SYNTHESIS OF OXYGEN CONTAINING HETEROCYCLIC COMPOUNDS THROUGH PALLADIUM CATALYZED AND FRIEDEL-CRAFTS REACTIONS

A Dissertation Submitted in the Partial Fulfillment for the Degree of Master of Philosopy (M. Phil) in Chemistry.

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Session: April 2000.

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THESIS ACCEPTANCE CERTIFICATE

The thesis titled "**Synthesis of Oxygen Containing Heterocyclic Compounds Through Palladium Catalyzed and Friedel-Crafts Reactions.**" Submitted by Mohammad Jahangir Alam. Roll No.# 040003106F, Registration No.# 00431, Session April 2000 has been accepted as satisfactory in partial fulfillment of the requirements for the degree of Master of Philosophy (M. Phil) on June 2002.

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DECLARATION

It is hereby declared that this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma.

(Mohammad Jahangir Alam)

PREFACE

Investigation embodied in this dissertation entitled "Synthesis of Oxygen containing Heterocyclic Compounds Through Palladium Catalyzed and Friedel-Crafts Reactions" were carried out in the Department of Chemistry, Bangladesh University of Engineering and Technology (BUET), Dhaka, Bangladesh, under the supervision of Dr. Md. Wahab Khan, Associate Professor, Department of Chemistry, BUET, Dhaka.

The present studies are directed towards the development of novel methodologies for the synthesis of heterocyclic compound containing benzofuran rings.

I take this opportunity to place on record my heartfelt gratitude to my supervisor Dr. Md. Wahab Khan, who introduced me to these areas. I am indebted to him for his keen interest, constant encouragement, moral support and helpful guidance in carrying out this work.

I am highly grateful to my honourable teacher Professor Dr. Enamul Huq, Department of Chemistry, BUET for his constant encouragement and cooperation during the entire period of my research work.

I express my gratitude to Professor Dr. Md. Rafique Ullah, Head, Department of Chemistry, BUET for helping me with laboratory facilities.

I am also grateful to Professor Dr. Nazrul Islam, Dr. Md. Abdur Rashid, Dr. A. K. M. Matior Rahman, Dr. Md. Manwarul Islam, Dr. Md. Monimul Huque, Mr. M. Nurul Islam, Dr. Al-Nakib Chowdhury and all other teachers of this department for their kind cooperation.

I am thankful to Mr. Nurul Islam, Assistant Professor, Department of Chemistry, BUET for supplying the UV spectra. I want to express my thanks to my labmates and friend Mr. Habib, Mr. Delower, Mukta, Milly for their generous help and co-operation. I express my thanks to all of my classmates and well-wishers.

I am thankful to Dr. Mozaffar Hossain and Mr. M. Shahidul Islam, Senior Scientific Officer, BCSIR, Dhaka for performing ^{1}HNMR and ^{13}CNMR spectra. I extend my thanks to Mr. Md. Shafiqul Islam, Senior Data Entry Assistant, Department of Mathematics, BUET for transcribing the entire manuscript.

I am grateful to Bangladesh University of Engineering and Technology for giving me opportunity to do my M.Phil program in the department of Chemistry, BUET, Dhaka.

I would like to acknowledge the Ministry of Science and Technology for providing the financial support to carry out my research work.

I am thankful to the office staff, Department of Chemistry, BUET for their help. Finally, I express my gratitude to the members of my family for their encouragement, sincere cooperation and sacrifice during the tenure of this work.

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ABSTRACT

o-Iodophenol underwent palladium catalyzed reaction with (trimethysilyl)acetylene to form o-(trimethylsilyl)ethylnyl phenol which was cyclized to 2-acyl(aroyl) benzo[b]furans through Friedel-Crafts acylation with acetyl(aroyl)chloride or acetic anhydride. Utilizing the same procedure 2-acyl(aroyl) benzofurans were obtained from o-acetoxyphenyliodide. A development of the heteroannulation of o-iodophenol with acetylenic substrates through palladium-copper catalysis leading to the synthesis of the 2-substituted benzofurans was also reported.

CONTENTS

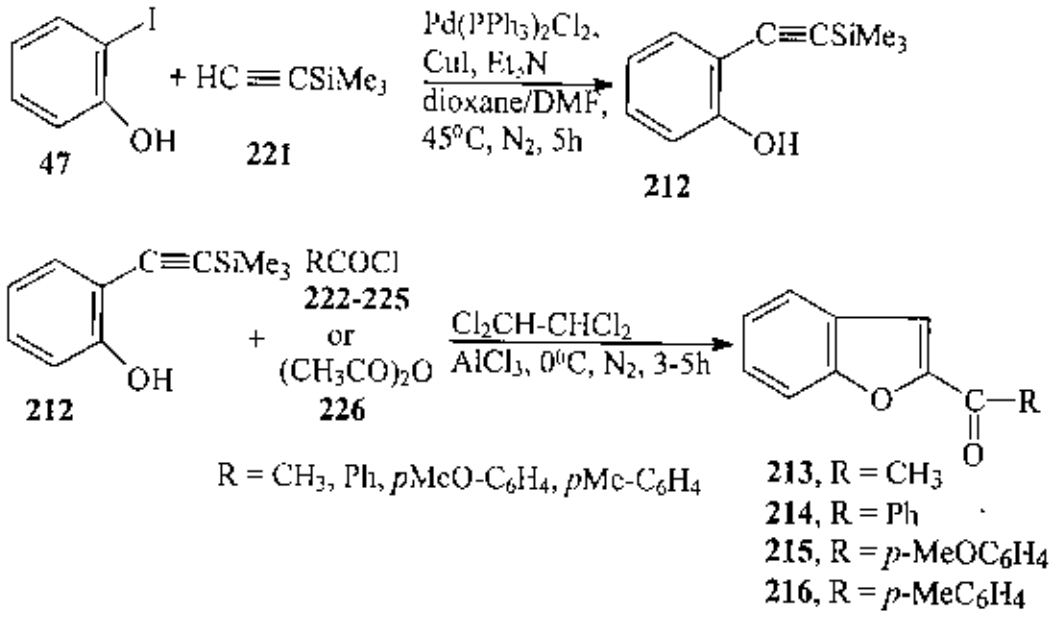
SUMMARY

Investigations incorporated in this dissertation entitled "**Synthesis of Oxygen Containing Heterocyclic Compounds Through Palladium Catalyzed and Friedel-Crafts Reactions**" have been presented in four sections. In section-1 background of biological importance and the important synthetic reactions involved in the synthesis are presented. Section-2, 3 and 4 deal with the detailed methodology and experimental procedures for the synthesis of the 2-substituted benzofurans.

Section one represents the importance and synthesis of benzofuran derivatives. Heterocyclic compounds containing the benzofuran moiety are of great interest because of their occurrence in nature and their fascinating pharmaceutical and medicinal activities. Although various methods have been developed previously for the synthesis of benzofurans, only a few of them were mediated through palladium catalysis. In section-2, we report a new strategy for the synthesis of 2-substituted benzofurans **213 – 216** through the palladium catalyzed and Friedel-Crafts reactions from *o*-iodophenol **47**. The reactions were usually carried out with trimethylsilyl acetylene **221** in the presence of Bistriphenyl phosphine palladium(II) chloride and copper(I) iodide at 45^0C to yield *o*-(trimethylsilyl)ethynyl phenol **212** in excellent yields. *o*-(Trimethylsilyl)ethynyl compound **212** was then subjected to Friedel-Crafts reaction with acid chlorides **222 – 225** or acetic anhydride **226** to afford the 2-substituted benzofurans in good yields as shown in **scheme-51**.

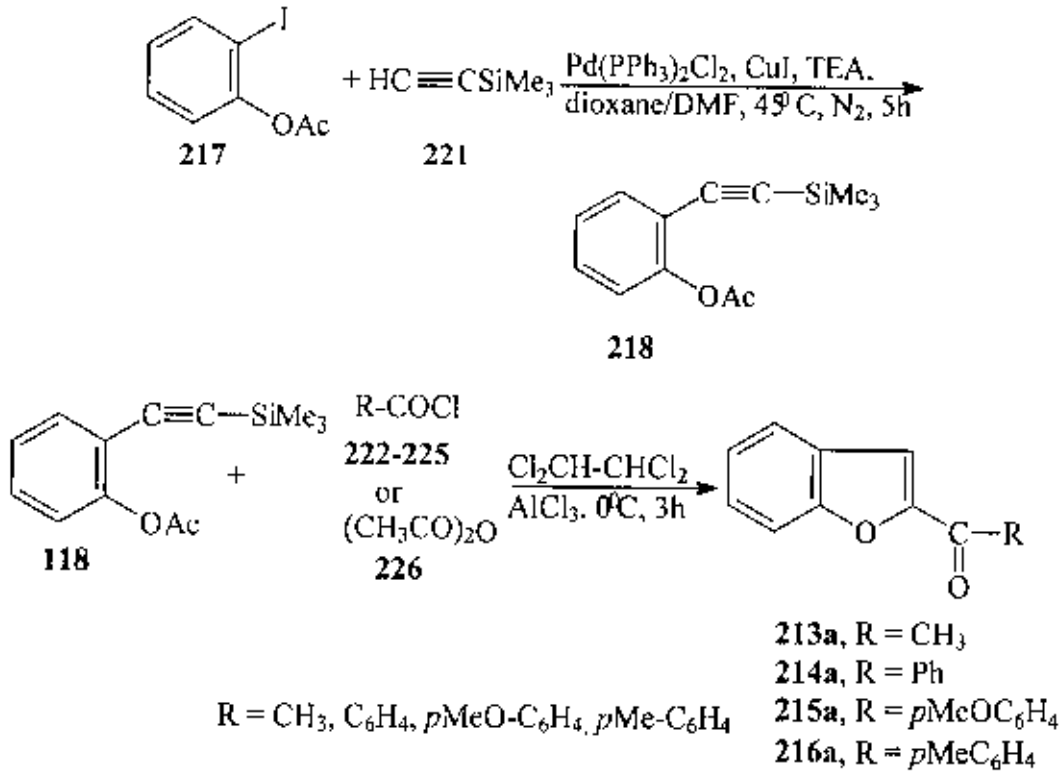
The starting materials, 2-iodophenol **47** and *o*-(trimethylsilyl)ethynyl phenol **212** were prepared from *o*-aminophenol according the known literature procedure.

Scheme - 51



We wanted to synthesis 2-substituted benzofurans from *o*-iodophenol through combined palladium catalyzed and Friedel-Crafts reactions But we have obtained a mixture of two isomeric product by that method. Later we decided to protect the OH group of *o*-iodophenol as acetate to develop the process for synthesizing 2-acylbenzofurans. In section-3, we demostrate a novel approach where a palladium catalyzed reaction was followed by Friedel-Crafts acylation and simultaneous cyclization to obtain 2-acylbenzofurans in excellent yields. *o*-Acetoxyphenyl iodide **217** underwent facile reaction with acetylenic compound **221** in the presence $(PPh_3)_2PdCl_2$ and CuI at 45^0C to yield *o*-(trimethylsilyl) ethynylphenyl acetate **218** in excellent yield. The compound **218** was then subjected to Friedel-Crafts reaction with acid chloride **222 – 225** or acetic anhydride **226** to afford the 2-substituted benzofurans **213a – 216a** in excellent yields as shown in **scheme-55**.

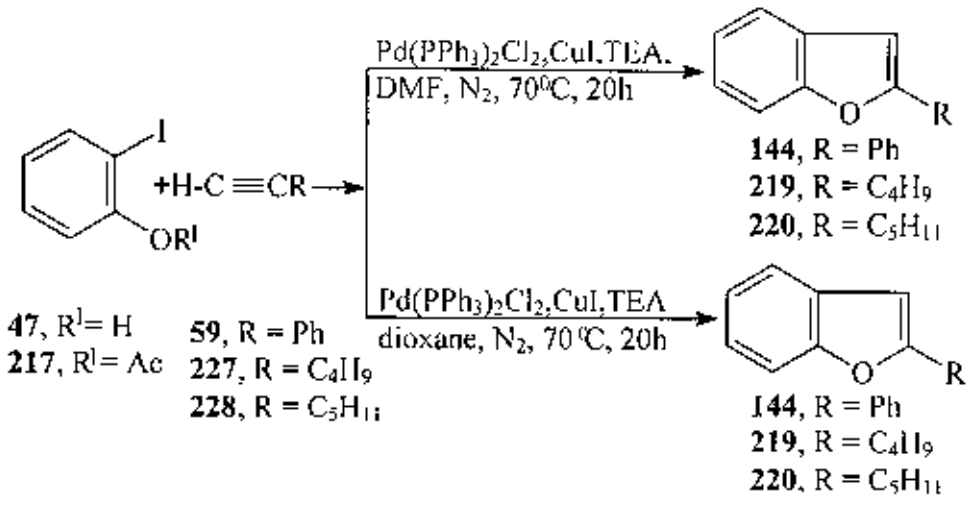
Scheme - 55



In the case of aroyl chloride we obtained a single product but in the case of acetyl chloride and acetic anhydride we also obtained mixture of two isomeric product. We obtained higher yield by this process than the earlier process.

In section-4, we have furnished a new strategy for the synthesis of 2-substituted benzofurans **144**, **215**, **220** with terminal alkynes **59**, **227**, **228**. The reactions were usually carried out by heating a mixture of *o*-iodo compounds **47** or **217** and alkynes **59**, **227**, **228** in dioxane or DMF at 70^{0}C for 15 hour in the presence of $(PPh_3)_2PdCl_2$ (2.5 mol %) copper (I) iodide (8 mol %) and triethylamine (10 ml) to afford the 2-substituted benzofurans as shown in **scheme - 59** In the case of hexyne **227** and heptyne **228** we obtained small amount of dimer with 2-substituted benzofurans which was not separable by column chromatography. We obtained good results when we used dioxane as a solvent.

Scheme - 59


Pd(PPh3)2Cl2,CuI,TEA,
DMF, N2, 70°C, 20h
+H-C≡CR
OR1
144, R = Ph
219, R = C4H9
220, R = C5H11
Pd(PPh3)2Cl2,CuI,TEA
dioxane, N2, 70 °C, 20h
47, R1= H
217, R1= Ac
59, R = Ph
227, R = C4H9
228, R = C5H11
144, R = Ph
219, R = C4H9
220, R = C5H11

PREFATORY NOTE

Unless otherwise stated the following procedures were used throughout the work.

1. Melting point (MP):

Melting points were determined on an electrothermal melting point apparatus (England) and paraffin oil bath were uncorrected.

2. Infra-red (IR) spectra and UV spectra:

The infra-red (IR) spectra were recorded on KBr disc for films with a Shimadzu FTIR spectrophotometer and the UV spectra were recorded in $CHCl_3$ with a Shimadzu UV visible spectrophotometer at the chemistry Department, BUET, Dhaka, Bangladesh.

3. Nuclear magnetic resonance (NMR) spectra:

^{1}HNMR and ^{13}CNMR spectra were recorded in $CDCl_3$ with a Ultra Shield (Bruker) spectrometer (400MHz) at BCSIR, Dhaka, Bangladesh.

4. All organic extracts were dried over anhydrous sodium sulphate (Na_2SO_4) before concentration.

5. Evaporation:

All evaporation were carried out under reduced pressure using Buchi Rotatory Evaporator.

a) Anhydrous 1,4-dioxane:

1,4-dioxane was shaken with sodium hydroxide pellets and kept standing overnight. Then the mixture was filtered and the filtrate thus obtained was distilled. The portion ranging 100 – 102^{0}C was collected and used as anhydrous 1,4-dioxane.

b) Anhydrous DMF:

DMF was distilled throughout.

c) Chloroform was distilled throughout.

d) n-Hexane was also distilled before use.

7. Techniques and application of thin layer chromatography (T.L.C):

Thin layer chromatography is considered to be one of the most useful methods for the separation, purification, progress of the reaction rate and identification of a mixture of organic compounds which involves an absorbent (usually silica gel) as stationary phase and a solvent or solvent mixture as a mobile phase. Due to the differential rate of absorption on the absorbent the compounds of the mixture migrated differently along the T.L.C. plates. In other words, due to the difference in mobility of the components, solvent follows the fact that the more polar compound makes faster the mobility of the components also depends on the polarity of the solvent or solvent mixture.

8. Procedure for the spotting and development of T.L.C. plates:

The silica gel coated alumina T.L.C. plates were used. To spot the plates, first a mark was made about 1 cm up from the bottom of each plate and the solution of the components were then spotted with thin glass capillaries. More spotting were applied upon the same place to concentrated the component when the first one was completely soaked in. In such a way another spotting was made in a horizontal straight line (base line). The plate was then placed vertically in a suitable solvent in a closed tank, but the spot was not covered by the solvent. The atmosphere inside the tank was saturated with the vapour of the same of the solvent. Development of the chromatogram accused by capillary movement of the solvent up the adsorbent layer. The plates were removed when the solvent front reached half a centimeter apart from a upper edge. The plates were then allowed to dry. If the component of the mixture were coloured, the spots were readily located. If the components were colourless the dried plate was developed with iodine vapour or UV light. For identification of the sample by T.L.C. at least three different solvent were tried and the R_f value computed and compared with each case but only the solvent conditions that gave the best results were mentioned. The ratio of the distance traveled by a component to the distance traveled by the solvent front was characteristic of each component and was known as R_f value, e.i.

$$R_f = \frac{\text{Distance traveled by the component front}}{\text{Distance traveled by the solvent front}}$$

True reproducibility in R_f values is however, rarely achived in practice due to minor changes in a number of variables such as :

i) The particle size of different batches of absorbent.

ii) The solvent composition.

iii) Prior activation and storage conditions of the plates.

iv) The thickness of the absorbent layer.

v) Chamber saturation etc.

Thus, when the R_f values for two different components are almost same or hardly distinguishable then to study the different characteristic is the only way to distinguish.

9. Column chromatography:

Column chromatography has been successfully applied to separate the individual components (having different R_f values) from the mixture obtained from the reaction. This technique was also employed for purification of the product.

A long cylindrical column (70 cm long and 2 cm in diameter usually a burette type is used) made of glass drown out at one end and packed with glass wool. To the lower constricted end of the column a stop cork was fitted in order to control the flow of the eluant. A separatory funnel fitted with a specially made quick fit stopper and filled with the eluant was placed at the top of the column and this served as a store of eluent.

The flow of the eluent was controlled by adjusting the stop cork. The column was prepared by slurry method, silica gel being used as the stationary phase, the column was made half filled with various type of solvents as light petroleum, ethyl acetate, chloroform, n-hexane etc. and slurry of silica gel in the chosen solvent was the poured into it, so that the packing was compact and uniform.

Air bubble was removed by making the column as quickly as possible and allowing the solvent to fall drop by drop through the stop cork of the column. The mixture of the components was then placed on the upper surface of the slurry of the silica gel and the mixture was covered in limited area by some amount of dry silica gel. Then the solvent mixture was passed through the column. The fractions were collected in test tubes about 20 to 30 ml in each at a regular interval of time and the respective fractions were detected by T.L.C. The solvent used for elution was chromatographically pure.

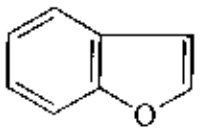
SECTION - 1

Background of the Present Work

1. Background of the Present Work

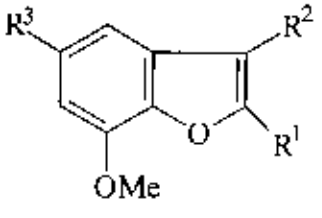
1.1 Introduction:

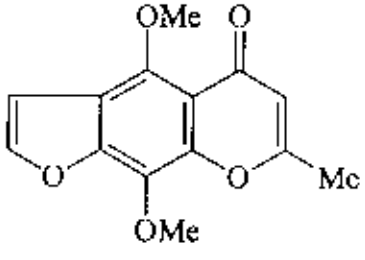
Benzofuran 1 and its derivatives have drown considerable attention due to their profound physiological and chemotherapeutic properties[1-2] and widespread occurrence among natural products.



I

There are many naturally occurring compounds containing the benzofuran skeleton. A few of them are cited here. Machicendiol[3] **2**, a constituent of the extracts of *Machilus gloucescens* (Lanraceae) is used in the treatment of asthma, rheumatism and ulcers. The active component, 5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)-3-benzo[b]furoncarbaldehyde[4] **3** of the aqueous extracts of *S. miltiarrhiza* Bunge "Danshen," widely used in China to treat acute myocardiac infraction and angina pectoris. A benzofuran derivative khellin **4** is effective against bronchial asthma[5]. Tremetone **5**, hydroxytremetone **6**, toxol **7** and dehydrotremetone **8** isolated from *Eupatorium utricaefolium* and *Aplopappus heterophyllus* are known to cause trembles in cattle and milk sickness in humans[6].





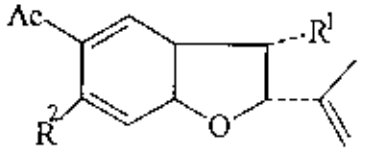
4

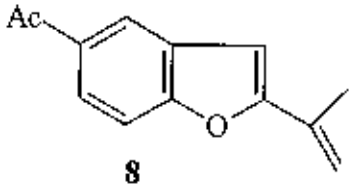
2. $R^1 = 3', 4'$ - methylenedioxyphenyl

$R^2 = H$, $R^3 = CH(OH)CH_2CH_2OH$

3. $R^1 = 3'$ – methoxy-4′ – hydroxyphenyl

$R^2 = CHO$, $R^3 = (CH_2)_3OH$





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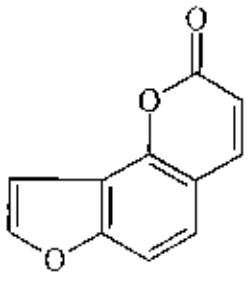
5. $R^1 = R^2 = H$

6. $R^1 = H,\ R^2 = OH$

7. $R^1 = OH,\ R^2 = H$

Naturally occurring furocoumarins e.g. psoralen **9** and methoxalen **10**, commercially obtained from seeds of *Amni majus* L, are used for treatment of psoriasis and other dermal diseases[7]. Furocoumarins, particularly psoralen, actively participate in elaboration of chlorophyll and as such are important for plant biosynthesis[8]. Substitution at some position of psoralen **9** reduce its photosensitizing activity, which decreases as the chain become longer[9]. Angelicin **11** possesses only 12% of the photosensitizing activity of psoralen. The study of photoreaction of psoralene **9** with DNA (UV rays, 365nm) showed that cycloaddition occurred with thymine involving one or two molecules of thymine[10]. Furoconmarins e.g. methoxalen, also known as xanthotoxin **10**, apparently increase the sensitivity of Ehrlich tumour cells to γ-rays[11]. The use of phototoxic furocoumarins as anticancer agents have been investigated[12]. 5,9-Dihydroxypsoralen **12** is used as a radiosensitizing drug[13], while 2,5,9-trimethylpsoralen **13** is used as a radioprotective agent[13]. Trimethylpsoralen and its derivatives **14** are effective photoreactive crosslinking reagents for nucleic acids[14].



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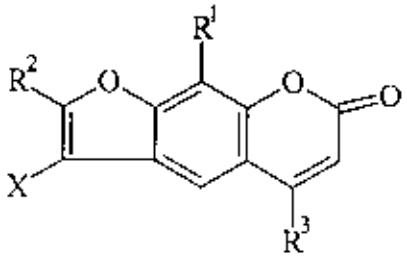


9. $R^1 = R^2 = R^3 = X = H$

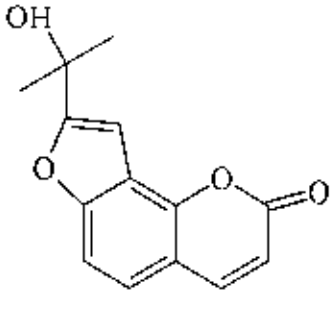
10. $R^2 = R^3 = X = H;\ R^1 = OMe$

12. $R^1 = X = H;\ R^2 = R^3 = OH$

13. $R^1 = R^2 = R^3 = Me;\ X = H$

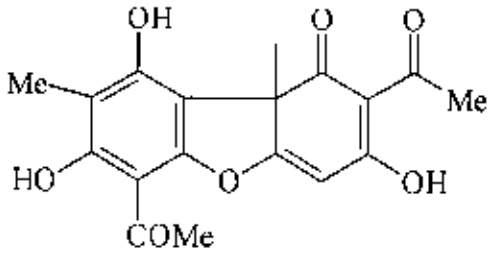
14. $R^1 = R^2 = R^3 = Me;\ X = CH_2OHCH_2\overset{+}{N}H_3$

Two terpenic coumarins, oroselol **15** and jatamansin have been isolated from *Nardostachys jatamansi*, a herb growing at great elevation upto 17000 ft. on the Himalayas[15].



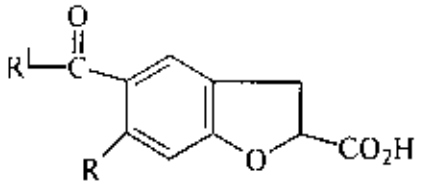
15

Usnic acid **16**, one of the most common lichen metabolites, shows inhibitory effect on Gram positive bacteria[16]. Probably it interferes with oxidative phosphorylation in the nucleus and in general, with functions associated with RNA[17]. In conjugation with streptomycin, it inhibits mycobacterium tuberculosis[18].



16

Substituted 5-acyl-2,3-dihydrobenzofuran-2-carboxylic acids **17** exhibit diurebic and antitussive activities[19].



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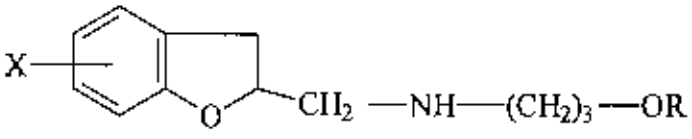
2-(3-Alkoxypropylaminomethyl)-2,3-dihydrobenzofuran analogues **18**, possess potent analgesic, spinal reflex-depressing and adrenergic α-bloking activity *in vivo*[20], while 2-amino-2,3-dihydrobenzofurans like **19** and **20** are useful antidepressants and hypotensive[21].



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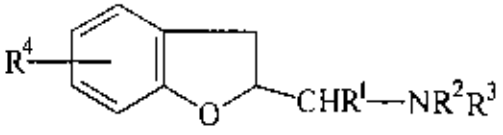

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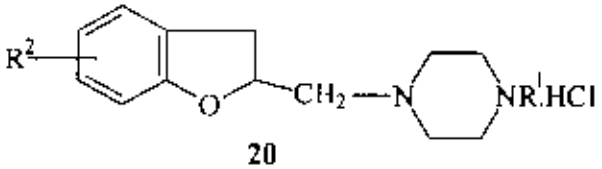

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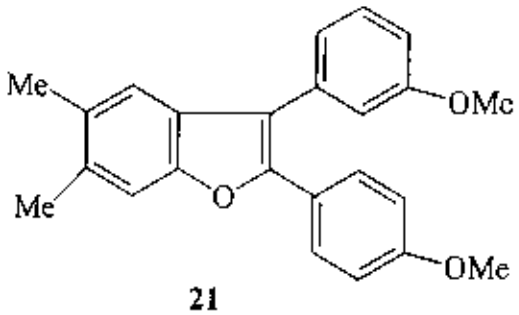
Among 2,3-diarylbenzofurans, 2,3-bis-(4-methoxyphenyl)-5,6-dimethylbenzofuran **21** is reported to have antiinflammatory properties[22]. while 6-methoxy-2-phenyl-3-[p-(2-pyrrolidylethoxy)phenyl]benzofuran hydrochloride **22** exhibits antifertility properties[23].



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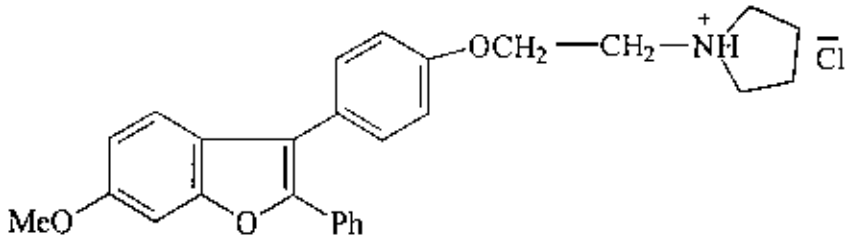
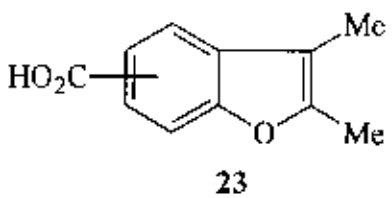


22

5,6-Dimethyl-2,3-diphenylbenzofurans are useful as scintillator for radiation measurement[24]. 2-Cyanobenzofuran-5-sulfonic acid esters and amids are used as color developers in photography[25], while 2,3-disubstituted compounds like **23** and **24** are used as brightening agents in textiles. wool, cellulose, nylon and paper industry[26].



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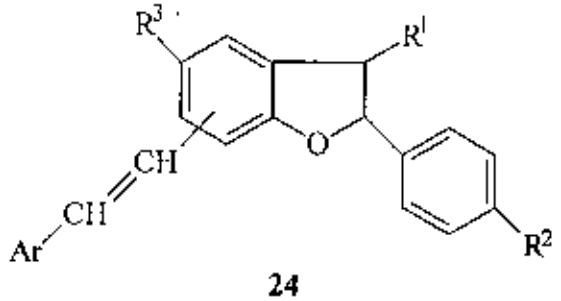

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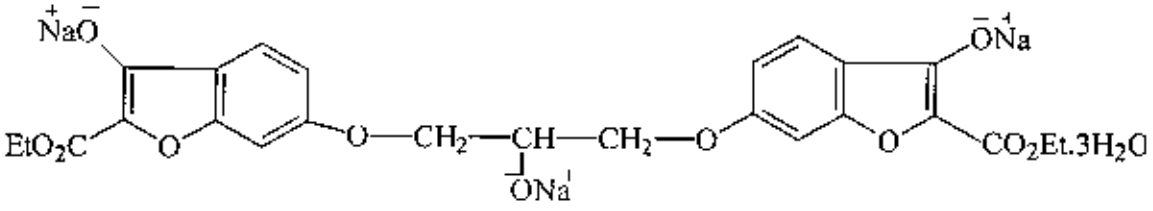
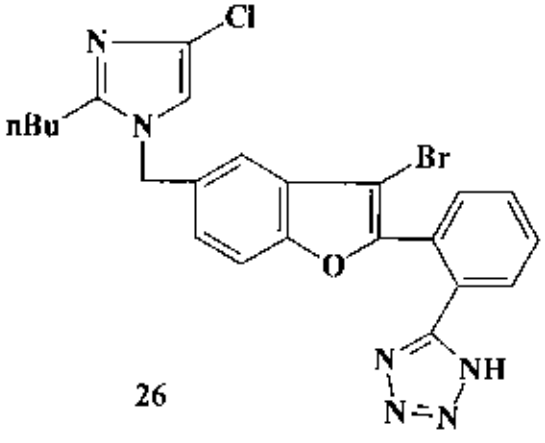
Several isosteric bisbenzofurans have been synthesized e.g. sodium chromoglycate (DSCC) **25** which is useful in human asthma[27].



25

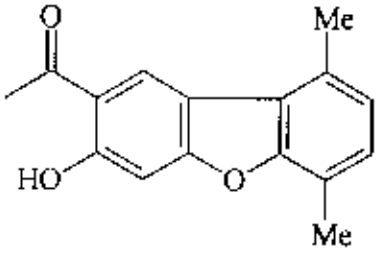
The synthesis and pharmacology of a novel series of benzofurans which are antagonists of anglotension II has been reported[28] e.g. GR 117289 **26** is a potent and specific antagonist which, after oral administration (10 mg/kg) causes marked and long lasting (<24 hours) fall in blood pressure in renal hypertensive rates[28]. Structure activity relationship based on **26** has been reported[29].



26

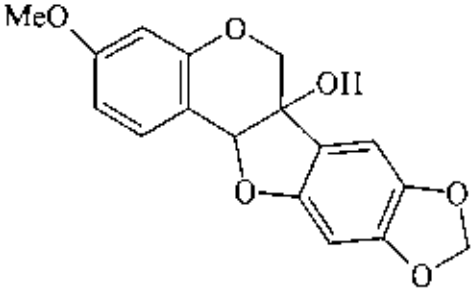
Polychlorodibenzofurans, which appear in a variety of industrial chemical products, are toxic to mammals and can cause chloracne and extensive liver damage[30].

Ruscodibenzofurans e.g. 2-acetyl-6,9-dimethyldibenzofuran-3-ol **27** have been isolated from *Ruscus aculeatus* (Liliaceae), extracts of which is known to have diurebic and antiinflammatory activity[31].

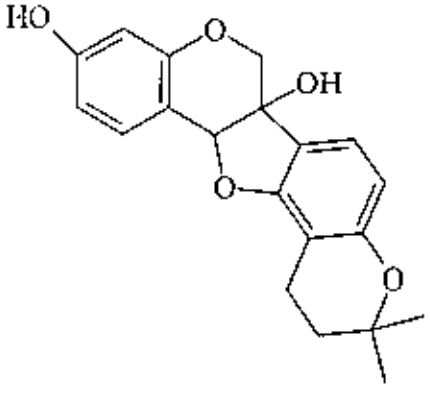


27

Pterocarpans (6a,11a-dihydro-6H-benzofuran[3,2-C] benzopyran) act as natural defence agents called phytoalexin, in plants[32]. The presence of a OH group at 6a position apparently enhances antifungal activity relative to pterocarpans e.g. pisatin **28** from *Pisum sativum*[33] and 6a-hydroxyphaseollin **29** from *phaseolus vulgaris*[34]. Phaseollin **30** exhibits antifungal and lipophilic activity[35].



28



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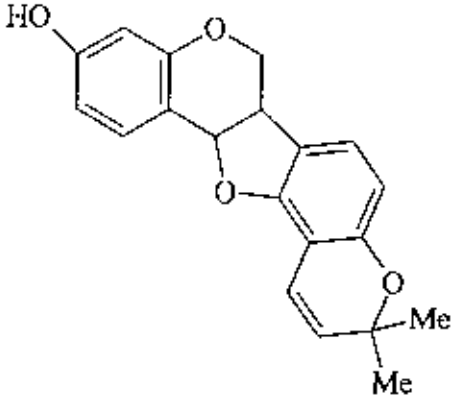
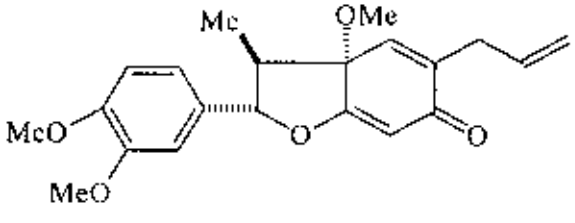


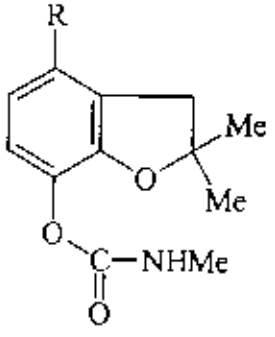
30

Neolignans are a group of secondary plants metabolites structurally characterized by the presence of two aryl propanoid units. One class of this group possesses the dihydrobenzofuran skeleton e.g. kadsurenone **31**, a potent and specific platlet activating factor (PAF) antagonist[36].



31

Benzofuranyl carbamates e.g. NIA 9242 i.e. methyl-2,3-dihydro-2,2-dimethyl-7-benzofuranyl carbamate **32**, its 4-chloroderivative NIA 10559 **33** and 4-methyl derivative NIA 10586 **34** are useful pesticides[2]. Benzofuran, 2,3-dibromobenzofuran, 2,3-dihydro-3-oxo-benzofuran and their derivatives exhibit low activity.

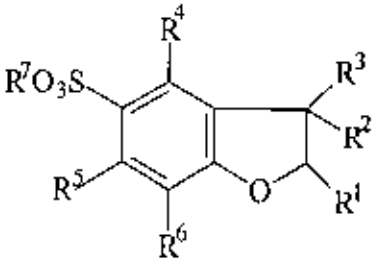


32. R = H

33. R = Cl

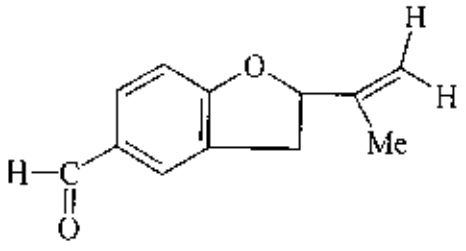
34. R = Me

Tremetone **5** the main constituent of termetol, seems to have insecticidal properties[2]. The carboxy derivatives of benzofurans are active growth regulators e.g. 5-benzofuranyl esters like **35** can be used to control grass[37].



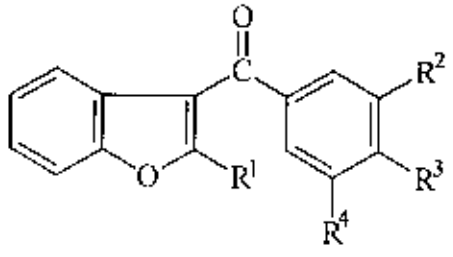
35

Fomannoxin **36** has been isolated from cultural broth of *Fomes annosus*, one of the few Basidiomycete fungi that causes death of host cell in living trees as well as extensive decay in the heartwood of diseased trees. Toxicity of fomannoxin is reported to be hundred times greater than that of fomannosin, a sesquiterpene previously isolated from the same source[38].



36

2-(4-Hydroxybenzoyl)benzofuran **37** exhibits relaxing effect on histamine and acetyl chloline spasm. However, estrogenic activity precludes clinical use[39-40]. Among several derivatives synthesized, **37** exhibits greatest estrogenic activity[39]. 2-Ethyl-3-(4-hydroxy-3,5-diiodobenzoyl)benzofuran **38** is superior to khellin as a coronary dilator. The corresponding dibromoderivative **39** is less active[41].



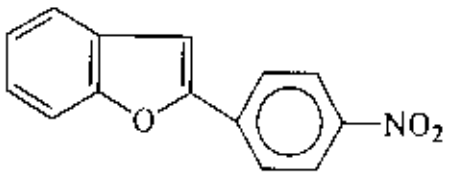
37. $R^1 = R^2 = R^4 = H,\ R^3 = OH$

38. $R^1 = CH_2CH_3,\ R^2 = R^4 = I,\ R^3 = OH$

39. $R^1 = CH_2CH_3,\ R^2 = R^3 = Br,\ R^3 = OH$

40. $R^1 = n-Bu,\ R^2 = R^4 = I,\ R^3 = OCH_2CH_2NEt_2$

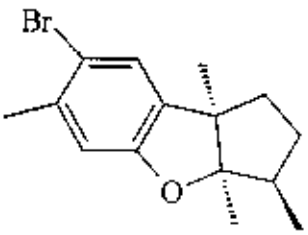
Both **38** and **39** are powerful uricoeliminators[2]. 2-Ethyl-3-(4-hydroxy-benzoyl)benzofuran exhibit angiotropic, antiinflammatory and fibronolytic properties[42]. 2-Butyl-3-[3,5-diiodo-4-(2-diethylaminoethoxy)benzoyl]benzofuran **40** is a powerful angiotropic[2], while 2-(4-nitrophenyl)benzofuran **41** shows high activity against straphylococci, pyocyaneae and E. coli. 3-(2-Hydroxy-3,5-dichlorophenyl)-5,7-dichlorobenzofuran exhibits bactericidal and bacteriostatic activity against *staphylococcus aureus*[43].



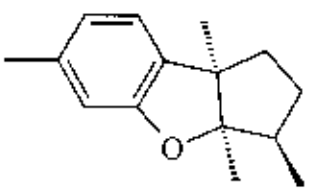
41

Recently there has been a growig interest in developing general and versatile synthetic methods for the synthesis of benzo[b]furan derivatives due to their activity as modulators of androgen biosynthesis (furanosteriod)[44] as inhibitors of 5-lipoxygenase[45], as antagonists of the angiotensin II receptor[46] and blood coagulation factor Xa inhabitors[47], and as ligands of adenosine A_1 receptor[48]. 1-[[(4-Aminoalkoxy)phenyl]sulphonyl] benzo[b]furan derivatives have been synthesized and tested as a potent class of calcium blockers[49].

Aplysin **42** was one of the first halogenated sesquiterpenes to be isolated from marine organisms. Found in the sea hare *Aplysia* and the red alga *Laurencia*[50], its antifeedant properties are believed to protect hosts from raptorial advances[51]. The co-occurrence of aplysin **42** and debromoaplysin **43** in all known natural sources has also prompted speculation that **43** is a biological precursor of aplysin and acts as an antioxidant by scavenging reactive halogens[52].

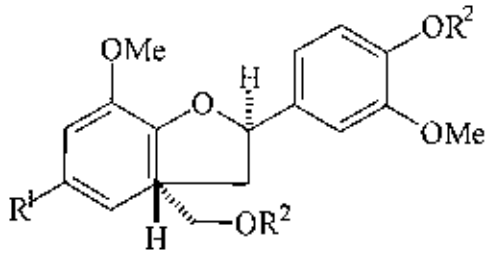


42



43

Neolignans possessing the 2,3-dihydrobenzo[b]furan skeleton are a class of naturally occurring heterocyclic compounds (**44a-d**) with hepatoprotective[53], hormone blocking[54,55] antibacterial[56], antifungal[57], plant growth regulator[58] antioxidant[59] and shows a significant PGI_2 inducing effect[60].



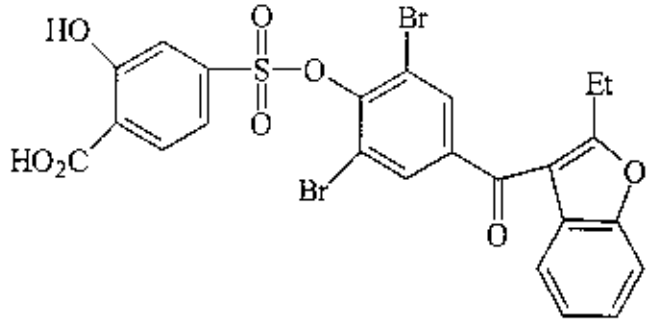
44a. $R^1 = (E) - CH = CH - CO_2CH_3$, $R^2 = H$

44b. $R^1 = R^2 = H$

44c. $R^1 = H$, $R^2 = Ac$

44d. $R^1 = Br$, $R_2 = Ac$

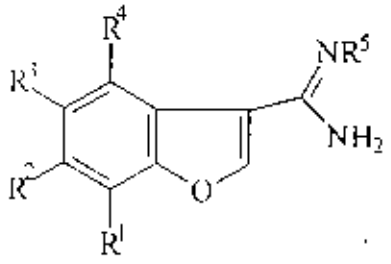
Benzofurans the title compound **45** are useful for thealing insulin resistance and hyperglyumia[61].



45

In 2000 Banskola *et al*[62] found that two novel benzofuran derivatives propolis benzofuran A and B, were isolated from the MeOH ext. of *Brazilian propolis* together with two known isoprenylated compounds. Both the new compounds exhibited mild cytotoxicity towards highly liver metastatic musine colon 16-L5 carcinoma and human HT1080 fifrosarcoma cells.

Benzofurancarboxamidines title compounds 46 acts as central nervous system agents[63].



46

$R^1 - R^4 = H$, halo,alkyl,alkoxy,aryl,benzyloxy,alkoxyalkyl,alkylsulphanyl,alkylsulphanylalkyl; $R^1, R^2 = OCH_2CH_3$; $R^5 = H, OH$ These type of compounds are useful for treatment of (migraine schizophrenia, anxiety strates, sleep disorders, anorexia, alzheimer's disease, addictions and disorders)[63] which result from damage to the head/brain or to the spinal column.

2-(4-Methoxphenol)-3-methyl-5-(E)-propenylbenzofuran, 2,3-dihydro-2-(4-hydroxyphenyl)-3- methyl-5-(E)propenylbenzofuran were isolated from the leaves of *piper magnibacum* C.DC. The antibacterial activity of the isolates were also investigated[64].

K. Ishibashi *et al*[65] reported that a series of 2-phenylbenzofuran derivatives with a carbonyl, alkylamino or alkoxy group at the 5 or 6 position of the benzofuran ring were synthesized and evaluated for rat and human testosterone 5α-reductase inhibitory activities *in vitro* Against rat enzyme, the carbonyl derivatives had more potent inhibitory activites than the alkylamino or alkyloxy derivatives. Against human enzyme the 6-substituted derivatives had more potent than the 5-substituted derivatives.

1.2 General Methods for the Synthesis of Benzo[b]furans:

A number of classical methods are available for the synthesis of benzo[b]furans, which can be classified under the following headings[66].

A) Synthesis of the heterocyclic ring from an aromatic substrate.

B) Synthesis of the heterocyclic ring from a non-aromatic substrate.

C) Fusion of the benzene ring to a furan substrate.

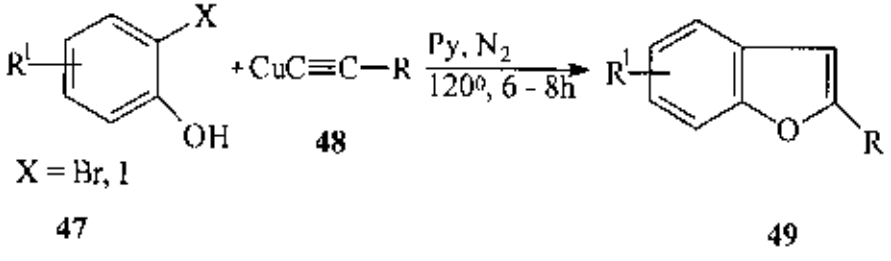
D) Synthesis of the heterocyclic ring from other heterocyclic compounds.

The classical methods for the synthesis of benzo[b]furans have been reviewed[66,67]. A number of them uses drastic reaction conditions and cannot accommodate sensitive groups like aldehyde and ketones. Usually, they display typical reactivity patterns and selectivities. This fact coupled with the chemotherapeutic importance of various benzofurans and their occurrence as natural products set the background for the search of more versatile methods to synthesize benzo[b]furans.

It becomes highly desirable to mention Castro-Stephen reaction[68a-c] for the synthesis of benzo[b]furans, because a number of catalytic synthesis have been developed in which copper salts are used to generate Pd(0) "*in situ*" from palladium (II).

When 2-halophenols **47** were refluxed with cuprous acetylides **48** in pyridine or DMF for 6-8 hours under nitrogen atmosphere, 2-substituted benzofurans **49** were obtained in moderate to excellent yields (**Scheme-1**). Presence of oxygen resulted in coupling of acetylenes, thus reducing the yields.

Scheme-1

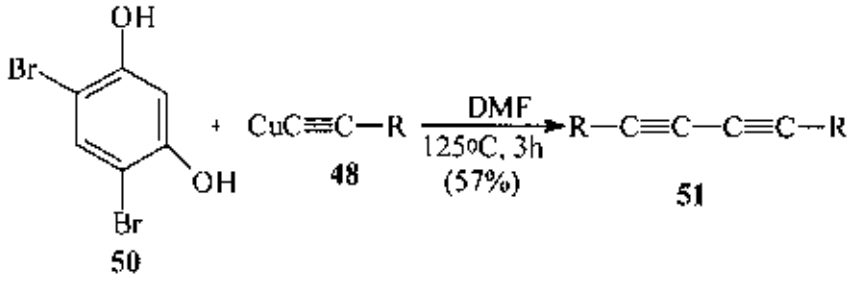


47 **48** **49**

The use of 2-iodophenols and DMF as solvent was found to give better results e.g. with 2-bromophenol **47** (X = Br, R^1 = H) and cuprous phenylacetylide **48** (R= Ph) a 56% yield of 2-phenylbenzofuran **49** (R^1= H, R = Ph) was obtained; for the corresponding reaction with 2-iodophenol **47** (R^1= H, X = I) in DMF, the yield was 85%.

Unreactive phenols e.g. 4,6-dibromoresorcinol **50** were found to promote oxidative coupling of the acetylides (**Scheme-2**)

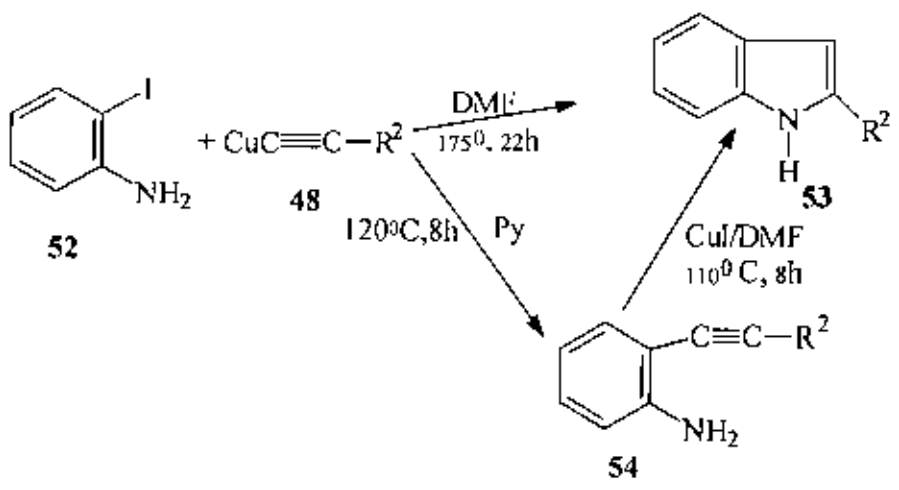
Scheme-2



50

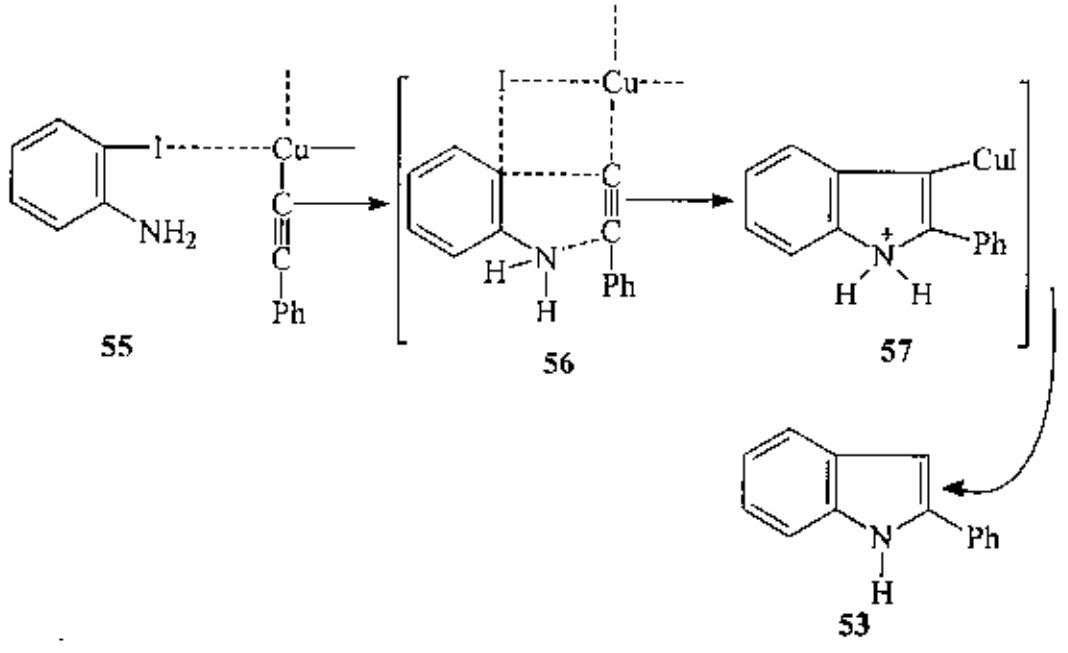
The reaction was found to be quite general in its scope. Heteroanulation occurred wherever the starting halide had an ortho-nucleophilic substituent. The effectiveness of an ortho-nucleophilic substituent to promote the heteroannulation was in the order COOH>OH>NH_2. In fact the reaction between 2-iodoaniline **52** and cuprous phenylacetylide **48** (R^2 = Ph) was found to be markedly solvent dependent. When DMF was used 2-phenylindole **53** (R^2 = Ph) was obtained in 89% yield. When pyridine was used 2-aminotolane **54** was obtained as the exclusive product. However **54** could be cyclized to 2-phenylindole **53** by warming with catalytic amount of cuprous iodide in DMF at 110^0C for 8 hours (**Scheme-3**).

Scheme-3



The reactivity of halides was found to be in the order I>Br>Cl. Furthermore the presence of N-ethylpiperidine was found to decrease the efficiency of benzofuran synthesis, indicating that strong coordination of copper could mask the ability of the metal to effect the initial alkylation or to coordinate with the acetylene[68c]. The substituent of halide and cyclization were thought to occur within the same copper complex[68a] **(Scheme-4)**

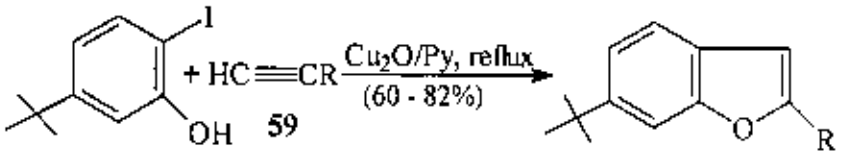
Scheme-4



In 1989, Doad *et al*[69a] observed that the usefulness of Castro-Stephen reaction was diminished by the requirement to prepare and isolate copper acetylides, some of which

are shock sensitive and explosive. Furthermore, several of the functionalized copper acetylides having hydroxyl, esters etc. were found to be soluble in or reactive towards the reaction mixture used in their preparation. They obtained 2-substituted benzofurans **60** good to excellent yields by refluxing a mixture of 5-t-butyl-2-iodophenol **58** with terminal acetylenes **59** in the presence of cuprous oxide in pyridine (**Scheme-5**).

Scheme-5

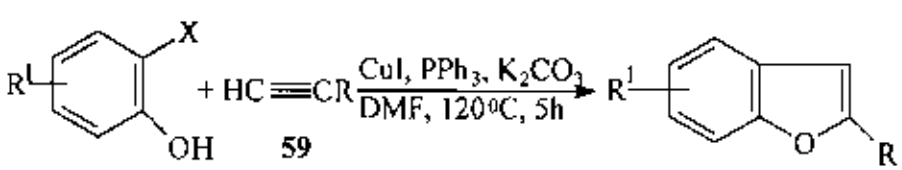


58 **60**

R = $(CH_2)_3CH_3$, CH_2CH_2OH, $CH_2CHOHCH_3$,$(CH_3)_3CN$, COOEt, CH=CHOMe.

Recently, Okuro *et al*[69b] developed a catalytic system consisting of cuprous iodide, triphenylphosphine and potassium carbonate as base, for carbon-carbon bond formation. Thus when a mixture of 2-iodophenol **47** (R^1=H, X=I) and phenyl acetylene **59** (R=Ph) was heated at 120^0C in the presence of catalytic amounts of cuprous iodide, triphenylphosphine and potassium carbonate, in DMF, for 5 hours, 2-phenylbenzofuran **49** (R^1=H, R=Ph) in 18% yield, along with phenol (15% yield) and 1,4-diphenylbutadiyne (15%) as side products were obtained (**Scheme-6**).

Scheme-6



47 **49**

R^1 = H, X = I, R = Ph

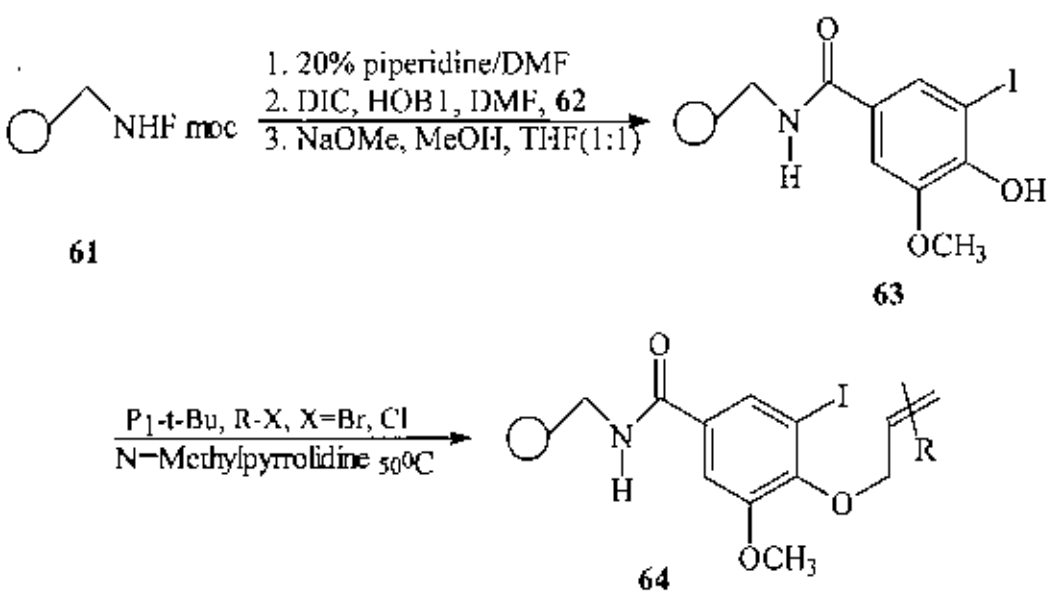
A higher yield 54% of 2-phenylbenzofuran **49** was obtained by using protected 2-iodophenol (as acetate).

The presence of a phosphine was found to be essential for the reaction. Although, other cuprous halides (cuprous bromide and cuprous chloride) as well as cuprous acetate could

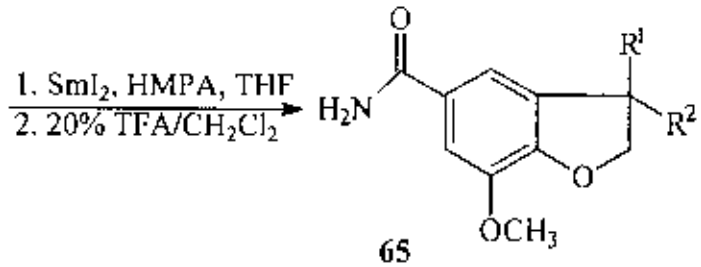
be used, cuprous oxide (which was used by Doad *et al*[69a]) was found to be ineffective. However, as far as heteroannulation was concerned, the reaction developed by Okuro *et al*[69b] was not of general nature (only one alkyne i.e. phenyl acetylene was utilized).

Recently progress in combinational library synthesis has focused on scope and limitation of reactions on solid support[70]. Few studies have been directed toward radical reactions on solid support[71], although they have emerged as a powerful synthetic strategy in solution in the past decade[72]. Balasubramanian *et al*[73] reported a study on tributyltin halide mediated radical cyclization on solid support to generate benzofuran and furan rings. R.W. Armstrong *et al*[74] reported an alternative synthesis of various benzofuran derivatives through SmI_2-mediated[75] aryl radical cyclizations on solid support[76,77]. The cyclization is mild, rapid and easy to carry out at room temperature. It thus offers an advantage over the harsher conditions used in tributyltin hydride-mediated synthesis of benzofuran derivatives in which heating to 80-100^{0}C for several hours to over night is usually needed[73,78]. Rink resin **61** was coupled to acid **62** (**Scheme-7**), the acetate group of the resin bound **62** could be clearly deprotectd by NaOMe in 1M MeOH/THF solution. Phenol **63** is readily coupled to a variety of allyl halides by using the Schwesinger base[79] P_1-t-Bu to generate **64**. Subsequent cyclization of **64** by SmI_2 and HMPA (is essential for the reaction on solid support) followed by TFA cleavage generated products **65**.

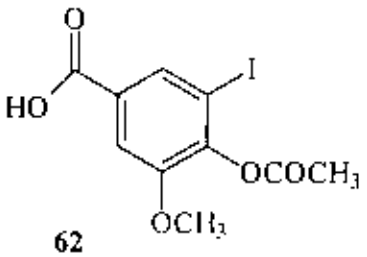
Scheme-7



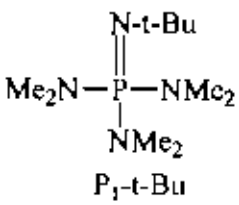
61 **63** **64**



65



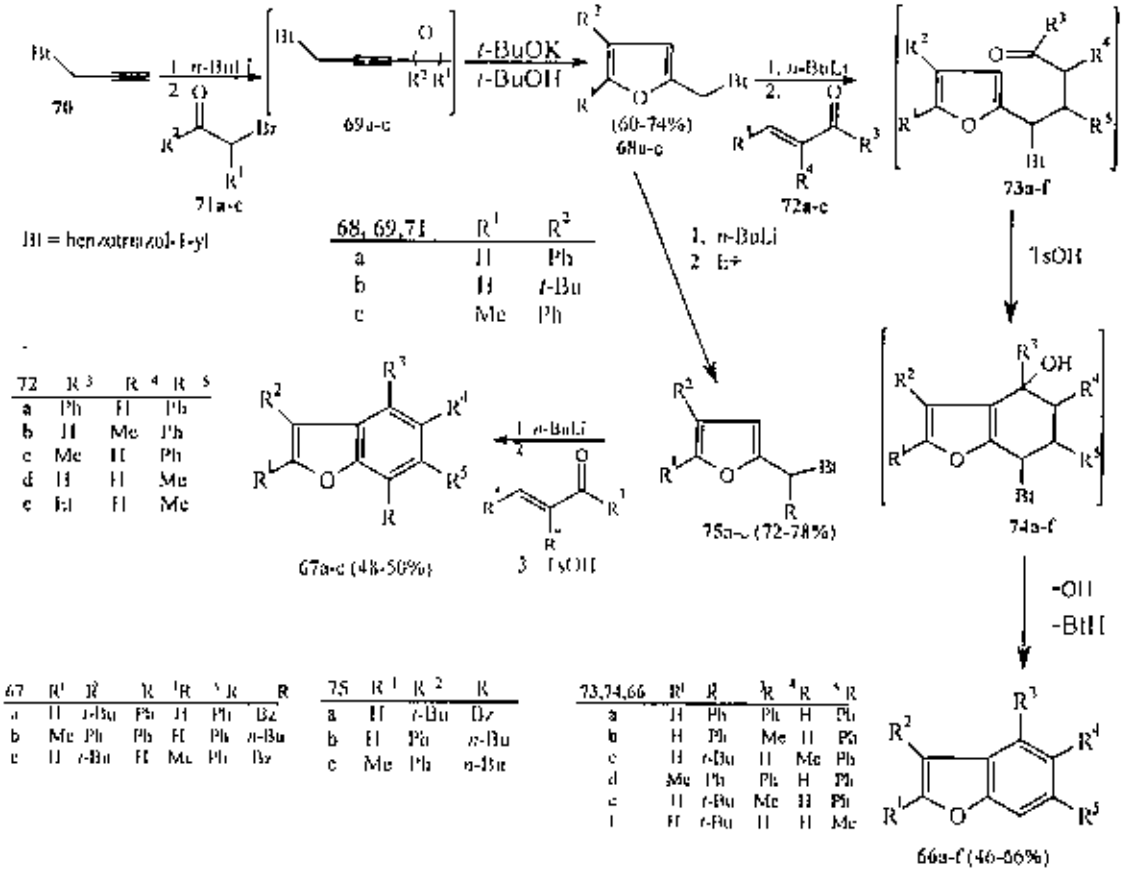
62



P_1-t-Bu

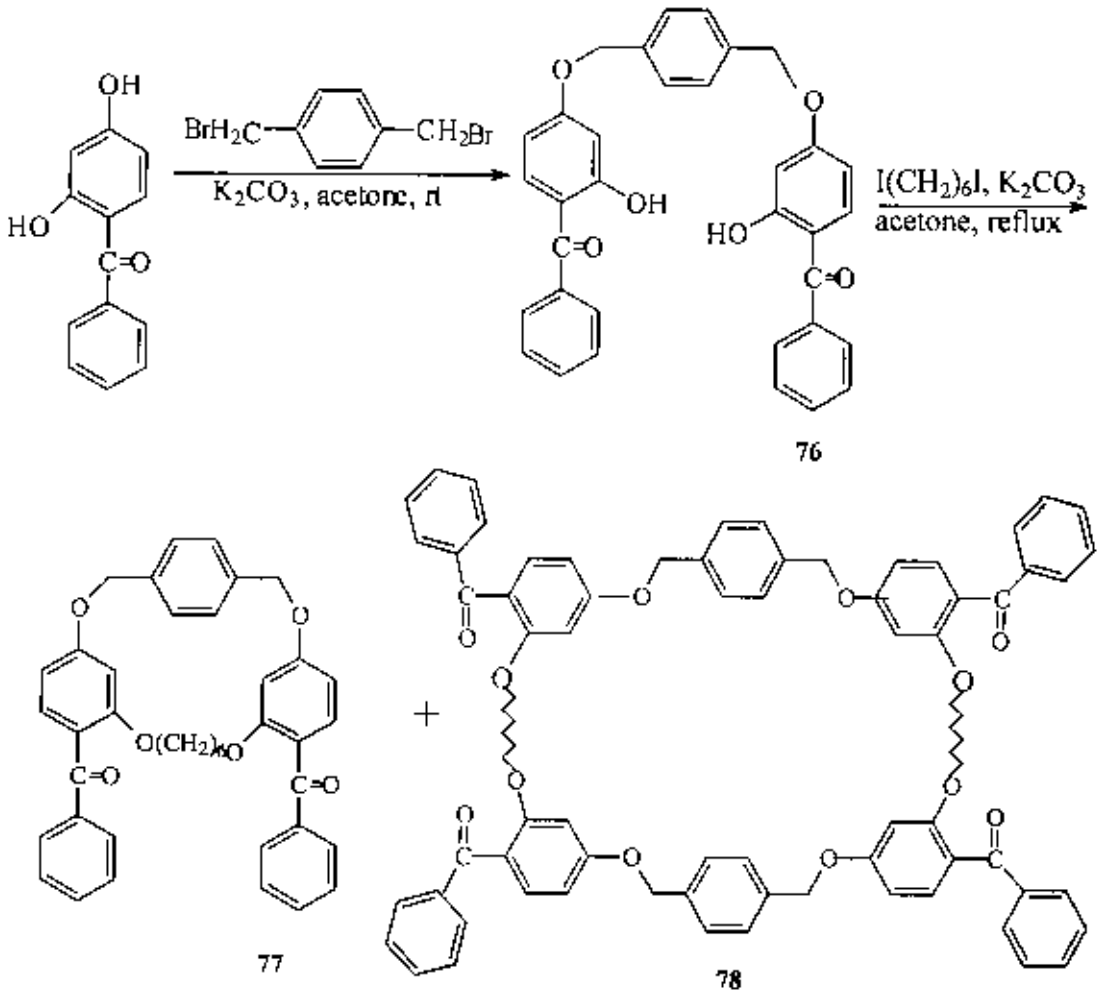
Various methods exist for the synthesis of benzo[b]furans[80] of which the intermolecular cyclization of a suitably substituted benzene is the most often employed[80n]. A.R. Katritzky *et al*[81] synthesized 2,3,5,6-substituted bezo[b]furans **66a** and 2,3,4,5,6-substituted benzo[b]furans **67a-c** by the intermolecular cyclization. When 2-(benzotriazol-1-ylmethyl)furans **68a-c** are readily available from alkynyloxiranes **69a-c**, themselves derived from 1-propergylbenzotriazole **70** and α-bromo ketons **71a-c**[82]. Treatment of **68a-c** with 1 equiv. of n-BuLi at - 78^{0}C, followed by 1 quiv. of α,β-unsaturated ketones or aldehydes **72a-e** gave 1,4-addition intermediates **73a-f**. The intermediates **73a-f** (obtained as mixtures of diastereisomers), without further purification were treated with *p*-toluene sulfuric acid in 1,4-dioxane under reflux to undergo intermolecular cyclization to intermediates **74a-f**. followed by spontaneous elimination of benzotriazole and water to give the benzo[b]furans 66a-f. They found that the best solvent was 1,4-dioxane; initial attempts to carry out these cyclization reactions in THF failed, probably due to the lower boiling temperature of THF. Alternatively the 2-(benzotriazol-1-yl)methyl moiety can be alkylated by lithiation of **68a-c** with 1 equiv of n-BuLi at -78^{0}C for 30 min, followed by reactions with n-butyl iodide or benzoyl bromide as electrophiles for 12h to give **75a-c** in good yields. Reactions of **75a-c** with α-β-unsaturated ketones followed by cyclization yielded polysubstituted benzo[b]furans **67a-c (Scheme-8)**.

Scheme-8

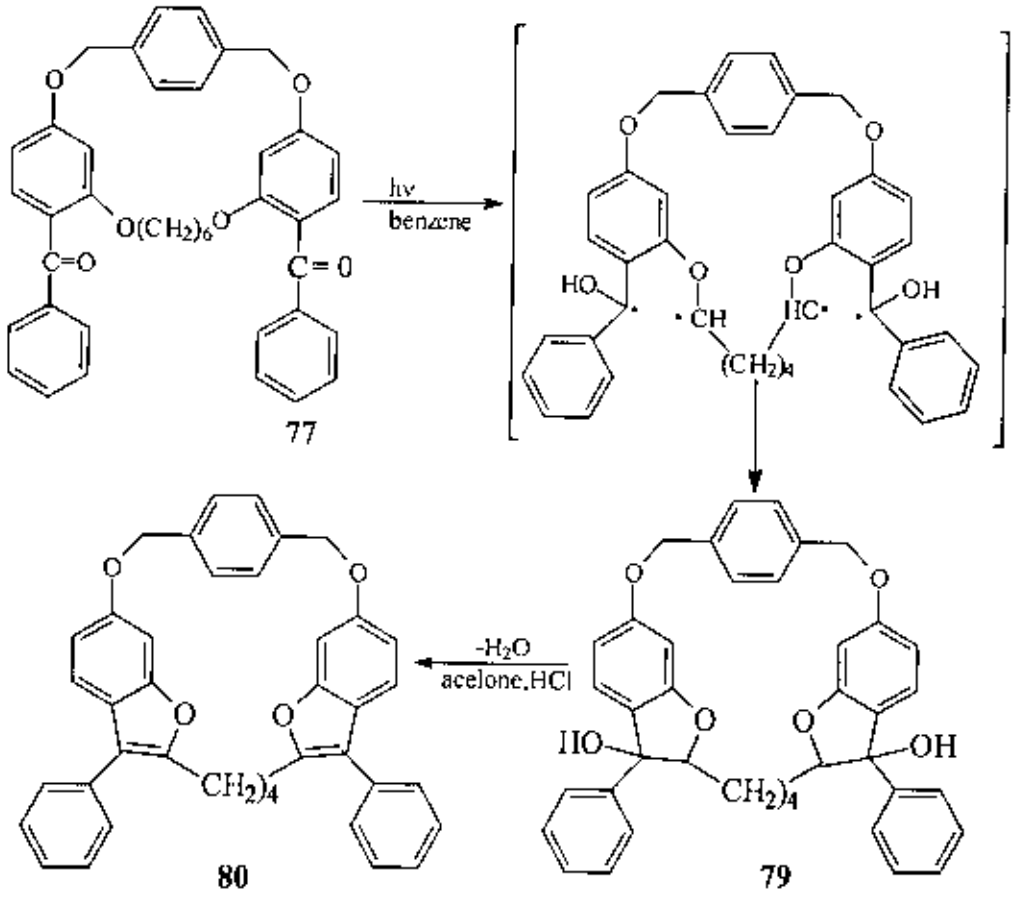


In 2000 K K. Park *et al*[83], described the synthesis of new macrocycles **77-78** utilizing 2,4-dihydroxbenzophenone as a connecting unit. Photochemical irradiation of **77** yielded benzo[b]furan ring-containing cyclophane **80** via intermolecular δ-hydrogen abstraction Schem-9 and Scheme-10. X-Rar analysis showed that **80** had a well defined rectangular cavity.

Scheme-9

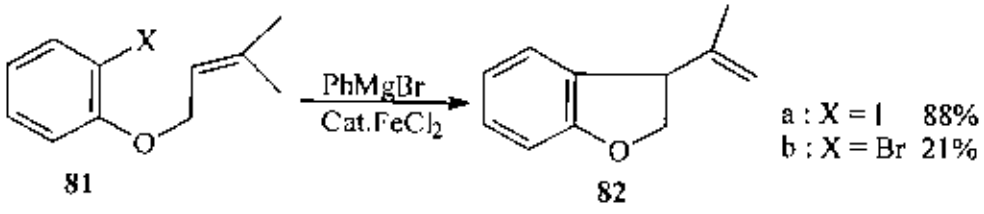

OH
HO
C=O
BrH2C
CH2Br
K2CO3, acetone, rt
O
OH
HO
C=O
I(CH2)6I, K2CO3
acetone, reflux
76
O(CH2)6O
77
78

Scheme-10



The radical cyclization of aryl iodide and aryl bromide bearing an alkenyl group was reported by K. Oshima *et al*[84]. Treatment of 2-iodophenyl prenyl ether **81** with PhMgBr in presence of catalytic amount of $FeCl_2$ provided benzofuran derivative **82** as a single product in 88% yield (**Scheme-11**). Saturated benzofuran derivative, 3-isopropyl-2,3-dihydrobenzofuran could not be detected in the reaction mixture. Cyclization of allyl 2-iodophenyl ether into a benzofuran derivative madiated by organozincate was also reported[85].

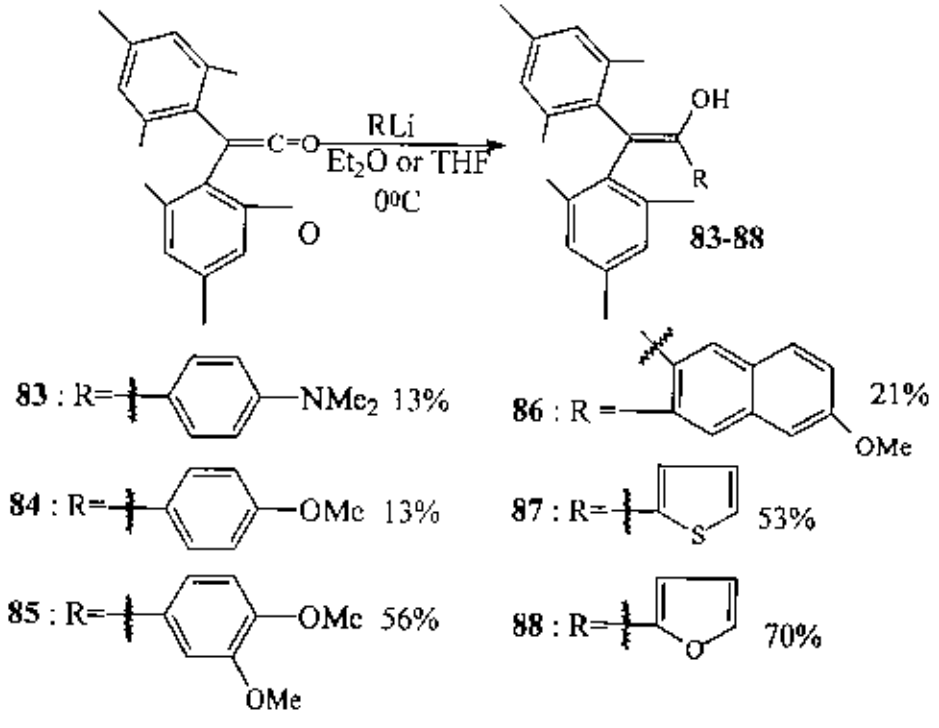
Scheme-11



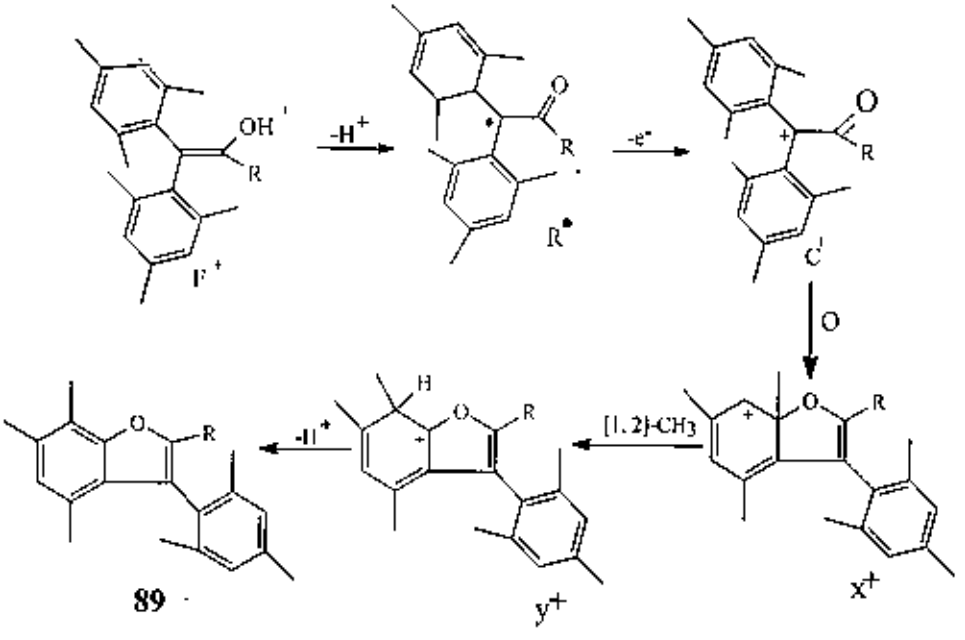
81 **82**

M. Schmittel *et al*[86] reported the synthesis and electro chemical investigation of six stable, simple enols **83-88** (**Scheme-12**) that were characterized by electron releasing substituents in α-position. Oxidative benzofuran formation from these enols was unusually slow because of key intermediate in the reaction, the dihydrobenzofuran cation X^+, was substantially stabilized vs rearrangement by the attached electron releasing substituents. The persistent cations X^+ were characterized by ^1H NMR and cyclic voltammetry and the kinetics of their rearrangement was followed by UV/vis. Notably upon one electron oxidation of X^+ to the radical dication, the formation of the benzofurans **89** was markedly accelerated by a factor of > 10^6 (**Scheme-13**).

Scheme-12

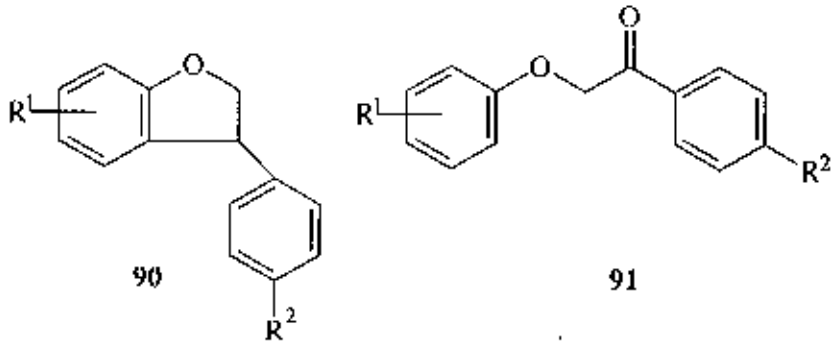


Scheme-13



Benzofuran derivatives were prepared[87] from α-chloro-α-(methylthio) ketones and phenols with *p*-cresol in CH_2Cl_2 in the presence of $ZnCl_2$ gave 78% of the corresponding $2-(2',4'-$dimethoxyphenyl)-3-(methylthio)benzo[b]furan. Reduction of which with Raney Ni in EtOH gave 92% of the corresponding $2-(2',4'-$dimethoxyphenyl) benzo[b]furan.

The preparation of 3-substituted benzofuran **90** from α-phenyl acetophenones **91** and related compounds using clay under microwave irradiation was described[88].



90 91

90, 91: R^1 = H, Me, Me_2CH, Br, EtO, Cl etc, R^2 = H, Me, Ph.

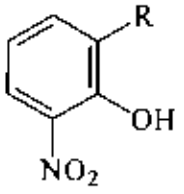
A solid phase synthesis of 3-arylbenzofurans were developed[89]. Polystyrene was sulfonated to give polystyrene supported benzenesulfonic acid. Treatment of the latter iodine/triphenylphosphine in benzene gave polystyrene-supported benzenethiol. Farther treatment of this with bromochloromethane/DBU gave polystyrene-supported [(Chloromethyl)thio]benzene condensation with (2-hydroxyphenol) phenyl methanone derivatives gave polystyrene-supported phenyl-[2-[(Phenylthio)methoxy]phenyl] methanone derivatives. Oxidation and epoxidation of the latter gave polystyrene-supported 2-phenyl-2-[2-[(phenylsulfonyl)methoxy]phenyl]oxirans. Cyclofragmentation of the latter gave the desired 3-aryl-benzofurans.

An efficient combinational route of substituted 3-phenyl benzofurans was achieved by the bromination of acetophenones to α-bromoacetophenones by polymer supported pyridinium bromide perbromide (PSPBP). The subsequent clean substitution of the obtained bromides by phenols using 1,5,7-triazobicyclo[4,4,0]dec-5-ene (TBD-P) and cyclodehydration of the resulting α-phenoxy-acetophenones using Amberlyst 15 affords pure products without the need for any chromatographic purification step.

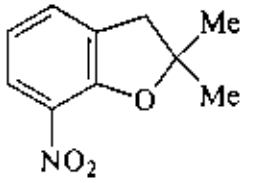
A new preparation of benzofurans was reported utilizing (trimethylsilyl)diazomethane[91]. 2-(Triisopropylsiloxy)aryl ketones and aldehydes smothly reacted with $Me_2SiC(Li)N_2$ to give [2-triisopropylsiloxy]phenyl acetylenes which were easily cyclized to benzofurans by treatment with $Bu_4N^+F^-$, 3-benzofuran methanols were obtanied when the reaction was conducted in the presence of carbonyl compounds.

A short and novel synthesis of unknown 3-alylbenzofurans was described[92]. Witting olefination of protected 2-hydroxybenzaldehydes followed by Claisen rearrangement resulted in the formation of 2-aryl-4-pentenals, which on deprotection and cyclodehydration gave 3-allylbenzofurans.

A facial synthesis of 7-nitro-2,3-dihydrobenzo[b]furan was reported by S.K. Kang *et al*[93]. Nitrophenols **92** were prepared and cyclized using $AlCl_3$ to give the title compounds **93**,



92



93

92 : R = allyl, $CH_2CMe : CH_2$, $CHMeCH : CH_2$, $CH_2 CH : CH$ Me

One pot synthesis method of benzofuran compounds was proposed by Z-L. Xu *et al*[93]. In the presence of base catalyst KF/Al_2O_3, the one pot reaction of 2-hydroxybenzaldehyde or 2-hydroxynapthaldehyde with Et-α-bromoacetate, α-bromoacetophenone, 4,4′-bis (chloromethyl)biphenyl and 1,5-bis(chloromethyl)napthalene gave the benzofuran compounds in 30-39% yield.

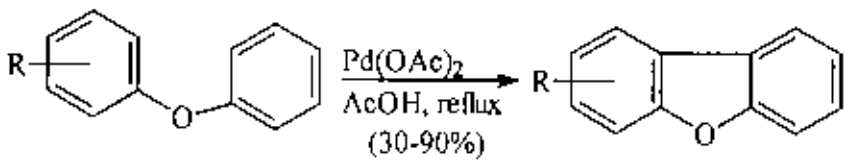
1.3 Palladium-Catalyzed Synthesis of Benzofurans:

Due to the versatility, availability and utility of organopalladium complexes, palladium is one of the most extensively used transition metal for synthetic purpose[94,95]. The recent trend is to develop palladium catalyzed heteroannulation procedure for the synthesis and functionalization of various heterocyclic moieties[94,95].

The initial reports of palladium catalyzed synthesis of benzofurans involved use of stoichiometric amount of costly palladium complexes. However, over the years, a number of very efficient catalytic systems has been developed, making the procedure competitive with the available methods of synthesis.

A stoichiometric palladium acetate catalyzed cyclization of diphenyl ethers **94** and related compounds in acetic acid was reported in 1975[96] **(Scheme-14).**

Scheme-14



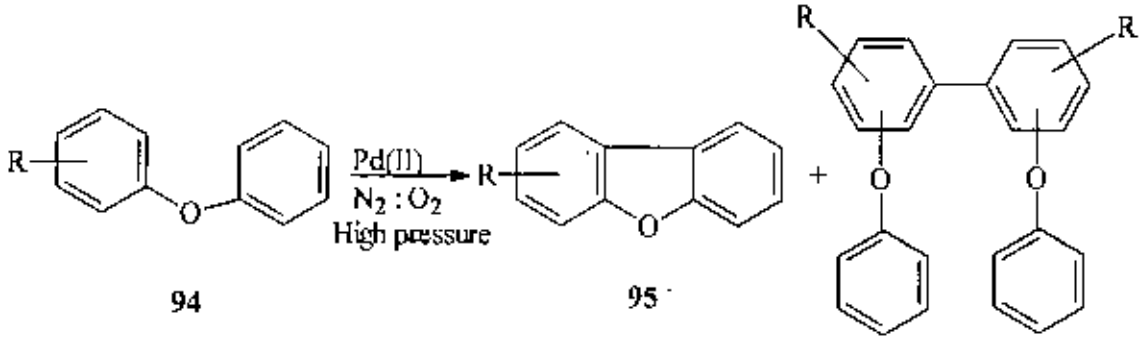
94 **95**

94:R = H

The rate of cyclization and required amount of palladium acetate were found to depend upon electron supply in the aromatic ring. In the presence of electron releasing groups cyclization was rapid (0.5–1h) and required one equivalent of the catalyst. Presence of electron withdrawing groups on the aromatic rings necessiated use of two equivalents of palladium acetate and the reaction took longer time ($\simeq$2 hours) to get completed. The reaction was found to be catalyzed by acids.

The palladium acetate catalyzed cyclization of diphenyl ethers **94** under acidic condition reported by Akermark *et al*[96] in 1975 required stoichiometric amounts of palladium acetate. It could be made catalytic by carrying out the reaction at high pressure in 1:1 mixture of nitrogen and oxygen[97]. However lack of selectivity led to intermolecular hydrogenative coupling to give **96** as a side product **(Scheme-15).**

Scheme-15

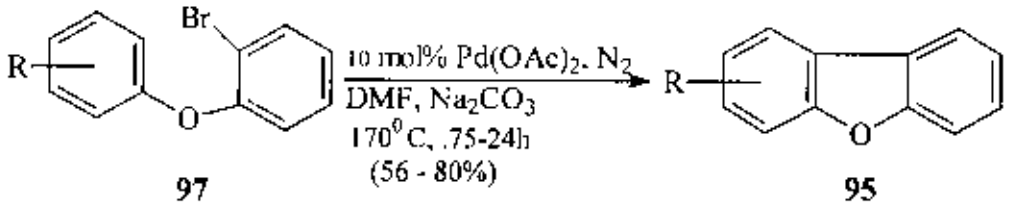


94 **95** **96**

A general procedure was reported[98] for cyclization of substituted 2-bromophenyl ethers **97** to obtain substituted dibenzofurans **95** under basic condition. The process required

only 10 mol% of palladium acetate and could tolerate electron withdrawing as well as electron releasing groups (**Scheme-16**).

Scheme-16

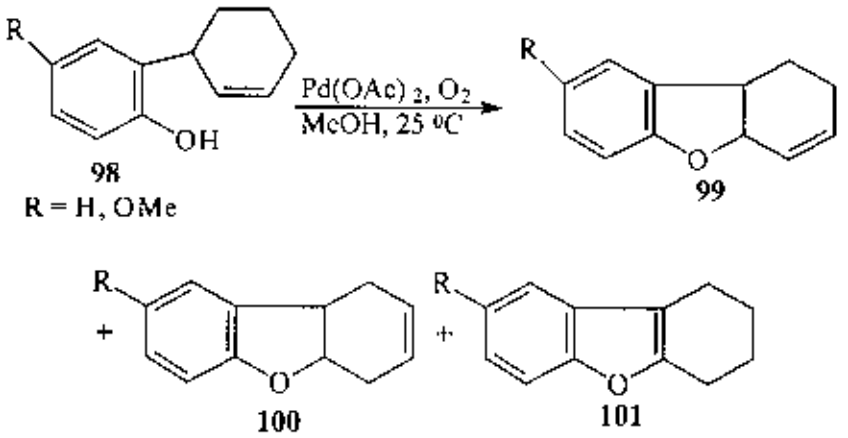


97 **95**

R = H, 2–NO_2, 3–NO_2, 4–NO_2, 4–OH–CH_2, 3–OH–CH_2, 4-COOH.

2-Allylphenols **98** having a cyclohexenyl moiety could be cyclized by an equimolecular amount of palladium acetate in methanol at room temperature and in the presence of air to give a mixture of cis-1,2,4a,9b-tetrahydrobenzofuran **99** and cis-1,4,4a,9b-tetrahydrobenzofuran **100** in 1:1 ratio, along with small amount of 2,3-butanobenzofuran **101 (Scheme-17)**[99].

Scheme-17



98
R = H, OMe

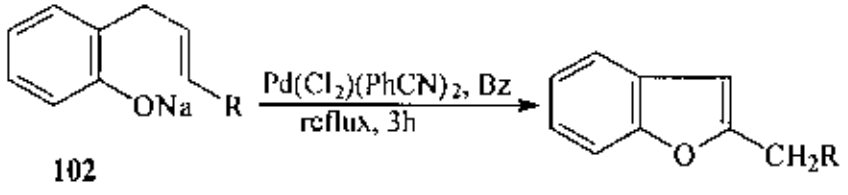
99 **100** **101**

The reaction could be carried out catalytically with respect to palladium catalyst in presence of oxygen (one atm.). For the production of one mole of cyclized product (**99** + **100** + **101**), 0.5 molar equivalent of oxygen was consumed under these condition; co-oxidants e.g. copper(II) were not required The distribution of the products (**99**, **100** and **101**) were found to depend upon substrate concentrations; e.g. in presence of excess substrate, the major product was **99**. Furthermore, addition of nine equivalents of cyclohexene was found to increase the proportion of **99** at the expense of **100** and **101**.

The observed change in product distribution was explained in terms of alternation of reaction palladium(II) species and interaction of palladium(II) complexes with olefins.

In 1973, Hosakawa *et al*[100] synthesized benzofurans **103**, **104** by refluxing sodium salt of 2-allylphenols **102** prepared from 2-allylphenol and sodium methoxide with a stoichiometric amount of dichlorobis(benzonitrile)palladium (**Scheme-18**).

Scheme-18



102

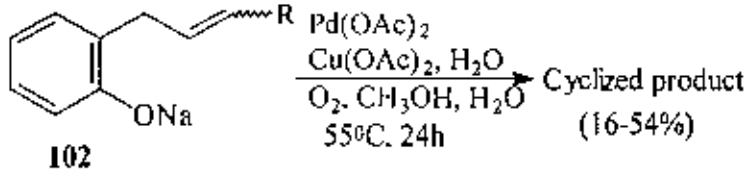
103, R = H (31%)

104, R = Ph (53%)

2-Propenylphenol could not be cyclized, indicating that cyclization proceeded not via first isomerization of starting olefin, but through coupling of oxygen and β-carbon of allyl group.

Later on, the cyclization was made catalytic by using palladium acetate, cupric acetate and oxygen[101] (**Scheme-19**). 2-Allylnaphth-1-ol did not undergo cyclization, but gave polymeric material, due to oxidation with oxygen.

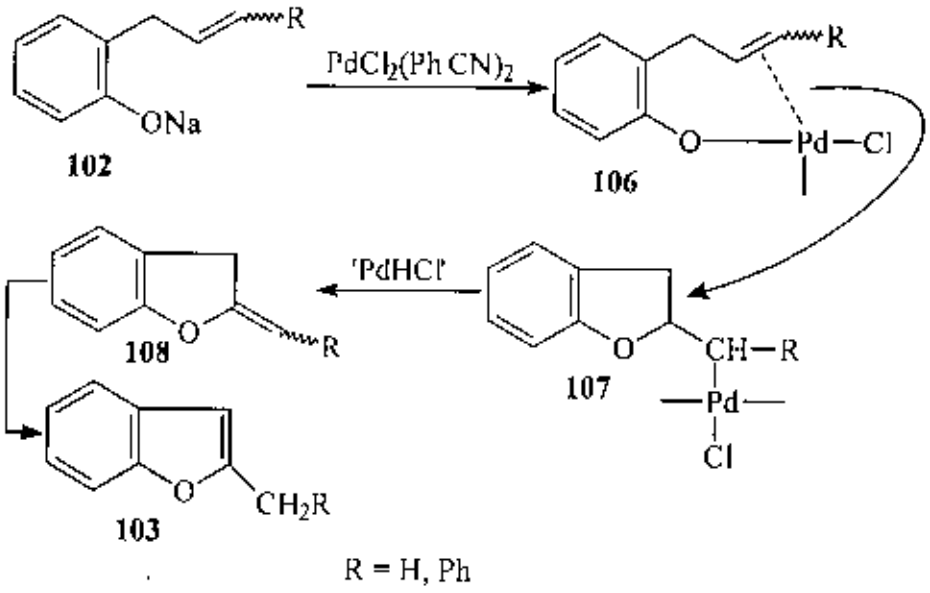
Scheme-19



102

The formation of cyclized products was explained by intramolecular oxypalladation followed by β-elimination of 'PdHCl' species (**Scheme-20**).

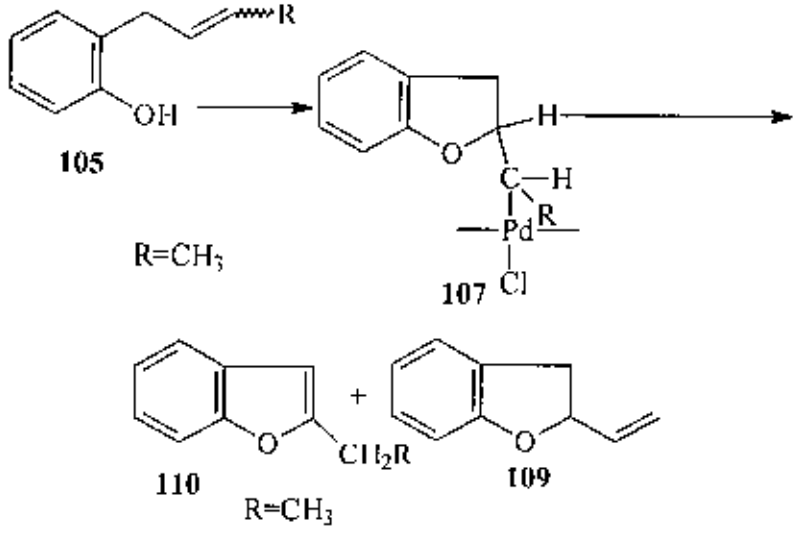
Scheme-20



R = H, Ph

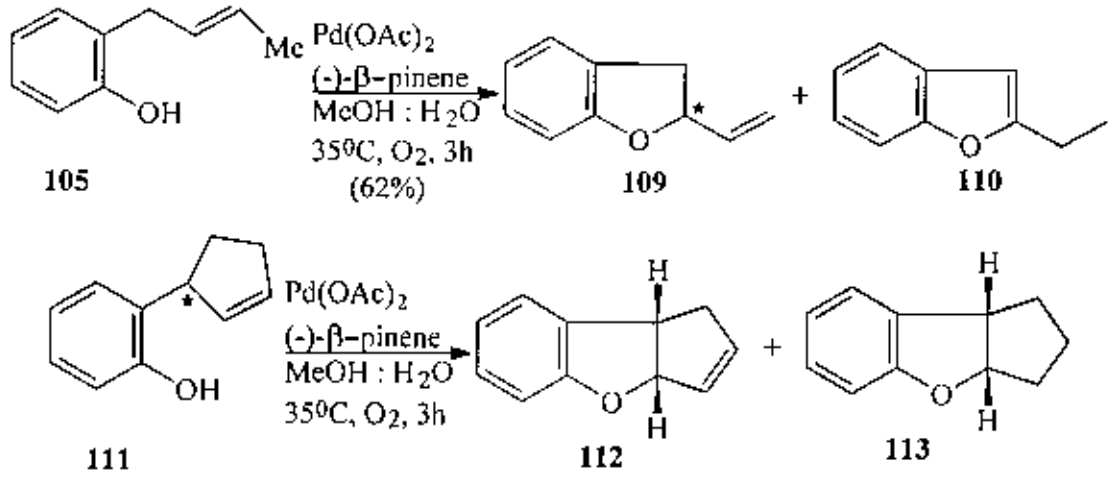
When R = H or Ph, the intermediate **107** showed that C-2 hydrogen was the only β-hydrogen that could be eliminated as 'PdHCl'. However when R = CH_3, two β-hydrogens were available. Predominance of unsaturated product **109** was in sharp contrast to stoichiometric cyclization, where 2-ethylbenzofurans **110** was the main product (**Scheme-21**).

Scheme-21



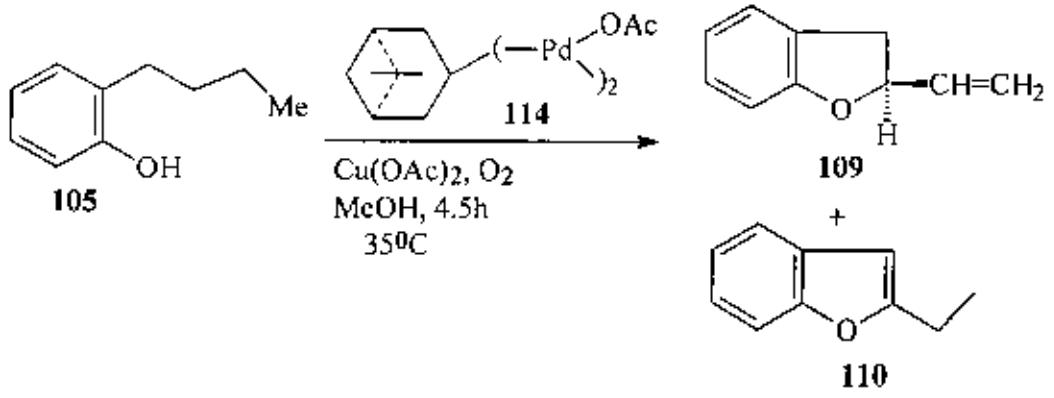
Hosokawa *et al*[102] reported a palladium(II) catalyzed asymmetric synthesis of 2,3-dihydrobenzofurans from 2-allylphenols **105** and **111** by using a catalytic amount of β-pinene as the source of chirality. The catalytic system consisted of 10 mol% palladium acetate, 10 mol% (–) β-pinene and one equivalent of cupric acetate. 19:1 (v/v) Methanol in water was used as solvent and the reaction was carried out at 35^{0}C under oxygen (**Scheme-22**). When an excess of β-pinene was used, no cyclization occurred with **105** as substrate; whereas (±)-2-(cyclopent-2-enyl)phenol **111** reacted with palladium acetate even in the presence of excess β-pinene.

Scheme-22



To gain an insight into the mechanism, the intramolecular cyclization of trans-2-(2-butenyl)phenol **105** was studied with 10 mol% (+)-(2,3,10-η-pinene)palladium(II) acetate **114** and 10 mol% cupric acetate in the presence of oxygen as effective catalytic system[103]. An overall yield of 77-81% was obtained as shown below in (**Scheme-23**).

Scheme-23



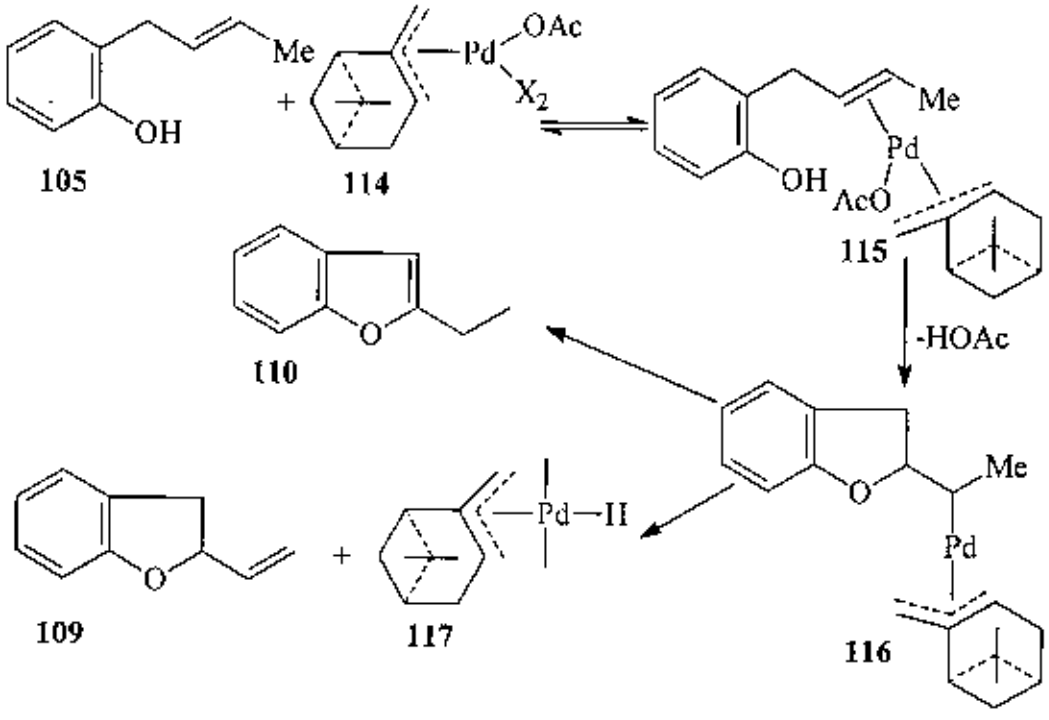
109 : 110 = 83 : 17

No cyclization occurred in coordinating solvents e.g. DMF or pyridine, while the reaction proceeded sluggishly in benzene, THF and acetic acid. The reaction was thought to proceed via reversible coordination of the substrate **105** to the dimeric palladium complex **114** to form the monomeric palladium(II) acetate **115**. Intramolecular nucleophelic attack by the phenoxy group and simultaneous removal of acetate ligand as acetic acid led to the oxypalladation species **116**. A look at this species showed the presence of two β-hydrogens making the following two pathways possible:

(i) Elimination of a β-hydrogen from the methyl group of **116** gave the product **109** and Pd-H species **117**.

(ii) Elimination of β-hydrogen from C-2, followed by rearrangement gave **110** (**Scheme-24**).

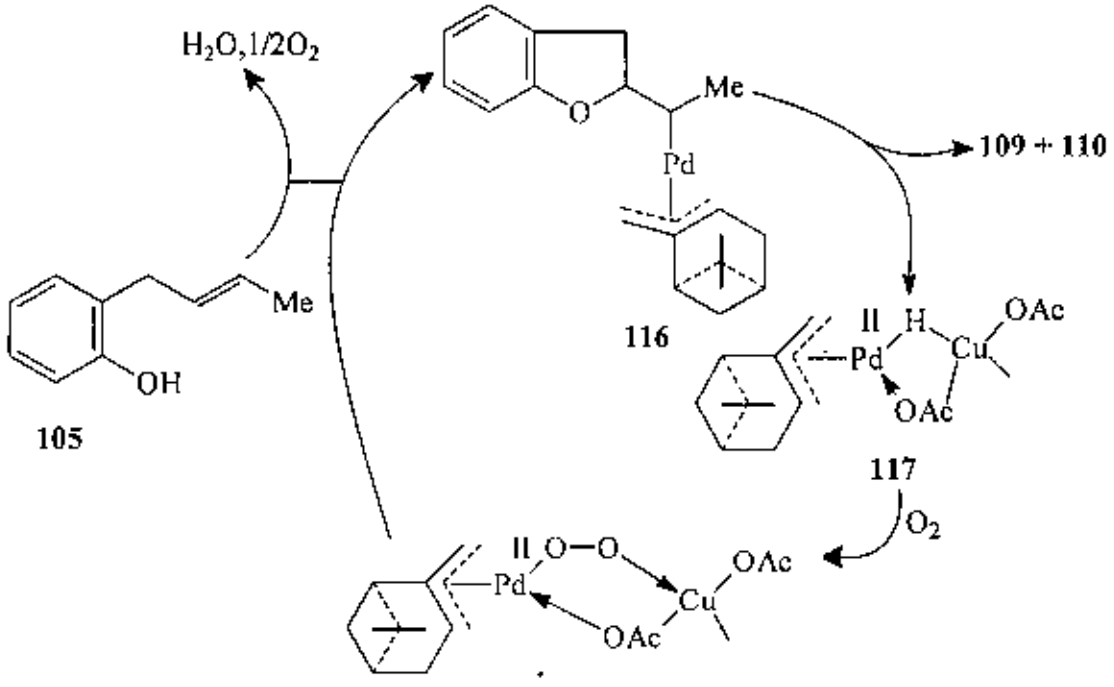
Scheme-24



The role played by cuprous acetate was not clear. The acetate ion may interact with palladium(II) due to its ready availability to form bridging legands.

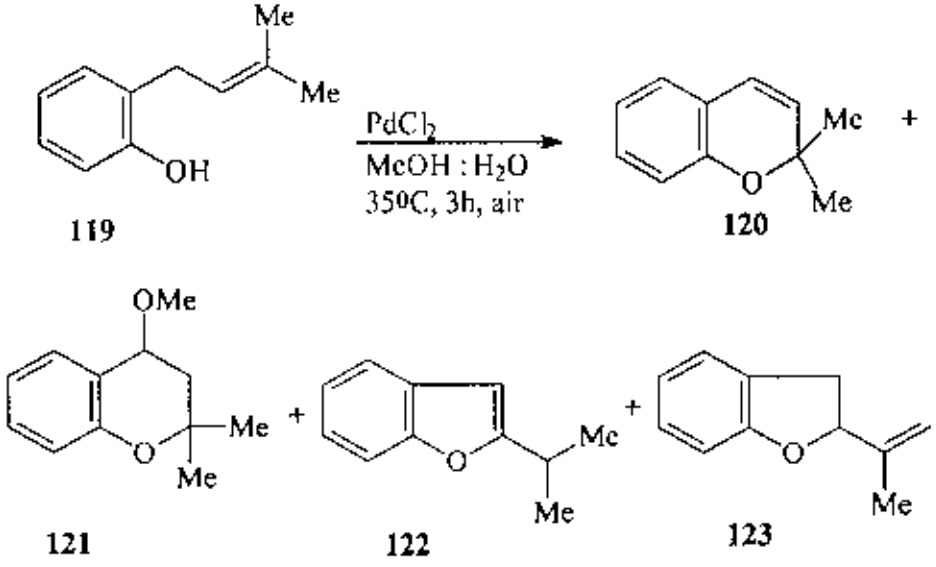
The regeneration of catalytically active species involved oxygenation of Pd-H bond in **116**. Thus formed palladium(II) hydroperoxide was supposed to be a Pd-Cu bimetallic complex, since regeneration of active catalyst required cupric acetate as well as oxygen. The presence of acetate bridge in **117** was supported by the experimental observation that reactivity and enantioselectivity were influenced by steric and electronic factors of the carboxylate ligands associated with copper (II) (**Scheme-25**).

Scheme-25



2-(3-Methyl-2-butenyl)phenol **119** underwent palladium chloride catalyzed to give 2,2-dimethylchromone **120** and 2,2-dimethyl-4-methoxychroman **121** as the predominant products along with < 2% 2-isopropylbenzofuran **122** and 2-isopropenyl-2,3-dihydrobenzofuran **123** (**Scheme-26**)[104].

Scheme-26



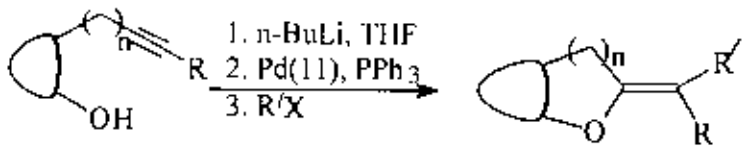
(**120** : **121** = 32:11)

Formation of these products could be explained by nucleophilic attack by phenoxy group at 2 or 3 position of the allylic side chain. Use of nitrogen or argon instead of air led to poorer yields although the relative ratios among the cyclized products did not change. While the presence of sodium salt of carboxylic acids bearing electron-withdrawing substituents resulted in predominant formation of six-membered products; addition of sodium salts of carboxylic acids bearing electron donars led to formation of benzofurans **122, 123** and six membered products **120, 121** in equal amounts.

Addition of sodium acetate or use of palladium acetate resulted in non-formation of **121**. Increase in the amount of sodium acetate added led to higher overall yield accompanied by an increase in the presence of **123**. These result were ascribed to change in palladium(11) species through coordination of sodium carboxylate to palladium. The resulting change in electron density of palladium seemed to affect the regioselectivity.

2-Alkylidenetetrahydrofurans and pyrans were synthesized by treating alkyl or aryl acetylenic alcohols **124** with n-butyl lithium in THF at 0^0C followed by addition of a solution of 10 mol% palladium acetate or palladium chloride and triphenylphosphine in THF and one equivalent of organic halide (**Scheme-27**). The reaction was highly regio and stereoselective[105].

Scheme-27

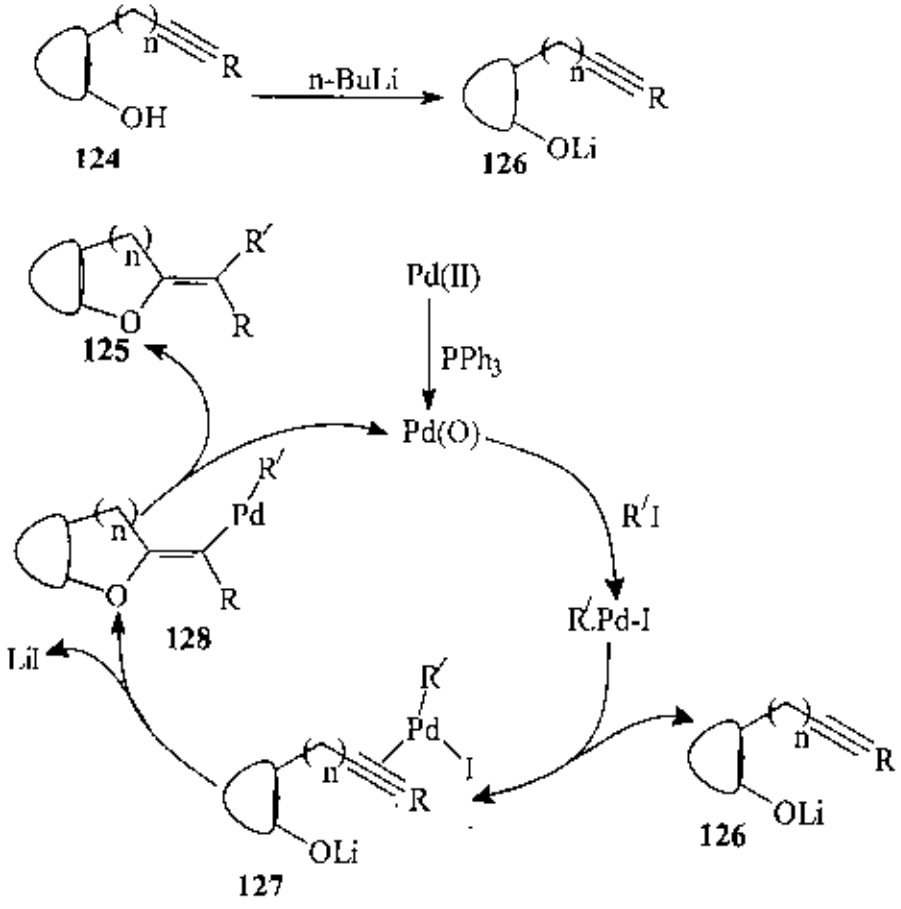


124 n = 1, 2 **125**
R = H, n-Bu, Ph
R/= Me, Ph, $PhCH_2$-, 2-thienyl

While palladium(II) catalysts like palladium acetate and palladium chloride were found to be effective, use of palladium(0) catalysts e.g. $(Ph_3P)_2PdCl_2$ and $Pd(PPh_3)_4$ resulted in poor yields. Use of chloroform, DMF, toluene or benzene instead of THF led poor yields (<3%). Most probably, palladium(II) consumed the excess n-butyllithium lowering the basicity of the reaction medium and thus minimizing the double bond migration in the initial products. Palladium(0) could not have done this.

The mechanism proposed by Luo *et al*[105] (**Scheme-28**) involved the following steps:

Scheme-28



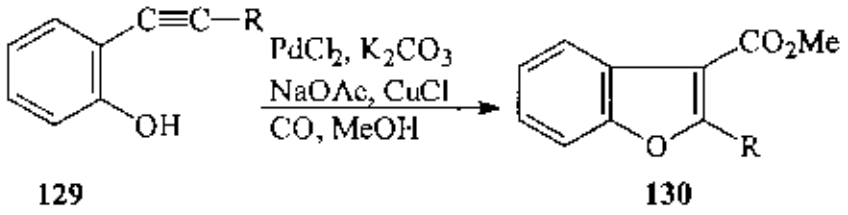
(i) Abstraction of proton from the alcohol **124** by n-BuLi.

(ii) Oxidative addition of organic halide to Pd(0) to form a σ-alkylpalladium halide complex. The latter underwent complexation with triple bond to produce **127**.

(iii) Reductive elimination from **128** gave the product **125** and Pd(0) was regenerated.

Carbonylation of 2-acetylenic phenols **129** with carbonmonoxide in methanol containing sodium acetate, cuprous chloride and palladium chloride led to intermolecular cycloaddition to give benzofurans **130** (**Scheme-29**)[106].

Scheme-29

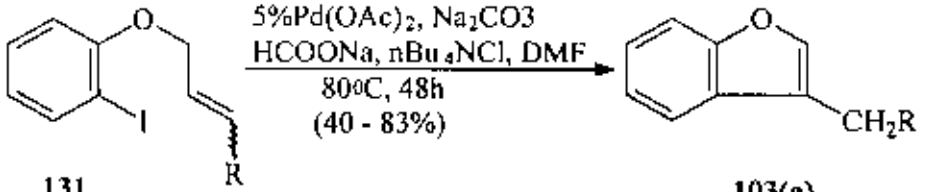


129 **130**

R = n-Bu, Ph

In 1988, Larock and Stinn[107] found that 2-iodoaryl allyl ethers **131** could be cyclized into 3-substituted benzofurans **103(a)** in the presence of 5% palladium acetate under phase transfer condition (**Scheme-30**).

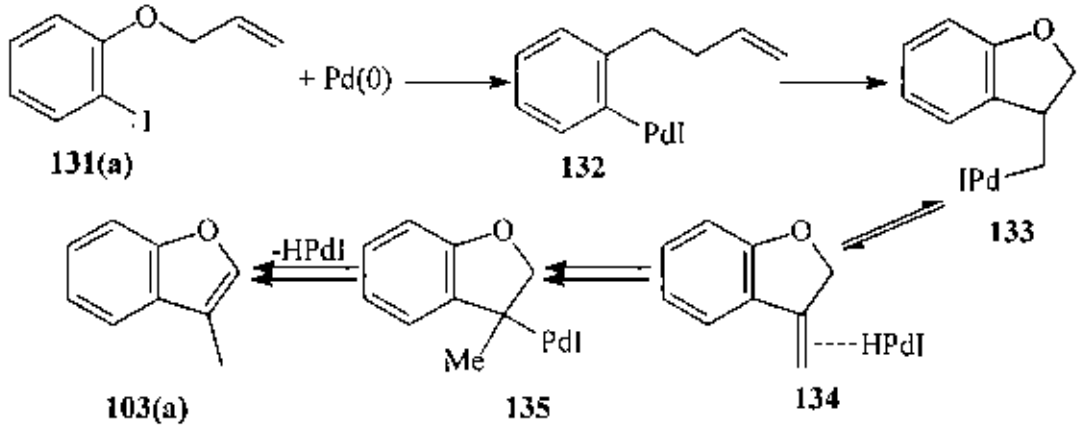
Scheme-30



131 R = CH_3, Ph **103(a)**

It was found that the yields of benzofurans **103** decreased with less hindered double bond and with better aryl leaving groups. The observation was consistent with the idea that insertion into the C-O bond was the major side reaction. The formation was thought to reduce a π-allylpalladium intermediate formed by C-O insertion and thus keeping the palladium(0) catalyst active. A mechanism was forwarded (**Scheme-31**)

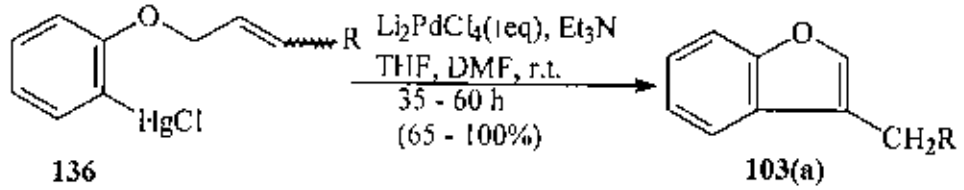
Scheme-31



131(a) **132** **133** **103(a)** **135** **134**

The palladium(II) catalyzed cyclization of analogus arylmercurials **136** were examined with an idea to improve the yield. Although, the yields were better (65-100%), the procedure required stoichiometric amounts of lithium tetrachloropalladate (**Scheme-32**)

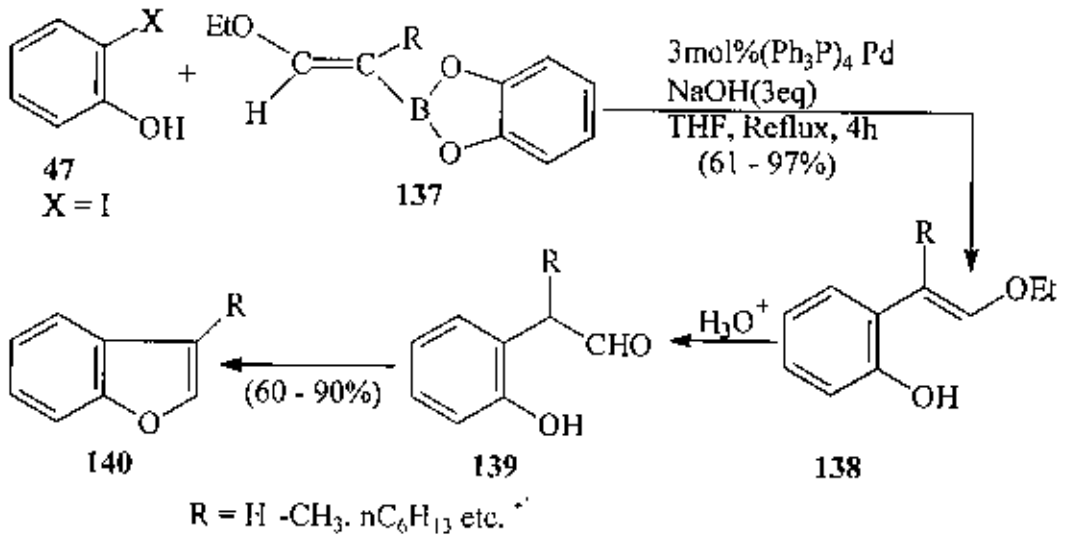
Scheme-32



136 **103(a)**

Palladium catalyzed cross coupling between (1-ethoxy-1-alken-2-yl)boranes **137** and 2-iodophenol **47** gave ortho-functionalized styryl ethers **138** in high yields. The latter could be converted into 3-substituted benzofurans **140** by cyclodehydration under acidic condition[108] (**Scheme-33**). The reaction could be utilized for the synthesis of indoles as well.

Scheme-33



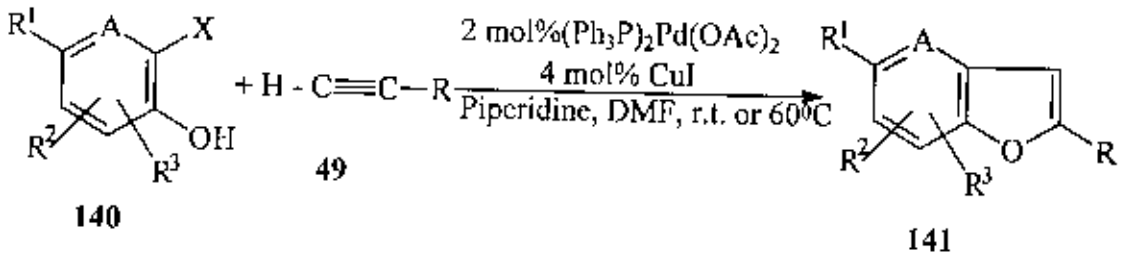
47 **137**
X = I

140 **139** **138**

R = H -CH_3, nC_6H_{13} etc.

Arcadi *et al*[109] found that when 2-hydroxyaryl or 2-hydroxyheteroaryl halides **140** were treated with terminal alkynes **49** in the presence of a base, $(Ph_3P)_2Pd(OAc)_2$ and cuprous iodide at room temperature or at 60°C. 2-substituted benzoburans **141** were obtained in good yields. The reaction could accommodate a variety of functional groups, both in the phenol and in the alkyne moiety. Piperidine was found to give the best results. Other bases like sodium acetate gave moderate yields, while use of n-tributyl amine led to Michael adduct in poor yields (**Scheme-34**).

Scheme-34



140 **49** **141**

A = CH, N

X = I, Br

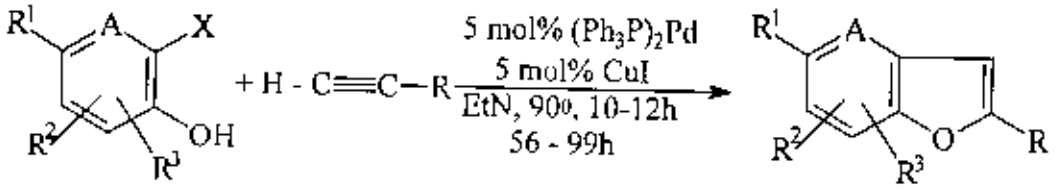
R^1 = H; R^2 = H, 2-Me, 1–CHO

R^3 = H, 3–OMe

R = $-C_4H_9$(n), C_6H_5, $-CH_2OH$, $-CH(OH)C_6H_5$ etc.

Latter, Torri *et al*[110] treated 2-hydroxylaryl on 2-hydroxyheteroaryl iodides **140** with terminal alkynes **49** in the presence of bis (triphenylphosphine) palladium (II) chloride (5 mol %) and cuprous iodide in triethylamine at 90°C for 10–12 hours, to obtain 2-substituted benzofurans **141** in 56 – 99% yields (**Scheme-35**).

Scheme-35



140 **141**

A = CH, N

X = I

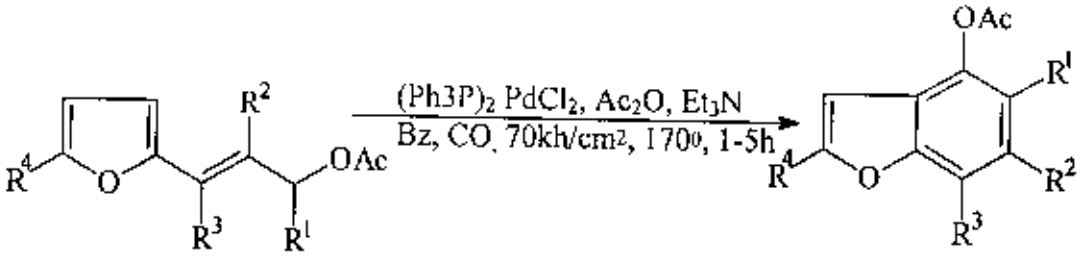
R^1 = H, Me, Cl

$R^2 = R^3$ = H; R = $-CH_2OTHP$, $-CMe_2OH$, $-C_6H_{13}$, Ph etc.

Cyclocarbonylation of 3-furylallyl acetates **142** in the presence of acetic anhydride, triethylamine and a calalytic amount of bis(triphenylphosphine)palladium(II) chloride at 130 – 170°C under 50 –70 atmospheric pressure of carbon monoxide was found to give acetoxybenzofurans **143** (**Scheme-36**). 3-(3-Furyl)allylacetate was found to cyclize selectively at the 2-position of the heterocyclic nucleus to give 7-acetoxybenzofuran. Reaction temperature >130°C was necessary to obtain high yield. At lower temperature,

side reactions gave unidentifiable high boiling by products. Triethylamine and acetic anhydride were used to esterify *in situ* the phenols produced.

Scheme-36

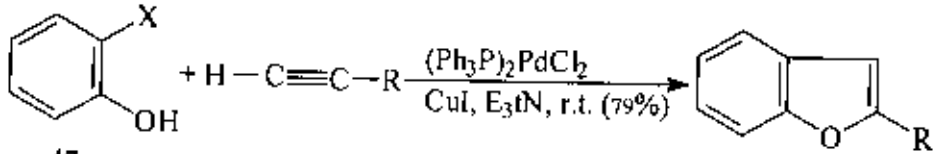


142 **143**

Secondary allyl acetate **142** ($R^1 = CH_3$, $R^2 = R^3 = R^4 = H$) did not undergo cyclocarbonylation due to elimination of acetic acid and polymerization of the resulting diene. Furtheremore γ-substituted allyl acetate **142** ($R^1 = R^2 = R^4 = H$, $R^3 = CH_3$) gave poor yield due to diene formation and subsequent polymerization.

It was found that 2-bromophenol **47** (X = Br) reacted with terminal acetylenes like phenylacetylene **59** (R = Ph) at room temperature, in the presence of a base, bis(triphenylphosphine)palladium(II) chloride and cuprous iodide[111] (**Scheme-37**) to give 2-substituted benzofruans **144**.

Scheme-37

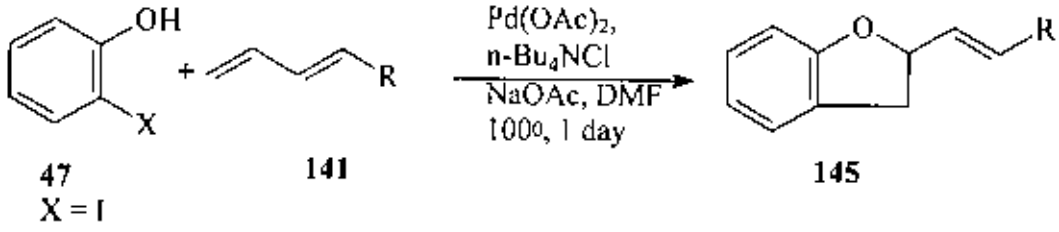


47 **59** **144**

X = Br R = Ph

Heteroatom-containing aryl iodides have been found to react with 1,3-dienes in the presence of a palladium catalyst and appropriate base to afford a variety of oxygen and nitrogen heterocycles. The catalytic system developed by Larok *et al*[112] to effect this reaction consisted of 5% $Pd(OAc)_2$ or $Pd(dba)_2$, one equivalent n-Bu_4NCl, 3.5 equivalent of appropriate base, with or without triphenyl phosphine (**Scheme-38**).

Scheme-38



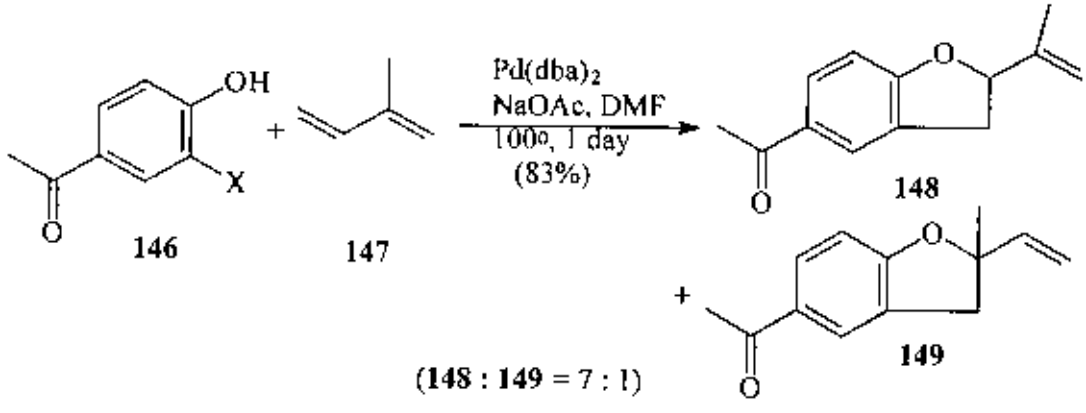
47
X = I

141

145

No single base was found to give best results consistently. A variety of 2-substituted aryl halide were found to undergo heteroannulation. Phenols having election withdrawing constituents were found to give higher yields. Even sensitive groups like aldehydes or ketones did not hampar the reaction. The reaction could be utilized as the most direct route to tremetone **148**, a toxic ketone isolated from white snake root and fomannoxin **151** a known phytopathogen (**Scheme-39**)

Scheme-39



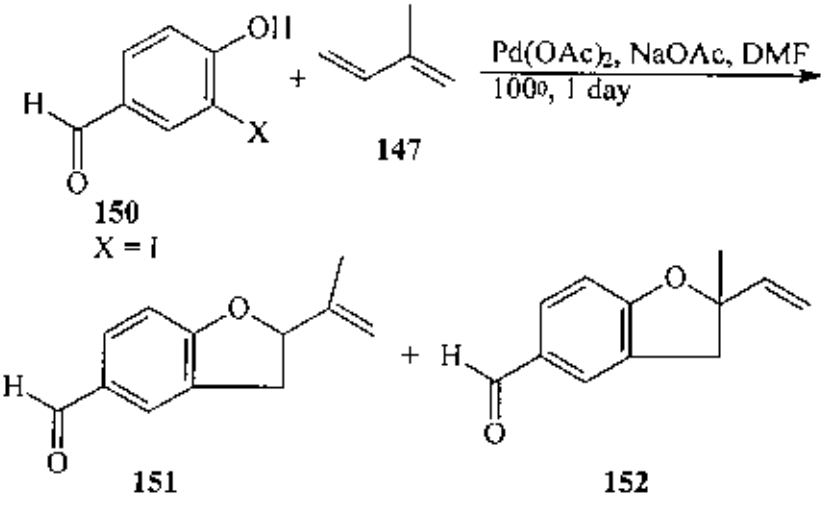
146

147

148

149

(148 : 149 = 7 : 1)



147

150
X = I

151

152

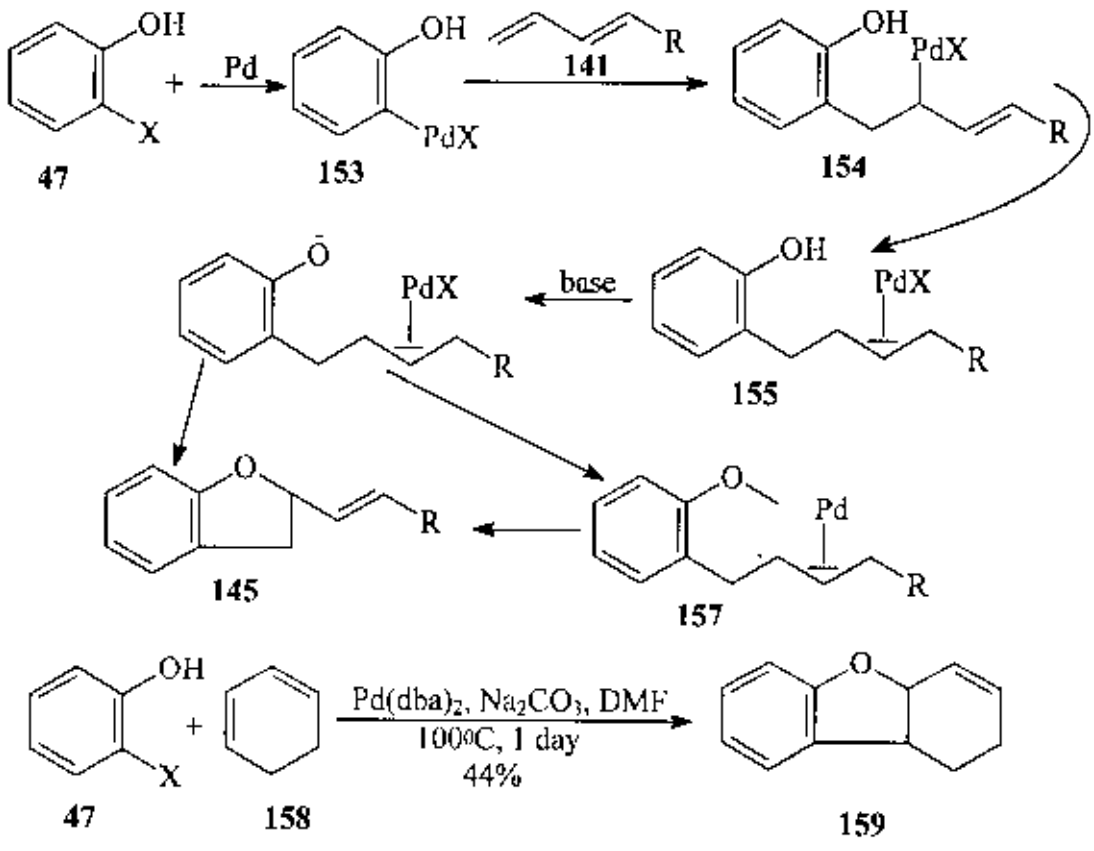
A possible mechanism was forwarded which required the reaction to proceed via aryl **153** and π-allyl palladium intermediates **155**. From the acyclic dienes the intermolecular palladium displacement may occur via

(i) path A - direct back side displacement or

(ii) path B - front side halide displacement and subsequent reductive elimination.

Formation of **159** from the reaction of 2-iodophenol **47** indicated the predominance of path B for the formation of five membered rings (**Scheme-40**)

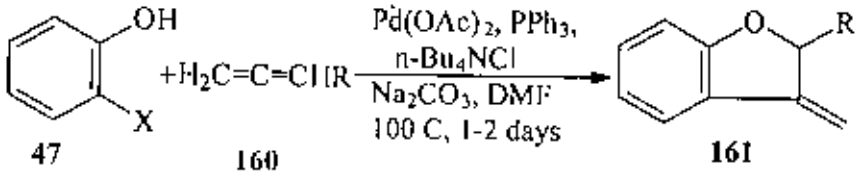
Scheme-40



Recently, aryl halides possessing a heteroatom or potential carbanion containing a functionality in the 2-position were found to undergo regioselective reaction with 1,2-dienes, in the presence of a palladium catalyst and a carbonate base, to give five and six membered cyclic compounds in heigh yields[113]. Regioselectivity of this annulation procedure was very high; most unsymmetrically substituted 1,2-dienes gave only one regioisomer. The formation of five membered ring involved exclusive annulation across the more highly substituted carbon-carbon double bond.

For the heteroannulation process 5% each of palladium acetate and triphenylphosphine, 1 equivalent of n-tetrabutyl ammonium chloride and 3 equivalent of carbonate base with DMF as solvent was found to give the best results (**Scheme-41**).

Scheme-41



47 160 161

Y. Nan *et al*[114] reported an efficient new synthetic technology for the synthesis of 2,3-disubstituted benzo[b]furans. A highly effective cocatalysis system (PdI_2-thiourea and corbon tetrabromide) was developed for carbonylative cyclization of both electron rich and electron deficient o-hydroxylarylacetylenes to the corresponding methyl benzo[b]furan-3--carboxylates.

The Pd-catalyzed reaction of 2-alkynylphenols with tertiary propargyl carbonates yielded 2-substituted-3-allenylbenzo[b]furans in moderate to good yields[115]. That heteroanulation promoted by a σ-allenylpalladium complex proceeded under nentral conditions.

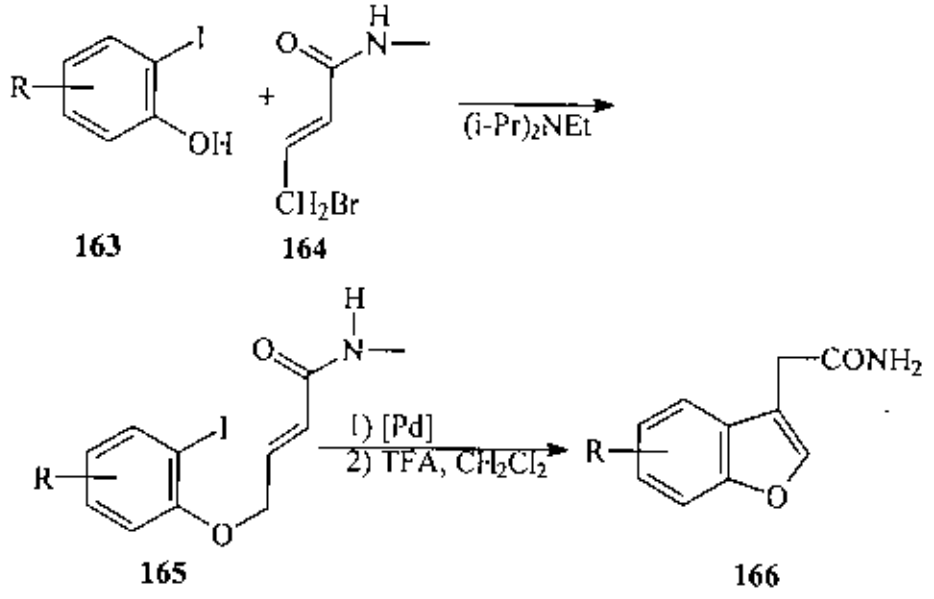
The Pd-catalyzed cross-coupling of *o*-allylic and *o*-vinylic phenols with vinylic halides and triflates produced substituted dihydrobenzopyrans and dihydrobenzofurans respectively in good to high yields[116]. The proposed mechanism involves vinylpalladium addition to the olefin, rearrangement to a π-allylpaladium intermediate and subsequent intermolecular nuclephilic displacement of palladium.

Substituted 2-methylbenzofurans were obtained from 2-allylphenols via Pd^{2+} catalyzed oxidative cyclization using $Cu(OAc)_2$- LiCl as a reoxidant and wet DMF as a solvent[117].

The Pd-catalyzed annulation of silyl-protected alkynols with $2\text{-}IC_6H_4OH$ gives silyl-protected (3-hydroxyalkyl) benzofurans[118]. The use of silyl-protected propynols bearing a free OH or an OFt_3Si protective group resulted in the formation of 1-oxa-2-silyclyclopent-3-enes as a major products. Removal of the silyl protective groups affords 3-(hydroxyalkyl)benzo[b]furans in good yields.

H.-C. Zhang *et al*[119] reported construction of indole and benzofuran synthesis on the solid phase via palladium mediated cyclization. Alkylation of the substituted 2-iodophenol **163a,b** with resin-bound alkylating agent **164** gave the resin-bound cyclization precursors **165a,b**, respectively. Palladium mediated intramolecular cyclization of **165a,b** followed by cleavage with 30% TFA in CH_2Cl_2 afforded the desired benzofuran derivatives **166a,b** with excellent yields (**Scheme-42**). The purity was tested by HPTC.

Scheme-42



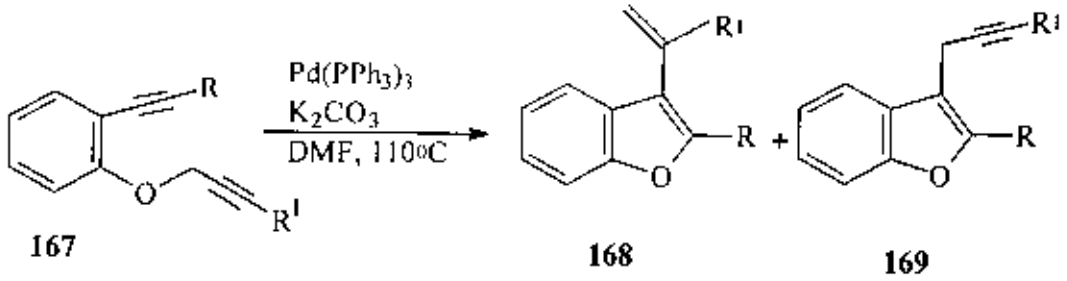
163 **164** **165** **166**

a : R = H (purifuid yield = 83%)

b : R = 5,5-di-Cl (Purified yield = 81%)

In 1998 S. Cacchi *et al*[120] reported 2-substituted-3-allylbenzo[b]furans through the palladium catalysed cyclization of propargylic-*o*-(Alkynl)phenyl ethers. They reported their preliminary results on the conversion of **167** into the 3-allynylbenzo[b]furans **168** (**Scheme-43**). The starting propargylic *o*-(alkynyl)phenyl ethers **167** have been prepared from *o*-alkynphenols **170** according to the sequence outline in (**Scheme-44**), through a one pot protocol which usually gives better results than the stepwise procedure.

Scheme-43

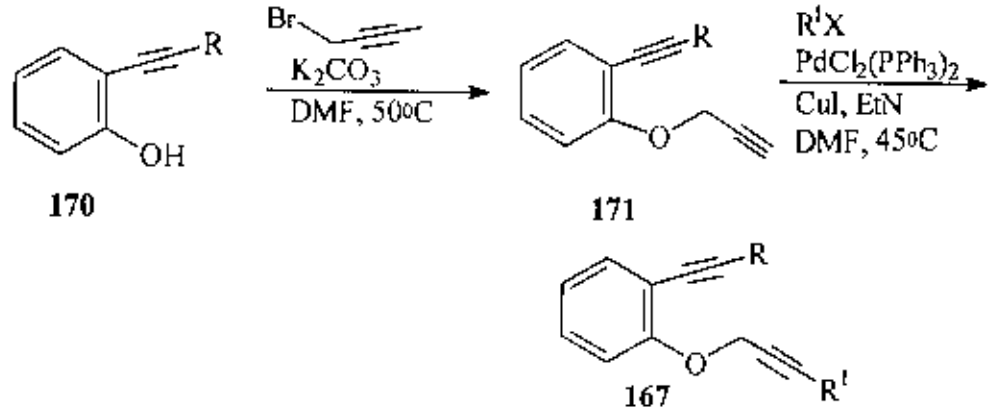


167 **168** **169**

R = Ph, n–C_5H_{11}, p –MeO–C_6H_5 etc.

R^1 = p –Me–C_6H_4, p – $MeOC_6H_4$, Ph etc.

Scheme-44



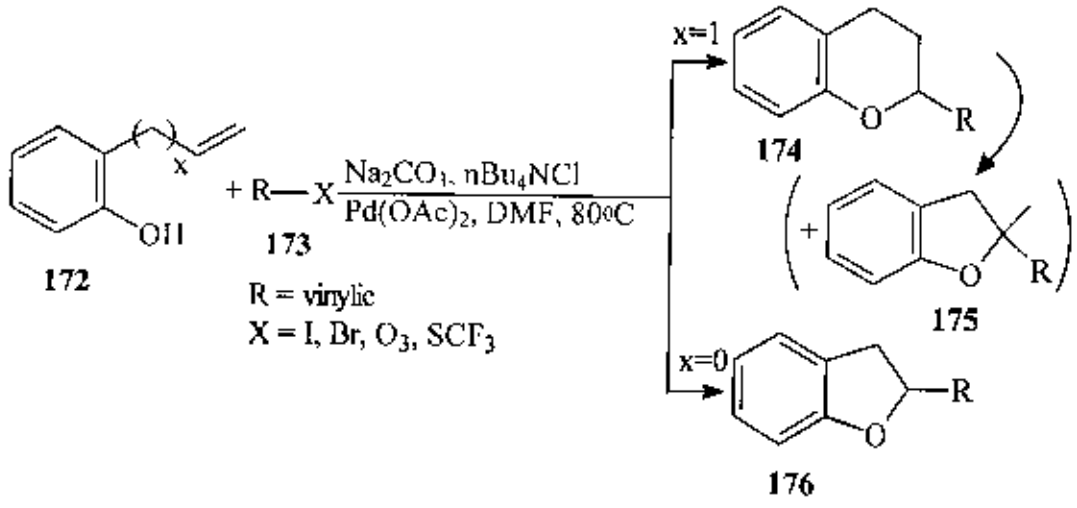
170 **171** **167**

R^1 = p –Me-C_6H_4, p – $MeOC_6H_4$, Ph etc.

R = Ph. n – C_5H_{11}, p – $MeOC_6H_5$, etc.

The palladium catalyzed cross coupling of *o*-allylic and *o*-vinylic phenols with vinylic halide and triflates produces substituted dihydrobenzopyrans and dihydrobenzofurans respectively in good to high yields. R. C. Larock *et al*[121] reported a conceptually related palladium-catalyzed coupling on vinylic halides and triflates with *o*-allylic and vinylic phenols, which provides a convenient, general route to dihydrobenzopyrans **174** and dihydrobenzofurans **176** respectively (**Scheme-45**)

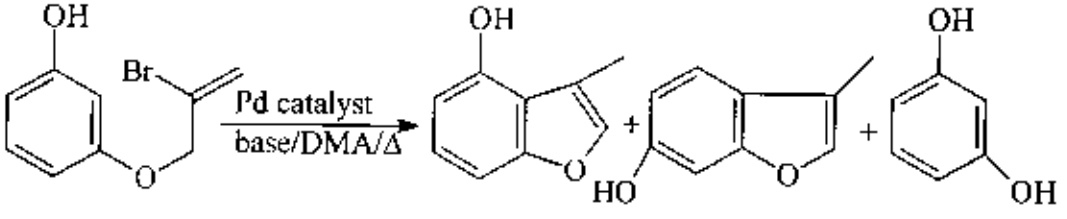
Scheme-45



172 173 174 175 176

The general strategy was illustrated through the cyclization of vinyl bromide **177** (**Scheme-46**). Heating a mixture of bromide **177** and Cs_2CO_3 in dimethylacetamide (DMA) in the presence of catalytic amount of Herrmann's palladacyclic catalyst (HC)[122] promoted cyclization to the ortho and para benzofurens **178** and **179** which were formed in a 1:1 ratio along with a small amount of resorcinol **180**.

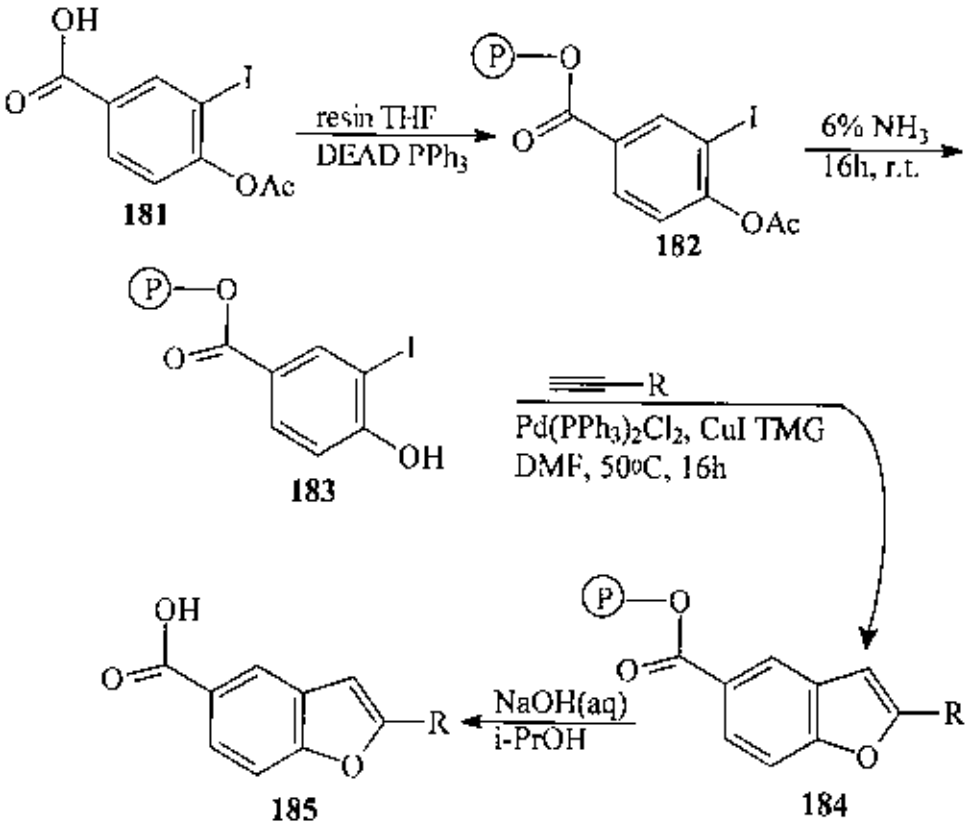
Scheme-46



177 178 179 180

In 1997, D Fancelli *et al*[124] reported a procedure for solid phase synthesis of 2-substituted benzofurn carboxylic acids which utillises a Pd-catalysed heteroannulation of terminal acetylenes in the presence of resin hound orthohydroxy aryl iodides (scheme **47**).

Scheme-47

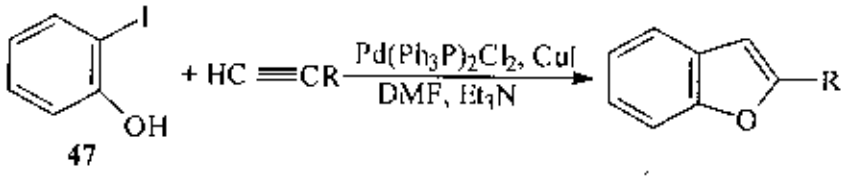


R = $(CH_2)_5CH_3$, $C(CH_3)_3$, ph,$(CH_2)_3Cl$, $(CH_2)_3OH$ etc.

The starting carboxylic acid **181** was directly linked to the comercial hydroxy resin TentaGel ™ S-OH using the Mitsunobu reaction, during the coupling the hydroxyl was protected as an acetate to avoid self-condensations. The protective group was then removed by mild alkaline hydrolysis and the resulting *o*-hydroxy iodide **183** reacted smoothly in the cyclization step to give the resin linked benzofurans **184**. Cleavage from the resin was performed with 1N aqueons sodium hydroxide / isopropyl alcohol. After Neutralization, HPLC quantitative assay showed that benzofurans **185** was obtained as essentially pure compounds in overall yields ranging from 40-70%.

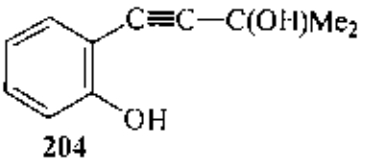
A mixture of *o*-iodophenyl **47** and an alkyne **59, 186 – 193** with a terminal acetylenic function, when heated in the prsence of a palladium catalyst, copper(I) iodide and a base in dimethylformamide, gave the 2-substituted benzofurans **144, 196 – 203** in good yields[125].

Scheme – 48



47

59	Ph	**144**
186	C_6H_4Cl-*m*	**196**
187	CH_2OH	**197**
188	CMe_2OH	**198**
189	CH_2OTHP	**199**
190	CH(OH)CH=CHMe	**200**
191	CH(OH)Ph	**201**
192	$CH(OH)C_6H_4Me$-*o*	**202**
193	$CH(OH)C_6H_4OMe$-*p*	**203**
194	CO_2Me	-
195	H	-



204

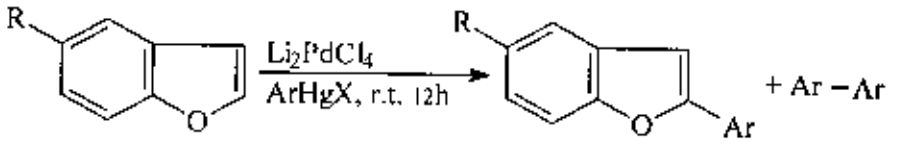
The reactions were usually carried out for 16h at 60^0C, lower temperature leading to poor yields. The reaction when carried out in DMF at room temperature in the presence of tetrabutylammonium chloride (PTC), gave a mixture of the cyclic product **198** and the corresponding acyclic product **204**. The overall yield and the proportion of the cyclic product increasing the time. At the higher temperature (50^0C) for 6h the cyclic product **198** was formed exclusively. This indicated the acyclic product **204** was an intermediate in the formation of the benzofuran **198**. However, with several aryl acetylenic carbinols a slightly higher temperature (80^0C) and longer reaction period were required to derive the optimum yields. The reaction could not be carried out with methoxycarbonyl **194** and acetylene gas **105**.

1.4 Palladium Catalyzed Functionalization of Benzofurans:

Due to their physiological and chemotherapeutic significance, benzofuran derivatives, particularly 2-substituted benzofurans are important synthetic targets. As such, palladium catalyzed functionalization of benzofurans, which could accomodate sensitive functional groups e.g. aldehyde, ketone etc. has received attention for synthetic organic chemists.

Benzofuran **205** was found[126] to undergo cross coupling with arylmercuryhalides in the presence of lithium tetrachloropalladate to give 2-aryl benzofurans **206** accompanied by small amounts of biaryl **207** (**Scheme – 49**)

Scheme – 49



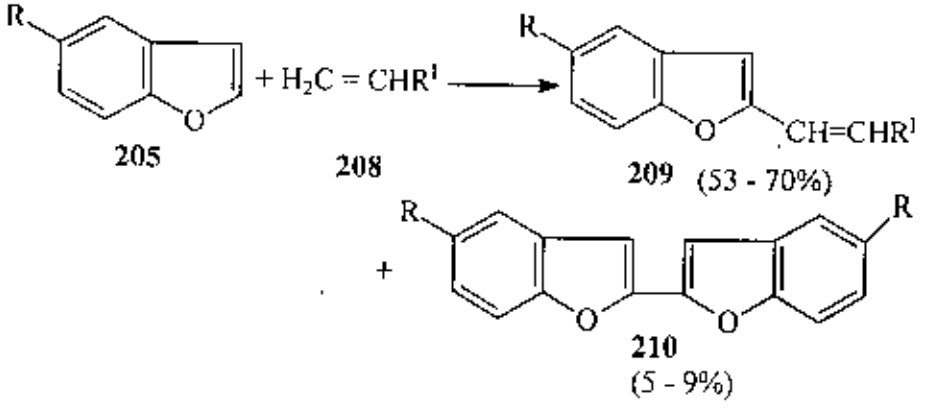
205 **206** (60-79%) **207** (5-8%)

205a, R = H Ar = Ph, C_6H_4Me-*p*, C_6H_4OMe-*p*,

205b, R = Me $C_6H_4NO_2$-*m*

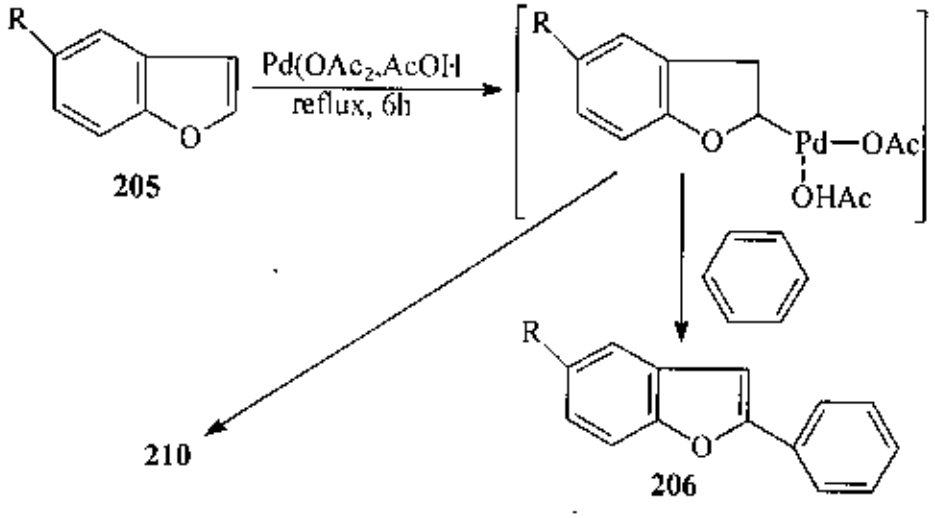
In the presence of palladium acetate in acetic acid, benzofuran **205** reacted with olifins **208** to give benzofurylsubstituted olifins **209** as major products (53-70%) and 2,2'-bibenzofuryl **210** as minor product. However, the latter **210** was the major product in the reaction between benzofuran **205** and aromatic halide in the presence of palladium acetate in benzene. 2-Arylbenzofuran was obtained in small amounts, indicating that reactivity of benzofuran **205** towards palladium acetate was far higher than that of benzene. No hydride shift was observed to take place during the reaction[127] (**Scheme-50**).

Scheme-50



R = H, Me

R^1 = H, CH_3, CH_2CH_3 etc.



SECTION - 2

Present Work

Synthesis of 2-Acylbenzofurans from *o*-Iodophenol Through Combined Palladium Catalyzed and Friedel-Crafts Reactions.

2. Present Work: Synthesis of 2-Acylbenzofurans from *o*-Iodophenol Through Combined Palladium Catalyzed and Fridel-Crafts Reactions.

2.1 Rationale:

Heterocyclic compounds containing the benzofuran skeleton have generated considerable interest in recent years as reflected by recent articles dealing with their synthesis and emphasizing their biological and medicinal properties. Our interest in benzo[b]furans stemmed from their fascinating chemistry, pharmaceutical and medicinal properties (as described in section-1). More recently progress in this area have been made though the development of methods involving (i) a modified Castro reaction[68c] using acetylenic substance with Cu_2O in pyridine[69a] (ii) solid support[70] (iii) intermolecular cyclization[81] (iv) radical cyclization[84]. Thus a number of synthesis of natural products containing the benzofuran nucleus have been reported[131].

Recent efforts, however have centred around the use of palladium catalysts for carbon-carbon bond formation[132] and carbon-heteroatom bond formation[94,95]. The palladium catalyzed synthesis of substituted benzofurans have been reported involving the cyclisation of 2-allylphenols[101] and palladium promoted cyclisation of *o*-iodoarylallyl ethers[107]. The palladium catalyzed reaction of *o*-iodophenols with 1,3-dienes and 1,2-dienes leading to the substituted benzofurans have also been accomplished[112,113]. The functionalization of pr-formed benzofurans under palladium catalyzed condition has also been reported[126a]. The cyclocarbonylation of 3-furylallyl acetates in the presence of palladium catalysts led to the acetoxybenzofurans[126b].

Acetylenic substrates have played a very significant role in palladium catalyzed reaction for carbon-carbon bond formation leading to cyclic and polycyclic structures[99], dihydrobenzofurans[102], 2-alkylidenetetrahydrofurans and pyrans[105]. The heteroannulation of *o*-iodophenols with acetylenic substrates containing a terminal acetylenic group leading to 2-snbstituted benzofurans have been reported by several group of investigators[109-111]. A somewhat different approach has been the palladium catalyzed carbonylation of 2-acetylenic phenols leading to substituted benzofurans[106]. Similarly, the

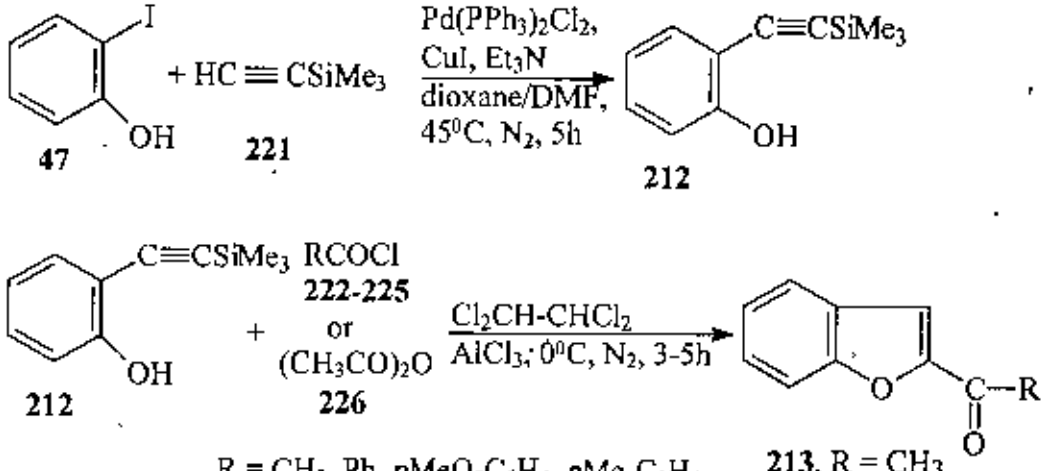
palladium catalyzed arylation of alkyl or aryl acetylenic phenols in the presence of butyllithium led to 2-alkylidenebenzofurans[105]. Kundu et al[125] reported a convenient method for the heteroannulation of acetylenic carbinols leading to 2-substituted benzofurans.

In view of the extensive natural occurrence and biological importance of benzofuran derivatives we planned to develop a general and facile method for the synthesis of 2-substituted benzofurans. We became interested in the palladium catalyzed heteroannulation and Friedel-Crafts acylation reaction for the synthesis of benzofurans.

2.2 Results and Discussion:

Here we demonstrate a novel approach where a palladium catalyzed reaction was followed by Friedel-Crafts acylation and simultaneous cyclization to obtain 2-acylbenzofurans in good to excellent yields. *o*-Iodophenol **47** underwent facile reaction with trimethylsilyl acetylene **221** in the presence of $(PPh_3)_2$ $PdCl_2$ and CuI at 45^0C to yield *o*-(trimethylsilyl)ethynyl phenol **212** in excellent yields. *o*-(Trimethylsilyl)ethynyl compound **212** was then subjected to Friedel-Crafts reaction with acid chlorides **222–225** or acetic anhydride **226** to afford the 2-substituted benzofurans **213–216** in good yields as shown in **Scheme-51**.

Scheme-51



R = CH_3, Ph, *p*MeO-C_6H_4, *p*Me-C_6H_4

213, R = CH_3
214, R = Ph
215, R = *p*-$MeOC_6H_4$
216, R = *p*-MeC_6H_4

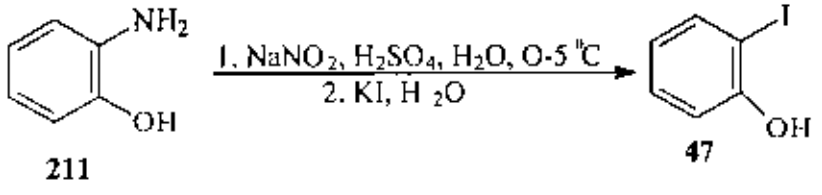
An ice cold solution of *o*-(trimethylsilyl)ethynyl phenol **212**, anhydrous aluminium chloride (4 mol eq) and acid chloride **222 – 225** or acetic anhydride **226** (1.5 mol eq) in tetrachloroethane was stirred at 0–25^{0}C for 1–2 h (acid chloride) or 3–4 h (acetic anhydride) to yield 2-acylbenzofurans **213–216**. In this case we have found two isomeric product which were not separable by column chromatography.

2.2.1 Starting Materials:

Synthesis of o-iodophenol 47:

o-Iodophenol **47** have been used as starting materials because of their easy availability from *o*-aminophenol **211**. Diazotization of o-aminophenol **211** followed by Sandmeyer iodination with potassium iodide afforded o-iodophenol **47** shown in **Scheme-52**. The product was characterized by its UV, IR, ^{1}HNMR. The ^{1}HNMR and IR spectra of the compound **47** showed absence of NH_2 group. In ^{1}HNMR spectrum of the compound **47** the chemical shift δ 5.3 (signlet) for OH proton was observed. The melting point of **47** was found to be 42––43^{0}C (lit[128] 43^{0}C) All spectral data of the compound **47** were identical to the reported data[128].

Scheme - 52



211 **47**

2.3 Characterization of products:

2-substituted benzofurans **213 – 216** were well characterized by their satisfactory spectroscopic (IR, UV, ^{1}HNMR and ^{13}C NMR) data. The IR spectra showed C = 0 stretching vibration in the range 1680 – 1778 cm^{-1}. Appearance of two singlet at δ 6.5 and δ 6.6 in the ^{1}HNMR spectra was assigned to be 3-H of 2-acetylbenzofuran **213**. The ^{1}HNMR spectra of the compound **213** showed two sharp singlet at δ 2.3 and 2.4 for $-COCH_3$ proton. In the case of 2-aryolbenzofurans the ^{1}HNMR spectra showed chemical shift positions at aromatic zone (7.0–7.3) for 3-H. The ^{1}HNMR spectra of the compound

2-anisoylbenzofuran **215** showed two sharp singlet at δ 3.87 and δ 3.82 for Ar-OCH_3 proton. Similarly the ^{1}HNMR spectra of the compound 2-toluoylbenzofuran **216** showed two singlet at δ 2.44 and δ 2.36 for Ar-CH_3 proton.

The ^{13}CNMR spectra of 2-acylbenzofurans showed two signals for C = 0 at δ_c 196 – 188, two signals at δ_c 55.67 and 56.54 for Ar-OCH_3 of compound **215** and two signals for each compound at δ_c 116–112 for C-3. Other signals for aromatic carbon were also found double.

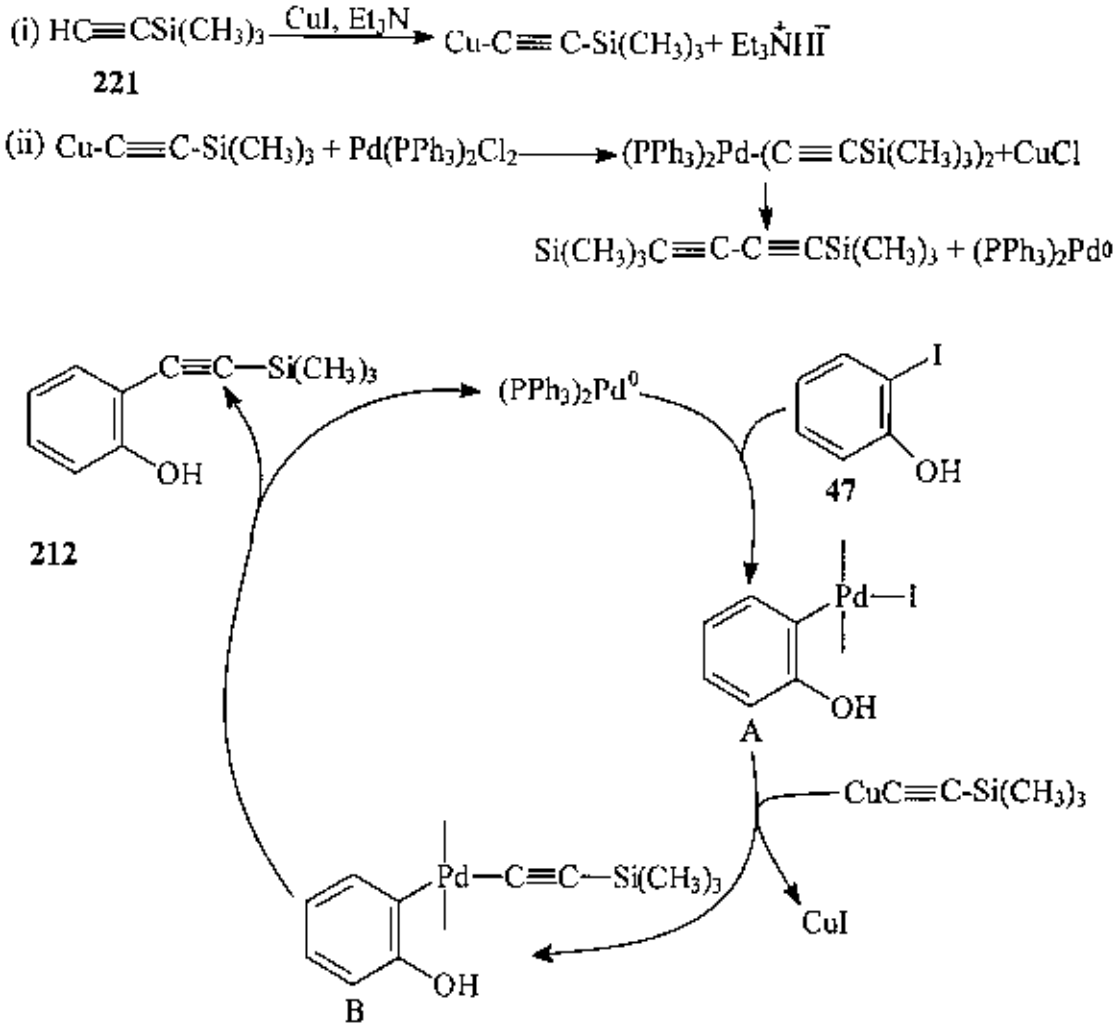
The ^{1}HNMR and ^{13}CNMR spectra indicate the presence of two isomer in each synthesized 2-acyl benzofurans. The UV spectra of all the compounds **213 – 216** showed absorption in the range λ_{max}/nm 320 – 250.

2.4. Mechanism:

a) A mechanism for the formation of *o*-(trimethylsilyl)ethynyl phenol **212** through palladium catalyzed reaction of *o*-iodophenol **47** with alkyne **221** having a terminal acetylenic group is illustrated in **Scheme - 53.**

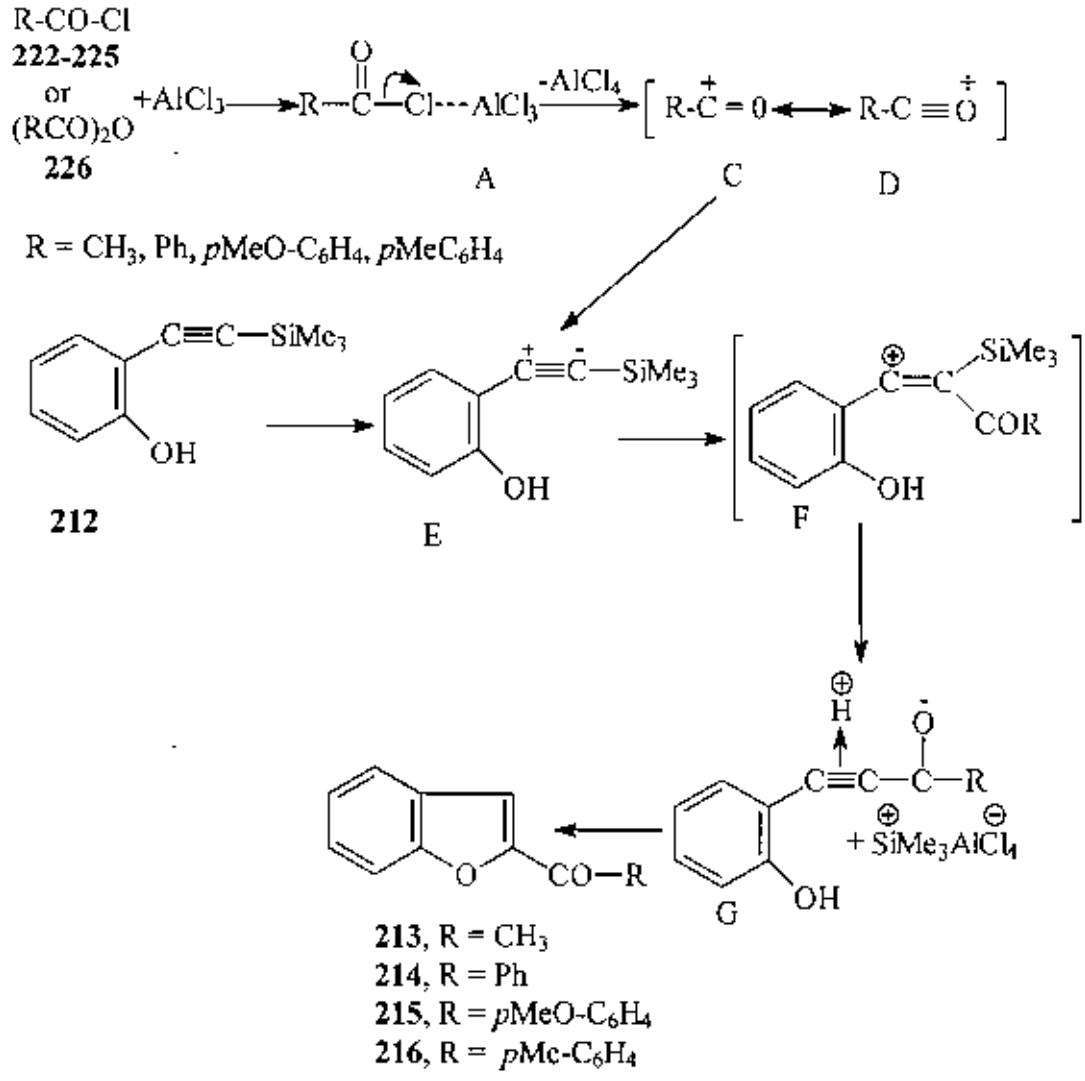
The formation of Pd^0 from the interaction of bis(triphenylphosphine)palladium (II) chloride and cuprous acetylide as shown in step (ii) was proposed by Hagihara *et al*[33]. Oxidative addition of *o*-iodophenol to Pd^0 complex gives a *o*-arylpalladium (II) complex (A) which then trans-metallates with cuprous acetylide to generate the arylalkynylpalladium (II) species (B). This on reductive elimination of Pd^0 then affords acyclic product **212**.

Scheme - 53



b) The acylation of *o*-(trimethylsilyl) product **212** was carried out by an acid chloride or acetic anhydride in the presence of a Lewis acid ($AlCl_3$). The most likely mechanism for Friedel-Crafts acylation is shown in **Scheme - 54**. In the Lewis acid catalyzed method, an acylium carbanion (C) is formed from the complex (A). Trimethylsilyl group acts as an electron donor and partial negative charge is developed on the terminal triple bond carbon **212**. The generated anion complex (E) is attacked by the acylium ion (C) to form the complex (F). Then the complex (F) undergoes the Michael addition to form the 2-acylbenzofurans **213 – 216**.

Scheme - 54



213, R = CH_3
214, R = Ph
215, R = *p*MeO-C_6H_4
216, R = *p*Mc-C_6H_4

2.5 Conclusion:

We have described for the first time a very convenient and elegant method for the synthesis of 2-acylbenzofurans from 2-iodophenol through palladium catalyzed reaction followed by Friedel-Crafts acylation. The method is characterized by readily available starting materials, relatively mild reaction condition and relatively good yields.

2.6 Experimentals :

o-Iodophenol 47:

10 g (0.09 mol) of *o*-aminophenol **211** was dissolved in a mixture of 11 g (6 ml) of concentrated H_2SO_4, 46 ml of water and 46 g of crushed ice in a large flask. The mixture was cooled in a freezing point and was stirred mechanically. Then was added during 1 hour a solutrion of 6.6 g (0.096 mol) of sodium nitrite in 13.6 ml of water. The solution was stirred for a further 20 minutes and then added 5.6 g (3.05 ml) of concentrated H_2SO_4. The cold diazonium solntion was poured into an ice cold solntion of 18.30 gm (0.11 mol) of potassium iodide in 20 ml water contained in a beaker provided with a mechanical stirrer. With continued stirring the solution was warmed slowly on a water bath. The temperature was maintained at 78 - 80^{0}C until the evolution on nitrogen ceases. The *o*-iodophenol was separated as a dark heavy oil. The residue was cooled to room temperature and extracted the reaction mixture with three 30 ml portions of chloroform, washed the combined extracts with dilute sodiumthiosulphate solution and dried with anhydrous sodium sulphate.

The solvent was removed on a waterbath. The compound was purified by steam distillation, extracted with chloroform and dried with anhydrous sodium sulphate. Solvent was removed to obtain the title compound 47 (16.96 g, 82.83%) as a solid, mp. 42–43^{0}C (lit.[128] 43^{0}C).

IR (KBr) : ν_{max} 3415, 1610, 1600, 1580, 845, 830, 730 cm^{-1}

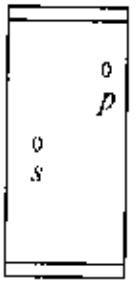
UV ($CHCl_3$) : λ_{max} 284.60, 277.20, 238.20 mm.

^{1}HNMR (400MHz, $CDCl_3$): δ 7.66 (dd, J=7.16, 1.48 Hz, 1H, ArH), 7.25 (m, 1H, ArH), 7.00 (dd, J=8.73, 1.44 Hz, 1H, ArH), 6.68 (ddd, J=7.59, 1.46 Hz, 1H, ArH), 5.30 (s,1H, ArOH).

o-(Trimethylsilyl)ethynyl phenol 212:

To a stirred solution of *o*-iodophenol **47** (4.00 g. 18.18 mmol) bis(triphenylphosphine) palladium (II) chloride (0.128 g, 0.18 mmol), copper (I) iodide (0.07 g, 0.36 mmol) and triethylamine (10 ml) in dioxane/DMF (10 ml) were added (trimelhylsilyl)acetylene (5 ml, 36.21 mmol). The reaction mixture was stirred at 45^{0}C for 5 hour (24 hour in the

case of DMF) under N_2 atmosphere. The progress of the reaction was monitored by T.L.C (hexane-chloroform, 6:1) (R_f value = 0.61) which indicated completion of the reaction with the formation of faster moving product.



The solvent was removed under reduce pressure. To a residue diethyl ether and 0.1NHCl were added and the organic layer was separated, neutralized with a saturated $NaHCO_3$ (3×50 ml) solution, washed with distilled water (3×50 ml), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The latter was purified by chromatography on a column of silica gel with hexane chloroform (7:1) to obtain the title comound **212** (3.6 g, 94.72% when dioxane was used as a solvent and the product was 70% when DMF was used as a solvent) as a solid, mp. 46–47^{0}C (lit[129] mp. 46–47).

IR (KBr) : ν_{max} 3450, 2146, 842, 775, 776 cm^{-1}

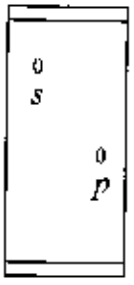
UV ($CHCl_3$) : λ_{max} 304.0, 295.8, 256.8, 288.6 nm.

^{1}HNMR (400MHz, $CDCl_3$) : δ 7.34 (dd, J=7.66, 1.39 Hz, 1H, ArH), 7.26 – 7.22 (m, 1H, ArH), 6.95 – 6.93 (m, 1H, ArH), 6.87 – 6.83 (m, 1H, ArH), 5.83 (s, ArOH), 0.28 [s, 9H, $Si(CH_3)_3$].

2-Acetylbenzofuran 213:

a) From acetyl chloride:

To an ice cold solution of *o*-(trimethylsilyl)ethynyl phenol **212** (200 mg, 1.1 mmol) in tetrachloroethane (10 ml), acetyl chloride (0.12 ml, 1.65 mmol) and anhydrous aluminium chloride (0.60 gm, 4.4 mmol) were added. The mixture was stirred under N_2 for 3 hour and the temperature of the reaction was raised from 0^{0}C to 25^{0}C. The progress of the reaction was monitored by T.L.C (hexane-chloroform 1:1) (R_f value = 0.51) which indicated completion of the reaction with the formation of slower moving product.



S = Reactant

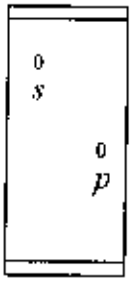
P = Product

Then the mixture was poured into an ice cold solution of dilute HCl (2 ml. 1–1.5 NHCl) and the organic layer was separated. The aqueous layer extracted with $CHCl_3$(3×25 ml). The combined organic extracts were washed with distilled H_2O (2×30 ml), saturated $NaHCO_3$ solution (2×30 ml) and distilled H_2O (2×30 ml) again. After drying over anhydrous Na_2SO_4 and removal of solvent a syrupy residue was obtained. The crude mass was purified by a silica gel column. Elution with hexane-chloroform (1:1) furnished the major product **213** (131.65 mg, 78.20%) as a homogeneous syrup.

IR (CCl_4) : ν_{max} 1776, 1676, 1548 and 1488 cm^{-1}.
UV ($CHCl_3$) : λ_{max} 275.2, 227.4 nm
^{1}HNMR (400 MHz, $CDCl_3$) : δ 7.70–7.11 (m, 8H, ArH) 6.61 (s, 1H, 3-H)
6.51 (s, 1H, 3-H), 2.43 [s, 3H, $COCH_3$, 2.37 (s, 3H, $COCH_3$).
^{13}CNMR (400 MHz, $CDCl_3$) : δc 196.49 (CO), 195.65 (CO), 169.05, 168.85, 168.77, 167.86, 153.05, 147.58, 134.40, 132.55, 131.72, 131.45, 126.35, 126.25, 122.80, 122.44, 114.45 (C-3), 114.25 (C-3), 29.93 (CH_3), 29.80 (CH_3).

b) From acetic anhydride:

To an ice-cold solution of **212** (200 mg, 1.1 mmol) in tetrachloroethane (10 ml), acetic anhydride (0.16 ml, 1.65 mmol) and anhydrous aluminium chloride (0.60 gm, 4.4 mmol) were added. The mixture was stirred under N_2 for 5 hour and the temperature of the reaction was raised from 0^0C to 25^0C. The progress of the reaction was monitored by T.L.C (hexane-chloroform 1:1) (R_f value = 0.51) which indicated completion of the reaction with the formation of slower moving product.



S = Reactant

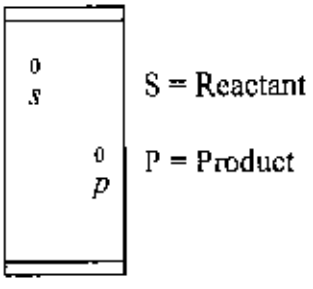
P = Product

Then the mixture was poured into a ice-cold solution of dilute HCl (2 ml, 1–1.5NHCl) and the organic layer was separated. The aqueous layer extracted with $CHCl_3$ (3×25 ml). The combined organic extracts were washed with distilled H_2O (2×30 ml), saturated $NaHCO_3$ solution (2×30 ml) and distilled H_2O (2×30 ml) again. After drying over anhydrous Na_2SO_4 and removal of solvent a syrupy residue was obtained. The crude mass was purified by column (silica-gel). Elution with hexane-chloroform (1:1) furnished the major product **213** (140 gm, 83.12%) as a homogenious syrupy.

IR, UV, ^{1}HNMR, ^{13}CNMR spectra of this compound was indistinguishable from those of the same sample prepared earlier from acetyl chloride.

2-Bezoylbenzofuran 214:

To an ice-cold solution of **212** (200 mg, 1.1 mmol) in tetrachloroethane (10 ml), benzoyl chloride (0.19 ml, 1.65 mmol) and anhydrous aluminium chloride (0.60 gm, 4.4 mmol) were added. The mixture was stirred under N_2 for 3 hour and the temperature of the reaction was raised from 0^0C to 25^0C. The progress of the reaction was monitored by T.L.C (hexane-chloroform 1:1) (R_f value = 0.36) which indicated completion of the reaction with the formation of slower moving product.



Then the mixture was poured into a ice-cold solution of dilute HCl (2 ml, 1–1.5NHCl) and the organic layer was separated. The aqueous layer extracted with $CHCl_3$ (3×25 ml). The combined organic extracts were washed with distilled H_2O (2×30 ml), saturated $NaHCO_3$ solution (2×30 ml) and distilled H_2O (2×30 ml) again. After drying over anhydrous Na_2SO_4 and removal of solvent a syrupy residue was obtained. The crude

mass was purified by column (silica-gel). Elution with hexane-chloroform (1:1) furnished the major product **214** (189 gm, 80.87%) as a solid, mp. 88–89^{0}C (lit.[39] 90^{0}C).

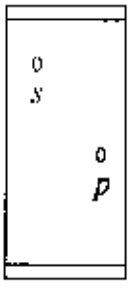
IR (KBr) : ν_{max} 1690, 1645, 1550 and 1548 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 310, 286, 241 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 8.32–8.13 (m, 2H, ArH), 7.99–7.09 (m, 18H, ArH).

2-(*p*-methoxybenzoyl)benzofuran 215:

To an ice-cold solution of **212** (200 mg, 1.1 mmol) in tetrachloroethane (10 ml), *p*-anisoyl chloride (0.22 ml, 1.65 mmol) and anhydrous aluminium chloride (0.60 gm, 4.4 mmol) were added. The mixture was stirred under N_2 for 3 hour and the temperature of the reaction was raised from 0^{0}C to 25^{0}C. The progress of the reaction was monitored by T.L.C (hexane-chloroform 1:1) (R_f value = 0.32) which indicated completion of the reaction with the formation of slower moving product



S = Reactant

P = Product

Then the mixture was poured into a ice-cold solution of dilute HCl (2 ml, 1–1.5NHCl) and the organic layer was separated. The aqueous layer extracted with $CHCl_3$ (3×25 ml). The combined organic extracts were washed with distilled H_2O (2×30 ml), saturated $NaHCO_3$ solution (2×30 ml) and distilled H_2O (2×30 ml) again. After drying over anhydrous Na_2SO_4 and removal of solvent a syrupy residue was obtained. The crude mass was purified by column (silica-gel). Elution with hexane-chloroform (1:1) furnished the major product **215** (220 mg, 82.92%) as a solid, mp.94–95^{0}C (lit.,[39] 95–96^{0}C).

IR (KBr) : ν_{max} 1739, 1640, 1549 and 1510 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 315.0, 265.2 nm.

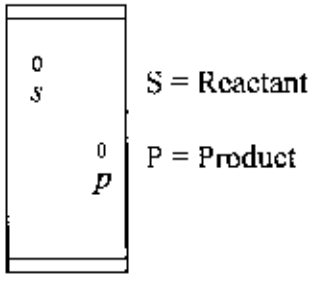
^{1}HNMR (400 MHz, $CDCl_3$) : δ 8.19–8.17 (m, 2H, ArH), 7.84–7.81 (m, 4H, ArH), 7.49–7.23, (m, 5H, ArH), 7.00–6.96 (m, 3H, ArH), 6.81–6.74 (m, 4H, ArH), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3).

^{13}CNMR (400 MHz, $CDCl_3$) : δc 189.77 (CO), 188.92 (CO), 164.78, 164.27, 163.91, 163.72, 148.01, 147.32, 142.67, 142.23, 136.63, 136.25, 132.70, 132.59, 132.45, 131.37, 131.08, 130.93, 130.33, 130.13, 127.11, 126.95, 126.33, 125.91, 123.62, 122.96, 114.14, 113.89, 113.80 (C-3), 113.75 (C-3), 55.67 (OCH_3) 55.54 (OCH_3).

^{13}CNMR (400MHz, $CDCl_3$, DEPT 135) : δc 132.61, 132.50, 132.36, 131.28, 130.99, 130.84, 130.04, 127.02, 126.86, 126.24, 125.83, 123.53, 122.87, 114.05, 113.80, 113.71(C-3), 113.65(C-3), 55.58(OCH_3), 55.43(OCH_3).

2-(*p*-Methylbenzoyl)benzofuran 216:

To an ice-cold solution of **212** (200 mg, 1.1 mmol) in tetrachloroethane (10 ml), *p*-toluoyl chloride (0.21 ml, 1.65 mmol) and anhydrous aluminium chloride (0.60 gm, 4.4 mmol were added. The mixture was stirred under N_2 for 3 hour and the temperature of the reaction was raised from 0^0C to 25^0C. The progress of the reaction was monitored by T.L.C (hexane-chloroform 1:1) (R_f value = 0.35) which indicated completion of the reaction with the formation of slower moving product.



Then the mixture was poured into a ice cold solution of dilute HCl (2 ml, 1–1.5NHCl) and the organic layer was separated. The aqueous layer extracted with $CHCl_3$ (3×25 ml). The combined organic extracts were washed with distilled H_2O (2×30 ml), saturated $NaHCO_3$ solution (2×30 ml) and distilled H_2O (2×30 ml) again. After drying over anhydrous Na_2SO_4 and removal of solvent a syrupy residue was obtained. The crude mass was purified by column (silica-gel). Elution with hexane-chloroform (1:1) furnished the major product **216** (200mg, 80.51%) as a homogeneous syrupy.

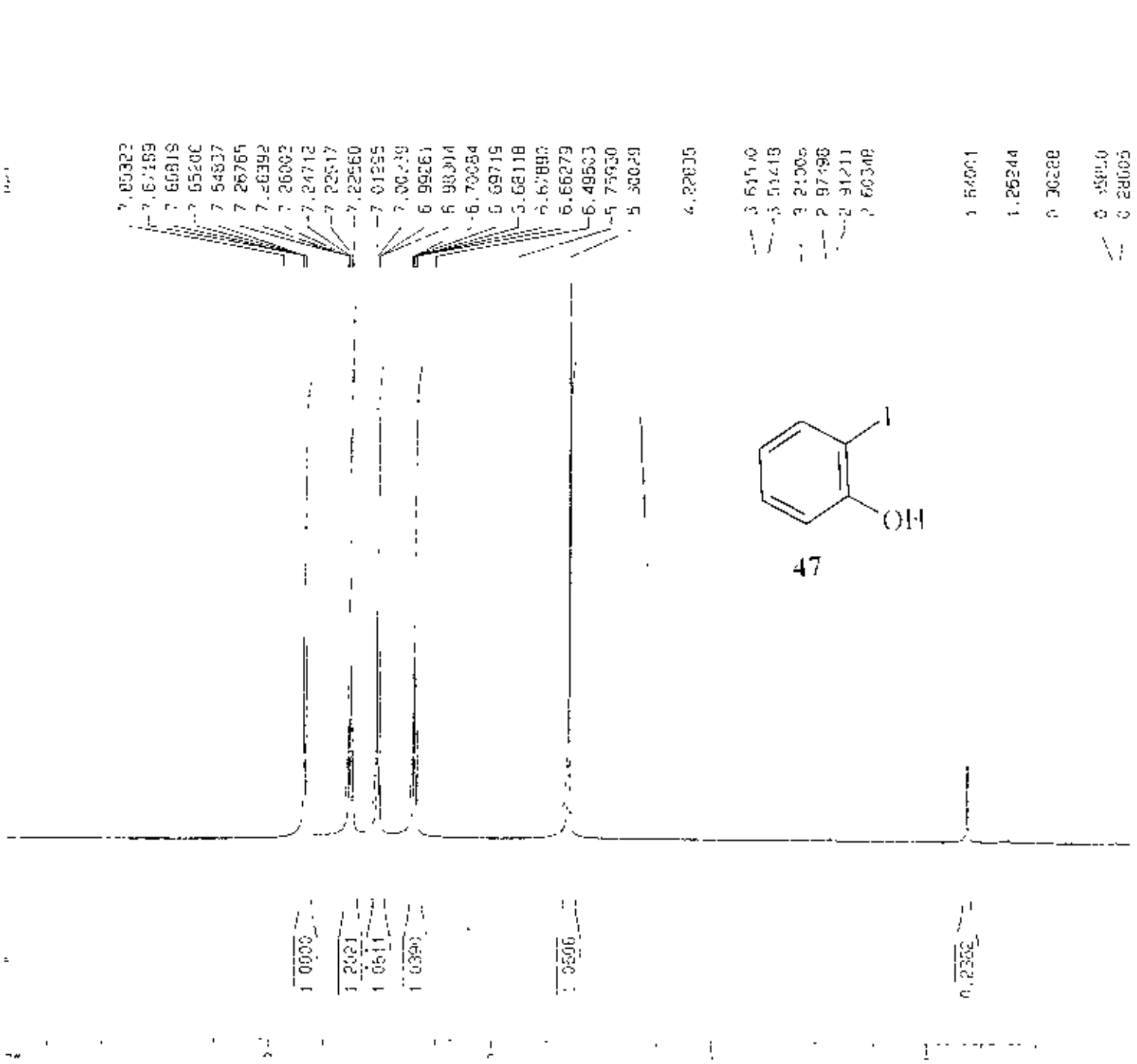
IR (CCl_4) : ν_{max} 1755, 1610, 1575, 1545 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 275.8, 244.2 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 8.19–8.09 (m, 2H, ArH), 7.88–6.60 (m, 16H, ArH), 2.44(s, 3H, CH_3) 2.36 (s, 3H, CH_3).

^{13}CNMR (400 MHz, $CDCl_3$) : δc 189.78 (CO), 188.20 (CO), 165.15, 153.06, 147.96, 144.42, 144.22, 132.16, 131.02, 130.73, 130.57, 130.38, 129.76, 129.62. 129.58, 129.40, 129.29, 129.22, 129.18, 129.06, 128.87, 126.40, 126.29, 123.61, 115.29 (C-3), 114.95 (C-3), 21.91 (CH_3), 21.86 (CH_3).

^{13}CNMR (400 MHz, $CDCl_3$, DEPT 135) : δc 131.02, 130.73, 130.60, 130.38, 129.76, 129.62, 129.58, 129.40, 129.30, 129.22, 129.28, 129.06, 128.87, 126.68, 126.40, 123.63, 115.29 (C-3), 114.99 (C-3), 21.90 (CH_3), 21.80 (CH_3).



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PROCNO 1

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FIDRES 0.146107 Hz
AQ 3.4210201 sec
RG 64
DW 104.400 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

======== CHANNEL f1 ======
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PL1 0.00 dB
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F2 - Processing parameters
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

1H NMR plot parameters
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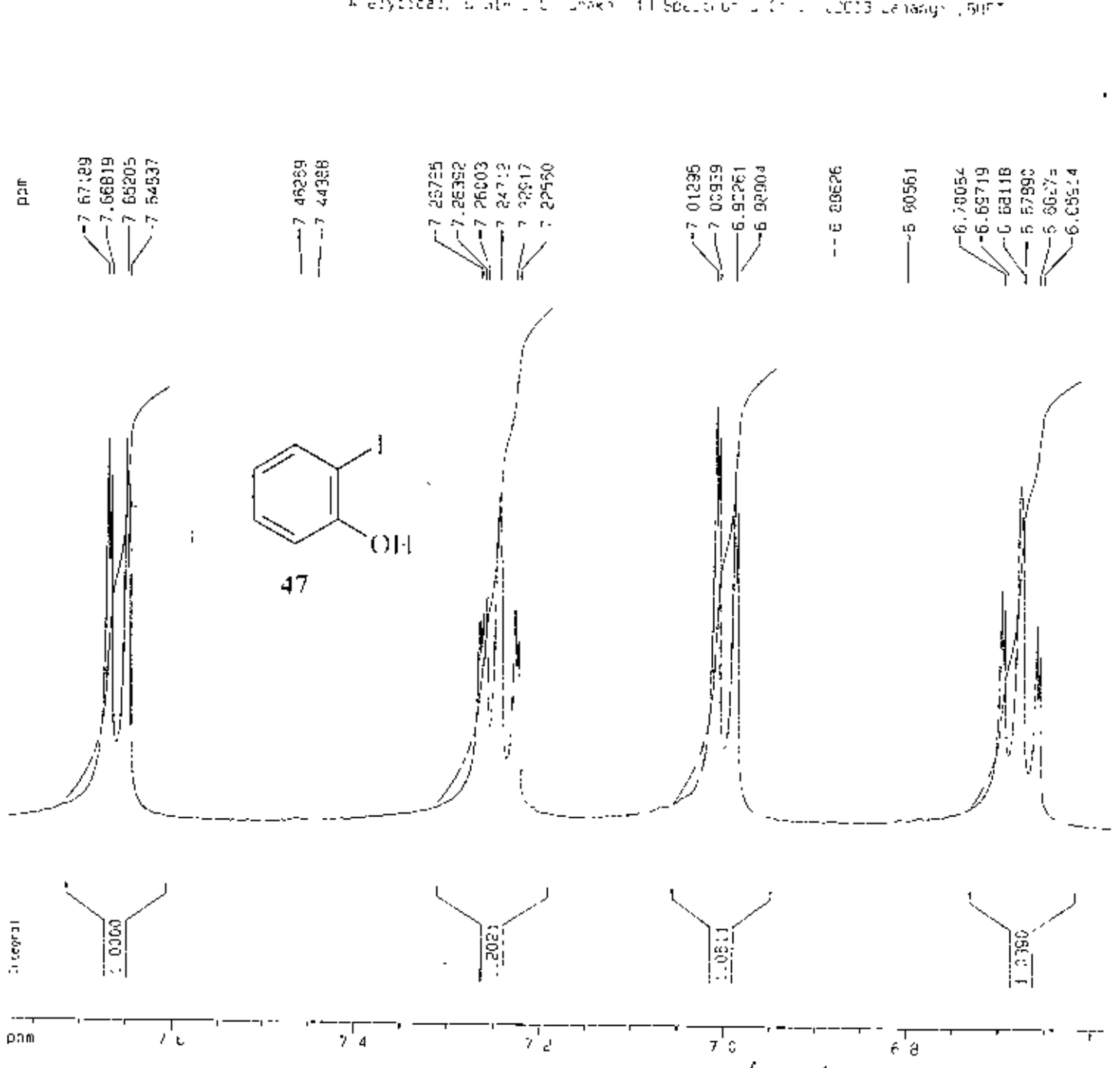
PPM 0.615% ppm/cm

62



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PROCNO 1

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SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210201 sec
RG 64
DW 104.400 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

======== CHANNEL f1 ======
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PL1 -6.00 dB
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F2 - Processing parameters
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1D NMR plot parameters
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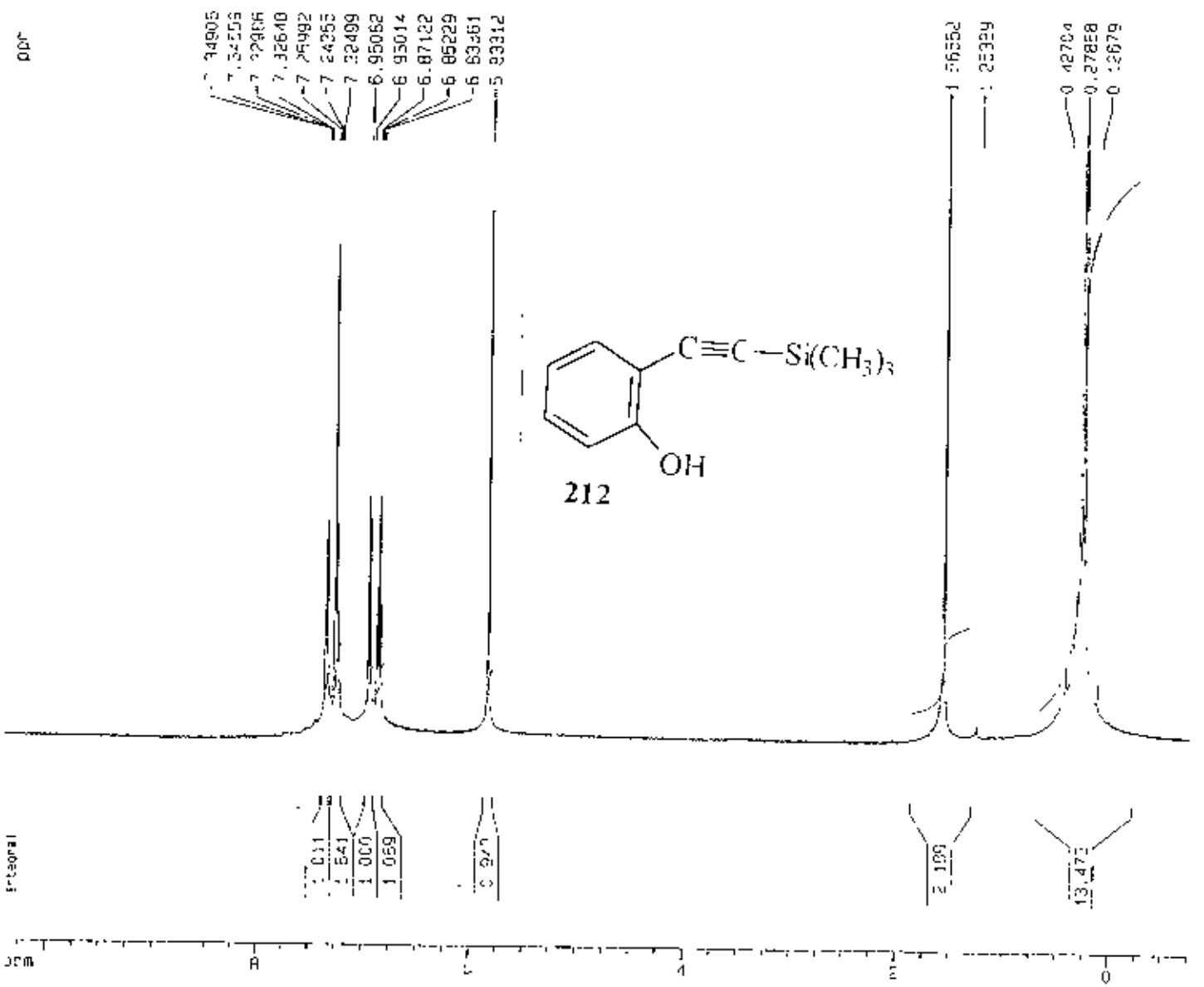
F2P 6.580 ppm
F2 2633.92 Hz
PPMCM 0.05994 ppm/cm
HZCM 23.98404 Hz/cm



212

Current Data Parameters

NAME	AJ/C
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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NS	128
DS	0
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	64
DW	104.400 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

======== CHANNEL f1 ======

NUC1	1H
P1	8.30 usec
PL1	-6.30 dB
SFO1	400.1400007 MHz

F2 - Processing parameters

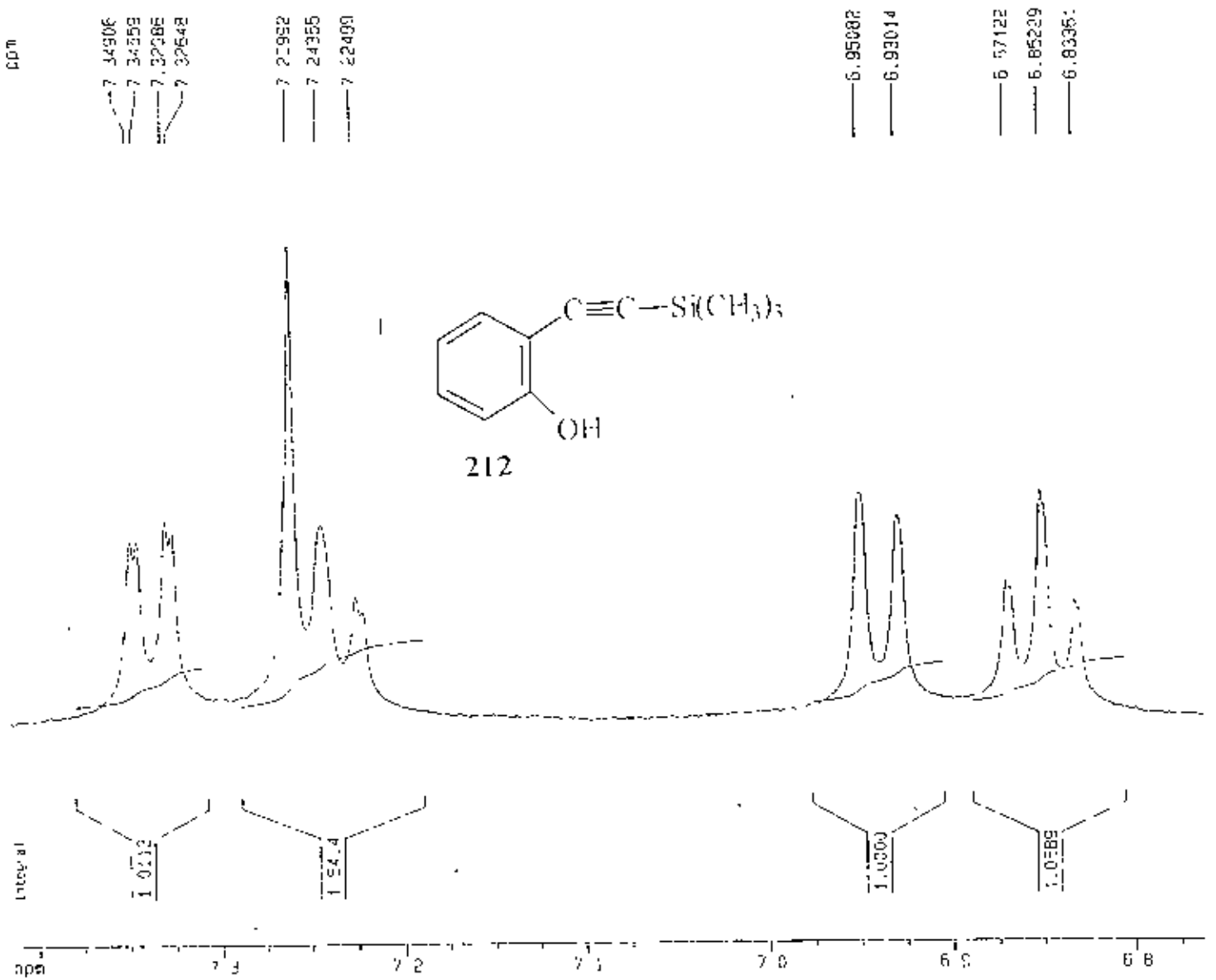
SI	32768
SF	400.1400082 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

2D NMR plot parameters

CX	20.00 cm
F1P	10.378 ppm
F1	4152.15 Hz
F2P	-0.752 ppm
F2	-301.00 Hz
PPMCM	0.55651 ppm/cm
HZCM	222.68250 Hz/cm

64

Analytical Chem. 1H Spectrum A-08 (a) in CDCl3 Jahangir



212

Current Data Parameters
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EXPNO 1
PROCNO 1

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PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 128
DS 0
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 64
DW 104.400 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

========== CHANNEL f1 ========== 65 ===
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P1 8.90 usec
PL1 -6.00 dB
SFO1 400.1420007 MHz

F2 - Processing parameters
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1D NMR plot parameters
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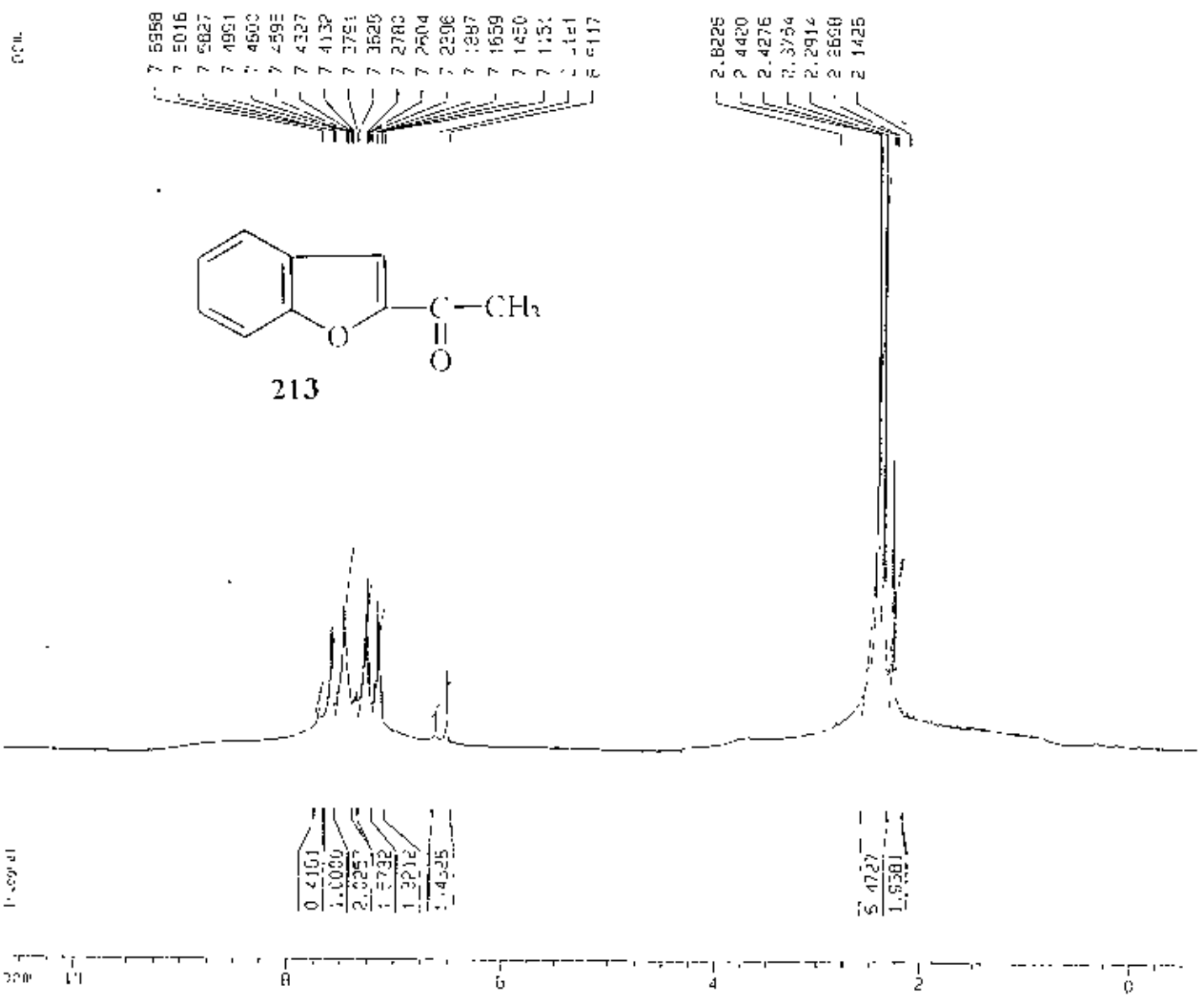

213

Current Data Parameters
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EXPNO 1
PROCNO 1

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FIDRES 0.146157 Hz
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RG 64
DW 104.400 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

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P1 9.30 usec
PL1 -6.00 dB
SFO1 400.1420007 MHz

F2 - Processing parameters
SI 32768
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
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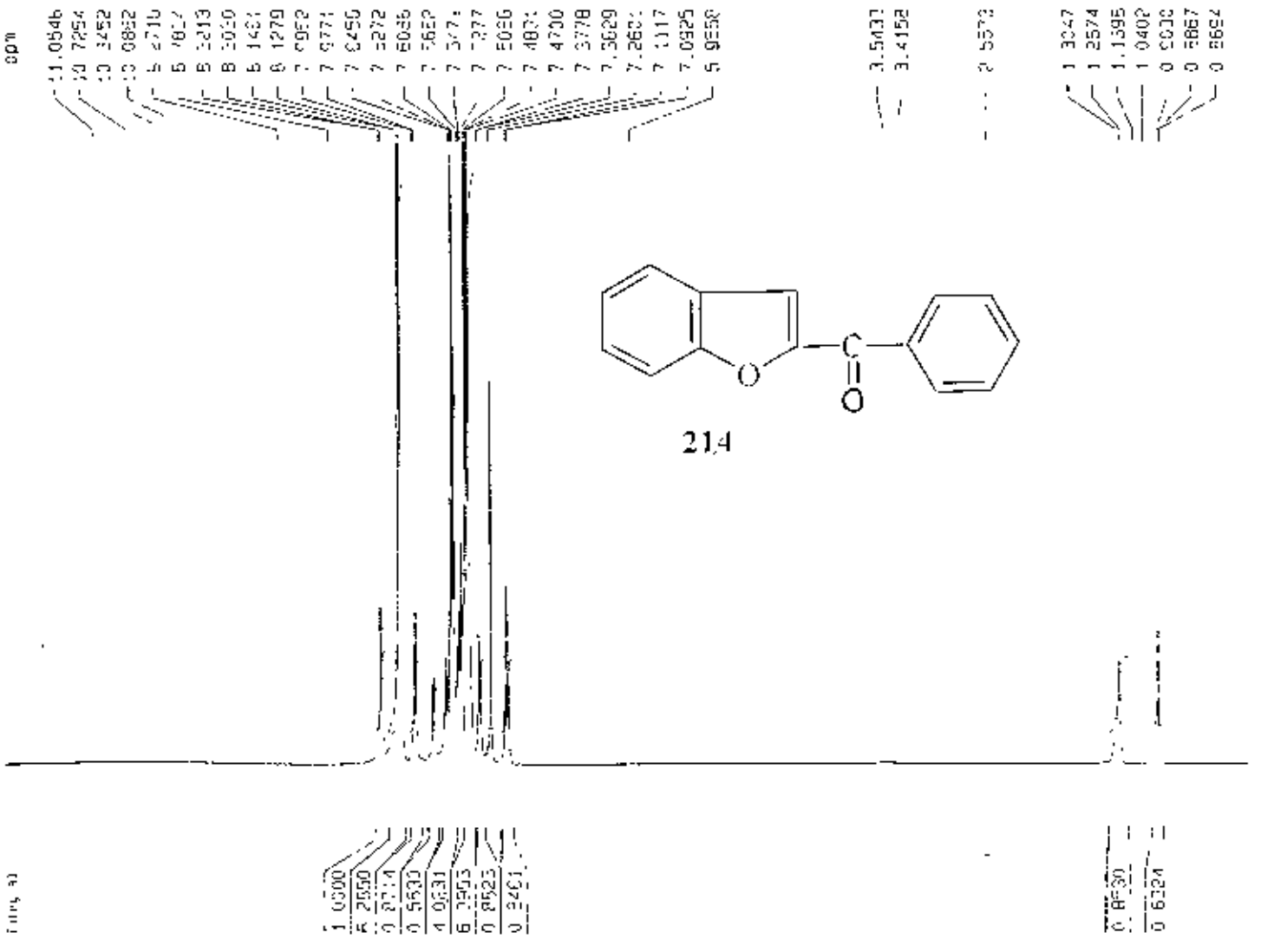
F1 4265.95 Hz
F2P -0.651 ppm
F2 -252.50 Hz
PPMCM 0.56499 ppm/cm
HZCM 226.07585 Hz/cm



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NAME A473
EXPNO 1
PROCNO 1

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PULPROG zg30
TD 32768
SOLVENT Acetone
NS 512
DS 0
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5559540 sec
RG 61
DW 78.000 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

========== CHANNEL f1 ========
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P1 8.30 usec
PL1 -6.00 dB
SFO1 400.1400010 MHz

F2 - Processing parameters
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SF 400.1400063 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
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F2 -0.51 Hz
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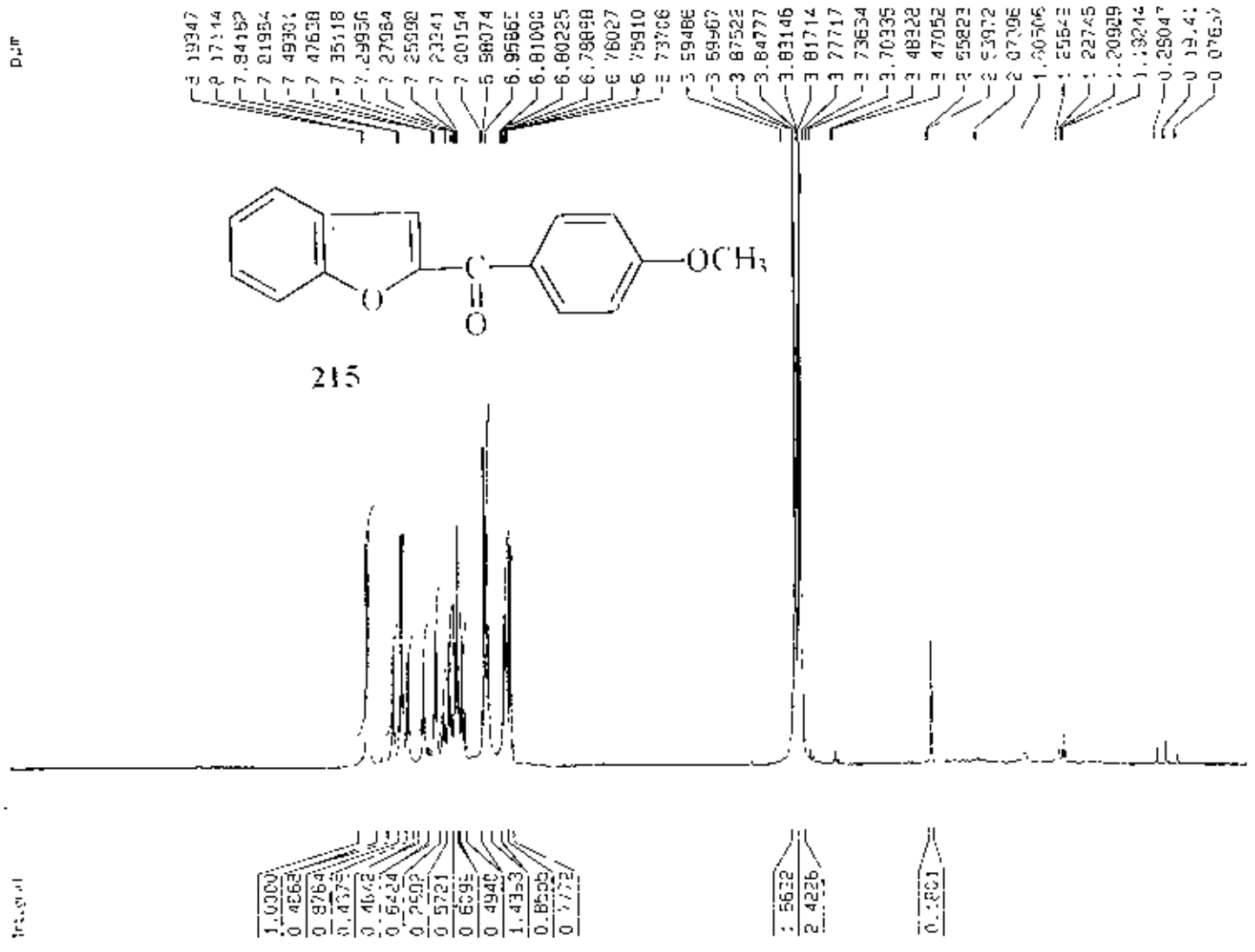

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EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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INSTRUM drx400
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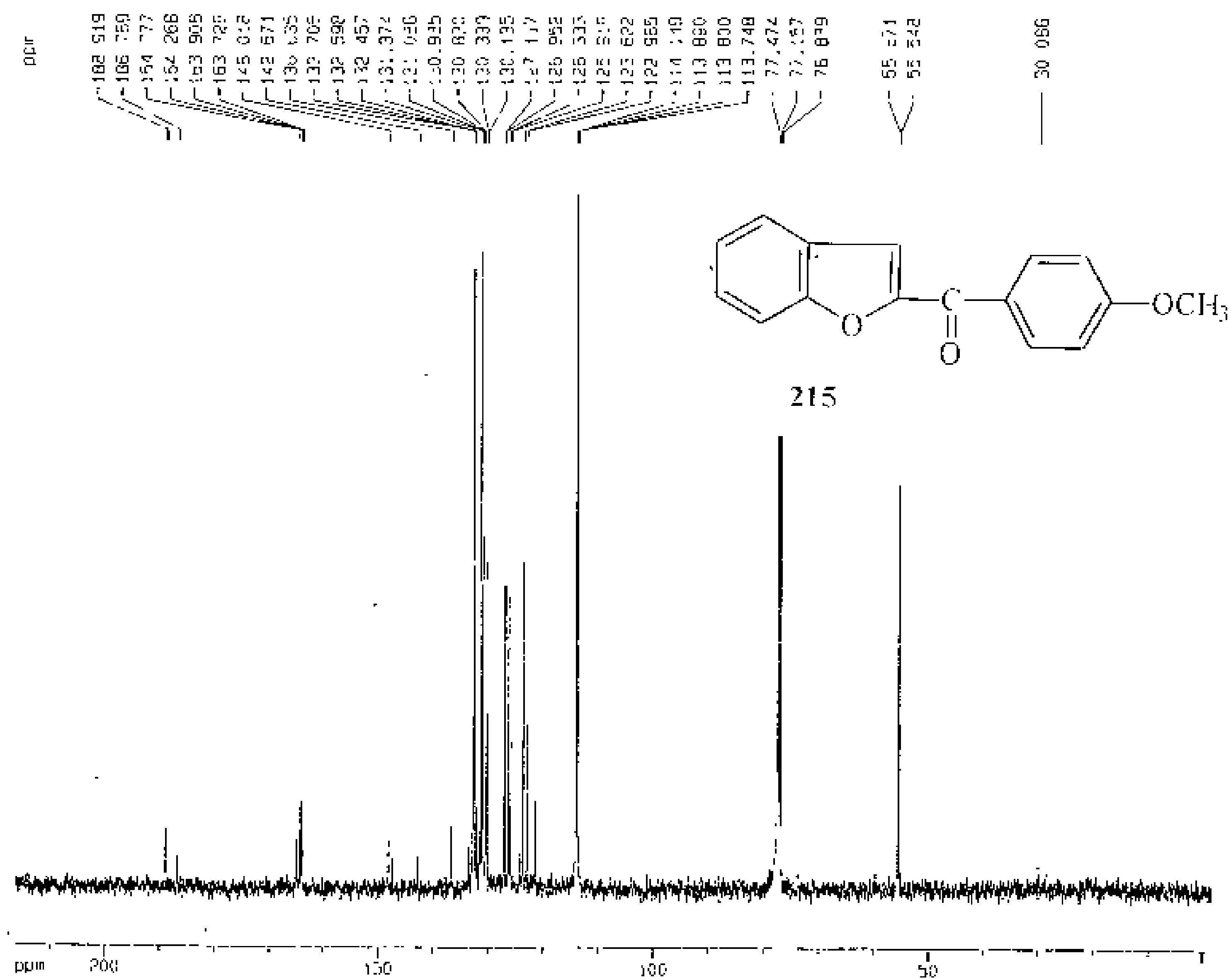
PULPROG zg30
TD 32765
SOLVENT Aceton
NS 60
DS 0
SWH 6410 256 Hz
FIDRES 0 195625 Hz
AQ 2 5559540 sec
RG 64
DW 78.000 usec
DE 3 00 usec
TE 310 0 K
D1 1 00000000 sec

======== CHANNEL f1 ======
NUC1 1H
P1 8 30 usec
PL1 -6 00 dB
SFO1 400 1428010 MHz

F2 - Processing parameters
SI 32768
SF 400 1400048 MHz
WDW EM
SSB 0
LB 0 30 Hz
GB 0
PC 1 40

1D NMR plot parameters
CX 20 00 cm
F1P 11 909 ppm
F1 4774 90 Hz
F2P -0 517 ppm
F2 -247 03 Hz
PPMCM 0 62127 ppm/cm
HZCM 248 59667 Hz/cm

Analytical BCSIR Lab Dhaka 13C Spectrum J-24(a-2) in CDCl3 Jahangir



215

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NAME 4534
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
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Time 16.57
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PROBHD 5 mm Multinuc
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 2577
DS 0
SWH 24154.590 Hz
FIDRES 0.737140 Hz
AQ 0.6783476 sec
RG 16384
DW 20.700 usec
DE 6.00 usec
TE 300.0 K
D1 1.50000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

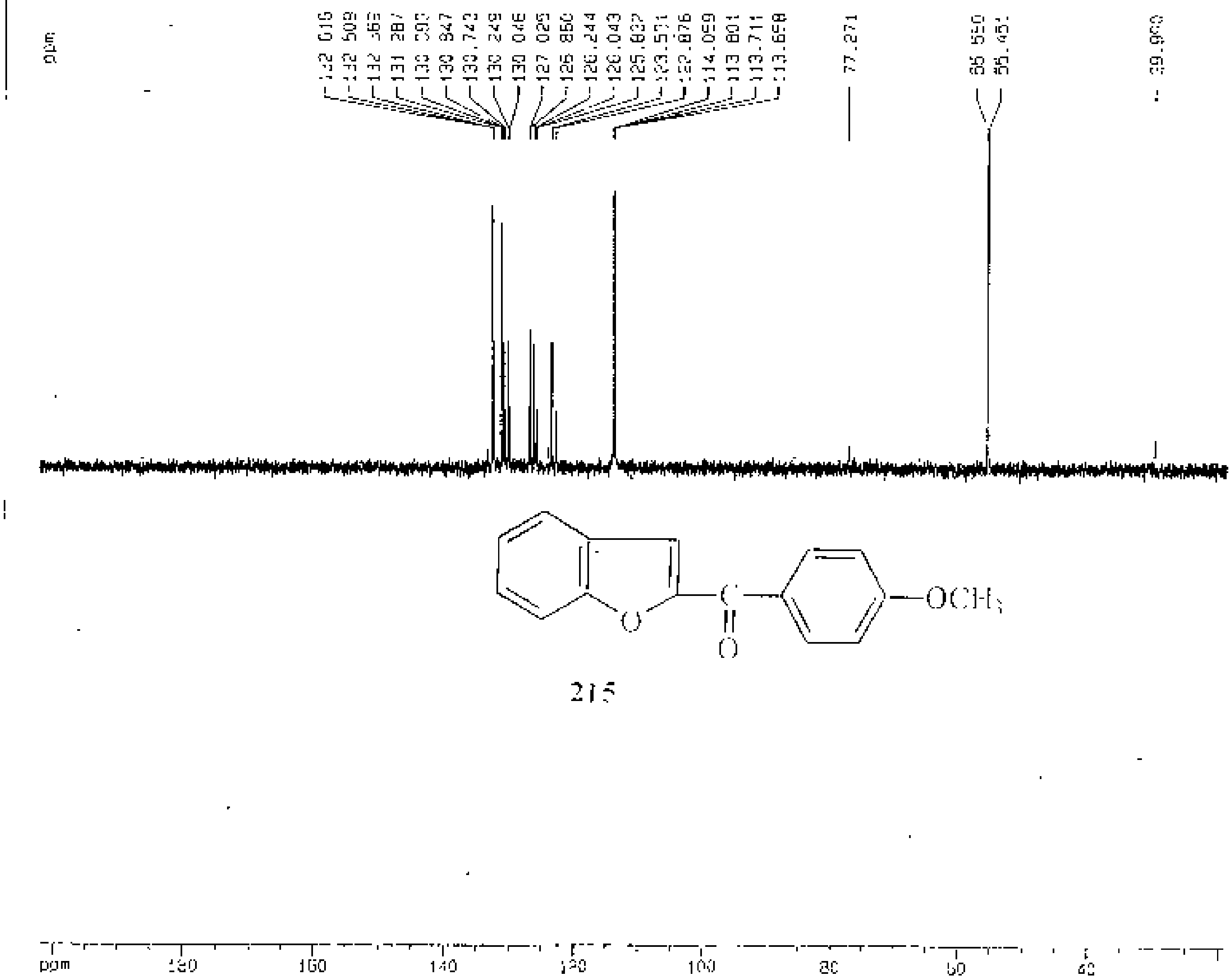
============ CHANNEL f1 ============
NUC1 13C
P1 9.50 us
PL1 -6.00 dB
SFO1 100.6228045 MHz

============ CHANNEL f2 ============
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -2.00 dB
PL12 14.00 dB
PL13 120.00 dB
SFO2 400.1416006 MHz

F2 - Processing parameters
SI 32768
SF 100.6127291 MHz
WDW EM
SSB 0
LB 3.50 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 216.371 ppm
F1 21770.21 Hz
F2P -1.580 ppm
F2 -158.96 Hz
PPMCM 10.90260 ppm/cm
HZCM 1096.99840 Hz/cm

Analytical 8G5IR Lab D.eve, c2c0135 in CDCl3 Jahangir 2DCT



215

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PROCNO 1

F2 - Acquisition Parameters
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Time 14.52
INSTRUM dpx250
PROBHD 5 mm Multinuc
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1470
DS 8
SWH 23075.055 Hz
FIDRES 0.673677 Hz
AQ 0.7242452 sec
RG 11004
DW 22.650 usec
DE 6.00 usec
TE 300.0 K
CNST2 145.0000000
D1 4.00000000 sec
d2 0.00341828 sec
d12 0.00002000 sec
DELTA 0.00000764 sec

======== CHANNEL f1 ========
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P1 6.00 usec
P2 12.00 usec
PL1 -6.00 dB
SFO1 100.6253615 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
P3 6.30 usec
P4 12.60 usec
PCPD2 90.00 usec
PL2 -6.00 dB
PL12 16.00 dB
SFO2 400.1420007 MHz

F2 - Processing parameters
SI 32768
SF 100.6157618 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
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F2P 18.904 ppm
F2 1901.00 Hz
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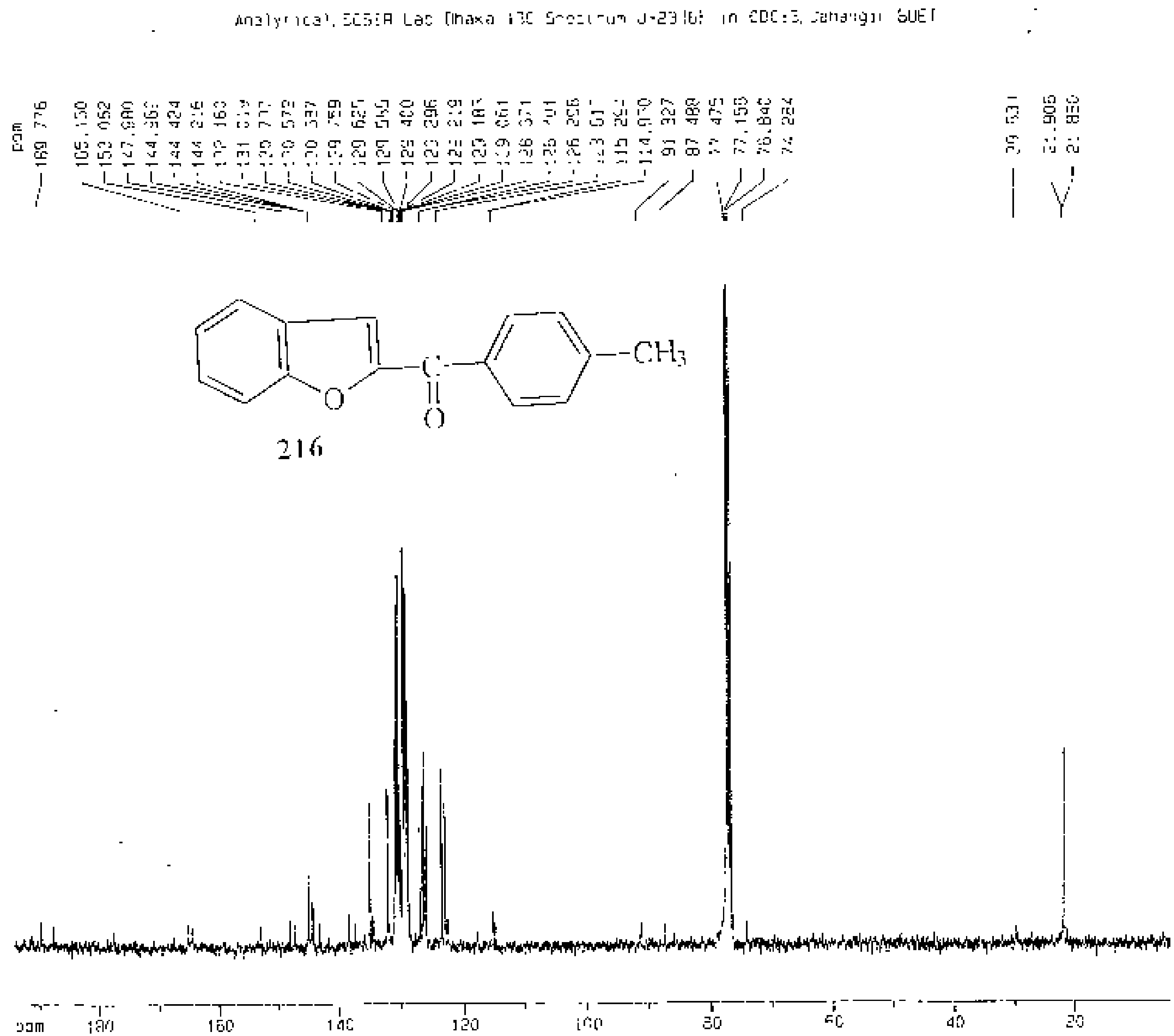
HZCM 920.37019 Hz/cm



Current Data Parameters

NAME	4507
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	24020323
Time	17.05
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PROBHD	5 mm Multinuc
PULPROG	zgpg
TD	32768
SOLVENT	CDCl3
NS	6690
DS	0
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	1.0790476 sec
RG	16384
DW	20.700 usec
DE	[illegible]
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	6.00 usec
PL1	-6.00 dB
SFO1	100.6257045 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-5.00 dB
PL12	15.00 dB
PL13	120.00 dB
SFO2	400.1400300 MHz

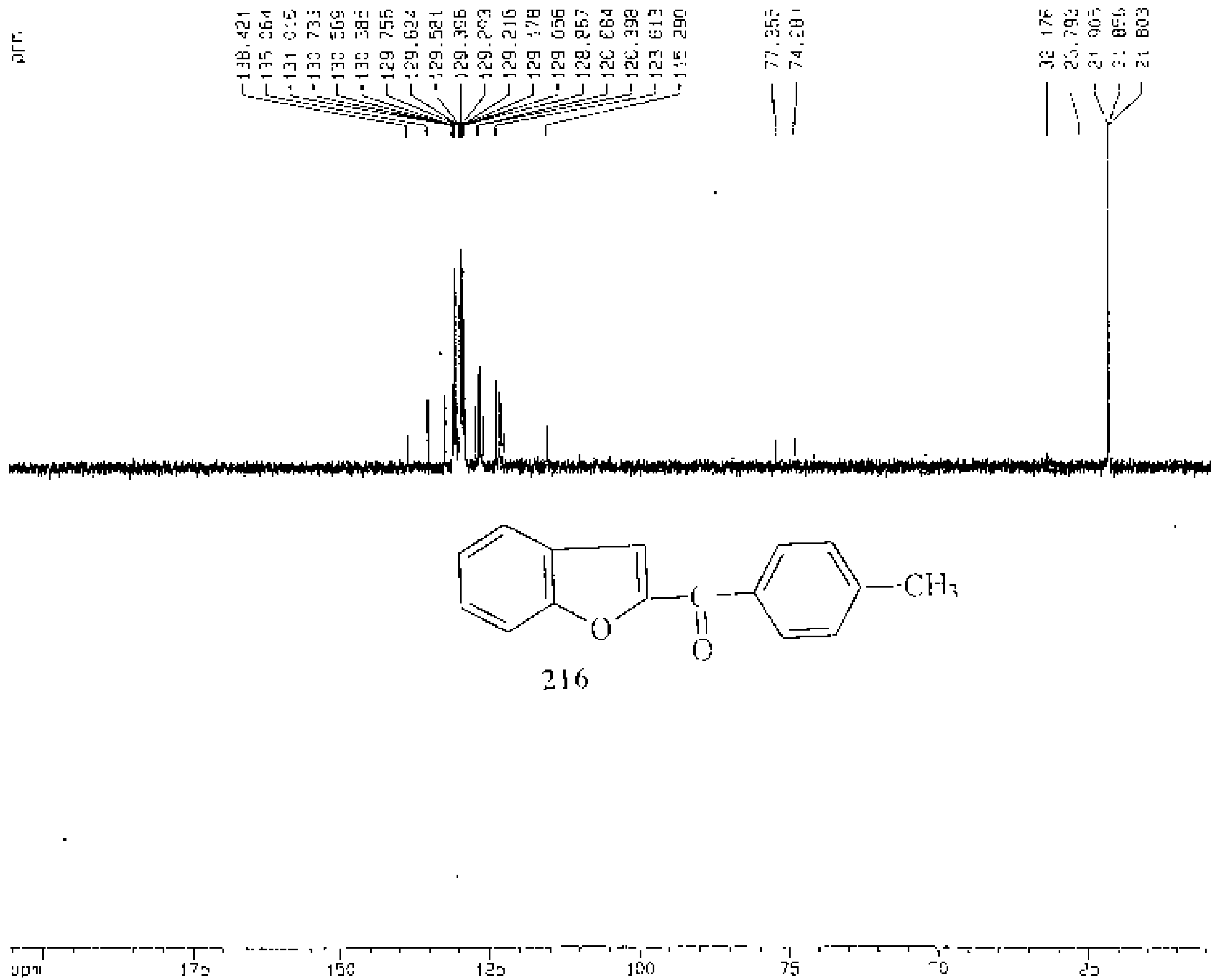
F2 - Processing parameters

SI	32768
SF	100.6127290 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

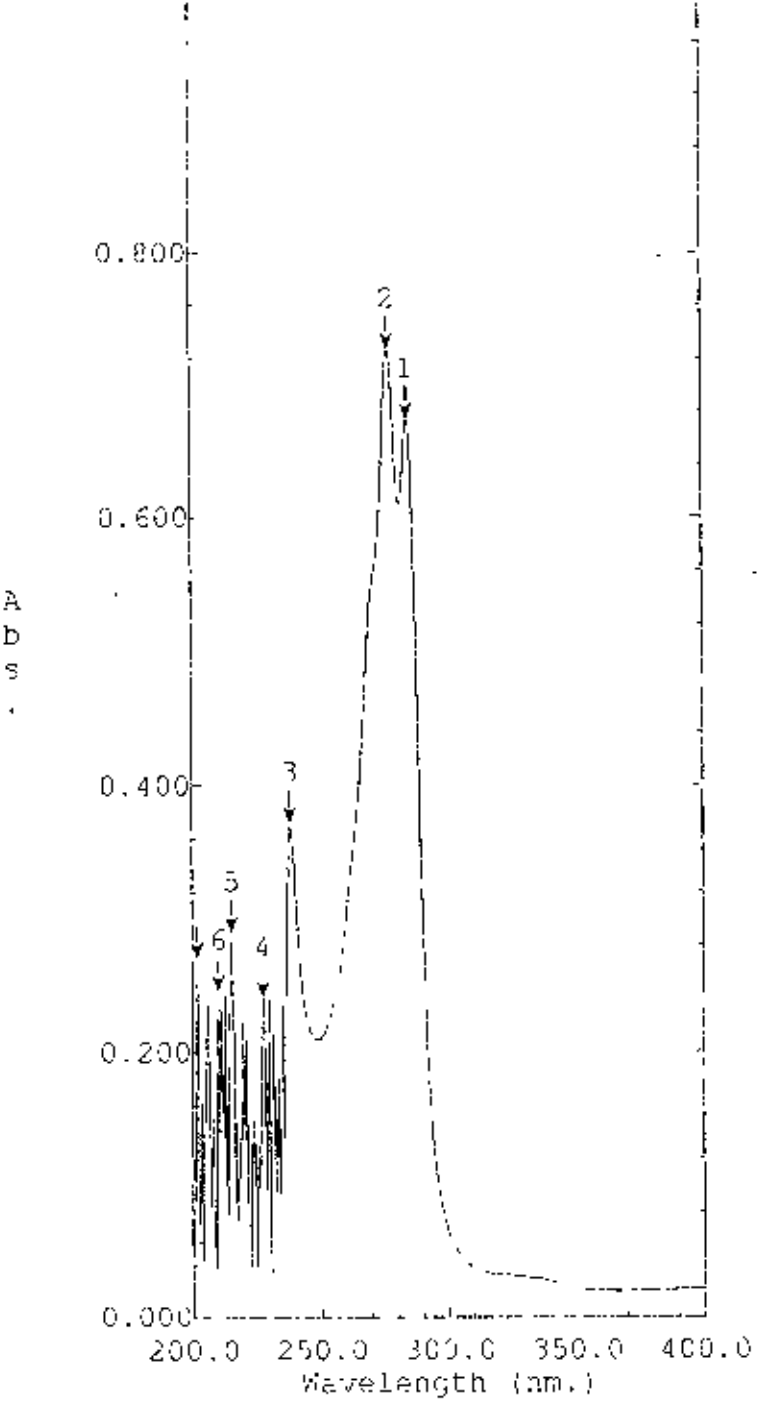
CX	20.00 cm
F1P	94.294 ppm
F1	19545.86 Hz
F2P	3.882 ppm
F2	390.60 Hz
PPMCM	9.52060 ppm/cm
HZCM	957.91303 Hz/cm

Analytical, BCSIR Lab Dhaka dept135 J-22 in CDCl3 Jahangir, Sat



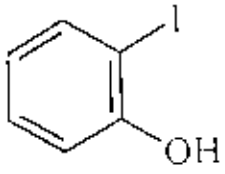
216

Current Data Parameters



Peak Pick

No.	Wavelength (nm.)	Abs.
1	284.60	0.6741
2	277.20	0.7267
3	238.20	0.3719
4	227.60	0.2407
5	215.40	0.2896
6	210.20	0.2455
7	202.00	0.2705

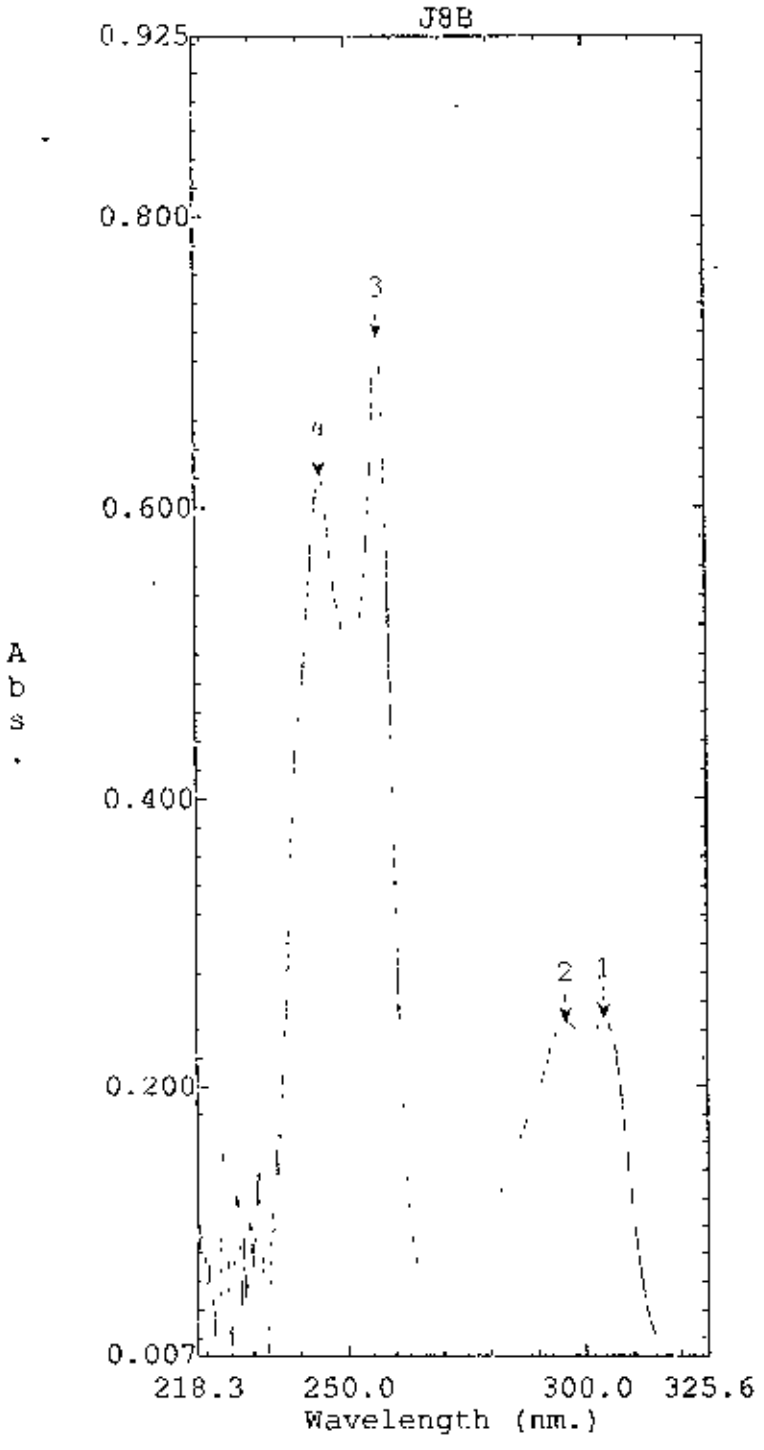


47

File Name: J13

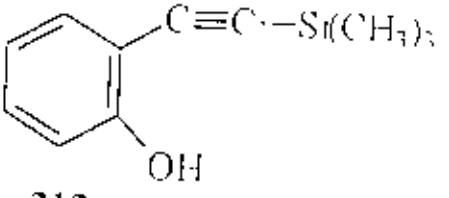
Created: 16:38 03/19/02
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2



Peak Pick

No.	Wavelength (nm.)	Abs.
1	304.00	0.2474
2	295.80	0.2451
3	256.80	0.7157
4	244.60	0.6206
5	207.00	0.2102
6	203.20	0.1952
7	201.00	0.2423

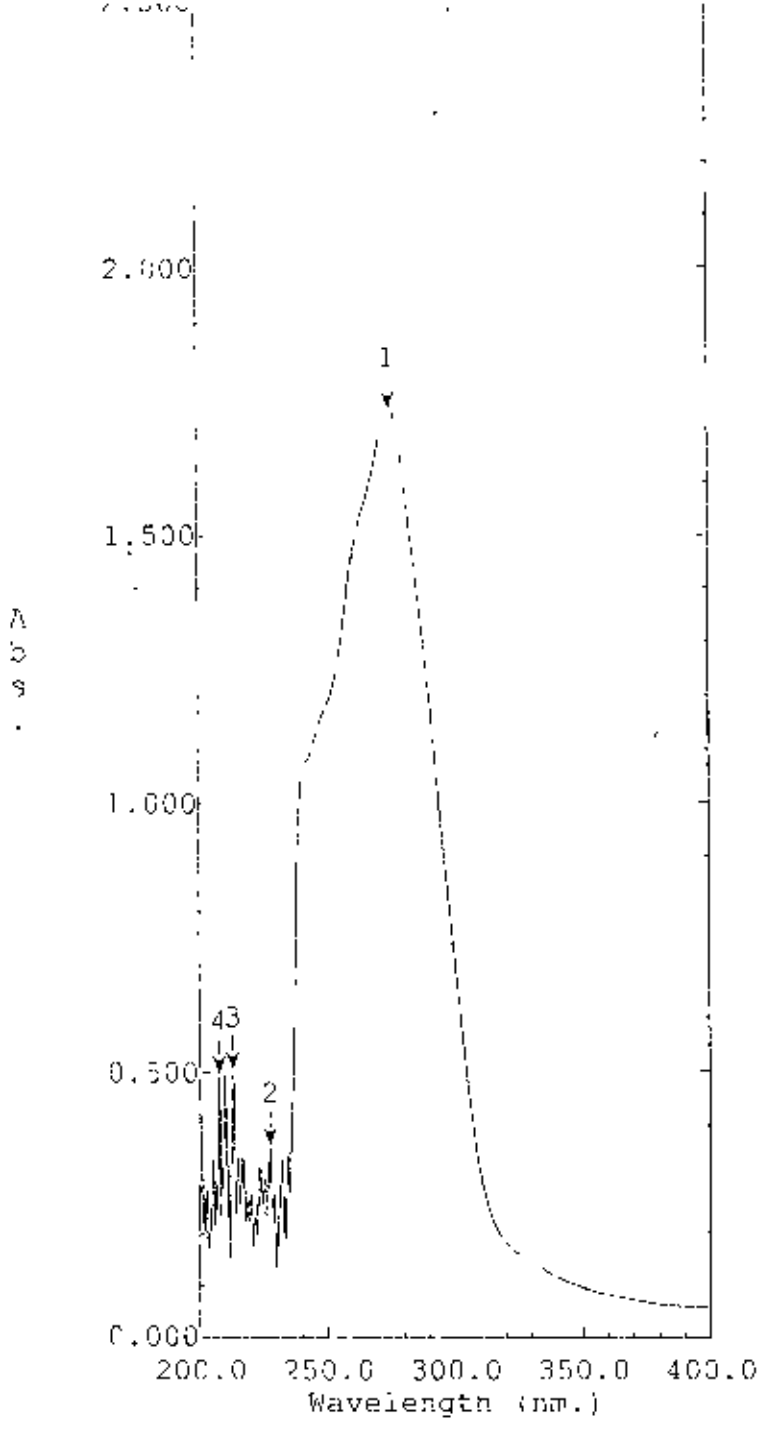


212

File Name: J8B

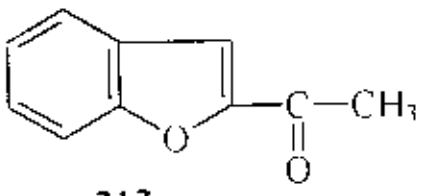
Created: 16:17 03/20/02
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2



Peak Pick

No.	Wavelength (nm.)	Abs.
1	275.20	1.7379
2	227.40	0.3669
3	213.00	0.5068
4	207.40	0.4999

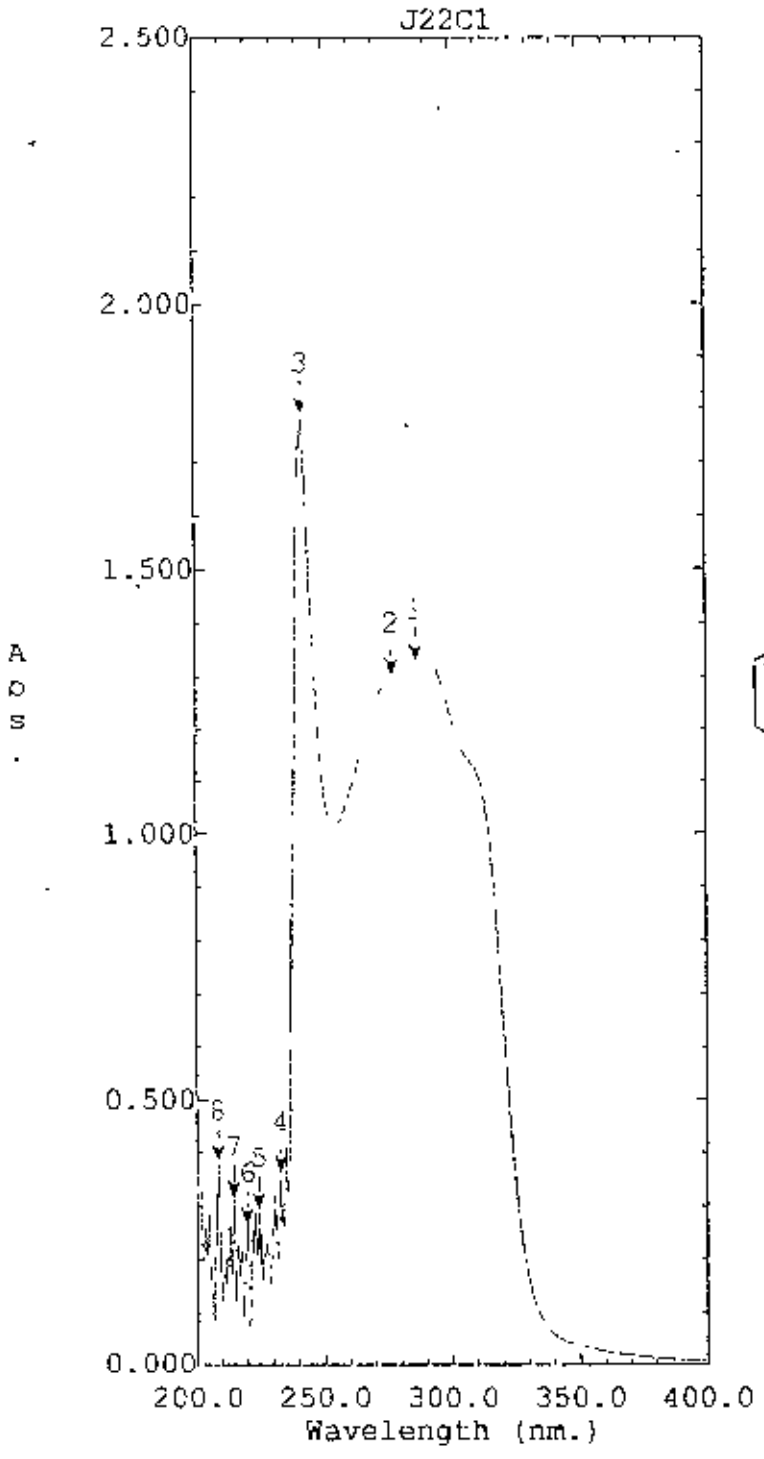


213

File Name: J19B

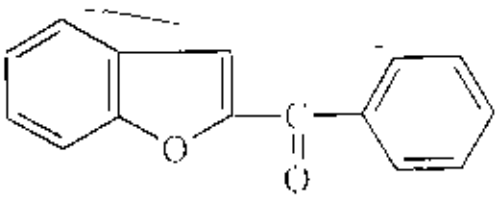
Created: 16:12 03/19/02
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2



Peak Pick

No.	Wavelength (nm.)	Abs.
1	286.20	1.328
2	276.80	1.303
3	241.60	1.793
4	232.80	0.365
5	224.00	0.295
6	219.40	0.266
7	214.20	0.316
8	208.00	0.384

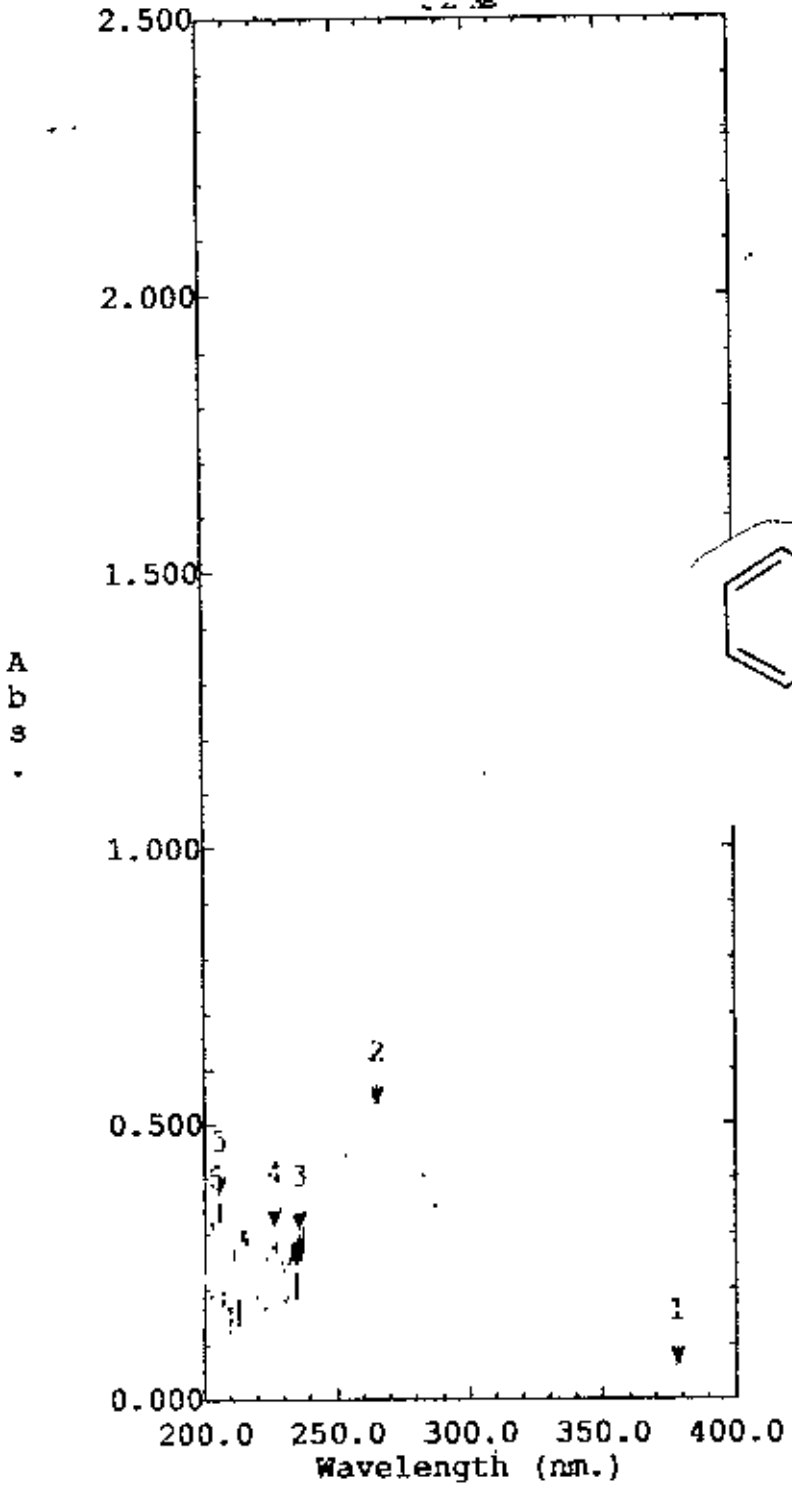


214

File Name: J22C1

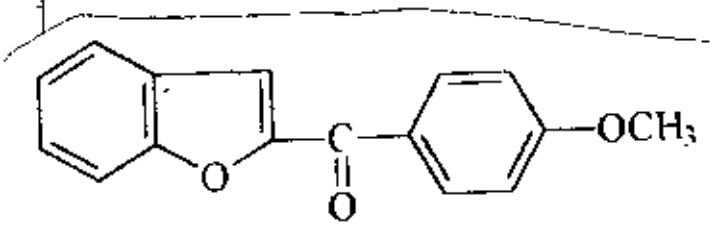
Created: 16:11 03/20/02
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2



Peak Pick

No.	Wavelength (nm.)	Abs.
1	378.20	0.065
2	265.20	0.53
3	235.60	0.31
4	226.40	0.31
5	205.60	0.37
6	203.60	0.30



215

File Name: J24B

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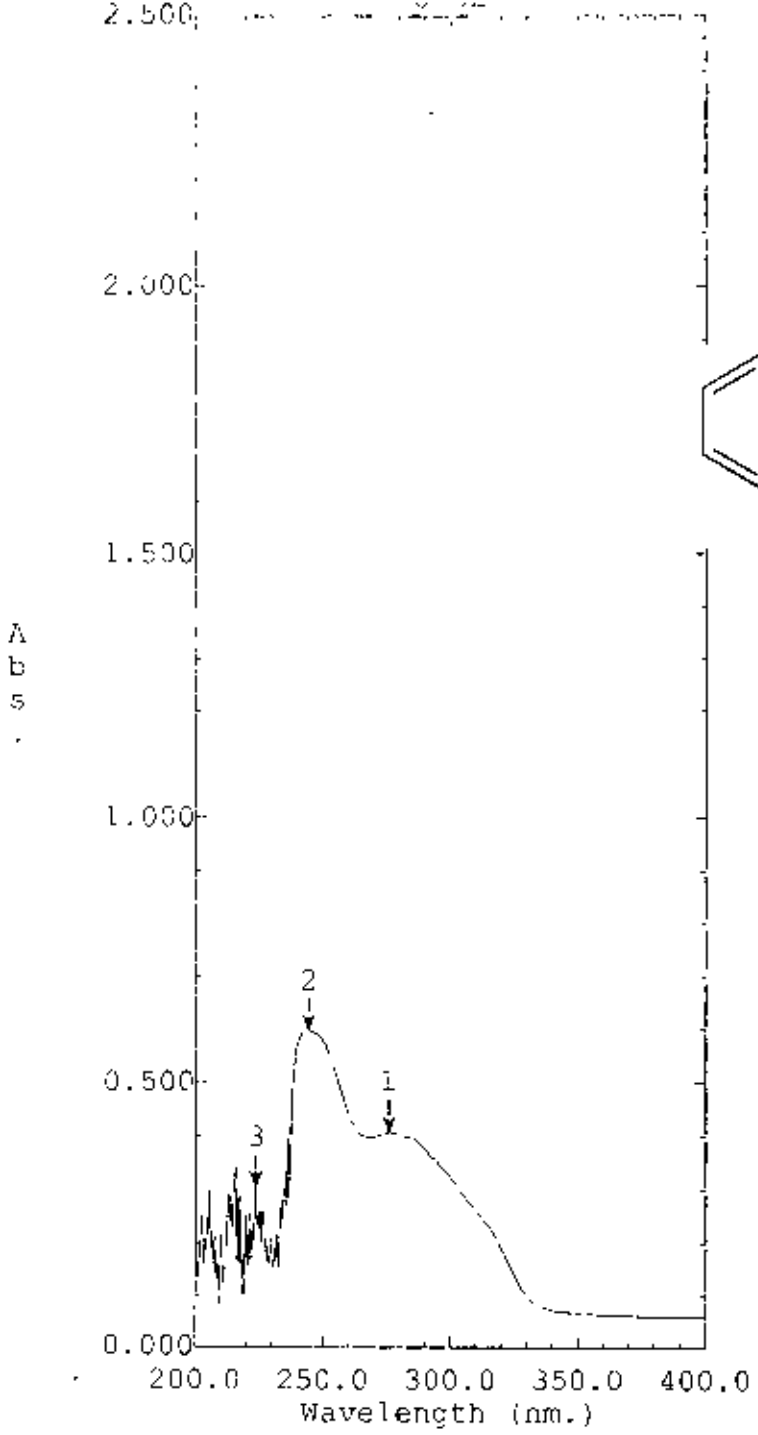
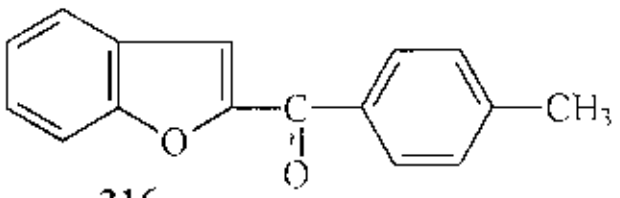
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2



Peak Pick

No.	Wavelength (nm.)	Abs.
1	275.80	0.4058
2	244.20	0.5959
3	223.40	0.3018

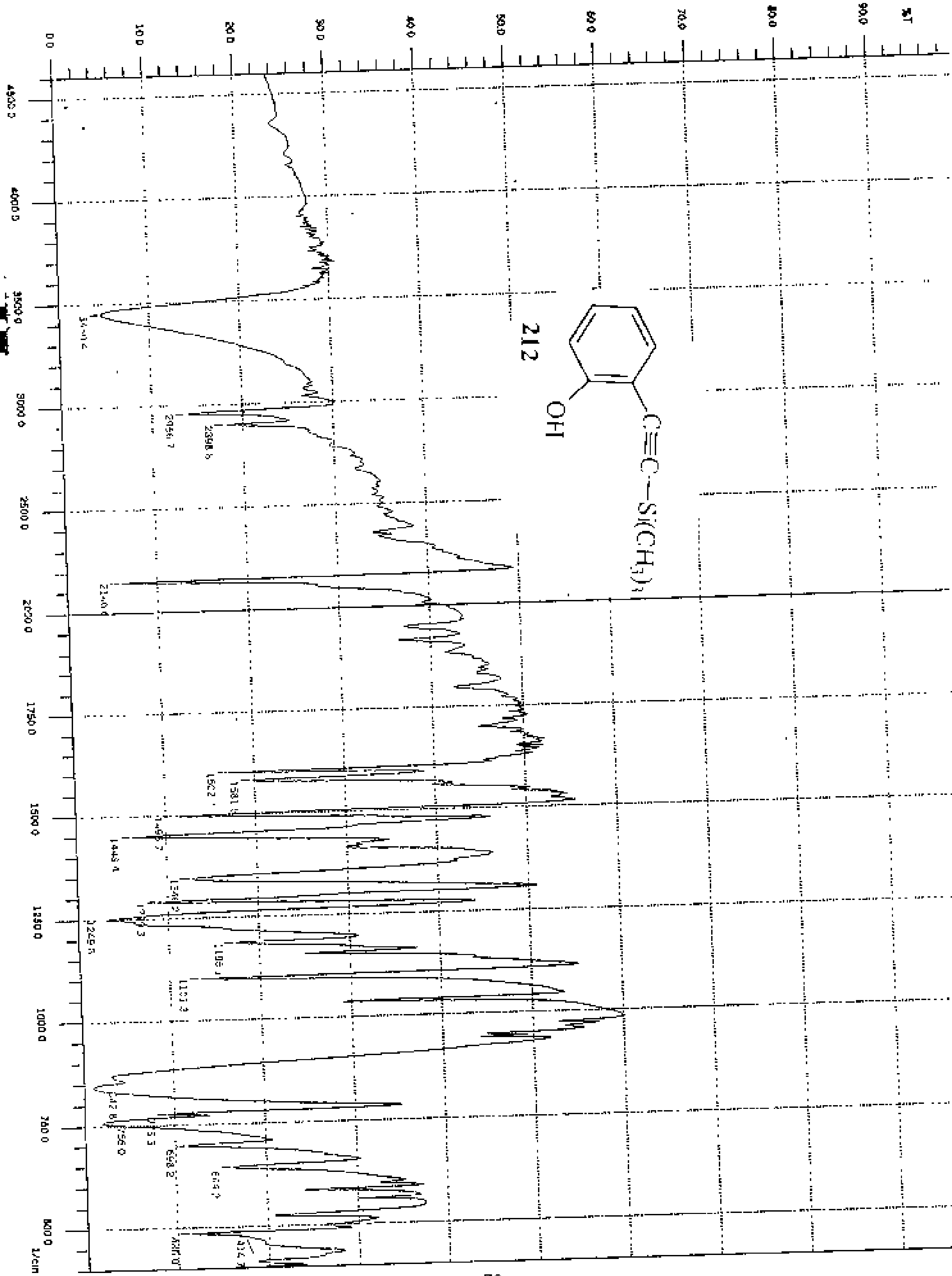


216

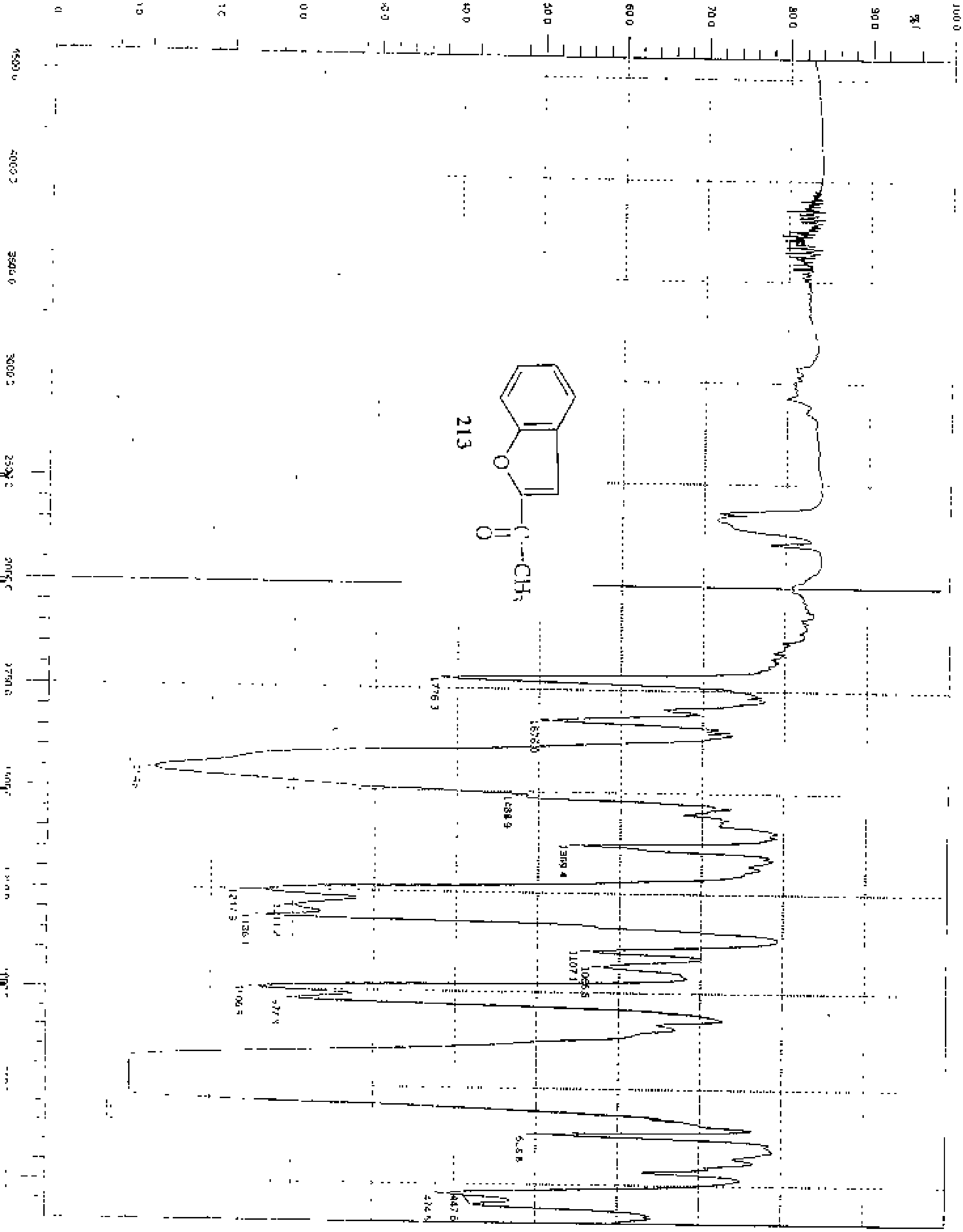
File Name: J23B

Created: 16:07 03/19/02
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2



212


213
1776.3
1359.4
1107.1
447.6

215
OCH3

SECTION - 3

Present Work

Synthesis of 2-Acylbenzofurans from *o*-Iodophenol Through Combined Palladium Catalyzed and Friedel-Crafts Reactions.

3. Present Work: Synthesis of 2-Acylbinzofurans from *o*-Iodophenol Through Combined Palladium Catalyzed and Friedel-Crafts Reactions.

3.1 Rationale :

We wanted to synthesis 2-acylbenzofuran from *o*-iodophenol through combined palladium catalyzed and Friedel-Crafts reaction. We have obtained a mixture of two isomeric product through palladium catalyzed and Friedel-Crafts reactions from *o*-iodophenol described in the section-2. Later we decided to protect the OH group of *o*-iodophenol as acetate to develop the process for synthesizing 2-acylbenzofurans.

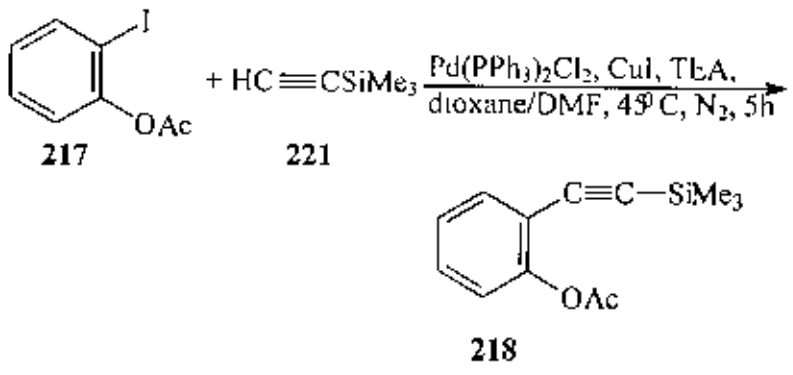
3.2 Results and Discussion :

Here we demonstrate a novel approach where a palladium catalyzed reaction was followed by Friedel-Crafts acylation and simultaneous cyclization to obtain 2-acylbenzofurans in excellent yields. *o*-Acetoxyphenyl iodide **217** underwent facile reaction with acetylenic compound **221** in the presence of $(PPh_3)_2PdCl_2$ and CuI at 45^0C to yield *o*-(trimethylsilyl)ethynylphenyl acetate **218** in excellent yield. The compound **218** was then subjected to Friedel-Crafts reaction with acid chlorides **222** – **225** or acetic anhydride **226** to afford the 2-substituted benzofurans **213a** – **216a** in excellent yields as shown in **scheme-55**.

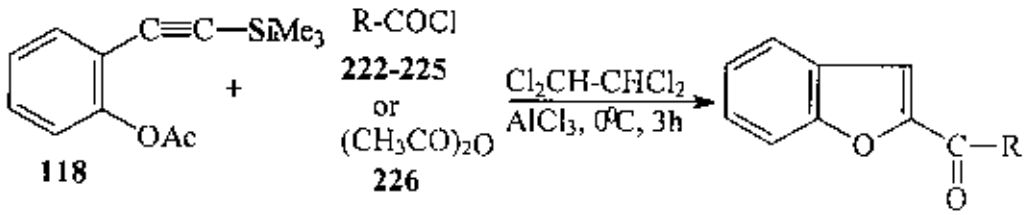
An ice cold solution of a *o*-(trimethylsilyl)ethynylphenyl acetate **218**, anhydrous aluminium chloride (4 mol eq) and acid chloride **222** – **225** (1.5 mol eq) or acetic anhydride **226** (1.5 mol eq) in tetrachloroethane was stirred at $0^0 - 25^0$C for 1 – 2 h (acid chloride) or 3–4h (acetic anhydride) to yield 2-substituted benzofurans **213a – 216a**.

In the case of acetyl chloride and acetic anhydride we also found two isomeric products. But in the case of aroyl chlorides **223** – **225** we obtained single product. The yield percentage was higher (91 – 95%) than the earlier process.

Scheme - 55



217 **221** **218**



118

R = CH_3, C_6H_4, *p*MeO-C_6H_4, *p*Me-C_6H_4

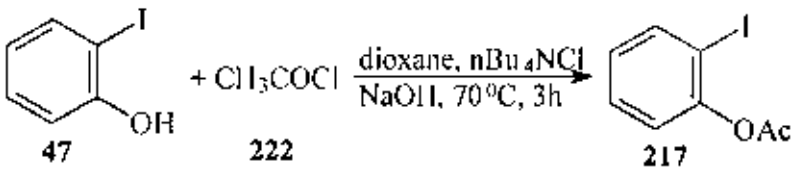
213a, R = CH_3
214a, R = Ph
215a, R = *p*McOC_6H_4
216a, R = *p*McC_6H_4

3.2.1 Starting Materials:

Synthesis of *o*-acetoxyphenyl iodide 217:

o-Acetoxyphenyl iodide have been used as starting materials because of their easy availability from *o*-iodophenol **47**. *o*-Iodophenol **47** was converted to *o*-acetoxyphenyl iodide **217** by heating with dioxane, n-Bu_4NCl, NaOH at 70^{0}C for 3 hour (shown in **scheme-56**). *o*-Acetoxyphenyl iodide **217** was characterized by its UV, IR, ^{1}HNMR. The ^{1}HNMR and IR spectra of the compound **217** showed absence of –OH group. In the IR spectrum C = 0 stretching vibration was observed at 1776 cm^{-1} and in the ^{1}HNMR sharp singlet at δ 2.38 was found for $COCH_3$. The compound *o*-acetoxyphenyl iodide was obtained as light yellow liquid.

Scheme-56



47 **222** **217**

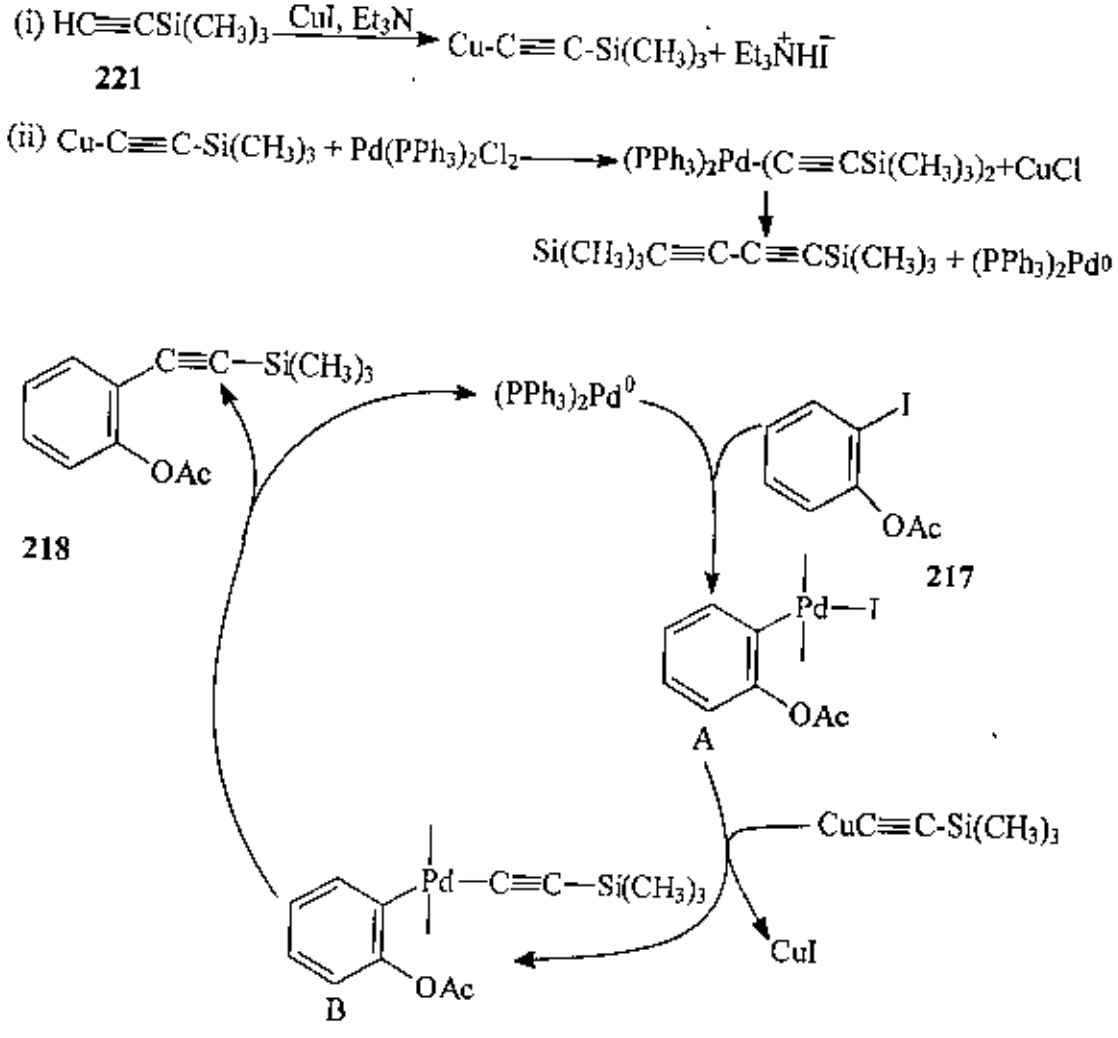
3.3 Characterization of Products:

2-Substituted benzofurans **213a** – **216a** were well characterized by their satisfactory spectroscopic (IR, UV, ^{1}HNMR and ^{13}CNMR) data. The IR spectra showed C = O stretching vibration in the range 1680–1778cm^{-1}. Appearance of two singlet at δ 6.5 and 6.6 in the ^{1}HNMR spectra was assigned to be 3-H of 2-acetyl benzofuran **213a**. The ^{1}HNMR spectra of the compound **213a** showed two sharp singlet at δ 2.3 and 2.40 for $COCH_3$ proton. In the case of aroyl benzofurans **214a** – **216a** the ^{1}HNMR spectra showed chemical shift positions at aromatic zone (7.0–7.3) for 3-H. The ^{1}HNMR spectra of the compund 2-anisoyl benzofuran **215a** showed a sharp singlet at δ 3.91 for $ArOCH_3$ proton. Similarly the ^{1}HNMR spectra of the compound 2-toluoylbenzofuran **216a** showed a singlet at δ 2.44 for $ArCH_3$ proton. The ^{13}CNMR spectra of 2-acetylbenzofuran showed two signals for C = O at δ_c **196** and **195** and two signals at δ_c 114.45 and 114.25 for C–3. The ^{13}CNMR spectra of 2-aroylbenzourans showed signal for –C = O at δ_c 196 – 188, one signal at δ_c 55.56 for $ArOCH_3$ group and one signal for each compound at δ_c 116 – 112 for C–3. The ^{1}HNMR and ^{13}CNMR spectra indicate the presence of two isomeric compound in the case of 2-acetylbezofuran **213a** and one compound in each synthesized 2-aroylbenzofurans **214a** – **216a**. The UV spectra of all the compounds **213a** – **216a** showed absorption in the range λ_{max} /nm 320 – 250.

3.4 Mechanism:

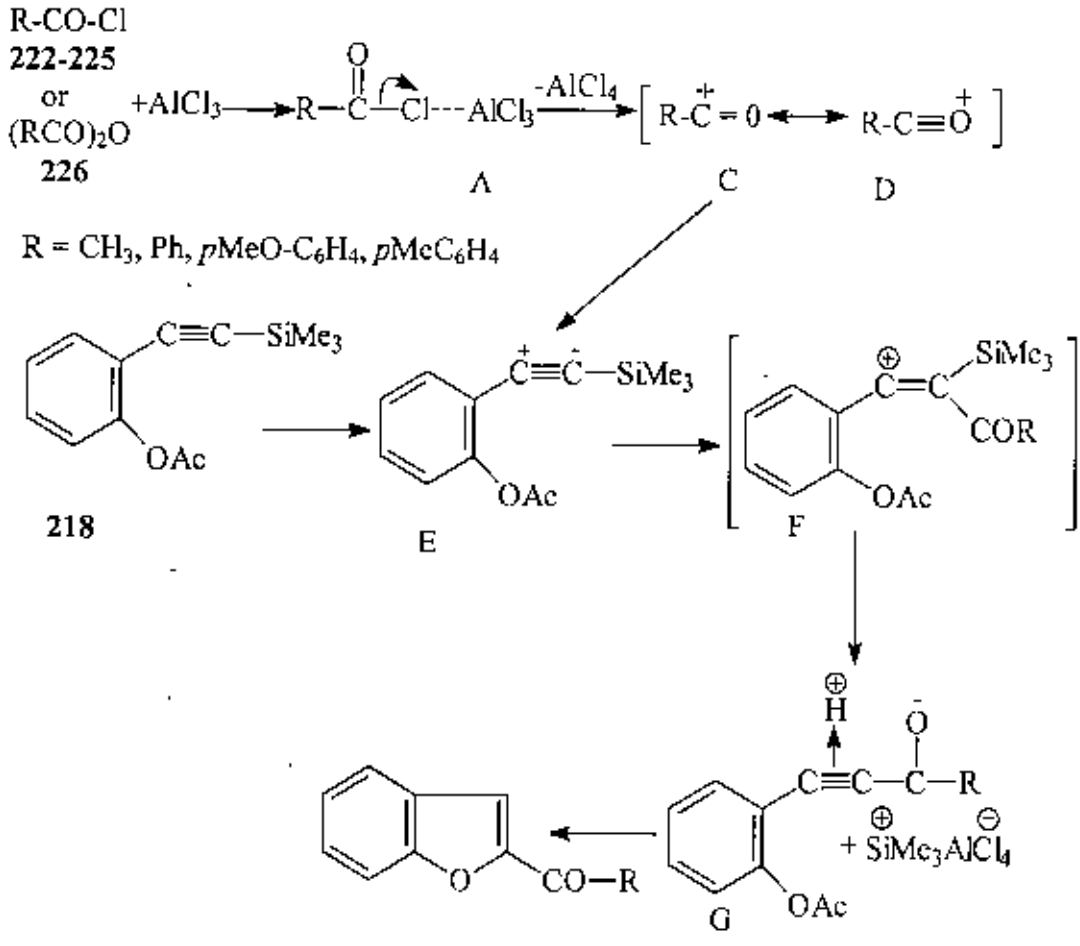
a) A mechanism for the formation of *o*-(trimethylsilyl)ethynylphenyl acelate **218** through palladium catalyzed reaction of *o*-acetoxyphenyl iodide **217** with alkyne **221** having a terminal acetylenic group as shown in **scheme-57** which is similar to **scheme-53** (described in section-2).

Scheme-57



b) The acylation of *o*-(trimethylsilyl) product **218** was carried out by an acid chloride or acetic anhydride in the presence of Lewis acid ($AlCl_3$). The mechanism of this reaction as shown in **scheme-58** which is similar to **scheme-54** (described in section-2).

Scheme-58



213a, R = CH_3
214a, R = Ph
215a, R = *p*MeO-C_6H_4
216a, R = *p*Me-C_6H_4

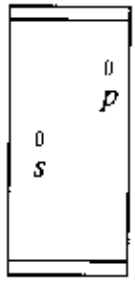
3.5 Conclusion:

In this section we have described a very convenient and elegant method for synthesis of 2-acylbenzofurans from *o*-acetoxyphenyl iodide through palladium catalyzed reaction followed by Friedel-Crafts acylation. In the case of aroyl chloride we obtained one isomer but in the case of acetyl chloride and acetic anhydride we also obtained two isomeric products.

3.6 Experimentals:

o-Acetoxy phenyliodide 217:

To a well-stirred mixture of *o*-iodophenol **47** (3 g, 13.64 mmol), dioxane (25 ml), *n*-Bu_4NCl (20 mg) and powdered NaOH (1 g), a solution of acetyl chloride (1.59 ml, 20.46 mmol) in dioxane (15 ml) was added dropwise over 30 min. at room temperature. The solution was stirred at 70^0C for 3 hour. The progress of the reaction was monitored by T.L.C. (hexane-chloroform, 6:1) (R_f value = 0.78) which indicated complete conversion of starting material into one faster moving product.



S = Reactant

P = Product

The mixture was filtered, washed with dioxane, evaporated and dried. The residue was purified through a silica gel column with hexane-chloroform (6:1) to obtain a title compound **217** as a syrupy (2.95 gm, 82.26%).

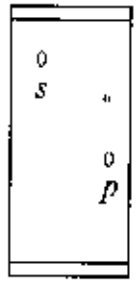
IR (CCl_4) : ν_{max} 1776, 1548, 1469, 1291, 840, 820, 730 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 284.6, 277.2, 238.2 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 7.84–6.96, (m, 4H, ArH), 2.38 (s, 3H, $COCH_3$).

o-(Trimethylsilyl)ethynylphenyl acetate 218:

To a stirred solution of *o*-acetoxyphenyliodid **217** (1 g, 4.82 mmol) $PdCl_2(PPh_3)_2$ (0.06 g, 0.09 mmol) copper(I)iodide(0.02 g, 0.10 mmol) and triethylamine (3 ml) in dioxane were added (trimethylsilyl)acetylene (1.5 ml, 10.86 mmol). The reaction mixture was stirred at 50^0C for 10 hour under N_2 atmosphere. The progress of the reaction was monitored by T.L.C (hexane-chloroform 3:1) (R_f value = 0.40) which indicated completion of the reaction with the formation of slower moving product.



The solvent was removed under reduce pressure. To a residue diethyl ether and 0.1 NHCl solution were added and the organic layer was separated, neutralized with a saturated $NaHCO_3$ (3×30 ml), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The latter was purified by silica gel column with hexane-chloroform (3:1) to obtain the compound **218** (2.06 gm, 91.15%) as a liquid.

IR (KBr) : ν_{max} 2289, 1776, 1548, 1258 cm^{-1}.

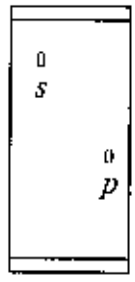
UV ($CHCl_3$) : λ_{max} 304.20, 296.00, 256.80, 244.60 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 7.50 (dd, J=7.65, 1.46 Hz, 1H, ArH), 7.33 (ddd, J=7.82, 1.54 Hz, 1H, ArH), 7.20–7.16 (m. 1H, ArH), 7.01 (d, J = 8.03 Hz, 1H, ArH), 2.33 (s, 3H, $COCH_3$), 0.24 [s, 9H, $Si(CH_3)_3$]

^{13}CNMR (400 MHz, $CDCl_3$) : δc 166.4, 151.9, 133.0, 129.5, 125.7, 125.6, 122.0, 117.1, 99.5, 77.0, –0.25.

2-Acetylbenzofuran 213a, 2-benzoylbenofuran 214a 2-(*p*-methoxybenzoyl)-benzofuran 215a and 2-(*p*-methylbenzoyl)benzofuran 216a:

To an ice-cold solution of *o*-(trimethylsilyl)ethynylphenyl acetate **218** (200 mg, 0.86 mmol) in tetrachloroethane (10 ml) acetyl chloride, acetic anhydride, benzoylchloride, *p*-anisoyl chlorid and *p*-toluoyl chloride (1.5 mol eq) and anhydrous $AlCl_3$ (4 mol eq) were added. The mixture was stirred under N_2 for 3–5h and the temperature of the reaction was raised from 0^0C to 25^0C. The progress of the reaction was monitored by T.L.C. which indicated completion of the reaction with the formation of slower moving product.



S = Reactant

P = Product

Usual work-up (as described earlier) and chromatographic purification (Hexane-Chloroform, 1:1 as eluant) afforded 2-substituted bezofurans **213a** (92.02%) (as syrupy) **214a** (93.42%) (as solid), **215a** (92.43%) (as solid) and **216a** (90.53%) (as liquid).

2-Acetylbenzofuran 213a:

IR (CCl_4) : ν_{max} 1776, 1676, 1548 and 1488 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 275.2, 227.4 nm

^{1}HNMR (400 MHz, $CDCl_3$) : δ 7.70–7.11 (m, 8H, ArH) 6.61 (s, 1H, 3-H)

6.51 (s, 1H, 3-H), 2.43 [s, 3H, $COCH_3$, 2.37 (s, 3H, $COCH_3$).

^{13}CNMR (400 MHz, $CDCl_3$) : δc 196.49 (CO), 195.65 (CO), 169.05, 168.85, 168.77, 167.86, 153.05, 147.58, 134.40, 132.55, 131.72, 131.45, 126.35, 126.25, 122.80, 122.44, 114.45 (C-3), 114.25 (C-3), 29.93 (CH_3), 29.80 (CH_3).

2-Bezoyl benzofuran 214a:

IR (KBr) : ν_{max} 1697, 1652, 1525 and 1548 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 310 and 220 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 8.64–8.60 (m, 1H, ArH), 8.50–8.49 (m, 1H, ArH), 8.31–8.28 (m, 2H, ArH, 8.08–8.05 (m. 1H, ArH), 7.98–7.77 (m 5H, ArH).

^{13}CNMR (400 MHz, $CDCl_3$) : δc 178.74 (CO), 170.81, 163.65, 156.36, 133.96, 133.65, 131.75, 130.06, 129.14, 128.48, 126.41, 125.81, 125.37, 124.92, 118.18 (C-3).

^{13}CNMR (400 MHz $CDCl_3$, DEPT, 135): δc 133.54, 132.97, 131.79, 130.25, 129.18, 128.87, 126.45, 125.85, 125.41, 118.23 (3-H).

2-(*p*-Methoxybenzoyl)benzofuran) 215a:

IR (KBr) : ν_{max} 1735, 1637, 1600 and 1510 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 315.0, 260.2 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 8.31–8.25 (m, 2H, ArH), 8.18–8.09 (m, 1H, ArH) 8.07–7.96 (m, 1H, ArH), 7.88–7.71 (m, 1H, ArH), 7.50–7.29 (m, 3H, ArH), 7.02–7.00 (m, 2H, ArH), 3.91 (s, 3H, OCH_3).

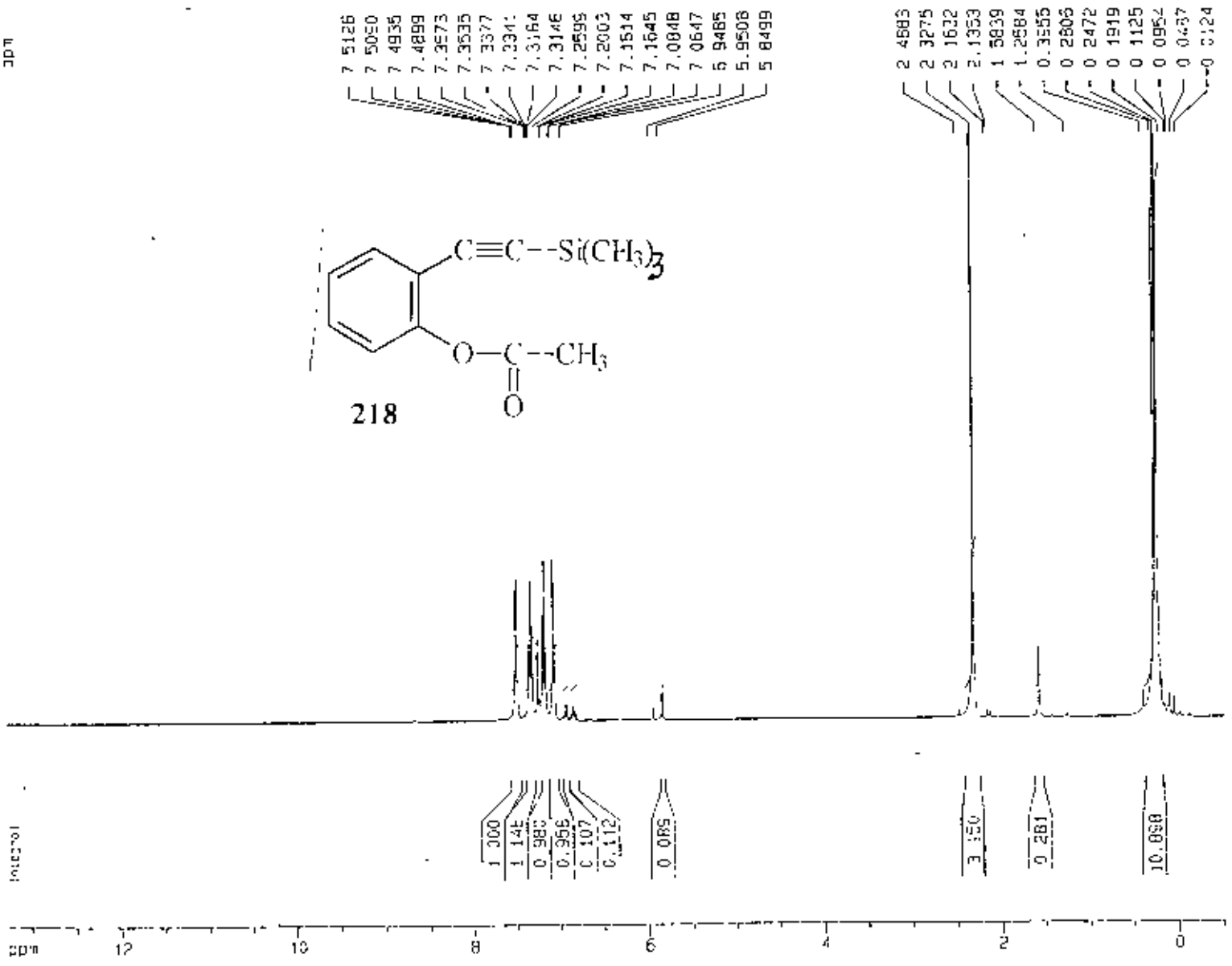
^{13}CNMR (400 MHz, $CDCl_3$) : δc 187.86 (CO), 164.23, 163.52, 147.95, 142.56, 136.69, 132.68, 131.91, 130.72, 130.24, 226.59, 126.01, 123.23, 114.37, 113.75 (C-3), 55.56 (OCH_3).

2-(*p*-Methylbenzoyl benzofuran) 216a :

IR (CCl_4) : ν_{max} 1765, 1610, 1575, 1545 cm^{-1}.

UV (CHCl3) : λ_{max} 275.8, 244.2 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 8.19–8.09 (m, 1H, ArH), 7.88–6.60 (m, 8II, ArH), 2.44 (s, 3H, CH_3).



218

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PROCNO                   1

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SWH              6410.256 Hz
FIDRES           0.195525 Hz
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RG                      64
DW                 78.000 usec
DE                  6.00 usec
TE                 310.0 K
D1               1.00000000 sec

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PL1                 -6.00 dB
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F2 - Processing parameters
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WDW                     EM
SSB                      0
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GB                       0
PC                    1.40

1D NMR plot parameters
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F1                  5314.44 Hz
F2P                 -0.510 ppm
F2                  -203.90 Hz
PPMCM             0.66603 ppm/cm
HZCM              262.52364 Hz/cm
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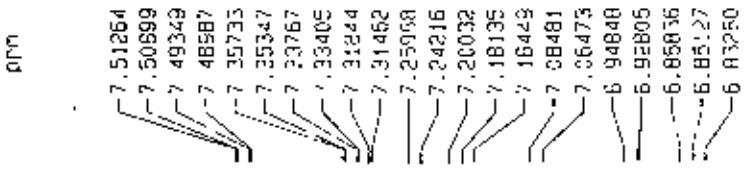
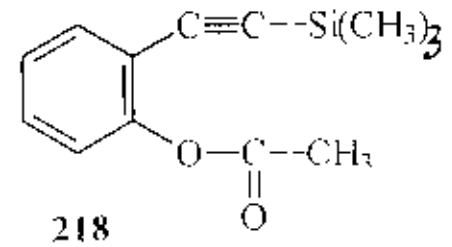
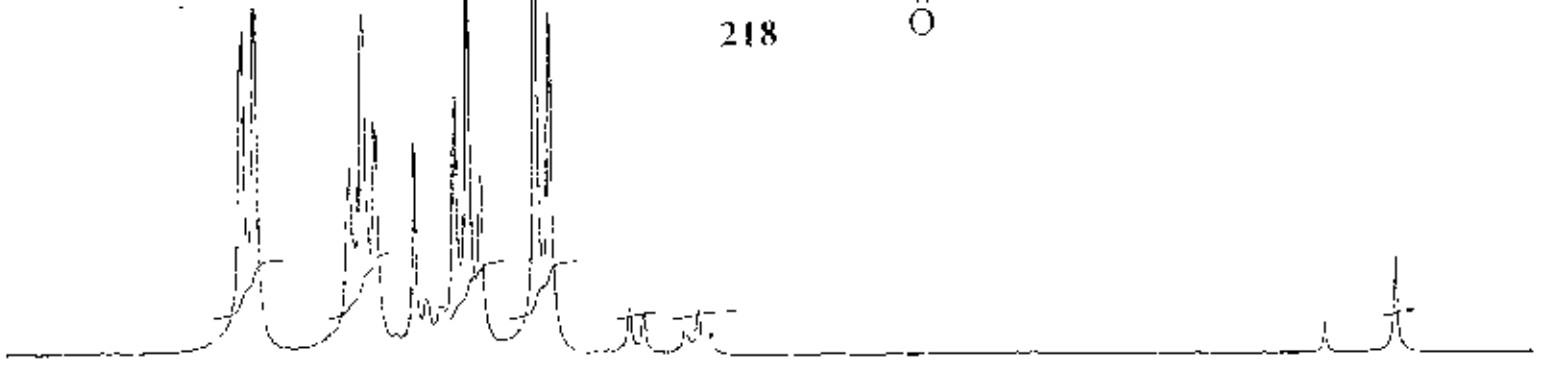
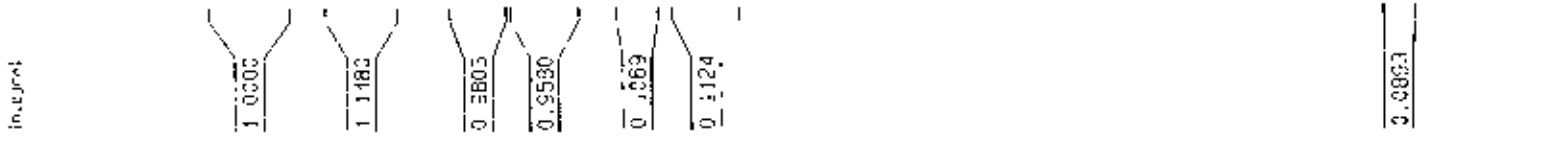
Analytical, BCSIR Lab Dhaka 1H Spectrum, 0.25%(W) in CDCl3 (Jahangir, DJE)





218





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PROCNO 1

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PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 128
DS 0
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5599540 sec
RG 64
DW 78.000 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==
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P1 8.30 usec
PL1 -6.00 dB
SFO1 400.1428010 MHz

F2 - Processing parameters
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SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 21.62 cm
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F2 2661.33 Hz
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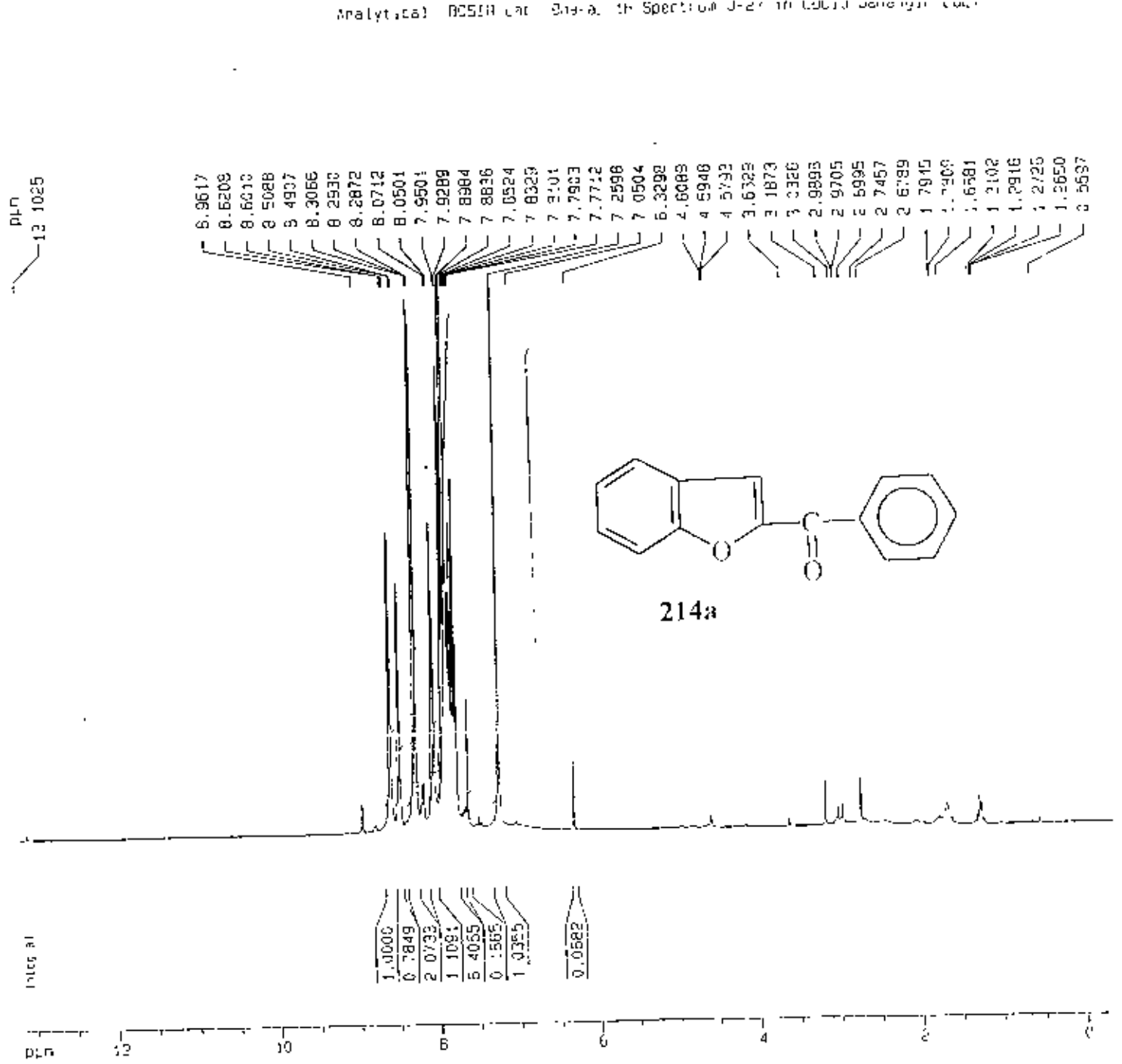
HZCM 41.94055 Hz/cm



Current Data Parameters

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EXPNO	1
PROCNO	1

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DS	0
SWH	6410 256 Hz
FIDRES	0 195625 Hz
AQ	2 5559540 sec
RG	64
DW	78.000 usec
DE	6.30 usec
TE	310 0 K
D1	1 00000000 sec

========== CHANNEL f1 ====

NUC1	1H
P1	8 30 usec
PL1	-6 00 dB
SFO1	400 1420010 MHz

F2 - Processing parameters

SI	32768
SF	400 1358504 MHz
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SSB	0
LB	0.30 Hz
GB	0
PC	1 40

1D NMR plot parameters

CX	20 00 cm
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F1	5276 75 Hz
F2P	-0 343 ppm
F2	-137 19 Hz
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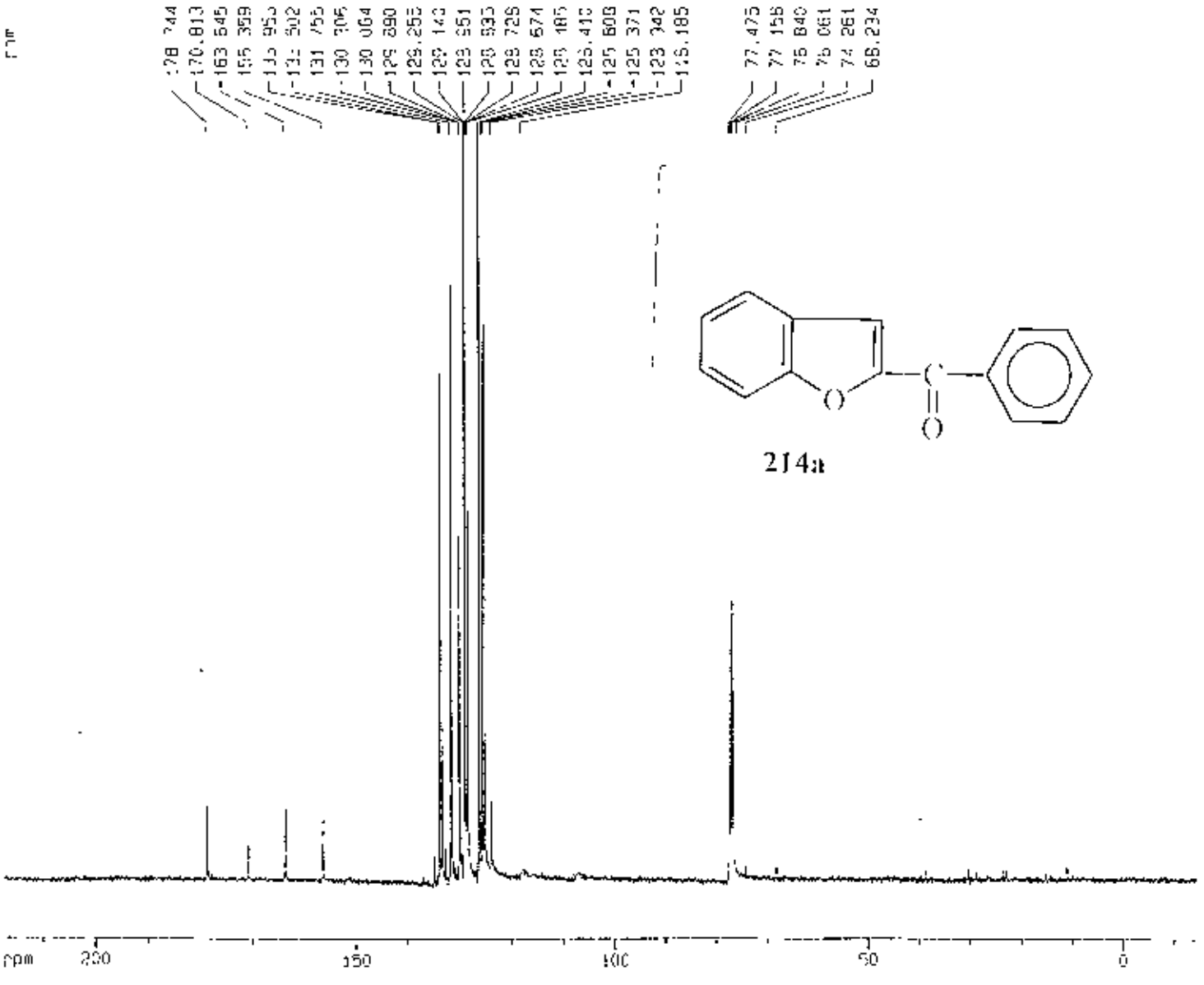
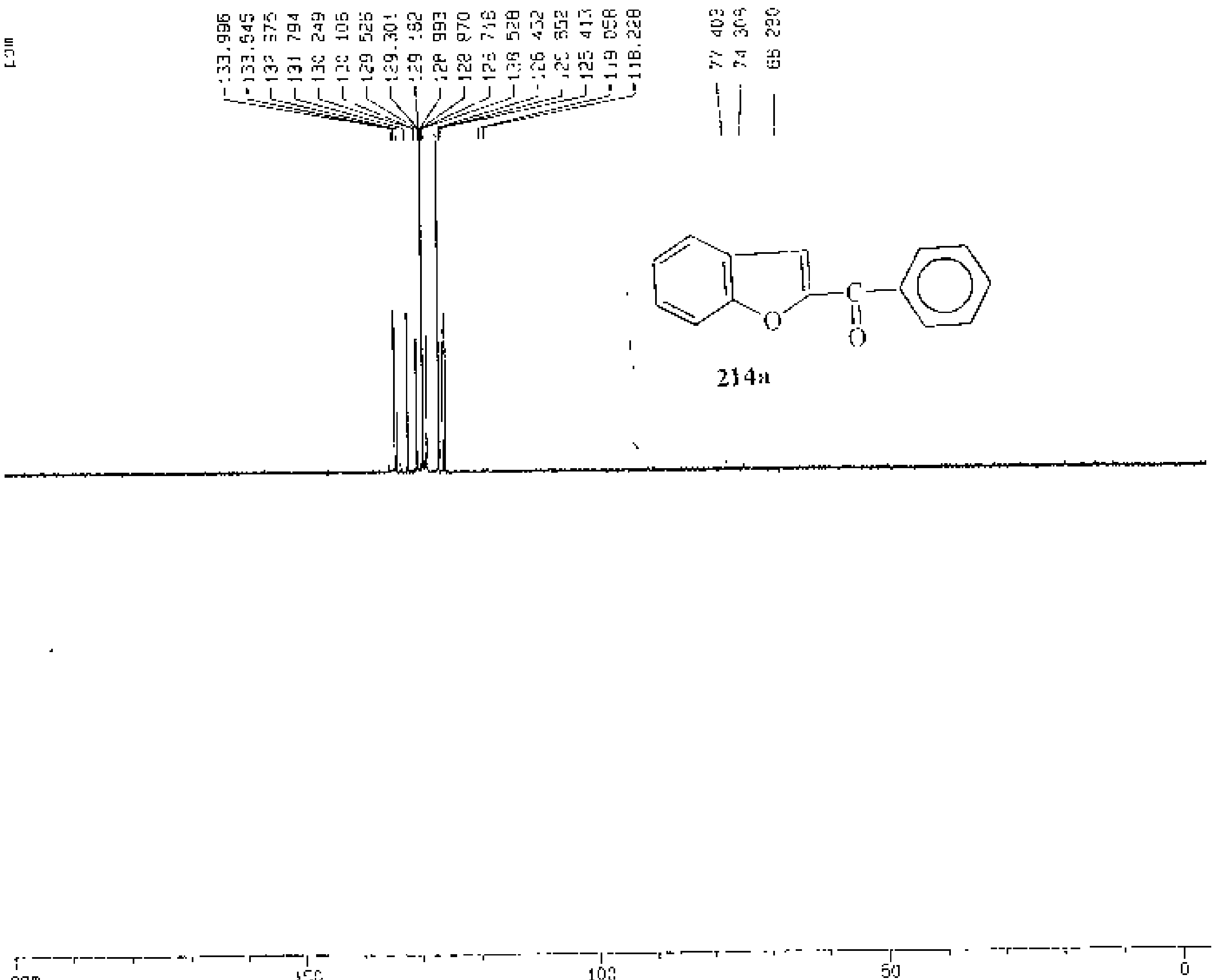
HZCM	270.69397 Hz/cm

Analytical, SCSIA Lab Dhaka 13C Spectrum J-27(b) in CDCl3 JahangirBUET



214a



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DS 8
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FIDRES 0.673677 Hz
AQ 0.7422452 sec
RG 13004
DW 22.650 usec
DE 6.00 usec
TE 300.0 K
CNST2 145.0000000
D1 4.00000000 sec
d2 0.00344828 sec
d12 0.00002000 sec
DELTA 0.00000704 sec

============ CHANNEL f1 ============
NUC1 13C
P1 6.00 usec
p2 12.00 usec
PL1 -6.00 dB
SFO1 100.6253046 MHz

============ CHANNEL f2 ============
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 6.00 dB
PL12 6.00 dB
SFO2 400.1420007 MHz

F2 - Processing parameters
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SF 100.6152727 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
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F2P -4.745 ppm
F2 -477.44 Hz
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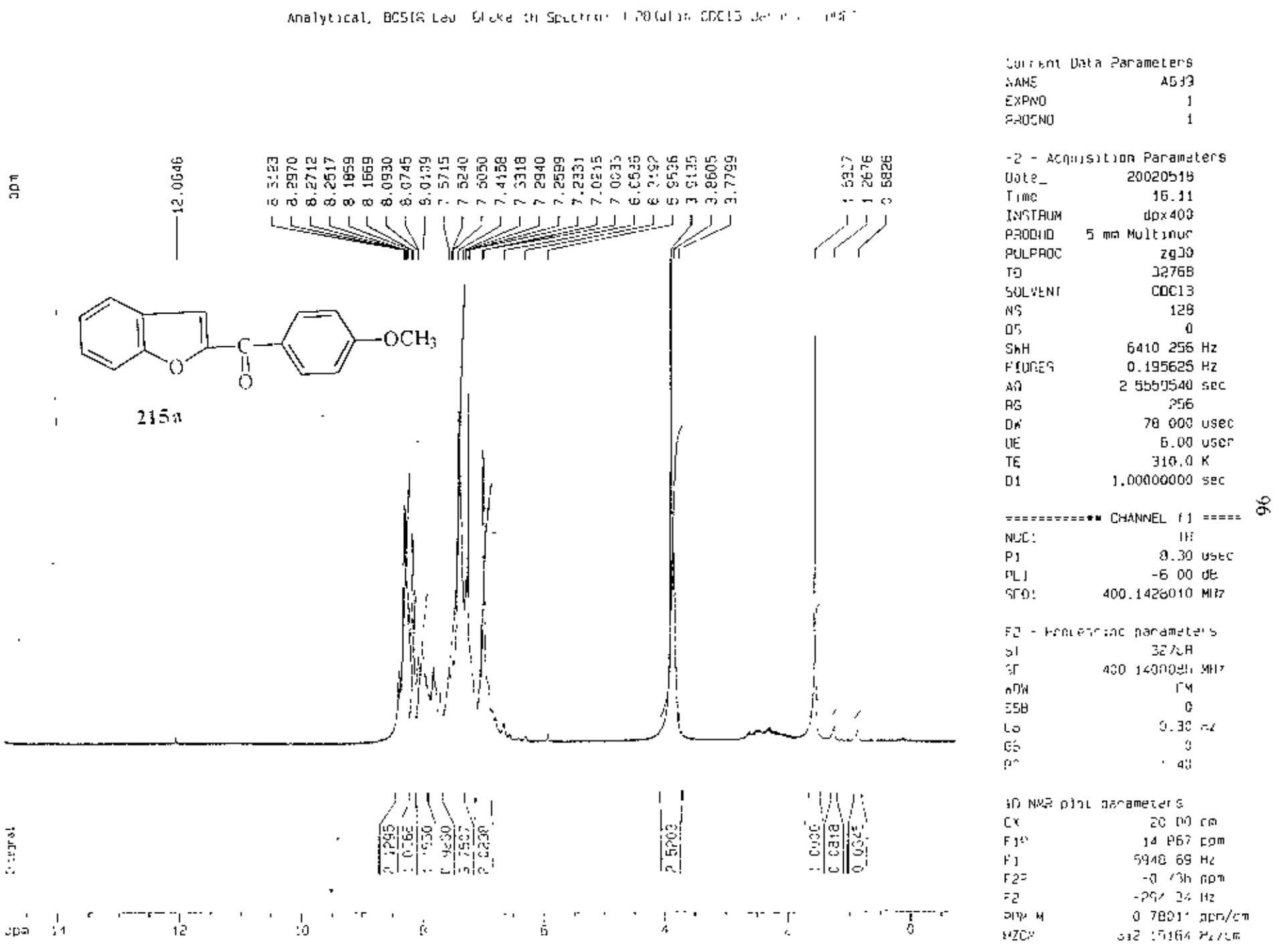
HZCM 1035.36804 Hz/cm



Current Data Parameters
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PROCNO 1

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TD 32768
SOLVENT CDCl3
NS 128
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FIDRES 0.195625 Hz
AQ 2.5550540 sec
RG 256
DW 78.000 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

========== CHANNEL f1 =====
NUC1 1H
P1 8.30 usec
PL1 -6.00 dB
SFO1 400.1426010 MHz

F2 - Processing parameters
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SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

1D NMR plot parameters
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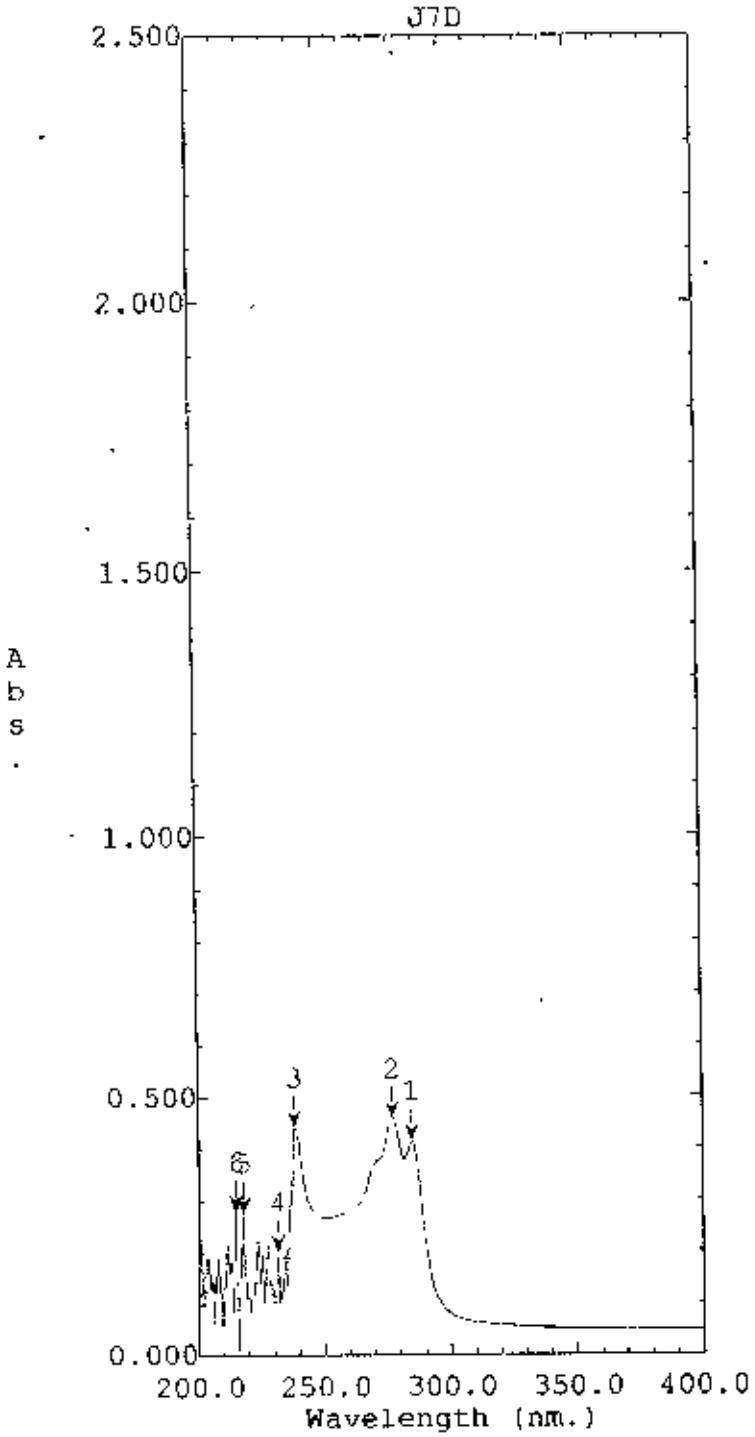
HZCM 312.15164 Hz/cm



Peak Pick

No.	Wavelength (nm.)	Abs.
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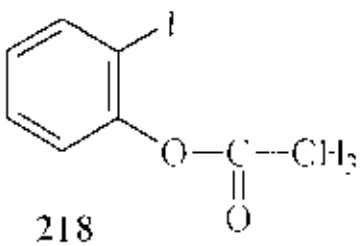
3	238.20	0.440
4	231.40	0.200
5	217.60	0.275
6	214.60	0.278



218

File Name: J7D

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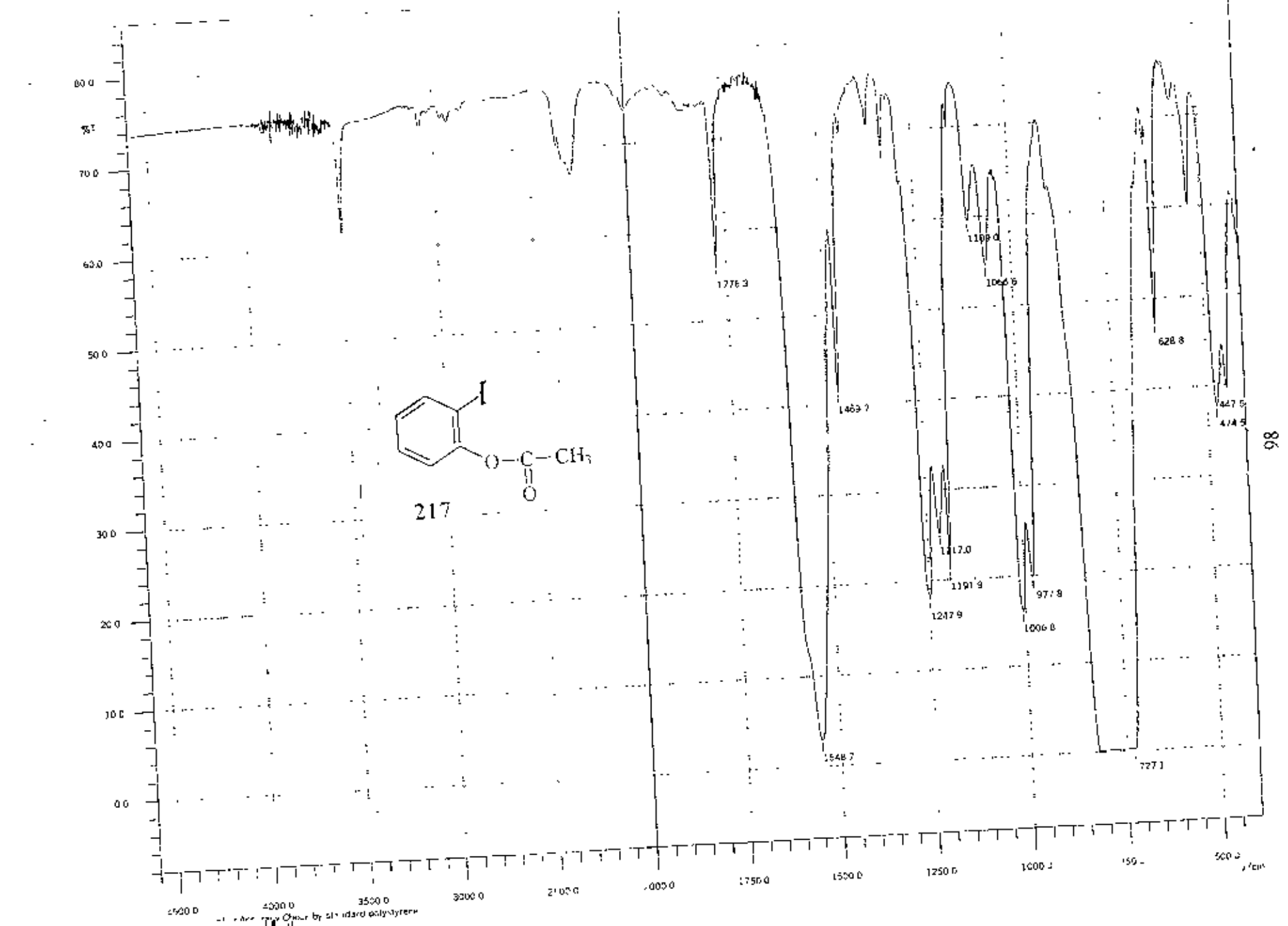
I
O
C
CH3
O
217
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1548.7
1217.0
1191.9
1247.9
1109.0
1066.9
1006.8
977.9
628.8
727.1
447.5
474.5
%T
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70.0
60.0
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40.0
30.0
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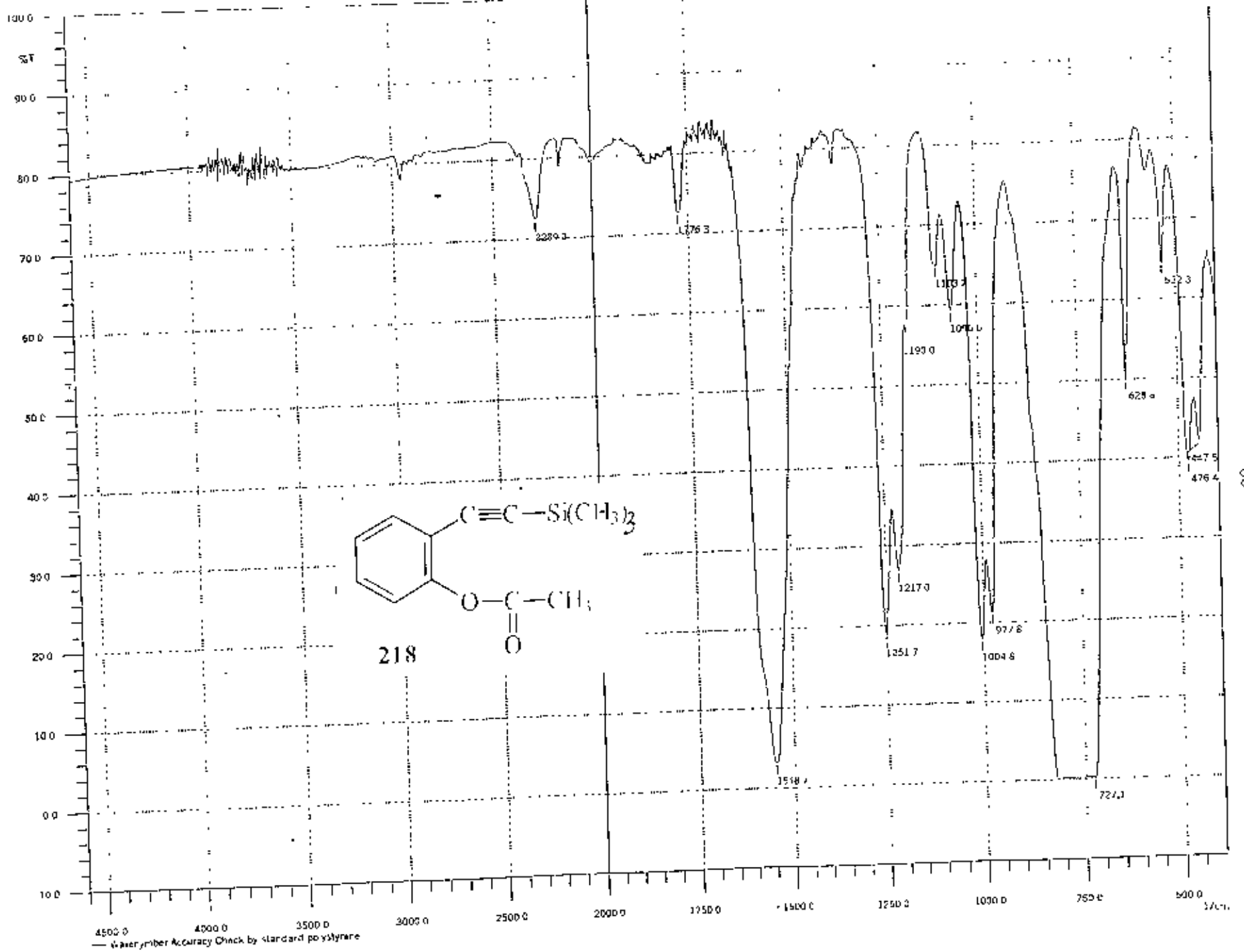
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1500.0
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500.0
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1763
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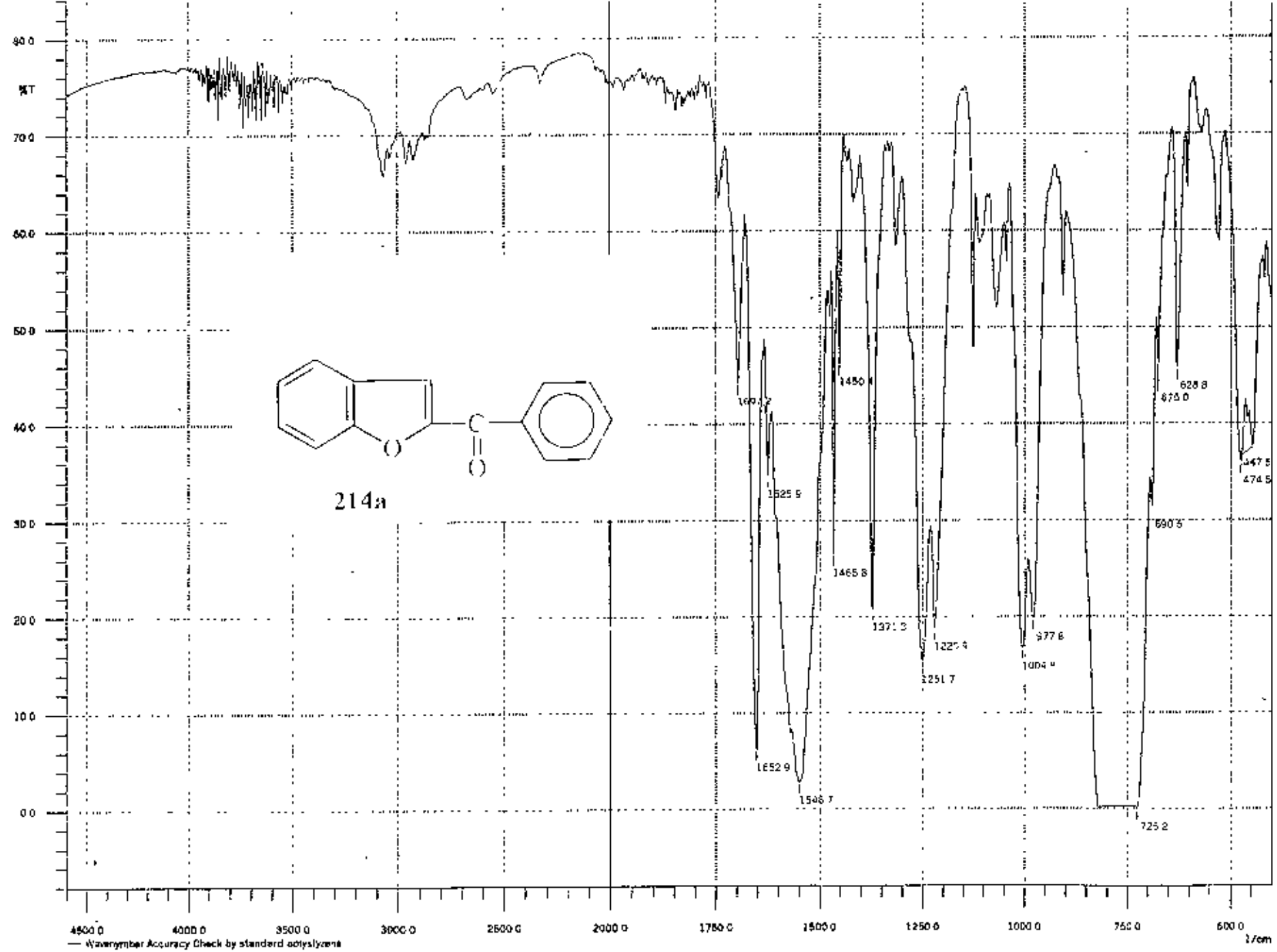
628.6
476.4
C≡C—Si(CH3)3
O—C—CH3
O
218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725.2
690.5
628.8
675.0
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474.5
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2500.0
2000.0
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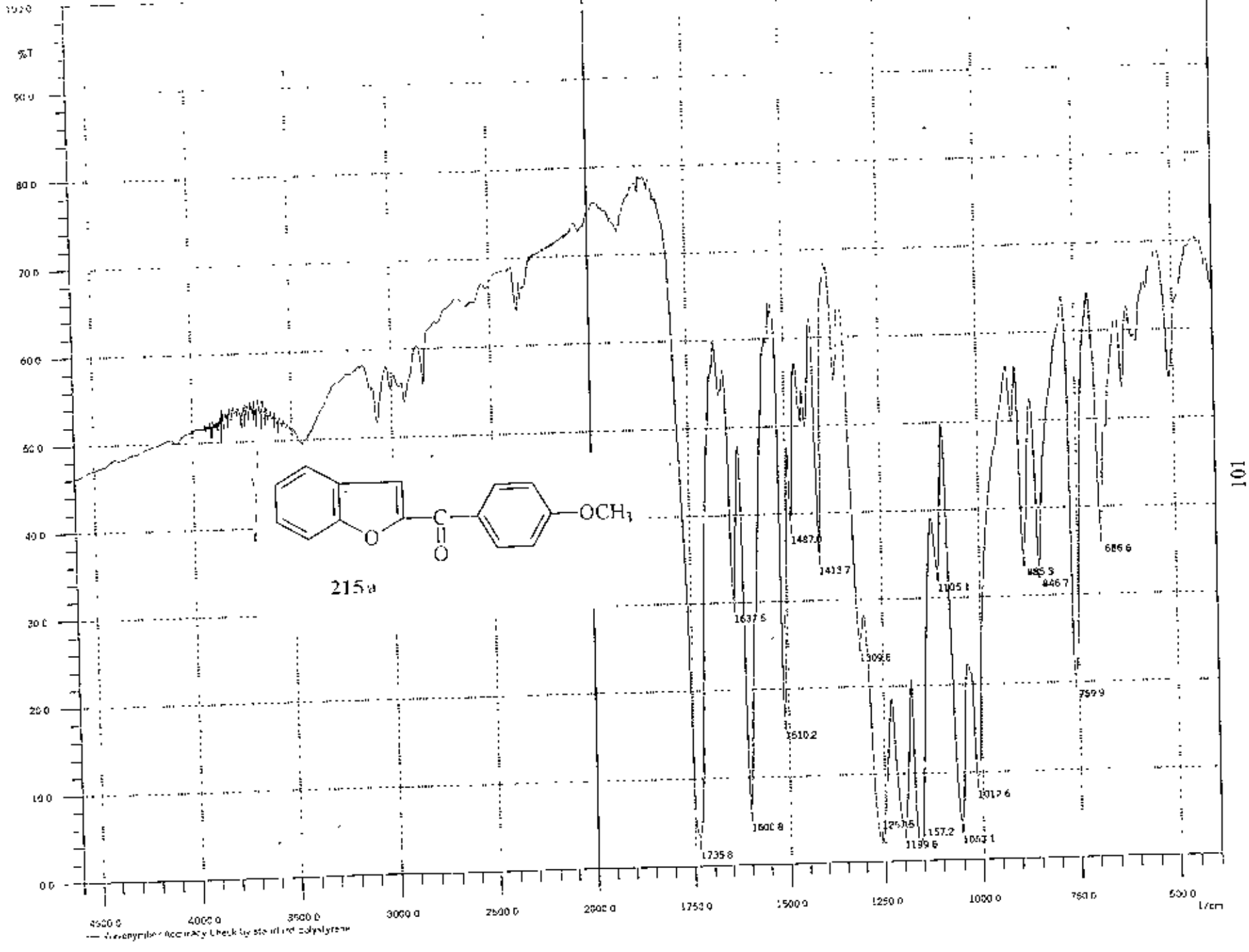
1/cm
Wavenymber Accuracy Check by standerd polystyrene
100

214a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1500.0
1250.0
1000.0
750.0
500.0
1/cm
1735.8
1637.5
1600.8
1510.2
1487.0
1413.7
1309.6
1257.5
1199.6
1157.2
1105.1
1057.1
1017.6
885.3
846.7
799.9
686.6
O
O
OCH3

215a

SECTION - 4

Present Work

One Pot Synthesis of 2-Alkyl or Aryl Benzofurans from *o*-Iodophenol Through Palladium Catalyzed Reactions.

4. Present Work: One Pot Synthesis of 2-Alkyl or Aryl Benzofurans from *o*-Iodophenol Through Palladium Catalyzed Reactions.

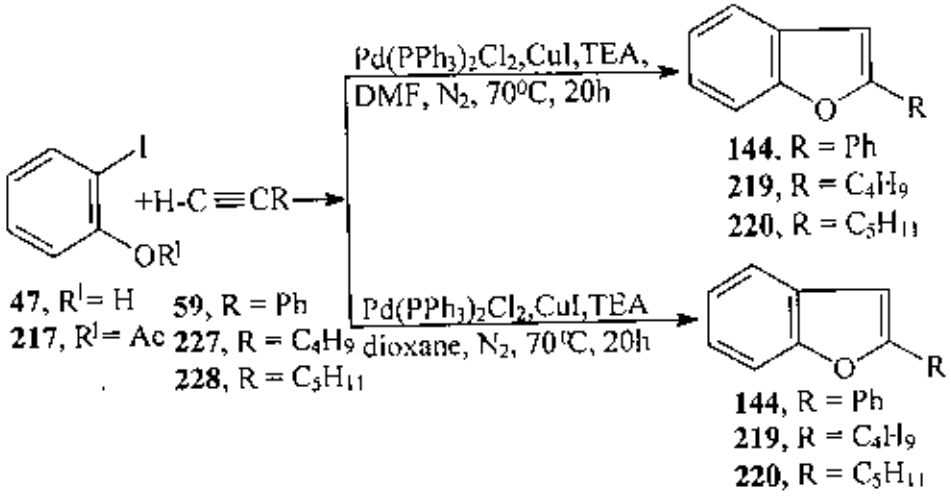
4.1 Rationale :

Benzofuran have been used as synthetic intermediates in the preparation of drugs and natural products. Some benzofuran derivatives display interesting biological activities which have been described in **section-1**. In **section-2** and **3**, the strategy was for the synthesis of 2-acyl benzofurans through combined palladium catalyzed and Friedel-Crafts reactions from 2-Iodophenol. We became interested in exploring the possibility of heteroannulation by using palladium catalyzed system. Furthermore, known chemotheraputic importance of a number of 2-substituted benzofurans provided the impetus to develop an alternative general method for their synthesis.

4.2 Results and Discussion:

We now report a new strategy for the synthesis of 2-substituted benzofurans **144**, **219**, **220** with terminal alkynes **59**, **227**, **228**. The reactions were usually carried out by heating a mixture of *o*-iodophenol **47** or *o*-acetoxy phenyliodide **217** and alkynes **59**, **227**, **228** in dioxane or DMF at 70^{0}C for 15 h in the presence of bis(triphenylphosphene)palladium (II) chloride (2.5 mol %), copper (I) iodide (8 mol %) and triethylamine (10 ml) to afford the 2-substituted benzofurans **144**, **219**. **220** in good yields as shown in **scheme-59**. In the case of hexyne **227** and heptyne **228** we obtained small amount of dimer with 2-substituted benzofurans which was not separable by column chromotography. When we used dioxane as a solvent we obtained better yields (80 – 90%) than DMF. In the case of protected iodophenol (as acetate) we obtained excellent (86–95%) yields.

Scheme - 59



The synthesis of *o*-iodophenol **47** and *o*-acetoxyphenyl iodide **217** was described in sectin-2 and section - 3.

4.3 Characterization of Products:

The products were characterized from their ^{1}HNMR, UV and IR spectra. ^{1}HNMR spectra showed the presence of a characteristic singlet peak, integrating for a single proton, at around 6.4–710 accounting for 3-H. All the benzofurans were found to give characteristic UV paterns λ_{max} / nm 329 – 250.

4.4 Mechanism:

A plausible mechanism involved which shown in **scheme-60**.

a) reduction of Pd(II) to Pd(0) in the presence of triethylamine, CuI and terminal alkynes.

b) Oxidative addition of *o*-iodophenol to the Pd(0) complex to form a σ-alkylpalladium (II) complex (A) which then trans metallates with cuprous acetylide to generate the arylalkynylpalladium (II) species (B). This on reductive elimination of Pd^0 then affords acyclic products **212**, **218**.

c) The latter on cyclisation in the presence of triethylamine where the phenoxide ion made an attack on the triple bond resulted in the formation of the benzofurans. Such cyclisations are favoured reactions[134] and are in accord with the known ability of 2-alkynylphenols to cyclise under alkaline condition[135].

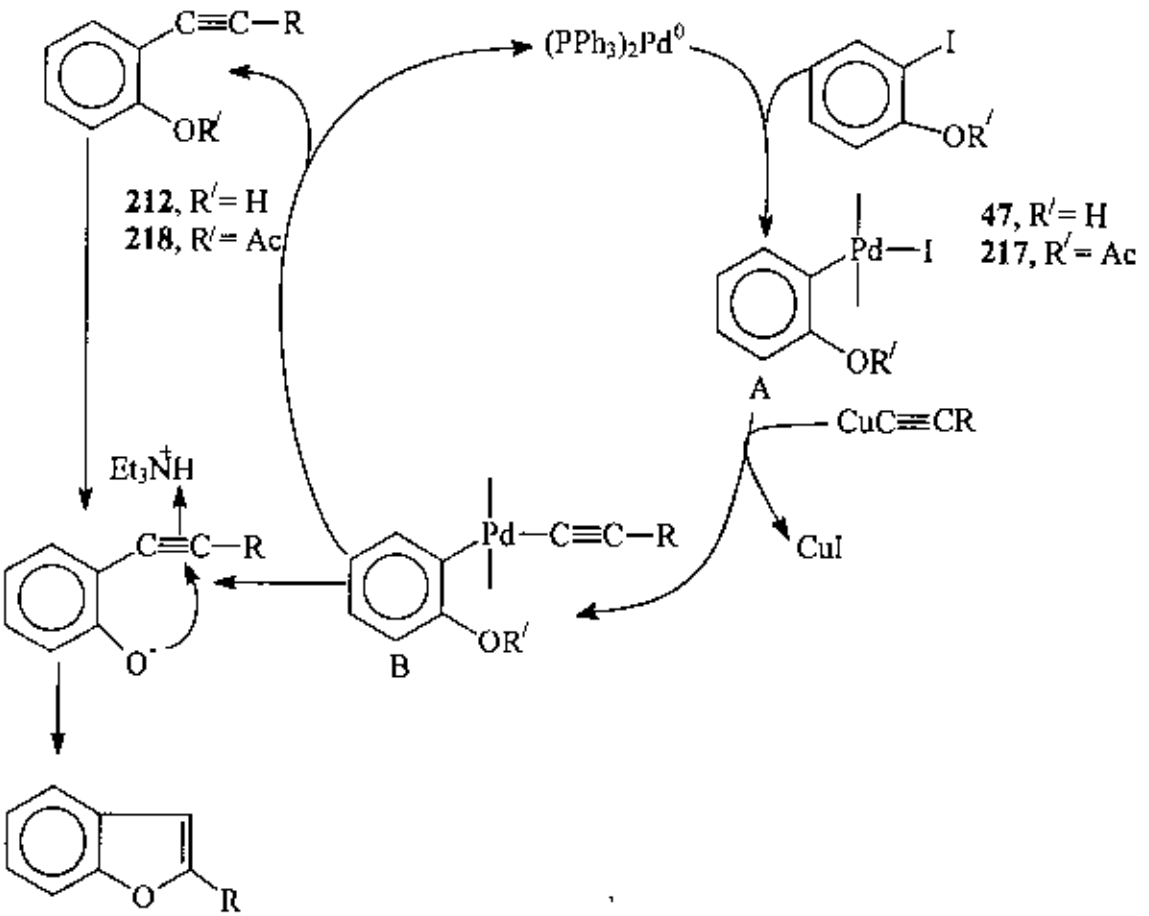
Scheme-60

(i) $HC\equiv C\text{-}R \xrightarrow{CuI,\ Et_3N} Cu\text{-}C\equiv C\text{-}R + Et_3\overset{+}{N}H\bar{I}$

59, R = Ph
227, R = C_4H_9
228, R = C_5H_{11}

(ii) $Cu\text{-}C\equiv C\text{-}R + Pd(PPh_3)_2Cl_2 \longrightarrow (PPh_3)_2Pd\text{-}(C\equiv CR)_2 + CuCl$

$RC\equiv C\text{-}C\equiv CR + (PPh_3)_2Pd^0$



144, R = Ph
219, R = C_4H_9
220, R = C_5H_{11}

4.5 Conclusion:

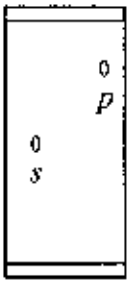
In this section, we have described a facile, one pot general method for the synthesis of 2-substituted benzfurans from *o*-iodophenol and *o*-acetoxyphenyl iodide. We used two different solvent DMF and dioxane. In the case of dioxane we obtained excellent yields. We obtained also good result in the case of protected iodophenol (as acetate) than *o*-iodophenol.

4.6 Experimentals:

2-Phenylbenzofuran 144:

a) From *o*-iodophenol 47:

To a well-stirred mixture of *o*-iodophenol **47** (500 mg, 2.275 mmol), $Pd(Ph_3P)_2Cl_2$ (3.5 mol%), CuI (6 mol%) and triethylamine (2 eq) in DME (6 ml)/dioxane (6 ml), phenyl acetylene (0.62 ml, 2 eq) was added under N_2 atmosphere. The mixture was stirred at 70^0C for 20 hour. The progress of the reaction was monitored by T.L.C (hexane 100%) (R_f value = 0.8) which indicated completion of the reaction with the formation of faster moving product.



S = Reactant

P = Product

Removal of the solvent under reduced pressure the mixture was then cooled, poured into distilled water (100 ml) and extracted with chloroform (3×30 ml). The combiued extracts were washed with 5 mol dm^{-3} aq NaOH (3×50 ml) and water (3×50 ml). The organic layer was dried by anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified through a silicagel column with hexane as eluant provided the 2-phenylbenzofuran **144**. (363 mg, 82.45% when dioxane was used as a solvent, 327 mg, 74.38% when DMF was used as a solvent) as a solid mp. 116–118^{0}C (lit.[130], 120.8–121.2^{0}C).

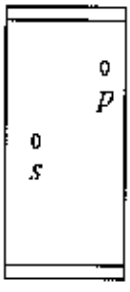
IR (KBr) : ν_{max} 1593, 1562, 1485, 1257, 806, 746, 688 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 318.60, 307.00, 261.40 and 240 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 7.89–7.87 (m, 1H, ArH), 7.60–7.26 (m, 8H, ArH), 7.04 (s, 1H, 3-H).

b) From *o*-acetoxyphenyliodide 217:

To a well-stirred mixture of *o*-acetoxyphenyliodide **217** (500 mg, 1.90 mmol), $Pd(Ph_3P)_2Cl_2$ (3.5 mol%), CuI (6 mol%) and triethylamine (2 eq) in DME (6 ml)/dioxane (6 ml), phenyl acetylene (0.62 ml, 2 eq) was added under N_2 atmosphere. The mixture was stirred at 70^{0}C for 20 hour. The progress of the reaction was monitored by T.L.C (hexane 100%) (R_f value = 0.8) which indicated completion of the reaction with the formation of faster moving product.



S = Reactant

P = Product

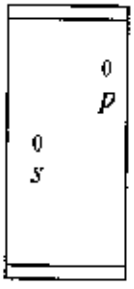
Removal of the solvent under reduced pressure the mixture was then cooled, poured into distilled water (100 ml) and extracted with chloroform (3×30 ml). The combined extracts were washed with 5 mol dm^{-3} aq NaOH (3×50 ml) and distilled water (3×50 ml). The organic layer was dried by anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified through a silicagel column with hexane as eluant provided the 2-phenylbenzofuran **144**. (347 mg, 94.12% when dioxane was used as a solvent, 313 mg, 86.92% when DMF was used as a solvent) as a solid mp.116–118^{0}C (lit.[130], mp. 120.8–121.2^{0}C).

IR, UV, ^{1}HNMR spectra of this compound was indistinguishable from those of the same compound prepared earlier from *o*-iodophenol **47**.

2-Butylbenofuran 219:

a) From *o*-iodophenol 47:

To a well-stirred mixture of *o*-iodophenol **47** (500 mg, 2.275 mmol), $Pd(Ph_3P)_2Cl_2$ (3.5 mol%), CuI (6 mol%) and triethylamine (2 eq) in DME (6 ml)/dioxane (6 ml), 1–hexyne (0.42 ml, 2 eq) was added under N_2 atmosphere. The mixture was stirred at 70^0C for 20 hour. The progress of the reaction was monitored by T.L.C (hexane 100%) (R_f value = 0.85) which indicated completion of the reaction with the formation of faster moving product.



S = Reactant

P = Product

Removal of the solvent under reduced pressure the mixture was then cooled, poured into distilled water (100 ml) and extracted with chloroform (3×30 ml). The combined extracts were washed with 5 mol dm^{-3} aq NaOH (3×50 ml) and distilled water (3×50 ml). The organic layer was dried by anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified through a silicagel column with hexane as eluant provided the 2-butylbenzofuran **219** which contained small amount of dimer (318 mg, 81.45% when dioxane was used as a solvent, 277 mg, 71.13% when DMF was used as a solvent) as a homogeneous syrupy.

IR (CCl_4) : ν_{max} 2240, 1590, 1570, 1480, 1250, cm^{-1}.

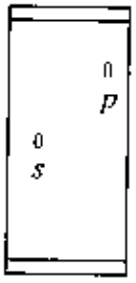
UV ($CHCl_3$) : λ_{max} 284.80, 277.80, 250.40 nm.

^{1}HNMR (400 MHz, $CDCl_3$) : δ 7.50–7.41, (m, 2H, ArH), 7.25–7.16 (m, 2H, ArH), 6.39 (s, 1H, 3-H), 2.81–2.25 (m, 6H, $-CH_2-(CH_2)_2-CH_3$), 1.77–1.42 (m, 12H, $-CH_2-(CH_2)_2-CH_3$, 0.99–0.91 (m, 9H, $CH_2-(CH_2)_2-CH_3$).

b) From *o*-acetoxyphenyliodide 217:

To a well-stirred mixture of *o*-acetloxyphenyliodide **217** (500 mg, 1.90 mmol), $Pd(Ph_3P)_2Cl_2$ (3.5 mol%), CuI (6 mol%) and triethylamine (2 eq) in DME (6 ml)/dioxane

(6 ml), 1-hexyne (0.42 ml, 2 eq) was added under N_2 atmosphere. The mixture was stirred at 70°C for 20 hour. The progress of the reaction was monitored by T.L.C (hexane 100%) (R_f value = 0.85) which indicated completion of the reaction with the formation of faster moving product.



S = Reactant

P = Product

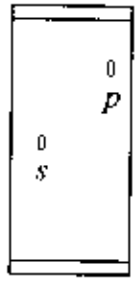
Removal of the solvent under reduced pressure the mixture was then cooled, poured into distilled water (100 ml) and extracted with chloroform (3×30 ml). The combined extracts were washed with 5 mol dm^{-3} aq NaOH (3×50 ml) and distilled water (3×50 ml) The organic layer was dried by anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified through a silicagel column with hexane as eluant provided the 2-butylbenzofuran **219** which contained small amount of dimer (310 mg, 93.67% when dioxane was used as a solvent, 278 mg, 84.06% when DMF was used as a solvent) as a homogeneous syrupy.

IR, UV and ^{1}HNMR spectra of this compound indistinguishable from those of the same compound prepared earlier from *o*-iodophenol 47.

2-Pentylbenzofuran 220:

a) From *o*-iodophenol 47:

To a well-stirred mixture of *o*-iodophenol 47 (500 mg, 2.275 mmol), $Pd(Ph_3P)_2Cl_2$ (3.5 mol%), CuI (6 mol%) and triethylamine (2 eq) in DME (6 ml)/dioxane (6 ml), 1-heptyne (0.48 ml, 2 eq) was added under N_2 atmosphere. The mixture was stirred at 70°C for 20 hour. The progress of the reaction was monitored by T.L.C (hexane 100%) (R_f value = 0.83) which indicated completion of the reaction with the formation of faster moving product.



S = Reactant

P = Product

Removal of the solvent under reduced pressure the mixture was then cooled, poured into distilled water (100 ml) and extracted with chloroform (3×30 ml). The combined extracts were washed with 5 mol dm^{-3} aq NaOH (3×50 ml) and distilled water (3×50 ml). The organic layer was dried by anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified through a silicagel column with hexane as eluant provided the 2-pentylbenzofuran **220** which contained small amount of dimer (358 mg, 83.45% when dioxane was used as a solvent, 310 mg, 74.89% when DMF was used as a solvent) as a homogeneous syrupy.

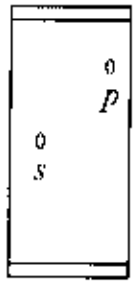
IR (CCl_4) : ν_{max} 2230, 1590, 1560, 1489, 1240 cm^{-1}.

UV ($CHCl_3$) : λ_{max} 284.80, 277.80, 250.00 nm.

1HNMR (400 MHz, $CDCl_3$) : δ 7.52–7.49 (m, 1H, ArH), 7.45–7.43 (m, 1H, ArH), 7.26–7.18 (m, 2H, ArH), 6.99 (s, 3-H), 2.81–2.53 (m. 6H, $-CH_2-(CH_2)_3-CH_3$), 1.80–1.33 (m, 18H, $-CH_2-(CH_2)_3-CH_3$), 0.98–0.91 (m, 9H, $-CH_2-(CH_2)_3-CH_3$).

b) From *o*-ocetoxyphenyliodide 217:

To a well-stirred mixture of *o*-acetoxyphenyliodide **217** (500 mg, 1.90 mmol), $Pd(Ph_3P)_2Cl_2$ (3.5 mol%), CuI (6 mol%) and triethylamine (2 eq) in DME (6 ml)/dioxane (6 ml), 1-heptyne (0.48 ml, 2 eq) was added under N_2 atmosphere. The mixture was stirred at 70^{0}C for 20 hour. The progress of the reaction was monitored by T.L.C (hexane 100%) (R_f value = 0.83) which indicated completion of the reaction with the formation of faster moving product.

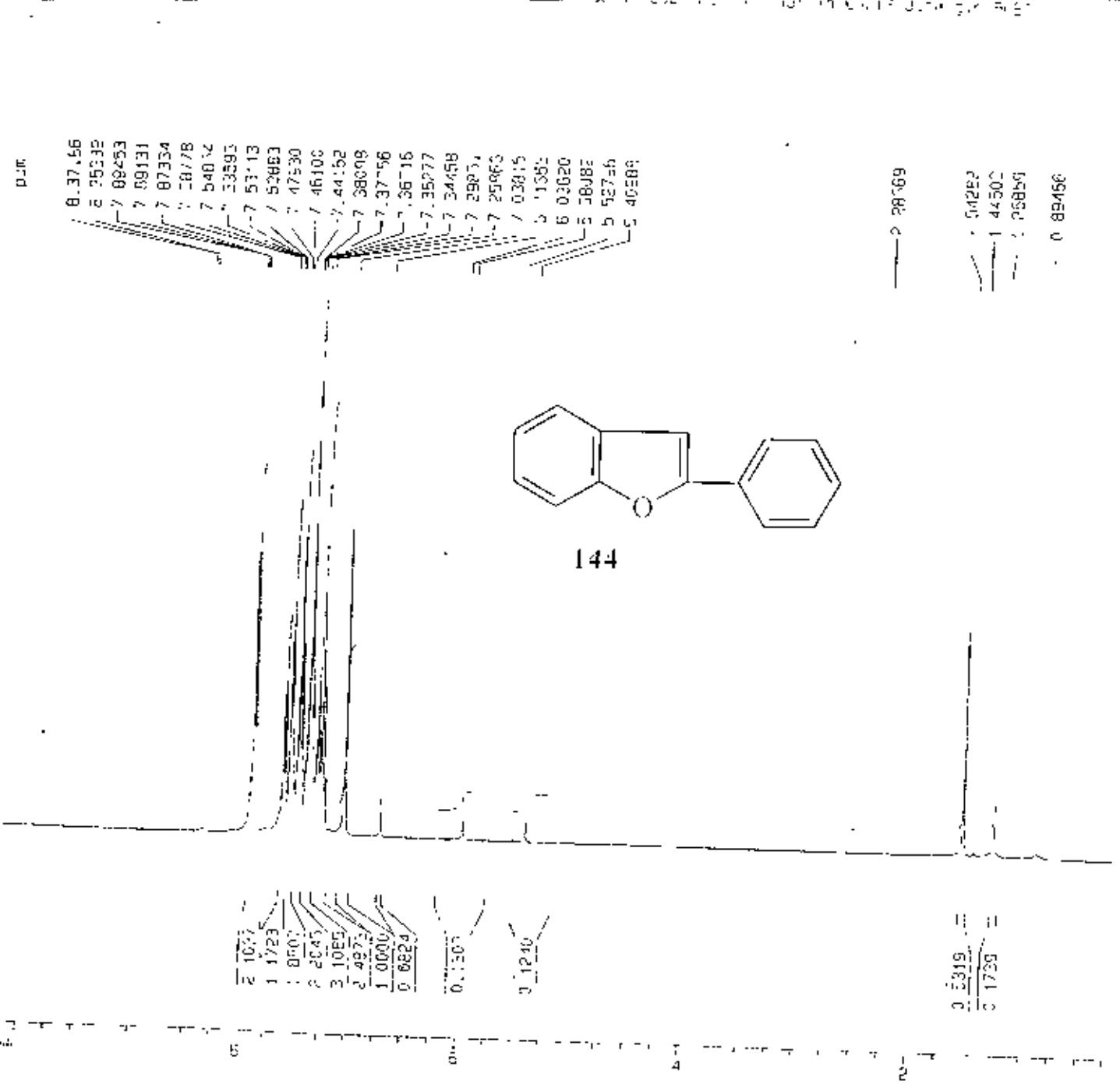


S = Reactant

P = Product

Removal of the solvent under reduced pressure the mixture was then cooled, poured into distilled water (100 ml) and extracted with chloroform (3×30 ml). The combined extracts were washed with 5 mol dm^{-3} aq NaOH (3×50 ml) and distilled water (3×50 ml). The organic layer was dried by anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified through a silicagel column with hexane as eluant provided the 2-pentylbenzofuran **220** which contained small amount of dimer (331 mg, 92.54% when dioxane was used as a solvent, 303 mg. 84.77% when DMF was used as a solvent) as a homogeneous syrup.

IR, UV and ^{1}HNMR spectra of this compound indistinguishable from those of the same compound prepared earlier from *o*-iodophenol **47**.



144

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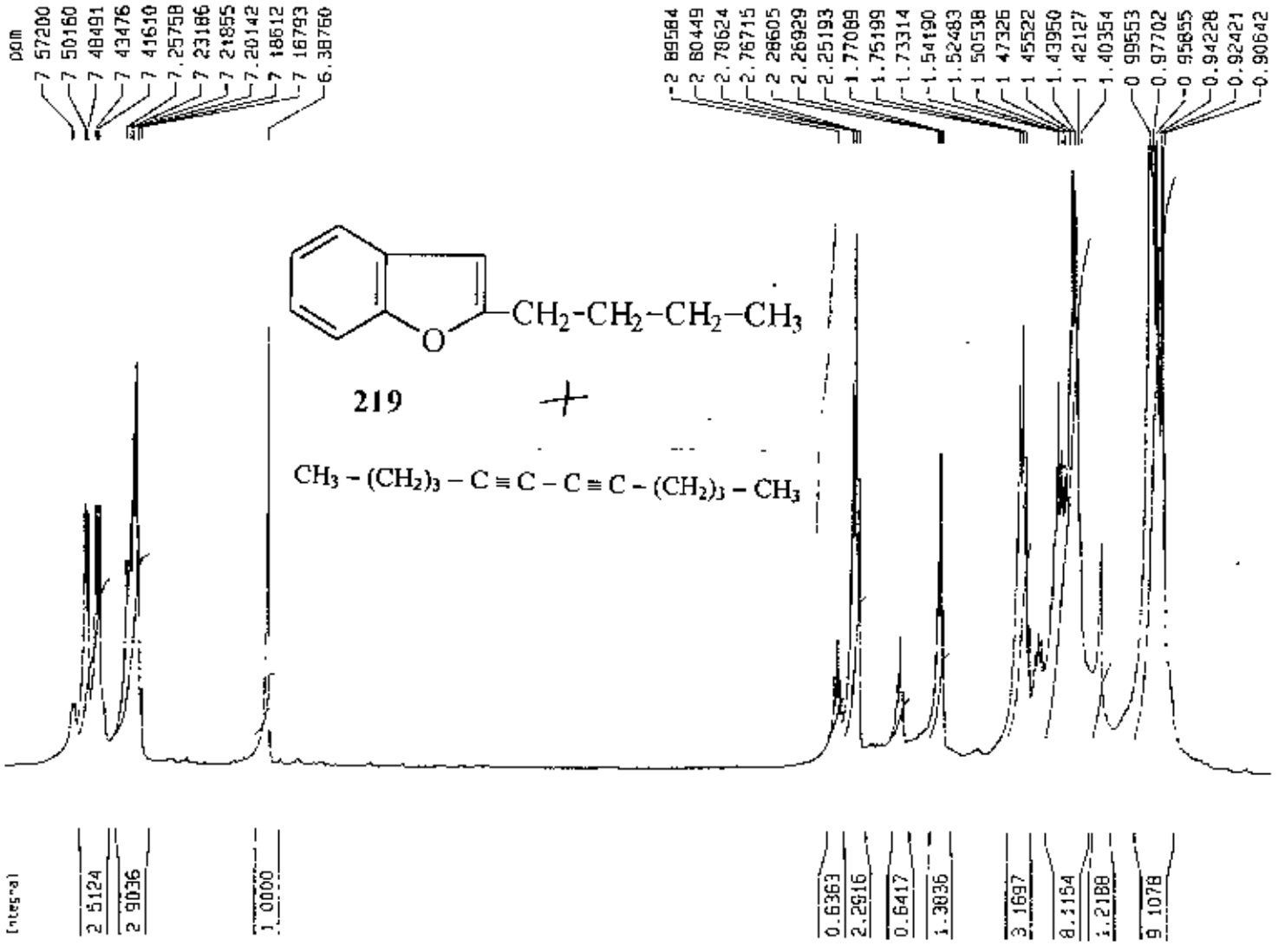

219 +

$CH_3 - (CH_2)_3 - C \equiv C - C \equiv C - (CH_2)_3 - CH_3$

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1D NMR plot parameters
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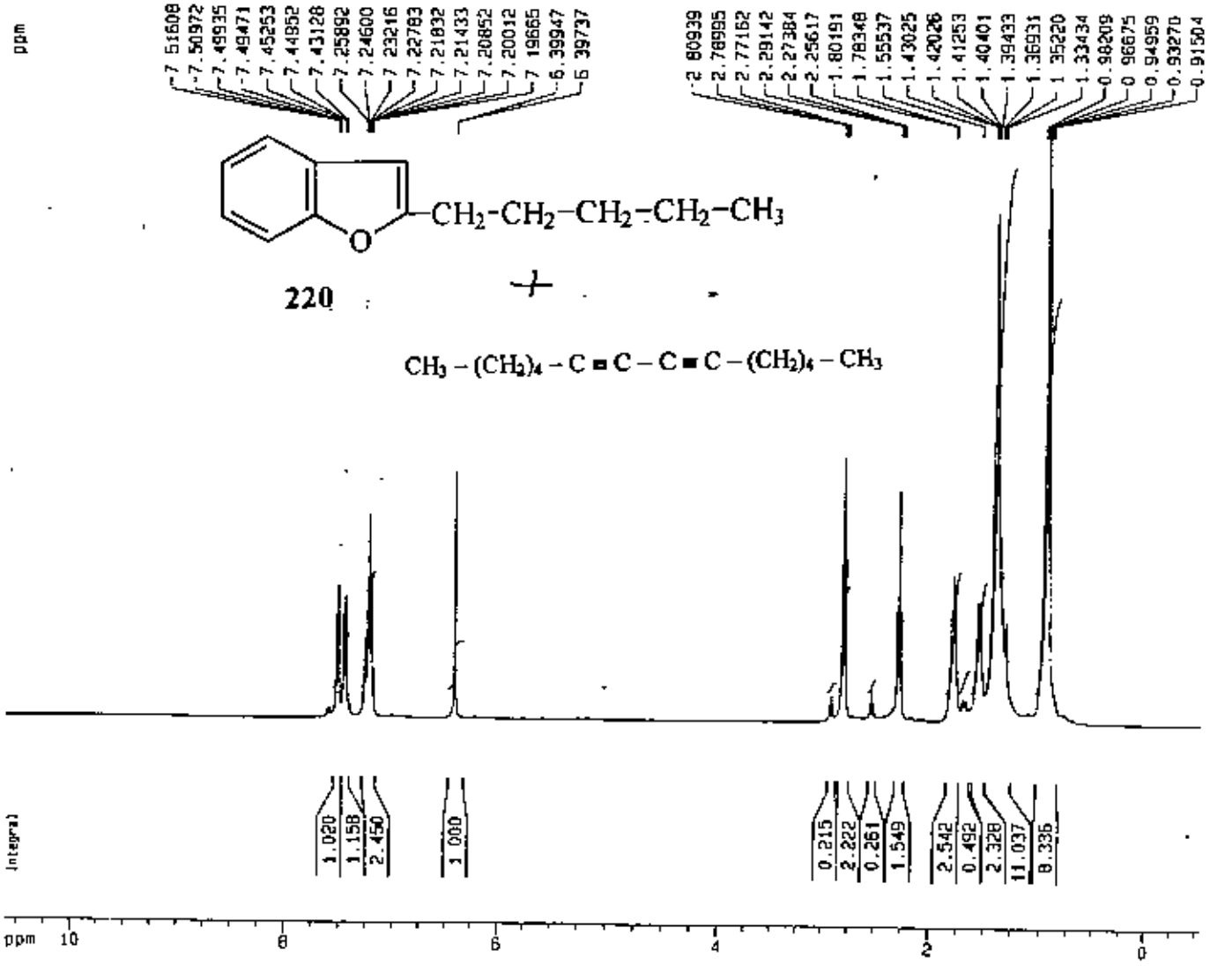

220

$$CH_3-(CH_2)_4-C\equiv C-C\equiv C-(CH_2)_4-CH_3$$

Current Data Parameters

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PROCNO	1

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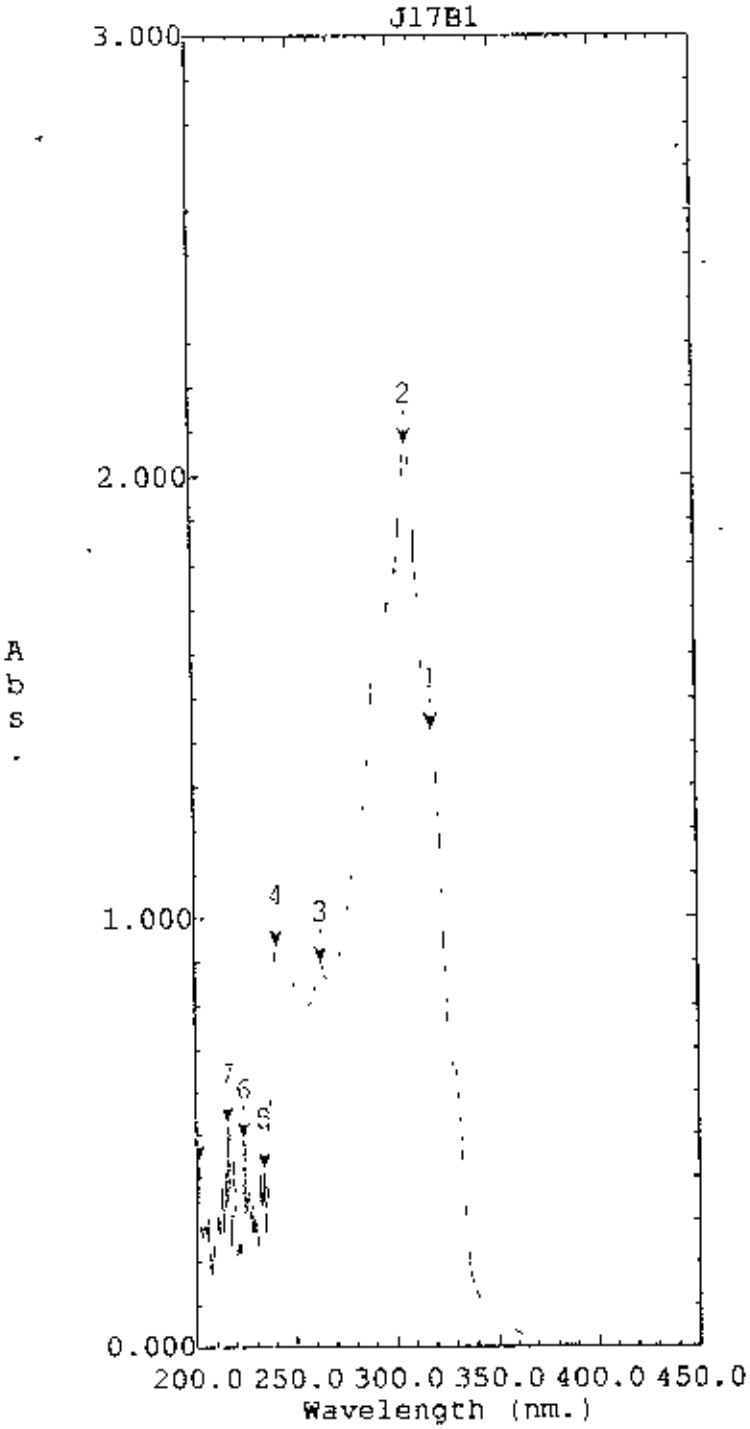

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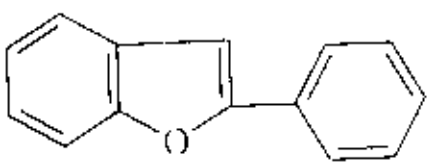
3	262.40	0.900
4	240.80	0.938
5	233.60	0.421
6	223.60	0.491
7	215.80	0.528
8	201.20	0.440



144

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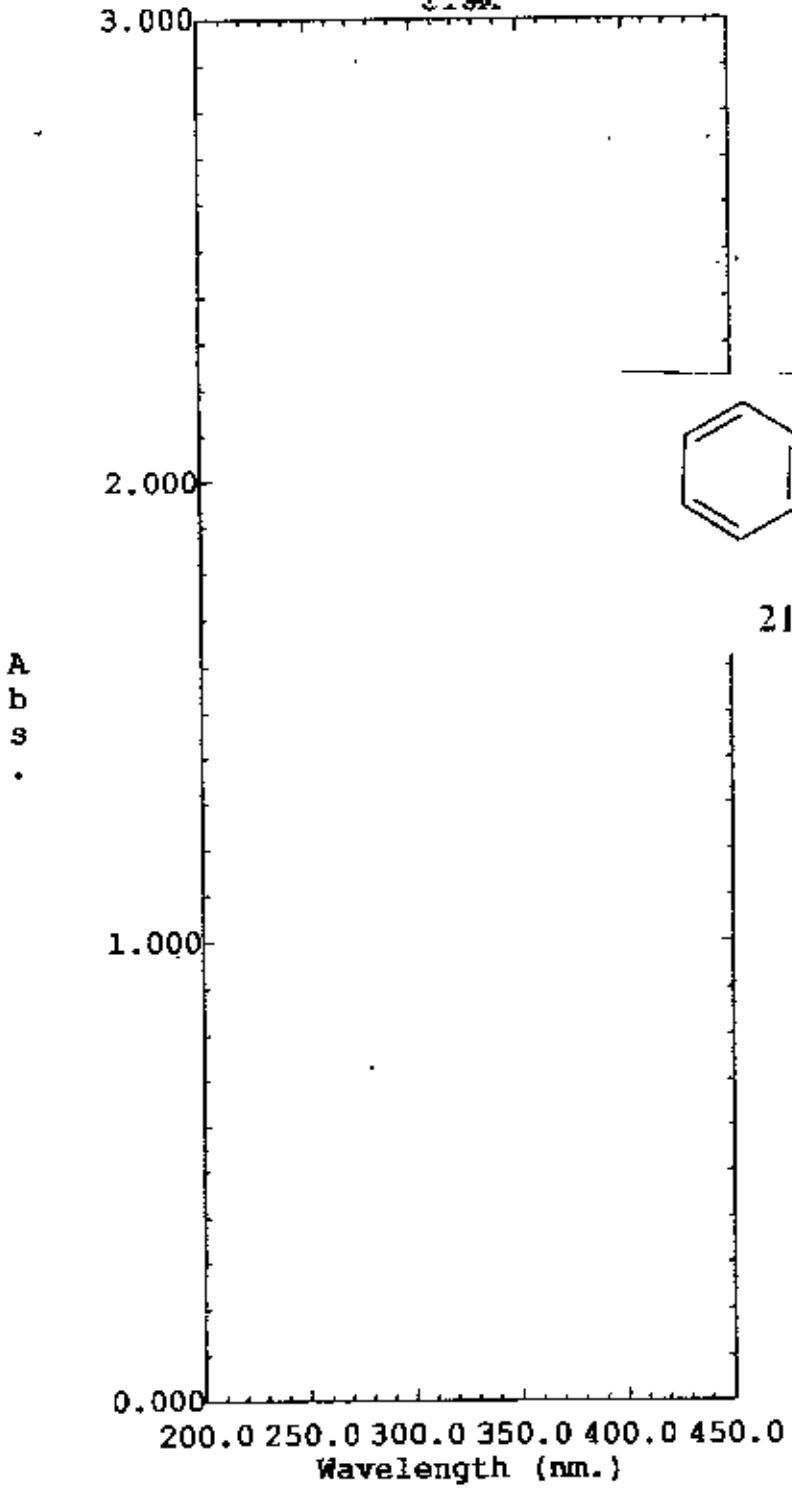

Peak Pick

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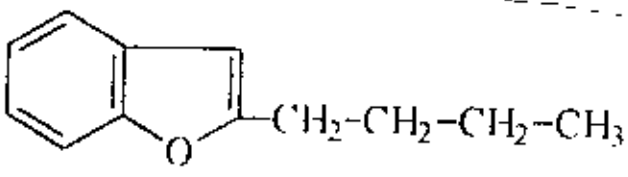

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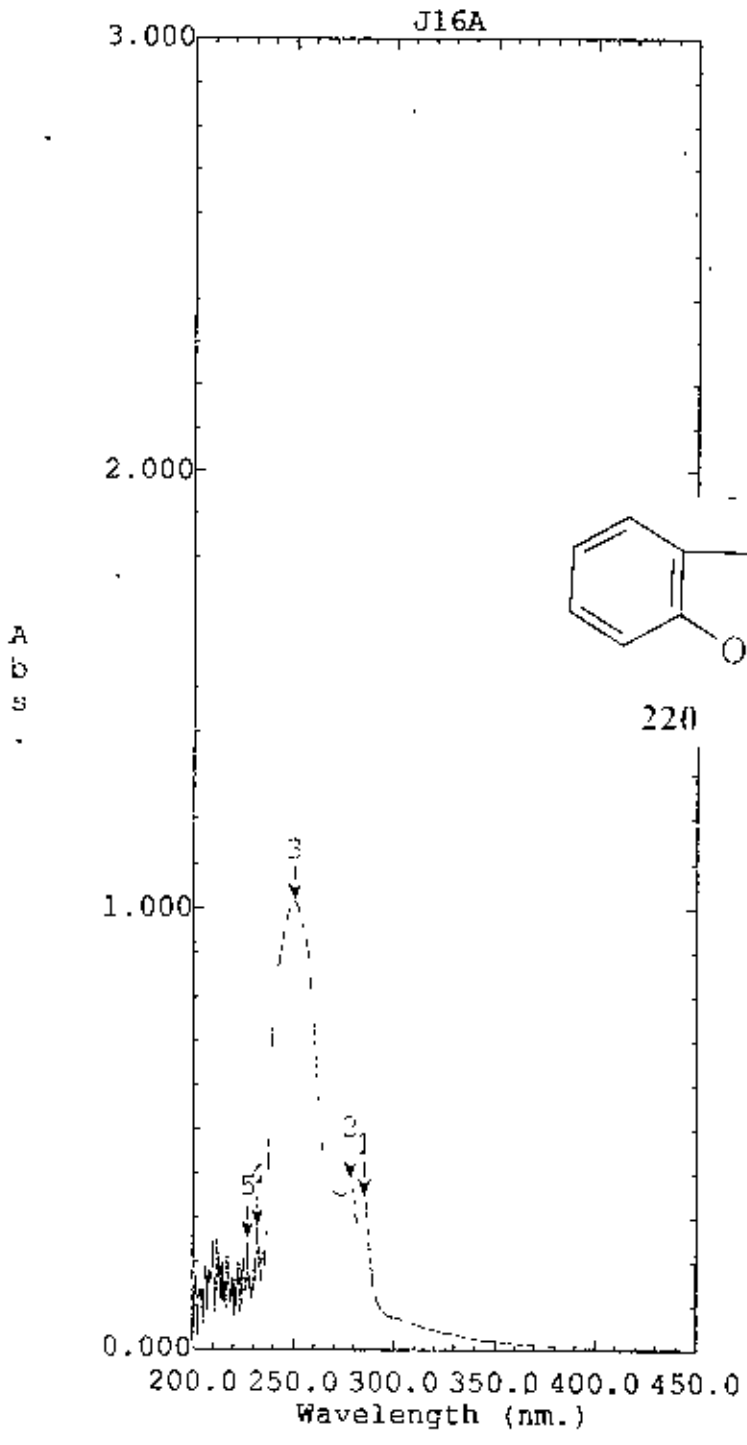

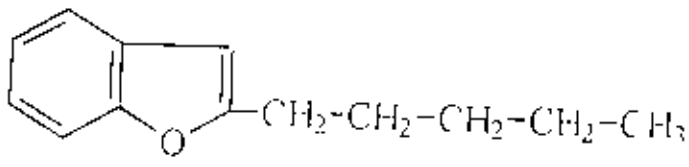

Peak Pick

No.	Wavelength (nm.)	Abs.
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3	250.00	1.0170
4	231.80	0.2836
5	227.00	0.2552

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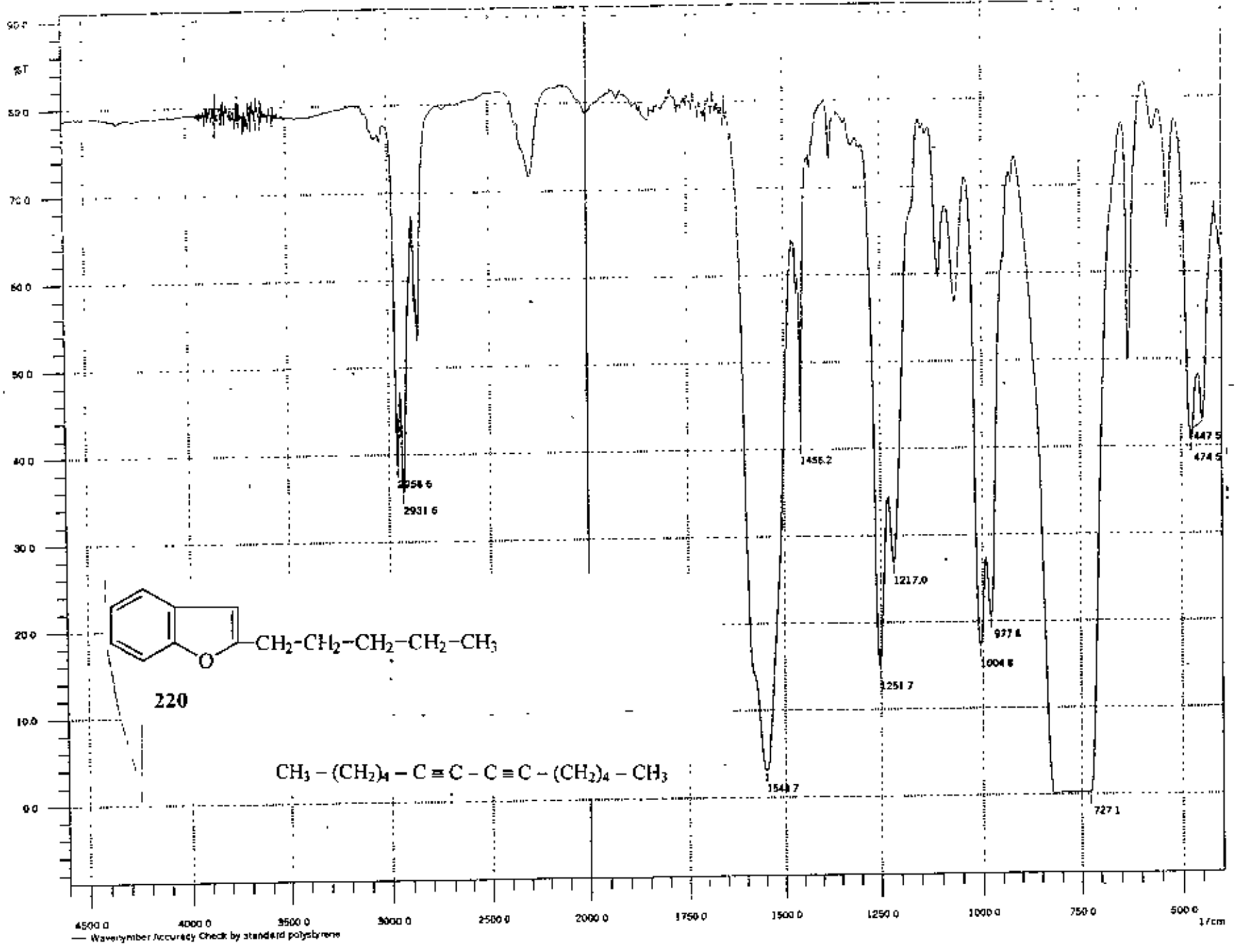
1-4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2931.6
1456.2
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1251.7
1004.8
977.6
1548.7
727.1
447.5
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4500.0
4000.0
3500.0
3000.0
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2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Wavenumber /Accuracy Check by standard polystyrene
CH2-CH2-CH2-CH2-CH3
O
220
CH3 – (CH2)4 – C ≡ C – C ≡ C – (CH2)4 – CH3

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