Aerobic Alcohol Oxidation Using a Cu(I)/TEMPO Catalyst System

Supplementary Material

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Experimental Notes

Although the experimental protocol is detailed only for the conversion of 4-nitrobenzyl alcohol to the corresponding aldehyde, the Cu(bpy)/TEMPO catalyst system described is effective for a range of *para*-substituted benzyl alcohols 4-R-$C_6H_4CH_2OH$ (R = Cl, Br, OMe, Me, ^{i}Pr) and also 3-nitrobenzyl alcohol.[1,2] The reactions proceed in standard glassware at room temperature with ambient air as the stoichiometric oxidant, and the entire procedure is readily completed within a 3-hour laboratory period. Reaction times range from 30-60 min, with average isolated yields of ~65%. The procedure has been successfully completed by >2000 undergraduate students in an introductory organic chemistry laboratory course at the University of Wisconsin-Madison.

The benzyl alcohol solution will turn from colorless/pale yellow to pale green upon addition of solid CuBr. It will turn deep red-brown upon addition of bpy and TEMPO, and will fade to a lighter red-brown upon drop-wise addition of NMI. Some students interpret the fading of color upon addition of NMI to be the color change mentioned in the lab procedure and quench the reaction before it has begun.

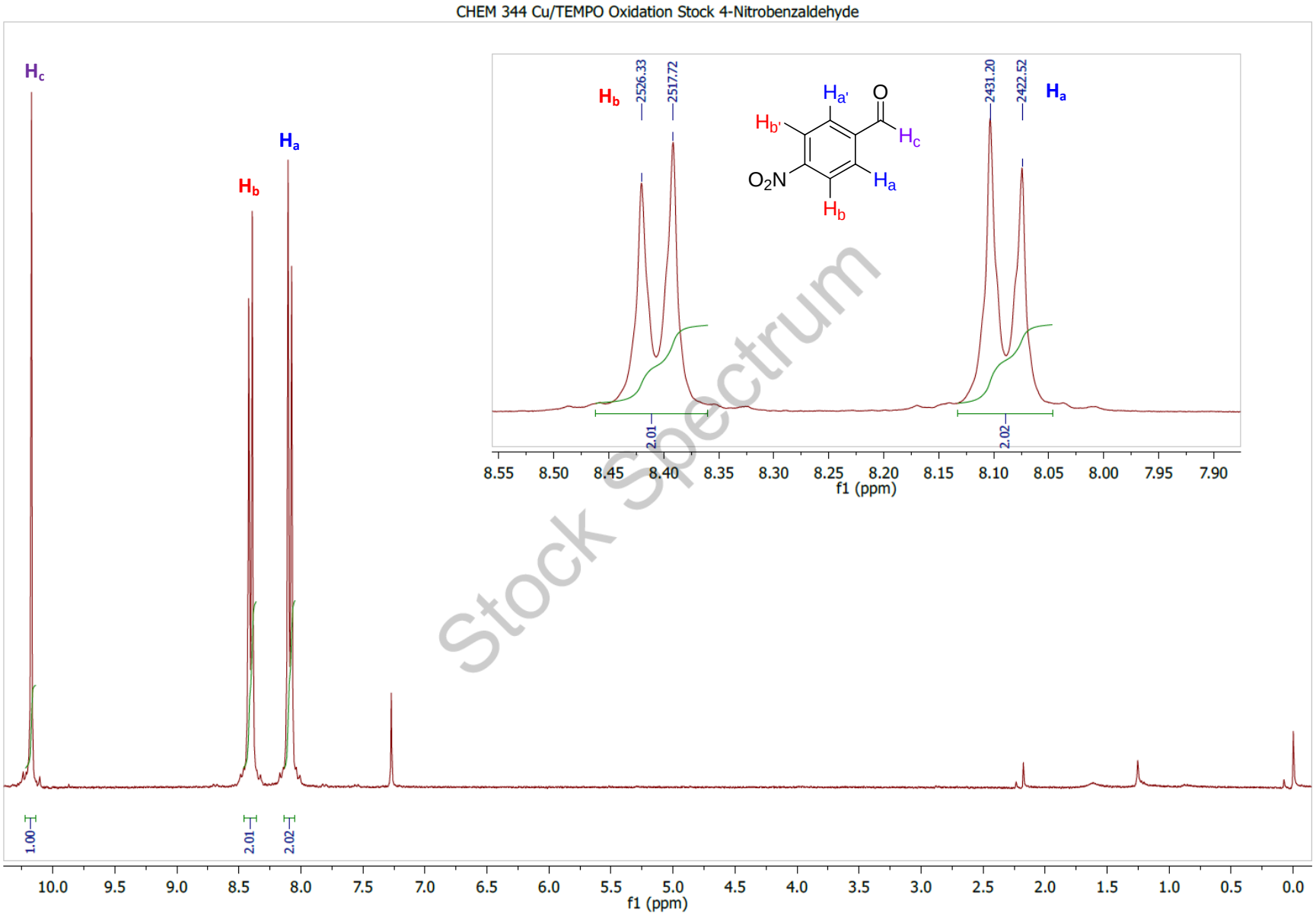
A color change from red-brown to a turbid green signifies complete consumption of the benzyl alcohol. Students should stir the reaction for ~5 min following the color change from red-brown to green while they prepare for the work-up and purification steps. Dilution of the reaction mixture with pentane and water should give a pale pink organic layer (residual TEMPO) and a blue aqueous layer ($[Cu(bpy)(OH)]_2Br_2$ complex) in the separatory funnel. During work-up, 4-nitrobenzaldehyde may precipitate in the separatory funnel upon addition of water to the reaction mixture. Addition of ~10 mL acetone is sufficient to dissolve the solid.

The aldehyde is isolated either as a solid (R = NO_2, Cl, Br) or an oil (R = OMe, Me, ^{i}Pr). The crude products may be tinged red-pink due to residual TEMPO. Rinsing the solids with cold pentane removes the TEMPO and leaves a colorless solid. Washing the oils with pentane is not effective. Significant TEMPO contamination of the aldehyde results in broadening of the ^{1}H-NMR signals.

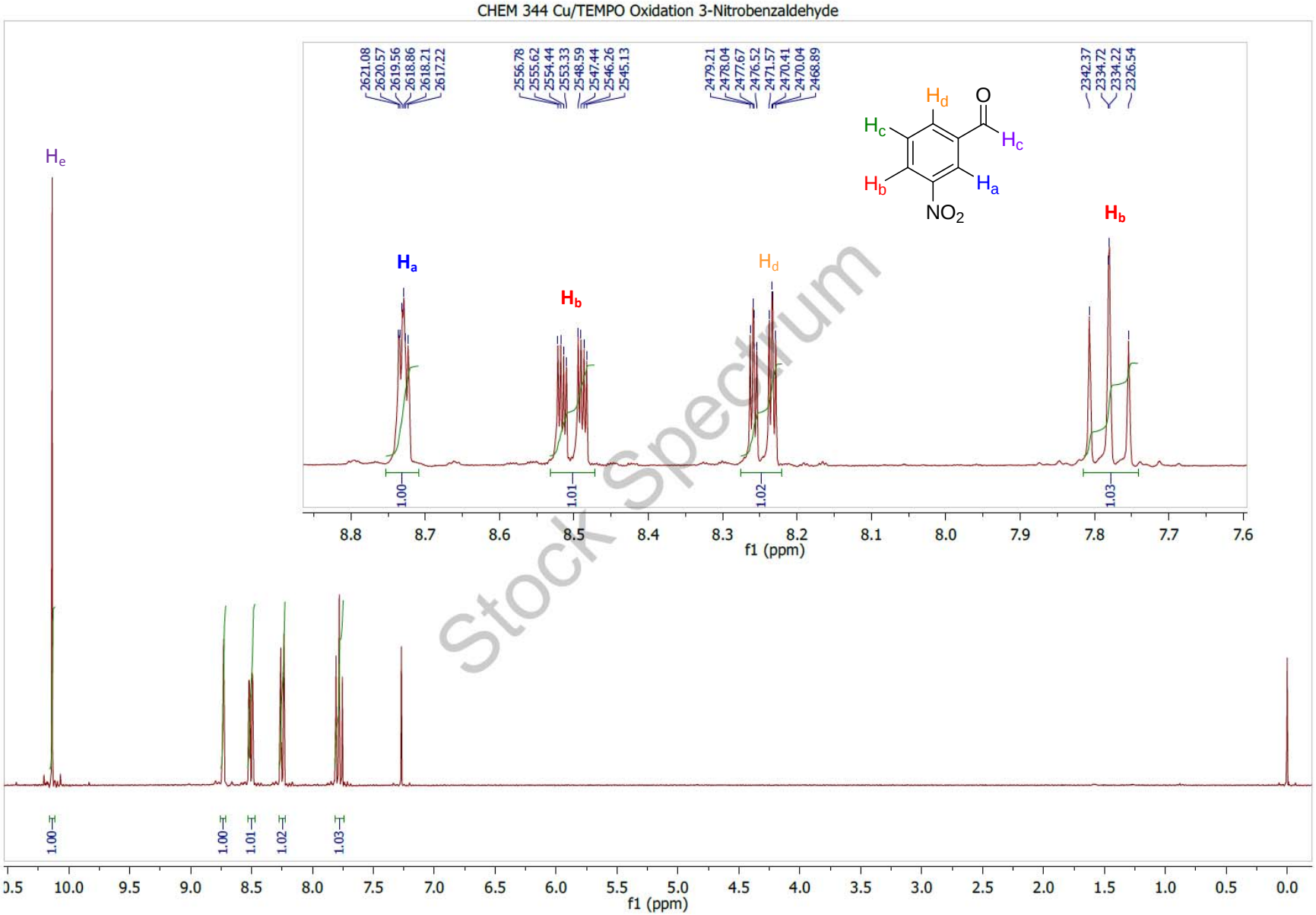
Provided that the recommended reaction conditions have been applied, students should not observe residual starting material in the NMR or IR spectra. Occasionally, however, students will quench the reaction before complete conversion of the benzylic alcohol to the aldehyde (signified by the red-to-green color change of the reaction mixture). In these cases, signals due to the starting benzaldehyde can be observed in the student ^{1}H-NMR spectrum. The benzaldehyde is not further oxidized to the corresponding benzoic acid under the reported reaction conditions, and thus signals due to a benzoic acid derivative should not be present in the student ^{1}H-NMR or IR spectra.

^{1}H-NMR Spectra of Substituted Benzaldehydes

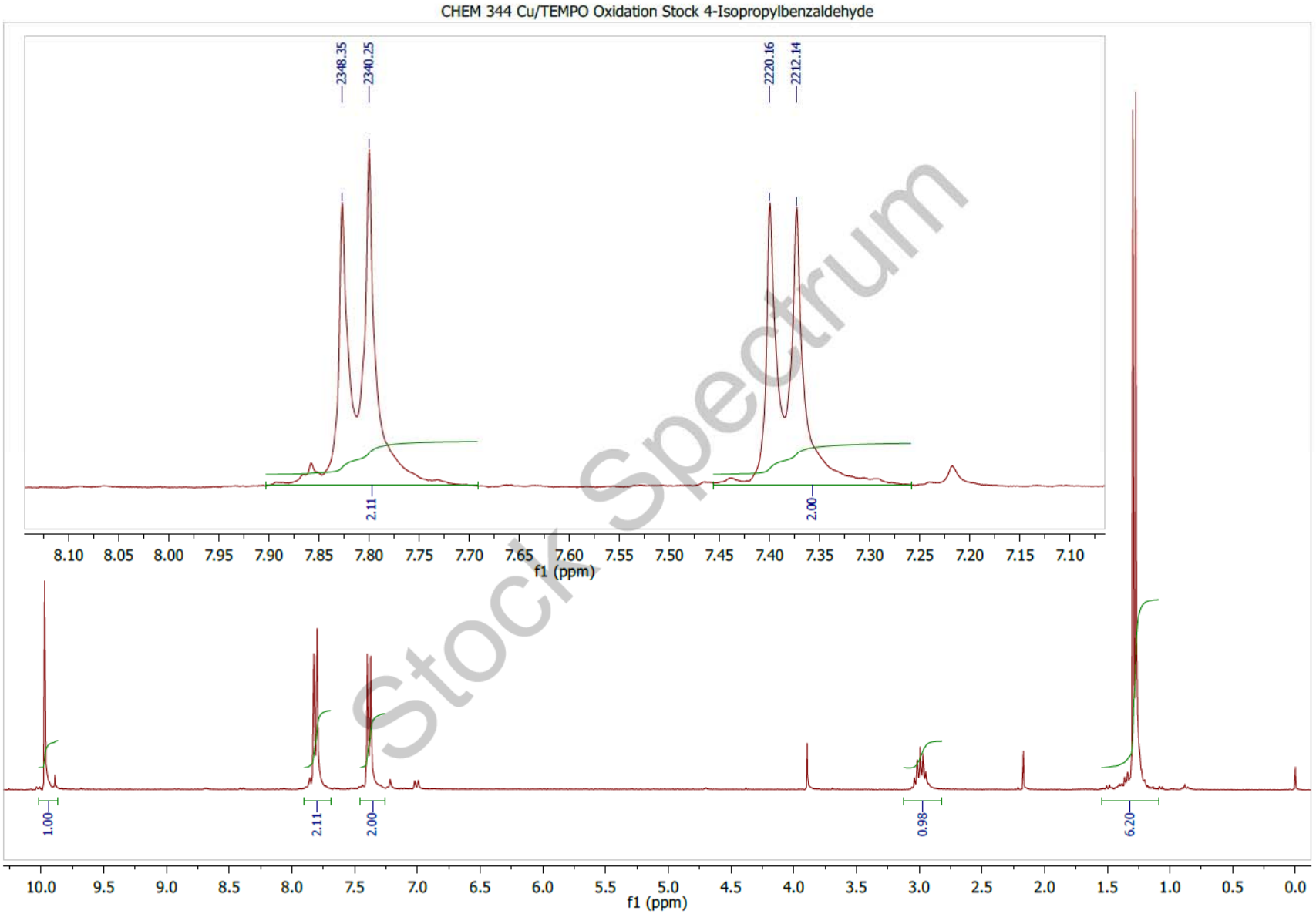
4-Nitrobenzaldehyde



3-Nitrobenzaldehyde

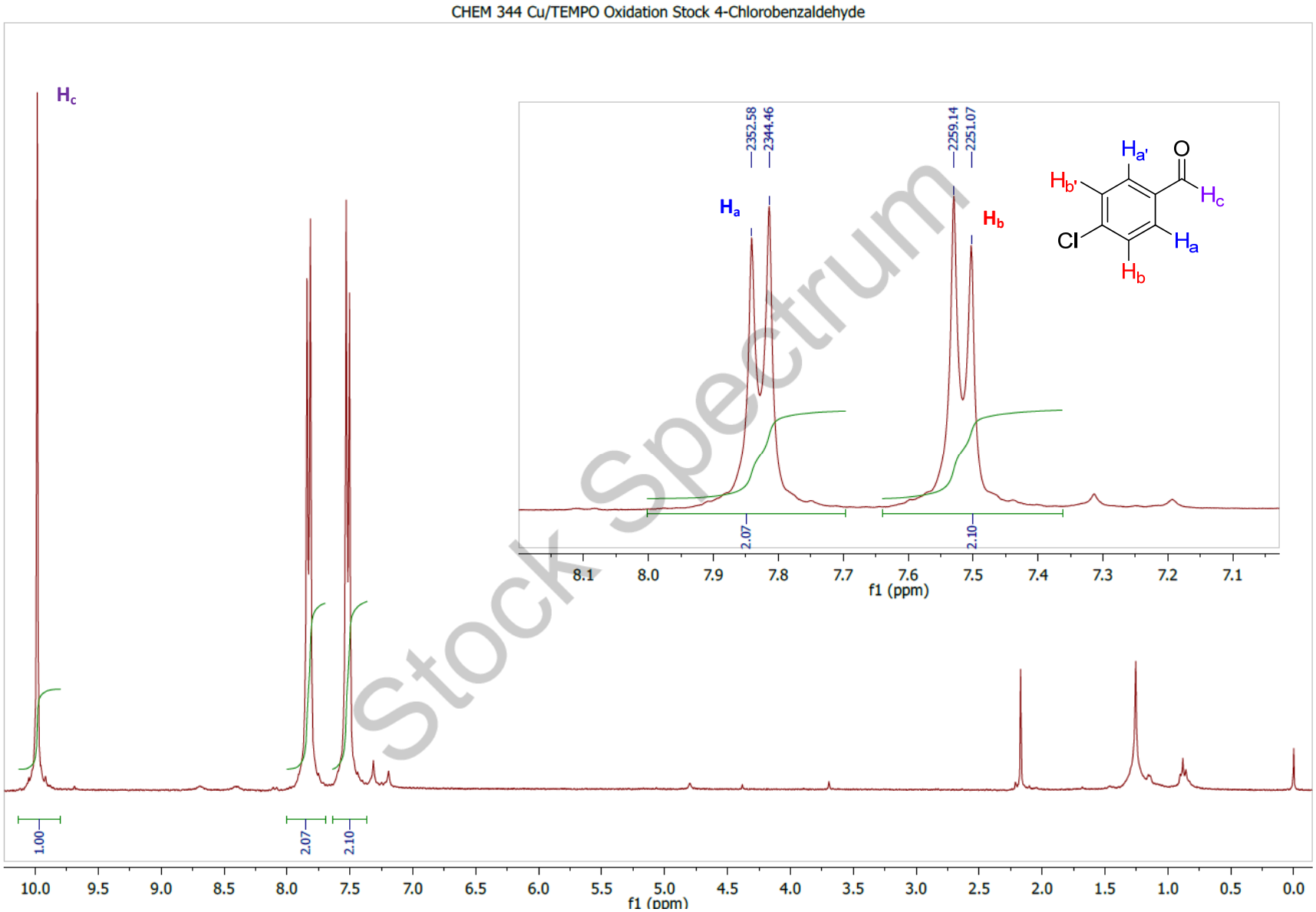


4-Isopropylbenzaldehyde

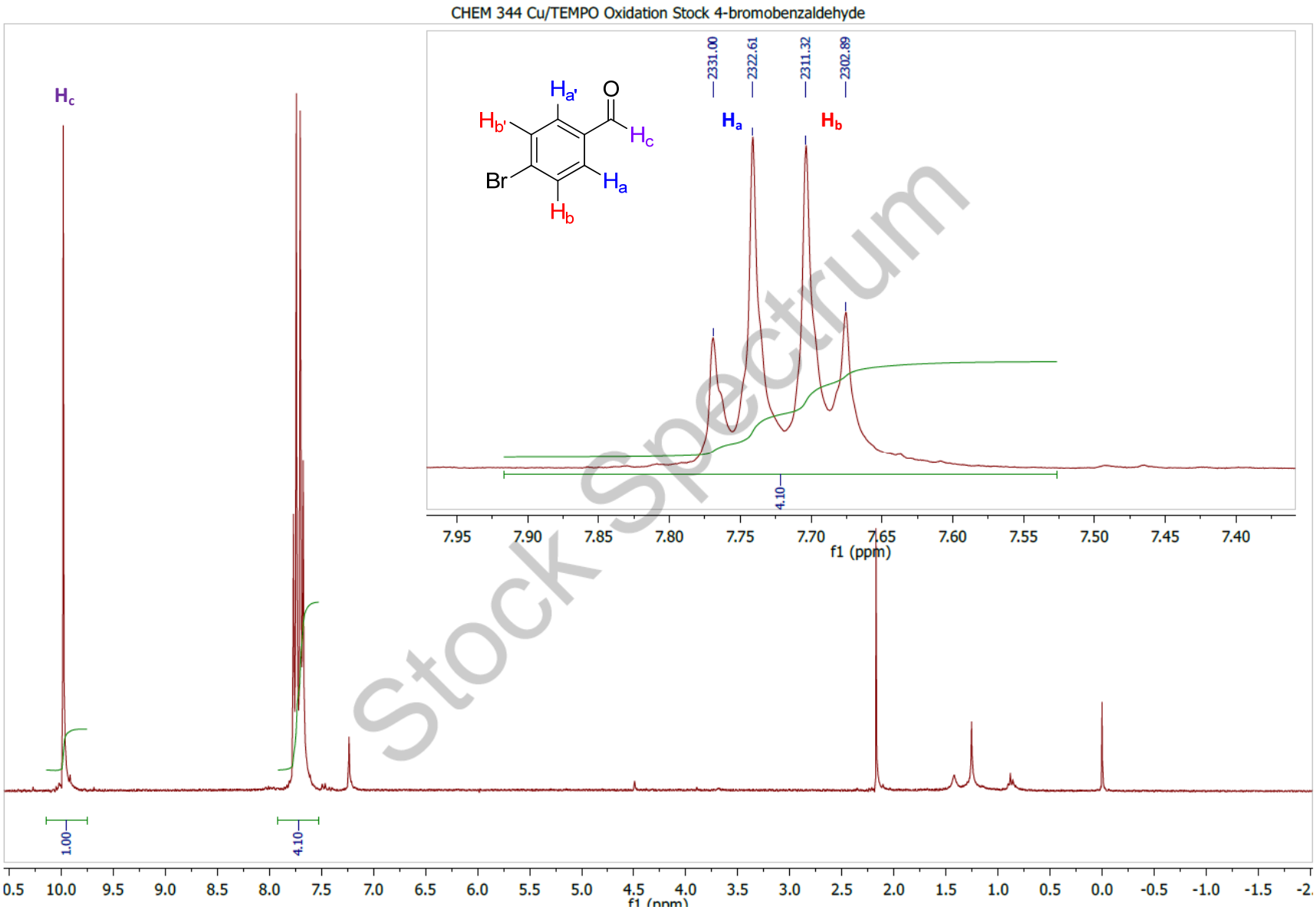


H_c

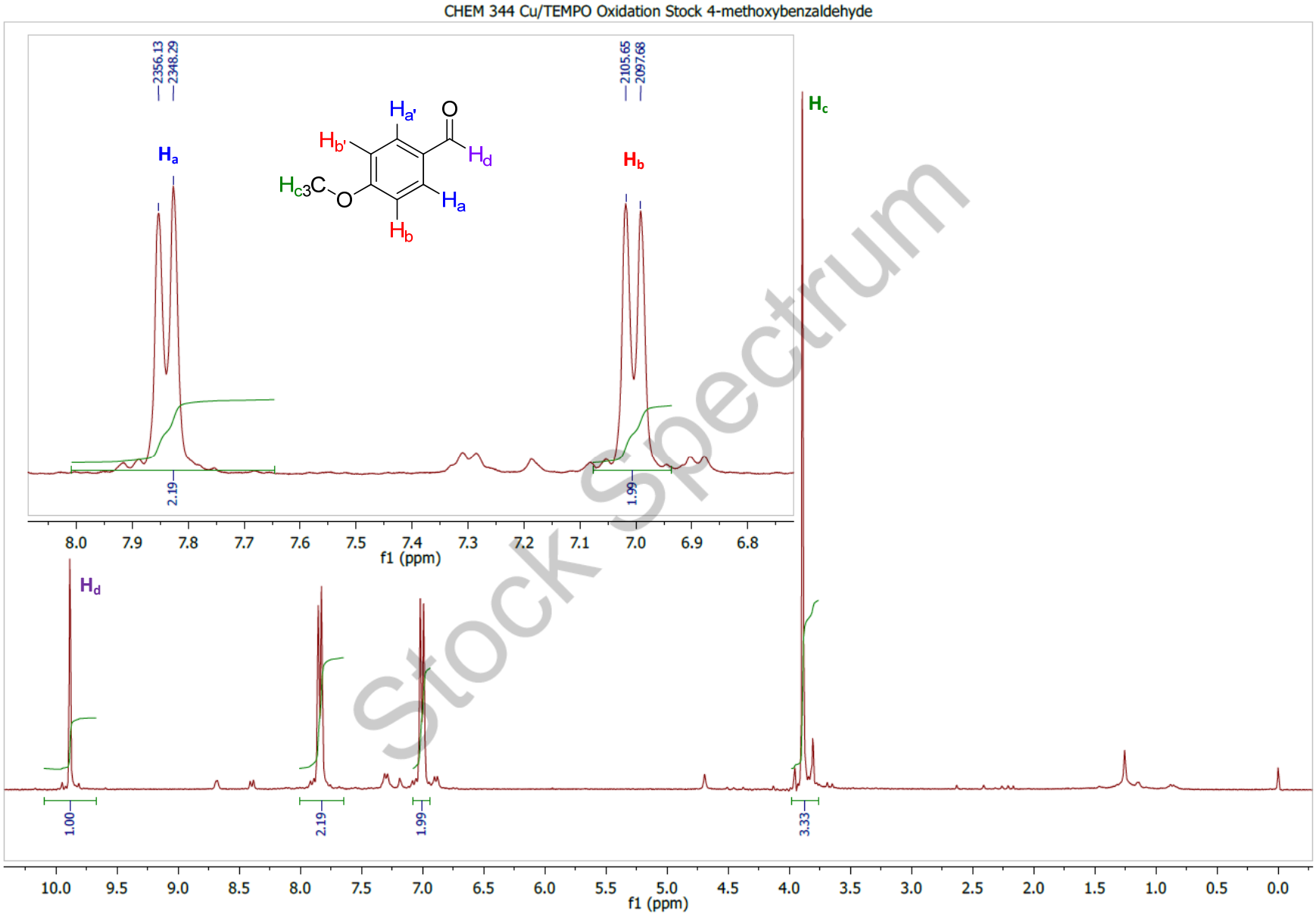
4-Chlorobenzaldehyde



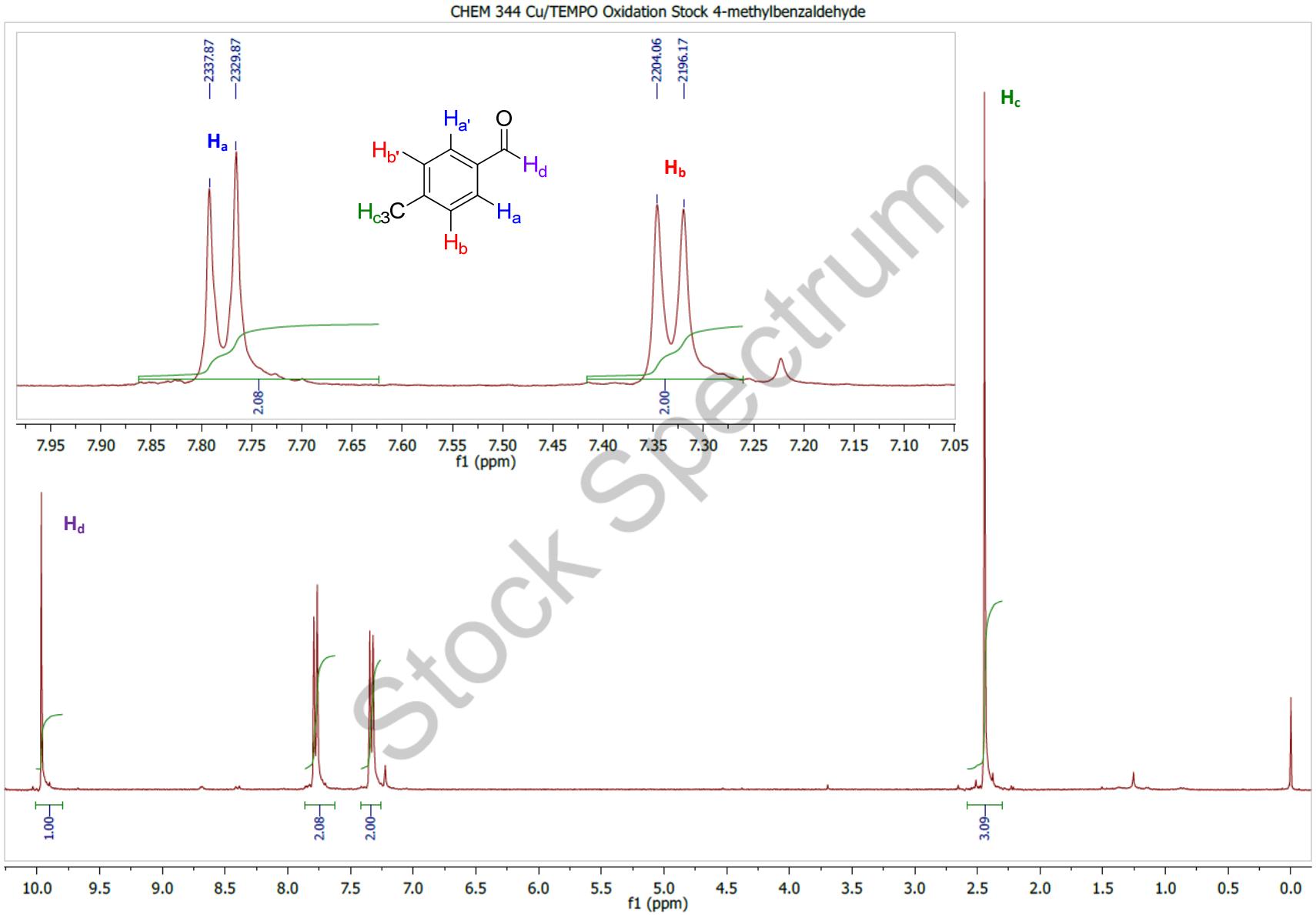
4-Bromobenzaldehyde



4-Methoxybenzaldehyde

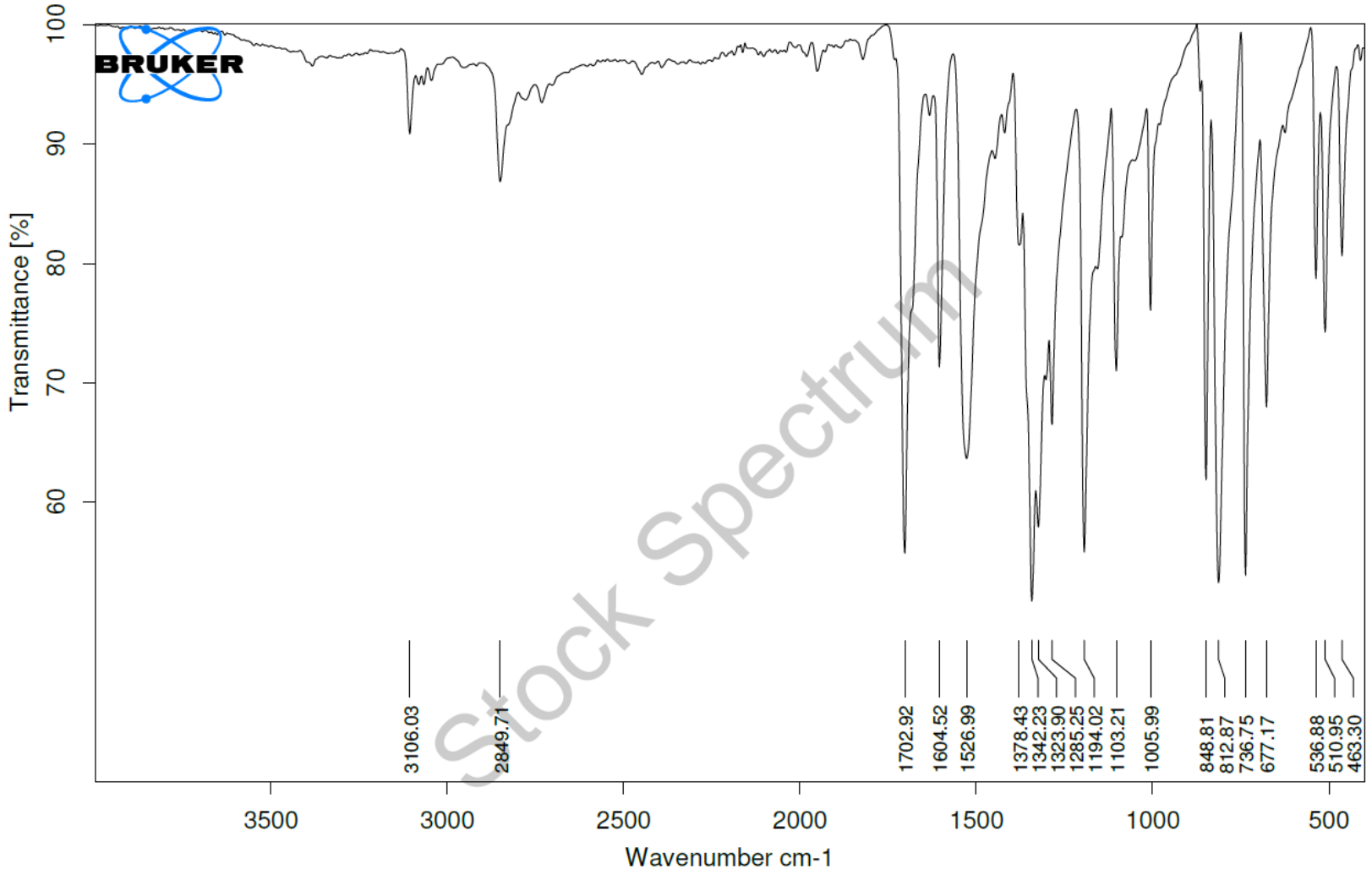


4-Methylbenzaldehyde



ATR-IR Spectra of Substituted Benzaldehydes

4-Nitrobenzaldehyde



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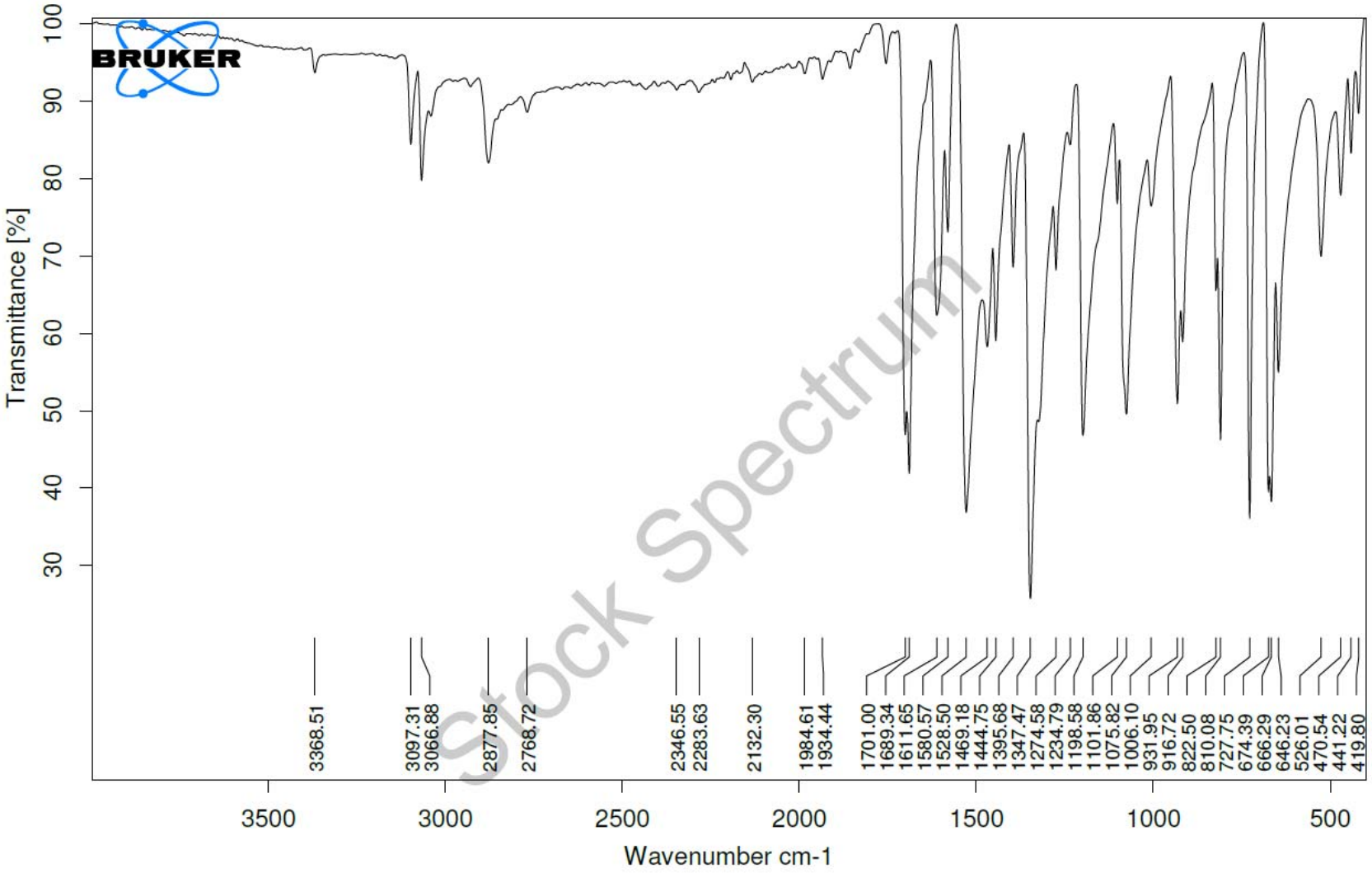
3-Nitrobenzaldehyde



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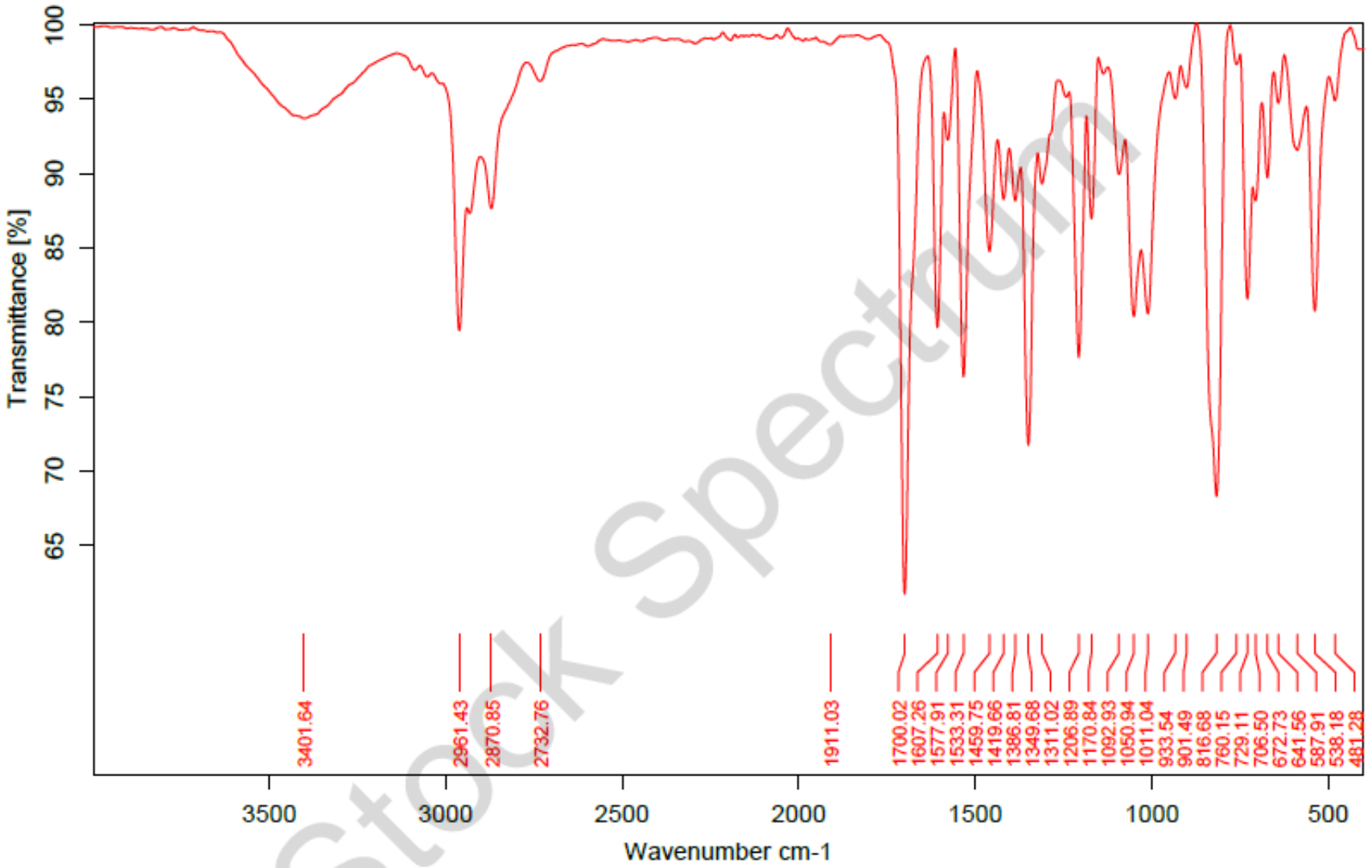
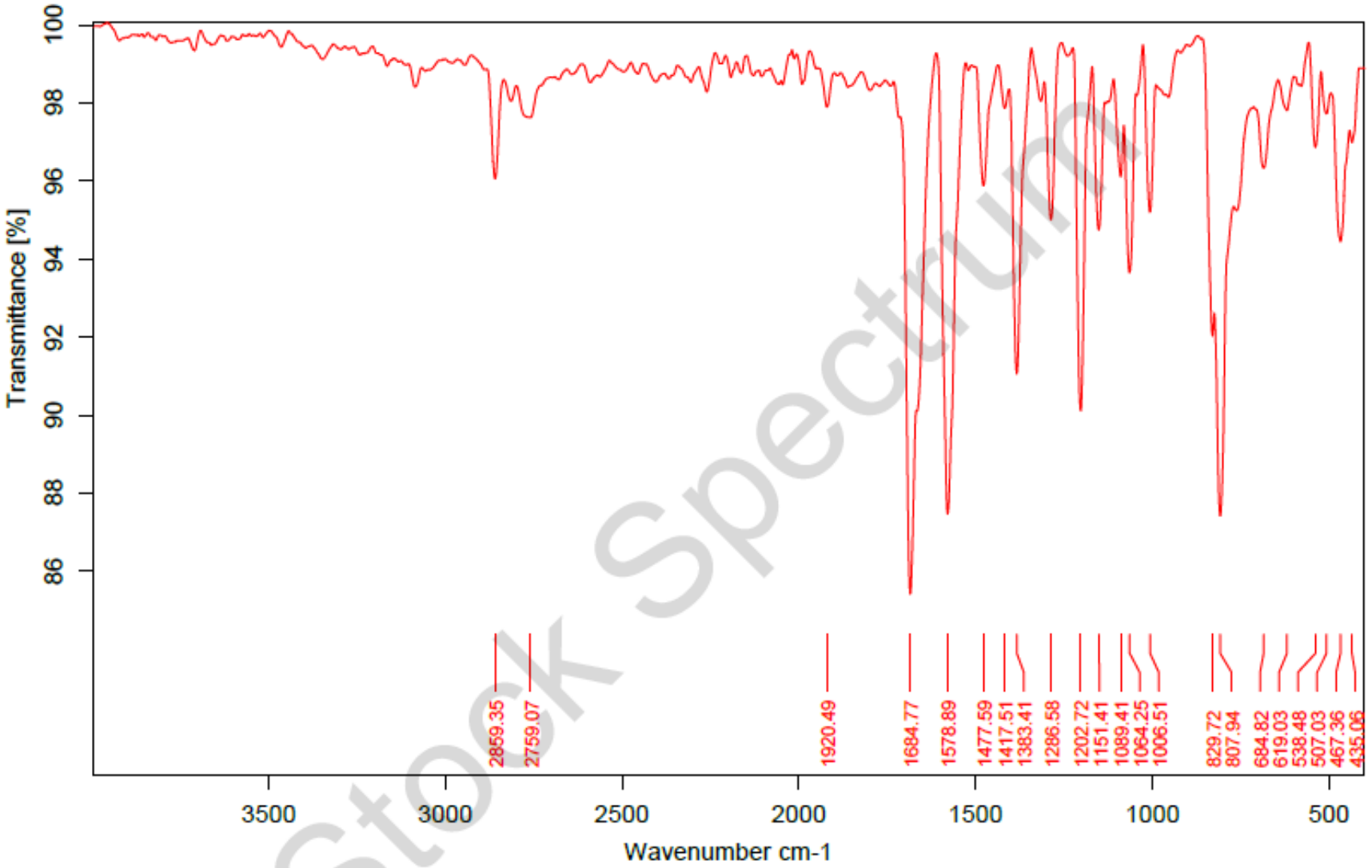
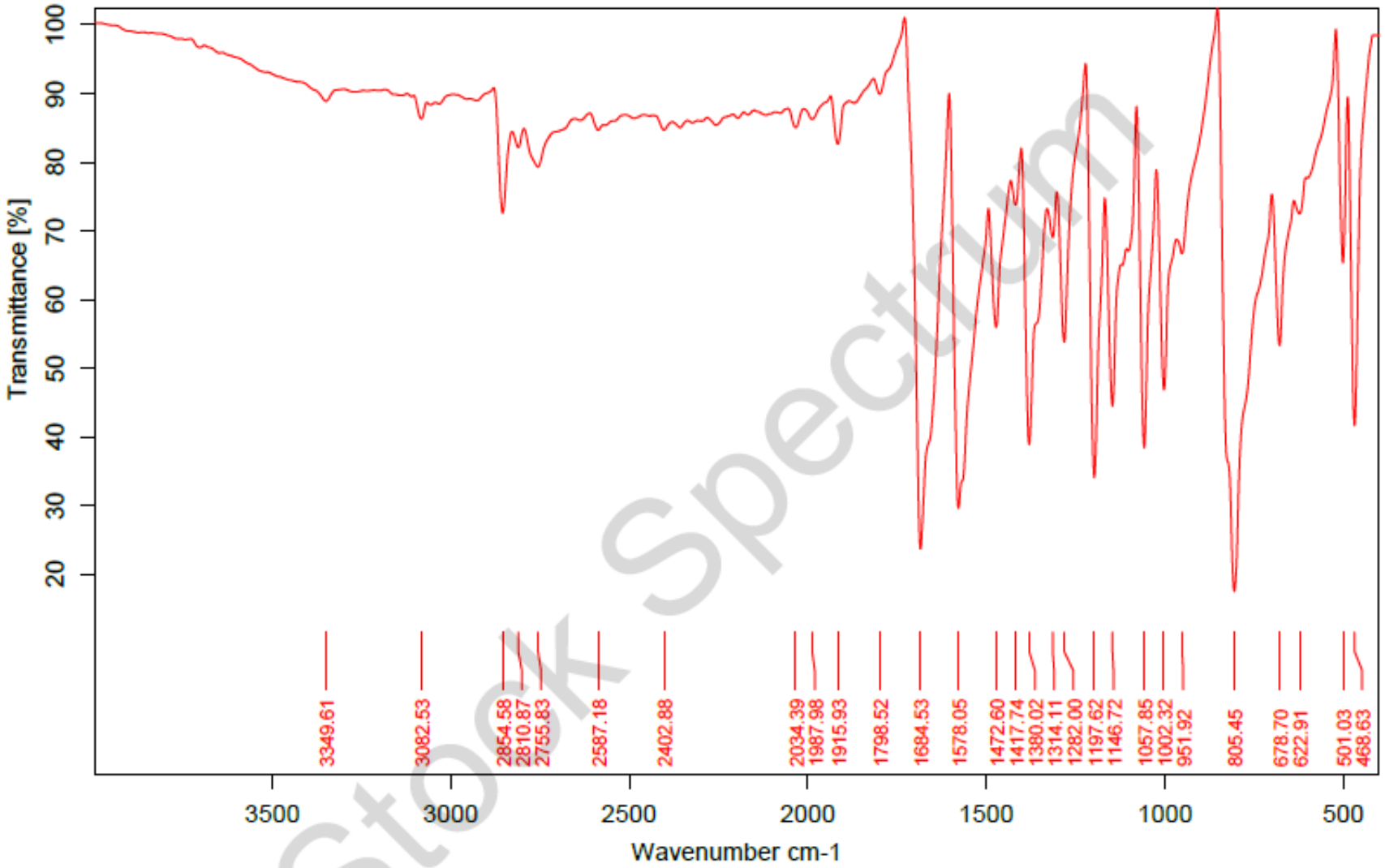
4-Isopropylbenzaldehyde



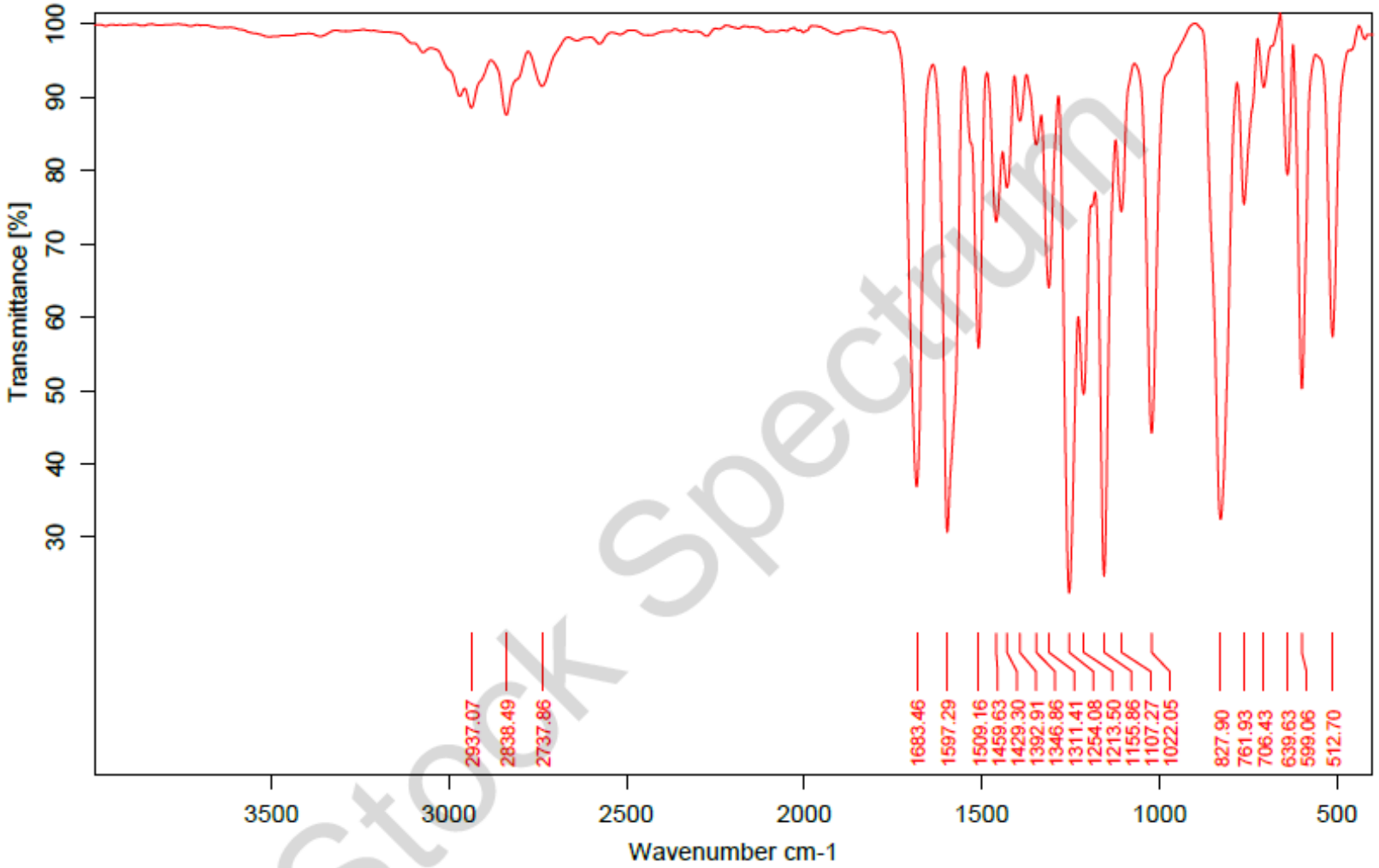
4-Chlorobenzaldehyde



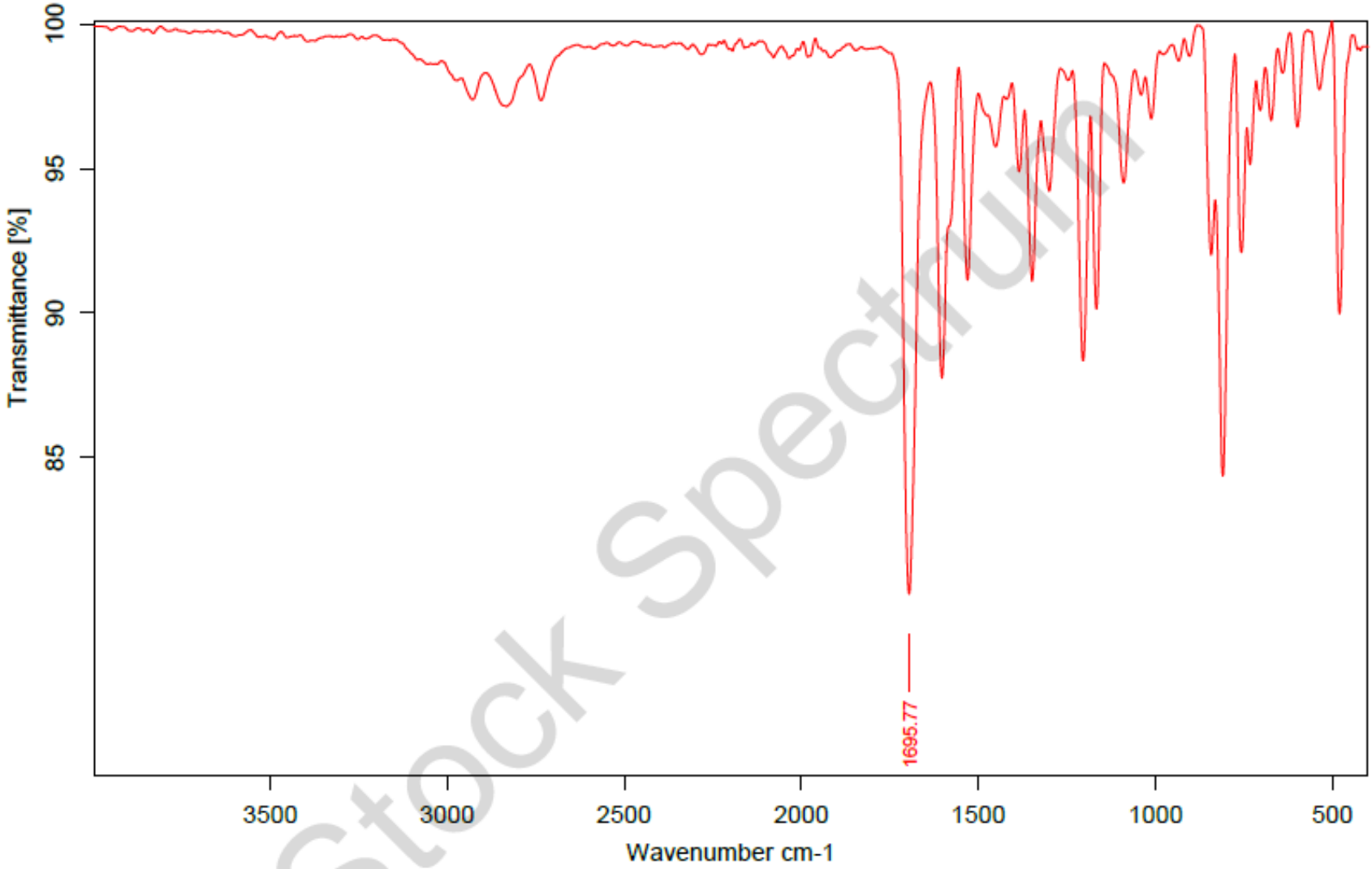
4-Bromoobenzaldehyde



4-Methoxybenzaldehyde



4-Methylbenzaldehyde



CAS Numbers for Reagents and Solvents

Compound	CAS Number
Acetone	67-64-1
2,2'-Bipyridyl (bpy)	366-18-7
Copper(I) bromide	7787-70-4
Deuterochloroform	865-49-6
N-Methyl imidazole (NMI)	616-47-7
(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO)	2564-83-2
4-Bromobenzyl alcohol	873-75-6
4-Bromobenzaldehyde	1122-91-4
4-Chlorobenzyl alcohol	873-76-7
4-Chlorobenzaldehyde	104-88-1
4-Isopropylbenzyl alcohol	536-60-7
4-Isopropylbenzaldehyde	122-03-2
4-Methoxylbenzyl alcohol	105-13-5
4-Methoxybenzaldehyde	123-11-5
4-Methylbenzyl alcohol	589-18-4
4-Methylbenzaldehyde	104-87-0
4-Nitrobenzyl alcohol	619-73-8
4-Nitrobenzaldehyde	555-16-8
3-Nitrobenzyl alcohol	619-25-0
3-Nitrobenzaldehyde	99-61-6

Magnesium sulfate (anhydrous)	7487-88-9
Pentane	109-66-0

References

1) For spectroscopic data for the starting benzyl alcohols, see: S. R. Roy, S. C. Sau, and S. K. Mandal, *J. Org. Chem*. 2014, **79**, 9150.

2) For spectroscopic data for the benzaldeyhde products, see: M. Iinuma, K. Moriyama, and H. Togo, *Tetrahedron,* 2013, **69**, 2961.

Chemoselective oxidation of 1,2-tetradecanediol

Supplementary Material

The main purpose of this experiment is to demonstrate the selectivity of oxidation with sodium hypochlorite in the presence of TEMPO as a catalyst. This catalytic system was efficiently used to oxidize the primary hydroxyl group to aldehydes even in the industrial procedures. The primary alcohol is oxidized also in the presence of secondary hydroxyl group, what is not usual selectivity.

The procedure described does not provide toxicity problems. Waste after reduction of hypochlorite (aqueous phase) does not contain any harmful compounds and can be easily removed. The substrate and the product of the reaction are insoluble in water.

This procedure was successfully implemented at the described scale. The reproducibility of the experiment was assessed by its execution by the group of six 2nd year Chemistry B.Sc. students.

Apparatus for the experiment is not complicated (Fig. **SM 12.1.2.**1) and the reaction itself is not demanding or labor intensive. Reaction is performed at room temperature; water bath (about 20°C) shown in the picture is not necessary. Optionally students can make the TLC to control the reaction progress.[1]

Figure SM 12.1.2.1 - Apparatus for oxidation of 1,2-tetradecanediol.

The TLC plate should be visualized by spraying with sulfuric acid and heating (charred blots, Fig. **SM 12.1.2.**2). Substances can be identified from their R_f (retardation factor) values. Calculate the ratio of distance covered by a substance (d) to the distance covered by the eluent (D).

$$\mathbf{R_f = d_{substance}/D_{eluent}}$$

Reaction is completed when the substrate is no longer observed in the reaction mixture (no spot on TLC). Because of visualization of the plate with sulfuric acid (30%soln.) preparation of TLC in this experiment is optional – not recommended for early bachelor students. The spots on TLC plate are hardly visible either in iodine or using UV lamp.

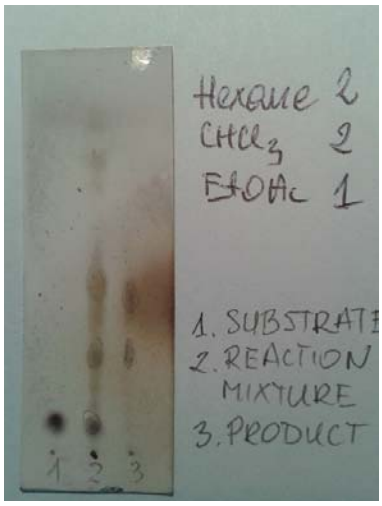


Figure SM 12.1.2.2 – TLC plate visualized using H_2SO_4 (30% soln.) and heating.

Because of dimerization the product is poorly soluble in most organic solvents (28 C atoms, long hydrocarbon chains). In described procedure chloroform was used for the extraction (it can be replaced with dichloromethane), and the extraction should be repeated several (at least 5) times.

Students should obtain about 2.2 g of the crude product, which can be purified by crystallization from the AcOEt (about 120 mL). After crystallization students can obtain 1.5-1.7 g of hemiacetal, which represents approximately 70% yield. The product is a mixture of diastereomers (also visible on TLC plate), that is why the melting point measured should be in the wide range (103-112°C).[2] Diastereoselectivity for this reaction was not determined.

Similar results can be obtained with 1,2-dodecanediol as the substrate, and the product is expected to be more soluble. The 1,4-pentanediol applied, gave 3-hydroxypentanal, which undergo intramolecular hemiacetal formation to 1-hydroxy-4-methyl-tetrahydrofurane.[2] The NMR spectra for substrate (Fig. **SM 12.1.2.**3) and product (Fig. **SM 12.1.2.**4) were performed in $CDCl_3$, using small concentration of the substance.

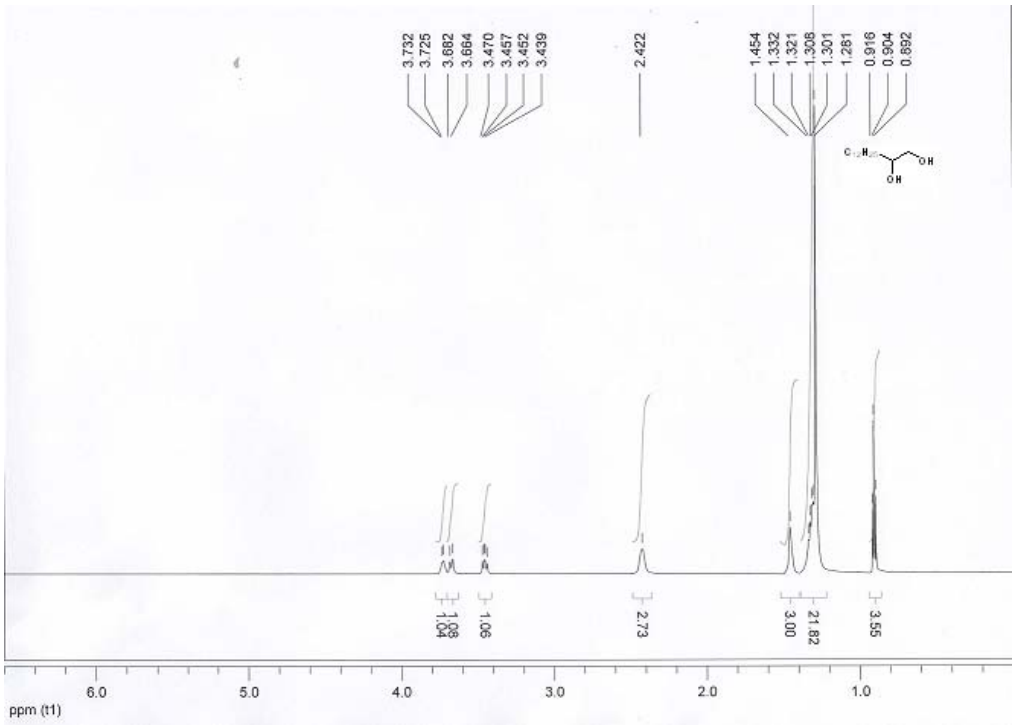


Figure SM 12.1.2.3 – ^{1}H NMR of the 1,2-tetradecanediol (600 MHz, $CDCl_3$).

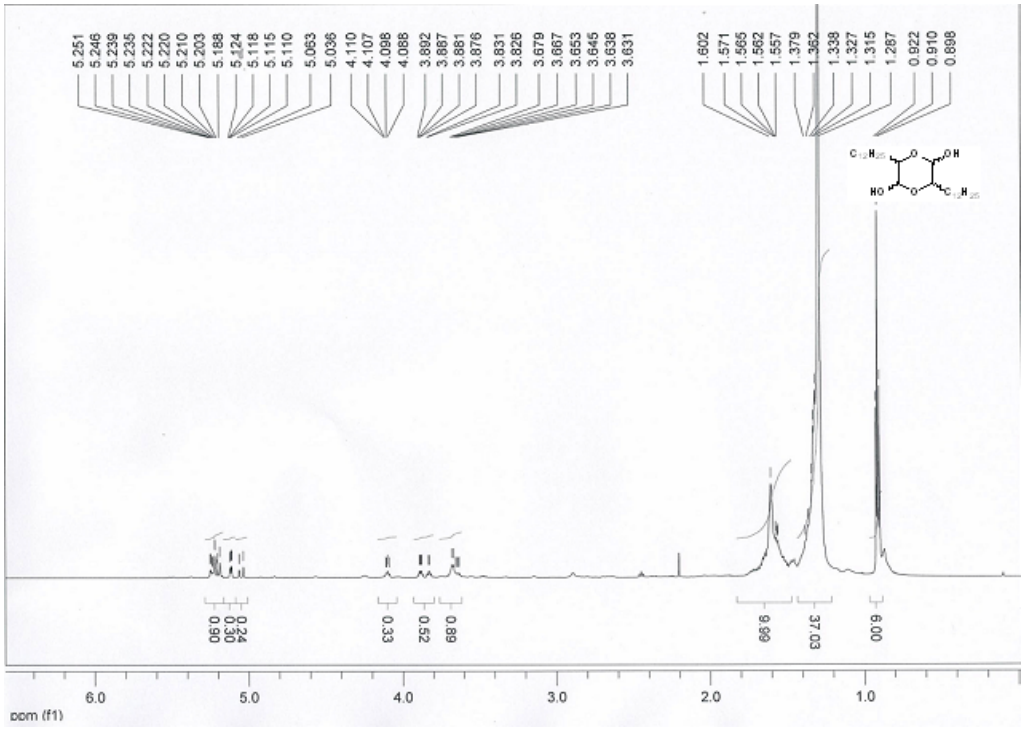


Figure SM 12.1.2.4 – ^{1}H NMR of the hemiacetal (600 MHz, $CDCl_3$).

[1] Theoretical basis of Thin Layer Chromatography: B. Spangenberg , C.F Poole, C. Weins; *Quantitative Thin-Layer Chromatography A Practical Survey*, Springer-Verlag Berlin Heidelberg 2011, p.13.

[2] R. Siedlecka, J. Skarżewski, J. Młochowski *Tetrahedron Letters* 1990, **31**, 2177.

Catalyzed Oxidation of Naphthalene to 1,4-Naphthoquinone

Supplementary Material

Experiment Notes

Figures

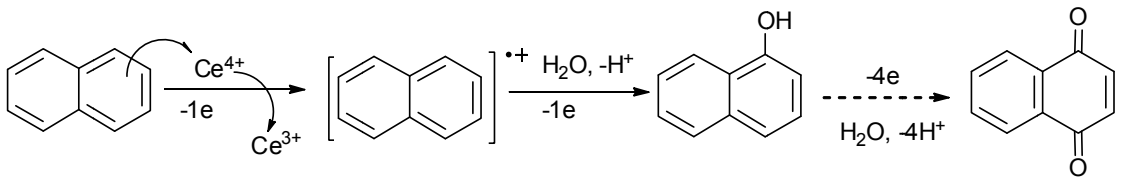
This experiment aims at the preparation of 1,4-naphthoquinone from the corresponding aromatic hydrocarbon (naphthalene). A classical method for this transformation involves application of CrO_3 in acetic acid and results in ca. 30% yield of the quinone.[1] Naphthalene can also be directly oxidized to the respective quinone with cerium ammonium sulphate (CAS).[2] However, such procedure is impractical because of the stoichiometry. The formation of one mole of the quinone (MW 158.15) requires six moles of the one-electron oxidant CAS (dihydrate MW 632.55). Thus the idea behind the applied method is the construction of a catalytic cascade, allowing for the fast reoxidation of the reduced Ce^{4+} ions. This can be done electrochemically[3] or using inexpensive chemical oxidant. Since CAS is a strong oxidant, the potential for reduction is about +1.44V, the respective chemical oxidant must be of the oxidation potential high enough. This condition fulfils ammonium persulfate (MW 228.18, two-electron oxidant, E° ca. 2.1V) Though, this oxidant reacts with the Ce^{3+} ions slowly and they are removed from the system, precipitating as the corresponding oxo-salts. The process needs an additional mediator. It has been found that the silver ions facilitate oxidation of Ce^{3+}.[4] Since the starting hydrocarbon is not soluble in the aqueous reaction medium, the reaction is facilitated by the presence of the emulsifying agent (SDS, sodium dodecyl sulfate). After the first step (ECEC), further oxidation of 1-naphthol goes easily to the final quinone (Scheme SM 12.1.3.1).[2]

$S_2O_8^{2-} + 2H^+ + Ag^+ \longrightarrow 2HSO_4^- + Ag^{3+}$

$Ag^{3+} + Ag^+ \longrightarrow 2Ag^{2+}$

$Ce^{3+} + Ag^{2+} \longrightarrow \mathbf{Ce^{4+}} + Ag^+$

Catalytic cascade



Scheme SM 12.1.3.1 Oxidation of naphthalene

The catalytic green procedure involves oxidation of polycyclic aromatic hydrocarbon in water.[5] Practically, the solid organic substrate together with ammonium persulfate is gradually added (small portions!) to a magnetically stirred aqueous solution of the catalysts: cerium ammonium sulfate, sodium dodecyl sulfate, silver nitrate and sulfuric acid at ca. 50 ˚C. Their concentration has been optimized.[5] The reaction is usually complete within 3-5 hrs. The corresponding quinone is extracted and recrystallized. The yield of pure product varied between 60-80%. For other examples of the oxidation of polycyclic aromatic hydrocarbons, see ref. [5]

Referring to **Experimental procedure**: Session 1

Points 6, 7 and 8: A sample of the reaction mixture should be checked by TLC for the presence of unreacted naphthalene. TLC: precoated silicagel 60 plate, eluent: n-hexane-ethyl aceteate 3 : 1 v/v, UV-lamp, naphthalene: R_f 0.60 and 1,4-naphthoquinone R_f 0.41. After 3 hours at 50 ˚C the reaction mixture still contained unreacted substrate. Their content is evaluated as ca. 44% of naphthalene and 56% of quinone (Fig. SM 12.1.3.1, ^{1}H NMR spectrum of the mixture after 3 h). The reaction time can be extended to 5-6 hours at 50 ˚C or the stirred mixture should be left at least overnight at room temperature. After that the oxidation is over, the mixture can wait for the final work-up even for a week. Typically 60 – 80 % yield of the recrystallized product was obtained.

Referring to **Experimental procedure**: Session 2

Point 8: The observed m.p. was 120-122 ˚C (recrystallized from methanol). Literature m.p.: 123-125 ˚C (from toluene-hexane) [5],124–125 °C (from petroleum ether) [1, 7].

Point 9: Fig. SM 12.1.3.2, ^{1}H NMR spectrum of the recrystallized 1,4-naphthoquinone. For comparison, see ref.[6, 7]

The aqueous solution of catalysts can be reused for next runs, however the next portion of SDS should be added. The surfactant used at 10^{-3} M concentration is hydrolysed/decomposed during the reaction.

The spent organic solvents can be distilled and reused. After the experiments are over, the spent aqueous catalytic solution is treated with sodium hydroxide, left overnight at room temperature, and the precipitates are filtered off for the separate disposal and the alkaline filtrate can be diluted and poured to the sink.

Referring to **Results interpretation and additional questions**

Question 4 (Write the catalytic reaction cascade and calculate the turn over number (TON) for the Ce^{4+} ions.)

Answer

$S_2O_8^{2-} + 2H^+ + Ag^+ \longrightarrow 2HSO_4^- + Ag^{3+}$

$Ag^{3+} + Ag^+ \longrightarrow 2Ag^{2+}$

$Ce^{3+} + Ag^{2+} \longrightarrow \mathbf{Ce^{4+}} + Ag^{+}$

Naphthalene + 2 H_2O (-6 electrones) $\longrightarrow$ 1,4-Naphthoquinone (+ $6H^{+}$)

Catalytic cascade

The oxidation of one mole of naphthalene to one mole of naphthoquinone requires 6 moles of Ce^{4+}-salt. For the catalytic system Turnover Number (TON) is number (no.) of mole of product produced by one mole (equivalent) of the catalyst used. Thus TON = Total no. of moles product / no. of mole (equivalent) catalyst.

In our specific case: for the reaction of naphthalene (5.3 g, 41.6 mmole) giving 1,4-naphthoquinone (5.08 g, 32.12 mmole, 77% yield) we have used 250 ml of 0.1 M CAS (25 mmole : 6 = 4.167 catalyst equivalents. Thus here TON = 32.12 / 4.167 = 7.71.

References

1. E. A. Braude, J. S. Fawcett, *Org. Synth. Coll. Vol. 4*, **1963**, 698; *Vogel's Textbook of Practical Organic Chemistry*, eds B. S. Furniss, A. J. Hannford, P. W. G. Smith, A. R. Tachell, Parsons-Prentice Hall, **1989**, p. 1033.
2. M. Periasamy, M. V. Bhatt, *Synthesis* **1977**, 330; M. V. Bhatt, M. Periasamy, ***J. Chem. Soc., Perkin Trans. 2*, 1993**, 1811.
3. I. M. Dalrymple, J. P. Millington, *J. Appl. Electrochem.* 1986, **16**, 885.
4. S. A. Fronaeus, C. O. Östman, *Acta Chem. Scand.* 1956, **10**, 320.
5. J. Skarżewski, *Tetrahedron* 1984, **40**, 4997.
6. D. W. Cameron, Feutrill, A. F. Patti, *Austr. J. Chem.* 1979, **32**, 575; A.-M. Abu-Elfotoh, K. Tsuzuki, T. B. Nguyen, S. Chanthamath, K. Shibatomi, S. Iwasa *Tetrahedron* 2013, **69**, 8612.
7. For further details on 1,4-naphthoquinone, see: data bases REAXYS (Beilstein Reg. no. 878524, ca. 2600 references) and SciFinder (Chemical Abstract, CAS No. 130-15-4, over 6600 references).

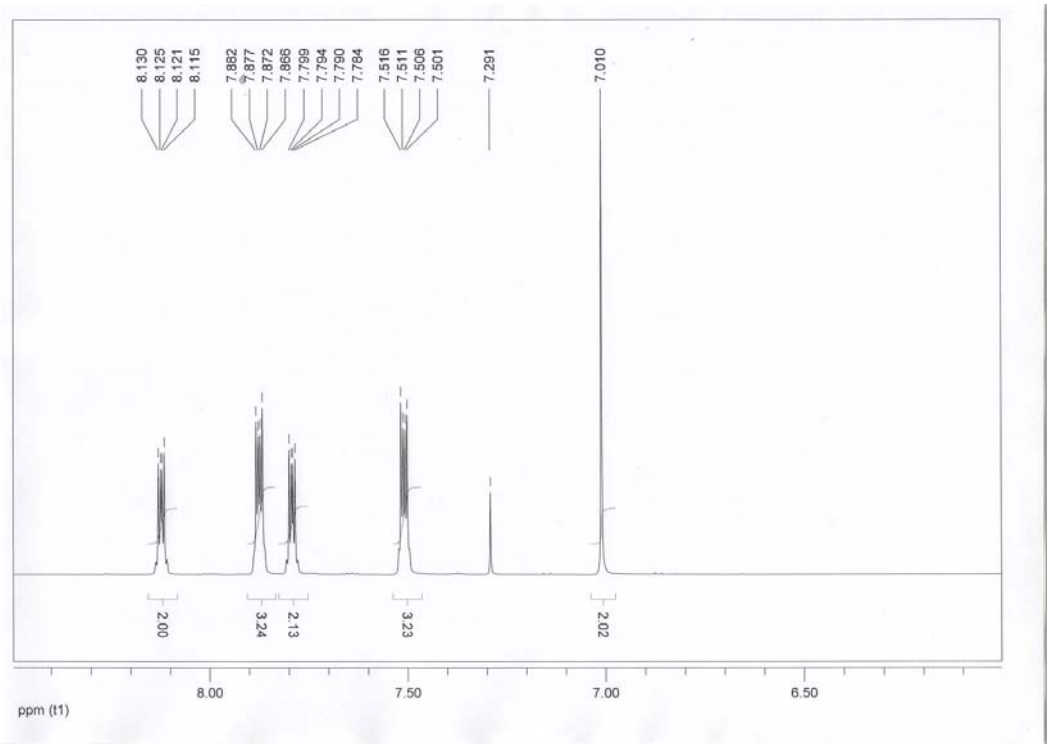


Figure SM 12.1.3.1. ^{1}H NMR spectrum (600MHz, $CDCl_3$) of the reaction mixture after 3 hours, naphthalene (44 %) and 1,4-naphthoquinone (56 %) by integration of the respective resonances.

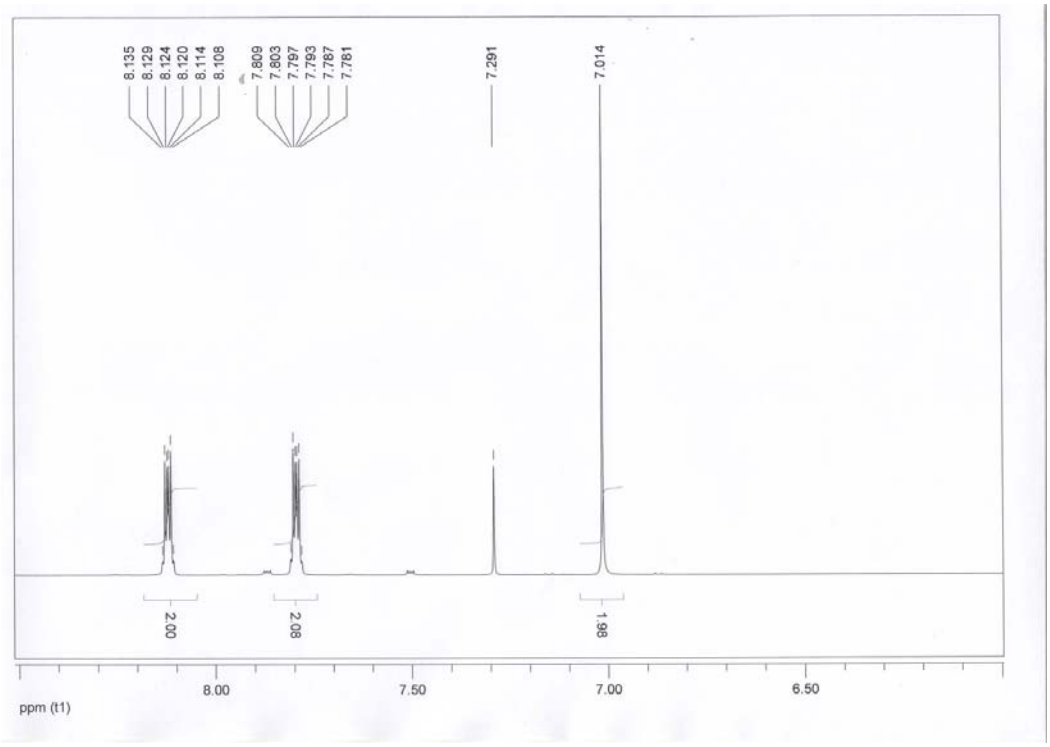
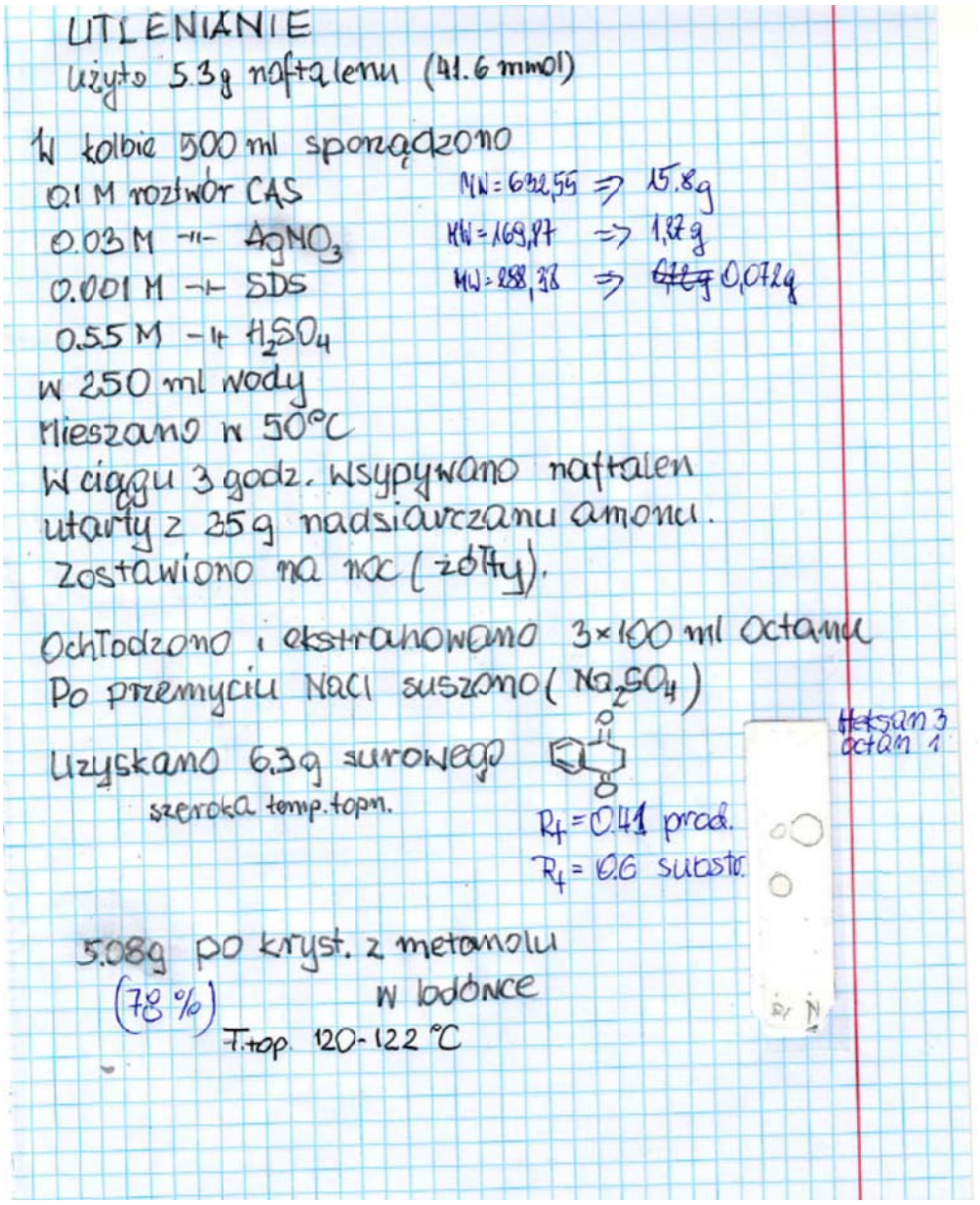
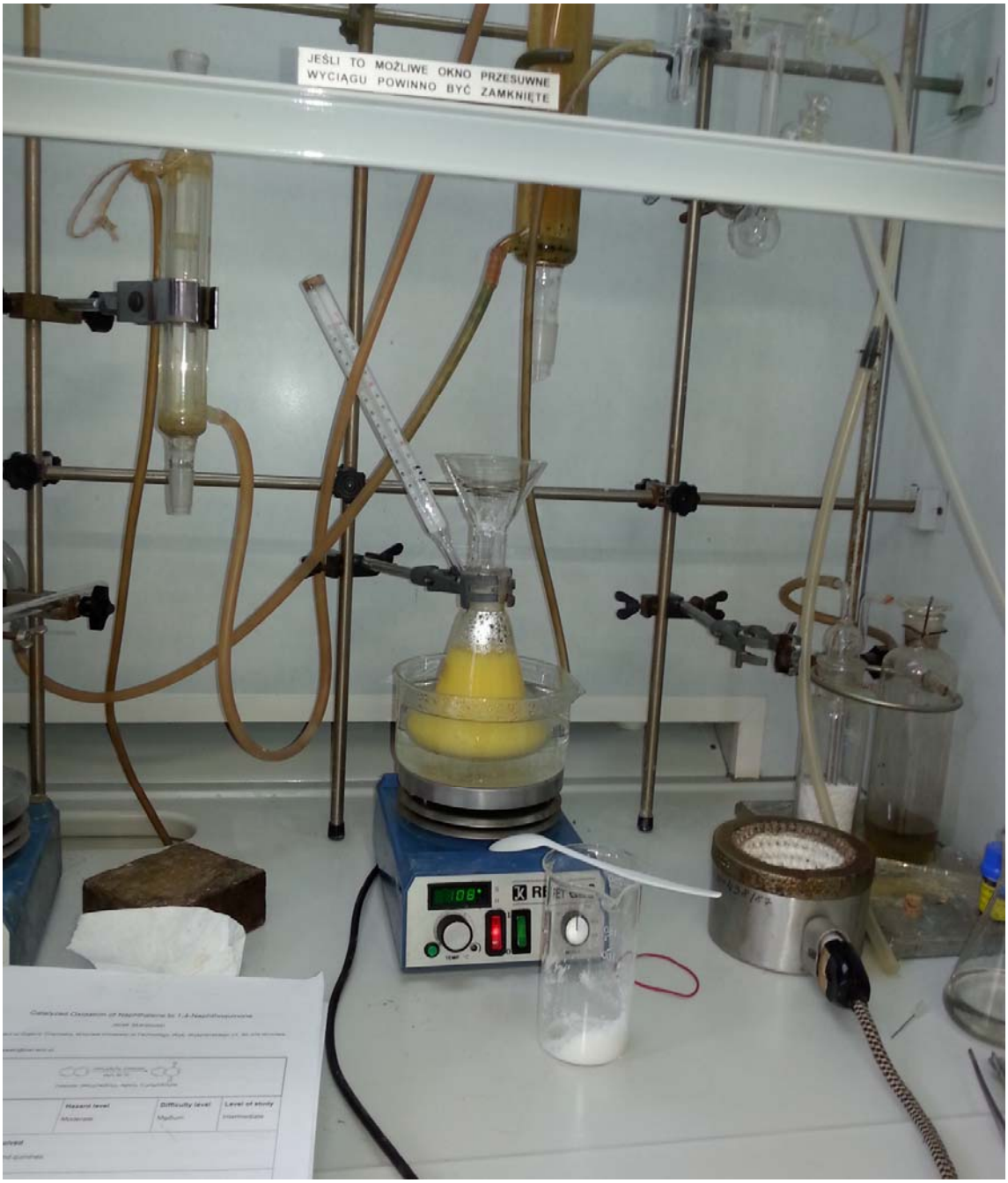


Figure SM 12.1.3.2. ^{1}H NMR spectrum (600MHz, $CDCl_3$) of the recrystallized 1,4-naphthoquinone (traces of naphthalene: δ 7.5 and 7.8 ppm)

Copy of the student's notebook





Alcohol oxidation: menthone preparation by menthol oxidation using pyridinium chlorochromate immobilized in silica gel

Supplementary Material

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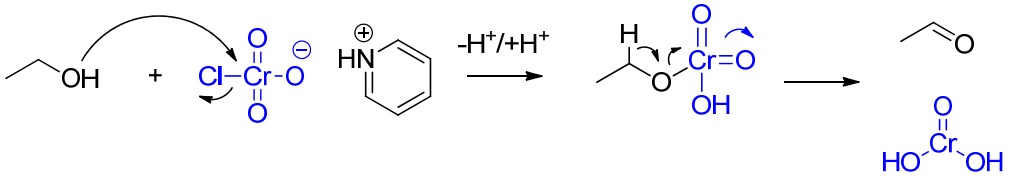
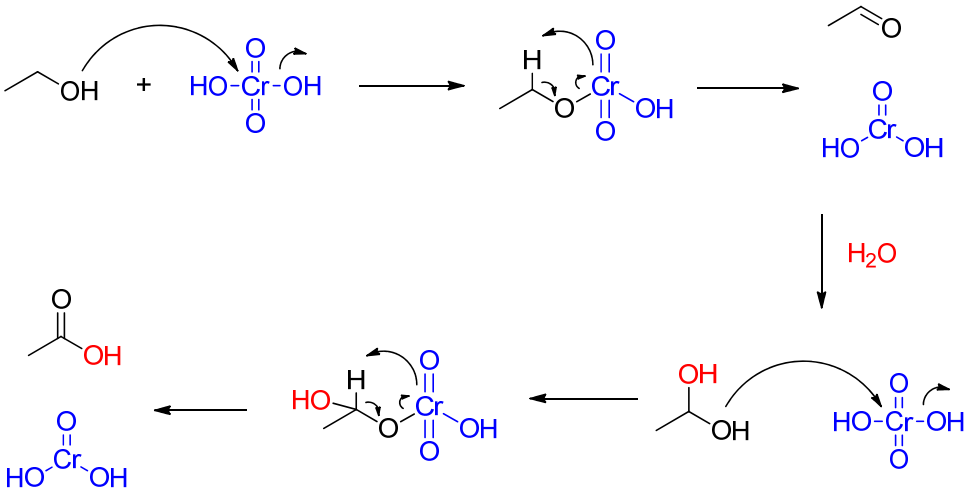
Oxidation of alcohols is a highly used method in organic chemistry. Several total synthesis of natural compounds for example need to use oxidation methods in order to achieve the final compound. Pyridinium chlorochromate (PCC) is a chromium catalyst used in the oxidation of alcohols into ketones and aldehydes. The mechanism involves the reduction of the chromium VI species into a chromium IV species (Scheme **SM 12.1.4.**1). Unlike the Jones reagent, PCC does not oxidize primary alcohols into carboxylic acids (Scheme **SM 12.1.4.**2.).



Scheme SM 12.1.4.1. PCC oxidation mechanism



Scheme SM 12.1.4.2. Jones oxidation mechanism

This experiment aims the preparation of menthone from (-)-menthol, using a chromium oxidant, PCC immobilized in silica. The procedure has been made by more than 30 groups of students (2

students/group) from the first year of organic chemistry course. Obtained yields were often above 80%, high purity. Due to the reaction time (less than 90min.), TLC can be used in different times allowing the visualization of the reaction progress (using hexane:diethyl ether 1:1 as eluent, menthol Rf 0,60, menthone Rf 0.65. After staining menthol appears as a white spot, menthone as a black spot). This will emphasize the technique as a routine procedure to follow a reaction.

The reaction mixture is initially orange from the PCC (Figures **SM 12.1.4.**1-2.) in 5 minutes at room temperature the solution becomes darker until it is completely black. After the addition of diethyl ether an orange precipitate will appear.

Sometimes the most appropriate silica (thinner) is not available or the laboratory does not have longer Buchner funnels (Figure **SM 12.1.4.**3). In those cases some contamination on the product with reduced Cr (brown color) was observed. According to the time and resources, further purification of the product can be done by column chromatography.

Measuring the optical rotation of menthol and menthone allows the comparison with the described commercial values and represent the influence of several asymmetric centers in the optical deviation. In this case, one center is lost and the optical deviation remains negative. Regarding to this point, the students may also read the reported experiment on the the acid catalyzed isomerization of (−)-menthone to (+)-isomenthone[1].

The fact that menthone has a nice aroma and different from menthol creates curiosity on the students about structure-property relations.

The experimental procedure and the attempt to reduce the residue contamination allow the discussion and presentation of more efficient methodologies. Some of the methodologies in this ‘greener’ context can be the palladium(II) or vanadium catalyzed aerobic oxidation of alcohols[2], the aerobic oxidation of aqueous ethanol to acetic acid over Au-on-Mg_2AlO_4 nanoparticles[2], the Ruthenium/TEMPO-Catalyzed Aerobic Oxidation of Alcohols[3,4] or even the photocatalytical oxidation of alcohols to ketones using no more than light described by Augugliaro *et al*[5.6].

At the end of this laboratory session the students should know about alcohol oxidation methods and the correspondent mechanisms. The student should know about the hazard of some toxic reagents and methods to reduce the dangers in their manipulation. In Figures **SM 12.1.4.**4-7 is provided the IR, ^{1}H and ^{13}C NMR spectra of the starting material menthol and the observed product menthone.

Figure SM 12.1.4.1. Grounded silica and PCC.

Figure SM 12.1.4.2. Oxidation mixture and menthol dissolved in DCM.

Figure SM 12.1.4.3. Silica filtration of the reaction mixture with a Buchner funnel.

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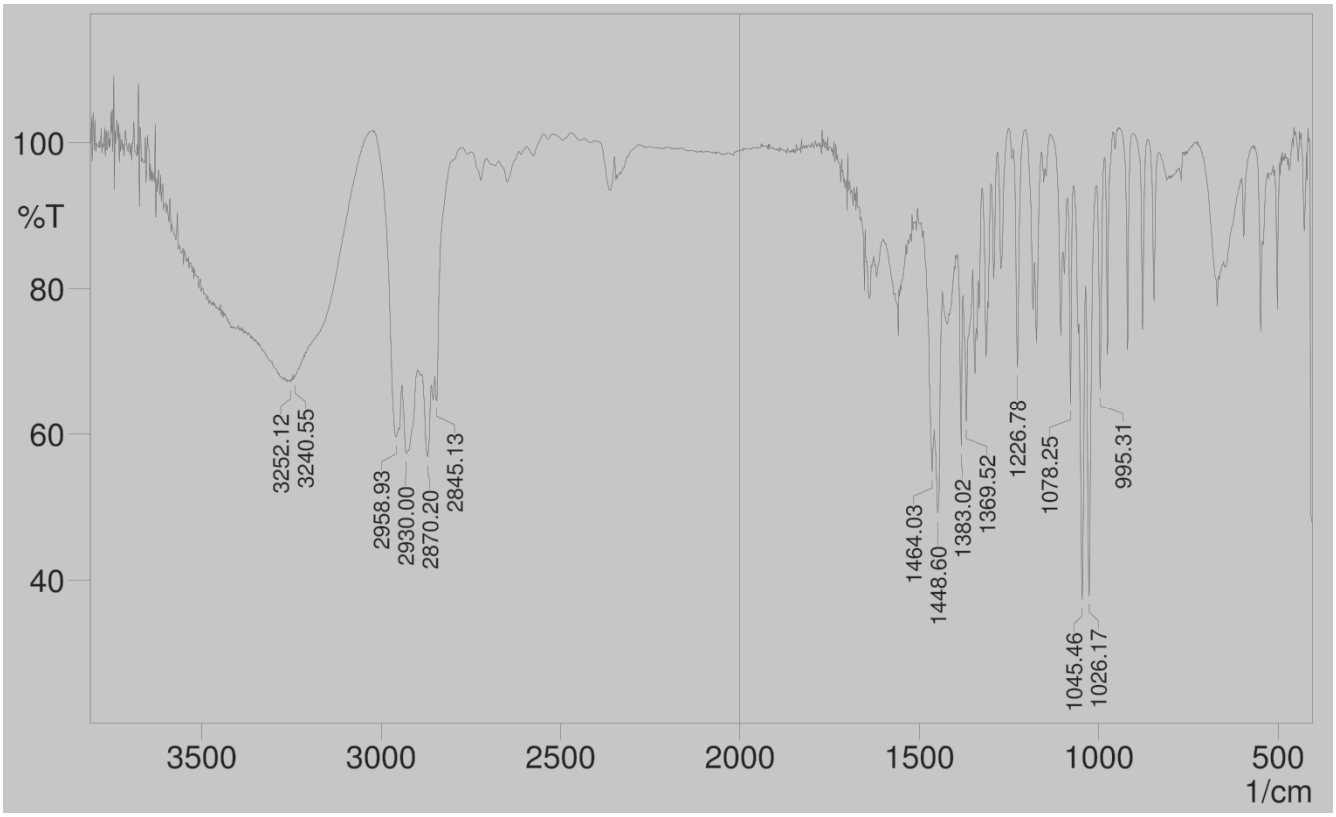

Figure SM 12.1.4.4 . IR Spectra of commercial menthol.

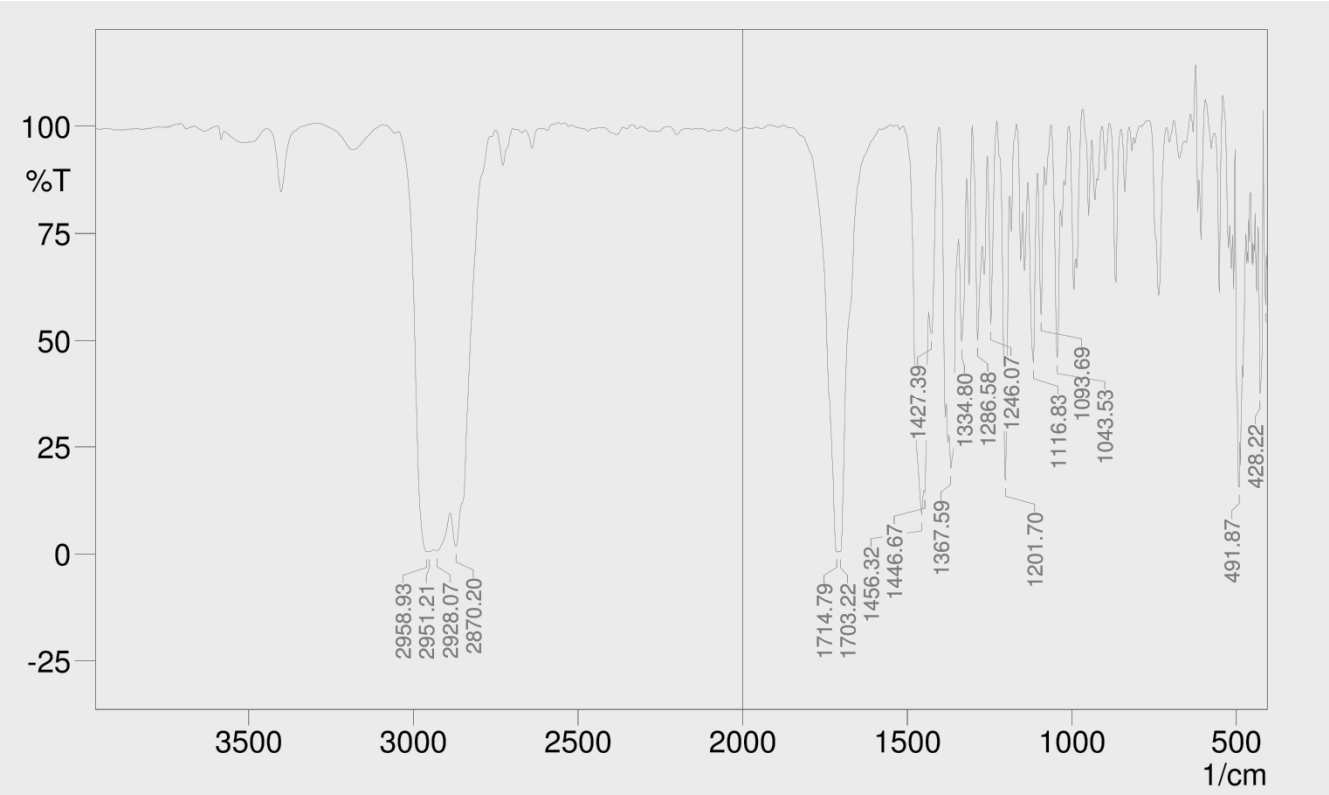

Figure SM 12.1.4.5 . IR spectra of obtained menthone (film).

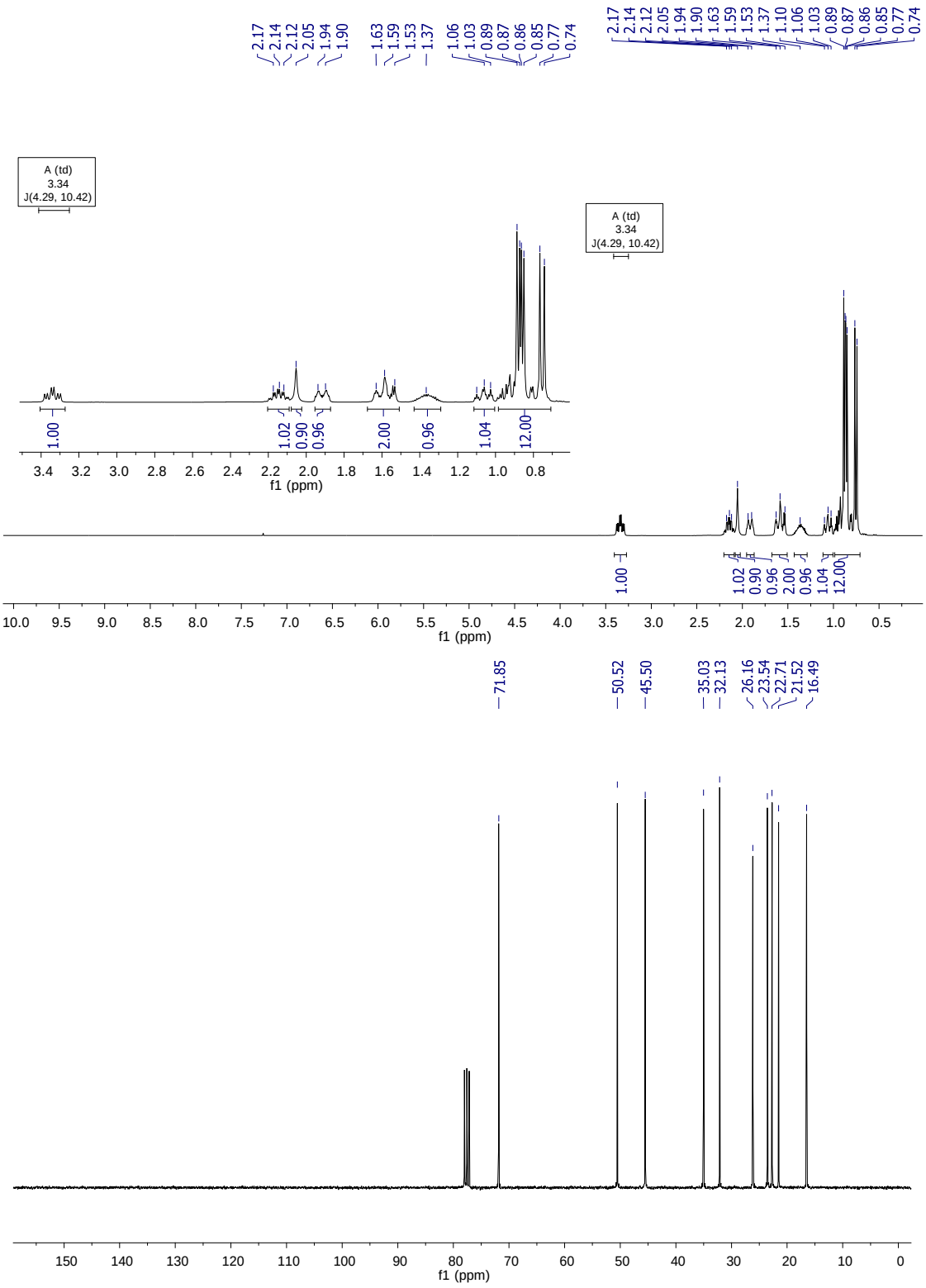

Figure SM 12.1.4.6 . ^{1}H-NMR (400 MHz) and ^{13}C-NMR ($CDCl_3$) spectra of commercial menthol.

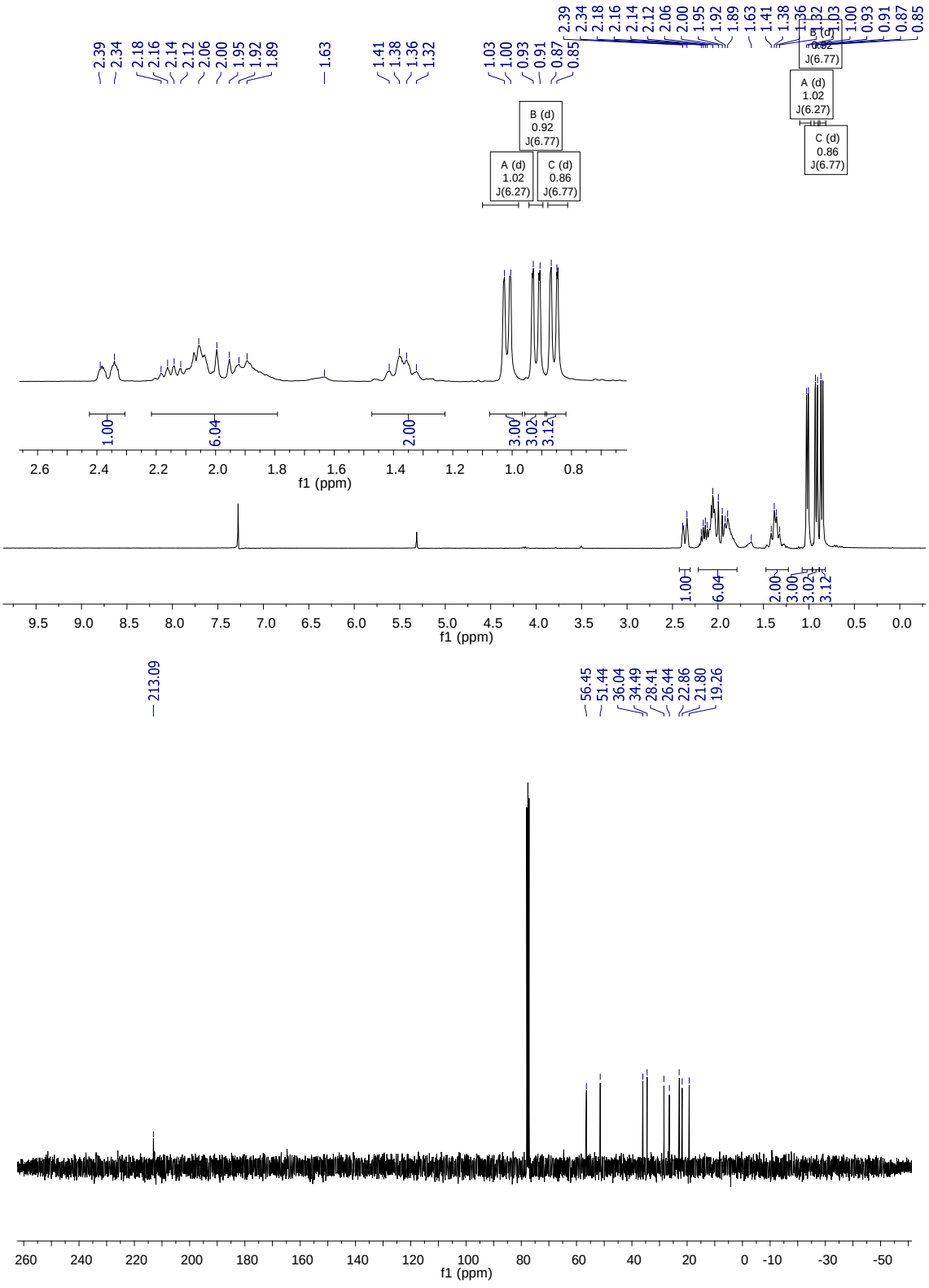

Figure SM 12.1.4.7 ^{1}H-NMR (400 MHz) and ^{13}C-NMR ($CDCl_3$) spectra of obtained menthone.

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Heterocyclic Target Synthesis – 3 Step syntheses from Benzaldehyde

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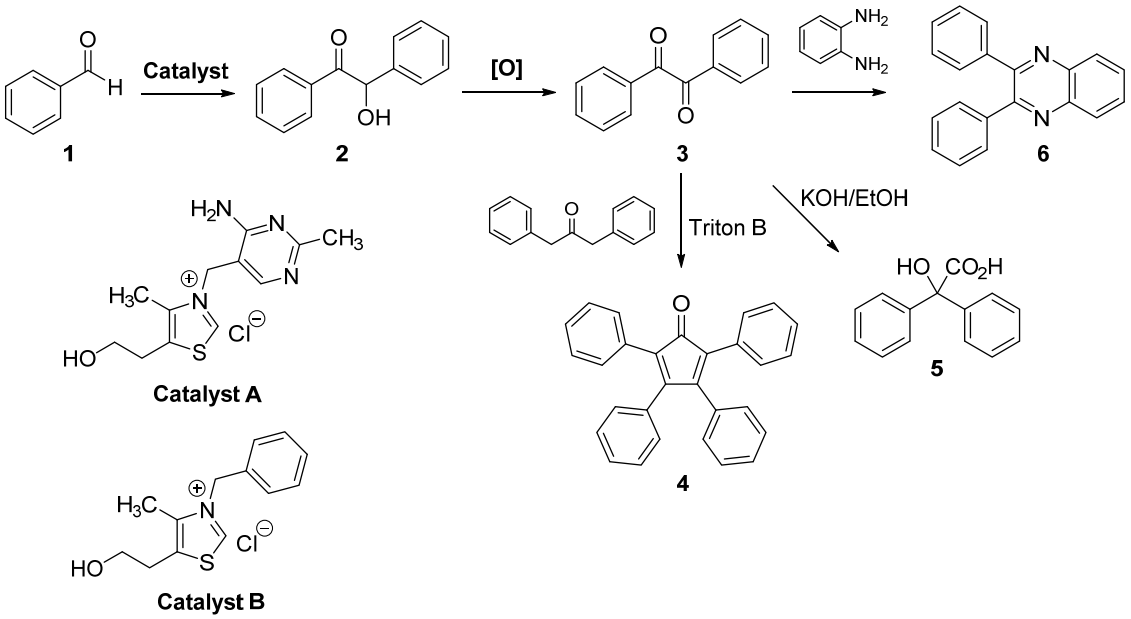
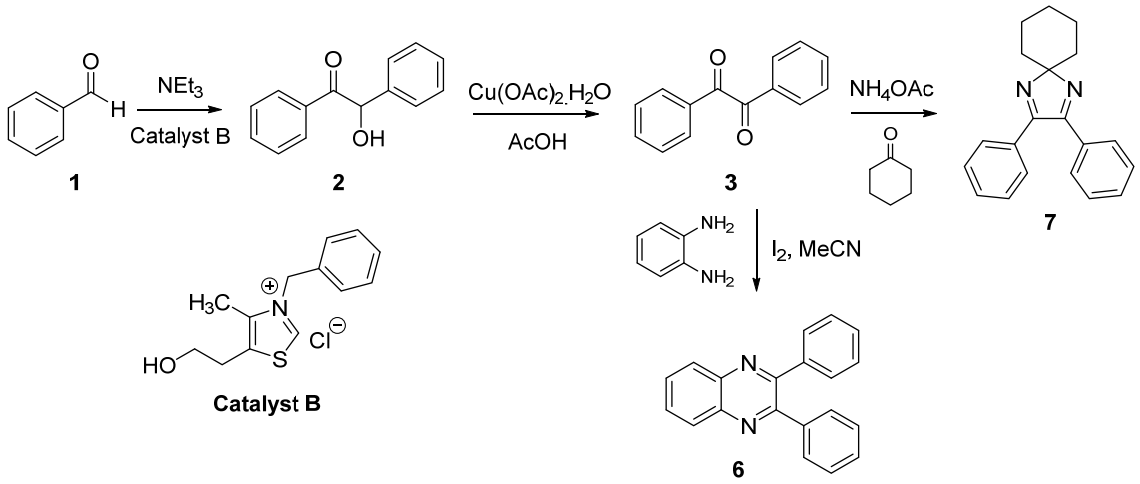
Supplementary Material

Multistep syntheses are an important feature of many advanced organic teaching laboratory courses; benzaldehyde (**1**) is a cheap, accessible and useful material for this type of exercise. A typical teaching laboratory sequence involves benzoin reaction of benzaldehyde (**1**), oxidation of benzoin[1] (**2**) to benzil (**3**) and then final conversion to one of the following targets: tetraphenylcyclopentadienone (**4**),[1] benzilic acid[2] (**5**) or 2,3-Diphenylquinoxaline[1] (**6**) (scheme **SM 12.1.5.**1).



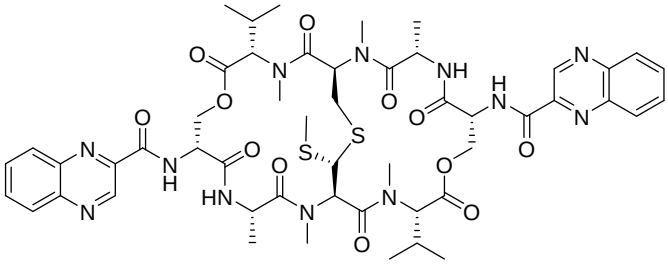
Scheme SM 12.1.5.1 Popular teaching laboratory reaction sequences starting from benzaldehyde

There are several catalysts[1,3,4] that can promote the conversion of benzaldehyde (**1**) to benzoin (**2**); sodium cyanide, potassium cyanide, thiamine (catalyst A, scheme **SM 12.1.5.**1) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride[3,4] (catalyst B, scheme **SM 12.1.5.**1) being the most common. Oxidation of benzoin (**2**) to benzil (**3**) can be accomplished using a variety of reagents, nitric acid is perhaps the most widely employed in a teaching laboratory setting.[1] The aim of this experiment is to prepare quinoxaline **6** by under and/or spiroimidazole **7**[5] as outlined in scheme **SM 12.1.5.**2. In this variant of the reaction sequence, alternative conditions from those more frequently described are used to convert **2** to **3** and **3** to **6**, further detail can be found in the "General notes for preparative steps" section.



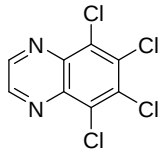
Scheme SM 12.1.5.2 Synthetic routes to quinoxaline **6** and spiroimidazole **7**

The synthesis of quinoxaline **6** is attractive for teaching purposes since the reaction sequence offers a relatively straightforward example of heterocyclic synthesis and the quinoxaline moiety is of interest to medicinal chemists and in agrochemistry (a selection of some example compounds and their use is provided in scheme **SM 12.1.5.**3).[6]



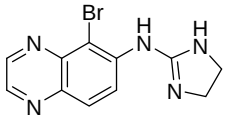
Echinomycin

antibiotic



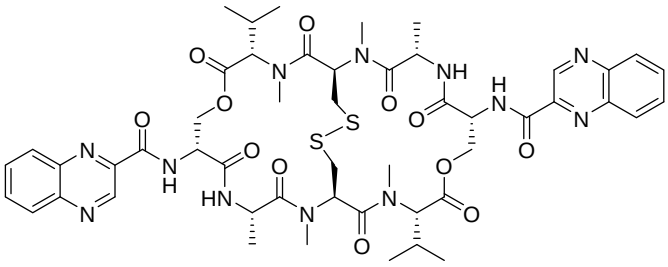
5,6,7,8-Tetrachloroquinoxaline

Pesticide



Brimonidine

the tartrate salt is marketed and used to treat ocular hypertension

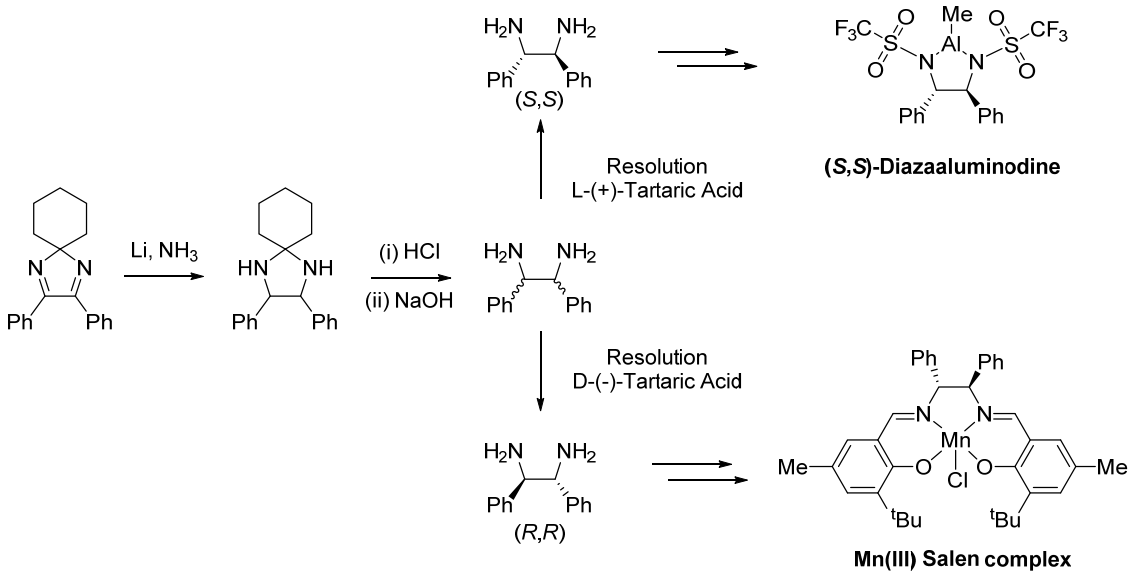


Triostin A

antibiotic

Scheme SM 12.1.5.3 Selected examples of compounds containing the quinoxaline moiety

This experiment also introduces spiroimidazole **7** as a synthetic target in a teaching laboratory exercise, the synthesis of **7**[5] offers an additional representative example of heterocyclic synthesis. In this case the target compound is of interest as a precursor to useful chiral reagents[7,8,9] and is a useful prompt for the discussion of chiral reagents/auxiliaries in organic synthesis (scheme **SM 12.1.5.**4). Diazaaluminodine **8**[7,8] and Mn(III) salen compex **9**[9] have been applied in the control of the stereochemical outcome of Diels-Alder reactions and alkene epoxidations respectively.



Scheme SM 12.1.5.4 Preparation of (R,R)- and (S,S)- 1,2-diphenyl-1,2-ethylenediamine and conversion to selected derivatives

This experiment is aimed at third year undergraduate students who have had training to an advanced level of synthetic organic chemistry work. The concepts covered are directly relevant to lecture material on synthetic and medicinal chemistry, associated lecture courses would be expected to cover heterocyclic chemistry. In addition to allowing students to practice assembly of key apparatus and techniques (recrystallization, glassware for heating under reflux and vacuum filtration), this exercise is useful for building planning skills and how to deal with synthetic problems. A representative example of this might be “can a reaction be scaled down if less product from an intermediate step is obtained than was expected?”. The experiment can be run in the format of a short project if desired. The identity of the products from each step in the sequence can be confirmed by melting point and ^{1}H NMR spectroscopy.

General notes for preparative steps.

Although benzaldehyde undergoes cyanide catalysed benzoin reaction in good yield, many teaching laboratories do not allow widespread use of cyanide salts. Thiamine[1] and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride[3,4] are good alternatives to cyanide salts, in our hands a modified version of the procedure of Stetter and Kuhlman has been found to work well.[4] 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (CAS number 4568-71-2) is readily sourced commercially and is stable on prolonged storage. The reaction is very reliable, the yields are typically 50-80% and the product is easily recrystallized. Melting point of benzoin is 133-134 °C (lit.)[13]

Oxidation of benzoin to benzil is traditionally accomplished in a teaching lab using concentrated nitric acid.[1] We sought alternatives in order to avoid large numbers of students manipulating concentrated nitric acid, the purity of the product made *via* this route has also been found to be variable (Clarke and Dreger[10] have suggested that it is difficult to avoid incomplete conversion of the starting material when using conc. Nitric acid). In our teaching laboratory course, the procedure of Depreux[11] *et al* has been found to be convenient. In this protocol copper acetate is the oxidant, the reaction is relatively fast and does not require the use of corrosive nitric acid. The copper waste generated is easy to safely dispose of since the cuprous oxide formed in the reaction can be filtered off and collected (in contrast to the potential disposal problems encountered when using other transition metal oxidants). The most convenient filtration method is to preheat a filter funnel plugged with glass wool in an oven (ca.120 °C) and use this to filter the hot reaction mixture. It is possible to decant the hot liquid off while leaving the bulk of the cuprous oxide in the reaction

flask (see figure SM 12.1.5.1). The yields for this step typically vary ~30-70% yield. Melting point of benzil is 95-96 °C (lit.)[13]

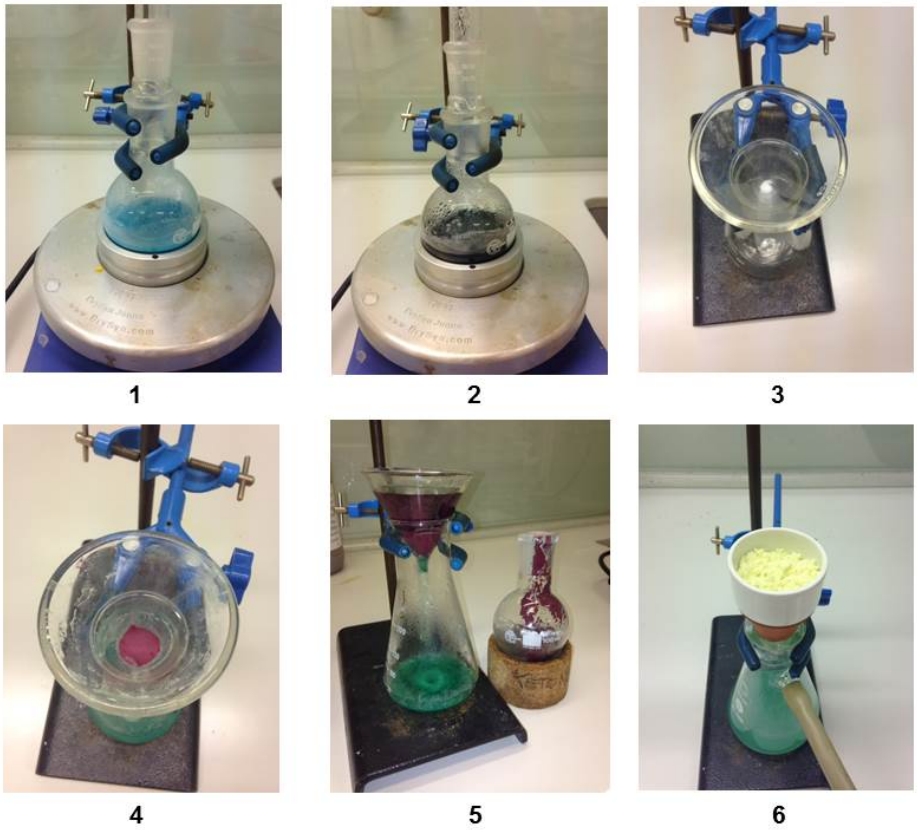


Figure SM 12.1.5.1 – Illustrations for oxidation of benzoin: Pictures 1 and 2 show the colour changes as the reaction is heated. Pictures 3, 4 and 5 show the hot filtration set up. The cuprous oxide can be clearly seen on top of the glass wool plug and retained in the reaction flask. As the filtrate cools, crude product precipitates out and the resulting material is filtered prior to recrystallization (picture 6).

Teaching laboratory procedures for the preparation of 2,3-diphenylquinoxaline are typically solventless and involve heating a mixture of benzil and 1,2-diaminobenzene in a boiling tube to form a melt.[1] We sought a set of conditions that were milder, ideally without the need for heating. Traditional procedures typically require that the 1,2-diaminobenzene starting material be purified by sublimation prior to performing

the reaction (failure to do this usually leads to a low yield of the desired quinoxaline). We have found a modified version of the protocol of Yao[12] *et al* is convenient for teaching laboratory use. The reaction is fast, does not require heating and does not suffer significantly lower yields if unpurified 1,2-diaminobenzene is used. The procedure Although the main procedure suggests purification of the product by recrystallization, the original publication suggests flash chromatography (silica gel) could be used instead (95:5 40-60 hexane:EtOAc). Typical yields range between 30 to 60%. Melting point of 2,3-diphenylquinoxaline is 125-126 °C (lit.)[1]

In this case the reliable large scale (0.75 mole) synthesis of spiroimidazole **7** (2,3-Diphenyl-1,4-diazaspiro[4.5]deca-1,3-diene) reported by Corey and Pikul[5] has been adapted for teaching laboratory work. The reaction requires a 1 hour period of heating under reflux, this can be extended to 1.5 hours if time allows, the yield tends to be higher if the reaction time is extended by 30-45 minutes (in the original report a yield of >95% was obtained after 1.5 hours). On cooling the reaction mixture is poured into water to afford a solid, on large scale it has been reported that large lumps may form that require breaking up. On the scale used here this is not normally necessary.

It is possible to alter scale of the reaction if required (it may be necessary to scale down some of the steps if a student gets poor yield). Attempts between 0.5 and 2 × the scale in the outlined procedure have been successfully attempted in our laboratory. Typical yields range between 20 to 60%. Melting point of 2,3-Diphenyl-1,4-diazaspiro[4.5]deca-1,3-diene is 107-108 °C (lit.)[5]

NMR samples and assignments

All the products are soluble in deuterochloroform. Assignments of spectra (and copies all the NMR spectra are provided) in the "Answers to additional questions" section.

References

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[11] P. Depreux, G. Bethegnies, and A. Marcincal-Lefebre, *J. Chem. Educ*., 1988, **65**, 553.
[12] S. V. More, M. N. V. Sastry, C-C. Wang and C-F. Yao, *Tetrahedron Lett.,* 2005, **46**, 6345.
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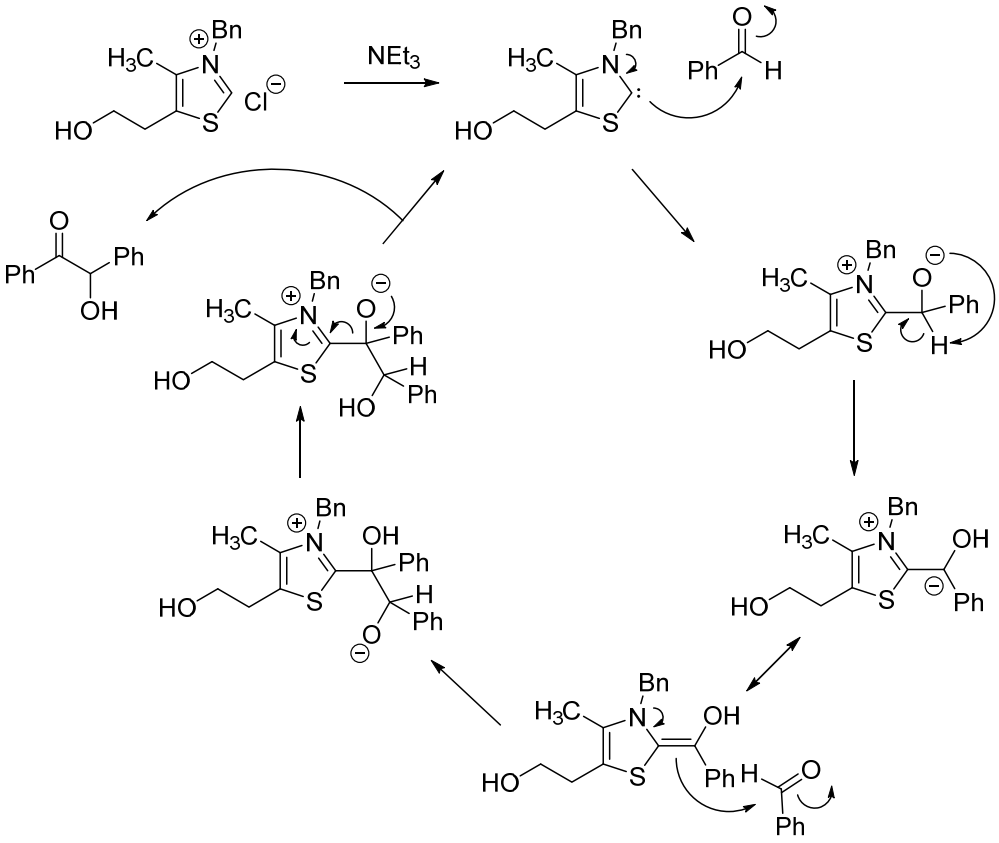
Answers to additional questions

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

The ^{1}H NMR spectra of benzoin and benzil are relatively straightforward to assign since they are largely comprised of multiplet signals that correspond to the aromatic protons in each molecule. The resulting spectra can be distinguished since benzoin does not possess the same level of symmetry as benzil and the benzoin spectrum contains signals for the hydroxyl proton and the proton in the α-position (6.00 and 4.62 ppm respectively – temperature, concentration, etc.[14] determine if coupling between the α-position and OH will be observed). The ^{1}H NMR spectrum of 2,3-diphenylquinoxaline is easily distinguished from that of the benzil precursor since the protons on the quinoxaline ring appear as distinctive AA'BB' multiplet patterns (8.17-8.23 ppm and 7.76-7.82 ppm). The Spiroimidazole can also be easily distinguished from the starting material since the ^{1}H NMR spectrum shows signals derived from the cyclohexane ring protons (between 1.83 and 1.69 ppm), in addition to those of the phenyl protons.

2. Provide a curly arrow mechanism for the benzoin reaction you carried out in step 1.

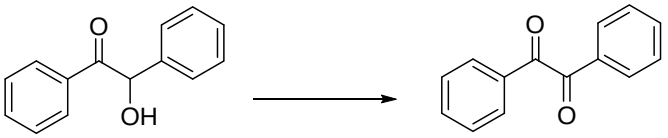
Plausible mechanism of thiazolium catalysed Benzoin reaction



3. Suggest what function the copper acetate has in the oxidation of benzoin to benzil.

Copper acetate mediated oxidation

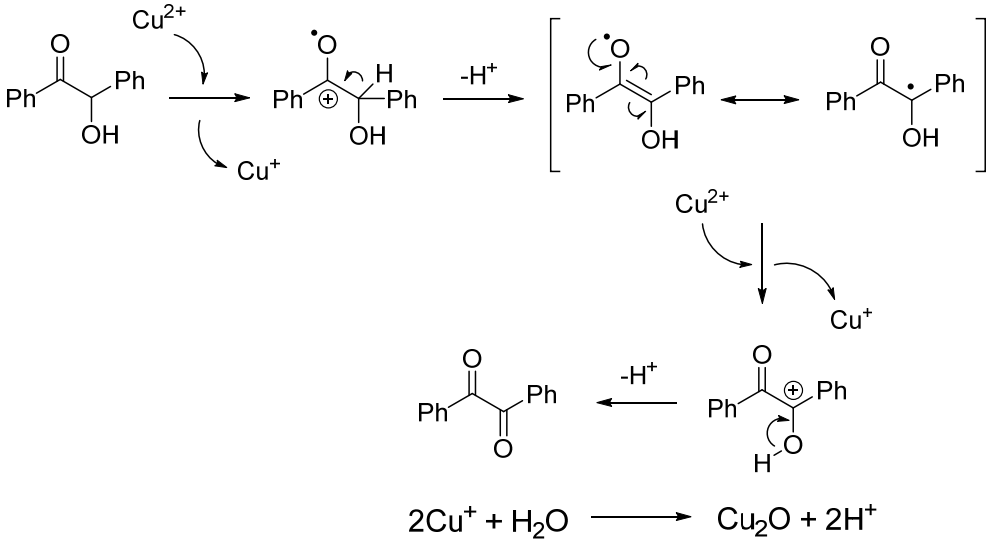
Overall Reaction



\+ $Cu(OAc)_2$ (aq) → + Cu_2O (s)

Copper acetate is a source of Cu^{2+} ion, this oxidises the secondary alcohol in benzoin. Cu^{2+} is reduced to Cu^{+}, which forms a red precipitate of cupric oxide.

Suggested Reaction Mechanism



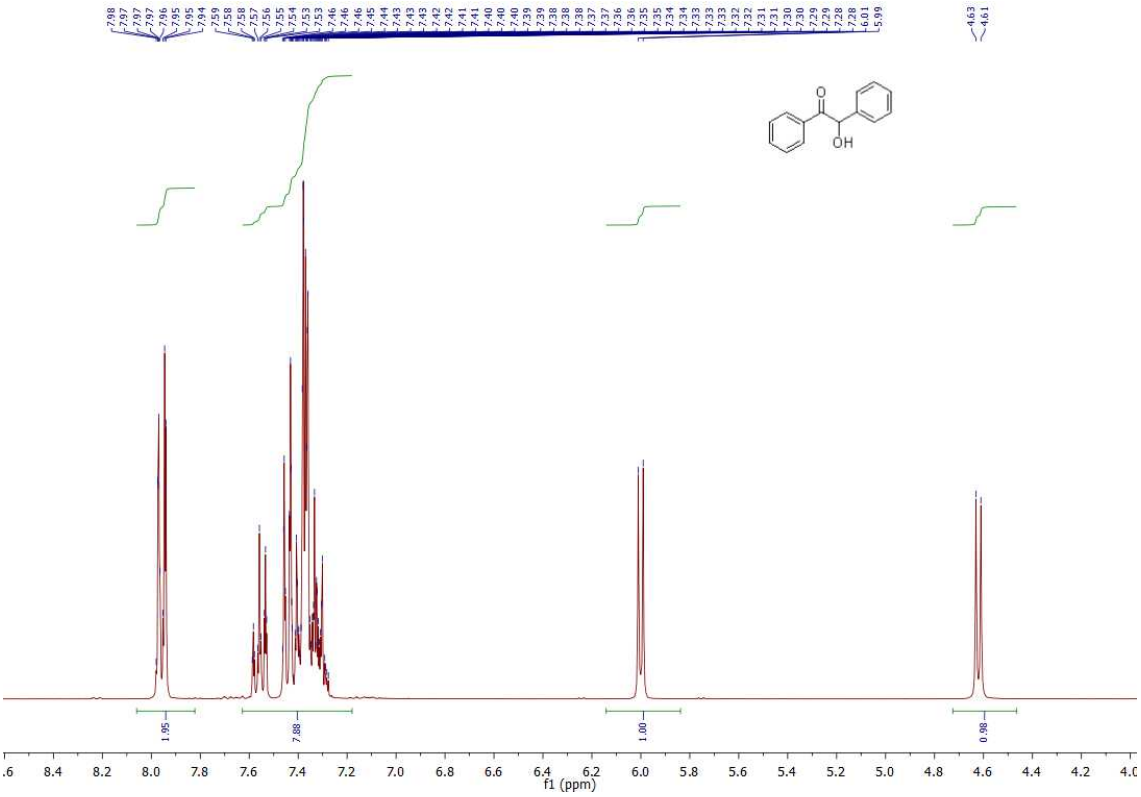
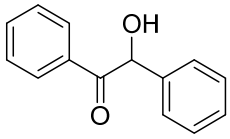


Figure SM 12.1.5.1 – ^{1}H NMR spectrum of Benzoin (**2**) (300 MHz, $CDCl_3$)



δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.94-7.98 (2H, m, Ar-H), 7.59-7.53 (2H, m, Ar-H), 7.28-7.46 (6H, m, Ar-H), 7.35-7.25 (5H, m, Ar-H), 6.00 (1H, d, $^{3}J_{HH}$ 6 Hz, C*H*(OH)) and 4.62 (1H, d, $^{3}J_{HH}$ 6 Hz, O*H*).

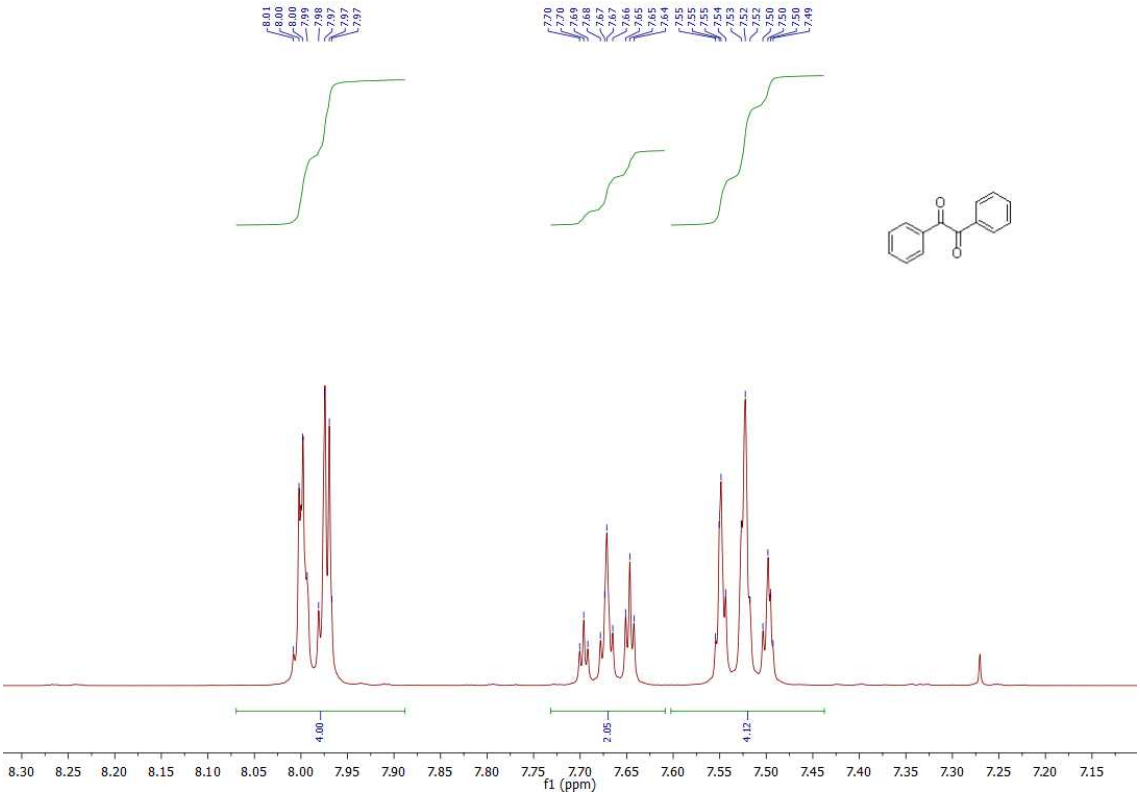
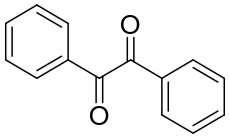


Figure SM 12.1.5.2 – ^{1}H NMR spectrum of Benzil (**3**) (300 MHz, $CDCl_3$)



δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.97-8.01 (4H, m, Ar-H), 7.64-7.70 (2H, m, Ar-H) and 7.49-7.55 (4H, m, Ar-H).

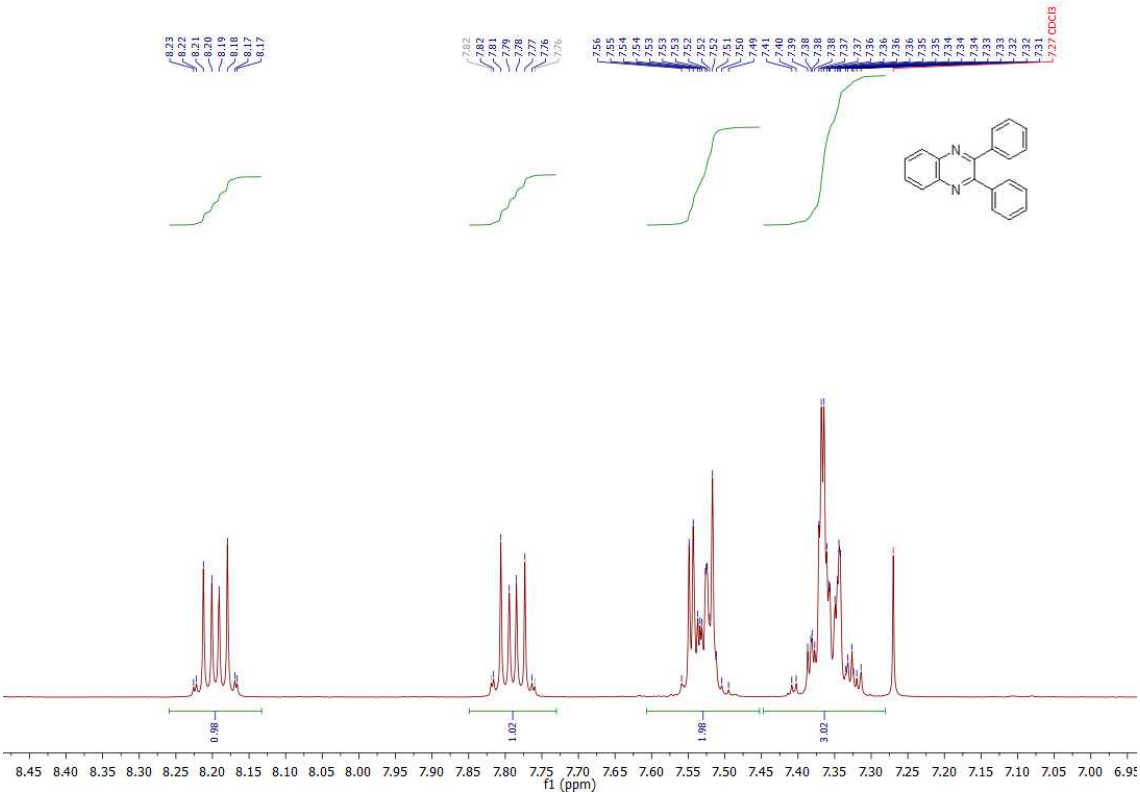
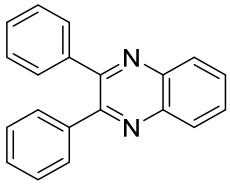


Figure SM 12.1.5.3 – ^{1}H NMR spectrum of quinoxaline **6** (2,3-Diphenylquinoxaline, 300 MHz, $CDCl_3$)



δ_H (300 MHz, $CDCl_3$, Me_4Si) 8.17-8.23 (2H, m, Ar-H), 7.76-7.82 (2H, m, Ar-H), 7.52-7.55 (4H, m, Ar-H) and 7.33-7.39 (6H, m, Ar-H).

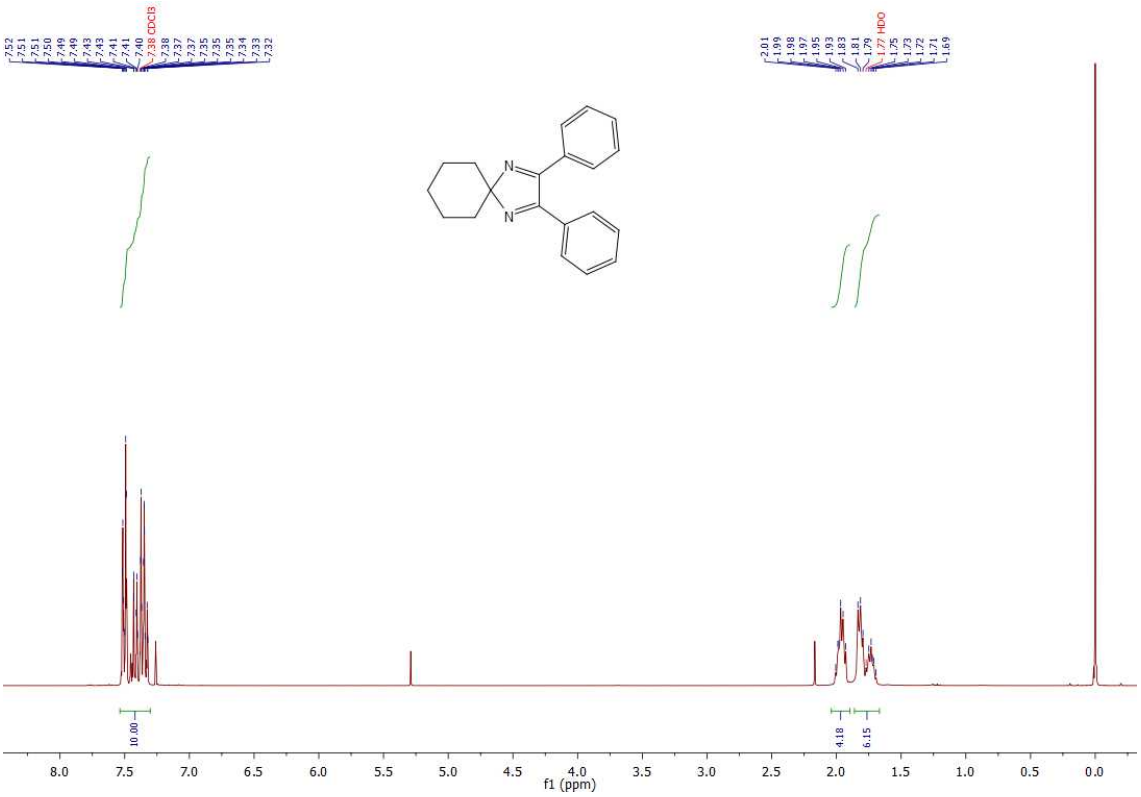
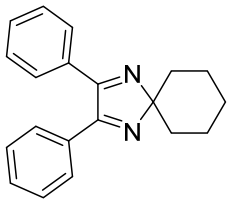


Figure SM 12.1.5.4 – ^{1}H NMR spectrum of spiroimidazole **7** (2,3-diphenyl-1,4-diazaspiro[4.5]deca-1,3-diene, 300 MHz, $CDCl_3$)



δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.49-7.52 (4H, m, Ar-H), 7.32-7.43 (6H, m, Ar-H), 2.01-1.93 (4H, m, C$\underline{H_2}$), 1.83-1.79 (4H, m, C$\underline{H_2}$) and 1.75-1.69 (2H, m, C$\underline{H_2}$).

Oxidation of activated phenols

Supplementary Material

Selective hydroxylation of aromatic compounds is among the most challenging of chemical reactions in synthetic organic chemistry in reason of lack of reagent for sinton $^{+}$OH group in a SEAr. The scope of this work covers other important issues in organic chemistry namely functional groups' reduction by metals, chromatography and NMR data interpretation.

The challenging occurrence of lateral reactions on the CAN oxidation can be explored by the students (Figure SM 12.1.6.1 and SM 12.1.6.2). The spectroscopic data of the lateral products is also provided.

o 1) information about the student body to whom the experiment was previously given to;

The experiment was developed by third year students of chemistry degree. The procedure is now robust enough to be applied to groups of students with good technical skills and ability to analyze spectroscopic data.

o 2) contextualization of the experiment in the organic chemistry subject at the proper level;

Considering the above arguments it is adequate to perform this work with students of the 3rd year of the bachelor degree.

At this stage students have properly assimilated knowledge of spectroscopy that allows them to interpret spectra without great difficulty and make comparisons with data from literature. Moreover the problem identification (lack of reagent for sinton +OH) can be done earlier by a chemistry student but the comprehension of the proposed solution arrives in a later stage.

o 3) the tricks needed to successfully perform the experiment in the classroom;

The solvent saturation with oxygen on the catalytic method is essential to avoid the use off an oxygen pressure above the atmospheric pressure. At atmospheric pressure the risk of oxygen use is reduced.

The oxygen saturated solution of DMF can be prepared before the laboratory session and provided to the students, avoiding the manipulation of gaseous oxygen during the class.

The phenol oxidation by CAN produces always lateral products as presented in Figure SM 12.1.6.1, resulting from coupling and nitration reactions. Those compounds are strongly colored (from orange to dark red), more polar than the desired quinone and can be isolated and characterized. If less solvent or non-acidic conditions are used they can become the main products.

o 4) parameters that can be changed in order to adapt the experiment to lab sessions of different duration;

The experiment can be reduced to only two sessions if the final objective is changed to the formation of the quinone product. A session is needed for the oxidation and a second one for chromatographic purification.

The same results can be obtained if the oxidant is changed to lead dioxide (PbO_2, 8 mmol), using acetic acid as solvent. The remaining conditions are unchanged. This lead procedure should be avoided by safety reasons.

o 5) experimental results obtain by students that performed this work;

At the end of work-up of the CAN oxidation, the residue weighs about 360 mg. The chromatography column was prepared with 25 g of silica with hexane / ethyl acetate (9.5: 0.5). Quinone was obtained as the less polar compound recovered from the chromatographic column as clear liquid (140 mg, yield 68%). From the same chromatographic column are usually also recovered, as pure compounds with increasing rf_s, 20 mg of the dimer (dark orange solid) and 10 mg and the nitro compound (yellow liquid).

At the end of work-up of oxidation by oxygen, the chromatographed residue weighs about 200 mg. In this reaction the desired quinone was the sole product (yields 15-30%) and was recovered always starting material (30-50%).

In some experiments performed by students small amounts of 5-hydroxycyclohex-2-ene-1,4-dione (Figure SM 12.1.6.2) are recovered witch can be rationalized by a conjugate addition to the desired quinone (question 4).

On the reduction of the quinone by metal were recovered 80 mg of a white solid (mp 101-109ºC).

Figure SM 12.1.6.1. Collection of products of propofol oxidation by CAN

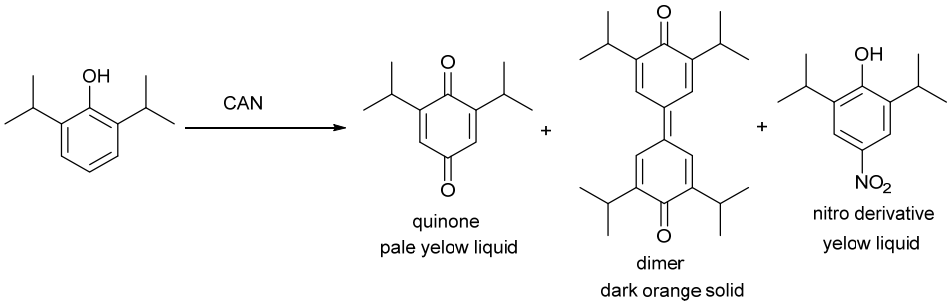


Figure SM 12.1.6.2. Proposed mechanism quinone attack by water.

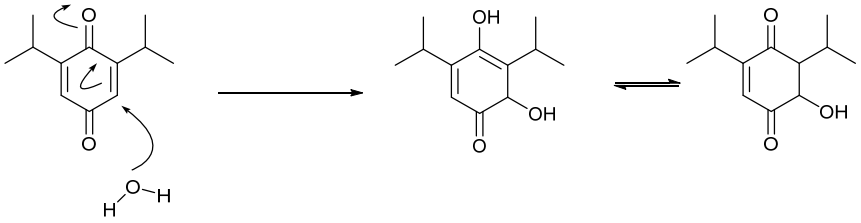


Figure SM 12.1.6.3. Quinone ^{1}H NMR spectra (400 MHz, $CDCl_3$).

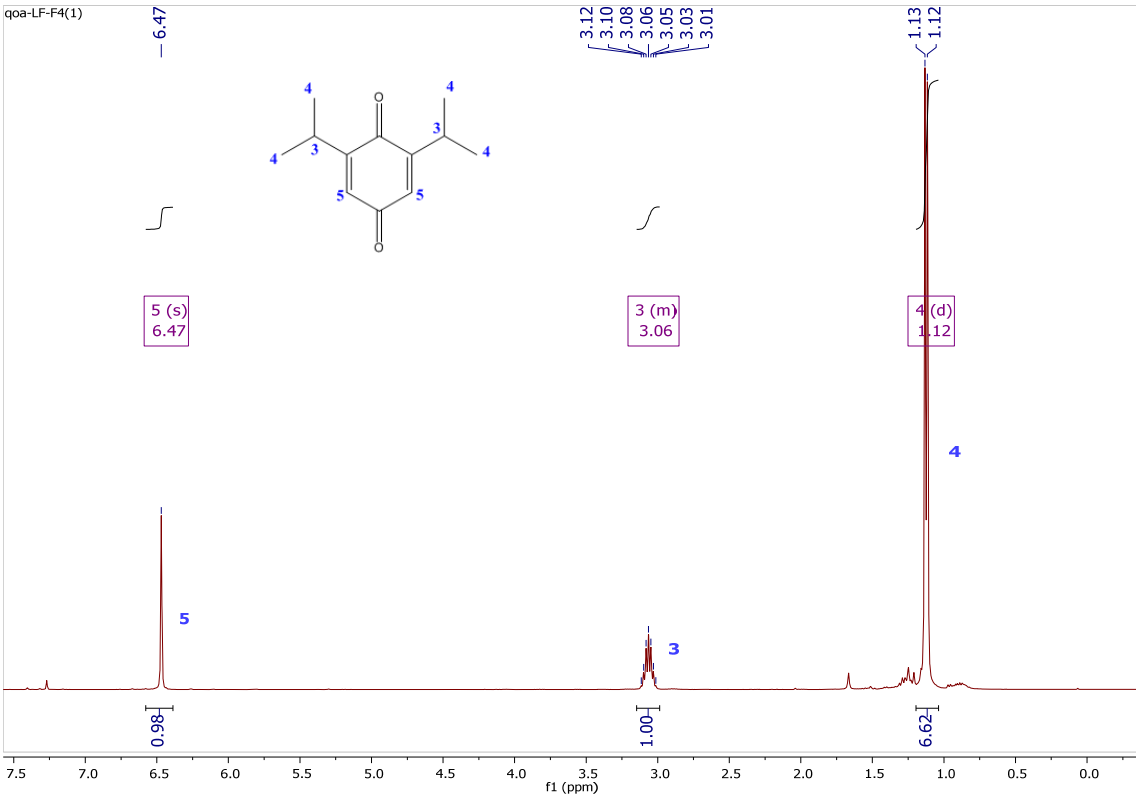


Figure SM 12.1.6.4. Quinone ^{13}C NMR spectra (101 MHz, $CDCl_3$)..

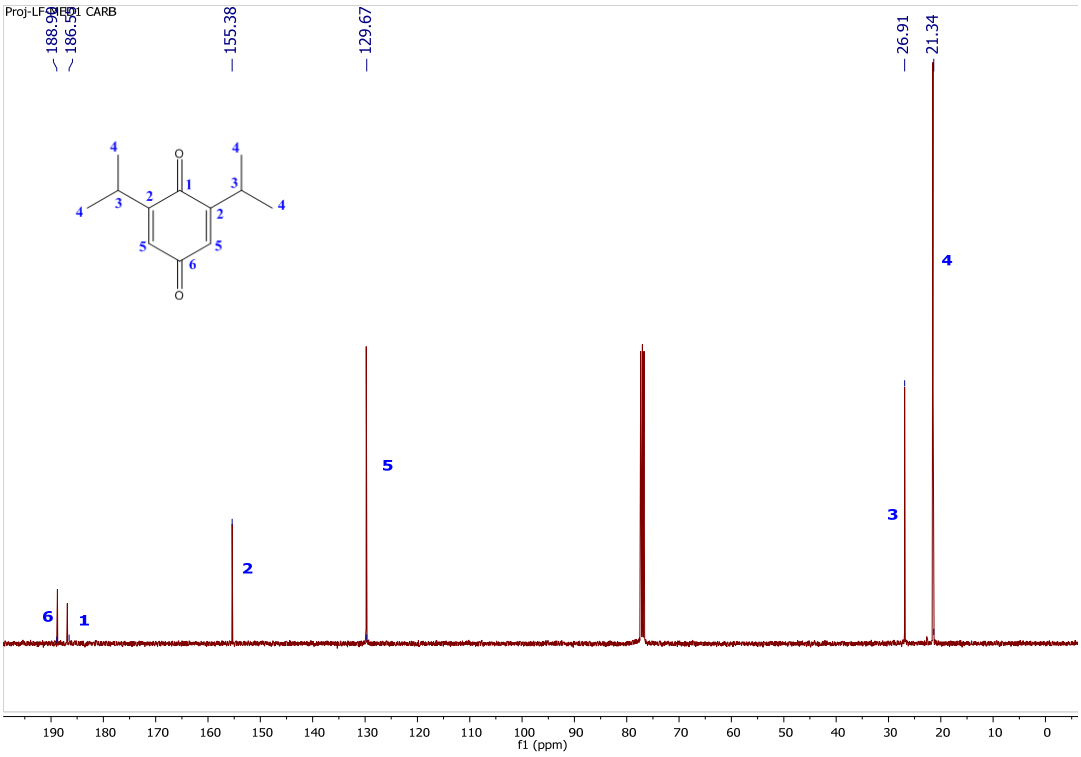


Figure SM 12.1.6.5. Quinone FTIR spectra (NaCl film).

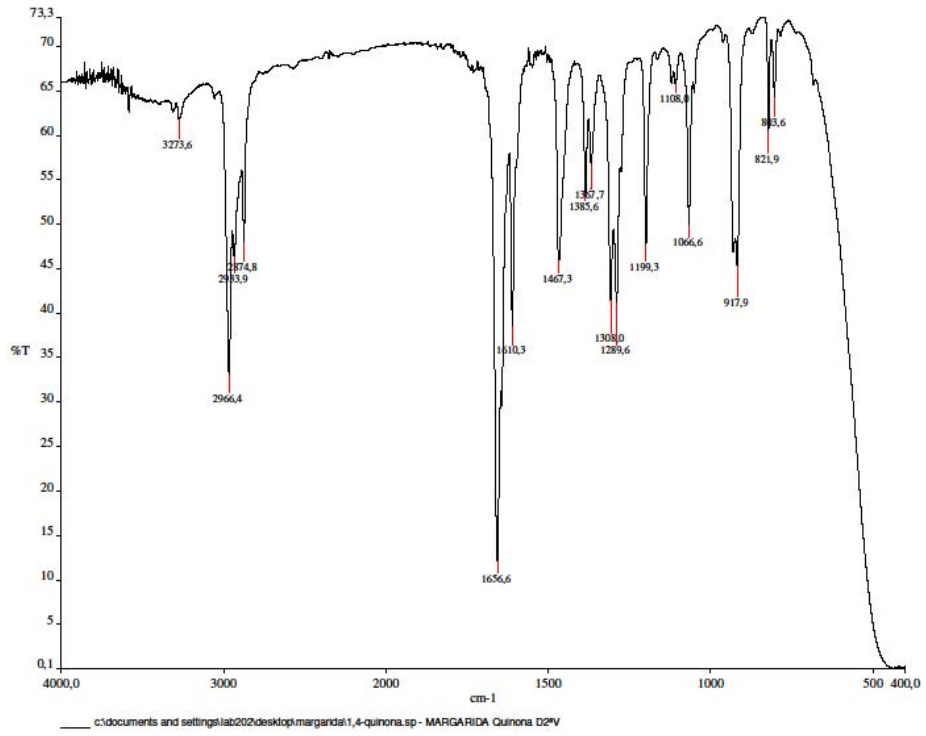


Figure SM 12.1.6.6. Dimer ^{1}H NMR spectra (400 MHz, $CDCl_3$).

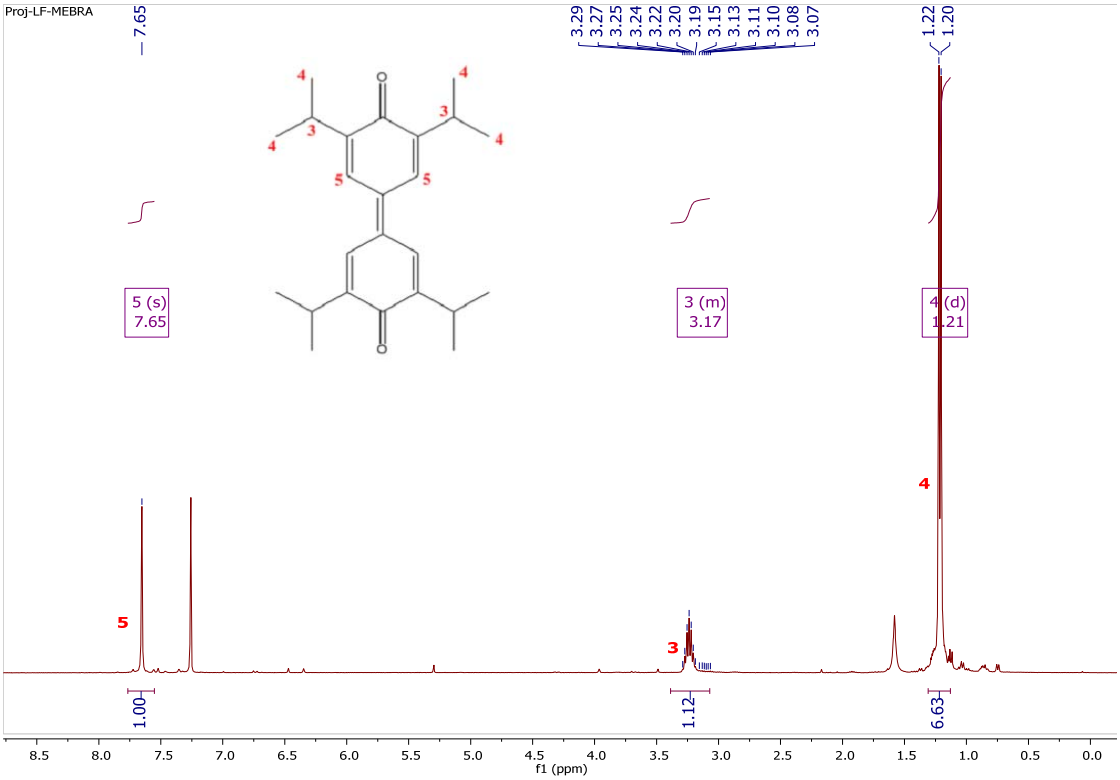


Figure SM 12.1.6.7. Dimer ^{13}C NMR spectra (101 MHz, $CDCl_3$).

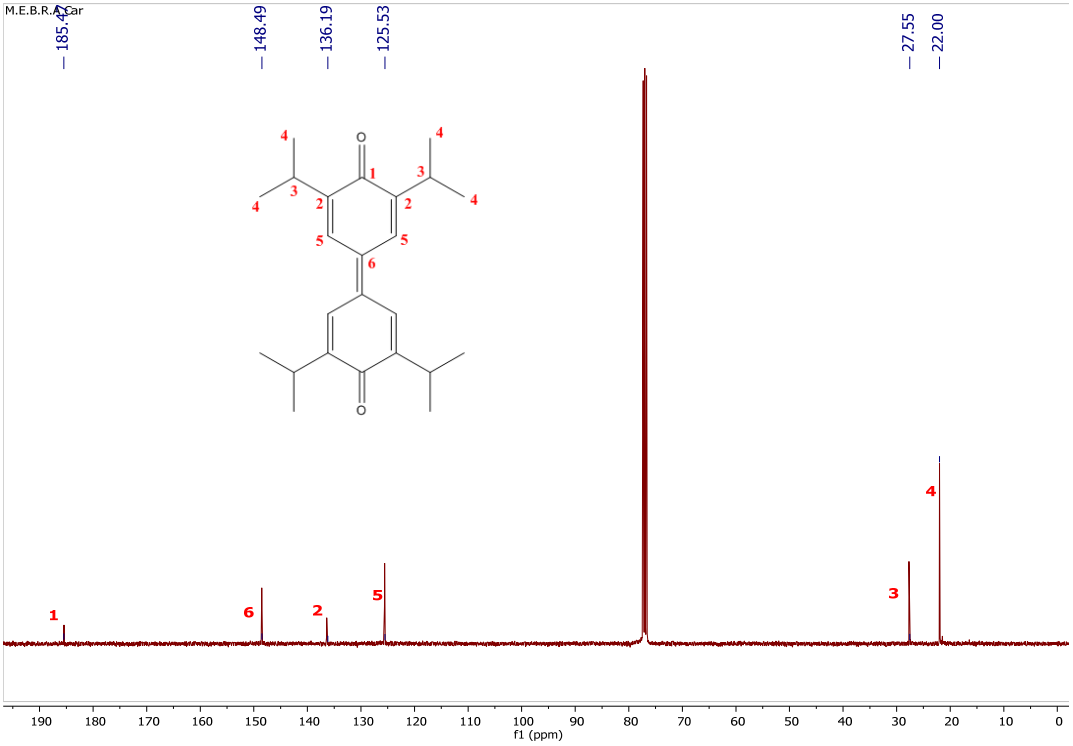


Figure SM 12.1.6.8. Dimer FTIR spectra (KBr pellet).

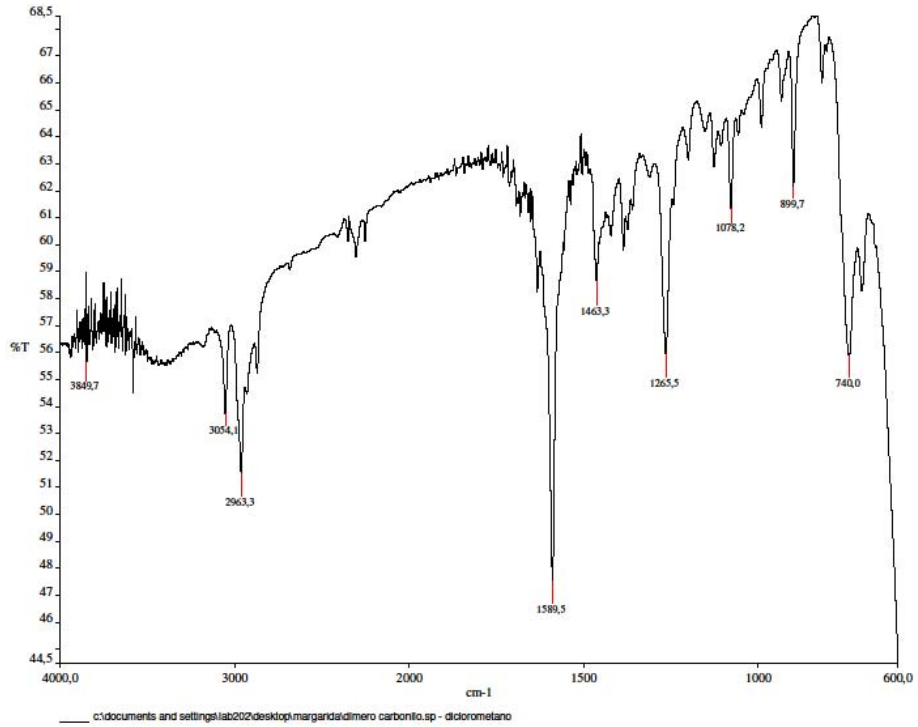


Figure SM 12.1.6.9. Nitro compound ^{1}H NMR spectra (400 MHz, $CDCl_3$).

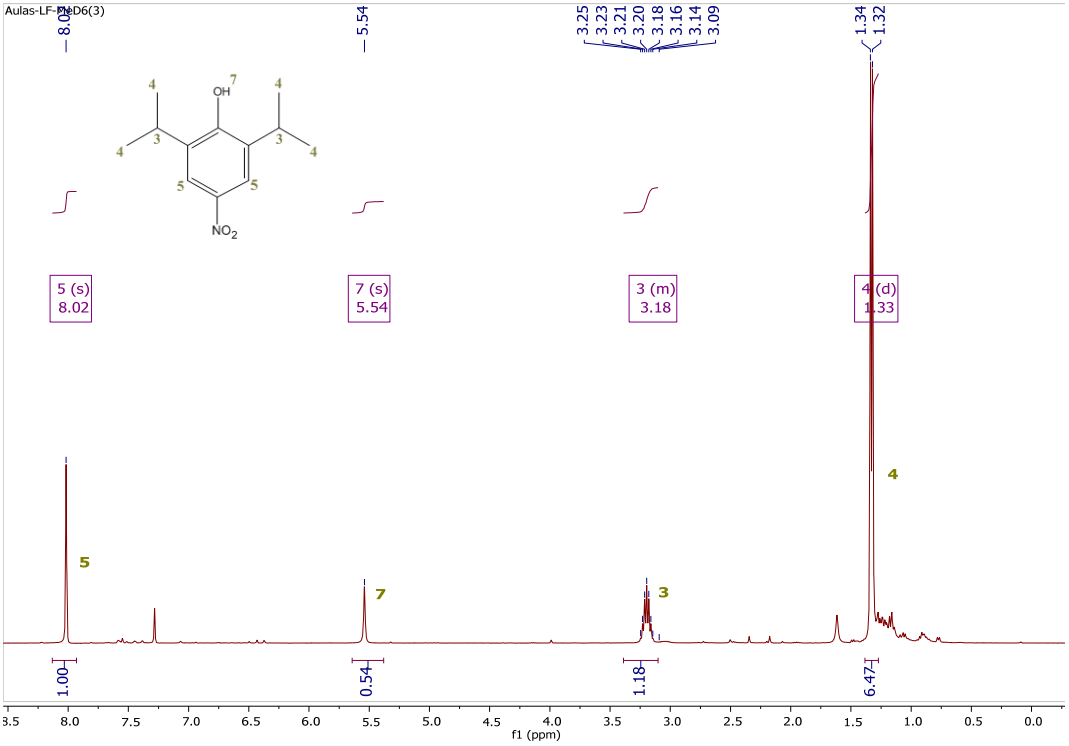


Figure SM 12.1.6.10. 4-hydroxy propofol ^{1}H NMR spectra (400 MHz, $CDCl_3$).

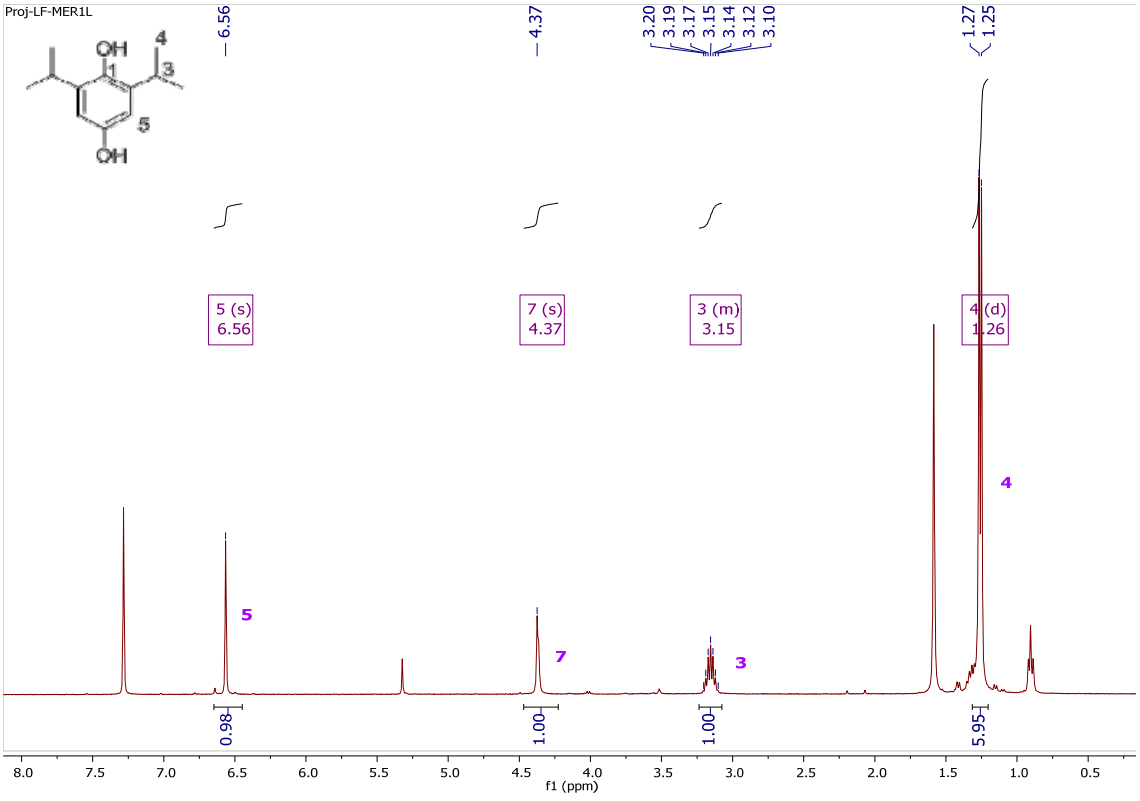


Figure SM 12.1.6.11. 4-hydroxy propofol ^{13}C NMR spectra (101 MHz, $CDCl_3$).

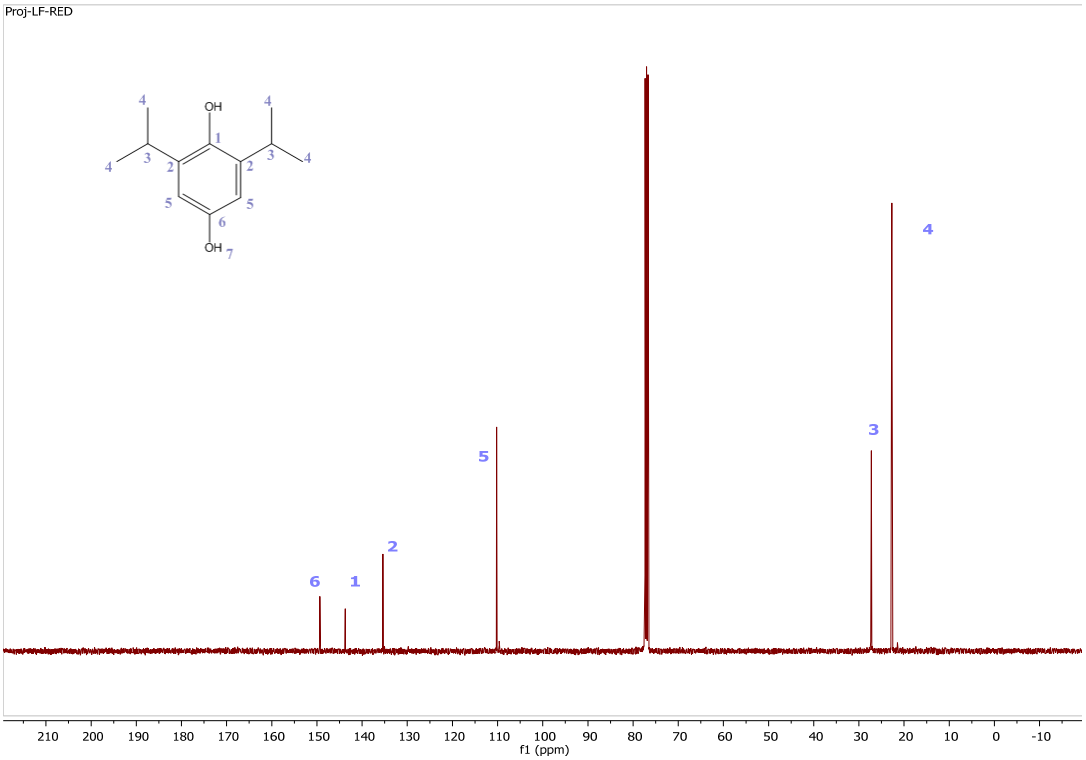


Figure SM 12.1.6.12. 4-hydroxy propofol FTIR spectra (KBr pellet).