Experiment 7

Multistep Synthesis (2)

Prepared by **Youngho Jang** KAIST

PURPOSE OF THE EXPERIMENT

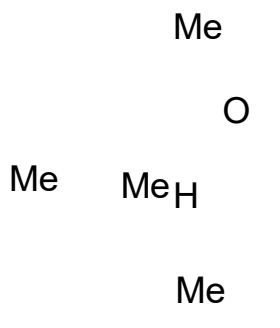
Conduct a multistep synthesis: Grignard reaction and Oxidation reaction.

BACKGROUND INFORMATION

Grignard reaction

The Grignard reaction is an organometallic chemical reation in which alkyl, vinyl, or aryl-magnesium halides add to a carbonyl group in an aldehyde or ketone.

Grignard reagents are made by reacting magnesium turnings with alkyl halides in ether solvents to form solutions of alkyl magnesium halide. Iodides, bromides, and chlorides can be used, as can both aryl and alkyl halides, though they cannot contain any functional groups that would react with the Grignard reagent once it is formed.



Oxidation

Tetrapropylammonium perruthenate, TPAP, is a readily soluble, nonvolatile, air stable oxidant for alcohols. The commericially available reagent can be used in catalytic amounts in the presence of a stoichiometric oxidant, operates at room temperature and is devoid of obnoxious or explosive side products. Suitable co-oxidants are hydroperoxides or *N*-methylmorpholine N-oxide (NMO), which seems to be most effective. In oxidations of primary alcohols, TPAP/NMO hives aldehydes rater than carboxylic acids in nonaqueous solutions in the presence of molecular sieves. The presence of water fosters an equilibrium concentration of the aldehyde hydrate, which can undergo further oxidation to the carboxylic acid.

EXPERIMENT A **Grignard reaction**

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	mmol*	*mp (^oC)*	bp (^oC)	*density (g/mL)*
β-Cyclocitral	1.0 g	152.23	6.569		62-63	0.943
CH3MgI 3.0 M in Et2O	3.3 mL	166.24	9.854			1.261
THF	50 mL	72.11		-108	65-67	0.889

*Calculate these values and find equivalency of the reaction

PROCEDURE

Caution: Wear lab coats and safety goggles at all times while in the lab. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Wearing contact lens is strictly prohibited.

Caution: Dichloromethane, ethyl acetate and hexane are toxic and irritating. Ultraviolet radiation can cause severe damage to the eyes. Do not look directly into the UV lamp.

1. Preparing TLC reference

Obtain standard samples of β-Cyclocitral (starting material) and product from your TA. Prepare a developing chamber by adding proper amount of ethyl acetate and hexane. By performing TLC analysis, find appropriate separation condition. View the plate under UV light to visualize the spots. Use the appropriate staining solution for this experiment (CAM).

2. Setting Up the Apparatus

Caution: Grignard reagents, it is important to exclude water and air, which rapidly destroy the reagent by protonolysis or oxidation.

In the fume hood, dissolved 1.0 g of β-Cyclocitral in 50 mL tetrahydrofuran in a 250 mL 1-neck round flask.
Methylmagnesium iodide solution was transferred dropwise to a solution of β-Cyclocitral at 0 °C. The reaction mixture was stirred for 1 h at room temperature. Saturated NH4Cl

solution of 50 mL was added to quench the reaction. The resulting mixture was then extracted with CH_2Cl_2 50 mL and the organic layer was washed with brine 50 mL and dried over MgSO4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatograpy (silica gel;hexaneEtOAc 4 : 1) to afford the desired alcohol product as a cololess oil. Rf 0.40 (4 : 1 hexanes/EtOAc)

3. Characterizing the Product

Obtain the NMR spectrum as directed by your TA.

EXPERIMENT B

Oxidation

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	mmol*	*mp (°C)*	bp (°C)	*density (g/mL)*
SM	1.0 g	168.28	5.942			
TPAP	48 mg	351.43	0.137	~160		
NMO	1.0 g	117.15	8.914	180-184		
4A MS		w/w 30%				
CH2Cl2	12 mL	84.93		-97	40	1.325

- TPAP = Tetrapropylammonium perruthenate
- NMO = 4-Methylmorpholine N-oxide

PROCEDURE

6. Conducting the Reaction

Note. Ask your TA for useful tips.

In the fume hood, dissolved 1.0 g of SM in 50 mL CH2Cl2 in a 250 mL 1-neck round flask. NMO, 4A molecular sieves, and TPAP were added successively to a solution of SM.
The reaction mixture was stirred for ~1 h at room temperature. The reaction mixture filtered through silica gel fad. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatograpy (silica gel;hexaneEtOAc 6 : 1) to afford the desired ketone product as a colorless oil. Rf 0.40 (6 : 1 hexanes/EtOAc)

8. Characterizing the Product

Obtain the NMR spectrum as directed by your TA.

Post-Laboratory Questions

Grignard reaction

1. Calculate the percent yield of the reaction
2. Use your TLC data to explain whether the Grignard

addition reaction went to completion.
3. Assign peaks in 1H NMR spectrum to confirm the formation of the desired product.

Oxidation reaction

1. Calculate the percent yield of the reaction
2. Use your TLC data to explain whether the Grignard addition reaction went to completion.
3. Assign peaks in 1H NMR spectrum to confirm the formation of the desired product.
4. What other options are there for this type oxidation? Provide 3 different type of oxidations conditions that might work for the specific substrate in this experiment.

Pre-Laboratory Questions

1. Write the MSDS of all reagents that is used in this experiment.
2. Organolithium reagent can also be used in this experiment. Compare the difference/similarity between organolithium reagent and organomagnesium reagent.