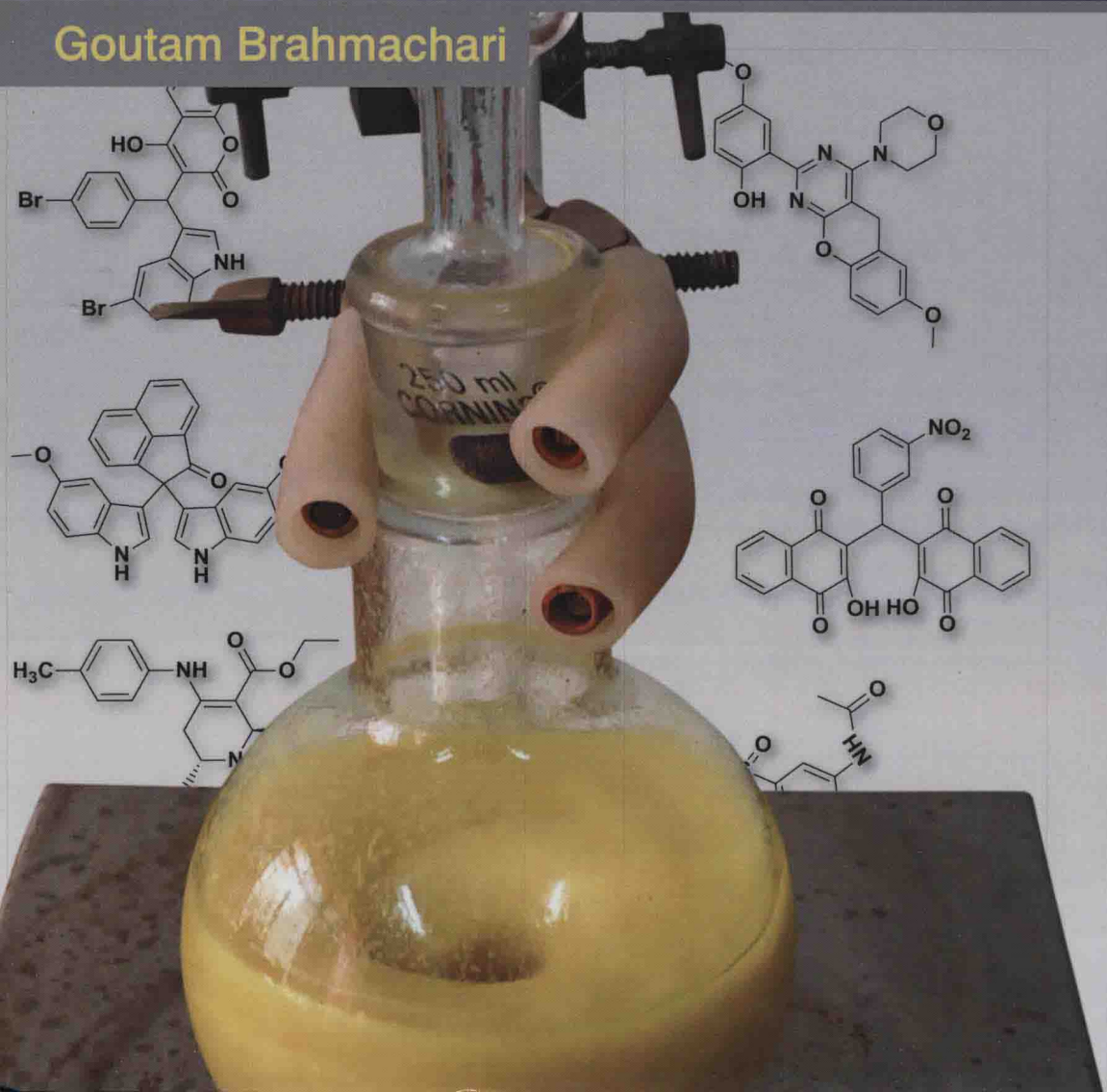


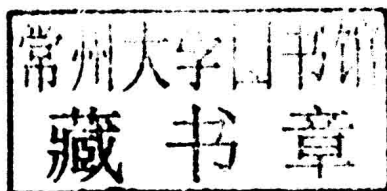
Room Temperature Organic Synthesis

Goutam Brahmachari



Room Temperature Organic Synthesis

Goutam Brahmachari



ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON • NEW YORK • OXFORD
PARIS • SAN DIEGO • SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Elsevier

Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK
225 Wyman Street, Waltham, MA 02451, USA

Copyright © 2015 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

For information on all Elsevier publications
visit our website at <http://store.elsevier.com/>

ISBN: 978-0-12-801025-9



Working together
to grow libraries in
developing countries

www.elsevier.com • www.bookaid.org

Room Temperature Organic Synthesis

Dedication

To my wife *PIYASI* who cares for me a lot!

Foreword

The topic of this book is both important and significant because it allows us to isolate an aspect of synthetic elegance that is all too often overlooked. The transformations of molecules that have been mastered over the past two centuries by synthetic chemists border on the miraculous. We are at a stage where nearly any chemical that can be drawn or represented computationally can be synthesized. And for that reason, the field of synthetic chemistry should be tremendously proud.

However, we also are well aware that many of the methods that have been invented over the years have required extraordinary measures in order to achieve these astonishing results. In some cases, the synthesis would be an extremely large number of steps while in other examples it may be that the results were achieved with an extremely poor yield. But one factor that is often employed is that many of the reactions that have allowed a significant number of the realized achievements over the years is the use of high temperatures.

The use of high temperature in synthesis when necessary us is understandable in order to obtain the desired molecule. However, the brilliance of the chemistry represented in this book, is that it represents the unwillingness of chemists to compromise in the never-ending quest for the ideal. By not accepting that synthetic methods have to be run at high temperatures and can be done at ambient conditions, is an important step toward along the path of continuous improvement.

It is true that running reactions at unnecessarily high temperatures is a waste of energy and is in opposition to the *Principles of Green Chemistry*. But even beyond that, it ignores the fact that so much of the most elegant chemistry, the most complex chemistry, the most important chemistry, is carried out by *Nature* at ambient temperatures. To ignore *Nature* as our most important chemistry teacher, mentor, and inspiration is unwise at best, and harmful and futile at worst.

My compliments and congratulations to Prof. Brahmachari for the important contribution that this book will be for our collective scientific knowledge and may it serve as a catalyst for further improvements in our collective mission in synthetic chemistry.

Paul T. Anastas
Yale University
New Haven
CT, USA

How to Read

As stated in the Preface, the book *Room Temperature Organic Synthesis* is designed with a motto to offer recent cutting-edge advances in developing organic synthetic protocols under ambient conditions, thereby satisfying the *sixth principle of green chemistry*, and features an in-depth and thorough coverage of a huge number of organic synthetic protocols at room temperature. This definite volume incorporates more than 200 sincerely screened organic synthetic protocols at room temperature for generation of carbon-carbon and carbon-heteroatom bonds resulting a wide spectrum of chemical compounds — aliphatic, aromatic, alicyclic and heterocycles. The reactions are classified in eight distinct chapters (Chapter 1 to 8) based on their bond forming strategies such as C – C, C – N, C – O, C – S, C – P, C – halogen, C – B, and miscellaneous bond forming reactions (*viz.* C – H, N – H, O – Si, S – N, S – O and S – S). Clearly structured for easy access to the information, each selected reaction is discussed in a very compact manner through point-wise discussion such as: Reaction type; Reaction conditions; Reaction strategy; Catalyst; Keywords; General reaction scheme; Mechanism; Representative examples; Experimental procedure; Characterization data of representative entries; Reference. Reaction scheme, plausible mechanism (if any) and illustrative examples relating to a particular reaction are presented under that reaction and are self-explanatory in nature. Each organic synthesis is supplemented with all its details including experimental procedure, representative examples and their physical and spectral properties so that one can reproduce the same with ease.

Preface

Organic synthesis is a special branch of chemical synthesis involved with the construction of organic compounds following certain distinct methodologies! It is truly a hardcore laboratory based set-up to carry out the desired organic reactions for the purpose. Over the past two centuries, synthetic organic chemistry has seen a tremendous all-round development, and the credits obviously go to the synthetic chemists at large!

Organic molecules often find their uses as key starting materials for a great number of major chemical industries. The production of organic chemicals as raw materials or reagents for other applications is a major sector of manufacturing polymers, pharmaceuticals, pesticides, paints, artificial fibres, food additives, *etc.* The overall outcome of an organic synthesis, *i.e.* the productivity, cost, safety, hazards, energy-efficiency, environmental-concerns *etc.*, is largely dependent on the generality and effectiveness of its synthetic method. Organic synthesis involves breakage and formation of chemical bonds! Formations of new bonds are broadly categorized as carbon-carbon and carbon-heteroatom bond forming reactions resulting a wide spectrum of chemical compounds — aliphatic, aromatic, alicyclic, heterocycles and so on. Hence, proper information on the recent development of novel and useful methods for carbon-carbon and carbon-heteroatom bond formation is of prime importance to the synthetic chemists.

With the advent of the twenty-first century, Anastas and Warner through their “*The Twelve Principles of Green Chemistry*” have developed a concept of “*Green Chemistry*” or “*Environmentally Benign Chemistry*”. This serves as guidelines for practicing chemists in developing and assessing how green a synthesis, compound, process, or technology is! The first principle espouses the basic tenet of green chemistry, namely, pollution prevention. Other principles deal with topics such as atom economy, toxicity, the use of solvents and auxiliary agents, energy usage, renewable *versus* non-renewable feedstocks, and decomposition of compounds into non-toxic, environmentally benign substances. The last decade has seen a huge interest in green chemistry, particularly as organic chemists look to “green” the methodologies/techniques for the synthesis of organic molecules of interest! As a result several methodologies/concepts such as solvent-free synthesis, organic reactions under aqueous conditions, organic reactions in non-aqueous media, greener organic reagents, development of heterogeneous catalysts and ionic liquids, waste management/recycling strategies, application of ultrasound, and microwave technology as a greener heating tool have emerged and are in extensive use at present-time.

The *sixth principle* is dedicated to “*Design of Energy Efficiency*”. That is to develop synthetic strategies that require less/minimum amount of energy to carry out a specific reaction with optimum productivity. During large-scale industrial production, energy usage is also a vital concern. For this purpose, use of microwave and application of ultrasound are in use as substitutes of conventional heating. *However, the most effective way-out to save energy is to develop strategies/protocols that are capable enough to carry out the transformations at ambient temperature!* In addition, room temperature condition is a mild reaction strategy, essentially required for many temperature-sensitive organic substrates as a key step in multi-step sequence reactions. That is why, as part of on-going developments on green synthetic

strategies, designing for room temperature conditions coupled with other green aspects is also an area of current choice. The concept of developing room temperature reaction strategy is now an emerging field of research in organic chemistry and is progressing largely.

The book *Room Temperature Organic Synthesis* is a first-time attempt to offer recent cutting-edge advances in developing organic synthetic protocols under ambient conditions, thereby satisfying the *sixth principle of green chemistry*, and features an in-depth and thorough coverage of a huge number of organic synthetic protocols at ambient temperature. This book is unique in its authoritative, thorough, and comprehensive inclusion of a wide variety of more than 200 sincerely screened organic synthetic protocols at room temperature for generation of carbon-carbon and carbon-heteroatom bonds resulting a wide spectrum of chemical compounds — aliphatic, aromatic, alicyclic and heterocycles. Clearly structured for easy access to the information, each selected reaction is discussed in a very compact manner through point-wise discussion such as: Reaction type; Reaction conditions; Reaction strategy; Catalyst; Keywords; General reaction scheme; Mechanism; Representative examples; Experimental procedure; Characterization data of representative entries; Reference.

The book successfully integrates research advances in designing energy-efficient reaction procedures for useful organic transformations to satisfy one of the notable green chemistry principles (*i.e.* reactions at ambient conditions) and their feasibility into industrial applications and process developments. A wide spectrum of important synthetic methodologies involving carbon-carbon and carbon-heteroatom bond forming reactions under mild conditions dealt in this book would surely make the work much interesting to the scientists deeply engaged in organic synthesis and related fields. This timely volume serves the purpose of also an outstanding source of information with regard to the industrial applications. It will serve not only as a valuable resource for researchers in their own fields, but also motivates young scientists to the dynamic field of organic synthesis and practice of green chemistry.

I would like to express my sincere thanks and deep sense of gratitude to Professor Paul T. Anastas, Director, Center for Green Chemistry and Green Engineering, Yale University, New Haven, CT, USA for his keen interest in the manuscript and for writing foreword to the book.

I would also like to express my deep sense of appreciation to all of the editorial and publishing staff members associated with Elsevier Inc., United States of America, for their keen interest in publishing the work as well as their all-round help so as to ensure that the highest standards of publication have been maintained in bringing out this book. My effort will be successful only when it is found helpful to the readers at large. Every step has been taken to make the manuscript error-free; in spite of that, some errors might have crept in. Any remaining error is, of course, of my own. Constructive comments and approach of the book from the readers will be highly appreciated.

Finally, I should thank my wife and my son for their well understanding and allowing me enough time throughout the entire period of writing; without their support, this work would not have been successful.

Goutam Brahmachari

Chemistry Department, Visva-Bharati University
Santiniketan, West Bengal, India
February 2015

Contents

| | | |
|-------------|--|------|
| Foreword | | ix |
| How to Read | | xi |
| Preface | | xiii |
| Chapter 1 | Carbon – Carbon Bond Forming Reactions at Room Temperature | 1 |
| Chapter 2 | Carbon – Nitrogen Bond Forming Reactions at Room Temperature | 75 |
| Chapter 3 | Carbon – Oxygen Bond Forming Reactions at Room Temperature | 189 |
| Chapter 4 | Carbon – Sulfur Bond Forming Reactions at Room Temperature | 241 |
| Chapter 5 | Carbon – Phosphorus Bond Forming Reactions at Room Temperature | 273 |
| Chapter 6 | Carbon – Halogen Bond Forming Reactions at Room Temperature | 299 |
| | Carbon – Fluorine Bond Forming Reactions | 299 |
| | Carbon – Iodine Bond Forming Reactions | 303 |
| Chapter 7 | Carbon – Boron Bond Forming Reactions at Room Temperature | 315 |
| Chapter 8 | Miscellaneous Bond Forming Reactions at Room Temperature | 325 |
| | Carbon – Hydrogen Bond Forming Reaction | 325 |
| | Nitrogen – Hydrogen Bond Forming Reaction | 326 |
| | Oxygen – Silicon Bond Forming Reactions | 328 |
| | Sulfur – Nitrogen Bond Forming Reaction | 334 |
| | Sulfur – Oxygen Bond Forming Reactions | 335 |
| | Sulfur – Sulfur Bond Forming Reactions | 339 |
| Index | | 345 |

Chapter 1

Carbon – Carbon Bond Forming Reactions at Room Temperature

C-C bond_1

Type of reaction: C-C bond formation

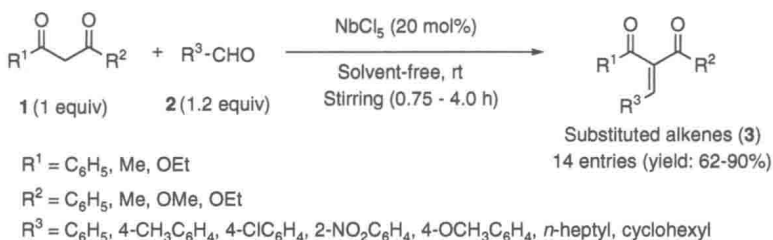
Reaction conditions: Solvent-free, room temperature

Synthetic strategy: One-step condensation

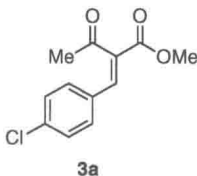
Catalyst: Niobium pentachloride (NbCl₅)

Keywords: 1,4-Dicarbonyls, aldehydes, niobium pentachloride (NbCl₅), homogeneous catalysis, solvent-free, room temperature, condensation, Knoevenagel reaction, trisubstituted alkenes

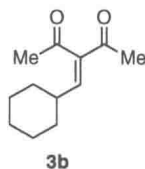
General reaction scheme



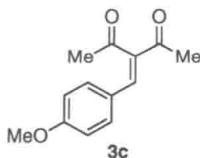
Representative entries



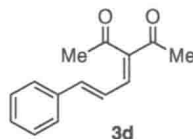
(*E*)-Methyl 2-(4-chlorobenzylidene)-3-oxobutanoate (**3a**): Reddish solid; mp 80 °C; reaction time: 1.5 h; yield: 80%



3-(Cyclohexylmethylene)pentane-2,4-dione (**3b**): Reaction time: 4.0 h; yield: 62%



3-(4-Methoxybenzylidene)pentane-2,4-dione (**3c**): Yellow liquid; reaction time: 1.5 h; yield: 80%



(*E*)-3-(3-Phenylallylidene)pentane-2,4-dione (**3d**): Reaction time: 3.0 h; yield: 65%

Experimental procedure

A round-bottomed flask was charged with a magnetic stir bar, 1,3-carbonyl compound (**1**; 1 mmol), and aldehyde (**2**; 1.2 mmol), followed by 20 mol% of NbCl₅. The reaction mixture

was then stirred at room temperature for required time-frame (0.75–4.0 h). After completion of the reaction, it was quenched by the addition of saturated aqueous NaHCO_3 solution and the product (**3**) was extracted with ethyl acetate. The product was purified by column chromatography using ethyl acetate/hexane as eluent. Structure of each of the products was verified from IR, ^1H NMR, ^{13}C NMR and HRMS studies.

Characterization data of two representative compounds

(*E*)-Methyl 2-(4-chlorobenzylidene)-3-oxobutanoate (**3a**): Reddish solid; mp 80 °C; IR (KBr): 821, 1088, 1250, 1618, 1654, 1733, 2362, 2855, 2932 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.16 (s, 3H), 2.58 (s, 3H), 6.11–6.12 (m, 4H), 6.27 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 26.5, 52.6, 129.1, 130.6, 136.8, 134.5, 140.0, 169.7, 194.3; ESIMS: m/z 261 ($\text{M}^+ + \text{Na}$); HRMS: Calcd for $\text{C}_{12}\text{H}_{11}\text{O}_3\text{NaCl}$, 261.0294; Found 261.0289.

3-(4-Methoxybenzylidene)pentane-2,4-dione (**3c**): Yellow liquid; IR (neat): 831, 1108, 1174, 1258, 1258, 1513, 1599, 1653, 1706, 2844, 2926, 3004 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.28 (s, 3H), 2.26 (s, 3H), 3.83 (s, 3H), 6.87 (d, $J=9.0$ Hz, 2H), 7.31 (d, $J=9.0$ Hz, 2H), 7.37 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 26.2, 31.6, 55.3, 114.5, 125.2, 131.6, 139.7, 140.6, 161.6, 196.4, 206.1; ESIMS: m/z 241 ($\text{M}^+ + \text{Na}$); HRMS: Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3\text{Na}$, 241.0840; Found 241.0833.

Reference

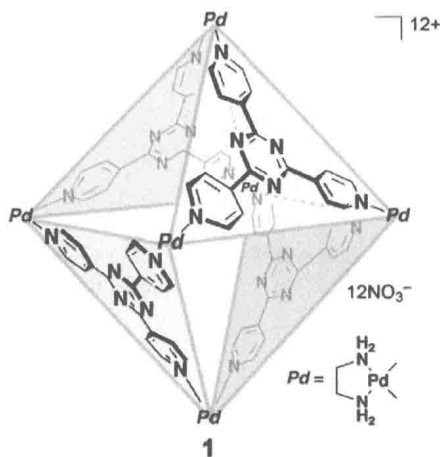
Yadav, J. S., Bhunia, D. C., Singh, V. K., and Srihari, P. (2009). Solvent-free NbCl_5 catalyzed condensation of 1,3-dicarbonyl compounds and aldehydes: A facile synthesis of trisubstituted alkenes. *Tetrahedron Lett.*, **50**, 2470–2473.

C-C bond_2

Type of reaction: C-C bond formation

Reaction conditions: Water, neutral conditions, room temperature

Synthetic strategy: One-step condensation



[Cage **1**: adapted from Murase *et al.* (2012), *J. Am. Chem. Soc.*, **134**, 162]