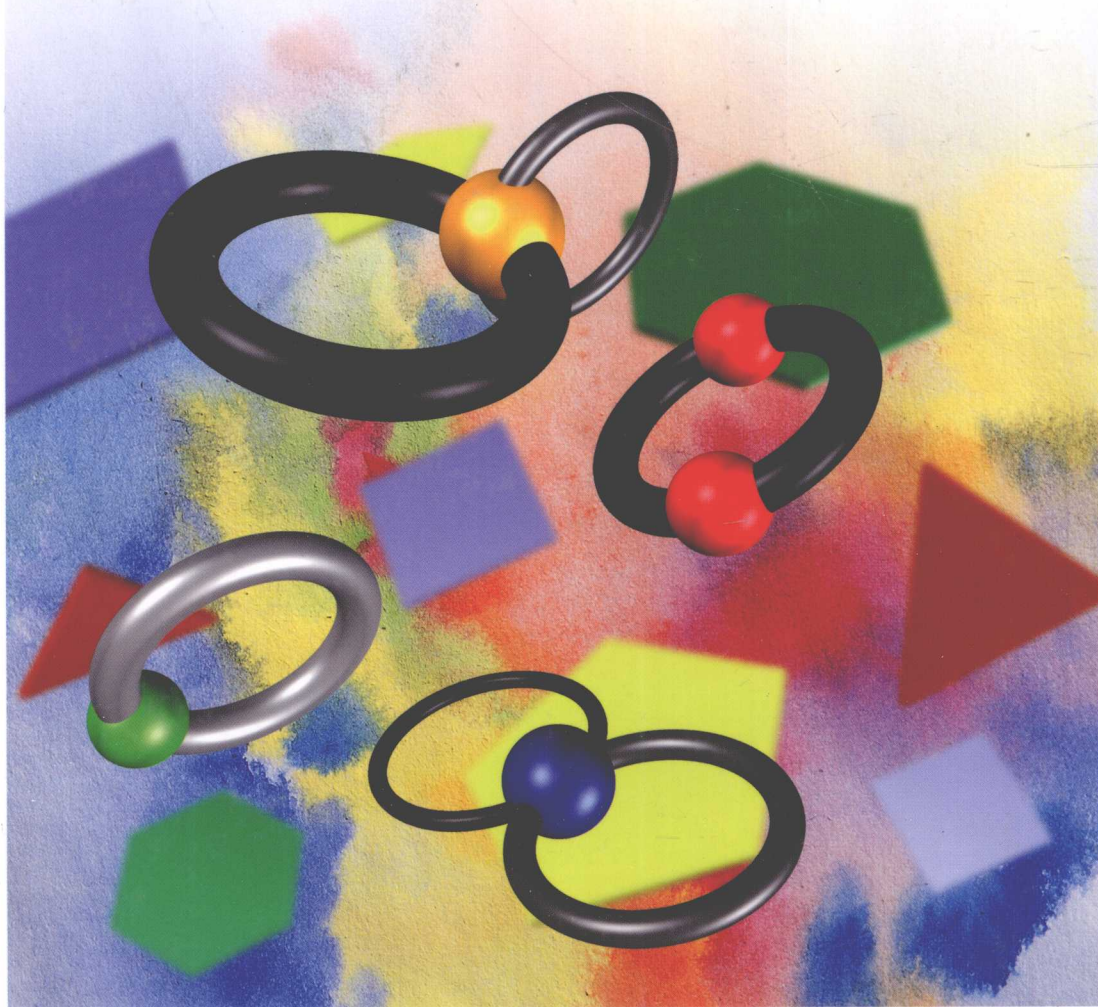


Edited by Julio Alvarez-Builla,
Juan J. Vaquero, and José Barluenga

 WILEY-VCH

Modern Heterocyclic Chemistry

Volume 4



Edited by
Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga

Modern Heterocyclic Chemistry

Volume 4



WILEY-VCH Verlag GmbH & Co. KGaA



The Editors

Prof. Dr. Julio Alvarez-Builla

Universidad de Alcalá
Facultad de Farmacia
Dpto. de Química Orgánica
Campus Universitario s.n.
Alcalá de Henares
28871 Madrid
Spain

Dr. Juan Jose Vaquero

Universidad de Alcalá
Dpto. de Química Orgánica
Ctra. Madrid-Barcelona km 33
Alcalá de Henares
28871 Madrid
Spain

Prof. Dr. José Barluenga

Universidad de Oviedo
Instituto Universitario de
Química Organometálica "Enrique Moles"
33071 Oviedo
Spain

All books published by **Wiley-VCH** are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

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

**Bibliographic information published by
the Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2011 Wiley-VCH Verlag & Co. KGaA,
Boschstr. 12, 69469 Weinheim, Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Typesetting Thomson Digital, Noida, India

Printing and Binding betz-druck GmbH, Darmstadt

Cover Design Schulz Grafik-Design, Fußgönheim

Printed in the Federal Republic of Germany

Printed on acid-free paper

Print ISBN: 978-3-527-33201-4

eBook ISBN: 978-3-527-63406-4

Edited by
Julio Alvarez-Builla,
Juan Jose Vaquero,
and José Barluenga

**Modern Heterocyclic
Chemistry**

Related Titles

Majumdar, K. C., Chattopadhyay, S. K. (eds.)

Heterocycles in Natural Product Synthesis

2011

ISBN: 978-3-527-32706-5

Eicher, T., Hauptmann, S., Speicher, A.

The Chemistry of Heterocycles

Structure, Reactions, Synthesis, and Applications

Third Edition

2011

ISBN: 978-3-527-32868-0

Yudin, A. K. (ed.)

Catalyzed Carbon-Heteroatom Bond Formation

2010

ISBN: 978-3-527-32428-6

Ma, S. (ed.)

Handbook of Cyclization Reactions

2009

ISBN: 978-3-527-32088-2

L. Ackermann (Ed.)

Modern Arylation Methods

2009

ISBN: 978-3-527-31937-4

H. Yamamoto, K. Ishihara (Eds.)

Acid Catalysis in Modern Organic Chemistry

2 Volumes

2008

ISBN: 978-3-527-31724-0

J. Royer (Ed.)

Asymmetric Synthesis of Nitrogen Heterocycles

2009

ISBN: 978-3-527-32036-9

List of Contributors

Ramón Alajarín

Universidad de Alcalá
Departamento de Química Orgánica
Alcalá de Henares
28871 Madrid
Spain

Benito Alcaide

Universidad Complutense de Madrid
Facultad de Química
Departamento de Química Orgánica I
28040 Madrid
Spain

Pedro Almendros

Instituto de Química Orgánica General
(CSIC)
Juan de la Cierva, 3
28006 Madrid
Spain

Julio Álvarez-Builla

Universidad de Alcalá
Facultad de Farmacia
Departamento de Química Orgánica
Alcalá de Henares
28871 Madrid
Spain

Venkataramanarao G. Anand

Regional Research Laboratory (CSIR)
Chemical Sciences and Technology
Division
Photosciences and Photonics Section
Trivandrum 695 019
India

José Barluenga

Universidad de Oviedo
Instituto Universitario de Química
Organometálica “Enrique Moles”
Julián Clavería 8
33006 Oviedo
Spain

Miguel Bayod

Asturpharma S.A.
Peña Brava 23
Polígono Industrial Silvota
33192 Llanera, Asturias
Spain

Jan Bergman

Karolinska Institute
Department of Biosciences and
Nutrition
Unit of Organic Chemistry
Novum Research Park
141 57 Huddinge
Sweden

Ulhas Bhatt

Albany Molecular Research, Inc.
Albany, NY 12212
USA

Carolina Burgos

Universidad de Alcalá
Departamento de Química Orgánica
Alcalá de Henares
28871 Madrid
Spain

María-Paz Cabal

Universidad de Oviedo
Instituto Universitario de Química
Organometálica "Enrique Moles"
Julián Clavería 8
33006 Oviedo
Spain

Luis Castedo

Universidad de Santiago de Compostela
Facultad de Química
Departamento de Química Orgánica
15782 Santiago de Compostela
Spain

Tavarekere K. Chandrashekar

Regional Research Laboratory (CSIR)
Chemical Sciences and Technology
Division
Photosciences and Photonics Section
Trivandrum 695 019
India

and

Indian Institute of Technology
Department of Chemistry
Kanpur 208 016
India

Ugo Chiacchio

Università di Catania
Dipartimento di Scienze Chimiche
Viale Andrea Doria 6
95125 Catania
Italy

Stefano Cicchi

Università degli Studi di Firenze
Dipartimento di Chimica "Ugo Schiff"
via della Lastruccia 13
50019 Sesto Fiorentino-Firenze
Italy

Ana M. Cuadro

Universidad de Alcalá
Departamento de Química Orgánica
Alcalá de Henares
28871 Madrid
Spain

José Elguero

University of Aveiro
Instituto de Química Médica (CSIC)
Department of Chemistry
Juan de la Cierva, 3
28006 Madrid
Spain

José L. García-Ivarez

Universidad de Oviedo
Instituto Universitario de Química
Organometálica "Enrique Moles"
Departamento de Química Orgánica e
Inorgánica
Unidad asociada al CSIC
Julian Claveria 8
33006 Oviedo
Spain

Cristina Gómez de la Oliva

Instituto de Química Médica (CSIC)
Juan de la Cierva, 3
28006 Madrid
Spain

Concepción González-Bello

Universidad de Santiago de Compostela
Facultad de Ciencias
Departamento de Química Orgánica
27002 Lugo
Spain

Pilar Goya Laza

Instituto de Química Médica (CSIC)
 Juan de la Cierva, 3
 28006 Madrid
 Spain

Bernardo Herradón

Instituto de Química Orgánica (CSIC)
 Juan de la Cierva, 3
 28006 Madrid
 Spain

Xue-Long Hou

The Chinese Academy of Sciences
 Shanghai Institute of Organic
 Chemistry
 Shanghai-Hong Kong Joint Laboratory
 in Chemical Synthesis and State Key
 Laboratory of Organometallic Chemistry
 354 Feng Lin Road
 Shanghai 200032
 China

Hui Huang

The Chinese Academy of Sciences
 Shanghai Institute of Organic
 Chemistry
 Shanghai-Hong Kong Joint Laboratory
 in Chemical Synthesis
 354 Feng Lin Road
 Shanghai 200032
 China

Tomasz Janosik

Karolinska Institute
 Department of Biosciences and
 Nutrition
 Unit of Organic Chemistry
 Novum Research Park
 141 57 Huddinge
 Sweden

Amparo Luna

Universidad Complutense de Madrid
 Facultad de Química
 Departamento de Química Orgánica I
 28040 Madrid
 Spain

Fabrizio Machetti

Instituto Chimica dei Composti
 Organometallica del CNR c/o
 Dipartimento di Chimica Organica
 "Ugo Schiff"
 Via Madonna del Piano 10
 50019 Sesto Fiorentino (Firenze)
 Italy

François Mathey

Nanyang Technical University
 School of Physical and Mathematical
 Sciences
 Division of Chemistry and Biological
 Chemistry
 21 Nanyang Link
 637371 Singapore
 Singapore

S. Shaun Murphree

Allegheny College
 Department of Chemistry
 520 N, Main Street
 Meadville, PA 16335
 USA

Carmen Ochoa de Ocariz

Instituto de Química Médica (CSIC)
 Juan de la Cierva, 3
 28006 Madrid
 Spain

Teresa M.V.D. Pinho e Melo

Universidade de Coimbra
 Departamento de Química
 3004-535 Coimbra
 Portugal

Julia Revuelta

Instituto de Química Orgánica General
(CSIC)
Grupo de Química Orgánica Biológica
C/Juan de la Cierva, 3
28006 Madrid
Spain

Sylvie Robin

Université de Paris-Sud
ICMMO
Laboratoire de Synthèse Organique et
Méthodologie
Université de Paris-Sud
91405 Orsay
France

Giovanni Romeo

Università di Messina
Dipartimento Farmaco-Chimico
Via SS Annunziata
98168 Messina
Italy

Gérard Rousseau

Université de Paris-Sud
ICMMO
Laboratoire de Synthèse Organique et
Méthodologie
Université de Paris-Sud
91405 Orsay
France

Javier Santamaría

Universidad de Oviedo
Instituto Universitario de Química
Organometálica "Enrique Moles"
Departamento de Química Orgánica e
Inorgánica
Unidad asociada al CSIC
Julian Clavería 8
33006 Oviedo
Spain

Artur M.S. Silva

University of Aveiro
Department of Chemistry
3810-193 Aveiro
Portugal

Alagar Srinivasan

Regional Research Laboratory (CSIR)
Chemical Sciences and Technology
Division
Photosciences and Photonics Section
Trivandrum 695 019
India

Augusto C. Tomé

University of Aveiro
Department of Chemistry
3810-193 Aveiro
Portugal

Carlos Valdés

Universidad de Oviedo
Instituto Universitario de Química
Organometálica "Enrique Moles"
Julián Clavería 8
33006 Oviedo
Spain

Juan J. Vaquero

Universidad de Alcalá
Departamento de Química Orgánica
Alcalá de Henares
28871 Madrid
Spain

José M. Villalgordo

Villalparma S.L.
Polígono Industrial Oeste
C/Paraguay, Parcela 7/5-A, Módulo A-1
30169 Murcia
Spain

David J. Wilkins

Key Organics Ltd.
Highfield Industrial State
Camelford
Cornwall PL32 9QZ
UK

Henry N.C. Wong

The Chinese University of Hong Kong
Institute of Chinese Medicine, and
Central Laboratory of the Institute of
Molecular Technology for Drug
Discovery and Synthesis
Department of Chemistry
Center of Novel Functional Molecules
Shatin, New Territories
Hong Kong SAR, China

and

The Chinese Academy of Sciences
Shanghai Institute of Organic
Chemistry
Shanghai-Hong Kong Joint Laboratory
in Chemical Synthesis
354 Feng Lin Road
Shanghai 200032
China

Jie Wu

Fudan University
Department of Chemistry
220 Handan Road
Shanghai 200433
China

Larry Yet

299 Georgetown Ct
Albany, NY 12203
USA

Kap-Sun Yeung

Bristol-Myers Squibb Pharmaceutical
Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492
USA

Contents

List of Contributors XV

Volume 1

- 1 **Heterocyclic Compounds: An Introduction** 1
Julio Álvarez-Builla and José Barluenga
- 2 **Three-Membered Heterocycles. Structure and Reactivity** 11
S. Shaun Murphree
- 3 **Four-Membered Heterocycles: Structure and Reactivity** 163
Gérard Rousseau and Sylvie Robin
- 4 **Five-Membered Heterocycles: Pyrrole and Related Systems** 269
Jan Bergman and Tomasz Janosik
- 5 **Five-Membered Heterocycles: Indole and Related Systems** 377
José Barluenga and Carlos Valdés
- 6 **Five-Membered Heterocycles: Furan** 533
Henry N.C. Wong, Xue-Long Hou, Kap-Sun Yeung, and Hui Huang
- 7 **Five-Membered Heterocycles: Benzofuran and Related Systems** 593
Jie Wu

Volume 2

- 8 **Five-Membered Heterocycles: 1,2-Azoles. Part 1. Pyrazoles** 635
José Elguero, Artur M.S. Silva, and Augusto C. Tomé
- 9 **Five-Membered Heterocycles: 1,2-Azoles. Part 2. Isoxazoles and Isothiazoles** 727
Artur M.S. Silva, Augusto C. Tomé, Teresa M.V.D. Pinho e Melo, and José Elguero

- 10 Five-Membered Heterocycles: 1,3-Azoles 809**
Julia Revuelta, Fabrizio Machetti, and Stefano Cicchi
- 11 Five-Membered Heterocycles with Two Heteroatoms:
 O and S Derivatives 925**
David J. Wilkins
- 12 Five-Membered Heterocycles with Three Heteroatoms: Triazoles 989**
Larry Yet
- 13 Oxadiazoles 1047**
Giovanni Romeo and Ugo Chiacchio

Volume 3

- 14 Thiadiazoles 1253**
Ugo Chiacchio and Giovanni Romeo
- 15 Five-Membered Heterocycles with Four Heteroatoms: Tetrazoles 1401**
Ulhas Bhatt
- 16 Six-Membered Heterocycles: Pyridines 1431**
Concepción González-Bello and Luis Castedo
- 17 Six-Membered Heterocycles: Quinoline and Isoquinoline 1527**
Ramón Alajarín and Carolina Burgos
- 18 Six-Membered Rings with One Oxygen: Pyrylium Ion,
 Related Systems and Benzo-Derivatives 1631**
Javier Santamaría and Carlos Valdés
- 19 Six-Membered Heterocycles: 1,2-, 1,3-, and 1,4-Diazines
 and Related Systems 1683**
María-Paz Cabal
- 20 Six-Membered Heterocycles: Triazines, Tetrazines and Other
 Polyaza Systems 1777**
Cristina Gómez de la Oliva, Pilar Goya Laza, and Carmen Ochoa de Ocariz

Volume 4

- 21 Seven-Membered Heterocycles: Azepines, Benzo Derivatives
 and Related Systems 1865**
Juan J. Vaquero, Ana M. Cuadro, and Bernardo Herradón
- 21.1 Introduction 1865**

- 21.2 Relevant Natural and Useful Compounds 1867
- 21.3 Relevant Computational Chemistry, Physicochemical, and Spectroscopic Data 1869
- 21.4 Valence Tautomerism in Seven-Membered Heterocycles 1874
- 21.5 Synthesis 1878
 - 21.5.1 Synthesis of Azepines 1878
 - 21.5.1.1 From Acyclic Compounds 1878
 - 21.5.1.2 From Cyclic Compounds 1883
 - 21.5.2 Synthesis of Oxepines 1885
 - 21.5.2.1 From Acyclic Compounds 1885
 - 21.5.2.2 From Cyclic Compounds 1890
 - 21.5.3 Synthesis of Thiepines 1896
 - 21.5.3.1 From Acyclic Compounds 1896
 - 21.5.3.2 From Cyclic Compounds 1897
 - 21.5.4 Synthesis of Azepanes, Oxepanes, and Thiepanes 1898
 - 21.5.5 Synthesis of Benzo Derivatives 1902
 - 21.5.5.1 Synthesis of Benzazepines 1902
 - 21.5.5.2 Synthesis of Benzoxepines 1906
 - 21.5.5.3 Synthesis of Benzothiepines 1907
- 21.6 Reactivity of Azepines 1911
 - 21.6.1 Reactivity of Azepines and Benzofused Derivatives 1911
 - 21.6.1.1 Cycloaddition Reactions 1911
 - 21.6.1.2 Reaction with Metal Carbonyl Complexes 1914
 - 21.6.1.3 Reactions through Metal Carbonyl Complexes 1916
 - 21.6.1.4 Pericyclic Reactions 1917
 - 21.6.1.5 Reactions with Electrophiles 1923
 - 21.6.1.6 Reactions with Nucleophiles 1927
 - 21.6.1.7 Reactions with Oxidants 1929
 - 21.6.1.8 Hydrogenation and Hydrogen Transfer 1932
 - 21.6.2 Reactivity of Partially Reduced Azepine Derivatives 1934
 - 21.6.2.1 Dihydroazepines 1934
 - 21.6.2.2 Tetrahydroazepines 1937
 - 21.6.2.3 Dihydroazepinones 1938
- 21.7 Reactivity of Oxepines 1943
 - 21.7.1 Reactivity of Oxepines and Benzofused Derivatives 1944
 - 21.7.1.1 Thermal and Photochemical Reactions 1944
 - 21.7.1.2 Cycloaddition Reactions 1945
 - 21.7.1.3 Reactions with Electrophiles 1948
 - 21.7.1.4 Reactions with Nucleophiles 1949
 - 21.7.1.5 Reactions with Oxidants 1951
 - 21.7.2 Reactivity of Partially Reduced Oxepines 1953
 - 21.7.2.1 Dihydrooxepines 1953
 - 21.7.2.2 Tetrahydrooxepines 1955
- 21.8 Reactivity of Thiepines 1958
 - 21.8.1 Reactivity of Thiepines and Benzofused Derivatives 1958

- 21.8.1.1 Reactions with Metal Carbonyl Complexes 1958
- 21.8.1.2 Cycloaddition Reactions 1959
- 21.8.1.3 Thermal and Photochemical Reactions 1962
- 21.8.1.4 Reactions with Electrophiles 1965
- 21.8.1.5 Reactions with Oxidants 1967
- 21.8.2 Reactivity of Partially Reduced Thiepine Derivatives 1968
- 21.8.2.1 Dihydrothiepinones 1968
- 21.8.2.2 Tetrahydrothiepinones 1972
- 21.8.2.3 Thiepinones 1975
- References 1975

22 Heterocycles Containing a Ring-Junction Nitrogen 1989

Juan J. Vaquero and Julio Alvarez-Builla

- 22.1 Introduction 1989
- 22.2 Pyrrolizines 1991
- 22.2.1 General Structure and Reactivity 1991
- 22.2.2 Relevant Natural and/or Useful Compounds 1991
- 22.2.3 Relevant Computational Chemistry and Physicochemical and Spectroscopic Data 1993
- 22.2.4 Synthesis of Pyrrolizines 1994
- 22.2.4.1 By Cyclization Reactions 1995
- 22.2.4.2 By [3 + 2] Approaches 1997
- 22.2.5 Reactivity of Pyrrolizines 1997
- 22.2.5.1 Electrophilic Attack 1997
- 22.2.5.2 Cycloaddition Reactions 2000
- 22.2.5.3 Reduction Reactions 2000
- 22.2.5.4 Ring-Opening Reactions 2001
- 22.2.6 Derivatives 2001
- 22.3 Indolizines 2003
- 22.3.1 General Structure and Reactivity 2003
- 22.3.2 Relevant Natural and/or Useful Compounds 2003
- 22.3.3 Relevant Physicochemical Data, Computational Chemistry, and NMR Data 2005
- 22.3.4 Synthesis of Indolizidines 2006
- 22.3.4.1 Intramolecular Condensation: Approaches Related to the Chichibabin Synthesis 2006
- 22.3.4.2 By a [3 + 2] Approach: 1,3-Dipolar Cycloaddition 2007
- 22.3.4.3 Organometallic Processes 2009
- 22.3.4.4 Rearrangement of Acetylenic Derivatives 2009
- 22.3.5 Reactivity of Indolizidines 2011
- 22.3.5.1 Reactions with Electrophilic Reagents 2011
- 22.3.5.2 Reactions with Oxidizing Agents 2016
- 22.3.5.3 Reactions with Nucleophilic Reagents 2016
- 22.3.5.4 Reactions with Bases 2017
- 22.3.5.5 Reactions with Reducing Agents 2017

22.3.5.6	Electrocyclic Reactions	2018
22.3.5.7	Reactions of C-Metallated Indolizines	2019
22.3.6	Derivatives	2020
22.4	Quinolizinium Salts	2020
22.4.1	General Structure and Reactivity	2020
22.4.2	Relevant Natural and/or Useful Compounds	2021
22.4.3	Relevant Computational Chemistry, and Physicochemical and Spectroscopic Data	2023
22.4.4	Synthesis of Quinolizinium Salts	2026
22.4.4.1	By [3 + 3] Approaches	2026
22.4.4.2	By [4 + 2] Approaches	2029
22.4.4.3	By Cyclization Reactions	2035
22.4.5	Reactivity of Quinolizinium Salts	2038
22.4.5.1	Reactions with Electrophilic Reagents	2039
22.4.5.2	Reactions with Nucleophilic Reagents: Ring-Opening Reactions	2040
22.4.5.3	Reactions with Reducing Reagents	2042
22.4.5.4	Cycloaddition Reactions	2042
22.4.6	Quinolizinium Derivatives	2043
22.4.6.1	Alkyl Derivatives	2043
22.4.6.2	Hydroxy and Amino Derivatives	2045
22.4.6.3	Halo Derivatives	2048
22.4.7	Benzoquinolizinium Salts and Related Systems	2052
	References	2062

23 Phosphorus Heterocycles 2071

François Mathey

23.1	Introduction	2071
23.2	Phospholes	2071
23.2.1	History and Nomenclature	2071
23.2.2	Spectral, Structural and Theoretical Studies	2072
23.2.3	Synthesis	2073
23.2.3.1	Synthesis of Phospholes	2073
23.2.3.2	Synthesis of Phospholide Ions	2075
23.2.4	Reactivity	2076
23.2.4.1	Reactions at Phosphorus	2076
23.2.4.2	Reactions at the Diene	2077
23.2.4.3	[1,5]-Sigmatropic Shifts	2079
23.2.4.4	Functionalization Reactions	2082
23.2.4.5	Ring Openings and Expansions	2082
23.2.4.6	Phospholes and Phospholides in Coordination Chemistry	2083
23.3	Phosphinines	2084
23.3.1	History and Nomenclature	2084
23.3.2	Spectral, Structural and Theoretical Studies	2085

23.3.3	Synthesis	2086
23.3.4	Reactivity	2089
23.3.4.1	Reactions at Phosphorus	2089
23.3.4.2	Substitution and Functionalization Reactions	2092
23.3.4.3	Cycloaddition Reactions	2095
23.3.4.4	Phosphinines in Coordination Chemistry	2096
23.4	Other P Heterocycles	2097
23.4.1	Three-Membered Rings: Phosphiranes and Phosphirenes	2097
23.4.2	Four-Membered Rings: Phosphetanes, Dihydrophosphetes and Phosphetes	2100
23.4.3	Five-Membered Rings: Phospholenes	2102
23.5	Applications of Phosphorus Heterocycles	2103
23.6	Addendum	2105
23.6.1	Phospholes	2105
23.6.2	Phosphinines	2107
	References	2109
24	The Chemistry of 2-Azetidinones (β-Lactams)	2117
	<i>Benito Alcaide, Pedro Almendros, and Amparo Luna</i>	
24.1	Monocyclic Derivatives	2117
24.1.1	Introduction	2117
24.1.2	Physicochemical Data	2117
24.1.2.1	Computational Chemistry	2117
24.1.2.2	Experimental Structural Methods	2119
24.1.3	Biologically Relevant Monocyclic β -Lactams	2120
24.1.4	2-Azetidinone Nucleus Synthesis	2121
24.1.4.1	Ketene-Imine Cycloaddition (Staudinger Reaction)	2121
24.1.4.2	Metalloester Enolate-Imine Condensation	2124
24.1.4.3	Isocyanate-Alkene Cyclocondensation	2125
24.1.4.4	Chromium Carbene-Imine Cyclization	2126
24.1.4.5	Cyclization of β -Amino Acids and Derivatives	2126
24.1.4.6	Hydroxamate Cyclization	2127
24.1.4.7	Metal-Catalyzed Insertions of Diazo Compounds	2127
24.1.4.8	Multicomponent Reactions	2129
24.1.4.9	Coupling of Terminal Alkynes and Nitrones (Kinugasa Reaction)	2130
24.1.4.10	Photochemical and Radical Methods	2130
24.1.4.11	Synthesis from Carbo- or Heterocycles	2131
24.1.4.12	Miscellaneous	2133
24.1.5	Reactivity of the 2-Azetidinone Ring	2134
24.1.5.1	Nucleophilic Attack at Carbon	2134
24.1.5.2	Electrophilic Attack at Carbon	2136
24.1.5.3	Electrophilic Attack at Nitrogen	2136

24.1.5.4	Radical Transformations	2137
24.1.5.5	Reduction Reactions	2138
24.1.5.6	Cis/Trans Isomerization	2139
24.1.5.7	Ring-Opening and Rearrangement Reactions	2140
24.1.5.8	Reactions of Substituents Attached to Carbon Atoms	2142
24.1.5.9	Reactions of Substituents Attached to Nitrogen Atom	2143
24.2	Penicillins and Cephalosporins	2144
24.2.1	Introduction	2144
24.2.2	Physicochemical Data	2146
24.2.2.1	Computational Chemistry	2146
24.2.2.2	Experimental Structural Methods	2147
24.2.3	Synthesis of Penicillins and Cephalosporins	2148
24.2.3.1	Classical Syntheses	2148
24.2.3.2	Industrial Production of β -Lactam Antibiotics	2150
24.2.4	Reactivity of Penicillins and Cephalosporins	2153
24.2.4.1	Basicity of β -Lactam Nitrogen	2153
24.2.4.2	Hydrolysis	2153
24.2.4.3	Alcoholysis, Thiolytic, and Aminolysis	2155
24.2.4.4	Destruction of β -Lactam Antibiotics by β -Lactamases	2156
24.2.4.5	Conversion of Penicillins into Cephalosporins	2158
24.2.4.6	Reactions for the Transformation of Functional Groups in Side Chains	2159
	References	2163
25	The Chemistry of Benzodiazepines	2175
	<i>Carlos Valdés and Miguel Bayod</i>	
25.1	Introduction	2175
25.1.1	General Introduction	2175
25.1.2	Structural Classification of Benzodiazepines	2177
25.2	Relevant Benzodiazepines	2177
25.2.1	Most Common 1,4-Benzodiazepines	2177
25.2.2	1,4-Benzodiazepines with a Heterocycle Condensed at sides <i>a</i> or <i>d</i>	2179
25.2.3	Other Benzodiazepines with Clinical Application	2181
25.2.4	Naturally Occurring Benzodiazepines	2181
25.3	1,4-Benzodiazepines: General Synthetic Methods	2182
25.3.1	1,4-Benzodiazepines Ring Synthesis: Introduction	2182
25.3.2	Ring Synthesis of 1,4-Benzodiazepin-2-ones	2182
25.3.2.1	Quinazoline <i>N</i> -Oxide Route: Sternbach's Classical Synthesis	2182
25.3.2.2	2-Aminobenzophenone Route	2184