PROGRESS IN HETEROCYCLIC CHEMISTRY

VOLUME 9

EDITORS
G. W. Gribble & T. L. Gilchrist

PERGAMON

PROGRESS

IN

HETEROCYCLIC CHEMISTRY

Volume 9

A critical review of the 1996 literature preceded by two chapters on current heterocyclic topics

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U.K. Elsevier Science Ltd. The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, U.K.
U.S.A. Elsevier Science Inc., 660 White Plains Road, Tarrytown, New York 10591-5153, U.S.A.

JAPAN Elsevier Science Japan, Higashi Azabu 1-chome Building 4F, 1-9-15 Higashi Azabu, Minato-ku, Tokyo 106, Japan

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First Edition 1997

Library of Congress Cataloging in Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0 08 0428010

Printed and bound in Great Britain
by Biddles Ltd, Guildford and King's Lynn

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Foreword

Progress in Heterocyclic Chemistry (PHC) Volume 9 reviews critically the heterocyclic literature published mainly in 1996. The first two chapters are review articles. Chapter 1 by C.J. Moody and K.J. Doyle deals with "The Synthesis of Oxazoles from Diazocarbonyl Compounds," and Chapter 2 by J.A. Sikorski provides a detailed account of the heterocyclic chemistry surrounding the remarkable herbicide glyphosate ("Roundup"®). This latter chapter illustrates the role that heterocyclic chemistry plays in other areas of modern chemistry, since glyphosate is a far cry from being heterocyclic!

The remaining chapters deal with recent advances in the field of heterocyclic chemistry arranged by increasing ring size. Once again, the reference system follows the system employed in *Comprehensive Heterocyclic Chemistry* (Pergamon, 1984).

We thank all authors for providing camera-ready scripts and disks, and most especially for adopting our new uniform format. In this regard, we welcome comments from readers about the style, presentation, and coverage.

We are much indebted to David Claridge of Elsevier Science for his invaluable help with the presentation of Chapters and with his input on the new format.

Finally, we wish to acknowledge retiring editor Hans Suschitzky not only for his outstanding contributions in all previous volumes of this series as co-editor, but, jointly with Eric Scriven, for launching the series. Heterocyclic chemists owe Hans and Eric a debt of gratitude.

Once again, we hope that our readers will find PHC-9 to be a useful and efficient guide to the field of modern heterocyclic chemistry.

G. W. Gribble

T. L. Gilchrist

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1997–1998

The International Society of Heterocyclic Chemistry is pleased to announce the establishment of its home page on the World Wide Web. Access can be gained from the following locations:

For USA, Americas, Japan:

http://euch6f.chem.emory.edu/ishc.html

for Europe:

http://www.ch.ic.ac.uk/ishc/

Contents

Foreword vii

Advisory Editorial Board Members viii

Chapter 1: The Synthesis of Oxazoles from Diazocarbonyl Compounds 1
Christopher J. Moody, *University of Exeter, Devon, UK* and Kevin J. Doyle *Loughborough University, Leicestershire, UK*

Chapter 2: The Heterocyclic Chemistry Associated with the Herbicide Glyphosate 17
James A. Sikorski, *Monsanto Company, St. Louis, MO 63198, USA*

Chapter 3: Three-Membered Ring Systems 43
S. Shaun Murphree, *Bayer Inc., SC, USA* and Albert Padwa, *Emory University, Atlanta, GA, USA*

Chapter 4: Four-Membered Ring Systems 64
J. Parrick and L. K. Mehta, *Brunel University, Uxbridge, UK*

Chapter 5: Five-Membered Ring Systems

Part 1. Thiophenes & Se, Te Analogs 77
Jeffery B. Press, *Galencia Pharmaceuticals, Inc., Frederick, MD, USA* and Erin T. Pelkey, *Dartmouth College, Hanover, NH, USA*

Part 2: Pyrroles and Benzo Derivatives 97
Daniel M. Ketcha, *Wright State University, Dayton, OH, USA*

Part 3: Furans and Benzo Derivatives 117
Stephan Reck and Willy Friedrichsen, *Institute of Organic Chemistry, University of Kiel, Germany*

Part 4: With More than One N Atom 148

Michael A. Walters, *Dartmouth College, Hanover, NH, USA* and J. Ramón Vargas, *Eastman Kodak Company, Rochester, NY, USA*

Part 5: With N & S (Se) Atoms 170
Paul A. Bradley and David J. Wilkins, *Knoll Pharmaceuticals, Research Department, Nottingham, England*

Part 6: With O & S (Se, Te) Atoms 192
R. Alan Aitken and Lawrence Hill, *University of St. Andrews, UK*

Part 7: With O & N Atoms 207
G. V. Boyd, *The Hebrew University, Jerusalem, Israel*

Chapter 6: Six-Membered Ring Systems

Part 1: Pyridine and Benzo Derivatives 222
Daniel L. Comins, *North Carolina State University, Raleigh, NC, USA* and Sean O'Connor, *Alliant Techsystems, Magna, UT, USA*

Part 2: Diazines and Benzo Derivatives 249
Michaël P. Groziak, *SRI International, Menlo Park, CA, USA*

Part 3: Triazines, Tetrazines and Fused Polyaza Systems 268
Derek T. Hurst, *Kingston University, Kingston upon Thames, UK*

Part 4: With O and/or S Atoms 289
John D. Hepworth and B. Mark Heron, *University of Central Lancashire, Preston, UK*

Chapter 7: Seven-Membered Ring s 318
David J. Le Count, *Formerly of Zeneca Pharmaceuticals, UK*
1, Vernon Avenue, Congleton, Cheshire, UK

Chapter 8: Eight-Membered and Larger Rings 334
George R. Newkome, *University of South Florida, Tampa, FL, USA*

Index 346

Chapter 1

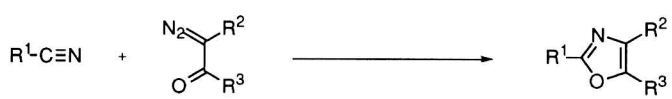
The Synthesis of Oxazoles from Diazocarbonyl Compounds

Christopher J. Moody
University of Exeter, Devon, UK

Kevin J. Doyle
Loughborough University, Leicestershire, UK

1.1 INTRODUCTION

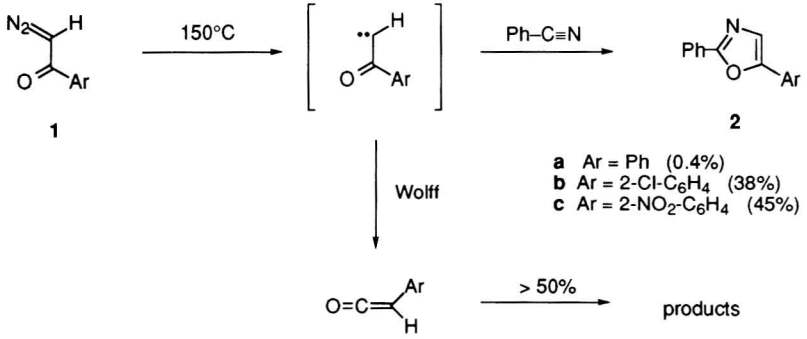
Oxazoles, which have been known for well over a hundred years, have been of considerable interest to organic chemists ever since the 1940's, when the intense research effort on penicillin led Cornforth and others to develop new routes to the oxazole ring. This work, summarised in the classic treatise in 1949,<B-49MI1> is the foundation of modern oxazole chemistry. The subsequent discovery during the 1950's by Kondrat'eva that oxazoles can function as azadienes in the Diels-Alder reaction, and by Huisgen that mesoionic oxazoles participate in 1,3-dipolar cycloaddition reactions prompted further research into the ring system.<86MI1> More recently the oxazole ring system has been found in an ever increasing range of natural products,<92JHC607, 93AG(E)1, 94NPR395, 95CRV2115, 95NPR135, 96NPR435> many of them "peptide alkaloids" in which the heterocyclic ring is most likely formed by a modification of a serine or threonine containing peptide.<96JOC778> The interesting biological activity associated with these natural products has not surprisingly prompted renewed interest in the synthesis of oxazoles. Although there are several methods available for the synthesis of oxazoles, this article focuses on just one route which has been used extensively in our own laboratory, namely that involving the reaction of diazocarbonyl compounds with nitriles (Scheme 1). Other aspects of diazocarbonyl chemistry have been widely reviewed.<86ACR348, 86CRV919, 87TCC(137)75, 91CRV263, 91T1765, 92T5385, 94AG(E)1797, 94CRV1091, 95T10811, 96AHC(65)93, 96CRV223>



Scheme 1

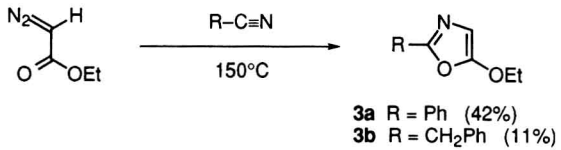
1.2 THERMAL AND PHOTOCHEMICAL REACTIONS

The formation of oxazoles from nitriles and diazocarbonyl compounds was investigated by Huisgen in the early 1960's during his classic studies on 1,3-dipolar cycloaddition reactions.<63AG(E)565, 64CB2628> He and co-workers found that the ketocarbene derived from diazoacetophenone **1a** by thermolysis at 150°C underwent formal cycloaddition with benzonitrile giving a 0.4% yield of 2,5-diphenyloxazole **2a** together with >50% of secondary products derived from a Wolff rearrangement (Scheme 2). The presence of electron withdrawing groups at the 2-position on the aromatic ring resulted in the formation of the oxazoles **2b** and **2c** in higher yield. The yield of oxazole **2a** was higher when the reaction was carried out in the presence of $Cu(acac)_2$.



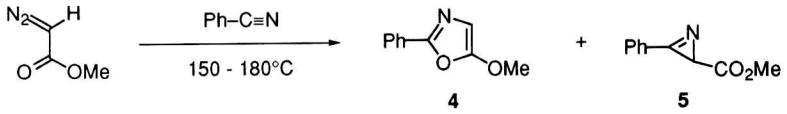
Scheme 2

Huisgen *et al.* also studied the thermal decomposition of ethyl diazoacetate in the presence of benzonitrile and phenylacetonitrile to give the corresponding 2-substituted-5-ethoxy oxazoles **3** in variable yields (Scheme 3).<64CB2864> The authors found that the solvent had an effect on the rate of decomposition of ethyl diazoacetate; in the polar solvent, nitrobenzene, the rate was found to be twice that in the hydrocarbon solvent, decalin.



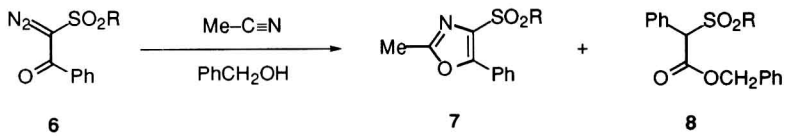
Scheme 3

Komendantov *et al.* found that thermal decomposition of methyl diazoacetate in the presence of benzonitrile yielded two products.<73JOU431> One is the expected 2-phenyl-5-methoxyoxazole **4** in about 35% yield and the other product was methyl 3-phenyl-2*H*-azirine-2-carboxylate **5** in around 1% yield (Scheme 4).



Scheme 4

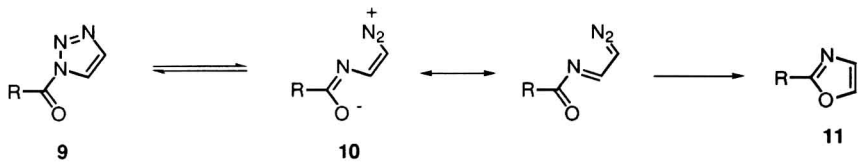
In studies on 1-diazo-2-ketosulfones, Shioiri *et al.* found that the thermal decomposition of benzoyl(sulfonyl)diazomethanes **6** with benzyl alcohol in acetonitrile also gave two products.<82CPB526> One is the 4-sulfonyloxazole **7** whereas the other product **8** results from rearrangement and reaction with the alcohol. The ratio of products varies with the nature of the sulfone substituent with the benzyl group giving highest yields of oxazole (Scheme 5).



R	*Yield / %* **7** : **8**
$PhCH_2$	59 : 41
t-Bu	24 : 62
4-Me-C_6H_4	24 : 33
4-MeO-C_6H_4	00 : 37

Scheme 5

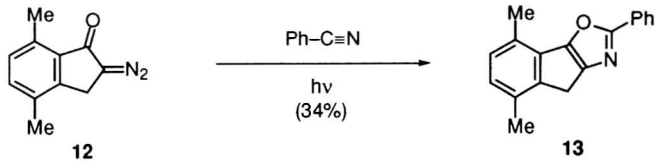
More recently, Williams has described the one pot synthesis of 2-substituted oxazoles **11** by the thermolysis of triazole amides **9**; the reaction does not proceed photochemically.<92TL1033> Although the reaction does not involve addition to a nitrile, it is an interesting application of a diazo compound since the proposed zwitterionic intermediate **10** is a resonance form of a diazo imine, so formally the reaction may be thought of as a thermal decomposition of a diazo imine (Scheme 6).



Scheme 6

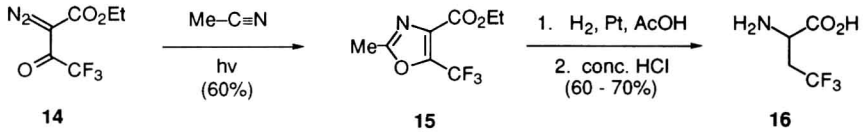
The photochemical decomposition of ethyl diazoacetate, methyl diazoacetate and diazoacetophenones **1** in benzonitrile has been studied by Huisgen and Komendantov. <64CB2864, 73JOU431> Ethyl diazoacetate failed to give any oxazole, whilst methyl diazoacetate gave a 20% yield of the oxazole **4**. As in the thermal reaction, the 2*H*-azirine **5** was isolated in ~2% yield. The photochemical decomposition of diazoacetophenone **1a** gave the oxazole **2a** in extremely low yield. Huisgen also found that the cyclic diazo ketone, 4,7-

dimethyl-2-diazoindan-1-one **12** underwent photolysis in benzonitrile to give the oxazole **13** in 34% yield (Scheme 7).<63AG(E)565, 64CB2628>



Scheme 7

The reaction of trifluoroacetyl diazoacetic ester **14** in acetonitrile has been studied by Weygand *et al.* who found that ethyl 2-methyl-5-trifluoromethyloxazole-4-carboxylate **15** could be formed photochemically in 60% yield. Further photolysis of the oxazole led to the formation of the dimeric species derived from a [2 + 2]-cycloaddition reaction in around 10% yield.<68CB302> The reaction has been exploited as a general approach for the preparation of 2-perfluoroalkylalanines **16**.<67AG(E)807> The oxazole ring is formed from the photolysis of the appropriate perfluoroacyl diazo esters in acetonitrile, and is then degraded under acid hydrogenolysis conditions to give the *N*-acetyl esters, which are then hydrolysed to the racemic 2-perfluoroalkylalanines **16** (Scheme 8).

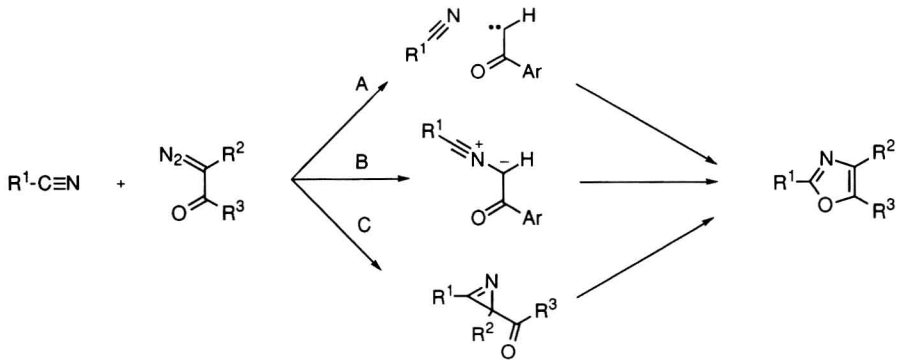


Scheme 8

1.3 MECHANISM

Oxazole formation can be envisaged as proceeding by three possible pathways: 1,3-dipolar cycloaddition of a free ketocarbene to the nitrile (Path A), the formation and subsequent 1,5-cyclisation of a nitrile ylide (Path B) or the formation and subsequent rearrangement of a 2-acyl-2*H*-azirine (Path C) (Scheme 9).

The mechanism of the thermal and photochemical formation of oxazoles from diazocarbonyls is often thought to involve the intermediacy of a free ketocarbene (Path A). In the thermal and photochemical decomposition of methyl diazoacetate in benzonitrile, the 2*H*-azirine **5** was formed along with the oxazole **4**.<73JOU431> However, when the photolysis was conducted in a 10 : 1 mixture of hexafluorobenzene and benzonitrile, the sole product was the oxazole in 20% yield. It was assumed that the formation of the 2*H*-azirine **5** and oxazole **4** was due to the reaction of methoxycarbonylcarbene in either its singlet or triplet state. The workers assumed that decomposition of the excited σ^2-singlet state led to the formation of the 2*H*-azirine, whilst the ground triplet state gave the oxazole. They rationalised the observed product ratio as being due to the presence of the inert solvent, hexafluorobenzene, and assumed it caused enhancement of the singlet-triplet transition, leading to more oxazole formation.



Scheme 9

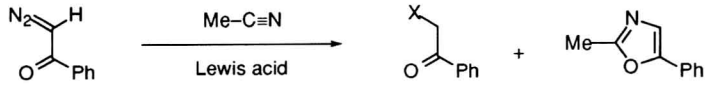
However, an investigation into the photodecomposition of diazoesters in acetonitrile, conducted by Buu and Edward,<72CJC3730> led to a different conclusion for the reaction of carbenes in their singlet and triplet states. These investigators found that only singlet ethoxycarbonylcarbene reacts with nitriles to yield oxazoles. Upon benzophenone sensitisation of the reaction mixture, no oxazole formation takes place; instead the triplet carbene reacts with benzophenone to give the diradical, which adds to acetonitrile yielding ethyl 5,5-diphenyl-2-methyl-4,5-dihydro-oxazole-4-carboxylate.

Despite the above, there is also considerable evidence to suggest that oxazole formation proceeds *via* an intermediate nitrile ylide, particularly in the catalysed reactions (see below). Nitrile ylides have been detected in laser flash photolysis studies of diazo compounds in the presence of nitriles, and stable nitrile ylides can be isolated in some cases.<94CRV1091>

Although 2-acyl-2*H*-azirines are known to give oxazoles upon irradiation, the reaction is wavelength dependent, and isoxazoles are formed at some wavelengths, as they are in the thermal rearrangement of 2-acyl-2*H*-azirines.<74TL29, 75JA4682> Since the thermal reaction of diazocarbonyl compounds with nitriles leads to oxazole formation, it would seem that mechanistic path C is unlikely in these reactions.

1.4 LEWIS ACID CATALYSED REACTIONS

The role of Lewis acids in the formation of oxazoles from diazocarbonyl compounds and nitriles has primarily been studied independently by two groups. Doyle *et al.* first reported the use of aluminium(III) chloride as a catalyst for the decomposition of diazoketones.<78TL2247> In a more detailed study, a range of Lewis acids was screened for catalytic activity, using diazoacetophenone **1a** and acetonitrile as the test reaction.<80JOC3657> Of the catalysts employed, boron trifluoride etherate was found to be the catalyst of choice, due to the low yield of the 1-halogenated side-product **17** (X = Cl or F) compared to 2-methyl-5-phenyloxazole **18**. Unfortunately, it was found that in the case of boron trifluoride etherate, the nitrile had to be used in a ten-fold excess, however the use of antimony(V) fluoride allowed the use of the nitrile in only a three fold excess (Table 1).

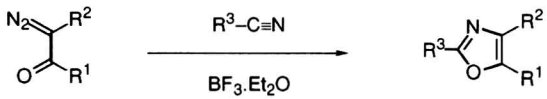


1a **17** **18**

Lewis Acid	*Ratio* **17: 18**	*Isolated Yield / %*
$AlCl_3$	36 : 64	91
$SnCl_4$	24 : 76	41
TiF_4	5 : 95	99
$FeCl_3$	0 : 100	76
$BF_3.Et_2O$	0 : 100	99
SbF_5	0 : 100	99

Table 1

The group of Ibata has also reported the effectiveness of boron trifluoride etherate in the formation of oxazoles.<79BCJ3597> They found that not only diazoketones, as reported by Doyle, but also diazoketoesters could be decomposed in the presence of nitriles to give oxazoles (Table 2). They also studied the range of nitriles that could be employed, finding that substituted thiocyanates and cyanamides,<84BCJ2450> along with chloroacetonitrile <89BCJ618> also participate in the reaction (Table 2).

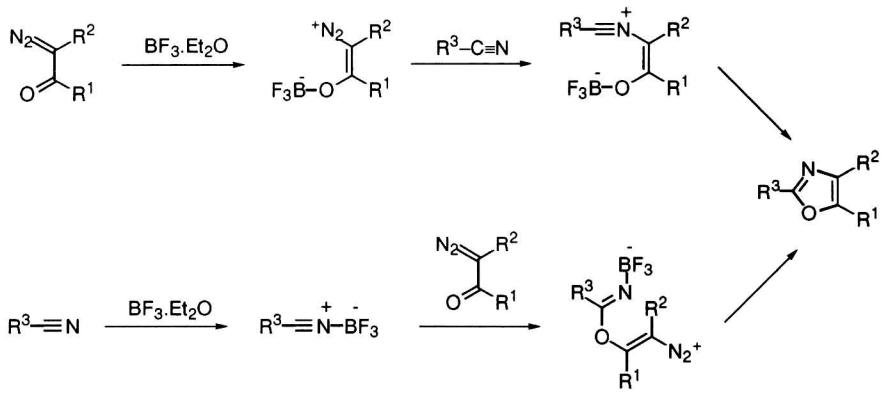


R^1	R^2	R^3	*Yield / %*
Ph	H	Me	94
Ph	H	MeO_2CCH_2	46
Ph	H	MeS	78
Ph	H	EtS	66
Ph	H	Me_2N	29
Ph	H	$ClCH_2$	84
4-NO_2-C_6H_4	H	Me	84
Me	MeO_2C	Me	80

Table 2

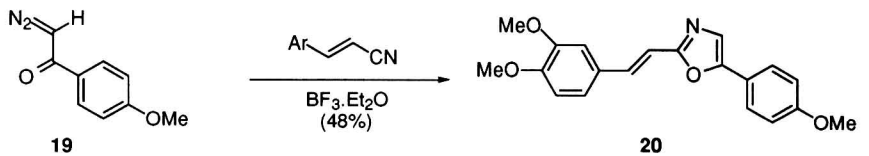
The use of protic acids in oxazole formation from diazoketones and nitriles has also been reported. Holt and co-workers found that diazoacetophenone **1a** in the presence of trifluoromethanesulfonic acid and acetonitrile gave 2-methyl-5-phenyl oxazole **18**.<79JCS(P1)1485> It was assumed that protonation of the diazo compound occurred to give a diazonium ion which underwent nucleophilic attack by acetonitrile to give a nitrilium ion which subsequently cyclised. On the other hand, two mechanisms for the Lewis acid mediated process have been advanced. Ibata favours initial attack by the Lewis acid on the diazocarbonyl oxygen to give a diazonium betaine which suffers nucleophilic attack by the nitrile to give, with loss of nitrogen, a nitrilium betaine which subsequently cyclises (Scheme

10).<79BCJ3597> Doyle however favours a mechanism involving the initial formation of a Lewis acid-nitrile adduct which suffers nucleophilic attack by the diazocarbonyl oxygen to give a 2-imidatoalkenediazonium salt, which cyclises, with extrusion of nitrogen gas, to the oxazole (Scheme 10).<80JOC3657>



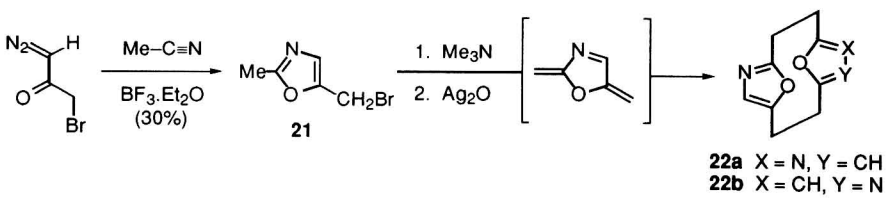
Scheme 10

The boron trifluoride etherate catalysed formation of oxazoles has been used in synthesis. Doyle has successfully employed the reaction in the synthesis of annuloline **20**, a disubstituted oxazole isolated from the roots of the annual rye grass. Thus, 1-diazo-4'-methoxyacetophenone **19** was reacted with 3,4-dimethoxycinnamonitrile in the presence of boron trifluoride etherate to yield the natural product **20** in 48% yield (Scheme 11).<80JOC3657>



Scheme 11

Keehn and Mashraqui, in their studies on cyclophanes, used this ring-formation reaction to prepare the oxazole **21**, which was then elaborated to give the [2,2]-(2,5)oxazolophanes **22**, *via* a Hofmann elimination (Scheme 12).<82JA4461>



Scheme 12