Honors Cup Synthetic Proposal

Section: 231-V
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Title: Synthesis of Ethyl 3-methyl-3-phenylglycidate (Strawberry Aldehyde) from Phenylmagnesium Bromide (A Grignard Reagent)

Introduction: Each of the steps in our synthesis utilizes basic chemical techniques to create Strawberry Aldehyde, an intriguing commercial compound. The first step involves using a Grignard Reagent to form a secondary alcohol. In the second step, Swern Oxidation produces acetophenone, which undergoes Darzens Condensation in step three to yield the final product. Strawberry Aldehyde’s unique aroma makes it highly sought after by perfume and flavor industries. This compound is often used as a sweet and pleasant base in perfumes, candies, beauty care products, and ice cream.

Overall synthetic reaction scheme:

A

\[
\begin{align*}
\text{Phenylmagnesium} & \quad \text{B} \\
\text{MgBr} & \quad \text{Acetaldehyde} \\
\text{Mg} & \quad \text{COCI}2, \text{DMSO}, \text{TEA, 2,4-DNP} \\
\text{H} & \quad \text{CH2Cl2} \\
\text{1-phenylethanol} & \quad \text{Ethyl chloroacetate} \\
\text{Mg} & \quad \text{CH3CN} \\
\text{NaH} & \quad \text{1-phenylethanone} \\
\text{Mg} & \quad \text{Ethyl 3-methyl-3-phenylglycidate} \\
\end{align*}
\]

Molecular Formulas and Weights:
- Phenylmagnesium Bromide: C₆H₅MgBr, Molecular Weight: 181.31 g/mol
- 1-Phenylethanol: C₆H₁₂O, Molecular Weight: 122.16 g/mol, m/z: 107 (100%), 79 (80%), 77 (42%)
- 1-Phenylethanone (Acetophenone): C₆H₆O, Molecular Weight: 120.15 g/mol, m/z: 105 (100%), 77 (75%)
- Ethyl 3-methyl-3-phenylglycidate: C₁₂H₁₄O₃, Molecular Weight: 206.24 g/mol
Step 1

Synthetic transformation 1:

\[
\begin{array}{c}
\text{Mg} \\
\text{Br} \\
\text{Mg} \\
\end{array}
\xrightarrow{\text{Acetaldehyde}}
\begin{array}{c}
\text{OH} \\
\text{H} \\
\end{array}
\]

Phenylmagnesium Bromide

1-phenylethanol

Experimental 1

Equipment must be completely dry before proceeding with reaction. (0.92 g, 5.07 mmol) phenylmagnesium bromide (A) in a solution of 10 ml ethyl acetate was placed in a 500 ml round bottom flask. With an addition funnel, (0.204 g, 4.61 mmol) of acetaldehyde in 10 ml of ethyl acetate was added slowly, drop wise. After two hours of stirring, the reaction was placed in an ice bath and 5mL concentrated hydrochloric acid was added until two distinct layers were present. The organic layer was separated using a separatory funnel. The aqueous layer was further extracted with 10ml of ethyl acetate. The two organic layers were combined and dried with MgSO\(_4\). The solute was removed by vacuum filtration and the remaining solution was evaporated using rotary evaporation. The solution is then distilled to leave 1-phenylethanol (B).

Expected yield: 75\% 0.423 g

Safety, disposal and green issues 1:

Phenylmagnesium Bromide – Extremely flammable, reacts violently with water, releasing flammable gas.

Acetaldehyde – Air sensitive, harmful by inhalation, ingestion and through skin absorption. May be anticipated to be a carcinogen. Contact with skin or eyes can cause severe irritation or burns.

Take care to dispose of waste properly, especially with acetaldehyde. Handle chemicals with gloves at all times.
Step 2

**Synthetic transformation 2:**

B

\[
\begin{align*}
\text{1-phenylethanol} & \quad \xrightarrow{\text{COCl}_2, \text{DMSO, TEA, 2,4- DNP}} \quad \text{1-phenylethanone} \\
\text{(Acetophenone)} & \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

**Experimental 2**

Note: The expected yield reported in the literature seems to be abnormally high (97%), so our expected yield is modified slightly to reflect expectable results in lab (92%). Oxalyl chloride (.439g, 3.457mmol) was dissolved in 25 mL CH\(_2\)Cl\(_2\) and placed in a 3 neck flask (modified from the 4 neck flask in the literature) equipped with a thermometer and two addition funnels. A magnetic stirrer was added to ensure mixing through the reaction. 0.590 g DMSO (7.544mmol) dissolved in CH\(_2\)Cl\(_2\) (5 mL) was added to one funnel. 1-phenylethanol (B) dissolved in 10 mL CH\(_2\)Cl\(_2\) was added to the other funnel. Contents of the flask were cooled to –60° C. DMSO solution was added dropwise over 5 minutes. The solution was left to stir for 10 minutes. The 1-phenylethanol solution was added slowly, dropwise. The mixture was stirred for 15 minutes and then followed by the addition of (.475g, 3.457mmol) TEA dropwise, for 5 minutes. The cooling bath was removed and water (30 mL) was added at room temperature, stirring continually for 10 minutes. The organic layer was separated with a separatory funnel. The solution was then condensed to 10 mL and treated with 2,4- DNP (1.982g in 100mL CH\(_2\)Cl\(_2\))*. After 30 minutes, the precipitated 2,4-DNP was filtered out of the solution to leave 1-phenylethanone (C).

*the values regarding our DNP solution were slightly ambiguous in the referenced procedure, which only noted the use of 110-112mL of .1M DNP solution. The figures we generated are derived from .1M of 2,4-DNP in 100mL of our solvent – CH\(_2\)Cl\(_2\).

**Expected yield:** 92% \(0.384\) g

**Safety, disposal and green issues 2:**

Oxalyl Chloride – avoid contact with water
DMSO – effects of overexposure include slight eye irritation, nausea, cramps, chills and drowsiness.

2,4-Dinitrophenylhydrazine – flammable and explosive if dry, harmful if absorbed through skin or ingested.
Triethylamine – Extremely flammable, corrosive, can cause burns to skin, eyes, respiratory tract.

Dispose of waste in proper container.
Step 3

**Synthetic transformation 3:** (Chemdraw picture of third transformation)

![Chemdraw diagram of synthetic transformation]

**Experimental 3** (notes if this transformation is not exactly the one reported in literature (e.g. on a different scale) and how it was modified):

Ethyl chloroacetate (.43g, 3.51mmol) and 1-phenylethanone (C) (.384g, 3.19mmol) were added to CH₃CN (450 mL) under vigorous stirring. The mixture is heated to 60° C, whereupon solid NaH (.085g, 3.51mmol) was added in small portions, taking care not to increase the temperature above 65° C. The addition process lasts a cumulative of 1.5 hours. The mixture was then stirred until all hydrogen was evolved and then heated under reflux for 30 minutes. The solvent was removed by distillation through a distilling column. The product was collected with water (150 mL) and CH₂Cl₂ (150 ml) then placed in a separatory funnel. The organic layer was extracted, dried with NaSO₄, and evaporated. The residue was distilled using vacuum distillation, resulting in Ethyl 3-methyl-3-phenylglycidate (Strawberry Aldehyde). TLC, IR, NMR were taken against our starting material.

**Expected yield:** 76% .501 g

**Safety, disposal and green issues 3:**

CH₃CN: toxic if inhaled or ingested, flammable. Work with under fume hood.
NaH: toxic if inhaled or ingested, flammable. Work with under fume hood.

Take care to dispose of waste properly.
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>Phenylmagnesium bromide</td>
<td>Aldrich</td>
<td>$0.08/mL of 3M solution</td>
<td>.92g</td>
<td>$0.14</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>Sigma-Aldrich</td>
<td>$0.18/mL</td>
<td>.204g</td>
<td>$0.04</td>
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<td>Oxalyl Chloride</td>
<td>Aldrich</td>
<td>$1.16/g</td>
<td>.439 g</td>
<td>$0.51</td>
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<td>Dimethyl sulfoxide</td>
<td>Sigma</td>
<td>$1.20/mL</td>
<td>.590 g</td>
<td>$0.65</td>
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<tr>
<td>Triethylamine</td>
<td>Sigma-Aldrich</td>
<td>$0.06/mL</td>
<td>.475 g</td>
<td>$0.04</td>
</tr>
<tr>
<td>2,4-Dinitrophenylhydrazine</td>
<td>Aldrich</td>
<td>$0.51/g</td>
<td>1.982g</td>
<td>$1.02</td>
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<tr>
<td>Ethyl chloroacetate</td>
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<td>.43 g</td>
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<td>Methyl Cyanide</td>
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<td>450 mL</td>
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<td>.085 g</td>
<td>$0.02</td>
</tr>
</tbody>
</table>

*Note: Chemical costs are estimated based on bulk prices from Sigma-Aldrich Catalogue.

**Ethyl acetate, Hydrochloric acid, Methylene chloride, and MgSO₄/ NaSO₄ are assumed to be common laboratory supplies, and so are not included in the cost.

Total costs per synthesis: $8.15

References:

1. **Step One: Product A to B**
   http://www.sonoma.edu/users/t/trowbrda/336/grignard.html

2. **Step Two: Product B to C**

3. **Step Three: Product C to D**
   Darzens, G. *Compt. Rend.;* 1904, 139, 1214.