TECHNIQUES & EXPERIMENTS FOR ADVANCED ORGANIC LABORATORY

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The Author of this manual has outlined extensive safety precautions in each experiment. Ultimately, it is your responsibility to practice safe, laboratory guidelines. The Author and Publisher disclaim any liability for any loss or damage claimed to have resulted from, or related to, the experiments.

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Preface

The transition from the Sophomore organic lab to doing research is complicated by several factors - differences in the size of reactions, the use of more sophisticated and expensive equipment, exposure to difficult-to-handle materials, a heavier reliance on analytical techniques and instrumentation, and the need to learn to design procedures for new reactions. Because of this, a need for a research-oriented organic laboratory course has been recognized at many schools. However, I (and others) had been unable to identify a suitable laboratory manual for such a laboratory. This manual was written to introduce students to a variety of techniques which are used in research, including the most useful instrumental analyses (NMR, capillary GC and GC-MS). Indeed, several of the experiments are designed to illustrate the power of modern instrumentation, particularly capillary GC and NMR. I have also attempted to choose especially interesting experiments, several of which require "detective work" to solve, similar to what is encountered in research. Finally, I have suggested optional ideas (not tested procedures) for more in-depth and independent studies in the "Exploring Further ..." sections. This text should be of use in Junior- or Senior-level advanced organic laboratories, as well as in the second semester of Sophomore organic laboratories where the instructor wishes to provide an especially rigorous laboratory experience.

The material in this text generally assumes an understanding of Sophomore-level organic laboratory techniques. It is intended that this laboratory manual be used in conjunction with a good spectroscopy text which gives a practical coverage of IR, proton and carbon NMR, and mass spectroscopy. In addition, we (and others) have used Zubrick's "The Organic Chemistry Laboratory Survival Manual" (John Wiley and Sons, 1992), which is a detailed and humorous discussion of laboratory pitfalls that is suitable for either a Sophomore or an advanced laboratory student.

Many participated in various aspects of this project. I am grateful to several at Wiley: Sharon Nobel and Joan Kalkut for early encouragement, and Jennifer Yee, Bonnie Cabot, and Nedah Rose for carrying the project to completion. Proofreading by Elisabeth Belfer greatly improved the consistency of the format. I wish to thank Dr. Robert Walkup of Texas Tech University for providing much of the Diels-Alder experiment and also for thorough reviews of the manuscript. I appreciate the initial encouraging reviews given by Kraig Steffan of Fairfield University and James Hansen of Seton Hall University. Most of the experiments were developed during four semesters (1993-96) of Chemistry 4237 (Advanced Organic Laboratory), a Junior/Senior-level laboratory course at Baylor University. Baylor students Farima Farzaneh and

especially the wonderful Lisa Alvarez helped work out experiments and collect spectra. Sunil Aggarwal worked out the procedure for the prediction of GC retention times. Finally, without the facilities provided by Baylor University and the Department of Chemistry, and their commitment to excellence in undergraduate education, this project could not have been accomplished. I would welcome any questions, comments or suggestions.

Charles M. Garner
October, 1996

About the author: Charles M. Garner is an Associate Professor of Chemistry at Baylor University. He received his B.S. from the University of Nevada, Las Vegas, and his Ph.D. from the University of Colorado. After working for a time in industry, he held an NIH postdoctoral fellowship at the University of Utah. In addition to conducting research in organic and organometallic chemistry, Professor Garner enjoys developing new experiments and applications of chemistry instrumentation in teaching laboratories. He has directed organic laboratories at both the Sophomore and advanced levels for several years.

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Purpose of the Text

This text is intended as an introduction to the most useful techniques encountered in organic chemistry research. This includes experience in handling very reactive materials, accomplishing difficult chromatographic separations, and especially becoming familiar with the most powerful methods of instrumental analysis. The experiments are designed to illustrate the power of NMR, IR, GC-MS, and gas chromatography in a variety of contexts. Capillary gas chromatography allows rapid, high-resolution analyses, yet tends to be quite under-utilized in organic lab courses, so I have placed some emphasis on this technique. Also, several experiments illustrate advanced aspects of NMR spectroscopy, including multinuclear NMR. It is intended that a spectroscopy text which provides a moderately advanced (yet practical) treatment of NMR, IR, and MS be used in conjunction with this lab manual. The intended result is that, given the necessary knowledge and tools, you will develop a practical understanding of and an appreciation for research in organic chemistry.

Equipment

On the next page are shown the major pieces of "macroscale" glassware; learn each type and keep them clean. If one of your pieces should become cracked, replace it immediately. Never apply vacuum or pressure to fractured glass! Round bottom flasks are especially susceptible to "star" fractures: watch for them.

Laboratory Safety

Safety in chemistry laboratories is of the utmost importance. As in previous lab courses you may have taken, safety glasses or goggles are required at **all** times. You should avoid wearing shorts or other types of clothing which leave significant portions of skin exposed. Likewise, shoes should fully cover the feet (no sandals). When in the lab, do not put anything in your mouth. All volatile toxic materials should be handled only in the fume hoods. Wear gloves when there exists a risk of skin contact with toxic materials. Be careful not to expose organic liquids or vapors to spark or flame sources. Dispose of chemical wastes only in a manner authorized by your instructor, which will generally **not** be in the sink or wastebasket. You are not allowed to work alone in the laboratory. Unauthorized experiments are prohibited.

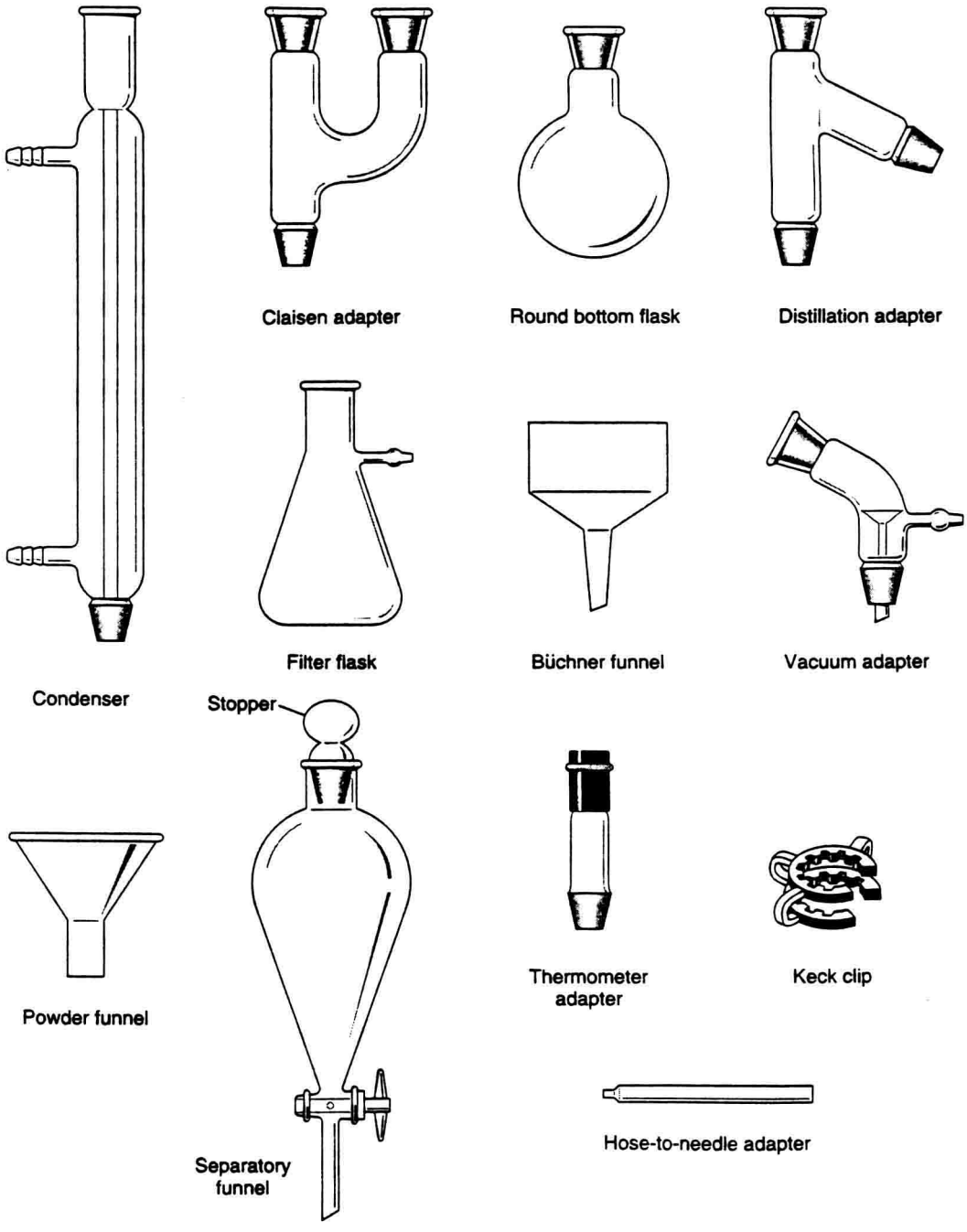


Figure 1: Common glassware and other items.

One aspect of advanced laboratory work is to develop an awareness of potential hazards various materials may present. The following terms are often used to describe particular hazards of various materials, and serve as an indication of how a given material should be handled. You should be familiar with these terms and their implications, and with common materials which have these properties. The label on a bottle may or may not note these hazards, but they should be given (when known) on the Material Safety Data Sheet (MSDS) provided by chemical suppliers.

Carcinogen: Causes cancer (e.g., methyl iodide, benzene, HMPA, chloroform, dioxane).

Deliquescent: Tending to absorb water from the air to the point of dissolving (e.g., $CaCl_2$, LiBr).

Hygroscopic: Absorbs water from the air (e.g., $MgSO_4$, DMSO, D_2O).

Lachrymator: Causes irritation and watering (tearing) of the eyes (e.g., benzyl bromide).

Mutagen: Causes mutations (e.g., 2-nitrobenzaldehyde).

Pyrophoric: Ignites spontaneously upon contact with air (e.g., t-butyllithium, trimethylaluminum, triethylborane, white phosphorus).

Sensitizer: Can cause serious allergic reactions on subsequent exposure (e.g., dicyclohexylcarbodiimide, iodomethane).

Sternutator: Causes sneezing and possibly lachrymation and vomiting (e.g., maleic anhydride, diphenylchloroarsine).

Teratogen: Causes birth defects (e.g., acrylamide, iodomethane, Thalidomide).

Vesicant: Causes blistering of skin (e.g., methyl iodide).

In addition, there are certain hazards particular to ethers. Diethyl ether and other low molecular weight ethers are extremely flammable. A more insidious hazard is that any ether with a CH bond next to the oxygen will slowly form peroxides upon exposure to air, which can cause two problems: (a) the peroxides can oxidize sensitive materials (like CuI), and (b) upon evaporation of the solvent, the higher-boiling peroxides concentrate and can detonate unexpectedly (an internal oxidation/reduction reaction). Diisopropyl ether is much worse that the other common ethers (diethyl ether and tetrahydrofuran). Prior to use, you should test any ethers which have had prolonged exposure to air (especially dry air) using commercially available starch/potassium iodide paper. This is done by evaporating a drop of the ether onto the paper followed by acidifying with 1 M HCl. An immediate change (within 1-3 seconds) to blue indicates the presence of peroxides. Slower color changes may be due to oxidation by atmospheric oxygen. Peroxide-contaminated ethers must be treated with an appropriate reducing agent followed by re-purification, or disposed of properly. The Aldrich catalog lists proper disposal procedures for the materials they sell.

Guidelines on Notebooks

Careful attention to thorough documentation of the laboratory notebook is extremely important in scientific training. Leave the first 2-3 pages of your notebook blank for a table of contents. Each experiment should always start on a new page. Always use a water-insoluble ink pen (**not** a felt-tip pen or a pencil) unless otherwise directed.

You should always:

- Date the experiment each day that you work in lab.

- Draw out the reaction that you hope will occur. You can also draw in possible undesired reactions if you wish.

- Note the purpose of the experiment.

- Reference the procedure you are following, if applicable.

- Provide a detailed table of reagents, which includes:

  - all the chemicals and solvents you will be using with a description of source and/or purity, if known (or appearance, if relevant).

  - the pertinent physical data for each compound (molecular weight, density for pure liquids, concentrations for solutions) required to calculate the mmoles used.

  - the actual amounts of materials you used, in the context you used them (if you weigh out a material, give the weight and not the volume that might correspond to).

  - the mmoles that each amount corresponds to (except for solvents).

  - the equivalents (i.e., mole ratios based on the limiting reagent) each amount corresponds to.

  - a very brief notation as to what hazards the material represents; this information may be obtained from the Aldrich catalog, or preferably from the material safety data sheets (MSDS) for that compound.

• Then describe what you did, including what size of flask you used, whether a stir bar was present, how you added the reagents and at what rate (if applicable), what temperatures were used, appearances during the experiment (especially color changes, homogeneity changes, gas or heat evolution, etc.). Be detailed enough that someone else could almost exactly reproduce your procedure using only your notebook. Date your notebook each new day you make an entry.

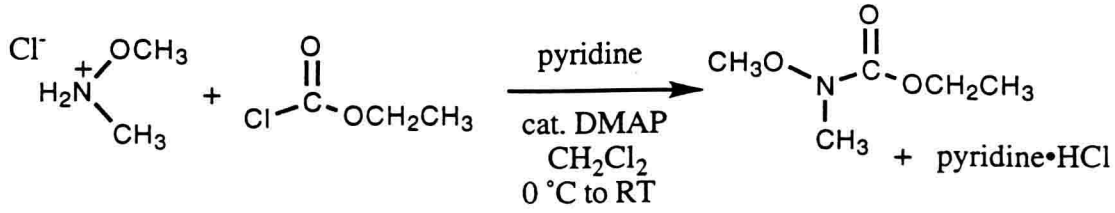
Note: Your instructor may or may not require you to use the third person when writing your notebook. The use of the first person is less formal, and in some cases may be more informative. For example, rather than writing "It was decided ...", something like "I decided ..." or "The instructor suggested ..." conveys more information. In more formal situations (for example, publications) the third person usually is used.

• All data from the characterization of products (such as product weight, yield, melting point, important IR frequencies, mass spectra peaks, and NMR chemical shifts and multiplicities, elemental analysis results, and GC retention times/area percents) should be entered into the notebook. *As much as possible, put a reduced copy of the spectrum or chromatogram into the notebook* (usually a 50 or 64% reduction of an appropriately sized original; we will work out good ways to do this for the various types of data). In addition to just *including* the data, you must also *interpret* it at an appropriate level. For example, what is it about your NMR spectrum or MS data that makes you think you have the correct compound? Always draw in pictures of important TLC plates (shade the spots with a pencil, but use ink for the rest; remember to note what solvent was used to develop the plate and what methods of visualization were used). In all reactions where you prepare and measure the amount of a product, you should calculate the percent yield (show your calculations).

• Complete the notebook with Conclusions, which includes a summary of the results and addresses any difficulties encountered, and then answer any questions which may have been assigned in the experiment.

An example of a notebook report with this general format follows.

Experiment 3: Preparation of Ethyl N-Methoxy-N-methylcarbamate
Date: 9-24-93



Purpose: Prepare carbamate derivative to use in conversion of organolithiums to ketones.
Reference: D. J. Hlast, J. J. Court Tetrahedron Lett. 1989, 30, 1773.

Table of Reagents

reagent	*mol. wt./density*	*amount*	*mmol*	*equiv.*	*hazards*
N,O-dimethylhydroxylamine hydrochloride	*97.55 g/mol*	*25.56 g*	*262*	*1.0*	*hygroscopic*
dichloromethane (dist. from CaH_2)		*210 mL*			*toxic, volatile*
4-dimethylaminopyridine (DMAP)	*122 g/mol*	*1.04 g*	*8.5*	*0.03*	*highly toxic*
ethyl chloroformate	*108.52 g/mol 1.135 g/mL*	*25.0 mL*	*262*	*1.0*	*highly toxic*
pyridine (dried over NaOH)	*79.10 g/mol 0.978 g/mL*	*47 mL*	*576*	*2.2*	*toxic, stench*

Procedure

The reaction was done in a 500 mL round bottom flask containing a large stir bar. The amine hydrochloride was weighed quickly in air and was then suspended in dichloromethane and cooled to 0 °C under inert atmosphere. Then dimethylaminopyridine and ethyl chloroformate were added; little or no reaction was evident at this point. Then pyridine was added by cannula over about a 5 minute period. The reaction mixture thickened considerably during the pyridine addition, to the point that magnetic stirring

became difficult. After about 5 minutes at 0 °C, the mixture was allowed to warm to room temperature over about a 15 minute period. The suspension thinned somewhat and became more stirable, with some heat evolution noted also. The reaction mixture was allowed to stir until next lab period.

9-26-93

The suspension was cooled to 0 °C, then filtered through a coarse porosity fritted-glass funnel, rinsing the solid well with dichloromethane. The filtrate was then transferred to a separatory funnel and washed twice with 125 mL portions of ice-cold 3 M aqueous HCl. During the first wash, the aqueous phase became yellow, but the second was colorless. The organic phase was dried over magnesium sulfate, filtered and concentrated by rotary evaporation with the flask at or below room temperature. This yielded a clear, light brownish-yellow liquid. This was subjected to simple distillation under aspirator vacuum. This yielded 31.8 g of a clear, colorless liquid, with a boiling point of 74-76 °C at 43 torr. A sample was prepared for capillary GC by diluting a small amount in dichloromethane using the 'paper clip' method. This showed the compound to be > 99% pure. GC-mass spectrometry was done, and ^{1}H and ^{13}C NMR were obtained at 360 and 90 MHz, respectively.

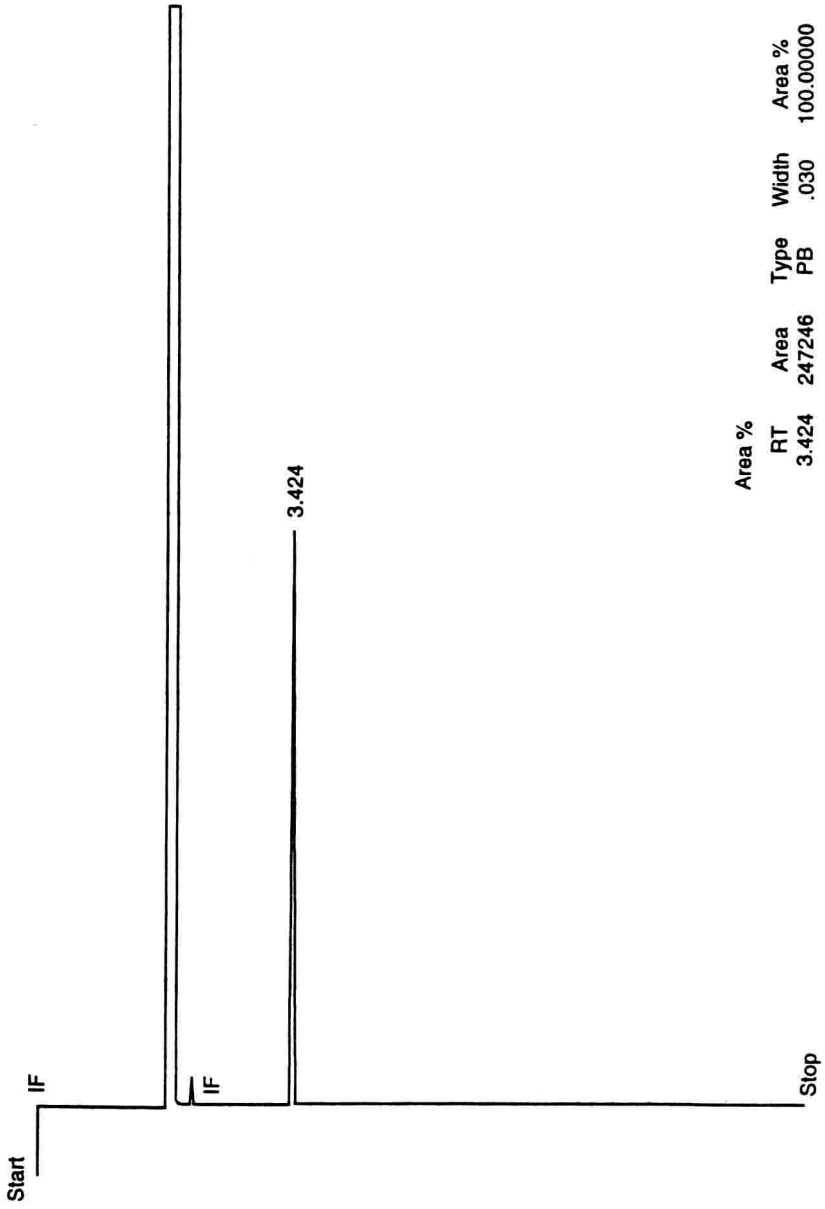
Percent yield calculations:

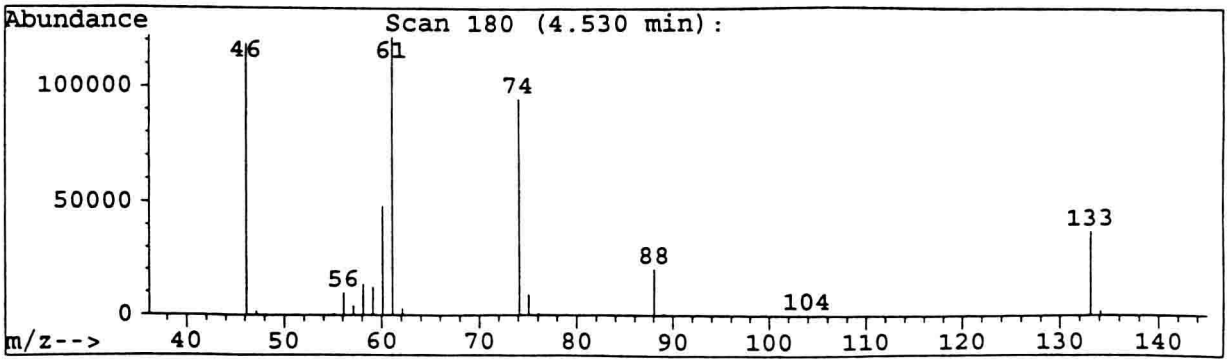
$$\frac{31.8\ g\ product}{133\ g/mol} \times \frac{1000\ mmol}{1\ mol} = 239\ mmol\ product$$

$$\frac{239\ mmol\ product}{262\ mmol\ limiting\ reagent} \times 100\% = 91\%\ yield\ of\ product$$

Conclusions: This reaction was a good example of nucleophilic acyl substitution and vacuum distillation, and proceeded in excellent yield.

Capillary GC and GC-MS for ethyl *N*-methoxy-*N*-methylcarbamate (80 °C to 150 °C at 5 °C per minute).





^{1}H and ^{13}C NMR spectra for ethyl *N*-methoxy-*N*-methylcarbamate (360 and 90 MHz, resp.)