).
1140. I. V. Smolanka, S. M. Khripak, and V. I. Staninets, *Ukr. Khim. Zh.*, **32**, 48 (1966); *Chem. Abstr.*, **64**, 19588y (1966).
1141. I. V. Smolanka, S. M. Khripak, and V. I. Staninets, *Ukr. Khim. Zh.*, **32**, 202 (1966); *Chem. Abstr.*, **64**, 15863c (1966).
1142. I. V. Smolanka, S. M. Khripak, V. I. Staninets, and V. S. Petrus, *Fiziol. Aktiv Veshchestva, Akad. Nauk. Ukr SSR. Respub. Mezhvedom*, 31 (1966); *Chem. Abstr.*, **67**, 64286p (1967).
1143. A. T. Balaban, A. Bota, G. N. Dorofeenko, V. D. Karpenko, and Y. I. Ryabukhin, *Tetrahedron*, **34**, 2035 (1978).
1144. G. Bonse, G. Marzolph, and H. U. Blank, Ger. Offen. DE 3,115,970 (1982); *Chem. Abstr.*, **98**, 96395b (1983).
1145. Y. I. Ryubkhin, V. D. Karpenko, and G. N. Dorofeenko, *Zh. Org. Khim.*, **18**, 230 (1982).
1146. A. N. Dorofeenko, V. D. Karpenko, and Y. I. Ryubkhin, *Khim. Geterosikl. Soedin.*, 702 (1977).
1147. Y. I. Ryubkhin, L. N. Faleeva, and G. N. Dorofeenko, *Khim. Geterosikl. Soedin.*, 1423 (1981).
1148. G. N. Dorofeenko, V. D. Karpenko, and Y. I. Ryubkhin, *Khim. Geterosikl. Soedin.*, 1905 (1978).
1149. T. P. Kosulina, Z. I. Zelikman, and V. G. Kulnevich, *Zh. Org. Khim.*, **12**, 1134 (1976).
1150. V. G. Kulnevich, T. P. Kosulina, F. Luebke, and Z. I. Zelikman, *Khim. Geterosikl. Soedin.*, 30 (1980).
1151. R. A. Slavinskaya, *Zh. Obsch. Khim.*, **50**, 126 (1980).
1152. N. A. Shenberg, L. S. Guseva, A. I. Ginak, and E. G. Sochilin, *Zh. Org. Khim.*, **14**, 1323 (1978).
1153. F. Troxler, *Helv. Chim. Acta.*, **56**, 1813 (1973).
1154. J. Sander, G. Buhr, and H. Ruckert, Ger. Offen. 2,829,512 (1980); *Chem. Abstr.*, **92**, 197475z (1980).
1155. B. R. Neustadt and N. Zampaglione, Ger. Offen. 2,711,330 (1978); *Chem. Abstr.*, **88**, 6868c (1978).
1156. C. Maselli, *Gazz. Chim. Ital.*, **35**, II 91 (1905).
1157. H. McCombie and J. W. Parkes, *J. Chem. Soc.*, **101**, 1991 (1912).
1158. D. L. Pain and R. Slack, *J. Chem. Soc.*, 2529 (1951).
1159. H. McCombie and H. A. Scarborough, *J. Chem. Soc.*, 103 (1913).
1160. K. vonAuwers and H. Mauss, *Biochem. Z.*, **192**, 200 (1928).
1161. R. Gompper, *Chem. Ber.*, **89**, 1748 (1956).
1162. R. Gompper, *Chem. Ber.*, **89**, 1762 (1956).
1163. G. Destevens, *J. Org. Chem.*, **23**, 1572 (1958).
1164. R. Gompper and H. Herlinger, *Chem. Ber.*, **89**, 2816 (1956).

1165. R. Gompper and H. Herlinger, *Chem. Ber.*, **89**, 2825 (1956).
1166. F. Cramer and W. Krum, *Chem. Ber.*, **86**, 1586 (1953).
1167. Serna, A. G., Ger. Offen. 2,518,882 (1977); *Chem. Abstr.*, **86**, 55419z (1977).
1168. Serna, A. G., Ger. Offen. 2,428,249 (1973); *Chem. Abstr.*, **82**, 15626v (1975).
1169. R. Hefli, U.S. Patent 3,895,024 (1975); *Chem. Abstr.*, **84**, 4935r (1976).
1170. V. M. Dziomko and A. V. Ivashchenko, *Zh. Org. Khim.*, **9**, 2191 (1973).
1171. V. M. Dziomko and A. V. Ivashchenko, USSR Patent 414,262 (1974); *Chem. Abstr.*, **80**, 133412j (1974).
1172. V. M. Dziomko and A. V. Ivashchenko, USSR Patent 427,015 (1974); *Chem. Abstr.*, **80**, 77899e (1974).
1173. B. Singh, U.S. Patent 4,150,030 (1979); *Chem. Abstr.*, **94**, 74598b (1979).
1174. S. Handa, T. Ueda, Y. Tanaka, and J. Nishihata, Japan Kokai 77,97965 (1977); *Chem. Abstr.*, **88**, 105308b (1977).
1175. S. Handa, T. Ueda, Y. Tanaka, and J. Nishihata, Japan Kokai 77,97966 (1977); *Chem. Abstr.*, **88**, 136602x (1977).
1176. B. Krieg and P. Konieczny, *Liebig's Ann. Chem.*, 1861 (1976).
1177. O. P. Shvaika and G. P. Klinisha, *Dopov. Akad. Ukr. RSR Ser.*, B32350 (1970); *Chem. Abstr.*, 733533t (1970).
1178. G. Cum, N. Uccella, M. C. Aversa, and M. Gattuso, *Atti. Soci. Peloritana Sci. Fis. Mat. Natur.*, **14**, 425 (1968); *Chem. Abstr.*, **74**, 3235u (1971).
1179. K. Sisido, K. Hukuoka, M. Toda, and H. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962).
1180. P. J. Stoffel and W. D. Dixon, *J. Org. Chem.*, **29**, 978 (1964).
1181. I. Renvall, *Acta Acad. Abo., Math. Phys.*, **30(b)** (1970); *Chem. Abstr.*, **75**, 5764k (1971).
1182. H. Siegel and H. Wittmann, *Monat. Chem.*, **113**, 1005 (1982).
1183. D. C. England, *J. Org. Chem.*, **46**, 147 (1981).
1184. D. C. England, *J. Org. Chem.*, **46**, 153 (1981).
1185. J. M. Lemmens, W. W. J. M. Blommerde, L. Thijs, and B. Zwanenburg, *J. Org. Chem.*, **49**, 2231 (1984).
1186. H. Bredereck, G. Simchen, and E. Goknel, *Chem. Ber.*, **103**, 236 (1970).
1187. R. Reiner and C. H. Eugster, *Helv. Chim. Acta*, **50**, 128 (1967).
1188. C. H. Eugster, *Tetrahedron Lett.*, 1813 (1965).
1189. H. Fritz, A. R. Gagneux, R. Zbinden, *Tetrahedron Lett.*, 2075 (1965).
1190. A. R. Gagneux and R. Goschke, *Tetrahedron Lett.*, 5451 (1966).
1191. M. Nakagawa, T. Nakamura, and K. Tomita, *Agr. Biol. Chem.*, **38**, 2205 (1974).
1192. H. Goth, A. R. Gagneux, C. H. Eugster, and H. Schmid, *Helv. Chim. Acta*, **50**, 137 (1967).
1193. K. H. Scholz, W. Hartmann, and H. G. Heine, Ger. Offen. 2,610,676 (1976); *Chem. Abstr.*, **88**, 6860u (1976).
1194. K. H. Scholz, H. G. Heine, and W. Hartmann, *Liebig's Ann. Chem.*, 1319 (1976).
1195. K. Gewald, H. Schafer, and B. Plumbohm, *J. Prakt. Chemie*, **315**, 41 (1973).
1196a. H. Fukumi, K. Oohata, and K. Takada, *Heterocycles*, **12**, 1297 (1979).
1196b. K. Oohata, H. Fukumi, and K. Takada, Japan Kokai 76,11763 (1976); *Chem. Abstr.*, **85**, 32987y (1976).
1197. R. Huisgen and H. Blaschke, *Chem. Ber.*, **98**, 1985 (1965).
1198. F. DeSarlo and G. Renz, *J. Chem. Soc. Perkin I*, 1113 (1978).
1199. F. DeSarlo, *J. Chem. Soc. Perkin I*, 385 (1980).

1200. F. DeSarlo, A. Guarna, P. Mascagni, R. Carrie, and P. Guenot, *J. Chem. Soc. Perkin I*, 1367 (1981).
1201. J. Roy and K. N. Mehrotra, *Ind. J. Chem.*, **22B**, 78 (1983).
1202. H. Greenberg, T. van Es, and O. G. Backeberg, *J. Org. Chem.*, **32**, 2964 (1967).
1203. B. G. Chatterjee and D. P. Sahu, *Z. Naturforsch., B. Anorg. Chem., Org. Chem.*, **32B**, 200 (1977); *Chem. Abstr.*, **86**, 189777y (1977).
1204. F. Bottari, E. Nanniperi, M. F. Saettone, M. F. Serafini, and N. Tellini, *J. Med. Chem.*, **15**, 39 (1972).
1205. F. Bottari, M. F. Saettone, M. F. Searfini, and N. Tellini, *Farmaco Ed. Sci.*, **24**, 672 (1969); *Chem. Abstr.*, **71**, 70524b (1969).
1206. F. Bottari, M. F. Saettoni, N. Tellini, and M. F. Serafini, Ger. Offen. 2,205,676 (1972); *Chem. Abstr.*, **77**, 140025b (1972).
1207. J. C. Sheehan and F. S. Guziec, *J. Am. Chem. Soc.*, **94**, 6561 (1972).
1208. J. C. Sheehan and F. S. Guziec, *J. Org. Chem.*, **38**, 3034 (1973).
1209. F. S. Guziec and J. C. Sheehan, *Chem. Biol. Pept. Proc.; Am. Pept. Symp.*, **320**, 321 (1972); *Chem. Abstr.*, **85**, 143435m (1976).
1210. N. L. Benoiton and P. Mathiapparanam, *Pept. Proc. Eur. Pept. Symp.* 16th (1980); *Chem. Abstr.*, **97**, 216647s (1982).
1211. E. Eimers and H. Rudolph, Ger. Offen. 2,304,589 (1974); *Chem. Abstr.*, **82**, 58461k (1975).
1212. O. Tsuge, K. Oe, and Y. Ueyama, *Chem. Lett.*, 425 (1976).
1213. G. H. Hakimelahi, C. B. Boyce, and H. S. Kasmai, *Helv. Chim. Acta*, **60**, 342 (1977).
1214. A. S. Dey and J. L. Neumeyer, *J. Med. Chem.*, **17**, 1095 (1974).
1215. I. Ninomiya, I. Furutani, O. Yamamoto, T. Kiguchi, and T. Naito, *Heterocycles*, **9**, 853 (1978).
1216. F. S. Guziec, Jr., and E. T. Tewes, *J. Het. Chem.*, **17**, 1807 (1980).
1217. R. Gompper, *Chem. Ber.*, **89**, 1762 (1956).
1218. J. F. Willems and A. Vandenberghe, *Bull. Soc. Chim. Belg.*, **70**, 745 (1961).
1219. S. Carboni, E. Grothe, and M. F. Saettone, *J. Pharm. Soc.*, **57**, 1063 (1968).
1220. M. F. Saettone, *J. Org. Chem.*, **31**, 1959 (1966).
1221. M. F. Saettone, *J. Pharm. Soc.*, **57**, 1798 (1968).
1222. B. Krieg and H. Lautenschlager, *Liebig's Ann. Chem.*, 1471 (1976).
1223. H. Lautenschlager, B. Heiner, and B. Stoll, Ger. Offen. 2,934,746 (1981); *Chem. Abstr.*, **95**, 43109w (1981).
1224. H. Lautenschlager, B. Heiner, B. Stoll, and M. Probst, Ger. Offen. 2,935,902 (1981); *Chem. Abstr.*, **95**, 43087n (1981).
1225. M. F. Saettone and A. Marsili, *Tet. Lett.*, 6009 (1966).
1226. V. B. Kalcheva and L. I. Tsvetanska, *Khim. Geterosikl. Soedin.*, 1028 (1981).
1227. B. Krieg and H. Lautenschlager, *Liebig's Ann. Chem.*, 208 (1976).
1228. B. Krieg and H. Lautenschlager, *Liebig's Ann. Chem.*, 788 (1976).
1229. G. Mukherjee-Muller, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **62**, 1429 (1979).
1230. B. Krieg and H. Lautenschlager, *Liebig's Ann. Chem.*, 1465 (1976).
1231. H. Lautenschlager, *Liebig's Ann. Chem.*, 566 (1978).
1232. R. Gompper and F. Effenberger, *Chem. Ber.*, **97**, 1928 (1959).
1233. A. Marsili, M. F. Saettone, and E. Bucci, *J. Org. Chem.*, **33**, 2884 (1968).
1234. R. Gompper, *Chem. Ber.*, **90**, 374 (1957).

1235. K. H. Scholz, H. G. Heine, and W. Hartmann, *Liebig's Ann. Chem.*, 2027 (1977).
1236. J. A. Deyrup and H. L. Gingrich, *Tetrahedron Lett.*, 3115 (1977).
1237. K. H. Scholz, H. G. Heine, and W. Hartmann, *Tetrahedron Lett.*, 1467 (1978).
1238. W. Hartmann, K. H. Scholz, and H. G. Heine, *Chem. Ber.*, **113**, 1884 (1980).
1239. K. H. Scholz, W. Hartmann, and H. H. Georg, Ger. Offen 2,754,493 (1979); *Chem. Abstr.*, **91**, 211398c (1979).
1240. S. Sekretar, J. Kopecky, and A. Martvan, *Coll. Czech. Chem. Commun.*, **47**, 1848 (1982).
1241. M. C. Aversa, G. Cum, P. D. Giannetto, G. Romeo, and N. Uccella, *J. Chem. Soc. Perkin I*, 209 (1974).
1242. G. Cum and N. Uccella, *Tetrahedron Lett.*, 1343 (1975).
1243. G. Sindona and N. Uccella, *Ann. Chim. (Rome)*, **70**, 405 (1980); *Chem. Abstr.*, **94**, 29658x (1981).
1244. G. Cum, P. Giannetto, G. Sindona, and N. Uccella, *Tetrahedron*, **36**, 745 (1980).
1245. T. Kunieda, Y. Abe, Y. Iitaka, and M. Hirobe, *J. Org. Chem.*, **47**, 4291 (1982).
1246. Y. Abe and T. Kunieda, *Fukusokan Kagaku Toronkai Koen Yoshishu*, 12th, 76 (1979).
1247. T. Kuneida, T. Higuchi, Y. Abe, and M. Hirobe, *Tetrahedron Lett.*, **23**, 1159 (1982).
1248. T. Kuneida, T. Higuchi, Y. Abe, and M. Hirobe, *Tetrahedron Lett.*, **21**, 3065 (1980).
1249. M. Kanaoka and Y. Kurata, *Chem. Pharm. Bull.*, **26**, 660 (1978).
1250. Y. Abe and T. Kuneida, *Tetrahedron Lett.*, 5007 (1979).
1251. T. Kuneida, Y. Abe, T. Higuchi, and M. Hirobe, *Tetrahedron Lett.*, **22**, 1257 (1981).
1252. T. Kuneida and M. Hirobe, *Yuki Gosei Kagaku Kyokaishi*, **41**, 77 (1982); *Chem. Abstr.*, **98**, 142566m (1982).
1253. T. Kuneida, T. Highuchi, Y. Abe, and M. Hirobe, *Tetrahedron*, **39**, 3253 (1983).
1254. G. B. Fregnan and M. Vidali, *Pharmacology*, **15**, 485 (1977).
1255. S.p.A. Montedisson, Belgian Patent 893,997 (1983); *Chem. Abstr.*, **98**, 198198k (1983).
1256. P. Moses and R. Dahlboom, *Acta Pharm. Suec.*, **15**, 175 (1978); *Chem. Abstr.*, **90**, 97468c (1979).
1257. E. Manghisi and G. Cascio, Ger. Offen. 2,351,948 (1974); *Chem. Abstr.*, **81**, 13484h (1974).
1258. V. V. Dovlatyan and E. N. Ambartsumyan, *Arm. Khim. Zh.*, **23**, 49 (1970); *Chem. Abstr.*, **73**, 14411d (1970).
1259. H. Hoffman, R. Wagner, and J. Uhl, *Chem. Ber.*, **104**, 2134 (1971).
1260. F. Benker, H. H. Credner, W. Laessig, E. Meier, and S. Schleger, Ger. Offen. 2,543,094 (1977); *Chem. Abstr.*, **87**, 39461x (1977).
1261. H. H. Credner, W. Laessig, E. Meier, E. Ranz, S. Schleger, and K. W. Schranz, Ger. Offen. 2,540,959 (1977); *Chem. Abstr.*, **87**, 93508f (1977).
1262. E. Meier, H. H. Credner, W. Laessig, K. Kuettner, and K. W. Schranz, Ger. Offen. 2,466,939 (1976); *Chem. Abstr.*, **86**, 99005r (1976).
1263. G. L'Abbe, A. Verbruggen, and S. Toppet, *Bull. Soc. Chim. Belg.*, **90**, 99 (1981).
1264. B. Caillaux, P. George, F. Tataruch, Z. Janousek, and H. G. Viehe, *Chimia*, **30**, 387 (1976).
1265. J. M. Lemmens, W. W. J. M. Blommerde, L. Thijs, and B. Zwannenburg, *J. Org. Chem.*, **49**, 223 (1984).
1266. J. Lukac and H. Heimgartner, *Helv. Chim. Acta*, **62**, 1236 (1979).

- 1267. H. Heimgartner, *Chimia*, **33**, 111 (1979).
- 1268. E. Schaumann and S. Grabley, *Liebig's Ann. Chem.*, 1568 (1978).
- 1269. G. Mukherjee, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, **62**, 1429 (1979).
- 1270. A. Ahlquist, *J. Prakt. Chem.*, **99**, 45 (1919); *Chem. Abstr.*, **14**, 1446 (1919).
- 1271. M. A. Spellman, *J. Am. Chem. Soc.*, **66**, 1244 (1944).
- 1272. J. S. H. Davies and W. H. Hook, *J. Chem. Soc.*, 30 (1950).
- 1273. J. S. Davidson, *Chem. & Ind.*, 618 (1977).
- 1274. E. Renk, F. Ostermeyer, and R. Dents, Swiss Patent 461,489 (1968); *Chem. Abstr.*, **70**, 68344r (1970).
- 1275. I. Baxter, D. W. Cameron, and M. R. Thoseby, *J. Chem. Soc. C.*, 850 (1970).
- 1276. J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 58 (1961).

CHAPTER 4

Mesoionic Oxazoles

HENRY L. GINGRICH and JONATHAN S. BAUM

FMC Corporation, Agricultural Chemicals Group, Princeton, New Jersey

4.1.	Introduction.	731
4.2.	1,3-Oxazolium 5-Oxides (Munchnones)	734
4.2.1.	Synthesis.	734
4.2.2.	Structure and Spectral Properties.	748
4.2.2.1.	Structure.	748
4.2.2.2.	Spectral Properties	750
4.2.3.	Reactions	760
4.2.3.1.	With Acylating Reagents.	760
4.2.3.2.	Nucleophilic Additions.	773
4.2.3.3.	Cycloaddition Reactions.	778
4.2.3.4.	Ring-Chain Valence Tautomerism.	906
4.3.	1,3-Oxazolium 5-Imines (Munchnone Imines).	922
4.3.1.	Synthesis.	922
4.3.2.	Structure and Spectral Properties.	924
4.3.2.1.	Infrared Spectra.	924
4.3.2.2.	Ultraviolet Spectra	925
4.3.2.3.	NMR Spectra	925
4.3.2.4.	Molecular Orbital Calculations	925
4.3.3.	Reactions	926
4.3.3.1.	With Nucleophiles.	926
4.3.3.2.	With Electrophiles	928
4.3.3.3.	Cycloaddition Reactions.	929
4.4.	1,3-Oxazolium 4-Oxides (Isomunchnones).	940
4.4.1.	Synthesis.	940
4.4.2.	Structure and Spectral Properties.	944
4.4.2.1.	Infrared and Ultraviolet Spectra.	944
4.4.2.2.	¹ H NMR Spectra	944
4.4.2.3.	Molecular Orbital Calculations	944
4.4.3.	Reactions	945
4.4.3.1.	With Nucleophiles.	945
4.4.3.2.	Cycloaddition Reactions.	946
4.5.	1,3-Oxazolium 4-Imines (Isomunchnone Imines)	953

4.1. INTRODUCTION

The representation of mesoionic ring systems as a hybrid of a number of charged forms is credited to Schonberg¹ in 1937 and is further elucidated by Baker and

Ollis² in 1949; yet several compounds that are now interpreted as being mesoionic indeed date back over 100 years.³ Since this time, the chemistry of mesoionic ring systems has been a rewarding area of pursuit for the synthetic, physical, and theoretical chemist. The study of mesoionic oxazoles is no exception, being an important part of the wealth of knowledge in mesoionic chemistry. Since the first description of the oxazolium mesoionic system in 1958,⁴ numerous papers have been published in the area. Clearly, as evidenced by the reactions of mesoionic oxazoles herein described, the ability of these systems to provide a variety of heterocyclic compounds inaccessible or poorly accessible by other routes makes this area an important and practical tool to the synthetic heterocyclic chemist.

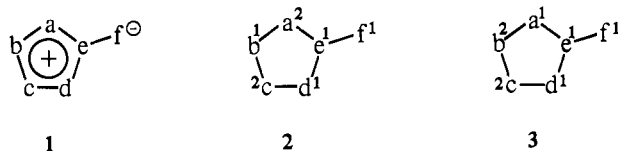
Previous reviews of mesoionic oxazoles have been part of a more general description of mesoionic ring systems⁵⁻¹² or have been included in summaries of the chemistry of oxazoles.^{13,14} In covering the literature to mid-1983, we attempt to be more comprehensive in scope than previous reviews yet acknowledge that due in part to the nature of synthesis of mesoionic oxazoles, omissions of references are to be expected. We hope that they are in the vast minority.

With the recognition of the general area of mesoionic (derived from mesomeric and ionic) chemistry came some confusion as to a good working definition of a mesoionic compound. A generally accepted definition was suggested by Ollis and Ramsden⁸ and later modified¹¹ to state:

"A compound may be appropriately called mesoionic if it is a five-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with the five atoms comprising the ring."

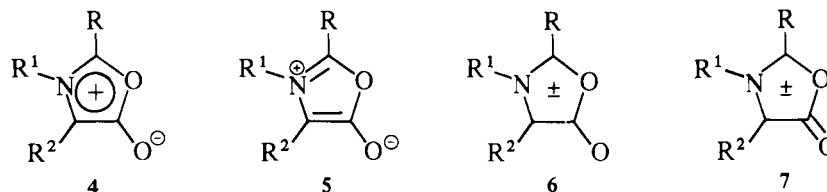
Both monocyclic and ring-fused mesoionic structures are applicable to the above definition.

In accord with this definition, mesoionic compounds are represented by formulae of the general type **1** where a-f are suitably substituted carbon atoms or heteroatoms. Mesoionic ring systems may be divided into two general types represented by structures **2** (type A) and **3** (type B) in which the superscripts indicate the origin of the electrons comprising the π -system.⁸ Mesoionic oxazoles (e.g., **4**) are a member of the type A classification.

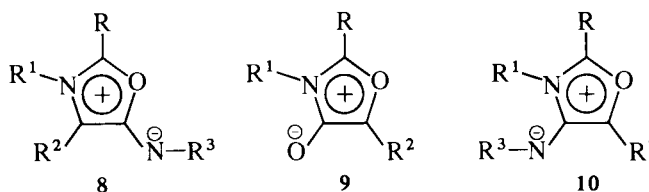


Several symbols (e.g., **4-7**) involving positive and negative signs can be found in the literature to represent 1,3-oxazolium 5-oxides. Obviously this situation can cause considerable confusion, particularly for those inexperienced in the field. Ollis and Ramsden⁸ advocate the exclusive use of symbolism **4**. While this symbolism implies that the oxazolone ring is associated with a partial positive charge and the exocyclic oxygen with a partial negative charge, it is not completely correct to

conclude that symbolism **4** "implies extensive polarization or the exhibition of properties or stability that can be characteristically associated with classical aromaticity."⁸ We agree with Ollis and Ramsden's recommendation, and therefore symbolism **4** will be used throughout this review.



It appears that no single convention for naming mesoionic compounds has been generally accepted in the literature. Thus **4** may be named satisfactorily as 2,3,4-trisubstituted 5-hydroxy-1,3-oxazolium hydroxide, inner salt; 2,3,4-trisubstituted 1,3-oxazolium-5-olate; or *anhydro*-2,3,4-trisubstituted 5-hydroxy-1,3-oxazolium hydroxide. We prefer the latter two usages as well as the shorter terminology (e.g., 1,3-oxazolium 5-oxide) for a description of **4**. Huisgen and co-workers have extensively studied the reactions of 1,3-oxazolium 5-oxides, particularly their 1,3-dipolar cycloadditions, and have named¹⁵ them "munchnones" in analogy to the related sydnones (1,2,3-oxadiazolium 5-oxides) first prepared at the University of Sydney. In the context of this review, no single method of naming mesoionic oxazoles will be applied. We state the above for purposes of clarity.



The mesoionic ring systems covered by this chapter include the 1,3-oxazolium 5-oxides (munchnones) **4**, the 1,3-oxazolium 5-imines (muchnone imines) **8**, the 1,3-oxazolium 4-oxides (isomunchnones) **9**, and the 1,3-oxazolium 4-imines (isomunchnone imines) **10**. Type A mesoionic compounds, including the oxazole ring system, as a consequence of the arrangement of heteroatoms contain masked 1,3-dipoles. These dipoles comprise three of the five-membered heterocycles' peripheral atom composition. Present in the 5-oxide **4** or 5-imine **8** system is the azomethine ylide **11** and correspondingly in the 4-oxide **9** or 4-imine **10** system is the carbonyl ylide **12**. Utilization of the dipolar character of oxazole mesoionic systems in cycloaddition reactions is well documented as described herein.

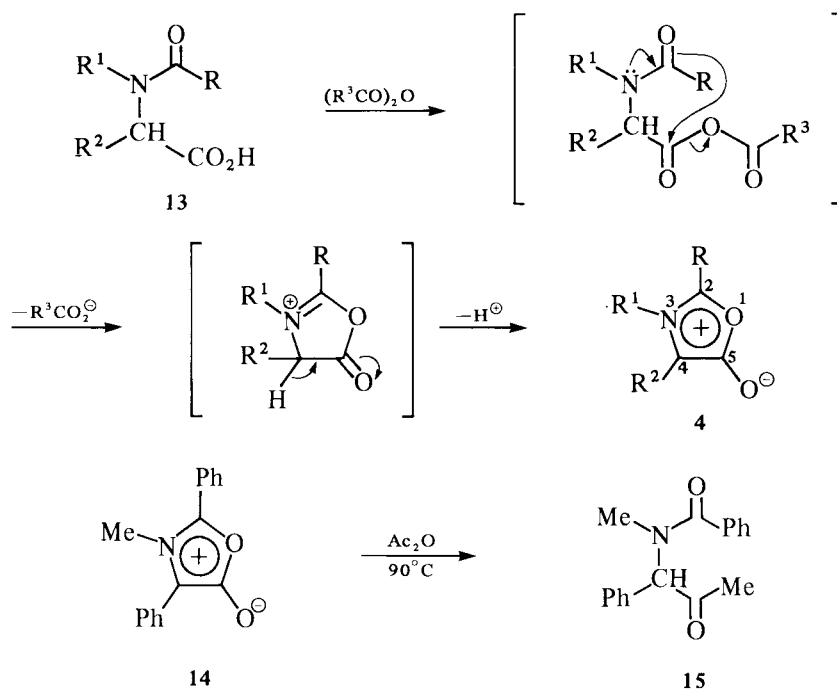


We have elected to separate each section of this chapter into a description of the synthesis, physical properties, and reactions of the four mesoionic oxazole ring systems **4** and **8–10**. Included in the text are numerous tables for rapid reference to the synthesis and cycloaddition reactions of mesoionic oxazoles.

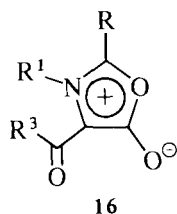
4.2. 1,3-OXAZOLIUM 5-OXIDES (MUNCHNONES)

4.2.1. Synthesis

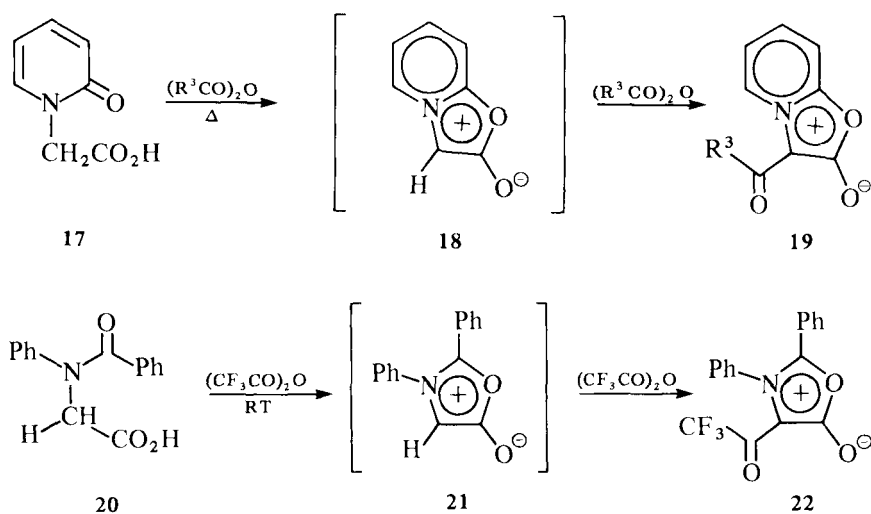
The classical preparation of 1,3-oxazolium 5-oxides (munchnones) **4** involves the cyclodehydration of an *N*-acylamino acid **13** with a carboxylic acid anhydride (usually acetic anhydride) at temperatures not exceeding 60°C.^{4,15–17} At higher temperatures, the carboxylic acid anhydride can react further with the munchnone in the Dakin–West reaction. For instance, 3-methyl-2,4-diphenyl-1,3-oxazolium 5-oxide **14** reacts with acetic anhydride at 90°C to give the α -acylaminoketone **15**.¹⁸



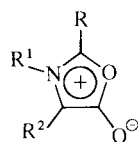
When R²=H, the munchnones **4** are readily acylated by the carboxylic acid anhydride to give 4-acyl-1,3-oxazolium 5-oxides **16**. Lawson and Miles reported the first examples of bicyclic mesoionic 1,3-oxazolium 5-oxides **19** by reacting 1,2-dihydro-2-oxo-1-pyridylacetic acid **17** with carboxylic acid anhydrides.^{4,16} The initially formed munchnones **18** were acylated under the reaction conditions to give



the 4-acyl mesoionic compounds **19**. Similarly, Singh and Singh prepared the monocyclic 4-acyl-1,3-oxazolium 5-oxide **22** upon reacting *N*-benzoyl-*N*-phenylglycine **20** with trifluoroacetic anhydride at room temperature (RT).¹⁹ Again the initially formed mesoionic compound **21** was acylated at the 4-position by trifluoroacetic anhydride. Additionally, the munchnones **4** are extremely moisture sensitive, hydrolyzing to the parent *N*-acylamino acids **13**.^{15,17} For these reasons, only a relatively small number of 1,3-oxazolium 5-oxides unacylated in the 4-position have actually been isolated using this procedure (see Table 4.1 for a compilation of isolable 1,3-oxazolium 5-oxides prepared by this method and other methods to be discussed shortly).

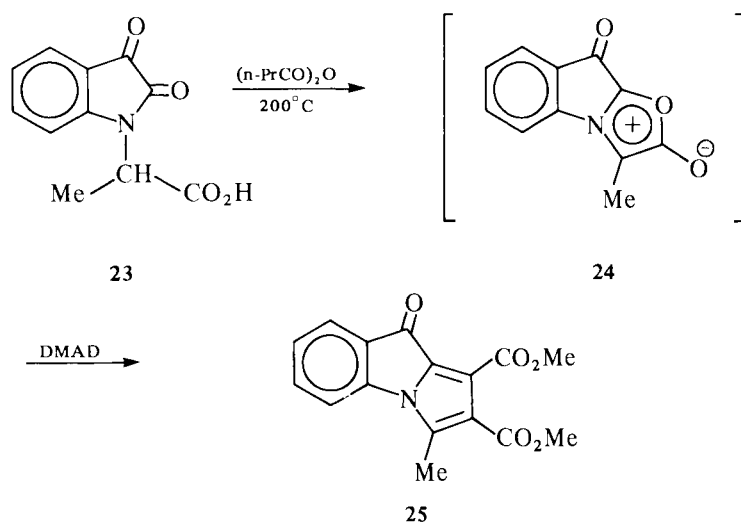


Fortunately, this cyclodehydration procedure is still extremely useful when the munchnone **4** is generated *in situ* from the *N*-acylamino acid precursor **13** in the presence of a suitable dipolarophile.^{17,24,26} Temperatures as high as 200°C have been employed, apparently without attack of the 1,3-oxazolium 5-oxide by the carboxylic acid anhydride cyclodehydrating reagent. For example, Anderson and Corey have reported the reaction of isatin-*N*-(α -methyl)acetic acid **23** with *n*-butyric anhydride in the presence of dimethyl acetylenedicarboxylate (DMAD) at 200°C to afford the 9*H*-pyrrolo[1,2-*a*]indole **25** in 62% yield.²⁷ The *in-situ*-generated munchnone **24** undergoes a 1,3-dipolar cycloaddition reaction with DMAD to give **25**. The mechanism of this 1,3-dipolar cycloaddition reaction will

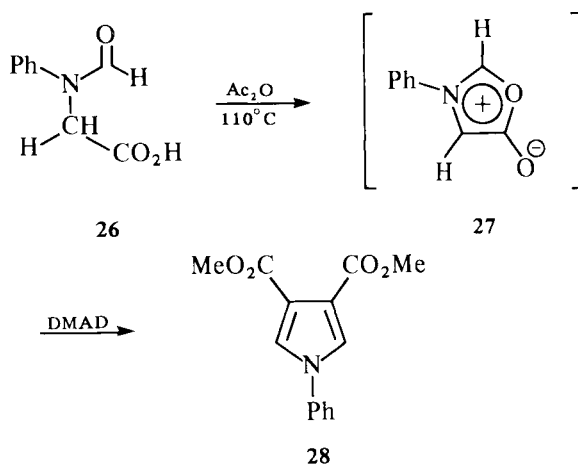
TABLE 4.1. ISOLATED *N*-SUBSTITUTED 1,3-OXAZOLIUM 5-OXIDES

Method of Preparation ^a	R	R ¹	R ²	Percent Yield	Reference
A	Ph	Me	Ph	87	15
B				50	15
C				37	20
A	<i>p</i> -MePh	Me	Ph	67	21
A				57	22
A	Ph	Me	<i>p</i> -MePh	74	21
A	<i>p</i> -MeOPh	Me	Ph	60	15
A	Ph	Me	<i>p</i> -MeOPh	73	15
A	<i>p</i> -MeOPh	Me	<i>p</i> -MeOPh	23	23
A	Ph	Me	<i>p</i> -NO ₂ Ph	44	15
A	<i>p</i> -NO ₂ Ph	Me	Ph	84	15
A	<i>p</i> -MeOPh	Me	<i>p</i> -NO ₂ Ph	51	15
A	<i>p</i> -NO ₂ Ph	Me	<i>p</i> -MeOPh	42	15
C	Ph	Me		58	20
A		Me	Ph	35	24
A	Ph	Me	1,4-Ph-(bismunchnone)	39	25
C	Ph	Ph	Ph	61	20
C	<i>p</i> -MeOPh	Ph	Ph	61	20
C	Ph	Ph	<i>p</i> -MeOPh	53	20
C	Ph	Ph	<i>p</i> -BrPh	57	20
C	Ph	<i>p</i> -MePh	Ph	65	20
C		<i>p</i> -MePh	Ph	38	20
C	Ph	<i>p</i> -MeOPh		58	20
C	Ph	<i>p</i> -ClPh	Ph	39	20

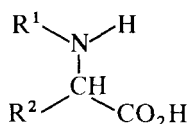
^aA, Cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, cyclodehydration of *N*-acylamino acid precursor with DCC; C, reaction of acyltetracarbonyl ferrate with imidoyl chloride.



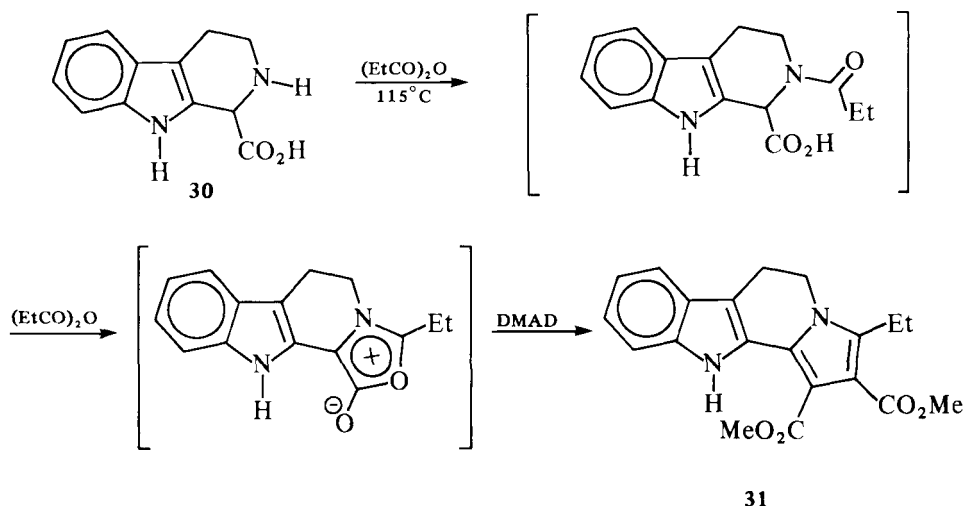
be discussed later (see Section 4.2.3.3). Additionally, unisolable 1,3-oxazolium 5-oxides **4** unsubstituted in the 2- and 4-positions can be generated and trapped in this manner. For instance, Huisgen and co-workers have prepared pyrrole **28** in 91% yield upon reacting *N*-phenyl-*N*-formylglycine **26** with acetic anhydride at 110°C in the presence of DMAD.^{17,24} Apparently, cycloaddition of the *in-situ*-generated munchnone **27** to the DMAD is faster than acylation of the 4-position of **27**.



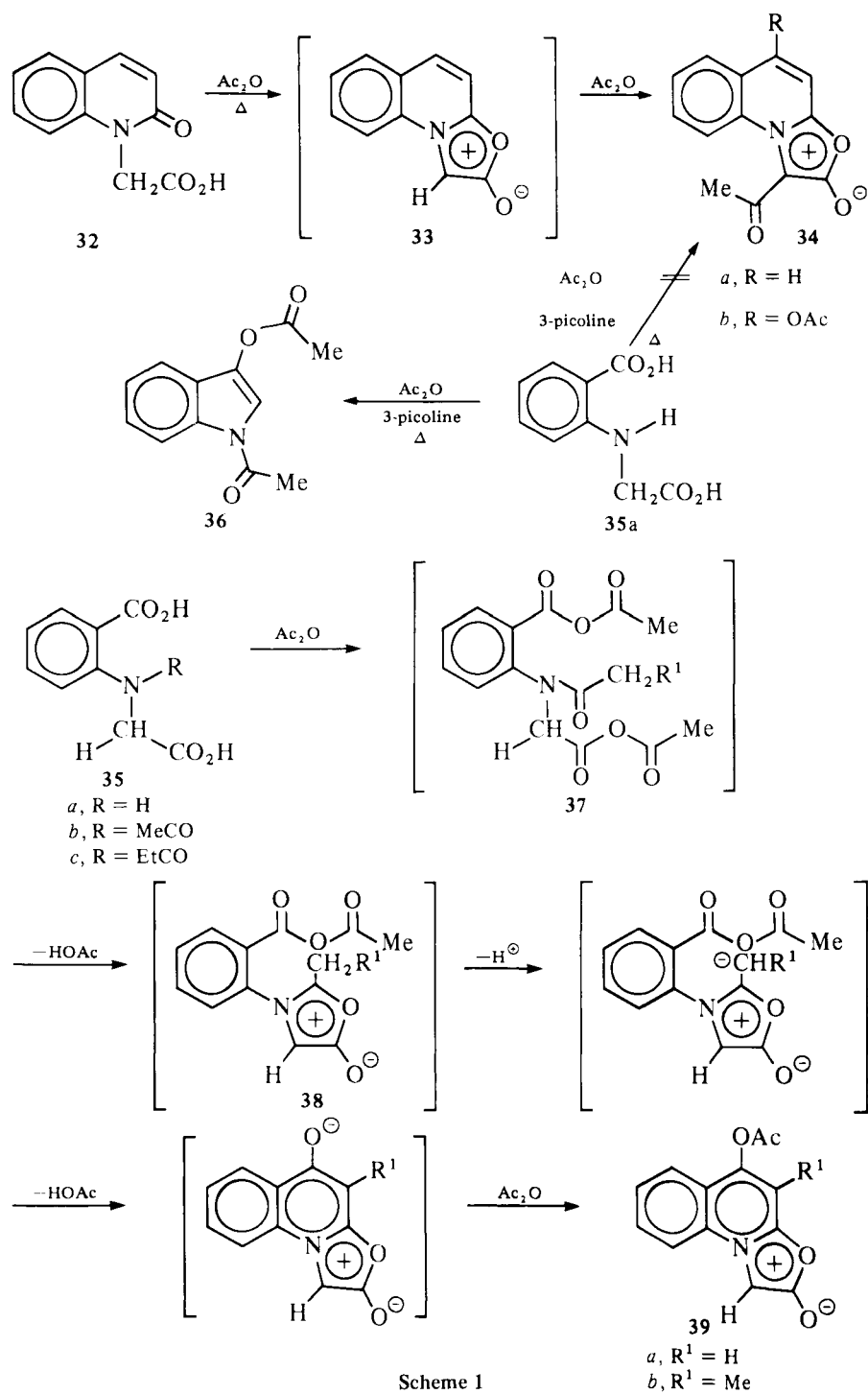
Another advantage of this *in situ* procedure is that amino acids **29** can also be used as 1,3-oxazolium 5-oxide **4** precursors. In this case, the *N*-acyl substituent is introduced by the carboxylic acid anhydride cyclodehydrating agent.^{17,24} An example of this sequence was reported by Hershenson involving the reaction of 1,2,3,4-tetrahydro- β -carboline-1-carboxylic acid **30** with propionic anhydride in

**29**

the presence of DMAD at 115°C to afford a 69% yield of the 5,6-dihydro-11*H*-indolizino[8,7-*b*]indole **31**.²⁸ In this case, propionic anhydride serves as both the *N*-acylating agent and as the cyclodehydrating agent. In short, a one-pot procedure involving *N*-acylation, cyclodehydration, and cycloaddition can be employed simply by heating a mixture of amino acid **29**, a carboxylic acid anhydride, and a suitable dipolarophile.



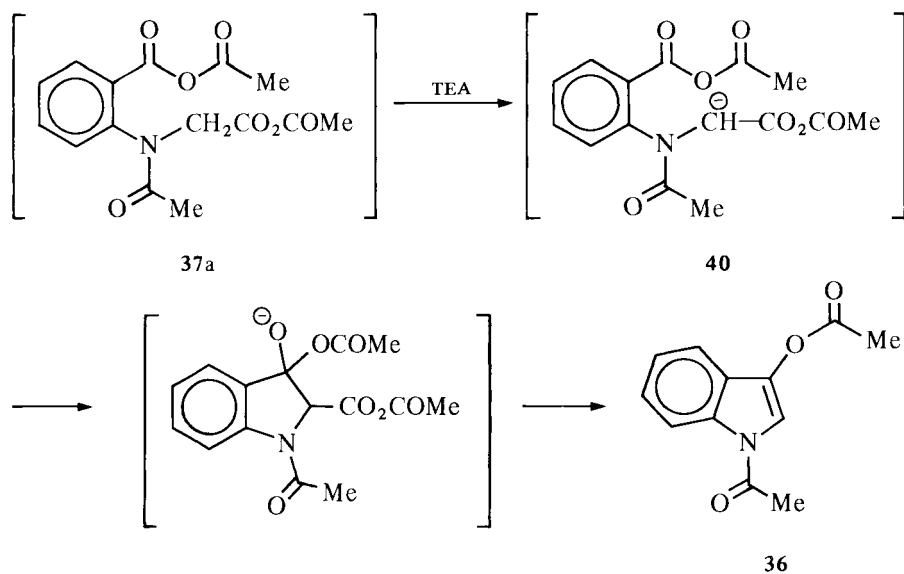
Lawson and Miles attempted to extend the scope of their earlier observation^{14,16} to the preparation of the 4-acyl mesoionic system **34a** but were unable to prepare the required 2-quinoline-*N*-acetic acid **32** starting material.¹⁶ (It should be noted that Potts and Yao subsequently successfully prepared **32** and trapped the *in-situ*-generated munchnone **33** with acetylenic dipolarophiles.²⁹) Utilizing a rather clever alternative approach, Lawson and Miles attempted the double cyclization of phenylglycine-*o*-carboxylic acid **35a** in refluxing acetic anhydride in the presence of 3-picoline.¹⁶ Instead of the desired mesoionic compound **34b**, they obtained *N,O*-diacetylindoxyl **36**.³⁰ More recently, Raileanu and co-workers reinvestigated the double cyclization of **35a** as depicted in Scheme 1.^{31,32} These workers were in fact able to isolate the 4-unsubstituted 1,3-oxazolium 5-oxide **39a** simply by heating **35a** in acetic anhydride in the absence of a base. The yield of **39a** was higher when the *N*-acetyl derivative **35b** was the starting material. Similarly, **39b** was obtained from **35c** and acetic anhydride. A plausible mechanism for the formation of the mesoionic compounds **39** is shown in Scheme 1.



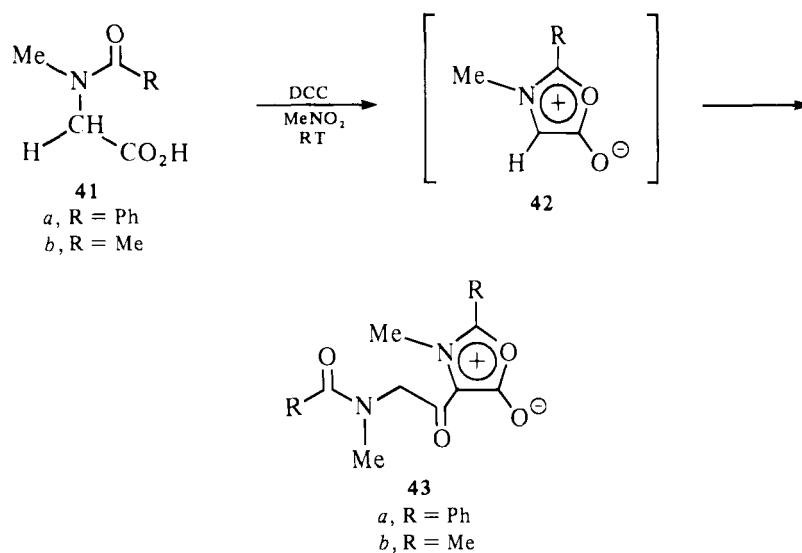
Scheme 1

Munchnones **39** (and a few related compounds) are the only stable 4-unsubstituted 1,3-oxazolium 5-oxides yet reported, as all others are known to undergo dimerization or acylation at the 4-position. In fact, attempts to acylate **39** at the 4-position with acetic anhydride, acetyl chloride, benzoyl chloride, or oxalyl chloride, even in the presence of pyridine or boron trifluoride etherate, failed. Acylation was successful only with trifluoroacetic anhydride. The stability of munchnones **39** toward "overacylation" was attributed to a decrease in reactivity at the 4-position due to the electron-withdrawing effect of the acyloxy substituent.^{31,32}

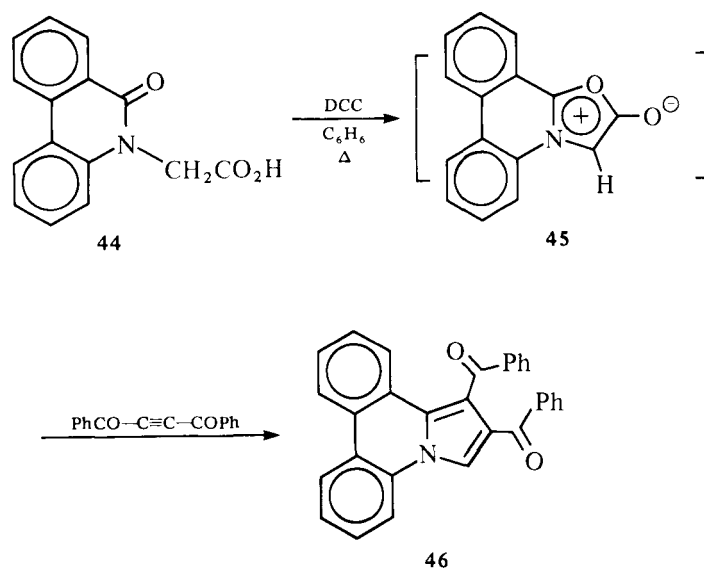
Interestingly, when **35a–b** were treated with refluxing acetic anhydride and triethylamine, *N,O*-diacetyloxyl **36** was obtained via the Heumann cyclization,^{31,32} as observed by Lawson and Miles with acetic anhydride and 3-picoline.³⁰ In the presence of triethylamine (TEA), deprotonation of the mixed anhydride **37a** to give intermediate **40** occurs, instead of cyclization to the 1,3-oxazolium 5-oxide **38**. If the triethylamine is replaced by a weaker base, such as pyridine, a mixture of **36** and **39a** is obtained.

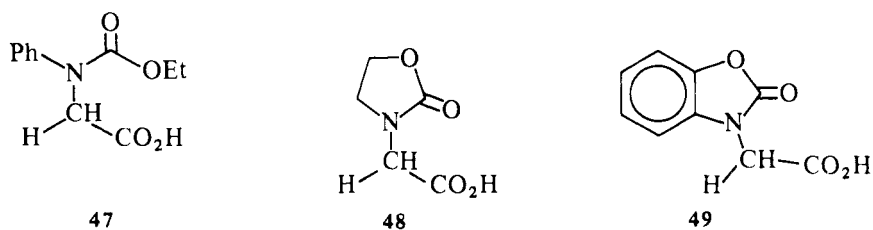


N,N'-Dicyclohexylcarbodiimide (DCC) has also been employed as a cyclodehydrating agent. Use of DCC avoids acylation of 1,3-oxazolium 5-oxides unsubstituted in the 4-position. However, most 4-unsubstituted munchnones **4** ($R^2 = H$) are too unstable to be isolated as they readily dimerize. Greco and co-workers reported³³ the cyclodehydration of *N*-benzoysarcosine **41a** and *N*-acetylsarcosine **41b** with DCC in nitromethane at room temperature to afford the 4-acylated 1,3-oxazolium 5-oxides **43**. The initially formed munchnones **42** dimerize under the reaction conditions. The mechanism of this dimerization will be discussed later (see Section 4.2.3.1). In the presence of a suitable dipolarophile, however, the 4-unsubstituted 1,3-oxazolium 5-oxides **4** ($R^2 = H$) can be trapped before they

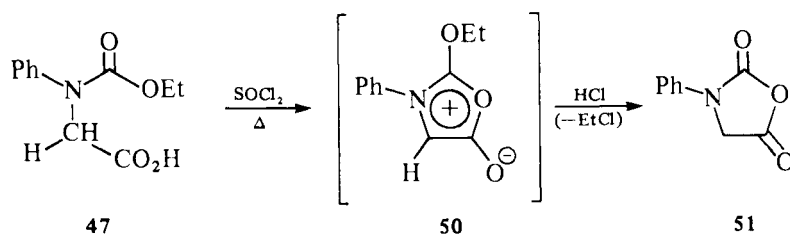


dimerize. For instance, Potts and Yao have intercepted the munchnone **45** generated from 6-oxo-5(6*H*)-phenanthridineacetic acid **44** and DCC in refluxing benzene with dibenzoylacetylene to afford the dibenzo[*e,g*]pyrrolo[1,2-*a*]pyridine **46** in 65% yield.²⁹ This reaction also illustrates an additional advantage of employing DCC as a cyclodehydrating agent for *in situ* 1,3-oxazolium 5-oxide **4** preparation — namely the simple work-up of the reaction mixture. Work-up normally involves filtration of the insoluble *N,N'*-dicyclohexylurea (DCU) by-product, followed by solvent removal.

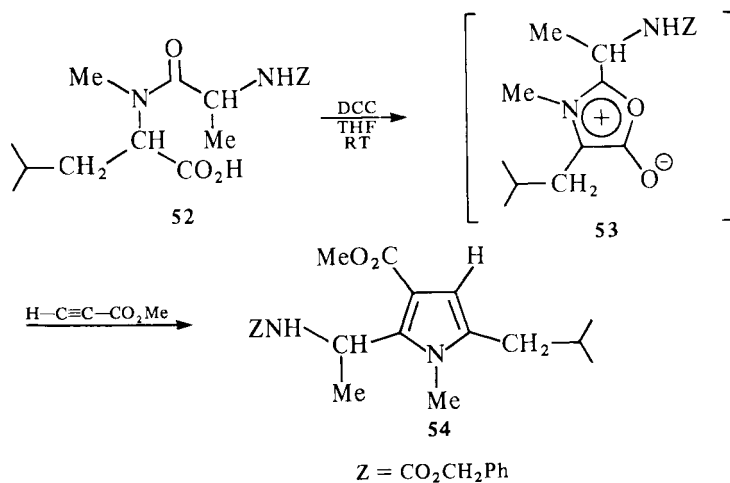


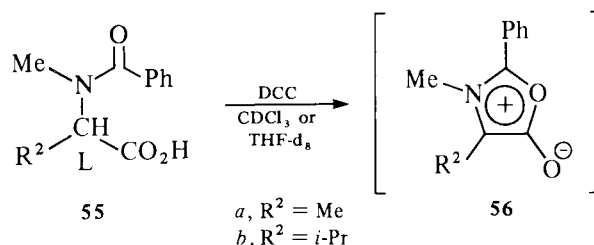


It should be noted that there are some limitations with regard to the cyclodehydration approach to munchnones **4**. Potts and co-workers noted the failure of amino acids **47–49** to form 1,3-oxazolium 5-oxides upon treatment with DCC and other cyclodehydrating agents.³⁴ These failures were attributed to the poor nucleophilicity of the carbonyl oxygen atoms in **47–49**. Reaction of *N*-(ethoxycarbonyl)-*N*-phenylglycine **47** with thionyl chloride, however, gives **51**, suggesting that munchnone **50** forms but undergoes rapid deethylation under the vigorous reaction conditions.

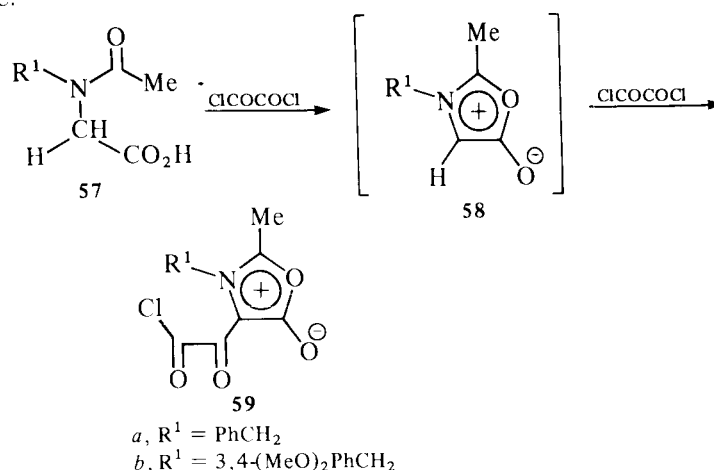


At this point a slight digression appears to be in order. 1,3-Oxazolium 5-oxides have been implicated by McDermott and Benoiton as racemization intermediates of *N*-methylamino acid residues during DCC-mediated peptide bond formation.³⁵ Racemization is promoted by polar solvents, which would be expected for a charged intermediate such as **4**. In fact, the munchnone **53** derived from *Z*-Ala-MeLeu **52** upon treatment with DCC in tetrahydrofuran at room temperature was

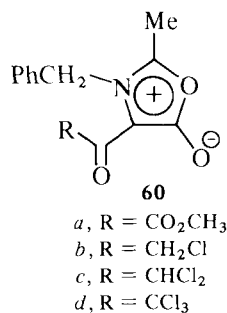




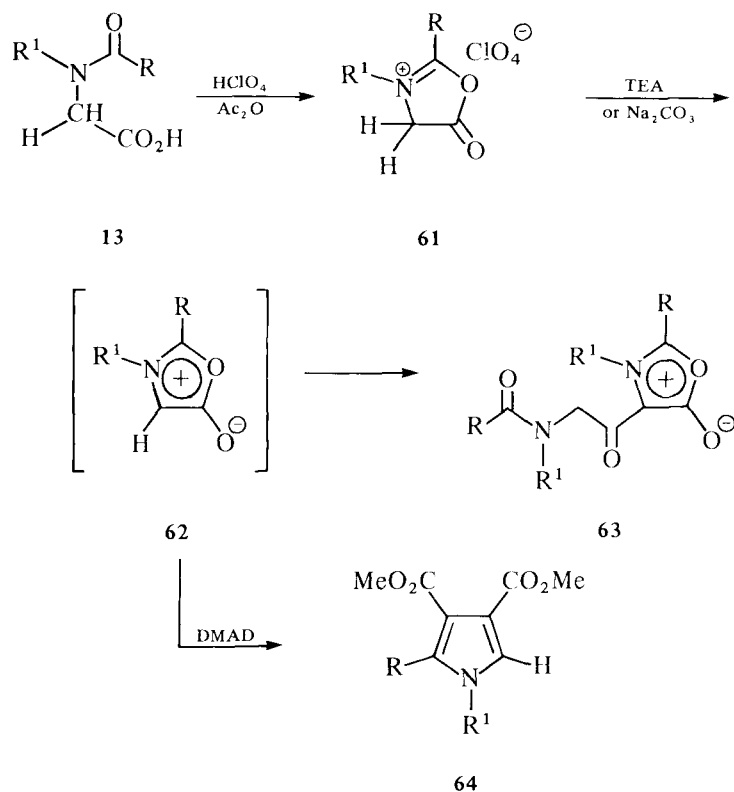
successfully trapped by methyl propiolate to afford pyrrole **54** in 79% yield. Additionally, Davies and Mohammed were able to observe by ^1H NMR spectroscopy the 1,3-oxazolium 5-oxides **56** formed upon treatment of *N*-benzoyl-*L*-*N*-methylamino acids **55** with DCC.³⁶ The authors found that formation of munchnones **56** was temperature dependent. Formation of **56** during DCC-mediated peptide coupling reactions and hence racemization could be reduced by carrying out the coupling reactions at ca. -5°C . Racemization could be completely eliminated upon addition of *N*-hydroxysuccinimide or *N*-hydroxybenzotriazole at -5°C .



Oxalyl chloride has also been reported as a cyclodehydrating agent for the preparation of 1,3-oxazolium 5-oxides. Burrows has reported that excellent yields of the 4-chloroglyoxyloxy-1,3-oxazolium 5-oxides **59** were obtained upon treating the *N*-acetyl-*N*-benzylglycines **57** with oxalyl chloride.³⁷ Again the initially formed 4-unsubstituted munchnones **58** were further acylated by oxalyl chloride to give the observed products **59**. Subsequently, Ohta and Mase³⁸ confirmed the formation of **59a** upon treatment of **57a** with oxalyl chloride. Additionally, these workers obtained the 4-acyl-1,3-oxazolium 5-oxides **60a–d** upon reacting **57a** with methyl oxalyl chloride, monochloro-, dichloro-, and trichloroacetyl chloride, respectively. Acetyl chloride, however, does not effect cyclodehydration of **57a** to a munchnone **58a**. To the best of our knowledge, 4-substituted 1,3-oxazolium 5-oxides **4** ($R^2 = \text{alkyl or aryl}$) have not been generated using oxalyl chloride or related acid chlorides as cyclodehydrating agents.

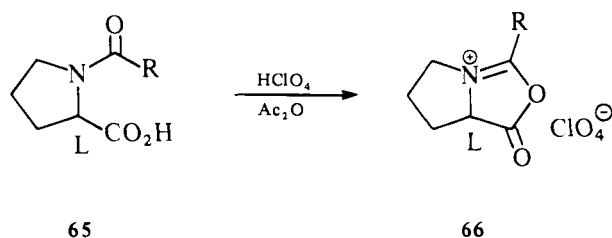


The preparation of 1,3-oxazolium 5-oxides **4** by the cyclodehydration of *N*-acylamino acids **13** with carboxylic acid anhydrides or DCC is complemented by a slight variation involving the formation of oxazolonium salts. *N*-Substituted oxazolonium salts **61** are readily prepared by cyclodehydration of *N*-alkyl- or *N*-aryl-*N*-acylamino acids **13** ($R^2 = H$) with a mixture of acetic anhydride and perchloric acid.³⁹⁻⁴² These oxazolonium salts **61** afford munchnones **62** upon treatment with base [e.g., triethylamine (TEA) or solid sodium carbonate] as shown in Scheme 2.



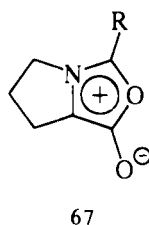
Scheme 2

As noted previously, most 4-unsubstituted 1,3-oxazolium 5-oxides are too unstable to be isolated as they readily dimerize unless they are generated in the presence of a suitable dipolarophile. Boyd and Wright, for instance, have reported that addition of triethylamine to a suspension of oxazolonium salt **61** ($R = \text{Ph}$, $R^1 = \text{Me}$) in methylene chloride immediately affords the 4-acylated 1,3-oxazolium 5-oxide **63** ($R = \text{Ph}$, $R^1 = \text{Me}$) in 83% yield as indicated in Scheme 2.⁴² However, when triethylamine was added to a mixture of **61** ($R = \text{Ph}$, $R^1 = \text{Me}$) and dimethyl acetylenedicarboxylate (DMAD), the munchnone **62** ($R = \text{Ph}$, $R^1 = \text{Me}$) undergoes a 1,3-dipolar cycloaddition reaction to give pyrrole **64** ($R = \text{Ph}$, $R^1 = \text{Me}$) in 81% yield.

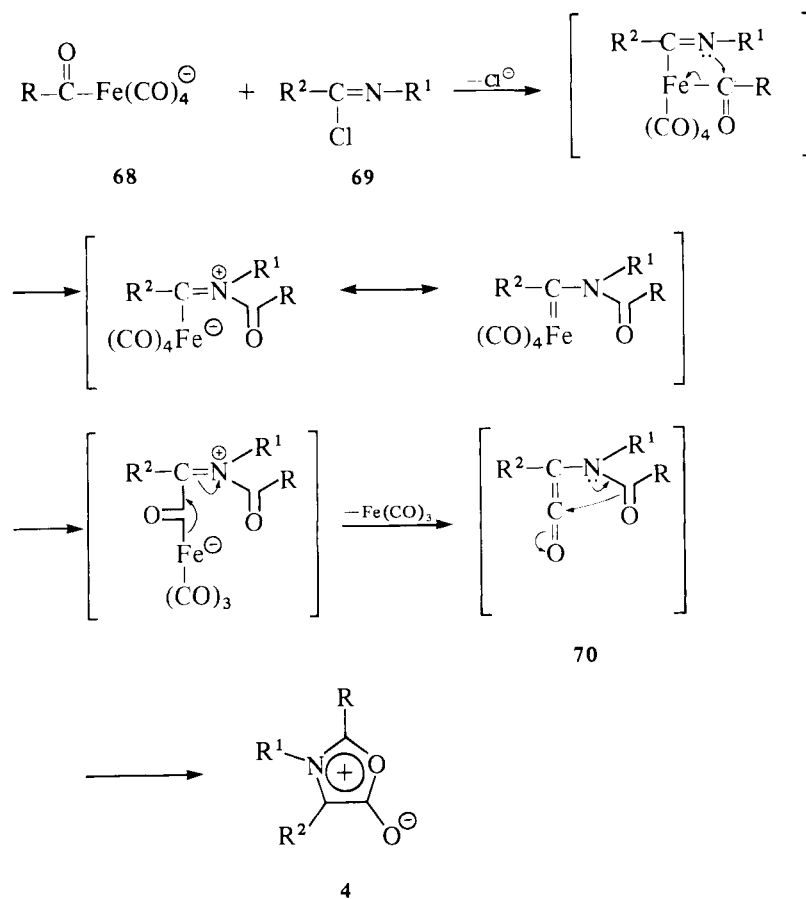


a, $R = p\text{-NO}_2\text{Ph}$
b, $R = \text{Ph}_2\text{N}$

Interestingly, apparently only 4-unsubstituted 1,3-oxazolium 5-oxides **62** have been generated by this procedure. In this regard, however, it is worth noting that treatment of *N*-*p*-nitrobenzoyl-L-proline **65a** with acetic anhydride and perchloric acid below 0°C affords the optically active oxazolonium perchlorate **66a**, which is hydrolyzed with water to afford **65a** with 97.5% optical retention.⁴¹ However, when the reaction mixture was kept at room temperature for 24 h before the perchlorate was precipitated, **66a** was optically inactive. This racemization was attributed to equilibration between **66a** and the munchnone **67a**. On the other hand, **65b** affords the optically active perchlorate **66b**, which upon hydrolysis, even with aqueous sodium hydroxide, regenerates **65b** with complete retention of optical activity. Presumably, the diphenyl amino substituent of **66b** stabilizes the cation toward deprotonation, avoiding the formation of **67b**.



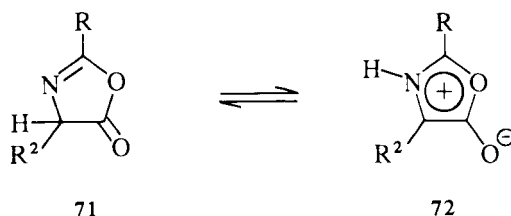
a, $R = p\text{-NO}_2\text{Ph}$
b, $R = \text{Ph}_2\text{N}$



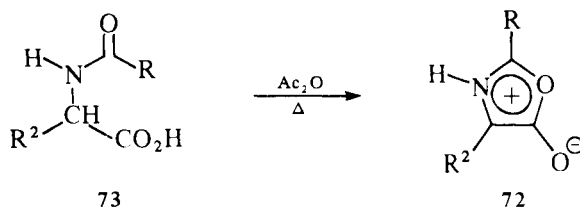
Scheme 3

Recently, Alper and Tanaka²⁰ reported a novel 1,3-oxazolium 5-oxide **4** synthesis involving the reaction of acyltetracarbonyl ferrates **68** and imidoyl chlorides **69** in methylene chloride at room temperature. A putative mechanism for this reaction is shown in Scheme 3. It should be noted that the controversial (see Section 4.2.3.4) ketene valence tautomers **70** are postulated as the immediate precursors of the munchnones **4**. Yields of the 1,3-oxazolium 5-oxides **4** prepared by this procedure were in the 37–65% range (see Table 4.1). Although this route allows the preparation of certain munchnones that are not readily accessible by the classical cyclodehydration of *N*-acylamino acids **13**, this approach also fails when either R or R² are alkyl, presumably due to the instability of such munchnones.

Finally, Huisgen and co-workers have shown that 2-oxazolin-5-ones (azlactones) **71** are in tautomeric equilibrium with the mesoionic oxazoles **72**.⁴³ This tautomeric equilibrium shows a marked solvent dependence. For instance, the colorless **71a** (R = R² = Ph) affords yellow solutions, particularly in polar solvents, due to the

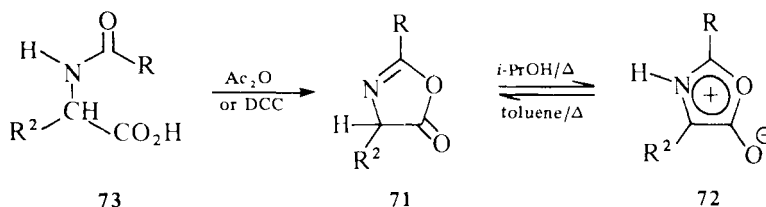


presence of tautomer **72a** ($R = R^2 = \text{Ph}$). Utilizing UV spectroscopy, these workers were able to estimate equilibrium concentrations of tautomer **72a** in the following solvents: dimethylformamide (49%), dimethylsulfoxide (32%), acetone (0.26%), and chloroform (0.007%). This equilibrium was also confirmed by IR spectroscopy.⁴³

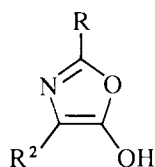


b; $R = p\text{-NO}_2\text{Ph}$, $R^2 = \text{Ph}$
c; $R = p\text{-ClPh}$, $R^2 = \text{Ph}$
d; $R = p\text{-ClPh}$, $R^2 = \text{CO}_2\text{Et}$

Killé and Fleury have, in fact, isolated and characterized the copper red *N*-unsubstituted mesoionic compound **72b** upon cyclodehydration of *N*-(4-nitrophenyl)-*C*-phenylglycine **73b** with acetic anhydride.⁴⁴ Similarly, Peterson reported the isolation of munchnones **72c** and **72d** upon heating **73c** and **73d** in acetic anhydride, followed by recrystallization from anhydrous ethanol.⁴⁵ More recently, Steglich and co-workers reported a procedure to isolate the *N*-unsubstituted 1,3-oxazolium 5-oxides **72a** and **72c** and to convert them to the corresponding 2-oxazolin-5-ones **71**.⁴⁶ When the azlactones **71a** and **71c** are dissolved in hot isopropyl alcohol, the pure mesoionic compounds **72a** and **72c** separate upon cooling. On the other hand, when **72a** and **72c** are heated in toluene, the azlactones **71a** and **71c** are obtained upon solvent removal. However, even upon prolonged heating in toluene, munchnones **72b** and **72e** ($R = \text{Ph}$, $R^2 = 4\text{-pyridyl}$) are not



a, $R = R^2 = \text{Ph}$
c; $R = p\text{-ClPh}$, $R^2 = \text{Ph}$



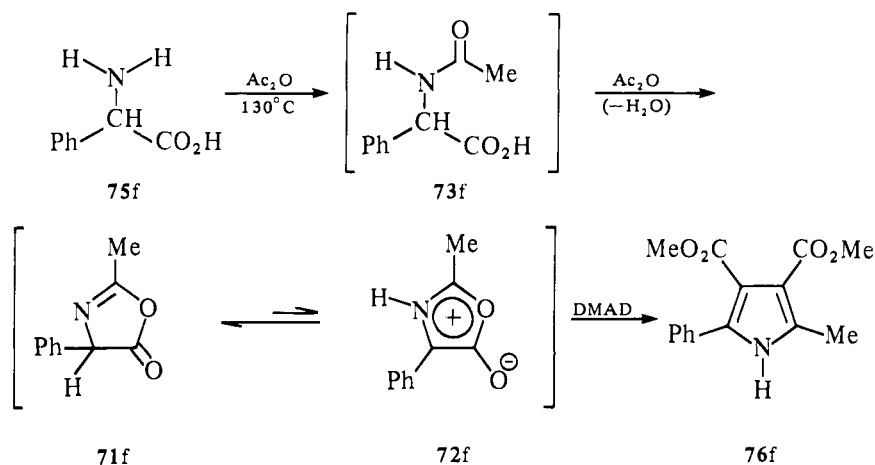
74

a, R = R² = Ph

e; R = Ph, R² = 4-pyridyl

converted to their corresponding azlactones. It should be noted that a comparison⁴⁶ of physical and spectral data reveals that compounds originally formulated as 5-hydroxyoxazoles **74a**⁴⁷ and **74e**⁴⁸ are, in fact, the *N*-unsubstituted 1,3-oxazolium 5-oxides **72a** and **72e**, respectively.

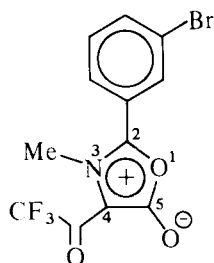
Huisgen and co-workers have shown that *N*-unsubstituted munchnones **72** also undergo 1,3-dipolar cycloaddition reactions with acetylenic^{43,49,50} and olefinic^{51,52} dipolarophiles (see Section 4.2.3.3). The 1,3-oxazolium 5-oxides **72**, however, do not need to be isolated as the *in situ* procedure also works well in this case. For instance, heating *C*-phenylglycine **75f** with dimethyl acetylenedicarboxylate (DMAD) in acetic anhydride at 130°C gives pyrrole **76f** in 75% yield.⁴³ In this way, it is possible to avoid handling the sensitive azlactone **71f**.



4.2.2. Structure and Spectral Properties

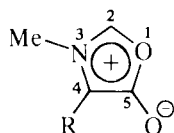
4.2.2.1. Structure

While it is obvious that 1,3-oxazolium 5-oxides conform to the definition of a mesoionic compound (see Section 4.1), the key issue structurally is their aromaticity; that is whether they are adequately represented by a structure that



77

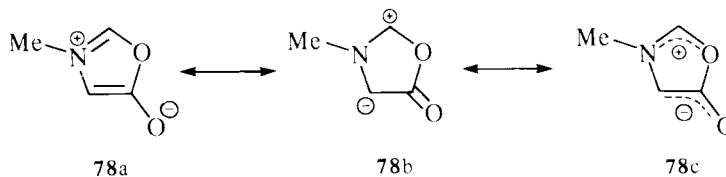
contains the aromatic 6π -oxazolium cation. Boyd and co-workers⁵³ have reported the crystal structure of 2-(*m*-bromophenyl)-3-methyl-4-trifluoroacetyl-1,3-oxazolium 5-oxide **77**. The molecular structure determined for **77** indicates that the *m*-bromophenyl substituent is tilted 44° from the planar oxazolone ring, while the trifluoroacetyl group is nearly coplanar. The bond distances within the oxazolone ring are short except for the O–C(5) bond, which is unexpectedly long. The endocyclic carbonyl bond is similar in length to carbonyl bonds found in γ -lactones and does not support an aromatic oxide structure. In short, the structure of **77** indicates extensive, but not full, conjugation over the oxazolone ring. It does not appear that **77** possesses much aromatic character, although the presence of the stabilizing 4-trifluoroacetyl substituent presumably causes some perturbation in this system.



78, R = H

79, R = CHO

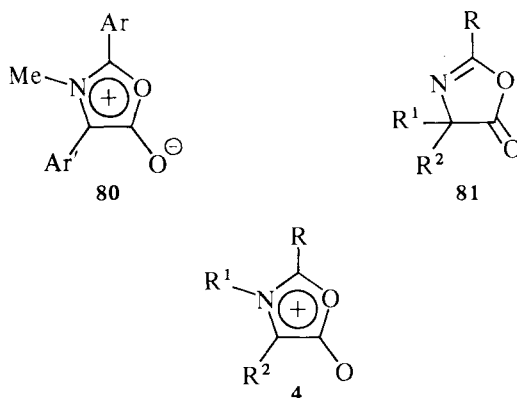
These workers have also performed self-consistent ω , β -calculations for 3-methyl-1,3-oxazolium 5-oxide **78**, as well as for its 4-formyl derivative **79**.⁵³ The calculated bond orders indicate the single-bond character of the O–C(5) bond and the double-bond character of the endocyclic carbonyl bond in both **78** and **79**, as well as showing the perturbing effect of the 4-acyl substituent. Dewar and Turchi have also calculated the geometry and distributions of formal charge for **78** by the MINDO/3 MO method.⁵⁴ Their calculations indicate that these species cannot be satisfactorily represented by single classical structures. Instead they are better represented by structures **78b** and **78c** (rather than **78a**), which implies that the oxazolone ring is nonaromatic.



4.2.2.2. *Spectral Properties*

4.2.2.2.1. INFRARED (IR) SPECTRA

Huisgen and co-workers have reported that a series of 2,4-diaryl-3-methyl-1,3-oxazolium 5-oxides **80** exhibit carbonyl stretching bands at $1690\text{--}1700\text{ cm}^{-1}$ (KBr) or at ca. 1710 cm^{-1} (CH_2Cl_2).¹⁵ These values should be compared to the observed frequency of ca. $1800\text{--}1820\text{ cm}^{-1}$ for the carbonyl stretching band in azlactones **81**. The lower observed frequency for the carbonyl stretch in **80** can be attributed to the reduced carbonyl bond order of **80** relative to **81**. Additionally, the high integrated intensities of the carbonyl stretches in **80** is also indicative of a reduced carbonyl bond order. Alper and Tanaka²⁰ have also reported carbonyl absorptions at $1700\text{--}1727\text{ cm}^{-1}$ (KBr) for additional munchnones **4**.

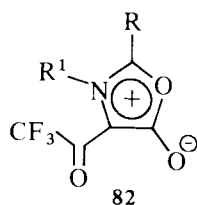


R = Ph, 2-furyl

R¹ = aryl, Me

R² = aryl, 2-furyl, 2-thienyl

Singh and Singh have reported that the 4-trifluoroacetyl-1,3-oxazolium 5-oxide **82a** exhibits a carbonyl doublet at 1802 and 1779 cm^{-1} , which were attributed to the ring carbonyl and trifluoroacetyl carbonyl groups, respectively.¹⁹ Greco and co-workers similarly reported that the IR (KBr) spectrum of **82b** shows a carbonyl doublet at 1800 and 1785 cm^{-1} , which were assigned to the trifluoroacetyl and ring carbonyl groups, respectively, as well as an intense band at 1625 cm^{-1} , which was attributed to the iminium group.³³ Boyd and Wright, however, do not concur with these assignments. These workers feel that the carbonyl doublet at 1802 and 1779 cm^{-1} for **82a** is due to the ring carbonyl and that an additional band at 1642 cm^{-1} is due to the trifluoroacetyl carbonyl group.⁴² The IR spectrum of **82c** also exhibits a doublet in the 1800 cm^{-1} region and an additional band at 1630 cm^{-1} . Boyd and Wright suggest that the trifluoroacetyl carbonyl group must be strongly polarized, and the shift to higher frequencies for the ring carbonyl indicates a greater lactone character for the 4-trifluoroacetyl munchnones **82** relative to 4-unacylated munchnones.⁴² It should be noted that their subsequent X-ray structure⁵³ of **77** does not appear to strongly support their arguments for a *strongly*

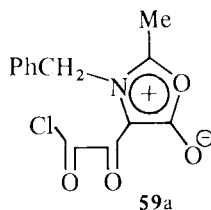


82

- a*, R = R¹ = Ph
b, R = R¹ = Me
c; R = Ph, R¹ = Me
d; R = SEt, R¹ = Me

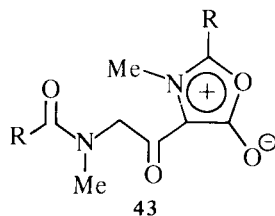
polarized trifluoroacetyl carbonyl group. Finally, Gotthardt and Rieter have reported that the IR (CH₂Cl₂) spectrum of **82d** exhibits a high-frequency absorption at 1800 cm⁻¹ due to the trifluoroacetyl carbonyl group and a pseudolactone carbonyl stretch at 1625 cm⁻¹.⁵⁵

Burrows has reported that the IR (KBr) spectrum of the 4-chloroglyoxyloxy-1,3-oxazolium 5-oxide **59a** exhibits strong bands at 1800 and 1785 cm⁻¹ due to the acid chloride and α-carbonyl groups, respectively, and a strong broad band at ca. 1610 cm⁻¹ attributed to the ring carbonyl and iminium groups.³⁷



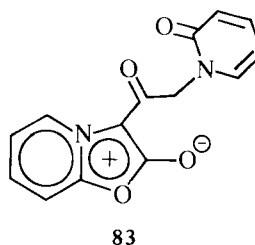
59a

Greco and co-workers have reported that the IR (KBr) spectra of the 4-acyl munchnone dimers **43** show an intense band at 1620 cm⁻¹ attributed to the iminium group and for **43b** a doublet at 1775 and 1750 cm⁻¹, which could be attributed to the ketone carbonyl and ring carbonyl groups, respectively.³³ However, Boyd and Wright⁴⁰ have reported that the IR (Nujol) spectrum of the bicyclic 4-acyl-1,3-oxazolium 5-oxide dimer **83** exhibits bands at 1766 (lactone carbonyl), 1653 (pyridone carbonyl), 1630, and 1574 cm⁻¹. Presumably one of the

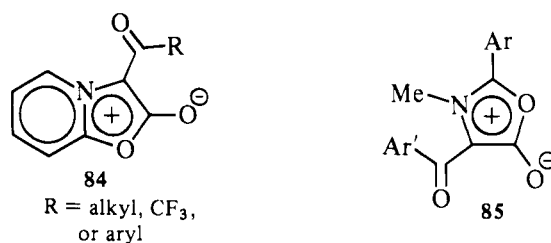


43

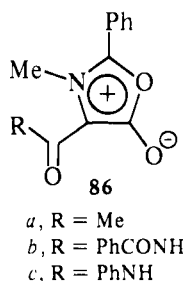
- a*, R = Ph
b, R = Me



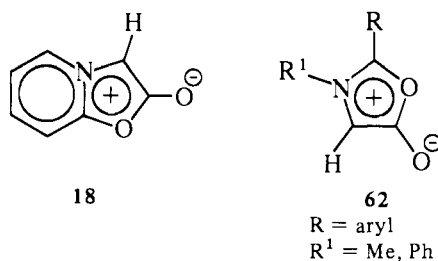
83

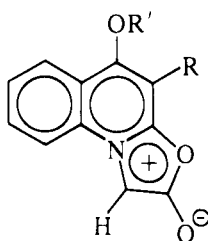


latter two bands is due to the ketone carbonyl group. Similarly, the IR (Nujol) spectra of the bicyclic 4-acyl munchnones **84** all exhibit high-frequency absorptions at 1750–1800 cm⁻¹, which were attributed to the ring carbonyl.⁴⁰ Additionally, for **84** (R = aryl) two additional bands appear at 1580–1600 cm⁻¹ and at 1560–1570 cm⁻¹. One of these bands was attributed to the polarized exocyclic carbonyl group and the other to the skeletal vibrations of the ring system. These two bands appear to overlap for **84** (R = alkyl or CF₃) since only a single broad band appears at ca. 1600 cm⁻¹. The IR spectra of the monocyclic 4-aroxy-1,3-oxazolium 5-oxides **85** exhibit ring carbonyl absorptions at ca. 1760 cm⁻¹ and a further band near 1610 cm⁻¹ due to the polarized exocyclic carbonyl group.⁴² Finally, Friedrichsen and Schröer have reported that the IR (KBr) spectrum of **86a** exhibits carbonyl stretches at 1745 and 1755 cm⁻¹, while **86b** shows several bands between 1670 and 1730 cm⁻¹.⁵⁶ Compound **86c** shows bands at 1653 and 1710 cm⁻¹.



Boyd and Wright have reported that freshly prepared methylene chloride solutions of the unstable bicyclic **18** and monocyclic 4-unsubstituted munchnones **62** exhibit two strong absorptions at 1728–1743 and 1693–1708 cm⁻¹, which gradually decrease in intensity as the 1,3-oxazolium 5-oxides decompose.^{40,42}

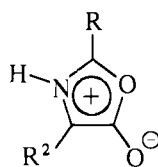


**39**

- a*; R = H, R' = MeCO
b; R = Me, R' = MeCO
c; R = H, R' = *p*-MePhSO₂

Raileanu and co-workers have reported that the pseudolactone carbonyl absorptions of the stable 4-unsubstituted munchnones **39a–b** are obscured by the acetoxy carbonyl absorption at ca. 1760 cm⁻¹ (KBr); however, the tosylate **39c** shows a carbonyl absorption at 1765 cm⁻¹.^{31,32} The C–H stretching vibrations for H₄ appear at 3178 and 3194 cm⁻¹ (KBr) for **39a** and **39b**, respectively. It should be noted that these C–H stretches could not be observed when the spectra were measured in solution.³²

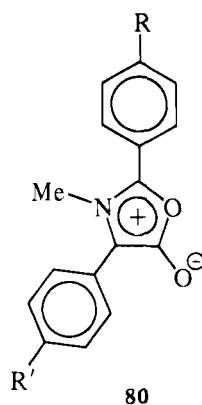
The IR spectra of the *N*-unsubstituted 1,3-oxazolium 5-oxides **72a–c** and **72e** have been reported to exhibit carbonyl absorptions in the 1650–1670-cm⁻¹ (KBr or Nujol) region, as well as broad absorptions in the 3100–2200-cm⁻¹ region presumably due to the N–H stretching band.^{44–46,48}

**72**

- a*, R = R² = Ph
b; R = *p*-NO₂Ph, R² = Ph
c; R = *p*-ClPh, R² = Ph
e; R = Ph, R² = 4-pyridyl

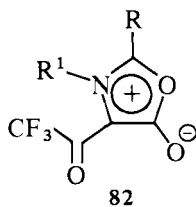
4.2.2.2. ULTRAVIOLET (UV) SPECTRA

Huisgen and co-workers have reported that the color and the long-wavelength UV absorption maxima ($\pi - \pi^*$) of a series of 2,4-diaryl-3-methyl-1,3-oxazolium 5-oxides **80** are dependent on the nature of the *p*-substituents on the aryl groups.¹⁵ For example, **80a** is orange yellow in color and exhibits a λ_{max} at 411.5 nm (CH₂Cl₂). Similarly, **80b** is green black (510 nm), **80c** is black violet (521 nm), and **80d** is bright red (396 nm).

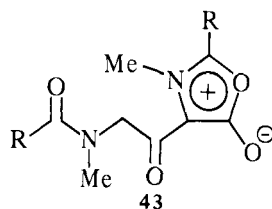


- a*, R = R' = H
b; R = NO₂, R' = H
c; R = NO₂, R' = MeO
d; R = MeO, R' = NO₂

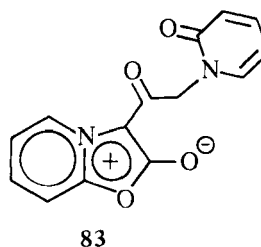
Greco and co-workers have reported $\lambda_{\max}$ (CHCl₃) for a series of 4-trifluoroacetyl munchnones **82a–c** and **82e** ranging from 310 to 370 nm.³³ These workers have also reported that the 4-acyl-1,3-oxazolium 5-oxide dimers **43a–b** exhibit $\lambda_{\max}$ (CHCl₃) at 352 and 300 nm, respectively. Similarly, dimer **83** exhibits a long-wavelength absorption at 340 nm (CH₂Cl₂).⁴⁰ Finally, Friedrichsen and Schröder have reported long-wavelength absorptions (CH₃CN) for **86a–c** at 343, 323, and 348 nm, respectively.⁵⁶

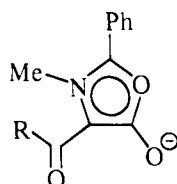


- a*, R = R¹ = Ph
b, R = R¹ = Me
c; R = Ph, R¹ = Me
e; R = Me, R¹ = Ph



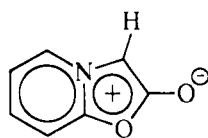
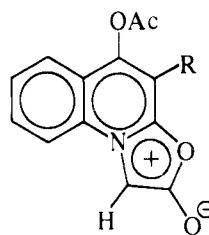
- a*, R = Ph
b, R = Me



**86**

- a*, R = Me
b, R = PhCONH
c, R = PhNH

Boyd and Wright have reported that the unstable 4-unsubstituted munchnone **18** gives a straw-colored solution in methylene chloride with a λ_{max} at 361 nm with a shoulder at 320 nm.⁴⁰ Similarly, Raileanu and co-workers have reported that the isolable 4-unsubstituted 1,3-oxazolium 5-oxides **39a–b** exhibit λ_{max} (CH₃CN) at 325 and 329 nm, respectively.³²

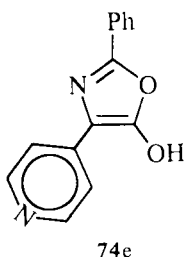
**18****39**

- a*, R = H
b, R = Me

The observation that the colorless 2,4-diphenyl-2-oxazolin-5-one **71a** produces yellow solutions, particularly in polar solvents, led Huisgen and co-workers to postulate a tautomeric equilibrium between **71a** and the *N*-unsubstituted munchnone **72a**.⁴³ The position and intensity of the band responsible for the yellow color (403–450 nm) shows a marked dependence on solvent polarity. These observations were rationalized by assuming an increase in the equilibrium concentration of the yellow **72a** in polar solvents. Killé and Fleury isolated the copper red *N*-unsubstituted 1,3-oxazolium 5-oxide **72b** and reported a λ_{max} at 520 nm in acetic



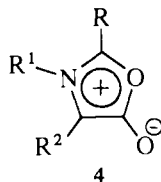
- a*, R = R² = Ph
b; R = *p*-NO₂Ph, R² = Ph
c; R = *p*-ClPh, R² = Ph
e; R = Ph, R² = 4-pyridyl



anhydride.⁴⁴ Similarly, Steglich and co-workers reported long-wavelength absorptions (ethanol) at 420 and 413 nm for **72a** and **72c**, respectively.⁴⁶ It is interesting to note that the *N*-unsubstituted munchnone **72e** was originally⁴⁸ formulated as the 5-hydroxyoxazole **74e**, but the structure has since been reassigned on the basis of its low solubility in organic solvents, its IR spectrum, and its UV absorptions (acetone) at 450 and 428 nm.⁴⁶

4.2.2.2.3. NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA

Alper and Tanaka²⁰ reported the ¹H NMR (CDCl₃) spectra of a series of tri-substituted 1,3-oxazolium 5-oxides **4**. Of particular interest were the chemical shifts of the *N*-methyl signals in **56c** and **56d** at δ 3.92 and 3.84 ppm, respectively.

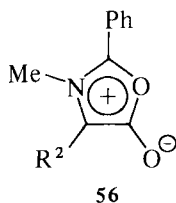


R = Ph, 2-furyl

R¹ = aryl, Me

R² = aryl, 2-furyl, 2-thienyl

Davies and Mohammed³⁶ reported that the *in-situ*-generated munchnones **56a** and **56b** show signals (CDCl₃) at δ 3.77 (N—CH₃) and 2.13 (C—CH₃) for **56a** and at δ 3.71 ppm (N—CH₃) for **56b**.

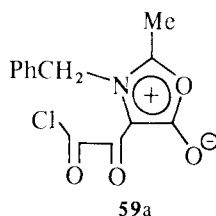


a, R² = Me

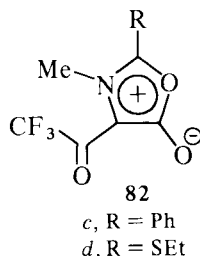
b, R² = *i*-Pr

c, R² = Ph

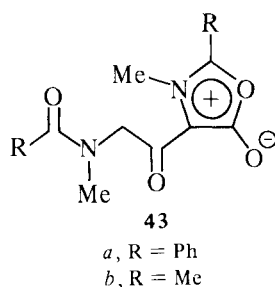
d, R² = 2-thienyl



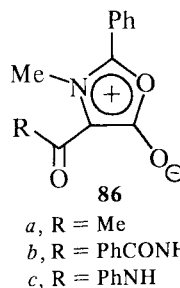
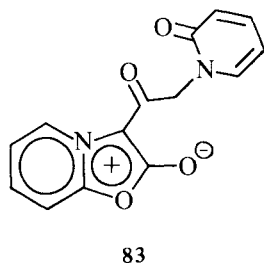
Burrows³⁷ has reported the NMR (acetone-*d*₆) spectrum of the 4-chloroglyoxyloxy-1,3-oxazolium 5-oxide **59a**. The *C*-methyl group has a chemical shift of δ 2.75 ppm, and the benzyl methylene protons appear as a singlet at δ 5.71 ppm.



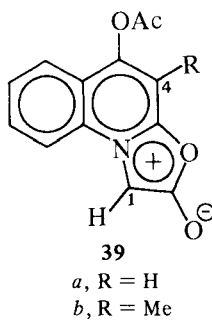
The NMR (CDCl₃) spectrum of 4-trifluoroacetyl munchnones **82c** and **82d** have been reported.^{55,56} The chemical shifts of the *N*-methyl signals are δ 4.13 and 3.85 ppm, respectively. Greco and co-workers³³ have reported the NMR (CDCl₃) spectra of the 4-acyl-1,3-oxazolium 5-oxide dimers **43**. For **43b**, the ring *N*-methyl group has a chemical shift of δ 3.92 ppm, while the *C*-methyl group appears at δ 2.55 ppm. The ring *N*-methyl signal in **43a** appears at a lower field (δ 4.15 ppm). It should be noted that for both dimers two sets of signals are observed at 30°C for the methylene and side-chain *N*-methyl groups, as well as the acyl methyl group of **43b**, due to restricted rotation about the side-chain amide bond. These signals coalesce in the spectrum of **43b** taken at 94°C (in DMSO-*d*₆). Boyd and Wright



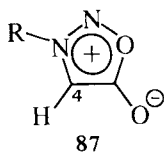
reported the NMR (CF₃CO₂H) spectrum of the bicyclic munchnone dimer **83**, although the dimer was evidently protonated by the NMR solvent.⁴⁰ Finally, Friedrichsen and Schröer⁵⁶ reported the NMR (CDCl₃) spectra of the 4-acyl-1,3-oxazolium 5-oxides **86a–c**. The *N*-methyl signals for these compounds appear at δ 4.15, 4.27, and 4.23 ppm, respectively.



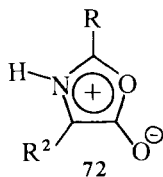
Raileanu and co-workers^{31,32} have reported the NMR (CDCl₃) spectra of the stable 4-unsubstituted munchnones **39**. For **39a**, H₁ appears as a doublet at δ 7.12 ppm, while H₄ also appears as a doublet at δ 5.72 ppm with $J_{1,4} = 2$ Hz. In **39b**,



H₁ appears as a singlet at δ 7.07 ppm. These workers feel that the low-field chemical shifts of H₁ suggest an appreciable aromatic character for these 1,3-oxazolium 5-oxides. It should be noted that in 4-unsubstituted sydnones **87**, H₄ appears at somewhat higher fields (i.e., δ 6.45–6.96 ppm).

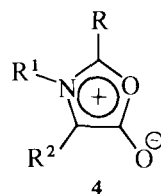


Apparently the ¹H NMR spectra of *N*-unsubstituted 1,3-oxazolium 5-oxides **72** have not been reported possible due to their poor solubility in organic NMR solvents. To the best of our knowledge, ¹³C NMR spectra of any type of 1,3-oxazolium 5-oxide have not been reported.



4.2.2.2.4. MASS SPECTRA

Alper and Tanaka²⁰ have reported that the molecular ion peaks were prominent in the mass spectra of a series of trisubstituted munchnones **4**.

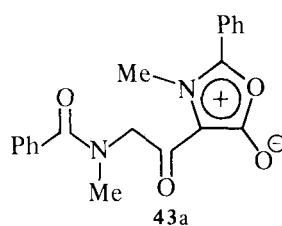
**4**

R = Ph, 2-furyl

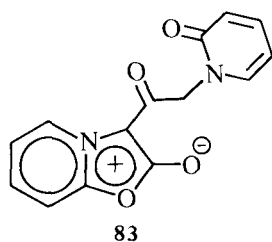
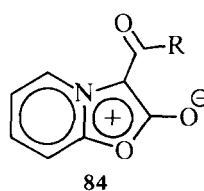
R¹ = Me, aryl

R² = aryl, 2-furyl, 2-thienyl

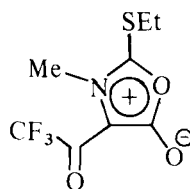
The mass spectral fragmentation analysis of the 4-acyl-1,3-oxazolium 5-oxide dimer **43a** has been reported by Greco and co-workers.³³ Similarly, Boyd and Wright⁴⁰ have reported the mass spectral fragmentation patterns for the bicyclic

**43a**

4-acyl munchnone dimer **83** and the bicyclic 4-aryl munchnones **84a, b**. Finally, Gotthardt, and Reiter⁵⁵ have reported the mass spectrum of the 4-trifluoroacetyl-1,3-oxazolium 5-oxide **82d**.

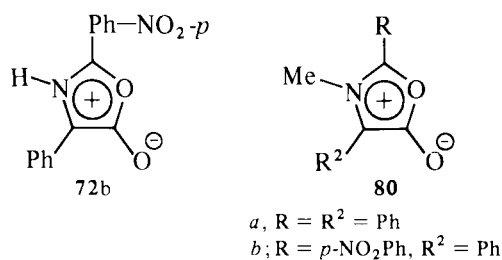
**83****84**

a, R = Ph
b, R = *p*-ClPh

**82d**

4.2.2.2.5. X-RAY PHOTOELECTRON SPECTRA

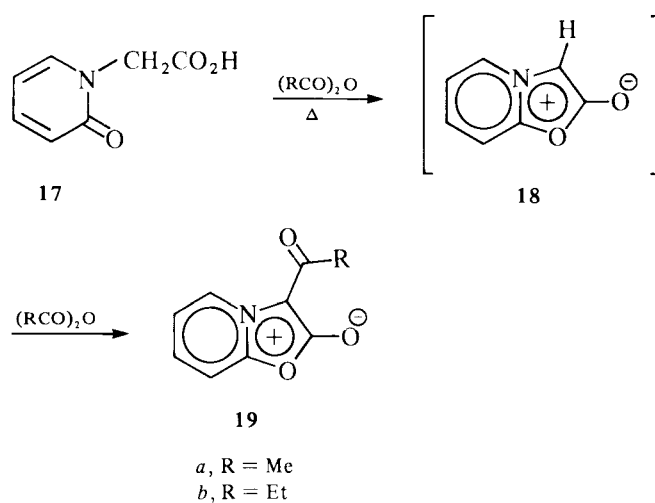
The X-ray photoelectron spectra of **72b** and **80a, b** have been reported.⁵⁷

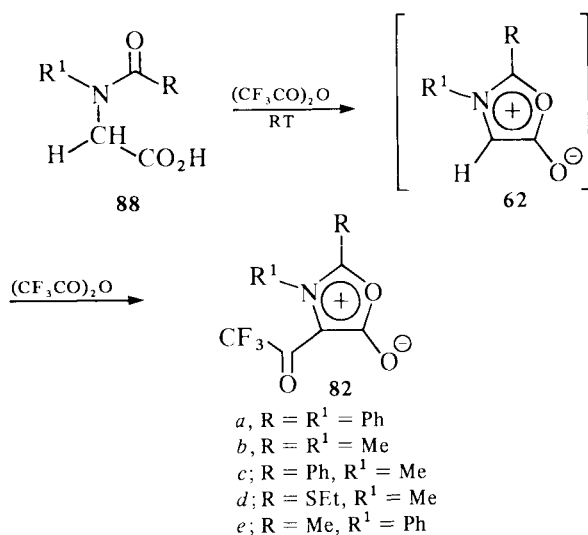


4.2.3. Reactions

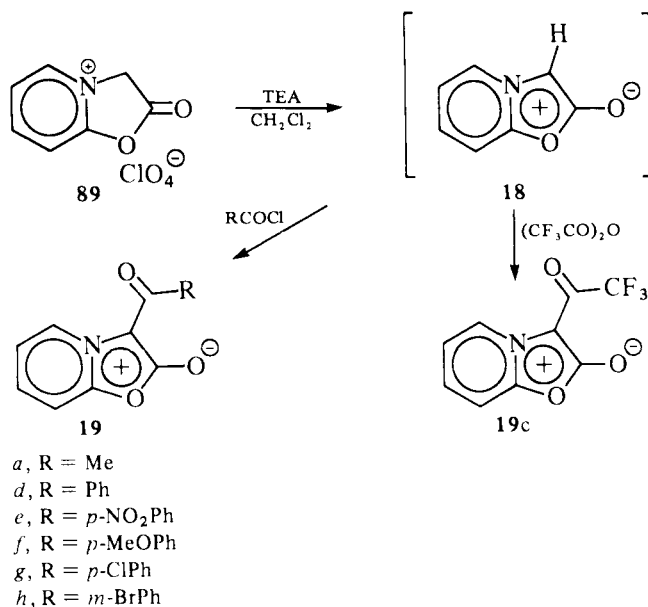
4.2.3.1. With Acylating Reagents

As noted previously, Lawson and Miles reported the preparation of the first recognized examples of 1,3-oxazolium 5-oxides **19** when they reacted 1,2-dihydro-2-oxo-1-pyridylacetic acid **17** with acetic anhydride.^{4,16} Similarly, Singh and Singh prepared the 4-trifluoroacetyl munchnone **82a** by reacting *N*-benzoyl-*N*-phenylglycine **88a** with trifluoroacetic anhydride at room temperature,¹⁹ while the 4-trifluoroacetyl munchnones **82b, c** and **82e** were prepared in an analogous manner by Greco and co-workers.³³ Gotthardt and Reiter also prepared the extremely hygroscopic **82d** upon treating *N*-[(ethylthio)carbonyl]sarcosine **88d** with trifluoroacetic anhydride.⁵⁵ In both cases the initially formed 1,3-oxazolium 5-oxides **18** and **62** were readily acylated at the 4-position by the cyclodehydrating agent to give the observed products **19** and **82**. These 4-acylated munchnones appear to be more stable than their corresponding unacylated munchnones.

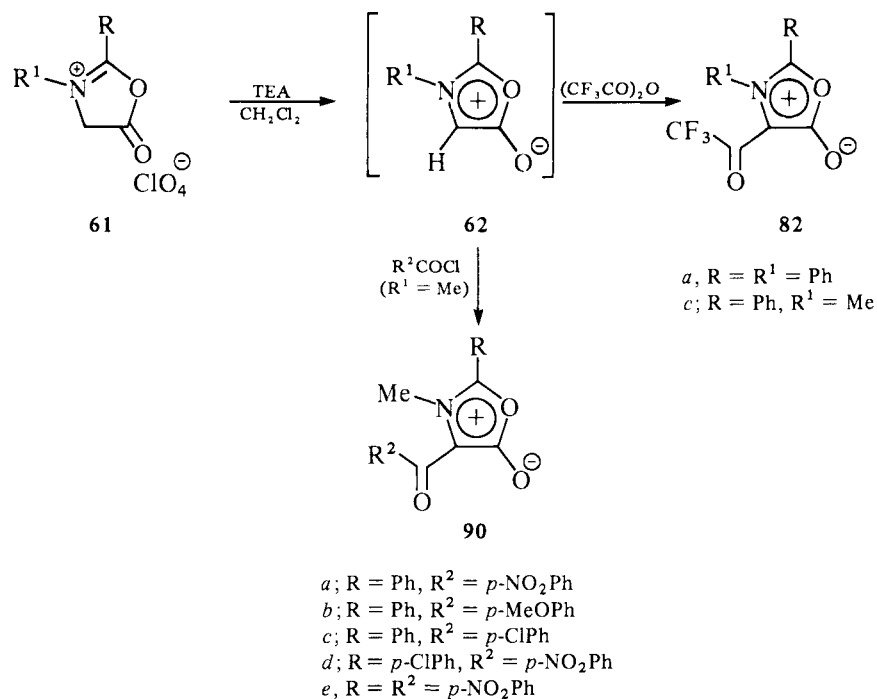




Boyd and Wright have reported the preparation of numerous additional 4-acyl-1,3-oxazolium 5-oxides **19**, **82**, and **90** utilizing their oxazolonium perchlorate technique as illustrated in Schemes 4⁴⁰ and 5.^{39,42} Using this technique, the acylating reagent was added to a freshly prepared solution of the unstable 4-unsubstituted munchnones **18** or **62**, which were prepared by adding the oxazolonium perchlorate salts **89** or **61** to a solution of triethylamine (TEA) in methylene chloride. Alternatively, triethylamine can be added to a mixture of **89** or **61** and the acylating reagent in methylene chloride.

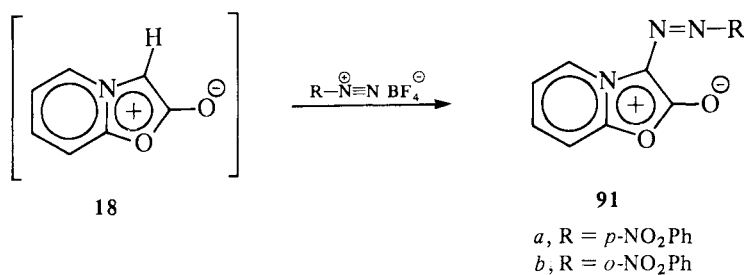


Scheme 4

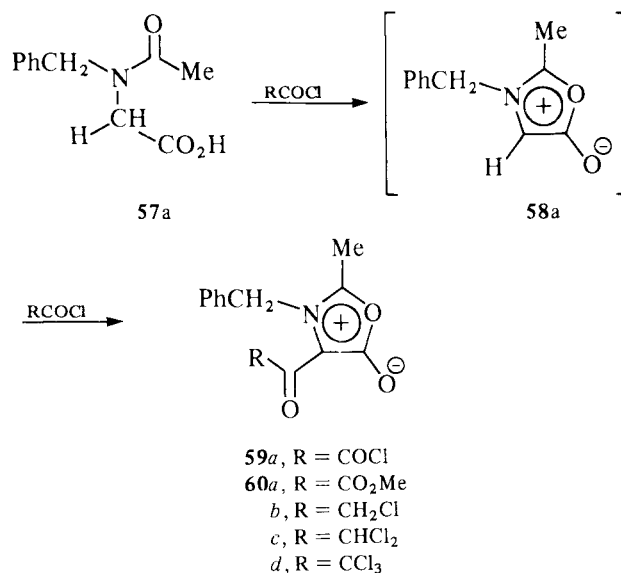


Scheme 5

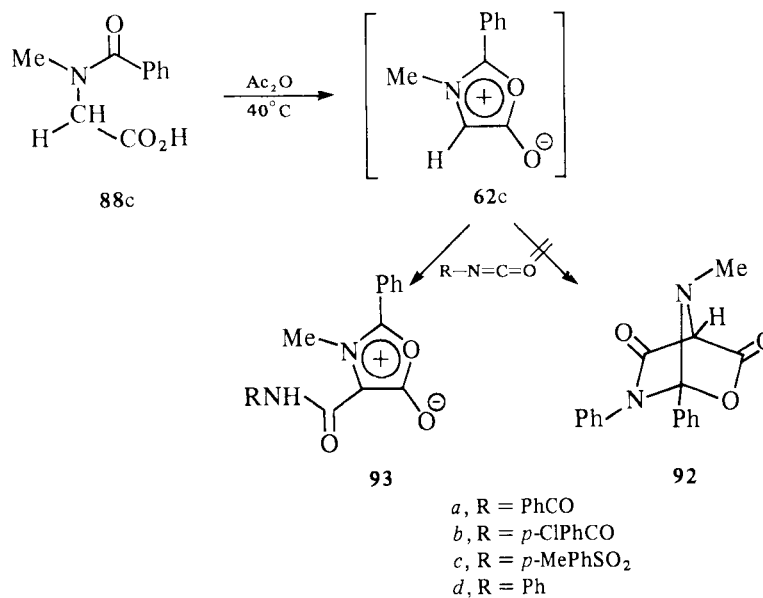
The azo compounds **91** were also prepared by adding solid aryldiazonium tetrafluoroborates to solutions of **18**.⁴⁰



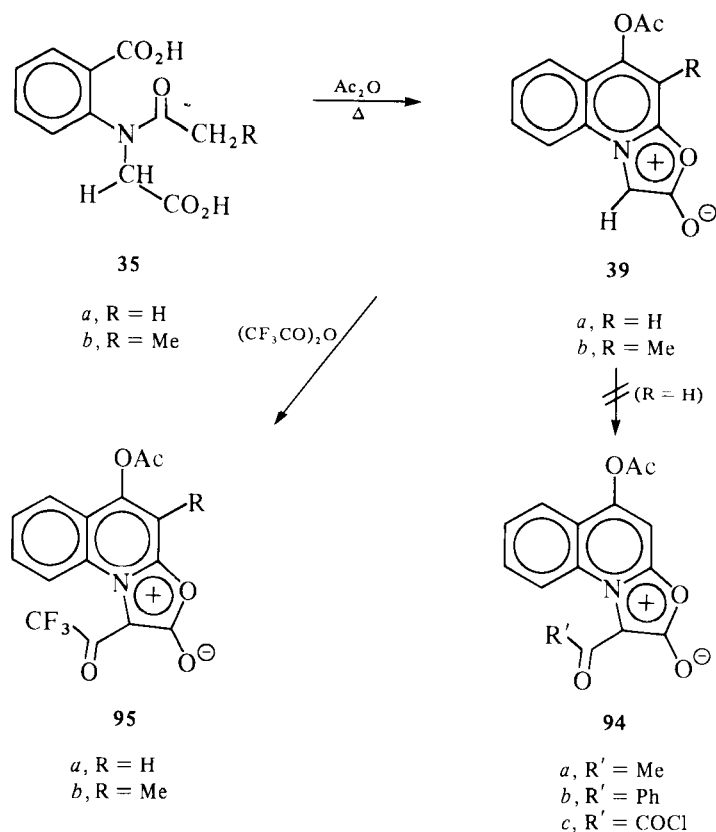
Burrows,³⁷ and subsequently Ohta and Mase,³⁸ reported that treatment of *N*-acetyl-*N*-benzylglycine **57a** with oxalyl chloride affords the 4-chloroglyoxyloxy-1,3-oxazolium 5-oxide **59a**. The initially formed 4-unsubstituted munchnone **58a** was readily acylated by the oxalyl chloride to afford **59a**. Ohta and Mase also reported the preparation of **60a–d** upon treating **57a** with methyl oxalyl chloride, monochloro-, dichloro-, and trichloroacetyl chloride.³⁸ Curiously, acetyl chloride did not effect cyclodehydration of **57a** to **58a**.



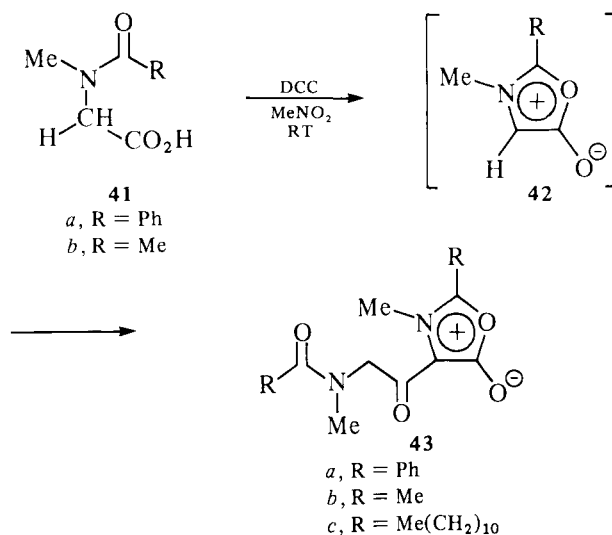
The 4-unsubstituted 1,3-oxazolium 5-oxide **62c** generated *in situ* from *N*-benzoylsarcosine **88c** and acetic anhydride at 40°C has been reported to react with activated isocyanates such as benzoyl, *p*-chlorobenzoyl, and *p*-toluenesulfonyl isocyanate.⁵⁸ The products of this reaction were originally formulated⁵⁸ as the primary cycloadducts **92a–c**; however, on the basis of spectral evidence^{56,59} these products now appear to be the 4-acyl munchnones **93a–c**. The reaction of **62c** and phenyl isocyanate to give **93d** has also been reported.⁵⁶



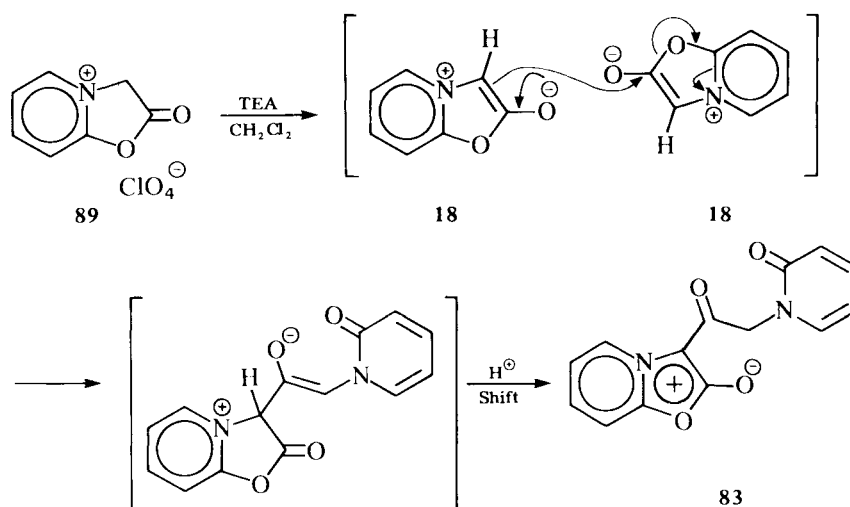
From the above discussion, it is obvious that 4-unsubstituted 1,3-oxazolium 5-oxides are readily acylated at the 4-position by carboxylic acid anhydrides, acid chlorides, and isocyanates. However, Raileanu and co-workers have reported the isolation of the stable 4-unsubstituted munchnones **39** upon heating the *N*-acyl-phenylglycine-*o*-carboxylic acids **35** with acetic anhydride.^{31,32} The mechanism of this double cyclization has been discussed previously (see Section 4.2.1). The 4-position of these 1,3-oxazolium 5-oxides **39** appears to be remarkably resistant to acylation as indicated by the failure to obtain 4-acyl derivatives **94** upon treatment of **39a** with acetic anhydride, acetyl chloride, benzoyl chloride, or oxalyl chloride, even in the presence of pyridine or boron trifluoride etherate. In fact, the only acyl derivatives of **39** that these workers were able to prepare were the 4-trifluoroacetyl derivatives **95** using trifluoroacetic anhydride. The stability of these 4-unsubstituted munchnones **39** towards acylation was attributed to the electron-withdrawing effect of the acyloxy substituent, which decreases the reactivity of the 4-position.



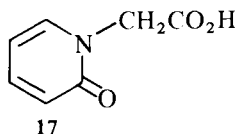
When 4-unsubstituted 1,3-oxazolium 5-oxides are generated in the absence of an acylating reagent, they undergo a self-condensation or dimerization reaction. Greco and co-workers reported the first examples of this reaction when they attempted the cyclodehydration of *N*-benzoylsarcosine **41a** and *N*-acetylsarcosine **41b** with



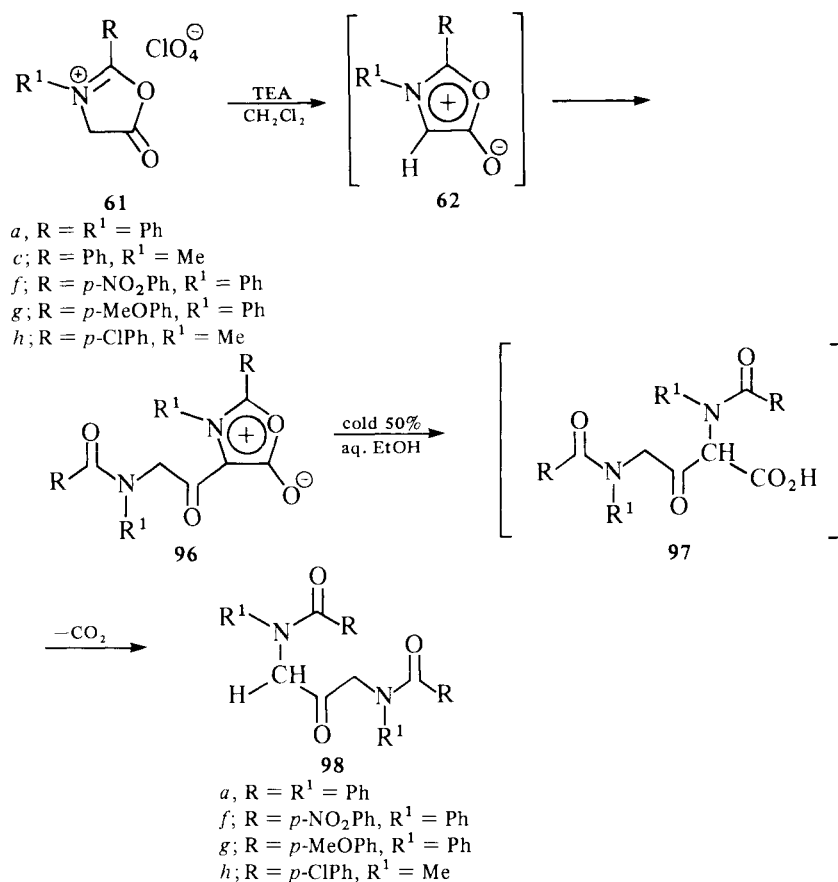
N,N'-dicyclohexylcarbodiimide (DCC).³³ Instead of the expected 4-unsubstituted munchnones **42**, they obtained the dimeric 4-acyl munchnones **43a, b**, respectively. Interestingly, **43c** has been patented as a fuel additive, as a detergent and corrosion inhibitor.⁶⁰ Boyd and Wright have studied this dimerization reaction in detail employing their oxazolonium perchlorate technique.^{40,42} When the bicyclic oxazolonium perchlorate **89** was added in small portions to a methylene chloride solution containing excess TEA, a straw-colored solution of the bicyclic 4-unsubstituted 1,3-oxazolium 5-oxide **18** was obtained.⁴⁰ This solution slowly deposited the colorless dimer **83**. It was proposed that dimer **83** is formed from monomer **18** when one molecule functions as an electrophile and another as a nucleophile. When triethylamine was added to a suspension of the oxazolonium



perchlorate **89** in methylene chloride, the dimer **83** was formed almost instantly. In this case, the dimer **83** is presumably formed by reaction of **18** with the more reactive electrophile cation **89**. Dimer **83** can also be obtained from 1,2-dihydro-2-oxo-1-pyridylacetic acid **17** upon treatment with DCC.⁴⁰



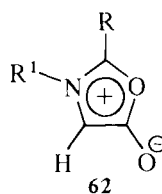
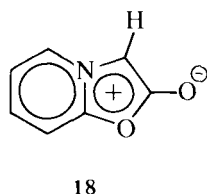
Boyd and Wright have also examined the dimerization reaction of the monocyclic 4-unsubstituted 1,3-oxazolium 5-oxides **62**, as illustrated in Scheme 6.⁴² When triethylamine was added to a suspension of the monocyclic oxazolonium perchlorate **61c** in methylene chloride, the munchnone dimer **96c** ($\equiv$ **43a**) previously reported by Greco and co-workers³³ formed almost instantly. As in the case of the bicyclic oxazolonium perchlorate **89**, when **61c** was slowly added to a



Scheme 6

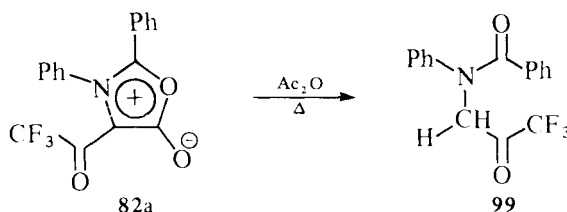
solution of triethylamine in methylene chloride, the resulting solution slowly deposited the dimer **96c**. However, deprotonation of the oxazolonium perchlorates **61a** and **61f, h** did not afford the dimers **96a** and **96f, h** but gave instead the acyclic ketones **98a** and **98f, h**, respectively.⁴² These results were rationalized by assuming that the dimers **96** undergo hydrolytic ring opening during work-up (cold 50% aqueous ethanol) to give the β -keto acids **97**, which upon subsequent decarboxylation afford the observed acyclic ketones **98**, as depicted in Scheme 6.

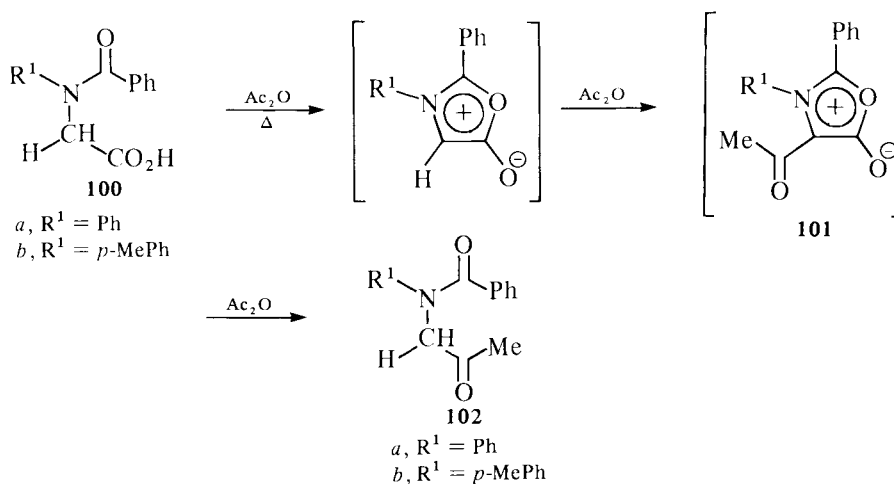
Boyd and Wright⁴² have also studied the rates of dimerization of the 4-unsubstituted 1,3-oxazolium 5-oxides **18** and **62** prepared by the deprotonation of their oxazolonium perchlorate precursors **89** and **61** in methylene chloride solution by using IR spectroscopy to measure the disappearance of **18** and **62**. The bicyclic munchnone **18** was the most stable of the compounds studied with a half-life of ca. 30 min at room temperature (in 0.1 M solution). The stability of **18** may be due to its comparatively low reactivity toward nucleophiles since dimerization involves the loss of one of the aromatic pyridinium rings. For the monocyclic munchnones **62**, the *N*-methyl compounds dimerize ca. 10 times more slowly than the *N*-phenyl compounds. Aryl substitution at C-2 also slows the dimerization, since the 2-methyl derivative **62e** dimerizes "immeasurably" fast. Finally, substituents on the C-2 aryl ring appear to have little effect on the dimerization rate.



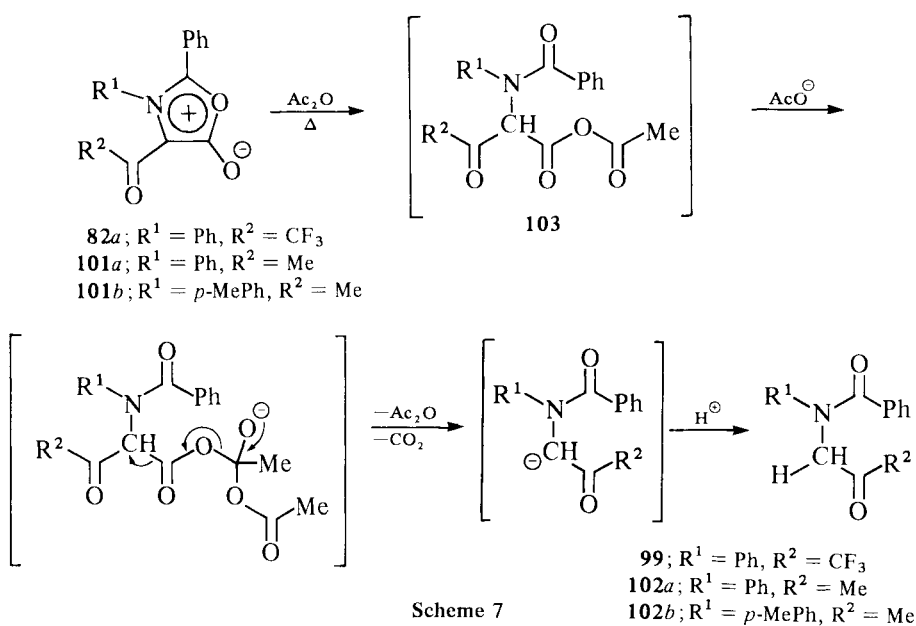
- a*, R = R¹ = Ph
c; R = Ph, R¹ = Me
e; R = Me, R¹ = Ph
f; R = *p*-NO₂Ph, R¹ = Ph
g; R = *p*-MeOPh, R¹ = Ph
h; R = *p*-ClPh, R¹ = Me
i; R = *p*-NO₂Ph, R¹ = Me

4-Acyl-1,3-oxazolium 5-oxides are capable of reacting further with carboxylic acid anhydrides. For example, Singh and Singh reported the formation of the α -acylaminoketone **99** when the 4-trifluoroacetyl munchnone **82a** and acetic anhydride were heated at reflux.¹⁹ Additionally, the reaction of *N*-benzoyl-*N*-phenyl-(**100a**) and *N*-benzoyl-*N*-(*p*-tolyl)glycine (**100b**) with acetic anhydride





affords only the α -acylaminoketones **102**, presumably through the intermediacy of the 4-acetyl-1,3-oxazolium 5-oxides **101**. The conversion of α -amino acids or *N*-acyl α -amino acids to their corresponding α -acylaminoketones upon heating with acetic anhydride and pyridine is known as the Dakin–West reaction.⁶¹ Based on their observations, Singh and Singh postulated that 4-acyl munchnones such as **82a** and **101** are intermediates in the Dakin–West reaction of *N*-acyl secondary amino acids with acetic anhydride.¹⁹ These workers rationalized the formation of the α -acylaminoketones **99** and **102** as indicated in Scheme 7. The 4-acyl-1,3-oxazolium 5-oxides **82a** and **101** are converted to the mixed anhydrides **103** upon heating with

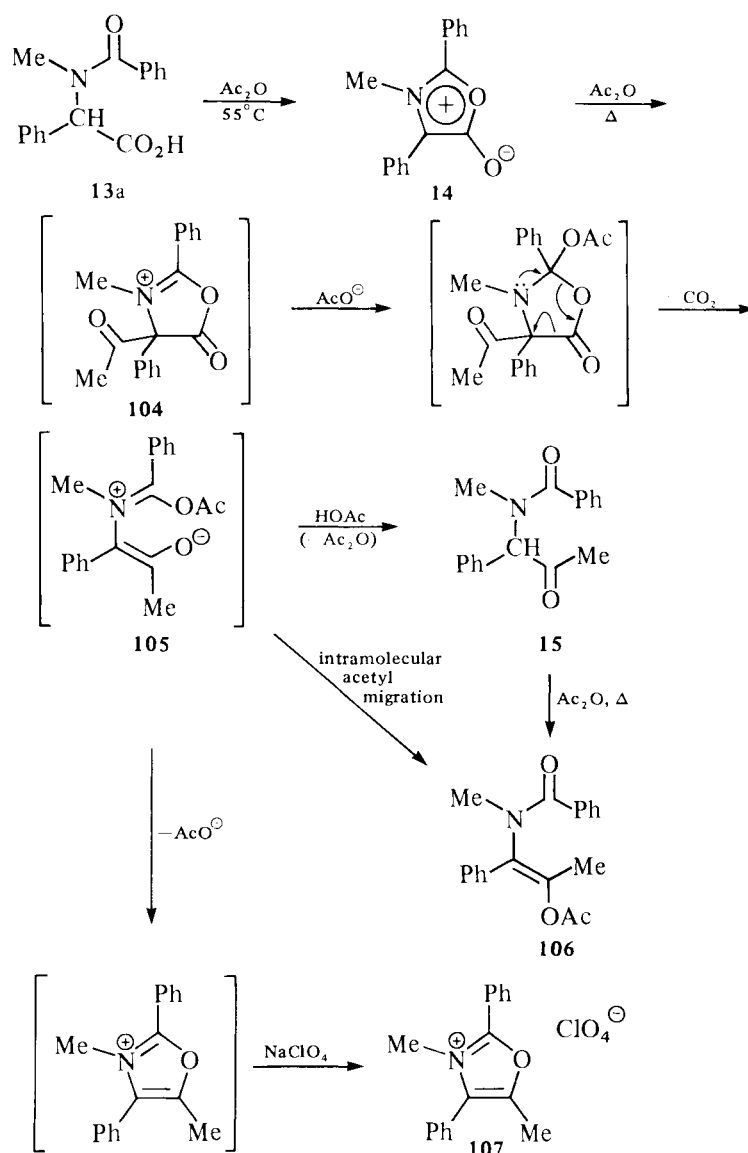


Scheme 7

99; $\text{R}^1 = \text{Ph}, \text{R}^2 = \text{CF}_3$
102a; $\text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me}$
102b; $\text{R}^1 = p\text{-MePh}, \text{R}^2 = \text{Me}$

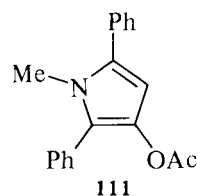
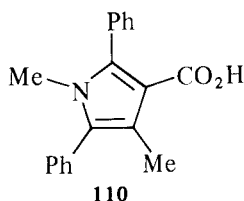
acetic anhydride. Acetate attack of mixed anhydrides **103** followed by decarboxylation affords the observed *N*-acylaminoketones **99** and **102**. It should be noted that the Dakin–West reaction of *N*-acyl primary amino acids with acetic anhydride requires the presence of pyridine and does not involve a munchnone intermediate.^{62, 63}

Knorr and Huisgen have studied the Dakin–West reaction of additional *N*-acyl secondary amino acids with an α -substituent. As indicated in Scheme 8, the



Scheme 8

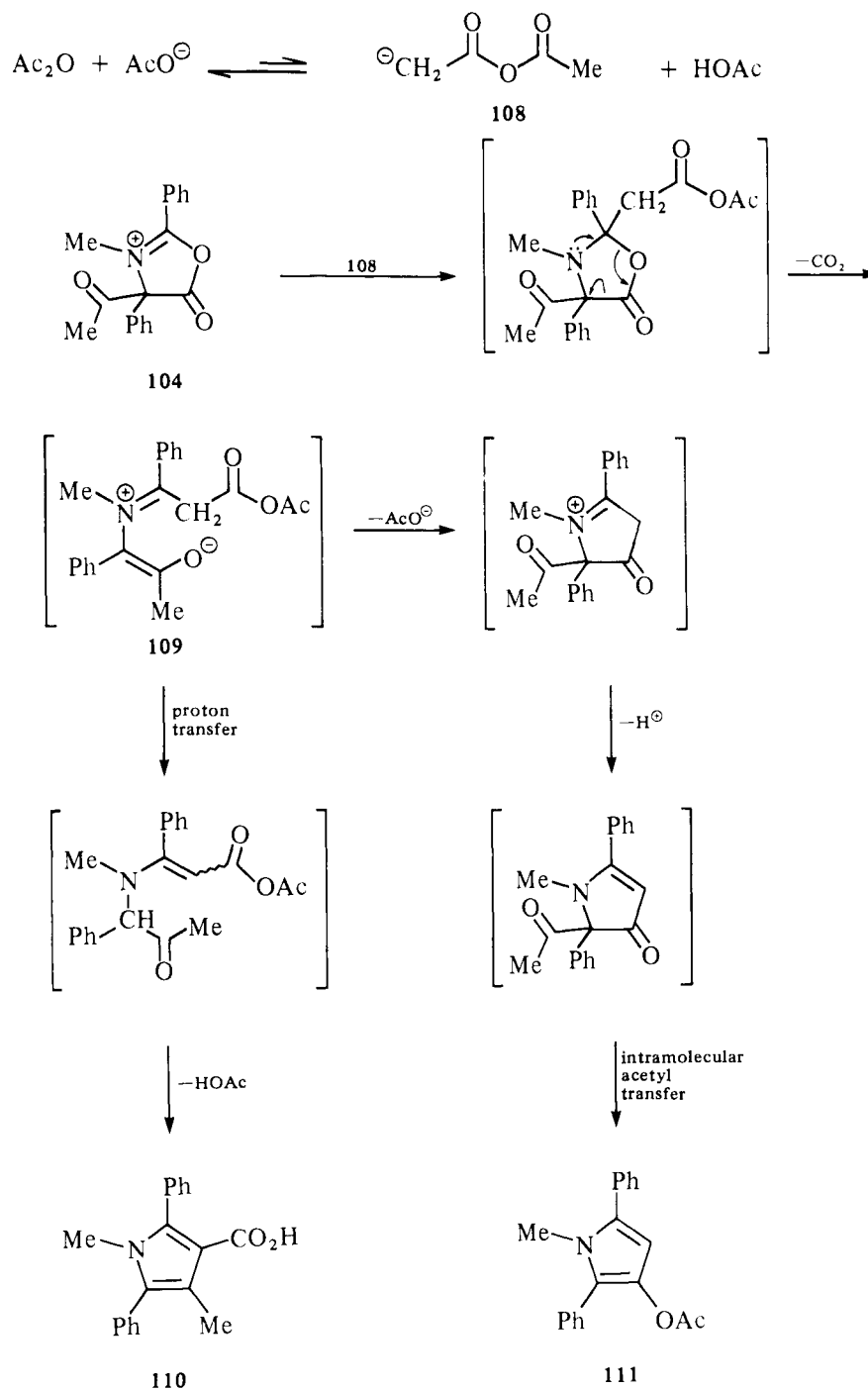
reaction of *N*-methyl-*N*-benzoyl-*C*-phenylglycine **13a** with acetic anhydride at 55°C affords the 1,3-oxazolium 5-oxide **14**.^{15,17} However, reaction of **13a** with acetic anhydride (containing 1.07 *M* acetic acid) at 90°C gave a 70% yield of the α -acylaminoketones **15**, the normal Dakin–West product.¹⁸ When the reaction mixture contains pyridine (1.24 *M*), only the enolacetate **106** is obtained. Refluxing acetic anhydride converts **15** to **106** in the absence of pyridine. The reaction of 1,3-oxazolium 5-oxide **14** with acetic anhydride containing a low concentration of acetic acid (0.1 *M*) at 90°C gave none of the Dakin–West product **15**. Instead, the enolacetate **106** (8%) was obtained, as well as three additional products: the pyrrolecarboxylic acid **110** (13%), the acetoxypyrrole **111** (7%), and the oxazolium salt **107** (0.4%), the major product upon reaction of **14** with acetyl chloride.



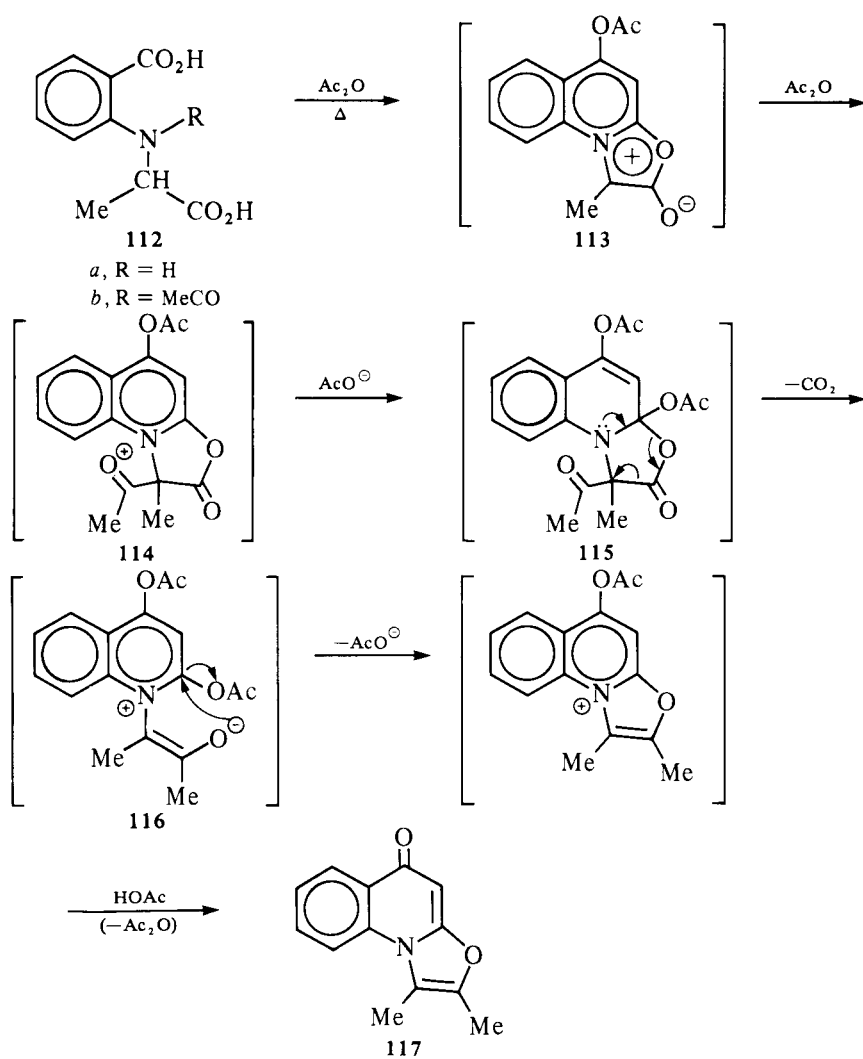
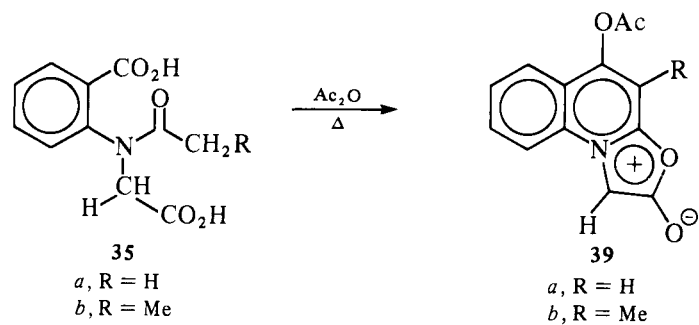
It is obvious that the product distribution is dependent on the acetic acid concentration in the acetic anhydride employed. High acetic acid concentrations afford the normal Dakin–West product **15**, while low acetic acid concentrations give **106**, **107**, **110**, and **111**. Knorr and Huisgen¹⁸ rationalized the formation of **15**, **106**, and **107** as shown in Scheme 8. The key zwitterionic intermediate **105** affords the normal Dakin–West product **15** when high concentrations of acetic acid are present. Zwitterion **105** can also cyclize to yield the oxazolonium salt **107** (upon addition of sodium perchlorate). Finally, zwitterion **105** can undergo an intramolecular acetyl transfer to give the enolacetate **106**.

The formation of the pyrroles **110** and **111** is somewhat more difficult to rationalize. The mechanism shown in Scheme 9 was proposed¹⁸ for the formation of **110** and **111**. The key intermediate in this pathway is the zwitterion **109**, which is formed by attack of anion **108** upon the 4-acetyloxazolonium ion **104**, followed by decarboxylation. With high concentrations of acetic acid, the concentration of anion **108** is low, and **108** cannot compete effectively with acetate for oxazolonium ion **104**. Zwitterion **109** affords pyrroles **110** and **111** as indicated in Scheme 9. Knorr and Huisgen also investigated the reaction of additional *N*-acyl secondary amino acids with acetic anhydride and acetic acid with similar results.¹⁸

As noted previously, Raileanu and co-workers have reported the isolation of the stable 4-unsubstituted 1,3-oxazolium 5-oxides **39**, which were remarkably resistant to acylation at the 4-position.^{31,32} The mechanism of this double cyclization of the *N*-acylphenylglycine-*o*-carboxylic acids **35** has been discussed (see Section 4.2.1). Interestingly, when the related phenylalanine-*o*-carboxylic acid **112a** or its *N*-acetyl derivative **112b** was refluxed in acetic anhydride, the expected munchnone **113** underwent acetylation at the 4-position as indicated in Scheme 10.^{31,32} The subsequent Dakin–West reaction ultimately affords the oxazolo-



Scheme 9



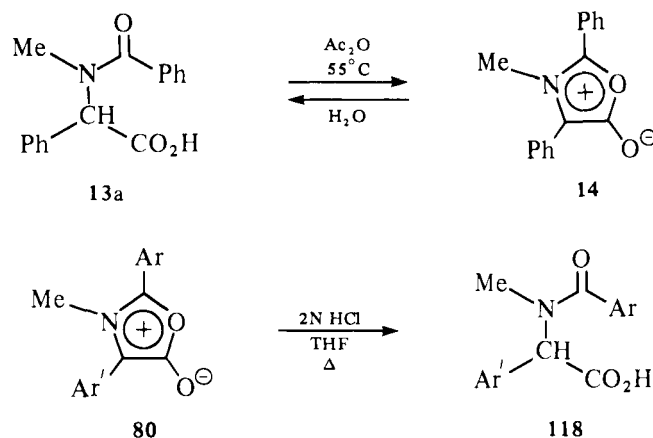
Scheme 10

[3,2-*a*]quinoline **117**. Presumably the electron-donating effect of the methyl group at the 4-position of **113** enhances the reactivity at this position, allowing acetylation to occur. It should be noted that the intermediates **114**–**116** correspond to the Dakin–West intermediates proposed by Knorr and Huisgen (see Scheme 8).¹⁸

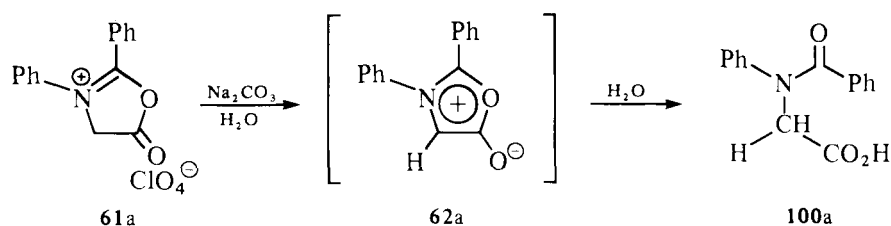
4.2.3.2. Nucleophilic Additions

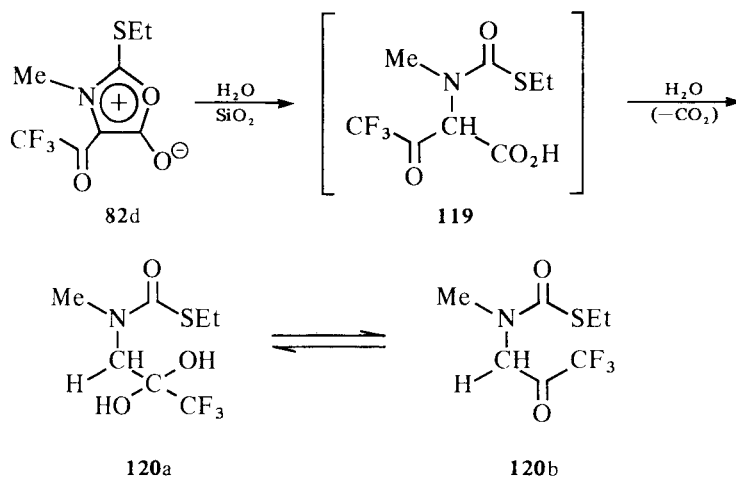
4.2.3.2.1. WATER AND ALCOHOL ADDITIONS

Upon isolating 3-methyl-2,4-diphenyl-1,3-oxazolium 5-oxide **14**, Huisgen and co-workers¹⁷ observed that it was readily hydrolyzed to its precursor *N*-aroylamino acid **13a**. In fact, this hydrolytic instability is probably one of the reasons munchnones had previously escaped notice. These workers have reported the rapid hydrolysis of additional 3-methyl-2,4-diaryl-1,3-oxazolium 5-oxides **80** to their *N*-aroylamino acid precursors **118** with 2 *N* HCl in tetrahydrofuran.¹⁵

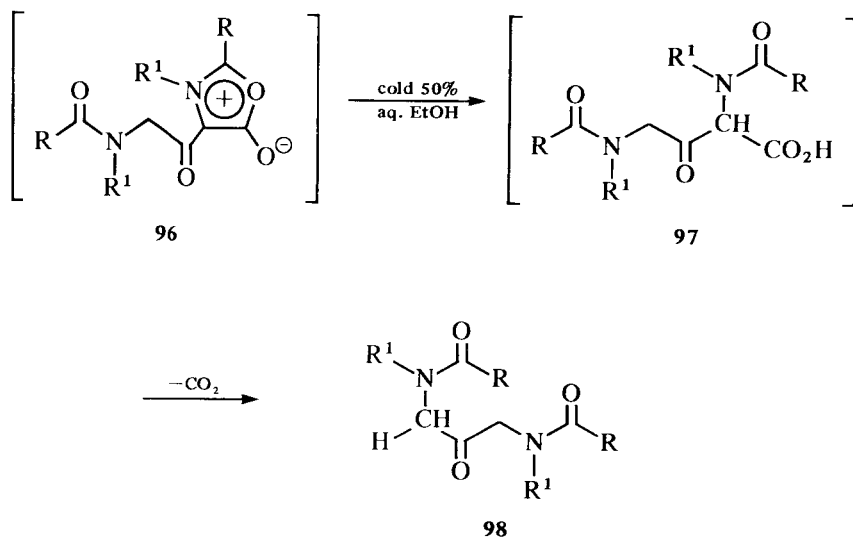


Boyd and Wright have reported that the oxazolonium perchlorate **61a** was readily hydrolyzed by water to give the parent *N*-aroylamino acid **100a** without the development of color in the reaction mixture.^{39,41} Presumably this hydrolysis proceeds by attack of water on the cation **61a**. However, hydrolysis with aqueous sodium carbonate appears to proceed at least in part via the munchnone **62a** since a transient yellow coloration is observed during the sodium carbonate hydrolysis.

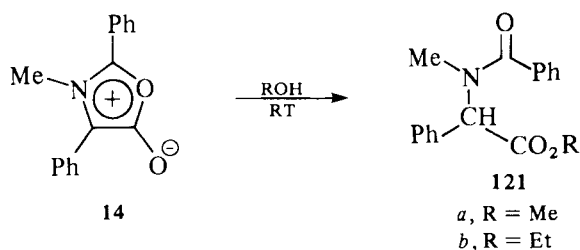




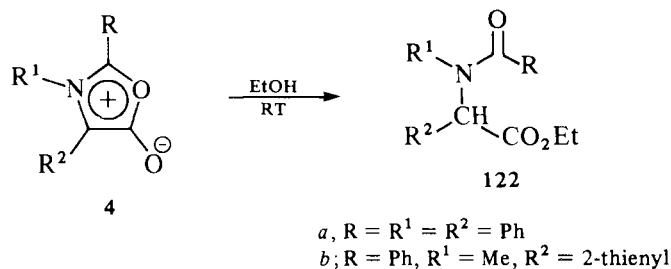
Upon attempted silica gel chromatography of the 4-trifluoroacetyl-1,3-oxazolium 5-oxide **82d**, Gotthardt and Reiter⁵⁵ obtained an 81% yield of the α -acylaminotrifluoromethylketone **120**, which was shown by ^1H NMR spectroscopy to exist as an equilibrium mixture favoring the monohydrate **120a** (75%). The formation of **120** was rationalized by initial water addition to **82d** to give the β -ketoacid **119**, followed by decarboxylation. Similarly, Boyd and Wright obtained the α -acylaminoketones **98** upon treating the 4-acyl munchnone dimers **96** with cold aqueous ethanol.⁴²



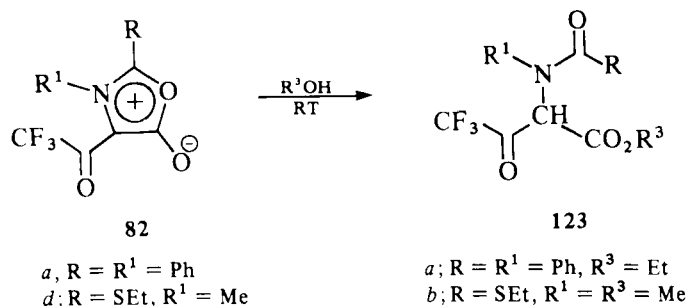
a, $\text{R} = \text{R}^1 = \text{Ph}$
f; $\text{R} = p\text{-NO}_2\text{Ph}$, $\text{R}^1 = \text{Ph}$
g; $\text{R} = p\text{-MeOPh}$, $\text{R}^1 = \text{Ph}$
h; $\text{R} = p\text{-ClPh}$, $\text{R}^1 = \text{Me}$

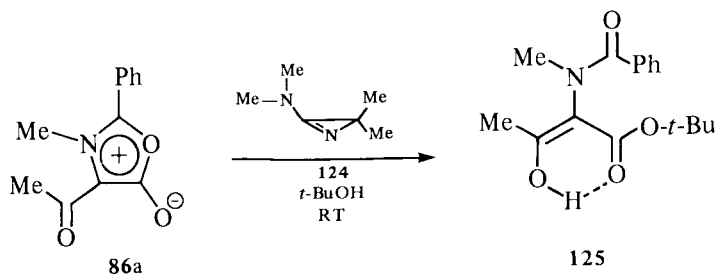


Huisgen and co-workers¹⁵ have also reported the addition of alcohols to the 1,3-oxazolium 5-oxide **14** to give esters **121**. Similarly, Alper and Tanaka²⁰ have reported several additional examples of the addition of ethanol to munchnones **4**.



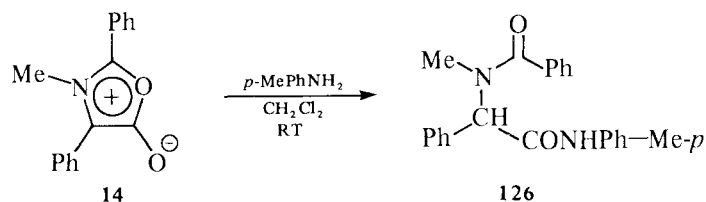
Singh and Singh¹⁹ have reported that the 4-trifluoroacetyl-1,3-oxazolium 5-oxide **82a** undergoes a facile and quantitative reaction with ethanol to afford the β-ketoester **123a**. Similarly, Gotthardt and Reiter⁵⁵ found that **82d** undergoes a spontaneous reaction at room temperature with absolute methanol to afford a quantitative yield of the β-ketoester **123b**, which appeared to exist as a keto–enol tautomeric mixture according to ¹H NMR spectroscopy. Finally, Lukáč and Heimgartner⁶⁴ have reported that 4-acetyl-1,3-oxazolium 5-oxide **86a** reacts with *t*-butyl alcohol in the presence of aminoazirine **124** at room temperature to afford a 69% yield of the β-ketoester **125**. Apparently, **125** was not formed under identical conditions in the absence of aminoazirine **124**. β-Ketoester **125** exists almost exclusively in the enol form in CDCl₃ solution as determined by ¹H NMR spectroscopy.



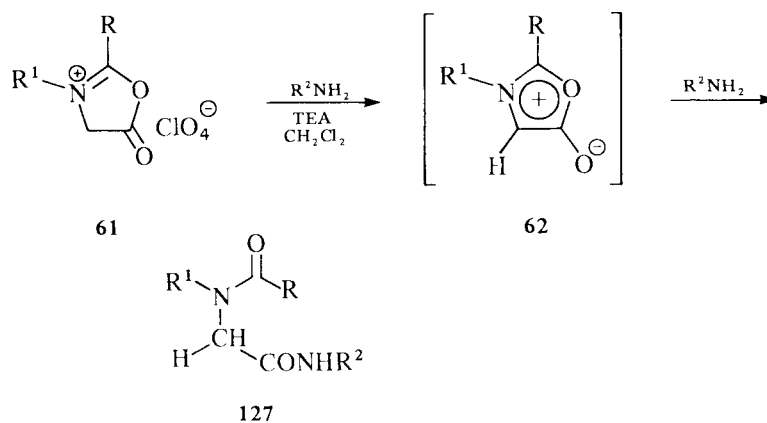


4.2.3.2.2. AMINE ADDITIONS

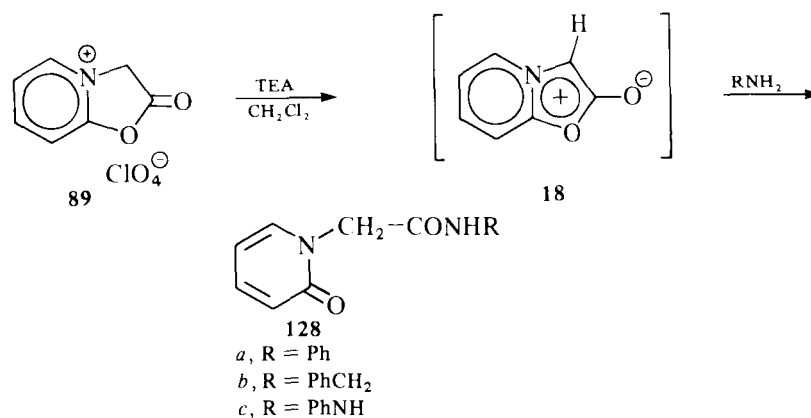
In a similar vein, Huisgen and co-workers¹⁵ have reported the addition of *p*-toluidine to munchnone **14** to give amide **126**.



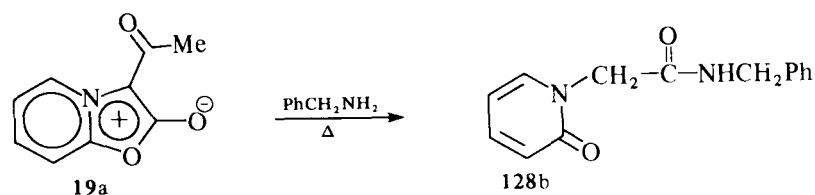
Boyd and Wright^{39,41} have reported that the portionwise addition of the oxazolonium perchlorates **61** to solutions of benzylamine or aniline and TEA in methylene chloride affords the amides **127**. These aminolysis reactions are accompanied by a transient yellow or orange coloration, which implicates the 1,3-oxazolium 5-oxides **62** as intermediates in these reactions. Similarly, these



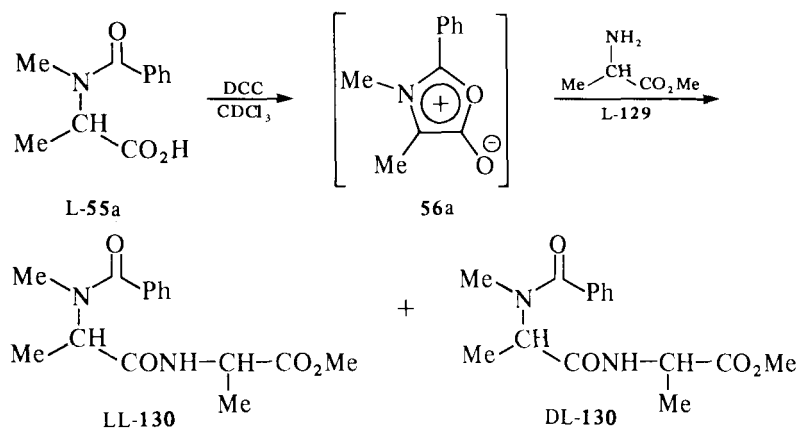
- a; R = R¹ = Ph, R² = PhCH₂
 b; R = *p*-MeOPh, R¹ = R² = Ph
 c; R = *p*-ClPh, R¹ = Me, R² = Ph
 d; R = *p*-NO₂Ph, R¹ = Me, R² = Ph
 e; R = Ph₂N, R¹ = Me, R² = PhCH₂



workers⁴⁰ have reported that solutions of the bicyclic 4-unsubstituted munchnone **18** react with aniline, benzylamine, and phenylhydrazine to give high yields of the amides **128**. The *N*-benzylamide **128b** was also obtained by Lawson and Miles upon heating the 4-acetyl-1,3-oxazolium 5-oxide **19a** with benzylamine.³⁰ In this case, ring opening was accompanied by deacetylation.

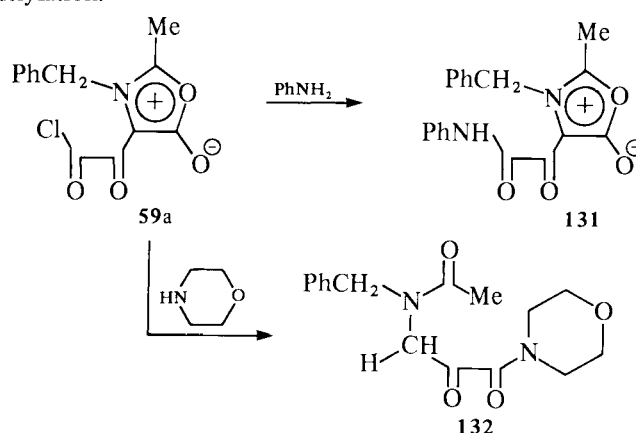


As noted previously (see Section 4.2.1), munchnones have been implicated as racemization intermediates of *N*-methylamino acid residues during *N,N'*-dicyclohexylcarbodiimide- (DCC-) mediated peptide bond formation.^{35,36} For instance,³⁶ coupling of *N*-benzoyl-*N*-methyl-L-alanine **55a** with L-alanine methyl ester **129** affords the racemic dipeptide **130**. The involvement of the 1,3-oxazolium 5-oxide



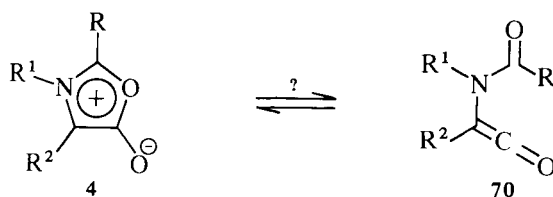
56a in such dipeptide coupling reactions is insidious in the respect that it is both responsible for the racemization of the amino acid residue **55a** and that it is a reaction intermediate, which upon aminolysis affords the observed dipeptide.

Finally, the reaction of the 4-chloroglyoxyloyl munchnone **59a** with amines deserves comment. Ohta and Kato have reported that reaction of **59a** with aniline gives the anilide **131** with retention of the mesoionic ring.⁷ On the other hand, reaction of **59a** with morpholine gives amide **132** upon hydrolytic ring opening and decarboxylation.



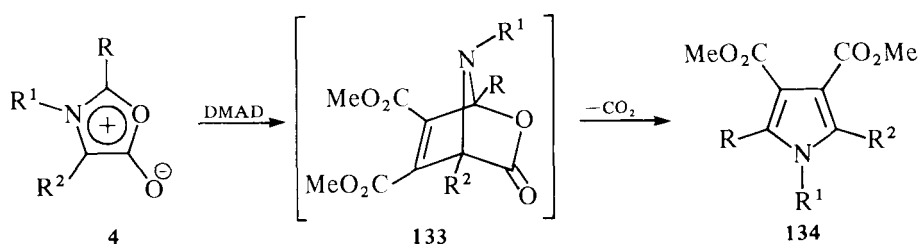
4.2.3.3. Cycloaddition Reactions

By far the most important reactions of 1,3-oxazolium 5-oxides from a synthetic point of view are 1,3-dipolar cycloaddition reactions. Huisgen and his school discovered that 1,3-oxazolium 5-oxides, behaving as cyclic azomethine ylides, undergo 1,3-dipolar cycloaddition reactions with a diverse group of dipolarophiles. As with most 1,3-dipolar cycloaddition reactions, this reaction is generally considered to be a single-step, concerted [$\pi_{4s} + \pi_{2s}$] cycloaddition, where the 1,3-dipole and the dipolarophile are envisioned as approaching each other in a “two-plane” orientation complex.⁶⁵ An alternate mechanism involving a spin-paired diradical intermediate has also been proposed.⁶⁶ Munchnones **4** undergo additional cycloaddition reactions, which at least in a formal sense involve [2 + 2] and [4 + 2] cycloaddition reactions of the presumed valence tautomer **70** (see Section 4.2.3.4).

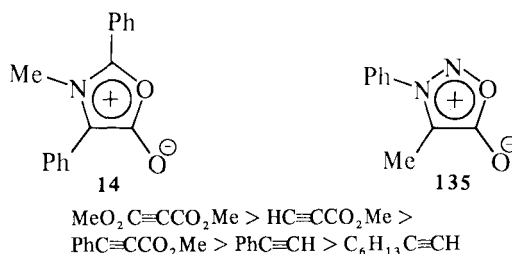


4.2.3.3.1. WITH ACETYLENIC DIPOLAROPHILES

The reaction of 1,3-oxazolium 5-oxides **4** with acetylenic dipolarophiles constitutes a pyrrole synthesis of broad scope.^{17,24,67} The reaction involves a 1,3-dipolar cycloaddition reaction of the munchnones **4** behaving as cyclic azomethine ylides to acetylenic dipolarophiles illustrated below with dimethyl acetylenedicarboxylate (DMAD). The primary cycloadducts **133**, which are rarely isolable, readily eliminate carbon dioxide to give pyrroles **134** in good yield. Kinetic studies involving the reactions of the isolable 3-methyl-2,4-diphenyl-1,3-oxazolium



5-oxide **14** with acetylenic dipolarophiles in benzonitrile obey a second-order rate law.⁶⁸ The activity order of dipolarophiles, indicated below, and the large negative activation entropies are characteristic of 1,3-dipolar cycloaddition reactions. Additionally, the rate constants of **14** are higher than for the corresponding cycloaddition reactions of the sydnone **135**; however, **14** exhibits the higher selectivity.⁶⁸



A compilation of 1,3-dipolar cycloaddition reactions of monocyclic and polycyclic munchnones with DMAD is contained in Tables 4.2 and 4.3, respectively. As has been noted previously, many 1,3-oxazolium 5-oxides are too unstable to be isolated.²⁴ The scope of this pyrrole synthesis is enhanced by employing *in situ* procedures in which the desired munchnone is generated in the presence of DMAD (or other acetylenic dipolarophiles). Suitable 1,3-oxazolium 5-oxide precursors are *N*-acylamino acids **13** and oxazolonium perchlorates **61**. With *N*-acylamino acid precursors **13**, carboxylic acid anhydrides,^{17,24,67} usually acetic anhydride, and

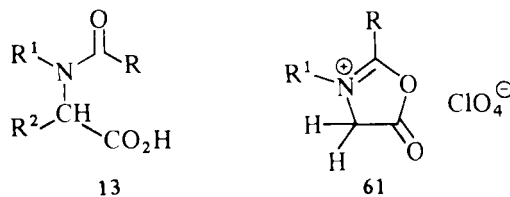
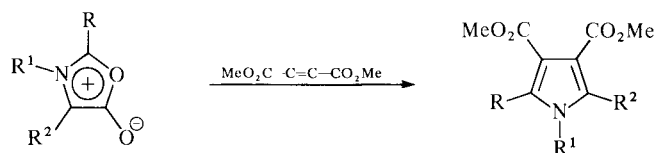
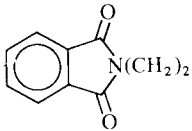


TABLE 4.2. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF MONOCYCLIC 1,3-OXAZOLIUM 5-OXIDES AND DIMETHYL ACETYLENEDICARBOXYLATE (DMAD)



Method of Munchnone Preparation ^a	R	R ¹	R ²	Percent Yield	Reference
B	H	Me	H	50	73
D				62	73
B	H	Ph	H	91	17, 24, 67
C	(Me) ^b	Me	H	36	17, 24, 67
C	(Me) ^b	Me	Me	87	24, 67
B	Me	Me	Ph	90	17, 24, 67
B	Me	Cyclo-C ₆ H ₁₁	Me	97	24, 67
B	Me	Ph	H	76	24, 67
E				79	42
B	Me	Ph	Me	80	17, 24, 67
B				88	69
C	(Me) ^b	Ph	Me	41	24
B	Me	4-MePh	Me	90	69
B	Me	4- <i>n</i> -BuPh	Me	71	69
B	Me	4-MeOPh	Me	98	69
B	Me	4-EtOPh	Me	83	69
B	Me	3,4-OCH ₂ OPh	Me	87	69
B	Me	4-FPh	Me	90	69
B	Me	4-ClPh	Me	99	69
B	Me	4-BrPh	Me	92	69
B	Me	3,4-Cl ₂ Ph	Me	95	69
B	Cyclo-C ₆ H ₁₁	Me	Ph	98	24, 67
A	EtS	Me	CF ₃ CO	6	55
B	MeO ₂ C(CH ₂) ₃	Me	H	57	75
A		Me	Ph	89	24
B	Ph	Me	H	68	26
D				84	74
E				81	42
F				73	42
B	Ph	Me	Me	83	17, 24, 67
B				85	70
A	Ph	Me	Ph	95	17, 24, 67
B				93	24, 67
A	Ph	Me	4-NO ₂ PhCO	93	42

TABLE 4.2. (CONTINUED)

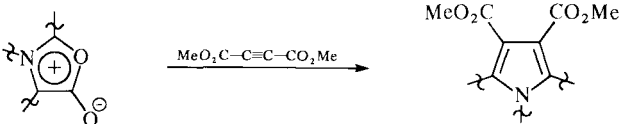
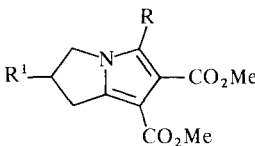
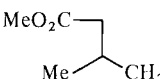
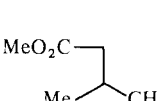
Method of Munchnone Preparation ^a	R	R ¹	R ²	Percent Yield	Reference
E	Ph	Ph	H	80	39, 42
E	4-NO ₂ Ph	Me	H	53	42
E	4-ClPh	Me	H	85	42
B	4-MePh	Me	Me	85	70
B	4- <i>t</i> -BuPh	Me	Me	93	70
B	4-MeOPh	Me	Me	91	70
B	4- <i>n</i> -BuOPh	Me	Me	89	70
B	4-MeSPh	Me	Me	94	70
B	4-MeSO ₂ Ph	Me	Me	75	70
B	4-NO ₂ Ph	Me	Me	99	70
B	4-FPh	Me	Me	96	70
B	4-ClPh	Me	Me	100	70
B	4-BrPh	Me	Me	93	70
B	3,4-Cl ₂ Ph	Me	Me	82	70
B	4-Ph-Ph	Me	Me	96	70
B	4-PhSPh	Me	Me	90	70
B	4-PhSO ₂ Ph	Me	Me	91	70
E	4-MeOPh	Ph	H	65	42
E	4-NO ₂ Ph	Ph	H	69	42
F				21	42
					
B		Me	H	59	72
B	Ph ₂ N	Me	H	40	42

^aA, Preformed; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride; D, *in situ* cyclodehydration of *N*-acylamino acid precursor with DCC; E, oxazolonium perchlorate precursor added to cold solution of DMAD in acetonitrile or benzene, followed by addition of triethylamine; F, oxazolonium perchlorate precursor added in small portions to cold solution of triethylamine in methylene chloride, followed by immediate addition of DMAD.

^bSubstituents in parentheses introduced by cyclodehydrating reagent.

N,N'-dicyclohexylcarbodiimide (DCC)^{29,35,73,74} are convenient *in situ* cyclodehydrating reagents. Treatment of the oxazolonium perchlorates **61** with base, usually TEA, liberates the corresponding munchnones *in situ*.^{39,42} Amino acids **29** can also be used as 1,3-oxazolium 5-oxide precursors.^{17,24,28,67} When carboxylic acid anhydrides are employed as the cyclodehydrating agent, the amino acids **29** initially undergo *N*-acylation to give **13**. Thus, in this case, the R substituent of the *in-situ*-generated munchnone **4** is introduced by the carboxylic acid anhydride cyclodehydrating agent.

TABLE 4.3. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF POLYCYCLIC 1,3-OXAZOLIUM 5-OXIDES AND DIMETHYL ACETYLENEDICARBOXYLATE (DMAD)

												
Method of Munchnone Preparation ^a	Structure of Product	Percent Yield	Reference									
												
	<table><tr><th>R</th><th>R¹</th></tr><tr><td>(Me)^b</td><td>H</td></tr><tr><td>(CF₃)^b</td><td>H</td></tr><tr><td>MeO₂C(CH₂)₃</td><td>H</td></tr></table>	R	R ¹	(Me) ^b	H	(CF ₃) ^b	H	MeO ₂ C(CH ₂) ₃	H			
R	R ¹											
(Me) ^b	H											
(CF ₃) ^b	H											
MeO ₂ C(CH ₂) ₃	H											
C	(Me) ^b	H	76	17, 24, 67								
C	(CF ₃) ^b	H	78	76								
A	MeO ₂ C(CH ₂) ₃	H	ca. 45	75								
A		H	—	78								
A			—	78								
A	Ph	H	87	76								
A	4-MeOPh	H	82	76								
A	4-FPh	H	99	76								
A	4-ClPh	H	90	76								
A	2,3-F ₂ Ph	H	55	77								
A	2,4-F ₂ Ph	H	76	77								
A	2,5-F ₂ Ph	H	80	77								
A	2,6-F ₂ Ph	H	63	77								
A	3,4-F ₂ Ph	H	84	77								
A	3,4-Cl ₂ Ph	H	91	76								

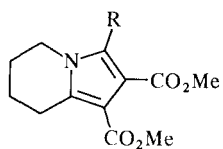


TABLE 4.3. (CONTINUED)

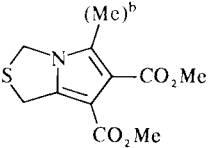
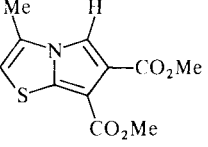
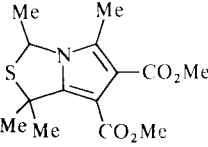
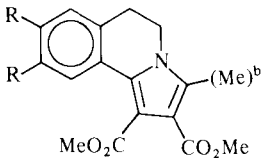
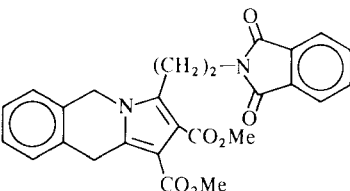
Method of Munchnone Preparation ^a	Structure of Product	Percent Yield	Reference
	R		
C	(Me) ^b	28	79
A	MeO ₂ C(CH ₂) ₃	ca. 38	75
C		49	80
A		83	81
A		51–56	82
			
	R		
C	H	62	83
C	MeO	78	83
A			72

TABLE 4.3. (CONTINUED)

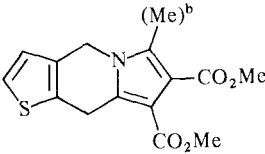
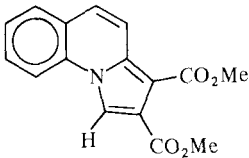
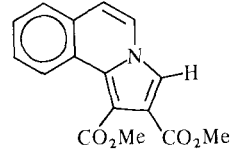
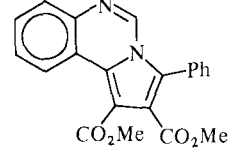
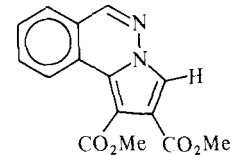
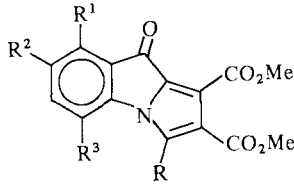
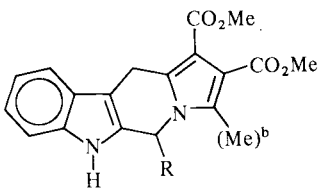
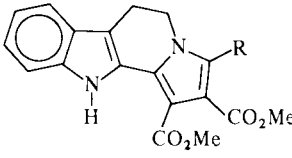
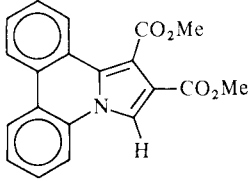
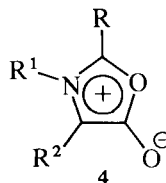
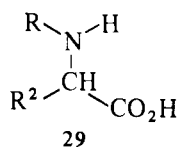
Method of Munchnane Preparation ^a	Structure of Product	Percent Yield	Reference
C		68	84
D		35	29
D		39	29
A		—	86
D		86	85
			
	R R ¹ R ² R ³		

TABLE 4.3. (CONTINUED)

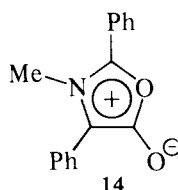
Method of Munchnone Preparation ^a	Structure of Product					Percent Yield	Reference
B	H	H	H	H		20	27
B	Me	H	H	H		62	27
A	Me	H	Me	H		70	27
A	Me	H	Cl	Cl		47	27
A	Me	H	Br	H		64	27
A	Me	Cl	H	MeO		29	27
A	Me	Cl	H	Cl		51	27
							
R							
C	H					64	28
C	PhCH ₂					27	28
C	4-MeOPh					49	28
							
R							
C	(Me) ^b					75	28
C	(Et) ^b					69	28
							
D						52	29

^aA, *In situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, *in situ* cyclodehydration of *N*-acylamino acid precursor in refluxing *n*-butyric anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with carboxylic acid anhydride; D, *in situ* cyclodehydration of *N*-acylamino acid precursor with DCC.

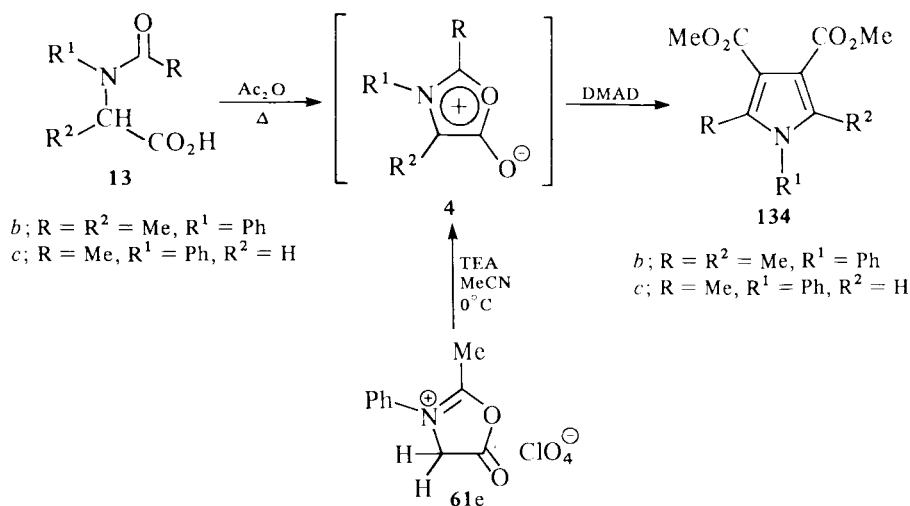
^bSubstituents in parentheses introduced by cyclodehydrating reagent.



In any case, whether isolable 1,3-oxazolium 5-oxides are employed or an *in situ* procedure is utilized, the reaction conditions (i.e., temperature and reaction time) required for the cycloaddition reaction of a munchnone and an acetylenic dipolarophile can be conveniently determined simply by monitoring carbon dioxide evolution. With regard to reaction temperature, several factors appear to be important. Of course, the nature of the acetylenic dipolarophile is crucial with electron-withdrawing substituents enhancing the rate of cycloaddition.⁶⁸ For example, the reaction of the isolable 1,3-oxazolium 5-oxide **14** with DMAD is quite exothermic and requires external cooling,^{17,24,67} while the reaction of **14** and 1-octyne proceeds at 90–100°C.²⁴

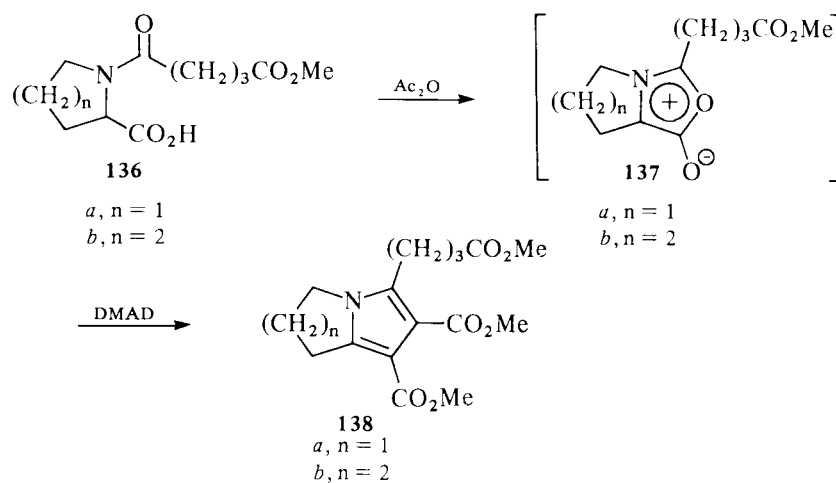


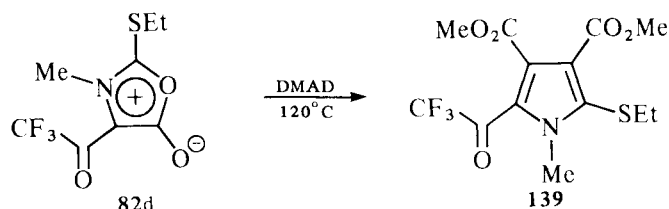
Because most munchnones are not isolable, data on the effect of the 1,3-oxazolium 5-oxide substituents on reactivity is not available. In principle, it should be possible to at least qualitatively determine the effect of the munchnone substituents on reactivity by comparing the reactivity of different *in-situ*-generated 1,3-oxazolium 5-oxides with a given dipolarophile. However, caution should be exercised when employing this approach since two reactions — the cyclodehydration reaction and the cycloaddition reaction — are involved in most cases. For instance, Huisgen and co-workers^{17,24,67} have reported that reaction of *N*-acetyl-*N*-phenylalanine **13b** with acetic anhydride in the presence of DMAD at 50°C affords the pyrrole **134b** in good yield. *N*-Acetyl-*N*-phenylglycine **13c** reacts with acetic anhydride in the presence of DMAD at 100°C to yield pyrrole **134c**, also in good yield.^{24,67} One conclusion that could be drawn from these results is that 4-unsubstituted munchnones **4** ($R^2 = H$) are less reactive 1,3-dipoles than 4-substituted munchnones **4** (e.g., $R^2 = Me$), despite the obvious steric considerations. While this may be true (as will be seen later), the relative rates of cyclodehydration of the *N*-acylamino acid precursors **13** also need to be considered. Boyd and Wright have also reported the 1,3-dipolar cycloaddition reaction of 1,3-oxazolium 5-oxide **4c** ($R = Me$, $R^1 = Ph$, $R^2 = H$) with DMAD to give pyrrole **134c** under appreciably milder conditions.⁴² In their case, the oxazolonium perchlorate **61e** was added to an ice-cold solution of DMAD in acetonitrile, followed by the addition of TEA. After 20 min, the reaction mixture was worked up to afford a



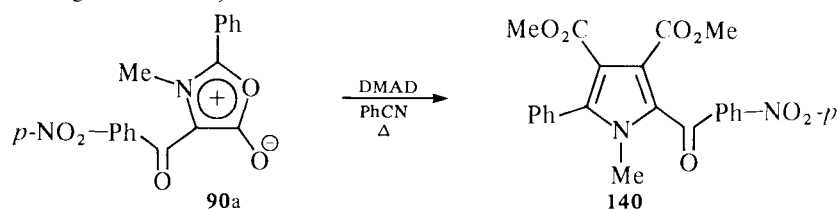
good yield of **134c**. Thus, it can be seen that the higher temperature required for the cycloaddition reaction of the munchnone derived from *N*-acylamino acid **13c** (relative to **13b**) is probably largely related to the cyclodehydration step rather than the cycloaddition step. That is, the cycloaddition rates of 1,3-oxazolium 5-oxides **4b** and **4c**, at least with DMAD, are probably comparable.

An additional example of a 1,3-dipolar cycloaddition reaction of an *in-situ*-generated munchnone with DMAD, where the cyclodehydration step appears to be the rate-determining step, is provided by Hershenson.⁷⁵ The reaction of the *N*-acylproline **136a** with acetic anhydride at $65\text{--}115^\circ\text{C}$ in the presence of DMAD affords the tetrahydropyrrolizine **138a**. On the other hand, the *N*-acylpipecolinic acid **136b** readily reacts with acetic anhydride and DMAD at room temperature to yield the tetrahydroindolizine **138b**. It appears likely that 1,3-oxazolium 5-oxide **137b** was formed much more readily than **137a**.

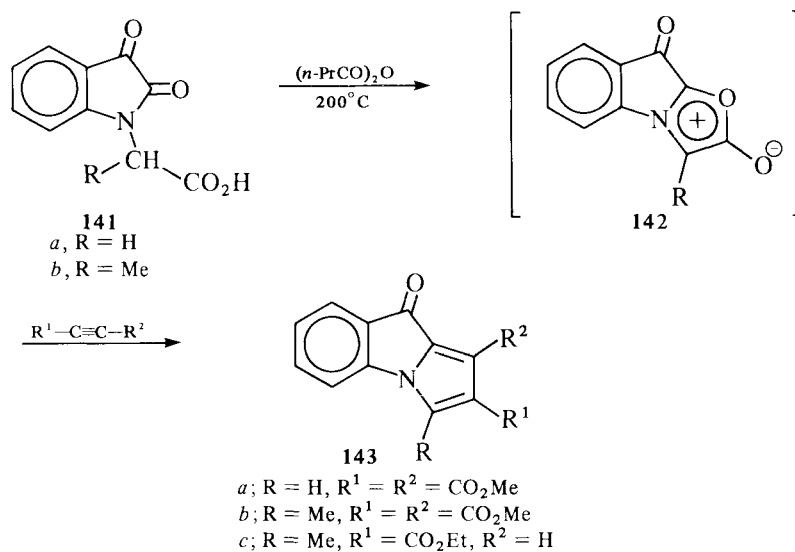




The introduction of an acyl substituent at the 4-position of a munchnone appears to retard 1,3-dipolar cycloaddition reactions. For example, Gotthardt and Reiter⁵⁵ have reported that the unique 1,3-oxazolium 5-oxide **82d**, which possesses an electron-donating substituent at the 2-position and an electron acceptor at the 4-position, affords only a 6% yield of the pyrrole **139** upon heating in DMAD at 120°C. Interestingly, Boyd and Wright have reported a 93% yield of pyrrole **140** upon reacting the 4-aryl munchnone **90a** with DMAD under forcing conditions (refluxing benzonitrile).⁴²

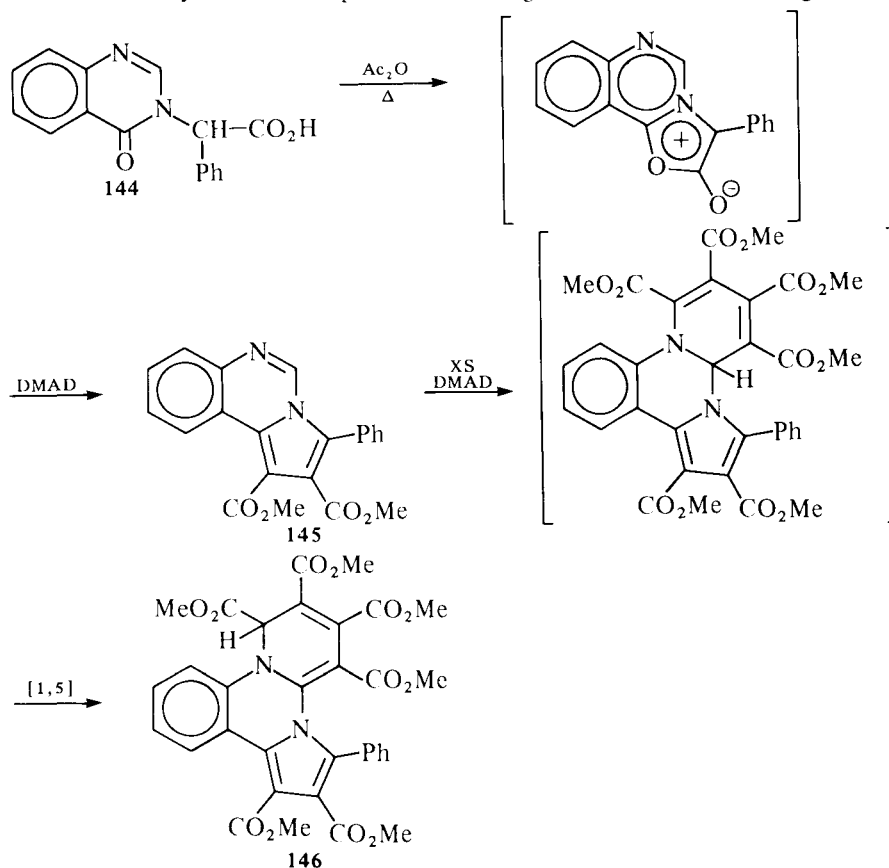


The presence of an acyl substituent at the 2-position of a 1,3-oxazolium 5-oxide also appears to retard 1,3-dipolar cycloaddition reactions. Anderson and Corey²⁷ have reported the reaction of the isatin-*N*-acetic acids **141a** and **141b** with DMAD in refluxing *n*-butyric anhydride (ca. 200°C) to give the 9-oxo-9*H*-pyrrolo[1,2-*a*]-indoles **143a** and **143b** in 20 and 62% yields, respectively. The harsh conditions



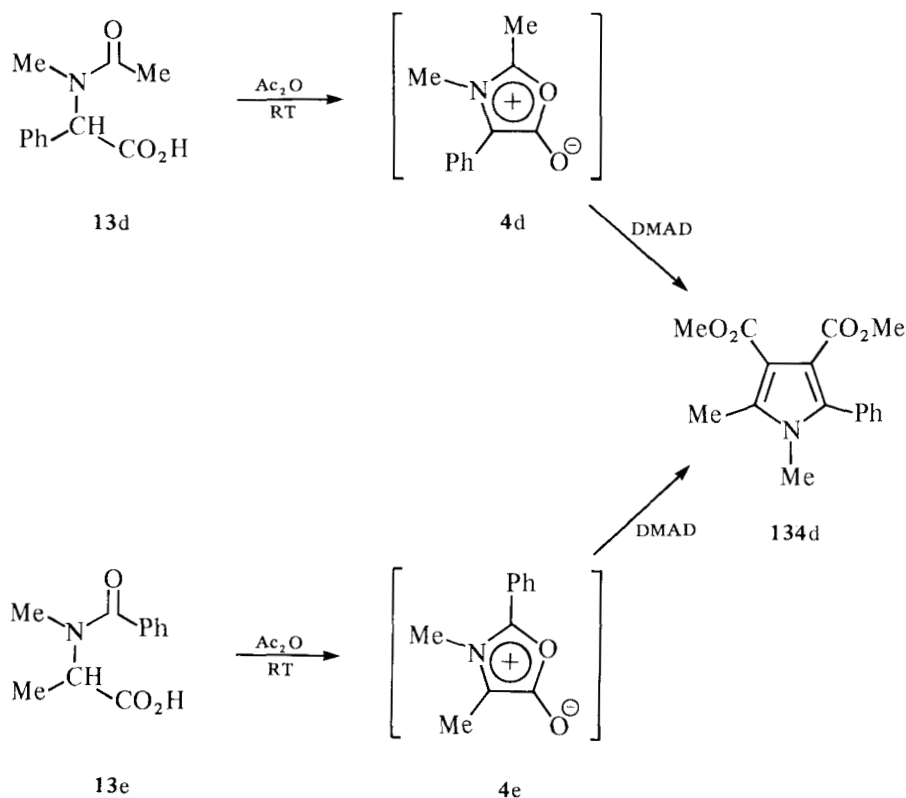
required for these reactions were attributed to either a decreased reactivity of the munchnones **142** due to charge delocalization by the carbonyl substituent at the 2-position of **142** or the sluggish rate at which **142** is formed. The development of a positively charged iminium group adjacent to the electron-withdrawing carbonyl substituent, as well as increased strain in this rigid system, may well retard the formation of **142**. While both factors are probably important, the apparent rate-enhancing effect of the 4-methyl substituent of **142b** is illustrated by the higher yield of **143b** (relative to **143a**). Additionally, **141b** reacts with *n*-butyric anhydride in the presence of ethyl propiolate, a less reactive dipolarophile than DMAD, to give a 49% yield of **143c**, while **141a** fails to react under these conditions.

From a practical point of view, most workers employ an excess of acetylenic dipolarophile when trapping a 1,3-oxazolium 5-oxide. Conditions ranging from a slight excess to using the dipolarophile as the reaction solvent have been utilized. Occasionally employing a large excess of acetylenic dipolarophile can affect the outcome of the 1,3-dipolar cycloaddition reaction, particularly if the product can react further with the dipolarophile. For example, Potts and co-workers⁸⁶ found that the reaction of the 4-oxo-3*H*-quinazoline-*N*-(α -phenyl)acetic acid **144** reacts with acetic anhydride in the presence of a slight excess of DMAD to give **145**.

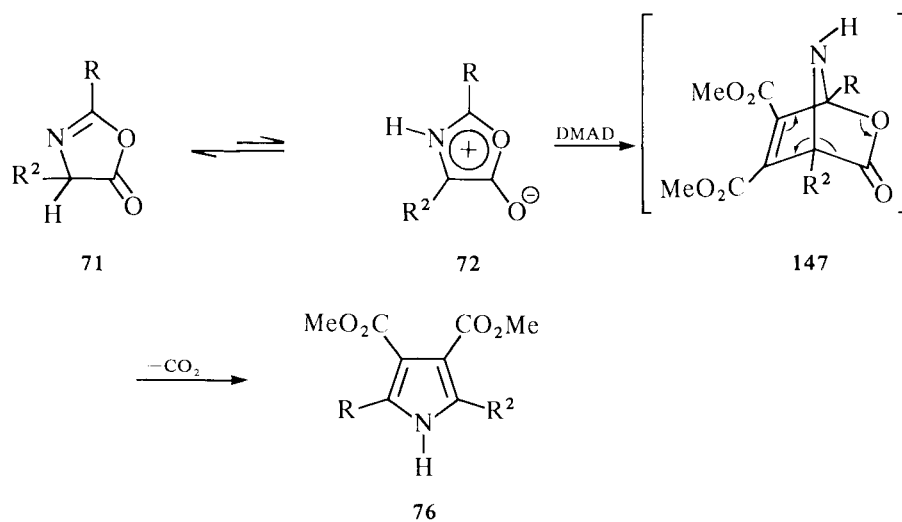


However, in the presence of a large excess of DMAD, **146** was obtained instead of **145**. Presumably the initially formed **145** reacts further with the excess DMAD to ultimately afford **146**. The structure of **146** was confirmed by X-ray crystallography.

An interesting feature of this pyrrole synthesis when symmetrical dipolarophiles such as DMAD are employed is that the R and R² substituents of the munchnones **4** occupy equivalent positions in the pyrrole product **134**. For instance,^{17,24,67} treatment of either *N*-acetyl-*N*-methyl-*C*-phenylglycine **13d** or *N*-benzoyl-*N*-methylalanine **13e** with acetic anhydride in the presence of DMAD affords pyrrole **134d**. In this case, neither route is preferred over the other since both **13d** and **13e** are readily accessible starting materials. Also reaction conditions and yields are comparable. However, as we shall see, this may not always be the case.

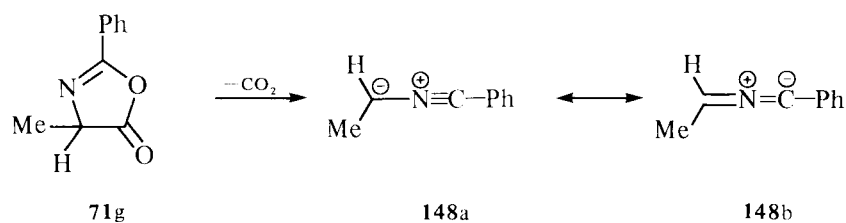


Huisgen and co-workers have also shown that 2-oxazolin-5-ones (azlactones) **71** undergo 1,3-dipolar cycloaddition reactions via their *N*-unsubstituted 1,3-oxazolium 5-oxide tautomers **72** with acetylenic dipolarophiles such as DMAD to give *N*-unsubstituted pyrroles **76** as indicated in Scheme 11.^{43,49,50,67} In general, the cycloaddition reactions of azlactones **71** require higher temperatures than the corresponding *N*-substituted 1,3-oxazolium 5-oxides **4**.

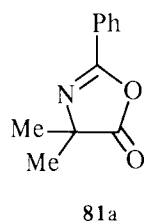


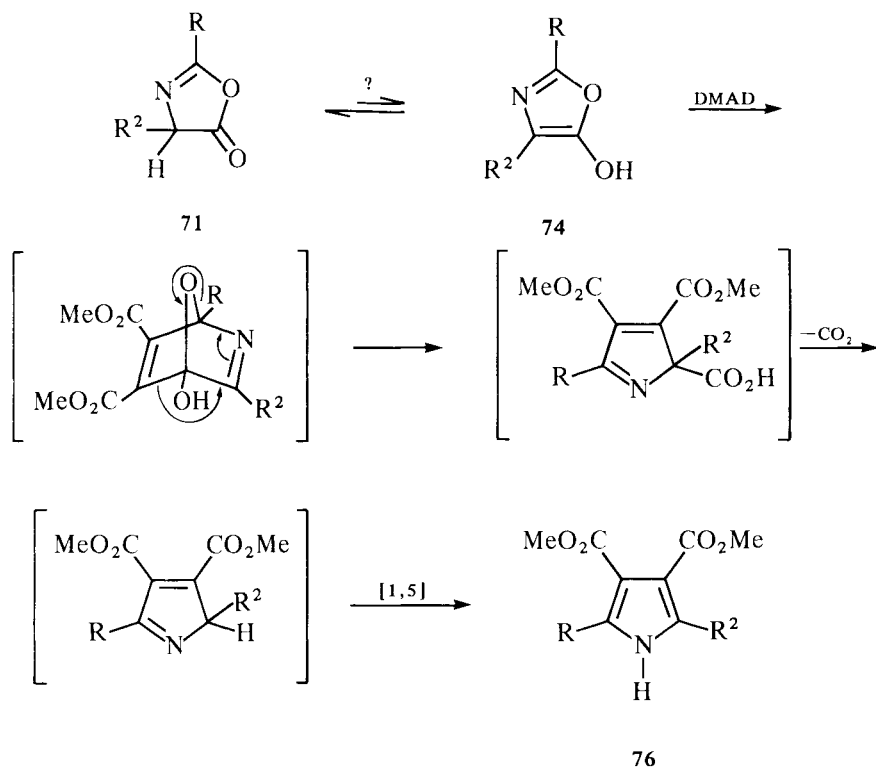
Scheme 11

The possibility that the azlactone **71g**, for example, loses carbon dioxide to afford the nitrile ylide **148**, which undergoes a 1,3-dipolar cycloaddition reaction with DMAD to give the observed pyrrole **76**, was ruled out since **71g** is stable in refluxing xylene (i.e., typical cycloaddition conditions).⁴³ Additionally, the 4,4-

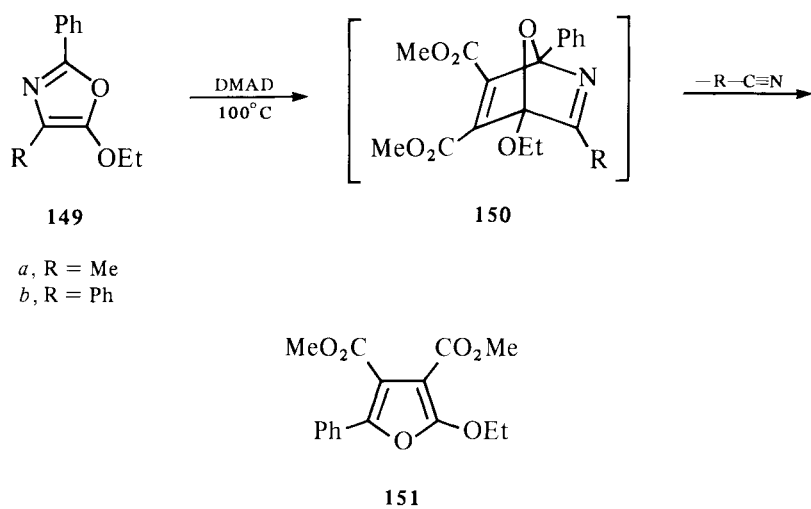


dimethylazlactone **81a** fails to react with DMAD in refluxing xylene.^{43,49} Huisgen and co-workers concluded that a reactive tautomer must be in equilibrium with the azlactone **71**. They considered the possibility that the azlactones were in tautomeric equilibrium with the 5-hydroxyoxazoles **74**, which could undergo cycloaddition reactions with DMAD to give the observed pyrroles **76**. To test this possibility, the reaction of the 5-ethoxyoxazoles **149** with DMAD was examined.





Upon heating **149** with DMAD at 100°C, the furan **151** is obtained in good yield. Furan **151** is presumably formed by a retro Diels–Alder reaction of the primary cycloadducts **150**. These results suggest that 5-hydroxyoxazoles **74** are not reactive intermediates in the reaction of azlactones **71** with DMAD.^{43,49}





Huisgen and co-workers concluded that the *N*-unsubstituted 1,3-oxazolium 5-oxides **72** are in tautomeric equilibrium with the azlactones **71** and that **72** undergo 1,3-dipolar cycloaddition reactions with DMAD, as indicated in Scheme 11.^{43,49,50,67} Additionally, utilizing UV spectroscopy, this tautomeric equilibrium was shown to be solvent dependent for the diphenylazlactone **71a** with the equilibrium concentration of the mesoionic tautomer **72a** increasing in polar solvent.⁴³ The *N*-unsubstituted munchnones **72** have subsequently been isolated in several instances.^{44–46}

A compilation of *N*-unsubstituted pyrroles **76**, which have been prepared by the 1,3-dipolar cycloaddition reaction of azlactones **71** with DMAD, is contained in Table 4.4. Although preformed azlactones **71** can be employed in this synthesis,

TABLE 4.4. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZLACTONES AND DIMETHYL ACETYLENEDICARBOXYLATE (DMAD)

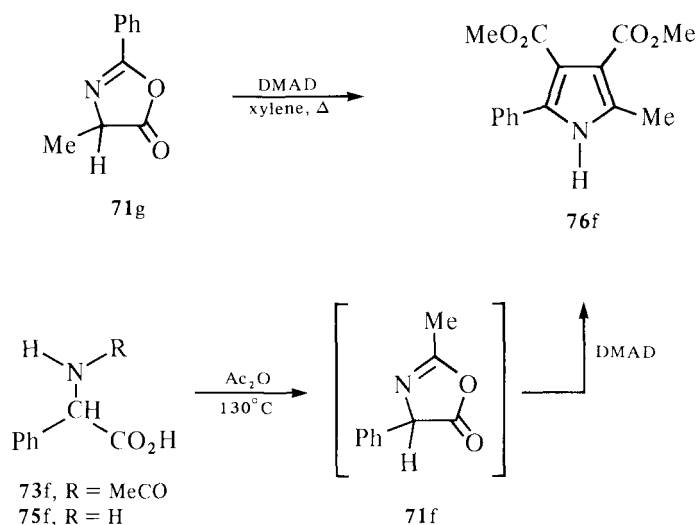
Method of Azlactone Preparation ^a	R	R ²	Percent Yield	Reference
B	Me	Ph	78	43, 49, 67
C	(Me) ^b	Ph	75	43, 67
B	Cyclo-C ₆ H ₁₁	Ph	93	50, 67
B	MeO ₂ C(CH ₂) ₃	Ph	ca. 95	75
A	Ph	Me	71	43, 49, 67
A	Ph	PhCH ₂	93	87
A	Ph	Ph	83	49, 50, 67
B			93	50, 67
A	Ph	2-NO ₂ Ph	60	49, 50, 67
A	4-MeOPh	Ph	65	50
B			98	49, 50, 67
B	4-NO ₂ Ph	Ph	98	50
B	4-ClPh	Ph	99	50, 67
B	α-Naphthyl	Ph	85	50, 67

^aA, Preformed azlactone; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride.

^bSubstituents in parentheses introduced by cyclodehydrating reagent.

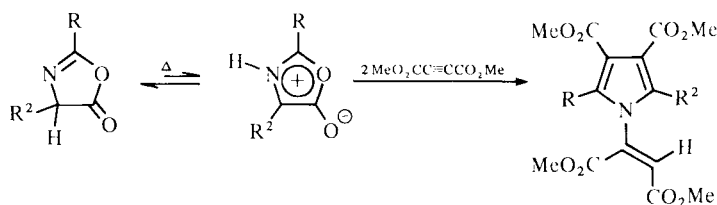


the *in situ* procedure^{43,49,50,67} employing the *N*-acylamino acid **73** and amino acid precursors **75** is more convenient since it avoids handling the sensitive azlactones **71**. For example, reaction of azlactone **71g** with DMAD in refluxing xylene affords a 71% yield of pyrrole **76f**, while reaction of *N*-acetyl-*C*-phenylglycine **73f** or *C*-phenylglycine **75f** with DMAD in acetic anhydride at 130°C also gives pyrrole **76f** via azlactone **71f** in yields of 78 and 75%, respectively.^{43,49,60} This sequence also illustrates that the 2- and 4-positions of the azlactone **71** become equivalent in this pyrrole synthesis when symmetrical acetylenic dipolarophiles such as DMAD are employed.



Inspection of Table 4.4 reveals that this pyrrole synthesis is only successful when either the R or R² substituent of the *N*-unsubstituted pyrrole product **76** is an aryl group. When the R and R² substituents of **76** are both alkyl or aralkyl,^{46,50,67} the *N*-unsubstituted pyrroles **76** are not isolable as they readily undergo Michael additions to DMAD to give the 1:2 products **152**. Examples of this secondary reaction are shown in Table 4.5. Reaction of DL-tryptophan **153** with DMAD in acetic anhydride at 120°C affords a 52% yield of a 1:2 product, which was assigned structure **154** based largely on its yellow color and inconclusive spectral data.^{50,67}

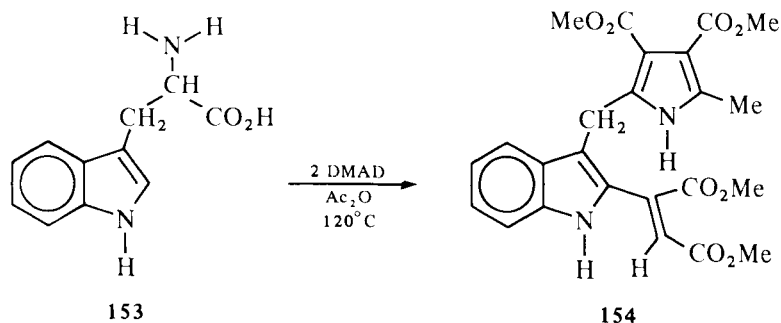
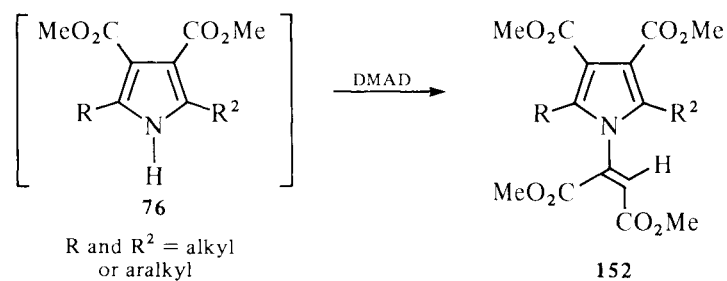
TABLE 4.5. 1:2 PRODUCTS FROM 2,4-DIALKYLAZLACTONES AND DIMETHYL ACETYLENEDICARBOXYLATE (DMAD)

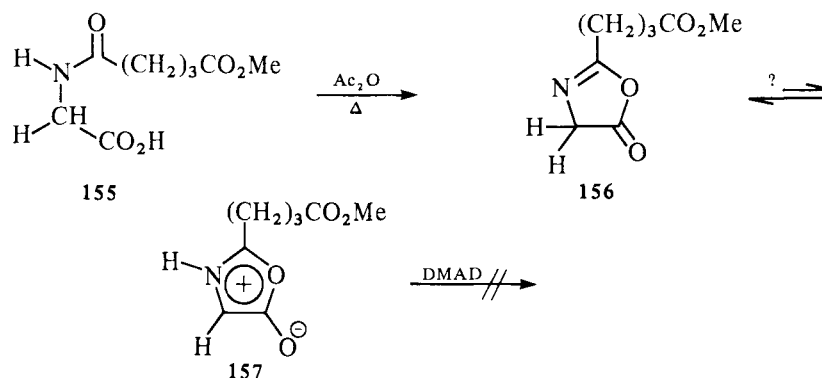


Method of Azlactone Preparation ^a	R	R ²	Percent Yield	Reference
B	(Me) ^b	Me	44	49, 50, 67
B	(Me) ^b	PhCH ₂	11	49, 50, 67
B	(Me) ^b	$\text{4-(MeC(=O)OPhCH}_2\text{)}$	43	50, 67
A	<i>i</i> -Pr	<i>i</i> -Pr	91	50, 67
A	<i>n</i> -C ₅ H ₁₁	<i>i</i> -Bu	88	50, 67
A	MeO ₂ C(CH ₂) ₃	Me	15	75
A	PhCH ₂	PhCH ₂	11	50, 67

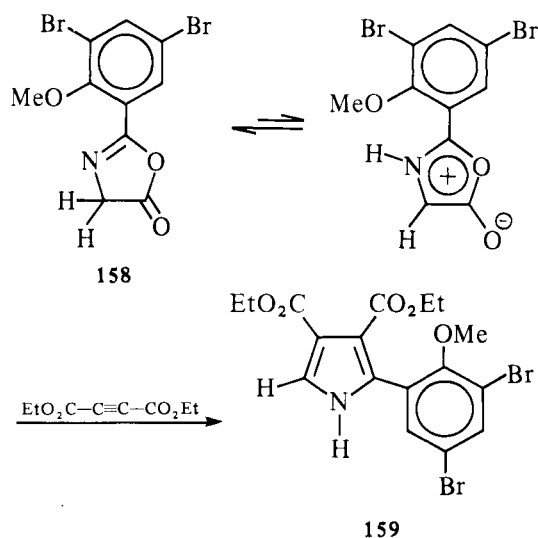
^aA, *In situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride.

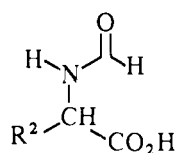
^bSubstituents in parentheses introduced by cyclodehydrating reagent.



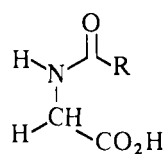


Another possible limitation of this pyrrole synthesis is that 4-unsubstituted azlactones **71** ($\text{R}^2 = \text{H}$) appear to react sluggishly with DMAD. For example, Hershenson has reported that upon heating the *N*-acylglycine **155** in acetic anhydride containing DMAD, carbon dioxide evolution was not observed even at the reflux temperature of acetic anhydride.⁷⁵ Although the azlactone **156** is formed under these conditions, either the equilibrium concentration of the required munchnone **157** is negligible or **157** fails to undergo a cycloaddition reaction with DMAD under these conditions. Interestingly, the reaction of the 4-unsubstituted azlactone **158** with diethyl acetylenedicarboxylate to afford pyrrole **159** has been reported;⁸⁸ however, the reaction conditions and yield of **159** were not specified. A possible solution to this apparent limitation would be to employ, when synthetically accessible, the corresponding *N*-formyl α -substituted amino acid **160** rather than the *N*-acylglycine **161** as the azlactone precursor, since the 2- and 4-positions of the pyrrole product become equivalent in this synthesis when symmetrical acetylenic dipolarophiles are employed. Such a strategy has been successfully





160



161

implemented by Benages and Albonico⁸⁹ in the reaction of azlactones **71** with 2-chloroacrylonitrile (see Section 4.2.3.3.3).

Thus far we have largely considered the 1,3-dipolar cycloaddition reactions of munchnones **4** or azlactones **71** with DMAD. Of course, other acetylenic dipolarophiles undergo cycloaddition reactions with **4** and **71**. Tables 4.6–4.8 include examples of cycloaddition reactions of monocyclic and polycyclic 1,3-oxazolium 5-oxides and azlactones, respectively, with other acetylenic dipolarophiles. These tables include only examples involving the cycloaddition of “symmetrical” munchnones **4** ($R = R^2$) and azlactones **71** ($R = R^2$) with symmetrical or unsymmetrical acetylenic dipolarophiles or “unsymmetrical” munchnones **4** ($R \neq R^2$) and azlactones **71** ($R \neq R^2$) with symmetrical acetylenic dipolarophiles. In either case, only a single pyrrole product is possible due to symmetry considerations.

A particularly interesting example of a 1,3-dipolar cycloaddition reaction of an “unsymmetrical” 1,3-oxazolium 5-oxide with a symmetrical acetylenic dipolarophile other than DMAD was reported by Matsumoto and co-workers.⁷⁹ Reaction of pipecolic acid **162** with acetic anhydride at 70°C in the presence of dibenzoylacetylene affords, via the munchnone **163**, a 10% yield of the primary cycloadduct **164**, as well as a 45% yield of the tetrahydroindolizine **165**. The primary cycloadduct **164** affords **165** upon thermolysis in refluxing xylene.

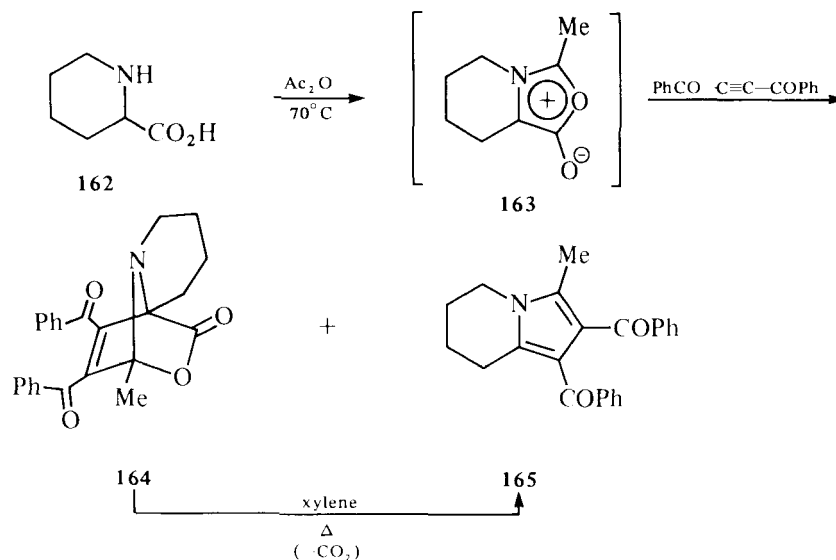
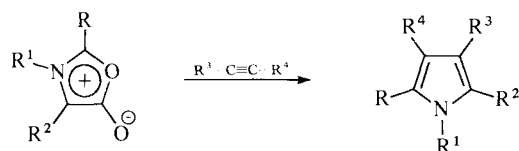


TABLE 4.6. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF MONOCYCLIC 1,3-OXAZOLIUM 5-OXIDES AND OTHER ACETYLENES



Method of Munchnone Preparation ^a	R	R ¹	R ²	R ³	R ⁴	Percent Yield	Reference
C	H	Me	H	CO ₂ Et	H	—	73
B	H	Me	H	Ph	CF ₃ SO ₂	60	90
C	H	Me	H	PhCO	PhCO	78	73
B	H	Ph	H	Ph	CF ₃ SO ₂	76	90
B	H	3-CF ₃ Ph	H	Ph	CF ₃ SO ₂	62	90
B	H	2,6-Me ₂ Ph	H	Ph	CF ₃ SO ₂	20	90
B	Me	PhCH ₂	Me	CO ₂ Et	H	80	91
B	Me	Ph	Me	CO ₂ Et	H	86	91
B	Me	Ph	Me	CO ₂ Et	Ph	80	17, 24, 67
B	Me	Ph	Me	Ph	H	75	24, 67
B	Ph	Me	H	PhCO	PhCO	65	92
C						89	74
A	Ph	Me	Ph	H	H	96	24, 67
A	Ph	Me	Ph	<i>n</i> -Bu	H	81	17, 24, 67
A	Ph	Me	Ph	<i>n</i> -C ₆ H ₁₃	H	51	24
A	Ph	Me	Ph	CO ₂ H	Me	27	24
A	Ph	Me	Ph	CO ₂ Me	H	94	17, 24, 67
B						90	67
B	Ph	Me	Ph	CO ₂ Et	Ph	87	17, 24, 67
A	Ph	Me	Ph		H	89	93
A	Ph	Me	Ph	Ph	H	66	24, 67
B						94	17, 24, 67
A	Ph	Me	Ph	Ph	Ph	11	24, 67
B						21	17, 24, 67
A	Ph	Me	Ph	PhCO	Ph	68	24, 67
B	Ph	Me	Ph	PhCO	PhCO	63	92
B	Ph	Me	Ph	2-C ₅ H ₄ N	H	95	94
B	Ph	Ph	H	PhCO	PhCO	57	92

^aA, Preformed; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; C, *in situ* cyclodehydration of *N*-acylamino acid precursor with DCC.

^bAfter neutralization of tetrafluoroborate salt with aqueous sodium carbonate.

TABLE 4.7. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF POLYCYCLIC 1,3-OXAZOLIUM 5-OXIDES AND OTHER ACETYLENES

Method of Munchnone Preparation ^a	Structure of Product	Percent Yield	Reference												
	<table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%;">R</th><th style="width: 25%;">R¹</th><th style="width: 25%;">R²</th></tr> <tr> <td>CO₂Et</td><td>CO₂Et</td><td>(Me)^b</td></tr> <tr> <td>PhCO</td><td>PhCO</td><td>(Me)^b</td></tr> <tr> <td>PhCO</td><td>PhCO</td><td>H</td></tr> </table>	R	R ¹	R ²	CO ₂ Et	CO ₂ Et	(Me) ^b	PhCO	PhCO	(Me) ^b	PhCO	PhCO	H		
R	R ¹	R ²													
CO ₂ Et	CO ₂ Et	(Me) ^b													
PhCO	PhCO	(Me) ^b													
PhCO	PhCO	H													
B	CO ₂ Et	CO ₂ Et	(Me) ^b	30	79										
B	PhCO	PhCO	(Me) ^b	45	79										
A	PhCO	PhCO	H	70	79										
	<table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%;">R</th><th style="width: 50%;">R¹</th></tr> <tr> <td>PhCO</td><td>PhCO</td></tr> </table>	R	R ¹	PhCO	PhCO	31	29								
R	R ¹														
PhCO	PhCO														
	<table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%;">R</th><th style="width: 50%;">R¹</th></tr> <tr> <td>PhCO</td><td>PhCO</td></tr> </table>	R	R ¹	PhCO	PhCO	71	29								
R	R ¹														
PhCO	PhCO														

TABLE 4.7. (CONTINUED)

Method of Munchnone Preparation ^a	Structure of Product			Percent Yield	Reference
	R	R ¹	R ²		
C	CO ₂ Et	CO ₂ Et	H	40	85
C	CO ₂ Et	CO ₂ Et	Ph	85	85

	R	R ¹			
C	PhCO	PhCO		65	29

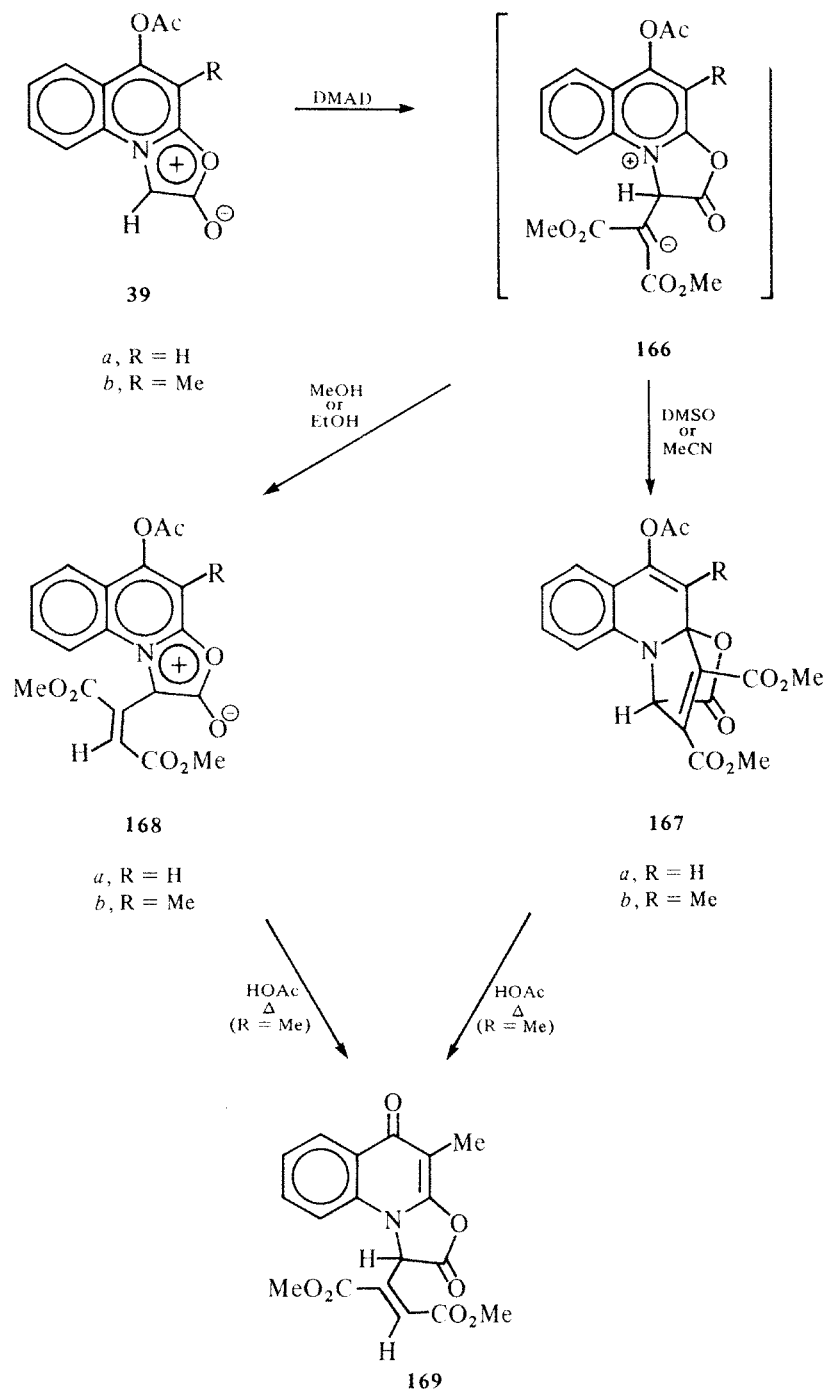
^aA, *In situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, *in situ N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride; C, *in situ* cyclodehydration of *N*-acylamino acid precursor with DCC.

^bSubstituents in parentheses introduced by cyclodehydrating reagent.

TABLE 4.8. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZLACTONES AND OTHER ACETYLENES

Method of Azlactone Preparation ^a	R	R ²	R ³	R ⁴	Percent Yield	Reference
A	Ph	Ph	CO ₂ Me	H	76	49, 50, 67
A	Ph	Ph	Ph	MeCO	12	67
A	4-NO ₂ Ph	PhCH ₂	CO ₂ Et	CO ₂ Et	33	95
A	3,5-Br ₂ -2-MeOPh	H	CO ₂ Et	CO ₂ Et	—	88

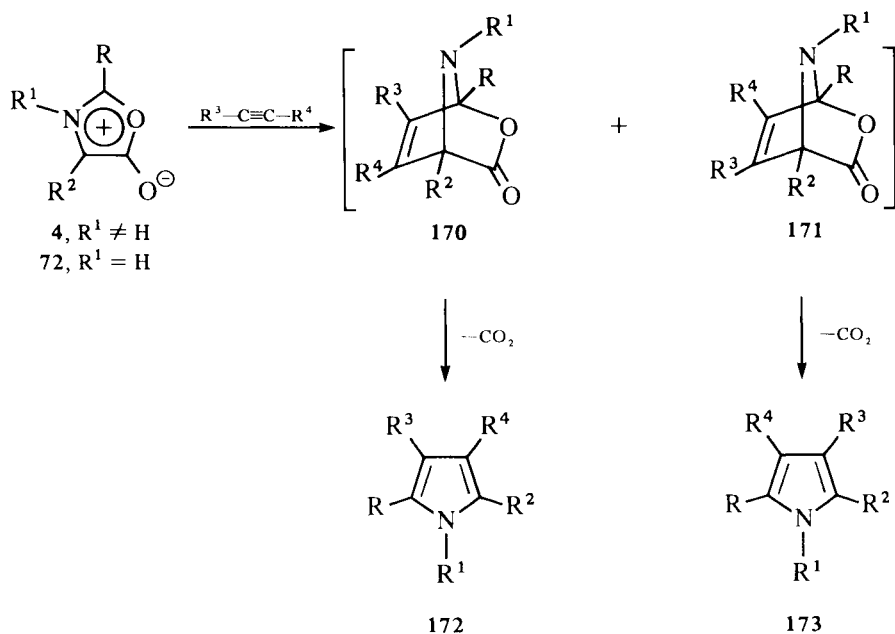
^aA, Preformed azlactone.



Scheme 12

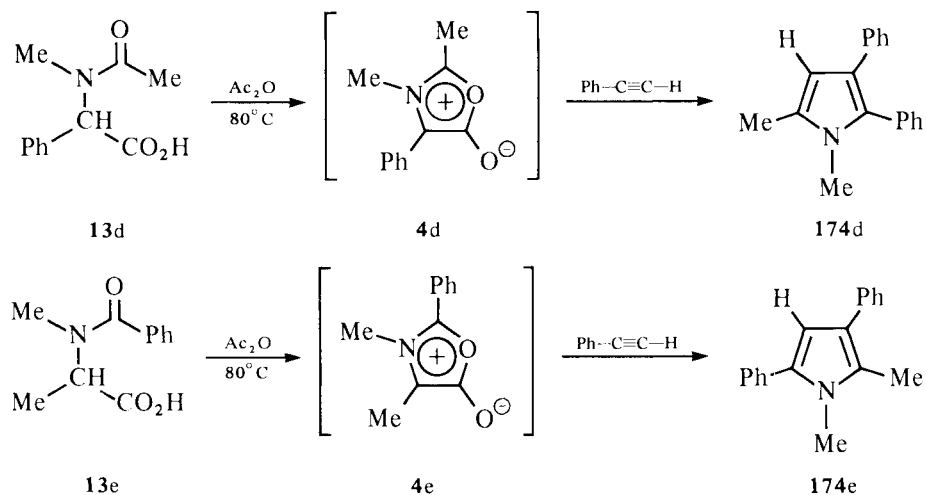
The isolation of a primary cycloadduct from the 1,3-dipolar cycloaddition reaction of a 1,3-oxazolium 5-oxide and an acetylenic dipolarophile is quite unusual. To the best of our knowledge, only two other examples have been reported. Raileanu and co-workers³¹ have reported that the reaction of the isolable 4-unsubstituted munchnones **39** with DMAD in aprotic solvents such as dimethyl sulfoxide or acetonitrile affords the primary cycloadducts **167**, as depicted in Scheme 12. However, when this reaction is run in methanol or ethanol, the Michael-type adducts **168** are obtained. Both **167b** and **168b** afford compound **169** upon deacetylation in refluxing glacial acetic acid. These workers postulated that the primary cycloadducts **167** and the Michael adducts **168** have a common intermediate, namely zwitterions **166**. The cycloaddition reactions of **39** with DMAD appear to represent a rare exception to the commonly accepted concerted⁶⁵ (or diradical⁶⁶) mechanism for 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxides, which was rationalized in this case by the exceptional charge delocalization in the intermediate zwitterions **166**.

The 1,3-dipolar cycloaddition reaction of unsymmetrical munchnones **4** or **72** ($R \neq R^2$) with unsymmetrical acetylenic dipolarophiles raises the interesting problem of the regiochemistry of the cycloaddition reaction. As illustrated in Scheme 13, two primary cycloadducts **170** and **171** can be formed, which afford pyrroles **172** and **173**, respectively, upon carbon dioxide elimination. Tables 4.9 and 4.10 contain a compilation of 1,3-dipolar cycloaddition reactions of unsymmetrical 1,3-oxazolium 5-oxides **4** or **72** with unsymmetrical acetylenic dipolarophiles.



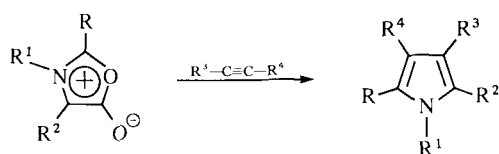
Scheme 13

An inspection of Tables 4.9 and 4.10 reveals that many of these cycloaddition reactions are regiospecific, particularly with polycyclic munchnones (see Table 4.10), or at least regioselective since minor isomers may not always have been detected or isolated. The regiospecificity of many of these 1,3-dipolar cycloadditions led early workers in this field to conclude that the direction of the cycloaddition was determined mainly by the nature of the 1,3-oxazolium 5-oxide ring and not by the nature of the substituents in the 2- and 4-positions of the munchnone ring. For instance, Huisgen and co-workers reported the cycloaddition reaction of the 1,3-oxazolium 5-oxide **4d** generated *in situ* from *N*-acetyl-*N*-methyl-*C*-phenylglycine **13d** with phenylacetylene affords only pyrrole **174d** in 89% yield.^{17,24,67} Under similar conditions, munchnone **4e** reacts with phenylacetylene to produce only pyrrole **174e** in 87% yield.²⁴ In both cases, it can be seen that the direction of cycloaddition is the same despite the differences in the R and R² substituents of **4d** and **4e**. In fact, all 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxides, including polycyclic 1,3-oxazolium 5-oxides,^{28,83} with phenylacetylene reported to date are regiospecific.



It is now appreciated that the nature of the munchnone substituents can markedly influence the direction of cycloaddition, at least with some acetylenic dipolarophiles. This situation is illustrated by the 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxides with propiolic esters. For example, Padwa and co-workers⁹⁶ have reported the cycloaddition reaction of munchnone **4c** generated *in situ* from *N*-acetyl-*N*-phenylglycine **13c** with ethyl propiolate affords a mixture of pyrroles **175c** and **176c** in a ratio of ca. 3:1, respectively, as shown in Scheme 14. However, reaction of *N*-phenylglycine **29** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$) with trifluoroacetic anhydride in the presence of ethyl propiolate furnishes, via **4f**, a ca. 1:9 mixture of pyrroles **175f** and **176f**, respectively. Thus, it can be seen that replacement of the $\text{R} = \text{Me}$ substituent with a trifluoromethyl group in **4** results in a pronounced change in the pyrrole product distribution. It is interesting to note

TABLE 4.9. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF MONOCYCLIC UNSYMMETRICAL 1,3-OXAZOLIUM 5-OXIDES AND UNSYMMETRICAL ACETYLENES

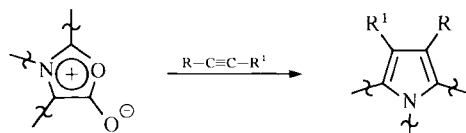


Method of Munchnone Preparation ^a	R	R ¹	R ²	R ³	R ⁴	Isomer Ratio	Percent Yield	Reference
D	Me	Me	H	H	CO ₂ Et	—	—	74
D	Me	Me	H	CO ₂ Et	H	—	—	
B	Me	Me	PhCH ₂	H	CO ₂ Me	45	69	96
B	Me	Me	PhCH ₂	CO ₂ Me	H	55		
B	Me	Me	Ph	H	CO ₂ Et	45	13	96
B	Me	Me	Ph	CO ₂ Et	H	55	16	
B	Me	Me	Ph	Ph	H	—	89	17, 24, 67
B	Me	Me	Ph	Ph	CO ₂ Et	—	75	17, 24, 67
B	Me	Ph	H	H	CO ₂ Et	3	32	96
B	Me	Ph	H	CO ₂ Et	H	1	9	
C	(CF ₃) ^b	Ph	H	H	CO ₂ Et	1	58	96
C	(CF ₃) ^b	Ph	H	CO ₂ Et	H	9		
B	CO ₂ Et	Me	Ph	2-C ₅ H ₄ N H	H	—	49	94
D		Me	<i>i</i> -Bu	H	CO ₂ Me	—	79	35
A	Ph	H	Me	H	CO ₂ Me	5	99	50
A	Ph	H	Me	CO ₂ Me	H	1		
B	Ph	H	Me	H	CO ₂ Me	—	98	49, 50, 67
B	Ph	H	Me	CO ₂ Me	H	—		
B	Ph	Me	H	H	CO ₂ Et	—	ca. 30	26
B	Ph	Me	H	Ph	CO ₂ Et	—	ca. 30	26
B	Ph	Me	Me	Ph	H	—	87	24

^aA, Performed azlactone; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with carboxylic acid anhydride; D, *in situ* cyclodehydration of *N*-acylamino acid with DCC.

^bSubstituents in parentheses introduced by cyclodehydrating reagent.

TABLE 4.10. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF POLYCYCLIC UNSYMMETRICAL 1,3-OXAZOLIUM 5-OXIDES AND UNSYMMETRICAL ACETYLENES



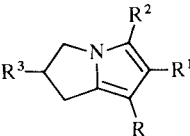
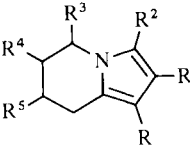
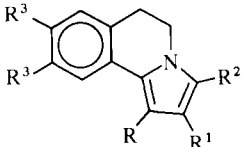
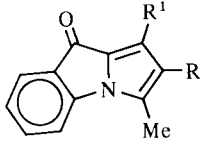
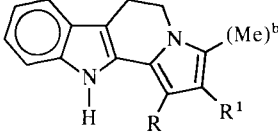
Method of Munchnone Preparation ^a	Structure of Product				Isomer Ratio	Percent Yield	Reference
							
	<u>R</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>			
A	CHO	H	H	H	—	40	97
A	CO₂Et	H	H	H	—	90	98
A	CO₂Et	H	H	OCHO	—	80	99, 100
							
	<u>R</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁴</u>	<u>R⁵</u>	
A	CO₂Et	H	H	H	H	H	— 82 101
A	CO₂Et	H	H	H	—C₆H₄—	—	— 70 101
A	CO₂Et	H	H	CO₂[Et] ^c	H	H	— 45 101
A	CO₂Et	H	Me	H	H	H	— 67 101
C	CO₂Et	H	(Me) ^b	CO₂[Et] ^c	H	H	— 70 101
							
	<u>R</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>			
C	Ph	H	(Me) ^b	H	—	69	83
A	Ph	H	Me	MeO	—	72	83
C	Ph	H	(Me) ^b	MeO	—	69	83
C	2-NO₂Ph	H	(Me) ^b	MeO	—	82	83

TABLE 4.10. (CONTINUED)

Method of Munchnone Preparation ^a	Structure of Product		Isomer Ratio	Percent Yield	Reference
					
	R	R¹			
B	CO ₂ Et	H	—	49	27
					
	R	R¹			
C	CO ₂ Et	H	5	51	28
C	H	CO ₂ Et	1	11	
C	Ph	H	—	34	28

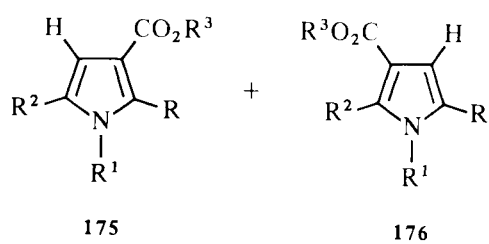
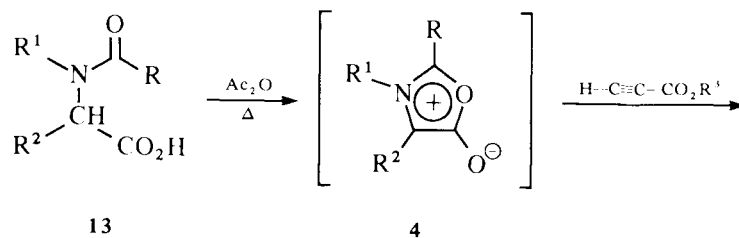
^aA, *In situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, *in situ* cyclodehydration of *N*-acylamino acid precursor in refluxing *n*-butyric anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride.

^bSubstituents in parentheses introduced by cyclodehydrating reagent.

^cSubstituents in brackets introduced upon transesterification of carboxylic acid substituent by excess ethyl propiolate.

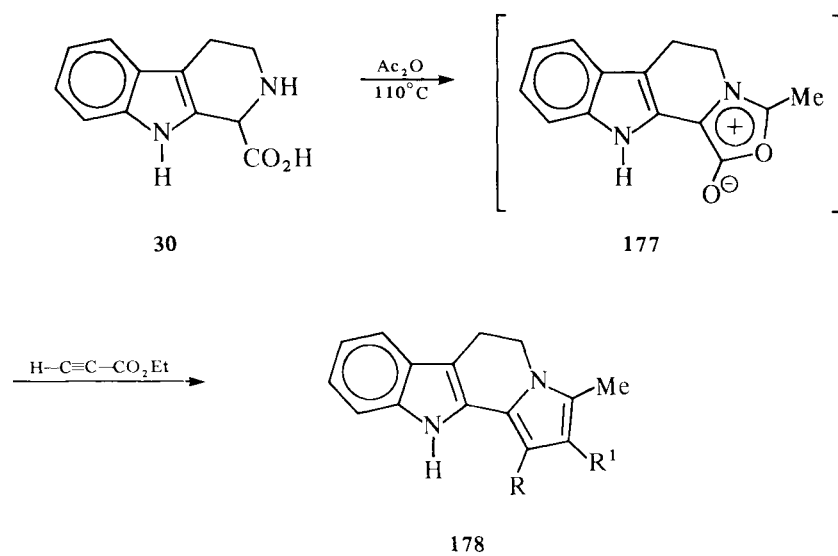
that 1,3-oxazolium 5-oxides **4d** and **4g** react with ethyl and methyl propiolate, respectively, to give in both cases approximately a 1 : 1 mixture of the corresponding pyrroles **175** and **176**.

Hershenson²⁸ has reported that the reaction of the munchnone **177** prepared *in situ* from 1,2,3,4-tetrahydro- β -carboline-1-carboxylic acid **30** with ethyl propiolate yields a 5 : 1 mixture of the indolizino[8,7-*b*]indoles **178a** and **178b**, respectively. It is interesting to note, however, that the 1,3-oxazolium 5-oxides **180** generated *in situ* from *N*-formylproline **179a** or the *N*-acylpipecolinic acids **179c** and **179d** react with ethyl propiolate to provide a regiospecific synthesis of the tetrahydropyrrolizine **181a** and the tetrahydroindolizines **181c** and **181d**, respectively, as indicated in Scheme 15.^{98, 101}

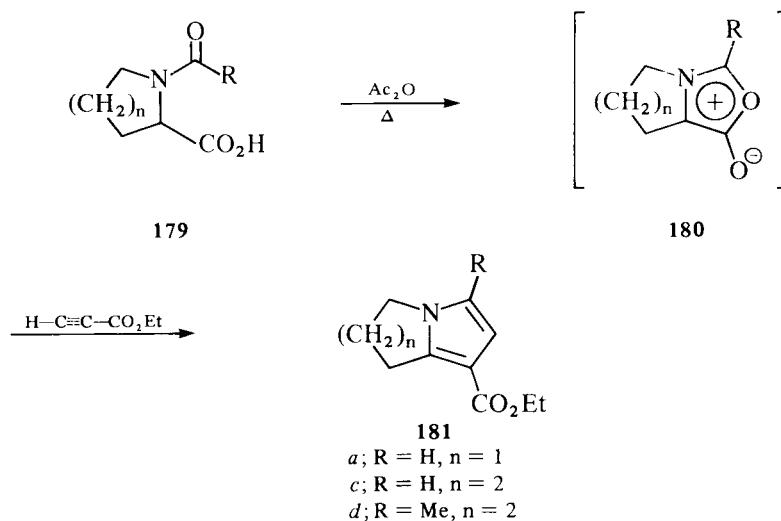


c; R = Me, R¹ = Ph, R² = H, R³ = Et
d; R = R¹ = Me, R² = Ph, R³ = Et
f; R = CF₃, R¹ = Ph, R² = H, R³ = Et
g; R = R¹ = R³ = Me, R² = PhCH₂

Scheme 14



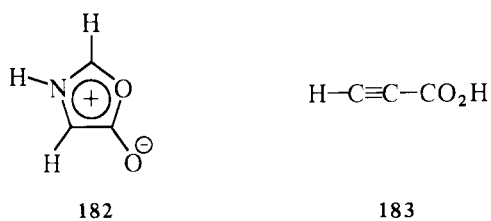
a; R = CO₂Et, R¹ = H
b; R = H, R¹ = CO₂Et



Scheme 15

Perhaps the best approach to rationalize or predict the regiochemistry of concerted 1,3-dipolar cycloaddition reactions is provided by the Frontier Molecular Orbital (FMO) theory.^{102,103} According to simple FMO theory, bond formation is dictated primarily by the charge transfer interaction energy determined by overlap of the HOMO(1,3-dipole)–LUMO(dipolarophile) and the LUMO(1,3-dipole)–HOMO(dipolarophile). Which of these interactions will dominate is sometimes determined by the relative energy differences of either pair of orbitals. The regioselectivity is then the result of the best orbital overlap (i.e., the atoms with the largest orbital coefficients combine preferentially).

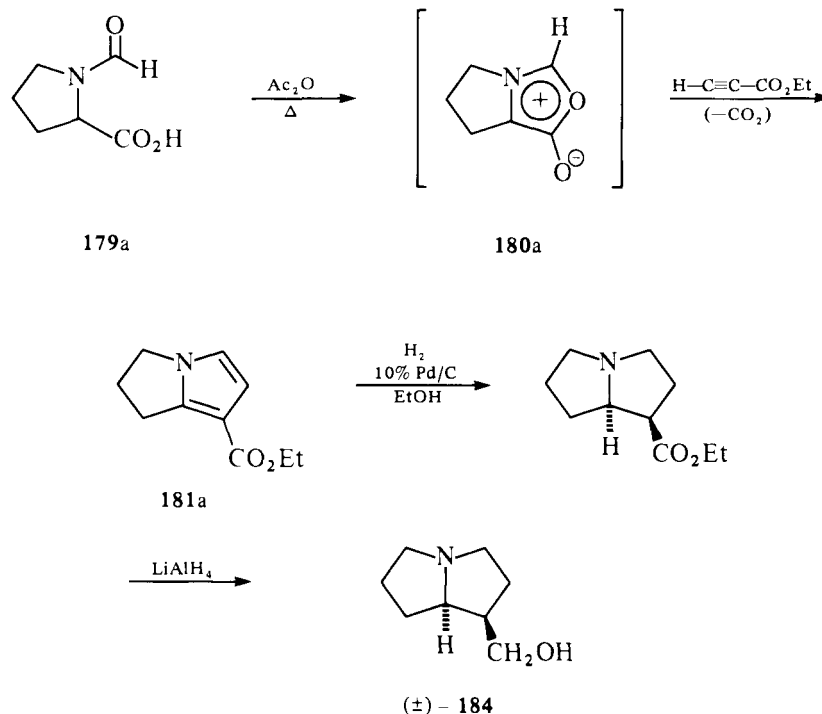
Houk has noted that unsymmetrically substituted azomethine ylides such as munchnones can form regioisomers with unsymmetrical dipolarophiles.¹⁰³ The regiochemistry of the cycloaddition will be caused by asymmetry in the 1,3-dipole frontier orbitals caused by the substituent groups. Fully geometry-energy optimized MINDO calculations performed on the parent 1,3-oxazolium 5-oxide **182** and propiolic acid **183** suggest that the regiochemistry exhibited in the cycloaddition reactions of munchnones with unsymmetrical acetylenic dipolarophiles has its basis in all possible frontier interactions.⁹⁶ Additionally, mesoionic compounds such as 1,3-oxazolium 5-oxides with high local charge densities give rise to a complex



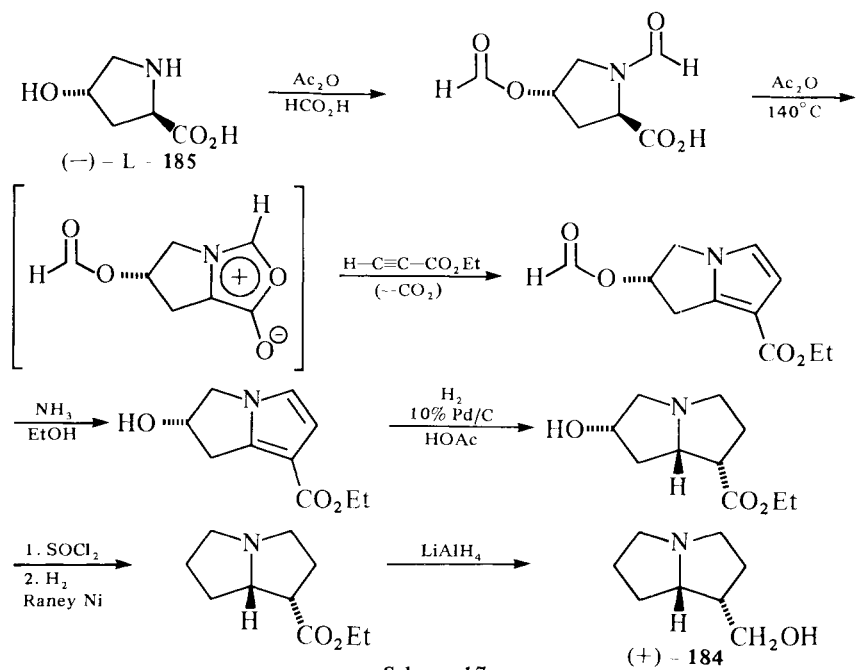
inhomogenous electric field in the vicinity of the approaching dipolarophile, and van der Waals energy considerations may be important and provide some insight into the regiochemistry of such cycloadditions.⁹⁶ Thus, it would appear that simple FMO theory does not readily rationalize the product distributions obtained from the cycloaddition reactions of unsymmetrical munchnones and unsymmetrical acetylenic dipolarophiles. Clearly it would be desirable to be able to easily rationalize the differences in the observed regiochemistry of the cycloaddition reactions of simple monocyclic 1,3-oxazolium 5-oxides such as **4b** and polycyclic 1,3-oxazolium 5-oxides such as **177** and **180** with ethyl propiolate.

An examination of Tables 4.2–4.10 reveals that the 1,3-dipolar cycloaddition reactions of munchnones and acetylenic dipolarophiles provides a vast array of pyrroles ranging from simple pyrroles to complex fused heterocyclic systems. At this point it appears worthwhile to briefly review some of the ways in which this pyrrole synthesis has been exploited to synthesize natural products, products of medicinal interest, and heterocyclic systems of even greater complexity.

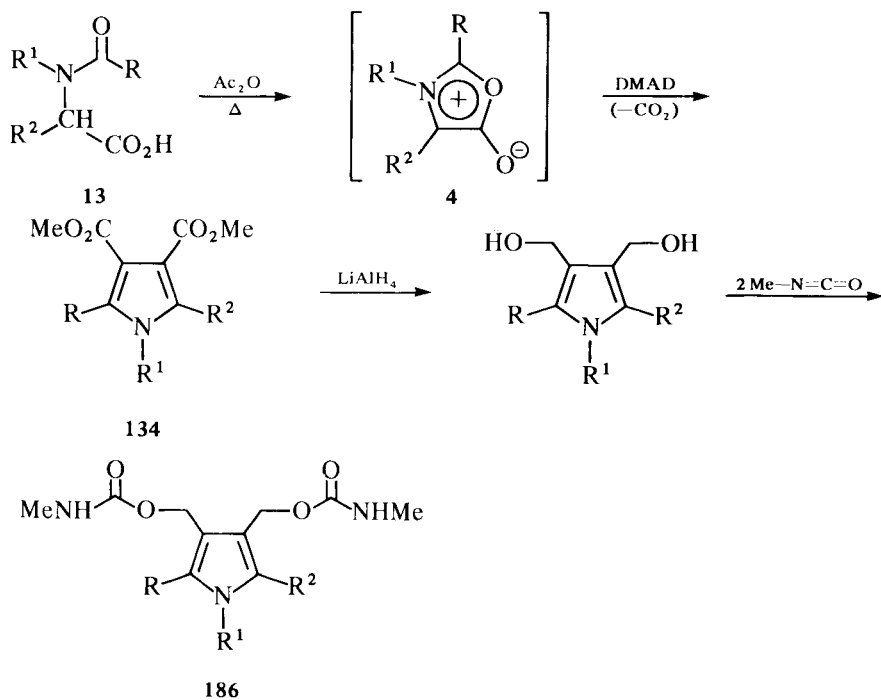
The tetrahydropyrrolizine and tetrahydroindolizine synthesis depicted in Scheme 15 has been exploited for the preparation of naturally occurring pyrrolizidine^{98–100} and indolizidine¹⁰¹ alkaloids. For example, Pizzorno and Albonico⁹⁸ prepared racemic isoretronecanol **184** from *N*-formylproline **179a** as shown in Scheme 16. By a modification of this procedure, illustrated in Scheme 17,



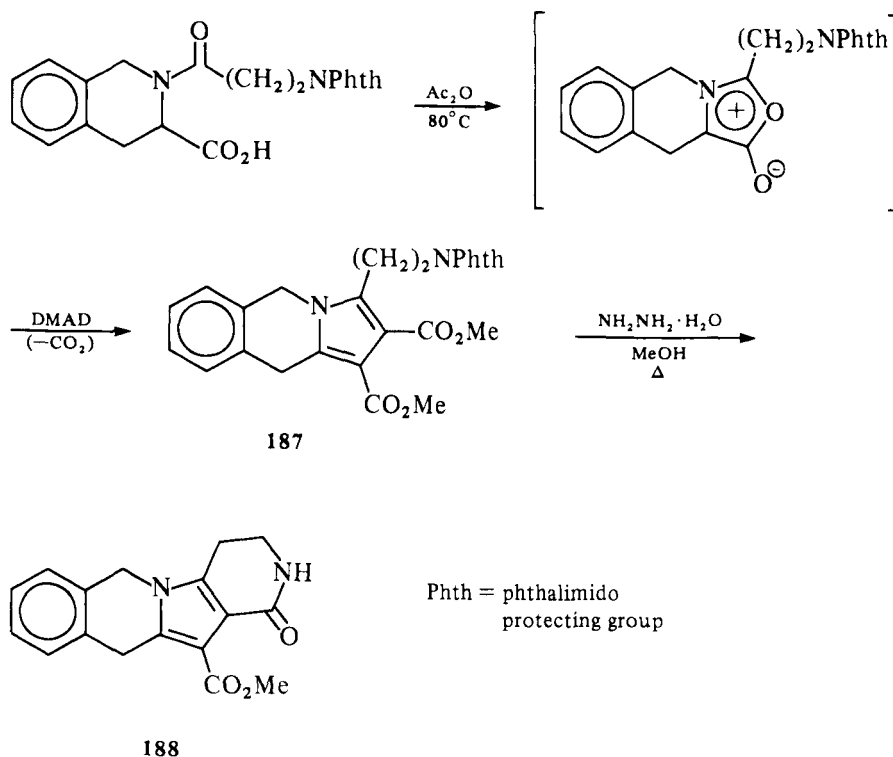
Scheme 16



Scheme 17



Scheme 18



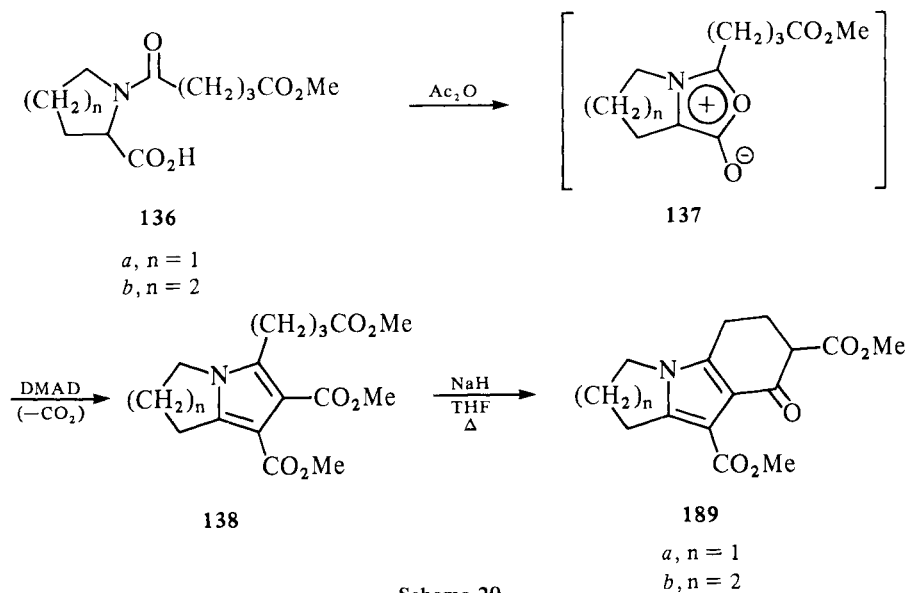
Scheme 19

Robins and Sakdarat^{99,100} have prepared (+)-isoretronecanol **184** in ca. 89% optical purity in an overall yield of 45% from (–)-4-hydroxy-L-proline **185**. Additional related pyrrolizidine alkaloids are available in >80% optical purity upon suitable synthetic modifications and strategic epimerizations.^{99,100}

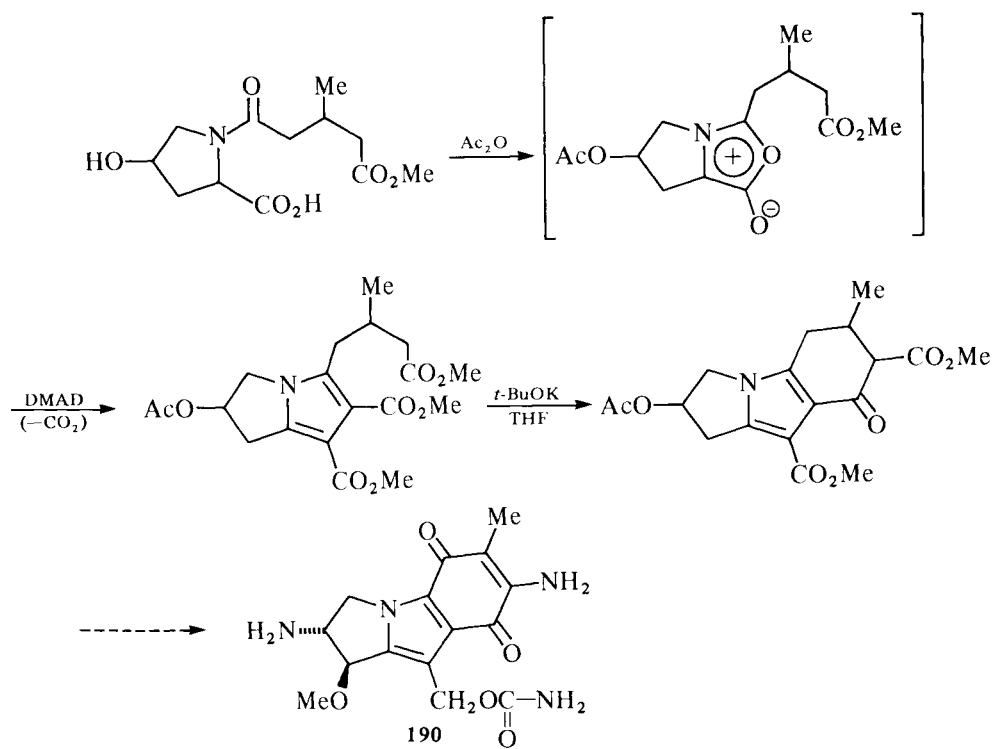
Anderson and co-workers^{69–71, 76, 77} have synthesized pyrrole biscarbamates **186** as potential antileukemic agents using the route indicated generically in Scheme 18.

This pyrrole synthesis can be extended to provide an even wider variety of fused heterocycles by including substituents capable of a subsequent ring closure reaction. This principle is nicely illustrated in Scheme 19 for the preparation of the hexahydropyrrodo[3',4':4,5]pyrrolo[1,2-*b*]isoquinoline **188** as reported by Hershenson.⁷² Removal of the phthalimido-protecting group from the cycloaddition product **187** results in lactamization to afford **188**.

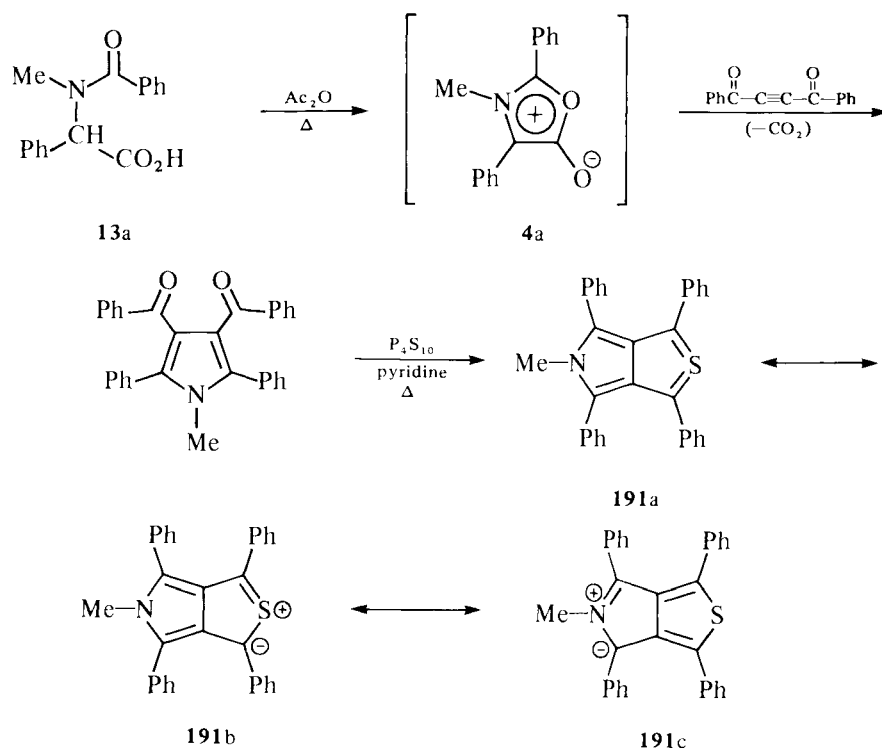
Hershenson⁷⁵ has also reported the preparation of the hexahydropyrrolo[1,2-*a*]-indole **189a** and the octahydropyrrodo[1,2-*a*]indole **189b** from the *N*-acylproline **136a** and the *N*-acylpipecolic acid **136b**, respectively, as depicted in Scheme 20. The cycloaddition products **138** were converted to **189** by a Dieckmann condensation. Rebek and co-workers^{78,104} have exploited this approach to synthesize the mitosene **190**, a chemical degradation product of mitomycin C, as outlined in Scheme 21.



Scheme 20



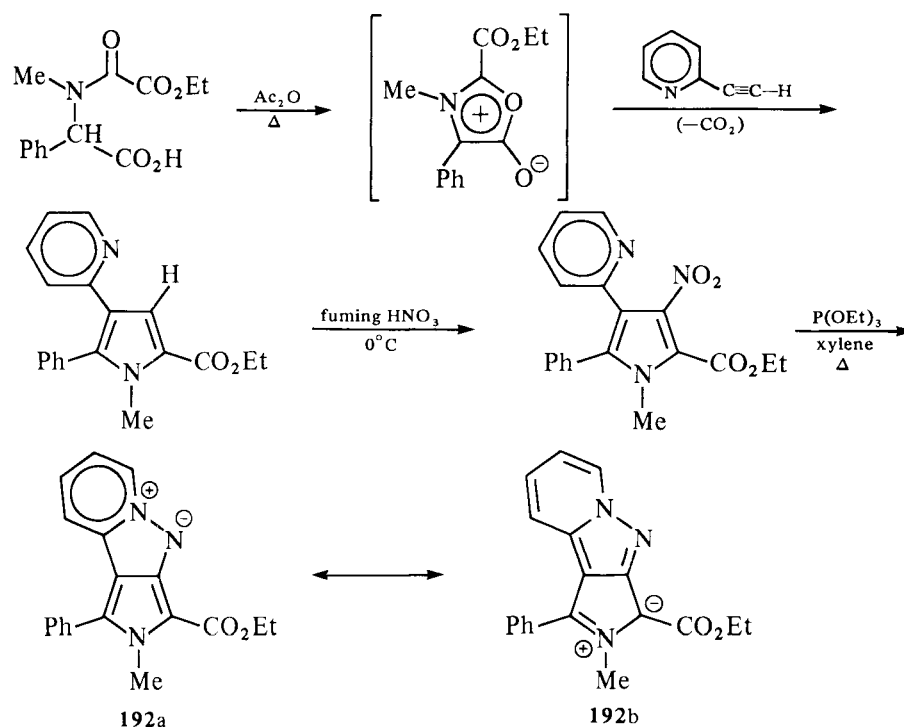
Scheme 21



Scheme 22

Potts and co-workers^{29,92,94} have demonstrated that the cycloaddition reactions of munchnones and acetylenic dipolarophiles provide convenient precursors to “nonclassical” heterocycles, as illustrated in Schemes 22⁹² and 23.⁹⁴ The thieno-[3,4-*c*]pyrrole **191** and the triazapentalene **192** undergo intriguing 1,3-dipolar cycloaddition reactions with selected acetylenes and olefins, which are beyond the scope of this review.

Manecke and Klawitter²⁵ have investigated the 1,3-dipolar cycloaddition reactions of bis(1,3-oxazolium 5-oxides) **194** with diacetylenic dipolarophiles **196** to form polymers **198**, which contain pyrrole units in the chain. By way of model studies, the cycloaddition reactions of the bismunchnones **194** with simple acetylenes were examined first. The results of this study are summarized in Table 4.11. In general, the bis(1,3-oxazolium 5-oxides) **194** are prepared *in situ* from their bis(*N*-acylamino acid) precursors **193** using acetic anhydride as the cyclodehydrating reagent and *N,N*-dimethylacetamide (DMA) as a solubilizing agent for **193** and **194**, although the bispyrrole products **195** are usually insoluble in DMA. However, these workers were able to isolate **194a** in a 39% yield. Because of the poor solubility of most of the bispyrroles **195** in CDCl₃, only the regiochemistry of the CDCl₃-soluble **195b** was assigned, as indicated, with the aid of ¹H NMR spectroscopy utilizing the shift reagent Eu(fod)₃.

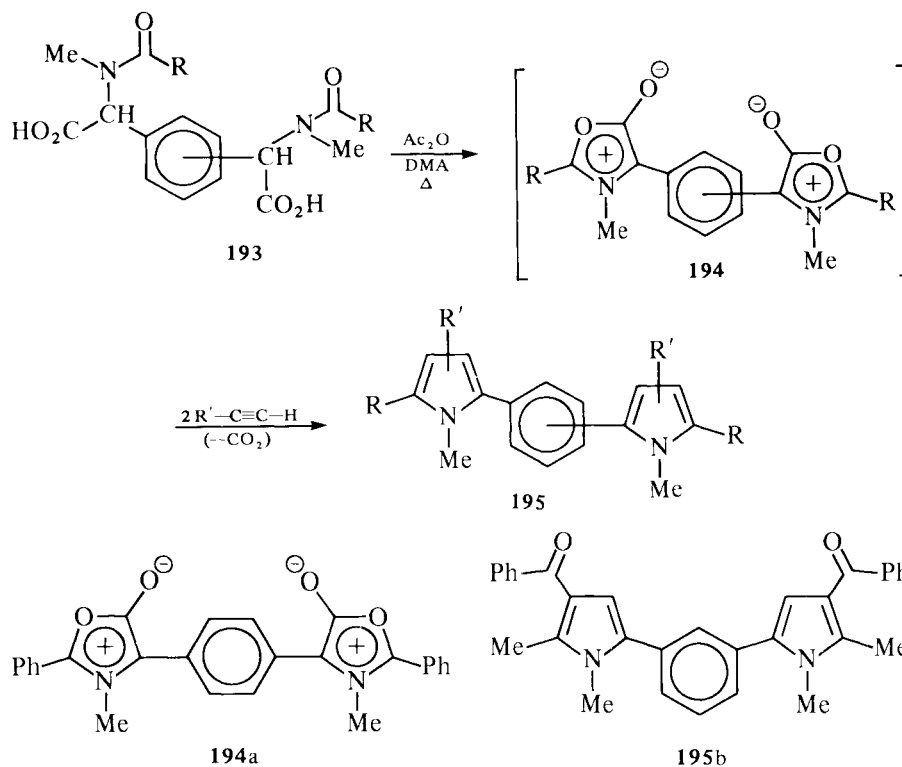


Scheme 23

TABLE 4.11. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF BIS(1,3-OXAZOLIUM 5-OXIDES) AND ACETYLENES²⁵

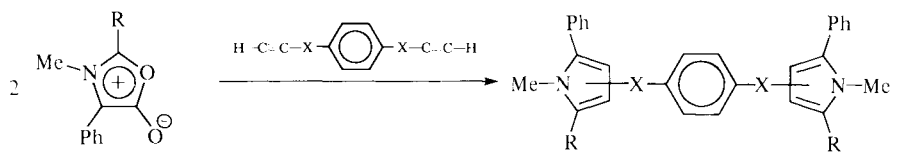
R	R ¹	Isomer	Percent Yield ^a
Me	Ph	1,3	78
Me	Ph	1,4	80
Me	PhCO	1,3	60
Me	PhCO	1,4	55
Ph	Ph	1,4	76
Ph	PhCO	1,4	49

^aThe bis(1,3-oxazolium 5-oxides) were prepared *in situ* by the cyclodehydration of the bis(*N*-acylamino acid) precursors with acetic anhydride in the presence of *N,N*-dimethylacetamide as solubilizing agent.



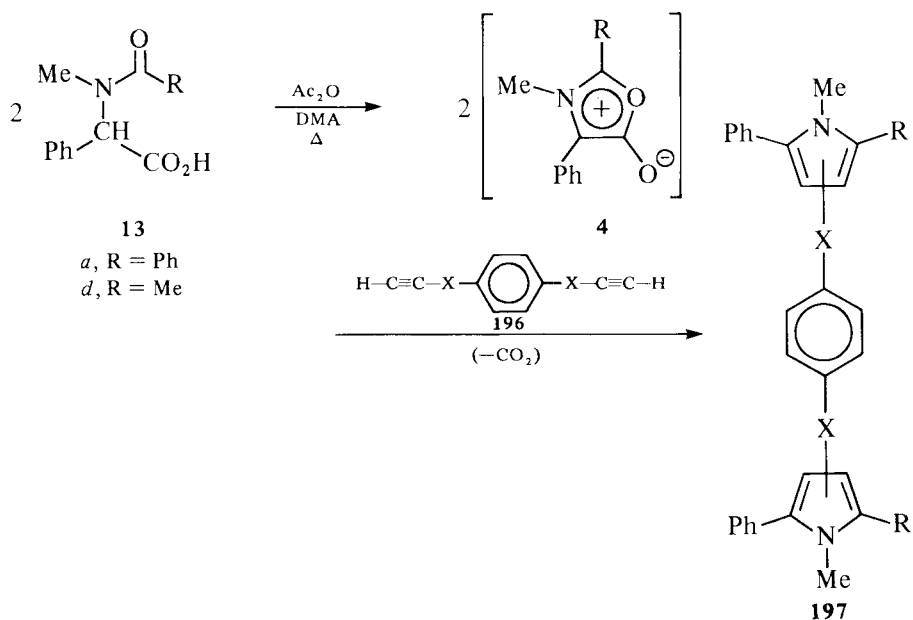
The cycloaddition reactions of the simple munchnones **4** and the diacetylenes **196** was next investigated.²⁵ A summary of these results is indicated in Table 4.12. The regiochemistry of the bispyrrole products **197** was not determined.

TABLE 4.12. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 1,3-OXAZOLIUM 5-OXIDES AND DIACETYLENES²⁵



R	X	Percent Yield ^a
Me	—	73
Me	C=O	74
Ph	—	23
Ph	C=O	59

^aMunchnones prepared *in situ* by cyclodehydration of *N*-acylamino acid precursors with acetic anhydride in presence of *N,N*-dimethylacetamide as solubilizing agent.



Finally, the cycloaddition reactions of the bis(1,3-oxazolium 5-oxides) **194** and the diacetylenes **196** was examined.²⁵ These results are summarized in Table 4.13. The gross structure of the polycycloaddition products **198** was confirmed by IR spectral comparison with the model compounds **195** and **197**, although the regiochemistry was not determined.

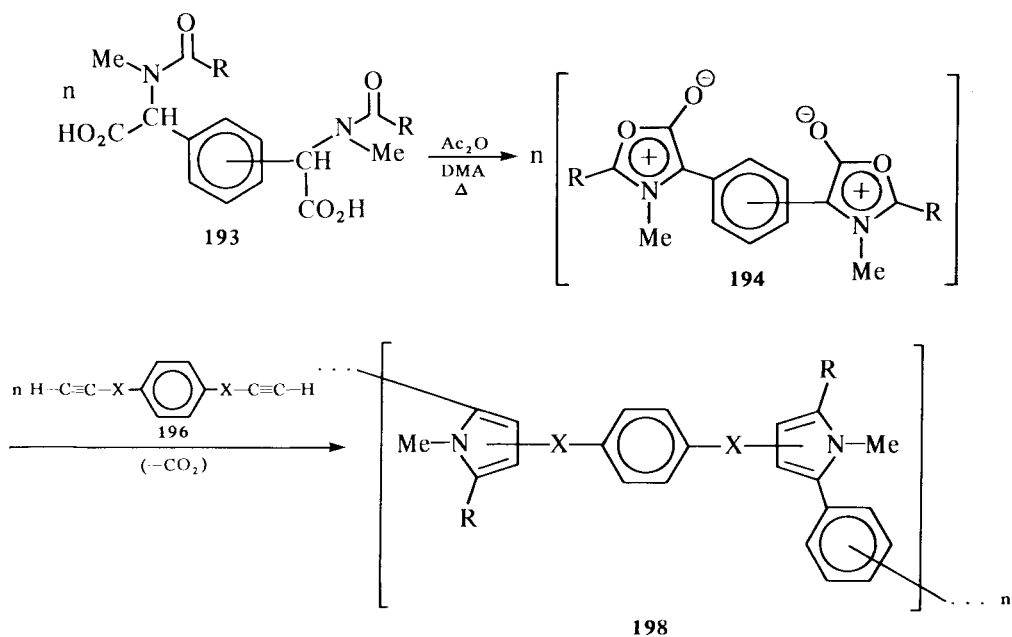
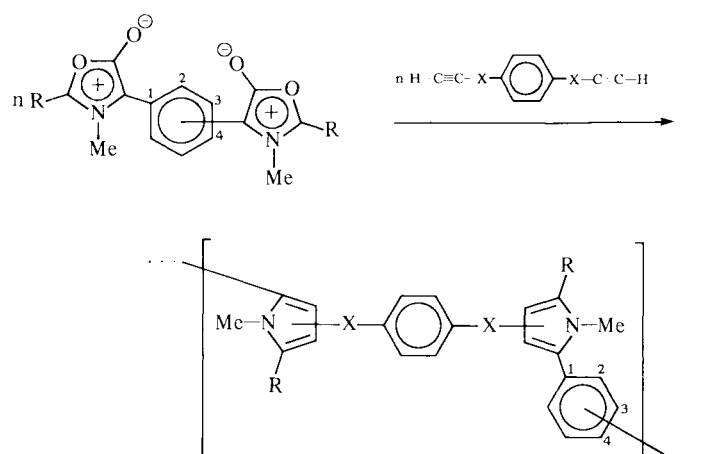


TABLE 4.13. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF BIS(1,3-OXAZOLIUM 5-OXIDES) AND DIACETYLENES²⁵

R	X	Isomer	Percent Yield ^a
Me	—	1,3	65
Me	—	1,4	37
Me	C=O	1,3	88
Me	C=O	1,4	64
Ph	C=O	1,4	56

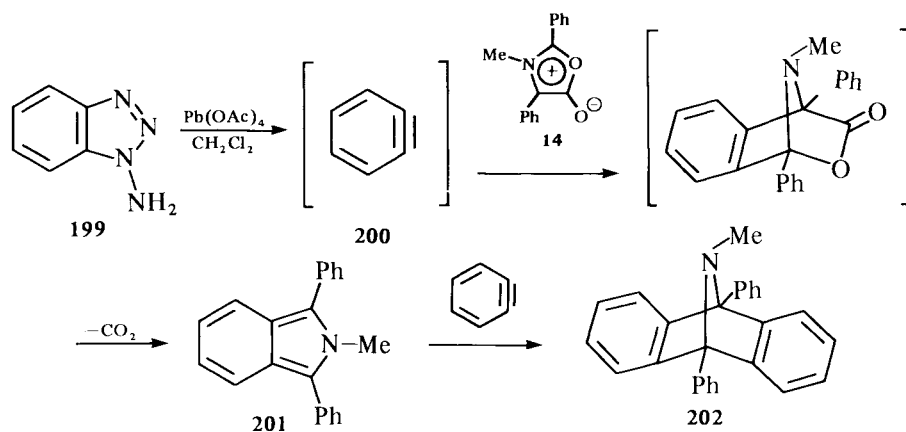
^aBismunchnones prepared *in situ* by cyclodehydration of bis(*N*-acylamino acid) precursors with acetic anhydride in presence of *N,N*-dimethylacetamide as solubilizing agent.

4.2.3.3.2. WITH ARYNE DIPOLAROPHILES

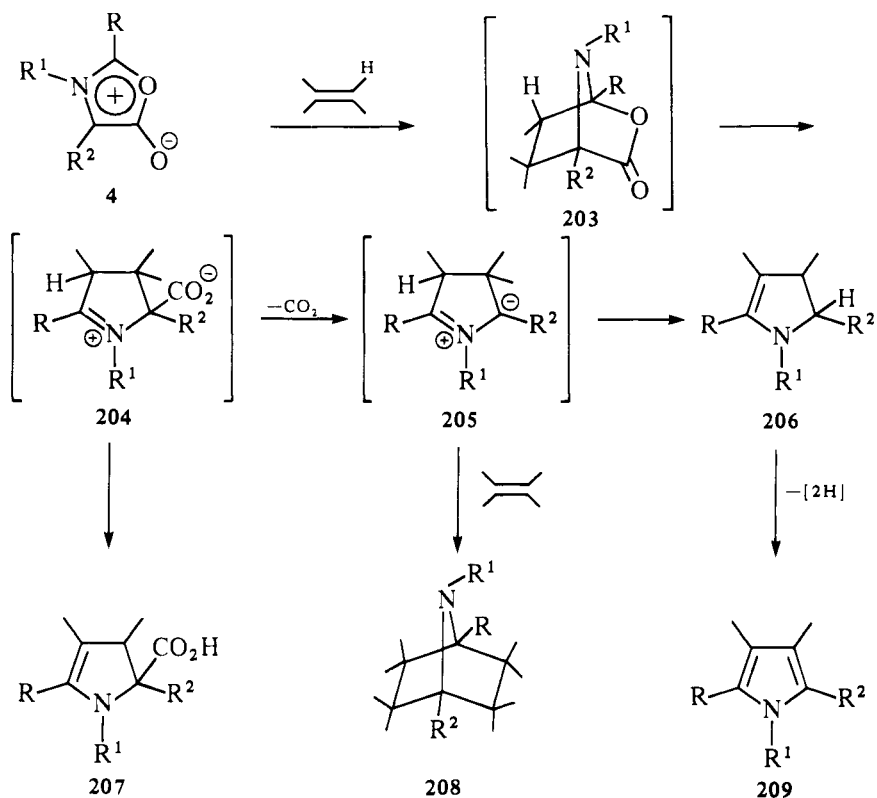
Only a single report involving the 1,3-dipolar cycloaddition reaction of a 1,3-oxazolium 5-oxide with an aryne has appeared. Kato and co-workers¹⁰⁵ have reported the reaction of the isolable munchnone **14** with benzyne **200**. This reaction affords only a 2% yield of the isoindole **201** and a 4% yield of the iminoanthracene **202**, the Diels–Alder adduct of **201** and benzyne. The low yields of **201** and **202** were attributed either to the instability of **14** to the oxidative conditions required to generate benzyne from 1-aminobenzotriazole **199** or to reaction of **14** with **199**.

4.2.3.3.3. WITH OLEFINIC DIPOLAROPHILES

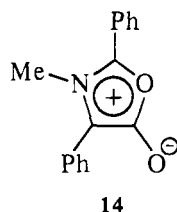
The 1,3-dipolar cycloaddition reactions of *N*-substituted 1,3-oxazolium 5-oxides **4** with olefins, shown in Scheme 24, yield cyclic azomethine ylides **205** after elimination of carbon dioxide from the primary cycloadducts **203**. The cyclic



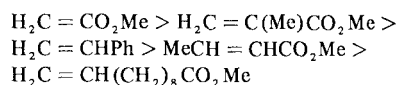
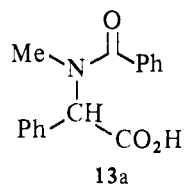
azomethine ylides **205** can then isomerize to Δ^2 -pyrrolines **206** or react with a second molecule of the olefinic dipolarophile to give 7-azabicyclo[2.2.1]heptane derivatives **208**.^{106,107} Although it was initially assumed that the cyclic azomethine ylides **205** are formed directly from the primary cycloadducts **203**, the betaines **204** may be involved, at least in some cases, since carboxylic acids **207** have been



Scheme 24



isolated under milder reaction conditions (*vide infra*).¹⁰⁸ Kinetic studies involving the reaction of the isolable munchnone **14** with olefinic dipolarophiles in benzonitrile obey a second-order rate law.⁶⁸ The activity order of olefinic dipolarophiles, indicated below, and the large negative activation entropies are characteristic for 1,3-dipolar cycloaddition reactions.



Huisgen and co-workers^{106,107} initially explored the scope of this Δ^2 -pyrroline synthesis by examining the reaction of the isolable 1,3-oxazolium 5-oxide **14** with various olefins at 50–120°C. Munchnone **14** was also generated *in situ* from its *N*-acylamino acid precursor **13a** using acetic anhydride as the cyclodehydrating reagent. The results of this investigation are summarized in Table 4.14. The Δ^2 -pyrrolines **206** were dehydrogenated to their corresponding pyrroles **209** with 10% Pd/C at 200–280°C to help establish their structure. However, occasionally, a “spontaneous” dehydrogenation occurs under the reaction conditions, affording pyrroles **209** as minor products or even sole products of the cycloaddition reaction. For example, reaction of **14** with 1-hexene affords only the pyrrole **209** ($\text{R} = \text{R}^2 = \text{Ph}$, $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{H}$, $\text{R}^5 = n\text{-Bu}$) in 57% yield. Similarly, reaction of **14** with acenaphthylene **210** gives the pyrrole **211** in 31% yield.^{106,107}

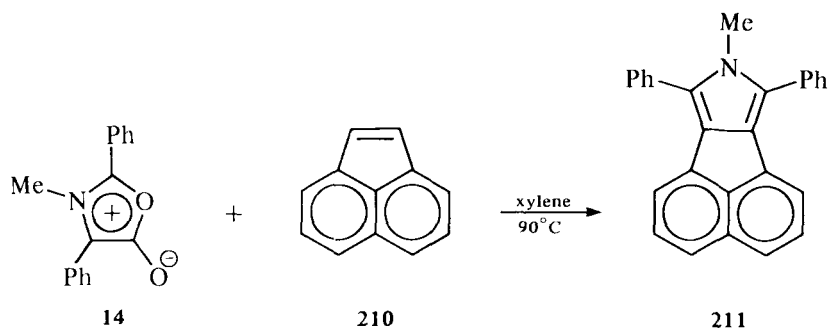
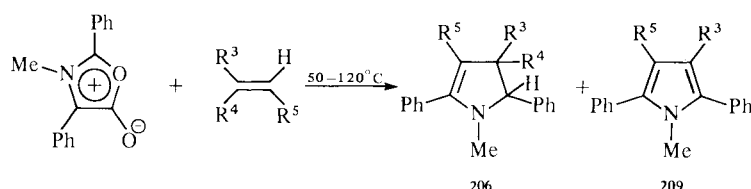


TABLE 4.14. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 3-METHYL-2,4-DIPHENYL-1,3-OXAZOLIUM 5-OXIDE (14) AND OLEFINS^{106,107}

Method of Munchnong Preparation ^a	R ³	R ⁴	R ⁵	Percent Yield	
				206	209
A	H	H	<i>n</i> -Bu	—	57
A	H	H	Ph	45	^b
B	—	—	—	—	37
A	H	CO ₂ Me	CO ₂ Me	31 ^c	—
B	—	—	—	20 ^c	—
B	Me	CO ₂ Me	H	74 ^d	—
A	CO ₂ Me	H	Me	87 ^e	—
B	—	—	—	75 ^e	—
A	CO ₂ Me	H	CO ₂ Me	43 ^c	—
B	—	—	—	49 ^c	—
A	CO ₂ Me	Me	CO ₂ Me	84 ^f	—
A	CO ₂ Et	H	Ph	g ^c	g
A	Ph	H	Ph	14	^b
A	Ph	Ph	H	64	—
A	PhCO	H	PhCO	64	—
B	—	—	—	70	—

^aA, Preformed; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride.

^bPyrrole **209** also formed in unspecified amount.

^cProduct probably has *cis* stereochemistry.

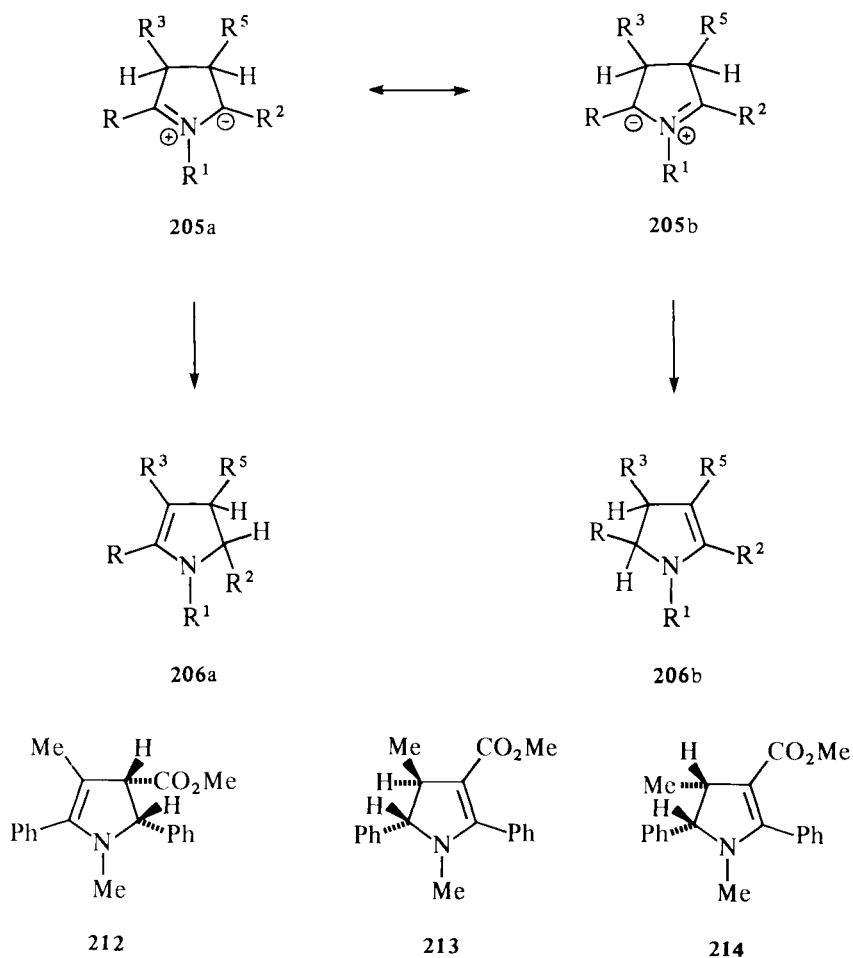
^dProduct was 40:60 *cis-trans* (with respect to phenyl and ester groups) mixture.

^eProduct was actually 70:30 mixture of **206** with *cis* stereochemistry and the other possible Δ^2 -pyrroline isomer as 1:1 *cis-trans* mixture.

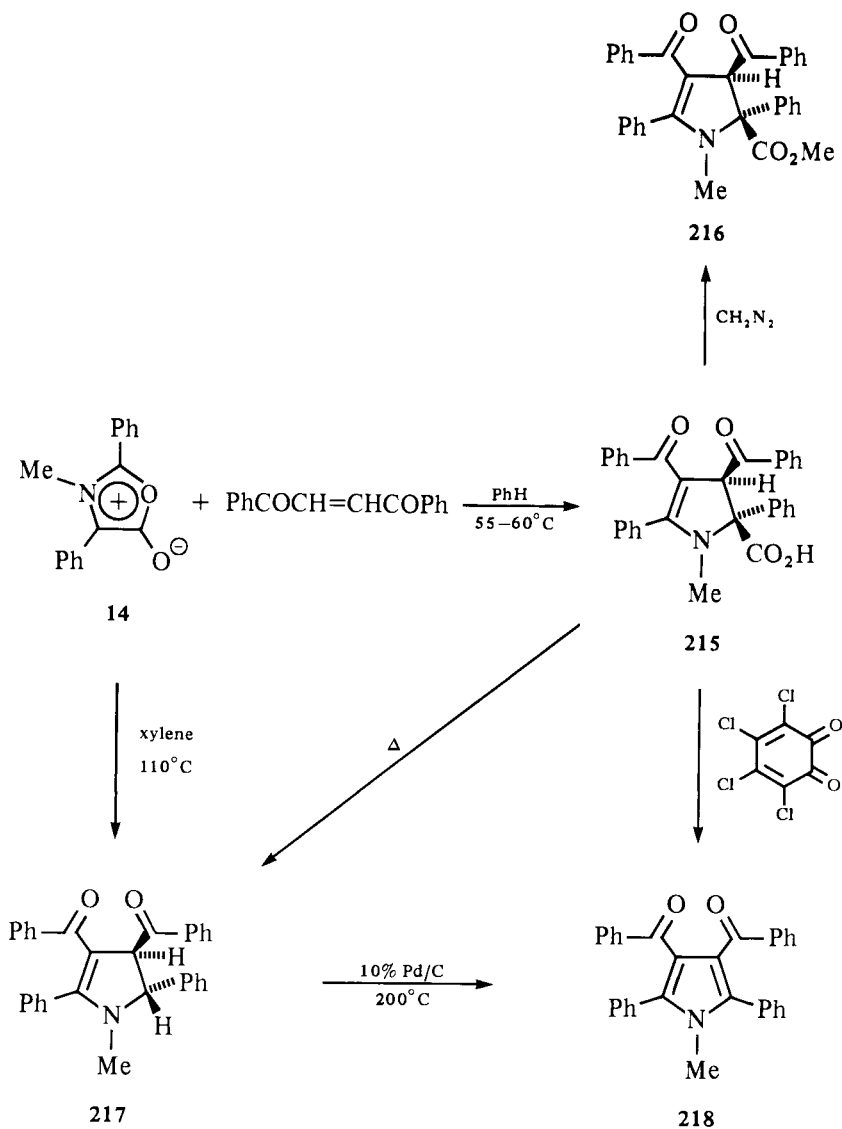
^fCrude Yield.

^gUnspecified mixture of **206** and **209** obtained in crude yield of 97%.

The position of the double bond in the Δ^2 -pyrrolines **206** is, of course, determined by the prototropic rearrangement **205** $\rightarrow$ **206**. However, since the negative charge can be on either the 2- or 5-position of **205**, the energetically favored Δ^2 -pyrroline should predominate. This perhaps, explains why dimethyl fumarate and maleate react with **14** to give the same Δ^2 -pyrroline. An interesting exception to this expectation is provided by the reaction of **14** and methyl crotonate, which gives a mixture of Δ^2 -pyrrolines **212**–**214** in a 70:15:15 ratio, respectively.¹⁰⁶

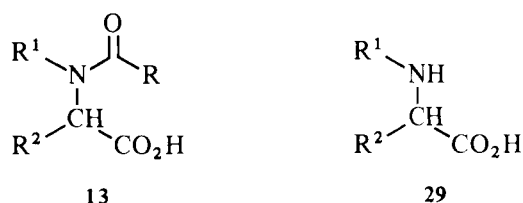


Huisgen and co-workers have reported that the reaction of the isolable 1,3-oxazolium 5-oxide **14** with *trans*-1,2-dibenzoyl ethylene in xylene at 110°C affords the Δ^2 -pyrroline **217** in 64% yield, as illustrated in Scheme 25.^{106,107} Δ^2 -Pyrroline **217** was dehydrogenated to pyrrole **218** with 10% Pd/C at 200°C in 73% yield.¹⁰⁶ However, Friedrichsen and Schröer have reported that the reaction of **14** and *cis*- or *trans*-1,2-dibenzoyl ethylene under milder conditions (presumably at 55–60°C in benzene) gives the Δ^2 -pyrroline carboxylic acid **215** in 74 and 79% yields, respectively.¹⁰⁸ Carboxylic acid **215** was converted to methyl ester **216** with diazomethane. Thermolysis of **215** affords the Δ^2 -pyrroline **217**. Treatment of **215** with *o*-chloranil at room temperature led to both decarboxylation and dehydrogenation to yield pyrrole **218**. The formation of **215** can be rationalized by the isomerization of the betaine **204** derived from the primary cycloadduct **203**, as indicated in Scheme 24.

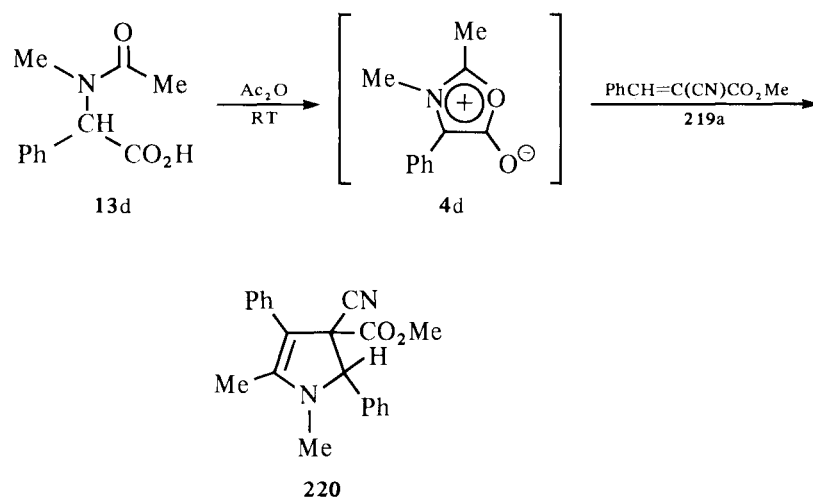


Scheme 25

There are only a few additional examples of the isolation of a Δ^2 -pyrroline carboxylic acid **207** from the reaction of a munchnone and an olefin, which will be discussed later.^{108,109} However, it appears likely that the formation of **207** is a general reaction under appropriate conditions. Unfortunately, most workers empirically determine the reaction temperature for the cycloaddition reaction of a 1,3-oxazolium 5-oxide and a dipolarophile by heating the reactants to a temperature required for carbon dioxide evolution. Hence, thermally labile products such as **207** are not normally observed.

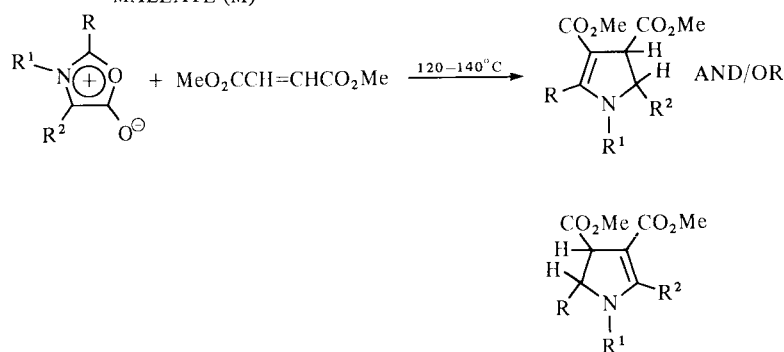


As noted previously, the isolable munchnone **14** could also be generated *in situ* from its *N*-acylamino acid precursor **13a** using acetic anhydride as the cyclodehydrating reagent. To further illustrate the utility of this *in situ* procedure, Huisgen and co-workers^{106,107} briefly examined the reaction of 1,3-oxazolium 5-oxides **4**, which cannot be isolated, with dimethyl fumarate and maleate at 120–140°C. These nonisolable munchnones were generated *in situ* from their *N*-acylamino acid **13** or amino acid precursors **29** again using acetic anhydride as the cyclodehydrating reagent. The results of these *in situ* reactions are summarized in Table 4.15. It should be noted that the products of these reactions were usually a mixture of Δ^2 -pyrroline isomers (positional and/or stereo), which were not separated or further structurally elucidated. Similarly, Texier and collaborators¹¹⁰ have reported that the reaction of 1,3-oxazolium 5-oxide **4d** generated *in situ* from the *N*-acetylamino acid **13d** and acetic anhydride with methyl α -cyanocinnamate **219a** affords the Δ^2 -pyrroline **220** in 65% yield.



Huisgen and co-workers have also reported the isolation of the 7-azabicyclo-[2.2.1]heptane derivative **221**, with the stereochemistry shown, in 31% yield from the reaction of munchnone **14** and excess *N*-phenylmaleimide.^{106,107} The formation of the 1:2 adduct **221** was rationalized by the addition of a second molecule of *N*-phenylmaleimide to the intermediate azomethine ylide **205**, as indicated in Scheme 24.

TABLE 4.15. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF *IN-SITU*-GENERATED 1,3-OXAZOLIUM 5-OXIDES AND DIMETHYL FUMARATE (F) OR MALEATE (M)^{106, 107}



R	R ¹	R ²	M/F	Percent Yield
H	Ph	H	F	20
(Me) ^a	Me	H	F	70 ^b
(Me) ^a	Me	Me	F	0 ^c
(Me) ^a	—(CH ₂) ₃ —	Me	F	86 ^b
Me	Cyclo-C ₆ H ₁₁	Me	M	31
Me	Ph	Me	F	83 ^d
Me	Ph	Me	M	79 ^d
Cyclo-C ₆ H ₁₁	Me	Ph	M	66 ^b

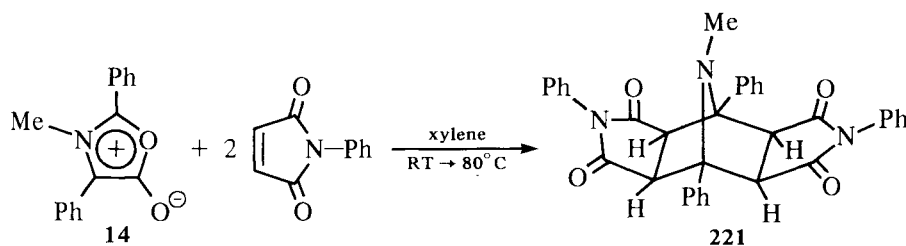
^aSubstituents in parentheses introduced by cyclodehydrating reagent, acetic anhydride.

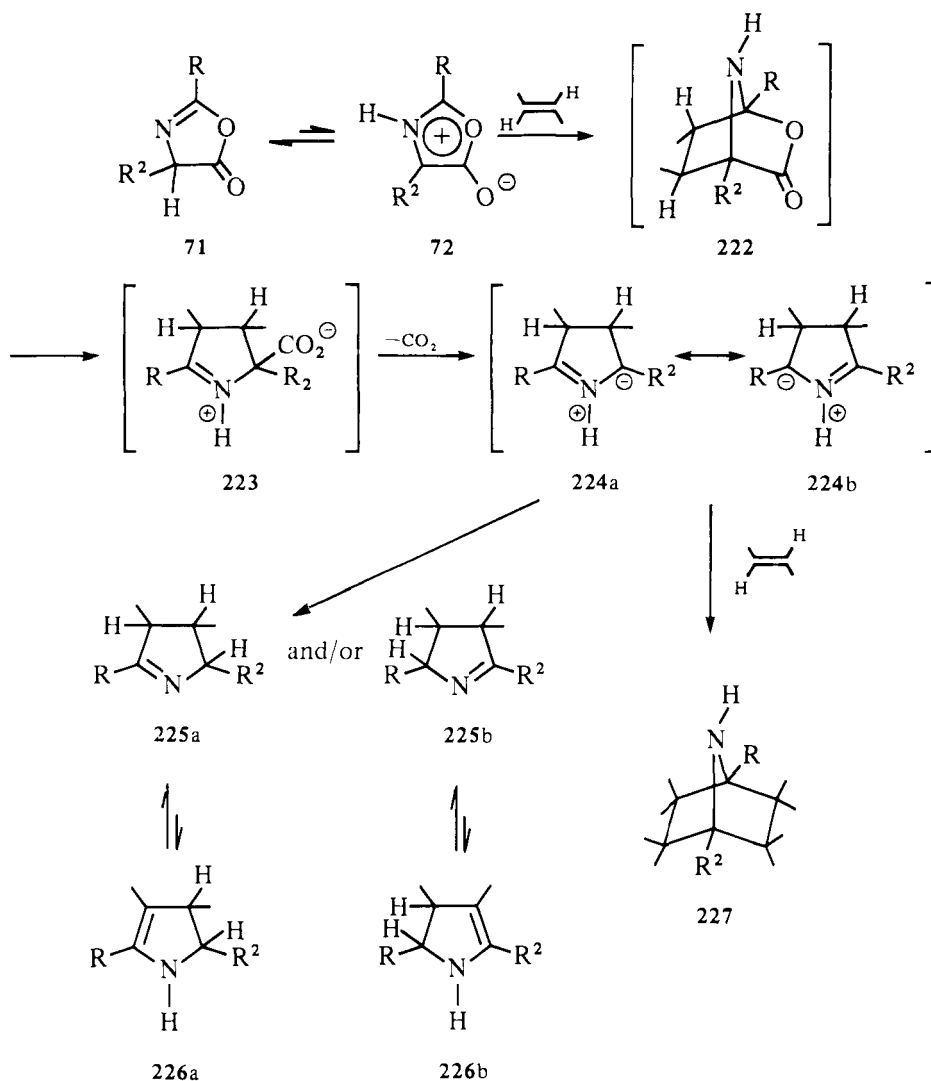
^bProbably a mixture of double-bond positional isomers.

^cCorresponding pyrrole obtained in 83% yield.

^dProbably a mixture of stereoisomers.

Huisgen and co-workers also examined the 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxide **14** with additional olefins, notably methyl acrylate and acrylonitrile, which gave complex mixtures.¹⁰⁶ No attempt was made to separate or structurally elucidate these mixtures. In general, this Δ^2 -pyrroline synthesis is not as broad in scope or range of application as the pyrrole synthesis from munchnones and acetylenic dipolarophiles. However, considering the synthetic accessibility of Δ^2 -pyrrolines, this approach still constitutes a valuable route to this class of compounds.

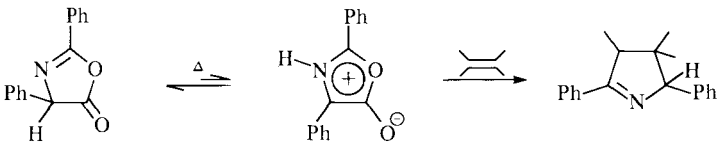
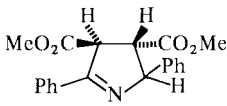
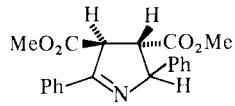
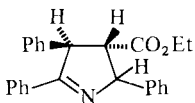
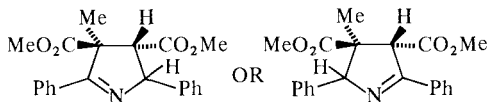
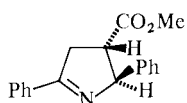
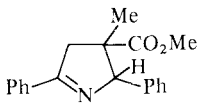
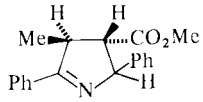




Scheme 26

2-Oxazolin-5-ones (azlactones) **71** also undergo 1,3-dipolar cycloaddition reactions via their *N*-unsubstituted 1,3-oxazolium 5-oxide tautomers **72** with activated olefins (α,β -unsaturated esters and nitriles), as illustrated in Scheme 26.^{51,52} Unlike the intermediate *N*-substituted azomethine ylides **205** (Scheme 24), the *N*-unsubstituted azomethine ylides **224** undergo intermolecular prototropic 1,2-shifts to afford Δ^1 -pyrrolines **225** rather than Δ^2 -pyrrolines. The *N*-unsubstituted azomethine ylides **224** also exhibit a greater propensity, presumably for steric reasons, to form 1:2 addition products **227** upon using high concentrations of reactive dipolarophiles. Again, it was initially assumed that the intermediate

TABLE 4.16. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 2,4-DIPHENYL-2-

	
Olefinic Dipolarophile	Product
Dimethyl fumarate	
Dimethyl maleate	
Ethyl cinnamate	
Dimethyl mesaconate	
Methyl acrylate	
Methyl methacrylate	
Methyl <i>trans</i> -crotonate	

OXAZOLIN-5-ONE AND OLEFINIC DIPOLAROPHILES

Percent Yield	Reference
67 ^a	51, 52, 113
45 ^a	51, 52
64	51, 52
16 ^b	52
—	113
^c	113
^c	113

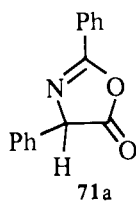
TABLE 4.16. (CONTINUED)

Olefinic Dipolarophile	Product
Acrylonitrile	
Methacrylonitrile	
<i>cis</i> - or <i>trans</i> -dicyanoethylene	
Methyl α -cyanocinnamate	

^aA 1:1 mixture of diastereomers.^bSingle component isolated by crystallization from methanol of a diastereomeric adduct mixture.^cUnspecified *cis*–*trans* mixture.^dA 90:10 *cis*–*trans* mixture. The major (*cis*) isomer isolated in crystalline form from methanol in 48% yield.^eA 1:1 *cis*–*trans* mixture. The *trans* (Ph:CN) isomer was isolated in crystalline form from methanol in 26% yield.^fStereochemistry not assigned.

azomethine ylides **224** were formed directly upon loss of carbon dioxide from the primary cycloadducts **222**; however, products derived from the betaines **223** have recently been isolated (*vide infra*).¹¹¹

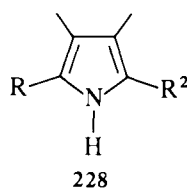
Huisgen and co-workers,^{51,52} as well as other researchers,^{112,113} have examined the reaction of the diphenylazlactone **71a** with α,β -unsaturated esters and nitriles. The results of these investigations are summarized in Table 4.16.

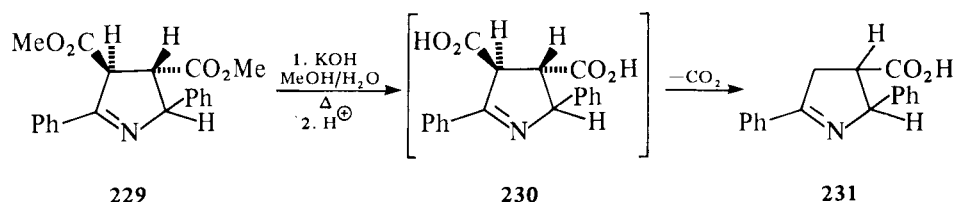


Percent Yield	Reference
90 ^d	51, 52, 113
88 ^e	51, 52, 113
^a	113
32 ^f	112

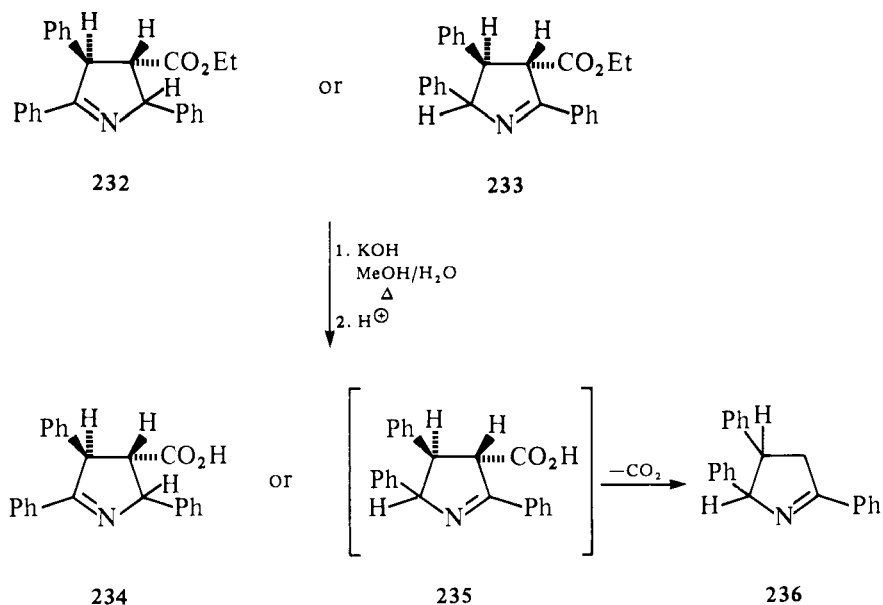
With very reactive dipolarophiles such as dimethyl fumarate the reactions are usually run in xylene at 120°C, avoiding a large excess of dipolarophile to minimize formation of the 1:2 addition products **227**. With less reactive dipolarophiles such as acrylonitrile the dipolarophiles are employed as the reaction solvent, and the reaction mixture is heated to the boiling point of the dipolarophile.

The structure of the Δ^1 -pyrroline products **225** was elucidated by ¹H NMR spectroscopy, by dehydrogenation to the corresponding pyrroles **228** with 10% Pd/C at 250–260°C,^{51,52} and by epimerizations.¹¹³ Another useful procedure for determining the position of the C=N in the Δ^1 -pyrroline products **225** is alkaline hydrolysis. For example,⁵² upon alkaline hydrolysis, Δ^1 -pyrroline **229**, the product of the cycloaddition reaction of azlactone **71a** and dimethyl fumarate, affords a

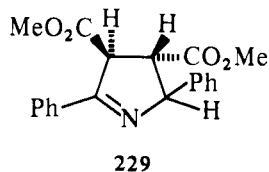


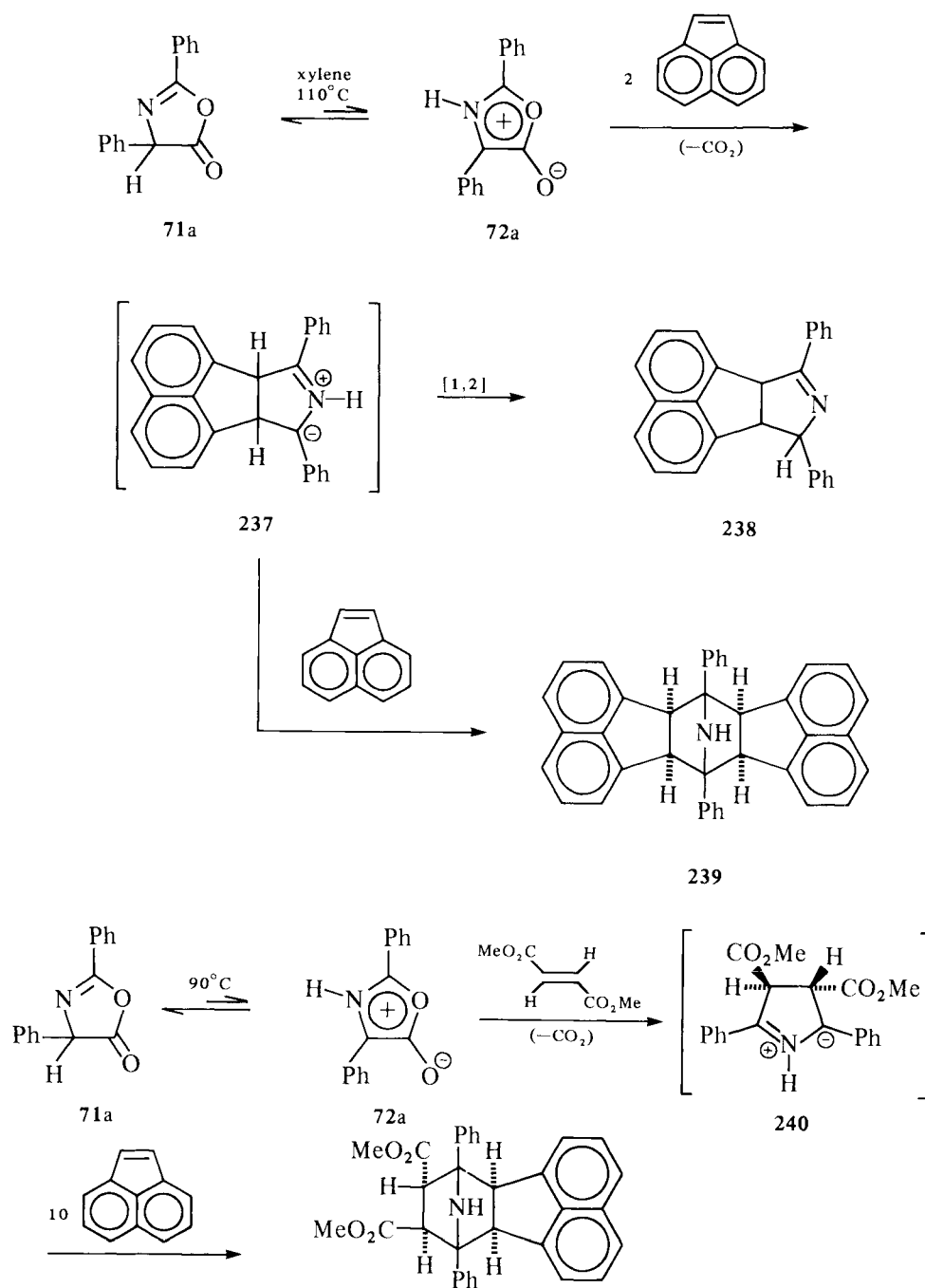


98% yield of the Δ^1 -pyrroline-4-carboxylic acid **231**. The intermediate β -imino-carboxylic acid **230** decarboxylates during hydrolysis. This procedure was employed to determine the structure of the Δ^1 -pyrroline **232** or **233** obtained from **71a** and ethyl cinnamate.⁵² Alkaline hydrolysis of **232/233** affords an isolable carboxylic acid, which has to be **234** since **235** would undergo decarboxylation to give **236**. Hence, the Δ^1 -pyrroline obtained from **71a** and ethyl cinnamate has structure **232** rather than **233**.



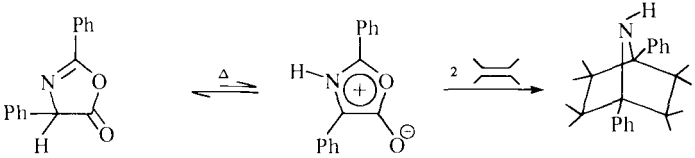
It is worth noting that the reaction of azlactone **71a** with dimethyl fumarate or maleate affords the same Δ^1 -pyrroline **229**.^{51,52} Presumably, a tautomeric equilibrium between Δ^1 -pyrroline **225** and the Δ^2 -pyrroline **226**, as indicated in Scheme 26, is responsible for this epimerization at C-3.





Scheme 27

TABLE 4.17. 1:2 ADDITION PRODUCTS FROM 2,4-DIPHENYL-2-OXAZOLIN-5-ONE

	
Olefinic Dipolarophile	Dipolarophile Concentration
Dimethyl fumarate	0.64 <i>M</i> /xylene
	2.2 <i>M</i> /xylene
	Dipolarophile Melt
Dimethyl maleate	0.7 <i>M</i> /xylene
	Dipolarophile as solvent
Maleic anhydride	0.9 <i>M</i> /xylene
	2.0 <i>M</i> /xylene
<i>N</i> -Phenylmaleimide	0.8 <i>M</i> /xylene

AND OLEFINIC DIPOLAROPHILES^{51,52}

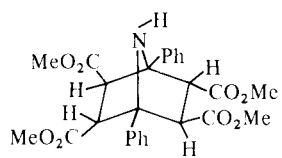
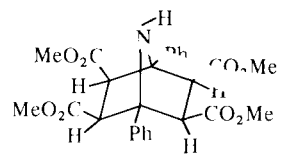
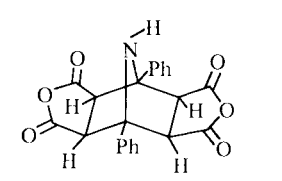
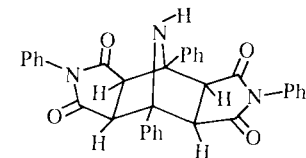
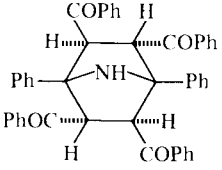
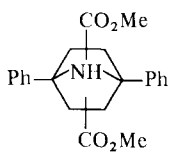
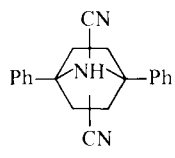
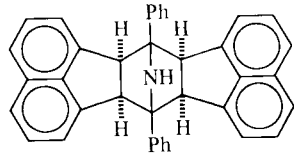
Product	Percent Yield
	Negligible
	46
	77
	2
	6
	76
	94
	67

TABLE 4.17. (CONTINUED)

Olefinic Dipolarophile	Dipolarophile Concentration
<i>trans</i> -1,2-Dibenzoylethylene	1 <i>M</i> /xylene
Methyl acrylate	Dipolarophile as solvent
Acrylonitrile	Dipolarophile as solvent
Acenaphthylene	1.8 <i>M</i> /xylene
	Dipolarophile Melt

Upon employing high concentrations of reactive olefinic dipolarophiles, azlactone **71a** affords 1:2 addition products **227**, as summarized in Table 4.17.^{51,52} The structures of these 7-azabicyclo[2.2.1]heptanes **227** were elucidated by ¹H NMR spectroscopy, by the preparation or attempted preparation of *N*-acetyl derivatives, and by the preparation of asymmetrical 7-azabicyclo[2.2.1]heptanes. It is important to note that treatment of the Δ^1 -pyrroline **225** with excess dipolarophile fails to yield the 1:2 addition products **227** and that dimethyl fumarate and maleate give different 1:2 addition products with **71a**, as depicted in Table 4.17. Both of these results suggest that the azomethine ylides **224** (Scheme 26) are common intermediates that can either undergo an intermolecular prototropic 1,2-shift to afford the Δ^1 -pyrroline **225** or add a second molecule of dipolarophile to

Product	Percent Yield
	77
	91
	0.6
	15
	70

give the 1:2 addition products **227**. The configuration of the 7-azabicyclo[2.2.1]-heptanes from **71a** and dimethyl fumarate and maleate is consistent with the addition of these dipolarophiles to the intermediate azomethine ylides **224** via a "two-plane" orientation complex.⁵²

One last result involving the formation of a 1:2 adduct from azlactone **71a** and an olefinic dipolarophile is worth noting. Huisgen and co-workers⁵² have reported that the reaction of **71a** with two equivalents of acenaphthylene in a 1.8*M* xylene solution at 110°C affords a 33% yield of the Δ^1 -pyrroline **238** and a 15% yield of the 1:2 addition product **239**, as shown in Scheme 27. However, when one equivalent of dimethyl fumarate is added to a solution of **71a** in 10 equivalents of acenaphthylene at 90°C (a temperature at which **71a** and acenaphthylene react

TABLE 4.18. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 2-OXAZOLIN-5-ONES

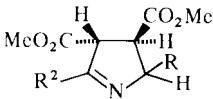
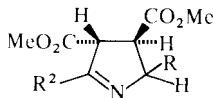
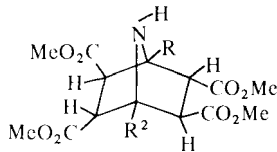
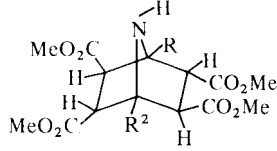
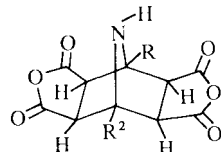
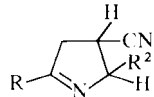
Method of Azlactone Preparation ^a	Dipolarophile	R
B	Dimethyl maleate	Cyclo-C ₆ H ₁₁
B	Dimethyl fumarate	4-ClPh
A	Dimethyl fumarate	
B	Maleic anhydride	4-MeOPh
A	Acrylonitrile	Ph

^a A, Preformed azlactone; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride.

^b Unspecified isomer mixture including the possibility of the other C=N positional isomer.

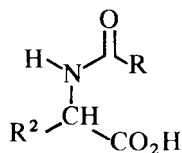
^c Unspecified *cis-trans* mixture.

AND OLEFINIC DIPOLAROPHILES

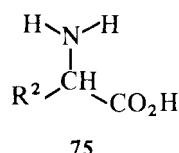
R ²	Product(s)	Percent Yield	Reference
Ph		100 ^b	52
Ph		91 ^b	52
		2	52
Ph		33	52
Ph		24	52
Me		^c	113

only sluggishly), a 68% yield of the 1:1:1 addition product **241** is obtained.^{51,52} This result suggests that the azomethine ylide **240** is a "hotter," less selective 1,3-dipole than the *N*-unsubstituted 1,3-oxazolium 5-oxide **72a**.

The reaction of several azlactones **71**, other than **71a**, with activated olefinic dipolarophiles has also been examined.^{52,113} The products of these reactions are Δ^1 -pyrroline **225** and/or 1:2 addition products **227**, depending on the reactivity or concentration of the dipolarophile employed. These results are summarized in Table 4.18. It should be noted that the azlactones **71** could be prepared *in situ* from their *N*-acylamino acid precursors **73** using acetic anhydride as the cyclodehydrating reagent without apparently changing the outcome of the reaction.⁵²

**73**

For this reason, the more recent results of Texier and collaborators involving the reaction of *in-situ*-generated azlactones **71** and activated olefins to give a plethora of products, not including Δ^1 -pyrrolines, is quite interesting.^{110-112,114} For example, reaction of azlactones **71** generated *in situ* from *N*-benzoylamino acids **73** (R = Ph) or amino acids **75** with methyl α -cyanocinnamate **219a** or methyl α -cyano(*p*-nitro)cinnamate **219b** in refluxing acetic anhydride (140°C) gives the *N*-acetyl Δ^2 -pyrrolines **242** and **243**, as summarized in Table 4.19.^{110,112,114} Reaction of preformed azlactones **71** with **219a** in refluxing acetic anhydride gives the same products, suggesting that the azlactones **71** are intermediates in the *in situ* reactions.¹¹⁴

**75****219**

a, R = H
b, R = NO₂

It appears plausible that the observed *N*-acetyl Δ^2 -pyrrolines **242** and **243** are formed upon *N*-acetylation of the expected Δ^1 -pyrrolines **244** and **245**. However, this possibility was ruled out since Δ^1 -pyrroline **244a**, which was obtained upon reacting azlactone **71a** and methyl α -cyanocinnamate **219a** in refluxing toluene, does not afford *N*-acetyl Δ^2 -pyrroline **242a** when heated with acetic anhydride in

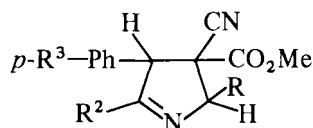
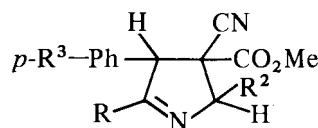
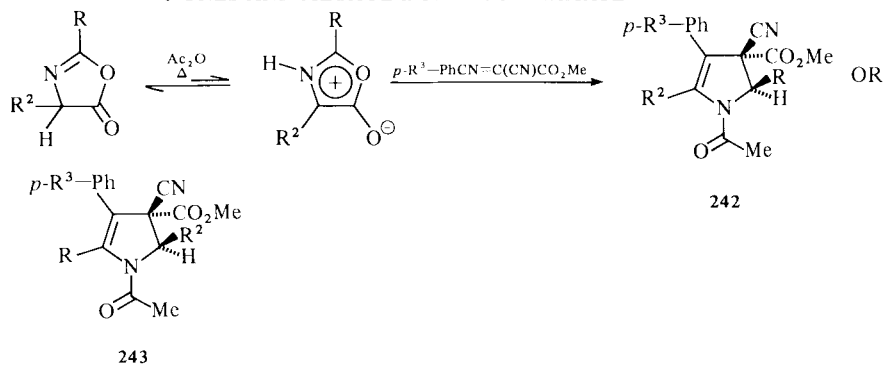
**244****245**

TABLE 4.19. *N*-ACETYL Δ^2 -PYRROLINES FROM *IN-SITU*-GENERATED 2-OXAZOLIN-5-ONES AND METHYL α -CYANOCINNAMATE^{110, 112, 114}



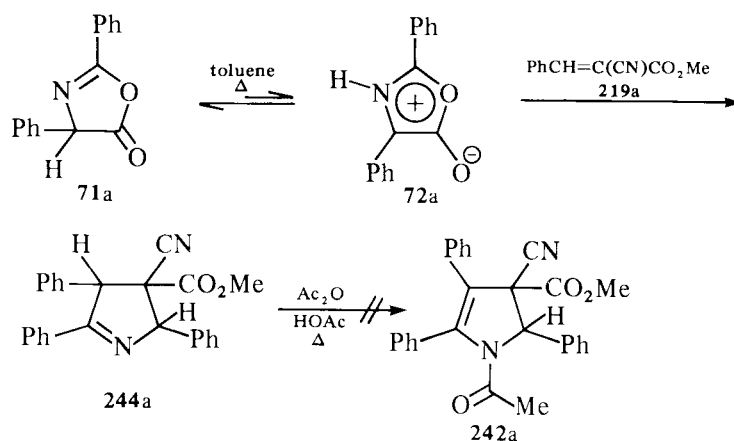
Method of Azlactone Preparation ^a	R	R ²	R ³	Product	Percent Yield
B	(Me) ^b	Me	H	242 = 243^c	43
B	(Me) ^b	PhCH ₂	H	242^c	72
B	(Me) ^b	Ph	H	243	85
B	(Me) ^b	Ph	NO ₂	243	78
A	Ph	Me	H	242	68
A	Ph	Me	NO ₂	242	65
A	Ph	Ph	H	242 = 243^d	78

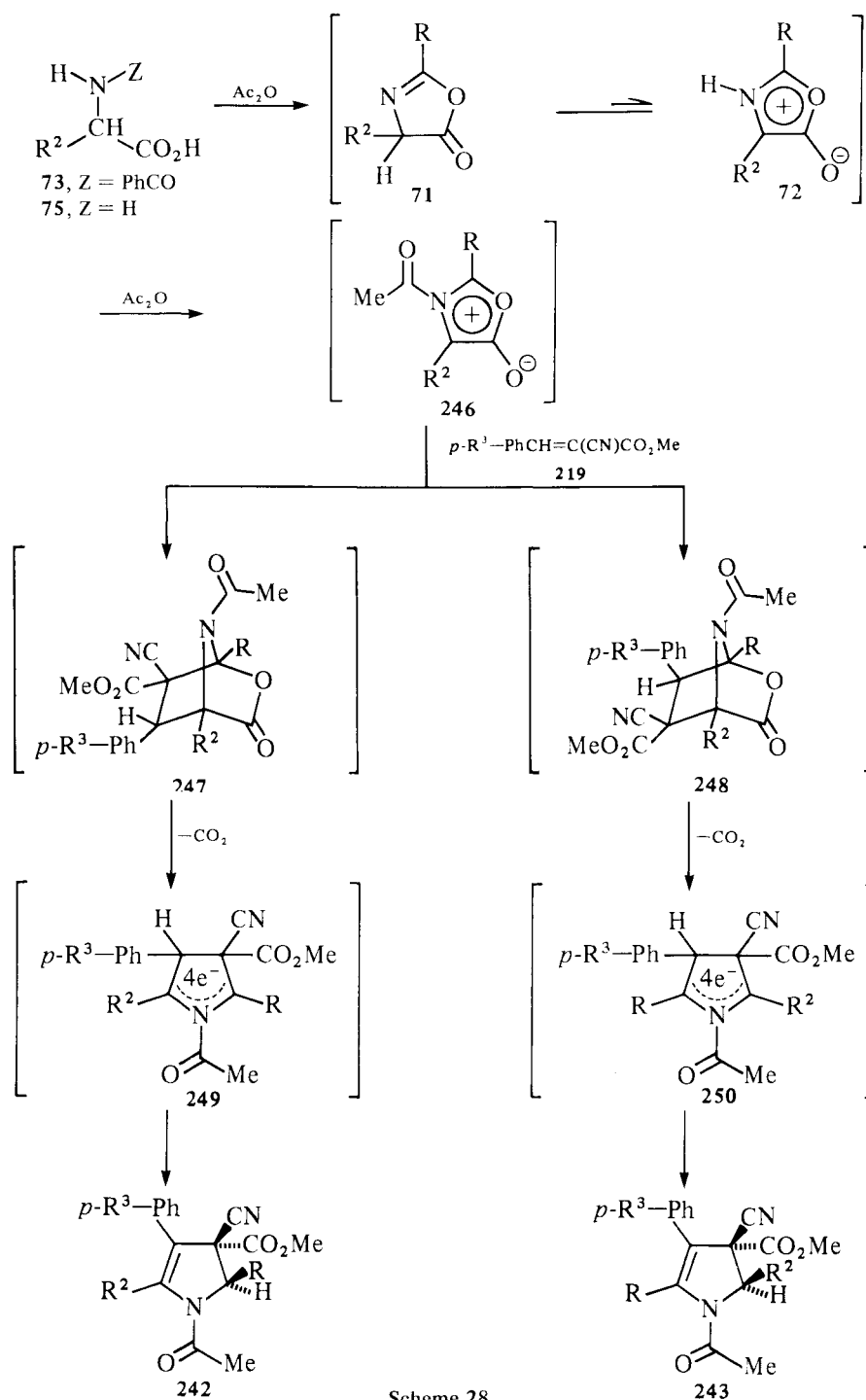
^a A, *In situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, *in situ* *N*-acetylation and cyclodehydration of amino acid precursor with acetic anhydride.

^b Substituents in parentheses introduced by cyclodehydrating reagent.

^c Stereochemistry of the product not assigned.

^d Mixture of *trans*-*cis* isomers, which were not separated, in a 78:22 ratio favoring the isomer with the stereochemistry depicted in **242 = 243**.

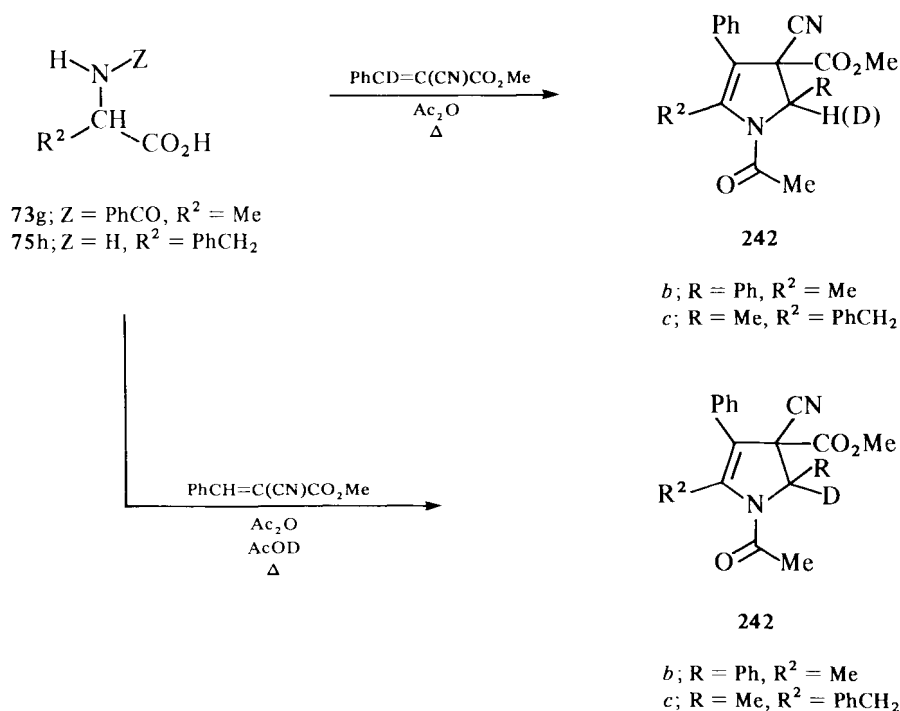




Scheme 28

the presence of acetic acid.¹¹² Accordingly, when the *N*-acetylation occurs appears to be a point of contention. Texier and co-workers favor the mechanism indicated in Scheme 28.^{112,114} The *N*-unsubstituted munchnones **72**, which are in tautomeric equilibrium with azlactones **71**, undergo acetylation to give the *N*-acetyl munchnones **246**. The 1,3-dipolar cycloaddition reaction of **246** and **219** affords the primary cycloadducts **247** or **248**, which eliminate carbon dioxide to give the *N*-acetyl azomethine ylides **249** or **250**, respectively. Prototropic isomerization of **249** or **250** then yields the observed *N*-acetyl Δ^2 -pyrrolines **242** or **243**. This mechanism seems unlikely as far as the intermediacy of the *N*-acetyl 1,3-oxazolium 5-oxides **246** are concerned since *N*-acetyl pyrroles have not been observed upon reaction of *in-situ*-generated azlactones **71** and acetylenic dipolarophiles.^{43,49,50,67} Possibly the mechanism of this reaction is similar to the one depicted in Scheme 26 except that the *N*-unsubstituted azomethine ylides **224** are acetylated to give the *N*-acetyl azomethine ylides **249** or **250**.

Texier and collaborators have demonstrated that the proton transfer that occurs during the **249** $\rightarrow$ **242** rearrangement is largely intermolecular in nature.^{112,114} Reaction of *N*-benzoylalanine **73g** and phenylalanine **75h** with methyl α -cyano-cinnamate with 98% β -deuteration in refluxing acetic anhydride affords *N*-acetyl Δ^2 -pyrrolines **242b** and **242c**, respectively, with less than 25% deuteration at C-5. On the other hand, reaction of **73g** and **75h** with methyl α -cyanocinnamate in refluxing acetic anhydride in the presence of deuterated acetic acid yields the C-5 deuterated *N*-acetyl Δ^2 -pyrrolines **242b** and **242c**.



The structure of the *N*-acetyl Δ^2 -pyrrolines **242** and **243**, as well as their stereochemistry (see Table 4.19), was determined largely by ^1H NMR spectroscopy.^{110,114} Treatment of *N*-acetyl Δ^2 -pyrrolines **242b** and **242c** with a stoichiometric quantity of deuterated acetic acid in acetic anhydride did not result in deuterium incorporation, suggesting that the *N*-acetyl Δ^2 -pyrrolines do not epimerize under the reaction conditions.

A careful examination of Table 4.19 reveals that the *in-situ*-generated azlactone **71f** ($R = \text{Me}$, $R^2 = \text{Ph}$) and the isomeric azlactone **71g** ($R = \text{Ph}$, $R^2 = \text{Me}$) afford the same *N*-acetyl Δ^2 -pyrroline **242b** $\equiv$ **243b** upon reaction with methyl α -cyano-cinnamate.^{110,114} Similarly, azlactones **71f** and **71g** both afford **242d** $\equiv$ **243d** upon reaction with methyl α -cyano(*p*-nitro)cinnamate. These results clearly indicate that the regiochemistry of these cycloadditions is not governed by the nature of the 1,3-oxazolium 5-oxide ring **72** but by the nature of the substituents R and R^2 . Texier and collaborators feel that PMO theory cannot readily explain these changes in regiochemistry. Accordingly, they offer an alternate rationale; that is, in the cycloaddition transition state the lactone group is elongated from its equilibrium

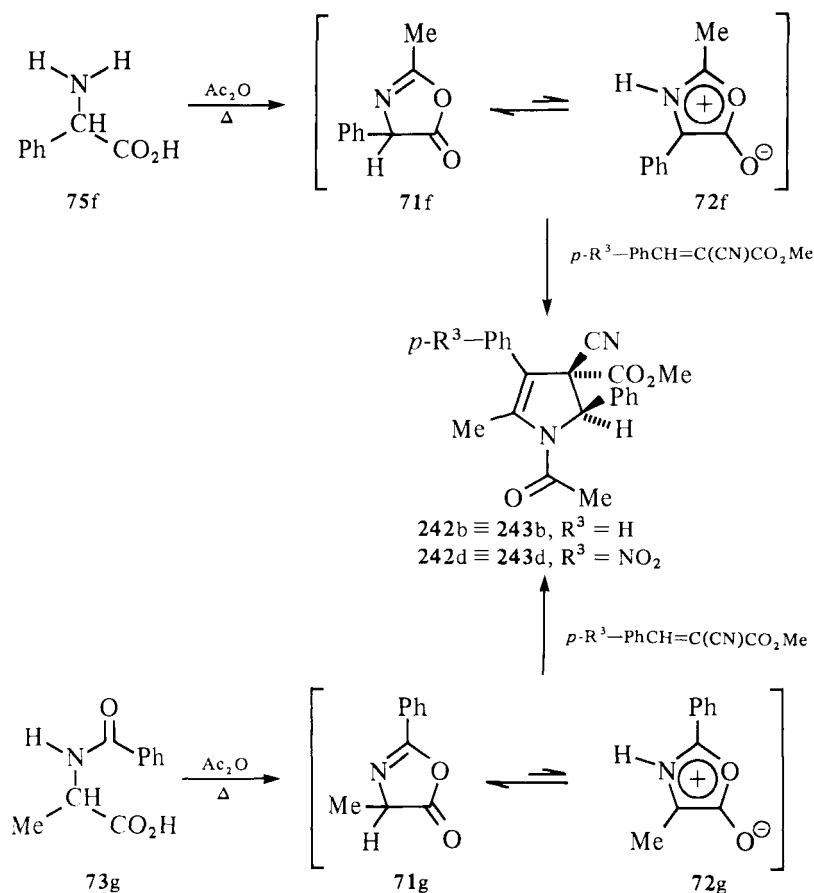
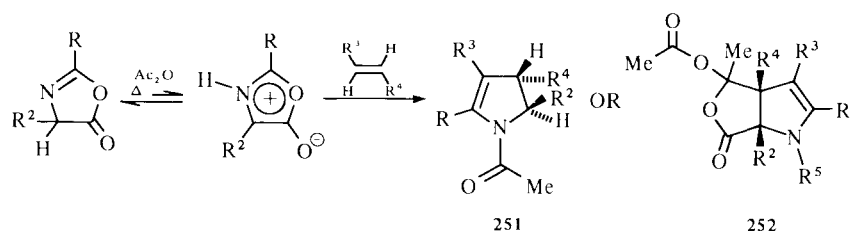


TABLE 4.20. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF *IN-SITU*-GENERATED 2-OXAZOLIN-5-ONES AND 1,2-DISUBSTITUTED OLEFINS

Method of Azlactone Preparation ^a	R	R ²	R ³	R ⁴	R ⁵	Product	Percent Yield	Reference
B	(Me) ^b	Me	CN	CN	MeCO	252	76	111
B	(Me) ^b	PhCH ₂	CN	CN	H	252	58	111
B	(Me) ^b	Ph	CN	CN	MeCO	252	72	111
B	(Me) ^b	Ph	CO ₂ Me	CO ₂ Me	—	251 ^c	58	112, 114
B	(Me) ^b	Ph	Ph	PhCO	—	251	63	110, 114
A	Ph	Me	CN	CN	H	252 ^d	56	111
A	Ph	Me	CO ₂ Me	CO ₂ Me	MeCO	252	46	111

^aA, *In situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride.

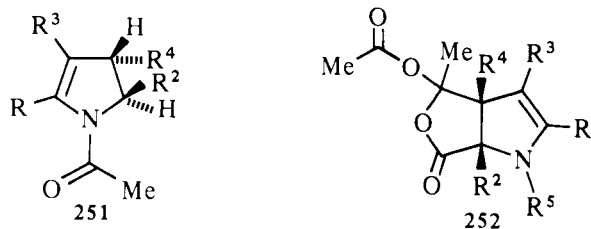
^bSubstituents in parentheses introduced by cyclodehydrating reagent.

^cMixture of *trans*–*cis* isomers, which were separated, in a 5 : 1 ratio.

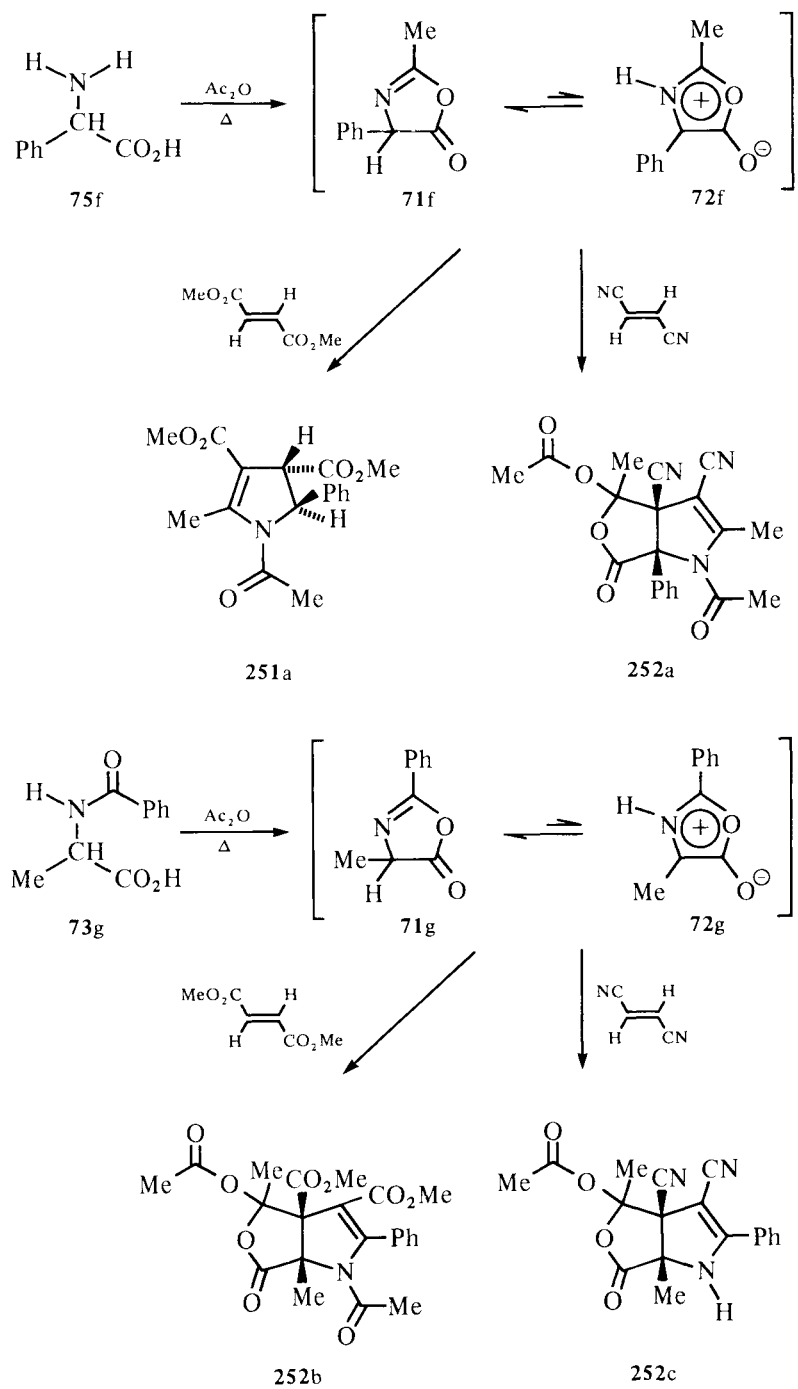
^dStructure confirmed by X-ray crystallography.

geometry such that the disymmetry of the C-2 and C-4 molecular orbitals induced by the lactone is practically negligible. Thus, the regiochemistry is governed by the R and R² substituents. This interpretation is supported by CNDO/2 calculations.¹¹⁰

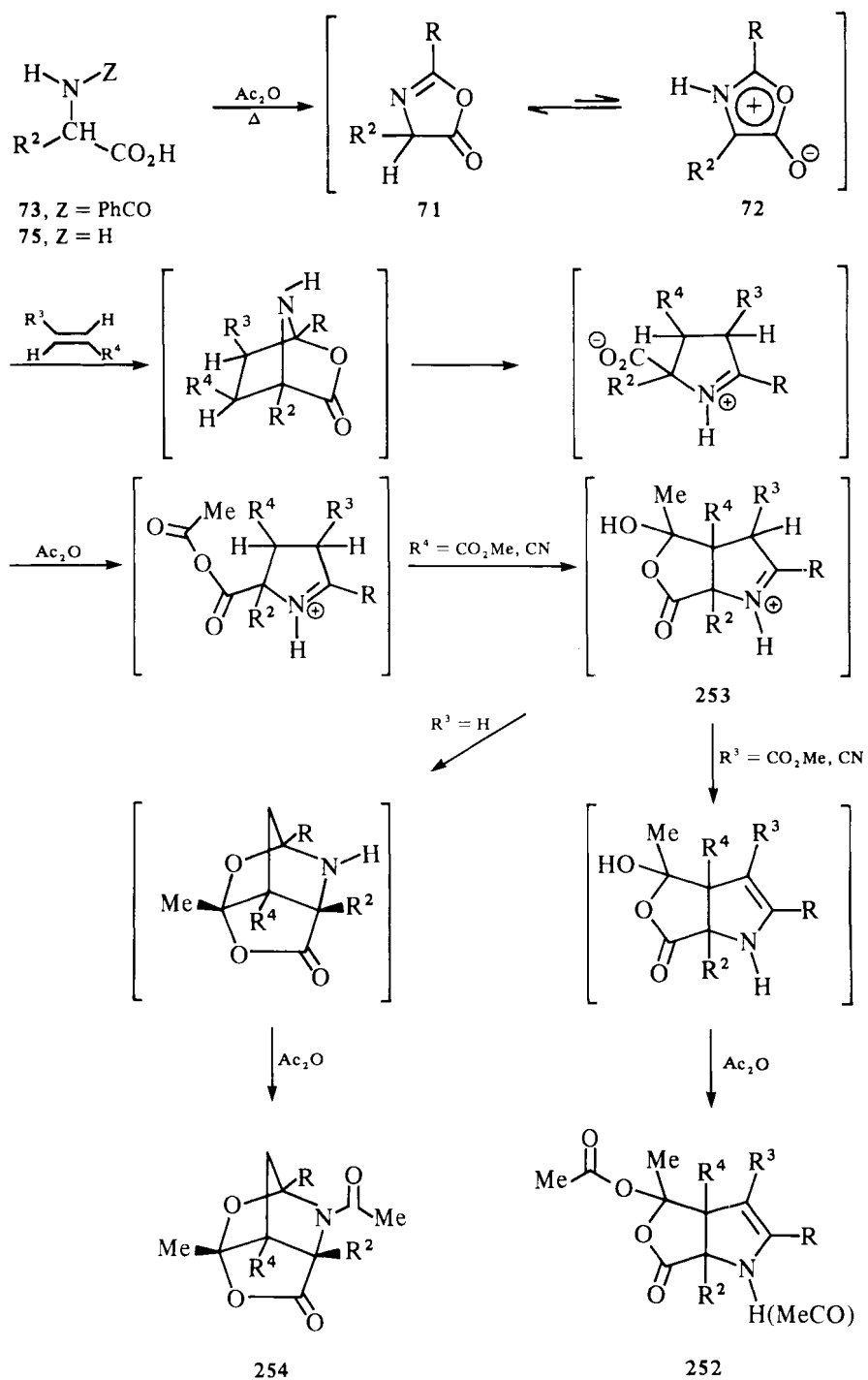
The reaction of azlactones **71** generated *in situ* from *N*-benzoylamino acids **73** (R = Ph) or amino acids **75** with 1,2-disubstituted olefins such as chalcone, dimethyl fumarate, or fumaronitrile in refluxing acetic anhydride affords either *N*-acetyl Δ²-pyrrolines **251** or the bicyclic carbolactones **252**, as summarized in Table 4.20.^{110–112, 114}



The complexity of this situation is best illustrated by considering the reactions of the isomeric azlactones **71f** and **71g** with dimethyl fumarate and fumaronitrile as shown in Scheme 29. The reaction of azlactone **71f** generated *in situ* from *C*-



Scheme 29

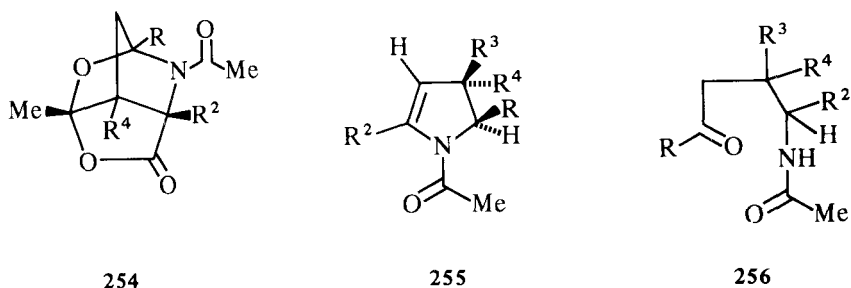


Scheme 30

phenylglycine **75f** with dimethyl fumarate in refluxing acetic anhydride affords the *N*-acetyl Δ^2 -pyrroline **251a**.^{112,114} Under the same conditions, azlactone **71f** with fumaronitrile gives the *N*-acetyl bicyclic carbolactone **252a**.¹¹¹ On the other hand, the isomeric azlactone **71g**, which was generated *in situ* from *N*-benzoylalanine **73g**, reacts with dimethyl fumarate in refluxing acetic anhydride to give the *N*-acetyl bicyclic carbolactone **252b**.¹¹¹ Under the same conditions, azlactone **71g** reacts with fumaronitrile to give the *N*-unacylated bicyclic carbolactone **252c**.¹¹¹

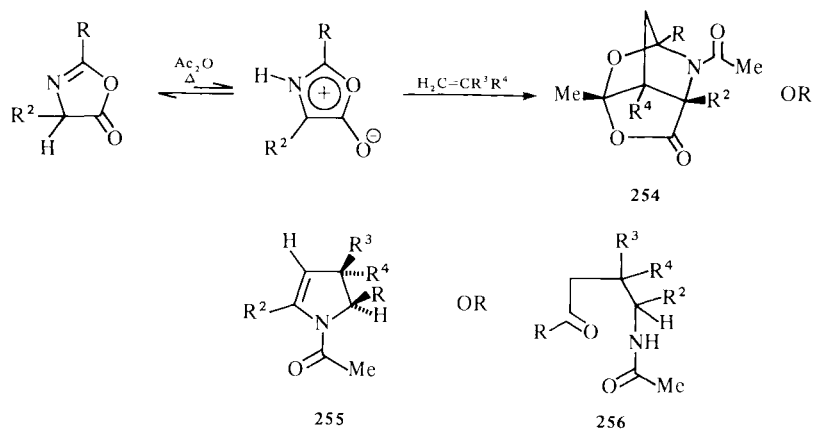
The structure of the bicyclic carbolactones **252** was determined largely by ¹H and ¹³C NMR spectroscopy, although the structure of **252c** was confirmed by X-ray crystallography.¹¹¹ Texier and collaborators have yet to publish a mechanism for the formation of carbolactones **252**. However, several points concerning this mechanism are worth mentioning. Two of the carbolactones **252** reported in Table 4.20 are not *N*-acetylated. This observation suggests that the initial step in the formation of **252** is not the *N*-acetylation of the *N*-unsubstituted munchnone tautomers **72** (to give the *N*-acetyl 1,3-oxazolium 5-oxides **246**) as suggested for the formation of the *N*-acetyl Δ^2 -pyrrolines **242** and **243** (see Scheme 28).^{112,114} Secondly, the structure of carbolactones **252** suggests that they are derived from a rearranged primary cycloadduct, which retains the elements of carbon dioxide, followed by further reaction with acetic anhydride.¹¹¹ We offer a putative mechanism for the formation of carbolactones **252** depicted in Scheme 30.

To further complicate matters, Texier and co-workers have reported that the reaction of azlactones **71** generated *in situ* from *N*-benzoylamino acids **73** (R = Ph) or amino acids **75** with monosubstituted olefins such as methyl or ethyl acrylate or acrylonitrile in refluxing acetic anhydride gives either *N*-acetyl tricyclic carbolactones **254**, *N*-acetyl Δ^2 -pyrrolines **255**, or amide ketones **256** depending on the nature of the azlactone substituents R and R².^{111,112,114} Under the same reaction conditions, 1,1-disubstituted olefins such as methyl methacrylate and methacrylonitrile afford the amide ketones **256**.¹¹⁴ These results are summarized in Table 4.21.



The formation of the *N*-acetyl Δ^2 -pyrrolines **255** has been rationalized previously. However, it should be noted that *N*-acetyl 3-unsubstituted Δ^2 -pyrrolines **255**, much like enamines, are particularly labile toward hydrolysis. For example, *N*-acetyl Δ^2 -pyrrolines **255a** and **255b** readily undergo hydrolysis to afford the amide ketones **256a** and **256b**, respectively.¹¹⁴ Accordingly, the isolation of the amide ketones **256** from the reaction of the *in-situ*-generated azlactones **71** and methyl acrylate, acrylonitrile, methyl methacrylate, or methacrylonitrile in

TABLE 4.21. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF *IN-SITU*-GENERATED 2-OXAZOLIN-5-ONES AND MONOSUBSTITUTED OR 1,1-DISUBSTITUTED OLEFINS

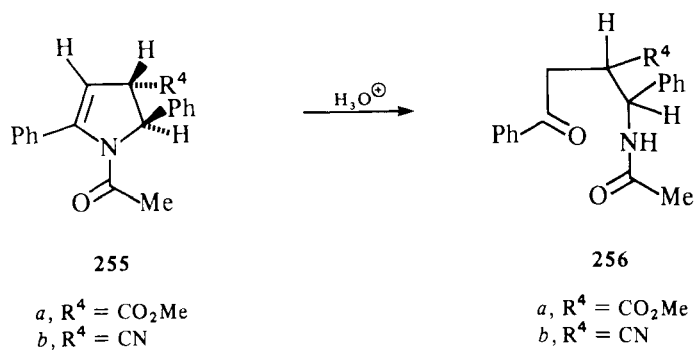


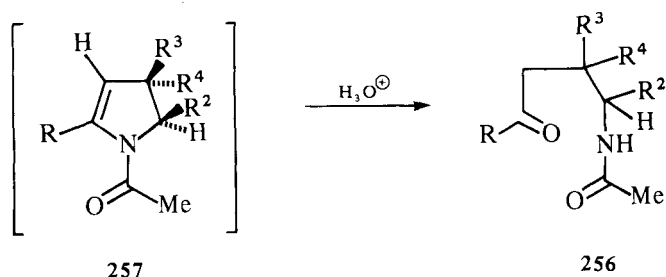
Method of Azlactone Preparation ^a	R	R ²	R ³	R ⁴	Product	Percent Yield	Reference
B	(Me) ^b	PhCH ₂	H	CO ₂ Me	254	53	111
B	(Me) ^b	PhCH ₂	H	CO ₂ Et	254 ^c	62	111
B	(Me) ^b	PhCH ₂	Me	CN	256	63	114
B	(Me) ^b	Ph	H	CN	256	42	114
B	(Me) ^b	Ph	H	CO ₂ Me	256	56	114
B	(Me) ^b	Ph	Me	CN	256	67	114
A	Ph	Ph	H	CN	255	52	112, 114
A	Ph	Ph	H	CO ₂ Me	255	65	112, 114
A	Ph	Ph	Me	CO ₂ Me	256	41	114

^aA, *In situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; B, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride.

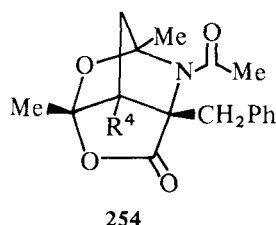
^bSubstituents in parentheses introduced by cyclodehydrating reagent.

^cStructure confirmed by X-ray crystallography.



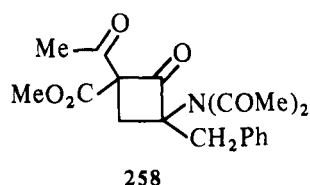


refluxing acetic anhydride has been attributed to the formation of the *N*-acetyl Δ^2 -pyrrolines **257**, which undergo hydrolysis presumably during the aqueous work-up.¹¹⁴



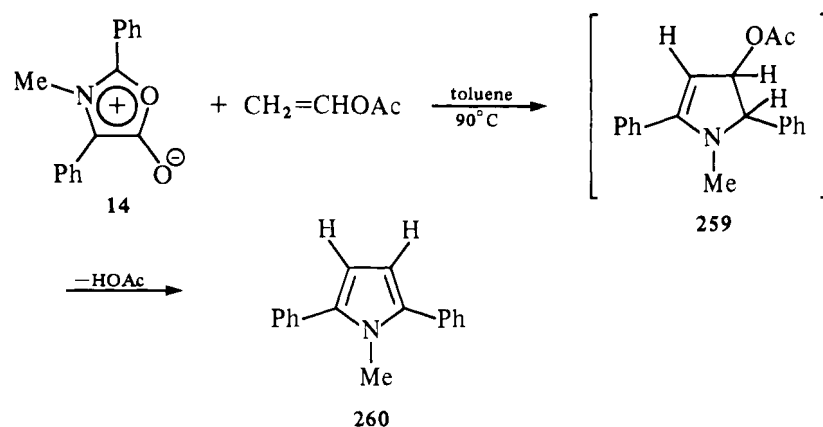
a, $R^4 = \text{CO}_2\text{Me}$
b, $R^4 = \text{CO}_2\text{Et}$

The structure of the *N*-acetyl tricyclic carbolactones **254** was determined largely by ^1H and ^{13}C NMR spectroscopy.^{111,112} The structure of **254b** was confirmed by X-ray crystallography.¹¹¹ It should be noted that the structure of **254a** was initially assigned as the cyclobutanone **258**.¹¹²

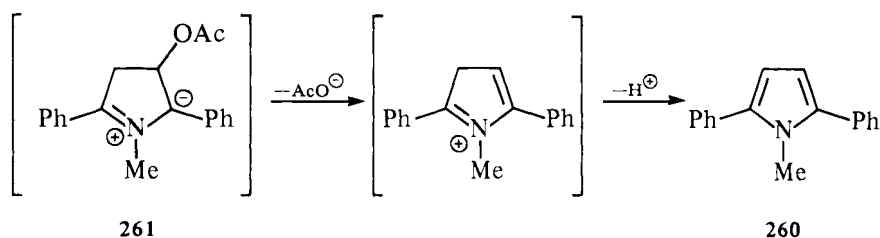


Texier and collaborators have not published a mechanism for the formation of the *N*-acetyl tricyclic carbolactones **254** at the time this review was written. However, the formation of **254** can be rationalized by employing the putative mechanism offered for the formation of the bicyclic carbolactones **252**. As indicated in Scheme 30, the intermediate **253** can afford either **252** or **254** depending on the nature of the R^3 substituent. When $R^3 = \text{CO}_2\text{Me}$ or CN , **253** should readily tautomerize to the Δ^2 -pyrroline, ultimately leading to **252**. On the other hand, when $R^3 = \text{H}$, tautomerization to the Δ^2 -pyrroline is slower and hydroxyl addition to the iminium group occurs intramolecularly to afford the tricyclic carbolactone **254** after *N*-acetylation. Although it is possible to rationalize

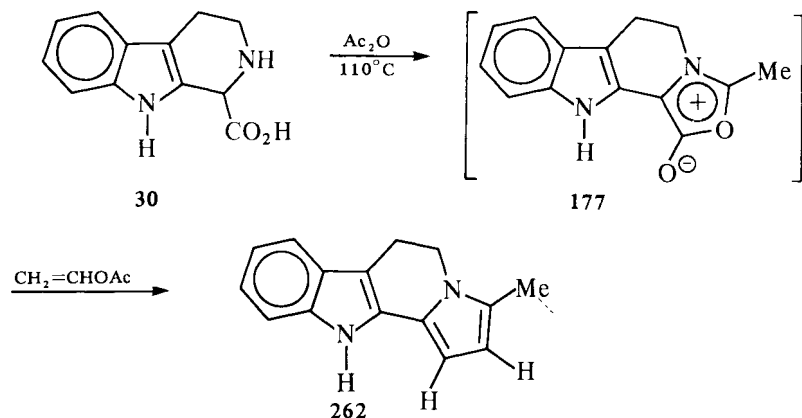
the formation of the *N*-acetyl Δ^2 -pyrrolines **251** and **255**, the carbolactones **252** and **254**, or the amide ketones **256**, it is not readily apparent which product will be obtained in a given reaction.



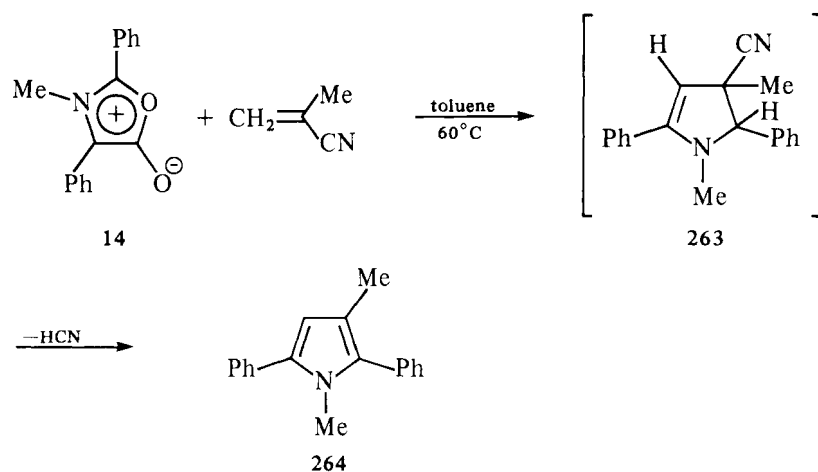
We have seen that *N*-substituted 1,3-oxazolium 5-oxides **4** react with olefins to afford Δ^2 -pyrrolines **206** (see Scheme 24).^{106,107} However, occasionally, a “spontaneous” dehydrogenation occurs under the reaction conditions, yielding pyrroles **209** as the minor or even sole products of the cycloaddition reaction. It is also possible to obtain pyrroles as the exclusive product of the cycloaddition reaction if the olefinic dipolarophile contains a substituent that can be readily eliminated under the reaction conditions. For example, Gotthardt and Huisgen have reported that the reaction of the isolable munchnone **14** with vinyl acetate gives pyrrole **260** in 50% yield.¹⁰⁶ In this reaction, the initially formed Δ^2 -pyrrolinium **259** presumably eliminates acetic acid to give the observed pyrrole **260**. However, the intermediate azomethine ylide **261** could also decompose to yield the observed product; that is,



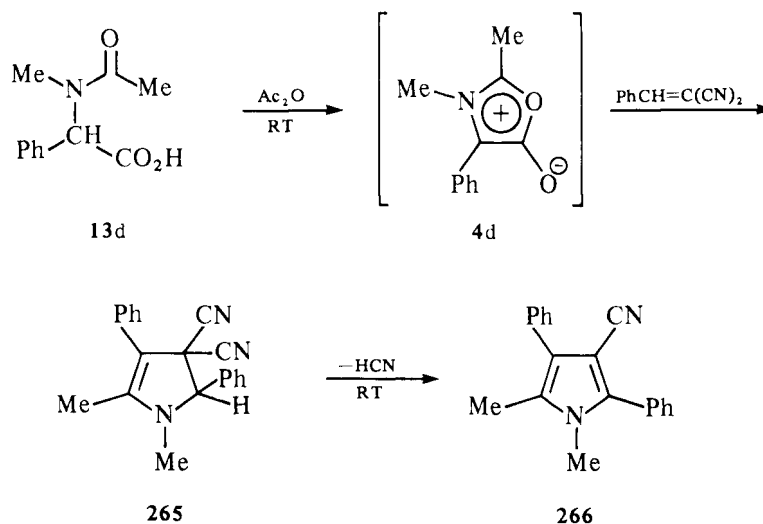
In either event, vinyl acetate behaves as an acetylene equivalent in this reaction. Similarly, Hershenson reported the reaction of 1,3-oxazolium 5-oxide **177**, generated *in situ* from 1,2,3,4-tetrahydro- β -carboline-1-carboxylic acid **30** with acetic anhydride, and vinyl acetate to afford the indolizino[8,7-*b*]indole **262** in 53% yield.²⁸



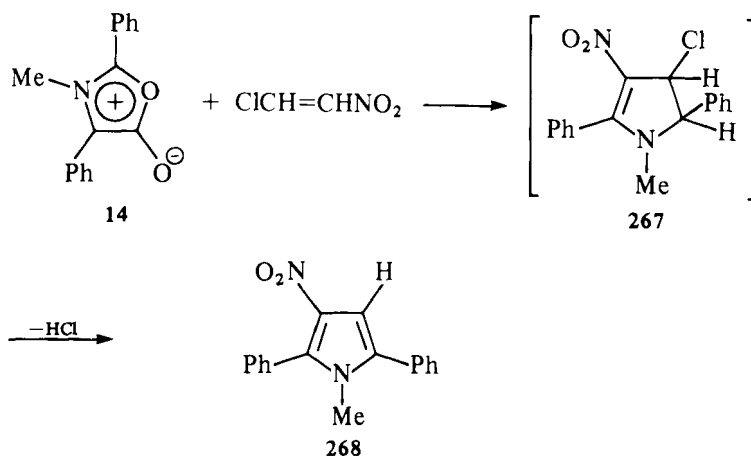
Gotthardt and Huisgen have also reported that methacrylonitrile behaves as a propyne equivalent in its reaction with **14** since the intermediate Δ^2 -pyrroline **263** eliminates hydrogen cyanide under the reaction conditions to yield pyrrole **264** in 65% yield.¹⁰⁶ Texier and co-workers have reported similar results from the reaction of munchnone **4d**, generated *in situ* from the *N*-acetylamino acid **13d** with acetic anhydride, and α -cyanocinnamonnitrile.¹¹⁰ However, in this case, the Δ^2 -pyrroline **265** was isolated in 62% yield. The slow elimination of hydrogen cyanide from **265** was observed at ambient temperature to afford cyanopyrrole **266**.



Verbruggen and Viehe¹¹⁵ have reported that 2-chloro-1-nitroethylene behaves as a nitroacetylene equivalent in its reaction with **14**. In this case, the intermediate Δ^2 -pyrroline **267** eliminates hydrochloric acid under the reaction conditions to yield the nitropyrrole **268** in 76% yield. Interestingly, Benages and Albonico have reported the 1,3-dipolar cycloaddition reactions of the bicyclic 1,3-oxazolium 5-oxides **180**, generated *in situ* from *N*-formyl-L-proline **179a**, L-proline **269**, *N*-

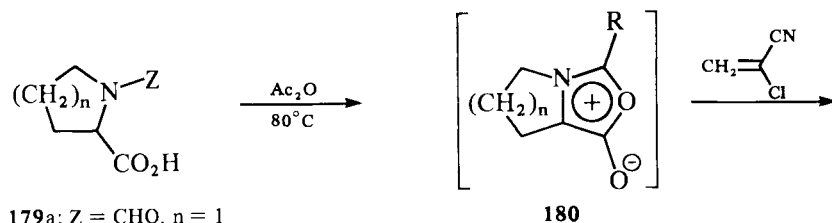


formylpipercolinic acid **179c**, or pipercolinic acid **162** with acetic anhydride, and 2-chloroacrylonitrile to give regiospecifically the cyanotetrahydropyrrolizines **271a** and **271b** and the cyanotetrahydroindolizines **271c** and **271d** in 65–77% yields.⁸⁹

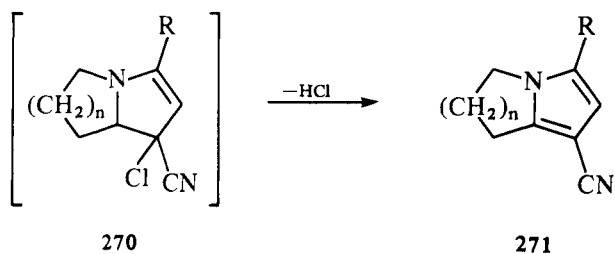


In this case, the intermediate Δ^2 -pyrroline **270** could lose hydrochloric acid to give the observed products **271** or hydrogen cyanide to give the chlorotetrahydropyrrolizines and chlorotetrahydroindolizines **272**, which were not detected. (The chlorotetrahydropyrrolizines and chlorotetrahydroindolizines **272**, if formed, may not have been stable to the reaction conditions.)

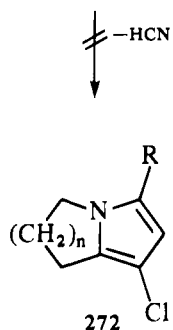
It is worth noting that the preparation of **271c** and **271d** was accompanied by the formation of smaller amounts of the 2-acetyl derivatives **273c** (14%) and **273d** (5%), respectively.⁸⁹ The yield of the 2-acetyl derivatives **273** is related to the



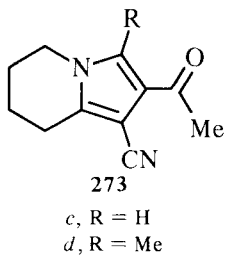
179a; Z = CHO, n = 1
 269; Z = H, n = 1
 179c; Z = CHO, n = 2
 162; Z = H, n = 2



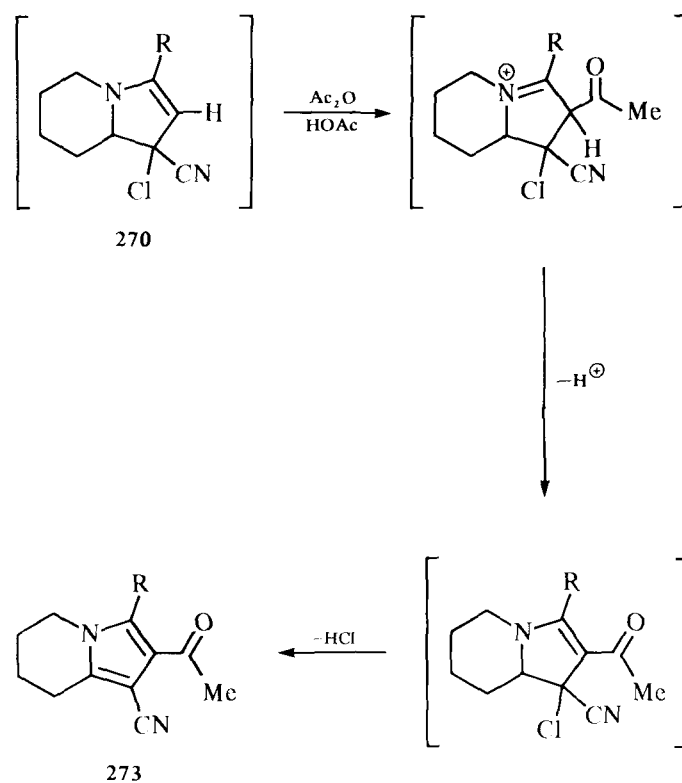
a; R = H, n = 1
 b; R = Me, n = 1
 c; R = H, n = 2
 d; R = Me, n = 2



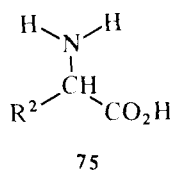
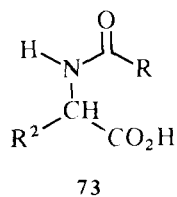
concentration of acetic acid in the reaction media since when acetic acid is added to the initial reaction mixtures, **273c** and **273d** become the major products of the reactions. Benages and Albonico also demonstrated that **273c** and **273d** are not formed from **271c** and **271d**, respectively, upon heating with acetic anhydride or

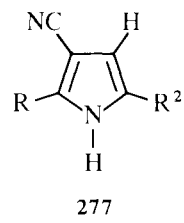
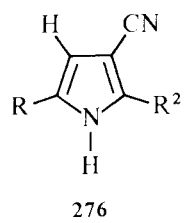
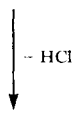
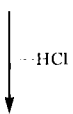
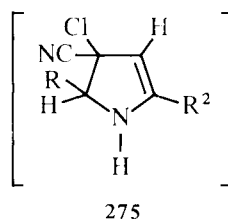
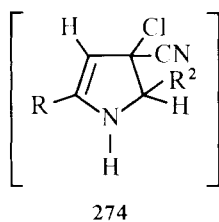
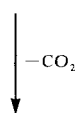
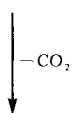
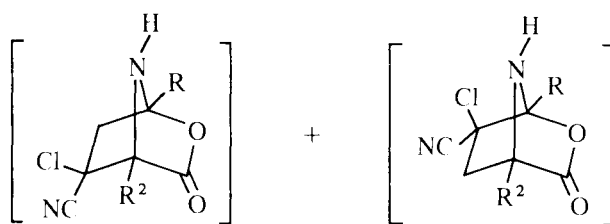
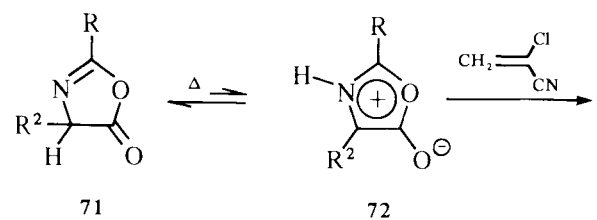


with acetic anhydride and acetic acid.⁸⁹ It appears plausible that the 2-acetyl derivatives **273** may result from acetylation of the intermediates **270**, which are essentially enamines, as indicated below.

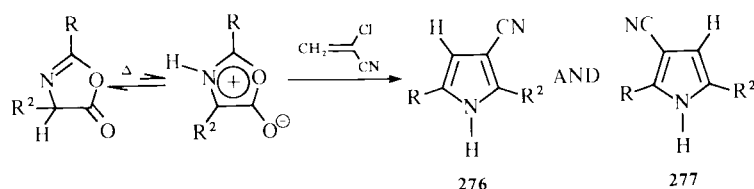


Benages and Albonico⁸⁹ have also demonstrated that 2-oxazolin-5-ones (azlactones) **71** react with 2-chloroacrylonitrile via their *N*-unsubstituted munchnone tautomers **72** to afford *N*-unsubstituted cyanopyrroles **276** and **277**, as depicted in Scheme 31. In most cases, the azlactones **71** were generated *in situ* from their *N*-acrylamino acid **73** or amino acid precursors **75** using acetic anhydride as the cyclodehydrating reagent. When $R \neq R^2$, it is possible to obtain both **276** and **277**, which occurs in several cases, as summarized in Table 4.22.





Scheme 31

TABLE 4.22. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 2-OXAZOLIN-5-ONES AND 2-CHLOROACRYLONITRILE⁸⁹

Method of Azlactone Preparation ^a	R	R ²	Product	Isomer Ratio	Percent Yield
B	H	Ph	276	—	64
C	(Me) ^b	Me	276 $\equiv$ 277	—	70
C	(Me) ^b	<i>i</i> -Bu	276	$\left. \begin{smallmatrix} c \\ c \end{smallmatrix} \right\}$	<i>d</i>
C	(Me) ^b	<i>i</i> -Bu	277		
C	(Me) ^b	Ph	276	$\left. \begin{smallmatrix} 2 \\ 1 \end{smallmatrix} \right\}$	80
C	(Me) ^b	Ph	277		
B	Ph	Me	276	$\left. \begin{smallmatrix} c \\ c \end{smallmatrix} \right\}$	70
B	Ph	Me	277		
A	Ph	Ph	276 $\equiv$ 277	—	70
B	Ph	Ph	276 $\equiv$ 277	—	78

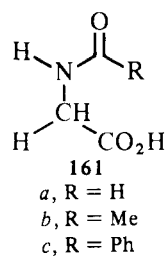
^aA, Preformed azlactone; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride.

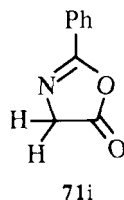
^bSubstituents in parentheses introduced by cyclodehydrating reagent.

^cUnspecified isomer mixture.

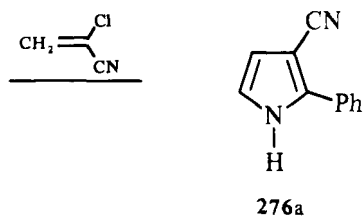
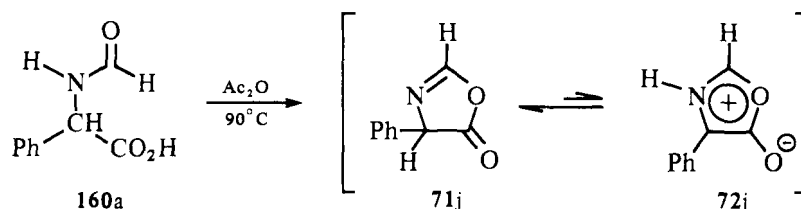
^dYield not reported.

A limitation of this reaction is that 4-unsubstituted azlactones **71** (R² = H) fail to react with 2-chloroacrylonitrile.⁸⁹ For example, *N*-formylglycine **161a**, *N*-acetylglycine **161b**, and hippuric acid **161c** all fail to react with 2-chloroacrylonitrile in acetic anhydride at 90°C. Even the isolated azlactone **71i** derived from hippuric acid **161c**, fails to react with 2-chloroacrylonitrile under these reaction

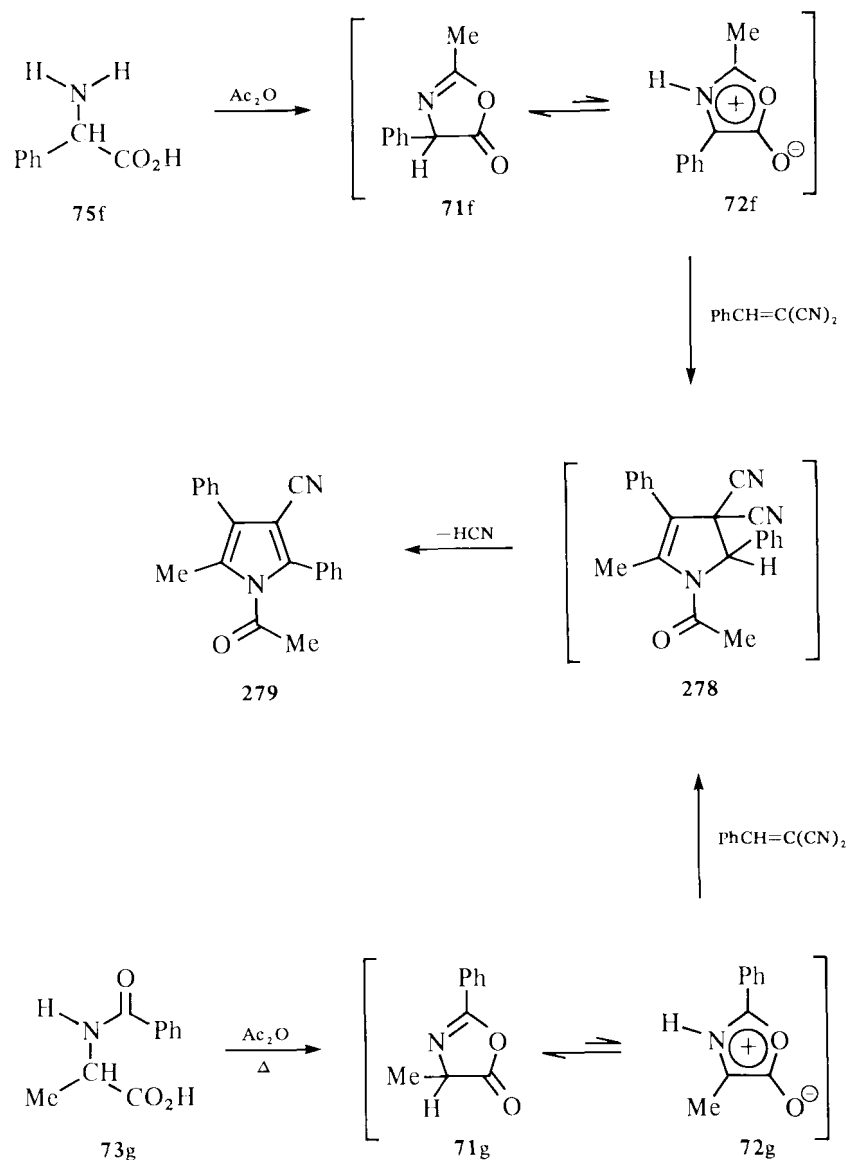




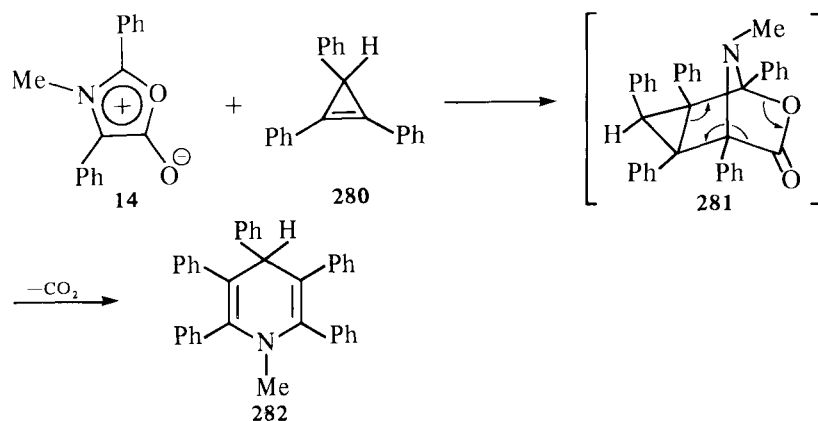
conditions. This problem was avoided, at least in the case of hippuric acid **161c**, by employing *N*-formyl-*C*-phenyl glycine **160a** as the starting material. In this way, the isomeric azlactone **71j** affords regiospecifically the *N*-unsubstituted cyanopyrrole **276a** in 64% yield.⁸⁹



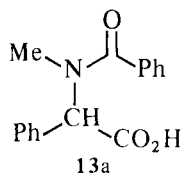
It is interesting to compare these results with the more recent results of Texier and collaborators.^{110,114} These researchers found that the reaction of azlactone **71f**, generated *in situ* from *C*-phenylglycine **75f**, or the isomeric azlactone **71g**, generated *in situ* from *N*-benzoylalanine **73g**, with α -cyanocinnamionitrile in refluxing acetic anhydride affords regiospecifically the same *N*-acetylcyanopyrrole **279**. Presumably, the isomeric *N*-unsubstituted 1,3-oxazolium 5-oxides **72f** and **72g** (or their corresponding *N*-acetyl-1,3-oxazolium 5-oxides **246**, as favored by Texier and co-workers) react with α -cyanocinnamionitrile to give the same *N*-acetyl Δ^2 -pyrroline **278**, which loses hydrogen cyanide under the reaction conditions to yield the observed pyrrole **279**. It is not apparent why **279** is *N*-acetylated, while Benages and Albonico's⁸⁹ pyrrole products are not. Possibly, the higher reaction temperature (140°C) employed by Texier and collaborators relative to the reaction temperatures (80–100°C) utilized by Benages and Albonico are responsible for this product discrepancy. Alternatively, perhaps, the acetic anhydride used by Texier and co-workers had a higher acetic acid concentration.



The 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxides **4** with strained cyclic olefinic dipolarophiles provides an interesting array of cycloaddition chemistry. Martin and Hekman¹¹⁶ reported the reaction of the isolable munchnone **14** with triphenylcyclopropene **280** to afford a 63% yield of the 1,4-dihydropyridine **282**. This reaction presumably involves a 1,3-dipolar cycloaddition reaction of **14** to the carbon–carbon double bond of **280** to yield the primary cycloadduct **281**. Cycloreversion of carbon dioxide from **281** and concomitant



(or subsequent) cleavage of the cyclopropane ring gives the observed **282**. This reaction was independently confirmed by Potts and co-workers employing an *in situ* preparation of **14** from its *N*-aroylamino acid precursor **13a** and acetic anhydride.^{117,118}



Three laboratories have independently investigated the 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxides **4** with cyclopropenone derivatives to afford 4-pyridones **284**,¹¹⁷⁻¹²¹ 4-pyridinethiones **285**,¹¹⁷⁻¹²¹ and 4-pyridineimines **286**.^{120,121} These results are summarized in Table 4.23. In all cases, the munch-nones **4** were generated *in situ* from their *N*-acylamino acid precursors **13** using acetic anhydride as the cyclodehydrating reagent. In only one case was the re-

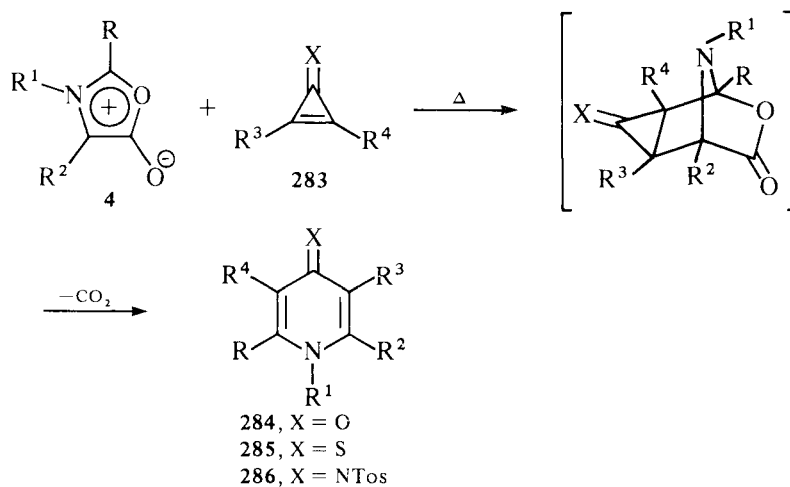
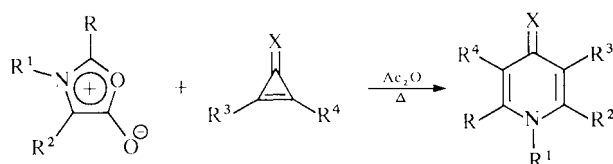
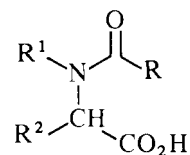


TABLE 4.23. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF *IN-SITU*-GENERATED 1,3-OXAZOLIUM 5-OXIDES^a AND CYCLOPROPENONE DERIVATIVES

R	R ¹	R ²	R ³	R ⁴	X	Percent Yield	Reference
Me	Me	Me	Ph	Ph	O	17	119
Me	Me	Ph	Ph	Me	O	59	119
Me	Me	Ph	Ph	Ph	O	51	119
Ph	Me	Ph	Me	Me	O	35	119
Ph	Me	Ph	Ph	Me	O	61	119
Ph	Me	Ph	Ph	Ph	O	29	117, 118
						63	119
						61	120, 121
4-NO ₂ Ph	Me	Ph	Ph	Ph	O	53	121
Ph	Me	Ph	Ph	Ph	S	68	117, 118
						58	119
						61	120, 121
4-NO ₂ Ph	Me	Ph	Ph	Ph	S	52	121
Ph	Me	Ph	Ph	Ph	NTos ^b	64	120, 121

^aThe 1,3-oxazolium 5-oxides were generated *in situ* by the cyclodehydration of their *N*-acylamino acid precursors with acetic anhydride.

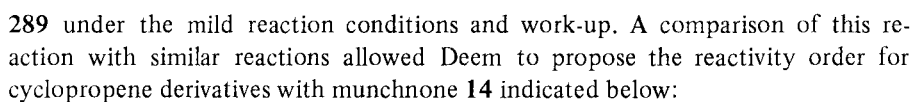
^bTos = *p*-toluenesulfonyl.



13

action of an unsymmetrical 1,3-oxazolium 5-oxide **4** ($R \neq R^2$) with an unsymmetrical cyclopropenone investigated. Eicher and Schäfer¹¹⁹ reported that the reaction of munchnone **4d**, generated *in situ* from its *N*-acylamino acid precursor **13d** with acetic anhydride, and 1-phenyl-2-methylcyclopropenone affords a single 4-pyridone in 59% yield. The ¹H NMR spectral data is consistent for both **284a** and **287**; however, structure **284a** is favored based on the observation of a mass spectral fragment at $m/e = 178$ for diphenylacetylene.

Deem¹²² has reported the reaction of **14** and tetrachlorocyclopropene at room temperature to afford the 4-pyridone **289**. Apparently, the intermediate 3,4,5-trichloropyridinium salt **288** undergoes hydrolysis to the observed 4-pyridone



In a similar fashion, two laboratories^{119–121} have independently reported the 1,3-dipolar cycloaddition reactions of *in-situ*-generated 1,3-oxazolium 5-oxides **4** with the endocyclic carbon–carbon double bond of 3-methylenecyclopropenes to yield 1,4-dihydro-4-methylenepyridines **290**. These results are summarized in

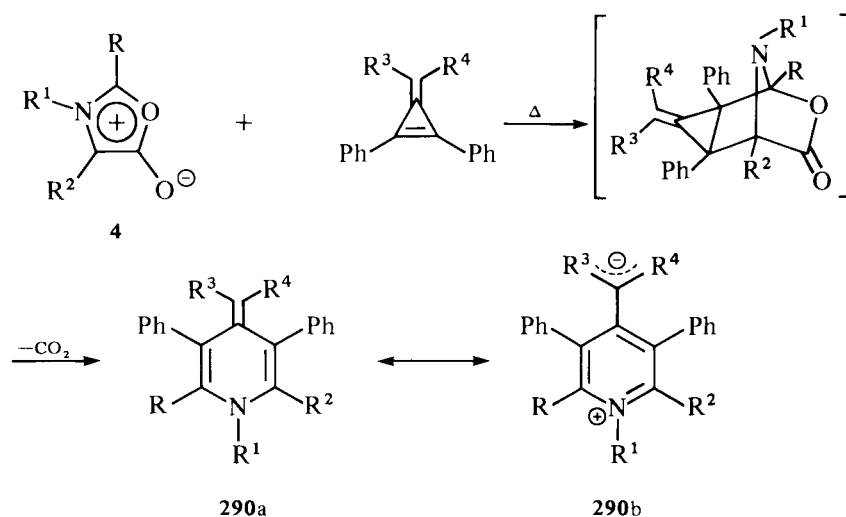
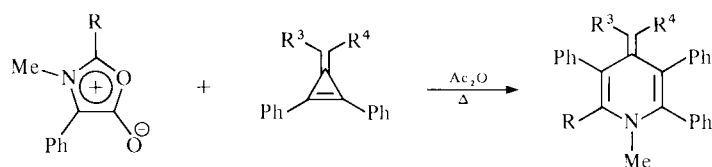


Table 4.24. The intense yellow- to red-colored merocyanine systems **290** exhibit marked solvatochromic and thermochromic properties.¹¹⁹

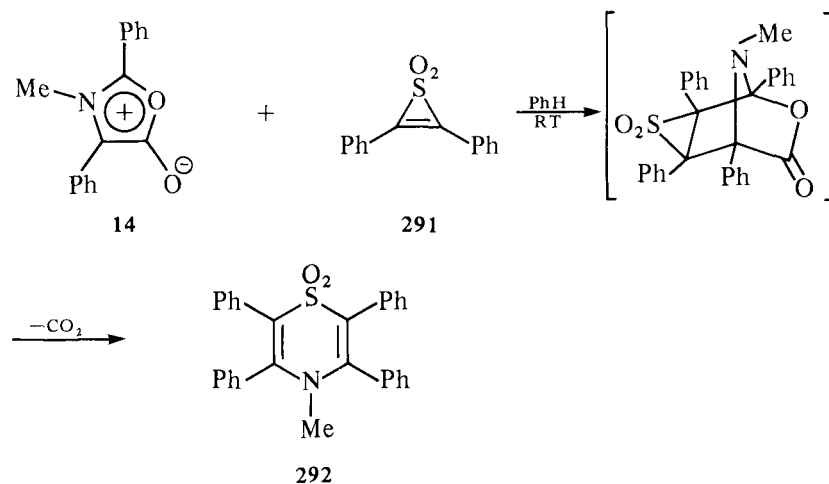
Similarly, Kato and co-workers¹²³ have reported the reaction of the isolable munchnone **14** and 2,3-diphenylthiirene dioxide **291** at room temperature to produce an 83% yield of the 1,4-thiazine 1,1-dioxide **292**. Heterocycle **292** was also formed in 63% yield upon reacting **291** with **14**, generated *in situ* from its

TABLE 4.24. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF *IN-SITU*-GENERATED 1,3-OXAZOLIUM 5-OXIDES^a AND METHYLENOCYCLOPROPENES

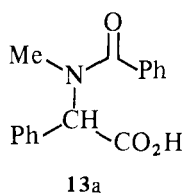


R	R ³	R ⁴	Percent Yield	Reference
Ph	CN	CN	31	119
			41	120, 121
Ph	CN	COPh	56	119
Ph	CN	CO ₂ Me	60	119
Ph	CN	CO ₂ Et	65	121
Ph	COMe	COMe	37	119
Ph	COPh	COPh	53	119
4-NO ₂ Ph	CN	CN	62	121

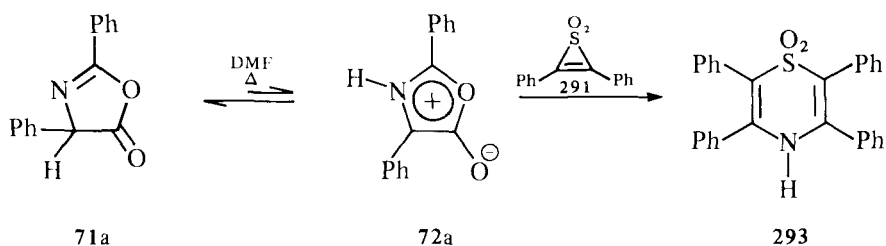
^aThe 1,3-oxazolium 5-oxides were generated *in situ* by the cyclodehydration of their *N*-acylamino acid precursors with acetic anhydride.



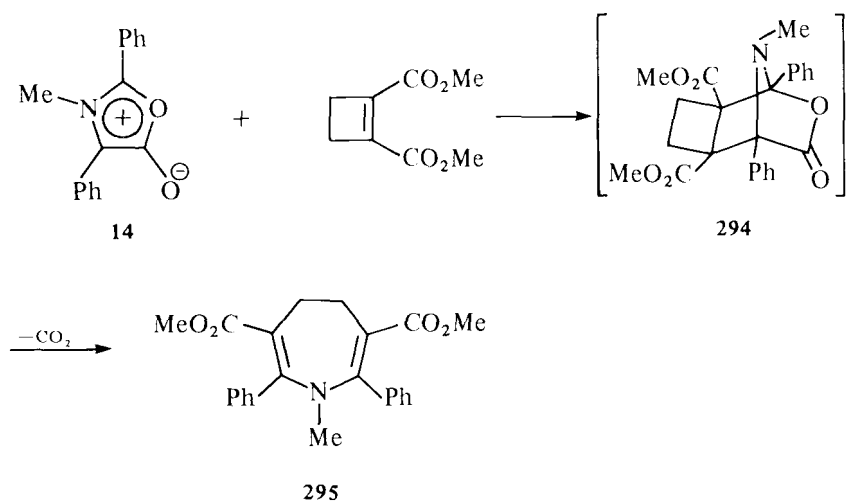
N-aroylamino acid precursor **13a** in acetic anhydride at 60°C. These researchers also investigated the reaction of **291** and 2,4-diphenyl-2-oxazolin-5-one **71a**. Attempted reaction of **71a** and **291** in benzene results only in decomposition of **291** to diphenylacetylene. However, in warm *N,N*-dimethylformamide (DMF),



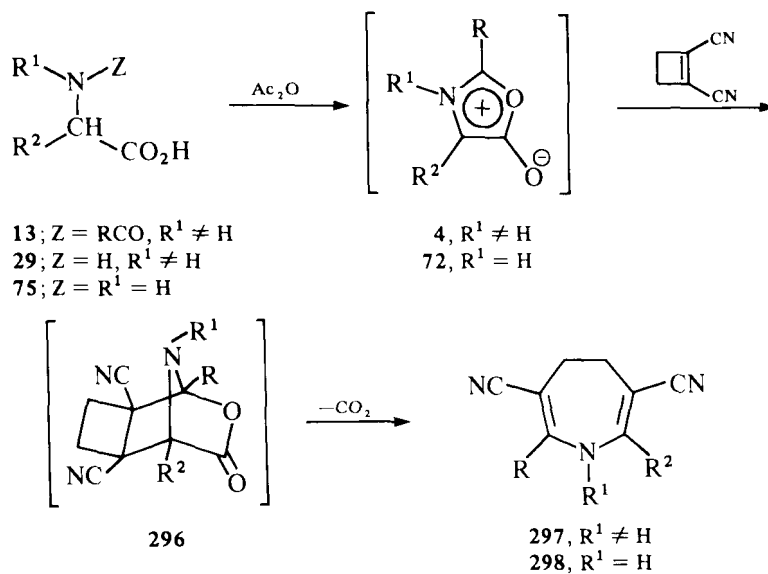
a 58% yield of the *N*-unsubstituted 1,4-thiazine 1,1-dioxide **293** is obtained. The more polar DMF shifts the **71/72** equilibrium toward the mesoionic oxazole **72a**, which is the reactive tautomer in this cycloaddition reaction.¹²³



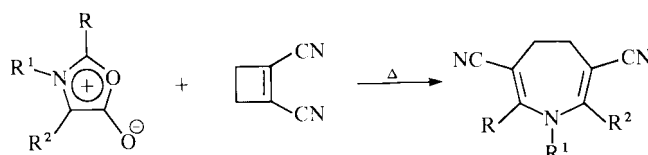
Cyclobutene derivatives also undergo 1,3-dipolar cycloaddition–extrusion ring expansion reactions with 1,3-oxazolium 5-oxides **4**. Martin and Hekman¹¹⁶ have reported the reaction of **14** with dimethyl 1,2-cyclobutenedicarboxylate to afford the 4,5-dihydroazepine **295**. This reaction involves the 1,3-dipolar cycloaddition reaction of **14** to the carbon–carbon double bond of the cyclobutene to



yield the primary cycloadduct **294**. Extrusion of carbon dioxide from **294** and concomitant (or subsequent) cleavage of the cyclobutane ring affords the observed dihydroazepine **295**.



Turchi and co-workers have exploited this approach to prepare a variety of 4,5-dihydroazepines **297** and **298** from the reaction of *N*-substituted 1,3-oxazolium 5-oxides **4** or 2-oxazolin-5-ones (azlactones) **71** (via their *N*-unsubstituted munchnone tautomers **72**) and 1,2-dicyanocyclobutene.¹²⁴ The 1,3-oxazolium 5-oxides **4** or azlactones **71** were generated *in situ* from the corresponding *N*-acylamino acid **13** or amino acid precursors **29** or **75** in acetic anhydride. These reactions are summarized in Table 4.25.

TABLE 4.25. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 1,3-OXAZOLIUM 5-OXIDES AND 2-OXAZOLIN-5-ONES WITH 1,2-DICYANOCYCLOBUTENE¹²⁴

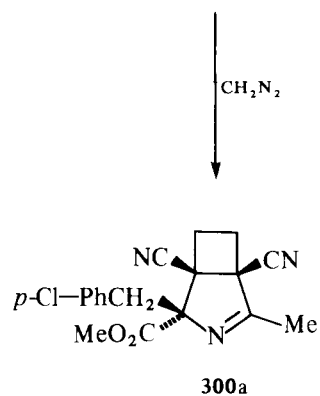
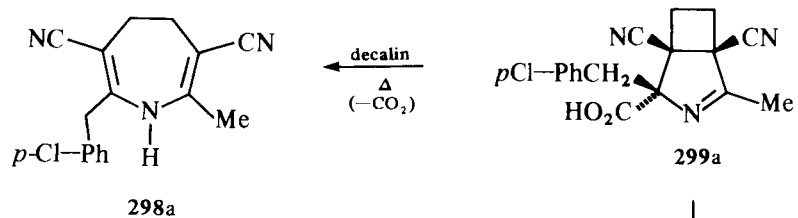
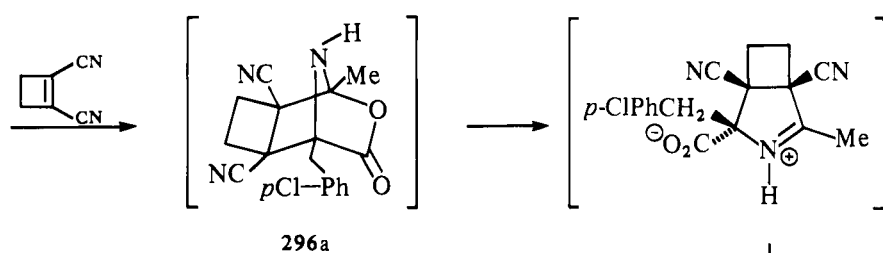
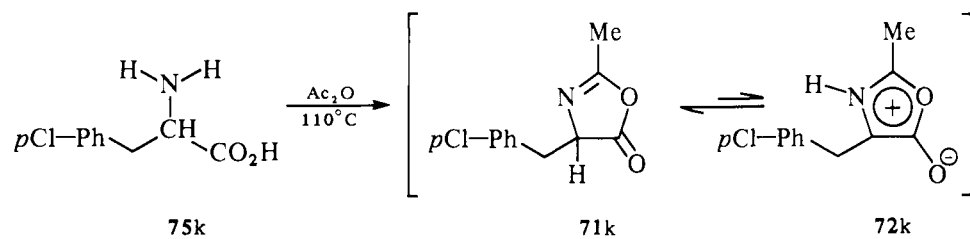
Method of Munchnone or Azlactone Preparation ^a	R	R ¹	R ²	Percent Yield
C	(Me) ^b	H	Me	76
C	(Me) ^b	H	PhCH ₂	84
C	(Me) ^b	Me	Me	93
A	Ph	Me	Ph	85
B				78
B	H	—(CH ₂) ₃ —		52
B	H	—(CH ₂) ₄ —		50
C	(Me) ^b	—(CH ₂) ₃ —		85
C	(Me) ^b	—(CH ₂) ₄ —		85
C	(Me) ^b	—(CH ₂) ₅ —		73
B	Ph	—(CH ₂) ₃ —		65

^aA, Preformed Munchnone; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride.

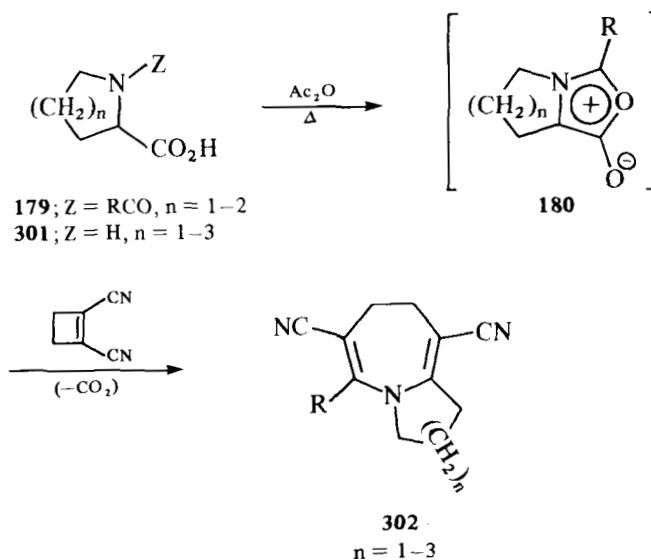
^bSubstituents in parentheses introduced by cyclodehydrating reagent.

Upon heating a mixture of *p*-chlorophenylalanine **75k** and 1,2-dicyanocyclobutene in acetic anhydride at 110°C for 5 h, these researchers¹⁰⁹ obtained a 70% yield of the bicyclic Δ^1 -pyrroline carboxylic acid **299a**, which precipitated from the reaction mixture as indicated in Scheme 32. Additionally, work-up of the filtrate affords the 4,5-dihydroazepine **298a** in 18% yield. Thermolysis of **299a** in decalin for 30 min affords **298a** in 79% yield. Carboxylic acid **299a** was converted to methyl ester **300a** with diazomethane. The structure and stereochemistry of **300a** was confirmed by X-ray crystallography. The formation of carboxylic acid **299a** can be rationalized by rearrangement of the primary cycloadduct **296a** without loss of carbon dioxide or cleavage of the cyclobutane ring as illustrated in Scheme 32. The isolation of carboxylic acid **299a** is significant since it indicates that loss of carbon dioxide (and ring expansion) from primary cycloadducts such as **296** need not be a concerted process.

Turchi and co-workers have also prepared bicyclic dihydroazepines **302** in good yields upon heating cyclic α -amino acids **301** or cyclic *N*-acyl- α -amino acids **179** in acetic anhydride in the presence of 1,2-dicyanocyclobutene.¹²⁴ These reactions,

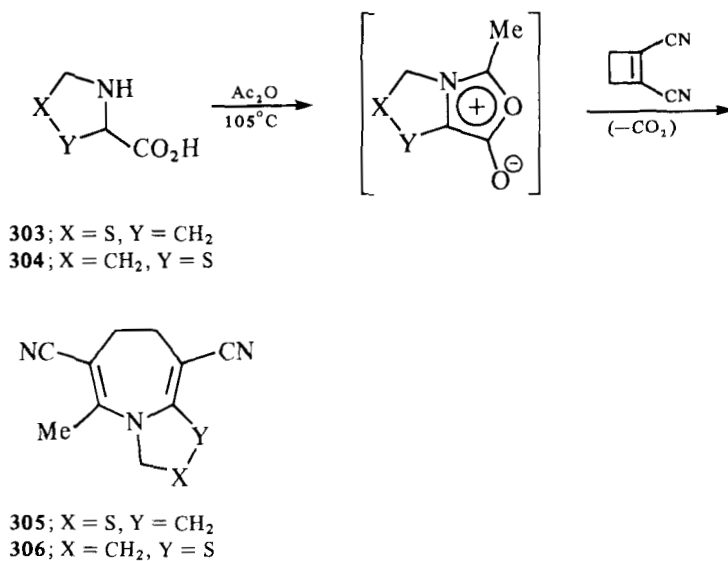


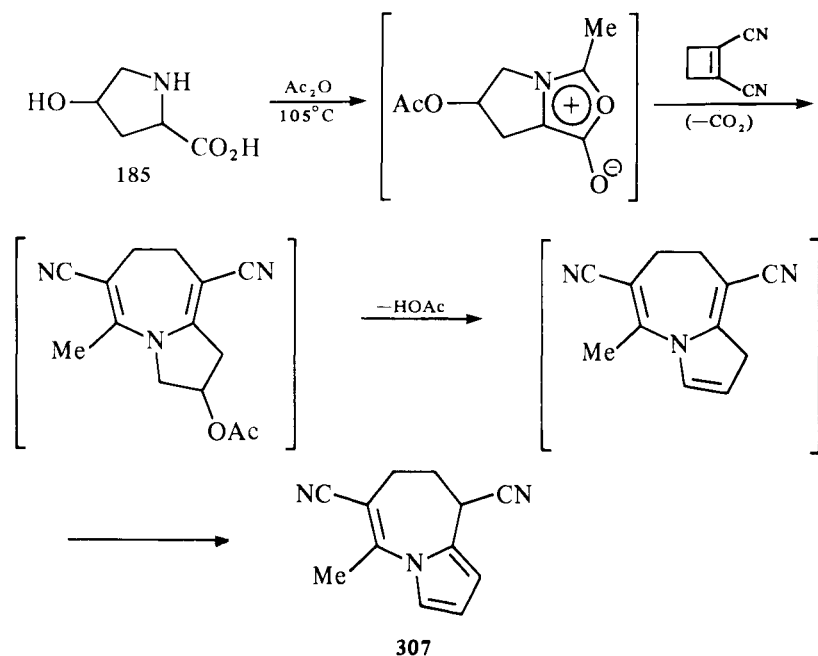
Scheme 32



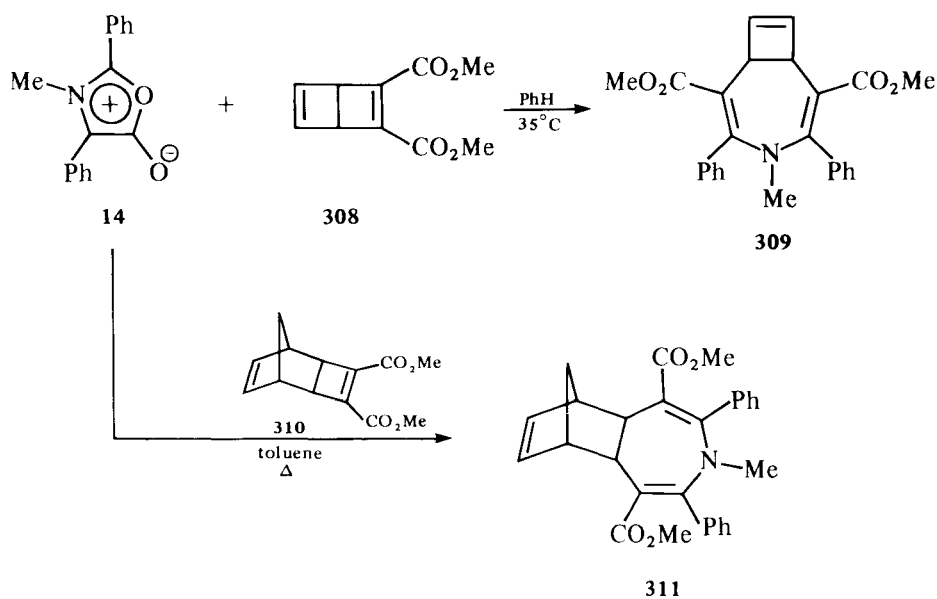
which involve the intermediacy of the bicyclic munchnones **180**, are also summarized in Table 4.25.

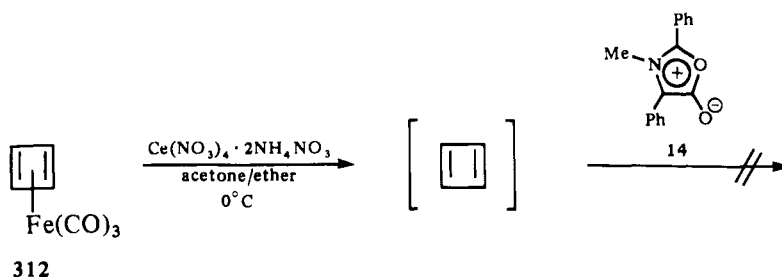
In a similar fashion, the thioproline **303** and **304** afford the bicyclic sulfur-containing dihydroazepines **305** and **306** in 79 and 77% yields, respectively, upon heating in acetic anhydride in the presence of 1,2-dicyanocyclobutene.¹⁰⁹ However, heating 4-hydroxyproline **185** in acetic anhydride in the presence of 1,2-dicyanocyclobutene gives the pyrrolotetrahydroazepine **307** in 46% yield as rationalized below.¹⁰⁹





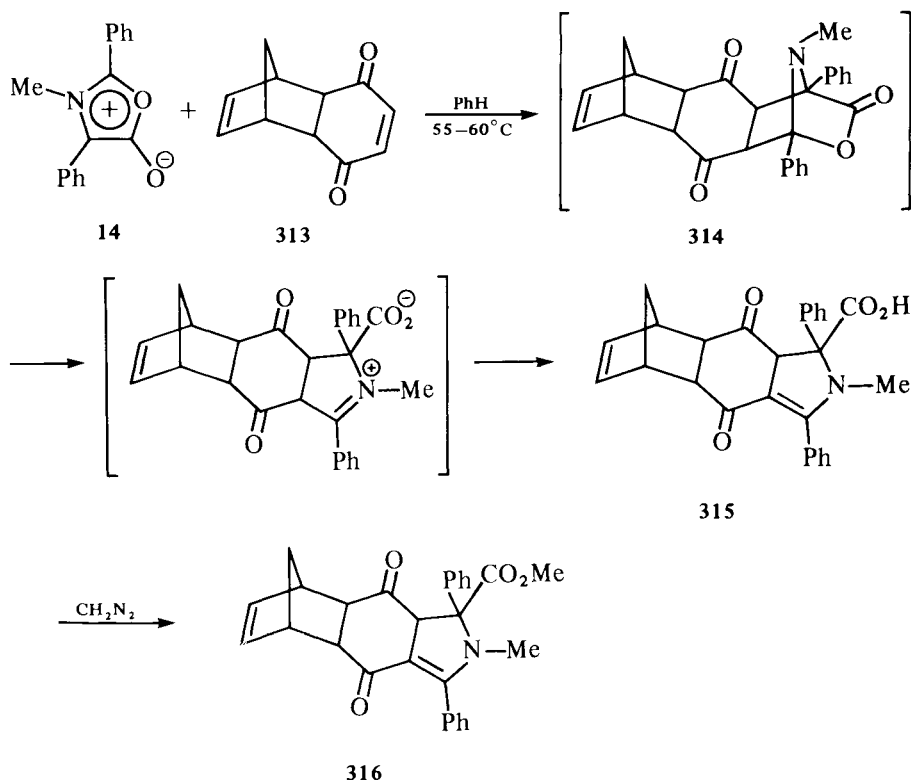
The reaction of more complex cyclobutenes with the isolable 1,3-oxazolium 5-oxide **14** has also been investigated. Martin and Hekman¹¹⁶ have reported the reaction of **14** and the Dewar benzene derivative **308** to yield the thermally labile 4-azabicyclo[5.2.0]nonatriene **309** in 20% yield, while Turchi and collaborators¹⁰⁹ prepared the dihydroazepine **311** in 38% yield from **14** and cyclobutene **310**.





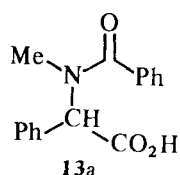
Finally, Rees and co-workers¹²⁵ attempted unsuccessfully to trap cyclobutadiene, generated from its iron tricarbonyl complex **312** by oxidation with cerium (IV) ammonium nitrate, with **14**. Presumably, **14** is too unreactive to compete effectively with the dimerization of cyclobutadiene.

Several laboratories have examined the 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxides **4** with 1,4-quinones. Myers and co-workers¹²⁶ have reported that the reaction of the isolable munchnone **14** with cyclopentadiene-quinone **313** in benzene at 55–60°C affords an 88% yield of a stable 1:1 adduct in which the elements of carbon dioxide have been retained, as shown in Scheme 33. The structure of this 1:1 adduct was initially assigned as the primary cyclo-

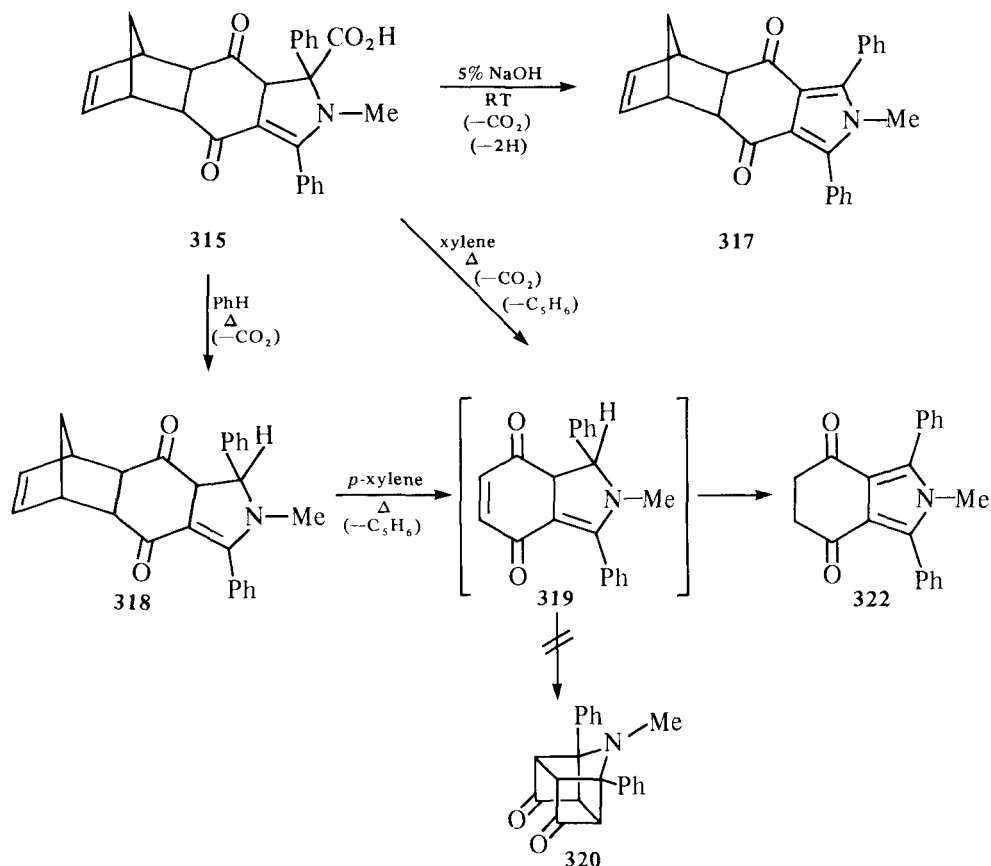


Scheme 33

adduct **314**. However, Friedrichsen and Schröer¹⁰⁸ subsequently demonstrated that the structure of this 1:1 adduct was actually the Δ^2 -pyrrolinecarboxylic acid **315**, which was presumably formed upon ring opening of the primary cycloadduct **314**, as depicted in Scheme 33. The Δ^2 -pyrrolinecarboxylic acid **315** gave ester **316** upon treatment with diazomethane. Matsukubo and Kato¹²⁷ have also reported the preparation of acid **315** in 92% yield upon reacting **313** and **14**, which was generated *in situ* from its *N*-aroylamino acid precursor **13a** in acetic anhydride at 55–60°C.

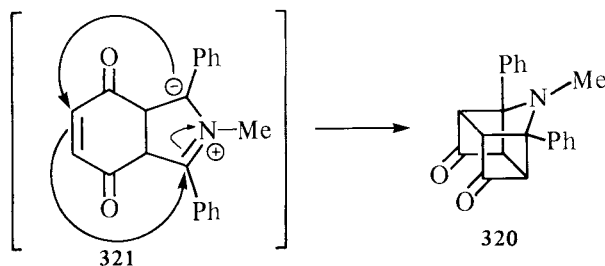


Myers and co-workers¹²⁶ studied the decomposition of the 1:1 adduct **315** as illustrated in Scheme 34. Treatment of **315** with 5% aqueous sodium hydroxide



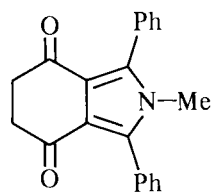
Scheme 34

gives a 54% yield of the pyrrole **317**, while thermal decomposition of **315** in refluxing benzene yields the Δ^2 -pyrroline **318** in 86% yield. Thermolysis of **315** in refluxing xylene affords a dark red, crystalline compound, which had lost cyclopentadiene along with carbon dioxide, in a 76% yield. This material is also produced in a 21% yield, along with pyrrole **317** (35%), upon thermal decomposition of Δ^2 -pyrroline **318** in refluxing xylene. The simple ^1H NMR spectrum of this thermolysis product, which consists of three singlets, is not consistent for the Δ^2 -pyrroline **319**, the product anticipated upon loss of cyclopentadiene from **318** via a retro Diels–Alder reaction or loss of both cyclopentadiene and carbon dioxide from **315**. Thus, Myers and co-workers¹²⁶ assigned the structure of this thermolysis product as the novel tetracyclic diketone **320**, the product of an intramolecular 1,3-dipolar cycloaddition reaction of the azomethine ylide **321**.

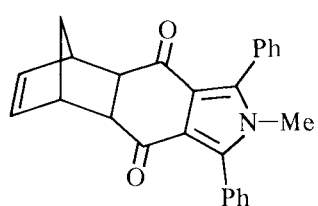
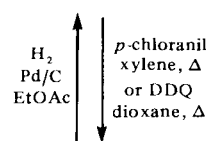


The IR and UV spectral data¹²⁶ reported for this thermolysis product do not appear to be consistent with the proposed structure **320**. For example, the carbonyl band at 1665 cm^{-1} is too low for a strained cyclobutanone, while the UV absorption maximum at 308 nm suggests a conjugated chromophore. These observations led at least three laboratories^{108,127,128} to independently reexamine the structure of this thermolysis product. All three laboratories reassigned the structure of this thermolysis product as the dihydroisindoleione **322**, which is presumably formed upon isomerization of the expected thermolysis product **319**, as indicated in Scheme 34. The structure of **322** was confirmed upon dehydrogenation to the isindoleione **323** with *p*-chloranil¹²⁷ or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).¹²⁸ Isoindoleione **323** was prepared independently by the 1,3-dipolar reaction of the munchnone **14** and *p*-benzoquinone,^{108,127} by thermolysis of pyrrole **317** in refluxing xylene,¹²⁷ or by *N*-methylation¹²⁸ of the *N*-unsubstituted isindoleione **324**, as summarized in Scheme 35. Alternately, dihydroisindoleione **322** was prepared from isindoleione **323** upon catalytic hydrogenation.¹⁰⁸

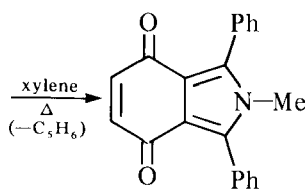
Myers and co-workers¹²⁶ have also reported the isolation of a 1:1 adduct in which the elements of carbon dioxide have been retained in an 89% yield upon reacting **14** and anthracenequinone **325** in benzene at $55\text{--}60^\circ\text{C}$, as indicated in Scheme 36. The structure of this 1:1 adduct was also assigned as the primary cycloadduct **326**. However, the absence of a carbonyl band above 1700 cm^{-1} in the reported IR spectrum of this adduct suggests that it should also be reassigned as the Δ^2 -pyrroline carboxylic acid **327**. The decomposition of **327** as investigated by Myers and co-workers¹²⁶ is also summarized in Scheme 36.



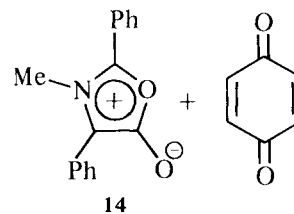
322



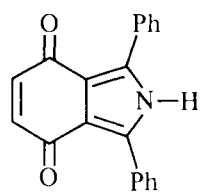
317



323

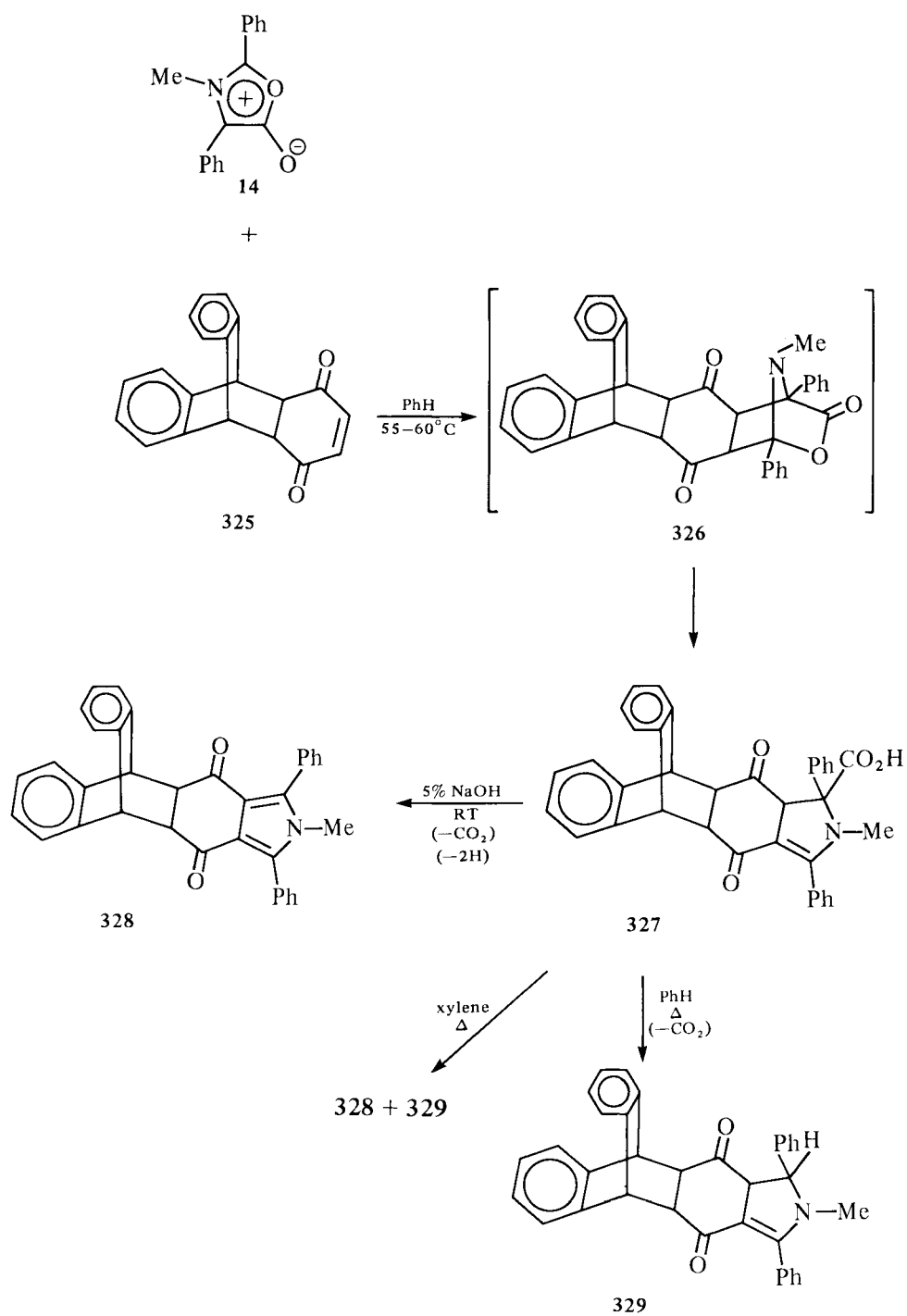


14



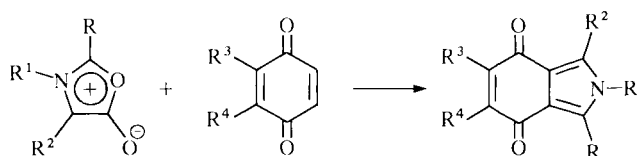
324

Scheme 35



Scheme 36

TABLE 4.26. 1,3-DIPOLAR CYCLOADDITION REACTIONS OF 1,3-OXAZOLIUM 5-OXIDES AND 1,4-QUINONES

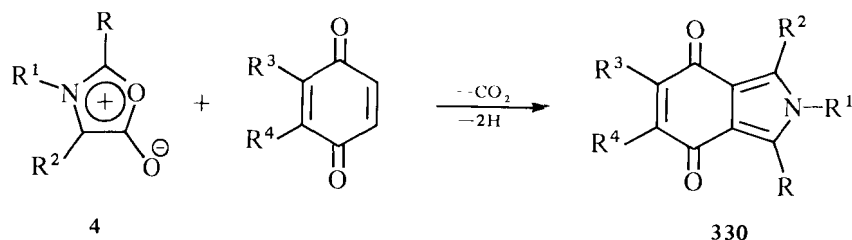


Method of Munchnone Preparation ^a	R	R ¹	R ²	R ³	R ⁴	Percent Yield	Reference
D	Me	Me	Ph	Me	H	33	129
	Me	Me	Ph	H	Me		
D	Me	Me	Ph	Me	MeO	41	129
	Me	Me	Ph	MeO	Me		
E	Me	Me	Ph	—CH=CHCH=CH—		10	129
A	Ph	Me	Ph	H	H	8	127
A						—	108
A	Ph	Me	Ph	Me	H	29	129
D						37	129
E						26	129
A	Ph	Me	Ph	Me	MeO	36	129
A	Ph	Me	Ph	—CH=CHCH=CH—		44	129
D						30	129
E						35	129
B	H	—(CH ₂) ₄ —	H		H	5	79
B	H	—(CH ₂) ₄ —	—CH=CHCH=CH—			34	79
C	(Me) ^b	—(CH ₂) ₄ —	H		H	19	79
C	(Me) ^b	—(CH ₂) ₄ —	—CH=CHCH=CH—			43	79
D	Ph	—(CH ₂) ₃ —	Me		H	28	129
	Ph	—(CH ₂) ₃ —	H		Me		
D	Ph	—(CH ₂) ₃ —	Me		MeO	39	129
	Ph	—(CH ₂) ₃ —	MeO		Me		
D	Ph	—(CH ₂) ₃ —	—CH=CHCH=CH—			40	129

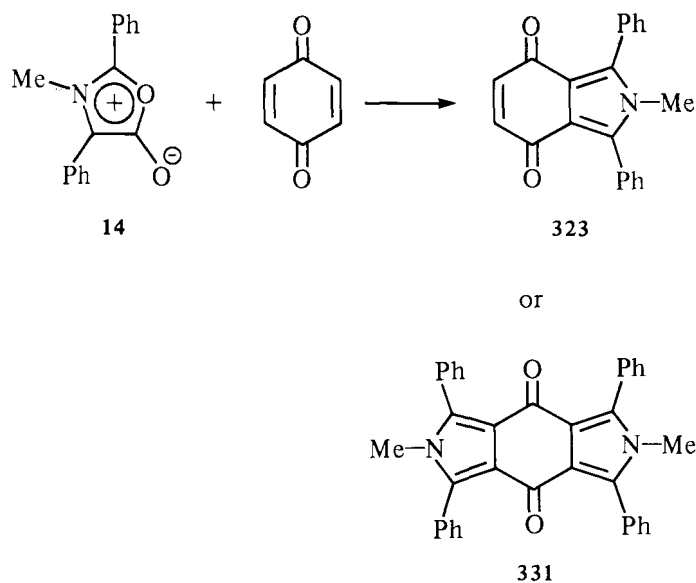
^aA, Preformed; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride; C, *in situ* *N*-acylation and cyclodehydration of amino acid precursor with acetic anhydride; D, *N*-Acylamino acid precursor heated at 55–60°C with equimolar amount of acetic anhydride in nonpolar solvent for 20–30 min. Sodium carbonate and sodium sulfate added, followed by the 1,4-quinone; E, equimolar amount of DCC added to suspension of *N*-acylamino acid precursor in methylene chloride. Mixture heated at reflux for 30–45 min. DCU removed by filtration and 1,4-quinone added to filtrate.

^bSubstituents in parentheses introduced by cyclodehydrating reagent.

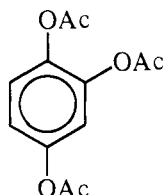
In general, in cases where 1:1 adducts are not isolated, the 1,3-dipolar cycloaddition reactions of 1,3-oxazolium 5-oxides **4** and 1,4-quinones provide a route to isoindolediones **330** in poor to fair yields. Reactions of this type are summarized in Table 4.26. As was noted previously (see Scheme 35), Matsukubo and Kato¹²⁷ reported that the reaction of the isolable munchnone **14** with an excess



of *p*-benzoquinone in benzene at 60°C affords the isoindoledione **323** in a yield of only 8%. This reaction was also reported by Friedrichsen and Schröer,¹⁰⁸ although no yield was given. However, upon reacting **14** with an equimolar amount of *p*-benzoquinone in tetrahydrofuran at room temperature, Myers and co-workers¹²⁹ obtained a 29% yield of the 2:1-adduct **331**. Friedrichsen and Schröer¹⁰⁸ also obtained **331** upon employing an excess of **14**. It should be noted that **331** represents the first 2:1-adduct from a 1,3-oxazolium 5-oxide and an olefinic dipolarophile, although 1:2-adducts had been observed previously (see Schemes 24 and 26).

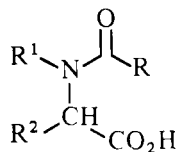


Upon attempting to generate munchnone **14** from its *N*-aroylamino acid precursor **13a** with acetic anhydride in the presence of *p*-benzoquinone, Myers and co-workers¹²⁹ obtained 1,2,4-triacetoxybenzene **332**. Presumably, the acetic acid produced in the cyclodehydration reaction acts as a catalyst for the Thiele acetylation of *p*-benzoquinone. In an attempt to prevent this type of side reaction, Myers and co-workers developed two modifications of the normal *in situ* procedure. In the first modification, the *N*-acylamino acid precursor **13** is warmed with an equimolar amount of acetic anhydride in a nonpolar solvent at 55–60°C for



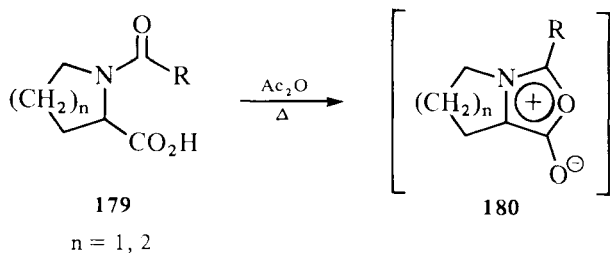
332

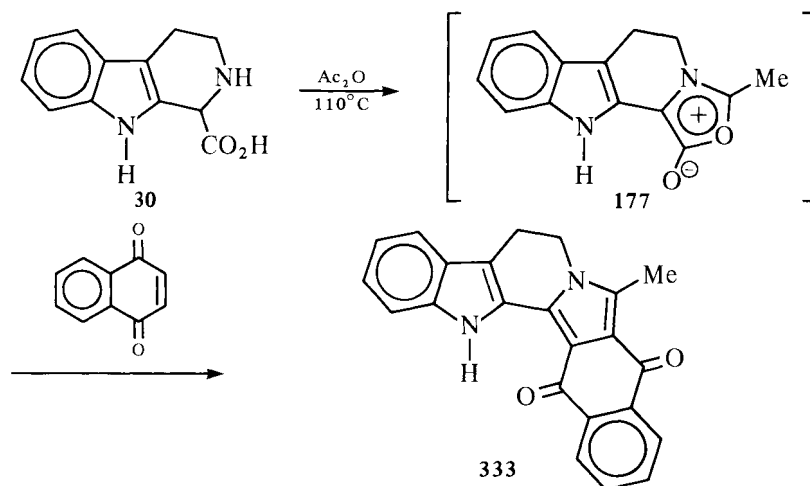
20–30 min. Sodium carbonate and sodium sulfate are then added to the solution of the 1,3-oxazolium 5-oxide **4** to neutralize acetic acid and absorb water. The 1,4-quinone is then added to this mixture at room temperature. Alternately, an equimolar amount of *N,N'*-dicyclohexylcarbodiimide (DCC) is added to a suspension of the *N*-acylamino acid precursor **13** in methylene chloride. The resulting mixture is heated at reflux for 30–45 min, and the *N,N'*-dicyclohexylurea (DCU) is removed by filtration to facilitate subsequent product isolation. The 1,4-quinone is then added to the methylene chloride solution of the munchnone **4** at room temperature.¹²⁹ In this manner, the reactions of unisolable 1,3-oxazolium 5-oxides **4** with 1,4-quinones were accessible, as illustrated in Table 4.26.



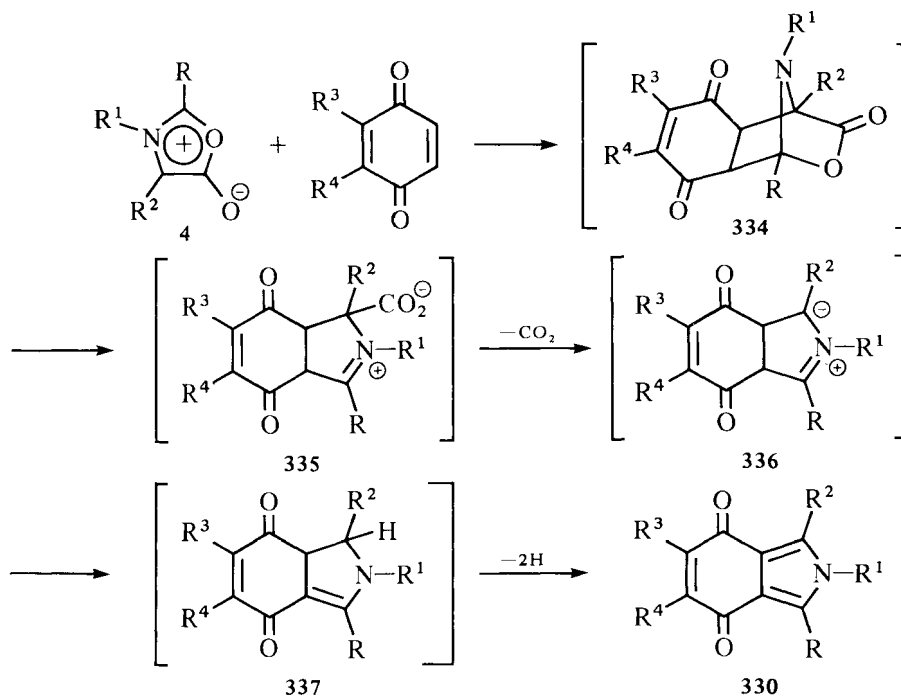
13

An examination of Table 4.26 also reveals that isoindolediones **330** are available not only from the reaction of 1,4-quinones with monocyclic 1,3-oxazolium 5-oxides but also from bicyclic 1,3-oxazolium 5-oxide **180** generated *in situ* from their *N*-acylamino acid precursors **179**.^{79,129} Hershenson²⁸ has also reported the reaction of the polycyclic munchnone **177**, generated *in situ* from 1,2,3,4-tetrahydro- β -carboline-1-carboxylic acid **30** with acetic anhydride, with 1,4-naphthoquinone to afford the indolizino[8,7-*b*]indole derivative **333** in 85% yield. It should also be noted that the reaction of unsymmetrical 1,3-oxazolium 5-oxides **4** ($R \neq R^2$) with unsymmetrical 1,4-quinones is not regiospecific, producing a mixture of both possible regioisomeric isoindolediones **330**, as indicated in Table 4.26.¹²⁹

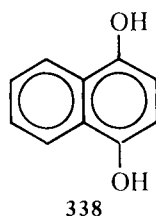




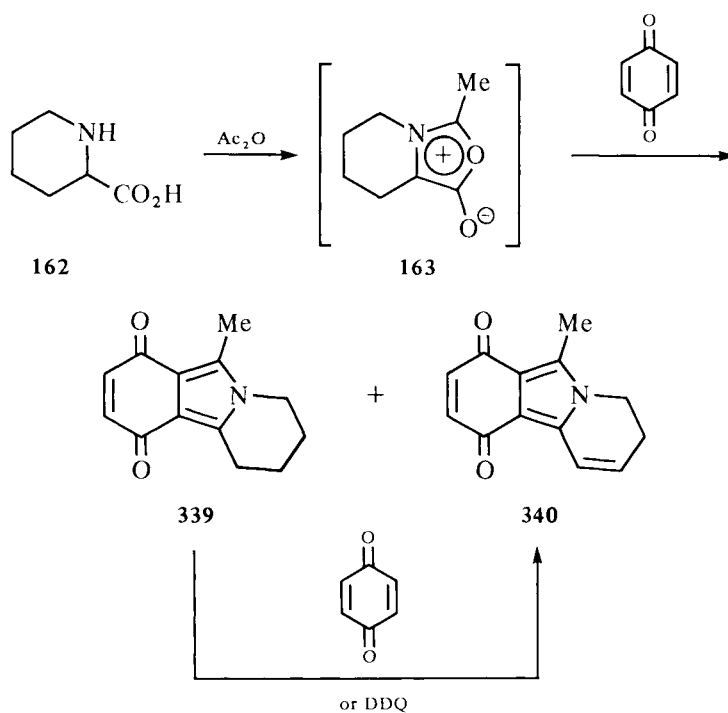
From a mechanistic point of view, the formation of isoindolediones **330** from the 1,3-dipolar cycloaddition reactions of munchnones **4** and 1,4-quinones can be rationalized as depicted in Scheme 37. Ring opening of the primary cycloadducts **334** affords the betaines **335**. Prototropic rearrangement of **335** gives Δ^2 -pyrroline carboxylic acids such as **315** and **327**, as discussed previously. However, loss of carbon dioxide yields the azomethine ylides **336**, which afford the dihydroiso-

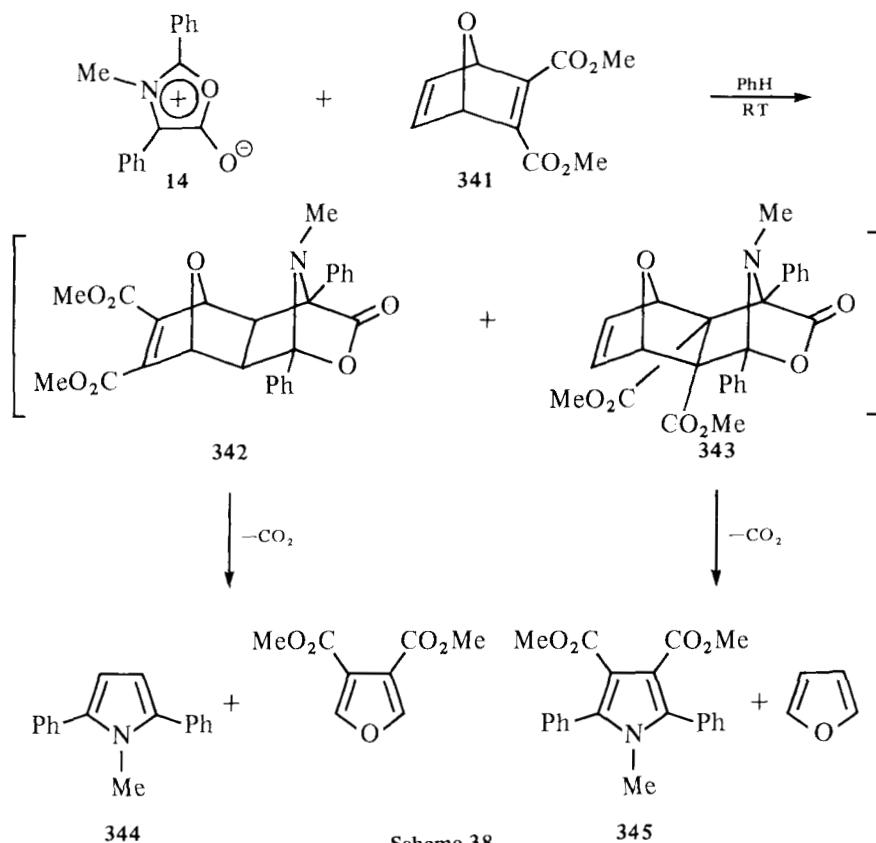


Scheme 37



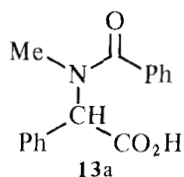
indolediones **337** upon a prototropic tautomerization. Dihydroisindolediones **337** are dehydrogenated under the reaction conditions to give the observed isoindolediones **330**. It appears reasonable that the 1,4-quinone dipolarophiles in these reactions are responsible for the dehydrogenation of **337** to **330** and may explain the relatively low yields of isoindolediones **330** obtained in these cycloaddition reactions.^{79,127,129} Evidence for this contention comes from the isolation of 1,4-naphthohydroquinone **338** from the reaction of 1,3-oxazolium 5-oxide **14** and 1,4-naphthoquinone.¹²⁹ Additionally, Matsumoto and co-workers⁷⁹ have reported that the reaction of *p*-benzoquinone and the bicyclic munchnone **163** generated *in situ* from pipecolinic acid **162** and acetic anhydride affords a 19% yield of the tetrahydroindolizine **339** and a 7% yield of the dihydroindolizine **340**. The formation of **340** is probably due to dehydrogenation of **339** by the *p*-benzoquinone dipolarophile, which was employed in excess. In fact, **339** exclusively yields **340** upon dehydrogenation with either *p*-benzoquinone or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).⁷⁹

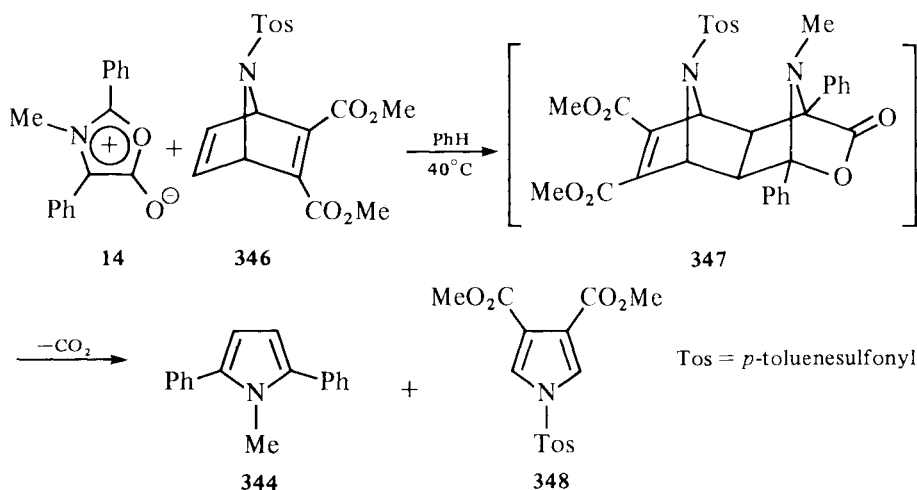




Scheme 38

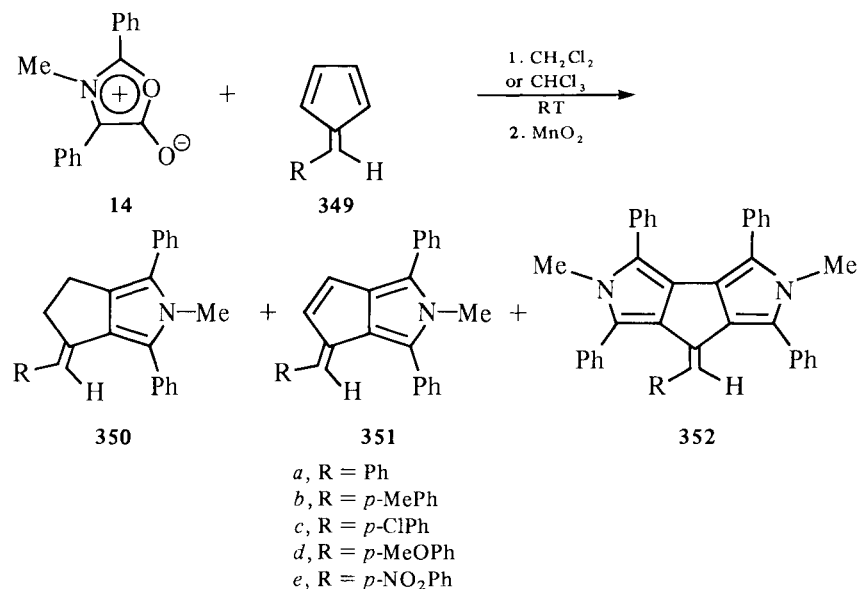
Matsukubo and Kato^{130,131} have reported the 1,3-dipolar cycloaddition reaction of the isolable 1,3-oxazolium 5-oxide **14** with the bridged diolefin **341** in benzene at room temperature as indicated in Scheme 38. The products of this reaction are the pyrroles **344** and **345** isolated in yields of 16 and 24%, respectively. The furan by-products were detected by ¹H NMR spectroscopy but were not isolated. The pyrroles **344** and **345** were also obtained in yields of 24 and 16%, respectively, upon reacting **341** and **14**, generated *in situ* from its *N*-aroylamino acid precursor **13a** in acetic anhydride at 50–55°C. These results indicate that the cycloaddition reaction of **14** and **341** occurs without periselectivity, giving both primary cycloadducts **342** and **343**, which then undergo a spontaneous double fragmentation to give the observed products. It was not possible to determine whether these double fragmentations are concerted or proceed in a stepwise fashion.



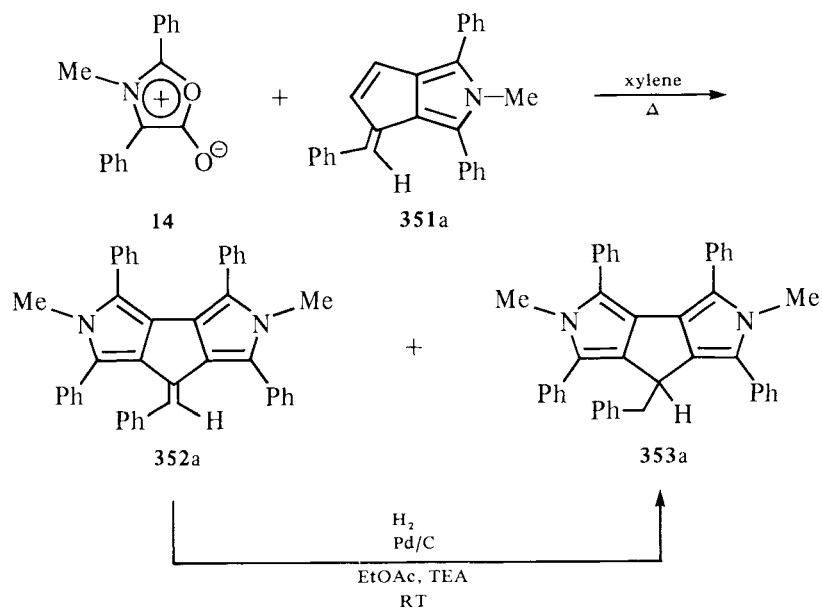


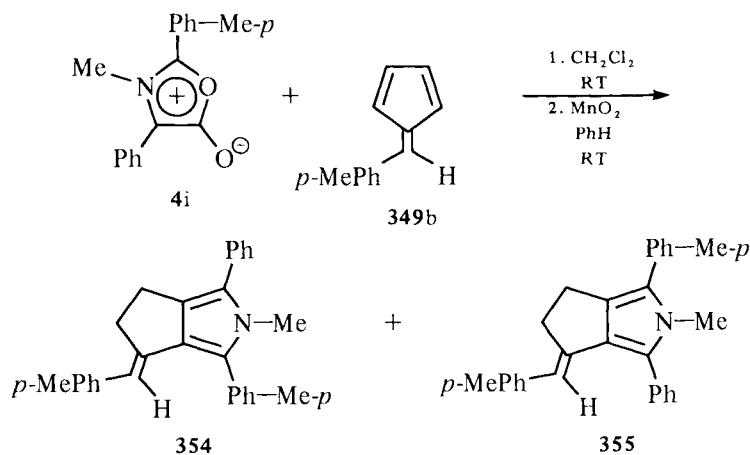
The reaction of **14** with the *N*-tosylazabicycloheptadiene **346** in benzene at 40°C, however, occurs with greater periselectivity.¹³² In this case, **14** adds selectively to the unsubstituted double bond of **346** to give the primary cycloadduct **347**, which then undergoes a spontaneous double fragmentation to afford pyrroles **344** and **348** in 55 and 56% yields, respectively. The greater periselectivity observed for the addition of **14** to **346** relative to **341** was rationalized on the basis of the greater steric bulk at the 7-position of **346** (since **14** approaches **341** and **346** from above the heteroatom bridge). Based on the results of the 1,3-dipolar cycloaddition reactions of some other mesoionic compounds with **346**, Matsukubo and Kato¹³² concluded that the double fragmentation of the primary cycloadduct **347** is probably not concerted but involves initial extrusion of carbon dioxide to give an unstable azomethine ylide, which then fragments to give pyrroles **344** and **348**.

Friedrichsen and co-workers^{133–135} have investigated the 1,3-dipolar cycloaddition reactions of the isolable munchnone **14** and fulvenes. The periselectivity of these cycloaddition reactions was determined by the fulvene substitution pattern. For example, reaction of **14** with the 6-monoarylfulvenes **349** affords a mixture of the dihydropyrrofulvenes **350**, the pyrrofulvenes **351**, and the bispyrrofulvenes **352**.¹³³ These reactions were run at room temperature in methylene chloride or chloroform, normally employing a 100% excess of **14**. The primary products of these reactions, pyrrolines, were not isolated but were instead oxidized to the observed products with manganese dioxide. The bispyrrofulvenes **352**, which were isolated in yields below 20%, were separated chromatographically from **350** and **351**. The pyrrofulvenes **351**, which were generally not isolated since they tended to decompose, were characterized as mixtures with **350** by ¹H NMR and UV spectroscopy. The dihydropyrrofulvenes **350** isolated in 10–20% yields were separated from **351** by fractional crystallization or by crystallization from ethanol containing acid. Under the latter conditions, **351** completely decomposed.



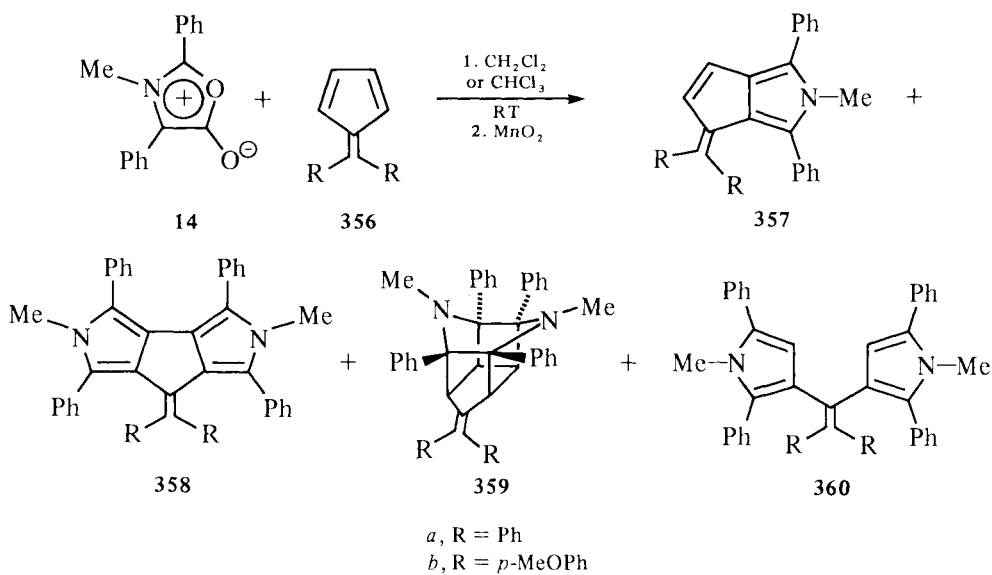
The structures of **350**, **351**, and **352** were secured by a combination of chemical and spectral methods.¹³³ The bispyrrofulvene **352a** was synthesized independently from **14** and **351a** under forcing conditions. A mixture of **14** and **351a** in xylene was heated at reflux to afford a mixture of **352a** and the dihydrobispyrrofulvene **353a** in yields of 34 and 32%, respectively. Dihydrobispyrrofulvene **353a** is also obtained in 78% yield from **352a** upon catalytic hydrogenation.



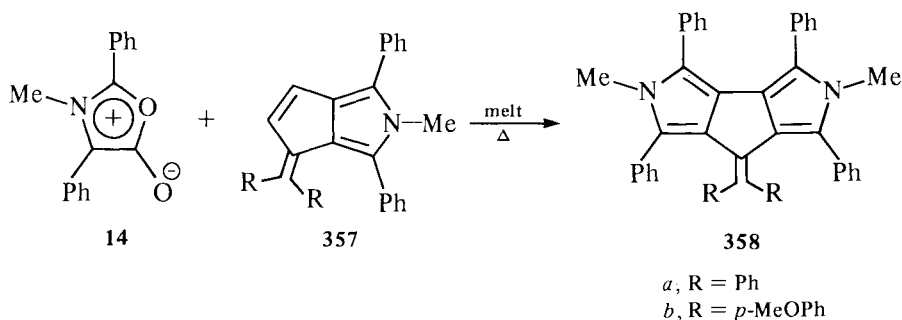


In an attempt to gain insight into the regiochemistry of the 1,3-dipolar cycloaddition reactions of unsymmetrical 1,3-oxazolium 5-oxides **4** ($\text{R} \neq \text{R}^2$) with 6-monoarylfulvenes **349**, Friedrichsen and co-workers¹³³ examined the reaction of the isolable munchnone **4i** and fulvene **349b**. In this case, a 1:1 mixture of regioisomeric dihydropyrrofulvenes **354** and **355**, as determined by ^1H NMR spectroscopy, was obtained in a 24% yield.

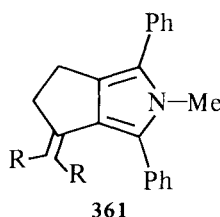
These researchers¹³⁴ next examined the reactions of **14** and the 6,6-disubstituted fulvenes **356**. Reaction of two equivalents of **14** with fulvene **356a** ($\text{R} = \text{Ph}$) in chloroform at room temperature for 15 h followed by dehydrogenation with manganese dioxide affords a mixture of pyrrofulvenes **357a**, bispyrrofulvene **358a**, and the novel cage compound **359a**, which were isolated in yields of 22, 0.5, and 11%, respectively. When the reaction time was reduced to 5 h, before



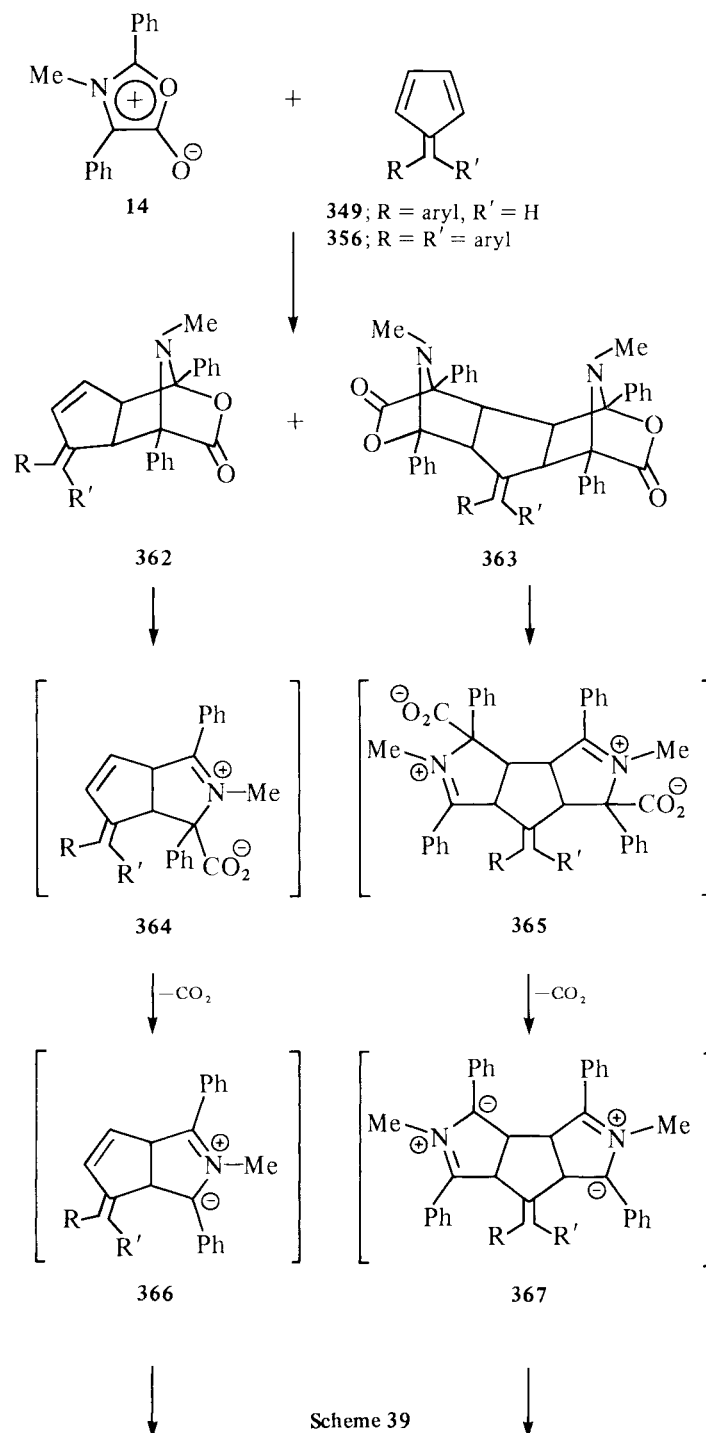
dehydrogenation, the same three products were obtained in yields of 43, 8, and 4%, respectively. A similar reaction of **14** and fulvene **356b** ($R = p\text{-MeOPh}$) in methylene chloride yields a mixture of **357b** (22%), **358b** (4%), and the dipyrrolylethylene **360b** (8%).

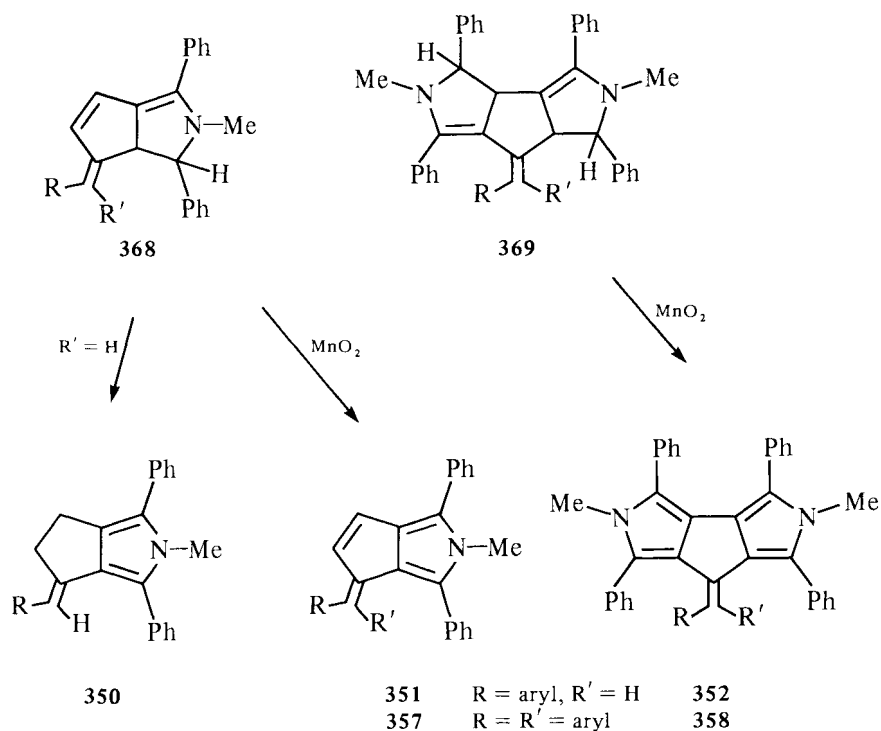


The bispyrrofulvenes **358** could be prepared independently in good yields under drastic conditions, that is, heating a melt of the pyrrofulvenes **357** and excess **14**. It is interesting to note that the corresponding dihydropyrrofulvenes **361** were not observed in these reactions, although they could be prepared in excellent yield upon catalytic hydrogenation of the pyrrofulvenes **357**.



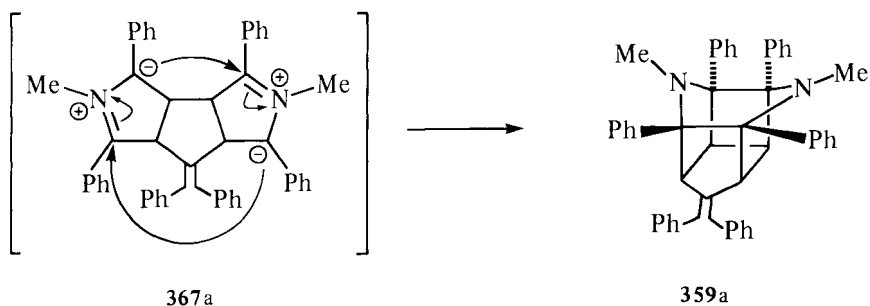
From a mechanistic point of view, the 1,3-dipolar cycloaddition reactions of münchnone **14** with fulvenes **349** and **356** can be rationalized as illustrated in Scheme 39.^{133,134} The 1,3-dipolar cycloaddition reaction of **14** to the endocyclic double bond of **349** and **356** affords the primary cycloadducts **362**. Ring opening of **362** yields the betaines **364**, which, upon loss of carbon dioxide, gives the azomethine ylides **366**. Prototropic rearrangement of **366** produces the Δ^2 -pyrrolines **368**. Dehydrogenation of **368** with manganese dioxide affords the observed pyrrofulvenes **351** and **357**. When $R' = \text{H}$, the Δ^2 -pyrrolines **368** can rearrange (presumably without manganese dioxide) to the dihydropyrrofulvenes **350**. This internal oxidation–reduction step is reminiscent of the **319** → **322** transformation noted previously (see Scheme 34). A similar sequence can be envisioned for the formation of the bispyrrofulvenes **352** and **358**, as also illustrated in Scheme 39. It should be appreciated that the exact stage at which the second molecule of **14** adds is open to debate. For example, **14** could add to **364** or **366** to give **365** or **367**, respectively. Additionally, the structures of **363**, **365**, **367**, and **369** could be envisioned as head-to-head structures rather than the head-to-tail structures depicted in Scheme 39.



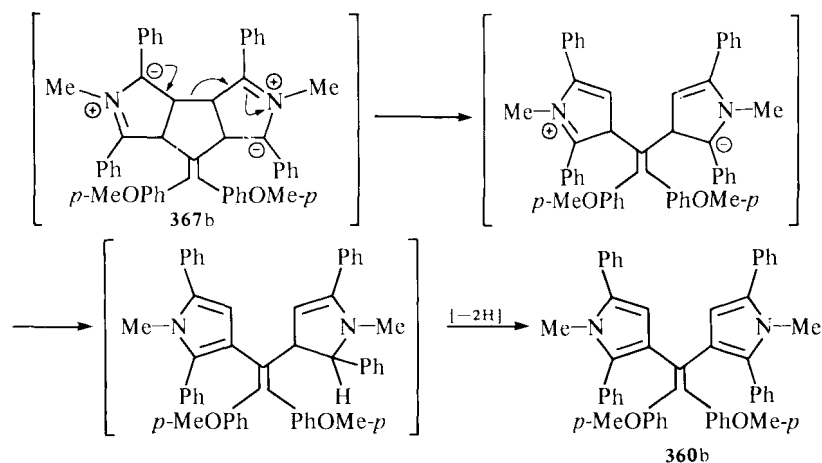


Scheme 39 (cont)

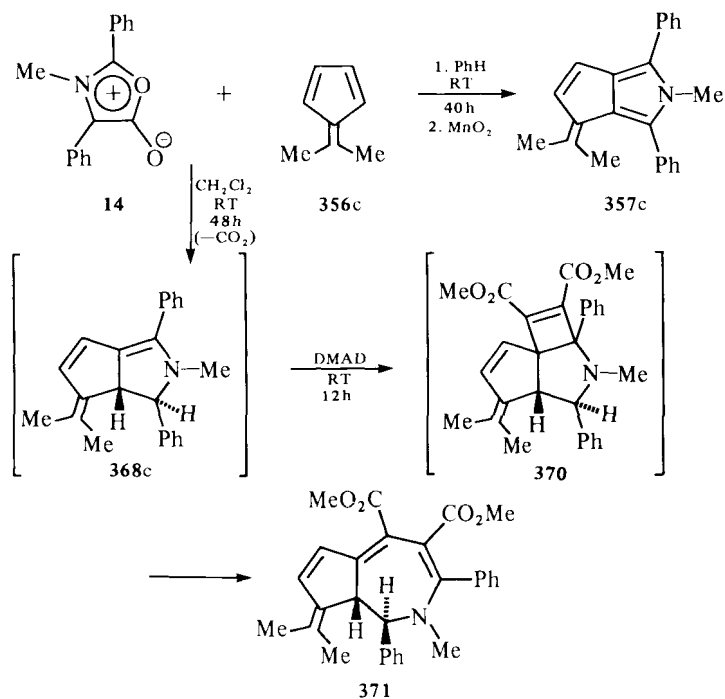
The formation of the novel cage compound **359a**, the structure of which was deduced by elemental and spectral (UV, IR, ^1H NMR, ^{13}C NMR) data, can be rationalized by the cyclization of the bisazomethine ylide **367a**.¹³⁴ Similarly, the formation of the dipyrrolethylene **360b** can be envisioned as involving an initial ring opening of the bisazomethine ylide **367b**, followed by a proton shift, and dehydrogenation as indicated below.¹³⁴

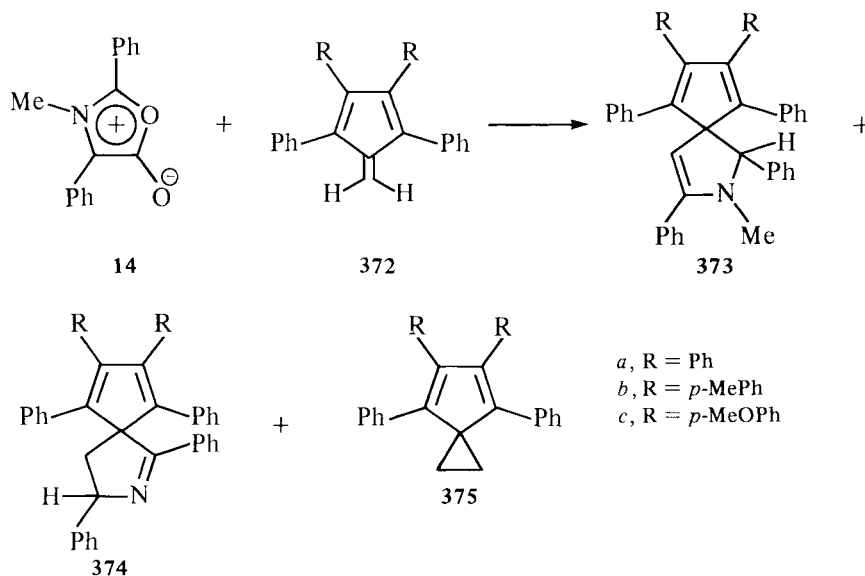


Friedrichsen and co-workers have also reported that the reaction of **14** with 6,6-dimethylfulvene **356c** ($R = \text{Me}$) followed by dehydrogenation with manganese dioxide affords the pyrrofulvene **357c** in only 7% yield.¹³⁴ However, if an excess



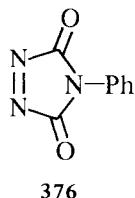
of dimethyl acetylenedicarboxylate (DMAD) is added to the reaction mixture in place of manganese dioxide, a 5% yield of the cyclopenta[*c*]azepine **371** was isolated, in addition to the known Diels–Alder adduct of **356c** and DMAD. The structure of **371** was confirmed by X-ray crystallography. The formation of **371** was rationalized by a [2 + 2]cycloaddition reaction of DMAD to the electron-rich double bond of the Δ^2 -pyrrole **368c** to initially give cycloadduct **370**, which undergoes ring opening to afford the observed **371**.



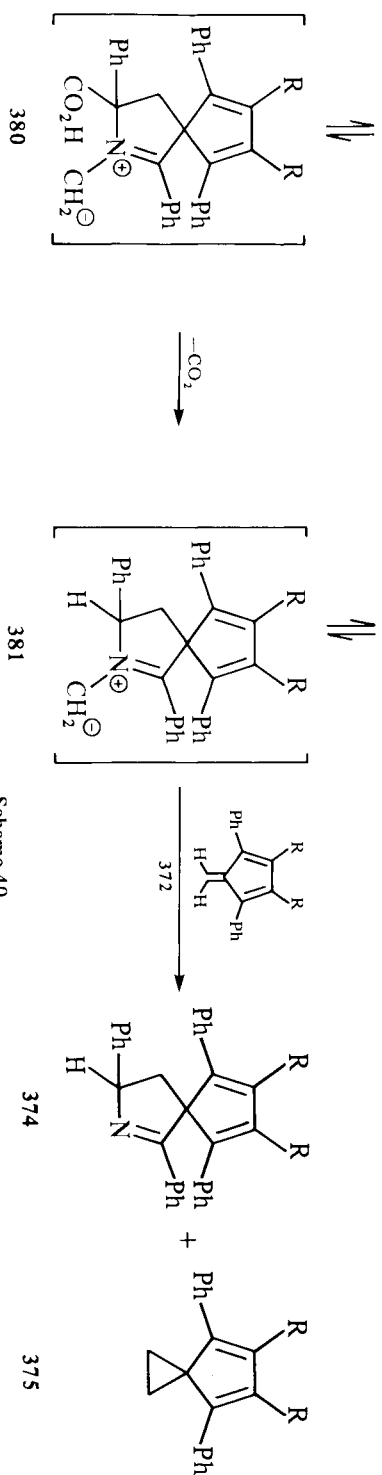
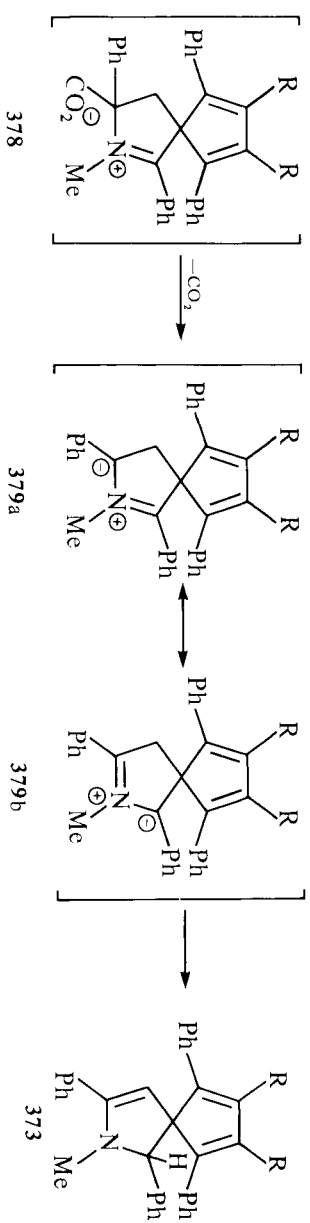
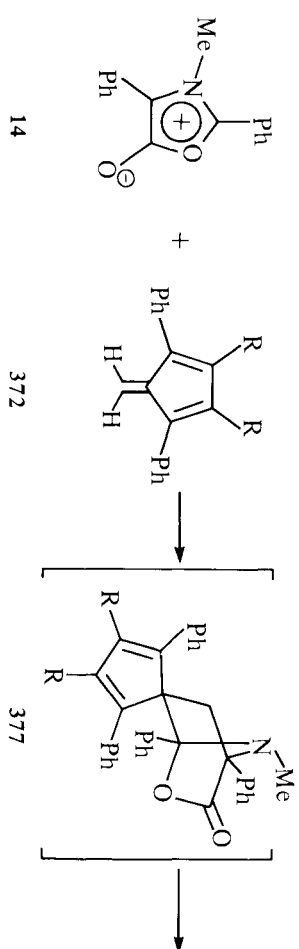


Finally, these researchers¹³⁵ examined the 1,3-dipolar cycloaddition reactions of munchnone **14** with 2,3,4,5-tetraarylfulvenes **372**. Three types of products — spiropyrrolines **373** and **374** and spiroheptadienes **375** — were obtained. These reactions were examined in two types of solvents since the product ratios were found to be dependent on the choice of solvent. For example, reaction of **14** with fulvene **372a** (R = Ph) in benzene at room temperature affords a 44% yield of **373a** and a 33% yield of **374a**, while in chloroform at room temperature **373a**, **374a**, and **375a** are obtained in yields of 11, 30, and 27%, respectively. In benzene the reaction components have relatively poor solubilities, and the reactions proceed slowly (5–20 h) at room temperature. However, when the reactions are run in chloroform or methylene chloride, the starting materials dissolve immediately, and vigorous carbon dioxide evolution occurs.

The spiroheptadienes **375** were prepared previously by Schröer and Friedrichsen from fulvenes **372** and dimethyloxosulfonium methylide.¹³⁶ The structures of the spiropyrrolines **373** and **374** were deduced from spectral data and chemical transformations, including Diels–Alder reactions of the cyclopentadiene moieties with 4-phenyl-1,2,4-triazoline-3,5-dione **376**.¹³⁵



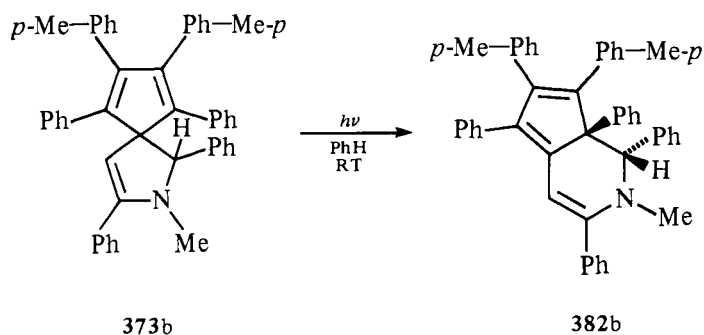
Friedrichsen and co-workers¹³⁵ have proposed the mechanism shown in Scheme 40 to account for the formation of **373**, **374**, and **375** from the reaction of **14**



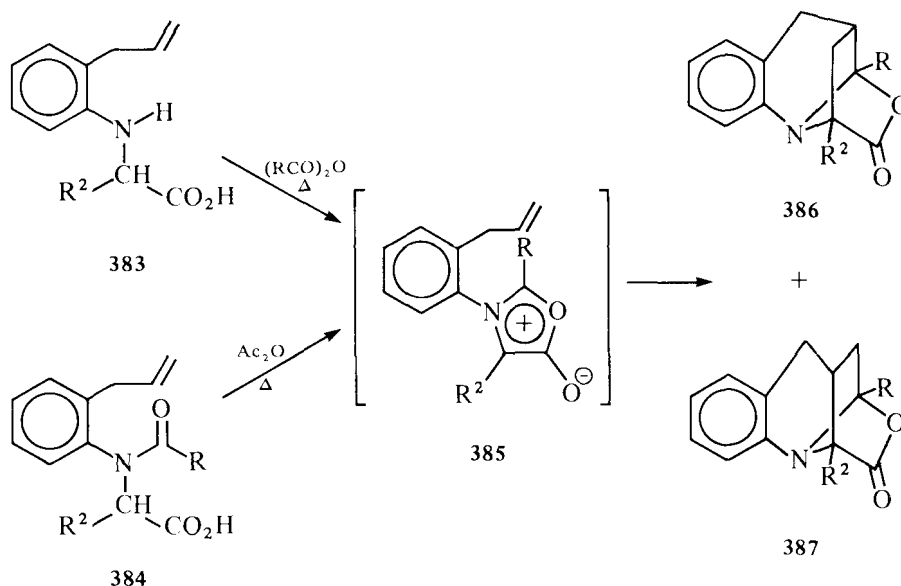
Scheme 40

and fulvenes **372**. Addition of 1,3-oxazolium 5-oxide **14** to the exocyclic double bond of **372** affords the primary cycloadducts **377**. Ring opening of **377** followed by loss of carbon dioxide yields the azomethine ylides **379**. Prototropic rearrangement of **379** gives the spiropyrrolines **373**. However, azomethine ylides **379** may be in equilibrium with the imonium ylides **381**. Transfer of a methylene group from **381** to additional fulvene **372** affords the spiropyrrolines **374** and the spiroheptadienes **375**. These workers suggest that the proposed equilibrium between **379** and **381** (or **378** and **380**) is supported by the observation that the product ratios are influenced by the solution concentration of the reactants **14** and **372**. It was noted that in chloroform or methylene chloride, where high concentrations of **14** and **372** exist, the yields of **374** and **375**, which are formed via a bimolecular secondary reaction, increase at the expense of **373**. In benzene, with a low stationary concentration of **14** and **372**, the yields of **374** and **375** decrease, while the yield of **373** increases.¹³⁵ However, inspection of the reported data reveals that while the yields of **373** and **375** are solvent dependent and inversely related, the yields of spiropyrrolines **374** appear to be relatively independent of the solvent type. It is also worth noting that the reactions of **14** with fulvenes **372a** ($R = \text{Ph}$) and **372b** ($R = p\text{-MePh}$) in benzene afford the spiropyrrolines **374a** and **374b** in yields of 33 and 25%, respectively. However, the corresponding spiroheptadienes **375a** and **375b** were apparently not observed.

When reactions of **14** and fulvenes **372** were run in benzene, the reaction mixtures were normally protected from light since the spiropyrrolines **373** are photolabile. For example, irradiation of a benzene solution of **373b** with a high-pressure mercury lamp affords an 80% yield of the dihydro-1*H*-cyclopenta[*c*]pyridine **382b**. The stereochemistry of **382b** was clarified by X-ray crystallography.¹³⁵



Intramolecular cycloaddition reactions of 1,3-dipoles bearing a functional group capable of serving as a dipolarophile constitute a general scheme for the synthesis of novel heterocyclic compounds.¹³⁷ Padwa and co-workers^{138,139} have reported the intramolecular 1,3-dipolar cycloaddition reactions of 3-(*o*-allylphenyl)-1,3-oxazolium 5-oxides **385**. Munchones **385** were generated *in situ* by *N*-acylation and cyclodehydration of the amino acid precursor **383** using an appropriate carboxylic acid anhydride or by cyclodehydration of the *N*-acylamino acid precursor **384** with acetic anhydride. The products of these intramolecular 1,3-di-



polar cycloaddition reactions are the oxazoloquinolinones **386** and **387**. These results are summarized in Table 4.27, along with some additional examples from our laboratory.⁹¹ The oxazoloquinolinones **386** and **387** represent the first examples of isolable primary cycloadducts obtained from the 1,3-dipolar cycloaddition reaction of a 1,3-oxazolium 5-oxide and an olefin.

Inspection of Table 4.27 reveals that the intramolecular cycloaddition reactions of munchnones **385** derived from *N*-(*o*-allylphenyl)alanines **383** ($\text{R}^2 = \text{Me}$) are regioselective, affording only the oxazoloquinolinones **386** regardless of the nature of the R substituent. However, the regiochemistry of the intramolecular cycloaddition reactions of **385** derived from *N*-(*o*-allylphenyl)-*C*-phenylglycines **383** ($\text{R}^2 = \text{Ph}$) is markedly dependent on the nature of the R substituent. When R = H, Me, or CF_3 , regioisomer **387** is favored; while, when R = Ph, regioisomer **386** predominates. The structures of the oxazoloquinolinones **386** and **387** are supported by IR and ^1H and ^{13}C NMR spectroscopy. The structures of **386a** and **386b** were confirmed by X-ray crystallography.^{138,139}

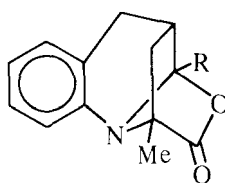
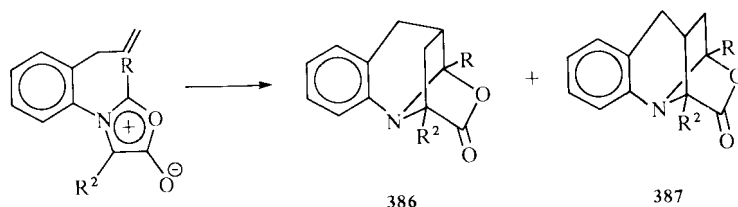
**386***a*, R = Me*b*, R = Ph

TABLE 4.27. INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION REACTIONS OF *N*-(*O*-ALLYLPHENYL)-1,3-OXAZOLIUM 5-OXIDE^{91, 138, 139}

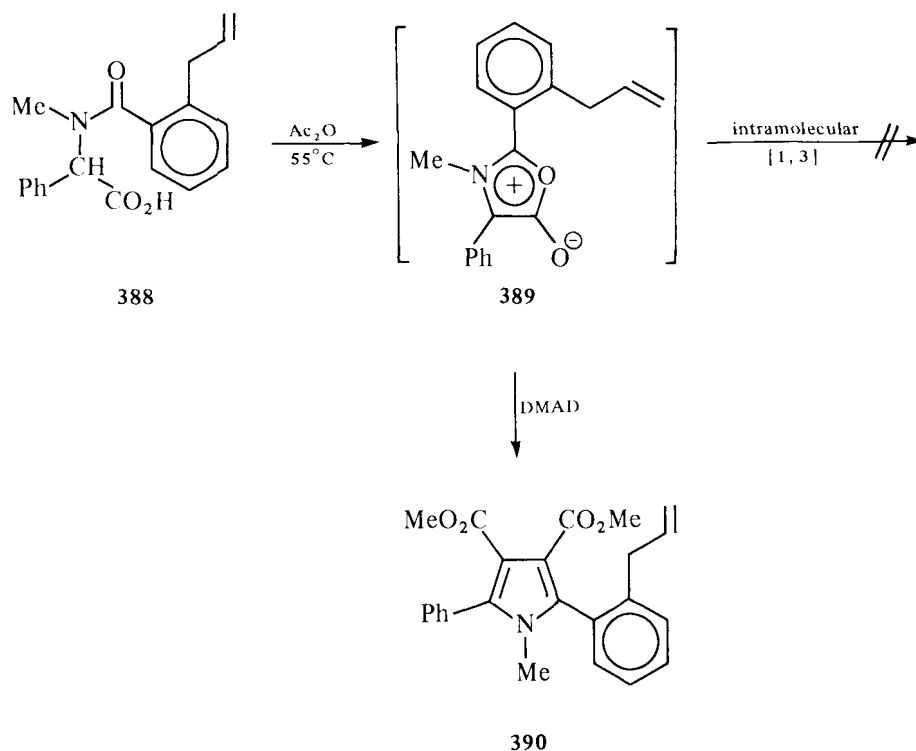
Method of Munchnone Preparation ^a	R	R ²	Product	Isomer Ratio	Percent Yield
B	H	Me	386	—	75
A	(Me) ^b	Me	386	—	54
A	(CF ₃) ^b	Me	386	—	70
A	(Ph) ^b	Me	386	—	81
B	Ph	Me	386	—	94
B	H	Ph	387	62	58
			386	38	26
A	(Me) ^b	Ph	387	83	62
			386	17	10
A	(CF ₃) ^b	Ph	387	90	78
			386	10	4
A	(Ph) ^b	Ph	386	67	65
			387	33	
B	Ph	Ph	386	67	
			387	33	92

^aA, *In situ* *N*-acylation and cyclodehydration of amino acid precursor with carboxylic acid anhydride; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride.

^bSubstituents in parentheses introduced by cyclodehydrating reagent.

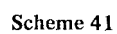
These researchers next examined 1,3-oxazolium 5-oxides, which contained an internal olefinic dipolarophile attached to the C-2 position of the munchnone rather than the N-3 position. Intramolecular 1,3-dipolar cycloaddition reactions of such systems proved to be less facile. For instance, all attempts to detect intramolecular cycloaddition products from 1,3-oxazolium 5-oxide **389** derived from *N*-methyl-*N*-(*o*-allylbenzoyl)-*C*-phenylglycine **388** and acetic anhydride failed.¹³⁹ However, treatment of **388** with acetic anhydride in the presence of dimethyl acetylenedicarboxylate (DMAD) at 55°C affords pyrrole **390** in 35% yield, indicating that munchnone **389** is formed under these conditions.

The failure of **389** to undergo an intramolecular 1,3-dipolar cycloaddition reaction was rationalized by poor overlap of the olefinic π bond with the munchnone 1,3-dipole.¹³⁹ However, molecular models indicate that in the homologous 1,3-oxazolium 5-oxides **392**, the required overlap should be better. Accordingly, the *N*-aroylamino acid **391a** (R¹ = Ph) and acetic anhydride at 55°C affords a

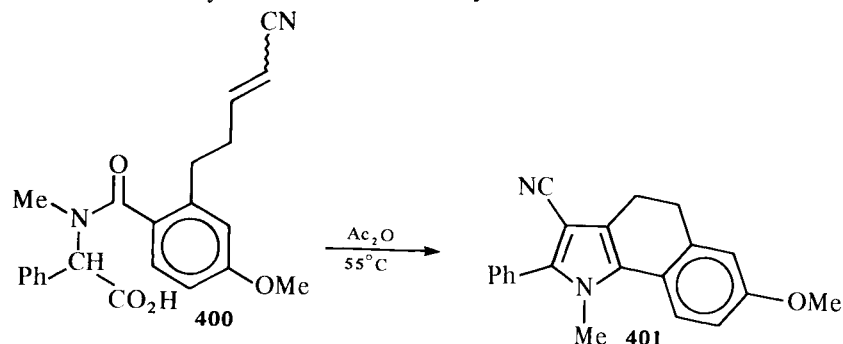


17% yield of the 4,5-dihydro-1*H*-benz[*g*]indole **397a**. The formation of this product was rationalized as indicated in Scheme 41. The intramolecular 1,3-dipolar cycloaddition reaction of munchnone **392a** generated from **391a** yields the primary cycloadduct **394a**. Loss of carbon dioxide from **394a** gives the azomethine ylide **395a**, which upon tautomerization produces the tetrahydro-1*H*-benz[*g*]indole **396a**. *In situ* dehydrogenation of **396a** affords the observed product **397a**. This intramolecular cycloaddition reaction could be completely suppressed when the reaction was run in the presence of excess DMAD. In this case, the only product observed was the pyrrole **393a** (33%).¹³⁹

Reaction of the related *N*-methyl-*N*-aroylamino acid **391b** ($R^1 = \text{Me}$) with acetic anhydride affords the corresponding 4,5-dihydro-1*H*-benz[*g*]indole **397b** in low yield (2%).¹³⁹ However, the major product obtained from this reaction was assigned as the 3-acetyltetrahydro-1*H*-benz[*g*]indole **398b**. Compound **398b** was oxidized to the 3-acetyl-1*H*-benz[*g*]indole **399b** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Presumably **398b** is formed upon acylation of the enamine moiety of the intermediate tetrahydro-1*H*-benz[*g*]indole **396b** as depicted in Scheme 41. The failure to obtain the corresponding 3-acetyl-*N*-phenyltetrahydro-1*H*-benz[*g*]indole **398a** from the reaction of the *N*-phenyl-*N*-aroylamino acid **391a** and acetic anhydride was rationalized on the basis of the reduced availability of the nitrogen lone pair of **396a**, which is delocalized onto the phenyl ring.¹³⁹



Finally, in an attempt to improve the efficiency of these intramolecular 1,3-dipolar cycloaddition reactions, Padwa and co-workers examined the reaction of the *N*-aroylamino acid **400**, which contains an electron-withdrawing substituent on the internal olefinic dipolarophile.¹³⁹ Accordingly, reaction of **400** with acetic anhydride at 55°C affords the expected 3-cyano-4,5-dihydrobenz[*g*]indole **401** in only 11% yield. Apparently, activation of the internal dipolarophile fails to increase the efficiency of the intramolecular cycloaddition reaction.



While the intramolecular cycloaddition reactions of mesoionic oxazoles appears to be in its infancy, these results clearly indicate the synthetic utility of this approach. To the best of our knowledge, the intramolecular 1,3-dipolar cycloaddition reactions of mesoionic oxazoles containing internal dipolarophiles other than olefins have not been investigated.

4.2.3.3.4. WITH CARBONYL COMPOUNDS

The 1,3-oxazolium 5-oxide system **4** ($R^1 = \text{Me}$) has been reported by Huisgen and co-workers to undergo cycloaddition reactions with aldehydes, α -diketones and α -keto carboxylic acid esters resulting in the formation of *N*-aroyl-*N*-alkenylamines **404**.^{140,141} The reaction is thought to proceed through an unstable 1:1 cycloadduct **402**, which extrudes carbon dioxide forming an azomethine ylide dipolar intermediate **403**. Upon ring opening, **403** leads to the stable products **404** (Table 4.28).

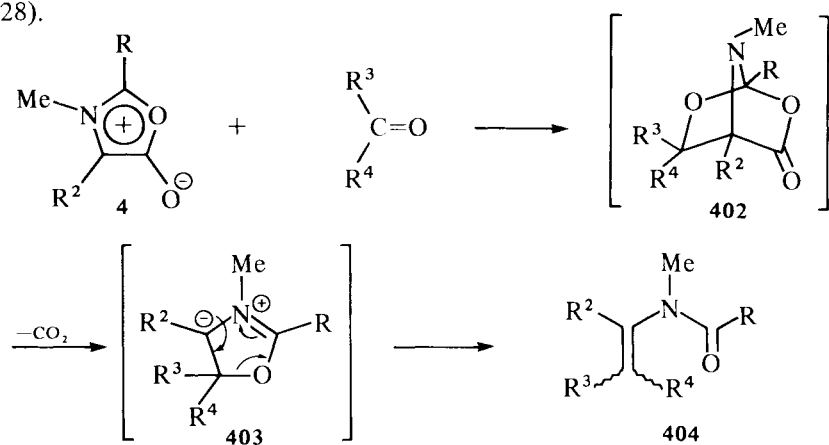
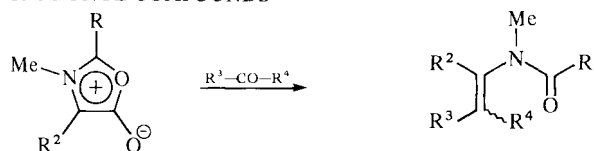
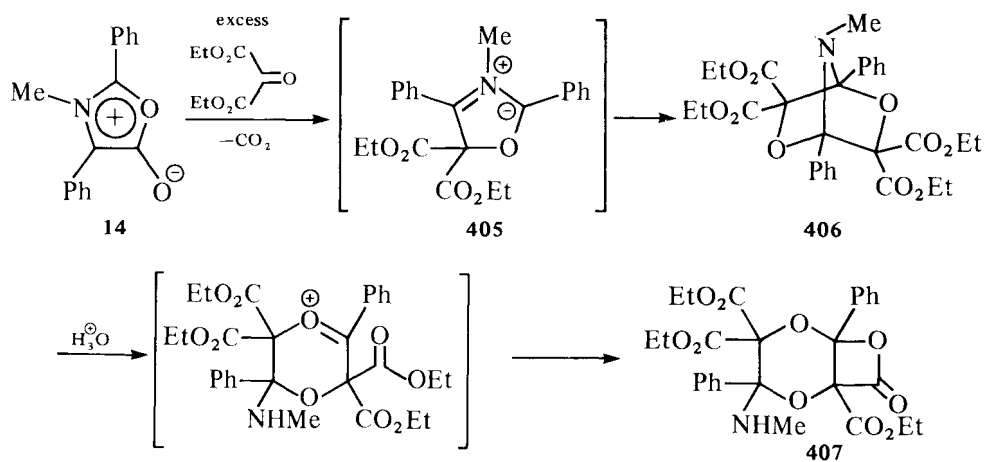
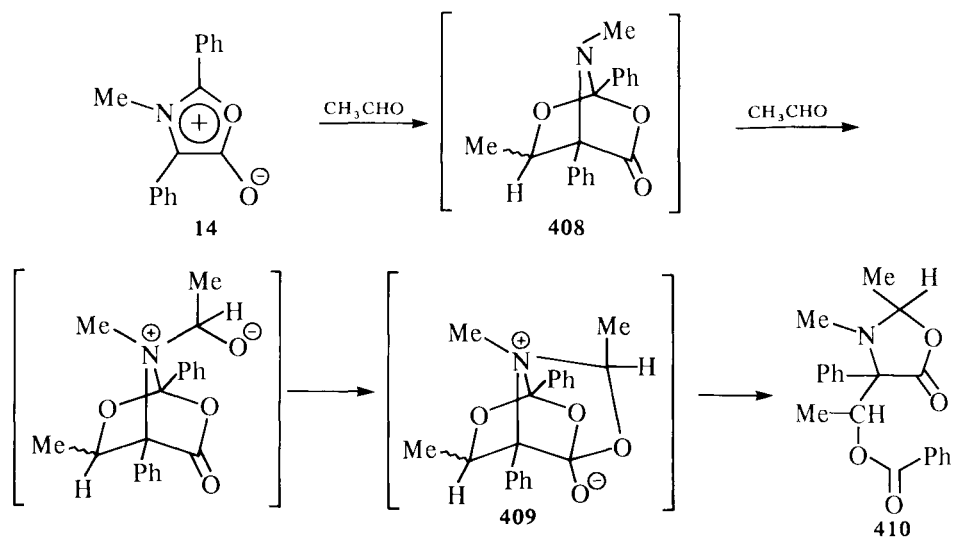


TABLE 4.28. *N*-AROYL-*N*-ALKENYLAMINES 404 FROM MUNCHNONES AND CARBONYL COMPOUNDS

R	R ²	R ³	R ⁴	Percent Yield	Reference
Ph	Ph	H	H	45	140
Ph	Ph	Me	H	32	140
Ph	Ph	Ph	H	46	140
Ph	Ph	<i>p</i> -ClPh	H	52	140
Ph	Ph	<i>p</i> -MePh	H	45	140
Ph	Ph	PhCO	Ph	60	140
Ph	Ph	Me	MeCO ₂	51	140
Ph	Ph	CO ₂ Et	CO ₂ Et	57	140
<i>p</i> -MeOPh	Ph	Ph	H	63	141
Ph	<i>p</i> -MeOPh	Ph	H	17	141
Me	Ph	Ph	H	71	141
Ph	Me	Ph	H	40	141
<i>p</i> -MeOPh	Ph	<i>p</i> -ClPh	H	51	141
<i>p</i> -MeOPh	Ph	Ph	COPh	36	141

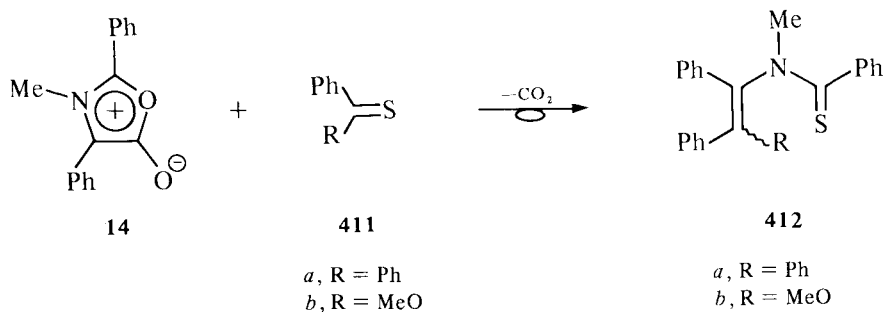
Both intermediates in the above reaction may be intercepted. Thus, **14**, when stirred slowly into an ethereal solution of an excess of diethyl mesoxalate, forms the bis-adduct **406** via trapping of the azomethine ylide **405**. Adduct **406**, upon mild hydrolysis, forms the β -lactone **407**.¹⁴⁰ Treatment of **14** with acetaldehyde at 0°C affords the bis-adduct **410**.¹⁴¹ Presumably, here the primary cycloadduct **408** is trapped by addition of a second molecule of acetaldehyde, which yields **409**. Ring opening thereof leads to the oxazolidinone **410**.



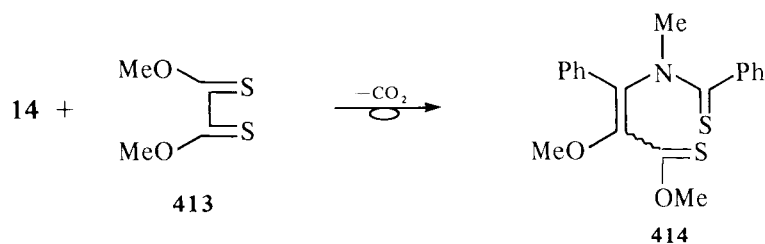


4.2.3.3.5. WITH THIOCARBONYL COMPOUNDS

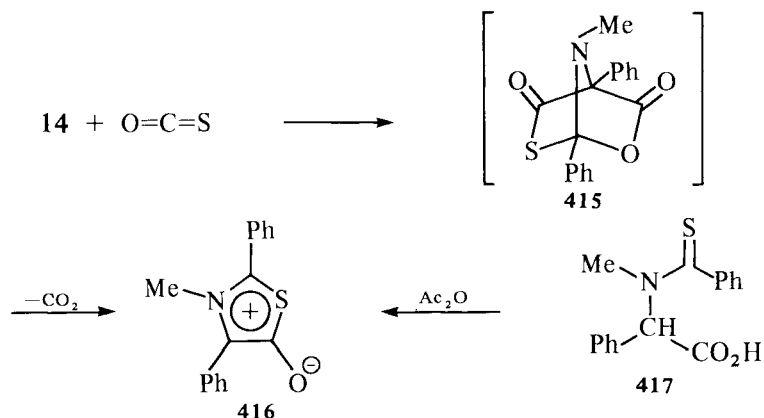
Thiobenzophenone **411a** at room temperature and methyl thiobenzoate **411b** at 80°C combine with 3-methyl-2,4-diphenyl-1,3-oxazolium 5-oxide **14** to give *N*-thiobenzoylenamines **412** in quantitative and 51% yields, respectively.^{142,143}



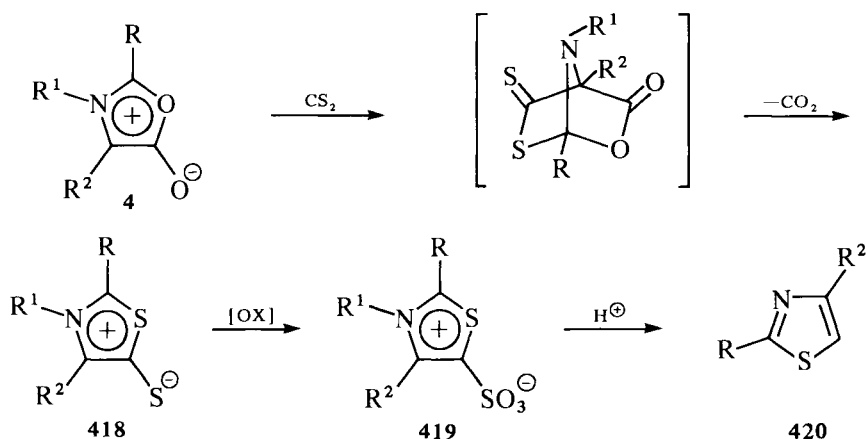
The reaction proceeds mechanistically analogous to carbonyl compound additions to **14** (Section 4.2.3.3.4). Via a similar process, **14** and *O,O*-dimethylthiooxalate **413** react at room temperature in benzene and form in 87% yield the analogous *N*-thiobenzoylenamine **414** as a 10:90 mixture of *E:Z*-isomers.¹⁴⁴



The interconversion of mesoionic systems is exemplified by the formation of the 1,3-thiazolium 5-oxide system **416** in 49% yield from treatment of **14** with carbonoxysulfide.^{142,143} Again the extrusion of carbon dioxide from a 1:1 cycloadduct **415** appears to be the plausible mechanistic pathway. That cycloaddition had occurred across the C–S double bond in carbonoxysulfide was proven by independent synthesis of **416** by cyclodehydration of thioamide **417**, available from acylation of *N*-methylphenylglycine with thiobenzoyl chloride.

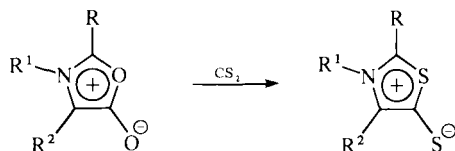


Analogous results are obtained from reactions of carbon disulfide and 1,3-oxazolium 5-oxides **4**, either preformed or generated *in situ* from *N*-acylamino acids and acetic anhydride.^{21,142,143} The reaction proceeds regiospecifically (Table 4.29), and the resultant 1,3-thiazolium 5-sulfides **418** can be oxidized. The resulting betaine **419** can be degraded to known 2,4-disubstituted thiazoles **420**.



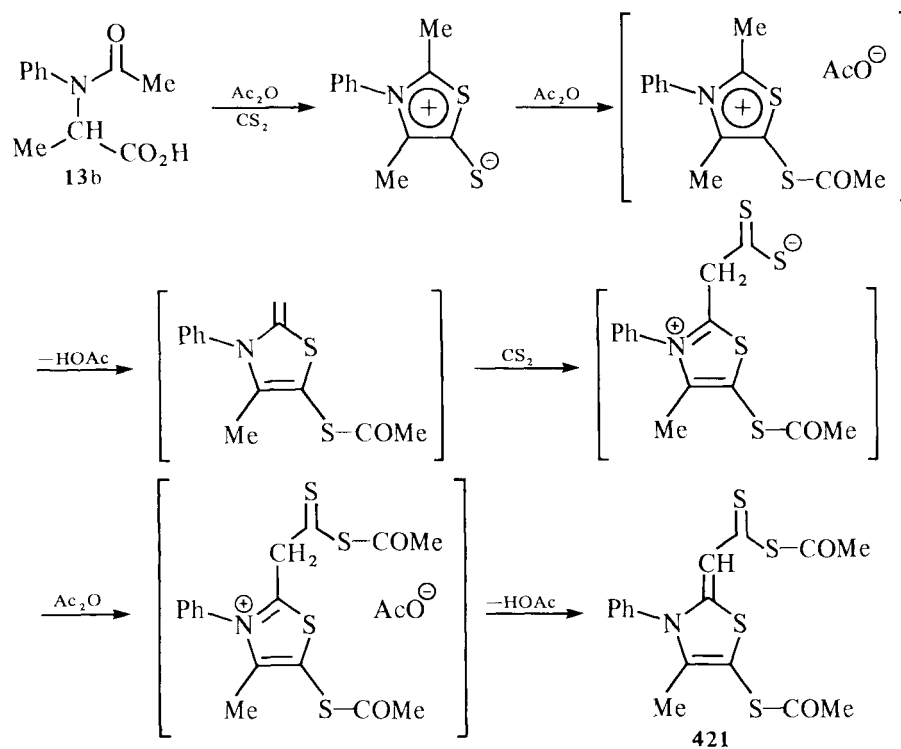
Under the conditions of acetic anhydride dehydration of *N*-acylamino acids to generate the mesoionic reactant, secondary products can be obtained.²¹ For example, **13b** with acetic anhydride and carbon disulfide affords **421** as depicted in Scheme 42.

TABLE 4.29. FORMATION OF 1,3-THIAZOLIUM 5-SULFIDES FROM 1,3-OXAZOLIUM 5-OXIDES AND CARBON DISULFIDE



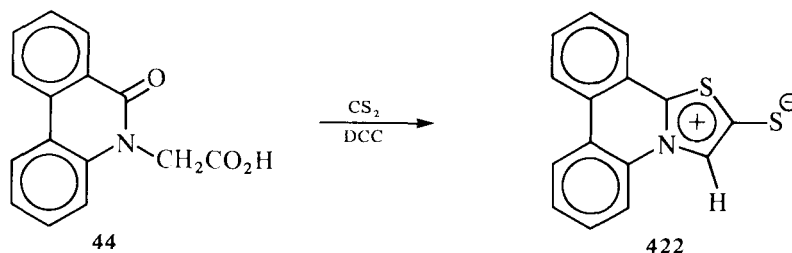
Method ^a	R	R ¹	R ²	Percent Yield	Reference
A	Ph	Me	Ph	100	142, 143
B	Ph	Me	Ph	96	142, 143
B	Me	Ph	Me	47	21, 142, 143
A	<i>p</i> -MePh	Me	Ph	95	21
A	Ph	Me	<i>p</i> -MePh	97	21
A	<i>p</i> -MeOPh	Me	Ph	84	21
A	Ph	Me	<i>p</i> -MeOPh	93	21
B	Me	Ph	Ph	32	21
B	Ph	Ph	Me	92	21

^aA, Preformed munchnone; B, *in situ* cyclodehydration of *N*-acylamino acid precursor with acetic anhydride.



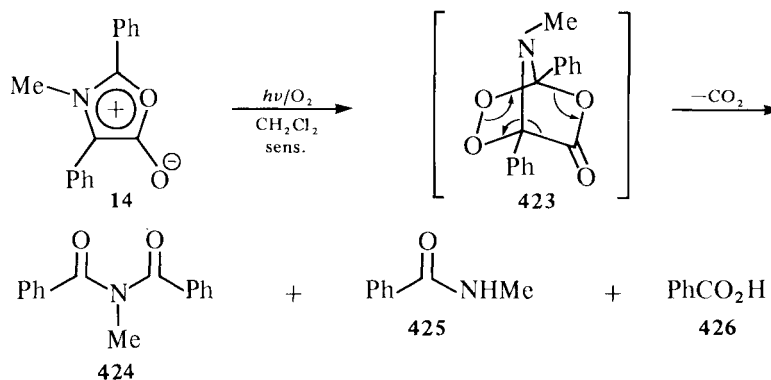
Scheme 42

The *in situ* technique has been applied by Potts and co-workers to 6-oxo-5-[6*H*]phenanthridineacetic acid **44**, which with *N,N'*-dicyclohexylcarbodiimide (DCC) and carbon disulfide provides the ring-fused 1,3-thiazolium 5-thiolate **422** in 40% yield.¹⁴⁵

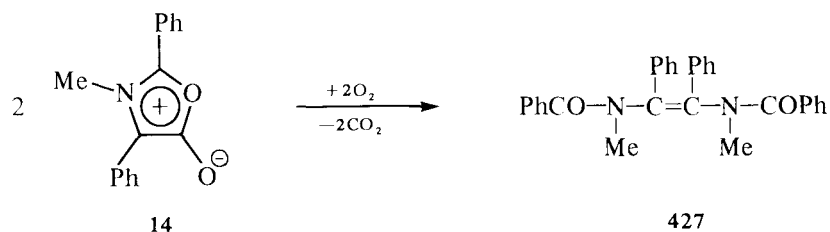


4.2.3.3.6. WITH OXYGEN

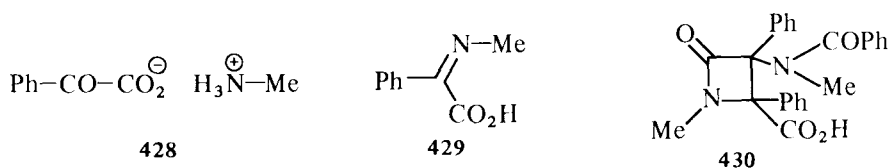
Irradiation of munchnone **14** in methylene chloride in the presence of methylene blue and oxygen and fractional sublimation of the products affords *N*-methyl-dibenzamide **424**, *N*-methylbenzamide **425**, and benzoic acid **426** in 29, 2, and 4% yields, respectively.¹⁴⁶ The reaction products may be rationalized from a $[4\pi + 2\pi]$ cycloaddition process forming the endoperoxide cycloadduct **423**, which in a retro process loses carbon dioxide to form **424**. The latter two products may arise from hydrolysis of **424**.



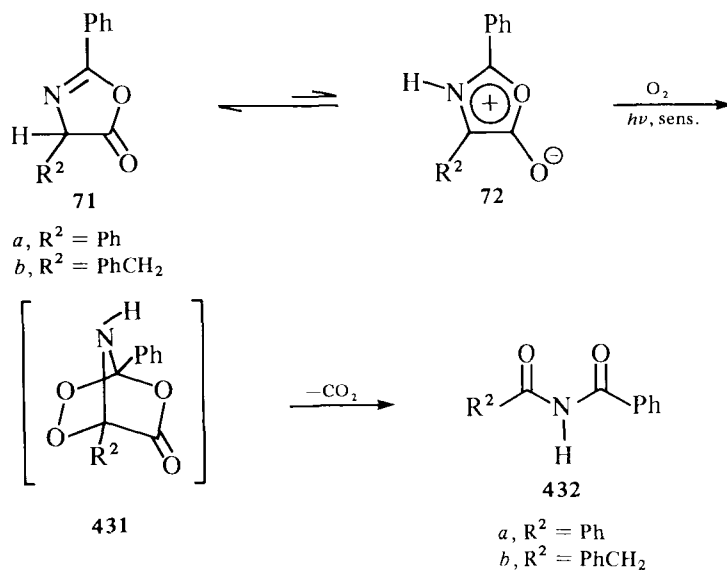
A product ascribed the structure **427** isolated during the reaction of **14** with tetrachlorocyclopropene (Section 4.2.3.3.3) corresponds to 2 mol of **14** plus 2 mol of oxygen minus 2 mol of carbon dioxide.¹²²



The above two reports differ somewhat from the original work by Huisgen¹⁵ on the identification of autooxidation products of 1,3-oxazolium 5-oxide **14**. In this case, action of oxygen under various conditions leads to the methylammonium salt of phenylglyoxylic acid **428**, *N*-methyliminophenylglyoxylic acid **429**, an unusual β -lactam **430**, and the dibenzamide **424**.

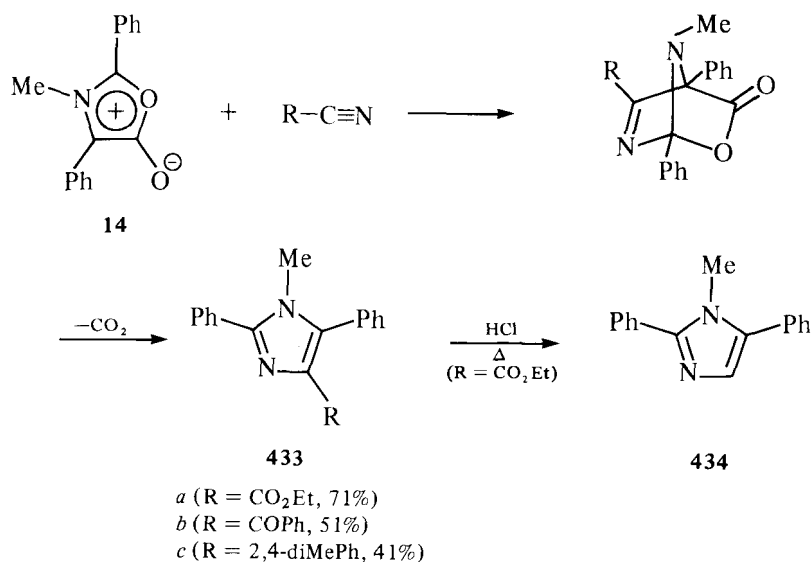


The tautomeric behavior of 2-oxazolin-5-ones **71** and the ability of the meso-ionic form **72** to undergo cycloaddition reactions (Sections 4.2.3.3.1 and 4.2.3.3.3) is reflected in reactions with oxygen under photolytic conditions.^{146,147} Imides **432** are isolated generally under polar conditions, which favor tautomer **72**. An analogous 1:1 adduct **431** is postulated as an intermediate. Products not derived from **72** are also obtained.

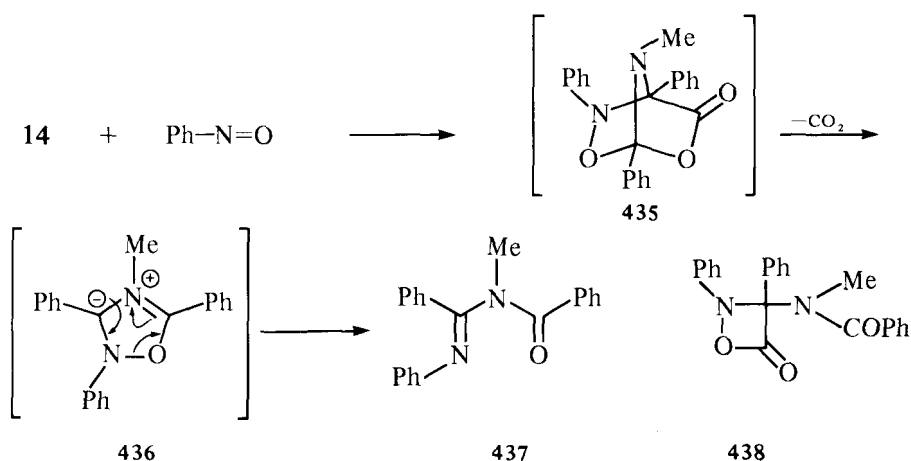


4.2.3.3.7. WITH NITROGEN-CONTAINING DIPOLAROPHILES

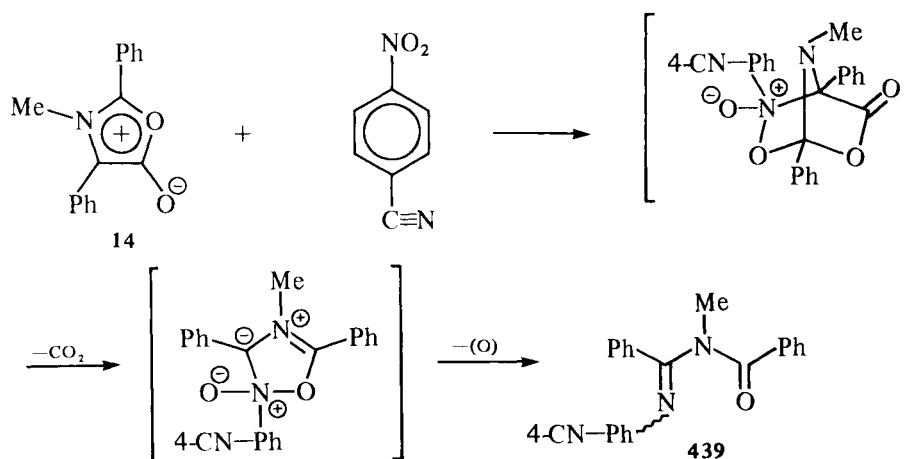
In analogy to the reactions of munchnone **14** with acetylenic dipolarophiles affording pyrroles (Section 4.2.3.3.1), Huisgen^{142,148} has reported that treatment of **14** with activated nitriles provides good yields of imidazoles **433**. The loss of carbon dioxide from a primary cycloadduct adequately rationalizes the formation of products. As a proof of structure, **433a** was degraded with concentrated HCl at 210°C , providing the known imidazole **434**.



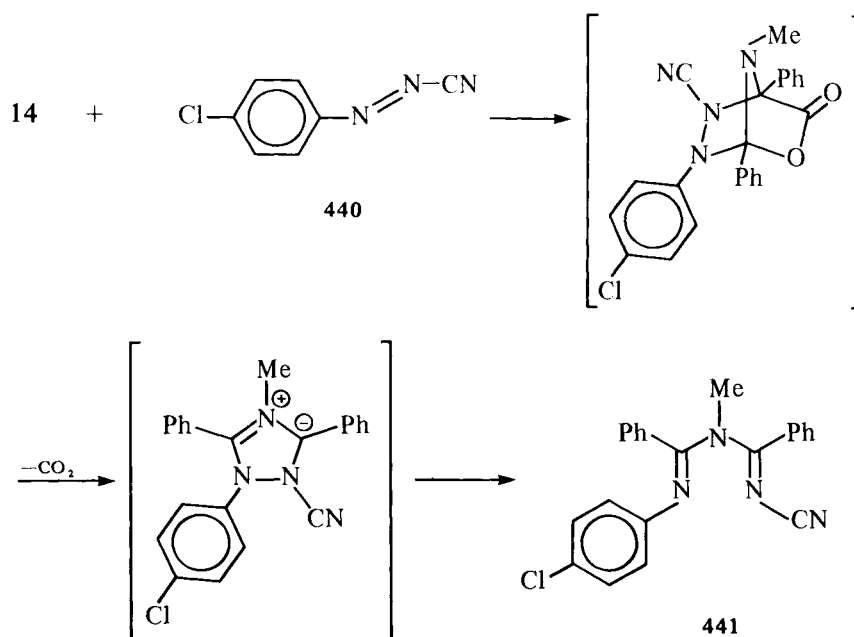
Also reported by the Huisgen group^{142,148} is the reaction of nitrosobenzene with 1,3-oxazolium 5-oxide **14**, which affords a 95% yield of *N*-methyl-*N'*-phenyl-*N*-benzoylbenzamidine **437**. The reaction is envisioned to proceed via the 1,3-dipolar cycloadduct **435**, loss of carbon dioxide, and subsequent rearrangement of the resultant cyclic ylide **436**, although an alternative mechanism involving the [2 + 2]adduct **438** originating from the ketene valence tautomer of **14** (see Section 4.2.3.4) cannot be discounted.



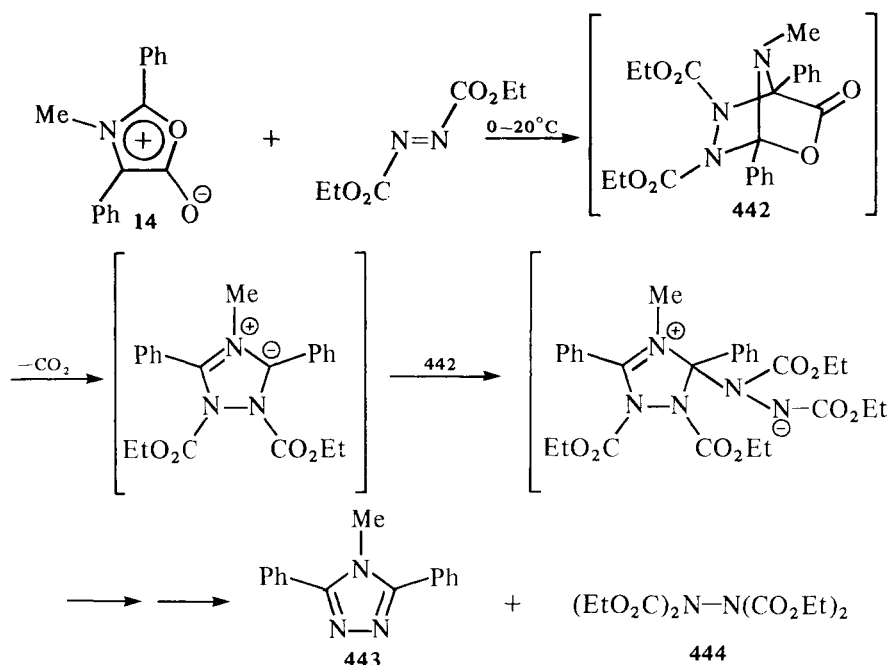
In contrast, 4-nitrobenzonitrile and **14** in xylene at 120°C was reported to give the analogous *N*-benzoylbenzamidine **439** via preferential cyclization across the nitro group, rearrangement after loss of carbon dioxide, and finally extrusion, in an undefined manner, of an oxygen atom.^{142,148}



4-Chlorobenzene *anti*-diazocyanide **440** readily reacts with **14** at the azo group to afford a 60% yield of a bisimine **441** via a similar mechanistic pathway.^{142,148}



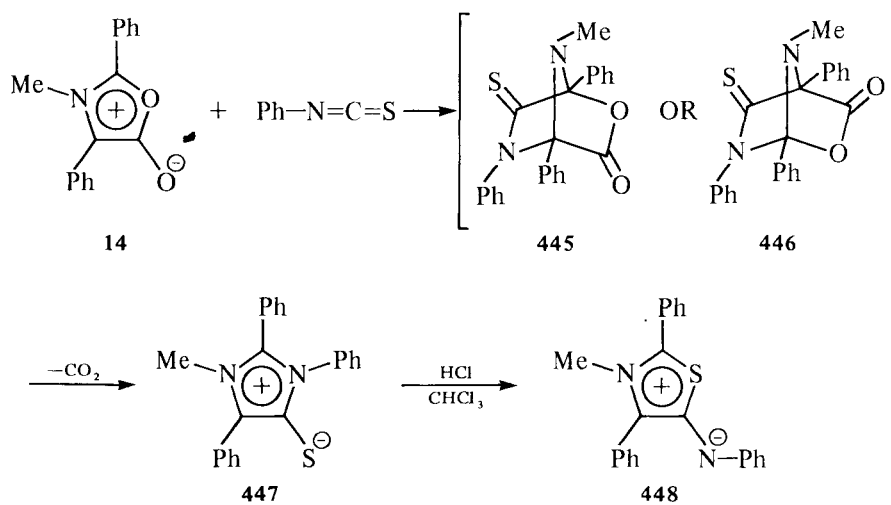
In a more complicated process, munchnone **14** is reported to react with 2 mol of ethyl diazodicarboxylate **442**, affording 4-methyl-3,5-diphenyl-1,2,4-triazole **443** and hydrazinetetracarboxylic ester **444** in 87 and 89% yields, respectively.^{142,148} A mechanism involving addition of the second equivalent of diazo-ester to an intermediate azomethine ylide and subsequent rearrangement can be invoked (Scheme 43).



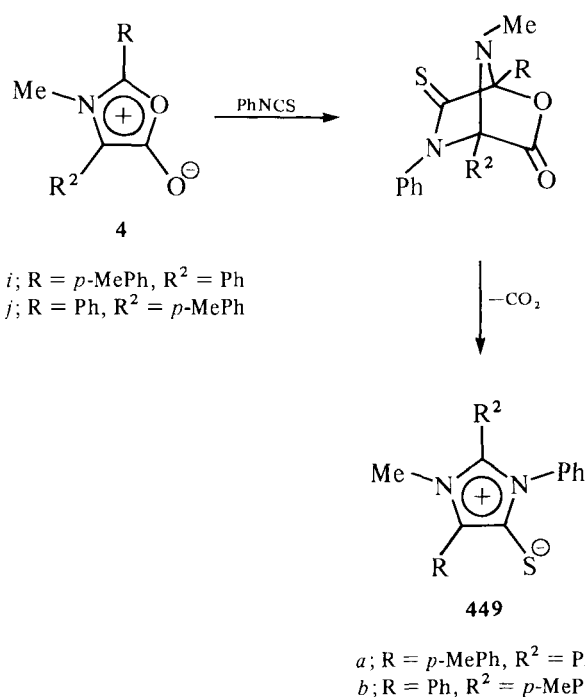
Scheme 43

4.2.3.3.8. WITH HETEROCUMULENES

Huisgen and co-workers have shown that treatment of munchnone **14** with phenyl isothiocyanate at 70°C in xylene affords the 1,3-imidazolium 4-thiolate **447** in 69% yield.¹⁴² The mesoionic imidazole **447** was observed to rearrange under the influence of HCl in chloroform at room temperature to the isomeric 1,3-thiazolium 5-imine **448**.

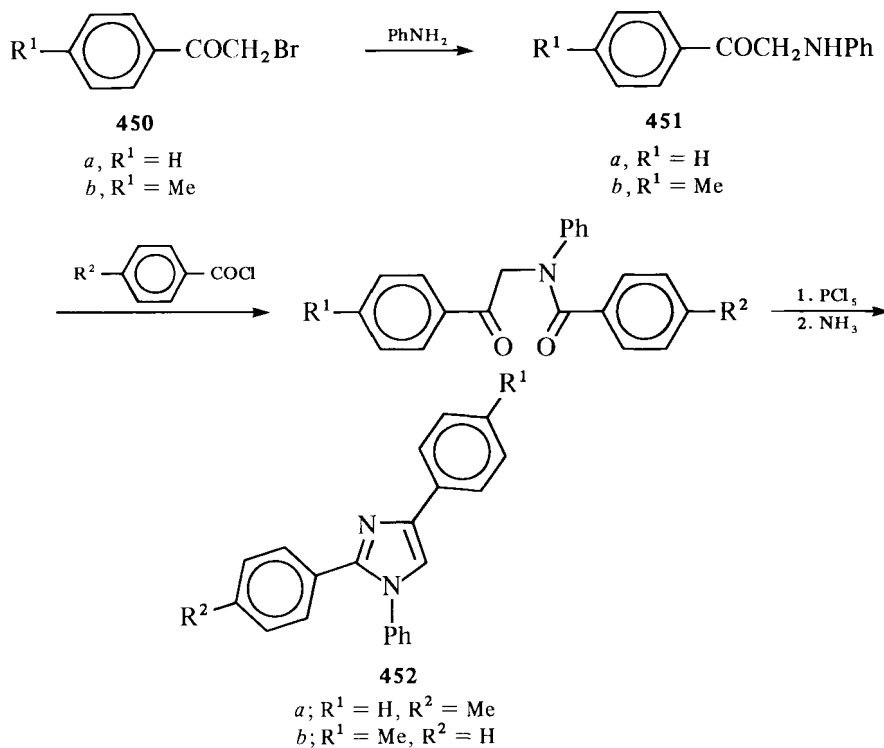


Subsequently, this reaction was extended to include *p*-tolyl isothiocyanate and *p*-nitrophenyl isothiocyanate, which gave analogous 1,3-imidazolium thiones in 87 and 61% yields, respectively.¹⁴⁹ Further investigation of this cycloaddition process indicates that the reaction is greater than 95% regioselective, as shown from the reactions of the asymmetrical munchnones **4i**, **j** with phenyl isothiocyanate.¹⁴⁹ In the case of 1,3-oxazolium 5-oxide **4i**, a 91% yield of 1,3-imidazolium 4-thiolate **449a** is obtained. The isomeric munchnone **4j** forms the corresponding 1,3-imidazolium 4-thiolate **449b** in 87% yield.



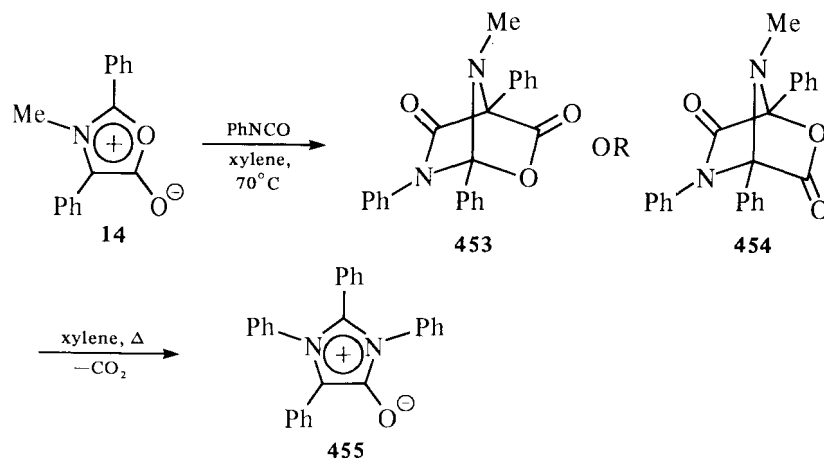
Analogous to the case with carbon disulfide cycloadducts (Section 4.2.3.3.5), the 1,3-imidazolium 4-thione system **449** may be oxidized to the sulfate betaine and then hydrolyzed under acidic conditions to afford two 1-phenyl-2,4-diaryl-imidazoles **452a**, **b**.¹⁴⁹ Proof of structure of these regioisomers was obtained by unambiguous synthesis. Thus, the corresponding phenacyl bromides **450** were treated with aniline, giving the anilinoacetophenones **451**. Subsequent benzoylation and ring closure with phosphorus pentachloride and ammonia gave imidazoles **452a** and **452b**, identical with products originating from **449a** and **449b**, respectively (Scheme 44).

The significance of this investigation is that munchnones **4** add regioselectively to aryl isothiocyanates, affording primary cycloadducts of type **445** rather than the regioisomer **446**. It should be noted that this orientation is opposite to that observed with cycloaddition reactions of munchnones to carbon disulfide (Section 4.2.3.3.5).

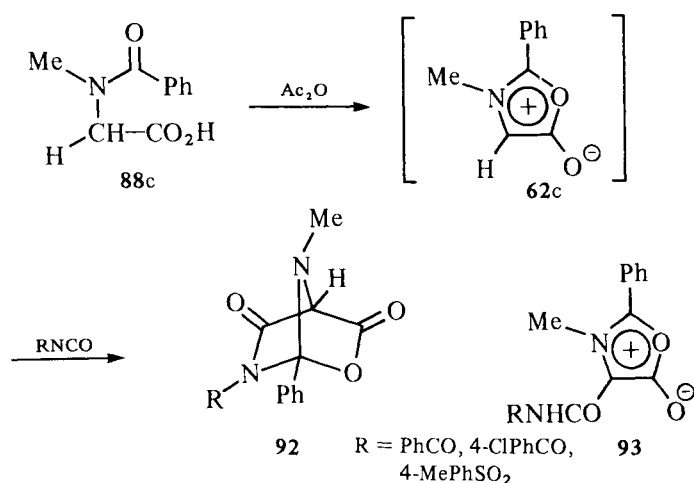


Scheme 44

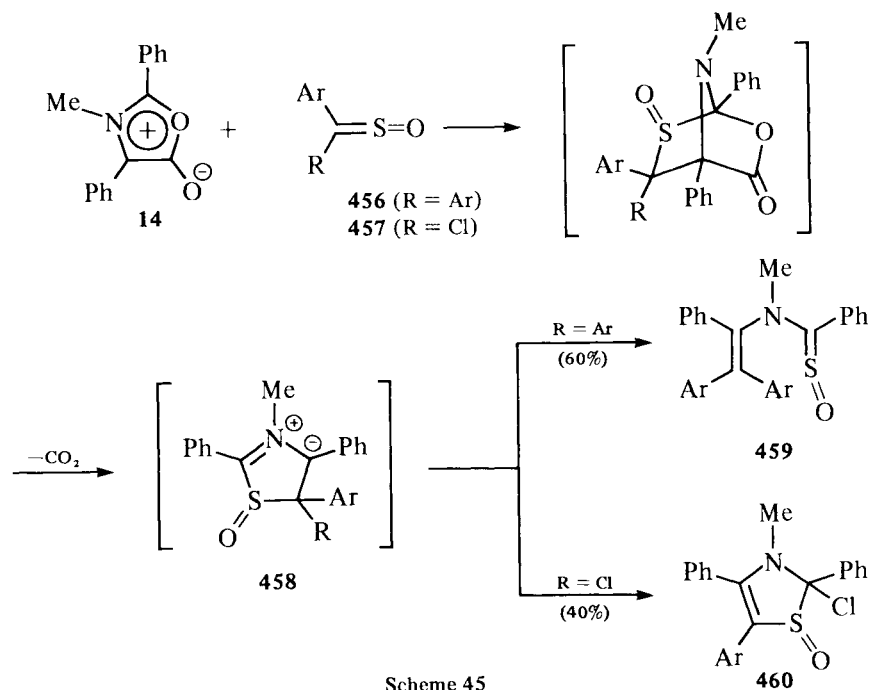
The corresponding reaction of 1,3-oxazolium 5-oxide **14** with phenyl isocyanate was reported by Kato.¹⁵⁰ In contrast to the other reactions with heterocumulenes, a 1:1 primary cycloadduct was *isolated* in 90% yield. This cycloadduct was converted to the 1,3-imidazolium 4-oxide **455** upon refluxing in xylene. The structure of the cycloadduct was formulated as either of two regioisomers **453** or **454**, although subsequent work by Friedrichsen⁵⁶ questions this structural assignment.



3-Methyl-2-phenyl-1,3-oxazolium 5-oxide **62c**, generated *in situ* from *N*-benzoyl-sarcosine **88c** and acetic anhydride, undergoes reaction with activated isocyanates from which 1:1 adducts may be isolated.⁵⁸ The original structural assignment of these adducts as **92** has been reformulated^{56,59} as the 4-acyl munchnones **93** (Section 4.2.3.1).



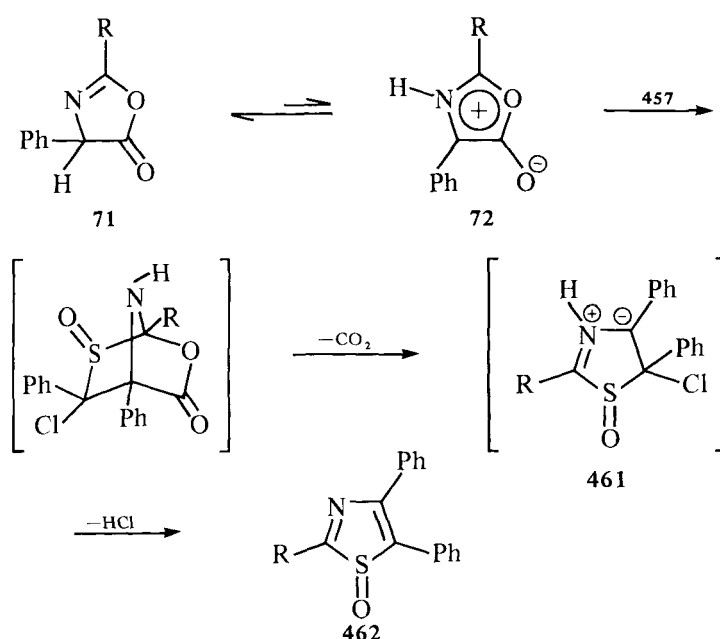
The reaction of sulfur-centered heterocumulenes, commonly called sulfines, with 1,3-oxazolium 5-oxide **14** has been reported by Zwanenburg¹⁵¹ to give two types of products. With the undefined diaryl sulfine **456** the formation of the thio-



Scheme 45

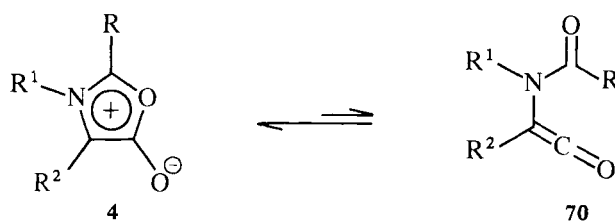
enamide *S*-oxide **459** was observed via rearrangement of the azomethine ylide dipolar intermediate **458**. The chlorosulfine **457** was reported to form a thiazoline *S*-oxide **460**, presumably from chloride transfer from the common intermediate **458** (Scheme 45).

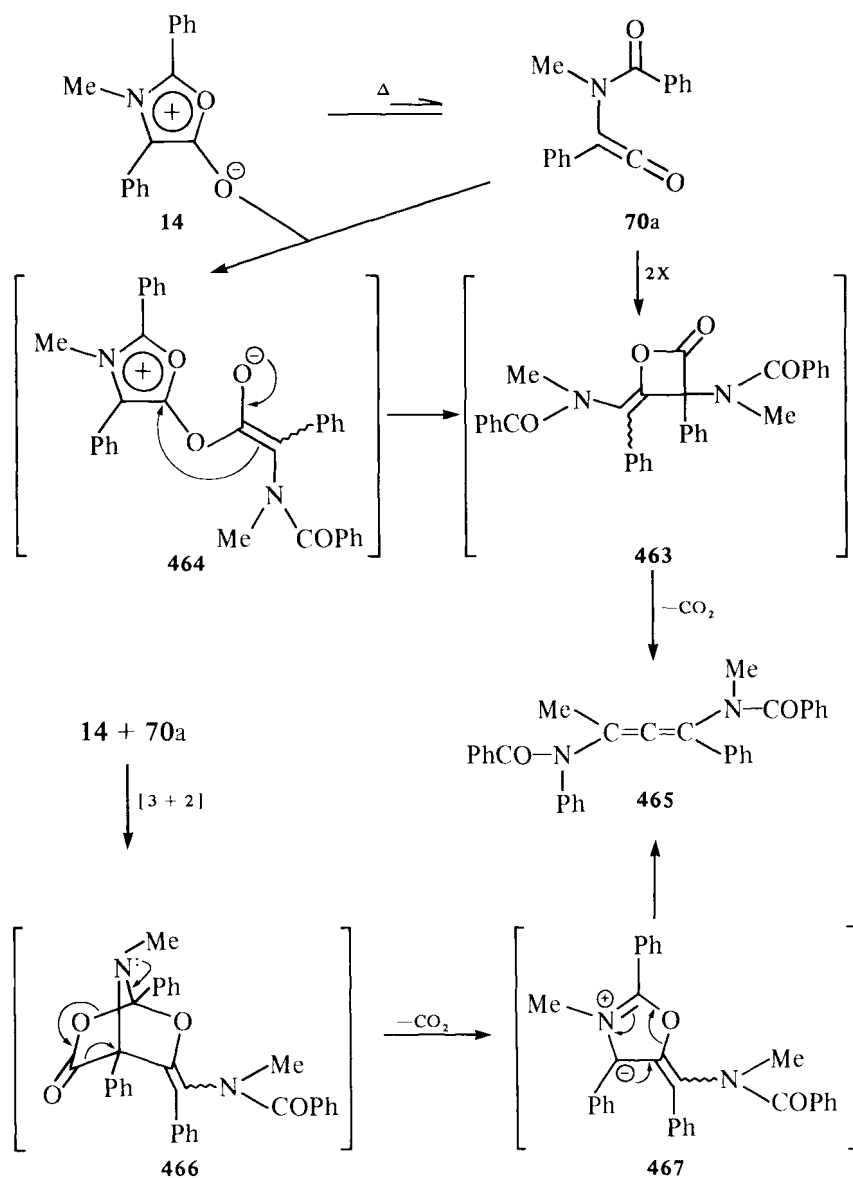
Az lactones **71**, presumably via their mesoionic tautomer **72**, were found¹⁵¹ to react similarly with **457**, providing the thiazole *S*-oxide **462**. In this case, loss of HCl from a dipolar intermediate **461** was postulated to explain the origin of the observed products (Scheme 46).



4.2.3.4. Ring-Chain Valence Tautomerism

As indicated in the preceding sections, 1,3-oxazolium 5-oxides **4** undergo a wide variety of cycloaddition reactions. There exist, however, several types of reactions of **4** that at least in a formal sense involve [2 + 2]- and [4 + 2]cycloadditions of the presumed valence tautomer ketene **70**.





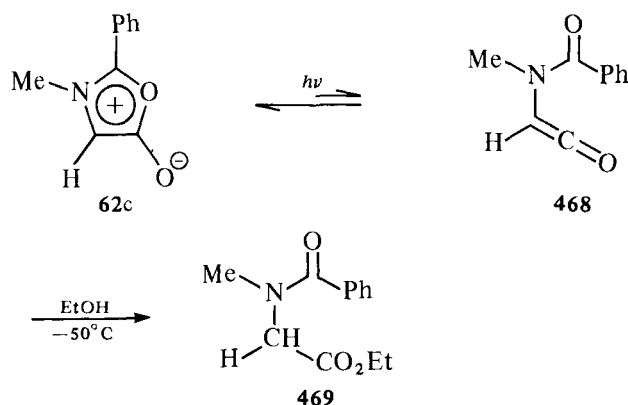
Scheme 47

During investigations into the chemistry of the isolable 1,3-oxazolium 5-oxide **14**, Huisgen observed upon thermolysis in dry xylene at 105°C that a tetrasubstituted allene **465** is formed in 83% yield along with the elimination of 1 mol of carbon dioxide (86% of theoretical).^{15,152} The reaction may be rationalized (Scheme 47) in terms of a dimerization of the ketene tautomer **70a**, followed by elimination of carbon dioxide from **463**. Another interpretation involves the addition

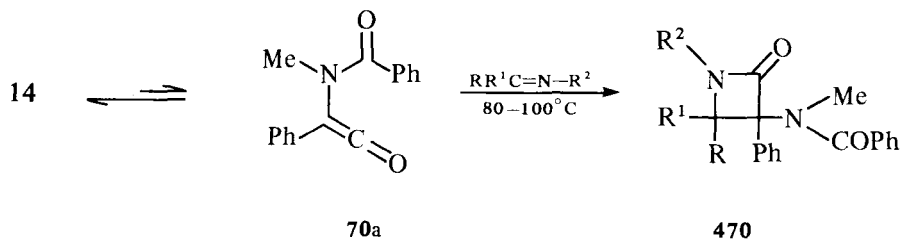
of **14** to **70a**, giving the adduct **464**, which may form allene **465** through cyclization to **463** and subsequent loss of carbon dioxide. Alternatively, 1,3-dipolar cycloaddition of **14** to **70a** would give cycloadduct **466** which, followed by loss of carbon dioxide and rearrangement of the resulting zwitterionic species **467**, would result in the formation of **465**.

Theoretical calculations⁵⁴ of formal charge distribution, heat of formation, dipole moment, and geometry for *N*-methylformamidoketene support the intermediacy of ketene **70** (perhaps only in low concentrations) in the thermolysis of mesoionic **14**.

Potts, Holm, and co-workers have reported¹⁵³ that photolysis of the mesoionic oxazole **62c**, presumably generated *in situ* (see Section 4.2.1), in 5% ethanol–chloroform at -50°C for 41 hr ($\lambda > 330\text{ nm}$) results in a 38% yield of ester **469**. Since no reaction between ethanol and **62c** was observed in the dark under identical reaction conditions, these workers concluded that the intermediary of ketene tautomer **468** best explains the formation of the observed product **469**.



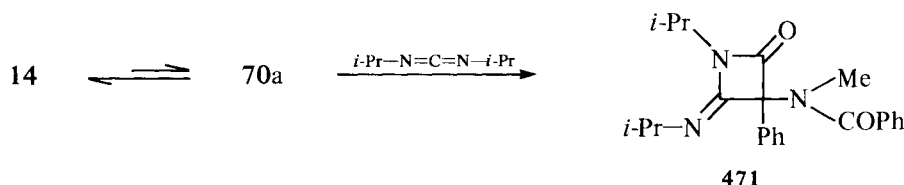
The ketene form **70a** may also be trapped by a [2 + 2] cycloaddition reaction with various imines affording α -acylamino β -lactams **470** in moderate yields^{152,154} (Table 4.30).



Munchedione **14** also reacts with diisopropylcarbodiimide at 137°C to give a similar [2 + 2] adduct **471** in 63% yield.^{152,154} Typical β -lactam carbonyl frequencies for **470** and **471** (ν_{CO} $1730-1808\text{ cm}^{-1}$) are observed.

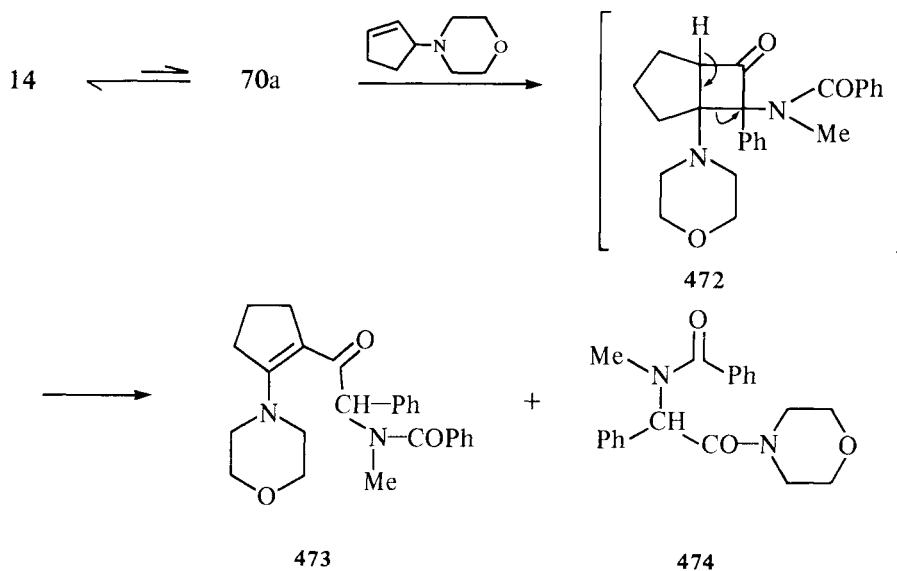
TABLE 4.30. FORMATION OF α -ACYLAMINO β -LACTAMS^{152,154}

R	R ¹	R ²	Percent Yield
H	Ph	Me	62
H	Ph	PhCH ₂	47
H	Ph	Ph	33
Ph	Ph	Ph	25
			56



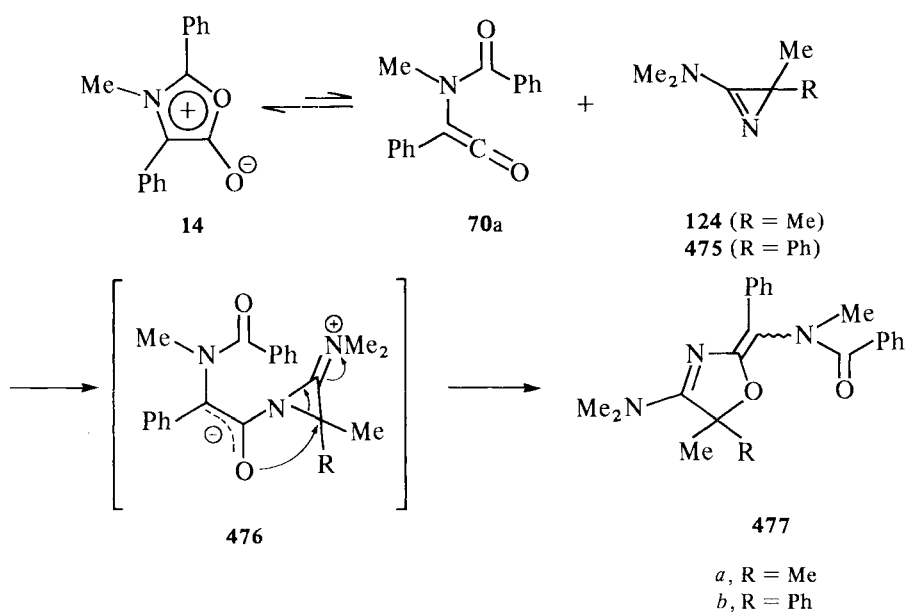
An additional example suggesting the involvement of the valence tautomeric ketene in certain reactions of **14** is provided from its reaction with the “ketenophilic” enamine: 1-morpholinocyclopentene.^{152,154} A 1:1-adduct **473** is formed in 45% yield, presumably through the [2 + 2] primary adduct **472**. The formation of **473** is accompanied by a secondary product **474** (16%), which may arise from the reaction of mesoionic **14** with morpholine (Scheme 48).

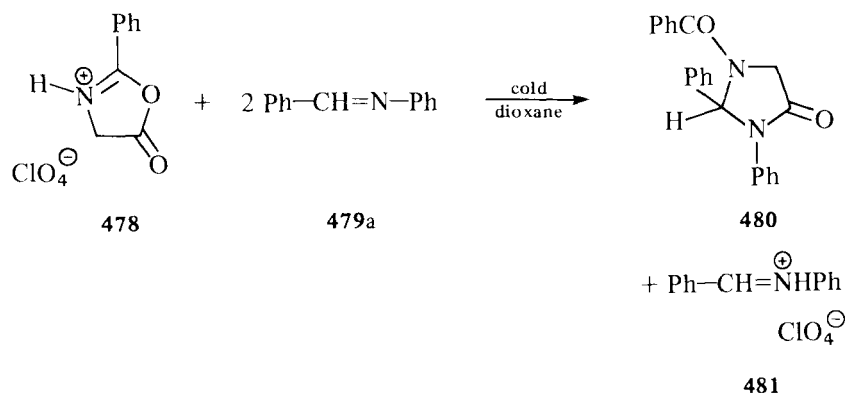
Heimgartner and collaborators found that treatment of 3-dimethylamino-2,2-dimethyl-2*H*-azirene **124** with **14** at room temperature in acetonitrile leads to the isolation in 73% yield of the 1:1-adduct (*Z*)-**477a**.^{64,155} The structure of **477a** was confirmed by X-ray crystallographic analysis. Similarly, reaction of **14** and 2-methyl-2-phenyl azirene **475** was found by these researchers to give adduct **477b** as an *E:Z* mixture. The overall reaction was rationalized by addition of the azirene to the ketene tautomer **70a** to form the zwitterionic intermediate **476** which is thus transformed into products. It should be appreciated that **476** can also be derived by attack of the aminoazirene onto the carbonyl of munchnone **14** without invoking the ketene tautomer **70a**.



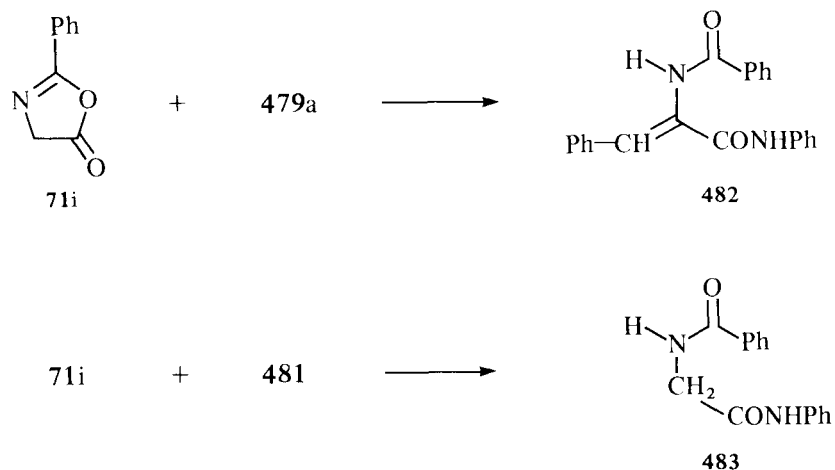
Scheme 48

In reactions of 2-oxazolin-5-ones (azlactones) and their perchlorate salts with Schiff bases, Knowles and co-workers offer an alternative explanation to the mechanistic course of the reaction of mesoionic oxazolones and various imines.¹⁵⁶ It was found that treatment of the oxazolonium perchlorate **478** with two equivalents of benzylideneaniline **479a** rapidly affords the known 1-benzoyl-2,3-diphenyl-

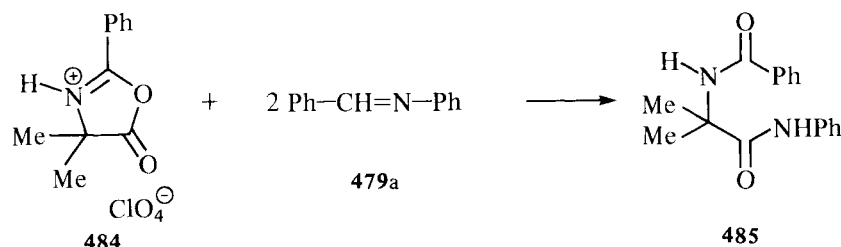




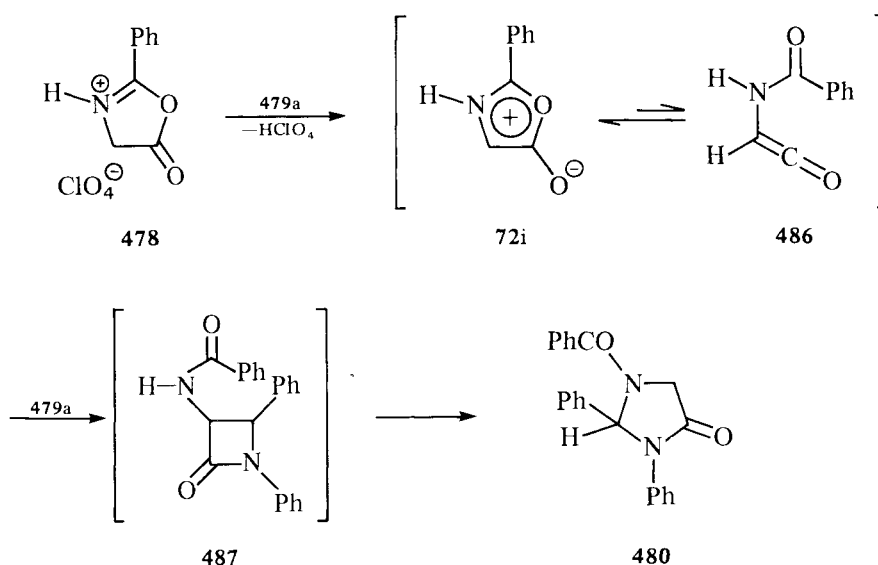
imidazoline-4-one **480** in 54% yield together with the theoretical amount of benzylideneanilinium perchlorate **481**. Accordingly, substituted Schiff bases form analogous imidazolidinones in 16–34% yield. Knowles points out certain reactions pertinent to the mechanistic course of the formation of **480**. First, initial proton transfer from perchlorate **478** to the Schiff base **479a** to form the oxazolone **71i** is ruled out since **71i** reacts with benzylideneaniline **479a** to yield α -benzamido-cinnamanilide **482** and with benzylideneanilinium perchlorate **481** to give hippuranilide **483**. Attack by **479a** onto the carbonyl group of **478** and subsequent



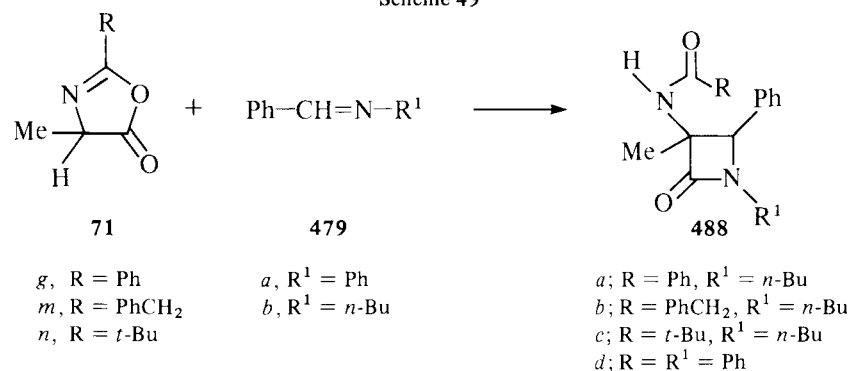
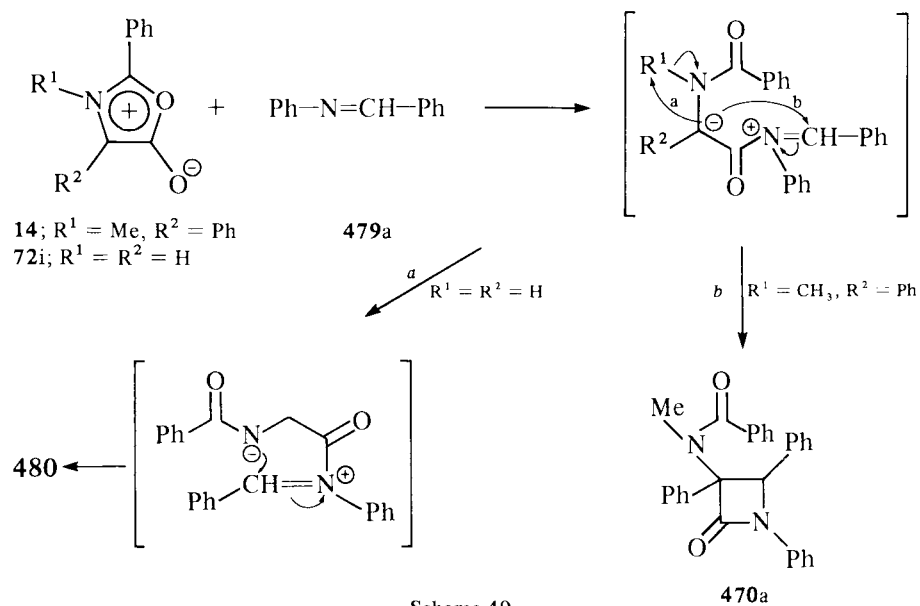
cyclization is not probable because the 4,4-disubstituted oxazolonium perchlorate **484** does not yield an imidazolidinone on treatment with **479a**; the anilide **485** is formed instead. One further explanation of the reaction course would be to involve the intermediacy of the mesoionic tautomer **72i**, formed upon deprotonation of **478** at the 4-position with benzylideneaniline **479a**. In this regard, it is important to note that the 4,4-disubstituted oxazolonium perchlorate **484** cannot undergo a similar deprotonation to form the corresponding *N*-unsubstituted munchnone. If analogous to the reactions of *N*-substituted mesoionic oxazolones with



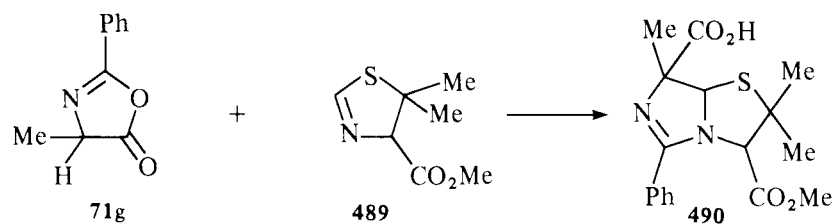
imines (loc. cit.), an azetidinone **487** would be formed via the valence ketene tautomer **486**. However, since **487** is known¹⁵⁷ to rearrange to the imidazolidinone **480** only at elevated temperatures, and no evidence was found for a strained ring carbonyl by following the course of the reaction by IR spectroscopy, the [2 + 2] mechanism was considered unlikely. Instead, the authors propose a mechanism that would explain the formation of products from both the *N*-unsubstituted munchnone tautomer **72i** and the *N*-substituted munchnone **14** with imines. Thus, both reactions may proceed by initial attack by the imine **479a** on the munchnone carbonyl; this is followed by carbon-carbon bond formation in the case of the *N*-substituted munchnone reaction to form azetidinone **470a** (path *b*), while in the case of **72i**, a prototropic shift intervenes and the imidazolidinone **480** is produced (path *a*) as summarized in Scheme 49.

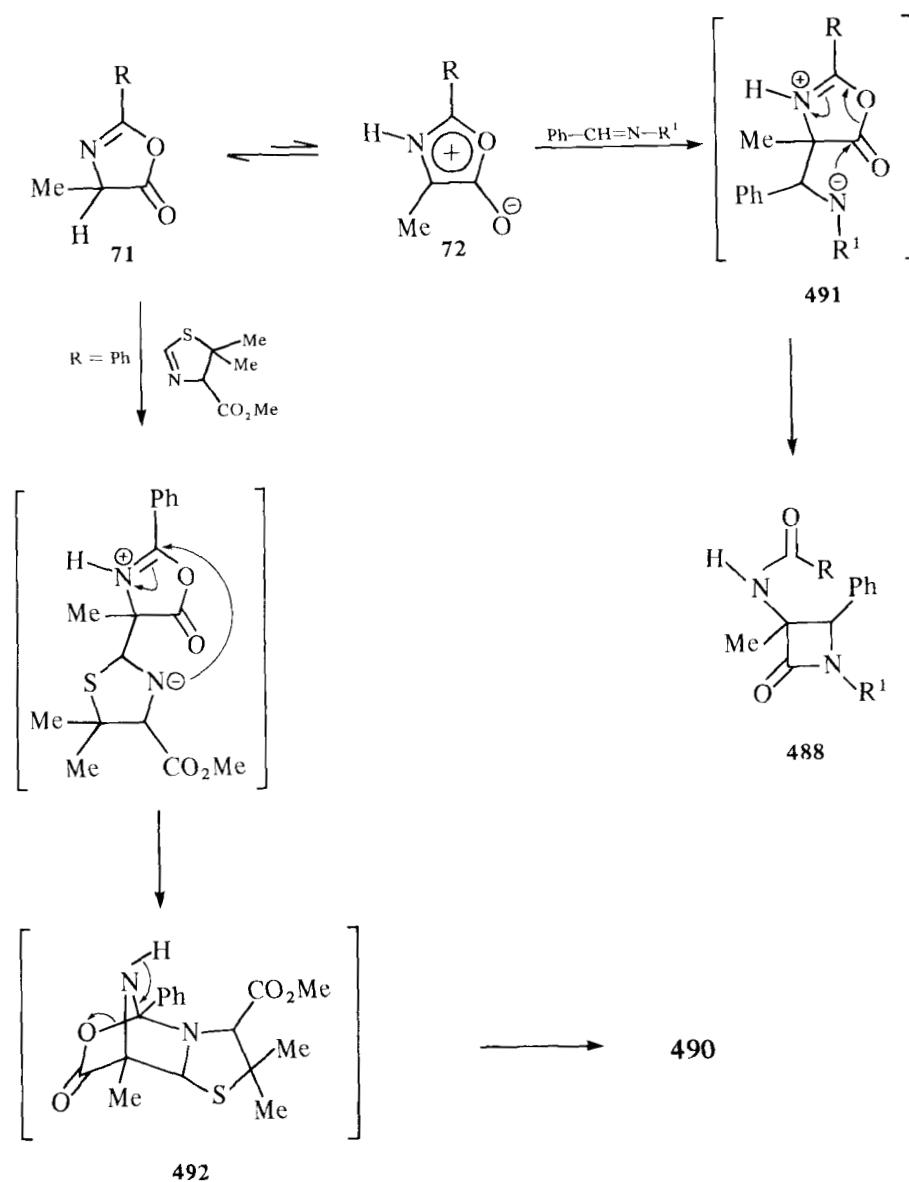


It is of interest to compare the above results with related work reported subsequently (and without reference to earlier work). Reactions of the 4-substituted azlactones **71** with imines **479a** and **479b** were described by Prasad and Petrizilka¹⁵⁸



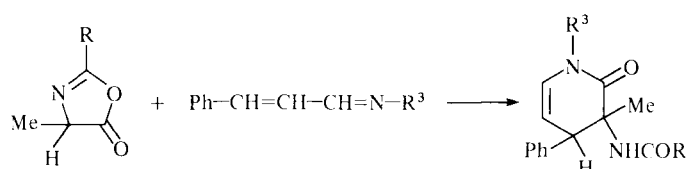
as forming products assigned the azetidinone structure **488**. The reaction of **71g** with the cyclic imine **489**, however, affords a product that was assigned structure **490**.¹⁵⁸ Mechanistically, both types of products were rationalized by an initial nucleophilic attack of mesoionic tautomer **72** onto the imine (Scheme 50) rather than attack by the imine nitrogen onto the C-5 position of munchnone **72i** (Scheme 49). In the case of acyclic imines, the resultant adduct **491** undergoes ring closure





Scheme 50

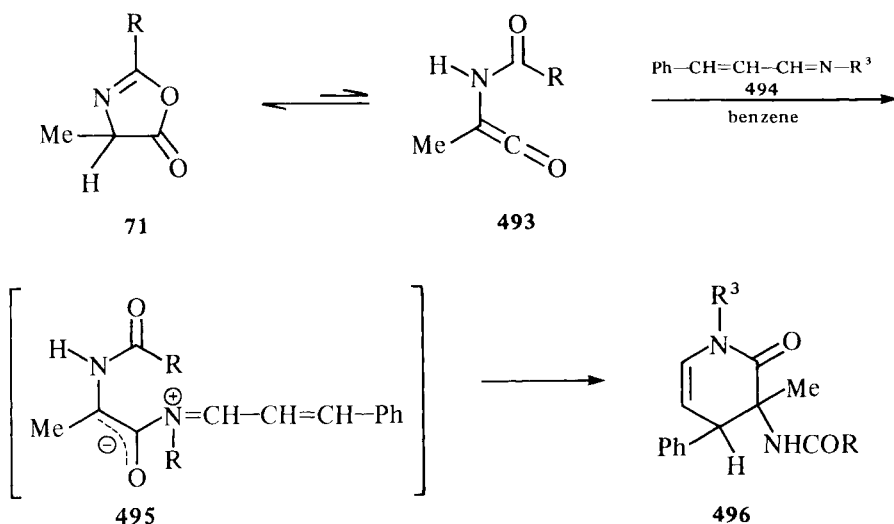
to **488** or, in the reaction with the thiazoline **489**, proceeds through a tricyclic adduct **492**, which rearranges to the assigned product **490**. It is curious that the presence of a methyl group at the C-4 position of **72** apparently changes the product of the reaction with benzilideneaniline **479a** from imidazolidinone **480** to the azetidinone **488d**. Intermediate **492** may also be formally derived as the primary cycloadduct of a 1,3-dipolar cycloaddition reaction of **72g** with thiazoline **489**.

TABLE 4.31. FORMATION OF α -PYRIDONES FROM OXAZOLONES AND CINNAMALDEHYDE ANILS

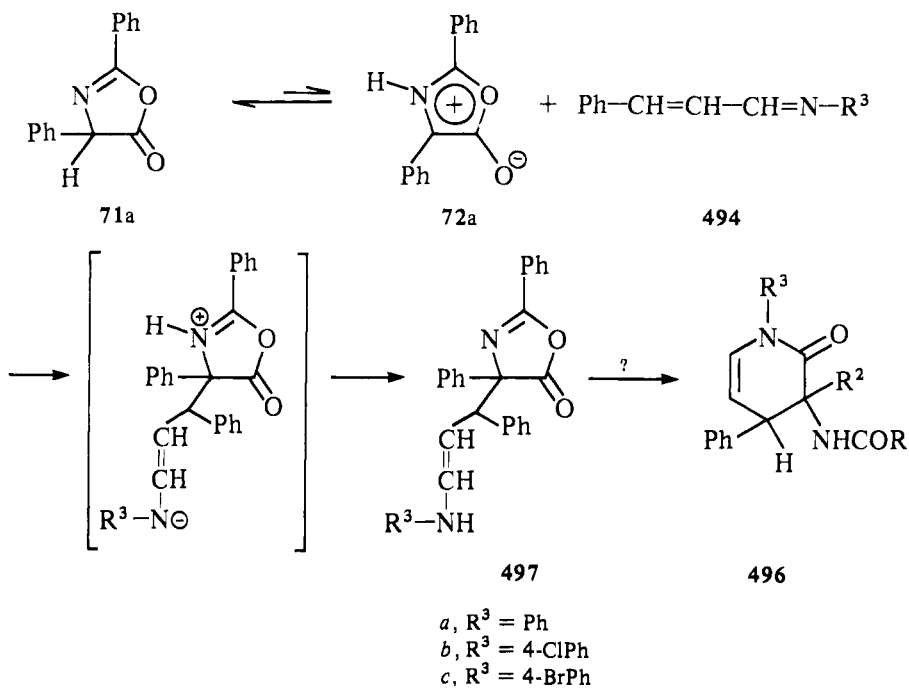
R	R ³	Percent Yield	Reference
Ph	Ph	85	159, 160
Ph	4-MeOPh	90	160
Ph	4-BrPh	90	160
Ph	4-ClPh	85	160
Ph	2,4-Cl ₂ Ph	25	160
Ph	4-MePh	90	160
Ph	Me	70	160
Ph	Cyclo-C ₆ H ₁₁	70	160
4-ClPh	Ph	74	161
4-ClPh	4-ClPh	72	161
4-ClPh	4-MePh	78	161
4-ClPh	4-MeOPh	80	161
4-MeOPh	Ph	80	161
4-MeOPh	4-ClPh	82	161
4-MeOPh	4-MePh	85	161
4-MeOPh	4-MeOPh	90	161
4-NO ₂ Ph	Ph	70	161
4-NO ₂ Ph	4-ClPh	68	161
4-NO ₂ Ph	4-MePh	72	161
4-NO ₂ Ph	4-MeOPh	75	161
PhCH ₂	Ph	75	161
PhCH ₂	4-ClPh	72	161
PhCH ₂	4-MePh	77	161
PhCH ₂	4-MeOPh	80	161

The reports from Sandhu and co-workers focus on the reaction of various 2-oxazolin-5-ones (azlactones) with α,β -unsaturated imines (i.e., cinnamaldehyde anils) and find that different type products are formed.¹⁵⁹⁻¹⁶² Thus, azlactones **71** ($R^2 = \text{Me}$), which may equilibrate with the ketene tautomer **493**, undergo reaction with the vinologous imines **494** to form α -pyridones **496** in yields ranging from 25 to 90% (Table 4.31). The intermediacy of the zwitterionic adduct **495** is implicated since the reaction rate was found to be dependent on the nucleophilicity of the imine nitrogen. Under no circumstances was evidence found for the formation of β -lactam or 1,3-dipolar cycloaddition products.

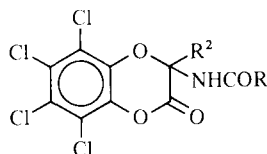
In a similar reaction with 2,4-diphenyl-2-oxazolin-5-one **71a**, the products isolated in 85–90% yield were assigned as the 4-substituted azlactones **497** (Scheme



51).¹⁶² The authors did not speculate, however, whether compounds of type **497** may actually be the intermediates formed during the preparation of α -pyridones **496** via nucleophilic attack of the enamine nitrogen onto the azlactone carbonyl with concomitant ring-opening and prototropic shift.



Scheme 51

TABLE 4.32. FORMATION OF DIOXINONES FROM *N*-ACYLAMINO ACIDS AND *O*-CHLORANIL^{163, 164}

R	R ²	Percent Yield
Ph	PhCH ₂	73
Ph	<i>i</i> -Pr	90
Ph	Me	95
Ph	H	61
Ph	Ph	93
Ph	<i>i</i> -Bu	88
Me	PhCH ₂	49

Another type of reaction of azlactones that in a formal sense might involve a ketene tautomer intermediate was reported by Stammer and collaborators.^{163, 164} Azlactones **71**, generated *in situ* by the reaction of either *N*-benzoylamino acids **73** (R = Ph) or D,L-phenylalanine **75h**, react with *o*-chloranil **498** to provide good yields (Table 4.32) of dioxinones **499**. The authors formulate an addition mechanism involving the tautomeric mesoionic form **72** and make no mention of the possibility of a ketene-type process.

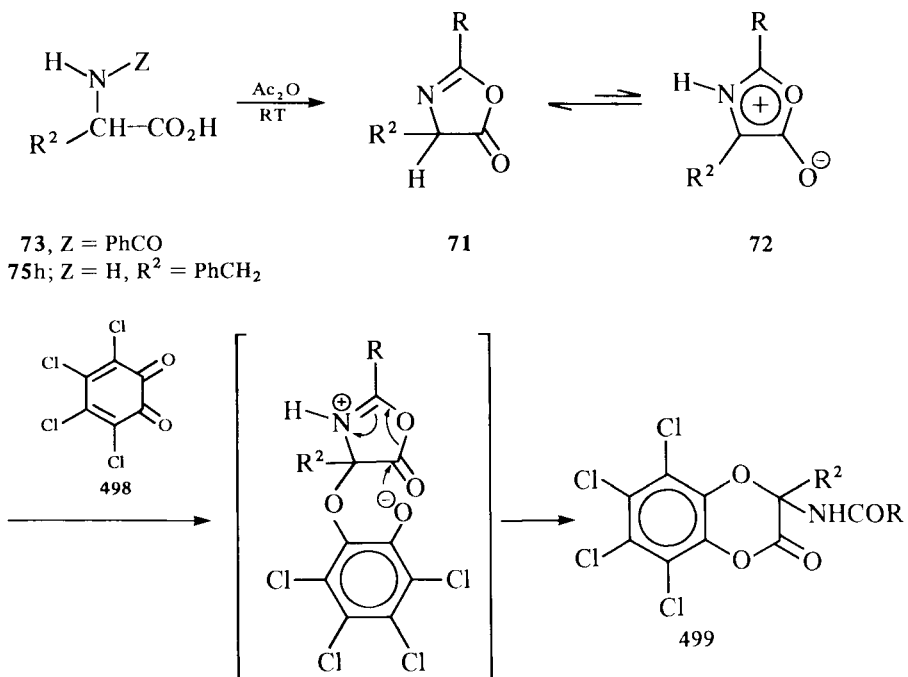
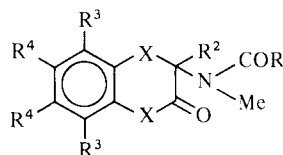
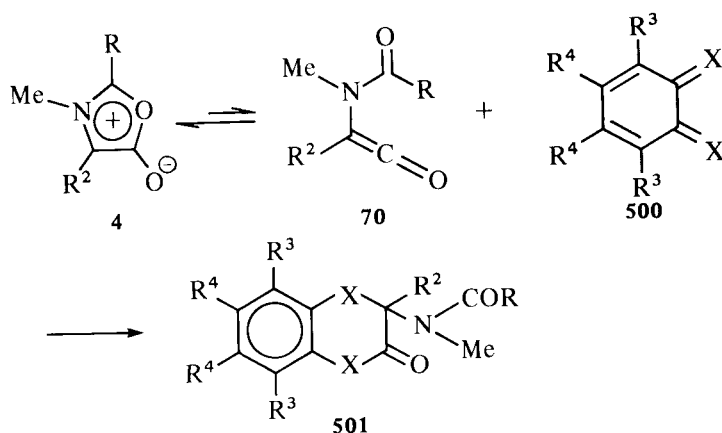
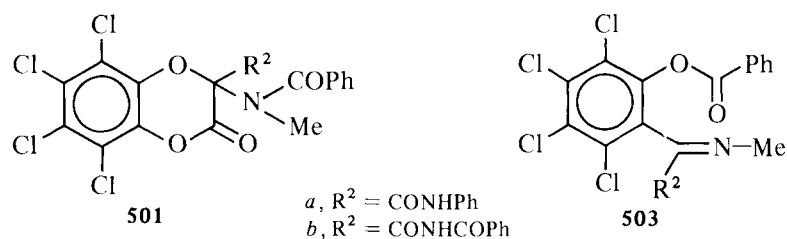


TABLE 4.33. FORMATION OF 1:1 CYCLOADDUCTS FROM 1,3-OXAZOLIUM 5-OXIDES AND *O*-QUINONES AND *O*-QUINONE IMINES

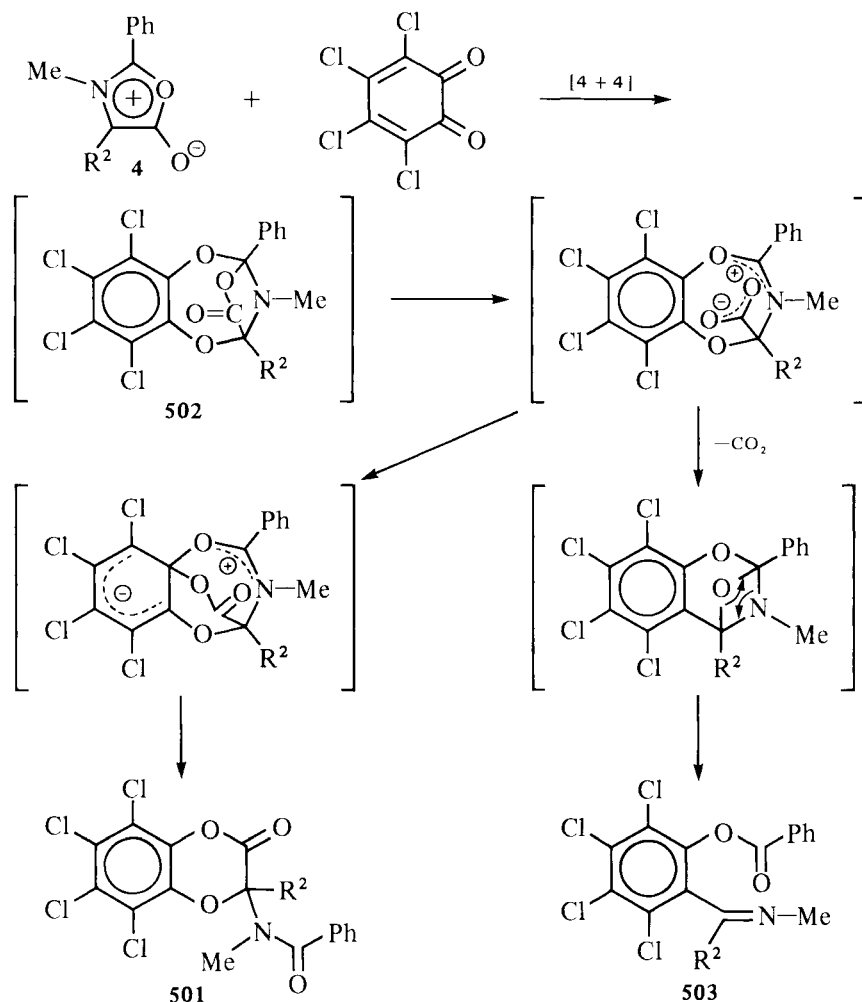
R	R ²	R ³	R ⁴	X	Percent Yield	Reference
Ph	Ph	H	H	O	49, 45	23, 165
Ph	Ph	Cl	Cl	O	96	23, 165
Ph	Ph	H	Me	NSO ₂ Ph	86, 74	23, 165
Ph	H	Cl	Cl	O	88	56
Ph	COMe	Cl	Cl	O	27	56
Ph	CONHPh	Cl	Cl	O	94	56
Ph	CONHCOPh	Cl	Cl	O	49	56
Ph	Ph	Br	Br	O	82	23
4-MeOPh	4-MeOPh	Cl	Cl	O	82	23
4-MeOPh	4-MeOPh	Br	Br	O	82	23
4-MeOPh	4-MeOPh	H	Me	NSO ₂ Ph	63	23

An extensive study of the reaction of *N*-substituted 1,3-oxazolium 5-oxides and similar *o*-quinoid compounds has recently been reported by Friedrichsen and collaborators.^{23,56,165,166} Thus, treatment of the isolable mesoionic system **4** ($R^1 = \text{Me}$) with substituted *o*-quinones or their diimine analogs **500** at room temperature provides respectable yields of 1:1 adducts **501** (Table 4.33). Although the reaction products **501** can formally be derived by a [4 + 2]cycloaddition process involving the ketene tautomer **70**, evidence is presented that strongly suggests instead that a [4 + 4]cycloaddition reaction of the mesoionic **4** and the *o*-quinoid partner **500** occurs forming a 1:1 adduct that then rearranges to more stable products. The following is representative of such evidence.

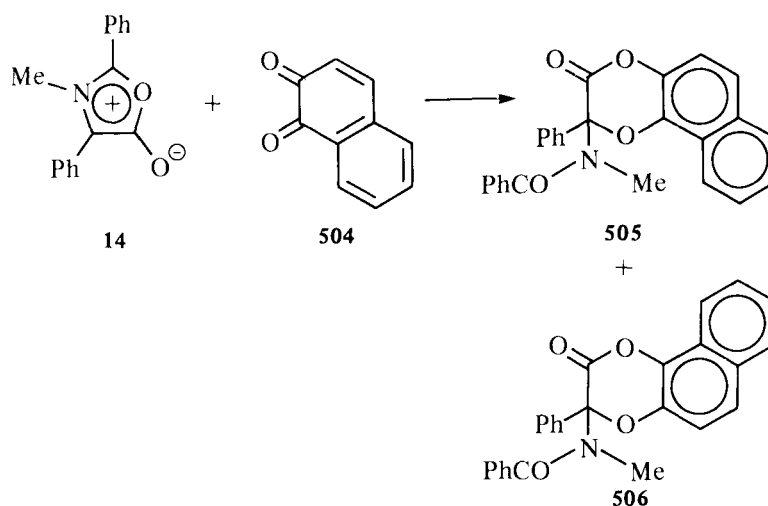




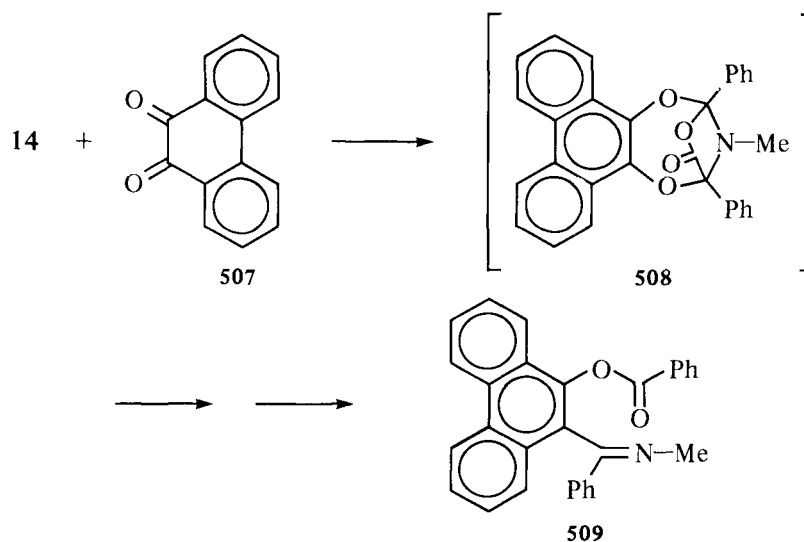
During the formation of **501a** and **501b**, additional products **503a** and **503b** were isolated, the structure of the latter being confirmed by X-ray analysis.⁵⁶ A detailed mechanism may be drawn that explains the formation of both **501** and **503** through the intermediacy of the [4 + 4]adduct **502** as indicated in Scheme 52.



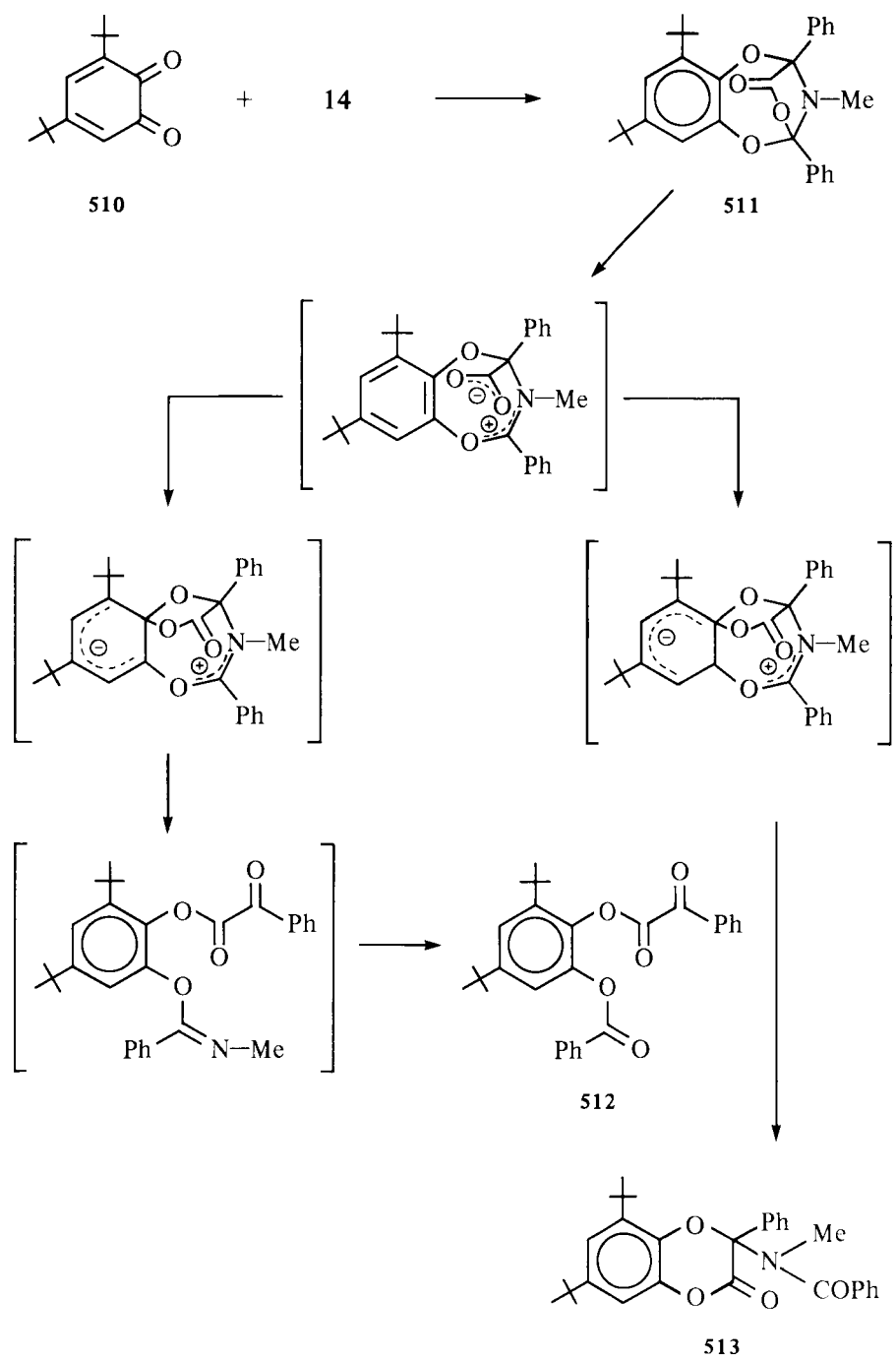
Scheme 52



α -Naphthoquinone **504** and **14** combine to provide low yields of regioisomeric 1:1-adducts **505** and **506**.²³ In contrast, 9,10-phenanthrenequinone **507** and **14** afford an 88% yield of **509**, similar in structure to **503**, which possibly results from an initially formed [4 + 4]adduct **508** with subsequent loss of carbon dioxide in a similar manner to that depicted in Scheme 52.²³



Finally, 3,5-di-*tert*-butyl-*o*-benzoquinone **510** was found to form an *isolable* [4 + 4]adduct **511** by reaction with munchnone **14**.¹⁶⁶ Under thermal conditions compound **511** rearranges to give **512** and **513** in 34 and 45% yields, respectively. The structure of **512** was confirmed by X-ray spectroscopic analysis. The route as depicted in Scheme 53 mechanistically shows the proposed derivation of the products.



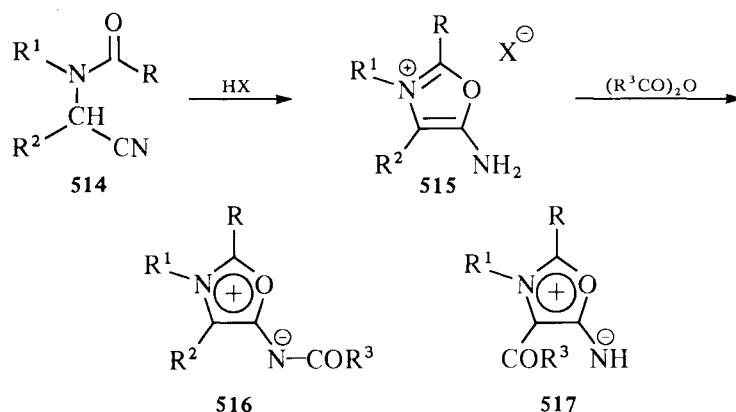
Scheme 53

In conclusion, the intermediacy of ketene tautomeric forms of mesoionic oxazoles in the reactions summarized above continues to be speculative. Although many products appear to be derived via a ketene cyclization process, no spectroscopic evidence has yet to be presented to support the ketene case, and several alternative mechanistic pathways are conceivable for the formation of the cycloaddition products. Perhaps future reports will clarify this issue.

4.3. 1,3-OXAZOLIUM 5-IMINES (MUNCHNONE IMINES)

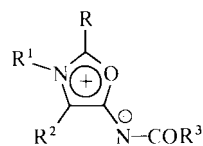
4.3.1. Synthesis

Heterocyclization of α -acylaminonitriles **514** with trifluoroacetic, chlorosulfonic, or hydrochloric acid affords 5-amino-1,3-oxazolium salts **515**.¹⁶⁷⁻¹⁷⁰ Further treatment of **515** or directly on **514** under Dakin–West conditions with acid anhydrides provides^{169,171,172} the *N*-acylated mesoionic 1,3-oxazolium 5-imines **516**. As seen in Table 4.34, only *N*-acylated munchnone imines are reported to be isolable. It is also interesting to note that even in the presence of excess acid anhydride that C-4-acylated products (**516** $R^2 = \text{COR}^3$) are not reported, in contrast to the ability of isoelectronic 4-unsubstituted 1,3-oxazolium 5-oxides to undergo C-4 acylations (Section 4.2.3.1). Roesler and Fleury,¹⁶⁹ in the original report on the mesoionic formation reaction from **514** ($R^2 = \text{H}$), assigned the structure as the C-4 acyl derivative **517**; however, further work by Götz and Zeile¹⁷¹ and an extensive reinvestigation by Fleury and co-workers¹⁷² gave proof of **516** as the correct structure. This was achieved through ¹³C NMR studies¹⁷² (Section 4.3.2), hydrolytic degradation¹⁷¹ (Section 4.3.3.1), and an unambiguous 1,3-dipolar cycloaddition reaction¹⁷² (Section 4.3.3.3.1).

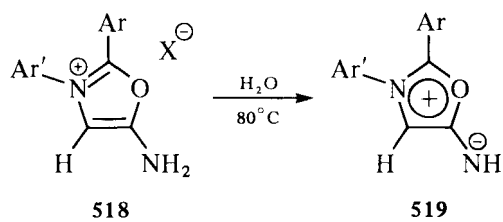


Fleury and collaborators also reported upon treatment of 1,3-oxazolium salts **518** with water at 80°C that highly colored, unpurified products could be isolated and postulated the mesoionic imine **519** as a possible structure.¹⁶⁹ Attempted recrystallization of **519c** from aqueous ethanol gave the amide **520**.

TABLE 4.34. ISOLABLE 1,3-OXAZOLIUM 5-ACYLIMINES

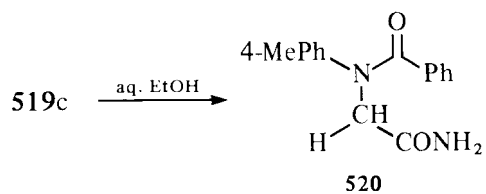


R	R ¹	R ²	R ³	Percent Yield	Reference
Ph	Ph	H	CF ₃	79	169
4-NO ₂ Ph	Ph	H	CF ₃	87	169
				85	172
Ph	4-MePh	H	CF ₃	81	169
Ph	4-ClPh	H	CF ₃	82	169, 171
Me	Me ₂ N	H	Me	83	171
Me	Me ₂ N	H	CCl ₃	53	171
4-ClPh		H	Me	73	171
PhCH ₂		Et	CF ₃	51	171
4-MePh		Et	CF ₃	59	171
Me	Me	H	CF ₃	58	171
4-NO ₂ Ph	Me	H	CF ₃	89	172



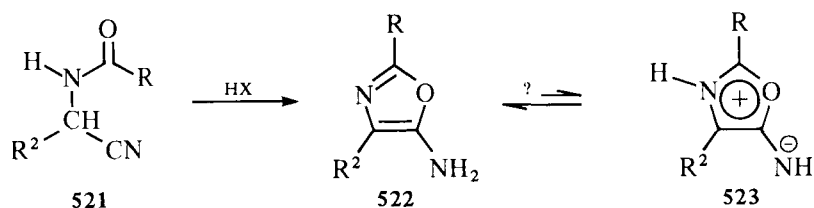
518

519

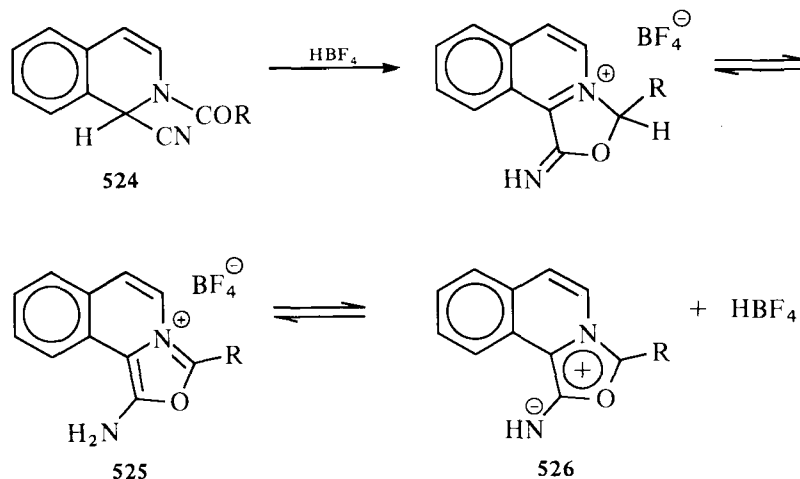
a; Ar = Ph, Ar' = Ph*b*; Ar = 4-NO₂Ph, Ar' = Ph*c*; Ar = Ph, Ar' = 4-MePh*d*; Ar = Ph, Ar' = 4-ClPh

520

5-Aminooxazoles **522** are prepared¹⁷³ by acidic cyclization of *N*-unsubstituted α -acylaminonitriles **521**. The contribution of the tautomeric *N*-unsubstituted mesoionic form **523** was considered unlikely in this case.



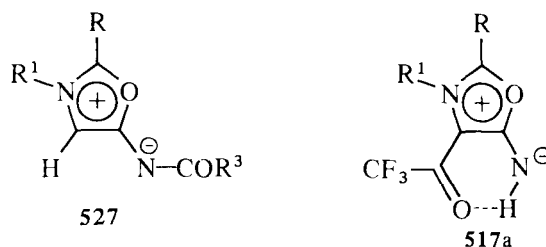
Reissert salts (e.g., **525**), which are derived from hydrofluoroboric acid treatment of the isoquinoline Reissert compound **524**, exist in solution as equilibrium mixtures of several forms, including the 1,3-oxazolium 5-imine **526**. Further discussion of the intermediacy of this form in cycloaddition reactions is provided in Section 4.3.3.3.2.



4.3.2. Structure and Spectral Properties

4.3.2.1. Infrared Spectra

Isolable 4-unsubstituted *N*-acylated-1,3-oxazolium 5-imines **527** are characterized by IR absorption bands between 3125 and 3200 cm⁻¹.^{169,171,172} These can be ascribed to a $\nu_{\text{C4-H}}$ stretching frequency; however, assignment of these bands to the intramolecularly H-bonded N-H of the alternative C-4-acylated isomer **517a** cannot be excluded.¹⁷² Other characteristic absorptions for **527** fall between 1654 and 1540 cm⁻¹. Thus, IR spectral evidence alone could not be used for definitive structural assignments.

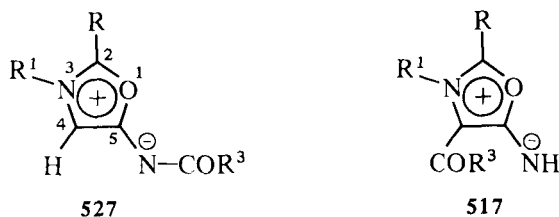


4.3.2.2. Ultraviolet Spectra

Fleury has measured UV spectra for the *N*-trifluoroacetyl munchnone imines **516**.^{169,170} Three absorption maxima are observed at 340–384, 245–253, and 194–196 nm. The first maximum is consistent with an oxazole ring. These compounds degrade rapidly in alcohol solvent used for UV determination, and thus extinction coefficients could not be accurately determined. Similarly, Götz has reported¹⁷¹ UV values for analogous acylated systems **516**.

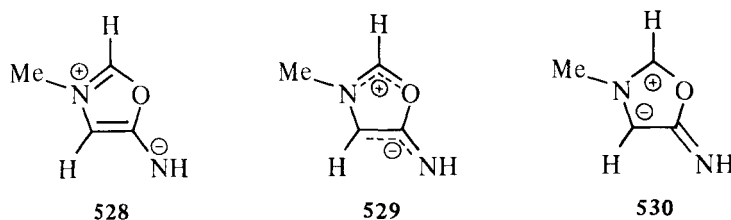
4.3.2.3. NMR Spectra

Proton NMR spectra were obtained for **527**. The assignment of the *N*-acylation product **527** versus the *C*-acylation product **517** is inconclusive based on these data due to aromatic masking of the C-4 hydrogen. The presence of an exchangeable NH proton was initially described by Fleury¹⁶⁹ yet was refuted by Götz¹⁷¹ from observations based on a similar series. An in-depth reinvestigation by Fleury and co-workers using ¹³C NMR spectroscopy clearly identified the position of attachment of the acyl group at the exocyclic 5-imino nitrogen.¹⁷² The off-resonance signal assigned to C-4 appears as a doublet, thus establishing the correct structure as **527**.



4.3.2.4. Molecular Orbital Calculations

A MINDO/3 study of mesoionic oxazoles was reported by Dewar and Turchi.⁵⁴ The theoretical 1,3-oxazolium 5-imine was subjected to molecular orbital treatment. The study emphasizes that these mesoionic species cannot be satisfactorily

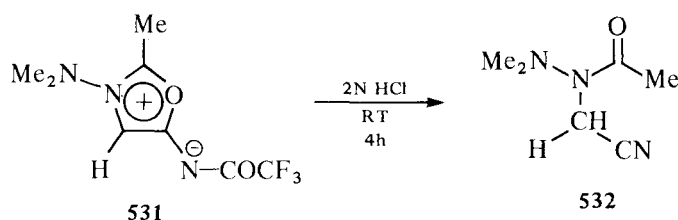


represented by single classical structures such as **528** but are better depicted from calculated charge distributions by structures **529** and **530**.

4.3.3. Reactions

4.3.3.1. With Nucleophiles

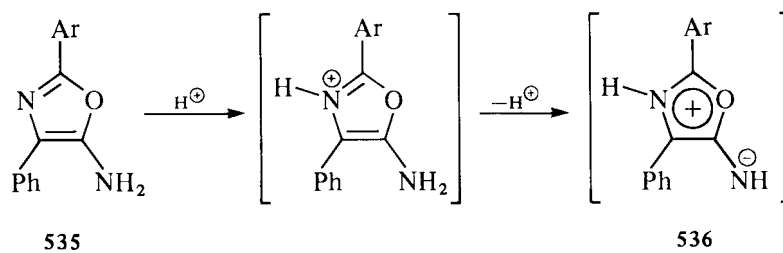
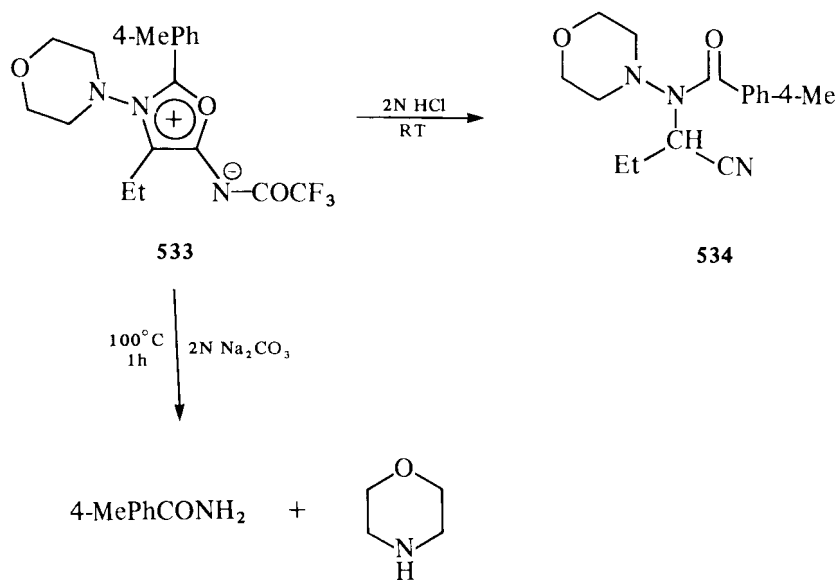
Mild acid hydrolysis of munchnone imine **531** affords its synthetic precursor **532** in 94% yield.¹⁷¹ This facile transformation was considered as additional evidence in favor of the *N*-acylated structure for **531** since hydrolysis of the isomeric C-4-acylated product would not be expected to take place under the conditions employed. The mesoionic compound **533** forms an analogous acid hydro-



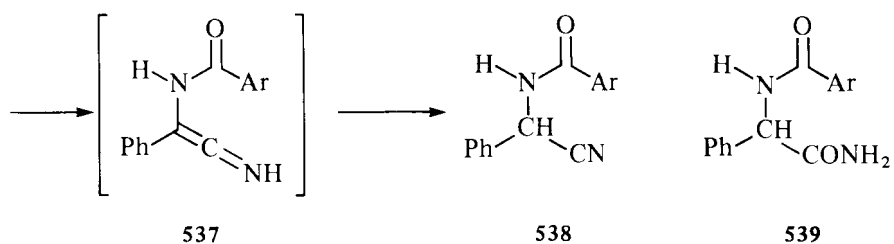
lysis product **534** but in contrast undergoes more complex degradation in hot sodium carbonate solution, from which only *p*-toluamide and morpholine were isolated. The reaction under basic conditions is presumed to occur by attack of hydroxyl at the electrophilic C-2 position of the intact mesoionic **533** since nitrile **534** is stable under identical conditions. Further hydrolytic products associated with carbons 4 and 5 of **533** could not be detected.¹⁷¹

Hydrolysis of 5-aminooxazoles **535** in refluxing water or aqueous ethanol is envisioned to pass through the intermediacy of mesoionic form **536** and its ketenimine tautomer **537** before formation of product α -acylamino nitriles **538**.¹⁷⁰ In a basic medium, where formation of **536** is unlikely, amides **539** are formed instead.¹⁷⁰

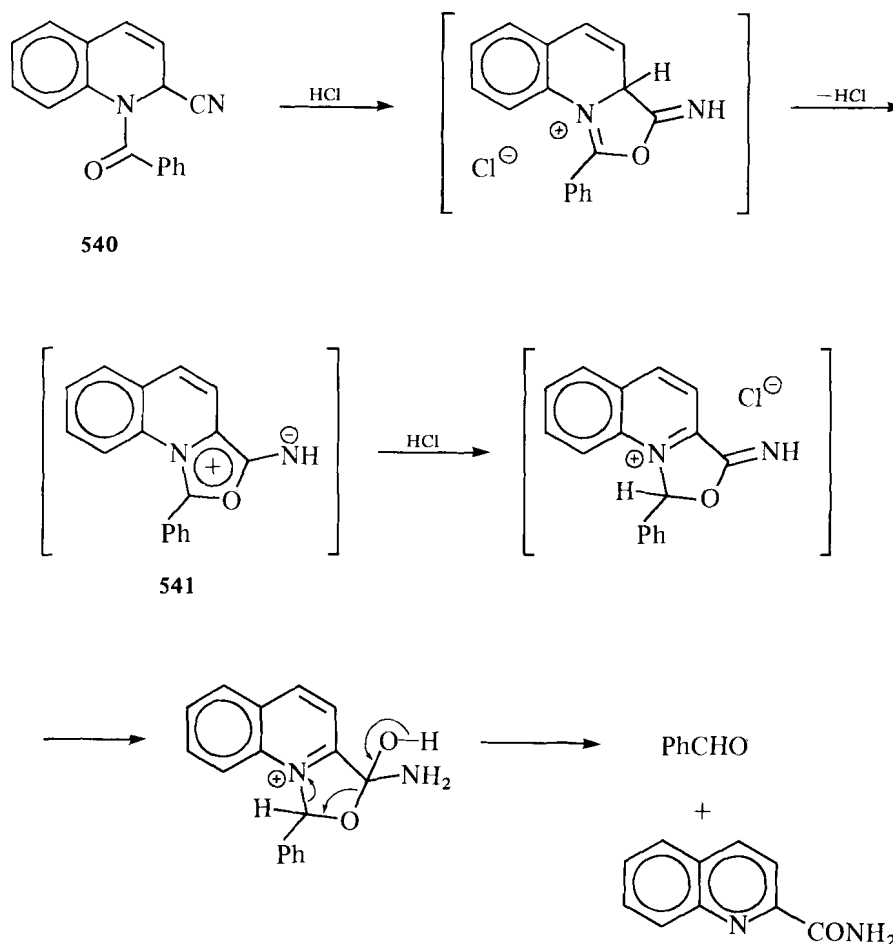
The acid-catalyzed hydrolysis of Reissert compound **540** is suggested¹⁷⁴ to possibly involve the mesoionic intermediate **541** (Scheme 54).



a, Ar = Ph
 b, Ar = 4-NO₂Ph
 c, Ar = 4-MeOPh



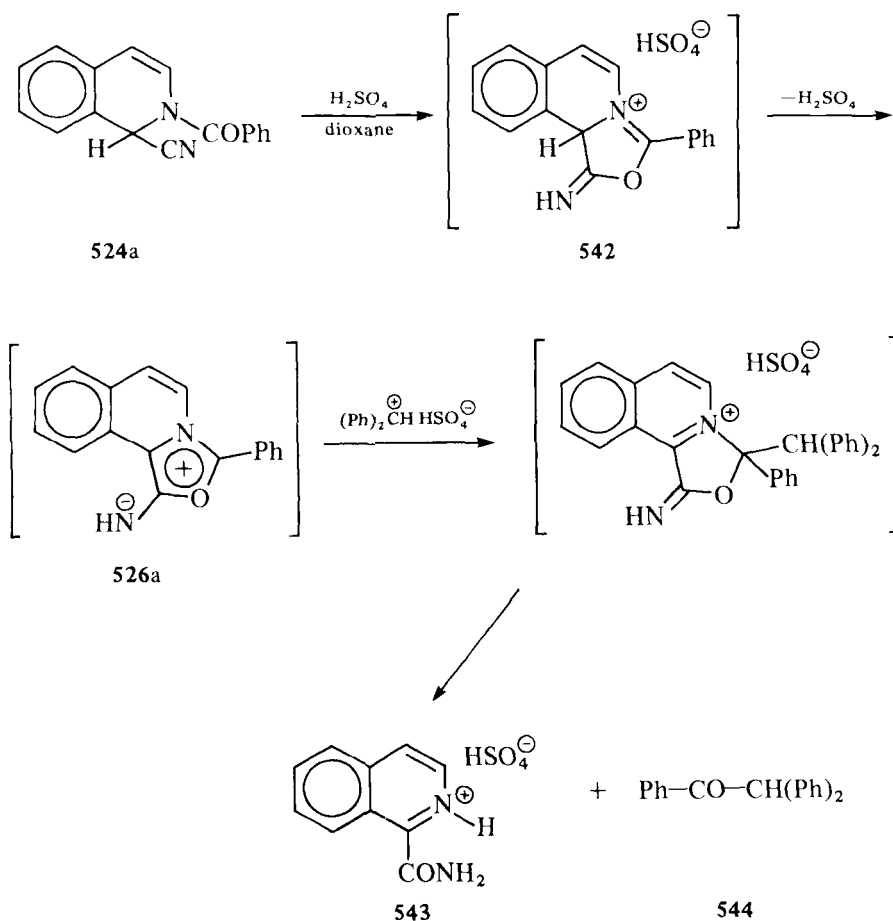
a, Ar = Ph
 b, Ar = 4-NO₂Ph
 c, Ar = 4-MeOPh



Scheme 54

4.3.3.2. With Electrophiles

Treatment of the Reissert compound 2-benzoyl-1,2-dihydroisoquinaldonitrile **524a** with benzhydrol and concentrated sulfuric acid in dioxane yields isoquin-aldamide bisulfate **543** and α,α -diphenylacetophenone **544**.¹⁷⁵ The reaction is presumed to proceed through the cyclic salt **542**, which could, although not demonstrated, be in equilibrium with the mesoionic intermediate **526a**. The interchangeable dipolar character of mesoionic compounds allows a resonance isomer at C-2 with negative charge, which is thus alkylated by the *in situ* benzhydryl cation. Hydrolysis and rearrangement gives the observed products (Scheme 55).

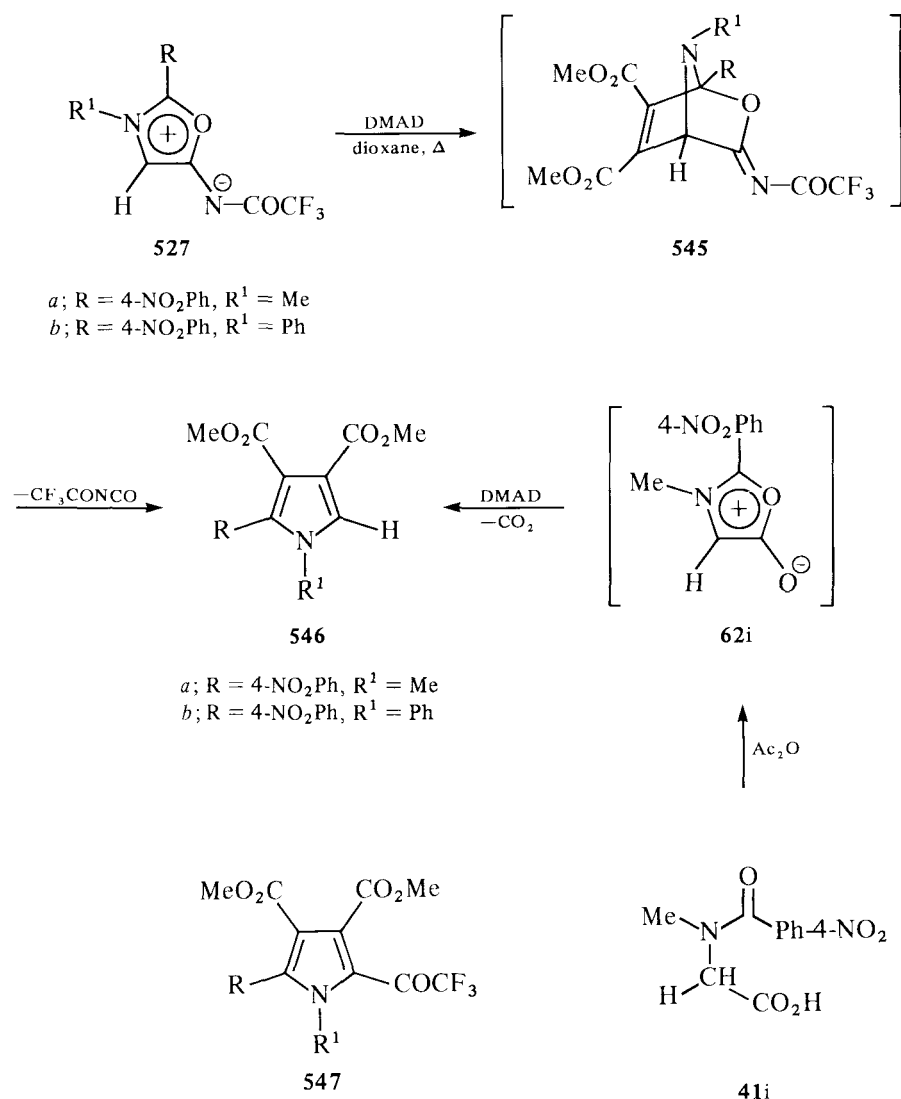


Scheme 55

4.3.3.3. Cycloaddition Reactions

4.3.3.3.1. FROM ISOLATED 1,3-OXAZOLIUM 5-IMINES

As a further proof of structure of 1,3-oxazolium 5-imines **527**, treatment with dimethyl acetylenedicarboxylate (DMAD) in refluxing dioxane gives the intermediate cycloadduct **545**, which undergoes elimination of trifluoroacetyl isocyanate to produce pyrroles **546a** and **546b** in 78 and 79% yields, respectively (Scheme 56).¹⁷² Pyrrole **546a** was unambiguously prepared¹⁷² in 88% yield from *N-p*-nitrobenzoylsarcosine **41i**, DMAD, and acetic anhydride via the *in situ* munchnone **62i** (see Section 4.2.3.3.1). It should be noted here that if the original structural assignment of **517** as the munchnone imine was correct, then the product of the cycloaddition reaction with DMAD would be **547**.



Scheme 56

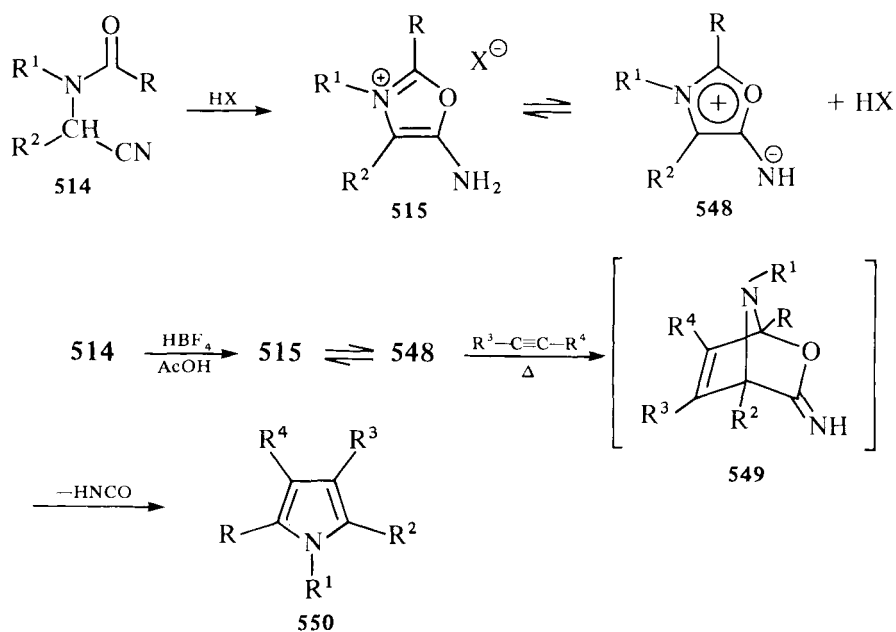
4.3.3.3.2. FROM *IN SITU* OR TAUTOMERIC INTERMEDIATES

Acid cyclization of α -acylaminonitriles **514** affords 5-amino-1,3-oxazolium salts **515** (Section 4.3.1). The aminonitriles **514** may also be considered as open-chain analogs of Reissert compounds,¹⁷⁶ which in solution may be transformed into the munchnone imine form **548**. The mesoionic intermediate was effectively trapped by reaction with DMAD or methyl propiolate to give 55–80% yields of pyrroles **550** via a 1,3-dipolar cycloadduct **549** (Table 4.35).¹⁷⁷

TABLE 4.35. PYRROLES DERIVED FROM 5-AMINO-1,3-OXAZOLIUM SALTS AND ACETYLENES¹⁷⁷

Method ^a	R	R ¹	R ²	R ³	R ⁴	Percent Yield
A	Ph	Ph	Ph	CO ₂ Me	CO ₂ Me	80
A	Ph	3-ClPh	Ph	CO ₂ Me	CO ₂ Me	73
A	Ph	4-MePh	Ph	CO ₂ Me	CO ₂ Me	55
A	Ph	PhCH ₂	Ph	CO ₂ Me	CO ₂ Me	—
B	Ph	Ph	Ph	CO ₂ Me	H	68

^aA, Treatment of tetrafluoroborate salt **515** with 12 equivalents of DMAD at 110°C for 10 hr; B, treatment of tetrafluoroborate salt **515** with 4 equivalents of methyl propiolate in refluxing ethanol for 10 hr.

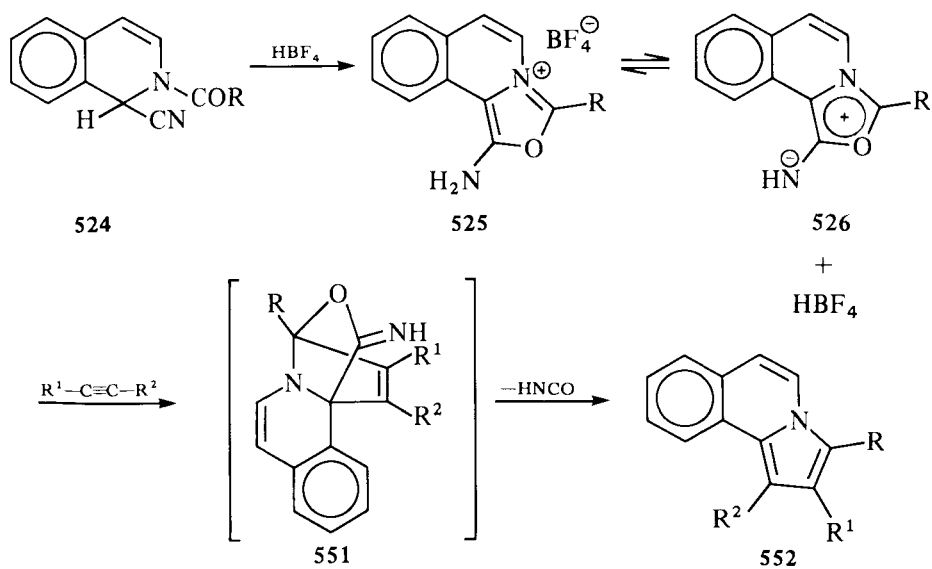


In an analogous reaction, isoquinoline-derived Reissert compounds **524** are known to form cyclic 1,3-oxazolium salts **525**, which in solution consist of several forms, including the 1,3-oxazolium 5-imine **526**. Trapping of **526** by a cycloaddition reaction with acetylenic dipolarophiles was readily accomplished, affording tricyclic pyrroles **552** via cycloadduct **551** (Table 4.36).¹⁷⁸⁻¹⁸³

TABLE 4.36. FUSED PYRROLES DERIVED FROM REISSERT COMPOUNDS AND ACETYLENIC DIPOLAROPHILES

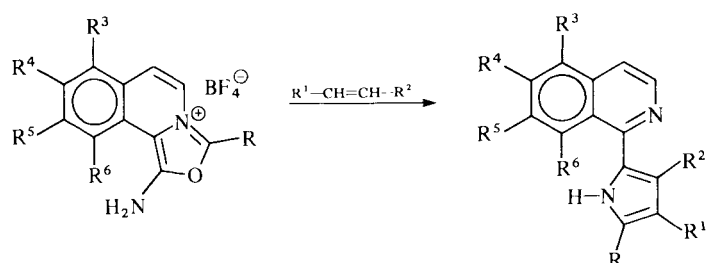
Method ^a	R	R ¹	R ²	Ratio	Percent Yield	Reference
A	Ph	CO ₂ Me	CO ₂ Me	—	90	178
A	Ph	CO ₂ Et	Ph	—	44	179
B	Ph	CO ₂ H	Me	—	—	179
C	Ph	H	Ph	—	57	182
C	Ph	Ph	Ph	—	28	182
C	Ph	4-MeOPh	Ph	1	12	181
	Ph	Ph	4-MeOPh	2		
C	Ph	4-NO ₂ Ph	Ph	1	31	181
	Ph	Ph	4-NO ₂ Ph	2		
C	Me	CO ₂ Me	CO ₂ Me	—	64	182
C	<i>i</i> -Pr	CO ₂ Me	CO ₂ Me	—	26	182
C	Cyclo-Pr	CO ₂ Me	CO ₂ Me	—	47	182
C	1-Naphthyl	CO ₂ Me	CO ₂ Me	—	40	182
D	Ph	H	H	—	19	183

^aA, Treatment of Reissert hydrofluoroborate salt with acetylenic dipolarophile in refluxing CH₂Cl₂–ethanol (5:95); B, conditions A, followed by base hydrolysis and acidification; C, treatment of Reissert salt and acetylenic dipolarophile in hot DMF; D, treatment of Reissert salt in DMSO at 25°C with acetylene gas.



Scheme 57

TABLE 4.37. 2-(1-ISOQUINOLYL)PYRROLES FROM REISSERT SALTS AND OLEFINIC



Olefin	R	R ¹
Acrylonitrile	Ph	H
<i>Trans</i> -stilbene	Ph	Ph
4-Nitro- <i>trans</i> -stilbene	Ph	Ph
4-Methoxy- <i>trans</i> -stilbene	Ph	Ph
	Ph	4-MeOPh
Ethyl acrylate	Ph	H
Styrene	Ph	H
Styrene	4-MeOPh	H
Styrene	4-MeOPh	H
1-(3,4-Dimethoxyphenyl)propene	4-MeOPh	Me
1-(3,4-Dimethoxyphenyl)propene	4-MeOPh	Me
Diethyl maleate	Ph	CO ₂ Et
Dimethyl maleate	Me	CO ₂ Me
	<i>i</i> -Pr	CO ₂ Me
	Cyclo-Pr	CO ₂ Me
	1-Naphthoyl	CO ₂ Me
Ethyl 4-nitrocinnamate	Ph	CO ₂ Et
	Ph	4-NO ₂ Ph
Ethyl cinnamate	Ph	CO ₂ Et
	Ph	Ph
Ethyl 4-methylcinnamate	Ph	CO ₂ Et
	Ph	4-MePh
Ethyl 4-methoxycinnamate	Ph	CO ₂ Et
	Ph	4-MeOPh
Ethyl cinnamate	3-FPh	CO ₂ Et
	3-FPh	Ph
	4-MeOPh	CO ₂ Et
	4-MeOPh	Ph
4-Chlorostyrene	Ph	H
4-Methylstyrene	Ph	H
4-Methoxystyrene	Ph	H

DIPOLAROPHILES^a

R ²	R ³	R ⁴	R ⁵	R ⁶	Percent Yield	Reference
CN	H	H	H	H	34	186
Ph	H	H	H	H	34	181, 182
4-NO ₂ Ph	H	H	H	H	45	181
4-MeOPh	H	H	H	H	18	181
Ph	H	H	H	H	9	
CO ₂ Et	H	H	H	H	67	187
Ph	H	H	H	H	66	182
Ph	H	H	MeO	MeO	16	182
Ph	MeO	MeO	MeO	H	60	182
3,4-(MeO) ₂ Ph	H	H	MeO	MeO	30	182
3,4-(MeO) ₂ Ph	MeO	MeO	MeO	H	13	182
CO ₂ Et	H	H	H	H	54	182
CO ₂ Me	H	H	H	H	76	182
CO ₂ Me	H	H	H	H	68	182
CO ₂ Me	H	H	H	H	70	182
CO ₂ Me	H	H	H	H	37	182
4-NO ₂ Ph	H	H	H	H	57	188
CO ₂ Et	H	H	H	H	5	188
Ph	H	H	H	H	43	188
CO ₂ Et	H	H	H	H	22	188
4-MePh	H	H	H	H	18	188
CO ₂ Et	H	H	H	H	7	188
4-MeOPh	H	H	H	H	17	188
CO ₂ Et	H	H	H	H	7	188
Ph	H	H	H	H	19	188
CO ₂ Et	H	H	H	H	9	188
Ph	H	H	H	H	20	188
CO ₂ Et	H	H	H	H	9	188
4-ClPh	H	H	H	H	44	188
4-MePh	H	H	H	H	52	188
4-MeOPh	H	H	H	H	30	188

TABLE 4.37 (continued)

Olefin	R	R ¹
4-Nitrostyrene	Ph	H
4-Dimethylaminostyrene	Ph	Ph
4-Methylstyrene	Ph	Ph
	Ph	4-MePh
4-Chloro- <i>trans</i> -stilbene	Ph	Ph
Ethylene	Ph	H
<i>N</i> -Phenylmaleimide	Ph	$\begin{array}{c} \text{Ph} \\ \parallel \\ -\text{CO}-\text{N}-\text{CO}- \end{array}$

^aReactions generally performed either in mixture of refluxing methylene chloride-ethanol or in dimethylformamide (RT → 150°C).

In one instance, reaction of **525** (R = Ph) with ethyl phenylpropiolate gives an *isolable* 1:1-cycloadduct **551** (R = R² = Ph, R¹ = CO₂Et) along with the expected pyrrole **552** (R = R² = Ph; R¹ = CO₂Et).¹⁷⁹ Single regioisomeric products are also obtained from ethyl tetrolate and phenylacetylene but with asymmetrical 4-methoxy- or 4-nitrotolan, mixtures of regioisomers are isolated.¹⁸¹ It should be noted here that pyrroles (Table 4.36) are the predominant products from reaction of Reissert salts with alkynes but not the sole products.^{181,182} In certain cases, substituted 2-(1-isoquinolyl)pyrroles **553**, predominant products from alkene cycloaddition reactions (Table 4.37), are also isolated in 5–10% yields. These observations were rationalized by assuming that both a 1,3-dipolar cycloaddition reaction involving the isomunchnone imine form **526** and a Diels-Alder reaction with the oxazolium salt **525** occur from the equilibrium mixtures derived from Reissert salts. The postulated mechanism for the preparation of pyrroles **553** is depicted in Scheme 57.

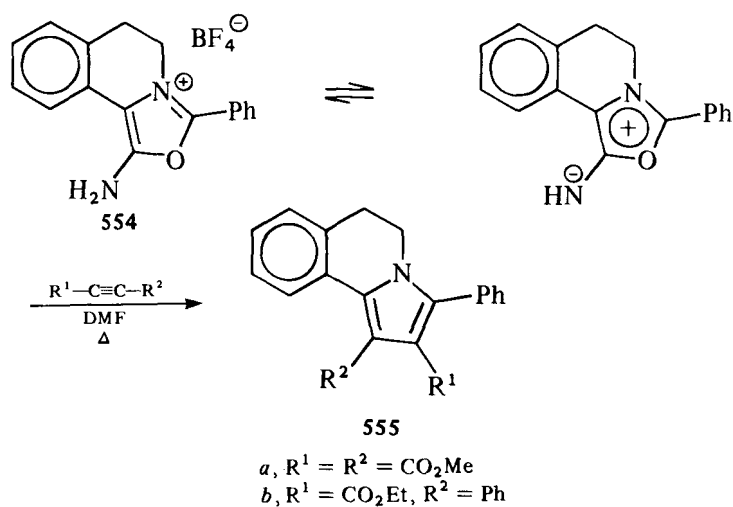
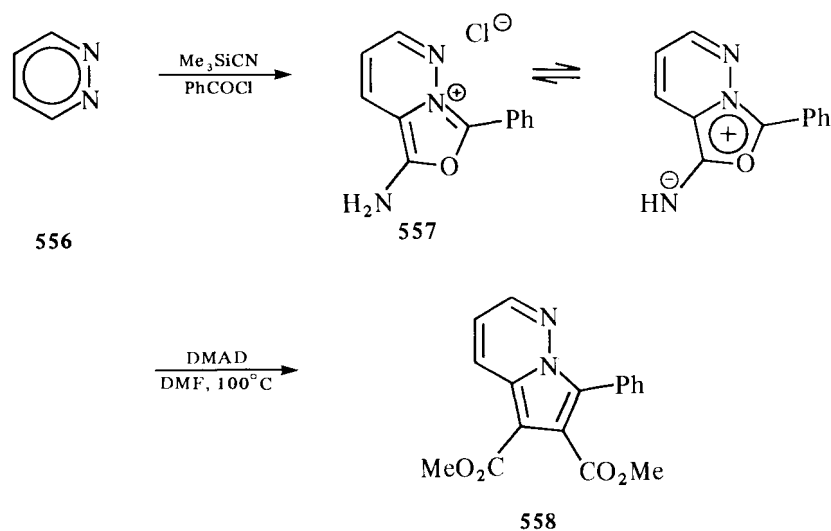


TABLE 4.37 (continued)

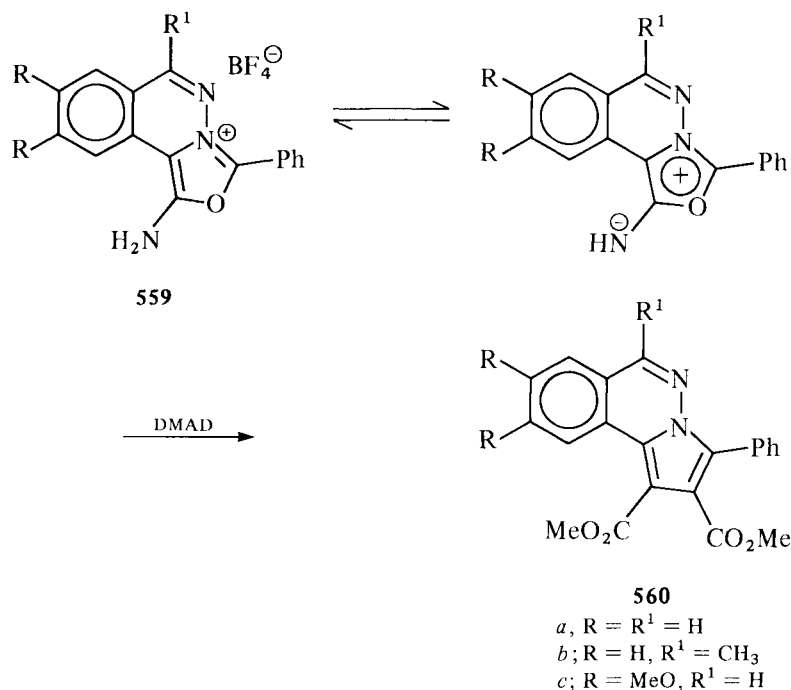
R ²	R ³	R ⁴	R ⁵	R ⁶	Percent Yield	Reference
4-NO ₂ Ph	H	H	H	H	38	188
4-NMe ₂ Ph	H	H	H	H	23	188
4-MePh	H	H	H	H	21	188
Ph	H	H	H	H	9	188
4-ClPh	H	H	H	H	35	188
H	H	H	H	H	24	183
	H	H	H	H	42	182

2-Benzoyl-1,2,3,4-tetrahydroquinaldonitrile hydrofluoroborate **554** undergoes reaction with DMAD or ethyl phenylpropiolate in hot dimethyl formamide (DMF) to provide analogous fused pyrroles **555** in 66 and 51% yields, respectively.¹⁸³

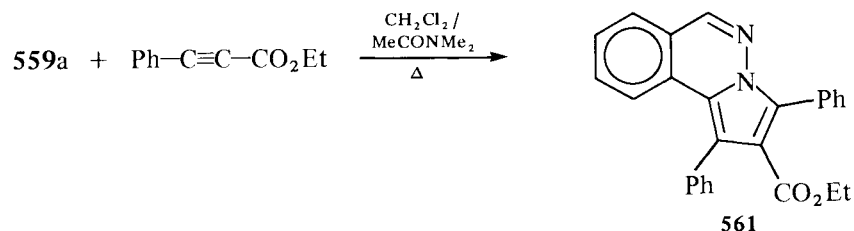
These alkyne cycloaddition reactions have been extended to monocyclic and benzo-fused phthalazine systems with analogous results. The deep-red Reissert salt **557**, derived from the reaction of pyridazine **556** with trimethylsilyl cyanide and undistilled benzoyl chloride, combines with DMAD to yield the pyrrolo[2,1-*a*]pyridazine **558**.¹⁸⁴



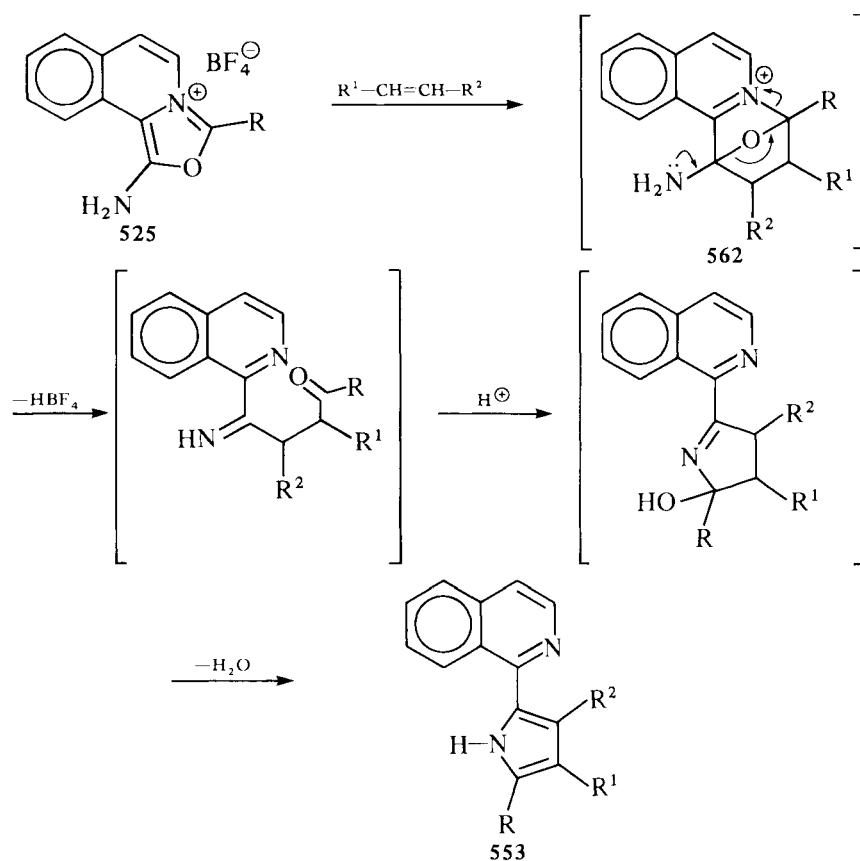
Similarly, the phthalazine Reissert salts **559** were found to react with DMAD in refluxing methylene chloride–ethanol or more efficiently in DMF at 100°C to give the pyrrolo[2,1-*a*]phthalazines **560** in 78–95% yields.¹⁸⁵



Treatment of **559a** with ethyl phenylpropiolate in refluxing methylene chloride—dimethylacetamide leads regiospecifically to the corresponding pyrrole **561** in 73% yield.¹⁸³

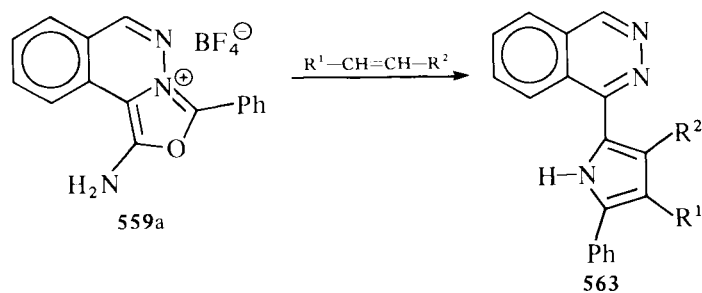


Reactions of isoquinolinium salts **525** with olefinic dipolarophiles are believed to involve a Diels–Alder cycloaddition to the 2 and 5 oxazole ring carbons forming a cycloadduct **562**, which rearranges to afford 2-(1-isoquinolyl)pyrroles **553**, as rationalized in Scheme 58.^{181–183,186–188} Table 4.37 exemplifies the product pyrroles **554** obtained from a wide variety of olefins. In the cases with unsymmetrical alkenes, the reaction was found to be predominantly regioselective with stilbenes and ethyl cinnamates; however, reactions with acrylonitrile and styrenes gave regiospecific single products. The orientation of the cycloadducts of Reissert salts and olefinic or acetylenic dipolarophiles, as cited above, was best rationalized by McEwen and collaborators by invoking the concept of merostabilized biradicaloid intermediates.¹⁸³



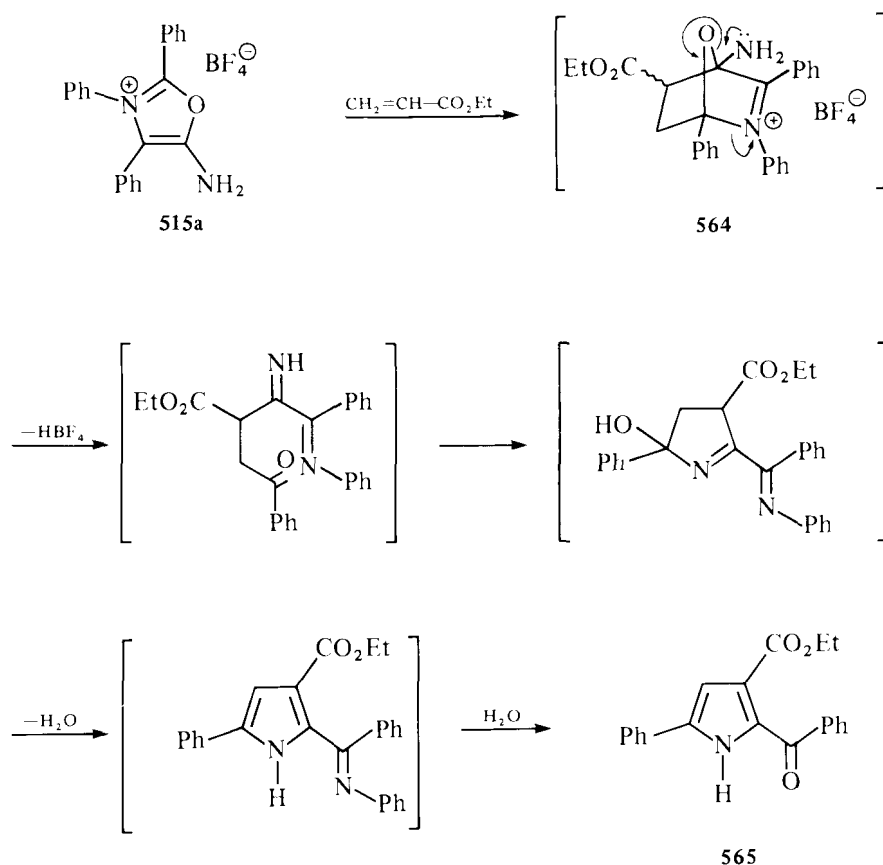
Scheme 58

Similarly, phthalazine salt **559a** was found to afford 2-(1-phthalazyl)pyrroles **563** by reaction with styrene and diethyl maleate in DMF at 150°C .¹⁸⁵



a; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$
b; $\text{R}^1 = \text{R}^2 = \text{CO}_2\text{Et}$

The reaction of salt **515a** with ethyl acrylate is presumed to proceed via a similar Diels–Alder cycloaddition process through adduct **564**, providing ethyl 2-benzoyl-5-phenylpyrrole-3-carboxylate **565** in 75% yield (Scheme 59).¹⁷⁷

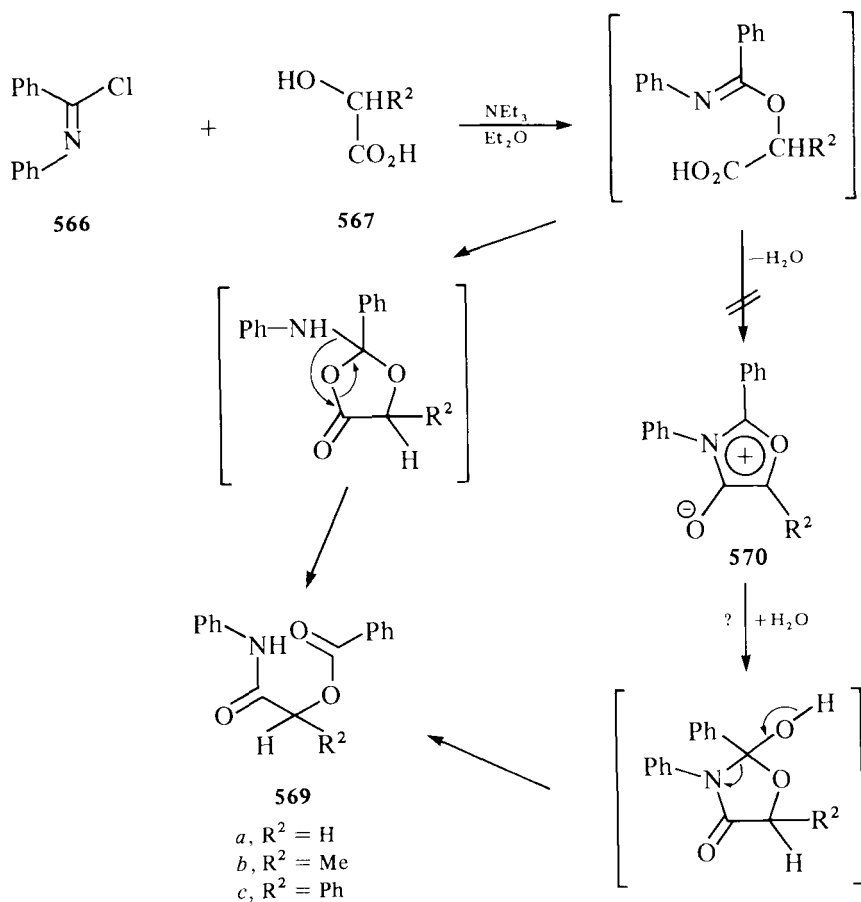


Scheme 59

4.4. 1,3-OXAZOLIUM 4-OXIDES (ISOMUNCHNONES)

4.4.1. Synthesis

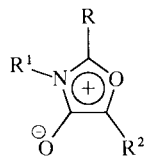
An initial attempt at the synthesis of the title mesoionic ring system was unsuccessful. Reaction of *N*-phenylbenzimidoyl chloride **566** with glycolic acid derivatives **567** gives benzoyloxyacetanilides **569** instead of the anticipated mesoionic oxazoles **570**.¹⁸⁹ The products were rationalized by the authors as arising from rearrangement of intermediate **568**. It should be noted, however, that benzoyloxyacetanilides **569** are formally hydrolysis products of the 1,3-oxazolium 4-oxides **570** (Section 4.4.3.1), and thus the formation of **569** may also be explained by invoking the intermediacy of the mesoionic **570** as depicted in Scheme 60.



Scheme 60

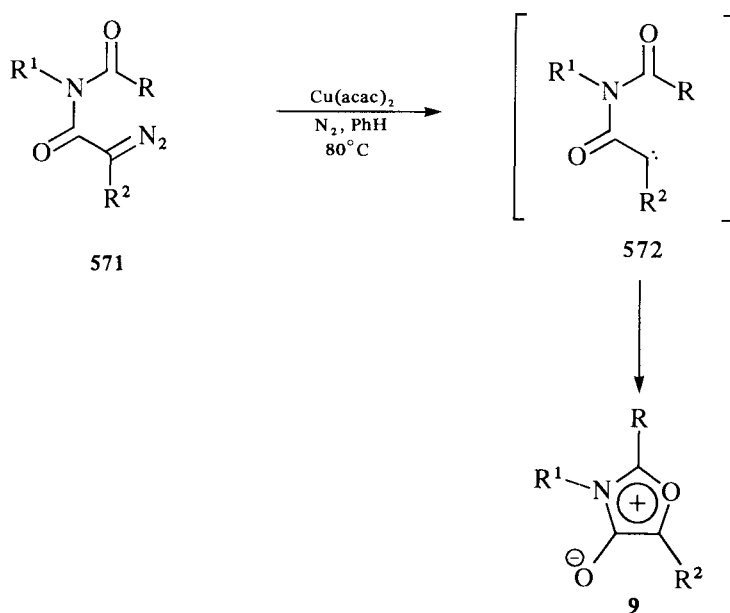
The first successful synthesis of the 1,3-oxazolium 4-oxide ring system was described by Hamaguchi and Ibata.¹⁹⁰ Diazoimides **571**, obtained by the Regitz¹⁹¹ diazo transfer reaction, are decomposed thermally in benzene solution (80°C) in the presence of catalytic cupric acetylacetonate from which red crystals of the air-stable 1,3-oxazolium 4-oxide **9** precipitates. The reaction is assumed to proceed through the carbene intermediate **572**, which undergoes cyclization via intramolecular attack on the imide carbonyl oxygen. Subsequent reports by Ibata and co-workers¹⁹²⁻¹⁹⁴ further detail this synthesis and are summarized in Table 4.38. The authors have given the name isomunchnone to the ring system **9** owing to its isoelectronic structure with the 1,3-oxazolium 5-oxide (munchnone) meso-ionic system (Section 4.2). The exceptional reactivity of this ring system in cyclo-addition reactions either from the isolated state or generated *in situ* is described in a succeeding section (Section 4.4.3.2).

TABLE 4.38. ISOLABLE 1,3-OXAZOLIUM 4-OXIDES

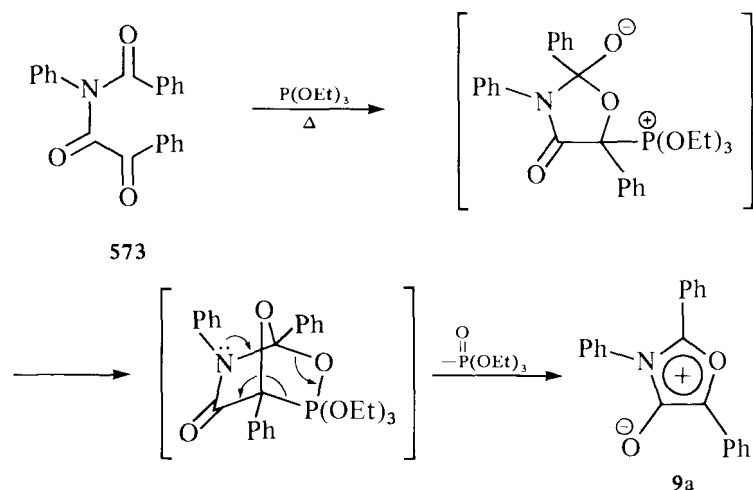


Method ^a	R	R ¹	R ²	Percent Yield	Reference
A	Ph	Me	4-NO ₂ Ph	85	190
A	4-MePh	Me	4-NO ₂ Ph	88	190
A	4-BrPh	Me	4-NO ₂ Ph	54	190
A	Me	Me	4-NO ₂ Ph	—	192
A	Ph	Ph	H	—	193
A	—CH ₂ —2—Ph—	—	4-NO ₂ Ph	—	194
B	Ph	Ph	Ph	50	195

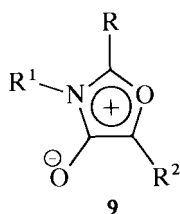
^aA, Decomposition of diazoimide with Cu(acac)₂ in benzene; B, treatment of *N*-benzoylphenylglyoxanilide with triethylphosphite.



Freeman and co-workers have recently described a novel synthesis of the iso-munchnone ring system by the reaction of *N*-benzoylphenylglyoxanilide **573** with triethyl phosphite.¹⁹⁵ The orange red *anhydro*-4-hydroxy-2,3,5-triphenyl-1,3-oxazolium hydroxide **9a** forms readily upon contact of the reagents (Table 4.38) via the postulated mechanism, as shown.



The preparation of the 1,3-oxazolium 4-oxide ring system by this method has recently been generalized by Haddadin and Tanous.¹⁹⁶ Although the types of isomunchnones **9** available by this route have been indicated, specific details have yet to be published.



R = Ph, 4-NO₂Ph, 4-MeOPh, Me, α -naphthyl
 R¹ = Ph, 2,6-Me₂Ph, β -naphthyl
 R² = Ph, 4-BrPh, 4-MePh

The ability of 2-oxazolin-4-ones **574** to undergo tautomerism with their meso-ionic isomer **575** has been recently exploited by Potts and Marshall¹⁹⁷ by trapping the *N*-unsubstituted isomunchnone species with acetylenic dipolarophiles (see Section 4.4.3.2).

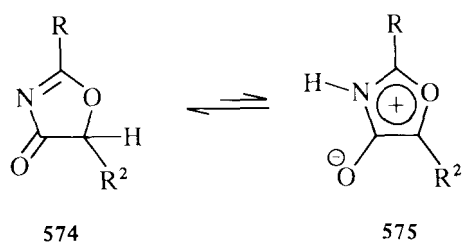
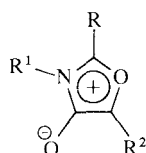


TABLE 4.39. 1,3-OXAZOLIUM 4-OXIDES: INFRARED AND ULTRAVIOLET SPECTRAL DATA



R	R ¹	R ²	ν_{CO} (cm ⁻¹)	UV nm	(Benzene) (ϵ)	Reference
Ph	Me	4-NO ₂ Ph	1672	475	(21,000)	190
4-MeOPh	Me	4-NO ₂ Ph	1670	482	(30,000)	190
4-BrPh	Me	4-NO ₂ Ph	1660	485	(24,000)	190
Ph	Ph	Ph	1665	—		195

4.4.2. Structure and Spectral Properties

4.4.2.1. Infrared and Ultraviolet Spectra

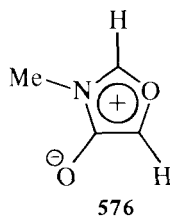
The infrared carbonyl absorptions and ultraviolet maxima for the 1,3-oxazolium 4-oxide system **9** are summarized in Table 4.39.

4.4.2.2. ¹H NMR Spectra

Lack of reported data prevents an extensive review of ¹H NMR spectral properties of the title mesoionic ring system. Derivatives possessing an N—Me group, as synthesized by Hamaguchi and Ibata,¹⁹⁵ exhibit resonances at δ 3.72–3.77 ppm, thus establishing the relative electropositive nature of the ring nitrogen atom.

4.4.2.3. Molecular Orbital Calculations

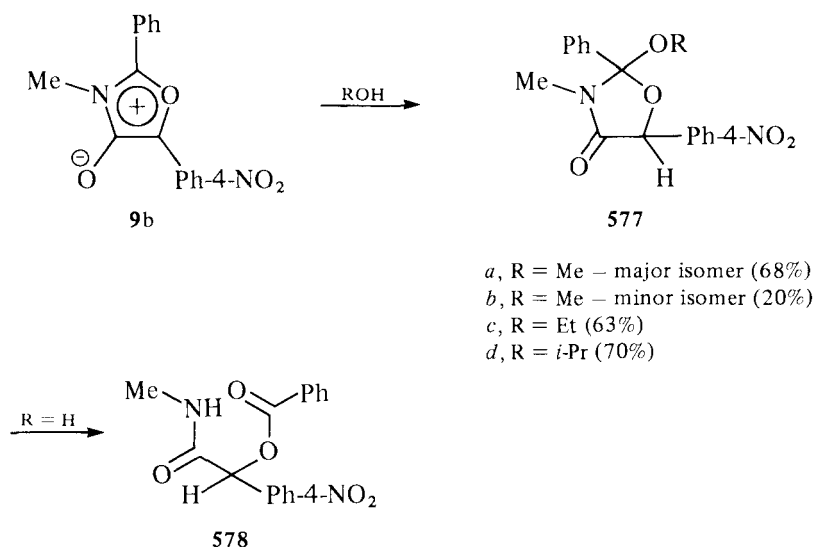
MINDO/3 calculations of geometries and distributions of formal charge on the theoretical system **576** have suggested that this is a species for which no single satisfactory classical structure can be written and should be represented by a series of mesomeric forms.⁵⁴



4.4.3. Reactions

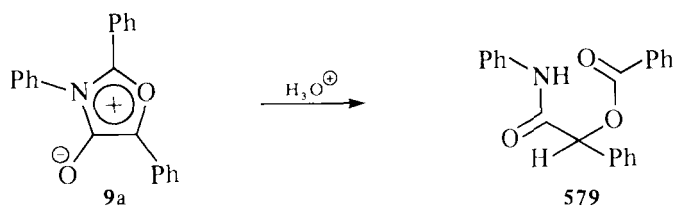
4.4.3.1. With Nucleophiles

The hydrolysis of isomunchnone **9b** in aqueous dioxane occurs readily at room temperature from which is isolated as the sole product, in quantitative yield, *N*-methyl- α -benzoyloxy- α -*p*-nitrophenylacetamide **578**.¹⁹⁴ Under alcholysis conditions, 1:1 adducts **577** are obtained as a mixture of isomers that differ in configuration at the C-2 position ($R = \text{Me}$) or as single isomers ($R = \text{Et}$, *i*-Pr).¹⁹⁴ *t*-Butyl alcohol failed to react with the 1,3-oxazolium 4-oxide system. Both the hydrolysis and alcholysis products can be explained by the addition of water or alcohol across the carbonyl ylide dipole inherent in the isomunchnone system **9b**, followed by, in the case of water, ring opening via C–N bond cleavage of the unstable intermediate 1:1 addition product **577** ($R = \text{H}$). These reactions are summarized in Scheme 61.

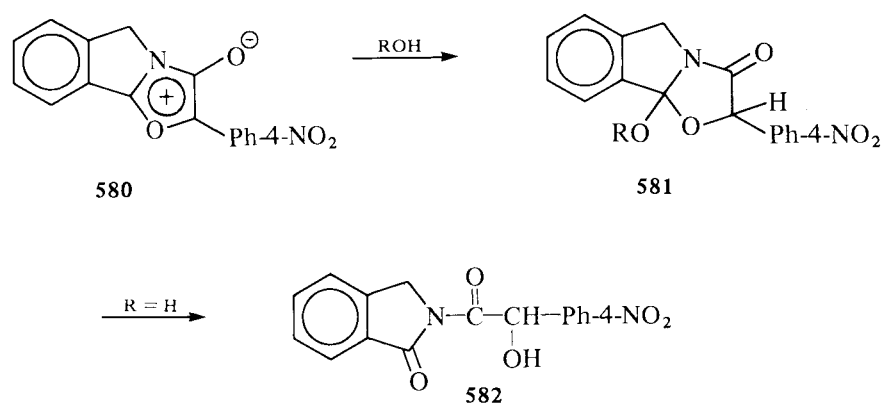


Scheme 61

Acid hydrolysis of the triphenylsubstituted isomunchnone **9a** occurs in an analogous fashion to provide *O*-benzoylmandelanilide **579** in 38% yield.^{195,198}



In contrast, the reaction of the bicyclic isomunchnone **580** with water affords *N*-(α -hydroxy-*p*-nitrophenylacetyl)phthalimidine **582**.¹⁹⁴ This can be rationalized via the addition product **581** ($R = H$), which undergoes C—O bond cleavage. A stable bicyclic addition product **581** ($R = Me$) could be isolated in 70% yield from addition of methanol to **580**.

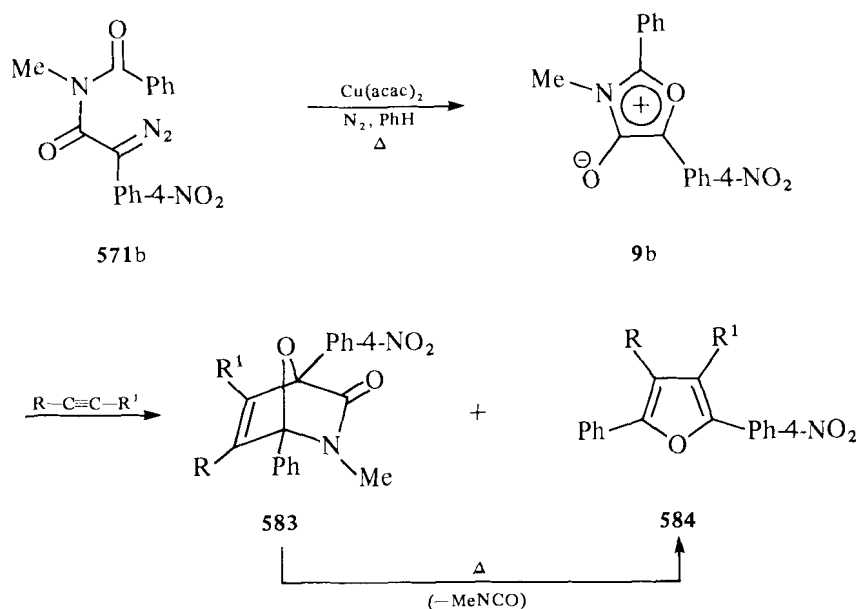


Hamaguchi and Iyata conclude that the facile addition of water and alcohols to isomunchnones indicates that these structures have a large degree of carbonyl ylide character.¹⁹⁴ This is borne out by the results summarized in the succeeding section.

4.4.3.2. Cycloaddition Reactions

The 1,3-oxazolium 4-oxide mesoionic system contains an extremely reactive carbonyl ylide dipole as evidenced by its ability to undergo a variety of cycloaddition reactions. As mentioned above, the first example of the isomunchnone system **9** was prepared from thermal decomposition of diazoimide **571b** in the presence of $Cu(acac)_2$ (Section 4.4.1). Cycloaddition reactions of **9b**, either in the isolated state or generated *in situ* from **571b**, in the presence of a small excess of acetylenic dipolarophiles result in the formation of 1:1-adducts **583** along with furans **584**.¹⁹²

The ratio of 1:1-adducts **583** to furans **584** was found to be dependent on the reaction conditions. High reaction temperatures favor formation of the furan products by thermal extrusion of methyl isocyanate (identified as *N*-methyl-*N'*-phenylurea) from the 1:1-adducts **583**. Reaction of isolated **9b** with dimethyl acetylenedicarboxylate (DMAD) at 30°C in benzene results in an almost exclusive formation of 1:1-adduct **583a** ($R = R^1 = CO_2Me$). The asymmetrical acetylene methyl propiolate gives only a single 1:1-adduct and a single furan, although the substituent orientation of the products has not been determined. Similarly, methyl tetrolate, methyl propiolate, and 1-hexyne give single furan isomers **584**; however, the 1:1-adducts **583** were not observed in these cases.



In contrast, phenylacetylene gives a mixture of regioisomeric furans in 82 and 3% yield, but details of structures of these products have not yet been reported. Finally, diphenylacetylene was found to react sluggishly and required higher reaction temperature to undergo cycloaddition with isomunchnones **9b**. These reactions are summarized in Table 4.40.

Curiously, the reaction of the isolated 1,3-oxazolium 4-oxide **9c** with DMAD in benzene at 30°C affords furan **586** in 94% yield. When generated *in situ* (Method B), reaction with DMAD in benzene at 80°C provides a mixture of 1:1-adduct **585** and furan **586** in 81 and 16% yields, respectively.¹⁹²

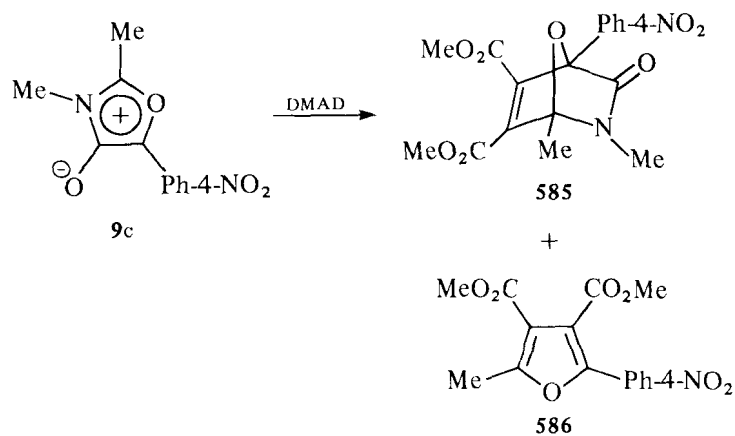


TABLE 4.40. PRIMARY CYCLOADDUCTS AND FURANS FROM ISOMUNCHNONE **9b** AND ACETYLENIC DIPOLAROPHILES¹⁹²

Acetylenes R-C≡C-R ¹ ^a	Reaction Conditions			Percent Yield	
	Temperature (°C)	Time (hr)	Method ^b	583	584
MeO ₂ C-C≡C-CO ₂ Me	30	2	B	92	5
	80	1	A	42	54
	120	1	A	—	83
PhCO-C≡C-COPh	30	1	B	69	—
	120	1	A	—	88
H-C≡C-CO ₂ Me	30	2	B	82	1
	80	1	A	35	44
Me-C≡C-CO ₂ Me	80	2	A	—	81
Ph-C≡C-CO ₂ Me	80	2	A	—	91
Ph-C≡C-Ph	120	3	A	—	27
H-C≡C-Ph	80	5	A	—	82
H-C≡C-Bu- <i>n</i>	100	2	A	—	3
				—	75

^aOrientation of substituents in **583** and **584** with unsymmetrical acetylenes not specified.^bA, diazoimide **571b** catalytically decomposed in presence of acetylenic dipolarophiles; B, isolated isomunchnone **9b** treated with acetylenic dipolarophiles.

Hamaguchi and Iyata have also investigated the 1,3-dipolar cycloaddition reactions of isomunchnone **9b** with olefinic derivatives.^{190,199} When generated *in situ*, **9b** and olefinic dipolarophiles provide isolable 1:1-adducts **587** in yields ranging from 17 to 100%.¹⁹⁹ These products are formed stereospecifically either as a mixture of adducts (*exo* and *endo*), as is the case with *trans*-1,2-dibenzoyl-ethylene, dimethyl maleate, maleic anhydride, and *trans*-stilbene, or as single isomers (*exo* or *endo*) with dimethyl fumarate, *N*-phenylmaleimide, acenaphthylene, norbornadiene, tetramethyl ethyltetra-carboxylate, and *cis*-stilbene. These reactions are summarized in Table 4.41.

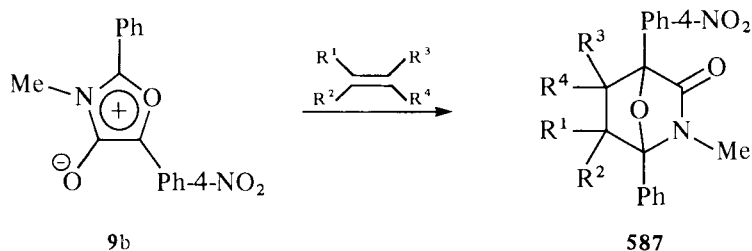
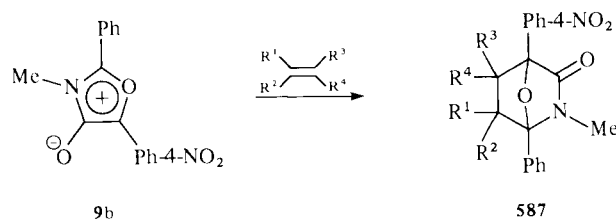
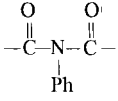
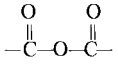
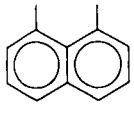
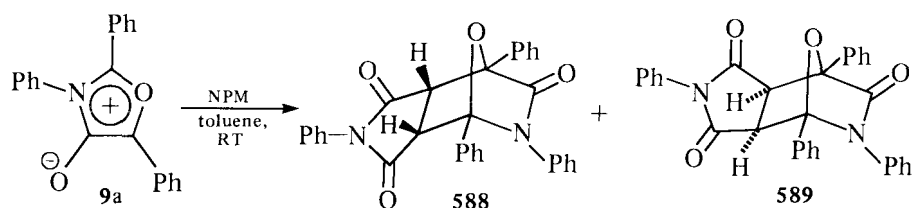


TABLE 4.41. PRIMARY CYCLOADDUCTS **587** FROM *IN SITU* ISOMUNCHNONE **9b** AND OLEFINIC DIPOLAROPHILES¹⁹⁹

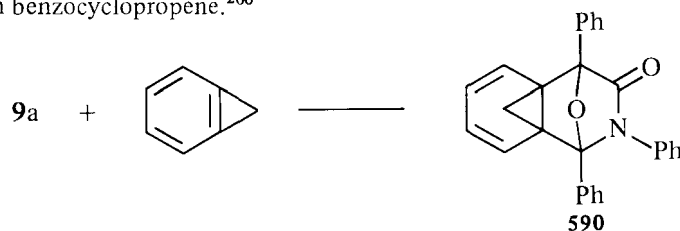
Olefin	Adduct				Percent Yield
	R ¹	R ⁴	R ²	R ³	
<i>Trans</i> -1,2-dibenzoyl ethylene	COPh	H	H	COPh	100 ^a
Dimethyl fumarate	CO ₂ Me	H	H	CO ₂ Me	100 ^b
Dimethyl maleate	CO ₂ Me	CO ₂ Me	H	H	34 ^c
	H	H	CO ₂ Me	CO ₂ Me	61 ^d
Tetramethyl ethylene-tetracarboxylate	CO ₂ Me	CO ₂ Me	CO ₂ Me	CO ₂ Me	31
<i>Trans</i> -stilbene	Ph	H	H	Ph	46 ^e
<i>Cis</i> -stilbene	Ph	Ph	H	H	59 ^f
<i>N</i> -Phenylmaleimide			H	H	87 ^c
Maleic anhydride			H	H	84 ^g
Acenaphthylene	H	H			100 ^d
Norbornadiene	H	H			55 ^d

^aA 23:77 mixture of unspecified *trans* adducts.^bSingle *trans* adduct of unspecified *exo-endo* stereochemistry.^c*Cis-endo* adduct.^d*Cis-exo* adduct.^eA 17:29 mixture of unspecified *trans* adducts.^fSingle *cis* adduct of unspecified *exo-endo* stereochemistry.^gMixture of *cis-exo/endo* adducts in 2:7 ratio, respectively.

The triphenyl-1,3-oxazolium 4-oxide **9a** was found by Freeman and co-workers¹⁹⁵ to react immediately with *N*-phenylmaleimide (NPM), giving a mixture of *endo* and *exo* adducts **588** and **589** in a ratio of 2:1, respectively. Heating the cycloadducts **588** or **589** above their melting points results in formation of a red product presumed to be **9a**.



Recently, Kato and collaborators isolated a cycloadduct **590** from the reaction of **9a** with benzocyclopropene.²⁰⁰



A thermal [4 + 4] cycloaddition reaction of 1,3-oxazolium 4-oxide **9b** with *o*-chloranil **498** and *N,N*-diphenylsulfonyl-4,5-dimethyl-*o*-benzoquinone diimine **592** in methylene chloride at room temperature results in the high yield formation of 1:1-adducts **591** and **593**, respectively.²⁰¹ The structure of **591** was confirmed by X-ray crystallography.

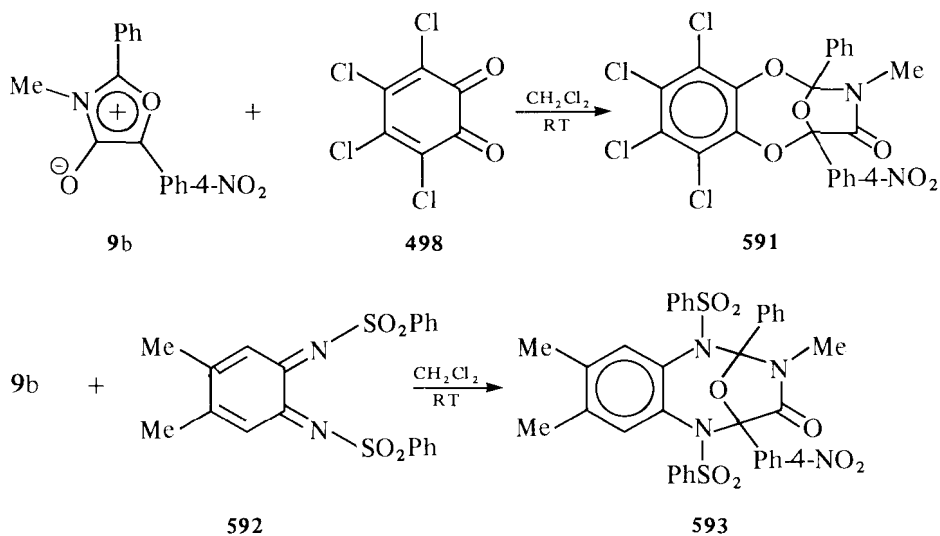
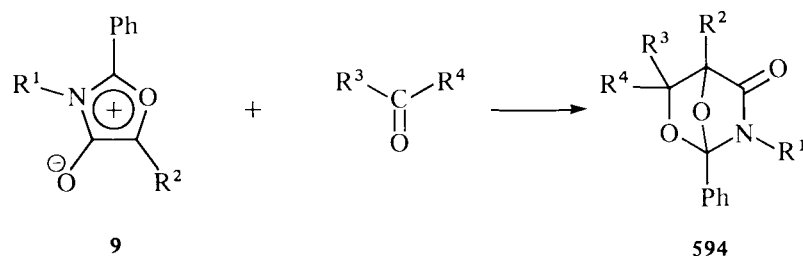


TABLE 4.42. PRIMARY CYCLOADDUCTS OF ISOMUNCHNONES AND CARBONYL COMPOUNDS¹⁹³

Method ^a	R ¹	R ²	R ³	R ⁴	Percent Yield
A	Me	4-NO ₂ Ph	4-ClPh	CH ₂ CHO	57
A	Ph	H	4-NO ₂ Ph	H	59
A	Ph	H	4-ClPh	H	65
A	Ph	H	4-NO ₂ Ph	Me	31
B	4-ClPh	H	4-NO ₂ Ph	H	55
B	4-ClPh	H	4-ClPh	H	34
B	4-ClPh	H	4-NO ₂ Ph	Me	57

^aA, Reaction of isolated isomunchnone and carbonyl compound; B, reaction of isomunchnone, generated *in situ* from the corresponding diazo compound, with carbonyl compound.

Hamaguchi has reported that the cycloadducts of type **594** are formed regio-specifically and in good yield upon reaction of isomunchnones **9** (R = Ph), either isolated or generated *in situ*, with carbonyl compounds.¹⁹³ It should be recalled that munchnones also react with carbonyl compounds, although in this case the primary adducts are not isolable (Section 4.2.3.3.4). The assignment of structure of the primary cycloadducts **594** was made on the basis of spectral evidence, primarily ¹H NMR data. It is interesting to note that reaction with 4-chlorobenzoyl-acetaldehyde preferentially takes place at the ketone functionality and not at the less hindered aldehyde group (Table 4.42).

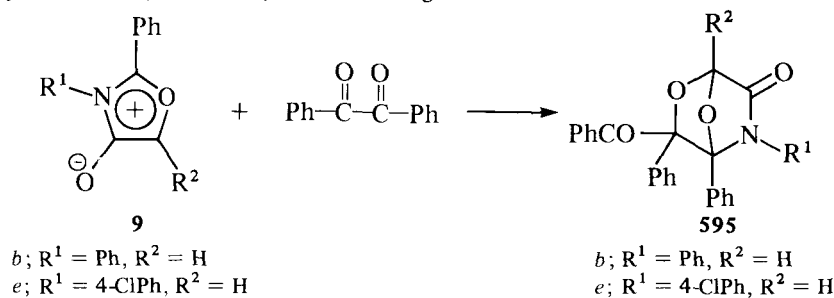


b; R¹ = Me, R² = 4-NO₂Ph

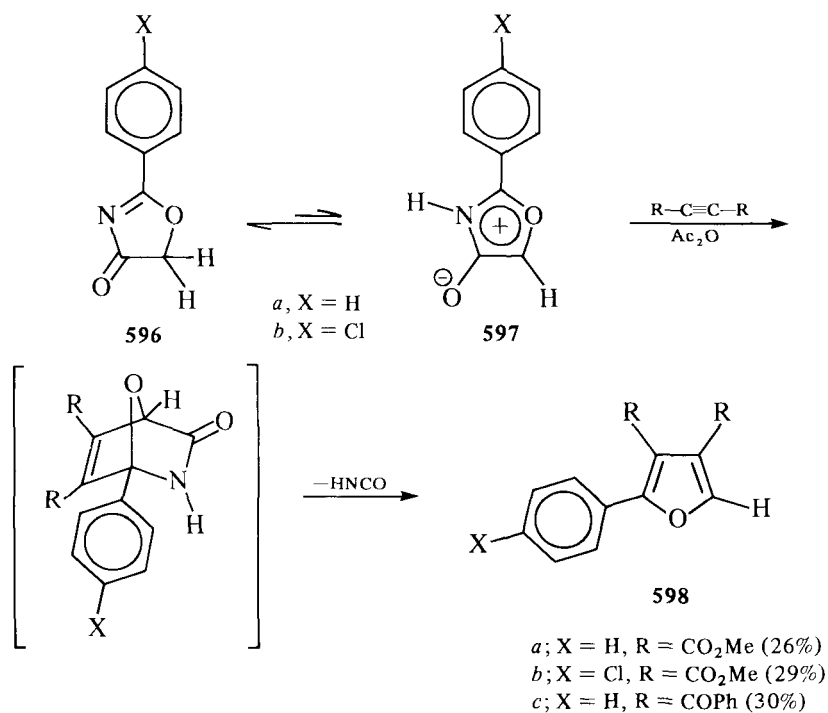
d; R¹ = Ph, R² = H

e; R¹ = 4-ClPh, R² = H

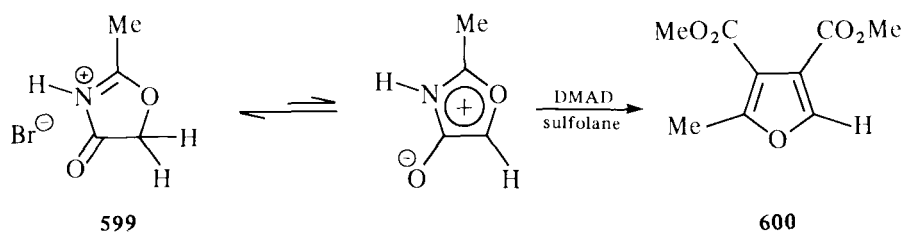
The regioisomeric adducts **595**, assigned on the basis of ^1H NMR spectral data, are obtained from reaction of isomunchnones **9b** and **9e** with benzil.¹⁹³ The lower field chemical shift of the bridgehead proton in **595b** as compared with other cycloadducts (Table 4.42) indicated a regioisomeric structure **595** for these adducts.



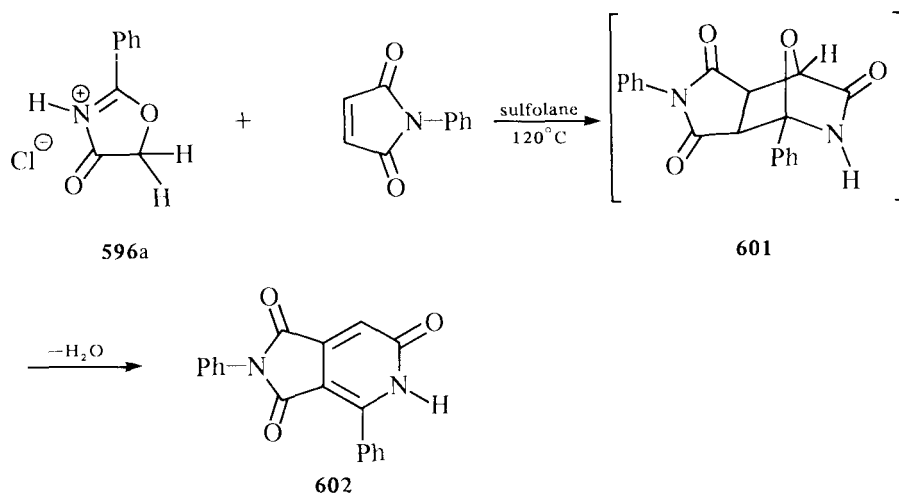
The trapping of the tautomeric mesoionic form **597** of the corresponding 2-oxazolin-4-one **596** is achieved through a cycloaddition reaction as reported by Potts and Marshall.¹⁹⁷ With DMAD or dibenzoylacetylene, furans **598** are formed. Evidence in favor of the intermediacy of the *N*-unsubstituted isomunchnone **597** was rationalized in terms of increased yield of **598a** by increase in reaction medium polarity. Thus, in changing from acetic anhydride to sulfolane, the reaction was completed in shorter time and the yield of **598a** increased from 26 to 45%. A further improvement to 61% yield of **598a** was realized by the use of the hydrochloride salt of **596a** in sulfolane as solvent.



Reaction of 2-methyl-2-oxazolin-4-one hydrobromide **599** and DMAD in sulfolane provides the corresponding 2-methyl furan **600** in 19% yield.¹⁹⁷

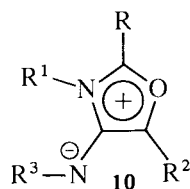


The ability of 2-oxazolin-4-ones to undergo cycloaddition reactions with acetylenic dipolarophiles is probably aided by the thermodynamic stability of the extruded fragment from the primary cycloadduct (HNCO) and of the furan produced.¹⁹⁷ Thus, the general inability of olefinic dipolarophiles, fumaronitrile, diethyl fumarate, and diethyl maleate to react is not surprising. Only *N*-phenylmaleimide was found to undergo cycloaddition with the hydrochloride salt of **596a** in sulfolane at 120°C from which was isolated in 22% yield a bicyclic pyridone **602**, derived from dehydration of the presumed primary cycloadduct **601**.¹⁹⁷

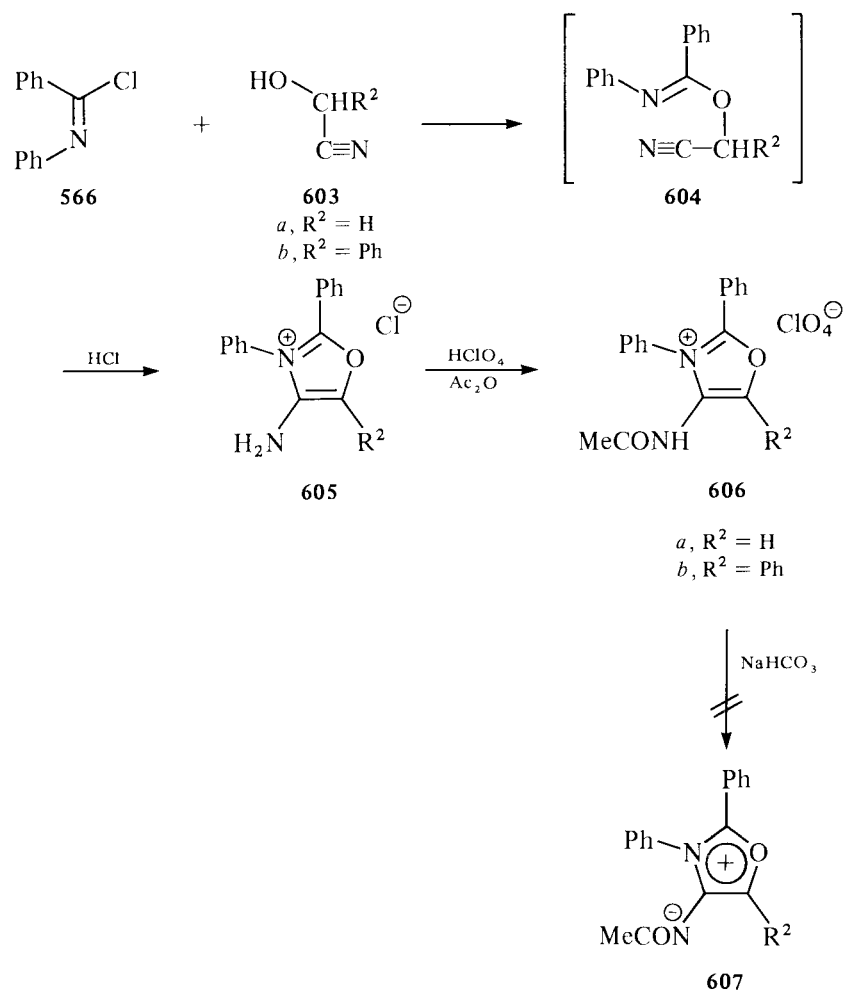


4.5. 1,3-OXAZOLIUM 4-IMINES (ISOMUNCHNONE IMINES)

To date, no example of the mesoionic ring system **10** has been reported. The conjugate acid **605** of the 1,3-oxazolium 4-imine system is prepared by the reaction of *N*-phenylbenzimidoyl chloride (see Section 4.4.1) with α -hydroxyacetonitriles **603**, followed by treatment of the unstable intermediate **604** with hydrogen chloride.¹⁸⁹ More stable perchlorate and picrate salts are also prepared. *N*-Acetyl perchlorates **606** are formed by treatment of **605** with perchloric acid and acetic

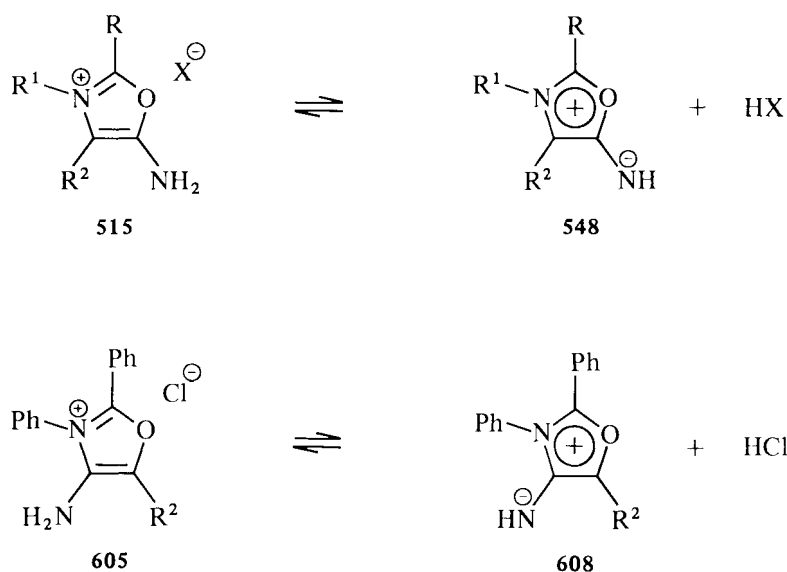


anhydride (Scheme 62). It was not reported, however, in analogy to the isolable *N*-acylated munchnone imines (Section 4.3.1), whether treatment of **605** solely with acetic or other acid anhydrides would lead to *N*-acylated isomunchnone imines **607**. The isolation of the free mesoionic system **607** via neutralization of salts **606** with sodium bicarbonate was unsuccessful; benzanilide, sodium perchlorate, and an unidentified compound were formed instead.



Scheme 62

The ability of isomeric 5-amino-1,3-oxazolium salts **515** to undergo cycloaddition reactions with acetylenic dipolarophiles via the munchnone imine tautomer **548** (Section 4.3.3.3.2) would lead to the speculation that the 4-amino-1,3-oxazolium system **605**, via the isomunchnone imine tautomer **608**, should behave analogously, yet this aspect of chemistry appears to be unreported.



Finally, a theoretical treatment of charge distributions and calculated geometries of the 1,3-oxazolium 4-imine system is available.⁵⁴

ACKNOWLEDGMENT

The authors wish to acknowledge the assistance of Nancy Pepper during the preparation of this manuscript, and the continued support of FMC Corporation.

REFERENCES

1. A. Schönberg, *J. Chem. Soc.*, 824 (1938).
2. W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.*, 307 (1949); *J. Chem. Soc.*, 1542 (1950).
3. E. Fischer and E. Besthorn, *Ann. Chem.*, **212**, 316 (1882).
4. A. Lawson and D. H. Miles, *Chem. Ind. (London)*, 461 (1958).
5. R. Huisgen, R. Grashey, and J. Sauer, in *The Chemistry of Alkenes*, S. Patai, Ed., Interscience, New York, 1964, pp. 806–878.

6. R. Huisgen, *Chem. Soc. Spec. Publ.*, No. 21, 51 (1967).
7. M. Ohta and H. Kato, in *Nonbenzenoid Aromatics*, J. P. Snyder, Ed., Academic Press, New York, 1969, pp. 117–248.
8. W. D. Ollis and C. A. Ramsden, *Adv. Heterocycl. Chem.*, **19**, 1 (1976).
9. K. T. Potts, *J. Heterocycl. Chem.*, **15**, 5–35 (1978).
10. C. A. Ramsden, in *Comprehensive Organic Chemistry*, Vol. 4, P. G. Sammes, Ed., Pergamon Press, New York, 1979, pp. 1171–1228.
11. C. G. Newton and C. A. Ramsden, *Tetrahedron*, **38**, 2965 (1982).
12. K. T. Potts, in *1,3-Dipolar Cycloaddition Chemistry*, A. Padwa, Ed., Wiley-Interscience, New York, 1984, Chapter 8.
13. I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
14. I. J. Turchi, *Ind. Eng. Chem. Prod. Res. Dev.*, **20**, 32 (1980).
15. H. O. Bayer, R. Huisgen, R. Knorr, and F. C. Schaefer, *Chem. Ber.*, **103**, 2581 (1970).
16. A. Lawson and D. H. Miles, *J. Chem. Soc.*, 2865 (1959).
17. R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem., Int. Ed. Engl.*, **3**, 136 (1964).
18. R. Knorr and R. Huisgen, *Chem. Ber.*, **103**, 2598 (1970).
19. G. Singh and S. Singh, *Tetrahedron Lett.*, 3789 (1964).
20. H. Alper and M. Tanaka, *J. Am. Chem. Soc.*, **101**, 4245 (1979).
21. R. Huisgen and T. Schmid, *Ann. Chem.*, 29 (1978).
22. W. Friedrichsen and W.-D. Schröer, *Ann. Chem.*, 476 (1981).
23. W. Friedrichsen, I. Schwarz, B. Epe, and K.-F. Hesse, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.*, **36B**, 622 (1981).
24. R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.*, **103**, 2611 (1970).
25. G. Manecke and J. Klawitter, *Makromol. Chem.*, **175**, 3383 (1974).
26. K. T. Potts and U. P. Singh, *J. Chem. Soc., Chem. Commun.*, 66 (1969).
27. W. K. Anderson and P. F. Corey, *J. Org. Chem.*, **42**, 559 (1977).
28. F. M. Hershenson, *J. Org. Chem.*, **37**, 3111 (1972).
29. K. T. Potts and S. Yao, *J. Org. Chem.*, **44**, 977 (1979).
30. A. Lawson and D. H. Miles, *J. Chem. Soc.*, 1945 (1960).
31. E. Tighineanu, F. Chiraleu, and D. Raileanu, *Tetrahedron Lett.*, 1887 (1978).
32. E. Tighineanu, F. Chiraleu, and D. Raileanu, *Tetradedron*, **36**, 1385 (1980).
33. C. V. Greco, R. P. Gray, and V. G. Grosso, *J. Org. Chem.*, **32**, 4101 (1967).
34. K. T. Potts, D. Bhattacharjee, and S. Kanemasa, *J. Org. Chem.*, **45**, 4985 (1980).
35. J. R. McDermott and N. L. Benoiton, *Can. J. Chem.*, **51**, 2562 (1973).
36. J. S. Davies and A. K. Mohammed, *J. Chem. Soc., Perkin Trans I*, 2982 (1981); *Pept., Proc. Eur. Pept. Symp. 16th*, 165 (1980); *Chem. Abstr.*, **98**, 89858e (1983).
37. W. D. Burrows, *J. Org. Chem.*, **31**, 3435 (1966).
38. M. Ohta and T. Mase, *Nippon Kagaku Zasshi*, **89**, 714 (1968); *Chem. Abstr.*, **70**, 11603v (1969).
39. G. V. Boyd, *J. Chem. Soc., Chem. Commun.*, 1410 (1968).
40. G. V. Boyd and P. H. Wright, *J. Chem. Soc., Chem. Commun.*, 182 (1969); *J. Chem. Soc. C*, 1485 (1970).
41. G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin Trans I*, 909 (1972).
42. G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin Trans I*, 914 (1972).
43. H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).

44. G. Killé and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 4636 (1968).
45. H. J. Petersen, *Tetrahedron Lett.*, 1557 (1969).
46. G. Höfle, W. Steglich, and H. Daniel, *Chem. Ber.*, **109**, 2648 (1976).
47. J. W. Cornforth, in *The Chemistry of Penicillin*, Princeton University Press, Princeton, NJ, 1949, p. 738.
48. W. Steglich and G. Höfle, *Chem. Ber.*, **102**, 1129 (1969).
49. R. Huisgen, H. Gotthardt, and H. O. Bayer, *Angew. Chem., Int. Ed. Engl.*, **3**, 135 (1964).
50. H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **103**, 2356 (1970).
51. R. Huisgen, H. Gotthardt, and H. O. Bayer, *Tetrahedron Lett.*, 481 (1964).
52. R. Huisgen, H. Gotthardt, and H. O. Bayer, *Chem. Ber.*, **103**, 2368 (1970).
53. G. V. Boyd, C. G. Davies, J. D. Donaldson, J. Silver, and P. H. Wright, *J. Chem. Soc., Perkin Trans II*, 1280 (1975).
54. M. J. S. Dewar and I. J. Turchi, *J. Chem. Soc., Perkin Trans II*, 548 (1976).
55. H. Gotthardt and F. Reiter, *Ann. Chem.*, 650 (1979).
56. W. Friedrichsen, W.-D. Schröer, and T. Debaerdemaeker, *Ann. Chem.*, 1836 (1980).
57. P. Espinasse, G. Killé, A. Kalt, and G. Nansé, *Tetrahedron Lett.*, 4587 (1977).
58. K. T. Potts, J. Baum, S. K. Datta, and E. Houghton, *J. Org. Chem.*, **41**, 813 (1976).
59. K. T. Potts, J. S. Baum, and M. Baum, unpublished results.
60. R. L. Sung and P. Dorn (to Texaco, Inc.), U.S. Patent 4,257,780 (1981).
61. H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91, 745, 757 (1928).
62. W. Steglich and G. Höfle, *Tetrahedron Lett.*, 1619 (1968).
63. W. Steglich and G. Höfle, *Chem. Ber.*, **104**, 3644 (1971).
64. J. Lukáč and H. Heimgartner, *Helv. Chim. Acta*, **62**, 1236 (1979).
65. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963); *J. Org. Chem.*, **33**, 2291 (1968); **41**, 403 (1976).
66. R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968); **37**, 2181 (1972); *J. Chem. Soc. A*, 1570 (1970); *Tetrahedron*, **33**, 3009 (1977).
67. R. K. Huisgen (to Union Carbide Corp.), U.S. Patent 3,285,931 (1966).
68. R. Knorr, R. Huisgen, and G. K. Staudinger, *Chem. Ber.*, **103**, 2639 (1970).
69. W. K. Anderson and P. F. Corey, *J. Med. Chem.*, **20**, 1691 (1977).
70. W. K. Anderson and M. J. Halat, *J. Med. Chem.*, **22**, 977 (1979).
71. W. K. Anderson, M. J. Halat, and A. C. Rick, *J. Med. Chem.*, **23**, 87 (1980).
72. F. M. Hershenson, *J. Heterocycl. Chem.*, **16**, 1093 (1979).
73. K. T. Potts and H. Y. Chen, personal communication.
74. K. T. Potts and J. Lorenc, personal communication.
75. F. M. Hershenson, *J. Org. Chem.*, **40**, 1260 (1975).
76. W. K. Anderson and P. F. Corey, *J. Med. Chem.*, **20**, 812 (1977).
77. W. K. Anderson and H. L. McPherson, Jr., *J. Med. Chem.*, **25**, 84 (1982).
78. J. Rebek, Jr. and J.-C. E. Gehret, *Tetrahedron Lett.*, 3027 (1977).
79. T. Uchida, S. Tsubokawa, K. Harihara, and K. Matsumoto, *J. Heterocycl. Chem.*, **15**, 1303 (1978).
80. J. M. Kane, *J. Org. Chem.*, **45**, 5396 (1980).
81. K. T. Potts and K. G. Bordeaux, personal communication.
82. H. T. Nagasawa, D. J. W. Goon, and F. N. Shirota, *J. Heterocycl. Chem.*, **18**, 1047 (1981).

83. F. M. Hershenson, *J. Org. Chem.*, **40**, 740 (1975).
84. J.-P. Maffrand, *Heterocycles*, **16**, 35 (1981).
85. K. T. Potts, K. G. Bordeaux, W. Kuehnling, and R. Salsbury, personal communication.
86. K. T. Potts, personal communication.
87. A. Padwa and L. Hamilton, *J. Heterocycl. Chem.*, **4**, 118 (1967).
88. J. W. ApSimon, D. G. Durham, and A. H. Rees, *Chem. Ind. (London)*, 275 (1973).
89. I. A. Benages and S. M. Albonico, *J. Org. Chem.*, **43**, 4273 (1978).
90. H. C. Berk and J. E. Franz, *Synth. Commun.*, **11**, 267 (1981).
91. H. L. Gingrich and S. M. Kellar, unpublished results.
92. K. T. Potts and D. McKeough, *J. Am. Chem. Soc.*, **96**, 4268 (1974).
93. J. S. Baum and H. G. Viehe, *J. Org. Chem.*, **41**, 183 (1976).
94. K. T. Potts, S. K. Datta, and J. L. Marshall, *J. Org. Chem.*, **44**, 622 (1979).
95. H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.*, **33**, 1097 (1968).
96. A. Padwa, E. M. Burgess, H. L. Gingrich, and D. M. Roush, *J. Org. Chem.*, **47**, 786 (1982).
97. M. T. Pizzorno and S. M. Albonico, *Chem. Ind. (London)*, 349 (1978).
98. M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **39**, 731 (1974).
99. D. J. Robins and S. Sakdarat, *J. Chem. Soc., Chem. Commun.*, 1181 (1979).
100. D. J. Robins and S. Sakdarat, *J. Chem. Soc., Perkin Trans I*, 909 (1981).
101. M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **42**, 909 (1977).
102. K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973).
103. K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).
104. J. Rebek, Jr., and S. H. Shaber, *Heterocycles*, **16**, 1173 (1981).
105. H. Kato, S. Nakazawa, T. Kiyosawa, and K. Hirakawa, *J. Chem. Soc., Perkin Trans I*, 672 (1976).
106. H. Gotthardt and R. Huisgen, *Chem. Ber.*, **103**, 2625 (1970).
107. H. Gotthardt, R. Huisgen, and F. C. Schaefer, *Tetrahedron Lett.*, 487 (1964).
108. W. Friedrichsen and W.-D. Schröer, *Tetrahedron Lett.*, 1603 (1977).
109. I. J. Turchi, C. A. Maryanoff, C. B. Karash, and E. Corey, personal communication.
110. O. Yebdri, O. Henri-Rousseau, and F. Texier, *Tetrahedron Lett.*, **24**, 369 (1983).
111. F. Texier, O. Yebdri, A. Laidoudi, B. Talbi, F. Balegroune, and G. Germain, *Tetrahedron Lett.*, **24**, 189 (1983).
112. F. Texier and O. Yebdri, *Tetrahedron Lett.*, 855 (1975).
113. A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **95**, 1945 (1973).
114. O. Yebdri and F. Texier, *Bull. Soc. Chim. Fr.*, II-195 (1983).
115. R. Verbruggen and H. G. Viehe, *Chimia*, **29**, 350 (1975).
116. H.-D. Martin and M. Heckman, *Angew. Chem., Int. Ed. Engl.*, **11**, 926 (1972).
117. K. T. Potts and J. Baum, *J. Chem. Soc., Chem. Commun.*, 833 (1973).
118. K. T. Potts, J. Baum, and E. Houghton, *J. Org. Chem.*, **41**, 818 (1976).
119. T. Eicher and V. Schäfer, *Tetrahedron*, **30**, 4025 (1974).
120. H. Matsukubo and H. Kato, *J. Chem. Soc., Chem. Commun.*, 412 (1974).
121. H. Matsukubo and H. Kato, *J. Chem. Soc., Perkin Trans I*, 632 (1975).
122. M. L. Deem, *Org. Prep. Proced. Int.*, **13**, 414 (1981).

123. H. Matsukubo, M. Kojima, and H. Kato, *Chem. Lett.*, 1153 (1975).
124. I. J. Turchi, C. A. Maryanoff, and A. R. Mastrocola, *J. Heterocycl. Chem.*, **17**, 1593 (1980).
125. T. L. Gilchrist, E. E. Nunn, and C. W. Rees, *J. Chem. Soc., Perkin Trans I*, 1262 (1974).
126. J. A. Myers, W. W. Wilkerson, and S. L. Council, *J. Org. Chem.*, **40**, 2875 (1975).
127. H. Matsukubo and H. Kato, *Bull. Chem. Soc. Jpn.*, **49**, 3333 (1976).
128. J. Lukáč, H. Heimgartner, and H. Schmid, *Chimia*, **31**, 138 (1977).
129. J. A. Myers, L. D. Moore, Jr., W. L. Whitter, S. L. Council, R. M. Waldo, J. L. Lanier, and B. U. Omoji, *J. Org. Chem.*, **45**, 1202 (1980).
130. H. Matsukubo and H. Kato, *J. Chem. Soc., Chem. Commun.*, 840 (1975).
131. H. Matsukubo and H. Kato, *J. Chem. Soc., Perkin Trans I*, 2565 (1976).
132. H. Matsukubo and H. Kato, *Bull. Chem. Soc. Jpn.*, **49**, 3314 (1976).
133. W. Friedrichsen and W.-D. Schröer, *Ann. Chem.*, 476 (1981).
134. W. Friedrichsen, W.-D. Schröer, and T. Debaerdemaeker, *Ann. Chem.*, 491 (1981).
135. T. Debaerdemaeker, W.-D. Schröer, and W. Friedrichsen, *Ann. Chem.*, 502 (1981).
136. W.-D. Schröer and W. Friedrichsen, *Ann. Chem.*, 1648 (1978).
137. A. Padwa, *Angew. Chem., Int. Ed. Engl.*, **15**, 123 (1976); in *New Synthetic Methods*, Vol. 5, Verlag Chemie, New York, 1979, pp. 25–69.
138. A. Padwa, H. L. Gingrich, and R. Lim, *Tetrahedron Lett.*, **21**, 3419 (1980).
139. A. Padwa, H. L. Gingrich, and R. Lim, *J. Org. Chem.*, **47**, 2447 (1982).
140. R. Huisgen and E. Funke, *Angew. Chem., Int. Ed. Engl.*, **6**, 365 (1967).
141. R. Huisgen, E. Funke, H. Gotthardt, and H.-L. Panke, *Chem. Ber.*, **104**, 1532 (1971).
142. R. Huisgen, E. Funke, F. C. Schaefer, H. Gotthardt, and E. Brunn, *Tetrahedron Lett.*, 1809 (1967).
143. E. Funke, R. Huisgen, and F. C. Schaefer, *Chem. Ber.*, **104**, 1550 (1971).
144. A. Kumar, K. Hartke, and J. Köster, *Chem. Zeitung*, 144 (1982).
145. K. T. Potts, S. J. Chen, and J. Szmuszkowicz, *J. Org. Chem.*, **42**, 2525 (1977).
146. H. Kato, K. Tani, H. Kurumisawa, and Y. Tamura, *Chem. Lett.*, 717 (1980).
147. V. M. Dixit, V. Bhat, A. M. Trozzolo, and M. V. George, *J. Org. Chem.*, **44**, 4169 (1979).
148. E. Brunn, E. Funke, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **104**, 1562 (1971).
149. T. Schmidt, Ph.D. dissertation, Univ. München (1975).
150. T. Shiba and H. Kato, *Bull. Chem. Soc. Jpn.*, **43**, 3941 (1970).
151. B. Zwanenburg, *Recueil, J. Royal Netherlands Chem. Soc.*, **101**, 1 (1982).
152. R. Huisgen, E. Funke, F. C. Schaefer, and R. Knorr, *Angew. Chem., Int. Ed. Engl.*, **6**, 367 (1967).
153. N. H. Toubro, B. Hansen, N. Harrit, A. Holm, and K. T. Potts, *Tetrahedron*, **35**, 229 (1979).
154. E. Funke and R. Huisgen, *Chem. Ber.*, **104**, 3222 (1971).
155. J. Lukáč, J. H. Bieri, and H. Heimgartner, *Helv. Chim. Acta*, **60**, 1657 (1977).
156. A. M. Knowles, A. Lawson, G. V. Boyd, and R. A. Newberry, *Tetrahedron Lett.*, 485 (1971).
157. C. W. Bird, *Tetrahedron Lett.*, 609 (1964); *Tetrahedron*, **22**, 2489 (1966).
158. K. K. Prasad and T. Petrzilka, *Helv. Chim. Acta*, **58**, 2504 (1975).
159. S. Mohan, B. Kumar, and J. S. Sandhu, *Chem. Ind. (London)*, 671 (1971).
160. B. Sain, G. Thyagarajan, and J. S. Sandhu, *Can. J. Chem.*, **58**, 2034 (1980).

161. B. Sain, J. N. Baruah, and J. S. Sandhu, *J. Heterocycl. Chem.*, **19**, 1511 (1982).
162. G. Thyagarajan, B. Sain, and J. S. Sandhu, *Chem. Ind. (London)*, 292 (1981).
163. J. M. Riordan and C. H. Stammer, *Tetrahedron Lett.*, 1247 (1976).
164. J. M. Riordan, M. Sato, and C. H. Stammer, *J. Org. Chem.*, **42**, 236 (1977).
165. W. Friedrichsen and I. Schwarz, *Tetrahedron Lett.*, 3581 (1977).
166. W. Friedrichsen, I. Schwarz, and T. Debaerdemaeker, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.*, **37B**, 663 (1982).
167. P. Roesler and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 4624 (1967).
168. S. Sato, T. Mase, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **41**, 2218 (1968).
169. P. Roesler and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 631 (1968).
170. G. Killé and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 4631 (1968).
171. M. Götz and K. Zeile, *Tetrahedron*, **26**, 3185 (1970).
172. D. Clerin, B. Meyer, J.-P. Fleury, and H. Fritz, *Tetrahedron*, **32**, 1055 (1976).
173. G. Killé and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 4619 (1967).
174. R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 5042 (1955).
175. T.-K. Liao and W. E. McEwen, *J. Org. Chem.*, **26**, 5257 (1961).
176. F. D. Popp, *Adv. Heterocycl. Chem.*, **24**, 187 (1979).
177. W. E. McEwen, A. V. Grossi, R. J. MacDonald, and A. P. Stamegna, *J. Org. Chem.*, **45**, 1301 (1980).
178. W. E. McEwen, I. C. Mineo, Y. H. Shen, and G. Y. Han, *Tetrahedron Lett.*, 5157 (1968).
179. W. E. McEwen, I. C. Mineo, and Y. H. Shen, *J. Am. Chem. Soc.*, **93**, 4479 (1971).
180. W. E. McEwen, K. B. Kanitkar, and W. M.-W. Hung, *J. Am. Chem. Soc.*, **93**, 4484 (1971).
181. W. E. McEwen, P. E. Stott, and C. M. Zepp, *J. Am. Chem. Soc.*, **95**, 8452 (1973).
182. W. E. McEwen, C. C. Cabello, M. A. Calabro, A. M. Ortega, P. E. Stott, A. J. Zapata, C. M. Zepp, and J. J. Lubinkowski, *J. Org. Chem.*, **44**, 111 (1979).
183. W. E. McEwen, I. C. W. Huang, C. P. C. Marin, F. McCarty, E. M. Segnini, C. M. Zepp, and J. J. Lubinkowski, *J. Org. Chem.*, **47**, 3098 (1982).
184. S. Veeraraghavan, D. Bhattacharjee, and F. D. Popp, *J. Heterocycl. Chem.*, **18**, 443 (1981).
185. D. Bhattacharjee and F. D. Popp, *J. Heterocycl. Chem.*, **17**, 1035 (1980).
186. E. K. Evangelidou and W. E. McEwen, *J. Org. Chem.*, **31**, 4110 (1966).
187. C.-F. Ling, R. P. Santella, Y. H. Shen, and W. E. McEwen, *J. Org. Chem.*, **40**, 661 (1975).
188. W. E. McEwen, M. A. Hernandez, C.-F. Ling, E. Marmugi, R. M. Padronaggio, C. M. Zepp, and J. J. Lubinkowski, *J. Org. Chem.*, **46**, 1656 (1981).
189. A. Chinone, S. Sato, T. Mase, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **42**, 2310 (1969).
190. M. Hamaguchi and T. Ibata, *Tetrahedron Lett.*, 4475 (1974).
191. M. Regitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 733 (1967).
192. T. Ibata, M. Hamaguchi, and H. Kiyohara, *Chem. Lett.*, 21 (1975).
193. M. Hamaguchi, *J. Chem. Soc., Chem. Commun.*, 247 (1978).
194. M. Hamaguchi and T. Ibata, *J. Chem. Soc., Chem. Commun.*, 230 (1980).
195. M. J. Haddadin, A. M. Kattan, and J. P. Freeman, *J. Org. Chem.*, **47**, 723 (1982).
196. M. J. Haddadin and H. Tanous, Abstract G-8, Ninth International Congress of Heterocyclic Chemistry, Tokyo, 1983.
197. K. T. Potts and J. L. Marshall, *J. Org. Chem.*, **44**, 626 (1979).

198. J. P. Freeman, M. J. Haddadin, W. H. Rastetter, and T. Chancellor, *Tetrahedron Lett.*, **23**, 815 (1982).
199. M. Hamaguchi and T. Ibata, *Chem. Lett.*, 499 (1975).
200. H. Kato, M. Hashimoto, and K. Ikoma, Abstract G-23, Ninth International Congress of Heterocyclic Chemistry, Tokyo, 1983.
201. W. Friedrichsen, W.-D. Schröer, and T. Debaerdemaeker, *Ann. Chem.*, 1850 (1980).

CHAPTER 5

Oxazoles and Oxazolines in Organic Synthesis

BRUCE E. MARYANOFF

Chemical Research Department, McNeil Pharmaceutical, Spring House, Pennsylvania

5.1.	Introduction	963
5.2.	Oxazolines	964
5.2.1.	Use as Protecting Groups	965
5.2.2.	Metalation Reactions	969
5.2.2.1.	Proton Abstraction	969
5.2.2.2.	Organometallic Addition	978
5.2.3.	Aromatic Nucleophilic Substitution	979
5.2.4.	Asymmetric Synthesis	981
5.2.4.1.	Alkylation of Metalated 2-Alkyl-2-oxazolines	981
5.2.4.2.	Aldol Reactions of 2-Alkyl-2-oxazolines	984
5.2.4.3.	Conjugate Addition Reactions	984
5.2.4.4.	Addition to α -Ketooxazolines	985
5.2.4.5.	<i>o</i> -Substituted-2-aryloxazolines	986
5.2.4.6.	Aromatic Nucleophilic Substitution	986
5.2.4.7.	Oxazolidines	987
5.2.5.	Oxazolinones	988
5.2.5.1.	Reactions with Nucleophiles	989
5.2.5.2.	Reactions with Electrophiles	991
5.2.5.3.	Cycloaddition Reactions	993
5.2.6.	Miscellaneous Applications and Reaction Intermediates	996
5.3.	Oxazoles	999
5.3.1.	Use as Protecting Groups	999
5.3.2.	Metalation Reactions	1002
5.3.3.	Cycloaddition Reactions	1005
5.4.	Concluding Remarks	1009

5.1. INTRODUCTION

Heterocycles, long relegated to the esoterica of organic chemistry by synthetic chemists, have emerged as important, effective agents for organic synthesis. No single publication has been more influential in promoting this modern viewpoint than the 1974 monograph by Meyers¹ on heterocycles in organic synthesis. Heterocyclic entities have served as latent functionalities² for the construction, elaboration, and functionalization of organic molecules. Also, heterocycles have been

used as groups for protecting sensitive moieties in synthetic sequences and for directing chemical reactions in a specific manner.

This chapter deals with the application of oxazolines and oxazoles in organic synthesis. Both heterocyclic units, of course, received treatment in Meyers' 1974 monograph.¹ Furthermore, oxazoles were exhaustively reviewed by Turchi in 1975 and 1981,^{3,4} as well as by Lakhan and Ternai in 1974.⁵ Some reactions of oxazoles were discussed in the Russian literature in 1969 and 1976.^{6,7} Oxazolines were the subject of general reviews in 1971⁸ and 1976,⁹ and three discussions by Meyers on their application in asymmetric synthesis appeared between 1978 and 1982.¹⁰⁻¹² Oxazolinones, a subclass of oxazolines, were reviewed by Filler and Rao in 1977.¹³ Thus, the chemical literature is well covered on oxazoles up to the beginning of 1980 and on oxazolines up to around 1977.

This chapter primarily reviews literature on the chemical applications of mononuclear oxazoles and oxazolines from 1977 to mid-1983. However, to illustrate certain key reactions, some earlier literature will also be tapped from time to time. Since the primary goal of the current survey is to delineate applications of oxazoles and oxazolines for the general elaboration of organic compounds, specialized heterocyclic ring transformations¹⁴ and heterocyclic substitution chemistry are substantially disregarded.

5.2. OXAZOLINES

Although an oxazoline five-membered ring can have the double bond located at the 2-, 3-, or 4-positions (giving 2-, 3-, or 4-oxazolines, respectively), only 2-oxazoline derivatives have been employed in organic synthetic procedures. The present discussion will therefore be restricted to the 2-oxazoline ring system. In the oxazolinone subclass, only the 2-oxazolin-5-ones (azlactones) have attracted sufficient synthetic interest to warrant consideration herein.

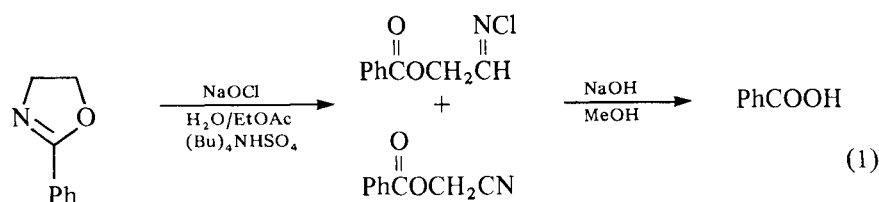
Preparation of the 2-oxazoline and 2-oxazolin-5-one ring systems is, for the most part, beyond the scope of this chapter. The interested reader should consult earlier reviews for such information.^{1,8,9,13}

Certain general chemical properties of 2-oxazolines confer utility as synthons for the assemblage of organic structures and as protecting groups. 2-Oxazolines are weak bases that form salts with mineral acids and quaternary derivatives with alkylating agents.^{8,9} The quaternary compounds can be readily reduced with sodium borohydride to oxazolidines, which can be hydrolyzed easily to release an aldehyde group.⁹ Although stable in cold aqueous acids and bases, they can be hydrolyzed rapidly by heating with dilute acids but more slowly by heating with aqueous bases.^{8,9} The electron-withdrawing C=N group activates the α -hydrogens on 2-alkyl substituents to proton abstraction, leading to aza-enolates that participate in typical carbanion chemistry.^{9-12,15} The 2-position proton can also be removed by strong bases to form carbanions that are acyl anion (formyl anion) equivalents having moderate synthetic utility.^{9,16-19} The oxazoline nucleus is also useful for (1) directing metalation, especially lithiation, to specific sites in an aromatic mole-

cule,⁹ constituting a form of heteroatom-facilitated lithiation,²⁰ and (2) activating aromatic substitution reactions.⁹ The 2-oxazolin-5-ones (Section 2.5) are useful because of the acidity of their 4-position protons, their ease of solvolysis or nucleophilic ring opening, and the presence of their nucleus in oxazolium-5-oxides (munchnones).¹³

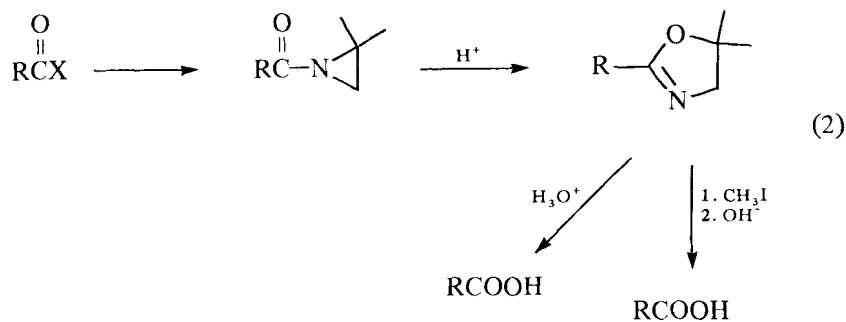
5.2.1. Use as Protecting Groups

Certain properties of 2-oxazolines make them serviceable intermediates for the protection of carboxylic acid and 1,2-aminoalcohol functionalities in the course of a synthetic program: (1) ease of formation from a variety of precursors, (2) stability to many harsh reagents, and (3) ease of unmasking.²¹ 2-Oxazolines may be generated from carboxylic acids, esters, acid chlorides, primary amides (via imidate esters), and nitriles under reasonably mild conditions.^{8, 9, 22-24} The original carboxylic acid or aminoalcohol group can be regenerated by hydrolysis of the 2-oxazoline with aqueous acid or base, albeit the latter requires more vigorous conditions (acidic alcoholysis to give esters is also possible).^{8, 9} Oxazolinium salts from quaternization of 2-oxazolines are readily hydrolyzed with mild aqueous alkali.^{9, 25} Recently, Weinreb reported a mild, high-yield method for conversion of a 2-oxazoline to its parent carboxylic acid by treatment with dilute NaOCl (5.25% commercial bleach) followed by gentle basic hydrolysis (Eq. 1).²⁶



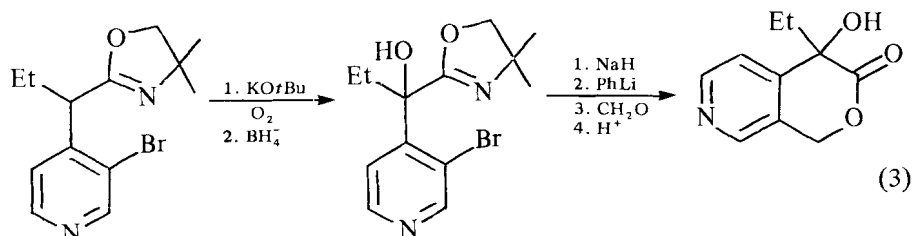
The 2-oxazoline ring is resistant to reaction with strongly basic or nucleophilic reagents, such as lithium aluminium hydride (LAH) or organomagnesium (Grignard) reagents, with strong oxidants, such as chromic oxide or alkaline permanganate, and with mild aqueous acid or alkali.^{8, 9, 15, 22} 2-Oxazolines are reduced by borane-tetrahydrofuran (borane-THF) to 1,2-aminoalcohols.²⁷ In the absence of a proton on the 2-position or α -protons on a 2-substituent (both susceptible to abstraction), the 2-oxazoline nucleus is also relatively inert to organolithium reagents.⁹

The use of a 2-oxazoline to mask the carboxylic acid group was first reported by Meyers in the early 1970s.^{22, 28, 29} Carboxylic acids, acid chlorides, or esters were converted to *N*-acylaziridines, which rearranged under mild, acidic conditions to 2-oxazolines; hydrolysis then regenerated the carboxylic acid (Eq. 2). Oxazoline protection allowed the preparation and use of Grignard reagents derived from bromobenzoic acids and selective reaction of the keto group of ketoacids with Grignard reagents or with LAH.

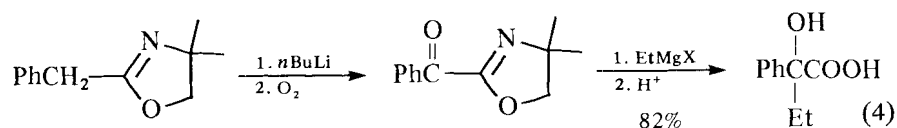


Ortho-lithiated 2-aryloxazolines represent an example of oxazoline protection analogous to that of the aromatic Grignard reagents. Although the lithiation chemistry illustrates carboxyl blocking methodology, discussion of the topic is largely reserved for Section 2.2.1 on metalation reactions. Aromatic nucleophilic substitution by organometallic reagents also exemplifies carboxyl protection but will be dealt with later as well (Section 2.3). Some specific applications of 2-oxazolines in the masking of carboxy and cyano functionalities are presented below.

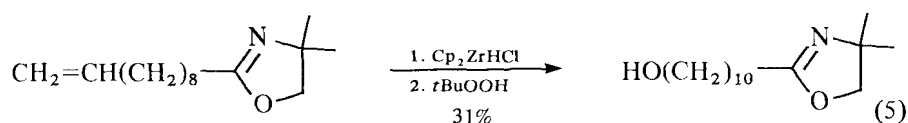
Synthesis of an intermediate to camptothecin³⁰:



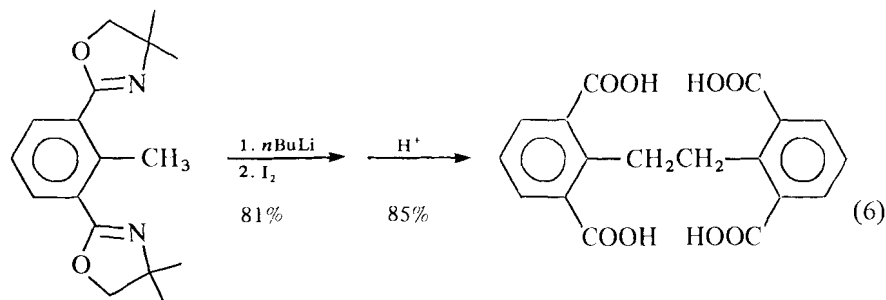
Preparation of mandelic acids³²:



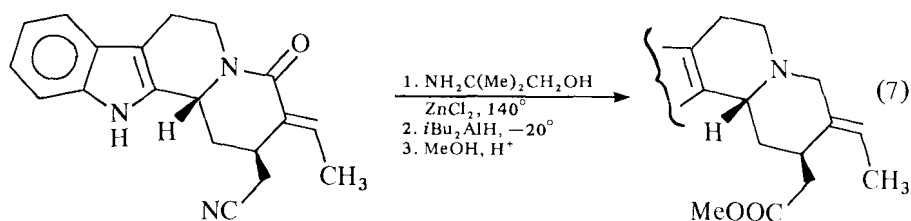
Hydrozirconation of unsaturated fatty acids³²:



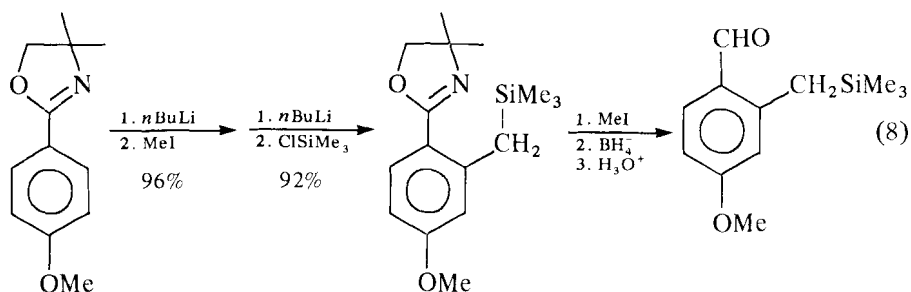
Synthesis of a diarylethane en route to [2.2.2] (1,2,3)-cyclophane³³:



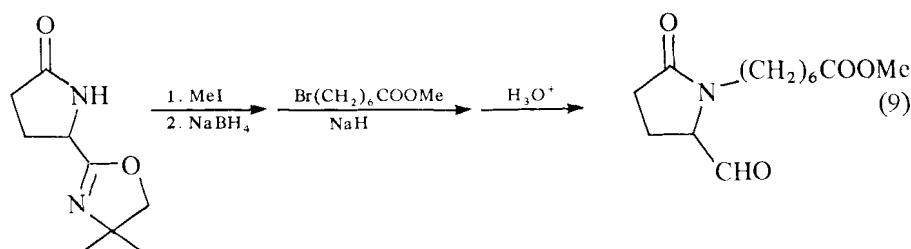
Protection of a cyano group during reduction of an amide group³⁴:

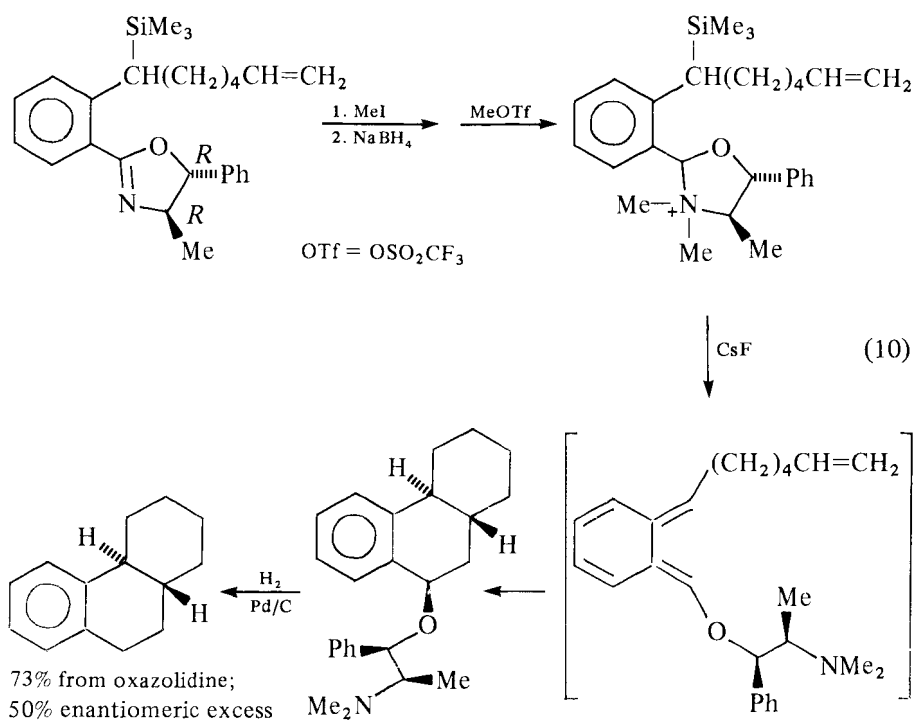


Synthesis of an intermediate to 11-hydroxyestrone methyl ether³⁵:

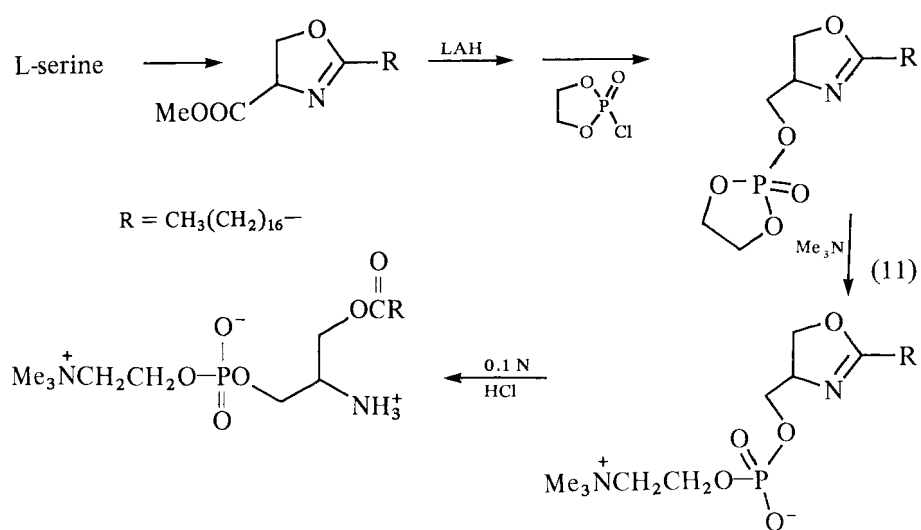


An extension of the carboxy group protection method involves generation of an oxazolidine from the oxazoline by methylation-reduction and hydrolysis to an aldehyde functionality.³⁶ Equation 8 depicts an example of this procedure.³⁵ Its utility in synthesis is also illustrated in a route to 8-azaprostaglandin E's in Eq. 9^{37, 38} and in an asymmetric synthesis of polycycles³⁹ (Eq. 10).





Oxazolines have been used to protect 1,2-aminoalcohols in syntheses of 2-deoxy-2-aminophospholipids⁴⁰⁻⁴² and a glycosphingolipid⁴³ starting with L-serine, in syntheses involving D-threonine as a starting material,^{44,45} and in aminoglycoside^{46a} and β -lactam^{46b} transformations. An application in phospholipid synthesis is shown in Eq. 11.⁴⁰



5.2.2. Metalation Reactions

Deprotonation of 2-oxazolines followed by reactions with electrophiles constitutes the major use of oxazolines in synthesis – both standard and asymmetric (aspects of asymmetric synthesis will be examined in Section 2.4).

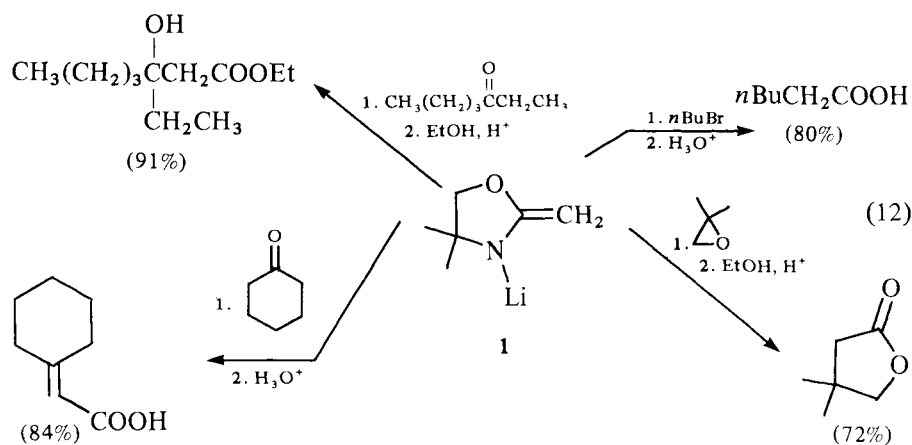
Metalation of a 2-alkyl substituent at the α -carbon gives rise to an aza-enolate, which can take part in the full range of enolate chemistry: alkylation, aldol condensation, acylation, and so on.^{9-12, 15} Metalation of 2-aryl substituents at the ortho position of the aryl ring occurs readily because of facilitation by the oxazoline heteroatoms and has been widely exploited.^{9, 20}

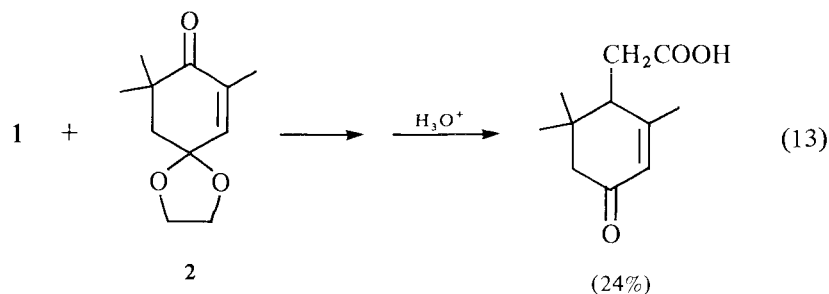
Organolithium compounds add to 2-(1-alkenyl)oxazolines at the β -carbon in Michael addition fashion to form aza-enolates like those obtained through deprotonation.⁹ Since most of the applications in this area have been in asymmetric synthesis, the main discussion will appear in Section 2.4.

5.2.2.1. Proton Abstraction

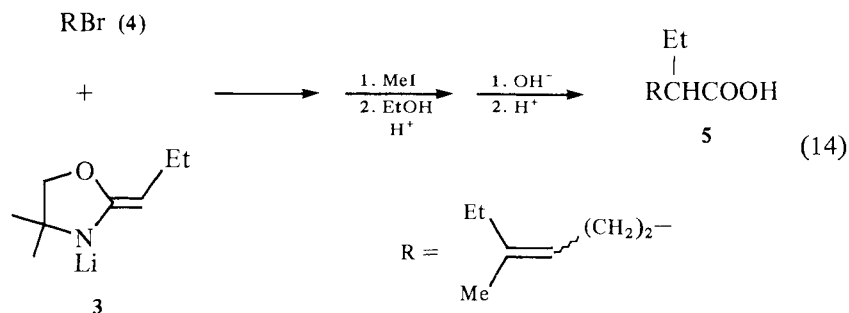
5.2.2.1.1. LITHIO 2-ALKYL-2-OXAZOLINES

The metalation of 2-alkyl-2-oxazolines is readily accomplished at low temperature (-78°C) with strong bases such as *n*-butyllithium or lithium diisopropylamide (LDA).^{1, 9, 15} The development of lithiooxazoline synthetic methodology was, to some degree, an extension of earlier 5,6-dihydro-1,3-oxazine chemistry.¹⁵ Much of the literature on the lithio oxazolines prior to 1976 has been surveyed by Meyers.⁹ Basically, the lithio 2-alkyl-2-oxazolines are synthons for LiCHRC(O)^- , useful in the synthesis of homologated acids, esters, ketones, and aldehydes of structure R'CHRC(O)^- . Alkylation with epoxides results in γ -butyrolactones, and condensation with aldehydes or ketones affords aldol products that may be converted to α,β -unsaturated acids or esters.⁹ The lithio oxazolines are best used at reduced temperatures since they are unstable in the vicinity of 0 – 25°C .⁴⁷ Representative chemical transformations are summarized in Eq. 12.

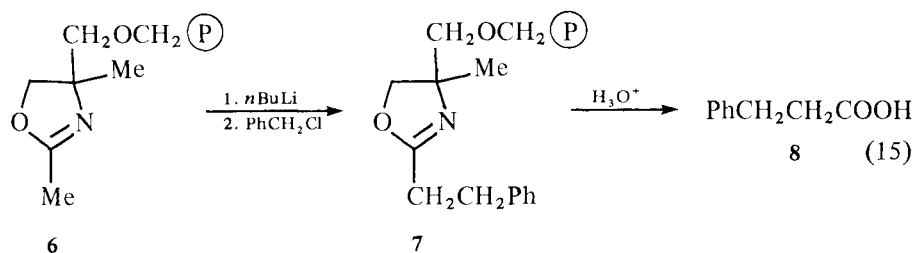




Use of lithio 2-alkyloxazolines has not attracted a large following in synthetic circles. One principal reason for this is competition from α -lithio ester enolates, convenient synthetic alternatives first introduced by Rathke.⁴⁸ A few reports on the use of lithio oxazolines have appeared since 1976. Shibata et al. described the addition of **1** to sterically hindered ketone **2** in low yield (Eq. 13).⁴⁹ A mandelic acid synthesis, mentioned in Section 2.1, was developed (Eq. 4).³¹ Kutney et al. alkylated lithio oxazoline **3** with *Z*- and *E*-bromides **4** in an inefficient route to isomeric mixture **5** (Eq. 14).⁵⁰



Polymer-bound oxazolines were studied by McManus.⁵¹ Oxazoline **6** [from chloromethylated poly(styrene-*co*-divinylbenzene)] was lithiated (at -43°C), then alkylated with excess benzyl chloride, to furnish **7**,⁵¹ which provided **8** in 81% yield on sluggish hydrolysis. The recovered aminoalcohol polymer was recyclable to **6**. Asymmetric synthesis with a polymeric oxazoline was also studied⁵¹ but this will be mentioned in Section 2.4.

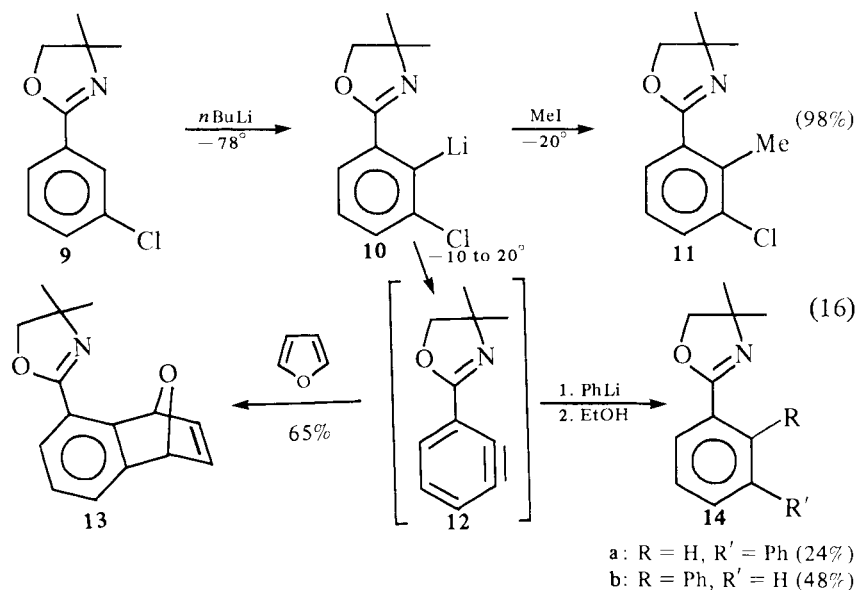


It should be kept in mind that 2-alkyl-2-oxazolines can undergo reactions at the α -carbon with certain electrophiles without metalation. The α -hydrogen is sufficiently labile to allow condensation with formaldehyde or aromatic aldehydes, giving α -hydroxymethyl (formaldehyde only: mono and bis) or 2-(1-alkenyl) derivatives.^{8,9,52} Other electrophiles such as halogens and 2-nitro alcohols (probably as the potent Michael-accepting nitroalkenes) also attack the α -carbon.⁸

5.2.2.1.2 AROMATIC RING LITHIATION

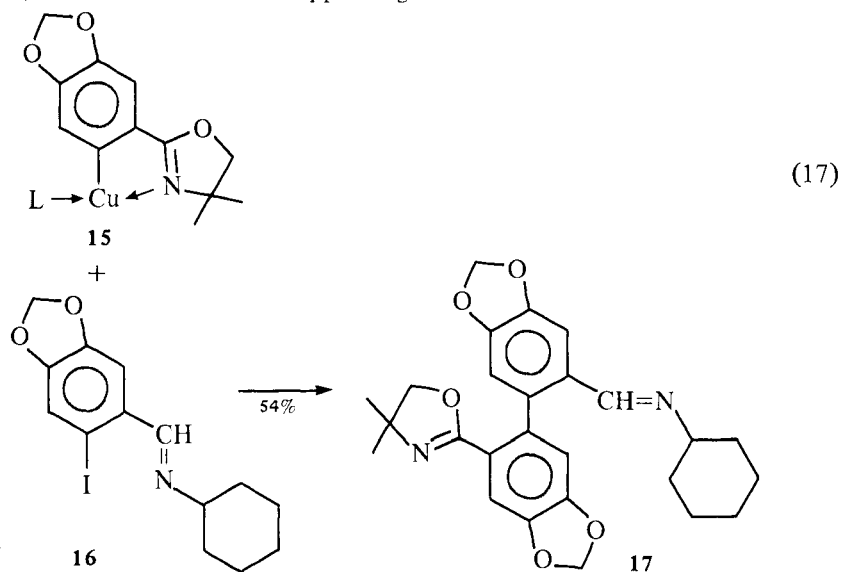
The 2-oxazoline group is a powerful activating and directing group for the lithiation of neighboring aryl CH and alkyl CH bonds. Presumably, the imino functionality in the oxazoline ring serves to (1) facilitate lithiation by coordination with the lithium atom of the organolithium reagent during deprotonation and (2) stabilize the resultant organolithium compound by cyclic coordination in a five- or six-membered ring. The use of a 2-oxazoline group for aromatic ortho lithiation, discovered independently by Meyers⁵³ and Gschwend,⁵⁴ has been widely exploited, in many cases for the production of highly substituted aromatic derivatives.^{9, 20, 23, 35, 55-75} The review by Gschwend on lithiation²⁰ covers literature on 2-aryloxazolines up to the middle of 1978; more recent papers are found elsewhere.^{23,35,55-75} Some representative applications follow.

(a) OXAZOLINYL BENZYNES (EQ. 16).⁶³ Lithiation of *m*-chlorophenyloxazoline **9** produces aryllithium **10**, which can be trapped with methyl iodide to afford **11** in 98% yield.^{63a} However, warming of **10** generates benzyne **12**, which reacts with certain dienes to form cycloadducts (e.g., **12** $\rightarrow$ **13**). Benzyne **12** also couples with organolithium reagents, giving new aryllithium compounds that may be reacted with electrophiles (e.g., **12** $\rightarrow$ **14**). It was first indicated that 2-lithio arenes form exclusively,^{63a} however, there are actually two modes of addition, the degree of

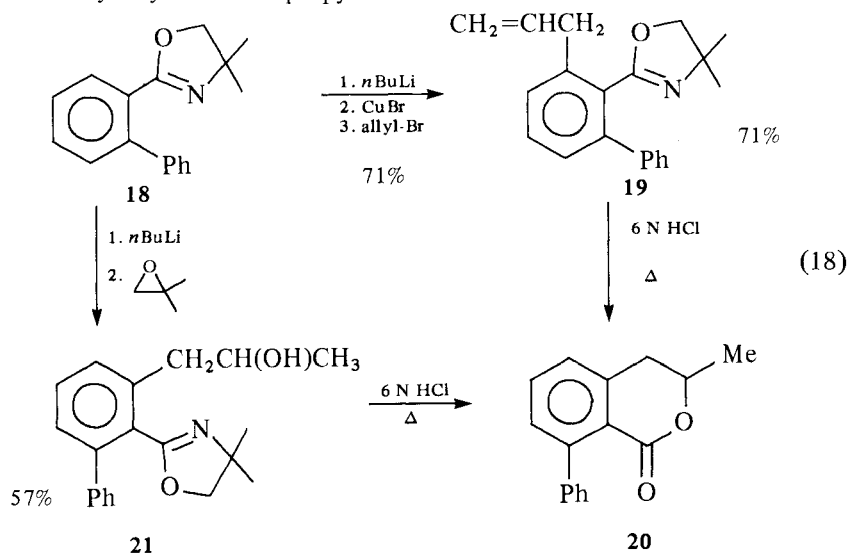


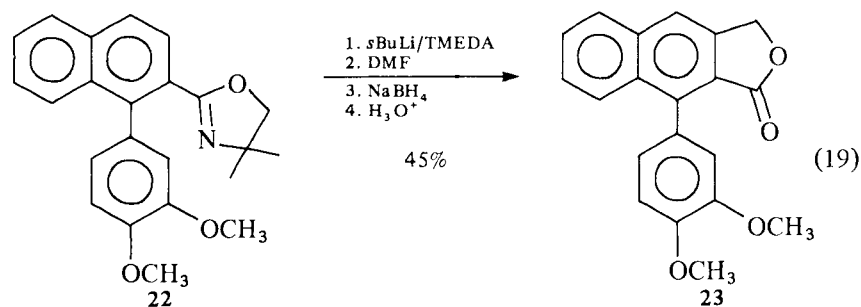
which depends on the type of organolithium.^{63b} Several alkyl- and aryllithiums generated 3-lithio (kinetic addition) products predominantly.^{63b}

(b) SYNTHESIS OF BIARYLS (EQ. 17).⁵⁵ Biaryl **17** was prepared by Ullmann coupling of oxazoline-stabilized copper reagent **15** and iodoimine **16**.

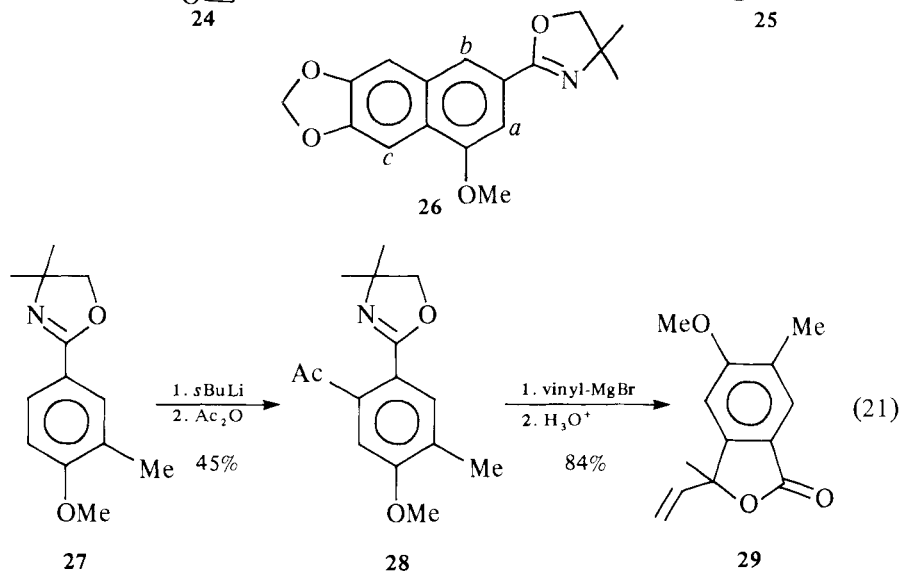
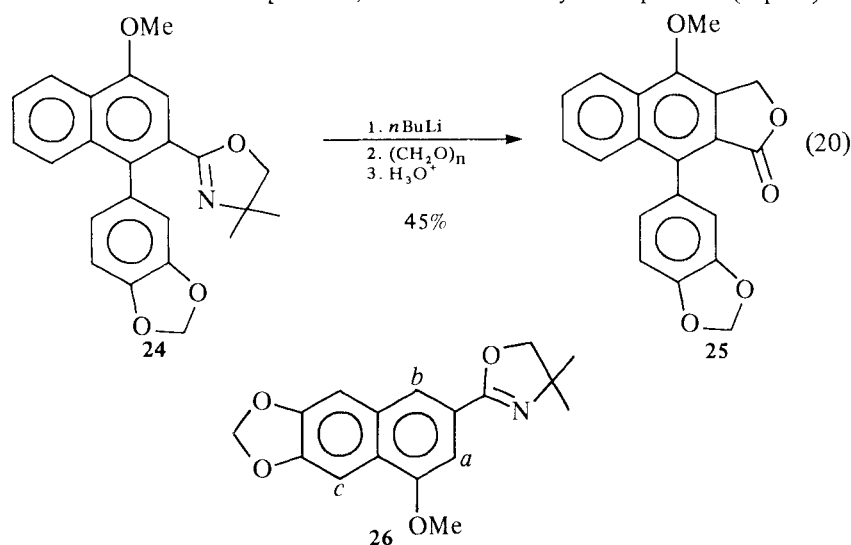


(c) SYNTHESIS OF FUSED LACTONES.^{23, 56-59, 65-71, 74, 75} Alkylation of the *o*-lithio oxazoline from **18** with allyl bromide gave **19** in only 19% yield, whereas alkylation of the arylcopper reagent proceeded in good yield (Eq. 18).⁵⁹ Iso-coumarin **20** was obtained from **19** or **21**, the latter prepared through lithiation of **18** followed by alkylation with propylene oxide.



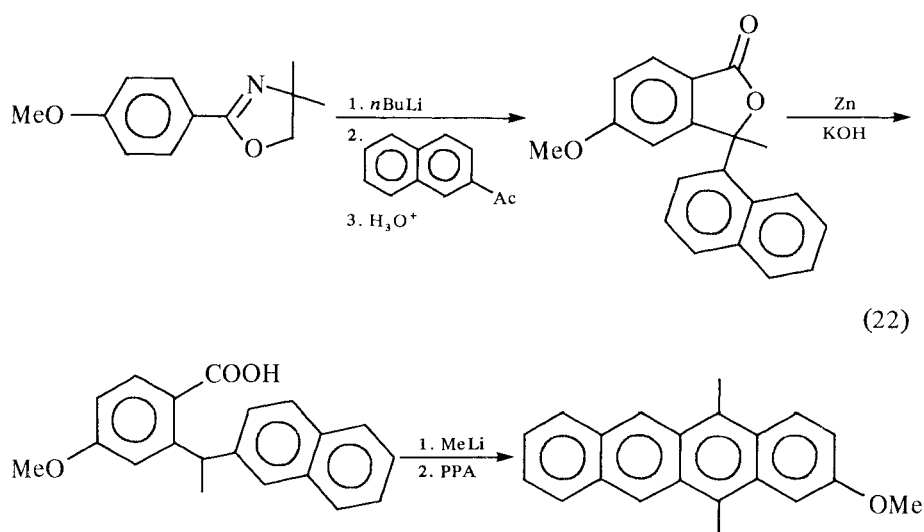


In the conversion of **22** to **23**, metalation of **22** could not be done effectively with *n*-butyllithium, so *s*-butyllithium and tetramethylethylenediamine (TMEDA) were employed (Eq. 19).²³ Although *n*-butyllithium did work well in metalating **24**, dimethylformamide (DMF) was ineffective as an electrophile, possibly because of steric effects (Eq. 20).²³ Attempted metalations of **26** resulted in mixtures of products arising from reaction at sites *a*, *b*, and *c*.²³ Metalation of **27** was regio-specific for the less hindered position; **28** was the sole acylation product (Eq. 21).⁵⁵



Adducts from the reaction of *o*-lithiated oxazolines with aliphatic aldehydes and ketones can yield *o*-alkenyl benzonitriles on reaction with phosphorus oxychloride in pyridine.^{64b}

Several papers have dealt with the synthesis of polyaromatic compounds via fused lactone intermediates (e.g., see Eq. 22).^{65-71, 74, 75}



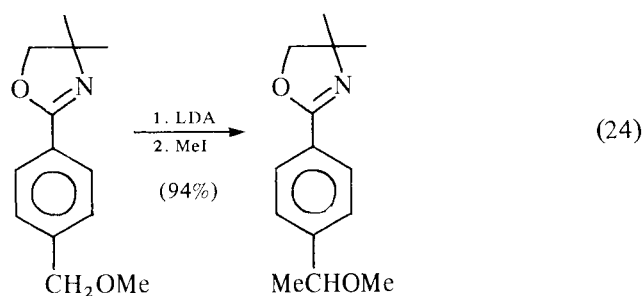
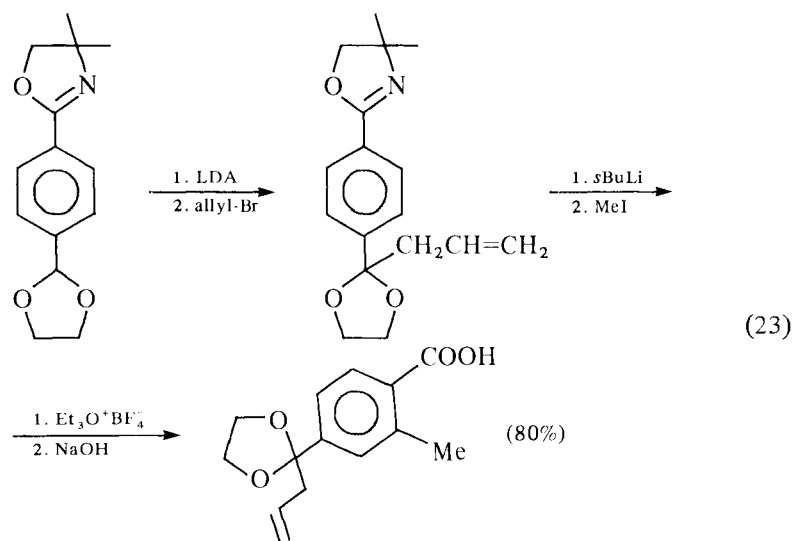
(d) METALATION OF HETEROCYCLES.⁷⁰⁻⁷⁵ Electron-rich, five-membered ring heterocycles (furan, *N*-R-pyrroles, and thiophene) generally undergo metalation at the α -position predominantly. An oxazoline substituent can be used to reinforce α -metalation or to direct metalation to the β -position. Della Vecchia and Vlattsas described selective lithiation of a 2-(2-thienyl)oxazoline at the 3-position,⁷⁵ although thiophene has a high preference for α -lithiation normally. Corresponding oxazolines of furan and *N*-methylpyrrole gave poor regioselectivity under the same conditions,⁷² but Chadwick et al. did establish conditions for the selective synthesis of 3-lithio derivatives.⁷²

Meyers and Gabel were able to lithiate 2-(3-pyridyl)- and 2-(4-pyridyl)-oxazolines at the 4- and 3-positions, respectively, with high regioselectivity.⁷¹ Methyl-lithium was preferred for lithiation in the 4-pyridyl series and lithium 2,2,6,6-tetramethylpiperidide was preferred for the 3-pyridyl series. In the 3-pyridyl series organometallic reagents were prone to add to the pyridine nucleus (see Section 2.2.2). Lithiation of the 4-pyridyl system, followed by fused lactone formation (see above), was used in the synthesis of ellipticine and its analogs.⁷⁴

Before leaving the subject of direct metalation, it should be noted that competition experiments have been performed to ascertain the relative ability of various substituents to orient metalation ortho on a benzene ring.⁶⁰⁻⁶² The tertiary amide function is the most effective in directing ortho lithiation. As a word of caution, selectivity in metalation reactions involving competing substituents can be highly dependent on the base and solvent employed.⁶²

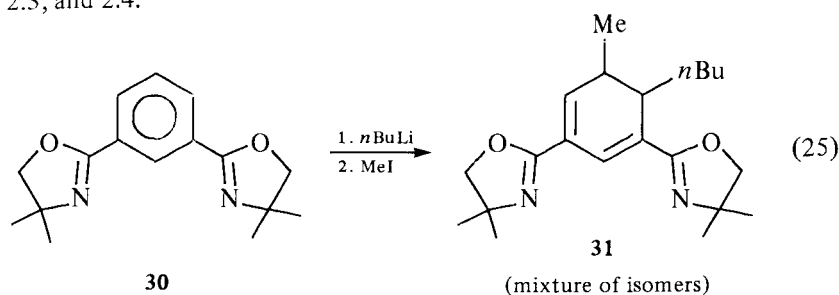
5.2.2.1.3. ALKYL GROUP LITHIATION

The properties of the 2-oxazoline group that promote ortho lithiation of aromatic rings can also be exploited for the lithiation of aliphatic groups. Facile lithiations of an aromatic methyl group adjacent to an oxazoline substituent have been reported by several research groups.^{33, 35, 76-78} One application was in an estrone synthesis³⁵ (Eq. 8) and another was in a berbine synthesis.⁷⁷ The ready metalation of a methyl group ortho to an oxazoline on a benzene ring may be due to vinylogous stabilization of the anion, as much as chelation of lithium by the oxazoline nitrogen. The stabilization of a carbanion by a 2-oxazoline group through vinylogy is aptly illustrated in the lithiation of 4-(2-oxazoliny)phenyl acetals and methoxymethyl ethers (Eqs. 23 and 24).⁷⁹

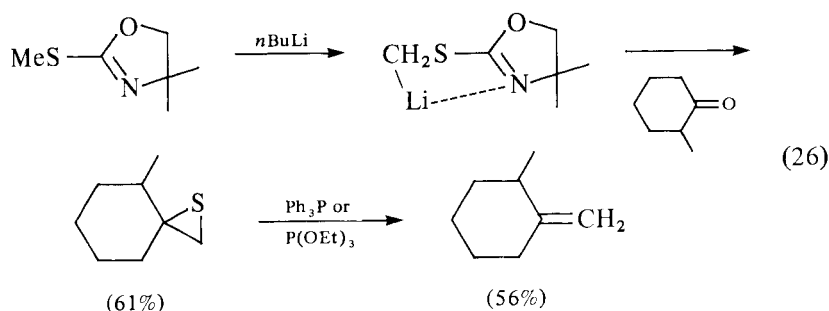


It is interesting to note that whereas the bisoxazoline in Eq. 6 was metalated on the aromatic methyl group with *n*-butyllithium,³³ bisoxazoline **30** suffered nucleophilic addition to the benzene ring, disrupting aromaticity (Eq. 25).⁷⁸ Successful aromatic ring metalation of **30** (between the two oxazoline substituents) was achieved with LDA (a non-nucleophilic base) and TMEDA.⁷⁸ The addition reaction

leading to **31** indicates the ability of a 2-oxazoline substituent to spur conjugate addition to carbon–carbon double bonds, a point to be discussed in Sections 2.2.2, 2.3, and 2.4.

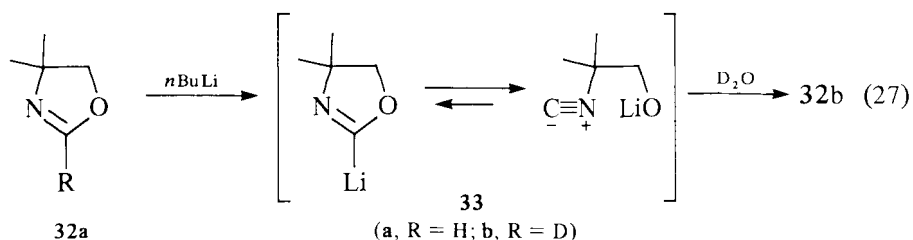


2-Alkylthio-2-oxazolines are metalated α to sulfur with *n*-butyllithium in THF at -78°C .^{80a} The new organolithium reagents serve as one-carbon homologating agents by their reaction with aldehydes and ketones to produce thiiranes, which are readily converted to alkenes (e.g., Eq. 26). Optically active thiiranes were prepared in low optical yields (ca. 20–30% ee), and optically active 2-methylmethylenecyclohexane was obtained after desulfurization (ca. 30% ee). A lithiomethylthio-oxazoline served as the linchpin of a thiophene synthesis.^{80b}

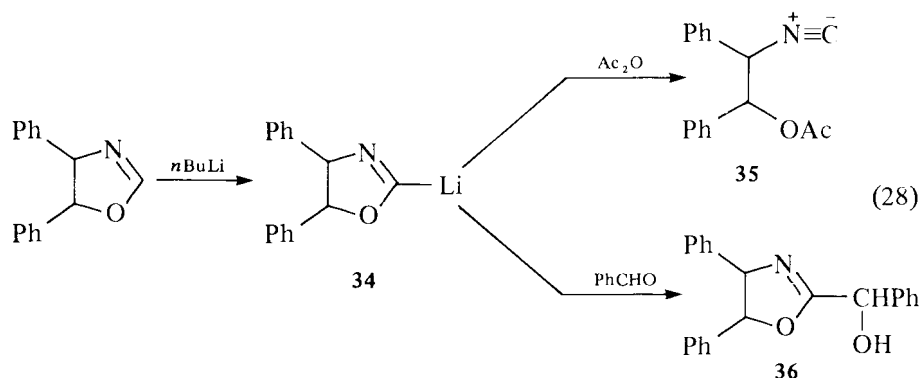


5.2.2.1.4. 2-LITHIO OXAZOLINES

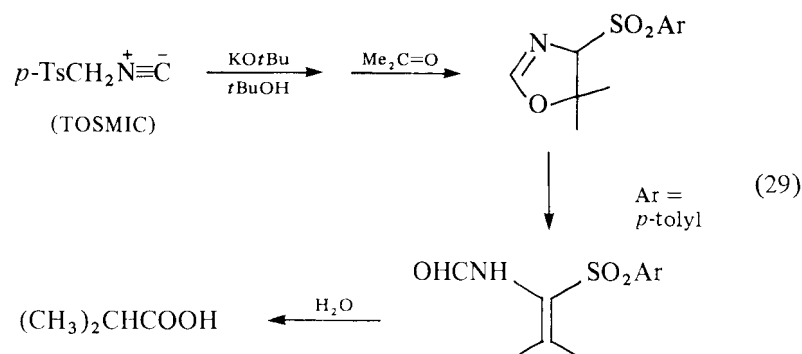
Metalation of the 2-position of a 2-unsubstituted oxazoline would yield an organo-metallic reagent that could function as a formyl anion equivalent. Such organo-metallic compounds can also be obtained via reaction of a metalated isocyanide with a ketone or aldehyde.¹⁶ Meyers and Collington⁸¹ deprotonated oxazoline **32a** with *n*-butyllithium to form an organolithium intermediate (**33**); quenching with deuterium oxide produced **32b**, as well as some isobutylene and LiOCN from deprotonation of the ring 5-position (Eq. 27). Note that 2-metalated 2-oxazolines exist in a mobile tautomeric equilibrium, lying strongly toward the ring-opened molecule (Eq. 27).¹⁶ Although alkaline hydrolysis (water, methanol) manages to capture the oxazoline form, because protonation of the ring-opened form is reversible, leading to thermodynamic product, irreversible quenching with acetic acid or acetic anhydride yields a 2-isocyano alcohol derivative.¹⁶



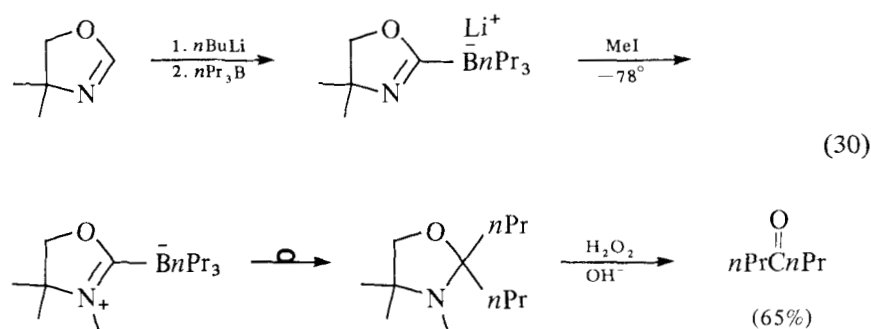
Reaction of lithio oxazoline **34** with acetic anhydride gave ring-opened product **35**, but reaction with benzaldehyde gave substituted oxazoline **36** (Eq. 28).^{16a} On the contrary, Pridgen and Killmer¹⁷ were unable to trap a 2-lithio-2-oxazoline in the absence of aromatic substituents on the 4- and/or 5-position of the oxazoline. Kozikowski and Ames⁸² trapped a 5-aryl 2-lithio oxazoline in the reaction of 2 equivalents of piperonal with 1 equivalent of lithiomethylisocyanide. Some similar quenching results were reported by Barrett et al.⁸³



The metalated isocyanide route to oxazolines has provided useful synthetic procedures for 2-hydroxy aldehydes,⁸⁴ α -amino acids,⁸⁵ alkenes,⁸⁶ carboxylic acids (Eq. 29),⁸⁷ and nitriles (see Section 2.6).^{88,89} The latter two represent one-carbon homologation of a carbonyl compound.⁸⁷⁻⁸⁹ A review on α -metalated isocyanide chemistry is available.^{16b}

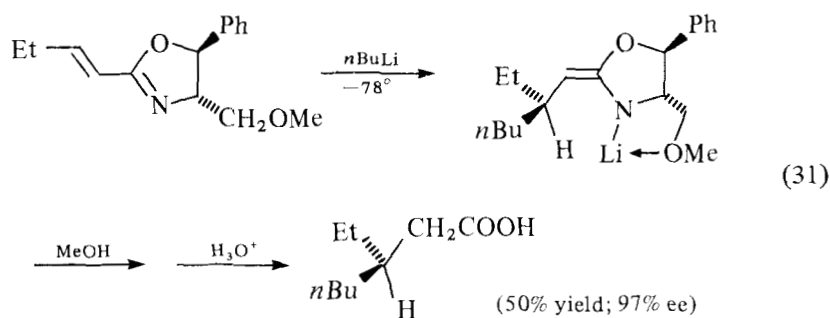


An interesting dialkyl ketone synthesis was devised by reacting a 2-lithio oxazoline with a trialkylborane (Eq. 30).⁹⁰

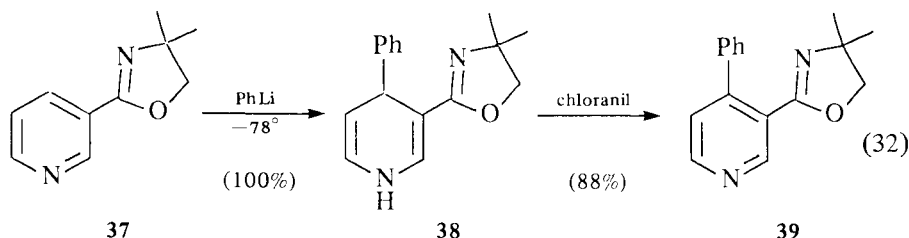


5.2.2.2. Organometallic Addition

2-(1-Alkenyl)oxazolines undergo conjugate addition of organolithium reagents to give aza-enolates analogous to those obtained from deprotonation of 2-alkyl-2-oxazolines (Section 2.2.1).⁹¹ This process has generally been reported in the realm of asymmetric synthesis, wherein 3-alkyl carboxylic acids were prepared in very high (92–99% ee) enantiomeric purity (see Section 2.4). An exemplary reaction is presented in Eq. 31.⁹¹



Nucleophilic addition in a 1,4 manner is also observed with 3-pyridyloxazolines.^{71, 92} Usually, strong nucleophilic species such as unstabilized organolithium compounds mainly add 1,2 to the pyridine nucleus. For 3-oxazolin-2-yl pyridine **37**, addition of methyllithium, *n*-butyllithium, ethylmagnesium bromide, and phenyllithium occurs almost exclusively 1,4 to give 4-substituted 1,4-dihydropyridines (e.g., **38**), which are readily oxidized to the corresponding 4-substituted pyridines (Eq. 31).^{71, 92}

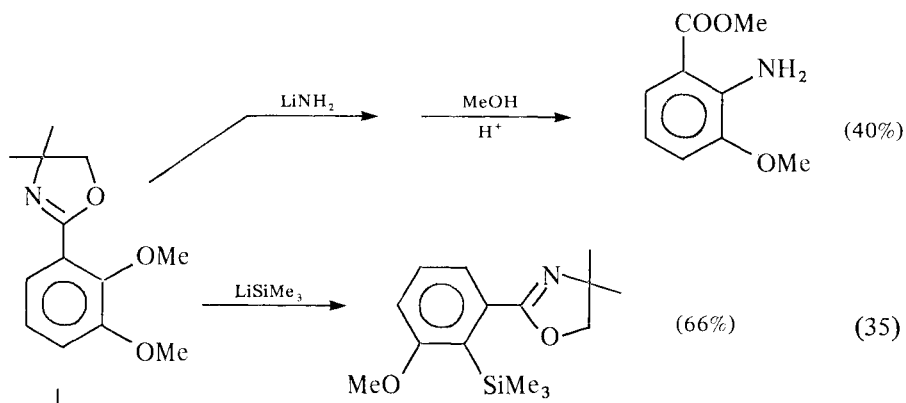
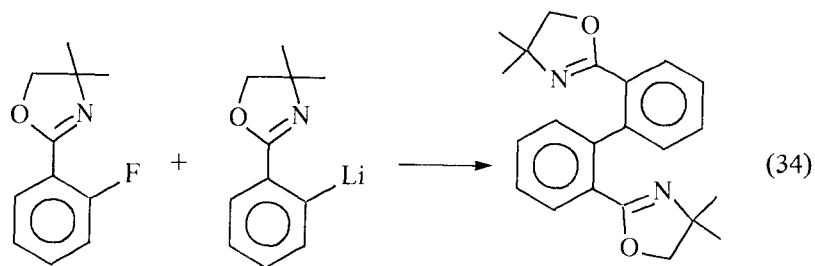
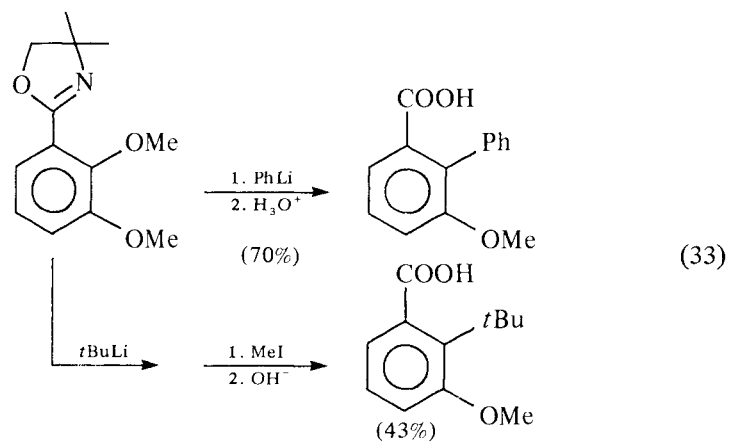


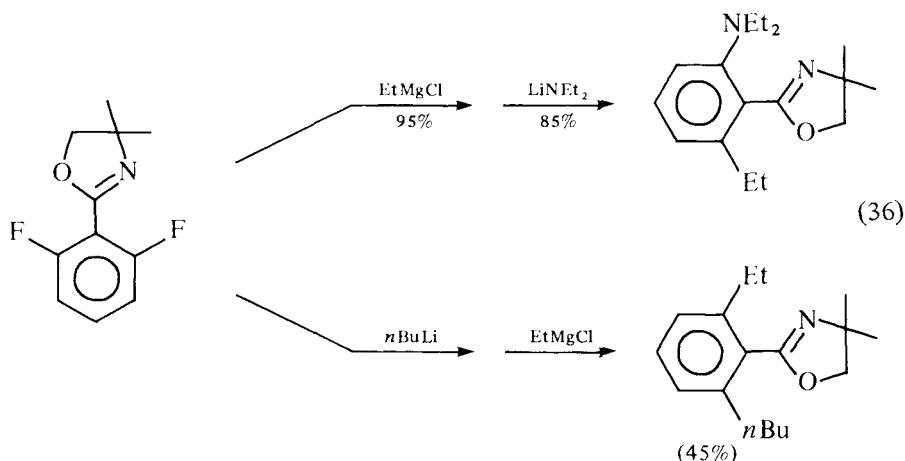
The activating power of the 2-oxazolinyl substituent for conjugate addition of organometallic reagents is evident from the addition of *n*-butyllithium to a benzene ring to give a dihydrobenzene compound (Eq. 25, Section 2.2.1), albeit two oxazoline groups are present in this case.⁷⁸ Significantly, Meyers has discovered that naphthyloxazolines have a tendency to experience “1,4-addition” of organolithium reagents.⁹³ In this same vein, one may perceive nucleophilic aromatic substitution reactions of certain ortho-substituted aryloxazolines to be a form of 1,4-addition, followed by elimination of the nucleofugic ortho substituent to give an aromatic derivative (this reaction is discussed in Section 2.3). The driving force for 1,4-addition to “aromatic” systems may reside in the thermodynamic stability of the aza-enolate species.

5.2.3. Aromatic Nucleophilic Substitution

As mentioned in Section 2.2.1, aryloxazolines are versatile intermediates for introducing various ortho substituents onto an aromatic ring through ortho lithiation followed by reaction with an electrophile. The utility of the oxazoline group was extended by Meyers’s discovery that oxazoline derivatives of *o*-methoxy^{25, 94, 95} and *o*-fluoro⁹⁶ benzoic acids experience displacement of the methoxy or fluoro groups by organolithium (or magnesium) reagents^{25, 94, 96} or lithium amides,^{95, 97, 98} rather than metalation of a vacant ortho position. The reaction probably occurs by an addition–elimination process, instead of a free-radical one.²⁵ As such, it can be viewed as a 1,4-addition to a 2-(1-alkenyl)oxazoline system, wherein the cyclohexadienylidene adduct is stabilized by complexation of lithium with the oxazoline nitrogen (see Section 2.2.2). The cyclohexadienylidene aza-enolate then suffers loss of lithium methoxide or fluoride in a final rearomatization step. Presumably, the methoxy or fluoro substituent facilitates addition to the aromatic nucleus by participating in metal complexation. The strong activating effect of the 2-oxazoline group toward aromatic substitution may be contrasted with the tertiary amide group, which, although a superactivator of ortho metalation, does not activate nucleophilic substitution well.²³

Several papers have demonstrated the power of this method in the synthesis of *o*-aryl, *o*-alkyl, *o*-silyl, *o*-amino, and *o*-(1-alkenyl) benzoic acids (or corresponding benzaldehydes).^{23, 25, 94–106} A sampling of representative chemistry is presented in Eqs. 33–36. Organometallic reagents stabilized by delocalization or strong intramolecular coordination (e.g., benzyl, allyl, 1,3-dithianyl reagents; metallo enolates)





are generally unsuitable for aromatic substitution.^{25, 96} However, this problem may be diminished in fluoro displacement compared with methoxy displacement, *q.v.* 2-thienyllithium^{25, 96} and *o*-dimethylaminomethylphenyllithium.¹⁰⁴ Sequential, double-displacement reactions can be performed (Eq. 36).^{25, 96}

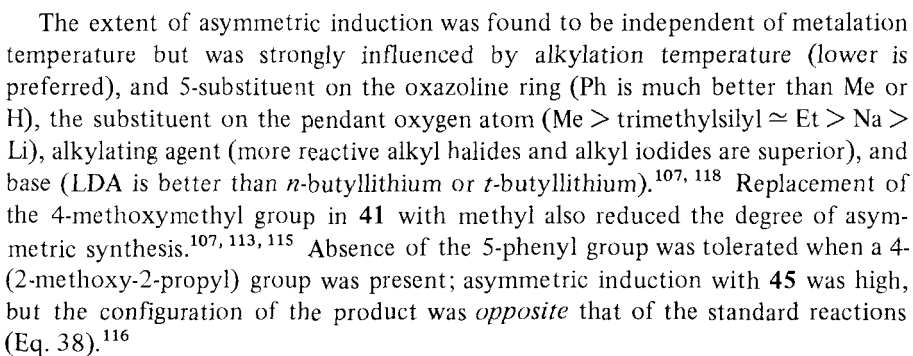
The methodology has been applied to the synthesis of cannabinol,¹⁰⁰ lignan lactones,²³ intermediates to diterpenes,^{102a} an anticoccidial natural product,⁹⁸ various benzo-fused ring systems,⁹⁷ and eupolauramine.^{102b} One should note, in particular, that the aromatic substitution chemistry has been highly useful for the synthesis of unsymmetrical biaryls^{23, 25, 94, 96, 99, 100, 103, 104} (for a different oxazoline-based biaryl synthesis see Eq. 17) and was parlayed by Cram¹⁰⁵ and Meyers¹⁰⁶ into an exquisite asymmetric synthesis of chiral binaphthyls (see Section 2.4).

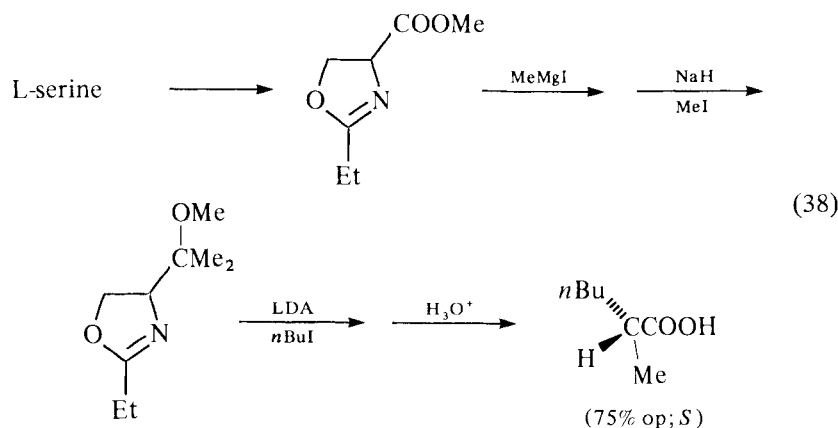
5.2.4. Asymmetric Synthesis

Perhaps the most remarkable applications of oxazolines in organic synthesis exist in the realm of asymmetric synthesis. Work in this area, initiated in Meyers' laboratory around 1974, had led to several very successful procedures for asymmetric induction. Since progress has been surveyed in some reviews,⁹⁻¹² one as recently as 1982,¹² discussion is mostly limited here to outlining the types of asymmetric reactions.

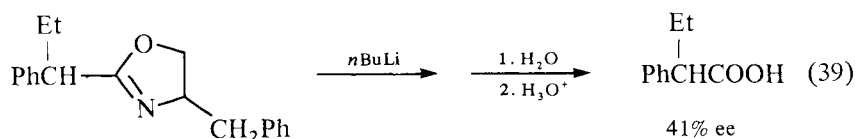
5.2.4.1. Alkylation of Metalated 2-Alkyl-2-oxazolines¹⁰⁷⁻¹²⁰

Lithiation of chiral 2-alkyl-2-oxazolines **41** comprised of (+)-amino diol component **40** affords chiral lithio aza-enolates **42**, which can be alkylated in the usual fashion (Section 2.2.1); hydrolysis then yields carboxylic acids **43** with a high proportion of one enantiomer (ca. 55–85% ee) (Eq. 37).¹⁰⁷ Amino alcohol by-product **44** can be recycled into oxazolines **41**. Both stereochemical configurations

$$\begin{array}{c} \text{OH} \\ | \\ \text{PhCHCHCH}_2\text{OH} \\ | \\ \text{NH}_2 \\ (+)\text{-40} \end{array}$$




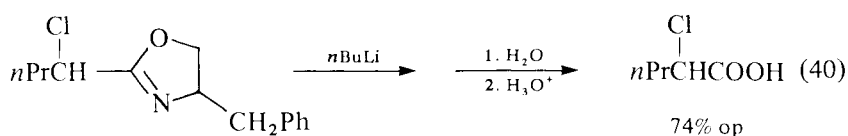
Chiral lithio oxazolines have also been alkylated with oxiranes to form γ -butyrolactones in high optical yields (60–85% ee); 3-trimethylsiloxyalkyl halides have been analogously used to prepare δ -valerolactones (50–70% ee).¹⁰⁸ Protonation or deuteration of chiral oxazolines has resulted in asymmetric transformations with optical yields ranging from ca. 30 to 75% (e.g., Eqs. 39 and 40).^{113, 114, 119}



Chiral lithio 4-methoxymethyl-5-phenyl oxazolines have been applied to the synthesis of optically active intermediates in routes to insect pheromones^{110, 111} (ca. 70% ee) and part of the cholesterol side chain.¹⁰⁹

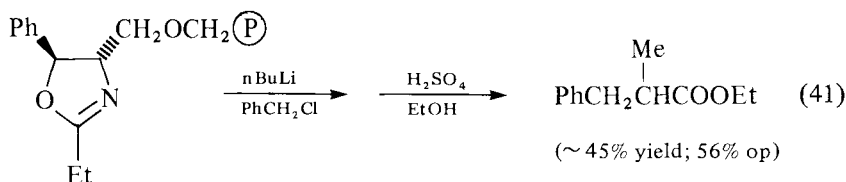
Polymer-bound chiral oxazolines have been studied as analogues of the parent procedure, with only a small loss in optical yields (Eq. 41).⁵¹ The chiral oxazoline method was employed, as well, to generate optically active polymers.¹¹²

The mechanism of asymmetric induction has been addressed.^{117, 118} It appears that lithiation of chiral 4-methoxymethyl-5-phenyloxazolines involves highly selective formation of the *Z*, as opposed to the *E*, lithio aza-enolate, both present as nonequilibrating kinetic products. Alkylation of such lithio anions occurs at similar rates, supporting the idea that asymmetric induction is determined chiefly by stereoselectivity in the deprotonation step, with alkylation favoring approach from the side of the methoxymethyl group.¹¹⁷

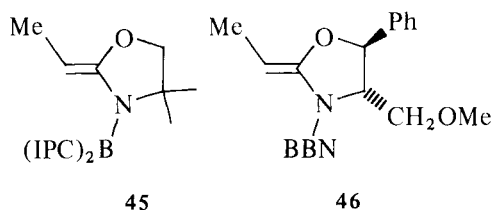


5.2.4.2. Aldol Reactions of 2-Alkyl-2-oxazolines^{121–124}

Condensation of racemic 2-ethyl-4-methoxymethyloxazoline with isobutyraldehyde gave aldol product having a 9:1 *threo*–*erythro* ratio, whereas the 4-unsubstituted oxazoline gave a 56:44 mixture.¹²¹ Optically active 2-ethyl-4-methoxymethyl-5-phenyloxazoline furnished a four-component mixture of adducts in an 18:2:2:1 ratio (*threo*–*erythro* = 82:18), wherein the major product was the *S,S* enantiomer (75% enantiomeric excess). The correspondent optically active 2-methyloxazoline showed comparatively low optical yields of 20–25%.¹²⁴



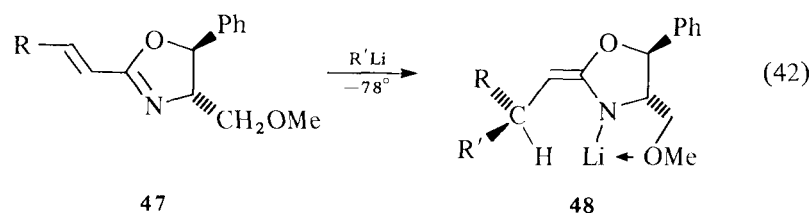
Boron aza-enolates, derived from oxazolines by low-temperature lithiation followed by borylation, were explored by Meyers.¹²² One boron enolate possessed a chiral boron auxiliary group (viz. **45**) and one possessed a chiral oxazoline ring (viz. **46**) (IPC = isopinocampheyl; BBN = 9-borabicyclonon-9-yl). Treatment of **45** with a variety of aldehydes afforded mainly *threo*- β -hydroxy esters (90–95% diastereomeric excess; 77–85% enantiomeric excess). By contrast, treatment of **46** with aldehydes afforded mainly *erythro* compounds (ca. 98% diastereomeric excess; 40–60% enantiomeric excess). Some other boron enolates have also received attention.¹²³ Evidently, boronated oxazoline enolates offer a nice method for acyclic stereoselection.¹²⁵



5.2.4.3. Conjugate Addition Reactions^{126–129}

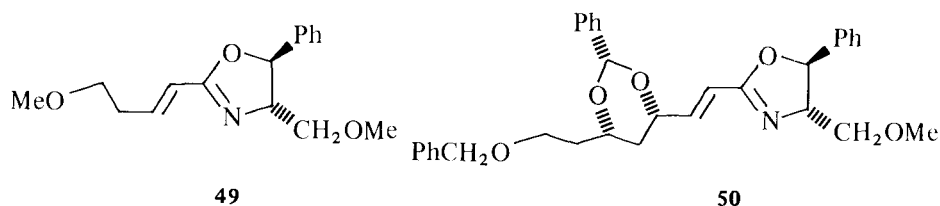
Chiral *E*-alkenyloxazolines **47** react as electrophiles with organolithium reagents, giving lithio aza-enolates **48** (Eq. 42; *Z*-alkenyl derivatives only undergo proton abstraction).^{91,126} Protonation of such aza-enolates with methanol, and acidic hydrolysis, produced chiral 3-substituting carboxylic acids with very high enantiomeric purity (91–99% ee). The notable enantioselectivity reflects on the very selective diastereofacial 1,4-addition of the organolithium reagent to **47**. Various

lithio oxazolines **48** combined with methyl iodide to afford α -methyloxazolines with ca. 99% stereoselectivity, which unfortunately was partially compromised by epimerization during hydrolysis to 2,3-disubstituted carboxylic acids possessing 77–82% diastereomeric purity.¹² The stereoselective methylation indicates that oxazolines **48** were virtually a single stereoisomeric species, a *Z*-lithio azaenolate that alkylates from the side of the 4-methoxymethyl group.¹² Chiral 1,4-addition was used to make several optically active 3-substituted six-membered-ring lactones in ca. 95% ee.¹²⁶ Absence of the 5-phenyl group (in **47**) did not significantly alter the asymmetric 1,4-addition.^{126, 127}



In the synthesis of **47**, where $R \neq \text{Ph}$, by the aldol route problems were experienced with the presence of undesired *Z*-1-alkenyl derivative, olefin positional isomerization, and polymerization. As an alternative, diisopropylphosphonate carbanion olefination was recommended.¹²⁶

Ziegler and Gilligan¹²⁸ reported a mild solvent effect on stereoselectivity in 1,4-addition to **49**. But more important, they observed dramatic reversals in stereochemistry for addition of alkyllithiums versus allyllithiums to **50**. Allyl and methallyl reagents give stereoselectivity opposite to that predicted by Meyers' model, although they reacted normally with **49**.



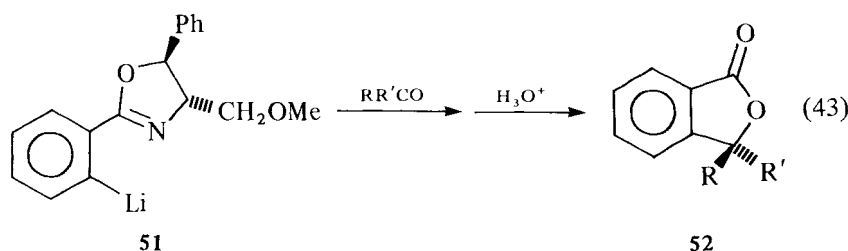
Addition of organometallics to 3-pyridyl-2-oxazolines resulted in 4-substituted 1,4-dihydropyridines, isolated as 1-carbomethoxy adducts, with 82–94% de.¹²⁹

5.2.4.4. Addition to α -Ketooxazolines^{130a}

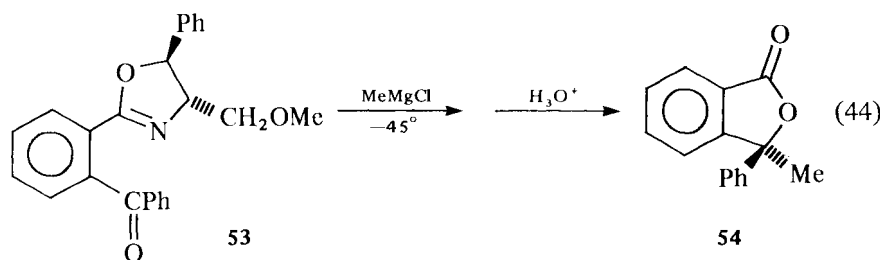
Meyers and Slade studied the addition of organometallic reagents to chiral α -ketooxazolines prepared by oxygenation of lithio oxazolines (achiral example given in Eq. 4).^{130a} α -Hydroxy carboxylic acids (generally *S* configuration) were obtained in 30–87% enantiomeric excess from the typical 4-methoxymethyl-5-phenyloxazolines. Other 4- and 5-substituted oxazolines gave less satisfactory results.

5.2.4.5. *o*-Substituted-2-aryloxazolines^{12, 130b}

Treatment of *o*-lithiophenyloxazoline **51** with carbonyl compounds yielded adducts of low diastereomeric purity (Eq. 43).^{12, 130b} Separation of diastereomeric adducts led to pure enantiomers of phthalides **52**.

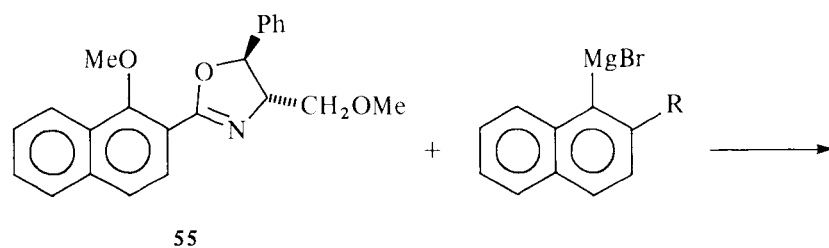


Addition of organolithium reagents to *o*-acylphenyloxazolines (such as **53**) occurred with poor diastereoselectivity; however, Grignard addition to **53** provided lactone **54** in high enantiomeric purity (Eq. 44).^{12, 130b}

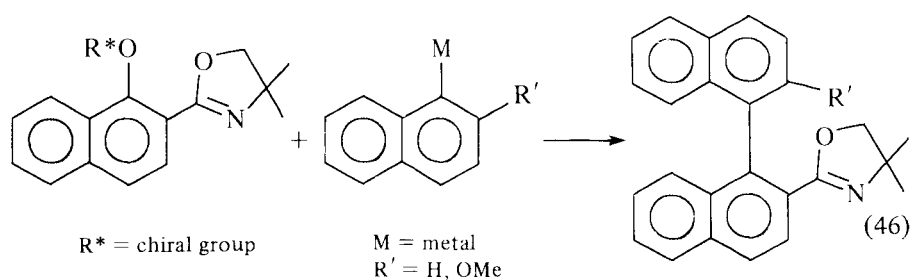
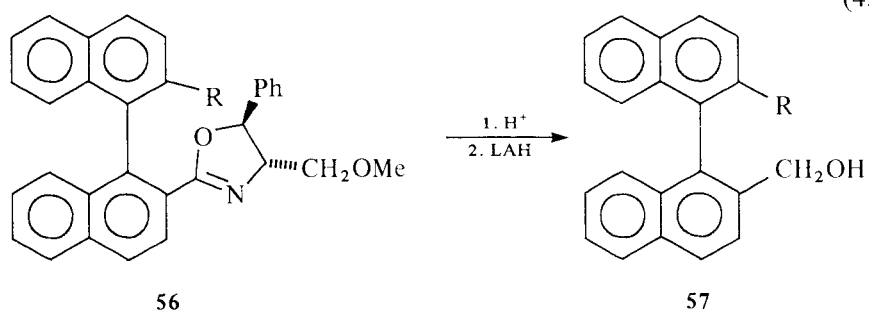
5.2.4.6. *Aromatic Nucleophilic Substitution*^{12, 105, 106}

Two elegant asymmetric syntheses of chiral binaphthyls have been developed utilizing oxazoline chemistry. Meyers and Lutomski¹⁰⁶ displaced the methoxy group in **55** with 1-naphthyl Grignard reagents to form adducts **56** having diastereomeric ratios of 87:13 ($R = H$), 76:24 ($R = Me$), and 92:8 ($R = OMe$) (Eq. 45). The sense of chirality at the binaphthyl chiral axis was identical in the first two cases, but not in the latter, representing an interesting reversal in stereoselectivity. Alcohol **57** ($R = OMe$) was obtained in nearly 100% ee due to enantiomeric enrichment during its production.

Wilson and Cram¹⁰⁵ used a chiral leaving group instead of a chiral oxazoline and achieved optical yields generally in the range of 50–95% (Eq. 46). Good enantioselectivities were found with *l*-menthoxy, quinoxoy, and quinidinoxy groups (>60% op), although *l*-menthoxy supplied the best chemical yields as well. 2-Methoxy-1-naphthyllithium rearranged in THF, but not in benzene, to the 3-lithium reagent, thus giving an optically active 1,3'-binaphthyl product.

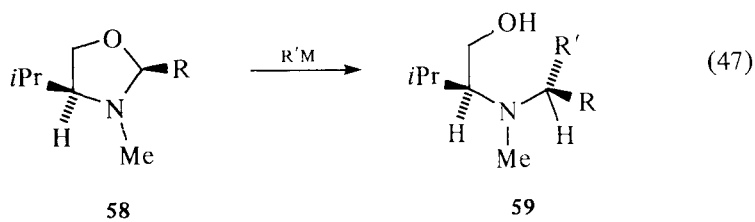


(45)

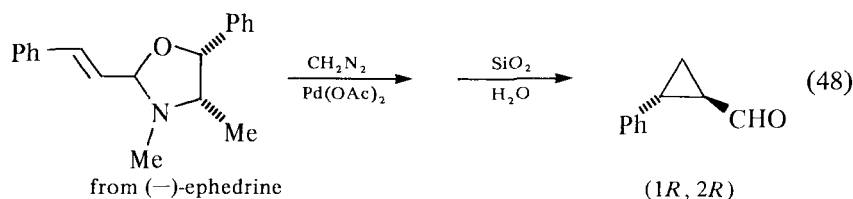


5.2.4.7. Oxazolidines¹³¹⁻¹³⁶

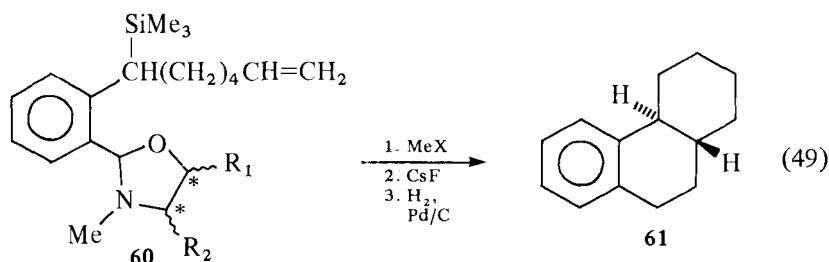
Although oxazolidines are not within the scope of this chapter, some asymmetric syntheses in this category are interesting or useful enough to warrant a brief discussion. Treatment of oxazolidines **58**, from (*S*)-*N*-methylvalinol and aldehydes, with EtMgBr or PhLi cleaved the C–O bond to give amino alcohols **59** in 80–90% diastereomeric purity (Eq. 47).¹³¹



Chiral formylcyclopropanes were synthesized in high enantiomeric purity (at least 90% ee) by carbene insertion into the double bond of 2-(1-alkenyl)oxazolidines derived from ephedrine (e.g., Eq. 48).^{132a} Related methyl copper addition reactions exhibited poor to moderate stereoselectivities.^{132b}



Ito et al.³⁹ methylated various chiral oxazolidinylbenzylsilanes of structure **60** on nitrogen and induced fragmentation of the quaternary salts with CsF to get transient *o*-quinodimethane species, which readily underwent cycloaddition to the alkene side chain (Eq. 49; also see Eq. 10). The resultant alkoxy *E*-octahydrophenanthrenes (e.g., Eq. 10) were then hydrogenolyzed to furnish *trans*-octahydrophenanthrene **61** with optical yields in the range of 28 to 55% ee.



Evans^{133–136} has described excellent asymmetric syntheses centered around lithium, boron, and zirconium enolates of *N*-acyloxazolidine derivatives. Zirconium enolates of chiral *N*-acyloxazolidines (based on valinol) reacted with aldehydes with 96–98% *erythro* diastereoselectivity and enantioselectivity of at least 50:1.¹³⁵ Lithium enolates of chiral *N*-acyloxazolidin-2-ones (imides based on valinol or norephedrine) were alkylated with 87–100% enantioselectivity; valinol- and norephedrine-based reactions afforded opposite enantiomers of β -substituted carboxylic acids.¹³³ Boron enolates of oxazolidinone imides derived from valinol or norephedrine condensed with aldehydes with >99% *erythro* stereoselectivity and generally >98% enantioselectivity (valinol- and norephedrine-based reactions gave opposite enantiomers).¹³⁶

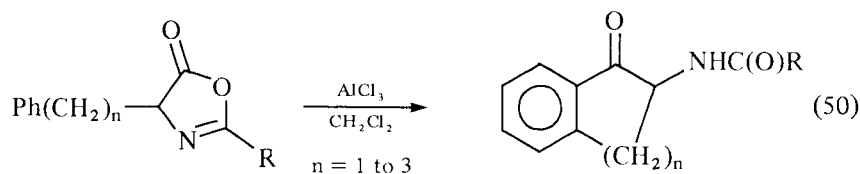
5.2.5. Oxazolinones

Oxazolinone chemistry was reviewed in 1965 and 1977.^{13, 137} Some minor exposure was also provided in monographs by Meyers¹ and van der Plas.¹⁴ 2-Oxazolin-5-ones are precursors to mesoionic oxazolium-5-oxides (munchnones), the chemistry

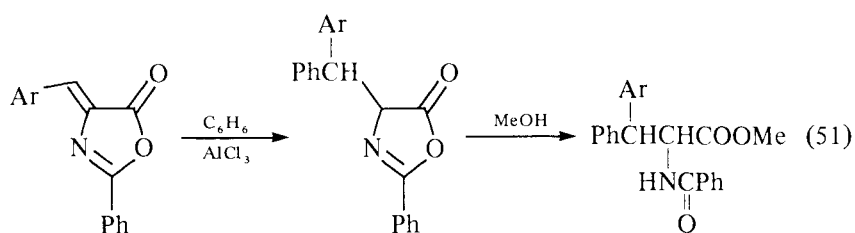
of which has been discussed elsewhere.^{3, 4, 138} Since we are concerned with applications of oxazolinones in organic synthesis, I have tended to disregard a fair body of literature in writing this section. The section will mainly deal with the 2-oxazolin-5-one (azlactone) system and slightly with the isomeric (by double-bond migration) 3-oxazolin-5-ones (pseudooxazolinones).

5.2.5.1. Reactions with Nucleophiles

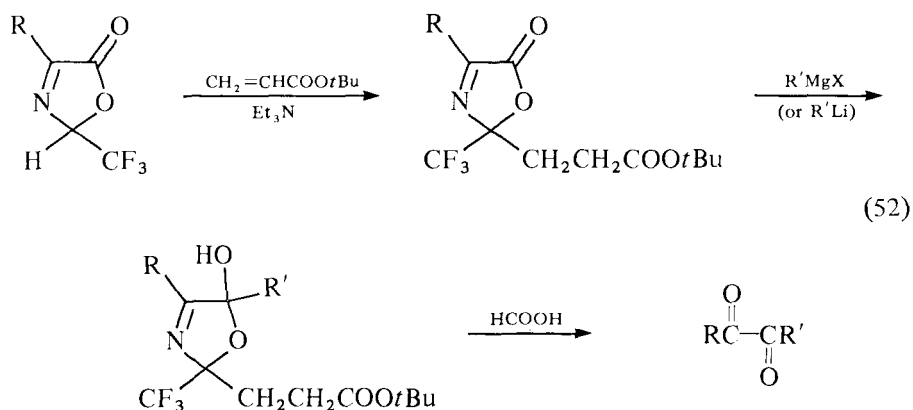
N-Acyl α -amino acids form 2-oxazolin-5-one derivatives via cyclodehydration; acylation of an amino acid and cyclization to an oxazolinone can be effected in a single step with carboxylic acid anhydrides.^{13, 137} 3-Oxazoline-5-ones arise from treatment of α -amino acids with trifluoroacetic anhydride.^{13, 137} Such oxazolinones are reasonably good acylating agents. The 2-oxazolin-5-ones react with water, alcohols, amines, hydrazines, hydrazoic acid, and phosphate anions to furnish α -amino acid derivatives.^{13, 137} Depending on conditions and nucleophilic reagent, attack on 2-oxazolin-5-ones may occur at the 2- or 5-position of the ring.^{13, 137}



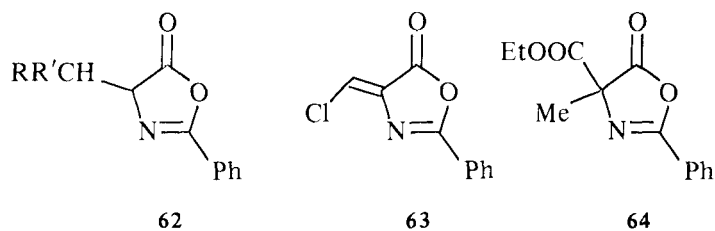
2-Oxazolin-5-ones have been induced to acylate aromatic compounds under Lewis acid catalysis to give *N*-acyl α -aminoketones, useful for making 2,5-disubstituted oxazoles.¹³⁷ This Friedel–Crafts process has been particularly valuable in the synthesis of cyclic compounds by means of intramolecular acylation (Eq. 50).¹³⁷ Since an oxazolinone species is involved, the chirality of the original amino acid is lost through racemization; however, an alternative procedure that transfers the original chirality has been reported.¹³⁹ Friedel–Crafts reactions of aromatic hydrocarbons with 4-arylidene 2-oxazolin-5-ones (Section 2.5.2) were used to introduce an aryl substituent, affording a route to diarylated α -amino acid derivatives (Eq. 51).^{1, 137}



Grignard reagents add to the 5-position of the oxazoline ring, generally resulting in ring cleavage.¹³⁷ 4-Alkylidene and 4-arylidenes 2-oxazolinones react with alkyl (not aryl) Grignard reagents by conjugate addition to give compounds **62**, sources of substituted α -amino acids.^{1, 137} Aryl Grignard and lithium reagents preferentially undergo 1,2-addition to the carbonyl group (5-position).¹³⁷ With 3-oxazolin-5-ones Grignard addition to the carbonyl formed the basis for an interesting unsymmetrical α -diketone synthesis (Eq. 52).¹⁴⁰ Use of copper (I) chloride in aryl Grignard addition to α,β -unsaturated 2-oxazolin-5-ones promotes 1,4-addition;¹³⁷ Michael addition also occurs with lithium alkylcuprates.¹⁴¹ Chlorovinylloxazoline **63** reacted with various organometallic compounds by 1,4-addition with subsequent chloride elimination to give substituted α,β -unsaturated 2-oxazolinones.¹ Condensation of Grignard reagents and carbethoxy 2-oxazolinone **64** resulted in α -keto- α -*N*-acylamino acid esters, which gave serine derivatives on reduction of the keto group with sodium borohydride.¹⁴² Michael addition of a β -ketoester enolate to an alkylidene 2-oxazolinone was successfully carried out in studies directed to the total synthesis of the tetracycline antibiotic terramycin; the C and D rings were constructed simultaneously by two Claisen condensations that also occurred during the reaction, one involving the acyl function of the oxazolinone ring.¹⁴³



Treatment of unsaturated 2-oxazolinones with diazomethane afforded cyclopropane adducts via attack at the carbon-carbon double bond; such adducts supplied the corresponding cyclopropyl α -amino acid derivatives on solvolysis.^{13, 144}

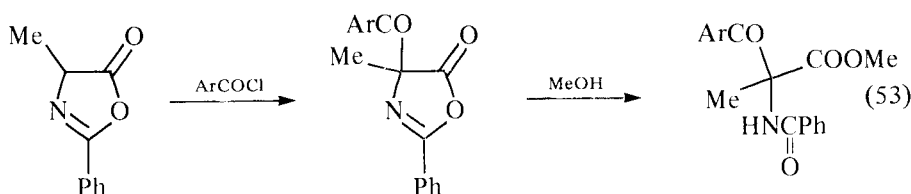


2-Oxazolin-5-ones have played a major role in the synthesis of dehydro α -amino acid derivatives^{137, 145–148} and dehydro peptides^{137, 149–154} (see Section 2.5.2). Reaction of α,β -unsaturated 2-oxazolinones with α -amino acid esters constitutes a good route to dehydro di- and tripeptides, the double bond of which can be hydrogenated with high stereoselectivity, furnishing natural or unnatural configurations.^{152, 153} Dehydro amino acids or unsaturated 2-oxazolinones have been converted into the corresponding α -keto carboxylic acids.^{145, 147} 3-Oxazolin-5-ones were also readily hydrolyzed to α -keto acids,¹³⁷ well exemplified by the synthesis of 3,4-dihydroxyphenylpyruvic acid in 70% yield.¹⁵⁵

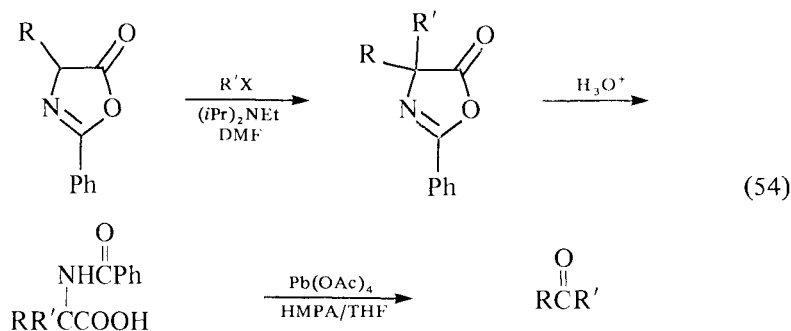
5.2.5.2. Reactions with Electrophiles

The protons on the 4-position of the 2-oxazolin-5-one ring are fairly acidic, which accounts for the racemization of optically active *N*-acyl α -amino acids via an oxazolinone intermediate.^{13, 156a} Aldehydes condense with 2-oxazolin-5-ones under the influence of a weak base, such as sodium acetate, to furnish α,β -unsaturated derivatives.^{13, 137, 156b, 157} Aldehyde condensations induced by acids, such as polyphosphoric acid,¹³ and lead (II) acetate^{157, 158} have also been conducted. Thus, complex α -amino acids such as those derived from carbohydrates¹⁵⁸ are readily available.

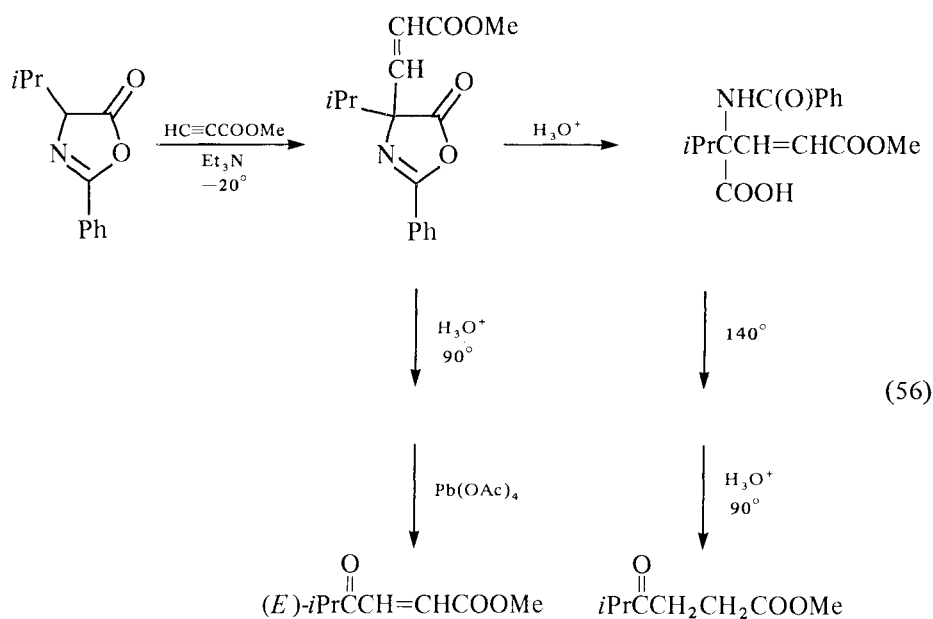
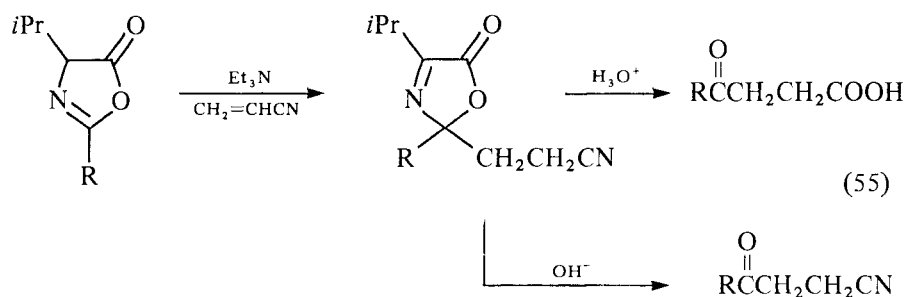
2-Oxazolines have also been reacted with acid chlorides at the 4-position to ultimately provide α -amino β -keto acids (Eq. 53).¹⁵⁹



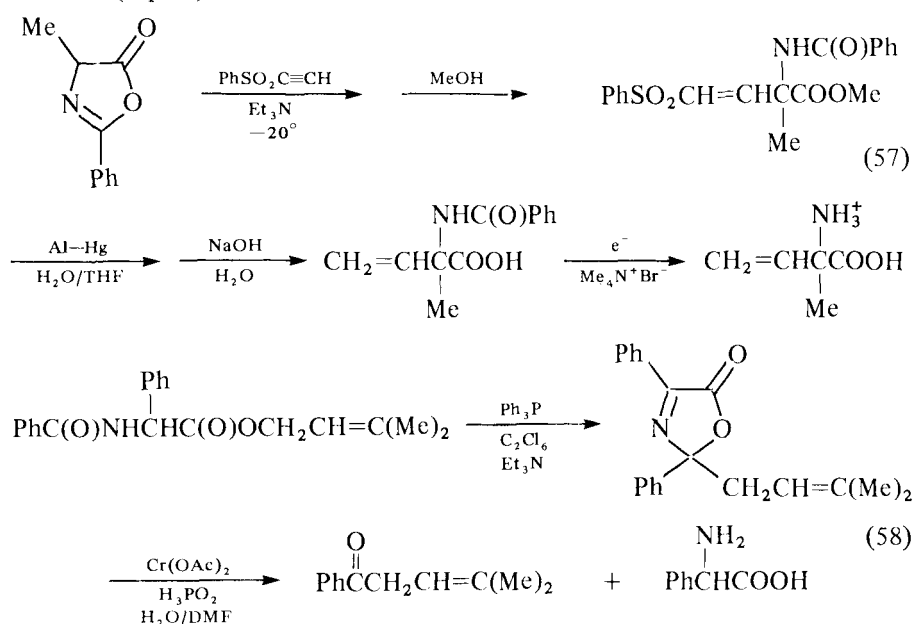
Base-promoted alkylation of 2-oxazolin-5-ones can take place at the 2- or 4-position.^{140, 141, 160–165} Suitable alkylating agents have been alkyl halides^{141, 162} and electron-deficient alkenes^{140, 161, 165} and alkynes.^{160, 163, 164} 2-Oxazolinones were used as acyl anion equivalents for the synthesis of ketones by reaction of alkyl halides at the 4-position (Eq. 54).^{141, 162} Elaborated aldehydes were also available through 1,4-addition of an alkyl cuprate to an α,β -unsaturated oxazolinone, followed by lead tetraacetate degradation.¹⁴¹ Reaction of *t*-butyl acrylate at the oxazolinone 2-position, to lock in the 3-oxazolin-5-one system, was employed in an α -diketone synthesis (Eq. 52).¹⁴⁰ Similarly, 3-keto nitriles and acids were prepared in 55–90% yields via reaction of acrylonitrile at the oxazolinone 2-position (Eq. 55).¹⁶⁵ On the contrary, oxazolinones with bulky 3-substituents underwent amine-catalyzed addition to activated alkenes exclusively at the 4-position of the ring; methyl vinyl ketone and acrylonitrile afforded 1,4-diketones and 4-oxonitriles, respectively, after lead tetraacetate oxidation.¹⁶¹



Treatment of 2-oxazolin-5-ones with methyl propiolate provided a route to 3-ketoesters or 3-acrylates (Eq. 56);¹⁶⁴ analogously, acetylenic ketones provided a route to 1,4-diketones.¹⁶⁰ Phenylsulfonylacetylene was used to obtain α -vinyl α -amino acids from oxazolinones (Eq. 57).¹⁶³

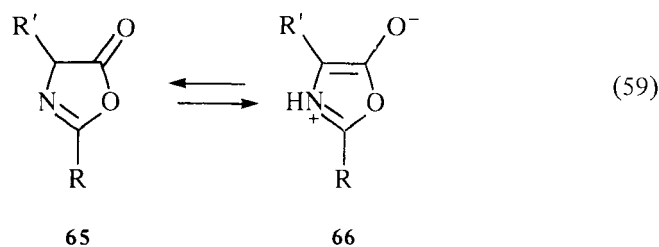


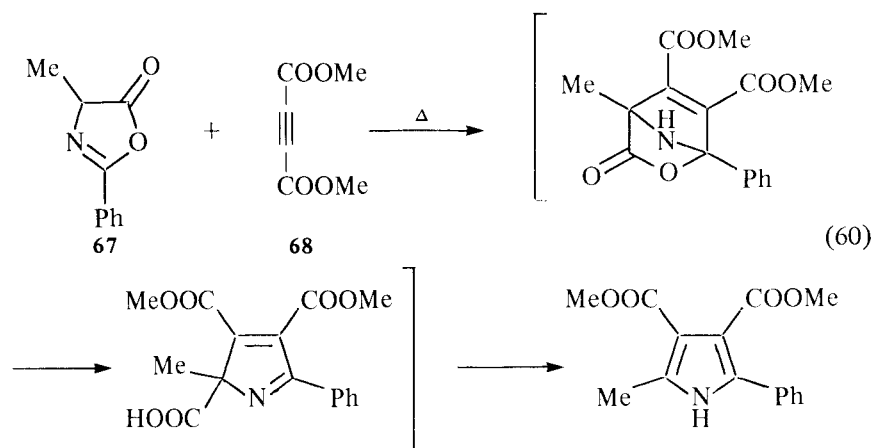
Allyl ketones were synthesized from allyl glycinate via 3-oxazolin-5-one intermediates (Eq. 58).¹⁶⁶



5.2.5.3. Cycloaddition Reactions

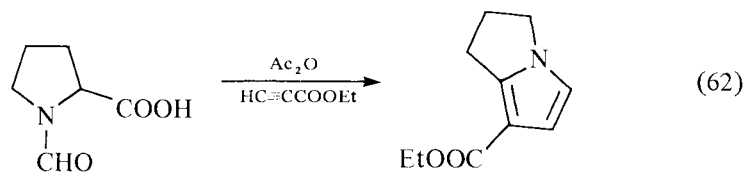
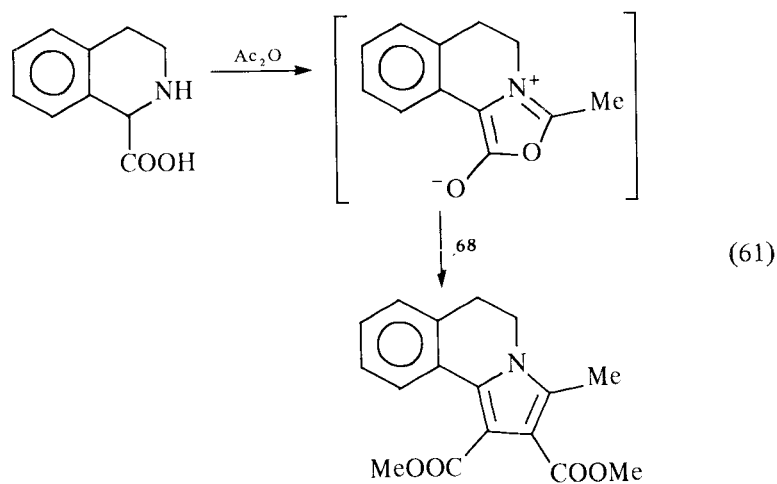
2-Oxazolin-5-ones (azlactones) are capable of existing in equilibrium with meso-ionic tautomers **65**, masked azomethine ylides (Eq. 59).^{167,168} Indeed, **65** with $R = R' = \text{Ph}$ has an equilibrium concentration of mesoionic species **66** ($R = R' = \text{Ph}$) of ca. 49% in dimethylformamide.¹⁶⁷ Oxazolium-5-oxide **66** accounts for the 1,3-dipolar cycloaddition reaction that occurs between 2-oxazolinones (e.g., **67**) and activated acetylene **68**, giving pyrrole products (Eq. 60).¹⁶⁷ Participation of **66**, as opposed to a nitrile ylide 1,3-dipolar entity, is supported by the fact that (1) **67** did not produce carbon dioxide on heating and (2) a 4,4-dialkyl-2-oxazolinone did not cycloadd to **68**.¹⁶⁷ 2-Oxazolin-5-ones were found to react as 1,3-dipoles with a variety of alkynes and alkenes.^{168, 169}

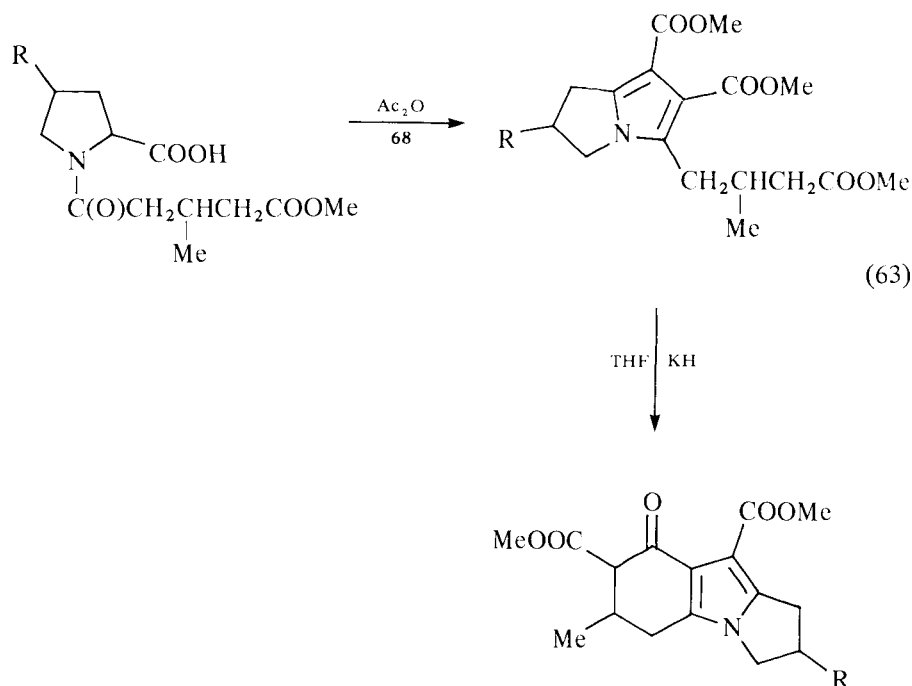




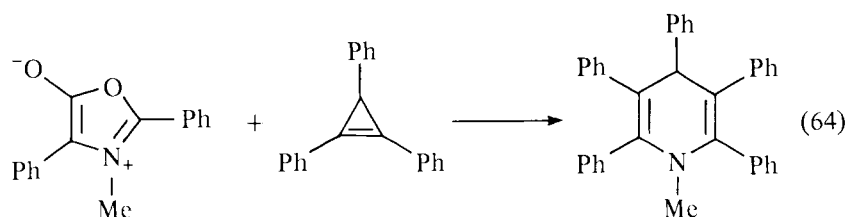
N-Substituted mesoionic oxazoles are prepared from *N*-acyl- α -amino acids by cyclodehydration with carboxylic acid anhydrides, oxalyl chloride, or dicyclohexylcarbodiimide.^{3,4,138} These *N*-substituted 1,3-dipoles readily engage in an assortment of cycloaddition reactions, many of which will not be discussed here (but are included in prior reviews^{3,4,138}).

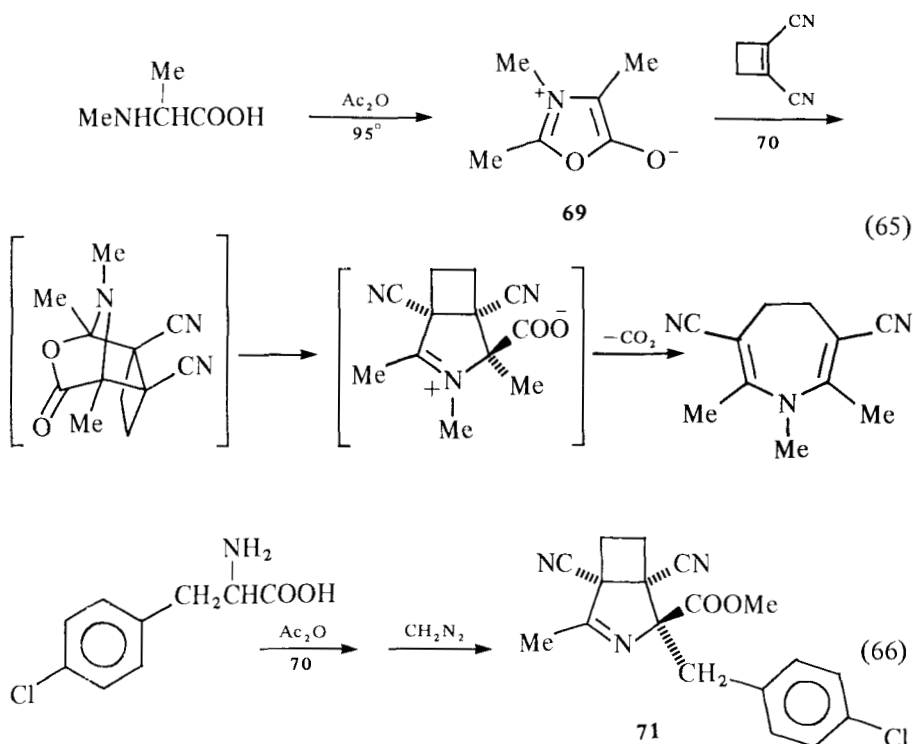
Reaction of oxazolium-5-oxides with acetylenes comprises a useful synthesis of a wide range of substituted pyrroles^{3,4} in the manner mentioned above. Fused pyrrole systems have been synthesized in good yields by this process from cyclic α -amino acids (Eqs. 61–63).^{4,170–173}





Oxazolium-5-oxides combine with simple alkenes to yield 1- or 2-pyrroline derivatives;^{3, 4, 138} but strained cyclic alkenes create sundry interesting products.⁴ For example, in a fashion related to simple alkenes, cyclopropenones, cyclopropenes (Eq. 64), and thirene-1,1-dioxides underwent cycloaddition to generate 4-pyridones, 1,4-dihydropyridines (Eq. 64), and thiazine-1,1-dioxides, respectively.^{4, 174, 175} Cyclobutenes also participate in this type of cycloaddition, followed by ring expansion.¹⁷⁶ Thus, condensation of **69** with 1,2-dicyanocyclobutene (**70**) resulted in excellent yields of 4,5-dihydroazepine (Eq. 65). In this reaction cyclic α -amino acids afforded a series of ring-fused dihydroazepine analogues in good yields.¹⁷⁶ In the 1,3-dipolar cycloaddition of *p*-chlorophenylalanine with **70**, a reaction intermediate was isolated and identified by X-ray crystallography as **71** (Eq. 66).¹⁷⁷ This revelation provided, for the first time, knowledge of the stereochemistry of oxazolium-5-oxide cycloaddition reactions (properly displayed in Eq. 65).



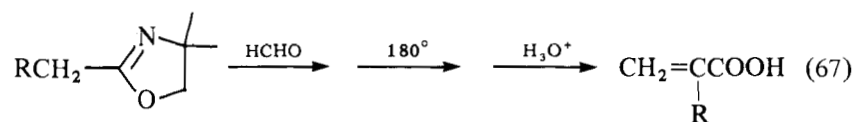


Cycloaddition of 1,3-dipolar species from 2-oxazolin-4-ones with acetylenes furnished substituted furans, by an analogous mechanism, in moderate yields.¹⁷⁸

Some similar cycloaddition chemistry has been performed with corresponding 2-oxazolin-5-imines,^{3, 4, 138} but this will not be discussed here.

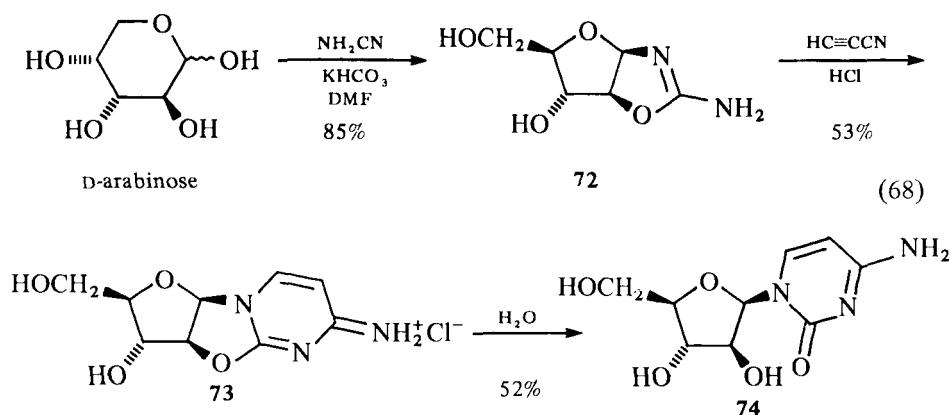
5.2.6. Miscellaneous Applications and Reaction Intermediates

Serota et al. developed a procedure for preparing acrylic acids in good yields by reaction of oxazoline derivatives of aliphatic carboxylic acids with formaldehyde (Eq. 67).⁵² The method was useful for obtaining fatty acrylic acids, but products contained about 10% of starting acid, which had to be removed by further purification.

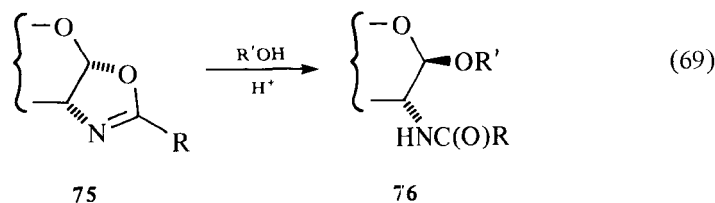


Oxazoline derivatives of carbohydrates have been employed in the synthesis of, *inter alia*, antitumor nucleosides.¹⁷⁹⁻¹⁸⁶ Arabinose and ribose combine with cyanamide on heating with a mild base to give 2-amino-2-oxazoline adducts (e.g., Eq.

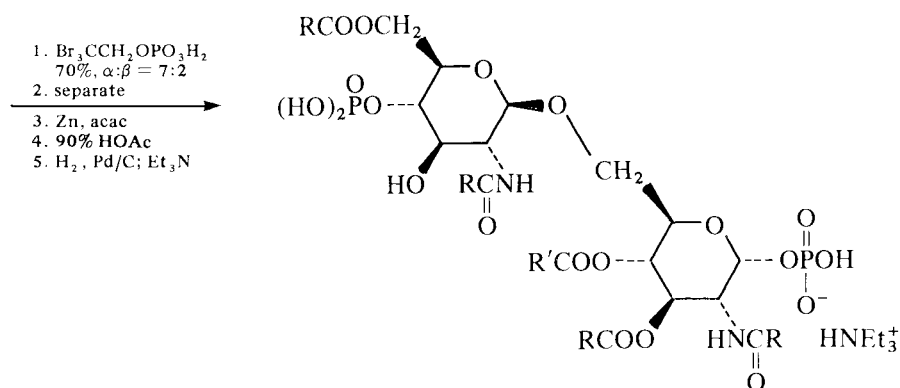
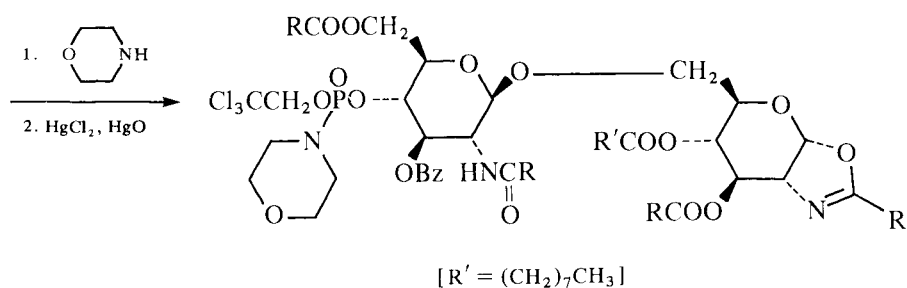
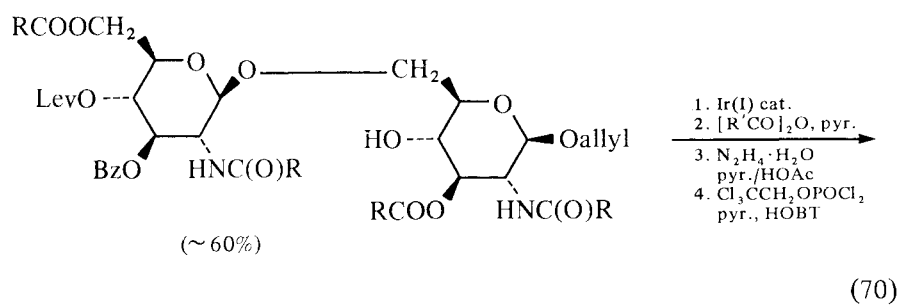
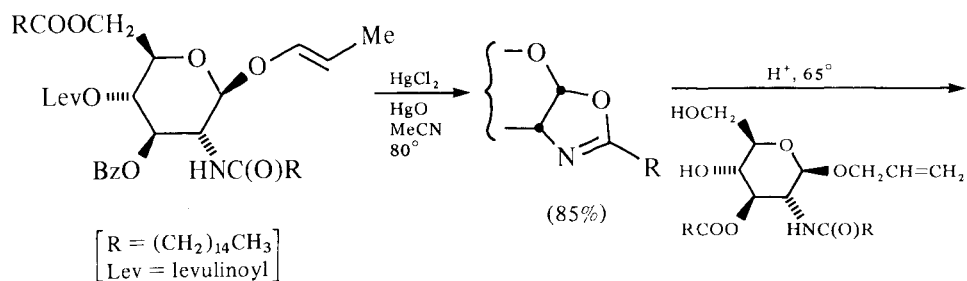
68).¹⁷⁹⁻¹⁸⁴ Condensation of oxazoline adduct **72** with propiolonitrile yielded an anhydro arabino-nucleoside, **73**, which was transformed to cytosine arabinoside (ara-C, **74**), a potent anticancer agent (Eq. 68).¹⁷⁹⁻¹⁸² Other pyrimidine nucleosides of ribose and arabinose have been synthesized by this route.^{180,182,183} From glycosyl amines, found to be more reactive with cyanamide, several pentose and hexose compounds were readily prepared.¹⁸⁵



cis-Glycosyl oxazolines of general structure **75** are useful in the synthesis of *trans*-aminoglycosides represented by **76** (Eq. 69).^{46,186-193} Protonation of the oxazoline generates an ionic species, akin to the well-recognized 1,3-dioxolanium ions, which is easily displaced from the anomeric center by weak nucleophiles, such as alcohols. The preparation of di- and oligosaccharides has benefitted from the oxazoline method, wherein the alcohol reactant ($R'OH$ in Eq. 69) is another sugar molecule.^{186-188,190-193} Besides using the oxazoline method for assembling a glycosidic ether linkage, van Boom and co-workers applied the method to introduction of an anomeric phosphate group in the synthesis of an analogue of the glycopospholipid, lipid A.¹⁹² Part of this elegant synthetic scheme is depicted in Eq. 70. It is interesting to note that the opening of the oxazoline intermediate with a phosphoric acid is not stereoselective for the β -isomer, as is the case for ring opening by alcohols.



A central aspect of the oxazoline method in carbohydrate chemistry is the propensity of an amide functionality vicinal to an electrophilic carbon center to cyclize to an oxazoline. Thus, activation of a hydroxy group in 2-amino alcohols by



reagents such as thionyl chloride or phosphorus oxychloride produces an oxazoline, which may suffer cleavage to a 2-amido alkyl halide.⁸ This process is implicated in the Pictet–Gams variation of the Bischler–Napieralski isoquinoline synthesis, which employs 2-amido alcohol reagents.^{194–197} Indeed, *erythro*-*N*-benzoyl- β -arylserines reacted with thionyl chloride with retention of stereochemistry, giving *erythro*- β -chloro- β -aryl alanine derivatives due to the involvement of oxazolines.¹⁹⁸

2-Oxazolines, or 2-oxazolin-2-yl carbanions, are intermediates in the addition of α -isocyano carbanions (which includes α -metalated isocyanides) to ketones and aldehydes (see Section 2.2.1).^{16b, 89, 199–208} This reaction has been used to synthesize the 1,2-aminoalcohol^{16b, 201–206} and *N*-vinyl amide^{16b, 199, 204, 207} functionalities, as well as β,γ -unsaturated α -amino acids.²⁰⁰ Addition of ethyl isocyanoacetate to aldehydes was highly stereoselective;^{202–206} a *trans*-substituted oxazoline ring was strongly favored. Condensation of D-glyceraldehyde acetonide with ethyl isocyanoacetate was, however, not especially stereoselective with regard to the position α to the aldehyde carbonyl group.^{202, 206} This reaction formed the basis of a synthesis of DL-threonine from acetaldehyde.^{204, 205} Ketones were reacted with tosylmethyl isocyanide in a one-step synthesis of nitriles, a facile one-carbon homologation procedure (Eq. 71).⁸⁹ In an analogous manner by a two-step process, Schöllkopf obtained carboxylic acids from ketones (see Eq. 29).^{87, 207, 208}



5.3. OXAZOLES

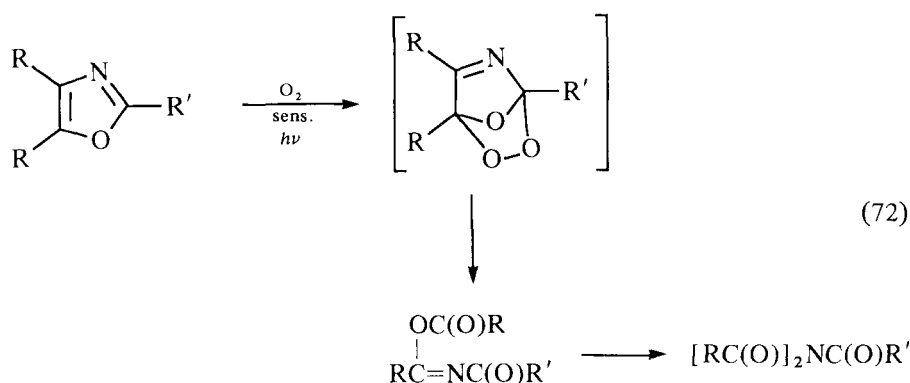
As mentioned in Section 5.1, oxazole chemistry has been the subject of five reviews in the last 15 years,^{3–7} three of which have been rather exhaustive.^{3–5} The purpose of this survey is to convey those aspects of oxazole chemistry that are particularly useful from an organic synthetic perspective. This chemistry falls into three broad categories: protecting groups, metalation reactions, and cycloaddition reactions.

5.3.1. Use as Protecting Groups

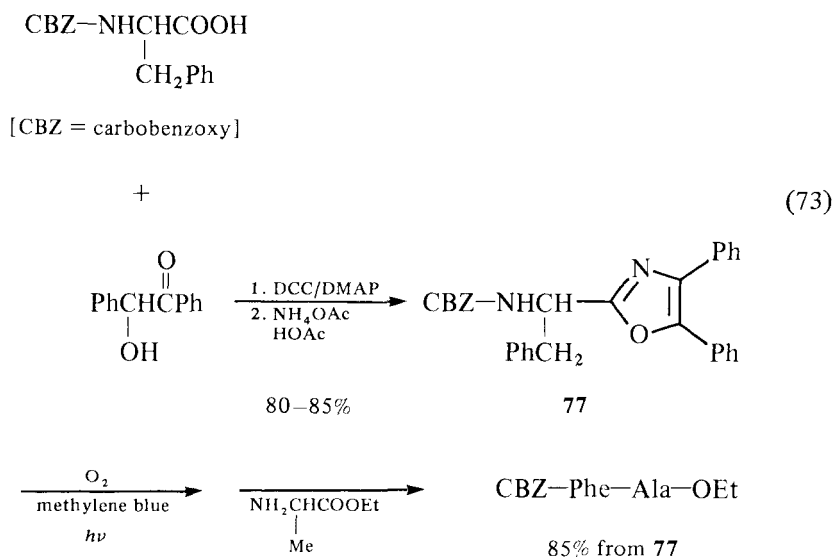
Carboxylic acids and their primary amides can be converted to oxazoles by well-known procedures.⁵ The acid route involves the reaction of ammonium acetate with ester derivatives of α -hydroxyketones, and the amide route involves condensation with α -haloketones.⁵ Aryl substituents on the α -hydroxy- or α -haloketone unit assist the reaction and contribute to high yields; thus, 4,5-diphenyloxazole derivatives are especially qualified for this application.⁵

The oxazole group is relatively unreactive to acid- and base-promoted hydrolysis and to many oxidizing and reducing agents.^{3–5} However, for an oxazole to serve as a protecting group, a convenient, mild method for its removal is required. Indeed, 4,5-disubstituted oxazoles readily undergo dye-sensitized photooxidation to yield

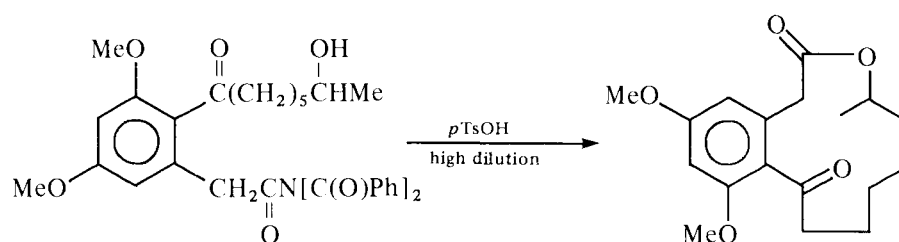
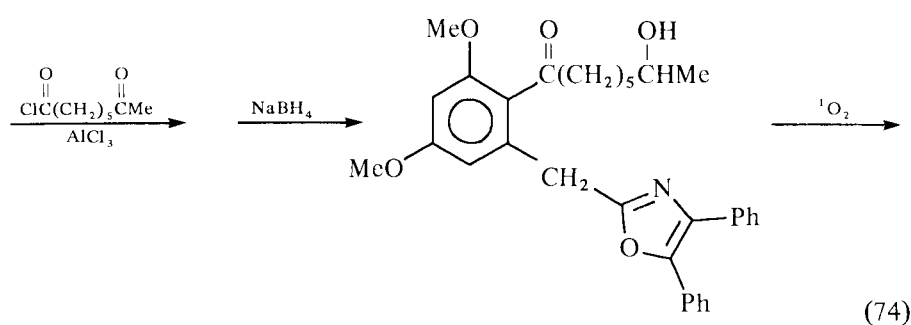
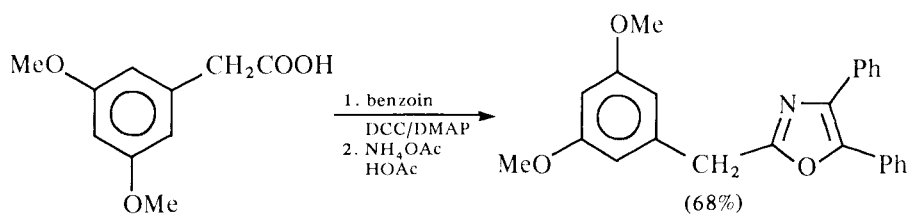
triamides, a reaction pioneered by Wasserman (Eq. 72).²⁰⁹⁻²¹² The process was indicated to proceed by initial 1,4-addition of singlet oxygen to the oxazole followed by rearrangement of the resultant 2,5-endoperoxide,²¹⁰ but a competing 1,2-addition pathway may also be operative.²¹³



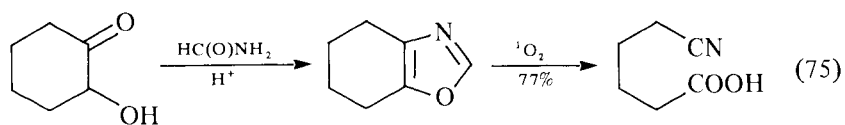
Wasserman employed the 4,5-diphenyloxazole group in this fashion to protect and activate the carboxyl group of *N*-acyl- α -amino acids in the course of dipeptide synthesis (Eq. 73).²¹⁴ The aliphatic acyl group on the triamide intermediate was selectively transferred over the two benzoyl groups to the nucleophilic reagent.



This 4,5-diphenyloxazole method has been exploited for lactonization reactions in the synthesis of macrolides,^{211,215-217} such as the curvularin skeleton (Eq. 74).^{211,217a}

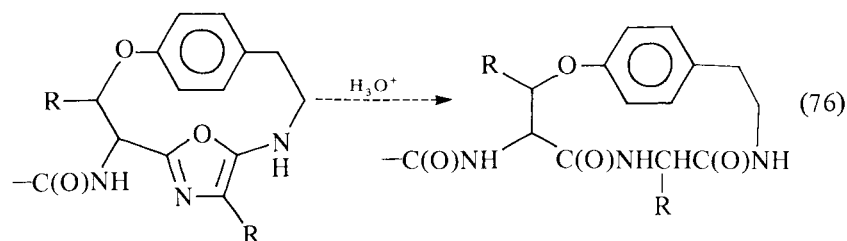


The singlet oxygen chemistry can also be used for the conversion of cyclic α -hydroxyketones (acyloins) via readily formed oxazoles²¹⁸ to ω -cyano acids (Eq. 75).^{5, 219}

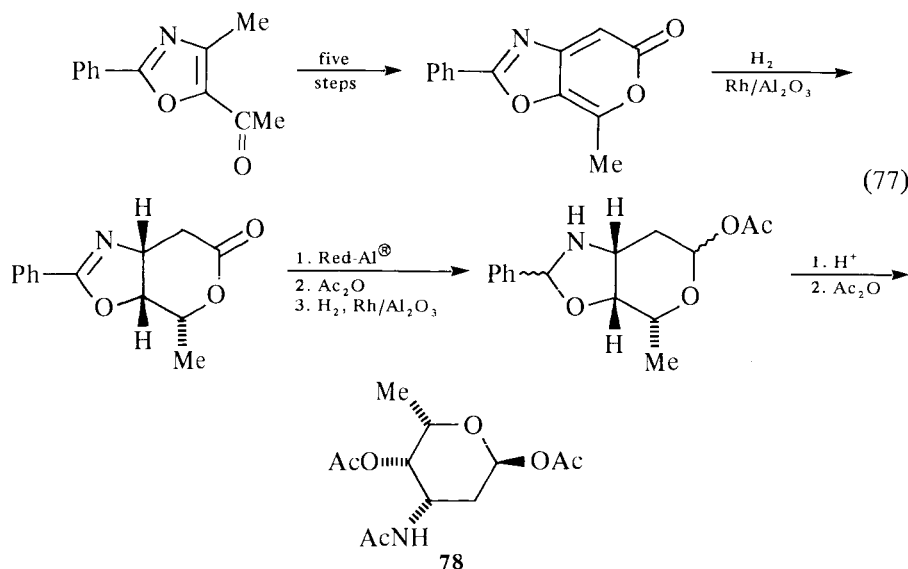


Instead of photo-generated singlet oxygen, one can consider thermally generated material. Triphenylphosphite ozonide is a convenient source of nonphotochemical singlet oxygen,²²⁰⁻²²² which may well be applicable in the oxazole-triamide rearrangement reactions.

In a different carboxyl protection approach, Lipshutz is investigating the potential of 5-aminooxazoles for the synthesis of cyclopeptide alkaloids (e.g. Eq. 76).²²³



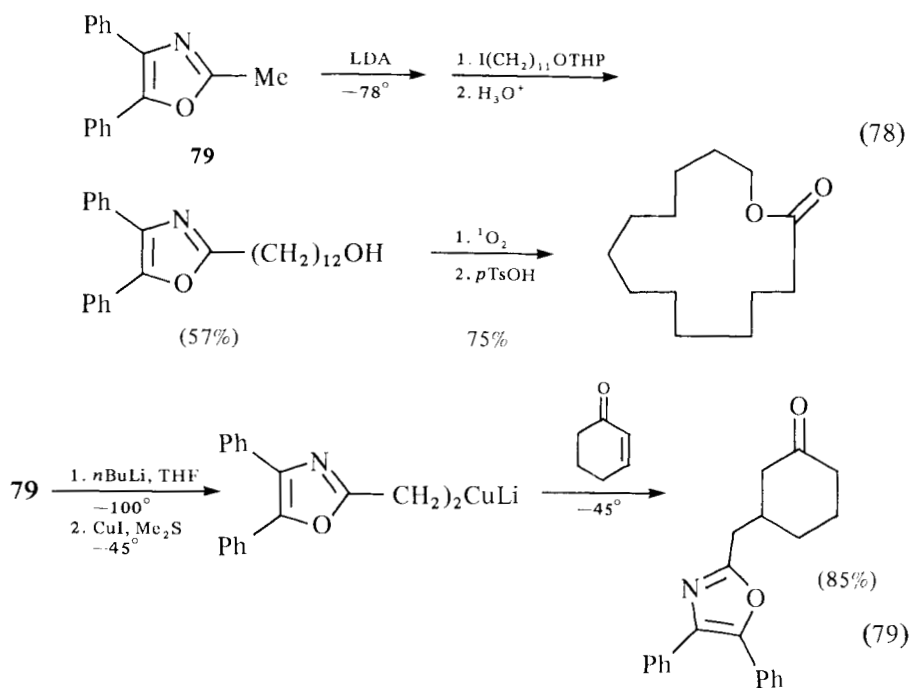
The oxazole nucleus was a key element in the synthesis of *dl*-triacetyldaunosamine **78** (Eq. 77).²²⁴ The oxazole, a latent 1,2-amino alcohol unit, served as a template for construction of the sugar ring.



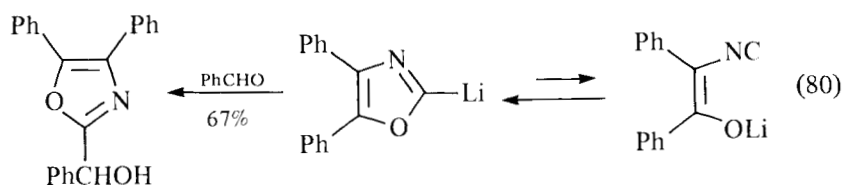
5.3.2. Metalation Reactions

Alkyl substituents on the 2-position of the oxazole ring possess activated, somewhat acidic α protons. Metalation has been effected with amide bases,^{5, 211, 216, 225} organolithium compounds,²²⁵ and even sodium hydride,⁷ and the resultant organometallics have been reacted with an assortment of electrophiles.^{5, 7, 225} This is illustrated in Wasserman's synthesis of macrocyclic lactones^{211, 216} (Eq. 78) and in a dialkylcuprate conjugate addition to cyclohexenone²²⁵ (Eq. 79).

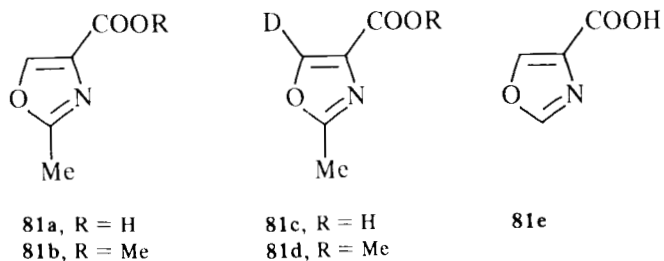
2-Metalated oxazoles have received some attention.^{82, 226, 227} 4,5-Diphenyl-oxazole was metalated at the 2-position with *n*-butyllithium.²²⁶ The 2-lithio compound was found to exist in a mobile equilibrium with a ring-opened species (Eq. 80). The lithio oxazole was trapped by benzaldehyde or deuterium oxide, whereas the isocyano enolate was trapped by trimethylsilyl chloride (on oxygen).²²⁶ In contrast, lithiation of 5-alkoxyoxazoles caused rapid, virtually irreversible ring

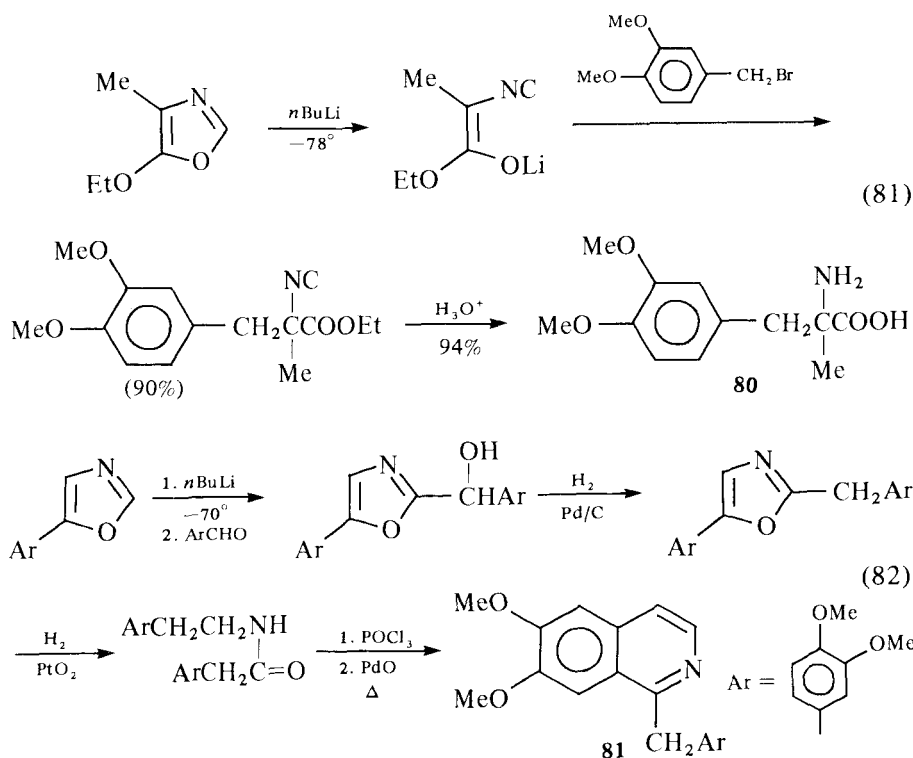


opening to isocyano ester enolates, which were *C*-alkylated in good yield (Eq. 81).²²⁶ Thus, the 5-alkoxyoxazole entity, via an ester enolate, constitutes an effective synthon for α -amino acid derivatives, such as di-*O*-methyl- α -methyldopa (**80**) (Eq. 81).

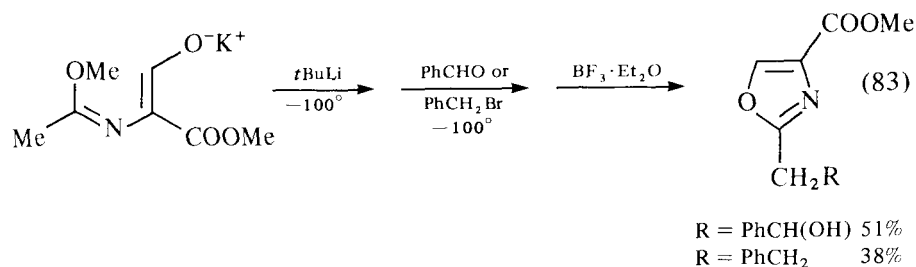


Kozikowski and Ames reacted 2-lithio-5-aryloxazoles with aromatic aldehydes to give 2,5-adducts in 50–90% yields, which were converted to 1-benzylisoquinolines, such as papaverine (**81**) (Eq. 82).⁸²





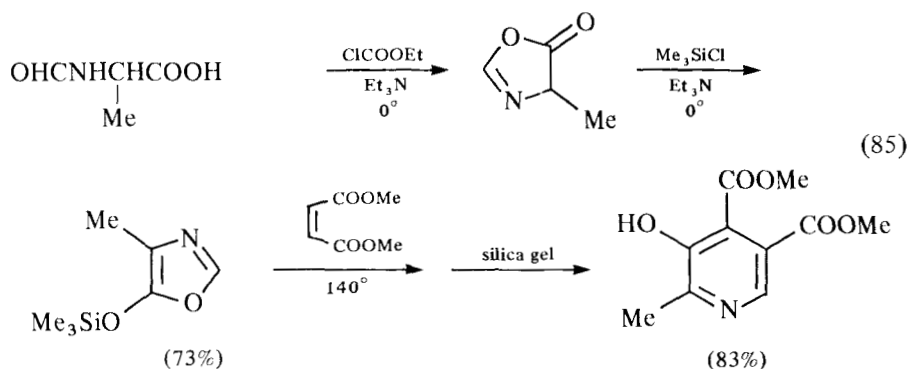
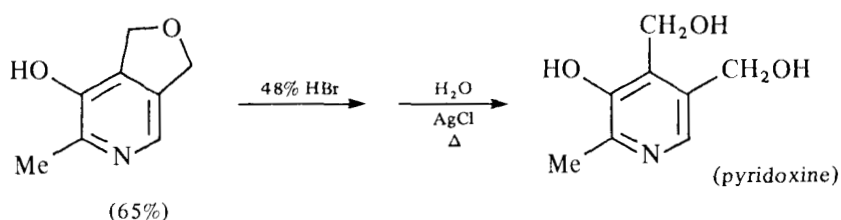
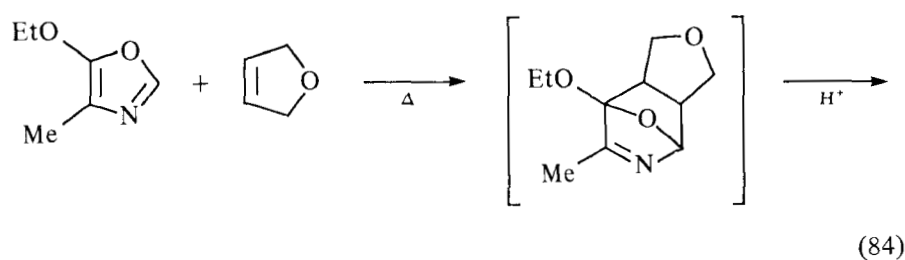
Attempts to metalate the 2-methyl group of **81a** or **81b** with *n*-butyllithium achieved only lithiation of the 5-position of the ring; no lithiation occurred at all with LDA.^{226a} Metalation of **81c**, which required *t*-butyllithium presumably because of a deuterium-isotope effect, occurred on C-5, not on the methyl group.^{226a} Proton exchange of **81d** with MeOD/OMe⁻ revealed only deuterium incorporation at the 5-position, indicating that this site is both kinetically and thermodynamically favored for attack by base. Additionally, oxazole **81e** was metalated exclusively on the 5-position, not the 2-position, with *n*-butyllithium. This anomalous lithiation behavior appears to be associated with the presence of a 4-carboxy substituent, which activates the adjacent ring proton. Meyers and Lawson managed to circumvent their metalation problem by lithiating an acyclic oxazole precursor (Eq. 83).

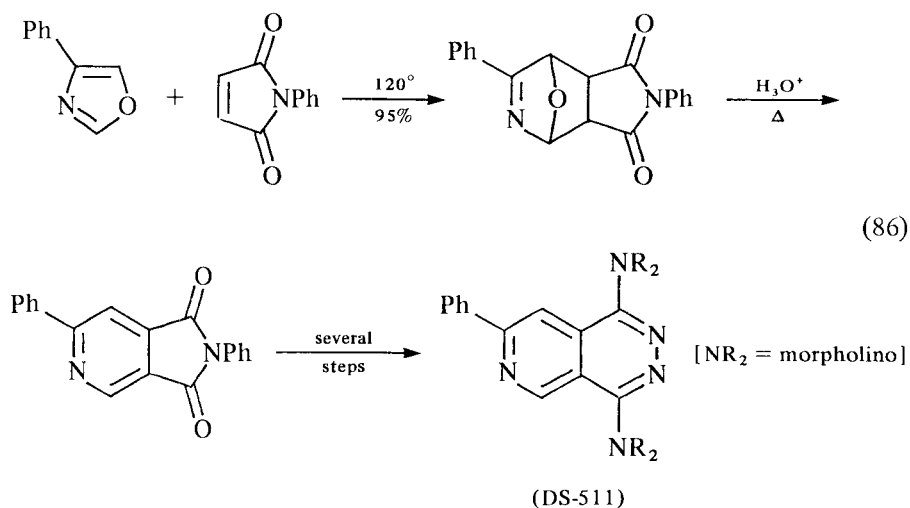


5.3.3. Cycloaddition Reactions

Oxazoles behave as azadienes in cycloaddition reactions with dienophiles. Since this Diels–Alder-type reaction has been extensively surveyed,^{3–6,14} the current discourse will be limited to (1) exemplification of reaction classes and (2) applications in organic synthesis, with an emphasis on post-1975 literature.

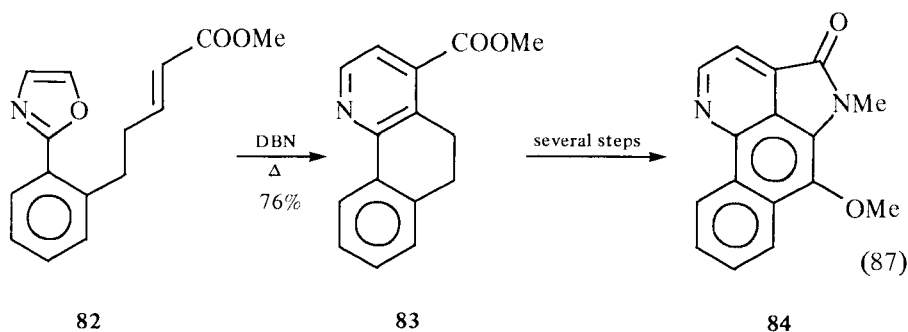
Cycloaddition of oxazoles with alkenes constitutes a useful synthesis of highly substituted pyridines.^{3–6,14} Much work has centered on the preparation of vitamin B-6 (pyridoxine) and its congeners.^{3,5,6,14} One of the classic Merck routes to pyridoxine is depicted in Eq. 84.^{228,229} Other dienophiles have also been employed to prepare pyridoxine and its analogues.^{3,5,6,14} Recently, various 5-silyloxy-oxazoles were used in Diels–Alder reactions with *N*-phenylmaleimide and dimethyl maleate to afford substituted pyridines in high yields (83–92%) (e.g., Eq. 85).²³⁰ Since the requisite oxazoles were readily obtained by silylation of 2-oxazolin-5-ones from *N*-formyl α -amino acids, an expeditious sequence from alanine to vitamin B-6 was realized (Eq. 85).²³⁰

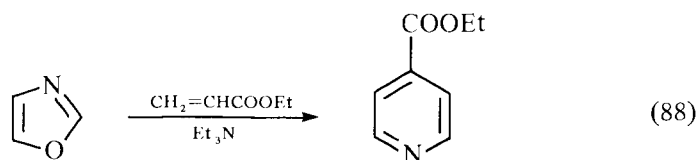




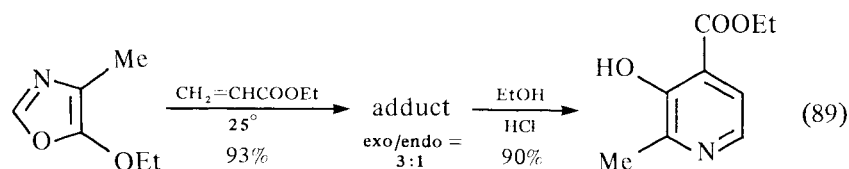
Oxazole cycloaddition to alkenes was also important in the synthesis of a series of potent pyrido[3,4-*d*]pyridazine diuretics, of which DS-511 is a prime prototype (Eq. 86).²³¹ Omura et al. isolated intermediate bicyclic adducts and identified the *exo* and *endo* stereoisomers, the ratio of which varied with reaction temperature. The cycloaddition shown in Eq. 86 gave *exo-endo* ratios of 2.4:1 and 9:1 in benzene at 25 and 80°C, respectively, and a ratio of >99:1 without solvent at ca. 120°C.

The facility with which oxazoles enter cycloaddition reactions depends on the ring substituents.³⁻⁶ As a rule of thumb, electron-releasing groups enhance reactivity and electron-attracting groups diminish it. For example, 5-alkoxy groups convey high reactivity and a phenyl group on the 2- or 5-position greatly attenuates reactivity, to an extent where cycloaddition becomes poor at best.⁵ However, in Weinreb's application of an intramolecular cycloaddition of an oxazole to an alkene, in the synthesis of eupolauramine (84), a 2-aryl substituent did not pose a serious problem (Eq. 87).^{102b} Interestingly, when the amidine base DBN was absent from the thermolysis of 82 (under argon), undesired pyridinols (not shown) were produced via "oxidative fragmentation," instead of 83.^{102b}

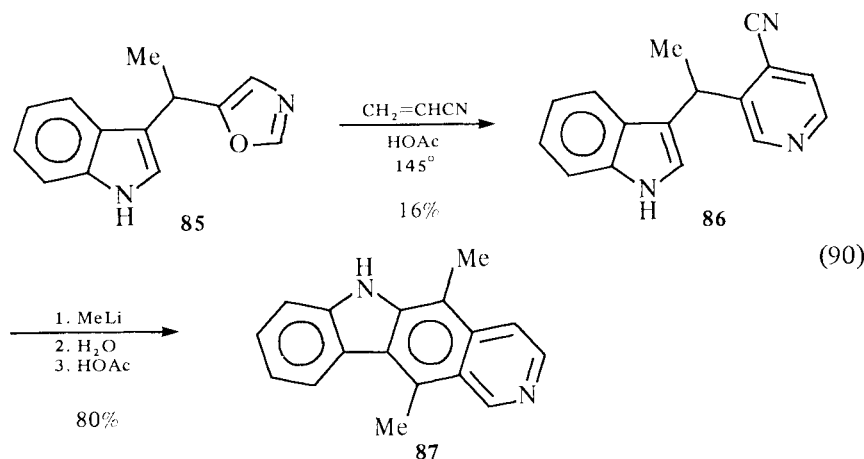




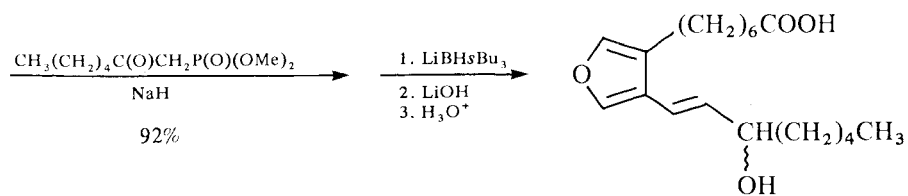
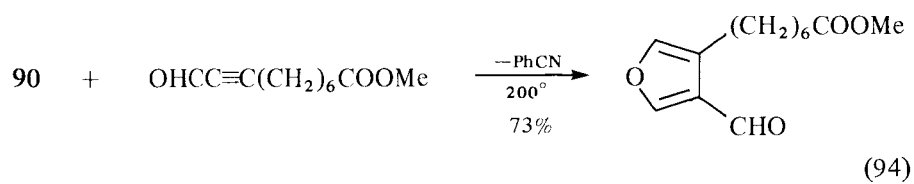
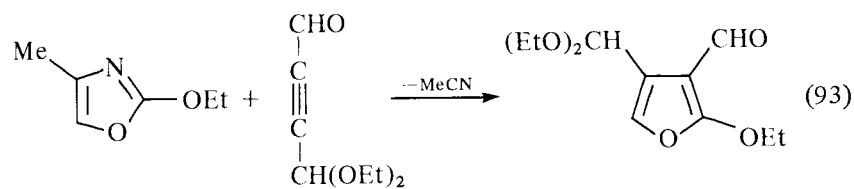
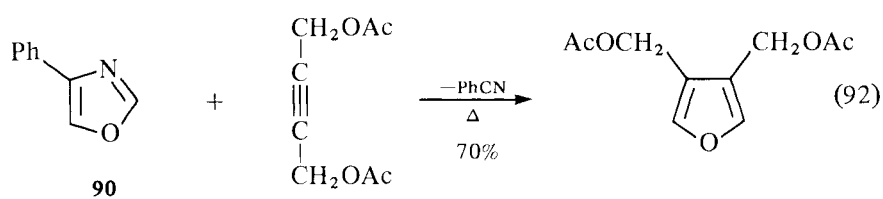
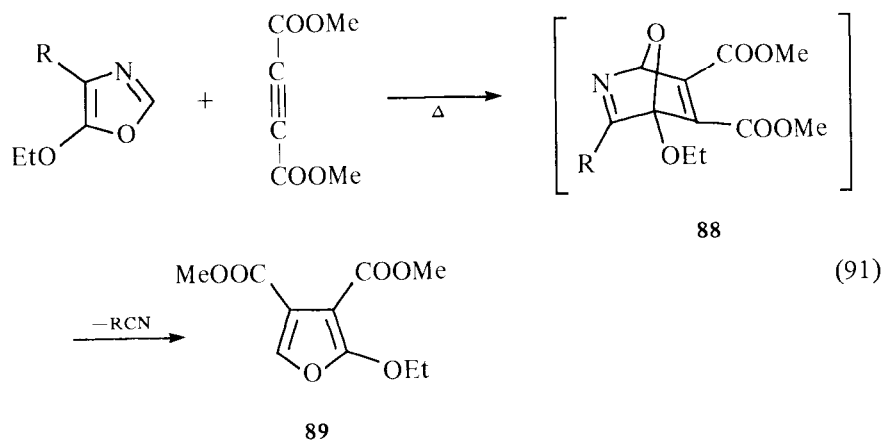
Oxazoles generally combine with unsymmetrical dienophiles to yield one of the two possible regioisomeric products.⁵ Thus, for example, isonicotinic acids and esters are formed almost exclusively in the reaction of oxazoles with acrylic acids and esters (e.g., Eq. 88).⁵ Recently, Johnsen and Undheim looked at a series of acrylic acid and acrylonitrile cyclocondensations with 5-ethoxyoxazoles and found high regioselectivity for 3-hydroxy-4-X-pyridines (e.g., Eq. 89).²³²

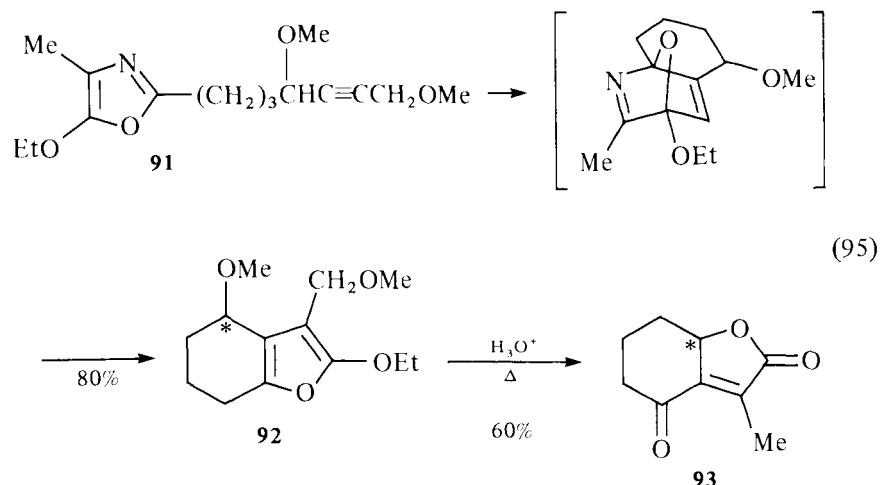


Reaction of oxazole **85** with acrylonitrile, a key step in the synthesis of the anti-tumor agent ellipticine (**87**), afforded cyanopyridine **86** in low yield (Eq. 90).²³³



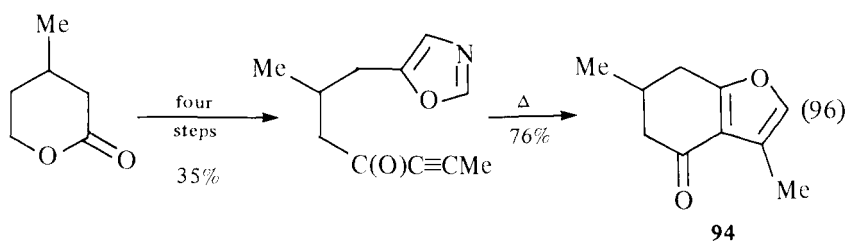
The cycloaddition reaction of oxazoles with acetylenes offers a useful method for the synthesis of substituted furans.^{3-6, 14} For instance, 5-ethoxyoxazoles cycloadd to dimethyl acetylenedicarboxylate to give furans **89** via transient bicyclic adducts **88** (Eq. 91).^{3-6, 14} Some examples of cycloadditions of oxazoles lacking a 5-alkoxy group are shown in Eqs. 92 and 93.^{234, 235} In a similar vein, reaction of 4-phenyloxazole **90** with acetylenic aldehyde **91** provided a central intermediate in the synthesis of furan prostanoids (Eq. 94).²³⁶ Recently, 4-phenyloxazole has been condensed with various unactivated acetylenes at ca. 200°C to furnish furans substituted on the 3- or 3,4-positions in good yields (50–95%).²³⁷





Intramolecular cycloaddition of oxazoles to acetylenic dienophiles, a process referred to as “bisheteroannulation,” has been exploited by Jacobi (Eqs. 95 and 96).^{238,239} Acetylenic oxazole **91** afforded furan **92**, which served as a precursor to butenolide **93** or to the related α -methylene lactone (not shown).²³⁸ In other studies, the furanosesquiterpene evodone **94** was constructed by means of this methodology (Eq. 96).^{239,240}

Cycloaddition reactions of oxazolium-5-oxides with dipolarophiles were already discussed in Section 2.5.



5.4. CONCLUDING REMARKS

The chemistry of oxazoles and oxazolines is legion.³⁻¹⁴ A fair portion of that chemistry, especially that of oxazoles, has little bearing on or application to general organic synthesis. In this chapter, an attempt was made to (1) extract that material of relevance to the synthetic organic chemist and (2) focus on the post-1975 chemical literature. Hopefully, reference to this concentrate of information will make it easier for chemists to recognize the potential utility of oxazoles and oxazolines in their particular synthetic endeavors.²⁴¹

ACKNOWLEDGMENTS

I wish to express appreciation to Dr. Norman Schwartz for extensive computer substructure searching of the chemical literature and to Ms. Deena DiStefano for valuable assistance with the literature work. Also, I am deeply grateful to Dr. Cynthia Maryanoff for support, encouragement, and advice.

REFERENCES

1. A. I. Meyers, *Heterocycles in Organic Synthesis*, Wiley-Interscience, New York, 1974.
2. D. Lednicer, *Adv. Org. Chem.*, **8**, 17 (1972).
3. I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
4. I. J. Turchi, *Ind. Eng. Chem. Prod. Res. Dev.*, **20**, 32 (1981).
5. R. Lakhan and B. Ternai, *Adv. Heterocycl. Chem.*, **17**, 99 (1974).
6. M. Y. Karpeiskii and V. L. Florent'ev, *Russ. Chem. Rev.*, **38**, 450 (1969).
7. P. B. Terent'ev and N. P. Lomakina, *Chem. Heterocycl. Compds.*, 483 (1976); original Russ. p. 579.
8. J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).
9. A. I. Meyers and E. D. Mihelich, *Angew. Chem. Intl. Edit.*, **15**, 270 (1976).
10. A. I. Meyers, *Accts. Chem. Res.*, **11**, 375 (1978).
11. A. I. Meyers, *Pure Appl. Chem.*, **51**, 1255 (1979).
12. A. I. Meyers, *Am. Chem. Soc. Sympos. Ser.*, **185**, 83 (1982).
13. R. Filler and Y. S. Rao, *Adv. Heterocycl. Chem.*, **21**, 175 (1977).
14. H. C. van der Plas, *Ring Transformations of Heterocycles*, Vol. 1, Academic Press, New York, 1973.
15. E. W. Collington, *Chem. Ind.*, 787 (1973).
16. (a) U. Schöllkopf, F. Gerhart, I. Hoppe, R. Harms, K. Hantke, K.-H. Scheunemann, E. Eilers, and E. Blume, *Justus Liebig's Ann. Chem.*, 183 (1976). (b) Also see the review: U. Schöllkopf, *Angew. Chem. Intl. Edit.*, **16**, 339 (1977).
17. L. N. Pridgen and L. B. Killmer, *J. Org. Chem.*, **46**, 5402 (1981).
18. A. P. Kozikowski and A. Ames, *J. Org. Chem.*, **45**, 2548 (1980).
19. J. R. Falck, S. Manna, and C. Mioskowski, *J. Org. Chem.*, **46**, 3742 (1981).
20. H. W. Gschwend and H. R. Rodriguez, *Org. Reactions*, **29**, 1 (1979).
21. Use of oxazolines was briefly discussed in a book on protecting group methodology: T. W. Greene, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, 1981, p. 185.
22. A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).
23. A. I. Meyers and W. B. Avila, *J. Org. Chem.*, **46**, 3881 (1981).
24. P. F. Hudrlik, A. M. Hudrlik, R. J. Rona, R. N. Misra, and G. P. Withers, *J. Am. Chem. Soc.*, **99**, 1993 (1977).
25. A. I. Meyers, R. Gabel, and E. D. Mihelich, *J. Org. Chem.*, **43**, 1372 (1978).
26. J. I. Levin and S. M. Weinreb, *Tetrahedron Lett.*, **23**, 2347 (1982).
27. L. N. Pridgen, L. B. Killmer, and R. L. Webb, *J. Org. Chem.*, **47**, 1985 (1982). [For

- more recent work on $i\text{Bu}_2\text{AlH}$ and Li/NH_3 reductions, see: A. I. Meyers, R. J. Himmelsbach, and M. Reuman, *J. Org. Chem.*, **48**, 4053 (1983).]
28. A. I. Meyers and D. L. Temple, *J. Am. Chem. Soc.*, **92**, 6646 (1970).
 29. D. Haidukewych and A. I. Meyers, *Tetrahedron Lett.*, 3031 (1972).
 30. J. F. Hansen, K. Kumata, and A. I. Meyers, *J. Heterocycl. Chem.*, **10**, 711 (1973).
 31. J. F. Hansen and S. Wang, *J. Org. Chem.*, **41**, 3635 (1976).
 32. R. Svenson and S. Gronowitz, *Chem. Scripta*, **19**, 149 (1982).
 33. B. Neuschwander and V. Boekelheide, *Isr. J. Chem.*, **20**, 288 (1980).
 34. B. J. Banks, M. J. Calverley, P. D. Edwards, and J. Harley-Mason, *Tetrahedron Lett.*, **22**, 1631 (1981).
 35. S. Djuric, T. Sarkar, and P. Magnus, *J. Am. Chem. Soc.*, **102**, 6885 (1980).
 36. I. C. Nordin, *J. Heterocycl. Chem.*, **3**, 531 (1966).
 37. P. A. Zoretic, B. Brauchaud, and N. D. Sinha, *J. Org. Chem.*, **42**, 3201 (1977).
 38. P. A. Zoretic, N. D. Sinha, and B. Brauchaud, *Syn. Commun.*, **7**, 299 (1977).
 39. Y. Ito, Y. Amino, M. Nakatsuka, and T. Saegusa, *J. Am. Chem. Soc.*, **105**, 1586 (1983).
 40. N. S. Chandrakumar and J. Hajdu, *J. Org. Chem.*, **47**, 2144 (1982).
 41. N. S. Chandrakumar and J. Hajdu, *J. Org. Chem.*, **48**, 1197 (1983).
 42. N. S. Chandrakumar and J. Hajdu, *Tetrahedron Lett.*, **23**, 1043 (1982).
 43. P. Tkaczuk and E. R. Thornton, *J. Org. Chem.*, **46**, 4393 (1981).
 44. R. A. Moss and M. Matsuo, *J. Am. Chem. Soc.*, **99**, 1643 (1977).
 45. B. Szechner, *Tetrahedron*, **37**, 949 (1981).
 - 46a. R. Gigg and R. Conant, *JCS Perkin Trans. I*, 2006 (1977), and relevant references cited therein. For other examples of oxazolines in carbohydrate chemistry, see Section 2.6.
 - 46b. D. Häbich, *Angew. Chem. Intl. Edit.*, **22**, 711 (1983); D. Häbich and W. Hartwig, *Tetrahedron*, **19**, 3667 (1984).
 47. A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2778 (1974).
 48. M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971). It should be noted that the ester enolate method was published after the first publication on the oxazoline method.
 49. S. Shibata, H. Matsushita, K. Kato, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, *Agric. Biol. Chem.*, **45**, 315 (1981).
 50. J. P. Kutney, M. J. McGrath, R. N. Young, and B. R. Worth, *Can. J. Chem.*, **57**, 3145 (1979). [Also, see: A. C. Oehlschlager, J. W. Wong, V. G. Verigin, and H. D. Pierce, Jr., *J. Org. Chem.*, **48**, 5009 (1983).]
 51. A. R. Colwell, L. R. Duckwall, R. Brooks, and S. P. McManus, *J. Org. Chem.*, **46**, 3097 (1981).
 52. S. Serota, J. R. Simon, E. B. Murray, and W. M. Linfield, *J. Org. Chem.*, **46**, 4147 (1981).
 53. A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 3158 (1975).
 54. H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **40**, 2008 (1975).
 55. F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuo, and N. D. Sinha, *J. Am. Chem. Soc.*, **102**, 790 (1980).
 56. A. B. Smith, III, S. R. Schow, J. D. Bloom, A. S. Thompson, and K. N. Winzenberg, *J. Am. Chem. Soc.*, **104**, 4015 (1982).
 57. J. A. Houbion, J. A. Miles, and J. A. Paton, *Org. Prep. Proced. Intl.*, **11**, 27 (1979).
 58. C. R. Ellefson and K. A. Prodan, *J. Med. Chem.*, **24**, 1107 (1981).

59. C. R. Ellefson, *J. Med. Chem.*, **44**, 1533 (1979).
60. P. Beak and R. A. Brown, *J. Org. Chem.*, **44**, 4463 (1979).
61. A. I. Meyers and K. Lutomski, *J. Org. Chem.*, **44**, 4464 (1979).
62. A. I. Meyers and W. B. Avila, *Tetrahedron Lett.*, **21**, 3335 (1980).
- 63a. A. I. Meyers and W. F. Rieker, *Tetrahedron Lett.*, **23**, 2091 (1982).
- 63b. A. I. Meyers and P. D. Pansegrau, *Tetrahedron Lett.*, **24**, 4935 (1983). [For regioselective addition of R_2CuLi , see: idem, *JCS Chem. Commun.*, 690 (1985).]
- 64a. K. J. Edgar and C. K. Bradsher, *J. Org. Chem.*, **47**, 1585 (1982).
- 64b. I. M. Dordor, J. M. Mellor, and P. D. Kennwell, *Tetrahedron Lett.*, **24**, 1437 (1983).
65. R. D. Thompson, M. Iwao, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **18**, 981 (1981).
66. R. Pratap, Y. Tominaga, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **19**, 865 (1982).
67. M. S. Newman and S. Kumar, *J. Org. Chem.*, **43**, 370 (1978).
68. M. S. Newman and R. Kannan, *J. Org. Chem.*, **44**, 3388 (1979).
69. M. S. Newman and K. Kanakarajan, *J. Org. Chem.*, **45**, 2301 (1980).
70. R. Pratap, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **18**, 1457 (1981).
71. A. I. Meyers and R. A. Gabel, *J. Org. Chem.*, **47**, 2633 (1982).
72. D. J. Chadwick, M. V. McKnight, and R. Ngochindo, *JCS Perkin Trans. I*, 1343 (1982).
73. M. E. K. Cartoon and G. W. H. Cheeseman, *J. Organometal. Chem.*, **234**, 123 (1982).
74. D. A. Taylor, M. M. Baradarani, S. J. Martinez, and J. A. Joule, *J. Chem. Res. (S)*, 387 (1979).
75. L. DellaVecchia and I. Vlattas, *J. Org. Chem.*, **42**, 2649 (1977). For more recent studies, see: A. J. Carpenter and D. J. Chadwick, *JCS Perkin Trans. I*, 173 (1985); P. Ribéreau and G. Queguiner, *Tetrahedron*, **40**, 2107 (1984).
76. G. S. Poindexter, *J. Org. Chem.*, **47**, 3787 (1982).
77. S. Takano, H. Numata, and K. Ogasawara, *Heterocycles*, **20**, 417 (1983).
78. T. D. Harris, B. Neuschwander, and V. Boekelheide, *J. Org. Chem.*, **43**, 727 (1978).
79. A. I. Meyers and A. L. Campbell, *Tetrahedron Lett.*, 4155 (1979).
- 80a. A. I. Meyers and M. E. Ford, *J. Org. Chem.*, **41**, 1735 (1976).
- 80b. C. A. H. Rasmussen and A. De Groot, *Synthesis*, 575 (1983).
81. A. I. Meyers and E. W. Collington, *J. Am. Chem. Soc.*, **92**, 6676 (1970).
82. A. P. Kozikowski and A. Ames, *J. Org. Chem.*, **45**, 2548 (1980).
83. A. G. M. Barrett, D. H. R. Barton, J. R. Falck, D. Papaioannou, and D. A. Widdowson, *JCS Perkin Trans. I*, 652 (1979).
84. O. H. Oldenzien and A. M. van Leusen, *Tetrahedron Lett.*, 163, 167 (1974).
85. U. Schöllkopf and D. Hoppe, *Angew. Chem. Intl. Edit.*, **9**, 459 (1970).
86. U. Schöllkopf and F. Gerhart, *Angew. Chem.*, **80**, 842 (1968).
87. U. Schöllkopf and R. Schröder, *Angew. Chem. Intl. Edit.*, **11**, 311 (1972).
88. O. H. Oldenzien and A. M. van Leusen, *Syn. Commun.*, **2**, 281 (1972).
89. O. H. Oldenzien, D. van Leusen, and A. M. van Leusen, *J. Org. Chem.*, **42**, 3114 (1977).
90. T. Baba and A. Suzuki, *Syn. Commun.*, **13**, 367 (1983).
91. A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, **97**, 6266 (1975).
92. A. E. Hauck and C.-S. Giam, *JCS Perkin Trans. I*, 2070 (1980).
93. A. I. Meyers, private communication, 1983. See: B. A. Barner and A. I. Meyers, *J. Am. Chem. Soc.*, **106**, 1865 (1984); A. I. Meyers and D. Hoyer, *Tetrahedron Lett.* **25**, 3667 (1984).

94. A. I. Meyers and E. D. Mihelich, *J. Am. Chem. Soc.*, **97**, 7383 (1975).
95. A. I. Meyers and R. Gabel, *J. Org. Chem.*, **42**, 2653 (1977).
96. A. I. Meyers and B. E. Williams, *Tetrahedron Lett.*, 223 (1978).
97. A. I. Meyers, M. Reuman, and R. A. Gabel, *J. Org. Chem.*, **46**, 783 (1981).
98. H. Tanaka, Y. Itoh, H. Ikushima, M. Okamoto, Y. Kawai, and H. Imanaka, *Tetrahedron Lett.*, **21**, 4359 (1980).
99. C. R. Ellefson, K. A. Prodan, L. R. Brougham, and A. Miller, *J. Med. Chem.*, **23**, 977 (1980).
100. J. Navak and C. A. Salemink, *Tetrahedron Lett.*, **23**, 253 (1982).
101. S. R. Wilson, D. T. Mao, and H. N. Khatri, *Syn. Commun.*, **10**, 17 (1980).
- 102a. S. R. Wilson and D. T. Mao, *J. Org. Chem.*, **44**, 3093 (1979).
- 102b. J. I. Levin and S. M. Weinreb, *J. Am. Chem. Soc.*, **105**, 1397 (1983). For a full account, see: idem, *J. Org. Chem.*, **49**, 4325 (1984).
- 102c. J. Novak and C. A. Salemink, *Tetrahedron Lett.*, **24**, 101 (1983).
103. A. I. Meyers and K. A. Lutomski, *Synthesis*, 105 (1983).
104. H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **47**, 3652 (1982).
105. J. M. Wilson and D. J. Cram, *J. Am. Chem. Soc.*, **104**, 881 (1982). For a full account, see: idem, *ibid.*, **49**, 4930 (1984).
106. A. I. Meyers and K. A. Lutomski, *J. Am. Chem. Soc.*, **104**, 879 (1982). [This reaction has been extended to biphenyls with generally lower stereoselectivity: A. I. Meyers and R. J. Himmelsbach, *ibid.*, **107**, 682 (1985).]
107. A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976).
108. A. I. Meyers, Y. Yamamoto, E. D. Mihelich, and R. A. Bell, *J. Org. Chem.*, **45**, 2792 (1980).
109. K.-P. Cheng, L. Bang, G. Ourisson, and J.-P. Beck, *J. Chem. Res. (S)*, 84 (1979).
110. S. Bystrom, H.-E. Hogberg, and T. Norin, *Tetrahedron*, **37**, 2249 (1981).
111. R. Rossi and M. Marasco, *Chim. Ind. (Milan)*, **62**, 314 (1980).
112. J. M. J. Frechet, W. Amaratunga, and J. Halgas, *Nouv. J. Chim.*, **6**, 609 (1982).
113. S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, *Chem. Lett.*, 217 (1981).
114. S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, *Heterocycles*, **16**, 1901 (1981).
115. A. I. Meyers, A. Mazzu, and C. E. Whitten, *Heterocycles*, **6**, 971 (1977).
116. J. F. Hansen and C. S. Cooper, *J. Org. Chem.*, **41**, 3220 (1976).
117. A. I. Meyers and K. Kamata, *J. Am. Chem. Soc.*, **98**, 2290 (1976).
118. A. I. Meyers, E. S. Snyder, and J. J. H. Ackerman, *J. Am. Chem. Soc.*, **100**, 8186 (1978).
119. M. A. Hoobler, D. E. Bergbreiter, and M. Newcomb, *J. Am. Chem. Soc.*, **100**, 8182 (1978).
120. S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi, and S. Yoshikawa, *Chem. Lett.*, 1983 (1982).
121. A. I. Meyers and P. J. Reider, *J. Am. Chem. Soc.*, **101**, 2501 (1979).
122. A. I. Meyers and Y. Yamamoto, *J. Am. Chem. Soc.*, **103**, 4278 (1981).
123. R. W. Hoffmann and T. Herold, *Chem. Ber.*, **114**, 375 (1981).
124. A. I. Meyers and G. Knaus, *Tetrahedron Lett.*, 1333 (1974).
125. For a review on acyclic stereoselection in the aldol reaction, see: C. H. Heathcock, *Science*, **214**, 395 (1981).

126. A. I. Meyers, R. K. Smith, and C. E. Whitten, *J. Org. Chem.*, **44**, 2250 (1979).
127. A. I. Meyers and C. E. Whitten, *Heterocycles*, **4**, 1687 (1976).
128. F. E. Ziegler and P. J. Gilligan, *J. Org. Chem.*, **46**, 3874 (1981).
129. A. I. Meyers, N. R. Natale, D. G. Wettlaufer, S. Raffii, and J. Clardy, *Tetrahedron Lett.*, **22**, 5123 (1981). [For some recent asymmetric addition reactions, see: A. I. Meyers and D. G. Wettlaufer, *J. Am. Chem. Soc.*, **106**, 1135 (1984); Reference 93.]
- 130a. A. I. Meyers and J. Slade, *J. Org. Chem.*, **45**, 2785 (1980).
- 130b. After the text of this review was prepared, an article on this chemistry appeared, see: A. I. Meyers, M. A. Hanagan, L. M. Trefonas, and R. V. Baker, *Tetrahedron*, **39**, 1991 (1983).
131. H. Takahashi, Y. Suzuki, and T. Kametani, *Heterocycles*, **20**, 607 (1983).
- 132a. H. Abdallah, R. Gree, and R. Carrie, *Tetrahedron Lett.*, **23**, 503 (1982).
- 132b. M. Hucho, J. Aubouet, G. Pourcelot, and J. Berlan, *Tetrahedron Lett.*, **24**, 585 (1983).
133. D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982).
134. D. A. Evans and J. Bartroli, *Tetrahedron Lett.*, **23**, 807 (1982).
135. D. A. Evans and L. R. McGee, *J. Am. Chem. Soc.*, **103**, 2878 (1981).
136. D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981).
137. R. Filler, *Adv. Heterocycl. Chem.*, **4**, 75 (1965).
138. W. D. Ollis and C. A. Ramsden, *Adv. Heterocycl. Chem.*, **19**, 1 (1976).
139. D. E. McClure, B. H. Arison, J. H. Jones, and J. J. Baldwin, *J. Org. Chem.*, **46**, 2433 (1981).
140. J. Leyendecker, U. Niewöhner, and W. Steglich, *Tetrahedron Lett.*, **24**, 2375 (1983).
141. R. Lohmar and W. Steglich, *Angew. Chem. Intl. Edit.*, **17**, 450 (1978).
142. S. H. Pines, S. Karady, and M. Sletzing, *J. Org. Chem.*, **33**, 1758 (1968).
143. H. Muxfeldt, G. Haas, G. Hardtmann, F. Kathawala, J. B. Mooberry, and E. Vedejs, *J. Am. Chem. Soc.*, **101**, 689 (1978).
144. S. W. King, J. M. Riordan, E. M. Holt, and C. H. Stammer, *J. Org. Chem.*, **47**, 3270 (1982). Also, see: J. M. Bland, C. H. Stammer, and K. I. Varughese, *ibid.*, **49**, 1634 (1984).
145. U. Hess and W. A. König, *Justus Liebig's Ann. Chem.*, 611 (1980).
146. R. S. Lott, E. G. Breitholle, and C. H. Stammer, *J. Org. Chem.*, **45**, 1151 (1980).
147. E. G. Breitholle and C. H. Stammer, *Tetrahedron Lett.*, 2381 (1975).
148. J. M. Riordan and C. H. Stammer, *J. Org. Chem.*, **39**, 654 (1974).
149. R. B. Morin and E. M. Gordon, *Tetrahedron Lett.*, 2163 (1973).
150. S. W. King and C. H. Stammer, *J. Org. Chem.*, **46**, 4780 (1981).
151. S. Konno and C. H. Stammer, *Synthesis*, 598 (1978).
152. I. Ojima and N. Yoda, *Tetrahedron Lett.*, **23**, 3913 (1982).
153. I. Ojima, T. Kogure, N. Yoda, T. Suzuki, M. Yatabe, and T. Tanaka, *J. Org. Chem.*, **47**, 1329 (1982).
154. J. S. Davies and M. N. Ibrahim, *Tetrahedron Lett.*, 1453 (1977).
155. M. L. Wilson and C. J. Coscia, *J. Org. Chem.*, **44**, 301 (1979).
- 156a. E.g., see V. Daffe and J. Fastrez, *JCS Perkin Trans. II*, 783 (1983) and ref 1–3 cited therein.
- 156b. A. Badshah, N. H. Khan, and A. R. Kidwai, *J. Org. Chem.*, **37**, 2916 (1972) and references cited therein.
157. H. E. Carter, *Org. React.*, **3**, 206 (1946).
158. A. Rosenthal and K. Dooley, *Carbohydr. Res.*, **60**, 193 (1978).

159. S. H. Pines and M. Sletzing, *Tetrahedron Lett.*, 727 (1969).
160. G. Schulz, P. Gruber, and W. Steglich, *Chem. Ber.*, **112**, 3221 (1979).
161. H. Wegmann and W. Steglich, *Chem. Ber.*, **114**, 2580 (1981).
162. R. Lohmar and W. Steglich, *Chem. Ber.*, **113**, 3706 (1980).
163. W. Steglich and H. Wegmann, *Synthesis*, 481 (1980).
164. H. Wegmann, G. Schulz, and W. Steglich, *Justus Liebig's Ann. Chem.*, 1736 (1980).
165. W. Steglich and P. Gruber, *Angew. Chem. Intl. Edit.*, **10**, 655 (1971).
166. U. Niewöhner and W. Steglich, *Angew. Chem. Intl. Edit.*, **20**, 395 (1981).
167. H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).
168. G. Höfle, W. Steglich, and H. Daniel, *Chem. Ber.*, **101**, 2648 (1976).
169. H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **103**, 2356 (1970).
170. R. Huisgen, H. Gotthardt, and H. O. Bayer, *Chem. Ber.*, **103**, 2368 (1970).
171. F. M. Hersenson, *J. Org. Chem.*, **40**, 740 (1975).
172. M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **39**, 731 (1974).
173. J. Rebek and J.-C. E. Gehret, *Tetrahedron Lett.*, 3027 (1977).
174. H.-D. Martin and M. Hekman, *Angew. Chem. Intl. Edit.*, **11**, 926 (1972).
175. H. Matsukubo, M. Kojima, and M. Kato, *Chem. Lett.*, 1153 (1975).
176. I. J. Turchi, C. A. Maryanoff, and A. M. Mastrocola, *J. Heterocycl. Chem.*, **17**, 1593 (1980).
177. C. A. Maryanoff, I. J. Turchi, and E. R. Corey, private communication, 1983.
178. K. T. Potts and J. L. Marshall, *J. Org. Chem.*, **44**, 626 (1979).
179. E. Hessler, *J. Org. Chem.*, **41**, 1828 (1976).
180. D. H. Shannahoff and R. A. Sanchez, *J. Org. Chem.*, **38**, 593 (1973).
181. D. T. Gish, G. L. Neil, and W. J. Wechter, *J. Med. Chem.*, **14**, 882 (1971).
182. W. Wierenga, B. E. Loughman, A. J. Gibbons, and H. E. Renis, *J. Med. Chem.*, **21**, 558 (1978).
183. A. Holy, *Tetrahedron Lett.*, 189 (1971).
184. D. Cech, J. König, H. Köppel, S. Möller, and G. Herrmann, *J. Prakt. Chem.*, **323**, 747 (1981).
185. R. M. Davidson, E. White, V. S. A. Margolis, and B. Coxon, *Carbohydr. Res.*, **116**, 239 (1983).
186. S. E. Zurabyan, T. P. Volosyuk, and A. J. Khorlin, *Carbohydr. Res.*, **9**, 215 (1969).
187. C. D. Warren and R. W. Jeanloz, *Carbohydr. Res.*, **59**, 67 (1977).
188. S. David and A. Veyrières, *Carbohydr. Res.*, **40**, 23 (1975).
189. M. A. Nashed, C. W. Slife, M. Kiso, and L. Anderson, *Carbohydr. Res.*, **82**, 237 (1980).
190. S. E. Zurbayan, T. S. Antonenko, and A. Y. Khorlin, *Carbohydr. Res.*, **15**, 21 (1970).
191. K. L. Matta and O. P. Bahl, *Carbohydr. Res.*, **21**, 469 (1972).
192. C. A. A. van Boeckel, J. P. G. Hermans, P. Westerduin, J. J. Oltvoort, G. A. van der Marel, and J. H. van Boom, *Tetrahedron Lett.*, **23**, 1951 (1982).
193. C. Augé, S. David, and A. Veyrières, *Nouv. J. Chim.*, **3**, 491 (1979).
194. N. Ardabilchi, A. O. Fitton, J. R. Frost, F. R. Oppong-Boachie, A. H. Hadi, and A. M. Sharif, *JCS Perkin Trans. I*, 539 (1979).
195. N. Ardabilchi and A. O. Fitton, *J. Chem. Res. (S)*, 310 (1979).
196. T. Kocpzyński and S. Goszczynski, *Pol. J. Chem.*, **55**, 393 (1981).
197. S. Goszczynski and T. Kocpzyński, *J. Org. Chem.*, **38**, 1245 (1973).
198. S. H. Pines and M. A. Kozłowski, *J. Org. Chem.*, **37**, 292 (1972).

199. H.-H. Bechtolsheimer and H. Kunz, *Angew. Chem. Intl. Edit.*, **21**, 630 (1982).
200. F. Heinzer and D. Bellus, *Helv. Chim. Acta*, **64**, 2279 (1981).
201. K. Bischofberger, A. J. Brink, O. G. De Villiers, R. H. Hall, and A. Jordaan, *Carbohydr. Res.*, **64**, 33 (1978).
202. I. Hoppe and U. Schöllkopf, *Justus Liebig's Ann. Chem.*, 1548 (1982).
203. Y. Ozaki, S. Maeda, M. Miyoshi, and K. Matsumoto, *Synthesis*, 216 (1979).
204. Y. Ozaki, K. Matsumoto, and M. Miyoshi, *Agric. Biol. Chem.*, **42**, 1565 (1978).
205. K. Matsumoto, Y. Ozaki, M. Suzuki, and M. Miyoshi, *Agric. Biol. Chem.*, **40**, 2045 (1976).
206. J.-C. Depezay, A. Dureault, and T. Prange, *Carbohydr. Res.*, **112**, 51 (1983).
207. U. Schöllkopf, R. Schröder, and E. Blume, *Justus Liebig's Ann. Chem.*, **766**, 130 (1972).
208. U. Schöllkopf and R. Schröder, *Angew. Chem. Intl. Edit.*, **12**, 407 (1973).
209. H. H. Wasserman and M. B. Floyd, *Tetrahedron, Suppl.* **7**, **22**, 441 (1966).
210. H. H. Wasserman, F. J. Vinick, and Y. C. Chang, *J. Am. Chem. Soc.*, **94**, 7180 (1972).
211. H. H. Wasserman, R. J. Gambale, and M. J. Pulwer, *Tetrahedron*, **37**, 4059 (1981).
212. For a review on singlet oxygen reactions with heterocycles, see: H. H. Wasserman and B. H. Lipshutz, in *Singlet Oxygen*, H. H. Wasserman and R. W. Murray, Eds., Academic Press, New York, 1979, Chapter 9.
213. M. L. Graziano, M. R. Iesce, and R. Scarpati, *J. Heterocycl. Chem.*, **15**, 1205 (1978).
214. H. H. Wasserman and T.-J. Lu, *Tetrahedron Lett.*, **23**, 3831 (1982).
215. H. H. Wasserman, J. E. Pickett, and F. S. Vinick, *Heterocycles*, **15**, 1069 (1981).
216. H. H. Wasserman, R. J. Gambale, and M. J. Pulwer, *Tetrahedron Lett.*, **22**, 1737 (1981).
- 217a. H. H. Wasserman and R. J. Gambale, *Tetrahedron Lett.*, **22**, 4849 (1981).
- 217b. H. H. Wasserman and R. J. Gambale, *J. Am. Chem. Soc.*, **107**, 1423 (1985).
218. H. Bredereck and R. Gompper, *Chem. Ber.*, **87**, 726 (1954).
219. H. H. Wasserman and E. Druckery, *J. Am. Chem. Soc.*, **90**, 2440 (1968).
220. R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **91**, 5358 (1969).
221. P. D. Bartlett and G. D. Mendenhall, *J. Am. Chem. Soc.*, **92**, 210 (1970).
222. A. P. Schaap and P. D. Bartlett, *J. Am. Chem. Soc.*, **92**, 6055 (1970).
223. B. H. Lipshutz, lecture at McNeil Pharmaceutical, November 1982. Some papers on this work have appeared: B. H. Lipshutz, R. W. Hungate, and K. E. McCarthy, *Tetrahedron Lett.*, **24**, 5155 (1983); idem, *J. Am. Chem. Soc.*, **105**, 7703 (1983).
224. C. M. Wong, T.-L. Ho, and W. P. Niemczura, *Can. J. Chem.*, **53**, 3144 (1975).
225. B. H. Lipshutz and R. W. Hungate, *J. Org. Chem.*, **46**, 1410 (1981) and references cited. [Also, see: R. D. Wood and B. Ganem, *Tetrahedron Lett.*, **24**, 4391 (1983).]
226. R. Schröder, U. Schöllkopf, E. Blume, and I. Hoppe, *Justus Liebig's Ann. Chem.*, 533 (1975).
- 226a. A. I. Meyers and J. P. Lawson, *Tetrahedron Lett.*, **22**, 3163 (1981). [Also, see A. I. Meyers and D. G. Walker, *J. Org. Chem.*, **47**, 2999 (1982) for some related chemistry.]
227. P. A. Jacobi, S. Ueng, and D. Carr, *J. Org. Chem.*, **44**, 2042 (1979).
228. E. E. Harris, R. A. Firestone, K. Pfister, III, R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, and W. Reuter, *J. Org. Chem.*, **27**, 2705 (1962).
229. R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron*, **23**, 943 (1967).
230. H. Takagaki, N. Yasuda, M. Asoaka, and H. Takei, *Chem. Lett.*, 183 (1979).
231. K. Omura, N. Tada, M. Tomimoto, Y. Usui, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.*, **24**, 2699 (1976).

- 232. B. A. Johnsen and K. Undheim, *Acta Chem. Scand.*, **B37**, 127 (1983). [Also, see: idem, *ibid.*, **B37**, 907 (1983).]
- 233. A. P. Kozikowski and N. M. Hasan, *J. Org. Chem.*, **42**, 2039 (1977).
- 234. J. Hutton, B. Potts, and P. F. Southern, *Syn. Commun.*, **9**, 789 (1979).
- 235. A. Gorgues and A. Le Coq, *Tetrahedron Lett.*, 4829 (1979).
- 236. M. F. Ansell, M. P. L. Caton, and P. C. North, *Tetrahedron Lett.*, **22**, 1727 (1981).
- 237. D. Liotta, M. Saindane, and W. Ott, *Tetrahedron Lett.*, **24**, 2473 (1983).
- 238. P. A. Jacobi and T. Craig, *J. Am. Chem. Soc.*, **100**, 7748 (1978).
- 239. P. A. Jacobi, D. G. Walker, and I. M. A. Odeh, *J. Org. Chem.*, **46**, 2065 (1981).
- 240. For some more recent work, see: P. A. Jacobi, C. S. R. Kaczmarck, and U. E. Udodong, *Tetrahedron Lett.*, **25**, 4859 (1984); P. A. Jacobi, T. A. Craig, D. G. Walker, B. A. Arrick, and R. F. Frechette, *J. Am. Chem. Soc.*, **106**, 5585 (1984); P. A. Jacobi and H. G. Selnick, *ibid.*, **106**, 3041 (1984).
- 241. After completion of this chapter, a review article on the use of oxazolines in aromatic substitution appeared (covering literature through 1983). It deals with nucleophilic substitution, metalation and electrophilic substitution, and organometallic addition; besides, it discusses chemistry for oxazoline removal. See: M. Reuman and A. I. Meyers, *Tetrahedron*, **41**, 837 (1985).

Author Index

- Abbe', J., 333
Abdallah, H., 1014
Abd-El-Gawad, 696, 701, 705
Abdel-Megeid, F. M. E., 693, 705
Abdel-Motaleb, R. M., 701
Abdin, T. M. S., 693
Abdul-Monem, M. A., 693
Abe, S., 325
Abe, Y., 728
Abou-Gharbia, M., 724
Abraham, E. P., 711
Abronin, I. A., 359
Acheson, R. M., 696, 704, 715
Ackerman, J. J. H., 1013
Ackerman, M. E., 335
Adamovich, A. I., 703
Adams, R., 325
Adelstein, G. W., 337
Adembri, G., 721, 722
Adiwidjaja, G., 332
Adkins, H., 338
Afanasiadi, L. S., 337, 702, 712, 714
Afifi, A. A., 697
Afridi, A. S., 328
Agarwal, R., 707
Agnello, S., 696
Agnesetti, P. A., 714
Ahlguist, A., 729
Aitzhanova, M. A., 331, 334, 340, 359
Akamatsu, N., 335
Akamatsu, T., 334
Akamori, R. N., 698
Akashi, H., 694
Akiba, M., 708, 721
Albanani, A. A. A., 712
Alberti, C. G., 334
Albonico, S. M., 958, 1015
Aldous, D. L., 324, 325
Ali, M., 703, 707
Ali, M. R., 707
Allan, A. W., 327
Allegrì, G., 708
Allinger, N. L., 695
Alonso, M. E., 327
Alper, H., 956
Al-Saigh, Z., 693
Altman, K., 709
Alvarez, E. P., 710
Amaratunga, W., 1013
Ambartsumyan, E. N., 728
Ambrus, G., 327
Ames, A., 325, 328, 1010, 1012
Ames, A. F., 720
Ames, A. J., 334
Ames, D. E., 720
Amino, Y., 1011
Amos, R. A., 333
Anderson, D. J., 328
Anderson, G. W., 340
Anderson, J. J., 716
Anderson, L., 1015
Anderson, N. K., 956, 957
Ando, M., 323, 326
Andrisano, R., 696
Angelo, H. R., 709
Angle, S., 324
Anhoury, M. L., 715
Anisimova, V. A., 695, 719
Ansell, M. F., 333, 1017
Antonenko, T. S., 1015
Antonova, A., 691
Antonov, V. K., 711
Aoyama, T., 329
Appiano, A., 360
ApSimon, J. W., 958
Aquilera, M. E., 702
Ardabilchi, N., 1015
Arenal, I., 698, 709
Arison, B. H., 1014
Aritomi, J., 325
Armstrong, M. D., 696, 698, 704
Arnold, D. R., 326, 327
Aronova, N. I., 695
Arora, R. K., 696
Arrick, B. A., 1017
Asahina, T., 710
Asai, H., 331
Asai, S., 340

- Asaoka, M., 328, 701, 1016
 Asaoka, N., 708
 Asaoka, S., 328
 Asher, R., 723
 Ashley, J. N., 714
 Asker, W., 693, 705, 707
 Asthana, B. P., 696
 Atala, S., 703
 Attenburrow, J., 697, 699
 Aubert, P., 700
 Aubouet, J., 1014
 Audier, H. E., 360
 Aue, D. H., 339
 Auerbach, L., 711
 Auge', C., 1015
 Austel, V., 703, 709, 721, 723
 Avaeva, S. M., 692
 Aversa, M. C., 726, 728
 Avila, W. B., 1010, 1012
 Awad, W. E., 693, 707, 709, 717
 Axelrod, B., 332
 Ayabe, G., 325
 Ayyangar, N. R., 699
 Azechi, K., 339
 Azimov, V. A., 719

 Baba, T., 1012
 Bacescu, M., 360, 706
 Bachstez, M., 334
 Backelberg, O. C., 325
 Badr, M. Z. A., 707
 Badshah, A., 703, 1014
 Baganz, H., 330, 340
 Bahl, O. P., 1015
 Baker, B. R., 716, 718
 Baker, J. H., 715
 Baker, R. V., 1014
 Baker, W., 699, 704, 711, 955
 Bakre, K. M., 339
 Balaban, A. T., 323, 360, 694, 706, 725
 Balashova, A. T., 719
 Balashova, E. G., 724
 Baldwin, J. E., 707
 Baldwin, J. J., 1014
 Balegroune, F., 958
 Ballantine, J. A., 710
 Ballhause, H., 340
 Bally, I., 360, 706
 Bal' on, Ya. G., 323
 Baltazzi, E., 691, 695, 697, 699, 700, 703
 Bambers, P., 715
 Banerji, K. D., 703
 Banfi, T. D., 714

 Bang, L., 1013
 Bangert, R., 327, 360
 Banks, B. J., 1011
 Baradarani, M. M., 1012
 Baran, G., 710
 Baranowski, T., 711
 Barber, H. J., 699, 718
 Barger, G., 711
 Barner, B. A., 1012
 Barnes, D. K., 707
 Barrett, A. G. M., 1012
 Barrett, G. C., 705
 Barta, I., 327
 Bartel, K., 332
 Barthwal, J. P., 707
 Bartlett, P. D., 1016
 Barton, D. H. R., 1012
 Bartroli, J., 1014
 Baruah, J. N., 709, 960
 Bashkir, E. A., 712
 Basova, Y. G., 724
 Bassi, D. A., 696
 Bassignana, P., 360
 Battersby, A. R., 713, 717
 Baudru, M., 327
 Bauer, E., 324
 Bauer, V. J., 326
 Baum, J., 957, 958
 Baum, M., 957
 Baumann, N., 701
 Baumgartel, H., 323
 Bausher, L. P., 340, 341, 359
 Bayer, H. O., 708, 956, 957, 1015
 Baysang, A., 331, 697
 Baxter, I., 729
 Beak, P., 1012
 Beccalli, E. M., 325
 Bechtolsheimer, H.-H., 1016
 Beck, J.-P., 1013
 Beckman, B. G., 697
 Beer, R. J. S., 714
 Beglinger, V., 713
 Behling, J., 717
 Behrens, O. K., 695, 716
 Behringer, H., 699, 705, 707
 Bekarek, V., 696
 Bekmukhametov, R. R., 328
 Belaya, Zh. N., 329, 332, 341
 Belgodere, E., 723
 Belikov, A. B., 333
 Bell, A. A., 705
 Bell, J. P., 715
 Bell, M. R., 712

- Bell, R. A., 1013
Bellus, D., 1016
Benages, I. A., 958
Bencze, W. L., 713
Bender, H., 719
Benker, F., 728
Bennett, E. L., 697, 710, 713
Benoiton, N. L., 727, 956
Bentley, R., 720
Beregi, L., 716
Berentsson, P. E., 703
Bergbreiter, D. E., 1013
Bergel, F., 705, 716
Bergman, J., 332
Bergmann, M., 698, 713, 720
Beriaru, V., 717
Berk, H. C., 709, 958
Berlan, J., 1014
Berlin, A. Y., 716
Bernabe, M., 698, 709, 710
Bernardi, L., 334
Bernstein, S., 718
Besprozvannaya, M. M., 329
Bestermann, H. H., 723
Bestermann, H. M., 708
Besthorn, E., 955
Beu, L., 323
Bexell, G., 340
Beyer, H., 326, 340, 341
Beyerman, H. C., 696
Bhat, V., 701, 959
Bhate, D. S., 333
Bhatia, S. B., 328
Bhatt, M. V., 324, 333
Bhattacharjee, D., 956, 960
Bhattacharya, B., 326, 707
Bieri, J. H., 959
Bilegan, C., 696, 700, 706, 707
Billek, G., 705
Binsch, G., 336, 339
Birch, H. F., 704
Bird, C. W., 696, 712, 723, 959
Birkofer, L., 691
Birladeanu, L., 360, 694, 705, 706
Birnbaum, G. I., 333
Bischofberger, K., 338, 1016
Bisson, R., 697
Bite, P., 720
Bittner, F., 705
Bland, J. M., 1014
Blank, H. U., 725
Blaschke, H., 328, 726
Blickens, D., 326
Block, F. H., 718
Blommerde, W. W. J. M., 726, 728
Blomquist, A. T., 713
Bloom, J. D., 1011
Blount, J., 341
Blount, J. F., 332, 333
Blume, E., 325, 328, 1010, 1016
Blümlein, F. O., 336
Bodea, C., 700, 702, 706, 710, 718, 720
Boeckelheide, V., 1011
Boernberg, S., 696
Boettcher, R. R., 1016
Bogdanov, V. S., 331, 334, 340, 359
Boksiner, E. I., 693
Bolanos, J. F., 704
Bolhofer, W. A., 323
Boll, W., 334, 336
Boltze, K. H., 717
Bonse, G., 725
Bonzom, A., 336
Booth, D. A., 696
Bordeaux, K. G., 957, 958
Bordignon, E., 712
Bordulina, S. N., 716
Borello, E., 360
Borg, R., 723
Borum, O. H., 323, 334
Bossert, F., 713
Bota, A., 725
Bottari, F., 727
Bottler, R., 724
Botvinik, M. M., 692
Boulton, A. J., 334
Bourne, E., 698
Bouteville, X., 715
Bower, B. H., 696, 958
Bowie, J. H., 324, 325, 359, 360
Boyd, G. V., 695, 696, 698, 707, 709, 720, 727, 956, 957, 959
Bradley, W., 718
Bradsher, C. K., 329, 1012
Branquet, J. P., 711
Brasch, J., 719
Brauchaud, B., 1011
Bredereck, H., 324, 327, 334, 336, 360, 726, 1016
Breitholle, E. G., 698, 701, 721, 723, 1014
Brenner, A. M., 713
Brenner, M., 692
Brettle, R., 696
Brewster, K., 716
Brink, A. J., 1016
Brink, M., 715

- Broadhead, G. D., 716
 Brocklehurst, K., 710, 711
 Brooker, L. G. S., 333, 700
 Brooks, R., 1011
 Brossi, A., 325
 Brougham, L. R., 1013
 Brovarets, V. S., 329
 Brown, A. G., 710
 Brown, C. J., 326
 Brown, D. J., 337, 359
 Brown, E. J., 724
 Brown, E. V., 325
 Brown, J. M., 711
 Brown, J. P., 705
 Brown, K., 324, 335, 337
 Brown, R. A., 1012
 Brown, R. F. C., 329
 Browne, E. J., 701
 Brunn, E., 959
 Brunova, B., 713
 Bruylants, A., 331
 Bucci, E., 727
 Bucciarelli, U., 329
 Buck, J. S., 697, 704
 Buckles, R. E., 697
 Budovski, E. I., 698, 707
 Buhr, G., 725
 Buhro, W. E., 324
 Bulka, E., 326
 Bullerwell, R. A. F., 696
 Bulow, W., 703
 Bundgaard, H., 709
 Bunge, K., 335
 Burdon, J., 698
 Burger, A., 709, 715, 716
 Burger, K., 326, 359, 721
 Burgess, E. M., 958
 Burghard, H., 708
 Burke, B., 333
 Burke, S. S., 325
 Burrows, E. T., 717
 Burrows, W. D., 956
 Bursock, H., 718
 Burton, H., 715
 Bushra, H., 719
 Butterick, J. R., 703
 Buu, N. T., 328
 Buurman, C. H., 703
 Buzas, A., 704
 Bykova, L. M., 338
 Bystrom, S., 1013
 Caballini, G., 716
 Cabello, C. C., 960
 Cahnmann, H. J., 704
 Caillaux, B., 728
 Calabro, M. A., 960
 Calverlez, M. J., 1011
 Camerino, B., 334
 Cameron, D. W., 729
 Campaign, E., 707
 Campbell, A. L., 1012
 Canada, E. J., 341
 Capmau, M-L., 333
 Cappelozzi, G., 324
 Caraculacu, G., 703
 Carboni, S., 727
 Carey, P. R., 710, 714, 715
 Caristi, C., 324
 Carlini, F. M., 722
 Carlsen, J., 712
 Carlson, J. A., 712
 Caron, E. L., 338
 Carotenuto, A., 334
 Carpenter, A. J., 1012
 Carpenter, F. H., 700, 718
 Carpino, L. A., 704
 Carr, D., 328, 1016
 Carrara, G., 338
 Carrie, R., 727, 1014
 Carriere, R. G., 714, 715
 Carter, H. E., 691, 692, 697, 698, 1014
 Cartoon, M. E. K., 1012
 Cartwright, N. J., 705
 Cartwright, W. F., 692
 Cascio, G., 728
 Casnati, G., 712, 720
 Cass, W. E., 335
 Castek, A., 334
 Castellucci, E., 360
 Castle, R. N., 324, 325, 1012
 Cativeira, C., 695
 Caton, M. P. L., 333, 1017
 Cavalla, J. F., 337
 Cavalleri, R., 720
 Cavallini, G., 700, 716
 Cavella, J. F., 337
 Cech, D., 1015
 Cedergren, R. J., 713
 Ceprini, M. Q., 695
 Ceriani, S., 323, 327
 Chadwick, D. J., 1012
 Chain, E. B., 711
 Chakaravarty, J., 703
 Chaloner, P. A., 711
 Chaloupka, S., 721
 Chaman, E. S., 691, 692, 697, 710, 714
 Chan, J., 716

- Chan, T. H., 692, 724
Chancellor, T., 961
Chandrakumar, N. S., 1011
Chane, J. P., 719
Chang, C. N., 719
Chang, Y. C., 327, 333, 1016
Chapman, J. R., 705
Charles, L., 333
Chase, G. O., 338
Chatten, L. G., 724
Chatterjea, J. N., 703, 704, 705
Chatterjee, B. G., 727
Chauvin, P., 327
Cheeseman, G. W. H., 1012
Chelli, M., 333, 723
Chel'tsova, G. V., 694, 698
Chemerdá, J. M., 339
Chen, E., 330
Chen, H. Y., 957
Chen, S. J., 959
Cheney, L. C., 328
Cheng, K.-P., 1013
Cheng-fan, J., 325
Cherkasova, I. S., 334
Chiancone, F. M., 338
Chien, S. W., 695
Chigira, Y., 698
Chiklis, C. E., 692
Chindris, E., 326
Chinone, A., 960
Chirac, G., 703
Chirahara, K. I., 719
Chiraleu, F., 956
Chirita, C., 696, 706
Chizhov, O. S., 334
Chliwner, I., 1011
Chouteau, J., 360
Christensen, S. A. K., 705
Christmann, O., 330
Chuaqui, C., 703
Chung, B. Y., 717
Chupp, J. P., 331
Chzhi-Khen, K., 330
Cier, A., 711
Cima, L., 323
Cinganotto, P., 712
Cioranescu, E., 360, 694, 706
Cioranescu, E. I., 705, 706
Ciordaru, V., 702
Claes, P. J., 709
Clardy, J., 1014
Clark, R. L., 699
Clarke, H. T., 691, 720
Clarke, K., 714
Clark-Lewis, J. W., 712
Clayton, J. C., 717
Cleaver, C. L., 701, 703
Cleland, G. H., 335
Clemans, S. D., 712
Clemo, G. R., 714, 715
Clerin, D., 331, 332, 334, 960
Cobb, R. L., 960
Cockerill, A. F., 330, 360
Coffen, D. L., 327
Cogrossi, C., 360
Cohen, L. A., 326, 333, 708, 717, 721
Cojocariu, I., 337
Cojocariu, Z., 337
Collington, E. W., 1010, 1012
Colwell, A. R., 1011
Conant, R., 1011
Cook, A. H., 332, 699, 714, 720
Cook, D. C., 700
Cook, E. W., 698, 700
Cooks, R. G., 325, 360
Cookson, E., 327, 699
Cooper, C. S., 1013
Cooper, J. L., 324
Cooper, R. D. G., 718
Copp, F. C., 712
Coppolla, G. M., 338
Corbett, D. F., 329, 709
Corbier, M., 713
Corbin, U., 328
Cordova, L., 719
Corey, E., 958
Corey, E. R., 1015
Corey, P. F., 956, 957
Cormos, L., 704, 716, 719
Cornforth, J. W., 322, 323, 327, 328, 329, 336, 691, 699, 700, 720, 957
Cornforth, R. H., 327, 328, 329, 336
Corse, J. W., 695, 716
Cort, L. A., 360
Coscia, C. J., 1014
Costa, C., 708
Council, S. L., 959
Coutts, R. T., 715
Coxon, B., 1015
Coyne, C. R., 720
Cragoe, E. J., Jr., 334
Craig, T., 339, 1017
Craig, T. A., 1017
Craig, P. N., 330
Cram, D. J., 1013
Cramer, F., 726
Crank, G., 330
Craat, L. B., 328

- Crawford, M., 692
 Credner, H. H., 728
 Crenshaw, R. R., 338
 Cromatie, R. I. T., 715
 Crooij, P., 715
 Crooy, P., 331
 Cross, F. J., 1016
 Crow, W. D., 332
 Crowe, B. F., 698, 710, 719
 Crunele, A. G., 702
 Cruz, J. R., 720
 Cullen, T. G., 334
 Cum, G., 726, 728
 Cuntze, U., 715
 Currie, R. B., 1016

 Dadkhah, M., 335
 Daffe, V., 1014
 Dahlboom, R., 728
 Dakin, H. D., 957
 Dalby, S., 712
 d'Alcontres, G. S., 324
 Dallacker, F., 338
 Dall Asta, L., 714
 D'Amato, V., 338
 D'Ambrosion, R., 716
 D'Amier, J. J., 331
 Dandiya, P. C., 696
 Dando, S. R., 707, 709
 D'Angeli, F., 692
 Daniel, H., 957, 1015
 Dann, O., 326, 335
 Dannenberg, D., 711
 Dannenberg, H., 711
 Dantsig, T. B., 689
 Dash, M., 330
 Datta, S., 326
 Datta, S. K., 957, 958
 Daub, G. H., 335
 Daubach, E., 701
 Dave, S. S., 696
 Davenport, H. F., 714
 David, S., 1015
 Davidenkov, L. R., 704
 Davidovich, Y. A., 693
 Davidson, D., 324, 711
 Davidson, J. G., 324
 Davidson, J. S., 729
 Davidson, R. M., 1015
 Davies, C. G., 957
 Davies, J. S., 956, 1014
 Davies, J. S. H., 709, 729
 Davis, E. A., 699

 Davis, J. W., 700
 Davis, M., 326
 Davis, S. G., 693
 Dawkins, A. W., 704
 Deacon, A., 330
 Dean, F. M., 704, 720
 Dean, P. M., 719
 DeAntoni, A., 708
 Dearnaley, D. P., 715
 Deasy, C. L., 718
 Deavenport, D. L., 359
 Debaerdemaeker, T., 957, 959, 960, 961
 deBuman, A., 360
 Declercq, J. P., 333
 de Díaz, R. G., 325, 330
 Decm, M. L., 958
 DeGroot, A., 324, 1012
 de Jersey, J., 711
 DellaVecchia, L., 1012
 Delofeu, V., 696
 Delpierre, G. R., 328
 DeMalleray, B. M., 719
 Demchenko, N. P., 323
 Demetrescu, C., 696, 706
 DeNet, R. W., 326
 Deneys, R., 715
 Denisova, L. I., 692
 Dents, R., 729
 Deorha, D. S., 704, 705
 Depezay, J.-C., 1016
 Derible, P. H., 326
 Deryckere, A., 324, 330
 DeSarlo, F., 726, 727
 Destevens, G., 713, 725
 Deulofeu, V., 709
 DeVilliers, O. G., 1016
 Dewar, M. J. S., 323, 329, 331, 359, 956, 957, 1010
 Dewhurst, B. D., 695
 Dey, A. S., 727
 Deyrup, J. A., 331, 728
 Dhane, D. L., 335
 Dharan, M., 709, 958
 Dhir, B. S., 701
 Diamond, J., 716
 Diaz-Azan, L., 702
 Diaz Palominos, S., 702
 DiBello, C., 692
 Diefenbach, H., 702
 Dietliker, K., 327, 332
 Diferrante, N., 709
 Dilthey, W., 325
 Dimsdale, M. J., 696

- DiPaco, G. F., 713
Diszler, E., 720
Dittrich, K., 326
Dixit, V. M., 701, 959
Dixon, W. D., 726
Djuric, S., 1011
Doenges, R., 326
Doherty, D. G., 713
Doktorova, N. D., 339
Dolby, L. J., 323, 333
Dolgushina, I., Ya., 332
Dominguez, X. A., 715
Donaghue, P. F., 324, 325, 359, 360
Donaldson, J. D., 957
Donati, D., 333
Dooley, K., 709, 1014
Dordor, I. M., 1012
Dorme, R., 713
Dorne, P., 957
Dornow, A., 330, 337
Dorofeenko, A. N., 725
Dorofeenko, G. N., 328, 332, 340, 725
Douchis, H., 331
Doyle, F. P., 700
Doyle, M. P., 324
Drach, B. S., 329, 331, 332, 340, 717
Drefahl, G., 326
Dren, A. T., 724
Dressler, V., 711
Dreyer, D. L., 332
Druckery, E., 1016
Dryanska, V., 325
Dubrakova, L., 696
Duckwall, L. R., 1011
Duclos, J. M., 340
Duesberg, P., 699
Duffin, G. F., 699, 700, 712, 720
Duffraisse, C., 712
Duggins, W. E., 698
Duhault, J., 716
Duke, R. E., Jr., 958
Dulenko, V. I., 340
Durant, F., 333
Durant, G. J., 326, 329, 337
Durckheimer, W., 718
Dureault, A., 1016
Durham, D. G., 958
Dürr, D., 334
duVigneaud, V., 700, 718
Duxbury, F. K., 714, 715
Dworschak, H., 327
Dyadyusha, G. G., 341
Dyer, E., 719
Dyumaev, K. M., 716
Dziomko, V. M., 326, 338, 726
Dzugaj, A., 692
Dzugat, A., 711
Dzyuban, A. D., 331
Eagles, J., 723
Earley, J. V., 332
Eastwood, F. W., 328
Edgar, K. J., 1012
Edward, J. T., 328
Edwards, H. D., 700
Edwards, P. D., 1011
Effenberger, F., 326, 727
Eggersdorfer, M., 721
Egorova, N. P., 337
Eguchi, S., 713, 718
Ehrhart, G., 714
Eicher, T., 958
Eiden, F., 696
Eilers, E., 1010
Eimers, E., 727
Eisenbrand, J., 709
Eitelman, S. J., 338
Ekeley, J. B., 707
Elargoudi, Z. E., 693
Elbanani, A. A. A., 693
Elbhail, S. A., 701
Elderfield, R. C., 691
El-Ebrashi, N. M., 707
Elguero, J., 359
El-Houseni, M. S., 696
Eliaers, J., 715
Elina, A. S., 697, 699
El-Kaschef, M. A., 693
El-Kaschef, M. A. F., 693, 705
Ellefson, C. R., 1011, 1012, 1013
Elliott, D. F., 697, 699, 717
Elliot, R. C., 324
Elnagdi, M. H., 701
El-Nagdi, M. H., 712
Eloy, F., 324, 330
Elphimoff-Felkin, I., 698
El-Sherief, H. A. H., 707
El'tsov, A. V., 329
Elvidge, J. A. E., 720
El'Yanov, B. S., 333
Emmett, J. C., 326, 329, 337
Emoto, S., 323, 326
Engel, N., 722, 723
Engelhardt, A., 696
England, D. C., 726
Ennis, M. D., 1014

- Epe, B., 956
 Erhardt, H., 701
 Erlenmeyer, E., 691
 Eschenmoser, A., 729
 Esfandiar, S., 359
 Espinasse, P., 957
 Essenburg, A. D., 323
 Essery, J. M., 328
 Estchenberg, E., 714
 Etchenberg, E., 717
 Eugster, C. H., 726
 Evangelidou, E. K., 960
 Evans, A. A., 718
 Evans, C. A., 720
 Evans, D. A., 1014
 Evans, D. L., 325
 Evans, R. H., 333
 Evrard, G., 333
 Ewiess, N. F., 708

 Fabrichinyi, B. P., 703
 Fahmy, A. F. M., 694, 697, 707
 Falck, J. R., 1010, 1012
 Faleeva, L. N., 725
 Falkenberg, K., 699
 Fanshawe, W. J., 326
 Farcasan, V., 705, 706, 710, 720
 Farkas, L., 704, 705
 Fastrez, J., 1014
 Fateen, A. K., 709
 Fattorusso, E., 328
 Favara, D., 327
 Fawaz, E., 327
 Fawre, R., 359
 Federsel, H.-J., 332
 Fedorova, N. S., 329
 Fehlhammer, W. P., 332
 Felkin, H., 698
 Fennoy, L., 715
 Fenwick, G. R., 723
 Fenwick, R., 710
 Ferber, R. H., 332
 Fernanadez-Bolanos, J., 720
 Fernandez-Alvarez, E., 698, 709
 Fernbach, R., 326, 335
 Ferrari, C., 693
 Ferrario, P., 714
 Ferrini, P. G., 336
 Ferris, J. P., 331, 336
 Ferrito, V., 723
 Fetizon, M., 360
 Feuerriegel, G., 323
 Fick, H., 326, 335

 Filippova, T. M., 334
 Filira, F., 692
 Filler, R., 691, 693, 697, 705, 710, 712,
 713, 714, 720, 721, 722, 724, 1010, 1014
 Finar, I. L., 697, 718
 Findlay, A., 723
 Fink, J., 702
 Firestone, R. A., 339, 957, 1016
 Firl, J., 326
 Fischer, E., 955
 Fischer, H., 703
 Fischer, J., 723
 Fisher, E., 323
 Fissekis, J. D., 695, 696
 Fitton, A. O., 697, 715, 1015
 Fitzi, K., 336, 720
 Fleifel, A. M., 705
 Fletcher, I. J., 334
 Fleury, J. P., 331, 332, 334, 697, 708, 709,
 957, 960
 Florent'ev, V. L., 334, 339, 1010
 Floss, H. G., 724
 Flowers, W. T., 341
 Floyd, M. B., 1016
 Foldi, Z., 712
 Fomenko, V. I., 332, 334
 Ford, M. E., 1012, 1013
 Forest, H. S., 715
 Forton, P., 693
 Foster, R. T., 704, 719
 Foucaud, A., 327
 Foulis, M. J., 330
 Fournair, P., 719
 Fowler, F. W., 325
 Fowler, K. W., 1011
 Francis, T., 704, 720
 Frangopol, P. T., 323, 360, 706
 Frankel, Z., 719
 Franz, J. E., 709, 958
 Frauendorfer, E., 722
 Frechet, J. M. J., 1013
 Frechette, R. F., 1017
 Freeman, J. P., 960, 961
 Fregnan, G. B., 728
 Frenkel, Z., 704, 716
 Freudenberg, K., 704, 705
 Fried, J., 710
 Friedman, B. S., 325
 Friedrichsen, W., 956, 957, 958, 959, 960,
 961
 Friedrichson, J., 325
 Fritz, H., 334, 726, 960
 Frost, J. R., 715, 1015

- Frump, J. A., 1010
 Frunze, T. M., 702
 Fry, D. J., 699
 Fryer, R. I., 332, 341
 Fuchs, O., 703
 Fuller, A. T., 715
 Fujimoto, K., 325
 Fujinuma, Y., 702
 Fujita, E., 341
 Fujiyama, F., 339
 Fukamoto, K., 702
 Fukumi, H., 726
 Fukumoto, K., 691, 714
 Fulmor, W., 723
 Funahashi, T., 328
 Funayama, M., 702
 Funke, E., 959
 Furer, B., 336
 Furlenmeier, A., 328
 Furutani, I., 727
 Futagawa, S., 718

 Gaarder, J. O., 703
 Gabel, R., 1010, 1013
 Gabel, R. A., 1012, 1013
 Gabor, V., 703
 Gabriel, S., 326, 334
 Gadallah, A. E. A., 693
 Gaffney, G. W., 709
 Gagneux, A. R., 726
 Gaiki, G. M., 335
 Gakis, N., 332, 721
 Galantay, E., 710
 Galat, A., 697
 Galey, J.-P., 359
 Gallagher, T. C., 325
 Gallina, C., 721
 Gambale, R. J., 325, 1016
 Gambaryan, N. P., 339, 718
 Gandhi, S. K., 697, 713
 Gandino, M., 360
 Ganellin, C. R., 326, 329, 337
 Ganem, B., 333, 1016
 Gante, J., 718
 Gardent, J., 712
 Garkusha, G. A., 338
 Garmatter, J., 360
 Garthe, E., 700
 Gaset, A., 701
 Gatsenko, L. G., 705
 Gattuso, M., 324, 726
 Gebhardt-Bauer, H. G., 717
 Gehret, J.-C. E., 957, 1015

 Geiszelt, A. O., 724
 Gemmili, C. L., 716
 Genghof, D. S., 700
 Georg, H. H., 728
 George, J. K., 958
 George, M. V., 701, 959
 George, P., 728
 Georgi, V., 718
 Geresh, S., 694
 Gerhart, F., 1010, 1012
 Germain, G., 333, 958
 Gever, G., 698
 Gewald, K., 330, 726
 Gezendanner, H., 721
 Ghosez, L., 336
 Ghosh, B. K., 707
 Ghosh, P. B., 334, 337, 359
 Ghosh, T. N., 326, 707
 Giam, C.-S., 1012
 Gianetto, P. D., 728
 Giannella, M., 330
 Giannetto, P., 728
 Gibbons, A. J., 1015
 Gigg, R., 1011
 Gilbert, W. W., 338
 Gilchrist, T. L., 326, 328, 959
 Gilgen, P., 324, 325, 327, 721
 Gillespie, H. B., 697, 714
 Gilligan, P. J., 1014
 Ginak, A. I., 724, 725
 Ginanneschi, M., 333, 360, 723
 Gingrich, H. L., 708, 728, 958, 959
 Ginoulhiac, E., 338
 Girard, T. A., 698
 Girault, P., 329
 Giroux, J., 713
 Gish, D. T., 1015
 Giudicelli, R., 723, 724
 Gizler, M., 710
 Glagoleva, E. A., 703
 Glaser, C. B., 692, 695
 Glaser, R., 694, 710
 Glennon, R. A., 331
 Glockner, U., 721
 Glushkov, R. G., 720
 Godfrey, J. C., 693
 Godfrey, K. E., 718
 Godreau, P. V., 711
 Godunova, L. F., 694, 703, 713
 Gohari, A. K. M. N., 707
 Goknel, E., 726
 Goldfarb, Y. L., 702, 703
 Goldsworthy, L. J., 327

- Golovner, B. M., 711
 Gomez, B., 715
 Gomez-Parra, V., 329
 Gompper, R., 324, 326, 327, 328, 329, 330, 334, 336, 360, 725, 726, 727, 1016
 Gonzalez, F. G., 704, 720
 Good, R. H., 327
 Goodman, M., 692, 695, 716
 Goon, D. J. W., 957
 Gordon, A. J., 725
 Gordon, E. M., 1014
 Gorques, A., 339, 1017
 Gorrichon, J. P., 701
 Goschke, R., 726
 Goszczynski, S., 1015
 Goth, H., 326, 359, 726
 Goto, Y., 325, 332, 333
 Gotsmann, U., 336
 Gotthardt, H., 708, 956, 957, 958, 959, 1015
 Gottsegen, A., 704
 Götz, M., 960
 Gotze, S., 708, 723
 Grabley, S., 332, 729
 Grabowski, Z., 359
 Gracian, D., 329
 Graf, F., 333
 Grafantini, M., 340
 Graham, R., 328
 Grahl-Nielsen, O., 692, 695, 711
 Grandsberg, P. T., 719
 Granger, R., 713
 Grashey, R., 955
 Gray, R. P., 708, 956
 Graziano, M. L., 328, 334, 1016
 Gream, G. E., 328
 Grebennikov, A. V., 332
 Greco, C. V., 708, 956
 Gree, R., 1014
 Green, B. S., 722
 Greenberg, H., 727
 Greene, T. W., 1010
 Grekov, A. P., 323
 Grell, W., 340
 Grethe, G., 717
 Grey, T. F., 720
 Griffin, D. M., 719
 Griffith, R. K., 697
 Grigg, R., 334
 Grigorev, I. A., 721
 Grigor'eva, V. I., 337
 Grimme, W., 707
 Grimova, J., 713
 Grimshaw, J., 696, 707
 Griss, G., 340
 Gronowitz, S., 1011
 Grossi, A. V., 960
 Grosso, V. G., 708, 956
 Grothe, E., 727
 Gruber, P., 694, 708, 712, 722, 723, 1015
 Grushina, L. E., 695, 719
 Gschwend, H. W., 1010, 1011, 1013
 Gualtieri, F., 330
 Guarna, A., 727
 Gudmundsno, A. G., 698
 Guenot, P., 727
 Guidicelli, R., 340
 Guitierrez, M. B., 714
 Gunar, V. I., 328, 333, 334, 338
 Gupta, A. A., 707
 Gupta, P., 705
 Gupta, R. C., 707
 Gupta, S. P., 696
 Gupta, V., 696
 Gupta, V. N., 696
 Guseva, L. S., 725
 Gustak, E., 334, 702
 Gustowski, W., 699
 Gutman, A. D., 324, 327
 Guzic, F. S., 727
 Gymer, G. E., 328
 Haagen—Smit, A. J., 718
 Haake, P., 340, 341, 359
 Haas, G., 1014
 Häbich, D., 1011
 Habild, G., 714
 Hachihama, M., 335
 Hackmann, J. T., 713
 Hackne, P. T., 713
 Haddadin, M. J., 960, 961
 Hadi, A. H., 1015
 Haefliger, W. E., 696
 Hafez, M. S., 693
 Hafferl, W., 340
 Hagesao, M., 722
 Haginiwa, J., 325
 Haidukewych, D., 1010, 1011
 Hajdu, J., 1011
 Hajós, A., 337, 714
 Hakimelahi, G. H., 727
 Halat, M. J., 957
 Halgas, J., 1013
 Halker, J. S. E., 714
 Hall, R. H., 338, 1016
 Hall, S. R., 333
 Hamada, Y., 327

- Hamaguchi, M., 960, 961
Hamana, M., 325
Hamburg, E., 719
Hamdan, A., 1011, 1013
Hamilton, L., 958
Hamilton, R., 707
Hammann, I., 330
Hammar, W. J., 326
Hammouda, M., 701
Han, G. Y., 960
Hanagan, M. A., 1014
Handa, S., 726
Handler, P., 697
Hanemann, K., 717
Hanna, C., 696, 710
Hansbury, E., 335
Hansel, W., 718
Hansen, B., 959
Hansen, G., 702
Hansen, H-J., 325, 332, 709, 721
Hansen, H. V., 716
Hansen, J. F., 1011, 1013
Hanson, A. W., 714
Hanson, K. R., 713, 717
Hantke, K., 1010
Hanumanthu, P., 707
Harborne, J. B., 704
Harder, R., 708
Hardtmann, G., 1014
Hardtmann, G. E., 338
Hardy, R. A., Jr., 723
Harhash, A. H., 693, 701, 705, 707, 712
Harhash, A. H. E., 693
Harigel, K. K., 708
Harihara, K., 957
Harley-Mason, J., 715, 1011
Harms, R., 1010
Harrington, C., 717
Harris, A. M., 696
Harris, E. E., 339, 1016
Harris, G., 699, 714
Harris, J. O., 714
Harrison, C. H., 359
Harrison, J. B., 692, 698
Harrison, R. G., 326, 330, 331
Harrit, N., 959
Hartke, K., 959
Hartmann, A., 713
Hartmann, W., 726, 728
Hartung, H., 718
Hartwig, W., 1011
Hartzel, M., 702
Haruki, E., 331
Harwood, H. J., 697
Hasan, N. M., 334, 1017
Hashem, A. I., 717
Hashimoto, M., 961
Hashimoto, N., 327, 331
Hassan, H. M., 705
Hassner, A., 325
Hata, N., 701
Hauck, A. E., 1012
Hauschildt, P., 340
Haverbeke, Y. V., 710, 717
Havinga, E., 713
Havir, E. A., 717
Haworth, J. W., 705
Hayami, M., 332, 335
Hayes, F. N., 326, 332, 335, 360
Healey, T. V., 704, 719
Hearn, W. R., 703
Heathcock, C. H., 1013
Hebron, L. M., 693
Hecht, S. M., 325
Heeres, J., 323
Hefli, R., 726
Hegedus, B., 717
Heiko, H., 702
Heilbron, I. M., 714
Heimgartner, H., 324, 325, 332, 693, 709, 721, 723, 727, 728, 729, 957, 959
Heimstra, H., 359
Heine, H. G., 726, 728
Heine, H. W., 958
Heinemann, U., 329
Heiner, B., 727
Heininger, H-U., 327, 723
Heinze, H., 718
Heinze, J., 323, 336
Heinzelman, W., 723
Heinzer, F., 1016
Hekman, M., 958, 1015
Hell, H., 330, 337
Heller, L., 722
Hellerman, L., 709
Hems, B. A., 717
Henneke, K., 323
Hennig, B., 326
Hennig, I., 714
Henri-Rousseau, O., 958
Henry, Y., 360
Herbison-Evans, D., 360
Herbst, D. M., 697
Herlinger, H., 725, 726
Hermans, J. P. G., 1015
Hernandez, M. A., 960

- Herold, T., 1013
 Herrin, T. R., 724
 Herrmann, E., 703
 Herrmann, G., 1015
 Hershenson, F. M., 956, 957, 958, 1015
 Hertwig, H., 718
 Herz, W., 719
 Hess, V., 1014
 Hesse, K.-F., 956
 Hessler, E., 1015
 Hetzheim, A., 332, 333, 341
 Heydt, A., 724
 Heyes, K., 698
 Hidisan-Tautean, L., 325
 Higuchi, T., 728
 Hilfman, L., 697
 Hill, R. K., 724
 Hilmy, M. K., 722
 Himmelsbach, R. J., 1011, 1013
 Hines, J. W., Jr., 698
 Hinman, J. W., 338, 697, 699
 Hiragi, M., 716
 Hirakawa, K., 958
 Hiraoka, T., 708, 712
 Hirobe, M., 331, 728
 Hirono, T., 702
 Hirose, Y., 325
 Hiyama, H., 335
 Hiyama, T., 336
 Hiyamoto, M., 698
 Ho, B. T., 704
 Ho, C. T., 336, 360
 Ho, T.-L., 337, 1016
 Hodgkin, J. H., 332
 Hoeksema, H., 338
 Hoekstra, J. W., 324
 Hoerger, E., 710
 Hoffer, M., 331
 Hoffmann, C., 704
 Hoffman, H., 718, 728
 Hoffmann, R. W., 1013
 Hoffmann-Poquette, H., 338
 Höfle, G., 325, 328, 339, 695, 706, 708, 721, 722, 723, 957, 1015
 Hogberg, H.-E., 1013
 Hohenlohe-Oehringen, K., 712, 723
 Holdrege, C. T., 693
 Holker, J. S. E., 705
 Holland, D. O., 713
 Holland, G. F., 338
 Holley, R. W., 700, 718
 Hollowood, J., 337
 Holm, A., 959
 Holt, E. M., 709, 1014
 Holt, G., 341
 Holubek, J., 713
 Holy, A., 1015
 Homberg, A., 715
 Honja, N., 333, 698
 Honma, T., 337
 Hoobler, M. A., 1013
 Hoogenboom, B. E., 323, 329, 359
 Hoogmartens, J., 709
 Hook, E. O., 698
 Hook, W. H., 729
 Hoppe, D., 323, 328, 712, 1012
 Hoppe, I., 325, 328, 1010, 1016
 Hora, I. M., 696
 Horan, H., 332
 Horgan, D. J., 711
 Horie, K., 722
 Horie, T., 697, 698
 Hornemann, V., 724
 Horner, L., 693, 703, 717
 Horrom, B. W., 724
 Horvath, G., 327
 Hosni, A. A., 708
 Houbion, J. A., 1011
 Houghton, E., 957, 958
 Houghton, P. G., 715
 Houk, K. N., 958
 Houwing, H. A., 323, 359
 Howard, J. C., 700
 Howe, R. K., 328, 341
 Howell, C. F., 723
 Hoyer, D., 1012
 Hrnicar, P., 719
 Hu, P. F., 715
 Huang, H. T., 700
 Huang, I. C. W., 960
 Huang, J. T., 704
 Hubacher, M. H., 696
 Hubert, A. J., 328
 Hubner, K., 712
 Huche, M., 1014
 Hudrlik, A. M., 1010
 Hudrlik, P. F., 1010
 Hudson, B. J. F., 704, 714
 Huebenett, F., 718
 Huebner, K., 691
 Hughes, P. G., 329
 Hugoh, P., 716
 Huisgen, R., 326, 328, 335, 336, 339, 695, 708, 726, 955, 956, 957, 958, 959, 1015
 Hukuoka, K., 726

- Hung, W. M.-W., 960
 Hungate, R. W., 325, 341, 1016
 Hunter, G. D., 332
 Hunter, J. H., 699
 Hunter, P. W. W., 359
 Hurley, L. H., 724
 Hurnaus, R., 694, 721
 Huttel, R., 718
 Hutton, J., 324, 1017
- Iasu, C., 705
 Ibata, T., 324, 960, 961
 Ibrahim, M. N., 1014
 Ichikawa, H., 698
 Ichikawa, N., 704
 Ida, H. I., 715, 717
 Ide, W. S., 697, 704
 Jesce, M. R., 334, 1016
 Iitaka, Y., 728
 Ikeda, K., 339
 Ikoma, K., 961
 Ikushima, H., 1013
 Illiceto, A., 323
 Imai, Y., 702, 703
 Imanaka, H., 331, 1013
 Imoto, E., 331
 Ingham, B. H., 336
 Ingraham, L. L., 340
 Inoue, M., 330
 Inoue, S., 335
 Inui, T., 718
 Ion, V., 696, 706
 Ionescu, M., 323, 325, 337
 Ionova, L. V., 339
 Irngartinger, H., 340
 Ishida, T., 330
 Ishidate, M., 333
 Ishiguro, M., 715
 Islam, A. M., 696
 Isobe, K., 339
 Isomura, K., 325
 Issatschenko, A. B., 336
 Ito, E., 333
 Ito, I., 330, 331, 720
 Ito, M., 339
 Ito, S., 328
 Ito, T., 694
 Ito, Y., 1011
 Itoh, Y., 1013
 Itov, Z. I., 328
 Ittyerah, P. I., 696, 715, 719
 Iur'ev, Iu. K., 333
 Ivanov, K., 325
- Ivanova, Z. N., 331
 Ivashchenko, A. V., 326, 338, 726
 Iwakura, Y., 323, 695, 698, 711, 720, 721, 722, 723
 Iwanami, M., 339
 Iwao, M., 1012
 Iwasaki, T., 338
 Iyengar, D. S., 707, 708, 710
 Izawa, K., 715
 Izzo, P. T., 724
- Jackson, B., 332, 721
 Jackson, J. L., 334
 Jackson, T. E., 329
 Jackson, W. G., 338
 Jacobi, P. A., 323, 328, 333, 339, 1016, 1017
 Jacquemin, C., 716
 Jaeggi, K. A., 714
 Jainamma, K. M., 719
 Jakobsen, H. J., 327
 Janicki, R. S., 724
 Jano, P., 327
 Janousek, Z., 728
 Jansen, A. B. A., 328
 Januszewski, H., 359
 Japp, F. R., 324, 723
 Jatzkewitz, H., 714
 Jaworski, S., 710
 Jaworski, T., 338, 340
 Jeanloz, R. W., 1015
 Jeffreys, R. A., 324, 332, 700, 720
 Jelling, M., 324
 Jendrzewski, S., 325, 708
 Jenkins, P. A., 713
 Jennings, K. F., 700, 702
 Jensen, A. B. A., 708
 Jensen, K. A., 705
 Jenssen, T., 712
 Jepson, J. B., 699
 Jeuring, H. J., 330
 Jezo, I., 696
 Jin, Q. Z., 360
 Joannic, M., 723
 Joannic-Voisinet, E., 723
 Johnsen, B. A., 1017
 Johnson, F. H., 719
 Johnson, J. R., 691, 720
 Johnson, P. C., 705
 Jolley, M. R. J., 331
 Jommi, G., 695, 701
 Jones, D. S., 711
 Jones, G., 327

- Jones, G. H., 337
 Jones, J. H., 712, 1014
 Jones, R. G., 695, 716
 Jones, W. G. M., 331, 709
 Jones, W. J., 329
 Jones, W. M., 717
 Jordaan, A., 1016
 Jordan, A., 338
 Jordis, U., 325
 Joshi, B. S., 333
 Joule, J. A., 1012
 Joullie, M. M., 716
 Julia, S., 336
 Just, G., 717

 Kabas, G., 360
 Kaczmarek, C. S. R., 1017
 Kaczorowski, Z., 695
 Kaigorodova, L. N., 694
 Kaiser, C., 715
 Kakehi, A., 328
 Kakiya, Y., 331
 Kalcheva, V., 330
 Kalcheva, V. B., 727
 Kalnin, I., 718
 Kalnin, I. K., 694
 Kalnina, J., 711
 Kalsi, P. S., 701
 Kalt, A., 957
 Kamata, K., 1013
 Kametani, T., 691, 702, 705, 708, 714, 715, 717, 1014
 Kamigata, N., 708
 Kaminski, Z. T., 692
 Kanakarajan, K., 1012
 Kanamori, Y., 331
 Kanaoka, M., 728
 Kane, J. M., 957
 Kaneko, E., 339
 Kaneko, H., 1011, 1013
 Kaneko, T., 698, 718
 Kanemasa, S., 956
 Kanfer, S. J., 1011
 Kang, H. H., 699
 Kanitkar, K. B., 960
 Kannan, R., 1012
 Kao, I., 716
 Kaplan, H. R., 323
 Kaplan, M. L., 1016
 Karady, S., 693, 1014
 Karash, C. B., 958
 Karchevnikov, A. P., 694, 713
 Karimoto, R. S., 332

 Kariyone, K., 695
 Karmarkar, S. S., 333
 Karnischky, L. A., 326
 Karpavicius, K., 716
 Karpeiskaya, E. I., 694, 698, 703, 711
 Karpeiskii, M. Y., 698, 707
 Karpeiskii, M. Y., 1010
 Karpeiskii, M. Ya., 334, 339
 Karpenko, V. D., 328, 332, 725
 Karpukhin, G. V., 717
 Karpukhin, O. N., 717
 Karrer, P., 711
 Kartev, V. G., 336
 Kashab, A. I., 693
 Kasmai, H. S., 727
 Kasperek, H., 700
 Kassab, N. A., 701
 Kassir, N. A. L., 693
 Kast, H., 702
 Kataoka, M., 334
 Katayama, K., 723
 Kathawala, F., 1014
 Kato, H., 325, 701, 709, 956, 958, 959, 961
 Kato, K., 1011
 Kato, M., 1015
 Kato, S., 334, 707
 Kato, T., 331
 Katritzky, A. R., 325, 328, 332, 333, 334, 360, 691, 720
 Katsuki, H., 722
 Katsura, H., 698, 718
 Kattan, A. M., 960
 Kaushik, A. C., 704
 Kawaguchi, Y., 722
 Kawai, Y., 1013
 Kawamura, H., 700, 702
 Kawashima, E., 341
 Kawazu, M., 339
 Kayahara, H., 693
 Keehn, P. M., 324
 Keighley, G., 718
 Keller, S. M., 958
 Keller, R., 711
 Kelley, J. A., 715
 Kellogg, R. M., 336
 Kemp, D. S., 695
 Kendall, J. D., 699, 700, 712, 720
 Kenner, G. W., 711, 712
 Kennwell, P. D., 1012
 Kermer, W. D., 702
 Kerr, V. N., 326, 332, 335
 Ketcha, D. M., 724
 Ketcham, R., 331

- Kettenes, D. K., 720
Keyes, G. H., 333, 700
Khalifa, M. A. E., 701, 707
Khalil, A. M., 696, 701, 705
Khan, N. H., 703, 707, 718, 1014
Kharchevnikov, A. P., 694
Khatri, H. N., 1013
Khatskevich, I. E., 694, 711, 718
Khokhar, A. R., 705
Khomutov, R. M., 698, 707
Khorana, H. G., 714
Khorlin, A. J., 1015
Khorlin, A. Y., 1015
Khozeeva, R. V., 329
Khripak, S. M., 725
Khromov, N. V., 715
Khromov-Borisov, N. V., 704
Kiaey, G., 330
Kibayashi, C., 715, 717
Kidwai, A. R., 703, 1014
Kigasawa, K., 716
Kiguchi, T., 727
Kikugawa, Y., 333
Kildisheva, O. V., 712, 716, 717
Kille', G., 331, 332, 708, 709, 957, 960
Killinsky, F., 712
Killion, K. K., 331
Killmer, L. B., 1010
Kim, J. H., 697
Kim, S., 717
King, F. E., 712
King, J. A., 335, 720
King, L. C., 335
King, S. W., 709, 1014
Kingdon, F. H., 702
Kingston, D. G. I., 328, 333
Kino, K., 702, 703
Kirby, G. W., 701, 713, 714
Kirono, T., 703
Kirsanov, A. V., 332
Kiryanov, A. N., 697
Kisfaludi, L., 695
Kishida, Y., 708
Kishor, K., 707
Kisilenko, A. A., 332
Kiso, M., 1015
Kitagawa, T., 323
Kitamura, T., 338
Kitatani, K., 336
Kiyohara, H., 960
Kiyosawa, T., 958
Kjellin, G., 329, 360, 707
Klabunovskii, E. I., 694, 720, 956
Klawitter, J., 720, 956
Kleemann, M., 340
Klemm, L. H., 719
Klimisha, G. P., 326, 340, 726
Klitgaard, N. A., 707
Klüpfel, K. W., 324
Knaus, G., 1013
Kneidl, F., 723
Knight, J. C., 704
Knoffler, G., 709
Knoll, A. G., 714
Knorr, R., 695, 956, 957, 959
Knorre, D. G., 692
Knott, E. B., 699, 700
Knowles, A. M., 695, 709, 959
Knowles, W. S., 703, 714
Knunyants, I. L., 339, 712, 717, 718, 720
Knyazkova, N. E., 706, 707
Kobayashi, K., 702
Koch, T. H., 724
Kochetkov, N. K., 698, 707
Kocpzynski, T., 1015
Koenig, H., 336
Koenig, V. L., 360
Kogure, T., 1014
Kohayakawa, A., 339
Kohayakawa, T., 339
Köhler, G., 341
Kohlmann, F. W., 340
Koike, Y., 707
Kojima, M., 336, 709, 959, 1015
Koller, W., 336
Kollinsky, F., 691
Kollonitsch, J., 337, 703, 714
Kolpak, M. X., 333
Koltai, E., 724
Komendantov, M. I., 328
Kondrat'eva, G. Ya., 330, 331, 334, 336, 339, 340
Konieczny, P., 726
König, H., 333, 334
König, J., 1015
König, W., 708, 722, 723
König, W. A., 1014
Konishi, M., 339
Konno, S., 1014
Kono, T., 714
Konyukhov, V., 703
Kopecky, J., 728
Koppel, H., 1015
Koremura, M., 337
Kormany, G., 360
Korol'chenko, G. A., 697

- Korshak, V. V., 693, 702
 Korte, F., 327, 360, 706
 Koshi, K., 336
 Kossmehl, G., 702
 Kost, A. N., 334, 336, 719
 Koster, H. F., 709
 Köster, J., 959
 Kostikov, R. R., 328
 Kosuigi, M., 722, 723
 Kosulina, T. P., 725
 Kotok, L. A., 702, 712
 Kovacs, J., 695
 Kovlatyan, V. V., 728
 Koyama, Y., 323, 333
 Kozikowski, A. P., 325, 334, 338, 339,
 1010, 1012, 1017
 Kozlov, L. V., 702
 Kozlowski, M. A., 1015
 Krasnavskaya, E. A., 703
 Krasovitskii, B. M., 325, 334, 335, 337,
 714
 Kratzer, P., 338
 Kratzl, K., 705
 Krause, H., 717
 Krieg, B., 726, 727
 Krishan, K., 701, 710
 Krishna, R. R., 339
 Krishnamurthy, A., 336
 Krivun, S. V., 717
 Kroha, H., 340
 Kroker, R., 702
 Krull, H., 724
 Krum, W., 726
 Ku, A., 330
 Kübel, B., 328, 694, 708, 722, 723
 Kubel, R., 712
 Kubota, T., 704
 Kuchar, M., 713
 Kudryashova, N. I., 704
 Kuehnling, W., 958
 Kuettner, K., 728
 Kuklina, E. T., 703
 Kukloja, S., 718
 Kulikova, L. B., 706, 707
 Kulka, M., 717
 Kulnevich, V. G., 725
 Kumar, A., 959
 Kumar, B., 708, 959
 Kumar, K., 710, 714
 Kumar, P., 691, 699, 701, 707
 Kumar, S., 701, 1012
 Kumashiro, I., 330
 Kumata, K., 1011
 Kuneida, T., 728
 Kunz, H., 1016
 Kuo, C. H., 691
 Kuo, S. J., 1011
 Kuo, Y.-C., 329
 Kurata, Y., 728
 Kurihara, T., 326
 Kurita, H., 698
 Kuriyama, S., 331
 Kurts, A. L., 711
 Kurumi, M., 700
 Kurumisawa, H., 701, 959
 Kurusu, K., 324
 Kusakawa, N., 323
 Kushner, S., 698, 700
 Kuskov, V. K., 701
 Kusunori, T., 703
 Kutney, J. P., 1011
 Kutulya, L. A., 337
 Kuwabura, T., 723
 Kvitko, N. Ya., 329
 L'Abbe, G. L., 728
 Labib, G. H., 715
 Labouchere, A., 703
 Lacasse, G., 329
 Lacova, M., 719
 Laessig, W., 728
 Lagowski, J. M., 325
 Laidoudi, A., 958
 Laizus, Z. K., 717
 Lakhani, R., 323, 326, 1010
 Lam, G., 331
 LaMattina, J. L., 323
 Lambooy, J. P., 696
 Lanet, J., 713
 Lanier, J. L., 959
 Lanm, B. B., 703
 Lanz, P., 328
 Lapvk, Y. A., 712
 Larsen, E. H., 327
 Lautenschläger, H., 325, 727
 Lavallee, R., 725
 Lavrenyuk, T. Ya., 340
 Lawesson, S.-O., 327
 Lawson, A., 325, 695, 696, 700, 709, 955,
 956, 959
 Lawson, J. P., 327, 1016
 LeCoq, A., 339, 1017
 Ledingham, A. E., 705
 Lednicer, D., 1010
 Lee, C. M., 724
 Lee, L. F., 328

- Lee, M. L., 1012
 Lee, W. S., 693
 Lee, W. W., 716
 LeGoffic, F., 333
 Leimgruber, W., 729
 Leipprand, H., 324
 Leising, F., 698
 Lemmens, J. M., 726, 728
 Lempert, K., 724
 Lenz, G. R., 333
 Lepetit, S. P. A., 698
 Lepikhova, S. V., 720
 Leplawy, M. T., 692, 711
 Lepone, G. E., 340
 LeRoy, G., 717
 Leschinsky, K. L., 331
 Lesiak, I., 705
 Lesiak, T., 719
 Leuchs, A., 718
 Levin, J. I., 334, 1010, 1013
 Levine, L., 695
 Levitina, E. S., 694
 Lewy, M., 336
 Leyendecker, J., 722, 1014
 Li, T., 716
 Li, T.-S., 335
 Liao, T.-K., 960
 Libman, D. D., 697
 Lichtenberger, J., 331
 Lier, R., 335
 Liesch, J. M., 327, 333
 Lim, R., 959
 Lind, E., 324
 Lindberg, H. A., 337
 Lindberg, V. H., 324, 340, 724
 Lindert, A., 1011
 Lindfield, W. M., 1011
 Ling, C.-F., 960
 Linkova, M., 717
 Liotta, D., 341, 1017
 Liphardt, B., 326
 Lipkin, A. E., 720
 Lipp, M., 338
 Lipshutz, B. H., 325, 341, 1016
 Lister, J., 335
 Literati-Kiraly, I., 329
 Little, W. T., 692
 Liu, C.-M., 333
 Liu, K.-C., 341
 Livermore, A. H., 700, 718
 Llinares, J., 359
 Lloyd, G., 705
 Lobanov, O. P., 329
 Lockhart, I. M., 720
 Locock, R. A., 724
 Lohmar, R., 694, 712, 1014, 1015
 Loiseau, J., 723, 724
 Lomakina, N. P., 334, 336, 360, 1010
 Long, L. M., 323
 Loop, W., 330, 340
 Lora-Tamayo, M., 324, 329
 Lord Todd, 328, 333
 Lorenc, J., 957
 Lott, R. S., 701, 1014
 Loudon, J. D., 704
 Loughman, B. E., 1015
 Louterman LeLoup, G., 717
 Lowe, H. J., 709
 Löwe, W., 326
 Lowy, P. H., 718
 Lu, T.-J., 324, 333, 1016
 Luanglath, K., 327
 Lubinkowski, J. J., 960
 Lubuzh, E. D., 694
 Lucente, G., 721
 Ludden, C. T., 334
 Luebke, F., 725
 Lukáč, J., 728, 957, 959
 Lukyanets, E. A., 337
 Lundin, R., 340
 Lupsa, I., 696, 700, 706, 707
 Lure, S. I., 697, 699, 705, 707, 710, 714
 Luryl, S. I., 691
 Luskus, L. J., 958
 Lutomski, K., 1012, 1013
 Lüttke, W., 326
 L'vov, A. I., 332
 L'vova, S. D., 328, 333, 334, 338
 Lykkeberg, J., 707
 Lynn, K. R., 715
 Lysova, I. V., 337, 702, 712, 714
 Macarovici, R., 323, 326
 McCarthy, K. E., 341, 1016
 McCarty, F., 960
 McCleery, P. P., 341
 McClure, D. E., 1014
 McCombie, H., 725
 McDermott, J. R., 956
 MacDonald, J. B., 721
 MacDonald, J. G., 708, 721
 MacDonald, R. J., 960
 MacDonald, S. F., 697
 McEwen, W. E., 960
 McGahren, W. J., 692, 695
 McGee, L. R., 1014

- McGrath, L., 714
 McGrath, M. J., 1011
 McGregor, D. N., 328
 Mach, M. H., 693
 McKenzie, J. B. D., 719
 McKeough, D., 958
 McKnight, M. V., 1012
 McLoughlin, V. C. R., 698
 McManus, S. P., 1011
 McMillan, A., 698, 704
 McMillan, F. H., 335, 720
 McNeal, J. P., 341
 McPherson, H. L., 957
 Madroñero, R., 324, 329
 Madsen, P., 327
 Maeda, I., 328, 340
 Maeda, M., 336
 Maeda, R., 334
 Maeda, S., 1016
 Mackawa, K., 719
 Maffrand, J.-P., 958
 Magdesieva, N. N., 719
 Magerlein, B. J., 692
 Magidson, O. Y., 697, 699, 720
 Magin, A., 324
 Magnus, P., 1011
 Mahapatra, G. N., 330
 Mahoney, C. L., 338
 Mahori, S. I., 716
 Maia, H. L., 692
 Maitra, S. S., 710
 Majori, L., 325
 Mak, A. L. C., 724
 Makhova, N. N., 695
 Makkay, C., 325, 329, 337
 Mallen, D. N. B., 360
 Mallicky, J. L., 715
 Mamaev, V. P., 696, 713, 719
 Mamiofe, S. M., 707
 Manabe, O., 335
 Mando, M., 323
 Manecke, G., 702, 720, 956
 Manghisi, E., 728
 Mani, N. V., 720
 Manna, S., 1010
 Mannschreck, A., 340
 Manrao, M. R., 701
 Manske, R. F. H., 705, 717
 Mantsch, H., 704
 Mao, D. T., 1013
 Maquestiau, A., 702, 710, 717, 718
 Marasco, M., 1013
 Marchesini, A., 325
 Marchetti, E., 323, 326, 335, 337
 Margolis, S. A., 1015
 Marin, C. P. C., 960
 Markert, G., 691, 700, 712
 Markova, L. V., 701
 Markovac-Prpic, A., 702
 Märky, M., 332, 721
 Marmugi, E., 960
 Marques, A., 703
 Marquez, A., 709
 Marrian, D. H., 714
 Marshall, J., 724
 Marshall, J. L., 958, 960, 1015
 Marsili, A., 727
 Martin, A. R., 331
 Martin, H.-D., 958, 1015
 Martin, W., 718
 Martinez, A. F., 716
 Martinez, J., 327
 Martinez, S. J., 1012
 Martinuzzi, C., 338
 Martvan, A., 728
 Martynyuk, A. P., 329, 717
 Martyres, G., 327
 Marxer, A., 336
 Maryanoff, C. A., 331, 359, 958, 959, 1015
 Marzolph, G., 725
 Masaki, M., 698
 Masamura, M., 698
 Mascagni, P., 727
 Mase, T., 956, 960
 Maselli, C., 725
 Mashraqui, S. H., 324
 Maslova, G., 718
 Massarini, E., 700, 716
 Mastrocola, A. R., 959, 1015
 Masumura, M., 697
 Matela, L., 707
 Mathiapparanam, P., 727
 Mathre, D. J., 1014
 Matiekno, L., 717
 Matsui, K., 719
 Matsui, M., 703
 Matsukawa, S., 722
 Matsukubo, H., 709, 958, 959, 1015
 Matsumoto, K., 338, 957, 1016
 Matsumura, K., 327, 331
 Matsuo, M., 334, 335, 1011
 Matsuo, T., 339, 718
 Matsura, T., 717, 719
 Matsushita, H., 1011, 1013
 Matta, K. L., 1015

- Matta, M. S., 715
 Mattalia, G., 323, 326, 329
 Matveev, V. K., 697
 Mauri, F., 701
 Mauri, L., 716
 Mauss, H., 725
 Mawri, F., 695
 May, H.-J., 330
 Mayer, D., 721
 Mazzu, A., 1013
 Mazzu, A. L., Jr., 325
 Medina-Castro, J., 703
 Medovshchikova, F. D., 715
 Medvedskaya, L. B., 339, 359
 Mehrhof, W., 718
 Mehrotra, K. N., 727
 Mehrotra, V. N., 703
 Meier, E., 728
 Meinwald, J., 339
 Melandez, E., 695
 Mella, F., 702
 Mellor, J. M., 1012
 Meltzer, R. I., 714, 716
 Melville, D. B., 697
 Mendenhall, G. D., 1016
 Menin, J., 340, 723, 724
 Menon, M. K., 696
 Mensink, C., 329
 Merchant, J. R., 327, 704, 710
 Merchant, J. P., 339
 Merrill, R. H., 719
 Merz, K. W., 702
 Metzger, J., 336
 Metzler, D. E., 340
 Meyer, B., 331, 960
 Meyer, H., 713
 Meyer, R. F., 323
 Meyer, W., 703
 Meyers, A. I., 325, 327, 333, 1010, 1011, 1012, 1013, 1014, 1016, 1017
 Mezentsova, N. N., 713, 719
 Mezheritskaya, L. V., 340
 Michael, J., 701, 714
 Michaels, R. J., 724
 Micheel, F., 710
 Michel, R., 716
 Mihelich, E. D., 1010, 1011, 1013
 Miki, T., 329, 339
 Miles, D. H., 955, 956
 Miles, J. A., 1011
 Mille, G., 360
 Miller, A., 1013
 Miller, A. L., 712
 Miller, W. B., 340, 359
 Millington, D. S., 327
 Mills, J. F., 704
 Mil'ner, R. S., 337
 Minami, S., 325
 Minato, A., 697
 Mineo, I. C., 960
 Minster, D. K., 325
 Mioskowski, C., 1010
 Mirgorodskaya, O. A., 692
 Misco, P. F., 328
 Mishra, H. D., 701
 Miskevich, G. N., 331, 717
 Misra, A. K., 699
 Misra, R. N., 1010
 Mitter, P. C., 710
 Mittra, A. S., 330
 Miyake, A., 697, 698
 Miyamoto, M., 697, 718
 Miyano, M., 703
 Miyashita, O., 327, 331
 Miyazaki, H., 697
 Miyazri, H., 698
 Miyoshi, M., 338, 1016
 Mizerski, T., 338
 Mizianty, M. F., 704
 Mizuno, D., 715
 Mocanu, M., 360
 Moevik, B., 711
 Mohammed, A. K., 956
 Mohan, S., 708, 959
 Mohri, K., 327
 Moise, I., 706
 Moldver, B. L., 716
 Möller, S., 1015
 Montastier, J., 333
 Monaco, M., 1016
 Monakhova, A. T., 719
 Monich, N. V., 329
 Moniotte, Ph., 328
 Montedisson, S. p. A., 728
 Mooberry, J. B., 1014
 Moore, L. D., Jr., 959
 Moreiko, O. V., 332
 Morel, J., 327
 Morgan, K. J., 693
 Morganstern, A. P., 710
 Mori, H., 722
 Morimoto, A., 698
 Morin, R. B., 718, 1014
 Morisawa, Y., 334
 Morita, N., 711
 Morita, S., 327

- Morita, T., 703
 Morita, Y., 339
 Moriyama, H., 709
 Morozova, L. F., 719
 Morrison, A. L., 705
 Mosalyk, R. E., 724
 Mosby, R. J., 698
 Mosebach, R., 724
 Moses, P., 728
 Moss, R. A., 1011
 Mostashari, A. J., 359
 Mostmans, J. H., 323
 Muchowski, J. M., 329
 Mueller, H. R., 702
 Mueller, I., 712
 Mukerjee, A. K., 691, 699, 701, 707
 Mukherjee, G., 729
 Mukherjee-Muller, G., 727
 Mulholland, T. P., 704
 Muller, E., 703
 Muller, J., 718
 Muller, L., 722
 Müller, R., 691
 Muller, R. N., 710, 717
 Murakami, M., 333, 339
 Murakami, S., 330, 703
 Muramoto, T., 337
 Murina, I. P., 694, 713
 Muroyama, Y., 335
 Murray, E. B., 1011
 Murray, R. W., 1016
 Murray, T. S., 324
 Mushrif, A. U., 335
 Mustafa, A., 693, 705, 707, 722
 Muste, A., 696, 706
 Muxfeldt, H., 715, 717, 718, 1014
 Myers, J. A., 959
 Nagakoshi, T., 335
 Nagamachi, T., 717
 Nagao, Y., 341
 Nagasawa, H. T., 957
 Nagato, K., 339
 Nagy, M., 337
 Nahm, H., 717
 Nair, M., 329
 Naito, T., 329, 336, 727
 Najer, H., 340, 723, 724
 Nakagawa, M., 726
 Nakahara, M., 718
 Nakajima, S., 707, 708
 Nakamori, R., 698
 Nakamura, A., 694
 Nakamura, T., 716, 726
 Nakanishi, T., 337
 Nakano, A., 338
 Nakano, H., 339
 Nakano, M., 704
 Nakao, H., 336
 Nakatsuka, M., 1011
 Nakazawa, J., 328, 337
 Nakazawa, S., 958
 Nalepa, K., 691, 696, 707
 Nanjo, K., 327
 Nanniperi, E., 727
 Nanse', G., 957
 Narasimhan, K., 699
 Narasimhan, N. S., 709
 Narayanan, K. V., 699
 Narayanaswami, S., 701, 713
 Nardi, O., 716
 Nari, D., 716
 Nasef, A. M., 707
 Nashed, M. A., 1015
 Nasi, F., 721
 Natale, N. R., 1014
 Nath, J. P., 330
 Nauta, W. Th., 710, 715
 Navarrette, P., 709
 Naya, Y., 704
 Nayak, A., 699
 Nayak, B. L., 330
 Nayler, J. H. C., 713
 Nazaki, H., 336
 Nazorova, Z. N., 719
 Neidlein, R., 724
 Neil, G. L., 1015
 Neish, W. J. P., 702
 Nel, W., 715
 Nemeck, O., 713
 Nenitzescu, C. D., 694
 Nesterenko, N. I., 331
 Nestor, J. J., 337
 Nesynov, E. P., 329
 Netsch, K. P., 723
 Neuberger, A., 691, 696
 Neudecker, T., 323
 Neugebauer, W., 324
 Neumeyer, J. L., 727
 Neupokoeva, E. S., 694, 703, 713
 Neuschwander, B., 1011
 Neustadt, B. R., 725
 Neville, M., 330
 Newberry, R. A., 337, 695, 709, 959
 Newcomb, M., 1013
 Newman, M. S., 1012

- Newton, C. G., 956
Ngochindo, R., 1012
Nicholas, E. S., 697, 711
Nichlaus, R. A., 328
Nieman, E., 691
Niemann, C., 335, 697, 708, 713
Niemczura, W. P., 337, 1016
Niewiadomsky, K. B., 716
Niewöhner, U., 722, 1014, 1015
Nikiforov, G. A., 716
Ninomiya, I., 727
Nishida, M., 330
Nishigaki, S., 331, 333
Nishihata, J., 726
Nishiki, H., 338
Nishinaga, A., 715, 717
Nishiwaki, T., 338, 339
Nishiyama, H., 324
Noguchi, H., 695
Noguchi, M., 709, 1011, 1013
Nolen, R. L., 1011
Nonaka, M., 339
Noras, K. A., 335
Nord, F. F., 697, 698, 710, 719
Nordin, I. C., 1011
Norin, T., 1013
Normura, T., 335
North, P. C., 333, 1017
Noureldeen, M. M., 722
Novak, J., 1013
Novák, J. J. K., 324, 336
Novar, H., 714
Novikov, V. N., 719
Nowak, K., 692, 695
Nozaki, H., 726
Numata, H., 1012
Nunami, K., 338
Nunez, J., 716
Nunn, E. E., 724, 959

Obata, K., 336
Obrecht, D., 693
O'Brien, J. L., 708
Oda, N., 331
Odek, I. M. A., 323, 1017
O'Donovan, D. G., 332
Oe, K., 727
Oehlschlager, A. C., 1011
Oesterlin, R., 712
Oettmeier, W., 331, 721
Offe, H. A., 714
Ogasawara, K., 708, 715, 1012
Ogawa, K., 337

Ohara, M., 708
Ohata, K., 335
Ohgo, Y., 703
Ohkubo, Y., 715
Ohle, H., 709
Ohler, E., 713
Ohnishi, S., 339
Ohshio, H., 718
Ohta, G., 336
Ohta, M., 325, 698, 956, 960
Ohtsuka, Y., 332, 333
Oikawa, Y., 327, 338
Oizumi, K., 698
Ojima, I., 1014
Ojrzynski, J., 711
Oka, Y., 336, 1016
Okada, I., 716
Okamoto, M., 1013
Okamoto, T., 331
Okamura, K., 720
Okawara, M., 324
Okolov, S. S., 716
Oku, H., 337
Okumura, F. S., 697, 698
Okumura, K., 338
Okumura, S., 697
Okutome, T., 700
Oldenzien, O. H., 1012
Ollis, W. D., 704, 955, 956, 1014
Olmsted, M. P., 330
Olsen, R. K., 709
Oltvoort, J. J., 1015
O'Mant, D. M., 324
Omoji, B. U., 959
Omote, Y., 702
Omura, K., 336, 1016
Omura, S., 336
Onaka, T., 324, 333
Onuma, K., 694
Oohata, K., 726
Ooi, N. S., 323
Opitz, W., 714, 717
Oppenhuizen, M., 324
Oppong-Boachie, F. R., 1015
Oprian, I., 700, 706, 710, 720
Orabi, M. O. A., 694
Orahovats, A., 721, 723
Orgel, L. E., 331
Orlowski, R. C., 710
Ortega, A. M., 960
Ortega, F. A., 696
Osborne, D. J., 330
Osgerby, J. M., 716

- Oskaja, V., 696
Ostermeyer, F., 714, 729
Ostrovskaya, Y. A., 703
Osuga, K., 339
Osugi, K., 698
Ota, B., 699
Ota, Y., 328
Otazo, E., 719
Ott, D. G., 326, 332, 335
Ott, W., 341, 1017
Ottlinger, R., 326, 359
Otvos, L., 714
Ourisson, G., 1013
Overman, L. E., 324, 330
Ozaki, Y., 1016
Ozawa, Y., 715
- Pacheco, H., 711
Pachler, K. G. R., 715
Padeiskaya, E. N., 724
Padronaggio, R. M., 960
Padwa, A., 324, 325, 326, 330, 708, 709, 721, 958, 959
Padyukova, N. Sh., 339
Pages, R. A., 709
Pain, D. L., 725
Paiu, F., 705
Palibroda, N., 326
Palling, S. J., 700
Pan, P. C., 716
Pande, C. S., 697, 713
Pandey, B. R., 707
Pandey, R. C., 327
Panetta, C., 712
Panke, H.-L., 959
Pansegrau, P. D., 1012
Papaioannou, D., 1012
Papantoniou, C. P., 336
Pappalardo, G., 697
Pare', P. J., 339
Parkes, J. W., 725
Parkins, H., 333
Parrish, S. L., 332
Partyka, R. A., 338
Pascdach, H., 340
Passeg, B. V., 693
Pastour, P., 327
Patel, C., 697
Patel, S. G., 720
Patil, V. D., 332
Paton, J. A., 1011
Pattanayak, B. K., 330
Paul, S. D., 335
- Paulissen, R., 328
Pauson, P. L., 716
Pauvlik, J. M., 724
Pavez, H., 709
Pavlov, V. A., 694
Pearson, D. P. J., 326
Pedersen, J., 324, 724
Pedrazzoli, A., 335, 710, 714
Pelz, J., 701
Pennewiss, H., 691, 711
Penny, G. F., 697
Pérez, J. D., 325, 330
Perrings, J. D., 360
Perron, Y. G., 693
Perronnet, J., 329
Pershin, G. N., 724
Person, H., 327
Pesaro, M., 729
Peshakova, L., 330
Petersen, H. J., 696, 697, 957
Peterson, D. E., 335
Peterson, E. R., 1016
Petri, W., 332
Petrova, T. D., 696
Petrov, V., 323
Petrus, V. S., 725
Petrzilka, T., 708, 959
Petzold, H. E., 709
Pfister, K., III, 1016
Pfister, O. R., 338
Pfister, R., 336
Pfleger, R., 327, 700, 701
Phelps, D. J., 697, 710, 711, 714
Piasek, E. J., 713, 721, 722
Pickett, J. E., 333, 1016
Pierce, H. D., Jr., 1011
Pietzner, B., 326, 335
Pifferi, G., 721
Pilyugin, G. T., 720
Pinder, R. M., 716
Pines, S. H., 339, 693, 695, 1014, 1015
Pini, H., 717
Pinto, T., 702
Pinza, M., 721
Piozzi, F., 720
Pirck, D., 702
Pizzorno, M. T., 958, 1015
Platt, K. L., 702
Platt, T. E., 692, 693
Ploch, J., 691
Plotnikoff, N. P., 724
Plumbohm, B., 330, 726
Plunkett, A. O., 715

- Poignant, J. C., 716
 Poindexter, G. S., 1012
 Poisel, H., 713
 Pojer, P. M., 705
 Polya, J. B., 701, 724
 Polyakov, V. K., 337
 Poole, V. D., 955
 Popa, A., 706
 Popp, F. D., 716, 960
 Porai-Koshits, A. E., 715
 Porter, C. C., 709
 Porter, V. C., 715
 Poschenreider, H., 708
 Possel, O., 323, 359
 Postiaux, R., 718
 Potts, B., 324, 1017
 Potts, K. T., 720, 724, 956, 957, 958, 959, 960, 1015
 Pouchan, C., 360
 Poupaert, J., 331
 Pourcelot, G., 1014
 Pourrat, H., 693
 Powers, D. D., 327
 Poznauskaya, E. M., 703
 Pracejus, H., 717
 Prain, H. D., 329
 Pramickiene, G., 716
 Prange, T., 360, 1016
 Prasad, K. K., 707, 708, 710, 959
 Prasad, N., 703
 Prasad, V. A. V., 724
 Pratap, R., 1012
 Pratt, B. C., 701, 703
 Preco, A., 713
 Prejzner, J., 340
 Preobrazhenskaya, M. N., 724
 Preston, J., 711, 712
 Price, H. S., 710
 Pridgen, L. N., 1010
 Prÿis, B., 328, 335
 Prime, D. M., 330
 Probst, M., 727
 Prodan, K. A., 1011, 1013
 Profft, E., 709
 Proinov, L., 719
 Prokof'ev, E. P., 698, 711
 Prosternik, M., 334
 Protopopova, G. V., 331
 Prouteau, M., 724
 Prox, A., 695, 703, 723
 Pschorr, R., 709
 Pullate, S., 709
 Pulwer, M. J., 325, 1016
 Pumpure, J., 711
 Purcell, F., 701
 Pusch, H., 332, 333
 Pushkaraeva, Z. V., 703, 715, 716, 720
 Pustovarov, V., 719
 Queguiner, G., 1012
 Quilico, A., 720
 Quinones, N. Q., 723
 Quitt, P., 328, 713
 Raab, R., 335
 Rachelle, J. R., 700
 Rachón, J., 332
 Raddatz, S., 714, 717
 Radina, L. B., 720
 Rae, I. D., 329, 705
 Raffü, S., 1014
 Rahimi, M. I., 334
 Rai, M., 701, 710
 Raiford, L. C., 703
 Raileanu, D., 956
 Rakshinda, M. A., 718
 Rall, G. J. H., 715
 Ralph, R. S., 720
 Ram, B., 336, 339
 Ramage, G. R., 331
 Ramirez, F., 328, 724
 Ramsden, C. A., 328, 956, 1014
 Ramsh, S. M., 724
 Rang, H. J., 720
 Ranjan, A., 712
 Ranz, E., 728
 Rao, K. B., 693
 Rao, P. S., 713
 Rao, S., 330
 Rao, Y. S., 691, 693, 695, 697, 705, 712, 713, 720, 724, 1010
 Rao Mohan Krishna, K. S. R., 338
 Rapi, G., 333, 723
 Rasadkina, E. N., 694
 Raschig, H., 339
 Rasmussen, C. A. H., 1012
 Rasmussen, J. K., 325
 Rasmussen, R. M., 724
 Rasmussen, R. S., 710
 Rastelkeve, L. P., 712
 Rastetter, W. H., 961
 Rastogi, S. N., 696
 Rathburn, D. W., 334
 Rathburn, R. W., 359
 Rathke, M. W., 1011
 Ratledge, C., 706

- Ratnam, C. V., 707
 Raut, R. K., 713
 Ravdel, G. A., 692, 697, 699, 710, 714
 Ravikovich, K. M., 707
 Rebek, J., 695, 1015
 Rebek, J., Jr., 957, 958
 Redaelli, S., 334
 Reddy, G. S., 324, 333
 Reddy, M. S., 707
 Redel, J., 715
 Reeder, E., 341
 Rees, A. H., 958
 Rees, C. W., 328, 720, 959
 Reeve, W., 339
 Regitz, M., 724, 960
 Regnier, G. L., 704
 Reich, F., 334, 336, 360
 Reichen, W., 697
 Reid, W., 701
 Reidalova, L. I., 331
 Reider, P. J., 1013
 Reincke, V., 718
 Reiner, R., 726
 Reinhouldt, D. N., 692, 696, 708
 Reisch, J., 324
 Reiter, F., 957
 Renis, H. E., 1015
 Renk, E., 729
 Renwall, I., 726
 Renz, G., 726
 Reppe, W., 324, 340
 Reuman, M., 1011, 1013, 1017
 Reuter, H., 703
 Reuter, W., 339, 1016
 Rhee, R. P., 701
 Riad, D. K., 334
 Ribbens, C., 715
 Ribéreau, P., 1012
 Ricca, A., 712
 Richards, K. D., 709
 Richards, R. E., 360
 Richtzenham, H., 704
 Rick, A. C., 957
 Ridge, B., 692
 Riebel, H.-J., 330
 Riebsomer, J. L., 324, 325
 Ried, W., 717, 719
 Rieker, W. F., 1012
 Rigby, C. W., 712
 Riggi, S. J., 326
 Rinderknecht, H., 705
 Rinderspacher, Th., 328
 Rinehart, K. L., 327
 Rinehart, K. L., Jr., 333
 Rio, G., 712
 Riordan, J. M., 692, 698, 709, 713, 960, 1014
 Risser, W. C., 697
 Riva, G., 695, 701
 Ro, M., 702
 Robertson, A., 704, 705, 714, 719, 720
 Robins, D. J., 958
 Robinson, C. A., 718
 Robinson, R., 335, 691, 695, 702, 703, 708, 711, 720
 Robinson, Sir Robert, 327
 Roche, J., 716
 Rodd, E. H., 691
 Rodda, H. J., 324, 325, 359, 360
 Rodehorst, R. M., 724
 Rodin, I. M., 340
 Rodionow, W. J., 692
 Rodriguez, H., 703, 709
 Rodriguez, H. R., 1010
 Roesler, P., 960
 Rogalski, W., 717, 718
 Rogers, B. S., 360
 Rogovik, V. I., 702, 703
 Rogozhin, S. V., 693
 Rohde, M. F., 715
 Rohklin, E. M., 339, 718
 Rolfson, S. T., 699
 Romeo, A., 721, 728
 Rona, R. J., 1010
 Ronzio, A. R., 697, 707
 Roos, J. P., 330
 Rooy, P. C., 715
 Rosebery, G., 717
 Roselius, W., 713, 715
 Rosenbaum, J. J., 335
 Rosenthal, A., 709, 1014
 Rosnati, V., 326
 Ross, R. M., 338
 Ross, W. J., 330
 Rossi, A. P. A., 713
 Rossi, R., 1013
 Rotberga, S., 696
 Rotbergs, J., 696
 Rousch, D. M., 958
 Rout, D. N., 330
 Rout, M. K., 696, 699, 700
 Roy, J., 727
 Roy, S. K., 703
 Rubtov, M. V., 720
 Ruckert, H., 725
 Rudolph, H., 727

- Rufenacht, K., 692, 713
 Ruggli, P., 701
 Rugheimer, L., 701
 Rühle, H., 326, 327
 Rulinda, J. B., 717
 Rumpf, P., 713
 Runnegar, M. T. C., 711
 Russell, P. B., 714
 Russo, H. F., 334
 Russey, P., 717
 Rustad, M. A., 326
 Ryabukin, Y. I., 725
 Ryabukin, Yu., 328, 332
 Rydan, H. N., 692
 Ryden, R., 330
 Rydon, H. N., 714

 Sabacky, M. J., 703, 714
 Saburi, M., 1011, 1013
 Saegusa, T., 1011
 Saeter, P. E., 337
 Saettone, M. F., 727
 Safir, S. R., 326, 718
 Sahu, D. P., 727
 Saikachi, H., 323
 Saikawa, I., 336
 Sain, B., 708, 709, 959, 960
 Saindane, M., 341, 1017
 Saito, N., 326, 338
 Sakaguchi, T., 334, 335
 Sakai, K., 328, 724
 Sakamoto, M., 724
 Sakdarat, S., 958
 Sakuragi, H., 701
 Sakurai, Y., 700
 Salama, T., 722
 Salat-Ferrer, C., 714
 Salemink, C. A., 1013
 Sallam, M. N. N., 693
 Sallmann, A., 720
 Salmond, W. G., 330, 338
 Salsbury, R., 958
 Sammour, A. E., 722
 Sammour, A. M. A., 707
 Sanchez, A. G., 704
 Sanchez, R. A., 1015
 Sanchez-Viesca, F., 704
 Sander, J., 725
 Sandhu, J. S., 708, 709, 959, 960
 Sandström, J., 329, 360
 Santella, R. P., 960
 Saraie, T., 331
 Sarin, P. S., 328

 Sarkar, T., 1011
 Sarma, C. R., 336, 339
 Sarret, M., 724
 Sarti-Fantoni, P., 722
 Sasaki, H., 323
 Sasaki, T., 333, 719
 Sasamoto, M., 704, 705
 Sato, H., 332
 Sato, J., 333
 Sato, M., 698, 713, 960
 Sato, R., 324, 331
 Sato, S., 325, 700, 960
 Sato, Y., 327, 328, 337, 715
 Satoh, K., 724
 Satrusallya, S. C., 330
 Satsangi, R. K., 707
 Sauer, J., 955
 Saukel, H., 701
 Saunders, J. C., 331
 Sauter, A., 700
 Sauvaitre, H., 360
 Sawdey, G. W., 701
 Saxena, N. K., 336
 Sbrana, G., 360
 Scarborough, H. A., 725
 Scarpati, R., 328, 334, 1016
 Scartazzini, R., 341
 Scatturin, A., 712
 Schaap, A. P., 1016
 Schaaf, F., 703
 Schaefer, F. C., 708, 956, 958, 959
 Schäfer, H., 330, 726
 Schäfer, V., 958
 Schall, E. D., 332
 Schaumann, E., 332, 729
 Scheffer, J. R., 324
 Schenider, G., 715
 Schetty, O., 701
 Scheunemann, K.-H., 1010
 Schiatti, P., 327
 Schickfluss, R., 702, 703
 Schiemann, G., 713, 715
 Schilling, H., 340
 Schlack, P., 336
 Schleger, S., 728
 Schleimer, B., 701
 Schleppinghoff, B., 710
 Schmid, H., 324, 325, 327, 332, 709, 721, 723, 726, 727, 729, 959
 Schmid, T., 956
 Schmid, U., 325
 Schmidhammer, L., 723
 Schmidt, T., 959

- Schmidt, U., 713
 Schnabel, E., 692
 Schneider, H., 715
 Schneider, R. S., 717
 Schneider, W., 713
 Schneiderahn, T., 718
 Schöberl, A., 691
 Schöllkopf, V., 323, 325, 328, 332, 1010, 1016
 Scholz, K. H., 726, 728
 Schönberg, A., 336, 955
 Schow, S. R., 1011
 Schranz, K. W., 728
 Schreiber, J., 729
 Schreier, K., 709
 Schröder, R., 325, 328, 1012, 1016
 Schroeder, D. C., 338
 Schröer, W.-D., 956, 957, 958, 959, 961
 Schroeter, H., 714
 Schubert, E. V., 724
 Schubert, H., 336
 Schudel, P., 729
 Schueler, F. W., 710
 Schuermann, H., 702
 Schuijt, C., 710
 Schukin, G. I., 721
 Schulte, K. E., 324
 Schultze, H., 340
 Schulz, G., 694, 723, 1015
 Schulz, O. E., 712
 Schulz, W., 699
 Schwann, H., 693
 Schwartz, I. L., 699
 Schwarz, I., 956, 960
 Scoffone, E., 323
 Scott, G. P., 702
 Scotton, M., 722
 Seefeldler, M., 340
 Sefcovic, P., 696
 Segnini, E. M., 960
 Seidel, M., 326
 Sekacis, J., 711
 Sekine, S., 714
 Sekiya, M., 331
 Sekretar, S., 728
 Selisko, L., 336
 Selnick, H. G., 1017
 Selva, A., 333
 Selva, D., 327
 Sen, P. K., 327
 Senda, S., 723
 Senga, K., 331, 333
 Sengupta, A. K., 707
 Serafini, C., 329
 Serafini, M. F., 727
 Serizawa, J., 705
 Serna, A. G., 726
 Serota, S., 1011
 Seshadri, T. R., 705
 Seshargiri Rao, C., 339
 Sethna, S., 719, 720
 Seto, M., 339
 Sevast'yanova, T. K., 323
 Severin, E. S., 698, 707
 Seyda, K., 705
 Seyferth, D., 328
 Shaber, S. H., 958
 Shafiee, A., 330
 Shah, V. P., 331
 Shalaev, V. K., 337
 Shalavina, I. F., 703
 Shalley, W. B., 705
 Shamina, L. P., 724
 Shannahoff, D. H., 1015
 Shannon, J. S., 329
 Shapiro, D., 698
 Sharanin, Yu. A., 340
 Sharif, A. M., 1015
 Sharma, P. K., 696
 Sharma, R. C., 701
 Shaturskü, Ya. P., 331
 Shaulova, E. M., 337
 Shaw, G., 699
 Shaw, K. N., 696
 Shaw, K. N. F., 698, 704
 Shchukina, M. N., 328
 Shechter, H., 329
 Sheehan, J. C., 698, 718, 724, 727
 Sheiaker, Y. N., 711
 Shemin, D., 697
 Shemyakin, M. M., 692
 Shen, Y. H., 960
 Shenberg, N. A., 725
 Shenouda, I. G., 697
 Sheppard, R. C., 711, 712
 Shershukov, V. M., 325, 334, 335
 Shetty, S. M., 710
 Shevchenko, A. E., 337
 Shiba, T., 704, 959
 Shibata, M., 330
 Shibata, S., 1011, 1013
 Shiboya, S., 715
 Shigorin, D. N., 710
 Shih, H., 328
 Shih, T. L., 1014
 Shimada, F., 714

- Shimada, J., 697
 Shimada, S., 329, 339
 Shimada, T., 698
 Shimadzu, H., 327, 331
 Shimamura, O., 719
 Shimanskaya, N. P., 702, 712
 Shimizu, A., 334
 Shimizu, I., 333
 Shimizu, M., 325
 Shimodoi, Y., 711
 Shimomura, O., 713, 718
 Shin, C., 327
 Shinooka, K., 722
 Shinra, K., 335
 Shioiri, T., 327, 329
 Shiozaki, M., 712
 Shirota, F. N., 957
 Shishkin, G. V., 713
 Shive, W., 695, 696
 Shkodinskaya, E. N., 716
 Shkurko, O. P., 719
 Shlyaputokh, K. V. Y., 717
 Shneur, S. A., 703
 Shokina, V. V., 712, 720
 Shokita, V. V., 712
 Shono, T., 335, 337
 Short, F. W., 323
 Shridhar, D. R., 336, 339
 Shriner, R. L., 707
 Shtamm, A. K., 715
 Shternberg, R., 705
 Shuyama, H., 325
 Shvaika, O. P., 326, 332, 334, 340, 726
 Shvorina, A. L., 337
 Sicher, J., 705
 Siddappa, S., 714
 Siddiqui, A. A., 703
 Siderius, H., 323, 329, 359
 Sidhu, G. S., 710
 Sieber, W., 712
 Siedel, W., 717
 Seigel, H., 726
 Siegrist, A. E., 326, 360
 Siemeniewsky, H., 692, 711
 Siemion, I. Z., 692, 695, 710, 711
 Sila, B., 705, 719
 Silberg, A., 704, 716, 719
 Silberg, I. A., 326
 Silberschmidt, R., 711
 Silver, J., 957
 Simchen, G., 726
 Simiti, I., 326, 719
 Simon, J. R., 1011
 Simon, Z., 360
 Simonov, A. M., 695, 719
 Simons, B. K., 324, 325, 360
 Simov, D., 330, 691
 Sims, J., 958
 Sindona, G., 728
 Singh, A., 701, 710
 Singh, B., 325, 726
 Singh, G., 708, 956
 Singh, H., 695
 Singh, P. P., 339
 Singh, S., 708, 956
 Singh, V. P., 956
 Singhal, O. P., 715, 719
 Sinha, N. D., 1011
 Sinita, A. D., 332
 Sisido, K., 726
 Sjoberg, B. O. H., 715
 Skinner, C. G., 695, 696
 Skinner, W. A., 716
 Slack, R., 699, 718, 725
 Slade, J., 1014
 Slater, G. L., 693
 Slates, H. L., 691, 721
 Slavinskaya, R. A., 725
 Sletzinger, M., 339, 693, 695, 1014, 1015
 Sli, F. A., 712
 Slife, C. W., 1015
 Slim, J., 715
 Sloan, A. D. B., 704
 Slouka, J., 696, 707
 Smale, T. C., 710
 Smaley, R. K., 697
 Smirnov, V. A., 323
 Smirnova, L. V., 715
 Smirnova, V. A., 329
 Smith, A. B., 958
 Smith, A. B., III, 1011
 Smith, C. P., 328
 Smith, C. W., 710
 Smith, F. X., 724
 Smith, R. D., 323
 Smith, R. K., 1014
 Smith, R. L., 334
 Smith, W. T., Jr., 696
 Smiti, I., 704
 Smolanka, I. V., 725
 Smolanoff, J., 325, 709, 958
 Sochilin, E. G., 725
 Sohar, P., 327
 Solheim, E., 692, 711
 Soll, H., 691
 Soma, N., 328, 337

- Somerville, A. W., 693
 Sommer, M., 324
 Sonn, A., 703
 Soper, Q. F., 695, 716
 Sorkhin, E., 715
 Soti, M., 327
 Southern, P. F., 324, 1017
 Snow, G. A., 706
 Snyder, E. S., 1013
 Snyder, H. R., 697, 704
 Spangler, R. J., 697
 Sparks, M., 325
 Spasokukotskü, N. S., 329
 Speedie, M. K., 724
 Spellman, M. A., 729
 Speroni, G., 722
 Spiess, B., 722
 Spitzer, E. L. T. M., 713
 Spoelhof, G. D., 324
 Spotswood, T. M., 724
 Sprague, R. H., 700
 Sprancmanis, V., 328
 Srinivasan, A., 709
 Srinivasan, K., 699
Srivastava, V. K., 707
 Staab, H. A., 340
 Stachel, H. D., 701, 708, 719
 Stacy, G. W., 700
 Stamegna, A. P., 960
 Stammer, C. H., 327, 692, 698, 701, 709,
 713, 721, 723, 960, 1014
 Stanaback, R. J., 714
 Stangl, H., 335
 Staninets, V. I., 725
 Stark, B. P., 712
 Staudinger, G. K., 695, 957
 Staunton, J., 705, 713, 717
 Stavri, N., 337
 Steckelberg, W., 703
 Stefanescu, A., 706
 Stefaniak, L., 359
 Stefanovich, G., 714
 Stefanovich, M., 714
 Steglich, W., 325, 327, 328, 331, 339,
 691, 694, 695, 703, 704, 706, 708, 709,
 712, 720, 721, 722, 723, 957, 1014,
 1015
 Stegmann, W., 332
 Stein, H. W., 705
 Stein, M. L., 340
 Steiner, K. V., 715
 Stepanova, S. V., 333, 334, 338
 Stephenson, O., 323
 Stern, F., 698, 720
 Sternhell, S., 329
 Steuben, K. C., 695
 Stevens, C. M., 697
 Stewart, J. M., 711
 Stickings, C. E., 699, 718
 Stiller, E. K., 719
 Stock, J. A., 716
 Stodola, F. H., 706
 Stoepel, K., 713
 Stoffel, P. J., 726
 Stoicescu-Crivat, L., 703
 Stokker, G. E., 334
 Stoll, B., 727
 Stoodley, R. J., 709, 721
 Stoops, J. K., 711
 Störiko, K., 327, 360, 706
 Storr, R. C., 325
 Stott, P. E., 960
 Strange, P. G., 717
 Stroh, J., 324
 Strong, F. M., 697
 Strozier, R. W., 958
 Strpvakov, V. M., 719
 Strukov, I. T., 338, 692, 699, 700, 718, 720
 Strzybny, P. P. E., 336
 Stuckwisch, C. G., 327
 Sturgeon, B., 323
 Sturm, H. J., 339
 Subba Rao, N. V., 338
 Sugasawa, S., 702, 716
 Sugihara, A., 339
 Sugimoto, K., 333
 Sugiyama, H., 327
 Sugiyama, N., 702
 Sukita, K. T., 717
 Summers, L. A., 704
 Suna, M., 701
 Sunagawa, G., 328, 336, 337
 Sung, R. L., 957
 Süs, O., 324
 Suschitzky, H., 715, 716
 Sustmann, S., 326
 Sutherland, J. K., 709
 Sutter, W., 329
 Suvorov, N. K., 719
 Suvorov, N. N., 724
 Suzuki, A., 1012
 Suzuki, H., 323, 695
 Suzuki, J., 331
 Suzuki, M., 338, 1016
 Suzuki, T., 1014
 Suzuki, Y., 1014

- Svenson, R., 1011
 Sviridov, E. P., 331, 332, 340
 Svoboda, M., 705
 Swaminathan, S., 699
 Swan, G. A., 692, 705
 Swan, J. M., 329, 692
 Sweet, C. S., 334
 Swern, D., 724
 Swindin, W. A., 712
 Sych, E. D., 332, 341
 Sycheva, T. P., 328
 Symonds, F. L., 707
 Syrkin, Y. K., 710
 Szabo, A., 710
 Szantho, V., 704
 Szechner, B., 1011
 Szelke, M., 328
 Szmuszkowicz, J., 959

 Tabei, K., 341
 Tada, N., 336, 1016
 Tada, Y., 337
 Tadros, M. E., 707
 Tai, C-K., 335
 Takada, K., 726
 Takada, T., 341
 Takagaki, H., 328, 708, 1016
 Takagaki, M., 701
 Takagi, E., 698
 Takahashi, H., 1014
 Takahashi, R., 334
 Takahashi, T., 332, 335
 Takamatsu, H., 325
 Takamizawa, A., 332
 Takano, S., 336, 1012
 Takase, Y., 325
 Take, H., 708
 Takehara, M., 334, 339, 340
 Takei, H., 328, 701, 1016
 Takei, Y., 337
 Takeuchi, S., 703
 Talbi, B., 958
 Talbot, A. M., 333
 Taliani, L., 326
 Tamas, V., 702, 718
 Tammam, G. H., 701
 Tamura, Y., 701, 959
 Tan, H. S., 696
 Tanabe, K., 330
 Tanabe, S., 328, 701
 Tanaka, C., 327, 330, 331, 338
 Tanaka, H., 1013
 Tanaka, K., 695
 Tanaka, M., 956
 Tanaka, T., 1014
 Tanaka, Y., 726
 Tani, K., 701, 959
 Taniguchi, H., 325
 Tanner, H., 704, 721, 722
 Tanous, H., 960
 Tansey, L. W., 704
 Tarzia, G., 323, 327
 Tashiro, M., 328, 724
 Tataruch, F., 728
 Tatlow, J. C., 698
 Tatsuoaka, S., 697, 698, 699
 Taub, D. S., 691
 Taul, H., 699
 Tavella, M., 324
 Taylor, D. A., 1012
 Taylor, E. C., 325, 719
 Taylor, G. F., 330
 Taylor, L. D., 692, 693
 Taylor, P. J., 360
 Taylor, W. I., 333
 Tchoubar, B., 698
 Tedeschi, P., 722
 Teitel, A., 706
 Telefus, C. D., 328, 724
 Tellini, N., 727
 Temperilli, A., 340
 Temple, D. L., 1010, 1011
 Teotino, U. M., 338
 Terent'ev, P. B., 334, 336, 360, 1010
 Ternai, B., 323, 326, 334, 1010
 Terpinski, J., 340
 Teuber, H. J., 717
 Tewes, E. T., 727
 Texier, F., 958
 Teyssié, Ph., 328
 Thaper, G. S., 336
 Theilig, G., 324
 Thibert, R. J., 697
 Thijs, L., 726, 728
 Thompsom, A. S., 1011
 Thompson, R. D., 1012
 Thomson, A., 693
 Thornton, E. R., 1011
 Thoseby, M. R., 729
 Threlfall, T., 729
 Thyagarajan, G., 708, 959, 960
 Tiege, W., 702
 Tietz, J., 715
 Tietzman, J. E., 713
 Tighineanu, E., 956
 Timasheff, S. N., 697

- Timofeeva, T. M., 338
 Tiwari, S. S., 707
 Tkaczuk, P., 1011
 Toda, F., 323, 695, 698, 711, 720, 721, 722, 723
 Toda, M., 726
 Todd, A., 330
 Todd, A. R., 714
 Todd, D., 700
 Togo, K., 328, 340
 Tokachev, V. N., 701
 Tokumaru, K., 701
 Tomida, I., 693, 723
 Tomimatsu, Y., 724
 Tomimoto, M., 336, 1016
 Tominaga, Y., 1012
 Tomioka, K., 722
 Tomita, K., 726
 Toppet, S., 728
 Torii, Y., 698, 711, 720, 721, 722, 723
 Torres-Gaone, R., 702
 Torricelli, C., 325
 Toubro, N. H., 959
 Townsend, L. B., 332
 Toyoshima, S., 334
 Trakhtenberg, P. L., 720
 Traldi, P., 360
 Tramier, B., 336
 Traube, W., 723
 Trefonas, L. M., 1014
 Treibs, A., 329
 Tremper, A., 325
 Treppendahl, S., 336
 Treu, T., 335
 Tricerri, S., 335
 Trimmer, R. W., 336
 Tripathy, P. B., 696, 700
 Trocha-Grimshaw, J., 707
 Trösken, O., 335
 Troxler, F., 725
 Trozzolo, A. M., 959
 Truitt, P., 703
 Trupp, T. Kh., 328
 Trybulski, E. J., 341
 Tschesche, R., 712
 Tsizin, Y. S., 701
 Tsuboi, S., 324, 330
 Tsubokawa, S., 957
 Tsuchiya, S., 704
 Tsuge, O., 328, 709, 724, 727
 Tsukerman, S. V., 337
 Tsuruta, S., 326
 Tsutsui, T., 335
 Tsvetanska, L. I., 727
 Tuorto, R. M., 336
 Turbanti, L., 713
 Turchi, I. J., 323, 325, 329, 331, 334, 359, 956, 957, 958, 959, 1010, 1015
 Turchin, K. F., 339, 724
 Turner, R. A., 700
 Twaik, M., 710
 Twibell, J. D., 696
 Uccella, N., 726, 728
 Uchida, T., 957
 Udodong, V. E., 1017
 Ueda, M., 702, 703
 Ueda, T., 334, 726
 Ueng, S., 328, 1016
 Ueyama, Y., 727
 Ueyanagi, J., 698, 699
 Uhl, J., 728
 Ulbricht, H., 340
 Ulff, B., 324, 340
 Ullate, S. P., 710
 Ullman, E. F., 325, 701
 Umezawa, O., 715
 Umio, S., 695
 Undheim, K., 1017
 Unma, G., 704
 Uno, I., 701
 Unrau, A. M., 703
 Unterstenhoefer, G., 330
 Urbach, H., 718
 Uritskaya, M. Y., 719
 Usui, Y., 336, 1016
 Uvarova, N. V., 724
 Vaghani, D. D., 704
 van Bergen, T. J., 336
 van Boeckel, C. A. A., 1015
 van Boom, J. H., 1015
 VandenBerg, G. E., 692
 Vandenberghe, A., 329, 727
 VanDenende, J. J., 702
 Vanden Eynde, J. J., 717
 Vanderhaege, H., 709
 van der Kamp, P. M. M., 692, 708
 van der Marel, G. A., 1015
 van der Plas, H. C., 1010
 Vander Stelt, C., 715
 Van Dyke, R. H., 700
 van Gennep, H. E., 329
 Vanghelovici, M., 696, 700, 706
 Van Haverbeke, Y., 702, 718
 Van Lare, E., 700

- van Leusen, A. M., 323, 329, 330, 359, 1012
vanLeusen, D., 1012
Vanloon, E. J., 697
van Nispen, S. P. J. M., 329, 330
VanOvervelt, J. C., 718
vans Es, T., 325, 336, 727
Van Zandt, G., 700
Varadarajan, S., 705
Varady, J., 704
Varughese, K. I., 1014
Vasileva, M. N., 716
Vasina, O. S., 716
Vaskovski, V. E., 713
Vastra, F., 703
Vater, W., 713
Vdovina, R. G., 710
Veal, C. J., 327, 709, 718
Vedejs, E., 1014
Vedenyapin, A. A., 694
Vecraraghavan, S., 960
Venkataratnam, R. V., 707, 708, 710
Venkatesh, M. S., 327
Veno, K., 329
Verbruggen, A., 728, 958
Vercellone, A., 334
Verge, J. P., 329, 330
Verigin, V. G., 1011
Vernigor, E. M., 337
Vernin, G., 336
Vettori, U., 360
Veyanagi, J., 697
Veyrières, A., 1015
Vichakanova, S. A., 701
Vickery, B. H., 337
Vida, J. A., 715
Vidali, M., 728
Viehe, H. G., 728, 958
Viel, C., 713
Vigdahl, R. L., 332
Vikhrova, N. M., 338
Vincent, E.-J., 359
Vineyard, B. D., 703, 714
Vinick, F. J., 323, 333
Vinick, F. S., 1016
Vinnick, F. S., 333
Vinograd, L. K., 719
Visconti, N., 338
Viscontini, M., 337, 339
Vlattas, I., 1012
Vogler, K., 328
Vogt, H., 327, 700
Vollbrecht, D., 717
Volodarskii, L. B., 323, 721
Volosyuk, T. P., 1015
Vompe, A. F., 329
vonAuwers, K., 725
von Phillipsborn, W., 332, 721
von Strandtmann, M., 327, 331, 700
Voronine, N., 723
Vorozhtsov, N. N., 696
Voticky, Z., 696
Wada, I., 339
Waddington, H. R. J., 699, 712, 720
Wade, R., 712
Wagatsuma, N., 716
Wagner, A., 691
Wagner, R., 728
Waldo, R. M., 959
Walkenhorst, E., 326, 335
Walker, D. G., 323, 327, 333, 1016, 1017
Walker, G. N., 700
Walker, J., 715
Wall, P. E., 696
Wallingford, H. P., 720
Walser, A., 341
Walter, B. H., 327
Walter, R., 699, 700, 701
Walton, E., 704, 714
Wamhoff, H., 340
Wang, G. L., 695
Wang, S., 1011
Wang, S. C., 710
Wang, T. S. T., 715
Warnecke, P., 712
Warnhoff, E. W., 697
Warren, C. D., 1015
Wassermann, H. H., 323, 324, 325, 333, 1016
Wasti, K., 716
Watanabe, M., 339
Watanabe, T., 328, 334, 337
Watson, L. S., 334
Watts, C. R., 958
Webb, E. C., 711
Webb, G. A., 359
Webb, R. L., 1010
Webber, J. A., 339
Weber, B., 724
Weber, S., 721
Weberndörfer, V., 333
Wechter, W. J., 1015
Wegmann, H., 694, 722, 1015
Wehrmüller, J., 713
Weinreb, S. M., 334, 1010, 1013
Weintraub, P. M., 332

- Weiss, M., 324
 Weitnauer, G., 698, 712
 Weitz, J. C., 715
 Welvert, Z., 698
 Wendler, N. J., 721
 Wendler, N. L., 691
 Wenis, E., 325
 Wentrup, C., 697, 708, 723
 Wermuth, C. G., 716
 Werner, L. H., 713
 West, R., 957
 Westerduin, P., 1015
 Westley, J. W., 333
 Wetmore, S. I., 709, 721, 958
 Wettlaufer, D. G., 1014
 Weygand, F., 327, 331, 698, 704, 721, 722, 723
 Whalley, W. B., 705, 715
 White, E. V., 1015
 White, F. L., 700
 White, J. D., 696, 701
 White, R. L., 329, 338
 Whitham, R. K., 693
 Whitten, C. E., 1012, 1013, 1014
 Whitter, W. L., 959
 Wibaut, J. P., 720
 Widdowson, D. A., 709, 1012
 Wiedlich, J., 702
 Wiegand, E. E., 334
 Wiegand, G. E., 326
 Wieland, T., 326, 691, 718
 Wierenga, W., 1015
 Wightman, R. H., 713
 Wilcke, F. W., 717
 Wild, A., 718
 Wild, H., 336
 Wildeman, J., 323, 330
 Wiley, R. H., 322, 323, 334
 Wilkerson, W. W., 959
 Wilkins, R. B., 721
 Wilkinson, S., 712
 Willems, J. F., 329, 727
 Williadsen, P., 711
 Williams, A., 711
 Williams, B. E., 1013
 Williams, D. H., 325, 328, 333, 360
 Williams, D. L., 697, 707
 Williams, L. A., 700
 Williamson, K., 710, 711
 Willner, D., 328
 Wilschowitz, L., 695
 Wilson, D. A., 323
 Wilson, J. M., 1013
 Wilson, M. L., 1014
 Wilson, S. R., 1013
 Wiltshire, H. R., 717
 Wineman, P. L., 702
 Winkelmann, E., 340
 Winkemuller, W., 715
 Winnefeld, K., 326
 Winter, H. W., 708
 Winzenberg, K. N., 1011
 Wisnar, J. D., 693
 Witkowski, M., 359
 Withers, G. P., 1010
 Wittig, G., 710
 Wittmann, H., 726
 Witty, M. J., 712
 Wolf, V., 340
 Wolfe, S., 693
 Wolinsky, J., 332
 Wolloch, A., 324
 Wong, C. M., 337, 1016
 Wong, J. W., 1011
 Wong, L. T., 692
 Wood, R. D., 333, 1016
 Woodier, A. B., 714
 Woodman, D. J., 692
 Woodward, R. B., 692
 Wooley, D. W., 711
 Worth, B. R., 1011
 Wotjanis, J., 705, 719
 Wrede, F., 323
 Wright, P. H., 696, 698, 956, 957
 Wu, M.-Th., 340
 Wunderlin, D. A., 325
 Wynberg, H., 324
 Yagi, K., 323
 Yagupol'skü, L. M., 335
 Yakhontov, L. N., 719, 720
 Yakobsen, G. G., 696
 Yakolev, V. G., 714
 Yamada, S., 341
 Yamaki, K., 702
 Yamamoto, O., 727
 Yamamoto, Y., 1013
 Yamanaka, K., 326
 Yamanaka, T., 339, 708
 Yamashita, T., 715
 Yamato, E., 720
 Yamauchi, K., 700
 Yamazaki, M., 325, 332, 333
 Yao, H. Y., 716
 Yao, S., 956
 Yassin, S. M., 693
 Yassin, S. M. A., 693, 705

- Yasuda, H., 339
Yasuda, N., 328, 708, 1016
Yasuda, S., 326
Yatabe, M., 1014
Yavari, I., 359
Yeats, R. B., 697
Yebdri, O., 958
Yeh, I., 719
Yoda, N., 1014
Yokosa, K., 323
Yokose, K., 333
Yokoyama, W., 719
Yoneda, N., 338
Yonemitsu, O., 327, 338
Yoshida, M., 340
Yoshida, N., 716
Yoshida, R., 328
Yoshida, Y., 334, 339
Yoshikawa, S., 1011, 1013
Yoshikawa, T., 336
Yoshimoto, M., 708
Yoshimura, J., 327, 703
Yoshioka, T., 327
Young, D. W., 327, 709, 718
Young, R. N., 1011
Young, T. E., 704
Yount, R. G., 340
Yranzo, G. I., 325, 330
Yuan, C. Y., 719
Yuki, H., 333
Yura, A., 324
Yura, Y., 324, 336
Yurev, Y. K., 713, 719
Yurugi, S., 336, 1016

Zabrocki, S., 692
Zack, J. F., Jr., 704

Zakharkin, L. I., 332
Zaleta, M. A., 324
Zampaglione, N., 725
Zapata, A. J., 960
Zaugg, H. E., 326
Zavyalov, S. I., 695, 706, 707
Zayed, E. M., 693, 707
Zayed, M. A., 709
Zbinder, R., 726
Zbiral, E., 324
Zecchina, A., 360
Zeeger-Huyskens, T., 717
Zeh, D., 326, 335
Zeile, K., 960
Zelikhover, Ya. B., 334
Zelikman, Z. I., 725
Zeller, P., 717
Zepp, C. M., 960
Zerner, B., 711
Zerweck, W., 703
Zhdanov, Y. A., 697
Zhdanovich, Y. V., 699
Zheltonog, N. G., 724
Zhukova, I. G., 333
Zia, A., 332, 333
Ziegler, F. E., 1011, 1014
Zimmer, H., 699, 700, 701
Zimmerman, J. P., 713
Zimmerman, N., 701
Zoltova, N. V., 717
Zoretic, P. A., 1011
Zubenko, V. G., 699
Zugravescu, I., 703
Zurabyan, S. E., 1015
Zvoristeanu, V., 337
Zwanenburg, B., 726, 728,
959

Subject Index

Italicized page numbers refer to tables.

- Acylamino derivatives, of oxazole, 268
 α -Acylamino ketones, from 2-[3H]oxazoles, 670
 α -Acylamino β -lactams, synthesis, 908–914
Acylanion equivalents, 964
N-Acylaziridines, 965
Acylazirines, photochemical conversion to oxazoles, 18, 19
N-Acylimines, from 5-[4H]oxazolones, 407
Acyloxycarbonylamino derivatives, of oxazole, 268
Acyloxy derivatives, of oxazole, 245
1-Acyloxyindazolones, from 5-[2H]oxazolones, 623
1,4-Addition, 969 [section 5.2.4.3], 984, 985
 to 2-(1-alkenyl)oxazolines, 969, 978
 with asymmetric synthesis, 978
 of alkylcuprate to α,β -unsaturated oxazolinone, 991
 chiral, 985
 dialkylcuprate addition, 1002
 Michael addition, 969
 of organolithium reagents to chiral *E*-alkenylloxazolines, 985
 of organolithium reagents to naphthylloxazolines, 979
 to 3-pyridyl-2-oxazolines, 985
Aldehyde derivatives, of oxazole, 231, 279
Alimine derivatives, of oxazole, 236
Aldol reactions, of 2-alkyl-2-oxazolines, 984
Alkenyl derivatives, of oxazole, 170
Alkoxy derivatives, of oxazole, 237
Alkoxyoxazole carboxaldehydes, 284
Alkoxyoxazole carboxamides, 280
Alkoxyoxazole carboxylic acid chlorides, 280
Alkoxyoxazole carboxylic acids, 280
Alkoxyoxazole carboxylic esters, 280
Alkoxyoxazole ketones, 284
Alkoxyoxazole nitriles, 280
Alkoxyoxazole thioamides, 280
Alkoxyoxazole thioesters, 280
Alkylation, 969
 of chiral lithio aza-enolates, 981
 of lithio 2-alkyl-2-oxazolines, 969
Alkyl derivatives, of oxazole, 138, 150, 154, 156, 157, 159, 161–164, 166–168, 186
2-Alkylidene-3-oxazolin-5-ones, 626
4-Alkylidene-2-oxazolin-5-ones, 498
2-Alkyl-2-oxazolines:
 aldol reactions, [section 5.2.4.2.], 984
 boron enolates, 984
 asymmetric synthesis, 970
 lithiation and alkylation of chiral, 981, 982
 metalation, 982
 reaction:
 with aromatic aldehydes, 971
 with electrophiles, 971
 halogens, 971
 2-nitroalcohols, 971
 with formaldehyde, 971
Alkylthioaminoxazoles, 297
Alkylthio derivatives, of oxazole, 246
Alkylthiooxazole carboxamides, 285
Alkylthiooxazole carboxylic esters, 285
Alkylthiooxazole dithioesters, 285
Alkylthiooxazole nitriles, 285
Alkylthiooxazole thioesters, 285
2-Alkylthio-2-oxazolines, 976
(5-Alkylthiooxazol-4-yl)triphenylphosphonium chlorides, synthesis, 73, 74
Allenes, from thermolysis of 1,3-oxazolium-5-oxides, 907, 908
Amide carboxylic acid derivatives, of oxazole, 230
Amide derivatives, of oxazole, 222
Amidino derivatives, of oxazole, 272
 α -Amino acids, 999, 1003, 1005
 from 5-[4H]oxazolones, 392, 989
2-Aminocyclobutanols, from 2-[3H]oxazolones, 671
Amino derivatives of oxazole, 254, 268, 286, 295–297
Aminoglycoside, 968
Aminohalooxazoles, 296

- 4-Aminomethylene-2-oxazoline-5-ones, 550
Aminooxazole carboxaldehydes, 295
Aminooxazole carboxamides, 286
Aminooxazole carboxylic acids, 286
Aminooxazole carboxylic esters, 286
Aminooxazole hydrazides, 286
Aminooxazole ketones, 295
Aminooxazole thioamides, 286
4-Amino-1,3-oxazolium salts:
 presumed equilibrium with 1,3-oxazolium-4-
 imines, 955
 synthesis, 953
5-Amino-1,3-oxazolium salts:
 equilibrium with 1,3-oxazolium-5-imines,
 930, 931, 955
 synthesis, 922, 930, 931
2-Amino-4-[5H]oxazolones:
 antidepressants, 644
 hunger suppressants, 644
 memory aids, 644
 synthesis, 644
 tranquilizers, 644
Anil derivatives, of oxazole, 272
Annuloline, structure, 109
Anomeric phosphate, 997
Alkyl derivatives, of oxazole, 138, 150, 154,
 157, 159, 161–164, 166–168, 172,
 186
Aromatic nucleophilic substitution:
 asymmetric synthesis of binaphthyls, 981
 with Grignard reagents, 979–981
 with organolithium reagents, 979–981
 synthesis of biaryls, 981
N-Aroyl-N-alkenylamines, synthesis, 893, 894
4-Aroylbenzils, from 2-[3H]oxazolones, 667
Aroyloxycarbonylamino derivatives, of oxazole,
 268
Arylacetic acids, from 5-[4H]oxazolones, 395
Arylacetonitriles, from 5-[4H]oxazolones, 395
Aryl derivatives, of oxazole, 138, 150, 154,
 156, 157, 159, 161, 164, 166–168,
 172, 186
2-Arylidene-3-oxazolin-5-ones, 626
 Friedel-Crafts reactions, 622
 photodimerization, 623
 reaction:
 with amines, 622
 with Grignard reagents, 622
 with hydrazines, 622
 synthesis, 617
4-Arylidene-2-oxazolin-5-ones, 432, 498, 510
 geometric isomerism, 415
 infrared spectra, 413
 mass spectra, 413
 NMR spectra, 414, 415
 synthesis:
 from N-chloroacetyl amino acids, 376
 from 4-chloromethylene-2-oxazolin-5-ones,
 380
 from 4-ethoxymethylene-2-oxazolin-5-ones,
 382
 from hydantoins, 380
 from β -hydroxy- α -acylamino acid, 374
 from α -hydroxyarylidene-2-oxazolin-5-ones,
 375
 from thiohydantoins, 380
 ultraviolet spectra, 412
2-Aryloxazolines, 966
 aromatic substitution, 979–981
 o-lithiated, 966, 971–974
Aryloxy derivatives, of oxazole, 237
Arylthioaminoxazoles, 297
Arylthio derivatives, of oxazole, 246
Arylthiooxazole carboxamides, 285
Arylthiooxazole carboxylic acids, 285
Arylthiooxazole carboxylic esters, 285
Arylthiooxazole nitriles, 285
Asymmetric synthesis, 969, 981 [section 5.2.4],
 988
 binaphthyl chiral axis, 986
 of binaphthyls, 981
 metalation, 982
 organometallic additions, 978
 with polymeric oxazolines, 970
 reactions:
 of boron enolates of oxazolinone imides,
 988
 of enolates of N-acyloxazolidines, 988
7-Azabicyclo[2.2.1]heptanes, synthesis, 818,
 823, 825, 828, 831–838
8-Azaprostaglandin Es, 967
Azetidin-2-ones:
 from oxazoles, 135
 from 5-[4H]oxazolones, 406
Azlactone-based merocyanines, 582
Azomethine ylides, 48
 in 1,3-oxazolium 5-imines, 733, 929–938
 in 1,3-oxazolium 5-oxides, 733, 778
 from 1,3-oxazolium 5-oxides and carbonyl
 dipolarophiles, 893, 894
 from 1,3-oxazolium 5-oxides and olefins, 817,
 818, 825
Benzothiazines, from 5-[2H]oxazolones, 623
Benzothiophenes, from 4-[5H] oxazolones,
 651

- Benzoyl glycolic acid amide, from 4-[5H]oxazolones, 649
- Benzynes, 971
- Berbine, 975
- Berninamycin, structure, 79
- Bioxazoles, 4, 53, 54
- Bisheteroannulation, 1009
- Bis(1,3-oxazolium 5-oxides):
acetylene cycloadditions, 813–817
synthesis, 813
- Bisoxazolones, 387–391, 556, 560
- Bisoxazolylbenzenes, synthesis, 4, 6
- Bispyrrofulvenes, synthesis, 879–884
- Boron enolates, 984
- Butenolides, from 5-[4H]oxazolones, 405
- Camptothecin, 966
- Carbohydrates, 996, 997
- Carbonyl nitrile ylides, 18, 19, 23, 51, 78, 93
- Carbonyl ylides, 24, 34
in 1,3-oxazolium 4-imines, 733, 955
in 1,3-oxazolium 4-oxides, 733, 946–953
- Carboxamidine derivatives, of oxazole, 230
- Carboxylic acid chloride derivatives, of oxazole, 221
- Carboxylic acid derivatives, of oxazole, 204
- Carboxylic acid hydrazide derivatives, of oxazole, 227
- Carboxylic ester derivatives, of oxazole, 208
- ¹³C-NMR spectra:
of 4-arylidene-2-oxazolin-5-ones, 415
of oxazoles, 348–353
chemical shifts, 343, 344, 348–352
proton-proton coupling, 352, 353
of 1,3-oxazolium-5-imines, 925
- Conglobatin, structure, 109, 110
- Coumarins, from oxazoles, 127
- Cyanamide derivatives, of oxazole, 272
- ω-Cyano acids, 1001
- Cyano derivatives, of oxazole, 228
- Cyanooxazole carboxylic acids, 230
- Cyanooxazole carboxylic esters, 230
- 4,5-Cycloalkaoxazoles, synthesis, 10
- Cyclopentadienes, from oxazoles, 136
- [2.2.2] (1,2,3)-Cyclophane, 967
- Cyclopropyl α-amino acid derivatives, 990
- Dakin-West reaction, 734, 767–773
- Dehydro α-amino acid derivatives, 991
- Dehydro peptides, 991
- N,O-Diacetyloxyl, synthesis, 738–740
- Diarylethane, 967
- Dicarboxamide derivatives, of oxazole, 226
- Dicarboxylic acid derivatives, of oxazole, 207
- Dicarboxylic ester derivatives, of oxazole, 220
- 4,5-Dihydroazepines, synthesis, 862–867
- 1,4-Dihydropyridine derivatives, synthesis, 857–861
- Dihydropyrrofulvenes, synthesis, 879–884
- (±)-Di-O-methylcurvularin, total synthesis, 112, 1000
- 1,2,4-Dioxazoles, from oxazoles, 126
- Dioxinones, synthesis, 917–921
- Dipeptide synthesis, 112, 1000
- 4,5-Diphenyloxazole, as protecting group, 999, 1000
for acids, 999, 1000
in dipeptide synthesis, 1000
for primary amides, 999, 1000
- 1,5-Dipolar electrocyclization, 23, 35, 48, 55, 56, 78, 92
- Disaccharides, 997
- Ellipticine, 1007
- Epoxide:
alkylation of *o*-lithio-2-aryl-2-oxazolines, 972
γ-butyrolactones from, 969
reaction with lithio 2-alkyl-2-oxazolines, 969
- Estrone, 975
- 5-Ethoxyoxazoles, 791, 792
- Ethyl isocyanoacetate, 999
- Eupolauramine, 128, 1006
- Evodone, 1009
- Fatty acid hydrozirconation, 966
- Formyl anion equivalents, 964, 976
- Furans:
from oxazoles, 114–116, 1007–1009
from 1,3-oxazolium-4-oxides, 946–948, 952
from 4-[5H]oxazolones, 650
- Gas chromatographic data:
on 5-[2H]oxazolones, 625
on 5-[4H]oxazolones, 415
- Geometric isomerism, of 4-arylidene-2-oxazolin-5-ones, 415
- Glycosphingolipid, 968, 997
- Grignard reagents, 965, 966
addition to oxazoline ring, 990
oxazoline as protection for carboxylic acids, 996
- Griseoviridin, structure, 109, 110
- Guanidine derivatives, of oxazole, 272
- Halfordinol:
structure, 109
synthesis, 10

- Halogeno derivatives, of oxazole, 200
Halooxazole carboxaldehydes, 279
Halooxazole carboxamides, 278
Halooxazole carboxylic acid chlorides, 278
Halooxazole carboxylic acids, 278
Halooxazole carboxylic esters, 278
Halooxazole nitriles, 278
Halooxazole thiazole thiazolidines, 279
Heumann cyclization, 740
¹H-NMR spectra:
 of 4-arylidene-2-oxazolin-5-ones, 414
 of oxazoles, 343–348
 chemical shifts, 344–348
 deuterium labeling, 343
 ¹⁴N quadrupole effect, 343
 spin-spin coupling, 343, 348
 of 1,3-oxazolium-5-imines, 925
 of 1,3-oxazolium-4-oxides, 944
 of 1,3-oxazolium-5-oxides, 743, 756–758
Hydrazine derivatives, of oxazole, 277
Hydrazone derivatives, of oxazole, 277
11-Hydroxyestrone, methyl ether, 967
5-Hydroxyoxazoles, 748, 791, 792

Imidate derivatives, of oxazole, 230
Imidazoles:
 from oxazoles, 119–122
 from oxazolium-5-oxides, 899, 900
Imidazolin-4-ones, synthesis, 910–914
1,3-Imidazolium-4-oxides, synthesis, 904
1,3-Imidazolium-4-sulfides, synthesis, 902, 903
Imidazolones:
 from 2-[3H]oxazolones, 667, 668
 from 5-[4H]oxazolones, 401
Imidazo[2,1-b]oxazoles, synthesis, 108, 109
Indolizidine alkaloids, synthesis, 809
Infrared spectra:
 of 4-arylidene-2-oxazolin-5-ones, 413
 of oxazoles, 358–359
 effect of solvent, 359
 NCO ring stretching frequency, 359
 of 1,3-oxazolium-5-imines, 924, 925
 of 1,3-oxazolium-4-oxides, 944
 of 1,3-oxazolium-5-oxides, 747, 750–753, 767
 of 2-[5H]oxazolones, 690
 of 5-[4H]oxazolones, 413
Isoindolediones, synthesis, 870, 871, 873–877
Isoquinoline, synthesis, 999
 2-amido alcohol conversion to oxazoline, 999
 1-benzylisoquinolines, 1003
 from oxazoles, 133, 1004
 from 5-[4H]oxazolones, 403

Isoxazoles:
 from oxazoles, 124, 125
 photochemical conversion to oxazoles, 18, 48
Isoxazolidones, from 5-[4H]oxazolones, 402

Ketene valence tautomer, 746, 778, 906–922
Ketimine derivatives, of oxazole, 236
 α -Keto acids, from 5-[4H]oxazolones, 394
Ketone derivatives, of oxazole, 232

Lactone synthesis, 974
 α -butyrolactones, optically active, 983
Lithio 2-alkyl-2-oxazolines, 969–971
 acid enolate equivalent, 969
 ester enolate equivalent, 969
 to give α,β -unsaturated acids, 969
 reaction:
 with aldehydes, 969
 with epoxides, 969
o-Lithio-2-aryl-2-oxazoline, 971–973
 reaction:
 with aldehydes, 973, 974
 with ketones, 974
Lithiomethylisocyanide, 977
 α -metalated isocyanide review, 977
 oxazoles from, 7–9
2-Lithio-2-oxazolines, 976–978
 borylation, 984
 with chiral auxiliary, 984
 reaction with trialkylboranes, 978
Lithium 2,2,6,6-tetramethylpiperidine, 974

Macrolides, 111, 112, 1000, 1001
Mandelic acids, synthesis, 966
Mass spectra:
 of 4-arylidene-2-oxazolin-5-ones, 413
 of oxazoles, 353–357
 appearance potential, 353
 deuterium labeling, 354, 355
 fragmentation, 353–357
 McLafferty rearrangement, 355, 356
 metastable ions, 353
 molecular orbital calculations, 353
 4-tropylium ion, 355
 of 1,3-oxazolium-5-oxides, 759
 of 5-[2H]oxazolones, 625
Mercury derivatives, of oxazole, 299
Mesoionic ring systems:
 definition, 732
 interconversion of, 896–898, 902–904
 nomenclature, 733
 symbolism, 732–733

- Metalation, 964, 969, 1002–1004
 2-alkyl-2-oxazolines, 969–971
 2-aryl-2-oxazolines, 971–974
 of furan, 974
 hydrogen/deuterium exchange, 1004
 of methoxymethyl ethers, 975
 of oxazoles, 24–28, 38
 of 4-(2-oxazoliny)phenyl acetals, 975
 of pyridines, 974
 of 2-(3-pyridyl)oxazolines, 974
 of 2-(4-pyridyl)oxazolines, 974
 of N-substituted pyrroles, 974
 of thiophene, 974
 of 2-unsubstituted oxazolines, 976–978
 α -Methylene lactone, 1009
 4-Methyleneoxazolines, 15, 16
 5-Methyleneoxazolines, synthesis, 14
 5-Methyleneoxazolinium salts, 14
 Mitosene, synthesis, 811, 812
 Molecular orbital calculations:
 of 1,3-oxazolium-4-imines, 955
 of 1,3-oxazolium-5-imines, 925, 926
 of 1,3-oxazolium-4-oxides, 944
 of 1,3-oxazolium-5-oxides, 749, 808, 809, 908

 Natural products, oxazole-containing, 109–111
 Nitrile ylides, 19, 20, 48, 72
 Nitro derivatives, of oxazole, 277
¹⁴N-NMR spectra of oxazoles, 353, 354
 chemical shifts, 353, 354
 correlation with calculated charge densities, 353
 “Nonclassical” heterocycles, synthesis, 813, 814
 Nucleosides, 996

 Oligosaccharides, 997
 ORD spectra, of 5-[4H] oxazolones, 413, 414
 Organometallic addition:
 1,4-to naphthyloxazolines, 979
 1,2-to pyridines, 978
 1,4-to pyridines, 978
 1,3-Oxazin-6-ones, from 5-[4H]oxazolones, 407
 1,4-Oxazin-3-ones, from oxazoles, 134, 135
 Oxazoles:
 4-acetoxy derivatives, 60
 5-acetoxymercury derivatives, reaction with halogens, 41
 4-acetoxymethyl derivatives, synthesis, 4, 24
 4-acetyl derivatives, oxidation, 49
 4-acetyl-N-oxide derivatives:
 deoxygenation, 80, 81
 synthesis, 80
 acyl cyanide derivatives, hydrolysis, 80
 aldimine derivatives, 236
 2-aldoxime, synthesis, 74
 alkoxyalkyl derivatives, synthesis, 43
 alkoxycarbonylalkyl derivatives, synthesis, 12
 4-alkoxycarbonyl-5-amino derivatives,
 synthesis, 90, 91, 98
 alkoxy derivatives, 237
 2-alkoxy derivatives, synthesis, 36, 37, 56, 57
 4-alkoxy derivatives, synthesis, 58, 59
 5-alkoxy derivatives:
 Diels-Alder reaction, 126, 130, 131
 reaction with singlet oxygen, 126
 synthesis, 61, 63, 64
 2-alkyl-5-aryl, synthesis, 6
 N-alkylation, 106–108
 alkyl derivatives, 138, 150, 154, 156, 157, 159, 161–164, 166–168, 186
 reaction with halogenating agents, 38, 40–42
 4-alkyl derivatives, synthesis, 15
 alkylthioalkyl derivatives, synthesis, 42, 43
 2-alkylthio-5-amino derivatives, synthesis, 94
 4-alkylthio-5-benzylideneamino derivatives,
 synthesis, 96
 alkylthio derivatives, 246
 2-alkylthio derivatives:
 oxidation, 68
 synthesis, 66–68
 4-alkylthio derivatives, synthesis, 68, 69
 5-alkylthio derivatives, synthesis, 70–74
 2-allyloxy derivatives:
 Claisen rearrangement of, 57, 58
 photochemistry, 57, 58
 synthesis, 57
 5-allyloxy derivatives, Claisen rearrangement, 61, 62
 aminoalkyl derivatives, synthesis, 12, 42
 2-amino-5-bromo derivatives, synthesis, 87
 2-amino-5-chloro derivatives, synthesis, 87
 amino derivatives, 254, 268, 272, 286, 295–297
 2-amino derivatives:
 acylation, 85
 alkylation, 85, 86
 halogenation, 87
 hydrogenolysis, 87, 88
 Mannich reaction, 86
 nitration, 87
 reaction:
 with isocyanates, 87
 with isothiocyanates, 87
 sulfonylation, 85
 synthesis, 36, 82–85

Oxazoles (*Continued*)

- 4-amino derivatives, 88, 89
- 5-amino derivatives:
 - acylation, 99
 - autooxidation, 101, 102
 - reaction:
 - with aryl diazonium salts, 99, 100
 - with isocyanates, 94
 - with orthoesters, 99
 - with toluenesulfonyl azide, 100
 - ring opening, 101
 - synthesis, 88–89
- 5-aminomethyl-4-carboxylic ester derivatives, synthesis, 47
- aryl derivatives, 138, 150, 154, 157, 159, 161–164, 166–168, 172, 186
- 4,5-aralkyl derivatives, synthesis, 9–11
- aryl derivatives, 138, 150, 154, 156, 157, 159, 161, 164, 166–168, 172, 186
 - reaction with halogenating agents, 38, 40–42
- 5-aryl derivatives, synthesis, 5–9, 20
- 2-aryl-4-hydroxymethyl derivatives, oxidation with sodium dichromate, 75
- 4-arylmethylideneamino derivatives, synthesis, 89
- 2-aryl-4-phenyl, synthesis, 5
- arylthio derivatives, 246
- 2-arylthio derivatives, synthesis, 67
- 2-aryl-4-trifluoro-5-fluoro derivatives:
 - reaction with nucleophiles, 42
 - synthesis, 39, 40
- 4-benzyl-5-phenyl, synthesis, 12
- boron derivatives, synthesis, 106
- 2-bromo derivatives, synthesis, 36
- 4-bromo, lithium-halogen exchange, 26
- 5-bromo, lithium-halogen exchange, 26
- bromomethyl derivatives, synthesis, 42
- 4-carbamates:
 - hydrogenolysis, 88, 89
 - synthesis, 88
- 5-carbamates:
 - alkylation, 99
 - synthesis, 97, 98
- carboxamide derivatives, 222
 - reaction:
 - with dehydrating agents, 53
 - with phosphorus pentasulfide, 53
 - synthesis, 53
- carboxamidine derivatives, 230
- 4-carboxamido-5-alkoxy derivatives, Cornforth rearrangement, 98
- 2-carboxamido-5-amino derivatives, synthesis, 92–94
- carboximidate derivatives, 230
- carboxylic acid azides, 227
 - Curtius rearrangement, 53
 - synthesis, 53
- carboxylic acid chloride derivatives, 221
 - Friedel-Crafts reaction, 80
 - reaction:
 - with diazomethane, 80
 - with diphenylcadmium, 80
 - with hydrogen cyanide, 80
 - Rosenmund reduction, 75, 76
- carboxylic acid derivatives, 204
 - conversion to acid chlorides, 53
 - decarboxylation, 53, 54
- carboxylic acid hydrazides, 227
 - synthesis, 53
- carboxylic ester derivatives, 43–51, 208
 - alkylthio, synthesis, 72
 - halo, synthesis, 55, 56
 - hydrolysis, 53
 - reaction with ammonia or amines, 53
- 2-carboxylic ester derivatives, synthesis, 43
- 4-carboxylic ester derivatives, synthesis, 43, 44, 46–49
- 5-carboxylic ester derivatives, synthesis, 49–51
- 2-chloroacetyl-4-methyl-5-(4-nitrophenyl), synthesis, 4
- 4-chloro-5-amino derivatives, synthesis, 95
- 2-chloro derivatives, synthesis, 36
- 2-(2-chloroethyl)-4,5-diphenyl, synthesis, 13
- 2-chloromethyl-4-alkyl-5-alkylthio derivatives, synthesis, 16
- 2-chloromethyl-4-alkyl-5-phenoxy derivatives, synthesis, 16
- chloromethyl derivatives, synthesis, 42
- 4-chloromethyl derivatives:
 - Sommelet reaction, 75
 - synthesis, 24
- 2-chloromethyl-4,5-diphenyl, synthesis, 13
- ¹³C-NMR spectra, 348–353
- cyanoacid derivatives, 230
- 2-(N-cyanoamino) derivatives:
 - decyanation, 86
 - reaction with amines, 86
- 4-cyano-5-amino derivatives, synthesis, 90, 91
- 2-(cyanobenzyl)-4,5-diphenyl, synthesis, 37
- cyano derivatives, 228
 - reaction:
 - with Grignard reagents, 78, 79
 - with hydrogen sulfide, 53
 - synthesis, 53

- 4-cyano derivatives, synthesis, 45, 52
- cyanoester derivatives, 230
- 2-deuteriomethyl derivatives, 27
- 2,4-dialkoxy derivatives, 60, 61
- 2,5-dialkyl derivatives, synthesis, 3
- 4,5-dialkyl derivatives, synthesis, 7, 8, 10, 11
- 2,5-diamino derivatives, synthesis, 102, 103
- 2,5-diaryl derivatives, synthesis, 3
- 4,5-diaryl derivatives, synthesis, 10, 11, 13
- diazoketone derivatives, synthesis, 80
- 2,5-di(4-bromophenyl)-4-chloro, synthesis, 5, 10
- dicarboxamide derivatives, 226
- 4,5-dicarboxylic acid derivatives, 207
 - decarboxylation, 53
 - synthesis, 53
- 4,5-dicarboxylic ester derivatives, 220
 - synthesis, 51–53
- Diels-Alder reaction, 114–116, 127–132
 - intramolecular, 116, 128, 130, 131
 - regiochemistry, 129
 - site selectivity, 131
- 2,5-dimethyl derivatives, synthesis, 6
- 2,5-diphenyl-4-chloro:
 - hydrogenolysis, 38
 - synthesis, 37, 38
- 2,5-diphenyl-4-deuterio, synthesis, 38
- 4,5-diphenyl, synthesis, 7, 13
- formyl derivatives, 231, 279
- 4-formyl derivatives:
 - bromination, 76, 77
 - Cornforth rearrangement, 78
 - reaction:
 - with nitromethane, 77
 - with penicillamine, 77, 78
 - synthesis, 75, 76
 - Wittig reaction, 77
- 5-formyl derivatives:
 - synthesis, 76
 - Wittig reaction, 77
- 2-formyl-4-styryl-5-ethoxy, synthesis, 65
- 2-guanidino derivatives, synthesis, 86
- haloalkyl derivatives, reaction with nucleophiles, 42, 43
- halo derivatives, 36–43, 200
 - reaction with dinitrogen tetroxide, 104
- 2-halo derivatives:
 - reaction with nucleophiles, 36, 37
 - synthesis, 36
- 5-halo derivatives:
 - reduction, 41
 - synthesis, 39–41
- 4-halo derivatives, synthesis, 37, 38
- 5-heteroaryl derivatives, 8
- ¹H-NMR spectra, 343–348
- hydrazino derivatives, 36, 277
- hydroxyalkyl derivatives, synthesis, 12
- 2-(2-Hydroxybenzyl)-5-aryl, synthesis, 25
- 2-(2-hydroxybenzyl)-4,5-diphenyl, synthesis, 25
- 2-Hydroxyethyl-4-carboxylic ester, derivatives, synthesis, 46
- 2-(2-hydroxyethyl)derivatives, synthesis, 27
- infrared spectra, 358, 359
- 2-iodo derivatives, synthesis, 36
- 2-iodo-4,5-diphenyl, synthesis, 36
- 4-isocyanates:
 - hydrolysis, 88
 - reaction:
 - with alcohols, 88
 - with amines, 88
 - synthesis, 88
- ketimine derivatives, 236
- keto derivatives, 232
 - reaction with Grignard reagents, 81
- 4-keto derivatives:
 - oxidation with selenium dioxide, 81, 82
 - reaction:
 - with malononitrile, 132, 133
 - with sulfuryl chloride, 82
 - synthesis, 79–81
- 5-keto derivatives:
 - reaction:
 - with ammonia, 134
 - with malononitrile, 136
 - synthesis, 81
- 2-keto derivatives, synthesis, 78, 79
- 4-lithio derivatives, 26
- 5-lithio derivatives, 26
- 2-lithio-4,5-diphenyl, 25
- 2-lithio-5-ethoxy, ring opening, 65
- 2-lithiomethyl derivatives, 26
 - reaction with electrophiles, 26, 27
- mass spectra, 353–357
- mercury derivatives, 299
 - reaction with halogens, 36, 41, 104
- 2-methoxymethyl-4,5-diphenyl, synthesis, 13
- 2-methyl-5-bromomethyl, synthesis, 18, 35
- 2-methyl derivatives, reaction:
 - with aryl aldehydes, 28
 - with *n*-butyllithium, 26
- 5-methyl derivatives, synthesis, 14
- 4-methyl-5-isocyanato, reaction with alcohols, 97, 98
- 4-methyl-5-(4-nitrophenyl), synthesis, 5, 34

Oxazoles (*Continued*)

- 2-methyl-4-phenyl-5-bromo, reaction with *n*-butyllithium, 38, 39
 - 2-methyl-4-phenyl-5-deuterio, synthesis, 42
 - 5-methyl, synthesis, 14
 - 2-methylthio-4,5-diphenyl, synthesis, 7
 - nitro derivatives, synthesis, 103, 104, 277
 - ¹⁴N-NMR spectra, 353, 354
 - N-oxides, 300
 - deoxygenation, 24
 - reaction:
 - with aryl isocyanates, 121, 122
 - with potassium cyanide/benzoyl chloride, 106
 - synthesis, 24, 106, 300
 - from 2-[3H]oxazolones, 669
 - from 5-[4H]oxazolones, 397, 408
 - 2-(1-pentenyl)-4-styryl-5-ethoxy:
 - oxidation, 65
 - synthesis, 65
 - 2-*n*-pentyl-4-styryl-5-ethoxy, oxidation, 65
 - 4-phenyl-5-benzyl, synthesis, 12
 - 2-phenyl-4-bromo-5-ethoxy, synthesis, 65
 - 2-phenyl-4-bromomethyl-5-bromo, synthesis, 41
 - 2-phenyl-4-chloromethyl-5-chloro, synthesis, 39, 40
 - phenyl derivatives, reaction with electrophiles, 28, 29
 - 2-phenyl-4-dichloromethyl-5-chloro, synthesis, 39, 40
 - 2-phenyl-5-ethoxy, bromination, 65
 - 2-phenyl-5-methyl, Vilsmeier formylation, 75
 - 4-phenyl, synthesis, 12
 - phosphorus derivatives, synthesis, 104, 105, 298
 - platinum derivatives, synthesis, 105, 299
 - pyridyl derivatives:
 - N-oxidation, 29
 - quaternization, 29
 - 2-(3-pyridyl)-5-(4-hydroxyphenyl), synthesis, 10
 - Raman spectrum, 359
 - reaction with singlet oxygen, 111–113
 - ring transformations to:
 - azetidin-2-ones, 135
 - coumarins, 127
 - cyclopentadienes, 136
 - 1,2,4-dioxazoles, 126
 - furans, 114–116
 - imidazoles, 119–122
 - isoquinolines, 133
 - isoxazoles, 124, 125
 - 1,4-oxazin-3-ones, 134, 135
 - oxetanes, 113, 114
 - pyrazoles, 123, 124
 - pyridines, 127–133
 - pyrimidines, 134
 - pyrroles, 117, 118
 - pyrrolidines, 118
 - pyrones, 126
 - quinazolones, 134
 - tetrones, 117
 - thiazoles, 122, 123
 - 1,2,4-triazines, 135, 136
 - triazoles, 125
 - 2-sulfinyl derivatives:
 - CNS depressant agents, 68
 - synthesis, 68
 - 2-sulfonyl derivatives:
 - herbicides, 68
 - synthesis, 68
 - 4-sulfonyl derivatives, 68–70
 - thioamide derivatives, 226
 - synthesis, 53
 - thioester derivatives, 229
 - 2-thioureido derivatives, synthesis, 87
 - 4-(4-toluenesulfonyl)-5-alkenyl derivatives,
 - synthesis, 68, 69
 - 2,4,5-trialkyl derivatives, synthesis, 3, 16
 - 2,4,5-triaryl derivatives, synthesis, 3, 16, 22, 34
 - 4-trifluoroacetyl-5-amino derivatives:
 - reaction with amines, 101
 - synthesis, 90, 101
 - 5-trimethylsilyloxy derivatives, synthesis, 63
 - ultraviolet spectra, 357, 358
 - 2-ureido derivatives, synthesis, 87
 - 4-ureido derivatives, synthesis, 88
- Oxazolidinediones, from 4-[5H]oxazolones, 649
- Oxazolidines, 964, 987, 988
 - carbene insertion into 2-(1-alkenyl)derivatives, 988
 - from sodium borohydride reduction of 2-oxazolinium salts, 964
- Oxazolidones, from 4-[5H]oxazolones, 650
- Oxazolines, metalated isocyanide route:
 - to alkenes, 977
 - to α-amino acids, 977
 - to carboxylic acids, 977
 - to hydroxy aldehydes, 977
 - to nitriles, 977
- 2-Oxazolines:
 - alkylation, 964–971
 - aromatic substitution, 966
 - lithiation of, 964, 965, 969–974

- metalation, 976–978
oxidation with nickel peroxide, 21, 22, 49
oxygenation of lithio derivatives, 985
polymer bound, 970, 983
reduction with:
 borane, 965
 diisobutyl aluminum hydride, 965
 lithium/ammonia, 965
resistance to:
 chromic oxide, 965
 Grignard reagents, 965
 lithium aluminum hydride, 965
 potassium permanganate, 965
synthesis, 965
Oxazolinium salts, 964
 reduction, 964
2-Oxazolin-5-thiones, alkylation, 73
4-Oxazolin-2-thiones:
 alkylation, 66
 synthesis, 667
1,3-Oxazolium-4-imines, attempted synthesis,
 953, 954
1,3-Oxazolium-5-imines:
 1,3-dipolar cycloadditions:
 with acetylenic dipolarophiles, 929–933,
 936–938
 isolable primary cycloadducts from, 936
 regiochemistry of, 932, 936, 938
 electrophilic addition of benzhydryl cation,
 928, 929
 hydrolysis of, 926–928
 infrared spectra, 924–925
 NMR spectra, 925
 synthesis:
 from α -acylaminonitriles, 922–924
 in situ generation, 930–940
 isolable derivatives of, 922–923
 from Reissert compounds, 924
 ultraviolet spectra, 925
1,3-Oxazolium-4-oxides:
 with acetylenic dipolarophiles, 946–948, 952,
 953
 with carbonyl dipolarophiles, 951, 952
 alcoholysis of, 945, 946
 [4 + 4]-cycloadditions with *o*-quinoid
 derivatives, 950
 1,3-dipolar cycloadditions:
 isolable primary cycloadducts, 946–952
 with olefinic dipolarophiles, 948–950, 953
 periselectivity of, 951
 regiochemistry of, 946–948, 951, 952
 hydrolysis of, 940, 941, 945, 946
 infrared spectra, 944
NMR spectra, 944
synthesis:
 from N-acyl-N-aryl glyoxanilides, 942, 943
 attempt from N-phenylbenzimidoyl chloride
 and glycolic acid derivatives, 940, 941
 from diazoimides, 941, 942
 in situ generation, 946–953
 isolable derivatives of, 941–943
 ultraviolet spectra, 944
1,3-Oxazolium-5-oxides:
 autooxidation, 899
 cycloadditions *via* the presumed ketene
 valence tautomer:
 allene formation upon thermolysis, 907,
 908
 with azirenes, 909, 910
 with cinnamaldehyde anils, 915, 916
 with diisopropylcarbodiimide, 908, 909
 with imines, 908–916
 isolable primary cycloadducts from, 920,
 921
 with 1-morpholinocyclopentene, 909, 910
 with nitrosobenzene, 900
 with *o*-quinones and *o*-quinone imines,
 917–921
 regiochemistry of, 920
 1,3-dipolar cycloadditions:
 with acetylenic dipolarophiles, 735, 737,
 738, 741–743, 745, 748, 779–817,
 890, 891, 929, 930, 993, 994
 with arynes, 817, 818
 with bridged diolefins, 878, 879
 with carbonyl dipolarophiles, 893–895
 1:2 cycloadducts, 818, 823, 825, 828,
 831–838, 894
 2:1 cycloadducts, 874, 879–885
 1:1:1 cycloadducts, 838
 with diazo dipolarophiles, 901, 902
 with fulvenes, 879–888
 intramolecular olefinic dipolarophiles,
 888–893
 with isocyanates, 904, 905
 isolable primary cycloadducts from, 797,
 801, 802, 889, 904
 with isothiocyanates, 902, 903
 kinetics, 779, 819
 with nitrile dipolarophiles, 899, 900
 with nitrobenzene, 900
 with 4-nitrobenzonitrile, 900, 901
 with olefinic dipolarophiles containing
 leaving group, 849–857
 with oxygen, 898, 899
 periselectivity, 878–888, 900, 901

1,3-Oxazolium-5-oxides (*Continued*)

- with 1,4-quinones, 868–877
 - rearranged primary cycloadducts, 821, 822, 843–849, 864, 865, 868–870, 872
 - regiochemistry of, 802–809, 842, 843, 853–857, 859, 860, 875, 889, 896, 903
 - with simple olefinic dipolarophiles, 817–849, 995
 - with strained cyclic olefins, 857–868, 995, 996
 - with sulfines, 905, 906
 - with thiocarbonyl dipolarophiles, 895–898
 - infrared spectra, 747, 750–753, 767
 - mass spectra, 759
 - NMR spectra, 743, 756–758
 - nucleophilic additions:
 - amine additions, 776–778
 - peptide bond formation, 742, 743, 777, 778
 - water and alcohol additions, 735, 766, 767, 773–776
 - reaction with acylating reagents:
 - acid chlorides, 743, 761, 762
 - aryldiazonium tetrafluoroborates, 762
 - carboxylic acid anhydrides, 734, 735, 740, 760–762, 764, 767–773
 - isocyanates, 763, 904, 905
 - self-condensation and dimerization, 740, 741, 745, 764–767
 - synthesis, 734–748
 - from N-acylamino acids, 734–743, 760–766
 - from acyltetracarbonyl ferrates and imidoyl chlorides, 736, 746
 - amino acid racemization, 742, 743, 745, 777, 778
 - in situ* generation, 735–738, 741–745, 748, 779, 781, 794, 874, 875
 - isolable derivatives, 735, 736, 740, 746–748, 813
 - from oxazolonium perchlorates, 744, 745, 761, 762
 - ultraviolet spectra, 753–756, 793
 - x-ray crystallography, 749
- Oxazolium salts, 302
- conversion to imidazoles, 120, 121
 - reaction:
 - with base, 108
 - with dialkyl acylphosphonates, 134, 135
 - with hydrazines, 135, 136
 - synthesis, 106–108
 - 2-vinyl-3-alkyl derivatives, 107, 108
- Oxazolocoumarins, synthesis, 49

2-[3H]Oxazolones, 674

- as amino acid protecting groups, 666
 - conversion:
 - to 2-acylamino ketones, 670
 - to 2-aminocyclobutanols, 671
 - to 4-arylbzils, 667
 - to imidazolones, 667, 668
 - to oxazoles, 669
 - to oxazolin-2-thiones, 667
 - to oxetanes, 671
 - to phenanthrenes, 666
 - to triazinones, 668
 - to 1,3,5-triazin-2,4,6-triones, 669
 - Diels-Alder reaction, 670
 - dimer formation, 672, 673
 - photolysis, 671
 - reaction:
 - with Grignard reagents, 670
 - with nitrones, 671
 - synthesis, 660–666
- 2-[5H]Oxazolones, 685, 686
- infrared spectra, 690
 - synthesis, 684–690
- 4-[5H]Oxazolones, 652
- conversion:
 - to benzothiophenes, 651
 - to benzoyl glycolic acid amide, 649
 - to furans, 650
 - to oxazolidinediones, 649
 - to oxazolidones, 650
 - to 4-oxazolin-2-ones, 651
 - to pyridones, 650
 - to triazoles, 651
 - photolysis, 651
 - reaction:
 - with hydrazines, 651
 - with phosphorus pentasulfide, 651
 - reduction, 650
 - ring opening, 649
 - synthesis:
 - from N-acylsulfilimines, 646
 - from 5-arylidene-2-thioxazolidin-4-ones, 648
 - from benzoyl isocyanates, 645
 - from α -haloamides, 646
 - tautomeric equilibrium with 1,3-oxazolium-5-oxides, 943, 952, 953
- 5-[2H]Oxazolones, 630
- conversion:
 - to 1-acyloxyindazolones, 623
 - to benzothiazines, 623
 - to pterines, 623
 - to pyridines, 624

- to pyrroles, 624
- to quinoxalines, 623
- gas chromatographic data, 625
- mass spectra, 625
- synthesis, 618, 619
- 5-[4H]Oxazolones, 418, 964, 965, 988
- alkylation, 368
- conversion:
 - to N-acyl- α -amino ketones, 989
 - to N-acylimines, 407
 - to α -amino acids, 392, 989
 - to arylacetic acids, 395
 - to arylacetoneitriles, 395
 - to azetidinones, 406
 - to butenolides, 405
 - to cyclopropyl α -amino acids, 990
 - to dehydro α -amino acids, 991
 - to dehydro peptides, 991
 - to imidazolones, 401
 - to isoquinolines, 403
 - to isoxazolidones, 402
 - to α -keto acids, 394
 - to 1,3-oxazin-6-ones, 407
 - to oxazoles, 397, 408
 - to oxazolo[5,4-b]quinolines, 403
 - to pyranones, 404
 - to pyrazolones, 398
 - to pyridines, 408
 - to pyridones, 406, 411
 - to pyrimidines, 406
 - to pyrrolidindiones, 408
 - to pyrrolines, 995
 - to pyrrolinones, 405
 - to tetrazoles, 400
 - to thiazolones, 396
 - to thienopyridines, 407
- gas chromatographic data, 415
- infrared spectra, 413
- optically active derivatives, 370
- ORD measurements, 413
- reaction:
 - with diazomethane, 990
 - with electrophiles, 991
 - with enzymes, 416
 - with Grignard reagents, 990
 - with lithium alkyl cuprates, 990
 - with nucleophiles, 989
- synthesis:
 - from α -acylamino acids, 363–366
 - from 4-arylidene-2-oxazolin-5-ones, 366–368
- tautomeric equilibrium with 1,3-oxazolium-5-oxides, 746–748, 790–793, 825, 862, 899
- 4-[5H]Oxazolonium perchlorates, 659
- Oxazolophanes, synthesis, 19, 35
- Oxazolo[3,2-a]pyridinium salts, synthesis, 78
- Oxazolo[4,5-d]pyrimidines, 89
- Oxazolo[5,4-d]pyrimidones, synthesis, 98
- Oxazolo[5,4-b]quinolines, from 5-[4H]oxazolones, 403
- Oxazoloquinolinones, synthesis, 888–890
- Oxazothiophenes, synthesis, 73
- 1-(2-Oxazolyl)-2-arylethylenes, synthesis, 28
- 1-(5-Oxazolyl)-2-arylethylenes, synthesis, 28
- Oxazoloyl, azides, 227
- 3-(5-Oxazoloyl)indoles, synthesis, 8
- Oxazolylthiazolidines, synthesis, 77, 78
- Oxetanes:
 - from oxazoles, 113, 114
 - from 2-[3H]oxazolones, 671
- Papaverine, total synthesis, 133, 1003
- Petasalbine, total synthesis, 116
- Phenanthrenes, from 2-[3H]oxazolones, 666
- Phospholipids, 968
- Phosphorus derivatives, of oxazole, 298
- Photooxidation, removal of oxazole protecting groups, 111, 999, 1000
- Pimpinine, structure, 109
- Platinum derivatives, of oxazole, 299
- Protecting groups:
 - for 1,2-aminoalcohols, 968
 - aminoglycoside, 968
 - for carboxylic acids, 965–967
 - glycosphingolipid, 968
 - oxazoles as, 1019
 - for phospholipids, 968
- removal:
 - of oxazoles, 111, 999, 1000
 - by photooxidation, 111, 999–1002
 - of oxazolines as, 965
- L-serine, 968
- D-threonine, 968
- Pterines, from 5-[2H]oxazolones, 623
- Pyranones, from 5-[4H]oxazolones, 404
- Pyrazoles, from oxazoles, 123, 124
- Pyrazolones, from 5-[4H]oxazolones, 398
- Pyridines:
 - from oxazoles, 127–133, 1005–1007, 1021
 - from 5-[2H]oxazolones, 624
 - from 5-[4H]oxazolones, 408
- Pyridones:
 - from 4-[5H]oxazolones, 650
 - from 5-[4H]oxazolones, 406, 411, 915, 916
- Pyrido[3,4-d]pyridazine, synthesis, 1006
- Pyrimidines, from oxazoles, 134

- Pyrindenes, from 5-[4H]oxazolones, 406
 Pyrones, from oxazoles, 126
 Pyrrofulvenes, synthesis, 879–885
 Pyrroles:
 from oxazoles, 117, 118
 from 1,3-oxazolium-5-oxides, 735, 737, 738, 741–743, 779–817, 819, 849–857, 926–940, 993
 from 5-[2H]oxazolones, 624
 secondary reactions of, 794, 795
 Pyrrolidindiones, from 5-[4H]oxazolones, 408
 Pyrrolidines, from oxazoles, 118
 Δ^1 Pyrrolines:
 from 1,3-oxazolium-5-oxides, 825–830, 835–839
 structure elucidation, 829, 830
 Δ^2 -Pyrrolines, from 1,3-oxazolium-5-oxides, 818–824, 838–849
 Pyrrolinones, from 5-[4H]oxazolones, 405
 Pyrrolizidine alkaloid, synthesis, 809–811

 Quinazolones, from oxazoles, 134
 Quinoxalines, from 5-[2H]oxazolones, 623

 Raman spectrum, of oxazole, 359
 ($\pm$)-Recifeolide, total synthesis, 111
 Regitz diazo transfer reaction, 941
 Reissert salts:
 Diels-Alder reactions:
 with acetylenic dienophiles, 933, 936
 with olefinic dienophiles, 934–940
 regiochemistry of, 938
 equilibrium with 1,3-oxazolium-5-imines, 924, 931–933, 936–938
 Robinson-Gabriel synthesis, 3–6
 cyclodehydration reagents, 3
 ^{18}O -labelling studies, 6

 L-Serine, 968
 Sulfinyl derivatives, of oxazole, 253
 Sulfonamide derivatives, of oxazole, 272
 Sulfonyl derivatives, of oxazole, 253
 Spiropyrrolines, synthesis, 886–888
 Spiroheptadienes, synthesis, 886–888

 Tetrazoles, from 5-[4H]oxazolones, 400
 Tetrones, from oxazoles, 117
 1,4-Thiazine-1,1-dioxides, synthesis, 861, 862

 Thiazoles, from oxazoles, 122, 123
 1,3-Thiazolium-5-imines, synthesis, 902
 1,3-Thiazolium-5-oxides, synthesis, 896
 1,3-Thiazolium-5-sulfides, synthesis, 896–898
 Thiazolones, from 5-[4H]oxazolones, 396
 Thiazolyloxazoles, synthesis, 53
 Thiele acetylation, 874
 Thienopyridines, from 5-[4H]oxazolones, 407
 Thiiranes, 976
 desulfurization, 976
 Thioamide carboxylic acid derivatives, of oxazole, 230
 Thioamide carboxylic ester derivatives, of oxazole, 230
 Thioamide derivatives, of oxazole, 226
 N-Thiobenzoyl enamines, synthesis, 895
 Thioester derivatives, of oxazole, 229
 Thiourea derivatives, of oxazole, 272
 D-Threonine, 968
 TMEDA, 973
 d1-Triacetyl-daunosamine, 1002
 1,2,4-Triazines, from oxazoles, 135, 136
 Triazinones, from 2-[3H]oxazolones, 668
 1,3,5-Triazin-2,4,6-triones, from 2-[3H]oxazolones, 669
 Triazoles:
 from oxazoles, 125
 from 4-[5H]oxazolones, 651
 Triphenylphosphite ozonide, 1001

 Ultraviolet spectra:
 of 4-arylidene-2-oxazolin-5-ones, 412
 of oxazoles, 357, 358
 effect of alkyl substitution, 357, 358
 extended conjugation, 357
 phenyl substituted, 357, 358
 of 1,3-oxazolium-5-imines, 925
 of 1,3-oxazolium-4-oxides, 944
 of 1,3-oxazolium-5-oxides, 753–756, 793
 Urea derivatives, of oxazole, 272

 Virginiamycin M, crystal structure, 111

 X-ray photoelectron spectroscopy, of 1,3-oxazolium-5-oxides, 760
 X-ray structure:
 of 1,3-oxazolium-5-oxides, 749
 of virginiamycin M, 111

Printed in the US/BNB