

The Discovery-Oriented Approach to Organic Chemistry.

6. Selective Reduction in Organic Chemistry: Reduction of Aldehydes in the Presence of Esters

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Experimental Overview

Chemoselective reductions are valuable in organic synthesis and are routinely discussed in a sophomore organic chemistry course. Yet, there are few examples of laboratory experiments that illustrate such chemoselectivity. A reaction that is routinely discussed in sophomore organic chemistry is the selective reduction of aldehydes and ketones using sodium borohydride. Esters are typically not affected by NaBH_4 . However, none of the lab experiments reported to date illustrate this chemoselectivity (1). We have developed a discovery-oriented lab experiment that illustrates the chemoselective nature of reductions using sodium borohydride. The experiments involve the reduction of vanillin acetate (Scheme I) and methyl 4-formylbenzoate (Scheme II), using sodium borohydride, followed by product identification using ^1H and ^{13}C NMR spectroscopy. Product identification is also achieved by classical qualitative functional group tests. Hence, this lab can be easily incorporated by departments that do not have access to an NMR spectrometer. The added element of discovery ensures that student interest and enthusiasm are retained (2). Products obtained are of sufficient purity to allow analysis by spectroscopy without further purification.

The entire reaction including work up takes about two hours. With the use of sufficient sample (ca. 100 mg), both ^1H and ^{13}C NMR spectra can be easily obtained in 15 minutes. Analysis of ^1H and ^{13}C NMR spectra of the products clearly indicates which functional group, the aldehyde or ester is reduced. Reaction progress can be easily followed by thin-layer chromatography. This also serves as a good exercise to illustrate the use of TLC techniques in monitoring reaction progress. Both the starting materials and products are UV active and hence spots on the TLC plate can be visualized under UV light. The starting materials contain an aldehyde group while the expected product does not. The absence of an aldehyde group in the product is easily shown by spraying the TLC plate with 2,4-dinitrophenylhydrazine, (2,4-DNP). TLC identification in this manner is much more convenient and desirable than the classical 2,4-DNP test as the latter results in waste production in the form of derivatives. The presence of the ester functionality in both the starting material and the product is confirmed by the hydroxylamine test.

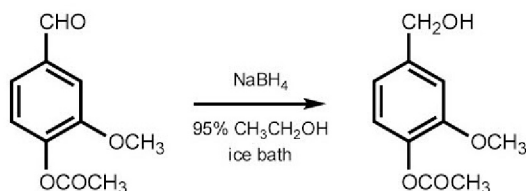
Students answer the following questions pertaining to the NMR spectra of the products and classical qualitative tests:

- Is there a peak for aldehyde hydrogens in the ^1H NMR spectrum? Aldehyde carbon in the ^{13}C NMR spectrum? How many carbonyl carbons are present in the ^{13}C NMR spectrum? (The expected aldehydic hydrogen peak and aldehydic carbon peak are no longer present in the product, indicating that the aldehyde has been reduced.)
- Is there a peak for the ester methyl group? (Both ^1H and ^{13}C NMR spectra indicate that the ester group is still intact.)
- Which compound(s), starting material or the product, or both, give a colored spot with the 2,4-DNP reagent?
- Which compound(s), starting material or the product, or both, test positive (formation of burgundy color) for an ester in the hydroxylamine test?

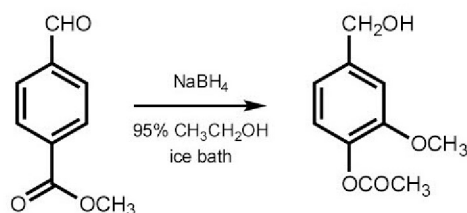
Experimental Section and Results

Chemicals and Instruments

^1H and ^{13}C NMR spectra were recorded on a JEOL NMR spectrometer at 270 MHz and 67.5 MHz, respectively. All chemicals used were reagent grade and were used as ob-



Scheme I. Reduction of vanillin acetate.



Scheme II. Reduction of methyl 4-formylbenzoate.

tained. Although vanillin acetate is commercially available, it was easily synthesized from vanillin by treatment with acetic anhydride. Methyl 4-formylbenzoate was purchased from Aldrich Chemical Co.

Reduction of Vanillin Acetate

A solution of vanillin acetate (0.5040 g, 2.596 mmol) in 95% ethanol (3.0 mL) was cooled in an ice bath and then NaBH_4 (0.2959 g, 7.822 mmol) was added in small portions over 5 minutes. The reaction mixture was stirred for 15 minutes while being cooled in the ice bath. TLC (ethyl acetate/hexane, 40:60, v/v) indicated that the reaction was complete. Water (10 mL) was added and the resulting mixture was stirred in the ice bath for an additional 2 minutes. The mixture was extracted with ether (2×15 mL) and the combined organic layers were washed with H_2O (10 mL) and saturated NaCl solution (15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed using a hot water bath to give 0.1785 g (35%) of the product as a viscous oil.

^1H NMR (270 MHz, CDCl_3 , δ): 2.26 (s, 3H, COCH_3), 3.1 (OH, broad), 3.73 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2O), 6.79–6.94 (m, 3H, aromatic).

^{13}C NMR (67.5 MHz, CDCl_3 , δ): 20.5, 55.6, 64.3, 110.8, 118.7, 122.4, 138.6, 140.1, 150.8, 169.3.

Reduction of Methyl-4-formylbenzoate

A solution of methyl-4-formylbenzoate (0.3288 g, 2.003 mmol) in 95% ethanol (3.0 mL) was cooled in an ice bath and then NaBH_4 (0.2292 g, 6.059 mmol) was added in small portions over two minutes. The reaction mixture was stirred for 15 minutes while being cooled in the ice bath. TLC (ethyl acetate/hexane, 40:60, v/v) indicated that the reaction was complete. Water (10 mL) was added and the resulting mixture was stirred in the ice bath for an additional 2 minutes. The mixture was extracted with ether (2×15 mL) and the combined organic layers were washed with H_2O (10 mL) and saturated NaCl solution (15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed using a hot water bath to give 0.1981 g (60%) of a white solid.

^1H NMR (270 MHz, CDCl_3 , δ): 2.33 (2 H, s, OH), 3.88 (3 H, s, COOCH_3), 4.72 (2 H, s, CH_2O), 7.39 (2 H, d, $J = 8.2$ Hz), 7.97 (2 H, d, $J = 8.2$ Hz).

^{13}C NMR (67.5 MHz, CDCl_3 , δ): 52.1, 64.5, 126.4, 129.1, 129.7, 146.0, 167.0.

Representative Procedure for Ester Test

The starting material or the product (ca. 50 mg), an equal quantity of hydroxylamine hydrochloride, a few drops of 95% ethanol and a pellet of solid KOH were placed in a large test tube and the mixture was heated to boiling using a Bunsen burner. (Caution: As soon as the ethanol starts to boil, the test tube must be removed from the burner and

cooled until the boiling subsides). This process was repeated eight times and then the test tube was cooled to room temperature. The mixture was made acidic using 2 mL of 4 M HCl and then a drop of 0.6 M aqueous FeCl_3 was added. A burgundy color was obtained confirming the presence of an ester group.

Hazards

Ether vapor is harmful and inhalation should be avoided. Ether is highly flammable and hence no flames should be present when ether is being used. Sodium borohydride can react violently with acids and hence all contact with acids should be avoided. 2,4-DNP reagent is toxic and all skin contact should be avoided. Hydroxylamine hydrochloride is toxic and hence skin contact should be avoided. Ethanol is flammable and toxic. Inhalation should be avoided.

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^WSupplemental Material

Notes for the instructor and NMR spectra are available in this issue of *JCE Online*.

Literature Cited

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