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Development of a method for the non-catalytic synthesis of *meta*-aryloxy phenols from 1,3-cyclohexanedione

8D07105 Chemical Technology of Organic Substances

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SYMBOLS AND ABBREVIATIONS

^{13}C NMR – Carbon-13 nuclear magnetic resonance
^{1}H NMR – Proton nuclear magnetic resonance
CPME – Cyclopentyl methyl ether
DBN – 1,5-Diazabicyclo[4.3.0]non-5-ene
DBU– 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM – Dichloromethane
DIAD – Diisopropyl-azodicarboxylate
DIPEA – *N*,*N*-Diisopropylethylamine
DMA – *N*,*N*-dimethylacetamide
DMF – Dimethyl formamide
DMG*HCl – *N*,*N*-3,3-dimethylglycine hydrochloride
DMS – Dimethyl sulfide
DMSO – Dimethylsulfoxide
DP – Desired product
EPC*HCl – *N*-ethylcarbodiimide hydrochloride
h – hour
HMPA – Hexamethylphosphoramide
HOBt – Hydroxybenzotriazole
IR – Infrared spectroscopy
LG – Leaving group
LiHMDS – Lithium bis(trimethylsilyl)amide
NBS – *N*-Bromosuccinimide
NMP – *N*-Methyl pyrrolidone
PCC – Pyridinium chlorochromate
rt – Room Temperature
TFA – Trifluoroacetic acid
THF – Tetrahydrofuran
Wt% – Percentage by weight

INTRODUCTION

General description of work. The focus of this project is to develop a method for the non-catalytic synthesis of *meta*-(aryloxy)phenols from 1,3-cyclohexanedione. The goal is on establishing a simple and efficient process for producing *meta*-substituted phenols using readily available starting materials.

Relevance of the research topic. *Meta*-(aryloxy)phenols have been widely studied for their efficient and versatile chemical properties. They serve as useful synthetic intermediates for the synthesis of natural and biologically active compounds such as pharmaceuticals, agrochemicals, and dyes. Additionally, *meta*-(aryloxy)phenols exhibit exceptional antioxidant, antimicrobial, and anti-inflammatory activities, which make them potential candidates for a broad range of industrial and medicinal applications.

Moreover, the *meta*-substituted nature of these phenols further enhances their efficiency by conferring unique steric and electronic properties that can be optimized for specific applications. This attribute enables the development of highly selective and efficient catalysts, ligands, and chiral auxiliaries that are employed in numerous chemical processes, including asymmetric synthesis, cross-coupling reactions, and polymerization.

The synthesis of *meta*-(aryloxy)phenols has been a long-standing challenge in organic chemistry due to the complex nature of the reaction and the difficulties associated with achieving high yields and selectivity. Traditional synthetic methods involve the use of transition metal catalysts, which can be expensive and often require rigorous reaction conditions that can lead to undesired byproducts and low yields. Additionally, the use of transition metals can pose environmental concerns, and the presence of metal residues in the final product may limit their applications in various industries, including pharmaceuticals and materials science.

Furthermore, the steric and electronic properties of *meta*-substituted phenols are highly dependent on the specific substituents present, which can make the synthesis of these compounds even more difficult. Achieving precise control over the position and nature of the substituents can be difficult, and small changes in reaction conditions can lead to significant changes in product distribution and properties.

Despite these challenges, the development of efficient and practical methods for the synthesis of *meta*-(aryloxy)phenols is of great importance due to their diverse range of applications, including their use as synthetic intermediates and in medicinal and industrial applications. As such, continued efforts are being made to develop more efficient and environmentally friendly methods for their synthesis, which will allow for their wider use in various fields of chemistry.

The degree of development of the problem. The current state of research on the synthesis of *meta*-(aryloxy)phenols has shown significant progress. While various methods have been developed to synthesize these compounds, the non-catalytic approach is of particular interest due to its potential for industrial-scale production and reduced cost. Recent studies have focused on optimizing reaction conditions and improving yields, as well as exploring the versatility of the resulting compounds in various applications.

Despite the progress made in the field, there is still room for further development of efficient and practical methods for the non-catalytic synthesis of *meta*-(aryloxy)phenols. Future research may focus on the use of alternative reaction conditions and reagents to improve yields and selectivity, as well as the development of new synthetic routes to access more complex and diverse structures.

The purpose of the dissertation research. The objective of the present dissertation research is to develop an efficient and novel method for the synthesis of *meta*-(aryloxy)phenols from 1,3-cyclohexanedione.

To accomplish this goal, the following tasks were undertaken:

- formation of 3-chlorocyclohex-2-en-1-one from cyclohexan-1,3-dione by utilizing the Vilsmeier reagent;
- conduction of research on the conditions of obtaining 3-(aryloxy)cyclohex-2-en-1-one by nucleophilic substitution reaction;
- introduction of a directing group by C(2) bromination of 3-(aryloxy)cyclohex-2-en-1-one;
- conduction of research on the conditions of synthesis of *meta*-(aryloxy)phenols by oxidative aromatization;
- structure analysis of synthesized compounds through various techniques such as IR spectroscopy, mass spectrometry, and NMR spectroscopy;
- representation technological schemes for the developed methods for the synthesis of intermediate and final compounds and calculate the material balance of production.

The main provisions of the dissertation submitted for defense:

1. A novel approach for synthesizing *meta*-(aryloxy)phenols via cyclohexane-1,3-dione has been devised, comprising a four-step synthesis protocol. The method has yielded eight *meta*-(aryloxy)phenols in high quantities, with an average yield of 66% for all eight compounds.
2. The method avoids the need for operations to bypass the *ortho-, para-* directing effect of oxygen, resulting in a simplified and streamlined synthesis process. The required 1,3-functional group relationship is inherent in the readily available cyclohexane-1,3-dione starting material, allowing for easy access to the desired *meta*-(aryloxy)phenols.
3. The synthesis method does not entail the use of heavy metals or ligands, rendering it a more ecologically sound and safer substitute to conventional techniques.

The objects of study in this dissertation research are cyclohexane-1,3-dione and its derivatives, as well as various reagents and conditions for the synthesis of *meta*-(aryloxy)phenols.

The subject of the study is the development of a new and efficient method for the synthesis of *meta*-(aryloxy)phenols from cyclohexane-1,3-dione.

Research methods - mass spectrometry, IR spectroscopy, ^{1}H, ^{13}C NMR spectroscopy.

The scientific novelty of the work.

- A new and efficient method for the non-catalytic synthesis of meta-aryloxyphenols from 1,3-cyclohexanedione in four steps. All steps don'trequired high temperature and don't involve any heavy metals or ligandswere developed.
- The method has been successfully utilized to synthesize eight distinct *meta*-aryloxy phenols, four of which have not been previously documented in the literature. Additionally, the method has yielded 16 intermediate products, 14 of which have not been previously reported in literature.
- The chemical structures of newly synthesized compounds have been characterized for the first time using a combination of analytical techniques.

Theoretical and practical significance. The theoretical significance of the developed method lies in the discovery of a new and efficient approach for the synthesis of *meta*-(aryloxy)phenols from 1,3-cyclohexanedione. This approach offers a unique alternative to the conventional methods that involve the use of heavy metals or ligands and require additional steps to bypass the *ortho*-, *para*- directing effect of oxygen.

The practical significance of this method lies in its potential for industrial applications, as it offers a cost-effective and environmentally friendly approach to the synthesis of *meta*-(aryloxy)phenols. These compounds have a wide range of applications in various fields, including pharmaceuticals, agrochemicals, and dyes, as well as in the development of highly selective and efficient catalysts, ligands, and chiral auxiliaries used in various chemical processes. The developed method can also be used as a platform for the synthesis of novel *meta*-substituted phenolic compounds with tailored steric and electronic properties, which can be optimized for specific industrial and medicinal applications.

Compliance with priority areas of science development or government programs. The dissertation was carried out aligning with the priorities of scientific development, as approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan. Specifically, it pertained to scientific research in the field of natural sciences.

The author's personal contribution. The author made a significant contribution to the development and implementation of experiments, the solution of theoretical and practical problems, and the interpretation of the results. She collaborated with researchers in the Dr. Clive group laboratory at the University of Alberta.

She also played a key role in the preparation and writing of a review article published in the journal "Molecules". Furthermore, the author synthesized 24 out of the 51 compounds discussed in an article published in the journal "Tetrahedron".

Approbation of work. Main provisions and results of the dissertation presented and discussed at the international conference: the «Фараби Әлемі – 2023» conference for students and young scientists in 2023.

Publications. During the course of the research conducted for this dissertation, three scientific papers were published. Including the article in the Q2-ranked journal Tetrahedron (with a 60% percentile) and another article in the Q2-ranked journal Molecules (with an 83% percentile). Additionally, the findings of this research have been presented and discussed in international conference, such as the «Фараби Әлемі – 2023» conference for students and young scientists in 2023.

The structure and scope of the dissertation. The dissertation is presented as 115 pages of typewritten text and includes abbreviations, an introduction, a literature review, a discussion of results, an experimental part, conclusions and a list of sources used from 128 items, and an appendix for 50 pages. The dissertation work contains 75 schemes, 5 figures and 25 tables.

1 LITERATURE REVIEW

Phenols are widely distributed in nature and are useful in synthetic organic chemistry for the construction of natural products, bioactive compounds, fine chemicals, and functional materials [1-4].

Conventional strategies for the synthesis of substituted phenols involve functionalizations and transformations of functional groups around the periphery of an existing aromatic ring [5-9]. These methods usually provide direct routes to *ortho*- and *para*-substituted phenols, but the regiospecific synthesis of meta-substituted phenols can be difficult due to the dependence of regioselectivity on the electronic effects of aromatic ring substituents [10-13].

Consequently, alternative approaches such as oxidative aromatization of non-aromatic precursors have been developed. Recent advances in metal-catalyzed oxidative aromatization of cyclohexenones to phenols have been made, although related metal-free approaches have been limited by issues such as the over-oxidation of products [14-16]. To overcome this, indirect protocols were used, such as: pre-installation of protect groups at sensitive positions of phenols or the use of pre-oxidized substrates obtained by elimination aromatization [17-28]. Therefore, it would be highly beneficial to develop a direct protocol for the regiospecific and facile synthesis of *meta*-substituted phenols without metal promoters, while avoiding overoxidation.

1.1 *meta*-Aryloxy phenols. Characterization and applications

meta-(Aryloxy)phenols are a class of compounds that have gained significant interest in recent years due to their unique properties and potential applications in a variety of fields. These compounds are characterized by a phenolic group with an attached aryl group linked through an oxygen atom.

meta-(Aryloxy)phenol derivatives possess a diverse range of properties and potential applications [29]. They have been investigated for their antioxidant and anti-inflammatory activities, which makes them potential candidates for the development of pharmaceuticals and nutraceuticals [30,31]. They have also been studied for their antibacterial, antifungal, and antiviral properties, making them promising agents for the development of antimicrobial agents [32-34]. Additionally, the optical properties of *meta*-(aryloxy)phenols have been explored, demonstrating their potential utility in the development of materials for optoelectronics and photonics [35,36].

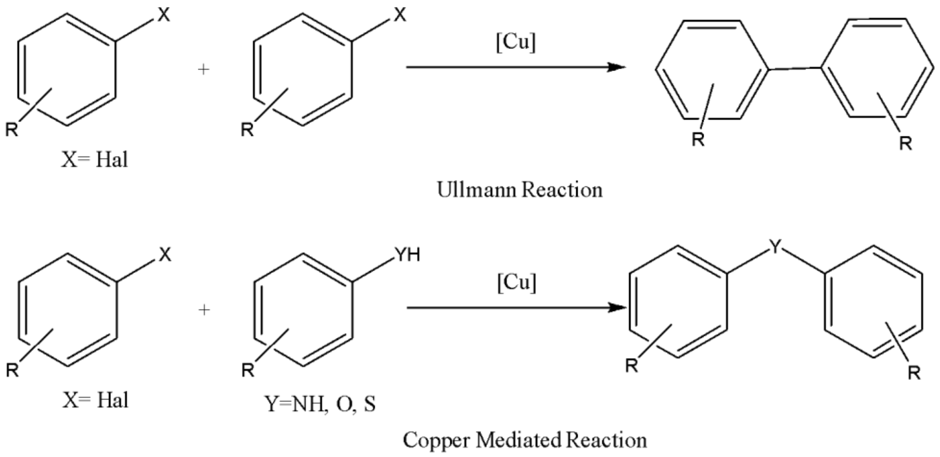
Overall, meta-(aryloxy)phenols are a versatile class of compounds with unique properties and promising potential applications. Further research into their synthesis, characterization, and potential applications is expected to continue in the coming years.

1.2 Synthesis of *meta*-aryloxy phenols

The synthesis of *meta*-(phenoxy)phenol has been of interest for its potential applications in various fields, including medicinal chemistry and materials science [29]. This compound has been shown to exhibit antibacterial and antifungal properties, and has been investigated as a potential agent for the treatment of bacterial infections. In addition, *meta*-(phenoxy)phenol has been used as a building block for the synthesis of other compounds, such as the herbicide mecoprop and the fungicide triflumizole [37,38].

The synthesis of *m* -aryloxy phenol can be achieved through a variety of methods, including the reaction of phenol with an aryl halide in the presence of a strong base, known as the Ullmann reaction. Another method involves the reaction of 3-bromophenol with phenylmagnesium bromide in the presence of a catalyst, such as copper (I) iodide.

The first diphenyl compound to be synthesized was biphenyl, which was accomplished by the German chemist Carl Gräbe in 1866. Gräbe utilized a method involving the oxidation of a mixture of two molecules of toluene with potassium permanganate [39]. However, the general method for diphenyl compound synthesis, known as the Ullmann reaction, was first reported by Fritz Ullmann in 1901(scheme 1.1). This reaction method has since been widely used for the synthesis of various diphenyl compounds.



Scheme 1.1 – Schematic representation of the Ullmann and the copper-mediated reaction

In the initial Ullmann reaction protocol, equimolar amounts of copper salts were employed at elevated reaction temperatures (equal to or greater than 200°C) and prolonged reaction times. However, contemporary adaptations of the Ullmann reaction have concentrated on the use of copper-mediated reactions (either stoichiometric or catalytic) between aryl halides and other reagents, such as amines, phenols, or thiophenols, to produce aryl-amine, -ether, or -thioether compounds, respectively [40-42].

Despite the broadened range of reactions that can be classified as Ullmann reactions, the term is primarily used to refer to the copper-catalyzed synthesis of biaryls from aryl halides. This protocol has been widely adopted due to its high efficiency and versatility in constructing complex biaryl compounds [43,44].

Since then, other methods for the synthesis of *meta*-(phenoxy)phenol have been reported, including the reaction of phenol with 3-chlorobenzyl chloride in the presence of a base, and the reaction of 3-iodophenol with phenylboronic acid in the presence of a palladium catalyst.

Overall, the synthesis of 3-(phenoxy)phenol has contributed to the development of new materials and compounds with potential applications in various fields. Its antibacterial and antifungal properties make it a promising compound for the development of new drugs and agricultural chemicals. The Ullmann reaction continues to be a crucial tool in modern organic synthesis and has played a significant role in the development of numerous natural products, pharmaceuticals, and materials.

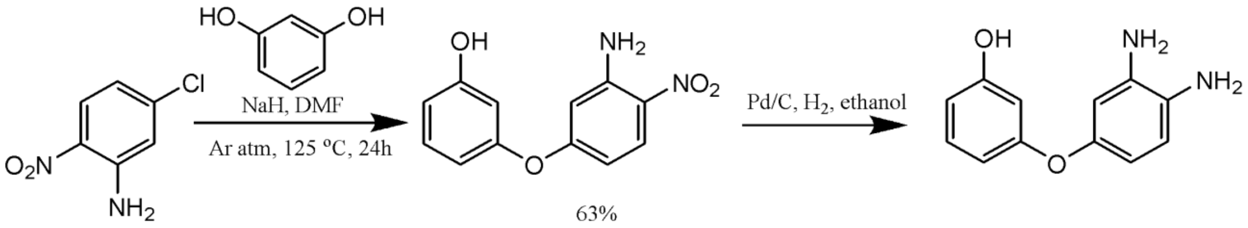
Recent developments in the synthesis of *meta*-(aryloxy)phenols have focused on employing advanced techniques and methodologies for the efficient construction of this class of compounds. One notable advancement involves the utilization of palladium-catalyzed cross-coupling reactions between aryl halides and phenols, which allows for the synthesis of a diverse range of *meta*-(aryloxy)phenols with high selectivity and efficiency.

Other approaches include the use of copper-catalyzed arylation reactions and transition metal-free methods, which have proven to be effective in constructing *meta*-(aryloxy)phenols in good yields and wild broad substrate scope. Additionally, the application of microwave-assisted and flow chemistry techniques has facilitated the rapid and streamlined synthesis of *meta*-(aryloxy)phenols. The following text describes the recent advances in the synthesis of *meta*-(aryloxy)phenols [29].

1.2.1 The Nucleophilic Aromatic Substitution Reaction between Aryl Halides and Resorcinol

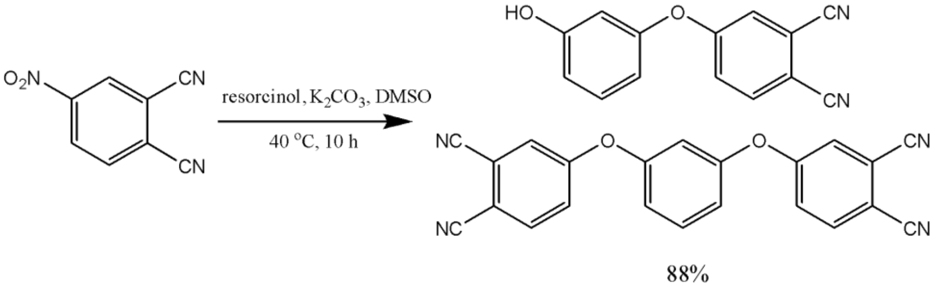
The nucleophilic aromatic substitution mechanism is involved in the reaction between aryl halides and 1,3-dihydroxybenzene (resorcinol). Under basic conditions, resorcinol is deprotonated and acts as a nucleophile on the aromatic ring of the aryl halide. This generates an intermediate species where the nucleophile attacks the ring, leading to the substitution of the halide group. The intermediate species contains an oxide anion, formed due to the loss of a proton. Finally, the reaction yields an aryloxy phenol as the product, which can be obtained in good yield with appropriate reaction conditions [45]. The following text will highlight some recent research studies that have been conducted.

Vagin and colleagues conducted a study in 2010 that described the synthesis of 5-(3-hydroxyphenoxy)-2-nitroanilin from 5-chloro-2-nitroaniline and resorcinol(scheme 1.2). The reaction was performed by heating the reaction mixture containing sodium hydride as a strong base and DMF as a solvent, under an argon atmosphere at 125°C for 24 h. Following this, they utilized a hydrogenation reaction with a Pd/C catalyst to obtain 4-(3-hydroxyphenoxy)-1,2-benzyldiamine as the final product. [46].



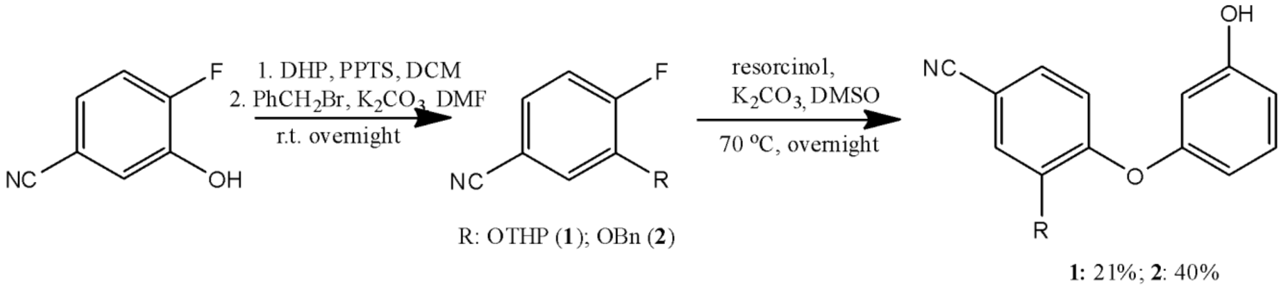
Scheme 1.2 – Hydrogenation reaction of 3-(3-amino-4-nitrophenoxy) phenol

Wang and his research team in 2015 created a self-promoted hydroxy-containing phthalonitrile system, which included 1,3-bis(3,4-dicyanophenoxy)benzene (BDB) and (4-hydroxyphenoxy)phthalonitrile (HPPH) through a one-pot nucleophilic displacement reaction by removing a nitro-substituent from 4-nitrophthalonitrile using a suitable reagent with resorcinol. They used potassium carbonate as a base, and DMSO as a solvent. The reaction goes in 40 ^{0}C(scheme 1.3) [47].



Scheme 1.3 – Synthesis of (4-hydroxyphenoxy)phthalonitrile and 1,3-bis(3,4-dicyanophenoxy) benzene

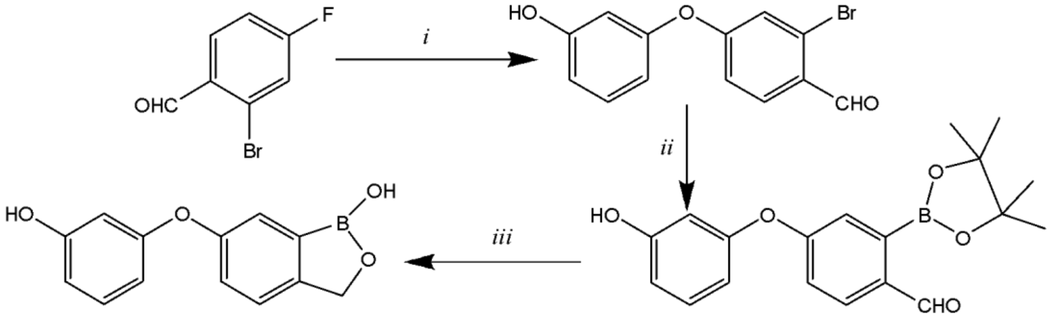
Bollini and colleagues published a study in 2011 that demonstrated the synthesis of 4-(3-hydroxyphenoxy)-3-[(tetrahydro-2H-pyran-2-yl)oxy]benzonitrile and 3-(benzyloxy)-4-(3-hydroxyphenoxy)benzonitrile from 3-hydroxy-4-fluorobenzonitrile using a two-step process(scheme 1.4) [48].



Scheme 1.4 – Synthesis of aryloxy phenols based on 3-aryloxy-4-fluorobenzonitrile and resorcinol

In the second step they used resorcinol, potassium carbonate as a base, and DMSO as a solvent. The reaction goes in 70 °C, overnight. The yields of the synthesis were 21% and 40%.

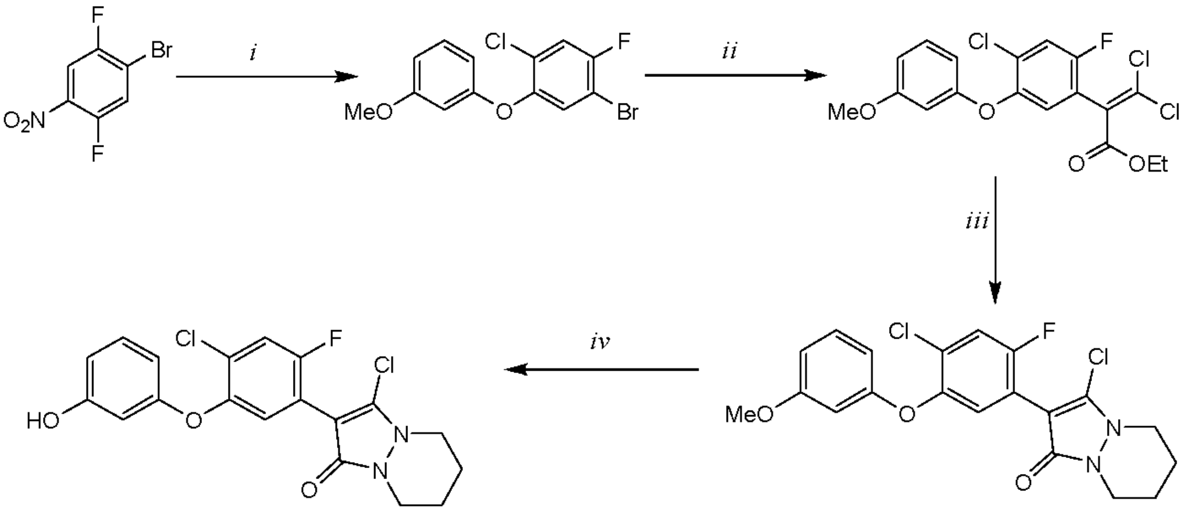
In 2011, a team led by Xia introduced a new category of benzoxaborole β-lactamase inhibitors via a three-step synthesis process. The initial step involved substituting 2-bromo-4-fluorobenzaldehyde with phenol to form an ether using nucleophilic substitution. Next, they utilized palladium-mediated boronylation on the ether to generate an aldehyde. Finally, the aldehyde was reduced with $NaBH_4$ and underwent acid-catalyzed cyclization to produce the final product, known as the (3-hydroxyphenoxy)benzoxaborole(scheme 1.5) [49,50].



(i) - resorcinol, Cs_2CO_3, DMF, 80 °C; *(ii)* - B_2pin_2, $PdCl_2(dppf)$, KOAc, dioxane, 80 °C;
(iii) - $NaBH_4$, MeOH-THF, 0 °C

Scheme 1.5 – Synthesis of the (3-hydroxyphenoxy)benzoxaborole

Kobayashi and his team accomplished the synthesis of 5-chloro-4-[4-chloro-2-fluoro-5-(3-hydroxyphenoxy)phenyl]-1,2-tetramethylene-4-pyrazolin-3-one in 2016 (scheme 1.6), using a seven-step process starting from 2,5-difluoro-4-bromonitrobenzene.

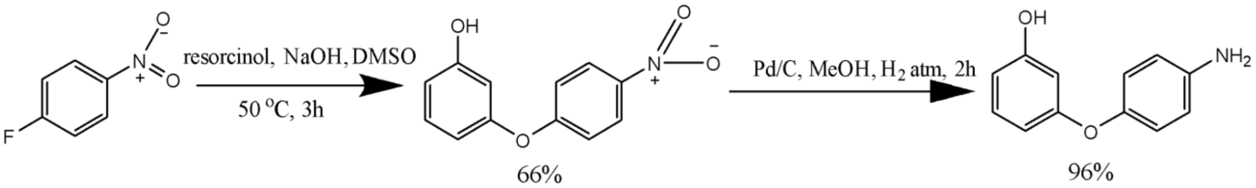


(i) - 3-methoxyphenol, NaOH, THF, 0 °C to rt., 1.5 h. Yield=87%; Fe, AcOH, H_2O, EtOAc, 0 °C to rt., 1h. 88%; CuCl, $CuCl_2$, isoamyl nitrile, MeCN, rt., 2 h. 99%; *(ii)* - I-PrMgCl*THF, Grignard rt, −40 °C to 0 °C, 2 h. 92%; CCl_4 PPh_3, DCM, 0 °C to rt., 17 h. 74%; *(iii)* - diazinane *2HBr, Et_3N, 1,4-dioxane, reflux, 22h. 83%; *(iv)* - BBr_3, DCM, rt, 2 h. 93%.

Scheme 1.6 – Synthesis of a polycyclic pyrazolinone derivative containing an aryloxy phenol fragment

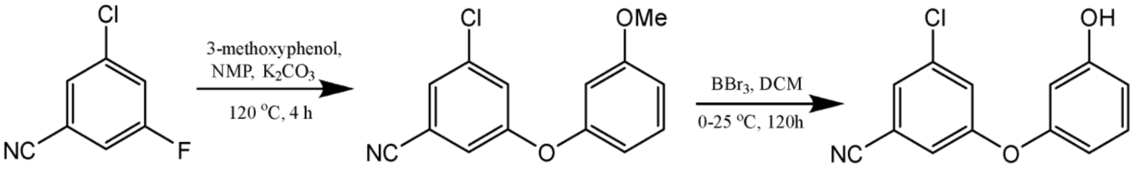
Their methodology entailed an electrophilic aromatic substitution reaction between 2,5-difluoro-4-bromonitrobenzene and 3-methoxyphenol, resulting in the formation of an ether. The final step involved the removal of a methyl group utilizing boron tribromide as a demethylation agent, yielding the desired 5-chloro-4-[4-chloro-2-fluoro-5-(3-hydroxyphenoxy-phenyl]-1,2-tetramethylene-4- pyrazolin-3-one [51].

In 2018, Kazuia and colleagues achieved synthesis of 4-(3-hydroxyphenoxy) benzamine from *para*-fluoronitrobenzene and resorcinol (scheme 1.7). The reaction was carried out at a temperature of 50°C for 3 h, utilizing sodium hydroxide and DMSO as reagents. The final product was obtained by hydrogenation using a Pd/C catalyst in methanol under a hydrogen atmosphere for 2 h [52].



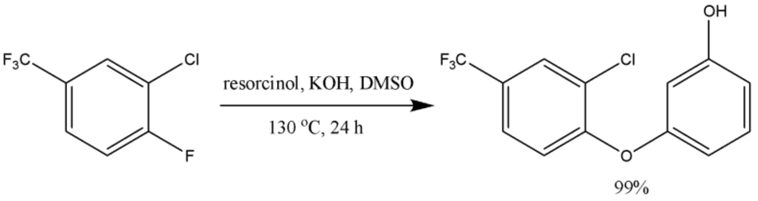
Scheme 1.7 – Synthesis of 4-(3-hydroxyphenoxy) benzamine

Frączk and his team reported the synthesis of 2-(3-hydroxyphenoxy)-5-chlorobenzonitrile in two steps in 2018(scheme 1.8). The first step involved the reaction of 5-chloro-3-fluorobenzonitrile with 3-methoxyphenol using NMP and potassium carbonate as reagents. In the second step, demethylation was performed using BBr_3 in DCM. The final product was 5-chloro-2-(3-hydroxyphenoxy)benzonitrile [53].



Scheme 1.8 – Synthesis of 5-chloro-2-(3-hydroxyphenoxy)benzonitrile

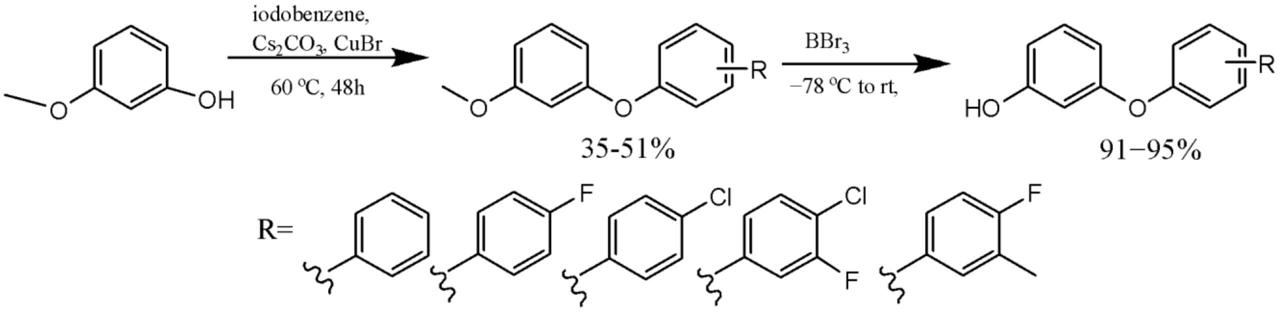
In 2022, Zhong and his team developed a synthesis approach for producing 3-[2-chloro-4-(trifluoromethyl)phenoxy]phenol(scheme 1.9). The synthesis was achieved through the displacement of 3-chloro-4-fluorobenzotrifluoride with resorcinol, requiring a high temperature of 130°C and an inert atmosphere for a 24-h reaction time. The desired product was 3-[2-chloro-4-(trifluoromethyl)phenoxy]phenol with 99% yield [54].



Scheme 1.9 – Synthesis of 3-(2-chloro-4-(trifluoromethyl)phenoxy) phenol

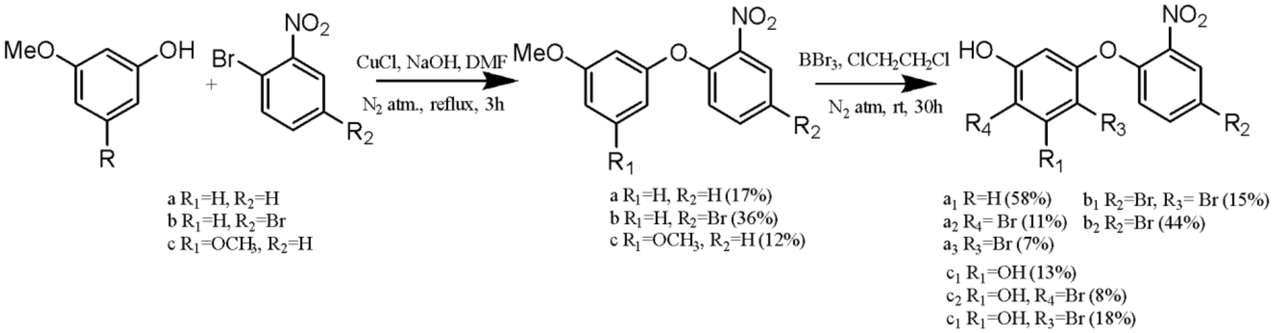
The use of a catalyst in the nucleophilic aromatic substitution reaction between an aryl halide and resorcinol has been extensively studied. The choice of a suitable catalyst depends on the reaction conditions and the desired outcome. Transition metal catalysts like palladium and copper have been shown to be effective in catalyzing this reaction, leading to an increase in reaction rate and/or improved regioselectivity. However, the use of a catalyst may also bring about practical disadvantages, such as higher cost and the need for specific handling and disposal procedures. Copper chloride (CuCl) has been found to be an effective catalyst in the reaction between an aryl halide and resorcinol, resulting in an enhancement in reaction rate and/or regioselectivity [55-58].

In 2010, Silverman and his team developed a two-step procedure for synthesizing *meta*-(aryloxy)phenols. They first carried out Ullmann couplings of *meta*-(methoxy)phenol with iodobenzene derivatives using Cs_2CO_3 and a small amount of CuBr as a catalyst to produce the intermediate compound. Next, they cleaved the methyl ethers using BBr_3, resulting in *meta*-(aryloxy)phenols in high yields(scheme 1.10) [59].



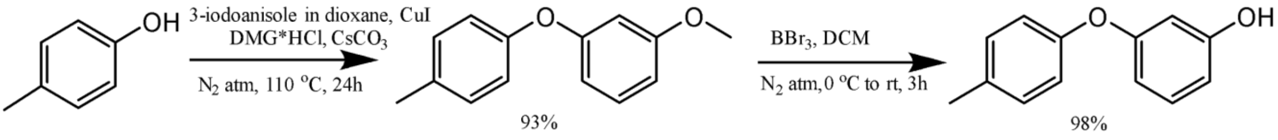
Scheme 1.10 – Synthesis of *meta*-(methoxy)phenol with iodobenzene derivatives using Cs_2CO_3 and a small amount of CuBr as a catalyst

In 2010, Sapkota and colleagues reported on a two-step copper catalyst-based synthesis of 8 *meta*-(aryloxy)phenols from methoxyphenols and 2-bromonitrobenzene or 2,4-dibromonitrobenzene. The yields of the final compounds varied between 6-44% (scheme 1.11) [60].



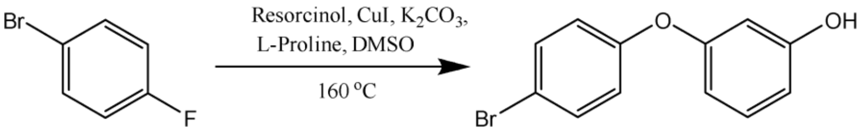
Scheme 1.11 – Two-stage synthesis of new meta-aryloxy phenols based on a copper catalyst

Bouey and her team synthesized 3-(*para*-tolyloxy)phenol from 3-iodoanisole and *para*-methylphenol through a two-step process in 2010(scheme 1.12). The first step involved utilizing copper iodide, *N,N*-dimethylglycine hydrochloride, and cesium carbonate to carry out etherification. In the second step, boron tribromide was used as a demethylation agent, with DCM serving as a solvent [61].



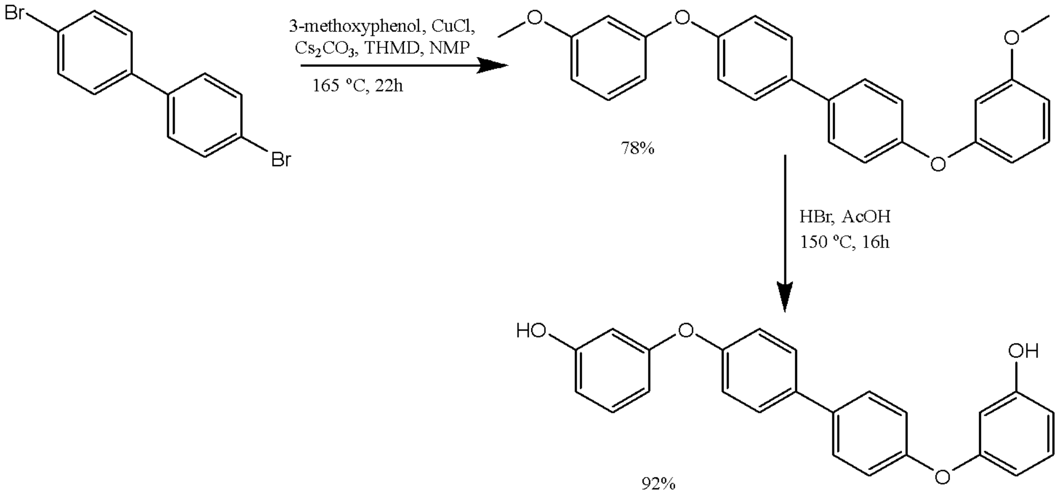
Scheme 1.12 – Synthesis of 3-(*para*-tolyloxy)phenol based on copper iodide as a catalyst

In a study published by Lee and colleagues, an Ullmann coupling reaction was employed for the synthesis of 3-(4-bromophenoxy)phenol, a derivative of *meta*-substituted phenol(scheme 1.13). The reaction was conducted in DMSO and utilized copper iodide, potassium carbonate, and L-proline as catalysts [62].



Scheme 1.13 – Synthesis of 3-(4-bromophenoxy)phenol

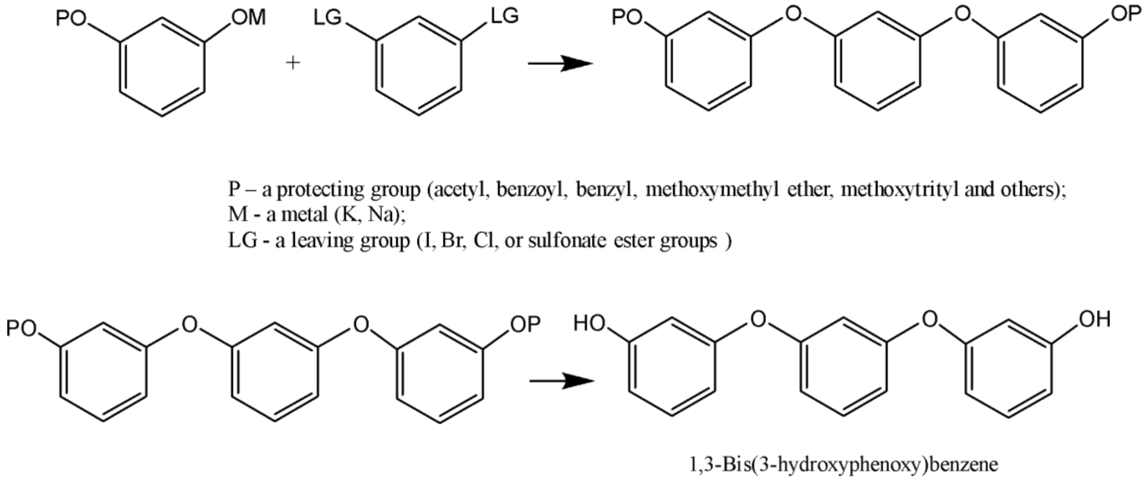
In 2012, Li and colleagues reported a two-step synthesis of bisphenol monomers using a copper catalyst(scheme 1.14). The starting materials were 4,4'-dibromo biphenyl and 3-methoxyphenol, and the reaction proceeded via an intermediate methoxy-terminated four-ring monomer.



Scheme 1.14 – Synthesis of bisphenol using a copper catalyst

The first step, which involved an Ullmann coupling reaction, using CuCl, Cs_2CO_3, 2,2,6,6-tetramethyl-3,5-heptanedione (THMD) and *N*-methyl pyrrolidone (NMP), was conducted at a high temperature of 165°C. The second step, which involved hydrolysis of the intermediate, was carried out at 150°C using hydrobromic acid in acetic acid to produce the final product [63].

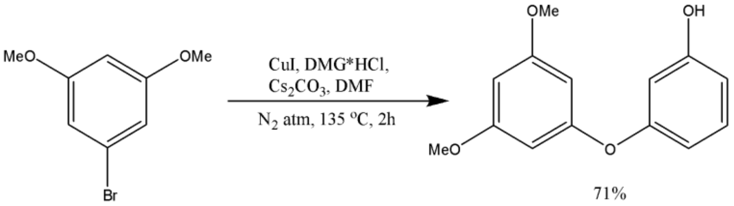
The paper [64] presents a modified method for synthesizing 1,3-di(3-hydroxyphenoxy)benzene, which involves two stages. The first stage involves the use of various activated *meta*-cresols with protected hydroxy groups and compounds containing leaving groups (LG) in the *meta* position in the presence of a catalyst such as copper (I) chloride, to produce 1,3-diaryl-substituted heterocycles. The second stage involves the interaction of these compounds with an acid catalyst to produce 1,3-di(3-hydroxyphenoxy)benzene(scheme 1.15). This method is a modification of a process previously published by L. Wang [65].



P – a protecting group (acetyl, benzoyl, benzyl, methoxymethyl ether, methoxytrityl and others);
M - a metal (K, Na);
LG - a leaving group (I, Br, Cl, or sulfonate ester groups)

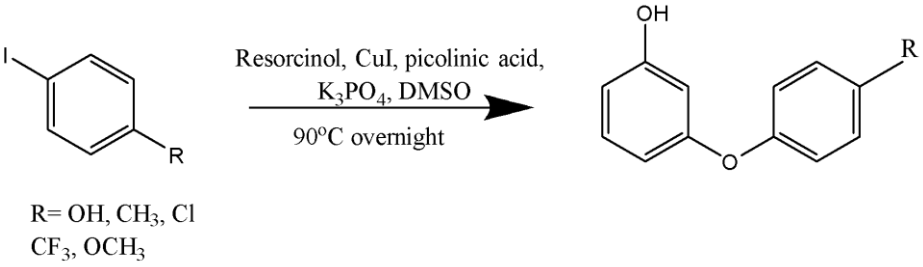
Scheme 1.15 – Synthesis of 1,3-di(3-hydroxyphenoxy)benzene

In 2013, a report was published by Bartholomeus et.al. detailing the synthesis of 3-(3,5-dimethoxyphenoxy)phenol through the application of the Ullmann-type coupling reaction(scheme 1.16). The synthesis process entailed mixing 1-bromo-3,5-dimethoxybenzene with resorcinol, in the presence of a copper iodide catalyst, *N,N*-dimethylglycine hydrochloride, cesium carbonate, and DMF as the solvent [66].



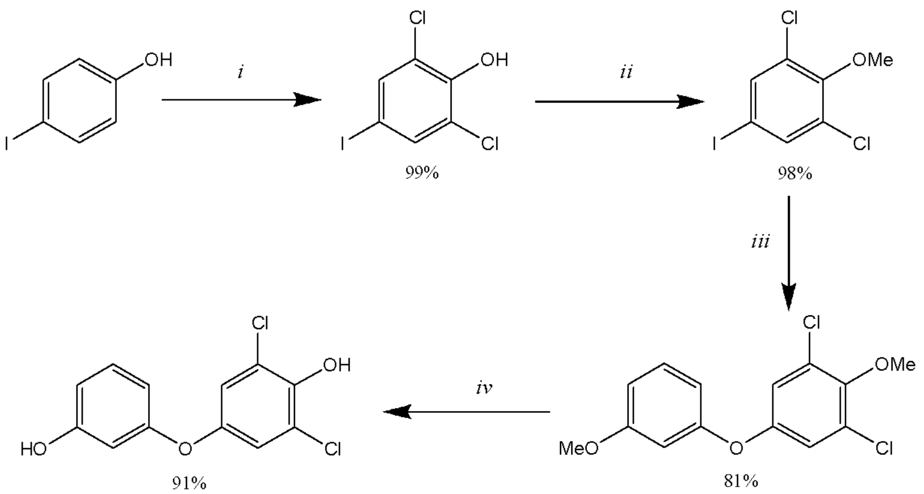
Scheme 1.16 – Synthesis of 3-(3,5-dimethoxyphenoxy)phenol

A methodology for the synthesis of 3-(*para*-substituted aryloxy) phenols via Ullmann coupling reaction was published by Gim and coworkers in 2015 (scheme 1.17). The process involved the amalgamation of resorcinol and aryl iodides with CuI with picolinic acid serving as catalyst. They used potassium phosphate as a base and dimethyl sulfoxide as a solvent for the synthesis. The reaction goes at 90°C overnight [67].



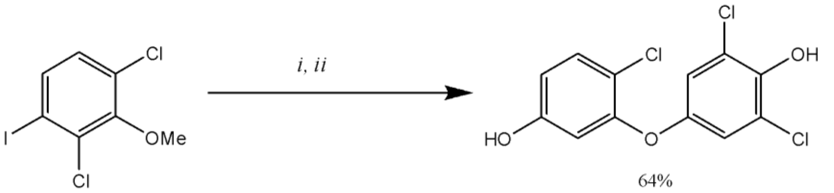
Scheme 1.17 – Synthesis of 3-(*para*-substituted aryloxy) phenols using CuI and picolinic acid as catalyst

In 2016, Yang and colleagues presented a 4-step approach for the synthesis of 3-(3,5-dichloro-4-hydroxyphenoxy)phenol from 4-iodophenol(scheme 1.18). The synthesis involved an Ullmann reaction catalyzed by copper, with 3-methoxyphenol serving as a co-reagent, followed by demethylation with HBr in acetic acid. All steps necessitated an inert atmosphere and exhibited high yields. Furthermore, the same process was employed by Hu et.al to synthesize 3-(3,5-dichloro-4-hydroxyphenoxy)-4-chlorophenol, as described in 2016 [68,69].



(i) - diisobutylamine, SO_2Cl_2, toluene, 70 °C, 1h; *(ii)* - MeI, Cs_2CO_3, DMF, r.t. 2h; *(iii)* - 3-methoxyphenol, CuI, DMG*HCl, Cs_2CO_3, dioxane, Ar atm., 90 °C, 24h; *(iv)* - HBr (48 wt%), AcOH, Ar atm., ref., 12h

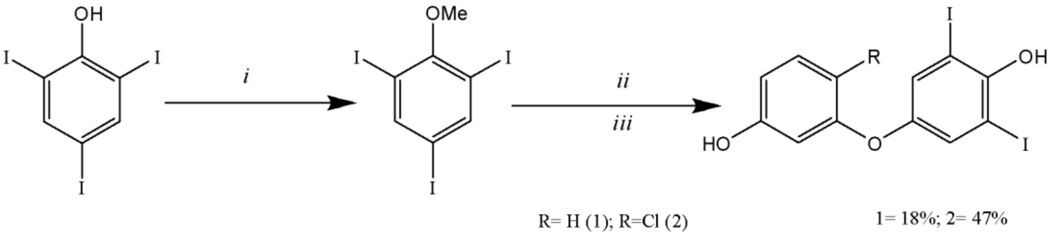
and



(i) - 4-chloro resorcinol, DMG*HCl, CuI, Cs_2CO_3, dioxane, 90 ⁰C; *(ii)* - HBr (48wt%), AcOH, ref, 12h

Scheme 1.18 – Synthesis of 3-(3,5-dichloro-4-hydroxyphenoxy)-phenol and 3-(3,5-dichloro-4-hydroxyphenoxy)-4-chlorophenol

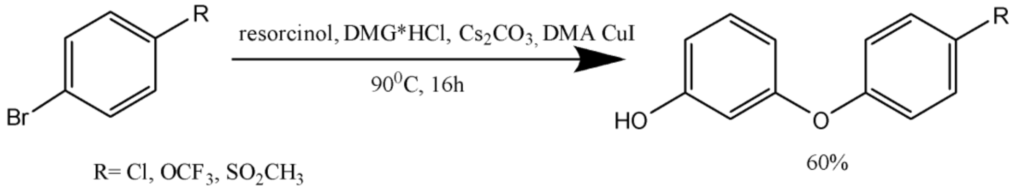
Bai and coworkers reported a 2-step method for synthesizing 3-(3,5-diiodo-4-hydroxyphenoxy)phenol and 4-chloro-3-(3,5-diiodo-4-hydroxyphenoxy)phenol from 2,4,6-triiodophenol, utilizing specific reagents. The ultimate stage of the process entailed using boron tribromide in DCM as a demethylation agent(scheme 1.19), as published in 2017 [70].



(i) - DMS, K_2CO_3, CH_3CN, ref., 2 h.; *(ii)* - 3-(MeO)-6-R-C_6H_3OH, CuI, DMG*HCl, Cs_2CO_3, 1,4-dioxane, 110 °C, 24h; *(iii)* - BBr_3, DCM, 0 °C, 3h

Scheme 1.19 – Synthesis of 3-(3,5-diiodo-4-hydroxyphenoxy)phenol and 3-(3,5-diiodo-4-hydroxyphenoxy)-4-chlorophenol

As per the 2010 patent by Breitenburcher et al. [71], the desired compounds were synthesized by treating the appropriate starting material with a CuI solution, in the presence of resorcinol, *N*,*N*-dimethylglycine HCl, and cesium carbonate in *N*,*N*-dimethylacetamide (DMA) (scheme 1.20).



Scheme 1.20 – Synthesis of 3-(*para*-substituted aryloxy) phenols using CuI and DMG*HCl as catalysts

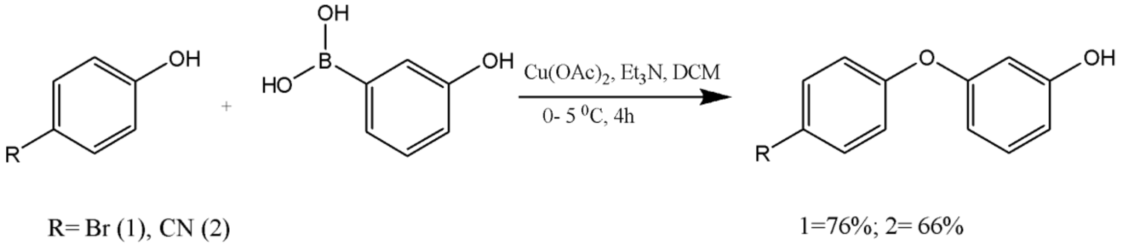
1.2.2 Sonogashira Coupling: A Copper-Catalyzed Method for Biaryl Synthesis

Over the past three decades, transition metal catalyzed reactions have become a versatile tool in organic chemistry due to their ability to easily form carbon-carbon bonds, making them useful in the synthesis of many pharmaceuticals and agrochemicals. These reactions have many desirable features such as mild reaction conditions, high efficiency, and good functional group tolerance. In 1975 [72-74], the Pd-catalyzed cross-coupling reactions between sp^2-C halides and terminal alkynes was independently reported by Heck, Cassar, and Sonogashira. Heck and Cassar utilized Pd catalysts for coupling between sp^2-C halide and terminal alkyne, while Sonogashira used a combination of Pd and Cu catalysts [75,76]. The Sonogashira-Hagihara reaction involves the cross-coupling reaction between an aryl halide (Cl, Br, I, OTf) and a terminal acetylene in the presence of catalytic amounts of a Pd complex, CuI salt, and a base to form an aryl acetylene. Typically, a combination of 1-10 mol% of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ and CuI is used as the catalyst system. However, due to the high cost of Pd, the use of the Sonogashira reaction in large scale production is restricted, and therefore, alternative catalyst systems are being actively researched [77]. As a result, replacing Pd with cheaper, more abundant, and less toxic Cu has become an area of active research.

The Sonogashira coupling reaction is a type of cross-coupling reaction that utilizes a copper catalyst and a strong base to facilitate the interaction between aryl boronic acids and phenols. Copper (II) acetate [$Cu(OAc)_2$] is commonly used as the copper catalyst, while potassium carbonate (K_2CO_3) serves as the base. The reaction mechanism involves the formation of a copper-phenol complex, which then reacts with the aryl boronic acid to generate an intermediate. This intermediate undergoes transmetallation to produce the final biaryl product. Due to its versatility and high efficiency, the Sonogashira coupling reaction is widely used in the synthesis of various compounds, including pharmaceuticals and agrochemicals [78,79].

The Sonogashira coupling reaction is known for its tolerance of various functional groups and can be performed under mild conditions. It has been utilized in the synthesis of a range of biaryl compounds, including natural products, such as strychnine, and bioactive molecules, such as anticancer agents. Despite its many benefits, the Sonogashira coupling reaction is not without limitations. For example, the reaction can be sensitive to steric hindrance, and the use of aryl chlorides or fluorides may require harsher reaction conditions or longer reaction times. Additionally, the use of toxic solvents, such as DMF or DMSO, may be required for certain substrates. Nevertheless, the Sonogashira coupling reaction remains an important tool for the formation of C-C bonds in organic synthesis.

In 2015, Bryan et al. summarized research efforts aimed at creating of the new carbon-heteroatom bonds using organoboron reagents through copper acetate-mediated reactions under ultrasound irradiation. The Chan-Evans-Lam reaction was modified by including of ultrasound irradiation to achieve *O*-arylation of phenols, *N*-arylation of anilines and indoles, and *S*-arylation of thiols. The use of ultrasound irradiation was found to drastically reduce reaction times from 72 h to 4 h, while also increasing product yields by an average of 20%. Scheme 1.21 illustrates the reaction [80].

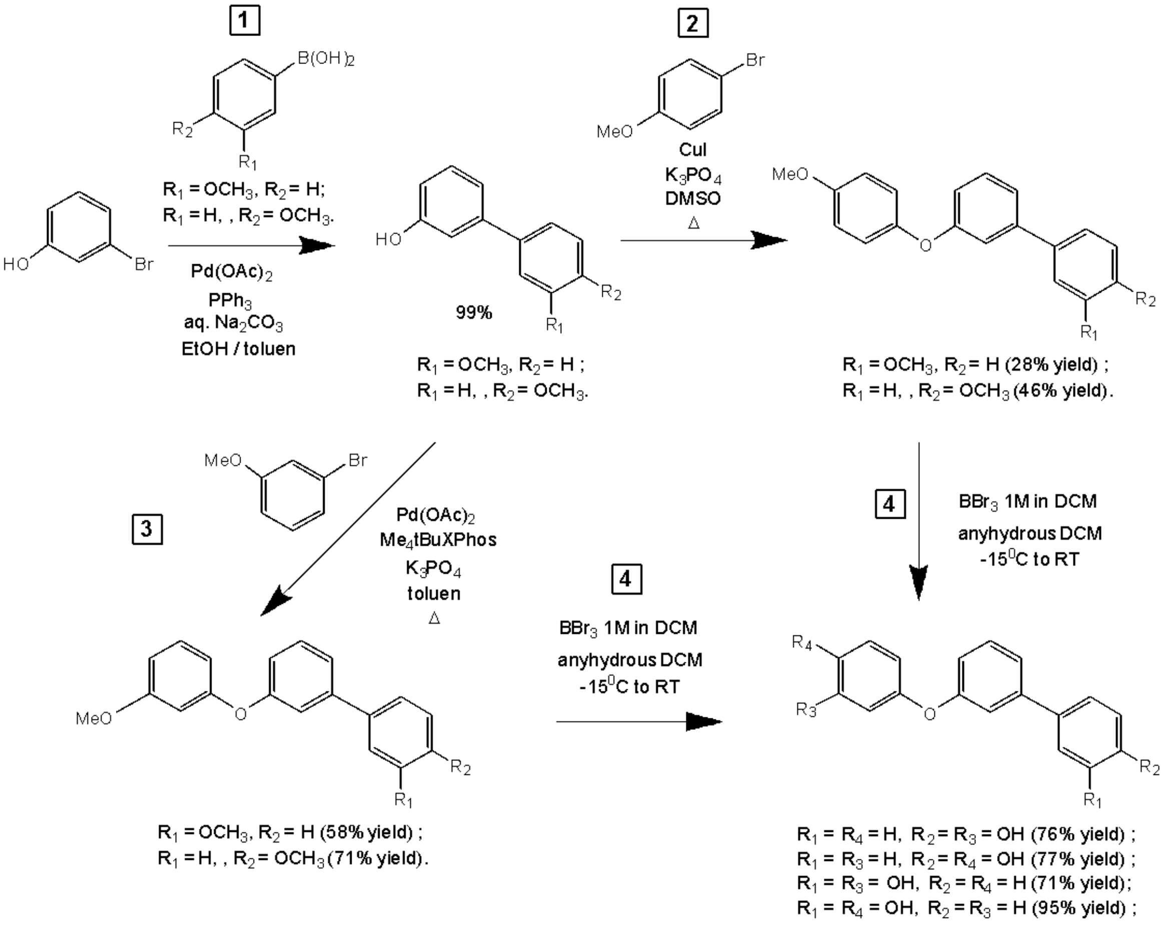


Scheme 1.21 – Synthesis of new aryloxy phenols by the Sonogashira reaction

A method for producing new diaryl ether phenolic compounds has been described by scientists at the University of Pisa. These compounds are composed of two peripheral phenolic rings with hydroxyl groups in the *meta*- and/or *para*-positions, which are linked by a central 1,3-disubstituted phenyl ring. The synthesis of these compounds involves four stages, as outlined in scheme 1.22.

Initially, commercially available 3-bromophenol is subjected to a cross-coupling reaction under bis(triphenylphosphine)palladium catalyzed Suzuki conditions with 3- or (4-methoxyphenyl)boronic acid to obtain diaryl derivatives - specifically, 3- and 4-(phenoxy)anisole with a quantitative yield (99% yield) in stage 1 of the synthesis process. The catalyst used for this reaction is a mixture of palladium acetate Pd(OAc)$_2$ and triphenylphosphine (PPh$_3$) in ethanol and toluene at rt in an inert gas environment.

Subsequently, the intermediates obtained in the first stage are subjected to a C-O bond interaction with 3- and 4-bromanisole in the presence of appropriate catalysts during heating, resulting in a ligand-free Ullmann-type reaction that forms 3- and 4-methoxy substituted derivatives of diaryl ether in stages 2 and 3 of the synthesis process. All the methoxy-substituted derivatives are then subjected to a common final synthetic step, which involves a BBr$_3$-promoted removal of the methoxy groups to obtain the desired diaryl ether phenolic compounds(stage 4 in scheme 1.22). The use of this dealkylating agent provides good yields of the target products (yield 71-95%) [81].



Scheme 1.22 – Synthesis of new diaryl ether phenolic compounds

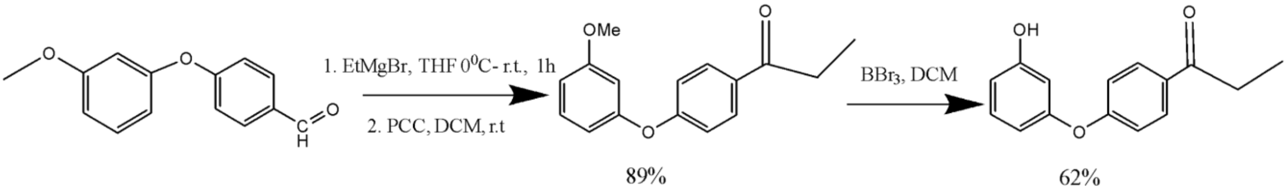
1.2.3 Synthesis of *meta*-(aryloxy)phenols using Grignard Reagents

In addition to their utility in the synthesis of aryloxy phenols, Grignard reagents have many other applications in organic chemistry. They can be used to synthesize a wide range of organic compounds, including alcohols, ethers, amines, and carboxylic acids, through reaction with various carbonyl compounds, halides, and other functional groups. They can also be used in cross-coupling reactions with other organic compounds, such as aryl halides, to form carbon-carbon bonds.

Grignard reagents have also been used in the synthesis of natural products and pharmaceuticals, as well as in the production of polymers and materials. They have played a critical role in the development of modern synthetic organic chemistry and continue to be an important tool for chemists in both academia and industry.

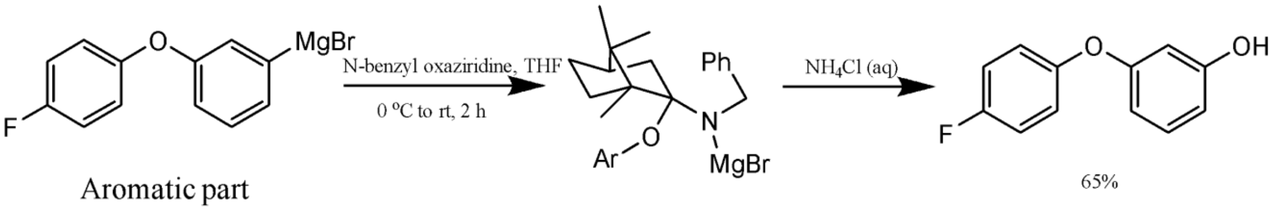
However, it is important to note that Grignard reagents can be highly reactive and potentially dangerous, especially when handled improperly. They can react violently with water and air, and can cause severe burns and other injuries. Proper safety precautions, such as appropriate protective equipment and storage conditions, must be taken when working with Grignard reagents [82].

In 2012, a team of researchers led by Chandrakala Pidathala employed 4-(3-methoxyphenoxy)benzaldehyde in a Grignard reaction, which yielded an intermediate alcohol(scheme 1.23). Subsequently, the alcohol was oxidized with PCC to produce 1-[4-(3-methoxyphenoxy)phenyl]propane-1-one, in a yield of 89%. Further, BBr_3 was utilized to eliminate the *O*-methyl group from the ketone, leading to the formation of 1-[4-(3-hydroxyphenoxy)phenyl]propane-1-one with a yield of 62% [83].



Scheme 1.23 – Synthesis of 1-[4-(3-hydroxyphenoxy)phenyl]propan-1-one

In a study conducted by Gao and colleagues, 3-(4-fluorophenoxy)phenol was synthesized from arylmetals via hydroxylation using *N*-benzyloxaziridine. The reaction took place at rt for 2 h. The researchers showed that N−H and N−alkyl oxaziridines, which are derived from economical terpenoid scaffolds, can act as effective primary aminating and hydroxylating reagents. This method allows for the direct production of primary arylamines and phenols from readily available aryl metals without the need for transition metal catalysts and under mild reaction conditions(scheme 1.24) [84].

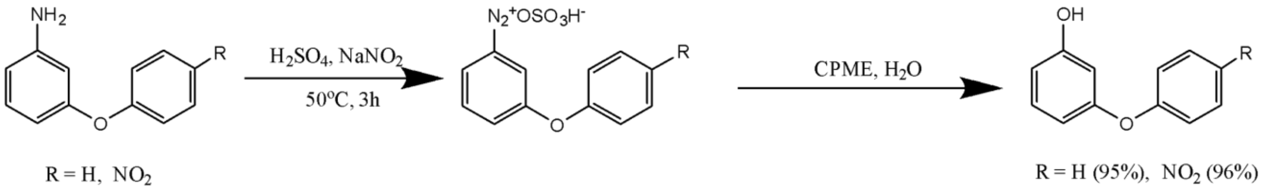


Scheme 1.24 – Synthesis of 3-(4-fluorophenoxy)phenol

1.2.4 Hydrolysis of Diazonium Salts Using a Two-Phase System

The synthesis of 3-(aryloxy)phenols through the hydrolysis of diazonium salts, derived from 3-(4-nitrophenoxy)aniline, was investigated with the goal of developing a safe, simple, low-cost, and high-yielding synthetic method [85]. However, the traditional textbook reactions were not practical and industrially feasible due to the formation of large amounts of tar during the reaction, making experimental manipulation difficult. To overcome this challenge, a two-phase system comprising an organic solvent and water was proposed. After extensive experimentation with various two-phase systems, the use of a mixture of cyclopentyl methyl ether (CPME) and water was found to be surprisingly effective.

In 2015, Taniguchi and colleagues reported a successful method for synthesizing 3-(phenoxy)phenol and 3-(4-nitrophenoxy)phenol(scheme 1.25). The process involved hydrolyzing intermediate diazonium salts derived from anilines using a two-phase system consisting of CPME and water. This approach resulted in high yields of the desired compounds, overcoming the challenge of forming large amounts of tar during the reaction and facilitating suitable experimental manipulation. This study represents the first example of using a two-phase system for the hydrolysis of diazonium salts [86].



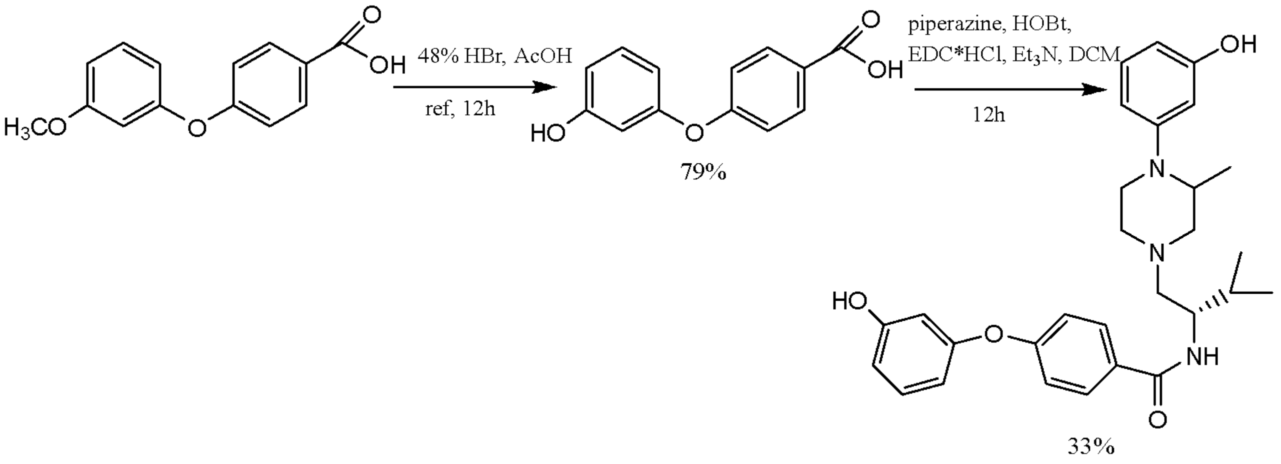
Scheme 1.25 – Synthesis of *meta*-aryloxy phenols

1.2.5 Synthesis of *meta*-aryloxy phenols by demethylation of *meta*-methoxy phenols

Demethylation is a process that involves the removal of a methyl group from a molecule. An example of this reaction is the conversion of *meta*-methoxy phenols to *meta*-aryloxy phenols. Demethylation can be achieved through various methods, such as chemical and catalytic approaches. Chemical methods involve the use of strong acids like sulfuric acid, hydrochloric acid, or nitric acid, which convert the methoxy group into the desired *meta*-aryloxy phenol [87].

In contrast, catalytic demethylation methods utilize transition metal catalysts like copper or palladium, and can occur through different mechanisms such as hydrogenation, transfer hydrogenation, or C-H bond activation. For instance, the use of the Bronsted acid - hydrogen bromide and boron tribromide (BBr_3) as a Lewis acid catalysts is a valuable approach for synthesizing *meta*-aryloxy phenols. These acids can coordinate with electron-rich sites in organic compounds, which enhances the efficiency of the demethylation reaction of *meta*-methoxy phenols to *meta*-aryloxy phenols [88,89].

Kormos and his team synthesized 4-(3-hydroxyphenoxy)benzoic acid from 4-(3-methoxyphenoxy)benzoic acid by refluxing with 48% hydrogen bromide in acetic acid(scheme 1.26). They then synthesized *N*-(1*S*)-1-{[(3*S*)-4-(3-hydroxyphenyl)-3-methylpiperazin-1-yl]methyl}-2-methylpropyl-4-(3-hydroxyphenoxy)benzamide by condensing 4-(3-hydroxyphenoxy)benzoic acid with piperazine using *N*-ethylcarbodiimide·hydrochloride (EDC·HCl) and a catalytic amount of hydroxybenzotriazole (HOBt) [90].



Scheme 1.26 – Synthesis of 4-(3-hydroxyphenoxy)benzoic acid and its derivative with piperazine amine

In 2022, Yamamoto's group reported the synthesis of *N*-(2-(3-hydroxyphenoxy)-4-nitrophenyl)methanesulfonamide(scheme 1.27) by demethylating the corresponding methoxy derivatives using BBr_3 as a dealkylating agent [91].

Scheme 1.27 – Synthesis of *N*-(2-(3-hydroxyphenoxy)-4-nitrophenyl)methanesulfonamide

In 2009, Yang [92] synthesized 3,3'-oxydiphenol by reacting 3-methoxyphenol with 3-bromanisole in the presence of a Cu-catalyst, followed by cleavage of the methyl groups with HBr in acetic acid.

1.3 Synthesis of phenol derivatives from cycloxenanone

Phenols are important building blocks for a variety of industrial chemicals, including pharmaceuticals and polymers. As previously described, the synthesis of phenols with specific patterns of functional groups around the aromatic ring is a significant challenge in organic chemistry. Traditional methods for introducing these functional groups, such as nucleophilic aromatic substitution reactions, are limited in their ability to produce *ortho*- and *para*-substituted derivatives due to strong electronic directing effects.

The process of aerobic dehydrogenation of substituted cyclohexanones to phenols involves the conversion of a substituted cyclohexanone molecule into a phenol molecule via a sequence of chemical reactions. The reaction is facilitated by a palladium catalyst, which is used to activate the C-H bonds of the cyclohexanone, leading to β-hydride elimination and the formation of a dienone intermediate. The dienone intermediate undergoes tautomerization to form the final phenol product.

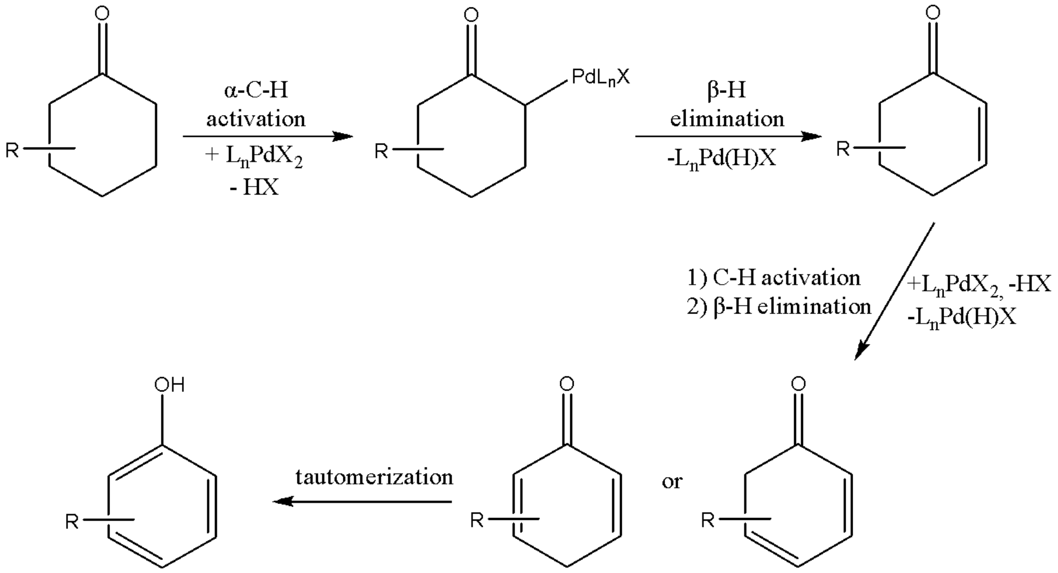
One of the major benefits of this reaction is that it can be carried out under aerobic conditions, meaning that oxygen can be used as the oxidant. As a result, the reaction is catalytic in palladium, and water is the only by-product. The reaction is particularly useful for the synthesis of a broad range of substituted phenols, including those with *meta*-substitution patterns, and it can be used in conjunction with other chemical reactions that provide access to substituted cyclohexanone precursors. This makes it a versatile and valuable method for the synthesis of phenols [93].

1.3.1 Transition-Metal based Dehydrogenative Aromatization of Cyclohexanones

The palladium-catalyzed aerobic dehydrogenation of substituted cyclohexanones to phenols is a chemical reaction that involves the conversion of a substituted cyclohexanone to a phenol molecule using a palladium catalyst. This reaction is a versatile method for the synthesis of substituted phenols that are important precursors for a range of industrial chemicals, including pharmaceuticals and polymers [94].

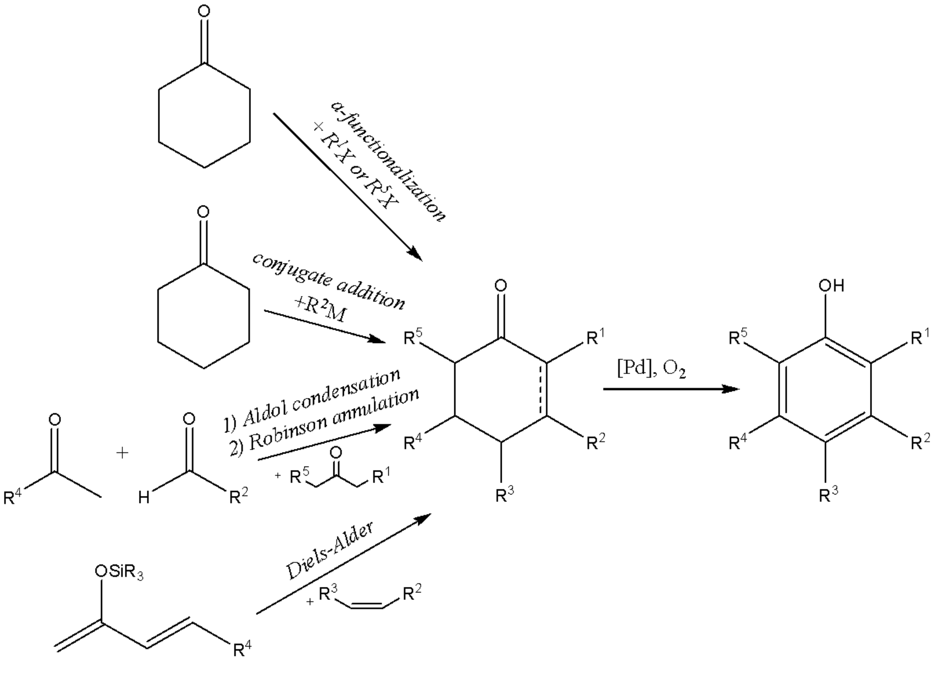
In this reaction, the palladium catalyst activates the C-H bond of the cyclohexanone molecule, followed by β-hydride elimination that leads to the formation of a dienone intermediate. The dienone intermediate then undergoes tautomerization to form the final phenol product. This reaction has the advantage of being carried out under aerobic conditions, where oxygen from the air serves as the oxidant, making water the only by-product and the reaction catalytic in palladium [95].

Based on recent progress in palladium-catalyzed aerobic oxidation reactions, it has been suggested that various phenol derivatives, even those with *meta* substitution, can be produced by dehydrogenating cyclohexanones through a sequential process involving Pd-mediated C-H activation and β-hydride elimination, followed by tautomerization of the resulting dienone product(scheme 1.28). This method is particularly attractive because Pd^{II}-hydride intermediates formed in this mechanism can be oxidized by molecular oxygen, leading to a catalytic process in Pd with water as the only by-product [96].



Scheme 1.28 – Stepwise sequence for Pd-mediated dehydrogenation of cyclohexanone

The availability of various chemical reactions that provide access to substituted cyclohexanones, including enolate arylation and alkylation methods, conjugate addition to cyclohexenones, Robinson annulation, and Diels-Alder reactions (as depicted in scheme 1.29), suggests that successful catalysts for this type of reaction could have broad applications [97].



Scheme 1.29 – Representative synthetic methods that afford facile access to substitute cyclohexanone derivatives

Enolate arylation and alkylation are versatile methods for synthesizing substituted cyclohexanones. In these reactions, an aryl or alkyl group is introduced onto a carbonyl compound, such as cyclohexanone, via an enolate intermediate, which is generated in the presence of a strong base. This intermediate then undergoes an electrophilic aromatic substitution reaction with an aryl or alkyl halide, yielding the desired substituted cyclohexanone product.

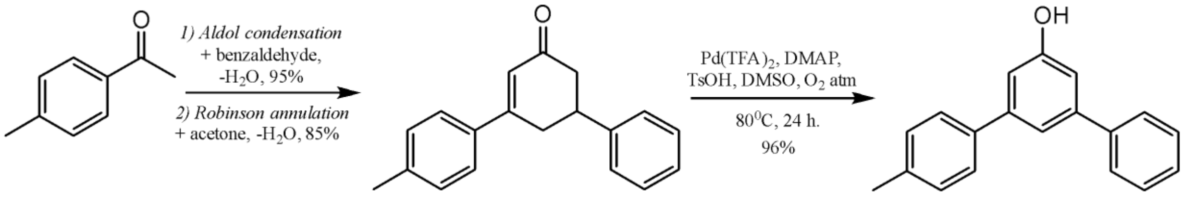
Conjugate addition to cyclohexenones is another effective method for preparing substituted cyclohexanones. In this reaction, a nucleophile is added to a cyclohexenone derivative in the presence of a base, leading to the formation of a new carbon-carbon bond and the desired substituted cyclohexanone product.

Robinson annulation, a type of reaction that involves the condensation of an α,β-unsaturated ketone with a carbonyl compound in the presence of a base, is a powerful method for producing substituted cyclohexanones that contain a six-membered ring.

The Diels-Alder reaction is a versatile cycloaddition reaction that can be used to synthesize a range of cyclohexanone derivatives with different substituent groups attached. This reaction involves the reaction of a diene with a dienophile to form a cyclic compound.

The availability of these various chemical reactions suggests that the development of efficient catalysts for these reactions could have wide-ranging applications. Catalysts can enhance both reaction rates and selectivity, without being consumed in the process. Thus, effective catalysts for these reactions could lead to more efficient and cost-effective methods for synthesizing a broad range of substituted cyclohexanones with diverse chemical properties, which could have important implications for fields such as chemistry, pharmaceuticals, and materials science.

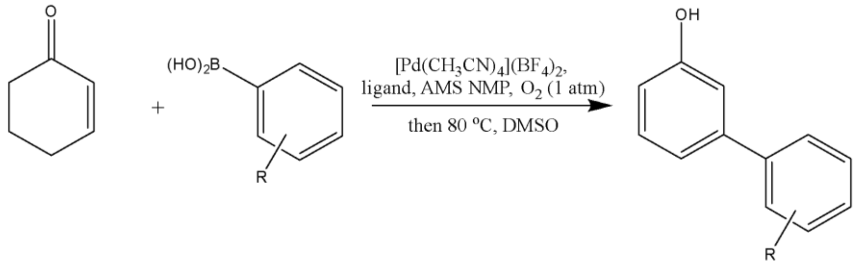
In 2011, the Stahl group reported the first successful synthesis of phenols from cyclohexanones in high yields and under conditions that are tolerant of various functional groups(scheme 1.30).



Scheme 1.30 – Synthesis of 3,5-diarylphenol by palladium-catalyzed aerobic dehydrogenation

The process involved using $Pd(TFA)_2$ as a catalyst in combination with 2-(*N*,*N*-dimethylamino)pyridine as a ligand and TsOH as a co-catalyst in the presence of oxygen. By utilizing this methodology, the Stahl group was able to produce a range of 3,5-disubstituted phenols from the corresponding cyclohexanones, with yields ranging from good to excellent. This breakthrough represents a significant advance in the production of *meta*-functionalized phenols [19,98]. One of them is the 3,5-diarylcyclohexenone which was obtained readily from very inexpensive starting materials, such as 4-methylacetophenone, benzaldehyde, and acetone, via sequential aldol condensation and Robinson annulation. Pd-catalyzed dehydrogenation of intermediate afforded final three-ring compound in excellent yield.

The Stahl group has made further progress in this area by developing a Pd-based catalyst system that enables the conjugate addition of a range of aryl boronic acids to cyclohexenones, followed by dehydrogenative aromatization to produce *meta*-functionalized phenols [99]. This efficient one-pot procedure employs $[Pd(CH_3CN)_4](BF_4)_2$ as the catalyst and bidentate bipyridine ligand in DMSO with molecular sieves at 80°C, under an atmosphere of O_2(scheme 1.31).

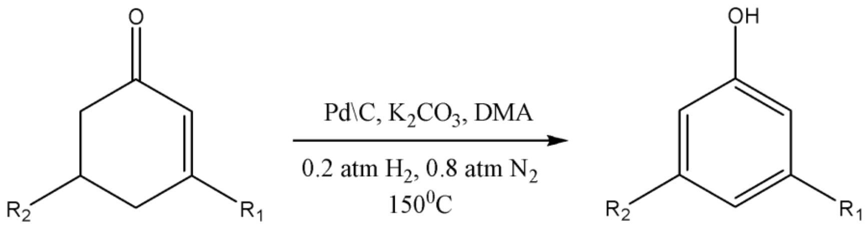


Entry	R	Time (h)	Yield (%)	Entry	R	Time (h)	Yield (%)
1	*para*-Me	32	91	10	*para*-CF_3	32	40
2	*para*-*tert*-Bu	36	85	11	*para*-CN	36	35
3	*para*- MeO	32	80	12	*para*-H	32	75
4	*para*- Cl	32	68	13	*meta*-MeO	36	47
5	*para*- Br	32	41	14	*meta*-Me	36	76
6	*para*-F	32	87	15	*meta*-NO_2	36	42
7	*para*-OH	32	64	16	*meta*-CF_3	32	60
8	*para*-Ph	36	63	17	*ortho*-Me	36	58
9	*para*-COOMe	32	74	18	*ortho*-F	36	66

Scheme 1.31 – Synthesis of *meta*-functionalized phenols using Pd-based catalysts

In 2015, the Liu group discovered that palladium on carbon (10 mol%) in the presence of potassium carbonate (20 mol%) in DMA at 150 °C could transform various cyclohexanones/cyclohexenones to their corresponding phenols without the need for external oxidants, instead utilizing a direct H_2 release mechanism [22,100]. Scheme 1.32 presents relevant examples, demonstrating that a wide range of substituted cyclohexenones can be dehydrogenated to yield the corresponding phenols in high isolated yields.

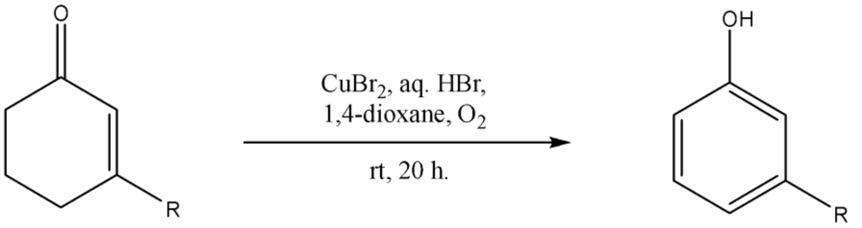
Moreover, the present dehydrogenation method effectively converts various 3-substituted cyclohexanones into their corresponding phenols, which may be useful in the synthesis of *meta*-fragment substituted phenol derivatives. Interestingly, the catalytic system smoothly converts sulfur-, nitrogen-, and oxygen-containing compounds into their corresponding phenols in high yields. This highlights the versatility of the catalytic system.



	R_1=	R_2=	Time (h)	Yield (%)
1	C_6H_5-NH	H	10	80
2	C_6H_5	H	10	83
3	4-Me-C_6H_4-S	H	22	71
4	C_6H_5	C_6H_5	10	94
5	$(CH_3)_2$-CH-CH_2	C_6H_5	13	83
6	4-MeO-C_6H_5	C_6H_5	10	90

Scheme 1.32 – The synthesis of phenol derivatives by dehydrogenation of substituted cyclohexanones and 2-cyclohexenones

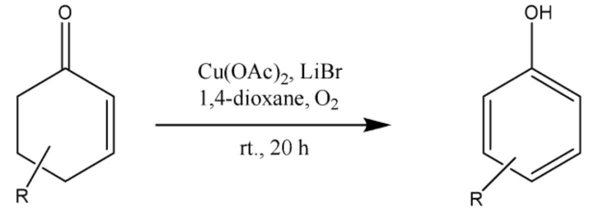
Various copper-mediated oxidative aromatization methods have been developed to produce phenols. The first such method was reported by Kikushima and Nishina in 2013, who utilized CuBr (5 mol%) and concentrated HBr (aq., 20 mol%) under an O_2 atmosphere to efficiently aromatize cyclohexenones(scheme 1.33). When excess HBr is present, this method can also produce brominated phenols with substitution governed by S_EAr selectivity[101]. The resulting reaction system demonstrated exceptional efficiency in generating diverse phenols, all under simple and affordable conditions.



	R=	Yield (%)		R=	Yield (%)
1	C_6H_5	99	6	3-Me-C_6H_4	99
2	4-Me-C_6H_4	98	7	2-Me-C_6H_4	99
3	4-MeO-C_6H_4	99	8	3,6-F_2-C_6H_3	97
4	4-Cl-C_6H_4	96	9	Naphtalen-1-yl	99
5	4-CF_3-C_6H_4	86			

Scheme 1.33 – The transformation of 2-cyclohexen-1-ones into phenols via copper-catalyzed oxidative aromatization

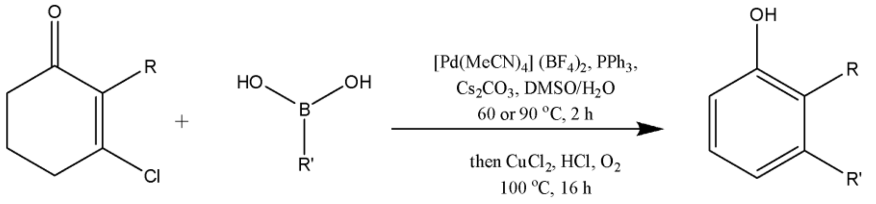
The Liu group reported similar conditions in 2014 [102], using $Cu(OAc)_2$ (4 mol%) and LiBr (0,5 equivalents) in a 2:1 mixture of acetonitrile/trifluoroacetic acid at 80°C to prepare phenols from cyclohexenones with moderate to excellent yields (scheme 1.34). Again, this method can produce brominated phenols with S_EAr selectivity when excess LiBr is present.



Entry	R	Yield (%)	Entry	R	Yield (%)
1	3,5-$(C_6H_5)_2$	65	5	3-Ph-4-(COOMe)-5-5-C_6H_4-*n*-Bu-*p*	60
2	3-Me-4-(COOMe)-5-Ph	58	6	3-Me	46
3	3-Me-4-(COOMe)-5-C_6H_4-NO_2-*p*	68	7	2-Me-5-*i*-Pr	97
4	3,5-diMe-4-(COOMe)	70	8	3-Me-4-(COOMe)-5-(C_4H_3S)	79

Scheme 1.34 – The copper-mediated methods for the synthesis of phenols

In 2017 [103], Wang and Orellana reported a one-pot procedure to convert 3-chlorohexenones to their corresponding 3-arylphenols using palladium-catalyzed Suzuki-Miyaura cross-coupling with aryl/heteroaryl boronic acids, followed by oxidative rearomatization using a $CuCl_2$ catalyst in the presence of HCl and O_2 as an oxidant(scheme 1.35).



Entry	R	R’	Yield (%)	Entry	R	R’	Yield (%)
1	H	4-(COMe)-C_6H_4	80	11	Me	Ph	70
2	H	4-(SO_2Me)-C_6H_4	75	12	Me	3,5-(MeO)- C_6H_3	54
3	H	3,5-(MeO)- C_6H_3	79	13	Et	Ph	48
4	H	2-Me- C_6H_4	81	14	Bn	Ph	66
5	H	2,6-$(Me)_2$- C_6H_3	63	15	Bn	4-(COMe)-C_6H_4	62
6	H	4-(C_2H_3)- C_6H_4	40	16	Me	C_6H_4-C_2HS	39
7	H	C_6H_5-C_2H_2	65	17	Me	2-Me- C_6H_4	57
8	H	C_6H_4-C_2HS	63	18	Me	2,6-$(Me)_2$- C_6H_3	52
9	H	C_6H_4-C_2HO	57	19	Me	5-(SOOMe)C_5H_4N	51
10	H	Ph	88	20	Bn	5-(SOOMe)C_5H_4N	52

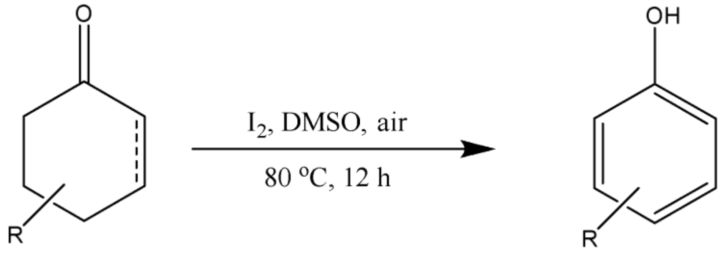
Scheme 1.35 – Synthesis of 3-arylphenols using palladium-catalyzed Suzuki-Miyaura cross-coupling with aryl/heteroaryl boronic acids

This method provides another approach to producing *meta*-substituted phenols, but is similarly limited to aryl/heteroaryl substituents in the *meta*-position.

1.3.2 Metal-free dehydrogenative aromatization of cyclohexanones

In 2018, the Jiao group introduced a unique approach for the metal-free dehydrogenative oxidation of cyclohexanones using iodine, which could produce either catechol or phenol depending on the substrate and conditions [104]. By treating various cyclohexanones with an I_2 catalyst in DMSO at 80°C under an air atmosphere, yields of catechol or phenol ranging from 25% to 91% were achieved(scheme 1.36). The proposed mechanism involves the I_2 catalyst trapping of the enol-tautomer of the cyclohexenone, generating the α-iodinated product that can undergo E2 elimination to give the cyclohexenone or Kornblum oxidation to produce the diketone. The E2 elimination product can undergo a second iodination/elimination process to generate a cyclohexadieneone, which can readily tautomerize to the aromatic phenol product. The diketone, on the other hand, can undergo subsequent iodination and elimination, followed by tautomerization to produce the catechol.

Highly substituted cyclohexanones have been observed to preferentially yield phenol rather than catechol due to the transition state energies involved in the initial elimination/Kornblum oxidation step. This is consistent with the conversion of cyclohexenones to the corresponding phenol, rather than catechol, when heated with I_2 and DMSO. The Jiao group demonstrated that a variety of cyclohexenones could be converted to the corresponding phenol using this methodology with yields ranging from 61-95% in 22 examples [105].



Entry	R	Yield (%)	Entry	R	Yield (%)
1	3-Me	61	5	3-Me-4-(COOMe)	73
2	2-Me-5-*i*-Pr	77	6	3-Me-4-(COOMe)-5-C_4H_3S	73
3	3-5-$(Ph)_2$	87	7	3-Et-4-(COOMe)-5-C_5H_4N-6-Me	78
4	3-Ph-5-C_4H_3S	95			

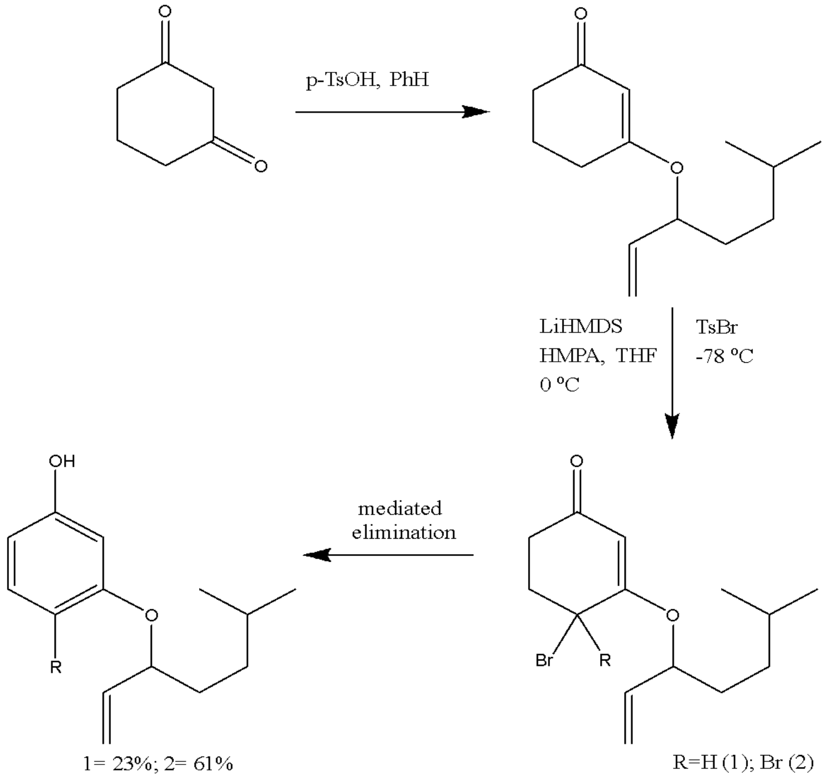
Scheme 1.36 – Synthesis of phenols by treating cyclohexanones with an I_2 catalyst

These results are supported by the Luo group's separate publication, which found that I_2 could effectively catalyze aromative oxidation of cyclohexenones in DMSO at

60 °C [106]. Since cyclohexenones can be readily functionalized at the 3-position through conjugate addition, this strategy allows for the production of various *meta*-functionalized phenols. These methodologies provide an interesting strategy to access these functional groups, particularly with regard to producing *meta*-functionalized phenols, and represent one of the first metal-free dehydrogenative oxidations of cyclohexanones to catechols/phenols [107].

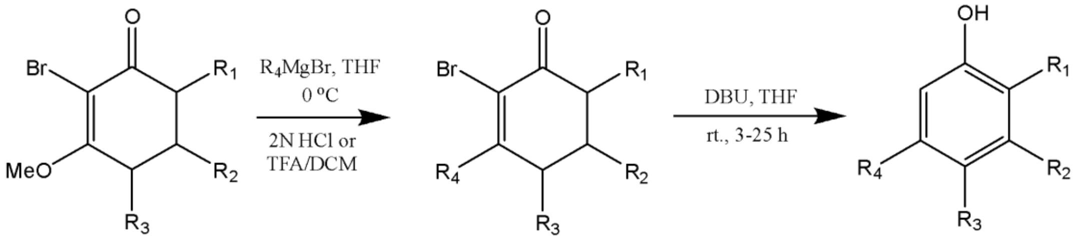
Mohr and colleagues developed a three-step synthesis of 3-[(6-methylhept-1-en-3-yl)oxy]phenol and 4-bromo-3-[(6-methylhept-1-en-3-yl)oxy]phenol from cyclohexan-1,3-dione in 2020 [108]. The first step involved a direct acid-catalyzed condensation between cyclohexadione and 2° allylic alcohol, resulting in a low yield of 23% on a 1 mmol scale, which decreased to 14% on a larger scale (5 mmol) (scheme 1.37).

To improve the yield, the Mitsunobu displacement process was utilized, which reversed the polarity of the coupling. The solution of diketone and alcohol in THF treated with a DIAD/PPh$_3$ mixture yielded the desired vinylogous ester in an improved yield of 58%, which was maintained on a larger scale. The vinylogous ester was then used in the key oxidative aromatization/bromination reaction using the established protocol (LiHMDS, HMPA, *para*-TsBr), which resulted in a yield of 61% for the desired γ-brominated arene product via a putative γ,γ-dibromoenone. Additionally, 3-[(6-methylhept-1-en-3-yl)oxy]phenol was obtained in a yield of 23%.



Scheme 1.37 – Synthesis of 3-[(6-methylhept-1-en-3-yl)oxy]phenol and 4-bromo-3-[(6-methylhept-1-en-3-yl)oxy]phenol

Clive discovered in 2016 that functionalized cyclohexenones could be obtained by adding Grignard or other organometallic reagents to 2-halocyclohex-2-en-1-ones, which could then be transformed to the corresponding phenol by treatment with DBU (scheme 1.38) [109].

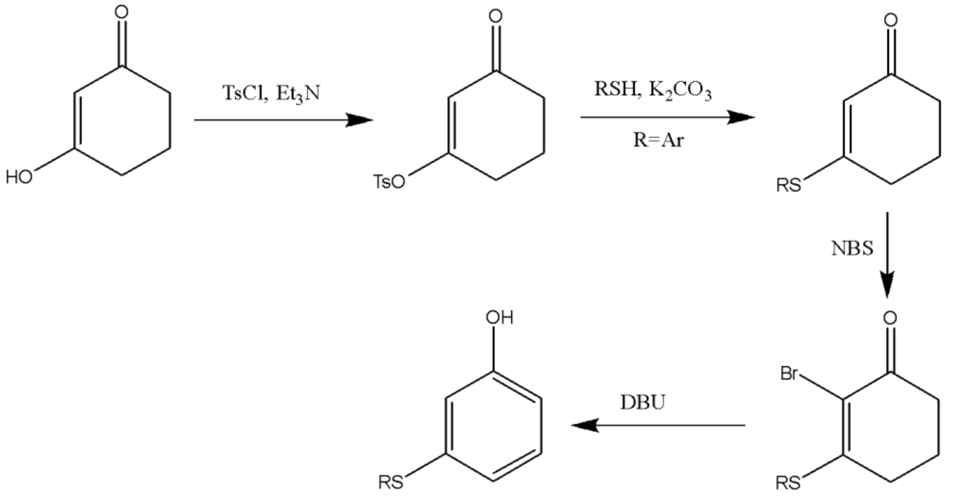


Entry	R_1	R_2	R_3	R_4	Yield (%)	Entry	R_1	R_2	R_3	R_4	Yield (%)
1	H	Me	H	Me	81	9	H	Me	H	3,5-$(CF_3)_2$-Ph	90
2	H	Me	H	*c*-Pr	84	10	H	Me	H	4-IPh	96
3	H	Me	H	C_2H_3	75	11	H	Me	H	naphtalen-1-yl	84
4	H	Me	H	Ph-C_2	85	12	H	Me	H	furan-1-yl	89
5	H	Me	H	Me_3Si-C_2	55	13	H	Me	H	thiophen-1-yl	98
6	H	Me	H	Ph	87	14	H	Ph	H	Ph	93
7	H	Me	H	2-MeO-Ph	91	15	H	Me	F	Me	87
8	F	Me	F	3,5-$(CF_3)_2$-Ph	81	16	F	Me	F	2-MeO-Ph	85

Scheme 1.38 – Synthesis of *meta*-substituted phenols using Grignard reagents

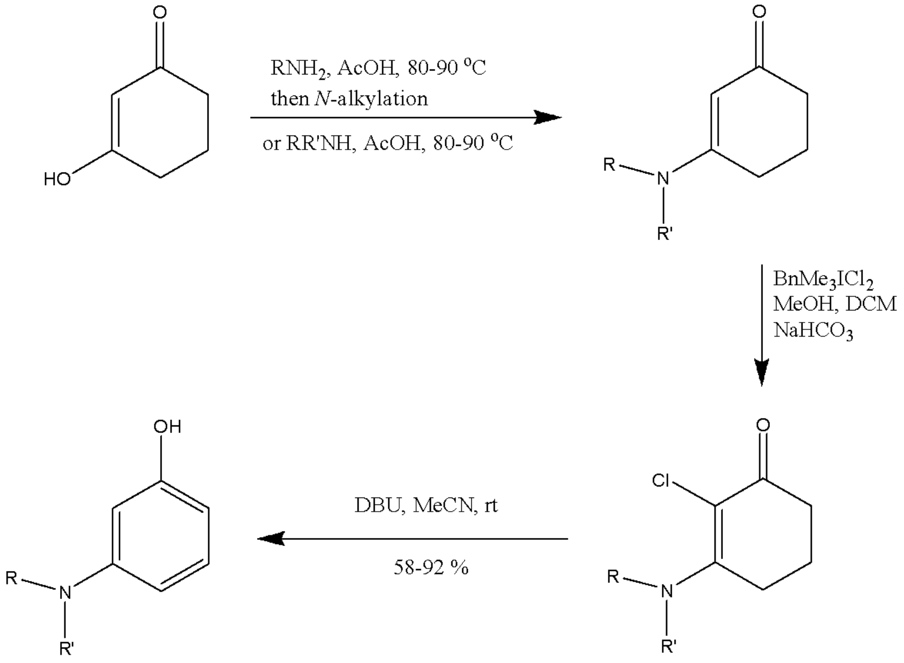
Clive developed a similar methodology in 2018 for the formation of *meta*-arylsulfanyl and *meta*-(alkylsulfanyl)phenols from brominated cyclohexane-1,3-diones, which expanded the types of substituents that can be tolerated at the *meta*-position to include heteroatoms(scheme 1.39). 3-(Tosyloxy)cyclohex-2-en-1-ones, which can be easily synthesized from cyclohexan-1,3-diones, can be converted to 3-(arylsulfanyl)- or 3-(alkylsulfanyl)cyclohex-2-en-1-ones by reacting with thiols in the presence of K_2CO_3 at rt. The resulting products can be brominated at C-2 using NBS in MeCN, and treatment with DBU in MeCN produces the corresponding 3-(arylsulfanyl)- or 3-(alkylsulfanyl)phenols. This reaction sequence occurs under mild conditions and does not require the use of heavy metals [110].

In 2021, Clive's group reported a synthesis of *meta*-aminophenols from cyclohexane-1,3-dione [111]. Cyclohexane-1,3-dione can be easily converted into 3-aminocyclohex-2-en-1-ones that have two substituents on the nitrogen atom, which are either both aryl or alkyl units, or one of each type(scheme 1.40). These compounds can be chlorinated at $C^{(2)}$ using the crystalline reagent $BnNMe_3{\cdot}ICl_2$, and the resulting chloro enaminones undergo aromatization at rt on treatment with DBU in MeCN. The average yield for the chlorination was 83% (12 examples), while the average yield for the aromatization was 73%.



Entry	R	Yield (%)	Entry	R	Yield (%)
1	Ph	89	6	2-MeC$_6$H$_4$	78
2	4-FC$_6$H$_4$	60	7	2-(MeO$_2$C)C6H4	72
3	4-MeOC$_6$H$_4$	86	8	Bn	65
4	4-BrC$_6$H$_4$	79	9	*tert*-Bu	25
5	4-MeC$_6$H$_4$	75	10		

Scheme 1.39 – Synthesis of meta-Sulfanylphenols



Entry	R	R’	Yield	Entry	R	R’	Yield
1	Me	Ph	82	7	Me	4-BrC$_6$H$_4$	74
2	Me	4-MeC$_6$H$_4$	75	8	Pmb	4-BrC$_6$H$_4$	84
3	Pmb	4-MeC$_6$H$_4$	73	9	Ph	Ph	79
4	Bn	4-BrC$_6$H$_4$	92	10	Me	Bn	59
5	Bn	2-MeC$_6$H$_4$	72	11	Bn	Bn	72
6	Bn	4-NCC$_6$H$_4$	62				

Scheme 1.40 – Synthesis of 3-aminophenols from cyclohexane-1,3-diones

Oxidative aromatization is an effective method for producing *meta*-functionalized phenols because 3-substituted cyclohexenones can be easily synthesized through conjugate addition. It is important to note that cyclohexanones/cyclohexenones are derived from aromatic precursors, which are either partially reduced phenols or products of cyclohexane oxidation (which is a product of benzene reduction) [112]. The production of phenols using this strategy illustrates how essential functionalization steps can occur via non-aromatic phenol precursors before undergoing rearomatization and phenol formation.

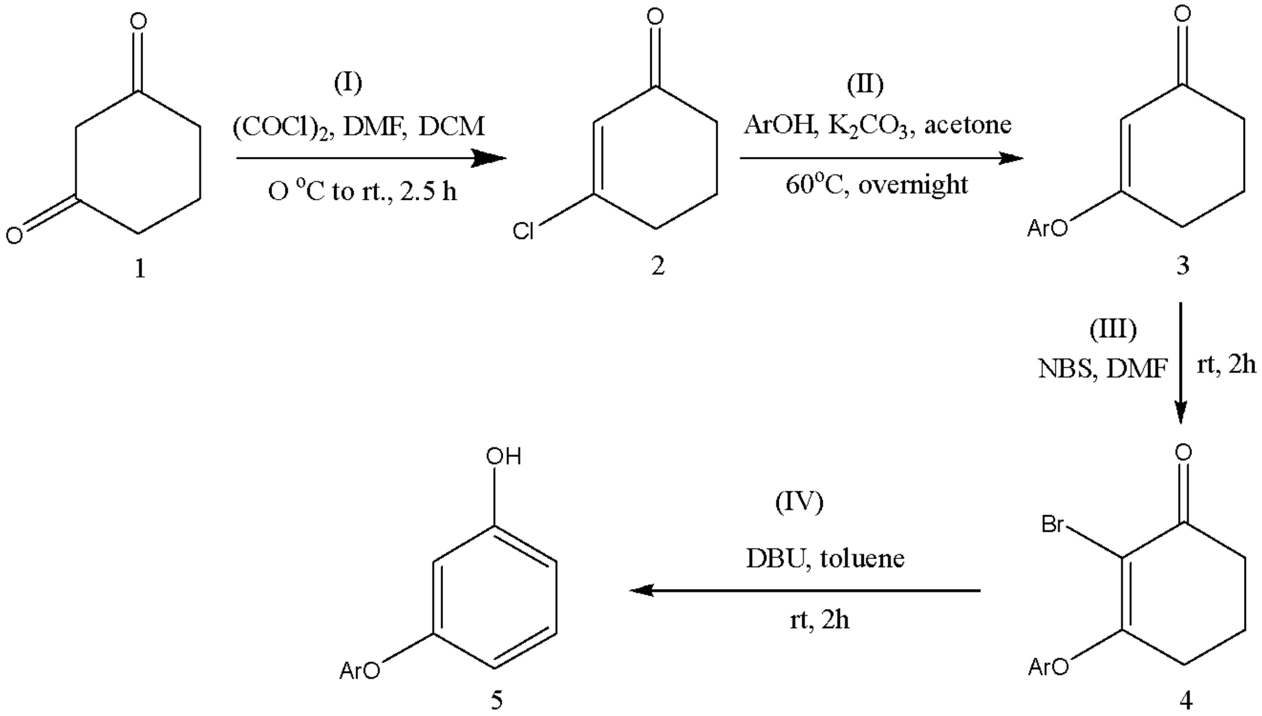
In conclusion, the literature review has provided a comprehensive understanding of the synthesis methods and potential applications of *meta*-aryloxy phenols. The reviewed studies have shed light on various approaches, including nucleophilic aromatic substitution reactions, Sonogashira coupling, Grignard reagent utilization, hydrolysis of diazonium salts, and demethylation of *meta*-methoxyphenols. Additionally, the synthesis of phenol derivatives from cycloxenanone has been explored, focusing on transition-metal based and metal-free dehydrogenative aromatization methods. This knowledge serves as a solid foundation for the subsequent experimental part, where we will implement and expand upon these synthesis strategies to develop a non-catalytic method for the synthesis of *meta*-aryloxy phenols from 1,3-cyclohexanedione.

2 RESULTS AND DISCUSSION

Chapter 1.2 outlines common strategies to prepare *meta*-aryloxy phenols, and chapter 1.3 describes synthesis of phenol *meta*-substituted derivatives by aerobic dehydrogenation of substituted cyclohexenones. From this survey, we identified a deficiency in the number of reactions that could provide *meta*-substituted derivatives. In this chapter, we will discuss our efforts to address this challenge through the development of a preparation of *meta*-(aryloxy)phenols from 3-chlorocyclohex-2-en-1-one in three steps [113].

Our approach for the preparation of *meta*-(aryloxy)phenols has been successfully implemented and offers a gentle alternative to the classical Ullmann reaction, as illustrated in Scheme 2.1. This development presents a universal method for synthesizing *meta*-aryloxy phenols from cost-effective and easily obtainable starting materials. The procedure involves a series of steps, which are described in detail in (scheme 2.1), including the synthesis of starting material (I), 3-chlorocyclohex-2-en-1-one (2) from cyclohexane-1,3-dione (1), the nucleophilic substitution reaction of 3-chlorocyclohex-2-en-1-one (2) with phenol derivatives (II), bromination (III) of 3-(aryloxy)cyclohex-2-en-1-ones (3), and finally, the aromatization step of 2-bromo-3-aryloxy-cyclohex-2-en-1-one (4) (IV) to obtain *meta*-aryloxy phenols (5). The synthesized compounds are outlined in figures 2.1 and 2.2.

Overall, our proposed methodology offers a practical and efficient pathway to access *meta*-(aryloxy)phenols, which have numerous applications in various fields.



Scheme 2.1 – Synthesis of *meta*-(aryloxy)phenols

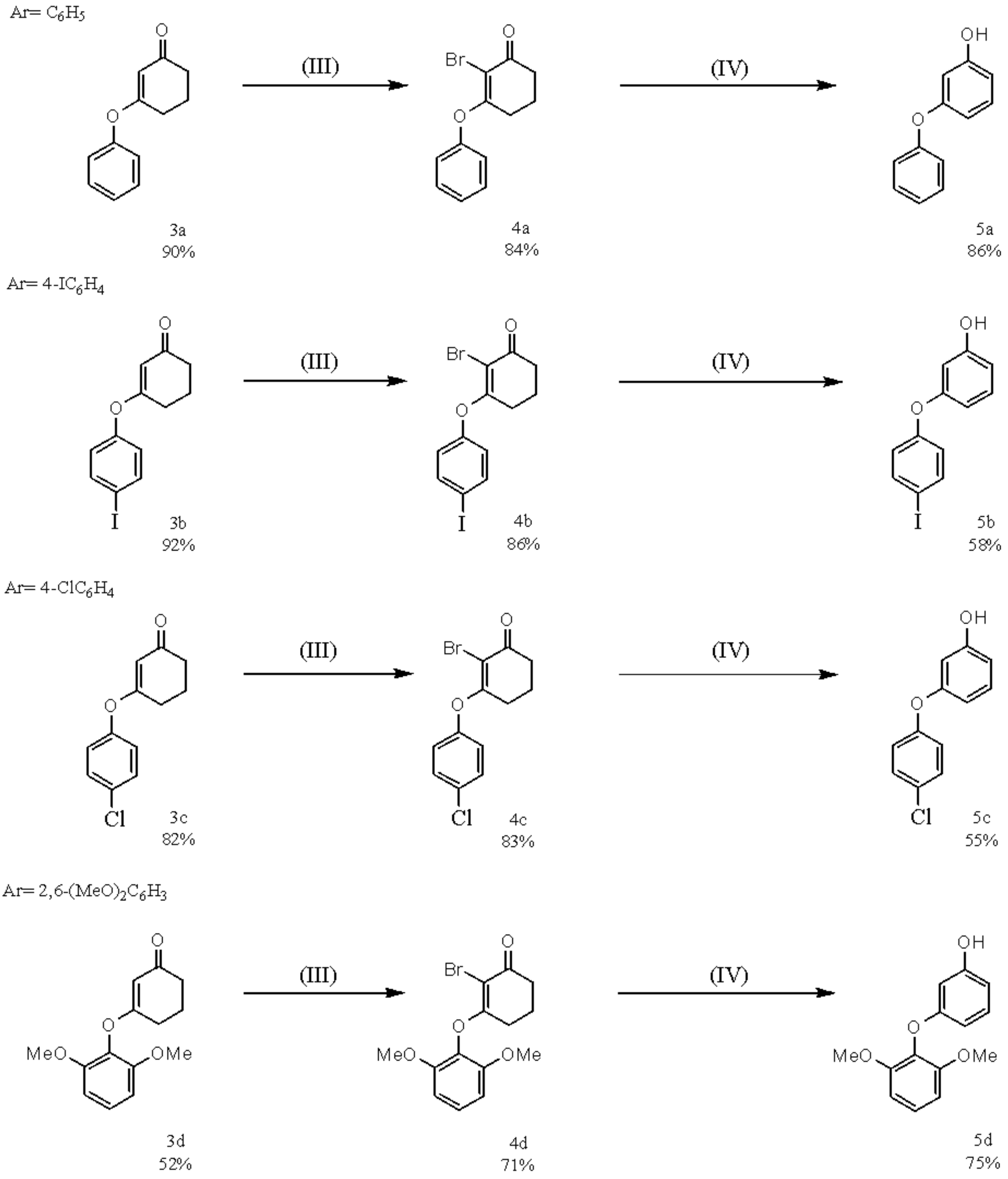
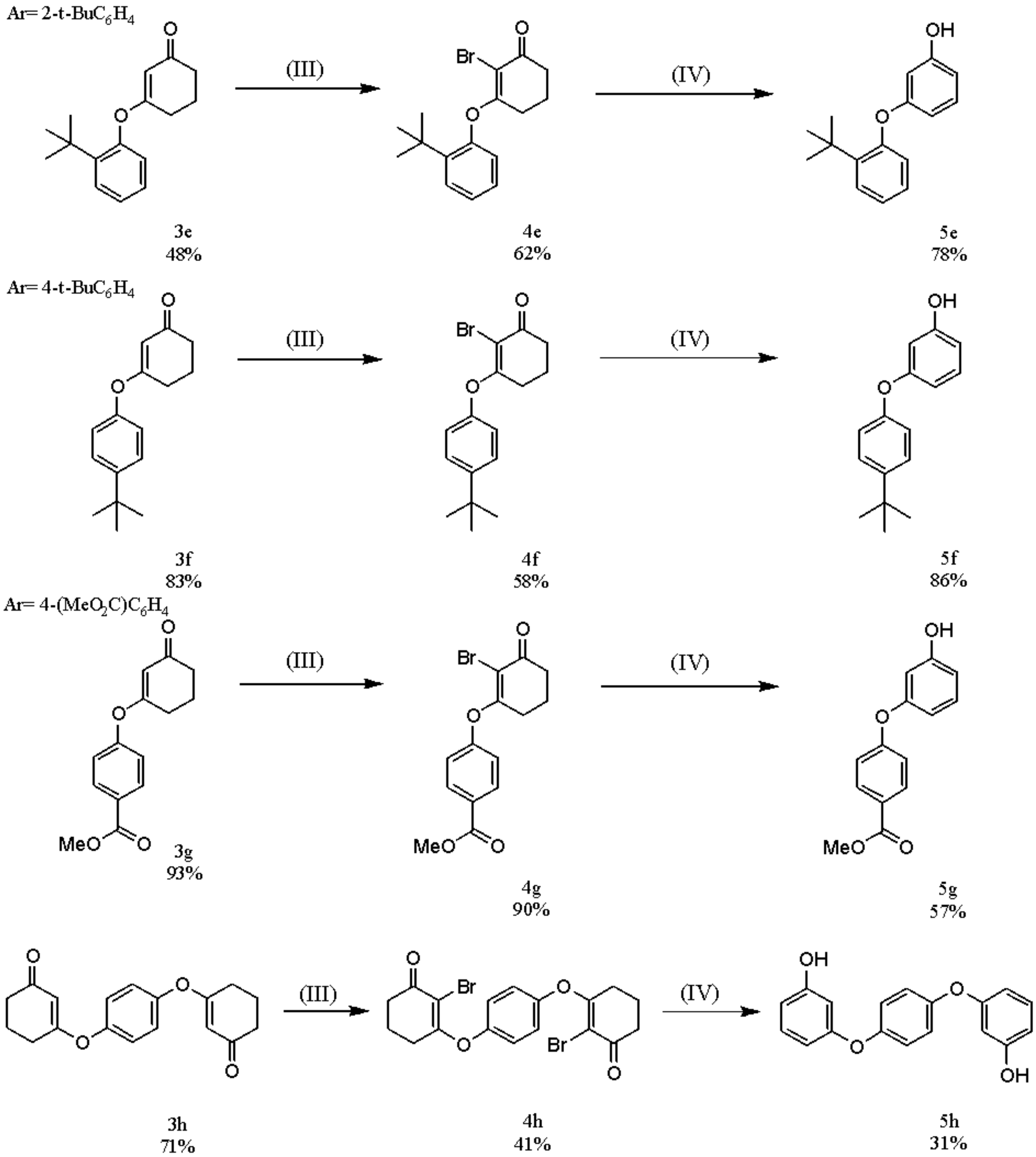


Figure 2.1 – Synthesized compounds (a-d)



3e 48%
4e 62%
5e 78%

3f 83%
4f 58%
5f 86%

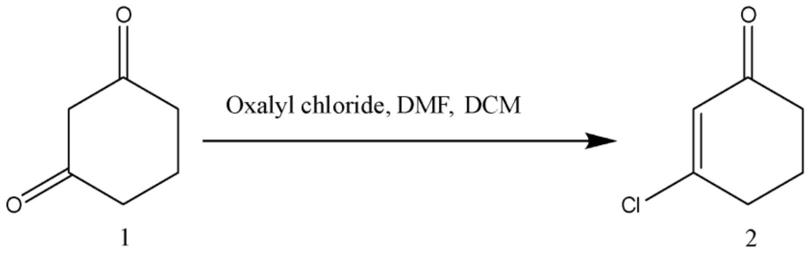
3g 93%
4g 90%
5g 57%

3h 71%
4h 41%
5h 31%

Figure 2.2 – Synthesized compounds (e-h)

2.1 Synthesis of 3-Chlorocyclohex-2-en-1-one (2)

3-Chlorocyclohex-2-en-1-one (2) is a chemical compound that serves as an important intermediate in various organic syntheses. It is typically prepared from 1,3-cyclohexandione by replacing one of its carbonyl groups with a chlorine atom via a substitution reaction(scheme 2.2).



Scheme 2.2 – Synthesis of 3-chlorocyclohex-2-en-1-one

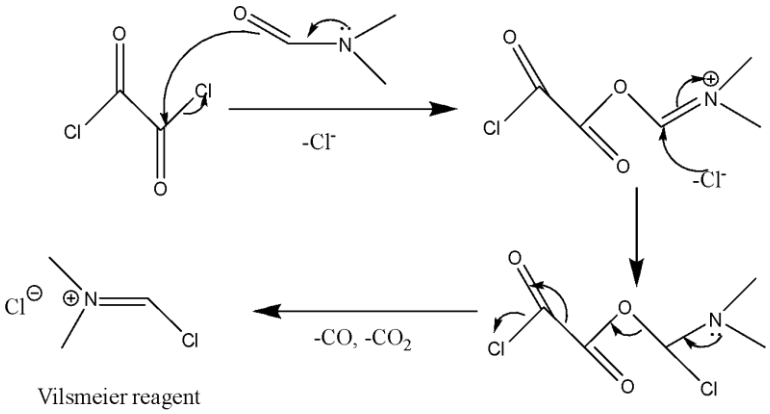
This compound contains a cyclohexene ring with a chloro group and a carbonyl group at the 1,3 positions. The presence of the chlorine atom in 3-chlorocyclohex-2-en-1-one makes it a versatile building block in organic synthesis, as it can undergo various reactions, including nucleophilic substitution, reduction, and addition reactions. 3- Chlorocyclohex-2-en-1-one has numerous applications in the synthesis of various organic compounds, including pharmaceuticals, agrochemicals, and materials.

3-Chlorocyclohex-2-en-1-one was used as an intermediate for the preparation of *meta*-aryloxy phenols first time because of its unique structural characteristics. The replacement of the chlorine atom with an aryloxy group leads to the formation of 3-(aryloxy)cyclohex-2-en-1-ones, which are then further transformed into *meta*-aryloxy phenols via an aromatization reaction. Moreover, the use of 3-chlorocyclohex-2-en-1-one as an intermediate in the synthesis of *meta*-aryloxy phenols allows for the preparation of a wide range of derivatives with various substituents, which makes it a versatile building block for the synthesis of organic compounds with diverse applications.

The formation of 3-chlorocyclohex-2-en-1-one (2) from 1,3-cyclohexandione (1) using oxalyl chloride and DMF in DCM proceeds through a multi-step mechanism [114].

Firstly, oxalyl chloride $(COCl)_2$ is activated by dimethylformamide (DMF) to form a Vilsmeier reagent(scheme 2.3).

Oxalyl chloride reacts with DMF first, and the DMF is catalytic, meaning that it only needs a substoichiometric amount of it. The mechanism of oxalyl chloride plus DMF overall loses CO_2 and CO and then forms an intermediate, Vilsmeier reagent, that reacts with the 1,3-cyclohexandione to form the 3-chlorocyclohex-2-en-1-one.



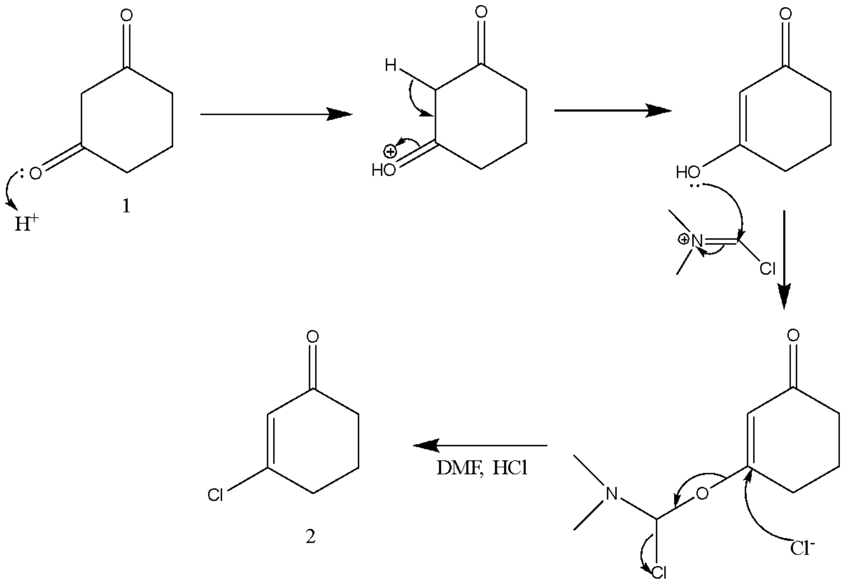
Scheme 2.3 – Mechanism of activation of oxalyl chloride by DMF

The resonance structure depicted in scheme 2.3 involves the transfer of the lone pair of electrons from nitrogen to oxygen of DMF, resulting in the formation of a charge-separated species which contained oxalyl chloride. This process entails the rupture of the pi bond and the formation of a new bond with carbon, while simultaneously breaking the σ bond to chlorine. Subsequently, the resulting species undergoes a collapse reaction, leading to the elimination of chlorine as chloride. The negatively charged chlorine species then attacks the carbon, leading to the formation of a neutral intermediate. This intermediate subsequently undergoes an elimination reaction initiated at the nitrogen center, leading to the rupture of bonds and an alpha elimination process that typically yields CO_2 and CO gases. Finally, the reaction generates an intermediate, which takes the form of a chloride salt.

The Vilsmeier reagent is a well-known and versatile reagent in synthetic organic chemistry that is typically utilized for the formylation of various organic compounds. This reagent, named after its discoverer, the German chemist Anton Vilsmeier, was first reported in 1927. The Vilsmeier reagent comprises a mixture of *N*,*N*-dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$), which readily reacts with a diverse range of organic compounds to form α-formylated derivatives [115].

In addition to its widespread use in formylation reactions, the Vilsmeier reagent has also been recognized as a valuable reagent for the activation of substrates for halogenation and cyclization reactions. The reagent activates the substrate towards nucleophilic attack by forming an electrophilic intermediate, which can subsequently undergo halogenation or cyclization depending on the nature of the substrate.

Firstly, the protonation of the lone pair of the carbonyl group on 1,3-cyclohexanedione by a hydrogen ion generates the enol tautomer, as shown in scheme 2.4.



Scheme 2.4 – The reaction mechanism for the formation of 3-chlorocyclohex-2-en-1-one

Upon reacting with the Vilsmeier reagent, 3-hydroxycyclohex-2-en-1-one produces 3-chlorocyclohex-2-en-1-one, which regenerates DMF and forms HCl. During this process, the oxygen atom of the hydroxyl group attacks the carbon of the Vilsmeier reagent, and the electrons from the pi bond are placed onto the nitrogen. Furthermore, the chloride ion attacks the β carbon. Subsequently, a β elimination takes place, breaking the C-O bond and forming 3-chlorocyclohex-2-en-1-one. This species then decomposes to eliminate the chloride ion. An acid-base reaction is then conducted, restoring the lone pair onto the nitrogen and regenerating DMF, while also producing HCl.

The use of oxalyl chloride and DMF in DCM provides mild reaction conditions and high yields, making this method suitable for large-scale synthesis.

The reaction product (2) is a yellow oil. Yield 83%. Spectroscopic data of 3-chlorocyclohex-2-en-1-one (2) was consistent with literature [116].

The FTIR (CH_2Cl_2, cast film) spectrum of compound (2) contains absorption bands of stretching vibrations of the (C-H) bond at 3200, cm^{-1}, methylene ($-CH_2-$) groups at 2955, 2927 cm^{-1}, carbonyl (C=O) group at 1717 cm^{-1}, (C=C) bond at 1680 cm^{-1}, and (C-Cl) bond at 1605 cm^{-1}.

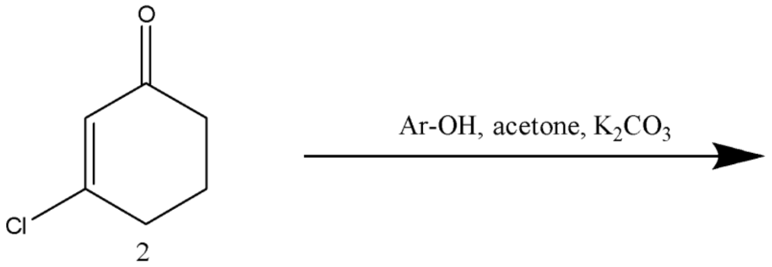
^1H NMR spectrum of 3-chlorocyclohex-2-en-1-one (figure A1 in an appendix A), ($CDCl_3$, 500 MHz). The first signal appears as a triplet at δ 6,22 with a coupling constant (t, J = 1,5 Hz, 1 H), indicating the presence of a hydrogen atom next to a carbon atom bearing a double bond. The second signal is a triplet of doublets at δ 2,68 (td, J = 6,1, 1,5 Hz, 2 H), indicating the presence of two hydrogen atoms attached to a carbon atom next to the chlorine atom. Signals appear as a multiplet and pentet δ 2,43-2,40 and 2,08, respectively, indicating the presence of two hydrogen atoms adjacent to the carbonyl group of the cyclohexene ring.

The $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) spectrum of 3-chlorocyclohex-2-en-1-one (figure A2 in an appendix A) shows six signals at the following chemical shifts: a signal appears at 196,8 ppm (singlet) indicating carbonyl carbon; the signal at 158,7 ppm (singlet) is assigned to the carbon adjacent to the chlorine atom; the signal at 128,5 ppm (doublet) corresponds to the carbon in the conjugated double bond; the triplets at 36,3, 33,9 and 22,2 ppm correspond to the three remaining carbons in the cyclohexane ring.

Mass- spectrum of 3-chlorocyclohex-2-en-1-one, exact mass (EI) *m/z* calcd for $C_6H_7{}^{35}ClO$ (M^+) 130,0854, found 130,01844.

2.2 Synthesis of 3-(aryloxy)cyclohex-2-en-1-one (3)

The nucleophilic substitution reaction of phenol derivatives with 3-chlorocyclohex-2-en-1-one (2) under refluxing acetone conditions in the presence of potassium carbonate (K_2CO_3) represents an efficient method for the synthesis of *meta* substituted cyclohex-2-en-1-ones (3) (scheme 2.5).



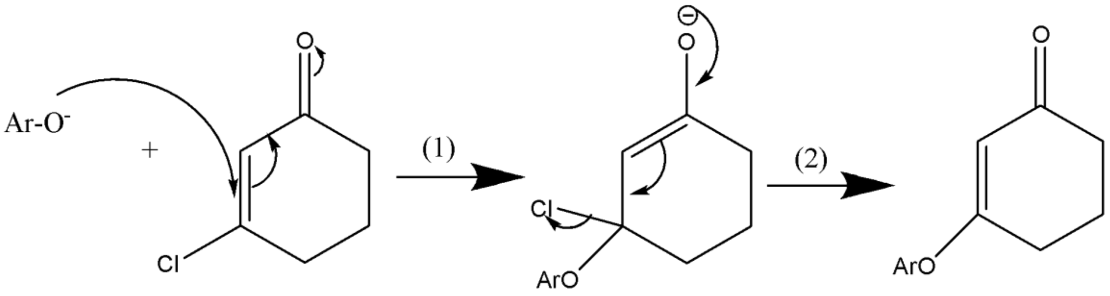
3a: ArOH= C_6H_5OH; **3b:** 4-IC_6H_4OH; **3c:** 4-ClC_6H_4OH; **3d:** 2,6-$(MeO)_2C_6H_3OH$;

3e: 2-t-BuC_6H_4OH; **3f:** 4-t-BuC_6H_4OH; **3g:** 4-$(MeO_2C)C_6H_4OH$; **3h:** 1,4-$(OH)_2C_6H_4$

Scheme 2.5 – The nucleophilic substitution reaction of
3-chlorocyclohex-2-en-1-one

The reaction mechanism, which was investigated by Dr. Clive’s group at the University of Alberta, can be summarized as follows(scheme 2.6): The potassium carbonate in the presence of acetone deprotonates the phenol derivatives to form the aryloxide ion. This acts as a nucleophile and attacks the electrophilic β carbon of 3-chlorocyclohex-2-en-1-one, resulting in the formation of a new carbon-oxygen bond, and forming an enolate (1). The enolate then ketonizes with expulsion of chloride (2).

This strategy provides a versatile and practical means for the construction of substituted cyclohexenones from readily available starting materials. The use of refluxing acetone as a solvent provides favorable reaction conditions, allowing for the generation of the expected substitution products.



Scheme 2.6 – The reaction mechanism for the formation of 3-aryloxy cyclohex-2-en-1-one

Average yield 76% for 8 examples(table 2.1).

Table 2.1 – Synthesized 3-aryloxy cyclohex-2-en-1-ones

	Name of compound	Solvent	Conditions	Yield (%)	State	Melting point (^{o}C)
3a	3-phenoxy cyclohex-2-en-1-one	acetone	60 ^{0}C, 20 h	90%	pale yellow oil	-
3b	3-(4-Iodophenoxy) cyclohex-2-en-1-one*	acetone	60 ^{0}C, 20 h	92%	oil which slowly crystallized	69–75
3c	3-(4-chlorophenoxy) cyclohex-2-en-1-one*	acetone	60 ^{0}C, 18 h	82%	white solid	72–75
3d	3-(2,6-dimethoxy phenoxy)cyclohex-2-en-1-one*	DMF	100 ^{0}C, 24 h	52%	white solid	76–78
3e	3-(2-*tert*-butylphenoxy) cyclohex-2-en-1-one	DMF	100 ^{0}C, 24 h	48%	yellowish oil	-
3f	3-(4-*tert*-butylphenoxy) cyclohex-2-en-1-one*	acetone	60 ^{0}C, 43 h	83%	white solid	92–96
3g	methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate*	acetone	60 ^{0}C, 18 h	93%	white solid	100–104
3h	3-{4-[(3-Oxo cyclohex-1-en-1-yl) oxy]phenoxy}cyclo hex-2-ene-1-one*	acetone	60 ^{0}C, 43 h	71%	light orange powder	209–212

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*- compounds have not been previously described in the literature

With 2,6-dimethoxyphenol the yield was only 23% even in refluxing butan-2-one but use of DMF at 100 °C raised the yield to 52%. The completion of the reaction was checked by TLC. The other hindered phenol we examined, 2-*t*-butylphenol, gave a yield of 21% in refluxing acetone and this result was also improved (48%) by using DMF at 100 °C. Mass, FTIR, ^{1}H-NMR, ^{13}C{^{1}H} NMR spectroscopic data for compounds 3a-3h are shown in the tables 2.2–2.5

Table 2.2 – Mass spectrum data for compounds 3a-3h

	Ionization technique	Formula	Calculated	Found
3a	Electron Ionization	$C_{11}H_{12}O_2$ (M^+)	188,08372	188,08356
3b	Electrospray Ionization	$C_{12}H_{12}IO_2$ $(M+H)^+$	313,9876	313,9878
3c	Electrospray Ionization	$C_{12}H_{11}{}^{35}ClO_2$ (M^+)	222,0448	222,0445
3d	Electron Ionization	$C_{14}H_{16}O_4$ $(M)^+$	248,10486	248,10488
3e	Electron Ionization	$C_{16}H_{20}O_2$ (M^+)	244,14633	244,13634
3f	Electron Ionization	$C_{16}H_{20}O_2$ (M^+)	244,1463	244,1461
3g	Electrospray Ionization	$C_{14}H_{15}O_4$ $(M+H)^+$	247,09650	247,0967
3h	Electrospray Ionization	$C_{18}H_{19}O_4$ $(M+H)^+$	299,1278	298,1280

Table 2.3 – IR data for compounds 3a-3h

Compound	Wave numbers of absorption bands, ν, cm-1						
	C-H of aromatic ring	C-H_2 of aliphatic chain	C=O of ketone group	C=C double bond of cyclohexenone ring	C=C in a aromatic ring	C-C in a aromatic ring	Note
3a	3065	2951, 2894, 2873	1661	1617	1587	1488	-
3b	-	2949	1666	1611	1653	1479	-
3c	-	-	1655	1614	1486	1374	-
3d	-	-	1651	1619	1585	1482	-
3e	-	2957	1663	1617	1599	1372	-
3f	-	2962	1669	1616	1656	1508	-
3g	-	-	1668	1620	1656	1598	1724 (C=O)
3h	3099, 3069	2940, 2892, 2870	1662	1614	-	1489	-

Table 2.4 – ^{1}H-NMR data for compounds 3a-3h

Compound	Chemical shift, ʃ, ppm			
	CH (aromatic protons)	C=CH	CH_2	CH_3
3a	7,42–7,39 (m, 2H), 7,29–7,24 (m, 1H) 7,06–7,04 (m, 2H)	5,14 (s, 1H)	2,65 (t, 2H), 2,41–2,38 (m, 2H) 2,08 (p, 2H)	-
3b	7,70 (d, 2 H), 6,80 (d, 2 H)	5,11 (s,1H)	2,63 (t, 2 H), 2,37 (t, 2 H), 2,08 (p, 2 H)	-
3c	7,37–7,35 (m, 2 H), 6,99–6,96 (m, 2 H)	5,10 (s, 1H)	2,64 (t, 2 H), 2,37 (t, 2 H), 2,07 (p, 2 H)	-
3d	7,12 (t, 1 H), 6,60 (d, 2 H)	5,08 (s, 1H)	2,70 (t, 2 H), 2,37 (t, 2 H), 2,08 (p, 2 H)	3,80 (s, 6H)
3e	7,39 (dd, 1 H), 7,18–7,13 (m, 2 H), 6,91 (dd, 1 H)	5,21 (s, 1H)	2,67 (t, 2 H), 2,39 (t, 2 H), 2,09 (p, 2 H)	1,32 (s, 9H)

Extension of table 2.4				
3f	7,39–7,37 (m, 2 H), 6,95–6,93 (m, 2 H)	5,12 (s, 1H)	2,65 (t, 2 H), 2,37 (t, 2 H), 2,08 (p, 2 H)	1,32 (s, 9H)
3g	8,10 (d, 2 H), 7,12 (d, 2 H)	5,16 (s, 1H)	2,67 (t, 2 H), 2,41 (t, 2 H), 2,11 (p, 2 H)	3,95 (s, 3H)
3h	7,08 (s, 4H)	5,15 (s, 2H)	2,67 (t, 4 H), 2,40 (t, 4 H), 2,11 (p, 4 H)	-

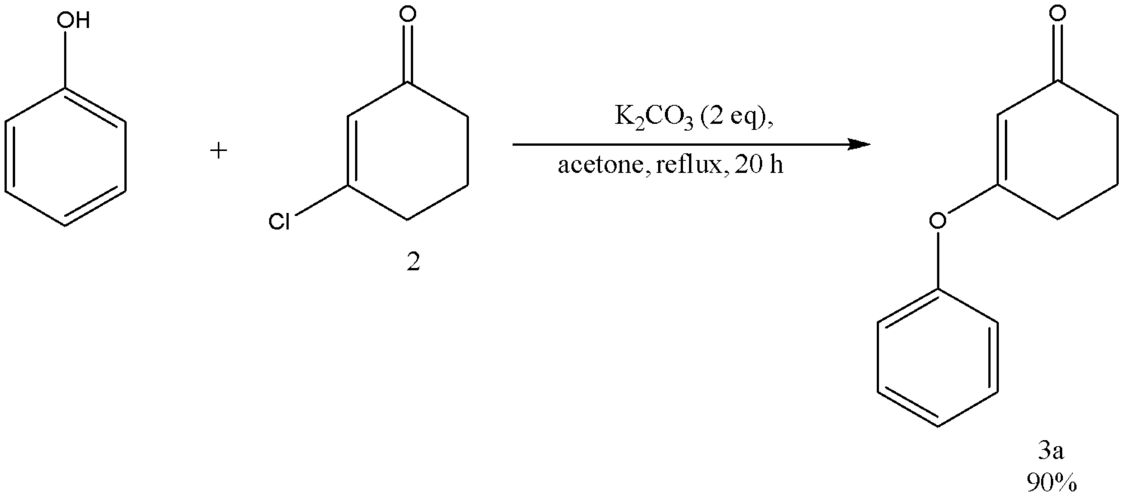
Table 2.5 – $^{13}C\{^{1}H\}$ NMR data for compounds 3a-3h

Compound	Chemical shift, ʃ, ppm							Note
	C=O	C-O Aromatic	C-O	=CH	-CH Aromatic carbons	-CH$_2$	-CH$_3$	-
3a	199,6 (s)	178,3 (s)	152,7 (s)	130,0 (d)	126,1 (d), 121,4 (d), 106,1 (d)	36,7 (t), 28,6 (t), 21,2 (t)	-	-
3b	199,3 (s)	177,7 (s)	152,6 (s)	139,1 (d)	123,6 (d), 106,3 (d)	36,6 (t), 28,4 (t), 21,1 (t)	-	90,0 (s) C-I
3c	199,3 (s)	177,8 (s)	151,2 (s)	130,2 (d)	122,8 (d), 106,2 (d)	36,6 (t), 28,5 (t), 21,2 (t)	-	131,6 (s) C-Cl
3d	200,2 (s)	177,8 (s)	152,3 (s)	130,2 (d)	126,5 (d), 105,1 (d), 104,8 (d)	36,7 (t), 28,0 (t), 21,3 (t)	56,1 (q)	-
3e	199,5 (s)	177,9 (s)	151,3 (s)	127,8 (d)	127,2 (d), 125,8 (d), 123,0 (d) 106,7 (d)	36,6 (t), 28,9 (t), 21,2 (t)	30,3 (q)	141,5 (s) C-*tert*-Bu, 34,6 (s) C-(CH$_3$)$_3$,
3f	199,9 (s)	178,7 (s)	150,4 (s)	126,9 (d)	120,8 (d) 106,0 (d)	36,7 (t), 28,6 (t), 21,3 (t)	31,5 (q)	149,2 (s) C-*tert*-Bu, 34,6 (s) C-(CH$_3$)$_3$,
3g	199,3 (s)	177,2 (s)	156,4 (s)	131,8 (d)	121,4 (d) 106,7 (d)	36,6 (t), 28,4 (t), 21,1 (t)	52,3 (q)	166,1 (s) C=O ester, 128,0 (s) C-(CO$_2$Me),
3h	199,4 (s)	177,9 (s)	150,2 (s)	122,9 (d)	106,2 (d)	36,6 (t), 28,4 (t), 21,1 (t)	-	-

2.2.1 3-(Phenoxy)cyclohex-2-en-1-one (3a)

3-(Phenoxy)cyclohex-2-en-1-one (3a) is a known organic compound that belongs to the class of cyclic ketones. That is primarily used as an intermediate in the synthesis of other organic compounds. It can be used to produce a variety of derivatives, including pharmaceuticals, agrochemicals, and fragrances.

3-(Phenoxy)cyclohex-2-en-1-one (3a) was synthesized by previously described general process(scheme 2.5) to prepare 3-(aryloxy)cyclohex-2-en-1-one using 1 equivalent of phenol as a reagent(scheme 2.7).



Scheme 2.7 – Synthesis of 3-(phenoxy)cyclohex-2-en-1-one

The reaction product (3a) is a pale yellow oil that crystallized in the fridge to form a white solid. Yield 90%. Physico-chemical data of 3-(phenoxy)cyclohex-2-en-1-one (3a) was consistent with literature [117].

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(phenoxy)cyclohex-2-en-1-one (3a) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3065 cm^{-1}, (C-H) of the aliphatic chain in the cyclohexene ring at 2951, 2894, 2873 cm^{-1}, (C=O) of the ketone functional group in the molecule at 1661 cm^{-1}, the (C=C) of the double bond in the cyclohexene ring at 1617 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1587 cm^{-1}, and the (C-C) bending vibration of the phenyl ring at 1488 cm^{-1}.

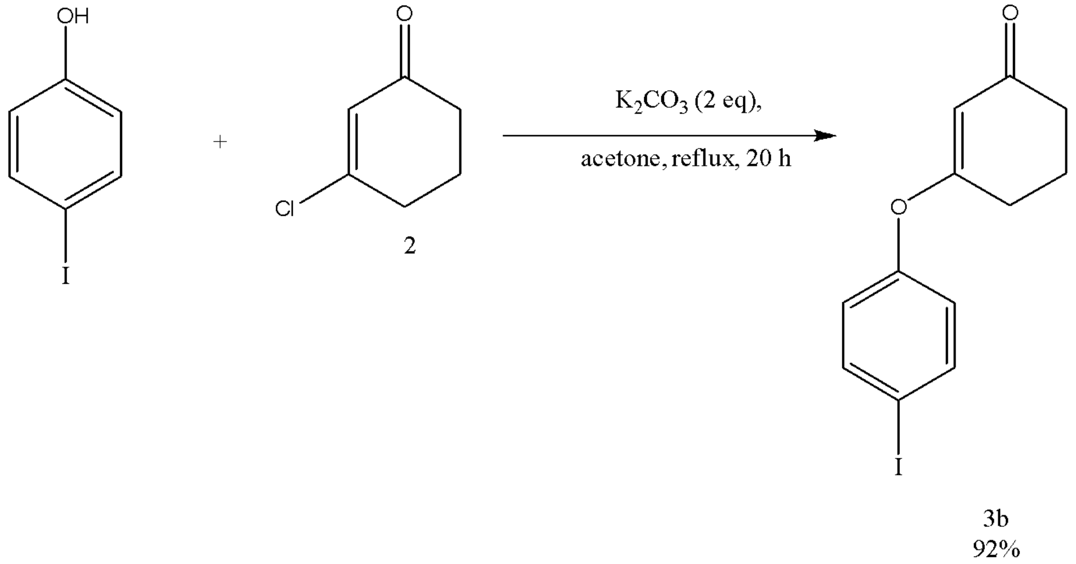
^{1}H NMR spectrum of 3-(phenoxy)cyclohex-2-en-1-one (3a) (figure A3), ($CDCl_3$, 500 MHz) shows the following peaks: the signals appear as multiplets at δ 7,42–7,39 (m, 2H), δ 7,29–7,24 (m, 1H) and 7,06–7,04 (m, 2H) are assigned to the aromatic protons in the phenoxy group; the signal appears as a singlet at δ 5,14 (s, 1H) is assigned to the proton on the double bond in the cyclohexene ring; the signals appear as multiplets at δ 2,65 (t, *J* = 6,3 Hz, 2H), δ 2,41–2,38 (m, 2H) and δ 2,08 (pentet, *J* = 6,5 Hz, 2H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring.

$^{13}C\{^1H\}$ NMR spectrum of 3-(phenoxy)cyclohex-2-en-1-one (3a) (figure A4) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal appears at 199,6 ppm (singlet) indicating carbonyl carbon; the signal appears at 178,3 ppm (singlet) indicating aromatic carbon attached to oxygen; the signal at 152,7 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal at 130,0 ppm (doublet) corresponds to the carbon in the conjugated double bond; the doublets appear at 126,1, 121,4 and 106,1 correspond to the aromatic carbons; the triplets at 36,7, 28,6 and 21,2 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.2.2 3-(4-Iodophenoxy)cyclohex-2-en-1-one (3b)

3-(4-Iodophenoxy)cyclohex-2-en-1-one (3b) is a compound that previously was not described in a literature.

The compound 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b) has been successfully synthesized through a previously described general process involving the preparation of 3-(aryloxy)cyclohex-2-en-1-one (3)(scheme 2.5). This synthetic route utilizes 3-chlorocyclohex-2-en-1-one (2), 1 equivalent of 4-iodophenol and 2 equivalents of potassium carbonate in acetone to obtain the desired compound 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b), as demonstrated in scheme 2.8.



Scheme 2.8 – Synthesis of 3-(4-iodophenoxy)cyclohex-2-en-1-one

The reaction product (3b) was as an oil which slowly crystallized: mp 69–75 °C. Yield 92%. The identification of the structure of 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR, and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b) contains absorption bands of stretching vibrations (C-H) of the aliphatic chain in the cyclohexene ring at 2949 cm^{-1}, (C=O) of the ketone functional group in the molecule at 1666 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1653 cm^{-1},the (C=C) of the double bond in the cyclohexene ring at 1611 cm^{-1}, and the (C-C) bending vibration of the phenyl ring at 1479 cm^{-1}.

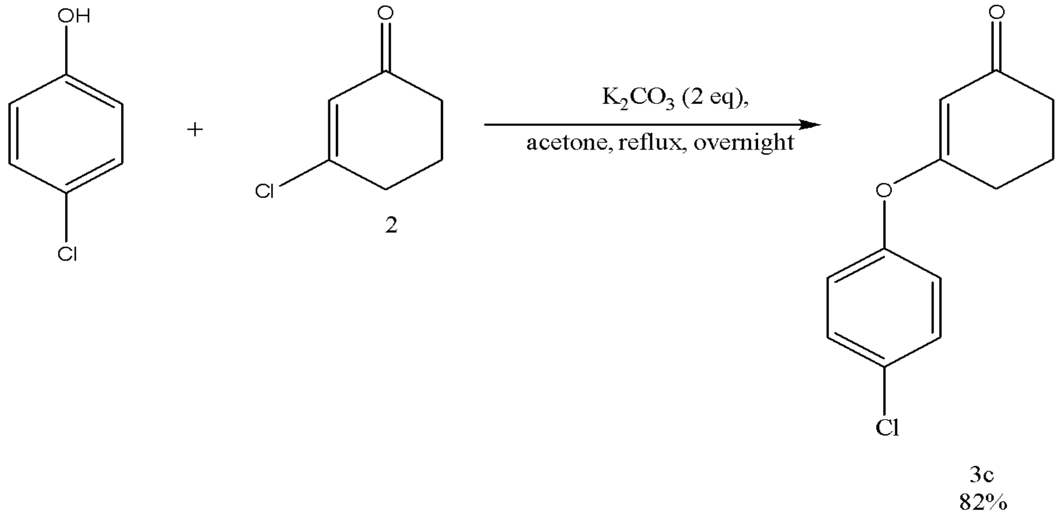
^{1}H NMR spectrum of 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b) (figure A5), ($CDCl_3$, 500 MHz) shows the following peaks: the signals appear as doublets at δ 7,70 (d, *J* = 9 Hz, 2 H), 6,80 (d, *J* = 9 Hz, 2 H) are assigned to the aromatic protons in the 4-iodophenoxy group; the signal appears as a singlet at δ 5,11 (s, 1H) is assigned to the proton on the double bond in the cyclohexene ring; the signals appear as triplets and pentet at δ 2,63 (t, *J* = 7 Hz, 2 H), 2,37 (t, *J* = 7 Hz, 2 H), 2,08 (pentet, *J* = 6,5 Hz, 2 H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring.

$^{13}C\{^1H\}$ NMR spectrum of 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b) (figure A6) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal appears at 199,3 ppm (singlet) indicating carbonyl carbon; the signal appears at 177,7 ppm (singlet) indicating aromatic carbon attached to oxygen atom; the signal at 152,6 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal at 139,1 ppm (doublet) corresponds to the carbon in the conjugated double bond; the doublets appear at 123,6, 106,3 correspond to the aromatic carbons; the signal at 90,0 ppm (singlet) is assigned to the aromatic carbon adjacent to the iodine atom; the triplets at 36,6, 28,4 and 21,1 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.2.3 3-(4-Chlorophenoxy)cyclohex-2-en-1-one (3c)

3-(4-Chlorophenoxy)cyclohex-2-en-1-one (3c) is a compound that previously was not described in a literature.

The compound 3-(4-chlorophenoxy)cyclohex-2-en-1-one (3c) has been successfully synthesized through a previously described general process (scheme 2.5) utilizing 4-chlorophenolas a reagent(scheme 2.9).



Scheme 2.9 – Synthesis of 3-(4-chlorophenoxy)cyclohex-2-en-1-one

The reaction product (3c) as a white solid: mp 72–75 °C. Yield 82%. The identification of the structure of 3-(4-chlorophenoxy)cyclohex-2-en-1-one (3c) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(4-chlorophenoxy)cyclohex-2-en-1-one (3c) contains absorption bands of stretching vibrations (C=O) of the ketone functional group in the molecule at 1655 cm^{-1},the (C=C) of the double bond in the cyclohexene ring at 1614 cm^{-1}, the (C=C) bending vibration of the phenyl ring at 1486 cm^{-1}, and the (C-C) of the double bond in the phenyl ring at 1374 cm^{-1}.

^{1}H NMR spectrum of 3-(4-chlorophenoxy)cyclohex-2-en-1-one (3c) (figure A7), ($CDCl_3$, 500 MHz) shows the following peaks: the signals appear as doublets at δ 7,37–7,35 (m, 2 H), 6,99–6,96 (m, 2 H) are assigned to the aromatic protons in the 4-chlorophenoxy group; the signal appears as a singlet at δ 5,10 (s, 1H) is assigned to the proton on the double bond in the cyclohexene ring; the signals appear as triplets and pentet at δ 2,64 (t, *J* = 6,5 Hz, 2 H), 2,37 (t, *J* = 6,5 Hz, 2 H), 2,07 (pentet, *J* = 6,5 Hz, 2 H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring.

^{13}C{^{1}H} NMR spectrum of 3-(4-chlorophenoxy)cyclohex-2-en-1-one (3c) (figure A8) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: the signal appears at 199,3 ppm (singlet) indicating carbonyl carbon; the signal appears at 177,8 ppm (singlet) indicating aromatic carbon attached to oxygen atom; the signal at 151,2 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal at 131,6 ppm (singlet) is assigned to the aromatic carbon adjacent to the chlorine atom; the signal at 130,2 ppm (doublet) corresponds to the carbon in the conjugated double bond; the doublets which appear at 122,8 and 106,2 correspond to the aromatic carbons; the triplets at 36,6, 28,5 and 21,2 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.2.4 3-(2,6-Dimethoxyphenoxy)cyclohex-2-en-1-one (3d)

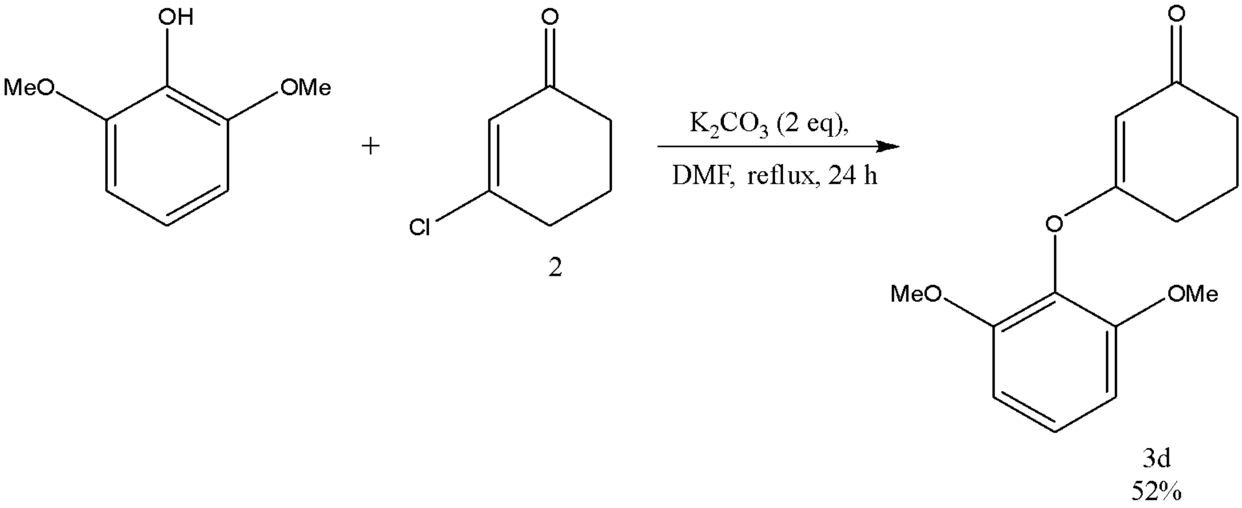
3-(2,6-Dimethoxyphenoxy)cyclohex-2-en-1-one (3d) is a compound that previously was not described in the literature.

The compound 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) has been synthesized through a general method(scheme 2.5) by using 1 equivalent of 2,6-dimethoxyphenol as a reagent and DMF as a solvent(scheme 2.10).

Our initial attempt at synthesizing 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) involved a universal approach. However, we encountered a low yield of product when using acetone as a solvent. To improve the yield, we tried using solvents with higher boiling points, such as butanone and DMF(table 2.6).

We first attempted to heat the reaction mixture with acetone at 55°C for 41 h, resulting in a pure product yield of only 5%. Increasing the refluxing temperature to 60°C for 47 h slightly improved the yield to 7%. Refluxing with butanone at 75°C for 66 h led to a more substantial yield of 23% pure product. Finally, when we utilized

DMF at 100°C for 24 h, the yield increased significantly to 52%. Using DMF helps to increase the yield and decrease the reaction time.



Scheme 2.10 – Synthesis of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one

Table 2.6 – Yield of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) with different solvents and refluxing temperatures

Solvent	Temperature (^{0}C)	Time (h)	Yield (%)
Acetone	55	41	5
Acetone	60	47	7
Butanone	75	66	23
DMF	100	24	52

The reaction product (3d) is a white solid: mp 76–78 °C. Yield 52%. The identification of the structure of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR, and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) contains absorption bands of stretching vibrations (C=O) of the ketone functional group in the molecule at 1651 cm^{-1}, the (C=C) of the double bond in the cyclohexene ring at 1619 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1585 cm^{-1}; and the (C-C) bending vibration of the phenyl ring at 1482 cm^{-1}.

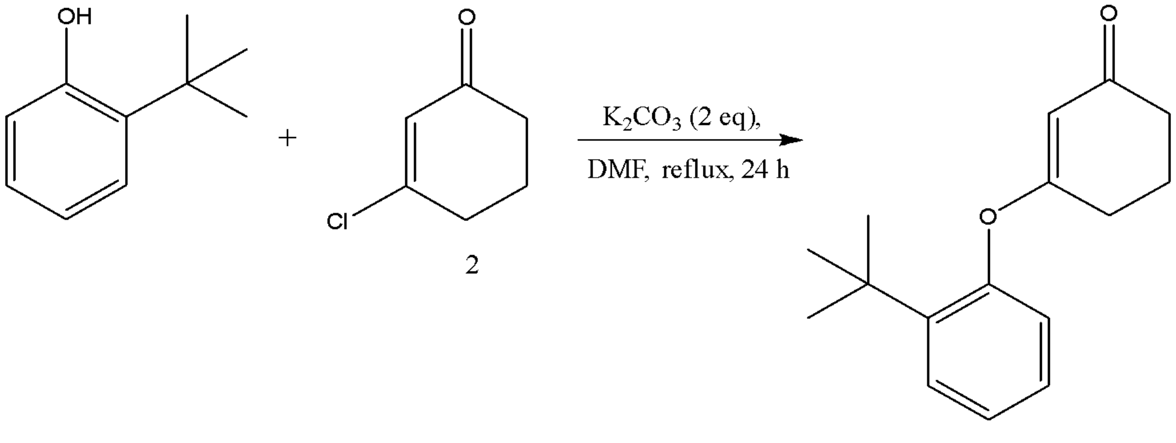
^{1}H NMR spectrum of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) (figure A9), ($CDCl_3$, 500 MHz) shows the following peaks: the signals appear as a triplet and doublet at δ 7,12 (t, J = 8,5 Hz, 1 H), 6,60 (d, J = 8,5 Hz, 2 H) are assigned to the aromatic protons in the 2,6-dimethoxyphenoxy group; the signal, that appears as a singlet at δ 5,08 (s, 1H) is assigned to the proton on the double bond in the cyclohexene ring; a signal appears as a singlet at δ 3,80 (s, 6H) indicating six protons of the two methyl oxy groups; the signals that appear as triplets and pentet at δ 2,70 (t, *J* = 6,5 Hz, 2 H), 2,37 (t, *J* = 6,5 Hz, 2 H), 2,08 (pentet, *J* = 6,5 Hz, 2 H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring.

$^{13}C\{^{1}H\}$ NMR spectrum of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) (figure A10) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: the signal that appears at 200,2 ppm (singlet) indicating carbonyl carbon; the signal that appears at 177,8 ppm (singlet) indicating aromatic carbon attached to oxygen atom; the signal at 152,3 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal at 130,2 ppm (doublet) corresponds to the carbon in the conjugated double bond; the doublets that appear at 126,5, 105,1 and 104,8 correspond to the aromatic carbons; the signal at 56,1 ppm (quartet) is assigned to the carbons of methoxy groups adjacent to the three protons; the triplets at 36,7, 28,0 and 21,3 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.2.5 3-(2-*tert*-Butylphenoxy)cyclohex-2-en-1-one (3e)

3-(2-*tert*-Butylphenoxy)cyclohex-2-en-1-one (3e) is a compound that previously was not described in the literature.

The compound 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e) has been successfully synthesized through a previously described process involving the preparation of 3-(aryloxy)cyclohex-2-en-1-one utilizing 2-*tert*-butylphenol as a reagent. This synthetic route, as depicted in scheme 2.5, has been employed and modified to obtain the desired compound 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one, as demonstrated in scheme 2.11.



Scheme 2.11 – Synthesis of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one

Our initial attempt at synthesizing 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e) involved a universal approach. However, we obtained a low yield of product when using acetone as a solvent. To improve the yield, we tried using solvents with higher boiling points, such as butanone and DMF (table 2.7). We first attempted to reflux the reaction mixture with acetone at 60 °C for 43 h, resulting in a pure product yield of only 21%. Refluxing with butanone at 75°C for 116 h led to losing product. Finally, when we utilized DMF at 100°C reaction was completed by TLC in 24 h, and the yield increased significantly to 48%.

The reaction product (3e) is a yellowish oil. Yield 48%. The identification of the structure of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

Table 2.7 – Yield of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e) with different solvents and refluxing temperatures

Solvent	Temperature (^{0}C)	Time (h)	Yield (%)
Acetone	60	43	21
Butanone	75	116	-
DMF	100	24	48

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e) contains absorption bands of stretching vibrations methylene (-CH_2-) groups in the 2957 cm^{-1}; (C=O) of the ketone functional group in the molecule at 1663 cm^{-1}; the (C=C) of the double bond in the cyclohexene ring at 1617 cm^{-1}; the (C=C) of the double bond in the phenyl ring at 1599 cm^{-1}; and the (C-C) bending vibration of the phenyl ring at 1372 cm^{-1}.

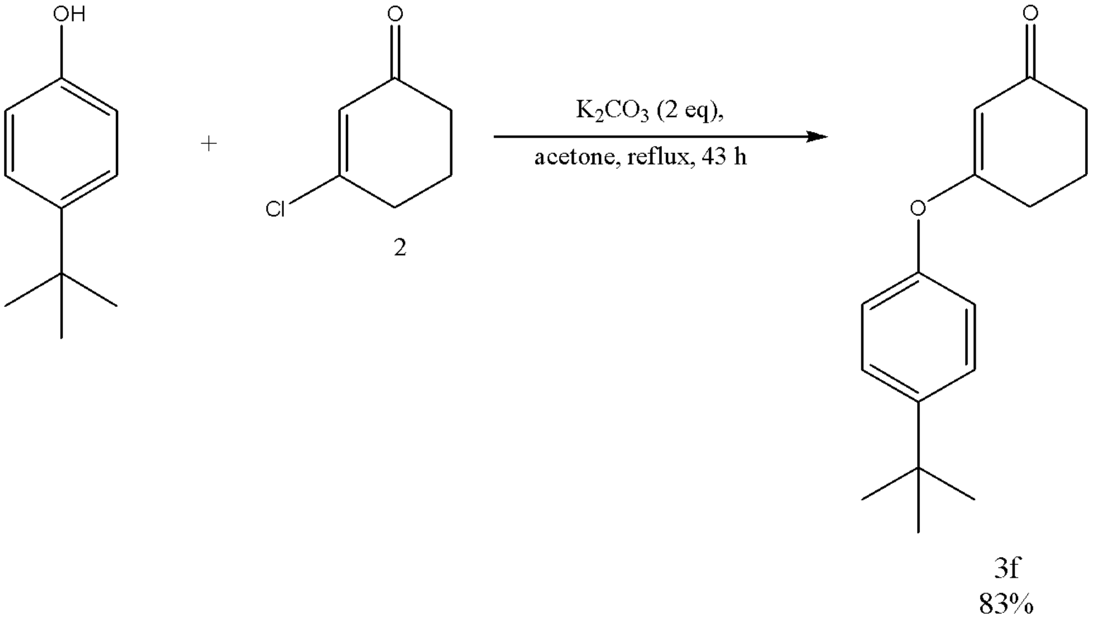
^{1}H NMR spectrum of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e) (figure A11), ($CDCl_3$, 600 MHz) shows the following peaks: the signals that appear at δ 7,39 (dd, *J* = 7,8, 1,8 Hz, 1 H), 7,18–7,13 (m, 2 H), 6,91 (dd, *J* = 7,8, 1,8 Hz, 1 H) are assigned to the aromatic protons in the 2-*tert*-butylphenoxy group; the signal that appears as a singlet at δ 5,21 (s, 1H) is assigned to the proton on the double bond in the cyclohexene ring; the signals that appear as triplets and pentet at δ 2,67 (t, *J* = 6 Hz, 2 H), 2,39 (t, *J* = 6 Hz, 2 H), 2,09 (pentet, *J* = 6 Hz, 2 H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring; the signal that appears as a singlet at δ 1,32 (s, 9H) indicating nine protons of the *tert*-butyl group.

^{13}C{^{1}H} NMR spectrum of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e) (figure A12) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: the signal that appears at 199,5 ppm (singlet) indicates carbonyl carbon; the signal that appears at 177,9 ppm (singlet) indicating aromatic carbon attached to oxygen atom; the signal at 151,3 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal that appears as a singlet at 141,5 ppm (singlet) is assigned to the aromatic carbon attached to *tert*-butyl group; the signal at 127,8 ppm (doublet) corresponds to the carbon in the conjugated double bond; the doublets appear at 127,2, 125,8, 123,0 and 106,7 correspond to the aromatic carbons; the signal at 34,6 ppm (singlet) is assigned to the carbon of *tert*-butyl group adjacent to the three methyl groups and aromatic ring;

the signal that appears as a quartet at 30,3 ppm is assigned to the carbons of methyl groups in *tert*-butyl group; the triplets at 36,6, 28,9 and 21,2 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.2.6 3-(4-*tert*-Butylphenoxy)cyclohex-2-en-1-one (3f)

The compound 3-(4-*tert*-Butylphenoxy)cyclohex-2-en-1-one (3f) has not been reported in the literature and hence, remains uncharacterized. The compound 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (3f) has been successfully synthesized through a previously described process involving the preparation of 3-(aryloxy)cyclohex-2-en-1-one from 3-chlorocyclohex-2-en-1-one(scheme 2.5) utilizing 4-*tert*-butylphenol as a reagent(scheme 2.12).



Scheme 2.12 – Synthesis of 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one

The reaction product (3f) is a white solid: mp 92–96 °C. Yield 83%. The identification of the structure of 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (3f) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (3f) contains absorption bands of stretching vibrations of methylene (-CH_2-) groups at 2962 cm^{-1}; (C=O) of the ketone functional group in the molecule at 1669 cm^{-1}; the (C=C) bending vibration of the phenyl ring at 1656 cm^{-1}; the (C=C) of the double bond in the cyclohexene ring at 1616 cm^{-1}; and the (C-C) of the bond the phenyl ring at 1508 cm^{-1};

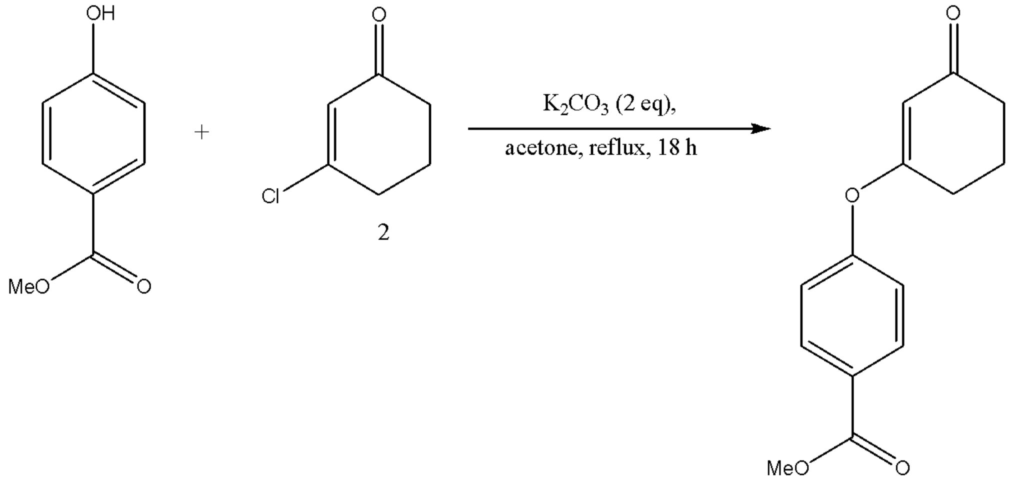
^{1}H NMR spectrum of 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (3f) (figure A13), ($CDCl_3$, 500 MHz) shows the following peaks: the signals that appear at δ 7,39–7,37 (m, 2 H), 6,95–6,93 (m, 2 H) are assigned to the aromatic protons in the 4-*tert*-butylphenoxy group; the signal that appears as a singlet at δ 5,12 (s, 1H) is assigned to the proton on the double bond in the cyclohexene ring; the signals that appear as triplets and pentet at δ 2,65 (t, J = 7 Hz, 2 H), 2,37 (t, J = 7 Hz, 2 H), 2,08 (pentet, J = 7,0 Hz, 2 H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring; the signal that appears as singlet at δ 1,32 (s, 9H) indicates nine protons of the *tert*-butyl group.

$^{13}C\{^1H\}$ NMR spectrum of 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (3f) (figure A14) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: the signal that appears at 199,9 ppm (singlet) indicating carbonyl carbon; the signal that appears at 178,7 ppm (singlet) indicates aromatic carbon attached to oxygen atom; the signal at 150,4 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal that appears as a singlet at 149,2 ppm (singlet) is assigned to the aromatic carbon attached to *tert*-butyl group; the signal at 126,9 ppm (doublet) corresponds to the carbon in the conjugated double bond; the doublets that appear at 120,8, 106,0 correspond to the aromatic carbons; the signal at 34,6 ppm (singlet) is assigned to the carbon of *tert*-butyl group adjacent to the three methyl groups and aromatic ring; the signal that appears as a quartet at 31,5 ppm is assigned to the carbons of methyl groups in *tert*-butyl group; the triplets at 36,7, 28,6 and 21,3 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.2.7 Methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g)

Methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g) is a compound that previously was not described in a literature.

Methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g) has been synthesized successfully by means of a previously described approach(scheme 2.5), which involves the use of methyl 4-hydroxybenzoate phenol derivatives as a reagent (scheme 2.13) for the preparation of 3 methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g).



3g
93%

Scheme 2.13 – Synthesis of methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate

The reaction product (3g) is a white solid: mp 100–104 °C. Yield 93%. The identification of the structure of methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g) contains absorption bands of stretching vibrations (C=O) of the ester functional group in the molecule at 1724 cm^{-1}; (C=O) of the ketone functional group in the molecule at 1668 cm$^-$1; the (C=C) bending vibration of the phenyl ring at 1656 cm^{-1}; the (C=C) of the double bond in the cyclohexene ring at 1620 cm^{-1}; and the (C-C) of the bond in the phenyl ring at 1598 cm^{-1}.

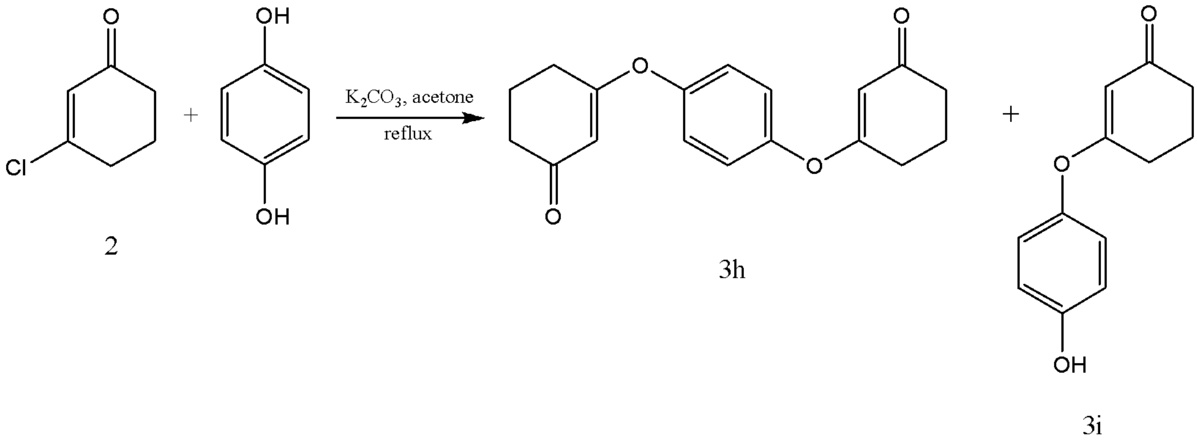
^{1}H NMR spectrum of methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g) (figure A15), ($CDCl_3$, 400 MHz) shows the following peaks: the signals that appear at δ 8,10 (d, *J* = 9 Hz, 2 H), 7,12 (d, *J* = 9 Hz, 2 H) are assigned to the aromatic protons; the signal that appears as a singlet at δ 5,16 (s, 1H) is assigned to the proton on the double bond in the cyclohexene ring; the signal that appears as a singlet at δ 3,95 (s, 3H) indicating three protons of the methyl group; the signals that appear as triplets and pentet at δ 2,67 (t, *J* = 6,6 Hz, 2 H), 2,41 (t, *J* = 6,6 Hz, 2 H), 2,11 (pentet, *J* = 6,6 Hz, 2 H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring.

^{13}C{^{1}H} NMR spectrum of methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g) (figure A16) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: the signal that appears at 199,3 ppm (singlet) indicates the carbonyl carbon; the signal that appears at 177,2 ppm (singlet) indicates the aromatic carbon attached to oxygen atom; the signal that appears as a singlet at 166,1 ppm indicates carbon of methyl ester; the signal at 156,4 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal at 131,8 ppm (doublet) corresponds to the carbon in the conjugated double bond; the signal that appear as a singlet at 128,0 ppm (singlet) is assigned to the aromatic carbon attached to (MeO_2C-) group; the doublets that appear at 121,4, 106,7 correspond to the aromatic carbons; the signal at 52,3 ppm (quartet) is assigned to the carbon of methyl group; the triplets at 36,6, 28,4 and 21,13 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.2.8 3-{4-[(3-Oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h)

The compound 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) has not been previously reported in the literature. 3-{4-[(3-Oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) has been synthesized through a previously described process involving the preparation of 3-(aryloxy)cyclohex-2-en-1-one utilizing hydroquinone as a reagent (scheme 2.14). However, when using 1 equivalent of 3-chlorocyclohex-2-en-1-one (2), 1 equivalent of hydroquinone and 2 equivalent of potassium carbonate in refluxing acetone for 41 h we got 69% of 3-(4-

hydroxyphenoxy)cyclohex-2-en-1-one (3i) and 13% of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) (table 2.8).



Scheme 2.14 – The synthesis of
3-{4-[(3-Oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) and
3-(4-hydroxyphenoxy)cyclohex-2-en-1-one (3i)

We can not continue synthesis with 3-(4-hydroxyphenoxy)cyclohex-2-en-1-one (3i) because of the ability of the hydroxyl group to react with bromine in the next step. Therefore, we worked on increasing the yield of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h).

Using 2 equivalent of 3-chlorocyclohex-2-en-1-one (2), 1 equivalent of hydroquinone and 2 equivalents of potassium carbonate in refluxing acetone for 41 h gave us 21% of pure 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) (table 2.8).

Finally, increasing the amount of potassium carbonate to 4 equivalents, and refluxing in acetone for 43 h gave us 71% of pure 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h).

Table 2.8 – Comparing different amounts of reagents to get 3h

Reagents, equivalent				Yield, %	
3-chloro cyclohex-2-en-1-one (2)	Hydroquinone	K_2CO_3	Reaction conditions	3-(4-hydroxyphenoxy) cyclohex-2-en-1-one (3i)	3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy} cyclohex-2-ene-1-one (3h)
1	1	2	Ref, 41h	69	13
2	1	2	Ref, 41h	-	21
2	1	4	Ref, 43 h	-	71

The yield of the reaction can be improved by increasing the concentration of the mild base potassium carbonate (K_2CO_3) used to facilitate the nucleophilic attack of hydroquinone on 3-chlorocyclohex-2-en-1-one (2). An increasing K_2CO_3 from 2 to 4 equivalents leads to higher base concentration, which improves the efficiency of deprotonation of hydroquinone and makes the nucleophilic attack more efficient, resulting in a higher yield of the desired product. Additionally, higher base concentration minimizes side reactions and increases the reaction rate, leading to a faster formation of the product. The longer reaction time observed with 4 equivalents of K_2CO_3 is compensated by the significant increase in the yield.

The reaction product (3h) is a light orange powder: mp 209–212 °C. Yield 71%. The identification of the structure of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) contains absorption bands (C-H) of the aromatic ring in the phenoxy groups at 3099, 3069 cm^{-1}, (C-H) of the aliphatic chain in the cyclohexene ring at 2940, 2892, 2870 cm^{-1}; (C=O) of the ketone functional group in the molecule at 1662 cm^{-}1; the (C=C) of the double bond in the cyclohexene ring at 1614 cm^{-1}; and the (C-C) of the bond in the phenyl ring at 1489 cm^{-1}.

^{1}H NMR spectrum of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) (figure A17), ($CDCl_3$, 500 MHz) shows the following peaks: the signal that appears as a singlet at δ 7,08 (s, 4 H) is assigned to the aromatic protons; the signal that appears as a singlet at δ 5,15 (s, 2H) is assigned to the protons on the double bond in the cyclohexene rings; the signals that appear as triplets and pentet at δ 2,67 (t, J = 6 Hz, 4 H), 2,40 (t, J = 7,2 Hz, 4 H), 2,11 (pentet, J = 6,6 Hz, 4 H) are assigned to the methylene protons in the aliphatic chain of the cyclohexene ring.

^{13}C{^{1}H} NMR spectrum of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h) (figure A18) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: the signal that appears at 199,4 ppm (singlet) indicates carbonyl carbon; the signal that appears at 177,9 ppm (singlet) indicates aromatic carbon attached to oxygen atom; the signal at 150,2 ppm (singlet) is assigned to the carbon adjacent to the oxygen atom; the signal at 122,9 ppm (doublet) corresponds to the carbon in the conjugated double bond; the doublet that appears at 106,2 corresponds to the aromatic carbons; the triplets at 36,6, 28,4 and 21,1 ppm correspond to the three remaining carbons in the cyclohexane ring.

2.3 Synthesis of 2-bromo-3-(aryloxy)cyclohex-2-en-1-one (4)

The introduction of a bromine atom, on the second carbon of a 3-(aryloxy)cyclohex-2-en-1-one (3) prior to the aromatization reaction is a commonly employed strategy. The bromine atom serves as an effective leaving group during the aromatization reaction.

To the best of my knowledge, in 1953 Nazarov [118] reported the first synthesis of 2-bromo-1,3-cyclohexanedione by brominating 1,3-cyclohexanedione using bromine in water, resulting in a yield of 60%. Additionally, Nazarov observed that 2-

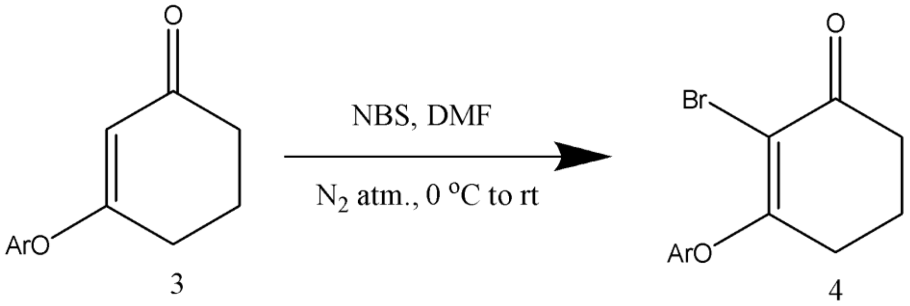
bromo-1,3-cyclohexanedione exhibited a higher degree of selectivity in reaction with organomagnesium compounds compared to 1,3-cyclohexanedione.

In 1987, Shepherd [119] described a method for synthesizing 2-bromo-3-methoxycyclohex-2-en-1-one from 3-methoxycyclohex-2-en-1-one using N-bromo-succinimide (NBS) in dichloromethane (DCM). Shepherd noted that the conversion of the resulting bromo enone to the corresponding phenol was difficult to achieve using aqueous conditions, but was easily accomplished under anhydrous conditions with acid catalysis, leading to a clean conversion.

This approach improves the selectivity of the reaction and streamlines the purification process. Therefore, the addition of bromine represents a crucial step in the synthetic pathway for the aromatization of 3-(aryloxy)cyclohex-2-en-1-one.

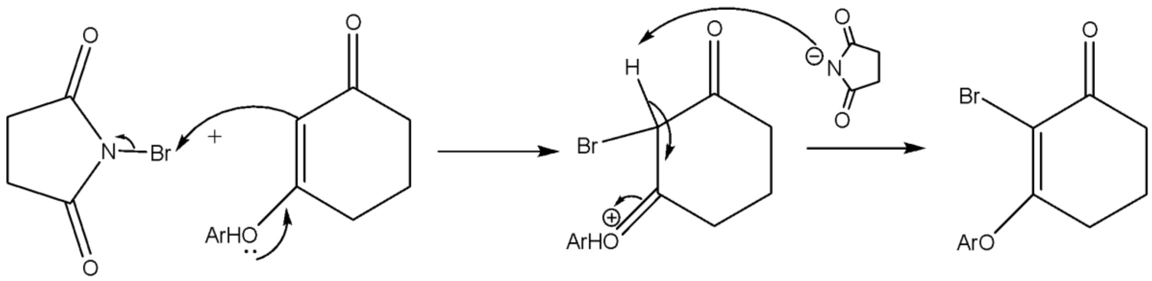
In our research, we synthesized 2-bromo-3-(aryloxy)cyclohex-2-en-1-one (4) from 3-(aryloxy)cyclohex-2-en-1-one (3) using NBS in DMF(scheme 2.15).

The mechanism for the synthesis of 2-bromo-3-(aryloxy)cyclohex-2-en-1-one (4) from 3-(aryloxy)cyclohex-2-en-1-one (3) using NBS in DMF, which was investigated by Dr. Clive's group at University of Alberta, may occur by the following mechanism (scheme 2.16).



4a: Ar= C_6H_5; **4b:** 4-IC_6H_4; **4c:** 4-ClC_6H_4; **4d:** 2,6-$(MeO)_2C_6H_3$; **4e:** 2-t-BuC_6H_4; **4f:** 4-t-BuC_6H_4; **4g:** 4-$(MeO_2C)C_6H_4$; **4h:** C_6H_7O-O-C_6H_4-

Scheme 2.15 – The synthesis of 2-bromo-3-(aryloxy)cyclohex-2-en-1-one



Scheme 2.16 – The mechanism for the synthesis of
2-bromo-3-aryloxy-cyclohex-2-en-1-one

The transfer of the lone pair of electrons from the oxygen of the aryloxy group of 3-(aryloxy)cyclohex-2-en-1-one (3) to the third carbon results in the breaking of the *pi* bond between the second and third carbons of the cyclohex-2-en-1-one ring and the formation of a new bond between the bromine atom from NBS and the second carbon.

The negatively charged succinimide ion, generated during the reaction, deprotonates the second carbon of the cyclohex-2-en-1-one ring. Subsequently, a *pi* bond forms between the second and third carbon atoms, causing the *pi* bond between the oxygen atom and the third carbon atom to break. This sequence of events leads to the formation of 2-bromo-3-(aryloxy)cyclohex-2-en-1-one (4), the desired product.

Initially, the bromination of 3-(aryloxy)cyclohex-2-en-1-ones (3) at C(2) proved to be challenging, until the discovery that NBS in DMF at 0 °C, followed by warming to rt, gave the required 2-bromo derivatives efficiently. Freshly recrystallized NBS from water was used as a matter of routine, and protection from light was necessary for clean halogenation. The amount of NBS needed to be controlled, with the best results obtained using just 1,1 equiv of the reagent, and DMF as the solvent was found to be important. Using a greater proportion of NBS led to the formation of polybromo compounds.

Before DMF was identified as the best solvent for bromination, other solvents and halogenating agents were examined, but none of them was satisfactory. Attempts to make the desired compounds through substitution reactions were also unsuccessful.

Average yield is 72% for 8 examples (table 2.9).

Table 2.9 – Synthesized 2-bromo-3-(aryloxy)cyclohex-2-en-1-ones

	Name of compound	Time (h)	Yield (%)	State	Melting point (^{o}C)
4a	2-bromo-3-(phenoxy)cyclohex-2-en-1-one	21	84	white solid	-
4b	2-bromo-3-(4-iodophenoxy) cyclohex-2-en-1-one*	24	86	white solid	157–159
4c	2-bromo-3-(4-chlorophenoxy) cyclohex-2-en-1-one*	18	83	white solid	149–150
4d	2-bromo-3-(2,6-dimethoxyphenoxy) cyclohex-2-en-1-one*	2	71	white solid	122–124
4e	2-bromo-3-(2-tert-butylphenoxy) cyclohex-2-en-1-one*	18	62	white solid	103–106
4f	2-bromo-3-(4-tert-butylphenoxy) cyclohex-2-en-1-one*	2	58	white solid	145
4g	methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate*	3,5	90	white solid	122–125
4h	2-bromo-3-{4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy] phenoxy}cyclohex-2-ene-1-one*	44	41	violet solid	-

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*- compounds have not been previously described in literature

2-Bromo-3-(phenoxy)cyclohex-2-en-1-one (4a) is a known compound, that previously was described by Harrowven et al., in 2007 [120]. They synthesized 2-bromo-3-(phenoxy)cyclohex-2-en-1-one (4a) from 3-(phenoxy)cyclohex-2-en-1-one (3a) using NBS in 1,2-dichloroethane (DCE). The reaction goes at 0 ^{o}C to RT, by stirring for 40 h. Yield of the DP is 74%. Other 7 compounds were not previously described in the literature.

The physical and chemical data for compounds 4a-4h were presented, including mass spectrum (table 2.10), IR (table 2.11), ^{1}H NMR (table 2.12), and ^{13}C{^{1}H} NMR (table 2.13) analyses. The spectrometers set for these analyses are listed in Appendix A. Further explanations of each data set for the corresponding compound are provided in their respective sections.

Table 2.10 – Mass spectrum data for compounds 4a-4h

	Ionization technique	Formula	Calculated	Found
4a	Electron Ionization	$C_{12}H_{11}{}^{79}BrO_2$ (M^+)	265,99423	265,99355
4b	Electron Ionization	$C_{12}H_{10}O_2{}^{81}BrI$ (M^+)	393,8880	393,8889
4c	Electron Ionization	$C_{12}H_{10}{}^{81}Br^{35}ClO_2$ (M^+)	301,9532	301,9533
4d	Electrospray Ionization	$C_{14}H_{16}{}^{79}BrO_4$ $(M+H)^+$	327,0226	327,0220
4e	Electrospray Ionization	$C_{16}H_{20}{}^{79}BrO_2$ $(M+H)^+$	322,0568	323,0639
4f	Electron Ionization	$C_{16}H_{19}{}^{79}BrO_2$ (M^+)	322,0569	322,0567
4g	Electron Ionization	$C_{14}H_{13}{}^{79}BrO_4$ (M^+)	323,999730	325,99964
4h	Electrospray Ionization	$C_{18}H_{17}{}^{79}Br_2NaO_4$ $(M+Na)^+$	476,9308	476,9304

Table 2.11 – IR data for compounds 4a-4h

Compound	Wave numbers of absorption bands, ν, cm-1							
	C-H of aromatic ring	C-H$_2$ of aliphatic chain	C=O of ketone group	C=C double bond of cyclohexenone ring	C=C in an aromatic ring	C-C in an aromatic ring	C-Br	Note
4a	3063	2954	1673	1608	1581	1489	1455	-
4b	-	2953	1666	-	1655	1479	1569	-
4c	-	-	1673	1607	-	-	1580	-
4d	-	-	1670	1599	1482	1494	1580	-
4e	-	2957	1674	-	1485	1597	1570	-
4f	3065	-	1665	-	-	-	1570	-
4g	-	-	1680	-	1503	1593	-	1721 (C=O ester)
4h	-	-	1655	1500	-	1417	1589	-

Table 2.12 – ^{1}H-NMR data for compounds 4a-4h

Compound	Chemical shift, ʃ, ppm		
	CH (aromatic protons)	CH$_2$	CH$_3$
4a	7,45–7,41 (m, 2H), 7,30–7,29 (m, 1H) 7,10–7,08 (m, 2H)	2,64-2,61 (m, 2H), 2,44 (t, 2H) 2,02 (p, 2H)	-
4b	7,71 (d, 2 H), 6,82 (d, 2 H)	2,60 (t, 2 H), 2,44 (t, 2 H), 2,01 (p, 2 H)	-
4c	7,39–7,36 (m, 2 H), 7,02 – 7,00 (m, 2 H)	2,61 (t, 2 H), 2,44 (t, 2 H), 2,02 (p, 2 H)	-
4d	7,15 (t, 1 H), 6,63 (d, 2 H)	2,57 (t, 2 H), 2,34 (t, 2 H), 1,96 (p, 2 H)	3,85 (s, 6H)
4e	7,44 (dd, 1 H), 7,24–7,17 (m, 2 H), 6,82 (dd, 1 H)	2,62 (t, 2 H), 2,44 (t, 2 H), 1,98 (p, 2 H)	1,40 (s, 9H)
4f	7,41–7,39 (m, 2 H), 6,99–6,97 (m, 2 H)	2,60 (t, 2 H), 2,45 (t, 2 H), 2,00 (p, 2 H)	1,33 (s, 9H)
4g	8,10 (d, 2 H), 7,10 (d, 2 H)	2,64 (t, 2 H), 2,52 (t, 2 H), 2,07 (p, 2 H)	3,96 (s, 3H)
4h	7,13 (s, 4H)	2,65 (t, 4 H), 2,49 (t, 4 H), 2,05 (p, 4 H)	-

Table 2.13 – $^{13}C\{^{1}H\}$ NMR data for compounds 4a-4h

Compound	Chemical shift, ʃ, ppm							Note
	C=O	C-O Aromatic carbon	C-O	=C-Br	-CH Aromatic carbons	$-CH_2$	$-CH_3$	-
4a	191,2 (s)	170,8 (s)	152,8 (s)	129,6 (s)	125,5 (d), 120,3 (d), 106,1 (d)	36,7 (t), 28,5 (t), 20,4 (t)	-	-
4b	191,5 (s)	170,3 (s)	153,1 (s)	107,5 (s)	139,1 (d), 122,6 (d)	37,1 (t), 28,9 (t), 20,8 (t)	-	89,5 (s) C-I
4c	191,5 (s)	170,5 (s)	151,7 (s)	107,3 (s)	130,1 (d), 121,9 (d)	37,1 (t), 28,9 (t), 20,8 (t)	-	131,3 (s) C-Cl
4d	191,9 (s)	173,3 (s)	152,7 (s)	131,0 (s)	126,6 (d), 105,3 (d)	37,1 (t), 27,5 (t), 20,6 (t)	56,4 (q)	-
4e	191,6 (s)	171,4 (s)	151,7 (s)	106,48 (s)	127,9 (d), 127,2 (d), 125,8 (d) 121,7 (d)	37,3 (t), 29,6 (t), 21,1 (t)	30,3 (q)	141,6 (s) C-*tert*-Bu, 34,8 (s) C-$(CH_3)_3$,
4f	191,7 (s)	171,6 (s)	150,8 (s)	106,0 (s)	126,9 (d) 120,2 (d)	37,2 (t), 29,0 (t), 20,8 (t)	31,4 (q)	149,1 (s) C-*tert*-Bu, 34,6 (s) C-$(CH_3)_3$,
4g	191,4 (s)	169,8 (s)	156,9 (s)	-	131,8 (d) 119,7 (d)	37,1 (t), 29,1 (t), 20,7 (t)	52,3 (q)	166,0 (s) C=O ester, 127,4 (s) C-(CO_2Me),
4h	199,4 (s)	177,9 (s)	150,2 (s)	122,9 (d)	106,2 (d)	36,6 (t), 28,4 (t), 21,1 (t)	-	-

In the FTIR spectra of compounds (4) several shifts in absorption bands are observed comparing with compounds (3). These shifts are associated with the (C-H) stretching vibrations of both the aromatic ring and aliphatic chain, the (C=O) vibration of the ketone group, the (C=C) vibrations of the double bonds in the cyclohexene and phenyl rings, and the (C-C) bending vibration of the phenyl ring. The observed shifts and the introduction of a new absorption band in the FTIR spectrum are a result of changes in the molecular structure of the compounds due to the substitution of a hydrogen atom with a bromine atom in compounds (4).

Bromine is significantly heavier than hydrogen, which directly influences the vibrational frequencies of the involved bonds and thereby alters the absorption bands. The presence of a bromine atom introduces a new vibrational mode, the (C-Br) bending vibration, which adds a new absorption band to the FTIR spectrum of (4) not seen in (3). Finally, the bromine atom, due to its size and electron-withdrawing nature, could impact the molecular environment surrounding the existing functional groups, further contributing to the shifts in the absorption bands. This can even induce a change in the (C-C) bending vibration of the phenyl ring.

In contrasting the ^{1}H NMR spectra of compounds (3a-3h) and (4a-4h) (figures in appendix A), distinct shifts and changes in signal distribution become evident.

The aromatic and aliphatic protons in (4) exhibit signals which display a shift when compared to the signals of (3). Additionally, the ^{1}H NMR spectrum of compounds 4 lacks the singlet at between δ 5,08-5,21 that is present in compounds 3, attributed to the proton on the double bond in the cyclohexene ring.

The observed variances are primarily attributable to modifications in the molecular structure and the proximate electronic environment of the protons.

- Chemical shift changes: These shifts result from the impact of the electron distribution around the protons. The addition of a bromine atom in (4), a much more electronegative element than hydrogen, alters the electron density surrounding nearby protons. This change can lead to a different shielding effect and thus affect the chemical shift of these protons.
- Influence of the bromine atom: Bromine, due to its larger size and different magnetic properties compared to hydrogen, can influence the magnetic field experienced by nearby protons, which can result in shifts in their peaks.
- Absence of the singlet: The disappearance of the singlet corresponding to the proton on the double bond in the cyclohexene ring in (4), compared to its presence in (3), could be due to the bromine substitution, affecting the electronic structure and consequently the chemical environment of this proton.

Analyzing the ^{13}C{^{1}H} NMR spectra of compounds (3a-3h) and (4a-4h), certain shifts are discernible, likely arising from the substitution of a bromine atom in (4).

Carbonyl Carbon: A downfield shift from around 199,2-200,2 ppm (in 3) to 191,2-191,9 ppm (in 4) is noted. This change might be due to the influence of the bromine atom, known for its higher electronegativity compared to hydrogen, which can alter the electronic environment around the carbonyl carbon, reducing its chemical shift.

Aromatic Carbon Attached to Oxygen: The downfield shift is probably a consequence of the bromine substitution as well, altering the electron distribution around the carbon atom connected to the oxygen.

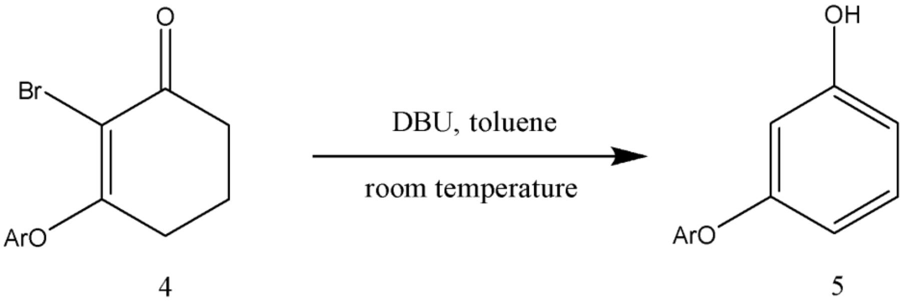
Carbon Adjacent to the Oxygen Atom: A slight upfield shift is seen. Although minor, this alteration may also be due to the effect of the bromine atom in 4, which influences the electron distribution around this carbon atom.

Carbon in the Conjugated Double Bond: A downfield shift suggests changes in the electronic environment due to the introduction of the bromine atom.

2.4 Synthesis of *meta*-aryloxy phenols (5)

In the first chapter, we delineated contemporary progress in the synthesis of *meta*-aryloxy phenols, encompassing a series of reactions such as nucleophilic substitution between aryl halides and resorcinol, Sonogashira coupling, demethylation processes, and the employment of Grignard reagents for the generation of *meta*-aryloxy phenols. Moreover, we examined the advancements in the production of *meta*-substituted phenols derived from *meta*-substituted cyclohex-2-en-1-ones via oxidative aromatization techniques.

In the course of our investigation, we successfully synthesized *meta*-aryloxy phenols (5) by employing 2-bromo-3-(aryloxy)cyclohex-2-en-1-one (4) as a starting material and utilizing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a toluene solvent(scheme 2.25). The reaction was conducted under ambient atmospheric conditions and at rt, typically requiring a duration of approximately two h to complete.

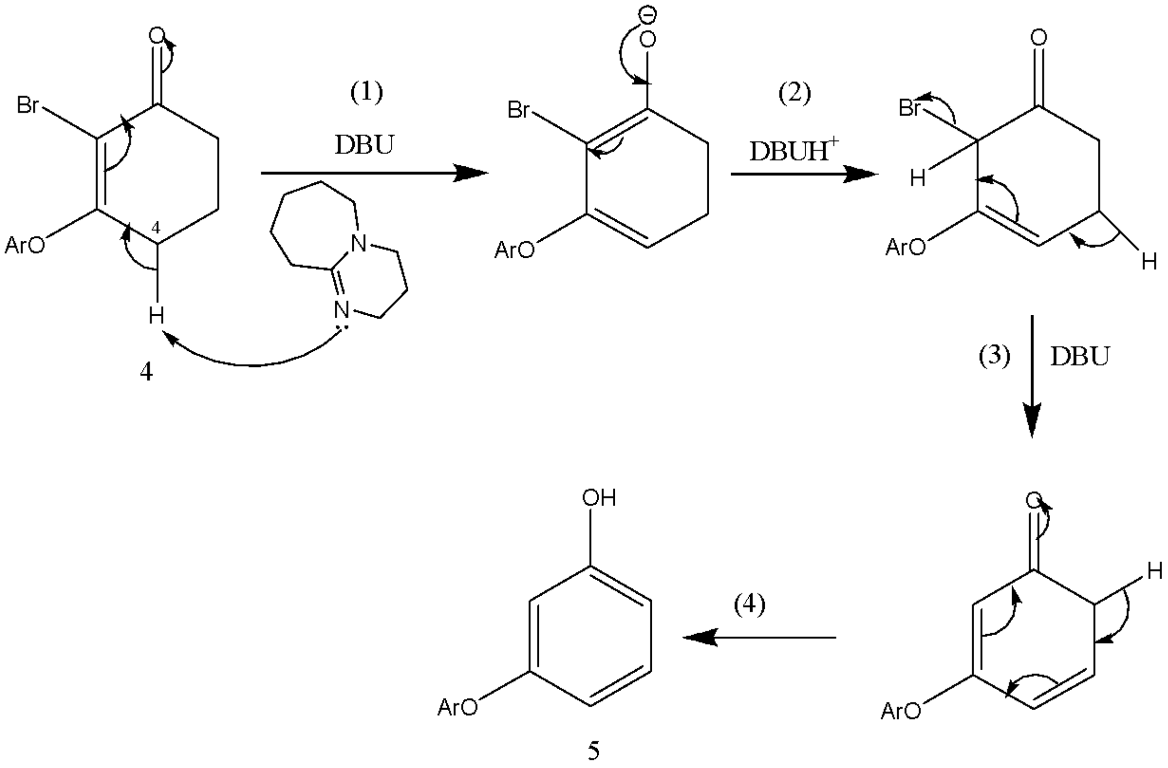


5a: Ar= C_6H_5; **5b:** 4-IC_6H_4; **5c:** 4-ClC_6H_4; **5d:** 2,6-$(MeO)_2C_6H_3$;
5e: 2-t-BuC_6H_4; **5f:** 4-t-BuC_6H_4; **5g:** 4-$(MeO_2C)C_6H_4$; **5h:** C_6H_6BrO-O-C_6H_4-

Scheme 2.25 – Synthesis of *meta*-aryloxy phenols

The reaction mechanism(scheme 2.26) for the synthesis of *meta*-aryloxy phenols (5) from 2-bromo-3-(aryloxy)cyclohex-2-en-1-one (4) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a toluene solvent can be elucidated as follows [113].

DBU, a strong organic base, deprotonates forth carbon in compound 4 which leads to a resonance-stabilized enolate anion (1). The enolate anion undergoes an intramolecular elimination (E2) reaction (2), facilitated by the electron-rich oxygen atom and positively charged protonated DBU ($DBUH^+$). This results in the protonation at C-2.



Scheme 2.26 – The mechanism for the synthesis of *meta*-aryloxy phenols

The second equivalent of the DBU deprotonates (C5) carbon on the cyclic compound (3), that leads to forming a new double bond in (C4) and transferring of the pi bond from (C3) to (C2), and a bromide ion is released as a leaving group. The resulting intermediate undergoes keto-enol tautomerization (4) to form the final *meta*-aryloxy phenol (5) product. The average yield is 66% for 8 compounds(table 2.14).

Table 2.14 – Synthesized *meta*-aryloxy phenols

	Name of compound	Time (h)	Yield (%)	State	Melting point (°C)
5a	3-(phenoxy)phenol	19	86	oil	-
5b	3-(4-iodophenoxy)phenol*	30	58	oil	-
5c	3-(4-chlorophenoxy)phenol	18	55	oil	-
5d	3-(2,6-dimethoxyphenoxy) phenol*	72	75	oil	-
5e	3-(2-*tert*-butylphenoxy)phenol*	72	78	oil	-
5f	3-(4-*tert*-butylphenoxy)phenol	22	86	solid	122–125
5g	methyl 4-[(2-bromo-3oxocyclohex-1-en-1yl)oxy]benzoate*	18	57	colorless gel	-
5h	3-[4-(3-hydroxyphenoxy) phenoxy]phenol	42	31	colorless solid	115–118

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*- compounds have not been previously described in the literature

We chose to let the aromatization reactions proceed for 24 h or longer without strict time constraints. However, we observed through TLC monitoring that the aromatization of the 2,6-dimethoxy compound (4d) and the 2-tert-butyl compound (4e) occurred at a slower rate. It is possible that in these instances, the aromatic substituents obstruct the base's access to the C(4) hydrogens in compounds 4d and 4e.

With compounds containing an electron-withdrawing group, for which we employed 4-iodophenol, 4-chlorophenol and methyl 4-hydroxybenzoate, as the original phenol. Once again, chloride displacement (2→ 3b, 3c,3g) and bromination (3b, 3c, 3g→4b, 4c, 4g) proceeded efficiently; however, treating with DBU in MeCN resulted in the formation of both the desired product (5b, 5c, 5g) and approximately of 4-iodophenol, 4-chlorophenol and methyl 4-hydroxybenzoate (determined by ^{1}H NMR), which was not present in the starting bromides (4b, 4c, 4g). In other instances, the degree of initial nucleophile expulsion must have been minimal, allowing the desired *meta*-(aryloxy)phenol to be isolated in a respectable yield (averaging 66% for 8 examples) using flash chromatography. In all cases, the final aromatized product retained only the substituents present in the starting 3-(aryloxy)enone.

The physical and chemical data for compounds 5a-5h were presented, including mass (table 2.15) IR (table 2.16), ^{1}H NMR (table 2.17), and ^{13}C{^{1}H} NMR (table 2.18) analyses. The spectrometers used for these analyses were listed in Appendix A. Further explanations of each data for the corresponding compound are provided in their respective sections.

Table 2.15 – Mass spectrum data for compounds 4a-4h

	Ionization technique	Formula	Calculated	Found
5a	Electrospray Ionization	$C_{12}H_9O_2$ (M–H)$^-$	185,0608	185,0606
5b	Electrospray Ionization	$C_{12}H_8IO_2$ (M–H)$^-$	310,9574	310,9571
5c	Electrospray Ionization	$C_{12}H_8{}^{35}ClO_2$ (M–H)$^-$	219,0218	219,0216
5d	Electrospray Ionization	$C_{14}H_{13}O_4$ (M–H)$^-$	245,0819	245,0818
5e	Electrospray Ionization	$C_{16}H_{17}O_2$ (M–H)$^-$	241,1234	241,1238
5f	Electrospray Ionization	$C_{16}H_{17}O_2$ (M–H)$^-$	241,1234	241,1232
5g	Electrospray Ionization	$C_{14}H_{11}O_4$ (M–H)$^-$	243,06630	243,06630
5h	Electrospray Ionization	$C_{18}H_{14}O_4$ (M–H)$^-$	293,0819	293,0821

Table 2.16 – IR data for compounds 5a-5h

Compound	Wave numbers of absorption bands, ν, cm-1				
	C-H of aromatic ring	C-OH	C=C in an aromatic ring	C-C in an aromatic ring	Note
5a	3065, 2927	2411	1590	1488	-
5b	3396	1581	1600	1478	-
5c	3407	1588	1600	1484	-
5d	3450	-	1601	1481	-
5e	3392	-	1596	1484	-
5f	3411, 2959	1592	1610	1498	-
5g	3392	1697	1598	-	1719 (C=O ester)
5h	3394	1599	1494	1276, 1137	-

Table 2.17 – ^{1}H-NMR data for compounds 5a-5h

Compound	Chemical shift, ∫, ppm		
	CH (aromatic protons)	OH	CH$_3$
5a	7,36–7,32 (m, 2H), 7,17 (t, 1H) 7,14–7,10 (m, 1H), 7,05 – 7,02 (m, 2H), 6,59 – 6,55 (m, 2H), 6,49 (t, 1H)	4,76 (s, 1H)	-
5b	7,62 (d, 2 H), 7,18 (t, 1 H), 6,79 (d, 2 H), 6,60–6,55 (m, 2 H), 6,49 (t, 1 H)	4,83 (s, 1H)	-
5c	7,31–7,26 (m, 2 H), 7,18 (t, 1 H), 6,98–6,94 (m, 2 H), 6,60–6,55 (m, 2 H), 6,49 (t, 1 H)	4,81 (s, 1H)	-
5d	7,14 (t, 1 H), 7,09 (t, 1 H), 6,66 (d, 2 H), 6,45–6,44 (m, 2 H), 6,35 (t, 1 H)	4,61 (s, 1H)	3,79 (s, 6H)
5e	7,40 (dd, 1 H), 7,18–7,14 (m, 2 H), 7,07 (td, 1 H), 6,87 (dd, 1 H), 6,57–6,53 (m, 2 H), 6,46 (t, 1 H)	4,73 (s, 1H)	1,41 (s, 9H)
5f	7,36–7,35 (m, 2 H), 7,16 (t, 1 H), 6,97–6,95 (m, 2 H), 6,59–6,53 (m, 2 H), 6,47 (t, 1 H)	4,74 (s, 1H)	1,33 (s, 9H)

Extension of the table 2.17			
5g	8,02 (d, 2 H), 7,25 (t, 1 H), 7,03 (d, 2 H), 6,70–6,63 (m, 2 H), 6,58 (t, 1 H)	5,17 (s, 1H)	3,93 (s, 3H)
5h	7,20 (t, 2 H), 7,04 (s, 4 H), 6,61–6,57 (m, 4 H), 6,50 (t, 2 H)	4,96 (br s, 2 H)	-

Table 2.18 – $^{13}C\{^1H\}$ NMR data for compounds 5a-5h

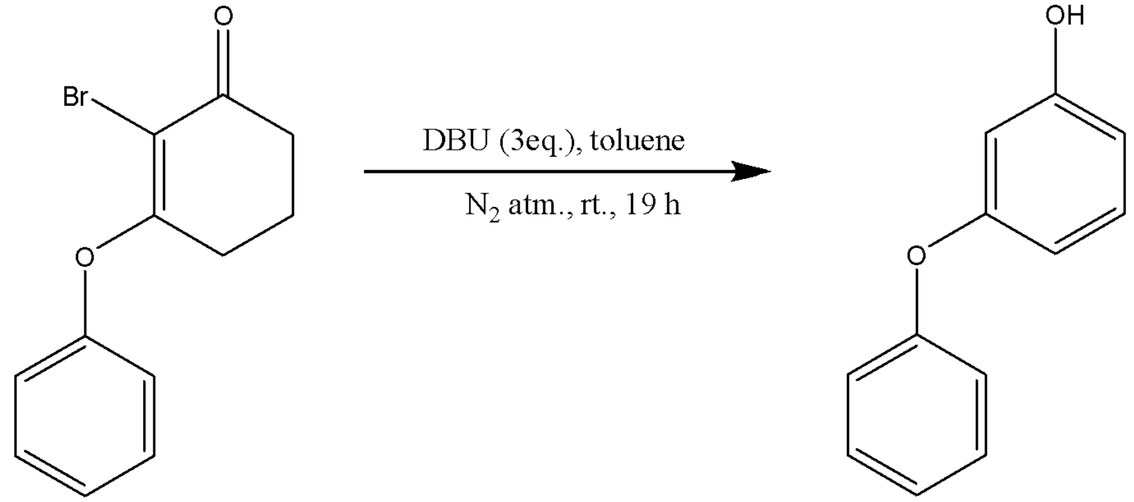
Compound	Chemical shift, ʃ, ppm				Note
	C-OH	C-O Aromatic carbon	-CH Aromatic carbons	-CH$_3$	-
5a	158,8 (s)	156,8 (s), 156,77 (s)	130,5 (d), 129,8 (d), 123,6 (d), 119,4 (d), 111,1 (d), 110,0 (d), 106,0 (d)	-	-
5b	158,0 (s)	157,0 (s), 156,9 (s)	138,7 (d), 130,6 (d), 121,3 (d), 111,2 (d), 110,7 (d), 106,3 (d)	-	86,3 (s) C-I
5c	158,3 (s)	156,9 (s), 155,5 (s)	130,6 (d), 129,8 (d), 120,5 (d), 111,0 (d), 110,6 (d) and 106,1 (d)	-	128,6 (s) C-Cl
5d	159,9 (s)	156,6 (s), 153,6 (s)	130,0 (d), 125,6 (d), 108,6 (d), 107,6 (d), 105,5 (d), 102,3 (d)	56,3 (q)	-
5e	159,3 (s)	156,8 (s), 155,4 (s)	130,4 (d), 127,3 (d), 127,2 (d), 123,6 (d), 120,7 (d), 111,0 (d), 109,6 (d), 105,8 (d)	30,2 (q)	141,2 (s) C-*tert*-Bu
5f	159,2 (s)	156,7 (s), 154,2 (s)	130,3 (d), 126,6 (d), 119,0 (d), 110,8 (d), 109,8 (d), 105,6 (d)	31,5 (q)	146,6 (s) C-*tert*-Bu, 34,4 (s) C-$(CH_3)_3$,
5g	167,1 (s)	161,6 (s), 157,3 (s)	131,7 (d), 130,7 (d), 117,6 (d), 112,0 (d), 111,7(d), 107,4 (d)	52,2 (q)	156,8 (s) C=O ester, 124,4 (s) C-(CO$_2$Me),
5h	159,3 (s)	157,0 (s), 152,4 (s)	130,4 (d), 121,0 (d), 110,4 (d), 110,0 (d), 105,3 (d)	-	-

2.4.1 3-(Phenoxy)phenol (5a)

3-(Phenoxy)phenol have gained considerable attention due to their diverse applications and properties. They serve as valuable intermediates in the synthesis of various organic compounds, including dyes, pharmaceuticals, and agrochemicals. Additionally, they exhibit a wide range of biological activities, such as antioxidant, antimicrobial, and anti-inflammatory properties, which contribute to their potential use in medicinal chemistry [121].

To the best of my knowledge, the initial synthesis of 3-(phenoxy)phenol can be traced back to the work of Armstrong et al. in 1983 [87]. In their research, they successfully synthesized 3-(methoxy)diphenyl ether in a 29% yield through the reaction of phenol and 3-bromoanisole. Subsequently, the resulting compound was subjected to a demethylation process employing boron tribromide as the reagent, which afforded the desired *meta*-(phenoxy)phenol in an appreciable yield of 83%.

In this research, we synthesized 3-(phenoxy)phenol (5a) from 2-bromo-3-(phenoxy)cyclohex-2-en-1-one (4a) using 3 equivalent of DBU and toluene as a solvent(scheme 2.27).



4a

5a
86%

Scheme 2.27 – Synthesis of 3-(phenoxy)phenol

In an effort to synthesize 3-(phenoxy)phenol, we explored various bases and solvents, as detailed in table 2.19. Experiments were conducted with DBU in solvents such as acetonitrile (MeCN), toluene, ethanol, and dimethyl sulfoxide (DMSO) under both rt and reflux conditions. A refluxed reaction using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in MeCN for 48 h yielded 43% of the desired product (DP) with impurities present.

Table 2.19 – Comparing of used solvents and bases in synthesis of 3-(phenoxy)phenol

	Base	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	DBU	MeCN	85	48	53
		MeCN	rt	48	No result
		Toluene	85	48	69
		Toluene	**rt**	**19**	**86**
		EtOH	80	48	54
		EtOH	rt	48	No result
		DMSO	80	70	43
		DMSO	90	44	55
		DMSO	rt	48	No result
2	DBN	MeCN	80	48	43, not pure
		MeCN	rt	48	No result
3	NaOAc	EtOH	rt	48	No result
		EtOH	80	48	36
		EtOH	80	74	57
4	DIPEA	MeCN	80	68	46
		MeCN	rt	48	No result
5	PhONa	MeCN	rt	45	38
		DMF	rt	48	28, not pure
		THF	rt	40	66
6	PhONa and DBU	MeCN	rt	48	40, not pure

When employing sodium acetate in ethanol, we initially observed no significant changes on thin-layer chromatography (TLC) after two days at rt. However, following two days of reflux, a 36% yield of DP was obtained, which increased to 57% after three days of reflux. Utilizing sodium carbonate under reflux for two days resulted in a 30% yield of DP.

A reaction involving *N*,*N*-diisopropylethylamine (DIPEA) in MeCN under reflux for 68 h produced a 46% yield of DP. We also experimented with sodium phenoxide alone in MeCN, DMF, and tetrahydrofuran (THF) under reflux for approximately 40 h. These reactions led to 38%, 28%, and 66% yields of purified DP, respectively. Lastly, the combination of DBU and sodium phenoxide in MeCN yielded a 40% mixture of DP and phenol.

The reaction product (5a) as an oil. Yield 86%. The physicochemical properties of the synthesized 3-(phenoxy)phenol were found to be consistent with previously reported literature data [87].

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(phenoxy)phenol (5a) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3065, 2927 cm^{-1}, the (C-O) of the hydroxyl group at 2411 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1590 cm^{-1}, and the (C-C) bending vibration of the phenyl ring at 1488 cm^{-1}.

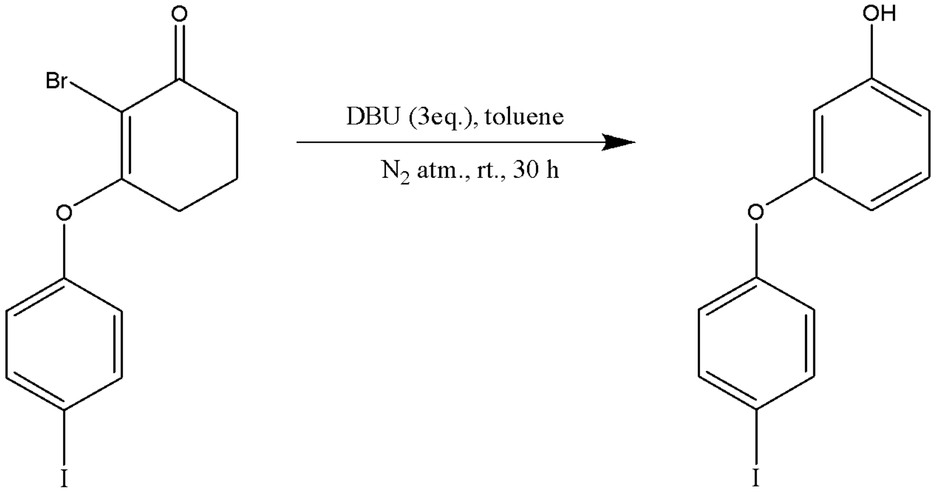
^{1}H NMR spectrum of 3-(phenoxy)phenol (5a) (figure A35), ($CDCl_3$, 500 MHz) shows the following peaks: the signals that appear as multiplets and triplets at δ 7,36–7,32 (m, 2 H), 7,17 (t, *J* = 8,2 Hz, 1 H), 7,14–7,10 (m, 1 H), 7,05–7,02 (m, 2 H), 6,59–6,55 (m, 2 H), 6,49 (t, *J* = 2,3 Hz, 1 H) are assigned to the aromatic protons of the two phenoxy groups; the signal that appears as a singlet at δ 4,76 (s, 1 H of -OH) assigned to the hydroxylic proton.

$^{13}C\{^1H\}$ NMR spectrum of 3-(phenoxy)phenol (5a) (figure A36) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 158,80 as a singlet indicates a carbon attached to the hydroxyl group; the signals that appear at 156,8, 156,77 ppm (singlet) indicates aromatic carbons attached to the oxygen atom; the doublets that appear at 130,5 (d), 129,8 (d), 123,6 (d), 119,4 (d), 111,1 (d), 110,0 (d) and 106,0 (d) correspond to the aromatic carbons;

2.4.2 3-(4-Iodophenoxy)phenol (5b)

3-(4-Iodophenoxy)phenol (5b) is a compound that previously was not described in the literature. The existence of iodine in compound 5b offers potential for additional transformations involving transition metals. Although iodides are compatible with copper-mediated Ullmann reactions [122] it is improbable that they would be well-suited for palladium-mediated variations [123,124] of the Ullmann reaction.

In this research work, we synthesized 3-(4-iodophenoxy)phenol (5b) from 2-bromo-3-(4-iodophenoxy)cyclohex-2-en-1-one (4b) by general synthetic method (scheme 2.25) using 3 equivalent of DBU and toluene(scheme 2.28).



4b

5b
58%

Scheme 2.28 – Synthesis of 3-(4-iodophenoxy)phenol

Reaction is done at rt for 30 h. In this case, we recognized expulsion of 4-iodophenol during the aromatization, which we could not separate by chromatography. Resulting compound contains 8 mol% of 4-iodophenol (^1H NMR). To remove the 4-iodophenol we used a Kugelrohr distillation (0.25 mmHg, oven temperature 110 °C) afforded **5b** (58%).

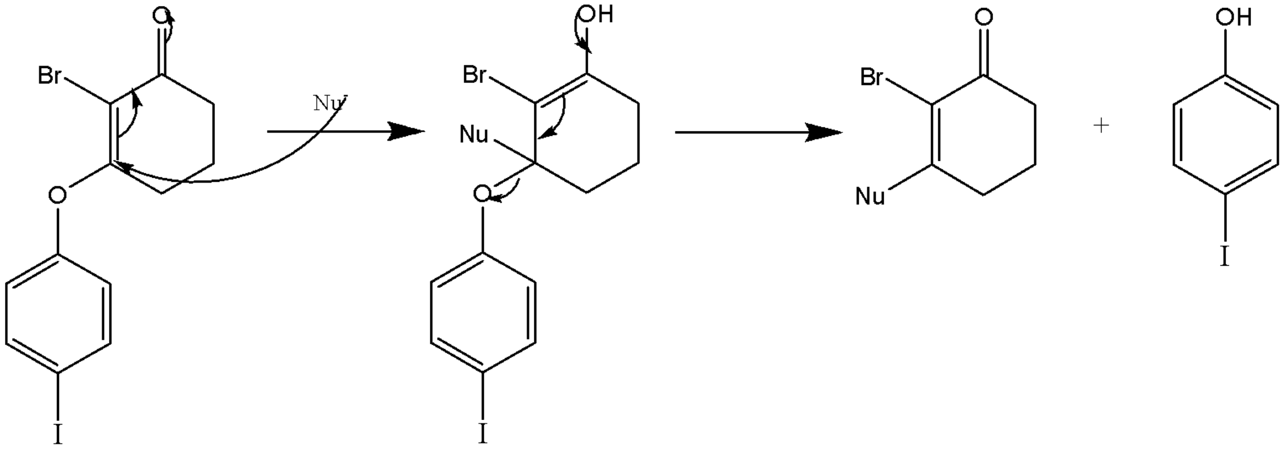
We investigated the impact of solvent choice on the aromatization process by examining the formation of compound 5b. We assessed DMF, DMSO, THF and toluene at rt. Toluene was determined to yield the most favorable outcome, as it minimized the production of unwanted by products(table 2.20).

Table 2.20 – Comparing of used solvents and bases in synthesis of 3-(4-iodophenoxy)phenol

	Solvent	Temperature (°C)	Time (h)	Yield (%) Not pure
1	MeCN	80	24	70
2	MeCN, Ac_2O	80	48	75
3	MeCN	rt	42	63
4	DMSO	rt	23	48
5	**Toluene**	rt	**2**	**86**

With compounds containing an electron-withdrawing group, for which we employed 4-iodophenol, 4-chlorophenol and methyl 4-hydroxybenzoate, as the original phenol, treating with DBU in MeCN resulted in the formation of both the desired product (5b, 5c, 5g) and approximately of 4-iodophenol, 4-chlorophenol and methyl 4-hydroxybenzoate (determined by ^1H NMR), which was not present in the starting bromides (4b, 4c, 4g).

In the current experiments, a competing reaction is observed. Theoretically, the release of the initial phenol (ArOH) might transpire through an addition-elimination mechanism, as outlined in scheme 2.29.



4b

Scheme 2.29 – Expulsion of 4-iodophenol

The reaction product (5b) as an oil. Yield 58%. The identification of the structure of 3-(4-iodophenoxy)phenol (5b) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(4-iodophenoxy)phenol (5b) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3396 cm^{-1}, the (C-O) of the hydroxyl group at 1581 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1600 cm^{-1}, and the (C=C) bending vibration of the phenyl ring at 1478 cm^{-1}.

^{1}H NMR spectrum of 3-(4-iodophenoxy)phenol (5b) (figure A37), ($CDCl_3$, 500 MHz) shows the following peaks: the signals that appear at δ 7,62 (d, *J* = 4,5 Hz, 2 H), 7,18 (t, *J* = 8 Hz, 1 H), 6,79 (d, *J* = 4,5 Hz, 2 H), 6,60–6,55 (m, 2 H), 6,49 (t, *J* = 2,5 Hz, 1 H), are assigned to the aromatic protons in the two phenoxy groups; the signal that appears as a singlet at δ 4,83 (s, 1 H of -OH) assigned to the hydroxylic proton.

^{13}C{^{1}H} NMR spectrum of 3-(4-iodophenoxy)phenol (5b) (figure A38) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 158,0 as a singlet indicates a carbon attached to the hydroxyl group; the signals that appear at 157,0 and 156,9 ppm (singlet) indicate aromatic carbons attached to the oxygen atom; the doublets that appear at 138,7 (d), 130,6 (d), 121,3 (d), 111,2 (d), 110,7 (d), 106,3 (d) correspond to the aromatic carbons; the singlet that appears at 86,3 (s) indicates the aromatic carbon attached to the iodine atom.

2.4.3 3-(4-Chloropenoxy)phenol (5c)

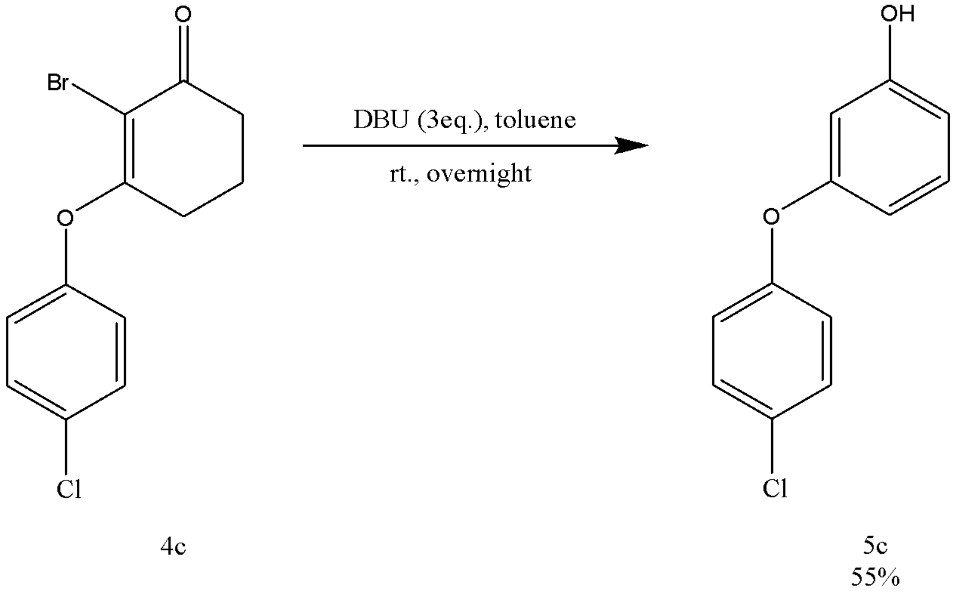
The 3-(4-chlorophenoxy)phenol (5c) demonstrates distinct characteristics stemming from the coexistence of both phenol and chlorophenoxy functional groups, thereby rendering it potentially advantageous for diverse applications.

As a derivative of phenol, 3-(4-chlorophenoxy)phenol (5c) could exhibit antioxidant properties, attributable to the hydroxyl group within the phenol moiety. Phenolic compounds are recognized for their capacity to donate hydrogen atoms or electrons to neutralize free radicals, consequently safeguarding cells from oxidative harm.

The incorporation of the 4-chlorophenoxy group in the compound imparts lipophilic attributes, which may influence its solubility and reactivity in assorted solvents. This characteristic could also affect its potential utility in agricultural or pharmaceutical contexts, such as functioning as a precursor for the synthesis of more intricate molecules or serving as an intermediate in the formulation of biologically active compounds.

The previous methods of the synthesis of 3-(4-chlorophenoxy)phenol (5c) were described in chapter 1. In this research work, we synthesized 3-(4-chlorophenoxy)phenol (5c) from 2-bromo-3-(4-chlorophenoxy)cyclohex-2-en-1-one (4c) using 3 equivalent of DBU in toluene(scheme 2.30). Reaction is done at rt overnight open to the atmosphere. Resulting the purification by column we got 78% of

DP with impurity, which was distilled (Kugelrohr, 0.2 mmHg, oven temperature 110 °C) to afford 5c (55%) containing a small amount of an aromatic impurity.



Scheme 2.30 – Synthesis of 3-(4-chlorophenoxy)phenol

Before toluene was determined as a best solvent, we tried MeCN, THF, DMSO, DMF, but reactions with all solvents gave DP with different amount of impurity (table 2.21).

Table 2.21 – Comparing of used solvents in synthesis of 3-(4-chlorophenoxy)phenol

	Solvent	Temperature (°C)	Time (h)	Yield (%) Not pure
1	MeCN	rt	41	73
2	THF	rt	27	70
3	DMSO	rt	23	43
4	DMSO	90	40	58
5	DMF	rt	24	47
6	Toluene	90	41	77
7	Toluene	rt	18	78

The physicochemical properties of the synthesized 3-(4-chlorophenoxy)phenol (5c) were found to be consistent with previously reported literature data [59].

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(4-chlorophenoxy)phenol (5c) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3407 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1600 cm^{-1}, the (C-O) of the hydroxyl group at 1588 cm^{-1}, and the (C-C) bending vibration of the phenyl ring at 1484 cm^{-1}.

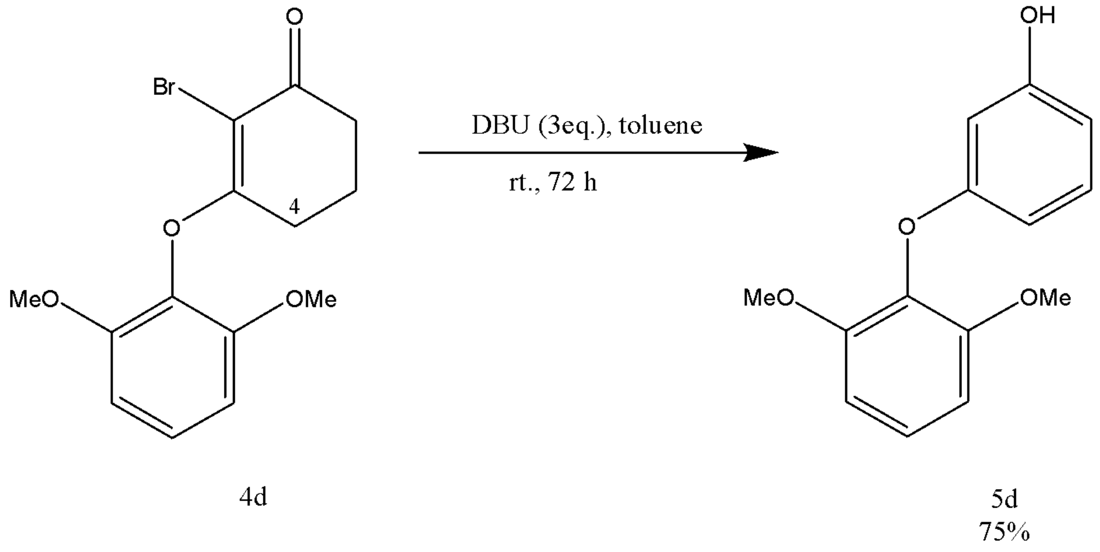
^{1}H NMR spectrum of 3-(4-chlorophenoxy)phenol (5c) (figure A39), (CDCl$_3$, 600 MHz) shows the following peaks: the signals that appear at δ 7,31–7,26 (m, 2 H), 7,18 (t, *J* = 8 Hz, 1 H), 6,98–6,94 (m, 2 H), 6,60–6,55 (m, 2 H), 6,49 (t, *J* = 2,5 Hz, 1 H) are assigned to the aromatic protons in the two phenoxy groups; the signal that appears as a singlet at δ 4,81 (s, 1 H of -OH) assigned to the hydroxylic proton.

^{13}C{^{1}H} NMR spectrum of 3-(4-chlorophenoxy)phenol (5c) (figure A40) (CDCl$_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 158,3 as a singlet indicates a carbon attached to the hydroxyl group; the signals that appear at 156,9 and 155,5 ppm (singlet) indicate aromatic carbons attached to the oxygen atom; the doublets that appear at 130,6 (d), 129,8 (d), 120,5 (d), 111,0 (d), 110,6 (d) and 106,1 (d) correspond to the aromatic carbons; the singlet that appears at 128,6 (s) indicates an aromatic carbon attached to the chlorine atom.

2.4.4 3-(2,6-Dimethoxyphenoxy)phenol (5d)

3-(2,6-Dimethoxyphenoxy)phenol (5d) has not been previously reported in the literature.

The compound (5d) was synthesized from 2-bromo-3-(2,6-dimethoxyphenoxy) cyclohex-2-en-1-one (4d) through the previously described general method(scheme 2.25) using 3 eq. of DBU and toluene at rt for 72 h(scheme 2.31).



Scheme 2.31 – Synthesis of 3-(2,6-dimethoxyphenoxy)phenol

Although we permitted the aromatization reactions to proceed for an arbitrary duration of 24 h or longer, we observed through thin-layer chromatography (TLC) monitoring that the aromatization of 2,6-dimethoxy compound 4d exhibited a slower pace. It is conceivable that, in these instances, the aromatic substituents obstruct the access of the base to the C(4) hydrogens in compound 4d.

The reaction product (5d) as an oil. Yield 75%. The identification of the structure of 3-(2,6-dimethoxyphenoxy)phenol (5d) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(2,6-dimethoxyphenoxy)phenol (5d) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3450 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1601 cm^{-1}, and the (C-C) bending vibration of the phenyl ring at 1481 cm^{-1}.

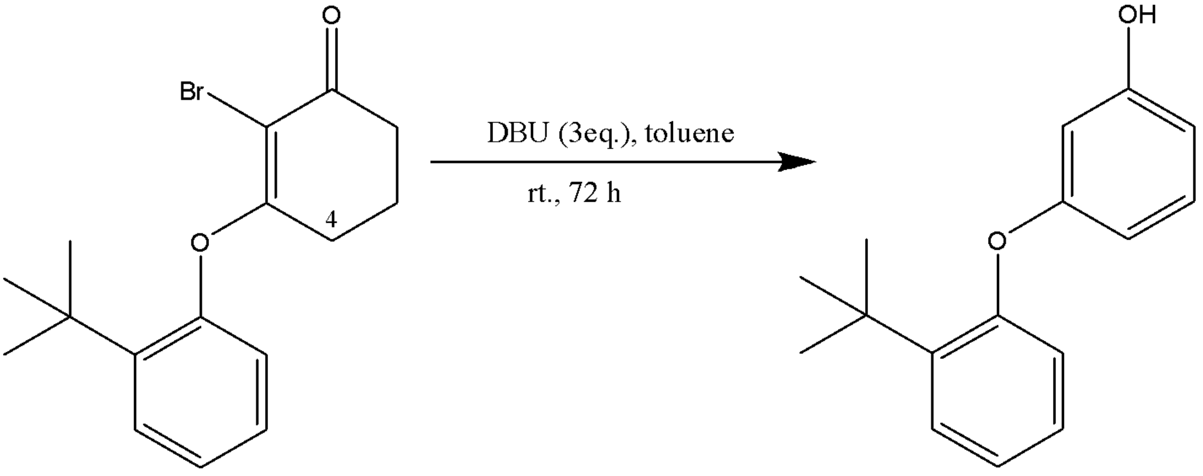
^{1}H NMR spectrum of 3-(2,6-dimethoxyphenoxy)phenol (5d) (figure A41), ($CDCl_3$, 500 MHz) shows the following peaks: the signals that appear at δ 7,14 (t, *J* = 8,5 Hz, 1 H), 7,09 (t, *J* = 8 Hz, 1 H), 6,66 (d, *J* = 8,5, 2 H), 6,45–6,44 (m, 2 H), 6,35 (t, *J* = 2 Hz, 1 H) are assigned to the aromatic protons in the two phenoxy groups; the signal that appears as a broad singlet at δ 4,61 (s, 1 H of -OH) assigned to the hydroxylic proton; the singlet that appears at 3,79 (s, 6H) indicates the six protons of the methyloxy groups.

^{13}C{^{1}H} NMR spectrum of 3-(2,6-dimethoxyphenoxy)phenol (5d) (figure A42) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 159,9 as a singlet indicates a carbon attached to the hydroxyl group; the signals that appear at 156,6, 153,6 ppm (singlet) indicates aromatic carbons attached to the oxygen atom; the doublets that appear at 130,0 (d), 125,6 (d), 108,6 (d), 107,6 (d), 105,5 (d), 102,3 (d) correspond to the aromatic carbons; the quartet that appears at 56,3 (q) indicates the carbons of the methyl groups.

2.4.5 3-(2-*tert*-Butylphenoxy)phenol (5e)

3-(2-*tert*-Butylphenoxy)phenol (5e) has not been previously reported in the literature.

The compound (5e) was synthesized from 2-bromo-3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (4e) through the previously described general method(scheme 2.25) using 3 equivalent of DBU and toluene in a rt for 72 h(scheme 2.32).



4e

5e
78%

Scheme 2.32 – Synthesis of 3-(2-tert-butylphenoxy)phenol

The reaction requires a longer duration as a previous synthesis of 3-(2,6-dimethoxyphenoxy)phenol (5d) because of the aromatic substituents obstruct the access of the base to the C(4) hydrogens in compound 4e.

The reaction product (5e) as an oil. Yield 78%. The identification of the structure of 3-(2-*tert*-butylphenoxy)phenol (5e) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(2-*tert*-butylphenoxy)phenol (5e) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3392 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1596 cm^{-1}, and the (C=C) bending vibration of the phenyl ring at 1484 cm^{-1}.

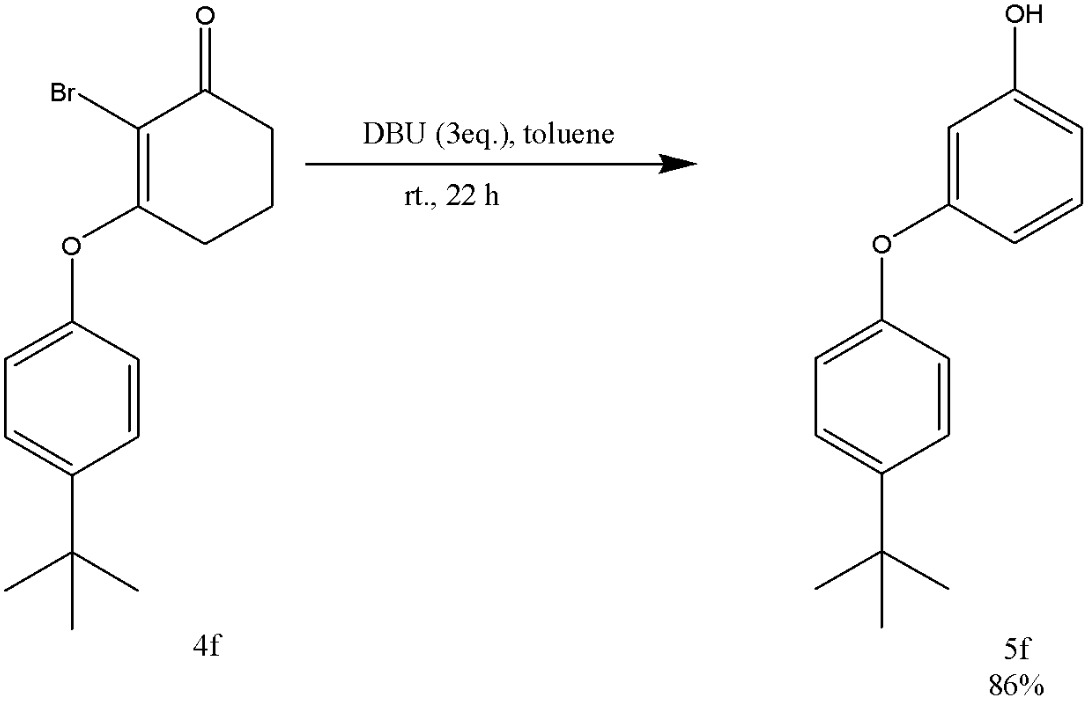
^{1}H NMR spectrum of 3-(2-*tert*-butylphenoxy)phenol (5e) (figure A43), ($CDCl_3$, 600 MHz) shows the following peaks: the signals that appear at δ 7,40 (dd, J = 7,8, 1,2, 1 H), 7,18–7,14 (m, 2 H), 7,07 (td, J = 7,8, 1,2, 1 H), 6,87 (dd, J = 7,8, 1,2, 1 H), 6,57–6,53 (m, 2 H), 6,46 (t, J = 2,4, 1 H) are assigned to the aromatic protons in the two phenoxy groups; the signal that appears as a broad singlet at δ 4,73 (s, 1 H of -OH) assigned to the hydroxylic proton; the singlet that appears at 1,41 (s, 9H) indicates the nine protons of the *tert*-butyl group.

^{13}C{^{1}H} NMR spectrum of 3-(2-*tert*-butylphenoxy)phenol (5e) (figure A44) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 159,3 as a singlet indicates a carbon attached to the hydroxyl group; the signals that appear at 156,8 and 155,4 ppm (singlet) indicate aromatic carbons attached to the oxygen atom; the singlet that appears at 141,2 ppm indicates an aromatic carbon attached to the *tert*-butyl group; the doublets that appear at 130,4 (d), 127,3 (d), 127,2 (d), 123,6 (d), 120,7 (d), 111,0 (d), 109,6 (d) and 105,8 (d) correspond to the aromatic carbons; the quartet appears at 30,2 (q) indicates the carbons of the methyl groups in *tert*-butyl.

2.4.6 3-(4-*tert*-Butylphenoxy)phenol (5f)

3-(4-*tert*-Butylphenoxy)phenol is an organic compound with the molecular formula $C_{16}H_{20}O_2$. It consists of a phenol moiety connected to a 4-*tert*-butylphenoxy group. The presence of both the phenol and the *tert*-butylphenoxy functional groups lends this compound unique properties, which could make it valuable for various applications.

The compound (5f) was synthesized from 2-bromo-3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (4f) through the previously described general method(scheme 2.25) using 3 equivalent of DBU and toluene in a rt for 22 h(scheme 2.33).



Scheme 2.33 – Synthesis of 3-(4-*tert*-butylphenoxy)phenol

The reaction product (5f) as a white solid: mp 122–125 °C. Yield 86%. The physicochemical properties of the synthesized 3-(4-*tert*-butylphenoxy)phenol (5f) were found to be consistent with previously reported literature data [125].

The FTIR (CH_2Cl_2, cast film) spectrum of 3-(4-*tert*-butylphenoxy)phenol (5f) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3411, 2959 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1610 cm^{-1}, the (C-OH) carbon attached to the hydroxyl group the phenyl ring at 1592 cm^{-1}, and the (C=C) bending vibration of the phenyl ring at 1498 cm^{-1}.

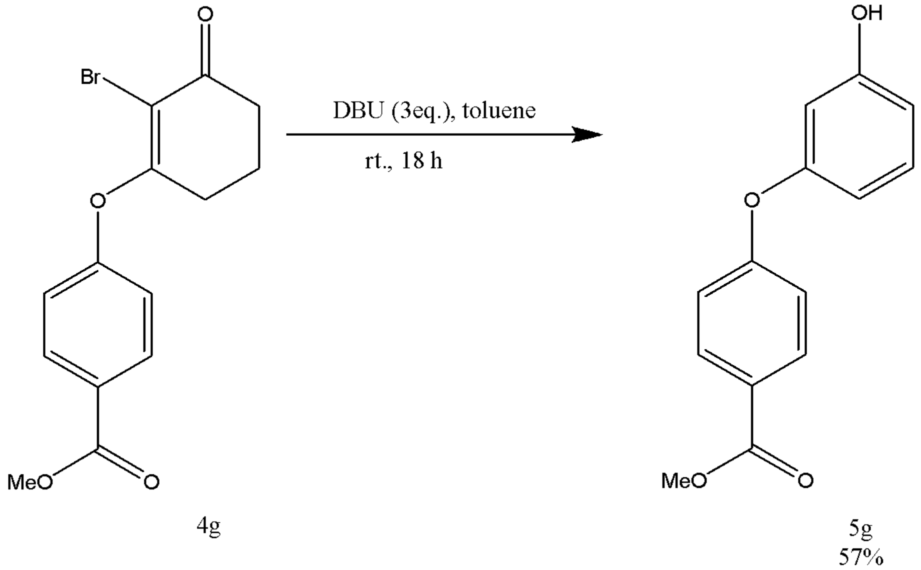
^1H NMR spectrum of 3-(4-*tert*-butylphenoxy)phenol (5f) (figure a45), ($CDCl_3$, 500 MHz) shows the following peaks: the signals that appear at δ 7,36–7,35 (m, 2 H), 7,16 (t, J = 8 Hz, 1 H), 6,97–6,95 (m, 2 H), 6,59–6,53 (m, 2 H), 6,47 (t, J = 2,0, 1 H) are assigned to the aromatic protons in the two phenoxy groups; the signal that appears as a broad singlet at δ 4,74 (s, 1 H of -OH) assigned to the hydroxylic proton; the singlet that appears at 1,33 (s, 9H) indicates the nine protons of the *tert*-butyl group.

$^{13}C\{^1H\}$ NMR spectrum of 3-(4-*tert*-butylphenoxy)phenol (5f) (figure a46) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 159,2 as a singlet indicates a carbon attached to the hydroxyl group; the signals appear at 156,7 and 154,2 ppm (singlet) indicate aromatic carbons attached to the oxygen atom; the singlet that appears at 146,6 ppm indicates the aromatic carbon attached to the *tert*-butyl group; the doublets that appear at 130,3 (d), 126,6 (d), 119,0 (d), 110,8 (d), 109,8 (d), 105,6 (d) correspond to the aromatic carbons; the singlet that appears at 34,4 ppm indicates a central carbon of the *tert*-butyl group attached to the three methyl groups; the quartet that appears at 31,5 (q) indicates the carbons of the methyl groups in *tert*-butyl.

2.4.7 Methyl 4-(3-hydroxyphenoxy)benzoate (5g)

Methyl 4-(3-hydroxyphenoxy)benzoate (5g) has not been previously reported in the literature.

The compound (5g) was synthesized from methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (4g) through the previously described general method (scheme 2.25) using 3 equivalent of DBU and toluene in a rt for 18 h(scheme 2.34).



Scheme 2.34 – Synthesis of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate

After purification by flash chromatography of the residue over silica gel (2 ´ 15 cm), using 20% EtOAc-hexane, gave 5g (89% as an oil which contained some impurities (^{1}H NMR). The material was subjected twice to Kugelrohr distillation under vacuum (0.5 mmHg, oven temp 120–140 °C) to afford 5g (57%) as a colorless gel.

In order to obtain pure 5g, prior to attempting Kugelrohr distillation, we explored the use of methyl 4-hydroxybenzoate sodium salt as a base, both independently and in combination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). We also tested various solvents, including acetonitrile (MeCN), dimethylformamide (DMF), and tetrahydrofuran (THF), as documented in table 2.22.

Table 2.22 – Comparing of used solvents and bases in synthesis of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate

	Base	Solvent	Temperature (^{o}C)	Time (h)	Yield (%) Not pure
1	methyl 4-hydroxybenzoate sodium salt	MeCN	rt	43	More than 100
		DMF	rt	71	81
		THF	65	42	Not pure
2	methyl 4-hydroxybenzoate sodium salt, DBU	MeCN	80	46	Not pure
3	DBU	toluene	rt	2	73
		toluene	rt	18	89
4	dried DBU	toluene	rt	26	90

We have also used azeotropically dried DBU with 4g, as opposed to using the purchased commercial material directly, but this made no difference to the extent of phenol expulsion.

The identification of the structure of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (5g) was accomplished through the use of IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy.

The FTIR (CH_2Cl_2, cast film) spectrum of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (5g) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3392 cm^{-1}, the (C=O) of the ester functional group in the molecule at 1719, the hydroxyl group attached to phenyl ring at 1697 cm^{-1}; and the (C=C) of the double bond in the phenyl ring at 1598 cm^{-1}.

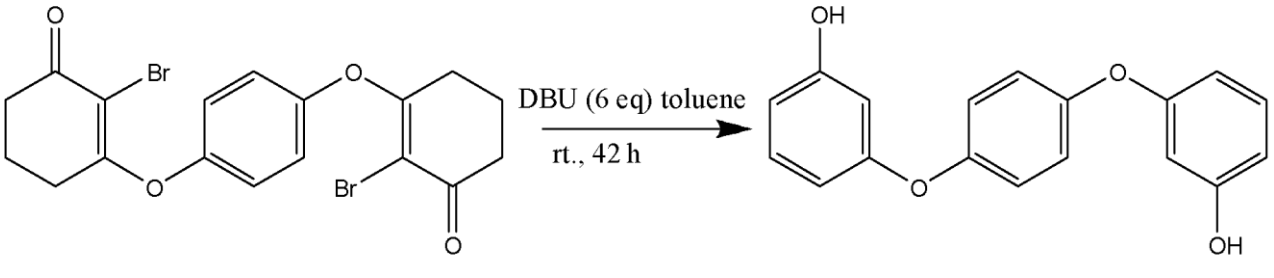
^{1}H NMR spectrum of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (5g) (figure A47), ($CDCl_3$, 500 MHz) shows the following peaks: the signals that appear at δ 8,02 (d, *J* = 8,4 Hz, 2 H), 7,25 (t, *J* = 8,4 Hz, 1 H), 7,03 (d, *J* = 9 Hz, 2 H), 6,70–6,63 (m, 2 H), 6,58 (t, *J* = 2,5 Hz, 1 H) are assigned to the aromatic protons in the two phenoxy groups; the signal that appears as a broad singlet at δ 5,17 (br s, 1 H) assigned to the hydroxylic proton; the singlet that appears at 3,93 (s, 3 H) indicates the three protons of the methyl group.

^{13}C{^{1}H} NMR spectrum of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (5g) (figure A48) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 167,1 as a singlet indicates a carbon attached to the hydroxyl group; the signals that appear at 161,6, 157,3 ppm (singlet) indicating aromatic carbons attached to the oxygen atom; the singlet that appears at 156,8 ppm indicates the carbon of the ester group; the doublets that appear at 131,7 (d), 130,7 (d), 117,6 (d), 112,0 (d), 111,7(d) and 107,4 (d) correspond to the aromatic carbons; the singlet that appears at 124,4 (s) indicates the aromatic carbon attached to the (MeO_2C-) group; the quartet that appears at 52,2 (q) indicates the carbons of the methyl group.

2.4.8 3-[4-(3-hydroxyphenoxy)phenoxy]phenol (5h)

3-[4-(3-Hydroxyphenoxy)phenoxy]phenol is an organic compound with the molecular formula $C_{18}H_{14}O_4$. It is comprised of a phenol moiety connected to a 4-(3-hydroxyphenoxy)phenoxy group. The compound's structure is characterized by the presence of both phenol and hydroxyphenoxy functional groups, which confer unique properties that may be applicable in various fields.

The compound (5h) was synthesized from 2-bromo-3-{4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]phenoxy} cyclohex-2-ene-1-one (4h) through the previously described general method(scheme 2.25) using 6 equivalent of DBU and toluene in a rt for 42 h(scheme 2.35).



4h

5h
31%

Scheme 2.35 – Synthesis of 3-[4-(3-hydroxyphenoxy)phenoxy]phenol

The reaction product (5h) as a solid which contained some aromatic impurities (^{1}H NMR): mp 115–118 °C. Yield 31%. The physicochemical properties of the synthesized 3-[4-(3-hydroxyphenoxy)phenoxy]phenol (5h) were found to be consistent with previously reported literature data [126].

The FTIR (CH_2Cl_2, cast film) spectrum of 3-[4-(3-hydroxyphenoxy)phenoxy]phenol (5h) contains absorption bands of stretching vibrations (C-H) of the aromatic ring in the phenoxy group at 3394 cm^{-1}, the (C-OH) of the hydroxyl group attached to the phenyl ring at 1599 cm^{-1}, the (C=C) of the double bond in the phenyl ring at 1494 cm^{-1}, and the (C-C) bending vibration of the phenyl ring at 1276, 1137 cm^{-1}.

^{1}H NMR spectrum of 3-[4-(3-hydroxyphenoxy)phenoxy]phenol (5h) (figure A49), ($CDCl_3$, 500 MHz) shows the following peaks: the signals that appear at δ 7,20 (t, *J* = 7,97 Hz, 2 H), 7,04 (s, 4 H), 6,61–6,57 (m, 4 H), 6,50 (t, *J* = 1,8 Hz, 2 H) are assigned to the aromatic protons in the two phenoxy groups; the signal that appears as a broad singlet at δ 4,96 (br s, 2 H) assigned to the hydroxylic protons.

$^{13}C\{^1H\}$ NMR spectrum of 3-[4-(3-hydroxyphenoxy)phenoxy]phenol (5h) (figure A50) ($CDCl_3$, 125 MHz) shows signals at the following chemical shifts: The signal that appears at 159,3 as a singlet indicates a carbon attached to the hydroxyl group; the signals that appear at 157,0, 152,4 ppm (singlet) indicates aromatic carbons attached to the oxygen atom; the doublets that appear at 130,4 (d), 121,0 (d), 110,4 (d), 110,0 (d), 105,3 (d) correspond to the aromatic carbons.

2.5 Technological schemes for developed methods

2.5.1 Technological schemes for obtaining compounds 3

The synthesis of 3-aryloxy-cyclohex-2-ene-1-one (3) is accomplished through a refluxing process of 3-chloro-cyclohex-2-ene-1-one (2) with phenol derivatives and potassium carbonate in acetone. The technological process is depicted in figure 2.3.

First, a mixture of acetone, 3-chloro-cyclohex-2-ene-1-one (2), phenol derivatives, and potassium carbonate is supplied in a ratio of 1:1:2 to reactor {1} equipped with a stirrer. The reaction mass is then heated to 65 ^{0}C and stirred until completion.

After completion, the reaction mass is transferred to celite filter {2} where filtration is carried out with dichloromethane (DCM). The filtrate is then dried using anhydrous magnesium sulfate and evaporated {3}. The evaporated DCM is distilled and returned to the filter for reuse.

The residue from the evaporator {3} is passed through a filtration column containing silica gel {4}, where it is cleaned with an ethyl acetate-hexane mixture. The resulting filtrate is evaporated {5} to obtain the desired product in a pure form.

In case of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d) and 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e), DMF was used as a solvent, and refluxing went ar 100 ^{o}C.

To obtain 3-{4-[(3-Oxocyclohex-1-en-1-yl)oxy]phenoxy} cyclohex-2-ene-1-one (3h) a ratio of entered 3-chloro-cyclohex-2-ene-1-one (2), hydroquinone, and potassium carbonate was changed to 2:1:4.

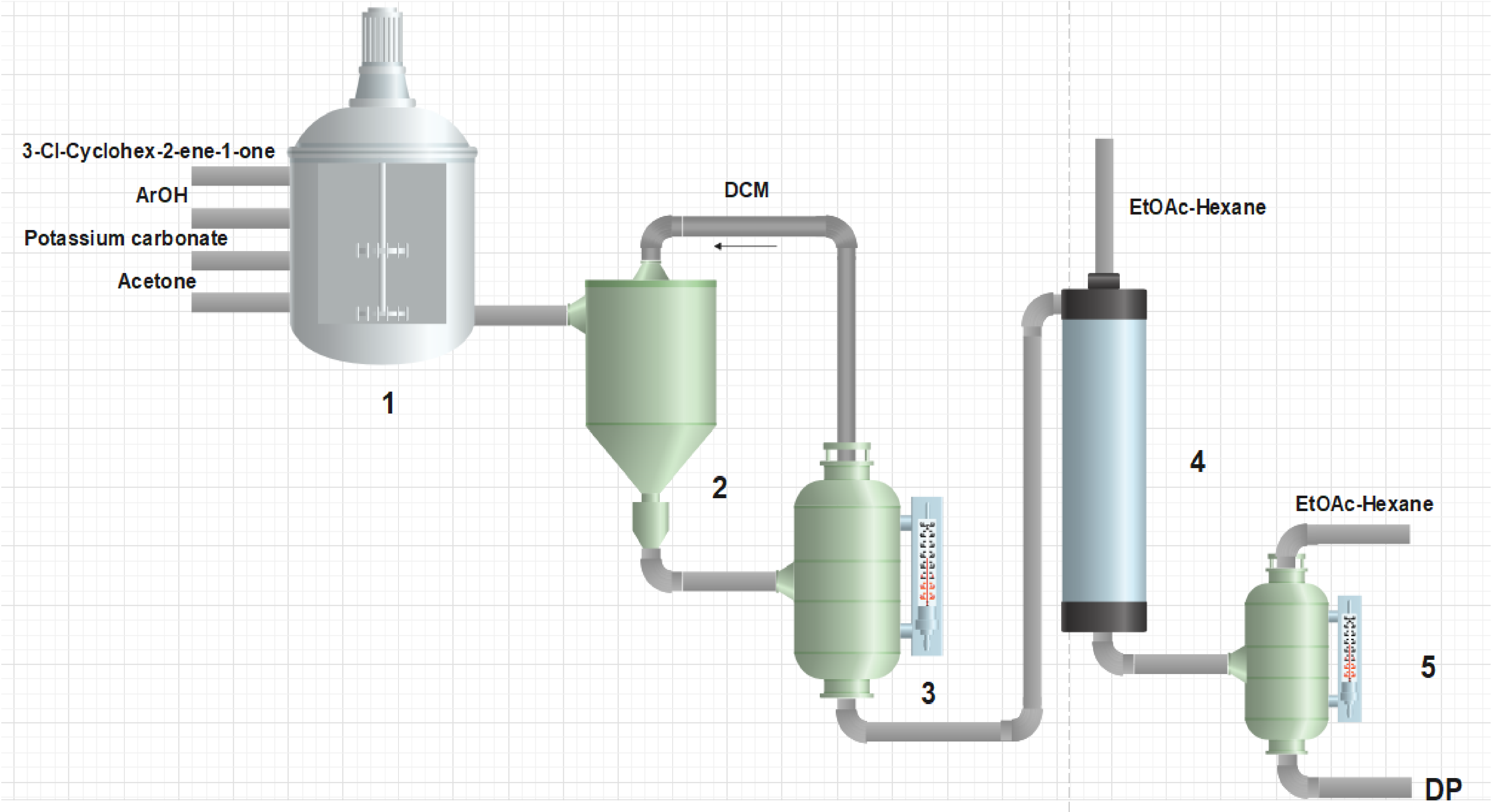
2.5.2 Material balance of 3-aryloxy-cyclohex-2-ene-1-one (3) synthesis

To evaluate the proposed production processes, calculation of the material balance for obtaining 3-aryloxy-cyclohex-2-ene-1-one (3) was calculated for 3-phenoxy-cyclohex-2-ene-1-one (3a).

To obtain ketone (3a) according to the proposed technological scheme used the reaction of interaction of 3-chlorocyclohex-2ene-1-one (2), phenol in the presence of potassium carbonate in acetone. The material balance is calculated for 100 kg of starting material - 3-chlorocyclohex-2enne-1-one (2).

Material balance equation: G1=G2+G3, where G1 is the mass of the initial substances, G2 is the mass of the finished product, G3 is the mass of material losses [127,138].

$$\text{Yield of DP:} \quad \eta = \frac{m\ pract}{m\ teor} \times 100$$



1- Reactor; 2 – filter; 3,5 – evaporators, 4 - filtration column

Figure 2.3 – The technological process for obtaining compounds 3

In the synthesis of 3a yield of DP was 90% or 2,01g. The loss of the original compounds will be 100%-90%=10%

The recirculating solvent is acetone.

Calculations on the material balance of the technological process ketone (3a) production is presented in table 2.23.

Table 2.23 – Material balance of production of 3-phenoxy-cyclohex-2-ene-1-one (3a)

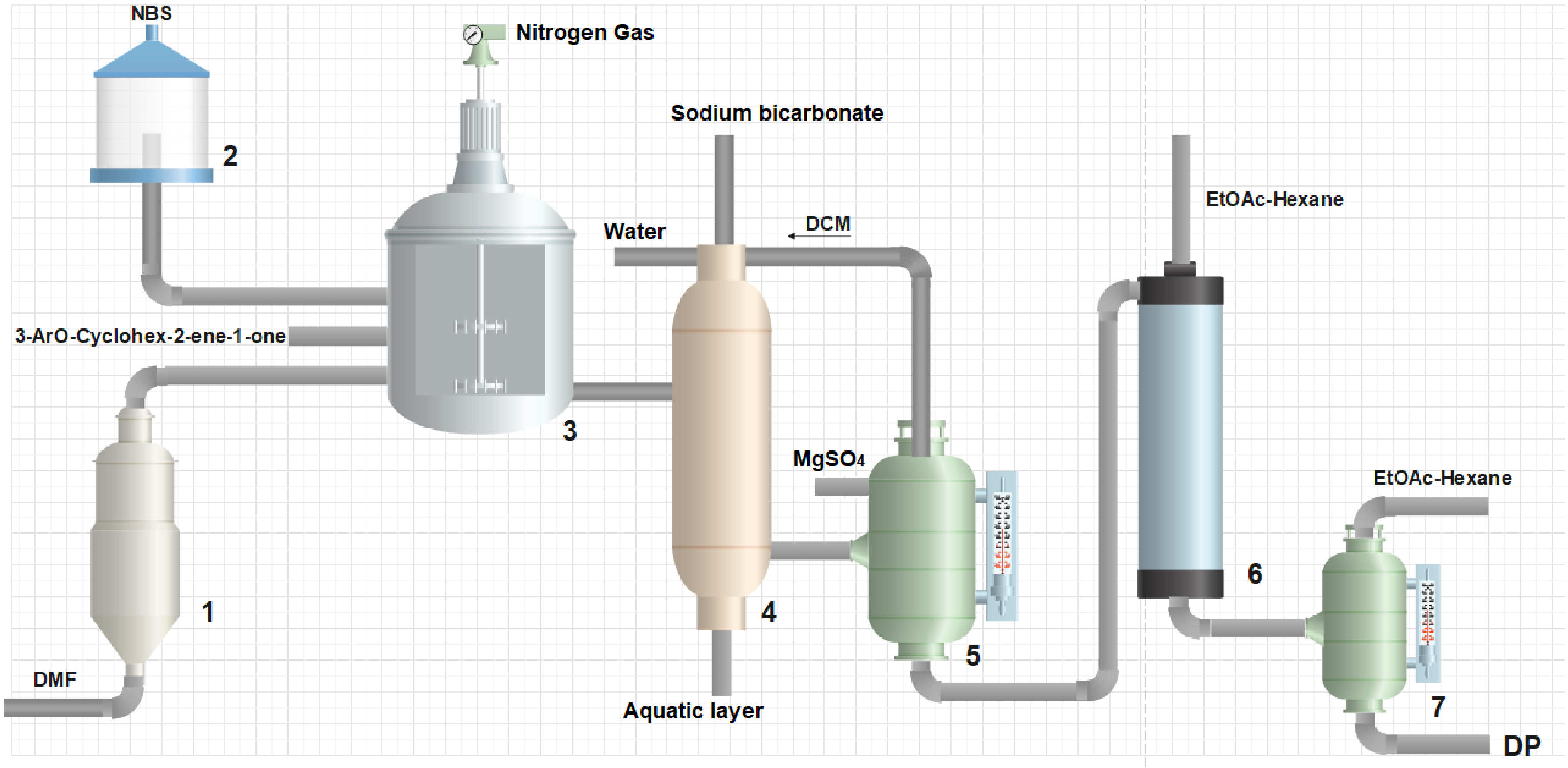
Incoming (kg)		Consumption (kg)	
3-chloro-cyclohex-2-ene-1-one (2)	100	Product: 3-phenoxy-cyclohex-2-ene-1-one (3a)	129,74
Phenol	72,08	SM loses	14,42
K_2CO_3	212,18	KCl	57,10
Acetone	452,60	Recirculate	407,34
		Solvent loses	45,26
		K_2CO_3	159,26
		CO_2	16,85
		Water	6,90
Total	836,86	Total	836,86

2.5.3 Technological schemes for obtaining compounds 4

The synthesis of 2-bromo-(3-aryloxy)cyclohex-2-ene-1-one (4) is accomplished by brominating process of 3-aryloxy-cyclohex-2-ene-1-one (3) with NBS in dry DMF in inert atmosphere at rt (figure 2.4).

Before adding compounds, DMF was distilled in distillatory column {1} and NBS was crystalized from water {2}. A mixture of dry DMF, 3-aryloxy-cyclohex-2-ene-1-one (3) and NBS is supplied in a ratio of 1:1.1 to reactor {3} equipped with a stirrer. The reaction mass is then stirred in nitrogen atmosphere at rt until completion.

After completion, saturated sodium carbonate and water were added to the mixture and organic layer was separated from aquatic layer by using DCM as a rinse {4}. Residue of the reaction was dried and evaporated from DCM in the evaporator {5}. Evaporated DCM was cleaned for reuse. The residue from the evaporator {5} is passed through a filtration column containing silica gel {6}, where it is cleaned with an ethyl acetate-hexane mixture. The resulting filtrate is evaporated {7} to obtain the desired product in a pure form.



1 – distillator; 2 - crystallizer; 3 - reactor; 4 – separator; 5,7 – evaporators, 6 - filtration column

Figure 2.4 – The technological process for obtaining compounds 4

2.5.4 Material balance of (4) synthesis

To evaluate the proposed production processes, calculation of the material balance for obtaining 2-bromo-(3-aryloxy)cyclohex-2-ene-1-one (4) was calculated for 2-bromo-(3-phenoxy)cyclohex-2-ene-1-one (4a).

To obtain (4a) according to the proposed technological scheme used the reaction of interaction of 3-phenoxy-cyclohex-2ene-1-one (3a) with NBS in DMF. The material balance is calculated for 100 kg of starting material (3a).

Material balance equation: G1=G2+G3, where G1 is the mass of the initial substances, G2 is the mass of the finished product, G3 is the mass of material losses.

$$\text{Yield of DP:} \quad ŋ = \frac{m\,pract}{m\,teor} \times 100\%$$

In the synthesis of 4a yield of DP was 84% or 128.7 mg. The loss of the original compounds will be 100%-84%=16%

The recirculating solvent is DMF.

Calculations on the material balance of the technological process (4a) production is presented in table 2.24.

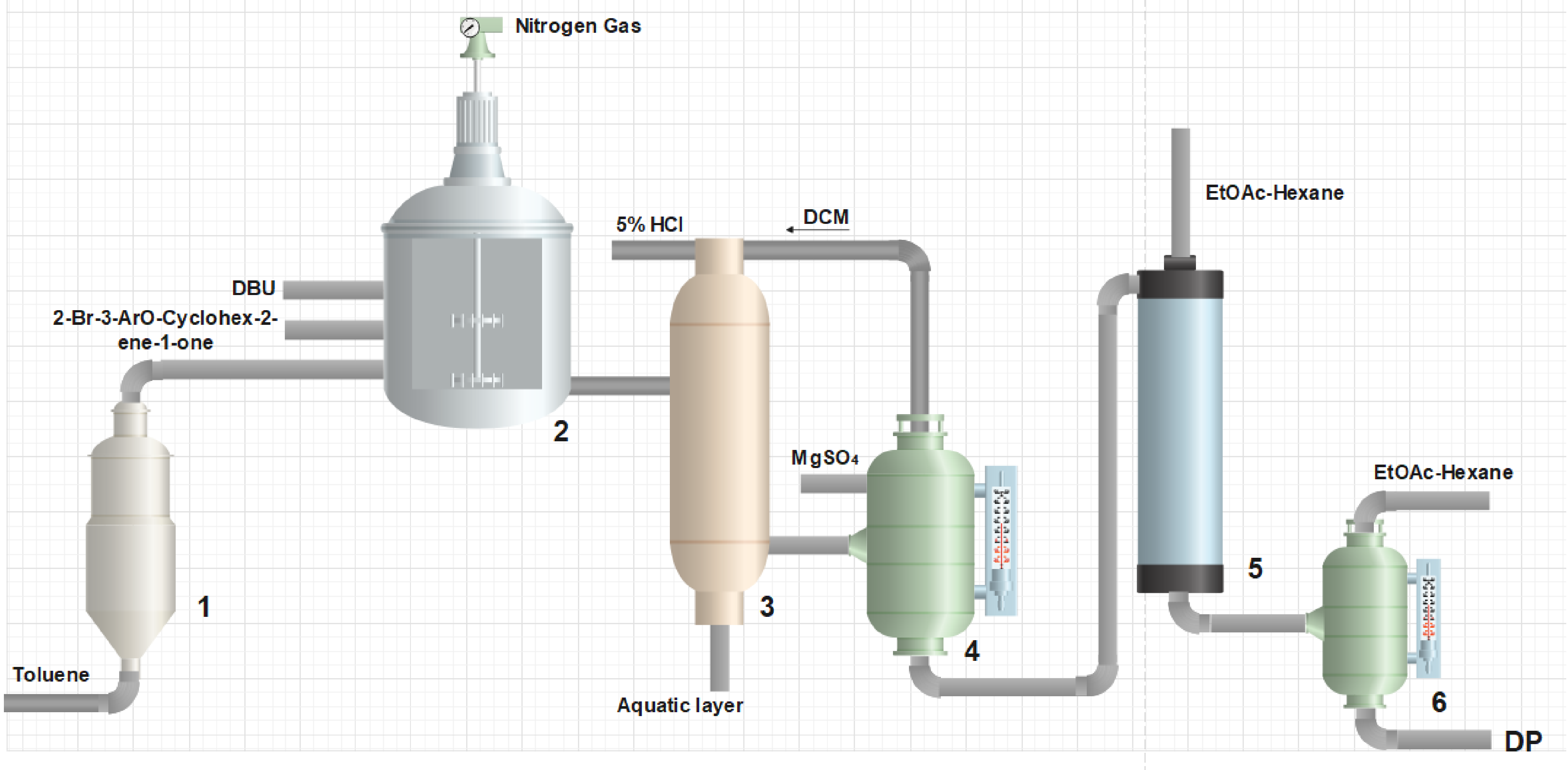
Table 2.24 – Material balance of production of 2-bromo-(3-phenoxy)cyclohex-2-ene-1-one (4a)

Incoming (kg)		Consumption (kg)	
3-phenoxy-cyclohex-2-ene-1-one (3a)	100	Product: 2-bromo-(3-phenoxy)cyclohex-2-ene-1-one (4a)	119,21
NBS	104,02	SM loses	22,71
DMF	189,6	Succinimide	52,65
		Recirculate	160,6
		Solvent loses	29
		NBS	9,45
Total	393,62	Total	393,62

2.5.5 Technological schemes for obtaining compounds 5

The synthesis of *meta*-aryloxy phenol (5) is accomplished by aromatization process of 2-bromo-(3-aryloxy)cyclohex-2-ene-1-one (4) with DBU in dry toluene in inert atmosphere at rt. The technological process is depicted in figure 2.5.

Before adding compounds, toluene was distilled in distillatory column {1}. To the dry toluene 2-bromo-(3-aryloxy)cyclohex-2-ene-1-one (4) and DBU is supplied in a ratio of 1:3 to reactor {3} equipped with a stirrer.



1 – distillator; 2 - reactor; 3 – separator; 4,6 – evaporators,   5 - filtration column

Figure 2.5 – The technological process for obtaining compounds 5

The reaction mass is then stirred in nitrogen atmosphere at rt until completion.

After completion, 5% aqueous hydrogen chloride was added to the mixture and organic layer was separated from aquatic layer by using DCM as a rinse {3}. Residue of the reaction was dried and evaporated from DCM in the evaporator {4}. Evaporated DCM was cleaned for reuse. The residue from the evaporator {4} is passed through a filtration column containing silica gel {5}, where it is cleaned with an ethyl acetate-hexane mixture. The resulting filtrate is evaporated {6} to obtain the desired product in a pure form.

2.5.6 Material balance of compound (5) synthesis

To evaluate the proposed production processes, calculation of the material balance for obtaining *meta*-aryloxy phenol (5) was calculated for 3-(phenoxy)phenol (5a). To obtain (5a) according to the proposed technological scheme used the reaction of interaction of (4a) with DBU in toluene. The material balance is calculated for 100 kg of starting material (4a).

In the synthesis of 5a yield of DP was 86% or 175,0 mg. The loss of the original compounds will be 100%-86%=14%

The recirculating solvent is a toluene.

Calculations on the material balance of the technological process (5a) production is presented in table 2.25.

Table 2.25 – Material balance of production of 3-(phenoxy)phenol (5a)

Incoming (kg)		Consumption (kg)	
2-bromo-(3-phenoxy)cyclohex-2-ene-1-one (4a)	100	Product: 3-(phenoxy)phenol (5a)	59,95
DBU	170,98	SM loses	9,76
Toluene	173,40	HBr	30,29
		Recirculate	156,90
		Solvent loses	16,50
		DBU	170,98
Total	444,38	Total	444,38

3 EXPERIMENTAL SECTION

- Solvents used for chromatography were distilled before use.
- Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used.
- Silica gel for flash chromatography was Merck type 60 (230−400 mesh).
- Dry solvents were prepared under an inert atmosphere (N_2) and transferred by syringe or cannula.
- Anhydrous K_2CO_3 was stored in an oven.
- In step gradient chromatography ca 100-mL portions were used with 10% increases of the more polar component.
- NBS was freshly recrystallized from water and dried under oil pump vacuum. The brominations were done under an inert atmosphere (N_2).
- The symbols s, d, t, and q used for $^{13}C\{^1H\}$ NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra.
- Solutions were evaporated under water pump vacuum, and the residue was then kept under oil pump vacuum.
- High resolution electrospray mass spectrometric analyses were done with an orthogonal time-of-flight analyzer, and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer.

*3-Chlorocyclohex-2-en-1-one (**2**).* $(COCl)_2$ (4,8 mL, 55 mmol) was added from a sidearm addition funnel over 30 min to a stirred and cooled (0 °C) solution of cyclohexane-1,3-dione (5,01 g, 44,7 mmol) in bench CH_2Cl_2 (111 mL) containing bench DMF (4,6 mL, 59,4 mmol) (HCl evolution). After the addition the ice bath was removed and stirring was continued for 2,5 h. Water (120 mL) was added and the mixture was extracted with Et_2O (3 · 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 · 15 cm), using 20% EtOAc-hexane, gave **2** (4,865 g, 83%) as a yellow oil: FTIR (CH_2Cl_2, cast film) 3200, 2955, 2927, 1717, 1680, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6,22 (t, J = 1,5 Hz, 1 H), 2,68 (td, J = 6,1, 1,5 Hz, 2 H), 2,43–2,40 (m, 2 H), 2,08 (pentet, J = 6,3 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 196,8 (s), 158,7 (s), 128,5 (d), 36,3 (t), 33,9 (t), 22,2 (t); exact mass (EI) *m/z* calcd for $C_6H_7{}^{35}ClO$ (M^+) 130,0854, found 130,01844.

*3-(Phenoxy)cyclohex-2-en-1-one (**3a**).* Phenol (1,02 g, 10,8 mmol) was added to a solution of 3-chlorocyclohex-2-en-1-one (1,56 g, 11,9 mmol) in reagent grade acetone (9 mL). Anhydrous K_2CO_3 (3,08 g, 22,3 mmol) was tipped into the solution and the mixture was stirred and refluxed for 20 h open to the atmosphere. The reaction mixture was allowed to cool to rt and filtered through a sintered disc funnel containing a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2,5 · 15 cm), using successive portions of EtOAc-hexane from 25% EtOAc to 50% EtOAc, gave **3a** (2,01 g, 90%) as a pale yellow oil that crystallized in the fridge to form a white solid: FTIR (CH_2Cl_2, cast film) 3065, 2951, 2894, 2873, 1661, 1617, 1587, 1488 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,42–7,39 (m, 2 H), 7,29–7,24 (m, 1 H), 7,06–7,04 (m, 2 H), 5,14 (s, 1 H), 2,65 (t, J = 6,3 Hz, 2 H), 2,41–2,38 (m, 2 H), 2,08 (pentet, J = 6,5 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 199,6 (s), 178,3 (s), 152,7 (s), 130,0 (d), 126,1 (d), 121,4 (d), 106,1 (d), 36,7 (t), 28,6 (t), 21,2 (t); exact mass (EI) m/z calcd for $C_{11}H_{12}O_2$ (M^+) 188,08372, found 188,08356.

*3-(4-Iodophenoxy)cyclohex-2-en-1-one (**3b**).* 4-Iodophenol (200 mg, 0,913 mmol) was added to a solution of 3-chlorocyclohex-2-en-1-one (131 mg, 1,0 mmol) in reagent grade acetone (12 mL). K_2CO_3 (272 mg, 1,97 mmol) was tipped into the solution and the mixture was stirred and refluxed for 20 h open to the atmosphere (no protection from light). The reaction mixture was allowed to cool to rt and filtered through a sintered disc funnel containing a pad (2 thick · 3 cm wide) of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 · 20 cm), using 40% EtOAc-hexane, gave **3b** (274 mg, 92%) as an oil which slowly crystallized: mp 69–75 °C; FTIR (CH_2Cl_2, cast film) 2949, 1666, 1653, 1611, 1479 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,70 (d, J = 9 Hz, 2 H), 6,80 (d, J = 9 Hz, 2 H), 5,11 (s, 1 H), 2,63 (t, J = 7 Hz, 2 H), 2,37 (t, J = 7 Hz, 2 H), 2,08 (pentet, J = 6,5 Hz, 2 H); $^{13}C\{^1H\}$ ($CDCl_3$, 125 MHz) δ 199,3 (s), 177,7 (s), 152,6 (s), 139,1 (d), 123,6 (d), 106,3 (d), 90,0 (s), 36,6 (t), 28,4 (t), 21,1 (t); exact mass (ESI) m/z calcd for $C_{12}H_{12}IO_2$ $(M+H)^+$ 313,9876, found 313,9878.

*3-(4-Chlorophenoxy)cyclohex-2-en-1-one (**3c**).* 4-Chlorophenol (149 mg, 1,14 mmol) was added to a solution of 3-chlorocyclohex-2-en-1-one (100 mg, 0,80 mmol) in reagent grade acetone (2 mL). Anhydrous K_2CO_3 (200 mg, 1,45 mmol) was tipped into the solution and the mixture was stirred and refluxed overnight open to the atmosphere. The reaction mixture was allowed to cool to rt and filtered through a sintered disc funnel containing a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 · 15 cm), using 30% EtOAc-hexane, gave **3c** (200 mg, 82%) as a white solid: mp 72–75 °C; FTIR (CH_2Cl_2, cast film) 1655, 1614, 1486, 1374 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,37–7,35 (m, 2 H), 6,99–6,96 (m, 2 H), 5,10 (s, 3 H), 2,64 (t, J = 6,5 Hz, 2 H), 2,37 (t, J = 6,5 Hz, 2 H), 2,07 (pentet, J = 6,5 Hz, 2 H); $^{13}C\{^1H\}$($CDCl_3$, 175 MHz) δ 199,3 (s), 177,8 (s), 151,2 (s), 131,6 (s), 130,2 (d), 122,8 (d), 106,2 (d), 36,6 (t), 28,5 (t), 21,2 (t); exact mass (ESI) m/z calcd for $C_{12}H_{11}{}^{35}ClO_2$ (M^+) 222,0448, found 222,0445.

*3-(2,6-Dimethoxyphenoxy)cyclohex-2-en-1-one (**3d**).* 2,6-Dimethoxyphenol (50 mg, 0,40 mmol) was added to a solution of 3-chlorocyclohex-2-en-1-one (60 mg, 0,45 mmol) in dry DMF (3 mL). K_2CO_3 (110 mg, 0,80 mmol) was tipped into the solution and the mixture was stirred and heated at 100 °C for 24 h open to the atmosphere. The reaction mixture was allowed to cool to rt and filtered through a sintered disc funnel containing a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 · 15 cm), using 20% EtOAc-CH_2Cl_2 gave **3d** (52 mg, 52%) as a white solid: mp 76–78 °C; FTIR (CH_2Cl_2, cast film) 1651, 1619, 1585, 1482 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,12 (t, J = 8,5 Hz, 1 H), 6,60 (d, J = 8,5 Hz, 2 H), 5,08 (s, 1 H), 3,80 (s, 6 H), 2,70 (t, J = 6,5 Hz, 2 H), 2,37 (t, J = 6,5 Hz, 2 H), 2,08 (pentet, J = 6,5 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 200,2 (s), 177,8 (s), 152,3 (s), 130,2 (s), 126,5 (d), 105,1 (d), 104,8 (d), 56,1 (q), 36,7 (t), 28,0 (t), 21,3 (t); (EI) *m*/*z* calcd for $C_{14}H_{16}O_4$ $(M)^+$ 248,10486, found 248,10488.

*3-(2-tert-Butylphenoxy)cyclohex-2-en-1-one (**3e**).* 2-*tert*-Butylphenol (95 mg, 0,63 mmol) was added to a solution of 3-chlorocyclohex-2-en-1-one (100 mg, 0,76 mmol) in dry DMF (6 mL). K_2CO_3 (140 mg, 1,0 mmol) was tipped into the solution and the mixture was stirred and heated at 100 °C for 24 h open to the atmosphere. The reaction mixture was allowed to cool to rt and filtered through a sintered disc funnel containing a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate under water pump vacuum and then under oil pump vacuum followed by flash chromatography of the residue over silica gel (2 · 15 cm), using 30% EtOAc-hexane, gave **3e** (52 mg, 48%) as a yellowish oil: FTIR (CH_2Cl_2, cast film) 2957, 1663, 1617, 1599, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7,39 (dd, J = 7,8, 1,8 Hz, 1 H), 7,18–7,13 (m, 2 H), 6,91 (dd, J = 7,8, 1,8 Hz, 1 H), 5,21 (s, 1 H), 2,67 (t, J = 6 Hz, 2 H), 2,39 (t, J = 6 Hz, 2 H), 2,09 (pentet, J = 6 Hz, 2 H), 1,32 (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 199,5 (s), 177,9 (s), 151,3 (s), 141,5 (s), 127,8 (d), 127,2 (d), 125,8 (d), 123,0 (d), 106,7 (d), 36,6 (t), 34,6 (s), 30,3 (q), 28,9 (t), 21,2 (t); (EI) *m*/*z* calcd for $C_{16}H_{20}O_2$ (M^+) 244,14633, found 244,13634.

*3-(4-tert-Butylphenoxy)cyclohex-2-en-1-one (**3f**).* 4-*tert*-Butylphenol (159 mg, 1,10 mmol) was added to a solution of 3-chlorocyclohex-2-en-1-one (171 mg, 1,32 mmol) in reagent grade acetone (6 mL). K_2CO_3 (292 mg, 2,11 mmol) was tipped into the solution and the mixture was stirred and refluxed for 43 h open to the atmosphere. The reaction mixture was allowed to cool to rt and filtered through a sintered disc funnel containing a pad of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 · 15 cm), using 30% EtOAc-hexane, gave **3f** (225 mg, 83%) as a white solid: mp 92–96 °C; FTIR (CH_2Cl_2, cast film) 2962, 1669, 1656, 1616 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,39–7,37 (m, 2 H), 6,95–6,93 (m, 2 H), 5,12 (s, 1 H), 2,65 (t, J = 7 Hz, 2 H), 2,37 (t, J = 7 Hz, 2 H), 2.08 (pentet, J = 7,0 Hz, 2 H), 1,32 (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 199,9 (s), 178,7 (s), 150,4 (s), 149,2 (s), 126,9 (d), 120,8 (d), 106,0 (d), 36,7 (t), 34,6 (s), 31,5 (q), 28,6 (t), 21,3 (t); exact mass (EI) *m/z* calcd for $C_{16}H_{20}O_2$ (M^+) 244,1463, found 244,1461.

*Methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (**3g**).* Methyl 4-hydroxybenzoate (739,9 mg, 4,863 mmol) was tipped into a solution of 3-chlorocyclohex-2-en-1-one (685,0 mg, 5,246 mmol) in reagent grade acetone (13 mL). K_2CO_3 (1,50 g, 10,9 mmol) was tipped into the solution and the mixture was stirred and refluxed for 18 h open to the atmosphere. The reaction mixture was allowed to cool to rt, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 · 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2,5 · 15 cm), using successive portions of EtOAc-hexane from 20% EtOAc to 50% EtOAc, gave **3g** (1,121 g, 93%) as a white solid: mp 100–104 °C; FTIR (CH_2Cl_2, cast film) 1724, 1668, 1620, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8,10 (d, J = 9 Hz, 2 H), 7,12 (d, J = 9 Hz, 2 H), 5,16 (s, 1 H), 3,95 (s, 3 H), 2,67 (t, J = 6,6 Hz, 2 H), 2,41 (t, J = 6,6 Hz, 2 H), 2,11 (pentet, J = 6,6 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 199,3 (s), 177,2 (s), 166,1 (s), 156,4 (s), 131,8 (d), 128,0 (s), 121,4 (d), 106,7 (d), 52,3 (q), 36,6 (t), 28,4 (t), 21,13 (t); (ESI) *m/z* calcd for $C_{14}H_{15}O_4$ $(M+H)^+$ 247,09650, found 247,0967.

*3-{4-[(3-Oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (**3h**).* Hydro-quinone (474,4 mg, 4,31 mmol) was tipped into a solution of 3-chlorocyclohex-2-en-1-one (1,12 g, 8,61 mmol) in dry acetone (15 mL). K_2CO_3 (2,38 g, 17,25 mmol) was tipped into the solution and the mixture was stirred and heated at 60 °C for 43 h open to the atmosphere (no protection from light). The reaction mixture was allowed to cool to rt and filtered through a pad of Celite (3 · 2 cm high), using CH_2Cl_2 as a rinse and the filtrate was evaporated. Flash chromatography of the residue over silica gel (2.5 · 15 cm), using 30% EtOAc-hexane (50 mL), 40% EtOAc-hexane (100 ml), 50% EtOAc-hexane (200 mL), 60% EtOAc-hexane (200 mL), 70% EtOAc-hexane (100 mL), 80% EtOAc-hexane (100 mL), gave **3h** (912,5 mg, 71%) as a light orange powder: mp 209–212 °C; FTIR (CH_2Cl_2, cast film) 3099, 3069, 2940, 2892, 2870, 1662, 1614, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,08 (s, 4 H), 5,15 (s, 2 H), 2,67 (t, J = 6 Hz, 4 H), 2,40 (t, J = 7,2 Hz, 4 H), 2,11 (pentet, J = 6,6 Hz, 4 H); $^{13}C\{^1H\}$ ($CDCl_3$, 125 MHz) δ 199,4 (s), 177,9 (s), 150,2 (s), 122,9 (d), 106,2 (d), 36,6 (t), 28,4 (t), 21,1 (t); exact mass (ESI) *m/z* calcd for $C_{18}H_{19}O_4$ $(M+H)^+$ 299,1278 found 298,1280.

*2-Bromo-3-(phenoxy)cyclohex-2-en-1-one (**4a**).* NBS (113,6 mg, 0,6383 mmol) was tipped into a stirred and cooled (0 °C) solution of **3a** (108,0 mg, 0,574 mmol) in dry DMF (2 mL) (protection from light, N_2 atmosphere). After 15 min the ice bath was removed and stirring was continued for 21 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (4 mL), followed by water (25 mL). The mixture was extracted with CH_2Cl_2 (3 · 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using successive portions of EtOAc-hexane from 10% EtOAc to 30% EtOAc, gave **4a** (128,7 mg, 84%) as a white solid: FTIR (CH_2Cl_2, cast film) 3063, 2954, 1673, 1608, 1581, 1489, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7,45–7,41 (m, 2 H), 7,30–7,29 (m, 1 H), 7,10–7,08 (m, 2 H), 2,64–2,61 (m, 2 H), 2,44 (t, J = 6,2 Hz, 2 H), 2,02 (pentet, J = 6,5 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 191,2 (s), 170,8 (s), 152,8 (s), 129,6 (d), 125,5 (d), 120,3 (d), 106,1 (d), 36,7 (t), 28,5 (t), 20,4 (t); exact mass (EI) *m/z* calcd for $C_{12}H_{11}{}^{79}BrO_2$ (M^+) 265,99423, found 265,99355.

*2-Bromo-3-(4-iodophenoxy)cyclohex-2-en-1-one (**4b**).* NBS (139 mg, 0,781 mmol) was tipped into a stirred and cooled (0 °C) solution of **3b** (212 mg, 0,675 mmol) in dry DMF (10 mL) (protection from light, N_2 atmosphere). After 15 min the ice bath was removed and stirring was continued for 24 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (8 mL) and then water (100 mL). The mixture was extracted with CH_2Cl_2 (3 · 30 mL) and the combined organic extracts were washed with water (2 · 70 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using 15% EtOAc-hexane, gave **4b** (224 mg, 86%) as a white solid: 157–159 °C; FTIR (CH_2Cl_2, cast film) 2953, 1666, 1655, 1569, 1479 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7,71 (d, J = 5,5 Hz, 2 H), 6,82 (d, J = 5,5 Hz, 2 H), 2,60 (t, J = 9 Hz, 2 H), 2,44 (t, J = 8 Hz, 2 H), 2,01 (pentet, J = 8 Hz, 2 H); $^{13}C\{^1H\}$ ($CDCl_3$, 175 MHz) δ 191,5 (s), 170,3 (s), 153,1 (s), 139,1 (d), 122,6 (d), 107,5 (s) 89,5 (s), 37,1 (t), 28,9 (t), 20,8 (t), ; exact mass (EI) *m/z* $C_{12}H_{10}O_2{}^{81}BrI$ (M^+) 393,8880, found 393,8889.

*2-Bromo-3-(4-Chlorophenoxy)cyclohex-2-en-1-one (**4c**).* NBS (100 mg, 0,60 mmol) was tipped into a stirred and cooled (0 °C) solution of **3c** (114 mg, 0,52 mmol) in dry DMF (2 mL) (protection from light, N_2 atmosphere). The ice bath was left in place but not recharged and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (4 mL). The turbid mixture was extracted with CH_2Cl_2 (3 · 10 mL) and the combined organic extracts were washed with brine (2 · 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using 30% EtOAc-hexane, gave **4c** (130 mg, 83%) as a white solid: mp 149–150 °C; FTIR (CH_2Cl_2, cast film) 1673, 1607, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7,39–7,36 (m, 2 H), 7,02–7,00 (m, 2 H), 2,61 (t, J = 8,5 Hz, 2 H), 2,44 (t, J = 8 Hz, 2 H), 2,02 (pentet J = 8 Hz, 2 H); $^{13}C\{^1H\}$($CDCl_3$, 175 MHz) δ 191,5 (s), 170,5 (s), 151,7 (s) 131,3 (s), 130,1 (d), 121,9 (d), 107,3 (s), 37,1 (t), 28,9 (t), 20,8 (t); exact mass (EI) *m/z* calcd for $C_{12}H_{10}{}^{81}Br^{35}ClO_2$ (M^+) 301,9532, found 301,9533.

*2-Bromo-3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (**4d**).* NBS (22 mg, 0,12 mmol) was tipped into a stirred and cooled (0 °C) solution of **3d** (27 mg, 0,11 mmol) in dry DMF (1 mL) (protection from light, N_2 atmosphere). After 15 min the ice bath was removed and stirring was continued for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (3 mL). The turbid mixture was extracted with CH_2Cl_2 (3 · 6 mL) and the combined organic extracts were washed with water (1 · 9 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 · 15 cm), using 40% EtOAc-hexane, gave **4d** (25 mg, 71%) as a white solid: mp 122–124 °C; FTIR (CH_2Cl_2, cast film) 1670, 1599, 1580, 1494, 1482 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,15 (t, J = 8,5 Hz, 1 H), 6,63 (t, J = 8,5 Hz, 2 H), 3,85 (s, 6 H), 2,57 (t, J = 6,5 Hz, 2 H), 2,34 (t, J = 6 Hz, 2 H), 1,96 (pentet, J = 6,5 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 191,9 (s), 173,3 (s), 152,7 (s), 131,0 (s), 126,6 (d), 105,3 (d), 103,6 (s), 56,4 (q), 37,1 (t), 27,50 (t), 20,6 (t); (ESI) m/z $C_{14}H_{16}{}^{79}BrO_4$ $(M+H)^+$ 327,0226, found 327,0220.

*2-Bromo-3-(2-tert-butylphenoxy)cyclohex-2-en-1-one (**4e**).* NBS (35 mg, 0,20 mmol) was tipped into a stirred and cooled (0 °C) solution of **3e** (45 mg, 0,14 mmol) in dry DMF (1 mL) (protection from light, N_2 atmosphere). After 15 min the ice bath was removed and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL). The turbid mixture was extracted with CH_2Cl_2 (3 · 10 mL) and the combined organic extracts were washed with water (1 · 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 · 15 cm), using 25% EtOAc-hexane, gave **4e** (40 mg, 62%) as a white solid: mp 103–106 °C; FTIR (CH_2Cl_2, cast film) 2957, 1674, 1597,1570, 1485 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7,44 (dd, J = 7,8, 1,8 Hz, 1 H), 7,24–7,17 (m, 2 H), 6,82 (dd, J = 7,8, 1,2 Hz, 1 H), 2,62 (t, J = 6,6 Hz, 2 H), 2,44 (s, 2 H), 1,98 (pentet, J = 6 Hz, 2 H), 1,40 (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 191,6 (s), 171,4 (s), 151,7 (s), 141,6 (s), 127,9 (d), 127,2 (d), 125,8 (d), 121,7 (d), 106,48 (s), 37,3 (t), 34,8 (s), 30,1 (q), 29,6 (t), 21,1 (t); (ESI) m/z calcd for $C_{16}H_{20}{}^{79}BrO_2$ $(M+H)^+$ 322,0568, found 323,0639.

*2-Bromo-3-(4-tert-butylphenoxy)cyclohex-2-en-1-one (**4f**).* NBS (160 mg, 0,90 mmol) was tipped into a stirred and cooled (0 °C) solution of **3f** (200 mg, 0,80 mmol) in dry DMF (2 mL) (protection from light, N_2 atmosphere). After 15 min the ice bath was removed and stirring was continued for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL). The turbid mixture was extracted with CH_2Cl_2 (3 · 20 mL) and the combined organic extracts were washed with water (1 · 40 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using 20% EtOAc-hexane, gave **4f** (150 mg, 58%) as a white solid: mp 145 °C; FTIR (CH_2Cl_2, cast film) 3056, 1665, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,41–7,39 (m, 2 H), 6,99–6,97 (m, 2 H), 2,60 (t, J = 6,5 Hz, 2 H), 2,45 (t, J = 6 Hz, 2 H), 2,00 (pentet, J = 6,5 Hz, 2 H), 1,33 (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ

191,7 (s), 171,6 (s), 150,8 (s), 149,1 (s), 126,9 (d), 120,2 (d), 106,0 (s), 37,2 (t), 34,6 (s), 31,4 (t), 29,0 (t), 20,8 (t); exact mass (EI) *m/z* calcd for $C_{16}H_{19}{}^{79}BrO_2$ (M^+) 322,0569, found 322,0567.

*Methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (**4g**).* NBS (303,3 mg, 1,363 mmol) was tipped into a stirred and cooled (0 °C) solution of **3g** (242,5 mg, 1,232 mmol) in dry DMF (3 mL) (protection from light, N_2 atmosphere). After 40 min the ice bath was removed and stirring was continued for 3,5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and water (50 mL). The mixture was extracted with CH_2Cl_2 (3 · 20 mL) and the combined organic extracts were washed with 6:1 water:brine (70 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2,5 · 15 cm), using successive portions of EtOAc-hexane from 30% EtOAc to 40% EtOAc, gave **4g** (361,7 mg, 90%) as a white solid: mp 122–125 °C; FTIR (CH_2Cl_2, cast film) 1721, 1680, 1593, 1503 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8,10 (d, *J* = 8,4 Hz, 2 H), 7,10 (d, *J* = 8,4 Hz, 2 H), 3,96 (s, 3 H), 2,64 (t, *J* = 6 Hz, 2 H), 2,52 (t, *J* = 6 Hz, 2 H), 2,07 (pentet, *J* = 6 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 191,4 (s), 169,8 (s), 166,0 (s), 156,9 (s), 131,8 (d), 127,4 (s), 119,7 (d), 108,8 (s), 52,3 (q), 37,1 (t), 29,1 (t), 20,7 (t); (EI) *m/z* calcd for $C_{14}H_{13}{}^{79}BrO_4$ (M^+) 323,999730, found 325,99964.

*2-Bromo-3-{4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (**4h**).* NBS (350,9 mg, 1,97 mmol) was tipped into a stirred and cooled (0 °C) solution of **3h** (243,3 mg, 0,82 mmol) in dry DMF (2,5 mL) (protection from light). The ice bath was removed 5 min after the addition and stirring was continued for 44 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (8 mL) and water (100 mL). The mixture was extracted with CH_2Cl_2 (3 · 30 mL) and the combined organic extracts were washed with water (1 · 70 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using 5% EtOAc-hexane, gave **4h** (150,9 mg, 41%) as a violet solid: FTIR (solid) 1655, 1589, 1500, 1417 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,13 (s, 4 H), 2,65 (t, *J* = 6 Hz, 4 H), 2,49 (t, *J* = 6 Hz, 4 H), 2,05 (pentet, *J* = 6,5 Hz, 4 H); $^{13}C\{^1H\}$ ($CDCl_3$, 125 MHz) δ 191,4 (s), 170,3 (s), 150,6 (s), 122,0 (d), 107,5 (s), 37,1 (t), 28,9 (t), 20,8 (t); exact mass (ESI) *m/z* calcd for $C_{18}H_{17}{}^{79}Br_2NaO_4$ ($(M+Na)^+$) 476,9308 found 476,9304.

*3-(Phenoxy)phenol (**5a**).* DBU (0,50 mL, 3,4 mmol) was added at a fast dropwise rate to a stirred solution of **4a** (290,6 mg, 1,088 mmol) in PhMe (6 mL) and stirring at rt was continued for 19 h (N_2 atmosphere). The mixture was diluted with 5%w/w hydrochloric acid (10 mL) and stirring was continued for 15 min. More 5%w/w hydrochloric acid (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 · 12 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2,5 · 15 cm), using 25% EtOAc-hexane, gave **5a** (175,0 mg, 86%) as an oil: FTIR (CH_2Cl_2, cast film) 3415 (br), 3065, 2927, 2411, 1590, 1488 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7,36–7,32 (m, 2 H), 7,17 (t, *J* = 8,2 Hz, 1 H), 7,14–7,10 (m, 1 H), 7,05–7,02 (m, 2 H), 6,59–6,55 (m, 2 H), 6,49 (t, *J* = 2,3 Hz, 1 H), 4,76 (s, 1 H of -OH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 158,80 (s), 156,77 (s), 156,8 (s), 130,5 (d), 129,8 (d), 123,6 (d), 119,4 (d), 111,1 (d), 110,0 (d), 106,0 (d); exact mass (ESI) *m/z* calcd for $C_{12}H_9O_2$ $(M–H)^-$ 185,0608, found 185,0606.

*3-(4-Iodophenoxy)phenol (**5b**).* DBU (31 mg, 0,203 mmol) was added at a fast dropwise rate to a stirred solution of **4b** (19 mg, 0,048 mmol) in PhMe (11 mL) and stirring at rt was continued for 30 h. The mixture was diluted with 5%w/w hydrochloric acid (30 mL) and stirred for 30 min. More 5%w/w hydrochloric acid (75 mL) was added and the mixture was extracted with CH_2Cl_2 (3 · 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using 15% EtOAc-hexane, gave **5b** containing 8 mol% of 4-iodophenol (^{1}H NMR). Kugelrohr distillation (0,25 mmHg, oven temperature 110 °C) afforded **5b** (9 mg, 58%) as an oil: FTIR (CH_2Cl_2, cast film) 3396, 1600, 1581, 1478 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7,62 (d, *J* = 4,5 Hz, 2 H), 7,18 (t, *J* = 8 Hz, 1 H), 6,79 (d, *J* = 4,5 Hz, 2 H), 6,60–6,55 (m, 2 H), 6,49 (t, *J* = 2,5 Hz, 1 H), 4,83 (s, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 158,0 (s), 157,0 (s), 156,9 (s), 138,7 (d), 130,6 (d), 121,3 (d), 111,2 (d), 110,7 (d), 106,3 (d), 86,3 (s); exact mass (ESI) *m/z* calcd for $C_{12}H_8IO_2$ $(M–H)^-$ 310,9574, found 310,9571.

*3-(4-Chlorophenoxy)phenol (**5c**).* DBU (120 mg, 0,79 mmol) was injected rapidly into a stirred solution of **4c** (203 mg, 0,70 mmol) in dry PhMe (6 mL) and stirring at rt was continued overnight open to the atmosphere. The mixture was diluted with 5%w/w hydrochloric acid (11 mL) and stirring was continued for 30 min. More 5%w/w hydrochloric acid (27 mL) was added and the mixture was extracted with CH_2Cl_2 (3 · 16 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using 10% EtOAc-hexane, gave material which was distilled (Kugelrohr, 0,2 mmHg, oven temperature 110 °C) to afford **5c** (83 mg, 55%) containing a small amount of an aromatic impurity. FTIR (CH_2Cl_2, cast film) 3407, 1600, 1588, 1484 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7,31–7,26 (m, 2 H), 7,18 (t, *J* = 8 Hz, 1 H), 6,98–6,94 (m, 2 H), 6,60–6,55 (m, 2 H), 6,49 (t, *J* = 2,5 Hz, 1 H), 4,81 (s, 1 H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 125 MHz) δ 158,3 (s), 156,9 (s), 155,5 (s), 130,6 (d), 129,8 (d), 128,6 (s), 120,5 (d), 111,0 (d), 110,6 (d), 106,1 (d); exact mass (ESI) *m/z* calcd for $C_{12}H_8{}^{35}ClO_2$ $(M–H)^-$ 219,0218, found 219,0216.

*3-(2,6-Dimethoxyphenoxy)phenol (**5d**).* DBU (35 mg, 0,20 mmol) was injected rapidly into a stirred solution of **4d** (22 mg, 0,07 mmol) in dry PhMe (1,5 mL) and stirring at rt was continued for 72 h open to the atmosphere. The mixture was diluted with 5%w/w hydrochloric acid (1,5 mL) and stirring was continued for 30 min. More

5%w/w hydrochloric acid (6 mL) was added and the mixture was extracted with CH_2Cl_2 (3 · 6 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 · 15 cm), using 40% EtOAc-hexane, gave **5d** (12 mg, 75%) as an oil: FTIR (CH_2Cl_2, cast film) 3450, 1601, 1481 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,14 (t, *J* = 8,5 Hz, 1 H), 7,09 (t, *J* = 8 Hz, 1 H), 6,66 (d, *J* = 8,5, 2 H), 6,45–6,44 (m, 2 H), 6,35 (t, *J* = 2 Hz, 1 H), 4,61 (br s, 1 H), 3,79 (s, 6 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 159,9 (s), 156,6 (s), 153,6 (s), 130,0 (d), 125,6 (d), 108,6 (d), 107,6 (d), 105,5 (d), 102,3 (d), 56,3 (q); (ESI) *m*/*z* calcd for $C_{14}H_{13}O_4$ $(M–H)^-$ 245,0819, found 245,0818.

3-(2-tert-Butylphenoxy)phenol (5e). DBU (30 mg, 0,20 mmol) was injected rapidly into a stirred solution of **4e** (35 mg, 0,14 mmol) in dry PhMe (2 mL) and stirring at rt was continued for 72 h open to the atmosphere. The mixture was diluted with 5%w/w hydrochloric acid (2 mL) and stirring was continued for 30 min. More 5%w/w hydrochloric acid (9 mL) was added and the mixture was extracted with CH_2Cl_2 (3 · 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 · 15 cm), using 20% EtOAc-hexane, gave **5e** (26 mg, 78%) as an oil: FTIR (CH_2Cl_2, cast film) 3392, 1596, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7,40 (dd, *J* = 7,8, 1,2, 1 H), 7,18–7,14 (m, 2 H), 7,07 (td, *J* = 7,8, 1,2, 1 H), 6,87 (dd, *J* = 7,8, 1,2, 1 H), 6,57–6,53 (m, 2 H), 6,46 (t, *J* = 2,4, 1 H), 4,73 (s, 1 H), 1,41 (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 159,3 (s), 156,8 (s), 155,4 (s), 141,2 (s), 130,4 (d), 127,3 (d), 127,2 (d), 123,6 (d), 120,7 (d), 111,0 (d), 109,6 (d), 105,8 (d), 34,8 (s), 30,2 (q); (ESI) *m*/*z* calcd for $C_{16}H_{17}O_2$ $(M–H)^-$ 241,1234, found 241,1238.

3-(4-tert-Butylphenoxy)phenol (5f). DBU (78 mg, 0.51 mmol) was injected rapidly into a stirred solution of **4f** (50 mg, 0,15 mmol) in dry PhMe (2 mL) and stirring at rt was continued for 22 h open to the atmosphere. The mixture was diluted with 5%w/w hydrochloric acid (3 mL) and stirring was continued for 30 min. More 5%w/w hydrochloric acid was added and the mixture was extracted with CH_2Cl_2 (3 · 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 · 15 cm), using 20% EtOAc-hexane, gave **5f** (31 mg, 86%) as a white solid: mp 122–125 °C; FTIR (CH_2Cl_2, cast film) 3411, 2959, 1610, 1592, 1498 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7,36–7,35 (m, 2 H), 7,16 (t, *J* = 8 Hz, 1 H), 6,97–6,95 (m, 2 H), 6,59–6,53 (m, 2 H), 6,47 (t, *J* = 2,0, 1 H), 4,74 (s, 1 H), 1,33 (s, 9 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 159,2 (s), 156,7 (s), 154,2 (s), 146,6 (s), 130,3 (d), 126,6 (d), 119,0 (d), 110,8 (d), 109,8 (d), 105,6 (d), 34,4 (s), 31,5 (q); exact mass (ESI) *m*/*z* calcd for $C_{16}H_{17}O_2$ $(M–H)^-$ 241,1234, found 241,1232.

*Methyl 4-(3-hydroxyphenoxy)benzoate (**5g**).* DBU (120,6 mg, 0,79 mmol) was injected rapidly into a stirred solution of **4g** (72,1 mg, 0,22 mmol) in dry PhMe (4 mL) and stirring at rt was continued for 18 h open to the atmosphere. The mixture was diluted with 5%w/w hydrochloric acid (3 mL) and stirring was continued for 10 min. More 5%w/w hydrochloric acid (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 · 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 · 15 cm), using 20% EtOAc-hexane, gave **5g** (48.2 mg as an oil which contained some impurities (^{1}H NMR). The material was subjected twice to Kugelrohr distillation under vacuum (0.5 mmHg, oven temp 120–140 °C) to afford **5g** (31 mg, 57%) as a colorless gel: FTIR (CH_2Cl_2, cast film) 3392, 1719, 1697, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8,02 (d, *J* = 8,4 Hz, 2 H), 7,25 (t, *J* = 8,4 Hz, 1 H), 7,03 (d, *J* = 9 Hz, 2 H), 6,70–6,63 (m, 2 H), 6,58 (t, *J* = 2,5 Hz, 1 H), 5,17 (br s, 1 H), 3,93 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 167,1 (s), 161,6 (s), 157,3 (s), 156,8 (s), 131,7 (d), 130,7 (d), 124,4 (s), 117,6 (d), 112,0 (d), 111,7(d), 107,4 (d), 52,2 (q); (ESI) *m/z* calcd for $C_{14}H_{11}O_4$ $(M-H)^-$ 243,06630, found 243,06630.

*3-[4-(3-hydroxyphenoxy)phenoxy]phenol (**5h**).* DBU (81,8 mg, 0,54 mmol) in PhMe (2 mL) was added rapidly to a stirred solution of **4h** (38,2 mg, 0,084 mmol) in PhMe (1 mL) and stirring was continued for 42 h at rt. The mixture was diluted with 5%w/w hydrochloric acid (3 mL) and stirred for 30 min. More 5%w/w hydrochloric acid (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 · 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 · 15 cm), using 50-mL portions of EtOAc-hexane mixtures from 5% EtOAc to 40% EtOAc, gave **5h** (7,6 mg, 31%) as a solid which contained some aromatic impurities (^{1}H NMR): mp 115–118 °C; FTIR (CH_2Cl_2, cast film) 3394, 1599, 1494, 1276, 1137 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7,20 (t, *J* = 7,97 Hz, 2 H), 7,04 (s, 4 H), 6,61–6,57 (m, 4 H), 6,50 (t, *J* = 1,8 Hz, 2 H), 4,96 (br s, 2 H); $^{13}C\{^1H\}$ ($CDCl_3$, 125 MHz) δ 159,3 (s), 157,0 (s), 152,4 (s), 130,4 (d), 121,0 (d), 110,4 (d), 110,0 (d), 105,3 (d); exact mass (ESI) *m/z* calcd for $C_{18}H_{13}Br_2O_4$ $(M-H)^-$ 293,0819, found 293,0821.

CONCLUSION

According to the results of the dissertation research, the following conclusions are made:

- 3-Chloro-cyclohex-2-en-1-one has been synthesized from cyclohexan-1,3-dione by utilizing Vilsmeier reagent.
- Systematic investigations were conducted to study the conditions for synthesizing 3-(aryloxy)cyclohex-2-en-1-one via nucleophilic substitution reaction. These studies aimed to systematically identify and optimize the reaction conditions for efficient and reliable synthesis of the target compound. 8 Compounds were synthesized by developed approach with average yield 76%; 7 of them have not been previously described in the literature.
- Bromination reaction of 3-(aryloxy)cyclohex-2-en-1-one at position C(2) was performed for further directional aromatization to exclude the synthesis of *para*- and *ortho*- substituted phenols. 8 Compounds were synthesized by developed approach with average yield 72%; 7 of them have not been previously described in the literature.
- A novel synthetic approach was developed for the synthesis of *meta*-aryloxy phenols via aromatization reaction. Through systematic experimentation, DBU was identified as an effective base for aromatizing 2-bromo-3-(aryloxy)cyclohex-2-en-1-one to achieve the desired *meta*-aryloxy phenols. 8 Final compounds were synthesized by developed approach with average yield 66%; 4 of them have not been previously described in the literature.
- The chemical structures of the synthesized compounds were confirmed using multiple analytical techniques, including infrared spectroscopy (IR), mass spectrometry (MS), and nuclear magnetic resonance (NMR) spectroscopy.
- Technological schemes detailing the developed methods for synthesizing intermediate and final compounds were presented. Additionally, material balances of production were calculated to assess the efficiency of the synthesis processes.

Assessment of the results of the work. The goals and objectives set in the dissertation work were completely achieved. Developed an efficient and novel non-catalytic method for the synthesis of *meta*-aryloxy phenols from 1,3-cyclohexanedione. The research conducted on the conditions for the synthesis of 3-(aryloxy)cyclohex-2-en-1-one by nucleophilic substitution reaction, the introduction of a directing group by C(2) bromination of 3-(aryloxy)cyclohex-2-en-1-one, and the synthesis of *meta*-aryloxy phenols by aromatization resulted in the development of new and efficient methods for the synthesis of intermediates and final compounds. The structural characterization of the synthesized compounds using various analytical techniques and the presentation of technological schemes for the synthesis processes and material balances of production further demonstrate the completeness of the solution of the tasks outlined in the dissertation work.

Recommendations and inputs for specific uses results of the study. The developed method for synthesizing *meta*-aryloxy phenols from cyclohexane-1,3-dione holds significant potential for diverse industrial applications. The compounds produced could serve as valuable precursors for the production of various organic compounds, including pharmaceuticals and agrochemicals.

Furthermore, the absence of heavy metals or ligands in the synthesis process renders this method a more environmentally sustainable and less hazardous alternative to conventional approaches. As such, this method could be adopted by industries to reduce the environmental impact of their chemical production processes.

Finally, the low-temperature operation of the method is conducive to decreased energy consumption and associated cost reductions, rendering it an attractive option for industries seeking to minimize their operational expenses. Overall, the results of this study demonstrate the promising potential of the developed method for synthesizing *meta*-aryloxy phenols, with potential benefits for both the environment and cost-effectiveness in industrial applications.

Assessment of the scientific level and economic efficiency of the work. The results obtained from this study exhibit a high level of both scientific rigor and practical applicability. The synthesized compounds have the potential to serve as the foundation for the synthesis and modification of various organic compounds, including pharmaceuticals and agrochemicals. Furthermore, the scientific caliber of this work has been assessed against the foremost accomplishments in this field, as evidenced by its publication in esteemed international scientific journals, including one article in the Q2-ranked journal Tetrahedron (with a 60% percentile) and another article in the Q2-ranked journal Molecules (with an 83% percentile). Additionally, the findings of this research have been presented and discussed in international conference, such as the «Фараби Әлемі – 2023» conference for students and young scientists in 2023.

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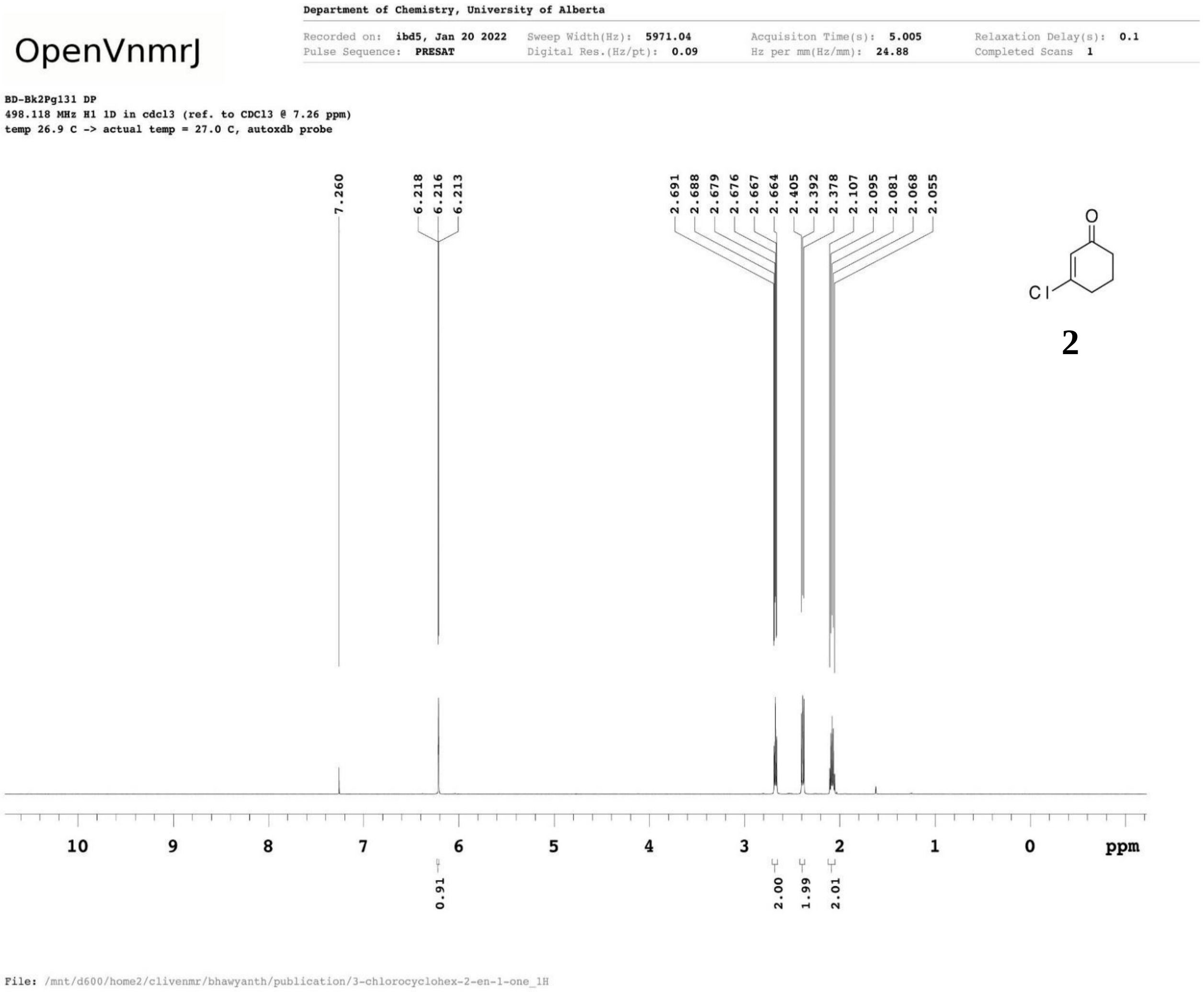
APPENDIX A



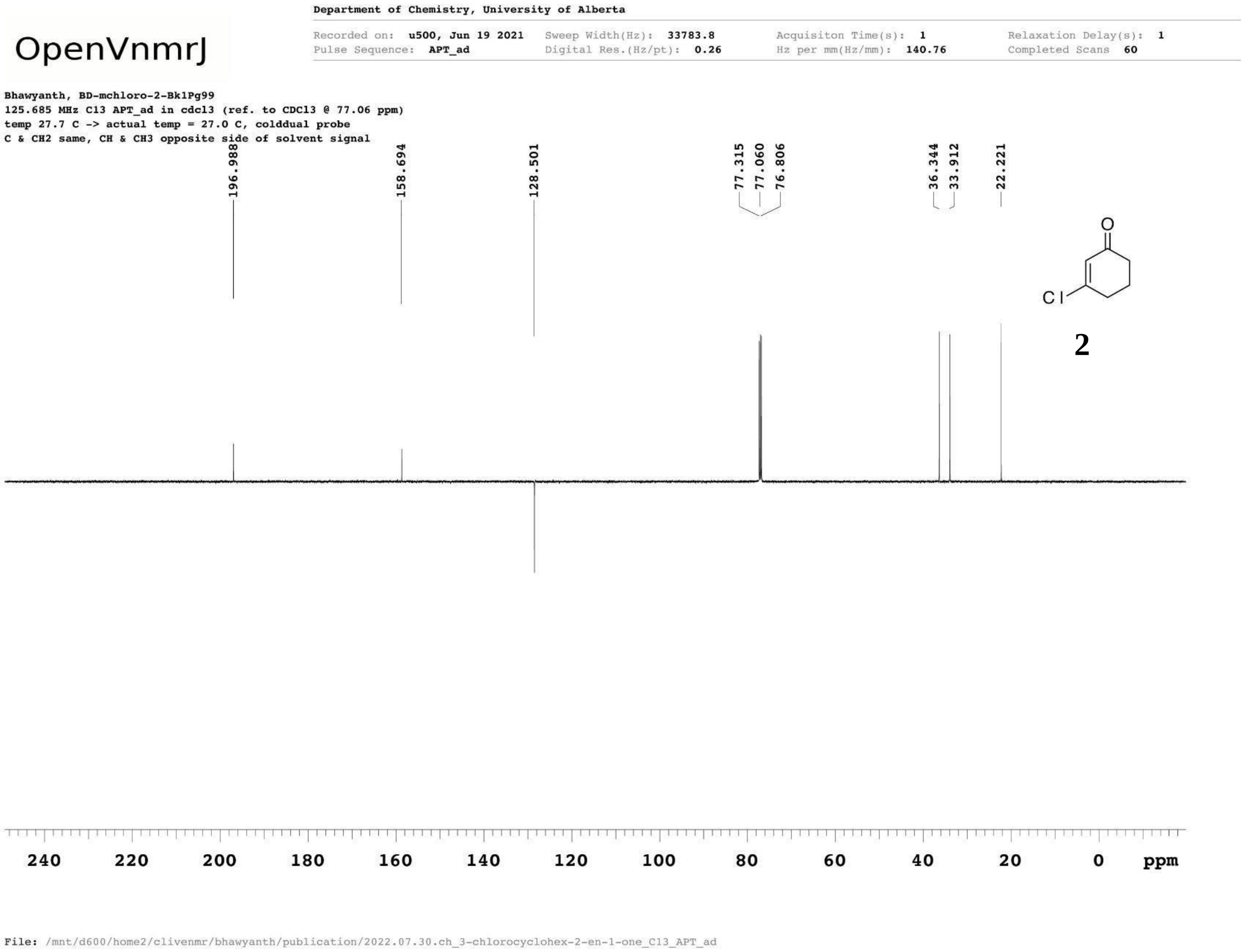
Department of Chemistry, University of Alberta

Recorded on: ibd5, Jan 20 2022 Sweep Width(Hz): 5971.04 Acquisiton Time(s): 5.005 Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT Digital Res.(Hz/pt): 0.09 Hz per mm(Hz/mm): 24.88 Completed Scans 1

BD-Bk2Pg131 DP
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/bhawyanth/publication/3-chlorocyclohex-2-en-1-one_1H

Figure A1 ^{1}H NMR spectrum of 3-chlorocyclohex-2-en-1-one (2).



Department of Chemistry, University of Alberta

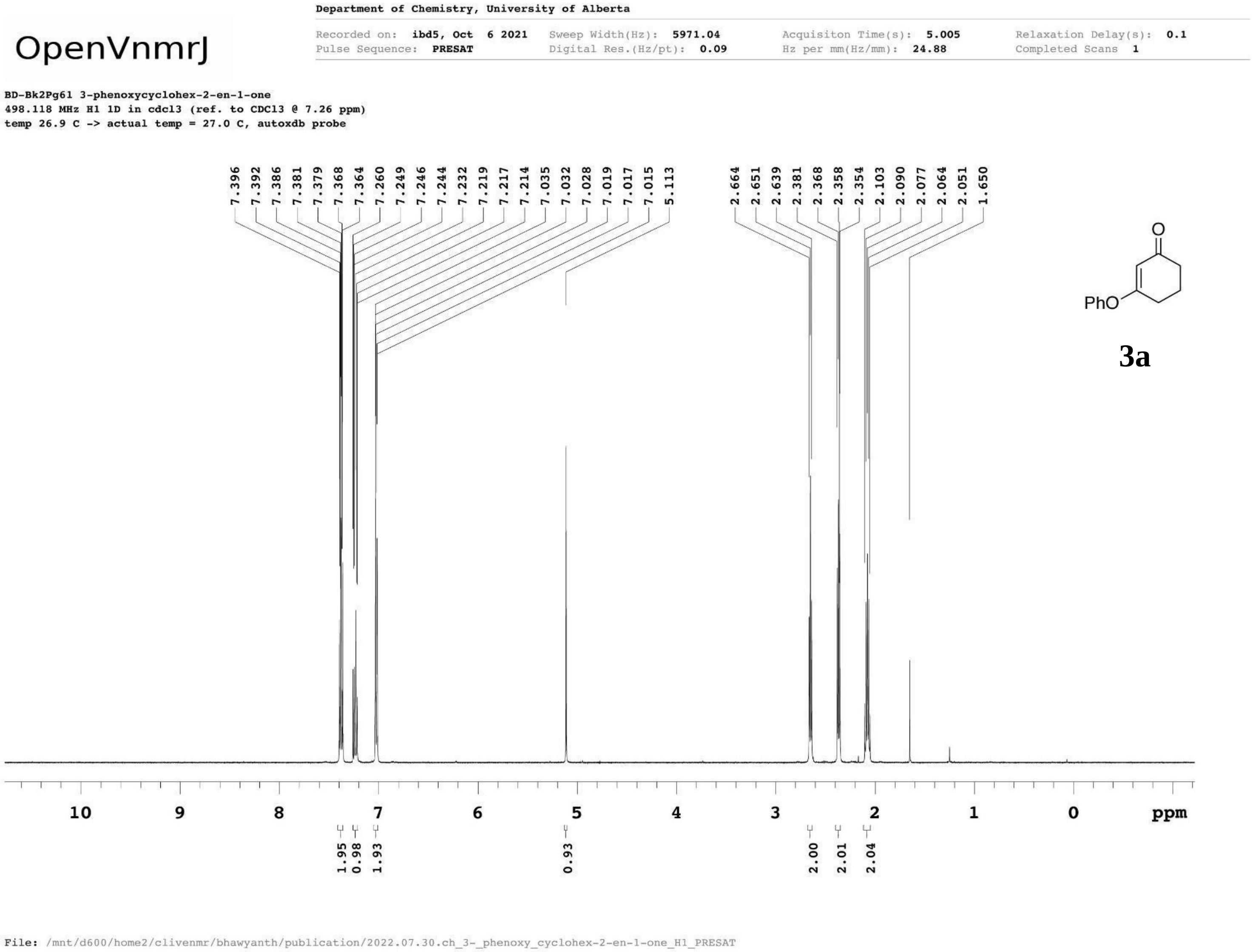
Recorded on: **u500, Jun 19 2021** Sweep Width(Hz): **33783.8** Acquisiton Time(s): **1** Relaxation Delay(s): **1**

Pulse Sequence: **APT_ad** Digital Res.(Hz/pt): **0.26** Hz per mm(Hz/mm): **140.76** Completed Scans **60**

Bhawyanth, BD-mchloro-2-Bk1Pg99
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/bhawyanth/publication/2022.07.30.ch_3-chlorocyclohex-2-en-1-one_C13_APT_ad

Figure A2 $^{13}C\{^1H\}$ NMR spectrum of 3-chlorocyclohex-2-en-1-one (2).



Department of Chemistry, University of Alberta

Recorded on: ibd5, Oct 6 2021 Sweep Width(Hz): 5971.04 Acquisiton Time(s): 5.005 Relaxation Delay(s): 0.1

Pulse Sequence: PRESAT Digital Res.(Hz/pt): 0.09 Hz per mm(Hz/mm): 24.88 Completed Scans 1

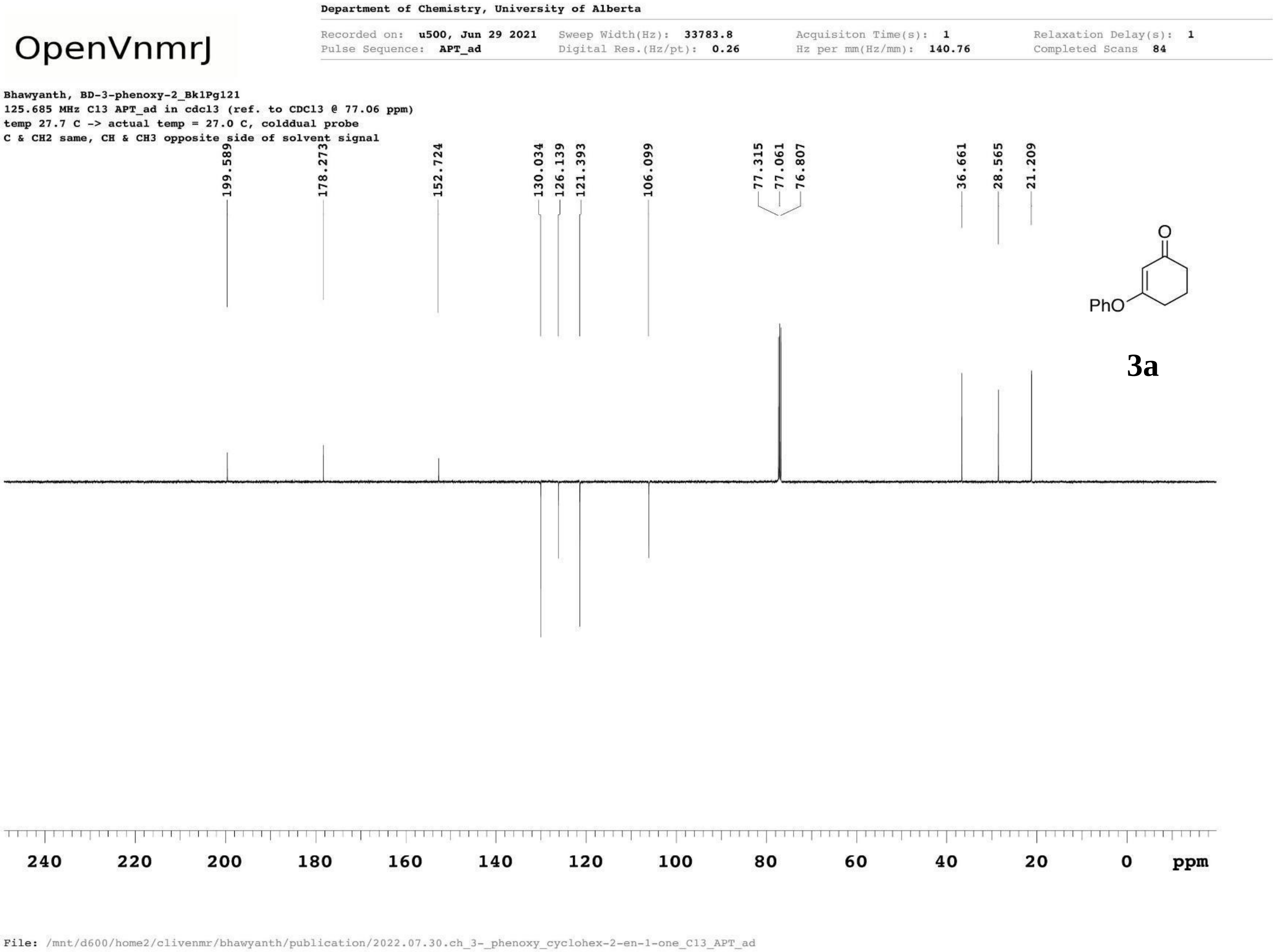
BD-Bk2Pg61 3-phenoxycyclohex-2-en-1-one

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/bhawyanth/publication/2022.07.30.ch_3-_phenoxy_cyclohex-2-en-1-one_H1_PRESAT

Figure A3 ^{1}H NMR spectrum of 3-(phenoxy)cyclohex-2-en-1-one (3a)



Department of Chemistry, University of Alberta

Recorded on: u500, Jun 29 2021 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1
Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 140.76 Completed Scans 84

Bhawyanth, BD-3-phenoxy-2_Bk1Pg121
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/bhawyanth/publication/2022.07.30.ch_3-_phenoxy_cyclohex-2-en-1-one_C13_APT_ad

Figure A4 $^{13}C\{^{1}H\}$ NMR spectrum of 3-(phenoxy)cyclohex-2-en-1-one (3a).

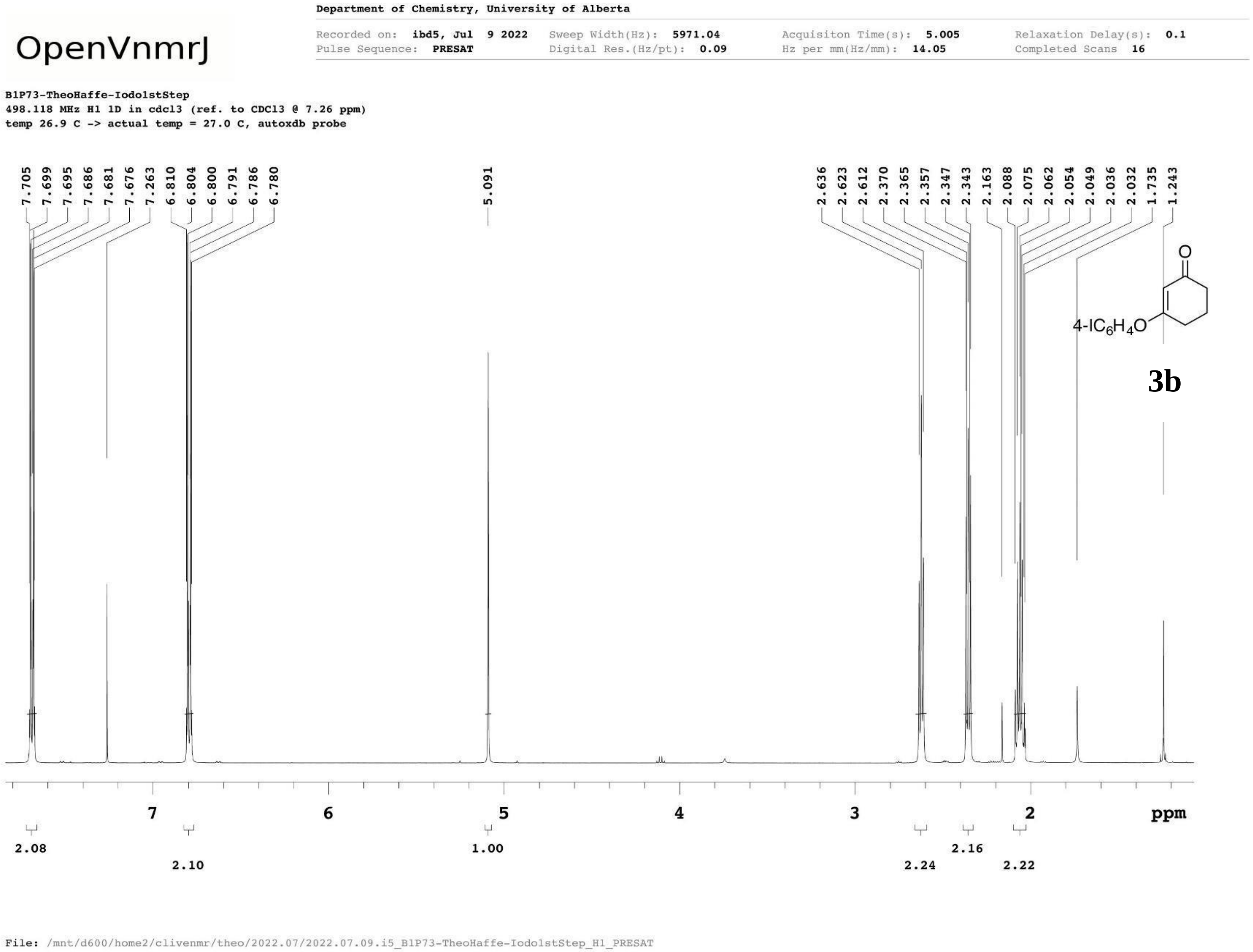


Figure A5 ^{1}H NMR spectrum of 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b).

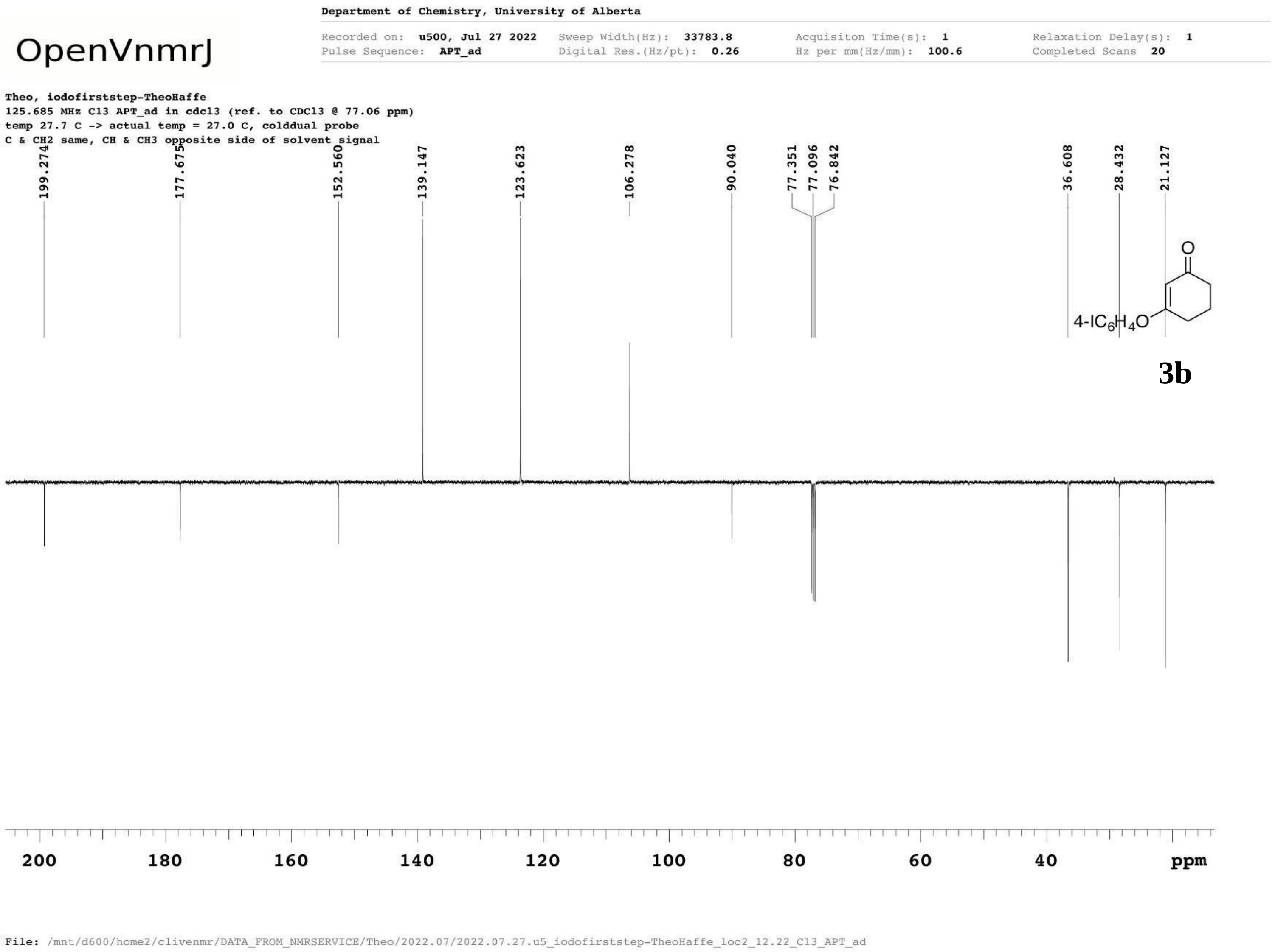
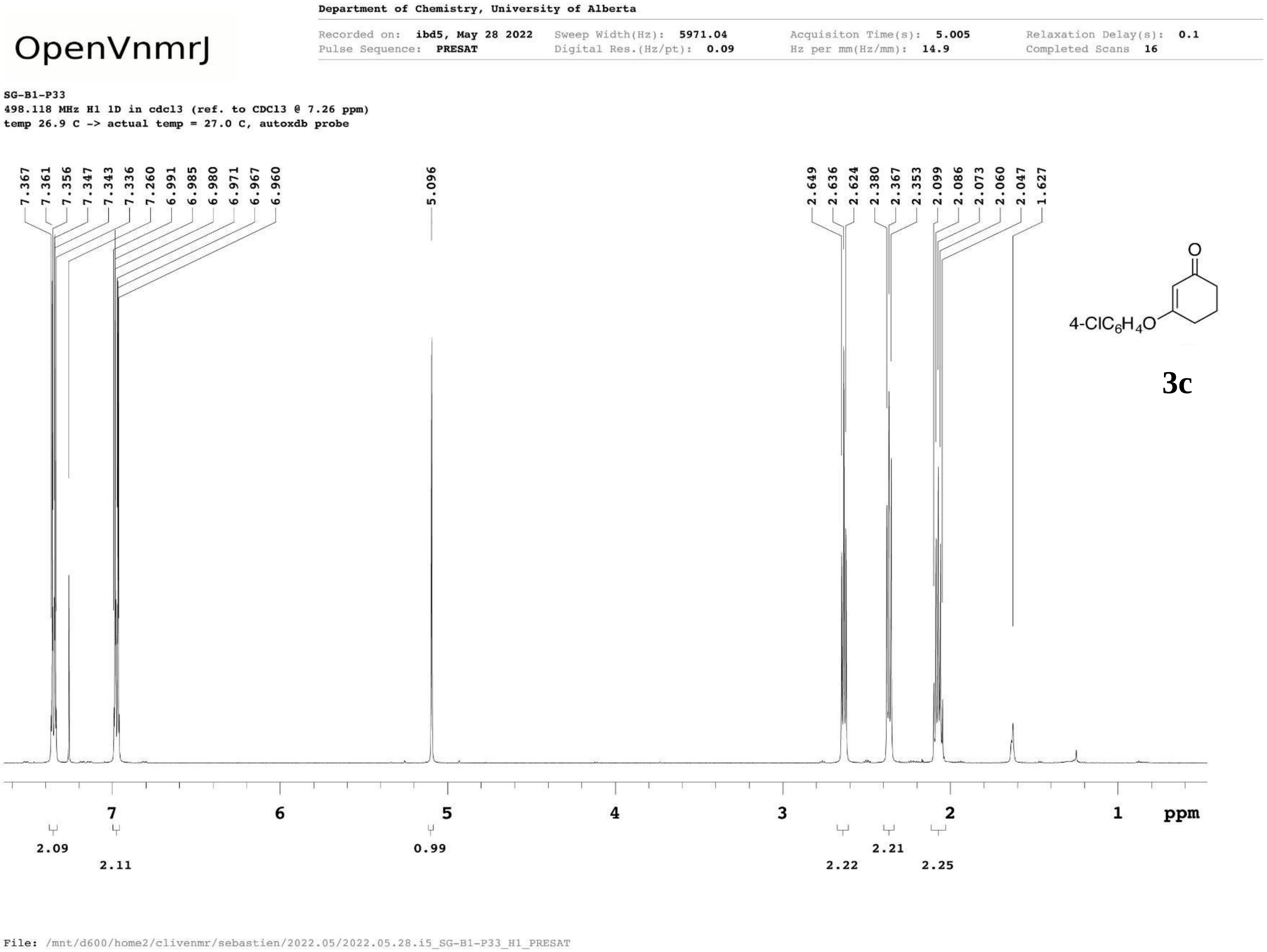


Figure A6 $^{13}C\{^{1}H\}$ NMR spectrum of 3-(4-iodophenoxy)cyclohex-2-en-1-one (3b).



Department of Chemistry, University of Alberta

Recorded on: ibd5, May 28 2022
Pulse Sequence: PRESAT
Sweep Width(Hz): 5971.04
Digital Res.(Hz/pt): 0.09
Acquisiton Time(s): 5.005
Hz per mm(Hz/mm): 14.9
Relaxation Delay(s): 0.1
Completed Scans 16

SG-B1-P33
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.05/2022.05.28.i5_SG-B1-P33_H1_PRESAT

Figure A7 ^{1}H NMR spectrum of 3-(4-chlorophenoxy)cyclohex-2-en-1-one (3c).

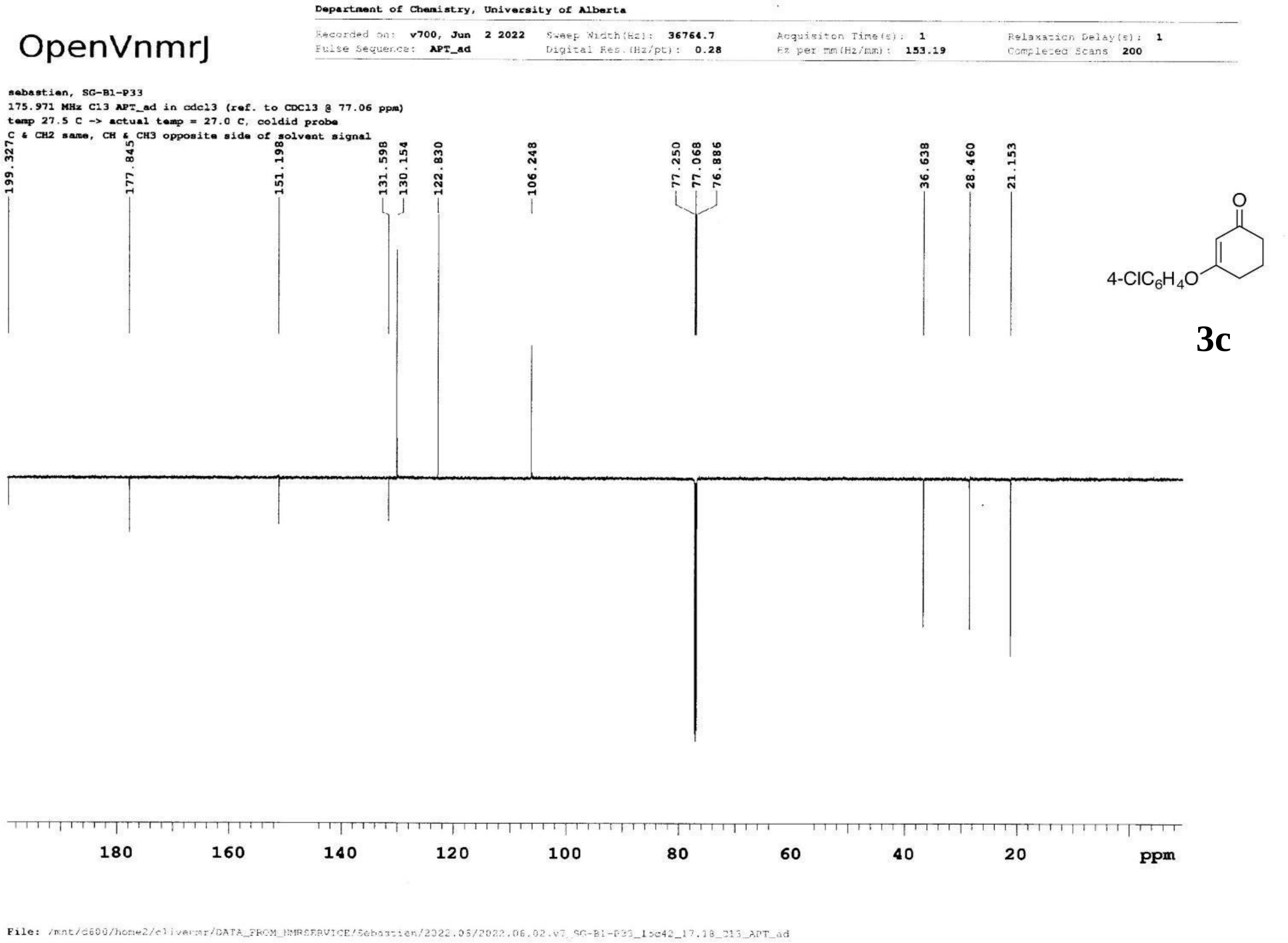
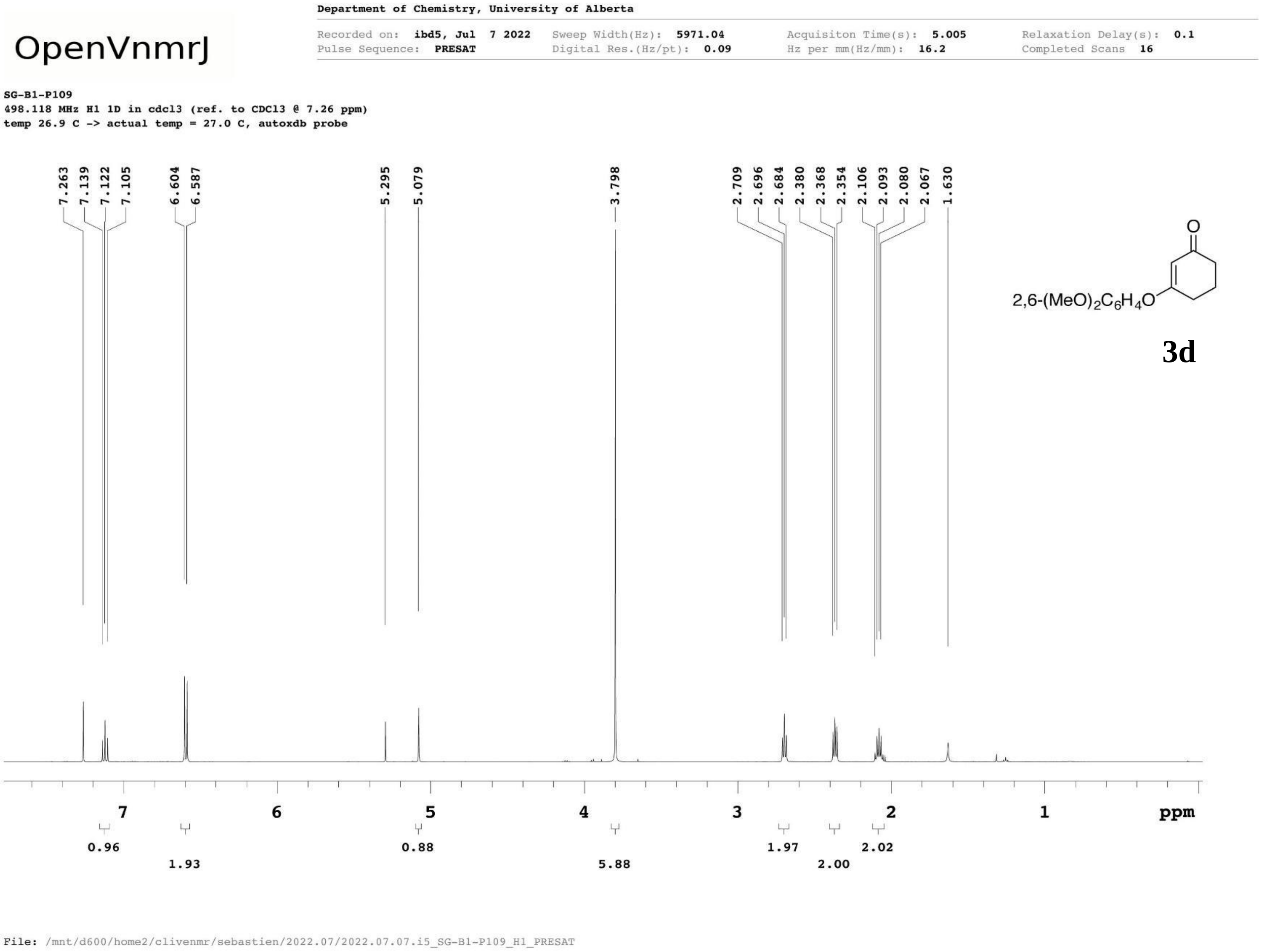


Figure A8 $^{13}C\{^{1}H\}$ NMR spectrum of 3-(4-chlorophenoxy)cyclohex-2-en-1-one (3c).



OpenVnmrJ

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Recorded on: ibd5, Jul 7 2022 Sweep Width(Hz): 5971.04 Acquisiton Time(s): 5.005 Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT Digital Res.(Hz/pt): 0.09 Hz per mm(Hz/mm): 16.2 Completed Scans 16

SG-B1-P109
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.07/2022.07.07.i5_SG-B1-P109_H1_PRESAT

Figure A9 ^{1}H NMR spectrum of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d).

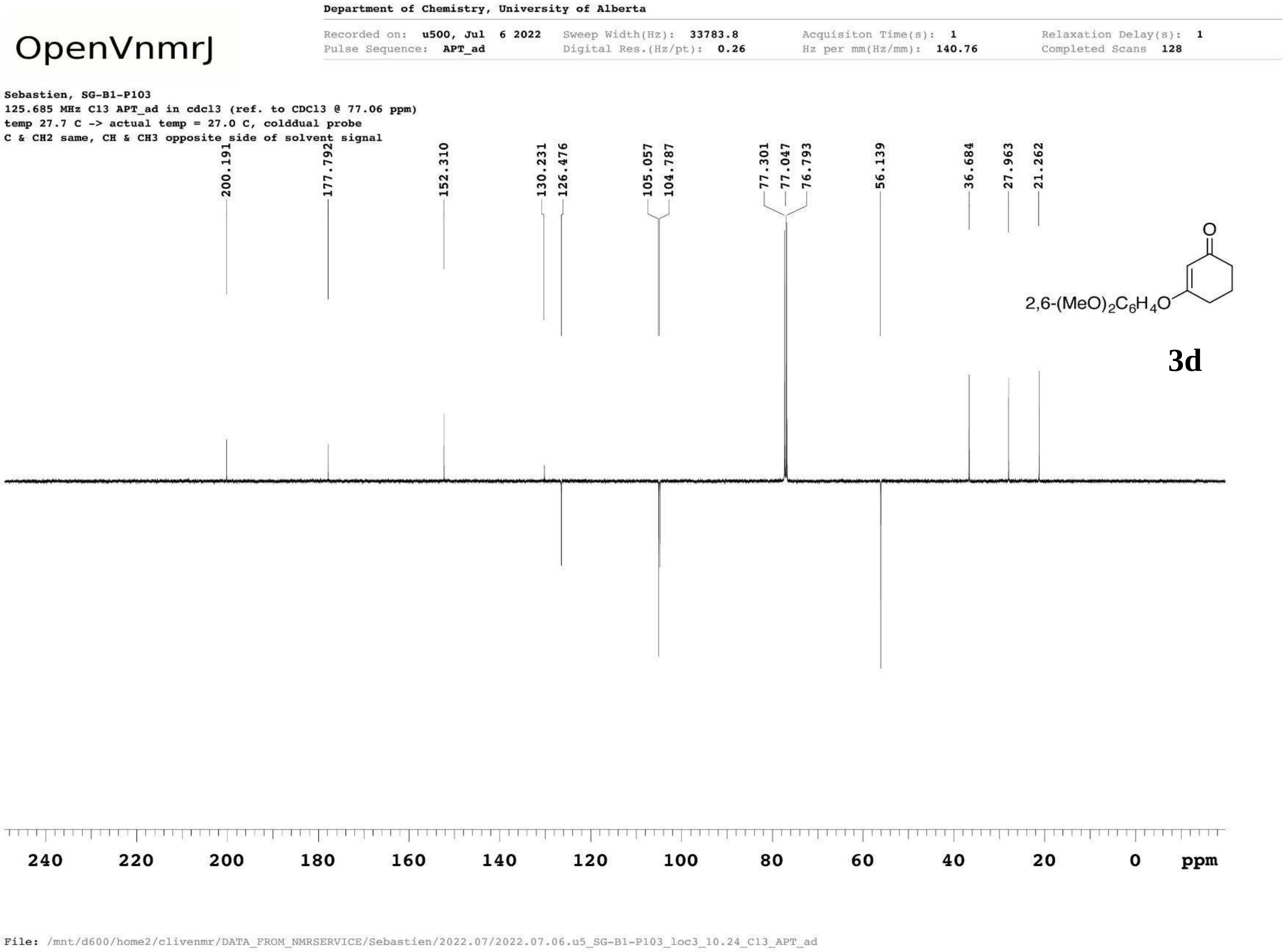


Figure A10 $^{13}C\{^1H\}$ NMR spectrum of 3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (3d).

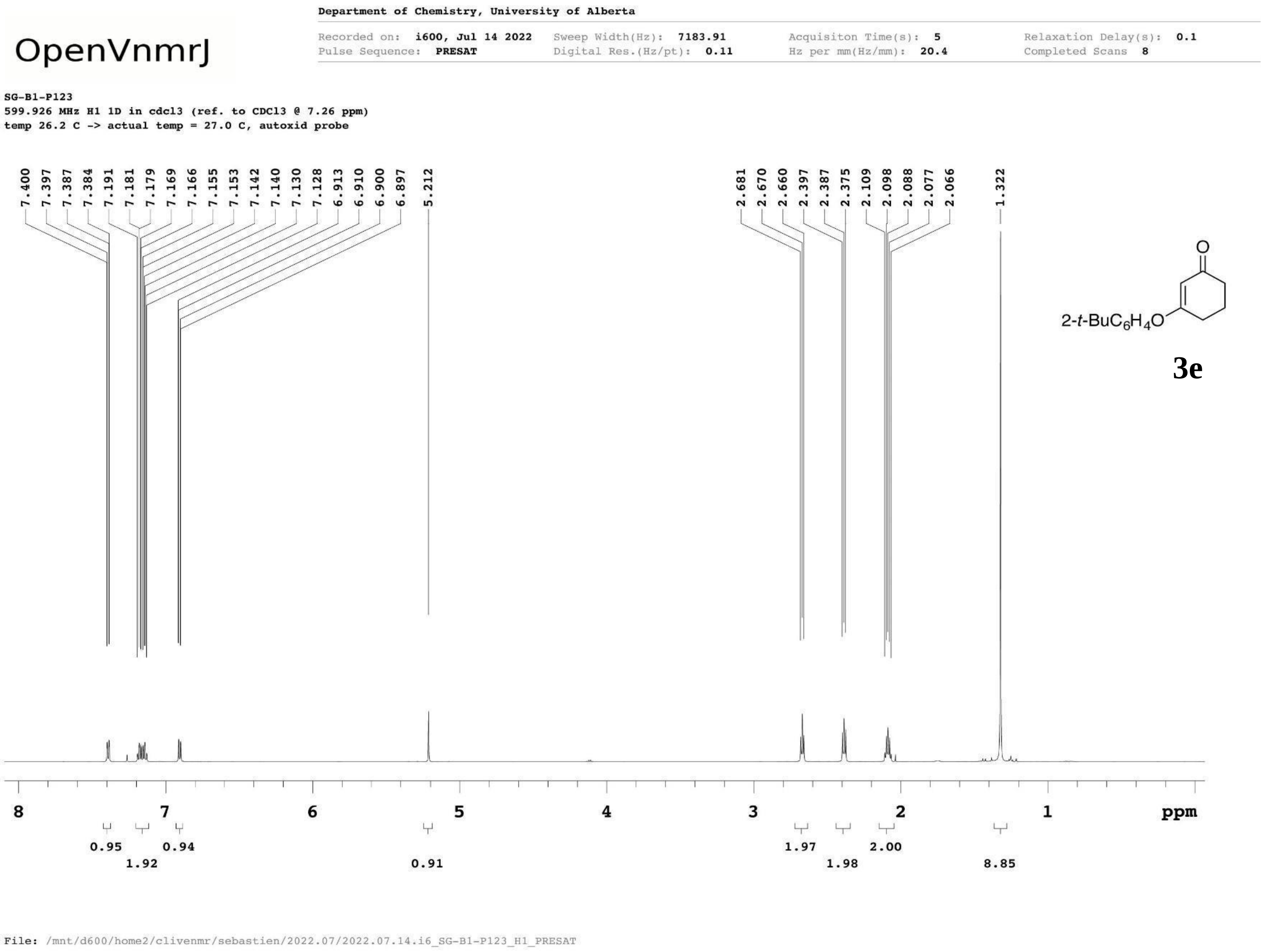
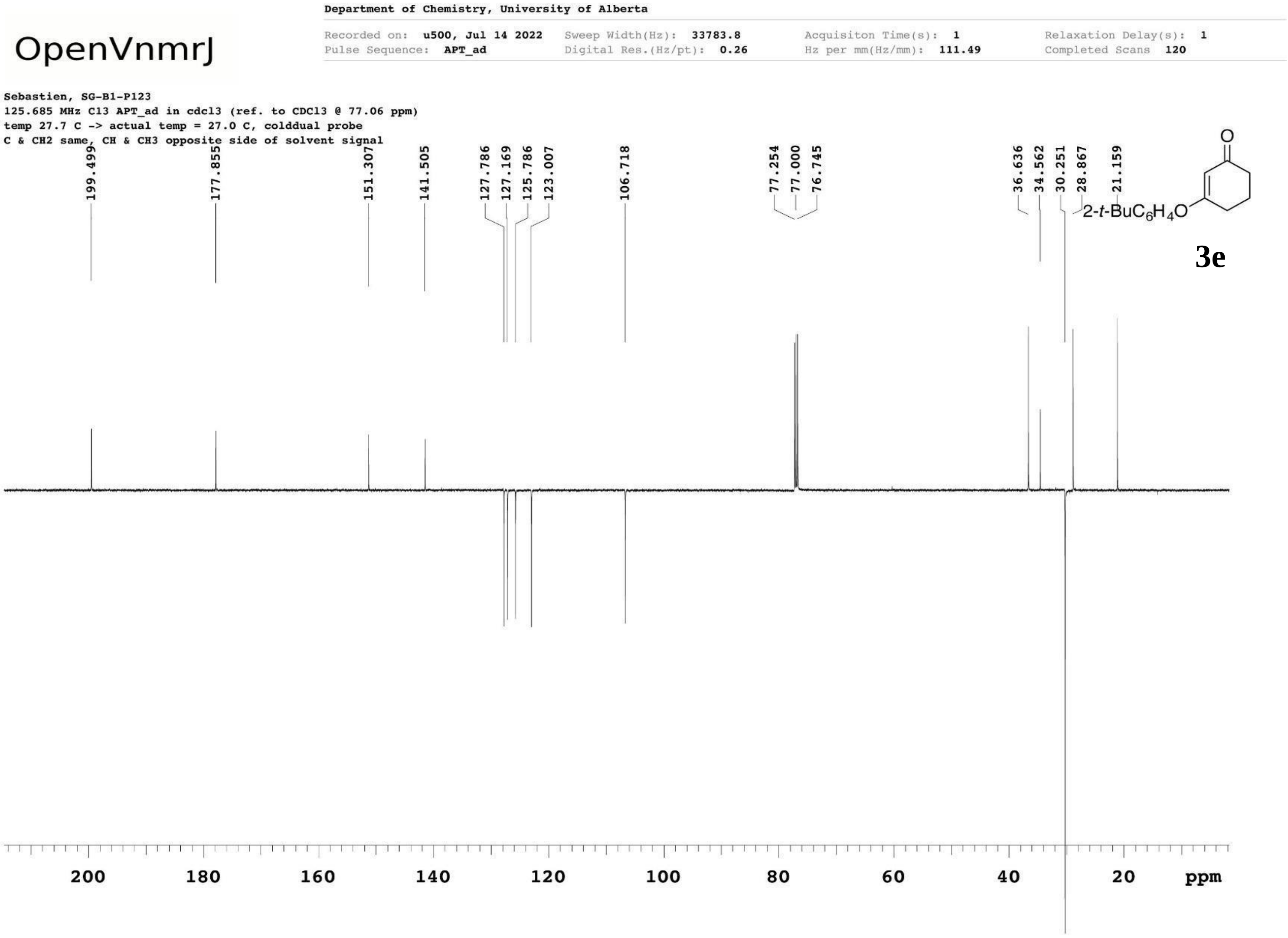


Figure A11 ^{1}H NMR spectrum of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e).



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OpenVnmrJ        Department of Chemistry, University of Alberta
                 Recorded on:  u500, Jul 14 2022   Sweep Width(Hz):  33783.8   Acquisiton Time(s):  1      Relaxation Delay(s):  1
                 Pulse Sequence:  APT_ad           Digital Res.(Hz/pt):  0.26  Hz per mm(Hz/mm):  111.49  Completed Scans  120
Sebastien, SG-B1-P123
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal
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File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Sebastien/2022.07/2022.07.14.u5_SG-B1-P123_loc7_15.32_C13_APT_ad
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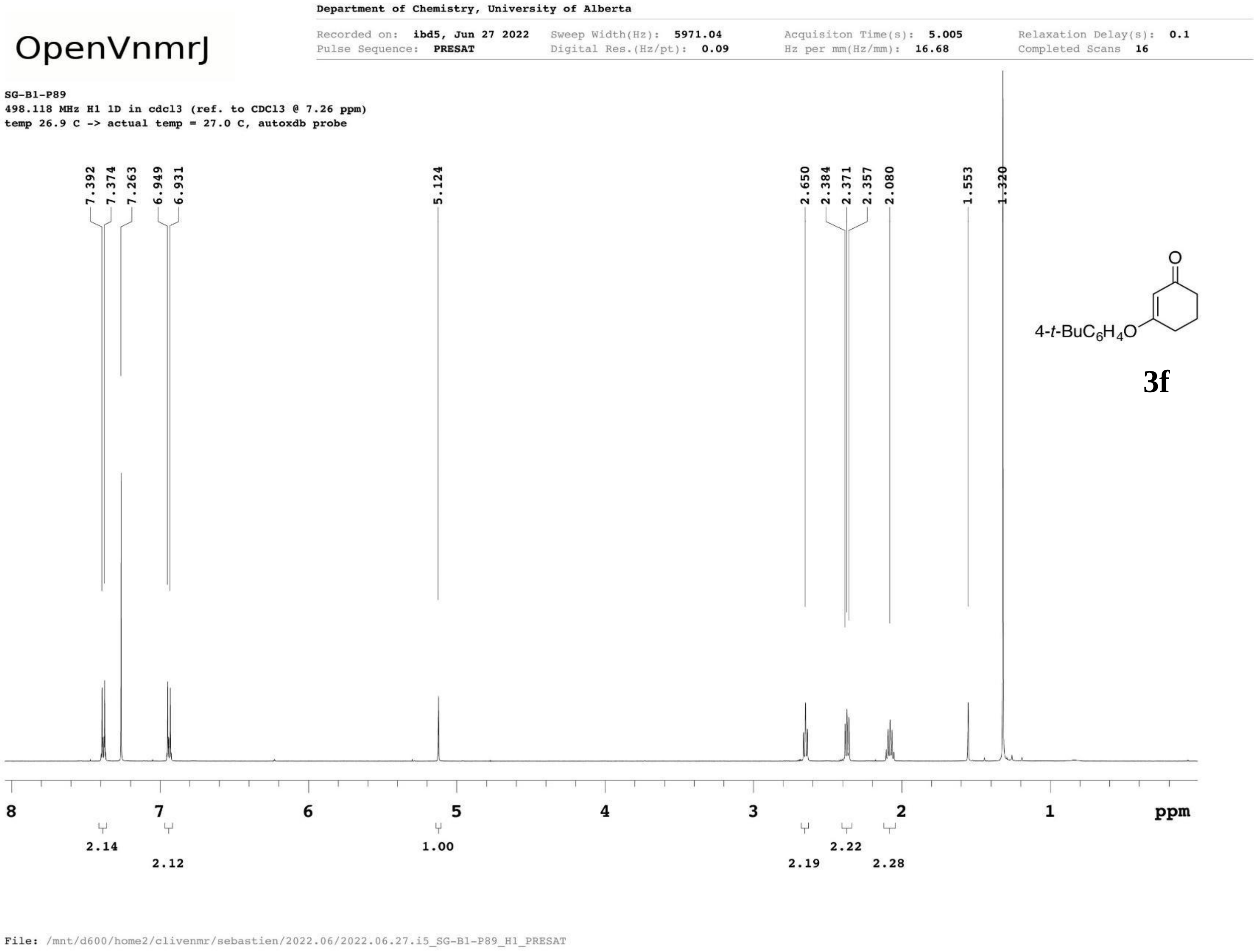
Figure A12 ^{13}C{^{1}H} NMR spectrum of 3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (3e).



Department of Chemistry, University of Alberta

Recorded on: ibd5, Jun 27 2022
Pulse Sequence: PRESAT
Sweep Width(Hz): 5971.04
Digital Res.(Hz/pt): 0.09
Acquisiton Time(s): 5.005
Hz per mm(Hz/mm): 16.68
Relaxation Delay(s): 0.1
Completed Scans 16

SG-B1-P89
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.06/2022.06.27.i5_SG-B1-P89_H1_PRESAT

Figure A13 ^{1}H NMR spectrum of 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (3f).

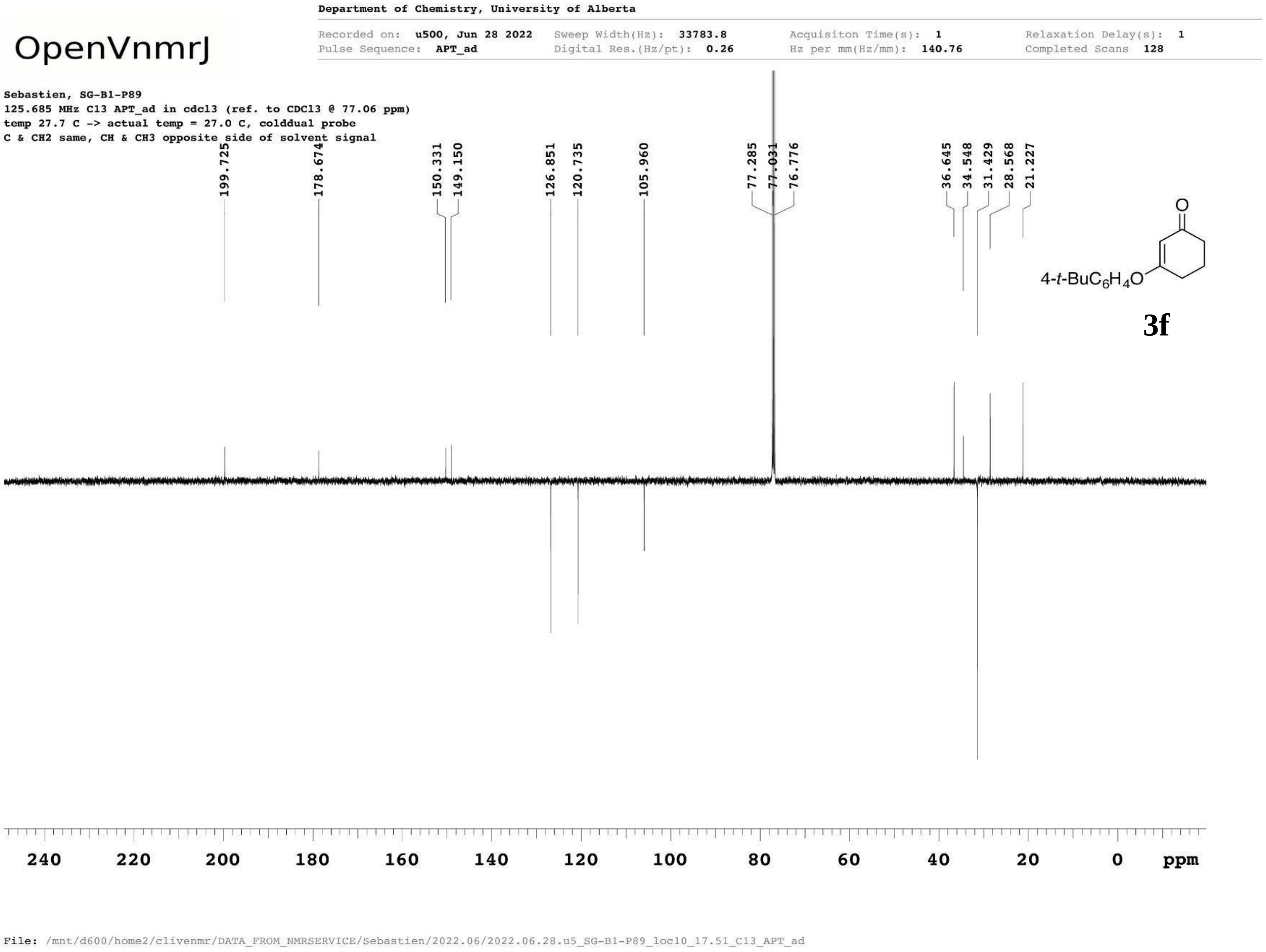
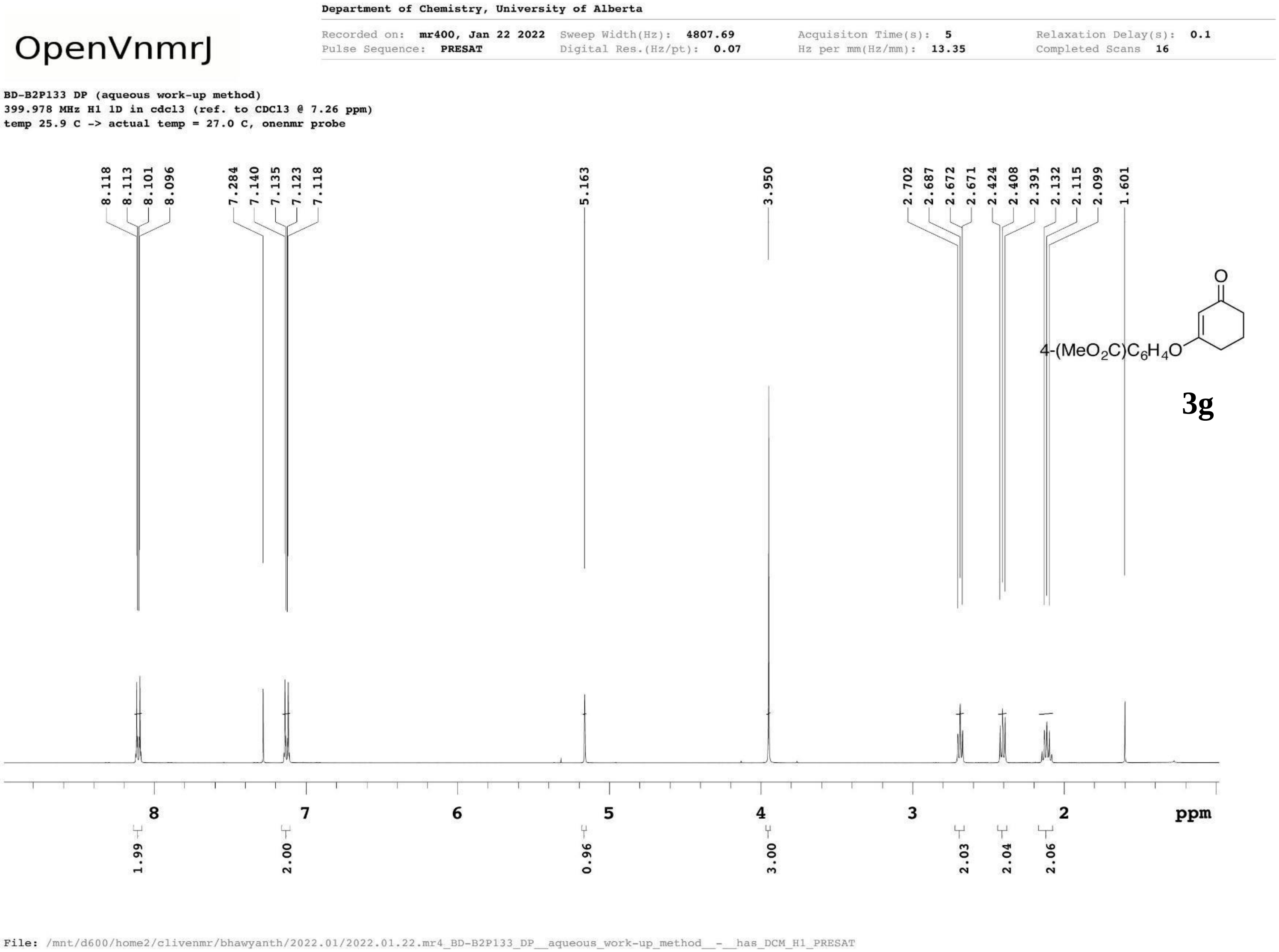


Figure A14 $^{13}C\{^1H\}$ NMR spectrum of 3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (3f).

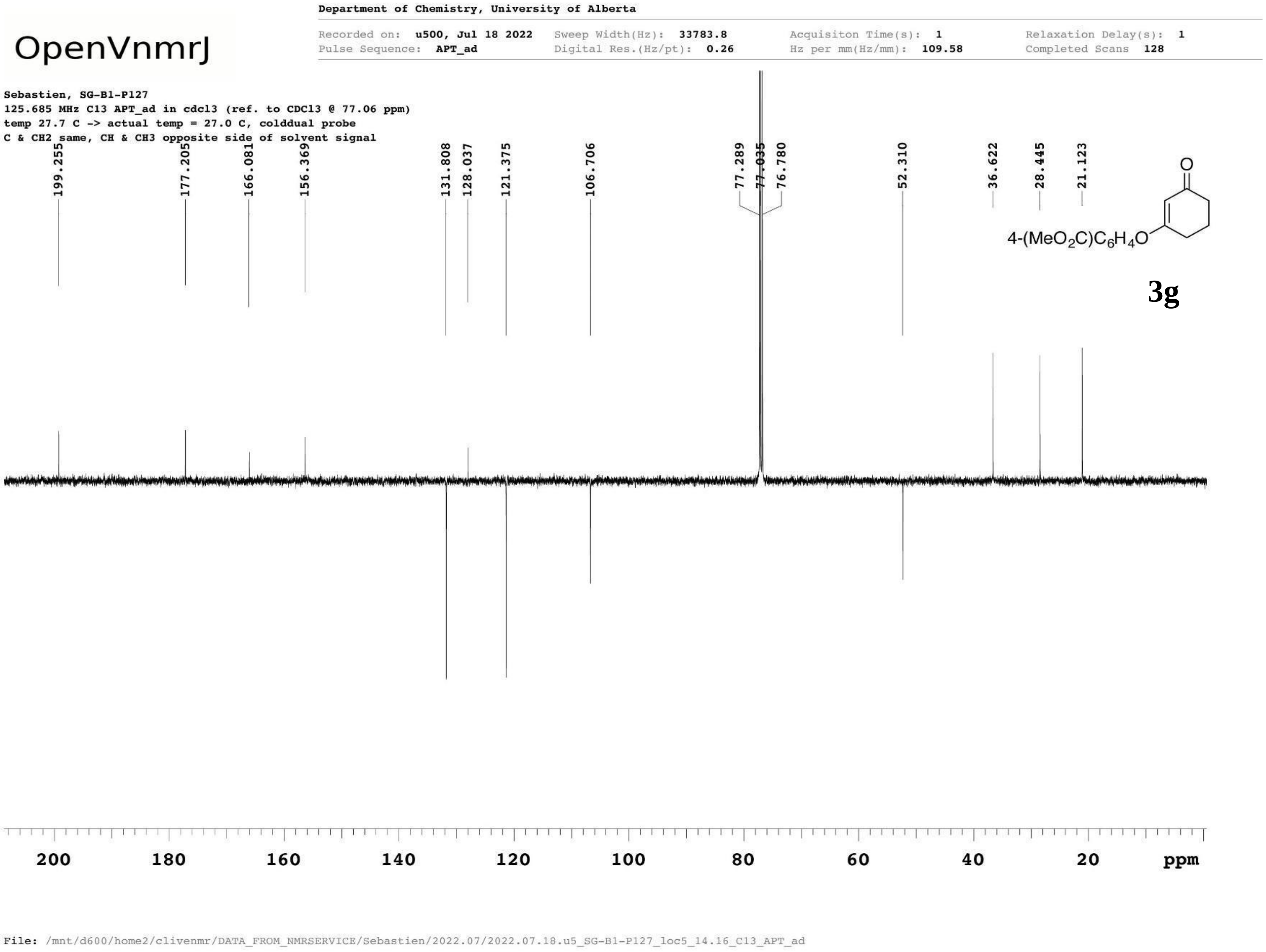

Department of Chemistry, University of Alberta

Recorded on: mr400, Jan 22 2022
Pulse Sequence: PRESAT
Sweep Width(Hz): 4807.69
Digital Res.(Hz/pt): 0.07
Acquisiton Time(s): 5
Hz per mm(Hz/mm): 13.35
Relaxation Delay(s): 0.1
Completed Scans 16

BD-B2P133 DP (aqueous work-up method)
399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

File: /mnt/d600/home2/clivenmr/bhawyanth/2022.01/2022.01.22.mr4_BD-B2P133_DP__aqueous_work-up_method__-__has_DCM_H1_PRESAT

Figure A15 ^{1}H NMR spectrum of methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g).



OpenVnmrJ

Department of Chemistry, University of Alberta

Recorded on: u500, Jul 18 2022 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1
Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 109.58 Completed Scans 128

Sebastien, SG-B1-P127
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Sebastien/2022.07/2022.07.18.u5_SG-B1-P127_loc5_14.16_C13_APT_ad

Figure A16 ^{13}C{^{1}H} NMR spectrum of methyl 4-[(3-oxocyclohex-1-en-1-yl)oxy]benzoate (3g).

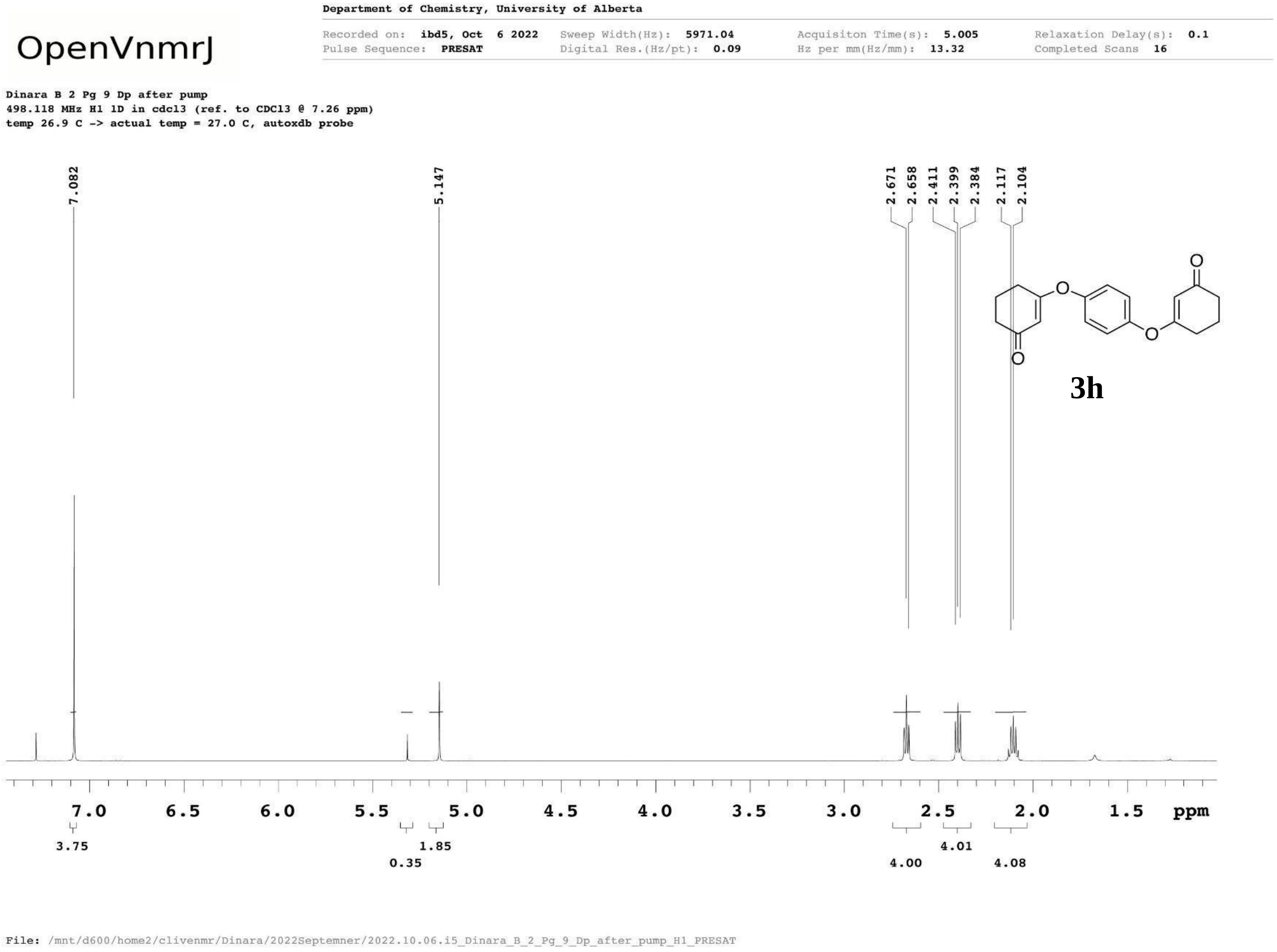


Figure A17 ^{1}H NMR spectrum of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h).

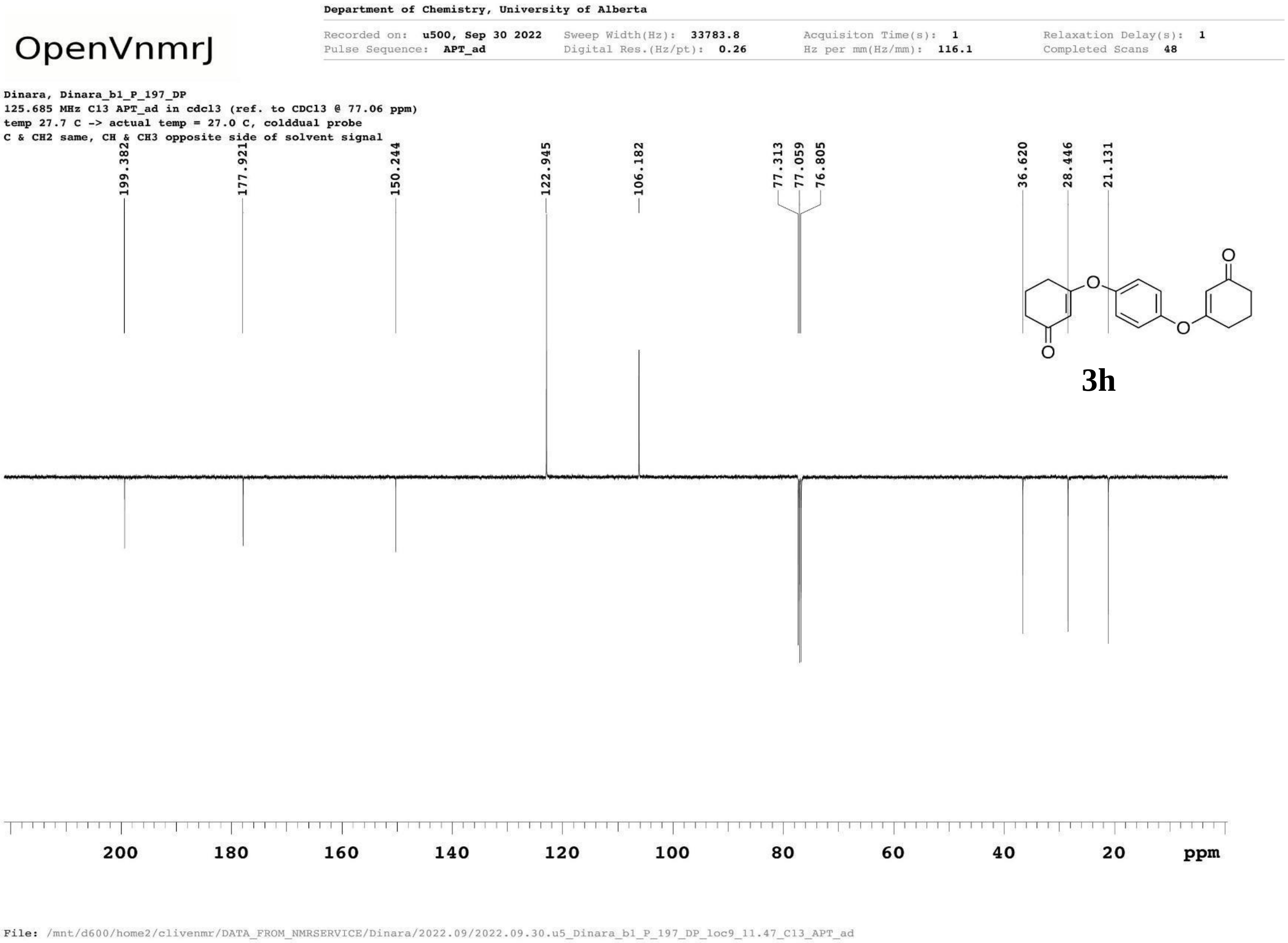
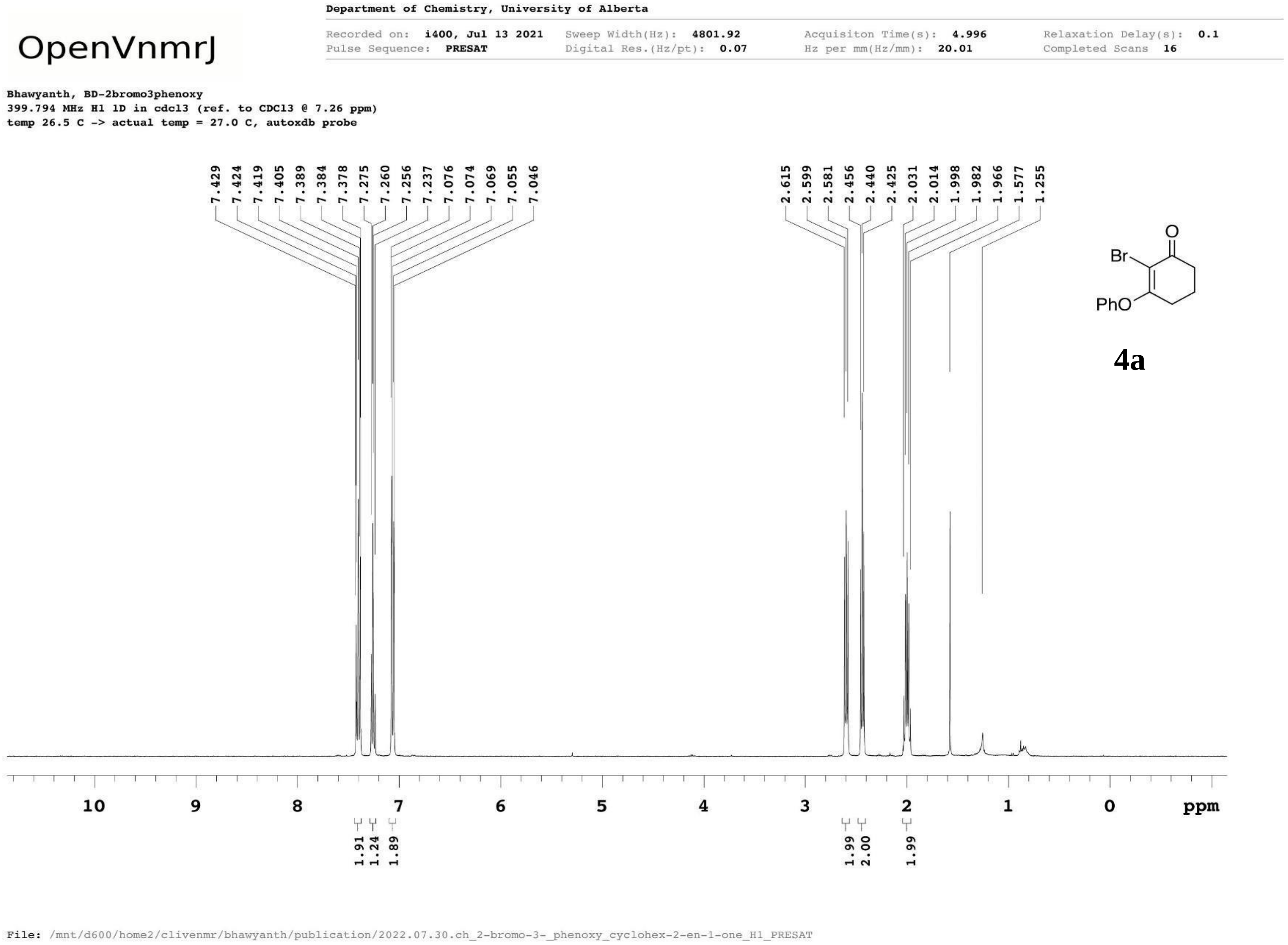


Figure A18 $^{13}C\{^{1}H\}$ NMR spectrum of 3-{4-[(3-oxocyclohex-1-en-1-yl)oxy]phenoxy}cyclohex-2-ene-1-one (3h).



Department of Chemistry, University of Alberta

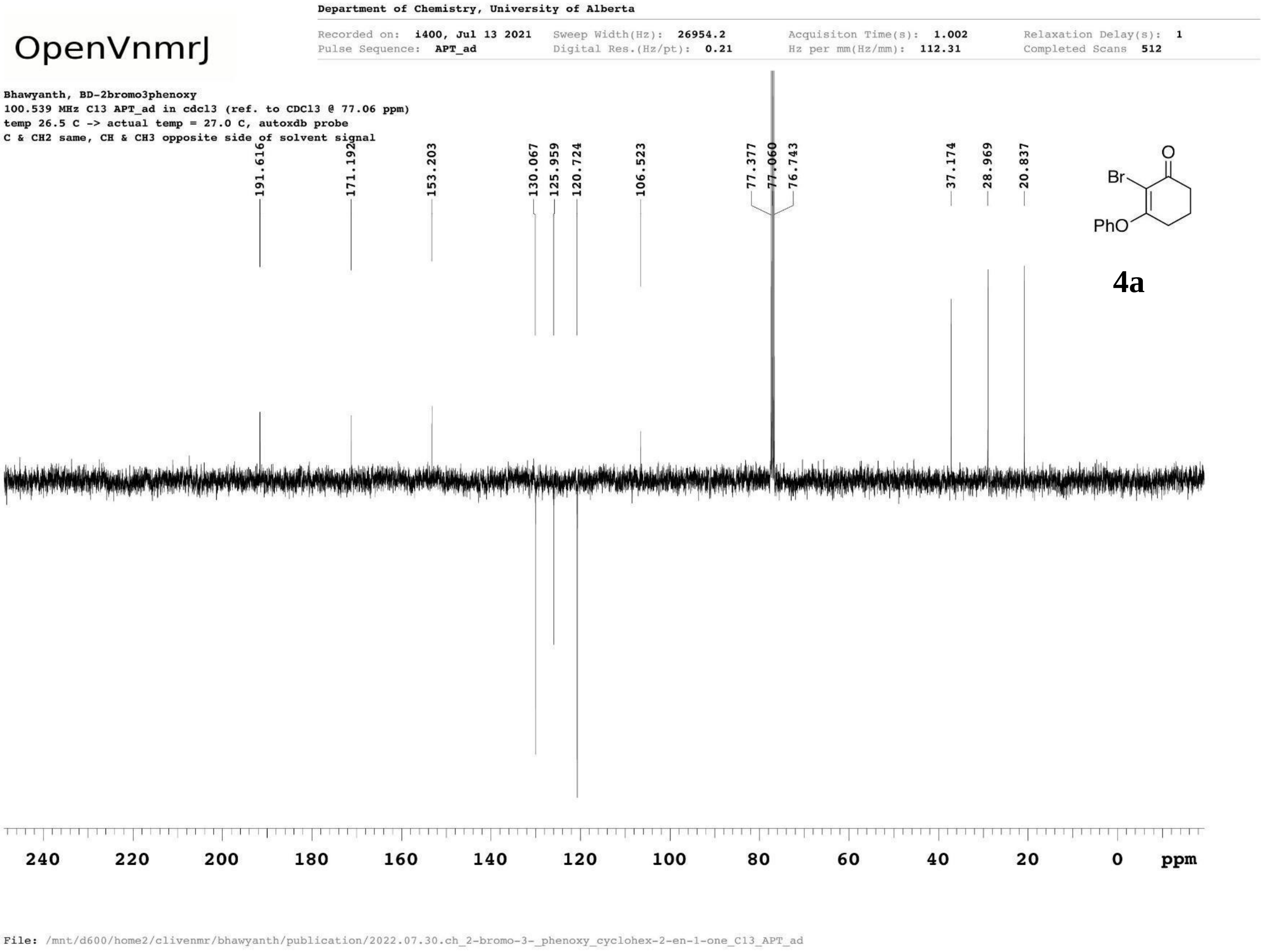
OpenVnmrJ

Recorded on: i400, Jul 13 2021 Sweep Width(Hz): 4801.92 Acquisiton Time(s): 4.996 Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT Digital Res.(Hz/pt): 0.07 Hz per mm(Hz/mm): 20.01 Completed Scans 16

Bhawyanth, BD-2bromo3phenoxy
399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/bhawyanth/publication/2022.07.30.ch_2-bromo-3-_phenoxy_cyclohex-2-en-1-one_H1_PRESAT

Figure A19 ^{1}H NMR spectrum of 2-bromo-3-(phenoxy)cyclohex-2-en-1-one (4a).



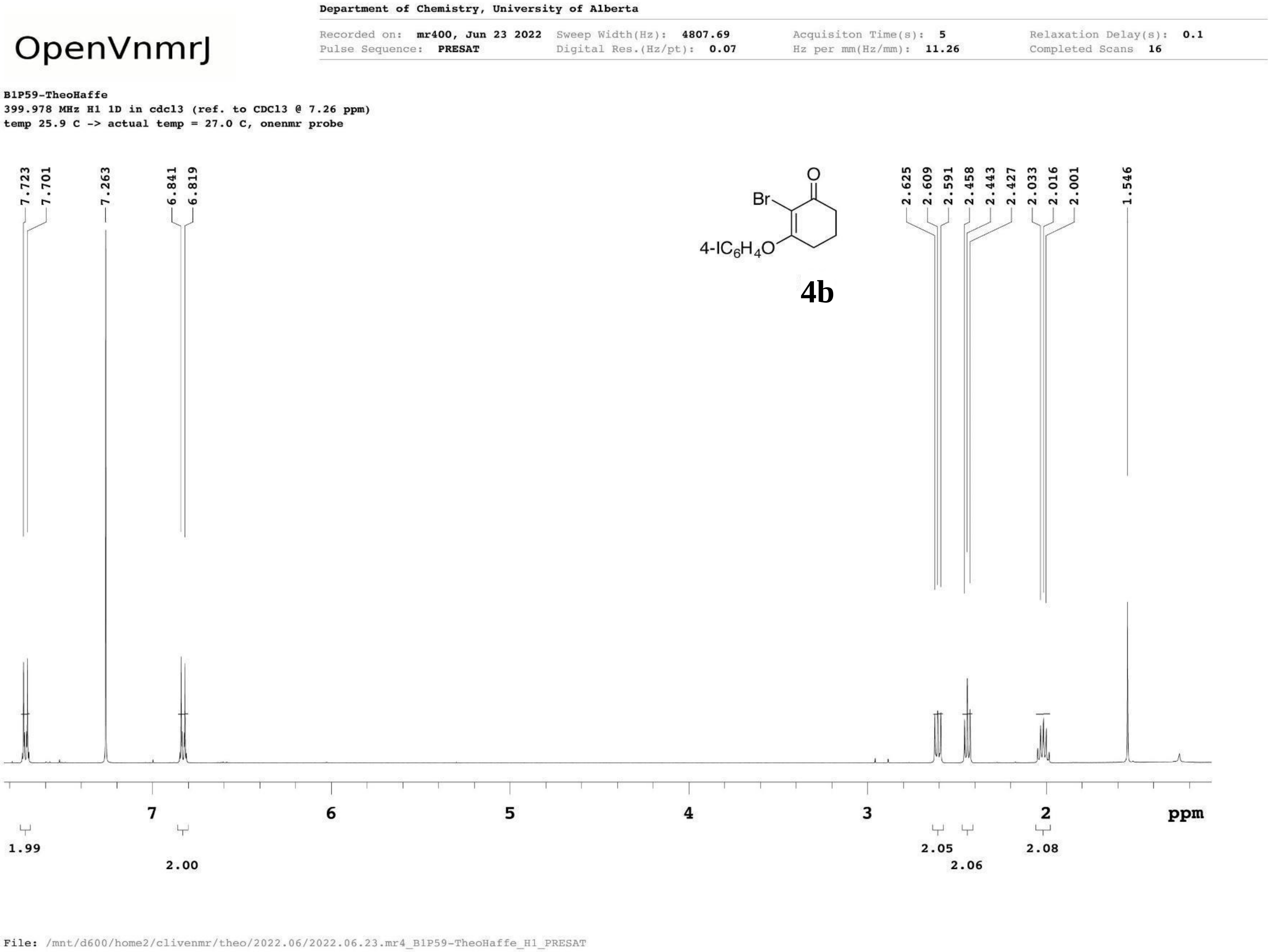
Department of Chemistry, University of Alberta

Recorded on: i400, Jul 13 2021 Sweep Width(Hz): 26954.2 Acquisiton Time(s): 1.002 Relaxation Delay(s): 1
Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.21 Hz per mm(Hz/mm): 112.31 Completed Scans 512

Bhawyanth, BD-2bromo3phenoxy
100.539 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 26.5 C -> actual temp = 27.0 C, autoxdb probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/bhawyanth/publication/2022.07.30.ch_2-bromo-3-_phenoxy_cyclohex-2-en-1-one_C13_APT_ad

Figure A20 $^{13}C\{^{1}H\}$ NMR spectrum of 2-bromo-3-(phenoxy)cyclohex-2-en-1-one (4a).



Department of Chemistry, University of Alberta

OpenVnmrJ

Recorded on: **mr400, Jun 23 2022**
Sweep Width(Hz): **4807.69**
Acquisiton Time(s): **5**
Relaxation Delay(s): **0.1**
Pulse Sequence: **PRESAT**
Digital Res.(Hz/pt): **0.07**
Hz per mm(Hz/mm): **11.26**
Completed Scans **16**

B1P59-TheoHaffe
399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

File: /mnt/d600/home2/clivenmr/theo/2022.06/2022.06.23.mr4_B1P59-TheoHaffe_H1_PRESAT

Figure A21 ^{1}H NMR spectrum of 2-bromo-3-(4-iodophenoxy)cyclohex-2-en-1-one (4b).

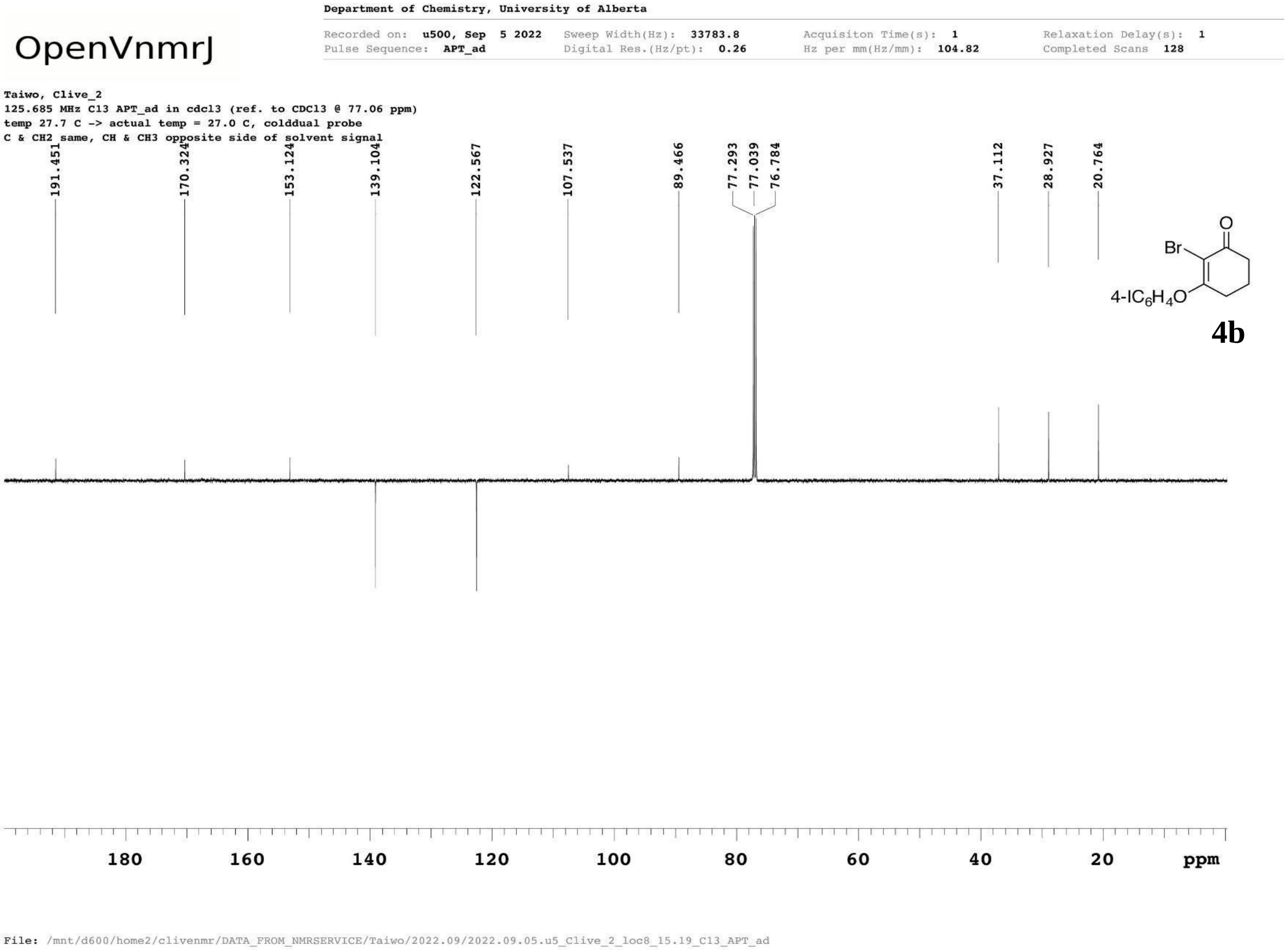
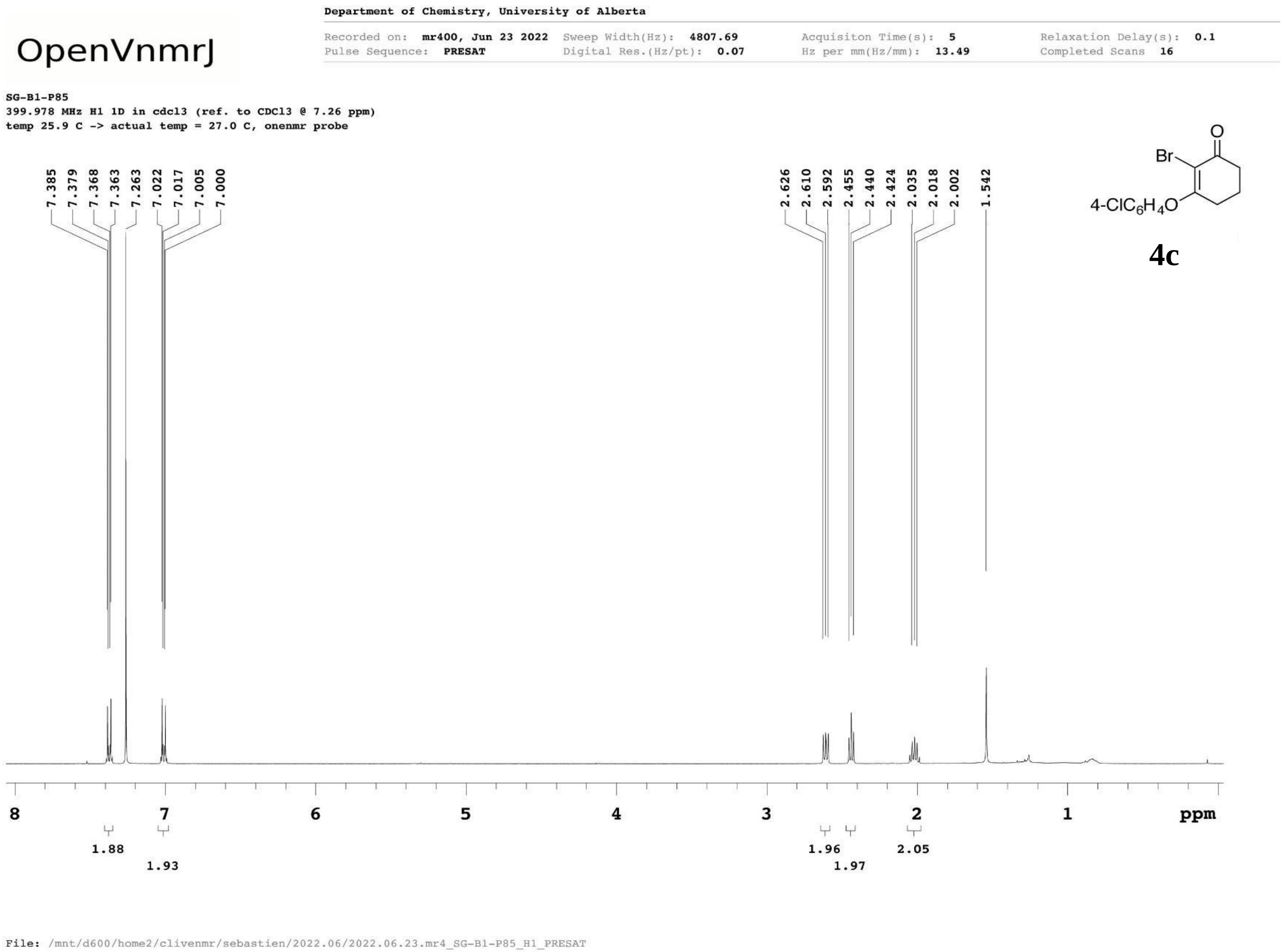


Figure A22 ^{13}C{^{1}H} NMR spectrum of 2-bromo-3-(4-iodophenoxy)cyclohex-2-en-1-one (4b).

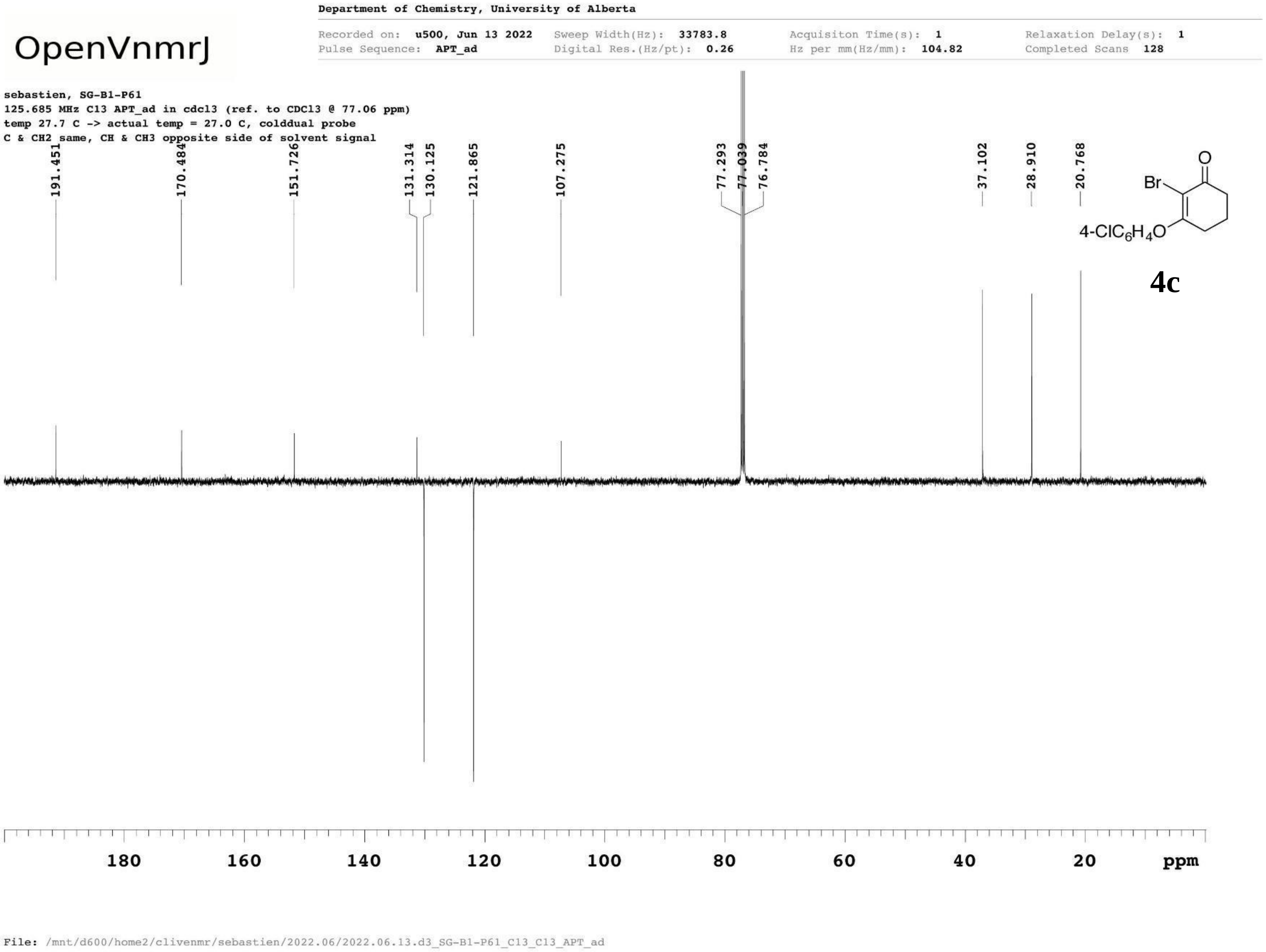

Department of Chemistry, University of Alberta

Recorded on: mr400, Jun 23 2022
Pulse Sequence: PRESAT
Sweep Width(Hz): 4807.69
Digital Res.(Hz/pt): 0.07
Acquisiton Time(s): 5
Hz per mm(Hz/mm): 13.49
Relaxation Delay(s): 0.1
Completed Scans 16

SG-B1-P85
399.978 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 25.9 C -> actual temp = 27.0 C, onenmr probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.06/2022.06.23.mr4_SG-B1-P85_H1_PRESAT

Figure A23 ^{1}H NMR spectrum of 2-bromo-3-(4-chlorophenoxy)cyclohex-2-en-1-one (4c).



OpenVnmrJ

Department of Chemistry, University of Alberta

Recorded on: u500, Jun 13 2022 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1

Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 104.82 Completed Scans 128

sebastien, SG-B1-P61

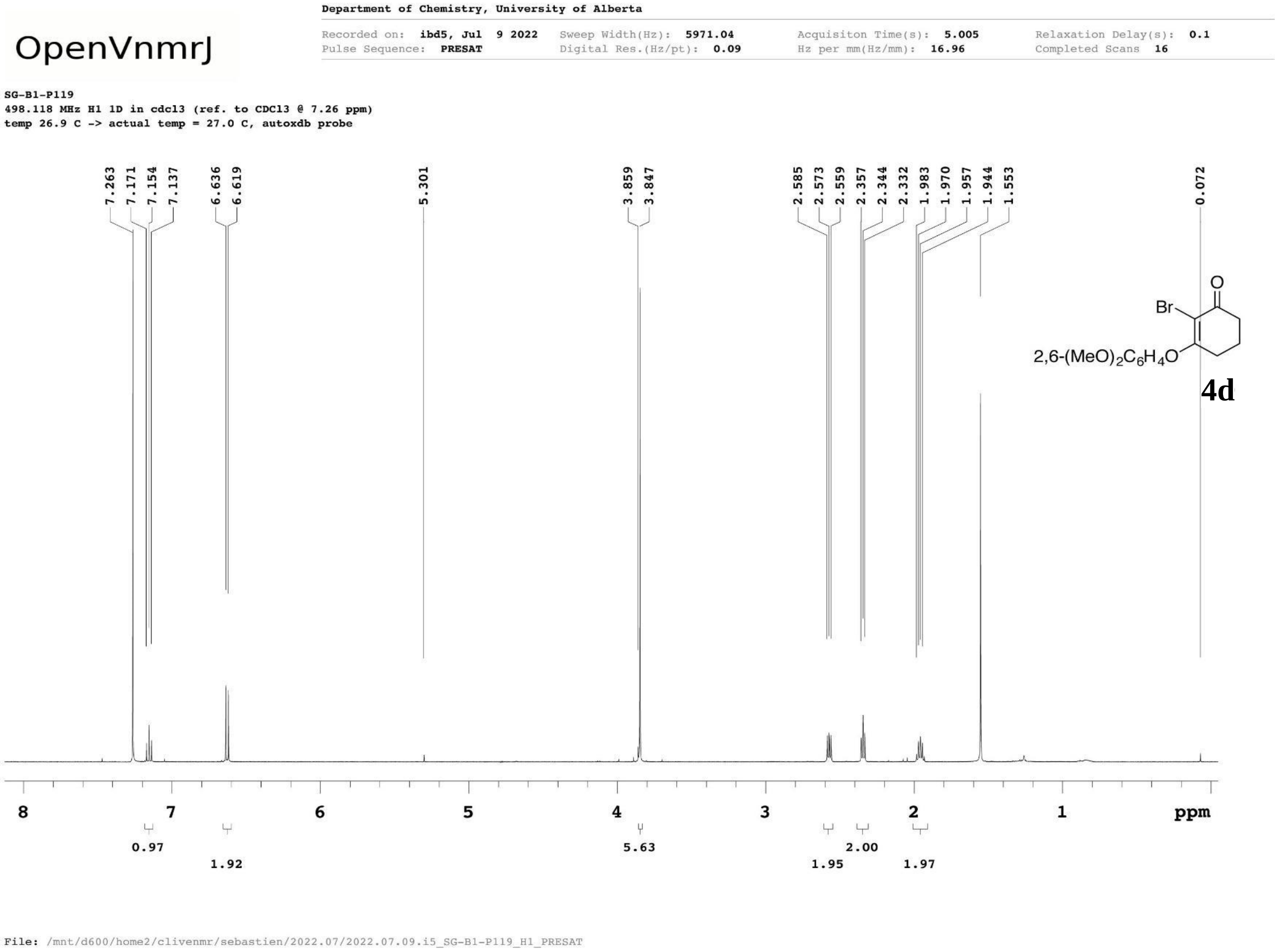
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

temp 27.7 C -> actual temp = 27.0 C, colddual probe

C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/sebastien/2022.06/2022.06.13.d3_SG-B1-P61_C13_C13_APT_ad

Figure A24 $^{13}C\{^1H\}$ NMR spectrum of 2-bromo-3-(4-chlorophenoxy)cyclohex-2-en-1-one (4c).



OpenVnmrJ

Department of Chemistry, University of Alberta

Recorded on: ibd5, Jul 9 2022 Sweep Width(Hz): 5971.04 Acquisiton Time(s): 5.005 Relaxation Delay(s): 0.1

Pulse Sequence: PRESAT Digital Res.(Hz/pt): 0.09 Hz per mm(Hz/mm): 16.96 Completed Scans 16

SG-B1-P119

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)

temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.07/2022.07.09.i5_SG-B1-P119_H1_PRESAT

Figure A25 ^{1}H NMR spectrum of 2-bromo-3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (4d).

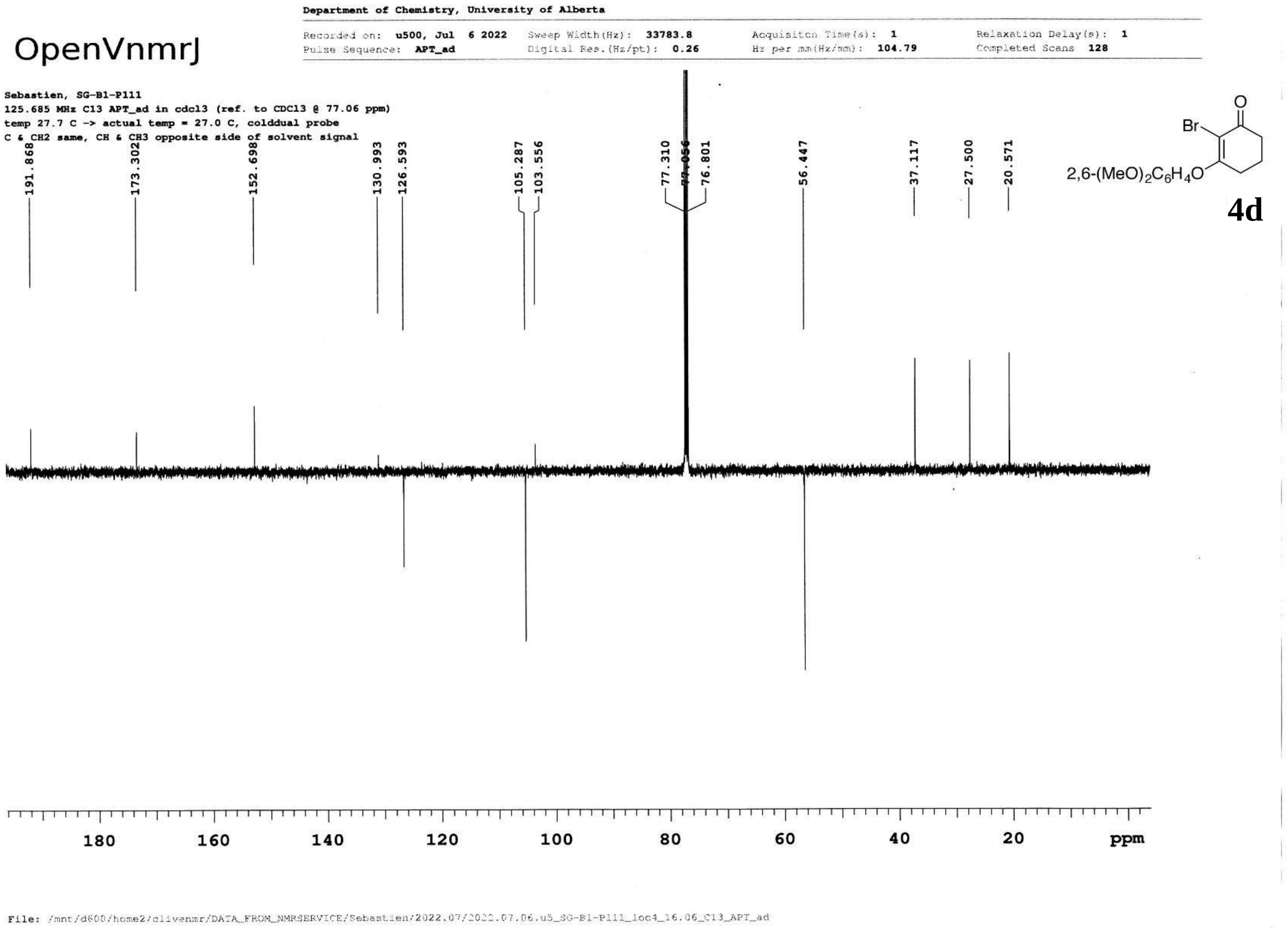
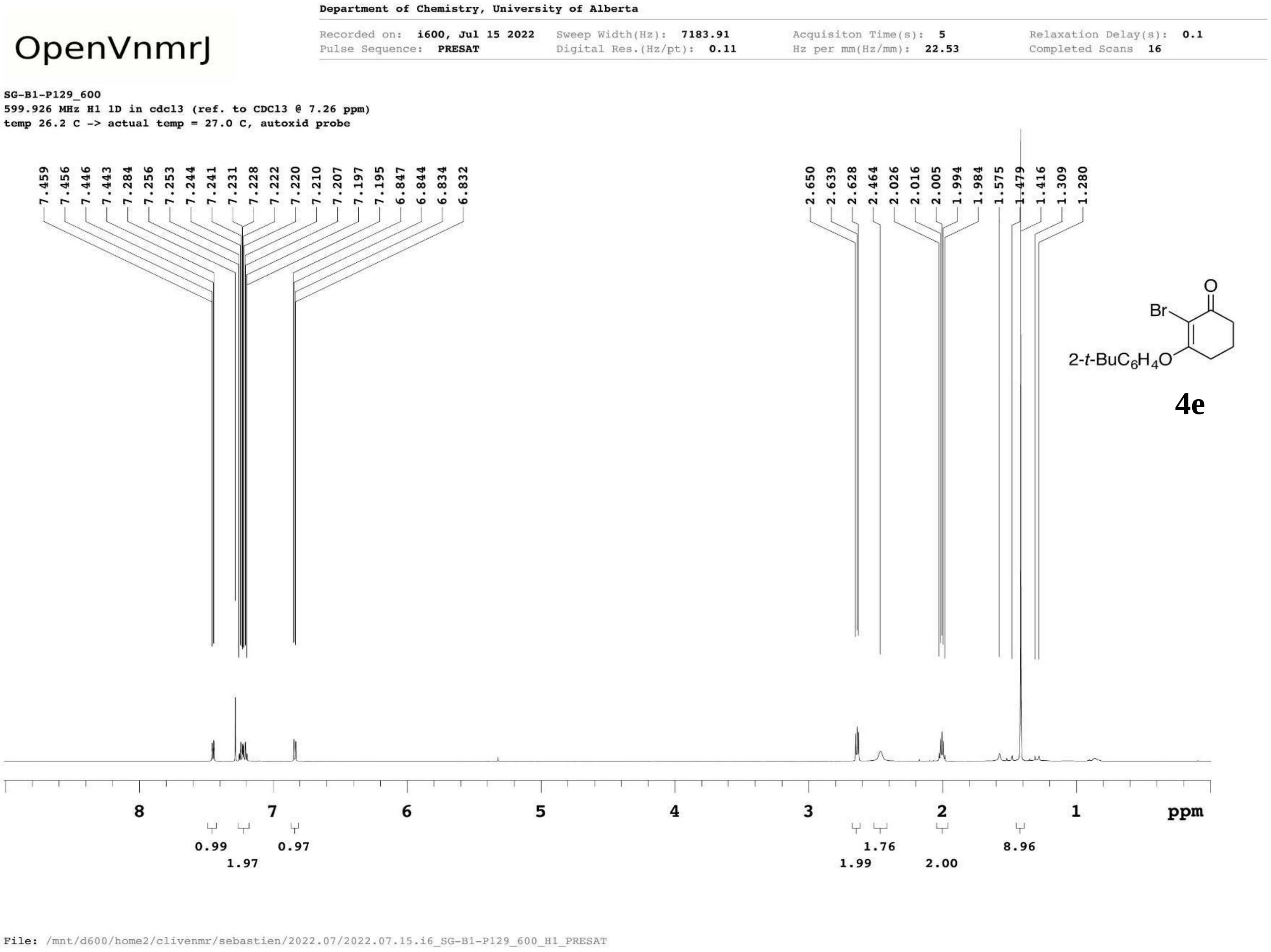


Figure A26 $^{13}C\{^1H\}$ NMR spectrum of 2-bromo-3-(2,6-dimethoxyphenoxy)cyclohex-2-en-1-one (4d).



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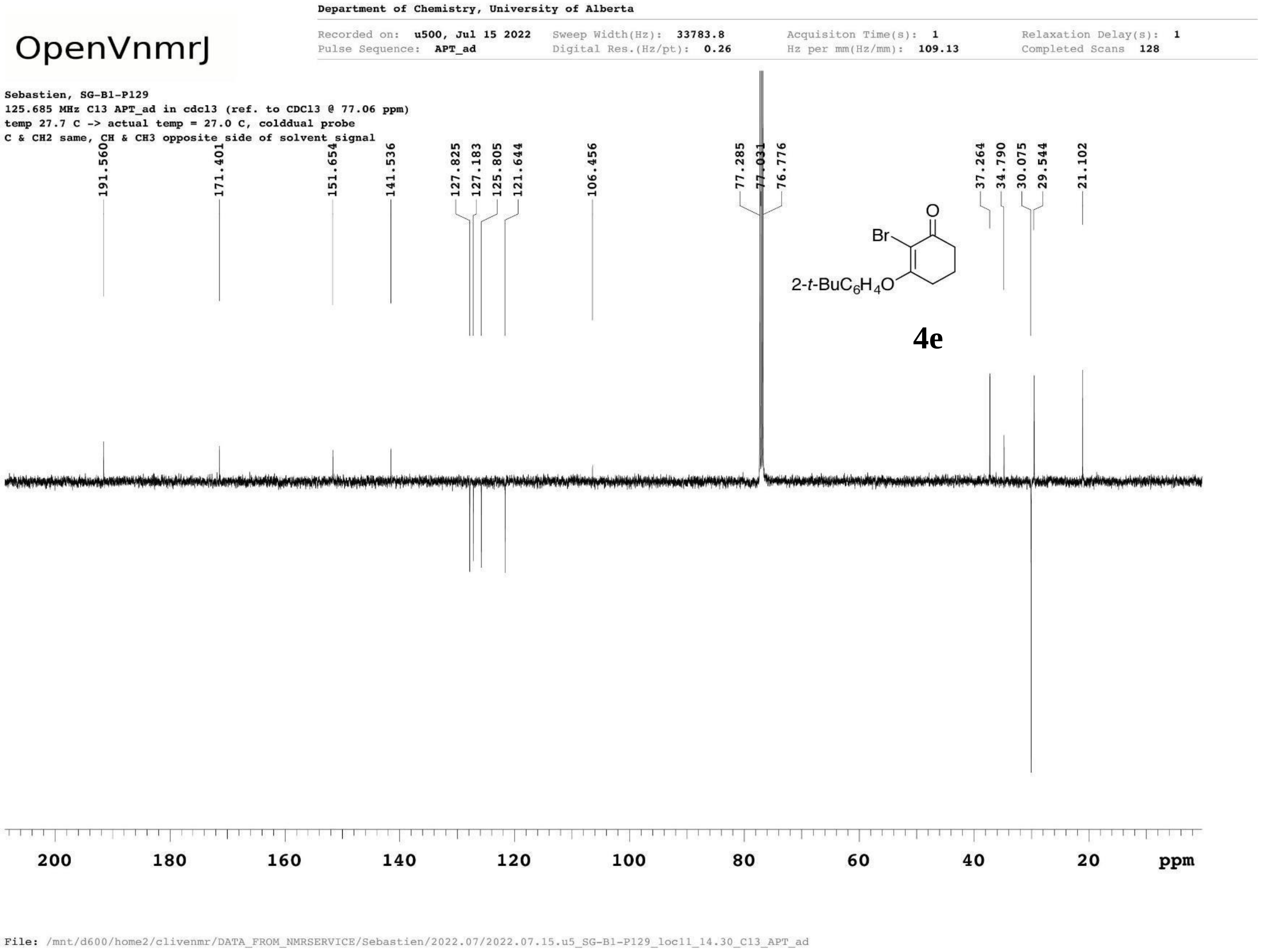
Recorded on: i600, Jul 15 2022 Sweep Width(Hz): 7183.91 Acquisiton Time(s): 5 Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT Digital Res.(Hz/pt): 0.11 Hz per mm(Hz/mm): 22.53 Completed Scans 16

SG-B1-P129_600
599.926 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.2 C -> actual temp = 27.0 C, autoxid probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.07/2022.07.15.i6_SG-B1-P129_600_H1_PRESAT

Figure A27 ^{1}H NMR spectrum of 2-bromo-3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (4e).



Department of Chemistry, University of Alberta

Recorded on: u500, Jul 15 2022 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1
Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 109.13 Completed Scans 128

Sebastien, SG-B1-P129
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Sebastien/2022.07/2022.07.15.u5_SG-B1-P129_loc11_14.30_C13_APT_ad

Figure A28 $^{13}C\{^1H\}$ NMR spectrum of 2-bromo-3-(2-*tert*-butylphenoxy)cyclohex-2-en-1-one (4e).

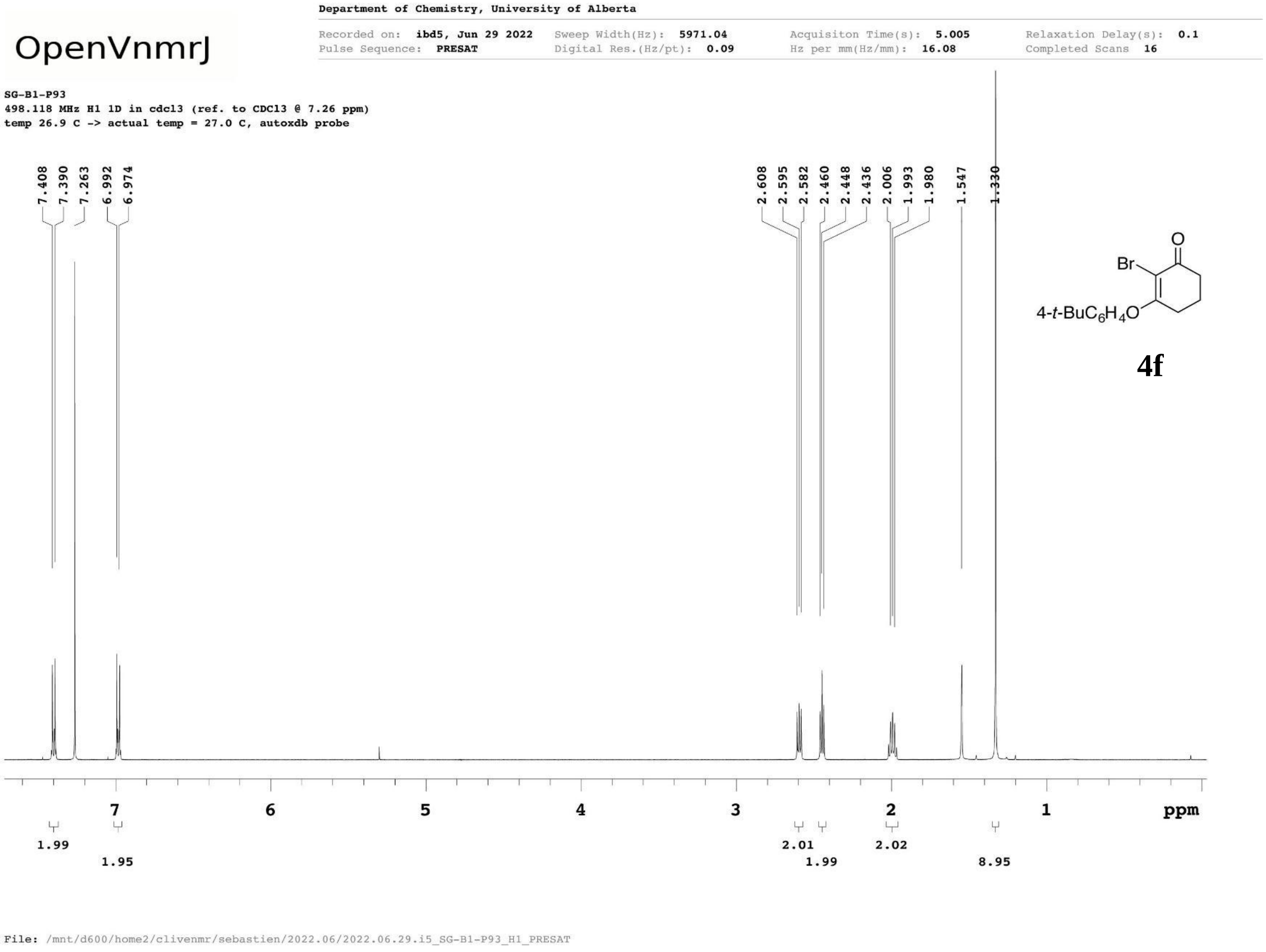


Figure A29 ^{1}H NMR spectrum of 2-bromo-3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (4f).

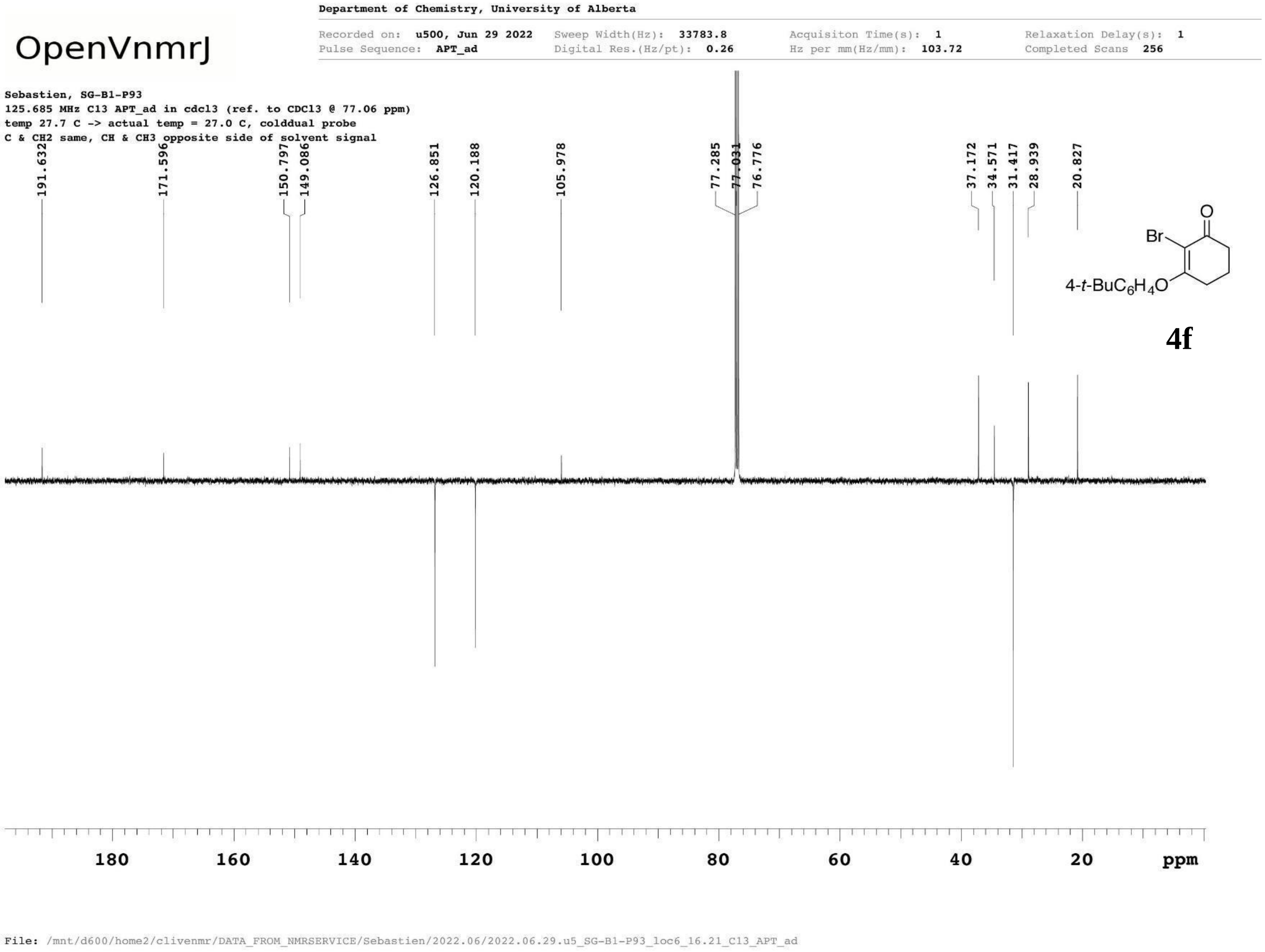


Figure A30 ^{13}C{^{1}H} NMR spectrum of 2-bromo-3-(4-*tert*-butylphenoxy)cyclohex-2-en-1-one (4f).

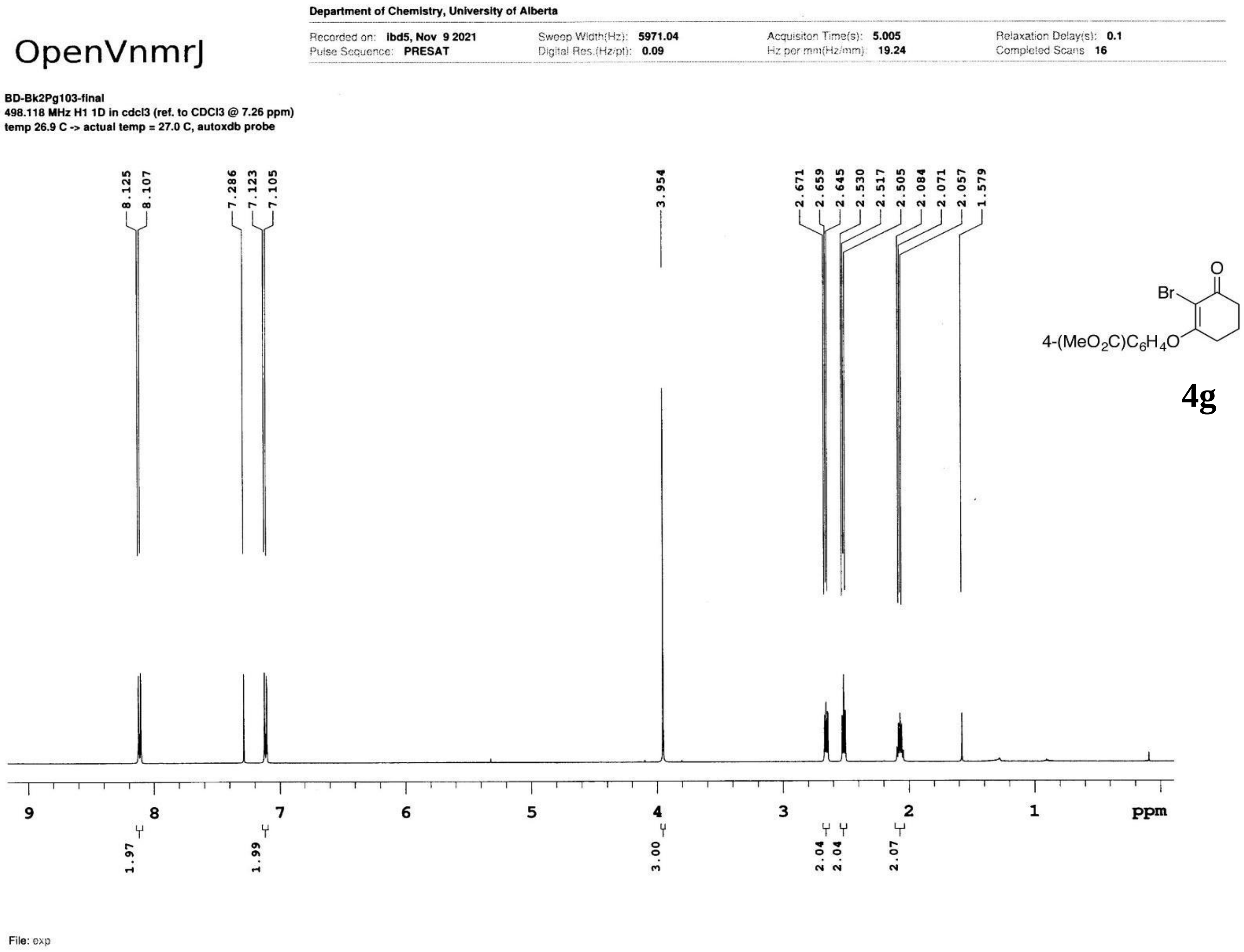
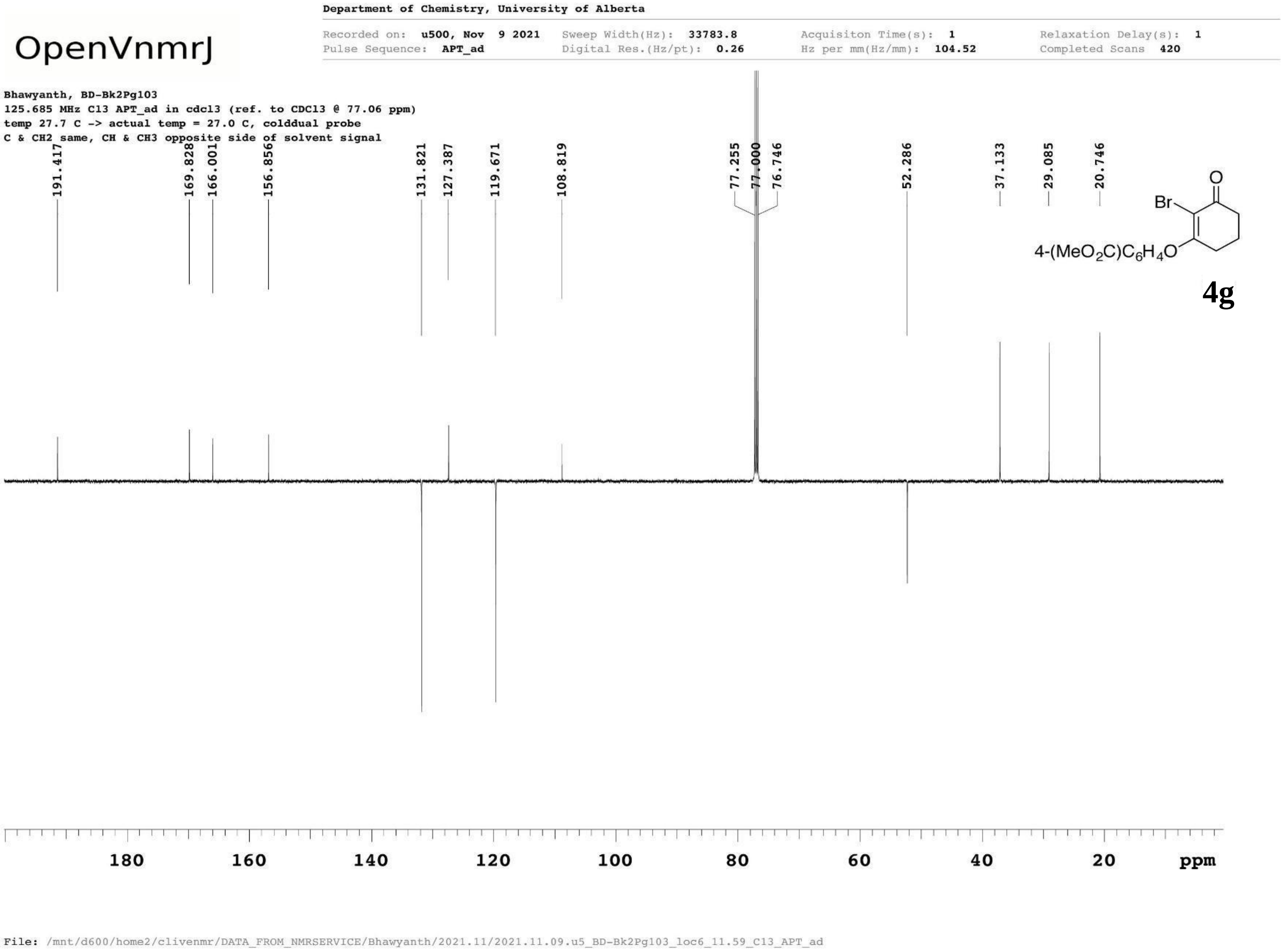


Figure A31 ^{1}H NMR spectrum of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (4g).



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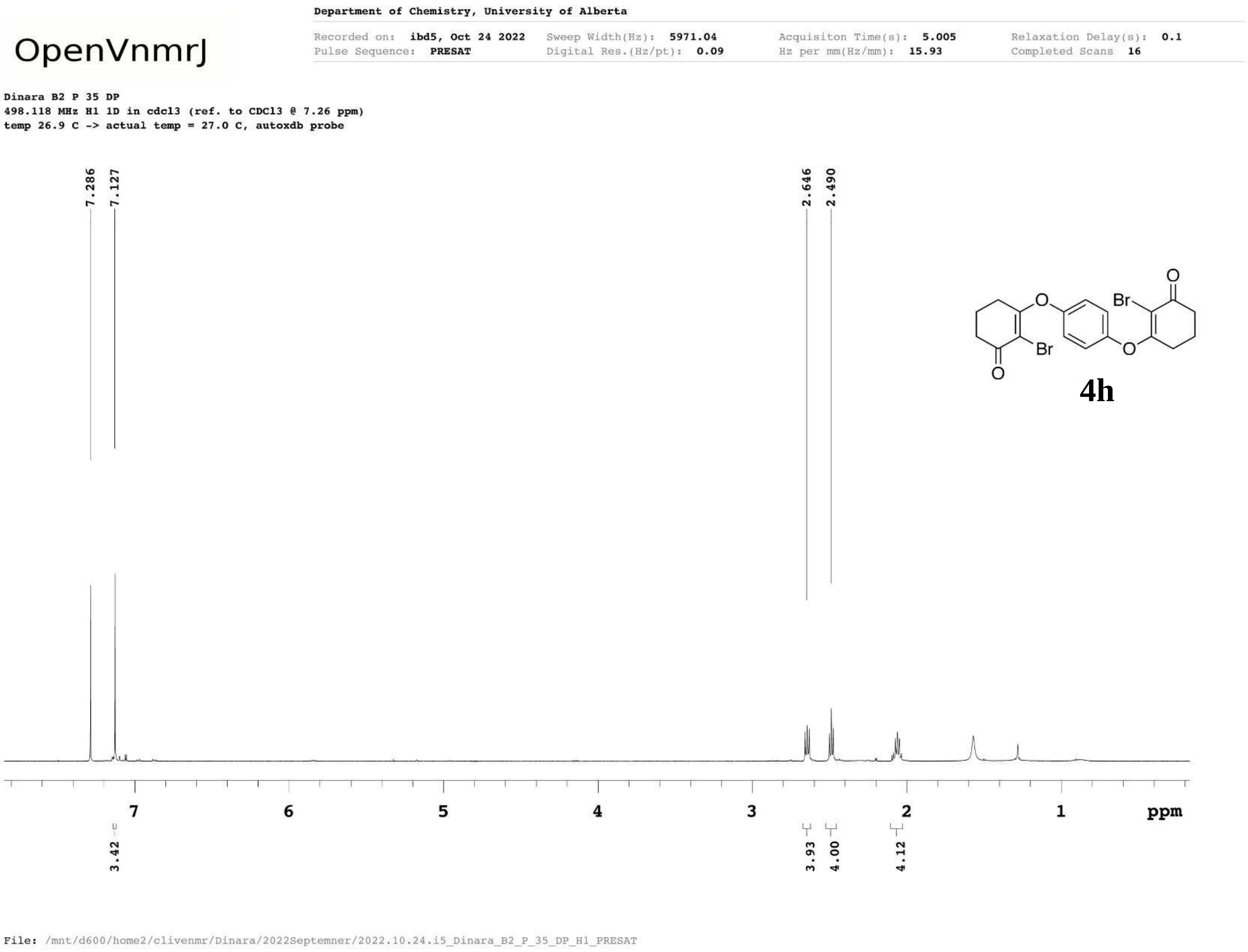
Department of Chemistry, University of Alberta

Recorded on:  u500, Nov  9 2021    Sweep Width(Hz):  33783.8      Acquisiton Time(s):  1        Relaxation Delay(s):  1
Pulse Sequence:  APT_ad             Digital Res.(Hz/pt):  0.26    Hz per mm(Hz/mm):  104.52    Completed Scans  420

Bhawyanth, BD-Bk2Pg103
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Bhawyanth/2021.11/2021.11.09.u5_BD-Bk2Pg103_loc6_11.59_C13_APT_ad
```

Figure A32 ^{13}C{^{1}H} NMR spectrum of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (4g).



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OpenVnmrJ

Recorded on: **ibd5, Oct 24 2022**
Pulse Sequence: **PRESAT**
Sweep Width(Hz): **5971.04**
Digital Res.(Hz/pt): **0.09**
Acquisiton Time(s): **5.005**
Hz per mm(Hz/mm): **15.93**
Relaxation Delay(s): **0.1**
Completed Scans **16**

Dinara B2 P 35 DP
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/Dinara/2022Septemner/2022.10.24.i5_Dinara_B2_P_35_DP_H1_PRESAT

Figure A33 ^{1}H NMR spectrum of 2-bromo-3-{4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]phenoxy} cyclohex-2-ene-1-one.

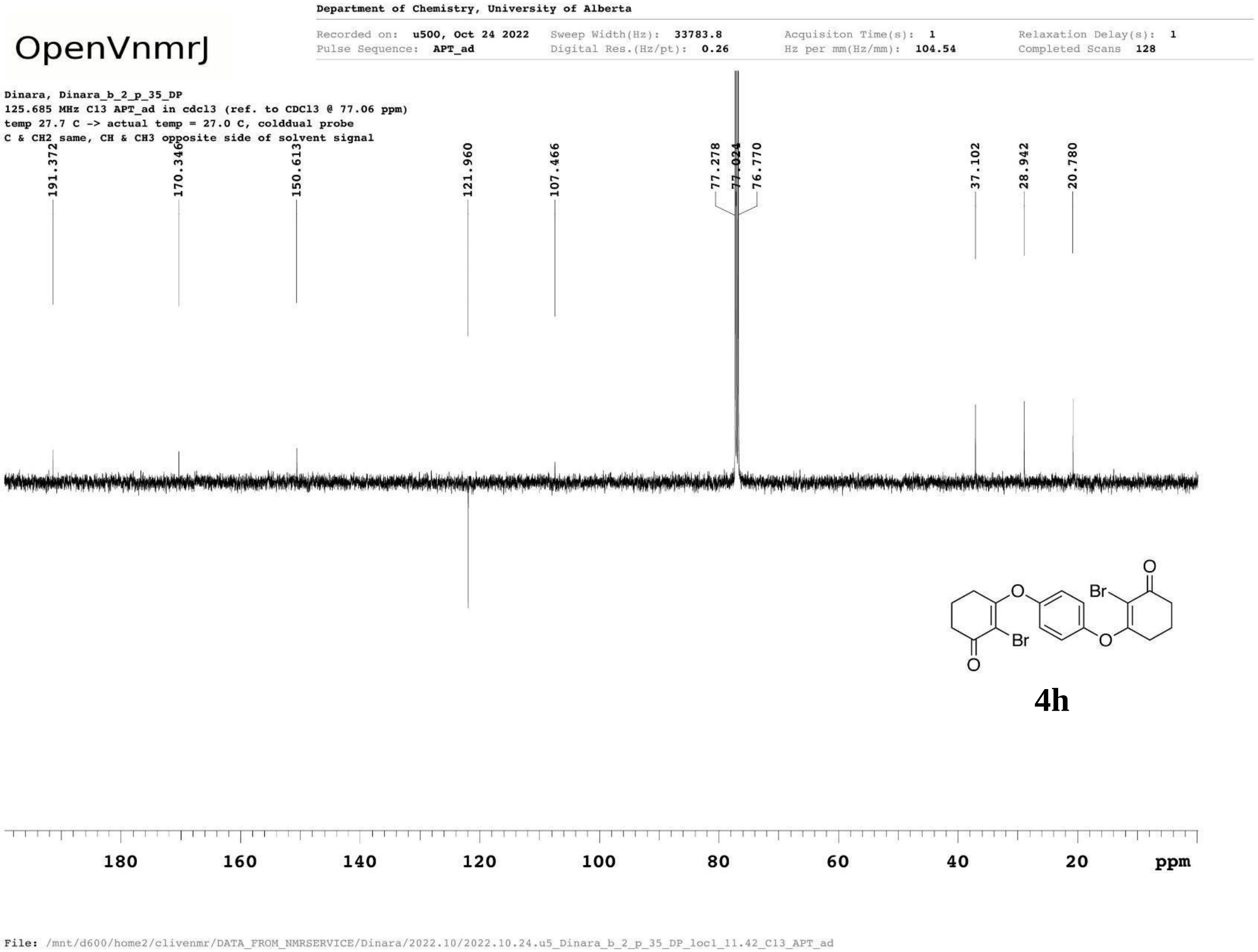


Figure A34 $^{13}C\{^{1}H\}$ NMR spectrum of 2-bromo-3-{4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]phenoxy} cyclohex-2-ene-1-one (4h).

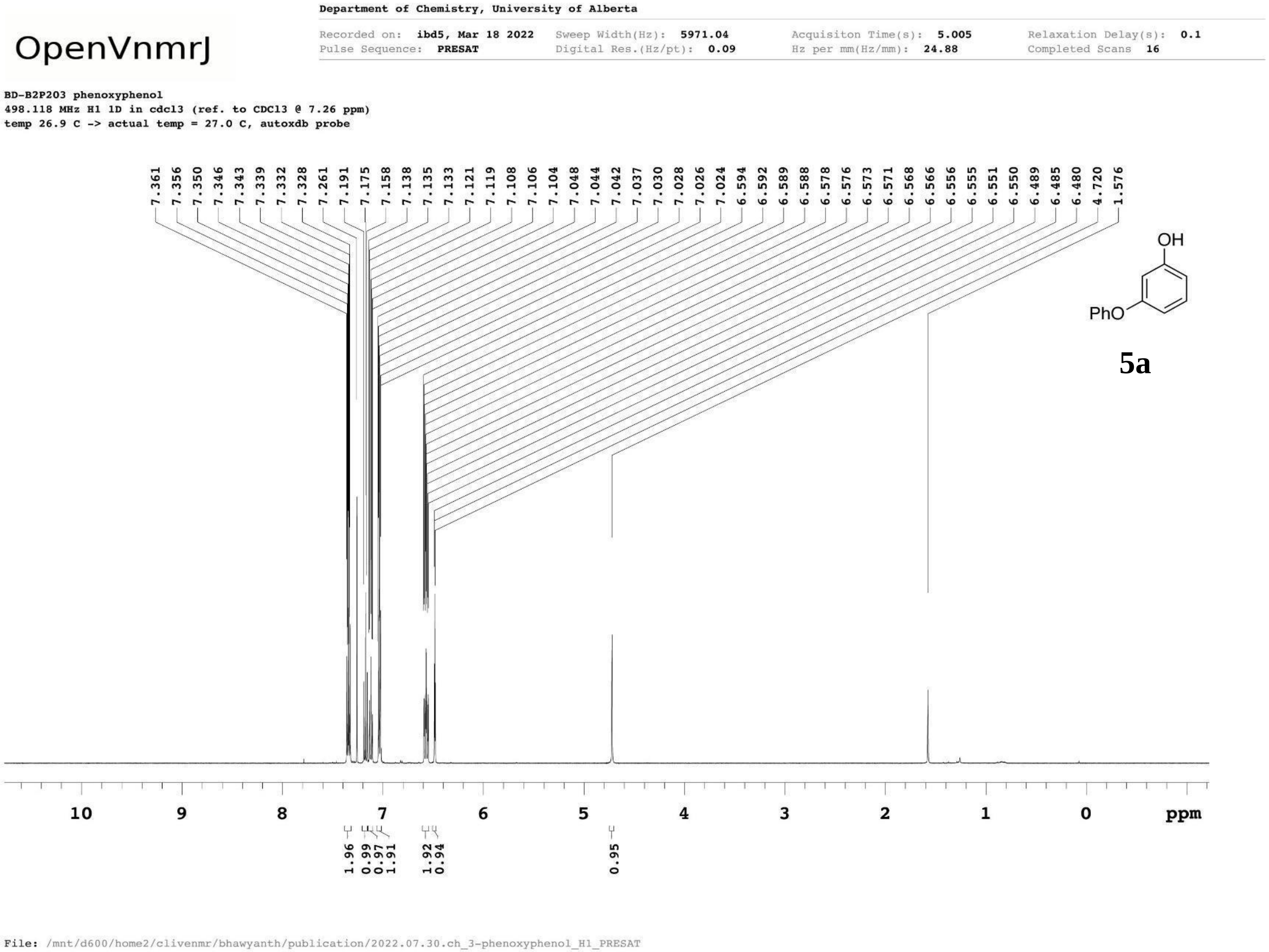
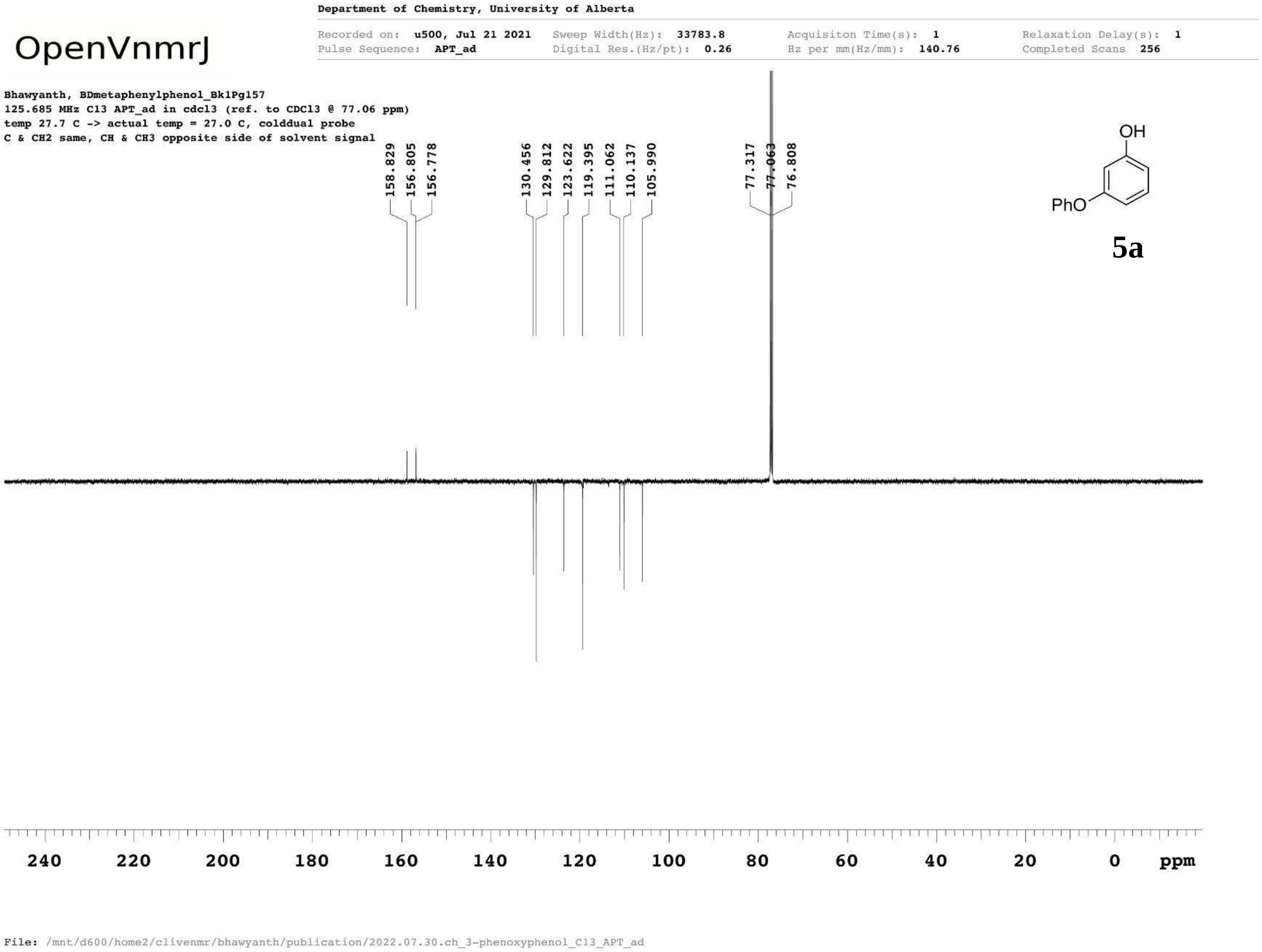


Figure A35 ^{1}H NMR spectrum of *meta*-(phenoxy)phenol (5a).



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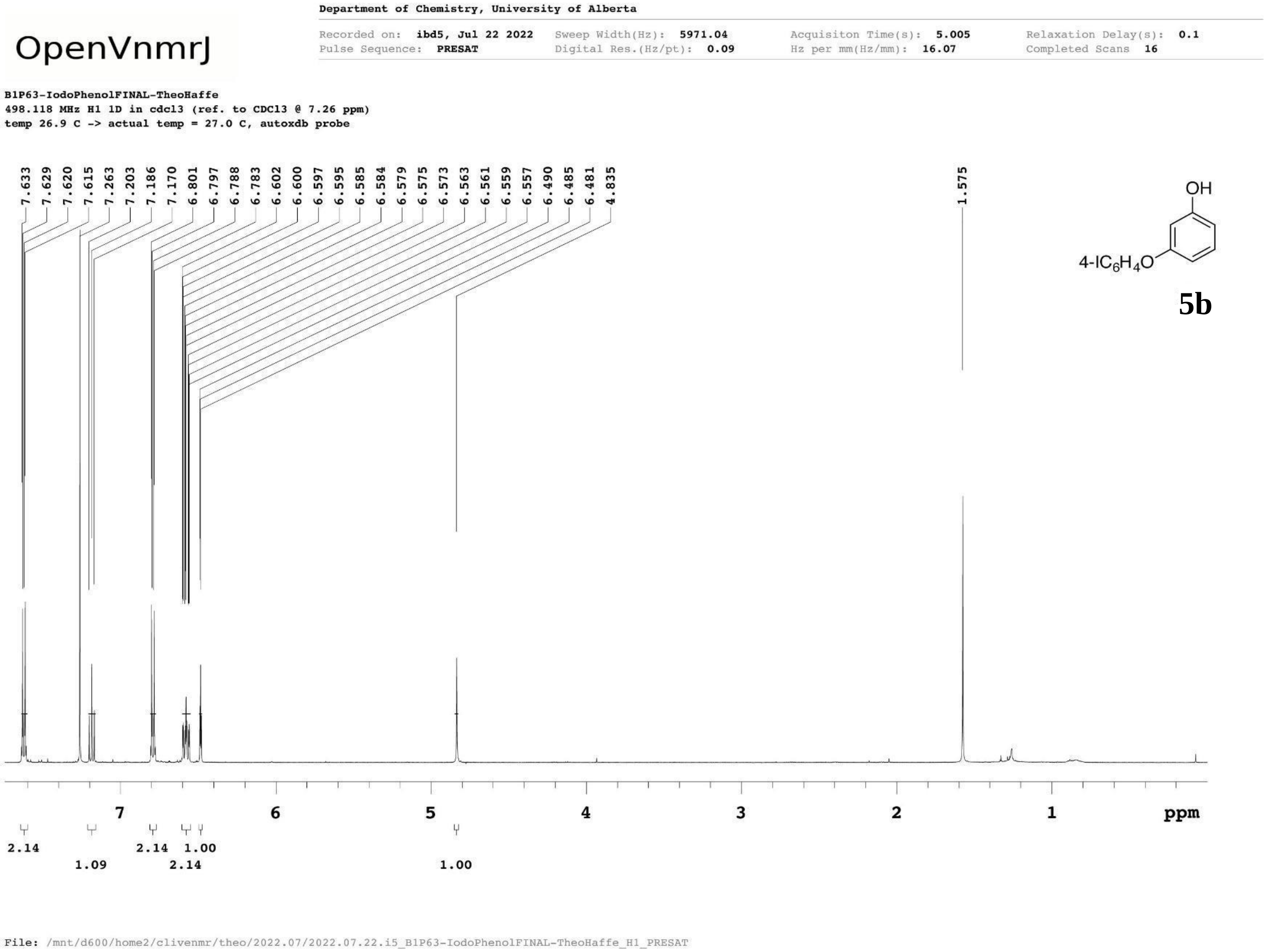
Recorded on: u500, Jul 21 2021
Pulse Sequence: APT_ad
Sweep Width(Hz): 33783.8
Digital Res.(Hz/pt): 0.26
Acquisiton Time(s): 1
Hz per mm(Hz/mm): 140.76
Relaxation Delay(s): 1
Completed Scans 256

Bhawyanth, BDmetaphenylphenol_Bk1Pg157
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/bhawyanth/publication/2022.07.30.ch_3-phenoxyphenol_C13_APT_ad

Figure A36 $^{13}C\{^{1}H\}$ NMR spectrum of *meta*-(phenoxy)phenol (5a).



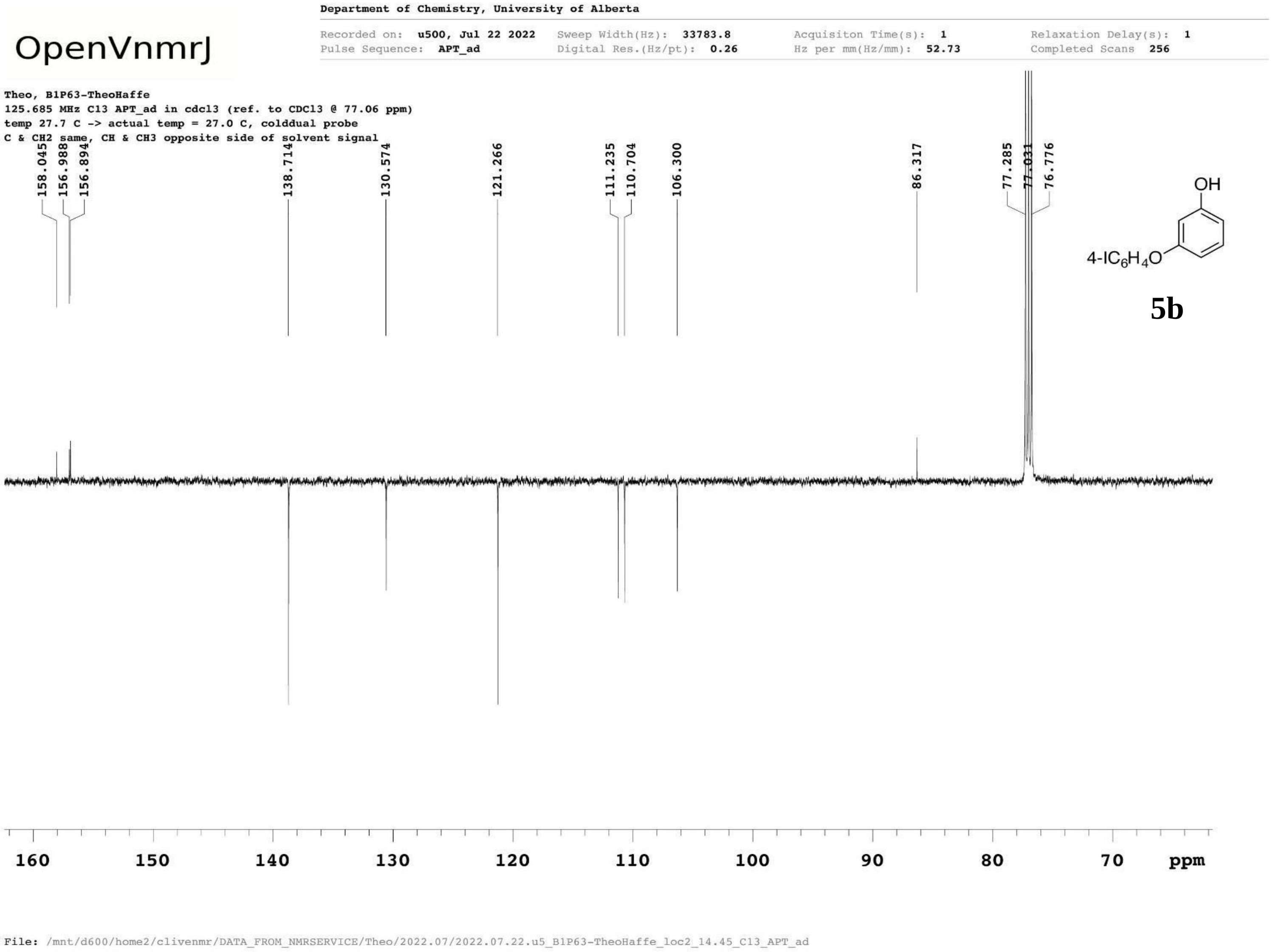
Department of Chemistry, University of Alberta

Recorded on:	**ibd5, Jul 22 2022**	Sweep Width(Hz):	**5971.04**	Acquisiton Time(s):	**5.005**	Relaxation Delay(s):	**0.1**
Pulse Sequence:	**PRESAT**	Digital Res.(Hz/pt):	**0.09**	Hz per mm(Hz/mm):	**16.07**	Completed Scans	**16**

B1P63-IodoPhenolFINAL-TheoHaffe
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/theo/2022.07/2022.07.22.i5_B1P63-IodoPhenolFINAL-TheoHaffe_H1_PRESAT

Figure A37 ^{1}H NMR spectrum of 3-(4-iodophenoxy)phenol (5b).



Department of Chemistry, University of Alberta

Recorded on: u500, Jul 22 2022 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1

Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 52.73 Completed Scans 256

Theo, B1P63-TheoHaffe

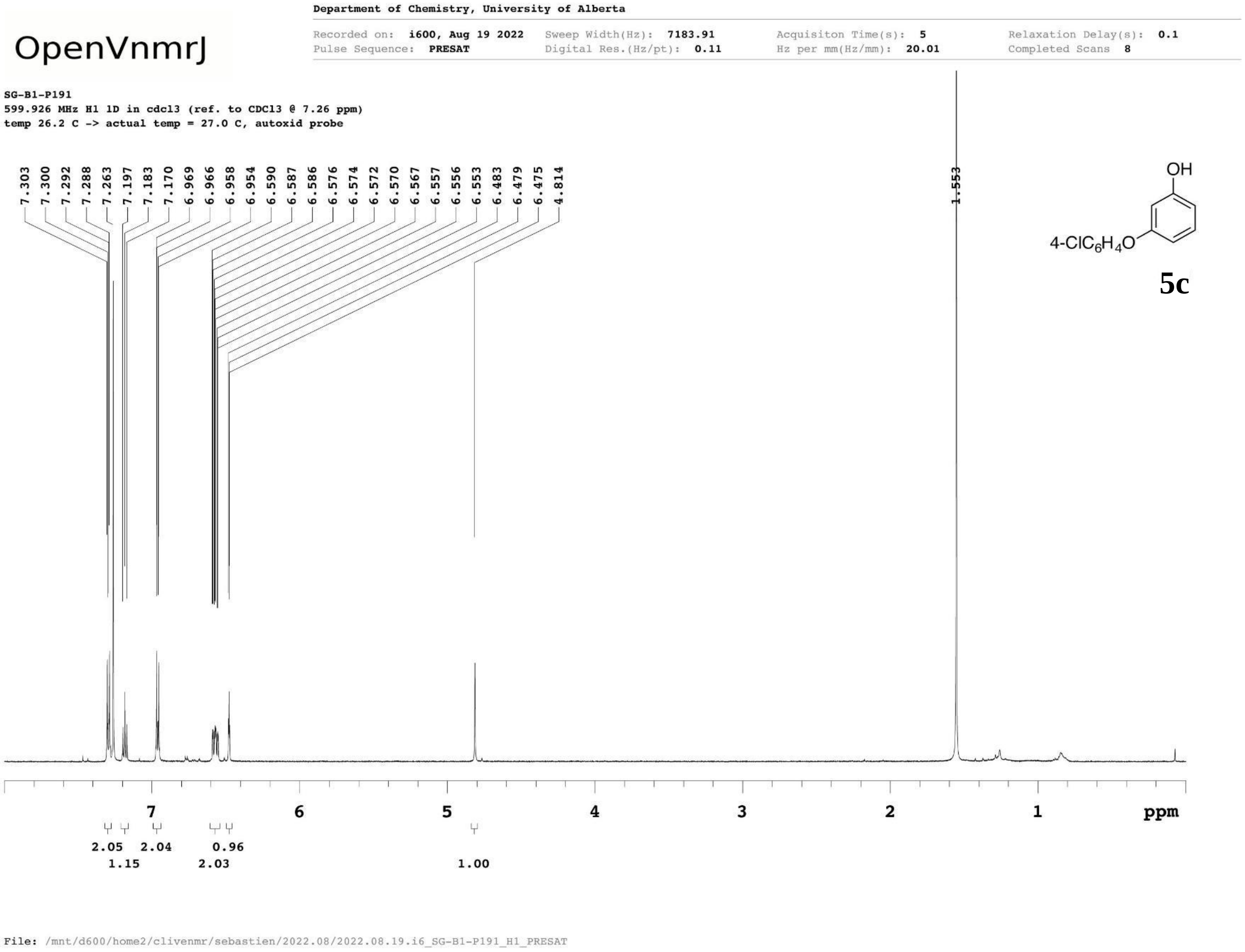
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

temp 27.7 C -> actual temp = 27.0 C, colddual probe

C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Theo/2022.07/2022.07.22.u5_B1P63-TheoHaffe_loc2_14.45_C13_APT_ad

Figure A38 $^{13}C\{^1H\}$ NMR spectrum of 3-(4-iodophenoxy)phenol (5b).



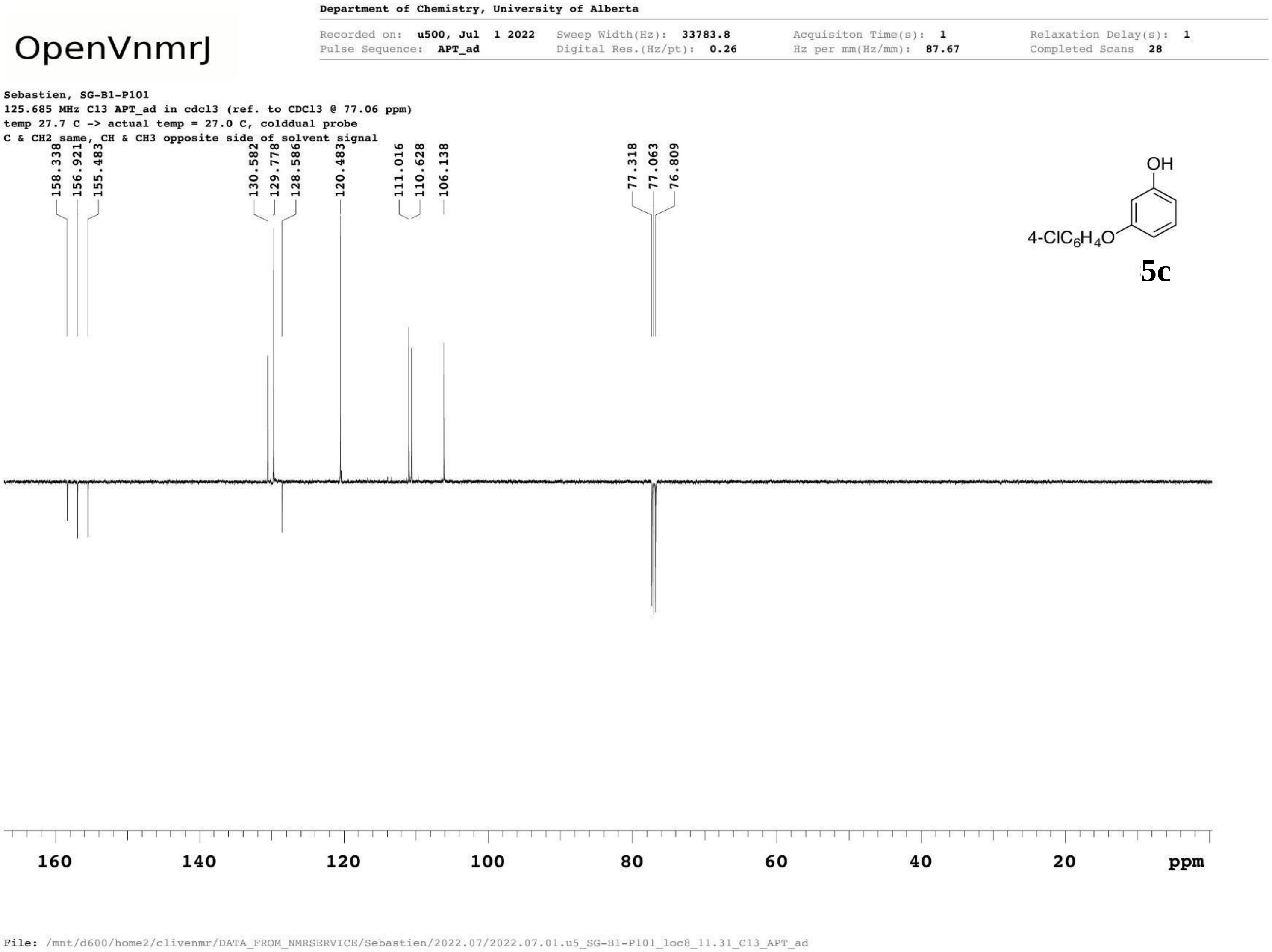
Department of Chemistry, University of Alberta

Recorded on: i600, Aug 19 2022
Pulse Sequence: PRESAT
Sweep Width(Hz): 7183.91
Digital Res.(Hz/pt): 0.11
Acquisiton Time(s): 5
Hz per mm(Hz/mm): 20.01
Relaxation Delay(s): 0.1
Completed Scans 8

SG-B1-P191
599.926 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.2 C -> actual temp = 27.0 C, autoxid probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.08/2022.08.19.i6_SG-B1-P191_H1_PRESAT

Figure A39 ^{1}H NMR spectrum of 3-(4-chlorophenoxy)phenol (5c).



Department of Chemistry, University of Alberta

Recorded on: u500, Jul 1 2022 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1
Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 87.67 Completed Scans 28

Sebastien, SG-B1-P101
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Sebastien/2022.07/2022.07.01.u5_SG-B1-P101_loc8_11.31_C13_APT_ad

Figure A40 ^{13}C{^{1}H} NMR spectrum of 3-(4-chlorophenoxy)phenol (5c).

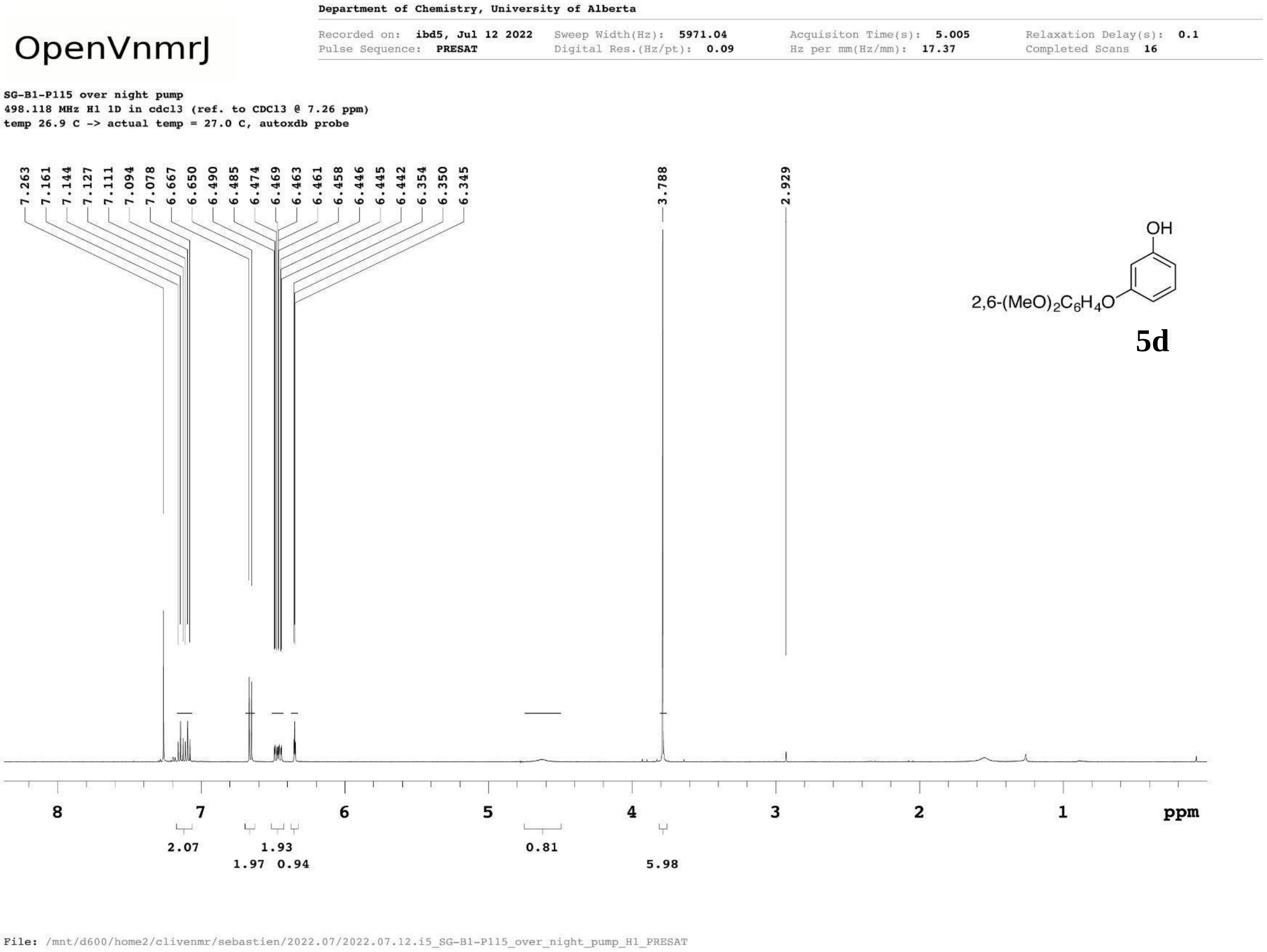
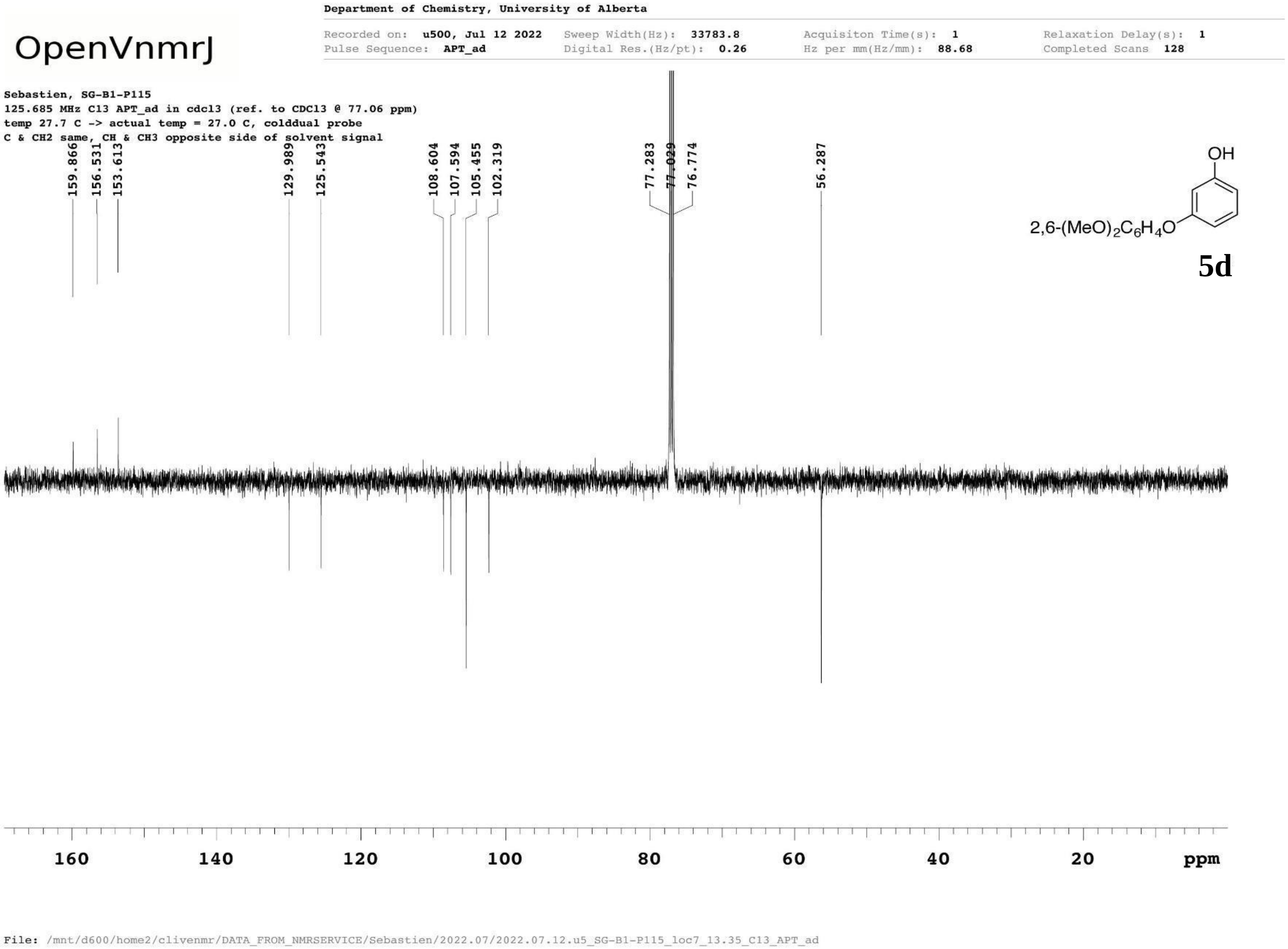


Figure A41 ^{1}H NMR spectrum of 3-(2,6-dimethoxyphenoxy)phenol (5d).



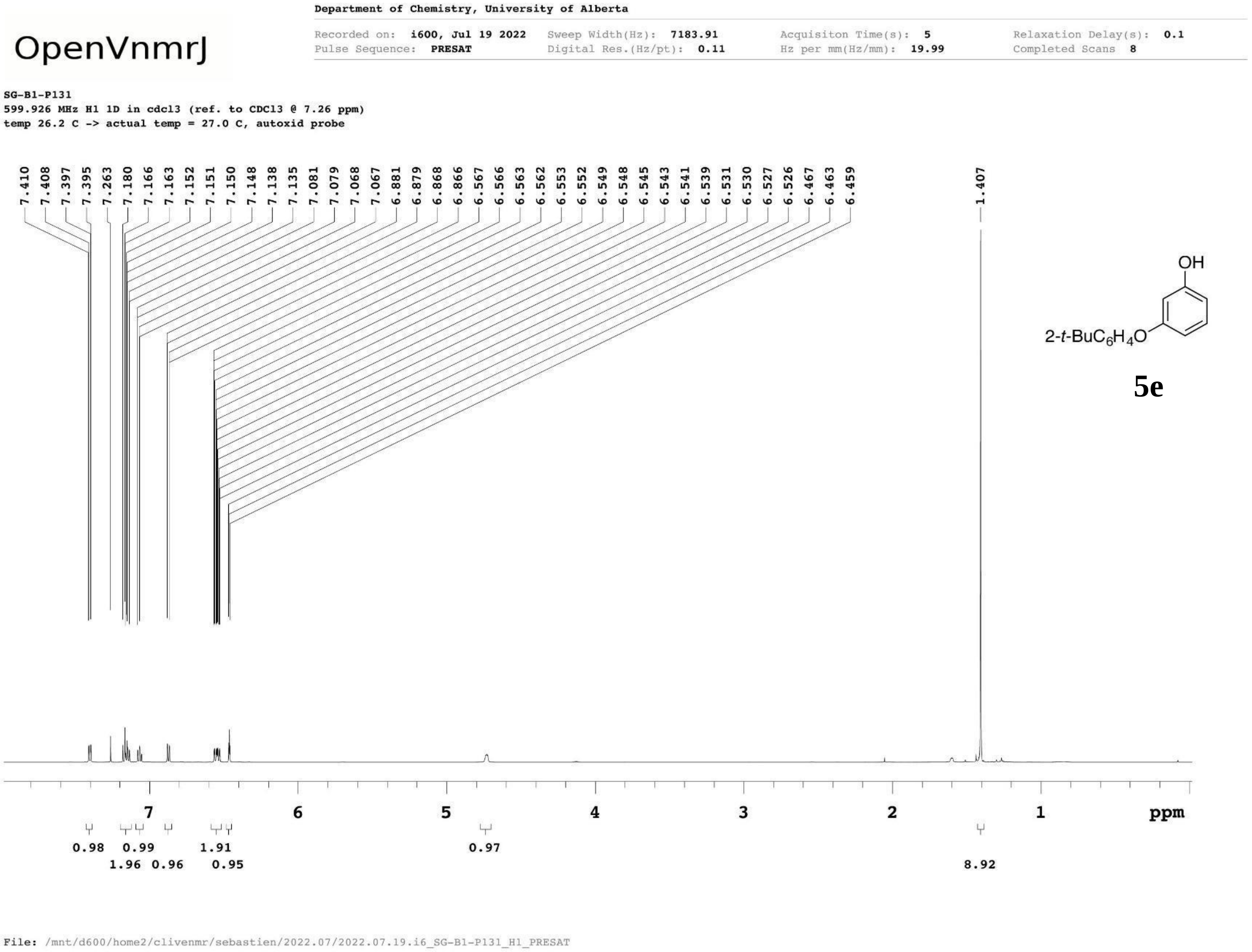
Department of Chemistry, University of Alberta

Recorded on: u500, Jul 12 2022
Pulse Sequence: APT_ad
Sweep Width(Hz): 33783.8
Digital Res.(Hz/pt): 0.26
Acquisiton Time(s): 1
Hz per mm(Hz/mm): 88.68
Relaxation Delay(s): 1
Completed Scans 128

Sebastien, SG-B1-P115
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Sebastien/2022.07/2022.07.12.u5_SG-B1-P115_loc7_13.35_C13_APT_ad

Figure A42 ^{13}C{^{1}H} NMR spectrum of 3-(2,6-dimethoxyphenoxy)phenol (5d).



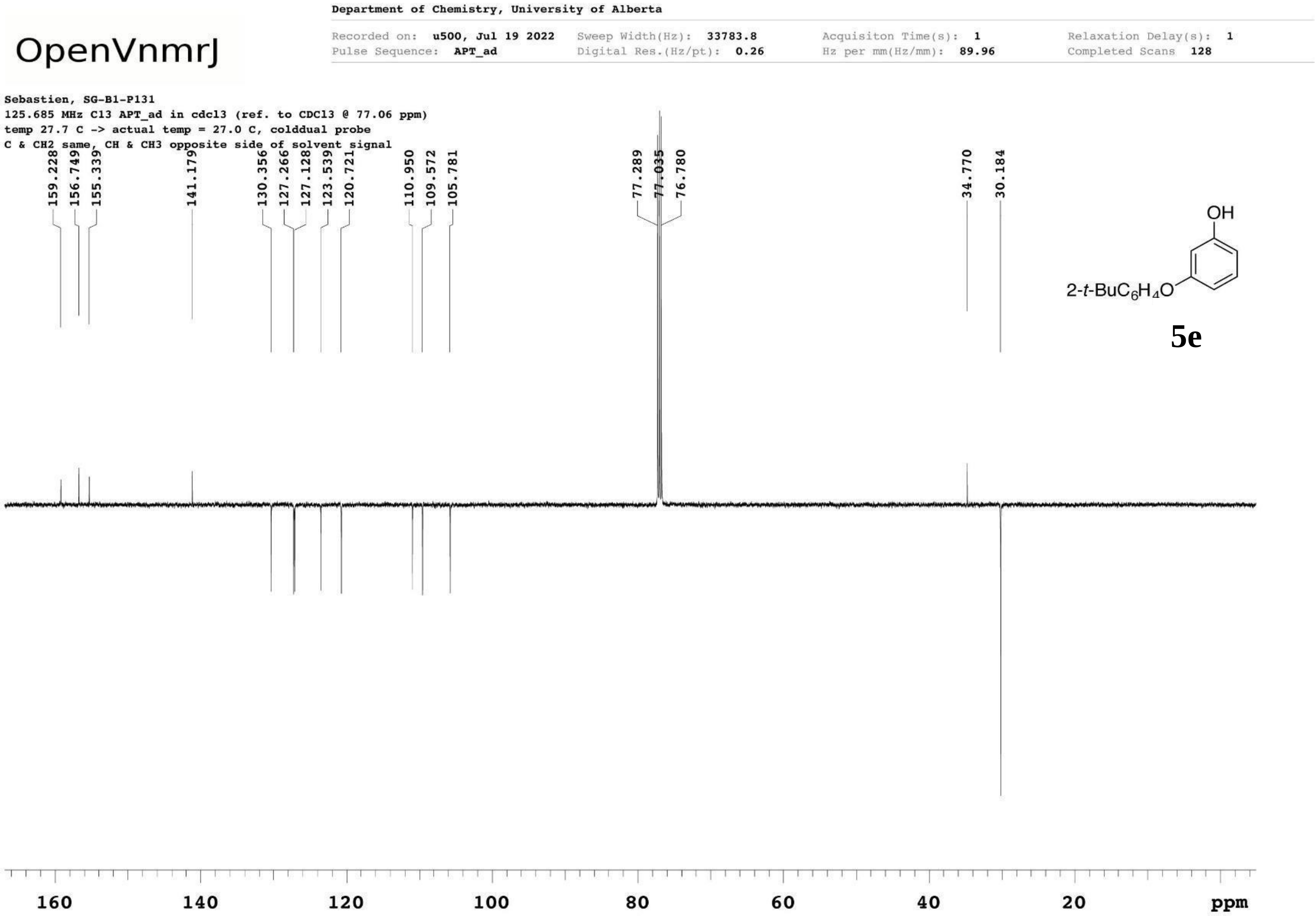
Department of Chemistry, University of Alberta

Recorded on: i600, Jul 19 2022   Sweep Width(Hz): 7183.91   Acquisiton Time(s): 5   Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT   Digital Res.(Hz/pt): 0.11   Hz per mm(Hz/mm): 19.99   Completed Scans 8

SG-B1-P131
599.926 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.2 C -> actual temp = 27.0 C, autoxid probe

File: /mnt/d600/home2/clivenmr/sebastien/2022.07/2022.07.19.i6_SG-B1-P131_H1_PRESAT

Figure A43 ^{1}H NMR spectrum of 3-(2-*tert*-butylphenoxy)phenol (5e).



OpenVnmrJ

Department of Chemistry, University of Alberta

Recorded on: u500, Jul 19 2022 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1

Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 89.96 Completed Scans 128

Sebastien, SG-B1-P131

125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)

temp 27.7 C -> actual temp = 27.0 C, colddual probe

C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Sebastien/2022.07/2022.07.19.u5_SG-B1-P131_loc2_16.10_C13_APT_ad

Figure A44 $^{13}C\{^{1}H\}$ NMR spectrum of 3-(2-*tert*-butylphenoxy)phenol (5e).

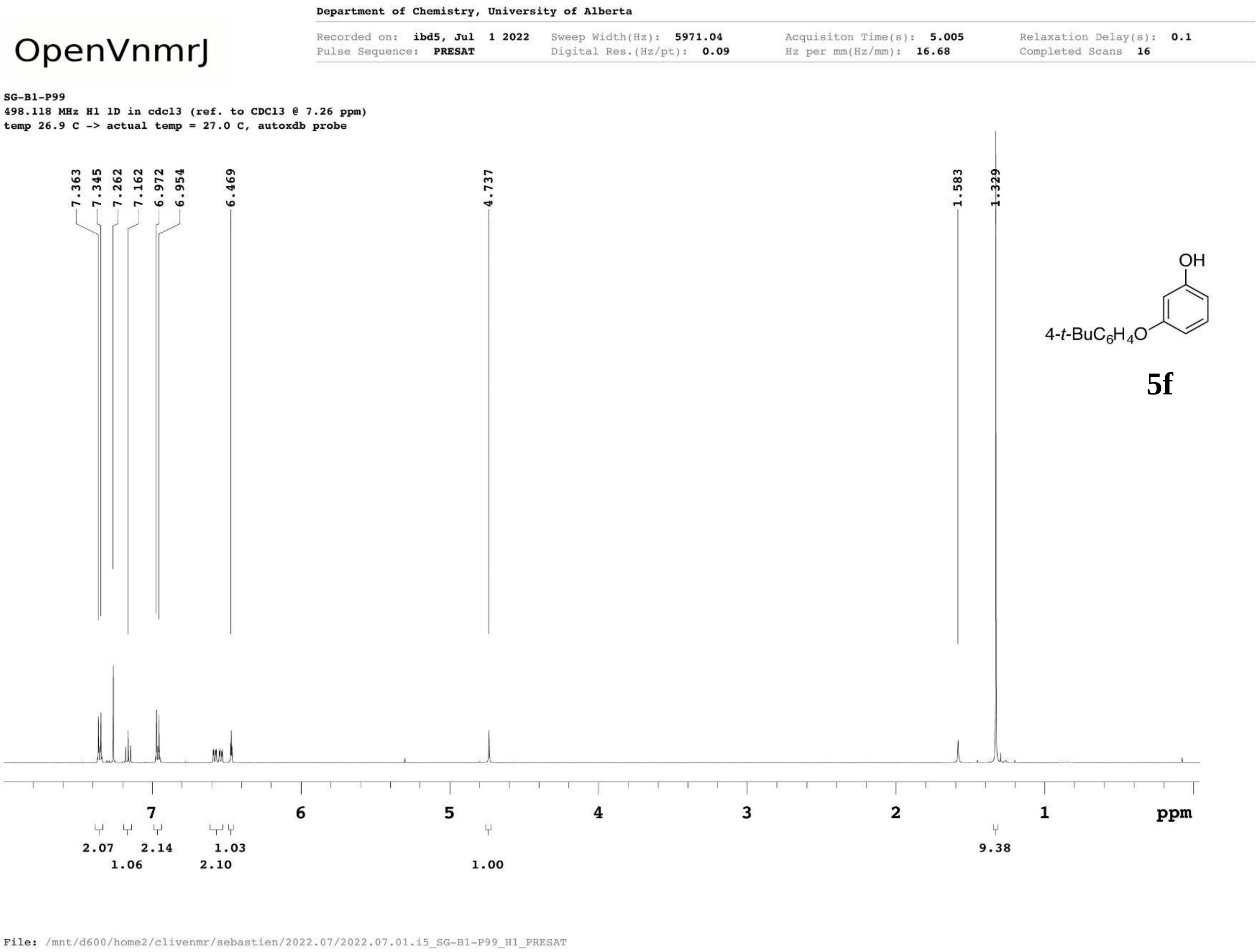


Figure A45 ^{1}H NMR spectrum of 3-(4-*tert*-butylphenoxy)phenol (5f).

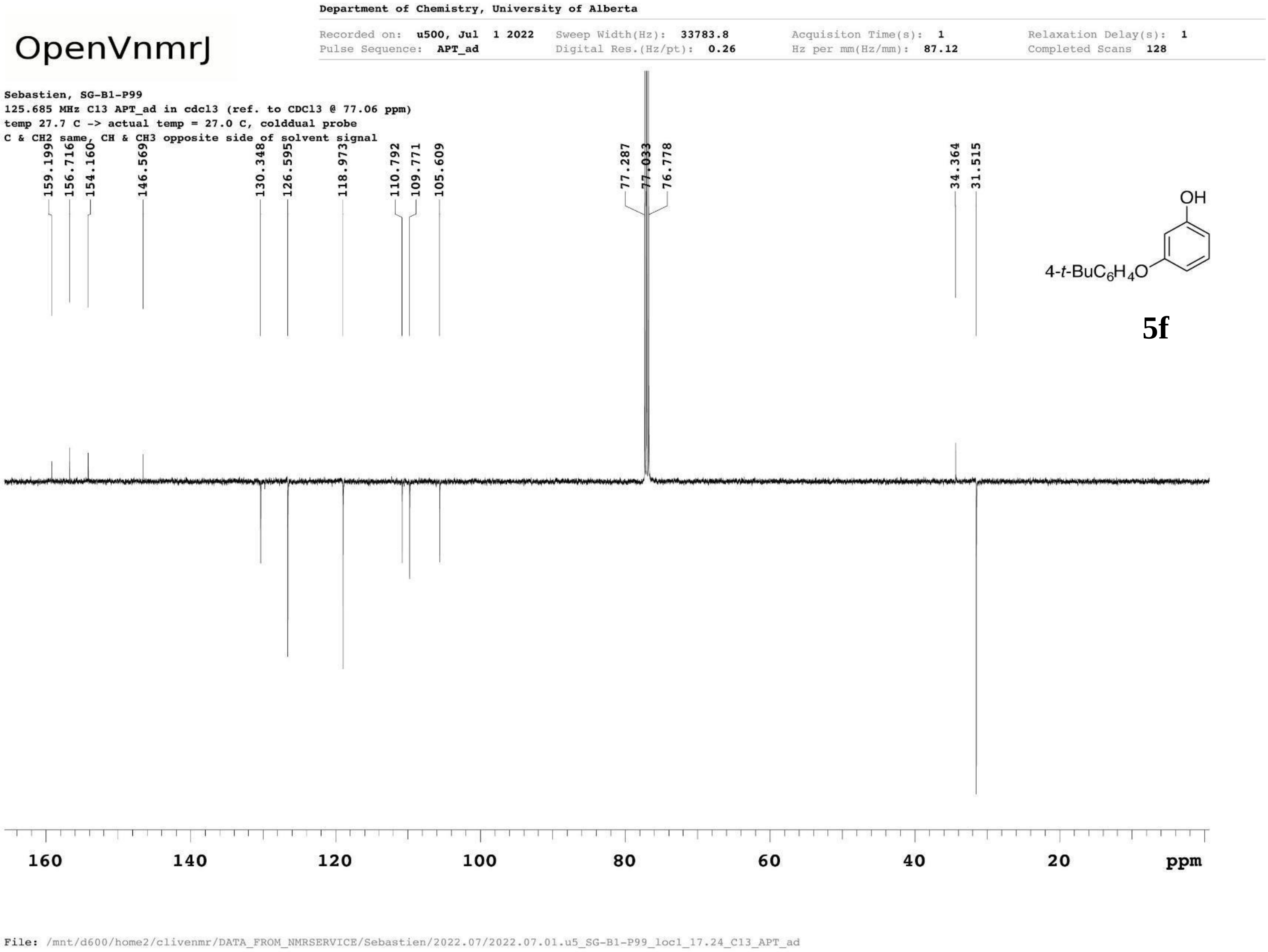


Figure A46 $^{13}C\{^1H\}$ NMR spectrum of 3-(4-*tert*-butylphenoxy)phenol (5f).

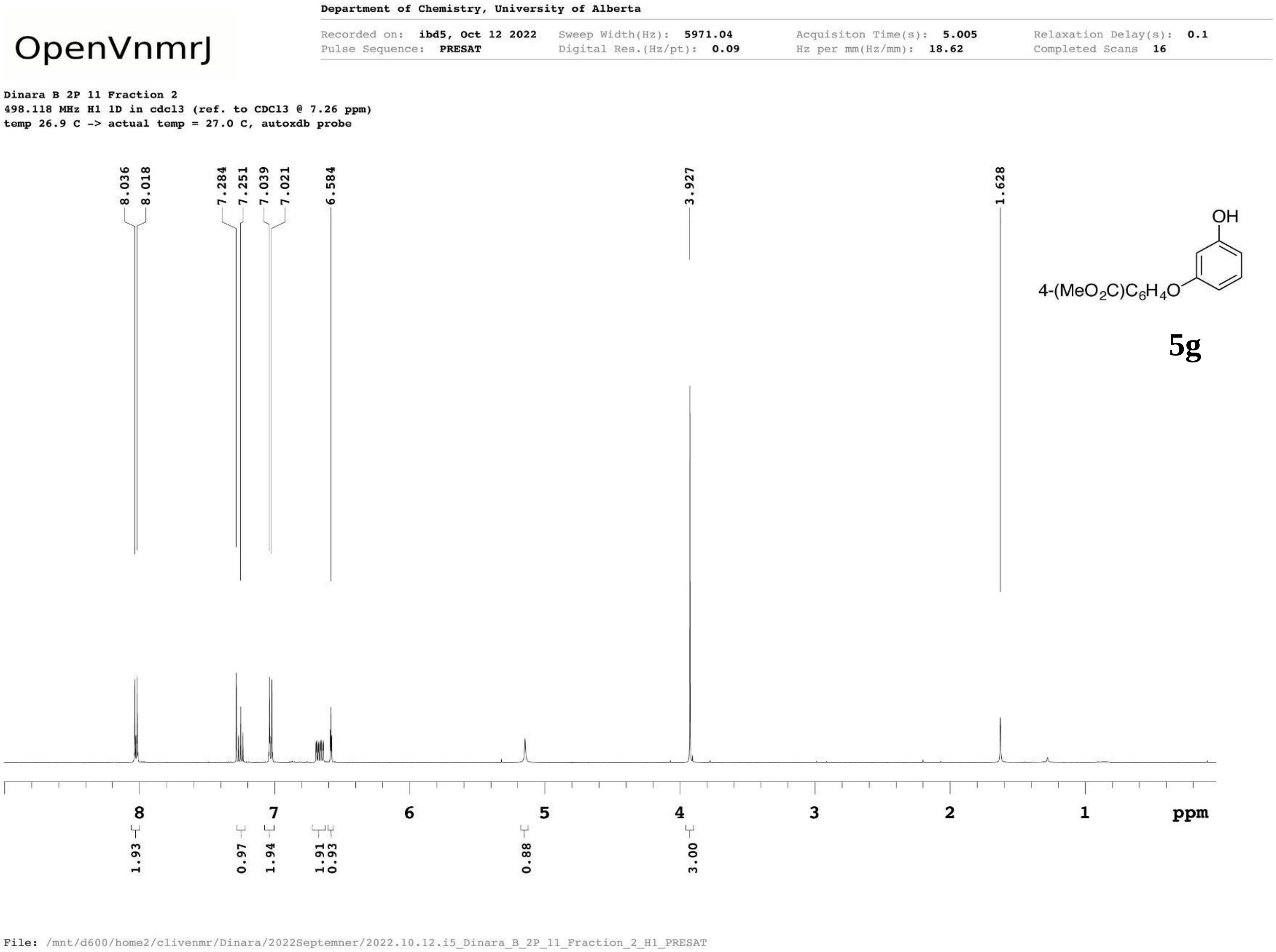
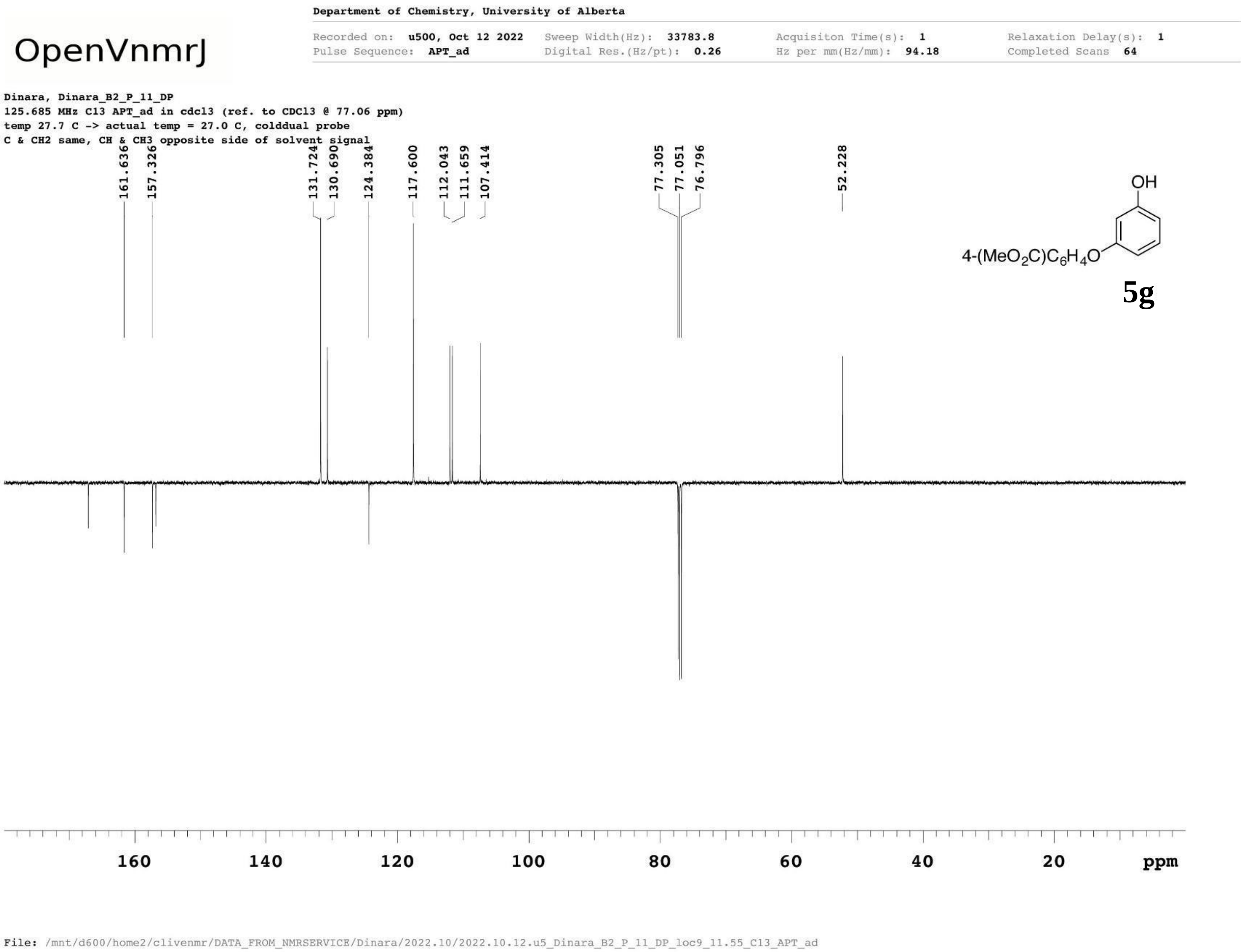


Figure A47 ^{1}H NMR spectrum of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (5g).



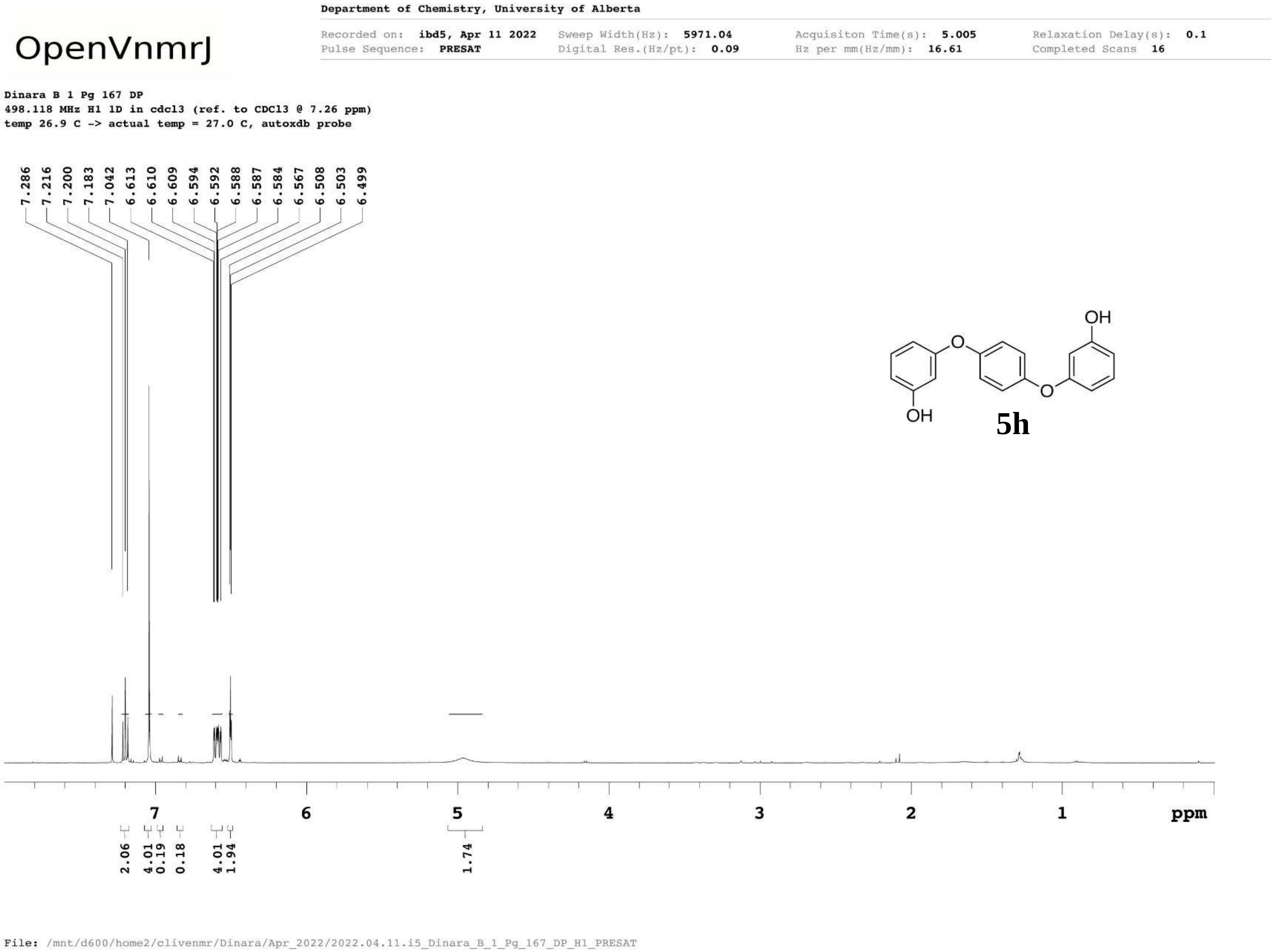
Department of Chemistry, University of Alberta

Recorded on: u500, Oct 12 2022 Sweep Width(Hz): 33783.8 Acquisiton Time(s): 1 Relaxation Delay(s): 1
Pulse Sequence: APT_ad Digital Res.(Hz/pt): 0.26 Hz per mm(Hz/mm): 94.18 Completed Scans 64

Dinara, Dinara_B2_P_11_DP
125.685 MHz C13 APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm)
temp 27.7 C -> actual temp = 27.0 C, colddual probe
C & CH2 same, CH & CH3 opposite side of solvent signal

File: /mnt/d600/home2/clivenmr/DATA_FROM_NMRSERVICE/Dinara/2022.10/2022.10.12.u5_Dinara_B2_P_11_DP_loc9_11.55_C13_APT_ad

Figure A48 ^{13}C{^{1}H} NMR spectrum of methyl 4-[(2-bromo-3-oxocyclohex-1-en-1-yl)oxy]benzoate (5g).



Department of Chemistry, University of Alberta

Recorded on: ibd5, Apr 11 2022 Sweep Width(Hz): 5971.04 Acquisiton Time(s): 5.005 Relaxation Delay(s): 0.1
Pulse Sequence: PRESAT Digital Res.(Hz/pt): 0.09 Hz per mm(Hz/mm): 16.61 Completed Scans 16

Dinara B 1 Pg 167 DP
498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm)
temp 26.9 C -> actual temp = 27.0 C, autoxdb probe

File: /mnt/d600/home2/clivenmr/Dinara/Apr_2022/2022.04.11.i5_Dinara_B_1_Pg_167_DP_H1_PRESAT

Figure A49 ^{1}H NMR spectrum of 3-[4-(3-hydroxyphenoxy)phenoxy]phenol (5h).

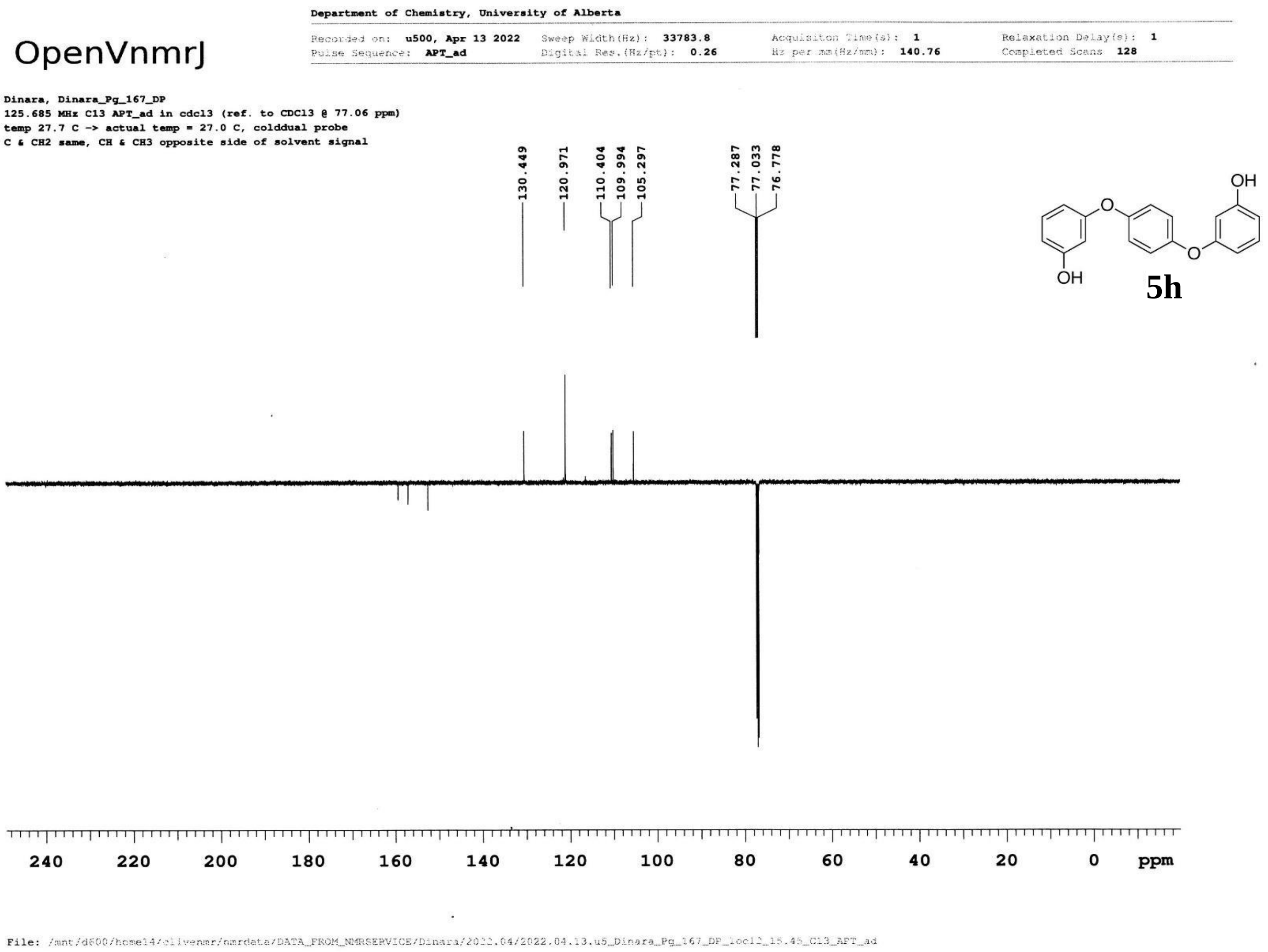


Figure A50 $^{13}C\{^1H\}$ NMR spectrum of 3-[4-(3-hydroxyphenoxy)phenoxy]phenol (5h)