CONVERSION TO DELTA 9 THCA USING TRIISOBUTYLALUMINUM

Equipment Needed to Perform the Reaction and Purify the End Product:

1 Heating Mantle with Magnetic Stirring

1 4-neck Round Bottom Boiling Flask (angled necks,24/40)

1 Cylinder of High Purity, Dry, Nitrogen Gas (22 cubic feet or larger)

1 Low Flow Nitrogen Regulator (1-15psi)

1 Laboratory Jack Stand (large enough to hold the heating mantle)

1 Reflux Condenser (at least 200mm in length, 24/40, preferably a Friedrichs or Dewar condenser)

1 Laboratory Recirculating Chiller (alternatively use a 5 gallon bucket of ice water with an aquarium pump. The aquarium pump should have at least a 10ft lift rating)

1 Length of 10mm Silicone Tubing (20ft)

1 Vacuum Flow Control Adapter (Female and Male Joints, 24/40)

2 Thermometer Adapters with Septum (24/40)

1 Claisen 3-Way Adapter (24/40)

10 Stainless Steel Keck Clips (24/40)

2 10mm Hose Barb Adapters (24/40)

3 Retort Stands (3 foot rod length)

6 Bosshead Retort Clamp Holders

5 Retort Clamps (remove rubber from clamp prongs used with the Reflux Apparatus)

1 24/40 Separatory Funnel with Glass Stopper (same volume as the boiling flask or larger)

1 24/40 Pressure Equalizing Addition Funnel with Glass Stopper (half the volume of the boiling flask or larger)

2 Mineral Oil Bubblers

1 Set of Graduated Beakers

1 Fritted Vacuum Buchner Funnel (same volume as the boiling flask or larger)

2 Graduated Erlenmeyer Flasks (the same volume as the boiling flask or larger)

1 Vacuum Filtration Pump

3 steritest vent needles

1 flammable storage fridge. STORE NO MORE THAN 1 MONTH SUPPLY!

1 24/40 Powder Funnel (at least 100mm in diameter)

1 Retort Ring (50-75% the diameter of the separatory funnel)

1 Magnetic Stir bar

1 pH meter pen

1 All Glass Syringe (luer lock)

1 Luer Syringe Needle (long enough to reach the bottom of your flask from the neck of the flask)

One bowl (large enough in diameter to hold the flask when the bowl is filled partially with ice water)

1 dual manifold schlenk line

3 nitrogen needle kits

1 laboratory fume hood with water/vacuum/nitrogen ports (can be ductless but in the event of fire ducted is best)

Materials Needed (Reactants and Solvents):

CBDA Isolate (99% purity or higher)

N-hexane, ACS 99.9% (2ml per 1 gram of CBD)

Activated Molecular Sieve (3a or 4a Zeolite, 0.70 grams per 1 gram of CBDA)

1M triisobutylaluminium solution(0.10ml of stock solution per 1g of CBD)

Aqueous Citric Acid solution [(pH 4) for final water washes]

Ice (for ice bath, optionally for aquarium pump based recirculating chiller)

Personal Protective Equipment (PPE):

1 Set of Laboratory Safety Goggles

1 Chemical Resistant Tyvek Suit (Alternatively one Lab Coat) Fire resistant is best

1 Set of Chemical Resistant Gloves

1 Vapor Respirator

1 Set of Thermally Insulated Gloves (800f rating at least)

1 eye wash station

1 chemical shower

1 laboratory face shield

1 chemical fire extinguisher

Nitrile gloves

Setting Up The Reaction:

IT IS WISE, ALTHOUGH NOT ALTOGETHER NECESSARY TO TAKE EXTRA PRECAUTION TO GREASE EVERY FITTING WITH VACUUM GREASE BEFORE ASSEMBLY.

Reflux Apparatus Assembly:

Assemble the equipment listed above. The heating mantle sits on the laboratory jack stand. The jack stand needs to be in a raised position. This will allow for the removal of the heating mantle during the end of the reaction. The boiling flask sits inside of the heating mantle and is held in place by a retort clamp attached to a retort stand. The reflux condenser plugs into one of the 4 necks on the boiling flask and is secured with a keck clip. Once the condenser is plugged in make sure to hold it in place with a retort clamp hooked up to a retort stand. Make sure that the reflux condenser is pointing straight up and is not sitting at an angle. Attach the nitrogen regulator to the nitrogen cylinder. Attach the 10mm silicone tubing to the nitrogen regulator. Attach the other end of the 10mm tubing to the 10mm hose barb adapter. Plug the nitrogen line into one of the necks on the flask with the hose barb adapter making sure to use a keck clip. Attach the Claisen 3-way adapter to one of the necks of the boiling flask using a keck clip. Insert one septum thermometer adapter into one of the necks on the flask with a keck clip. Insert the second septum thermometer adapter into the straight neck on the Claisen 3-way adapter and secure it with a keck clip. Insert the vacuum flow control adapter into the curved neck of

the Claisen 3-way adapter with a keck clip. Insert the thermometer probe of the heating mantle into the thermometer adapter attached to either of the thermometer adapters with septums. To do this you must pierce the septum of the adapter with the thermometer probe. Make sure that your thermometer probe reaches far enough into your flask to be partially submerged by liquid during the reaction, but not so deep that it comes into contact with your stir bar. Plug a 10mm hose barb adapter into the top of the condenser with a keck clip. Attach a short length of 10mm silicone tubing to this hose barb and then attach the other end of the 10mm tubing to the hose barb on the mineral oil bubbler. Attach the mineral oil bubbler to the retort stand with a retort clamp. The reflux apparatus used to carry out the reaction is now set up. When carrying out the reaction one must be able to assemble this apparatus from memory.

Separatory Funnel Apparatus Assembly:

Place a retort stand in a separate space from the reflux apparatus. Attach to the retort stand 1 retort clamp and 1 retort ring. Use the clamp to hold the 24/40 joint on top of the funnel. The bottom conical portion of the funnel slips into and is held up by the retort ring. The apparatus used to hold the separatory funnel is now set up. Keep in mind that the separatory funnel should come with a 24/40 stopper which plugs into the joint of the funnel. Make sure that this stopper is accounted for as it will be needed to operate the separatory funnel. Before filling with liquid make sure that the stopcock valve is closed.

Buchner Funnel Vacuum Filtration Apparatus Assembly:

Attach to the retort stand 1 retort clamp. Clamp into place 1 Erlenmeyer flask. Plug the vacuum Buchner funnel into the neck of the Erlenmeyer flask and secure it with a keck clip. Attach a length of 10mm silicone tubing to the hose barb of the vacuum Buchner funnel. Attach the other end of the 10mm tubing to the lab vacuum filtration pump. The apparatus used for vacuum filtration is now set up.

Optional Assembly of Aquarium Pump/Bucket Chiller:

In a pinch one can replace a laboratory recirculating chiller with a 5 gallon bucket filled with ice water and an aquarium pump. Make sure that the aquarium pump has a 10ft lift rating or greater. ALWAYS have an identical second aquarium pump on hand in case of the primary pump failing.

Attach silicone tubing to the barb on the aquarium pump. Attach the pump to the bottom of the 5 gallon bucket using the suction cups located at the bottom of the pump. Fill the bucket with an ice water slurry. Attach the silicone tubing from the aquarium pump to the inlet barb of the reflux condenser. Run a length of tubing from the outlet barb of the condenser to the bucket, making sure that the outlet hose is partially submerged in the ice water. Plug in the aquarium pump and cold ice water will begin circulating from the bucket, through the condenser, and back into the bucket.

Preparing The Cannabinoid Solution:

In a flask add the CBDA isolate and the prescribed volume of N-Hexane. Stir and heat LIGHTLY until all of the CBDA has been dissolved. Store for later use or proceed to the sparging section.

Solution Sparging:

To prepare the solution for use one must first sparge it. Sparging involves running a stream of inert gas through your solvent for roughly 6 hours. In order to do this one must fill an appropriate container with solvent, insert a long stem inlet adapter, and bubble nitrogen gas through the solvent for 24 hours. Alternatively use a gas washing bottle or sparging stone. When the solution is appropriately sparged it must be dried with an absorbent prior to use.

Solution Drying With Absorbent:

Remove the stopper from the pressure equalizing addition funnel. Make sure that the stopcock valve on the funnel is turned closed. Plug in the 24/40 powder funnel to the pressure equalizing funnel. Fill the pressure equalizing addition funnel 50% by volume with activated zeolite (3a or 4a Molecular Sieve.) Next, fill the rest of the pressure equalizing funnel with sparged solvent. Remove the 24/40 powder funnel and plug back in the stopper. Store the pressure equalizing funnel filled with solvent and activated zeolite for 24 hours or more before use. Ensure that the storage conditions are adequate given that the funnel is now filled with volatile solvent. Store in a dark cool place.

For larger scale applications where use of the pressure equalizing funnel is inadequate use a large boiling flask or reactor to dry the solution. Add 0.5g of activated zeolite per 2ml of solution to the flask or reactor and stir for 24 hours under a stream of inert gas.

The Reaction:

To start, one must first dry out the glassware that will be used. Place all glassware used in the reaction into an oven set to 200f or higher. Using a Vacuum Oven in order to pull vac is advised but not necessary to attain decent yields. Heat glassware in the oven for at least 4 hours before use. Make sure that thermally insulated gloves are worn while handling hot glass. Remove the glassware from the oven one piece at a time as needed. First remove the 4-neck boiling flask, then the reflux condenser. Make sure that the heating mantle is in a raised position (adjust the laboratory jack stand to the raised position.) Next assemble the condenser and round bottom flask, making sure that both are securely held in place with retort clamps. The round bottom flask should be sitting inside of the mantle as well. Hook up the nitrogen regulator to the round bottom flask. Turn the regulator and begin replacing the atmosphere within the flask with inert gas. This should take place at around 15psi. Hook up the thermometer adapter, and the Claisen 3-way adapter, to the flask. Make sure that the Claisen adapter has the vacuum flow controller and thermometer adapter plugged into it. Make sure the vacuum flow controller valve is shut off. Allow inert gas to flow through the reflux apparatus for 20 minutes or until glassware is cooled… Insert the temperature probe of the mantle

into one of the thermometer adapter septums. Fill the mineral oil bubbler a third of it's volume with mineral oil and attach it to the condenser with the hose adapter and tubing. Hook up the recirculating chiller (or improvised chiller) to the hose barbs on the condenser. Coolant should flow into the lowest barb of the condenser and exit the highest barb. The coolant should be 32f or lower. Adjust the flow of nitrogen to 1-5psi. Remove stopper and insert powder funnel into one of the necks of the boiling flask. Pour into the flask by way of the powder funnel all dry reactants (Activated Zeolite.) Once all dry reactants are inside of the flask replace the powder funnel with a stopper. At this point the dry solvent and catalyst must be added to the flask. Hook up the pressure equalizing addition funnel containing the dry solvent to the vacuum flow control adapter attached to the Claisen 3-way. Leave the stopper plugged into the pressure equalizing funnel. Open the valve on the flow control adapter. Then open the valve on the pressure equalizing funnel. Dried, sparged, cannabinoid solution will begin to enter the round bottom flask. Once that is complete close the valve on the flow control adapter. Then remove the pressure equalizing funnel. Using a syringe with luer lock needle, draw up the catalyst in hexane's solution. To draw up catalyst insert nitrogen needle into head space of catalyst solution. Connect vent needle to external bubbler. Insert needle of syringe into catalyst solution headspace and sparge the needle. Insert needle into solution and draw the solution in. Pull solution slowly so no air bubbles are formed. Pull needle out slightly into head space of solution bottle and draw in a bit of nitrogen. Remove needle. Insert the needle through the septum of the available thermometer adapter. Push solution into flask and then remove the needle from the septum. Quench needle with hexane/isopropanol/water. Dispose of quenching agents as hazardous waste. Cap solution bottle and return to

flammable fridge. Turn on the heating and stirring functions of the mantle. Increase temperature until the boiling point of the solvent is reached. To do this safely: increase the temperature setting on the mantle 5-10 degrees at a time- slowly raising the temperature from room temp to 125 degrees Fahrenheit. Once the desired temperature is reached one must reflux the reaction for roughly 9 hours. To ensure that all of the CBDA is consumed, one can periodically remove a small sample of the liquid inside of the flask by piercing the septum thermometer adapter with the glass syringe and long needle. Monitor with in house analytics. Once the reaction is complete the heating function of the mantle must be turned off and the mantle should be removed (lower the jack stand, lowering the mantle with it.) Replace the mantle with the magnetic stirrer and a bowl of Isopropyl and dry ice slurry. Ensure that the glass has cooled down to close to RT before submerging the glass in ice bath. The magnetic stirrer should be turned on and actively stirring the stir bar inside of the flask. Using the jack stand, raise the ice bath into place, and submerge the flask within the ice bath.

Quench the reaction.
THIS WILL TAKE TIME AND PATIENCE. PLEASE DO NOT RUSH THIS STEP.

This can only be done safely while the round bottom flask is in the ice bath and the reactants inside are chilled. Add isopropanol at ⅓ volume (or until solution stops bubbling/exotherm is controlled) drop wise via septum and stir for 30 minutes. Add methanol at ⅓ volume drop wise and stir for 30 minutes. Remove the hose adapter attached to the mineral oil bubbler from the top of the condenser. Add water drop wise to the top of the condenser so that water drips slowly into the boiling flask.

Remove water bath and replace stirrer. Warm to room temperature and stir for 30 minutes. This SOP calls for an overabundance of water to be used during the quench. Please record the volume of water added to the flask. This number will be used later during the first water wash. The quench is complete when the flask is filled completely both with reactants and water. The reaction is now complete. The next steps involve purifying your product prior to distillation.

Purification:

Vacuum Filtration to Remove Solids:

(Please reference the assembly of vacuum filtration apparatus section prior to attempting vacuum filtration. The vacuum filtration apparatus should be fully assembled prior to use.)

With the reaction quenched by water, and the boiling flask filled up, begin vacuum filtration to remove solids from the mixture. Pour the contents of the round bottom flask into the Buchner vacuum funnel. Establish vacuum in the system by turning on the vacuum filtration pump. The liquid will slowly exit the funnel and begin filling up the Erlenmeyer flask. Once the Erlenmeyer flask is full the buchner funnel should only contain the solids used in the reaction (in this case activated zeolite.) The filtered mixture within the Erlenmeyer flask should be visibly free of any solid contaminants. The next step is to remove the acid catalyst from the mixture. This is done using the separatory funnel apparatus and is covered by the next section.

Liquid- Liquid Extraction (Water Washing):

Before the final product is considered purified one must remove the water and acid catalyst solution from the mixture left in the Erlenmeyer flask. Remove the glass stopper from the top of the separatory funnel and plug in a clean 24/40 powder funnel. Pour the contents of the Erlenmeyer flask into the separatory funnel by way of the powder funnel. Replace the powder funnel with the glass stopper and secure it with a keck clip. The apparatus is now ready to be used.

With the separatory funnel full, begin gently shaking the funnel in order to thoroughly mix the contents together. Make sure every few shakes that you orient the stopcock valve upwards and open the valve. This is done to ensure that positive pressure doesn't build within the separatory funnel leading to the glass rupturing. It is crucial that this step is not skipped. Pressure must be relieved frequently during the mixing of the contents to avoid rupture. After the contents are thoroughly mixed, and pressure has been relieved within the funnel, secure the funnel to a retort stand with a retort clamp and a retort ring. Allow the contents of the funnel to separate into layers. This takes some time so be patient. Once completed there should be 2 distinct layers within the funnel. The top layer (organic layer) contains a solution of solvent and THC isomers. The bottom layer (aqueous layer) contains a solution of water and the catalyst used in the reaction.

In order to separate the layers one must open the valve on the funnel and drain the bottom (aqueous) layer into a beaker. The stopper on the top of the funnel must be removed in order for the liquid inside the funnel to flow out. If the stopper is still in then the liquid will begin to flow out but will abruptly stop flowing at some point. The draining of the aqueous layer is most easily accomplished if one recorded the amount of water used to

quench the reaction. That volumetric amount is the same amount to be drained from the separatory funnel and discarded. Once the aqueous layer has been drained and discarded, what remains inside of the funnel is the solution of solvent and THC isomers.

Split the solution containing cannabinoids (organic layer) into three equal parts. Repeat the water washes with each part separately making sure to fill the funnel fully. There should be significantly more water in the funnel than solution for these washes. Please record the volume of water added to the funnel for each water wash. At the end of each wash, it is that number that determines the volume of the aqueous layer to be drained. Do at least 6 water washes on each of the three equal parts of cannabinoid solution obtained from the first wash. Before discarding the aqueous layer, check the pH of the water with the pH pen. Continue washing the organic layer until the pH is 7. Finish with several washes of PH 4 with an 20 % aqueous citric acid solution.Then do at least 4 washes with ½ saturated brine. If PH is not 6-7 upon completion then wash with distilled water until PH is achieved.

Solvent Drying Prior to Distillation:

Once water washing is complete there will be a small residual water content to the cannabinoid solution. To remove this residual water fill a 24/40 Erlenmeyer flask half way with activated zeolite and fill in the remaining volume with the cannabinoid solution and put a stopper in the top joint of the

flask. Stir on a magnetic stirrer for 24 hours. Then filter through the vacuum Buchner funnel (see vacuum filtration section of SOP) to remove the solids from the solution. This is a second and separate round of vacuum filtration as this should have been done once before water washing. Once that is complete the solvent should be evaporated and purged completely from the product prior to distillation which is optional.

PRO TIPS: In some cases during and prior to distillation an violet hue can be observed in the final product. This is due to rapid oxidation. One way that this can be combated is to provide a scavenger for oxygen radicals. The best way that we have found is using 99.9% copper scrubbies to “pack” the distillation head. It is worth noting that these scrubbies will often have a factory “coating” that is undesirable/may produce side chain reactions. Before packing make sure to wash your scrubbies in citric acid and distilled water then dry appropriately in a vacuum oven before use.

SAFETY:

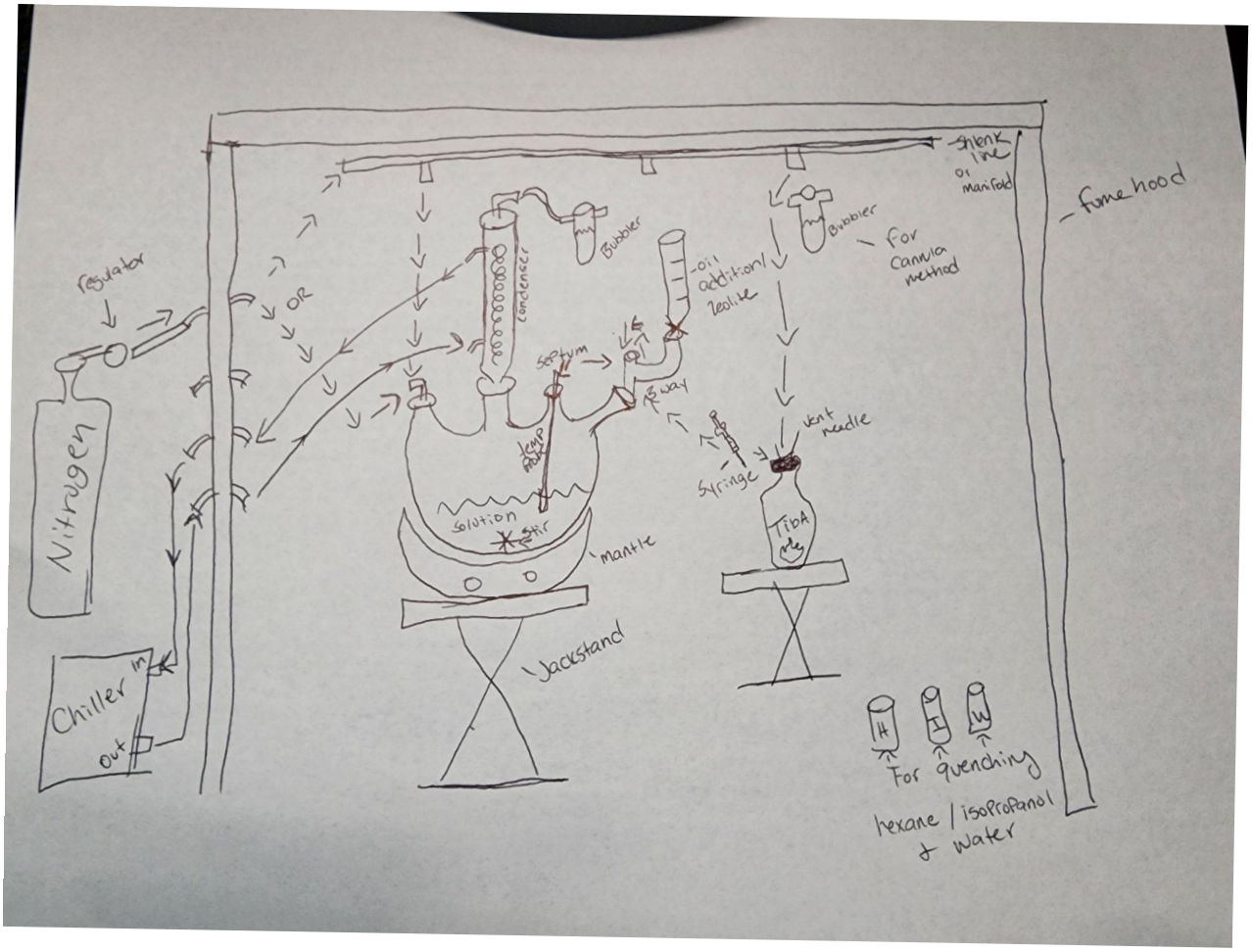
1. Never work alone. Two is good three is better. Alert all other workers in the area of your intentions to use pyrophoric reagents.
2. Keep a fire extinguisher and quenching sand readily available no further than 10 feet from the reaction station for rapid deployment.
3. ALWAYS inspect all glassware for integrity before set up.

4. Set up your reaction and call another chemist over to double check your work.
5. Wear proper PPE at all times.
6. If something feels wrong. DO NOT PROCEED.
7. PRACTICE PRACTICE PRACTICE. Reactions can be done multiple times with just hexane to ensure you are confident and precise without any waste before moving forward with the reagent portion.
8. Remove all other flammable materials and ignition sources from the work area.
9. A small spark can sometimes happen at the end of the syringe if improper discharge of reagent has taken place. Do not panic. This is what your sand is for.
10. Reaction and quench is not time sensitive. Take your time. You will build speed as your confidence increases.

VIDEOS TO WATCH TO INCREASE CONFIDENCE:

A. Synthesis of cannabinoids/ Handling of pyrophoric c…
B. Transferring Pyrophoric Liquids Eps 2

REACTION SET UP ROUGH DIAGRAM.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