Imperial College London	Department of Chemistry Third Year Advanced Practical Organic Chemistry

Experiment 5

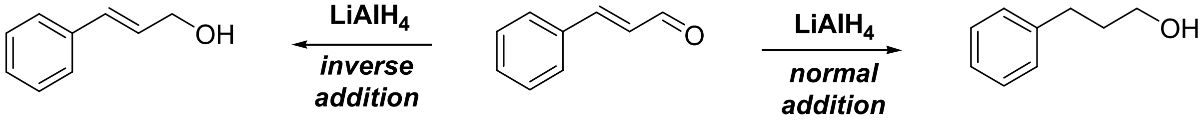
Reductions with Lithium Aluminium Hydride

EXPERIMENT 5:

REDUCTIONS WITH LITHIUM ALUMINIUM HYDRIDE

Aims of the experiment

To demonstrate the control of reactivity in $LiAlH_4$ reductions possible by altering the mode of addition, by reducing cinnamaldehyde *either* to cinnamyl alcohol OR dihydrocinnamyl alcohol.



Techniques used/learned:

Handling of pyrophoric and moisture sensitive reagents ($LiAlH_4$); vacuum distillation.

Introduction[1]

Lithium aluminium hydride is an excellent reagent for the reduction and hydrolysis of certain polar groups. For example, –COCl, $-CO_2H$, $–CO_2Et$, and –CHO are reduced to $–CH_2OH$; >CO to >CHOH; –CH=NOH and $–CONH_2$ to $–CH_2NH_2$. Provided the correct solvent is used, primary and secondary halides can be reduced to hydrocarbons. Carbon-carbon double and triple bonds are generally unaffected except when they are $\alpha\beta$- to a polar group.

The reductions often proceed at room temperature or below and are usually rapid and free from side reactions. The compound to be reduced is added slowly (by continuous extraction if it is sparingly soluble) to an excess of the reagent suspended or dissolved in an ether.

Selective reduction of polar groups in the presence of other reducible functions can frequently be achieved by an inverse addition method: the reagent is added slowly to the substance to be reduced, so that the reagent is never present in excess. Thus by inverse addition –C≡N can be reduced to –CH=NH (normal addition gives $–CH_2NH_2$) and cinnamaldehyde to cinnamyl alcohol (normal addition gives hydrocinnamyl alcohol).

Selective reduction of functional groups can also be achieved by chemical modification of the reagent, *e.g.* as $LiAlH(OBu^t)_3$, or by the use of the related complex hydrides, lithium and sodium borohydrides. Useful modifications in the properties of lithium aluminium hydride is also effected with aluminium chloride and other Lewis acids.

HAZARD DATA - READ THIS BEFORE GOING ANY FURTHER!

LITHIUM ALUMINIUM HYDRIDE:

CONTACT WITH WATER LIBERATES EXTREMELY FLAMMABLE GASES

A white microcrystalline powder and lumps; decomposes above 125°C; reacts rapidly with water with evolution of hydrogen. Prevent skin, eye and clothing contact.

Toxic effects: Reaction with water produces LiOH which is corrosive to skin and eyes.

Fire hazard: Arises from contact with small quantities of water. Extinguish with *sand*, **not** CO_2.

Hazardous reactions: May ignite when ground with a pestle. Reacts vigorously on solution if solvents not rigorously dried. ***See special warning below***.

Spillage disposal: Clear area, shut off all sources of ignition. Wear face shield goggles and gloves. If contained, destroy cautiously with isopropanol. If scattered, cover with solid sodium carbonate, shovel into buckets and remove to safe place for destruction with isopropanol.

CINNAMALDEHYDE:

HARMFUL BY INGESTION, INHALATION, AND SKIN CONTACT

Colourless/ pale yellow liquid with characterisitic odour; b.p. 125°C (11 mmHg), m.p. -4°C.

Toxic effects: Harmful by ingestion and inhalation. Harmful by skin contact

Hazardous reactions: May react with oxidising agents

Spillage disposal: Clear area, shut off all sources of ignition. Wear face shield goggles and gloves. Absorb onto sand and place in container for disposal

TETRAHYDROFURAN:

IRRITATING TO EYES AND RESPIRATORY TRACT
MAY FORM EXPLOSIVE PEROXIDES
HIGHLY FLAMMABLE

Colourless volatile liquid with ethereal odour; b.p. 66°C; miscible with water. Liable to form explosive peroxides on exposure to light/air. Peroxides removed by treatment with aqueous sodium metabisulfite. Avoid breathing vapour, eye and skin contact. OEL 295 mgm^{-3}.

Toxic effects: The vapour irritates eyes and respiratory system; high concentrations have narcotic effect. Absorption or ingestion may cause liver damage.

Hazardous reactions: Explosive peroxides formed on exposure to air/light. NaOH/KOH can cause explosion with peroxided material.

Fire hazard: Flash point –17°C; ignition temp. 321°C; extinguish fire with CO_2.

Spillage & disposal: Clear area, shut off all sources of ignition. Wear goggles, gloves, and laboratory coat. Mop up with plenty of water and run to waste. Organise effective ventilation and evaporate remaining liquid.

DIETHYL ETHER:

HARMFUL BY INHALATION, AND INGESTION
MAY FORM EXPLOSIVE PEROXIDES
EXTREMELY FLAMMABLE

Colourless highly volatile liquid with characteristic odour; b.p. 34°C; immiscible with water. Liable to form explosive peroxides on exposure to light/air. Peroxides removed by treatment with aqueous sodium metabisulfite. Avoid breathing vapour. OEL 1200 mgm$^{-3.}$

Toxic effects: Inhalation of the vapour may cause drowsiness, dizziness, mental confusion, faintness and, in high concentrations, unconsciousness. Ingestion may also produce these effects. Continued inhalation of low concentrations may cause loss of appetite, dizziness, fatigue and nausea.

Hazardous reactions Peroxide formation can result in subsequent explosion. Powerful oxidants can cause explosion. Reacts vigorously with sulfuryl chloride.

Fire Hazard Flash point –45°C, ignition temp. 180°C; extinguish fire with CO_2.

Spillage & disposal Clear area, shut off all sources of ignition. Organise effective ventilation and allow to evaporate. Diethyl ether should be placed in the non-chlorinated waste container for central disposal

WARNING ON THE USE OF LITHIUM ALUMINIUM HYDRIDE (LAH)

Powdered lithium aluminium hydride must never be allowed to come into contact with water.

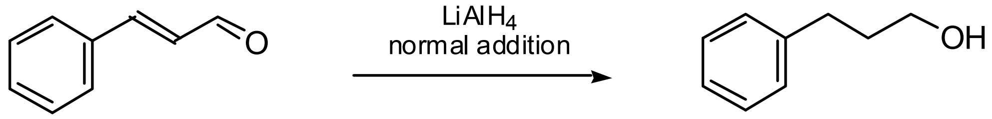
1. All apparatus and reactants should be perfectly dry, and reactions should be run rigorously under nitrogen, with the reaction temperature below 70°C at all times.
2. Order of addition is important. **Always** first add the hydride to the solvent in the nitrogen purged apparatus before mixing with any reactant.
3. The hydride should never be allowed to form a crust above the level of the liquid or to settle to the bottom of a heated flask, so gentle efficient stirring is essential.
4. To prevent local overheating of the reaction vessel, heating mantles should never be used. Use an intermediate medium such as oil or graphite bath.
5. After reaction, destroy excess LAH by slow careful addition of ethyl acetate (diluted with an inert solvent such as dry THF), under nitrogen, keeping the temperature below 50°C. ***All LAH reactions should be carried out behind protective screens.***
6. Any spillages of LAH should be reported to the demonstrators who will advise on procedures for clearing up the spillage.

EXPERIMENTAL PROCEDURES

Note that *only one of these experiments* is to be carried out. You will have been allocated one (see the master-plan of the experimental assignments). **Before carrying out the reduction**, you will need to purify the cinnamaldehyde by distillation.

NB: Experiment 5a = 'inverse' addition (METHOD 2, below)
Experiment 5b = 'normal' addition (METHOD 1, below)

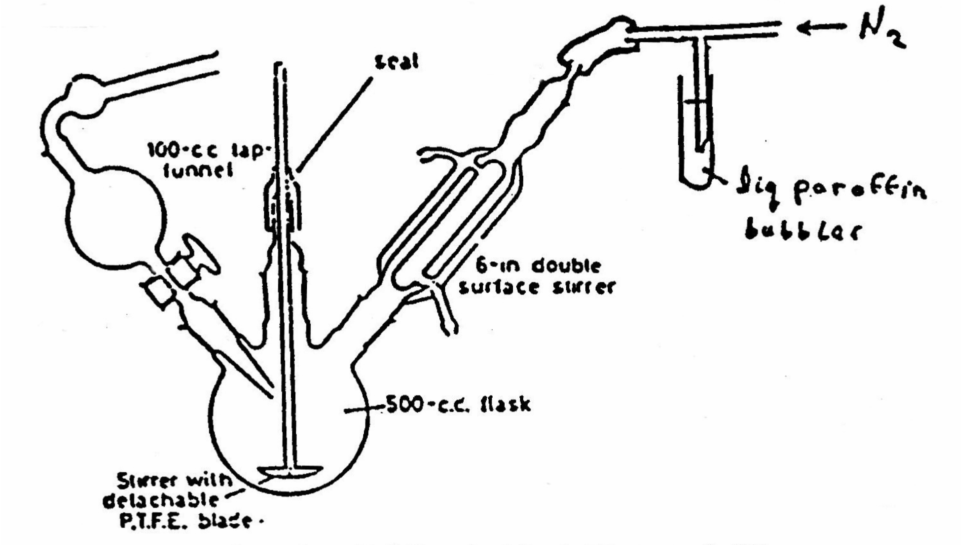
1. *Reduction of Cinnamaldehyde to Hydrocinnamyl Alcohol: Normal Addition.*[2]



Dry, in an oven, a 250 ml three-necked flask, a 100 ml tap-funnel and a double surface condenser.

In a dry fume cupboard weigh out lithium aluminium hydride (2.9 g) and introduce it into a 3-necked flask *via* a powder funnel. Rinse in any residues with *dry* THF (~20 ml) and at once fit a stirrer, condenser and tap-funnel and set up the apparatus as in Figure 1. Use a Citenco brushless motor for the stirrer, a magnetic stirrer is not sufficiently powerful.

Pass a slow stream of purified nitrogen into the reaction flask, switch on the stirrer and heat the flask to a gentle reflux. From the dropping funnel add a solution of redistilled cinnamaldehyde (5 g) in dry THF (50 ml), very slowly and at such a rate that the THF in the flask maintains the gentle reflux. At intervals check the reaction mixture by tlc using silica plates developed in dichloromethane.



Apparatus for reactions with lithium aluminium hydride : normal addition

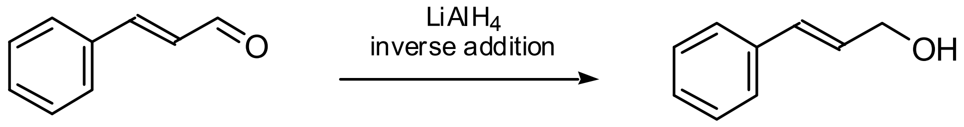
Figure 1

When the reaction is complete (> 10 min) cool the flask in water and ice and cautiously add saturated aqueous sodium sulfate (12 ml) dropwise to the stirred reaction mixture to decompose the excess of reagent. An aqueous solution is safe here because only a small quantity of reagent is present and it is in solution under an atmosphere of nitrogen. It is important to ensure that all of the excess reagent is destroyed before continuing (ask a demonstrator if in doubt). Then add 10% (v/v) sulfuric acid (95 ml). Separate the two layers (if present) and re-extract the aqueous layers with ether (4 x 30 ml). Dry the combined organic layers over anhydrous sodium sulfate.

Evaporate the solvent under reduced pressure (Rotavapor) and distil the residual oil under reduced pressure. Isolate the hydrocinnamyl alcohol (b.p. 120-121°C/13 mm Hg pressure). Record the yield, b.p. refractive index and i.r. and n.m.r. spectra and so confirm (or otherwise) the absence of cinnamaldehyde.

In the fume cupboard, clean any contaminated glassware by decomposing the lithium aluminium hydride with ethyl acetate (see above for details; contact a demonstrator if you are unsure what to do!).

2. *Reduction of Cinnamaldehyde to Cinnamyl alcohol: Inverse Addition.*[3]



Dry, in an oven, a 250 ml three-necked flask, a 100 ml tap-funnel and a side arm adapter (see Figure 2). Make up a solution/suspension of lithium aluminium hydride (0.72 g, 1.1 H^- equiv) in dry ethyl ether (50 ml) in the 100 ml tap funnel. Set up the dried apparatus as in Figure 2 with a solution of cinnamaldehyde (redistilled, 10 g) in dry ether (25 ml) in the flask.

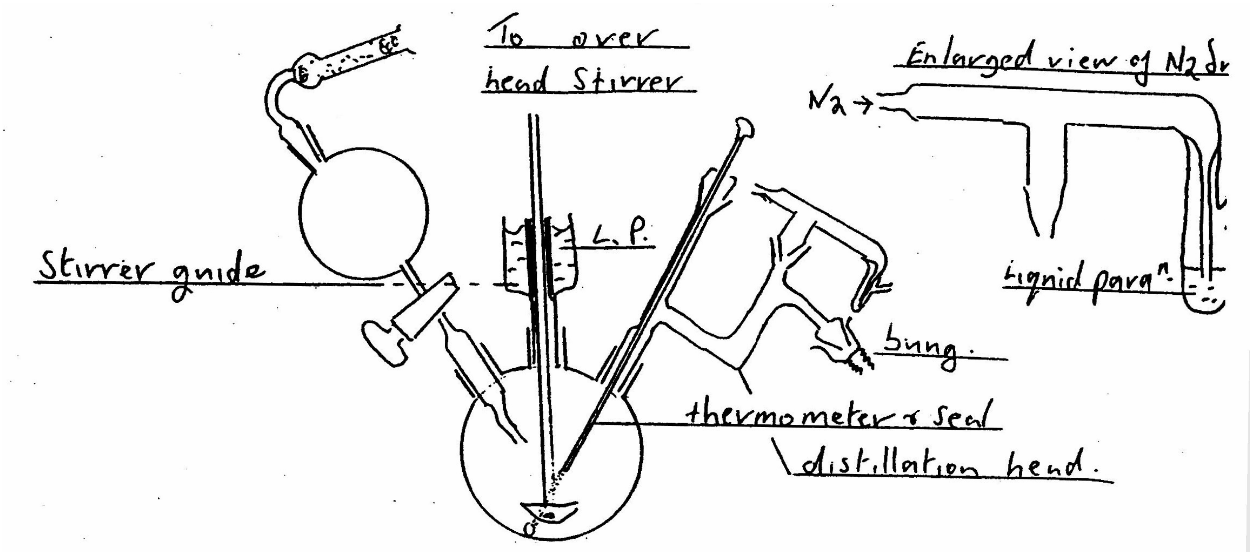


Figure 2

Switch on the stirrer, cool the flask with an ice-salt bath until the internal temperature is –10°C (pentane or alcohol thermometer) and add the solution/suspension of lithium aluminium hydride in ether during ~ 30 min so that the temperature remains below +10°C. Follow the reaction by tlc on silica plates developed in dichloromethane. If necessary add more lithium aluminium hydride in diethyl ether (carefully weighed out in the dry fume cupboard).

When the reaction is complete, add water (3 ml) to decompose the excess of the reagent. It is important to ensure that all of the excess reagent is destroyed before continuing (ask a demonstrator if in doubt). Add 10% (v/v) sulfuric acid (25 ml), then separate the ether layer and extract the aqueous layer with ether (2 x 50 ml). The combined layers are dried over anhydrous sodium sulfate. Evaporate the ether (Rotavapor) and by distil the residue under reduced pressure to isolate the cinnamyl alcohol (b.p. 139°C/14 mmHg). It should crystallise when cooled, m.p. 33°C. Record the yield, refractive index, and nmr and infra-red spectra and interpret the spectra. Transfer the material to a labelled tube.

If a sample fails to crystallise, purify it as follows: transfer the crude alcohol to a 250 ml conical flask, and dissolve it in dry ether (35 ml for each 5 g). Add powdered calcium chloride (10 g) and leave the mixture overnight under N_2.

Next day collect the calcium chloride-cinnamyl alcohol solvate under N_2, wash it with dry ether (20 ml) and then add it to water (25 ml). Extract the mixture with ether (3 x 25 ml), dry the extract over solid sulfate, filter the solution and evaporate the ether (Rotavapor) to obtain crystalline cinnamyl alcohol.

3. *Disposal of Lithium Aluminium Hydride*

Do this away from flames or other sources of ignition, in the fume-cupboard, and **WEAR GOGGLES OR A VISOR**. Dispose of the reagent, both solid and solution, by cautiously adding it to a solution of ethyl acetate in dry THF (1:2) under an atmosphere of nitrogen. **NEVER** add reagent residues to water or alcohols: there might be a violent explosion. Treat contaminated apparatus with ethyl acetate. Later, after at least 1 hour, wash the apparatus with water and dilute hydrochloric acid, and then re-rinse it with water.

Write Up

The write up should conform to *Organic and Biomolecular Chemistry* style (Title, Abstract, Introduction, Results and Discussion, Experimental, References). Your introduction must include discussion of the following points:

1. A discussion of the mechanism of the particular reduction you have undertaken.
2. One example from the recent (2003 or later) literature of the use of MODIFIED metalhydride reagents in organic synthesis (*eg* to obtain superior chemical, diastereo- or enantioselectivity).

References and Notes

1. H.C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567; E.R.H. Walker, *Chem. Soc. Rev.*, 1976, **5**, 23; N.G. Gaylord, "Complex Metal Hydrides", Wiley-Interscience, New York, 1956, p. 107.
2. R.F. Nystrom and W.G.Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197, 2548; *ibid.*, 1948, **78**, 3738.
3. A.J. Hill and E.H. Nason, *J. Amer. Chem. Soc.*, 1924, **46**, 2236.