

Contents

Preface XIII

List of Contributors XV

1	Chiral Nonracemic Isocyanides	1
	<i>Luca Banfi, Andrea Basso, and Renata Riva</i>	
1.1	Introduction	1
1.2	Simple Unfunctionalized Isocyanides	1
1.3	Isocyanides Containing Carboxylic, Sulfonyl, or Phosphonyl Groups	4
1.3.1	α -Isocyano Esters	4
1.3.2	α -Isocyano Amides	7
1.3.3	Other Isocyano Esters or Amides	9
1.3.4	Chiral Sulfonylmethyl or Phosphonylmethyl Isocyanides	10
1.4	Isocyanides Containing Amino or Alcoholic Functionalities	11
1.4.1	Chiral Amino or Azido Isocyanides	11
1.4.2	Chiral Hydroxy Isocyanides	12
1.5	Natural Isocyanides	16
1.5.1	Isolation and Natural Sources	16
1.5.2	Synthesis of Naturally Occurring Isocyanides	17
1.6	Isocyanides Used in the Synthesis of Chiral Polyisocyanides	23
1.6.1	Properties	24
1.6.2	Synthesis	25
1.6.3	Applications	26
	References	26
2	General Aspects of Isocyanide Reactivity	35
	<i>Maxim A. Mironov</i>	
2.1	Introduction	35
2.2	Isocyanide–Cyanide Rearrangement	37
2.3	Oxidation/Reduction of the Isocyano Group	41
2.3.1	Oxidation of the Isocyano Group	41
2.3.2	Reactions with Sulfur and Selenium	43

2.3.3	Reduction of the Isocyano Group	45
2.4	Reactions of Isocyanides with Electrophiles	47
2.4.1	Reaction with Acids	49
2.4.2	Reactions with Halogens and Acyl Halides	52
2.4.3	Reactions with Activated Alkenes and Alkynes	55
2.4.4	Reactions with Carbonyl Compounds and Imines	58
2.4.5	Reactions with Activated Heterocumulens	60
2.5	Reactions of Isocyanides with Nucleophiles	62
2.5.1	Reactions with Organometallic Compounds	62
2.5.2	Reactions with Hydroxide, Alcohols, and Amines	64
2.6	Conclusions	66
	References	67

3 **α -Acidic Isocyanides in Multicomponent Chemistry** 75

Niels Elders, Eelco Ruijter, Valentine G. Nenajdenko, and Romano V.A. Orru

3.1	Introduction	75
3.2	Synthesis of α -Acidic Isocyanides	76
3.3	Reactivity of α -Acidic Isocyanides	78
3.4	MCRs Involving α -Acidic Isocyanides	80
3.4.1	van Leusen Imidazole MCR	81
3.4.2	2,6,7-Trisubstituted Quinoxaline MCR	82
3.4.3	4,5-Disubstituted Oxazole MCR	83
3.4.4	Nitropyrrole MCR	83
3.4.5	2,4,5-Trisubstituted Oxazole MCR	84
3.4.5.1	2,4,5-Trisubstituted Oxazoles	84
3.4.5.2	Variations on the 2,4,5-Trisubstituted Oxazole MCR	86
3.4.5.3	Oxazole MCR and <i>In-Situ</i> Domino Processes	88
3.4.6	2-Imidazoline MCR	91
3.4.6.1	2-Imidazoline MCR in the Union of MCRs	93
3.4.7	Dihydropyridone MCR	95
3.5	Conclusions	97
	References	98

4 **Synthetic Application of Isocyanoacetic Acid Derivatives** 109

Anton V. Gulevich, Alexander G. Zhdanko, Romano V.A. Orru, and Valentine G. Nenajdenko

4.1	Introduction	109
4.2	Synthesis of α -Isocyanoacetate Derivatives	109
4.3	Alkylation of Isocyanoacetic Acid Derivatives	113
4.4	α -Isocyanoacetates as Michael Donors	115
4.5	Reaction of Isocyanoacetic Acids with Alkynes: Synthesis of Pyrroles	119
4.6	Reaction of Isocyanoacetic Acid Derivatives with Carbonyl Compounds and Imines	121
4.6.1	Aldol-Type Reaction of Isocyanoacetic Acids with Aldehydes: Synthesis of Oxazolines	122

4.6.2	Transition Metal-Catalyzed Aldol-Type Reactions	124
4.6.3	Reaction of Isocyanoacetic Acids with Imines: Imidazoline Formation	126
4.7	Reaction with Acylating Agents	129
4.8	Multicomponent Reactions of Isocyanoacetic Acid Derivatives	133
4.9	Chemistry of Isocyanoacetates Bearing an Additional Functional Group	134
4.10	Reactions of Isocyanoacetic Acids with Sulfur Electrophiles	138
4.11	Miscellaneous Reactions	139
4.12	Concluding Remarks	144
4.13	Notes Added in Proof	145
	References	145
5	Ugi and Passerini Reactions with Carboxylic Acid Surrogates	159
	<i>Laurent El Kaïm and Laurence Grimaud</i>	
5.1	Introduction	159
5.2	Carboxylic Acid Surrogates	160
5.2.1	Thiocarboxylic Acids	160
5.2.2	Carbonic Acid and Derivatives	163
5.2.3	Selenide and Sulfide	165
5.2.4	Silanol	165
5.2.5	Isocyanic Acid and Derivatives	166
5.2.6	Hydrazoic Acid	167
5.2.7	Phenols and Derivatives	171
5.2.8	Cyanamide	179
5.3	Use of Mineral and Lewis Acids	180
5.3.1	Ugi and Passerini Reactions Triggered by Mineral Acids	181
5.3.2	Ugi and Passerini Reactions Triggered by Lewis Acids	184
5.4	Conclusions	189
	References	189
6	Amine (Imine) Component Surrogates in the Ugi Reaction and Related Isocyanide-Based Multicomponent Reactions	195
	<i>Mikhail Krasavin</i>	
6.1	Introduction	195
6.2	Hydroxylamine Components in the Ugi Reaction	196
6.3	Hydrazine Components in the Ugi Reaction	200
6.4	Miscellaneous Amine Surrogates for the Ugi Reaction	218
6.5	Activated Azines in Reactions with Isocyanides	220
6.6	Enamines, Masked Imines, and Cyclic Imines in the Ugi Reaction	223
6.7	Concluding Remarks	227
	Acknowledgments	227
	References	227

7	Multiple Multicomponent Reactions with Isocyanides	233
	<i>Ludger A. Wessjohann, Ricardo A.W. Neves Filho, and Daniel G. Rivera</i>	
7.1	Introduction	233
7.2	One-Pot Multiple IMCRs	234
7.2.1	Synthesis of Multivalent Glycoconjugates	236
7.2.2	Synthesis of Hybrid Peptide–Peptoid Podands	237
7.2.3	Covalent Modification and Immobilization of Proteins	240
7.2.4	Assembly of Polysaccharide Networks as Synthetic Hydrogels	241
7.2.5	Synthesis of Macromolecules by Multicomponent Polymerization	243
7.3	Isocyanide-Based Multiple Multicomponent Macrocyclizations	243
7.3.1	Synthesis of Hybrid Macrocycles by Double Ugi-4CR-Based Macrocyclizations	244
7.3.2	Synthesis of Macrobicycles by Threefold Ugi-4CR-Based Macrocyclization	246
7.4	Sequential Isocyanide-Based MCRs	248
7.4.1	Sequential Approaches to Linear and Branched Scaffolds	248
7.4.2	Sequential Approaches to Macrocycles	254
7.4.3	Convergent Approach to Natural Product Mimics	256
7.5	Conclusions	257
	References	258
8	Zwitterions and Zwitterion-Trapping Agents in Isocyanide Chemistry	263
	<i>Ahmad Shaabani, Afshin Sarvary, and Ali Maleki</i>	
8.1	Introduction	263
8.2	Generation of Zwitterionic Species by the Addition of Isocyanides to Alkynes	265
8.2.1	CH-Acids as Zwitterion-Trapping Agents	266
8.2.2	NH-Acids as Zwitterion-Trapping Agents	271
8.2.3	OH-Acids as Zwitterion-Trapping Agents	273
8.2.4	Carbonyl Compounds as Zwitterion-Trapping Agents	275
8.2.5	Imine Compounds as Zwitterion-Trapping Agents	278
8.2.6	Electron-Deficient Olefins as Zwitterion-Trapping Agents	279
8.2.7	Miscellaneous Compounds as Zwitterion-Trapping Agents	280
8.3	Generation of Zwitterionic Species by the Addition of Isocyanides to Arynes	283
8.4	Generation of Zwitterionic Species by the Addition of Isocyanides to Electron-Deficient Olefins	284
8.5	Miscellaneous Reports for the Generation of Zwitterionic Species	286
8.6	Isocyanides as Zwitterion-Trapping Agents	287
8.7	Conclusions	289
	Acknowledgments	289
	References	289

9	Recent Progress in Nonclassical Isocyanide-Based MCRs	299
	<i>Rosario Ramón, Nicola Kielland, and Rodolfo Lavilla</i>	
9.1	Introduction	299
9.2	Type I MCRs: Isocyanide Attack on Activated Species	300
9.3	Type II MCRs: Isocyanide Activation	308
9.4	Type III MCRs: Formal Isocyanide Insertion Processes	320
9.5	Conclusions	327
	Acknowledgments	327
	References	327
 10	 Applications of Isocyanides in IMCRs for the Rapid Generation of Molecular Diversity	 335
	<i>Muhammad Ayaz, Fabio De Moliner, Justin Dietrich, and Christopher Hulme</i>	
10.1	Introduction	335
10.2	Ugi/Deprotect/Cyclize (UDC) Methodology	337
10.2.1	Ugi-4CC: One Internal Nucleophile	337
10.2.2	TMSN ₃ -Modified Ugi-4CC: One Internal Nucleophile	343
10.2.3	Ugi-4CC: Two Internal Nucleophiles	344
10.2.4	Ugi-4CC: Three Internal Nucleophiles	347
10.2.5	Ugi-5CC: One Internal Nucleophile	348
10.3	Secondary Reactions of Ugi Products	350
10.3.1	Nucleophilic Additions and Substitutions	351
10.3.1.1	Alkylations	351
10.3.1.2	Mitsunobu Reactions	352
10.3.1.3	Lactonization and Lactamization	354
10.3.2	Base- or Acid-Promoted Condensations	355
10.3.3	Nucleophilic Aromatic Substitutions	355
10.3.4	Palladium-Mediated Reactions	356
10.3.5	Ring-Closing Metatheses	358
10.3.6	Staudinger–aza-Wittig Reactions	358
10.3.7	Cycloadditions	359
10.4	The Bifunctional Approach (BIFA)	361
10.4.1	Applications of Amino Acids	363
10.4.2	Applications of Cyclic Imines	365
10.4.3	Applications of Tethered Aldehyde and Keto Acids	366
10.4.4	Heterocyclic Amidines as a Tethered Ugi Input	371
10.4.5	Combined Bifunctional and Post-Condensation Modifications	372
	Acknowledgments	375
	Abbreviations	375
	References	376

11	Synthesis of Pyrroles and Their Derivatives from Isocyanides	385
	<i>Noboru Ono and Tetsuo Okujima</i>	
11.1	Introduction	385
11.2	Synthesis of Pyrroles Using TosMIC	386
11.3	Synthesis of Pyrroles Using Isocyanoacetates	391
11.3.1	Synthesis from Nitroalkenes	391
11.3.2	Synthesis from α,β -Unsaturated Sulfones	396
11.3.3	Synthesis from Alkynes	401
11.3.4	Synthesis from Aromatic Nitro Compounds: Isoindole Derivatives	402
11.4	Synthesis of Porphyrins and Related Compounds	407
11.4.1	Tetramerization	407
11.4.2	Meso-Tetraarylporphyrins via the Lindsey Procedure	412
11.4.3	[3+2] and [2+2] Methods	414
11.4.4	Expanded, Contracted, and Isomeric Porphyrins	414
11.4.5	Functional Dyes from Pyrroles	420
11.5	Conclusion	423
	References	424
12	Isocyanide-Based Multicomponent Reactions towards Benzodiazepines	431
	<i>Yijun Huang and Alexander Dömling</i>	
12.1	Introduction	431
12.2	1,4-Benzodiazepine Scaffolds Assembled via IMCR Chemistry	433
12.2.1	Two-Ring Systems	433
12.2.2	Fused-Ring Systems	440
12.3	1,5-Benzodiazepine Scaffolds Assembled via IMCR Chemistry	443
12.4	Outlook	446
	References	446
13	Applications of Isocyanides in the Synthesis of Heterocycles	451
	<i>Irini Akritopoulou-Zanze</i>	
13.1	Introduction	451
13.2	Furans	451
13.3	Pyrroles	453
13.4	Oxazoles	459
13.5	Isoxazoles	461
13.6	Thiazoles	464
13.7	Imidazoles	466
13.8	Pyrazoles	466
13.9	Oxadiazoles and Triazoles	470
13.10	Tetrazoles	471
13.11	Benzofurans and Benzimidazoles	473
13.12	Indoles	473
13.13	Quinolines	477

13.14	Quinoxaline	479
	Abbreviations	480
	References	480
14	Renaissance of Isocyanoarenes as Ligands in Low-Valent Organometallics	493
	<i>Mikhail V. Barybin, John J. Meyers, Jr, and Brad M. Neal</i>	
14.1	Historical Perspective	493
14.2	Isocyanidemetalates and Related Low-Valent Complexes	497
14.2.1	Introduction	497
14.2.2	Four-Coordinate Isocyanidemetalates and Redox-Related Complexes	497
14.2.3	Five-Coordinate Isocyanidemetalates	502
14.2.4	Six-Coordinate Isocyanidemetalates and Redox-Related Complexes	504
14.3	Coordination and Surface Chemistry of Nonbenzenoid Isocyanoarenes	508
14.3.1	Isocyanoazulenes	508
14.3.2	Organometallic η^5 -Isocyanocyclopentadienides	509
14.3.3	Homoleptic Complexes of Nonbenzenoid Isocyanoarenes	510
14.3.4	Bridging Nonbenzenoid Isocyanoarenes	514
14.3.5	Self-Assembled Monolayer Films of Nonbenzenoid Isocyano- and Diisocyanoarenes on Gold Surfaces	517
14.4	Conclusions and Outlook	521
	Acknowledgments	522
	References	523
15	Carbene Complexes Derived from Metal-Bound Isocyanides: Recent Advances	531
	<i>Konstantin V. Luzyanin and Armando J.L. Pombeiro</i>	
15.1	Introduction	531
15.2	Coupling of the Isocyanide Ligand with Simple Amines or Alcohols	532
15.3	Coupling of the Isocyanide Ligand with Functionalized Amines or Alcohols	537
15.4	Coupling of the Isocyanide Ligand with a Hydrazine or Hydrazone	537
15.5	Coupling of the Isocyanide Ligand with an Imine or Amidine	538
15.6	Intramolecular Cyclizations of Functionalized Isocyanide Ligands	540
15.7	Coupling of Isocyanides with Dipoles	543
15.8	Other Reactions	544
15.9	Final Remarks	546
	Acknowledgments	546
	References	547

16	Polyisocyanides	551
	<i>Niels Akeroyd, Roeland J.M. Nolte, and Alan E. Rowan</i>	
16.1	Introduction	551
16.1.1	Chiral Polymers	551
16.1.2	Polyisocyanides and Their Monomers	553
16.2	The Polymerization Mechanism	553
16.3	Conformation of the Polymeric Backbone	556
16.4	Polyisocyanopeptides	561
16.5	Polyisocyanides as Scaffolds for the Anchoring of Chromophoric Molecules	563
16.6	Functional Polyisocyanides	570
16.7	Conclusions and Outlook	575
	References	576
	Index	587