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Published in:
Journal of Chemical Education

DOI:
[10.1021/ed068p71](https://doi.org/10.1021/ed068p71)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1991

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Jong, E. A. D., & Feringa, B. (1991). The Synthesis of 2-Methyl-4-Heptanone. *Journal of Chemical Education*, 68(1). <https://doi.org/10.1021/ed068p71>

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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 alarm 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-methylpropane. The Grignard synthesis of 2-methyl-4-heptanol (**1**) was first performed by Levene and Marker (4), using 1-bromo-2-methylpropane. 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-methylpropane and butanal. First the Grignard reagent is prepared from 1-chloro-2-methylpropane and magnesium. The use of a primary alkyl halide (1-chloro-2-methylpropane) instead of a secondary alkyl halide (2-bromo-pentane is used in the synthesis of 4-methyl-3-heptanol, mentioned above) reduces the relative importance of the Grignard cou-

pling 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 alcohol². 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 (11) 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-methylpropane 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 azeotrope (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-methylpropane 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-

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² Alternatively 2-methyl-4-heptanol (**1**) may be oxidized by adding 2.00 g (0.015) mol of the alcohol dropwise to a sodium dichromate/dilute sulfuric acid solution, which contains 3.2 g (0.01 mol) sodium dichromate, 2 mL concentrated sulfuric acid, and 20 mL water. Stirring at room temperature for 1.5 h and workup by adding ether and washing the ethereal solution with 1 N aqueous NaOH yields the ketone (**2**) in 86%.

gnard solution. After addition, the mixture is refluxed for an additional 20 min. Carefully, and with efficient stirring, 5 mL of water is added dropwise. Subsequently 35 mL of 5% aqueous HCl is added dropwise. The major part of the solution is decanted from the magnesium, and the remaining magnesium is washed with ether and removed by gravity filtration. The decanted solution is combined with the filtrate, and the layers are separated. The ethereal solution is washed with 30 mL 5% aqueous NaOH and dried over Na₂SO₄. The ether is removed by means of a rotary evaporator. Mind the product's boiling point! A colorless liquid, 2-methyl-4-heptanol remains.

Yield: 3.60 g (27.6 mmol; 83%); bulb-to-bulb distillation or fractionation under reduced pressure, bp¹⁰: 61–62 °C; lit (13): bp⁷⁵²: 164–164.5 °C yields 3.53 g (27.1 mmol; 81%) colorless liquid; *n*_D: 1.4214²⁰; lit (13): 1.4220²⁰.

IR(neat): 3330(s), 2940(s), 1460(m), 1375(m), 1150(m), 1130(m), 1075(m), 1020(m), 950(m), 850(m).

¹H NMR (300 MHz, CDCl₃, TMS): δ 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): δ 13.95(q); 18.63(t); 21.90(q); 23.33(q); 24.42(d); 40.11(t); 46.67(t); 69.42(d).

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

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-heptanol 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 com-

bined 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%). Bulb-to-bulb distillation or fractionation under reduced pressure, bp¹⁰: 40 °C(lit (14): 155⁷⁵⁰) yields 1.50 g (11.7 mmol, 77%) colorless liquid. Refractive index³: 1.4105²⁰ (lit (15): 1.4220²⁰; lit (16): 0.8088²²).

IR(neat): 2950(s), 2200(w), 1710(s), 1470(m), 1375(s), 1150(m), 1045(m).

¹H NMR (300 MHz, CDCl₃, TMS): δ 0.9 (m, 9 H); 1.55 (m, 2 H); 2.1 (m, 1 H); 2.25 (d, 2 H, J 1.1 Hz); 2.35 (t, 2 H, J 1.5 Hz).

¹³C NMR (75 MHz, CDCl₃): δ 13.58(q); 17.03(t); 22.41(q, 2 CH₃); 24.41(d); 45.07(t); 51.67(t); 210.88(s).

Analysis: calculated: %C: 74.94 %H: 12.58; found: %C: 74.67 %H: 12.48.

Literature Cited

- Trave, R.; Pavan, M. *Chem. Ind. Milano* **1956**, 38, 1015–1019.
- Pavan, M.; Trave, R. *Insect. Soc* **1958**, 5, 299–308.
- Hefetz, A.; Lloyd, H. *J. Chem. Ecol.* **1983**, 9, 607–613.
- Levene, P. A.; Merker, R. E. *J. Biol. Chem.* **1931**, 90, 674.
- Einterz, R. M.; Ponder, J. W.; Lenox, R. S. *J. Chem. Educ.* **1977**, 54, 383.
- Hoffman, R. V.; Alexander, M. D.; Buntain, G.; Hardenstein, R.; Mattox, C.; McLaughlin, S.; McMin, D.; Spray, S.; White, S. *J. Chem. Educ.* **1983**, 60, 78.
- March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 402.
- Kharasch, M. S.; Rheinmuth, O. *Grignard Reaction of Nonmetallic Substances*; Prentice-Hall: New York, 1954; p 20.
- Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, 45, 2030–2032.
- Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizzati, K. F. *Tet. Lett.* **1982**, 23, 4647–4650.
- Vogel, A. I. *A Textbook of Quantitative Inorganic Analysis*, 4th ed.; Longman: New York, 1978; p 382.
- Smith, T. E.; Bonner, R. F. *Ind. Eng. Chem.* **1951**, 43, 1169.
- Boit, H. G., Ed. *Beilsteins Handbuch der Organischen Chemie*; Springer: Berlin, 1973; Band 1, E.W. IV, p 1781.
- Weast, R. C., Ed. *Handbook of Chemistry and Physics*, 64th ed.; C.R.C.: Boca Raton, FL, 1983.
- Boit, H. G., Ed. *Beilsteins Handbuch der Organischen Chemie*; Springer: Berlin, 1973; Band 1, E.W. IV, p 3343.
- Bellassoued, M.; Gaudemar, M. *J. Organomet. Chem.* **1974**, 81, 139–144.

³ 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.