

## Honors Cup Synthetic Proposal (231-II Tu PM W'08)

Section: 231

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### Title: Total Synthesis of Phenylpropanolamine

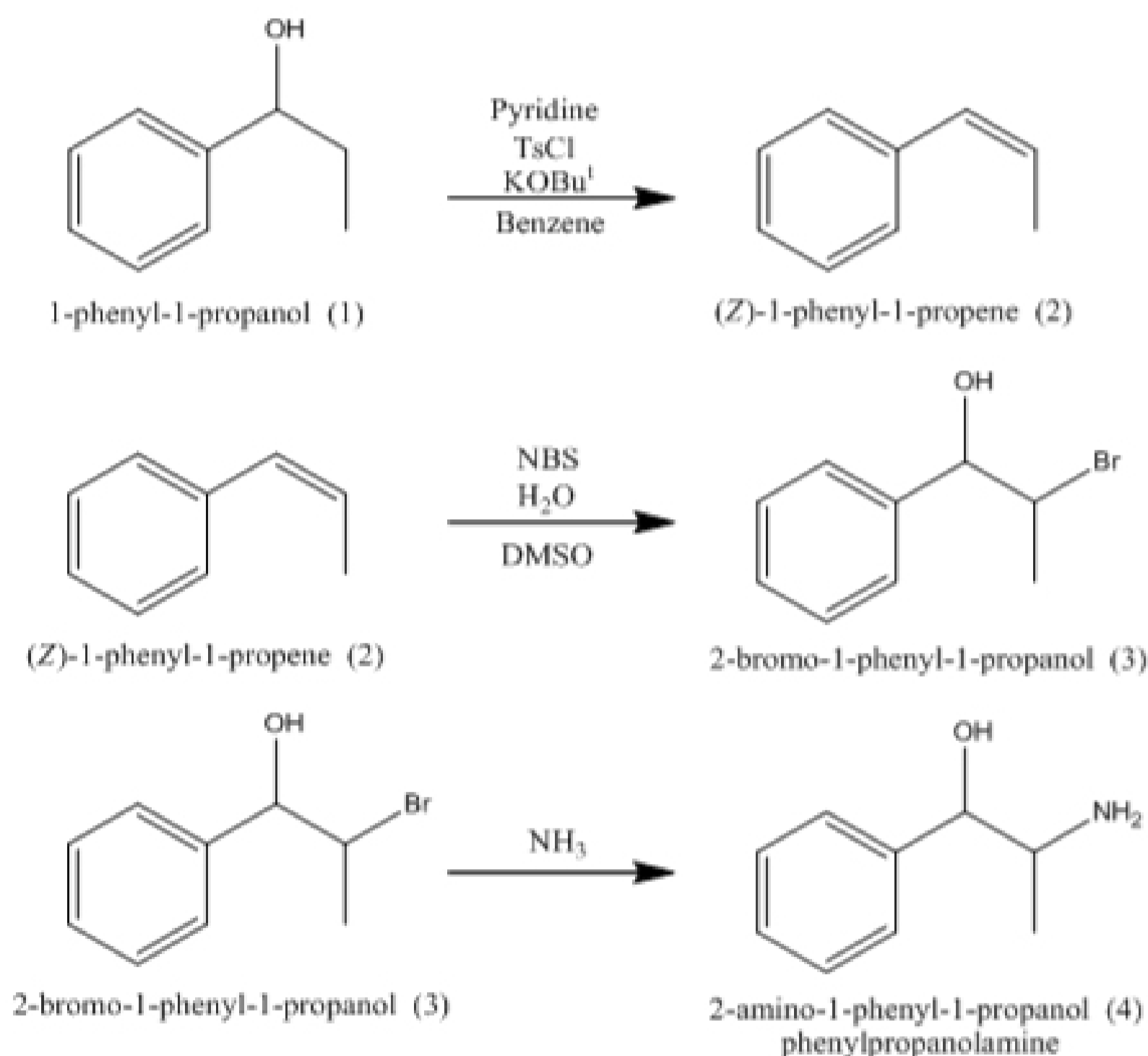
#### Introduction:

Phenylpropanolamine (PPA) is a compound which was used as a decongestant in common cough and cold medicines, and was also used as an appetite suppressant in OTC weight loss products. PPA isn't found in modern medicines in the United States because of an FDA recall due to side effects of hemorrhagic strokes in women, and the ability for PPA to be reduced into amphetamines.

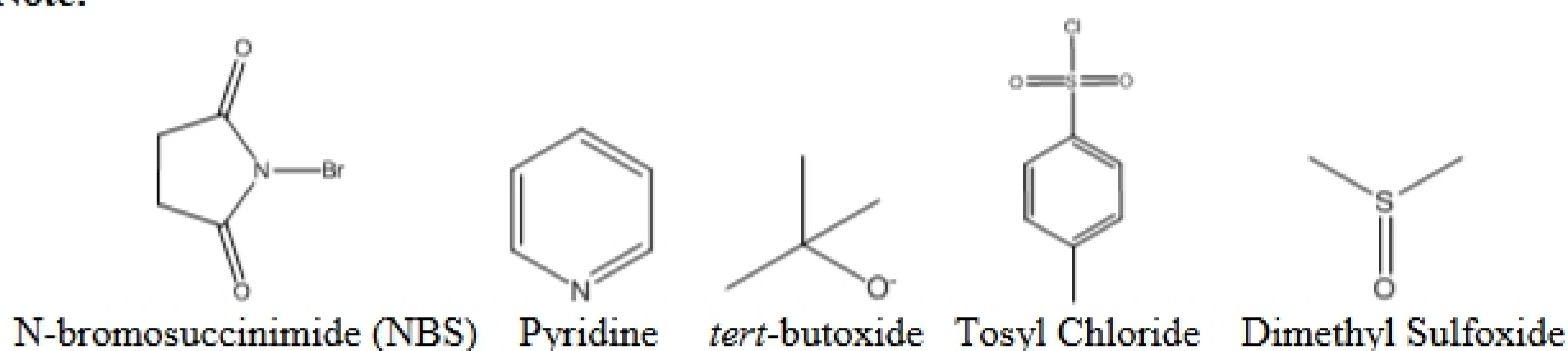
There are four possible stereoisomers of PPA due to the two chiral centers found in the compound. All of the stereoisomers however serve the same basic function as a decongestant. The (1*R*, 2*S*) isomer (D-norpseudoephedrine) is used most often with European medications because it is naturally found in the flowering stimulant plant khat.

The compound reduces swelling of the mucous membrane in the nasal passages. It causes a response from adrenoreceptors in cells that increase cardiac output and dilate the bronchial walls. This process increases airflow in the body, allowing for better breathing.

#### Overall synthetic reaction scheme:

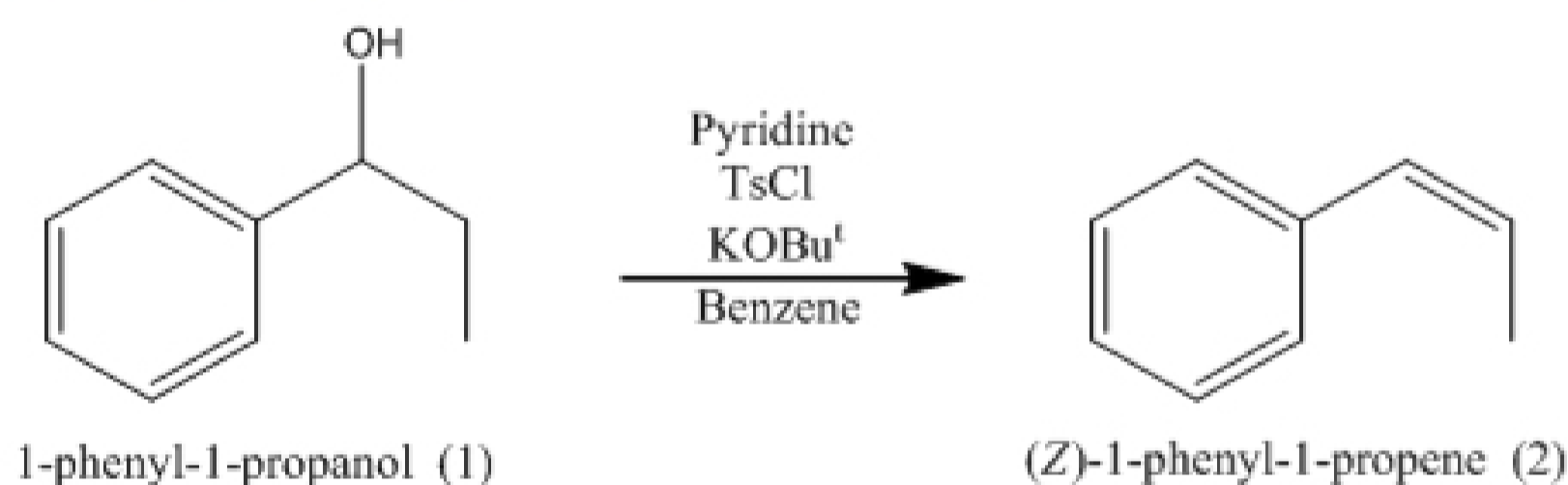


**Note:**



**Step 1**

**Synthesis of (*Z*)-1-phenyl-1-propene:**



**Experimental 1**

The procedure for the first step of this three step synthesis was changed from the literature. The starting material is different from the one in the article to make the designated product. The article provided the basis of tosylation. Methylene chloride was used instead of ether because of the availability of the methylene chloride and the familiarity with it from the students.

1-phenyl-1-propanol (3.00 g, 0.022 mol) was added to a 100-mL round bottomed flask. Pyridine (25 mL) and Tosyl Chloride (8 g, 0.042 mol) were added to the solution. It was stirred for 90 minutes with slight heat. HCl (1 M, 5 mL) and H<sub>2</sub>O (15 mL) were mixed then added to the solution. The resulting mixture was extracted with ether twice. The ether layers were washed with water twice, and then with brine. It was then dried over MgSO<sub>4</sub>. After removing the drying agent by gravity filtration, the ether was removed by rotary evaporation.

The tosylate was dissolved with benzene (10 mL), and Potassium *tert*-butoxide (4 g, 0.036 mol) was added. The solution was allowed to complete while stirring under slight heat for two hours. After the reaction completed, it was poured into HCl (1 M, 15 mL), and extracted with ether twice. Wash the ether layers with water twice, then with brine, and dry over MgSO<sub>4</sub>. After removing the drying agent by gravity filtration, the ether was removed by rotary evaporation.

**Expected yield: 70 % 1.82 g**

## Safety, disposal and green issues 1:

### **Safety:**

1-phenyl-1-propanol: It is harmful if swallowed or inhaled. Use under the fume hood. It is also a skin irritant. In case of contact with skin, wash skin thoroughly. Always use goggles, gloves, aprons, and the fume hood.

Hydrochloric Acid: It is harmful if swallowed. It may cause intense irritation and burns if in contact with skin or eyes. It is highly corrosive. Always use gloves, goggles, aprons, and fume hoods.

Ether: It is highly flammable and harmful. It may cause irritation to skin and eyes. It is not to be mixed with halogens and some metals. Always use gloves, goggles, aprons, and fume hoods.

Magnesium Sulfate: Do not breathe in dust. Avoid contact with eyes. Always use gloves, goggles, aprons, and fume hoods.

Potassium *tert*-butoxide: It is harmful and corrosive. Reacts violently with water and acids. Always use gloves, goggles, aprons, and the fume hood.

Tosyl Chloride: It is highly corrosive and causes burns. It may cause irritation if in contact with skin or eyes. Vapors may be harmful. Always use gloves, goggles, aprons, and the fume hood.

Benzene: It is highly flammable and toxic. It may cause irritation if in contact with skin or eyes. It is a known carcinogen. Do not breathe in vapors. Always use gloves, goggles, aprons, and the fume hood.

### **Disposal:**

The methylene chloride should be disposed of in a halogenated bottle. The hydrochloric acid should be disposed of in the halogenated acid bottle. The potassium *tert*-butoxide should be disposed of in a base bottle.

### **Green:**

The materials are not harmful if disposed of properly. If not disposed of properly, they may be dangerous when mixing with water and other environmental compounds.

All MSDS information taken from:

"Compound Search." Sigma-Aldrich. 2007. 2 Feb. 2008

<[http://www.sigmaaldrich.com/Area\\_of\\_Interest/The\\_Americas/United\\_States.html](http://www.sigmaaldrich.com/Area_of_Interest/The_Americas/United_States.html)>.