CLEAVAGE OF 4-(2, 4-DINITROPHENOXY)-3-METHOXYBENZALDEHYDE WITH AMINES

A thesis submitted in partial fulfilments of requirement for the degree of

Master of Science in Chemistry

Submitted by	**Supervisor**
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DEDICATED TO MY PARENTS

Acknowledgement

Foremost, I would like to express my sincere appreciation to my advisor Dr. Manmohan Chhibber, Associate Professor at School of Chemistry and Biochemistry. He has been a tremendous mentor for me and his continuous support patience, motivation, enthusiasm and immense knowledge helped me throughout my project work and writing this thesis.

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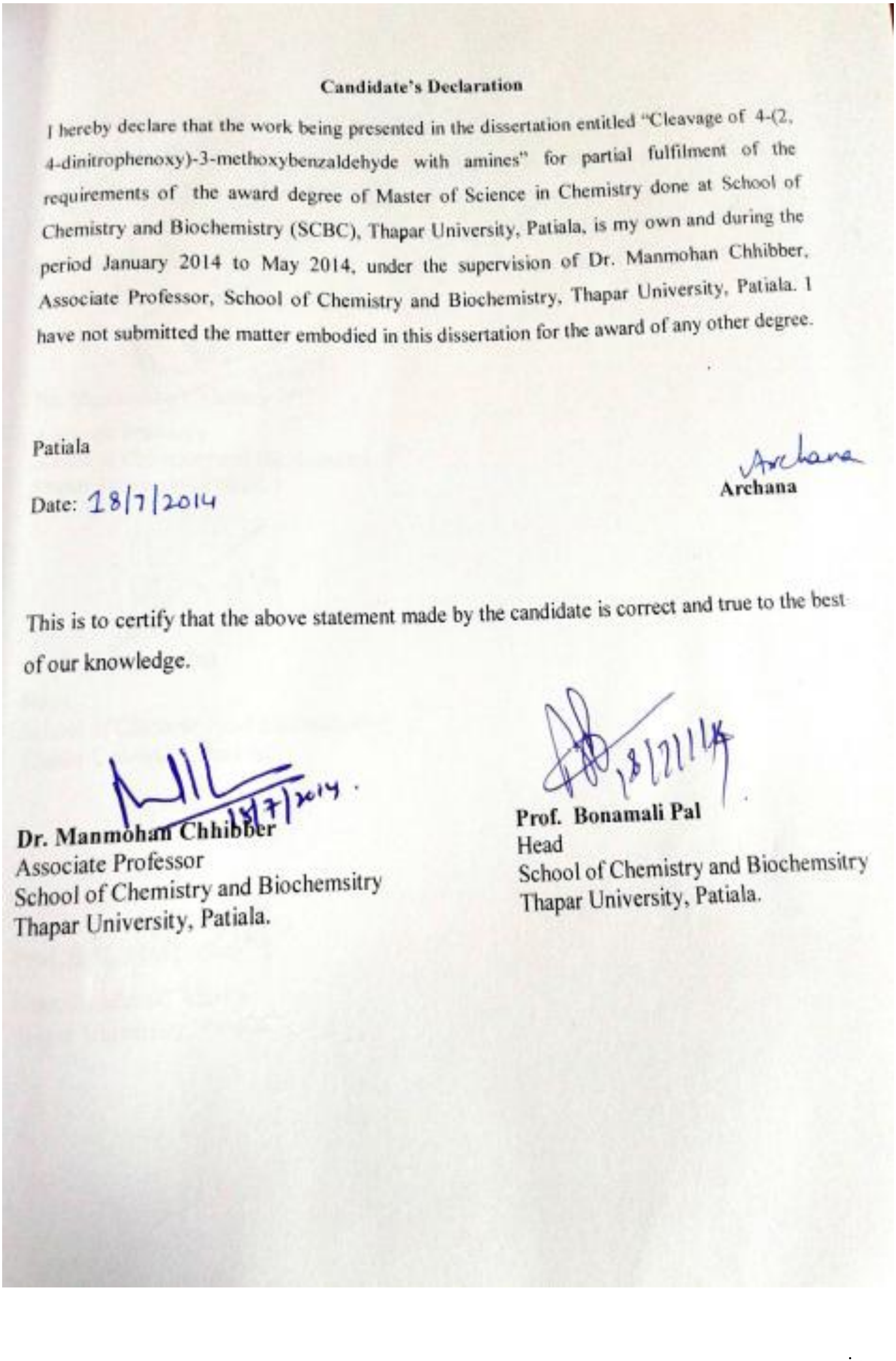
Date: 18/7/2014



Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled "Cleavage of 4-(2, 4-dinitrophenoxy)-3-methoxybenzaldehyde with amines" for partial fulfilment of the requirements of the award degree of Master of Science in Chemistry done at School of Chemistry and Biochemistry (SCBC), Thapar University, Patiala, is my own and during the period January 2014 to May 2014, under the supervision of Dr. Manmohan Chhibber, Associate Professor, School of Chemistry and Biochemistry, Thapar University, Patiala. I have not submitted the matter embodied in this dissertation for the award of any other degree.

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Date: 18/7/2014

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This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

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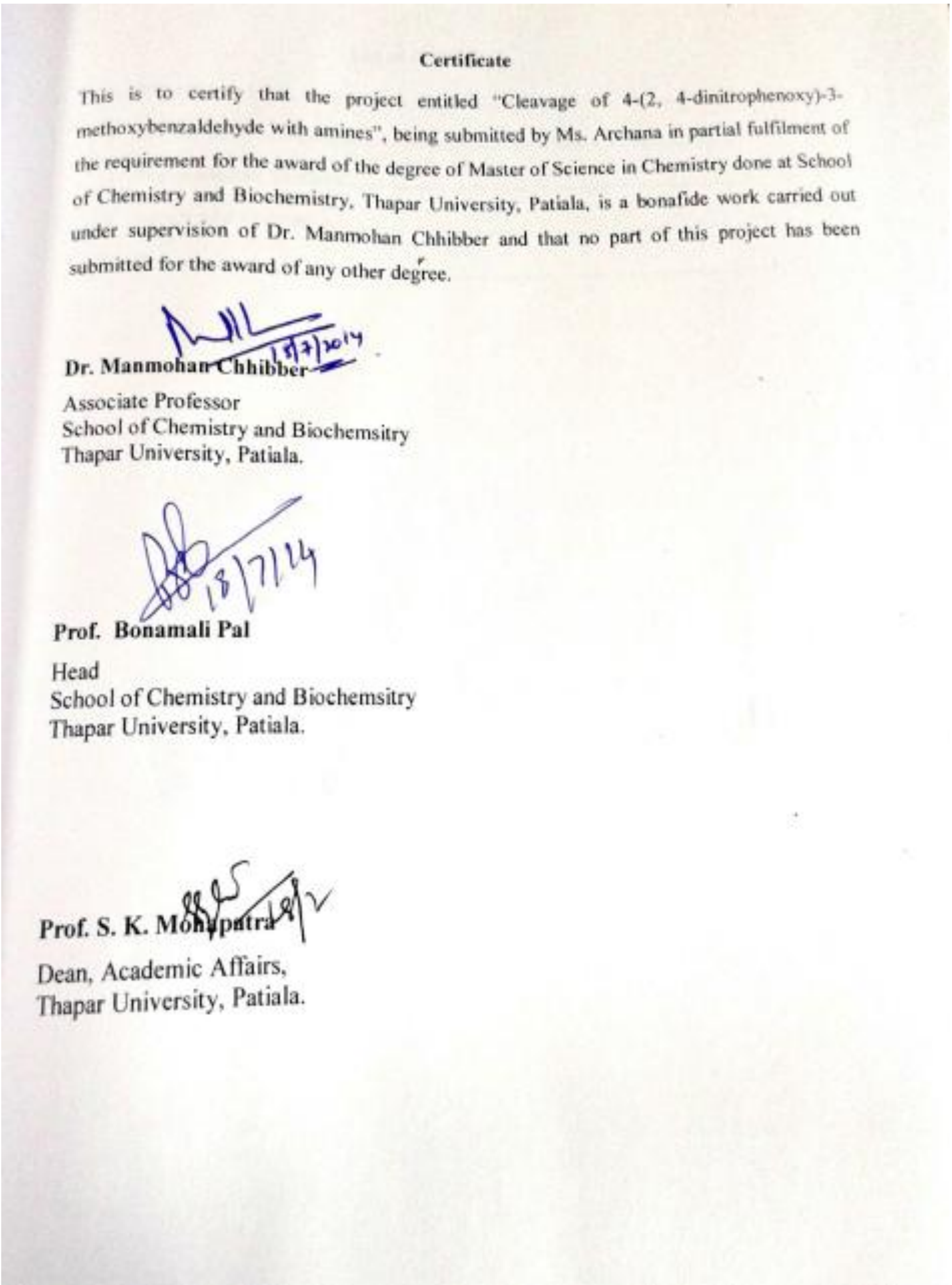

Certificate

This is to certify that the project entitled "Cleavage of 4-(2, 4-dinitrophenoxy)-3-methoxybenzaldehyde with amines", being submitted by Ms. Archana in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry done at School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonafide work carried out under supervision of Dr. Manmohan Chhibber and that no part of this project has been submitted for the award of any other degree.

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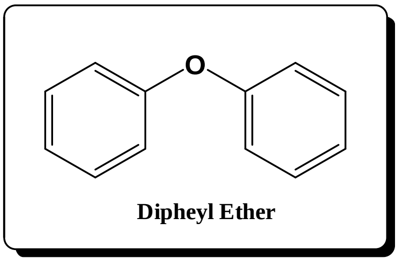
INTRODUCTION

Diphenyl ethers (DPE) are the compounds where two phenyl rings are attached by oxygen. Such compounds are known for more than hundred years but of late have found use in various applications like flame retarding agents, antimalarial[1], antifungal[2] and antituberculosis[3] agents. Diphenyl ethers[4] and the motifs containing diphenyl ethers have also been isolated various natural resources. Triclosan, a known diphenylether is widely used in soaps, perfumery, and in the production of polyesters due to its antibacterial properties.



Dipheyl Ether

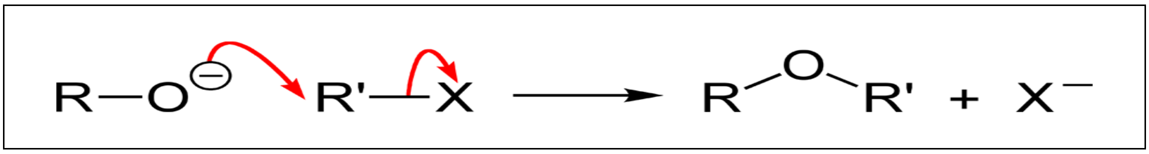
Polybrominated diphenyl ethers (PBDEs) are widely used as flame retardant polymers due to their excellent stability[5]. These compounds are also used as heat – transfer medium is due to its extraordinary heat stability. The studies showed that activated diphenyl ethers are unreactive thermally at 350^0C but aqueous chemistry provides ionic pathways for cleavage of ether cross links which are abundant in coals. Diphenyl ethers are stable and unreactive at 350^0C [6].

REVIEW OF LITRATURE

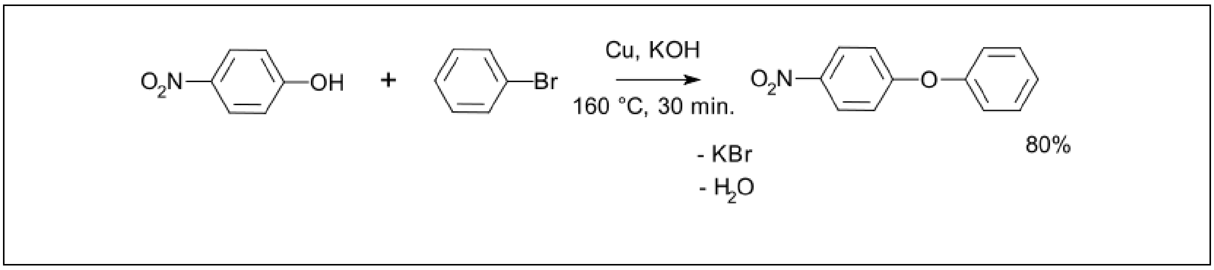
Synthesis of dipheylethers

Diphenyl ether was synthesized in 1854 by List and Limpricht [7] by the dry distillation of copper benzoate. The product was later on shown to be the mixture of diphenyl ether and diphenyl by Hoffmeister [8] who isolate the pure substance by separating mixture. It was also synthesized by the reaction of benzenediazonium sulfate and phenol but gave poor yield. However, an improvement in yield of diphenyl ether was done by preparing them with benzene diazonium chloride [9]. Diphenyl ether and many of its properties were reported in 1901 [10].

Williamson developed another synthesis of such compounds by reaction of an alkoxide ion with a primary alkyl halide via S_N2 reaction[11] where alkoxide ion (a nucleophile) is attacking the alkyl/aryl halide causing the displacement of halide ion and ultimately leading to the formation an desired ether as shown in the figure below.

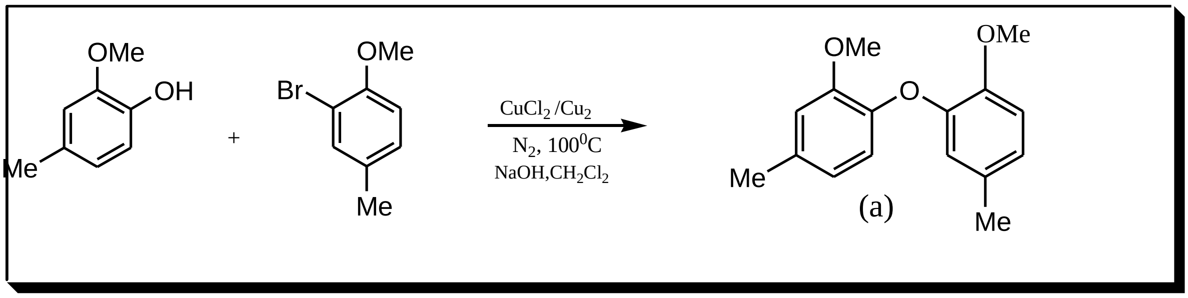


Another one of the most important synthetic reaction commonly used for the synthesis of ethers is the Ullmann condensation or Ullmann ether synthesis which is a variation of the Ullmann reaction. In this, a phenol is coupled to an aryl halide to create a diaryl ether in the presence of a copper compound, named after Fritz Ullmann[12]. An example is the synthesis of p-nitrophenyl phenyl ether [13].

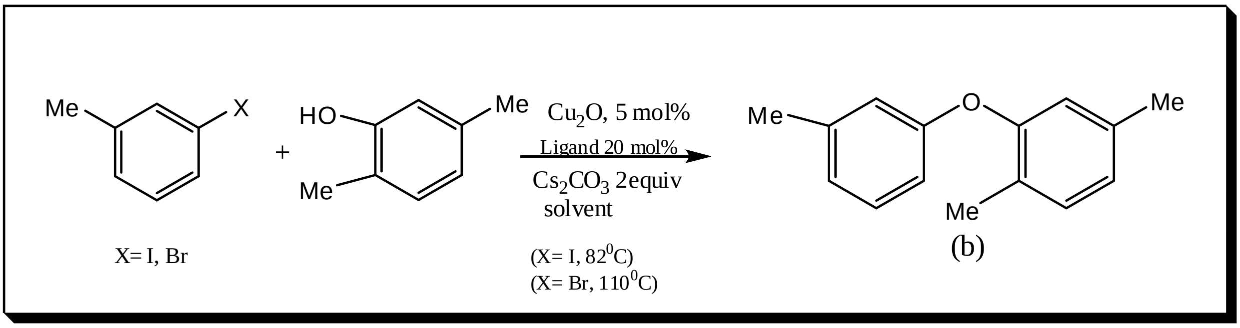


An active copper powder that is required for this reaction can be prepared by the reduction of copper sulfate by zinc metal in hot water causing the precipitation of elemental copper. The reaction often requires high-boiling polar solvents such as N-methylpyrrolidone, nitrobenzene or dimethylformamide and high temperatures (often in excess of 210°C) with stoichiometric amounts of copper. The aryl halide is activated by electron-withdrawing groups or carries a carboxylic acid group in the aromatic ortho position[14].

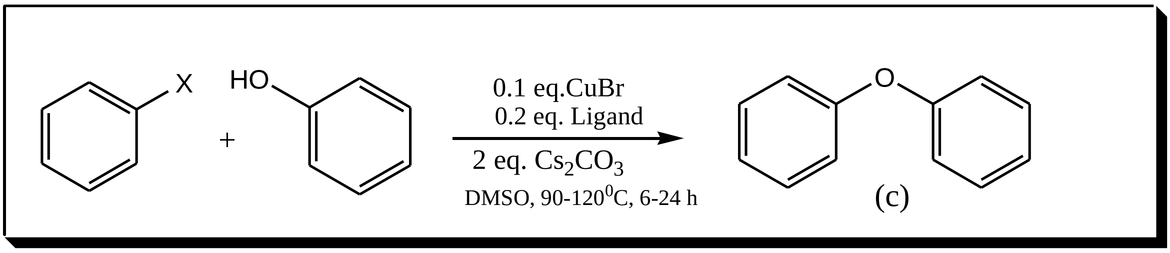
In 1978 Roabe *et al* [15] have reported the synthesis of a diphenyl ether using the above mentioned ullmann ether synthesis where 2-methoxy-4-methylphenol is coupled with 2-bromo-1-methoxy-4-methylbenzene to form the desired diphenyl ether (a) as a product.



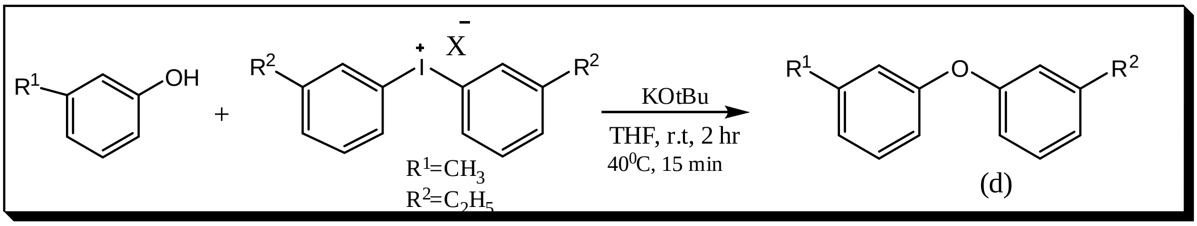
Cristan et al [16] also reported the below given synthesis of diphenyl ether (b) in which 3, 5-dimethyl phenol coupled with substituted aryl iodide and gave the high selectivity at low temperature (82^{0}C). This method shows broad functional group tolerance on both coupling partners with the exception of electron poor phenol and gives away to palladium chemistry.



Ding et al [17] have reported that copper-catalyzed couplings reactions of aryl halides with various phenols under mild conditions using (2-pyridl) acetone as ligand with good yields shown in below reaction (c). This reaction displays great functional groups compatibility and excellent selectivity.



Diphenyl ethers also synthesized with the use of mild and metal-free conditions. Jalalian et al have synthesized diphenyl ether (d) from phenol and diphenyliodonium salt in the presence of strong base like potassium tertiary butoxide in THF at room temperature gave high yield[18].

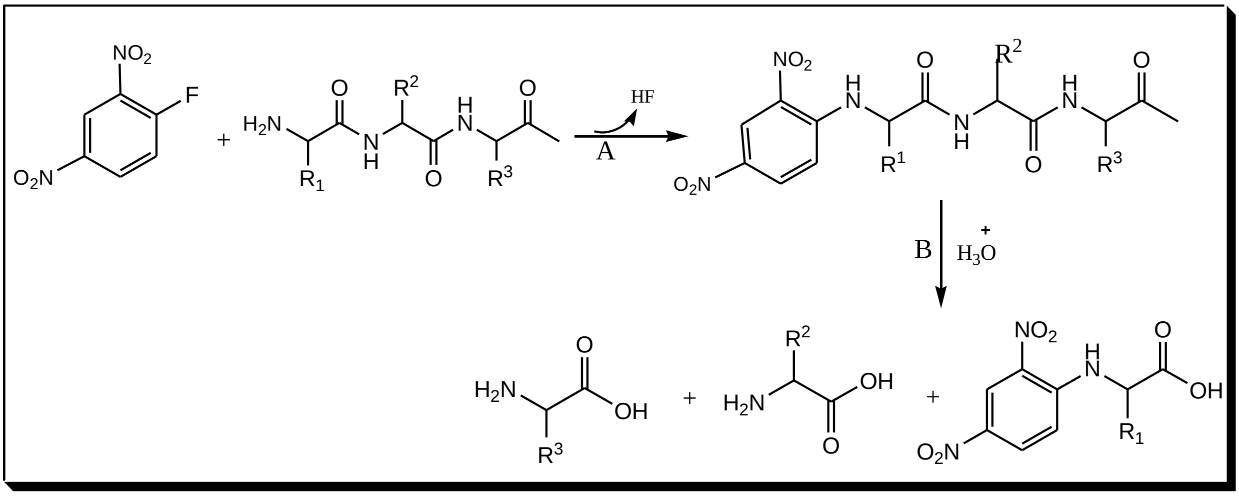


Stability of Dipheyl ethers

Thermal reactivity of aryl ethers is of interest to various fields of chemistry since these structures are present as base units in natural polymeric materials like lignin and coal. The strength of the alkyl-phenoxyl bond is, relative to other carbon-oxygen bonds, substantially lowered due to the resonance stabilization in the product (phenoxyl) radical. Stronger carbon-oxygen bonds can be expected with two sp^2 carbons adjacent to oxygen such as in diphenyl ether (DPE) [19]. Owing to the high bond strengths of ether bond, they are quite stable. The carbon oxygen bond in diphenyl ether is cleaved only under drastic conditions, e.g with alkalis at high temperature and pressure. Phenolic ether can be alkylated or acylated by Friedel-crafts reactions[20]. Ethers feature C-O-C linkage defined by a bond angle of about 104° and C-O distances of about 140 pm. The barrier to rotation about the C-O bond is low. Ethers are quite stable chemical compounds which do not react with bases, active metals, dilute acids, oxidising agents and reducing agents.

Sanger's Reagent and its use

1-fluoro-2, 4-dinitrobenzene, or Sanger's Reagent (commonly called as dinitro fluorobenzene or DNFB), is a chemical used for polypeptide sequencing. Gottlieb has been synthesized DNFB in 1936 from 1-chloro-2, 4-dinitrobenzene reacted with potassium fluoridemin nitrobenzene[21]. In 1945, Frederick Sanger described its use for determining the N-terminal amino acid in polypeptide chains, in particular insulin[22]. Dinitrofluorobenzene reacts with the amine group in amino acids to produce dinitrophenyl-amino acids. These DNP-amino acids are moderately stable under acid hydrolysis conditions that break peptide bonds.



The DNP-amino acids can then be recovered, and the identity of those amino acids can be discovered through chromatography. More recently, Sanger's reagent has also been used for the rather difficult analysis of distinguishing between the reduced and oxidized forms of glutathione and cysteine in biological systems in conjunction with HPLC [23, 24].

Sanger's method of peptide end-group analysis: **A)** derivatization of *N*-terminal end with Sanger's reagent (DNFB), **B)** total acid hydrolysis of the dinitrophenyl peptide.

Present work makes use of Sanger's reagent to synthesize dipheyl ether which has been described later. The presence of two nitro groups at ortho and para position to ether linkage make the synthesized dipheyl ether linkage a very weak one that has been exploited in this work.

MATERIALS AND METHODS

All the reagents and solvent except amines amine were purchased from S.D Fine Chemicals, Mumbai. The amines used were procured from Aldrich. Toluene and silica gel (60-120 mesh) from column chromatography were recycled for purification of diphenyl ether. Toluene was distilled before use silica washed with methanol. TLC analysis was done on silica coated aluminium plates (Aluchrosep Silica Gel) were also purchased from S.D. Fine Chemicals, Mumbai.

Experimental Section

Synthesis of 4-(2, 4-Dinitrophenoxy)-3-methoxybenzaldehyde (1)

1-Fluoro-2, 4 dinitrobenzene (0.48g, 2.5 mmol) and vanillin (0.5g, 3.2 mmol) in presence of K_2CO_3 (1.48g, 10.8 mmol) were taken in 250 ml round bottom flask. To this was added DMF (10 ml) 18-crown-6 (25 mg.01mmol) and stirred under the room temperature for 12 hrs. TLC was done to monitor the progress of reaction using toluene as a solvent. After completion of reaction, was washed with aqueous NaOH (0.1). Resulting solid was filtered and was neutralized with 2% HCl followed by washing with water (3-4 times) to remove excess of the solvent. The crude product was dried under vacuum and was purified by column chromatography using toluene as an eluent. Light yellow colored solid (0.7207g) 66 % was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.8(s, 3H), 6.9 (d, J=9.16 Hz, 2H), 7.3 (m, 1H), 7.6 (m, 2H), 8.3 (dd, 1H), 8.9(d, J=2.76 Hz, 1H), 10.0 (s, 1H).

Synthesis of N-Octyl-2, 4-dinitro benzenamine (2)

Compound (1) (0.2g, 0.6 mmol) was taken in 100 ml round bottom flask. To this was added methanol (10 ml) and octyl amine (200µl, 1.2 mmol) was added. The reaction mixture refluxed and TLC monitoring done. After 2hrs the spot for compound (1) disappeared completely and a new spot appeared. Evaporation of the methanol using rotary evaporator gave crude product that was purified by using petroleum ether and ethyl acetate as a solvents. . Yellow colored liquid was analyzed by ^{1}H and ^{13}C NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.57 (s,1H, NH), 8.26 (dd, 1H), 6.91 (dd, 1H), 3.40 (m, 2H), 1.78 (m, 2H), 1.49 (m, 2H), 1.32 (m, 8H) and 0.892 (t, j=7.8, 3H). ^{13}C NMR ($CDCl_3$): δ 148.3, 136.0, 130.5, 129.9, 124.4, 113.8, 43.6, 31.7, 29.1, 29.0, 28.6, 26.9, 22.5 and 14.07.

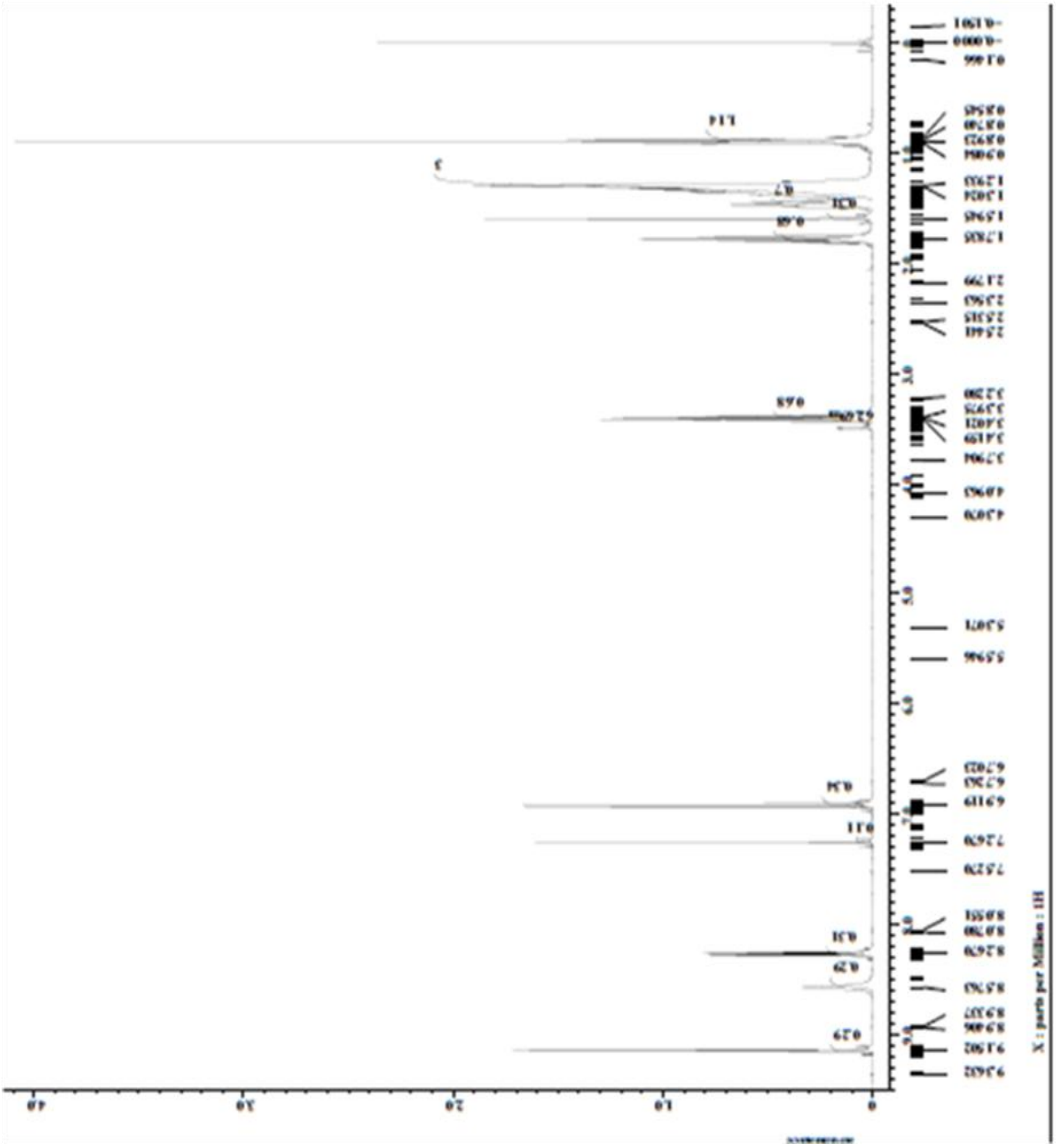
Synthesis of N-Benzyl-2, 4-dinitrobenzenamine (3)

Compound (1) (0.2g, 0.6 mmol) was taken in 100 ml round bottom flask containing methanol (10 ml). To this was added benzyl amine (200µl, 1.83 mmol) was added. The reaction mixture was refluxed and TLC monitoring done using ethyl acetate: petroleum ether. After 2 hrs spot of compound (1) was replaced by a new one. The solvent was evaporated and the product purified using column chromatography using same solvent system as for TLC. Product synthesis was analyzed and confirmed by ^{1}H and ^{13}C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.16 (d, 1H), 8.9 (s, 1H), 8.24 (m, 1H), 7.39 (m, 5H), 6.92 (d, 1H) and 4.65 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 148.1, 136.4, 135.5, 130.7, 130.3, 129.2, 128.3, 127.0, 124.2, 114.3 and 47.5

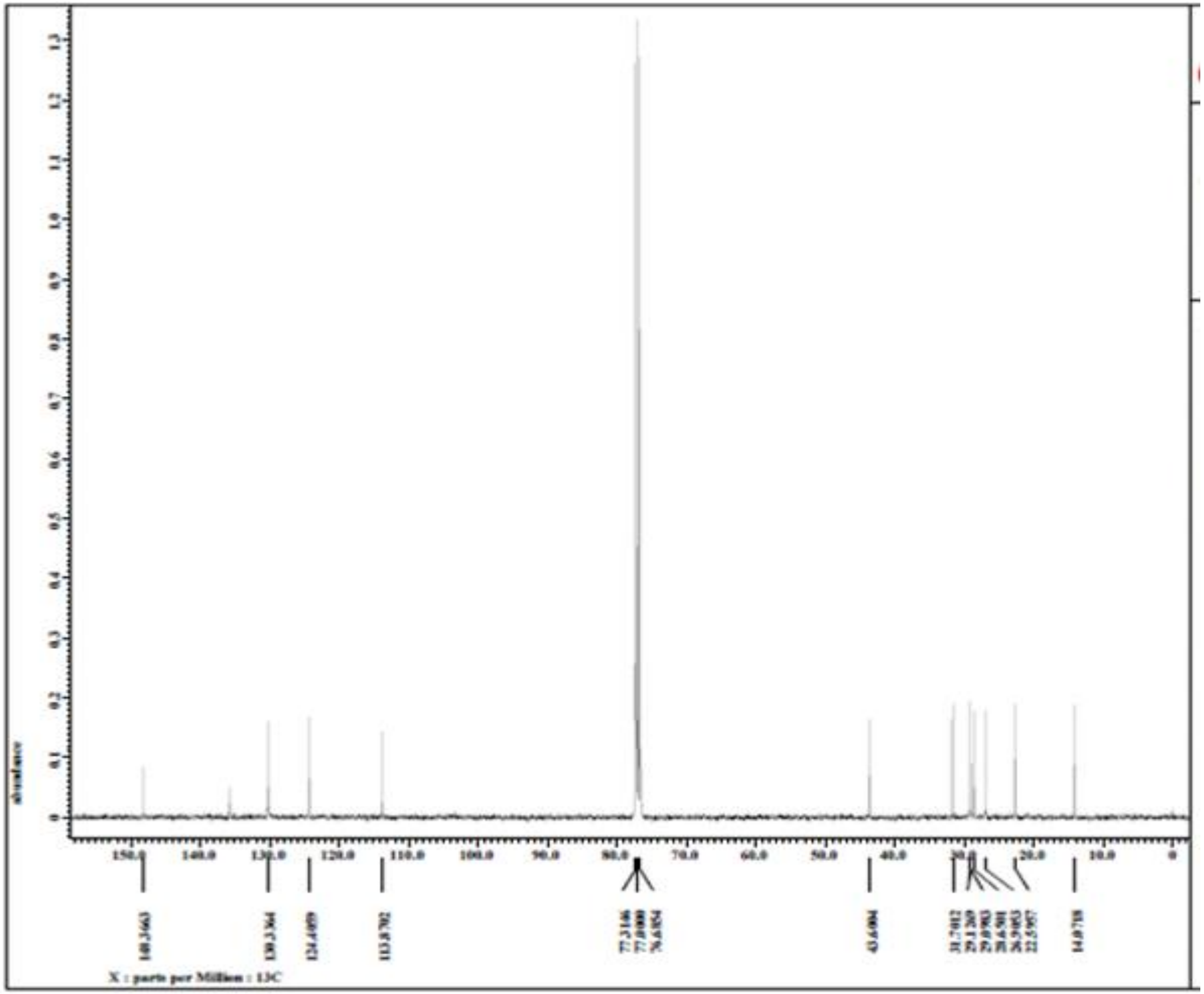
Synthesis of 2,4-Dinitro- N-phenylaniline (4)

Compound (1) (0.2g, 0.6 mmol) was taken in round bottom flask. To this was added methanol (10 ml) and aniline (200µl, 2.19 mmol) was added. The reaction mixture was refluxed TLC monitoring was done using ethyl acetate and pet ether showed appearance of new spot instead of diphenyl ether (1). Evaporation of the organic solvent through rotary evaporator gave corresponding crude product which was purified column chromatography in petroleum ether and ethyl acetate (65/35) as a solvents system. Product synthesis was analyzed and confirmed by ^{1}H and ^{13}C. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.0 (s, 1H, N-H), 9.19 (d, 1H), 8.19(s, 1H), 8.16(d, 1H), 7.15(s, 2H), 7.2(s, 2H), 7.17(s, 2H). ^{13}C NMR ($CDCl_3$): δ 147.16, 137.38, 136.58, 131.07, 130.25, 129.93, 127.7, 125.51, 124.11, 116.01.

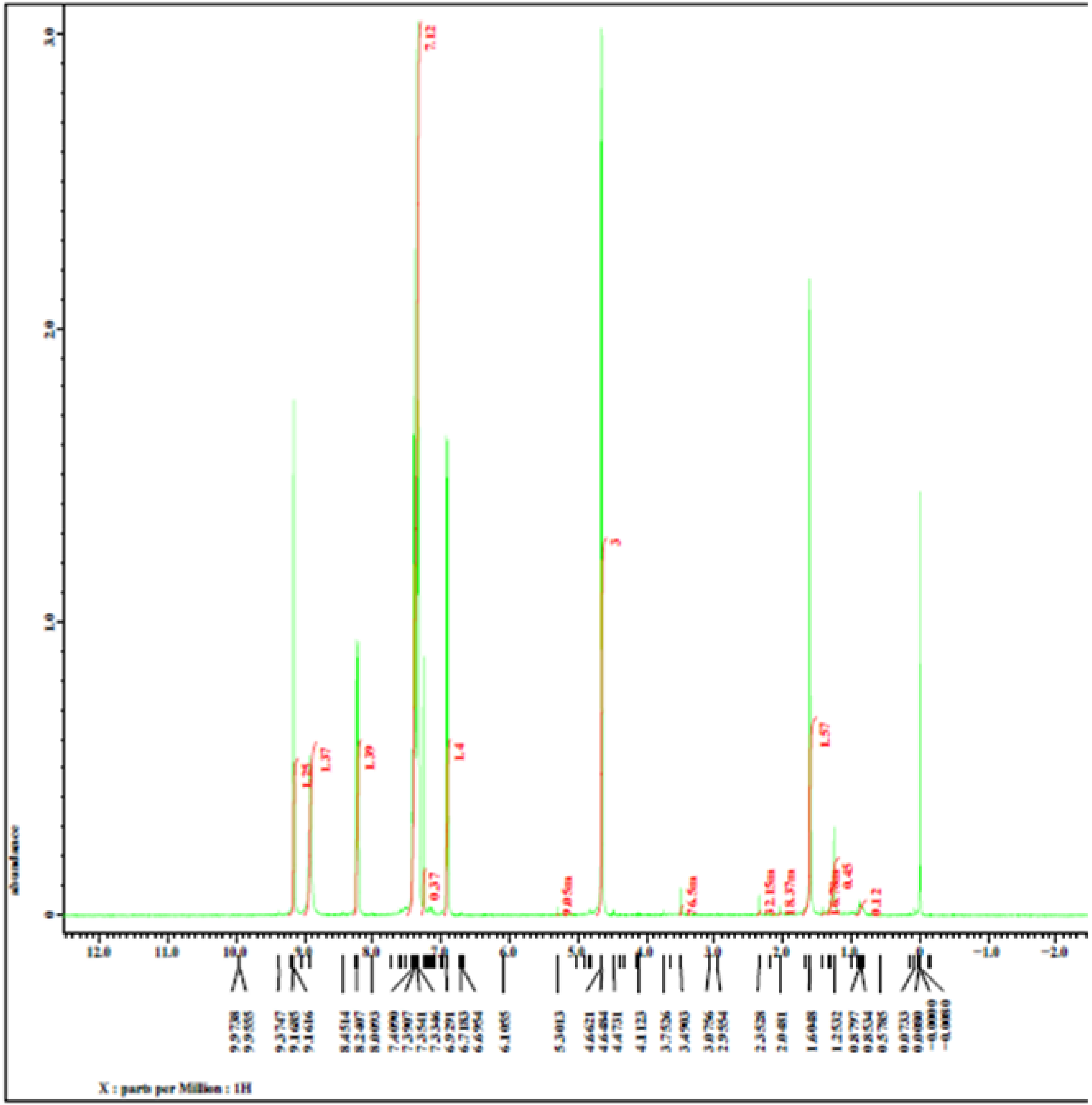
NMR SPECTRA



^{1}H NMR Spectra of N-Octyl 2,4 dinitrobenzenamine



^{13}C NMR Spectra of N-Octyl-2, 4-dinitro benzenamine



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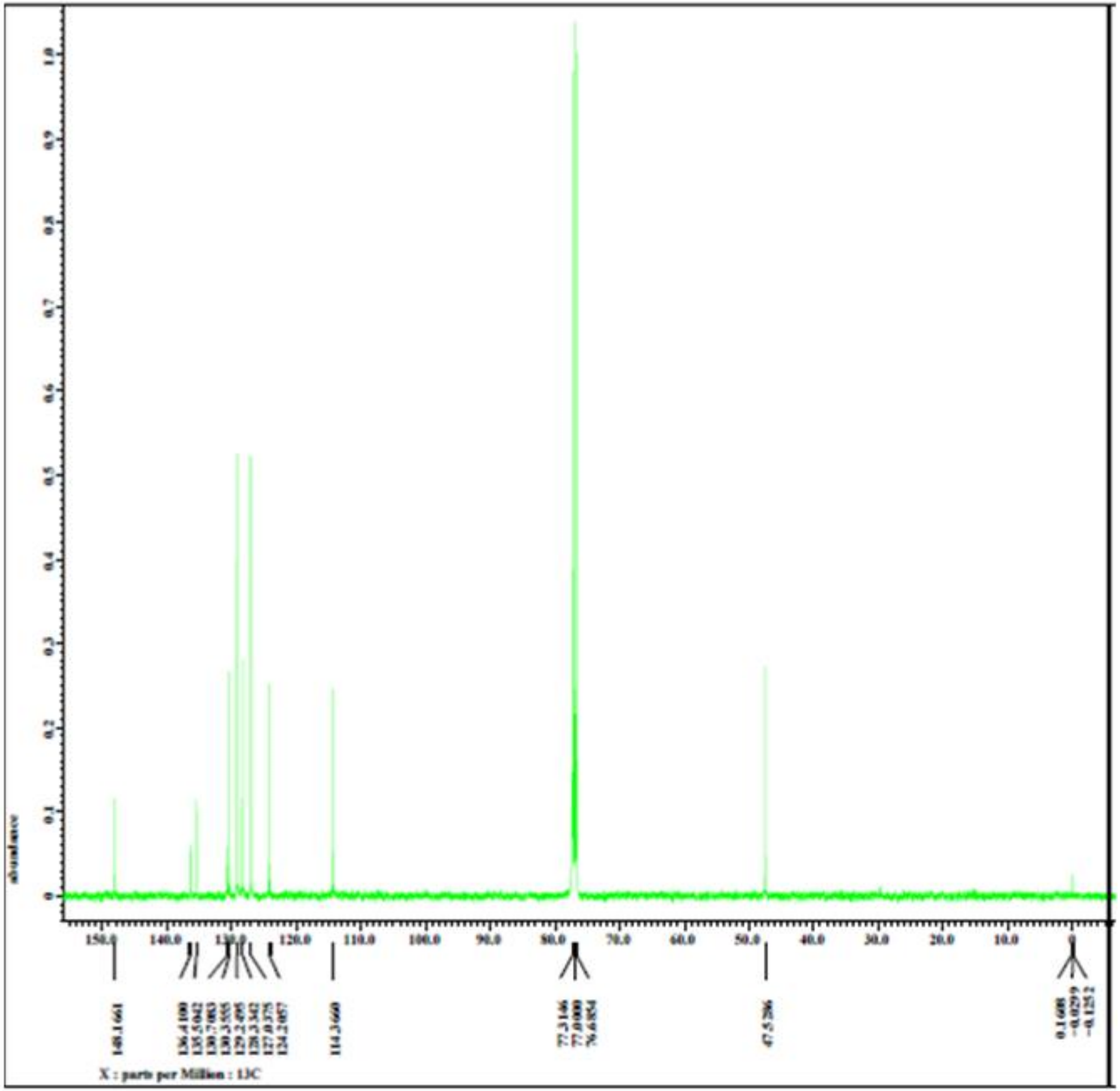
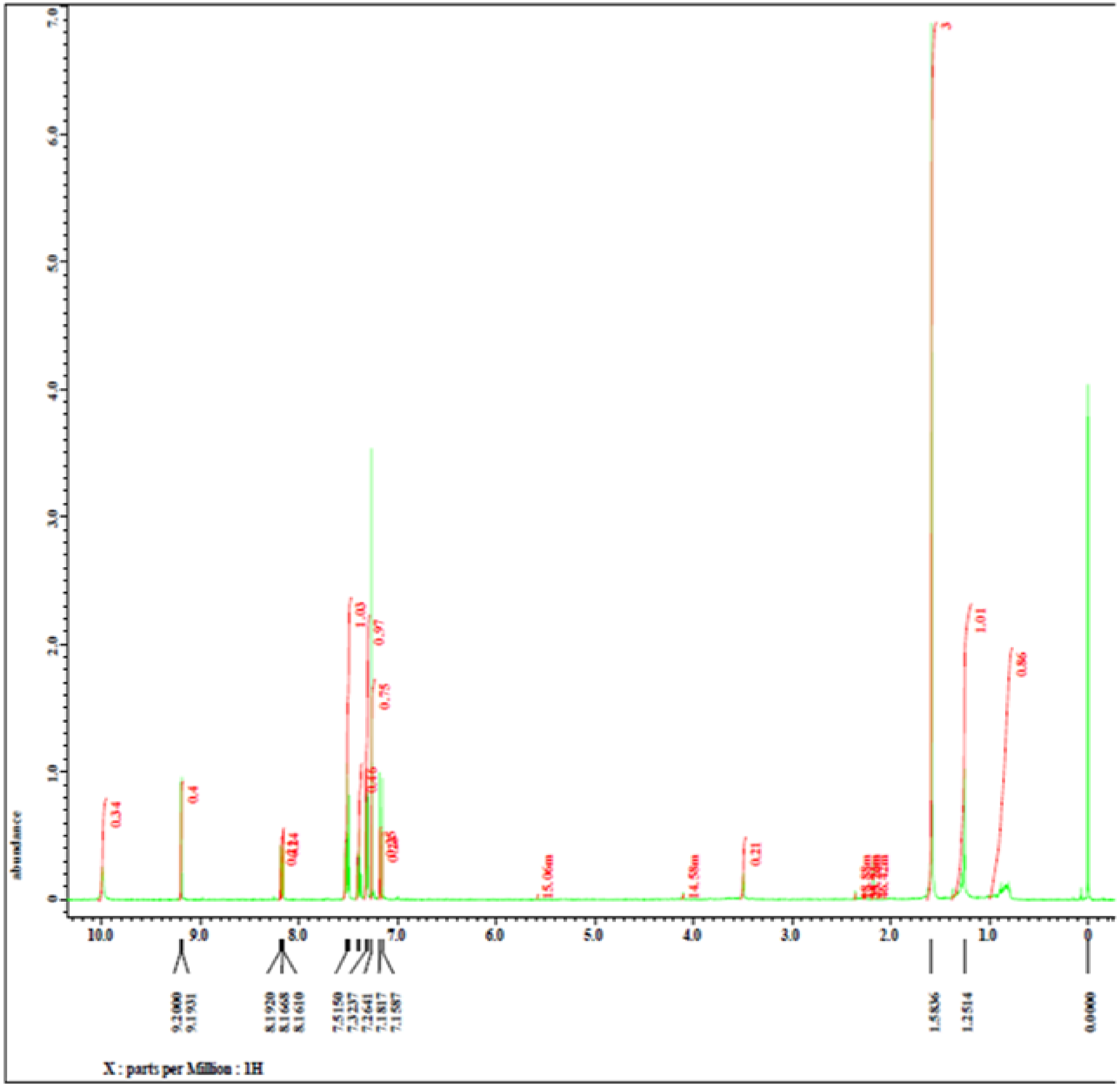
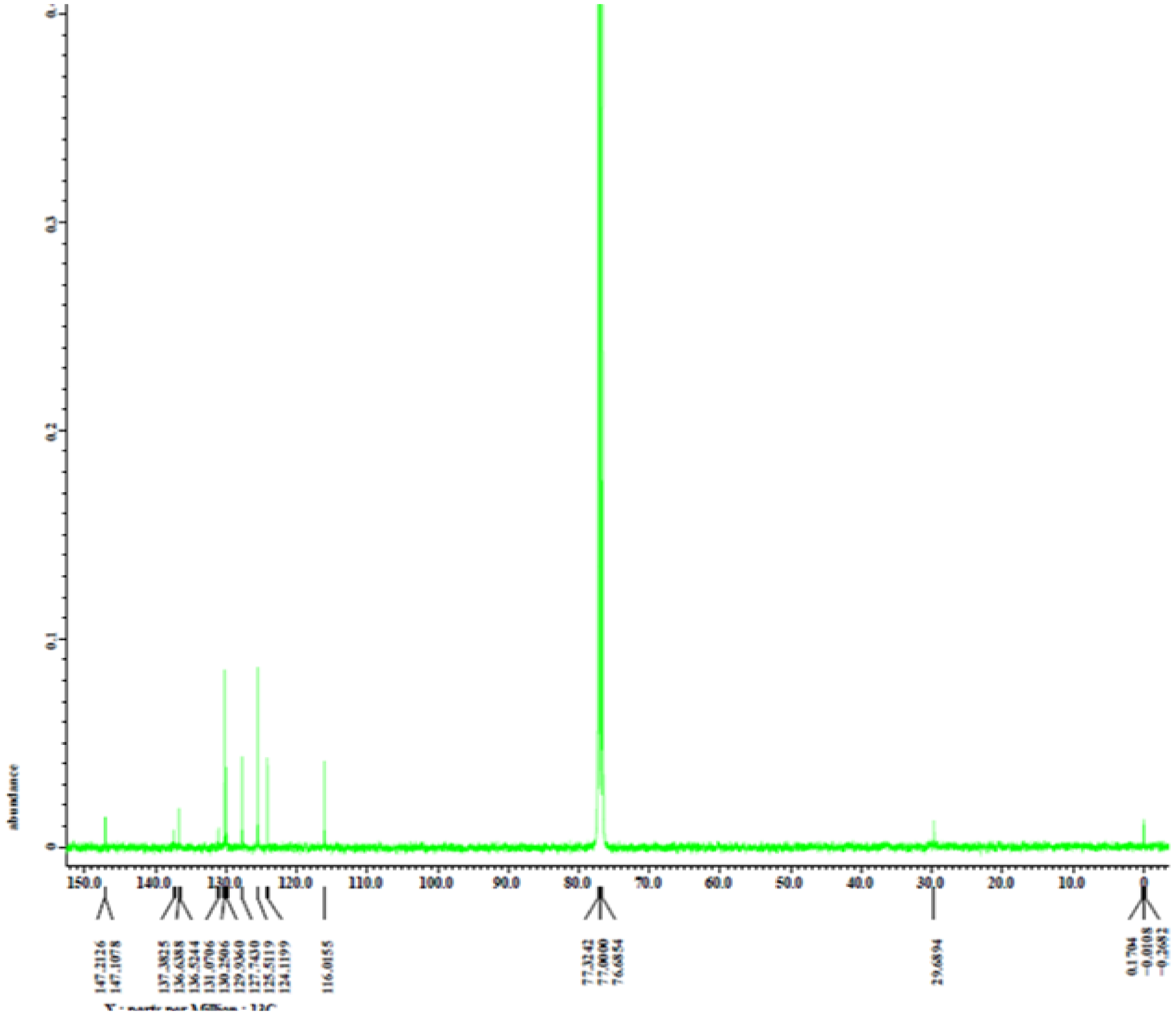


^{13}C NMR Spectra of N-Benzyl-2, 4-dinitrobenzenamine



^{1}H NMR Spectra of 2,4-Dinitro- N-phenylaniline



^{13}C NMR Spectra of 2,4-Dinitro- N-phenylaniline

RESULT AND DISCUSSION

Synthesis of diphenyl ether has generated lot of interest in last one decade due to their antibacterial activity. Triclosan **(Figure-1)**, a diphenyl ether, is known antibacterial and is commonly used in toothpaste, mouthwashes and deodorants. In order to explore other interesting properties of diphenyl ethers different attempts have been made. Gagandeep Bansal attempted imparting it liquid crystal properties by making Schiff base of compound (1) with long chain aliphatic amine (Scheme-1) [25]. However, it resulted in an unexpected major product having structure as shown in (Figure-2).

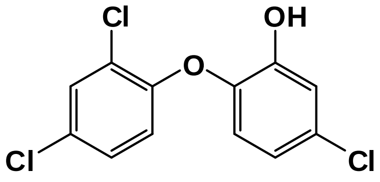


Figure - 1

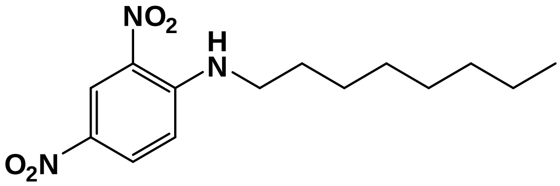
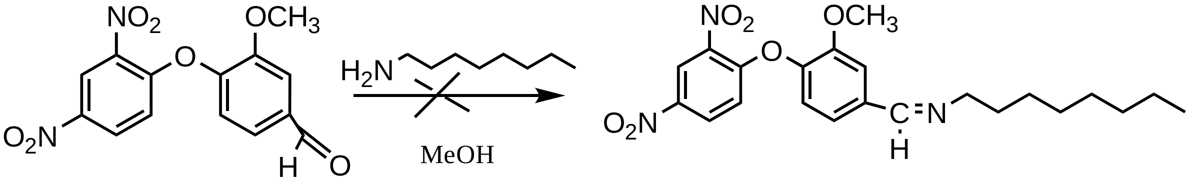


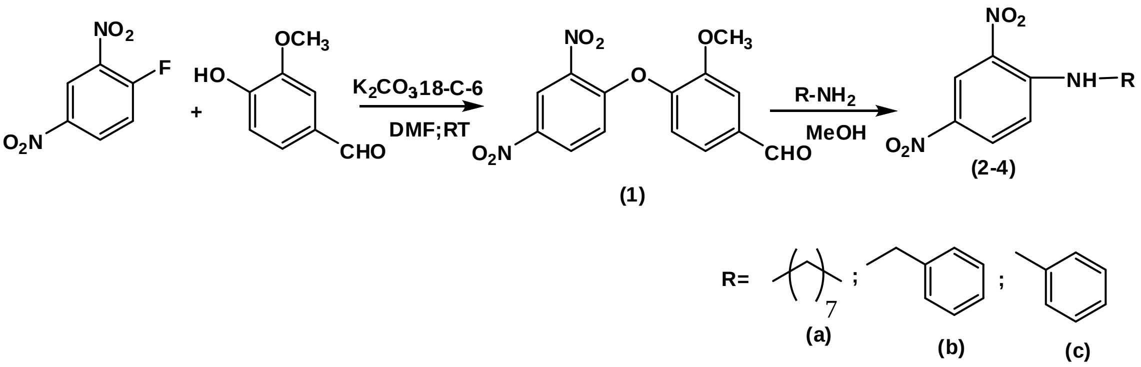
Figure - 2

Present study has been taken with an objective to explore this unexpected reaction pathway. Compound (1) was synthesized by nucleophile aromatic substitution using (2,4-dinitroflurobenzene), vanillin in the presence of mild base, potassium carbonate and catalytic amount of 18-Crown-6 in aprotic solvent, DMF. The known compound was compared for its purity and structure by TLC and ^{1}HNMR.



Scheme-1: Expected formation of Schiff's Base in presence of an aldehyde and amine

Compound (1) was subjected to reaction with octyl amine (a) in methanol in refluxing conditions to afford the compound shown in figure-2. However, the amount of amine required for completion of reaction was to equivalents. Equimolar amount of amine gave partial reaction, as confirmed by TLC. Product obtained was purified by column chromatography and analysed by ^{1}H and ^{13}C NMR techniques.



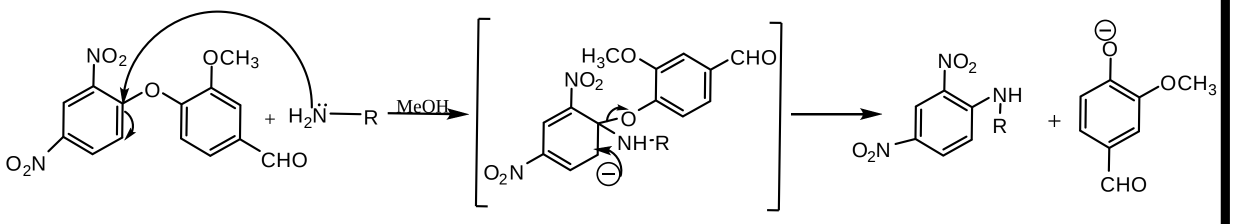
Scheme-2

Reaction of compound (1) under parallel conditions was carried out with other amines also to give similar results. Benzyl amine (b) and aromatic amine, aniline (c), gave similar results. Purification and spectroscopic analysis of compounds 3 and 4 confirmed the formation of proposed structures as in Scheme-2.

The formation and cleavage of diphenyl ether in Scheme-2 takes place by nucleophile for electron deficient carbon attached to fluorine. The use of potassium carbonate in combination with 18-crown-6 increases the nucleophilicity of phenoxide ion. Also the two nitro groups attached at ortho and para positions make carbon attached to fluorine as a good nucleophile centre.

Interstingly, in the second step (Scheme-2) the amine itself acts as a base and nucleophile. The well known reaction of amines in the presence of an aldehydes, formation of Schiff's base, does not take place in this case and nucleophile aromatic substitution is more preferred. The reason for this preference over formation of Schiff base is again presence of two nitro groups at ortho and para position to diphenyl ether linkage. The proposed mechanism of the second step of reaction has been shown in Scheme-3.

Proposed Mechanism



Scheme-3

To conclude, present work has tried to explore the cleavage of diphenyl ether in the presence of amines under simple reaction conditions. The cleavage is a preferred reaction over the formation of Schiff base and has been confirmed with aliphatic, aromatic and benzylic amines in the presence of protic solvent. There is scope for further exploration by investigating cleavage of diphenyl ethers containing other electron withdrawing groups in the presence of different solvent conditions.

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