

52

Topics in Heterocyclic Chemistry

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Aims and Scope

The series Topics in Heterocyclic Chemistry presents critical reviews on present and future trends in the research of heterocyclic compounds. Overall the scope is to cover topics dealing with all areas within heterocyclic chemistry, both experimental and theoretical, of interest to the general heterocyclic chemistry community.

The series consists of topic related volumes edited by renowned editors with contributions of experts in the field. All chapters from Topics in Heterocyclic Chemistry are published OnlineFirst with an individual DOI. In references, Topics in Heterocyclic Chemistry is abbreviated as Top Heterocycl Chem and cited as a journal.

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Viktor Krchňák

Editor

Solid-Phase Synthesis of Nitrogenous Heterocycles

With contributions by

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A. La-Venia · E.G. Mata · M. Meldal · E. Schütznerová ·
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ISSN 1861-9282 ISSN 1861-9290 (electronic)
Topics in Heterocyclic Chemistry
ISBN 978-3-319-58615-1 ISBN 978-3-319-58616-8 (eBook)
DOI 10.1007/978-3-319-58616-8

Library of Congress Control Number: 2017942797

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The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

In 1963 Robert Bruce Merrifield forever changed peptide synthesis when he revealed the concept of solid-phase (SP) peptide synthesis [1]. Merrifield's approach simplified isolation of intermediates during traditional stepwise peptide synthesis. The carboxy-terminal *N*-protected amino acid was covalently attached to insoluble polymeric support. Resin beads of polystyrene cross-linked with divinylbenzene served as the solid phase. Even to this day, this support is the most frequently used in all aspects of SP synthesis. In practice, SP peptide synthesis consisted of repetitive use of two steps: removing the amino acid *N*-protecting group and coupling of the next *N*-protected amino acid. After each step, simply washing the resin beads can isolate the resin-bound intermediates.

The potential of SP synthesis for general organic chemistry was soon recognized, including Henry Rapoport [2] who realized the unique advantages of SP synthesis. However, it was not until the era of combinatorial chemistry, started in the early 1990s by Kit Lam [3] and Richard A. Houghten [4], that SP organic synthesis started to flourish. Pooling of resin-bound intermediates enabled synthesis of large chemical libraries. The first SP heterocycle synthesis was reported from Jonathan A. Elman's laboratory [5].

SP synthesis of heterocycles expanded Merrifield's original idea by applying a sequence of unrelated organic reactions on resin-bound intermediates. Obviously, each step of the SP heterocycle synthesis needs to be fine-tuned to provide the highest possible purity of resin-bound intermediates, because the intermediates cannot be purified. The successful SP synthesis needs to master not only two reactions used for peptide synthesis (acylation and *N*-protecting group cleavage), but to optimize all reactions involved in synthesis.

Critical advantages of SP synthesis include very efficient isolation of intermediates by simply washing reagents away from the resin beads with organic solvents. Unlike synthesis in solution, the isolation timing is therefore very predictable and allows multiple syntheses to be conducted at the same time. Because of simple reaction solvent removal, high boiling solvents such as DMF and DMSO can beneficially be used without the need for evaporation.

On the other hand, SP synthesis requires detailed optimization of reaction conditions for each step of the synthesis, excess of reagents to drive the reaction to completion, and excludes chemical transformations using heterogeneous components (e.g. catalyst).

The five chapters in this book describe different facets of SP heterocycle synthesis. The first chapter by Greg A. Slough is included to inspire novices in SP synthesis and describes details of each of the SP synthesis aspect. He has proven that SP synthesis can be carried out in any organic chemistry laboratory, without significant investment, using a plastic syringe equipped with a porous disc served as a reaction vessel for manual SP synthesis.

Veronika Fülöpová and Miroslav Soural summarize the rich literature dedicated to the synthesis of seven-membered nitrogenous heterocycles including notoriously known pharmacophores such as benzodiazepines. This chapter shows that numerous different routes are applicable for SP synthesis of the same type of heterocycle, and chemists can select a route best suited for a given project's needs.

Morten Meldal's laboratory dedicates substantial effort to developing very powerful cyclic iminium – nucleophilic addition cascade reactions. Together with Frederik Diness and Yuanyuan Wang as co-authors they contribute a chapter documenting the power of this cascade reaction for SP synthesis of diverse fused and bridged molecular scaffolds applicable as peptidomimetics.

Agustina La-Venia, Carina M. L. Delpiccolo and Ernesto G. Mata focus on methodology and their chapter discusses metal-mediated synthesis of heterocyclic compounds. This area, in particular, is a growth area in heterocyclic chemistry, and we can expect more critical contributions in coming years.

The last contribution by Eva Schütznerová and Viktor Krcchňák describes syntheses of diverse nitrogenous heterocycles based on C-arylation reaction of 2-nitrobenzene sulfonamides. Interestingly, these synthetic routes were developed for SP in an arena with no precedents for synthesis in solution.

To conclude, individual chapters in this book document that SP synthesis can provide the ultimate solution to very efficient synthesis of structurally diverse heterocyclic compounds.

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Viktor Krcchňák

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Contents

Solid-Phase Synthesis of Heterocycles in Practice	1
Greg A. Slough	
Solid-Phase Synthesis of Seven-Membered Heterocycles with Two Nitrogen Atoms	23
Veronika Fülöpová and Miroslav Soral	
Intramolecular N-Acyliminium Cascade (INAIC) Reactions in Cyclization of Peptide-Like Molecules	65
Frederik Diness, Yuanyuan Wang, and Morten Meldal	
Advances in Metal-Mediated Solid-Phase Synthesis of Heterocyclic Compounds	95
Agustina La-Venia, Carina M.L. Delpiccolo, and Ernesto G. Mata	
Intramolecular Arylation of 2-Nitrobenzenesulfonamides: A Route to Diverse Nitrogenous Heterocycles	139
Eva Schütznerová and Viktor Krchňák	
Index	167