COMPREHENSIVE ORGANIC CHEMISTRY

The Synthesis and Reactions of Organic Compounds

SIR DEREK BARTON, F.R.S.

AND

W. DAVID OLLIS, F.R.S.

Volume 2 Nitrogen Compounds, Carboxylic Acids, Phosphorus Compounds

Foreword

During more than a century, the development of organic chemistry has been associated with extensive documentation. Vast numbers of textbooks, monographs, and reviews have been published with the objective of summarizing and correlating the results obtained by many thousands of organic chemists working in academic and industrial research laboratories. However, out of this colossal literature there is but a relatively small number of textbooks and multi-volumed works which have become generally accepted as representing real steps forward in the presentation of our subject.

During the classical era of organic chemistry (1820–1940), textbooks which had a profound influence on the teaching of the subject included, for example, works by Armstrong (1874), van't Hoff (1875), Roscoe–Schorlemmer (1878), Richter (1888), Gattermann (1895), van't Hoff–Werner–Eiloart (1898), Meyer–Jacobson (1902), Schmidt–Rule (1926), Karrer (1928), Freudenberg (1933), Richter–Anschütz (1935), and Gilman (1938). These texts provide an opportunity to comment on the relationship between the history of organic chemistry and its associated publications. The *Treatise on Chemistry* by Roscoe and Schorlemmer consisted of three volumes (5343 pages) published in nine parts over the period 1878–1892: the major component was Volume III (6 parts, 3516 pages) which was devoted to organic chemistry. Another instructive example is the important work *Lehrbuch der Organischen Chemie*, produced by Victor Meyer and Paul Jacobson. The increase in size from the edition (1735 pages) published during 1902–1903 to the edition (5115 pages) published over the period 1913–1924 is striking.

Many have expressed concern about the problems of maintaining effective contact with the expanding literature of organic chemistry, but few have allowed themselves to become involved with attempted solutions. The decision to publish Comprehensive Organic Chemistry was not taken lightly. The absence of a work reflecting the current rapid development of modern organic chemistry has been lamented by many eminent chemists, including the late Sir Robert Robinson (1886–1975) who played an important role in the initiation of this project shortly before his death. Comprehensive Organic Chemistry was conceived, designed, and produced in order to meet this deficiency. We realised that the current rate of growth of organic chemistry demanded speedy publication and, furthermore, that its interaction with other subjects including biochemistry, inorganic chemistry, molecular biology, medicinal chemistry, and pharmacology required the collaboration of many authors. The selection of topics to be included in order to justify the work as being comprehensive has not been easy. We recognize that some areas of organic chemistry have not been given the detailed treatment which can be justified, but we have done our best to meet the expectations of the majority of readers. In particular, we have not made a special section for Theoretical Organic Chemistry. This is not because of any lack of appreciation on our part of the importance of Theory. It is because a correct treatment of Theory cannot be made comprehensible in an abbreviated form. It is also because Theory changes with time more rapidly than the facts of the subject. Theory is better treated in our view in specialist monographs. The same arguments apply equally to the fundamental subject of Stereochemistry. Any comments regarding errors and omissions will be appreciated so that they can be dealt with in future editions.

The contents of each volume have been brought together so as to reflect what are judged to be the truly important facets of modern organic chemistry. The information is presented in a concise and logical manner with mechanistic organic chemistry being adopted to provide a constant and correlative theme. The dominating intention of the Editorial Board has been to ensure the publication of a contribution to the literature of organic chemistry which will be genuinely useful and stimulating. Emphasis has therefore been given throughout to the properties and reactions of all the important classes of organic compounds, including the remarkable array of different compounds prepared by synthesis as well as natural products created by biosynthesis. Of course, the study of natural products provided the original foundation stones on which modern synthetic organic chemistry now firmly stands.

As a major presentation of modern organic chemistry, Comprehensive Organic Chemistry will be doubly useful because we have provided, in a separate volume, an extensive index. Not only have the contents of the work been indexed in the ordinary way, but we have also added a substantial number of additional references from the original literature. These do not appear in the text itself. Thus, the reader who wishes to obtain additional information about reactions and reagents mentioned in the text will quickly be able to consult the original literature. The Index volume has been prepared by a team from Pergamon Press.

Our debt to the Authors and to the Volume Editors is considerable. We are very grateful to all our colleagues for the efficient way in which they have tried to meet the challenges (and the deadlines!) which have been presented to them. We hope that the Authors have enjoyed their association with this venture. In a lighter vein, we also trust that their feelings are different from the statement 'this task put system into my soul but not much money into my purse' attributed to Henry Edward Armstrong (1848–1937) after he had written his *Introduction to Organic Chemistry* in 1874.

We are delighted to acknowledge the masterly way in which Robert Maxwell, the Publisher, and the staff at Pergamon Press have supported the Volume Editors and the Authors in our endeavour to produce a work which correctly portrays the relevance and achievements of organic chemists and their contributions to knowledge by research.

D. H. R. BARTON
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W. D. OLLIS
Deputy Chairman

Preface to Volume 2

The classification of organic chemistry in terms of the chemistry of functional groups is a long-standing tradition whose value has not been diminished by other approaches, such as those based upon reaction mechanisms. The traditional approach that has been adopted for Comprehensive Organic Chemistry has ensured that emphasis has been placed upon the reactions of organic compounds and modern synthetic methods. Information on these topics is a major need for organic chemists, both for research and for teaching. It is hoped that the organization of the volume will enable the expert and those for whom organic chemistry is less familiar to locate the information that they require with reasonable ease.

The major works of organic chemistry, such as Houben–Weyl, present a truly comprehensive array of synthetic methods and reactions and there is a large number of monographs which cover specialized areas of organic chemistry in similar detail. Comprehensive Organic Chemistry is an attempt at a compromise between specialization and the forbidding dimensions of a totally comprehensive text. Emphasis has therefore been placed upon a critical selection of the topics to be included and this has placed a considerable responsibility upon the contributors. The success with which they have met this challenge may well determine the reception that organic chemists give to this book.

The development of new synthetic methods and the extension of the range of functional groups available for the organic chemist have been features of research during the last two decades. These advances have been made possible by the skill and enthusiasm of gifted research workers in association with physical methods for structure determination, efficient separation techniques, and a general appreciation of the guidelines laid down by physical organic chemistry. The incentives have been provided by the challenge presented by the total syntheses of the complex structures of natural products. Landmarks include strychnine, reserpine, vitamin B_{12}, macrolide antibiotics, β-lactam antibiotics, and the prostaglandins. The requirement for purely synthetic compounds designed to meet a specific need, for example in the pharmaceutical industry, has also provided a continual incentive for the invention of efficient synthetic methods.

Some scientists, seldom organic chemists, note these successes and consider that organic chemistry is a fully developed, or even moribund, science and point to the biological sciences as an area of allegedly greater activity, challenge, and excitement. The narrowness of this view is apparent from inspection of the contents of Comprehensive Organic Chemistry. In spite of an ever-increasing armoury of sophisticated ideas and techniques it is still seldom possible to achieve in laboratory syntheses the total stereospecificity and regiospecificity that is a characteristic of biochemical processes. Furthermore, ideas of substrate specificity, other than those proposed in terms of functionality, are virtually undeveloped. It is to be expected that the final two decades of this century will see considerable progress towards the achievement of the chemical efficiency of biological systems by the organic chemist in his laboratory. It is hoped that Comprehensive Organic Chemistry, in a modest way, will make its contribution as a source of information, and even of inspiration, for the present generation of organic chemists.

Volume 2 covers the chemistry of compounds with functional groups containing nitrogen and phosphorus together with an account of the chemistry of carboxylic acids and their derivatives. The reader will find that some areas have developed considerably more than others in recent years and this is reflected in the references. Thus in general the high proportion of references to the recent literature indicates the progress in synthetic organic chemistry to which reference has already been made, but in some of the more traditional fields development has been less marked in recent years and the proportion of earlier literature references is correspondingly greater. In both circumstances the objective has been to provide the reader with a contemporary view of organic chemistry.

Any volume of this type is a product of its contributors and I should like to express my very sincere thanks to all of them. The printing schedule has set deadlines that have been difficult to meet and authors have responded in a very positive way to meet this challenge. Thanks are also due to Pergamon Press and Dr Colin Drayton for the energetic and efficient way in which they dealt with what appeared to be an overwhelming flood of manuscripts. The inspiration for the project was provided by Sir Derek Barton and Professor David Ollis and the completion of the work has owed much to their drive and enthusiasm. All those involved will also wish to thank Jeanne Bovett who has dealt patiently and effectively with the administrative matters and the unreasonable requests of at least one volume editor.

Liverpool I. O. SUTHERLAND

Contributors to Volume 2

Dr. R. S. Atkinson
Department of Chemistry, University of Leicester

Dr. J. M. Brown
Dyson Perrins Laboratory, University of Oxford

Dr. B. C. Challis
Department of Chemistry, Imperial College of Science and Technology, University of London

Dr. J. A. Challis
The Open University, Milton Keynes

Dr. E. W. Colvin
Chemistry Department, University of Glasgow

Dr. R. G. Coombes
Department of Chemistry, The City University, London

Dr. A. Cox, Department of Molecular Sciences, University of Warwick

Dr. R. S. Edmundson
School of Chemistry, University of Bradford

Dr. T. L. Gilchrist
Robert Robinson Laboratories, University of Liverpool

Dr. J. M. Z. Gladych
Allen and Hanburys Research Ltd., Ware

Dr. D. Hartley
Allen and Hanburys Research Ltd., Ware

Dr. A. F. Hegarty
Department of Chemistry, University College, Cork

Dr. J. H. Jones
Dyson Perrins Laboratory, University of Oxford

Mr. R. J. Lindsay
Imperial Chemical Industries Organics Division, Manchester

Dr. J. R. Malpass
Department of Chemistry, University of Leicester

Dr. I. S. Roberts
Department of Chemistry, University of Stirling

Dr. S. M. Roberts
Department of Chemistry, University of Salford

Dr. D. J. H. Smith
Department of Chemistry, University of Leicester

Professor I. O. Sutherland
Robert Robinson Laboratories, University of Liverpool

Dr. G. Tennant
Department of Chemistry, University of Edinburgh

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PART 6

AMINES AND RELATED COMPOUNDS

6.1

Aliphatic, Acyclic, and Cyclic Amines

J. R. MALPASS
University of Leicester

6.1.1 PREPARATION OF AMINES

The range of preparative methods for amines is vast. Many reactions are old but have stood the test of time; others have been handed down from review to review without finding wide applications, whilst the scope of more recent reactions has yet to be established. The following range is a selected and condensed fraction of a large volume of work and, since amines are inevitably used widely in making other amines, the balance between this section and Section 6.1.3 (reactions of amines) is a matter of convenience and personal taste. Comprehensive reviews[1-8] of amine preparation are available for further exploration of many reactions. Leading references from the recent literature have been selected where possible, even though this may occasionally appear to deny original authors their due credit.

6.1.1.1 Alkylation and dealkylation of amines[1,9,10]

The most straightforward route to an amine, in principle, is alkylation of ammonia or another amine with an alkyl halide. However, the reaction carries with it the possibility of further alkylation according to equations (1)–(4) (which cover a wide range of amines and alkylating reagents by variation of the groups R and X). The reactions cannot be expected to stop at any specific stage on the basis of intrinsic differences in amine nucleophilicity, and the value of the reaction in the laboratory is generally limited. However, primary or secondary amines may often be prepared reasonably successfully with a suitable excess of ammonia or primary amine respectively (where this does not introduce difficulties of economics or separation), and secondary amines can give useful yields of tertiary amines with one molar equivalent of alkylating agent. Intramolecular amination of substituted alkanes to give cyclic amines is a most useful reaction (p. 19).

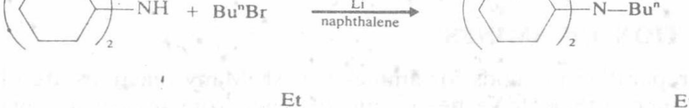
$$RX + NH_3 \longrightarrow R\overset{+}{N}H_3\,X^- \longrightarrow RNH_2 \text{ (primary)} \qquad (1)$$

$$RX + RNH_2 \longrightarrow R_2\overset{+}{N}H_2\,X^- \longrightarrow R_2NH \text{ (secondary)} \qquad (2)$$

$$RX + R_2NH \longrightarrow R_3\overset{+}{N}H\,X^- \longrightarrow R_3N \text{ (tertiary)} \qquad (3)$$

$$RX + R_3N \longrightarrow R_4\overset{+}{N}\,X^- \quad \text{(quaternary ammonium salt)} \qquad (4)$$

Amongst alkyl halides, the reactivity order $I > Br \gg Cl \gg F$ is observed, and iodide ion may be added to promote halogen exchange and thereby increase reactivity when other halides are used. Reactivity decreases with increasing substitution in the amine or RX, a factor which may be used to advantage in stopping the sequence (1)–(4) at an early stage. Greater alkyl branching in RX brings with it an ever-increasing probability of competing amine-induced β-elimination in substrates having suitably placed hydrogens. Elimination is also a potential problem whenever an amide ion R_2N^- is used as the nucleophile in order to achieve an increase in reactivity over the corresponding amine. The preparation of primary amines from primary alkyl halides with sodamide is usually satisfactory, however (minor amounts of alkene are easily removed), and the conversion of secondary amines to their lithium salts *in situ* may be of assistance in the preparation of tertiary amines (equation 5).[11] The use of unsaturated halides with an ultimate hydrogenation step may help to avoid elimination of HX and also allow the formation of amines which are inaccessible by direct reaction on steric grounds (equation 6).[12]



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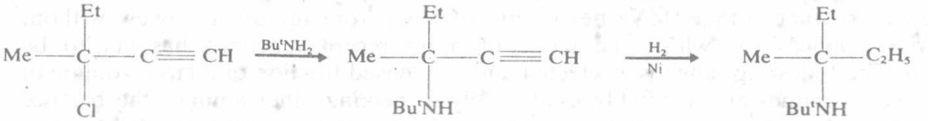
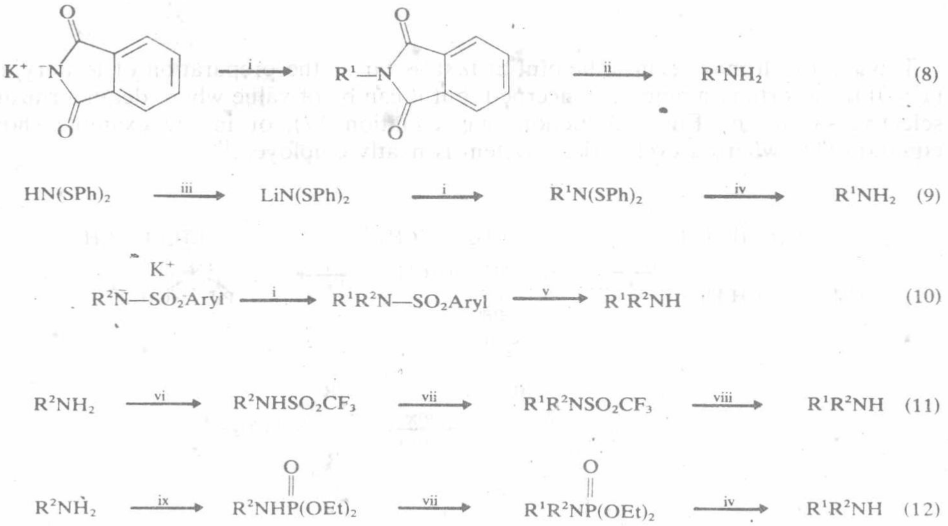


$$Me-\underset{Cl}{\overset{Et}{C}}-C\equiv CH \xrightarrow{Bu^tNH_2} Me-\underset{Bu^tNH}{\overset{Et}{C}}-C\equiv CH \xrightarrow[Ni]{H_2} Me-\underset{Bu^tNH}{\overset{Et}{C}}-C_2H_5 \qquad (6)$$

Equations (1)–(4) are not limited to X = halogen. Whilst direct conversion of alcohols to amines may be achieved commercially with suitable catalysts, ester derivatives are almost invariably used in the laboratory. A number of examples will be encountered, but sulphonate esters (*e.g.* X = toluene-*p*-sulphonyloxy) are widely used, for example in the preparation of amino sugars and amino steroids, and the stereospecificity expected of an S_N2 reaction is observed. Phosphonium salts derived from alcohols react cleanly and efficiently with primary and secondary amines to give secondary and tertiary amines, respectively (equation 7).[13]

$$R^1R^2NH + R{-}O{-}\overset{+}{P}Ph_3 \xrightarrow[\text{or benzene}]{\text{DMF}} \underset{\text{(after liberation with base)}}{R^1R^2NR} + O{=}PPh_3 \qquad (7)$$

In general, however, the efficient preparation of specific primary, secondary, or tertiary amines by alkylation demands approaches which are subject to a greater degree of control. Successful routes to amines bearing a number of hydrogens $x(0, 1, 2)$ on nitrogen fall mainly into two groups. First (for primary and secondary amines) a number of positions equal to x may be temporarily blocked with substituents, at least one of which also reduces the reactivity of the amine. The remaining proton on nitrogen may then be removed with base and mono-alkylation achieved without the problems of further alkylation or competing elimination (where RX is primary or secondary). Removal of the blocking group(s) completes the synthesis. Scheme 1 includes the long-established Gabriel[14] (designated equation 8) and Hinsberg[1,2] (equation 10) syntheses together with more recent reactions (equations 9,[15] 11,[16] and 12[17]) which have the particular advantage of using milder conditions for the final step.



i, R^1X; ii, N_2H_4; iii, BuLi, THF, −20 °C; iv, HCl; v, conc. acid or base; vi, $(CF_3SO_2)_2O$, CH_2Cl_2, NEt_3, −78 °C; vii, R^1X, base; viii, $LiAlH_4$; ix, $(EtO)_2POH$, CCl_4.

SCHEME 1

In the second approach, the formation of a quaternary salt is used to advantage in the alkylation of a substrate in which $(x+1)$ positions are blocked, followed by deblocking to give the required amine as shown in Scheme 2. The Délépine (equation 13) and Ritter (equation 14) reactions are traditional.[1,2] The Ritter reaction also applies to carbonium ions formed from alkyl halides with Lewis acids and from alkenes with proton acids, but potential carbonium ion rearrangements must be borne in mind. Imines (azomethines, Schiff bases) derived from amine and carbonyl compound are important in many amine