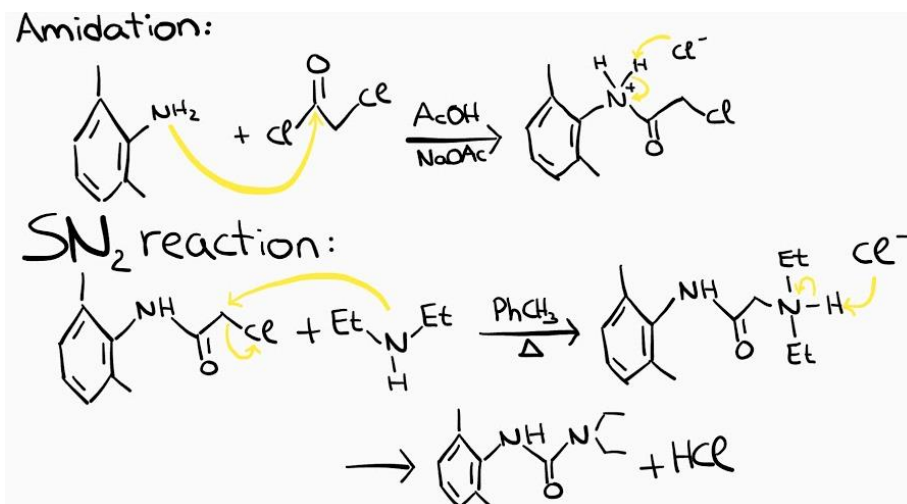


EXPERIMENTATION IN ORGANIC CHEMISTRY: 3rd Practice: Addition Elimination

A. Main Features of the practice:

1. Main objective of the practice:
 - Perform an amidation reaction and a nucleophilic substitution (S_N2 reaction) in order to synthesize Lidocaine a very typical anaesthetic compound used by odontologists.
2. Mechanism of the reaction:



3. Dangerous reagents, preventive measures; H and P phrases

Dangerous Reagents	Preventive Measures; H and P phrases
2,6-Dimethylaniline	H302: Harmful if swallowed H312: Harmful if contact with skin H315: Causes skin irritation H332: Harmful if inhaled H335: May cause respiratory irritation. H351: Suspected of causing cancer. H411: toxic to aquatic life with long lasting effects. P201: Obtain special instructions before use. P202: Do not handle until all safety precautions have been read and understood. P261: Avoid breathing dust/fume/gas/mist/vapours/spray. P264: Wash thoroughly after handling. P270: Do not eat, drink or smoke when using this product. P271: Use only outdoors or in a well-ventilated area. P273: Avoid release to the environment. P280: Wear protective gloves/protective clothing/eye protection/face protection. P281: Use personal protective equipment as required. P301+P312: IF SWALLOWED: call a POISON CENTER/doctor/... IF you feel unwell. P302+P352: IF ON SKIN: wash with plenty of water. P304+P312: IF INHALED: Call a POISON CENTER/doctor/... if you feel unwell.

2,6-Dimethylaniline	<p>P304+P340: IF INHALED: Remove person to fresh air and keep comfortable for breathing.</p> <p>P308+P313: IF exposed or concerned: Get medical advice/attention.</p> <p>P312: Call a POISON CENTER or doctor/... if you feel unwell.</p> <p>P321: Specific treatment (see ... on this label).</p> <p>P322: Specific measures (see ...on this label).</p> <p>P330: Rinse mouth.</p> <p>P332+P313: IF SKIN irritation occurs: Get medical advice/attention.</p> <p>P362: Take off contaminated clothing.</p> <p>P363: Wash contaminated clothing before reuse.</p> <p>P391: Collect spillage.</p> <p>P403+P233: Store in a well-ventilated place. Keep container tightly closed.</p> <p>P405: Store locked up.</p> <p>P501: Dispose of contents/container to...</p>
Chloroacetyl chloride	<p>H301+H311+H331: Toxic if swallowed, in contact with skin or if inhaled.</p> <p>H314: Causes severe skin burns and eye damage.</p> <p>H372: Causes damage to organs through prolonged or repeated exposure.</p> <p>H410: Very toxic to aquatic life with long lasting effects</p> <p>P260: Do not breathe dust/fume/gas/mist/vapours/spray.</p> <p>P280: Wear protective gloves/protective clothing/eye protection/face protection.</p> <p>P303: If on skin (or hair): Remove/take off immediately all contaminated clothing. Rinse skin with water/shower</p> <p>P304+P310: IF INHALED: Call a POISON CENTER/doctor/... if you feel unwell.</p> <p>P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses if present and easy to do - continue rinsing.</p>
Sodium acetate	<p>H319: Causes serious eye irritation.</p> <p>P264: Wash (hands) thoroughly after handling.</p> <p>P280: wear (protective gloves/protective clothing/eye protection/face protection).</p> <p>P305+P351+P338: If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.</p> <p>P337+P313: If eye irritation persists, get medical advice/attention.</p>
Hydrochloric acid	<p>H290: May be corrosive to metals</p> <p>H314: Causes severe skin burns and eye damage.</p> <p>P260: Do not breathe dusts or mists.</p> <p>P280: Wear eye protection/face protection.</p> <p>P303+P361+P353: If on skin (or hair): Remove/Take off immediately all contaminated clothing.</p> <p>P305+P351+P338: If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.</p> <p>P390: Absorb spillage to prevent material damage.</p> <p>P501: Dispose of contents/container to industrial combustion plant.</p>

Sodium Sulphate Anhydrous	H412: Harmful to aquatic life with long lasting effects. P273: Avoid release to the environment. P501: Dispose of contents/container to an approved waste disposal plant.
Pentane	H225: Highly flammable liquid and vapour. H304: May be fatal if swallowed and enters airways. H336: May cause drowsiness or dizziness. H411: Toxic to aquatic life with long lasting effects. P210: Keep away from heat/sparks/open flames/hot surfaces. No smoking. P261: Avoid breathing dust/fume/gas/mist/vapours/spray. P273: Avoid release to the environment. P301+P310: If swallowed: Immediately call a poison centre or doctor/physician. P331: Do not induce vomiting.
Potassium hydroxide	H302: Harmful if swallowed. H314: Causes severe skin burns and eye damage. H402: Harmful to aquatic life. P260: Don't breathe dust. P264: Wash exposed skin thoroughly after handling. P270: Do not eat, drink, or smoke when using this product. P273: Avoid release to the environment. P280: Wear protective gloves, protective clothing, eye protection, face protection. P301+P330+P331: If swallowed: Rinse mouth. Do NOT induce vomiting.
Toluene	H225: Highly flammable liquid and vapor. H304: May be fatal if swallowed and enters airways. H315: Causes skin irritation. H336: May cause drowsiness or dizziness. H361: suspected of damaging the unborn child. H373: Causes damage to organs through prolonged or repeated exposure. P201: Obtain special instructions before use. P202: Do not handle until all safety precautions have been read and understood. P210: Keep away from heat, hot surface, sparks, open flames and other ignition sources. No smoking. P233: Keep container tightly closed. P240: Ground/bond container and receiving equipment. P241: Use explosion-proof (electrical/ ventilating/ lighting/...) equipment. P242: Use only non-sparking tools. P243: Take precautionary measures against static discharge.

Toluene	<p>P260: Do not breathe dust/fume/gas/mist/vapours/spray. P261: Avoid breathing dust/fume/gas/mist/vapours/spray. P264: Wash ... thoroughly after handling. P271: Use only outdoors or in a well-ventilated area. P280: Wear protective gloves/ protective clothing / eye protection/ face protection. P281: Use personal protective equipment as required. P304+P310: If inhaled, immediately call a POISON CENTER or doctor/physician. P302+P352: If on skin: wash with plenty of water. P303+P361+P353: If on skin (or hair): Take off immediately all contaminated clothing. Rinse SKIN with water (or shower). P304+P340: IF INHALED: Call a POISON CENTER/ doctor/... if you feel unwell. P312: Call a POISON CENTER/ doctor/... if you feel unwell. P314: Get medical advice/attention if you feel unwell. P321: Specific treatment (see... on this label). P331: Do NOT induce vomiting. P332+P313: If SKIN irritation occurs: Get medical advice/attention. P362: Take off contaminated clothing. P370+P378: In case of fire: Use ... to extinguish. P403+P233: Store in a well-ventilated place. Keep container tightly closed. P403+P235: Store in a well-ventilated place. Keep cool. P405: Store locked up. P501: Dispose of contents/container to...</p>
Diethylamine	<p>H225: Highly flammable liquid and vapour. H302: Harmful if swallowed. H302+H332: Harmful if swallowed or if inhaled. H311: Toxic in contact with skin. H315: Causes skin irritation. H317: May cause an allergic skin reaction. H318: Causes serious eye damage. H332: Harmful if inhaled. H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled. H402: Harmful to aquatic life. P210 Keep away from heat/sparks/open flames/hot surfaces. No smoking. P233: Keep container tightly closed. P240: Ground/bond container and receiving equipment. P241: Use explosion-proof electrical/ventilating/lighting/equipment. P242: Use only non-sparking tools. P243: Take precautionary measures against static discharge. P261: Avoid breathing dust/fume/gas/mist/vapours/spray. P264: Wash skin thoroughly after handling. P270: Do not eat, drink or smoke when using this product. P271: Use only outdoors or in a well-ventilated area. P272: Contaminated work clothing should not be allowed out of the workplace. P273: Avoid release to the environment.</p>

Diethylamine	<p>P280: Wear protective gloves/ protective clothing/ eye protection/ face protection.</p> <p>P285: In case of inadequate ventilation wear respiratory protection.</p> <p>P301+P312: IF SWALLOWED: Call a POISON CENTER or doctor/ physician if you feel unwell.</p> <p>P303+P361+P353: IF ON SKIN (or hair): Remove/ Take off immediately all contaminated clothing. Rinse skin with water/ shower.</p> <p>P304+P340: IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.</p> <p>P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.</p> <p>P310: Immediately call a POISON CENTER or doctor/physician.</p> <p>P322: Specific measures (see supplemental first aid instructions on this label).</p> <p>P330: Rinse mouth.</p> <p>P333+P313: If skin irritation or rash occurs: Get medical advice/attention.</p> <p>P361: Remove/ Take off immediately all contaminated clothing.</p> <p>P370+P378: In case of fire: Use dry sand, dry chemical or alcohol-resistant foam for extinction.</p> <p>P403+P235: Store in a well-ventilated place. Keep cool.</p> <p>P405: Store locked up.</p> <p>P501: Dispose of contents/container to an approved waste disposal plant.</p>
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4. Experimental Procedure and Observations:

Amidation Reaction and its purification:

- Put 2,5 mL of 2,6-Dimethylaniline and 1 mL of Acetic acid into a 250 mL Erlenmeyer Flask.
- Shake the mixture until it is homogeneous.
- Pour 1,8 mL of Chloroacetyl chloride carefully using an addition funnel while it is stirred vigorously. This must be done in the fume hood because the reagents emit tear-producing gases.
- Then the mixture is heated to 45°C for approximately 5 minutes.
- Add 50 mL of %5 aqueous solution of Sodium acetate while the solution is stirred. A precipitate might appear; cool it down in an ice bath and then vacuum filtrate it with the aid of a Büchner and a Kitasato. Moreover, wash the solid four times with 40 mL of water each time.
- Move the solid to a watch glass and let it dry overnight.
- Weigh the solid and calculate the yield.

SN₂ Reaction and its purification:

- Dissolve 1 g of α -chloro-2,6-dimethylanilide in 10 mL of toluene at a 50 mL round bottomed flask with a stir bar.
- Add 1,5 mL of dimethylamine to the solution.
- Connect the condenser and heat under reflux for 1h.
- Let it cool down to room temperature.

- If some crystals appear, get rid of them by vacuum filtration with a Büchner and a Kitasato. Wash the solid with 10 mL of toluene and add the toluene used for washing to the filtrate.
- Put the filtrate in a separation funnel where we add 20 mL of HCl.
- Shake the mixture and collect the aqueous phase (the lower phase) in an Erlenmeyer flask.
- Wash the organic phase again with 20 mL of HCl and the water phase is as well added to the Erlenmeyer.
- The organic phase is received in another flask.
- Cool down the water phase containing Erlenmeyer with an ice/water bath keeping the temperature below 10°C.
- Dropwise add KOH until a precipitate is formed while we control the temperature.
- Add a bit more KOH to assure that there is no more lidocaine left.
- Warm up the solution to room temperature and place it in a separation funnel.
- Add 20 mL of pentanes slowly shaking the funnel.
- Eliminate the aqueous phase.
- Wash the organic phase with 15 mL of water and shake.
- Eliminate again the water phase and dry the organic one bias Na₂SO₄. Afterwards, filtrate to eliminate the solid.
- Use the rotavapor to eliminate the solvent and acquire the pure lidocaine.
- Weigh the product.

B. Results:

1.

Molecular formula	MW (g/mol)	Density (g/cm ³)	State	Colour
C ₈ H ₉ NH ₂	121,19	0,956	Liquid	Colourless
C ₂ H ₂ Cl ₂ O	112,94	1,42	Liquid	Colourless/ yellow
C ₁₀ H ₁₂ ClNO	197,66	1,187	Solid	White
C ₄ H ₁₀ NH	73,14	0,707	Liquid	Colourless
C ₁₄ H ₂₂ N ₂ O	234,34	1,026	Solid	White / Slightly yellow

Calculations of n:

- Amidation reaction:

$$n_{C_8H_9NH_2} = 2,5 \text{ mL} \times \frac{0,956 \text{ g}}{1 \text{ mL}} \times \frac{1 \text{ mol}}{121,19 \text{ g}} = 0,0197 \text{ mol } C_8H_9NH_2$$

$$n_{C_2H_2Cl_2O} = 1,8 \text{ mL} \times \frac{1,42 \text{ g}}{1 \text{ mL}} \times \frac{1 \text{ mol}}{121,19 \text{ g}} = 0,0211 \text{ mol } C_2H_2Cl_2O$$

→The limiting reactant will be 2,6-Dimethylaniline.

- SN₂ reaction:

$$n_{C_{10}H_{12}ClNO} = 1 \text{ g} \times \frac{1 \text{ mol}}{197,66 \text{ g}} = 0,00506 \text{ mol } C_{10}H_{12}ClNO$$

$$n_{C_4H_{10}NH} = 1,5 \text{ mL} \times \frac{0,707 \text{ g}}{1 \text{ mL}} \times \frac{1 \text{ mol}}{73,14 \text{ g}} = 0,01400 \text{ mol } C_4H_{10}NH$$

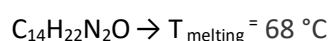
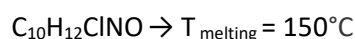
→The limiting reactant will be 2-Chloro-N-(2,6-dimethylphenyl)acetamide.

Theoretical weight or volume of final product:

$$m_{C_{10}H_{12}ClNO} = 0,0197 \times \frac{197,66 \text{ g}}{1 \text{ mol}} = 3,894 \text{ g } C_{10}H_{12}ClNO$$

$$m_{C_{14}H_{22}N_2O} = 0,00506 \text{ mol} \times \frac{234,34 \text{ g}}{1 \text{ mol}} = 1,186 \text{ g } C_6H_{10}Br_2$$

Theoretical Melting or Boiling point (°C):



2. Yield. Analysis of the results:

- Yield of the amidation reaction

$$\text{Yield} = \frac{m_{\text{experimental}}}{m_{\text{theoretical}}} \times 100 = \% 90 = \frac{m_{\text{experimental}}}{3,894} \rightarrow m_{\text{experimental}} = 3,505 \text{ g}$$

- Yield of the SN₂ reaction

$$\text{Yield} = \frac{1,00}{1,186} \times 100 = \% 84,32$$

3. Spectroscopic Data:

H-NMR of α -chloro-2,6-dimethylanilide:

This molecule has some symmetry elements so some of the signals will only appear once due to this effect.

- δ 7.92: this signal belongs to the N attached to the N. It is near electron density subtracting groups such as the amide or the aromatic cycle. Causing the H to be very deprotected.
- δ 7.20-7.02: This range of signals belong to the aromatic ring. Its chemical shift is very characteristic.
- δ 4.20: This singlet belongs to the CH₂ between the chlorine and the carbonyl group.
- δ 2.22: This singlet belongs to the CH₃ groups attached to the benzene.

C-NMR of α -chloro-2,6-dimethylanilide:

- δ 164.6: This signal belongs to the carbonyl group. Its signal is very characteristic.
- δ 135.4: The carbons in meta position from the methyl groups cause this signal.
- δ 132.8: This signal belongs to the carbons in ortho position regarding the methyl groups.
- δ 128.3: This signal belongs to the carbons attached to the methyl groups.
- δ 127.9: This signal belongs to the C attached to the N of the aniline group.

- δ 42.8: This signal belongs to the carbon next to the chlorine.
- δ 18.3: This signal belongs to the methyl groups.

IR spectra of α -chloro-2,6-dimethylanilide:

We have three interesting signals: at around 3200 cm^{-1} we can see the N-H bond. Moreover, at the range of 1750-1900 we see some small ups and downs and another peak can also be seen 1540, these signals are of the benzene ring. Additionally, the peak at 1640 belongs to the carbonyl group.

H-NMR of Lidocaine:

This molecule has some symmetry elements so some of the signals will only appear once due to this effect.

- δ 8.93: This singlet belongs to the H attached to the N.
- δ 7.09: This signal belongs to the aromatic ring. Its signal is very characteristic.
- δ 3.22: The singlet belongs to the CH_2 hydrogens between carbonyl and the ethylamine.
- δ 2.69: The quadruplet is made by the CH_2 of the ethyl groups of the amine.
- δ 2.24: a singlet that belongs to both methyl groups.
- δ 1.14: This triplet are caused by the CH_3 of ethyl groups of the amine.

C-NMR of Lidocaine:

- δ 170.3: This signal belongs to the carbon of the carbonyl group. This signal is very characteristic.
- δ 135.1: This is caused by the C-s that are attached to the methyl groups.
- δ 134.0: The C attached to the amine causes this signal.
- δ 128.2: This signal is created by the carbon in meta position to the methyl groups.
- δ 127.1: This signal corresponds to the C in ortho position to the methyl groups.
- δ 57.5: This signal is related to the C between the carbonyl and the diethylamine.
- δ 49.0: The signal belong the ethyl groups, exactly to the C next to the amine.
- δ 18.6: The signal is created by the C of the methyl groups.

4. Conclusions:

Even though we did not have the chance to access to the lab and make the experiment ourselves, we have been able to see a method to synthetize a very useful compound in the health sector. Moreover, we have been able to see some of the concepts learnt in Kimika Organikoa I into practice which can be very beneficial for our comprehension in the matter.