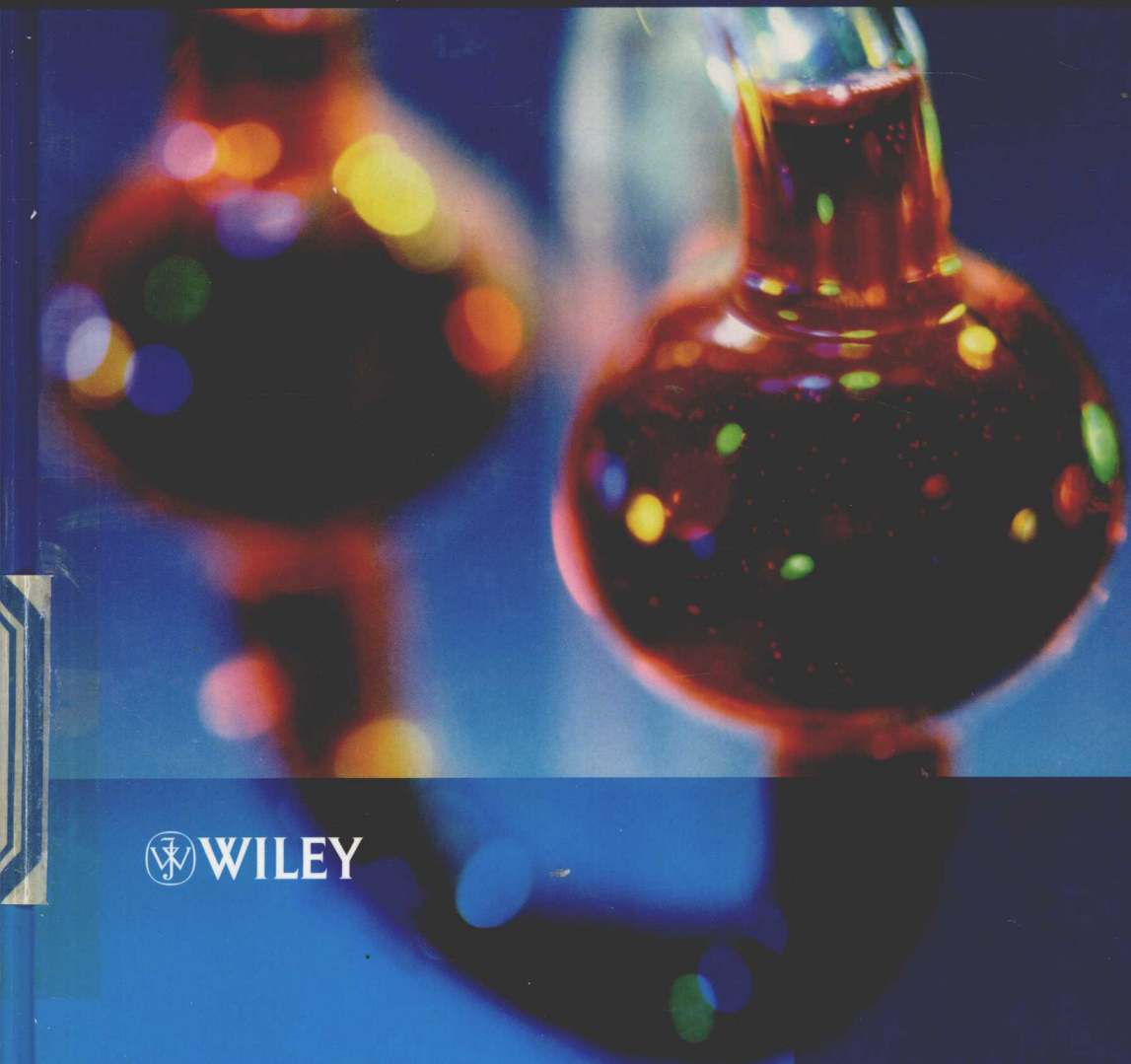
R. KEESE | M.P. BRÄNDLE | T.P. TOUBE

Practical Organic Synthesis

A STUDENT'S GUIDE



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Practical Organic Synthesis: A Student's Guide

Reinhart Keese
University of Bern, Bern, Switzerland

and

Martin P. Brändle
ETH Zürich, Zürich, Switzerland

Translated by

Trevor P. Toube
Queen Mary, University of London, London, UK

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Preface

Basic laboratory techniques in organic chemistry are an essential element in the training of chemists, who must learn to employ their experimental skills in the preparative organic laboratory in order to undertake the safe, careful and successful synthesis of compounds.

This guide was originally developed in concept by R. Scheffold at the ETH Zürich as the basis for a successful course in practical organic chemistry. Further contributions by many teaching assistants, first at the ETH and later together with R. K. Müller, A. Pfaltz and R. K.'s students at the University of Berne, led to the publication of *Grundoperationen der präparativen organischen Chemie, eine Einführung*, now in its 6th edition, which has been used successfully as a teaching tool in the first laboratory course of preparative organic chemistry.

Many suggestions and comments from experts, colleagues and friends have augmented the information presented. Safety precautions and environmental considerations in the handling and disposal of reagents are nowadays significant concerns of the responsible experimentalist. The main chapters deal with practical procedures and guidelines for organisational aspects of preparing compounds. The chapter on searching the literature, illustrated by worked examples, is particularly useful in providing efficient access to chemical information; this material was developed by Martin Brändle, an information specialist at the ETH.

In addition to proving invaluable to the aspiring undergraduate, experience has shown that this practical guide is also useful to advanced students as a handbook or desktop manual in the laboratory: it contains many details about solvents, handling of air sensitive compounds, the synthesis and analysis of optically active compounds, and the disposal and deactivation of hazardous chemicals. Beyond the teaching aspects of this practical guide, we believe that our hints and suggestions may also provide a stimulus for chemists searching for solutions to practical problems in the preparative laboratory.

Mrs. H. Mischler-Brühwiler's cartoons and illustrations make this practical guide entertaining as well as instructive. Thanks are also due to P. Schär, who provided the pages from his laboratory notebook.

Practical Organic Chemistry contains a wealth of useful information, laid out in a clear, stimulating style, designed to appeal to novices and experts in this field. It is an essential guide to young students, a text to which they will return again and again throughout their careers.

Berne, February 2006

Reinhart Keese
Martin P. Brändle
Trevor P. Toube

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Chapter 1

Accident Prevention and First Aid

1.1 SAFETY

Chemicals must always be handled with great care and attention. Many are potentially dangerous to health, possibly even poisonous and some are explosive. The majority of organic solvents are flammable, some have very low boiling points and may catch fire even on a hot surface at these low temperatures. Chapters 2 and 13 give details of the properties of some compounds.

It is essential that one is aware of possible hazards and prevents accidents.

1.1.1 Safety in the Laboratory

(a) *Laboratory Equipment*
A typical, well-equipped laboratory has workbenches with cupboards beneath them, shelving, rotary evaporators and fume hoods with movable vertical shields at the front.
There should be provision for leaving reactions running safely overnight.
Separate waste bottles should be available for chlorinated and non-chlorinated solvents. Broken glass, chromatographic supports and drying agents should be collected separately (see Chapter 13).

(b) *Safety Apparatus*
A laboratory should contain eyebaths, fire extinguishers as well as (often outside the actual laboratory) fire blankets, showers, bandages and fire alarms.

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Before you start work make sure you know where the eyebaths, fire extinguishers, fire blankets, showers and bandages are located as well as the emergency exit routes.

Read the local fire rules and think about them, *e.g.* what happens when an alarm is set off? Always obey instructions from those in charge.

(c) *Personal Equipment*

(i) *Laboratory Coat*

Ideally one made of cotton, as synthetic materials can cause severe burns if there is a fire.

(ii) *Safety Spectacles*

Must be worn at all times. Contact lenses are a hazard, as solvents or other liquids can be drawn behind them by capillary action and then cannot be washed away quickly. Prescription spectacles are available for those who wear glasses.

(iii) *Gloves*

Rubber or latex gloves usually prevent skin contact with undesired substances.

(iv) *Shoes*

Wear closed, skid-proof shoes.

1.1.2 Some Rules About Conduct and Safety

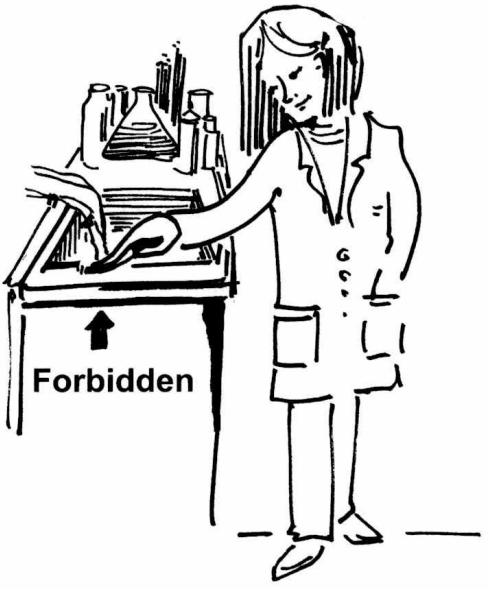
(a) *Flames*

- Bunsen burners: ideally, one should use a flame only when other heat sources are unavailable or inadequate. Bunsen burners should only be used in exceptional circumstances, and then in a fume hood. Even in such cases, it is essential that one makes sure that there are no flammable materials near the flame.

- Many fires are caused by inappropriate destruction of reactive compounds (see Chapter 13).

(b) *Smoking*

- Smoking is totally forbidden in the laboratory.



(c) *Glass Apparatus*

- Because glass is fragile, it must always be handled with care.
- Avoid increasing the internal pressure in vessels. Make sure that reaction or distillation apparatus is not a sealed system; use a drying tube or gas valve.
- Check that flasks do not have any cracks or flaws.
- Be particularly careful when opening ampoules; always cool in ice first.

(d) *Vacuum Work*

- Do not evacuate flat-bottomed flasks; they may implode.
- Use a safety cage when evacuating vacuum desiccators.
- Rotary evaporators can be made safer by enclosing the condenser in plastic netting.

(e) *Liquid N_2*

- Fill apparatus from the reservoir behind a safety shield.
- Wear safety glasses, gloves and solid shoes.
- Cover the open Dewar flask with a cloth when transporting it.
- Immerse cold traps in liquid N_2 slowly and under vacuum.

1.1.3 General Rules About Handling Chemicals

- A knowledge of the correct handling of chemicals and of potential hazards is an essential characteristic of a responsible chemist (see Chapters 2 and 15).
- Label all containers with a description of their contents. It is essential that contents are clearly identified.
- Always wear safety glasses and gloves when handling concentrated H_2SO_4. If acid gets onto the skin, wipe it off immediately with cotton wool or a cloth, rinse with plenty of water and then seek medical attention. To dilute concentrated H_2SO_4, add acid carefully to water (not *vice versa*). Sulfuric acid must not come into contact with chlorates, permanganates, concentrated ammonia or alkalis, or alkaline earth hydroxides, as they may react explosively.
- Contact with HF or its vapour is exceptionally dangerous. Burns are extremely painful. If you have to use HF, make sure you have read all the safety precautions first.
- Exceptional care is needed in handling carcinogenic substances:

  Do not use them except when unavoidable.
  Carcinogenic reagents and solvent can often be substituted by less hazardous substances.
  It is often possible to avoid the use of carcinogens by choosing alternative synthetic routes.
  Risks can be substantially reduced if one has the required skills and implements all the requisite safety precautions.
  Work in a fume hood, use disposable gloves, wear a dust mask and cover the work surface with aluminium foil.
  Handle carcinogenic material only in closed vessels.
  Destroy any excess reagents or reaction residues promptly.

- See Chapter 2: Environmentally Responsible Handling of Chemicals and Solvents.
- See Chapter 13: Disposal and Destruction of Dangerous Materials.

1.2 AVOIDING ACCIDENTS

1.2.1 First Aid

(a) *Eye Injuries*

If any chemical gets into the eyes, the eye should be washed at once with water at the nearest tap or eyebath. Washing should continue for at least 10 minutes. It is particularly efficacious and the injury becomes almost painless if the tap in the laboratory is fitted with a moveable mixing nozzle. The help of a second person in holding the head and holding open the eyelids to ensure thorough washing is desirable. This procedure is appropriate for accidents involving acids, strong bases (especially dangerous as they disintegrate the tissues and allow the contaminant to penetrate more deeply) and other chemicals.

Under no circumstances should acid splashed in the eye be washed out with bases (or *vice versa*), as this generally does more harm than good. After the eyes have been thoroughly rinsed with water for a sufficient period, professional medical attention should be sought. Contact lenses should not be worn in the laboratory as chemicals may be drawn under the lenses by capillary action and cannot easily be rinsed out.

(b) *Skin Burns*

Cool at once with running water. Larger burns may need to be covered with cloths soaked in cold water. These procedures also reduce the pain. Then seek professional medical attention. Do not cover burns with oily or greasy ointments. Do not puncture blisters.

(c) *Cuts*

Most cuts occur when handling glass. Many accidents can be prevented if glass is handled with a glass cloth or leather gloves, especially when being pushed through holes in stoppers, etc.

Take particular care to cool ampoules thoroughly in ice before opening them.

(i) *Treatment*

Small cuts:	Allow to bleed, disinfect, bandage.
Larger cuts:	If necessary stop bleeding, cover with a bandage (without disinfectant) and get medical attention.
Cut fingers:	Remove rings; unless they are obviously difficult, cuts on the fingers should be examined by a doctor.

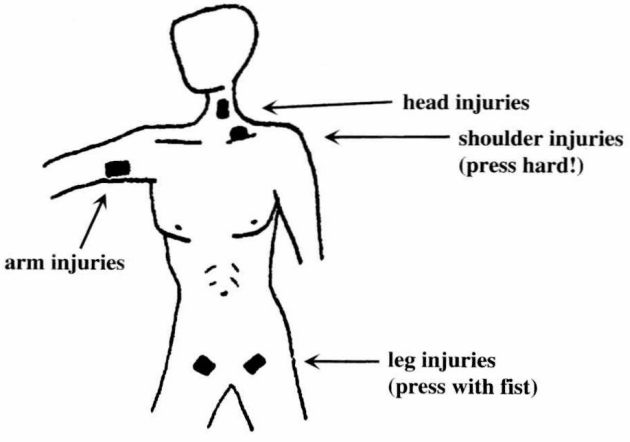
(ii) *Bleeding*

Stop the bleeding by:

- raising the affected limb;
- if this is not sufficient, applying pressure at the appropriate pressure point (requires practice!) or applying pressure directly over the wound, using a large dressing.

Make sure bleeding has stopped.

Seek medical attention.



(d) *Poisoning*
Medical treatment is easier if the nature of the poison can be established (obtain a sample of the substance, gas, vomit, *etc.*).

General Procedure

- elimination of the poison;
- medical treatment.

(i) *Oral Poisoning*
Induce vomiting by giving warm salt water (three heaped teaspoons of NaCl per glass) to drink. Repeat until vomit is clear. Then seek medical aid.

Do not induce vomiting if unconscious or if solvent, acid or alkali has been swallowed.

If solvent has been swallowed, do not induce vomiting, but give 200 cm^3 of pure liquid paraffin to drink.

Then seek medical aid.

(ii) *Gas Poisoning*
Remove victim from the danger zone (wear compressed air breathing apparatus, if necessary), keep him/her quiet and transport to doctor on a horizontal stretcher. Painful coughing may be assuaged somewhat by inhalation of alcohol vapour (using a cotton wool pad soaked in ethanol).

(iii) *Percutaneous Poisoning*
Remove contaminated clothing immediately, wash the affected area thoroughly and then seek medical assistance.

In acute cases, the time factor is critical. Carry out the above first aid procedures and get medical attention immediately. Clothing must be washed and aired before re-use.

Knowledge of the toxicity of chemical substances is an essential part of the training of a responsible chemist.

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Links to information about safety in chemical laboratories

http://www.hse.gov.uk/chemicals is the official government source for the UK and is legally binding.

Online access to a large variety of information about safety (and many other aspects of chemistry and chemicals) is avaibable via PSIgate: http://www.psigate.ac.uk/ → chemistry → safety.

Information about occupational exposure to hazardous chemicals in laboratories is published by the Occupational Safety & Health Administration of the U.S. Department of Labor:

http://www.osha.gov/

Chapter 2

Environmentally Responsible Handling of Chemicals and Solvents

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A wise head foresees problems!

Laboratory experiments should be planned to avoid danger as far as possible and to minimise the amount of refuse. Wherever possible, unreacted starting materials should be recovered and solvents recycled. Inappropriate handling of chemicals and solvents and careless behaviour must be avoided. One should also be aware of how to deal with any accidental mishaps which may occur.

It is essential that every chemist knows how to handle dangerous chemicals safely.

Before every experiment one should assess the possible dangers and health hazards, and consider what safety precautions are necessary. One should consider whether any of the substances involved are irritant, corrosive, flammable or explosive.

The following suggestions about appropriate experimental practice should prompt consideration of how one can protect oneself and others from danger, and awareness of the environmental effects of waste disposal.

The existing standards provide a minimum framework for safety precautions and procedures that should be observed in any laboratory. Obviously, local regulations supersede them in every case.

The following section merely indicates the immediate standards that need to be observed in a laboratory. It is intended to draw suitable attention to hazards and safety precautions.

2.1 DANGEROUS MATERIALS: POISONS, LAWS, REGULATIONS AND CLASSES

Poisons may be defined as substances which, by ingestion or contact, can endanger the health of people or animals by their chemical or physico-chemical effects even in relatively small amounts and which therefore need to be handled with particular care.

The framework for regulations for working with poisonous materials follows from this definition.

Poison Regulations describe the legal provisions covering poisons, prescribing in detail who may deal with them and what precautions have to be taken when handling them.

Poisons are subject to formal classification on the basis of their acute oral LD_{50} values in rats, but also taking account of data on toxicity, their effects on skin and mucous membranes, and absorption via the skin or by inhalation, as well as any available information on their behaviour in humans. A list of these poison classes is given in the following table.

2.2 EU POISON REGULATIONS

The European Union has guidelines and legal provisions aimed at harmonising the various national laws and regulations covering poisons and other dangerous materials,

so that uniform grades can be established on toxicity, ecological effects and physico-chemical properties of substances.

Substances, including laboratory chemicals, are classified into three groups based on their toxicity and their potential danger.

EU danger designations	Swiss classifications
Very poisonous	1
Poisonous and corrosive	2
Health hazard; irritant	3 and 4

From 2005 new EU regulations came into force, incorporating the following *R* and *S* phrases and symbols (which are already widely used). A complete list is given in chapter 15.

Code	Hazard symbol	Danger descriptor	Safety precautions
T+ T		Very poisonous poisonous	Avoid any contact with the body as there may be serious health risks
C		Corrosive	Avoid contact with skin or eyes. Do not inhale vapour
Xn Xi		Health risk irritant	Avoid contact with skin or eyes. Do not inhale vapour
E		Explosive	Avoid sparks, heat, friction, shock or impact
F+ F		Highly flammable Flammable	Keep well away from flames and heat sources
O		Promotes burning oxidizing	
N		Environmental danger	

R Phrases (risk indicators)

Poisonous substances, including laboratory chemicals, are classified according to their potential hazards using the so-called *R* phrases. For example, R11 means 'highly flammable' [*e.g.* ether] and R34 means 'irritant' [*e.g.* phenol]. Combinations