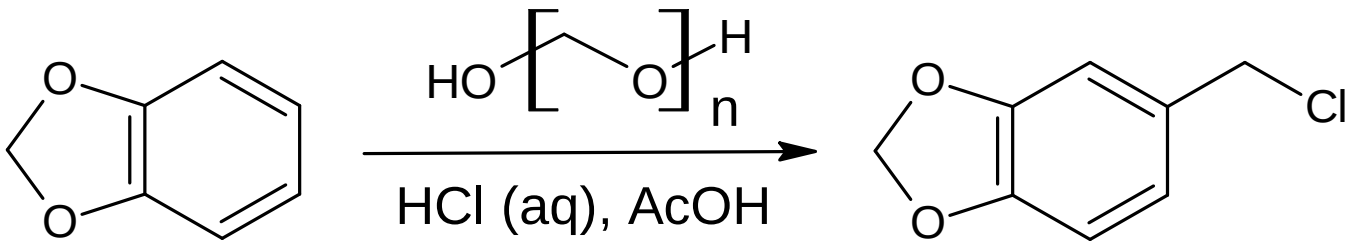
DISCLAIMER:

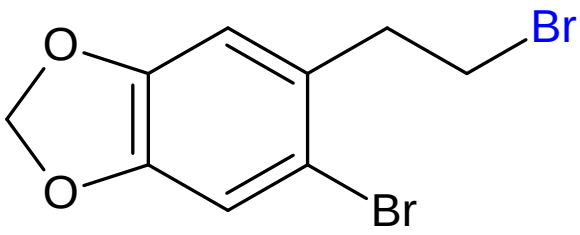
This content is intended for educational and/or entertainment purposes only. Many of the chemicals used in this research are hazardous and should be handled only by properly trained adults who are familiar with the physical/chemical properties and the techniques for handling/transferring them. We assume 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.

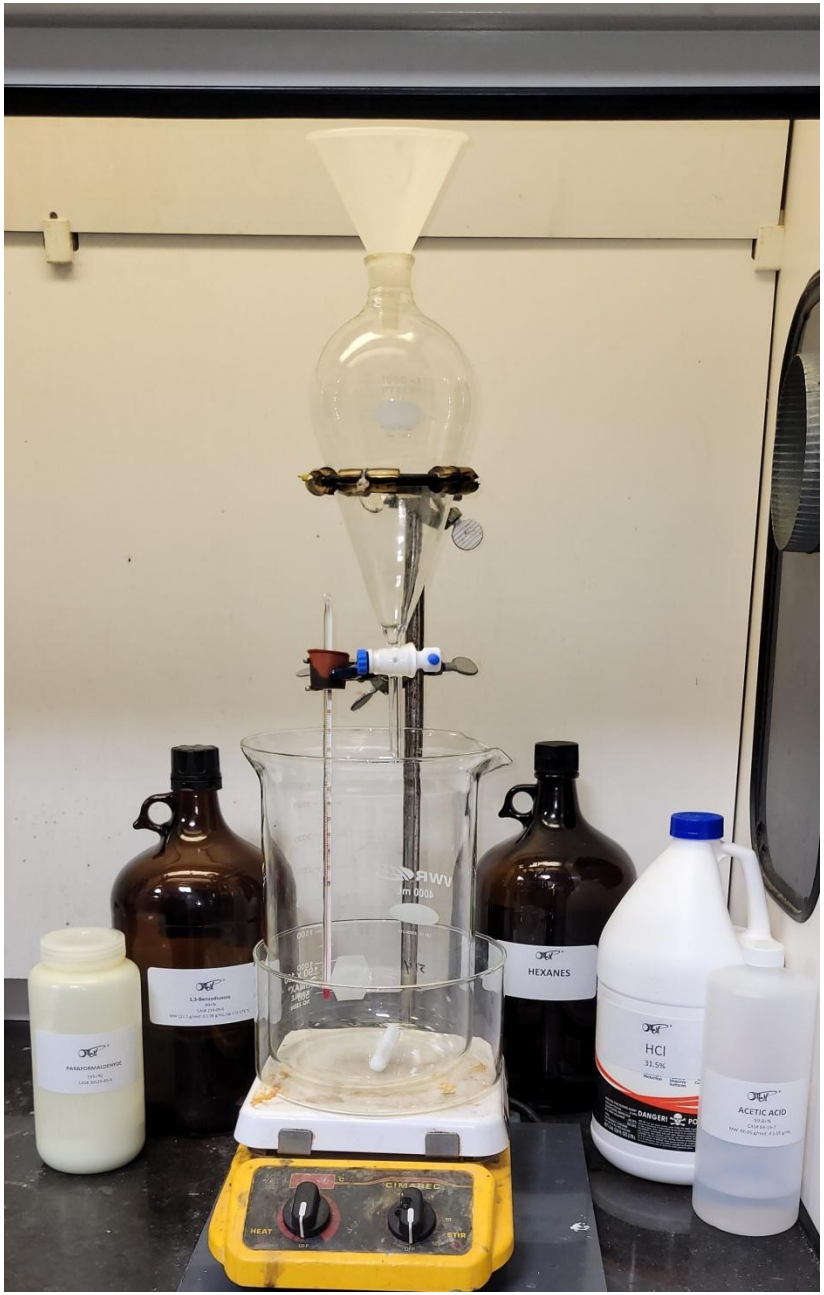
Chloromethylation of 1,3-Benzodioxole (Route A, Conditions A)



Step 1 of one of our routes to a key intermediate (alkyl bromide)→

used in a total synthesis of Berberine published in 2021 (Konno, et al.)





RAW MATERIALS:

1_Paraformaldehyde (95%)

2_1,3-Benzodioxole (99+%)

3_Hexanes (or Toluene)

4_Concentrated HCl (31.5% was used, 37% is preferred)

5_Acetic acid (glacial)

QUANTITIES:

1,3-Benzodioxole (MW 122.1 g/mol)
400 g, 3.28 mol, 1 eq

Paraformaldehyde MW (monomer) = 30 g/mol
112 g, 3.73 mol, 1.14 eq

Hydrochloric acid (31.45%, MW 36.5 g/mol)
1600 g, 13.79 mol, 4.2 eq

Acetic acid
600 g

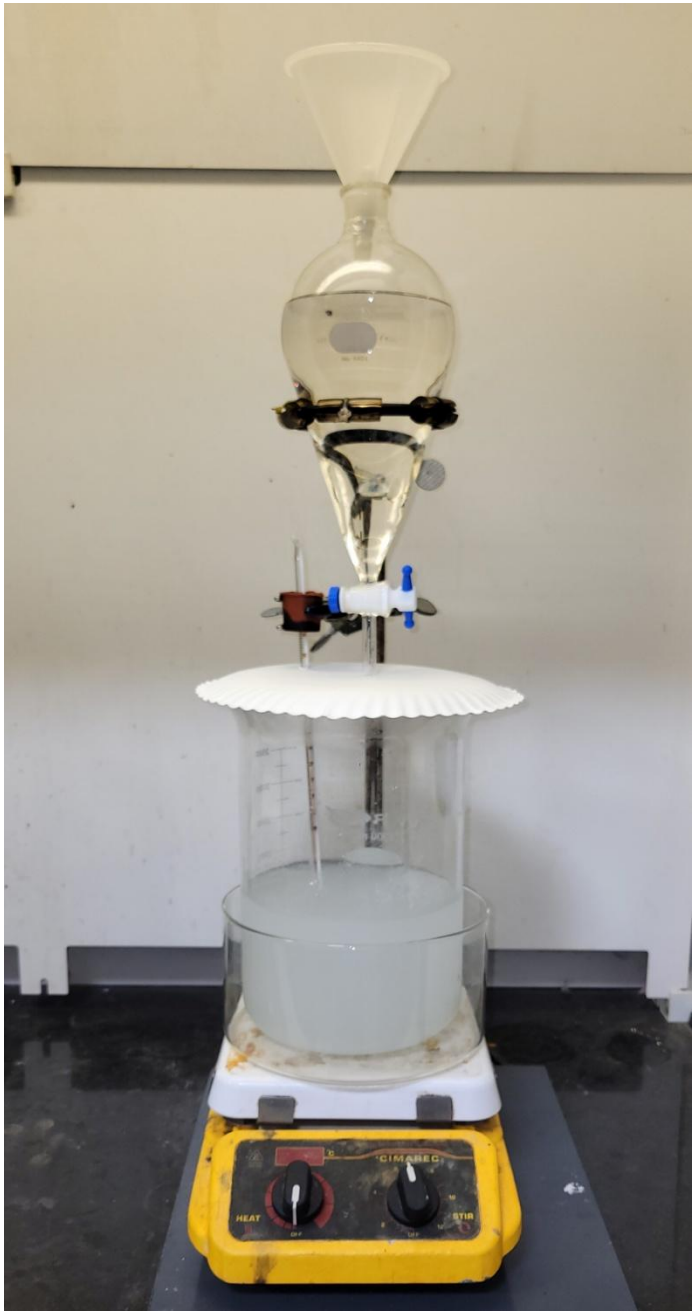
PROCEDURE:
[Note: IT = Internal Temperature (°C), RM = Reaction Mixture]

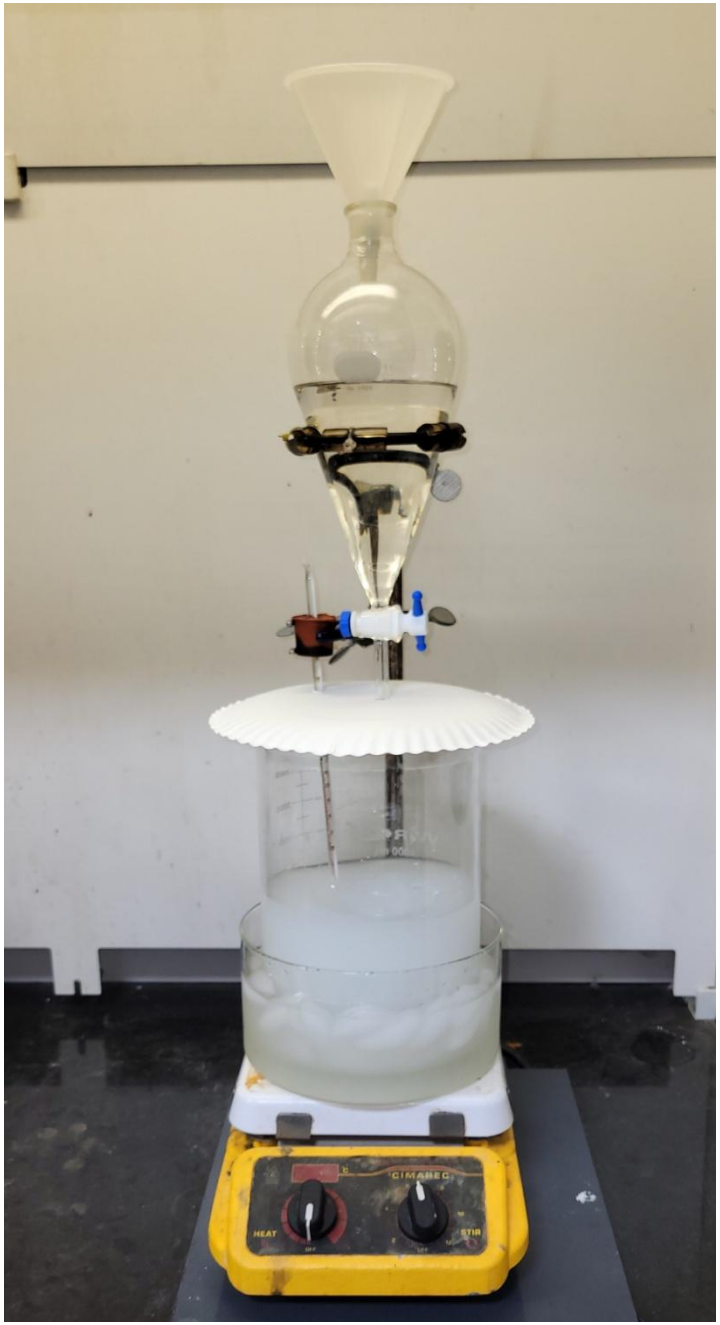
1_(11:45 am, IT = 23) Added aq HCl to a 4 L beaker (in empty 190 mm crystallizing dish) containing a 3” stir bar.

2_(11:50 am, IT = 23) Added paraformaldehyde to aq HCl in one portion (endothermic). Topped beaker with inverted paper plate to reduce fumes

3_(11:55 am) Charged 1 L separatory funnel with 1,3-benzodioxole dissolved in AcOH

4_(12 pm, IT = 16) Began adding benzodioxole-AcOH solution as a heavy stream





PROCEDURE (cont'd):

5_(12:05 pm, IT = 17) Filled crystallizing dish halfway with water

6_(12:07 pm, IT = 18) Added ~10 ice cubes to water bath

7_(12:20 pm, IT = 18) Addition of benzodioxole-AcOH solution complete

8_(12:30 pm, IT = 18) Ice completely melted

9_(12:42 pm, IT = 19.5) Removed some water from bath using a 50 mL glass pipet (see photo next slide)

PROCEDURE (cont'd):

10 _(12:55 pm, IT = 21) Added 3 ice cubes to bath

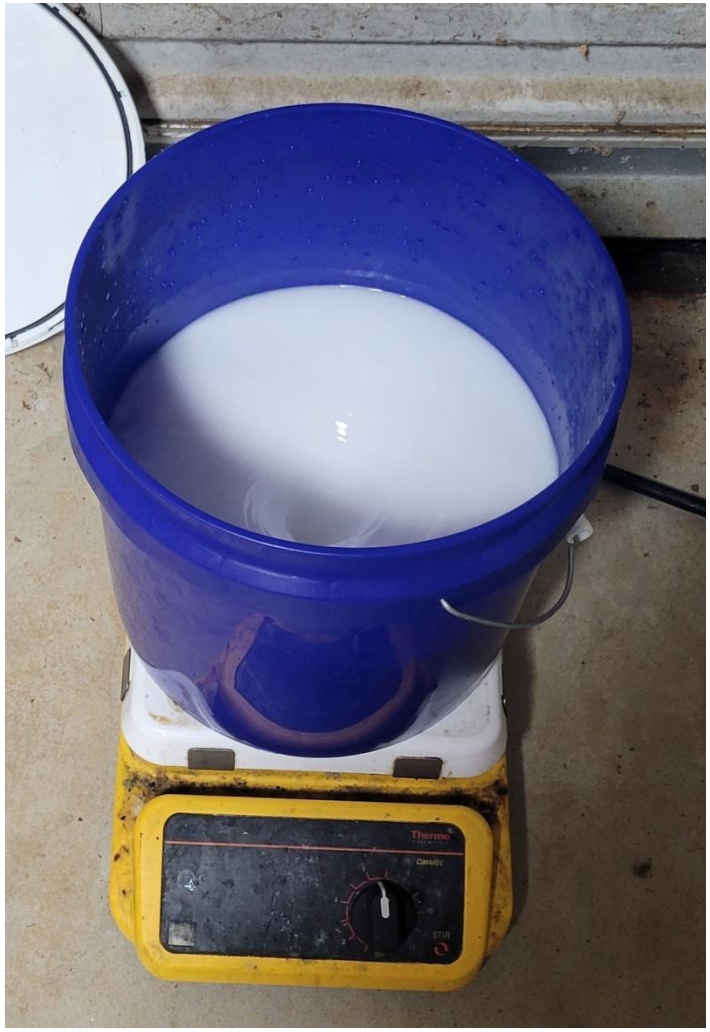
11_(1:10 pm, IT = 21) Added 3 ice cubes to bath

12_(1:25 pm, IT = 21) Added 3 ice cubes to bath

13_(2 pm, IT = 21) Added 3 ice cubes to bath

14_(2:15 pm, IT = 21.5) Removed some water from bath and added 5 ice cubes

15_(2:35 pm, IT = 21) Added 5 ice cubes to bath and left to run an errand



PROCEDURE (cont'd):

16_(3:10 pm, IT = 22) Returned, added 5 ice cubes to bath

17_(3:45 pm, IT = 23) Added 5 ice cubes to bath

18_(4:15 pm, IT = 23) Poured RM into 2 gallon bucket containing 800 g (stirring) hexanes and stirred 20 min

PROCEDURE (cont'd):

19_(4:40 pm) Filtered (gravity, SLOW) into 5 gallon bucket

20_(4:45 pm) Covered funnel with lid to reduce fumes

PROCEDURE (cont'd):

21_(6:30 pm) Wrung out (polymeric) solids wearing heavy duty rubber gloves (this filter paper is doubled commercial coffee/tea filter paper (originally 24" diameter cut to size for this application)

PROCEDURE (cont'd):

22_Transferred filtrate to a 4 L separatory funnel

23_Drained (lower) aqueous layer back into (white) 5 gallon bucket and (upper) hexane layer into (blue) 2 gallon bucket

PROCEDURE (cont'd):

24_Added 800 g hexanes (2nd extraction) to aqueous layer and stirred 10 min (below)

25_Filtered into 4 L separatory funnel (right)

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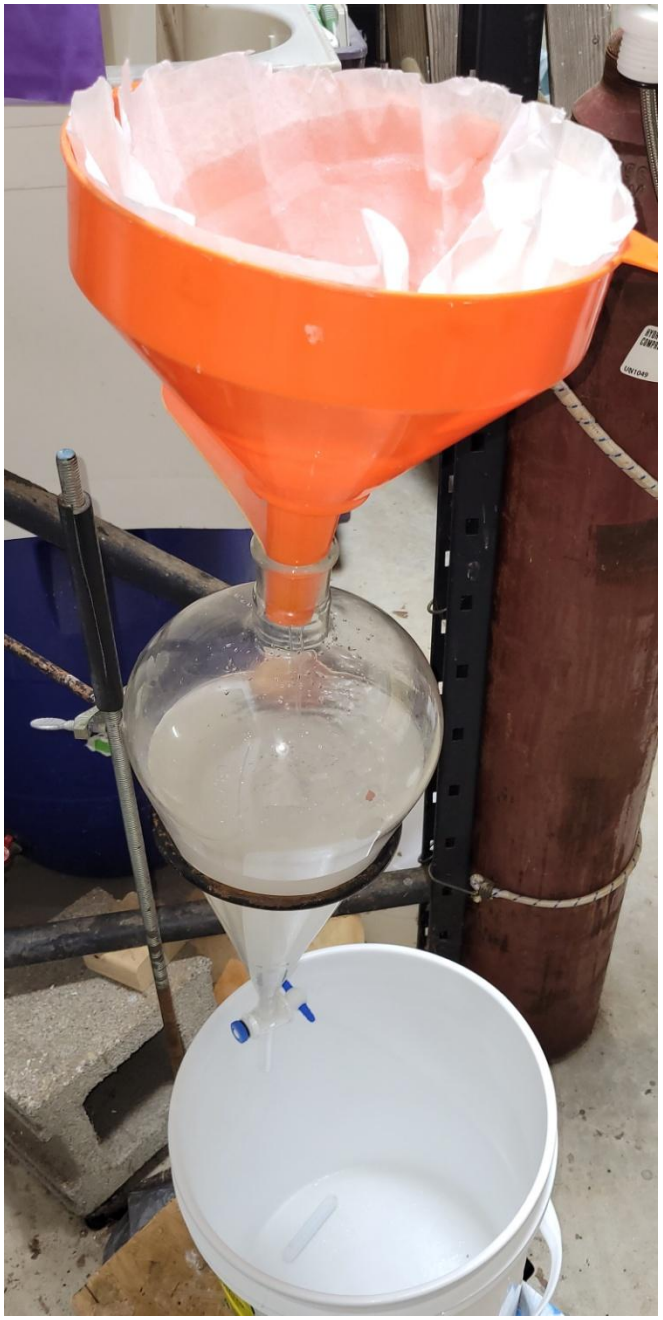


PROCEDURE (cont'd):

26_Drained (lower) aqueous layer back into (white) 5 gallon bucket. Drained (upper) hexane layer into (blue) 2 gallon bucket containing first extract

27_Added 400 g hexanes (3rd extraction) to aqueous phase, stirred 10 min (left), then poured into sep funnel. Drained (lower) aqueous layer back into 5 gallon bucket and (upper) hexane layer into 2 gallon bucket containing first and second hexane extracts

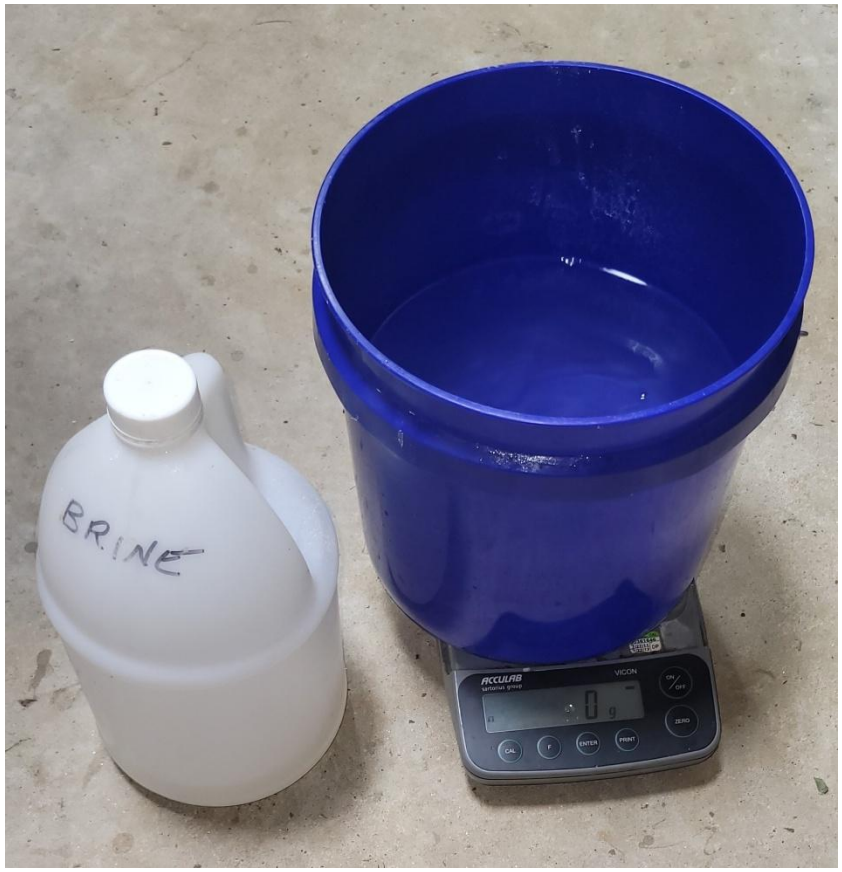
PROCEDURE (cont'd):

28_To (stirring) combined hexane extracts in (blue) 2 gallon bucket was added 800 g distilled water (right) and mixture stirred 10 min.

29_ Filtered (gravity- slow) into sep funnel. Drained aqueous layer into 5 gallon bucket and hexane layer into 2 gallon bucket. Added 800 g distilled water to blue bucket and stirred 10 min (2nd wash). Drained aqueous layer into 5 gallon bucket and hexane layer into 2 gallon bucket.

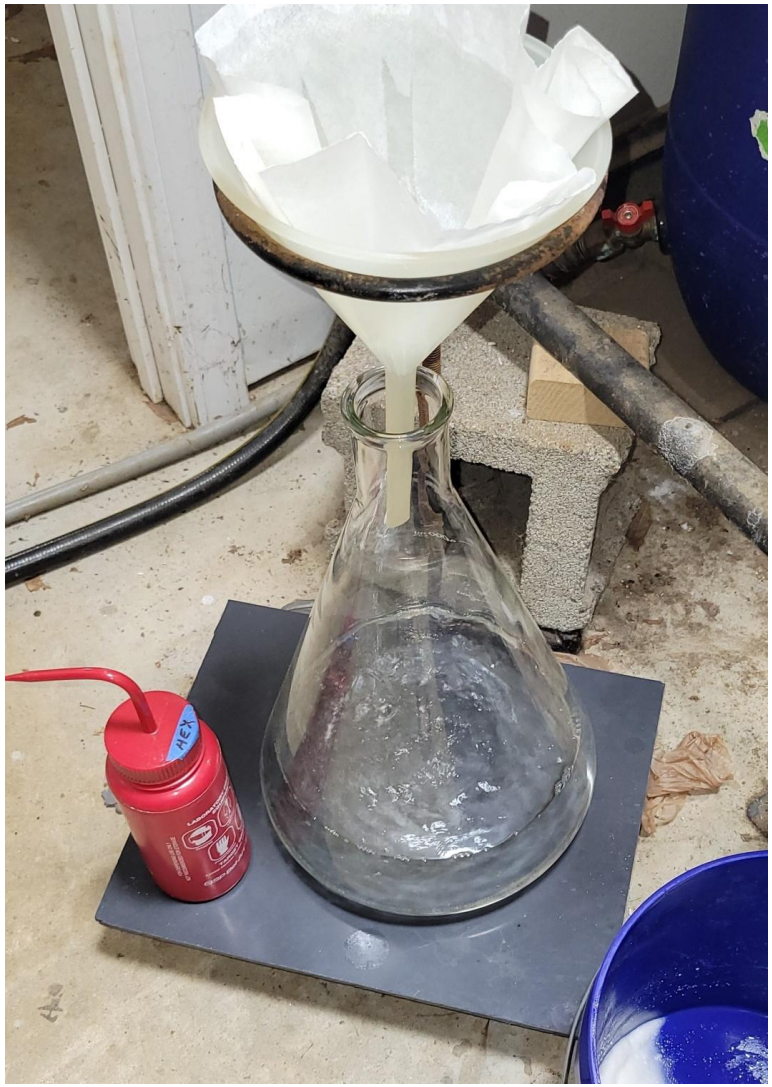
PROCEDURE (cont'd):

30_To blue bucket containing washed hexane layer (below) was added brine (1 Kg). Mixture stirred 10 min (right) then transferred to separatory funnel and separated



PROCEDURE (cont'd):

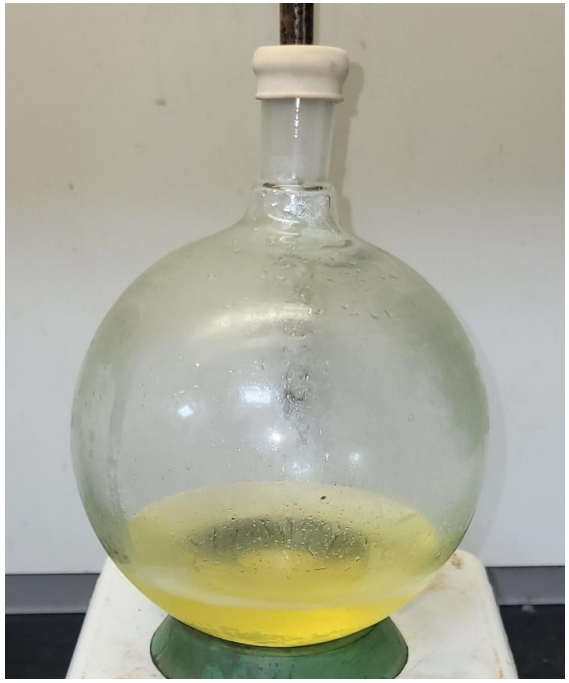
31_Brine-dried hexane layer was then dried over anhydrous Na2SO4 (below, left) and filtered into a 6 L Erlenmeyer flask (below, right)



PROCEDURE (cont'd):

32_Transferred (portionwise) to a 2 L round bottom flask and stripped on rotovap. Ultimately full vacuum (measuring 20-25 mmHg, water bath temp = 50 °C) was applied and held only for 5 minutes to minimize loss of unreacted benzodioxole which will be recovered later

33_Crude product (332 g, 59%, see photo next slide) was stored in freezer until carried forward (see "Grignard reaction to MDPAA")



COMMENTS:

1_For comments on this chemistry, see our “Grignard reaction to MDPAA” pdf in which this material is carried forward.

2_Please consider https://orbitnaturalproductderivatives.com/ when sourcing materials for your research needs.