

**Radicals in Organic Synthesis:
Formation of Carbon–Carbon Bonds**

BERND GIESE

Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds

BERND GIESE

Institut für Organische Chemie und Biochemie, Technische Hochschule Darmstadt,
Federal Republic of Germany

PERGAMON PRESS

OXFORD · NEW YORK · BEIJING · FRANKFURT
SÃO PAULO · SYDNEY · TOKYO · TORONTO

U.K.	Pergamon Press, Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press, Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
PEOPLE'S REPUBLIC OF CHINA	Pergamon Press, Qianmen Hotel, Beijing, People's Republic of China
FEDERAL REPUBLIC OF GERMANY	Pergamon Press, Hammerweg 6, D-6242 Kronberg, Federal Republic of Germany
BRAZIL	Pergamon Editora, Rua Eça de Queiros, 346, CEP 04011, São Paulo, Brazil
AUSTRALIA	Pergamon Press Australia, P.O. Box 544, Potts Point, N.S.W. 2011, Australia
JAPAN	Pergamon Press, 8th Floor, Matsushita Central Building, 1-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160, Japan
CANADA	Pergamon Press Canada, Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada

Copyright © 1986 Pergamon Books Ltd.

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means: electronic, electrostatic, magnetic tape, mechanical, photocopying, recording or otherwise, without permission in writing from the publishers.

2nd edition, 1986

Library of Congress Cataloging in Publication Data

Giese, Bernd, 1940-

Radicals in organic synthesis.

(Organic chemistry series ; v. 5)

Includes bibliographies and index.

1. Chemistry, Organic — Synthesis. 2. Radicals (Chemistry) I. Title.

II. Series: Organic chemistry series (Pergamon Press) ; v. 5.

QD262.G48 1986 547'.2 86-17052

British Library Cataloguing in Publication Data

Giese, Bernd

Radicals in organic synthesis : formation of carbon-carbon bonds. —
(Organic chemistry series ; v. 5)

1. Free radicals (Chemistry) 2. Reactivity (Chemistry) 3. Chemistry,
physical organic

I. Title II. Series

547.1'224 QD471

ISBN 0-08-032493-2 Hardcover

ISBN 0-08-032494-0 Flexicover

In order to make this volume available as economically and as rapidly as possible the author's typescript has been reproduced in its original form. This method unfortunately has its typographical limitations but it is hoped that they in no way distract the reader

Printed in Great Britain by A. Wheaton & Co. Ltd., Exeter

Foreword

The past twenty years have witnessed an unparalleled development of new synthetic methods in the field of organic chemistry. Many of these new methodologies involve the same basic ionic processes which were involved in the early development of the mechanistic picture of organic chemistry. Although of great power these ionic processes do suffer from limitations, in particular the problems of compatibility of functional groups. This is especially so in highly functionalised molecules.

Within the last decade however a new approach to bond formation has been emerging, namely the use of homolytic or radical reactions. It is already evident that these processes, well known of course in the polymer industry, have a great role to play in the synthesis of complex molecules. Professor Bernd Giese is a pioneer of this new development. In this book he describes in a masterly fashion the developments which have occurred and in particular how the practising synthetic chemist can make use of them in his work. The book will be of wide use to all chemists involved in synthesis both in industry and academia.

J E Baldwin, FRS
Dyson Perrins Laboratory
University of Oxford

Acknowledgements

First of all I would like to thank my American postdoctorate collaborator Dr. D.B. Gerth for helping me to make my English more readable and for the numerous suggestions he has made throughout the writing of the manuscript. Furthermore, I am indebted to a large group of coworkers who have proofread the original manuscript as well as the references, namely:
D. Bartmann, J.A. González-Gómez, K. Gröninger, T. Haßkerl, K. Jäger, M. Leising, W. Mehl, M. Nix, B. Rückert, R. Rupaner, G. Thoma, and T. Witzel. The manuscript was patiently typed by Mrs. E. Schmieg and the extensive art work was superbly done by Mrs. H. Roth and Mrs. E. John. Final proofreading was done by A. Ghosez and Dr. D.B. Gerth. I would also like to thank all of the colleagues who have send me preprints of their work, which have allowed me to cover literature references up to mid 1986.

Abbreviations

Ac	acetyl
AIBN	azoisobutyronitrile
Ad	adamantyl
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
Cbz	carbobenzyloxy
Co(dmgh) ₂ py	cobaloxime (see p. 102)
DBU	diazabicycloundecane
DEAD	diethylazodicarboxylate
DHP	dihydropyran
DME	dimethoxyethane
DTBP	di- <i>t</i> -butylperoxide
e ⁻	electron
Et	ethyl
HMPA	hexamethylphosphortriamide
Im	imidazolyl
LDA	lithium diisopropylamide
MCPBA	m-chloroperbenzoic acid
Me	methyl
NBS	N-bromosuccinimide
OGlu(OAc) ₄	tetraacetylglucoside
PCC	pyridinium chlorochromate
Pr	propyl
TBHP	<i>t</i> -butylhydroperoxide
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
Tol	p-tolyl

Contents

ABBREVIATIONS	xiii
CHAPTER ONE	
INTRODUCTION	1
REFERENCES	2
CHAPTER TWO	
BASIC PRINCIPLES	
A. GENERAL ASPECTS OF SYNTHESSES WITH RADICALS	4
1. Reactions between radicals	5
2. Reactions between radicals and non-radicals	6
a. Selectivity requirement	7
b. Reactivity requirement	12
B. ELEMENTARY REACTION STEPS BETWEEN RADICALS AND NON-RADICALS	13
1. Introduction	13
2. Addition	14
3. Substitution	17
4. Elimination	18
5. Rearrangement	19
6. Electron transfer	20

C. COMPARISON OF RADICALS AND IONS IN SYNTHESSES	22
1. Chemoselectivity	22
2. Regioselectivity	24
3. Stereoselectivity	26
4. Umpolung	29
5. Racemization	31
REFERENCES	32
CHAPTER THREE	
INTERMOLECULAR FORMATION OF ALIPHATIC C-C BONDS	36
A. INTRODUCTION	36
B. TRAPPING WITH HYDROGEN DONORS.	38
1. Mercury hydride	38
a. Halides	40
b. Alkenes	41
c. Cyclopropanes	49
d. Ketones	54
2. Tin hydride	56
a. Halides	57
b. Alcohols and selenides	64
c. Nitro compounds	65
3. Germanium hydride	67
4. "Carbon hydride"	69
a. Alcohols, ethers, and acetals	70
b. Aldehydes and formic acid derivatives	72
c. Ketones	73
d. Esters and lactones	74
e. Amines	75
f. Amides and lactams	76
g. Chloroform	76
h. Hydrocarbons	77

C. TRAPPING WITH HETEROATOM DONORS	77
1. Halogen donor	77
2. Thio donor	82
3. Boron donor	86
D. TRAPPING BY ELECTRON TRANSFER REACTIONS	89
1. Oxidation by metal ions	89
2. Anodic oxidation	94
3. Syntheses via $S_{RN}1$ reactions	95
E. FRAGMENTATION	97
1. Cleavage of carbon-heteroatom bonds	98
a. Carbon-tin bonds	98
b. Carbon-cobalt bonds	102
c. Carbon-sulfur bonds	104
2. Cleavage of oxygen-oxygen bonds	106
F. MISCELLANEOUS RADICAL ADDITION REACTIONS	107
G. RADICAL-RADICAL REACTIONS	113
1. Oxidative coupling	113
a. Oxidation of anions	113
b. Dehydrodimerization	119
2. Reductive coupling	122
3. Diacylperoxides and azo compounds	125
REFERENCES	127

CHAPTER FOUR

INTRAMOLECULAR FORMATION OF ALIPHATIC C-C BONDS	141
A. INTRODUCTION	141
1. Regioselectivity	144
2. Stereoselectivity	147
B. TRAPPING WITH HYDROGEN DONORS	151
1. Mercury hydride	151
2. Tin hydride	154
3. "Carbon hydride"	170-

C. TRAPPING WITH HETEROATOM DONORS	173
1. Halogen donor	173
2. Thio donor	176
3. Oxygen donor	178
4. Metal donor	179
D. TRAPPING BY ELECTRON TRANSFER REACTIONS	182
1. Oxidation	182
2. Reduction	185
E. FRAGMENTATION AND DISPLACEMENT	189
F. BIRADICALS	192
1. Reductive cyclization	192
2. Photolytical cyclization of ketones	193
3. Diazenes	197
REFERENCES	203

CHAPTER FIVE

C-C BOND FORMATION OF AROMATIC SYSTEMS	210
A. INTRODUCTION	210
B. REACTIONS WITH CARBOCYCLIC AROMATIC COMPOUNDS	212
1. Electrophilic radicals	213
2. σ -Radicals	216
3. Nucleophilic π -radicals	220
C. REACTIONS WITH HETEROCYCLIC AROMATIC COMPOUNDS	221
1. Alkylation	225
a. Hydrocarbons	225
b. Alkyl iodides	226
c. Alcohols and ethers	227
d. Alkenes	230
e. Derivatives of aldehydes and ketones	231
f. Carboxylic acids	233
g. Dialkylamides	234

2. Acylation	235
a. Formation of aldehydes	235
b. Formation of ketones	236
c. Formation of carboxylic acids	236
3. Miscellaneous C-C bond formations	237
D. REACTIONS OF ARYL RADICALS	241
1. Aryldiazonium salts	242
2. Arylhalide/tin hydride	246
3. $S_{RN}1$ reaction	247
a. Conjugated hydrocarbons	249
b. Ketones	250
c. Aldehydes, esters and amides	253
E. RADICAL IONS	255
1. Radical cations	256
2. Radical anions	259
REFERENCES	261

CHAPTER SIX

METHODS OF RADICAL FORMATION	267
A. CARBON-HALOGEN BONDS	268
B. CARBON-OXYGEN BONDS	269
1. Alcohols	269
2. Aldehydes, ketones, and esters	270
C. CARBON-SULFUR AND CARBON-SELENIUM BONDS	272
1. Alkylsulfides, arylsulfides, alkylselenides, and acylselenides	272
D. CARBON-NITROGEN BONDS	273
1. Amines	273
2. Nitro compounds	273
3. Diazonium salts	274
4. Azo compounds	274

E. CARBON-CARBON BONDS	275
1. Carboxylic acids	275
2. Ketones	276
3. Cyclopropanes	276
4. Alkenes	277
5. Alkenes and aromatic compounds	278
F. CARBON-HYDROGEN BONDS	279
G. CARBANIONS	280
H. CARBON-BORON BONDS	280
I. CARBON-MERCURY BONDS	281
J. CARBON-COBALT BONDS	281
 AUTHOR INDEX	 282
SUBJECT INDEX	291

Chapter 1

Introduction

Radical chemistry dates back to 1900 when Gomberg¹ investigated the formation and reactions of the triphenylmethyl radical. In the 1920's Paneth² showed that less stabilized alkyl radicals also exist and measured the lifetime of these radicals in the gas phase. Organic synthesis with radicals began in 1937 when Hey and Waters³ described the phenylation of aromatic compounds by benzoyl peroxide as a radical reaction. The same year, Kharasch⁴ recognized that the anti-Markovnikov addition of hydrogen bromide to alkenes proceeds via a radical chain process. In the following years, Mayo, Walling, and Lewis⁵ discovered the rules of radical copolymerization reactions. The results of these early investigations were presented in two texts on radical chemistry.⁶

The deeper insights into the formation, structure, and reactions of radicals gained in the 1950's and 60's were collected (1973) in a two-volume work edited by Kochi.⁷ In the following years, the work of Ingold and others made available the absolute rate constants of the major radical reactions in solution. These rate data have only recently been compiled in the Landoldt-Börnstein edited by Fischer.⁸

However, the 1970's also witnessed the start of new synthetic methods involving radicals, particularly in substitution

reactions of aromatic compounds.^{9,10} The last years have brought a rapid development in the use of alkyl radicals for the formation of aliphatic C-C bonds and in the synthesis of target molecules.¹¹

This monograph is an attempt to bring together the principles that have to be followed when radicals are used in synthesis and to demonstrate how carbon-carbon bonds can be formed in radical reactions. Since radical chemistry provides mild reaction conditions for the formation of C-C bonds and these bonds constitute the backbone of organic compounds, this book will focus on this topic.

It is suggested that the chapter on the basic principles be read first, because one must have at least some knowledge of the reactivity of radicals in order to successfully apply radical reactions to synthesis.

REFERENCES

1. M. Gomberg, *J. Am. Chem. Soc.* **1900**, *22*, 757; M. Gomberg *Chem. Ber.* **1900**, *33*, 3150.
2. F. Paneth, W. Hofeditz, *Chem. Ber.* **1929**, *62*, 1335.
3. D.H. Hey, W.A. Waters, *Chem. Rev.* **1937**, *21*, 169.
4. M.S. Kharasch, E.T. Margolis, F.R. Mayo, *J. Org. Chem.* **1937**, *2*, 393.
5. F.R. Mayo, F.M. Lewis, *J. Am. Chem. Soc.* **1944**, *66*, 1594; F.R. Mayo, F.M. Lewis, C. Walling, *Discuss. Faraday Soc.* **1947**, *2*, 285.
6. W.A. Waters: *The Chemistry of Free Radicals*, Clarendon Press, Oxford 1946; C. Walling: *Free Radicals in Solution*, Wiley, New York 1957.
7. J.K. Kochi (ed.): *Free Radicals*, Wiley, New York 1973.
8. H. Fischer (ed.), Landoldt-Börnstein, New Series, Vol. 13, Springer, Berlin since 1983.

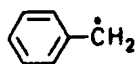
9. J.F. Bunnett, *Acc. Chem. Res.* **1978**, 11, 413.
10. F. Minisci, *Top. Curr. Chem.* **1976**, 62, 1.
11. D.H.R. Barton, W.B. Motherwell in B.M. Trost;
C.R. Hutchinson: *Organic Synthesis Today and Tomorrow*,
Pergamon Press, Oxford 1981; D.J. Hart, *Science* **1984**,
223, 883; B. Giese, *Angew. Chem. Int. Ed. Engl.* **1985**, 24,
553; B. Giese (ed.): *Selectivity and Synthetic Applica-*
tions of Radical Reactions, Tetrahedron "Symposia-in-
Print" Number 22, Tetrahedron **1985**, 41, 3887 ff.

Chapter 2

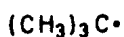
Basic Principles

A. General Aspects of Syntheses with Radicals

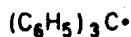
Radicals are species with at least one unpaired electron which, in contrast to organic anions or cations, react easily with themselves in bond forming reactions. In the liquid phase most of these reactions occur with diffusion controlled rates. Radical-radical reactions can be slowed down only if radicals are stabilized by electronic effects (stable radicals) or shielded by steric effects (persistent radicals). But these effects are not strong enough to prevent diffusion controlled recombination of, for example, benzyl radicals 1¹ or tert-butyl radicals 2.² Only in extreme cases, e.g. the triphenylmethyl radical 3 or the di-tert-butyl methyl radical 4,³ recombination rates are low. While the recombination rate of the triphenylmethyl radical 3 is reduced due to both steric and radical stabilizing effects, the steric effect alone slows down the recombination of the di-tert-butyl methyl radical 4. Since 3 and 4 have no C-H bonds β to the radical center, disproportionation reactions, in which the hydrogen atom is transferred, cannot occur.



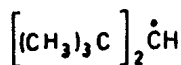
1



2



3



4

1. Reactions between radicals

The fact that reactions between radicals are in most cases very fast could lead to the conclusion that direct radical-radical combination is the most synthetically useful reaction mode. This, however, is not the case because direct radical-radical reactions have several disadvantages:

- In the recombination reactions, the radical character is destroyed so that one has to work with at least equivalent amounts of radical initiators.
- The diffusion controlled rates in radical-radical reactions give rise to low selectivities which cannot be influenced by reaction conditions.
- The concentrations of radicals are so low that reactions with non-radicals, like the solvents, which are present in high concentrations, are often hard to prevent.

Nevertheless, there are useful synthetic applications in which new bonds are formed from radical-radical combination, for example, the Kolbe electrolysis of carboxylates (5+7), with the modern developments by Schäfer,⁴ and the radical induced dehydrodimerization (8+7), which has been studied extensively in the last years by Viehe.⁵