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Medicinal Chemistry

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Multistep Organic Synthesis

Practical Course

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Introduction

Most of organic syntheses are dedicated to the creation of large, multifunctional molecules, having desired properties. Simple and easily accessible substrates are transformed into more complicated compounds, which can be used as pharmaceuticals, food additives, herbicides or polymers. During the Organic Chemistry course students are familiarized with many groups of compounds and their properties, but still it is not so easy to plan and perform synthesis of complex molecules.
"Multistep Organic Synthesis" laboratory should enhance students' knowledge and skills in two aspects:

- how to design an efficient synthesis,
- how to carry out all the planned experiments step by step.

Bearing this in mind, this manuscript contains a short theoretical part devoted to selected basic ideas to be considered when planning the synthesis, descriptions of some more often used experimental techniques and methods, and finally a selection of recommended experiments starting from fundamental to the advanced one. The teachers are free to modify each student program individually using this selection and their own suggested procedures.

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1. Safety in the Chemical Laboratory

The chemistry laboratory is a dangerous environment because chemists regularly use hazardous materials. However, with sensible precautions the laboratory is probably no more dangerous than your home, where you usually have contact with drugs, bleach, herbicides, insecticides, natural gas, electrical equipment, kitchen knives and so on. It is easy to familiarize yourselves with good laboratory practice and to minimize this way the dangers of organic chemistry.

Essential rules for laboratory safety:

1. *Be prepared* – study carefully the procedure before starting the experiment; you should know which chemicals you are going to use, what properties they have an how to deal with them (check the Material Safety Data Sheets); you should also know about the techniques you are to use; *think through the next step* you are going to perform before starting it.
2. *Wear approved protective clothing* (goggles, apron, gloves) – tie back long hair and loose items of clothing to avoid dropping them into a reagent or getting near flame.
3. *Check where there are the precautionary measures in your lab* – locate the nearest eye wash, fire extinguisher, spray shower, fire blanket, emergency exit.
4. *Do not put anything in your mouth while in laboratory*, including food, drinks and pipettes.
5. *Minimize your contact with any chemicals* (by skin or inhalation) – keep the bottles closed, work in a fume hood whenever it is possible.
6. *Be sure that you have proper chemicals for your reaction* – check labels carefully, use exact amounts you need and don't leave the substances in unmarked flasks/containers.
7. *Keep things clean* – laboratory bench surface and glassware; clean also means dry – water can disturb your reaction; wash and put unused apparatus away; wipe up or take care of spills on the bench or on the floor.
8. *Be careful while assembling glass and using electrical apparatus;* check if all the connections are tight and stable; when dealing with electricity make sure that your hands are dry and there is no other possibility of contact with water.
9. *Do not work alone*; you may need assistance or help.
10. *Pay attention to proper waste disposal* – only a few (water soluble materials) may be disposed of to the sink, other wastes should go into special containers (follow their labels).

2. How to Design an Efficient Synthesis

Looking *i.e.* at the most popular prescription drugs and their number of functional groups, it is common to have at least a dozen individual transformations, whereby the product of one reaction is then used as the starting material for the next reaction. Before starting the experiments it is necessary to carefully think over the strategy. You should choose an inexpensive, readily available starting material and to predict how many and what kind of transformations to apply in order to get the target molecule. If you do not have any ready procedure, prepare yourself for rather long literature study.

Several rules should be followed while planning the step by step synthesis. Two factors are of major importance: synthetic efficiency and selectivity of each individual step.

Criteria for evaluating synthetic efficiency:

1. Number of steps – should be minimized.
2. Yield for each step – should be maximized (high-yielding reactions should be chosen).
3. Reaction conditions – difficult conditions (temperature, pressure), toxic materials, intricate equipment are not desirable.
4. Ease of purification – simple work-up procedures that can be performed on a large scale are preferred.
5. Total cost – reagents and materials used should be cheap and easy handled; waste disposal also becomes very important.

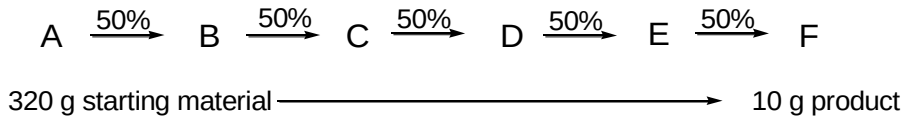
Overall synthetic yield is defined as the product of all the individual yields (expressed as decimals) multiplied by 100%. One problem, which becomes apparent is that the yield of the final product will be limited by the lowest yielding individual reaction. Therefore, each reaction in the sequence must be high yielding.

Table 1. Dependence of the overall yield versus number of steps in multistep procedures.

Number of steps	Yield depending on step (%)			
	99	***90***	***75***	***50***
1	99	90	75	50
2	98	81	56	25
3	97	73	42	12
4	96	66	32	6
5	95	53	18	3

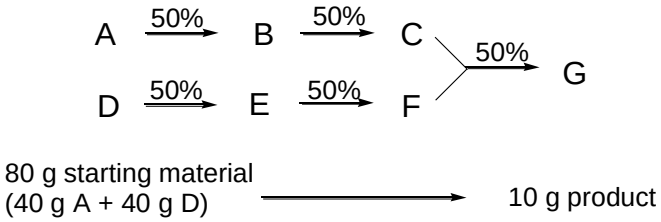
For example: a two-step synthesis with a 50% yield per step is not as efficient as a five-step synthesis with a 90% yield per step (see Table 1).
To modify the synthetic efficiency, instead of linear synthesis, one can perform convergent synthesis. Different ways of achieving the same number of steps can result in very different overall final product yield.

Linear synthesis – when the product of one reaction is then used as the starting material for the next step and so on.



Total yield in this synthesis goes down strongly with increasing the number of steps even when the individual step yield is “not so bad”.

Convergent synthesis – if the target molecule can be divided into two or more fragments (building blocks), which can be synthesized independently (in parallel).



With the same number of steps and the same yield per step, the total yield is much better in this case (all calculations assume similar molecular weight of substrates and product).

In the professional world of organic synthesis, most molecules are polyfunctional. Furthermore some functional groups may be similar to one another and may have similar reactivity. One of the most important challenges for organic chemist is the ability to transform one functional group within a molecule without affecting other groups, or to produce one particular functionality replacing another. This ability is called the **selectivity** of a particular reaction.

Types of selectivity:

1. **Chemoselectivity** – the ability of a reagent to react with one molecule or functional group over other similar molecules or groups in the same system.
2. **Regioselectivity** – when a reaction can potentially produce two or more constitutional isomers affords exclusively or predominately one of them.
3. **Stereoselectivity** – a reaction in which a non-stereospecific substrate is converted into predominately one of the possible stereochemical outcomes; enantioselectivity – the ability of a reagent to react with one enantiomer over another or to produce one enantiomer over another.

Proper selection of the reactions, and sometimes even the order of their execution is very important. The more complex structure of the synthesized compound is, the greater importance have the correct planning of the sequence of experiments.

Selectivity determines the usefulness of the process and possibilities of its application in synthesis.

3. Laboratory Equipment and Techniques

There is no particular collection of glassware for this laboratory. Students will use mostly the same equipment and the same techniques they had learned earlier within the general Organic Laboratory. Some examples are given in Fig. 1. Taking pieces from this collection, including clamps and connectors, it is possible to assemble simple (*e.g*. just test tube or beaker with heating) or more complicated sets, suitable for most experiments and processes.

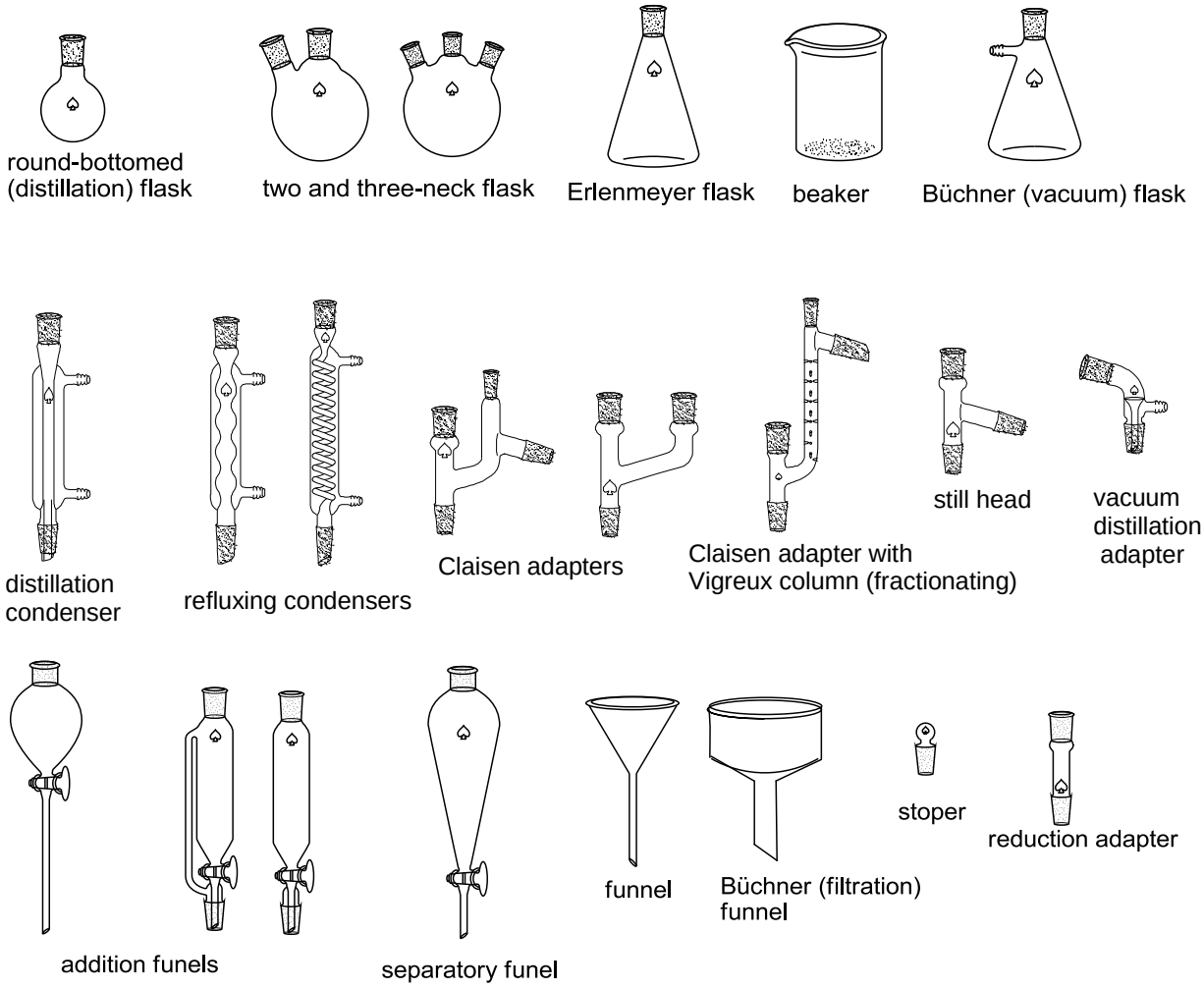


Figure 1. Glass equipment with standard ground glass joints.

Organic reactions should always be carried out in an apparatus that is suitable for the particular task. The proper choice of apparatus will allow you to combine the reactants in the right order and at the right rate, stir the mixture if necessary, control the reaction temperature and exclude moisture

and/or maintain an inert atmosphere, if required (see Fig. 2-4). It should be always remembered to match the size of glass-equipment with the amounts of used reactants and solvents (scale of the experiment). We have chosen to illustrate just a few apparatus assemblies that, in our opinion, will cover requirements of this laboratory.

3.1. Assembling the selected apparatus

3.1.1. Carrying out the reaction

The simplest apparatus for this purpose is just a beaker or a flask in which two chemicals are mixed and optionally heated. But sometimes the reagents are air and/or moisture sensitive, additionally you have to control the temperature (by heating or cooling) or addition rate of the reagents. Examples of apparatus suitable for carrying such experiments are presented in Fig. 2-4.

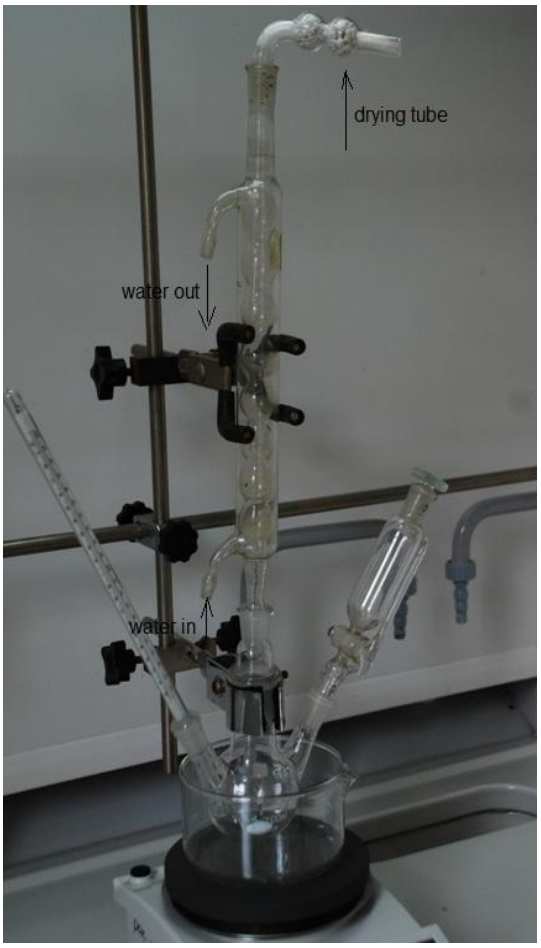


Figure 2. Stirring with addition of reagent and heating, protected from the moisture with drying tube on top of the condenser.

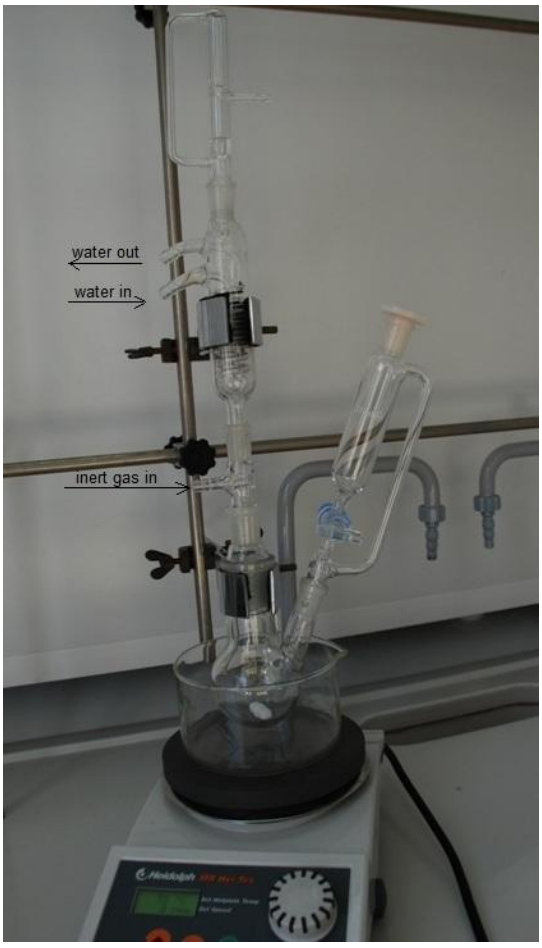


Figure 3. Stirring with addition of reagent and heating under inert atmosphere.

Apparatus given in Fig. 4 is recommended for small scale experiments, which additionaly need low temperature. For heating, except the heating mantle, water (0-80°C) or silicone oil (0-250°C) baths are mostly used. For cooling usualy the ice-salt mixtures are used (Table 2).

Table 2. Ice-salt cooling mixtures.

Salt	Ratio (salt : ice)	Lowest temp. (°C)
$CaCl_2 \cdot 6H_2O$	1:2.5	-10
NH_4Cl	1:4	-15
NaCl	1:3	-20
$CaCl_2 \cdot 6H_2O$	1:0.8	-40

The lower temperature cooling baths are based on solid CO_2 in connection with some organic solvents (even down to -78°C with acetone).

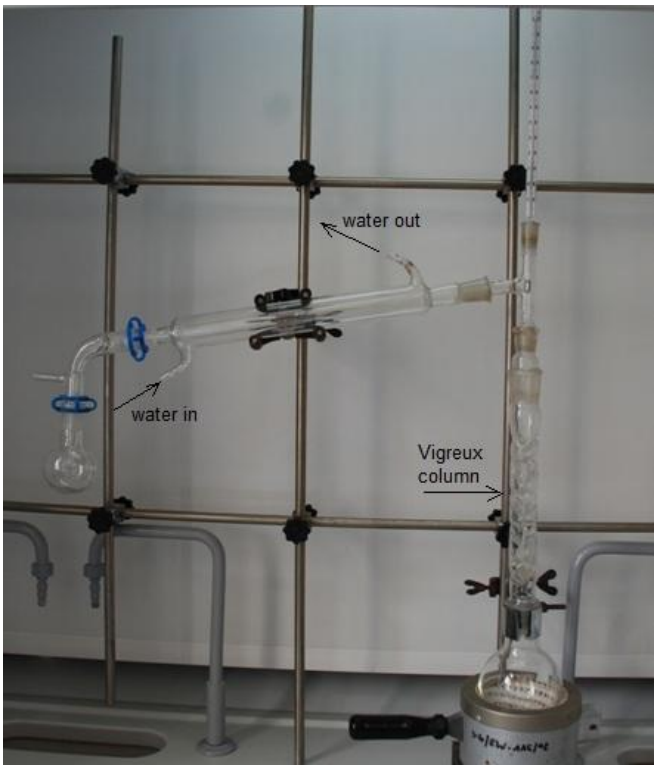
Figure 4. Stirring with addition of reagents via syringe under inert atmosphere; suitable for small scale experiments requiring low temperature.

3.1.2. Separation via destillation (purification)

Distillation is one of the mainly used techniques for purification in Organic Laboratory. It always involves vapourising the mixture by heating it, and then condensing the vapour back to a liquid. The choice of distillation procedure depends on the properties of the liquid (mixture) which you have to purify.

Simple distillation can be carried out when you have to separate two liquids, which widely differ in boiling temperature (> 40°C), or to purify solvents. For microscale distillation the apparatus given in Fig. 5 can be used.

Figure 5. Set for microscale distillation.



For separation of components with similar boiling points it is recommended to perform **fractional distillation**. The only difference between apparatus for fractional and simple distillation is the fractional (e.g. Vigreux) column inserted between the distillation flask and the still head (Fig. 6). To prevent the fractionating column from heat loss, it needs to be insulated (wrapped with aluminum foil). Sometimes a modified receiver adapter is used (named “cow”) to collect separate fractions in several flasks without disconnecting the set.

Figure 6. Apparatus for fractional distillation.

Many of organic compounds undergo decomposition at high temperature, therefore it is recommended to carry out the **distillation under reduced pressure** (vacuum distillation) if the normal boiling point is greater than 150°C. Firstly, it is necessary to decide how high vacuum is required and what the b.p. would be. Using the water aspirator it is possible to achieve the vacuum about 10-20 mm Hg, which can reduce the boiling point by about 100°C. Vacuum pump, which operate down to about 0.1 mm Hg pressure, will reduce the boiling point by about 150°C. More accurate estimation of the boiling point at reduced pressure can be obtained from a *nomograph* shown in Fig. 7.

How to use the pressure nomograph?

The basic principle is that a line through two known points on any two different scales (A, B and C) can be used to read off the value on the third scale.

There are two ways in which a pressure nomograph (Fig. 7) can be used:

1. <u>to determine the boiling point at atmospheric pressure</u> (760 mm Hg) – given the boiling point at a lower pressure and
2. <u>to determine the boiling point at a lower pressure</u> – given the boiling point at atmospheric pressure.

Note that the pressure in mm Hg and in torr means the same value.

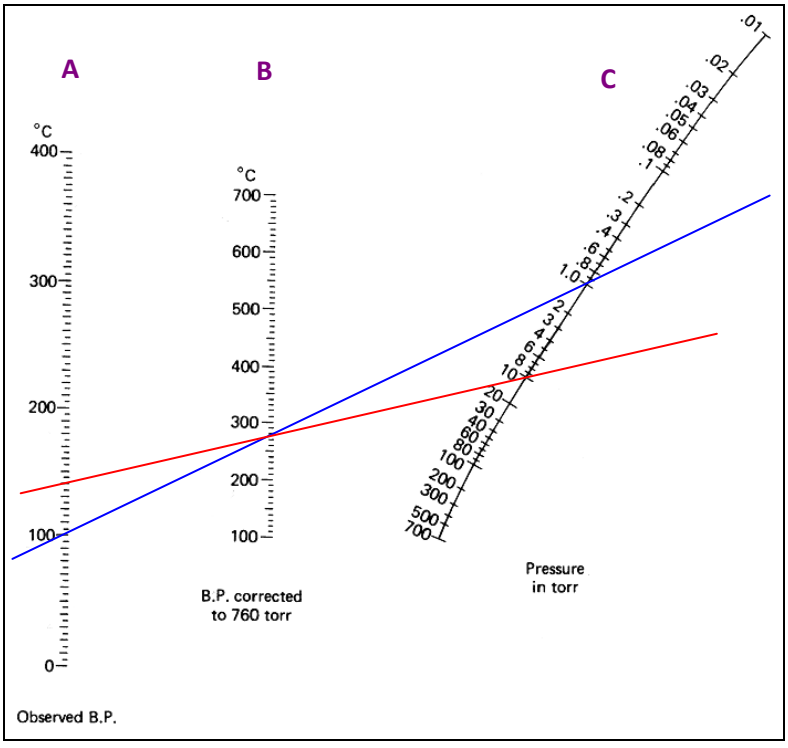


Figure 7. Nomograph for estimating the boiling point of a liquid at a particular pressure.

Interpretation examples

1. First, let's say we have a compound with a boiling point of 100°C at 1 mm Hg pressure. What is the boiling point at 760 mm Hg?
To do this we need to draw a line from 100°C on scale A (left side, observed b.p.) to 1.0 mm Hg on scale C (right side, pressure in torr) – blue line. We can then read off the boiling point at 760 mm on line B, it is about 280°C.

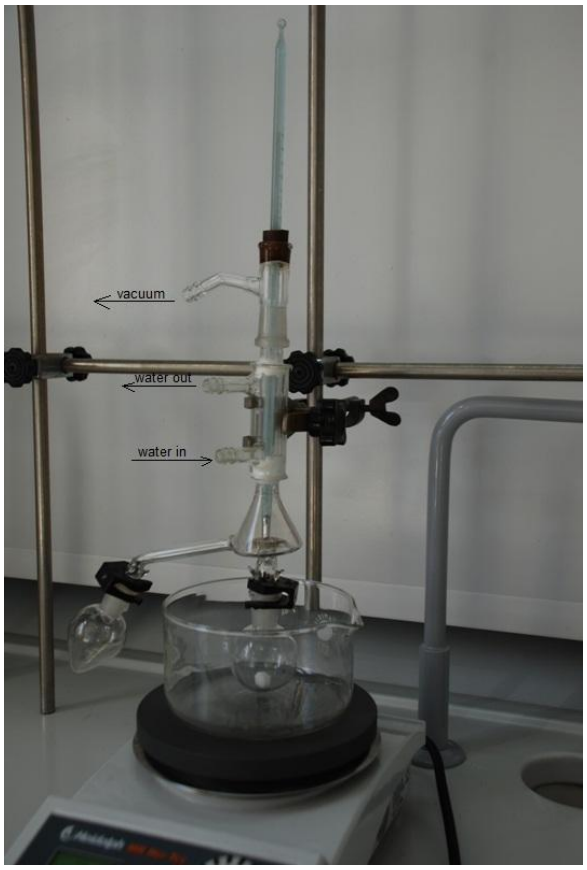
2. Now, at what temperature would that same compound boil at 10 mm Hg pressure? Now we draw a line that passes through 280°C on scale B (middle scale, the boiling point at 760 mm Hg) and to 10 mm Hg on scale C – red line. By extending that line to scale A, we can read off the new boiling point on scale A (left side) as being about 140°C.

*<u>Warning</u>**:** All readings are approximate. The exact data depends on the nature of the distilled compound, and may differ by ten percent or so.*

Two sets of apparatus for vacuum distillation are shown below (Fig. 8 and Fig. 9). Previousy, both sets required using the vacuum grease to seal all the joints, in order to connect tightly all components. Nowadays, as highly efficient vacuum pumps are used, application of grease is not recommended.

The first set-up (Fig. 8) contains a capilary (*very fine!*) – instead of boiling stones – to ensure smooth boiling. However, if the organic compound is likely to oxidize with air, the capillary should be connected to a nitrogen supply.

Figure 8. Apparatus for vacuum distillation with a capilary.



A simpler technique that works in most cases is to put a small magnetic stirrer bar in the distillation flask, and stir the liquid rapidly. Some set-up similar to the previously shown (Fig. 5) can be adopted for this purpose, or the apparatus with the Hickman still can be used (Fig. 9), particularly for a small scale distillation.

A safety flask and some pressure gauge should be incorporated between the apparatus and the vacuum source.

<u>Remember</u> to record both: the boiling point and the pressure.

Figure 9. Microscale vacuum distillation using a Hickman still.

Steam distillation is another very effitient way to distill liquids below their boiling point. Steam distillation is a technique relying on distillation of an immiscible mixture of an organic compound and

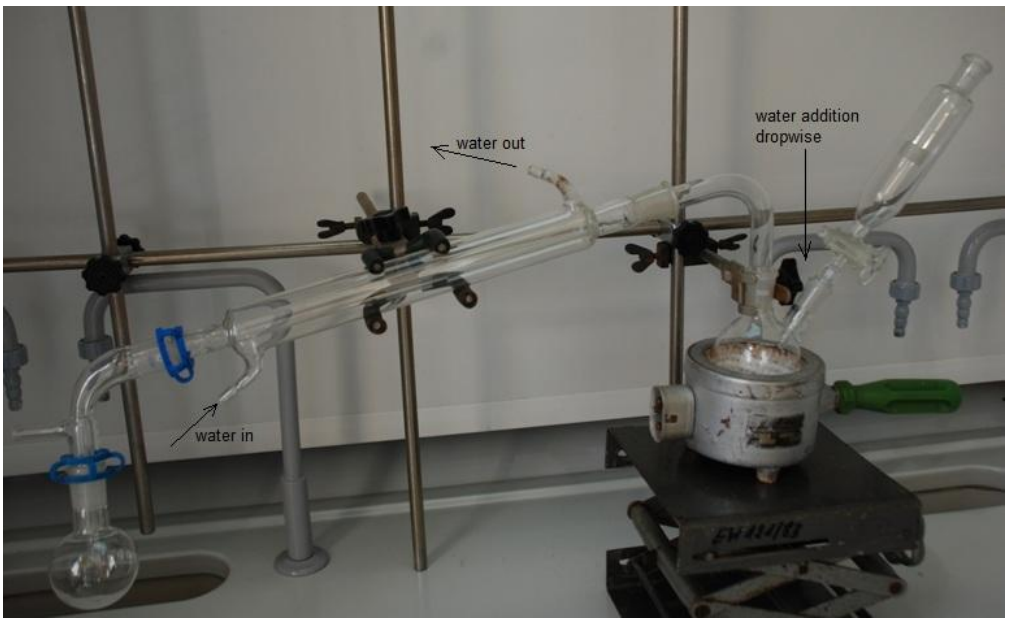


Figure 10. Modified apparatus for steam distillation.

water (steam). Immiscible mixtures do not distill in the same way as miscible liquids; the components exert their own vapor pressure independently. The total vapor pressure is the sum of vapor pressures of the pure individual components. When this sum equals external (atmospheric) pressure the mixture will boil at a lower temperature than either of the pure liquids. This way co-distillation of an immiscible mixture of an organic compound plus water will result in the distillation of the organic compound below 100°C. The traditional method of carrying out a steam distillation is to pass steam (generated separately) into the liquid in the distillation flask. Much easier way is shown in Fig. 10. You can place the mixture of organic compound and water in the distillation flask, and carry out the simple distillation.

Remember: water distils out and should be replenished from the addition funnel.

3.2. Preparation of anhydrous solvents[1,2]

Ethanol

Dehydration of the rectified spirit (95-96%) with CaO. A round bottomed flask is charged with CaO and technical ethanol (200 g per 1 L, CaO should be freshly heated in a muffle furnace), and equipped with a double coated condenser with a drying tube filled with $CaCl_2$. The mixture is gently refluxed for 6 h and left overnight. The flask is equipped with a drop catcher adapter and connected to the same condenser, now used for distillation. A receiving adapter should be also equipped with a drying tube. Ethanol is slowly distilled, removing the first 20 mL, preferentially to the final receiving bottle. Absolute ethanol (99.5%) should be stored tightly closed.

Anhydrous ethanol (the Lund and Bjerrum method). A round bottomed 1.5-2 L flask is charged with clean and dry magnesium turnings (5 g per 1 L), iodine (0.5 g) and 50-75 mL of absolute or dehydrated ethanol (the water contents < 1%), and equipped with a double coated condenser with a drying tube. The mixture is warmed until the iodine color has disappeared. If intensive hydrogen evolution is not observed, a further 0.5 g of iodine is added. Heating is continued until all the magnesium is converted into ethanolate. Then, 900 mL of absolute ethanol is added and the mixture is refluxed for 0.5 h. The alcohol is distilled directly to the dedicated vessel, using a procedure and apparatus as describe above. The product is highly hygroscopic and should be stored over molecular sieves 4A.

***N,N*-Dimethylformamide**

A round bottomed 1.5-2 L flask is charged with 900 mL of *N,N*-dimethylformamide (DMF), benzene (40 mL) and water (60 mL). The mixture is distilled under atmospheric pressure to collect a water-benzene azeotrop (70-75°C). The remaining solvent is distilled under reduced pressure (40°C/10 mm Hg). The product is recommended to be stored over molecular sieves 4A.

Tetrahydrofuran

To obtain absolute and oxygen free tetrahydrofuran (THF), a round bottomed 1 L flask is charged with solvent (750 mL), potassium or finely cut sodium (4-5 g) and benzophenone (8-10 g). The mixture is refluxed under a condenser closed with an oil bubbler until the deep purple-blue color persists (2-12 h, depending on the solvent purity). A demanded portion of anhydrous THF is distilled

off from potassium (sodium) benzophenone ketyl directly to the dedicated reaction vessel using the distillation apparatus protected with a drying tube. The residue is tightly closed and can be used several times for preparation of fresh portions of solvent. Pre-heating to achieve the ink color, and occasional addition of an alkali metal and benzophenone can be necessary. The product is highly hygroscopic and, as easily available, should not be stored.

THF should not be distilled to dryness. For safety reason, a residue greater than typically should be left in the flask. To quench this residue, a 100 mL portion of ethyl acetate is added to the flask under reflux condenser, preferentially also under inert gas, and left for several hours. When the reaction proceeds, methanol (50 mL) can be added to complete the alkali decomposition.

Chloroform

To dry and to remove stabilizing additive of ethanol (~ 1%), chloroform is passed though a broad column filled with a basic aluminum oxide (10 g of Al_2O_3 per 14 mL of $CHCl_3$). Additionally, the filtrate is distilled over P_2O_5 using a distillation apparatus equipped with a receiving adapter protected with a drying tube. The product should be kept in darkness and used immediately. Longer storage cause dangerous evolution of phosgene.

Prepared according to:

1. A. I. Vogel, Preparatyka Organiczna, Ed. 2, WNT, Warszawa 1984.
2. B. Bochwic, Preparatyka Organiczna, PWN, 1975

3.3. Handling organolithium reagents (pyrophoric liquids)[1]

Examples of **pyrophoric materials** applied in Organic Chemistry laboratory are: organometallic reagents (lithium, zinc and Grignard reagents), alkali metals, finely powdered metals, white phosphorus, metal and nonmetal hydrides and their alkylated derivatives, metal carbonyls, etc…

Organometallic reagents dissolved in hydrocarbon solvents (e.g. *n-butyllithium in hexane*) are **pyrophoric liquids** the most commonly used in organic synthesis. They may ignite spontaneously upon exposure to air, reacting violently with oxygen and water, thus, *they must be handled with particular care!* The Aldrich technical bulletin on handling air-sensitive reagents (AL-134), and accompanying one on handling pyrophoric reagents (AL-164), are the recommended sources that describe safe operation with those materials.

The SigmaAldrich Sure/Seal™ packaging system

Air-sensitive and pyrophoric reagents can be distributed and stored in a convenient and safe manner with the use of the Sure/Seal system (Fig. 11). The reagents are dispensed using a syringe or double-tipped needle inserted through the hole in the metal cap. Upon withdrawal of the needle, a small hole remaining in the teflon/elastomer liner will self-seal under normal circumstances. To avoid the reagent deterioration on long-term storage, it is recommended to use an additional plastic cap or Oxford Sure/Seal valve-cap.

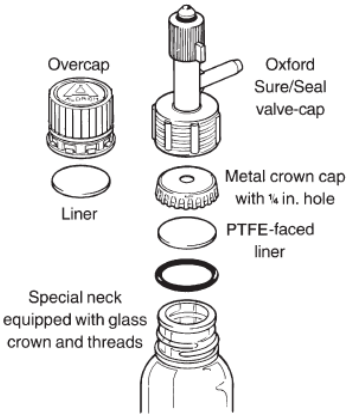


Figure 11. The components of Sure/ Seal packaging system.

Reactions involving air-sensitive reagents can be carried out in common glass apparatus, oven-dried prior to use. Other required pieces of equipment are: a source of an inert gas, a septum inlet, a bubbler, and syringes with suitable needles.

Figure 12. Equipment for handling pyrophoric liquids: syringes, inert gas inlet, septum and bubbler.

Instruction for transferring reagents with syringe (Fig. 13)

Install firmly the reagent bottle and receiving vessel in a fume hood. Spike the Sure/Seal septum introducing an open input line of inert gas to the reagent bottle (gentle flow, excess pressure is regulated with an exit bubbler). Flush the syringe with inert gas. Insert the syringe into the Sure/Seal bottle (the tip of the needle below the level of the liquid) and withdraw an excess volume of the liquid. Invert the syringe and force back the excess of the reagent and gas bubbles into the bottle. Clear the needle out of the material gently pulling the plunger. With the empty needle transfer quickly the liquid to the reaction apparatus by puncturing a rubber septum.

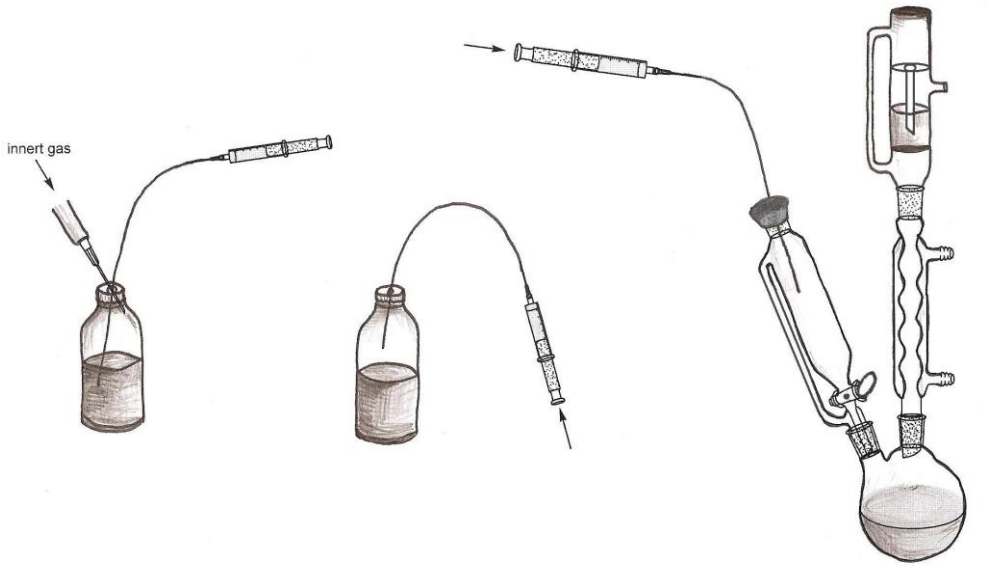


Figure 13. Transferring pyrophoric liquids with syringe.

Instruction for transferring reagents with cannula (double-tipped needle, Fig. 14)

Pressurize the Sure/Seal bottle with inert gas. Insert the double tipped needle through the septum to the reagent bottle above the reagent (the cannula is flushed with inert gas). Insert the other end through the septum on the reaction apparatus (to a calibrated addition funnel). Push the needle into the liquid in the Sure/Seal reagent bottle. Transfer the desired volume. When transferred immediately withdraw the tip of the needle above the liquid level.

Recommended when transferring volume exceeds 50 mL!

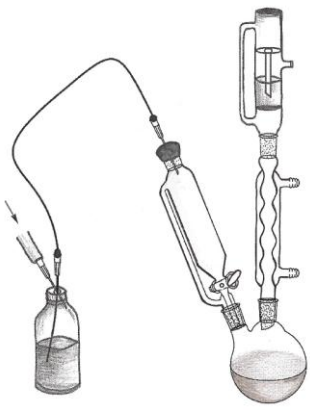


Figure 14. Transferring pyrophoric liquids with cannula.

Safety remarks

1. Any unused or waste pyrophoric materials must be destroyed. To do this, transfer the materials to an appropriate apparatus. Quench the reagent carefully in inert gas atmosphere and with ice/water bath cooling. *Be aware of gas evolution!* Add *n*-butanol first, then ethanol or methanol and finally water. When reaction is completed, use hydrochloric or citric acid for neutralization the basic solution.

2. *Do not use a carbon dioxide fire extinguisher or water to extinguish a pyrophoric material!* Sand or lime (soda ash) is useful to extinguish a small fire.

1. Images and procedures based on Sigma-Aldrich Technical Bulletins.

3.4. *T*hin-*L*ayer *C*hromatography (TLC)

Thin-layer chromatography is a very common technique in synthetic and organic chemistry, used mostly for analytical separation. TLC requires minimum quantity of the compound (ng), it is fast and can be simply performed. Main applications of thin-layer chromatography concern:

• compounds identification (by comparison to the reference samples),

• qualitative determination of compounds purity,

• following the progress of a reaction,

• control the process of purification *e.g.* column chromatography: optimization of the solvent system and analysis of fractions.

Definitions

1. **The stationary phase:** a finely ground matrix, typically silica gel (SiO_2) or alumina (Al_2O_3), coated on glass, metal or rigid plastic sheets as a thin layer (~ 0.25 mm). Commonly, it contains additives, such as: gypsum to improve binding to the plate surface and a **fluorescent dye** for visualization in final analysis.
2. **The mobile phase (eluent):** a solvent / a mixture of solvents.

Performing a TLC experiment

1. Preparing the plate. Cut the plate, typically 2.5-4 cm wide and 5-8 cm long. Important: *do not touch the stationary phase surface*! To obtain a start line, draw lightly with a pencil a line 1 cm from the end of the plate (Fig. 15). Important: *do not scratch the stationary phase surface*!

2. Spotting the plate. Load a spotting capillary with a dilute solution of an analyte and touch the plate briefly at the start line. After solvent evaporation, spot at the same place few times to obtain concentrated and small spot (1-3 mm optimally, Fig. 15). Important: *avoid using too much material and spot broadening, because these deteriorate the quality of the separation!* The spots should be far enough away from the edges and from each other. If possible, apply the starting materials and the products as internal standards.

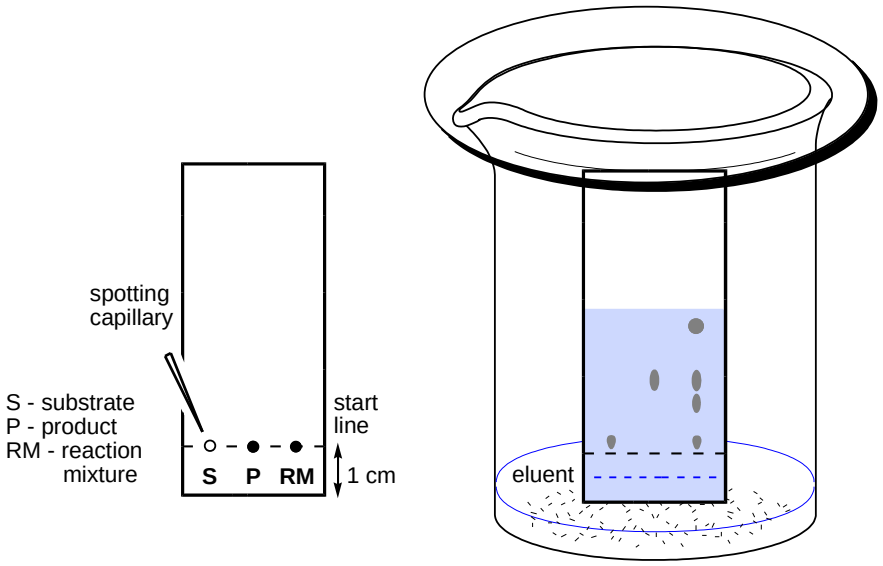


Figure 15. Preparing, spotting and developing a TLC plate.

3. Developing a plate. A TLC plate has to be developed in a covered beaker or in a closed jar. Fill this glass container with a small amount of the mobile phase (~ 0.5 cm in depth, *below the starting line!*). Place the TLC plate inside the chamber standing, somewhat tilted and leaned against the wall (Fig. 15). The eluent travels up capillary action, moving the compounds at various rates because of their different interaction between the stationary and mobile phases. Leave the plate until the eluent has advanced the level ~ 1 cm from the top. Take the plate out and mark the solvent front line. Important: *do not allow the solvent to travel up to the edge!* Let the solvent evaporate completely or dry the plate (< 50-60°C for those coated onto plastic).

4. Visualization. Rarely, the substances are colored so that the spots can be seen directly. The most general techniques to visualize colorless compounds are:

• iodination (place a dry plate in a chamber containing a few crystals of iodine, once the spots are visible outline them with a pencil, coloration is not permanent),

• treatment with sulfuric acid and heat (charred blots),

• UV light, for the plates containing a fluorescent dye (the substance dark spots, lacking of fluorescence, are visible on the yellow-green background, Fig. 16).

5. Analysis. Substances can be identified from their R_f (retardation factor) values. Measure the distance to the solvent front line (D). Measure the distances from the bottom start line to the center

of each spot (d). Divide d by D to obtain individual R_f values (obviously, between 0.0 and 1.0). Compare the R_f of your analytes to those of the known reference materials (Fig. 16).

<u>Important:</u> the R_f depends on the solvent system, absorbent parameters, amount of material spotted, temperature, etc., so it is unique for an individual experiment!

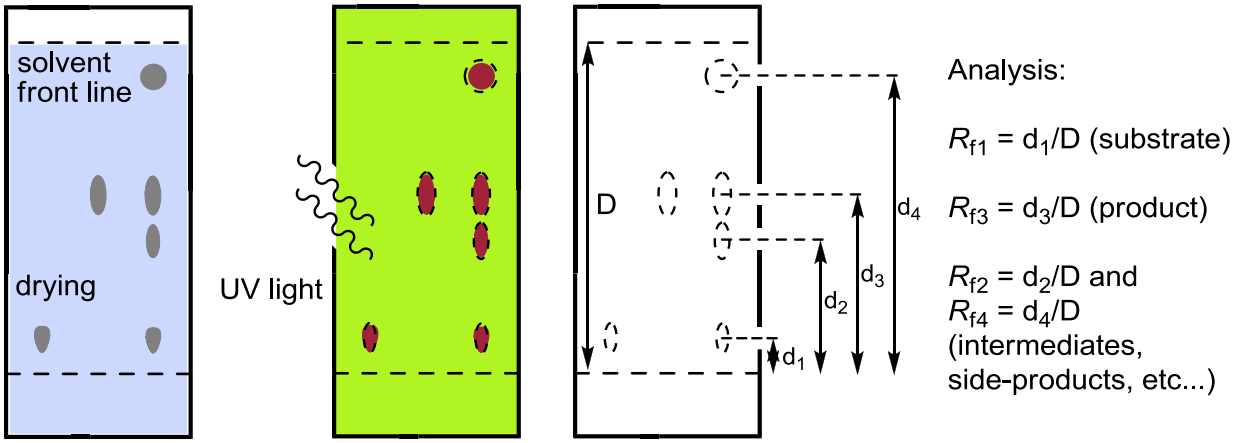


Figure 16. Visualization and analysis of a TLC plate.

3.5. The specific rotation, polarimetry

If a substance is optically active, the plane of the polarized light passing through its solution change the orientation. The phenomenon is quantitatively described by the **specific rotation** value. The specific rotation [α] is the observed angle of optical rotation of the plane-polarized light passing along a path length of 1 decimeter and with a sample concentration of 1 gram per 1 milliliter.

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{c \times l}$$

α – observed angle of optical rotation

c – sample concentration (in grams per milliliter !)

l – length of the sample tube (typically 1 dm)

The specific rotation of a pure compound is an intrinsic property of that substance at a given wavelength (λ) and temperature (T). Values should always be accompanied by the wavelength, the temperature at which the measurement was performed and the solvent in which the material was dissolved. If the wavelength of the light used is 589.3 nanometers (the sodium D line), the symbol "*D*" is used. If not specified; it is assumed the measurement has been performed at room temperature.

The formal unit for specific rotation values is [(deg × cm^3)/(dm × g)] but the scientific literature uses just values, without any units. Ability to rotate the plane of polarized light to the right (clockwise) means **dextrorotatory** rotation (+, a positive value). A negative value (-) means **levorotatory** rotation (anticlockwise).

Optical rotation is measured with an instrument called a **polarimeter** by introducing a tube containing a solution with the substance to be measured dissolved in appropriate solvent on the rails.

Measurement of the optical activity

1. Turn on the polarimeter to allow the instrument to warm up.
2. Prepare a solution of known concentration (~ 0.5-3%) by weighting the precise amount of the substance and dissolving to an exact final volume.
3. Fill the polarimeter cell with prepared solution into. *Be careful not to leave air bubbles!*
4. Adjust the instrument to zero.

5. Place the cell inside the instrument on the rails, the direction does not matter.
6. Measure the optical rotation several times, take the average for calculations. Mind the sign.

Specific rotation can be directly calculated by an input of the cell length and the concentration on the instrument options.

Exemplified calculations

1. Calculate the specific rotation for 0.095 g of a substance dissolved in 5 mL of ethanol. The optical rotation measured in an 1 dm cell tube at 589.3 nm and 20°C is +2.58.

$$[\alpha]_D^{20} = +\frac{2.58}{0.019 \times 1}$$

$$[\alpha]_D^{20} = +\textbf{13.6 (c = 1.9\% in EtOH)}$$

2. Determine **the optical purity (the enantiomeric excess, ee)** of a sample that shows the specific rotation [α] = -15.6. The specific rotation measured in the same conditions for the pure enantiomer is -26.0.

Optical purity (ee) = $[\alpha]_{mixture} / [\alpha]_{pure\ enantiomer} \times 100\% = 15.6/26.0 \times 100\% = 60\%$

The optical purity is defined as: (moles of one enantiomer – moles of the other enantiomer) divided by (moles of both enantiomers), this means that the mixture consists of enantiomers in ratio: **80% : 20%** ((80 - 20)/(80 + 20) × 100% = 60%).

Problems

For a compound that displays a very large rotation value (over 180), measurements at several different concentrations, or a cell of a shorter length, can help in determination of the correct value. In the cases of very small or very large angles, switching wavelength can be also useful.

4. Writing a Lab Report

A laboratory report in the notebook should contain:

1. *Title of the experiment*. Give the title of the experiment (the name of the final product) and the date on which each step is performed.
2. *Reaction scheme.* Present the overall reaction scheme including the used reagents. You may put the amounts of reactants and products under the balanced equations for the reaction.
3. *Physicochemical and safety data.* List the molecular weight, melting point, boiling point, density, solubility, etc., and hazard and safety data of all chemicals used in the experiment: substrates, products, reagents and solvents (preferably in a tabular form).
4. *Calculations.* Calculate the amounts of reactants in moles and grams for solids, and in moles and mL for liquids. Select the limiting reagent and calculate the theoretical yield of the product.
5. *The original (literature) procedure.* Copy the procedure to be followed. You may write it in the form of a brief but complete plan. Illustrate each newly performed technique with an appropriate apparatus graphic.

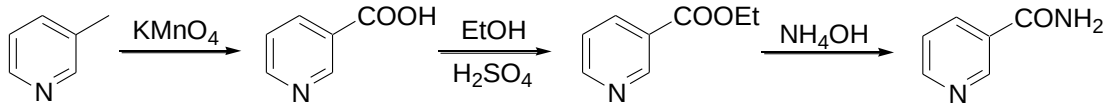
Points 1-5 are pre-requisites and should be prepared before the beginning of the experiment!

6. *Observations.* Write observations of the experiment (color changes, appearance of crystals, formation of an emulsion, boiling temperatures, test results, etc.). These data should facilitate any chemist to repeat the experiment. Evidence the weights of reactants and products, and tare weights.
7. *Results and conclusions.* Indicate and discuss the amount of obtained compound, its yield (percent), purity and identity (m.p., TLC, NMR, etc…). Comment the performed procedure, discuss the errors.
8. *Calculate the overall yield of the procedure after the final step.*

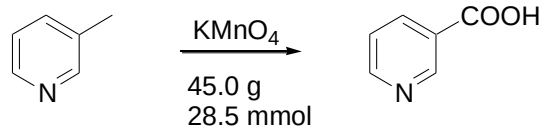
The report should be ready for the next classes after the completion of the experiment!

AN EXAMPLE

Nicotinic acid amide (Vitamin PP)



FIRST STEP: Preparation of nicotinic acid by oxidation of β-picoline ***06/13.12.2010***



10.0 g
10.4 mL
10.7 mmol

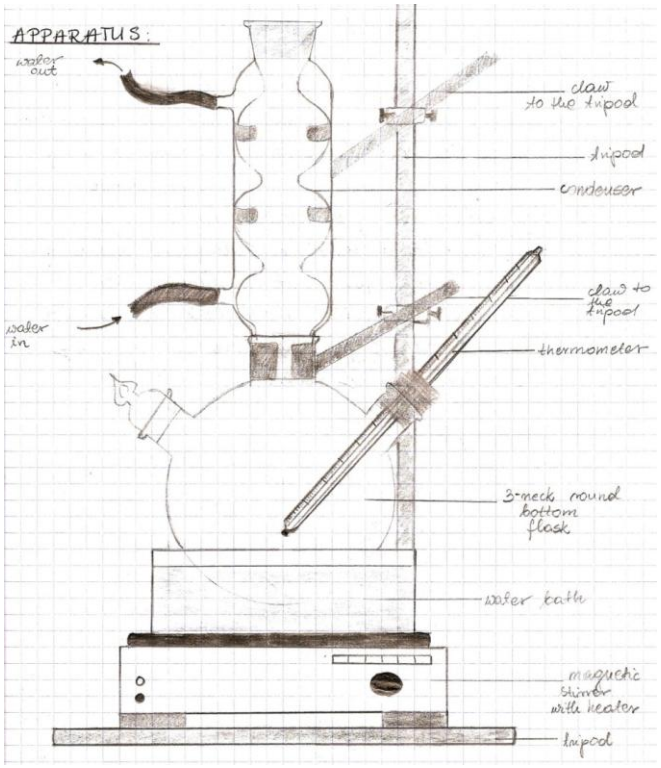
13.2 g (theor.)
10.7 mmol

	MW (g/mol)	*Mp (°C)*	*Bp (°C)*	*Density (g/cm³)*	*Safety data*
β-picoline	*93.13*	*-18*	*141*	*0.961*	*Corrosive; skin contact may cause burns. Harmful if swallowed. Severe skin and eye irritant. Flammable (Flash point: 36°C).*
nicotinic acid	*123.11*	*237*	*-*	*1.473*	*Actually not toxic, but moderately irritant to the eye and to skin (rare cases of skin flushing). Irritating to respiratory system.*
$KMnO_4$	*158.03*	*ca. 240 (decom.)*	*-*	*2.7*	*Strong oxidant. Contact with other material may cause fire. Corrosive. Causes burns to any area of contact. Harmful if swallowed or inhaled. Irritant. Readily absorbed through skin.*

Calculations:

β-Picoline (substrate)	*10 g (10.4 mL)*	*10.7 mmol*
$KMnO_4$ (reagent)	*45 g*	*28.5 mmol*
Nicotinic acid (product)	*13.2 g (theor.)*	*10.7 mmol*

Plan of the synthesis:	*Observations and remarks:*
	06.12.2010
1. Construction of the apparatus	*Use an efficient magnetic stirring bar!*
2. Loading the flask with 10 g of β-picoline and 100 mL of water. Heating the mixture to 70°C with stirring.	*The mixture was heated with a heating magnetic stirrer in a water bath.*
3. Addition to the solution of 45 g of $KMnO_4$ with small portions in a period of 4 hrs (wait until the mixture will decolorize after the last portion).	*$KMnO_4$ was added with several portions within 3 hrs. To facilitate the transfer into the flask, a funnel for solids was used and washed with minimal portions of water.*
4. Filtration off MnO_2 from the hot mixture through fluting filter paper (soft) and washing it with hot water (4 x 40 mL).	*Purple-violet color changed into brown, a dark solid was formed. The mixture was filtered and the solution was left for one week.*
5. Evaporation of the collected filtrate to c.a. 100 mL on the rotary evaporator.	
	13.12.2010
6. Acidification with conc. HCl to pH 3.5 and leave the mixture for precipitation.	*pH 3 was achieved, white solid precipitated. The mixture was cooled in the ice bath before filtration.*
7. Filtration of the solid nicotinic acid and washing with cold water (3 x 5 mL). Concentration of the filtrate to half volume, leaving in a refrigerator for precipitation and filtration of the second fraction of product.	*Second precipitation yielded only tiny amount of a solid (~ 100 mg), and was discarded*
8. Recrystallization of combined products from hot water.	
9. Drying (note the yield and m.p. of pure nicotinic acid).	*The final product was dried on air for one week and used for the next step.*



Picture by Aleksandra Stróżyk

Results and conclusions:

The mass of dry nicotinic acid: *m = 4.76 g*

The yield of the reaction: *36%* *4.74 g (obtained) / 13.2 g (theoretical)*

Melting point: *235.5°C (literature 237°C)*

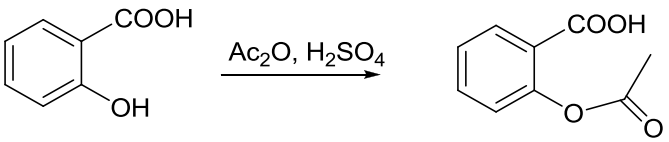
Sharp and correct m.p. indicate the correct product of high purity. Low yield can be caused by partial loose of the material during washing of the separated product with water (too much in volume and not cold enough). Etc…

5. Experiments

5.1. One step procedures

5.1.1 Acetylsalicylic acid[1]

(Aspirin)



Materials:

salicylic acid 5.0 g, 0.036 mol,

acetic anhydride 7.5 g, 6.95 mL, 0.072 mol.

Solvents: ethanol.

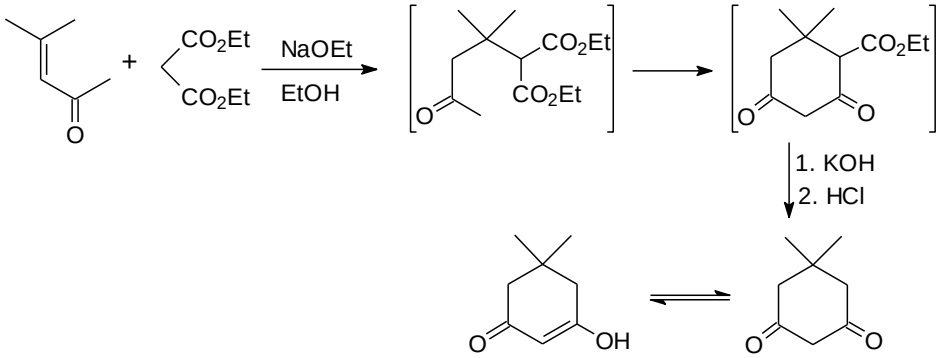
Other: concentrated H_2SO_4 (3 drops).

Place 5 g of salicylic acid in a 100-mL Erlenmeyer flask. Add 7.5 g of acetic anhydride and 3 drops of conc. H_2SO_4. Heat the solution on the water bath keeping the temp. in range of 50-60°C for 15 min with occasional stirring. After that time allow the solution to cool and pour it into the beaker containing 75 mL of cold water. Filter off precipitated crude acetylsalicylic acid under suction, and wash with water (3 × 10 mL). Purify the product by crystallization. Dissolve the product in 15 mL of ethanol by heating and pour the solution into 40 mL of water – beginning of precipitation can be observed. Heat the mixture until dissolve again and leave to cool for precipitation. Filter off the crystals, measure the yield and m.p. of pure acetylsalicylic acid.

Prepared according to:

1. A. I. Vogel, Elementary Practical Organic Chemistry, Part I: Small Scale Preparation, 2nd Edition, *Longman*, London 1965, p. 364.

5.1.2 5,5-Dimethylcyclohexane-1,3-dione[1] (Dimedone)



Materials:

sodium	1.15 g, 0.05 mol,
diethyl malonate	8.0 g, 7.5 mL, 0.05 mol,
mesityl oxide	4.9 g, 5.7 mL, 0.05 mol.

Solvents: absolute ethanol, diethyl ether, light petroleum, acetone.

Other: KOH (6.3 g), concentrated HCl.

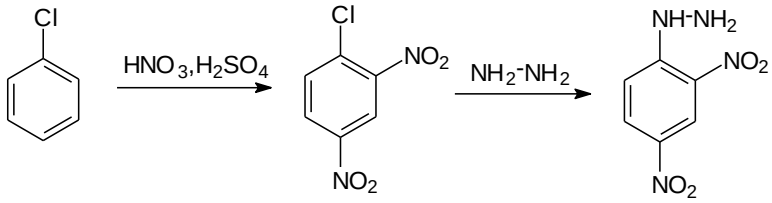
All apparatus must be thoroughly dried before use! Place 30 mL absolute ethanol in a 2-neck 100-mL flask fitted with a magnetic stirrer bar, reflux condenser carrying a drying tube fitted with $CaCl_2$, and an addition funnel. Add the sodium piece by piece *(carefully!*) down the condenser to the ethanol with gentle stirring at such a rate that the mixture boils. Replace the drying tube after each addition. When all the sodium has dissolved, add diethyl malonate from the addition funnel over 5 min followed by 5 mL absolute ethanol. Similarly add the mesityl oxide over 5 min, followed by 5 mL absolute ethanol, and then reflux the mixture gently for 45 min. After this time, dissolve the KOH in 25 mL water, add this solution through the addition funnel and continue refluxing for a further 45 min. Allow the mixture to cool, remove the condenser and addition funnel and arrange the apparatus for distillation. Distil off *c.a.* 35 mL of the ethanol-water mixture, cool the residue in ice and extract with 25 mL diethyl ether*, retaining the aqueous layer*. Return the aqueous layer to the reaction flask, acidify it to pH 1 with conc. HCl and reflux for 15 min. Allow the mixture to cool in an ice bath until crystallization is completed. Filter off the crude product under suction, wash it with 25 mL of water and 25 mL of light petroleum. Dry the product in air, record the yield. Recrystallize *c.a.* 1 g from aqueous acetone.

Prepared according to:

1. Organic Syntheses, Coll. Vol. 2, p. 200 (1943); Vol. 15, p. 14 (1935).

5.2. Two steps procedures

5.2.1 2,4-Dinitrophenylhydrazine[1]



Materials:

chlorobenzene	3.0 g, 2.71 mL, 0.027 mol,
concentrated H_2SO_4	15 mL,
concentrated HNO_3	5 mL,
hydrazine hydrate sol. (85%)	c.a. 2.0 g.

Solvents: methanol.

FIRST STEP: **Preparation of 2,4-dinitrochlorobenzene**

Place 5 mL of conc. HNO_3 and then 15 mL of conc. H_2SO_4 in the 100-mL Erlenmeyer flask. Both acids should be mixed carefully. Add chlorobenzene (3.0 g) and heat the mixture on a water bath for 20 min with occasional vigorous swirling in order to ensure good mixing. The evolving nitrogen oxides should be removed using a rubber tube connected to the water aspirator. After 20 min. pour the mixture into the 250 mL beaker containing *c.a.* 50 g of crushed ice and use a glass rod to start the crystallization (by scratching the side of the flask).

Caution: Avoid contact with skin – 2,4-dinitrochlorobenzene is a potential skin irritant.

Filter off the precipitated solid under suction using Büchner funnel and wash the residue on the funnel with water. Transfer the wet and slightly oily product to 250-mL of Erlenmeyer flask and recrystallize from methanol. Dissolve the solid in as small amount of methanol as it is possible without heating and after dissolving cool it on ice-water bath. Filter off the crystals under suction and leave the product to dry in the air. Record the yield and m.p. of obtained 2,4-dinitrochlorobenzene.

Dilute the methanolic filtrate with double amount of water and cool it to obtain the second fraction. Analyze the obtained oily solid isolated previously and both recrystallized fractions of the product by TLC using chloroform as the eluent. Record the retardation factors (R_f) of all compounds. Explain, what compounds can be found in the mother liquor after crystallization next to 2,4-dinitrochlorobenzene?

SECOND STEP: **Reaction of 2,4-dinitrochlorobenzene with hydrazine**

Place the obtained 2,4-dinitrochlorobenzene in the 100-mL Erlenmeyer flask and dissolve it in methanol (10 mL per 1 g). Using a small cylinder, measure out the proper amount of hydrazine hydrate solution (85%) – 1 mL per 1 g of 2,4-dinitrochlorobenzene and dilute with 5 mL of methanol. **Determine the molar ratio of used hydrazine and 2,4-dinitrochlorobenzene.**

Add the hydrazine solution to the methanolic 2,4-dinitrochlorobenzene solution and leave for precipitation. After 15 min. filter the precipitated solid under suction and wash it at the funnel with small amount of cold methanol. Dry the product in the air at room temperature and note the yield and m.p. of obtained 2,4-dinitrophenylhydrazine.

Identification of carbonyl compounds

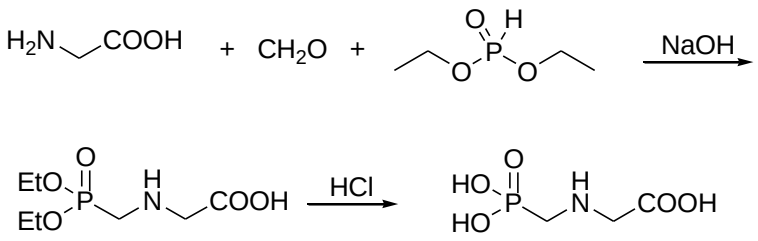
Dissolve 0.2 g of 2,4-dinitrophenylhydrazine in 1 mL of conc. H_2SO_4 and add the solution to the mixture of 1.5 mL H_2O and 5 mL EtOH. Use these solution for identification of carbonyl compounds.

Prepared according to:

1. J. A. Moore, D. L. Dalrymple, Ćwiczenia z Chemii Organicznej, PWN, Warszawa 1976, p. 164.

5.2.2 *N*-Phosphonomethylglycine[1,2]

(Glyphosate, active component of Roundup™)



Materials:

NaOH	4.0 g, 0.1 mol,
glycine	7.5 g, 0.1 mol,
formaline, 37%	8.6 g, 7.9 mL, 0.1 mol,
diethyl phosphite	13.8 g, 12.9 mL, 0.1 mol.

Solvents: ethanol, acetone.

Other: concentrated HCl, charcoal.

FIRST STEP: **Three-component Mannich-type condensation**

A 250-mL three necked round-bottomed flask, equipped with a thermometer, a dropping funnel, a reflux condenser and a magnetic stir-bar, is charged with a solution of 4.0 g (0.1 mol) of sodium hydroxide in 40 mL of water and 7.5 g (0.1 mol) of glycine. To the stirred solution, cooled to 0-5°C in a water-ice bath, 8.6 g (7.9 mL) of 37% formaline (0.1 mol) is added dropwise (*slowly*, < 5°C). After 0.5 h of additional stirring at this temperature, 13.8 g (12.9 mL, 0.1 mol) of diethyl phosphite is added, and stirring is continued for 2 h at 90°C to 100°C. The reaction mixture is cooled and acidified with hydrochloric acid.

Diethyl *N*-carboxymethylaminomethylphosphonate (mp 132-134°C, decomposition) can be extracted from the acidified solution or directly hydrolyzed (see the next step).

SECOND STEP: **Hydrolysis**

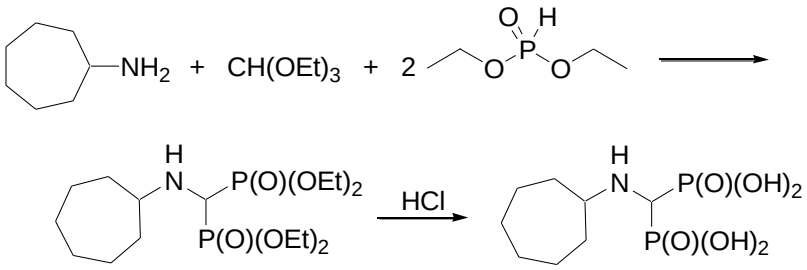
The reaction mixture is cooled, acidified with 60 mL of concentrated hydrochloric acid and refluxed for 2 hours. The reaction mixture is concentrated under a reduced pressure (80 to 100 mm Hg) on a rotary evaporator. The residue is triturated with 150 mL of ethanol and warmed for 5 min. The precipitated NaCl is filtered off from still warm solution. The solid substance precipitating after cooling is filtered and recrystallized as follows. The crude solid is dissolved in 30-35 mL of hot water, the solution is decolorized with charcoal, cooled, and the product is precipitated with 45 mL of acetone to yield 8.5-10.0 g. (50-60%, overall yield of two steps) of *N*-phosphonomethylglycine, m.p. 224-6°C.

Prepared according to:

1. US Patent 4.065.491 (1977).
2. US Patent 4.368.162 (1983).

5.2.3 **Incadronate™** (An antiosteoporotic agent)[1]

(A general procedure for the synthesis of α-aminomethylenebisphosphonic acids)



Materials:

cycloheptylamine	5.7 g, 6.4 mL, 0.05 mol,
triethyl orthoformate	7.4 g, 8.3 mL, 0.05 mol,
diethyl phosphite	13.8 g, 12.9 mL, 0.1 mol.

Solvents: ethanol, acetone.

Other: concentrated HCl, charcoal.

FIRST STEP: **Three-component condensation**

A 250-mL round-bottomed flask is charged with 6.4 mL (0.05 mol) of cycloheptylamine, 8.3 mL (0.05 mol) of triethyl orthoformate and 12.9 mL (0.1 mol) of diethyl phosphite. The mixture is heated at gentle reflux for 12 h. After cooling, volatile components are removed under reduced pressure in a rotary evaporator.

SECOND STEP: **Hydrolysis**

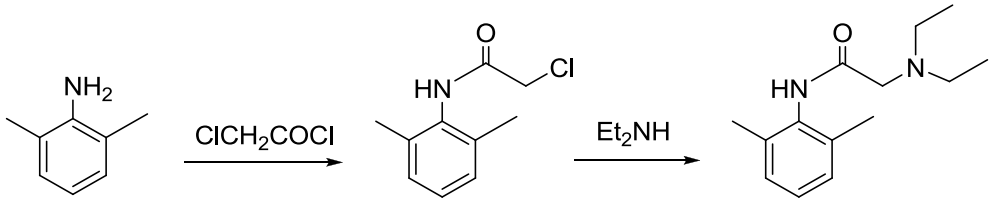
The residue is hydrolyzed in 100 mL of concentrated hydrochloric acid at reflux for 8 h. The acid is removed under reduced pressure in a rotary evaporator. The residue is worked up with water, the product is filtered, and washed with water and ethanol to yield 7.2-8.0 g. (50-55%, overall yield of two steps) of *N*-cycloheptylaminomethylenebisphosphonic acids. The crude acid can be recrystallized from hot water (if necessary the solution is decolorized with charcoal). The precipitated product is filtered, and washed with water, ethanol and acetone.

Prepared according to:

1. Polish Patent PL 172268 B1 (1997).

5.2.4 α-Diethylamino-2,6-dimethylacetanilide[1]

(Lidocaine)



Materials:

2,6-dimethyl aniline	6.0 g, 6.17 mL, 0.050 mol,
chloroacetic chloride (*lachrymator*)	5.6 g, 3.95 mL, 0.050 mol,
sodium acetate trihydrate	8.0 g, 0.060 mol,
diethylamine	15.6 mL, 0.150 mol.

Solvents: glacial acetic acid (30 mL), toluene (50 mL).

Other: 3 M HCl, 3 M NaOH.

Safety notes

Handle all chemicals with care – avoid inhaling vapors or contact with skin.

Flush affected areas with plenty of water if any of these come in contact with your skin.

FIRST STEP: **Preparation of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide**

Work under the fume hood! In a dry 100-mL Erlenmeyer flask mix 6.0 g (6.2 mL, 50 mmol) of 2,6-dimethylaniline, 30 mL of glacial acetic acid and 5.6 g (4.0 mL, 50 mmol) of chloroacetyl chloride in that order. Gently warm this mixture on the hot plate with mixing for 5 minutes, then remove from the heat and add a solution of sodium acetate (8.0 g, 60 mmol) in distilled water (60 mL). Cool the mixture in an ice bath and collect the solid product by vacuum filtration. Wash the solid with small portion of cold water, and then dry it in the Büchner funnel for 15 min (draw air through it). Determine the weight of the product and its m.p. Calculate the yield of the first step.

SECOND STEP: **Preparation of Lidocaine**

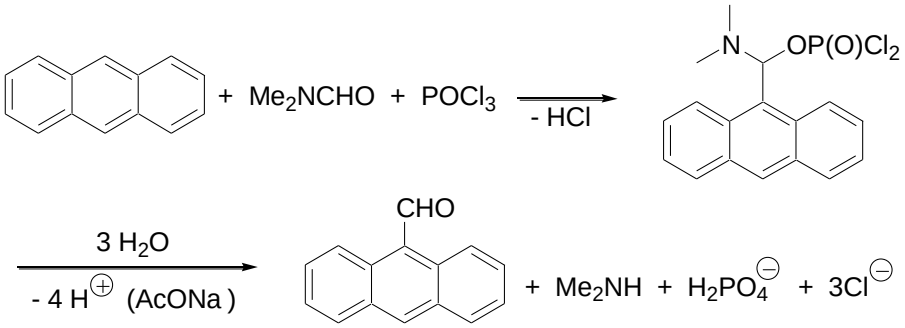
Put the product from the first step in clean, dry 100-mL round bottom flask. Add 50 mL of toluene, 15.6 mL (150 mmol) of diethylamine, and a stirring bar. Reflux the solution with stirring for 45 minutes. Cool the reaction mixture to room temp. Using direct vacuum connection the excess of diethylamine can be removed (b.p. 56°C). Carefully transfer the mixture to a large separatory funnel (by pipette). Wash the flask with 5-10 mL o toluene to complete the transfer. Wash the toluene phase with four 10-mL portions of water. Extract the organic layer with three 20-mL portions of 3 M HCl. If you observe white solid in your funnel, you will need to use more toluene. You may also need to do the extraction in portions. *Do not shake vigorously!* – it may cause the emulsion formation. Combine the aqueous extracts in 250 mL Erlenmeyer flask (or large beaker), cool the solution in an ice/salt bath, and neutralize it by addition of 3 M NaOH in portions, with stirring (check with pH paper). Collect the Lidocaine precipitate by filtration and wash with small portions of cold water. Allow the product to air dry. Determine the weight and m.p. Calculate the final yield.

Prepared according to:

1. Reilly, T. J. *J. Chem. Ed*. **1999**, *76*, 1557.

5.2.5 9-Formylanthracene[1]

(The Vilsmeier-Haack formylation reaction of electron-rich arenes)



Materials:

anthracene	8.9 g, 0.05 mol,
DMF (dimethylformamide)	9.5 g, 10 mL, 0.13 mol,
$POCl_3$	13.5g, 8 mL, 0.0875 mol.

Solvents: *o*-dichlorobenzene (10 mL).

Other: sodium acetate hydrate (50 g).

FIRST STEP: **Condensation**

8.9 g (0.05 mol) of anthracene, 10 mL (0.13 mol) of DMF and 10 mL of *o*-dichlorobenzene is placed in a 250-mL three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser (protected by a drying tube containing $CaCl_2$) and a dropping funnel. The flask is placed in a water bath and the dropping funnel is charged with 8 mL (0.0875 mol) of $POCl_3$ (*work under a fume hood!*). Phosphorus oxychloride is added to the stirred solution dropwise and the mixture is heated on boiling water bath for 2 hours.

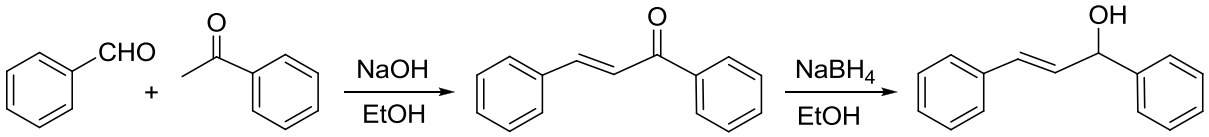
SECOND STEP: **Hydrolysis**

The flask is cooled in an ice/NaCl bath and the mixture is neutralized by a solution of sodium acetate (earlier prepared, approximately 50 g of the AcONa hydrate in 87 mL of water) using a Congo paper as an indicator. Then, the mixture is diluted with water to 1 L and left for 2 h at 0°C. The crude yellow product is filtered off and recrystallized from aqueous solution of acetic acid to give 6.0 g (58%) of 9-formylanthracene, m.p. 104°C.

Prepared according to:

1. A. I. Vogel, Preparatyka Organiczna, Ed. 2, WNT, Warszawa 1984, p. 651.

5.2.6 1,3-Diphenyl-2-propen-1-ol[1,2]



Materials:

acetophenone	26.0 g, 0.22 mol,
benzaldehyde	22.0 mL, 0.22 mol,
sodium borohydride	1.0 g, 0.026 mol.

Solvents: ethanol.

Other: sodium hydroxide (11.0 g).

FIRST STEP: **Preparation of benzylideneacetophenone (chalcone)[1]**

Place a solution of sodium hydroxide (11.0 g) in ice-water (100 mL) and 50 mL of rectified ethanol in a flask provided with a mechanical stirrer. Immerse the flask in an ice bath, pour in 26.0 g of freshly distilled acetophenone and start mixing. Add 23.0 g of pure benzaldehyde from the addition funnel, keeping the temperature about 25°C (*if necessary remove the cooling bath*). Stir the mixture until became thick (2-3 hrs). Remove the stirrer and leave the flask in refrigerator overnight. Filter off the product and wash with cold water until the washings are neutral (pH ~ 7), and then with 10 mL of cold ethanol. Recrystallize it from ethanol (*c.a.* 5 mL per gram). Dry the pure benzylideneaceto-phenone in the air, measure the weight and m.p.

Be careful, the product can be skin irritant!

SECOND STEP: **Preparation of 1,3-diphenyl-2-propen-1-ol[2]**

To a round-bottomed flask containing the solution of 20.0 g of benzylideneacetophenone in 50 mL of ethanol, add 1.0 g of sodium borohydride portion by portion, while the solution was stirred at room temperature. If there are problems with solubility, warm the solution a little bit (30-50°C) using water bath. The mixture should be stirred for 3 hrs; at the end add 50 mL of water. Transfer the solution

to the separatory funnel and extract with dichloromethane (3 × 20 mL).The combined organic layers should be washed with brine and dried over anhydrous sodium sulfate. The evaporation of the solvent afforded crystals which should be recrystalized from hexane. Measure the m.p. and calculate the yield of obtained product.

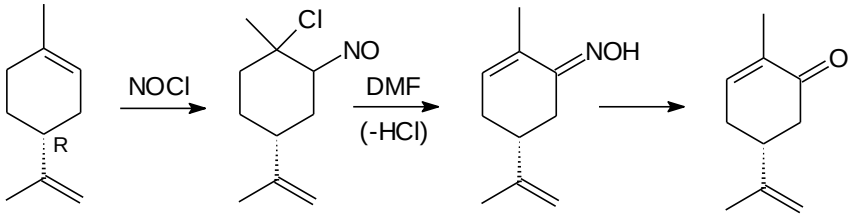
Prepared according to:

1. Vogel's Textbook of Practical Organic Chemistry (fifth ed.), *J. Wiley & Sons*, New York, 1989, p. 1034.

2. Sato, T.; Homma, I. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 1885.

5.3. Three steps procedures

5.3.1 (*R*)-(-)-Carvone[1]



Materials:

(*R*)-(+)-limonene 4.1 g, 0.03 mol,

$NaNO_2$ 2.1 g.

Solvents: propan-2-ol (24 mL), DMF (2 mL), methanol, dichloromethane.

Other: oxalic acid (5% solution, 30 mL), concentrated HCl (12 mL), $MgSO_4$.

FIRST STEP: **Preparation of (*R*)-limonene nitrosochloride**

Place (*R*)-(+)-limonene (4.1 g) and propan-2-ol (4 mL) in 100-mL three-neck round bottom flask fitted with two addition funnels, thermometer and magnetic stirrer bar. To this stirred solution add dropwise, at the same time, the solution of conc. HCl (12 mL) in 2-propanol (8 mL) from one addition funnel and saturated water solution of $NaNO_2$ (2.1 g) from the second. Keep the temperature below 10°C during the addition. Continue stirring for a further 15 min. and then leave the mixture in the refrigerator for 1 hr for precipitation. Filter off the solid precipitate, wash it with cold methanol and dry at room temperature. Measure the yield and m.p. of obtained (*R*)-limonene nitrosochloride.

Caution: The product decomposes by standing with liberation of HCl giving carvone oxime.

SECOND STEP: **Preparation of (*R*)-(-)-carvone oxime**

Place the obtained in the first step (*R*)-limonene nitrosochloride (4.0 g), DMF (2 mL) and 2-propanol (12 mL) in 50 mL round bottom flask fitted with condenser and heat the reaction mixture to reflux for 30 min. Pour the hot solution to the 250 mL beaker containing ice and water (75 mL) and stir the

mixture for 15 min. Filter off the solid product with suction using Büchner funnel, wash the residue with water (3 × 5 mL) and cold methanol (3 mL). Dry the product in the air. Record the yield and m.p. The product can be used for further experiments without purification.

THIRD STEP: **Preparation of (*R*)-(-)-carvone**

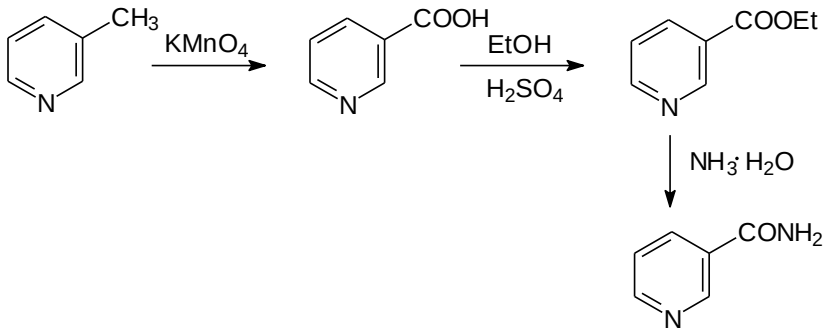
Place the carvooxime (3.3 g) and 5% solution of oxalic acid (30 mL) in the 100 mL round bottom flask. Set up the condenser and heat the reaction mixture to reflux for 30 min. Set up the apparatus for steam distillation and collect two layers distillate. When the distillation is completed you shall observe in the condenser clear distillate (water) with no oily drops evident. Transfer the solution to the separatory funnel and extract the product with dichloromethane (3 × 5 mL). Dry the combined dichloromethane solution over anhydrous $MgSO_4$. Remove the solvent under reduced pressure on the rotary evaporator to obtain the crude product (oil). Measure the yield and optical rotation of (*R*)-(-)-carvone.

Prepared according to:

1. J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit, Współczesna Synteza Organiczna, PWN, Warszawa, 2004, p. 275.

5.3.2 Nicotinic acid amide

(Vitamin PP)



Materials:

β-picoline 10.0 g, 10.45 mL (0.107 mol),

$KMnO_4$ 45 g.

Solvents: anhydrous EtOH (65 mL), diethyl ether, toluene.

Other: concentrated HCl (11 mL), H_2SO_4 (3 mL), Na_2CO_3, NaCl (15 g), Na_2SO_4, ammonia (30%).

FIRST STEP: **Preparation of nicotinic acid**

Place 10.0 g of β-picoline to the 3-neck 500-mL round bottom flask equipped with condenser, thermometer and magnetic stirrer bar. Add 100 mL of water and heat the mixture up to 70°C with stirring. Within a period of 4 hrs add 45 g of $KMnO_4$ in small portions to the solution. During the addition, raise the temperature to 90°C. After adding the last portion wait until the mixture decolorizes. Filter off the solid MnO_2 from the hot mixture through fluting filter paper (soft) and wash it with hot water (4 × 40 mL). Reduce volume of the collected filtrate to *c.a.* 100 mL on the rotary evaporator and acidify with conc. HCl to pH 3.5 (about 11 mL). Leave the mixture for precipitation. Filter off the solid nicotinic acid and wash with cold water (3 × 5 mL). Concentrate the filtrate on rotary evaporator (half volume) and leave it in a refrigerator for precipitation. Filter off the second portion of product, slightly impured by KCl. Combine the products and for purification, recrystallize from hot water. Note the yield and m.p. of pure nicotinic acid.

SECOND STEP: **Preparation of ethyl ester of nicotinic acid**

Set up the 2-neck 250-mL round bottom flask with reflux condenser and addition funnel. Place nicotinic acid (6.0 g) to the flask and add 60 mL of anhydrous ethanol. Protect the condenser at the top with a calcium chloride guard tube and from the dropping funnel add 3 mL of conc. H_2SO_4 – observe the precipitation of white solid nicotinic acid sulfate. Keep the solution refluxing for 10 hrs. Remove about 50 mL of EtOH on rotary evaporator. Cool the residue to *c.a.* 0°C, add about 25 g of crushed ice and neutralize with cold (~ 0°C) solution of Na_2CO_3. Add 15 g of NaCl and extract the solution with diethyl ether (3 × 25 mL). Dry combined ether extracts over anh. Na_2SO_4. Remove the solvent on the rotary evaporator and distill the product under reduced pressure collecting fraction boiling at 107-108°C/17 Tr. Record the yield and n_D^{20} of pure nicotinic acid ethyl ester.

THIRD STEP: **Preparation of nicotinic acid amide**

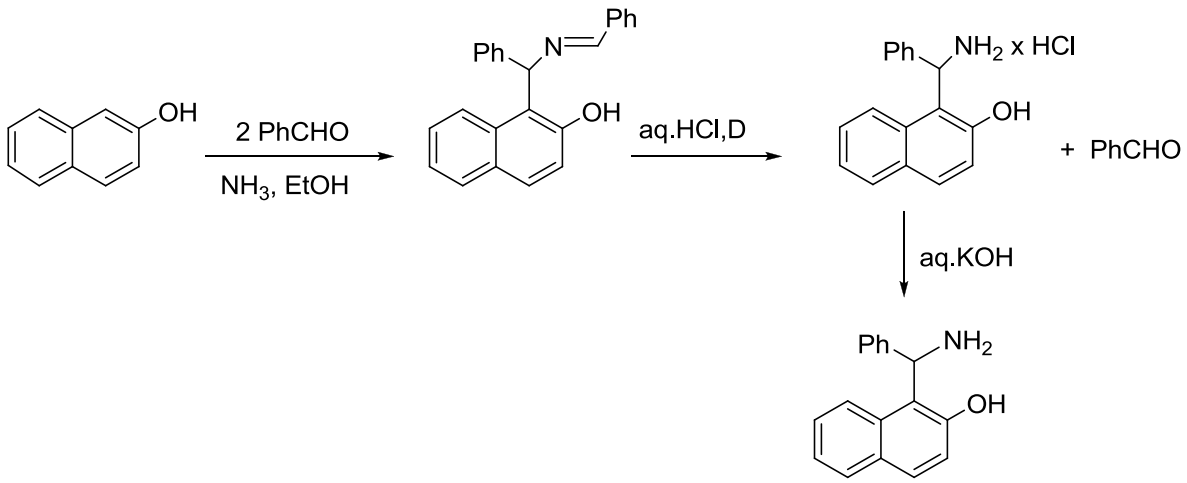
Place nicotinic acid ethyl ester (3.0 g) and 25 mL of ammonia (30%) in the 100-mL Erlenmeyer flask with well fitted stopper. The reaction mixture should be shaken for 2 hrs. Remove the unreacted ammonia, water and ethanol on the rotary evaporator. Dissolve the residue in 5 mL of anh. EtOH , add the same amount of anh. diethyl ether and leave the solution in a refrigerator. Filter off the precipitated solid amide on sintered glass filter funnel and dry the product in vacuum desiccator over calcium chloride. Record the yield and m.p. of obtained nicotinic acid amide. For purification crystallize the product from toluene.

Prepared according to:

1. S. Biniecki, Preparatyka Środków Leczniczych dla Studentów Farmacji, PZWL, Warszawa 1980, p. 88.

5.3.3 1-(α-Aminobenzyl)-2-naphthol[1]

(Betti base)



Materials:

β-naphthol	14.4 g, 0.1 mol,
benzaldehyde	21.2 g, 20.3 mL (0.2 mol),
ammonium (25%)	20 mL.

Solvents: ethanol, ethyl acetate, diethyl ether.

Other: HCl 6 M (70 mL), NaOH 10%, brine, anhydrous Na_2SO_4.

FIRST STEP: **Preparation of benzylidene-1-(α-aminobenzyl)-2-naphthol**

In a 250-mL round-bottomed flask 14.4 g of β-naphthol and 80 mL of 95% alcohol are placed. To this solution first 21.2 g of freshly distilled benzaldehyde and then about 20 mL 25% aqueous ammonia is added. The solution becomes red and warms up spontaneously and after several minutes appeared the second layer. The flask is stoppered and allowed to stay until next week (excess ammonia is allowed to escape). The condensation product solidifies (white needles). Filter off the product with suction and wash with alcohol (4 × 10 mL). The filtrate, on standing for three days, deposits an additional portion of the condensation product. Measure the yield and m.p. of obtained benzylidene-1-(α-aminobenzyl)-2-naphthol.

SECOND STEP: **Preparation of 1-(α-aminobenzyl)-2-naphthol hydrochloride**

Put 20.0 g of obtained benzylidene-1-(α-aminobenzyl)-2-naphthol into a 250-mL round-bottom flask equipped with a condenser, add 6 M HCl (70 mL) and reflux for 2 hrs. There are oily drops of benzaldehyde formed by the hydrolysis observed in the condenser. Allow the mixture to cool and filter off precipitated 1-(α-aminobenzyl)-2-naphthol hydrochloride with suction. Wash the solid first with water (3 × 30 mL) and then with ethyl acetate (5 × 10 mL) in order to remove benzaldehyde. The hydrochloride thus obtained varies from pure white to a light red in color, depending on the purity of the original reagents and on the length of time required for the hydrolysis.

The salt is somewhat more stable than the free base, and, if the reagent is to be stored for some time, it should be kept in this form.

THIRD STEP: **Preparation of 1-(α-aminobenzyl)-2-naphthol**

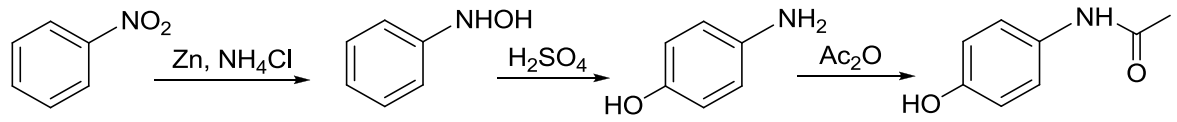
In order to obtain the amine, 10.0 g of finely divided hydrochloride is placed in a 250-mL beaker and stirred into a smooth paste with 15 mL of water. Add 5.0 g of crushed ice, and to the mixture cooled in an ice bath add slowly 10% aqueous NaOH with stirring until a nearly clear solution results (about 30 mL). Add ethyl acetate (30 mL) to the cold solution with vigorous stirring. Transfer the solution to a separatory funnel and separate the water layer. Wash the organic layer with water (3 × 30 mL) and with brine. Dry the organic phase over anh. Na_2SO_4. Remove 2/3 of the solvent on the rotary evaporator, add 50 mL of diethyl ether to the residue and leave in a refrigerator for precipitation. Filter off the solid product under suction, wash with cold diethyl ether and dry in air. Record the yield and m.p. of pure 1-(α-aminobenzyl)-2-naphthol.

Prepared according to:

1. Organic Syntheses, Coll. Vol. 1, p. 381 (1941).

5.3.4 *p*-Hydroxyacetanilide[1-3]

(Paracetamol)



Materials:

nitrobenzene	12.3 g, 10.3 mL, 0.10 mol,
ammonium chloride	6.4 g, 0.12 mol,
zinc dust	13.4 g, 0.205 mol,
acetic anhydride	6.12 g, 5.7 mL, 0.06 mol.

Solvents: diethyl ether.

Other: NaCl, conc. sulfuric acid (20 mL), potassium dichromate 10 % (5 mL), $NaHCO_3$, $MgSO_4$.

FIRST STEP: **Preparation of *N*-fenylhydroxylamine**

To a 500-mL, three-necked, round-bottomed flask equipped with a condenser, thermometer and mechanical stirrer, put ammonium chloride (6.4 g, 0.12 mol), 200 mL of water and nitrobenzene (12.3 g, 10.3 mL, 0.10 mol). To the vigorously stirred solution add 0.205 mol of zinc dust, portion by portion, and maintain the temperature about 60-65°C during the time of addition. Stir the mixture for additional 15 min. Filter the hot mixture using Büchner funnel (to remove the zinc oxide) and wash with hot water. Transfer the filtrate to an Erlenmeyer flask, saturate with NaCl and cool for 1 h keeping in the ice bath. Light pink crystals of *N*-fenylhydroxylamine should precipitate. Filter off the solid and dry keeping at the Büchner funnel with the water aspirator on. Dissolve the solid in 50 mL of diethyl ether – not dissolved impurities should be filtered under gravity using the pleated filter paper. Organic solution should be dried over anhydrous sodium sulfate. Evaporate the solvent, check the weight of the product and measure the m.p.

SECOND STEP: **Preparation of *p*-aminophenol**

To the 1-L beaker containing 20 mL of conc. sulfuric acid and ~ 70 g of ice, on the ice bath, add slowly 0.05 mol of *N*-fenylhydroxylamine. After finishing the addition, dilute the solution with water (400 mL) and warm gently until the moment, when after addition the potassium dichromate solution to a small sample (in a test tube) you can feel the smell of almonds (nitrobenzene). Then cool the solution and neutralize with sodium bicarbonate (*caution, foaming!*). Saturate the solution with NaCl and extract with diethyl ether (2 × 30 mL). Dry the etherate solution with magnesium sulfate and then remove the solvent with rotary evaporator. Weight the crude product and measure its m.p.

THIRD STEP: **Preparation of *p*-hydroxyacetanilide**

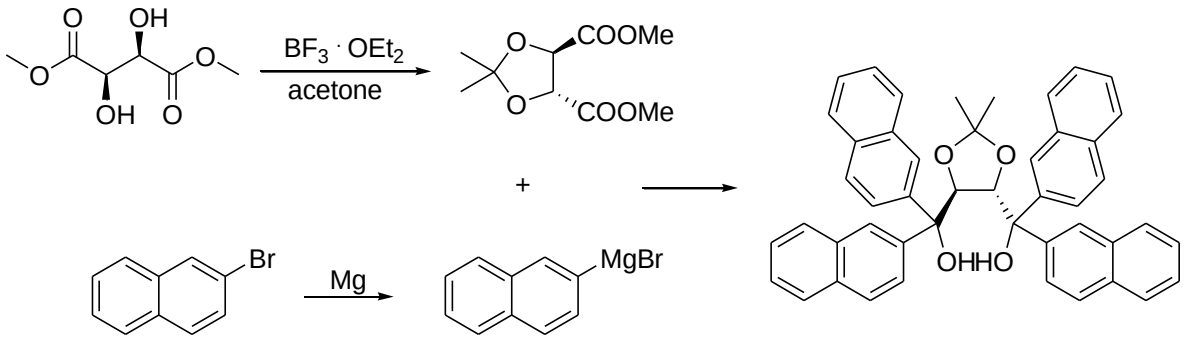
Work in the fume hood! Place 5.5 g of *p*-aminophenol (0.05 mol), 15 mL of water and 5.7 mL of acetic anhydride in the 100-mL Erlenmeyer flask fitted with condenser. The suspension should be refluxed for 15 min. During this time the *p*-aminophenol should dissolve. Leave the solution to cool, the precipitation of solid product should be observed. If not, add a bit of water (5-10 mL) and mix the solution. The crude product filter off under suction and wash three times with water. Purify the product by crystallization from water (40 mL). Filter off the product and dry on air. Measure the weight of the product and m.p. Calculate the overall yield of this experiment.

Prepared according to:

1. Organic Syntheses, Coll. Vol. 1, p. 445 (1941); Vol. 4, p. 57 (1925).
2. Organic Syntheses, Coll. Vol. 4, p. 148 (1963); Vol. 35, p. 22 (1955).
3. Vogel's Textbook of Practical Organic Chemistry (fifth ed.), *J. Wiley & Sons*, New York, 1989, p. 985.

5.3.5 (*4R,5R*)-2,2-Dimethyl-α,α,α',α'-tetra(naphth-2-yl)-1,3-dioxolane-4,5-dimethanol[1]

(TADDOL derivative)



Materials:

(*R,R*)-dimethyl tartrate	17.8 g, 0.1 mol,
$BF_3 \times Et_2O$, 48%	16.5 mL, 60 mmol,
magnesium (turnings)	5.0 g, 0.205 mol,
2-bromonaphthalene	40.4 g, 0.195 mol.

Solvents: acetone, ethyl acetate, tetrahydrofuran, diethyl ether, ethanol, toluene, hexane.

Other: aqueous saturated sodium bicarbonate and ammonium chloride solution, iodine, 10% hydrochloric acid, magnesium sulfate.

FIRST STEP: **(*R,R*)-Dimethyl *O,O*-isopropylidenetartrate**

Under an inert atmosphere a 500-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar and a pressure-equalized addition funnel, is charged with (*R,R*)-dimethyl tartrate (17.8 g, 0.1 mol) dissolved in acetone (180 mL). At room temperature, boron trifluoride diethyl etherate (16.5 mL, 48% solution, 60 mmol) is added to the clear solution over 20 min (< 30°C). The resulting yellow solution is stirred for an additional 3 h when the color of the solution becomes red-brown. For workup the reaction mixture is poured into an aqueous saturated sodium bicarbonate solution (750 mL in a 2 L beaker) (*vigorous evolution of carbon dioxide takes place, foaming*). The turbid mixture is extracted three times with ethyl acetate (3 × 100 mL). The combined organic layers are washed twice with water (2 × 200 mL) and dried over anhydrous magnesium sulfate. After filtration, the solvent is removed by rotary evaporation at ca. 45°C/20 mm. The yellow oil that is obtained (~ 20 g) is purified by fractional distillation using a 15-cm Vigreux column (b.p. 92-95°C/1.5 mm Hg) to

afford 16.9 g (77%) of product as a yellowish oil with a specific rotation of $[\alpha]_D$ -62.0 (neat), -44.0 ($CHCl_3$, *c* = 1).

SECOND STEP: **2-Naphthylmagnesium bromide (Grignard reagent)**

Under an inert atmosphere a 1-L, three-necked, round-bottomed flask, fitted with a reflux condenser, pressure-equalized addition funnel, a stirring bar and a thermometer, is charged with magnesium turnings (5.0 g, 0.205 mol, 1.05 eq.) and some iodine crystals. Then 20 mL of a solution of 2-bromonaphthalene (40.4 g, 0.195 mol) in dry tetrahydrofuran (150 mL) is added. As soon as the reaction has started (*usually warming with a heat gun is necessary to start the reaction*), the remaining tetrahydrofuran solution is added at such a rate that a gentle reflux is maintained. After complete addition, reflux is continued for 1 h. Finally, the reaction mixture is allowed to cool to room temperature.

THIRD STEP: **(*4R,5R*)-2,2-Dimethyl-α,α,α',α'-tetra(naphth-2-yl)-1,3-dioxolane-4,5-dimethanol**

A solution of (*R,R*)-dimethyl *O,O*-isopropylidenetartrate (9.6 g, 44 mmol) (obtained in the first step) in tetrahydrofuran (90 mL) is added to the Grignard solution obtained in the second step, with stirring and cooling by an ice bath. During the addition, the internal temperature should not exceed 20°C (*slowly*). After completion of the addition, the reaction mixture is heated at reflux for 1.5 h, then cooled to room temperature. For workup, an aqueous saturated ammonium chloride solution (320 mL) is carefully added, cooling the mixture with an ice bath (if pH of 7-8 is not achieved, an appropriate amount of 10% hydrochloric acid should be added). The mixture is extracted once with ethyl acetate (150 mL). After separation of the layers, the aqueous phase is extracted twice with ethyl acetate (2 × 50 mL). The combined organic layers are washed twice with brine (2 × 100 mL) and dried over anhydrous magnesium sulfate, and the solvent is evaporated on a rotary evaporator at 45°C/100 mm Hg (*foaming*).

The resulting yellowish foam (~ 40 g) is dissolved in diethyl ether (20 mL) followed by the addition of ethanol (80 mL). After a few minutes a white solid precipitates that is the clathrate of the product with ethanol. After leaving for several hours (or overnight), the crystals are filtered, washed with ethanol/diethyl ether (60 mL, 4:1), and ethanol (20 mL), and then dried overnight at 50°C/8 mm Hg to give 25-26 g of colorless crystals. In order to remove the ethanol, the crystals are dissolved in toluene (3 mL per 1 g of clathrate) at 70°C, and the solution is evaporated to dryness on a rotary

evaporator at 45°C/100 mm Hg. This procedure is repeated once more. A portion of the solid obtained in that way (~ 14 g) is mixed with toluene (160 mL) at 80°C in a 500-mL, two-necked, round-bottomed flask equipped with an mechanical stirrer, until the TADDOL derivative is completely dissolved. Hexane (160 mL) is slowly added to the solution maintained between 65-70°C. On cooling, a white precipitate starts to form. The mixture is allowed to cool completely to room temperature, and the resulting thick slurry is stirred overnight. Further solvent (100 mL of a 1:1 mixture of toluene-hexane) is added to unstirrable suspension. The mixture is shaken vigorously to give a stirrable slurry. The solid is removed by vacuum filtration and washed first with the mother liquor, then with a 1:1 toluene/hexane mixture (50 mL), and finally with hexane (50 mL). The resulting solid is dried under high vacuum (0.3 mbar) at 90°C for 10 h in a vacuum oven to give the title ligand as a white solid (8.4 g, 61%).

The mother liquor is concentrated under vacuum to give a yellow solid (~ 5 g) that can be again purified as described above by recrystallization from 60 mL of toluene and 60 mL of hexane to give a second crop of the product (2.9 g, 21%), for a combined yield of 11.3 g (82%), m.p. 204-208°C (sintering at 155°C), $[\alpha]_D$ -115.4 (ethyl acetate, *c* = 1). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.18 (s, 2 CH_3), 4.22 (s, 2 OH), 4.98 (s, 2 H-C-O), 7.21-8.19 (m, arom. H).

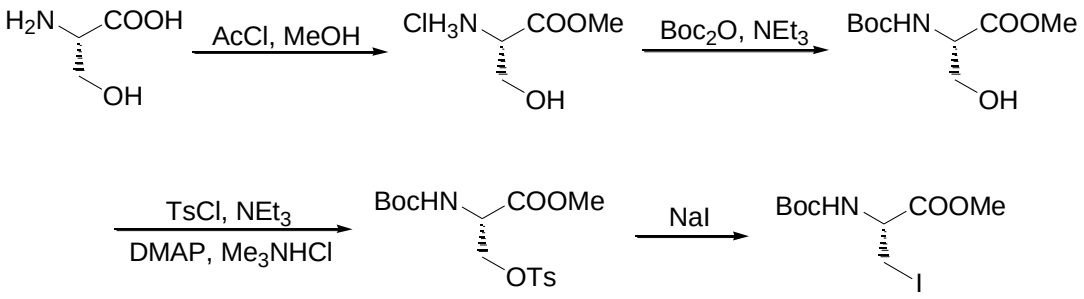
Prepared according to:

1. Organic Syntheses, Coll. Vol. 10, p. 349 (2004); Vol. 76, p. 12 (1999).

5.4. Four steps procedures

5.4.1 *N*-(*tert*-Butoxycarbonyl)-β-iodoalanine methyl ester[1,2]

(A useful building block in the synthesis of non-natural α-amino acids via palladium catalyzed cross coupling reactions)



Materials:

L-serine	12.0 g, 114 mmol,
acetyl chloride	23 mL,
di-*tert*-butyl dicarbonate	14.3 g, 63.6 mmol,
triethylamine	22.5 g, 0.2 mol,
4-dimethylaminopyridine	0.35 g, 3.0 mmol,
Me_3NHCl	0.55 g, 6.0 mmol,
p-toluenesulfonyl chloride	11.4 g, 60 mmol,
NaI	8.35 g, 56.0 mmol.

Solvents: methanol, tetrahydrofuran, diethyl ether, CH_2Cl_2, acetone, petroleum ether.

Other: 2 M HCl, saturated aqueous bicarbonate solution, 1 M sodium thiosulfate ($Na_2S_2O_3$), brine, sodium sulfate, magnesium sulfate.

FIRST STEP: ***L*-Serine methyl ester hydrochloride**

A 250-mL, three-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with a dropping funnel, reflux condenser protected from moisture by a calcium chloride-filled drying tube and a rubber septum. The dropping funnel is charged with 23 mL of acetyl chloride (*work in a fume hood!)*. The flask is charged with 150 mL of methanol and cooled with an ice-water bath under

nitrogen. Acetyl chloride is added dropwise within 10 min. The solution is stirred for a further 5 min, then solid *L*-serine, (12.0 g, 114 mmol) is added in one portion. The solution is slowly heated to reflux. The reflux is continued for 2 h, then the solution is allowed to cool to room temperature and the solvent is removed under reduced pressure to give 17.5-17.7 g of crude methyl serinate hydrochloride (98-99% yield) as a white crystalline solid that is used without further purification.

SECOND STEP: ***N*-*tert*-Butyloxycarbonyl protection**

A 500-mL, three-necked, round-bottomed flask, is equipped with a magnetic stirring bar, thermometer, reflux condenser protected from moisture by a calcium chloride-filled drying tube, and a pressure-equalizing dropping funnel that is connected to a nitrogen flow line. The dropping funnel is charged with a solution of di-*tert*-butyl dicarbonate (14.3 g, 63.6 mmol) in tetrahydrofuran (100 mL). Methyl serinate hydrochloride (10.0 g, 64.3 mmol) is suspended in the flask in tetrahydrofuran (200 mL) and triethylamine (14.0 g, 138 mmol). The solution of di-*tert*-butyl dicarbonate is added dropwise over a period of 1 h to the suspension cooled with an ice-water bath. After 10 min of additional stirring, the ice-water bath is removed and the suspension is stirred overnight at room temperature, then warmed at 50°C for a further 3 h. The solvent is removed under reduced pressure and the residue is partitioned between diethyl ether (200 mL) and saturated aqueous bicarbonate solution (250 mL). The aqueous phase is extracted with three 150-mL portions of diethyl ether. The combined organic phases are dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 13.4-14.0 g (95-99% crude yield) of *N*-Boc-*L*-serine methyl ester as a colorless oil that is used without further purification.

THIRD STEP: ***O*-Tosylation**

A one-necked, 250-mL, round-bottomed flask equipped with a rubber septum and magnetic stir-bar is charged with 13.0 g (60 mmol) of *N*-(*tert*-butoxycarbonyl)-*L*-serine methyl ester and 200 mL of CH_2Cl_2. The solution is cooled in an ice bath at 0°C while 0.35 g (3.0 mmol) of 4-dimethylamino-pyridine (4-DMAP), 0.55 g (6.0 mmol) of Me_3NHCl, and 11.4 g (60 mmol) of freshly recrystallized* *p*-toluenesulfonyl chloride (TsCl) are added. The septum is replaced with a dropping funnel charged with 8.5 mL (60 mmol) of triethylamine (Et_3N) in 25 ml of CH_2Cl_2 which is added dropwise to the reaction mixture at 0°C over 30 min (*carefully!*). The resulting slurry is stirred at 0°C for 2 hr and then poured into a mixture of 50 mL of ice, 50 mL of water, and 25 mL of 2 M HCl solution. The aqueous

layer is extracted with 100 mL of CH_2Cl_2, and the combined organic layers are washed with two 30-mL portions of brine, dried over magnesium sulfate, and concentrated by rotary evaporation to yield ~ 30 g of a light yellow solid. This product may contain *c.a.* 15% of starting material and TsCl that can be efficiently removed by crystallization according to the following procedure. The solid is dissolved in 70 mL of hot diethyl ether, filtered, and the filtrate is allowed to cool to room temperature and then to 0°C. Once crystallization begins (*scratching*), a total of 250 mL of petroleum ether is added in five portions over 2 h and then crystallization is allowed to proceed at -20°C overnight. The crystals are collected by suction filtration on a Büchner funnel and air-dried to give 14.2-15.4 g (65-69%) of a white solid, m.p. 74-76°C; R_f 0.24 (petroleum ether/EtOAc, 3:1); ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9 H), 2.46 (s, 3 H), 3.71 (s, 3 H), 4.29 (dd, *J* = 10.1, 3.1 Hz, 1 H), 4.40 (dd, *J* = 10.1, 3.1 Hz, 1 H), 4.50-4.53 (m, 1 H), 5.30 (d, *J* = 7.9 Hz, NH), 7.37 (app d, *J* = 7.9 Hz, 2 H), 7.77 (app d, *J* = 8.2 Hz, 2 H).

* *p*-Toluenesulfonyl chloride (85 g) is dissolved in 150 mL of hot $CHCl_3$ and 200 mL of petroleum ether (room temperature) is added in one portion to the clear, colorless solution. The resulting cloudy solution is clarified by addition of ca. 5 g of charcoal, stirred for 1 min, and filtered on a Büchner funnel. The filtrate is concentrated to ca. 1/5th of its original volume by rotary evaporation, and the solid which appears is collected by filtration and dried under reduced pressure to afford 68 g of TsCl as bright white crystals.

FOURTH STEP: **Substitution**

A one-necked, 250-mL, round-bottomed flask equipped with a rubber septum and magnetic stir-bar is charged with 13.9 g (37.0 mmol) of *N*-(*tert*-butoxycarbonyl)-*O*-(*p*-toluenesulfonyl)-*L*-serine methyl ester and 80 mL of acetone. The solution is stirred at room temperature and 6.7 g (45.0 mmol) of NaI is added in one portion. The reaction mixture is stirred in the dark for 3 days, after which an additional 1.65 g (11 mmol) of NaI is added and stirring is continued for an additional day. The reaction mixture is then suction filtered through a sintered glass funnel and the filtrate is collected in a one-necked, 250-mL, round-bottomed flask. The solid is washed with acetone until it is colorless. The solid is discarded and the filtrate is concentrated by rotary evaporation under reduced pressure. The residual yellow oil is partitioned between 100 mL of diethyl ether and 50 mL of 1 M sodium thiosulfate ($Na_2S_2O_3$) solution. The organic layer is separated and washed with 50 mL of 1 M $Na_2S_2O_3$,

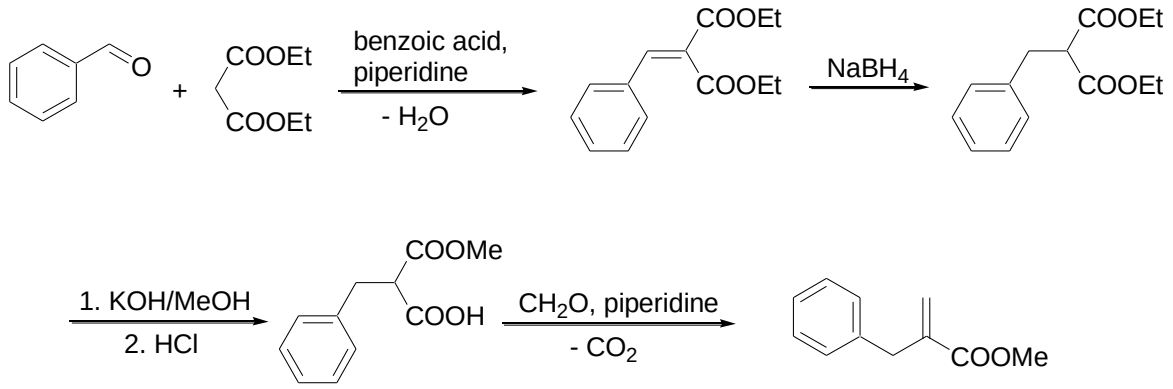
50 mL of brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to afford 11.6 g of a colorless oil that solidifies on leaving at 0°C. The solid is dissolved in 15 mL of hot (40°C) petroleum ether (b.p. 35-45°C), cooled to room temperature and then to 0°C. Once a precipitate appears, the mixture is cooled at -20°C for 1 h and the white solid is collected on a Büchner funnel and washed with cold petroleum ether to yield 9.7-10.0 g (80-82%) of *N*-(*tert*-butoxycarbonyl)-β-iodoalanine methyl ester as white to pale yellow crystals, m.p. 45-47°C; R_f 0.60 (petroleum ether/AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9 H), 3.55-3.67 (m, 2 H), 3.81 (s, 3 H), 4.53-4.54 (m, 1 H), 5.36 (d, J = 6.4 Hz, 1 H).

Prepared according to:

1. Organic Syntheses, Coll. Vol. 10, p. 320 (2004); Vol. 77, p. 64 (2000).
2. Organic Syntheses, Vol. 81, p. 77 (2005).

5.4.2 Methyl α-benzylacrylate[1,2]

(Steps III and IV – a general procedure to prepare α-substituted acrylates starting from alkyl malonates)



Materials:

diethyl malonate	100 g, 0.63 mole,
benzaldehyde	72-76 g (technical, containing benzoic acid),
piperidine	2-7 ml,
sodium borohydride, $NaBH_4$	10.4 g, 0.275 mol,
KOH	14.0 g, 0.25 mol,
piperidine	2.13 g, 2.5 mL, 25 mmol,
paraformaldehyde	6.0 g, 0.2 mol.

Solvents: benzene (or toluene), methanol, ethyl acetate, ether, pyridine.

Other: 1 M hydrochloric acid, concentrated HCl, saturated solution of sodium bicarbonate, 5% $NaHCO_3$, 5% $NaHSO_4$, sodium sulfate, magnesium sulfate, hydroquinone.

FIRST STEP: **Ethyl benylidenemalonate**

In an 1-L round-bottomed flask, which is fitted with a unit for continuous removal of water (Dean & Stark trap) and surmounted by a reflux condenser, 100 g (0.63 mol) of diethyl malonate, about 72-76 g of commercial benzaldehyde, 2-7 mL of piperidine (1.2 mL per gram of benzoic acid) and 200 mL of benzene (or toluene) are placed. The mixture is refluxed until no more water (total, 12-13 mL) is collected; this operation requires 11-18 h. After the mixture has been cooled, 100 mL of benzene is added and the solution is washed with two 100-mL portions of water, with two 100-mL portions of

1 M hydrochloric acid, and then with 100 mL of a saturated solution of sodium bicarbonate. The aqueous wash solutions are shaken with a single 50-mL portion of benzene, the benzene extract is added to the original organic layer, and the organic solution is dried with 30 g of anhydrous sodium sulfate. After the benzene has been removed under reduced pressure, the residue is distilled under reduced pressure. The yield of colorless ethyl benzylidenemalonate boiling at 185-190°C/12 mm Hg is 137-142 g (89-91%).

SECOND STEP: **Reduction to ethyl benzylmalonate**

A 1-L round-bottomed flask is charged with ethyl benzylidenemalonate (62.0 g, 0.25 mol) dissolved in 300 mL of methanol, and equipped with an efficient magnetic stir-bar. The solution is cooled to 0°C in a water/ice bath. Solid sodium borohydride $NaBH_4$ (10.4 g, 0.275 mol) is added to the solution with small portions (*gas evolution*) within 1-2 h. The solution is allowed to stir overnight, slowly warming to room temperature. Methanol is evaporated under reduced pressure at room temperature. The residue is partitioned between 5% aqueous $NaHSO_4$ and ethyl acetate (250 mL : 250 mL) and stirred in the same reaction flask. Additional portions of solid $NaHSO_4$ are added until the pH of the water phase is 3. The phases are separated, the organic one is washed with brine and dried over sodium sulfate. Evaporation of the solvent gives ~ 55-60 g of crude* ethyl benzylmalonate that is directly used in the next step.

*The yield is not evaluated as the malonate is partially transesterified to the methyl ester. Transesterification is completed in the next step.

THIRD STEP: **Hydrolysis**

In a 500-mL round-bottomed flask, equipped with pressure equalizing dropping funnel and a magnetic stir-bar, crude ethyl benzylmalonate is dissolved in 200 mL of methanol. A solution of KOH (14.0 g, 0.25 mol) dissolved in methanol (100 mL) is added dropwise within 0.5-1 h to the solution stirred without cooling. Stirring is continued overnight, then methanol is evaporated under reduced pressure, finally warming a water bath to 60-70°C. After cooling, the dense oil residue is dissolved in 50 mL of water. The flask is cooled in a water/ice bath and concentrated HCl (22 mL) is added within 20 min. The contents of the flask is transferred to a separatory funnel using portions of ethyl ether (300-400 mL totally) and water (50-100 mL totally). The water phase is separated and extracted with another portion of ether (150 mL). Combined ether phases are washed with brine and dried over

20 g of $MgSO_4$ with stirring for 1.5 h. The drying agent is filtered off and ether is removed under reduced pressure. Crude benzylmalonate monomethyl ester (40-45 g) is directly used in the next step.

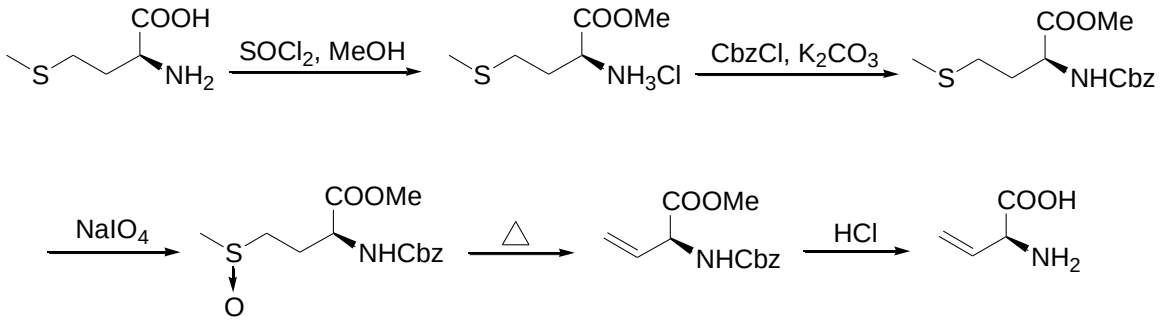
FOURTH STEP: **Benzyl acrylate**

In a 250-mL round-bottomed flask, equipped with a condenser surmounted with a bubbler, crude benzylmalonate monomethyl ester (40-45 g), pyridine (50 mL), piperidine (2.13 g, 2.5 mL, 25 mmol) and paraformaldehyde (6.0 g, 0.2 mol) are warmed under gentle reflux until intensive evolution of CO_2 stops (1-2 h). After cooling, volatile components are removed under reduced pressure. The residue is partitioned between ethyl acetate and water (150 mL : 100 mL) and transferred to a separatory funnel. The water phase is separated and extracted with another portion of ethyl acetate (150 mL). Combined organic phases are washed successively with: diluted HCl, pH 2-3 (three times), 5% $NaHCO_3$ and brine. The solution is dried over Na_2SO_4 with addition of hydroquinone (0.5 g). The drying agent is filtered off and ethyl acetate is removed under reduced pressure. The residue is distilled under reduced pressure. The yield of colorless benzyl acrylate boiling at 125-130°C/12-15 mm Hg (water pump) is 18-20 g (41-45%, total yield for three steps II-IV). The products should be stored in dark with stabilizing addition of hydroquinone.

Prepared according to:

1. Organic Syntheses, Coll. Vol. 3, p. 377 (1955); Vol. 25, p. 42 (1945).
2. Stetter, H.; Kuhlmann, H. *Synthesis* **1979**, 29.

5.4.3 *N*-(Benzyloxycarbonyl)-*L*-vinylglycine methyl ester / *L*-vinylglycine[1,2]



Materials:

L-methionine	10.0 g, 67 mmol,
thionyl chloride	8.8 g, 5.4 mL, 74 mmol,
potassium bicarbonate	28.2 g, 0.28 mol,
benzyl chloroformate	10.5 g, 8.9 mL, 62 mmol,
glycine	0.85 g, 11 mmol,
sodium periodate ($NaIO_4$)	13.1 g, 61 mmol.

Solvents: methanol, diethyl ether, chloroform, ethyl acetate, hexane.

Other: 0.01 M HCl, brine, sodium sulfate.

FIRST STEP: ***L*-Methionine methyl ester hydrochloride**

A 250-mL flask, containing a magnetic stirring bar, is charged with *L*-methionine (10.0 g, 67 mmol) and methanol (70 mL), and equipped with a pressure-equalizing dropping funnel. The dropping funnel is charged with thionyl chloride (8.8 g, 5.4 mL, 74 mmol, 1.1 eq.). $SOCl_2$ is added dropwise to the solution cooled to 0°C. The reaction is left overnight for stirring, slowly warming up to room temperature. Then, the volatile materials are evaporated under reduced pressure. Further drying under reduced pressure gives *L*-methionine methyl ester hydrochloride as a white solid (13.2 g, 99%), that is suitable for most purposes. It can be recrystallized by dissolving in hot methanol (50 mL) and precipitating with ether (100 mL) to give the pure hydrochloride: 11.8 g, 88%, m.p. 152-153°C.

SECOND STEP: ***N*-Benzyloxycarbonyl protection**

A 500-mL, two-necked flask, containing a magnetic stirring bar, equipped with thermometer and a pressure-equalizing dropping funnel, is charged with *L*-methionine methyl ester hydrochloride (11.8 g, 56 mmol), potassium bicarbonate (28.2 g, 0.28 mol, 5 times molar excess), water (75 mL), and ether (75 mL), and the solution is cooled to 0°C. The dropping funnel is charged with benzyl chloroformate (10.5 g, 8.9 mL, 62 mmol, 1.10 eq.) which is added dropwise. After 1 h the cooling bath is removed, and the solution is stirred for 5 h. Glycine (0.85 g, 11 mmol, 0.2 eq.) is added to scavenge excess chloroformate and the solution is stirred for additional 18 h. The organic layer is separated, and the aqueous layer is extracted with ether (2 × 50 mL). The combined organic layers are washed with 0.01 M hydrochloric acid (2 × 100 mL), water (2 × 100 mL), and saturated brine (100 mL), and then dried (Na_2SO_4), filtered, and evaporated on a rotary evaporator. The resulting oil is further dried under reduced pressure to leave product as a clear oil that solidifies upon cooling: 16.5-16.6 g (98-99%), m.p. 42-43°C.

THIRD STEP: **Oxidation**

A 500-mL, two-necked flask, containing a magnetic stirring bar, equipped with thermometer and a pressure-equalizing dropping funnel, is charged with *N*-benzyloxycarbonyl-*L*-methionine methyl ester (16.6 g, 56 mmol) and methanol (150 mL), and the solution is cooled to 0°C. A solution of sodium periodate ($NaIO_4$) (13.1 g, 61 mmol, 1.10 eq.) in water (200 mL) is added dropwise over a period of 0.5 h. The cooling bath is removed and the mixture is stirred for 18 h. The product is extracted with chloroform (3 × 100 mL), washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated by rotary evaporation (bath temperature < 30°C). The resulting oil is further dried under reduced pressure, yielding the product as a waxy solid: 17.3 g, 99%.

FOURTH STEP: **Elimination**

Sulfoxide of *N*-(benzyloxycarbonyl)-*L*-methionine methyl ester (3.2 g, 10 mmol) is placed in a 50-mL, round-bottomed flask, and distilled from a preheated Kugelrohr apparatus (150°C, 3 mm, *stench*) or a corresponding apparatus for vacuum distillation. The yellow brown product oil is chromatographed on a column by silica gel, eluting with hexane/ethyl acetate (85/15) to give 2.0 g (80%) of *N*-(benzyloxycarbonyl)-*L*-vinylglycine methyl ester as a light yellow oil contaminated with 2% of its (*Z*)-α,β-isomer (TLC: hexane/ethyl acetate; 2/1, the major product, R_f = 0.37, (*E*)- and (*Z*)-α,β-unsaturated isomers R_f = 0.40 and 0.30, respectively).

To obtain a pure analytical sample, a subsequent purification step (column chromatography, hexane/ethyl acetate, 9/1) can be applied.

***L*-Vinylglycine hydrochloride** can be obtained from *N*-(benzyloxycarbonyl)-*L*-vinylglycine methyl ester in almost quantitative yield by refluxing in 6 M hydrochloric acid for 1 h.

Prepared according to:

1. Organic Syntheses, Coll. Vol. 9, p. 63 (1998); Vol. 70, p. 29 (1992).
2. Afzali-Ardakani. A.; Rapaport, H. *J. Org. Chem.* **1980**, *45*, 4817.