Experiment 1.
Ketone Reduction by Sodium Borohydride:
3-Nitroacetophenone and 9*H*-Fluoren-9-one

Introduction: The reduction of aldehydes, ketones, and esters is a fundamental transformation often used in organic synthesis. The resulting alcohol may be the desired final product, or it may be transformed into a leaving group for subsequent reactions such as nucleophilic substitution or elimination. Since carbonyl reduction (i.e., net addition of dihydrogen) is so important to synthetic organic chemistry, a wide variety of reducing agents have been developed. Some hydride ($H:^-$) donors will react with most members of the large family of carbonyl-containing functional groups. For instance, lithium aluminum hydride ($LiAlH_4$) will reduce, in most cases, aldehydes, ketones, esters, and amides, but the "mild" reducing agent sodium borohydride (or tetrahydridoborate) ($NaBH_4$) will generally only react with aldehydes and ketones (the more reactive of the common carbonyl-containing functional groups) to give primary or secondary alcohols, respectively.

R = alkyl, aryl
R' = OH, OR, H, R

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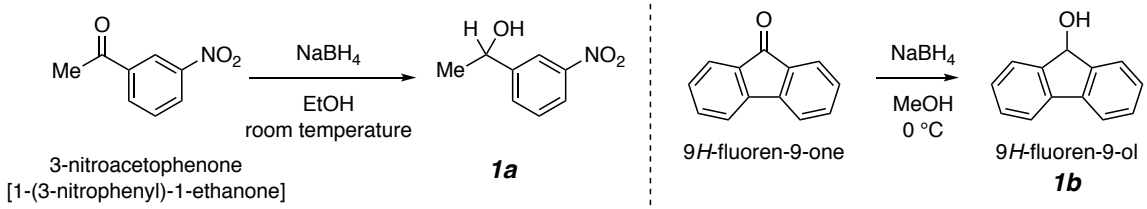
Experiment: In this experiment you will carry out the two reactions indicated in Scheme 1. Each is a reduction of a ketone substrate (3-nitroacetophenone or 9*H*-fluoren-9-one) to the corresponding alcohol product (**1a** or **1b**, respectively). You will take ~2-3 mmol of each of the ketones from its bottle; one is a yellow, the other a colorless (or "white") solid at ambient temperature. *Only use a clean and dry spatula (or disposable pipette) to remove solid (or liquid) from any commercial bottle of a chemical, reagent, or solvent in order to prevent contamination both of what you have removed as well as that of the bulk supply remaining in the bottle.*

Scheme 1



3-nitroacetophenone
[1-(3-nitrophenyl)-1-ethanone]

1a

9*H*-fluoren-9-one

9*H*-fluoren-9-ol

1b

You will use $NaBH_4$ as the hydride reducing agent. You should follow (i.e., monitor) the progress of *every reaction* you perform in organic chemistry; thin-layer chromatography (TLC; see/read Mohrig) is the most commonly used technique for doing this. You may be wondering, "How much $NaBH_4$ should I use?" In theory each of the four hydrides in $NaBH_4$ is available to reduce a molecule of ketone. In other words, one mole of $NaBH_4$ can, in principle, reduce four moles of ketone. In practice, chemists often use at least two equivalents of hydride ion per ketone carbonyl group when using this reagent.

You may be wondering, "On what scale should I perform this reaction?" Use ~300 mg (~0.3 g) of the 3-nitroacetophenone as the substrate for your first reduction and perform the reaction in ethanol – the reaction solvent or medium – at ambient (aka "room") temperature. You may be wondering, "How much solvent should I use – a drop, 5 gal, …?" The initial concentration of your substrate in the alcohol solvent should be ~0.25 M. You may be wondering, "How will I get my product away from the solvent and inorganic byproducts from the $NaBH_4$?" You will need to devise a "workup" procedure. Initial removal of the majority of the alcohol solvent on the rotary evaporator will aid in a subsequent partitioning between water and diethyl ether in an extractive (see/read Mohrig) work-up. The product alcohol **1a** should be purified by simple flash column chromatography (see/read Mohrig) on silica gel.

You may be wondering, "How will I determine the structure of my product?" You will use GC-MS, IR, and NMR analyses to characterize the principal product(s) of each of your reactions.

Once you have successfully reduced 3-nitroacetophenone, perform a similar reduction reaction, this time using 9*H*-fluoren-9-one as the substrate (aka starting material or reactant). Perform this reduction using ca. 2.5 mmol of the ketone in methanol solution in a 0 °C cooling bath. Again, monitor the reaction progress by tlc (see Mohrig), workup the reaction mixture, and record the crude mass recovery [remember to tare* in advance the flask in which you put your dried ether extraction solution prior to removing the solvent on a rotary evaporator]. Record the mass of the organic material you obtain following the extraction (i.e, the crude mass recovery). Purify this crude product, which should be a solid, by a small-scale recrystallization (see/read Mohrig). Place most of the crude solid into a tared, 25 mL round-bottomed flask (RBF). Weigh the exact amount you have transferred into the flask. Preheat/equilibrate a beaker of water, large enough to accept the RBF, on a hot plate to ca. 85 °C. Add ca. 5-7 mL of hexanes, a non-polar solvent, into the RBF and immerse it in the water bath. The contents will soon be boiling. If you dally at this point, increasing amounts of the hexanes will boil away. Plan ahead to have reached the saturation point by addition of EtOAc to the hot mixture (see more details below) in, say, ≤10 minutes. Use of a wooden "applicator stick" that contacts the bottom of the slurry (or suspension) will allow for smooth boiling as well as provide a means to break up chunks of the solid to help increase surface area of the solid and speed up the rate of dissolution. Not all of the solid will dissolve because there is not enough hexanes to reach the saturation concentration (hexanes is not a particular good solvent for dissolving the polar alcohol **1b**). Now add ethyl acetate (EtOAc) *dropwise* to the hot suspension. You should be able to observe a slow, progressive reduction in the amount of solid; EtOAc is a very good solvent for **1b** and you are increasing the polarity of this, now, mixed solvent system. Keep adding, slowly, EtOAc until the last bit of solid goes into solution. The goal of this is to have 'sneaked up' on the saturation

concentration at the boiling point of the solvent mixture. Take care to not allow a significant portion of the hexanes to boil away; if so, replenish a bit of the hexanes. Remove the flask from the heating bath and allow it to stand and cool to room temperature. Crystals of **1b** should grow because the compound is less soluble at lower temperature. Allow this mixture to stand for at least an hour; overnight is fine, although place a yellow plastic cap-plug (or glass stopper) gently on the opening of the flask to prevent evaporation of a significant portion of the solvent. To isolate your solid, you can either: a) carefully draw off the supernatant solvent with a pipet, leaving all of the solid in the flask (the TAs can show you how to use a pipet pulled to a capillary to make a finer diameter tip, if you like) or b) use a vacuum filtration through a Hirsh funnel, although this is less favorable in my mind because of inherent inefficiency due to inevitable mechanical loss, especially so on a small-ish scale. Allow the solid, now freed of all bulk solvent, to air dry overnight. Weigh the recovered solid (you did tare and record the mass of the flask in your notebook at the outset, didn't you !?!). This represents your yield of purified product. Provide the yields of both crude and purified material in your lab report. Collect the full battery of spectral data (MS, IR, NMR) on this purified sample. Also, record its melting point (mp). Always observe and record a *temperature range* when taking a melting point. The range (from initial softening of the sample to final disappearance of all of the crystals) reflects the purity of the sample.

For the 9-fluorenol product, I recommend that you submit your purified product as two different samples, one dissolved in $CDCl_3$, the other in DMSO-d_6. You should see some differences in these two spectra that will help in the interpretation and assignment of the resonances.

There are reports that the alcohol **1b** is susceptible to air (more specifically, O_2) oxidation back to the ketone. 2018 was the first year we made this product, and we have not observed any difficulties associated with the oxidative instability of **1b**.

* "tare weight" = "unladen weight" from shipping; "to tare" means to determine the mass of a container prior to adding contents.

NMR spectral data files of a related ketone: We have recorded the proton (at 500 MHz) and carbon (at 125 MHz) NMR spectra of a related 1,3-disubstituted benzene derivative: namely, 3-chloroacetophenone. The file names are:

3-Chloroacetophenone-1H-proton
3-Chloroacetophenone-13C-carbon

I will email these to you in a zipped file (that turns out to be the easiest way to deliver them – they are not large, there are just many small but necessary files in each of the two folders to maintain the integrity of the data). These data will help you answer several of the Questions on the following page.

You need to have downloaded and installed onto your computer the application **MNova**, which we will use to process NMR data throughout the term. As a reminder and if not, go to one of the following files on the 2312H website: Installation Instructions for Mnova - Mac - 2022.txt (for Mac) or Installation Instructions for Mnova - Windows - 2022.txt for installation instructions. You should also read the information in the "NMR Data Retrieval Guidelines" PDF on the website.

Provide answers to the following questions at the end of your lab report for this experiment (Report #1):

Questions:

1. What would be the TLC (on silica gel) relative retention factor (R_f) values for the following compounds: cyclohexanone, cyclohexanol, 2,2-dimethylcyclohexanone? List them from lowest R_f (most polar) to highest R_f (least polar). Why (briefly)?

2. What are the boiling points (in °C) of toluene, 1-hexanol, *p*-xylene, and acetophenone at one atmosphere of pressure (aka the atmospheric boiling point)? Which of these four would you predict to have the shortest and which the longest retention time on a gc column coated with a 5%-phenyl silicone liquid phase (like the HP-5 column in our GC-MS instrument in 491 Kolthoff)?

3. How many unique proton resonances do you expect to see in the ^{1}H NMR spectrum of each of the ketones 3-chlorotoluene, benzophenone, and benzaldehyde?

4. Describe (briefly) the concept of monitoring the reduction of a ketone to its alcohol by TLC. Include in your description the concept of co-spotting for TLC analysis. Discuss (briefly) how you might deduce the half-life ($t_{1/2}$) for this reaction by monitoring the reaction by GC. [Hint: this involves taking aliquots of the reaction mixture and analyzing their contents over time.]

5. What would the product of reduction of 1-indanone (look up its structure) be if you used the deuterated reducing agent $NaBD_4$ in CH_3OH solvent? Draw each of the two enantiomers of this chiral molecule and label each as having the *R* or the *S* absolute configuration.

6. What would you obtain if you treated 3-methylphenol (*m*-cresol) with an excess of deuterium oxide (D_2O)?

7. Assign the resonances for each of the four aromatic protons in the ^{1}H NMR spectrum of 3-chloroacetophenone.

8. How many carbon resonances are there in the ^{13}C NMR spectrum of 3-chloroacetophenone? Why are two of the six resonances for the aromatic carbons less intense than those of the other four?

9. Explain the change in color of the reaction mixture you observed during the reduction of 9*H*-fluoren-9-one with $NaBH_4$.

10. What macroscopic observation, easily seen with the human eye, could you make to judge whether the air oxidation of alcohol **1b** is occurring?