Honors Cup Synthetic Proposal

Section: 221

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Title: **Synthesis of Vanillin from Catechol**

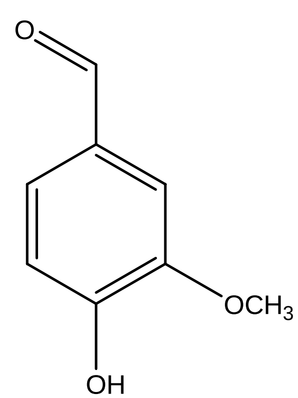
Introduction:

Vanillin (*4-hydroxy-3-methoxybenzaldehyde*) is a synthetic compound used extensively as a flavoring agent in many foods like chocolate, ice cream, and baked goods. It is also used for its pleasant scent in perfumes and is a flavoring agent in beverages. A large amount of vanillin (about 40% of all synthesized) is used as a pharmaceutical intermediate as well.

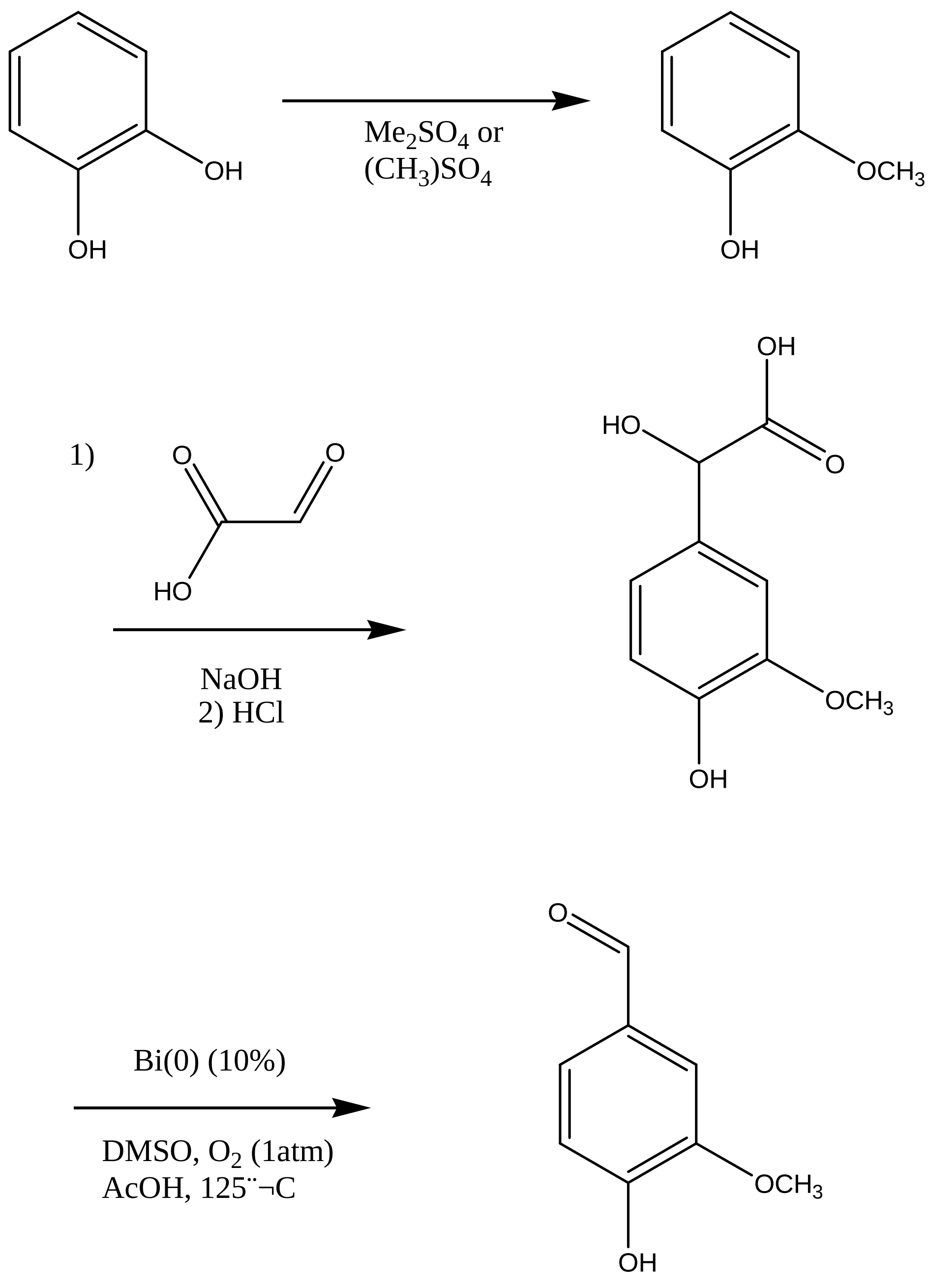
Vanillin is available from three different sources: the vanilla bean itself, from guaiacol, or from lignin. The following synthesis uses, as most of the chemical industry does, the guaiacol route. However, to be more cost efficient, we will synthesize guaiacol from catechol. Thus, the first step of the synthesis will be making guaiacol from catechol. Then, the guaiacol will be changed into vanillylmandelic acid (VMA). Finally, the VMA will be converted into vanillin.

Target Molecule:

Vanillin
4-hydroxy-3-methoxybenzaldehyde ($C_8H_8O_3$)

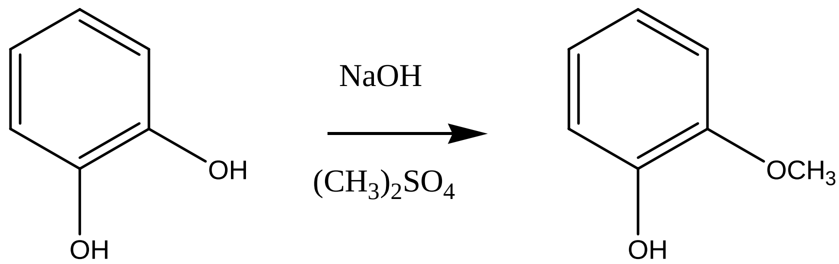


Overall synthetic reaction scheme:



Step 1

Synthetic transformation 1:



Experimental 1

Monomethylation of Catechol

All reagents were obtained from commercial suppliers and used without further purification. 0.10 mol of catechol was added to a solution of NaOH (40%, 10 mL, 0.1 mol) and dissolved under heating. Water was evaporated under reduced pressure. Polyethylene glycol – PEG400 – (1.6 grams or about 0.04 mol) and .11 mol of dimethyl sulfate were added to the reaction system while vigorously stirring. The reaction was heated and monitored with TLC until the conversion of phenol was complete. Then, the mixture was poured into a hot NaOH solution (5%) or water (80-90 degrees Celsius, 100 mL) with stirring. The mixture was allowed to precipitate or separate into layers. The precipitate or organic layer was then washed with water (3x50mL). If a higher purity is desired, recrystallisation with a suitable solvent or distillation in vacuum may be used.

Expected yield: 86%

Safety, disposal and green issues 1:

Safety

Safety is a concern when dealing with many aromatic compounds, and catechol is no different. It is stable but care should be taken to limit exposure to air and light. It is a mutagen, tumorigen, and reproductive effector. It may also cause burns. It is harmful when inhaled, ingested, or absorbed by the skin. Dimethyl sulfate is a dangerous chemical. It is extremely toxic and carcinogenic as well as flammable. It is very important to wear goggles, gloves, cap the bottle, and keep it under a hood when dealing with these chemicals. Sodium hydroxide is very corrosive and should be used with care also.

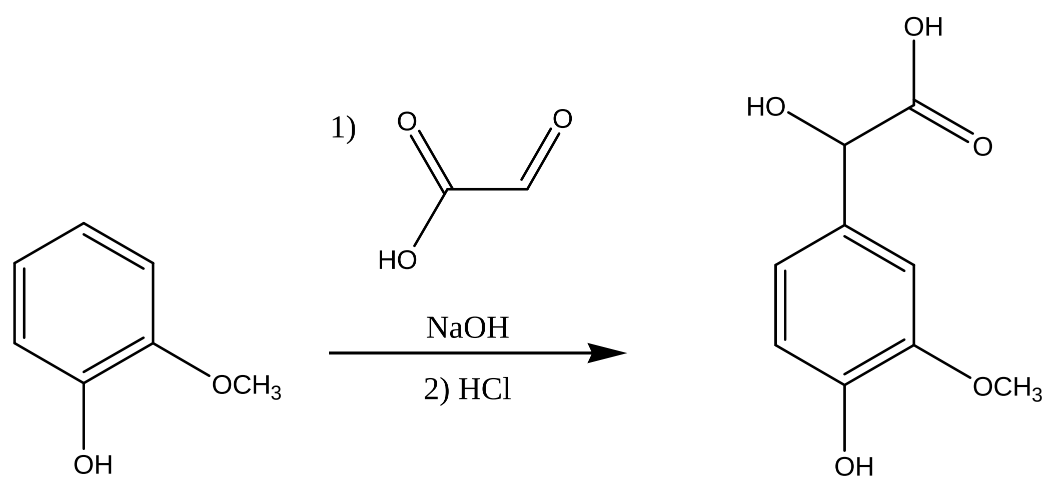
Disposal

When disposed of, catechol should be separated from strong oxidants and kept in the dark. Ventilation is also suggested. Sodium hydroxide should be stored in a container with similar bases. Dimethyl sulfate should be in a dry, well-ventilated area with containers closed. It should also be away from direct sunlight, heat, and not with strong oxidizers or alkalines. Discard waste materials based on the following categories unless otherwise indicated: acids, bases, halogenated, and non-halogenated. See federal, state, and local regulations for more information.

Green
Catechol is a relatively inexpensive chemical. It is about $0.33 per gram. NaOH is a substance already found in the lab, which costs around 10 cents a gram, depending on the type used. Dimethyl sulfate is inexpensive as well, at roughly 5 cents per milliliter.

Step 2

Synthetic transformation 2:



Experimental 2

Electrophilic Substitution of Glyoxylic Acid on Guaiacol

A solution of 176 g (4.4 mol) of NaOH in 100 mL of water (15 degrees Celsius) was combined with 1 kg of crushed ice. 250 g (2.014 mol) of guaiacol (our previous product) was added to this mixture, surrounded by an ice-salt bath, while stirring. While stirring, an ice-cold solution of 225 g (2.5 mol) of glyoxylic acid monohydrate in 400 mL of water was introduced dropwise during 4 hours. The reaction was kept at 0 to -5 degrees Celsius. A precipitate may form as an indicator of adding the glyoxylic acid too quickly but will disappear on stirring. The solution was stirred for an additional 20 hours while the temperature slowly returned about 20 degrees Celcius. 375 mL of concentrated hydrochloric acid was added to the dark-brown solution. This is then saturated with 700 g of salt and extracted with benzene (3x100mL). The benzene extract was dried with sodium sulfate. The aqueous layer was then extracted with ethyl acetate (15x250mL). The extracts were combined, dried again with sodium sulfate, treated with 3g of acid-washed charcoal. Then this mixture is concentrated into a syrup using the rotary evaporator. The syrup was cooled, and the product crystallized. This was filtered and washed with cold ethyl acetate to give almost colorless crystals.

Expected yield: 40%

Safety, disposal and green issues 2:

Safety

Guaiacol (the product of step 1) is not known to be extremely toxic, but may affect the central nervous system. It is hazardous with eye contact, ingestion, or inhalation. It is also slightly hazardous with skin contact as an irritant. It should be used only in a well-ventilated area. Glyoxylic acid is somewhat corrosive, so skin contact should be avoided, as with sodium hydroxide. Handle concentrated HCl and beneze with extreme care as HCl is corrosive and benzene is carcinogenic and flammable.

Disposal

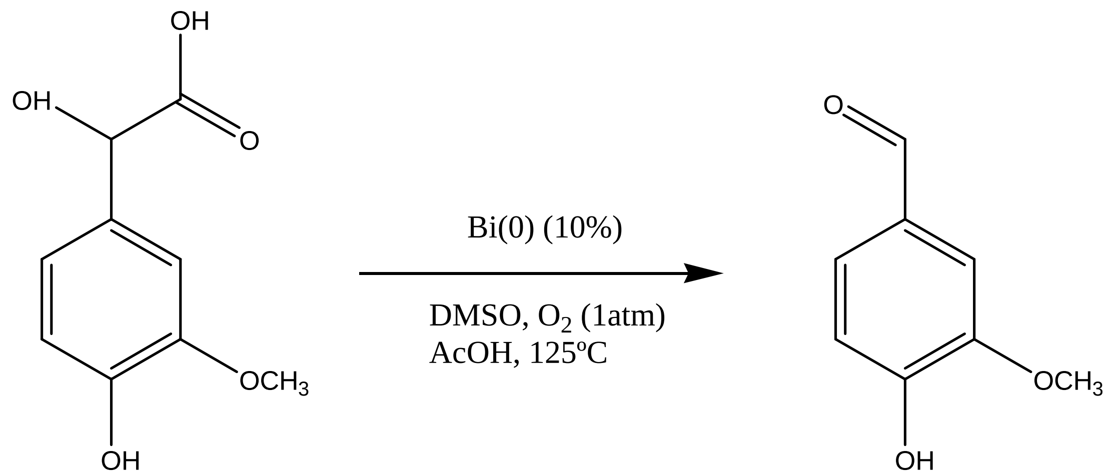
Guaiacol should be kept in a cool, well-ventilated area. It should not be stored near oxidizing agents, acids, or bases. Glyoxylic acid should be kept around room temperature, but is relatively stable. Sodium hydroxide should be stored with other bases. Discard waste materials based on the following categories unless otherwise indicated: acids, bases, halogenated, and non-halogenated. See federal, state, and local regulations for more information.

Green

In this step, guaiacol has been synthesized, so we do not need to purchase it. NaOH has already been purchased, and H_2O can be taken directly from the labs' faucets. The only compound to be purchased for this step is glyoxylic acid. This is inexpensive, at 81 cents per gram for glyoxylic acid monohydrate. In a 50:50 solution with water, it is 18 cents per milliliter.

Step 3

Synthetic transformation 3:



Experimental 3

Catalytic Oxidative Decarboxylation of VMA

The commercially available products were used without further purification. The reactions were carried out under atmospheric pressure of molecular oxygen. 4-hydroxy-3-methoxy mandelic acid (vanillylmandelic acid or VMA) (2 mmol) was dissolved in DMSO (5 mL) in the presence of Bi(0) powder (0.2 mmol) and 3 mmol of ACOH (50% aqueous solution). The mixture was stirred at 125ºC for 40 minutes. The crude reaction mixture was hydrolysed with 5 mL aqueous 1 M HCl solution saturated with NaCl, and extracted with ethyl acetate (5×10 mL). Organic phases were collected and washed twice with an aqueous 0.1 M HCl solution saturated with NaCl, dried over $MgSO_4$ and filtered off.

Expected yield: 87%

Safety, disposal and green issues 3:

Safety

DMSO is a skin, eye, and respiratory irritant. Bismuth powder is not significantly toxic. Acetic acid and and hydrochloric acid are corrosive, so care should be taken to avoid exposure to skin and eyes. HCl especially shouldn't be inhaled and kept under a hood. Sodium chloride is relatively safe, causing only eye irritation if exposed. Ethyl acetate is an irritant, but only significantly harmful if swallowed. Magnesium sulfate may be harmful if swallowed and is an irritant.

Disposal

DMSO shouldn't be stored with acid chlorides, strong acids, strong oxidizing agents, strong reducing agents, phosphorus halides, moisture, copper wool + trichloroacetic acid because it can react violently with a number of agents. Bismuth should not be stored with strong acids, strong oxidizing agents, nitrosyl fluoride, fused ammonium nitrate, interhalogen compounds, and chlorine. It is also potentially flammable. Acetic acid should be stored with other acids, avoiding metals, oxidizing agents, alcohols, aldehydes, etc. Hydrochloric acid shouldn't be stored with metals, strong bases, carbonates, etc. Sodium chloride shouldn't be stored with strong oxidizing agents but is otherwise stable. Ethyl acetate should be kept in a dry place, out of contact with strong oxidizing agents. $MgSO_4$ is stable and can be stored under many conditions. Discard waste materials based on the following categories unless otherwise indicated: acids, bases, halogenated, and non-halogenated. See federal, state, and local regulations for more information.

Green

DMSO is relatively expensive at about $1.56 per mL; however, only 5 mL are needed. Bismuth powder is about $2.30 per gram. Again, a very slight amount is needed. Acetic acid is about 80 cents per gram. HCl is inexpensive at around 7 cents per milliliter. NaCl is found at a price of about 10 cents per gram. Ethyl acetate is about 20 cents per milliliter. Magnesium sulfate is $4.50 per gram but is only needed for the purposes of drying. This might seem expensive, however, hydrochloric acid, sodium chloride, ethyl acetate, and magnesium sulfate are all currently found in the lab.

Overall budget:

Chemical	Supplier	Cost	Amt. Needed	Total
Catechol	Sigma-Aldrich	30.00/100G	11g/ 0.10 mol	$3.30
NaOH	SAJ	50.00/500G	stock	
$(CH_3)_2SO_4$	Aldrich	47.00/1L	13.64g/0.11 mol	$0.49
Glyoxylic acid	Aldrich	16.70/10G	225 g	$375.75
DMSO	Sigma	39.00/25mL	5 mL	$7.80
Bi powder	Aldrich	57.10/25G	0.418 g/2 mmol	$1.76
HCl	Sigma-Aldrich	34.30/500mL	5 mL	$0.34
Ethyl acetate	Sigma-Aldrich	29.90/500mL	50 mL	$2.99
$MgSO_4$	Sigma-Aldrich	19.10/5G	5 g	$19.10
Benzene	Aldrich	23.00/100mL	300mL	$69.00
Na_2SO_4	Aldrich	59.80/1G	Sufficient amt	

Total costs per synthesis: $480.53

References:

Step 1:

Bjorsvik, H.R.; Liguori, L.; Minisci, F. *Organic Process Research & Development*. **2000**, *4*, 534-543.

Cao, Y.Q.; Pei, B.J. *Synthetic Communications*. **2000**, *30*, 1759-1766.

Step 2:

Bjorsvik, H.R.; Liguori, L.; Minisci, F. *Organic Process Research & Development*. **2000**, *4*, 534-543.

Fatiadi, A.J.; Schaffer, R. *Journal of Research of the National Bureau of Standards, Section A: Physics and Chemistry*, **1974**, *78*, 411-412.

Step 3:

Favier, I.; Dunach, E. *Tetrahedron*. **2003**, *59*, 1823-1830.

Favier, I.; Giulieri, F.; Dunach, E.; Hebrault, D.; Desmurs, J.R. *Eur. J. Org. Chem*. **2002**, 1984-1988.