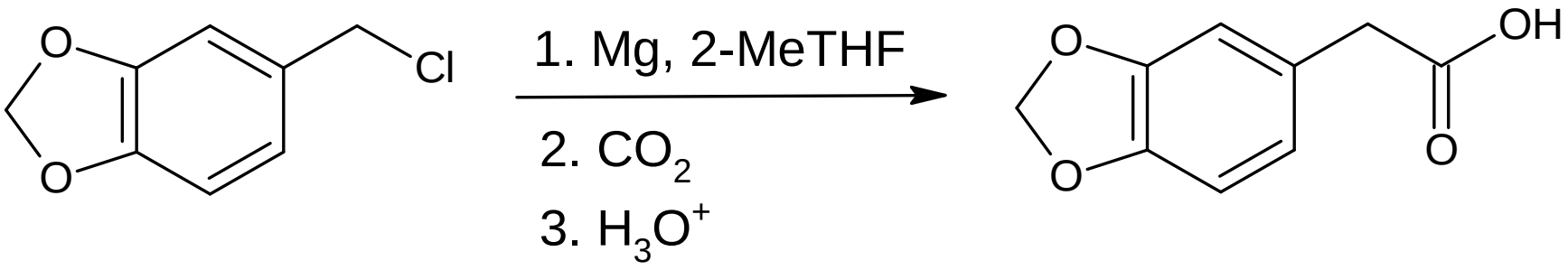
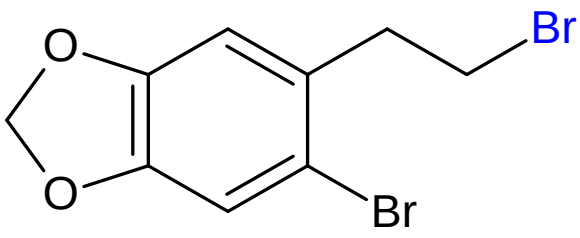
DISCLAIMER:

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.

Grignard Reaction: Synthesis of 3,4-(Methylenedioxy)phenylacetic acid



Step 2 (Route A) of our synthesis of a key intermediate (alkyl bromide)→ used in a total synthesis of Berberine published in 2021 (Konno, et al.)



RAW MATERIALS:

1_Piperonyl chloride (Right photo, from our previous chloromethylation of 1,3-benzodioxole)

2_Magnesium (turnings)

3_Iodine (small crystal)

4_2-Methyltetrahydrofuran (anhydrous) (may substitute THF or diethyl ether)

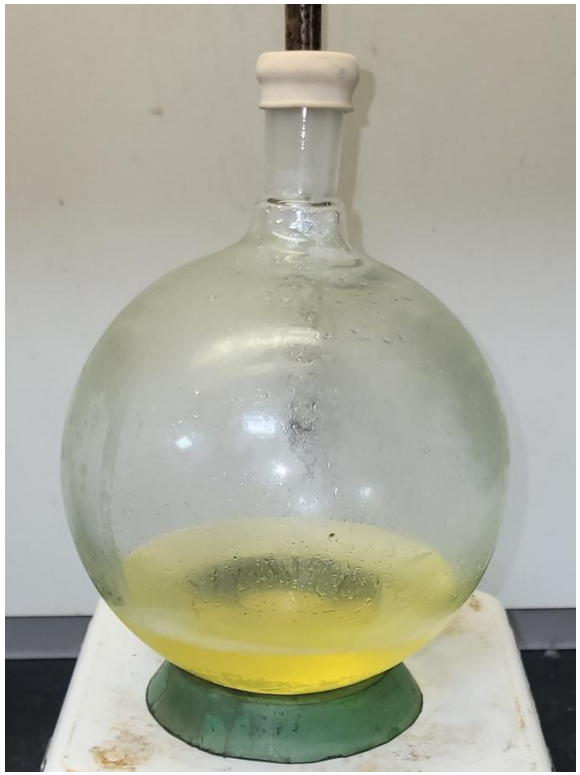
5_Carbon dioxide

6_Hydrochloric acid

7_Sodium hydroxide

8_Isopropyl acetate (or toluene or ether)

9_Toluene



QUANTITIES:

Piperonyl chloride (MW 170.6 g/mol) 332 g, 1.95 mol, 1 eq

Magnesium (MW 24.3 g/mol) 38.4 g, 1.58 mol, 0.81 eq

2-Methyltetrahydrofuran (489 g, anhydrous- dried & distilled)

Iodine (small crystal)

Carbon dioxide (dry ice, 200 g)

Hydrochloric acid (450 g of ~15% and 165 g of 31.5%)

Sodium hydroxide (5% w/w) 700 g

Isopropyl acetate (200 g)

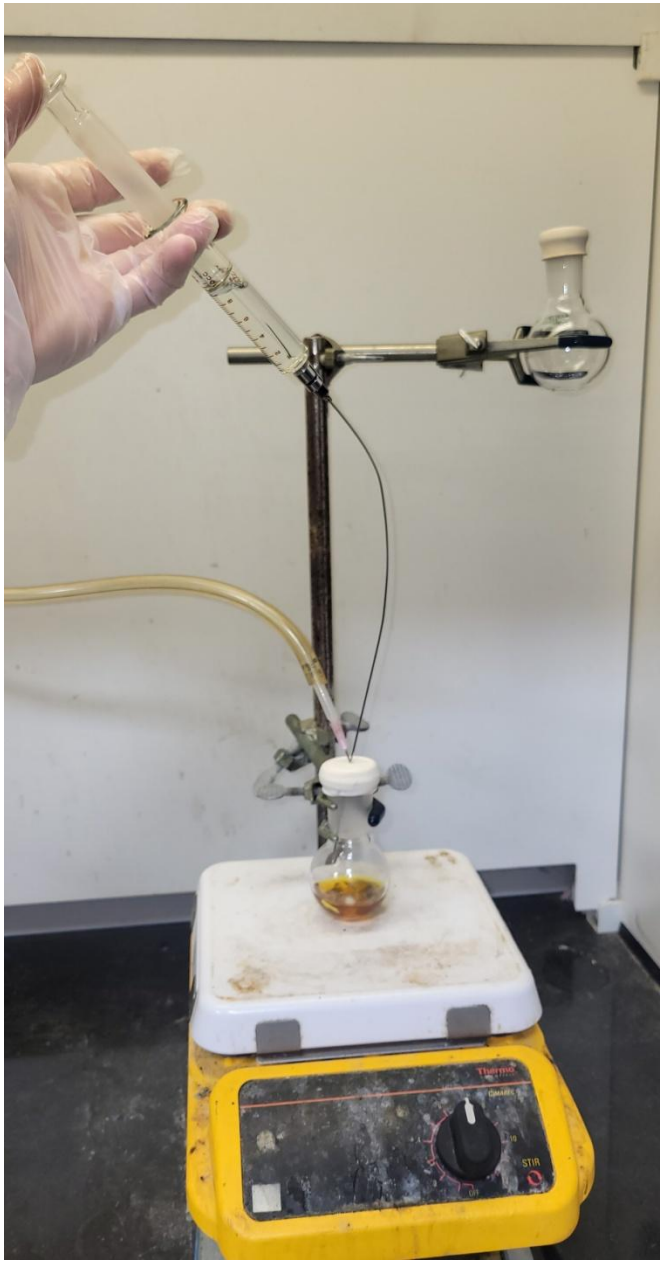
Toluene (307 g)

PROCEDURE:
[Note: IT = Internal Temperature (°C), RT = Room Temperature, RM = Reaction Mixture, RB = Round Bottom, EOC = Evaporated Outdoors Covered]

1_To a (heat gun-dried, N2-flushed) 50 mL RB flask containing Mg (436 mg) was added 2-MeTHF (7.7 g) followed by one small crystal of I2

2_In a separate (100 mL) RB flask, a solution consisting of (crude) piperonyl chloride (4 g) in 2-MeTHF (6.3 g) was prepared

3_Approximately 1/3 of the piperonyl chloride solution was added (under N2) dropwise via syringe to the RB flask containing Mg in 2-MeTHF (photo- Right)



PROCEDURE (cont'd):

4_After ~10 min, the brown color (of I2) began to lighten and give way to a clear solution (photo- Left)

5_RM began to generate heat and the clear solution began to darken. A (RT) water bath was incorporated (see Left photo next slide) and the remaining 2/3 piperonyl chloride solution was added over 30 min.

6_RM was stirred ~1.5 h then transferred (under N2, via cannula) to a 2 L Morton RB flask containing a (stirring) suspension of Mg (38 g) in 2-MeTHF (325 g)- see Right photo next slide


Thermo
STIR

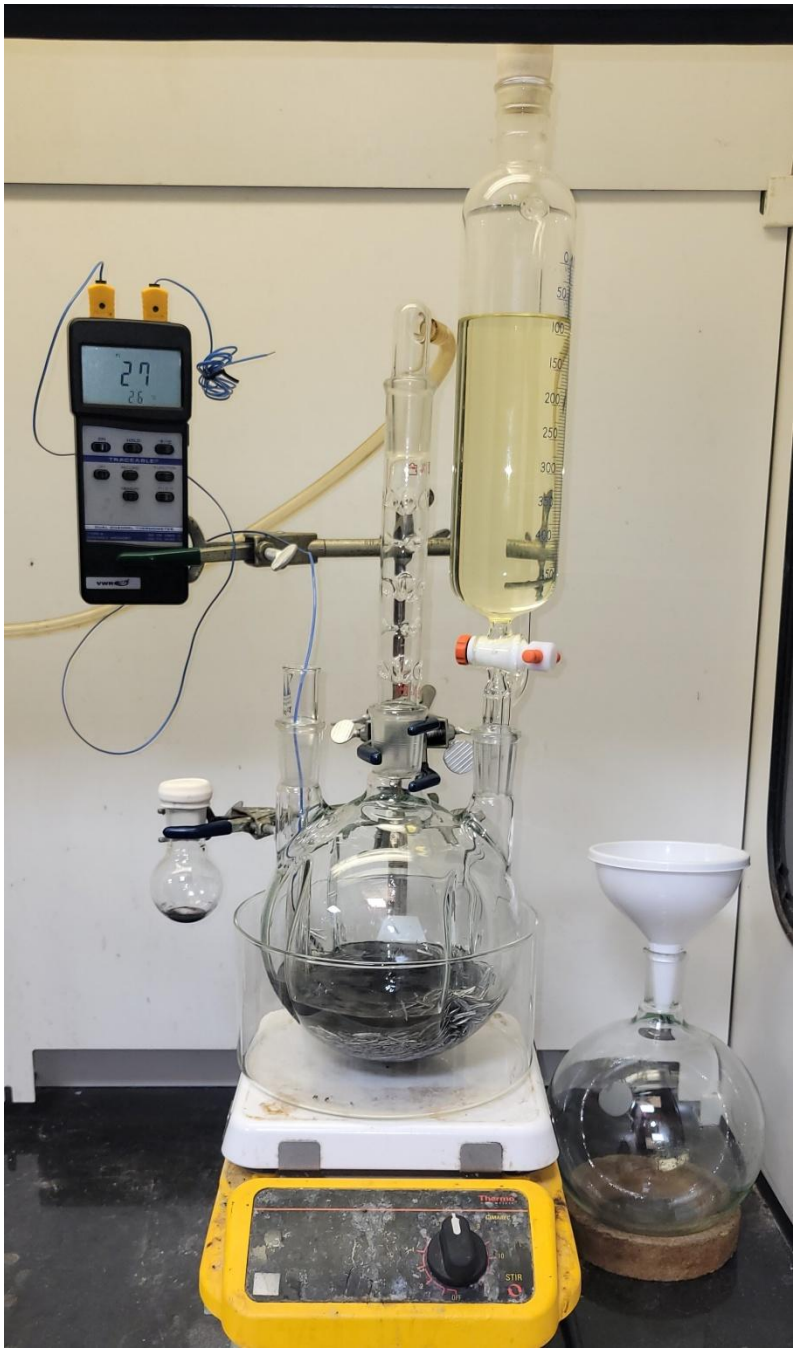

25
TRACEABLE
Thermo
STIR

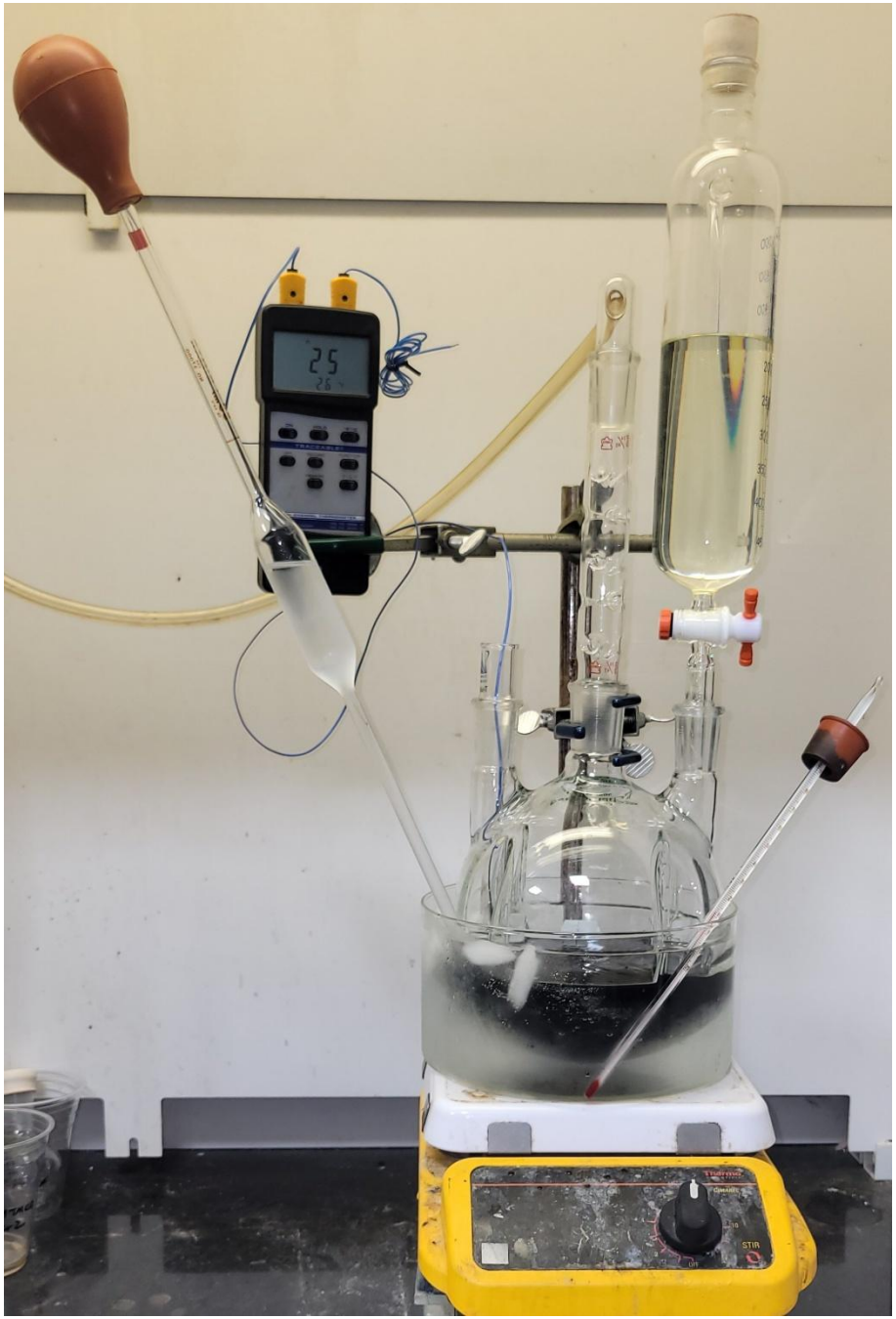
PROCEDURE (cont'd):

7_ A 500 mL addition funnel was incorporated and charged with a solution of piperonyl chloride (328 g) in 2-MeTHF (150 g)- see photo- Right.

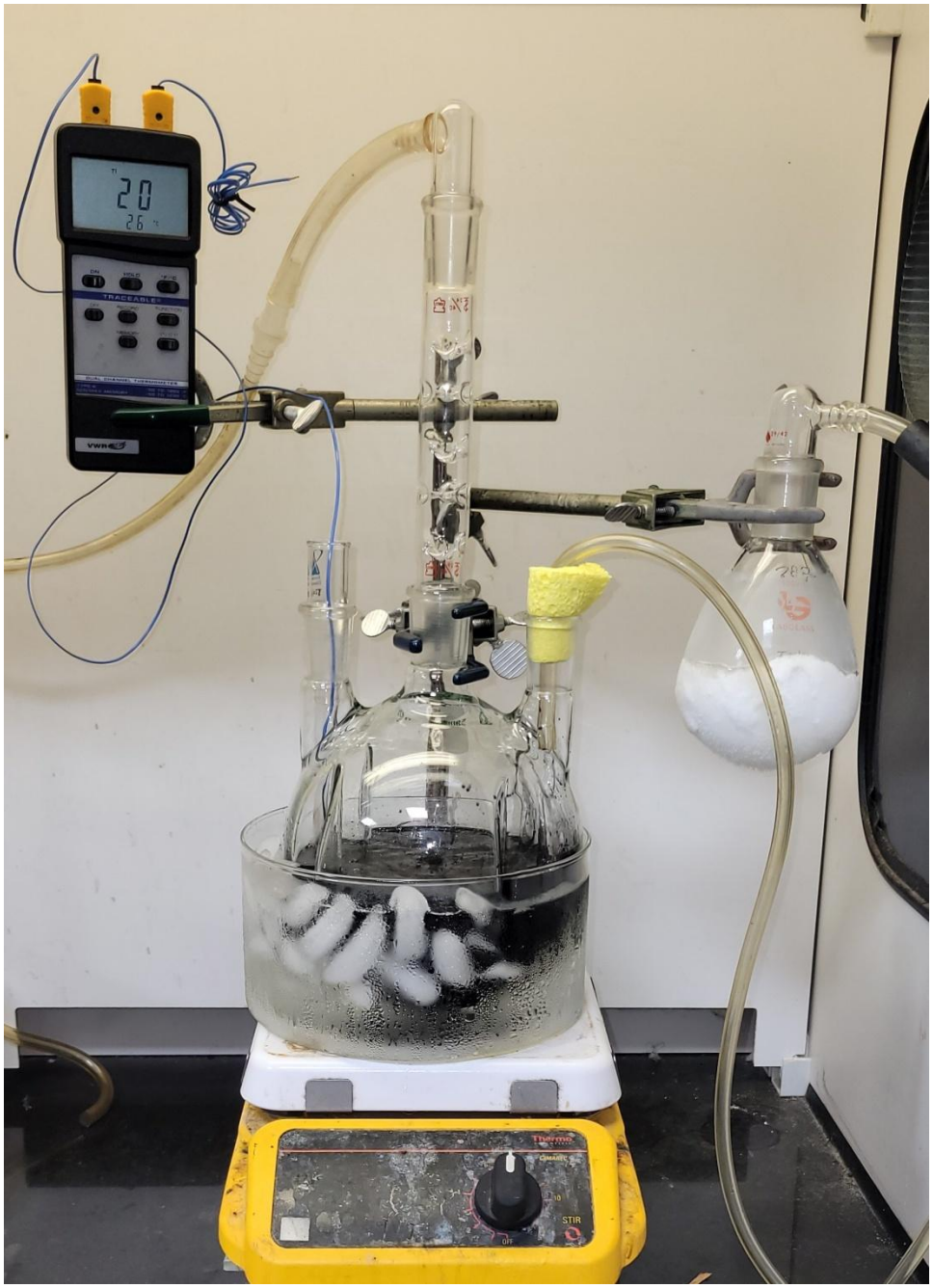
8_(1:30 pm, IT = 27) Began adding the piperonyl chloride solution. Soon after, water and some ice cubes were added to the bath. Addition rate was controlled such that IT stayed around 25 °C. This was accomplished by maintaining the ice/water bath ~10-15 °C. At one point, some water had to be removed from the bath (via 50 mL pipet)- see Left photo next slide

9 _(3:40 pm, IT = 25) Addition complete (see Right photo next slide)




25
26
STIR


25
26
STIR



PROCEDURE (cont'd):

10_ Let RM stir at RT ~1.5 h and then cooled to 5 °C. Began bubbling in CO_2 (from a 500 mL RB flask loaded with 200 g dry ice) through Tygon tubing and a glass pipet (see photo- Left)

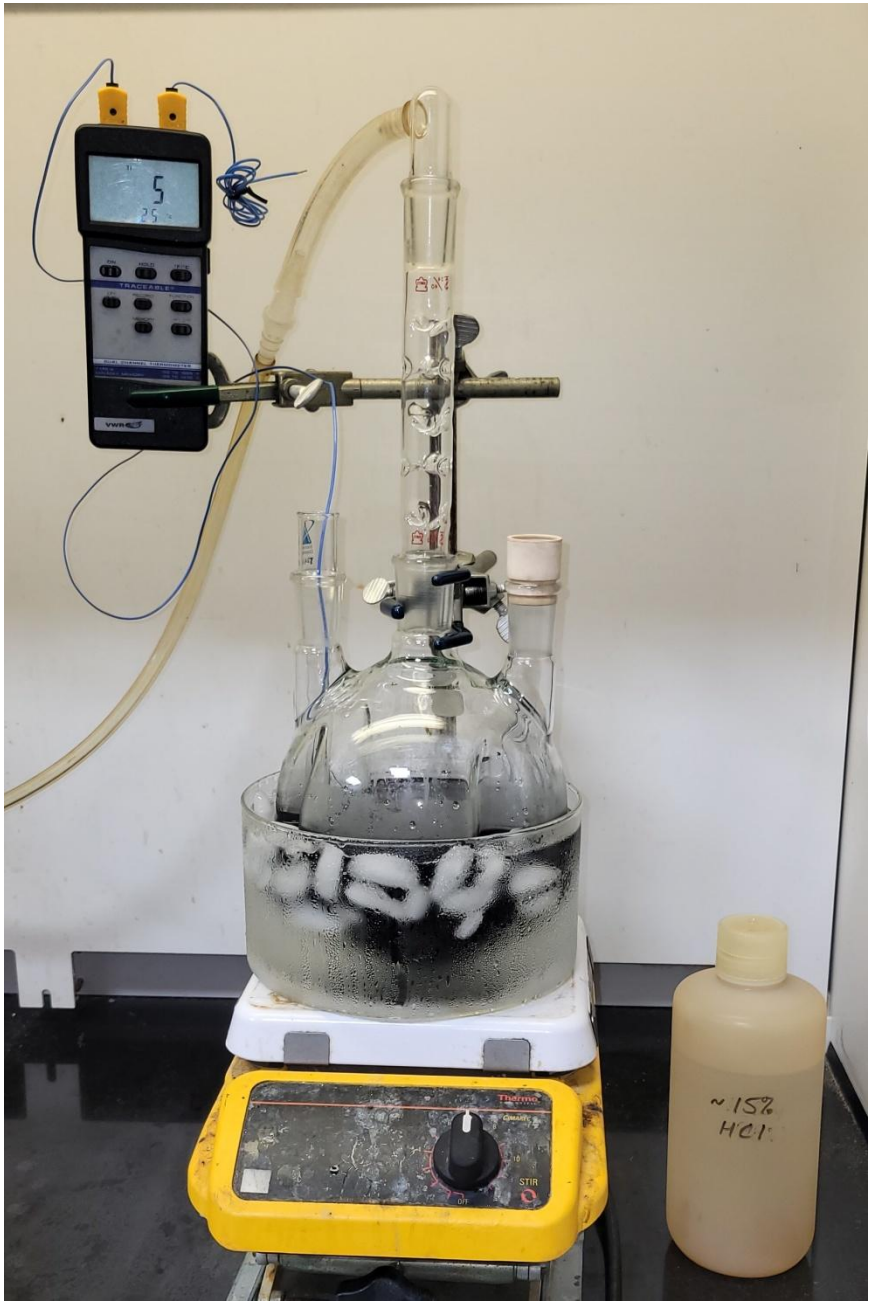
11_Addition was exothermic, with IT ultimately rising to 21 °C. CO_2 was bubbled in for 2 h before cooling RM again (to 5 °C).

12_Added distilled water dropwise (6 g initally – Exothermic!). Added a total of 112 g water (over ~45 min) then let RM stir overnight (out of time for today).

PROCEDURE (cont'd):

13_ Next day added ice bath and cooled to 5 °C. Added ~15% HCl (SLOWLY, 350 g over 30 min) and let stir. Added another 50 g 15% HCl after 5 h and again let stir overnight.

14_ Next day added another 50 g 15% HCl. Stirred another 2 h then filtered (gravity) into 4 L sep funnel (see photo next slide). This required ~1 h and filter paper was wrung out (using heavy duty rubber gloves) at the end.



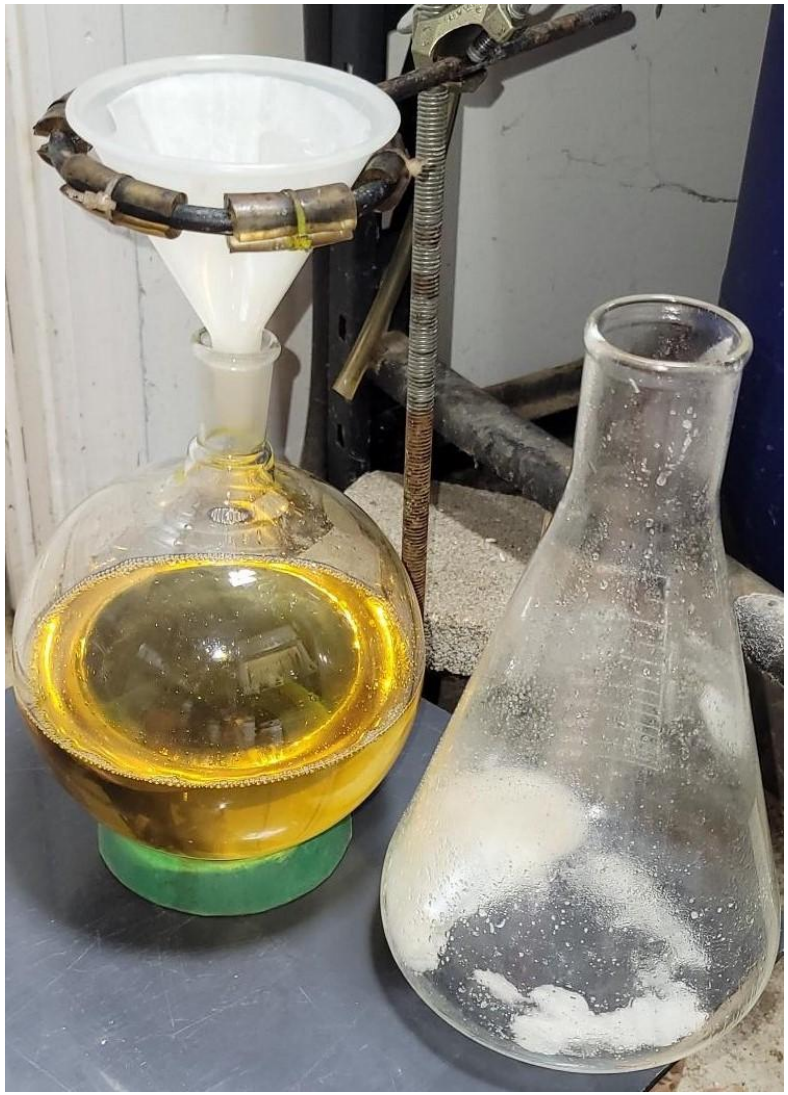
PROCEDURE (cont'd):

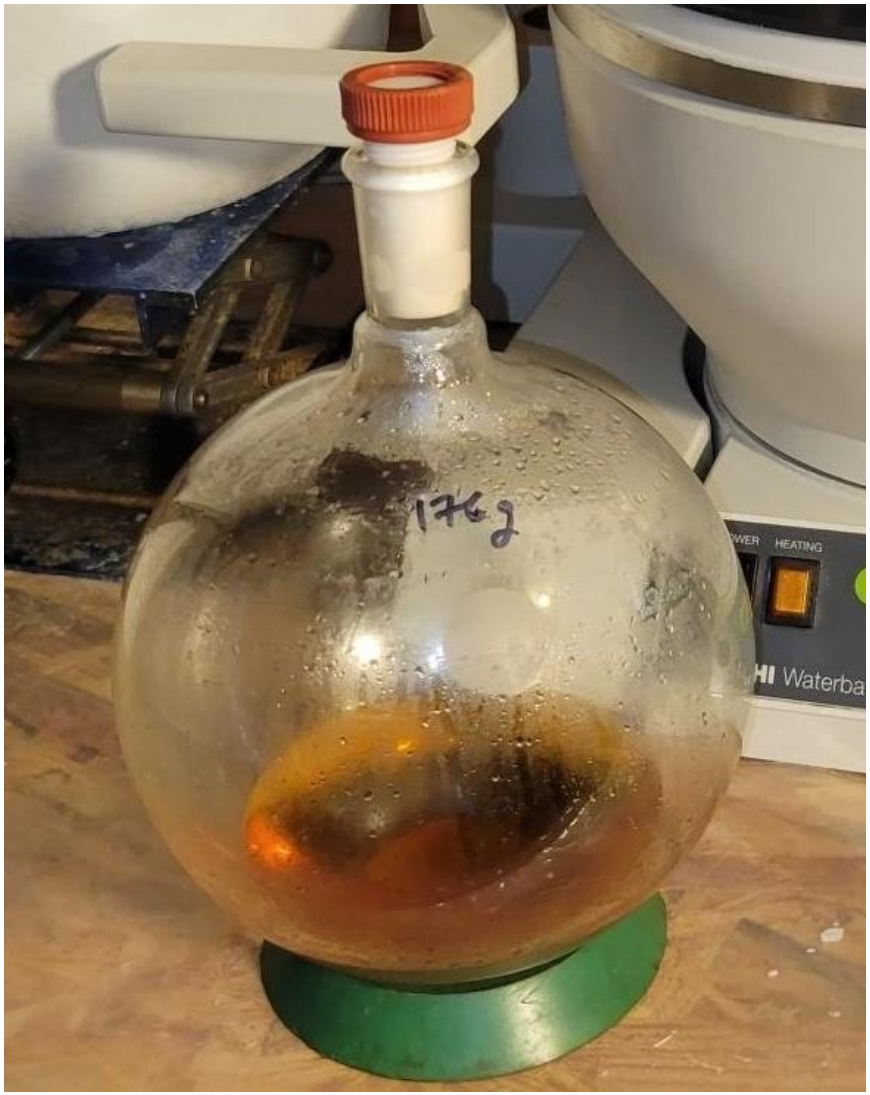
15_ Layers were separated and to the (top) 2-MeTHF (organic) layer (in a 4 L beaker containing a 3" stir bar) was added 300 g DI water. After stirring vigorously, poured back into sep funnel. [Note this aqueous wash was unnecessary (skip next time) as separation of layers was slow (EMULSION)]. Let sit in sep funnel 20 h after which time the emulsion completely broke.

16_ Separated layers. The organic layer was sealed with Al foil and sat for 2 days then extracted (see photo next slide) three times: 1 x 400 g 5% NaOH, 1 x 300 g 5% NaOH, then 1 x 200 g DI water.

PROCEDURE (cont'd):

17_The organic layer, following aqueous NaOH extraction, was washed with brine, dried over Na_2SO_4 and filtered into a 2 L RB flask (see left photo next slide). After sitting ~1 week, it was rotovapped (holding full vacuum for 5 min @ ~50 °C water bath temp). Residue weighed 176 g (see right photo next slide). This will be distilled later to recover unreacted 1,3-benzodioxole

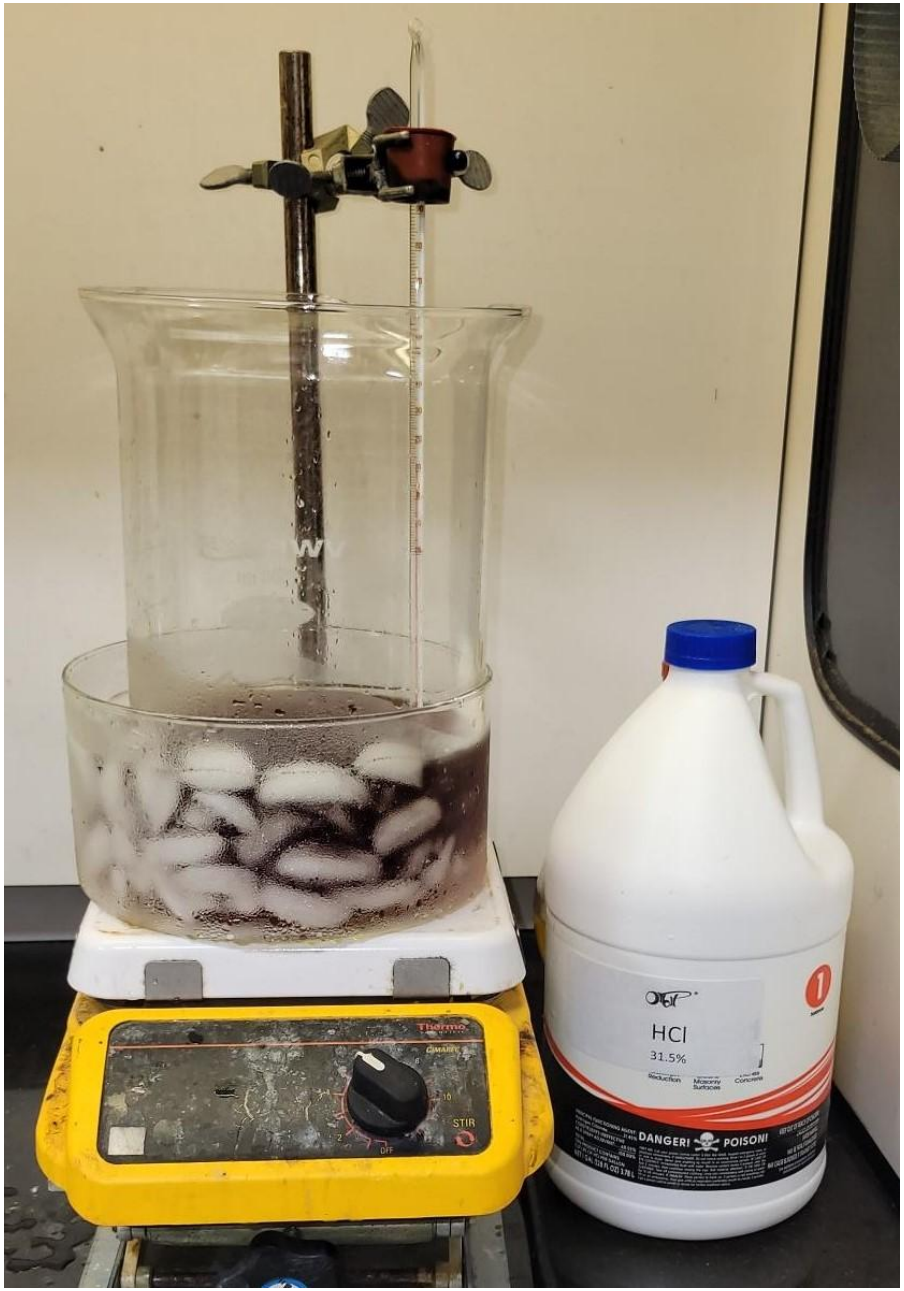



176 g
HEATING

PROCEDURE (cont'd):

19_Combined aqueous extracts (from #16) were washed (see photo- right) with 2 x 100 g IpOAc (Note: Combined washings were EOCd to 1.5 g of a dark brown oil which was discarded).

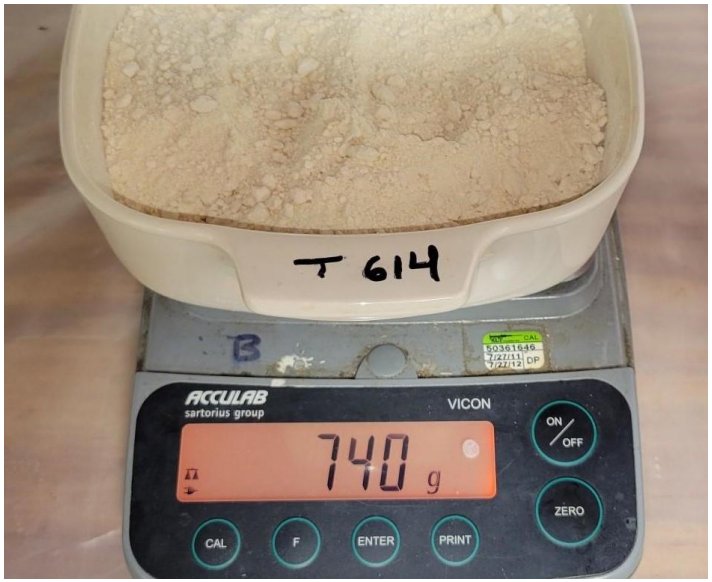
20_Washed aqueous extract (in 4 L beaker) was put on ice bath and cooled to 10 °C (see left photo next slide). Concentrated (31.5%) HCl was added SLOWLY portionwise with stirring (3" stir bar). After adding ~100 g, stirring was ceased by a massive precipitation of product. Continued to stir manually with a paddle until a total of 165 g had been added (see right photo next slide).

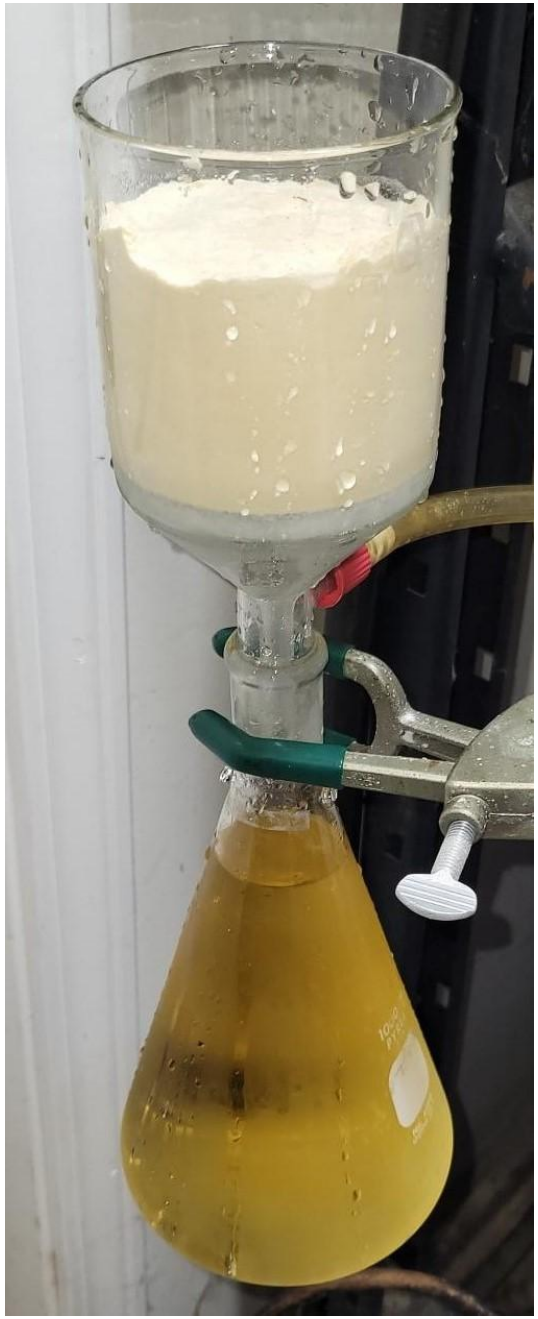

HCl
31.5%
DANGER! POISON!
STIR


STIR

PROCEDURE (cont'd):

21_Filtered (aspirator) thru an extra coarse fritted funnel (see photo- right). Washed solids well with water and sucked dry 5-10 min. After 24 h, (still very wet) solids were spread in shallow ceramic pan and fan-dried (under mesh), stirring occasionally. After ~1 week a constant weight of 126 g (36%) was observed (see photo below).





PROCEDURE (cont'd):

22_ Crude solid was added to 256 g (stirring) boiling toluene (in 600 mL beaker) and heated to ~100 °C before hot-filtering into a 2nd 600 mL beaker (a substantial amount of dark brown insolubles were removed this way). Sealed beaker with Al foil, let cool slowly and then let stand overnight. In AM used spatula to break up chunks and scrape walls of beaker. Filtered (aspirator, Buchner funnel, see left photo) and washed solids with toluene (51 g). Air-dried in funnel 48 h then spread onto shallow glass pan to dry another 48 h. A constant weight of 103 g (29%, mp 132-133 °C) was observed.

COMMENTS:

1_The low (29%) yield was undoubtedly carried forward from the previous chloromethylation reaction. A 51% (crude) yield was reported for piperonyl chloride in US patent 7402709B2 (in which toluene and 37% HCl were used). It would be interesting to repeat this work using those conditions for comparison. Higher yields (ie. >80%) have been reported using anhydrous HCl (see WO2020250018A1). Other (Blanc-type) methods for chloromethylation have been reported using ZnX2/dimethoxymethane.

2_2-MeTHF is a recommended solvent for Grignard reactions such as this one (*Green Chem*., **2013**, *15*, 1880-1888).

3_Please consider https://orbitnaturalproductderivatives.com/ when sourcing materials for your research.