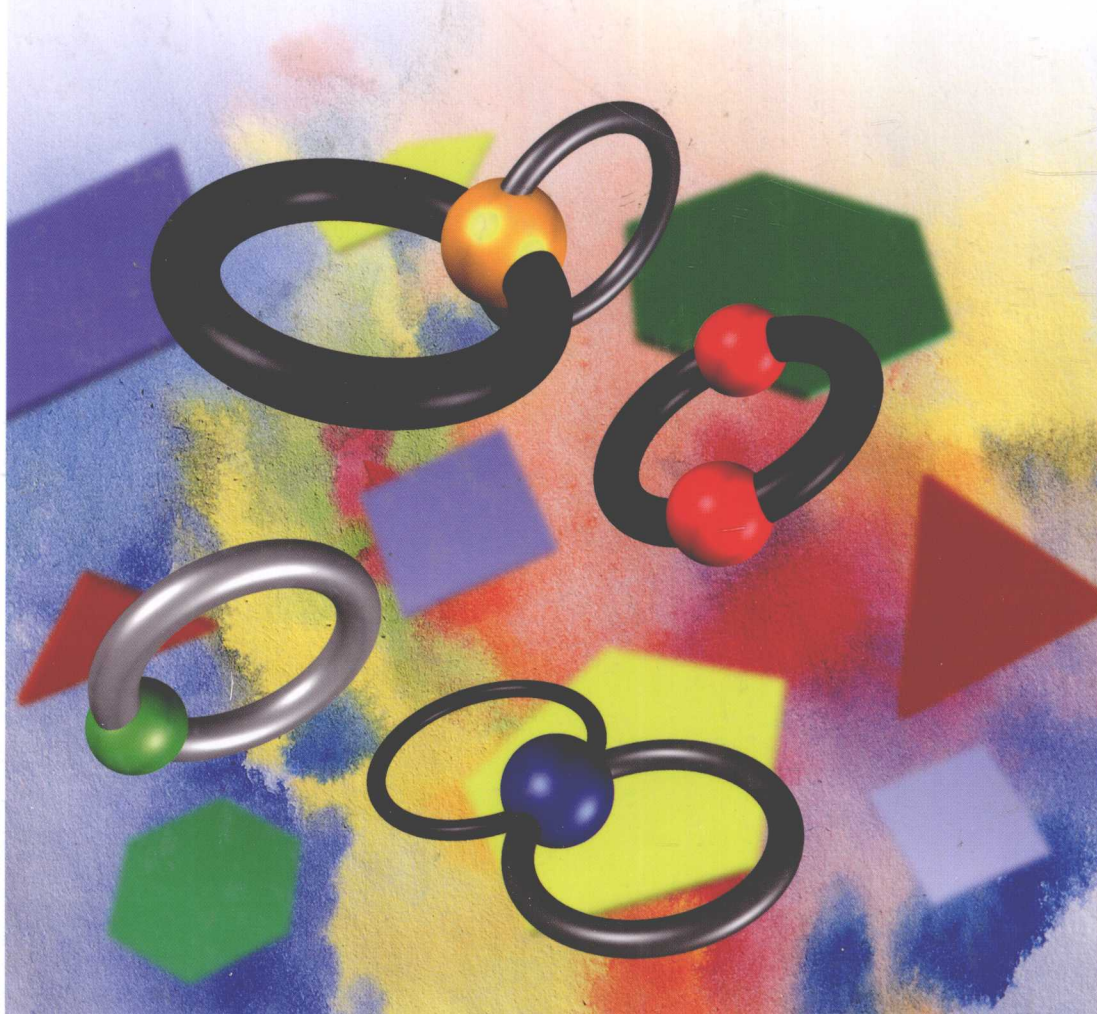


Edited by Julio Alvarez-Builla,
Juan J. Vaquero, and José Barluenga

 WILEY-VCH

Modern Heterocyclic Chemistry

Volume 1

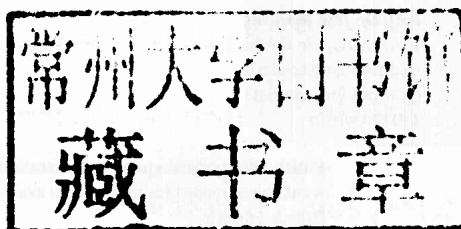


Edited by

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

Modern Heterocyclic Chemistry

Volume 1



**WILEY-
VCH**

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"
Julian Clavería 8
33006 Oviedo
Spain

Juan J. Vaquero

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

José M. Villalgorido

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
 - 1.1 Heterocyclic Compounds: An Introduction 1
 - 1.2 Structure and Reactivity of Aromatic Five-Membered Systems 5
 - 1.3 Structure and Reactivity of Aromatic Six-Membered Systems 6
 - 1.4 Basic Literature on Heterocyclic Compounds 8
 - References 9
- 2 Three-Membered Heterocycles. Structure and Reactivity 11**
S. Shaun Murphree
 - 2.1 Aziridines 11
 - 2.1.1 Properties of Aziridines 11
 - 2.1.2 Synthesis of Aziridines 12
 - 2.1.2.1 Aziridination of Alkenes 12
 - 2.1.2.2 Aziridination of Imines 23
 - 2.1.2.3 Ring Closure of Amines 27
 - 2.1.2.4 Ring Contraction of Other Heterocycles 29
 - 2.1.3 Reactivity of Aziridines 30
 - 2.1.3.1 Nucleophilic Ring Opening 30
 - 2.1.3.2 N-Elaboration Reactions 35
 - 2.1.3.3 Azirdinyl Anion Chemistry 37
 - 2.1.3.4 Ring Expansions 38
 - 2.2 2*H*-Azirines 41
 - 2.2.1 Properties of Azirines 41
 - 2.2.2 Synthesis of Azirines 42
 - 2.2.2.1 Neber Route 42
 - 2.2.2.2 From Vinyl Azides 45

2.2.2.3	From Other Heterocycles	48
2.2.3	Reactivity of Azirines	50
2.2.3.1	Addition of Nucleophiles	50
2.2.3.2	Cycloadditions	54
2.2.3.3	Rearrangements into other Heterocycles	55
2.3	Oxiranes	55
2.3.1	Properties of Oxiranes	56
2.3.2	Synthesis of Oxiranes	58
2.3.2.1	Using Dioxiranes	59
2.3.2.2	Using other Oxidants without Metal Catalysts	64
2.3.2.3	Metal-Catalyzed Epoxidation of Alkenes	69
2.3.2.4	Epoxidation of Electron-Deficient Alkenes	83
2.3.2.5	Epoxidation of Carbonyl Compounds	86
2.3.2.6	Ring-Closing Reactions	90
2.3.3	Reactivity of Oxiranes	92
2.3.3.1	Nucleophilic Ring Opening	92
2.3.3.2	Rearrangements	98
2.3.3.3	Radical Chemistry	104
2.3.3.4	Reduction and Deoxygenation	104
2.3.3.5	Oxiranyl Anions	107
2.4	Thiiranes	109
2.4.1	Properties of Thiiranes	109
2.4.2	Synthesis of Thiiranes	110
2.4.2.1	From Epoxides	110
2.4.2.2	From Alkenes	113
2.4.2.3	From Haloketones	113
2.4.3	Reactivity of Thiiranes	114
2.4.3.1	Nucleophilic Ring Opening	114
2.4.3.2	Desulfurization	116
2.5	Diaziridines	117
2.5.1	Properties of Diaziridines	117
2.5.2	Synthesis of Diaziridines	119
2.5.2.1	Oxidative Methods using Hypohalites	119
2.5.2.2	Via Hydroxylamine Derivatives	120
2.5.2.3	Other Methods	121
2.5.3	Reactivity of Diaziridines	122
2.5.3.1	Diaziridines	122
2.5.3.2	Diaziridinones and Diaziridinimines	123
2.6	3 <i>H</i> -Diazirines	124
2.6.1	Properties of Diazirines	124
2.6.2	Synthesis of Diazirines	124
2.6.3	Reactivity of Diazirines	126
2.7	Oxaziridines	129
2.7.1	Properties of Oxaziridines	129
2.7.2	Synthesis of Oxaziridines	129

2.7.3	Reactivity of Oxaziridines	131
2.7.3.1	Nitrogen Transfer Reactions	131
2.7.3.2	Oxygen Transfer Reactions	133
2.7.3.3	Rearrangements	133
2.8	Dioxiranes	135
2.8.1	Properties of Dioxiranes	135
2.8.2	Synthesis of Dioxiranes	136
2.8.3	Reactivity of Dioxiranes	137
2.8.3.1	Epoxidation of Alkenes	137
2.8.3.2	Hydroxylation of Alkanes	137
2.8.3.3	Oxidation of Sulfur	138
	References	140
3	Four-Membered Heterocycles: Structure and Reactivity	163
	<i>G�rard Rousseau and Sylvie Robin</i>	
3.1	Azetidines	163
3.1.1	Introduction	163
3.1.2	Physicochemical Data	165
3.1.3	Synthesis	166
3.1.3.1	Cyclization Reactions	166
3.1.3.2	Ring Transformations	173
3.1.3.3	Cycloadditions	176
3.1.4	Reactivity and Useful Reactions	177
3.1.4.1	Reactions at the Nitrogen Atom	177
3.1.4.2	Oxidizing Reactions	180
3.1.4.3	Reactions with Nucleophiles and Bases	181
3.1.4.4	Reactions of C-Metallated Azetidines	182
3.1.4.5	Ring Expansions	182
3.1.4.6	Cleavage of the Azetidine Ring	186
3.1.4.7	Enzymatic Resolutions of Azetidines	186
3.2	Oxetanes	188
3.2.1	Introduction	188
3.2.2	Physicochemical Data	188
3.2.2.1	NMR Data	189
3.2.2.2	Infrared Spectroscopy	189
3.2.3	Natural or Bioactive Compounds	189
3.2.4	Synthesis of Oxetanes and Oxetan-2-ones	191
3.2.4.1	[2+2] Paterno-B�chi Cyclizations	191
3.2.4.2	Catalyzed [2+2] Cyclizations	193
3.2.4.3	Ring Contraction of Butanolides	194
3.2.4.4	Oxirane Ring Opening by Carbanionic Attacks	195
3.2.4.5	Williamson Reactions	195
3.2.4.6	Isomerization of Oxiranyl Hydroxyls	195
3.2.4.7	Oxirane Ring Expansions	196
3.2.4.8	Electrophilic Cyclizations	196

3.2.4.9	[2+2] Cycloaddition of Ketene and Carbonyl Compounds	197
3.2.4.10	Acyl Halide–Aldehyde Cyclocondensations	198
3.2.4.11	C–H Insertions	200
3.2.4.12	Carbonylative Ring Expansion Reactions	201
3.2.4.13	β -Hydroxy Acid Cyclizations	202
3.2.5	Reactivity	202
3.2.5.1	β -Lactones	202
3.2.5.2	Oxetanes	208
3.3	Thietanes	214
3.3.1	Introduction	214
3.3.2	Physicochemical Data	215
3.3.3	Natural and Bioactive Compounds	215
3.3.4	Synthesis of Thietanes	216
3.3.4.1	Synthesis by Formation of a S–C Bond	216
3.3.4.2	Synthesis by Formation of a C–C Bond	221
3.3.4.3	Synthesis by Formation of Two S–C Bonds	221
3.3.4.4	Synthesis from Other Sulfur Heterocycles	224
3.3.4.5	Synthesis by [2+2] Cycloaddition	228
3.3.4.6	Synthesis by Miscellaneous Methods	230
3.3.5	Reactivity and Useful Reactions	231
3.3.5.1	Reactions with Electrophilic Reagents	231
3.3.5.2	Reactions with Oxidizing Agents	231
3.3.5.3	Reactions with Nucleophilic Reagents	233
3.3.5.4	Reactions with Bases	233
3.3.5.5	Reactions with Metal Complexes and Salts	234
3.3.5.6	Electrocyclic Reactions	235
3.3.5.7	Cleavage and Other Reactions	237
3.4	Other Four-Membered Heterocycles	238
3.4.1	Selenetanes	238
3.4.1.1	Introduction	238
3.4.1.2	Synthesis of Selenetanes	239
3.4.1.3	Reactivity	242
3.4.2	Telluretanes	244
3.4.3	Phosphetanes	244
3.4.4	Arsetanes	244
3.4.5	Siletanes	245
3.4.5.1	Introduction	245
3.4.5.2	Preparation of Siletanes	246
3.4.5.3	Reactivity	249
3.4.6	Germetanes	252
3.4.6.1	Introduction	252
3.4.6.2	Preparations	252
3.4.6.3	Reactivity	253
3.4.7	Bismetanes and Stibetanes	254
	References	254

4	Five-Membered Heterocycles: Pyrrole and Related Systems	269
	<i>Jan Bergman and Tomasz Janosik</i>	
4.1	Introduction	269
4.1.1	Nomenclature	269
4.2	General Reactivity	270
4.2.1	Relevant Physicochemical Data, Computational Chemistry, and NMR Data	270
4.2.2	Fundamental Reactivity Patterns	271
4.3	Relevant Natural and/or Useful Compounds	273
4.4	Pyrrole Ring Synthesis	274
4.4.1	Paal–Knorr Synthesis and Related Methods (4+1 Strategy)	275
4.4.2	Other Cyclizations of Four-Carbon Precursors (5+0 and 4+1 Strategies)	278
4.4.3	Knorr Synthesis and Related Routes (3+2 Strategy)	281
4.4.4	Hantzsch Synthesis and Related Approaches (2+2+1 or 3+2 Strategy)	284
4.4.5	Syntheses Involving Glycine Esters (3+2 Strategy)	284
4.4.6	Van Leusen Method (3+2 Strategy)	285
4.4.7	Barton–Zard Synthesis (3+2 Strategy)	287
4.4.8	Trofimov Synthesis (3+2 Strategy)	288
4.4.9	Cycloaddition Reactions and Related Approaches (3+2 Strategy)	289
4.4.10	Multi-Component Reactions (2+2+1 Strategy)	291
4.4.11	Miscellaneous Transition Metal Catalyzed Methods (3+2 and 5+0 Strategies)	291
4.5	Reactivity	293
4.5.1	Reactions with Electrophilic Reagents	293
4.5.1.1	General Aspects of Reactivity and Regioselectivity in Electrophilic Substitution	293
4.5.1.2	Protonation	294
4.5.1.3	Halogenation	295
4.5.1.4	Nitration	299
4.5.1.5	Reactions with Sulfur-Containing Electrophiles	299
4.5.1.6	Acylation	302
4.5.1.7	Reactions with Aldehydes, Ketones, Nitriles and Iminium Ions	306
4.5.1.8	Conjugate Addition to α,β -Unsaturated Carbonyl Compounds	309
4.5.2	Reactions with Oxidants	310
4.5.3	Reactions with Nucleophiles	312
4.5.4	Reactions with Bases	313
4.5.4.1	N-Metallated Pyrroles	313
4.5.4.2	C-Metallated Pyrroles	314
4.5.5	Reactions with Radical Reagents	318
4.5.6	Reactions with Reducing Agents	320

4.5.7	Cycloaddition Reactions	322
4.5.8	Reactions with Carbenes and Carbenoids	328
4.5.9	Photochemical Reactions	330
4.5.10	Pyrrol-C-X Compounds: Synthesis and Reactions	331
4.5.11	Transition Metal Catalyzed Coupling Reactions	333
4.6	Pyrrole Derivatives	336
4.6.1	Alkyl Derivatives	336
4.6.2	Pyrrole Carboxylic Acids and Carboxylates	337
4.6.3	Oxy Derivatives	338
4.6.4	Aminopyrroles	342
4.6.5	Dihydro- and Tetrahydro-Derivatives	344
4.7	Addendum	349
	References	355
5	Five-Membered Heterocycles: Indole and Related Systems	377
	<i>José Barluenga and Carlos Valdés</i>	
5.1	Introduction	377
5.1.1	General Introduction	377
5.1.2	System Isomers and Nomenclature	378
5.2	General Properties	379
5.2.1	Physicochemical Data	379
5.2.2	General Reactivity	379
5.3	Relevant Natural and/or Useful Compounds	383
5.4	Indole Synthesis	384
5.4.1	Introduction	384
5.4.2	Synthesis of the Indole Ring from a Benzene Ring	385
5.4.2.1	Indole Synthesis Involving a Sigmatropic Rearrangement	385
5.4.2.2	Cyclization by Formation of the N–C2 Bond	398
5.4.2.3	Ring Synthesis by Formation of the C3–C3a Bond	415
5.4.2.4	Ring Synthesis by Formation of the C2–C3 Bond	421
5.4.2.5	Cyclizations with Formation of the N–C7a Bond	427
5.4.3	Synthesis of the Indole Ring by Annelation of Pyrroles	431
5.4.3.1	Synthesis by Electrophilic Cyclization	431
5.4.3.2	Palladium-Catalyzed Cyclizations	433
5.4.3.3	Electrocyclizations	435
5.4.3.4	[4 + 2] Cycloadditions	435
5.4.3.5	Indoles from 3-Alkynylpyrrole-2-Carboxaldehydes	435
5.5	Reactivity of Indole	436
5.5.1	Reactions with Electrophiles	436
5.5.1.1	Protonation	438
5.5.1.2	Friedel–Crafts Alkylations of Indole	438
5.5.1.3	Nitration	449
5.5.1.4	Acylation	451
5.5.1.5	Halogenation	452

5.5.2	Reactions with Bases	453
5.5.2.1	N-Metallation of Indoles	453
5.5.2.2	C-Metallation of Indoles	454
5.5.3	Transition Metal Catalyzed Reactions	457
5.5.3.1	General Considerations on Palladium-Catalyzed Cross-Coupling Reactions	457
5.5.3.2	Reactions with Alkenes and Alkynes: Heck Reactions	457
5.5.3.3	Sonogashira Reaction	458
5.5.3.4	Cross-Coupling Reactions with Organometallic Reagents	460
5.5.3.5	C–N Bond-Forming Reactions	463
5.5.3.6	Transition Metal Catalyzed C–H Activation	464
5.5.4	Radical Reactions	470
5.5.5	Oxidation Reactions	475
5.5.6	Reduction of the Heterocyclic Ring	478
5.5.6.1	Catalytic Hydrogenation	478
5.5.6.2	Metal-Promoted Reductions	479
5.5.6.3	Metal Hydride Complexes	479
5.5.7	Pericyclic Reactions Involving the Heterocyclic Ring	480
5.5.7.1	Cycloaddition Reactions	480
5.5.7.2	Electrocyclizations	488
5.5.7.3	Sigmatropic Rearrangements	488
5.5.8	Photochemical Reactions	489
5.5.9	Reactions with Carbenes and Carbenoids	491
5.6	Chemistry of Indole Derivatives	491
5.6.1	Alkylindoles	491
5.6.2	Oxiderivatives	494
5.6.2.1	Oxindole	495
5.6.2.2	N-Hydroxyindoles	498
5.6.3	Aminoindoles	500
5.6.4	Indole Carboxylic Acids	500
5.7	Addendum	501
5.7.1	Ring Synthesis	501
5.7.1.1	Fischer Indole Synthesis	501
5.7.2	Reactivity	508
5.7.2.1	Reactions with Electrophiles	508
5.7.2.2	Transition Metal Catalyzed Reactions	509
	References	513
6	Five-Membered Heterocycles: Furan	533
	<i>Henry N.C. Wong, Xue-Long Hou, Kap-Sun Yeung, and Hui Huang</i>	
6.1	Introduction	533
6.1.1	Nomenclature	534
6.1.2	General Reactivity	534
6.1.3	Relevant Physicochemical Data	538
6.1.4	Relevant Natural and Useful Compounds	540