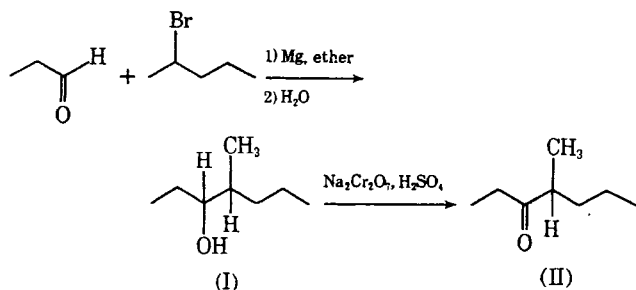


The Synthesis of 4-Methyl-3-heptanol and 4-Methyl-3-heptanone

Two easily synthesized insect pheromones

Although the synthesis of alcohols from Grignard reagents is frequently discussed in textbooks of organic chemistry, laboratory manuals normally suggest the syntheses of relatively simple and biologically uninteresting compounds such as triphenylcarbinol (1, 2) or cyclohexyl phenyl carbinol (3) to demonstrate the utility of the reaction. The same is true of the oxidation of secondary alcohols to the corresponding ketones; a suggested synthesis in available laboratory manuals is that of cyclohexanone from cyclohexanol (2, 3).

We would like to suggest as an interesting alternative to these preparations a two step reaction sequence involving the Grignard synthesis of an alcohol followed by oxidation of this alcohol to the corresponding ketone. The alcohol, 4-methyl-3-heptanol (I), is prepared from propanal, 2-bromopentane, and magnesium and, interestingly, is one of three known compounds used as the aggregation pheromone of *Scolytus multistriatus*, the European elm beetle, which is chiefly responsible for the spread of Dutch elm disease (4). 4-Methyl-3-heptanone (II), which can be produced by dichromate oxidation of (I), is known to function as the alarm pheromone for *Pogonomyrmex barbatus* (the harvester ant), *Atta texana* (the Texas leaf-cutting ant), and other related ant species (5, 6). This is reported to be the only branched-chain compound yet reported from ants which does not obey the isoprene rule (5).



We feel that the preparation, isolation, and characterization of compounds (I) and (II) should provide a useful and stimulating laboratory synthesis for students enrolled in organic chemistry courses. Not only are vital synthetic and isolation techniques employed, but also the interest of students, particularly those who have a background in biology, is enhanced. It is of interest to note that the Grignard synthesis of (I) followed by oxidation to compound (II) is not described elsewhere in the chemical literature.

Discussion

Several fundamental aspects of stereochemistry are illustrated by this reaction sequence. For example, 4-methyl-3-heptanol (I) has two chiral centers. When commercially available racemic 2-bromopentane is used as the starting material, diastereomeric pairs of enantiomers of (I) are formed. These can be easily separated by gas-liquid phase chromatography and thus a student should be able to see that equal quantities of diastereomers are formed. This separation can be effected using even a nonpolar 3-ft 10% SE-30 column; the separation using a more polar column packing such as Carbowax is much more dramatic.

Purification of (I) by distillation at atmospheric pressure also offers some insight into the physical properties of diastereomers. A reasonably pure sample of the diastereomers can be obtained by collecting the fraction boiling between 150–165°C. This broad range, atypical of what a student would consider normal behavior for a

“pure” compound, emphasizes the difference in physical properties of diastereomers. Literature references to the boiling point of this compound may also interest the student. Two different references to two different sharp boiling points (7, 8) are given; the authors of these references do not seem to take into account the existence of diastereomers.

Dichromate oxidation of the mixture of diastereomers of (I) affords 4-methyl-3-heptanone (II). This compound has only one chiral center as chirality at C-3 is destroyed upon formation of the carbonyl group. The presence of only one chiral center means that the student now is working with a mixture of enantiomers which have identical boiling points. This is vividly illustrated by the narrow boiling point range (156–157°C) observed for (II) at atmospheric pressure (745 mm).

Only simple laboratory equipment is necessary to effect this synthetic sequence. Although more sophisticated equipment can be employed if desired, the methods described in the experimental section will enable students with a minimum amount of glassware to perform the reactions and obtain satisfactory yields.

Experimental

General

Both propanal and 2-bromopentane were purchased from Aldrich Chemical Company. Propanal was distilled immediately before using as significant quantities of propionic acid were found to be present. Ether was dried before use by distilling from calcium hydride; the dried solvent was stored over sodium shavings. Magnesium shavings were dried by heating before use.

4-Methyl-3-heptanol (I)

A dry 200-ml round bottom flask with a single 24/40 joint is fitted with a reflux condenser; a calcium chloride drying tube is placed at the top of the condenser. To the flask is added 7.3 g (0.30 mole) of dry magnesium shavings, 100 ml of dry ethyl ether and a Teflon coated magnetic stirring bar. The apparatus is then assembled and 2.4 g (0.016 mole) of 2-bromopentane added through the top of the condenser. The drying tube is replaced and stirring commenced. If formation of the Grignard reagent has not started after 5 min, 6–10 drops of methyl iodide and a crystal of iodine may be added to initiate the reaction.

Once formation of the desired organometallic has begun, 27.9 g (0.184 mole) of 2-bromopentane is added in small portions over a period of 30 min through the top of the condenser. The drying tube should remain in place between additions. When addition of the bromide is complete, the reaction mixture is stirred for an additional 15 min.

Propanal (11.6 g, 0.20 mole) is then added *slowly* to the solution of Grignard reagent through the top of the condenser and the reaction mixture stirred for an additional 15 min. Water (50 ml) is then added slowly to protonate the magnesium salt of (I), followed by sufficient 5% aqueous HCl to dissolve all inorganic salts. Excess magnesium can be removed from the mixture by gravity filtration through a glass wool plug.

The organic layer is separated, washed with 50 ml of 5% aqueous NaOH and dried over MgSO₄. Isolation and purification of the substance is done by evaporating the ether and distilling the oily residue at atmospheric pressure. The fraction boiling from 150–165°C (745 Torr) is collected (lit. bp 160–161°C (7); 155.4°C (8) to give 13.9 g (0.107 mole, 36%) of 4-methyl-3-heptanol; refractive index, 1.429; (lit. (9), 1.430). The infrared spectrum is identical to a published spectrum (9).

4-Methyl-3-heptanone (II)

To a 200-ml round bottom flask mounted in an ice-water bath is added 100 ml of deionized water. Concentrated sulfuric acid (17.6 g, 0.18 mole) is slowly added and the solution is stirred with a magnetic stirring bar. Sodium dichromate (22.2 g, 0.074 mole) is then added and

stirring continued until all materials are dissolved. At this point, 4-methyl-3-heptanol (I) (13.9 g, 0.107 mole) is slowly added; the color of the reaction mixture should gradually change to green. The mixture is then stirred for an additional 15 min.

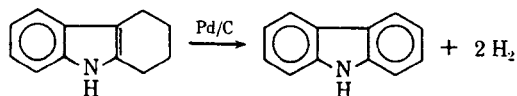
When the reaction is complete, the reaction mixture is transferred to a 250-ml separatory funnel and the organic layer is isolated and washed with four 50-ml portions of 10% sodium hydroxide solution. The organic layer is then dried with magnesium sulfate and ether removed by heating on a steam bath to give 10.3 g (0.08 mole) of (II) as a yellow liquid. This can be distilled at atmospheric pressure (156–157°C, 745 mm) to give 7.0 g (0.055 mole, 51%) of (II) as a clear liquid; refractive index, 1.416; (lit. (9), 1.416). The infrared (9) and nmr spectra (5) are found to be identical to published spectra.

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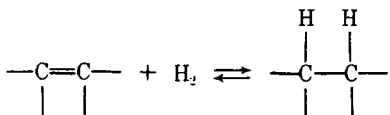
Catalytic Dehydrogenation of Tetrahydrocarbazole

An organic laboratory experiment

Although dehydrogenation is a process of considerable importance in the synthesis of aromatic molecules (1), experiments involving its use are rarely included in organic laboratory textbooks. Presumably a major reason for this is that dehydrogenations at conventional laboratory temperatures usually require reaction periods which extend far beyond the few hours per week allotted to a sophomore laboratory. This paper describes a simple experiment in catalytic dehydrogenation which has been modified so that it can be completed within the limits of the usual 3 or 4-hour laboratory period. The reaction, conversion of 1,2,3,4-tetrahydrocarbazole to carbazole, is of additional value in that it illustrates the synthesis of a common heterocyclic system.



In considering the experimental conditions needed for catalytic dehydrogenation, it is helpful to recognize the fact that the reaction is simply the reverse of hydrogenation



One consequence of this is that the catalysts most useful for hydrogenation, the transition metals of Group VIII, in particular palladium, platinum, rhodium, and nickel, are also effective for dehydrogenation. Palladium, usually supported on carbon, has been most often used.

Since addition of hydrogen to a carbon-carbon double bond is exothermic by about 28 kcal mole⁻¹, dehydrogenation is, in itself, a thermodynamically unfavorable process. The accompanying positive entropy change of approximately 30 cal mole⁻¹ °K⁻¹ is, however, a mitigating factor, and, where only one double bond is needed to complete an aromatic π -system, the resulting increase in resonance energy may be sufficient to provide a negative ΔG . Nevertheless, in the most common applications where at least two new double bonds are introduced, the reactions are significantly endergonic.

The success of these reactions, then, usually depends on displacement of an unfavorable equilibrium. This is accomplished most simply by allowing the liberated hydrogen to escape into the atmosphere. The use of a vigorously boiling reaction mixture aids the expulsion of hydrogen from the solution, and may be essential to the success of a dehydrogenation. Sweeping the atmosphere above the reaction mixture with a slow stream of nitrogen or other inert gas is also helpful, and the time required for complete dehydrogenation is often considerably reduced by the use of this technique.

A high reaction temperature is usually necessary, since most de-

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hydrogenations, as a result of their endothermicity, have rather high activation energies. Moreover, at higher temperatures, owing to the increased equilibrium constant and the decreased solubility of hydrogen, the equilibrium concentration of hydrogen is more likely to be beyond the limit of its solubility in the medium used. Di- and trialkylbenzenes having boiling points of 140°C or more are often employed as solvents. In some cases, the reagents are heated together without solvent to temperatures as high as 375°C, or, in gas-phase processes, sometimes much higher.

The amount of catalyst used can be an important consideration, since rates of hydrogenation and dehydrogenation are, as a rule, dependent on the amount of catalyst. The reaction rate is also dependent on the activity of the catalyst, which may be a function of how it is prepared. The presence of impurities in the reaction mixture which poison the catalyst will lower its activity; even nominally pure reagents and solvents may contain traces of catalyst poisons.

Horning, Horning, and Walker (2) found that a 95% yield of carbazole could be obtained after only 2 hr refluxing of a solution of tetrahydrocarbazole in redistilled trimethylbenzene (b.p. 168–172°C) with their own preparation of 5% palladium-on-carbon. With commercially available catalysts and solvents, however, our experience is that, under similar conditions, yields approaching complete conversion can be obtained only after a much longer reaction time. Similar results were indicated by Campaigne and Lake (3), who reported a 91% yield of carbazole after 12 hr in refluxing xylene (b.p. ~140°C). A substantial reduction in the time can, however, be achieved by employing a relatively large amount of catalyst. With a 1:2 catalyst-substrate ratio and *p*-cymene (b.p. 177°C) as solvent, a reasonable conversion (~75%) can be obtained within 1½ hr.

Procedure

Into a 25- or 50-ml round-bottomed flask² are placed 1.00 g of 1,2,3,4-tetrahydrocarbazole (4), 0.5 g of 5% Pd/C, and 10 ml of *p*-cymene. Boiling stones are added and the mixture is refluxed gently for 1.5 hr over a microburner flame, with occasional swirling to wash down catalyst deposited on the flask walls. The flask is then allowed to cool; 10 ml of ethyl acetate is added and the mixture is warmed gently, if necessary, to dissolve the precipitated carbazole. The catalyst is removed by vacuum filtration, using a carefully fitted double

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²A 25-ml flask is perhaps preferable, but the 50-ml size found in most standard-taper glassware kits was used in the studies reported here, and was found to be quite adequate. Since the flask is well under half full, the burner flame should be adjusted carefully to avoid superheating the flask walls above the surface of the liquid; the use of a shield of asbestos board with a small hole cut in the center may be advantageous, but is not necessary if reasonable care is taken.