UMPOLED SYNTHONS

A Survey of Sources and Uses in Synthesis

Edited by

TAPIO A. HASE

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University of Helsinki
Helsinki, Finland

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CONTRIBUTORS

DAVID J. AGER, Department of Chemistry, University of Toledo, Toledo, Ohio

TAPIO A. HASE, Department of Chemistry, University of Helsinki, Helsinki, Finland

MICHAEL KOLB, Strasbourg Research Center, Merrell Dow Research Institute, Strasbourg, France

JORMA K. KOSKIMIES, Department of Chemistry, University of Helsinki, Helsinki, Finland

JOSEPH E. SAAVEDRA, Frederick Cancer Research Facility, National Cancer Institute, Frederick, Maryland

NICK H. WERSTIUK, Department of Chemistry, McMaster University, Hamilton, Ontario

FOREWORD

In 1981 Professor Tapio A. Hase and his associate Jorma K. Koskimies published an excellent compilation of acyl anion equivalents in *Aldrichimica Acta*. During a vist to Helsinki in June of 1982, I encouraged Dr. Hase to undertake the writing of an extensive and more general publication on synthetic equivalents, because the earlier brief review was so useful. The present volume represents the completion of the first phase of this major effort. It places at the disposal of synthetic chemists a large and well-organized body of information drawn mainly from developments in synthesis over the past 20 years.

Contemporary activity in organic synthesis is impressive by any standard. Each year scores of new syntheses are described which are remarkable for the ingenuity underlying their design, the elegance and inventiveness with which known and new chemistry are applied, and the effectiveness of laboratory execution. Reviews such as this text play a significant role in the achievement of this level of accomplishment.

Most contemporary syntheses are planned with the guidance of retrosynthetic analysis and appropriate higher level strategies, e.g., topological, stereochemical, or those centered on the identification of key-reactions or key-intermediates. The chemist must perceive critical information extracted from the target structure and each precursor structure generated in the analysis, and couple this with the vast body of chemical knowledge, to derive potentially valid synthetic sequences. The number of possibilities to be analyzed is awesome. Yet, before proceeding with the execution of a particular plan, the chemist is well advised to carry out a very extensive analysis. This is one of the areas in which critical and comprehensive compendia of synthetic information are of great importance.

I sincerely hope that practicing synthetic chemists will utilize fully this valuable source of information on synthetic equivalents.

E. J. COREY

PREFACE

Following E. J. Corey's introduction in 1967 of the concept of synthons, it has become common among practitioners of organic synthesis to treat numerous synthetic reactions as simple combinations of the appropriate synthons instead of writing out the actual reagents in full. Thus, for a Grignard reaction, it is convenient to write

$$^{+}\text{CHR—OH} + {}^{-}\text{R}' \longrightarrow \text{R}'\text{—CHR—OH}$$

and to dispense with the Mg and the halide anion that do not appear in the final isolated product. Similarly, an alkyl halide RX (an electrophilic reagent) may be simplified to R^+ which, barring side-reactions, clearly will combine with another synthon bearing a negative charge. For synthetic purposes this can be done irrespective of S_N1/S_N2 mechanistic considerations, although in practice the various limitations of a particular synthon, reaction conditions, and reactivities must of course be kept in mind.

The emergence of the concept of "umpolung" (Seebach) or "symmetrization of reactivity" (Corey) has made the synthon approach even more important. At the same time, the use of synthons has become more demanding because the new umpoled species no longer necessarily look very much like the actual reagents. A case in point is the acyl cation/acyl anion synthon pair. Although it is obvious to treat an acyl halide as an acyl cation synthon, it may be less clear that, say, 1-methyl-3,5-dithiazolidine is in fact a source for the formyl anion synthon, $^{-}$CH=O. Also, unlike the classical synthons, which are usually obtained by a simple disconnection from a reagent, many of the new umpoled synthons are more or less obviously incapable of actual existence ($^{-}$COOH, for example) and are seldom available by a simple disconnection.

Synthons originally were introduced as a vehicle for performing the analysis of organic syntheses. If one were to use synthons in planning an actual synthesis, it would be convenient to have access to a catalog of synthons, showing the various sources (i.e., reagents) for any given synthon, along with key information on reaction conditions, reactivities, and possible limitations.

However, professional synthetic workers do not need to be reminded that

aralkyl ketones, for example, can be made in a Friedel-Crafts reaction using an acyl cation synthon derived from the acyl halide. Indeed, most synthetists could probably run a simple Friedel-Crafts acylation without consulting the literature. In any case, most of the reliable classical reactions have been discussed thoroughly and reviewed over the years, and ample digested information is available on these reactions.

The purpose of this book is to provide chemists who plan their synthetic routes manually with information on some of the new umpoled synthons. The introductory chapter examines, in general, the use of synthons in planning organic syntheses. Concluding the introduction is a fairly detailed list of generally convenient synthons that are, however, extraneous to the main contents of the book. A major portion of the book is devoted to acyl anions, hydroxycarbonyl and related anions, carbonyl α-cations, and carbonyl β-anions. A further group comprises carbanionic synthons in which the carbon atom carries a singly bonded heteroatom (O, S, N, or halogen). In appropriate chapters, the above synthons are surveyed with emphasis on the aspects relating to synthetic use. The book concludes with a tabular presentation of known applications of these synthons, with relevant data on the sources, auxiliary reagents, yields, and restrictions. Each table has been prepared by the author of the corresponding chapter, with the exception of Tables 6.1.–6.9., which were prepared by Dr. Koskimies.

Although well over 2000 references have been cited, it is quite possible that some important references have been overlooked, and sincere apologies are offered to anyone feeling neglected in this respect. However, in addition to plain ignorance, the omissions may also be due to the Editor's feeling that the most recent work should be cited preferentially, and references to previous work then can be easily located. For the same reason, references are usually omitted to preliminary communications that have been followed up by full papers.

In closing, it is a great pleasure for me to thank Professor E. J. Corey, without whose initiative and encouragement this book would not have been started. The members of the Organic Chemistry Laboratory at the University of Helsinki who have been involved with the editing and writing of the book are most sincerely thanked. Professor Gösta Brunow and Dr. Jorma Koskimies read through all chapters and provided criticism and valuable suggestions. Kristiina Wähälä, M.Sc., was exceedingly helpful and resourceful in checking and sorting out the literature references and taking care of numerous other editing details. Lasse Koskinen and later Hannu Hirvonen gave invaluable assistance in the operation and maintenance of our laboratory text processing system for the needs of compiling this book.

TAPIO A. HASE

Helsinki, Finland
January 1987

ABBREVIATIONS AND CONVENTIONS

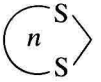
Ac	Acetyl
AcF_3	Trifluoroacetyl
AcOH	Acetic acid
tAm, Am-t	1,1-Dimethylpropyl
Ar	Aryl
Bu	Butyl
iBu, Bu-i	Isobutyl
sBu, Bu-s	*sec*-Butyl
tBu, Bu-t	*tert*-Butyl
Bzl	Benzyl
cat.	Catalysis, catalyst
Cb	Carboxybenzyl
Cp	Cyclopentadienyl
Cx	Cyclohexyl
d	Day
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNPH	2,4-Dinitrophenylhydrazone
ee	Enantiomeric excess
El	Electrophile
Et	Ethyl
h	Hour
(H)	Reduction
$h\nu$	Photolysis, photochemical reaction
het	Heterocycle
Hex	Hexyl
HMPA	Hexamethyl phosphorictriamide

KDA	Potassium diisopropylamide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LDCA	Lithium dicyclohexylamide
LDMAN	Lithium 1-dimethylaminonaphthalenide
LN	Lithium naphthalenide
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
MCPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MEM	2-Methoxyethoxymethyl
Met	Metal
Mes	Mesityl (2,4,6-trimethylphenyl)
Ms	Methanesulfonyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMP	1-Methyl-2-pyrrolidone
Np	Naphthyl
Nu	Nucleophile
(O)	Oxidation
PbTA	Lead tetraacetate
Pe	Pentyl
Ph	Phenyl
Phth	Phthalyl
Pr	Propyl
iPr, Pr-i	Isopropyl
PTC	Phase-transfer catalysis or catalyst
py	Pyridine
R	Alkyl
R—Ni	Raney nickel
rt	Room temperature, ambient temperature
Tf	Trifluoroacetyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMEDA	Tetramethylethylenediamine
TMSCN	Trimethylsilyl cyanide
Tol	*p*-Tolyl
TosMIC	Toluene 4-sulfonylmethyl isocyanide
Ts	*p*-Toluenesulfonyl
X	Halogen
xs	Excess
$\rightarrow$	Reaction (synthetic direction)
$\Rightarrow$	Disconnection (retrosynthetic direction)
Δ	Heat

In some structural formulas, unessential substitutents are stripped for clarity. Such formulas apply to cases where the structure given is general in terms of degree of alkyl substitution. Thus, C═C—COOH is short for R—CR′═CR″—COOH where R, R′, and R″ can be any combination of H and alkyl groups. Cases where generality is lacking or was not studied, or where just a single structure is possible, are given in full.

In indicating ring sizes, the "*n*" accounts for all ring atoms:

cyclopentene and larger if $n \geq 5$



1,3-dithiane if $n = 6$

CONTENTS

TABULAR SURVEY OF UMPOLED SYNTHONS

1

INTRODUCTION: CLASSICAL AND UMPOLED SYNTHONS

Tapio A. Hase

In 1967, E.J. Corey[1] introduced the new concept of *synthons,* defining them as "structural units within a molecule which are related to possible synthetic operations." He went on to point out how the synthetic chemist has learned by experience to recognize within a target molecule these units that can be synthesized, modified, or joined by known or conceivable synthetic operations. Certainly, any reasonably proficient pre–1967 synthetic chemist requiring an alkyl aryl ketone would immediately have thought of joining an aryl fragment to an acyl group by using the Friedel-Crafts reaction of an arene with an acyl halide. Whether having thought or not in terms of the aryl and acyl fragments, that is, synthons, he or she would have written out the synthesis as

$$\mathrm{ArH} + \mathrm{RCOCl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArCOR} \; (+\mathrm{HCl})$$

Synthons are formally obtainable from a molecule by the disconnection of a single bond. Although any such bond may be disconnected, as far as actual synthesis is concerned the most useful disconnections will involve carbon–carbon bonds. Thus, an alkyl aryl ketone can be seen to furnish the synthons Ar, RCO, R, and ArCO, with Ar and RCO being used in the above example. In this context, it should be pointed out that disconnections of double bonds, although feasible, actually correspond to two-step synthetic processes and do not give conveniently handled synthons.[2]

Synthons were first introduced as a means for performing the analysis of organic syntheses, that is, for retrosynthetic operations. As originally defined, synthons were not visualized as carrying a charge or an unpaired electron. Later, as the use of synthons in planning actual syntheses became widespread and many previously unexpected synthons were being developed deliberately and were in routine use, it became useful to view disconnection as a heterolytic

(or homolytic) process that gives two cation/anion pairs (or two radicals), as shown in Scheme (1).

$$\text{ArCOR} \begin{cases} \nearrow \; \text{Ar}^+ + {}^-\text{COR (or Ar}^- + {}^+\text{COR)} \\ \searrow \; \text{ArCO}^+ + \text{R}^- \text{ (or ArCO}^- + \text{R}^+) \end{cases} \tag{1}$$

Now, the above Friedel-Crafts acylation can be represented as

$$\text{Ar}^- + \text{RCO}^+ \longrightarrow \text{ArCOR} \tag{2}$$

Unquestionably, this is a very efficient and concise way of indicating a Friedel-Crafts reaction, and our pre–1967 chemist would presumably have understood what is meant by this expression. However, he or she might also have made two pertinent remarks in this connection. First, it would have been noted that the alkyl aryl ketone can be made from the same acyl halide under at least one other set of conditions, that is, by using the diarylcadmium reagent Ar_2Cd. This then must be another source for the Ar^- synthon. Possibly, yet other routes from the acyl halide to the ketone could have been found. Obviously, there can be several sources for any given synthon; thus it is clear that one must have a good grasp of the vast number of organic reactions to be able to use synthons effectively in planning syntheses. Alternatively, a "menu" of the available synthons would be highly useful. A further difficulty arises when one realizes that there are many synthons that clearly cannot exist, or in any case are unlikely to exist as such, for example, $^-$COOH or $^-CH_2CH_2Cl$. This however is not a problem as long as the menu provides the synthetist with suitable multistep sequences that correspond overall to the change required, for example, R—Br → R—COOH.

Second, reaction (2), even if taken to represent a Friedel-Crafts acylation, tells one nothing about the compatibility of existing functionality in the aromatic ring, for example. To take this and similar aspects into account, one must either be very familiar with the reaction in question, or consult the literature. Most conveniently, the menu referred to previously should include information about the applicability and restrictions of the various synthons.

The bulk of this book is intended to serve as precisely such a menu, at least for some of the less accessible but important synthons of recent origin. Partial listings of various types of synthons, based on one unifying theme or another, have appeared in the literature.[3–9] Additional references to previous reviews are given in the introductory remarks in the chapters that follow.

DEFINING SYNTHONS

We visualize synthons as purely conceptual entities that may or may not actually exist, however fleetingly, in a reaction. For our purposes, synthons

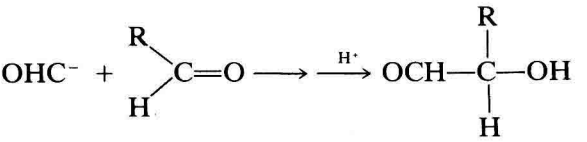
are defined as cationic or anionic fragments of a neutral molecule, formally obtained from the latter by heterolysis of one single bond. Two pairs of synthons can always be written for the heterolysis, or disconnection, of a single bond (Scheme 1). Therefore, the combination of a cationic and an anionic synthon gives a neutral molecule. In this book, a full positive or negative charge will always be shown irrespective of whether in the actual reagents a full or partial charge would be more appropriate.

It is unfortunate that in current usage the word "synthon" sometimes has quite another meaning. Instead of indicating fragments of a molecule, as pointed out above and set out below in more detail, the word is used as a synonym for "reagent" or "synthetic equivalent," or "convenient starting material," such as in the expression "mannitol is a synthon for (R)-glyceraldehyde." This practice is redundant, does not agree with the original definition, and should be abandoned.

There is also another matter of definitions we would like to bring up at this point. Homologations of carbonyl compounds, such as those based on the Wittig and related reactions,

$$R{-}CHO \longrightarrow R{-}CH_2CHO \ (\textit{via}\ RCH{=}CH{-}OR')$$

are sometimes referred to as corresponding to operation with an acyl anion synthon (here ^-CHO). This is not entirely correct because the addition of the formyl anion synthon to another aldehyde will obviously give, after proton quench, a homologated α-hydroxyaldehyde (Scheme 3):



(3)

It is as if the starting aldehyde RCHO in the Wittig homologation reaction acts as a source for the RCH_2^+ synthon. However, in Grignard reactions an aldehyde's synthon equivalent normally is RCH^+OH, as is easily seen by writing down a Grignard reaction of this sort, and as is in fact apparent from Scheme (3). It is true that any aldehyde RCH_2CHO can be disconnected to give the ^-CHO synthon (which is to say it can be thought to be formed using the formyl anion synthon). However, the cationic counterpart to ^-CHO is then necessarily RCH_2^+, available from RCH_2Br, for example. The discrepancy is now apparent: The nonphosphorus component in the Wittig reaction is RCHO, not RCH_2Br. The problem only arises because the Wittig reaction is a multistep process involving an elimination step, the latter being a reaction that cannot be handled using synthons. This example shows that careless use of terminology will very easily obscure the admirably simple yet useful basic concept of synthons.

It follows from our definition that only single-step substitution and addition