Honors Cup Synthetic Proposal

Section: 250; Group IV
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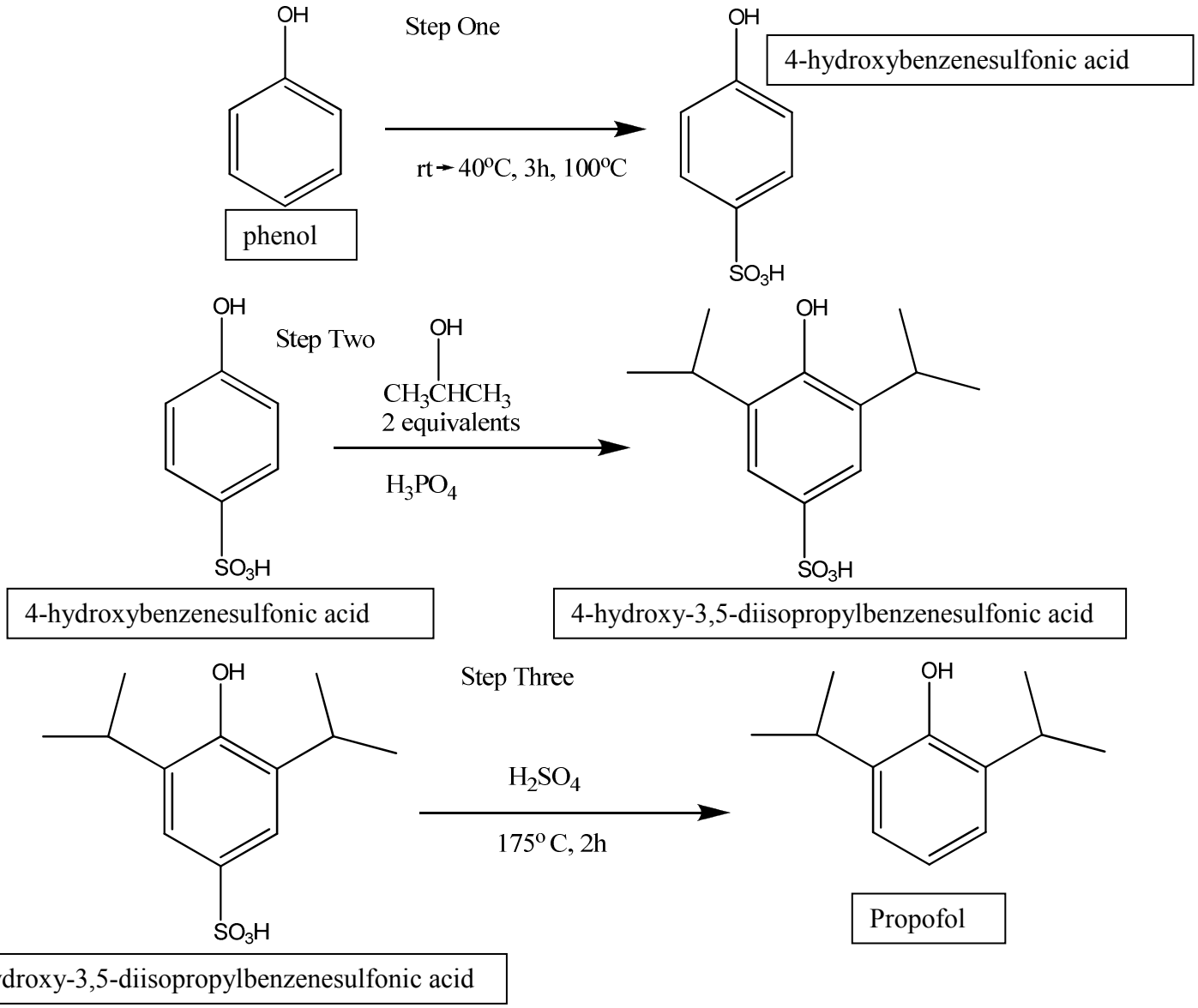
Title: Three Step Synthesis of Propofol (2,6-diisopropylphenol)

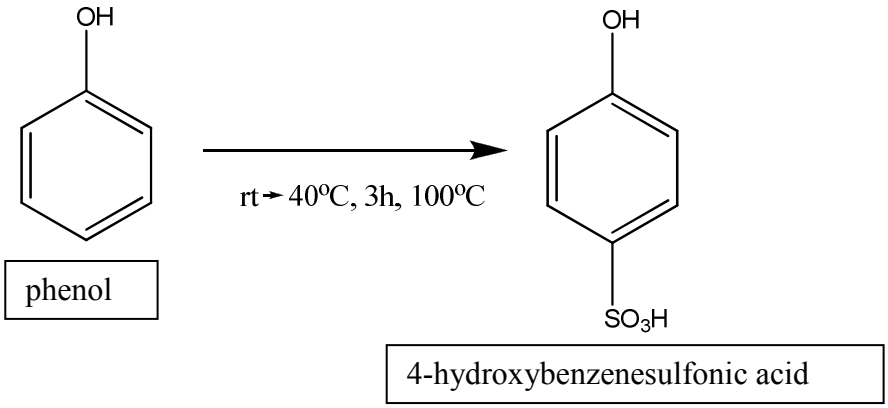
Introduction: Propofol is a short-acting, intravenous anesthetic. In other words, it allows medical patients the peace of mind that comes from knowing that one can sleep through his own surgery and still wake up within a reasonable period of time. Propofol is useful for maintaining anesthesia in patients two months of age and older, including domesticated animals as well as humans. Clearly, Propofol's versatility is undisputable. Although very effective for inducing and maintaining anesthetic unconsciousness, Propofol provides no analgesia, so it must be used in conjunction with some other pain killing agent. Propofol is sold commercially under the name Diprivan.

Overall synthetic reaction scheme:



Step 1

Synthetic transformation 1:



phenol

4-hydroxybenzenesulfonic acid

Experimental 1

In a 500 mL three-neck flask, add 10.07 mmol of phenol and a magnetic stir bar. To one neck, attach a thermometer. To the middle neck, attach a reflux condenser, and to the third neck, attach an addition funnel. Heat the flask to roughly 40 degrees Celsius. Once the phenol has melted, add 40 mmol sulfuric acid and stir the mixture well. Increase the reaction temperature to 100 degrees Celsius. Allow the reaction mixture to reflux for three hours. Remove the reaction mixture from heat and allow it to sit for a week. To purify, place the reaction mixture in a separatory funnel and basify with aqueous sodium acetate. Add 20 mL of methylene chloride to the sep funnel to wash out remaining phenol. Repeat this wash twice. Add 20 mL of HCl to the aqueous layer in the sep funnel to reprotonate the desired product. Add 20 mL of methylene chloride to extract the desired product. Remove the organic layer from the sep funnel. Repeat this wash twice. Dry the organic layer over $MgSO_4$. Discard the aqueous layer. Save the organic layer for step two.

Alterations:

The Obermiller and Cerfontain articles reported slightly different reaction conditions, mainly in temperature of reaction. Because Cerfontain tended to be less thorough with procedural details, the Obermiller figures were used predominantly for the sake of uniformity.

Obermiller's procedures called for 200 g of phenol and, in most cases, 800 g of phenol. We have simply adjusted the amounts to fit this project, but kept the 1:4 ratio by mass.

Additionally, Obermiller calls for 6-8 hours of reflux; because we do not have this kind of time in lab, the reflux had to be shortened to three hours.

Obermiller also implies that, over time, the undesired ortho-product will undergo unimolecular desulfonation, in most cases converting into the desired para form and in other cases reverting to phenol. Therefore, we allowed a week for this process to occur. Note that Cerfontain did not even provide purification data. Overmiller provided several alternative methods. The separatory funnel technique used above is a combination of 211 and 216 techniques with Overmiller's general recommendations.

Expected yield: 85% 1.49 g

Note: The yield reported by Obermiller for both para and ortho products is 95% (60% and 35%, respectively). However, it was not possible to estimate what percent of the ortho products would convert into para products over the week. Therefore, this expected yield is an estimate.

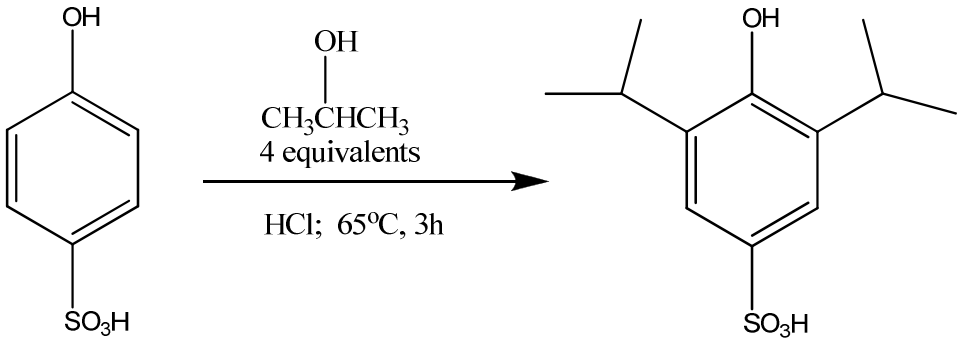
Safety, disposal and green issues 1:

Phenol is very toxic if ingested or taken into the body in any way, and so should be treated with extreme caution. However, phenol is used in many surgical scenarios, including cosmetic surgery, so its presence should not pose a safety threat in the lab, so long as sensible safety precautions are taken. As a member of the alcohol group, phenol should be disposed of in the designated alcohol container in the lab waste hood. If properly disposed of, phenol will not present an environmental hazard.

Sulfuric acid is highly corrosive and can cause burns on the skin. Accordingly, it should be kept covered and in a fume hood or designated acid storage container at all times. Exposure to fumes should be limited. Still, it should not present a safety hazard so long as reasonable precautions and careful common sense are used. Sulfuric acid should be disposed of with other inorganic acids, and it should not pose an environmental hazard is properly disposed of.

Step 2

Synthetic transformation 2:



4-hydroxybenzenesulfonic acid

4-hydroxy-3,5-diisopropylbenzenesulfonic acid

Experimental 2

Place the product from synthesis step one into a 25 mL round-bottom flask along with a magnetic stir bar. Add four molar equivalents of isopropyl alcohol and 1 mL of hydrochloric acid. Attach a reflux condenser to the flask and heat the reaction mixture to 65 degrees Celsius. Reflux for three hours. Allow the reaction to cool to room temperature and quench with water and 5% sodium bicarbonate. Use the separatory funnel technique to isolate the product from ions created by the addition of acids and bases. Note that the separatory funnel will not be used here to isolate the product from any remaining starting material.

Alterations

No experimental data could be found for reactions in which 4-hydroxybenzenesulfonic acid was the reactant, so analogous reactions had to be used in which the reactant *p*-bromophenol. Because both protecting groups are electron withdrawing and ring deactivating, they should function in the same way.

Hart and Cassis used isobutylene rather than isopropyl alcohol for their alkylation. Propene would not have been practical in our experiment because it is a gas at room temperature. However, it was taught in 210 that the two reactions are analogous and will yield the same products.

Hart and Cassis also used .5 mol of starting material and 2 moles of alkene. We kept this 1:4 molar ratio, but the amount of starting material will be whatever quantity was produced in step one. Additionally, hydrochloric was used in place of sulfuric acid, because sulfuric acid is known to desulfonate both the reactant and product of the above reaction.

Finally, the reflux had to be shortened from ten (Hart and Cassis) or 7.5 (Katsumi et al.) hours to three hours due to time constraints in the lab.

Expected yield: 35.6 % .79 g

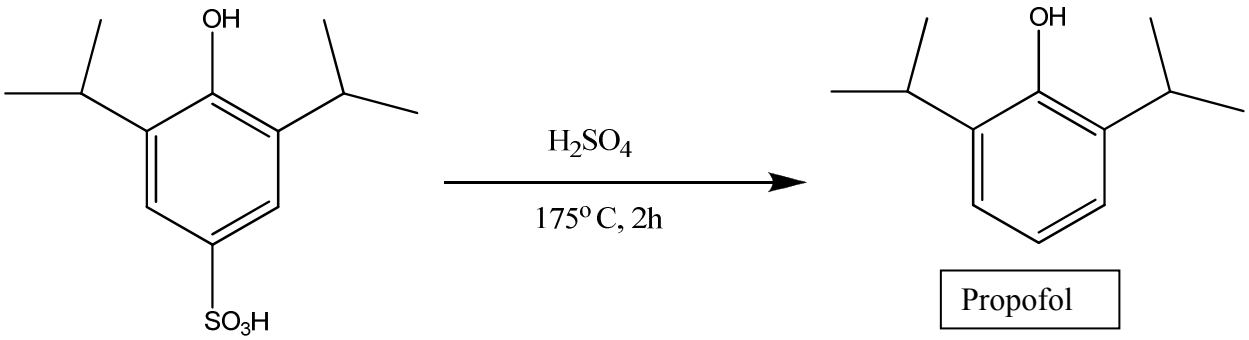
Safety, disposal and green issues 2:

Isopropyl alcohol is flammable, so it should be kept away from open flame. The reflux condenser must be employed to assure that isopropyl alcohol vapors are not released to the open air. Isopropyl alcohol can also act as an irritant if ingested, inhaled, or if it comes into contact with skin, so all work should be done under a fume hood with minimal exposed skin. It should be disposed of with other alcohols; if properly disposed of, isopropyl alcohol should pose no environmental threat.

Hydrochloric acid is corrosive and should be kept sealed and properly stored when not in use. It should be handled only in a fume hood for proper ventilation. Hydrochloric acid will burn skin on contact, so exposed skin should be avoided whenever possible. If a student feels ill after exposure to hydrochloric acid, medical attention should be sought immediately.

Step 3

Synthetic transformation 3:



4-hydroxy-3,5-diisopropylbenzenesulfonic acid

Propofol

Experimental 3

Place the product from step two into a 25 mL round bottom flask. Add 1 mL of pure sulfuric acid and slowly add .33 mL of water. Heat the reaction mixture to 175 degrees Celsius (if practicable; otherwise, heat the reaction mixture as high as possible and prudent) and reflux for two hours (or longer, if possible). Allow the reaction to sit overnight.

Add sodium hydroxide to neutralize the reaction mixture. To separate the product from any leftover starting material, acidify the reaction mixture with sodium acetate. Place this mixture in a separatory funnel and add methylene chloride to extract the product. Remove the organic layer; set aside for further use. Repeat the extract with methylene chloride twice. Discard the aqueous layer. Combine the organic layers and dry them over $MgSO_4$. Use gravity filtration to remove the magnesium sulfate after drying is complete.

Any leftover starting material from step two would have been desulfonated to phenol. Use column chromatography to separate Propofol from phenol.

Alterations:

Neither of the articles used for this reaction gave specific times necessary for this reaction to occur. Therefore, the reaction mixture will be allowed to reflux for a reasonable amount of time and then allowed to sit overnight to allow the reaction to go to completion.

Kelbe carried out the reaction on a much larger scale. We maintained his ratios but reduced the number of moles used for each reactant.

Expected yield: 92 % .5 g

Safety, disposal and green issues 3:

Sulfuric acid is highly corrosive, so it should be kept tightly sealed and properly stored. Sulfuric acid is also harmful when it is inhaled or comes into contact with skin or the eyes, so full protective gear should be worn to minimize exposed skin, and all work should be done under the fume hood. If sulfuric acid comes into contact with the eyes, they should be rinsed thoroughly with water and medical care should be sought immediately. All waste products should be effectively discarded in the appropriate bins in the waste hood. If properly disposed of, no environmental hazard should be posed.

Overall budget:

Chemical	Supplier	Cost ($ per mL)	Amt. Needed	Total ($)
Phenol	Aldrich	.17	.948 g (.886 mL)	.15
Isopropyl Alcohol	Aldrich	.43	2.06 g (2.62 mL)	1.13
Sulfuric Acid	Aldrich	.02	3.13 mL	.06
Sodium Acetate	Sigma-Aldrich	.37	10 mL	3.70

Total costs per synthesis: $5.04

Other chemicals are assumed to be readily available in the lab, and therefore of negligible cost.

References

Step One

Major Sources

Cerfontain, H.; Coombes, R.G. *J. Chem. Soc. Perkin Trans. II* **1985**, *5*, 659-667.

Obermiller *Chem. Ber.* **1907**, *40*, 3637-3641.

Additional Reading

Paul *Z. Ang.* **1896**, *9*, 590.

Kekule *Zeitschrift für Chemie* **1867**, 199.

Step Two

Major Sources

Hart, H.; Cassis, F. A *J. Am. Chem. Soc.* **1951**, *73*, 3179-3182.

Katsumi, I.; Kondo, H.; Yamashita, K.; Hidaka, T.; Hosoe, K.; Yamashita, T.; Watanabe, K. *Chem. Pharm. Bull.* **1986**, *34*, 121-129.

Additional Reading

Kolka, A. J.; Napolitano, J. P.; Filbey, A. H.; Ecke, G. G. *J. Org. Chem.* **1957**, *22*, 642-646.

Chemistry 216H; Winter 2008; Experiment One Procedure

Step Three

Major Sources

Kelbe, W. *Chem. Ber.* **1886**, *19*, 92-94.

Armstrong, H. E.; Miller, A. K. *J. Chem. Soc.* **1884**, *45*, 148-153.