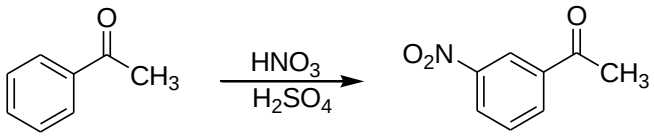
Synthesis of 3-nitroacetophenone

Reaction:



Procedure:

Take a 250 cm^3 flask with three necks with a mechanic stirrer, dropping funnel and a thermometer impinging the reaction mixture and pour 37 cm^3 of concentrated sulphuric acid. Switch on the stirrer, cool down the flask (cooling mixture: ethanol-dry ice) until the temperature in the flask drops to 0 °C.

Then carefully add drop by drop 0.125 mol of acetophenone so that the temperature inside the flask does not exceed 5 °C. Then cool the mixture down to -7 °C and be adding a cooled nitration mixture consisting of 15 cm^3 of concentrated sulfuric acid and 10 cm^3 of concentrated nitric acid a rate so that the whole operation does not take more than 30 minutes and the temperature of the reaction mixture is still within -5-0 °C. After adding the nitration mixture maintain the cooling and stirring for next 10 minutes. Then stir the mixture with a glass rod and during the stirring pour it on a crushed ice mixture of 165 g of ice and 375 cm^3 of water. By the stirring the product is precipitated as a yellow wax or solid substance.

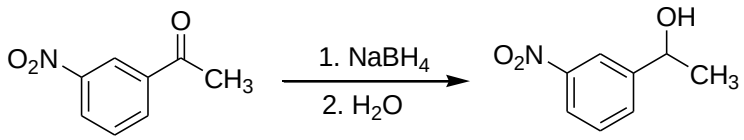
Once the ice is melted suck off the nitro compound and remove water on a filter by pressing with a glass stopper. After bringing it into a glass beaker wash it out twice with 75 cm^3 of water and blend it in 8 cm^3 of ethanol. After each of these three washing suck up the product and squeeze it out perfectly with a glass stopper. Then re-crystallize the product from 25-35 cm^3 of ethanol with addition of activated carbon. Filter the hot solution into 250 cm^3 of cold water at intensive stirring with glass rod. After several minutes of standing suck up the product, wash it with 50 cm^3 of cold water and squeeze it to dry as much as possible. Do the second re-crystallization from about 30 cm^3 of ethanol at using activated carbon. Suck up the created yellow crystals and let them dry in the air. Determine the yield and measure the melting point (temperature). **Store the product in a marked vessel for next lab task – synthesis of 1-(3-nitrohpenyl)ethanol and 3-aminoacetophenone!**

Additional questions:

1. Why must be the reaction mixture cooled during the synthesis of 3-nitroacetophenone?
2. Why takes the substitution the position meta?
3. Why is acetophenone first dropped to sulphuric acid and afterwards the nitration mixture is added?

Synthesis of 1-(3-nitrophenyl)ethanol

Reaction:



Procedure:

Dissolve 0.013 mol of 3-nitroacetophenone in 30 cm^3 of methanol in a 250cm^3 flask with a reflux condenser and heat it on a heating bath until complete dissolution of 3-nitroacetophenone. Then cool the solution with an external ice bath. Slowly add to the suspension 0.016 mol of sodium tetrahydridoborate and shake the created mixture occasionally for 15 min. Then add 20 cm^3 of distilled water and boil the mixture 30 min under the reflux condenser. Then extract the cooled reaction mixture with 30 cm^3 of ether. Do it twice. If the two phases are not separated after shaking in the extraction funnel add 25 cm^3 of a saline solution. Wash the conjoined etheric extracts with 25 cm^3 of the saline solution and then dry it carefully with anhydrous magnesium sulphate. Filter out the drying agent and remove ether by distillation with a rotary evaporator. Re-crystallize the product from toluene with an appropriate adsorbent. Determine the yield of reaction and measure the melting point (temperature). The product purity can be verified with infrared spectroscopy. The spectra can be compared with those of the starting substance.

Properties:

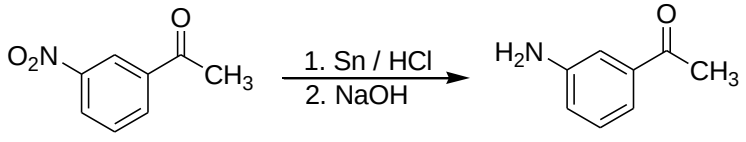
1-(3-Nitrophenyl)ethanol is a solid crystalline substance with melting point of 62 °C.

Additional questions:

1. Why is the reaction mixture boiled with water after the end of the reaction?

Synthesis of 3-aminoacetophenone

Reaction:



Procedure:

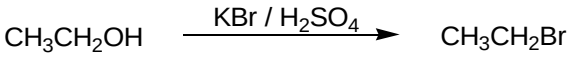
Mix 0.013 mol of 3-nitroacetophenone and 0.034 mol of fine granulated tin in an NZ 29 100cm^3 flat bottom flask with a reflux condenser, add a mixture of 29 cm^3 of water and 11 cm^3 of concentrated hydrochloric acid. Reflux it on an electromagnetic stirrer under permanent stirring for 90 min. Then filter the cooled reaction mixture and add to the filtrate under permanent stirring and cooling in an ice bath 24 cm^3 of 40% sodium hydroxide solution. Suck up the created precipitate, wash it with cold water and re-crystallize it from about 80 cm^3 of water with addition of activated carbon. Determine the product yield and measure the melting point (temperature). The product purity can be verified with infrared spectroscopy. The spectra can be compared with those of the starting substance.

Additional questions:

1. Which substance reduces the nitro group to amino group in the reaction mixture?
2. How many electrons are exchanged during this reaction?
3. Why is 40% solution of sodium hydroxide added to the reaction mixture after the end of the reaction?

Synthesis of bromoethane

Reaction:



Procedure:

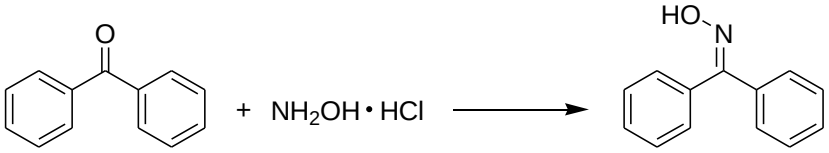
Take a 500 cm^3 flask, insert 55 cm^3 of concentrated sulfuric acid and then carefully add under permanent stirring step by step 0.60 mol of ethanol. Afterwards cool the hot mixture externally with cold water to 10–15 °C, add 40 g of ice and then 0.42 mol of potassium bromide. Connect the flask to the distillation apparatus and distil the mixture carefully on a chemical mesh using a burner so that the mixture does not boil over into the condenser. Fill the receiving flask of the distillation apparatus to one half with mixture of water with crushed ice and adjust the allonge with help of a tubing so that its outflow is situated just slightly under the water level in the receiving flask. The receiving flask should be externally cooled with ice. The reaction is over when oil droplets move no more into the receiving flask. The receiving flask is being filled with the liquid and thus it is necessary to check the apparatus that the product liquid does not enter back through the condenser to the hot distillation flask at the underpressure! This can occur when the heating is interrupted. The tubing of the allonge must be still tightly under the liquid level in the receiving flask! Ethyl bromide should be separated from water in a divider funnel. It creates the lower layer in the funnel. Then it should be dried with anhydrous calcium chloride in a dry flask. After drying the drying agent is removed by filtration (caution: ethyl bromide is a very volatile substance). The raw product is then re-distilled from the water bath to a dry receiving flask externally cooled with ice. Use the distillation bridge with NZ 14 standard joints. Write the boiling temperature, determine the product yield, measure its refractive index and analyse the product with gas chromatography. **Store the product in a marked vial for next laboratory task – synthesis of ethyl magnesium bromide!**

Additional questions:

1. Why is added ice into the reaction medium at the synthesis of ethyl bromide?
2. Which side products can be created at the synthesis of ethyl bromide?
3. What is the reaction mechanism and why?
4. Why is necessary the presence of sulphuric acid at the synthesis of ethyl bromide?
5. Why is ethyl bromide collected under the water level with crushed ice?

Synthesis of benzophenone-oxime

Reaction:



Procedure:

Weigh 0.01 mol of benzophenone, insert it into a 50cm^3 flask and add 15 cm^3 of ethanol. Take two beakers and in each beaker dissolve separately in 4 cm^3 of water 0.02 mol of hydrochloride hydroxylamine and 0.04 mol of NaOH and add both these solutions into a flask. Heat the flask content under a reflux condenser to moderate boiling. Monitor the progress of the reaction with thin layer chromatography (TLC). Make the first analysis even before the heating. Every 20 min interrupt the heating and after cooling the solution use a capillary to bring a part of the solution on a Silufol plate.

In addition to the reaction mixture bring also standards of the initial substances. Let the chromatogram elute with mobile phase containing hexane and ethyl-acetate in the ratio of 4:1. Continue the heating until TLC shows no benzophenone in the reaction mixture. When the reaction is finished cool the flask in ice bath and its content then pour in the mixture of 10 cm^3 of concentrated hydrochloric acid, 10 g of ice and 30 cm^3 of water. Suck up the precipitate and wash it carefully on a filter with 3 × 20 cm^3 of water.

Use a Büchner funnel to remove water from the product by precise squeezing. Re-crystallize the product from methanol (about 5 ml for 1 g of the raw product) using an appropriate adsorbent. After drying the product in a vacuum dryer determine its melting point and measure infrared spectrum in a KBr pellet.

Properties:

Benzophenone-oxime is a white crystalline substance with melting point of 143.5–144.5 °C. The substance must be stored in an inert protective atmosphere because it is slowly decomposed to benzophenone and nitric acid in contact with air.

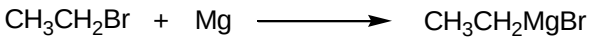
Additional questions:

1. Determine the retention factor of benzophenone and its oxime. Which factors can influence the R_f of a substance?
2. Oximes show the possibility of tautomer equilibrium presence. Make a sketch of the second tautomer structure of benzophenone-oxime.
3. Oximes of asymmetrically substituted carbonyl compounds can exist as two stereoisomers. What kind of stereoisomerism is it and what is the difference between these stereoisomers?

Diastereoselective syntheis of 1,2-diphenylbutane-1,2-diol

Preparation of Grignard reagent

Reaction:



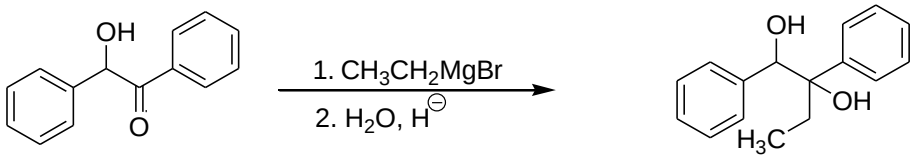
Procedure:

Weigh into a 250cm^3 three neck flask 0.047 mol of magnesium, add a grain of iodine and a Teflon stirrer. Complete the apparatus – connect to the bottle a dropping funnel and a reflux condenser; close the flask and the dropping funnel with stopper and attach to the condenser a chlorcalcium stopper. Pour in the flask 20 cm^3 of anhydrous diethyl ether, prepare in the dropping funnel a solution of 0.047 mol of bromoethane in 20 cm^3 of anhydrous diethyl ether. Place an electromagnetic stirrer under the flask. Drain partly from the dropping funnel into the flask about 1/10 of its content, stir the flask content shortly, then let it be until the moment of initiation of the reaction. Then add the bromoethane solution drop by drop so that the reaction is not too stormy.

After adding of all bromoethane heat the mixture shortly to boil. In case of higher amount of remaining magnesium in the mixture add drop by drop the solution of 0.008 mol of bromoethane in 10 cm^3 of anhydrous diethyl ether until the dissolving of nearly all the magnesium. Then cool the solution by immersing the flask in an ice bath.

Addition of Grignard reagent to benzoin

Reaction:



Procedure:

Prepare into the dropping funnel a solution of 0.0094 mol of benzoin in 30 cm^3 of anhydrous dichloromethane. Then add the solution drop by drop to the solution of Grignard reagent at intensive stirring in a three neck flask immersed in an ice bath during about 10 min. After adding of all the Grignard reagent remove the ice bath and heat the solution for about 20 min to a moderate boil. Then disconnect the three neck flask from the apparatus, add in the mixture about 30 g of ice and 25 cm^3 of 10% solution of H_2SO_4. Close the flask and stir the mixture carefully. Then pour the mixture in the dividing funnel. Separate the organic layer and extract once more the water layer with 25 cm^3 of diethyl ether. Wash the adjoined organic extracts with 25 cm^3 of 10% solution of Na_2CO_3, 25 cm^3 saturated water solution of NaCl

(saline solution) and dry the extract with anhydrous $MgSO_4$. Filter the drying agent out and evaporate the organic solvents in a flask (**weighed in advance!**) of a vacuum evaporator.

A yellowish liquid remains after the evaporation. This liquid is solidified after cooling. Re-crystallize the raw product from toluene using an appropriate sorbent. Dry the re-crystallized product in a vacuum drier. Determine the melting point of the product and analyse it with thin layer chromatography.

Comment:

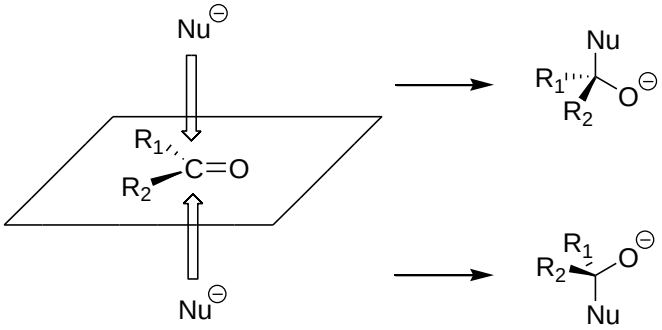
Based on the melting point it is possible to determine which diastereomer is the principal reaction product. Racemic mixture (1*R*,2*R*) and (1*S*,2*S*)-1,2-diphenylbutane-1,2-diol shows the melting point 105-106 °C, racemic product consisting of (1*R*,2*S*) and (1*S*,2*R*)-1,2-diphenylbutane-1,2-diol shows the melting point 116-117 °C. Summarize your observations in protocol!

Additional questions:

1. Why is the Grignard reagent prepared in a dry atmosphere without air humidity?
2. What would happen if water would enter the reaction environment before and/or after the preparation of the Grignard reagent?
3. Is it possible to use also some other solvent than diethyl ether for preparation of the Grignard reagent? Which?
4. During the addition of ethyl magnesium bromide to benzoin a huge excess of Grignard reagent over benzoin is used. Try to explain it.
5. Which methods can be used (except comparison of product melting point with tabulated values of particular diastereomers) for confirmation of the spatial configuration of the molecule of the prevailing product?
6. What is diastereomeric excess and what is its definition? How can you determine the diastereomeric excess of your product?

Stereospecific addition of the nucleophile to the carbonyl group

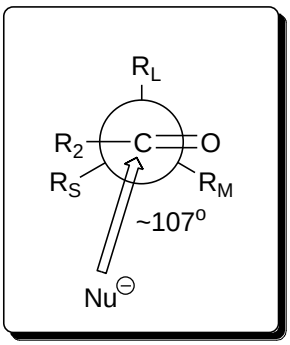
Atoms of the C=O group and the atoms tightly bonded to the carbonyl atom of carbon are situated in one plane in ideal case. In case of a nucleophile addition to the polar bond C=O, the nucleophile can approach the carbon atom from one or another side of this plane.

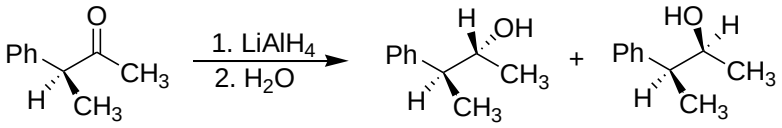


If the substituents R_1 and R_2 are the same the addition does not lead to creation of stereoisomers.

If there are two different groups on the carbonyl atom of carbon, the addition produces a mixture of enantiomers, in case there is no external chiral influence it is a racemic mixture. If the carbonyl compound is chiral due to the presence of the stereogenic centre in the molecule the addition creates two diastereomers in unequal amounts because the products internal energies are different as well as their activation energies of these reactions producing these diastereomers. It can be usually said that the closer is the stereogenic centre to the carbonyl function the bigger is its influence on the ratio of the product stereoisomers. The reaction runs stereoselectively if one of the stereoisomers is created excessively.

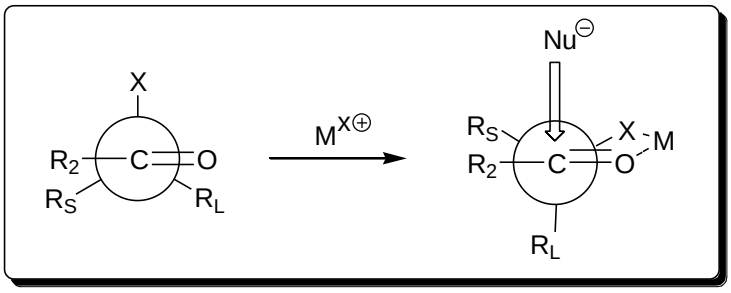
A stereoselectivne way of addition of cyanide anion to chiral saccharides was observed by Emil Fischer. Systematic studies of additions of nucleophiles (mostly Grignard reagents) to chiral carbonyl compounds started in fifties of 20th century. The first model capable of explaining stereoselectivity of these additions to carbonyl compounds, in which the stereogenic centre is an atom tightly bonded to carbonyl (α-carbon atom), was designed by Donald J. Cram. Nowadays it is a widely accepted Felkin-Ahn model. This model supposes that during the addition there are crucial steric interactions between the second substituent of the carbonyl R_2 and substituents on the first atom of the group R_1 and further between the coming nucleophile and the most voluminous group on the first atom of the group R_1. If we want to predict the prevailing product of the nucleophile addition using this model it is necessary to separate the substituents bonded to the carbon atom of the group R_1, which is also a stereogenic centre, by their steric need to R_L (largest), R_M (medium) a R_S (smallest). During the addition the molecule gets a conformation in which is the largest substituent R_L oriented orthogonally to the plane of the carbonyl group so that the group R_2 is closer to the smallest substituent R_S. The nucleophile then comes from the side opposite to the side occupied with R_L. The development of the addition is depicted below.

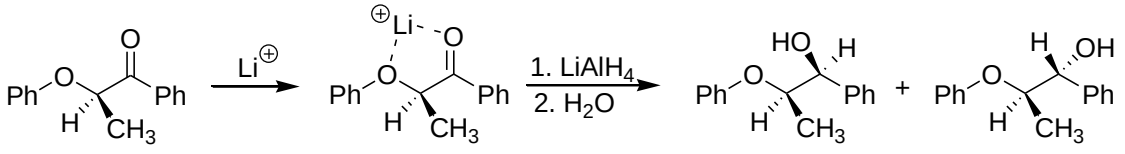




74 % 26 %

The addition is not orthogonal to the plane of the carbonyl group. The nucleophile is coming in the trajectory forming an angle with the C=O bond 107° app. The addition of organometallic reagents to the carbonyl function is usually connected with coordination of the particular metal (by Lewis acid) to an oxygen atom of the C=O group. However, if there is a group capable of coordination with a metallic ion (typically -OH, -OR) on the α-carbon atom stable pentamerous chelates are formed which can substantially change the addition of the nucleophile. In this case the rules described above are not applicable. The spatial conformation of the substituents is locked by a created chelate. The nucleophile is approaching the carbonyl atom of carbon from the side occupied by the smaller one of the two remaining substituents. It can be seen in figure below.

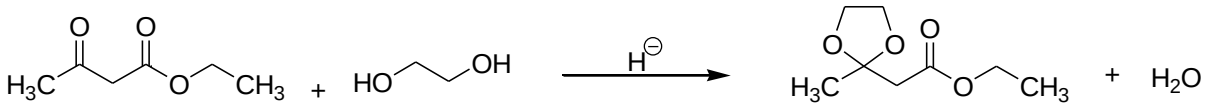




72 % 28 %

Synthesis of ethyleneacetal of ethyl 3-oxobutanoate

Reaction:



Procedure:

Pour in a 250cm^3 flask 0.23 mol of ethyl 3-oxobutanoate (ethyl acetoacetate), 0.24 mol of ethylene glycol and add 0.2 g of *p*-toluensulfonic acid monohydrate and 100 cm^3 of toluene. Append an azeotropic attachment with a reflux condenser to the flask and let the solution being refluxed until you can see that no water drops are forming in the attachment. Cool the reaction mixture down to the lab temperature and wash it with 35 cm^3 of sodium hydroxide in a dividing flask, two times with 50 cm^3 of water and then dry it with anhydrous magnesium sulphate in the flask. After filtration evaporate toluene in a rotary vacuum evaporator and make a vacuum re- distillation of the raw product. Observe and record the temperature progress of the distillation. Determine the product yield, refractive index for all the fractions of the distillation and also determine the composition of these fractions with gas chromatography.

Properties:

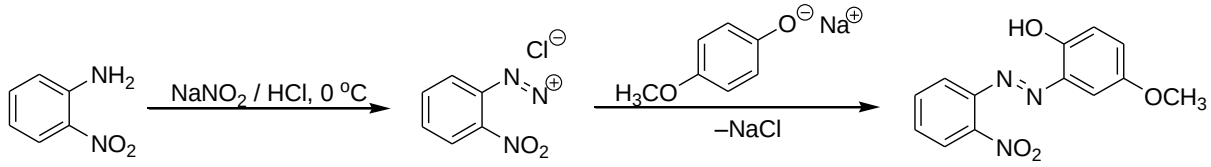
Ethyleneacetal of ethyl 3-oxobutanoate is a liquid with a characteristic aroma, boiling point 70–80 °C at the pressure of 1 torr, refractive index n_{20D} = 1.4360.

Additional questions:

1. What is the difference between a water and an oil vacuum pump which are used for vacuum generation at the vacuum distillation?
2. Why is it necessary to add *p*-toluensulfonic acid in the reaction mixture?
3. Why is done azeotropic distillation?
4. What is a cold trap and what is it used for?
5. Why is done vacuum distillation?
6. What is the reason of washing the reaction mixture with the solution of sodium hydroxide after the end of the reaction?
7. In the reaction mixture there can be except the catalysed creation of acetal also acid catalysed transeterification of the original substance with ethylene glycol at the creation of 2-hydroxyethyl 3-oxobutanoate. Why is acetal the main reaction product? Try to explain it.
8. What is the use of the reaction product ethyleneacetal of ethyl 3-oxobutanoate?

Synthesis of 4-methoxy-2-(2-nitrophenylazo)phenol

Reaction:



Procedure:

Weigh into a 250cm^3 beaker 0.02 mol of NaOH, 0.1 mol of K_2CO_3 and 0.02 mol of 4-methoxyphenol. Add 60 cm^3 of water, heat the mixture to 80-90 °C and stir it until all components are dissolved. Then cool the mixture down to 0 °C. Prepare a solution of 1.5 g of $NaNO_2$ in 5 cm^3 of water and cool the solution down to 0 °C. To prepare the diazonium salt weight 0.02 mol of 2-nitroaniline into 100 cm^3 beaker, triturate it with 5.4 cm^3 of concentrated hydrochloric acid, add 10 g of ice and at intensive stirring add solution of $NaNO_2$ in water. Cool the beaker with the mixture in ice bath during the reaction. Stir the suspension until the crystals of 2-nitroaniline dissolve (15 min). The end of the reaction should be determined using a starch-iodide reagent paper. Filter the solution of diazonium salt into the alkaline solution of 4-methoxyphenolate at permanent stirring. Add to the funnel a piece of ice for cooling of the filtrated solution. After addition of the diazonium salt let the mixture 30 min in the ice bath and stir it occasionally. Then suck off the product using a Büchner funnel, wash it with water and dry the raw product in a heated vacuum heater. Take several crystals of the crude product for thin layer chromatography, take 0.06 g for column chromatography. Re-crystallize the remaining crude product from ethanol using a charcoal as a adsorbent. Dry the re-crystallized product in a vacuum drier. Determine the melting point of the product (lit. 133–135 °C) and analyse it with thin layer chromatography.

Additional questions:

1. Why is coupling performed in alkali environment?
2. Which group of reactions includes coupling?
3. Why must be temperature maintained between 0-5 °C at the synthesis of the diazonium salt?
4. The product can exist as several tautomeric forms. Try to draw their structures.

Separation of the reaction products with column chromatography:

The reaction products will be separated in a silica gel column using toluene as a mobile phase. When doing column chromatography usually 30 times more silica gel is used than the weight of the separated substance. However, in our case it will be even more. The chromatographic column should be filled with a suspension of the sorbent in a solvent which is usual method for silica gel columns. In order to ensure the best possible separation efficiency, the column must be well kept out of the reach of heat sources and direct sunlight.

a) Fasten the housing of the chromatographic column to a stand in vertical position. Fill the tube leading to the valve with a piece of cotton wool and peen carefully the cotton wool with a glass rod so that no solid particles of the column filling can escape from the column. Fill the narrower part of the column over the cotton wool stopper with sea sand.

b) Cover the sea sand on the column bottom with about 10 cm high column of the mobile phase. Do it very carefully to not stir up the sea sand. In case of roughness creation on the sea sand surface it is possible to straighten the surface by soft knocking on the column housing.

c) Weigh into a 400cm^3 beaker the required amount of silica gel (25 g), mix the silica gel with a small amount of the mobile phase and stir the resulting suspension carefully several minutes until you can see no escaping bubbles and the silica gel is well wetted by the mobile phase. To speed up the process the suspension can be immersed in an ultrasonic bath for several minutes.

d) Using a wide funnel pour the silica gel suspension slowly into the column. Do it very carefully to not stir up the sea sand on the bottom and to let the silica gel settle evenly in the column. Stir the suspension in the beaker with a glass rod all the time of pouring to prevent sedimentation in the beaker. When the suspension is poured in the column open the column valve and let the mobile phase escape into a clean beaker. Observe the silica gel sedimentation. When the sedimentation is finished there should be a several centimetres thick layer of the mobile phase over the silica gel column. Fasten a reduction piece with a rubber bulb to the end of the chromatographic column. Press the bulb to increase the pressure in the column and to speed up the outflow of the mobile phase. Close the valve in the moment when the mobile phase column is about 2 cm height over the silica gel column. All the time of operations with the column and silica gel be very careful that the silica gel is not dried and the column filling thus not devalued! Put a circle of filter paper on the silica gel column and then pour a half centimetre layer of the sea sand. If you are just not working with the column close it with a normalized joint stopper to prevent drying of the mobile phase.

e) Dissolve 50–60 mg of the raw product in a test tube in 0.5 cm^3 of mobile phase. Open the valve of the chromatographic column and let the mobile phase escape so long that the sea sand on the silica gel is dry. Caution! The silica gel, however, must not be dried! Using a pipette cover the sand layer evenly with the substance solution. Once more let the mobile phase escape so long that the sea sand on the silica gel is dry. Repeat once more the covering the sand layer with a small amount of the substance solution. Let the mobile phase escape and repeat this cycle until the mobile phase covering the sand is no more coloured with the mixture of dyes being separated. Then it is possible to pour a bigger amount of the mobile phase over the silica gel column and to start the chromatographic separation.

f) Open the valve of the chromatographic column and collect the escaping mobile phase in a clean beaker. Observe the motion of colour zones together with the mobile phase through the column. Thanks to the fact that the separated substances are coloured you can see all the imperfections of the filling of the column. If the filling is perfect no channels with faster streams of the liquid or moreover some bubbles should be in the column. The mobile phase flow should be the same in every part of the column cross section. In the moment when the first colour zone approaches the bottom end of the column start the collection of the flowing solution into numbered test tubes or small beakers. The fraction volume should be 10–15 cm^3. Stop the collection of the fractions if the product is washed out of the column. Periodically observe the level of the mobile phase and if needed add some amount of the mobile phase to not let the silica gel column dry.

g) Analyse the collected fractions using thin layer chromatography (TLC). Put the individual fractions on one TLC plate in one line and also the solution of the raw product. Identify the individual fractions containing only the required product, put those fractions together and evaporate their solution carefully in a rotary vacuum evaporator in a flask weighed in advance.

h) Determine the pure product yield and its melting point. Do also TLC which provides a comparison of the composition of the raw product, re-crystallized product and product yielded from the chromatographic separation. Determine also R_f of the main reaction product. Finally comment all the results in the protocol!

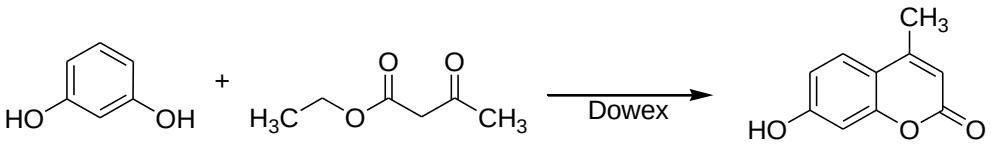
i) When the chromatographic separation is finished let the mobile phase flow off from the column, put a stopper with a drilled hole on the outflow of the column and put it on a suction flask. Connect the flask to a source of vacuum and let the air streaming through the silica gel until the silica gel is dry. Then put the silica gel into a bottle for chemical waste.

j) Pour all the remaining waste solutions containing toluene as well as toluene evaporated in the rotary vacuum evaporator into marked waste bottles!

Green synthesis of 4-methylumbelliferone

Coumarins are natural products occurring in a variety of plants, including those used as traditional herbal medicines. The physical and chemical properties of the coumarins have been exploited in a wealth of practical applications, ranging from cosmetics, sunscreens, flavorings, and laser dyes to pharmaceuticals, including well-known anticoagulants.
Umbelliferone, or 7-hydroxycoumarin, and a number of its methyl derivatives are found in plants of the family Umbelliferae, including carrots, parsley, cumin, and celery. Umbelliferones have recently found applications in fluorometric enzyme assays, anti-inflammatory agents, dyes, and fluorescent pH indicators.
The Pechmann condensation produces coumarins via the acid-catalyzed reaction of a phenol with a β-keto ester. Whereas high temperatures and extreme reagents such as H_2SO_4 and $POCl_3$ were originally used to effect the transformation, the reaction has been improved upon by the development of protocols involving recyclable, solid acid catalysts.

Reaction:



Procedure:
50 cm^3 Erlenmeyer flask or beaker is charged with 2.0 cm^3 of ethyl acetoacetate (ethyl 3-oxobutanoate), 1.6 g of resorcinol, and 2.0 g of Dowex 50WX12 beads. The flask is placed in a water bath on a hot plate. The reaction proceeds at a reasonable rate at temperatures 80–90 °C. The commencement of the reaction is indicated by gentle bubbling. The mixture is occasionally stirred with a glass rod until bubbling ceases and the mixture solidifies to a tan solid (typically 20-30 min). A small volume, 10 cm^3, of acetone is added to dissolve the solid and then the remaining beads are filtered off. The beads are rinsed with additional 2 portions of acetone (10 cm^3) and dried. The used catalyst is collected in dedicated container. The solution is evaporated with rotatory vacuum evaporator. The remaining crude product is dissolved in 4-6 cm^3 of hot ethanol. While heating, hot water is added until the solution becomes slightly cloudy and then the flask is removed from the hot bath and the mixture is allowed to cool slowly to room temperature. The white to off-white crystalline precipitate is isolated by vacuum filtration and is washed with water. The product is allowed to dry before determining the melting point (lit. 181–183 °C) and carrying out spectral analysis (IR).

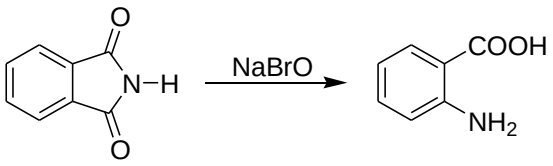
Additional questions:

1. Determine yield of the reaction.
2. Describe chemical structure of Dowex 50 ion-exchange resin.

3. Outline mechanism of the reaction.
4. Why can be the synthesis characterized by an adjective “green”?
5. Which of the reagents limits overall yield of the synthesis?
6. Which gas is released during the reaction as bubbles?

Synthesis of anthranilic acid

Reaction:



Procedure:

Weight 14 g of NaOH in 150cm^3 beaker and dissolve it in 80 cm^3 of water. Cool the solution to about −5 °C using ethanol-dry ice bath. Add 3,6 cm^3 of bromine dropwise at intensive stirring. Stir until bromine dissolves. Make sure that temperature of the mixture does not exceed 5 °C. Mix 10 g of ftalimide and 15 cm^3 of water in another 150 cm^3 beaker. Cool the suspension of ftalimide in the cooling bath. Then slowly transfer the solution of sodium hypobromite in water to the suspension of ftalimide at continuous stirring. Keep stirring of the mixture in cooling bath for 20 min after ftalimide dissolves. Rise the temperature to 80 °C, add 8 g of NaOH and held there for two minutes. Brought it back to room temperature using cold water. Transferred the mixture to a 1000cm^3 beaker and neutralized it with concentrated hydrochloric acid. The pH should be 7.0–7.5. Then add 10 cm^3 of acetic acid at intensive stirring. Remove precipitate by filtration and wash the crystals with small amount of cold water. Re-crystallize crude product from approximately 100 cm^3 of water using charcoal as an absorbent. The product is allowed to dry before determining the melting point.

Synthesis of potassium hydrogensulphate

Reaction:

Neutralization reactions are some of the most common ways for the preparation of salts. In aqueous solutions of acids and basis there takes place a dissociation to oxonium cations and hydroxide anions in a lesser (weak acids and bases) or in a greater degree (strong acids and bases). If an insoluble salt is not formed simultaneously then the most important equilibrium process in the resultant solution is determined by the ionic product of water ($Kw = [H_3O^+]\cdot[OH^-] = 10^{-14}$). That´s why the gist of the neutralization of some acid by a base is not the direct interaction for example K^+ with HSO_4^- but it is always a pairing H_3O^+ and OH^- in order to form two molecules of water so that the mentioned equilibrium between dissociated and undissociated water molecules is maintained. Even the heats of various neutralization reactions testify about it. They are practically identical (cca –57 kJ mol^{-1} at 25 °C) and correspond to the formation of water molecules from ions. Then we reach the desired salt only by its isolation from the aqueous solution, thus by crystallization after its concentrating, cooling or precipitating with an organic solvent in which is the salt poorly soluble.

The reactive base doesn´t have to be only a hydroxide necessarily, it can be some compound which provides OH^- ions only secondarily after its dissolution in water during the reaction with water. As an example we can name potassium carbonate which actually doesn´t contain hydroxide ions in its structure however OH^- will appear in the solution anyway due to a hydrolysis of CO_3^{2-} anions. Some similar examples of compounds, which generate OH^- during the reaction with water, are some alkaline oxides, ionic hydrides or organic bases.
The neutralization reactions are important also in a quantitative analytical chemistry where they are used in a volumetric analysis during an acid-base titrations. During the determination of acids concentration, it is used an aqueous NaOH solution with known molar concentration and from its demand we can then calculate a substance amount, respectively a molarity of a determined acid. The most important is to capture so-called equivalence point during the titration or the volume of NaOH solution which causes the exact equilibration of substance amounts of H_3O^+ and OH^- in a titration flask. We can determine the equivalency either visually – based on a change of colouration of acid-base indicator or electrochemically – with the help of pH-meter. But it is necessary to perceive that the equivalence point doesn´t have to necessarily correspond to the neutral solution after the titration (pH = 7) and it makes a difference if we titrate a weak acid or strong one. We come to the neutral solution in the equivalence point only during the determination of strong acids meanwhile during a titration of weak acids the resulting salts cause an increase of the pH due to a hydrolysis. With respect to the expected pH of the final solution it is necessary to choose the indicator during a visually controlled titration so that its change in colour should occur just close to this pH. In the case of polybasic acids there naturally exists several equivalence points corresponding the neutralization of acids into first, second or further stages.

We prepare the pure potassium hydrogensulphate by crystallization from solutions, which arise from the reaction of potassium hydroxide and potassium carbonate with surplus of sulfuric acid:

$$KOH + H_2SO_4 \rightarrow KHSO_4 + H_2O$$
$$K_2CO_3 + 2H_2SO_4 \rightarrow 2KHSO_4 + CO_2 + H_2O$$

Procedure:

We dissolve **15,0 g** of K_2CO_3 in **15 cm^3** of water in a 600 cm^3 beaker and while stirring we pour the twice of calculated amount of 60% H_2SO_4 solution in small portions. The content of the beaker strongly peddles during that and it heats up almost to boiling point. After complete reaction the solution reacts acidly. We pour it to another beaker (150 cm^3), we cool it down with water and then with the mixture of water + ice to the temperature of **0**–**2 °C**. We let the solution in the ice bath at least for **20 minutes**. We filter the precipitated $KHSO_4$ on the frit and after a thorough suction and a squeezing of the mother solution we pour the filtrate to a clean beaker for further treatment. Then we wash the $KHSO_4$ crystals with ice water gradually and with ethanol twice. With **disconnected vacuum pump** we pour such amount of a liquid on crystals that the height of its bar will be approximately equal to the height of a filter cake, we quickly stir the mixture with a stamen and we filter immediately the resulting solution off with the vacuum. We let the well suctioned $KHSO_4$ crystals dry in an open vessel, for example in a Petri dish, in a hot air oven at **100 °C**. To the mother solution, which we pour from a suction flask to a beaker before **washing $KHSO_4$ crystals**, we pour **80 cm^3** of ethanolwhile stirring and we precipitate a second fraction of $KHSO_4$ which we filter again, wash and dry but we won´t mix it with the first fraction.

Purity check:

We carry out the purity control of $KHSO_4$ by an alkalimetric titration of $KHSO_4$ solution with NaOH solution (c = 0,1 mol dm^{-3}). We weigh the sample of $KHSO_4$ on a weighting boat using an analytical balance we flush quantitavely the sample weight via a funnel into a 100 cm^3 volumetric flask with water from a wash bottle and we supply the solution in the flask to the mark with water. We close the volumetric flaks with a stopper and we mix up the solution inside. For an individual analysis we always pipette 20 cm^3 of the prepared solution and we titrate by NaOH solution (0,1 mol dm^{-3}) with phenolphtalein till a red-purple colour. We titrate it three times. We choose the sample weight so that the consumption of NaOH solution with a concentration of 0,1 mol dm^{-3} should be in the range of **15**–**20 cm^3** for the titration of 20 cm^3 $KHSO_4$ solution. All data and results write in the table.

Properties:

Potassium hydrogensulphate creates colourless crystals with a melting point of 210 °C. It is very well soluble in water; it is insoluble in ethanol.

Comment:

Carbonates applications:

We generally understand the reaction between K_2CO_3 and H_2SO_4 as the neutralization reaction of H_3O^+ cations, which are created by the dissociation of sulfuric acid, with OH^- anions, which are created by the hydrolysis of carbonate anion. On the other hand, we can also talk about the displacement of weak carbonic acid from its salt by strong sulfuric acid. Whereas we use the first description rather with regard to the resulting salt ($KHSO_4$) we can use the second alternative in the case that the centre of our focus is the preparation of the weak acid (H_2CO_3). Despite the formal site of description, the products are of course the same.

Carbonates solubility:

Alkali metal and Tl(I) carbonates are characterized by a significant solubility in water. Other metal carbonates including alkaline earth metal carbonates are slightly soluble. That´s why we can easily remove impurities by washing them with water and guarantee the purity of the starting reactant. For this reason, they are used even as an intermediate at binary substitutions (conversion methods for the preparation of salts - see the preparation of $CoCl_2 \cdot 6H_2O$).

Washing:

Note about the disconnected vacuum pump during the washing crystals on the frit has a considerable importance. Approach when a student pour water on the crystals on the frit without stirring, while vacuum pump is connected, is totally unsuitable especially in the case when the product is grossly crystalline and the frit is very porous. Then there takes place very fast suction of the pouring liquid and only a narrow column of a filter cake is washed. To make the washing really effective a solvent has to get into the whole volume of crystals. This can be ensured only with the disconnected pump and with stirring. In practise we can either disconnect a hose of a vacuum water pump from a suction flask, wash the product and then we can put the hose back and filter a solvent off or we can hold the frit with one hand over the flask while pump is connected to it and meanwhile we can wash a precipitate with the second hand and finally put the frit back into the neck of the suction flask. The second approach is probably preferable in cases when the precipitate is very well soluble in a washing solvent and every delay means significant loses of the yield.

Precipitation:

The precipitation with ethanol, to obtain the second fraction of $KHSO_4$, is relatively fast and often nearly a quantitative method for an isolation of the dissolved salt. It is a general separation method which can be used even for non-aqueous solutions and the precipitating substance also doesn´t have to be a salt. The choice of a precipitant depends on components of

the solution from which we want do the precipitation. The precipitant a, has to be miscible with the solution, b, doesn´t have to react with any component of the solution and has to precipitate the required product i.e. the product doesn´t have to be soluble in it, c, the precipitant should not to precipitate other side products from the solution (ideally). A simple mixing of the precipitant with the solution leads to the formation of very tiny crystals. If we require crystals which are more evolved it is necessary to slow down the process of a precipitant-solution mixing. We can achieve that by a slow diffusion of a liquid precipitant or by its vapour.

Additional questions:

1. Why is it necessary to wash $KHSO_4$ precipitate with ice water and ethanol?
2. Why is it necessary to use double the amount of H_2SO_4 compared the theoretical one?
3. How can we determine the precise concentration of NaOH volumetric solution and how the factor of solution is determined?
4. Draw the electron structural (Lewis) formula of SO_4^{2-} and CO_3^{2-}.
5. Determine the structure of SO_4^{2-} and CO_3^{2-} anions according to VSEPR model.
6. Cite examples of compounds which can create OH^- ions in water although they don´t contain them in their structure. Express the course of their reactions with water by chemical equations.
7. Write down the hydrolysis of hydrogencarbonate and carbonate anions with the help of chemical equations.
8. Arrange the following compounds according to the increasing acidity of their aqueous solution: H_2SO_4, K_2SO_4, $KHSO_4$, $KHSO_3$.
9. Draw titration curves for the titration of a strong acid with a strong base and of a weak acid with a weak acid.
10. Write down formulas for the calculation of pH of strong and weak acids and bases.
11. What properties does the solvent must have when we use it for the precipitation of substance from a solution? From the following liquids choose those which certainly couldn´t replace ethanol during the precipitating of $KHSO_4$ from its aqueous solution and justify it: acetone, hexane, dichloromethane, methanol.

Synthesis of boric acid

Reaction:

We prepare trihydrogenboric (orthoboric) acid by decomposition of sodium tetraborate $Na_2B_4O_7 \cdot 10H_2O$ (borax) with hydrochloric acid. This is the typical example of a displacement of a weak acid with stronger one.

$$Na_2B_4O_7 + 2HCl + 5H_2O \rightarrow 4H_3BO_3 + 2NaCl$$

Procedure:

We dissolve the required quantity of borax which is needed for the preparation of **30,0 g** H_3BO_3 in **60,0 cm^3** of hot water and under continuous stirring we pour a calculated amount of concentrated HCl solution to the formed solution which is heated to **100 °C**. Trihydrogenboric acid will crystallize by cooling an obtained solution with water and with an ice bath. We filter the crystalline product with a Büchner funnel and we squeeze thoroughly its mother solution on filter. We purify the obtained trihydrogenboric acid by a recrystallization from a saturated solution at **80 °C**. We put H_3BO_3 into a beaker we add **80 cm^3** of water and if all H_3BO_3 is not dissolved at the temperature of **80 °C** we add carefully more water with a wash bottle. If it´s necessary, we filter thus prepared saturated H_3BO_3 solution by a hot filtration funnel and we cool the filtrate down to the lowest possible temperature in an ice bath. We filter the recrystallized H_3BO_3 with a frit and again we thoroughly squeeze the mother solution from it with a glass rod with an expanded end. We wash it by **20 cm^3** of ethanol and we let an air flow through crystals on the frit for a few minutes. **We keep the product in a labelled bottle until next exercise for the synthesis of boric oxide and trimethyl borate!**

Properties:

H_3BO_3 forms a white transparent flaky crystal with some pearly shine which are greasy to touch. It is slightly soluble in a cold water, i tis well soluble in a hot water, its aqueous solutions have a mild antiseptic effects.

Comment:

Trihydrogenboric acid is a final product of a majority of boron compounds hydrolysis. It is a very weak monobasic acid (pK_a = 9.25) which acts as an acceptor of hydroxide anion OH^-:

$$B(OH)_3 + 2H_2O \leftrightarrow H_3O^+ + B(OH)_4^-$$

The acidity of its aqueous solutions significantly increases by complexation (formation of chelates) with polyhydric alcohols, for example with glycerine, mannitol, etc. It allows its alkalimetry determination (pK_a of chelate with mannitol is 5.15).

Additional questions:

1. Draw a structural formula of an anion which is located in borax.
2. What are the borax pearls?

3. How does an aqueous borax solution react (acidly, alkaline, neutrally)? Give your reasons.
4. Cite which other acids we usually prepare through the displacement with stronger acids from its salts and write down with equations some particular preparation methods.
5. Explain why we wash the obtained trihydrogenboric acid with ethanol at the end of its preparation.
6. What impurities can we find in the prepared trihydrogenboric acid?
7. Cite proper procedure of compound washing with a frit, describe individual steps.
8. What is the final product of the reaction between phosphorous pentoxide and water?
9. Write down the reaction between lithium oxide and water by a chemical equation.
10. Determine the type of hybridization of a boron atom in H_3BO_3.