Synthesis of Simazine – an example of a Triazine Herbicide

Results obtained by the 1917 Branding Boys. Bevo I with his 13-0 ‘Aggie’ brand

Herbicides

1. Herbicides are defined as agents used to destroy or inhibit plant growth. Some herbicides will kill any plant. The more desirable herbicides are those which do not harm the desired crop, but kill all undesired plants (defined as weeds).

2. Most herbicides are man-made small molecules that interfere in some way with the biological processes necessary for plant growth. Several different methods of growth inhibition have been documented for herbicides.
Herbicides – Mechanisms of Action

7 Auxin Growth Regulators (applied to foliage)
These herbicides mimic natural auxins and result in abnormal connective tissue (lack of nutrients).
An example is 2,4-D.

7 Amino Acid Synthesis Inhibitors. (foliage or soil)
These herbicides inhibit the enzymes necessary for synthesis of amino acids and stunt growth from lack of necessary protein precursors.
An example is glyphosate.

Herbicides – Mechanisms of Action

7 Cell Membrane Disruptors (foliage and soil)
These herbicides result in oxidation of cell membrane lipids (necessary for cell wall integrity) and lead to leaf and stem death.
An example is oxyfluorfen.

7 Lipid Biosynthesis Inhibitors (foliage)
These herbicides inhibit the enzymes of lipid biosynthesis that results in stunted growth and death.
An example is diclofop.
Herbicides – Mechanisms of Action

7 Pigment Inhibitors (primarily soil)
These herbicides inhibit carotinoid biosynthesis, which results in loss of chlorophyll and of the photosynthesis process.
Examples are fluridone and amitrol

7 Shoot Growth Inhibitors (soil)
These exact mechanism of action of these herbicides has not been established, but they inhibit new shoot growth.
All examples have a thiocarbamate functionality.

7 Cell Division Disruptors (soil)
These herbicides are applied in the soil and disrupt the cell division of roots and thus prevent sufficient nutrient uptake.
Examples are trifluralin and naproamide.

7 Cell Membrane Disruptors (foliage)
These herbicides directly or indirectly disrupt the cell membranes and result in rapid leaf and stem death.
Examples include paraquat and glufosinate.

7 Acids, oils, and soaps used as herbicides also act by this mechanism.
Herbicides – Mechanisms of Action

7 Photosynthesis Inhibitors (soil)
This final class of herbicides block electron transport in photosynthesis resulting in yellowing of leaves and death.
Examples are atrazine, simazine and diuron.
7 We will be synthesizing simazine in the lab today.

Use of Atrazine and Simazine

7 Atrazine, simazine, and related herbicides are the most widely used herbicides on crops of corn, sorghum, and sugarcane. They are applied to the soil and can result in contamination of ground water and drinking water.
7 Although these herbicides are metabolized in soil, the process is slow.
7 The areas of heaviest use of atrazine are shown on the map on next slide.
Although atrazine herbicides and some of the metabolites are potent poisons of the photosynthetic machinery of many plants, the target crops (corn, sorghum and sugarcane) are resistant to the herbicide and its metabolites, but the weeds problematic to these crops are destroyed.

This selectivity is not found in other currently available herbicides.
Health Risks vs. Economic Impact

Potential health risks associated with atrazine have led the E.P.A. to consider restricting or banning the use of this class of herbicides in this country. Atrazine is currently banned in Europe. However, economic considerations – and the lack of suitable alternatives – have required its continued use. The E.P.A. estimated that longterm costs associated with banning atrazine would range between $295-$665 million/yr (in 1994 dollars).

Structure of Triazine Herbicides

Atrazine is just one of several herbicides that are called triazine herbicides. They all contain a central aromatic ring with three nitrogens.
Simazine – a symmetrical triazine

7 We are going to synthesize simazine, because of its symmetrical structure – both aminoalkyl sidechains are identical.

Simazine Tradenames

7 Tradenames for simazine herbicides include Aquazine, Caliber, Cekusan, Cekusima, Framed, Gesatop, Primatol S, Princep, Simadex, Simanex, Sim-Trol, Tanzine and Totazine.

7 It is sometimes formulated as a mixture with other herbicides under other tradenames.
Atrazine – Mechanism of Action

1. How do triazine herbicides such as atrazine and simazine inhibit the photosynthesis mechanism?
2. The molecular basis for killing plants results from the triazine herbicide being able to effectively mimic an essential small molecule, plastoquinone, and displace it from its binding site in the photosynthetic apparatus.
3. Plastoquinone is a critical component in the electron-transport process involved in photosynthesis.

Atrazine – Mechanism of Action

1. Figure A shows plastoquinone binding to a protein and being reduced. Figure B shows atrazine in the binding site preventing access of plastoquinone to the active site.
Health Risks - Simazine

- Simazine is essentially non-toxic to humans and birds. However, sheep and cattle are more sensitive!
- Patch tests have indicated that simazine is not a skin irritant or sensitizer.
- The environmental concern has not been high toxicity, but the fact that these compounds have been detected in ground water and drinking water at low concentrations.
- In today’s lab, the starting materials are of more concern than the product in terms of safety.

Synthetic Methods

- Triazine herbicides are prepared by nucleophilic aromatic substitution – the replacement of a leaving group on an aromatic ring by a nucleophile. This attack by a nucleophile generates an anionic intermediate, whereas the more common electrophilic aromatic substitution generates a cationic intermediate.
Synthetic Methods

7 Nucleophilic attack on an aromatic ring will occur only if the aromatic ring contains functionality that will stabilize the negative charge generated. Thus, electron-withdrawing groups and electronegative atoms are required for such substitution.

\[
\text{Nu}^\ominus + \text{Nu} \rightarrow \text{Nu}^\ominus
\]

Synthetic Methods

7 Below are some examples of nucleophilic aromatic substitution reactions.

\[
\text{ClNO}_2 \ + \ \text{NaOH} \rightarrow \text{OHNO}_2 + \text{NaCl}
\]

\[
\text{BrN} \ + \ \text{H}_2\text{O} \rightarrow \text{OHNO} + \text{HBr}
\]
Synthetic Methods

These reactions are very similar to the nucleophilic substitution of acid chlorides. The nucleophile adds to an sp² carbon to form a tetrahedral intermediate, then the original substituent is released to form the substitution product.

\[
\begin{align*}
\text{OCl} & \quad + \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{O}^+\text{OH}_2\text{Cl} \quad \rightarrow \quad \text{O}^-\text{OH}_2\text{Cl} \\
\text{NClClCl} & \quad + \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{N}^+\text{OH}_2\text{Cl} \quad \rightarrow \quad \text{N}^-\text{OH}_2\text{Cl}
\end{align*}
\]

Synthesis of Simazine

In the synthesis of simazine in today’s laboratory experiment, the reaction involves the substitution of two of the three chlorine atoms of cyanuric chloride with two ethylamine groups as shown below.

\[
\begin{align*}
\text{ClClCl} & \quad + \quad 4\text{NH}_2 \quad \xrightarrow{\text{acetone} \ 0^\circ\text{C} - 25^\circ\text{C}} \quad \text{NHNHNH} \quad + \quad 2\text{NH}_3^+\text{Cl}^-
\end{align*}
\]
Synthesis of Simazine

7 Each substitution step releases a molecule of HCl, which will form an ammonium salt with some of the ethyl amine. Therefore two ethylamine molecules are required for each chlorine molecule replaced in this reaction.

\[
\text{Cyanuric Chloride} + 4 \text{NH}_2 \xrightarrow{\text{acetone 0}^\circ \text{C - 25}^\circ \text{C}} \text{Simazine} + 2 \text{NH}_3^+ \text{Cl}^-\n\]

Through control of the amount of nucleophile added and of the reaction temperature, one, two, or even all three chlorides of cyanuric chloride can be replaced.

Today, you need to ensure that the reaction temperature remains low enough to prevent formation of significant amounts of the tri-substituted product.
SAFETY!

7 Both cyanuric chloride and ethyl amine are irritants. Cyanuric chloride is a lachrymator since it liberates HCl upon reaction with water. Be sure to wear the pair of nitrile gloves provided for the entire lab period. You will find the gloves in one of the hoods at the back of the room.

7 Promptly clean up any spills. Use the ammonia solution in the spray bottle to ‘neutralize’ any spilled cyanuric chloride.

SAFETY!

7 The reagent solutions will be dispensed from bottles in the reagent hood using an autodispenser.

7 Follow the procedure given in the lab manual carefully. Use aluminum foil to cover your graduated cylinder and the reaction flask after you add the reagents to avoid introducing HCl or ethyl amine vapors into the air.
Product Characterization

1. You will use TLC to compare the purity of the crude product (before the methanol wash) with the purity of the product after washing with methanol. The impurities are more soluble in methanol than the desired product.

2. Dry your sample as much as possible, then obtain a weight to calculate yield and take a melting point of your product to compare with the literature melting point.

CLEAN-UP PROCEDURES!

1. Dispose of solid crystals, filter paper, and TLC plates in the solid waste container provided.

2. Dispose of the nitrile gloves and aluminum foil in the designated waste beaker in the hood.

3. Dispose of liquid waste in appropriately labeled liquid waste bottle.

4. Wash all glassware with soap and water and rinse with acetone.
Course Evaluation

7 Course evaluations for both organic lab and lecture courses are now available on e-learning (WebCT/Blackboard).
7 Computers will be available for your use in the organic lab instrument rooms between 8-5 PM weekdays until the end of classes.
7 Please provide a responsible evaluation for this course and your TA.