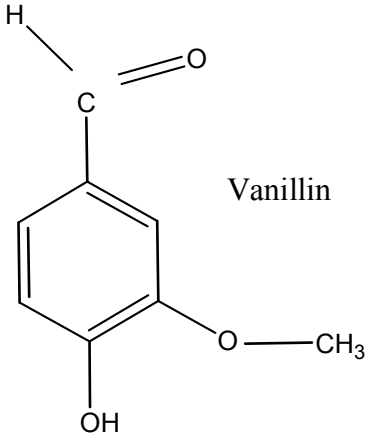
Honors Cup Synthetic Proposal

Section: 290
Group Members: Surbhi Gupta, Anne Mathew, and Shoko Asei

Title: Synthesis of Vanillin (4-hydroxy-3-methoxybenzaldehyde)

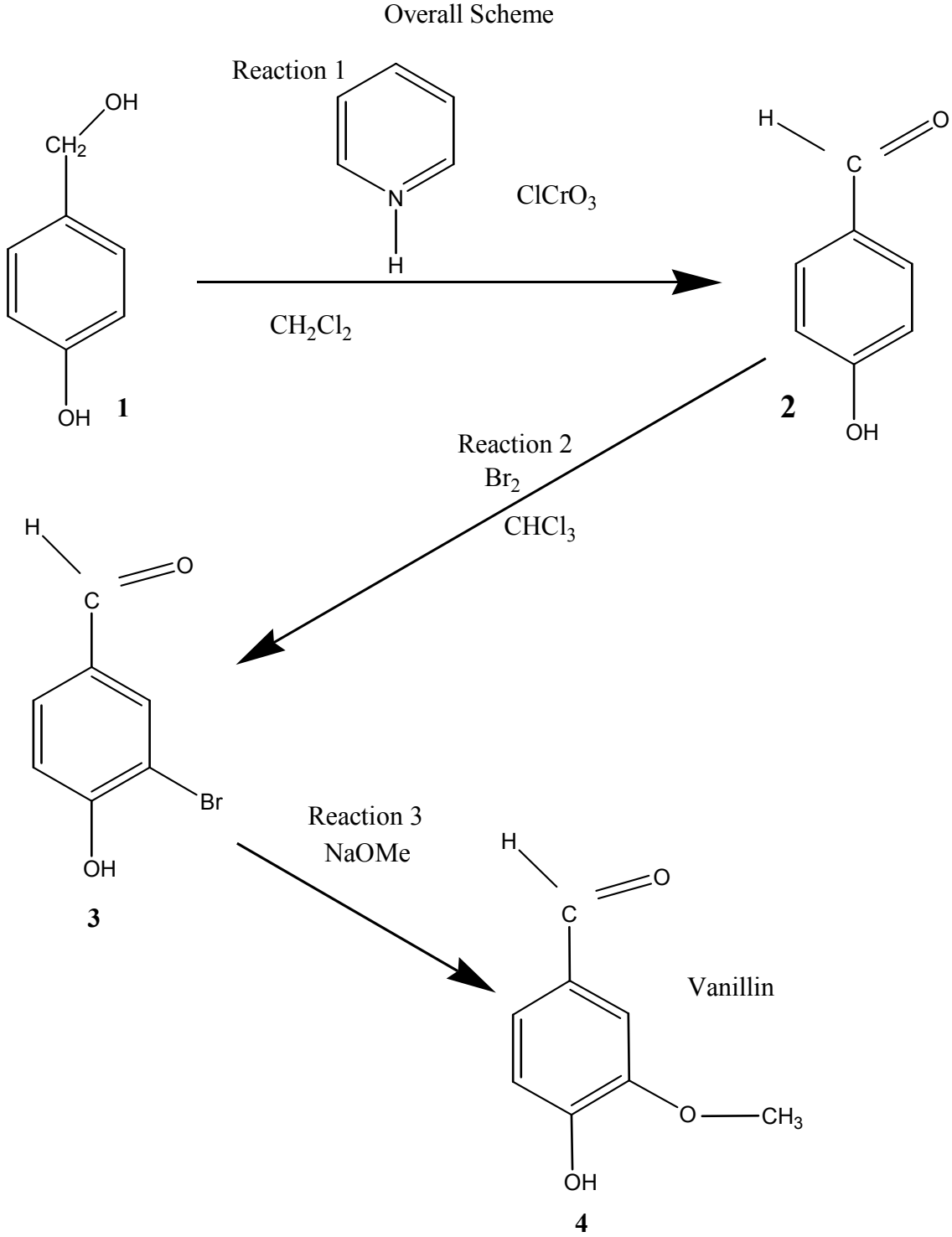


4

Introduction:

Vanillin is a commercial compound used in several different food and non-food products to produce a vanilla flavor or scent. It is an antioxidant as well, and has antibacterial properties, so it helps to preserve food. Vanillin is also reported that cattle fed with vanilla-flavored feed gain more weight because they eat more. 3-methoxy-4-hydroxybenzaldehyde (vanillin) was used as the synthetic vanilla flavoring agent. As you can see there are many applications of vanillin from everything to foods, fragrances, lotions, candles and air fresheners. (The Chemical Industry Education Centre [CIEC], 1988)

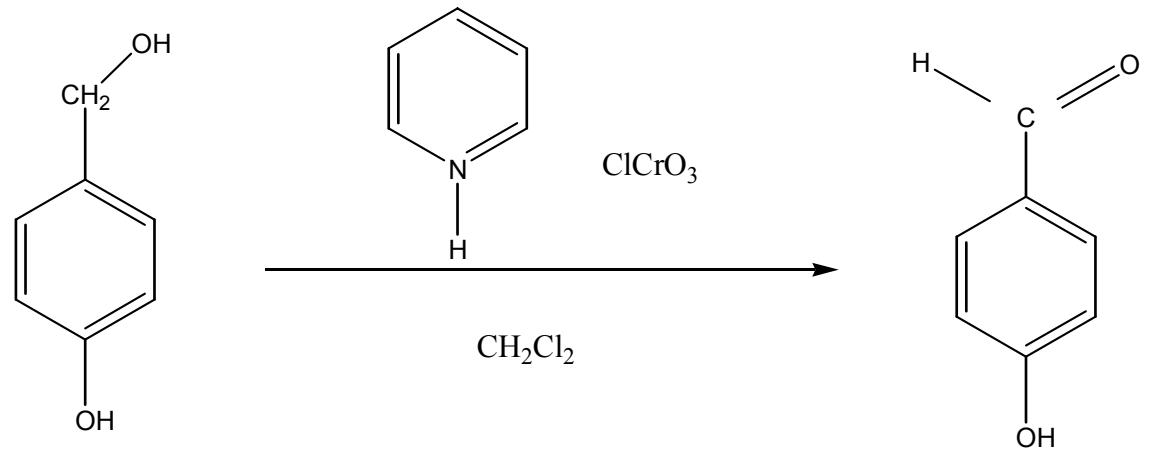
Overall synthetic reaction scheme:



Step 1

Synthetic transformation 1:

Reaction 1



4- Hydroxybenzyl Alcohol

1

4 - Hydroxybenzaldehyde

2

Experimental 1

Oxidation of primary alcohol **(1)** to acid to produce 4-hydrozybenzoic acid **(2)** using PCC (Pyridinium chlorochromate): Mix 6.75 g of 4-Hydroxybenzyl Alcohol in CH_2Cl_2 (30 ml). Take PCC (2equivalents based on the number of mmols of alcohol you select) and the same weight of silica gel and mix these together in a mortor. Suspend the powder in CH_2Cl_2 (10ml) at room temperature and add the alcohol solution in one portion with stirring. Follow the reaction by tlc and after 1.5-2.5 hours (when all the alcohol has reacted) filter the mixture through a pad of celite in a funnel. Rinse the pad with ether and evaporate all of the filtrate together (Corey, 1975).

Expected yield: 40 %, 2.70 g

Safety, disposal and green issues 1:

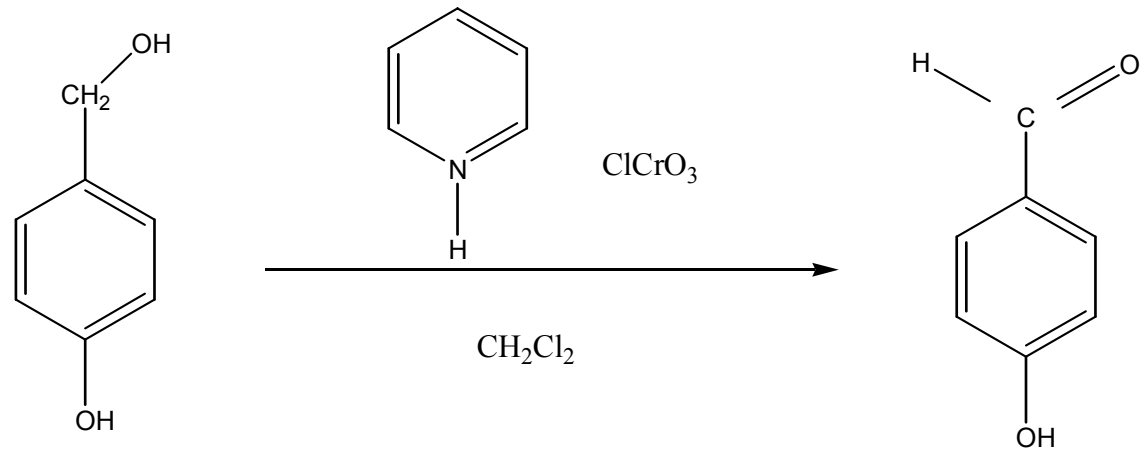
4-Hydroxybenzyl alcohol has no safety concerns (Joint FAO/ WHO Expert Committee on Food Additives, 2003).

"Handle PCC as a carcinogen. Safety glasses, gloves, good ventilation"
"Stable. May react with easily oxidized materials. Incompatible with reducing agents, combustible material"(Physical and Theoretical Chemistry Laboratory Oxford University, 2003).

Step 2

Synthetic transformation 2:

Reaction 1



4- Hydroxybenzyl Alcohol

1

4 - Hydroxybenzaldehyde

2

Experimental 2

Bromination of 4-Hydroxybenzaldehyde **(2)** to produce 3-Bromo-4-hydroxybenzaldehyde **(3)**:
A mixed solution of Br_2 (1.21 ml, 2.1mmol) and $CHCl_3$ (22ml) was added drop wise to a stirred solution of **2** (2.70g, 2.00mmol) in $CHCl_3$ (55ml). The mixture was stirred for 30 minutes at room temperature and for one hour at 40 degrees Celsius. After this time, the reaction was worked up by washing with saturated $NaHCO_3$ and the organic layer was dried over with anhydrous $MgSO_4$. (Torii, Tanaka, Siroi, and Akacla, 1979)

Theoretically, treatment of 4-Hydroxybenzaldehyde with Br_2-$CHCl_3$ gave 3-Bromo-4-hydroxybenzaldehyde gives 90% yield (Torii, Tanaka, Siroi, and Akacla, 1979)

Expected yield: 70% 0.755g

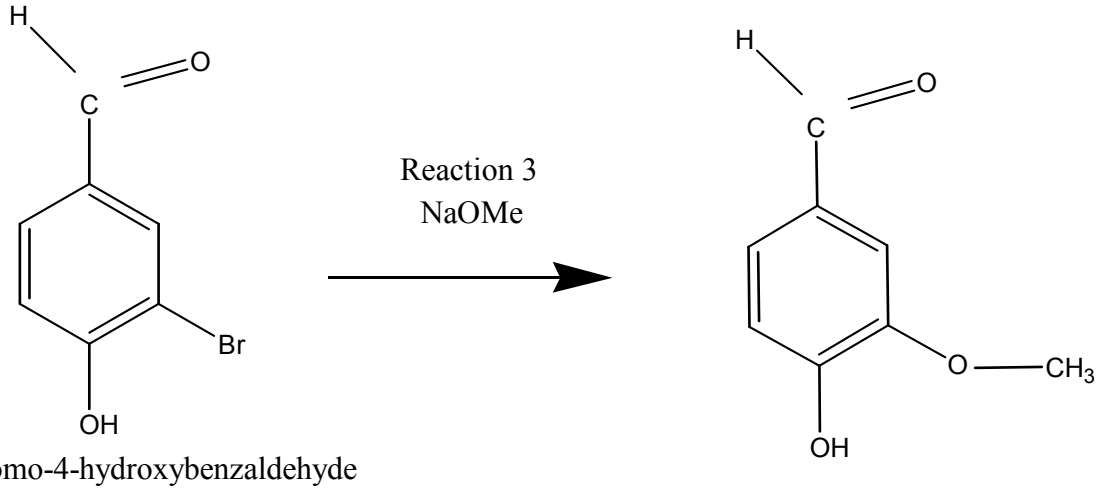
Safety, disposal and green issues 2:

Bromine is toxic since it is highly corrosive to metal and skin. Handle it with care, and weigh out only what is necessary. Also keep it in a hood and work quickly but safely. (Environmental Health & Safety, 2004)

Chloroform is hazardous chemical and listed as a probable human carcinogen. It is harmful by inhalation and irritating to skin. Handle it with care and keep it in a hood.
(New Jersey Department of Health, 1988)

Step 3

Synthetic transformation 3:



3-Bromo-4-hydroxybenzaldehyde

3

Vanillin

4

Experimental 3

The solution was "obtained by refluxing a mixture of NaOH (335 mg, 7.80 mmol) and CaO (1.11 g, 19.8 mmol) in MeOH (5 mL) for 7 hours under nitrogen gas. This step is not necessary for the reaction because NaOMe has already deprotonated. The amounts of the 3-bromo-4-hydroxybenzaldehyde **(3)** are changed to result in a yield of 0.5 g with a 75% yield. (Torii, Tanaka, Siroi, and Akacla, 1979)

Sn2 reaction of 3-Bromo-4-hydroxybenzaldehyde **(3)** to produce vanillin **(4)**:
NaOMe (5 mL) was added to a mixture of 3-bromo-4-hydroxybenzaldehyde **(3)** (70 mg, 0.348 mmol) and $CuCl_2$ (28 mg, 0.208 mmol) in DMF (2 mL). The solution was stirred for 3 hours at 110 degrees Celsius. Most solvent was removed by reduced pressure at 110 degrees Celsius. The reaction was quenched by HCl (5 %, aq). Ether was used to extract the organic layer. The reaction was worked up by washing with saturated $NaHCO_3$ and the organic layer was dried over with anhydrous $MgSO_4$. (Torii, Tanaka, Siroi, and Akacla, 1979)

Theoretically, the yield gives 94% yield. (Torii, Tanaka, Siroi, and Akacla, 1979)

Expected yield: 71% 0.50 g

Safety, disposal and green issues 3:

Sodium Methoxide is a flammable solvent that must be kept away from water, acids, and chlorinated solvents. It is a strong reducing agent. It is important to consider safety because the substance is corrosive to skin and a respiratory irritant. (The Physical and Theoretical Chemistry Laboratory, 2004)

Ether is a volatile liquid and vapor. A large leak causes serious environmental concerns. (Merck Source, 2004)

Budget:

The cost for the reactants of the synthesis has been estimated through the Aldrich catalog. The reactants are, for the most part, inexpensive because the synthesis of vanillin is common. (The Sigma-Aldrich Family, 2004)

Chemical	**Supplier**	**Cost**	**Amount Needed**	**Total**
4-hydroxybenzyl	Aldrich	10 g/ $30.60	6.75 g	$20.66
Pyridinium Chlorochromium	Aldrich	50 g/ $111.80	13.5 g	$30.19
Br_2	Aldrich	100 mL/ $44.20	1.21 mL	$0.53
sodium methoxide	Aldrich	100 mL/$37.90	5 mL	$1.90
$CuCl_2$	Aldrich	10 g/ $25.70	0.28 g	$0.72
Ether	Aldrich	100 mL/ $20.60	25 mL est.	$5.15

Total costs per synthesis: $59.15

References:

Aldrich: Handbook of Fine Chemicals and Laboratory Equipment: United States. (2004). The Sigma-Aldrich Family.

Bromine: *Material Safety Data Sheet.* (2004). Environmental Health & Safety. Retrieved Jan.25, 2005 from http://www.jtbaker.com/msds/englishhtml/b3905.htm.

Chloroform: Hazardous Substance Fact Sheet.(1988). New Jersey Department of Health. Retrieved Jan. 25, 2005 from http://home.earthlink.net/~clearh2orev/toxchloroform.html

Corey, E. J.; Suggs, J. W. *Tetrahedron Letters*, **1975**, 2647-2650.

4-hydroxybenzyl alcohol. (2003). Joint FAO/ WHO Expert Committee on Food Additives. Retrieved Feb 3, 2005 from http://www.inchem.org/documents/jecfa/jeceval/jec_931.htm

Prager, R.; Tan, Y. *Tetrahedron Lett.* **1967**, *38*, 3661-3664.

Production Methods Summary. (1988) The Chemical Industry Education Centre. Retrieved Feb.3, 2005 from http://www.uyseg.org/greener_industry/pages/vanillin/4Vanillin_PMS.htm.

Protroleum Ether. (2004). Merck Source. Retrieved Jan. 25, 2005 from http://www.mercksource.com/pp/us/cns/cns_hl_dorlands.jspzQzpgzEzzSzppdocszSzuszSzcommonzSzdorlandszSzdorlandzSzdmd_p_15zPzhtm#1073685

Safety (MSDS) data for pyridinium chlorochromate. (2003). Physical and Theoretical Chemistry Laboratory Oxford University. Retrieved Feb 3, 2005 from http://ptcl.chem.ox.ac.uk/MSDS/PY/pyridinium_chlorochromate.html

Safety (MSDS) data for sodium methoxide. (2004). The Physical and Theoretical Chemistry Laboratory Oxford University. Retrieved Jan. 25, 2005 from http://physchem.ox.ac.uk/MSDS/SO/sodium_methoxide.html

Torii, S.; Tanaka, H.; Siroi, T.; Akacla, M. *J. Org. Chem.* **1979**, *44*, 3305-3310.