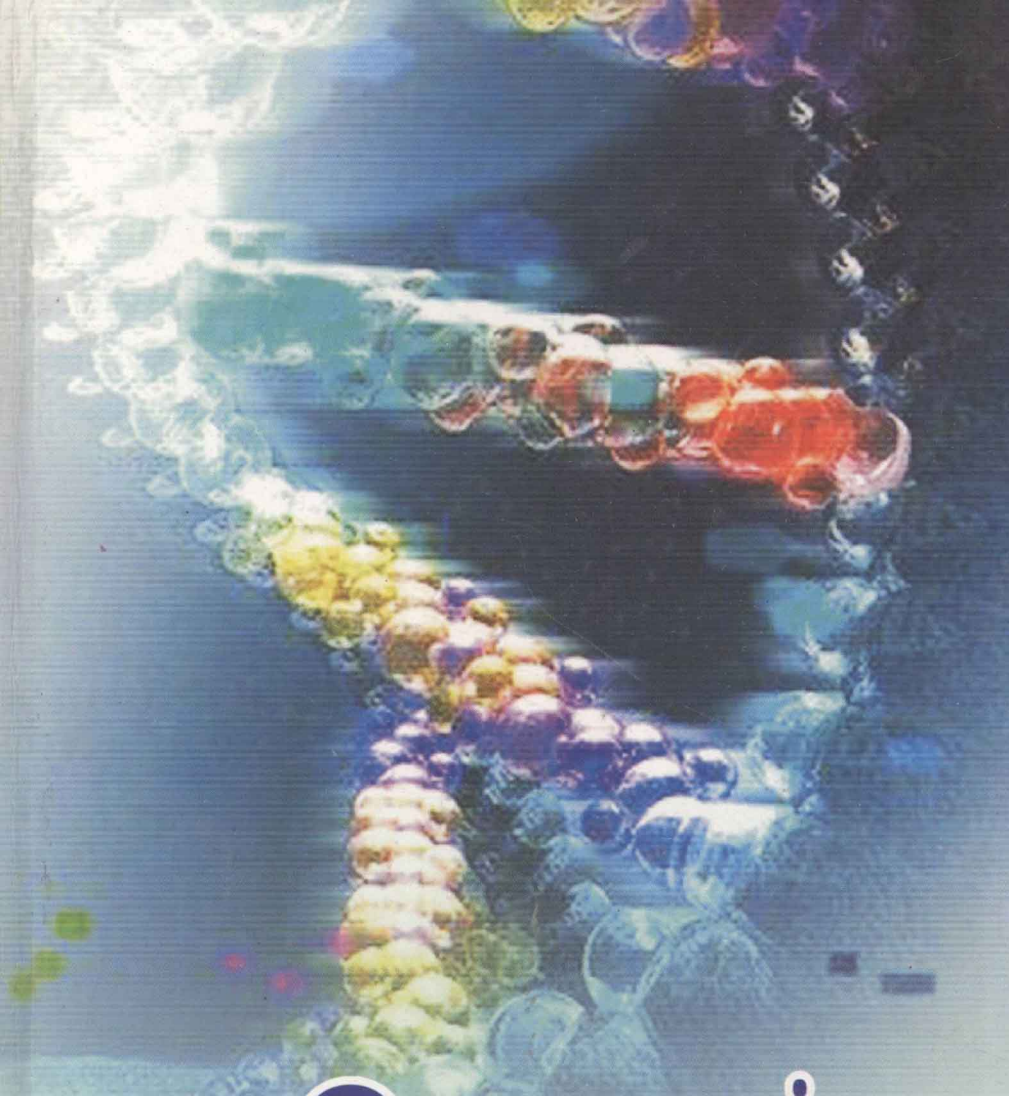

Organic Synthesis

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Preface

As a science in its own right, organic synthesis emerged at the beginning of 20th century, when chemists started to master the skills of manipulating compounds in a controlled and predictable fashion which eventually elaborated an arsenal of tools required for the preparation of various target products from simple starting materials. The spectacular progress achieved from this, complemented by the discovery of new approaches to the analysis of synthetic problems, changed the very image of organic synthesis dramatically. The complexity of tasks increased tremendously and by now one may safely claim that almost any compounds, isolated from natural sources or conceived in the chemists minds, can be synthesized with a reasonable amount of time and effort.

A successful synthesis of an organic compound requires a sound grasp of functional group chemistry, reaction mechanisms and stereochemistry in order for the student to be able to understand the methods of making bonds. It then requires a good grasp of their structural consequences in order to analyses a target molecule in terms of the bonds that can be disconnected to reveal suitable synthetic steps.

This book is an effort to provide an overview of the role of organic synthesis in chemistry and, in general, in science. It introduces the major methods of creating carbon-carbon and carbon-nitrogen bonds, along with functional group inter-conversions. The use of protecting groups and solid-phase methods are also discussed. The analysis of the structure of

target molecule, in terms of the structural consequences of synthetic reactions, is introduced to enable the student to identify key dissections and building blocks and hence develop a suitable synthetic method. It will be a highly valuable reference tool for organic chemistry professionals, students, and those who used to have a rather peripheral contact with this area of organic chemistry.

While writing this book, I have made references from various sources and have freely used the writings of outstanding scholars and researchers. I, hereby, acknowledge their contribution with sincerity and gratitude.

I am thankful to the publisher for bringing out this book within a very short period.

Dr. Akhilesh K. Verma

Contents

Introduction

Of all 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 beginnings of the subject, and thus has a history stretching back over many centuries. It has to be admitted, however, than 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, the chemist has been able to set himself 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.

The fundamental ideas which lie behind this revolution are neither complicated nor new. They consist in recognizing that a covalent bond is formed, in the vast majority or synthetically useful processes, by the interaction of an electrophilic and a nucleophilic atom: and in recognising 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 rarely been included in undergraduate textbooks (or, we suspect, in lecture courses).

In 1835, the German chemist, Friedrich Wohler, who was one of the pioneers of organic synthesis, wrote a letter to his mentor, the great Jons Jacob Berzelius, which included the following often quoted remarks.

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.

If any reader of this introduction feels like that about organic synthesis, let him read on. This guidebook has been written especially for him and those who share his view. It may not lead provide a reliable pathway, over solid ground, as far as the first clearing.

1

Biosynthetic Pathways

The complex organic compounds found in living organisms on this planet originate from photosynthesis, an endothermic reductive condensation of carbon dioxide requiring light energy and the pigment chlorophyll.

$$x\ CO_2 + x\ H_2O + \text{energy} \longrightarrow C_xH_{2x}O_x + x\ O_2$$

The products of photosynthesis are a class of compounds called carbohydrates, the most common and important of which is glucose ($C_6H_{12}O_6$). Subsequent reactions effect an oxidative cleavage of glucose to pyruvic acid (CH_3COCO_2H), and this in turn is transformed to the two-carbon building block, acetate.

The multitude of lipid structures described here are constructed from acetate by enzymatic reactions that in many respects correspond to reactions used by chemists for laboratory syntheses of similar compounds. However, an important restriction is that the reagents and conditions must be compatible with the aqueous medium and moderate temperatures found in living cells. Consequently, the condensation, alkylation, oxidation and reduction reactions that accomplish the biosynthesis of lipids

will not make use of the very strong bases, alkyl halides, chromate oxidants or metal hydride reducing agents that are employed in laboratory work.

1.1 Condensations

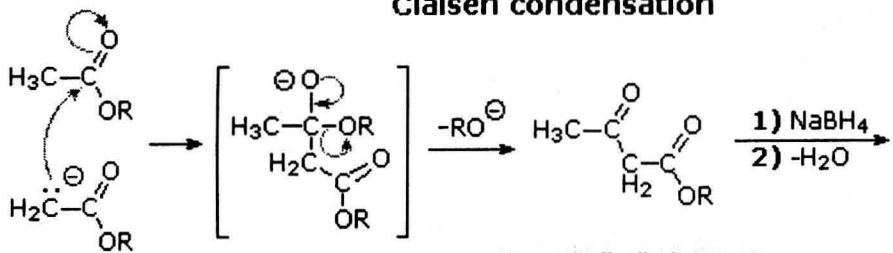
Claisen condensation of ethyl acetate (or other acetate esters) forms an *acetoacetate ester*, as illustrated by the top equation in the diagram of the following page . Reduction, dehydration and further reduction of this product would yield an ester of butyric acid, the overall effect being the elongation of the acetate starting material by two carbons. In principle, repetition of this sequence would lead to longer chain acids, made up of an even number of carbon atoms.

Since most of the common natural fatty acids have even numbers of carbon atoms, this is an attractive hypothesis for their biosynthesis. Nature's solution to carrying out a Claisen-like condensation in a living cell is shown in the bottom equation of the diagram. Thioesters are more reactive as acceptor reactants than are ordinary esters, and preliminary conversion of acetate to malonate increases the donor reactivity of this species. The thiol portion of the thioester is usually a protein of some kind, with efficient acetyl transport occuring by way of acetyl coenzyme A.

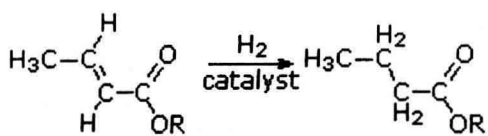
Depending on the enzymes involved, the condensation product may be reduced and then further elongated so as to produce fatty acids, or elongated by further condensations to polyketone intermediates that are precursors to a variety of natural phenolic compounds.

The reduction steps (designated by [H] in the equations) and the intervening dehydrations needed for fatty acid synthesis require unique coenzymes and phosphorylating reagents. The pyridine ring of nicotinamide adenine dinucleotide (NAD) and its 2'-phosphate derivative (NADP) function as hydride acceptors, and the corresponding reduced species (NADH & NADPH) as a hydride donors.

Claisen condensation

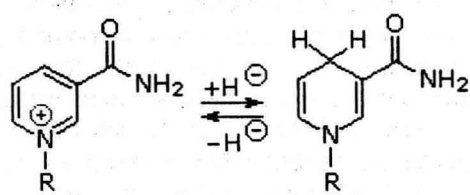


R = small alkyl group



thioester condensation
CO2
enzymes
-RS⊖
-CO2
[H]
-H2O
[H]
R = Coenzyme A or a carrier protein

Partial structures for these important redox reagents are shown below.



NAD ⊕ NADH
NADP ⊕ NADPH

The hydroxyl group is a poor anionic leaving group (hydroxide anion is a strong base). Phosphorylation converts a hydroxyl group into a phosphate (PO_4) or pyrophosphate (P_2O_7) ester, making it a much better leaving group (the pK_as at pH near 7 are 7.2 and 6.6 respectively).The chief biological phosphorylation reagents are phosphate derivatives of adenosine (a ribose compound). The strongest of these is the triphosphate ATP, with the diphosphate and monophosphate being less powerful.

The overall process of fatty acid synthesis is summarized for palmitic acid, $CH_3(CH_2)_{14}CO_2H$, in the following equation:

$$8\ CH_3CO\text{-}CoA + 14\ NADPH + 14\ H^{(+)} + 7\ ATP + H_2O \longrightarrow CH_3(CH_2)_{14}CO_2H + 8\ CoA + 14\ NADP^{(+)} + 7\ ADP + 7\ H_2PO_4^{(-)}$$

1.2 Alkylations

The branched chain and cyclic structures of the terpenes and steroids are constructed by sequential alkylation reactions of unsaturated isopentyl pyrophosphate units. As depicted in the diagram of the next page, these 5-carbon reactants are made from three acetate units by way of an aldol-like addition of a malonate intermediate to acetoacetate.