ADVANCED PRACTICAL ORGANIC CHEMISTRY

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Dedicated to Professor Gilbert Stork
In recognition of the skills and enthusiasm for chemistry
gained in his laboratories

Preface

The preparation of organic compounds is central to many areas of scientific research, from the most applied to the most academic, and is not limited to chemists. Any research which uses new organic chemicals, or those which are not available commercially, will at some time require the synthesis of such compounds.

This highly practical book, covering the most up-to-date techniques commonly used in organic synthesis, is based on our experience of establishing research groups in synthetic organic chemistry and our association with some of the leading laboratories in the field. It is not claimed to be a comprehensive compilation of information to meet all possible needs and circumstances; rather, the intention has been to provide sufficient guidance to allow the researcher to carry out reactions under conditions which offer the highest chance of success.

The book is written for postgraduate and advanced level undergraduate organic chemists and for chemists in industry, particularly those involved in pharmaceutical, agrochemical and other fine chemicals research. Biologists, biochemists, genetic engineers, material scientists and polymer researchers in university and industry will find the book a useful source of reference.

Contents

CHAPTER 1

General Introduction

The preparation of organic compounds is central to many areas of scientific research, from the most applied to the most academic, and is not limited to chemists alone. Any research which uses new organic chemicals, or those which are not available commercially, will at some time require the synthesis of such compounds. Accordingly the biologist, biochemist, genetic engineer, materials scientist, and polymer researcher in university or industry all might find themselves faced with the task of carrying out an organic preparation, along with those involved in pharmaceutical, agrochemical, and other fine chemicals research.

These scientists share with the new organic chemistry graduate student a need to be able to carry out modern organic synthesis with confidence and in such a way as to maximize the chance of success. The techniques, methods, and reagents used in organic synthesis are numerous, and increasing every year. Many of these demand particular conditions and care at several stages of the process, and it is unrealistic to expect an undergraduate course to prepare the chemist for all the situations which might be met in the research laboratories. The non-specialist is even more likely not to be conversant with most modern techniques and reagents.

Nevertheless, it is perfectly possible for both the non-specialist and the graduate student beginning research in organic chemistry to carry out such reactions with success, provided that the appropriate precautions are taken and the proper experimental protocol is observed.

Much of this is common sense, given a knowledge of the properties of the reagents being used, as most general techniques are relatively straightforward. However, it is often very difficult for the beginner or non-specialist to find the appropriate information.

At Salford, we found ourselves handing out to students beginning research in organic chemistry a compilation of what we hoped was useful information on the practical aspects of organic synthesis, based on the authors' recent associations with some of the top synthetic organic research laboratories. We have gathered this information together in this book, and expanded it to cover some other areas, in the hope that it will be an aid to the specialists and non-specialists alike. Of course most research groups will have their own modifications and requirements, but on the whole the basic principles will remain the same.

This book is intended to be a guide to carrying out the types of reactions which are widely used in modern organic synthesis, and is concerned with basic technique. It is not intended to be a comprehensive survey of reagents and methods. A few representative procedures are given, and the appendix contains some information on commonly used reagents.

If we have achieved our aims, users of this book should be able to approach their synthetic tasks with confidence. Organic synthesis is both exciting and satisfying, and provides opportunity for real creativity. If our book helps anyone along this particular path then our efforts will have been worthwhile.

CHAPTER 2

Keeping Records of Laboratory Work

2.1 Introduction

No matter how high the standard of experimental technique employed during a reaction, the results will be of little use unless an accurate record is kept of how that reaction was carried out and of the data obtained on the product(s). Individuals or individual research groups will develop their own style for recording experimental data, but no matter what format you choose to follow, there are certain pieces of vital information which should always be included. In this section a format for keeping records of experimental data will be suggested and although this need not be strictly adhered to, it will be used to point out the essential features which should be included. It is suggested that records of experimental work and experimental data be kept in two complementarv forms: *The lab notebook* should be a diary of experiments performed and should contain exact details of how experiments were carried out; A *data book* or set of *data sheets* should also be kept to record the physical data and preferred experimental procedure for each individual compound which has been synthesized.

2.2 The laboratory notebook

2.2.1 *Why keep a lab book ?*

Before any practical work is undertaken in the laboratory a sturdy hard-backed lab notebook should be obtained and a standard format for keeping the notebook should be decided upon. A good deal of thought should go into the layout of the lab book. It should be stressed that a lab book is not a format for polished report writing, but a daily log of work carried out in the lab. Some of the main reasons for keeping a lab book are:

1. In order that the exact procedure followed for a reaction can be referred to later. This can be very important even if the reaction was not successful. For instance, after several attempts to bring about a reaction have failed, it is often possible to review what has been done then carry out a more successful experiment.
2. It should be the main index point that will enable you to find experimental, literature and spectroscopic data on any compound which you have synthesized.
3. It is the main source of reference when you come to write reports, papers, theses etc.
4. It is a chronological diary of the experiments carried out and thus it should allow you to say exactly when a particular experiment was carried out.
5. In order that another worker can follow your work, it is very important to use a lab book style which is easily understood by others.

2.2.2 How to write a lab book

One of the most important points about keeping a lab book is that it is kept on the bench and written up as you perform the experiments. *It is bad practice to keep rough notes about experiments, then transfer the details to a lab book later.* This can cause many problems, for instance: the original notes can be lost; even with the strongest will, the exact truth often becomes distorted in transferring information to the lab book and small facts which may at the time seem unimportant are left out; it is also very easy to forget to rewrite an experiment altogether, especially if the reaction failed, and this can lead to much time wasting later. It is more important that the lab book be an accurate record of the way an experiment was performed, than for it to be in your neatest writing, although of course it should be legible.

An example of a format that is effective for general synthetic chemistry is outlined on page 6. This can be adjusted to personal needs but its essential features, which are listed below, should be included in any format chosen.

2.2.3 Suggested notebook format (Fig. 2.1)

1. *General layout*

   It is good practice to start each new experiment on the next free right hand page of the notebook. This makes finding any particular experiment easier.

2. *Experiment number*

   The experiment number is in the top right hand corner of the page and this is very important since it is used to reference all the compounds which are prepared. If a notebook with numbered pages is used, it is common for the experiment number to be the number of the page on which the experiment starts. The way in which the notebook is indexed is open to personal preference. In this system a researcher's first book is book *A*, then *B,C,D* etc. Figure 2.1 therefore shows experiment *23* of book *A*. Compounds isolated from this experiment all carry the number *A23*, prefixed with the researchers initials (in this case *BB*). When more than one product is isolated from a reaction a suffix, *a, b, c* etc. is added to the reference number, *a* being the spot running highest on tlc, *b* the next, and so on. Thus, for this experiment two products were isolated and these carry reference numbers *BB A23a* and *BB A23b*. Using this system the origin of any synthetic sample can be determined very quickly.

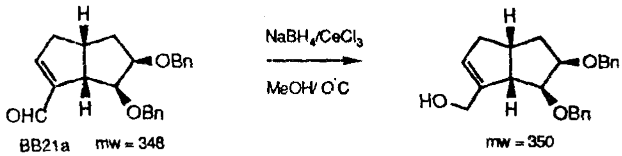
3. *The date*

   It is important that the date is always included.

4. *A reaction scheme indicating the proposed transformation*

   This is always included at the top of the page so that an individual experiment is easily found. If the reaction proceeded as desired the scheme is left intact, but if the desired product was not obtained it can be crossed through in red to indicate this. If other products were also obtained they can be added, again in a different colour ink if desired. Thus, simply flicking through the lab book, looking at the schemes, can quickly provide a good deal of information. Some people prefer to write only the left-hand side of the equation until the experiment is complete.

9 March 2000 *A23*



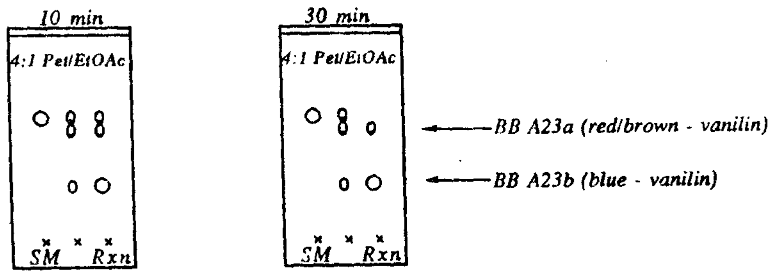
Ref., J.-L. Luche, L. Rodriguez-Hahn and P Crabbe, J. Chem. Soc., Chem. Commun., 1978, 601

Substance	*Quant.*	*Mol. wt.*	*m.moles*	*Equiv.*	*Source*
BB A21a	*200mg*	*348*	*0.57*		*p.A21*
$NaBH_4$	*27mg*	*38*	*0.71*	*2.84*	*Aldrich*
$CeCl_3$(0.4M/MeOH)	*2ml*		*0.8*	*1.4*	
MeOH	*25ml*				

Method:

The aldehyde (200mg) and $CeCl_3$ solution 2ml) in MeOH (25ml), was cooled to 0^oC, then treated with $NaBH_4$ (27mg in MeOH, 8ml).

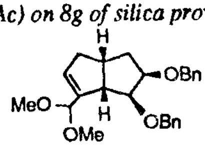
TLC



After 30 min tlc shows no SM, but two products. MeOH was evaporated, CH_2Cl_2 (30ml) added and the mixture washed with 10% HCl (10ml) followed by satd. $NaHCO_3$ (3 X10ml), dried and evaporated. (210mg crude)

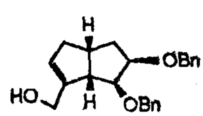
Flash chromatography using 9:1 (pet. ether/EtOAc) on 8g of silica provided:

BB A23a 27mg (12%)- NMR (BB28), MS (BB19), IR (BB27), Data sheet 6 - looks like:



$C_{25}H_{30}O_4$
mw = 394

BB A23b 140 mg (69% yield) - NMR (BB29), MS (BB20), IR (BB28), Data sheet 5 - OK for:



$C_{23}H_{26}O_3$
mw = 350

Comment:

Next time use aqueous solvent - may avoid ketal formation

Figure 2.1