Honors Cup Synthetic Proposal

Section: 220
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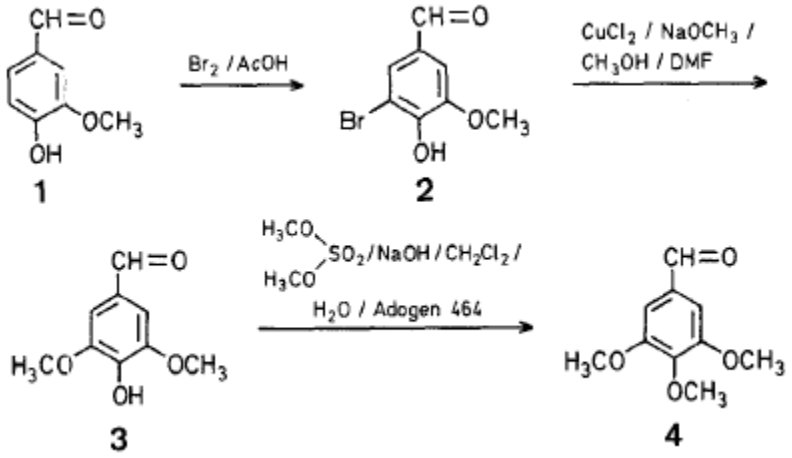
Title: Synthesis of 3,4,5-Trimethoxybenzaldehyde

Introduction: (what makes your target interesting?)
This molecule is interesting to us because it is a very versatile molecule. It has many different uses spanning various different fields of life. One of the more important uses for Trimethozybenzaldehyde is that it is used to make pharmaceutical products. It is an intermediate step which is more economically efficient than methods previously used. One of the important medications that Trimethoxybenzaldehyde helps to make is Trimethoprim (an antibiotic that interferes with the production of folic acid – helping to treat numerous bacterial infections – mostly used for urinary tract infections). In addition to its very important pharmaceutical use, Trimethoxybenzaldehyde is also used in many other areas of life. Trimethoxybenzaldehyde is essential in the world of the culinary arts, as it is used to help create the flavoring compounds used in not only cooking but in the flavoring of beverages as well. Also, Trimethoxybenzaldehyde can help with the development of fragrances used in perfumes and other air fresheners. In addition to the wide range of uses that Trimethoxybenzaldehyde has, it can also be used in the production of plastic additives.

Overall synthetic reaction scheme: (a Chemdraw or similar drawing of all three steps)



Compound 1: Vanillin

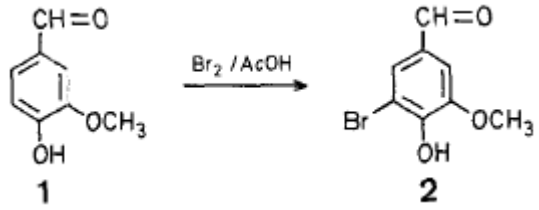
Compound 2: 5-Bromovanillin

Compound 3: 4-Hydroxy-3,5-dimethoxybenzaldehyde

Compound 4: 3,4,5-trimethoxybenzaldehyde

Step 1

Synthetic transformation 1: (Chemdraw picture of first transformation)



Experimental 1 (notes if this transformation is not exactly the one reported in literature (e.g. on a different scale) and how it was modified):

The scale of the experiment is adjusted to synthesize approximately l g of product, as the scale given produced 2.94g of 3,4,5-trimethoxybenzaldehyde.

5-Bromovanillin

Add vanillin (6 g, 0.1 mol) in glacial acetic acid (29.6 ml) to bromine (6.95 g, 0.11 mol). Stir for 1 hour and dilute with ice water (80 ml). Filter the precipitated solid, wash with water and dry it.

Expected yield: % g

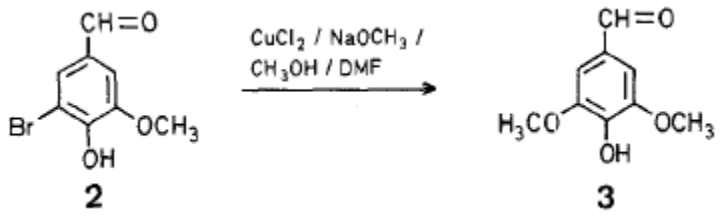
6g of vanillin to start 0.0395 moles
Assume 65% yield: 0.0257 moles or 5.937g

Safety, disposal and green issues 1:

Vanillin is harmful or toxic to contact with the skin or swallowing. To prevent contact, we will wear gloves in the laboratory. It is dangerous to inhale bromine, so we will work under the hood to prevent inhalation. Bromine may also cause harm to an unborn child, or to breast-fed babies. We do not believe this applies to anyone in the laboratory. To minimize risks, we can wear aprons. Acetic acid is flammable and reacts violently with water. It is important for us to glassware cleaned with acetone and not water. It is also important for us to work under the hood, in a inert nitrogen environment. Gloves and protective clothing are recommended, and acetic acid must be disposed of in the appropriate hazardous waste bottle instead of the drain. Bromine and vanillin can also be disposed of in the appropriate hazardous waste bottle.

Step 2

Synthetic transformation 2: (Chemdraw picture of second transformation)



Experimental 2 (notes if this transformation is not exactly the one reported in literature (e.g. on a different scale) and how it was modified):

4-Hydroxy-3,5-dimethoxybenzaldehyde

Equip a two-necked round bottom flask with a Claisen distillation head, a thermometer, and a magnetic stir bar. Dissolve fresh sodium (1.93g, .0214 mol) in dry methanol (39.5 ml). After distilling 12–14 ml of methanol, the product from step 1 (4.6 g, .0497 mol) and anhydrous copper (II) chloride (1.066 g, .02 mol) in dimethylformamide (19.7 ml) is added and distillation continued. The oil bath temperature should be at 110-115° C. After 1 hour, the reaction will reach 100° C and the reaction will be complete. After 10 minutes (methanol distilled will be 40 ml), the reaction mixture is diluted with water (40 ml), acidified with 6 normal hydrochloric acid (20 ml), and extracted twice with ethyl acetate (2 x 30 ml). The extract is washed with water and dried with magnesium sulfate and rotary evaporated.

The procedure values are reduced by 2.53 to get approximately expected final product of 1 g.

Expected yield: % g

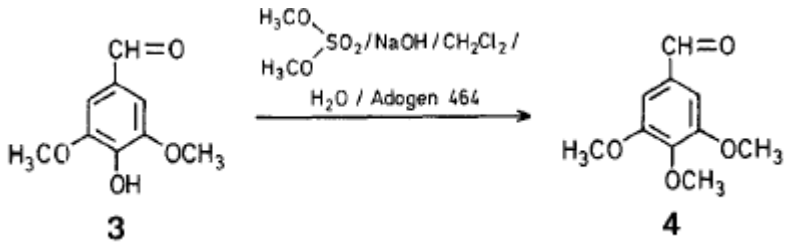
Start with 5.5g (0.0237 moles) of the step 1 intermediate.
Assuming 55% yield, 2.385g of this intermediate is expected

Safety, disposal and green issues 2:

When copper(II) chloride comes into contact with acids, a toxic gas is produced. It is necessary to clean glassware used in the previous step thoroughly, work under the hood, and keep the copper(II) chloride sealed when not in use. Gloves will prevent harmful contact with the skin. Sodium reacts violently with water, so this experiment should be performed in a water-free (nitrogen) environment. Dry methanol should also be kept away from moisture, and capped securely when not in use. The experimental setup should be capped with a septum to avoid inhalation of sodium. In addition, protective clothing and eyewear should be worn to protect against dry methanol. In working with the solvent DMF (N,N-dimethylformamide) it is necessary to take similar precautions as other chemical reagents and solvent in this experiment require. DMF is irritating to the eyes; goggles should be worn and hands washed thoroughly after working in the laboratory. These solvents and reagents should be disposed of in the appropriate hazardous waste bottle.

Step 3

Synthetic transformation 3: (Chemdraw picture of third transformation)



Experimental 3 (notes if this transformation is not exactly the one reported in literature (e.g. on a different scale) and how it was modified):

3,4,5-trimethoxybenzaldehyde

The product from step 2 (1.2 g, 0.0164 mol), sodium hydroxide (.68 g, 0.0425 mol), dimethyl sulfate (0.92ml, 0.0246), phase-transfer catalyst (0.088 ml), and dichloromethane (20 ml) is vigorously stirred at room temperature. The solution is left for a week, and an aqueous layer forms with traces of starting material. The organic layer is separated, and the aqueous layer is extracted with dichloromethane (19.74 ml). The two dichloromethane extracts are combined and washed with ammonium hydroxide (10-12 ml of 30% NH_4OH is diluted to 40 ml), and dried with magnesium sulfate. The solvent is removed by rotary evaporation.

The values have been reduced by 2.53 to give approximately 1g of final product. The original process was to stir the solution for 16 hours, but we changed it to stirring until the end of the lab period and sitting until the next lab period. The product can be recrystallized from cyclohexane to purify it (90%).

Expected yield: % g

Start with 2.0g (0.0109 moles) of the intermediate from step 2.
Assuming 55% yield, 1.18g (0.006 moles) of product is expected after recrystallization.

Safety, disposal and green issues 3:

The use of sodium hydroxide should be restricted to under the hood and in a nitrogen environment to avoid potentially toxic reactions. As usual, gloves and protective eyewear should be worn to a safety precaution. Dimethyl sulfate should also be used in a nitrogen atmosphere to prevent inhalation, as this is toxic. Gloves should be worn to avoid contact with the skin. Extra care should be taken to avoid unnecessary contact with dimethyl sulfate as it is carcinogenic. The phase transfer catalyst Andogen® 464 should be kept under the hood in a nitrogen atmosphere as well. It is highly flammable and produces toxic gas, so do not heat the reaction mixture. The use of dichloromethane (methylene chloride) and ethyl acetate does not require any precautions in addition to the previously mentioned precautions. Cyclohexene is another reagent for which it is necessary to work in a nitrogen atmosphere, as it is flammable in air. Disposal of these chemicals should occur via the hazardous waste bottles.

Overall budget:

Chemical	Supplier	Cost	Amt. Needed	Total ($)
Vanillin	Sigma	$13.80/100g	6g	0.83
Bromine	Aldrich	325.50/250g	6.95g	9.04
Glacial Acetic Acid	Sigma	$73.70/2.5L	29.6ml	0.87
Sodium	Aldrich	$59.80/100g	1.93g	1.15
Dry Methanol	Aldrich	$17.40/1L	39.5ml	0.70
Anhydrous Copper Chloride	Sigma	$92.50/1kg	1.066g	0.10
Dimethylformamide	Aldrich	$26.80/500ml	19.737ml	1.18
Dimethyl Sulfate	Aldrich	$33.90/1L	0.92ml	0.05
Adogen 464	Ashland	$32.9/500ml	.0879ml	0.01
Dichloromethane	Aldrich	$35.00/1L	19.737ml	0.69
30% Ammonium Hydroxide	Aldrich	$187.00/1L	9.868-11.84ml	1.85-2.21

Total for synthesis: $16.47 - $16.83

References (include at least two different sources for your experimentals):

3,4,5-Trimethoxybenzaldehyde. 2005. Chemicalland21.com. 5 Feb. 2005 <http://www.chemicalland21.com/arokorhi/lifescience/phar/3,4,5-TRIMETHOXYBENZALDEHYDE.htm>.

CHEMINFO: Benzaldehyde. 2004. Canadian Centre for Occupational Health and Safety. 5 Feb. 2005 <http://www.intox.org/databank/documents/chemical/benzald/cie232.htm>.

Rao, D. V.; Stuber, F. A. *Synthesis* **1983**, 308.

Sigma-Aldrich Co. Equipment, Supplies & Books. 2005. Sigma-Aldrich Co. 6 Feb. 2005.

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Sodium Benzoate, Potassium Benzoate, Specialty Chemicals. 2005. Noveon, Inc. 4 Feb. 2005 <http://www.noveon.com/products/NoveonKalama/kciprodn.asp#Bzald>.

Trimethoprim. 31 Jan. 1997. MedicineNet.com. 5 Feb. 2005 <http://www.medicinenet.com/trimethoprim/article.htm>.

Step 1-3 use the Aldrich website and the actual article from *Synthesis*.