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Book Reviews *

Microwave Assisted Organic Synthesis. Edited by J. P. Tierney and P. Lidstrom. Blackwell Publishing: Oxford. 2005. 280 pp. £89.50. ISBN 1-4051-1560-2. (Also published by CRC Press in U.S.A. and Canada, ISBN 0-8493-2371-1.)

In the two decades since microwave-assisted organic chemistry was first reported, there has been an exponential growth in the number of publications in the field. The last two books on this topic (by Andre Loupy and Brittany Hayes) were both published in 2002, and although new purpose-built equipment for organic synthesis was described, the fact is that the majority of the organic chemistry reviewed in these books was performed in what were essentially domestic microwave ovens. The literature results were therefore accompanied by uncertainties relating to both reproducibility and safety.

Over the last 5 years or so, purpose-built microwave units for synthetic organic chemists have become commercially available and affordable and have largely addressed the issues of reproducibility and safety. Such microwave reactors are now widely deployed in academia and industry across the world. Thus, the almost simultaneous publication, in 2005, of *two* new books on microwave-assisted organic chemistry is timely and valuable. Both of the new books are reviewed here.

The first of these books is edited by Jason Tierney (of GSK) and Pelle Lidstrom (of Biotage), (both first-hand experts in the field) and consists of nine chapters, each written independently by different authors.

Chapter 1 (by D. Michael P. Mingos) describes the theoretical aspects of microwave dielectric heating. Chapter 2 (by Kristofer Olofsson and Mats Larhed) focuses on microwave-accelerated metal catalysis (with the amusing subtitle "organic transformations at warp speed"), where the usual array of Stille, Heck, Suzuki, Negishi, and Sonogashira couplings are reviewed, along with cyanation, allylic alkylation, and carbonylation. Chapter 3 (by Thierry Besson and Christopher Brain) turns the emphasis on a systematic review of microwave-enhanced heterocycle synthesis, while Chapter 4 (by Timothy Danks and Gabriele Wagner) focuses on microwave-assisted reductions. Multicomponent reactions such as the Hantzsch, Biginelli, and Ugi reactions form the basis of Chapter 5 (by Jacob Westman), while Steve Ley and co-workers provide a perspective regarding the application of solid-supported reagents under microwave conditions (Chapter 6). The authors of the other new book (reviewed below), Alexander Stadler and Oliver Kappe, contribute a chapter on microwave-assisted solid-phase synthesis (Chapter 7). The book concludes with what were to me the two most interesting and entertaining chapters: Chapter 8 entitled "Timesavings Associated with Microwave-Assisted Synthesis: A Quantitative Approach" (by Christopher Sarko of Boehringer Ingelheim) and Chapter 9 entitled "Scale-up of Microwave-Assisted Organic Synthesis (by Brett Roberts and Christopher Strauss).

Because of the multiple authors and the somewhat piecemeal approach taken, this is a somewhat disjointed book, with quite a bit of overlap across the chapters. Some of the chapters are more readily navigated than others, but nevertheless, there is much of value to be found.

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Microwaves in Organic and Medicinal Chemistry. By C. Oliver Kappe and Alexander Stadler. Wiley VCH: Weinheim. 2005. 409 pp. £139. ISBN 3-527-31210-8. (Volume 25 in Methods and Principles in Medicinal Chemistry. Series Editors R. Mannhold, H. Kubinyi, and G. Folkers.)

The second microwave synthesis book being reviewed here deals with both synthetic applications of microwaves and, as the title indicates, with typical applications in medicinal chemistry.

The book opens with a short history of the evolution of microwaves in synthesis, followed by a nicely pitched theoretical chapter, providing just enough theory for the organic chemist to grasp the essentials, without going into a level of physical depth which would lead many to turn the page with glazed eyes. The third chapter is a useful equipment review in which all of the currently commercially available equipment is critically assessed. Chapter 4 describes different microwave processing techniques such as solvent-free reactions, phase-transfer catalysis, reactions using solvents, open- versus closed-vessel conditions, parallel processing, etc. There is a six-page section on "scale-up in batch and continuous flow", which the process chemist may find of interest. Chapter 5 is entitled "Starting with Microwave Chemistry" and takes the reader step by step through the various considerations which must be borne in mind when approaching microwave chemistry. Limitations and safety aspects are also briefly addressed. The remainder (indeed the bulk) of the book consists of a literature survey, split into "General Organic Synthesis" (Chapter 7, 183 pages), and Combinatorial Chemistry and High-Throughput Organic Synthesis" (Chapter 8, 100 pages), with a primary focus on the literature of 2002−2004. Organic reactions (almost any reaction you can think of) are discussed in a systematic

*Unsigned book reviews are by the Editor.

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manner in the general chapter, while the combinatorial chapter covers solid-phase, polymer-supported, fluorous phase, and other technologies. Finally, there is a very short concluding chapter, which assesses the outlook for microwaves in organic chemistry.

This is a well-thought out and nicely constructed book which has been carefully written with its audience in mind. It is more than just a literature review, it is a handbook of "how to do it", which will be extremely useful to the practitioner. In my view, this is now the seminal text for chemists (especially, but not exclusively, medicinal chemists) using microwaves on laboratory scale. I can warmly recommend this book, and would expect it to end up on the shelves in most synthetic organic laboratories.

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Preparative Enantioselective Chromatography. Edited by Geoffrey B. Cox. Blackwell Publishing: Oxford, UK. 2005. 330 pp. ISBN: 1-4051-1870-9.

Over the past 15 years enantioselective chromatography has grown from pure analytical applications to wide use as a preparative tool. Enantioselective or so-called chiral chromatography is applied in lab- and pilot scale, as well as in production, mostly in the pharmaceutical industry. Cox's book provides chemists and chemical engineers with valuable hints and advice. The authors are, in part, experienced practitioners in industry and, in part, academics at the forefront of this field.

The book is a delight to read. Its 330 pages are appropriately divided into 11 chapters, allowing ready access to the material presented. It begins by outlining the support of chiral chromatography in pharmaceutical process research, followed by a recall of fundamentals of preparative chromatography. Important data and an extended overview of all types of chiral stationary phases are presented in chapter 3. Chapters 4 and 5 review method development and scaling-up procedure. The chapters 6, 7, and 8 are devoted to simulated moving bed (SMB) technology, steady-state recycling (SSR) and supercritical fluid chromatography (SFC). In chapter 9, function and design of equipment in detail is introduced. A case study of a chiral separation in multimetric-ton scale is discussed in chapter 10. This case study can be seen as an evidence that enantioselective chromatography can be a competitive low-cost process if process development is done in a proper manner. Contract manufacturing and outsourcing considerations are the focus in chapter 11. The book concludes with an appendix highlighting advanced concepts.

At every stage, material is logically presented and easy to access. My only criticism is that the fundamentals are only discussed in short; more details would especially enable newcomers to have access to more support.

In summary, this is an excellently compiled book with well-produced text. It will be of use to practising chromatographers in the enantioselective field.

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Active Pharmaceutical Ingredients; Development Manufacturing and Regulation. Edited by S. H. Nusim. Taylor and Francis: Boca Raton, FL, 2005. £79.99. xiv + 337 pp. ISBN 0-8247-0293-X

There are few books which cover the subject of API development and manufacture so this title is a welcome addition to the library of all who work in the pharmaceutical industry. After a brief introduction by the editor, the subject of process development is covered in 83 pages by Carlos Rosas, who was formerly with Merck and now at Rutgers University. He provides a chemical engineer's view of process R&D, and chemists should read this account to familiarise themselves with a different approach. Little is said about choice of synthetic route for an API, or indeed optimisation of each step of the route. Instead the focus is on the "philosophy of the development process". He divides this into the preparative stage, development stage (including scale-up), the consolidation stage, and the technology transfer stage.

This chapter also discusses taking a process "from the bench to the pilot plant" and beyond, which includes sections on scale-up, pilot plants, and new technologies. An important section on physiochemical attributes of the bulk drug follows. Other areas covered in this chapter are the process body of knowledge (the dossier), processing responsibility (including hazards, industrial hygiene, and environmental issues), and outsourcing.

The chapter is well written and is a useful overview. It would have been improved by detailed examples and case studies from the author's experiences in industry and by some pictures or diagrams of equipment in the pilot plant discussion.

The second chapter (Bulk Drugs, Process Design, Technology Transfer, and First Manufacture), also written by Dr. Rosas, will be useful for managers, but scientists and engineers unfamiliar with the topic would learn more if a good case study had been incorporated. Further chapters are on Design and Construction of Facilities, Regulatory Affairs, Validation, Quality Assurance and Control, Plant Operations, Materials Management, and Plant Maintenance.

For those readers wishing to have a general introduction to the chapter topics, the book will provide for their needs. For those chemists and engineers requiring more information, the generalisations, lack of detail, and omissions will soon be noticed. For example, topics which I would have expected to be included in detail in such a work are specifications

(raw material, intermediate, final API) including residual solvents and process impurities; polymorphism, solvation, and amorphous forms of APIs; importance of Design of Experiments for evaluating critical process parameters and robustness testing when performing experiments leading to validation protocols; choice of "regulatory" starting material; which steps in a synthesis have to be to GMP; and something on generic drugs. Thus, residual solvents are mentioned in an Appendix, but no guidance on the type and level of solvents allowed in APIs is given, nor is there reference to the ICH guidelines on residual solvents.

Overall, most chapters are too general and would benefit from detailed analysis and use of examples and case studies. In conclusion, the book can only be recommended to those requiring a general introduction to the topic.

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Chemical Engineering, Trends and Developments. Edited by Miguel A. Galan and Eva Martin del Valle. Wiley: Hoboken, NJ. 2005. 400 pp. $125.00/£65/99.90 Euro/160 SFR. ISBN: 0-470-02498-4.

The title might lead one to believe that this is an introductory chemical engineering text. Quite the contrary. The editors have collected here a series of very advanced monographs on a number of loosely related engineering topics by experts in industry and academia. It's *raison d'*etre is to call attention to some groundbreaking work being carried out in the ever-expanding discipline of modern chemical engineering.

The opening chapter "The Art and Science of Upscaling" offers up a very in-depth treatment of some of the pitfalls and limitations of applying standard differential equations to the case of homogeneous and heterogeneous catalytic reactions.

Later chapters discuss the merits of using small, inexpensive peptides as ligands in affinity chromatography, and the use of SMB together with immobilized-metal affinity chromatography (IMAC) for protein purification. Together these represent potentially important advances in processing for the biotech industry.

Other sections deal with modeling gas and vapor solubility in polymeric membranes, important in many thin-film applications, the use of nanostructured microporous materials in bioprocessing and tissue engineering, the scale-up and application of modern encapsulation technology, and advances in the preparation of fine-structured coatings and films, including so-called Langmuir−Blodgett (monomolecular) films.

Additional topics include heterogeneous catalysis for wastewater remediation and cleanup of CO from hydrogen for fuel cells, the design of homogeneous and heterogeneous photoreactors, advances in logic-based optimization of process integration and supply chain management, and the integration of process systems engineering to risk management and other enterprise-related endeavors.

All in all, a weighty tome, this, with a strong emphasis on theory and mathematical modeling. The common threads that emerge are the application of engineering principles to the development of membranes and thin films and to the burgeoning field of biotechnology. Organizing the 12 chapters along such lines might have helped highlight those connections and make the book feel a little more focused.

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Design and Optimization in Organic Synthesis, 2nd revised and enlarged edition. Rolf Carlson and Johan E. Carlson. Elsevier: Dordrecht, The Netherlands. 2005. 574 pp (+ CD). Price: £180, $290, 265 Euro. ISBN 0-444-51527-5.

This is a welcome re-issue for a modern classic of the organic chemistry literature. Rolf Carlson's 1992 text provided a fresh, some would say controversial, approach to process investigation and optimization. Now, assisted by his son, he presents a revised and enlarged edition, incorporating some fresh material, updated references, and novel strategies.

The central point of the book remains encouraging chemists to use principles of statistics and matrix algebra to plan the most informative set of experiments, consistent with the goals of their investigations. This has the potential to be an extremely dry topic, but here it is presented in a lucid and provocative style, making it an accessible read even for the most mathematics-averse synthetic chemist. The examples come mostly from the authors' extensive experience in synthetic chemistry. Thus, they never allow purely mathematical aspects to dominate the discussions but always strive to relate the numerical results to real chemical phenomena.

The early chapters describe the standard methodologies of factorial design, fractional factorials, simplexes, steepest ascent methods, and response surface analysis. These are mainly useful for straightforward problems where variables are continuous and a limited number of response measurements are considered. Subsequent to the original publication, numerous software packages have become available to help the chemist use these methods effectively. However, Carlson believes that even greater insight can be obtained by canonical analysis of the data, which has largely been overlooked by software developers and thus requires a greater degree of mathematical persistence on the chemist's part. For the more difficult problem of designing experiments to choose among discrete alternatives—such as different solvents or catalysts—a number of strategies are presented in the later chapters, mainly hinging on the concept of "principle properties". There is also advice on how to deal with many different responses, such as situations in which a large number of different impurities must be minimised or

eliminated. The techniques of Principle Component Analysis and Partial Least Squares modelling are strongly recommended here.

Over the past decade, the value of these chemometric techniques has become fairly well appreciated by development chemists working in industry, and regular readers of *Organic Process Research & Development* will be familiar with the many examples which have appeared in these pages. But reading the book afresh has made me realise what an untapped potential exists here for academic research also—where these methods appear to be still largely unknown. The authors recall (page 201) surveying recent literature to identify reactions for inclusion in a course on preparative organic chemistry; of over 2000 papers scrutinized, "only 4 presented methods which had been adequately optimized". This means that across the world professors are systematically selling their own ideas short—when with a modest number of designed experiments they could obtain true perspective on the scopes of their new reactions, as well as insight into how to get them to work with the more recalcitrant substrates. This book has also shown how statistically designed experiments can provide insight into the kinetics and fundamental mechanisms of many reactions.

One useful innovation in the second edition is an accompanying CD, on which can be found the extensive tables of data which were previously printed in the book: tables which collate the measured properties of solvents, Lewis acids, aldehydes, ketones, and amines. One slight quibble I have is that the calculated principle properties, which were given in the first edition, are now missing. Perhaps we are now expected to work these out for ourselves, and indeed the CD also contains a MATLAB routine which will perform the necessary Principle Components Analyses. MATLAB routines are also supplied for canonical analysis, PLS modelling, Singular Value Decomposition, and the extraction of kinetic information from suitable studies.

The absurdly high price will make it difficult for everyone to acquire a personal copy, but I would urge all organic chemists to read this book and become acquainted with these valuable tools. To quote from the authors' concluding remarks: "Statistics is always secondary to chemistry in the domain of organic synthesis", but it "provides methods by which good chemists will be able to do even better chemistry."

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