Practical Process Research & Development

Neal G. Anderson

Forewords by
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Additional Praise for

Practical Process Research & Development

"This volume was clearly written by someone experienced with (a) the transition from being a classical organic chemist to being a process chemist and (b) taking laboratory chemical conversions into manufacturable chemical processes. Anderson's use of "tips," real-life examples, and summary tables makes this a must reference on every process chemist's (both the novice's and the experienced practitioner's) desk. This will be required reading by all new chemists, engineers, and analysts in my department."

—Sean T. Nugent, *Senior Director, Chemical Sciences, Searle Research and Development*

"Neal Anderson has assembled an immense amount of practical information that is absolutely essential to the design and execution of safe, reliable, and efficient large-scale syntheses. Critical facts once hidden in obscure sources or chemical folklore are now organized for ready access. Countless illustrative reactions and sequences from the latest literature are discussed lucidly, and impress upon the reader the scope and sophistication of modern organic process chemistry. This book is a must for beginners and old hands alike."

—Raymond Conrow, *Assistant Technical Director, Chemical Preparations Research, Alcon Laboratories*

"In writing this book, Anderson has done a great service to the chemical community, especially those chemists who are starting industrial R&D positions after their academic work. He has done a superb job of identifying the key elements of best practices in process R&D by providing a large number of judiciously chosen examples to illustrate these practices. In addition, plenty of useful data on key reagents, and practical suggestions on how to use these data in process chemistry, can be found throughout the book. Even though the book is primarily aimed at process chemists, others in academic laboratories as well as in pharmaceutical and agricultural discovery groups will find it immensely valuable. The new awareness that this book brings might even help to dispel some of our old inherently unsafe and environmentally questionable habits. To those of us who are in the teaching business, this book will serve as an eye-opener by showing the disparity between what we teach and what we practice. I predict that this book will also become a standard reference book used by synthetic chemists everywhere."

—T. V. RajanBabu, *Professor of Chemistry, The Ohio State University*

Practical Process Research & Development

To Hope

for all her love and support

Foreword by K. Barry Sharpless

Process chemists are a breed apart. While their backgrounds may vary, they share a common preoccupation with understanding chemical reactivity. The best ones seem able to anticipate much of what can go wrong in a proposed reaction sequence, and thus avoid most of the traps, barriers, and dead ends that impede the rest of us. They gain profound satisfaction from being able to steer a complex reaction along one of many possible paths, creating the sense, albeit whimsical, of wielding "power over the molecules."

The process chemist's special sense for which reaction variables offer the most leverage in a given case is founded on the ability to absorb vast amounts of information about factors that affect reactivity and to sort them into a coherent and flexible "intuition." Information, both theoretical and empirical in nature, is continuously added and intuition is thus continuously refined. It is therefore virtually impossible for a young process chemist to avoid learning many crucial lessons the hard way. Whenever old-timers are in the mood for giving out "tips" (vide infra), I *always* pay attention.

Process chemists thus play a crucial role in advancing both basic and applied chemistry. Given that man-made chemical products would not exist without their skills, it is odd and unfortunate that they rarely have much say in selecting the molecular targets for which they must devise practical commercial syntheses. Nowhere is the exclusion of process chemists from the discovery process more unfortunate than in the pharmaceutical industry. Here discovery takes the form of a "sky's-the-limit" search, wherein chemistry that is feasible, let alone ideal, for application on a practical scale is all but ignored. The pharmaceutical industry therefore needs more process chemists than any other field, and the challenges they face are by far the most daunting of chemists in any area of pure or applied chemistry.

Neal Anderson, one of the outstanding practioners of pharmaceutical process research and development, has given us here the best text ever written on the

subject. This accomplishment is all the more impressive because the aforementioned "no holds barred" chemistry style favored by the discovery team means that the process chemist has to be ready and willing to deal with organic synthesis challenges reaching from simple to nearly impossible. "Everything you always wanted to know" about process research is here, and this monograph will no doubt be pored over carefully by all newcomers as well as afficionados of this subject. Readers will especially enjoy the many highlighted "tips," ranging from all manner of advice on experimental detail and procedures to general issues and trends concerning the process chemist's world. This desire to pass on the tricks of the craft for controlling and simplifying a reaction is the distinguishing trait shared by all "real" process chemists. In this way at least, I too fit the description: for the past several years, I have based my TSRI graduate course lectures on files accumulated over the years describing various "best" procedures, advice, tips, etc., on a wide and eclectic range of processes. These arise, in some guise or other, almost daily in the work of a process chemist.

I first realized I was a process chemist after Seemon Pines invited me to the "Organic Reactions and Processes" Gordon Conference almost 30 years ago. This meeting has drawn the process chemistry faithful to New Hampshire for the past 40 summers. While the attendees bring with them a diverse range of experiences and specific interests, their differences are barely noticeable next to the main passion they all share, which is the discovery, development, and large-scale implementation of *useful* reactions and reaction sequences. Since the "discovery" part of the dream is fulfilled only on rare and unpredictable occasions (always in someone else's laboratory!), it is not a reliable generator of new material for presentation and discussion. Fortunately, process chemists are delighted by the more everyday "strategy/control" aspect of their field, and for good reason. Choosing the right sequence of reactions for a large-scale synthesis and then optimizing each of them demands many talents, with mechanistic acuity at the head of the list. Even a "simple" reaction step like acylation can misbehave and ruin an otherwise promising synthetic route. The very best process chemists seem to have built their reputations by repeatedly finding fixes for ailing reactions. These accomplishments, rarely as simple as they may appear after the fact, rely on an uncanny interplay of experience and mechanistic insight.

It is therefore fitting that whenever I've heard gifted process chemists like Merck's Edward Grabowski telling their favorite stories, it is clear that they too are proudest of these "all-or-nothing-at-all" quick "instinctive" fixes, more so because they chuckle about the trivial nature of the answer they found. The handful of people who are world class in pulling such "simple" solutions out of thin air bring to mind my two favorite quotes by scientists:

> The art of concluding from experience and observations consists in evaluating probabilities, in estimating if they are high or numerous enough to constitute proof. This type of calculation is more complicated than one might think.
>
> —Antoine Lavoisier

> Mediocre spirits demand of science the kind of certainty which it cannot give, a sort of religious satisfaction. Only the real, rare, true scientific minds can endure doubt, which is attached to all our knowledge."
>
> —Sigmund Freud

These insights of Lavoisier and Freud into the importance of welcoming doubt as the natural companion of all scientific inquiries seem apt in the present context. The process chemist is routinely asked to solve problems of great and often irreducible complexity. Since such ill-defined problems are encountered at nearly every stage in perfecting a reaction sequence that runs reliably at scale, it is not surprising that the best practitioners of the art relish working on the edge of chaos, fully expecting to find the trick(s) for taming a poorly understood reaction type. What really attracts them (and me) to these unpredictable systems is the awareness that here too lies the most fertile ground for stumbling on new reactivity, the origin of all useful new reactions.

> The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole.
>
> —Sir John Cornforth

Cornforth's old saw on the "perfect" industrial reaction reminds us how far we still have to go. This is especially so in the area of pharmaceutical manufacturing, which stands in stark contrast to the modern petrochemical industry. The latter has been on a much happier path since its birth, and, to the great benefit of humans, many of its workhorse reaction processes are already approaching perfection. Hence, the two biggest industrial applications for organic reactions and processes have evolved in nearly opposite directions.

Historically, the pharmaceutical industry has watched its drugs become progressively harder to synthesize, whereas the petrochemical industry, finding elegance and profit in simplicity, has moved steadily toward ever more direct and efficient processes. All petrochemical products depend on a handful of remarkably efficient gas-phase processes through which the abundant, but chemically uninteresting, fossil hydrocarbons are selectively transformed into about a dozen small, functionalized organic building blocks. The modular assembly of these few reactive blocks/monomers is then accomplished using a variety of unique processes and catalysts, each known to selectively and reliably catalyze a particular bonding pattern once the reacting block(s) is specified. This deceptively simple strategy of combining a few uniquely reactive blocks under the control of a few exquisitely selective catalysts is solely responsible for the astonishing productivity and versatility of the modern petrochemical industry. It has given us myriad new substances, with almost tunable properties, and often made on a massive scale.

Although on a tiny scale by comparison, the identical, small set of petrochemical-derived blocks (vide supra) is also the ultimate source of starting materials for about 90% of all the organic compounds used for any purpose by the pharmaceutical industry. However, the theme of gaining reliability and efficiency through a

modular synthetic strategy, so dominant in petrochemical organic synthesis and organic synthesis as practiced by living systems, has so far had negligible effect on the style of organic synthesis used to search for new medicines. But whatever else the future holds, to the extent that the insights and attitudes of process chemists become better inculcated in our students and better known throughout the synthetic community, new medicines should become easier to discover and to manufacture. Careful attention to this book will take us a long way down this highly desirable path.

Professor K. Barry Sharpless
Dreyfuss Professor of Chemistry and Molecular Biology
The Scripps Institute for Medical Research

Foreword by Jerome L. Moniot

The key role of process chemistry and process development in the economic success of the large-scale preparation of fine chemicals and the manufacture of pharmaceuticals in particular has frequently been underappreciated. In the pharmaceutical industry at large, organic chemists are employed in the discovery process to determine which molecules to make and also in the development/manufacturing role to determine how to make those selected molecules. Although organic chemistry is the common denominator in these functions, the discovery chemist is additionally focused on the biological activity and novel aspects of the compounds, while the development/manufacturing chemists are focused primarily on the practicality and elegance of the process to manufacture the compounds. The approaches to the use of organic chemistry may differ, but the goals of both groups of chemists are the same, namely, to enhance human life through new and effective medicines.

The evolution of a manufacturing process for an active pharmaceutical ingredient has several distinct phases of development. Beginning with the discovery or selection of the target molecule, the development of a practical route to full evaluation of toxicological and pharmacologic attributes is undertaken. Once the route is defined, initial scale-up development and the transition to process equipment proceed, followed by process optimization and refinement for manufacturing operations for each synthetic step through pilot trials.

Effective process development is an amalgam of synthetic organic methodology, physicochemical properties, purification technologies, chemical engineering principles, and practical mechanics orchestrated with a view toward safety, product quality, reproducibility, ruggedness, and cost efficiency. The simple translation of a description of a laboratory synthetic process into the series of sequential unit operations required to replicate the procedure in process equipment reveals the complexity involved. The numbers and sizes of vessels (head tanks for reagents, reactors, distillate receivers, phase splitting vessels, filtrate hold tanks, crystallizers,

etc.), as well as the numbers and types of filtration devices, product drying equipment, transfer lines, pumps, and valves, all need to be selected for chemical compatability and operational suitability. These determinations are frequently the focus of laboratory experimentation and safety hazard studies and involve close interactions with chemical engineers.

One development concern that is not immediately intuitive to laboratory-based organic chemists beginning development work is the effect of physical size on the progress and eventual outcome of an organic reaction, beyond those obvious effects due to the length of time required for operations. An example is surface addition of a reaction component. The design of a laboratory experiment to determine the effect of adding a reagent at the surface of a large-scale reaction is challenging. Rather than a few inches of mixture separating the surface of the reaction from the agitation device, the 6- to 12-foot separation in a mid-sized process vessel can lead to troublesome mixing gradients and localized stoichiometric imbalances (hot spots). As the text highlights, mixing is critical to the successful execution of an organic reaction and requires that process chemists and engineers work together closely to minimize difficulties with this aspect of process scale-up during development.

As Dr. Anderson points out, a key to many a successful process is the careful integration of physical phenomena, such as insolubility, preferential solvent phase distribution, and volatility, with control rates of desirable reactions or the rates of undesirable side reactions.

One of the thrusts of synthetic chemistry that distinguishes process development work is the emphasis on the postreaction workup and purification/isolation aspects of a process. Isolated intermediates must necessarily be filterable solids, and the tolerance of the chosen purification methods for impurities in the solution will have a profound effect on both yield and quality of the product.

Dr. Anderson has produced a very insightful and informative book for a process development team in pursuit of their ultimate goal. That goal can be summarized as the definition of a process that is characterized as being high throughput, safe, reproducible, and rugged and one in which a minimum number of different solvents are used to carry out the maximum amount of synthetic construction in the shortest amount of time, with the highest isolated yield of high-quality product, for the lowest cost per kilogram.

Dr. Anderson's text ably highlights many of the interrelations of the key facets of the development process, along with many practical reference tables to facilitate parameter selections for evaluation.

Dr. Jerome L. Moniot
Vice President of Technical Operations
Bristol–Meyers Squibb Co., Inc.

Preface

My goal with this book is to provide a comprehensive, step-by-step, hands-on approach to organic process research and development for the preparation of "small molecules." It should be useful to those in the pharmaceutical, fine chemical, and agricultural chemical industries and to those academicians who wish an insight into process R&D in these industries. I hope it will ease the transition for those who are entering industrial process R&D labs fresh from academia. More experienced readers may find some useful tips and ideas.

This book has been developed primarily from my experiences at Bristol–Myers Squibb. The principles discussed are illustrated by examples from the chemical literature, patents, and my personal experience in the laboratory, pilot plants, and manufacturing plants. Many of the guidelines for implementing processes on scale (Chapter 14) were developed by the New Brunswick staff of BMS, and the thoughts there represent many collective years of experience.

I have selected examples from the literature primarily through the middle of 1999. Some reaction schemes are used in several chapters because they provide insights into different areas of process development. The interested reader could consult many of the process papers mentioned in this book for additional examples of successful process R&D. Some tips are repeated in the hope that readers who examine chapters out of sequence will not miss valuable points.

There are many people to thank. Dave Burdick, Ed Delaney, Kumar Gadamasetti, Marc Halpern, Sean Nugent, Bob Polomski, Rob Waltermire, Steve Weissman, and especially Ray Conrow reviewed my draft chapters and gave me insightful technical comments. Alice McKee, Phyllis Minicuci, Donna Gibson, Charlee Sevenski, Marion Morgan, and Cindie Good were very kind to let me use the New Brunswick Bristol–Myers Squibb library. Julie Arnheim and her staff at the Princeton University Chemistry Library were very helpful. I have had many illuminating discussions with Barbara Ciaramella, Bill Ferguson, David Kacsur, San Kiang, Atul Kotnis, Ken Morris, Larry Parker, J. D. Pipkin, Larry Steele,

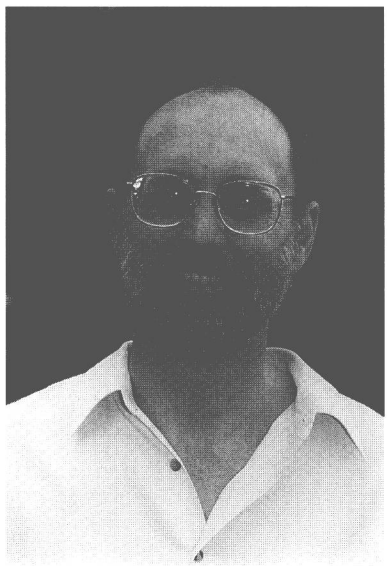
Steve Taylor, Ajit Thakur, Bill Winter, and other past and current employees of Bristol–Myers Squibb. Professor Rich Lawton and John R. Carson taught me so much and allowed me room to learn. Jerry Moniot first mentioned to me the concept of snapshot, and we have spent many hours discussing problem-solving and details of process development. Barry Sharpless kindly gave his thoughts on this work. Don Doell and Christine Williams provided useful information on process reactors. Colleen Saggese supported me in the crunch and helped me marshal the details to complete the manuscript. David Packer at Academic Press had faith in this project. Gail Savage made my manuscript much more powerful and readable, and I appreciate her writing lessons. Linda Gustafson was very responsive with the production of the pages. Participants in my courses have given me valuable feedback and encouragement. Many, many thanks to all these people.

I also must thank Bristol–Myers Squibb for many rewarding years. BMS provided world-class laboratories for learning about technology and people.

Discerning readers will undoubtedly find some exceptions to the general guidelines offered here. I welcome comments on the book and will appreciate mention of the inevitable errors.

Neal G. Anderson

About the Author



Neal G. Anderson, Ph.D., has worked for over 20 years in chemical process R&D in the pharmaceutical industry. He earned a B.S. from the University of Illinois and a Ph.D. in medicinal chemistry from the University of Michigan and completed postdoctoral studies at McNeil Laboratories. With almost 18 years in process R&D at Bristol–Myers Squibb Co. in New Brunswick, New Jersey, Dr. Anderson has extensive hands-on experience in laboratory, pilot plant, and manufacturing facilities. He has made key contributions to processes for the manufacture of four major drug substances, including captopril, has participated in 12 manufacturing start-ups, and has successfully introduced many processes to pilot plants. He received the Bristol–Myers Squibb President's Award and spot awards, and his final position was Principal Scientist.

In 1997, Dr. Anderson established Process Solutions L.L.C., a consulting firm offering practical guidance on developing and implementing processes for bulk pharmaceuticals and fine chemicals. As part of these consulting services, he presents courses on selected aspects of practical process R&D. He also practices chemistry in the kitchen, by home-brewing beer.

Contents