Honors Cup Synthetic Proposal

Section: 216H.221, Group C
Group Members: Frank Bartley, Phillip Lombard, Joe Pawlowski, Thomas Antoni Peter

Title: Three-step synthesis of trans-cinnamaldehyde from cinnamic acid

Introduction

Trans-cinnamaldehyde is the molecule that is responsible for cinnamon’s characteristic taste and smell. It is found in the bark of cinnamon trees. Typical cinnamon-scented products contain only a few tenths of a percent of this very strong compound. Cinnamaldehyde is also used as an agricultural fungicide.

Overall Synthetic Reaction Scheme

Figure 1: Overview of three-step trans-cinnamaldehyde synthesis
**Synthetic Transformation I**

![Chemical Structure](image)

Figure 2: Transformation I

**Experimental I**

The first step of this synthesis involves the transformation of cinnamic acid to its acyl chloride form, cinnamyl chloride. This well-known reaction\(^1\)\(^2\) is performed by heating cinnamic acid (2 g, 13.50 mmol) and freshly distilled thionyl chloride (2.29 mL, 31.5 mmol) under reflux and stirring for two hours. The excess thionyl chloride is then distilled off. Yields range from 58 to 87\(^\%\)\(^1\). Even in the case of 58\(^\%\) yield, enough product will be formed to reach our target goal of 0.5 g of *trans*-cinnamaldehyde. Yields for the remainder of this proposal will reflect the maximum 87\(^\%\) yield.

**Expected yield:** 87\(^\%\), 1.79 g

**Safety, Disposal and Green Issues of Transformation I**

Cinnamic acid is an eye, respiratory, and skin irritant and should be handled under a fume hood. In case of eye contact, wash with plenty of water for at least 15 minutes and seek medical advice. Be sure to wear suitable clothing when handling cinnamic acid. In case of swallowing, wash mouth out with water *if person is conscious* and call a physician. If cinnamic acid comes in contact with skin, wash with soap for at least 15 minutes. If inhaled, remove person to fresh air and give artificial respiration in case the person stops breathing. In case of ignition, use carbon dioxide, dry chemical powder, or appropriate foam. Cinnamic acid emits toxic fumes under fire conditions and appropriate breathing apparatus and clothing should be worn during fire fighting. Cinnamaldehyde should be disposed of by mixing with a combustible solvent. Solution should then be burned in a chemical incinerator with afterburner and scrubber.

Thionyl chloride is corrosive and reacts vigorously with water. Contact with water also releases toxic gas. Contact of this gas with metal surfaces can form explosive hydrogen gas. Thionyl chloride is harmful if inhaled and if swallowed. Skin contact can also produce severe burns, and this compound also has an unpleasant odor. In case of skin or eye contact, inhalation, or ignition, follow instructions given for cinnamic acid. The same applies for ingestion, and *by no means* induce vomiting. Thionyl chloride may decompose into harmful carbon dioxide, carbon monoxide, and hydrogen chloride gases over extended periods of time. Disposal instructions for thionyl chloride are the same as cinnamon acid disposal (above).

Cinnamyl chloride is highly toxic and may cause sensitization and/or burns on skin contact. In case of ingestion, skin or eye contact, or ignition, follow instructions given for cinnamic acid. Excessive inhalation of cinnamyl chloride causes respiratory depression and can be fatal.
Disposal instructions for cinnamyl chloride are the same as cinnamon acid and thionyl chloride disposal (above).
Synthetic Transformation II

![Reaction Scheme]

Figure 3: Transformation II

Experimental II

Cinnamyl chloride is reduced to its corresponding alcohol (cinnamyl alcohol) in exceptional yield. The resulting 1.79 g (11.73 mmol) of cinnamyl chloride from transformation I is added to 60 mL of dry tetrahydrofuran, followed by adding sodium borohydride (1.32 g, 35 mmol) in a round-bottomed flask. Methanol (4.5 mL) is then added dropwise via an addition funnel to the solution for an hour at room temperature. Next, 1N hydrochloric acid (3.0 mL) is added and the solution is stirred for 10 minutes. The methanol and THF is then evaporated. Ether is used to extract the reaction mixture, and is subsequently washed with water and brine. Magnesium sulfate is then used to dry the ether layer. Finally, the solvent is evaporated at a reduced pressure (i.e. rotary evaporation).

Expected yield: 95%, 1.50 g

Safety, Disposal and Green Issues of Transformation II

Tetrahydrofuran is flammable and may form explosive peroxides. It is a possible carcinogen that targets the central nervous system as well as the liver. THF is harmful if swallowed and is a skin, respiratory, and eye irritant. In case of ingestion, eye or skin contact, or inhalation, follow the instructions that were given for cinnamic acid, thionyl chloride, or cinnamyl chloride. For small fires, use “alcohol” foam, dry chemical, or carbon dioxide. In case of a large fire, use large quantities of water in mist or spray form, as streaming water may be ineffective. Refer to explanation given in cinnamic acid description for firefighting gear that should be worn. Use the same disposal instructions already given when dealing with THF.

Sodium borohydride is a flammable and toxic solid that causes burns on skin contact. Contact of sodium borohydride with water forms extremely flammable gasses. Typical (see above) procedure should be executed in case of ingestion or inhalation. In case of ignition, do not use water, foam, or carbon dioxide, but rather dry chemical powder. Typical firefighting gear applies. Sodium borohydride can decompose over time to produce harmful borane/boron oxides, sodium oxide, and hydrogen gas. Use care when disposing of this compound, as environmental exposure causes a pH shift which can be harmful to aquatic life. Contact a licensed professional for disposal of sodium borohydride.

Anhydrous methanol is very toxic and can cause serious, irreversible effects in case of ingestion, inhalation, and skin contact. Ingestion could lead to blindness or death. Typical procedure
applies in case of ingestion, inhalation, and skin or eye contact. In case of fire, use water spray, carbon dioxide, chemical powder, or appropriate foam. Use standard firefighting gear. To dispose of methanol, use the instructions given for THF or the like.

Cinnamyl alcohol is harmful if swallowed and irritating to the eyes and skin. See methanol for procedure in case of ingestion, inhalation, skin or eye contact, ignition, firefighting gear, and disposal.
Synthetic transformation III

![Figure 4: Transformation III](image)

**Experimental III**

Finally, cinnamyl alcohol is oxidized to form *trans*-cinnamaldehyde. Potassium permanganate, an extremely common oxidizer, is used. However, potassium permanganate usually yields uncontrolled oxidation, usually oxidizing primary alcohols to an aldehyde and then its respective carboxylic acid form. To control the oxidation process so that it halts at the aldehyde stage, a solid support such as Kieselguhr is used\(^4\,^5\).

To begin, 1.34 g of cinnamyl alcohol (10 mmol) product of the 1.50 g (11.18 mmol) from the last transformation is mixed with 20 g of the KMnO\(_4\)-Kieselguhr reagent\(^6\) and is shaken for 20 minutes at 65-70\(^\circ\) C. Note that the time and amount of KMnO\(_4\)-Kieselguhr reagent are educated guesses derived from the resources and may not be precise. To ensure that *trans*-cinnamaldehyde is being formed, the reaction is monitored by TLC (using aluminum-backed silica gel plates and 8:2 hexane : ethyl acetate as an eluent). Once the reaction is complete, wash the reaction mixture with diethyl ether three times. The filtrates are then evaporated and purified by distilling with a Vigreux column under reduced pressure.

**Expected yield:** 94%, 1.24 g

**Safety, Disposal and Green Issues of Transformation III**

Potassium permanganate, as already mentioned, is an extreme oxidizer and should be handled with care. Contact with combustible material may cause fire. Harmful if swallowed. See methanol for procedure in case of ingestion, inhalation, skin or eye contact, ignition, and firefighting gear. This compound is an extreme environmental hazard and can cause long-term adverse affects to aquatic life. Contact a licensed professional waste disposal service to dispose of KMnO\(_4\).

Kieselguhr is a carcinogen and should not be inhaled. Typical procedure should be applied in case of ingestion, inhalation, or skin or eye contact. This compound is not flammable, but emits toxic fumes under fire conditions. To dispose of Kieselguhr, use the instructions given for THF or the like.
## Overall Budget

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Supplier</th>
<th>Product No.</th>
<th>Cost</th>
<th>Amt. Needed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinnamic acid</td>
<td>Aldrich</td>
<td>C80857</td>
<td>$0.22/g</td>
<td>2.0 g</td>
<td>$0.44</td>
</tr>
<tr>
<td>Thionyl chloride</td>
<td>Sigma-Aldrich</td>
<td>320544</td>
<td>$0.09/mL</td>
<td>2.29 mL</td>
<td>$0.21</td>
</tr>
<tr>
<td>Anhydrous THF</td>
<td>Aldrich</td>
<td>401757</td>
<td>$0.06/mL</td>
<td>60 mL</td>
<td>$3.60</td>
</tr>
<tr>
<td>Sodium borohydride</td>
<td>Sigma-Aldrich</td>
<td>213462</td>
<td>$1.59/g</td>
<td>1.32 g</td>
<td>$2.10</td>
</tr>
<tr>
<td>Anhydrous methanol</td>
<td>Aldrich</td>
<td>322415</td>
<td>$0.03/mL</td>
<td>4.5 mL</td>
<td>$0.14</td>
</tr>
<tr>
<td>1N hydrochloric acid</td>
<td>Sigma</td>
<td>H3162</td>
<td>$0.01/mL</td>
<td>3.0 mL</td>
<td>$0.03</td>
</tr>
<tr>
<td>Potassium permanganate</td>
<td>Sigma-Aldrich</td>
<td>207985</td>
<td>$0.05/g</td>
<td>20 g*</td>
<td>$1.00</td>
</tr>
<tr>
<td>Kieselguhr</td>
<td>Sigma-Aldrich</td>
<td>392545</td>
<td>$0.02/g</td>
<td>20 g*</td>
<td>$0.40</td>
</tr>
</tbody>
</table>

**TOTAL:** $7.92

*Exact amount needed is unknown (see transformation III). 20 g is the absolute maximum that could possibly be used.

## References

1: Pau, A; Boatto, G; Asproni, B; Palomba, M; Auzzas, L; Cerri, R; Palagiano, F; Filippelli, W; Falcone, G; Motola, G; *Il Farmaco* 2000 55(6-7) 439-447

2: Kampmeier, J; Harris, S; Rodehorst, R; *J. Am. Chem. Soc.* 1981 103(6) 1478-1485


4: Lou, J; Wang, M; Zhu, L; Fang, Z; *Catalysis Communications* 2003 4(12) 647-649

5*: Lou, J; Chen, X; Wang, M; *Oxidation Communications* 2004 27(3) 610-613

6: Lou, J; Lou, W; *Synthetic Communications* 1997 27(21) 3697-3699

*Resource was, unfortunately, not available at any University of Michigan library.