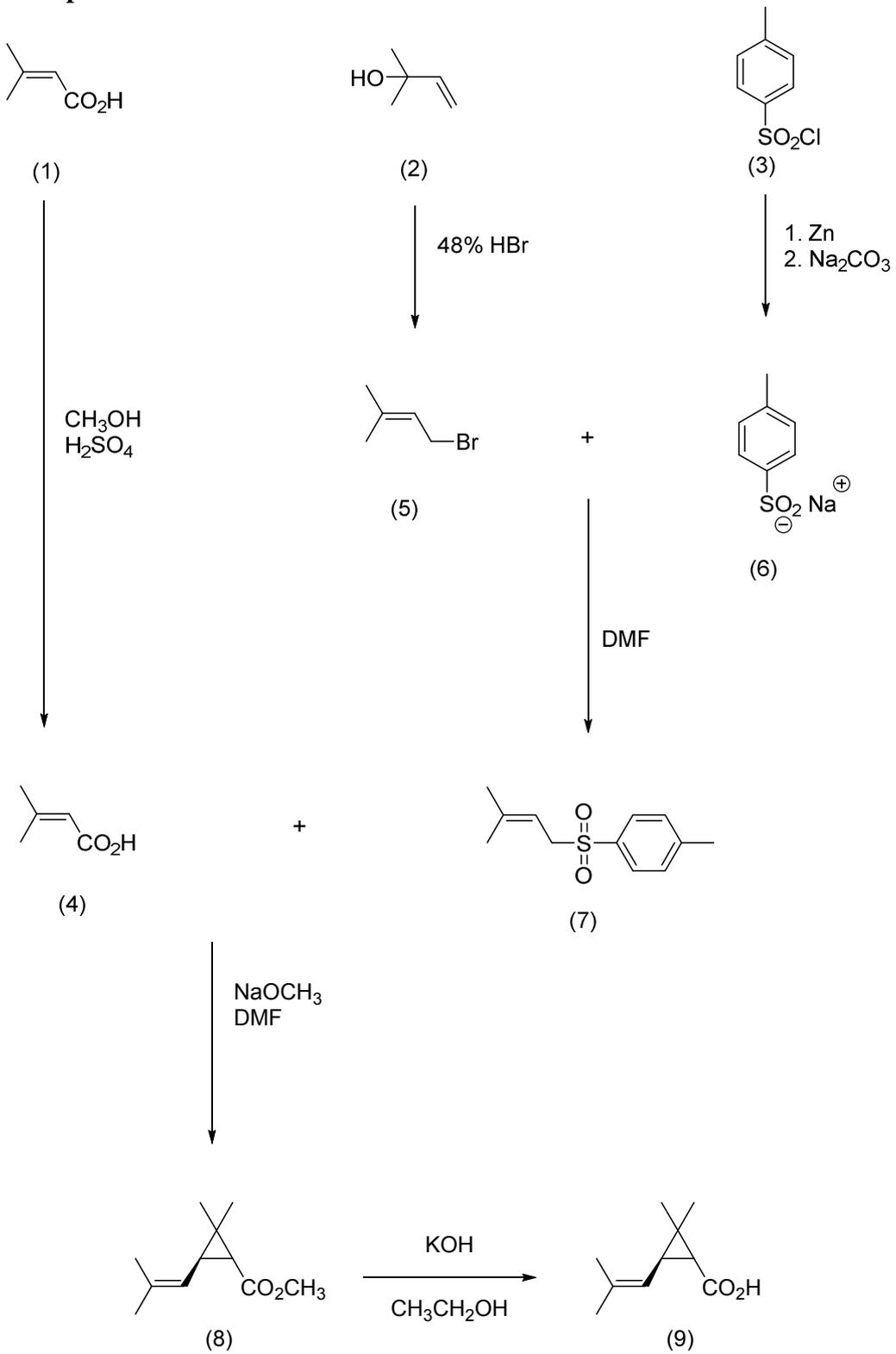


Action Plan

Reaction Steps:



Key:

1. 3-methyl-2-butenic acid
2. 2-methyl-3-buten-2-ol
3. p-toluene sulfonyl chloride
4. Methyl 3-methyl-2-butenate
5. 1-bromo-3-methyl-2-butene
6. Sodium p-toluene-sulfonate
7. 3-methyl-2-butenyl p-tolyl sulfone
8. Methyl chrysanthemate
9. Chrysanthemic acid

Physical Data:

Name	MW (amu)	Mp°C	Bp°C	Density (g/mL)	Solubility	Hazards
3-methyl-2-butenic acid	100.1158	65-70	194-195	0.969	-	-
Methanol	32.04	-93.9	65	0.791	w, al, eth, ace, bz, chl	flammable, poisonous
Sulfuric acid	98.08	-64	337	1.39	W	Caustic
Water	18.02	-	100	1.00	-	-
Ether	74.12	-116.2	34.5	0.7138	Al, ace, bz, chl	Flammable, irritant
Sodium chloride	58.44	801	-	2.165	w, al	-
Magnesium sulfate	120.37	1127	-	2.65	W, al	Irritant, mutagen
Zinc	65.38	419.53	907	7.140	-	Irritant, flammable
p-toluene sulfonyl chloride	190.65	65-69	134	1006	Dcm	Corrosive, toxic
Sodium hydroxide	40.00	681	145	1.515	w	corrosive, toxic
Sodium carbonate	105.99	851	D	2.532	W, al	Irritant, hy- groscopic
Sodium p-toluene-sulfonate dihydrate	194.18	>300	-	-	W	Irritant
Dimethyl formamide	73.09	-61	153	0.948	W	Flammable, hygroscopic

1-bromo-3-methyl-2-butene	149.03	-	129-133	1.293	-	Irritant
Hydrobromic acid	80.91	-87	-67	1.49	W	Hygroscopic, irritant
2-methyl-3-buten-2-ol	86.13	-43	98-99	0.824	Al	Irritant
Sodium bicarbonate	84.01	-	-	2.159	W, al	-
3-methyl-2-butenyl p-tolyl sulfone	224.313	82-84	-	-	-	-
Isopropyl alcohol	60.1	-89.5	82	0.785	Benz	-
Methyl 3-methyl-2-butenoate	114.14	-41	70-75	0.935	-	Irritant
Sodium methoxide	54.02	-	-	-	W, al	Flammable, solid, corrosive
Hydrochloric acid	36.46	-114.9	-85.06	1.18	w	toxic, corrosive
Pentane	72.15	-130	36.1	0.6262	Al, eth, ace, bz, chl	Flammable, irritant
Potassium hydroxide	56.11	361	1320	1.450	W	Corrosive
Ethanol	46.07	-117.3	78	0.789	w, eth, ace, bz	highly toxic, flammable
Chloroform	119.38	-63	61	1.492	W	Suspected carcinogen
Methyl chrysanthemate	182.26	-	56-59	1.004	Eth	-
trans-chrysanthemic acid	168.23	17-21	80	1.01	W, eth	Toxic, irritant
dichloromethane	84.93	-95.1	40	1.3266	Al, eth	Toxic, irritant

*Data from Handbook for Organic Chemistry, 10th ed., <http://pubchem.gov>, <http://chemsynthesis.com> and <http://chemicalbook.com>

Masses and Volumes of Reagents:

- 9 g 3-methyl-2-butenoic acid
- 23 g zinc dust
- 25 g p-toluene sulfonyl chloride
- 20 g solid Na₂CO₃
- 90 mL dimethyl formamide

- 25 mL hydrobromic acid
- 5 g 2-methyl-3-buten-2-ol
- Anhydrous magnesium sulfate (dependent on amount of water in sample)
- 5 g methyl 3-methyl-2-buten-2-yl 2-methylpropanoate
- 5 g sodium methoxide
- 125 mL pentane
- 3 g potassium hydroxide
- The rest of the reagents will be specified in the procedure, as they will be freely available per the multistep project description.

Procedure: Adjusted from Paul F. Schatz's procedure, University of Wisconsin

NMR will be submitted w/ chloroform, and IR w/ DCM.

Step 1- Synthesis of Methyl 3-methyl-2-buten-2-yl 2-methylpropanoate

- Take clean 250 mL round flask w/stir bar and add 9 g 3-methyl-2-buten-2-yl 2-methylpropanoic acid, 50 mL methanol, then 5 mL conc. sulfuric acid
- Attach to water cooled condenser and reflux for 1.5 hours to 2 hours. Allow to cool.
- Pour cooled mix into 50 mL of ice water. Extract w/ 3 parts of 38 mL ether.
- Combine ether extracts and wash w/ 50 mL sat. NaCl. Dry over anhydrous magnesium sulfate
- Use rotovap to reduce volume down to 20-30 mL
- Transfer residue to smaller flask and distill at 130-138 deg Celsius. Take mass of clean flask and collect distillate. Save the methyl 3-methyl-2-buten-2-yl 2-methylpropanoate for later step. Run NMR, IR.

Step 2- Synthesis of Sodium p-toluene-sulfonate

- Take 1 L beaker and put in 250 mL water, then heat to 70 deg Celsius on a steam bath (ask TA about possibility of set-up or to use hot plate instead)
- Add magnetic stir bar, and mass 23 g zinc dust. Add to beaker. Then slowly add 25 g of finely ground p-toluene sulfonyl chloride. Addition of p-toluene sulfonyl chloride should take about 10 minutes so add accordingly.
- Stir for 10 more minutes on the steam bath (or hot plate)
- Add 13 mL NaOH (12g/25mL water)
- Add sodium carbonate 2.5 to 5 g at a time until mixture has pH higher than 7. Can use pH testing paper to test. During addition, some bubbling may occur.
- Filter the mix on Buchner funnel while it is still hot and save the filtrate (liquid), and then add solids to 75-125 mL of water as it heats on the steam bath (or hot plate) make sure the mix is being stirred w/ another magnetic stir bar
- Again filter the mix and save the liquid. Combine with the liquid (filtrate) from previous step
- Can use reduced pressure in side arm flask or rotovap to remove solvent until volume goes down to 50 to 85 mL, or let stand until water evaporates and crystals start to form. Can ask TA which method will be more efficient

- Let mix cool so the crystals will form, then filter the Sodium p-toluene-sulfonate dihydrate. Let the crystals air dry, can use reduced pressure and Buchner funnel. Can collect melting point if desired, as well as NMR and IR.

Step 3- Synthesis of 3-methyl-2-butenyl p-tolyl sulfone

- Take 100-250 mL round flask w/ 3 necks and attach condenser, dropping funnel and glass stopper. Add stir bar.
- Add 13.5 g Sodium p-toluene-sulfonate dihydrate to flask. Measure and add 50 mL DMF
- Stir mix at room temp. In the separatory funnel (or addition funnel) add 25 mL 48% hydrobromic acid, then add 4.15 g (5 mL) 2-methyl-3-buten-2-ol.
- Thoroughly shake sep funnel 15 min. Drain lower aqueous layer. Wash organic layer w/ 25 mL sodium bicarbonate. Collect lower (organic) layer. Drain aqueous layer and replace w/ organic in the sep funnel.
- Add contents of funnel over 10 min period (1-bromo-3-methyl-2-butene). Heat and stir at 80-90 deg Celsius for 1.5-2 hrs.
- After previous step, add mix to 250 mL of water and stir one hour. Crystals will appear white. Filter w/ Buchner funnel.
- If desired, can recrystallize w/ isopropyl alcohol (1 mL per 1 g of product). Crystals will be pointy and colorless. Take melting point, IR, and NMR.

Step 4- Synthesis of Methyl Chrysanthemate

- Take clean and dry 250 mL round flask w/ stir bar and set up in nitrogen atmosphere (w/ nitrogen inlet)
- Mass 4.5 g Methyl 3-methyl-2-butenate from step 1 and add to flask. Also add 7.5 g 3-methyl-2-butenyl p-tolyl sulfone from step 3, then 37.5-38 mL DMF.
- Add 5 g sodium methoxide, then stir at room temp (in N₂ atmosphere) for 24-48 hrs
- Afterward, add 12.5 mL HCl, 25 mL water, and 25 g ice into a large beaker. Transfer mix from previous step into same beaker.
- Extract mix w/ 5 parts of 25 mL pentane. Organic layer on top, drain aqueous. Wash combined layers w/ 50 mL sodium bicarbonate, then 50 mL NaCl. Use magnesium sulfate to dry layer.
- Use rotovap to remove pentane
- Distill residue leftover in flask under vacuum (ask TA). Run IR, NMR and mp if possible.

Step 5- Chrysanthemic acid

- Take 100 mL round flask and add 2.5 g Methyl Chrysanthemate, then 2.5 g potassium hydroxide, then 37.5 mL 95% ethanol.
- Reflux mix for 2 hrs
- Rotovap to remove ethanol
- Add 50 mL water to solid product, then extract w/ 25 mL ether.
- Save aqueous layer and add 50% HCl to acidify. Get rid of ether extract. Test w/ pH paper, should be 1-2.
- Extract aqueous layer in 3 parts of 17.5-18 mL ether. Save these ether layers and dry w/ more magnesium sulfate.
- Use rotovap to remove ether. Then distill under vacuum. Product should be an oil and may become solid. If solid, take melting point, lit from referenced procedure says 50-52

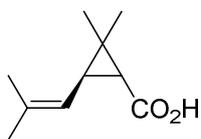
deg Celsius, therefore should compare w/ lit from data table. Also take IR and submit NMR.

Background Information and Relevance

Chrysanthemic acid is known to be a natural insecticide with the added benefit of being biodegradable. This is very significant as the use of this compound leaves a negligible environmental footprint. It is also nontoxic to mammals, making it safe to use around children and pets.

Structure and Interesting Properties

The compound Chrysanthemic acid has a tricyclic ring as part of the structure. There is a COOH group coming off the ring which makes the compound a carboxylic acid. There is also a double bond in the structure pointing out of the page off of the ring, making the compound an alkene. There are also two methyl groups coming off of the top of the ring. The structure of chrysanthemic acid is shown below:



Methods and Synthesis

The synthesis was organized into five steps, with four intermediates and the resulting product, chrysanthemic acid. The experiment was designed for 8-10 four-hour lab periods, or 32-40 hours for the entire synthesis. Time constraints limited the lab to 18 hours, so embarking on the task of synthesizing chrysanthemic acid within the allotted time was admittedly ambitious.

Step 1 was to synthesize methyl 3-methyl-2-butenate via acid catalyzed esterification. All the measurements during the synthesis were scaled down to one half of the literature values to reduce waste and as an attempt to reduce the time needed to conduct the experiment. The literature used a 250 mL round bottom flask and 18 g of the off-white colored 3-methyl-2-butenic acid, but was adjusted to 100 mL and 9.0309 g. To the flask, 49.5 mL of methanol and 5 mL of concentrated sulfuric acid were added and allowed to reflux for 1 hour and 50 minutes. The mixture was poured into cool water and the yellow layers were extracted by 3 parts of ether, a total volume of 114 mL. Afterward the rotary evaporator was used to reduce the volume of the liquid to about 30 mL, and the mixture became dark yellow. The resulting residue was distilled at 130 degrees Celsius, and gave a distillate that was colorless with a very strong odor. Leftover residue in the round flask had a reddish color. 7.5882 g of product was collected, giving a yield of 73.73%. The literature described a yield of 69%, so these results were quite satisfying. On the IR spectrum taken of the compound, there were peaks at around 2800-2900 cm⁻¹ that indicated the compound had C-H bonds, peaks at 3100 cm⁻¹ that indicated an alkene, and more peaks at the carbonyl region that 1715-1730 cm⁻¹ that suggested the presence of an ester. Each peak on the attached NMR neatly matched the structure of the compound, indicating the presence of methyl 3-methyl-2-butenate.

Synthesizing sodium p-toluenesulfinate was the next step, and was started at the same time as step 1 in order to make good use of time. The reaction was a zinc reduction, with 23.0242 g of dark grey zinc dust combined with 25.0064 g of p-toluene sulfonyl chloride. The literature had suggested a slow addition to prevent thickening the mixture too rapidly, but the p-toluene sulfonyl chloride was accidentally added all at once and led to a thick sludge/slurry. The grayish sludge that resulted strongly resembled cement in appearance; special care was taken when handling and kept under the student hood because of its strong odor. The addition of 14 mL of

6M NaOH made the mixture somewhat looser, as well as one hour of stirring. Treatment with a total of 7.5627 g of sodium carbonate followed and led to vigorous bubbling; much of the mixture had to be quickly salvaged with another container as it was spilling up and out. The mixture was filtered with a Buchner funnel and resulted in filtrate and a dense grey filter cake. Again the solids were filtered but in 130 mL of hot water. Care was taken to make sure the filtrate was not discarded in order to retrieve the intermediate, and the filter cake was properly disposed of. A large 500 mL Erlenmeyer flask was used to contain the reaction, so boiling down the water took several hours; no other large beakers were available, but in hindsight would have significantly sped up the process of evaporation. Eventually when enough water boiled off, the liquid was transferred to a 250 mL beaker and the rest of the process was fairly quick. Using the rotary evaporator was considered, but was decidedly less efficient than boiling. The crystals of p-toluenesulfonate were large, flat and white, with a mass of 13.5554 g and a yield of 53.21%. The literature reported yields of 72% so the yield for this experiment was fairly low. Much of the product was stuck in the sludge-cake, resulting in a lower yield. Characterization was fairly difficult, as p-toluenesulfonate is soluble in water and could not be tested by IR. The NMR showed water instead of the compound so next the melting point was attempted. The digimelt apparatus had a threshold of 260 degrees Celsius while the compound had a melting point >300 degrees Celsius so it could not be measured in the lab. The intermediate didn't melt at the digimelt's highest setting, so this suggested the correct compound had been synthesized.

Step 3 was the synthesis of 3-methyl-2-butenyl p-tolyl sulfone. 10.6863 g of p-toluenesulfonate from the last step was measured and added to a 3-neck 100 mL round bottom flask with an attached condenser and addition funnel. The crystals were added to 49 mL of DMF and the peach colored mixture was stirred. In a separatory funnel was added 25 mL of fuming 48% hydrobromic acid. 2-methyl-3-buten-2-ol was added to the separatory funnel, and the resulting cloudy organic layer was washed with sodium bicarbonate in an SN1 reaction. The separatory mixture was placed into the addition funnel and added slowly over a 10 minute period, then heated and stirred for 2 hours in an SN2 reaction. When the mixture was then added to water, it became milky white and was stirred for another hour. The crystals of 3-methyl-2-butenyl p-tolyl sulfone were filtered and appeared off-white and powdery. 6.6429 g were collected, which was a yield of 53.82%. The literature reported a yield of 66%, so the experimental yield was only a little lower. Its melting point was close to the literature value of 82-84 degrees Celsius at 83.1-84.5 degrees Celsius, indicating the purity of the compound. The IR was not taken, but the attached NMR showed very little contamination and matched nicely with the structure of the compound.

Step 4 was the synthesis of methyl chrysanthemate, and was basically a 24-48 hour reaction under inert nitrogen gas atmosphere followed by extraction and evaporation. 4.5300 g of methyl-3-methyl-2-butanoate was combined with DMF and sodium methoxide and left to react while stirring. At the beginning of the reaction the mixture was shades of orange, but by the end had turned into a deep dark brown viscous fluid. The mix was added to 12M HCl, water and ice to prevent the mixture from getting too hot, and vapors appeared on top of the mixture. The mixture was extracted with ether and the yellow organic layer was collected. Washing with saturated sodium bicarbonate and NaCl resulted in a bright yellow liquid. After being reduced in volume by the rotary evaporator, the residue was brown and viscous, similar in appearance to honey. The yield was not determined as distillation was the last part of the step and the NMR was a mess, but the IR showed peaks at 2900 cm⁻¹ for the double bond, 3100 cm⁻¹ for the C-H

bonds, and 1724 cm⁻¹ for the carboxylic acid group which indicated the presence of methyl chrysanthemate.

Step 5 was the last and final step of the synthesis of chrysanthemic acid, but time did not permit the completion of the step. It involved basic hydrolysis using KOH to convert the methyl chrysanthemate to a carboxylic acid via reflux, evaporation, acidification, extraction, and distillation. In the future, care will be taken to plan and take the necessary time in order to finish the synthesis.

References

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