# Lokaskýrsla til Kennslumálasjóðs vegna styrks

Kennslumálasjóður úthlutaði verkefninu *Þróun og nútímavæðing verklegra æfinga í efnafræði* styrk eftir B-leið í úthlutun sinni 2023.
Styrkféð var notað til að ráða sumarstarfsmann til að vinna að endurskoðun verklegu æfinganna í verklegu lífrænu námskeiðum námsbrautarinnar. Sumarstarfið var auglýst meðal nemenda sem höfðu lokið þessum verklegu námskeiðum á síðustliðnum 2 skólaárum. Sigrún Elísa Eyjólfsdóttir var ráðinn eftir yfirferð umsókna.

Vinna Sigrúnar fólst fyrst og fremst í eftirfarandi:

- Yfirfara núverandi æfingar og veita endurgjöf um hvaða æfingar mætti helst skipta út, t.d. ef þær voru of langar miðað við tíma æfinganna í stundatöflu, eða óþarfa endurtekning á kostnað annarra atriða sem mætti þjálfa betur í æfingunum.
- Leita að hugmyndum að nýjum æfingum, t.d. í kennslutímaritum (*Journal of Chemical Education*) og kennsluheftum annarra háskóla fyrir samsvarandi námskeið sem kennarar námsbrautar hafa aðgang að og heimasíðum annarra skóla.
- Prófa efnilegar æfingar til að sjá hversu praktískar æfingarnar væru.
- Taka saman niðurstöðurnar í skýrslu fyrir námsbrautina.

Benjamín Ragnar, ábyrgðaraðili verkefnis, var Sigrúnu innan handar sem leiðbeinandi yfir sumarið.

Hér á eftir fylgir skýrslan frá Sigrúnu Elísu. Kennarar námskeiðanna *Verkleg lífræn efnafræði 1* og *Verkleg lífræn efnafræði 2* hafa þessa skýrslu nú undir höndum og munu vinna að því að prófa að skipta út æfingum næstu árin út frá þessum tillögum, en líklegt er að þær breytingar muni taka nokkur ár í viðbót þar sem 1-2 æfingum er skipt út á ári til að sjá hægt og rólega hvernig æfingarnar ganga í hópastærðunum sem eru í þessum námskeiðum, og til að geta tryggt að það sé til staðar reynsla af meirihluta æfinganna hverju sinni, frekar en að skipta út öllu í einu.

Virðingarfyllst,

Benjamín R. S.

Benjamín Ragnar Sveinbjörnsson
Ábyrgðaraðili verkefnis

# Endurskoðun á verkleg lífræn efnafræði 1 & 2 námskeið

***Verkleg lífræn efnafræði 1 núna:***

- Æfing nr. 1: Endurkristöllun og ákvörðun á bræðslumarki
- Æfing nr. 2: Útdráttur, eiming og ákvörðun á suðumarki
- Æfing nr. 3: Þunnlagsskiljun (TLC)
- Æfing nr. 4: Brómun límonens
- Æfing nr. 5: Skiptihvarf (alkóhól => alkyl halíð)
- Æfing nr. 6: Samkeppni í skiptihvarfi (Cl vs Br)
- Æfing nr. 7: Diels-Alder + NMR
- Æfing nr. 8: Diels-Alder + NMR
- Æfing nr. 9: NMR (óþekkt alkóhól => ester)

***Tillaga að breytingu fyrir verklegu lífrænni efnafræði 1:***

- Æfing nr. 1: Endurkristöllun og ákvörðun á bræðslumarki
- Æfing nr. 2: Útdráttur, eiming og ákvörðun á suðumarki
- Æfing nr. 3: NBS hvarf (TLC æfing) *

  eða
- Æfing nr. 3: Samanburður á hreinleika efnis (endurkristöllun vs. mini-súla) *
- Æfing nr. 4: Brómun límonens
- Æfing nr. 5: Efnasmíði á aspiríni og NMR *
- Æfing nr. 6: Samkeppni í skiptihvarfi (Cl vs Br)
- Æfing nr. 7: Diels-Alder + NMR
- Æfing nr. 8: Diels-Alder + NMR
- Æfing nr. 9: NMR (óþekkt alkóhól => ester)

* Uppástungur á nýjum æfingum / tillaga að breytingu

**Athugasemdir**:

1. Persónulega fannst mér æfing nr. 3 (sem er núna í gangi) ekki kenna almennilega á TLC og í þeirri æfingu þarf að notast við 2,4-DNP afleiður sem er ekki kennt fyrr en í verklegri lífrænni efnafræði 2. Þess vegna gæti verið sniðugt að breyta æfingu 3.

***Verkleg lífræn efnafræði 2 núna:***

- Æfing 1: Friedel-Crafts alkylun
    - Hópur A: Phenylbenzen + tert-butyl chloride
    - Hópur B: Benzen + tert-butyl chloride
    - Hópur C: *p*-Dimethoxybenzen + tert-butyl alcohol

- Æfing 2: Oxun (alkóhól => ketón) + 2,4-DNP afleiða
    - Hópur A: Cyclohexanól
    - Hópur B: 4-metýlcyclohexanól
    - Hópur C: 2-metýlcyclohexanól

- Æfing 3:
    - Hópur A: Aldól þétting (val um 3 mismunandi aldehýð)
    - Hópur B: Beckmann umröðun oxíms
    - Hópur C: Claisen-Schmidt þétting

- Æfing 4:
    - Hópur A: Þétting, oxun og afoxun *
    - Hópur B: Beckmann umröðun oxíms
    - Hópur C: Sýruafleiður (klóríð og amíð)

- Æfing 5:
    - Hópur A: Nítrun og estrun **
    - Hópur B: Oxun og estrun **
    - Hópur C: Nítrun og vatnsrof **

- Æfing 6: Hvarfgirni arómata við brómun
    - Hópur A: Anilín
    - Hópur B: Anisól
    - Hópur C: Acetanilíð

- Æfing 7:
    - Hópur A: Sýruafleiður og Hofmann umröðun ***
    - Hópur B: Sýruafleiður og Hofmann umröðun
    - Hópur C: Sýruafleiður og Hofmann umröðun ***

- Æfing 8: Efnagreining á óþekktri blöndu

**Athugasemdir**:

* Æfing sem er þó nokkuð löng miðað við athugasemdum frá fyrri nemendum (fólk að klára um kl. 19)

** Æfing sem hefur ekki getað náð að klára að fullu vegna tímaraskana (gera bara fyrri hlutann af æfingunni) og einnig hefur orðið á því að fólk sé að mæta aukalega til að gera mælingar á myndefni.

*** Hér gera allir sömu æfinguna (7B) því æfingar 7A og 7C í verklega heftinu eru tímafrekar.

***Tillaga að breytingu fyrir verklegu lífrænni efnafræði 2:***

- Æfing 1: Friedel-Crafts alkylun
    - Hópur A: Phenylbenzen + tert-butyl chloride
    - Hópur B: Benzen + tert-butyl chloride

    - Hópur C: *p*-Dimethoxybenzen + tert-butyl alcohol

- Æfing 2: Oxun (alkóhól => ketón) + 2,4-DNP afleiða
    - Hópur A: Cyclohexanól
    - Hópur B: 4-metýlcyclohexanól
    - Hópur C: 2-metýlcyclohexanól

- Æfing 3:
    - Hópur A: Aldól þétting (val um 3 mismunandi aldehýð)
    - Hópur B: Beckmann umröðun oxíms
    - Hópur C: Claisen-Schmidt þétting

- Æfing 4:
    - Hópur A: Efnasmíði á phenacetin **
    - Hópur B: Beckmann umröðun oxíms
    - Hópur C: Sýruafleiður (klóríð og amíð)

- Æfing 5: Williamson-Ether efnasmíði og NMR **
    - Hópur A: 1-bromopentane
    - Hópur B: 1-bromo-3-methylbutane
    - Hópur C: 1-bromobutane

- Æfing 6: Hvarfgirni arómata við brómun
    - Hópur A: Anilín
    - Hópur B: Anisól
    - Hópur C: Acetanilíð

- Æfing 7:
    - Hópur A: Sandmeyer hvarf **
    - Hópur B: Sýruafleiður og Hofmann umröðun
    - Hópur C: Wolff-Kishner afoxun **

- Æfing 8: Efnagreining á óþekktri blöndu

** Uppástungur á nýjum æfingum / tillaga að breytingu

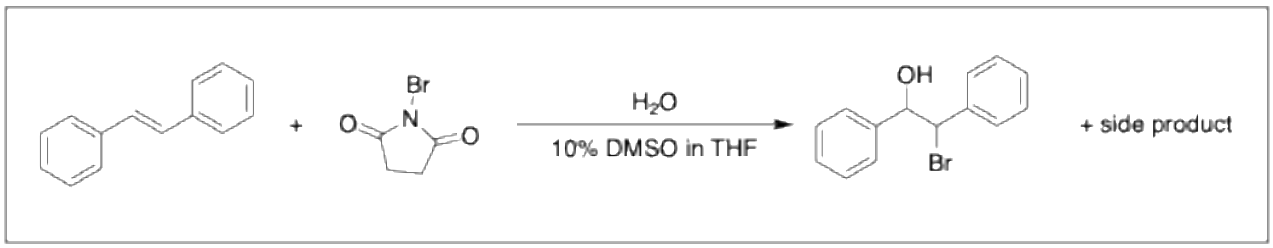
**Athugasemdir:**

1. Mér myndi finnast sniðugt að bæta við sérstaklega æfingu 5 (bæði TLC + column chromatography æfing) til að fá smá innsýn inn í verklegri lífrænni efnafræði 3 og til að fá upprifjun frá verklegri lífrænni efnafræði 1 varðandi TLC þar sem það var aldrei tekið fyrir í verklegri lífrænni efnafræði nema einu sinni. Einnig sniðugt að fá NMR æfingu líka í þessum áfanga þar sem það er ekkert NMR tekið fyrir nema í verklegri lífrænni 1 (en það er svo sem tekið fyrir í efnagreiningartækni en kannski gaman að taka það líka fyrir hér)

## Hugmyndir að nýjum æfingum

**NBS hvarf (TLC æfing)**

- Hugmynd að æfingu 3 fyrir verklegri lífrænni efnafræði 1
- Grein: https://pubs.acs.org/doi/10.1021/acs.jchemed.9b00256




Working in small groups, the class will collaboratively determine the best TLC conditions to separate compounds on a TLC plate (7.5 x 2.5 cm). The compounds you will be working with are the starting materials and a known byproduct for the reaction you will run. Working out the TLC conditions before running a reaction is common practice among organic chemists. Knowing which TLC spots are the starting materials and byproducts helps us to better understand how the reaction is progressing and when to stop a reaction!

**Determination of a suitable developing solvent system:**

1. Working in your small group (3-4 people), obtain the following samples for spotting on TLC plates:
    a. *trans*-stilbene
    b. *N*-bromosuccinimide (NBS)
    c. Succinimide
2. Figure out which TLC developing solvent systems your small group will be responsible for testing. Each small group will test two TLC developing solvent systems (you can allocate yourselves to group 1 to 4, see **Table 1**).
3. Set up two TLC chambers (one for each solvent system) with filter paper and the assigned developing solvent.
4. Prepare two TLC plates with 3 tick marks along the baseline. Carefully spot *trans*-stilbene, N-bromosuccinimide and succinimide at different tick marks on the baseline. Make sure you label which tick mark contains which compound, under the baseline with abbreviations.
5. Run the TLC plates in your group's developing solvents.
6. Visualize the TLC plates under UV light and trace each spot you see with a pencil.
7. Visualize the TLC plates using iodine staining and trace the new spots that have appeared (if any).
8. Calculate the $R_f$ value for each spot in each lane.
9. Record your data with the class and compare your results to determine the best developing solvent system (*Hint*: You want your compounds to have different $R_f$ values and the best separation)

P.S. Á bls. 8 í þessu skjali er stuttur viðauki hvernig TLC er gert þannig fólk viti hvað *TLC chamber* þýðir t.d. en ég get líka endurorðað þetta.

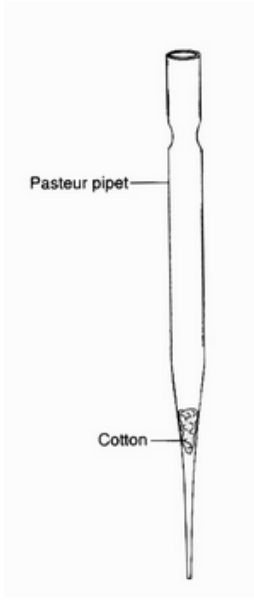
Once you have determined the appropriate TLC conditions, you can now prepare to run your reaction.

**Procedure**:
Before starting the reaction, prepare a TLC plate and label it with 3 tick marks (''SM'' for starting material, 1 min and 30 min) as shown in the figure to the right.


Weigh out *trans*-stilbene (0.2 mmol) and place it into a 10 mL round bottom flask. Add 0.1 mL of deionized water into 3 mL of the 10% DMSO/THF stock solution. Add this solution to the round bottom flask. Stir until the trans-stilbene dissolves. Spot the dissolved trans-stilbene on the SM mark on your TLC plate.

Add NBS (0.2 mmol) to the round bottom flask and continue stirring (note any color changes). After adding the NBS, wait 1 min. Then, spot the reaction on your TLC plate for the 1 min. mark. Allow the reaction to run for 30 min. Spot the reaction mixture on your TLC plate after 30 min. Run the TLC plate in the solvent system you determined, then visualize the TLC spots using both UV light and iodine staining. Draw what you see on the TLC plate and include it on your report, as well as the calculated $R_f$ values of each spot (**Note 1**).

*Purification: Column Chromatography*




As you will probably see on the TLC plate, more than one product is in the reaction mixture after 30 minutes. Therefore you will need to purify it to obtain the desired final product which we can do by setting up a silica column. This can be done by taking a long Pasteur pipette and lightly push a small ball of cotton into the base of the pipette (shown in the figure to the right). This pipette will serve as your column. Take your pipette to the fume hood and add silica to about two-thirds of the pipette (**Note 2**). Carefully, clamp the pipette to a stand so the pipette is positioned vertically. Next, make up a solution of hexane/ethyl acetate (1:19). Using a fresh pipette, transfer some of this eluent to your column and allow the eluent to slowly pass through the column collecting the liquid in a beaker. Make sure to never let the column run dry. Once most of the eluent has eluted through the column (again, make sure the silica gel does not run dry), place a clean test tube under the tip of the pipette. Add your reaction mixture to the surface of the silica in the pipette (without disturbing the silica gel). Pass all the reaction mixture through the column and collect approximately 2 mL of the eluent in numbered test tubes (This is also known as 'collecting fractions' in column chromatography) (**Note 3**). Collect ~2 mL fractions in at least 10 separate test tubes. Once all reaction mixture has passed through, add 3 mL of hexane/ethyl acetate (1:19) to make sure all the product has passed through the silica.

On a TLC plate (you may need 2 plates), spot all collected fractions to determine if you have collected the desired final product from the column and in which fractions it is contained in. Develop the TLC plates using the same eluent as last time and visualize with a UV light and iodine staining. Combine all fractions that contain only the desired final product and remove the solvent by evaporation. Record the weight of the compound and calculate the yield. Make sure to record your TLC plates in your lab report from the column.

**Table 1**: Group assignments for testing different developing solvent systems (**Note 4**)

| Group number | Developing solvent system | |
|---|---|---|
| 1 | hexane/ethyl acetate (2:3) | hexane/ethyl acetate (3:2) |
| 2 | hexane/ethyl acetate (3:7) | hexane/ethyl acetate (7:3) |
| 3 | hexane/ethyl acetate (4:1) | hexane/ethyl acetate (1:4) |
| 4 | hexane/ethyl acetate (1:1) | hexane/ethyl acetate (1:9) |

**Notes**:

1. For spots that have the same $R_f$ and appear in more than one lane, you only need to calculate and label the $R_f$ value once.
2. Always work in a fume hood when handling with silica as it is harmful when inhaled (!). Handle with caution.
3. The numbered test tubes, or the fractions collected from the column, are labelled as 1 (the first fraction collected from the column), 2 (the second fraction collected from the column), and so on.
4. To explain the abbrevations: for example the 2:3 in hexane/ethyl acetate (2:3) means 5 parts total (2 + 3 = 5). This implies that there are 2 parts of hexane and 3 parts of ethyl acetate in the total solvent mixture. For example, if you need 50 mL of eluent, you would need 20 mL of hexane and 30 mL of ethyl acetate.

**Spurningar:**

1. Which TLC developing solvent condition was best for this reaction according to the data from the class? Why did you choose this TLC developing solvent condition?
2. Skoðaðu TLC plötuna hjá þér. Hvaða efni eru til staðar í ‘’SM’’, ‘’1 min’’ og ‘’30 min’’ markinu á TLC plötunni?
3. Hvaða hliðarmyndefni myndaðist í hvarfinu? Geturu séð það á TLC plötunni? Ef já, hvað er $R_f$ gildi þess?

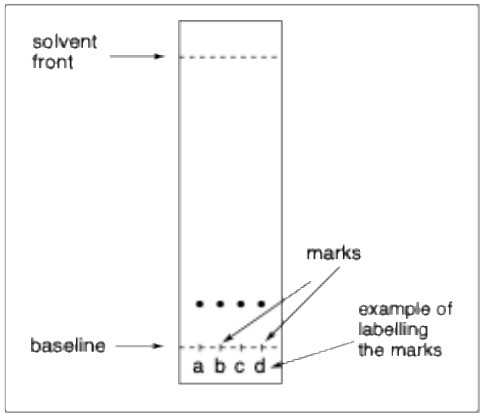
**Athugasemd**:

1. NBS hvarfið er tekið fyrir í bóklega hlutanum í lífrænni efnafræði 1 og þess vegna gæti þetta hvarf verið sniðugt að taka fyrir í verklega hlutanum. Nemendurnir myndu læra hvernig TLC plötur eru notaðar í lífrænum efnasmíðum og hvernig það er notað til að fylgjast með efnahvarfi, sem er vanalega ekki kennt nema í verklegri lífrænni efnafræði 3.

## Viðauki fyrir NBS æfinguna

**Technique of TLC**

1. To perform a TLC, you will need the following items: a small beaker (50-100 mL), watch glass, TLC spotter, filter paper, silica-coated TLC plates, pencil, ruler and tweezers.
2. Slide filter paper into the beaker so it is flat against the wall. Adding filter paper minimizes evaporation of the mobile phase (the developing solvent) during the procedure. Measure an appropriate amount of the developing solvent and pour the developing solvent into the beaker. You do not need to be precise with the volume added to the beaker, as it will not affect the results as long as the top of the developing solvent is BELOW where the samples are spotted on your TLC plate (i.e. the baseline must be above the developing solvent once the TLC plate is placed into the beaker). Ensure the filter paper is completely moistened and place the watch glass over the beaker.




3. To prepare the TLC plate, face the silica-coated surface up. Use a pencil to draw a horizontal line (this is the baseline) about 2 cm from the bottom of the plate. Mark no more than 4, roughly evenly spaced, small marks on the baseline; these marks are where you spot the samples. Label these small marks below the baseline with the appropriate abbreviations. Draw another horizontal line 5 cm above the baseline (7 cm from the bottom of the plate). This second line will serve to mark your solvent front.
    a. Most of the time, the sample (if solid) must be diluted in a solvent such as ethyl acetate, hexane, or dichloromethane before spotting onto the TLC plate. If a volatile solvent is used, the spotted solvent evaporates within a few seconds of spotting and giving no results on the TLC.
4. Once the plate has been spotted, use tweezers to place the plate in the beaker. **Make sure the developing solvent level is below the baseline**. Place the watch glass over the beaker and wait until the developing solvent reaches the line that marks the solvent front. At this point, remove the TLC plate from the beaker using tweezers.
5. The spots on the TLC plate can be visualized in many ways, for example using UV light or iodine staining. Use a pencil to draw a circle around each spot you see when using these visualizations.
6. The retention factor ($R_f$) can then be calculated once the spots have been drawn with the following equation:

$$R_f = \frac{Distance\ traveled\ by\ the\ compound\ (X)}{Distance\ traveled\ by\ the\ solvent\ (Y)}$$

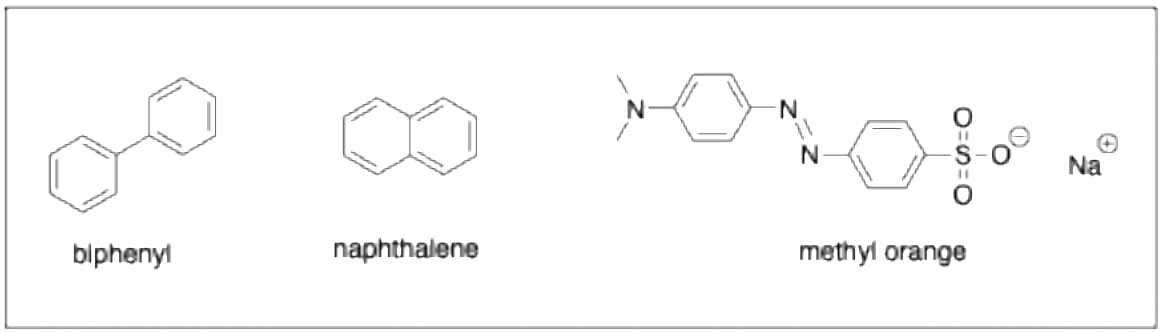
where X is the distance from the baseline to the center of the spot. If the compound appears as a streak rather than a round spot, measure to where the spot signal is densest (darkest in color). Y is the distance from the baseline to the solvent front. The $R_f$ value should always be between 0 – 1.

**Troubleshooting tips for TLC:**

1. **The spots are too big**: After developing your plate, if the spots are too big (e.g. running into other spots or forming a long streak), you will need to dilute your sample and run the TLC again.
2. **You don't see any spots**: There are several reasons for this. (1) Your sample is too dilute. (2) The visualization method is not appropriate. (3) The baseline was submerged below the developing solvent resulting in dissolution of your sample.
3. **The solvent ran to the top of the plate**: The $R_f$ values will be inaccurate, so you will need to run a new TLC plate.

**Samanburður á hreinleika efnis (endurkristöllun vs. aðskiljun efna með súlu)**

- Hugmynd að æfingu 3 fyrir verklegri lífrænni efnafræði 1
- Grein: https://pubs.acs.org/doi/10.1021/ed101039m




In this exercise, you will be handed a sample that contains a non-polar organic chemical compound (either biphenyl or naphthalene) mixed with a polar organic dye (methyl orange). Ask your teacher which non-polar compound you received. You will do a comparative analysis on different purification methods, between recrystallization and column chromatography by comparing the melting points of the purified products (as well as the crude sample before recrystallization).

**Procedure**:

**1. Recrystallization analysis**

First, you will require five test tubes. Knowing which non-polar compound you have, determine the solubility of the pure compound (not the sample mixture you were handed) using the solvents listed below, where each test tube contains a different solvent.

Methanol Acetone Dichloromethane Toluene Hexane

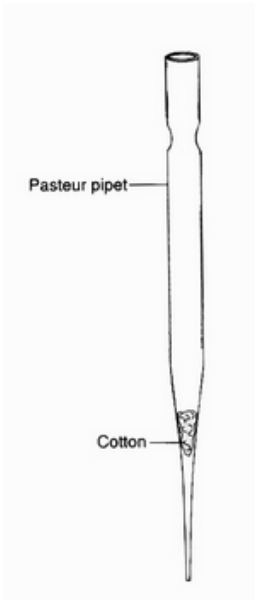
Place about 10 mg of the pure non-polar component into each test tube and then add a few drops of each solvent into the corresponding test tube. Record your observations for the solubility of the compound in room temperature and under heating. The aim is to find a solvent that will not dissolve your non-polar compound at room temperature, but will dissolve when hot. The suitable solvent will then be used to recrystallize your product.

Next, weigh and transfer approximately 50 mg of your sample mixture to an Erlenmeyer flask and record the amount of the sample you used. Keep the rest of the sample for later. Over a steam bath, slowly add the solvent which gave the best results for recrystallization until no more solid dissolves. Remove the dye by vacuum filtration into a *preweighed* side arm flask. Let the vacuum run until all the solvent has evaporated from the side arm flask. Record the weight of the crude non-polar compound in the filter flask. Recrystallize the non-polar compound in the filter flask, prepare a hot saturated solution by adding a minimum amount of hot methanol *dropwise* until all the solid has dissolved. Swirl the flask over the heat source with one hand while slowly adding the hot solvent using the other hand. When all the solid has dissolved, remove the solution from the steam bath, allowing the hot saturated solution to cool to room temperature. Then place the flask into an ice bath and let the crystals form. Collect the crystals by vacuum filtration then using ice-cold methanol rinse the flask and wash the crystals. Record the weight of the dried crystals. Measure the melting point of the crystals once dried.

## 2. Column chromatography analysis

Set up two clean, dry test tubes and label them as 'Crude' and 'Recrystallized compound'. Transfer a *small* amount (e.g. the tip of a spatula) of your recrystallized sample to the appropriately labelled test tube. Add 1 mL of dichloromethane and shake to dissolve. Next place a small amount of crude compound into the second labelled test tube and add 1 mL of dichloromethane to dissolve.

On a silica TLC plate, draw a baseline and mark 2 positions on the baseline for the 'Crude' and 'Recrystallized compound'. Spot each of the solutions above onto the corresponding position on the TLC plate. Use hexane:ethyl acetate (4:1) (**Note 1**) as the eluent to develop the TLC plate and then visualize it under a UV lamp. Draw up all the spots you see under the UV light on the TLC plate with a pencil. Make sure to draw up the TLC plate and record the $R_f$ values for each spot you see for your report.




Next take a long Pasteur pipette and lightly push a small ball of cotton into the base of the pipette, see figure to the right (**Note 2**). This pipette will serve as your column. Take your pipette to the fume hood and add silica to about two-thirds of the pipette (**Note 3**). Carefully, clamp the pipette to a stand so the pipette is positioned vertically. In a 10 mL graduated cylinder, make up a 4:1 solution of hexane:ethyl acetate. Using a fresh pipette, transfer some of this eluent to your column and allow the eluent to slowly pass through the column (*make sure the column doesn't run dry*). Place a clean test tube under the tip of the column to collect the eluent that passes through. Once most of the eluent has eluted through the column, add 50 mg of your sample mixture (dissolved in a minimum amount of acetone, about 2 drops) to the surface of the silica in the pipette (**Note 4**). Pass the dissolved sample mixture through the column and collect approximately 1 mL of the eluent in numbered test tubes (This is also known as 'collecting fractions' in column chromatography) (**Note 5**). Collect 1 mL fractions until a colored band can be observed in the middle of the pipette column (collect at least 3 fractions in 3 separate test tubes).

On a TLC plate, spot all 3 of these fractions alongside the crude sample mixture and the previously recrystallized sample to determine if you have collected the pure non-polar compound from the column and in which fraction it is contained in. Develop the TLC plate using the same eluent as last time and visualize with a UV lamp. Combine the fractions that contain the pure non-polar compound and remove the solvent by evaporation. Transfer the dried, pure compound to a pre-weighed watch glass. Record the weight of the dried compound and measure the melting point.

Determine the melting points for the following samples and assess the purity of the samples using melting point data:

a. The original sample mixture (mixture of non-polar compound and methyl orange)
b. The recrystallized compound
c. The compound purified by column chromatography

**Notes**:

1. The 4:1 in *hexane/ethyl acetate (4:1)* means 5 parts total (4 + 1 = 5). This implies that there are 4 parts of hexane and 1 part of ethyl acetate in the total solvent mixture. For example, if you need 50 mL of eluent, you would need 40 mL of hexane and 10 mL of ethyl acetate.

2. Make sure the cotton wool stays in place; we do not want the cotton wool to be too tight or too loose at the bottom of the pipette.
3. Always work in a fume hood when handling with silica as it is harmful when inhaled (!). Handle with caution.
4. Due to acetone's polarity, adding *too much* can damage the column. So make sure to add as little as possible for it to dissolve, 2-3 drops of acetone should do the trick.
5. The numbered test tubes, or the fractions collected from the column, are labelled as 1 (the first fraction collected from the column), 2 (the second fraction collected from the column), and so on.

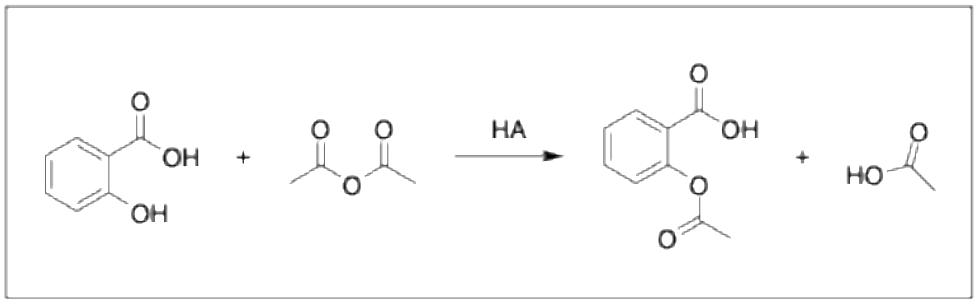
| **Compound** | **Melting point (°C)** |
|---|---|
| Biphenyl | 68 – 70 |
| Napthalene | 80 – 82 |

**Athugasemd:**

1. Kennari afhendir ca 700 mg af óskautaða efninu (biphenyl eða napthalene) og 10 mg af methyl orange litvísinum (þarf ekki of mikið magn fyrir þessa æfingu)
    a. Gæti verið sniðugt að láta nemendurna vita fyrirfram hvaða efni þau eru með (biphenyl eða naphthalene) en gæti líka verið skemmtilegt ef þau fá ekki að vita það. En það gæti kannski verið smá flókið þegar reynt er að ákvarða besta leysinn fyrir endurkristöllunina?
2. Mér finnst þessi æfing góð þar sem það kynnir nemendum fyrir column chromatography sem er ekki sérstaklega kynnt nema í verklegri lífrænni efnafræði 3.

**Efnasmíði á aspiríni og NMR**

- Hugmynd að æfingu 5 fyrir verklegri lífrænni efnafræði 1
- Fengið úr hefti Pomona College: Organic Chemistry Laboratory Manual




**Procedure:**

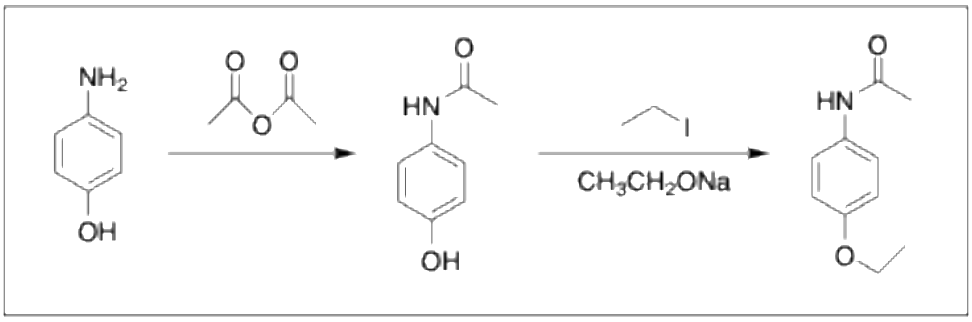
Place 5 g (0.363 mol) of salicylic acid (o-hydroxybenzoic acid) and 7.5 g (7.0 mL, 0.074 mol) of acetic anhydride in a small conical flask, add 3 drops of concentrated sulphuric acid and rotate the flask in order to secure thorough mixing. Warm on a water bath to about 50-60 °C, stirring with a thermometer (carefully!) for about 15 minutes. Allow the mixture to cool and stir occasionally. Add 75 mL of water, stir well and filter at the pump. Dissolve the solid in about 15 mL of hot ethanol and pour the solution into about 37.5 mL of warm water: if a solid separates at this point, warm the mixture until solution is complete and then allow the clear solution to cool slowly. Beautiful needle-like crystals will separate. The air-dried crude product may also be recrystallized from ether-light petroleum (b.p. 40-60 °C).

Acetylsalicylic acid (aspirin) decomposes when heated and does not possess a true, clearly defined m.p. Decomposition points varying from 128 to 135 °C have been recorded: a value of 129-133 °C is obtained on an electric hot plate. Some decomposition may occur if the compound is recrystallised from a solvent of high boiling point or if the boiling period during recrystallization is unduly prolonged.

Collect both a $^{1}H$ NMR spectrum for both the crystallized product and the starting material, salicylic acid, to compare the two spectra for your lab report.

**Efnasmíði á phenacetin**

- Hugmynd að æfingu 4A fyrir verklegri lífrænni efnafræði 2
- Æfing tekin úr eftirfarandi bók: https://books.google.is/books?hl=en&lr=&id=-Or4DwAAQBAJ&oi=fnd&pg=PR1&ots=7KGqj9Gej-&sig=5dzDPzoG2HOXk7vmLwPbvhINncI&redir_esc=y#v=onepage&q=wolff-kishner&f=false




**Procedure**:

Synthesis of paracetamol

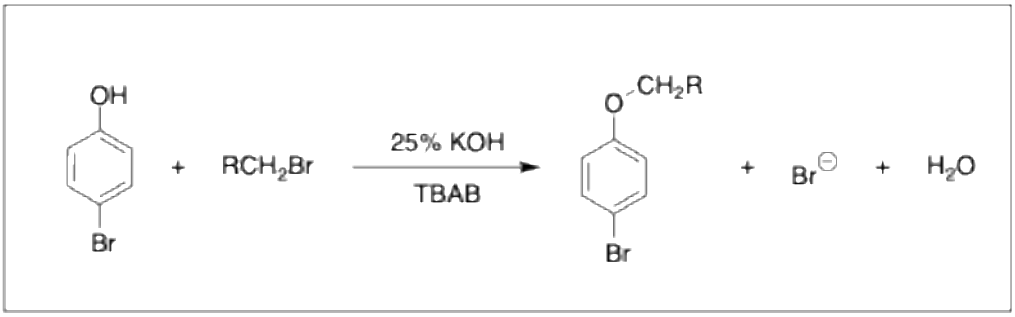
Add *p*-aminophenol (2.0 g, 18.32 mmol), acetic anhydride (2.2 mL, 23.28 mmol) and water (10 mL) to a 50 mL Erlenmeyer flask. Place the flask in a water bath and heat the solution near the boiling point for 20 min. Stir the mixture regularly, using a glass rod, until the complete dissolution of the *p*-aminophenol. Once dissolved, continue heating for a further 10 min. Cool the flask in an ice bath for 10 min. and watch the formation of paracetamol crystals. Filter out the solid using vacuum filtration. Use small amounts of cold water to help remove any residual product from the flask and to wash the product. Recrystallize the product from water. Place the product in a flask, add water (10 mL) and heat in a heating plate until the complete dissolution of the product. Remove the flask and allow it to cool slowly to room temperature. Place the flask in an ice bath for 15 min and collect the crystals by filtration. Dry the product in an oven and measure the weight afterwards. Make sure to take aside a small sample of the dried crystals for melting point analysis later on.

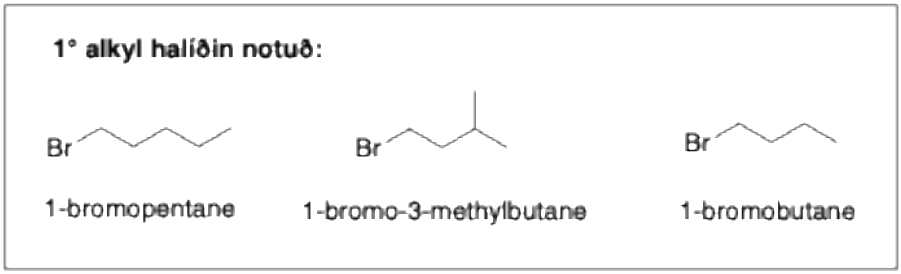
Synthesis of phenacetin

While the product is drying, place ethanol (10 mL) in a 50 mL round-bottom flask and carefully add metallic sodium (0.275 g, 11.96 mmol) and heat the reaction mixture under reflux for 15 min. until the complete consumption of the sodium. Cool the flask to room temperature. Add paracetamol (1.7 g, 11.24 mmol) and ethyl iodide (1.4 mL, 17.41 mmol) drop by drop over 1 min. Heat the reaction mixture under reflux for 80 minutes. Cool the flask to room temperature, add 10 mL of water and place it in an ice bath. Watch the formation of phenacetin crystals. Filter out the crystals using vacuum filtration. Use small amounts of cold water to help remove any residual product from the flask and to wash the product with cold water. Once the product is dried, weigh it and calculate the yield. Record the melting point.

**Williamson-Ether efnasmíði og NMR**

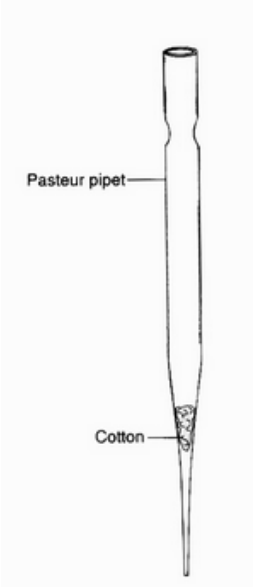
- Hugmynd að æfingu 5 fyrir verklegri lífrænni efnafræði 2 fyrir hópa A, B og C
- Grein: https://pubs.acs.org/doi/10.1021/acs.jchemed.9b00503




Í þessari æfingu fáið þið afhent óþekkt alkyl halíð. Þegar búið er að hreinsa lokamyndefnið er tekið $^{1}$H NMR róf af því og út frá rófinu er hægt að finna út hvaða halíð var afhent ykkur!

**Procedure:**
Add 346 mg of 4-bromo-phenol, 712 mg of 25% aqueous KOH and a magnet to a small round bottom flask. Add 290 mg of tetrabutylammonium bromide (TBAB) to the flask and allow it to dissolve while spinning. Add 302 mg of your unknown alkyl halide to the flask. Reflux the solution for 60 minutes at ~100 °C. After the reaction is complete, allow to cool for about 10 minutes to room temperature. Cool the flask further in an ice bath for 2 minutes. Remove the magnet and rinse the magnet with 1-2 mL diethyl ether into the flask. Add 1-2 mL distilled water to the flask, and separate the resulting aqueous layer. Extract the aqueous layer with 2 mL of diethyl ether. Combine the ether extract and organic contents of the flask into another flask. Wash the combined ether layers three times with 2 mL of 5% aqueous KOH, setting aside the aqueous layer after each wash. Dry the ether layer with sodium sulfate.




To isolate the final product, a Pasteur pipette column will be used. To prepare the column, insert a small amount of cotton through the top of the pipette and push it through with a wire until the pipette is plugged (see figure to the right). Fill about 75% of the pipette with silica gel (**Note 1**). Secure the pipette with a small clamp, positioning the pipette vertically. Before adding your product mixture into the pipette, add a steady amount of methylene chloride through the top of the pipette using a second, clean pipette. It is crucial that the methylene chloride is continuously added until you are ready to use the plug. This plug (the silica gel) must not be allowed to be dry (**Note 2**). When ready to isolate your product, add your product mixture into the plug using a clean pipette. Once all of your product mixture is added to the plug, add 2 mL of dichloromethane to the plug after all the product mixture has been added to ensure all product is collected into a clear, pre-weighed round-bottom flask.

Carefully concentrate your product using rotary evaporation. While concentrating the sample, spot 4-bromophenol dissolved in DCM and your alkyl bromide onto a TLC plate, leaving room for a third spot for your final concentrated product. After the solvent has been removed, determine the mass of your final product. Afterwards, spot the TLC plate with the final purified product and run the plate in DCM. Visualize the TLC plate using a UV light. Collect a $^{1}$H NMR spectrum of your sample and determine the unknown alkyl halide.

**Notes**:

1. Always work in a fume hood when handling with silica as it is harmful when inhaled (!). Handle with caution.
2. You can recycle the methylene chloride that is being used to pack the plug by collecting all liquid that runs down the pipette in a small beaker and adding it back into the plug until you are ready to use it.

**Spurningar**

1. Why are we using TBAB in this experiment? What does it do?

**Athugasemdir:**

1. Á næstu síðu er hægt að finna $^{1}$H NMR af myndefnunum sem nemendur geta fengið til að vinna úr í skýrslu sinni.

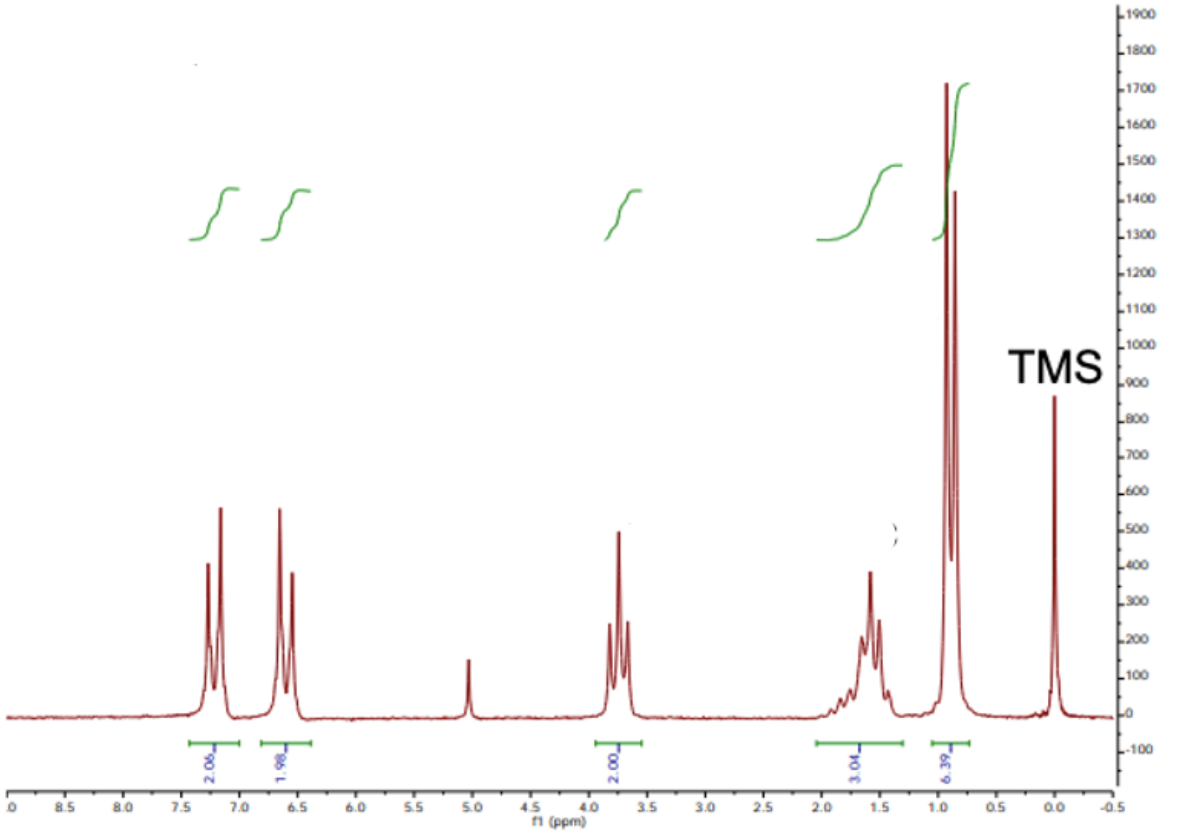



*Figure 1: $^{1}H$ NMR róf af 1-bromo-4-(isopentyloxy)benzene, þar sem alkyl halíðið 1-bromo-3-methylbutane var notað*

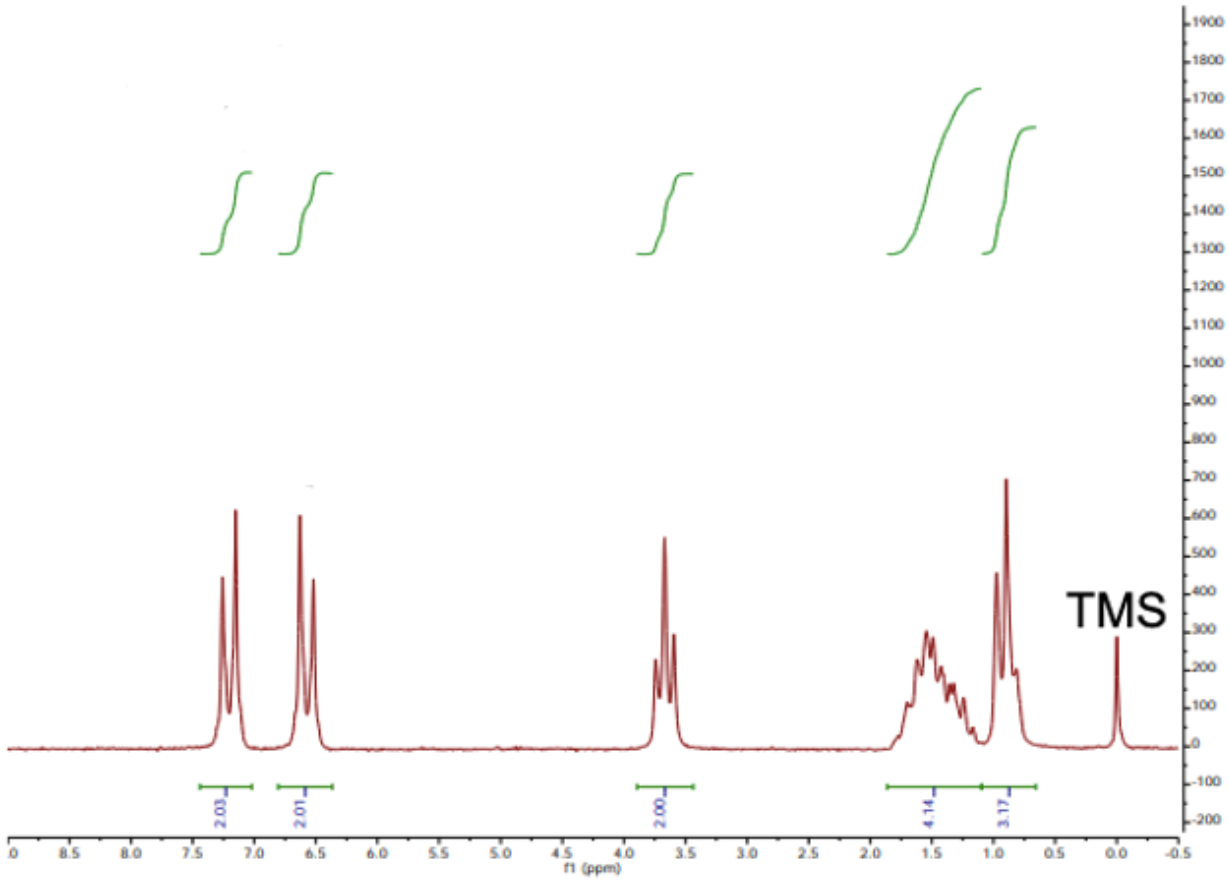



*Figure 2: 1H NMR róf af 1-bromo-4-butoxybenzene, þar sem alkyl halíðið 1-bromobutane var notað*

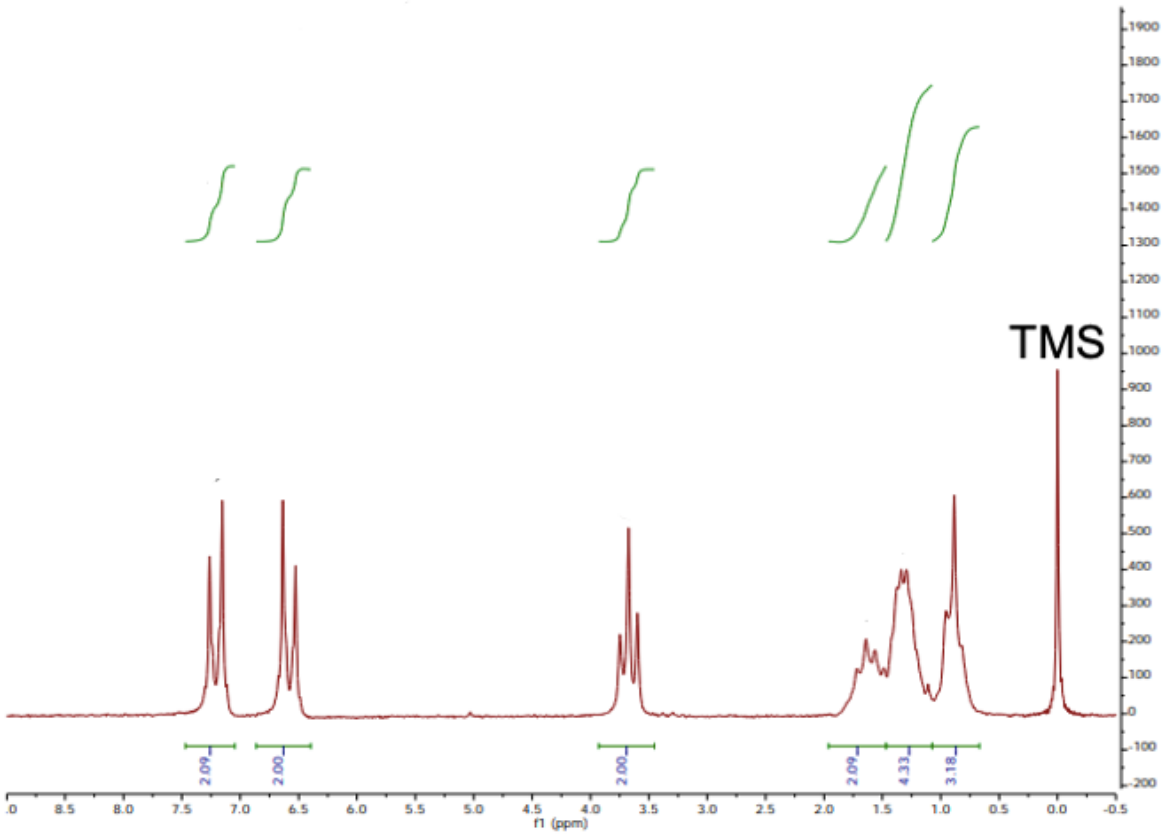
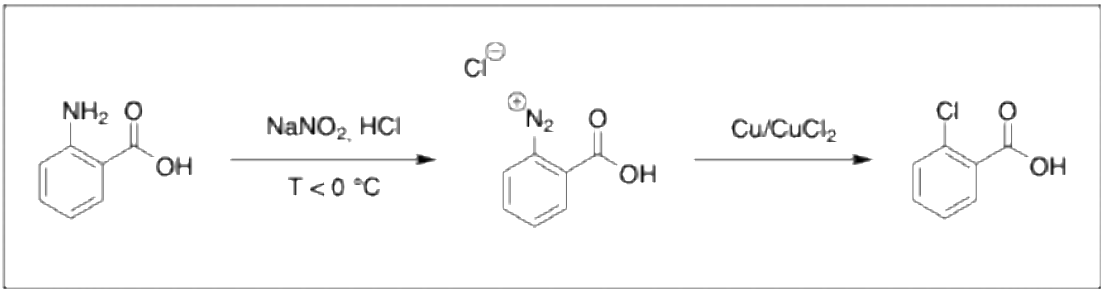



*Figure 3: 1H NMR róf af 1-bromo-4-pentoxybenzene, þar sem alkyl halíðið 1-bromopentane var notað*

**Sandmeyer hvarf: Efnasmíði á o-chlorobenzoic acid**

- Hugmynd að æfingu 7A eða 7C fyrir verklegri lífrænni efnafræði 2
- Æfing fengin úr eftirfarandi hefti: https://komar.edu.iq/wp-content/uploads/2018/09/Organic-Chemistry-Lab-Manual.pdf




**Procedure**:

I) In a Erlenmeyer flask weigh 4.7 g of $CuCl_2.2H_2O$. Add 20 mL of water and stir until complete dissolution. Next add 15 mL of concentrated HCl and 3.5 g copper metal and heat the mixture until it boils gently. Keep boiling for about 15 minutes after which decoloration should be observed. Meanwhile, carry out part II.

II) Measure 10 mL concentrated HCl and transfer it to a 250 mL Erlenmeyer flask and add 50 mL water. Add 5.5 g of N-phenyl anthranilic acid to the flask and dissolve it by heating slightly and then cool the solution in an ice-salt bath and leave it there. While monitoring the temperature, in a clean beaker prepare a solution of $NaNO_2$ by dissolving 2.8 g of $NaNO_2$ in 10 mL water. Add dropwise of this solution to the anthranilic acid solution in the 250 mL Erlenmeyer flask. *Note that the temperature of the mixture should not exceed 0 °C*. Once the addition is over, keep the Erlenmeyer flask in the ice-salt bath.

III) In a 600 mL beaker, add the $CuCl_2$ solution from part I and cool it down quickly below 0 °C. Add the diazonium salt from part II gradually while stirring vigorously with a glass rod. (**Note 1**). Keep stirring for 30 minutes. Then, filter over a Buchner funnel, and wash the precipitate first with cold ~8 M $HNO_2$ (**Note 2**), then with cold water until the filtrate gets colorless. Dry the precipitate over vacuum/distillation. Weigh the mass of crude product (o-chlorobenzoic acid) obtained.

**Notes**:

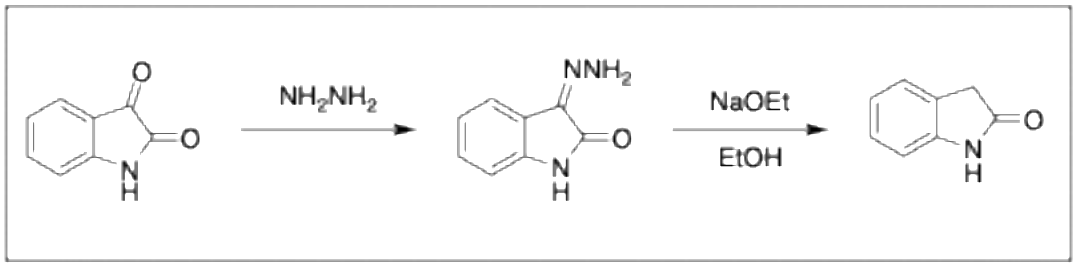
1. Large amount of foam is produced due to the release of nitrogen gas.
2. This 8 M solution needs to be prepared on-site and it needs to be used immediately once prepared as it can decompose. Dissolved sodium nitrite ($NaNO_2$) mixed with dilute acid while maintained at a low temperature should stabilize the $HNO_2$ solution and minimize decomposition.

**Spurningar**:

1. What is the purpose of washing the anthranilic acid with $HNO_2$ solution?

**Wolff-Kishner afoxun**

- Hugmynd að æfingu 7A eða 7C fyrir verklegri lífrænni efnafræði 2
- Grein: https://pubs.acs.org/doi/epdf/10.1021/ed070p332?ref=article_openPDF




**Procedure**:
Isatin (25.0 g, 0.17 mol) is suspended in mixture of 200 mL of anhydrous methanol. Hydrazine hydrate (30.0 g, 0.425 mol) is then added in one portion. The solution is heated to a gentle reflux for one hour. The solution is then cooled in an ice bath and the yellow crystals are filtered after 30 min.

While the yellow crystals are left on a watch glass to air dry, sodium metal (2.0 g) is dissolved in 50.0 mL of absolute ethanol in a 100 mL round-bottom flask (**Note 1**). When the sodium has completely dissolved, 5.0 g of the hydrazone derivative is added in small portions, while shaking, at 60-70 °C over a 10-min interval. The solution is heated to reflux until the evolution of nitrogen gas has ceased (~ 30 min). The brown solution is then carefully poured on ice and acidified to pH = 1 with 10% HCl solution. The mixture is extracted with 2 x 25 mL of ether, dried over calcium chloride, filtered and concentrated to yield a crude, light-orange residue. The mass is recrystallized from 50 mL of water (a small amount of charcoal is added) to yield oxindole (3.0 g, 73% yield) as white needles (m.p: 125-127 °C).

**Spurningar**:

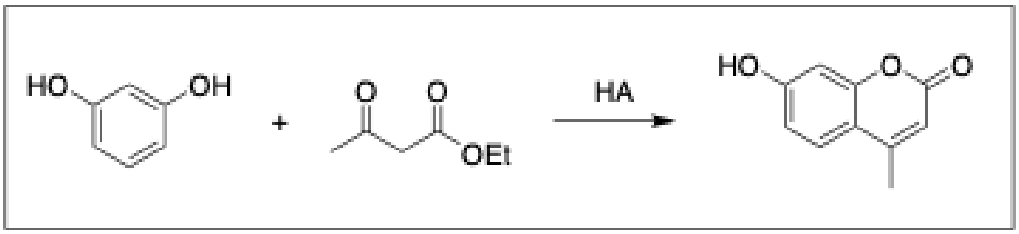
1. Why do you rinse your crude product with water?
2. Why does the color of the fluorescence change when you add base or acid to your coumarin product?

**Notes**:

1. Caution: Hydrogen gas evolution.

**Pechmann condensation**

- Hugmynd að æfingu fyrir verklegri lífrænni efnafræði 2
- Fengið frá vefsíðu: https://open.bu.edu/handle/2144/43653




**Procedure**:
In this lab you will be reacting resorcinol and ethyl acetoacetate using sulfuric acid as a catalyst to make the coumarin shown below. The product is fluorescent and you will study the effect of the pH on the color of the florescence.

Add resorcinol (4.54 mmol, 1 equiv) and ethyl acetoacetate (1 equiv) to a 3 mL conical vial with a spin vane. Stir the mixture 10 min at 90 °C in a water bath. Add concentrated $H_2SO_4$ (0.11 mL) very slowly dropwise. Start by adding one drop, then wait until the reaction is bubbling less vigorously then add another drop and continue until all of it has been added. Stir the mixture at 90 °C for 1 hour.

Cool the mixture to room temperature. Set-up a vacuum filtration and use 10 mL of distilled water to help aid in the transfer of the solid to your funnel. Pull vacuum through your product for a couple of minutes to dry your solid. Transfer your product to a 25 mL Erlenmeyer flask and recrystallize with 95% ethanol. Vacuum filter your crystals and wash them with 5 mL of cold 95% ethanol. Pull vacuum through your product for at least 5 minutes to dry your solid and transfer to a tared glass vial.

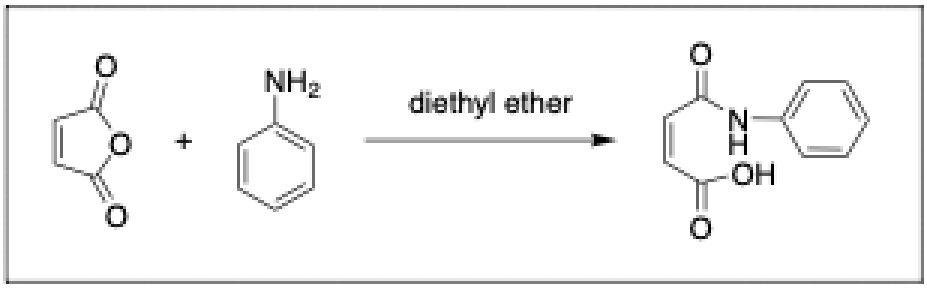
*Fluorescence*
To observe fluorescence, dissolve a small amount (20 mg) of product in 2-3 mL of ethanol (95%) in three test tubes or scintillation vials. Alter the pH of two of the samples by adding 2 mL of a 10% HCl solution in one and 2 mL of a 10% $Na_2CO_3$ solution to the other. Place samples under a UV lamp and record your observations.

**Athugasemdir**:

1. Fannst þetta áhugaverð æfing, skemmtilegt að kenna hvernig hægt er að skoða fluorescence á myndefninu og einnig skemmtilegur hvarfgangur fyrir skýrsluna.

**Efnasmíði á N-arylmaleamic sýrur (anhydride aminolysis)**

- Hugmynd að æfingu fyrir verklegri lífrænni efnafræði 2
- Æfing tekin úr eftirfarandi bók: https://books.google.is/books?hl=en&lr=&id=-Or4DwAAQBAJ&oi=fnd&pg=PR1&ots=7KGqj9Gej-&sig=5dzDPzoG2HOXk7vmLwPbvhINncI&redir_esc=y#v=onepage&q=wolff-kishner&f=false




**Procedure**:
In a fume hood, prepare a 250 mL two neck-round bottomed flask with a magnetic stir bar, a condenser and an addition funnel. Place maleic anhydride (10 g, 0.102 mmol) in the flask, add 100 mL of diethyl ether and stir the suspension until complete dissolution of the anhydride. Put the flask in a water bath at room temperature with the condenser and the addition funnel. Prepare a solution of the aniline (0.1 mol) in 25 mL of diethyl ether. Using the addition funnel, add *dropwise* the aniline solution to the maleic anhydride solution (**Note 1)**. Warm up the water bath to 40-45 °C and keep the reaction mixture stirring for about 90 min.

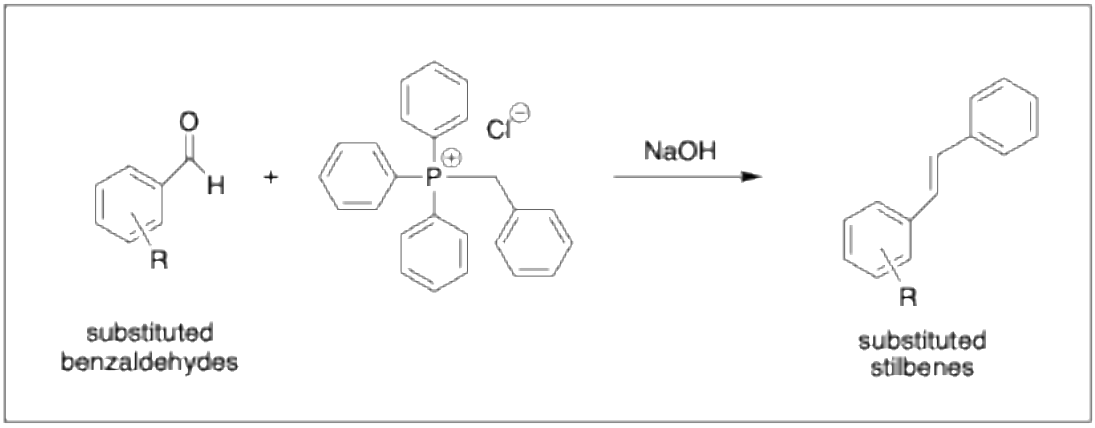
After cooling to room temperature, filter the suspension that was formed by filtration. Transfer the solid to a pre-weighed glass watch and put it in the oven at 75 °C for 20 – 25 min. Weigh the product obtained and calculate the yield.

**Notes**:

1. Caution: The reaction is exothermic.

**Wittig hvarf**

- Hugmynd að æfingu fyrir verklegri lífrænni efnafræði 2 (fyrir þá hópa A, B og C þar sem þau hafa mismunandi upphafsefni)
- Grein: https://pubs.acs.org/doi/10.1021/ed400408k




**Procedure**:
Obtain amounts of the starting aromatic aldehyde and the benzyltriphenylphosphonium chloride in a 1.0:1.1 equivalent mole ratio. Start with 500 mg of the aldehyde and calculate the amount of the phosphonium salt needed. To do this, you need to determine the moles of the aldehyde, and then calculate the slight excess (1.1 times the moles of aldehyde) of the phosphonium material. Combine materials in 25 mL Erlenmeyer flask along with a magnetic stir bar. Measure 5 mL 10 N sodium hydroxide (NaOH). Add the NaOH to the reaction flask, place on a stir plate and stir for 30 minutes.

When the 30 minutes is nearly complete, obtain 20mL ethanol and begin to heat to boiling for recrystallization. Assemble a vacuum filtration apparatus and filter product. Wash the crude product with water until the filtrate is no longer basic.

Transfer the crude product to a 25 mL Erlenmeyer flask. Add a minimum amount of boiling ethanol to the product until it is completely dissolved. Let the solution cool to room temperature on the counter without disturbing, and then place in an ice bath for about 30 minutes. Vacuum filter and weigh the crystalline product.

*TLC*
The recrystallized product can be analyzed by thin layer chromatography using 10/90 ethyl acetate/ heptane. It should be possible to see both the Z and E isomers on the TLC plate.

→ *Do you see a pronounced difference between the TLC of the crude and recrystallized in terms of Z/E products?*

*$^1$H NMR*
Dissolve a small amount of your product in $CDCl_3$ for analysis by $^1$H NMR.

→ *Where do aldehydes show up in $^1$H NMR? Is there still an aldehyde peak present in the spectra?*

→ *Where do alkenes typically show up in $^1$H NMR? Which signal do you think is resulting from the alkene protons?*

Tafla af arómatískum aldehýðum sem var notað fyrir æfinguna

| **Efni** | **CAS númer (ef það er áhugi)** |
|---|---|
| *o*-nitrobenzaldehyde (Aldrich) | CAS: 99-61-6 |
| *p*-anisaldehyde (Acros Organics) | CAS: 123-11-5 |
| benzaldehyde (Alfa Aesar) | CAS: 100-52-7 |
| 4-chlorobenzaldehyde (Acros) | CAS 104-88-1 |
| *p*-tolualdehyde (Aldrich) | CAS 104-87-0 |
| mesitaldehyde (Aldrich) | CAS 487-68-3 |
| 4-(dimethylamino)benzaldehyde | CAS 100-10-7 |