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

Modern Heterocyclic Chemistry

Volume 1
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 Aziridinyl Anion Chemistry 37
2.1.3.4 Ring Expansions 38
2.2 2H-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
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.2.3 From Other Heterocycles</td>
<td>48</td>
</tr>
<tr>
<td>2.2.3 Reactivity of Azirines</td>
<td>50</td>
</tr>
<tr>
<td>2.2.3.1 Addition of Nucleophiles</td>
<td>50</td>
</tr>
<tr>
<td>2.2.3.2 Cycloadditions</td>
<td>54</td>
</tr>
<tr>
<td>2.2.3.3 Rearrangements into other Heterocycles</td>
<td>55</td>
</tr>
<tr>
<td>2.3 Oxiranes</td>
<td>55</td>
</tr>
<tr>
<td>2.3.1 Properties of Oxiranes</td>
<td>56</td>
</tr>
<tr>
<td>2.3.2 Synthesis of Oxiranes</td>
<td>58</td>
</tr>
<tr>
<td>2.3.2.1 Using Dioxiranes</td>
<td>59</td>
</tr>
<tr>
<td>2.3.2.2 Using other Oxidants without Metal Catalysts</td>
<td>64</td>
</tr>
<tr>
<td>2.3.2.3 Metal-Catalyzed Epoxidation of Alkenes</td>
<td>69</td>
</tr>
<tr>
<td>2.3.2.4 Epoxidation of Electron-Deficient Alkenes</td>
<td>83</td>
</tr>
<tr>
<td>2.3.2.5 Epoxidation of Carbonyl Compounds</td>
<td>86</td>
</tr>
<tr>
<td>2.3.2.6 Ring-Closing Reactions</td>
<td>90</td>
</tr>
<tr>
<td>2.3.3 Reactivity of Oxiranes</td>
<td>92</td>
</tr>
<tr>
<td>2.3.3.1 Nucleophilic Ring Opening</td>
<td>92</td>
</tr>
<tr>
<td>2.3.3.2 Rearrangements</td>
<td>98</td>
</tr>
<tr>
<td>2.3.3.3 Radical Chemistry</td>
<td>104</td>
</tr>
<tr>
<td>2.3.3.4 Reduction and Deoxygenation</td>
<td>104</td>
</tr>
<tr>
<td>2.3.3.5 Oxiranyl Anions</td>
<td>107</td>
</tr>
<tr>
<td>2.4 Thiiranes</td>
<td>109</td>
</tr>
<tr>
<td>2.4.1 Properties of Thiiranes</td>
<td>109</td>
</tr>
<tr>
<td>2.4.2 Synthesis of Thiiranes</td>
<td>110</td>
</tr>
<tr>
<td>2.4.2.1 From Epoxides</td>
<td>110</td>
</tr>
<tr>
<td>2.4.2.2 From Alkenes</td>
<td>113</td>
</tr>
<tr>
<td>2.4.2.3 From Haloketones</td>
<td>113</td>
</tr>
<tr>
<td>2.4.3 Reactivity of Thiiranes</td>
<td>114</td>
</tr>
<tr>
<td>2.4.3.1 Nucleophilic Ring Opening</td>
<td>114</td>
</tr>
<tr>
<td>2.4.3.2 Desulfurization</td>
<td>116</td>
</tr>
<tr>
<td>2.5 Diaziridines</td>
<td>117</td>
</tr>
<tr>
<td>2.5.1 Properties of Diaziridines</td>
<td>117</td>
</tr>
<tr>
<td>2.5.2 Synthesis of Diaziridines</td>
<td>119</td>
</tr>
<tr>
<td>2.5.2.1 Oxidative Methods using Hypohalites</td>
<td>119</td>
</tr>
<tr>
<td>2.5.2.2 Via Hydroxylamine Derivatives</td>
<td>120</td>
</tr>
<tr>
<td>2.5.2.3 Other Methods</td>
<td>121</td>
</tr>
<tr>
<td>2.5.3 Reactivity of Diaziridines</td>
<td>122</td>
</tr>
<tr>
<td>2.5.3.1 Diaziridines</td>
<td>122</td>
</tr>
<tr>
<td>2.5.3.2 Diaziridinones and Diaziridinimines</td>
<td>123</td>
</tr>
<tr>
<td>2.6 3H-Diazirines</td>
<td>124</td>
</tr>
<tr>
<td>2.6.1 Properties of Diazirines</td>
<td>124</td>
</tr>
<tr>
<td>2.6.2 Synthesis of Diazirines</td>
<td>124</td>
</tr>
<tr>
<td>2.6.3 Reactivity of Diazirines</td>
<td>126</td>
</tr>
<tr>
<td>2.7 Oxaziridines</td>
<td>129</td>
</tr>
<tr>
<td>2.7.1 Properties of Oxaziridines</td>
<td>129</td>
</tr>
<tr>
<td>2.7.2 Synthesis of Oxaziridines</td>
<td>129</td>
</tr>
</tbody>
</table>


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
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5.7</td>
<td>Cycloaddition Reactions</td>
<td>322</td>
</tr>
<tr>
<td>4.5.8</td>
<td>Reactions with Carbenes and Carbenoids</td>
<td>328</td>
</tr>
<tr>
<td>4.5.9</td>
<td>Photochemical Reactions</td>
<td>330</td>
</tr>
<tr>
<td>4.5.10</td>
<td>Pyrryl-C-X Compounds: Synthesis and Reactions</td>
<td>331</td>
</tr>
<tr>
<td>4.5.11</td>
<td>Transition Metal Catalyzed Coupling Reactions</td>
<td>333</td>
</tr>
<tr>
<td>4.6</td>
<td>Pyrrole Derivatives</td>
<td>336</td>
</tr>
<tr>
<td>4.6.1</td>
<td>Alkyl Derivatives</td>
<td>336</td>
</tr>
<tr>
<td>4.6.2</td>
<td>Pyrrole Carboxylic Acids and Carboxylates</td>
<td>337</td>
</tr>
<tr>
<td>4.6.3</td>
<td>Oxy Derivatives</td>
<td>338</td>
</tr>
<tr>
<td>4.6.4</td>
<td>Aminopyrroles</td>
<td>342</td>
</tr>
<tr>
<td>4.6.5</td>
<td>Dihydro- and Tetrahydro-Derivatives</td>
<td>344</td>
</tr>
<tr>
<td>4.7</td>
<td>Addendum</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>355</td>
</tr>
</tbody>
</table>

5 Five-Membered Heterocycles: Indole and Related Systems 377

José Barluenga and Carlos Valdés

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] Cycloaditions 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
5.7.2.3 Metal-Promoted Reductions 511
5.7.2.4 Metal Hydride Complexes 517
5.7.3 Pericyclic Reactions Involving the Heterocyclic Ring 518
5.7.3.1 Cycloaddition Reactions 518
5.7.3.2 Electrocyclizations 526
5.7.3.3 Sigmatropic Rearrangements 526
5.7.4 Photochemical Reactions 527
6 Five-Membered Heterocycles: Furan 533
Henry N.C. Wong, Xue-Long Hou, Kap-Sun Yeung, and Hui Huang
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