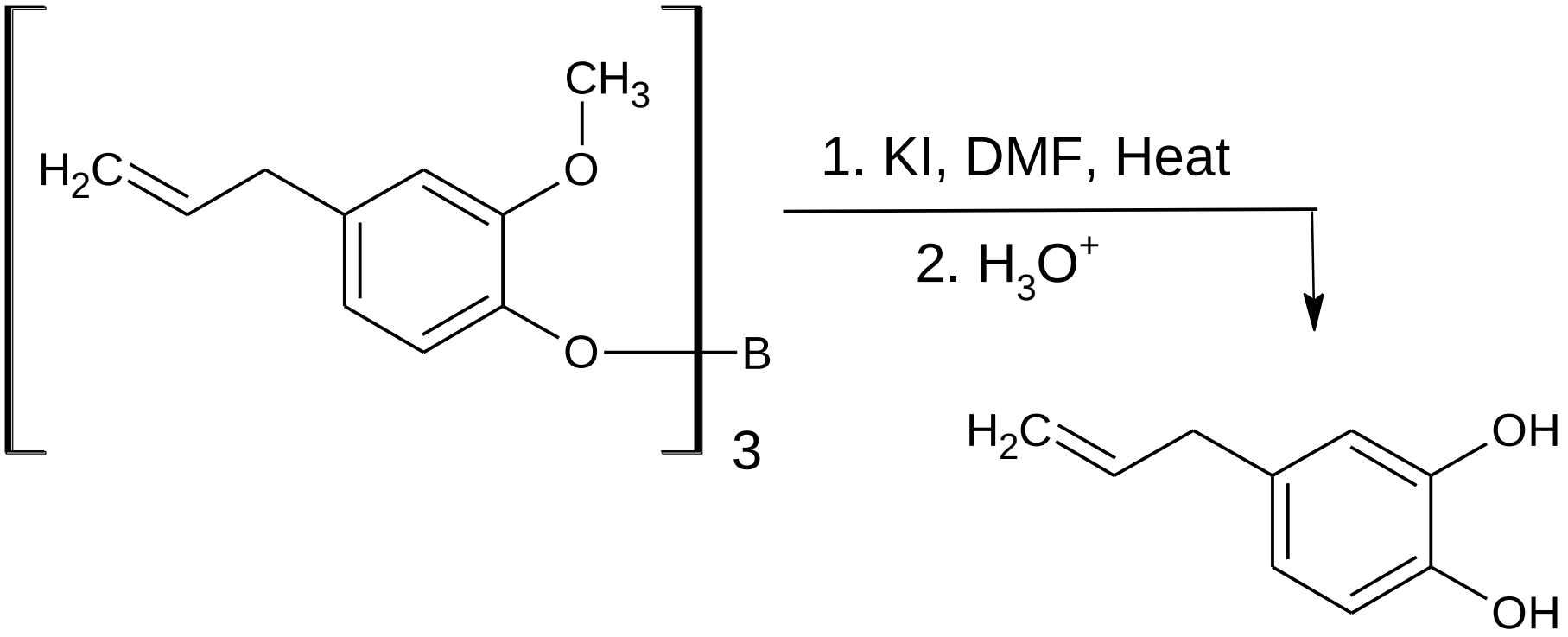
DISCLAIMER:

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. That said, we have a passion for chemistry and seek to assist other chemical researchers in the implementation of safe practices that lead to success in their research and manufacturing endeavors.

Demethylation of Eugenol via Trieugenyl borate using Potassium Iodide in Dimethylformamide



RAW MATERIALS:

1_Trieugenyl borate* (crude, old stock from 2017, stored refrigerated until ~4 months ago)
2_N,N-Dimethylformamide* (recently distilled)
3_Potassium Iodide
4_Hydrochloric acid (31.5%)
5_Isopropyl acetate (other suitable extraction solvent could be substituted)
6_Hexanes, EtOAc, Silica gel (not shown)

GLASS/EQUIPMENT:

Magnetic stirrer, RB Flask (1 L, 3-necks), Digital thermometer/thermowell (glass thermometer/adapter may be substituted), Hickman Still (Dean-Stark trap may be substituted), Condenser (with cold water circulation), N2 manifold/bubbler (may substitute argon/balloon or carry out in air), heating mantle (1 L) & variac (not shown)

*These materials had already been added in the photo on the right and on the next page


28
Isopropyl Acetate
HCl
31.5%
POTASSIUM IODIDE
N,N-DIMETHYLFORMAMIDE
TRIEUGENYL BORATE

QUANTITIES:

Trieugenyl borate = “TEB”
(MW 500.4 g/mol) 150 g, 0.3 mol, 1 eq

Potassium Iodide (KI)
(MW 166 g/mol) 154 g, 0.93 mol, 3.1 eq

Dimethylformamide (DMF)
(d = 0.94 g/mL) 400 g (425 mL)

NOTES:

Eugenol = “EUG” (MW 164.2 g/mol)
Hydroxychavicol = “HC” (MW 150.2 g/mol)
Iodomethane = “MeI” (MW 141.94 g/mol, d 2.28 g/mL, bp ~42 °C)
Theoretical MeI produced = 3 eq, 0.9 mol, 127.6 g, 56 mL
Theoretical yield HC = 3 eq, 0.9 mol, 135 g

PROCEDURE:

[Note: IT = Internal Temperature (°C), RT = Room Temperature, HT = Head Temp, RXN = Reaction, RM = Reaction Mixture, RB = Round Bottom]

1_(~9 am) Weighed out TEB followed by DMF into RB Flask. Assembled system and flushed with N2 (see previous two photos)
2_(9:45 am, IT = 15) Turned on variac and set to 25%
3_(11:20 am, IT = 74) Initiated water flow through condenser*
4_(11:30 am, IT = 78) Added portion (52 g) of KI (not exothermic)
5_(11:38 am, IT = 83) Added remaining KI (102 g)
6_(12 pm, IT = 89) Insulated RB and neck extending to Hickman (see photo- Right)

*This rxn was carried out in December and the (tap) water temperature was 14 oC (must be cold enough to efficiently condense MeI (bp 42 C))

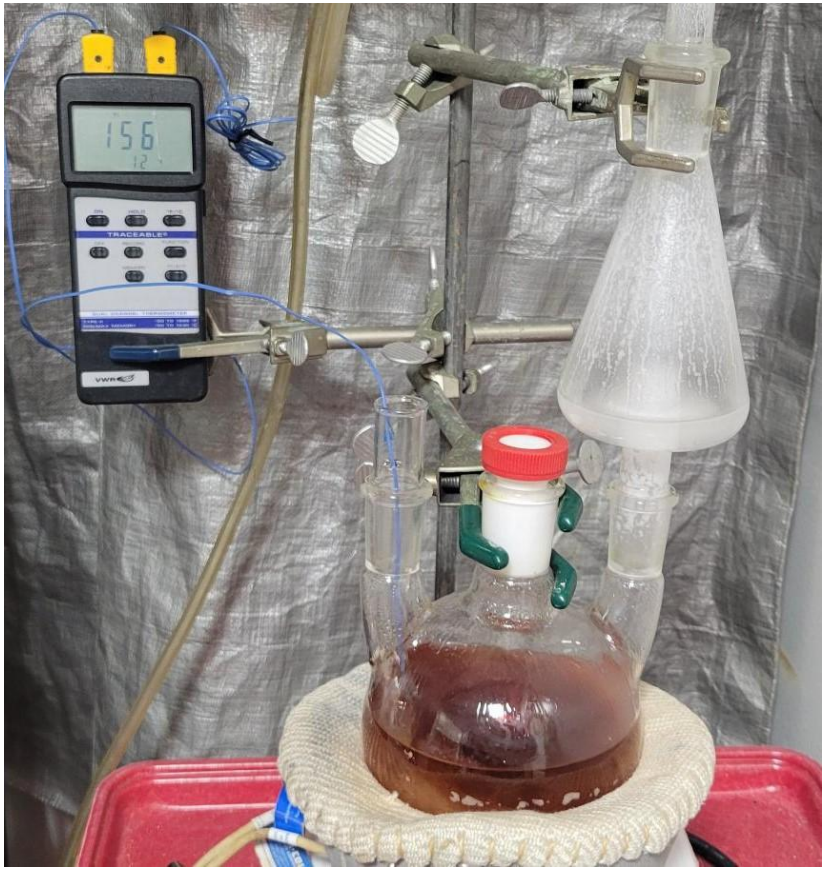
7_(12:35 pm, IT = 103) Left to run an errand
8_(2:05 pm, IT = 133) Returned and observed distillate beginning to collect in Hickman (see photo- Right)

9_(2:30 pm, IT = 136) Left for lunch
10_(4:45 pm, IT = 143) Returned and observed distillate continuing to accumulate (see photo- left)
11_(5:30 pm, IT = 144)
12_(6 pm, IT = 144)
13_(7 pm, IT = 145)
14_(8 pm, IT = 146)
15_(8:30 pm, IT = 147)

16_(8:35 pm, IT = 147) Took photo (see above)
17_(8:45 pm, IT = 147) Left for the evening

18_(3:20 am, IT = 160) Returned & turned off heat. Observed some solids in Hickman (salts of boric acid?).

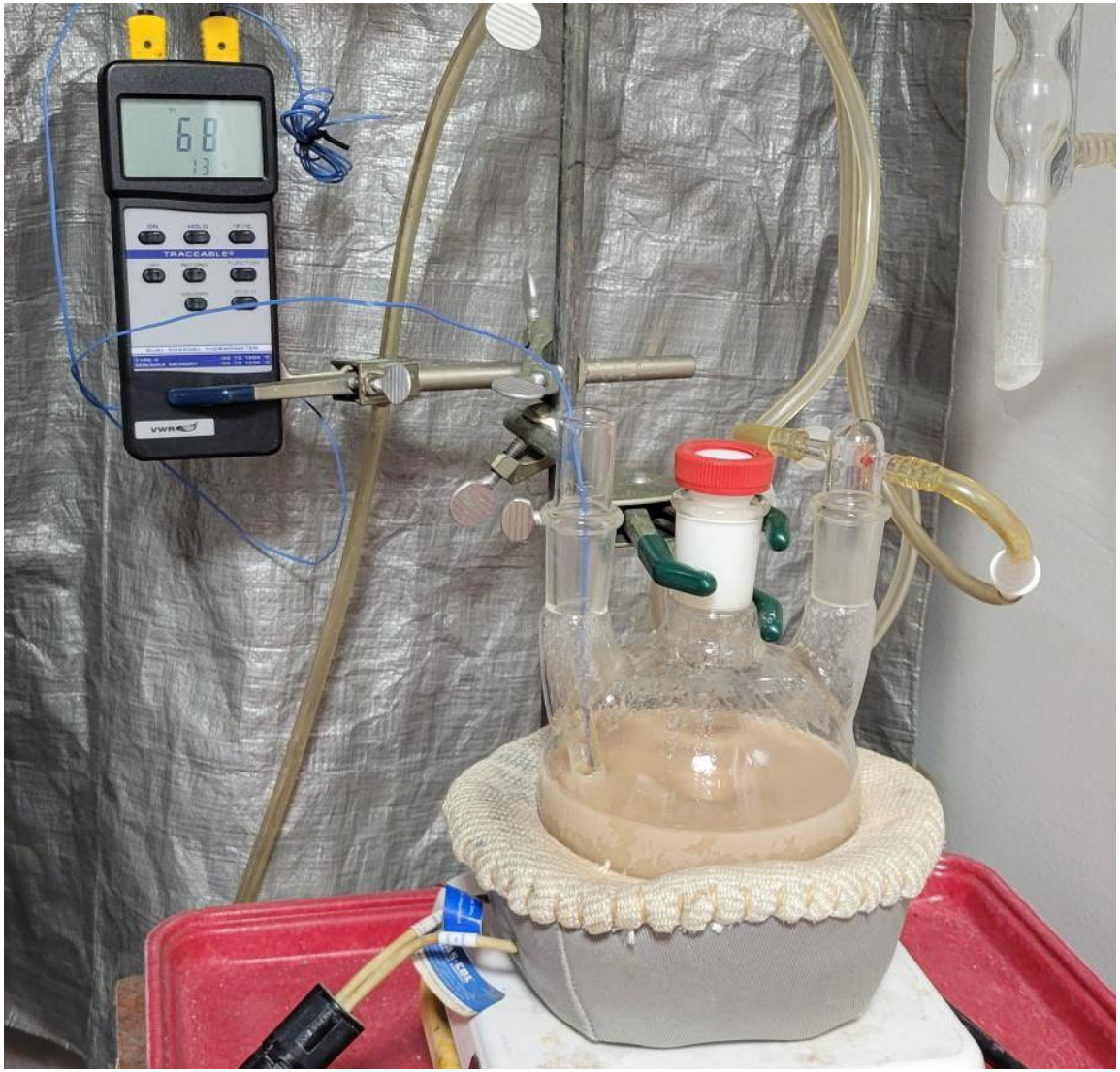
19_(3:29 am, IT = 156) Removed insulation & took photo (Right). Some solids observed in RM



20_(4:03 am, IT = 105)

21_(4:31 am, IT = 80) Heavy precipitation observed in RM as it slowly cooled (see photo- Left)

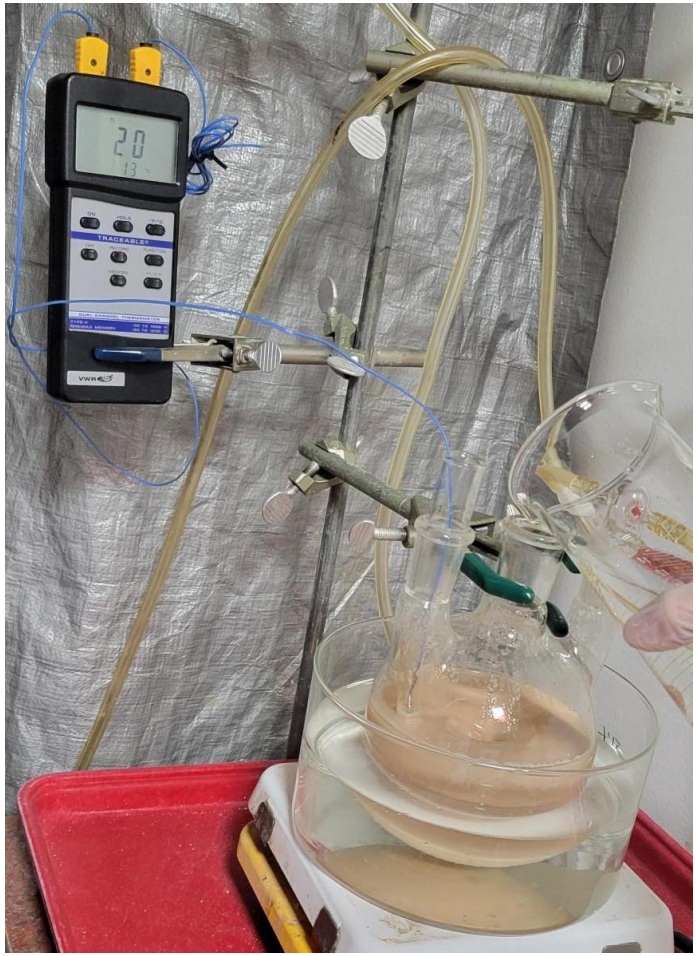
22_(4:50 am, IT = 68)
Removed Hickman still* & condenser and replaced with N2 inlet (see photo-Right)
22_(5 am, IT = 63)
Removed heating mantle
23_(5:20 am, IT = 48)
Incorporated RT water bath (see photo on next page).
24_(~5:30 am)
Prepared an ice-cold solution of ~5 M HCl (300 g)

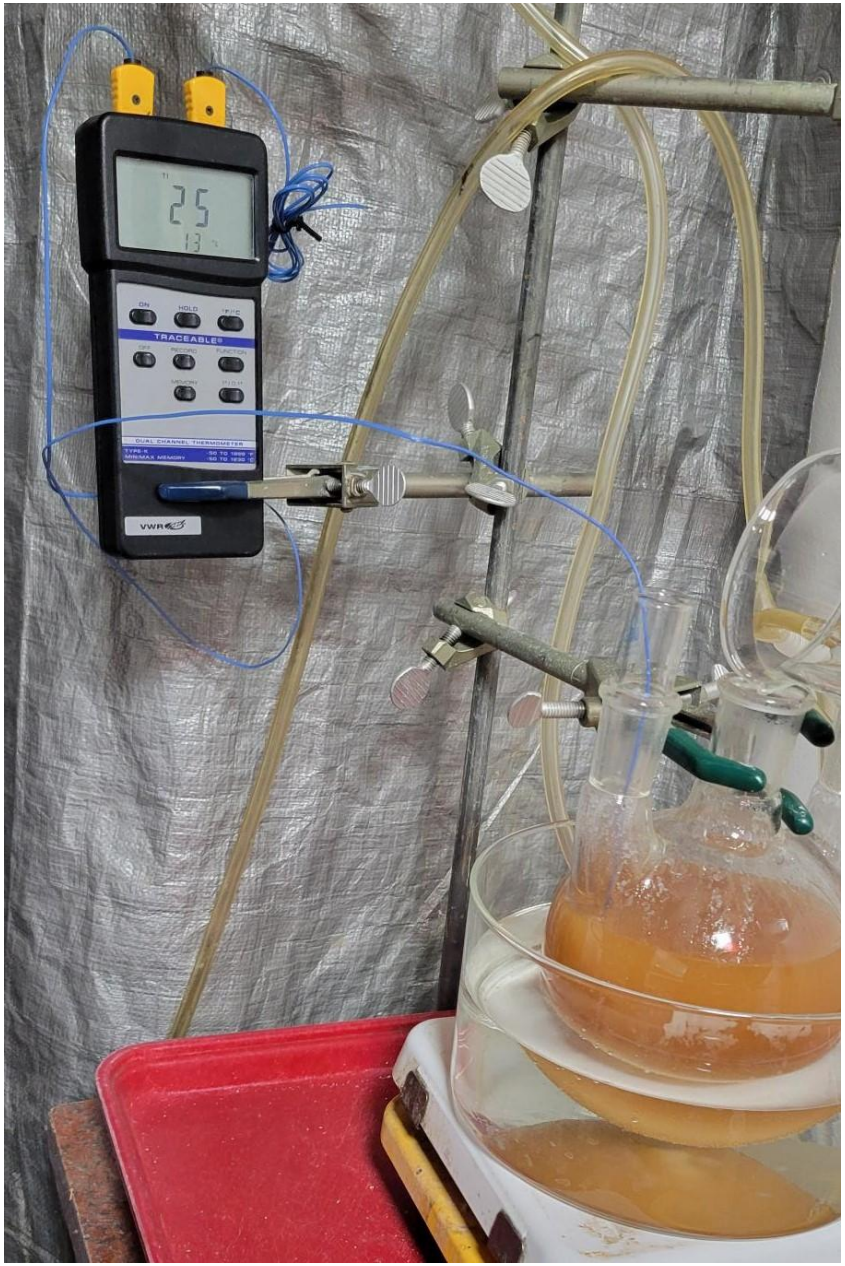


*The distillate (50 g) was transferred to a separate flask which was sealed and refrigerated. This was later distilled to recover (some of) the MeI produced (see #48).

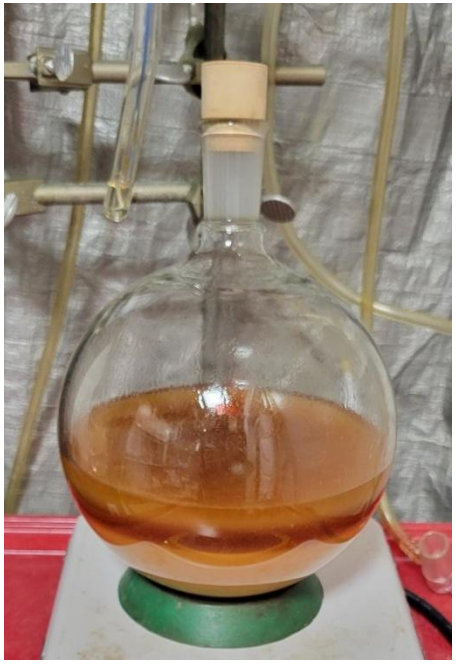

48
TRACEABLE
VWR

25_(5:45 am, IT = 20) Slowly added ice-cold HCl (exothermic-caused IT ↑ to 26 °C) See photos



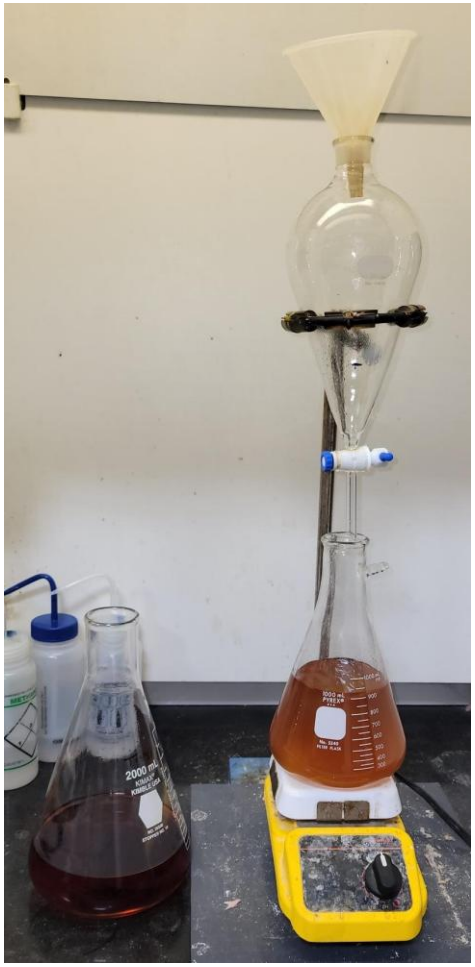


26_(6 am) Checked pH of mixture using pH strip (see photo- Left)
27_(6:05 am) Turned off N2 and water to condenser
28_(6:16 am) Transferred RM to a 2 L (single neck) RB flask (see photo- Right); Rinsed 3-neck RB with EtOAc (~50 mL), flushed with N2 and sealed with rubber septum (see photo- Middle)



29_Stripped on rotovap (to 575 g) and stored in freezer
30_ Added 205 g IpOAc (actually used recovered IpOAc/EtOAc) and DI water (200 g) and mixed well.
31_Much undissolved solids present so added another 150 g water
32_Filtered (Buchner funnel/ aspirator) to remove remaining solids and washed (extracted) solids well with 100 g IpOAc (not shown)

33_Transferred mixture to a 1 L sep funnel and separated layers (see Left photo next page). The aqueous layer was then extracted two more times with IpOAc/EtOAc (2 x ~150 g). The combined organic layers were then washed with water (200 g), brine (250 g) and dried over Na2SO4 before filtering (gravity- see Middle photo next page) into a clean RB flask which was subsequently flushed with N2 and sealed (see Right photo next page).

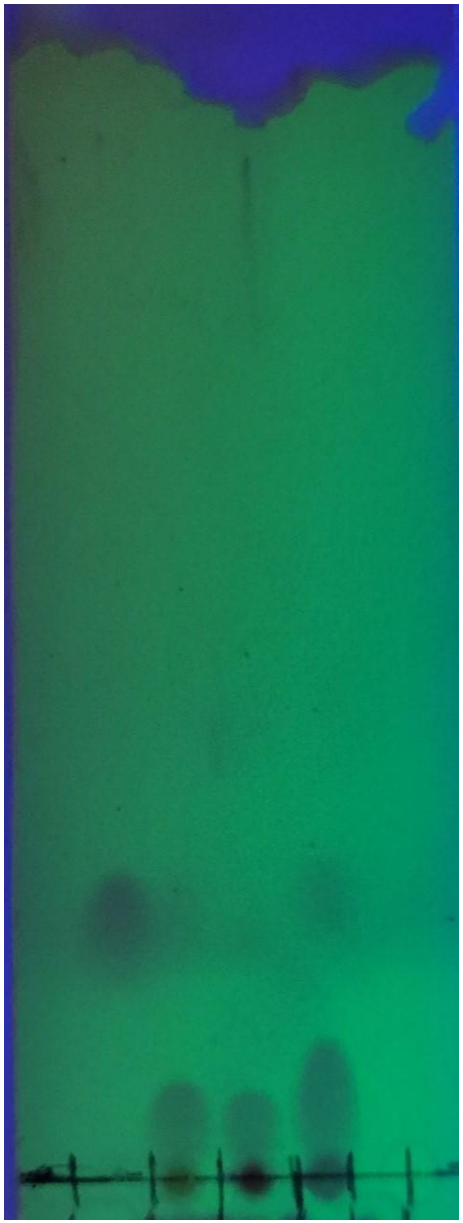


34_After stripping again on rotovap (to full vacuum), the crude yield was determined to be 134 g (99%).

35_TLC* was carried out to compare this crude product with EUG as well as two old (freezer-stored) samples of HC (see photo- Right)

TLC* (10:1 w/w Hex:EtOAc) Spotted Left to Right:
1_EUG
2_HC (old sample- KI method)
3_HC (old sample- Thiourea method)
4_HC (sample of this 134 g crude)

36_Prepared a column using 100% hexanes and silica gel (240 g)- see Left photo next page
37_Loaded (133 of 134 g) crude HC on column (see Middle photo next page). A period of 5 hours was required for complete absorption onto the gel.
38_Once completely absorbed, a layer of sand was carefully added followed by a (cup-shaped) piece of aluminum foil (both of which serve to protect the band of crude material from being disturbed by solvent addition (see Right photo next page).



*Multiply-used plate

39_Hexanes were carefully added until the column was nearly full. The top of the column was then covered with aluminum foil to minimize evaporative losses (see Left photo- next page).

40_Initally the drip rate was painfully slow, especially for the first hour. Collected about 200 mL each in the first two fractions, and this was returned to the column. Subsequent fraction volumes varied from ~350-450 mL.

41_Ran something like 2.5 L of pure hexanes before switching to 10:1 w/w Hexanes:EtOAc, of which ~6 L was used before switching to 5:1 (which was held for about 2 L).*

*This was a relatively large solvent requirement, however the solvent was recovered and will be reused in other experiments.

42_Column was continued until a greenish band had completely eluted. (See Right photo at fraction 15 with greenish band partially eluted).
43_TLCs (not shown) of the 27 fractions were then carried out* to determine which to combine.

*Some fractions were very dilute so multiple spotting was required for UV observation

44_After combining the intial 27 fractions into 6 fractions (see Top photo next page), it was decided to strip most of the solvent from each before running a final TLC.
45_The 6 (rotovap-concentrated, though not fully) fractions (see Bottom photo next page) were then (singly) spotted for a final TLC (see photo-Right)

TLC* (10:1 Hex:EtOAc) Spotted Left to Right:
1_Fractions 3-8
2_Fraction 9a
3_Fractions 9b-9c
4_Fraction 10
5_Fractions 11-23
6_Fractions 24-25

46_Following this TLC (which clearly shows that complete separation was not achieved), each of the 6 fractions were stripped to full vacuum.

*Ignore baseline spots (multiple-reuse plate)


3-8
9a
9b-9c
10
11-23
24-25

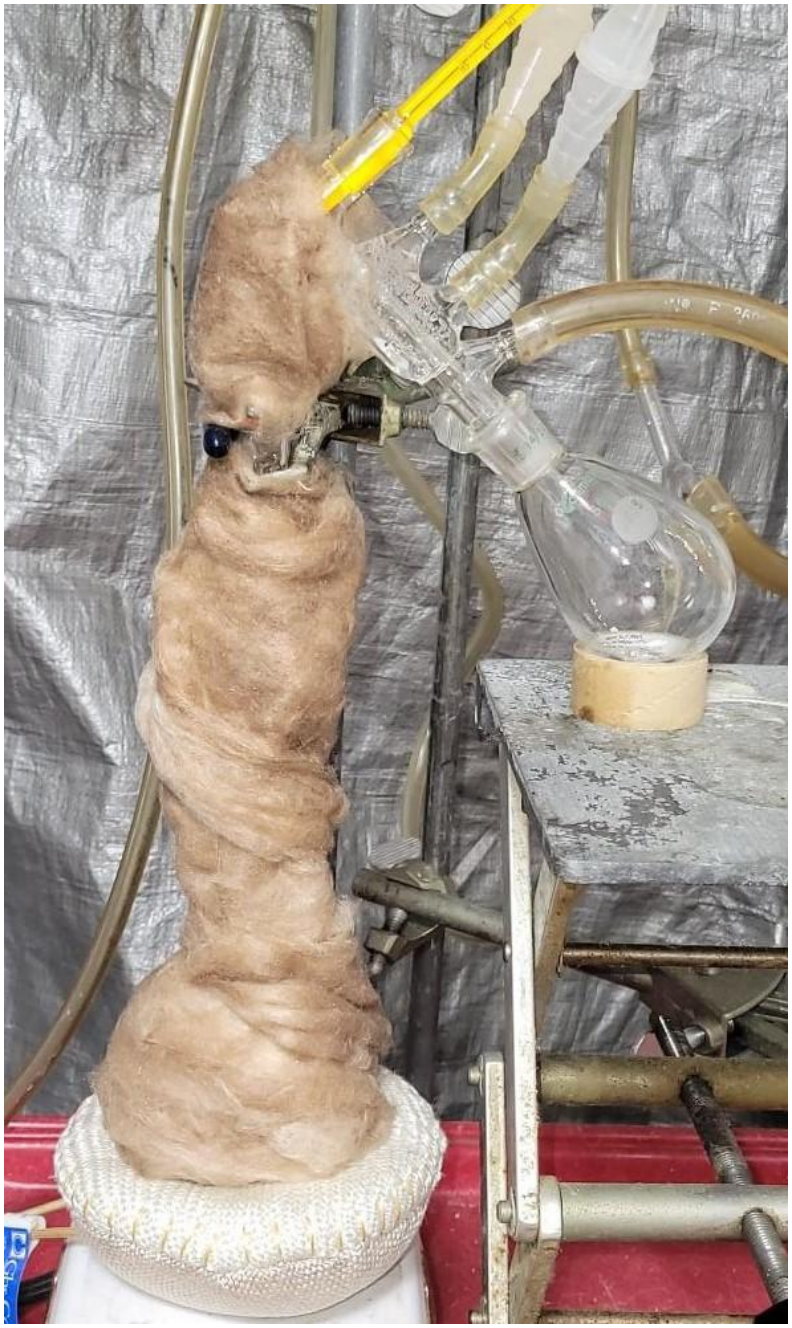

3-8
9a
9b-9c
10
11-23
24-25

47_Created chart (below) with visual descriptions and masses recorded for each fraction. Fractions 11-23 (78 g, 58%) seems to be clean HC (see previous TLC and photo on last page). Fraction 9b-9c and fraction 10 had a combined mass of 18.4 g. If these fractions contain 50% HC, then a yield of 65% was possible.* Also worth noting is that ~15% EUG was present which is useful for comparison with experiments using freshly prepared TEB.

Fraction(s)	Appearance	Mass (g)
3-8	Pale (almost water-white) yellow oil	9.7
9a	Light amber oil	2.0
9b-9c	Amber oil	4.5
10	Darker Amber oil which partially crystallized in freezer	13.9
11-23	Darker Amber oil which completely crystallized in freezer	78.0
24-25	Oiled out (small quantity) after stripping Hex/EtOAc to ~20 mL	N/A (discarded)
	Total	**108.1**

***A mass ratio (silica gel:crude HC) of 1.8 was employed for this separation. Increasing that ratio to say 2.3 would have likely resulted in complete separation of EUG & HC.

48_The by-product (MeI-containing) distillate (50 g) was transferred to a single neck 100 mL (14/20) RB flask and a distillation apparatus was set up (which included a short-path still head with N2 inlet & water inlet/outlet and a 7” vigreux column- see Left photo).



49_Notes were taken to create a chart (below):

TIME (pm)	Head Temp (°C)*	ACTION
12:30	RT	Set variac to 12%
1:30	RT	Increased variac to 15%
2:00	RT	Insulated RB, vigreux, and still head (see Right photo on previous page)
2:30	RT	Increased variac to 20%
3:00	RT	Increased variac to 25%
3:10	35	First drops appeared
~3:40	38	Changed fractions (Note: Fraction 1 mass = 1.0 g collected at HT ≤38 °C)
3:50	45	HT stabilized; Left for an errand
5:30	42	Returned and changed fractions (Note: Fraction 2 mass = 14.6 g collected at HT 38-45 °C ← LIKELY USABLE MeI); Increased variac to 30%
~6:00	57	Once HT stabilized at 57 °C, changed fractions (Note: Fraction 3 mass = 2.05 g collected at HT 45-57 °C)
6:30	56	Once HT fell to 56 °C, changed fractions and turned off heat (Note: Fraction 4 mass = 6.14 g collected at HT = 57 °C ← CAN ONLY GUESS- SEE COMMENTS)

*Head temperature s (HTs) were estimated as multiple breaks were present in the (Hg) thermometer

COMMENTS:

1_A 50% yield of HC was reported* by refluxing EUG in DMF with a large excess (6 eq) of (presumably anhydrous) LiCl. This salt was briefly explored using our method and found to also be effective, however this needs to be revisited as a purified yield was not established at that time.

2_The low recovery of MeI could be partially due to the formation of $B(OMe)_3$ (bp 68-69 °C) forming azeotrope? though this is just speculation

3_We plan to post an HC synthesis which includes a TEB prep as well as at least one *in situ* method

4_Please consider https://orbitnaturalproductderivatives.com/ when sourcing raw materials for your research and fragrance products.

*This online link disappeared- I have a copy for reference (though unsure of the original source)

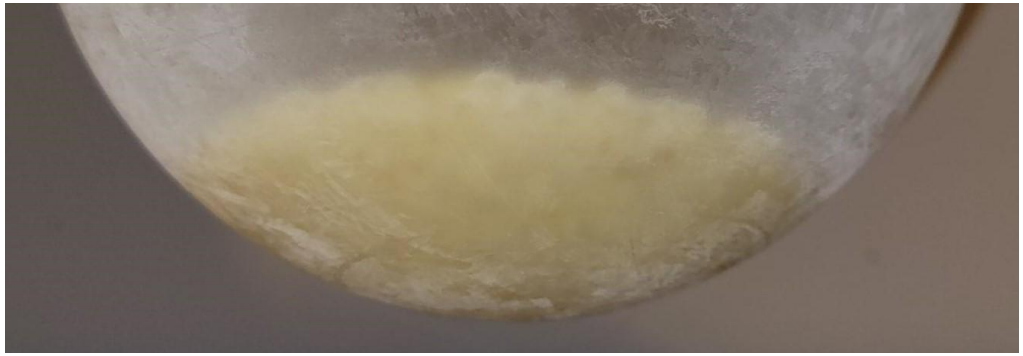


Photo of (frozen) HC product