Synthesis of Methyl orange

Supplementary Material

Students are often enthusiastic about the synthesis of a dye, since it is a kind of product that they contact daily. The synthesis of methyl orange has been performed since the 1960s by students from different courses and it is an excellent example to illustrate a diazo coupling, allowing them to understand reactivity and orientation in electrophilic aromatic substitution using diazonium salts as electrophiles. The experimental procedure is quite simple and ideal for first and second-years undergraduate students.

Additional notes on the preparation of methyl orange:

The described procedure[1] was adapted along the time. All heating steps can be made using a heating plate and stirring can be done manually. The test to detect the presence of free nitrous acid with potassium iodide-starch paper is always positive (dark brown spot) and it is not necessary to add any extra $NaNO_2$ solution. This step may be skipped if the instructor decides so. The acid (red) form of methyl orange (**SM 5.1.1.1**) gradually separates before addition of NaOH (aq.) that turns to a uniform orange color, due to the precipitation of the sodium salt of methyl orange. This alkaline solution also eliminates the possible phenol formed by conversion in the water soluble phenoxide anion.

SM 5.1.1.1: Acid (red) form of methyl orange before NaOH (aq.)

The product can be recrystallized from water, although unnecessary once the melting point is not measured. Methyl orange (**SM 5.1.1.2**) is obtained in an average yield of 50-60%.

SM 5.1.1.2: Vacuum filtration of methyl orange

Different colors for alkaline and acid aqueous solutions of methyl orange are shown in **SM 5.1.1.3**.

SM 5.1.1.3: Alkaline (left) and acidic (right) aqueous solutions of methyl orange

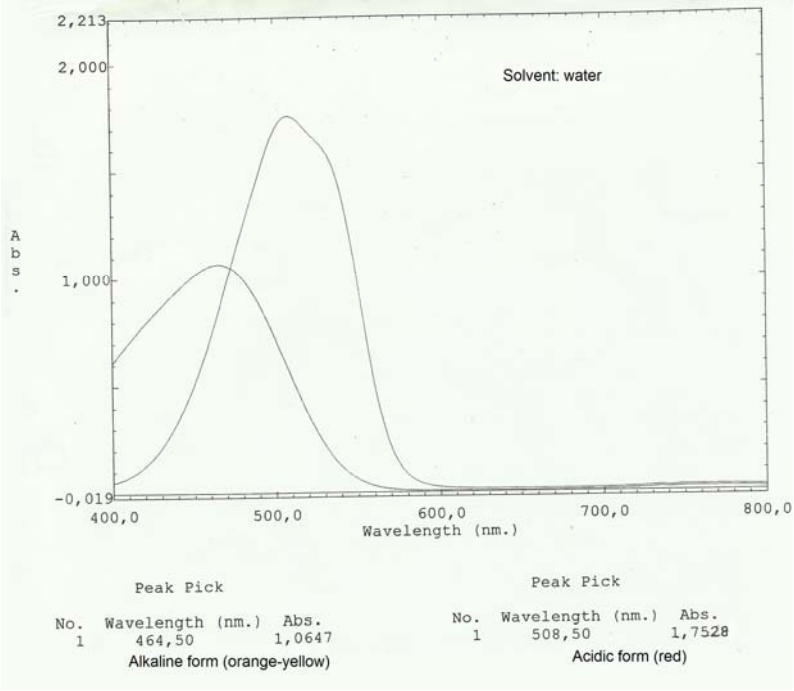
UV-vis spectrum (**SM 5.1.1.4**) was also recorded for both forms of the dye (alkaline and acidic) using water as solvent. Students can calculate the molar extinction coefficient (ε_{max}) according Lambert-

Beer's Law express as A = εbc, where: A = absorbance, ε = molar extinction coefficient, b = path length in cm (1.0 cm) and c = molar concentration (5.2×10^{-5} M).

Methyl Orange (alkaline form) ε_{max}= 2.05×10^4 $Lmol^{-1}cm^{-1}$

Methyl Orange (acidic form) ε_{max}= 3.37×10^4 $Lmol^{-1}cm^{-1}$

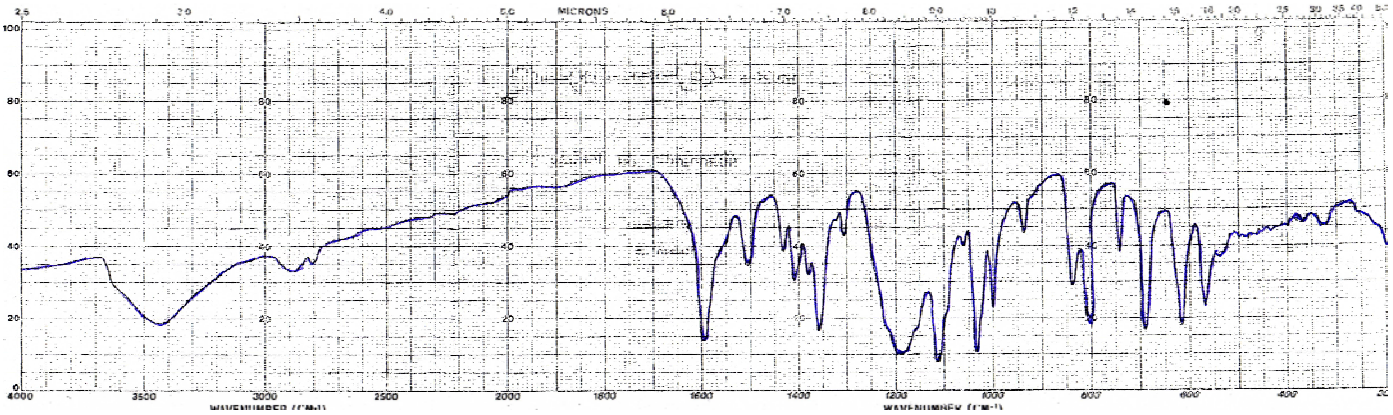
The results obtained by students are similar to the ones found in literature[2].



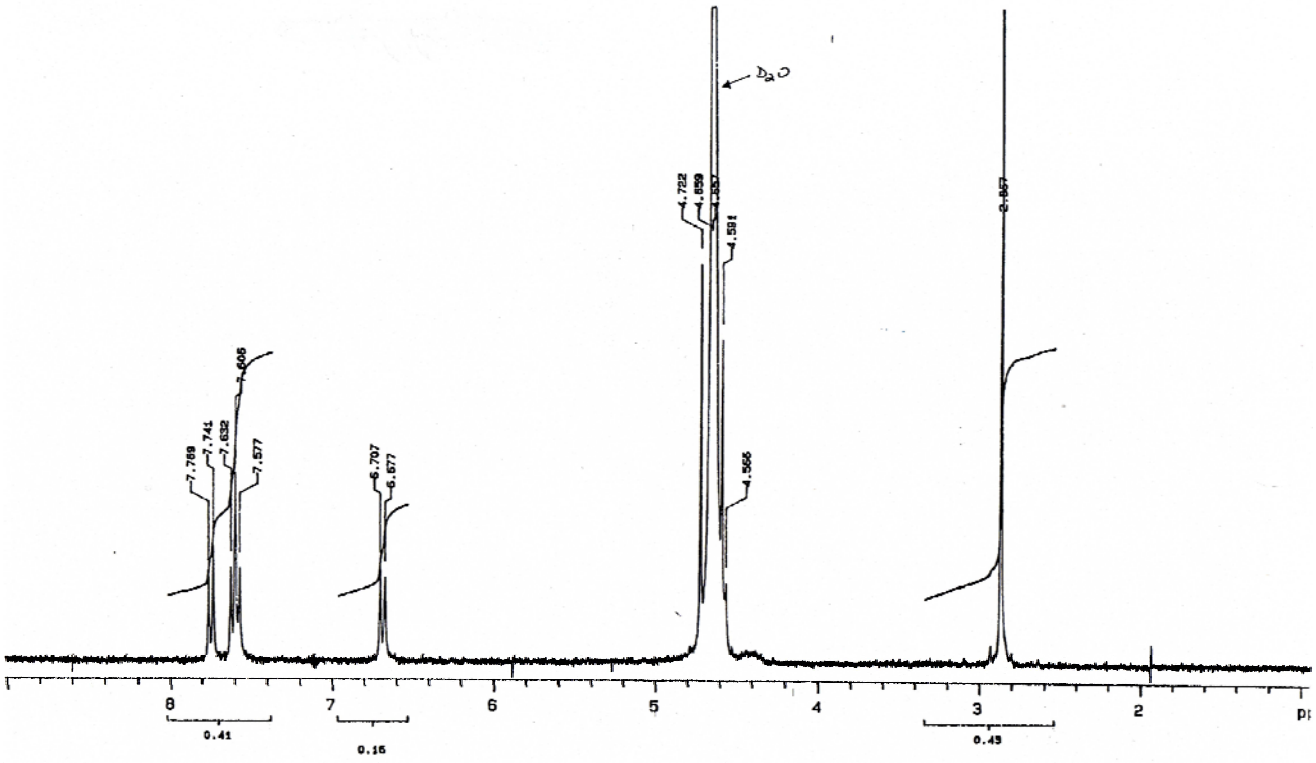
SM 5.1.1.4: UV-vis spectra of alkaline and acidic form of methyl orange (conc. 5.2×10^{-5} M) in water.

IR, ^{1}H NMR:

In the IR spectrum (**SM 5.1.1.5)** can be observed a broad absorption near 3400 cm^{-1} (O-H from water) due to insufficient drying of the product and several absorptions bands in the region 1400 - 650 cm cm^{-1} (S=O stretching). N=N stretching vibration is also visible at 1420 cm^{-1}.



SM 5.1.1.5: IR (KBr) of methyl orange



SM 5.1.1.6: ^{1}H NMR (D_2O) of methyl orange

In the ^{1}H NMR spectrum (**SM 5.1.1.6**) students identify easily aromatic and aliphatic protons. Spectral data (IR, ^{13}C NMR and ^{1}H NMR) for methyl orange can be found on SDBS[2] under number 2632.

[1] A.I. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific and Technical, 5th Ed., 1989, 951.
[2] *Handbook of Chemistry and Physics*, CRC Press,59th ed., C-378.
[3] http://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_frame_disp.cgi

Halogenation reactions of Vanillin

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Supplementary Material

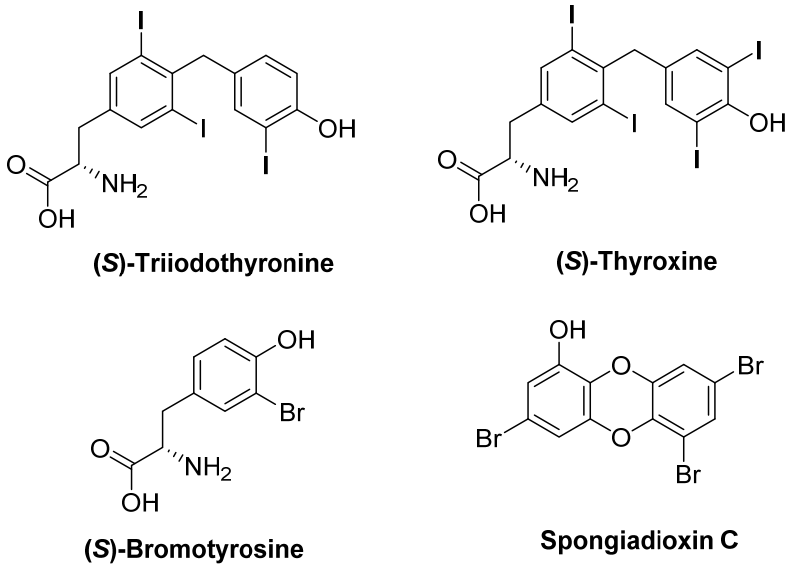
Vanillin (4-hydroxy-3-methoxybenzaldehyde) has found many uses in organic chemistry teaching laboratories, there are many examples where vanillin features as a reactant or as a target molecule in synthesis/isolation exercises. Vanillin lends itself well for use in teaching laboratories[1-9] since it is a familiar molecule to students (it's pleasant odour usually is!), it is multifunctional, not particularly toxic and vanillin is cheap/readily sourced.

Bromination reactions of unactivated aromatic compounds usually require additional reagents[10,11] (most frequently a Lewis acid, common examples being $FeBr_3$ or $FeCl_3$) in order to proceed. Phenols and aromatic amines on the other hand are usually reactive enough to be brominated without the need for additional reagents, although the level of bromination can be difficult to control.[12]

Iodination of aromatic compounds is usually not as straightforward due to Iodine being less reactive than the other halogens.[10,11] In contrast to bromination, iodination of vanillin does not normally proceed on treatment solely with the parent halogen. Most procedures employ an oxidant to convert iodine to a more reactive electrophile, the mechanism of this type of reaction is not fully understood since the iodine species in each case is believed to be different.[13] Addition of a base can be effective

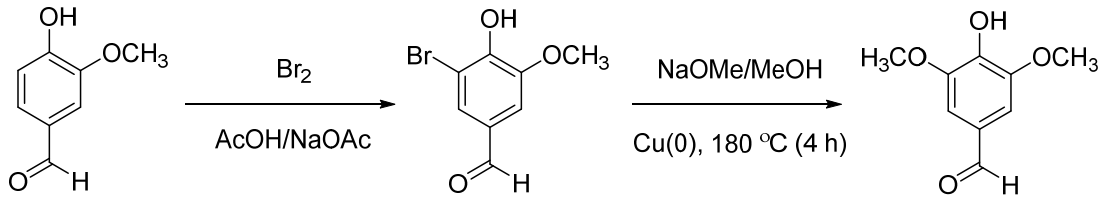
since the resulting phenoxide ion can be reactive enough to react directly with iodine.[14]

The aim of this experiment is to demonstrate electrophilic addition of bromine and iodine to vanillin. The targets are of interest since they are related to more complex halogenated natural products and some are medicinally relevant (scheme 5.1.2.1).[15,16,17]



Scheme 5.1.2.1 Selected examples of naturally occurring halogenated phenols

3-Bromo-4-hydroxy-5-methoxybenzaldehyde derived from vanillin has been used to prepare syringaldehyde[18] Syringaldehyde and vanillin are valuable products that can be obtained from lignin, the amounts of both are dependent on the wood from which they are isolated. Syringaldehyde is usually isolated in smaller quantities[19] but can be obtained from vanillin by the reaction sequence outlined in scheme 5.1.2.2.[18]



Vanillin **Syringaldehyde**

Scheme 5.1.2.2 Conversion of Vanillin to Syringaldehyde

This experiment is aimed at second or third year undergraduate students who have had training to an introductory/intermediate level of synthetic organic chemistry work. The concepts covered are directly relevant to core lecture material on aromatic chemistry although there are more general links to process/industrial chemistry (and possibly medicinal chemistry). In addition to allowing students to practice assembly of key apparatus and techniques (recrystallization, and vacuum filtration), this exercise can be used to introduce the safety and manipulation skills required for the use of toxic and corrosive materials (Bromine in particular). The identity of the products from each step in the sequence can be confirmed by melting point analysis and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of the products demonstrate that halogenation is regioselective for the same position in each case (NMR spectra are discussed in “Answers to additional questions” section).

General notes for preparative steps.

In the bromination reaction it is **advised that neat bromine is NOT added directly to the vanillin/acetic acid mixture**, this may result in a less controllable addition and initial reaction. It is safer to prepare a solution of bromine in acetic acid and then add this in portions to a mixture of vanillin in acetic acid. For use in larger classes, we have set up a burette containing bromine in a fume hood. This arrangement allows small volumes of bromine to be safely dispensed by laboratory demonstrators

into a flask containing acetic acid (provided by each student). The resulting bromine/acetic acid mixture contained within the stoppered flask can be stored in a fume hood for a short period of time until it is required. An alternative approach may be that a member of staff prepares a larger volume of bromine/acetic acid mix immediately before the class, and that a burette containing this solution is made available. The crude product is likely to precipitate out as the reaction progresses; the remainder is recovered when the solution is added to ice water. The product is particularly amenable to purification by recrystallization, indeed very good quality material is obtained if the product is allowed to slowly crystallise from ethanol overnight (figure 5.1.2.1). Typical yields range between 30 to 75%. Melting point of 3-Bromo-4-hydroxy-5-methoxybenzaldehyde is 163-164 °C (lit)[1].

Figure 5.1.2.1 Large crystals of 3-Bromo-4-hydroxy-5-methoxybenzaldehyde obtained from slow overnight recrystallisation.

The iodination reaction normally proceeds smoothly. The reaction mixture should become a dirty orange colour as the iodine is added to the initial slurry. The crude product is usually dark brown, this can be redissolved and washed with more sodium thiosulfate if desired, however recrystallization usually affords product of an acceptable standard. The longer reaction time potentially posed a problem for laboratories that do not have the facilities to magnetically stir reactions overnight, however if this is a problem satisfactory results are obtained by allowing the reaction mixture to stand overnight. Typical yields range between 25 to 65%. Melting point of 4-hydroxy-3-iodo-5-methoxybenzaldehyde is 179-180 °C (lit)[20].

During review of the initial manuscript of this set experiments, the referees suggested that hazard/risk could be managed further by scaling the reactions down by as much as 50% without any detrimental effect on yield. The authors are very grateful for this insight from the referee's previous experience.

NMR samples and assignments

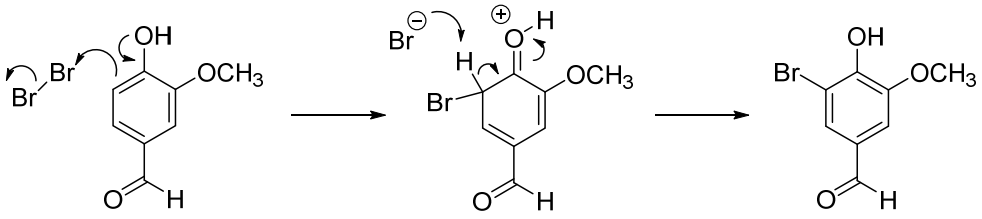
The products are partially soluble in deuterochloroform; small yet satisfactory amounts (ca. 15 mg) for ^{1}H NMR analysis will dissolve if well mixed. Deuterated DMSO can be used instead as an alternative if preferred. Assignments of spectra (and copies all the NMR spectra are provided) in the "Answers to additional questions" section.

Answers to additional questions

1. Interpret the ^{1}H NMR spectra you obtained from both reaction steps. Use the NMR spectra and melting points to confirm the structure of your compounds unambiguously.

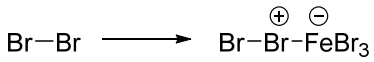
The ^{1}H NMR spectra (see Figures 5.1.2.2 and 5.1.2.3) in conjunction with melting points allow unambiguous identification of both products. The ^{1}H NMR spectra of the products are relatively simple since there are only 2 protons attached to the aromatic ring of both products. The aldehyde and methyl group signals appear as sharp singlets as may be expected. The ring protons are *meta* to each other, the relatively small coupling constants (ca. <2 Hz) provide good evidence for this substitution pattern. If halogenation were to take place adjacent to the methoxy group, the ring protons would be expected to appear as doublets with *J* values consistent with ortho coupling (ca. 6-9 Hz). If halogenation were to take place *para* to the methoxy group, the ring protons would be *para* to each other and the resulting coupling constant should be different to that observed for 3-Bromo-4-hydroxy-5-methoxybenzaldehyde.

2. Provide a curly arrow mechanism for the bromination of vanillin.

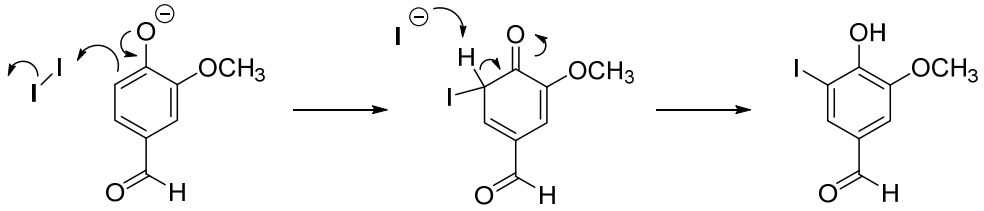


3. Account for the following observations. Bromination of phenol occurs rapidly in the presence of bromine while bromination of nitrobenzene requires heating and addition of ferric bromide as a catalyst in addition to bromine in order to obtain the desired product.

The phenolic hydroxyl group is an electron donating and "activating" substituent. The aromatic system in this case is very reactive toward bromine. In contrast, nitrobenzene is a deactivated by the electron-withdrawing nitro group. The aromatic system in this case is not very reactive toward bromine, however addition of $FeBr_3$ increases the electrophilic character of the bromine and facilitates the reaction.



4. Account for the following observations: Iodination of vanillin does not efficiently proceed without addition of a base; in contrast bromination of vanillin is favourable without addition of other reagents.



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Supplementary information for *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom*

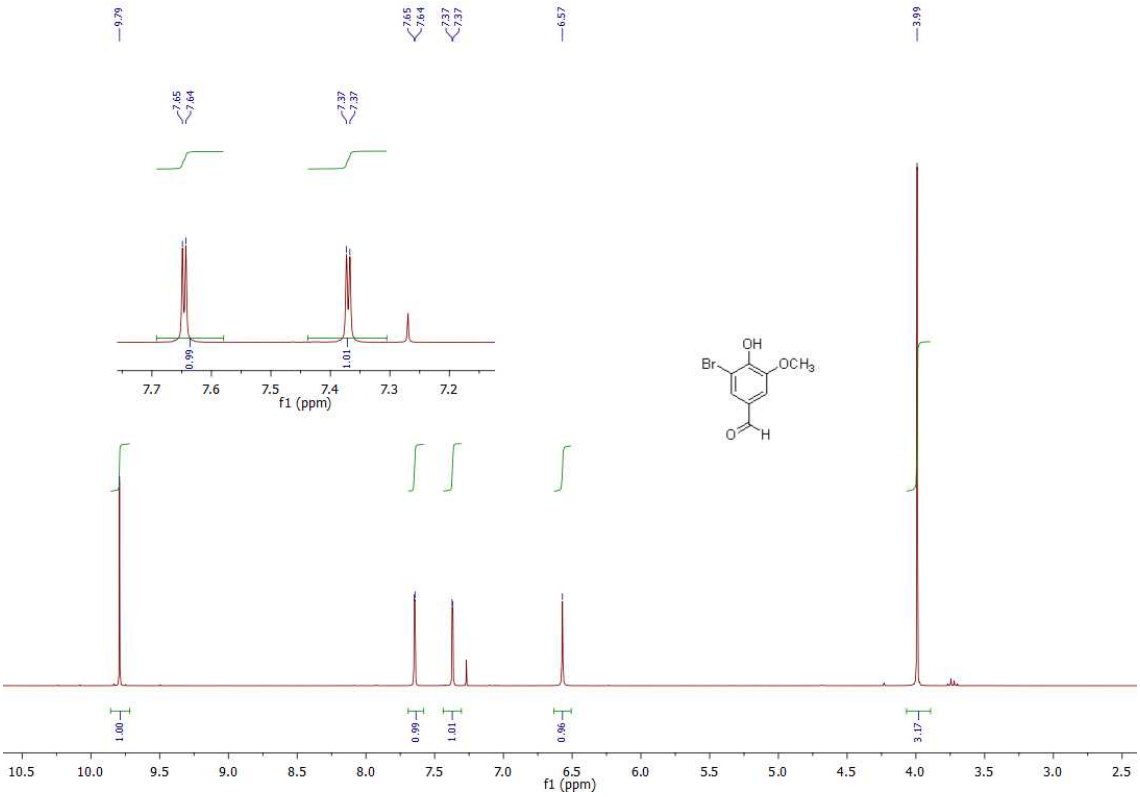
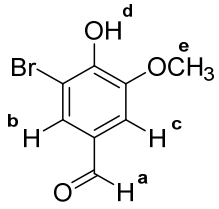


Figure 5.1.2.2 – ^{1}H NMR spectrum of 3-Bromo-4-hydroxy-5-methoxybenzaldehyde



δ_H (300 MHz, $CDCl_3$) 9.79 (1H, s, H-a), 7.64 (1H, d, $^{4}J_{HH}$ = 1.7 Hz, H-b), 7.37 (1H, d, $^{4}J_{HH}$ = 1.7 Hz, H-c), 6.57 (1H, s, H-d), 3.99 (3H, s, H-e).

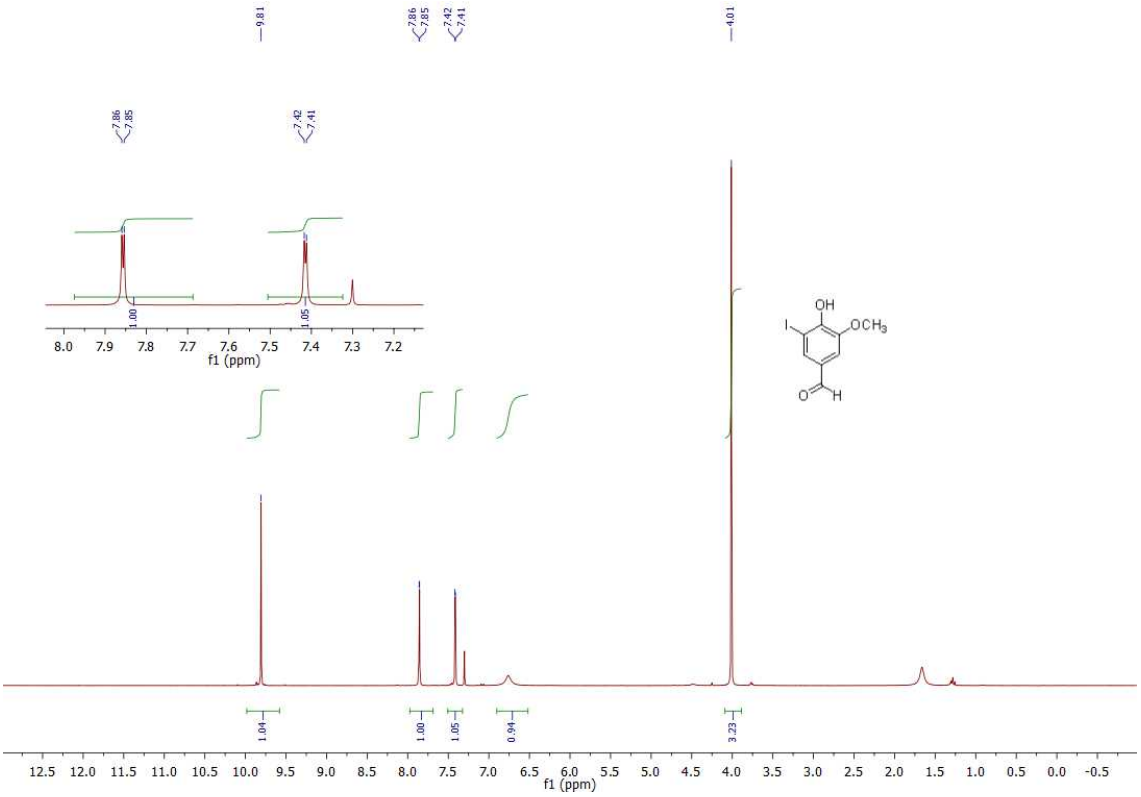
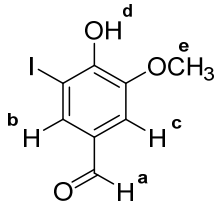


Figure 5.1.2.3 – ^{1}H NMR spectrum of 4-hydroxy-3-iodo-5-methoxybenzaldehyde



δ_H (300 MHz, $CDCl_3$) 9.81 (1H, s, H-a), 7.86 (1H, d, $^{4}J_{HH}$ = 1.5 Hz, H-b), 7.42 (1H, d, $^{4}J_{HH}$ = 1.5 Hz, H-c), 6.74 (1H, br s, H-d) and 4.01 (3H, s, H-e).

Synthesis of 2-(2,4-dinitrobenzyl)pyridine

Supplementary Material

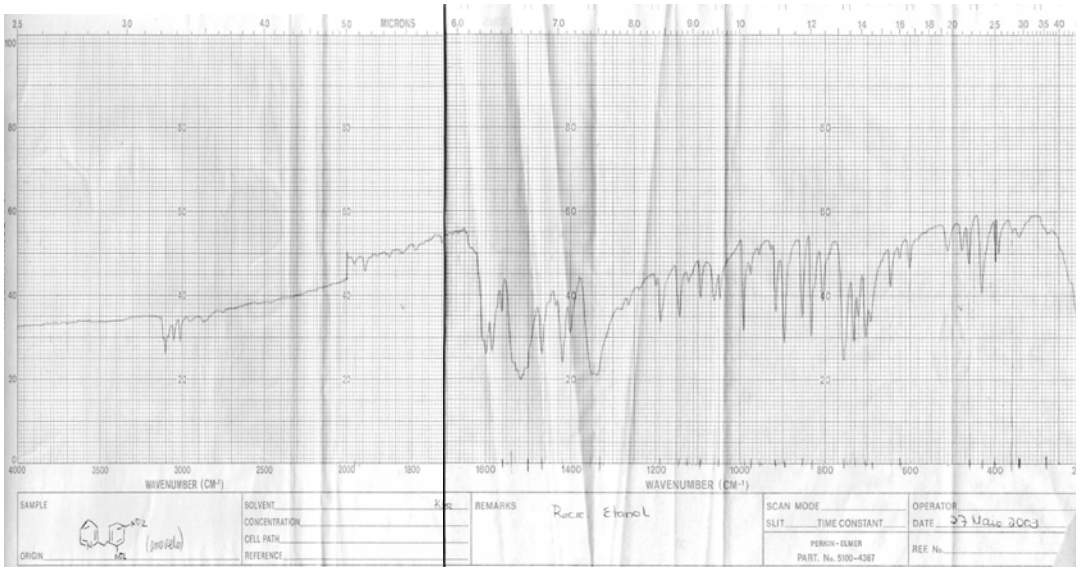
This experiment proposal was tested by students of elementary organic chemistry in which the concepts of electrophilic aromatic substitution were taught. The synthesis of a photochromic compounds increase the interest of all students for this kind of experiments. Experimental procedure can be easily performed by them, but the handling of toxic chemicals requires the use of fume hoods. This work is a great example to illustrate how substituent can affect both reactivity and orientation in electrophilic aromatic substitution in particular relative reactivities of pyridine and phenyl rings. Additionally allow to understand photochromism phenomenon and tautomerism.

Additional notes on 2-(2,4-dinitrobenzyl)pyridine

The yield is around 30-50 % and melting point 89-90ºC (91-93ºC[1,2]). Temperature control is important. It should remain below 10ºC, otherwise an oil could be formed resulting in difficult precipitation. That way, 2-benzylpyridine and fuming nitric acid should be cooled in ice bath before funnel addition. It was found in the literature that this reaction can be performed with an equivalent amount of concentrated nitric acid (cheaper) instead fuming nitric acid (yield from 25-50%)[3]. It is advisable work in small scale to avoid handling large volumes of reaction mixture. Photochromic behavior is easily visible when some crystals are exposed to direct sun light. That way, prolonged exposure to light during the experiment and particularly during recrystallization should be avoid. In the absence of sun, a 60 Watts lamp can be used, but the change of color is slower.

SM 5.1.3.1 - Crystals of 2-(2,4-dinitrobenzyl)pyridine stored at dark (sandy) and after sun light exposition (dark blue)

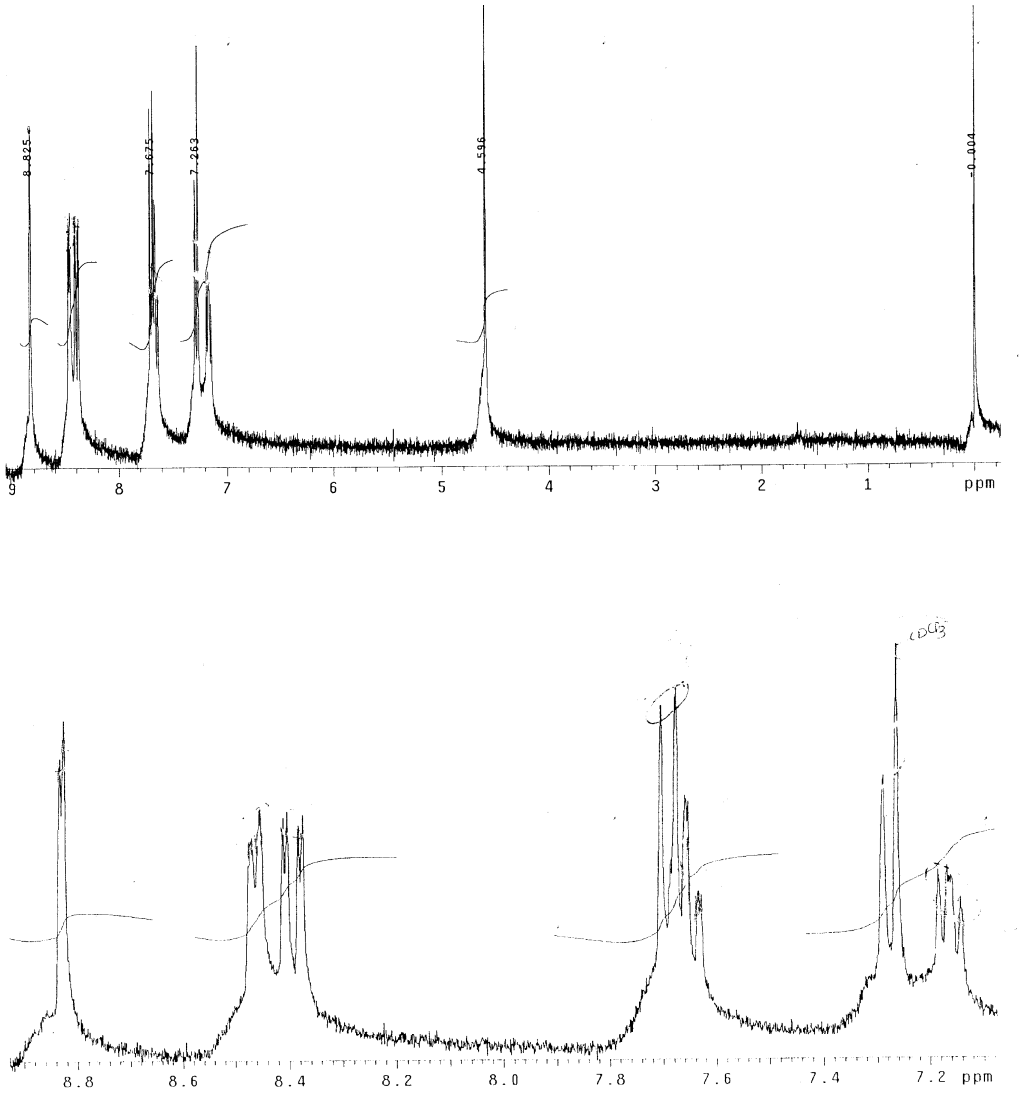
IR spectra:



SM 5.1.3.2 - IR (KBr) of 2-(2,4-dinitrobenzyl)pyridine

IR spectrum of 2-(2,4-dinitrobenzyl)pyridine is also available in SDBS (nº 11226)[4].

NMR spectra:



SM 5.1.3.3 - ^{1}H RMN of 2-(2,4-dinitrobenzyl)pyridine (300 MHz, $CDCl_3$)

There is no NMR data available for 2-(2,4-dinitrobenzyl)pyridine but it can be found for 4-(2,4-dinitrobenzyl)pyridine in SDBS (nº 41100)[4].

[1] C. A. M. Afonso, D. P. Simão, L. P. Ferreira, M. S. Serra, M. M. M. Raposo, *100 Experiências de Química Orgânica*, Copyright © IST Press, 2011, 361.
[2] A. Ault, *J. Chem. Educ.* 2000, **77**, 1386-1387.
[3] N. M. Zaczek; W. D. Levy; M. L. Jordan; J. A. Niemyer, *J. Chem. Educ.* 1982, **59**, 705.
[4] URL: http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi

Regioselectivity in the nitration of acylanilines by electrophilic aromatic substitution

Supplementary material

Electrophilic aromatic substitution is a key transformation in the aromatic chemistry for the functionalization of aromatic compounds. Some of the most important electrophilic aromatic substitutions are nitration, halogenation, sulfonation, acylation and alkylating by Friedel–Crafts reactions.

Regioselectivity in EAS (orientation effects) can be anticipated and the product distribution is the result of a kinetically controlled process, either by electronic or stereochemical hindrance effects. Both the regioselectivity and the speed of an electrophilic aromatic substitution are affected by the substituents already attached to the benzene ring.

In the current experiment, the acetamide, the methyl and the succinmidyl groups are all activating (+R) and *ortho/para* directing groups. The groups are ordered by their decreasing activity ability for the EAS reaction. The succinimidyl derivative can be regarded as a “double amide” and, due to strong electron-withdrawing inductive effect, it is only slightly activating for the EAS reaction.

In terms of regioselectivity, all groups already present in the aromatic ring promote substitution at the *ortho* or *para* positions. The nitrogen atom of the acetyl and succinimidyl groups can act as electron-donors to the ring and *ortho/para* substitution is preferred. The methyl group also stabilizes the cationic intermediate for *ortho/para* substitution.

The formation of N-acetyl amides of aniline and 4-methylaniline and their nitration were performed routinely in our laboratory course for first and second year undergraduate student of MsC students during a 15 year period. Using the procedure described above, and at that reaction scale, the experiment produced consistent results (yield and quality). The succinimidyl derivatives, their

nitrations and HPLC analysis were performed by three different students and at least five times each step. The yield and quality results were consistent as long as the temperature control is efficient.

Hints for result interpretation and answers

N-acylaniline nitration

Nitration on the *para* position of N-acetylaniline is preferred, since the stereochemical hindrance reduces the amount of the *ortho* substitution product. The succinimidyl group is also ortho/*para* directing, but less electron-releasing than the acetyl group, so the distribution of the product is much more even.

N-acyl-4-methylaniline nitration

In the case of the N-acetyl-4-methylaniline, the acetyl group is the stronger directing group for the EAS: the main product is *ortho* relative to the N-acyl group. However, when the N-succimidyl 4-methylaniline is nitrated, almost only the 3-nitroderivative is obtained (*ortho* to the methyl group). This means that the alkyl group (methyl) is now directing the nitration.

N-acetyl-2-methylaniline nitration

Using the N-acetyl derivative, 2-methyl-4-nitroaniline is obtained as the major product, the acetyl group being the stronger directing group for the EAS. Nitration occurs mainly at the *para* position to the N-acetylamine group. However, the nitration of the N-succinimidyl derivative produces mainly 2-methyl-5-nitroaniline. In this latter case, the succinimidyl group cannot donate efficiently its nitrogen electrons to the ring due to stereochemical constraints and the methyl group becomes the stronger activating group for the EAS.

Notes for the instructor

Preparation of the acetanilide derivatives

This reaction is highly exothermic but can be slow at low temperatures. The addition of the acetic anhydride should not start below 25ºC as the reaction is slow below this temperature and an accumulation of the anhydride may occur. The rate of the addition of the anhydride is controlled to keep the temperature below 80ºC. After the filtration, the product cake must be well washed with water to remove the acetic acid.

Preparation of the succinimidyl derivatives

The reaction mixture is slowly heated in a glass beaker standing directly on a heat plate over 3 hours, until 200ºC is reached. During the first hour, it is advisable that the temperature should not exceed 120ºC, allowing most of water formed in the reaction to be released. Using the glass rod or a spatula, scrap the walls of the beaker to run some solid product that might be stuck into the main liquid. Caution: hot water vapour is released during the transformation.

Nitration of the protected aniline

The nitration is exothermic and the reaction temperature is controlled below 10ºC by the rate of the addition of the nitrating solution. A water/ice/salt bath is needed to control the heat release (a water/ice bath is not enough to cool the reaction mixture properly).

Photographs of the experimental equipment

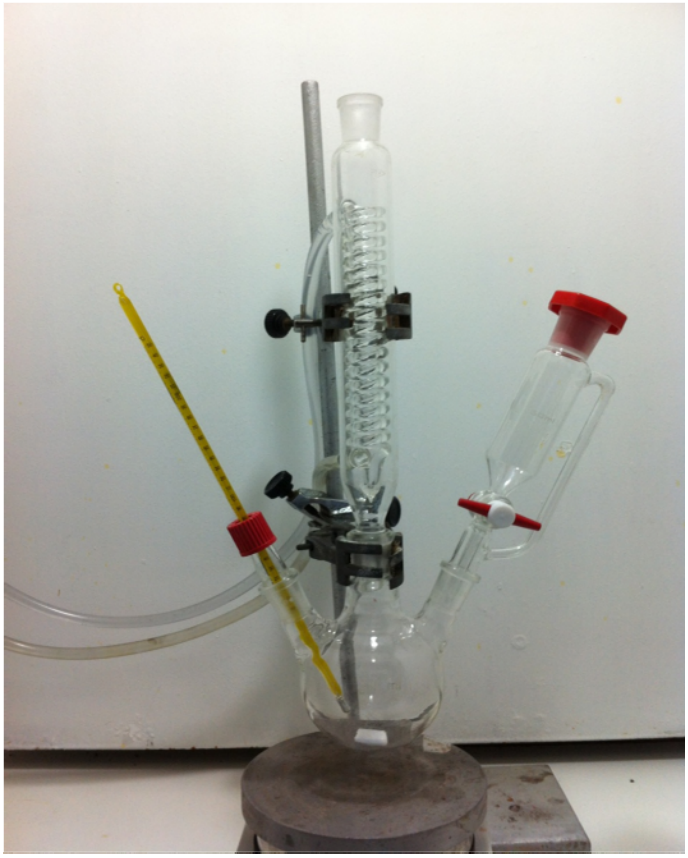
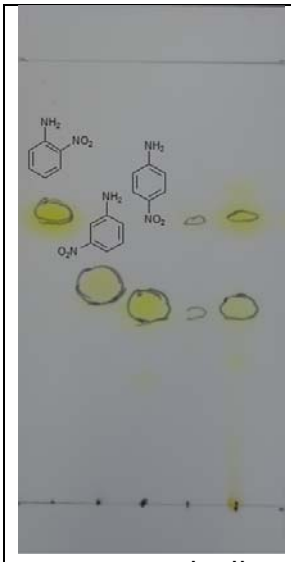


Figure SM 5.1.4.1 – Amide formation and nitration apparatus.

Product analysis and quantification by HPLC

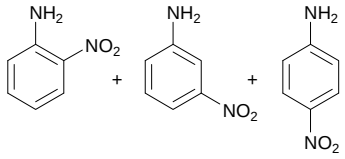
a) by TLC

A rough analysis of the predominant product of each reaction can be performed by TLC. Reference nitroaniline compounds are available from common chemical reagent suppliers and may be purchased as standards for TLC and HPLC analysis. Typical TLC plates are shown below.



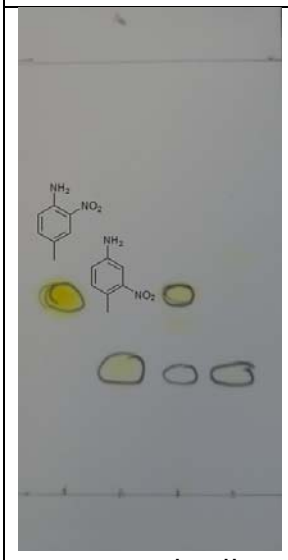
I II

R_f (silica, CH_2Cl_2/heptane, 1:1, eluted twice);
2-nitroaniline 0.65;
3-nitroaniline 0.48;
4-nitroaniline 0.44.



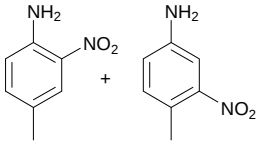
I- from acetyl	1 %	1 %	98 %
II - from succinimidyl	42 %	13 %	45 %

(% mol by HPLC)



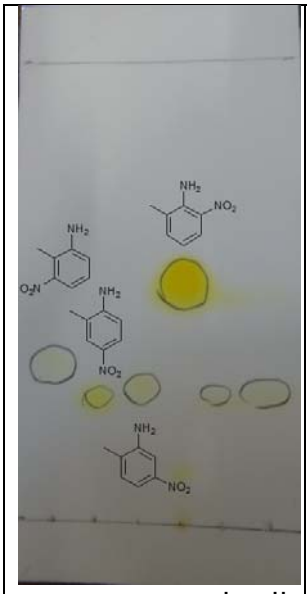
I II

R_f (silica, CH_2Cl_2/heptane, 7:3);
4-Methyl-2-nitroaniline 0.44;
4-Methyl-3-nitroaniline 0.28.



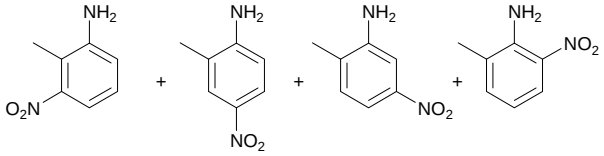
I- from acetyl	95 %	4 %
II- from succinimidyl	1 %	99 %

(% mol by HPLC)



I II

Rf (silica, CH_2Cl_2/heptane, 7:3);
2-Methyl-3-nitroaniline 0.35;
2-Methyl-4-nitroaniline 0.28;
2-Methyl-5-nitroaniline 0.28;
2-Methyl-6-nitroaniline 0.48
or
Rf (silica, CH_2Cl_2/heptane, 1:1, eluted twice, shown in photo);
2-Methyl-3-nitroaniline 0.33;
2-Methyl-4-nitroaniline 0.25;
2-Methyl-5-nitroaniline 0.28;
2-Methyl-6-nitroaniline 0.50.

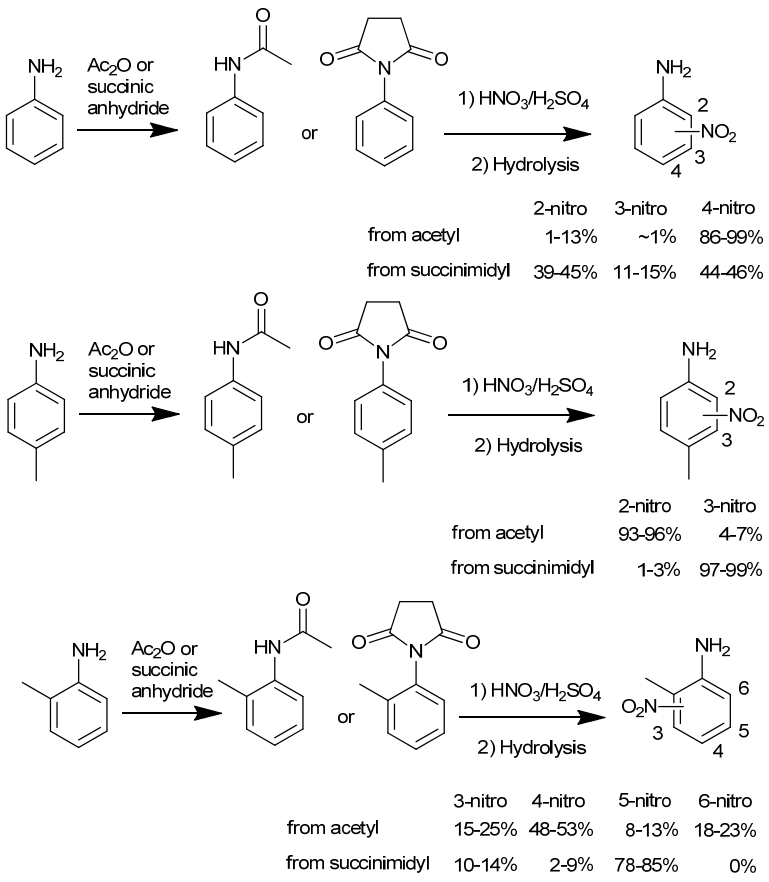


I- from acetyl	20 %	50 %	10 %	20 %
II- from succinimidyl	13 %	4 %	83 %	0 %

(% mol by HPLC)

b) Product analysis by HPLC

The molar percentage of the various products can be calculated using the response factors included in the experiment. Common product distribution is shown in Scheme SM 5.1.4.1.



Scheme SM 5.1.4.1 – Common distribution of the nitroaromatic products obtained in this work.

Synthesis of 2-nitro-4-methtylaniline

Supplementary Material

This experiment proposal was tested by students of elementary organic chemistry in which the concepts of electrophilic aromatic substitution were taught[1]. This work is a great example to illustrate the use of amine protection and how disubstituted benzenes can affect both reactivity and orientation in electrophilic aromatic substitution. Steric hindrance can be also discussed. The presence of methyl group in *para* position leads only to *ortho* nitration product. So, this work is an alternative to aniline nitration where, *ortho* and *para* products (mainly *para*) are obtained. Experimental procedure can be easily performed by them, but the handling of toxic chemicals requires the use of fume hoods. This work has been successfully performed by second-year undergraduate chemistry students since 1999 (each laboratory class with 14 students that work in pairs, 5 days per week).

Additional notes on the preparation of N-acetyl-4-methylamine:

The acetylation with acetic anhydride is performed with dry toluene instead of benzene[2], due to its lower toxicity. Acetic anhydride should be distilled prior to its use (Figure **SM 5.1.5.1**).

SM 5.1.5.1 – Reaction set-up apparatus for N-acetyl-4-methylamine

Although not described in the experimental procedure, we observed that ethanol/water (4:1) was the best solvent to recrystallize the crude product (Figure **SM 5.1.5.2**). N-Acetyl-4-methylamine is obtained with an average yield of 55-65% and a melting point of 146-147ºC (lit.: 148.5ºC[3]).

SM 5.1.5.2 – Vacuum filtration set-up and copper funnel (previously heated by flame) for hot filtration

If heating is prolonged and excess of acetic anhydride is employed variable amounts of the diacetyl derivative are formed. In general however the diacetyl derivatives are unstable in the presence of water undergoing hydrolysis to the monoacetyl compound, so that when they are crystallized from a aqueous solvent e.g. dilute ethanol, only the monoacetyl derivative is obtained.

Additional notes on the preparation of N-acetyl-2-nitro-4-methylaniline:

The procedure for the nitration follows a different synthetic route from the one reported in literature[1]. A mixture of nitric and sulfuric acids is used instead of an 80% nitric acid solution. It is necessary to use mechanical stirring instead of magnetic to guarantee an efficient cooling of the reaction mixture during nitration (Figure **SM 5.1.5.3**).

SM 5.1.5.3 – Reaction set-up apparatus for N-acetyl-2-nitro-4-methylaniline

N-Acetyl-4-methylamine is a granular substance, and will dissolve better if grinded with a pestle and mortar. The stirring time can be reduced to 30 minutes without consequences in the yield. Recrystallization in warm petroleum ether requires a large quantity of solvent (c.a. 200 mL). Average yield is 25-30%, while the melting point is between 87 and 92ºC, with a melting point range of 1-2ºC (lit.: 96ºC[4]).

Additional notes on the preparation of 2-nitro-4-methylaniline:

Reaction set-up apparatus for 2-nitro-4-methylaniline can be seen in figure **SM 5.1.5.4**. After removal of the heat, the pressure-equalized dropping funnel is fitted on top of the condenser as in figure **SM**

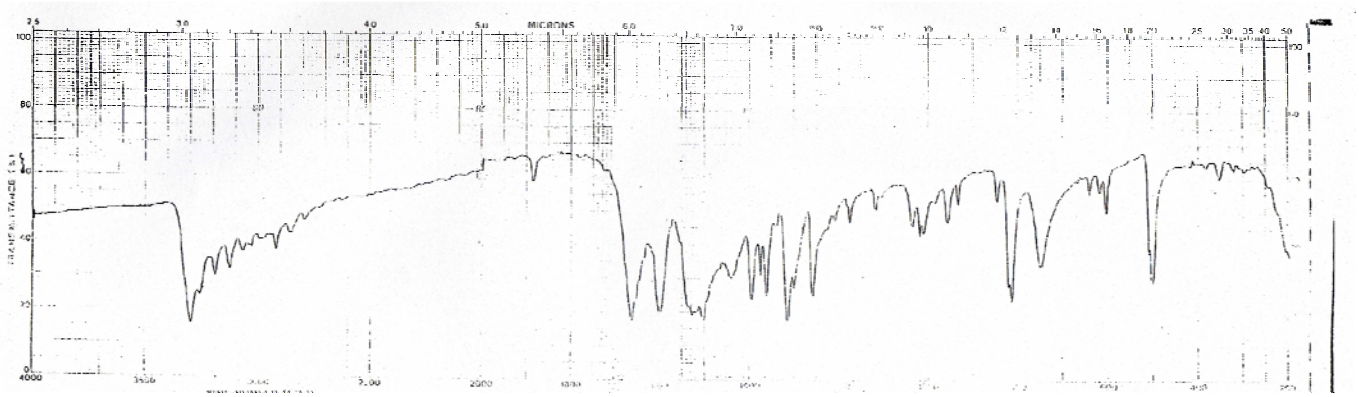
5.1.5.5 to add water. Average yield of this product is 35-40% and the melting point is 113-114ºC (lit.: 117ºC[5]).

SM 5.1.5.4 – Reaction set-up apparatus for 2-nitro-4-methylaniline

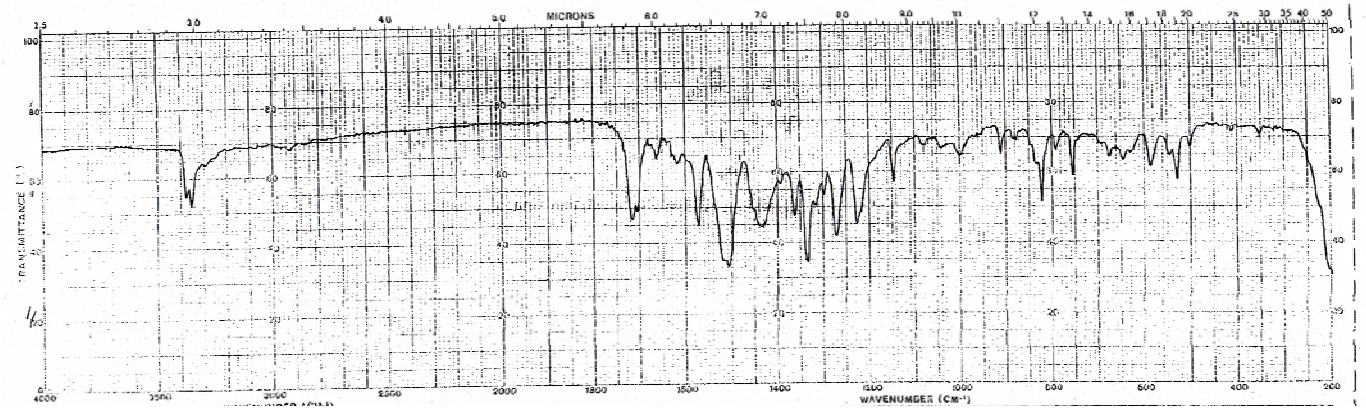
SM 5.1.5.5 – Setup after removal of heating bath and addition of water.

IR spectra:

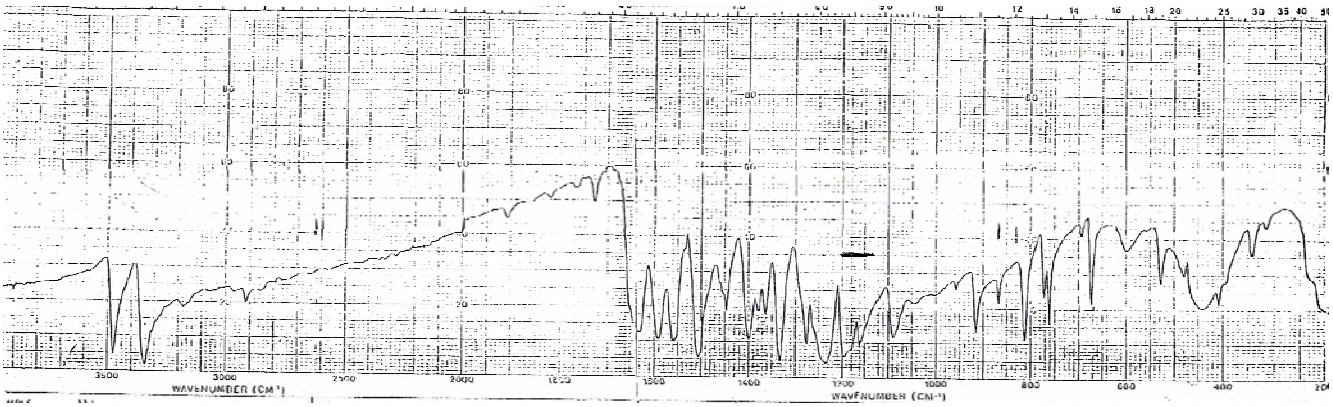
Students easily identify in the Figure **SM 5.1.5.6** and **SM 5.1.5.7** absorption bands near 3400-3350 cm^{-1} due to N-H stretching vibration. For 2-nitro-4-methylaniline (Figure **SM 5.1.5.8**) two N-H stretching bands at 3320 and 3480 cm^{-1} can be observed by them. Strong absorption bands due to C=O stretching vibration is also visible near 1700 cm^{-1} in figure **SM 5.1.5.6** and **SM 5.1.5.7**. N=O stretching vibrations can also be seen at 1500 cm^{-1} for N-acetyl-2-nitro-4-methylaniline and 2-nitro-4-methylaniline.



SM 5.1.5.6: IR (KBr) of N-acetyl-4-methylamine



SM 5.1.5.7: IR (KBr) of N-acetyl-2-nitro-4-methylaniline

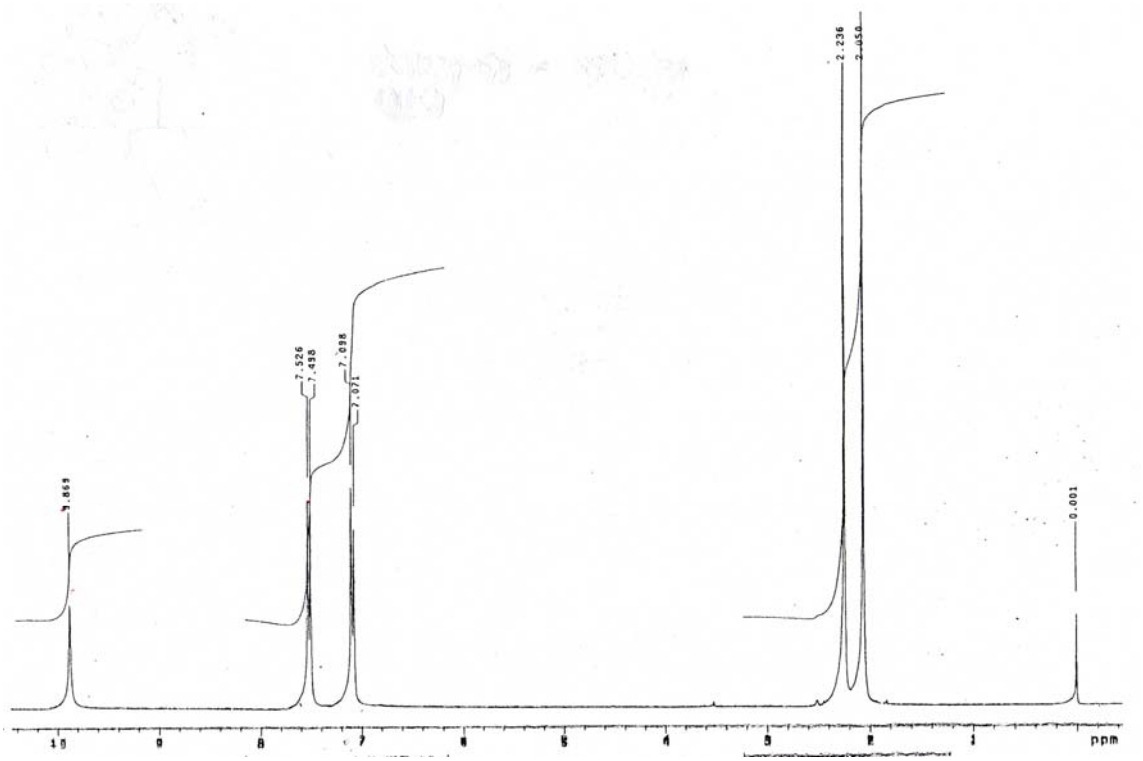


SM 5.1.5.8: IR (KBr) of 2-nitro-4-methylaniline

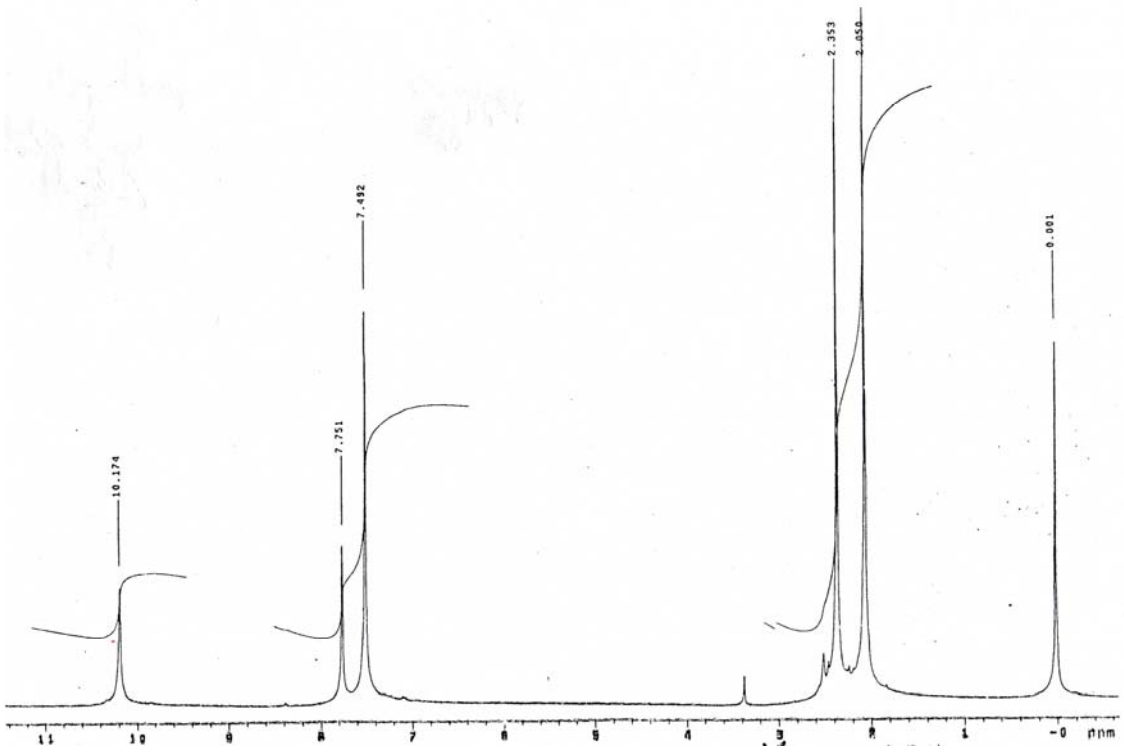
IR spectra of all products are available in the literature on SDBS (Spectral Database for Organic Compounds)[6] under numbers 6377 (N-acetyl-4-methylamine), 34164 (N-acetyl-2-nitro-4-methylaniline), and 3254 (2-nitro-4-methylaniline).

NMR spectra:

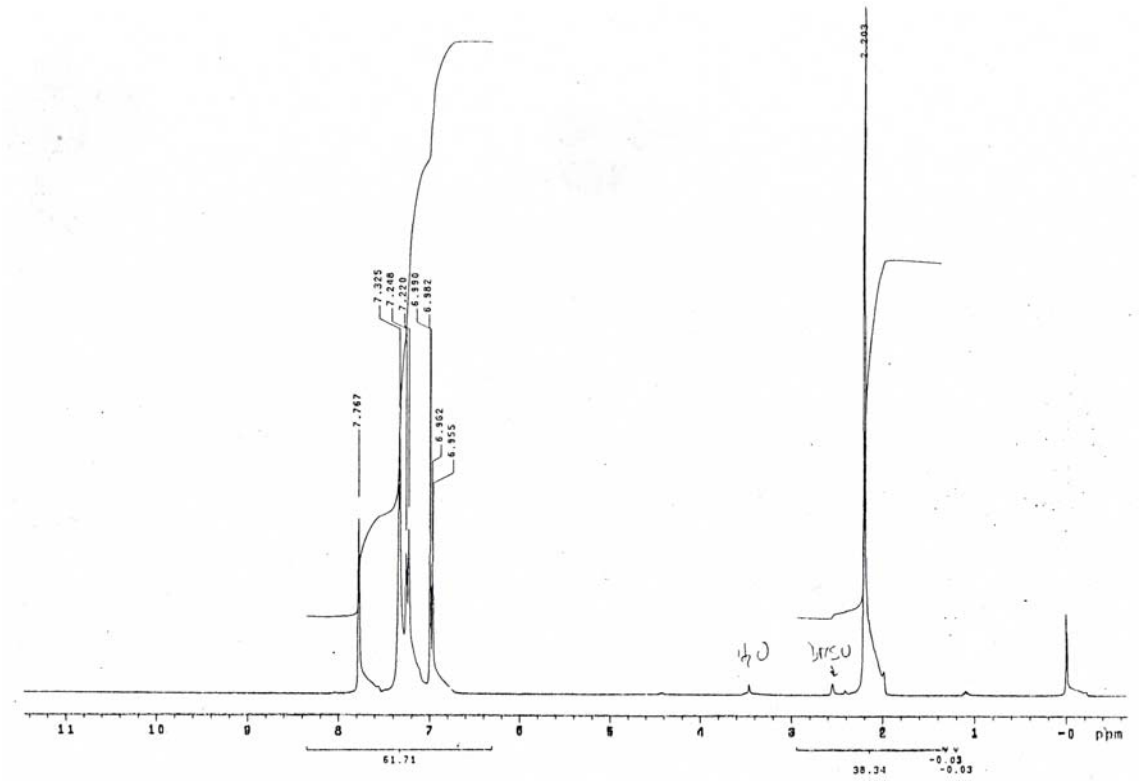
NMR spectra were obtained with student's samples. Students easily identify the aromatic protons, and the two different protons of methyl groups. N-H protons show a broad absorption centered about δ 10 ppm for N-acetyl-4-methylamine and N-acetyl-2-nitro-4-methylaniline (Figure **SM 5.1.5.9** and **SM 5.1.5.10**) and at 7.3 ppm for 2-nitro-4-methylaniline (Figure **SM 5.1.5.11**). The Figure **SM 5.1.5.12** shows the recorded ^{1}H NMR spectrum after addition of deuterated water where this peak is missing due to the exchangeability of N-H proton with the solvent. ^{1}H NMR spectra of N-acetyl-4-methylamine and 2-nitro-4-methylaniline are available in the literature[6] (SDBS numbers 6377 (N-acetyl-4-methylamine), and 3254 (2-nitro-4-methylaniline)).



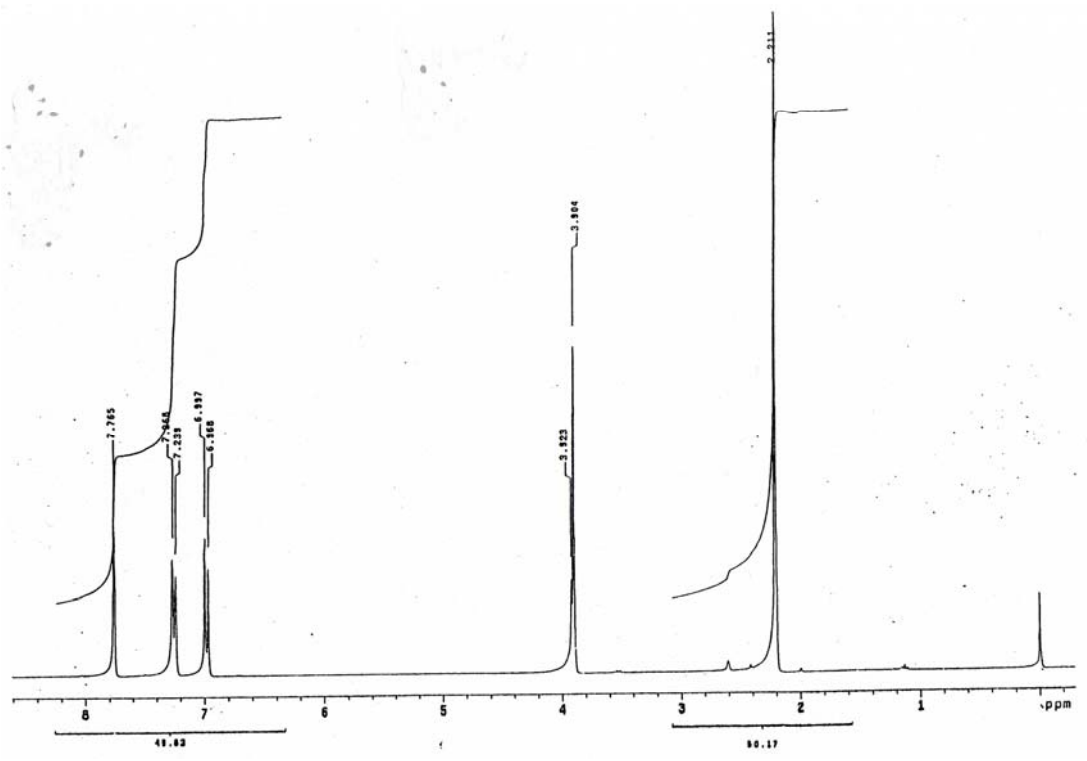
SM 5.1.5.9: ^{1}H NMR (DMSO-d_6) of N-acetyl-4-methylamine



SM 5.1.5.10: ^{1}H NMR (DMSO-d_6) of N-acetyl-2-nitro-4-methylaniline



SM 5.1.5.11: ^{1}H NMR (DMSO-d_6) of 2-nitro-4-methylaniline



SM 5.1.5.12: ^{1}H NMR (DMSO-d_6) of 2-nitro-4-methylaniline after adding D_2O

[1] C. A. M. Afonso, D. P. Simão, L. P. Ferreira, M. S. Serra, M. M. M. Raposo, *100 Experiências de Química Orgânica*, IST Press, 2011, 353.
[2] L. F. Tietze, T. Eicher, *Reactions and Synthesis in the Organic Chemistry Laboratory*, University Science Books, 1989, 141.
[3] *Handbook of Chemistry and Physics*, CRC Press,1st Student ed., C-46.
[4] *Handbook of Chemistry and Physics*, CRC Press,1st Student ed., C-47.
[5] *Handbook of Chemistry and Physics*, CRC Press,1st Student ed., C-527.
[6] http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi, access in Sep 2015.

Synthesis of 1-Nitronaphthalene

Supplementary Material

More than three hundred students finished synthesis of 1-nitronaphthalene in the last fourteen years. This is one of experiments of aromatic electrophilic substitution in our Organic Chemistry Laboratory. The yields of all experiments are 65-82%. The student melting points are from 52-54^{o}C to 58.5-60^{o}C.

Sometimes traces of naphthalene are in final products after recrystallization (no more than 3% of students).

No additional tricks are needed to perform the experiment.

There is a need to leave crystals for one day for drying. It is strongly recommended not to store the product in an open vessel due a slight sublimation of 1-nitronaphthalene.

We do not recommend interpretations of ^{13}C NMR spectra because of their complexity.

We use horizontal TLC chamber (see attached photo – Figure 5.1.6.2). However, vertical TLC chamber is also convenient. 1-Nitroaphthalene is noticeable much better in UV light.

Additional purification can be done by passing even 100 mg of the final product by Pasteur pipette using toluene/ethyl acetate 4:1 (v:v) as eluent (Figure 5.1.6.3). Yellow impurity is less than 0,4% at the top of the column. Yellowish 1-nitronaphthalene is at the bottom of the column. The melting point of pure 1-nitronaphthalene after CC is 60-61^{o}C.

-- naphthalene

-- 1-nitronaphthalene

-- nitrosulphonated impurity

Figure 5.1.6.1. TLC plate of naphthalene and the student's 1-nitronaphthalene in UV lamp 254nm

Figure 5.1.6.2. Vertical chamber used for TLC of 1-nitronaphthalene

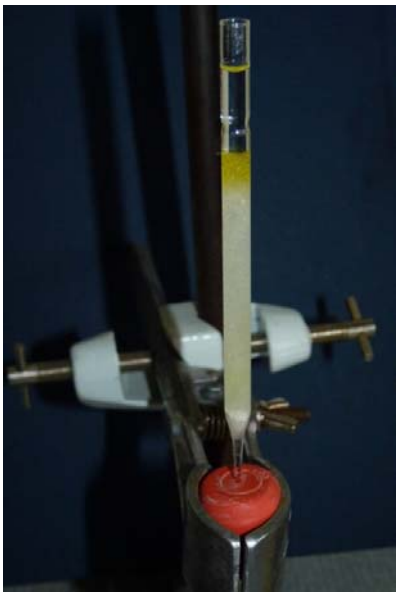


Figure 5.1.6.3. Column chromatography of the final student's product.

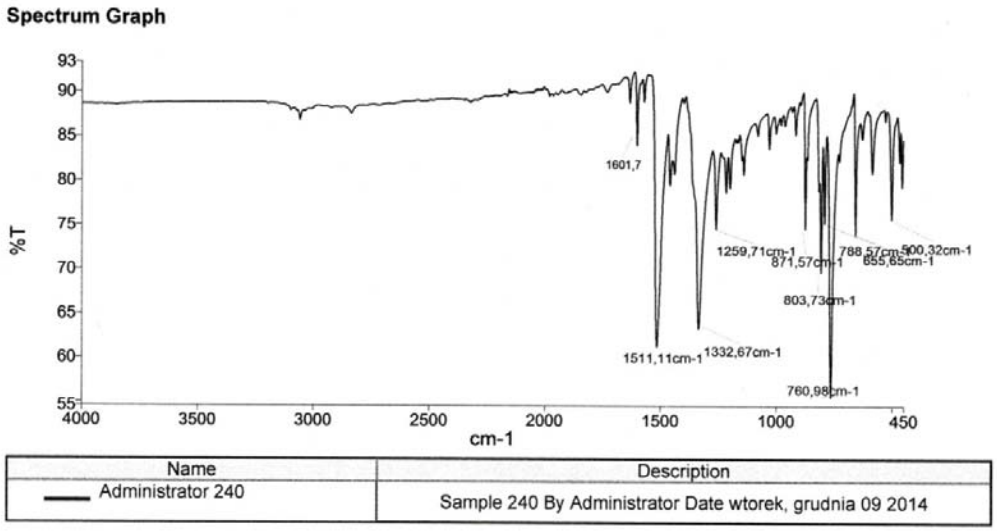


Figure 5.1.6.4. IR spectrum of the student 1-nitronaphthalene (neat) recorded by Perkin Elmer Spectrum Two

^{1}H NMR analysis

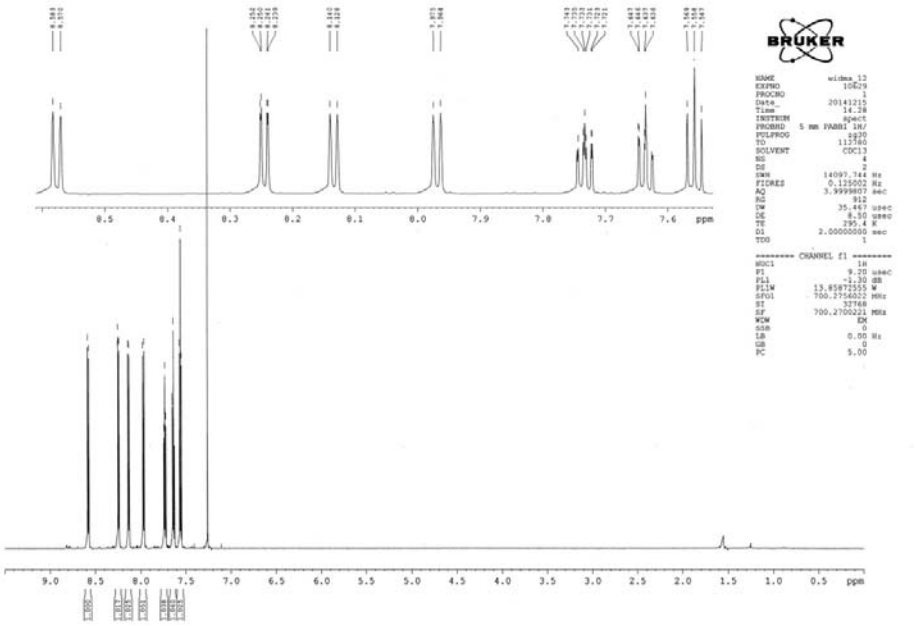


Figure 5.1.6.5. ^{1}H NMR spectrum of pure 1-nitronaphthalene

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.58 (d, 1H, J = 9.1, 8-CH), 8.25 (dd, 1H, J = 1.4, J = 8.0, 2-CH), 8.13 (d, 1H, J = 8.4, 4-CH), 7.97 (d, 1H, J = 7.7, 5-CH), 7.73 (dt, 1H, J = 1,4, J = 7.7, 6-CH or 7-CH), 7.64 (dt, 1H, J = 1,4, J = 7.0, 6-CH or 7-CH), 7.56 (t, 1H, J = 7.7, 3-CH).

Selective Boc-protection and bromination of pyrazoles

Supplementary Material

Thomas A. Logothetis

Experiment notes

The described sequence of two reactions starts with the products obtained from a preceding practical in which the pyrazole has been synthesised in a two-step procedure from an aldol condensation of a *para*-substituted benzaldehyde with 3-quinuclidinone hydrochloride followed by a pyrazole formation using hydrazine hydrate. Details are described in the chapter "***Synthesis of pyrazole heterocycles***" ***(Experiment 4.2.2.8)***. To the best of the author's knowledge the pyrazole starting material (**X.1**) for this practical is currently not commercially available. However, the synthesis thereof comprises of two high yielding steps that could be executed by an experienced laboratory technician to prepare sufficient starting material for the project described herein.

The TLC monitoring for both reactions involves a mini-work-up, *i.e.* the partitioning of an aliquot of the reaction mixture between water and diethyl ether, and utilising the organic layer for TLC analysis.

Reaction 1 – Synthesis of tert*-butyl 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine-1-carboxylate*

Tert-Butyl pyrocarbonate is typically stored in a fridge but should only be weighed once the bottle and contents have reached RT (to avoid condensation of moisture which slowly degrades the reagent).

The reaction is typically finished within 30-50 minutes according to TLC while monitoring the disappearance of the limiting starting material (**X.1**). Note that the polar eluent (CH_2Cl_2:MeOH:NH_3 15:4:1) causes the base to move up on the TLC plate. However, it is easily distinguished from the starting ma-

terial and product as it is UV inactive whereas oxidation (*e.g.* with permanganate dip) readily forms a positive reaction (*i.e.* formation of TEA *N*-oxide). Eluting the TLC with neat diethyl ether can be used to monitor the product (**X.2**) formation. If the reaction has not turned over all limiting starting material (**X.1**) addition of an extra aliquot of Boc_2O is helpful – the reason is likely to be partially hydrolysed anhydride.

The rotary evaporation sometimes produces a foam that solidifies once all solvent has been removed. If not all solvents are removed by rotary evaporation due to an ineffective pump, it might be necessary to use a more efficient high vacuum pump for last traces. Trituration is necessary in any case to purify the crude product.

An optional feature of this reaction is that instead of using triethylamine as an organic base the reaction can be run biphasic using saturated sodium bicarbonate.

Reaction 2: Synthesis of tert-*butyl 4-[4-bromo-5-(4-chlorophenyl)-1*H-*pyrazol-3-yl]piperidine-1-carboxylate*

The reaction takes typically 30 – 45 minutes after complete addition of NBS. Longer reaction times are encountered with low quality NBS. It is sensible in such cases to either increase the excess beyond 10 % (faster) or to add an additional aliquot if TLC monitoring indicates incomplete turnover after circa 40 minutes stirring at RT (better).

Trituration is necessary to produce pure a product, however, as it removes by-products it seemingly decreases the yield, which is particularly evident to those determining the crude and purified yield.

Optional features

An optional feature includes variation of the halogenation of the pyrazole ring, *e.g.* utilising NCS or NIS instead of NBS to generate a library of products, *e.g.* to showcase more complex isotope patterns in

mass spectra (X_1Y_1 or X_2 pattern, for X and Y being different halogens with isotopes, *i.e.* Cl, Br) or for subsequent testing of palladium-catalysed modifications of the scaffold. This has not been investigated, though.

Another variation depends on the nature of the residue on the phenyl ring. Although this script only describes the synthesis starting from the 4-chlorophenyl derivative, three more *para*-substituted phenyl derivatives have been tested and used in practicals (see tabulation of experimental results below) employing the same conditions.

Experimental results

The following tables summarise the results achieved with second year undergraduate students averaged over several years. Starting materials have *para*-substituted phenyl rings, *i.e.* 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, and 4-tolyl). The products of both reactions are amorphous white solids for all tested derivatives.

*Typical melting points and yields for products of reaction 1 (*Boc *protection):*

Residue	mp [°C]	trituration solvent	Yield [%]
R = Cl	207-209	light petroleum ether	85±5
R = Br	214-216	light petroleum ether	85±5
R = F	183-185	light petroleum ether	85±5
R = Me	174-175	light petroleum ether	80±5

Table 5.1.7.1: Data for *tert*-butyl 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine-1-carboxylate

Typical melting points and yields for products of reaction 2 (bromination):

Residue	mp [°C]	trituration mixture	Yield [%]
R = Cl	210-211	diethyl ether / petroleum ether (1:1)	70±5
R = Br	210-212	ethanol *recrystallisation*	55±5
R = F	199-200	diethyl ether / petroleum ether (1:1)	65±5
R = Me	212-214	petroleum ether	60±5

Table 5.1.7.2: Data for *tert*-butyl 4-[4-bromo-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine-1-carboxylate

Photos of the products

Figure 5.1.7.1: *Boc*-protected product (left) and brominated product (right)

Typical TLC plates for both reactions

Reaction 1 (Boc protection):
Due to the strongly different polarity of the starting material (SM) and the product (P) it is advised to use two

different eluents to follow the reaction (R). In the more polar eluent trimethylamine becomes visible under oxidative staining.

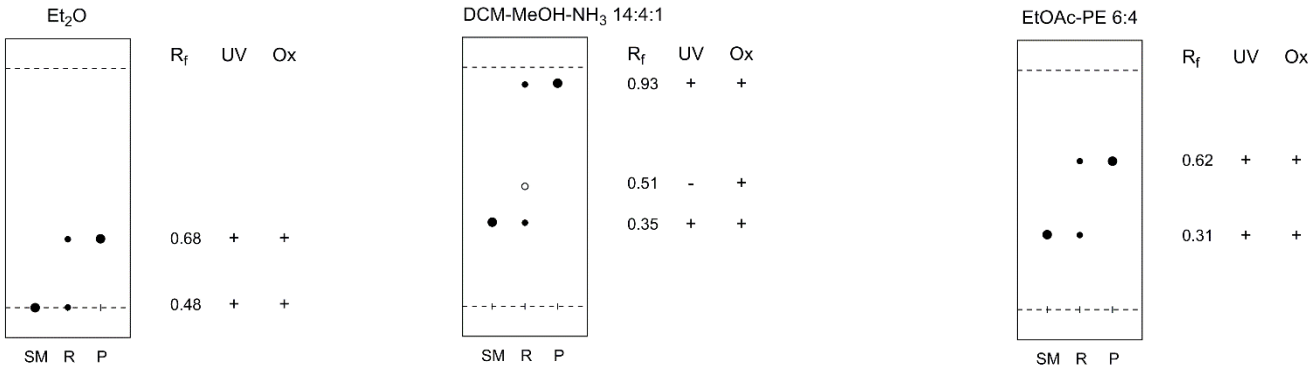


Figure 5.1.7.2: Exemplary observations on TLC plates when monitoring reaction 1 (left & middle) and reaction 2 (right)

Reaction 2 (bromination):
Both, starting material and product can easily be observed under UV light only and only one eluent is necessary.

Spectra

The spectra depicted here illustrate the chloro-derivatives only. For reasons stated below and due to the overwhelming signal of the *tert*-butyl moiety the ^{1}H NMR spectra have been found impractical for analysis in our teaching setting and thus have been omitted here, but this remains an optional feature. NMR spectra stemming from the fluoro-derivatives would exhibit additional coupling between ^{1}H and ^{19}F nuclei as well as between ^{13}C and ^{19}F nuclei. In infrared spectra the ν(C-Cl) could be observed in the region of 1030 – 1100 cm^{-1} depending on the resolution and spectral width of the spectrometer. The carbamate typically absorbs around 1670 cm^{-1}. Mass spectra (ES+) are an optional feature and would exhibit isotope patterns depending on the presence of chlorine and bromine.

In this practical only IR and ^{13}C NMR / DEPT spectra have been employed to analyse the products. In the ^{13}C NMR spectra the quaternary carbon atoms next to the pyrazole nitrogen atoms as well as the CH_2N of the piperidine ring exhibit strong line broadening due to flexibility / inversion at these centres. If desired, an adaption of NMR acquisition parameters helps producing stronger signals.

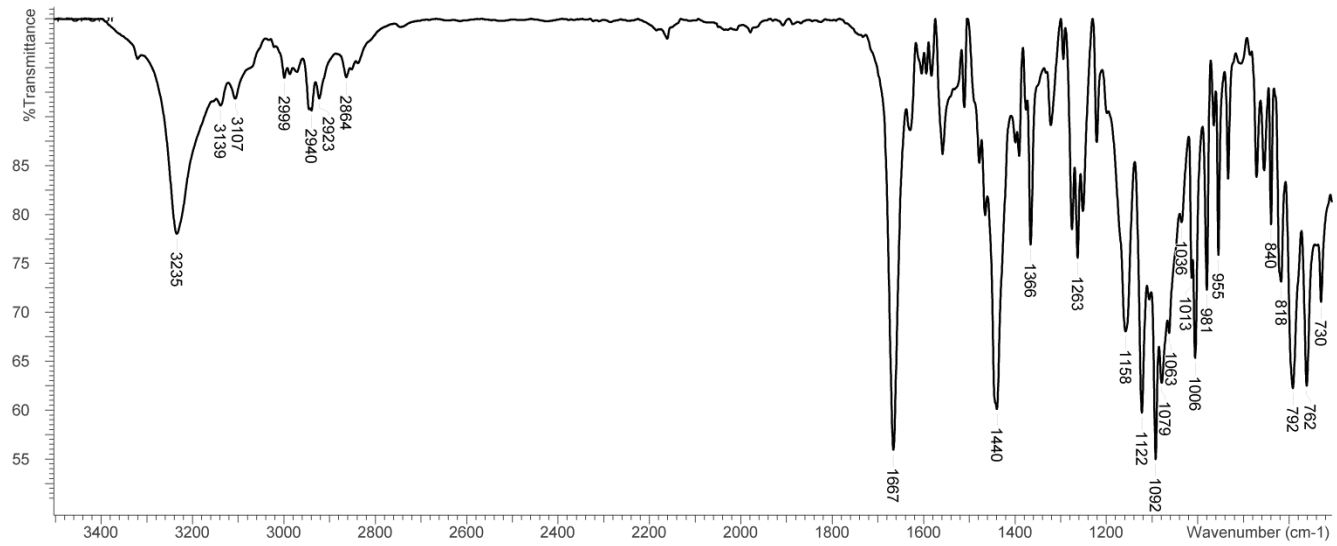
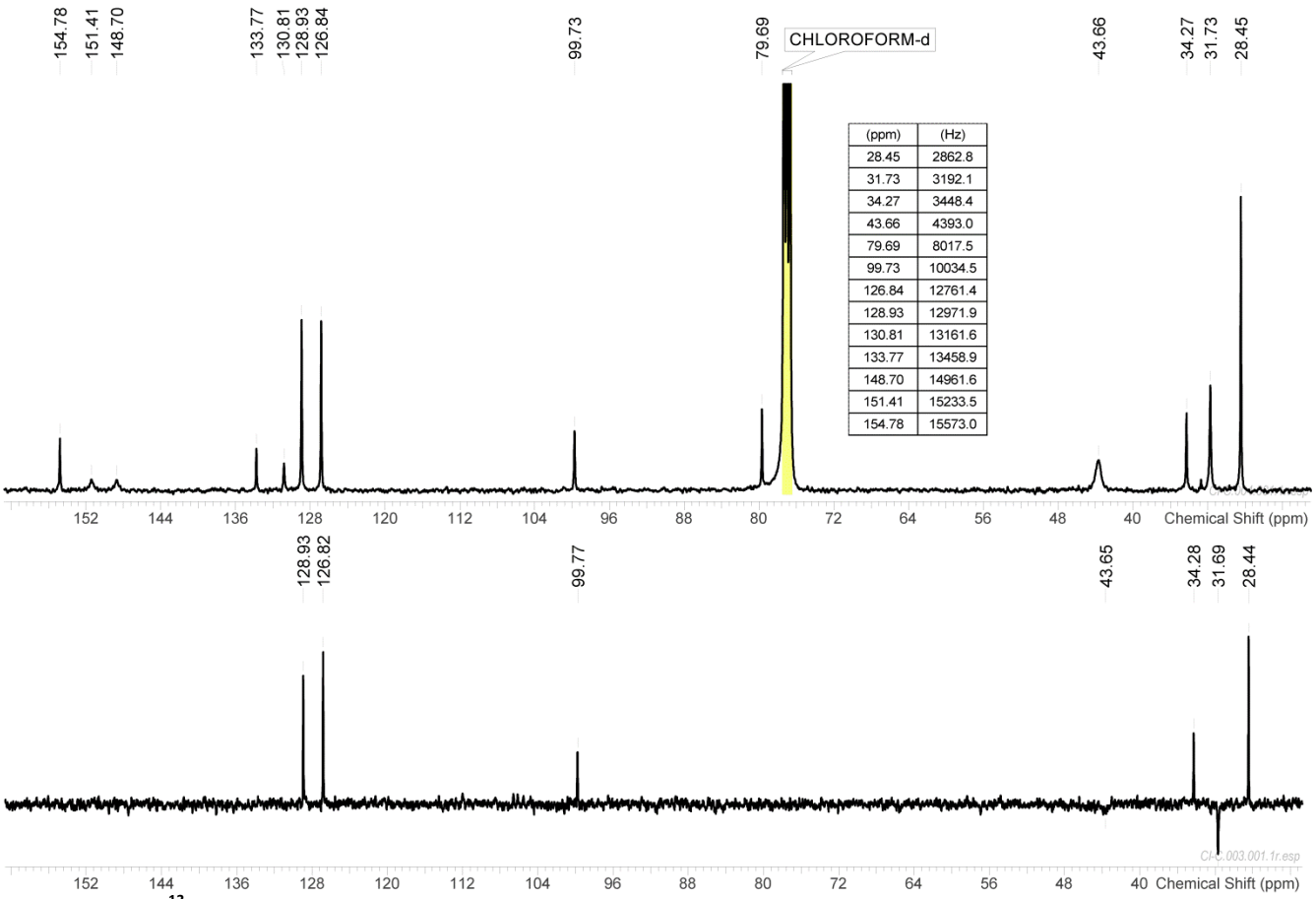


Figure 5.1.7.3: IR (ATR) of *tert*-butyl 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine-1-carboxylate



(ppm)	(Hz)
28.45	2862.8
31.73	3192.1
34.27	3448.4
43.66	4393.0
79.69	8017.5
99.73	10034.5
126.84	12761.4
128.93	12971.9
130.81	13161.6
133.77	13458.9
148.70	14961.6
151.41	15233.5
154.78	15573.0

Figure 5.1.7.4: ^{13}C NMR & DEPT-135 (100 MHz, $CDCl_3$) of *tert*-butyl 4-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine-1-carboxylate

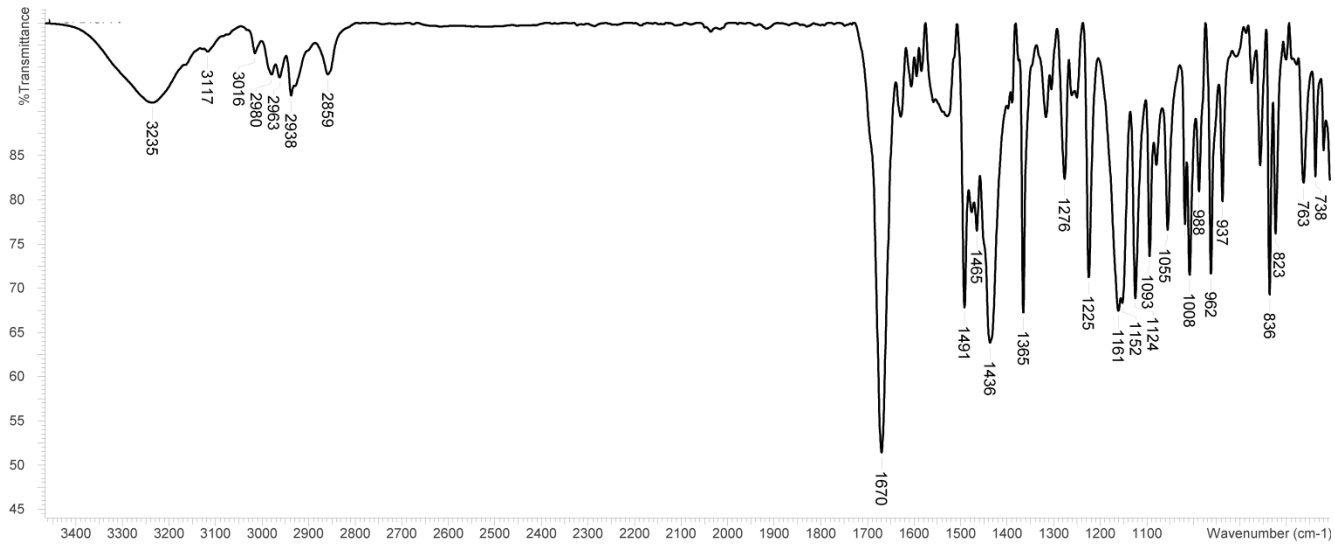


Figure 5.1.7.5: IR (ATR) of *tert*-butyl 4-[4-bromo-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine-1-carboxylate

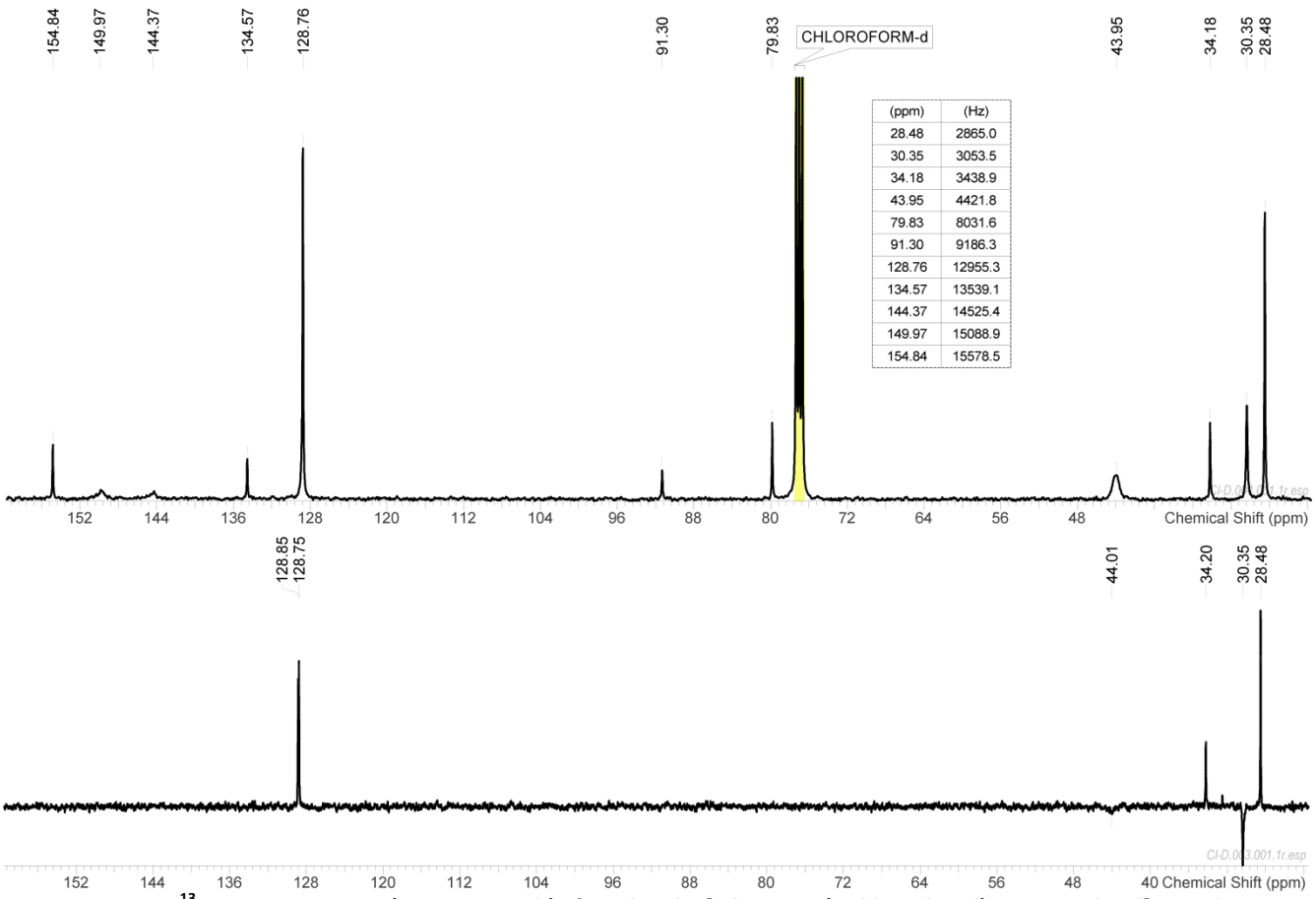
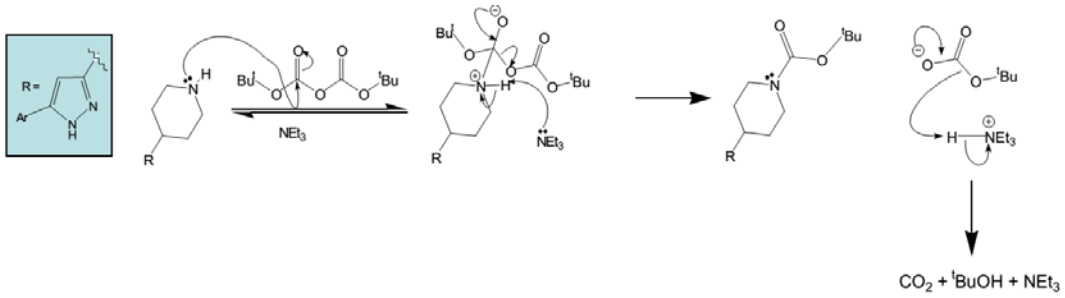


Figure 5.1.7.6: ^{13}C NMR & DEPT-135 (100 MHz, $CDCl_3$) of *tert*-butyl 4-[4-bromo-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]piperidine-1-carboxylate

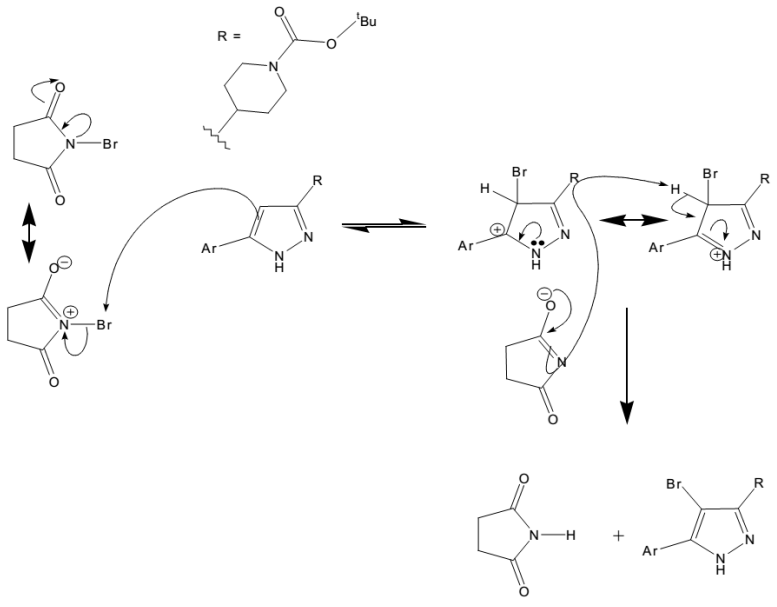
Mechanistic details

The Boc protection is driven by the release of carbon dioxide. The pyrazole (pK_a 14) is aromatic and this feature is retained, wheres the piperdine (pK_a 11) is attacked and the intermediate deprotonated by the base.



Scheme 5.1.7.1: Mechanism for reaction 1

In the second reaction the reagent as well as the intermediate is resonance-stabilised which facilitates the bromination of the pyrazole ring.



Scheme 5.1.7.2: Mechanism for reaction 2

Preparation of *p*-bromoaniline

Supplementary Material

Experimental notes

Figures

Experimental notes

Background topics

This experiment aims to illustrate a multi-step aromatic synthesis and the strategy of introduction and removal of protective groups.

The experiment is appropriate to intermediate level students, who are encouraged to rationalise the chemistry of aromatic compounds (and to distinguish it from that of other unsaturated compounds) and some experimental details through the answers to a set of additional questions.

This three-step synthesis was already realized by over 120 students of the Faculty of Sciences and Technology, Universidade Nova de Lisboa (in classes of 22 students/class, 11 groups of two), who accomplished the work in two (3 hours) laboratory sessions. Alternatively, the work may also be realized in three sessions for a more detailed discussion of the results (including spectral interpretation).

It is important that the students understand the necessity of using a multistep synthesis instead of a direct electrophilic substitution reaction. Ask them about the advantages. Try also to sensitize them to the strategy of using protective groups (giving other examples).

Hints for the answers to the proposed questions and topics to discussion:

1. The first reaction is a nucleophilic addition of the amino group of aniline to the carbonyl group of acetic anhydride; the second is an aromatic electrophilic substitution; the last one is the basic hydrolysis of the amide.
2. If equimolar quantities of aniline and bromine are used, in a direct bromination of aniline, a mixture of tri- (major product), di- and mono-brominated products would be formed, leading to a decrease in the yield and purity of the desired compound.
3. Acetamido is less electron-donating than amino.
4. In acidic medium, Zn^{0} reduces the oxidation products of aniline.
5. Bisulphite reduces bromine to bromide, which is much less hazardous.

Experimental details

Experimentally the work has a medium difficulty and a high hazard level (use of bromine and aniline, which require special care, as indicated in Safety and Experimental procedure sections).

Concerning the third step of the synthesis (preparation of *p*-bromoaniline), the classical experimental procedure[1] recommends to add water to the reaction mixture and to extract the aqueous solution with ethyl ether. After collecting the extract, drying and evaporating the solvent, the residue is poured over ice cold water in order to precipitate the product. However, the procedure here proposed for this experiment revealed to be efficient to obtain the final product and much less time consuming. It would be interesting, if there is availability, to suggest a group of students to use one technique and another group to use the other one, and then compare the results.

Considering the three products sequentially prepared – acetanilide, *p*-bromoacetanilide and *p*-bromoaniline – the students are asked to purify only the last one (by recrystallization) and to characterize it by IR and ^{1}H-NMR spectroscopies. However, they are also asked to keep a sample of each one of the two first crude products. They can measure the three melting points (as asked in the Results interpretation section) but, if the instructor considers convenient, it is also possible to acquire the spectra of all prepared compounds.

To evaluate the eventual formation of by-products (e.g. *o*-bromoaniline, tribromoaniline) a simple TLC test can be performed. For this purpose a silica gel coated aluminium plate with fluorescence indicator and methylene chloride (dichloromethane) as eluent can be used. After development and revelation of a sample of the final (purified) product, the presence of a single spot indicates the formation of *p*-bromoaniline as the unique product. If other spots are detected, by-products have also been formed, that can be compared with standards, if available.

Some experimental results obtained by the students in the laboratory are presented in Table 5.1.8.1.

Table 5.1.8.1. Typical experimental results obtained in the Laboratory

Yield of crude acetanilide	Not significant. The crude product contains a large amount of water and drying is not necessary for the next step.
Melting point of crude acetanilide	74-77ºC
Yield of crude *p*-bromoacetanilide	70%
Melting point of crude *p*-bromoacetanilide	158-160ºC
Yield of purified *p*-bromoaniline	55%
Melting point of purified *p*-bromoaniline	44-46 ºC

To prepare samples for IR spectroscopy, use a small amount of a dried sample of the compound and dry KBr and the adequate material.

For ^{1}H-NMR spectroscopy deuterochloroform, acetone-d_6 or DMSO-d_6 are suitable solvents.

Figures

Photos of the experiment

Step 1

Figure 5.1.8.1. Acetylation of aniline

Figure 5.1.8.2. Precipitation of acetanilde

Step 2

Figure 5.1.8.3. Set-up for the bromination step

Figure 5.1.8.4. Formation of *p*-bromoacetanilde

Figure 5.1.8.5. Precipitation of *p*-bromoacetanilde

Figure 5.1.8.6. Crude *p*-bromoacetanilde

Step 3

Figure 5.1.8.7. Hydrolysis of *p*-bromoacetanilde

Figure 5.1.8.8. Crude *p*-bromoaniline

Figure 5.1.8.9. Recrystallization of *p*-bromoaniline

Figure 5.1.8.10. Purified *p*-bromoaniline

Spectra

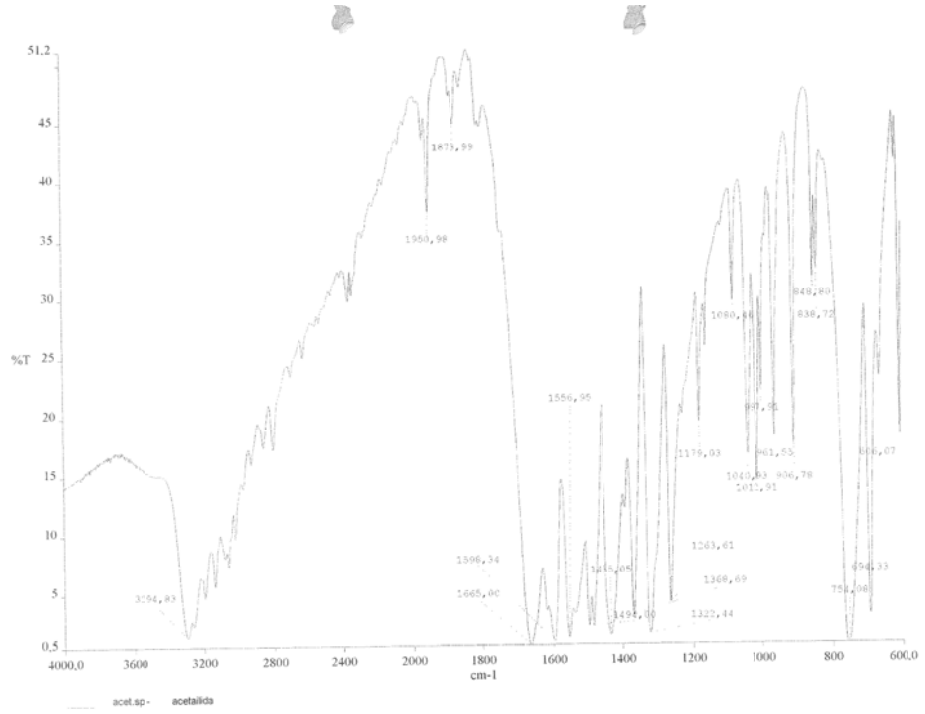


Figure 5.1.8.11. IR spectrum (in KBr) of acetanilide

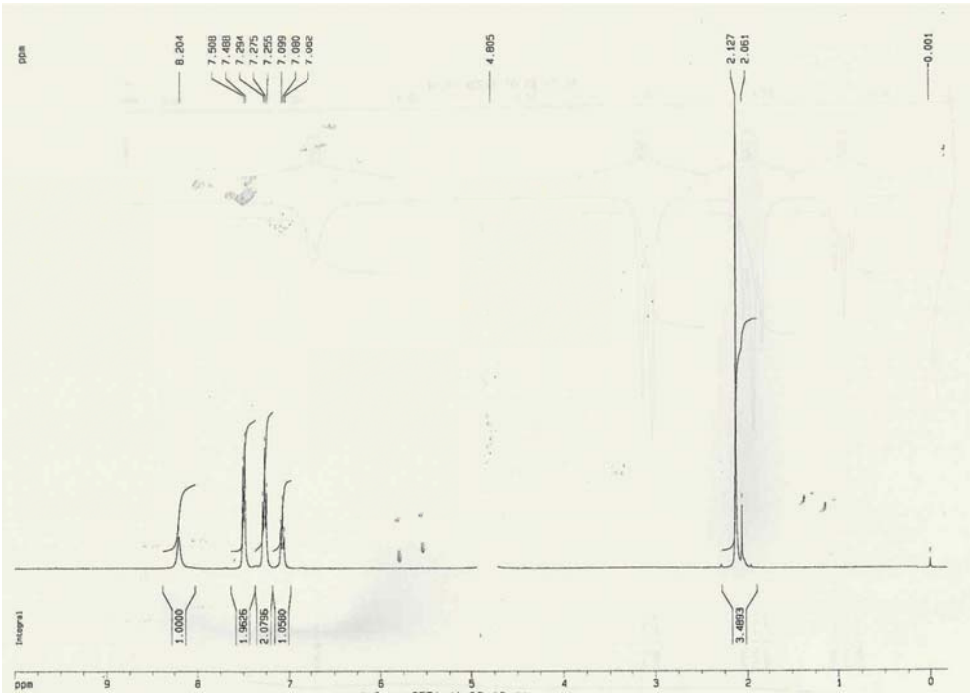


Figure 5.1.8.12. ^{1}H-NMR spectrum (in $CDCl_3$) of acetanilide

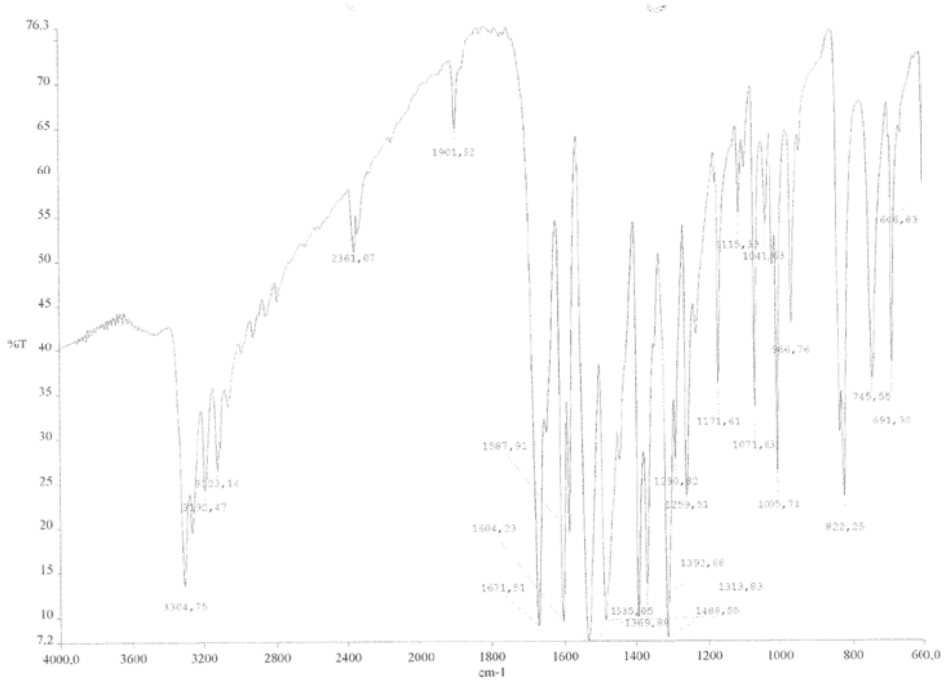


Figure 5.1.8.13. IR spectrum (in KBr) of *p*-bromoacetanilide

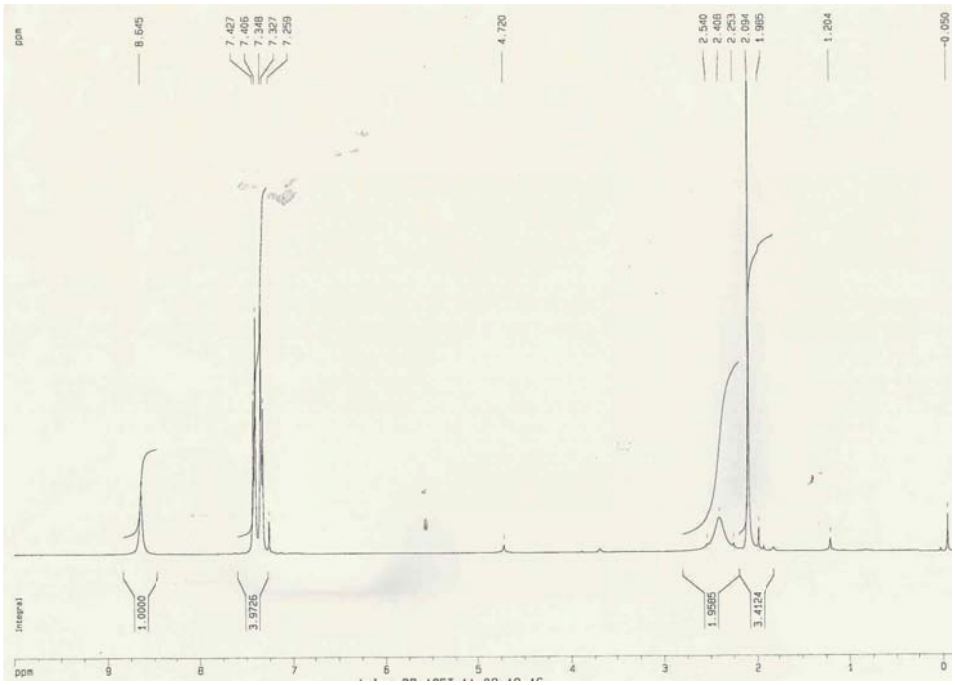


Figure 5.1.8.14. ^{1}H-NMR spectrum (in $CDCl_3$) of *p*-bromoacetanilide

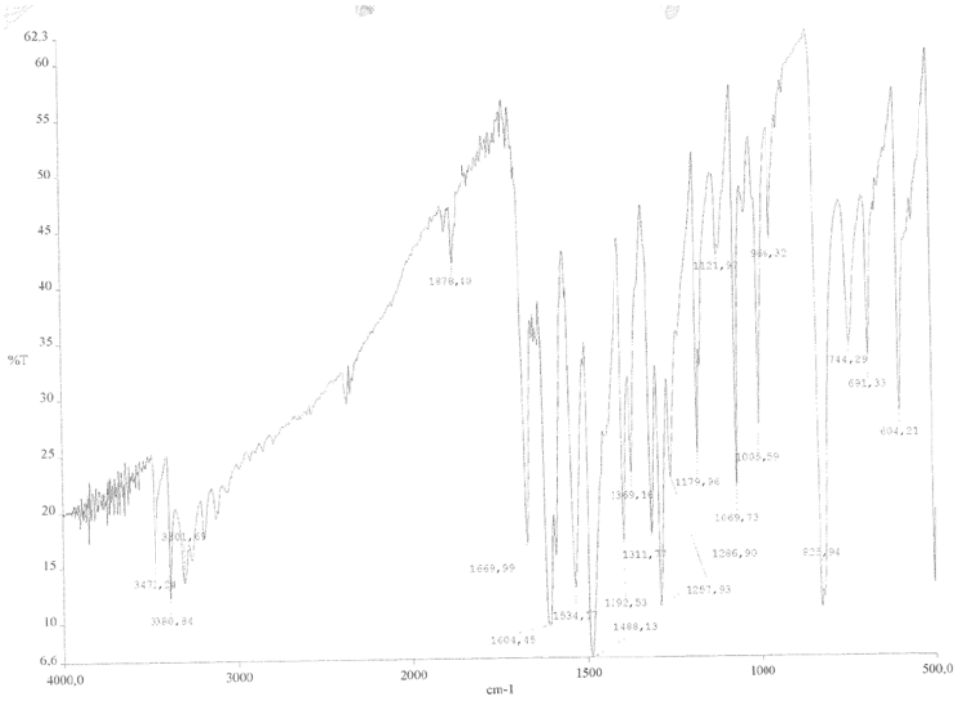


Figure 5.1.8.15. IR spectrum (in KBr) of *p*-bromoaniline

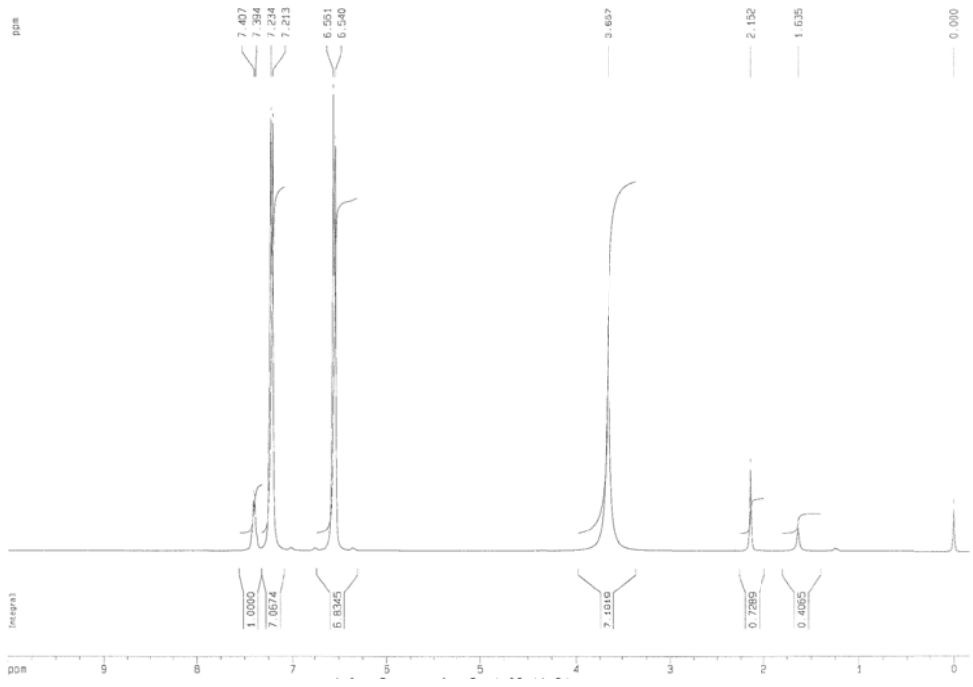


Figure 5.1.8.16. ^{1}H-NMR spectrum (in $CDCl_3$) of *p*-bromoaniline

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[1] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, *VOGEL's Textbook of Practical Organic Chemistry*, Longman Scientific & Technical, 5th Ed., 1989, 6, 916