Scheme 3: N-Acylation

Synthesis of N-Crotonates

\[ \text{6a-e (from Scheme 2) } \quad \text{or 6f (from Scheme 4)} \]

\[ \text{Crotonic Acid (86.0 g/mol)} \]

\[ \text{NEt}_3 (139 \text{ mL/mol)} \]

\[ \text{dry CH}_2\text{Cl}_2 \]

\[ \text{Dimethylaminopyridine (122 g/mol, catalyst)} \]

\[ \text{or Crotonic Acid (86.0 g/mol)} \]

\[ \text{or 6f (from Scheme 4)} \]

\[ \text{255.6 g/mol} \]

**Scheme 3 Procedure: N-Acylation of Pyrazolidinone 6a-f Using Crotonic Acid and Mukayama’s Reagent (9)**

**Scheme 3, Part 1: Starting the Reaction for N-Acylation, 6 \( \rightarrow \) 10**

1. Determine the number of mmol of pyrazolidinone 6 that you have in your Erlenmeyer.
   - You should have calculated your mass yield, as well as the molar mass and the number of mmol for your version of 6, during the previous Scheme.
   - Note: Your substrate 6 might be somewhat contaminated, so you may not actually have as many mmol of 6 as you calculated based on mass alone.

2. Add 25 mL of dry anhydrous CH\(_2\)Cl\(_2\)
   - add a white rubber septum to exclude air, if you aren’t ready to continue with following steps very quickly.

3. Hopefully the sample will dissolve on its own within a few minutes. If not, you may wish to add a reflux condenser and heat the mixture (hot plate 5) until it dissolves. If you did heat it, to facilitate dissolving, then turn the hot plate off as soon as things are dissolved, and take the flask away from the hot plate to cool for 5 minutes.

4. Based on how many mmol of pyrazolidinone 6 you have, add 1.1 equivalents of crotonic acid 8 (86.0 g/mol).
   - In other words, if you have 10 mmol of 6, add 11 mmol of 8.

5. Then add 1 mmol of dimethylaminopyridine (122 g/mol). This is a catalyst, so the exact amount isn’t crucial, and we’re using a lot less of this than of the other reactants.

6. Weigh out and add 1.3 equivalents of 2-chloro-1-methylpyridinium iodide (Mukayama’s Reagent, 9, 255.6 g/mol).
   - Immediately reclose the bottle from which you took reagent 9, since it is moisture sensitive. If you leave it uncovered, it will go bad and everybody who uses it after you will have problems.

7. Record all of your observations. (Is the mixture homogeneous or heterogeneous, etc.)

8. Syringe in 2.8 equivalents of triethylamine (139 mL/mol).
   - This will get the reaction started.
   - Record observations. Does anything happen? Exotherm or anything? Color change? Solubility changes?

9. Add a septum into your flask, and poke a syringe needle through it to serve as a pressure vent.

**THIS IS AN IDEAL PLACE TO STOP AT THE END OF WEEK TWO. LET THINGS STIR FOR 5 MINUTES, MAKE SURE THERE IS A SEPTUM TO YOUR FLASK WITH A SYRINGE NEEDLE POKING IN TO SERVE AS A PRESSURE VENT, AND STASH IT IN YOUR DRAWER TILL NEXT WEEK.**

10. Emergency Note: If you don’t get this far during week two, be sure that you come in and get the reaction set up at least a day before your lab period.
Scheme 3, Part Two: Workup/Isolation of Product 10 (Week Three Begins Here)

11. Weigh out 3 equivalents (relative to your reactant $6$) of solid ammonium chloride (0.0535 g/mmol), and dissolve it into 50 mL of tap water.
   • It’s possible that there will be an NH$_4$Cl/water mixture already prepared.
12. Get about 45 mL of ether.
13. Pour about half of the ether and about half of the NH$_4$Cl/water into your reaction flask. Stir the mixture for a minute.
14. Pour the contents of your reaction flask into a separatory funnel.
15. Add the rest of the ether and NH$_4$Cl/water into your Erlenmeyer, rinse them around, and then add that to your separatory funnel.
   • The purpose of the NH$_4$Cl/water wash is to convert the neutral triethylamine into ionic triethylamine-hydrochloride, which will extract into the aqueous layer.
16. Shake cautiously, with venting, then allow the mixture to settle.
   • The organic layer will probably be more strongly colored
   • The top layer will normally be the organic layer, but if you aren’t sure, add some extra water to see which layer gets bigger.
   • If the layers separate poorly, consult the instructor and we can improvise.
17. Prepare a clean 125-mL Erlenmeyer flask with a ground-glass joint, with a long stir bar inside, and with the mass of the combination recorded.
   • This could be the same flask/stirrer you’ve used and weighed before. If so, clean it by rinsing/brushing with water, then with acetone.
18. Find a fritted filter column (the one with the 6-inch column above a white fritted filter, with a ground-glass joint on the bottom, and with a vacuum connector on the side.)
19. Weigh out 20 g of silica, pour it into the filter funnel, and attach the filter funnel into the 150-mL Erlenmeyer.
   • This is a lot more silica than was used in Scheme 2. When the dry silica is poured into your fritted filter column, it should fill about half of the space from the frit to the top of the column. If not, consult instructor. If the column is too short, contaminants will get through.
   • The silica layer is meant to absorb some polar, sticky byproduct from the Mukayama Reagent 9, and also any triethylamine hydrochloride that did not get removed by the separatory funnel treatment. We are doing a crude but rapid “flash chromatography” to try to partially purify your product $10$.
20. Weigh out 30 g of sodium sulfate, and pour this on top of the silica bed.
   • The sodium sulfate will function to absorb water.
21. Assuming the top layer in the separatory funnel is the organic phase, carefully drain out the lower aqueous layer into a beaker, and pour the organic solution onto the filter column.
   • Try to pour it carefully/evenly so that the surface of the column doesn’t get all pitted. If pouring it in makes a big pit, the effective length may be compromised.
   • If you scissor-cut a piece of filter paper to kind of lay on top of the sodium sulfate, that can help to protect against pitting. Probably not needed.
22. Carefully/gradually open up the vacuum so that liquid gets pulled through without boiling out and getting sucked into the vacuum tube.
23. Pour the aqueous phase back into the separatory funnel. Add an additional 25 mL of 2/1 ether/dichloromethane, and shake it up briefly. The organic layer will probably again be the top layer. If so, pour off the aqueous layer into a beaker (this will get thrown away), and then pour the organic phase onto the filter column. Rinse this through the filter column to try to make sure that no desired product is left stuck on the silica.
24. **Concentrate this solution.** Attach a reflux condenser with no water flow, and with a vacuum adaptor on top. While stirring and with no heat turned on, slowly open the vacuum. Things
will bubble a lot at first. Crack open the vacuum as aggressively as you can get away with without causing the mixture to foam over.

- Within about 2 minutes you should be able to get the vacuum fully opened.
- Notice the condensation (and perhaps ice) that forms on the outside of the flask.

25. Once you’ve been able to safely open the vacuum fully, turn the hot plate on at a setting of 5, and heat/boil/vacuum the mixture while continuing to stir (setting 6) for 20 minutes.

  - Try to wipe off the frost from the walls as early as possible.
  - The mixture should be pretty thick and concentrated by the end, with limited bubbling.
  - In some cases, the material will foam up like cotton candy or taffy. With continued heating, though, usually the entrapped solvent does escape, and the material collapses back to a thick paste.

26. After the vacuum-heating, turn off your vacuum first, then turn off the heat, remove the flask from the heat, detach the vacuum hose, and remove the condenser.

27. Immediately, while the mixture is still hot and hopefully liquid, dip in with a long-stem pipet and draw up a quarter inch of material. Immediately place the pipet into an NMR tube. The material will probably harden/freeze as soon as it cools.

28. Use 1.0 mL of CDCl3 to make up your NMR sample. Add a red cap to this one.

  - We won’t run a GC on this one. The product is so big that it doesn’t vaporize well.

29. Submit your NMR-10 to the NMR queue.

30. See the section about NMR’s to review expectations in terms of data, analysis, and presentation.

31. Weigh your flask, so that you can determine mass, millimoles, and percent yield.

  - It is well possible that your mass recovery will exceed your theoretical yield. That would be impossible if the material was all and only desired product 10x. But there were a lot of side products, and solvents, to try to remove in a short purification sequence. If the yield exceeds 100%, perhaps by a lot, that’s evidence that the purification/distillation was imperfect. (Perhaps badly so….)

Yield Analysis: Calculate the % yield for both the final step, but also for the overall process. (If every step of the synthesis had worked perfectly, you’d end up with 20 mmol of product. So 20 mmol is your theoretical number of moles.)

**Scheme 3 Part Three: Cleaning Up and Pooling Products**

1. **BE SURE THAT YOU’RE PUTTING YOUR PRODUCT INTO THE CORRECT CONTAINER. WE DON’T WANT ANY 10a GOING INTO THE 10b CONTAINER, ETC.**

2. **IF POSSIBLE, AND IF YOU’VE GOTTEN AN NMR FOR YOUR PRODUCT, SHOW IT TO THE INSTRUCTOR BEFORE PUTTING YOUR PRODUCT INTO THE COLLECTION JAR. IF YOUR STUFF IS JUNK FOR SOME REASON, WE DON’T WANT IT TO BE CONTAMINATING THE GOOD PRODUCT CONTRIBUTED BY OTHER STUDENTS.**

**Process for transferring your product into the collection jar:**

1. Add 10 mL of dichloromethane to your flask, and try to dissolve up all of your product with that. If that doesn’t succeed, try heating the mixture on a hot plate for a few minutes to facilitate solubility, and/or perhaps add some additional dichloromethane.

2. Once the product is dissolved, simply pour the solution into the appropriately labeled collection jar.

  - Make sure you’re putting your stuff into the correct jar!
**Final Report Data Sheet.**

Which Scheme 2 Did I use, 2A or 2B? _________________________

Draw pictures for each of your products 3, 6, and 10 on the bottom of the page, or on an attached page, or on the back of this page. Draw the labels for each chemical underneath it.

**GC Results Table:**

<table>
<thead>
<tr>
<th>Substrate ID</th>
<th>Retention Time</th>
<th>Product Purity</th>
<th>Was the Peak Reasonably Sharp or Really Broad?</th>
<th>Did the molecular ion show in the mass spec?</th>
<th>Retention Times and %’s for Major Impurities</th>
<th>Identification Of Major Impurities If Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mass and % Yields Results Table:**

<table>
<thead>
<tr>
<th>Substrate ID</th>
<th>Molar Mass</th>
<th>Yield in grams</th>
<th>Yield in mmol</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NMR Results Table.**
Unless the header indicates otherwise, enter the chemical shifts. Some of the boxes will be blank, depending on the structure. For example, products 3 don’t have any benzyl hydrogens, and only the “e” family has a methyl group attached to the β-carbon.

<table>
<thead>
<tr>
<th>Substrate ID</th>
<th>β-H</th>
<th>α-H’s (list both)</th>
<th>Benzyl H’s (list both)</th>
<th>Methyl Doublet (in the “e” series)</th>
<th>4-Methyl Singlet (in the “b” series)</th>
<th>4-methoxy Singlet (in the “c” series)</th>
<th>Crotonate Methyl group (only in product 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>