

SYNTHESIS AND CHARACTERIZATION OF AMINE AND EUGENOL BASED DIPHENYLEETHERS

**A THESIS
SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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IN
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Submitted by

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Certificate

This is to certify that the thesis entitled “**Synthesis and Characterization of Amine and Eugenol based Diphenylethers**” being submitted in the partial fulfilment of requirements for the award of degree of **Master of Science in Chemistry** submitted in **School of Chemistry and Biochemistry, Thapar University, Patiala** is a bonafide work carried under the supervision of **Dr. Manmohan Chhibber** Associate Professor, School of Chemistry and Biochemistry, Thapar University, Patiala and that no part of this project has been submitted for the award of any other degree.

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Declaration

I hereby declared that the work presented in this thesis entitled “**Synthesis and Characterization of Amine and Eugenol based Diphenylethers**” submitted in the partial fulfilment of requirements for the award of degree of **Master of Science in Chemistry** submitted in **School of Chemistry and Biochemistry, Thapar University, Patiala** is an authentic record of my own work carried out under a bonafide work carried out under our guidance and supervision and that no part of this project has been submitted for the award of any other degree.

Date: July, 2016

Place: Patiala


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Needless to say errors and omissions are solely mine.


Ramanpreet Kaur Sandhu

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SYNTHESIS AND CHARACTERIZATION OF AMINE AND EUGENOL BASED DIPHENYLEETHERS

Abstract

The work described in the thesis involves synthesis of dipheylamine (**Compound-1**) by reaction of 2-nitrofluorobenzene and 2-aminophenol. Besides that allylic group of another eugenol based dipheyl ether (**Compound-2**) was converted to its corresponding iodohydrin (**Compound-3**) in the presence of sodium iodide and hydrogen peroxide in acidic medium. All the synthesized compounds were characterized by ^1H , ^{13}C NMR spectroscopy. GCMS and IR was also done for **Compound- 3**.

Introduction

Diphenyl ether is an organic compound with the formula $O(C_6H_5)_2$. The molecule is subject to reactions typical of other phenylrings, including hydroxylation, nitration, sulphonation and Friedel–Crafts alkylation and acylation.¹

It is used as heat transfer medium as an eutectic mixture with biphenyls because of relatively large temperature range in its liquid state. Dowtherm A is a commercially available eutectic mixture containing 73.5% diphenyl ether and 26.5% diphenyl. This compound is also a starting material for the production of phenoxathiin via the Ferrasiorreaction.² Phenoxathiin find applications in the synthesis of polyamide and polyimide production.³

Many diphenyl ethers due to their high stability, low price and germicide action find wide use in soaps and perfumes.⁴ Besides this, they find application as biocides, flame retardant, functional fluids and motifs in many natural products. Oxyfluorfen (**Compound A**) and triclosan (**Compound B**) are used as herbicide and antibacterial agents respectively. Oxyfluorfen kills plants by cell lysis by the action of light which induces per oxidative degradation of cellular constituents, especially membrane lipids.⁵ Triclosan, on the other hand kills bacteria by inhibiting an essential enzyme that is responsible for the fatty acid biosynthesis in the bacteria.⁶ Several polybrominated diphenylethers (PBDEs) also find use as flame retardants. Decabromodiphenyl oxide is one of the very common flame retarding material sold under the trade name Saytex 102 (**Compound C**) in the manufacture of paints and reinforced plastics.

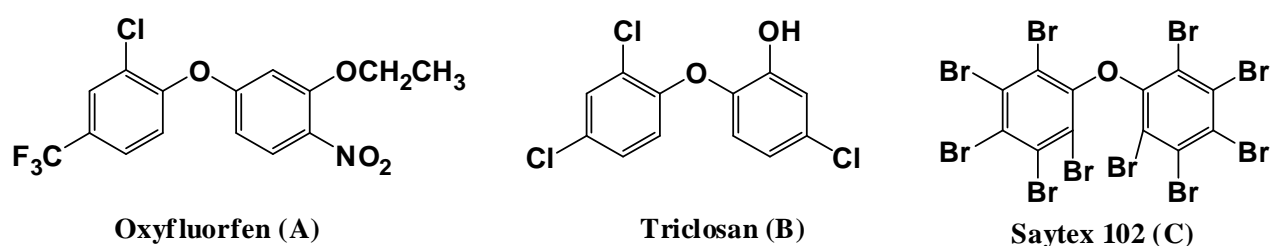


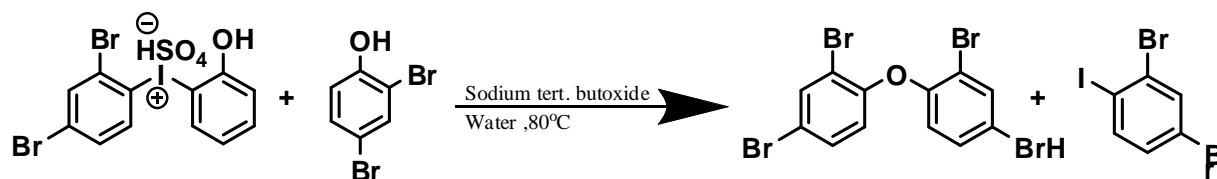
Figure-1 : Diphenyl ethers used as herbicide (A) as antibacterial agents (B) and as flame retardant (C)

The work presented in this thesis involves synthesis of some diphenyl ethers and reactions on already synthesized diphenyl ethers to create new moieties.

Review of Literature

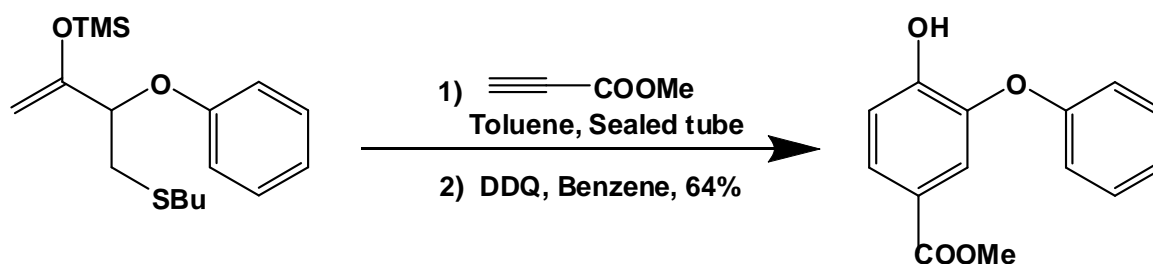
Diphenyl ether was prepared in 1854 by List and Lmpricht ⁷ by dry distillation of copper benzoate. Hoffmeister ⁸ was the first to isolate the pure diphenyl ether and conclude that the mixture consisted of diphenyl ether and biphenyl. Later, dipheyl ether was also prepared by the reaction of benzenediazonium sulfate with phenol ⁹. The yields were poor in either case. Improved yields of diphenyl ether from benzenediazonium chloride were claimed by Kirsch ¹⁰. Diphenyl ether is obtained among other products from the distillation of calcium phenyl salicylate. It is formed in 40-50 % yield when a mixture of sodium benzenesulfonate and potassium phenoxide is distilled ¹¹. Most of above methods of synthesizing dipheyl ethers were explored between mid nineteen century and early twentieth century. Interestingly, the importance of these molecules has increased tremendously over the years due to their varied applications. Therefore new methodologies were developed for improved yield and new applications.

Scheme -1



Recently, diphenyl ethers have been synthesized by heating phenol with symmetrical diphenyliodonium salt ¹² in presence of sodium tertiary butyl dioxane and water (**Scheme -1**) The preparation of the iodonium salts is done by oxidation of iodine to iodylsufate $(\text{IO})_2(\text{SO})_4$ with the help of nitric and sulphuric acid at about 75⁰ C which is then reacted with a benzene to obtain the iodonium salt. . The methodology is expected to be of high utility in the synthesis of complex molecules and in the pharmaceutical industry.

Scheme - 2

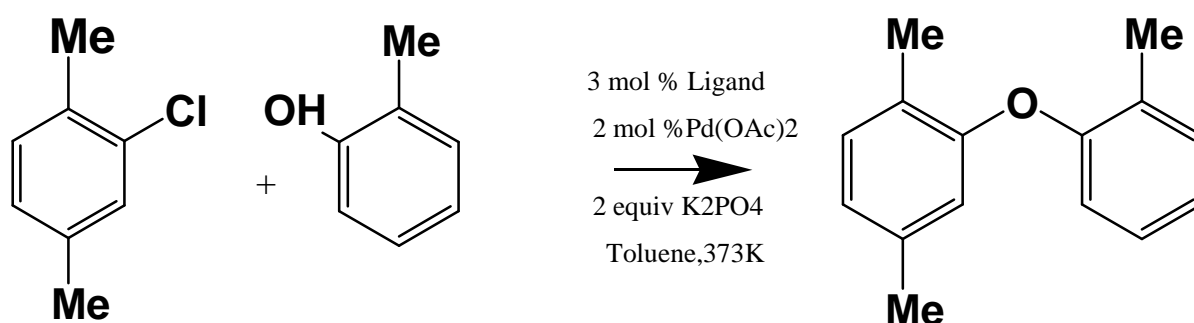


Synthesis of diaryl ether has been developed where diene was condensed with methyl propiolate and resulting cyclo adduct was oxidized with DDQ to provide diarylether (**Scheme - 2**). The yield was poor. Improved yields were then obtained when diene reacted with dienophile to give isodityrosine derivative that was isolated after silica gel chromatography to give 77% yield.¹³

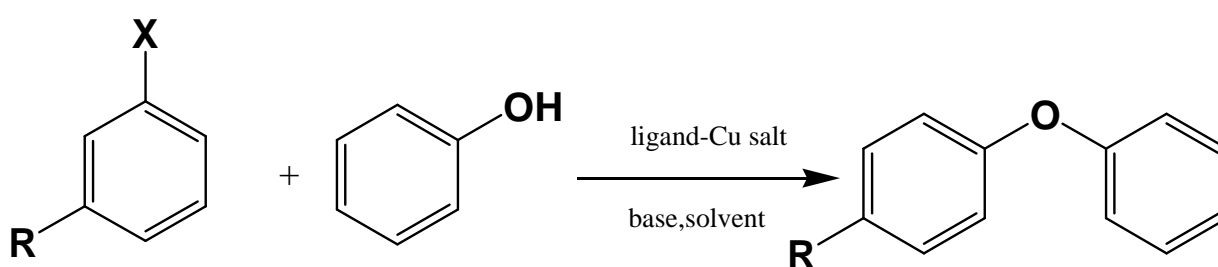
Use of transition metal-catalyzed cross-coupling reactions such as palladium and copper has gained importance for the synthesis of diaryl ethers. Thus, Pd-catalyst was used for the coupling of aryl halides and phenol for the synthesis of diarylether.¹⁴ (**Scheme - 3a**) However, high cost of palladium salt, and multistep processes involved in the synthesis of these ligands have edge over traditional Ullmann and Stein methodology if no of steps can be reduced. Westonp et. al. have developed best laboratory method for the preparation of diphenyl ethers that uses copper¹⁵ catalyzes the reaction between alkali phenoxides and aryl halides (**Scheme - 3b**).

Scheme - 3

(a)

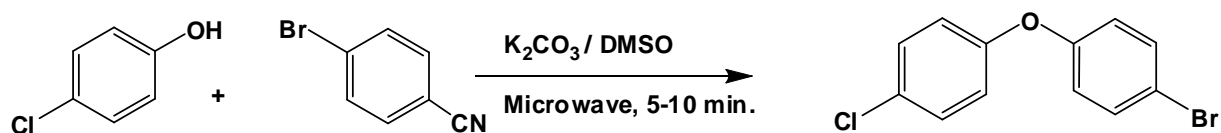


(b)



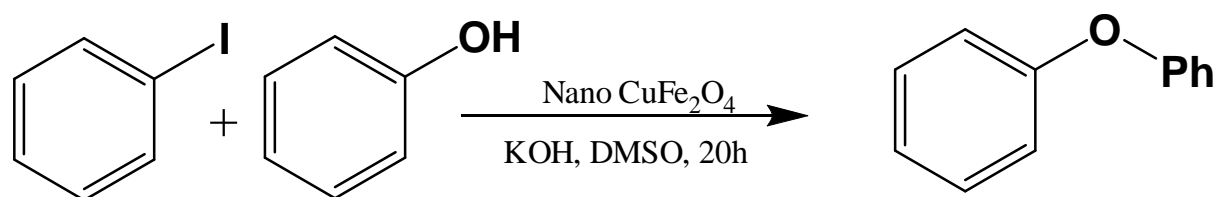
One of the important methods for the synthesis of diphenylether was improvement of original Ullmann method with assistance of microwave irradiation. **Scheme - 4** shows nucleophilic S_NAr reaction of activated aryl halides with phenol under microwave irradiation results in 98% yield in basic conditions.¹⁶ Copper catalysts can be advantageous from the standpoints of cost and toxicity. Therefore, use of CuI as pre-catalyst, the cross-coupling of phenols with aryl iodide can be accomplished at room temperature.¹⁷

Scheme - 4



Avudoddi et. al have accomplished the synthesis of aryl / alkyl ether using recyclable catalyst CuFe_2O_4 nanopowder (Scheme - 5). The reaction between aryl halides and phenols/alcohols in the presence of, air-stable, inexpensive, magnetically separable and recyclable, catalyst gives the ether. The catalyst is recyclable up to four cycles¹⁸.

Scheme - 5



Besides above synthetic methodologies a number of diphenyl ethers have been synthesized for direct applications in the material science. For example poly phenyl ethers¹⁹ (Figure-2) possess many properties desirable for functional fluids such as lubricants. This is because aromatic compounds are much more resistant to radiation than aliphatic compounds and possess better properties such as viscosity, temperature coefficient and oxidation, thermal and radiation stabilities for such applications. Such lubricants²⁰ are capable of lubricating high speed bearings and moderately-loaded gear trains.

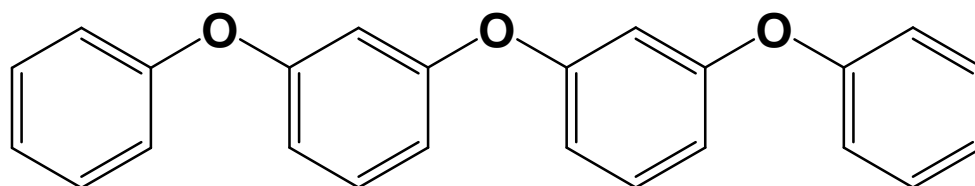


Figure-2: Bis(m-phenoxy phenyl)ether finds application as lubricant

The work described in following chapters describes synthesis and characterization of some diphenyl ethers and reactions on already synthesized diphenyl ethers to create new moieties.

Experimental

All the chemicals used for synthesis were procured from Avra Synthesis Pvt Ltd, Hyderabad, India. Solvents were purchased from Merck India, Mumbai. ^1H and ^{13}C NMR spectral analysis were performed on JEOL ECS400 MHz spectrometer and mass analysis was done on BRUKER GC-MS(SHS-40) instrument using turbo spray.

Synthesis of 2-(2-nitrophenoxy) aniline (1)

In a 100 ml round bottom flask were added 2-aminophenol (0.232 g, 2.126mmol), 2-fluoronitrobenzene (0.250g, 1mmol), K_2CO_3 (0.612g, 4.428mmol) and 2-drops of 18-crown-6. The mixture was magnetically stirred overnight. Progress of the reaction was monitored by TLC. After completion of the reaction work-up was done by quenching the reaction with water and extracting the organic product with dichloromethane (DCM) (3 X25ml). The organic layer was washed with water till neutral and then organic layer was dried over Na_2SO_4 to remove any traces of moisture. Evaporation of the product gave crude product that was purified by column chromatography using hexane and ethyl acetate as mobile phase (Yield = 0.57 gm, 52.1%). $^1\text{H-NMR}$ -(400MHz, CDCl_3): δ 4.0(s,2H), 7.15(m,1H), 7.47(d,8Hz,1H), 7.92(t,7.6Hz,1H), 8.23(d,1.20Hz,1H); $^{13}\text{C NMR}$ (CDCl_3): δ 117, 118.1, 119, 121.3, 122.5, 125.7, 126.48, 134, 139.2, 141, 151.2.

Synthesis of 1-[4(2,4-dinitrophenoxy)-3-methoxy-phenyl]-3-iodopropan-2-ol (3)

In a 100 ml round bottom flask was added NaI (0.227g, 1.51mmol), compound 2 (0.5g, 1.52mmol) and solvent (THF:H₂O= 5ml:1ml). The mixture was cooled in an ice water bath and magnetically stirred. To this vigorously stirred reaction mixture were added sequentially, H₂SO₄ (0.5 ml) and H₂O₂ (0.5 ml). The development of dark red color with exothermic reaction in the solution was noticed. After 15 minutes, the cooling bath was removed and the mixture further stirred until colorless. THF was then removed under vacuum and the resulting mixture extracted with DCM (150 ml). The organic layer was washed with Na₂S₂O₃ (30 ml of 5% aqueous solution) to remove any iodide present in the reaction mixture. Finally, the organic layer was dried over Na_2SO_4 and solvent evaporated to obtain crude product. This was purified by column chromatography (hexane/EtOAc) to get pure iodohydrins. (Yield = 0.8 gm, 46.3 %), $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 2.16(d,4Hz,2H), 2.94(d,8Hz,2H), 3.77(s,1H), 3.8(m,1H), 6.91(s,1H),

6.95(d,4Hz,1H), 6.96(d,2Hz,1H), 7.15(d,8Hz,1H), 8.29(d,4Hz,1H), 8.87(s,1H). ¹³C-NMR (CDCl₃): δ14.8, 42.5, 55.9, 71.5, 110, 113, 114, 117.28, 122.2, 128.6, 132.9, 137.4, 141, 150.8, 154, 156.4. **GC-MS** : m/z=347[M⁺ for C₁₆H₁₅N₂O₇], m/z=164[M⁺ for C₁₀H₁₂O₂⁺], m/z=113[M⁺ for C₆H₁₁O⁺], m/z=92[M⁺ for C₇H₇⁺]; IR: peak of NO₂ at 1341cm⁻¹ (stretching vibration), -OH at 3358cm⁻¹ (broad), C-O-C at 1238cm⁻¹, -CH₂- at 1270cm⁻¹ (wagging).

Synthesis of 1-[4(2,4-dinitrophenoxy)-3-methoxy-phenyl]-3-bromopropan-2-bromide (4)

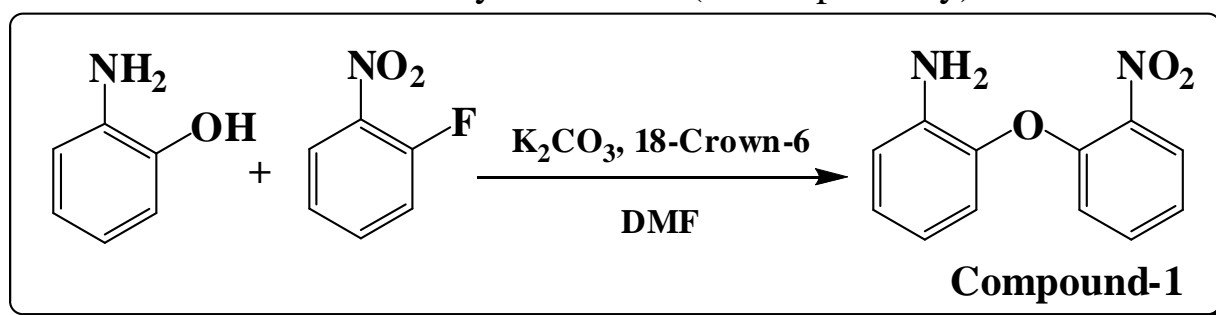
To a reaction vial with magnetic needle was added solution of compound **2** (0.2 gm, 1 mmol) in CHCl₃ (0.6 ml, 1 ml per mmol of substrate) and 48 % aqueous HBr (0.5 ml, 5 equiv) along with DMSO (0.6 ml, 1ml in 5 mmol of substrate). The reaction mixture was capped and stirred in water bath at 65°C until complete disappearance of starting material was observed by TLC. The reaction was then transferred to the separatory funnel containing water and extracted with ethyl acetate (3X 50 ml). The combined organic extracts were dried over Na₂SO₄ and the solvent was removed under vacuum to get crude product that was purified by column chromatography (gradient elution of hexane and EtOAc). (Yield = 0.3 gm, 46.15 %). However ¹H NMR spectra of the compound was similar to that of compound **2**.

Result and discussion

The work describes the synthesis and characterization of two diphenyl ethers namely 2-(2-nitrophenoxy)aniline (**Compound-1**), 1-[4(2,4-dinitrophenoxy)-3-methoxy-phenyl]-3-iodopropan-2-ol (**Compound-3**) and an attempt to synthesize 4-(2,3-dibromopropyl)-1-(2,4-dinitrophenoxy)-2-methoxybenzene (**Compound-4**).

Compound-1 was prepared by nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene by phenolate ion of 2-aminophenol (**Scheme-6**). The phenolate ion required for the purpose was generated in aprotic solvent, dimethylformamide (DMF), by excess of potassium carbonate. Purification of crude product by column chromatography and analysis by ^1H and ^{13}C NMR confirmed the synthesis of **compound-1**.

Scheme - 6 : Synthesis of 2-(2-nitrophenoxy)aniline



The formation of product was verified by ^1H and ^{13}C NMR spectroscopy. Broad singlet at 3.95 ppm indicated the presence of two protons due to amine group along with eight protons between 6.7 to 7.9 ppm due to phenyl rings. ^{13}C -NMR showed four quaternary carbons that appeared downfield from 139.0-151.3 ppm due to presence of nitro and amino groups. **Figure- 3** shows the ^{13}C NMR spectra of the compound.

This is interesting to note that despite presence of two nucleophilic groups, phenolic and amino, in 2-aminophenol major product was obtained was from the phenolate ion. This was due to high acidity of phenolic protons as compared to amine protons due to which phenolate ion was formed even in the presence of mild base. Amines generally require use of a ligand along with a lewis acid, a metal salt, to form diphenyl amines ¹⁴. A number of ligands like proline, glycerol have been used for the formation of diphenyl amines.

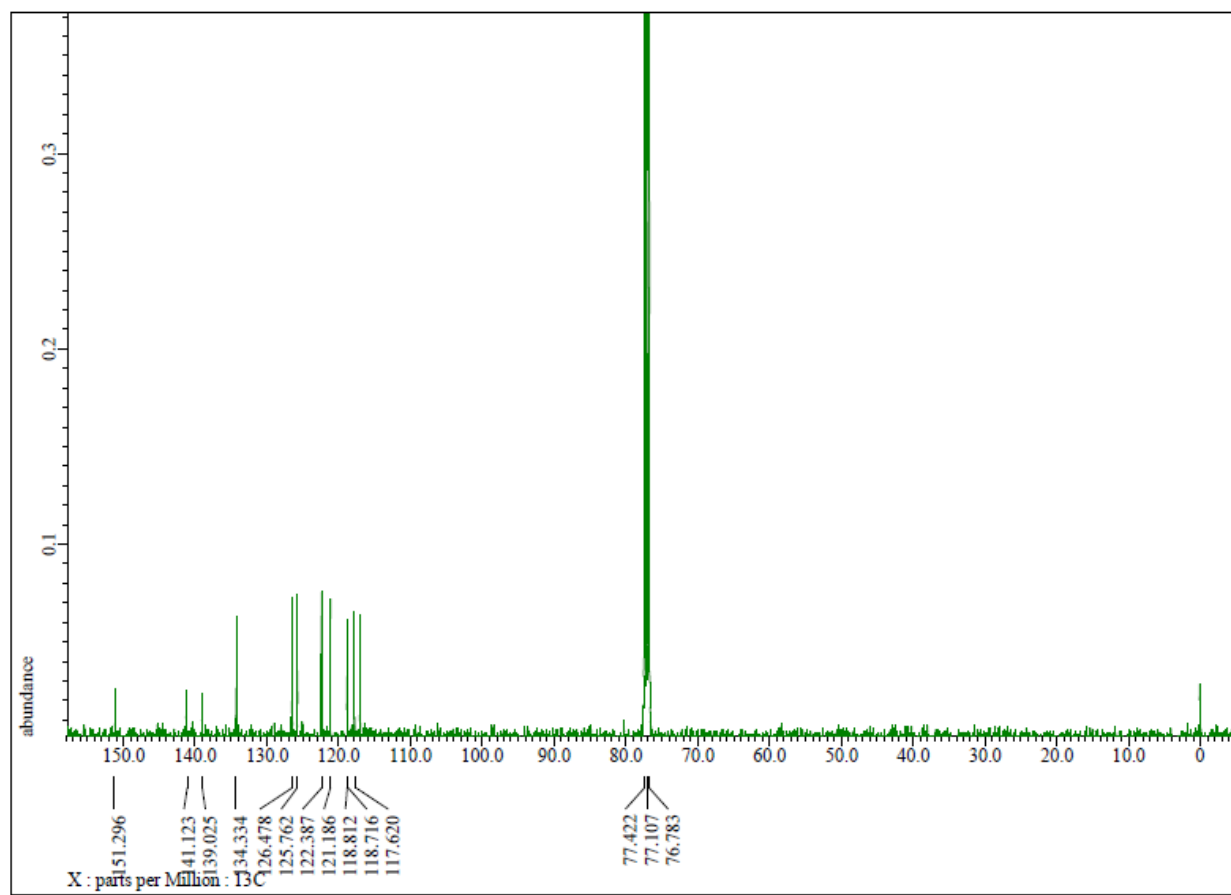
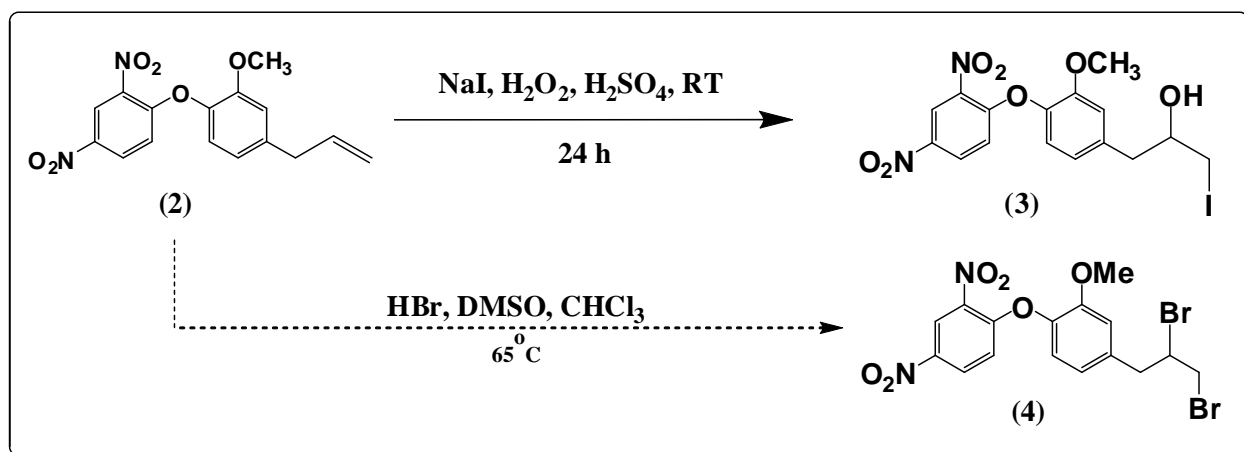


Figure- 3: ^{13}C NMR spectra of 2-(2-nitrophenoxy)aniline (**Compound-1**)

Work done earlier in our research group synthesized 4-allyl-1-(2,4-dinitrophenoxy)-2-methoxybenzene (**Compound-2**)²¹. This work further explored the chemistry of allylic group in the molecule.

Barluenga *et. al.* have reported an efficient method of synthesizing iodohydrins using sodium iodide and hydrogen peroxide in aqueous media²². The reaction is facilitated by *in situ* formation of IOH, which further attacks at the allylic position to give halohydrin with hydroxyl group at carbon having lesser number of hydrogens. Thus, reaction of **compound-2** with sodium iodide (NaI) and hydrogen peroxide (H_2O_2) in the presence of closed vessel as described in above chapter gave **compound-3** (**Scheme - 7**). The compound after purification via column chromatography was analyzed using ^1H -NMR, ^{13}C -NMR, GC-MS and IR spectroscopy. ^1H -NMR of the compound shows singlet due to methoxy ($-\text{OCH}_3$) group and proton attached to hydroxyl group together at 3.7 ppm. **Figure 4** shows ^1H NMR of the compound.

Scheme-7 : Synthesis of 1-[4(2,4-dinitrophenoxy)-3-methoxy-phenyl]-3-iodopropan-2-ol (**3**) and attempted synthesis of 4-(2,3-dibromopropyl)-1-(2,4-dinitrophenoxy)-2-methoxybenzene (**4**)



Protons due to terminal allylic group are replaced by two separate protons attached to the terminal iodo group at 3.2 and 3.4 ppm shows the presence of iodo compound. Other aliphatic protons attached to phenyl ring appear at 2.1 and 2.9 ppm. Six aromatic protons in the range 6.8 to 8.8 ppm show that diphenyl ether moiety is intact during the reaction.

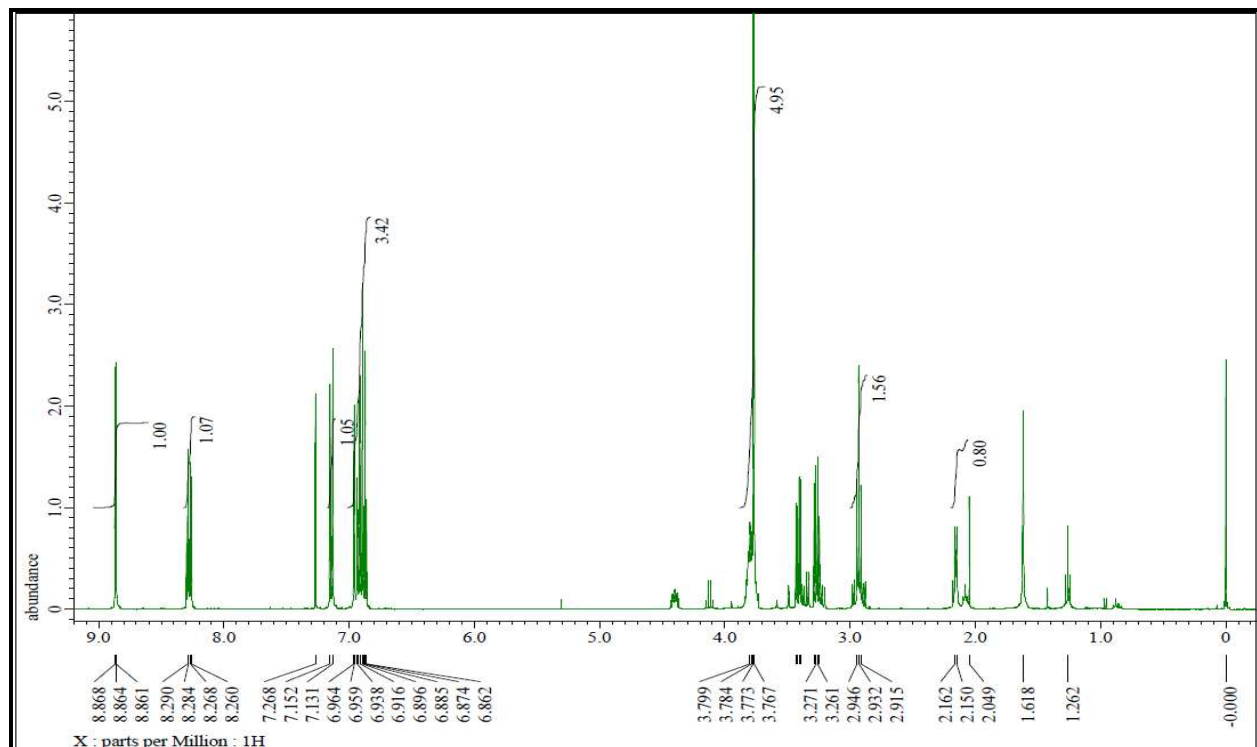


Figure - 4: ^1H NMR spectra of 1-[4(2,4-dinitrophenoxy)-3-methoxyphenyl]-3-iodopropan-2-ol (**3**)

^{13}C -NMR spectra displayed four aliphatic carbons, at 14.85, 42.54, 71.50 and 55.97 due to carbons attached to iodo group, phenyl ring, hydroxyl groups and due to methoxy group respectively. All aromatic carbons appeared in the range of 114-156 ppm.

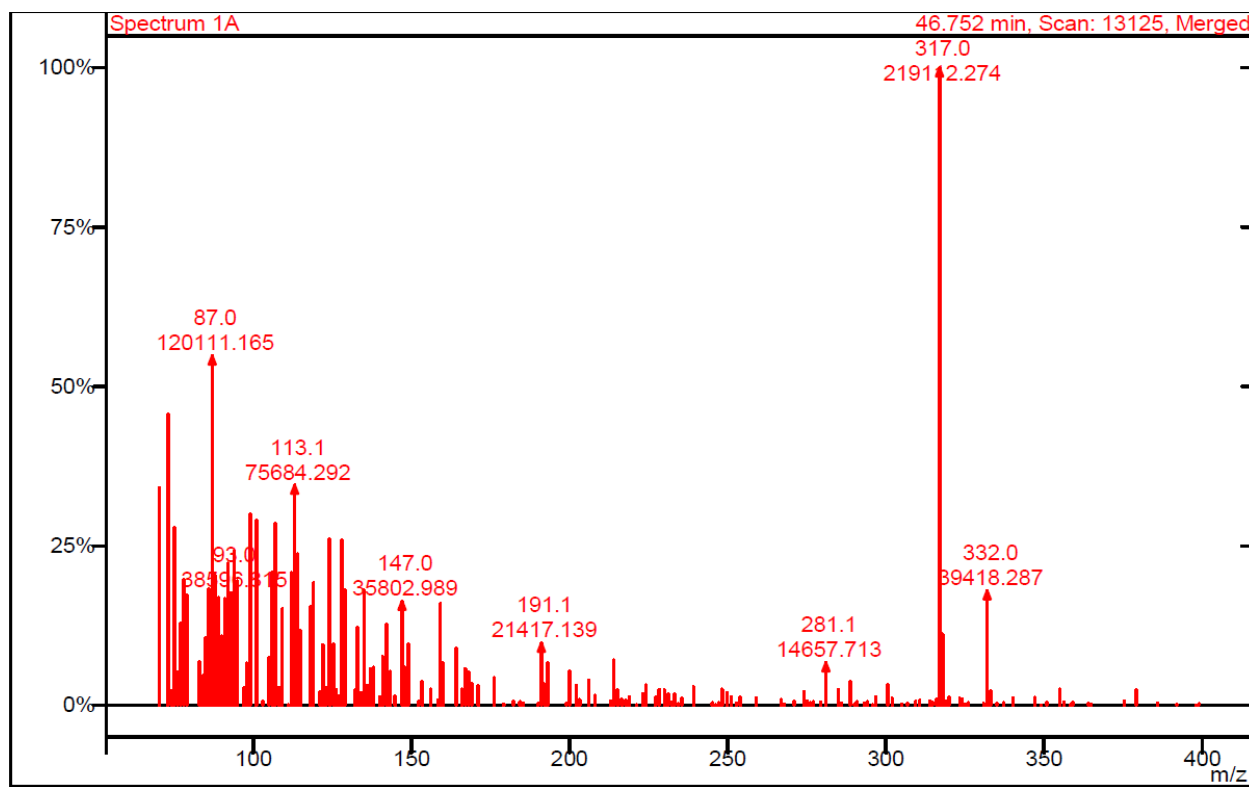
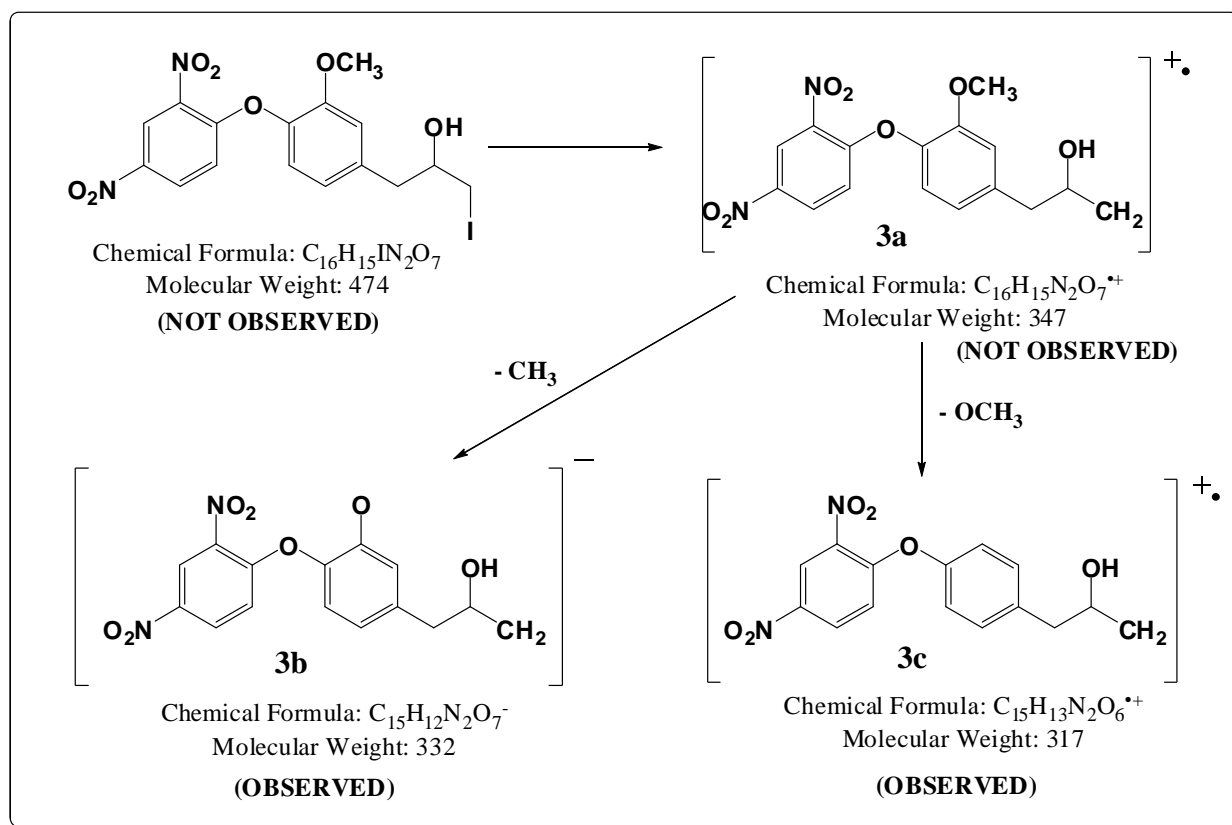


Figure- 5: Mass spectra obtained for 1-[4(2,4-dinitrophenoxy)-3-methoxy-phenyl]-3-iodopropan-2-ol (**3**) using GC-MS.

Mass fragments of **compound-3** displayed two prominent peaks at $m/z = 332.0$ and $m/z = 317.0$ due to loss of methyl (**3b**) and methoxy fragment (**3c**) from phenyl ring along with simultaneous loss of iodide moiety (**Figure-5**). The fragment due to loss of only iodide (**3a**) was very unstable and never observed in the MS. The molecular ion peak corresponding to molecular weight of the compound was also not observed in the spectra. **Scheme- 8** below shows the fragmentation pattern for the **compound-3**.

Comparison of infra red spectra of starting compound-2 and iodohydrin (**compound-3**) showed signal due to presence of $-\text{OH}$ group from 3358 cm^{-1} in later confirming the presence of hydroxyl group.

Scheme-8 Fragmentation pattern for **Compound-3** as observed in its mass spectra



Recently, Karki et. al. have shown a very inexpensive method of brominating alkenes with Aq. HBr and dimethyl sulphoxide.²³ We envisaged brominating the allylic double bond in **compound-3** to corresponding dibromo product. Thus the reaction was set up at 65°C in a voil containing required quantities of 48% aqueous HBr, DMSO and chloroform. Although TLC of the reaction displayed presence of products other than reactants, purification of the product after column chromatography and subsequently its 1H NMR gave spectra corresponding to the starting material. It can thus be concluded that product was formed in very low yield.

In conclusion, we have synthesized a dipheyl ether by reaction of 2-nitrofluorobenzene and 2-amino phenol. In case of other dipheyl ether the allylic group was converted to its corresponding iodohydrin by commonly available reagents. An attempt was made to convert the allylic group of the dipheyl ether into corresponding dibromo compound. Iodohydrin synthesized was characterized by 1H , ^{13}C NMR mass spectroscopy and IR techniques.

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