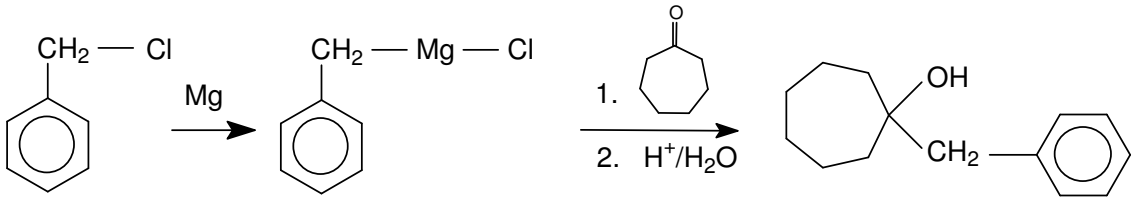
Preparation of 1-Benzyl-cycloheptane-1-ol

1-Benzyl-cycloheptane-1-ol is the first intermediate by the synthesis of a medicine called Bencyclane Fumarate produced by EGIS Ltd. We carry out the laboratory scale synthesis of this compound as described below.

Reagents

4.86 g (0.2 mol) magnesium turnings	in a round bottomed-flask on the table
tetrahydrofuran (boiling point 65-67 ^{o}C)	in fume cupboard
solution of of 23.8 g (0.188 mol)benzyl chloride in 20 ml of dry tetrahydrofuran	in an Erlenmeyer flask on the table
ammonia-ethanol mixture	in fume cupboard
acetone	in fume cupboard
solution of 13.9 g (0.122 mol) of cycloheptanone in 20 ml dry tetrahydrofuran	on the table
50 % acetic acid	in fume cupboard
diluted HCl	in fume cupboard
1,2-dichloroethane (boiling point 83 ^{o}C)	in fume cupboard
10 % acetic acid	in fume cupboard
sodium sulphate	at the balance
ice	
ethanol	
dry ice	
warm water	
filter paper	

Reaction scheme



Procedure

All parts of the apparatus used for the synthesis of the Grignard reagent must be thoroughly dry.

1

Place in a 250-ml round-bottomed flask equipped with magnetic stir bar and charged with 4.86 g (0.2 mol) of magnesium turnings 40 ml of dry tetrahydrofuran. Mount

the flask on a magnetic stirrer unit so that it may be heated on a water bath and equip it a special dropping funnel and reflux condenser (Fig. 1). Place calcium chloride guard-tube on the top of the condenser. Using a small funnel introduce a solution of 23.8 g (0.188 mol) of benzyl chloride in 20 ml of dry tetrahydrofuran into the dropping funnel and if needed close the top of the funnel with cotton-wool. (The necessary amount of the benzyl chlorid solution can be found in an Erlenmeyer flask on the table.)

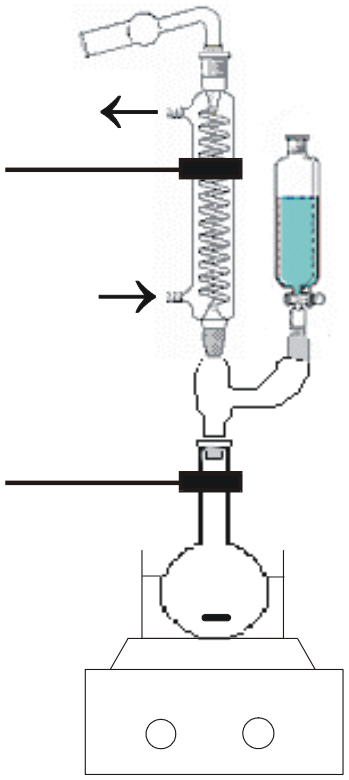


Fig. 1

The small funnel and the Erlenmeyer flask contaminated with benzyl chloride must be washed in a fume cupboard with ammonia-ethanol mixture and acetone.

Under stirring introduce in one portion about 20% of the benzyl chloride solution from the dropping funnel into the flask. After 2-5 min. initiation the reaction commences which is accompanied by the development of cloudiness and bubbles being released from the metal surface. Run in the remainder of the benzyl chloride solution at such a rate that the mixture refluxes gently (about 30-35 min.). After the addition is completed continue the stirring at 60-80^{o}C in a water bath for 15 min. (place warm water in the glass cup and turn on the heating).

2

Using a small funnel place a solution of 13.9 g (0.122 mol) of cycloheptanone in 20 ml dry tetrahydrofuran into the dropping funnel and remove the water bath. Under continuous stirring add the cycloheptanone solution to the Grignard reagent at such a rate

that the mixture refluxes gently (10-15 min.) than heat the flask on a water bath at 60-80 ^{o}C for additional 30 min.

Replace the water bath by an ice bath and cool the mixture for 6-8 min. During about 5 min. add 22 ml of 50% acetic acid from the dropping funnel to the reaction mixture (50% acetic acid can be found under the fume cupboard). Because the precipitating magnesium salts block the stir bar, to maintain the stirring move carefully the support stand.

After the addition remove the reflux condenser and the dropping funnel and rub the mixture with a glass rod in an ice bath until the cake containing the magnesium salts disintegrates.

3

Filter the mixture through a fluted filter paper into a 250-ml round-bottomed flask, wash the solid residue with 10 ml of tetrahydrofuran. Remove the stir bar from the solid residue and clean it. Put the contaminated filter paper into the waste-container under the fume cupboard. Wash the 250-ml reaction flask containing the magnesium salts under the fume cupboard with diluted hydrochloric acid and introduce the acidic solution into the corresponding waste-container.

4

Assemble a vacuum distillation apparatus as shown in Fig. 2. (a magnetic stirrer unit with water bath, a 250-ml round-bottomed distillation flask equipped with magnetic stir bar and charged with the filtrate, distillation head, two-necked or one-necked flask with side arm as receiver connected to the water pump, dry ice-ethanol cooling bath: (The latter can be made by carefully adding of small pieces of dry ice to ethanol until the lumps of solid carbon dioxide no longer evaporate vigorously).

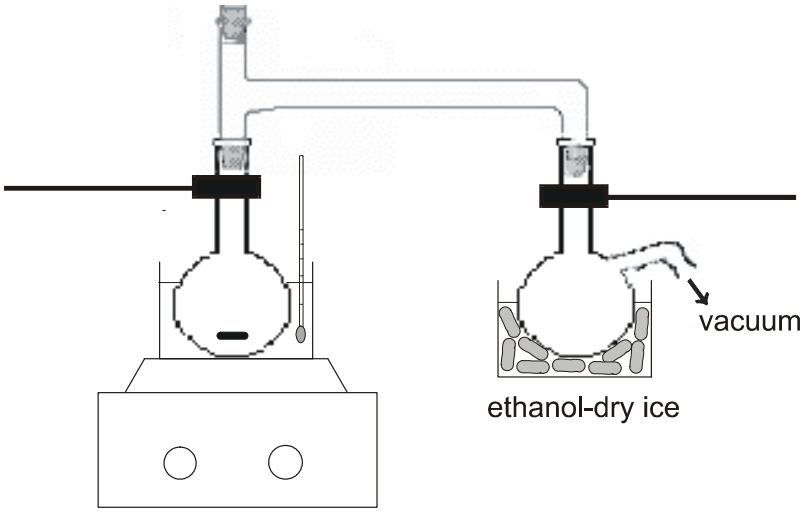


Fig. 2.

Under continuous stirring distil the tetrahydrofuran from the filtrate in water pump vacuum. At the beginning regulate the vacuum with the three-way tap so that no foaming takes place. When a steady pressure is attained (without foaming), use an about 30 ^{o}C

water bath and during the distillation increase the temperature of the bath to about 50 ^{o}C. If needed use Teflon foil to improve the tightness of the joints. Put the distillate into the corresponding waste-container in the fume cupboard.

5

Remove the water bath and the distillation head and add to the oily residue remained in the distillation flask 40 ml of 1,2-dichloroethane, pour the solution into a 100-ml separatory funnel and wash it with 20 ml of 10% acetic acid then with 2 x 20 ml of water.(Collect the water layer and put it into the appropriate waste-container under the fume cupboard). Note that the dichloroethane solution is always the under layer. After washing put the organic layer into a clean and dry 100-ml Erlenmeyer flask and dry it for 15 min. over 5 g of sodium sulphate. After drying filter the mixture through a fluted filter paper into a clean and dry 100-150-ml round-bottomed flask, wash the sodium sulphate with 10 ml of 1,2-dichloroethane. Put the contaminated filter paper into the waste-container under the fume cupboard.

6

Distil the 1,2-dichloroethane in water pump vacuum as described above (Fig. 2) (45 – 50 ^{o}C and about 30 min). Pour the distillate (1,2-dichloroethane) into the corresponding waste-container.

7

Dissolve the oily residue remained in the distillation flask in 15 ml of ethanol, pour the solution into a 100-ml clean and dry Erlenmeyer flask, cool it gradually and carefully in ethanol-dry ice bath. The flask should be scratched below the surface of the solution with a glass rod in order to initialise the crystallisation of the product. Cool the mixture only to such an extent that it can be filtered with suction filter flask with side arm, rubber ring, fritted glass funnel).

Cool 20 ml of ethanol in a 100-ml Erlenmeyer flask in dry ice-ethanol bath and pour a small amount of the cooled ethanol (in a thin layer) onto the fritted glass funnel to precool it. After few seconds start the suction with the water pump, pour the cooled crystal-suspension quickly onto the fritted glass funnel, press it with at the end flattened glass rod, get the total amount of the crystals with small amounts of cooled ethanol onto the funnel. Pour the filtrate back into the 100-ml Erlenmeyer flask, cool it again in the dry ice-ethanol bath to a larger extent as in the first time and filter the crystals with suction as described above. If crystallisation takes place on cooling the filtrate the procedure can be repeated again. At the end wash the product with small amounts of cooled ethanol and continue the suction until the funnel warms up to room temperature. Mind that a thorough pressing of the filter cake is needed for the removing of the impurities from the product. Do not smear with the suspension the side of the funnel: only this way can be avoided water condensation on the product. Pour the last filtrate into the corresponding waste-container.

8

Collect the white crystalline product in a bottle with cap and weigh it.
Wash up the equipment (for the washing up make the best use of your time: you can wash up also during the procedure).