Honors Cup Synthetic Proposal

Section: 220
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Title: Synthesis of Trans-Cinnamaldehyde using Nobel Prize winning Grubbs Catalyst, 1st Generation

Introduction:
Trans-Cinnamaldehyde, in its naturally occurring form, gives cinnamon its spice. Cinnamaldehyde is used for the flavoring in candy, ice cream, and chewing gum. Besides flavoring and scents, this compound has many other practical uses. Cinnamaldehyde is also used as a fungicide applied to the root systems of many crops. Because of its low levels of toxicity, it is perfect for agricultural applications. It is sometimes used as an insecticide, and its scent is used to repel certain animals such as cats and dogs. Clearly, this compound has many practical uses. This compound would be very interesting for the Chemistry 216H lab because the students would be producing a compound that they recognize by its distinct smell. Students feel more involved in the chemistry when they can identify with the compounds being produced, and everyone can identify with cinnamon flavoring and the great smell it produces. Everybody in the chemistry building will appreciate the lab rooms smelling like cinnamon candy! This method of synthesis is also particularly interesting because the catalyst used won the Nobel Prize this year. Both the compound being produced and the synthesis by which it is made are both tremendously interesting.

Overall synthetic reaction scheme:

Step 1:

\[
\text{Styrene} + \text{1,1,1-Trichloromethane (Chloroform)} \xrightarrow{\text{Catalyst 1}} \text{(1,3,3-trichloropropyl)benzene} \]

Step 2:

\[
\text{(1,3,3-trichloropropyl)benzene} \xrightarrow{10\% \text{H}_2\text{SO}_4, 180{\degree}\text{C}, 6:15 \text{h}} \text{Trans-cinnamaldehyde} \]
Catalyst 1: (Grubb’s Catalyst 1st Generation)

\[ \begin{align*}
\text{Catalyst 1: (Grubb’s Catalyst 1st Generation)} \\
\text{Grubbs Catalyst, 1st Generation}
\end{align*} \]

**Step 1**

**Synthetic transformation 1:**

\[ \begin{align*}
\text{Styrene} & \quad + \quad \text{1,1,1-Trichloromethane} \\
& \quad \xrightarrow{\text{Catalyst 1}} \quad \text{(1,3,3-Trichloropropyl)benzene}
\end{align*} \]

- Catalyst on second page

**Experimental 1**

Product: (1,3,3-Trichloro-propyl)-benzene. To a Schlenk flask equipped with a reflux condenser was added catalyst 1 (210 mg, 0.247 mmol), 1,1,1-trichloromethane (10 mL) and styrene (2) (.531 g, 4.94 mmol). The reaction was heated to 75 8C under N2 atm. for 1.5 h. The reaction was concentrated and purified by silica gel chromatography (pentanes) to give (1,3,3-Trichloro-propyl)-benzene (1.15 g, 4.74 mmol, 96% yield) as a colorless oil.

*The molar values for the original reaction were divided by 1.94 in order to compensate for the desired intermediate yield.*

*This step corresponds to the formation of a different compound, (1,3,3-Trichloro-butyl)-benzene, but we confirmed with Dr. Koreeda that this generic process applies to our molecules as well.*

**Expected yield: 96 % 1.1 g**

**Safety, disposal and green issues 1:**

Grubb’s Catalyst is classified as an irritant to the eyes skin and respiratory system. Grubb’s catalyst should also never come into contact with water and should be handled with care as it has a limited shelf life. However, it is a very effective catalyst in that it is less reactive than some others, including Shrock’s catalysts. Grubb’s catalyst should not under any circumstances be disposed of down a drain, but may be
disposed of in a regular waste container. Grubb’s catalyst is significant to green chemistry because it enables reactions to be more efficient, thereby requiring fewer resources and creating less waste. It also allows for more environmentally nontoxic reactions by requiring less hazardous solvents and creating less hazardous waste. Styrene is classified as a harmful substance and as a possible carcinogen by the EPA. It is toxic through external contact with the skin, and inhalation or swallowing. It is also flammable and must be handled with extreme care under a hood to avoid inhalation. Styrene should be disposed of in a hazardous waste container. Styrene dissolves in most organic solvents, and should eventually be disposed of dissolved in a combustible solvent and then burned in a chemical incinerator containing an afterburner and scrubber. Proponents of green chemistry have been attempting to produce styrene via a more environmentally friendly route, which involves using xylenes instead of benzene, but styrene itself is still considered to be quite toxic. Chloroform is also a harmful substance in the same ways as styrene is, through contact with skin, eyes, and inhalation, and should never be handled without gloves. It should also be disposed of in a hazardous waste container and then through controlled incineration, preferably when mixed with another combustible material, such as styrene. Chloroform has some green issues. Currently there is a move to decrease its use in industry to limit exposure to it. During the procedure of this part of the experiment, precaution should be taken while heating the reactants, thus the inclusion of the reflux condenser to prevent overheating. The system should be kept closed from the air as two of the reactants are flammable. All procedures should be performed in a hood for safety purposes to minimize the risk of inhaling the catalyst. Groves and safety goggles should be worn at all times during the experiment.

**Step 2**

**Synthetic transformation 2:**

\[
\begin{align*}
(1,3,3\text{-trichloropropyl})\text{benzene} & \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \\
& \quad \text{10} \% \text{ H}_2\text{SO}_4 \\
& \quad 180 \, ^\circ\text{C}, \, 6:15 \text{ h} \\
\rightarrow & \quad \text{H} \\
\end{align*}
\]

Trans-cinnamaldehyde

### Experimental 2

Alternative hydrolysis. To a heavy walled reaction tube was added compound 6 (1.1 g, 4.88 mmol), and H2SO4 (28% aq., 1.0 mL). The tube was sealed with a Teflone screw cap and heated to 180 °C (oil bath temp) for 6.5 h. The reaction was partitioned between Et2O and H2O. The organic layer was separated, concentrated, and purified by silica gel chromatography (pentanes/Et2O, 10:1) to give trans-cinnamaldehyde (14) (500 mg, 3.78 mmol, 77% yield) as a yellow oil.

*The molar values were multiplied by 15.75 to scale for desired product yield.

**Expected yield: 77% 0.5 g**
Safety, disposal and green issues 2:

(1,3,3-Trichloro-propyl)-benzene is classified as an irritant, particularly so to the skin, so gloves should be worn at all times during the experiment, and care should be taken not to allow it to come into contact with exposed skin. Inhalation and contact with the eyes should also be avoided. It should be disposed of in organic halogenated solvents in a hazardous waste container, and, importantly, the container must not be made of aluminum. It is considered a polluting substance, and therefore does not comply strictly with the methodology of green chemistry. Trans-cinnamaldehyde is classified as an irritant. It is irritating to the skin and poses serious threat to the eyes, so safety goggles and gloves should be worn throughout the entire experiment. Work should be done in a hood and water should not be added to trans-cinnamaldehyde and it should not be disposed of down the drain, but instead in an approved hazardous waste disposal container, although as this is our target molecule, it is not likely that we will have to worry about disposing it right away. Trans-cinnamaldehyde is combustible and may eventually be disposed through incineration as well. It is sensitive to air. However, it is not generally considered to be as harmful as styrene and chloroform in the previous steps. There is no documentation of health risks associated with prolonged exposure to the chemical. Nevertheless, precautions should still be taken to minimize direct exposure. Trans-cinnamaldehyde is generally considered to comply with green chemistry regulations, and is found in cinnamon bark in small quantities and is what gives cinnamon its distinctive odor and flavor. Sulfuric acid, H2SO4, is not flammable but is considered corrosive and can cause severe burns, so it should always be handled with care and only when wearing gloves. It is also very dangerous to the respiratory system and may be fatal by inhalation, or ingestion. Always work with sulfuric acid under a hood to minimize inhalation, and if inhalation, ingestion, or contact with eyes does occur, medical help should be sought immediately. Due to its corrosive nature, sulfuric acid is not considered to be particularly compliant with the methods and principles of green chemistry. Sulfuric acid should be disposed of in an appropriate hazardous waste container. Diethyl ether, Et2O, is harmful and extremely flammable. When exposed to oxidizing reagents diethyl ether can become extremely explosive and should be kept out of the presence of water. It is toxic and harmful through contact with skin, inhalation, and eyes. Work should be done in a hood and such precautions as goggles and gloves. Diethyl ether should not be disposed of down the drain. It should be disposed of in a hazardous waste container and later incinerated. It diethyl ether is released into the soil or water, it will not biodegrade and bioaccumulation does not occur. Diethyl ether is not toxic to aquatic life. Water is safe for the environment, and may be disposed of down the drain. There are no safety issues associated with working with it or handling it. During the procedure, take care to make sure that the oil bath doesn’t overheat. Keep a thermometer in the oil bath to make sure that the temperature is maintained. An oil bath must be used, since the reaction must be heated at 180 °C, and water will boil significantly before that. Always do all work under hood while wearing goggles and gloves.
Overall budget:

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Supplier</th>
<th>Cost</th>
<th>Amt. Needed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrene</td>
<td>Reagent Plus</td>
<td>$0.0216/g</td>
<td>0.531g</td>
<td>$0.0114</td>
</tr>
<tr>
<td>Grubb’s Cat.</td>
<td>Aldrich</td>
<td>$47.00/g (in bulk)</td>
<td>0.21g</td>
<td>$9.87</td>
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<td>Chloroform</td>
<td>Reagent Plus</td>
<td>$34.90/L</td>
<td>10mL</td>
<td>$0.35</td>
</tr>
</tbody>
</table>

*Sulfuric acid (1mL of 28%) The cost is negligible.

Total costs per synthesis: **$10.23**

*Note: We confirmed with Dr. Hicks that the deviation from the normal price range was acceptable.

References

**Step 1:**

**Step 2:**

*Note:*
Step 2 is a hydrolysis reaction followed by an elimination reaction. A similar reaction takes place in scheme 4 from molecules 10 to 12, and the reactions in scheme 5 of (Tutar, et.al.).

Safety, disposal, and green issues references

Green Chemistry. 3 Feb. 2006.
Material Safety Data Sheet. 5 Feb. 2006.
   <http://www.conncoll.edu/offices/envhealth/MSDS/chemistry/C/trans-Cinnamaldehyde-99.html>
MSDS for TRANS-CINNAMALDEHYDE. 3 Feb. 2006.
   <http://cast.csufresno.edu/graduatelab/msds/C/TRANS-CINNAMALDEHYDE>
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   <http://www.camd.lsu.edu/msds/p/polystyrene-co-divinylbenzene.htm#Disposal>
Product Info: 3-Phenylpropyl chloride. 5 Feb. 2006.
   <http://chemdat.merck.de/pls/pi03/web2.zoom_in?text=818624&screen=110&cid=xcsfs&pg=0&s=&l ang=4>
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