The Synthesis of 2-Methyl-4-Heptanone
An Ant Alarm Pheromone
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In order to stimulate students’ interest in synthetic organic laboratory courses, it is fruitful to combine basic synthetic methodology with the presentation of target molecules of biological origin. We present a two-step route to such a molecule (2) using common preparations, i.e., the Grignard reaction and the oxidation of secondary alcohols.

An ant pheromone of two ant species, Tapinoma nigerrimum (1, 2) and Tapinoma simrothi (3), is 2-methyl-4-heptanone (2). Both ant species are common in the Mediterranean area. The alarm pheromones are secreted by anal glands, located at the tip of the ant’s abdomen. The synthesis of 2-methyl-4-heptanone (2) proceeds in two steps from butanal and 1-chloro-2-methyl-propane. The Grignard synthesis of 2-methyl-4-heptanol (1) was first performed by Levene and Marker (4), using 1-bromo-2-methyl-propane. The Grignard reaction followed by the oxidation makes the experiment described here a valuable alternative to the synthesis of 4-methyl-3-heptanone, the alarm pheromone of the harvester ant, reported earlier in this Journal (5).

The synthesis of 4-methyl-3-heptanone has some severe drawbacks, as we and others (6) experienced. The intermediate product 4-methyl-3-heptanol, synthesized in the Grignard reaction is contaminated with the ketone, 4-methyl-3-heptanone (13%) and the Grignard coupling product, 4,5-dimethyloctane (15–25%). The three products cannot be separated easily by distillation.

The synthesis of 2-methyl-4-heptanone (2) presented here does not suffer the drawbacks mentioned above. It is simple and proceeds in high yield. 2-Methyl-4-heptanol (1) is prepared by the Grignard reaction between 1-chloro-2-methyl propane and butanal. First the Grignard reagent is prepared from 1-chloro-2-methyl-propane and magnesium. The use of a primary alkyl halide (1-chloro-2-methylpropane) instead of a secondary alkyl halide (2-bromopentane used in the synthesis of 4-methyl-3-heptanol, mentioned above) reduces the relative importance of the Grignard coupling reaction (7). In addition the less reactive alkyl chloride instead of the more reactive alkyl bromide generally shows a lower reactivity in side reactions (8). Common side reactions are: Grignard coupling, reduction of the starting carbonyl compound to the alcohol by the Grignard reagent, and reaction of the Grignard reagent with a proton α to the carbonyl functionality (enolization). The product, 2-methyl-4-heptanol (1), can be identified by its refractive index and IR and 1H NMR spectrum. The OH signal position in the NMR spectrum may be established by adding a few drops of D2O to the sample and shaking vigorously. A recorded spectrum shows the disappearance of the OH signal.

The ketone, 2-methyl-4-heptanone (2) is produced by sodium hypochlorite oxidation of the alcohol(2). This simple method yields ketones from secondary alcohols in high yield (9, 10). We used a sodium hypochlorite solution that is commercially available as a cleaning agent. As obtained, it was determined by titration (71) to be 2.1 molar (12.7% available chlorine by weight). The ketone is identified by its refractive index, 1H NMR and IR spectrum.

The synthesis of 1 and 2 combines a number of important techniques in preparation, isolation, and identification, with a target molecule of natural origin. In addition it focuses students’ attention on the important field of insect pheromones.

Experimental

2-Methyl-4-heptanol (1)

A 250-mL three-necked flask, a pressure-equalized dropping funnel, a glass stopper, a CaCl2 tube, a double surface reflux condenser and an egg-shaped magnetic stirring bar, are dried for 1 night in an oven at 80 °C before use. The reaction is performed in a hood, in a nitrogen atmosphere. Ether is distilled from P2O5 before use. 1-Chloro-2-methyl-propane is dried over Na2SO4 for 1 night. Commercially available butanal contains considerable amounts of water. For the purpose of the reaction 50 mL butanal is first dried over Na2SO4 and then fractionally distilled. The butanal/water azetropes (12) boils at 68 °C. The fraction boiling from 75 °C to 76 °C is used in the reaction. The magnesium is activated just before the start of the reaction, by agitating it together with a few crystals of iodine in a mortar.

A 250-mL three-necked flask is fitted with a condenser with CaCl2 tube, a pressure-equalized dropping funnel with N2 inlet, an egg-shaped magnetic stirring bar and a glass stopper. The flask is flushed thoroughly with N2 and then filled with N2. The dropping funnel is charged with a solution of 4,81 g (5.45 mL, 52.0 mmol) 1-chloro-2-methyl-propane in 30 mL dry ether. Subsequently 1.9 g (78 mmol) of activated magnesium is added to the flask along with a few crystals of iodine. By means of a heating gun the iodine is sublimed onto the magnesium turnings. The 1-chloro-2-methylpropane solution is added dropwise at such a rate that a gentle reflux is maintained. The start of the reaction is indicated by a light effervescence on the magnesium particles. The reaction mixture assumes a gray/brown color. When all of the magnesium in the flask is covered by liquid, the stirrer is started. After complete addition (approximately 20 min), reflux is maintained by means of an electric heating mantle for an additional 20 min. The solution is cooled down to room temperature and a solution of 2.40 g (2.94 mL, 33.3 mmol) butanal in 10 mL anhydrous ether is added dropwise with stirring to the Gri-
2-Methyl-4-heptanone (2)

A 100-mL three-necked flask is equipped with a dropping funnel, a CaCl₂ tube, a stopper, and a magnetic stirring bar. The flask is charged with a solution of 2.00 g (15.3 mmol) 2-methyl-4-heptanone in 10 mL acetic acid. The flask is placed in a cold water bath. To the solution, 14.5 mL of an aqueous 2.1 M NaOCl solution (2 equiv.) is added dropwise in 30 min. The temperature is kept at 15–25 °C. After the addition the water bath is removed, and stirring is continued for 1.5 h. To the yellow solution 50 mL of water is added, and the solution is extracted twice with 60 mL dichloromethane. The combined organic layers are extracted twice with a saturated NaHCO₃ solution (caution: foaming) and twice with a 5% NaHSO₃ solution, after which a potassium iodide-starch test was negative. Subsequently the solution was dried over Na₂SO₄ and the dichloromethane removed by means of a rotary evaporator. Mind the product’s boiling point! A colorless liquid, 2-methyl-4-heptanone remains.

Yield: 1.78 g (13.9 mmol, 91%).

Conclusions

Bulb-to-bulb distillation or fractionation under reduced pressure, bp³⁵ 40 °C (14)–153.7° yields 1.50 g (11.7 mmol, 77%) colorless liquid. Refractive index¹: 1.4105²⁰ (lit (15): 1.4220²⁰; lit (16): 0.8088²⁰).

IR(neat): 3330(s), 2940(s), 1460(m), 1375(m), 1150(m), 1130(m), 1075(m), 1020(m), 850(m), 650(m).

¹H NMR (300 MHz, CDCl₃, TMS): 8 0.9 (m, 9 H); 1.25 (m, 2 H); 1.35 (m, 4 H); 1.75 (m, 1 H); 1.9 (s, 1 H); 3.65 (m, 1 H).

¹³C NMR (75 MHz, CDCl₃): 8 13.95(q); 18.63(t); 21.90(q); 23.33(q); 24.42(d); 40.11(d); 46.67(t); 69.42(d).

Analysis: calculated: %C: 73.78; %H: 13.93; %C: 73.70; %H: 13.85.

The refractive index differs considerably from the values reported in the literature (15, 16). However, as our spectra and analysis are in accordance with a pure product, the refractive index found by us is very likely to be the most correct one.