Honors Cup Synthetic Proposal

Section: 210 .
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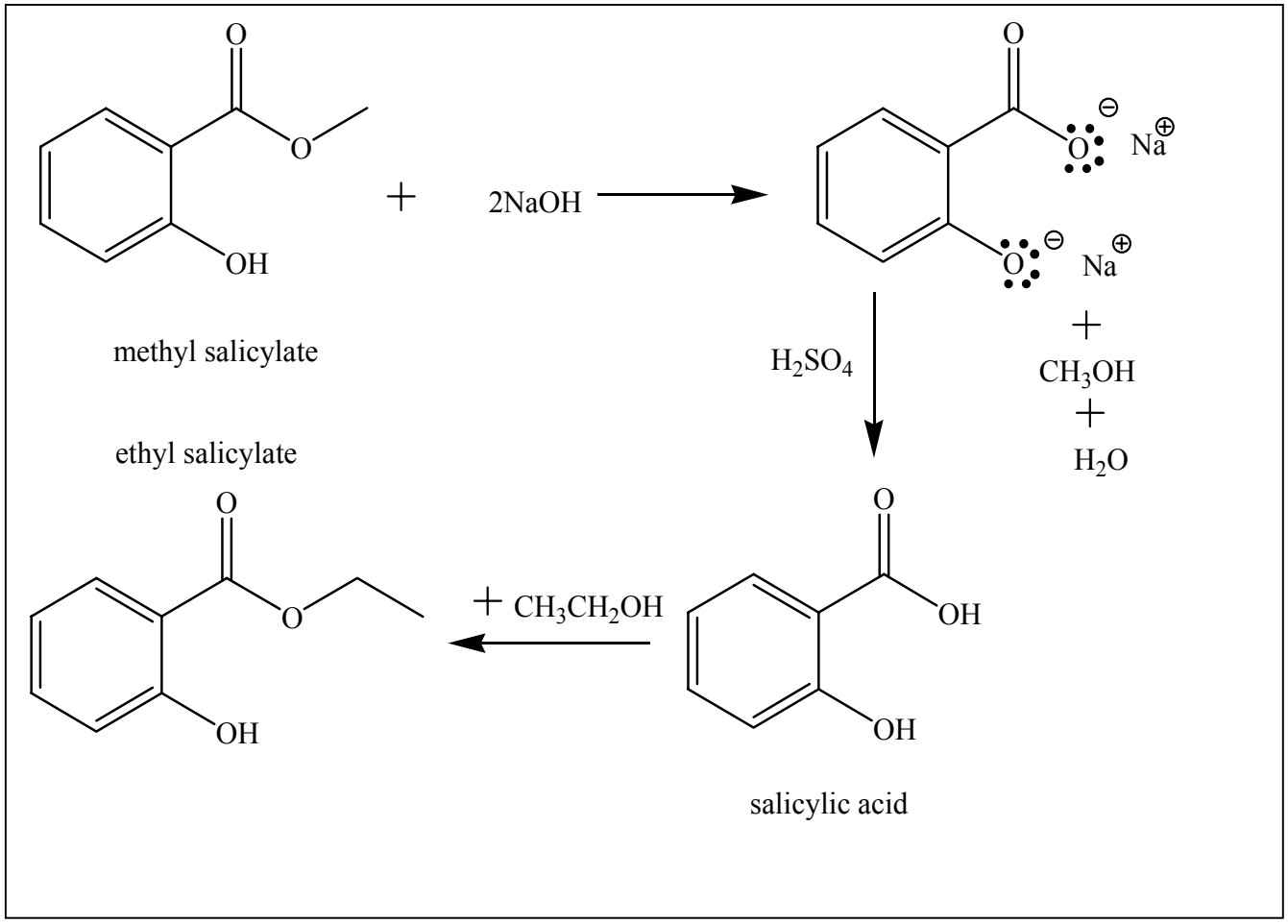
Title: Synthesis of Ethyl Salicylate

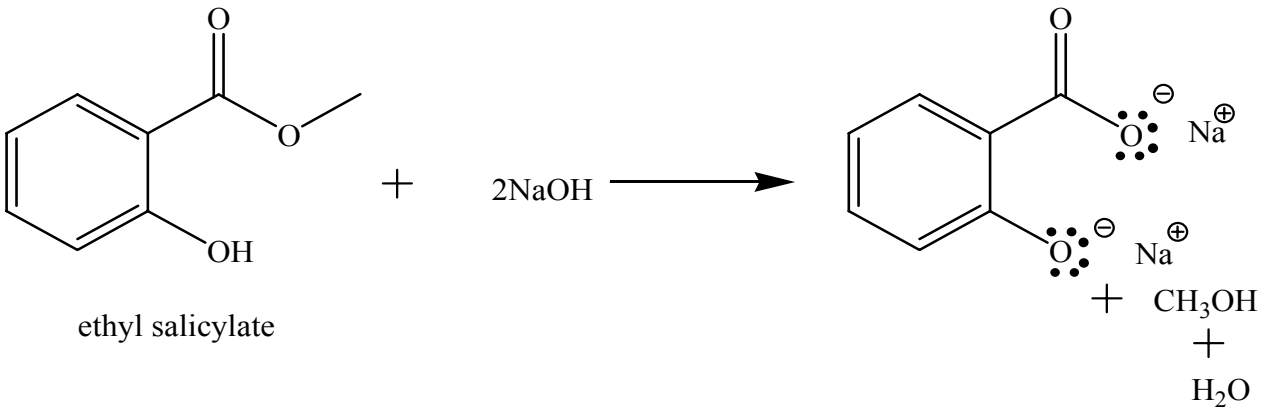
Introduction: Ethyl salicylate is a molecule that is naturally occurring in plants, fruits & vegetables. It is a natural preservative that is used in perfume and cosmetics and also has uses as an analgesic, antiseptic, and antipyretic. It has the odor of wintergreen/mint and is used in sweet floral, tutti frutti and spicy balsam essences. Ethyl salicylate is an ideal synthetic product because of the ease with which it can be identified due to its distinctive smell. Methyl salicylate also has a distinctive smell and the olfactory characteristics of these salicylate esters will help to reassure researchers that they are following the procedure correctly.

Overall synthetic reaction scheme:



Step 1

Synthetic transformation 1:



ethyl salicylate

Experimental 1

Dissolve 16 g of NaOH in 80 mL of water. Allow the solution to cool to room temperature and add it to 8 g of methyl salicylate in a 200 mL round-bottom flask. Add two boiling chips and attach a reflux condenser with greased joints. Using a heating mantle, heat the solution slowly at first, then at vigorous boil for 10 to 20 minutes until the oily ester appears to be gone. Set aside one quarter of the solution for characterization.

To characterize the resulting ionic intermediate of this step, distill the solution to remove excess ethanol. Prepare the sample for IR, and for H-NMR use D_2O as the solvent.
(Lambert & Mazzola 2004)

The scale has been doubled so that there will be enough product for characterization and further steps.

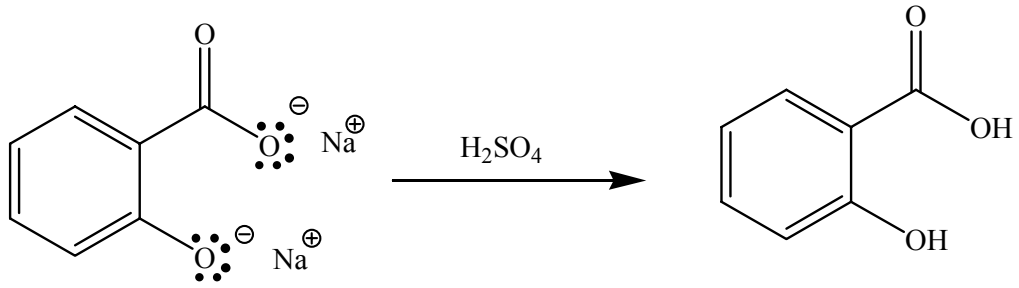
Expected yield: Ideal: 100% yield, 7.16 g. Due to error 60% yield expected, 4.30 g.

Safety, disposal and green issues 1:

Distillation will result in methanol as a byproduct. This can be disposed in the waste hood.

Step 2

Synthetic transformation 2:



salicylic acid

Experimental 2

Cool the reaction solution from experiment 1 in a ice water bath. Pour it into a 100 mL beaker and cautiously add with stirring enough 3 M sulfuric acid to make the pH of the solution about 1. This will be approximately about 5 to 6 mL. With occasional stirring, cool the mixture of liquid and precipitate in an ice water bath to about 5ºC. Collect the precipitate by vacuum filtration, rinse with ice cold water. Recrystallize the impure product from water in a 100 mL Erlenmeyer flask. Characterize the product using IR, NMR and TLC.

Expected yield: Ideal 100% 5.45 g. Due to error, 60% yield expected, 3.27 g.

Note: These molar amounts will not correspond to those of step 1 due to the fact that one quarter of the solution from step 1 was removed prior to beginning step 2.

Safety, disposal and green issues 2:

Excess methanol will be filtered out as a byproduct. This can be disposed in the waste hood.

Step 3

Synthetic transformation 3:

Experimental 3

Using 3 g of dried salicylic acid from step 2, put the reagent in a 150 mL Erlenmeyer flask. Add 6 mL of 100% ethanol, 0.25 g boric acid and 2-3 boiling stones. Set up reaction on a heat plate and attach reflux condenser. Heat until the ethanol is boiling, and continue heating under reflux for 2 hours. After the allotted 2 hours, allow the reaction mixture to come to room temperature using an ice bath. Transfer the solution to a separatory funnel. Add 5 mL of 2 M NaOH. The bottom (organic) layer will turn milky. Separate the bottom layer into a beaker, and dry the ester with anhydrous $MgSO_4$, roughly .1 g. Use vacuum filtration to separate remaining aqueous material. The remaining substance in the Erlenmeyer flask will be ethyl salicylate. This can be identified by its less potent wintergreen fragrance and clear/oily appearance. Characterize this compound using IR, NMR, and TLC.

The scale has been halved due to the margin of error expected from Step 2.

Expected yield: Ideal 100% 3.60 g. Due to error, 60% expected, 2.16 g.

Safety, disposal and green issues 3:

The aqueous layer will be disposed in the waste hood. The aqueous layer combined with $MgSO_4$ will be disposed in the solid waste bucket in the waste hood.

Overall budget:

Chemical	Supplier	Cost	Amt. Available/ Amount per synthesis	Total/ Total per synthesis
Methyl salicylate	Aldrich	23.30	100 g / 8 g	23.30/ 1.86
Boric acid	Aldrich	12.60	100 g / 0.25	12.60/ 0.03
D_2O for H-NMR	Aldrich	23.10	5 mL	23.10

Other materials such as ethanol, sulfuric acid, sodium hydroxide, magnesium sulfate and boiling stones can be found in the lab.

Total costs per synthesis: 1.89
Additional cost for H-NMR solvent: 23.10

References:

1. Solomon, S.; Hur, C.; Lee, A.; Smith, K. *J. Chem. Educ.* **1996**, *73,* 173-175. (Title of article: "Synthesis of Ethyl Salicylate using Household Chemicals")
2. Kirumaki, S.R.; Nagaraju, N.; Murthy, K.V.; Narayanan, S. *Applied Catalysis A: General* **2002**, *226,* 175-182. (Title of article: "Esterification of salicylic acid over zeolites")
3. Kakkar, T.; Maersohn, M.J. *Chromatogr.* **1998,** *718*, 69-75. (Title of Article: "Simultaneous quantitative analysis of methyl salicylate, ethyl salicylate and salicylic acid from biological fluids using gas chromatography- mass spectrometry)
4. Lamber, J.B.; Mazzola, E.P. *Nuclear Magnetic Resonance Spectroscopy: An Introduction to Principus, Applications, and Experimental Methods.* New Jersey: Pearson Education, Inc; **2004;** pp 33-34.
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