Comprehensive Organic Functional Group Transformations

Volume 2

Comprehensive Organic Functional Group Transformations

UK	Elsevier Science Ltd., The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK
USA	Elsevier Science Inc., 660 White Plains Road, Tarrytown, New York 10591-5153, USA
JAPAN	Elsevier Science Japan, Tsunashima Building Annex, 3-20-12 Yushima, Bunkyo-ku, Tokyo 113, Japan

First edition 1995

Library of Congress Cataloging in Publication Data
Comprehensive organic functional group transformations / editors-in-chief, Alan R. Katritzky, Otto Meth-Cohn, Charles W. Rees. — 1st ed.
p. ; cm.
Includes indexes.
Contents: v. 1. Synthesis: carbon with no attached heteroatoms / edited by Stanley M. Roberts — v. 2. Synthesis: carbon with one heteroatom attached by a single bond / edited by Steven V. Ley — v. 3. Synthesis: carbon with one heteroatom attached by a multiple bond / edited by Gerald Pattenden — v. 4. Synthesis: carbon with two heteroatoms, each attached by a single bond / edited by Gordon W. Kirby — v. 5. Synthesis: carbon with two attached heteroatoms with at least one carbon-to-heteroatom multiple link / edited by Christopher J. Moody — v. 6. Synthesis: carbon with three or four attached heteroatoms / edited by Thomas L. Gilchrist — v. 7. Indexes.
1. Organic compounds—Synthesis. I. Katritzky, Alan R. II. Meth-Cohn, Otto. III. Rees, Charles W.
QD262.C534 1995
547'.2—dc20 95–31088

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library.

ISBN 0–08–040604–1 (set : alk. paper)
ISBN 0–08–042323–X (Volume 2)

♾™ The paper used in this publication meets the minimum requirements of the American National Standard for Information Sciences—Permanence of Paper for Printed Library Materials, ANSI Z39.48–1984.

Printed and bound in Great Britain by Cambridge University Press, Cambridge, UK.

Preface

Some years ago the three of us met in a London club reviewing an ongoing publishing venture in Organic Synthesis. The conversation drifted to a consideration of volumes on the synthesis of key functional groups. No doubt the good wine helped since we actually broached the idea of a work on the synthesis of *all* functional groups. Would it be useful? Definitely. Would it be feasible? How would it be organized? Where do you start? We recognized that functionality was based on the coordination and heteroatom attachment of a carbon atom. But putting together a complete framework seemed particularly daunting. Two of us became very interested in the fascinating bouquet of the Muscat de Beaumes de Venise.

At our next dinner together Alan announced that he had solved the problems posed last time—problems that Charles and I hoped he had forgotten! He brought out a remarkable matrix analysis of *all* functional groups, analysed rigorously and logically. Even unknown functions were covered. Although we were all very impressed, the practicalities of the idea still seemed daunting. Those who know Alan's terrier instincts will appreciate that he would not give up such a challenge so easily. Our twice yearly club get-togethers, occasionally with friends from Pergamon, refined our thinking. Alan's cosmic vision was tempered by Charles's intuitive realism and fully supported by the publishers.

Another major problem remained: how to reduce our thinking into a practical handbook for authors—a dismaying task for three busy chemists. We settled on a seven-volume work and the indomitable ARK produced a rough breakdown to fit such a format. Putting flesh on these bones became feasible during a fortuitous three-month break between jobs by myself, and the largest handbook ever assembled by Pergamon (120 pages) was written and page allocations agreed—even for little or unknown functional groups. Sample chapters were commissioned and finally proved very encouraging, despite our first chosen topic uncovering virtually no known examples!

Contracts were defined and agreed, volume editors approached, and potential authors considered during a pleasant preconference stay in Grasmere. Following the sale of Pergamon to Elsevier Science Ltd there was a lull in the project but soon *Comprehensive Organic Functional Group Transformations* was back on track, and everyone adhered to a very businesslike timetable.

OTTO METH-COHN
Sunderland

CHARLES W. REES
London

ALAN R. KATRITZKY
Florida

Contributors to Volume 2

Dr K. I. Booker-Milburn
School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

Dr W. R. Bowman
Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire LE11 3TU, UK

Dr C. K.-F. Chiu
Pfizer Inc. Central Research, Eastern Point Road, Groton, CT 06340, USA

Dr D. Choueiry
Department of Chemistry, Purdue University, West Lafayette, IN 47907-1393, USA

Dr E. W. Colvin
Chemistry Department, University of Glasgow, Glasgow G12 8QQ, UK

Dr I. G. C. Coutts
Department of Chemistry, Faculty of Sciences and Mathematics, The Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, UK

Dr D. G. Genov
School of Sciences, Staffordshire University, College Road, Stoke-on-Trent ST4 2DE, UK

Professor L. Hevesi
Laboratoire de Chimie Organique, Département de Chimie, Facultés Universitaires N.-D. de la Paix, Rue de Bruxelles 61, B-5000 Namur, Belgium

Dr A. D. Hobson
Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK

Dr P. R. Huddleston
Department of Chemistry, Faculty of Sciences and Mathematics, The Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, UK

Professor T. Kataoka
Department of Organic and Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan

Professor W. Kitching
Department of Chemistry, The University of Queensland, Brisbane, Qld 4072, Australia

Dr C. Kouklovsky
Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

Dr K. Kwetkat
HÜLS AG, Paul-Baumann Strasse 1, D-45764 Marl, Germany

Professor S. V. Ley
Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

Dr S. D. Lindell
AgrEvo UK Ltd, Chesterfield Park Research Station, Saffron Walden, Essex CB10 1XL, UK

Dr R. T. Marmon
Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire LE11 3TU, UK

Dr C. M. Marson
Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK

Professor T. Minami
Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Sensui-cho, Tobata-ku, Kitakyushu 804, Japan

Professor E.-I. Negishi
Department of Chemistry, Purdue University, West Lafayette, IN 47907-1393, USA

Dr K. Okuma
Department of Chemistry, Faculty of Science, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka 814-01, Japan

Dr P. C. B. Page
Department of Chemistry, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK

Dr V. S. Rao†
Bristol Myers Squibb Pharmaceutical Research Institute, 100 Boulevard de l'Industrie, Candiac, PQ J5R 1J1, Canada

Dr R. W. Read
Department of Organic Chemistry, Heffron Building, Room 400D2, The University of New South Wales, Barker Street, Gate 14, Kensington, Sydney, NSW 2052, Australia

Dr D. Reynolds
Department of Chemistry, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK

Professor G. Sauvé
Immunology Research Center, Institut Armand-Frappier, 531 Boulevard des Prairies, Case Postale 100 Laval, PQ H7N 4Z3, Canada

Dr P. L. Spargo
Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK

Profesor P. J. Stang
Department of Chemistry, University of Utah, Henry Eyring Building, Salt Lake City, UT 84112, USA

Dr J. B. Sweeney
School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK

Dr P. C. Taylor
Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK

Professor J. C. Tebby
School of Sciences, Staffordshire University, College Road, Stoke-on-Trent ST4 2DE, UK

Dr C. J. Urch
ZENECA Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY, UK

Dr M.-X. Wang
Institute of Chemistry, Academia Sinica, Beijing 100080, China

Dr J. W. Wheeler
School of Sciences, Staffordshire University, College Road, Stoke-on-Trent ST4 2DE, UK

Dr R. D. Wilkes
Department of Chemistry, University of Liverpool, PO Box 147, Liverpool L69 3BX, UK

Dr M. Wills
School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

Dr M. Yoshimatsu
Department of Organic and Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan

Dr V. V. Zhdankin
Department of Chemistry, University of Minnesota-Duluth, Duluth, MN 55812, USA

Introduction

OBJECTIVES, SCOPE, AND COVERAGE

Comprehensive Organic Functional Group Transformations (COFGT) aims to present the vast subject of organic synthesis in terms of the introduction and interconversion of functional groups. All organic structures can be considered as skeletal frameworks of carbon atoms to which functional groups are attached[a]; it is the latter which are mainly responsible for chemical reactivity and which are highlighted in COFGT. All known functional groups fit a logical and comprehensive pattern and this forms the basis for the detailed list of contents. The format of the present work was designed with the intention to cover systematically all the possible arrangements of atoms around a carbon, including those which are quite unfamiliar. The work also considers the possibility of as yet unknown functional groups which may be constructed in the future and prove to be important; thus COFGT also indicates what is not known and so points the way to new research areas.

The philosophy of the present work has been to rationalize this enormous subject within as logical and formal a framework as possible, in a scholarly and critical fashion. COFGT is designed to provide the first point of entry to the literature for synthetic organic chemists, together with an unrivalled source for anyone interested in less common, obscure, or unknown functional groups.

All functional groups are viewed as being carbon based (even if the group contains no carbon). Thus, a nitro compound is considered from the standpoint of the immediately attached carbon atom, whether di- (sp), tri- (sp^2), or tetracoordinated(sp^3). The work is organized on the basis of formation or rupture of bonds to a carbon atom and it is the nature of the carbon atom left after the transformation that determines the classification of the overall sequence. Several key criteria have been used to organize the work and to minimize overlap. These are, in order of priority:

1. the number of attached heteroatoms;
2. the coordination of the carbon atom involved in the functional group;
3. the nature of the immediately attached heteroatom(s); and
4. the Latest Placement Principle.

These four key principles have been used to determine the content of each volume, and to develop the detailed chapter breakdown within each volume.

Thus, according to the number of attached heteroatoms:

Volume 1 deals with synthetic reactions which result in the alteration of bonding at carbon atoms which are left with *no* attached heteroatoms.

Volume 2 deals with syntheses which result in carbon atoms attached to *one* heteroatom by a single bond.

Volume 3 deals with syntheses which result in carbon atoms attached to *one* heteroatom by a double or by a triple bond.

Volume 4 deals with syntheses which result in carbon atoms attached to *two* heteroatoms, each by a single bond.

Volume 5 deals with syntheses which result in carbon atoms attached to *two* heteroatoms by one single and one double bond, or by two double bonds, or by one single and one triple bond.

Volume 6 deals with syntheses which result in carbon atoms attached to *three* or *four* heteroatoms.

Volume 7 comprises the author and subject indexes.

Certain key principles apply to all the volumes because all functional groups are viewed as carbon based (e.g. a nitro group is either alkyl-, vinyl-, aryl-, or alkynyl-); these are:

(a) Volumes are subdivided according to the *coordination* of the carbon atom which is the product of the reaction, i.e., tetra- coming before tri- before di- before monocoordinated carbon functions.

[a] The major exception to this lies in heterocyclic compounds, where the cyclic heteroatoms are more logically considered as part of the framework. The subject of heterocycles has been treated elsewhere in the companion work *Comprehensive Heterocyclic Chemistry* published in 1984 with a second edition to be published in 1996.

In Volumes 1 and 6, reactions producing four-coordinated carbon are considered first, followed by three- and then two-coordinated carbon. The other volumes contain a more limited range of coordination types (Volumes 2 and 4 only four-coordinated, Volumes 3 and 5 only two- or three-coordinated). Each type of coordination is allocated a separate section in each volume.

(b) Attached *heteroatoms* are discussed in the following order of priority:

Halogens—F, Cl, Br, I
Chalcogens—O, S, Se, Te
Nitrogen—N
Other group 15 elements—P, As, Sb, Bi
Metalloids—B, Si, Ge
Main group metals—Sn, Pb, Al, Ga, In, Tl, Be, Mg, Ca, Sr, Ba, Li, Na, K, Rb, Cs
Transition metals—Cu, Ag, Au, Zn, Cd, Hg, Ti, Zr, Hf, Cr, Mo, W, Mn, Fe, Co, Ni, Pd, Pt, and others.

Higher coordination of heteroatoms is treated after lower. Thus, in sections dealing with iodo compounds, monocoordinate (e.g. iodides) are discussed before dicoordinate (e.g. iodoxyls) and tricoordinate functions.

(c) The *Latest Placement Principle* (or Last Position Principle) is used to avoid undue overlap in the work. Thus, the carbon attached to the heteroatom is discussed at the last possible position in the above prioritizing of heteroatoms. Examples of its application are noted later. On this basis, for example, when both C—C and C—H bonds are formed the reaction will appear in the latest chapter (i.e. Chapters 1.04–1.10 rather than in the earlier Chapters 1.01–1.03), and when both C—C and C=C bonds are formed, this will be found in the later Chapter 1.17. The Latest Placement Principle is particularly important in determining where to find electrocyclic reactions in Volume 1. If C—H, =C—C, and C=C bonds are all formed in a reaction, then the latest appropriate chapter will deal with the reaction. Only if a change in heterofunction occurs is the reaction left to a later volume.

Exceptions to the above principles are rare. However the reactions of heteroarenes are mentioned along with those of arenes. If on reduction no change in the heterofunction occurs (e.g. in going from thiophene to tetrahydrothiophene or from pyridine to 2,3,4,5-tetrahydropyridine) the reaction is found in Volume 1. However, when the function changes (e.g. pyridine to piperidine), the conversion is considered in Volume 2. Conversion of methyl phenyl sulfone into methyl cyclohexyl sulfone appears in Volume 2, whereas the formation of cyclohexyl methyl ketone is treated in Volume 1, since the coordination of the carbon atom to the heteroatoms is changed in the first but not in the second hydrogenation.

Some further exceptions to the rigorous ordering of the work have been made for the purpose of easy reference. Thus, in Volume 1, a special chapter on ions, radicals, and carbenes is added: this chapter is limited to the treatment of species capable of more than a transitory existence. Throughout the work aspects of the Latest Placement Principle are occasionally ignored for reasons of clarity. Thus metal ligands that are incidental to the chemistry under discussion are not considered when prioritizing. Also, references to aromatic substituents, some of which involve a heteroatom (e.g. pyridyl, thienyl, etc.) but are incidental to the chemistry being described, are not viewed as changing the priority.

Within each section, we have endeavored to explain the influence of important secondary effects such as inclusion in a ring, degree of strain, degree of substitution, various types of activation, influence of stereochemistry, and so on, on the transformation under consideration. General synthetic methods are treated before specific methods.

Transient intermediates, as such, do not fall within the scope of this work. Although there is clearly no sharp division, we have attempted to restrict coverage of radicals, etc., to more stable, longer lived species. It is the aim of this work to consider all organic functional groups provided that the molecules which incorporate them, though they may be unstable, can have a finite lifetime and chemistry. The whole work deals with the generation and transformation of functional groups, *not* of molecules such as CO_2, COS, CS_2, ClCN, etc. Such simple carbon derivatives are not treated unless a further carbon is attached (e.g. RN=C=O).

VOLUME 1 SYNTHESIS: CARBON WITH NO ATTACHED HETEROATOMS

Volume 1 deals solely with the formation of nonheteroatom functional groups and as such is different in style to the remaining volumes.

In addition to the general principles, Volume 1 is further organized as follows:

1. By the type of bond formed (i.e. C—H before C—C).
2. By the type of reaction involved (i.e. substitution, then addition, then rearrangement). With C=C bond formation the order is addition, elimination, condensation, then electrocyclic and other methods. One rearrangement chapter only is devoted to each of the Parts I and II.
3. In Parts II and III the treatment of formation of ions, radicals, and carbenes is added at the end of the section dealing solely with those species with a significant rather than a transient lifetime.

In Volume 1, the heteroatom sequence is a secondary feature since only remote heteroatom functions are involved in the products: but the standard order pertains in reactants that contain heteroatoms (see, e.g. Chapters 1.01 and 1.02).

All the major structural influences that are treated throughout this work apply equally (or perhaps more importantly) in Volume 1. Thus the effects of conjugation, remote substituents, rings, stereochemistry, strain, kinetic or thermodynamic factors, solvation, primary, secondary and tertiary nature, etc., are mentioned whenever relevant.

VOLUME 2 SYNTHESIS: CARBON WITH ONE HETEROATOM ATTACHED BY A SINGLE BOND

Volume 2 is arranged in three parts: I, II and III, dealing respectively with sp^3, sp^2, and sp carbon linked to the heteroatom. In each chapter we have endeavored to explain important effects due to such features as the primary, secondary, tertiary nature, ring effects, strain activation, effect of beta, gamma, and more remote functionality, stereochemical effects, and so on. Methods that are common to a larger group are dealt with at their first appearance and suitably cross-referenced.

Volumes 2–6 all deal with the synthesis of functions involving at least one heteroatom. To avoid major overlap we have applied the Latest Placement Principle; that is, the chemistry is discussed at the last possible position based on the prioritization of the carbon attached to the heteroatom. Thus the compound CH_3ONH_2 is treated under "Alkyl Chalcogenides" in the subsection "Functions Based on the RON-Unit" (i.e. 2.02.6). However, CH_3ONHCH_3 appears under "Alkyl Nitrogen Compounds" (2.06.2.3) since the Latest Placement Principle prevails. Also, dialkyl ethers appear in Part I of Volume 2 (Functions Linked by a Single Bond to an sp^3 Carbon Atom), while alkyl aryl ethers appear in Part II of Volume 2 (Functions Linked by a Single Bond to an sp^2 Carbon Atom). Exceptions to the rule are:

(a) When a fully unsaturated heterocyclic substituent (e.g. thienyl, pyridyl, etc.) is used as an example of an aryl group, the ring heteroatom(s) is (are) not taken into account (e.g. 2-methoxypyridine should strictly appear in Volume 6, but is covered in Volume 2 along with 3- and 4-methoxypyridine).

(b) Carbon-based metal ligands that are incidental to the synthesis under discussion (e.g. carbonyls, cyclopentadienyls, etc.) are not taken into consideration.

VOLUME 3 SYNTHESIS: CARBON WITH ONE HETEROATOM ATTACHED BY A MULTIPLE BOND

Volume 3 follows the logical development indicated in Volume 2. Thus, according to the Last Placement Principle, the imines, RCH=N—R, appear in Volume 3 rather than in Volume 2 (where functions singly bonded to carbon are treated). Furthermore, acetophenone, $PhCOCH_3$, is treated under α,β-unsaturated ketones (3.05) rather than saturated ketones (3.04). Chloronitroacrylonitriles would appear under the section "α,β-Vinylic Nitriles with Nitrogen-based Substituents" (3.19.2.7), not under the related earlier section dealing with halo-substituents (3.19.2.3).

VOLUME 4 SYNTHESIS: CARBON WITH TWO HETEROATOMS, EACH ATTACHED BY A SINGLE BOND

Volume 4 is in three parts. Part I deals with tetracoordinated carbon bearing two heteroatoms, Part II with tricoordinated carbon bearing two heteroatoms, and Part III (a brief chapter) with stabilized radicals, ions, and the like bearing two heteroatoms. The material is arranged according

to the Latest Placement Principle: thus, the synthesis of $CHBr_2CHI_2$ would appear in the section dealing with diiodo, not dibromo functions (i.e. in 4.01.5, not 4.01.4), and the synthesis of CF_3CH-BrCl is discussed in Volume 6 (carbons bearing three heteroatoms), rather than in Volume 4.

VOLUME 5 SYNTHESIS: CARBON WITH TWO ATTACHED HETEROATOMS WITH AT LEAST ONE CARBON-TO-HETEROATOM MULTIPLE BOND

Volume 5 is in three parts. Part I deals with functions with one doubly bonded and one singly bonded heteroatom, Part II with functions containing two doubly bonded heteroatoms and Part III with one triply bonded and one singly bonded heteroatom. Part I constitutes the bulk of Volume 5.

The arrangement of the chemistry in each part follows the same logical sequence. The multiply bonded heteroatom is focused on first and then the other heteroatom in a secondary classification, both following the priority rules already described. Each section excludes the coverage of the previous sections. Thus, all carbonyl derivatives will appear in Chapters 5.01–5.10 but not in Chapters 5.11, *et seq.*

According to the Latest Placement Principle structure RC(O)OC(S)R is discussed in the chapter dealing with carbons bearing a doubly bonded sulfur and singly bonded oxygen (5.12.3), *not* in that dealing with doubly and singly bonded oxygen (5.04.1). Another effect of the Latest Placement Principle is that the amides RCONMePh are discussed under *N*-arylalkanoamides (5.06.2.4), rather than *N*-alkylalkanoamides (5.06.2.2). Again, exceptions are made to the latest placement rules for: (a) hetaryl rings used as examples of aryl substituents which are not viewed as functional groups. Thus, 2-methylimidazole is not considered as an example of an amidine function and 2-methoxypyridine is not an example of a doubly bonded nitrogen, singly bonded oxygen function; (b) metal ligands that are incidental to the organic chemistry under discussion are not viewed as functions in priority considerations.

VOLUME 6 SYNTHESIS: CARBON WITH THREE OR FOUR ATTACHED HETEROATOMS

Volume 6 is in four parts. Part I deals with tetracoordinate carbons bearing three heteroatoms. Part II covers tetracoordinate compounds bearing four heteroatoms, i.e. substituted methanes, and Part III deals with tricoordinate systems bearing three heteroatoms, i.e. where one heteroatom is attached by a double bond. Part IV is brief and deals with stabilized radicals and ions. Not surprisingly, the coverage of Volume 6 is very large—and also shows that many gaps in the development of organic chemistry still exist.

The organization within the three sections not only follows the same broad logic developed in the previous volumes, but also has a structure unique to the multiheteroatom volume. According to the Latest Placement Principle $CF_3C(NR_2)_3$ appears in the section dealing with carbons bearing three nitrogens (6.05.1.1), not that dealing with carbons bearing three halogens (6.01.2), while $(CF_3CH_2O)_2CO$ appears in Part III, not in Part I.

In the chapter dealing with iminocarbonyl functions in Part III, the substituents on nitrogen are discussed in each appropriate subsection in the order outlined above. Thus, the RN= group would be first considered with R = H, then alkyl, alkenyl, aryl and hetaryl, alkynyl and then heteroatom substituents in the usual order.

In each relevant section, we have endeavored to explain the influence of important secondary effects on the synthesis such as structure (primary, secondary, etc.), ring effects, strain, activation, stereochemistry, remote substituent effects, etc.

The arrangement of the chemistry in each of Parts I–III follows a similar pattern. Thus, each section commences with functions containing at least one halogen. This section deals with all combinations of halogen with other heteroatoms in the described order. The next section deals with functions containing at least one chalcogen in combination with any other heteroatoms except halogens. Subsequent sections each exclude the previous title heteroatom functions.

VOLUME 7 INDEXES

Subject Indexes are included in each of Volumes 1–6 and Cumulative Subject and Author Indexes appear in Volume 7. Most entries in the Subject Index consist of two or three lines: the first line is the entry itself (e.g. Lactones) and the second line is descriptive of that entry (e.g. reduction); in many cases more detail is given (e.g. with 9-BBN).

REFERENCES

The references are handled by the system previously used successfully in *Comprehensive Heterocyclic Chemistry*. In this system reference numbers appear neither in the text, nor as footnotes, nor at the end of chapters. Instead, each time a reference is cited in the text there appears (in parentheses) a two-letter code assigned to the journal being cited, which is preceded by the year (tens and units only for twentieth-century references) and followed by the page number. For example: "It was shown ⟨80TL1327⟩ that . . .". In this phrase, "80" refers to 1980, "TL" to *Tetrahedron Letters*, and "1327" to the page number. For those journals which are published in parts, or which have more than one volume number per year, the appropriate part of the volume is indicated, e.g. as in ⟨73JCS(P2)1594⟩ or ⟨78JOM(162)611⟩, where the first example refers to *J. Chem. Soc., Perkin Trans 2*, 1973, page 1594, and the second to *J. Organomet. Chem.*, 1978, volume 162. page 611.

This reference system is adopted because it is far more useful to the reader than the conventional "superscript number" system. It enables readers to go directly to the literature reference cited, without first having to consult the bibliography at the end of each chapter.

References to the last century quote the year in full. Books have a prefix "B-" and if they are commonly quoted (e.g. *Organic Reactions*) they will have a code. Otherwise, as with uncommon journals, they are given a miscellaneous code (MI) and numbered arbitrarily *abb1*, *abb2*, etc., where *abb* refers to the volume and chapter number and *1*, *2*, etc., are assigned sequentially. Patents are assigned appropriate three-letter codes.

The references are given in full at the end of each volume. They include *Chemical Abstract* references when these are likely to help; in particular, they are given for all patents, and for less accessible sources such as journals in languages other than English, French, or German, company reports, obscure books, and theses.

Contents

2.01
Alkyl Halides

PETER L. SPARGO
Pfizer Central Research, Sandwich, UK

2.01.1 GENERAL METHODS FOR ALKYL HALIDES

The chemistry and preparation of halogen-containing compounds have been reviewed in *Houben-Weyl* ⟨60HOU(5/4)1, 62HOU(5/3)1⟩, in *Comprehensive Organic Chemistry* ⟨79COC(1)493⟩, and in an excellent review by Hudlicky and Hudlicky in *The Chemistry of Functional Groups* series ⟨B-83MI 201-01⟩. The latter review includes some useful 'Halogenation Tables' (reproduced from an earlier publication ⟨78OPP181⟩ which correlate starting materials, halogenating agents and products in such a way that the reader can quickly identify generally useful methods, as well as the compatibility of functional groups with halogenating agents. A review in *Comprehensive Organic Synthesis* ⟨91COS(6)203⟩ provides an account of nucleophilic halogenation methods, while the synthesis and reactivity of α-halogenated ketones, aldehydes and imines is the subject of an update volume of the Patai series ⟨B-88MI 201-01⟩. Many classical methods for the synthesis of alkyl halides are still widely used, and the *Houben-Weyl* volumes ⟨60HOU(5/4)1, 62HOU(5/3)1⟩, despite their age, provide detailed procedures and numerous tables from which much useful information may be gleaned. Literature procedures up to and including 1987 have been clearly tabulated in easily accessible form in Larock's *Comprehensive Organic Transformations* ⟨B-89MI 201-01⟩. In addition, an annual review of the synthesis of organic halides can be found in the new journal *Contemporary Organic Synthesis* ⟨94MI 201-01⟩.

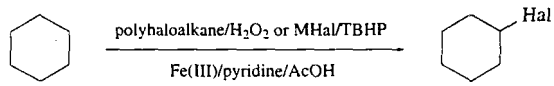
It would be impossible here to provide a truly comprehensive review of alkyl halide synthesis, so coverage has been restricted primarily to those methods which would appear to have the greatest general synthetic utility. Mechanistic details have necessarily been kept to a minimum and are only discussed where they have a direct bearing on regio-, stereo- or chemoselectivity. Brief mention of some less well used methods is also made.

Because of the large differences in reactivity of fluorides, chlorides, bromides and iodides, there are very few methods which are generally applicable to all four halogens. In particular, the unique properties of fluorine mean that special methods have had to be developed for this halogen (Section 2.01.2). Alkyl chlorides and bromides are synthetically the most widely used alkyl halides and their chemistry is often closely related (Sections 2.01.3 and 2.01.4). Although alkyl iodides are often prepared using methods similar to those used to prepare alkyl bromides, they are much less common synthetic targets or intermediates (Section 2.01.5).

In this section a range of general synthetic approaches to alkyl halides is described. Certain transformations are discussed in detail in this section, while others are expanded in the later sections specific to each halogen. The reader is therefore encouraged to consult the relevant subsection within each of the five sections in this chapter for a balanced coverage.

2.01.1.1 Alkyl Halides from Alkanes

Direct halogenation of unactivated alkanes with elemental halogen, often in the presence of visible or ultraviolet light ⟨see reviews B-69MI 201-01, B-69MI 201-02, B-73MI 201-02, B-73MI 201-03⟩, is generally indiscriminate and therefore not preparatively useful, except in cases where symmetry dictates that all of the replaceable hydrogens are equivalent (e.g., cyclohexane, ethane). There are scattered reports of halogenations of unactivated hydrocarbons with a variety of different reagents ⟨B-89MI 201-01⟩, but yields are often low, and none of the methods appears general. The most recent work in this area has been by Barton *et al.* in the early 1990s, and their chemistry, which can be used to prepare chlorides, bromides and iodides (but not fluorides), is exemplified by Equation (1) ⟨92T9195, 92TL3413, 93TL1871, 93TL5689, 94T31⟩. For a short review on this and related chemistry see ⟨92ACR504⟩.

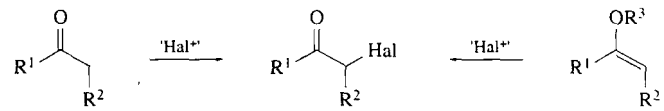


(1)

polyhaloalkane = CCl_4, CBr_4, $CBrCl_3$, CBr_2Cl_2, etc.
M = Li, Na
Hal = Cl, Br, I

While the existence of radical intermediates in the processes above has been the source of some dispute ⟨94TL1427, 94TL1431⟩, the radical nature of halogenation at allylic and benzylic sites is universally accepted ⟨B-72MI 201-01⟩. The latter reaction is most commonly applied in the synthesis of allylic and benzylic bromides using *N*-bromosuccinimide (the Wohl–Ziegler reaction) (Section 2.01.4.1).

Alkane activation by an electron-withdrawing group greatly widens the scope of reagents and reaction conditions for halogenation, since ionic mechanisms may then operate. Aldehydes and ketones (often in an enol form such as silyl enol ether or an enol acetate) can be halogenated in the α-position with a variety of reagents, including elemental fluorine, chlorine, bromine and iodine (Scheme 1). The most difficult of these is fluorination, but a range of useful procedures have been devised to overcome this problem (Section 2.01.2.1).

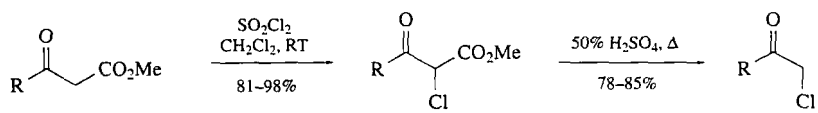


R^3 = alkyl, acyl, silyl

Scheme 1

As a general rule, clean monohalogenation (with minimal dihalogenated by-product formation) is more easily achieved under acidic rather than basic conditions, although there are nevertheless many examples of the latter. For unsymmetrical ketones, halogenation under acidic conditions generally occurs at the more substituted α-carbon, because the reaction proceeds under thermodynamic control through the more stable enol tautomer.

Halide ions can also be used to α-halogenate carbonyl compounds and their enol derivatives in the presence of a suitable oxidant such as lead tetraacetate ⟨82S1021⟩, benzoyl peroxide, hydrogen peroxide or mcpba ⟨76CPB820⟩. α-Chloro-, bromo- and iodocarbonyl compounds have all been prepared using these methods. For a detailed review of the preparation of α-halo aldehydes, ketones and imines, see ⟨B-88MI 201-01⟩. Ketals have been brominated and occasionally chlorinated (but apparently not fluorinated or iodinated) at the β-carbon, probably via transient enolic intermediates (Section 2.01.4.1). Carboxylic esters, amides and acids are also straightforwardly α-halogenated, as are nitriles ⟨48JA165⟩. Thionyl chloride converts acid chlorides to α-chloro-, α-bromo- or α-iodoacid chlorides when combined with NCS, NBS or iodine respectively ⟨75JOC3420⟩. A surprisingly little-used alternative approach to α-haloketones exploits the reactivity of the active methylene group in β-ketoesters or malonates by halogenation with NBS, NCS, SO_2Cl_2 or Br_2, followed by hydrolysis and decarboxylation (Scheme 2) ⟨83TL163, 87S188⟩ or deacetylation ⟨49JA3107, 72TL4067, 87TL5505⟩. A related method for preparing α-fluoroketones has also been described ⟨89CL577⟩.



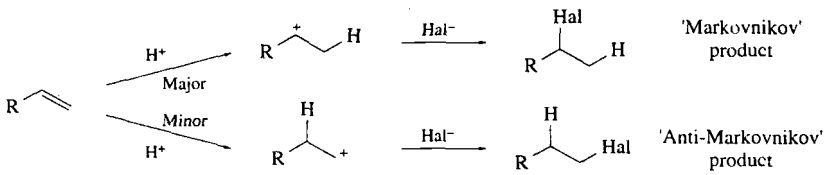
Scheme 2

2.01.1.2 Alkyl Halides from Alkenes

A wide variety of 2-functionalised alkyl halides can be prepared by addition of Hal—Y (Y = O, N, S, Se, etc.) to alkenes ⟨93S1177⟩. In accordance with the 'rule of latest placement' applied to the organisation of this publication, most of these are covered in later chapters. In this chapter the discussion focuses on the addition of halogen–hydrogen and halogen–halogen only.

2.01.1.2.1 Alkyl halides by hydrohalogenation of alkenes

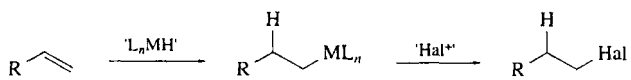
The direct addition of HHal (Hal = F, Cl, Br, I) to alkenes is not a particularly widely used synthetic approach to alkyl halides, and there are a number of reasons for this. Among these is the fact that mixtures of regioisomers and rearranged products are often obtained (see reviews ⟨40CRV351, 62CRV599⟩ and hydrobromination ⟨63OR(13)150, B-77MI 201-01, 91COS(4)269⟩). Commonly, the reaction proceeds through an ionic mechanism via the more stable of the two possible carbocation intermediates to give the Markovnikov product as indicated in Scheme 3 for a terminal alkene.



Scheme 3

A general method for Markovnikov addition of HHal (Hal = Cl, Br, I) to alkenes using phase-transfer catalysis has been reported ⟨80JOC3527⟩ and a polymer-supported phase transfer catalyst can be conveniently used for this purpose ⟨88IJC(B)1129⟩. It has also been shown that Markovnikov hydrohalogenation can be facilitated by performing the reaction in the presence of an inorganic support such as silica or alumina. Furthermore, under these latter conditions there is no need to use HHal itself, since it can be generated *in situ* from species such as $SOCl_2$, $(COCl)_2$, TMS-Cl, TMS-Br, TMS-I or PI_3 ⟨90JA7433, 93JA3071⟩. Hydrohalogenation of alkenes bearing an electron-withdrawing group gives the β-halogenated product exclusively, as expected on electronic grounds. Anti-Markovnikov addition to alkenes is often observed in hydrobromination with HBr, and suggests a free-radical or four-centre addition mechanism. Indeed, if Markovnikov addition of HBr is required, it is often necessary to take precautions to exclude peroxides or to add free radical inhibitors ⟨40CRV351⟩.

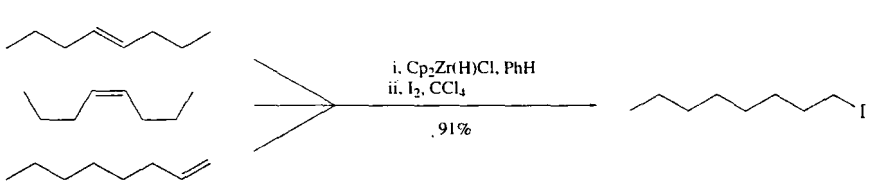
Anti-Markovnikov addition of HCl, HBr or HI is generally achieved via hydrometallation, usually hydroboration ⟨81JCR(S)376, 81JOC2582, 81JOC3113, 83HCA1018⟩ or hydroalumination ⟨76JOM(122)C25, 78CL833⟩, followed by treatment with an electrophilic halogen source (Scheme 4).



M = B, Al, Zr, Si
L = Ligand (including carbon-bonded ligands)
Hal = Cl, Br, I

Scheme 4

The halogenolysis of organoboranes has been briefly reviewed ⟨85OR(33)1, 91COS(7)593⟩, as has its applications to the incorporation of radioactive halogen isotopes ⟨84ACR215⟩. BCl_3 and BBr_3 are recent additions to the list of reagents suitable for this purpose ⟨93S973⟩. Hydrosilylation followed by treatment with Cl_2, Br_2, I_2, NBS or copper(II) chloride or bromide also gives access to the anti-Markovnikov products ⟨78JA290, 78TL1809, 82OM355, 82OM369⟩. In addition, it has been shown that hydrozirconation of a substituted alkene leads to migration such that, on quenching with NCS, NBS, iodine, bromine or iodobenzene dichloride, the terminal primary alkyl halide is obtained (Scheme 5, ⟨74JA8115⟩; see also ⟨76AG(E)333, 81JOC1821⟩).



Scheme 5