

# Guidebook to Organic Synthesis

3rd Edition

有机合成指南 第3版

Raymond K Mackie  
David M Smith  
R Alan Aitken

世界图书出版公司

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Third Edition

Raymond K. Mackie, David M. Smith and R. Alan Aitken

*School of Chemistry, University of St Andrews*

世界图书出版公司

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## Foreword

by Professor Sir John Cadogan, C.B.E., F.R.S.

It is now eight years since the publication of the second edition of this remarkably useful Guidebook to the art and science of organic synthesis, a subject which is now even more important.

It is arguable that in this century we have seen five major scientific and engineering events that have changed the world. We began with the revolution in understanding of chemistry in all its forms, which led inexorably to the key place still occupied by the world's chemical and pharmaceutical industries. Then came powered flight, nuclear fission and the transistor. Now, as we enter the new Millennium, we have the cracking of the human genome code, based on the amazing revelation of the chemical structure of DNA.

The post-genome world will be a startlingly different place. The 100,000 or so genes will become books of instruction about the living world. But they are not books of information. We first have to uncover the function of each gene and the resulting big proteins and hence, through modelling and combinatorial chemistry, the nature of the vital small molecules which will be needed to exploit the potential of this genomic intelligence. This is where the artists – the synthetic organic chemists – will have their new day. They will be needed more rather than less.

The authors are extraordinarily well placed to lay the foundations of organic synthesis in the minds of the new generation. Through their long experience with teaching and guiding generations of students at first bemused by the increasing multitudes of synthetic methods, routes, approaches, concepts, scenarios, they can show the way with confidence. This Guidebook is for the benefit of these students, and builds on the remarkable success of the first two editions. The authors have contrived to combine the traditional with the new to give a readable and easily digested guide to the essentials of organic synthesis, which will be even more valuable to the new generations of students – and their teachers!

John Cadogan

Imperial College, London

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## Preface to the third edition

Eight years have passed since the second edition of this book was published, and it is now almost 20 years since two of us (R.K.M. and D.M.S.) began work on the original *Guidebook*. This new version, like its predecessors, is designed for students who are beginning a serious and detailed study of organic synthesis. It is assumed that they will already have completed a course in elementary organic chemistry which includes the reactions of simple functional groups, and the basic concepts of reaction mechanism and stereochemistry. We have particularly in mind students in the third and fourth years of a Scottish Honours Chemistry course (including the still-new M.Chem. degree programme) and their counterparts elsewhere in the world.

The evident timeliness of the original *Guidebook*, and the continuing popularity of its successor, have persuaded our publishers to commission a third edition. Organic synthesis continues to be a rapidly developing subject at the present time, and it behoves every author to keep abreast of the most recent developments. On the other hand, the fundamental principles upon which synthetic methodology is based do not change, and we believe that students must have mastered these basic ideas before they will be able to appreciate the more advanced aspects of the subject.

In this third edition, only one chapter is completely new, *viz.* Chapter 10 (Protective groups). This chapter was not updated in the second edition, and the many recent protective group developments in, for example, the syntheses of biologically active compounds made a new version of this chapter essential. A section on regiochemistry and stereochemistry has been added to Chapter 2, which has been given a new title; Chapter 5 has been expanded to include sections on sulfonium ylides and nucleophilic acylation; Chapter 8 (Reduction) and Chapter 9 (Oxidation) have been enlarged; and we have of course taken the opportunity to make minor additions and amendments elsewhere, wherever appropriate.

Those readers who are familiar with the second edition will note a number of changes in the format of this new version. A summary is provided at the end of each chapter, in the hope that this will help students to appreciate the chapter's salient points more easily. The structural formulae throughout the book have been redrawn, using a more up-to-date computer package, and the clarity of

the figures is thereby greatly improved. All the footnotes have been collected at the end of the text and the further reading list has been updated to the end of 1997.

As in the previous editions of this book, we have made extensive cross-reference throughout the text to Dr Peter Sykes' *A Guidebook to Mechanism in Organic Chemistry*, the page numbers referring to the sixth edition (Longman, 1986), and we have taken the opportunity to make cross-references to Dr Sheila Buxton and Professor Stanley Roberts' *Guide to Organic Stereochemistry* (Longman, 1996). Dr Sykes' newer and shorter book, *A Primer to Mechanism in Organic Chemistry* (Longman, 1995), although not specifically mentioned in cross-references, nevertheless offers guidance on fundamental mechanistic principles which will be of value to the less experienced reader.

As in the two previous editions, we have not provided a chapter, or chapters, on the use of transition metals in organic synthesis. While we acknowledge the importance of, and the current interest in, such processes, and while we apologize to any who may be offended by this omission, the choice of material for a book of this size and at this level is not an easy one, and there are more specialized textbooks devoted exclusively to transition-metal-mediated organic reactions.

As always, we remain grateful to our students here, and to our colleagues in St Andrews and elsewhere, for their helpful comments and suggestions, and (usually helpful!) criticisms. We are also grateful for the continuing friendly collaboration with Longman's staff, among whom we thank especially Alexandra Seabrook, Shuet-Kei Cheung and Pauline Gillett.

St. Andrews  
April 1998

R.K.M.  
D.M.S.  
R.A.A.

### **Important notice**

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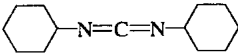
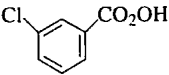
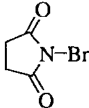



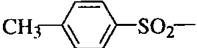
This book is not intended to be a 'recipe book' for the experimentalist. The reactions cited here should be regarded merely as an illustration of the general principles; readers seeking to use these reactions in practice are *strongly advised* to refer first to the original literature for experimental details.

Readers are also reminded of the various hazards entailed in organic chemical reactions, and of the consequent need for proper safety precautions. The fire hazard associated with many common solvents is well known, but particular care must also be taken where a compound is liable to be explosive (e.g. azides, diazo-compounds), corrosive (e.g. phenols), skin-irritant, toxic (e.g. methylating agents) or carcinogenic (e.g. benzene, *N*-nitroso compounds and certain arylamines). Further details of such hazards, and safety precautions, are to be found in practical handbooks, e.g. in Vogel's *Textbook of Practical Organic Chemistry* (fifth edition, Longman, 1989).



## Abbreviations and trivial names

The following terms are used throughout the text without further explanation. Other abbreviations which are used only in specific chapters are explained at the appropriate point in the text.

DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide	
Diglyme	Diethylene glycol dimethyl ether	$\text{CH}_3\text{O}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OCH}_3$
Digol	Diethylene glycol	$\text{HO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OH}$
DME	1,2-Dimethoxyethane	$\text{CH}_3\text{O}(\text{CH}_2)_2\text{OCH}_3$
DMF	<i>N,N</i> -Dimethylformamide	$(\text{CH}_3)_2\text{NCHO}$
DMSO	Dimethyl sulfoxide	$(\text{CH}_3)_2\text{SO}$
HMPA	Hexamethylphosphoramide	$[(\text{CH}_3)_2\text{N}]_3\text{P}=\text{O}$
LDA	Lithium diisopropylamide	$[(\text{CH}_3)_2\text{CH}]_2\text{N}^- \text{Li}^+$
MCPBA	<i>m</i> -Chloroperoxybenzoic acid	
NBS	<i>N</i> -Bromosuccinimide	
Ph	Phenyl	
Sulfolane	Tetramethylene sulfone (tetrahydrothiophene dioxide)	
THF	Tetrahydrofuran	
Ts or tosyl	<i>p</i> -Toluenesulfonyl	

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## Chapter 1

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### Introduction

Of the principal constituent parts of present-day organic chemistry, synthesis is the one with perhaps the longest history. The ideas of functionality and stereochemistry, for example, have their origins in the second half of the nineteenth century, and the concepts of bonding and reaction mechanism, as we know them today, undoubtedly belong to the present century. Synthesis, however, has constituted an important part of organic chemistry from the very beginning of the subject and thus has a history stretching back over many centuries. It has to be admitted, however, that most of the early work was fragmentary in character, depending as it did on starting materials isolated from natural sources in doubtful states of purity; the *development* of organic synthesis on a systematic basis belongs to the nineteenth century, even if its *origins* are much earlier.

In more recent times, the growth of organic synthesis has kept pace with the growth of organic chemistry as a whole. As understanding of structural and theoretical chemistry has increased, and as experimental methods have been developed and refined, chemists have been able to set themselves more and more ambitious synthetic objectives. These lead in turn to the discovery of new reactions and to the perfection of new experimental methods, and thence to new synthetic targets, and so on. Thus present-day organic synthesis often appears to the student as a vast assembly of factual information without much by way of structure or rationale.

During the 1950s and 1960s, the teaching of functional group chemistry was revolutionized, and in most cases greatly simplified, by the use of reaction mechanism. The corresponding revolution in the teaching of synthesis belongs mainly to the 1970s and early 1980s, and is now well established.

The fundamental ideas which lie behind this revolution, however, are neither complicated nor new. They consist of recognizing that a covalent bond is formed, in the vast majority of synthetically useful processes, by the interaction of an electrophilic atom and a nucleophilic atom, and in recognizing the various structural units (called *synthons*) which go to make up a given synthetic target molecule. These ideas have been familiar to synthetic chemists for decades but have been formalized only in relatively recent times.

[It should be noted that the word *synthon*, which was introduced by the American chemist E. J. Corey around 30 years ago, has become one of the



most misused words in organic chemistry. Many present-day authors use the word, incorrectly, to describe the *reagent* which serves as a means of introducing a particular grouping or functionality into a molecule.]

In 1835, the German chemist Friedrich Wöhler, who was one of the pioneers of organic synthesis, wrote a letter to his mentor, the great Jöns Jacob Berzelius, which included the following often-quoted remarks:<sup>1</sup>

Organic chemistry just now is enough to drive one mad. It gives me the impression of a primeval tropical forest, full of the most remarkable things; a monstrous and boundless thicket, with no way of escape, into which one may well dread to enter.

Any readers of this book who feel like that about organic *synthesis* are encouraged to read on. This Guidebook has been written especially for them. It may not lead them right through the forest, but we hope that it will at least provide a reliable pathway, over solid ground, as far as the first clearing.