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Synthesis of *p*-Nitroaniline *via* a Multi-Step Sequence

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Contents

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Objectives

The principal aims of these experiments are to provide experience in the synthesis, isolation, purification and characterisation of simple aromatic compounds. In particular, you will study aromatic substitution reactions in which functional groups greatly influence further substitution of monosubstituted benzenes. The main characterisation technique utilised in these experiments is ^{1}H NMR spectroscopy using the benchtop Spinsolve NMR spectrometer.

Introduction

Nitroanilines are important chemical intermediates in the manufacture of dyes.[1] In this series of experiments, you will synthesise *p*-nitroaniline (Figure 1) *via* a multi-step sequence.* This particular compound is used in the synthesis of the azo dye Para Red.[2] The synthetic sequence to prepare *p*-nitroaniline from acetophenone involves the transformation of one functional group on a monosubstituted benzene into another through chemical reactions, then performing an electrophilic aromatic substitution reaction to obtain the target compound. The various compounds prepared will be characterised by ^{1}H NMR spectroscopy.

*** In these experiments, *ortho*, *meta* and *para* (omp) nomenclature is used to indicate the substituent position in disubstituted benzenes in place of IUPAC (systematic) nomenclature.**

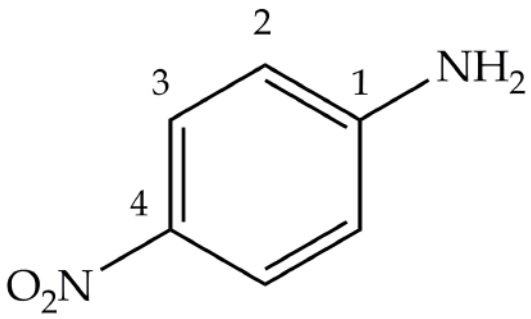


Figure 1. *p*-Nitroaniline.

Synthesis of acetophenone oxime

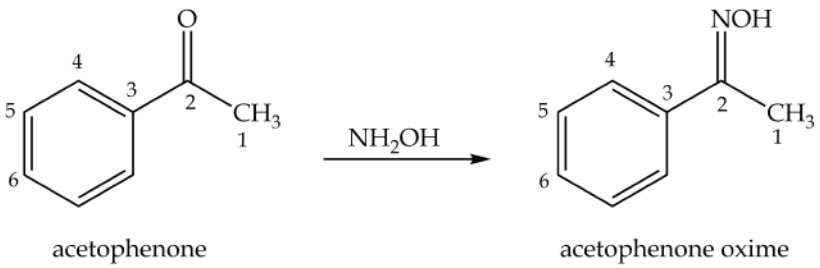
The first step in the synthesis of *p*-nitroaniline is the preparation of acetophenone oxime from acetophenone (Scheme 1). Oximes are highly crystalline compounds that feature a carbon-nitrogen double bond, with an OH group on the nitrogen atom (>C=N–OH).[3] They are used extensively in synthetic organic chemistry for the protection, purification and characterisation of carbonyl compounds.[4] Oximes are also versatile building blocks for the synthesis of nitrogen-containing compounds.[3]

Safety

Ethanol is flammable; handle with care. Acetophenone, sodium acetate trihydrate ($CH_3COONa.3H_2O$) and acetophenone oxime are irritating to the skin, eyes and respiratory system. Avoid contact and do not ingest or inhale. Hydroxylamine hydrochloride ($NH_2OH.HCl$) is corrosive, avoid all contact and handle with caution. Deuterochloroform ($CDCl_3$) is toxic, handle with care.

Procedure

To a solution of water (30 mL) and ethanol (10 mL) in a 100 mL round bottom flask, add acetophenone (3.75 mL), hydrated sodium acetate crystals (7.50 g) and hydroxylamine hydrochloride (3.75 g). Heat the reaction mixture with stirring on a hot water bath for 10 min (Figure 2). Colourless oil droplets should form on top of the solution. Cool the mixture in an ice bath for 30 min, during which time the oil should solidify. If necessary, induce crystallisation by scratching the sides of the flask with a glass rod. Collect the white solid by filtration, wash with cold water and dry in the air. Recrystallise the crude product from boiling water (60 mL),[5] making sure that all oil droplets have dissolved. Filter and dry the purified product, and record your yield (Figure 3).



Scheme 1. Synthesis of acetophenone oxime.

Figure 2. Experimental setup for the synthesis of acetophenone oxime.

Figure 3. Purified acetophenone oxime.

Tasks & Questions

- Calculate the theoretical and percentage yields of acetophenone oxime.
- Record the ^{1}H NMR spectra of acetophenone and acetophenone oxime using the Spinsolve NMR spectrometer. Prepare the NMR samples using 1 drop of acetophenone and 30 mg of acetophenone oxime in 0.6 mL of $CDCl_3$ each.
- Record and assign the IR spectra of acetophenone and acetophenone oxime.
- Record the melting points of acetophenone and acetophenone oxime.
- Assign the ^{1}H NMR spectra of acetophenone and acetophenone oxime.
- Give a mechanism for the transformation of acetophenone into acetophenone oxime.
- Why is sodium acetate used in the reaction?
- Show how acetophenone oxime can exist as geometric stereoisomers.

^{1}H NMR Spectra

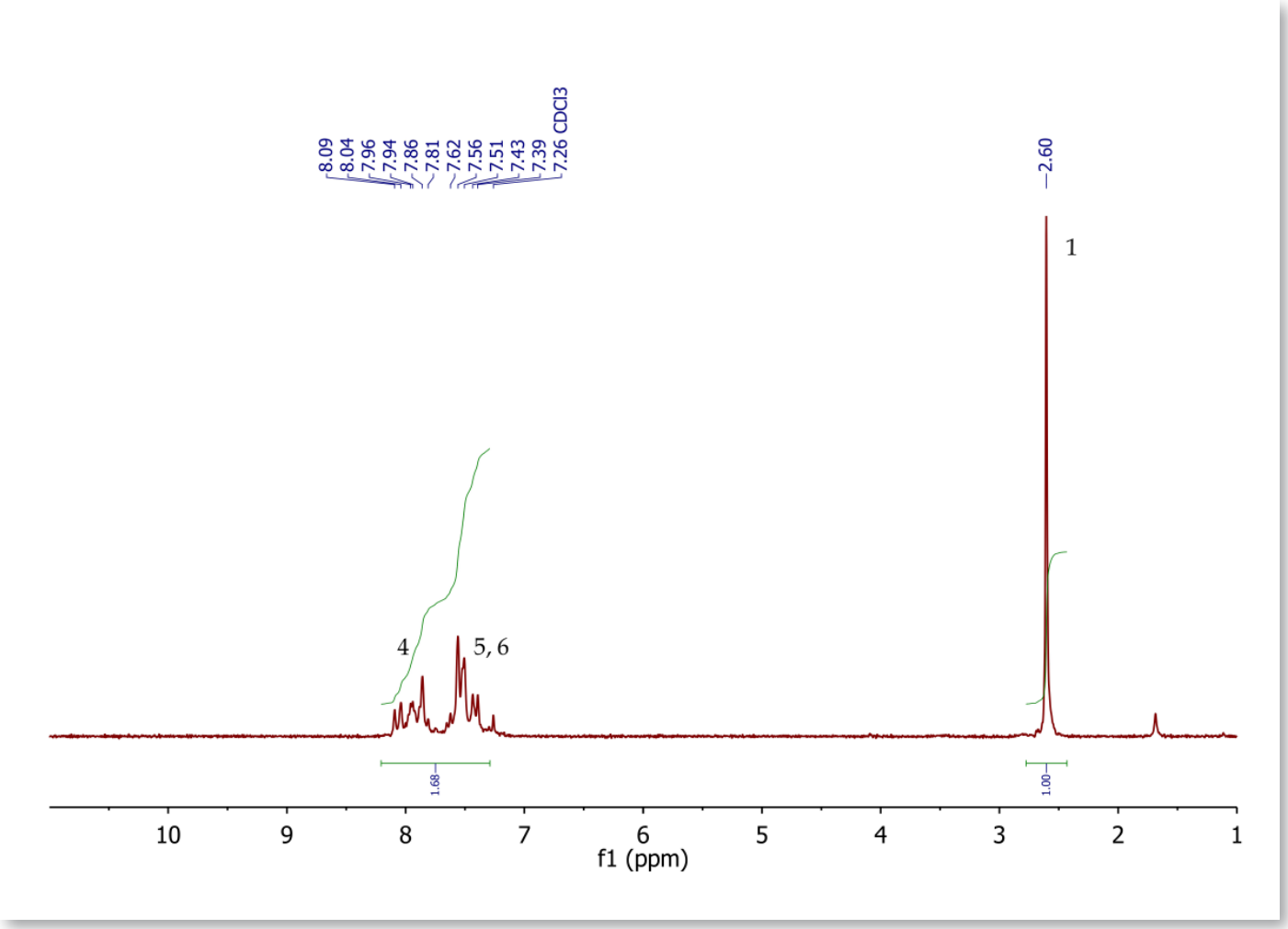


Figure 4. ^{1}H NMR spectrum of acetophenone, $CDCl_3$.

The ^{1}H NMR spectrum of acetophenone (Figure 4) shows a singlet (3H) at 2.60 ppm, corresponding to the methyl group at position 1. The five aromatic protons at positions 4, 5 and 6 resonate as a multiplet between 7.39-8.09 ppm.

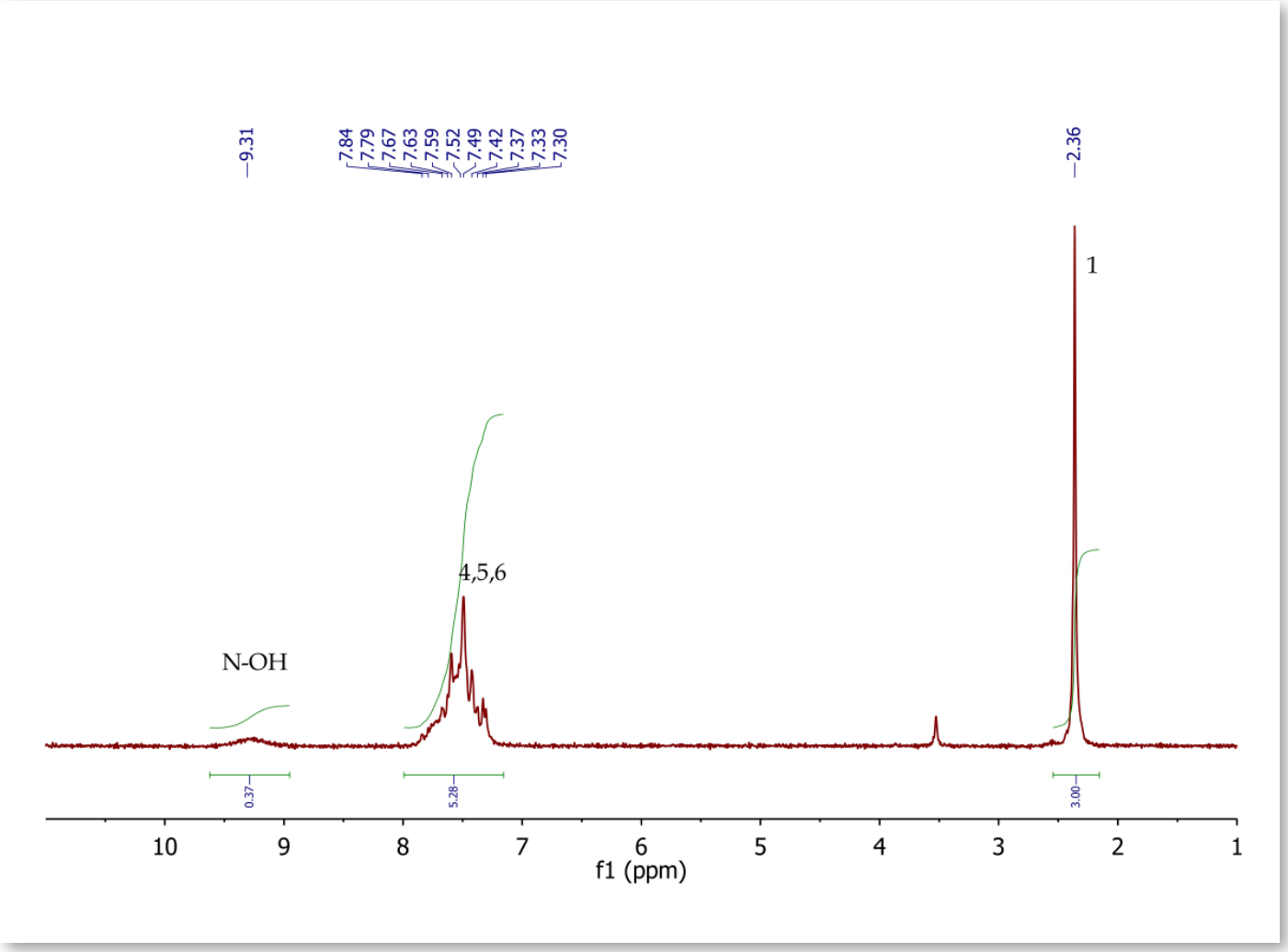


Figure 5. ^{1}H NMR spectrum of acetophenone oxime, $CDCl_3$.

The ^{1}H NMR spectrum of acetophenone oxime (Figure 5) shows a singlet (3H) at 2.36 ppm, corresponding to the methyl group at position 1. The five aromatic protons at positions 4, 5 and 6 resonate as a broad multiplet between 7.30-7.84 ppm. The exchangeable NOH proton is observed at 9.31 ppm as a broad singlet with a low peak integration value.

Synthesis of acetanilide: the Beckmann rearrangement

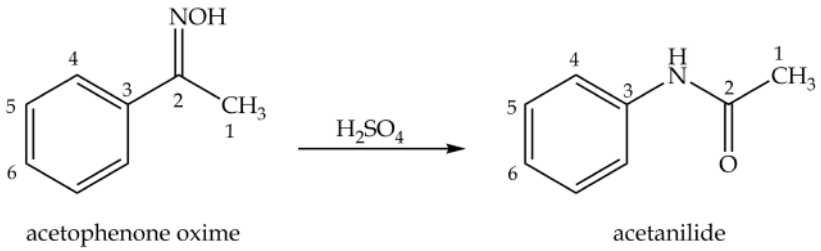
The second step in the synthesis of *p*-nitroaniline is the preparation of acetanilide from acetophenone oxime (Scheme 2). In the presence of strong acids, oximes can undergo molecular rearrangement to form amides *via* the Beckmann rearrangement.[3] This isomerisation reaction provides a powerful synthetic method to efficiently incorporate a nitrogen atom into compounds.

Safety

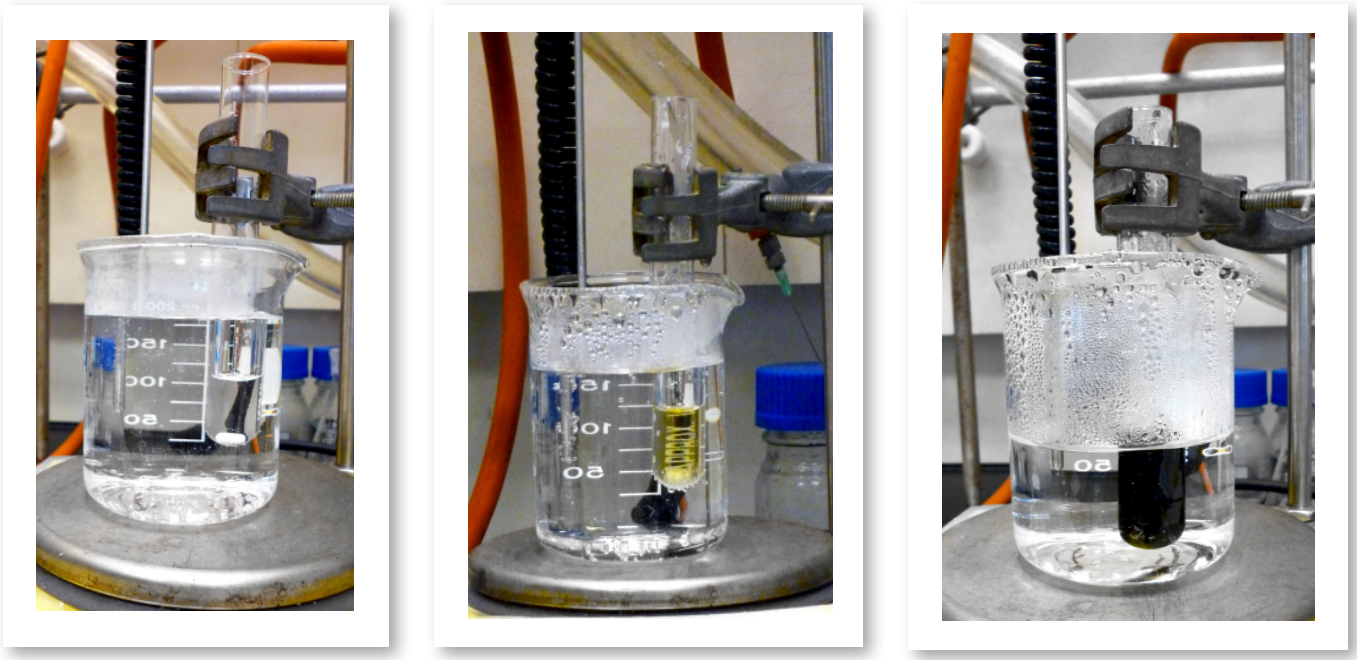
Sulfuric acid is highly corrosive; use with caution and perform the experiment in a fume hood with the protective glass door pulled down. Acetanilide is an irritant, handle with care.

Procedure

Place concentrated sulfuric acid (3 mL) in a boiling tube and heat in a hot water bath until the temperature of the acid reaches approximately 90 °C. Add acetophenone oxime (3 g) in small portions with stirring over a period of 20 min. Heat and stir the reaction mixture for a further 15 min (Figure 6). Pour the cool mixture onto crushed ice (50 g) to precipitate the title compound. Collect the solid by filtration and wash with cold water. Recrystallise the crude product from 50 mL of water and record your yield (Figure 7).

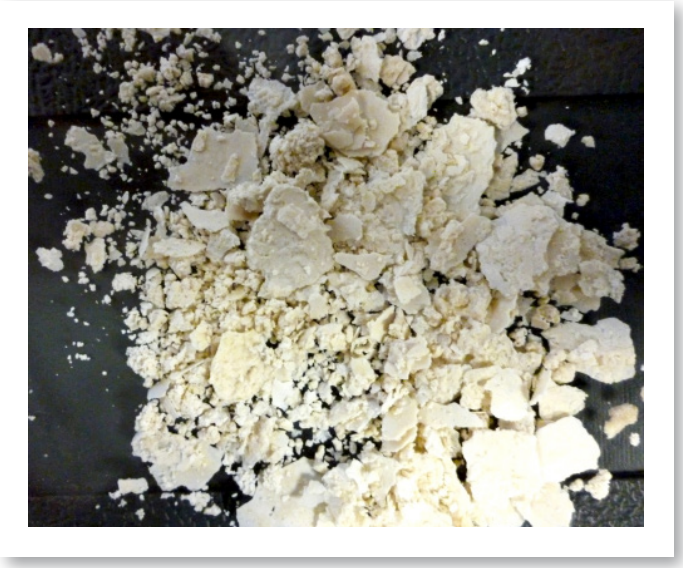


Scheme 2. Synthesis of acetanilide.



(a) (b) (c)

Figure 6(a)-(c). Reaction mixture colour changes observed during the synthesis of acetanilide.



(a)

(b)

Figure 7(a)-(b). Crude and recrystallised acetanilide.

Tasks & Questions

- Calculate the theoretical and percentage yields of acetanilide.
- Record the ^{1}H NMR spectrum of acetanilide using the Spinsolve NMR spectrometer. Prepare the NMR sample using 30 mg of acetanilide in 0.6 mL of $CDCl_3$.
- Record the IR spectrum of acetanilide.
- Record the melting point of acetanilide.
- Assign the IR and ^{1}H NMR spectra of acetanilide.
- Give a mechanism for the transformation of acetophenone oxime into acetanilide.

^{1}H NMR Spectra

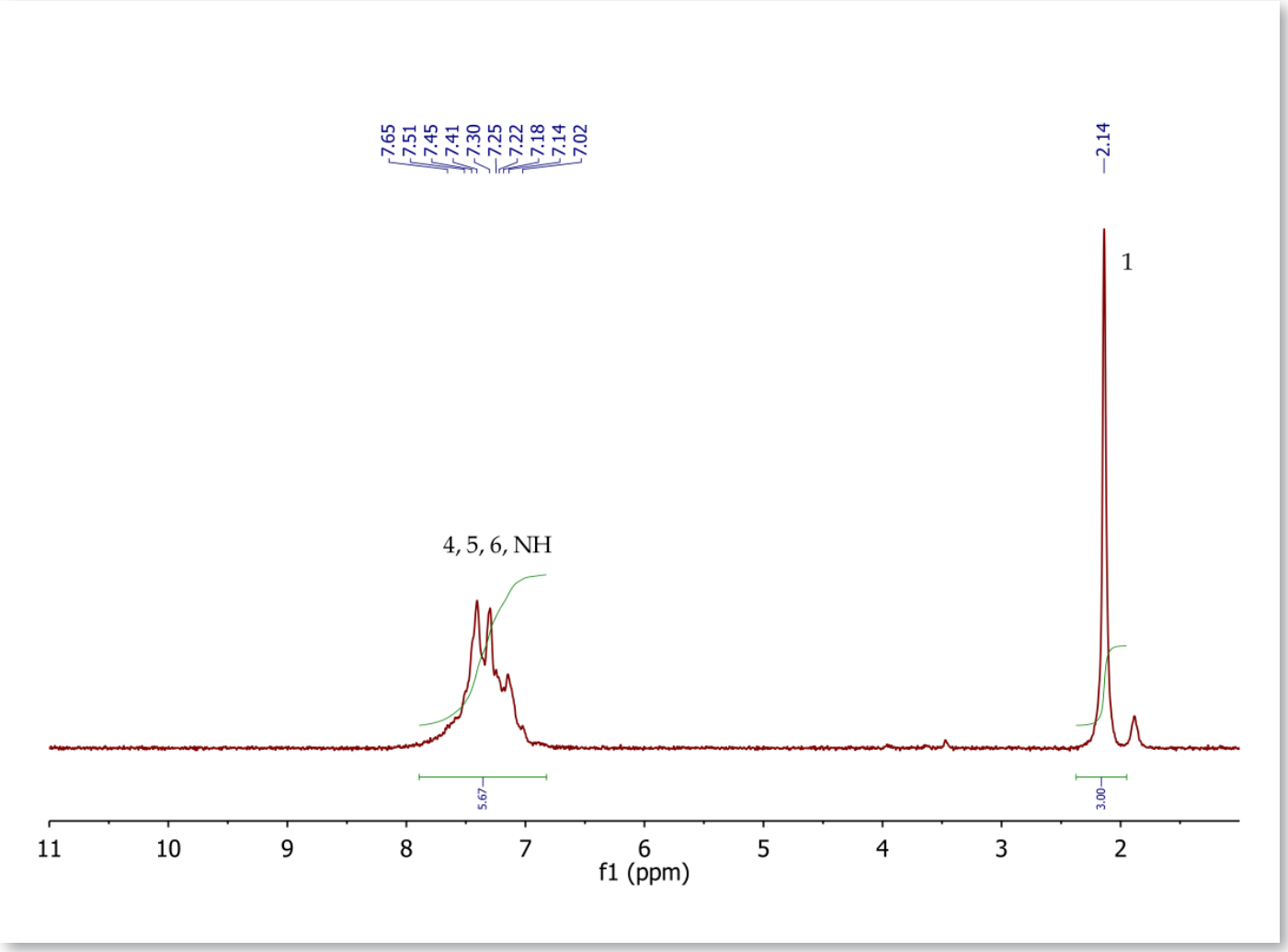


Figure 8. ^{1}H NMR spectrum of acetanilide, $CDCl_3$.

The ^{1}H NMR spectrum of acetanilide (Figure 8) shows a singlet (3H) at 2.14 ppm, corresponding to the methyl group at position 1. The five aromatic protons at positions 4, 5 and 6 resonate as a broad multiplet between 7.02-7.65 ppm. The signal for the exchangeable NH proton may also be overlapping with the multiplet as suggested by the peak integration value.

Nitration of acetanilide

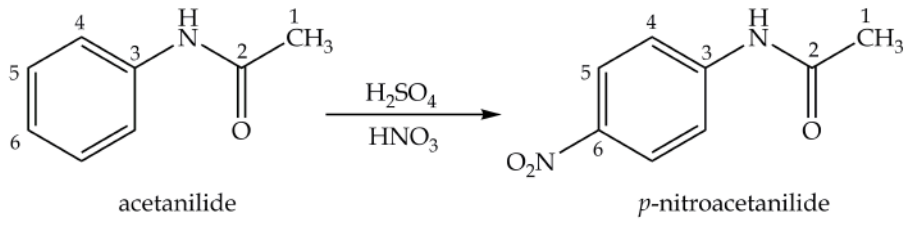
The third step in the synthesis of *p*-nitroaniline is nitration of acetanilide using a mixture of concentrated sulfuric and nitric acids to obtain nitroacetanilide (Scheme 3). In this electrophilic aromatic substitution reaction, the acetamido group (–$NHCOCH_3$) directs the nitronium ion ($^+NO_2$) to the *ortho* and *para* positions of the aromatic ring.[6] Thus, nitration of acetanilide principally produces *ortho*- and *para*-nitroacetanilides, with the *para* compound being the major product. Separation of the *ortho*- and *para*-nitroacetanilides is achieved by recrystallistion from ethanol. The colourless major product, *p*-nitroacetanilide, is almost insoluble in ethanol and can be filtered out, while the yellow *ortho* isomer remains in the filtrate.

Safety

Fuming nitric acid, sulfuric acid and glacial acetic acid are highly corrosive, use with caution and perform the experiment in a fume hood with the protective glass door pulled down. *p*-Nitroacetanilide is an irritant, avoid contact with skin, eyes and clothing. Deuterated dimethyl sulfoxide (DMSO-d_6) is dangerous because it increases the permeability of the skin to other substances. Avoid all contact with skin and clothing.

Procedure

Place glacial acetic acid (1.5 mL) in a boiling tube and add 1.5 g of acetanilide. Stir the mixture and add concentrated sulfuric acid (3 mL). Cool the hot reaction mixture in an ice/salt bath until the temperature drops to about 0.5 °C. With stirring, slowly add fuming nitric acid (0.6 mL), making sure that the temperature does not rise above 20 °C. Once addition is complete, bring the reaction mixture to room temperature and allow to stand for 20 min. Pour the mixture onto ice (15 g) and allow to stand for a further 20 min. Collect the crude yellow solid by filtration, wash thoroughly with water and dry in the air. Recrystallise from the minimum amount of hot ethanol to obtain *p*-nitroacetanilide as a cream-coloured crystalline solid (Figure 9). Dry in the air and record your yield.



Scheme 3. Synthesis of *p*-nitroacetanilide.

(a) Crude *p*-nitroacetanilide

(b) Purified *p*-nitroacetanilide

Figure 9(a)-(b). Crude and recrystallised *p*-nitroacetanilide.

Tasks & Questions

- Calculate the theoretical and percentage yields of *p*-nitroacetanilide.
- Record the ^{1}H NMR spectra of acetanilide and *p*-nitroacetanilide using the Spinsolve NMR spectrometer. Prepare the NMR samples using 30 mg of each compound in 0.6 mL of DMSO-d_6.
- Record and assign the IR spectrum of *p*-nitroacetanilide.
- Record the melting point of p-nitroacetanilide.
- Assign the ^{1}H NMR spectra of acetanilide and *p*-nitroacetanilide.
- Give a mechanism for the formation of *p*-nitroacetanilide from acetanilide.
- Why is *o*-nitroacetanilide the minor product in this reaction?

^{1}H NMR Spectra

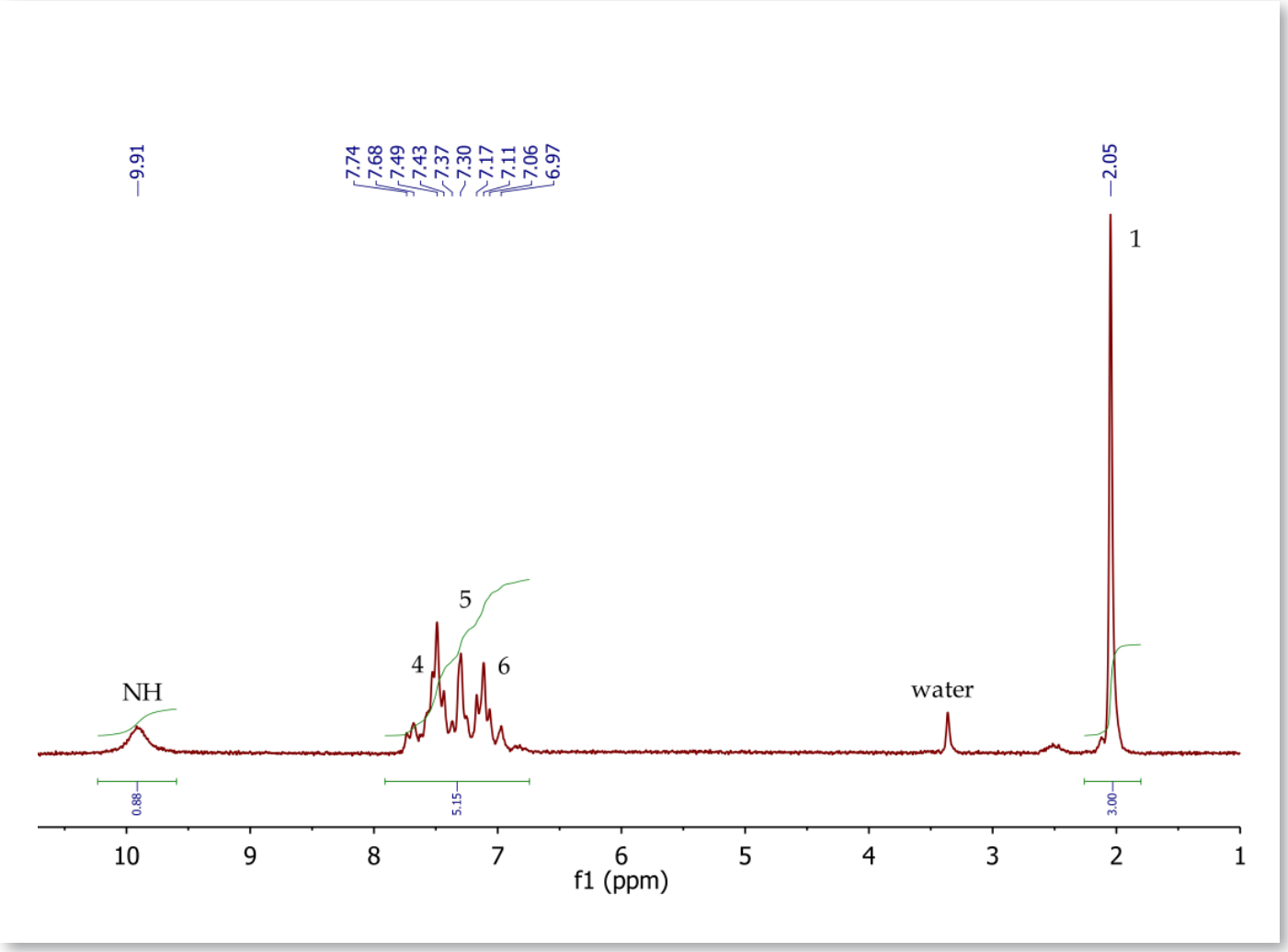


Figure 10. ^{1}H NMR spectrum of acetanilide, DMSO-d_6.

The ^{1}H NMR spectrum of acetanilide (Figure 10) shows a singlet (3H) at 2.05 ppm, corresponding to the methyl group at position 1. The five aromatic protons at positions 4, 5 and 6 resonate as a broad multiplet between 6.97-7.74 ppm. The exchangeable NH proton is also observed in DMSO-d_6 at 9.91 ppm as a broad singlet.

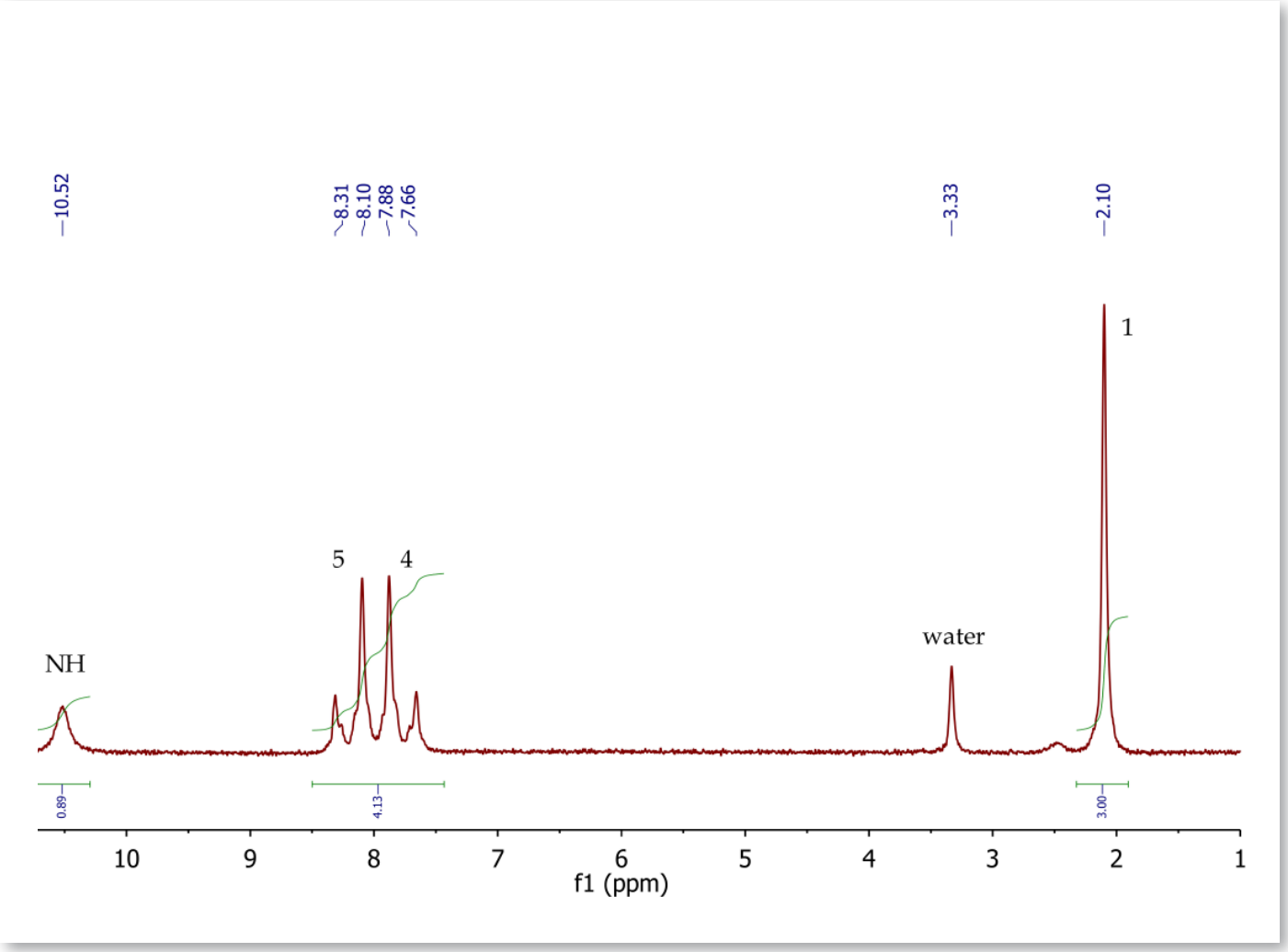


Figure 11. ^{1}H NMR spectrum of *p*-nitroacetanilide, DMSO-d_6.

The ^{1}H NMR spectrum of *p*-nitroacetanilide (Figure 11) shows a singlet (3H) at 2.10 ppm, corresponding to the methyl group at position 1. The four aromatic protons at positions 4 and 5 appear as a second order AA'BB' system, with two multiplets centred at 7.77 and 8.21 ppm. The exchangeable NH proton is observed at 10.52 ppm as a broad singlet.

Synthesis of *p*-nitroaniline

The final step in the synthesis of *p*-nitroaniline is the hydrolysis of *p*-nitroacetanilide under acidic conditions (Scheme 4).

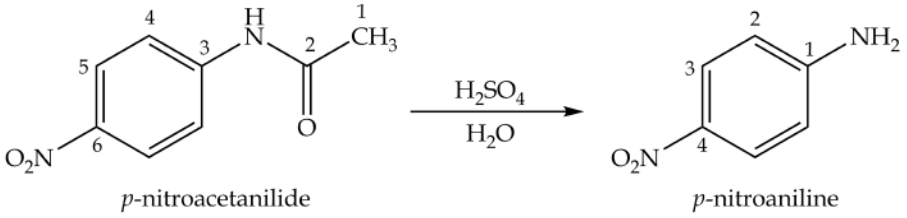
Safety

Perform the experiment in a fume hood with the protective glass door pulled down since corrosive sulfuric acid and sodium hydroxide solution are being used. *p*-Nitroaniline is toxic, avoid contact with skin, eyes and clothing and handle with care.

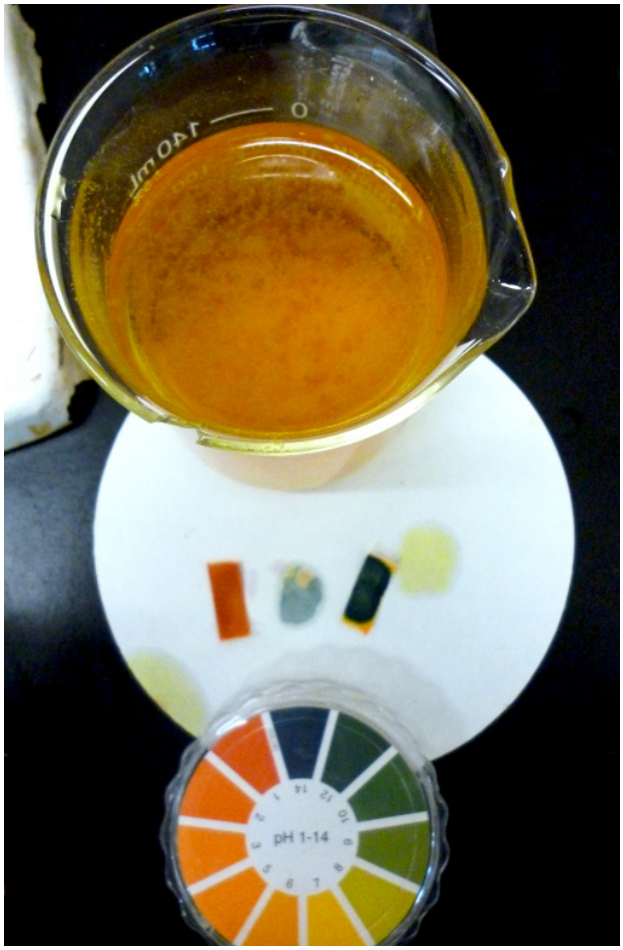
Procedure

Charge a 25 mL round bottom flask with a solution of concentrated sulfuric acid (4 mL) and water (3 mL).+ Add *p*-nitroacetanilide (0.7 g) and heat the reaction mixture gently under reflux for 20 min. Pour the hot mixture into cold water (20 mL), and adjust the pH of the solution with sodium hydroxide solution (2 M, approximately 120 mL) until alkaline and a yellow precipitate is obtained (Figure 12a-b). Cool the mixture in an ice bath. Collect the crude yellow solid by filtration (Figure 12c), wash thoroughly with water and dry in the air. Recrystallise from 1:1 ethanol/water mixture to obtain bright yellow crystals of the title compound (Figure 12d). Record your yield.

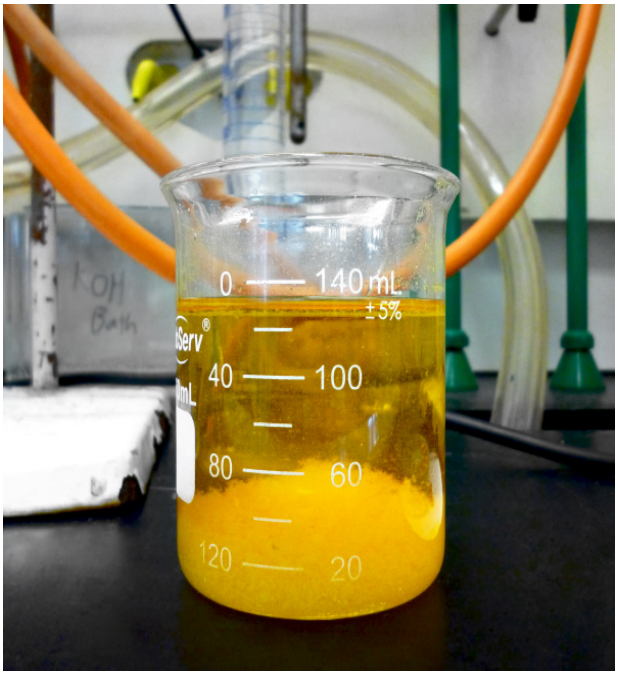
+ **Sulfuric acid reacts violently with water in an exothermic reaction. Prepare the solution by slowly adding the concentrated sulfuric acid to water.**



Scheme 4. Synthesis of *p*-nitroacetanilide.



(a) Alkaline reaction mixture



(b) Yellow *p*-nitroaniline precipitate

(c) Crude *p*-nitroaniline

(d) Purified *p*-nitroaniline

Figure 12(a)-(d). Precipitation and recrystallisation of *p*-nitroaniline.

Tasks & Questions

- Calculate the theoretical and percentage yields of *p*-nitroaniline.
- Record the ^{1}H NMR spectrum of *p*-nitroaniline using the Spinsolve NMR spectrometer. Prepare the NMR sample using 30 mg of *p*-nitroaniline in 0.6 mL of DMSO-d_6.
- Record the IR spectrum of *p*-nitroaniline.
- Record the melting point of *p*-nitroaniline.
- Assign the ^{1}H NMR and IR spectra of *p*-nitroaniline.
- Give a mechanism for the hydrolysis of p-nitroacetanilide to give *p*-nitroaniline.

^{1}H NMR Spectra

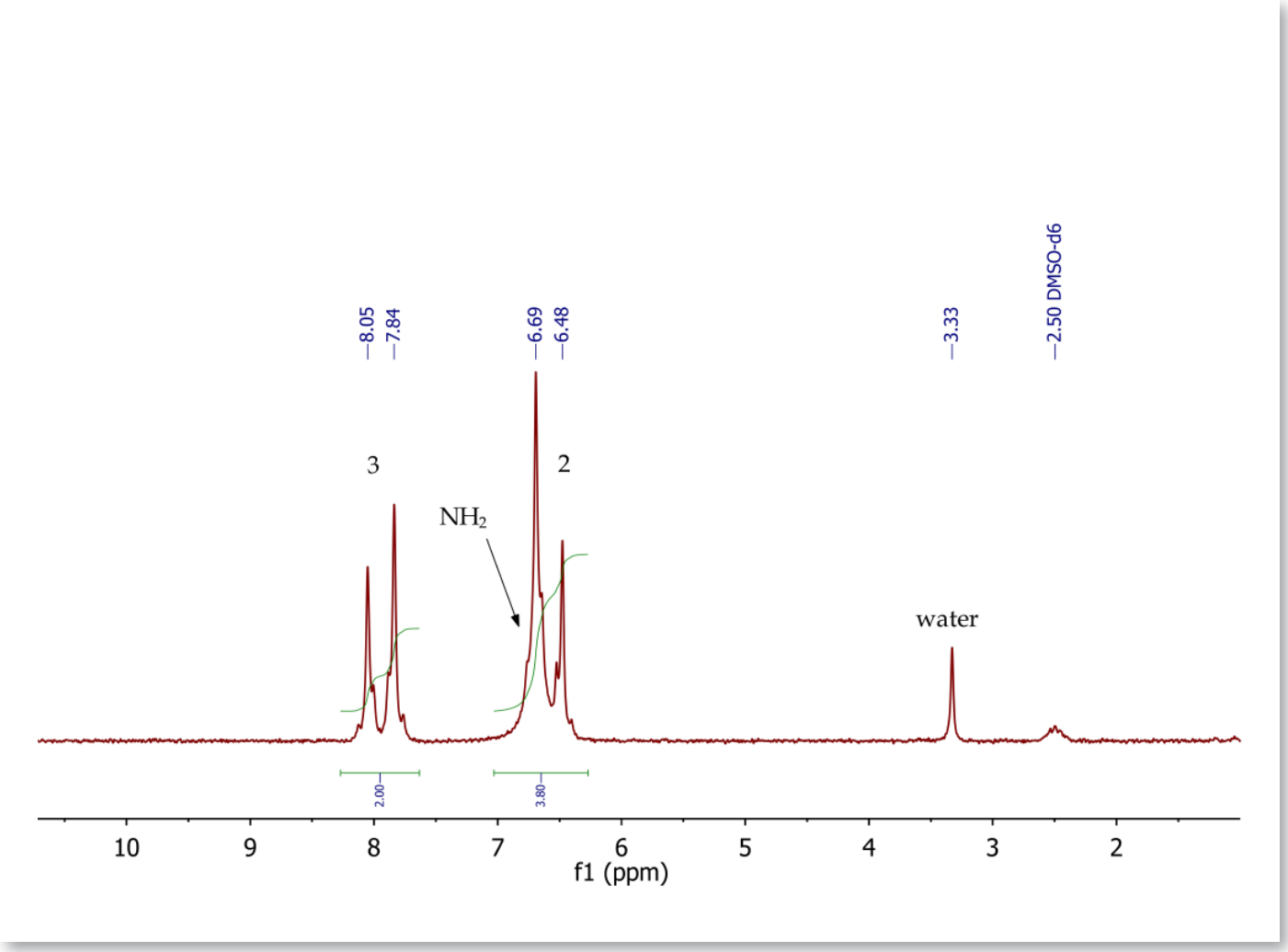


Figure 13. ^{1}H NMR spectrum of *p*-nitroanilide, DMSO-d_6.

The ^{1}H NMR spectrum of *p*-nitroacetanilide (Figure 13) shows two doublets at 6.59 and 7.95 ppm, corresponding to the four aromatic protons at positions 2 and 3 respectively. The signal for the exchangeable NH_2 protons is overlapping with the doublet at 6.59 ppm, as indicated by the 2:1 peak integration values.

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