Edited by
J. Zhu, H. Bienaymé

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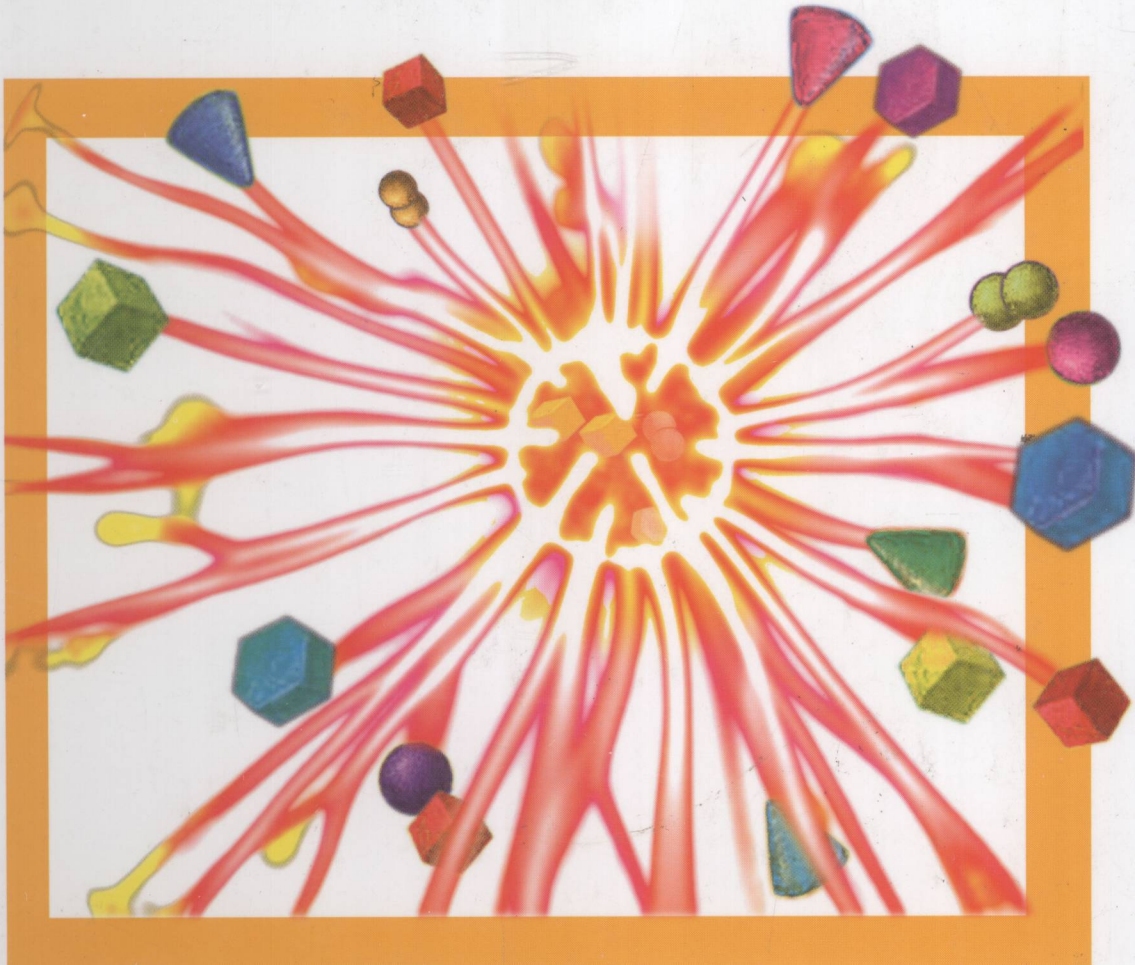

Multicomponent Reactions

Edited by Jieping Zhu, Hugues Bienaymé

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Preface

The length of a synthesis is dependent upon the average molecular complexity produced per operation, which depends in turn on the number of chemical bonds being created. Therefore, devising reactions that achieve multi-bond formation in one operation is becoming one of the major challenges in searching for step-economic syntheses. By today's standards, besides being regio-, chemo- and stereoselective, an ideal multi-bond-forming process should satisfy the following additional criteria: (a) readily available starting materials; (b) operationally simple; (c) easily automatable; (d) resource effective (personnel, time, cost etc); (e) atom economical; and (f) ecologically benign. Multicomponent reaction (MCR) processes, in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the components, naturally comply with many of these stringent requirements for ideal organic syntheses.

Multicomponent reactions, though fashionable these days, have in fact a long history. Indeed, many important reactions such as the Strecker amino acid synthesis (1850), the Hantsch dihydropyridine synthesis (1882), the Biginelli dihydropyrimidine synthesis (1891), the Mannich reaction (1912), and the isocyanide-based Passerini reactions (1921) and Ugi four-component reactions (Ugi-4CRs) (1959), among others, are all multicomponent in nature. In spite of the significant contribution of MCRs to the state of the art of modern organic chemistry and their potential use in complex organic syntheses, little attention was paid to the development of novel MCRs in the second half of the twentieth century. However, with the introduction of molecular biology and high-throughput biological screening, the demand on the *number* and the *quality* of compounds for drug discovery has increased enormously. By virtue of their inherent convergence and high productivity, together with their exploratory and complexity-generating power, MCRs have naturally become a rapidly evolving field of research and have attracted the attention of both academic and industrial scientists.

The development of novel MCRs is an intellectually challenging task since one has to consider not only the reactivity match of the starting materials but also the reactivities of the intermediate molecules generated *in situ*, their compatibility, and their compartmentalization. With advances in both theory and mechanistic insights into various classic bimolecular reactions that allow for predictive analysis of reaction sequences, the development and control of new reactive chemical

entities, and the availability of new technologies that activate otherwise "inactive" functional groups, we are optimistic that many new and synthetically useful MCRs will be developed in the coming years.

As enabling technology, the development and application of MCRs are now an integral part of the work of any major medical research unit. It is nevertheless important to point out that MCRs have contributed to drug development, from lead discovery and lead optimization to production, long before the advent of combinatorial technologies. The one-step synthesis of *nifedipine* (Adalat®), a highly active calcium antagonist, by a Hantsch reaction is a classic demonstration. A more recent example is the synthesis of piperazine-2-carboxamide, the core structure of the HIV protease inhibitor Crixivan®, by a Ugi-4CR. We believe that the impact of MCRs on both target-oriented and diversity-oriented syntheses will become stronger and stronger as we enter the post-genomic era in this new millennium.

In editing this book, we were fortunate to be associated with more than a dozen experts who were willing to devote the time and effort required to write their contributions. These distinguished chemists are highly knowledgeable in the area reviewed, have contributed to its development, and are uniquely able to provide valuable perspectives. We are truly indebted to all the authors for their professionalism, their adherence to schedules, their enthusiasm, and most of all, their high-quality contributions. We thank all of our collaborators at Wiley-VCH, especially Dr. Elke Maase for her invaluable help from the conception to the realization of this project.

We hope that this monograph will be of value to both expert and novice practitioners in this area, further stimulating the development and application of novel MCRs and providing an appropriate perspective with which to evaluate the significance of new results.

Gif-sur-Yvette and Lyon, France
September 2004

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Contents

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1
Asymmetric Isocyanide-based MCRs

Luca Banfi, Andrea Basso, Giuseppe Guanti, and Renata Riva

1.1
Introduction

Although the great utility of isonitrile-based multicomponent reactions in assembling complex pharmacologically important structures in a small number of steps and with the possibility of several diverse inputs is widely recognized [1, 2], the stereochemical issues still represent a challenge. Usually in Passerini and Ugi reactions (P-3CRs and U-4CRs) a new stereogenic center is generated, but most reactions reported so far suffer from low or absent stereoselectivity. It seems that MCRs are following the evolutionary trend experienced in the past by conventional organic syntheses. While in the 1960s and 1970s the main efforts were directed toward the discovery of new reactions, in the 1980s and 1990s the focus moved towards selectivity, in particular stereoselectivity, leading to highly efficient methodologies. For MCRs it is probable that the same thing will happen. Promising results are already appearing in the literature. We can foresee that in the next 20 years more and more researchers will dedicate their skills and ingenuity to devise methods to control the stereoselectivity in P-3CR and U-4CR, as well as in other less well-known isonitrile-based MCRs. We hope that this chapter may help to stimulate these efforts by describing the present state of the art.

1.2
Racemization Issues

Since asymmetric induction in P-3CRs or U-4CRs is achieved in most cases by using one or more chiral components in enantiomerically pure form, it is important to assess the possibility of racemization under the reaction conditions. While this does not seem to be a problem for carboxylic acid and amine components, there are some reports of racemization of chiral aldehydes or isocyanides.

For example, aldehydes having an α-alkyl substituent have been reported to be stereochemically unstable during Ugi condensation [3]. On the contrary, α-alkoxy substituted aldehydes do not racemize.

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