

SYNTHESIS, SPECTROSCOPY AND PHOTOCHEMISTRY OF BENZOPHENONES

Integrated Laboratory Project - CH 463 & CH 463H (WIC)

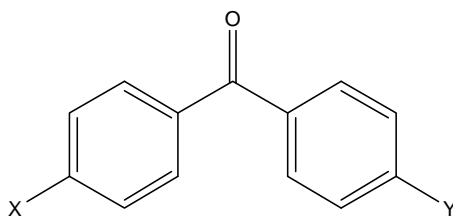
Department of Chemistry - Oregon State University

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I. Overview of the Experiment.

Each student in the class will be assigned an individual substituted benzophenone,



where X and Y are halogen, methyl, etc., substituents. Students will be assigned a method to use to synthesize their assigned compound which requires making a new C-C bond using one of five reaction routes. Two routes are Friedel - Crafts reactions using AlCl_3 as the catalyst, three routes are organometallic routes: (i) the phenylmagnesium Grignard reagent and benzaldehyde to make a secondary alcohol and subsequent oxidation with MnO_2 to the ketone; (ii) t-butyl lithium (pyrophoric and usually not done in this class); and (iii) Pd catalyzed cross coupling of a substituted phenyl boronic acid with an anhydride (a “greener” Suzuki-Miyaura reaction). The synthetic method will also be assigned. Before beginning the experimental work, each student will conduct a literature search for specific information on the assigned compound and route of synthesis, starting with secondary reference sources and leading to the primary published reviewed journal literature (e.g., scientific publications, such as but not limited to, JACS, Syn Comm, etc.). Primary literature is located by using both Scifinder Scholar (search engine for American based Chemical Abstracts), and Reaxys (search engine for German based Beilstein and Gmelin Abstracts), plus other secondary references, e.g., vendor catalogs, books, other reputable online sources, which will point to primary references. Students will locate the primary journal articles either online through these scientific search engines or using Inter Library Loan (ILL). The assigned compound is to be prepared, isolated, purified and characterized by tlc, mp, IR, 1 and 2D NMR, GCMS to give a sufficient quantity to carry out the analytical and physical and photochemical studies in the rest of this project.

The physical studies are designed to give the photophysical parameters for the photochemical active excited triplet electronic state (T_1) originating in the carbonyl moiety and for the excited electronic singlet state(s) (S_1 , S_2 , S_3 , etc) and the electronic singlet ground state (S_0) for both the carbonyl and the aromatic ring. The integrated UV absorption spectrum of the substituted benzophenone will be

determined in a suitable solvent, e.g. ethanol and/or cyclohexane, at room temperature and the effect of solvent polarity on the UV transitions will be investigated. The integrated UV absorption spectrum yields the integrated absorption coefficient (IAC) for each transition. The UV phosphorescence emission spectrum will be determined at 77 K (liquid N₂ temperature) and the phosphorescence quantum yield can be determined. The UV phosphorescence excitation spectrum and the phosphorescence lifetime will be measured at 77 K. The IAC for each observed electronic transition leads to the oscillator strength for the transition, the transition rate constants (Einstein coefficients), and the value for the transition dipole moment. A comparison of the photophysical parameters will be made for ground state versus excited state transitions and a Jablonski diagram will be constructed for the carbonyl and for the aromatic ring electronic transitions. An option for some students wishing to get some experience with polymers, is to encase the ketone in optically clear polymer (PMMA) and analyze the phosphorescence of this sample at room temperature for comparison to the data collected at 77 K.

The photochemical reduction of the substituted benzophenone by UV irradiation in a suitable solvent will be carried out as a synthetic route to the substituted benzopinacol. The photoreduction quantum efficiency will be determined using quantitative FTIR analysis. The photochemical principles behind this reaction are emphasized.

II. Literature Search and Report for Your Substituted Benzophenone.

Your first task is to find secondary and primary references and prepare a research proposal after a search of the primary literature. Your proposal should cover all information and pertinent data that has been published on your assigned substituted benzophenone using your assigned chemical reagents and method. The first week, particular emphasis is to be placed on information about the synthesis, work up, isolation, and purification of the compound, and in following weeks your job is to locate as much information as possible on the electronic spectroscopy and photochemical reactivity for your compound. You should pay special attention to the physical properties of significance to you in this experiment, e.g., melting points, solubility and solvents suitable for recrystallization, boiling points at various pressures, etc. Has anyone synthesized your compound

by the same method you are going to use or by a closely related method? What were the conditions, methods of working up the reaction mixture, yields, etc.? Previous literature reports on the absorption spectra (UV, IR, Raman), NMR, phosphorescence behavior, photochemical reduction, and properties of the photoreduction product, benzopinacol, are also important.

The two most useful secondary reference sources that are locators for the primary literature are the scientific search engines: SciFinder Scholar (Chemical Abstracts), and Reaxsys (the German Beilstein's Handbuch der Organischen Chemie and Gmelin). The first day you will use these search engines to search for primary references for the synthesis and characterization of your assigned compound. These user interfaces have been installed on the computers in the lab and you can also register to use these programs on your own laptops - see the Valley Library web page for electronic databases. You may still need to go to Valley Library to retrieve paper copies of primary literature sources from the stacks and/or request electronic copies using InterLibrary Loan for any journals that OSU does not have access to. The librarians at the Valley Library Science-Technology desk are also available to help you. The reference indexes (in print), Chem Abstracts System Source Index (CASSI, QD1.A532) is a useful guide to find the standard abbreviations for journals and this information can often be found online as well. There are several helpful links on the CH 463 web page (Supplemental Materials).

Beilstein is a major structure and factual database of organic chemistry and is comprised of abstracts written from a critical review of the primary literature (this is different than just listing references). Some abstracts written after 1959 are unreviewed organic substance records (registry numbers, structures, formula and weight, chemical name, general chemical data including preparation and property data). Citations to Beilstein and Gmelin are common in the Handbook of Chemistry and Physics (CRC), Lange's Handbook, and the Aldrich catalog/handbook, for example.

Examples of additional secondary references:

- SDBS data base online at course web page- supplementals
- NIST web \book availab on line at course web page- supplementals
- Chemical Vendor web sites, e.g., Sigma Aldrich and TCI web sites

- CRC Atlas of Spectral Data and Physical Constants of Organic Compounds, 2nd Ed. Vol. II (QD291/A8(ref));
- Atlas of Absorption Spectra, L. Láng (QC437.L27);
- Phillips, Freedman, Craig, Organic Electronic Spectral Data (QD 95.O7, V. 6), G. Olah, Friedel-Crafts and Related Reactions, 4 Vols. (QD501.O6); etc.

The secondary reference sources will direct you to the original primary journal articles. Your job is to use these secondary references to locate the primary articles. The original papers may well be in German, French, Italian, or Russian - but don't worry! Scientific/chemical dictionaries and your instructors will assist you in reading these if you bring a legible copy (note: please treat old journals with care - they are not easily replaced). There are some on-line scientific dictionaries for translation purposes as well (see course web page).

Before starting your synthetic work the second week, you are required to turn in your research proposal and detailed draft of your proposed synthetic work and receive approval from the main course instructors (Pastorek or Firpo). This proposal should be 1-2 pages of written text (see class handout for more directions) and you should give specific details based on what you found in the literature explaining on how you plan to carry out the synthesis, work up, isolation, purification and characterization for your assigned compound.

Tips on Searching the Scientific Literature for Benzophenone Project.

For the first part of the project you are looking for information and details on the synthesis and characterization of your assigned compound. Clues are often found in unlikely places, such as in figures and tables in published articles, and information that you are looking for may not be the main emphasis of the publication, or your compound may appear in a table in a paper reporting a systematic study of many substituted benzophenones that all have a common preparation scheme. Usually one clue leads to another, and eventually you will find enough published information (presumably reviewed by reputable scientists) to design your synthesis. Often it pays to follow up on secondary leads by consulting the reference list at the end of promising journal articles and search for those sources. A good place to start is by searching the secondary references such as handbooks,

catalogs and databases that lead you to the primary journal articles. The goal is to find the original published reviewed journal articles that have the information that you need. The following is a flow chart of sorts on how to start your search.

1. Find the Chemical Abstracts Registry number (CAS) or Registry Number (RN) for your compound. This is a unique identifier and can be a useful tag to search on instead of using a chemical name. The RN/CAS's can be found for example in the Aldrich Catalog/Handbook and in the MSDS. For example the RN/CAS for unsubstituted benzophenone is: [119-61-9]. [Note square brackets are used to designate the CAS].

2. Locate a few proper chemical names for your compound. For example, **benzophenone is a parent name but in IUPAC language it also known as diphenyl methanone**. Symmetrically substituted benzophenones are named either as *bis* (phenyl) methanone, e.g., *bis* (4-iodophenyl) methanone, or as 4,4-di(substituent)benzophenone, e.g., 4,4'-diiodobenzophenone. For non-symmetrically substituted benzophenones, for example, 4-iodophenyl-4-nitrophenyl methanone is the same as 4-iodo-4'-nitrobenzophenone.

3. OSU currently has unlimited user licenses for the entire campus (~\$200K/yr) for Scifinder Scholar and Reaxsys. You can access these through the OSU Library site and setup a login using your onid email. The search results you locate depend on how you search and which database is searched (there are several databases that are part of SciFinder, such as, Registry, CAracts, etc.). Success also depends on the date the journal article was published. For example, it is usually more efficient to search using the chemical name or the CAS number as a RESEARCH TOPIC rather than searching the compound using a structure search - try both methods. Searching the structure should at a minimum lead to the CAS number if you can't find it somewhere else. If you get a lot of hits after entering a search string, refine your search by searching the first hit list with another TOPIC such as synthesis of, preparation of, spectroscopy of, etc. to narrow down the choices. Once you have a hit list of references, you can check the box next to the likely candidates to view the abstract and often download a pdf of the full text of the paper through an interface called CAS Port. If OSU

owns a license for the electronic version of a particular journal, you can download a pdf file of the actual article. If OSU owns a hardcopy license, you can take the list of references and go to Valley Library and retrieve the paper journal from the stacks. If OSU does not own rights to the journal you can request a copy of the article by InterLibrary Loan (ILL) on line. This means that if a library in the consortium of University libraries that OSU belongs to has the journal, they will email you a pdf within a few days to a few weeks. To request ILL, use the electronic form on the Valley web page.

4. You might have to physically go to the stacks at Valley Library on the first floor. Occasionally but rarely, the abstracts are detailed enough so you can design your synthesis without the physical copy of the primary article.

5. Don't get discouraged, there are often false trails. Keep on trying and check with your Instructors frequently!

6. Check the Valley Library Catalog and Orbis, a consortium of university libraries that share resources. See the link on Valley library web page.

7. Check your organic text book and other organic text books for Friedel-Crafts acylation using aluminum chloride catalyst and Pd catalyzed cross coupling reactions using boronic acids. Also consult the references cited in your text book.

8. If you can't find ANYTHING on your compound, try searching for information on a similar benzophenone and adapt that procedure after discussion with one of your instructors. For example, if you are assigned 4-chloro-4'-propylbenzophenone and can't find ANYTHING, try looking up a preparation for a more simple but similar benzophenone, e.g., 4-chlorobenzophenone or 4-chloro-4'-methylbenzophenone or 4-propylbenzophenone and design your own synthesis (the Instructors are available to help). Method 2 in the lab manual can be useful as a general guide in these cases.

Key words to watch for in your search

Part A of Project - Synthesis and characterization

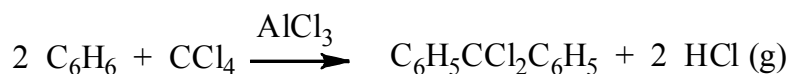
- Friedel-Crafts acylation synthesis
- Aluminum Chloride catalyst; AlCl_3 ; carbon disulfide (solvent), CS_2
- Pd catalyzed cross coupling reactions using phenyl boronic acid
- melting point
- boiling point (pressure?)
- solubility in various solvents - sometimes this shows up in published work on the spectroscopy, or is listed along with melting points
- IR, NMR, Raman spectra for main peaks.

Keep your eyes open for references for the physical chemistry/analytical study for the Photophysics and Photochemistry and note pertinent references so you can retrieve and read these later:

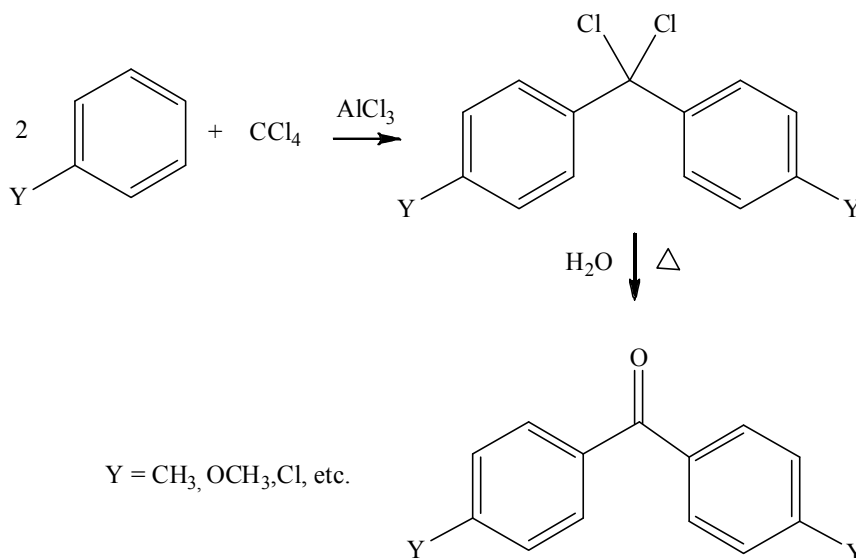
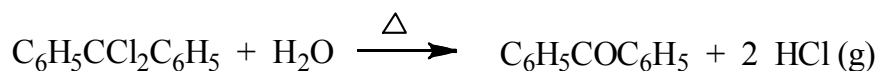
- UV absorption spectrum; solvent?
- molar absorptivity, extinction coefficient
- lambda max
- emission wavelength; solvent?
- excitation wavelength; solvent?
- integrated absorption coefficient
- Singlet (S_1) and Triplet (T_1) UV transitions; $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions
- emission lifetime, phosphorescence lifetime; solvent?
- phosphorescence quantum efficiency; solvent?
- photochemical reduction by sun light or UV light to the benzopinacol
- photochemical reduction efficiency
- mp, IR, NMR for your benzopinacol.

III. Three Routes for Synthesis of Benzophenone.

Benzophenone can be prepared conveniently by a Friedel-Crafts reaction by either of two routes, each making use of a very effective catalyst, anhydrous aluminum chloride. The *first route* uses carbon tetrachloride as the source of the carbonyl group, and two steps are involved. The first step joins the two benzenes to the CCl_4 to make a dichlorodiphenylmethane. We don't usually assign the FC alkylation method in CH 463 because it can lead to tarry byproducts that are hard to separate, is hard to control to stop at the addition of two rings, and can lead to benzhydrol (an alcohol instead of ketone). There are two steps in the alkylation:

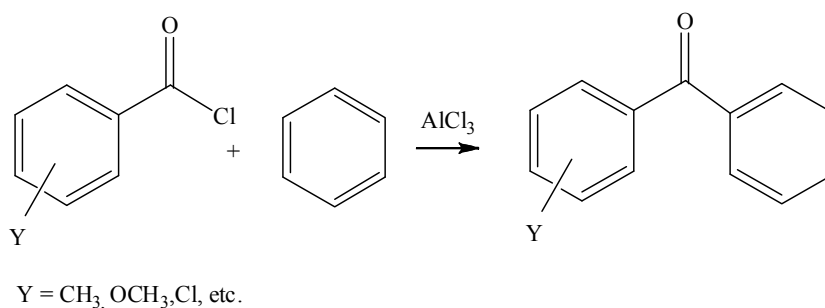


uses steam to hydrolyze the CCl_2 group to a carbonyl group. and the second

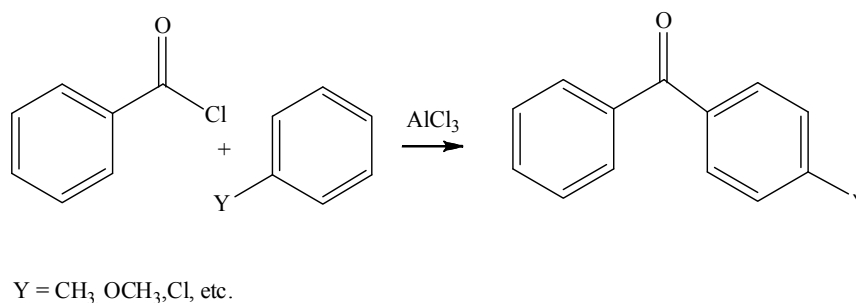


Clearly this route is limited to the preparation of symmetrically substituted benzophenones. Substitution occurs almost exclusively in the para position on each ring.

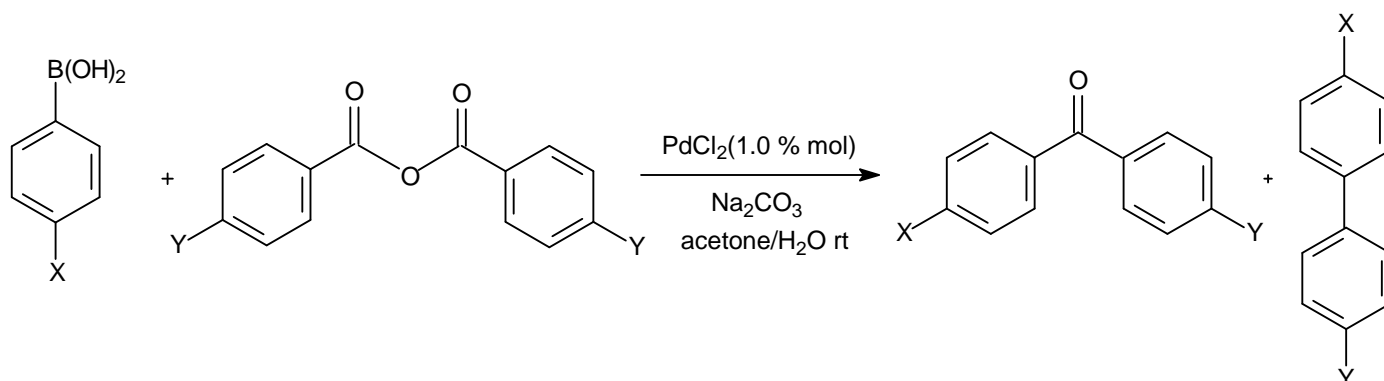
The **second route** uses an acylchloride, and the benzophenone is obtained directly from the Friedel-Crafts reaction.



This reaction is suited to the preparation of either symmetrically or unsymmetrically substituted benzophenones. When benzoyl chloride reacts with a substituted benzene the reaction again occurs predominantly in the para position. However, with a substituted benzoyl chloride the substituent can be in ortho, meta or para positions.



A **third route** uses PdCl_2 in a coupling reaction between a substituted phenylboronic acid and a substituted symmetrical benzoic anhydride to produce the 4,4' substituted benzophenone.



METHOD 1:

The synthesis of unsubstituted benzophenone will be described for illustration purposes only.

ALL OF THESE REACTIONS ARE TO BE DONE IN THE HOOD.

Formation of the dichlorodiphenylmethane.

Equip a 500 mL round-bottomed three-necked flask with a condenser, an efficient mechanical stirrer, a dropping funnel and a thermometer as shown in Figure 1. Note that the thermometer must dip into the liquid in the flask, but must be so adjusted that the stirrer does not hit the bulb. A mineral oil bubbler to indicate the rate of hydrogen chloride evolution should be attached to the top of the condenser. It is important that the exhaust from the bubbler passes out near the surface of the aqueous sodium hydroxide, to hold down room air pollution.

Place in the flask 45 g. (0.34 mol) of ¹anhydrous aluminum chloride and 100 mL of dry carbon tetrachloride. (Commercial carbon tetrachloride can be dried by distilling it and rejecting the first 10% of the distillate). The flask is immersed in an ice bath and the stirrer is started. When the temperature of the material in the flask is between 15° and 10°C, 5 mL of dry thiophene-free benzene is added in one batch from the dropping funnel. Evolution of hydrogen chloride indicates the reaction has started. If the temperature is below 10° the reaction will not start. Immediately after the reaction has begun, salt should be mixed into the ice bath to cause more effective cooling, and when the temperature in the reacting mixture falls below 10°, a mixture of 55 mL of benzene in carbon tetrachloride is added at a rate which keeps the temperature between 5 - 10°. Below 5° the reaction proceeds too slowly and above 10° more tarry by-products will be formed and the yield will be lowered. After the addition has been completed the reaction mixture is stirred for 3 hrs. while keeping the temperature at 10°. The stirrer is then stopped and the reaction mixture is allowed to stand at room temperature until the next lab period.

¹Anhydrous $AlCl_3$ is extremely reactive. Handle with caution. Carbon tetrachloride is toxic and benzene is a class B carcinogen, handle both with caution, wear gloves, and work under the hood.

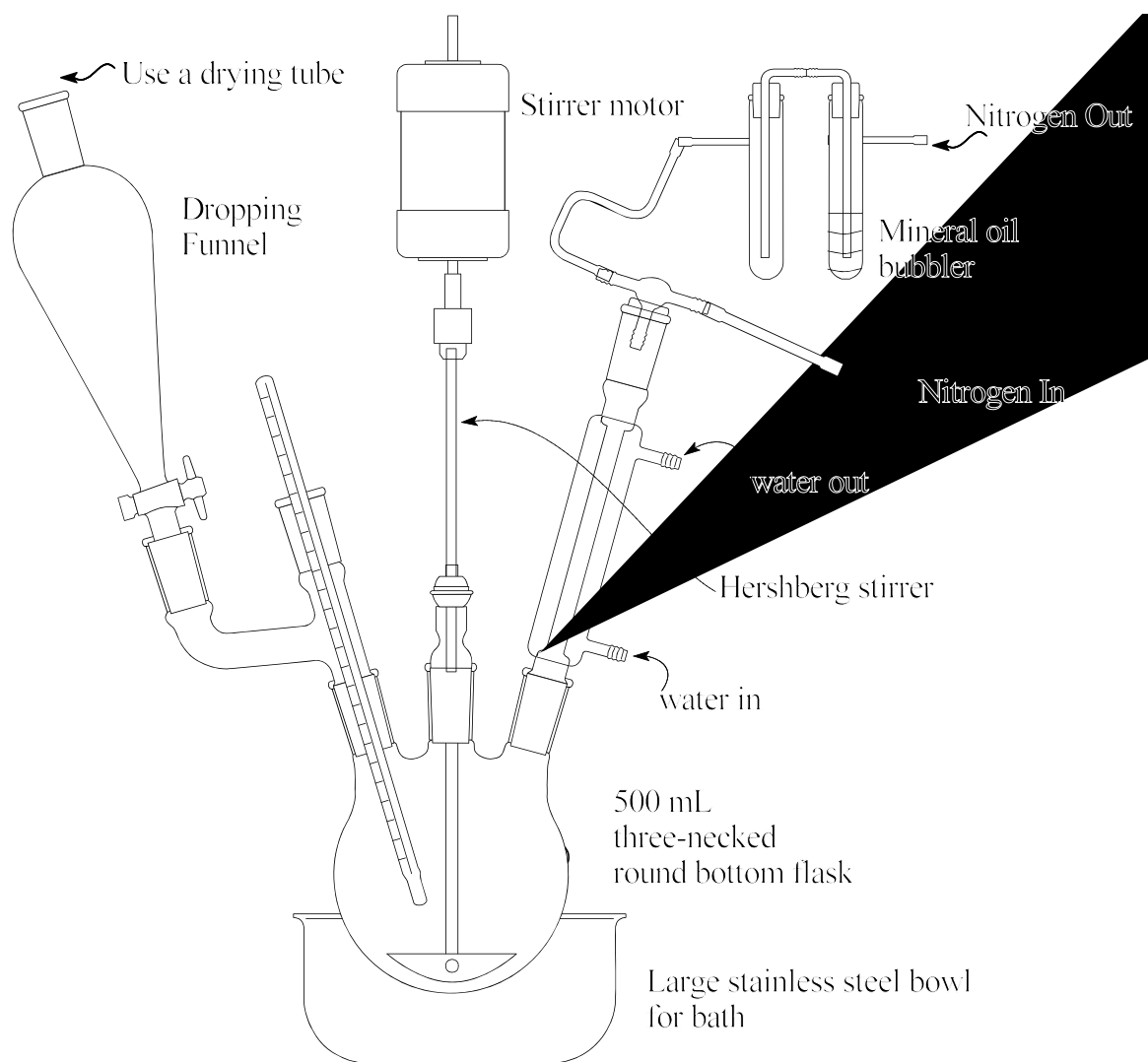


Figure 1. Reaction set-up for both methods.

Hydrolysis of dichlorodiphenylmethane to benzophenone.

At the next lab period the stirrer is started, the ice bath is filled with ice, and 50 mL of water is added slowly and be alert to a lag in reaction time. It will do no harm if the reaction mixture gets hot enough to boil the carbon tetrachloride during this addition. The mixture is allowed to cool, and the stirrer, thermometer and dropping funnel are removed. The side necks are stoppered, and the apparatus is set up for distillation (as in Figure 2 except the steam inlet is omitted). Most of the excess carbon tetrachloride is distilled. At this point the steam inlet is put in place and the mixture is steamed distilled for 1 hr. During this steam distillation the remaining carbon tetrachloride distills and the dichlorodiphenylmethane is hydrolyzed.

To bring about steam distillation in a convenient fashion, steam is passed through a heated mixture of water and the organic materials. When a source of steam from a steam line is not available, a steam generator can be constructed or water is added to the reaction mixture and the mixture heated to produce steam *in situ*. **We will use this last method.**

For organic compounds which are insoluble in water, **steam distillation** amounts to a co-distillation of water and the organic compound. When the sum of the vapor pressures at a given temperature equals atmospheric pressure, distillation will occur. For any compound, the ratio of moles of the compound to moles of water which distill will equal the ratio of the vapor pressures.

$$\frac{W_X / M_X}{W_{H_2O} / 18} = \frac{P_X}{P_{H_2O}} \quad \text{or} \quad \frac{W_X}{W_{H_2O}} = \frac{M_X P_X}{18 P_{H_2O}}$$

Obviously, carbon tetrachloride would be removed quickly. Any excess of the volatile aromatic reagents will co-distill with water (some form azeotropes). However, benzophenone is a relatively non-volatile compound whose vapor pressure at 100° is about 0.5 torr.

$$\frac{W_{C_{13}H_{10}O}}{W_{H_2O}} = \frac{182}{18} \times \frac{0.5}{760} = 7 \times 10^{-3} = 0.7 \%$$

For every 100 g of water distilled, less than 1 g of benzophenone will be co-distilled. Therefore, the product is to be found in the residue in the still pot.

After the residual material in the reaction flask has cooled, the upper benzophenone layer is separated, the aqueous layer is extracted with 25 mL of benzene. The extract is combined with the benzophenone and the mixture is separated by distillation. Most of the benzene is removed at atmospheric pressure, then the benzophenone is distilled under reduced pressure, b.p. 188-190 (15 mm). The product solidifies to a white solid, m.p. 47-48°, and 49-55 g (80-89%) should be obtained.

METHOD 2:

For illustration purposes only the synthesis of unsubstituted benzophenone will be described.

REMINDER: THESE REACTIONS ARE TO BE DONE IN THE HOOD.

Set up a 500 mL three-necked round-bottomed flask equipped with an efficient mechanical stirrer, a condenser topped by a bubbler and a trap for hydrogen chloride, and a stopper in the third neck (Fig. 1). In the flask place 35 g (0.25 mol) of benzoyl chloride and 250 mL of anhydrous thiophene-free benzene. In a dry Erlenmeyer flask weigh out 36 g (0.27 mol) of ²anhydrous aluminum chloride and stopper the flask immediately. Using a dry powder funnel add the aluminum chloride in one batch to the reaction flask and stopper the flask again quickly. When the initial hydrogen chloride evolution slows, start the stirrer and heat the mixture to reflux for 3.5 hrs.

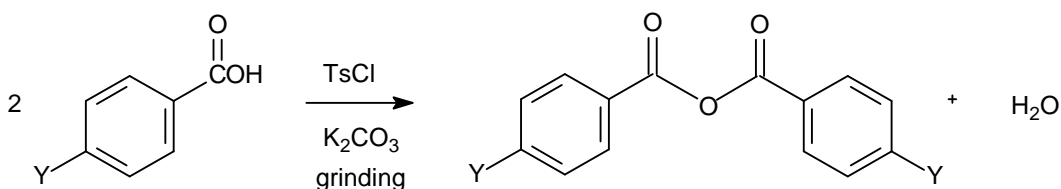
While the reaction mixture is cooling, mix 50 mL of concentrated hydrochloric acid with approximately 250 g of ice in a 1 L beaker. In the hood carefully pour the reaction mixture into the ice-acid mixture, stirring with a stirring rod as this is done. If all of the ice melts before the entire reaction mixture is added throw in enough ice to keep the solution cool while the remainder is added. When the ice has melted separate the organic layer. Steam distill the excess benzene (see note on steam distillation in Method 1, p 15). Cool the residual material in the still pot and add 100 mL of ether. **Separate the aqueous layer and wash the ether layer with 25 mL of 10% sodium hydroxide solution or until basic (IMPORTANT-Why?).** Wash the ether layer with water until a neutral pH is achieved and finally wash with saturated NaCl solution. Dry the ether solution over anhydrous magnesium sulfate then remove the excess ether with a rotary evaporator. The yield of

²Anhydrous AlCl₃ is extremely reactive. Handle with caution. Benzoyl chloride is a lachrymator and benzene is a class B carcinogen. Wear gloves and work under the hood when working with these chemicals. Neutralize the residual benzoyl chloride before removing used glassware from the hood.

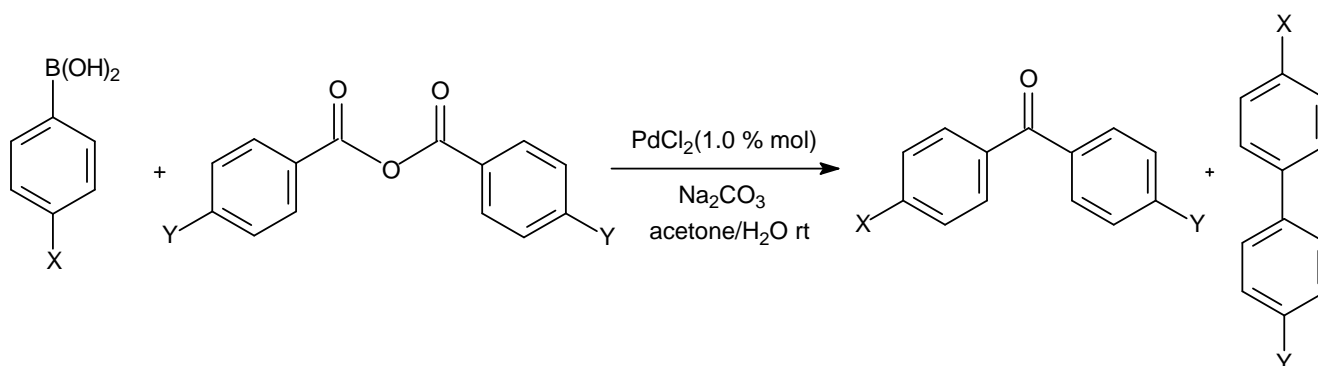
crude benzophenone should be 32-36 g. Purification may be achieved by recrystallization from ethyl alcohol. Note: substituted benzophenones are best purified by vacuum distillation.

METHOD 3: (under development 2012-14)

This method uses PdCl₂ in a coupling reaction between a substituted phenylboronic acid and a substituted symmetrical benzoic anhydride to produce the 4,4' substituted benzophenone. The first step is making the anhydride:



After making the desired anhydride, it is reacted with a para substituted boronic acid at room temperature, open to the air in acetone and water. The biaryl is an undesirable byproduct that is



removed using column chromatography.