

TARGETS IN HETEROCYCLIC SYSTEMS

Chemistry and Properties

Volume 13 (2009)

Table of Contents

The N→C=O interaction: a weak bond with attractive properties for the deliberate exploitation in medicinal and supramolecular chemistry 1

Jens Hasserodt, Arnaud Gautier, Romain Barbe and Michael Waibel

1. The N→C=O interaction in natural products
 - 1.1. Discovery of a class of medium-sized cyclic alkaloids
 - 1.2. Crystal structure characterization: the Bürgi-Dunitz angle
 2. Physicochemical studies: dipole moment, pKa and spectroscopy
 3. Factors favouring the observation of the N→C=O interaction
 - 3.1. Preorganization
 - 3.2. Influence by the nature of the amine and carbonyl substituents
 - 3.3. Solvent influence and constitutional equilibria
 4. Molecular modeling: MM/QM
 5. Deliberate incorporation of the N→C=O motif by molecular design
 - 5.1. Enzyme inhibitor design
 - 5.1.1. General notions about aspartic peptidases
 - 5.1.2. Design of inhibitors for HIV-1 peptidase
 - 5.1.3. The N→C=O motifs as a transition state mimic in the design of HIV-1 peptidase inhibitors
 - 5.2. Foldamer design
 6. Conclusions
- Acknowledgments
- References

Multicomponent reactions involving heterocyclic surrogates of oxocarbenium and iminium ions 27

Federica Catti and Rodolfo Lavilla

1. Introduction
2. Povarov-type reactions
 - 2.1. Dihydropyridine-based Povarov reactions
 - 2.2. Four-component reactions with enol ethers
 - 2.3. Enol esters in Mannich-type multicomponent reactions
3. Isocyanide-based multicomponent reactions
 - 3.1. Hydro-, halo- and seleno-carbamoylation of cyclic enol ethers and dihydropyridines
 - 3.2. Benzimidazolium salts

- 3.3. Isocyanide addition to pyridinium salts
- 3.4. Reissert-Ugi reactions
- 4. Conclusions
- Acknowledgments
- References

Synthesis and chemistry of 3(2*H*)-furanones

57

Timm T. Haug and Stefan F. Kirsch

- 1. Introduction
- 2. Structural motif in natural compounds
 - 2.1. Spirocyclic furanones
 - 2.2. Germacranolides
 - 2.3. Non-spirocyclic 3(2*H*)-furanones
- 3. Medicinal chemistry
- 4. Synthetic strategies
 - 4.1. Cyclization/elimination approaches
 - 4.1.1. Bond formation between O1 and C5
 - 4.1.2. Bond formation between C4 and C5
 - 4.1.3. Bond formation between C2 and C3
 - 4.2. Substitution approaches
 - 4.3. Addition approaches
 - 4.4. Miscellaneous reactions
- 5. Selected applications in total synthesis
 - 5.1. Bullatenone
 - 5.2. Geiparvarin
 - 5.3. Jatrophone
 - 5.4. Longianone
 - 5.5. Trachyspic acid
 - 5.6. Azaspirene, pseurotin A and pseurotin F₂
 - 5.7. Eremantholide A
- 6. Reactivity of 3(2*H*)-furanones
 - 6.1. Alkylations and related reactions
 - 6.2. Ring modifications
 - 6.3. Photochemical reactions
 - 6.4. Cycloadditions
- 7. Conclusions
- Acknowledgments
- References

Ethynylation of pyrrole nucleus with haloacetylenes on active surfaces

92

Boris A. Trofimov and Lyubov N. Sobenina

1. Introduction
 2. Reactions of pyrroles, 4,5,6,7-tetrahydroindoles and indoles with haloacetylenes on active surfaces
 - 2.1. Discovery of the reaction of pyrroles with haloacylacetylenes on active surfaces
 - 2.2. A deeper insight into the reaction of 2-arylpyrroles with benzoylbromoacetylene
 - 2.3. The ethynylation of 1-vinylpyrroles with benzoylbromoacetylene on alumina
 - 2.4. Effect of active surfaces on the pyrrole ethynylation with haloacetylenes
 - 2.5. The ethynylation of 4,5,6,7-tetrahydroindoles with halopropynoates on active surfaces
 - 2.6. The ethynylation of indoles with benzoylbromoacetylene on alumina
 3. A peculiarity of the C-ethynylpyrroles and -indoles reactivity
 4. Rotational isomerism of 2-(2-benzoylethynyl)-5-phenylpyrrole in crystal state
 5. Conclusions
- Acknowledgments
- References

Access to spirocyclic piperidines, important building blocks in medicinal chemistry

120

Yves Troin and Marie-Eve Sinibaldi

1. Introduction
2. 3-Spiropiperidines
 - 2.1. General retrosynthetic pathways
 - 2.2. Approaches by construction of the spirocycle from a preformed piperidine ring
 - 2.2.1. From 1,5-dicarbonyl compounds (*route I-A*)
 - 2.2.2. Reductive cyclization (*route I-A*)
 - 2.2.3. RCM (*route I-A*)
 - 2.2.4. Mitsunobu reaction (*route I-B*)
 - 2.2.5. Metal-catalyzed cyclizations (*route I-B*)
 - 2.2.6. Use of phenyloxazolopiperidine (*route I-B*)
 - 2.2.7. [1-3]-Dipolar cycloaddition (*route I-B*)
 - 2.2.8. Diels-Alder (*route I-C*)
 - 2.3. Approaches by construction of the piperidine ring from a carbocyclic ring in place
 - 2.3.1. Radical cyclization (*route II-D*)
 - 2.3.2. Photocyclization (*route II-D*)
 - 2.3.3. N-Acyliiminium ion cyclization (*route II-D*)
 - 2.3.4. Use of cyclohexadiene-Fe(CO)₃ (*route II-D*)
 - 2.3.5. Lactamization (*route II-E*)
 - 2.3.6. Hydroamination (*route II-E*)
3. 4-Spiropiperidines
 - 3.1. General retrosynthetic pathways
 - 3.2. Approaches by construction of the spirocycle from a preformed piperidine ring

- 3.2.1. Fischer indole reaction (*route III-F*)
- 3.2.2. Palladium-catalyzed cyclization (*route III-F*)
- 3.2.3. Radical cyclization (*route III-F*)
- 3.2.4. From 4-piperidone (*route III-G*)
- 3.3. Approaches by construction of the piperidine ring
 - 3.3.1. Amine condensation (*route IV-H*)
 - 3.3.2. Nucleophilic substitution (*route IV-H*)
 - 3.3.3. Anionic cycloacylation of carbamate (*route IV-I*)
- 3.4. Multi-component reaction
- 4. Conclusion
- References

Most relevant recent enantioselective synthesis of pyrrolidenes and piperidines

147

Xavier Companyó, Andrea-Nekane Alba and Ramon Rios

- 1. Introduction
- 2. Enantioselective synthesis of piperidines
 - 2.1. Metal catalyzed approaches
 - 2.2. Organocatalytic approaches
- 3. Enantioselective synthesis of pyrrolidines
 - 3.1. Metal catalyzed approaches
 - 3.2. Organocatalytic approaches
- 4. Conclusions
- References

Synthesis of pyridines by [2+2+2]-cyclootrimerization of alkynes with nitriles

175

Pavel Turek and Martin Kotora

- 1. General considerations
 - 1.1. History
 - 1.2. Reaction mechanism and regiochemistry
 - 1.3. Catalysts
 - 1.4. Regioselectivity
- 2. Synthesis of natural compounds and their congeners
- 3. Synthesis of potentially biologically active compounds
- 4. Synthesis of pyridines and bipyridines
- 5. Synthesis of pyridine based chiral ligands and catalysts
- 6. Enantioselective cyclootrimerization catalyzed by chiral catalysts
- 7. Other applications
- 8. Conclusion
- Acknowledgment
- References

Recent developments in the synthesis of dihydropyridines (DHPs) and dihydropyrimidines (DHPMs)

201

Julie Moreau, Jean-Pierre Hurvois, Mbaye Diagne Mbaye and Jean-Luc Renaud

1. Introduction
 2. Brønsted and Lewis acids catalyzed Hantzsch type synthesis of 1,4-dihydropyridines (DHPs)
 - 2.1. Recent synthesis of 1,4-DHPs
 - 2.1.1. Brønsted acid catalysis
 - 2.1.2. Lewis acid catalysis
 - 2.2. Synthesis of optically active 1,4-DHPs
 - 2.2.1. Enzyme-catalyzed enantioselective differentiation
 - 2.2.2. Diastereoselective synthesis of 1,4-DHPs
 - 2.2.2.1. Diastereoselective cyclizations
 - 2.2.2.2. Selective reduction of pyridines and pyridinium salts
 - 2.3. Enantioselective catalytic syntheses of 1,4-DHPs
 3. Brønsted and Lewis acids catalyzed Biginelli reaction
 - 3.1. Recent synthesis of dihydropyrimidines (DHPMs)
 - 3.1.1. Lewis acid catalysis
 - 3.1.2. Brønsted acid catalysis
 - 3.1.3. Miscellaneous
 - 3.2. Synthesis of chiral DHPMs
 - 3.2.1. Chemical and enzymatic resolution of racemic DHPMs
 - 3.2.2. Diastereoselective approaches
 - 3.2.3. Enantioselective synthesis
 4. Conclusion
- Acknowledgments
- References

C2-Functionalized furans as dienes in [4+3] cycloaddition reactions

231

Ángel M. Montaña, Pedro M. Grima and Consuelo Batalla

1. Introduction
 - 1.1. The [4+3] cycloaddition reaction
 - 1.2. Concerted and stepwise mechanisms
2. C2-Functionalized furans as dienes in [4+3] cycloadditions: a study of the stereo-electronic factors controlling the diastereoselectivity
3. General method of assignment of relative stereochemistry in C-1 substituted cycloadducts by ¹H- and ¹³C-NMR correlations
 - 3.1. Complete assignment of the ¹H- and ¹³C-NMR spectra of the diastereomeric pairs
 - 3.2. Comparative analysis of ¹H-NMR spectra for **20a** and **20b**
 - 3.3. Correlation of ¹³C spectra of **20a** and **20b**
 - 3.4. General method of relative stereochemistry assignment based on NMR correlation

4. Improvement and optimization of the [4+3] cycloaddition reaction: generation of oxyallyl cations by reduction of α,α' -diiodoketones under very mild sonochemical or thermal conditions

Acknowledgments

References

Methods for the synthesis of rhazinilam and its analogues

252

Inga Kholod and Reinhard Neier

1. Pyrrole containing natural products
2. Isolation and structure determination of rhazinilam and its analogues
 - 2.1. Isolation of rhazinilam
 - 2.2. Structure determination of rhazinilam
 - 2.3. Putative formation of (*R*)-(-)-rhazinilam from other natural products
 - 2.4. Isolation of analogues of rhazinilam
3. Overview of the published total syntheses of *rac*-rhazinilam and of (*R*)-(-)-rhazinilam
 - 3.1. Published total syntheses of rhazinilam
 - 3.1.1. First total synthesis of rhazinilam by Smith
 - 3.1.2. The two total syntheses of rhazinilam of Sames: *rac*-rhazinilam and (*R*)-(-)-rhazinilam
 - 3.1.2.1. The first total synthesis of racemic rhazinilam of Sames
 - 3.1.2.2. Sames' second enantioselective total synthesis of (*R*)-(-)-rhazinilam
 - 3.1.3. Total synthesis of *rac*-rhazinilam of Magnus
 - 3.1.4. Total synthesis of *rac*-rhazinilam of Trauner
 - 3.1.5. Total synthesis of (*R*)-(-)-rhazinilam of Nelson
 - 3.1.6. Total synthesis of (*R*)-(-)-rhazinilam of Banwell
 - 3.2. Overview of the published total syntheses of analogues of rhazinilam
 - 3.2.1. Rhazinal
 - 3.2.1.1. Total syntheses of *rac*- and (*R*)-(-)-rhazinal of Banwell
 - 3.2.1.2. Total synthesis of *rac*-rhazinal of Trauner
 - 3.2.2. Rhazinicine
 - 3.2.3. Leuconolam and *epi*-leuconolam
4. Summary and conclusions

Acknowledgments

References

Metal-catalyzed electrophilic cyclization reactions in the synthesis of heterocycles

273

Félix Rodríguez and Francisco J. Fañanás

1. Introduction
2. Mechanism and general aspects of the metal-catalyzed electrophilic cyclization
3. Oxygen-centred nucleophiles

- 3.1. Cyclization of alcohols
 - 3.1.1. Intramolecular addition to alkynes
 - 3.1.2. Intramolecular addition to alkenes
 - 3.1.3. Intramolecular addition to allenes
 - 3.2. Cyclization of carboxylic acids
 - 3.2.1. Intramolecular addition to alkynes
 - 3.2.2. Intramolecular addition to alkenes
 - 3.2.3. Intramolecular addition to allenes
 - 3.3. Cyclization of amides, carbonates and carbamates
 - 3.4. Cyclization of aldehydes and ketones
 - 3.4.1. Intramolecular addition to alkynes
 - 3.4.2. Intramolecular addition to allenes
 - 3.5. Cyclization of ethers and acetals. Intramolecular addition to alkynes
 - 4. Nitrogen-centred nucleophiles
 - 4.1. Cyclization of amines
 - 4.1.1. Intramolecular addition to alkynes
 - 4.1.2. Intramolecular addition to alkenes
 - 4.1.3. Intramolecular addition to allenes
 - 4.2. Cyclization of amides, carbamates and trichloroacetimidates
 - 4.2.1. Intramolecular addition to alkynes
 - 4.2.2. Intramolecular addition to allenes
 - 4.3. Cyclization of imines
 - 5. Cascade reactions initiated by a metal-catalyzed electrophilic cyclization
 - 6. Conclusions
- Acknowledgments
- References

Stereoselective synthesis of optically active pyridyl alcohols. Part I: pyridyl *sec*-alcohols

303

Giorgio Chelucci

- 1. Introduction
- 2. Pyridyl *sec*-alcohols
 - 2.1. Addition of 2-pyridyllithium derivatives to chiral aldehydes
 - 2.2. Addition of chiral 2-pyridyllithium derivatives to aldehydes
 - 2.3. Stereoselective addition of organometallic reagents to pyridyl carboxaldehydes
 - 2.3.1. Enantioselective addition
 - 2.3.2. Diastereoselective addition
 - 2.4. Rearrangement of pyridine *N*-oxides
 - 2.5. Reduction of pyridyl ketones
 - 2.5.1. Stoichiometric enantioselective reduction
 - 2.5.2. Catalytic enantioselective reduction

- 2.5.2.1. Borane reduction
- 2.5.2.2. Hydrogenation transfer reactions
- 2.5.2.3. Hydrogenation
- 2.5.3. Stoichiometric diastereoselective reduction
- 2.5.4. Catalytic diastereoselective reduction
- 2.6. Cyclotrimerization of chiral 2-hydroxynitriles
- 2.7. Asymmetric dihydroxylation
- 2.8. Chiral aziridine and epoxide ring opening
- 3. Conclusion
- 4. Note added in proof
- Acknowledgments
- References

ISBN 978-88-86208-62-8 ISSN 1724-9449

XII+346 pp

Euro 80.00 + postal expenses