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An Expedited, Regiospecific para-Bromination of Activated Aryls

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AN EXPEDITED, REGIOSPECIFIC *PARA*-BROMINATION OF ACTIVATED ARYLS

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AN EXPEDITED, REGIOSPECIFIC *PARA*-BROMINATION OF ACTIVATED ARYLS

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Dean, Graduate Studies and Research Date

I dedicate this thesis to my mom, Susan Dudley, whose persistence in encouragement has allowed me to never give up on finishing my goals. Through her own struggles, she managed to win her battle while insisting I win mine. I am forever grateful for such endless support and reassurance.

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Directed by: Donald W. Slocum, Rui Zhang, and Darwin Dahl

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Electrophilic Aromatic Substitution (EAS) is one of the most frequently used aryl substitution methods. Aside from the fact that most EAS reactions require an acid and an oxidizer to proceed, the reactions involving activated aryls typically produce a mixture of *ortho*- and *para*- products as well as an *ortho*-/*para*- disubstituted product. Regiospecificity in aromatic substitution is key in the production of many compounds in a variety of disciplines. Since EAS is one of the most often used substitution methods, it is extremely important to develop an efficient method for regiospecific substitutions. Previous research developed a method of *ortho*-substitution by using hydrocarbon media, a less hazardous, greener medium, which was modified to develop a method of *p*-iodination (bromination), but with extensive time periods. The research presented here not only reveals an expedient, rapid method for regiospecific *p*-bromination, but also does so without the need for an acid or an oxidizer. The conditions for *p*-bromination involve the use of acetone (sometimes with cyclohexane) and NBS resulting in GC yields of *p*-brominated product approaching 100% in a cost and time efficient manner without the concerns of hazardous materials or byproducts like Br_2 or HBr. The reaction mechanism is briefly examined as well.

I. INTRODUCTION

A. Electrophilic Aromatic Substitution

Electrophilic Aromatic Substitution (EAS) is one of the most commonly used methods for adding a substituent to an aromatic ring. Displacement of a hydrogen atom via a two-step mechanism results in a carbocation intermediate. The importance of EAS can be widely seen in the synthesis of a variety of chemicals for uses in industrial, pharmaceutical, agrochemical, and fine chemicals.[1] In EAS, Figure 1 shows the resonance that occurs within the ring causing a carbocation to form at various locations on the ring structure thereby lowering the overall activation energy of the transition state. This resonance within the ring is required for substitution to occur, and is known as a Wheland adduct, sigma complex, or Ingold-Hughes arenium ion.[2-4] The process of the carbocation rearranging itself among the aromatic ring is an energy lowering aspect of the electrophilic aromatic substitution reaction.[5] Once the hydrogen is displaced, the pi bond is reformed, thus satisfying the completion of the reaction to a stable molecule. EAS typically requires the use of strongly acidic, oxidative conditions through the use of a Lewis or a Brønsted acid, which commonly results in metallic or acidic waste products.[6]

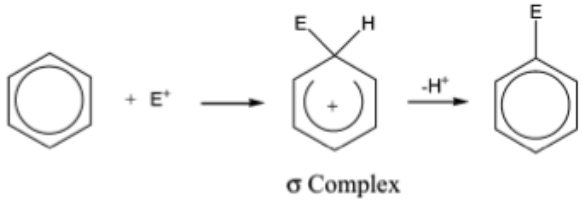


Figure 1. Electrophilic aromatic substitution reaction showing the sigma complex, Wheland adduct, or Ingold-Hughes arenium ion.[4]

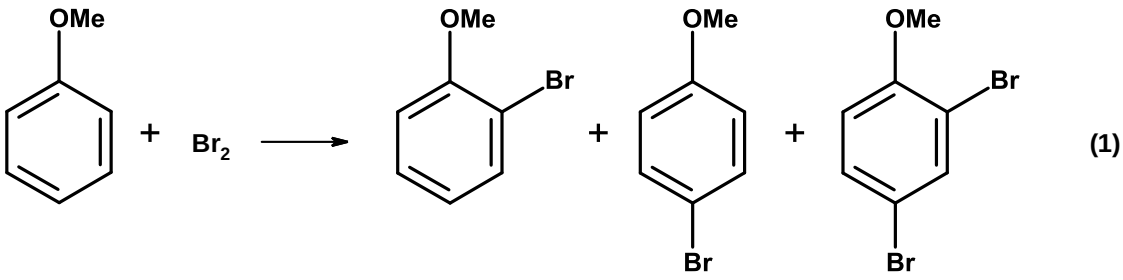
Dewar first proposed the concept that a pi complex intermediate may occur prior to the sigma complex.[4] However, uncertainty remains as to whether the pi complex is required for electrophilic aromatic substitution to occur. The sigma complex is the pivotal intermediate in dictating the location where substitution will occur along with the properties of the substituent on the ring.[2,7] In instances where a substituent is located on the aromatic ring, there are two different types of chemical behavior observed. These substituents are divided into two different groups: those that are activating and those that are deactivating.

When the substituent on the ring is an activating group, it tends to be electron rich, and is known as an electron donating, or releasing, group (EDG/ERG).[8] The electron rich molecules, which are also electronegative, cause the bonded aromatic carbon to obtain a partially positive charge, as well as the 3 and 5 positions within the aromatic ring.[2] The remaining 2, 4, and 6 positions, therefore, obtain a partially negative charge. Because an electrophile is an "electron loving" atom, the electrophile will react with said 2, 4, and 6 positions more readily than the 3 or 5 positions, ultimately resulting in a mixture of *ortho*- and *para*- substitution reactions. Activating groups, such as $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-CH_3$, -OH, $-OCH_3$,and $-OCOCH_3$ act as *ortho*- and *para*- directors, and are considered to be like an "off" switch for *meta*- substitution.[2] Although activating groups do not allow for *meta*- substitution to occur, the opposite effect occurs for deactivating groups.

A deactivating group contains a partial positive charge, and is known as an electron withdrawing group (EWG).[8] The partial positive charge from the substituent causes the bonded aromatic carbon to become partially negative alongside the 3 and 5

positions, resulting in a partially positive charge to occur at the 2, 4, and 6 positions. The electrophile, therefore, prefers to attack at the 3 and 5 positions, which results in a strictly *meta*- substitution reaction. Deactivating groups, such as halogens, -NO_2, -CHO, -CO_2H, -$COCH_3$, -CO_2CH_3, and -CN, act as a type of "on" switch for *meta*- substitution to occur.[2]

One of the greatest difficulties of an activating group substituent is the tendency for reaction to occur at both the *ortho*- and *para*- sites, resulting in a mixture of products in similar ratios including the common *ortho*-, *para*- disubstitution product. Equation 1 shows the bromination of anisole using Br_2, which results in a mixture of these three products.



(1)

This causes a problem in trying to isolate one product over the other, especially when the *ortho*- and *para*- products have similar melting points, boiling points, and solubilities. Forbes studied the effects on product placement of EWG disubstituted, EDG disubstituted, and EWG/EDG disubstituted substituents, and noticed a trend consistent with what one would expect.[8] Steric hinderance promotes products to substitute at positions that are farthest away from the substituents, which can be seen in figure 2. Regioselectivity seems to be greatest for an EDG substituent when an EWG is located at the 2 position, thus making the *meta*- position for the EWG, which is the *para*- position for the EDG, the likely position for EAS to occur.[8] Even though this seems to be the

primary positioning for EAS, most of the remaining disubstitutions still present multiple locations for substitution to happen resulting in multiple products in similar ratios. By using a combination of activating and deactivating groups on an aromatic ring, regioselectivity can become greatly enhanced.

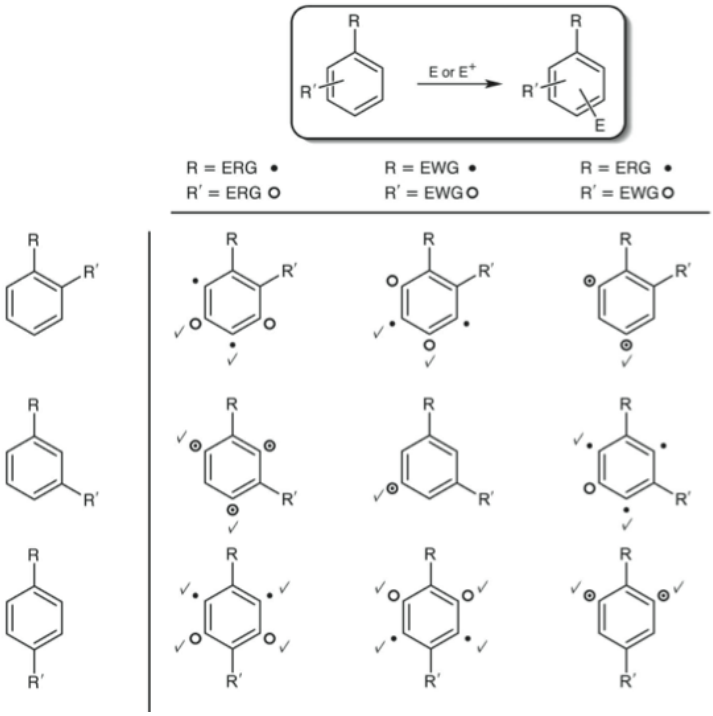
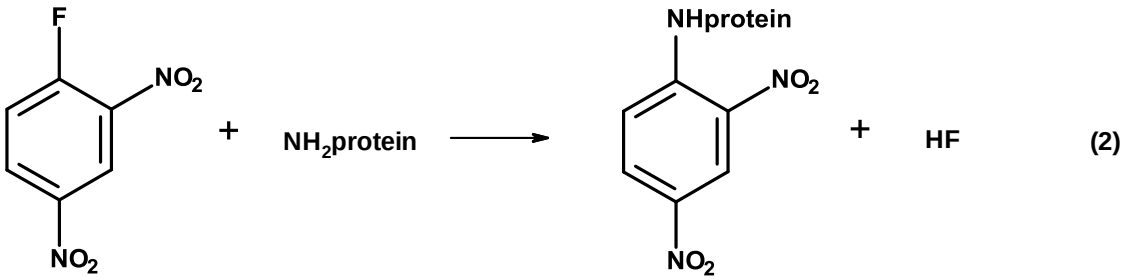


Figure 2. Shown are various types of disubstituted molecules with the dots showing locations of potential electrophile placement for ERG (or EDG) groups and circles representing the locations of potential electrophile placement for EWG groups. Check marks represent the found locations for actual electrophile placement in reactions.[8]

B. Regiospecific Aromatic Substitutions

There are a number of alternatives to EAS for aromatic substitutions. Notably, all provide regiospecificity. In contrast to multi-positional substitution with EAS, Nucleophilic Aromatic Substitution (NAS) reactions will always occur at the position

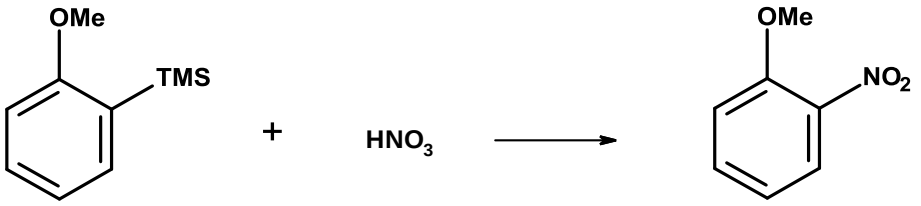
with the strongest leaving group, making regiospecificity somewhat of a non-issue. NAS differs from EAS in that the leaving group of the reaction is not a hydrogen on an aryl ring. Various types of nucleophilic substitution include an S_N1 reaction, a metal-mediated substitution reaction, as well as the most frequently used NAS reaction, the addition-elimination two-step substitution reaction.[9] One characteristic of all types of NAS is that the reaction must have a good leaving group, such as a halogen, for substitution to occur. One classic example of an NAS reaction would be the Sanger reagent 2,4-dinitrofluorobenzene, which has now been used in a vast number of biochemical reactions to determine the N-terminus of proteins by exchanging positions with the flouride ion as can be seen in Equation 2.[10]



(2)

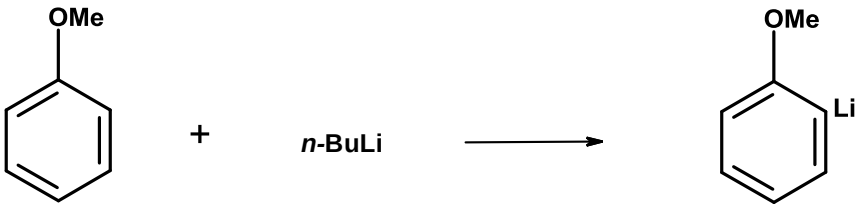
In *ipso*-Electrophilic Aromatic Substitution, the substitution reaction occurs on a non-hydrogen location of the aryl. Most commonly, substitution happens at a –trimethylsilyl (-TMS) substituent position due to its reactivity being around 10^4 times greater than that of a hydrogen atom. A typical example is the nitration of *o*-TMS-anisole using nitric acid to produce *o*-nitroanisole, which can be prepared via directed *ortho*-metalation (DoM) with a TMS-Cl quench as shown in Equation 3. In previous research involving directed *ortho*-metalation (DoM) and/or the halogen/metal exchange, the use of -TMS to show our extent of metalation (EoM) is exceptionally useful. The

-TMS at the metalation site gives us the ability to know where our regiospecific *ipso*-substitution should occur.



(3)

One of the most well known DoM reactions involves the use of *n*-butyllithium to form *o*-lithio intermediates for *ipso*-electrophilic aromatic substitution. Gilman *et. al.* and Wittig *et. al.* came up with a method of *ortho*-lithiating *p*-bromoanisole by using alkyllithiums and phenyllithiums, respectively, as metalating agents in ether, a hazardous, water miscible, hydroscopic solvent.[11-15] With a strong directing metalating group (DMG), *o*-lithiation proceeds with high yields at the position *ortho*- to the heteroatom.[16-17] In studying the effects of anisole vs. *N*,*N*-dimethylaniline, nitrogen is less electronegative than oxygen making the oxygen a stronger directing group, for example, the methoxy substituent of *N*,*N*-dimethyl-*p*-anisidine is a stronger DMG resulting in *o*-lithiation adjacent to the methoxy group.[16] Equation 4 illustrates the use of anisole, one of the most studied DMG's, with *n*-BuLi to form *o*-lithioanisole, a regiospecific substitution reaction that takes place in the *ortho*-position.

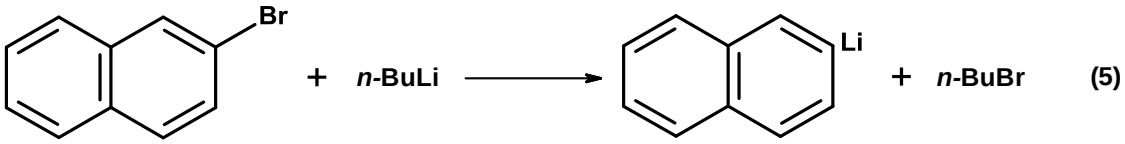


(4)

The progression of this reaction allows for carbon-carbon bond formation, most notably a carbonation reaction where a $–CO_2H$ substitutent replaces the –Li ion after workup.

The intermediate of this reaction, with the *ortho*-substitution of the lithium ion, is known as a hydrogen-metal exchange.

Another reaction involving the use of alkyllithiums as a metalating agent is the aromatic substitution reaction, the halogen/metal exchange. The substitution of lithium for the bromine on 1-bromonaphthalene using *n*-BuLi to yield 1-lithionaphthalene and *n*-BuBr, as seen in equation 5, displays a simplistic view of how the halogen/metal can yield a regiospecific product. One of the first metal activated halogen intermediates is



(5)

the Grignard reagent,which uses an aryl magnesium bromide to form a variety of products involving carbon-carbon bond formation.[18]

C. Background

Of all EAS's, regiospecific halogenations play an important role in the synthesis of many compounds. For the research presented here, the focus will be mainly on regiospecific *para*-brominations. Bromoaromatics, specifically aromatic haloamines, are prevalent in the production of many important compounds such as rubber chemicals and polyurethanes, and a wide range of biologically active molecules including agrochemicals like pesticides, fungicides, pharmaceuticals, as well as antibacterial, antineoplastic, antiviral, and antioxidant agents.[19-25] The versatility of these bromoaromatics can be seen in their ability to be converted to carbon-carbon bonds through various processes including transmetalation processes like Heck, Stille and Suzuki methods, as well as being used in the Grignard formation or halogen/metal

exchange process.[19,26] The problem still persists of how to develop such regiospecifically substituted bromoaromatics in high yields at low costs.

Many of the issues with producing *para*-brominated agents lies in the conditions required for their synthesis. Aside from harsh conditions needed for oxidative bromination to occur, greater quantities of brominating agent are typically required in comparison to that of the arene, which can increase the likelihood for polysubstitution to occur.[27] In some cases, even the steps required to allow for the bromination to occur are more extreme than necessary. As an example, to achieve monobromination of aryls, such as aniline, conversion to an anilide, such as acetanilide, is necessary due to the high EAS reactivity of the primary aromatic amine.[19,28] In some instances, reactions were being performed with additional steps, some requiring microwaving of an ionic liquid media for activation or necessitating that the bromine source be produced through the use of blue LED's to induce a photoredox catalysis.[29-30] These steps are time consuming and often are not necessary. Even when the conditions are harsh and there are these additional complex steps, the yields still tend to be low or moderate along with low regioselectivity, and the reaction times are greater than desired.[31-33]

Another difficulty in the regiospecificity as well these harsh conditions come from the various bromine sources used in the bromination process. For a while, molecular bromine, Br_2, was used as the bromine source in such bromination reactions. Using Br_2 as a brominating agent becomes somewhat of a concern in that half of the Br_2 is used while the other half is converted to hydrobromic acid as a waste product.[34] Handling molecular bromine alone can be considered rather hazardous due to the equipment needed as well as the dangers involved in the large scale uses, not to mention

the HBr waste produced.[35] With HBr as the by-product of the reaction, the acid must be neutralized before proceeding with disposal for safety purposes. For these reasons, many researchers have sought another bromine source for their reactions.

A vast number of bromine sources have been used instead of Br_2 ranging in complexity from as simple as HBr or LiBr to some convoluted compounds such as hexamethylenetetramine-bromine complexes.[19,35-38] Most of these methods require temperature changes and extensive time frames to produce moderate to high yields, as well as some sort of ionic solvent, oxidation agent, or catalyst. For many of the various bromine sources, a vast number of individuals appear to be using dichloromethane, trichloromethane (chloroform), or tetrachloromethane (carbon tetrachloride) as their solvent choice.[37,39-43] All of these solvents pose serious health risks through inhalation, ingestion, and even skin contact, yet alone the fact that all three are considered carcinogenic. Such threats increase the desire to find a more simplistic, safer, cost and time efficient method for bromination reactions.

Using N-Bromosuccinimide (NBS) as a brominating agent has become more prevalent in recent studies as a safer alternative to the hazardous bromine sources mentioned above. Early on, the Wohl-Ziegler bromination reaction converted NBS to Br_2 using HBr and carbon tetrachloride as a solvent before the bromine source would attack an allylic location.[44] Use of NBS as a bromination agent has become drastically less complicated in comparson to methods like the Wohl-Ziegler reaction such that the conversion of NBS to any other bromine source is completely unnecessary, not to mention the fact that HBr and carbon tetrachloride are dangerous materials. Plus,

converting the safer NBS to a more hazardous Br_2 is nonsensical when considering other reaction possibilities.

Studies show using NBS becomes more effective when paired with a polar solvent such as DMF, acetonitrile, or propylene carbonate; however, DMF poses difficulties in solvent removal due to its high boiling point and water miscibility.[42,45-47] When NBS began to be used, a catalyst or zeolite was typically a necessity to allow the reaction to proceed in high yields with enhanced selectivity including SiO_2, HZSM-5, HBF_4•Et_2O, silica, tetrabutylammonium bromide (TBAB), palladium, and Cu-Mn spinel oxide to name a few.[31,33,38-39,43,46,48] The research here shows a method that does not require a catalyst for the reaction to proceed in high yields, though, it does use a polar solvent, acetone, to assist in solubility of the brominating agent.

Through previous studies, Slocum *et. al.* discovered the use of a completely nonpolar solvent, cyclohexane, as a greener solvent choice.[11,24,49] For many years, the focus of the research within our group was not just regiospecific substitution, but rather very specifically directed *ortho*- metalation (DoM) as mentioned earlier. As mentioned earlier, Gilman and Wittig had come up with DoM using alkyllithiums and phenyllithiums, respectively, with ether to produce *ortho*-lithiated intermediates. Such methods present problems when PhLi is utilized due to the production of benzene, a well-known carcinogen, as a waste product. Slocum *et. al.* came up with a safer method of metalating by using another metalating agent with a comparable basicity and a lower nucleophilicity to phenylithium, *o*-lithiodimethylaniline (*o*-LiDMA), in the safer hydrocarbon solvent, cyclohexane.[11]

The use of cyclohexane continued in advancing the methods found for the DoM reactions. Further research showed the use of an ether or an amine, such as tetramethylethylenediamine (TMEDA) at 60°C or 3 equiv. of THF, acted as a catalyst in the production of *ortho*-metalation when using bulk cyclohexane as solvent.[49] Extent of metalation (EoM) is analyzed using ClTMS to observe *o*-TMS formation. Relatively higher yields and lower times were observed with the use of such catalysts.

Once cyclohexane became implemented as the novel, choice solvent, research progressed to the discovery of a method for *para*-iodination without the need for an oxidant, as previous halogenation methods had required.[24] Though this reaction still had a wide range of times from 0.5 hours to 24 hours, the reaction allowed for a green, regiospecific halogenation using hydrocarbon media. From here, the thought process was that if a weaker electrophile like iodine was able to go through regiospecific *p*-iodination, why should bromine not be able to perform under the same conditions? Through the *p*-iodination reaction, the *p*-bromination reaction was born, beginning with the use of cyclohexane as the solvent medium. The yields for such reaction were high, but required nearly 24 hours for most substrates for the bromination to occur because NBS was only sparingly soluble in cyclohexane. Once acetone was found to completely dissolve NBS, the reaction progress improved dramatically to just one minute for most substrates.

Now, with the use of acetone as an even greener, polar solvent, we give rise to a more cost and time efficient method of regiospecific *p*-bromination. Though the high flammability of acetone presents some concerns in the usage of the solvent, the lower boiling point allows for rapid stripping of the solvent. The water miscibility of acetone

allows any remnants of the solvent left over in the crude product to be triturated with DI water or hexanes along with waste products HBr and succinimide leaving a rather pure product.

II. MATERIALS AND METHODS

A. Basic Setup

All chemicals were purchased from Sigma Aldrich unless otherwise noted. All equipment used including glass syringes, round-bottom flasks, stir bars, and needles were washed then rinsed with acetone and methanol before being placed in a 35°C oven to dry completely. All reactions were run at room temperature with a slightly positive pressure of nitrogen (N_2) or argon (Ar) through needles inserted in the top of the septum sealed, single-neck, round-bottom flasks that had been previously purged with an N_2 or Ar line. All reactions were quenched with approximately 20 mL of DI water before being transferred to a separatory funnel.

For the extractions, around 20 mL of brine and 20 mL methyl *tert*-butyl ether (MTBE) were added to the separatory funnel, rinsing the 50 mL round-bottom flasks in the process. Each product migrates from the aqueous layer to the MTBE organic layer, and is then washed with brine twice more before the organic layer is dropped into a 250 mL Ehrlenmeyer flask. The product and MTBE is then dried with sodium sulfate before filtering the organic solution into a 24/40 neck round-bottom flask. The solvent is then removed using a rotary evaporator to reveal either a solid or an oil product. To ensure purification, most solid products were triturated using around 10 mL of DI water unless otherwise noted. For the oils, they were transferred to sample vials with approximately 5

mL of DI water and shaken to transfer any remaining starting material or residual succinimide to the DI water. At that point, the aqueous layer was removed from the vial before adding another 5 mL of DI water to repeat the process. Then, MTBE was added along with sodium sulfate to dry the remaining organic layer before filtering the solution again into a 24/40 single neck, round-bottom flask to concentrate the product again using the rotary evaporator.

B. Instrumentation

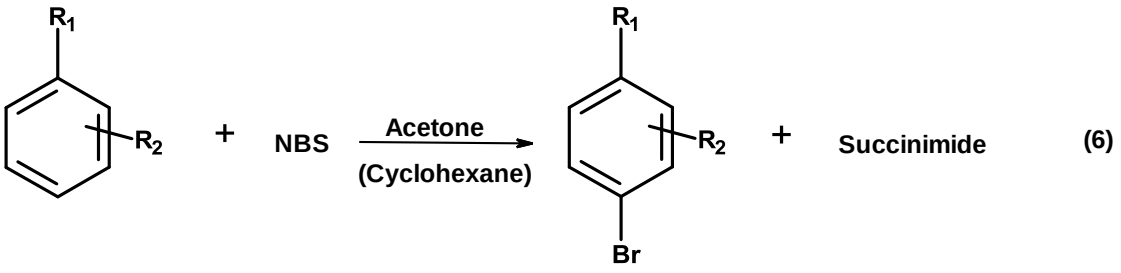
The products were analyzed using an Agilent 6850 gas chromatograph (GC) containing a flame ionization detector (FID) set at a temperature of 300°C in combination with an OV-17 packed column sustained at an inlet pressure of 10.0 psi. Nitrogen (N_2) is the carrier gas for this GC instrument. The successful products were then run through an Agilent 5973 MSD gas chromatograph-mass spectrometer (GC-MS) also containing an FID linked with a 6890 N Network system to verify that the expected product exhibited the same major MS peak signal as what was anticipated. The parameters for the instrument were such that the temperature of the oven was set to 60°C, the column flow pressure was set to 3.0 psi, and the inlet flow temperature was set to 250°C. Helium (He) is the carrier gas for the GC-MS instrument. ^{1}H NMR spectrums were executed on a 90 MHz NMR unless otherwise noted. Melting point ranges were determined through the use of a Mel-Temp® instrument connected to a digital thermometer.

C. Sample Preparation

0.25 mL samples were taken from the reactions using a 1 mL syringe introduced through the septum in the 50 mL round-bottom flask. The aliquot was then transferred to

a 10 mL pyrex sample vial containing approximately 2 mL of DI water to quench the reaction. Around 5 mL of MTBE was then added to the sample vial before shaken on a vortex mixer. Depending on the concentration of the product in MTBE, a GC vial was filled with the product solution directly from the 10 mL sample vial or a portion was put into the vial and diluted with MTBE so that the GC spectrum total area was at or near 4000. The samples were then analyzed via GC and GC-MS instrumentation. Isolated products were prepared for NMR analysis by dissolving a small sample in about 1 mL of chloroform-d with 1% v/v TMS except for the *m*-cresol product, which was dissolved in methanol-d.

D. Experimental



A summary of MS analytical data for all *p*-brominated aryls is listed at the end of the experimental section.

1. General Procedure For Aniline Derivatives

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, 1 equiv. of NBS is combined with 19 mL of acetone and 1 mL of cyclohexane (unless noted otherwise) until dissolved. If the NBS does not dissolve readily, a heat gun is used to assist in dissolving the NBS. The solution is then transferred using a 20 mL syringe to a clean, dry 50 mL round-bottom flask equipped with a medium stir bar

containing 1 equiv. of substrate while stirring. Reaction is then quenched after one minute of stirring using 20 mL of DI water, unless otherwise noted. Those reactions that produced a solid were then triturated using 10 mL of DI water, and those reactions that produced oils were then re-extracted using DI water and MTBE before being rotovaped again. Isolated solids were characterized using NMR and mp, while oils were characterized just using NMR.

a. Acetanilide

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 19 mL of acetone and 1 mL of cyclohexane until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of acetanilide (1.35 g, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the acetanilide using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 98.3% GC yield of *p*-bromoacetanilide. The solid isolated after trituration appeared to decompose between 196.0-199.5 °C.

b. Aniline

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 19 mL of acetone and 1 mL of cyclohexane until dissolved.* To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of aniline (0.92 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the aniline using a glass syringe while

stirring. Quench of the reaction after one minute of stirring resulted in a 95.3% GC yield of *p*-bromoanailine. The solid isolated after trituration had a melting point of 56.1-60.3 °C. ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 2H), 6.50-6.59 (d, 2H), 7.18-7.27 (d, 2H) (Appendix NMR #1)

c. Anthranilic Acid

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of anthranilic acid (1.37 g, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the anthranlic acid using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield of 2-amino-5-bromobenzoic acid. The solid isolated after trituration had a melting point of 202.0-203.5 °C.

d. *o*-Toluidine

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *o*-toluidine (1.08 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *o*-toluidine using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield of

4-bromo-2-methylaniline. Isolation of the product produced an oil. ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.45 (s, 2H), 6.45-6.55 (d, 1H), 7.03-7.14 (complex m, 2H) (Appendix NMR #2)

e. *m*-Toluidine

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1.1 equiv. of NBS (1.78 g, 10 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *m*-toluidine (1.08 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *m*-toluidine using a glass syringe while stirring. Quench of the reaction after five minutes of stirring resulted in a 100% GC yield of 4-bromo-3-methylaniline. The solid isolated after trituration had a melting point of 72.7-74.6 °C. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.59 (s, 2H), 6.45-6.58 (complex m, 2H), 7.20-7.30 (complex m, 1H) (Appendix NMR #3)

f. *o*-Anisidine

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 19 mL of acetone and 1 mL of cyclohexane until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *o*-anisidine (1.13 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *o*-anisidine using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield of 4-bromo-2-methoxyaniline. The solid isolated after trituration had a melting

point of 50.4-52.3 °C. ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 5H), 6.51-6.61 (d, 1H), 6.87-6.96 (complex m, 2H) (Appendix NMR #4)

g. *m*-Anisidine

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 19 mL of acetone and 1 mL of cyclohexane until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of 97% *m*-anisidine (1.16 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *m*-anisidine using a glass syringe while stirring. Quench of the reaction after one minute resulted in a 46.5% GC yield of 4-bromo-3-methoxyaniline, which was not purified further.

2. General Procedure For *N*-Methylated Aniline Derivatives

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, 1 equiv. of NBS is combined with 1 equiv. of cyclohexane and 20 mL acetone (unless noted otherwise) until dissolved. If the NBS does not dissolve readily, a heat gun is used to assist in dissolving the NBS. The solution is then transferred using a 20 mL syringe to a clean, dry 50 mL round-bottom flask equipped with a medium stir bar containing 1 equiv. of substrate while stirring. Reaction is then quenched after one minute of stirring using 20 mL of DI water, unless otherwise noted. Those reactions that produced a solid were then triturated using 10 mL of DI water, and those reactions that produced oils were then re-extracted using DI water and MTBE before being rotovaped

again. Isolated solids were characterized using NMR and mp, while oils were characterized just using NMR.

h. *N*-Methylaniline

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 1 equiv. of cyclohexane (1.08 mL, 10 mmol) and 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *N*-methylaniline (1.08 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *N*-methylaniline using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 98.4% GC yield of 4-bromo-*N*-methylaniline. Isolation of the product produced an oil. 1H NMR ($CDCl_3$) δ 2.80 (s, 3H), 2.86 (s, 1H), 6.43-6.52 (dd, 2H), 7.2-7.3 (dd, 2H) (Appendix NMR #5)

i. *N*,*N*-Dimethylaniline

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 1 equiv. of cyclohexane (1.08 mL, 10 mmol) and 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of 99% *N*,*N*-dimethylaniline (1.28 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *N*,*N*-dimethylaniline using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 96.9% GC yield of 4-bromo-*N*,*N*-dimethylaniline. The solid isolated after trituration had a melting point of 49.7-52.0 °C.

^{1}H NMR ($CDCl_3$) δ 2.92 (s, 6H), 6.53-6.63 (dd, 2H), 7.25-7.35 (dd, 2H) (Appendix NMR #6)

j. *N*,*N*-Dimethyl-*o*-Toluidine

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 1 equiv. of cyclohexane (1.08 mL, 10 mmol) and 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of 99% *N*,*N*-dimethyl-*o*-toluidine (1.46 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *N*,*N*-dimethyl-*o*-toluidine using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 96.2% GC yield of 4-bromo-*N*,*N*-2-trimethylaniline. Isolation of the product produced an oil. ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.64 (s, 6H), 6.80-6.90 (d, 1H), 7.17-7.27 (complex m, 2H) (Appendix NMR #7)

k. *N*,*N*-Dimethyl-*m*-Toluidine

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 1 equiv. of cyclohexane (1.08 mL, 10 mmol) and 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of 97% *N*,*N*-dimethyl-*m*-toluidine (1.28 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *N*,*N*-dimethyl-*m*-toluidine using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 94.6% GC yield of 4-bromo-*N*,*N*-3-trimethylaniline. The solid isolated after trituration had a melting

point of 47.4-49.6 °C. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.91 (s, 6H), 6.4-6.58 (complex m, 2H), 7.27 (cross coupling, 1H) (Appendix NMR #8)

l. Indoline

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 1 equiv. of cyclohexane (1.08 mL, 10 mmol) and 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of indoline (1.13 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the indoline using a glass syringe while stirring. Quench of the reaction after one hour of stirring resulted in an 81.1% GC yield of 5-bromoindoline.

3. General Procedure For Anisole Derivatives

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, 1 equiv. of NBS is combined with 20 mL of acetone (unless noted otherwise) until dissolved. The solution is then transferred using a 20 mL syringe to a clean, dry 50 mL round-bottom flask equipped with a medium stir bar containing 1 equiv. of substrate while stirring. Reaction is then quenched after designated stirring time using 20 mL of DI water. Those reactions that produced a solid were then triturated using 10 mL of DI water, and those reactions that produced oils were then re-extracted using DI water and MTBE before being rotovaped again. Isolated solids were characterized using NMR and mp, while oils were characterized just using NMR.

m. Anisole

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 18 mL of acetone and 2 mL of cyclohexane until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of anisole (1.09 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the anisole using a glass syringe while stirring. Quench of the reaction after two hours of stirring resulted in a 100% GC yield of 4-bromoanisole. Isolation of the product produced an oil. ^{1}H NMR ($CDCl_3$) δ 3.75 ppm (s, 3H), 6.70-6.80 (d, 2H), 7.31-7.41 (d, 2H) (Appendix NMR #9)

n. *m*-Nitroanisole

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *m*-nitroanisole (1.22 g, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *m*-nitroanisole using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield of 4-bromo-3-nitroanisole. The solid isolated after trituration had a melting point of 28.8-30.2 °C. ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.18-7.52 (complex m, 1H), 7.73-7.87 (m, 2H) (Appendix NMR #10)

o. *m*-Iodoanisole

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *m*-iodoanisole (1.19 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *m*-Iodoanisole using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield 4-bromo-3-iodoanisole. Isolation of the product produced an oil. ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 6.68-6.81 (dd, 1H), 7.35-7.50 (m, 2H) (Appendix NMR #11)

4. General Procedure For Phenol Derivatives

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, a designated amount of NBS is combined with 20 mL of acetone (unless noted otherwise) until dissolved. If the NBS does not dissolve readily, a heat gun is used to assist in dissolving the NBS. The solution is then transferred using a 20 mL syringe to a clean, dry 50 mL round-bottom flask equipped with a medium stir bar containing 1 equiv. of substrate while stirring. Reaction is then quenched after one minute of stirring using 20 mL of DI water, unless otherwise noted. Those reactions that produced a solid were then triturated using 10 mL of DI water, and those reactions that produced oils were then re-extracted using DI water and MTBE before being rotovaped again. Isolated solids were characterized using NMR and mp, while oils were characterized just using NMR.

p. Phenol

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1.2 equiv. of NBS (2.14 g, 12 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of phenol (0.95 g, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the phenol using a glass syringe while stirring. Quench of the reaction after ten minutes of stirring resulted in a 96.4% GC yield of 4-bromophenol. Isolation of the product produced an impure oil that was not triturated further. ^{1}H NMR ($CDCl_3$) δ 4.61 (s, OH), 6.66-6.93 (d, 2H), 7.27-7.57 (d, 2H) (Appendix NMR #12)

q. Salicylic Acid

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 15 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of salicylic acid (1.38 g, 10 mmol) with 5 mL of acetone. Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the salicylic acid and acetone mixture using a glass syringe while stirring. Quench of the reaction the reaction after one minute of stirring resulted in a 100% GC yield of 5-bromo-2-hydroxybenzoic acid. The solid isolated after trituration had a melting point of 134-146 °C.

r. *o*-Cresol

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1.1 equiv. of NBS (1.96 g, 10 mmol) with 20 mL of acetone

until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *o*-cresol (1.08 g, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *o*-cresol using a glass syringe while stirring. Quench of the reaction after ten minutes of stirring resulted in a 98.1% GC yield of 4-bromo-2-methylphenol. Isolation of the product produced an oil. ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H), 4.71 (s, OH), 6.59-6.68 (d, 1H), 7.14-7.23 (complex m, 2H) (Appendix NMR #13)

s. *m*-Cresol

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1.1 equiv. of NBS (1.96 g, 10 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of *m*-cresol (1.05 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *m*-cresol using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield of 4-bromo-3-methylphenol. Isolation of the product produced an impure oil, which was not further triturated. ^{1}H NMR (CD_3OD) δ 1.23 (s, 3H), 3.26 (s, OH), 6.47-6.85 (m, 2H), 7.26-7.35 (d, 1H)

t. Guaiacol (2-Methoxyphenol)

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 18 mL of acetone and 2 mL of cyclohexane until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of guaiacol (1.10 mL, 10 mmol). Once the

NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the guaiacol using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield of 4-bromo-2-methoxyphenol. Isolation of the product produced an oil. ^{1}H (500MHz) NMR ($CDCl_3$) δ 3.87-3.91 (s, 3H), 5.54 (s, OH), 6.78-6.80 (dd, 1H), 6.96-6.99 (dd, 1H), 7.25 (s, 1H) (Appendix NMR #15)

u. 3-Methoxyphenol

To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1.5 equiv. of NBS (2.67 g, 10 mmol) with 20 mL of acetone until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of 3-methoxyphenol (1.10 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the 3-methoxyphenol using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in a 100% GC yield of 4-bromo-3-methoxyphenol. Isolation of the product produced an impure oil, which was not further triturated. ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H), 3.67 (s, OH), 5.10-5.41 (m, 2H), 6.04-6.14 (d, 1H) (Appendix NMR #16)

E. Mechanistic Inquiries

The procedures for making both *o*-TMSAnisole and *o*-TMS-*N*,*N*-dimethylaniline were done according to Slocum *et. al*.[49] The procedures then follow the general procedures as listed above.

1. *o*-TMS-*N*,*N*-Dimethylaniline

The procedure used to make *o*-TMS-*N*,*N*-dimethylaniline yielded a 90% product.[49] To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 1 equiv. of cyclohexane (1.08 mL, 10 mmol) and 20 mL of acetone until dissolved using a heat gun, if necessary. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of 90% *o*-TMS-*N*,*N*-dimethylaniline (2.30 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *o*-TMS-*N*,*N*-dimethylaniline using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in GC yield of 30.1% *o*-bromo-*N*,*N*-dimethylaniline and 55.3% *o*-TMS-*p*-bromo-*N*,*N*-dimethylaniline.

2. *o*-TMS-Anisole

The procedure used to make *o*-TMS-anisole yielded a 96% product.[50] To a clean, dry 25 mL round-bottom flask equipped with a medium stir bar, combine 1 equiv. of NBS (1.78 g, 10 mmol) with 18 mL of acetone and 2 mL of cyclohexane until dissolved. To a clean, dry 50 mL round-bottom flask equipped with a medium stir bar, add 1 equiv. of 96% *o*-TMS-anisole (2.06 mL, 10 mmol). Once the NBS has dissolved into the solution, transfer the contents of the 25 mL round-bottom flask to the 50 mL round-bottom flask containing the *o*-TMS-anisole using a glass syringe while stirring. Quench of the reaction after one minute of stirring resulted in GC yields of 65.8% *o*-bromoanisole and 17.5% *o*-TMS-*p*-bromoanisole.

Table 1. Summary of Analytical Data for Aryl *p*-Brominations

	Products	GC% Yield	Lit. M^+ Ion	Exp. M^+ Ion	Lit MP °C	Exp MP °C
a	4-Bromoacetanilide	98.3	214.06	213.1/215.1	165-169	196.0-199.5
b	4-Bromoaniline	95.3	172.02	171.0/173.0	56-62	56.1-60.3
c	2-Amino-4-Bromobenzoic Acid	100	216.03	215.0/217.0	213-215	202.0-203.5
d	4-Bromo-2-Methylaniline	100	186.05	185.0/187.0	57-59	Oil
e	4-Bromo-3-Methylaniline	100	186.05	185.0/187.0	80-82	72.7-74.6
f	4-Bromo-2-Methoxyaniline	100	202.05	201.0/203.0	58-60	50.4-52.3
g	4-Bromo-3-Methoxyaniline	46.5	202.05	201.0/203.0	--	--
h	4-Bromo-*N*-Methylaniline	98.4	186.05	185.0/187.0	Oil	Oil
i	4-Bromo-*N*,*N*-Dimethylaniline	96.9	200.08	199.1/201.1	52-54	49.7-52.0
j	4-Bromo-*N*,*N*,2-Trimethylaniline	96.2	214.1	213.1/215.1	Oil	Oil
k	4-Bromo-*N*,*N*,3-Trimethylaniline	94.6	214.1	213.1/215.1	55	47.4-49.6
l	5-Bromoindoline	81.1	198.06	197.0/199.0	--	--
m	4-Bromoanisole	100	198.06	197.0/199.0	--	--
n	4-Bromo-3-Nitroanisole	100	232.03	231.0.233.0	32-34	28.8-30.2
o	4-Bromo-3-Iodoanisole	100	312.93	311.1/313.1	66-68	Oil
p	4-Bromophenol	96.4	173.01	172.0/174.0	61-64	Oil
q	5-Bromo-2-Hydroxybenzoic Acid	100	217.02	216.0/218.0	159-162	134-136

r	2-Methylphenol	98.1	187.03	186.0/188.0	63-67	Oil
s	3-Methylphenol	100	187.03	186.0/188.0	59-61	Oil
t	2-Methoxyphenol	100	203.03	202.0/204.0	34-37	Oil
u	3-Methoxyphenol	100	203.03	202.0/204.0	77-82	Oil

III. RESULTS AND DISCUSSION

One of the greatest advances in regiospecificity in aromatic substitution was our group's discovery of a method for *p*-iodinations.[24] Use of hydrocarbon media as the select solvent choice for the *p*-iodination reactions allowed for a much safer alternative in comparison to the methods found in the literature. With the realization that iodine can react regiospecificly *para* in a safer way, a more electronegative atom like bromine should react even better. The progression of the research here began with *p*-iodinations, then advanced to *p*-brominations, and becomes more novel with the extreme reduction in time. Using cyclohexane, the *p*-iodinations as well as the *p*-brominations require extensive amounts of time for the reaction to proceed in high yields, with reaction times as long as 24 hours. Acetone as the solvent has reduced the reaction time to very short periods, though, in some cases such as anisole, the reaction time is two hours. Table 2 shows the difference in times between compounds that had been *p*-brominated with acetone and cyclohexane in our research. Note that most *p*-brominated reactions performed in cyclohexane were studied using methoxybenzenes while the focus of this thesis research was primarily on aryl amines, so few comparisons can be represented here.

In using NBS for our bromination reactions, we tried to find a means of dissolving the solid brominating agent to assist in the bromination process. This gave us the ability for the reaction to proceed in a more rapid fashion as opposed to being a surface reaction. Most of the acetone reactions can be completed in just one minute, and afford *p*-bromination at room temperature with few signs of bromoacetone formation. These findings allow for speedier product development. Most of the initial studies were completed on *N*,*N*-Dimethylaniline (DMA), which allowed us to develop a method that worked for the various *N*-Methylated anilines.

Table 2. Comparison of % GC Yields and Time for *p*-Bromination of Substrates Using Cyclohexane and Acetone.

Substrate	**Product**	**% GC Yields in Cyclohexane**	**% GC Yields in Acetone**
N,*N*-Dimethylaniline	4-Bromo-*N*,*N*-Dimethylaniline	90 (24h)	96.9 (1min)
N,*N*-Dimethyl-*o*-Toluidine	4-Bromo-*N*,*N*,2-Trimethylaniline	97 (20h)	96.2 (1 min)
N,*N*-Dimethyl-*m*-Toluidine	4-Bromo-*N*,*N*,3-Trimethylaniline	88 (2h)	94.6 (1 min)
Anisole	4-Bromoanisole	95 (24h)	100 (2 hr)
m-Iodoanisole	4-Bromo-3-Iodoanisole	95 (24h)	100 (1 min)
Phenol	4-Bromophenol	40 (24h)	96.4 (10 min)

DMA was studied under numerous conditions to see how the substrate reacted to different media environments. In studying whether the reaction needed to run in the dark, no difference was detected whether light was involved or not as the results were

similar in time and yield. Different grades of acetone were also used to see if it was mandatory that the bulk solvent be as pure as the 99.9% acetone or if acetone from a 20 gallon drum used in our cleaning procedure could be used to further decrease the cost. The drum acetone resulted in lower, inconsistent yields in comparison to the 99.9% acetone, so we continued using the higher grade for the remainder of the experimentation.

We also studied whether or not the experiment required the use of an air sensitive environment by running the reaction under either Argon (Ar) or Nitrogen (N_2) or if the reaction could be performed under open air. When the reaction was performed under Ar or N_2, we saw consistent, high yields, whereas the open air reaction seemed to give us varied results, and not necessarily as high of yields. Therefore, we decided to continue to use the Ar and N_2. At one point in time, we noticed our reactions were not proceeding as normal, which is when we discovered that our acetone had been contaminated. It is possible these conditional reactions for open air experimentation were performed using our contaminated acetone, which would require further studies to be done on determining if open air experimentation could still be a possibility.

We also tried variation of reactant ratios and orders of adding the materials since we were having varied results. Changing the order of addition made results consistent, though the process became slightly longer than just adding NBS last until dissolved. By allowing the NBS to fully dissolve in the acetone or acetone/cyclohexane mixture, then transferring the solution to the substrate, higher, consistent yields were produced. When the substrate was added to the NBS solution, we noticed a higher percentage of disubstitution reactions occurring, possibly due to the rapid reaction happening as the

substrate was being added to the flask. For this reason, we added the NBS solution to the substrate as opposed to reversing the order.

We varied the number of equiv. of cyclohexane used with *N*,*N*-dimethylaniline because we could not find a consistent method of producing high yields of product. We found the most success with 1 equiv. cyclohexane. By finding a method that worked best for *N*,*N*- dimethylaniline, we were able to use a similar procedure for all *N*-methylated derivatives, including indoline, resulting in high yields for each substrate.

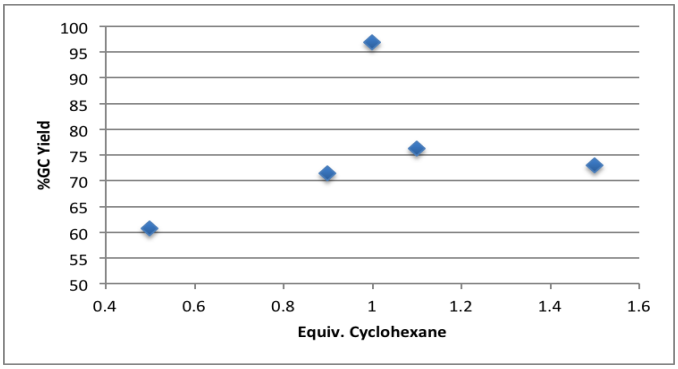


Figure 3. Graph of the % GC yield vs. equiv. cyclohexane used in the reaction with 1 equiv. *N*,*N*-dimethylaniline and 1 equiv. NBS in 20 mL of acetone.

With nitrogen being less electronegative than oxygen, the amine group of aniline is more of an activating group than the methoxy group of anisole. This could account for the reason that most of the aniline reactions occur in one minute whereas the anisole reaction takes two hours. We studied varied amounts of cyclohexane and acetone totaling 20 mL (i.e. 18 mL of acetone with 2 mL of cyclohexane, 19 mL of acetone with 1 mL cyclohexane, 20 mL acetone with 0 mL of cyclohexane) for anilines, anisoles, and phenols in an attempt to increase yield/time ratios.

We tried using a similar method for aniline to see if the equiv. of cyclohexane needed to be varied as was done for *N*,*N*-dimethylaniline and the other *N*-methylated

anilines. None of the reactions using an equiv. of cyclohexane gave a 100% GC yield as did using 19 mL of acetone with 1 mL of cyclohexane. For the remainder of the anilines, 19 mL of acetone and 1 mL of cyclohexane were used as a starting point, and if 100% GC yields were achieved, we typically ceased attempts at any other acetone/cyclohexane combinations, though, not every time.

For acetanilide, varying the amount of acetone to cyclohexane did not make a tremendous amount of difference. Whether it was 18 mL of acetone with 2 mL of cyclohexane (96.8% GC yield), 19 mL of acetone with 1 mL cyclohexane (98.3% GC yield), or 20 mL of acetone with 0 mL of cyclohexane (96.5% GC yield), the results still show high yields. Reported in the procedure is the greatest GC yield value, that for 19 mL acetone and 1 mL of cyclohexane; however, if an individual finds he or she lacks cyclohexane, it is still possible to successfully *p*-brominate acetanilide using 0 mL of cyclohexane and 20 mL of acetone.

The same method was used to find the most successful method of *p*-brominating *o*-toluidine. More of a difference was seen in comparison between the different acetone/cyclohexane ratios. With 18 mL of acetone and 2 mL of cyclohexane, the yields were much lower (78.2% GC yield), but were not as low for 19 mL acetone and 1 mL of cyclohexane (96.1% GC yield. The greatest success was found using 20 mL of acetone with 0 mL of acetone resulting in the 100% GC yield. Because of the high success, the same procedure was used for *m*-toluidine. While the reaction was not as fast (10 minutes), the result was still a 100% GC yield. By increasing the equiv. of NBS to 1.1, we were able to reduce the amount of time to 5 minutes to produce 100% *p*-bromination of *m*-toluidine.

Anthranilic acid gave 100 % GC-MS yields whether it was performed using 19 mL of acetone and 1 mL of cyclohexane or 20 mL of acetone and 0 mL of cyclohexane. For this reason, reported is the 20 mL of acetone with 0 mL of cyclohexane run to show the most simplistic form of the reaction. The product had to be run through the GC-MS (as did salicylic acid) because the carboxyl group can cause problems with the regular GC's packed column.

o-Anisidine gave a 100% GC yield with the 19 mL of acetone and 1 mL of cyclohexane combination, so no further studies were performed. We expected *m*-anisidine to produce great results due to two activating groups, one in the one position and the other in the 3 position, both of which would prefer the reaction to proceed in the 4 position. We believe that it may be possibly due to steric hindrance that the bromination of the *para*- position was simply not achievable, thus resulting in our low GC yield of 46.5%.

Moving from anilines to anisoles, we had a less efficient donor as our -EDG, which resulted in a longer period for *p*-bromination. Anisole was one of the original compounds experimented on for *p*-bromination, and used the 18 mL of acetone with 2 mL of cyclohexane, but took two hours early in our studies. Because like many of the previous *m*- substituted compounds worked most successfully with 20 mL of acetone with no cyclohexane, we began performing our *m*-substituted anisoles with those conditions, which gave us 100% GC yields much quicker than the bromination of anisole itself. The reaction of *m*-nitroanisole resulting in *p*-bromination shows that even though the nitro substituent is a strong -EWG, the conditions in this research gives strictly *para*- substitution, irrespective of other directing groups. When running the

reaction with anisole itself in 20 mL of neat acetone, we received considerably lower yields (77.4%) in the same period.

The phenols presented a number of difficulties in comparison to the anilines and anisoles. This may be due to the –OH group being a slightly stronger EDG in comparison to the methoxy substituent. No matter what variation of acetone and cyclohexane combinations were used, the results still remained between 65% and 75% GC yields, except for when 20 mL of neat acetone was used (85% GC yield). From here, the equiv. of NBS was varied, as seen in Figure 4, up to 1.2 equiv, where we found the best results.

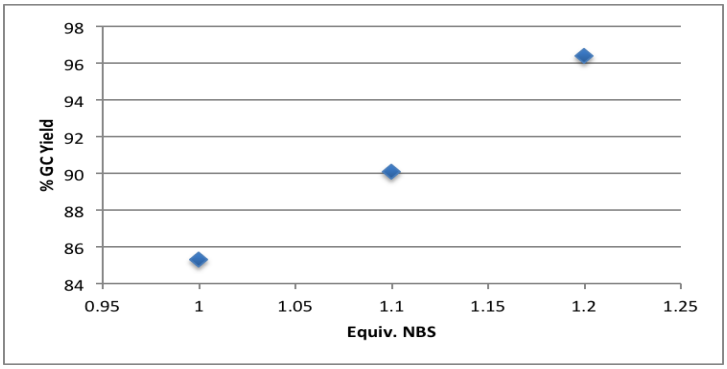


Figure 4. Graph of the % GC yield vs. equiv. of NBS used in the reaction of 1 equiv. phenol with 20 mL of acetone.

For the substituted phenols, most were found to have the greatest success with 20 mL of neat acetone. Salicylic acid still used neat acetone; however, to assist in the speed of the reaction, the acetone was split between the NBS (15 mL) and salicylic acid (5 mL) so both were in solution once the reaction started. This allowed for 100% GC-MS yields in one minute. With the lower amount of acetone combined with NBS, a heat gun was necessary to assist in dissolving the solid into solution.

20 mL of acetone was also used for both *o*-cresol and *m*-cresol, but as was done for phenol, the equiv. of NBS needed to be varied as well. We did test variations of acetone/cyclohexane combinations, but the yields were still greatest with 20 mL of acetone. We never got our *o*-cresol reaction to reach 100% GC yields, but we did get extremely close. Figure 5 shows our progression of yields for the varied equiv. of NBS in the *o*-cresol reaction. As with phenol, we tested 1 equiv., 1.1 equiv., and 1.2 equiv. Unlike phone, however, *o*-cresol with 1.2 equiv. of NBS resulted in a lower GC yield in comparison to 1.1 equiv. of NBS. *m*-Cresol had more success than *o*-cresol, giving 100% GC yields, but with various times. As with other *m*-substituted compounds and phenols in general, 20 mL of acetone resulted in the greatest GC yields. With just 1 equiv. of NBS, 100% GC yields were found in 5 minutes; however, the time increased to just 1 minute with both 1.1 equiv. NBS and 1.2 equiv. NBS. For that reason, we reported the lower quantity of NBS needed for the reaction to proceed with the most success, 1.1 equiv.

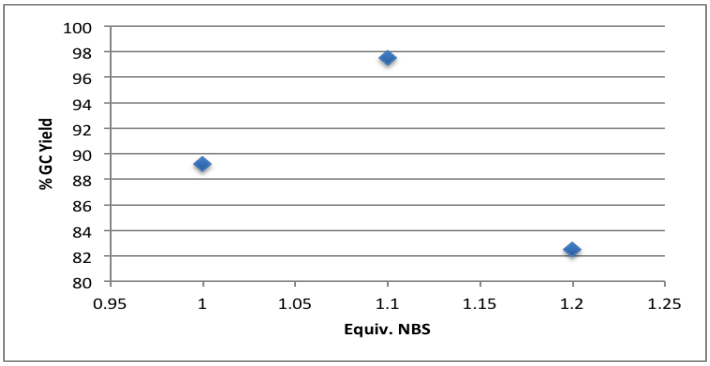


Figure 5. Graph of % GC yield vs. equiv. of NBS used in the reaction of 1 equiv. *o*-cresol with 20 mL of acetone.

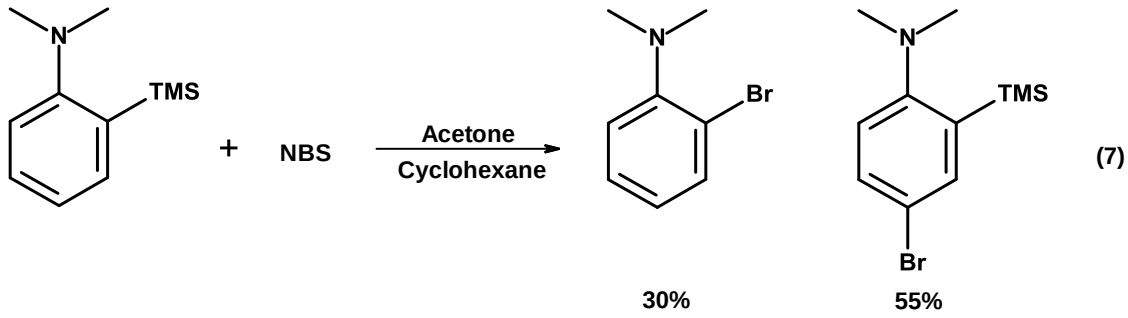
The methoxyphenols were interesting compounds to examine due to there being two EDG's on the ring. Guaiacol, or 2-methoxyphenol, was studied around the time

anisole was studied, which is where our use of 18 mL of acetone with 2 mL of cyclohexane in the reaction arose. Since we attained 100% GC yields with that acetone/cyclohexane combination, we did not experiment any further on whether the reaction will still proceed in neat acetone, which could be another portion that may be investigated in the future. The difficulty would have been to determine whether the reaction occurred *para*- to the phenol group or the methoxy group. The NMR shows that there is, in fact, *p*-bromination, but it's the melting point that suggests the reaction more likely occurred *para*- to the phenol group. The melting point of 4-bromo-2-methoxyphenol is 34-37°C whereas the melting point for 5-bromo-2-methoxyphenol is 63-65°C. Because our reaction yielded an oil, it is more likely that the reaction produced 4-bromo-2-methoxyphenol.

While the question of whether or not the reaction would proceed *para*- to the alcohol group or the methoxy group became an issue for guaiacol, we expected the reaction of 3-methoxyphenol to be less of a challenge since the methoxy group would support the bromination of the 4 position as an *ortho*- substitution. The reaction ended up yielding monobromination at the 4 as well as the 6 position, when reacting with 1 equiv. of NBS with the same acetone/cyclohexane combination as guaiacol. Even when the reaction was performed at 0°C, there were higher yields (71.9%) of *p*-bromination, but there remained a persistent amount of the isomer. As we began to vary the acetone/cyclohexane combinations with 1 equiv. NBS, the yields ranged from as little as 37.7% to as high as 71.5%, not showing much improvement from performing the conditions at 0°C. In correspondence with other *m*-substitutions, our best results came

from 20 mL of acetone with 1.5 equiv. of NBS giving us 100% GC yields of *p*-bromation, presumably *para* to the –OH substituent, in just one minute.

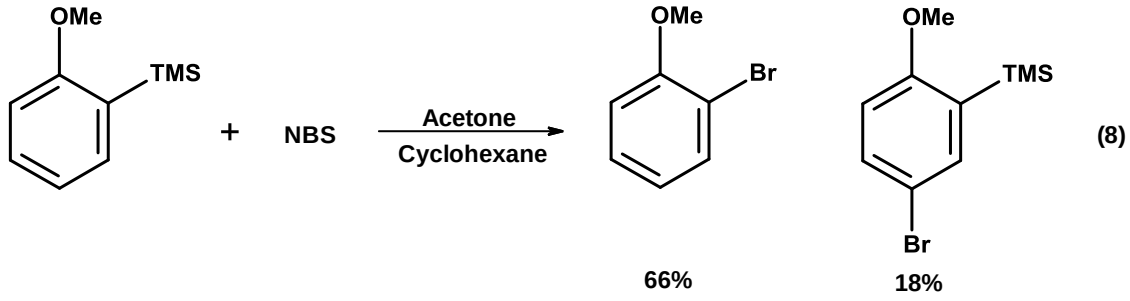
In a typical EAS reaction, it is known that a TMS substituent will react at a magnitude of 10^4 times faster than a hydrogen on the aromatic ring. Since most EAS reactions occur with a partition between *ortho*- and *para*- products, the regiospecific *para*- substitution reactions discovered were analyzed as to whether the reaction is, in fact, proceeding under standard EAS mechanisms. Since typical EAS conditions require the use of an oxidizing agent as well as a Lewis acid, and the research here is a neutral reaction without either of these elements, we have to wonder if this is actually an EAS reaction. For this purpose, we studied *o*-TMS-anisole as well as *o*-TMS-*N*,*N*-dimethylaniline to see whether or not the reaction would take place at the *ortho*- position as we would suspect for typical EAS reactions involving the –TMS substituent.



(7)

As seen in equations 7 and 8, two very different outcomes occur with the same reaction setup. *N*,*N*-Dimethylaniline reacts in one minute as does *o*-TMS-*N*,*N*-dimethylaniline. With the rapid substitution, a greater amount of product becomes substituted in the *para*- position, which defies the traditional EAS rules. With traditional EAS, the reaction would become substituted in a greater magnitude at the *o*-TMS location to produce *o*-bromo-*N*,*N*-dimethylaniline. Our research shows that this is not

the case. A variation of this result occurred when *o*-TMS-anisole under the same conditions.



In equation 8, we see that a greater amount of product forms at the *o*-TMS position. Interestingly, the research shows that the procedure for producing *p*-bromoanisole requires two hours to complete. The reaction of NBS with *o*-TMS-anisole yields a greater quantity of *o*-bromoanisole in just one minute. It could be that because the typical reaction for anisole requires a longer period of time, the shorter time frame resulted in a traditional EAS reaction. Because of the two different outcomes of our mechanistic inquiry, we are still unsure of the exact mechanism involved in this research.

IV. CONCLUSIONS

For many years, the focus of research within our group consisted of regiospecific halogen/metal exchange and hydrogen/metal exchange by the use of lithium reagents. For halogen/metal exchange, it could occur at any position on an aryl where a -Br or –I is located, whether it's *ortho*-, *meta*-, or *para*- to a substituent. With the hydrogen/metal exchange reactions, the substitution is strictly *ortho*- to the substituent. Because EAS is one of the most vastly used methods for aromatic substitution, it is imperative for

regiospecific substitution to be available at both *ortho*- and *para*- locations. This illustrates the extreme importance of the research presented here.

As mentioned in the introduction, substitution where there is a lithium substituent allows for carbon-carbon bond formation, which can be used in a vast number of disciplines. In DoM, lithium substitution occurs in the *ortho*- position whereas the halogen/metal exchange requires a halogen to be on the ring. This research allows for a *para*-bromination (iodination), resulting in the ability for the halogen/metal exchange to occur strictly *para*-, permitting carbon-carbon bond formation to be possible in a regiospecific manner. Previously, *p*-brominated substrates had to be purchased to perform the halogen/metal exchange with ease. Now, we can generate 100% GC yields of certain activated aryls in an expedited fashion with simple, low cost materials.

The novelty of the research method here lies in the ability to strip acetone from the product solution with ease to leave a mostly pure product. In a minimal amount of time, we can produce a *para*-brominated compound and have it readily available to go through the halogen/metal exchange. Since our previous research used cyclohexane, we can strip the acetone, add cyclohexane, and not worry about adverse solvent effects. After the halogen/metal exchange is performed, we could then use the compound for DoM, which can further create more complex compounds.

Our work is focused on creating safer, greener, cost efficient methods for aryl substitutions. From discovering a method of performing the halogen/metal exchange and hydrogen/metal DoM with using cyclohexane instead of an hazardous solvent such as ether, to being able to *p*-iodinate and *p*-brominate with the use of cyclohexane, and now

being able to rapidly *p*-brominate in acetone media, we have managed to advance our research towards accomplishing our goals.

Future work would involve testing the reaction scheme proposed, as well as testing more activated aryls not researched here. There would also need to be a greater amount of research performed on discovering the logistics of the mechanism involved in this substitution reaction. Further advancement in decreasing the amount of time it takes to *para*-brominate the longer substrates like anisole are currently being studied with the use of another solvent, acetonitrile.

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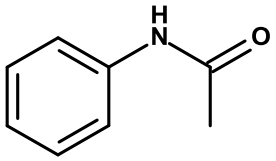
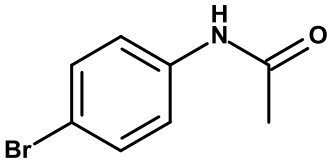
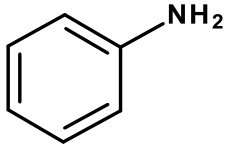
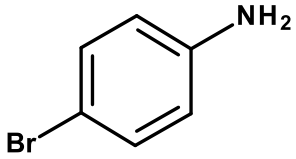
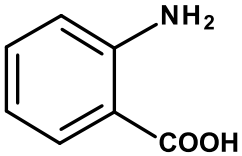
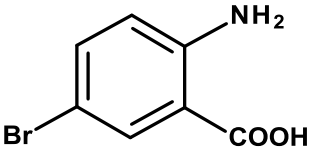
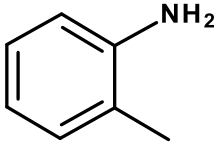
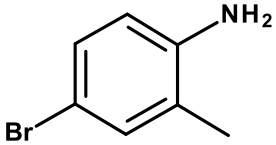
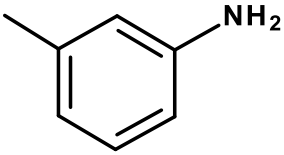
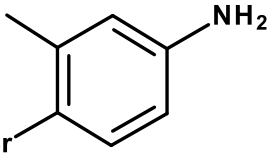
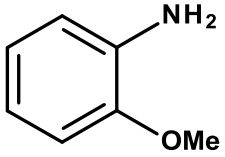
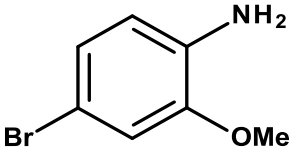
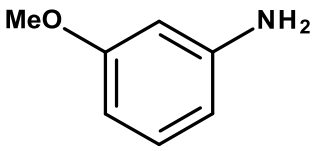
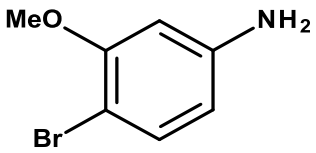
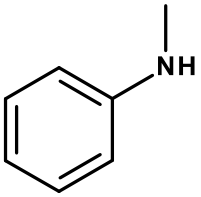
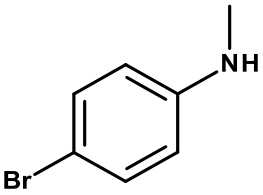
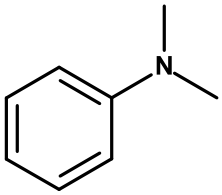
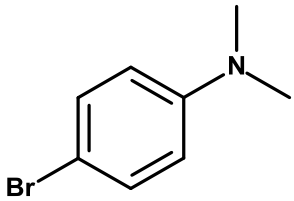
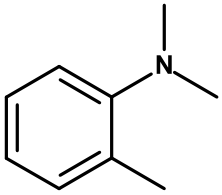
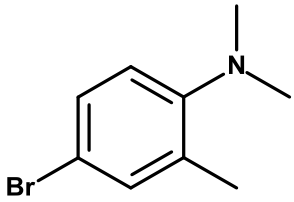
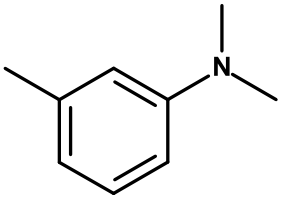
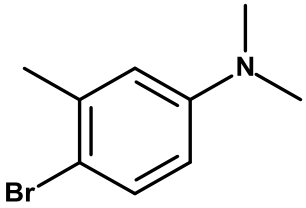
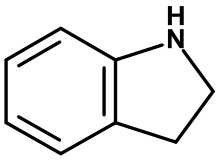
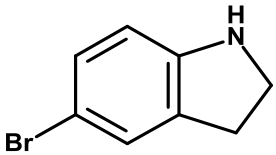
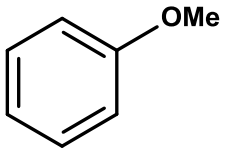
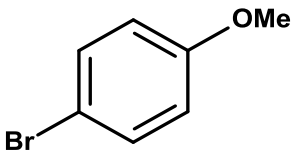
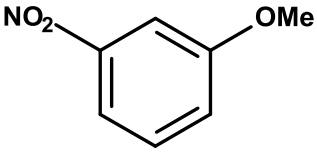
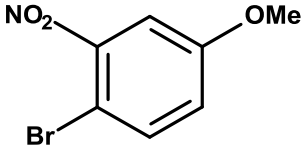
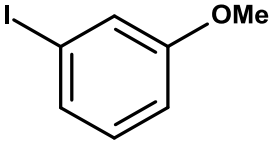
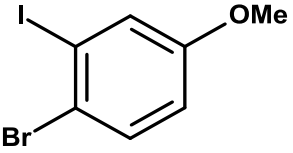
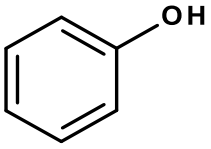
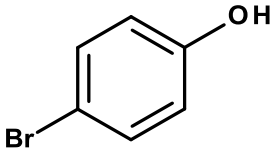
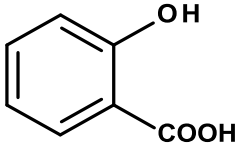
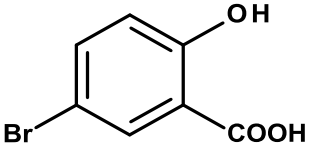
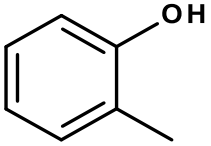
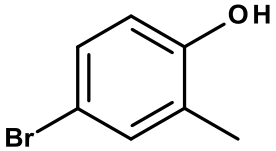
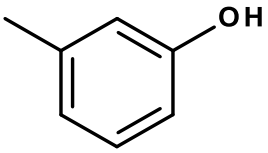
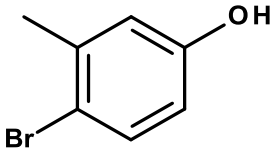
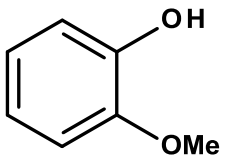
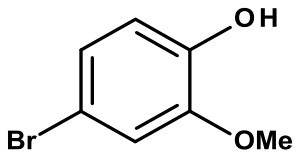
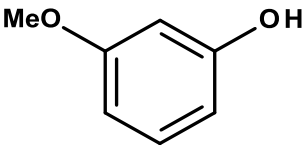
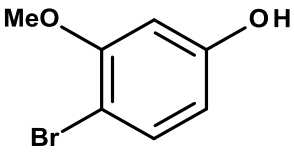
VI. APPENDIX

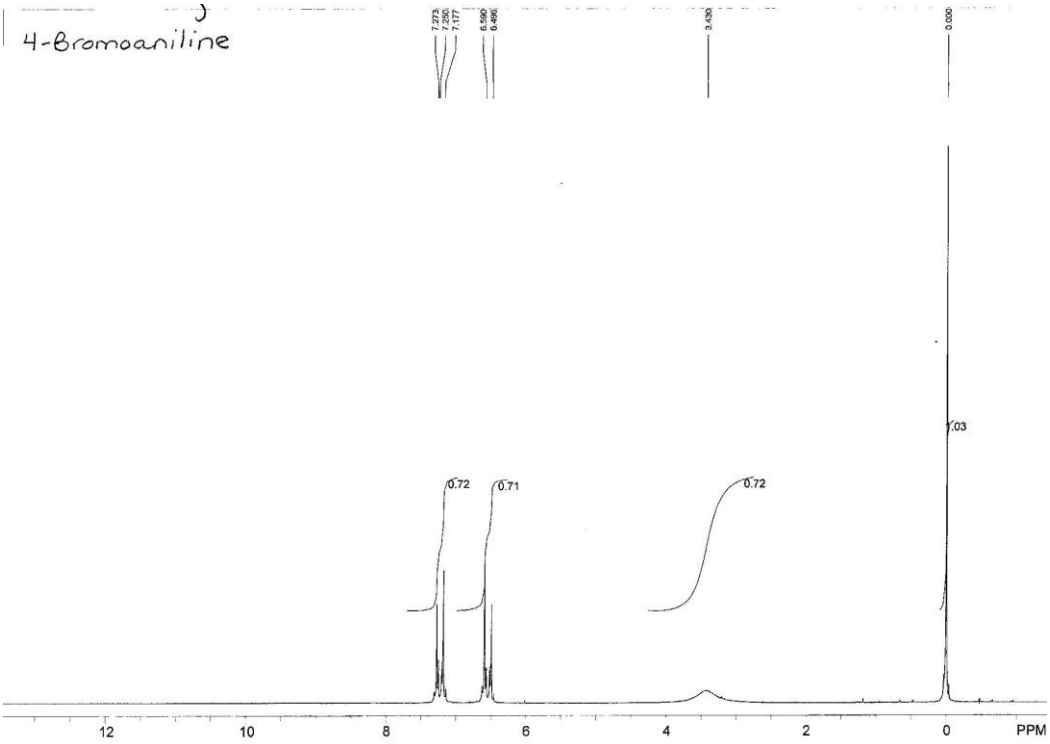
	Substrate	**Product**
a	 Acetanilide	 4-Bromoacetanilide
b	 Aniline	 4-Bromoanline
c	 Anthranilic Acid	 2-Amino-5-Bromobenzoic Acid
d	 *o*-Toluidine	 4-Bromo-2-Methylaniline
e	 *m*-Toluidine	 4-Bromo-3-Methylaniline
f	 *o*-Anisidine	 4-Bromo-2-Methoxyaniline

g	 *m*-Anisidine	 4-Bromo-3-Methoxyaniline
h	 *N*-Methylaniline	 4-Bromo-*N*-Methylaniline
i	 *N*,*N*-Dimethylaniline	 4-Bromo-*N*,*N*-Dimethylaniline
j	 *N*,*N*-Dimethyl-*o*-Toluidine	 4-Bromo-*N*,*N*,2-Trimethylaniline
k	 *N*,*N*-Dimethyl-*m*-Toluidine	 4-Bromo-*N*,*N*,3-Trimethylaniline
l	 Indoline	 4-Bromoindoline

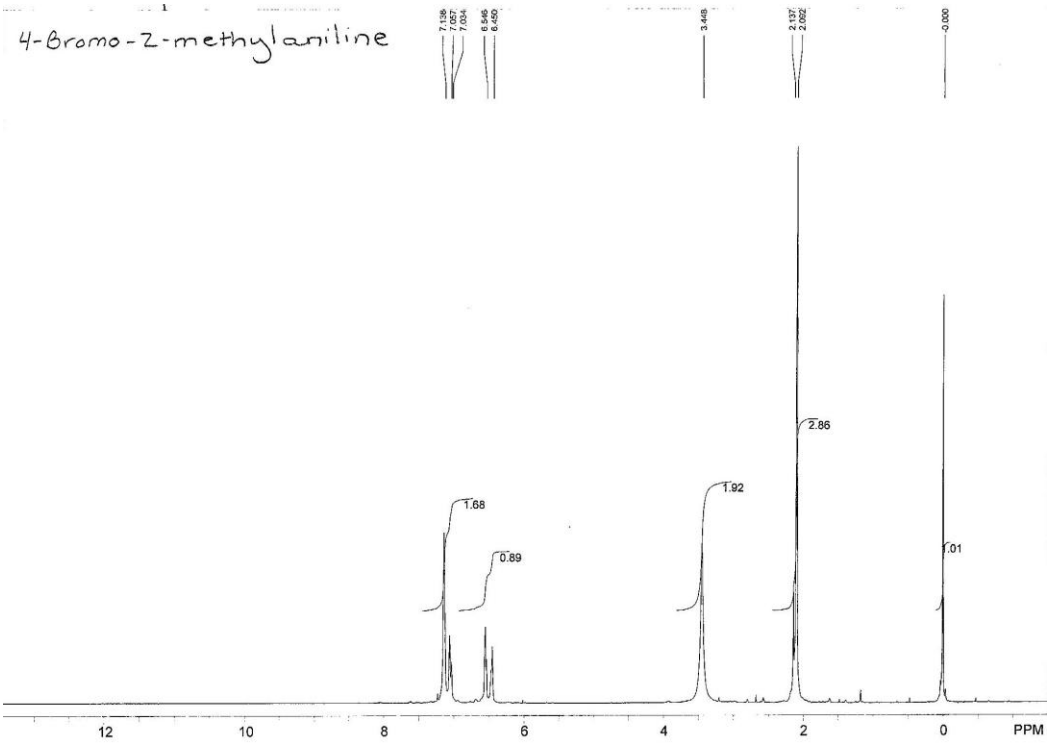
m	 Anisole	 4-Bromoanisole
n	 *m*-Nitroanisole	 4-Bromo-3-Nitroanisole
o	 *m*-Iodoanisole	 4-Bromo-3-Iodoanisole
p	 Phenol	 4-Bromophenol
q	 Salicylic Acid	 4-Bromo-2-Hydroxybenzoic Acid
r	 *o*-Cresol	 4-Bromo-2-Methylphenol
s	 *m*-Cresol	 4-Bromo-3-Methylphenol

t	 Guaiacol	 4-Bromo-2-Methoxyphenol
u	 3-Methoxyphenol	 4-Bromo-3-Methoxyphenol

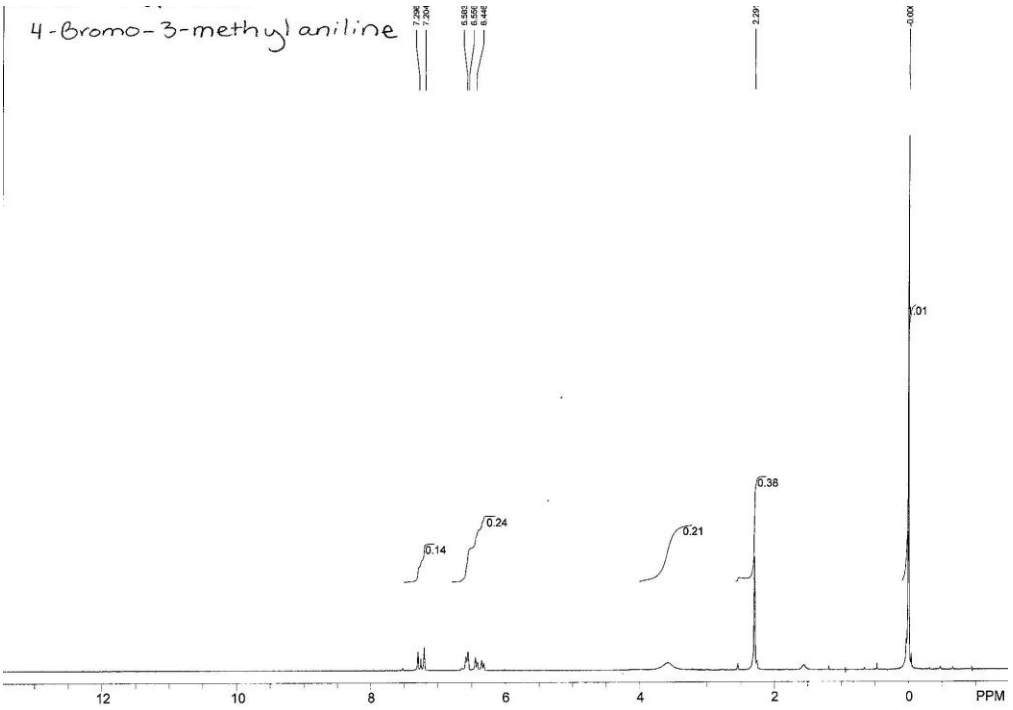
NMR #1 (4-Bromoaniline)



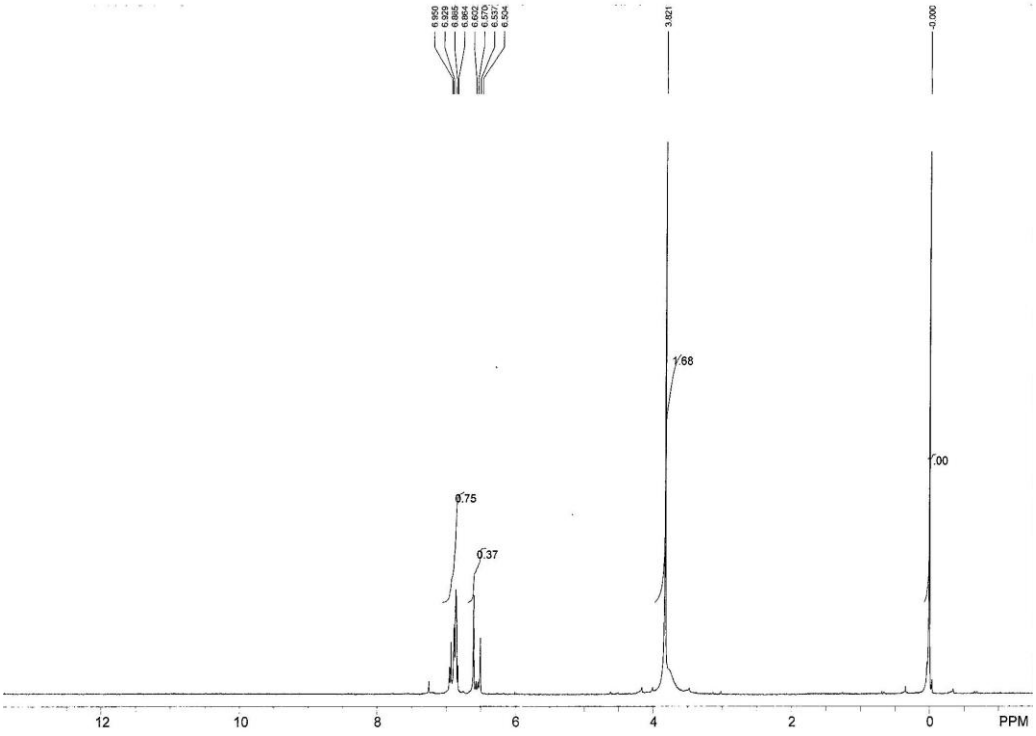
NMR #2 (4-Bromo-2-Methylaniline)



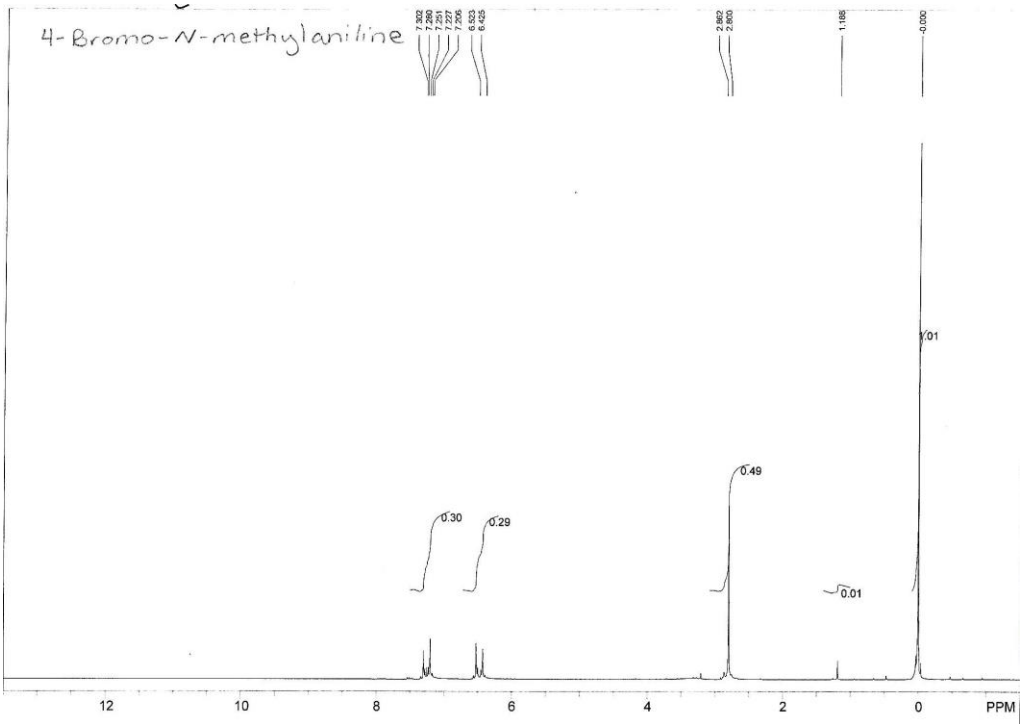
NMR #3 (4-Bromo-3-Methylaniline)



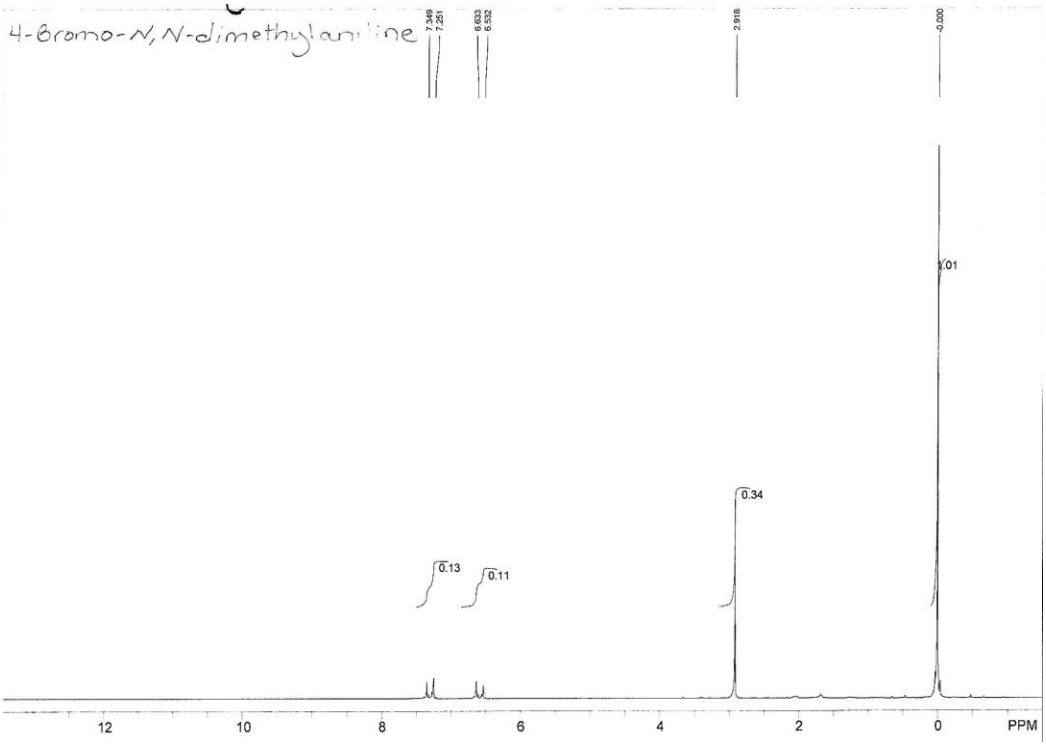
NMR #4 (4-Bromo-2-Methoxyaniline)



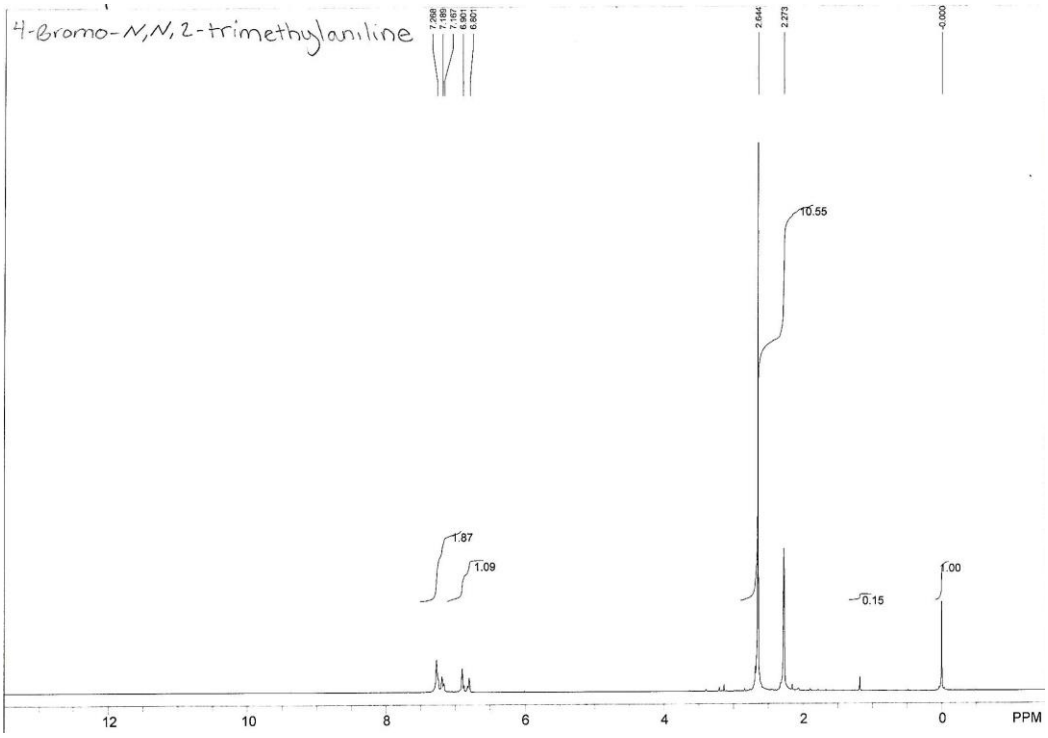
NMR #5 (4-Bromo-*N*-Methylaniline)



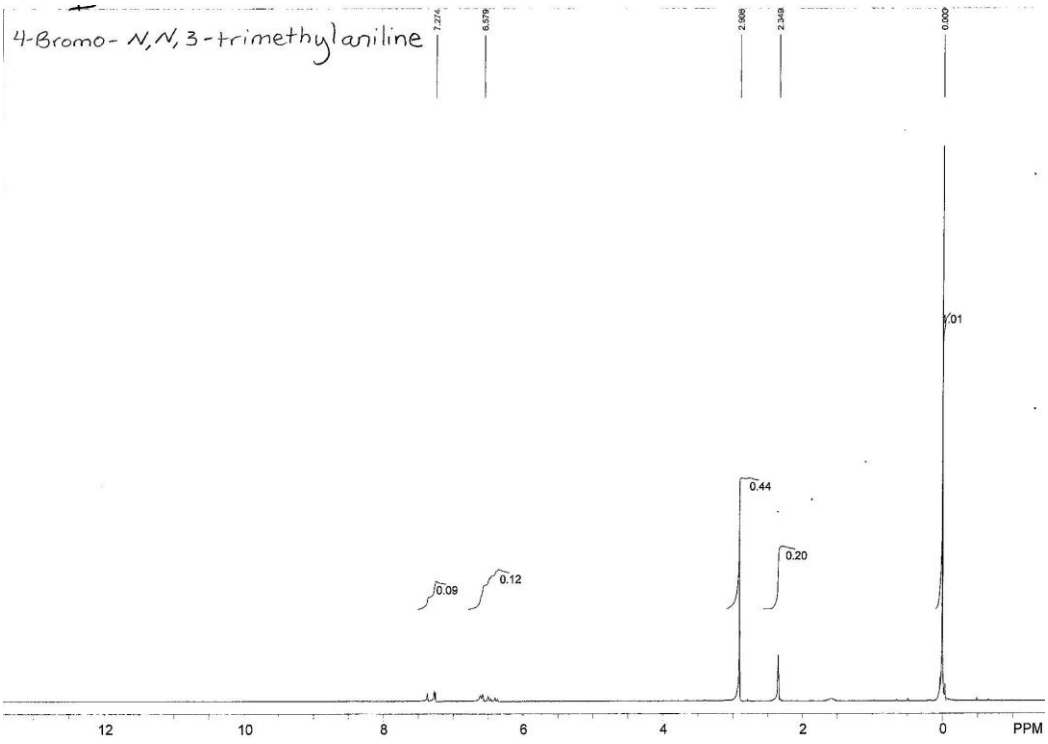
NMR #6 (4-Bromo-*N*,*N*-Dimethylaniline)



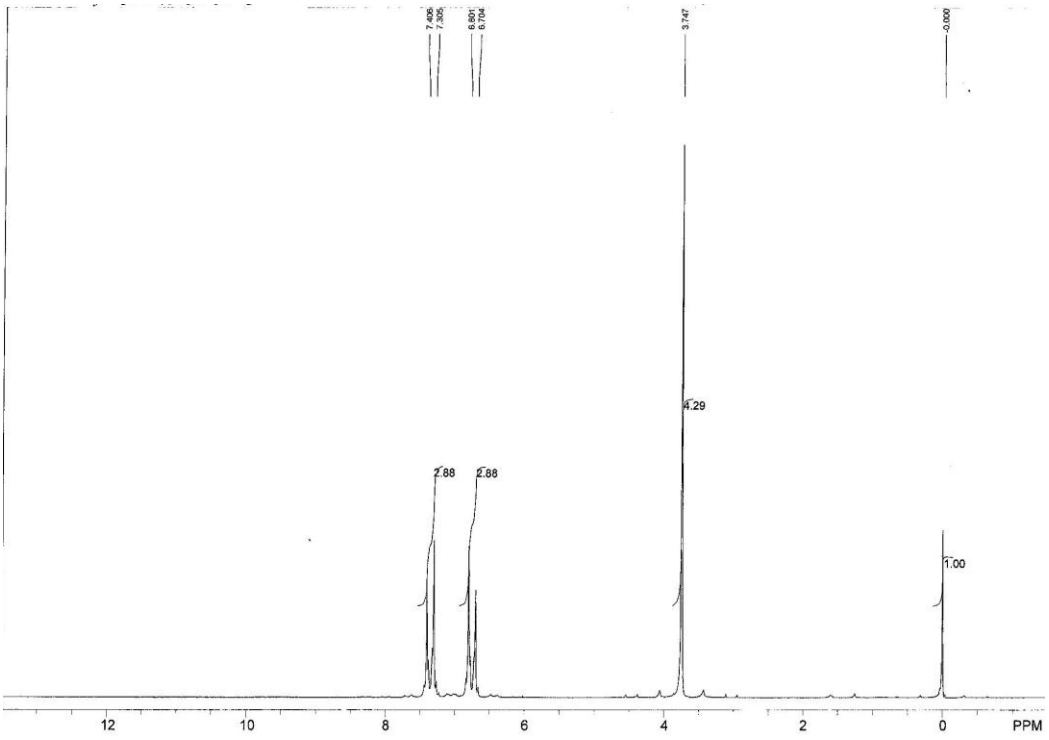
NMR #7 (4-Bromo-*N*,*N*,2-Trimethylaniline)



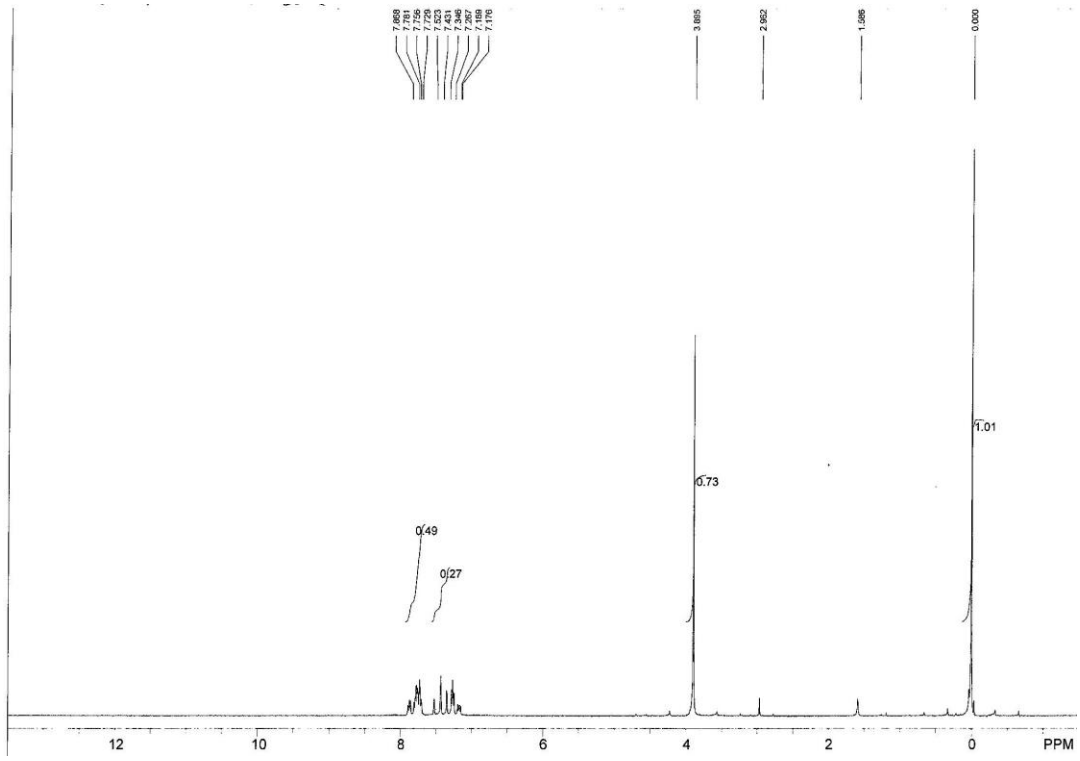
NMR #8 (4-Bromo-*N*,*N*,3-Trimethylaniline)



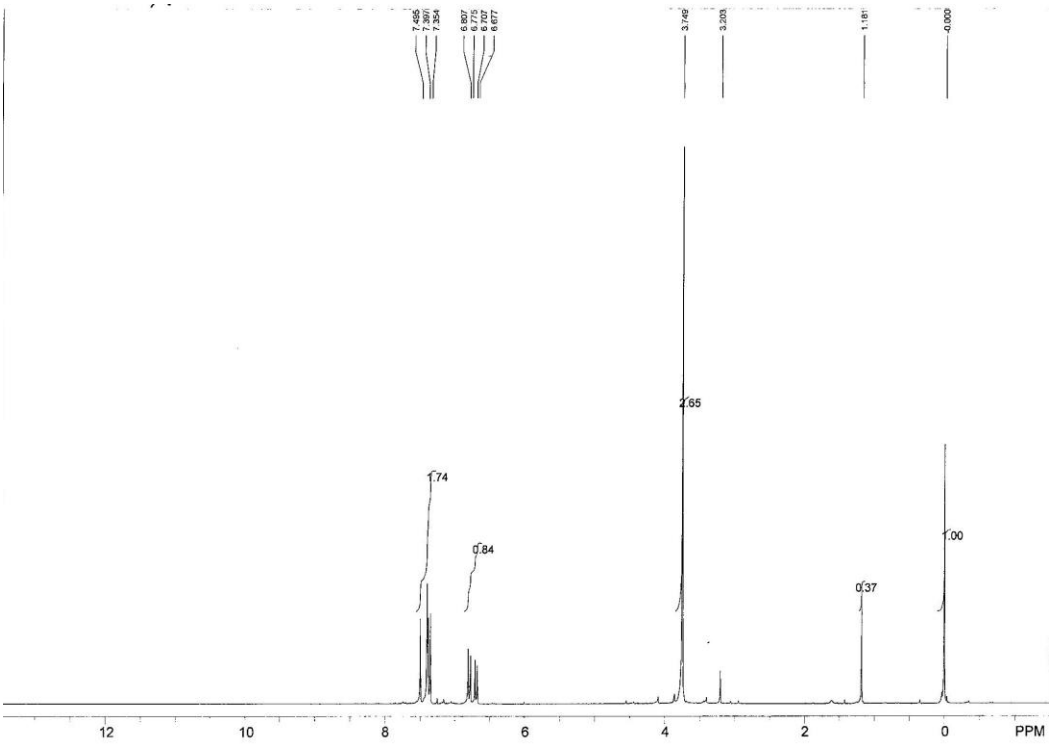
NMR #9 (4-Bromoanisole)



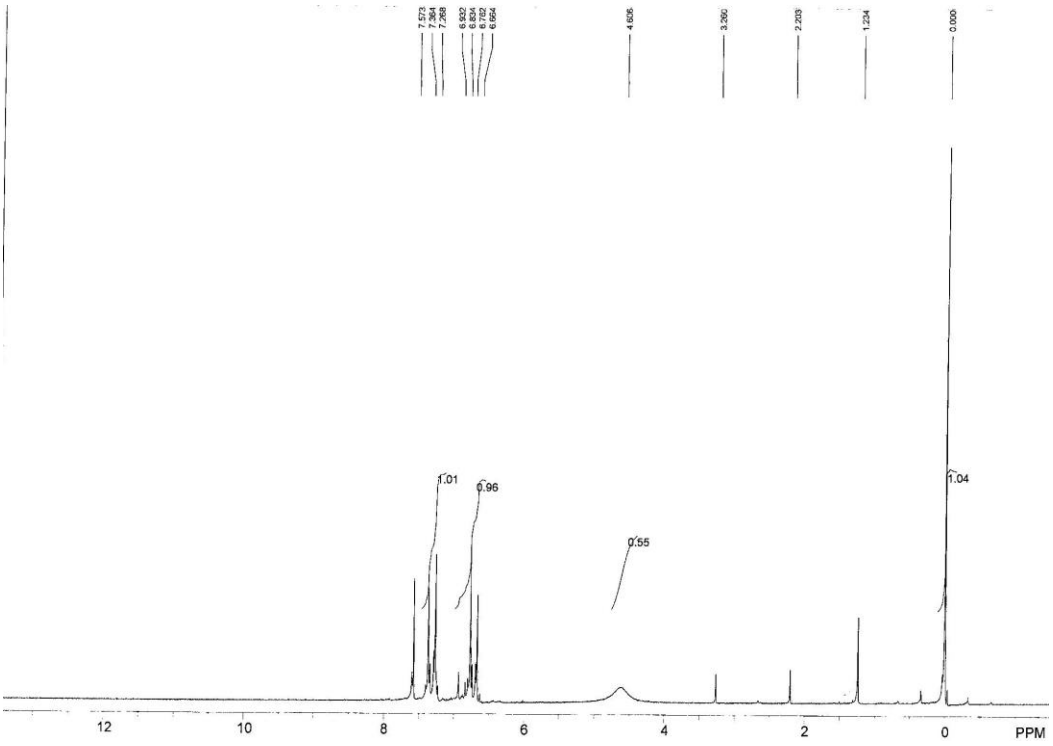
NMR #10 (4-Bromo-3-Nitroanisole)



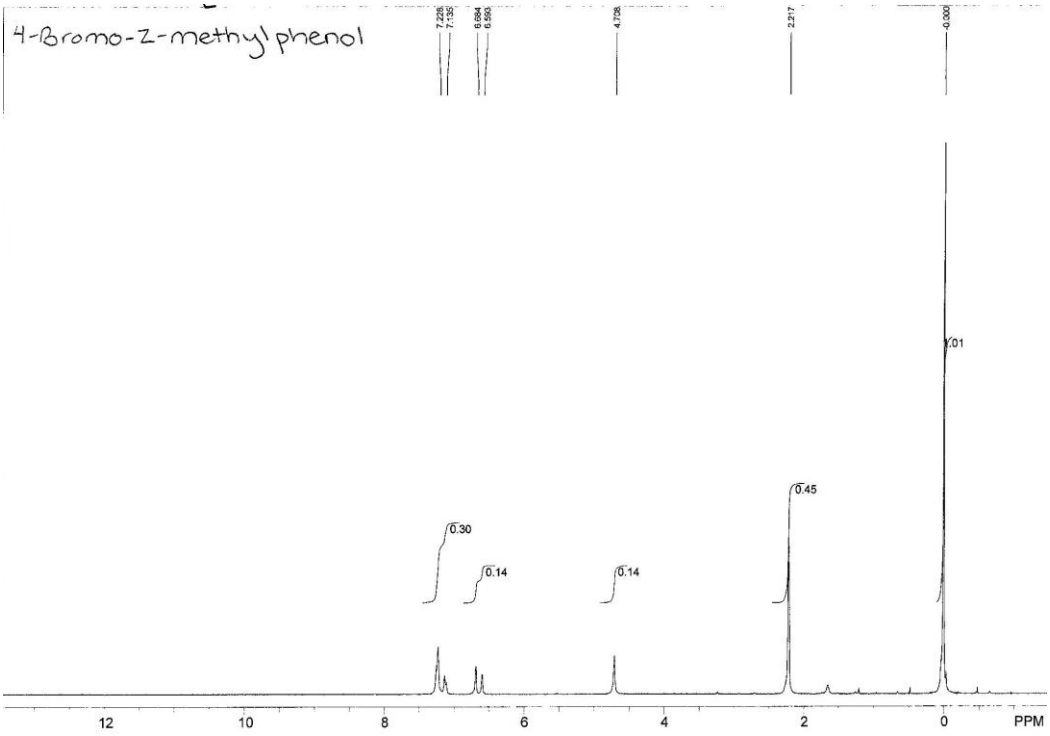
NMR #11 (4-Bromo-3-Iodoanisole)



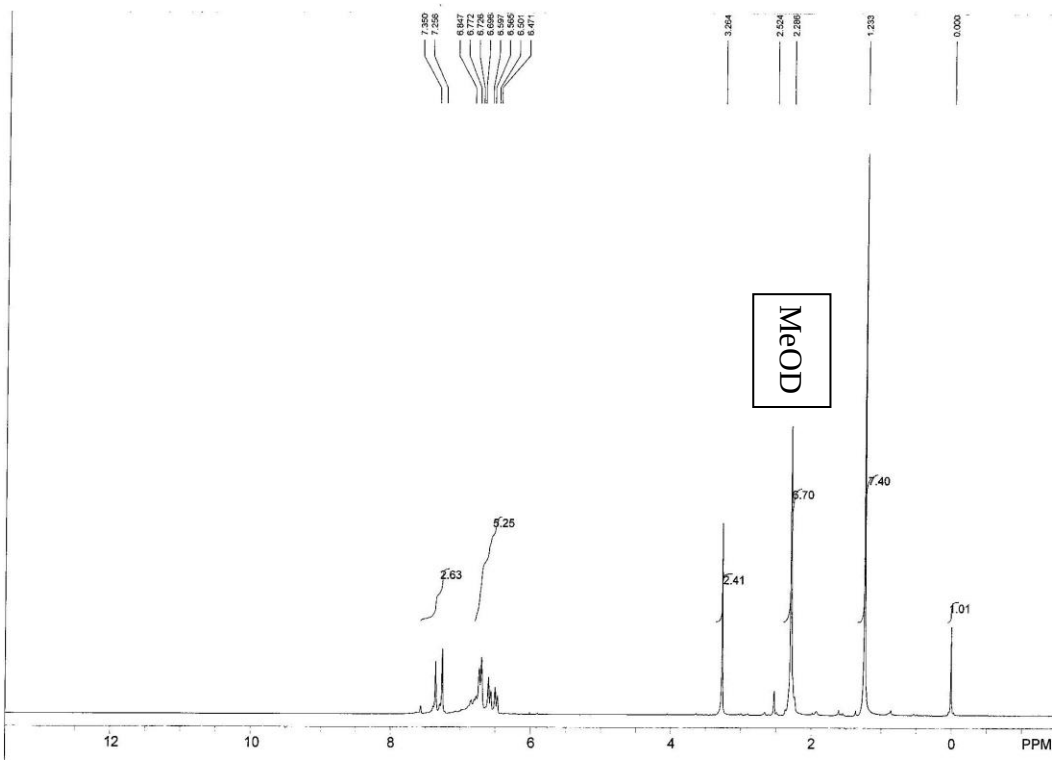
NMR #12 (4-Bromophenol)



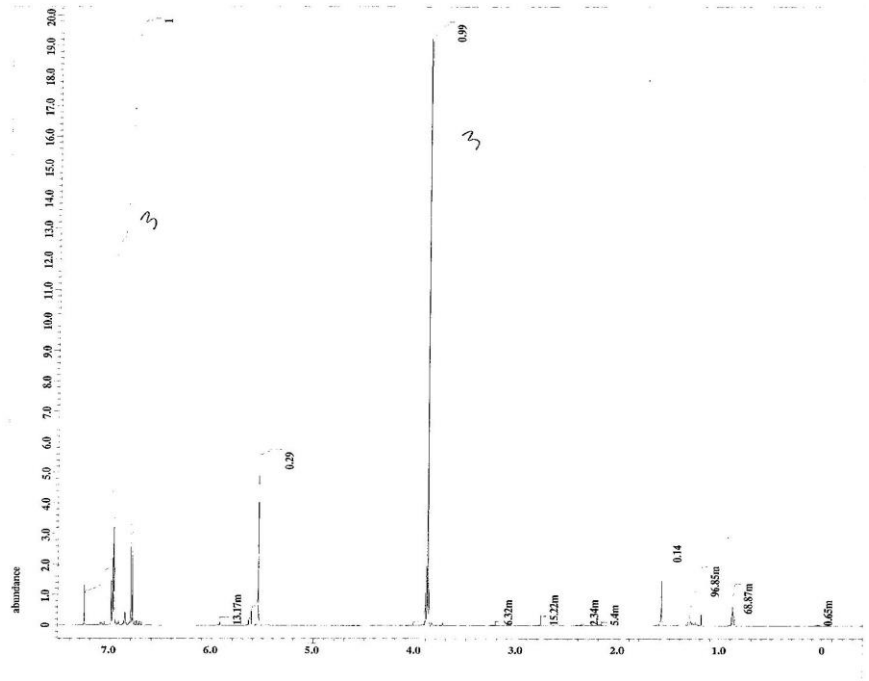
NMR # 13 (4-Bromo-2-Methylphenol)



NMR #14 (4-Bromo-3-Methylphenol)



NMR #15 (4-Bromo-2-Methoxyphenol)



NMR #16 (4-Bromo-3-Methoxyphenol)