HETEROCYCLES IN ORGANIC SYNTHESIS

A. I. MEYERS

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Colorado State University

A Wiley-Interscience Publication

JOHN WILEY & SONS, New York . London . Sydney . Toronto

Library of Congress Cataloging in Publication Data:
Meyers, Albert Irving, 1932-
Heterocycles in organic synthesis.

(General heterocyclic chemistry series)
"A Wiley-Interscience publication."
1. Chemistry, Organic–Synthesis.
2. Heterocyclic compounds. I. Title.

QD262.M56 547'.59 73-17355
ISBN 0-471-60065-2

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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GENERAL HETEROCYCLIC CHEMISTRY SERIES

Edward C. Taylor and Arnold Weissberger, Editors

MASS SPECTROMETRY OF HETEROCYCLIC COMPOUNDS
by Q. N. Porter and J. Baldas

NMR SPECTRA OF SIMPLE HETEROCYCLES
by T. J. Batterham

HETEROCYCLES IN ORGANIC SYNTHESIS
by A. I. Meyers

INTRODUCTION TO THE SERIES

General Heterocyclic Chemistry

The series, "The Chemistry of Heterocyclic Compounds," published since 1950 by Wiley-Interscience, is organized according to compound classes. Each volume deals with syntheses, reactions, properties, structure, physical chemistry, etc., of compounds belonging to a specific class, such as pyridines, thiophenes, pyrimidines, three-membered ring systems. This series has become the basic reference collection for information on heterocyclic compounds.

Many aspects of heterocyclic chemistry have been established as disciplines of *general* significance and application. Furthermore, many reactions, transformations, and uses of heterocyclic compounds have specific significance. We plan, therefore, to publish monographs that will treat such topics as nuclear magnetic resonance of heterocyclic compounds, mass spectra of heterocyclic compounds, photochemistry of heterocyclic compounds, X-ray structure determination of heterocyclic compounds, UV and IR spectroscopy of heterocyclic compounds, and the utility of heterocyclic compounds in organic synthesis. These treatises should be of interest to *all* organic chemists as well as to those whose particular concern is heterocyclic chemistry. The new series, organized as described above, will survey under each title *the whole field of heterocyclic chemistry* and is entitled "General Heterocyclic Chemistry," The editors express their profound gratitude to Dr. D. J. Brown of Canberra for his invaluable help in establishing the new series.

Department of Chemistry
Princeton University
Princeton, New Jersey

Edward C. Taylor

Research Laboratories
Eastman Kodak Company
Rochester, New York

Arnold Weissberger

PREFACE

For too many years organic chemistry has witnessed a trend toward over-specialization within the discipline. We have jokingly referred to specialists in the 17-position of steroids, 3-position in pyridines, and so on. Although much of this specialization is necessary for maximum competence in many complex areas of organic chemistry and although it has undoubtedly led to many exciting developments, the students in both introductory and advanced courses are easily frustrated by attempts to absorb the results of this information explosion. In particular, heterocyclic chemistry has become what many students feel is the sole domain of the dye and medicinal chemist and has little pedogogical value as far as principles and utility in the broad area of organic synthesis are concerned. It is somewhat disappointing to find that this stigma attached to heterocyclic chemistry which was recognized more than 25 years ago in Professor A. A. Morton's monograph on *The Chemistry of Heterocyclic Compounds*[1] remains essentially unchanged. In the preface to this book, which was the first attempt to integrate heterocyclic chemistry into the broad areas of organic chemistry, he wrote:

A generous third of the compounds listed in Beilstein have heterocyclic nuclei; over half of the types of compounds produced by nature have heterocyclic systems; the greater share of the drugs and medicinals and nearly all the alkaloids contain such structures; the large majority of the colors produced by nature and by man have these nuclei as essential components. Yet this wealth of chemical interest, and much more, is scarcely touched in the average textbook. Such compounds as are mentioned are usually treated as individual substances, not as members of a great class of compounds. And if classes of compounds are mentioned, the treatment is too sketchy to be worthwhile or to provide a working knowledge of the subject. Accordingly, the average student of organic chemistry comes to regard heterocyclic compounds as a very special field, to be entered if he desires to be a specialist of a kind, but certainly not to be eagerly studied as the fruition of his efforts to understand the principles of organic chemistry.

Most chemists will agree that investigators in heterocyclic chemistry spend the majority of their effort studying routes to more elaborate systems, improved methods to increase the versatility of heterocyclic syntheses, or the transposition of substituents. On the other hand, chemists who work with nonheterocyclic systems rarely turn to the heterocyclic molecule as a possible solution to their synthetic problems. It is significant that Professor Morton, in his effort to find acceptance of heterocyclic chemistry in general synthesis, actually devoted a small section of his chapter on furans to the "Preparation of Nonfuran Products from Furan Compounds" and began by stating that "Heterocyclic compounds are frequently very useful as sources of non-heterocyclic materials." This was followed by citing the formation of α-(*t*-alkyl) carboxylic acids from 5-(*t*-alkyl) furoate esters.

This philosophy, briefly touched upon in 1946, has nevertheless been widely overlooked both by the teacher and by the researcher in organic chemistry. For several years I have been primarily concerned with establishing this concept in synthesis, which has resulted in an accumulation of data from both the literature and my own laboratory.

It is, therefore, the main goal of this work to demonstrate that many useful (as well as superior) methods for obtaining functionalized organic compounds and structures of diverse architecture can be found by employing a heterocycle either as a precursor, reagent, or vehicle for formation. This approach would serve two valuable purposes. First, it would illustrate to the beginning student that a place in the repertoire of organic compounds should be reserved for heterocycles. Second, it would stimulate the imagination of investigators into looking at a heterocyclic system with the renewed interest in its potential synthetic utility.

The book is divided into chapters devoted to functional groups or classes of organic compounds, in much the same manner in which an introductory organic chemistry text is presented. This means that a variety of different heterocycles appear in each chapter, and many heterocycles reappear in other chapters. The sole requirement for various heterocycles discussed in a given section is that they, in some way, assist or be responsible for the formation of the same class of organic compound. For those interested in the behavior of a particular heterocycle, the index contains references to various classes of compounds derived from each heterocyclic system.

To appreciate the synthetic utility of a heterocycle, some knowledge is required regarding its chemical properties. To present, in a single volume, the synthetic routes and properties of heterocyclic compounds would be undoubtedly presumptuous and incomplete. Only those synthetic schemes and chemical properties that have a bearing on the philosophy already set forth are

[1]A. A. Morton, *The Chemistry of Heterocyclic Compounds*, McGraw-Hill, New York, 1946.

mentioned. For the reader concerned with detailed description of synthesis and chemical properties of heterocyclic molecules, the traditional source material is recommended.[2,3]

Searching the literature for the information that constitutes the body of this monograph proved to be a rather difficult task primarily because the chemical literature is not aligned to this particular subject. For this reason, many interesting and useful synthetic methods derived from heterocycles are certain to have been overlooked. Significant contributions were made by many researchers who replied to a form letter requesting reprints, unpublished materials, and examples known to them that would add to this effort. I am grateful for their time and concern.

Acknowledgment is warmly extended to Mrs. Linda Benedict who typed the manuscript with care and concern. Finally, a debt of gratitude is rendered to Professor E. C. Taylor for his encouragement, enthusiasm, and unending patience in reading the manuscript.

A. I. Meyers

Fort Collins, Colorado
September 1973

[2]The most extensive works dealing specifically with heterocyclic compounds are in the following series of volumes:

(a) *The Chemistry of Heterocyclic Compounds*, A. Weissberger and E. C. Taylor, eds., Interscience, New York.
(b) *Heterocyclic Compounds*, R. C. Elderfield, ed., Wiley, New York.
(c) *Advances in Heterocyclic Chemistry*, A. R. Katritzky, ed., Academic Press, New York. In Volume 7 (p. 225) of this series, source material in heterocyclic chemistry has been summarized.

[3]Monographs of recent vintage that incorporate many of today's modern mechanistic concepts related to heterocycles should also be consulted:

(a) L. A. Paquette, *Modern Heterocyclic Chemistry*, Benjamin, New York, 1968.
(b) A. Albert, *Heterocyclic Chemistry*, Oxford University Press, New York, 1968.
(c) M. H. Palmer, *The Structure and Reactions of Heterocyclic Compounds*, Arnold, London, 1967.

CONTENTS

1 GENERAL CONSIDERATIONS CONCERNING SYNTHETICALLY USEFUL HETEROCYCLIC COMPOUNDS

In the usual planning of a synthetic program, the target molecule is mentally dissected into small and recognizable fragments, which are then considered individually with regard to their accessibility. These "accessible fragments" then become the subject of an assembling process such that they can be physically reconstructed to achieve the synthetic goal. The assembling process—or organic synthesis as chemists prefer to call it—depends invariably on appropriate carbon skeletons and introduction and manipulation of functional groups that serve as "links" to allow all the fragments to be incorporated into the desired product. For the large part, "accessible fragments" have always been nonheterocyclic compounds since heterocycles are not normally considered to be qualified candidates for service in a synthetic program. To blame their lack of utility on inaccessibility would be a gross distortion of fact, as evidenced by the enormous literature pertaining to heterocyclic chemistry.

By contemplating various heterocyclic compounds as an aid in synthesis one may be surprised to learn that considerable functionality, appropriate carbon skeletons, and needed driving forces to achieve a chemical transformation are already "built in" and await the command to perform. To be sure, the chemical behavior of heterocyclic compounds is governed by the same factors that govern *all* chemical behavior, and they respond alike to electronic and solvent effects, as well as to orbital and strain theories. Hence no revolutionary concepts of synthesis need be invoked—merely recognition of their inherent abilities to carry out the desired task. To focus attention by recognition of the unique properties of heterocycles that result in useful synthetic reactions is undoubtedly the *raison d'être* of this monograph.