DISCLAIMER:

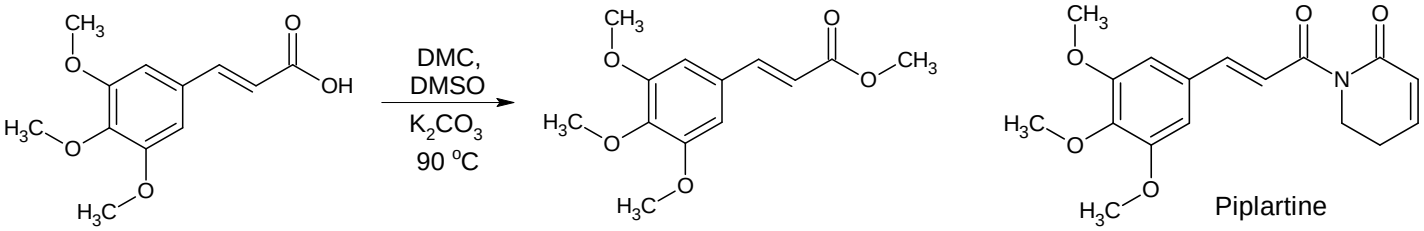
This content is intended for educational and/or entertainment purposes only. Many of the chemicals used in this research are hazardous and should be handled only by properly trained adults who are familiar with the physical/chemical properties and the techniques for handling/transferring them. We assume no liability for accidents or injuries to individuals or property caused by the use or misuse of our products or information.

Esterification of two cinnamic acids using Dimethylcarbonate

In order to investigate certain synthetic methods for use in natural product synthesis, we needed the methyl esters of two particular aryl-substituted cinnamic acids. Seeking a "green" method and avoiding Fisher esterification (which is incompatible with acid-sensitive substrates), dimethylcarbonate (DMC)[1] was chosen as an alternative to classical (toxic) methylating reagents such as iodomethane and dimethyl sulfate. We referred to a 2013 publication[2] by Gorin, et al.., which used DMSO/catalytic K_2CO_3 in refluxing DMC.

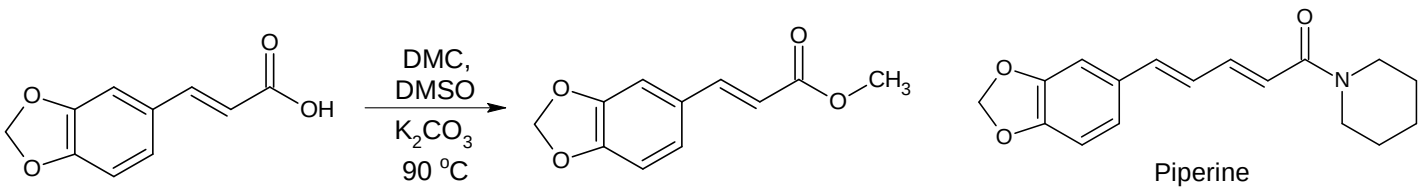
Part 1. Synthesis of Methyl-3,4,5-trimethoxycinnamate

3,4,5-trimethoxycinnamic acid (a natural product itself) and its methyl ester are common precursors to numerous natural products contained in plants used in Ayurvedic medicine. One example is Piperlongumine (*aka* Piplartine), an alkaloid found in Long Pepper *(Piper longum*- which is known as "Pippali" in India) and in Black Pepper[3] (*Piper Nigrum*-*aka* "Maricha"). Another example is Colchicine, found in *Colchicum luteum*, *aka* "Suranjana."



Part 2. Synthesis of Methyl-3-(1,3-benzodioxol-5-yl)-2-propenoate

3,4-(methylenedioxy)cinnamic acid (and its methyl ester) are precursors to fragrances and a multitude of natural products used in homeopathic & Ayurvedic medicine. A well-known example is Piperine, the alkaloid of highest concentration in Black Pepper[3,4], which is known to enhance the absorption of supplements or drugs. Another example is Methysticin, a biologically active lactone found in the roots of the Kava (*Piper methysticum*) plant. We were mainly interested in the ester for synthetic method development and for use in the synthesis (Route D) of Berberine.



1. See last page page for list of abbreviations
2. "Catalytic Methyl Transfer from Dimethylcarbonate to Carboxylic Acids." Yuan Ji, Jessica Sweeney, Jillian Zoglio & David J. Gorin* *J. Org. Chem.*, **2013**, *78*, 11606-11.
3. "Piperine-Type Amides: Review of the Chemical and Biological Characteristics." *International Journal of Chemistry*; Vol. 5, No. 3; **2013**.
4. **"**Black Pepper, the "King of Spices": Chemical composition to applications." *Arabian Journal of Chemical and Environmental Research* Vol. 06 Issue 1, **2019**, 12–56.

Part 1a. Synthesis of Methyl-3,4,5-trimethoxycinnamate (22 g scale)

3,4,5-Trimethoxycinnamic acid (TMCA, MW 238.26 g/mol) 22 g, 92.3 mmol, 1 eq
Potassium carbonate K2CO3 (MW 138.2 g/mol) 5.1 g, 36.9 mmol, 0.4 eq
DMSO (MW 78.13 g/mol, d 1.1 g/mL) 92 g, 1.18 mol, 12.75 eq
DMC (MW 90.08 g/mol, d 1.07 g/mL, BP 90 °C) 92 g, 1.02 mol, 11 eq
NOTE: Product (TMCAME) MW = 252.26 g/mol [20329-96-8] or [7560-49-8] Rep MPs: 91-92 °C, 99-100 °C, 108-110 °C

06/19/25			
TIME	**EXSBT (°C)**	**Variac (%)**	**ACTION**
10:25 am	N/A	N/A	Added DMSO followed by TMCA followed by DMC to 350 mL glass PV equipped with stir bar. Stirred. Once TMCA dissolved, added K2CO3. Flushed with N2 and sealed.
11 am	"	"	Turned on variac (15%)
12 pm	62	15	
1 pm	73	"	Vented
1:30 pm	75.5	"	↑d variac to 18%
2 pm	85	18	Took photo (2:22 pm)- See **PHOTO A**
2:30 pm	89	"	
2:45 pm	90	"	Vented
3:15 pm	91	"	
3:30 pm	92	"	
3:45 pm	93	"	
4 pm	94	"	Vented
4:15 pm	"	"	
4:30 pm	"	"	
5 pm	95	"	Vented, backed off variac to 17%
5:30 pm	93	17	
6 pm	"	"	
6:30 pm	"	"	Vented one last time and left for evening

PHOTO A (06/19/25) 2:22 pm

PHOTO B (06/20/25) 9:07 am

06/20/25			
8:30 am	91	17	Vented and then carried out TLC (5:1 Hex:EtOAc, **PHOTO B:** 1_TMCA, 2_TMCAME from a previous 1 g scale rxn, 3_ALQ from this rxn (diluted ~1:1:1 with IpOAc:H2O)
2:45 pm	92	"	Turned off heat and removed HM; continued stirring
5:15 pm	N/A	N/A	Poured RM into mixture of IpOAc (165 g) + DI water (165 g) in 1 L EFlask and stirred 5 min; Sealed with AL foil and let sit over weekend
06/23/25			
Separated layers & extracted AQ 2 more times (1 x 75 g & 1 x 50 g). Combined IpOAc layers & washed with DI water (2 x 150 g) then brine (1 x 125 g). EOCd in shallow pyrex pan.			
06/24/25			
Mass of (solid) residue (with slight DMS odor): 17 g			
06/25/25			
Added this crude solid to 40 g boiling IPA in a 100 mL beaker then hot-filtered into a clean 250 mL beaker. Washed (extr) filtered solids with 5 g boiling IPA. Sealed beaker with AL foil and let stand.			
06/26/25			
Decanted ML from crystalline mass into clean 100 mL beaker. Dried under stream of air overnight. Sealed beaker containing ML and refrigerated (cooler fridge ~10 ^{o}C).			
06/27/25			
Crop1 mass = 13.8 g (MP 100-101 ^{o}C)			
06/30/25			
Beaker containing ML was removed from cooler fridge and put on ice bath for 1 h before decanting ML from 2nd crop of crystals. Crop2 mass = 800 mg (MP 100-102 oC) so total yield = 13.8 g + 0.8 g = 14.6 g (63%).			

Part 1b. Synthesis of Methyl-3,4,5-trimethoxycinnamate (110 g scale)

3,4,5-Trimethoxycinnamic acid (TMCA, MW 238.26 g/mol) 110 g, 462 mmol, 1 eq
K2CO3 (MW 138.2 g/mol) 32 g, 231 mmol, 0.5 eq
DMSO (MW 78.13 g/mol, d 1.1 g/mL) 541 g, 6.93 mol, 15 eq
DMC (MW 90.08 g/mol, d 1.07 g/mL, BP 90 °C) 624 g, 6.93 mol, 15 eq
NOTE: Product (TMCAME) MW = 252.26 g/mol; CAS#s: 7560-49-8, 20329-96-8; Rep MPs: 91-92, 99-100, 108-110 °C

08/07/25				
TIME	**IT (°C)**	**EXSBT (°C)**	**VARIAC (%)**	**ACTION**
~2 pm	N/A	N/A	N/A	Weighed DMSO, DMC, K2CO3, & TMCA (**PHOTO A**) into 3 L RBF equipped with thermowell
~2:30 pm	"	"	"	Assembled glass (Hickman Still under 16" vigreux column with N2 inlet) & flushed with N2 (used a separate bubbler); Turned on variac & set to 15%
3:30 pm	NC	NC	15	Insulated RBF
4 pm	39	NC	"	↑d variac setting to 16%
4:42 pm	46	54	16	
4:55 pm	49	56	"	↑d variac setting to 18%
6:02 pm	61	68	18	Took photo (**PHOTO B**)
10:45 pm	88	90	"	Condensation present in neck of Hickman still but nothing (ie. MeOH) collected
08/08/25				
10:18 am	95	96	"	~10 droplets collected in Hickman still; RM has yellowed; questioning if magnetic stirring is adequate
~5 pm	"	"	"	Set timer to cut variac (heat) off ~8:30 am Sunday- so considering as ~60 h at IT ≥88 oC

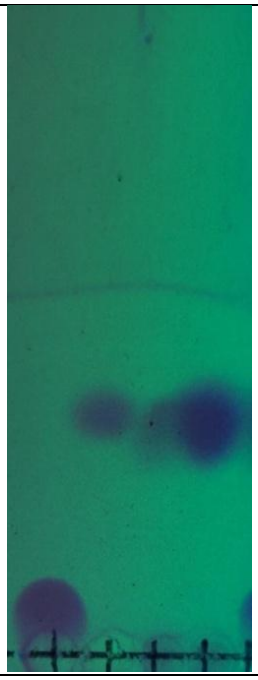
08/11/25→08/14/25

Poured RM into a 4 L FFlask containing (stirring = 3" stir bar) IpOAc & DI water (500 g + 500 g) which was pre-cooled in an in an ice bath to 13 oC (**PHOTO C**). This dilution was exothermic and caused an ↑ in IT (13 oC → 27 oC). The RBF and funnel was rinsed with IpOAc followed by DI water (200 g & 300 g, respectively). Stirred the mixture a few minutes then sealed with AL foil and let sit 24 h. Transferred mixture to 4 L sep funnel and separated layers. Extracted AQ layer again with IpOAc (225 g). Combined IpOAc layers were washed with DI water (2 x 200 g) followed by brine (1 x 250 g). Carried out TLC (**PHOTO D**). Evaporated to a mass of 149 g with a strong smell of DMS.

08/07/25 (~2 pm) PHOTO A
MATERIALS

08/07/25 (6:02 pm) PHOTO B

08/11/25 (1:21 pm) PHOTO C (ABOVE↑)
08/13/25 (6:40 pm) PHOTO D (RIGHT→)
TLC (~3:1 Hex:EtOAc): 1_TMCA (SM), 2_TMCAME (authentic), 3_DHTMCAME (authentic), 4_RM following AQ workup



08/15/25

Further EOCd to mass of 120 g. Still strong smell of DMS. Transferred bulk of crude from glass evap bowl to 600 mL beaker equipped with stir bar. Heated IPA (120 g) in a 600 mL beaker to near boiling and used this hot IPA to extract residue which was adhered to walls of bowl. Did this a 2nd time (120 g IPA) and added both solvent rinses to 600 mL beaker containing the bulk of crude product. Heated to boiling (and measured mass of solvent was 222 g after evap losses) and then hot-filtered (gravity-filter paper) into another clean 600 mL beaker. Sealed with AL foil and let stand. Crystals were observed on the bottom of the beaker in minutes following the hot filtration.

08/18/25

Broke up crystals with spatula, freeing from sides and bottom of beaker. Filtered crystals (aspirator, coarse fritted funnel, no wash); left on aspirator for ~10 min then spread crystals onto shallow glass pan to air dry.

08/19/25

Mass of (dry) Crop1 crystals = 108 g (93%, MP 101-102 oC) **PHOTO E**

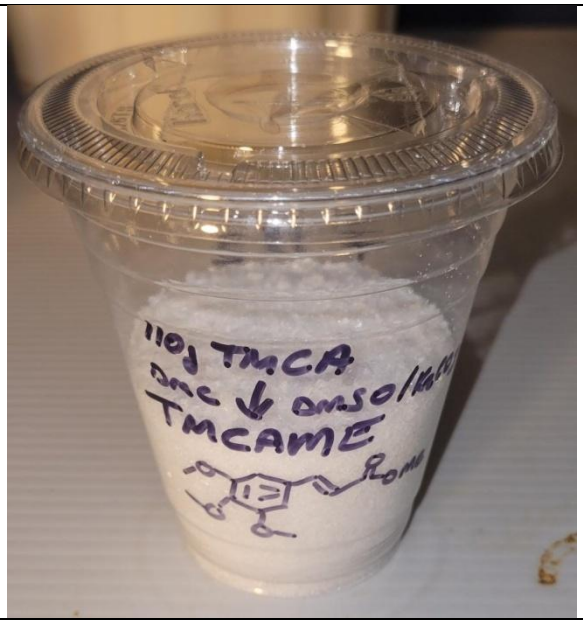


PHOTO E

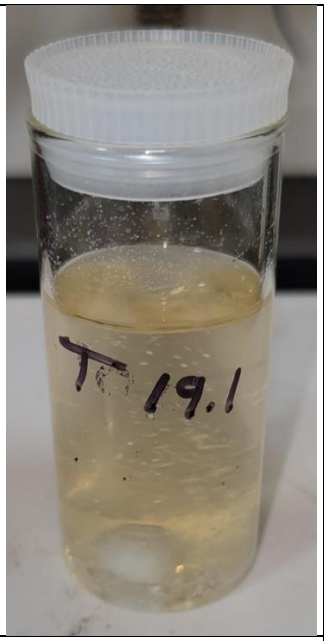
Part 2. Synthesis of Methyl-3-(1,3-benzodioxol-5-yl)-2-propenoate (38.4 g scale)

3,4-Methylenedioxycinnamic acid ("MDCA" MW 192.17 g/mol, MP 242-244 °C) 38.4 g, 0.2 mol, 1 eq
Potassium carbonate (K_2CO_3) MW 138.2 g/mol 13.8 g, 0.1 mol, 0.5 eq
DMSO (MW 78.13 g/mol, d 1.1 g/mL) 234 g, 3 mol, 15 eq
DMC (MW 90.08 g/mol, d 1.07 g/mL, BP 90 °C) (270 g, 3 mol, 15 eq) + (81 g, 0.9 mol, 4.5 eq) = 19.5 eq
NOTE: Product (MDCAME) MW = 206.2 g/mol; MP (rep) 133-134 °C

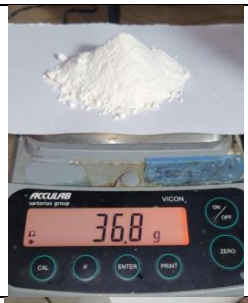
06/10/26			
TIME	**IT (°C)**	**Variac (%)**	**ACTION**
~8:30 pm	N/A-RT	N/A	Took photo of SM, reagents, & solvents (besides extraction solvents) **PHOTO A**
06/11/26			
~2 pm	"	"	Testing solubility on a small scale prior to rxn: To a 1 oz glass shell vial equipped with stir bar was added DMSO (10 g) followed by MDCA (1.64 g)← dissolved quickly. DMC (11.5 g) was added← MDCA remained dissolved. Added K2CO3 (590 mg)→ remained mostly undissolved (which was expected). Stirred & did not observe any solubility issues (**PHOTO B**)
2:11 pm	"	"	Added DMSO (224 g) to a 1 L (3-neck) RBF equipped with stir bar & thermowell (**PHOTO C**)
2:14 pm	"	"	Weighed out MDCA (minus qty in shell vial)- **PHOTO D**
2:17 pm	"	"	Added MDCA to (stirring) DMSO in 1 L RBF via paper funnel (**PHOTO E**)
2:23 pm	22	"	MDCA dissolved (**PHOTO F**)
2:28 pm	"	"	Added DMC (258 g)- **PHOTO G** & stirred (**PHOTO H**)
2:30 pm	"	"	Weighed out K2CO3 (minus qty in shell vial, **PHOTO I**) & added to (stirring) solution (**PHOTO J**)
2:35 pm	"	"	Added contents of shell vial to 1 L RBF (**PHOTO K**)
2:45 pm	23	"	Added 16" vigreux column/N2 inlet/bubbler & flushed system with N2 (**PHOTO L**) & added HM (**PHOTO M**)
2:51 pm	24	"	Stoppered RBF; adjusted N2 with slight positive pressure & powered ON variac/set to 20% (**PHOTOS N & O**)

space

06/10/26 (8:33 pm) PHOTO A

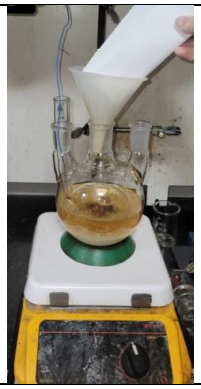


06/11/26 (2:08 pm) PHOTO B

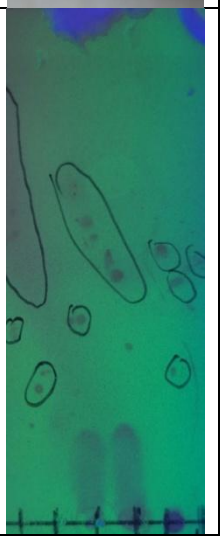


06/11/26
PHOTO C (2:11 pm) Above
PHOTO D (2:14 pm) Top Right; PHOTO E (2:17 pm) Bottom Right

space

			 	
06/11/26 (2:23 pm) PHOTO F	**06/11/26 (2:28 pm) PHOTO G**	**06/11/26 (2:29 pm) PHOTO H**	**06/11/26 PHOTO I (2:30 pm) TOP; PHOTO J (2:33 pm) BOTTOM**	**06/11/26 (2:35 pm) PHOTO K**

space

		 		 
06/11/26 (2:45 pm) PHOTO L	**06/11/26 (2:47 pm) PHOTO M**	**06/11/26 PHOTO N (2:51 pm) TOP PHOTO O (2:52 pm) BOTTOM**	**06/11/26 PHOTO P (6:44 pm) ABOVE PHOTO Q (7:31 pm) TOP RIGHT PHOTO R (7:59 pm) TLC BOTTOM RIGHT** (Ignore circled spots)	

space

06/11/26 (continued)			
TIME	**IT (°C)**	**Variac (%)**	**ACTION**
3 pm	28	20	
3:30 pm	45	"	

4 pm	58	"	
4:30 pm	67	"	
4:45 pm	70	"	
5:04 pm	74	"	
5:15 pm	75	"	
5:33 pm	76	"	
6:18 pm	79	"	
6:32 pm	"	"	↑d variac to 21%
6:41 pm	"	21	↑d variac to 22%
7 pm	81	22	
7:30 pm	82	"	
8 pm	84	"	
8:15 pm	85	"	
9 pm	88	"	↓d variac to 21%
9:20 pm	87	21	↓d variac to 20%
06/12/26			
7:20 am	85	20	
6:44 p→ ~7:30 pm	83	"	Drew a (~1 g) ALQ for TLC using a glass pipet (**PHOTO P**); Let cool to RT then added ~1 g ice + ~1 g 10% HCl + 1 g Et2O & mixed well; Some insolubles present so transferred to a (larger) 2nd shell vial & added enough EtOAc to give 2 clear layers (**PHOTO Q**); ↑d variac to 21%
~7:45 pm	NC	21	Carried out TLC (~2:1 Hex:EtOAc): 1_MDCA (MeOH solution) vs 2_RXN ALQ (**PHOTO R**): NO RXN YET!!
8:28 pm	87	"	Added Hickman Still between RBF & vigreux column
06/13/26			
9 am	88	"	↑d variac to 24%
5:30 pm	100	24	Took **PHOTO S**; 1-2 mL water in Hickman Still
5:35 pm	"	"	Insulated RB & replaced Hickman Still with larger one containing anhydrous Na2SO4 (70 g); SLOWLY added more DMC (81 g) to RM (**PHOTO T**)
6:10 pm	101	"	Condensate beginning to appear in Hickman Still (**PHOTO U**)
6:55 pm	103	"	Hickman Still now ~2/3 full of solvent; ↓d variac to 23%
7:02 pm	104	23	Returned the other Hickman Still positioned above the first one (to potentially collect MeOH)- **PHOTO V**

space

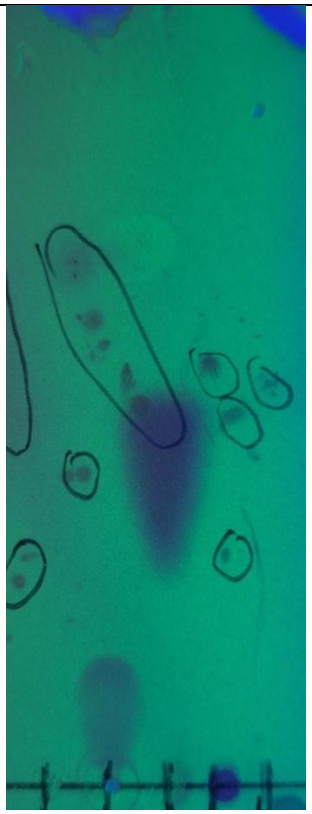
			
06/13/26 (5:33 pm) PHOTO S	**06/13/26 (5:42 pm) PHOTO T**	**06/13/26 (6:10 pm) PHOTO U**	**06/13/26 (7:04 pm) PHOTO V**

space

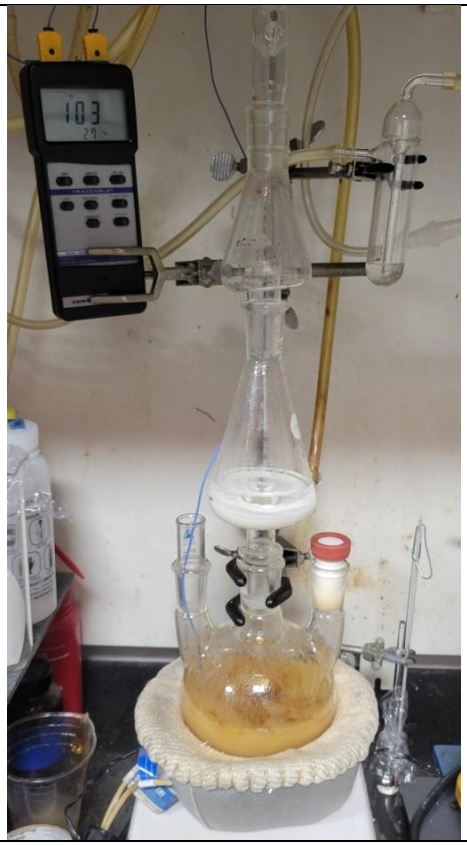
06/14/26			
TIME	**IT (°C)**	**Variac (%)**	**ACTION**
11:33 am	107	23	Maybe 1-2 mL in top Hickman Still
3:41 pm	108	"	~3-4 mL in top Hickman Still (**PHOTO W**) & distinct color change in RM (**PHOTO X**)
~3:45 pm	"	"	Drew ALQ (& diluted into EtOAc/5% HCl) & carried out TLC (**PHOTO Y**)- Looks done!!
4:05 pm	103	"	Turned variac power OFF, removed insulation, & took **PHOTO Z**; Left to stir & cool slowly to RT

space

06/14/26 (3:41 pm)
PHOTO W (TOP)
PHOTO X (BOTTOM)



06/14/26
PHOTO Y (4:05 pm) TLC (~2:1 Hex:EtOAc): 1_MDCA; 2_ALQ (Ignore circled spots = permanent stains)



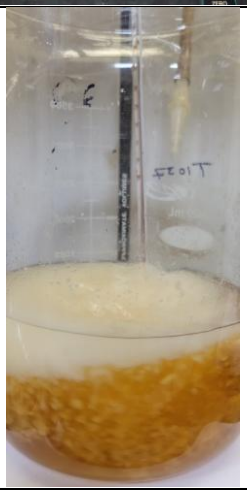
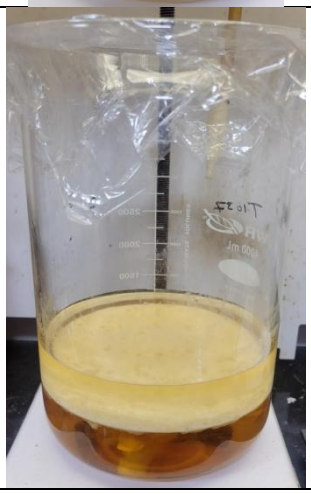
06/14/26 PHOTO Z (4:06 pm) ABOVE

06/15/26 PHOTO ZA (3:50 pm) TOP RIGHT
PHOTO ZB (3:55 pm) ⟶

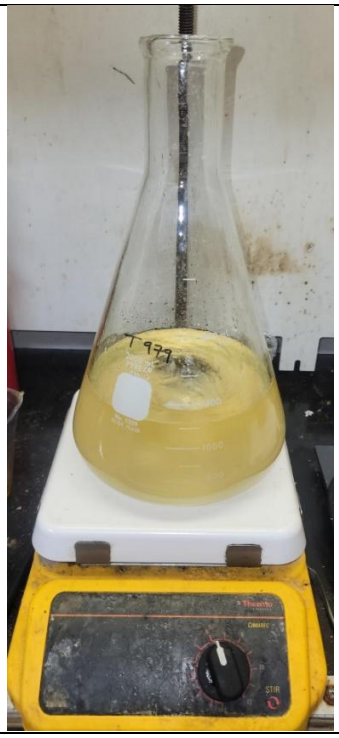
space

06/15/26			
TIME	**IT (°C)**	**Variac (%)**	**ACTION**
2:50 pm	25	N/A	
3:50 pm	"	"	Decanted most of the supernatant liquid into 4 L beaker via large orange funnel (**PHOTO ZA**)
3:55 pm	"	"	Added filter paper & filtered remaining liquid **+** solids (K2CO3); Washed (extr) RBF & filtered solids twice with Et2O (200 g **+** 150 g)- **PHOTO ZB**
4:36 pm	23	"	Added 3" stir bar & suspended thermometer & stirred mixture at a low setting; Slowly added DI water (~400 g, **PHOTOS ZC & ZD**); Addition of water was exothermic: IT ↑d to 30 oC (**PHOTO ZE**)
~4:40 pm	30	"	Stirred vigorously for ~1 min (**PHOTO ZF**) then let stand; Some solids present at interface (**PHOTO ZG**)
~5 pm	RT	"	Filtered (thru filter paper in orange funnel) into a 2 L sep funnel (**PHOTO ZH**)
~5 pm→ ~6 pm	"	"	Separated layers & extracted (lower) AQ layer again with IpOAc (250 g); Separated layers & combined Et2O & IpOAc extracts in a 2 L EFlask; Washed combined organic extracts (twice) with DI water (2 x ~300 g)← **PHOTOS ZI & ZJ** followed by brine (~300 g)← **PHOTOS ZK & ZL**
6:19 pm	"	"	Sealed 2 L EFlask with plastic wrap/AL foil for later processing (**PHOTO ZM**)

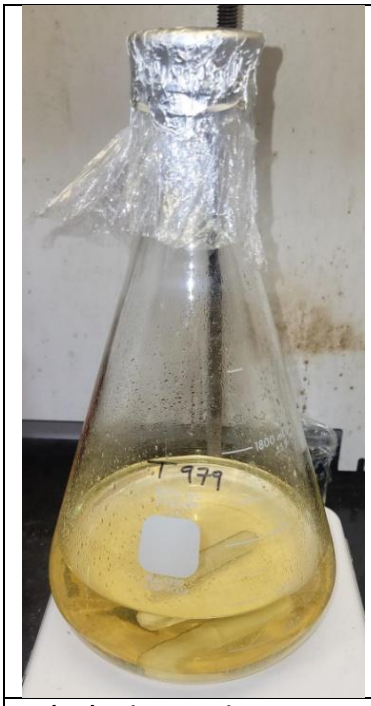
space

			
			
06/15/26 (4:38 pm) **PHOTO ZC**	**06/15/26** **PHOTO ZD (4:39 pm) TOP** **PHOTO ZE (4:40 pm) BOTTOM**	**06/15/26** **PHOTO ZF (4:41 pm) TOP** **PHOTO ZG (4:55 pm) BOTTOM**	**06/15/26** **PHOTO ZH (5 pm)**

space

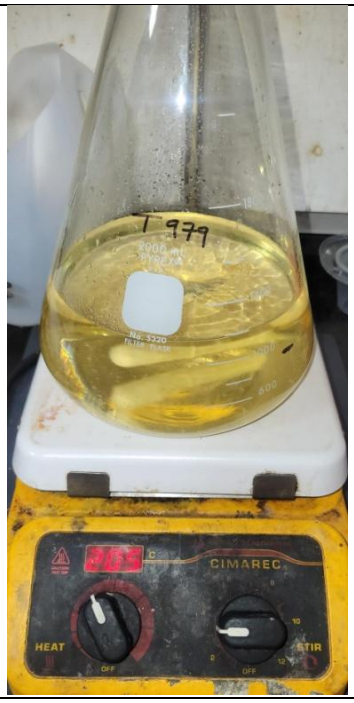
			
06/15/26 (5:46 pm) PHOTO ZI	**06/15/26 (5:52 pm)** **PHOTO ZJ**	**06/15/26 (6:03 pm) PHOTO ZK**	**06/15/26 (6:08 pm) PHOTO ZL**

space



06/15/26 (6:19 pm) PHOTO ZM

06/17/26
PHOTO ZN (1:56 pm) TOP
PHOTO ZO (2:01 pm) BOTTOM



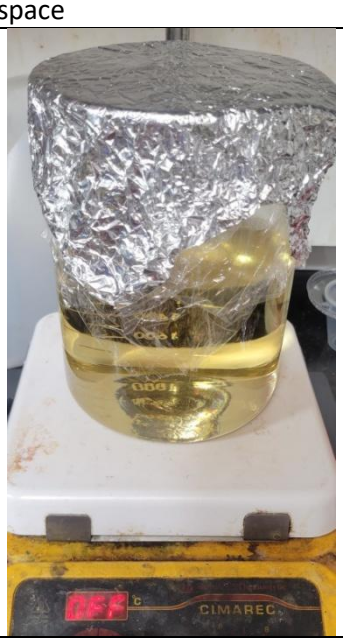
06/17/26 (2:02 pm) PHOTO ZP

06/17/26
PHOTO ZQ (2:09 pm) TOP
PHOTO ZR (2:10 pm) BOTTOM

space

06/17/26			
TIME	**IT (°C)**	**Variac (%)**	**ACTION**
1:56 pm	RT	N/A	Observed that a small amount of crystals had formed in EFlask (**PHOTO ZN**)
~2 pm	"	"	Added Hex (195 g, **PHOTO ZO**) & heated crystals back into solution (**PHOTO ZP**)
~2:05 pm →2:10 p	"	"	Added ~3 teaspoons anhydrous Na2SO4 & stirred warm solution (**PHOTO ZQ**) before decanting into a 2 L beaker (**PHOTO ZR**); The EFlask was then rinsed with Et2O (~50 g) & decanted again.
~2:15 pm	"	"	The 2 L beaker was sealed with plastic wrap & AL foil (**PHOTO ZS**) & let stand to cool slowly to RT
~4:30 pm	"	"	After a couple of hours, the sealed beaker was put on an ice bath in a styrofoam cooler (**PHOTO ZT**)

space



06/17/26 (2:15 pm) PHOTO ZS

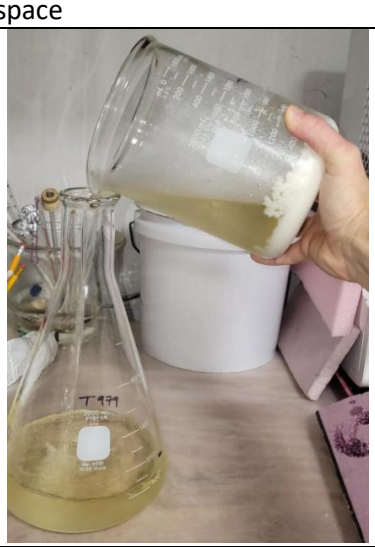
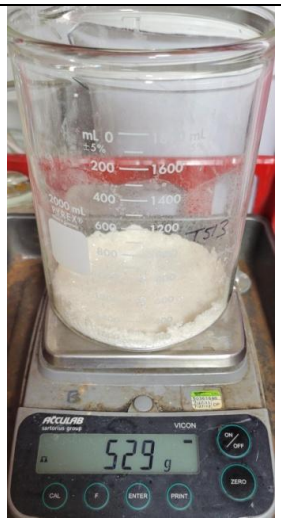
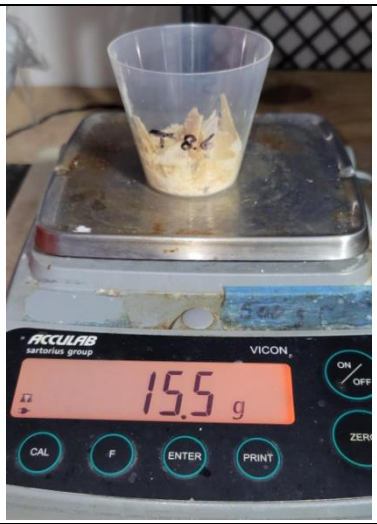
06/17/26 (4:29 pm) PHOTO ZT

06/18/26 (9:33 am) PHOTO ZU

space

06/18/26			
TIME	**IT (°C)**	**Variac (%)**	**ACTION**
~9:30 am	~0	N/A	Removed beaker & took **PHOTO ZU**; Immediately returned beaker to styrofoam cooler & replenished ice
~4:30 pm→ 5 p	"	"	Removed beaker & decanted ML into 2 L EFlask (**PHOTO ZV**); Left beaker suspended using a chain clamp to let last bit of ML drip into flammable waste bottle (**PHOTO ZW**).
06/19/26			
1:05 pm	RT	N/A	Mass of crystals (Crop1) = 16 g (**PHOTO ZX**)
~1:45 pm	"	"	Evaporated volatiles from Crop1 ML to afford a 2nd crop of 6.9 g (which will require recrystallization) (**PHOTO ZY**); Yield = 22.9 g (56%)
06/26/26			
~7 pm	"	"	MP (Crop1) = 139-141 °C

space

			
06/18/26 (4:38 pm) PHOTO ZV	**06/18/26 (4:49 pm) PHOTO ZW**	**06/19/26 (1:05 pm) PHOTO ZX** Crop1	**06/23/26 (6:11 pm) PHOTO ZY** Crop2

ABBREVIATIONS:
AQ = aqueous
AL = aluminum
ALQ = aliquot
DI = deionized (ie. distilled)
DMS = dimethyl sulfide
DMSO = dimethyl sulfoxide
EFlask = erlenmeyer flask
EOCd = evaporated outdoors covered
Et2O = diethyl ether
EtOAc = ethyl acetate
extr = extracted
EXSBT = external sand bath temperature
FFlask = filter flask
g = gram(s)
h = hour(s)
HCl = hydrochloric acid
Hex = hexanes
HM = heating mantle
IPA = isopropyl alcohol
IT = internal temperature
IpOAc = isopropyl acetate
L = Liter(s)
min = minute(s)
mg = milligram(s)
mL = milliliter(s)
ML = mother liquor
MP = melting point
MW = molecular weight
N2 = nitrogen
PV = pressure vessel
qty = quantity
RB = round bottom
RBF = round bottom flask
RM = reaction mixture
RT = room temperature
RXN = reaction
SEP = separatory
SM = starting material
TLC = thin layer chromatography
↑ = increase
↓ = decrease
↑d = increased
↓d = decreased