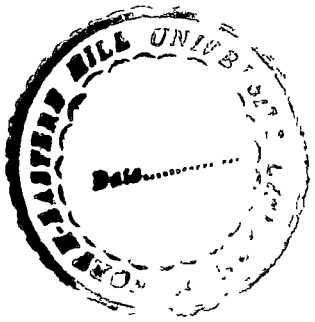
I. SYNTHETIC INVESTIGATION ON AROMATIC AND HETEROAROMATIC ANNELATION REACTION

II. HYDROGEN PEROXIDE/ BORIC ACID OXIDATIONS OF ORGANIC SUBSTRATES



By

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Thesis

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I Miss Amrita Roy, hereby declare that the subject matter of this thesis is the record of work done by me, that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else, and that the thesis has not been submitted by me for any research degree in any other University/ Institute.

This is being submitted to the North-Eastern Hill University for the Doctor of Philosophy degree in Chemistry.

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Dedicated

To

My Parents

And

Pishimoni

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PREFACE

Polysubstituted aromatic and heteroaromatic compounds have been the synthetic targets of chemists since an early period. An important approach for the synthesis of these type of compounds involve application of annelation methods, that is; construction of cyclic compounds from open chain precursors. This approach is well applicable for heteroaromatic annelation method for the synthesis of benzoheterocycles. The importance of benzoheterocycles in natural product chemistry as well as pharmacology is the driving force for developing new efficient methods for their construction which, became a part of the on going research programme.

The thesis consists of four chapters.

Chapter I consists of two parts. The first part contains a general introduction on aromatic and heteroaromatic annelation reactions. The second part gives a brief outline of the present investigation.

The second chapter deals with the synthesis of benzo[*a*]quinolizines by the reaction of 6,7-dihydro-3,4-dimethoxy-1-methylisoquinoline with β-oxodithioates in the presence of triethylamine.

The third chapter deals with the synthesis of substituted Indazolone derivatives involving *in situ* generation of pyrazolo-3,4-dienolate as diene reacting with various dienophiles.

The fourth chapter of this thesis deals with the Dakin type oxidation using boric acid and hydrogen peroxide in presence of sulphuric acid for the conversion of aromatic aldehydes and ketones to phenols.

Chapters 2, 3 and 4 are framed with an introduction, followed by results and discussion, conclusion and experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter. The references of the published work of the present investigation are cited in the respective chapters.

CHAPTER-I

AROMATIC AND HETEROAROMATIC ANNELATION: A BRIEF INTRODUCTION

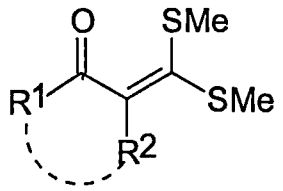
The invention of efficient methods for the synthesis of substituted aromatic compounds has been the interest of chemists since the time of the earliest synthetic organic investigations in the 19^{th} century. Classical approaches to substituted aromatic compounds exploited readily available benzene derivatives and relied on electrophilic and nucleophilic substitution reactions. In recent years, directed metalation reactions have joined the classical substitution methods as another means for the introduction of substituents onto preexisting aromatic rings.

A second approach to highly substituted aromatic compounds involves the application of annelation methods in which the aromatic system is assembled from acyclic precursors[1] and the substitution pattern of the aromatic

ring, is governed by the functionalities and the structure of the starting materials. Annelation strategies enjoy several advantages over substitution strategies, especially when applied to the preparation of highly substituted target molecules. It provides access to substitution patterns that cannot be easily obtained by the classical electrophilic and nucleophilic aromatic substitutions and also facilitates the efficient assembly of highly substituted aromatics that would require long, multistep routes using classical substitution methodology.

The most commonly employed synthetic strategies for the construction of aromatic compounds from open chain precursors are methods based on Diels-Alder chemistry[2] and condensation of 1,3-carbonyl compounds with appropriate 3-carbon fragments.[1] A number of approaches have been developed on the basis of carbonyl condensation reactions for the synthesis of benzene derivatives and their condensed analogs[3,4]. Recently few other methods have been developed which include use of Fisher vinyl carbenes[5], ring expansion of cyclobutenones[6] and cycloaddition of quinodimethane intermediates[7]. In our laboratory, a new method has been developed for the construction of aromatic compounds starting from open chain precursors.[8] This strategy consists of [3+3] annelation approach involving use of α-oxoketene dithioacetals (as 3-carbon 1,3-electrophilic species). Therefore, it is considered appropriate to give a brief introduction to α-oxoketene dithioacetals at this juncture.

The α-oxoketene dithioacetals[9] of general formula **1** are among the simplest synthetic intermediates in organic synthesis which can be conveniently prepared from any active methylene compound by treatment with base, carbon disulfide followed by alkylation. They have been recognized as useful building blocks in many synthetic operations.



1

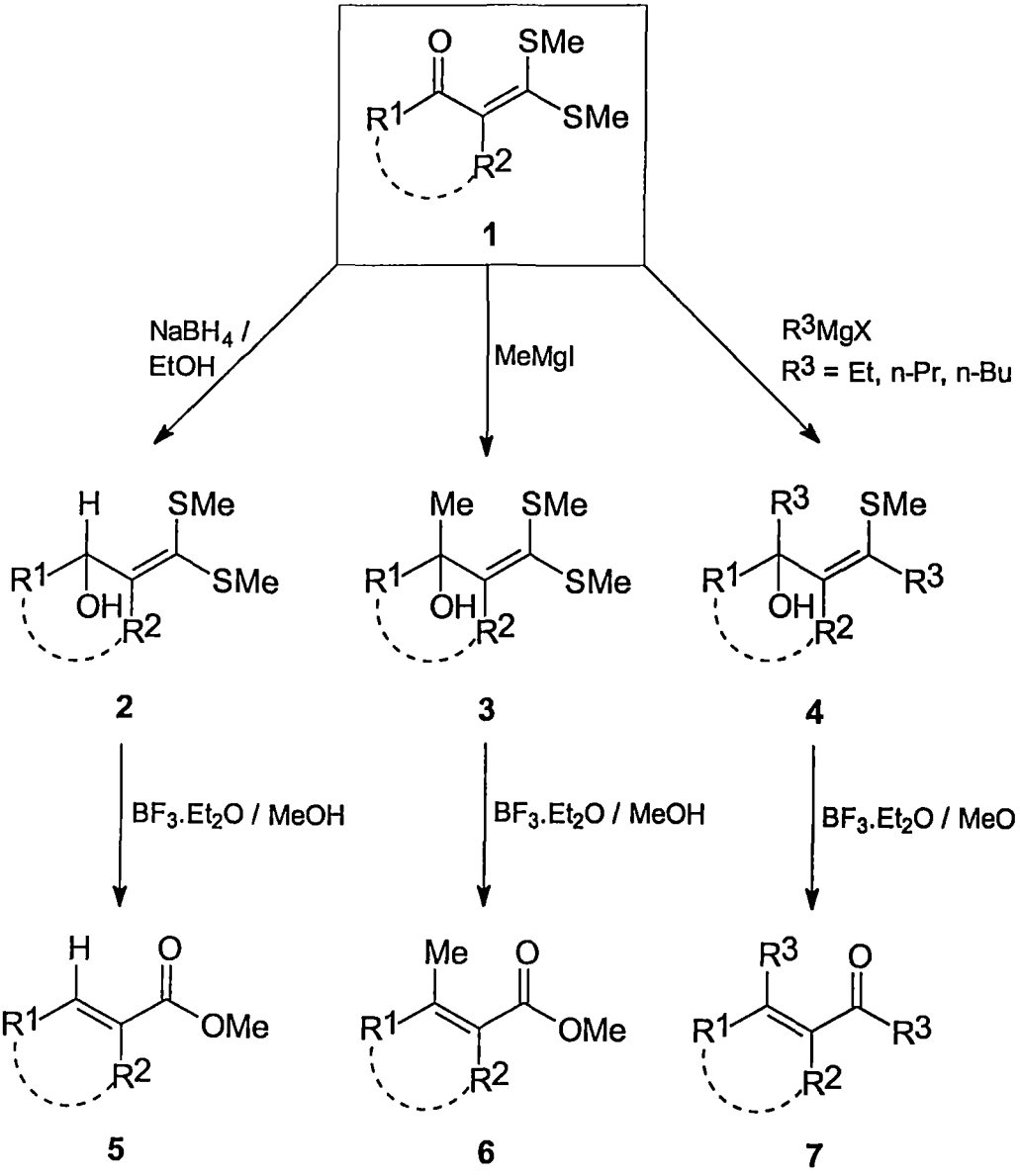
The first synthesis of α-oxoketene dithioacetal was reported by Kelber and co-workers in 1910[10-12]. However, the chemistry of these intermediates remained unexplored, until Thuillier and co-workers[13-16] prepared these compounds in high yields in one pot reaction by reacting the active methylene ketones with carbon disulfide in the presence of sodium amylate followed by alkylation. Later on several modifications in the reaction conditions have been made for obtaining higher yields of α-oxoketene dithioacetals.[17-21]

The oxoketene dithioacetals can be visualized as masked β-ketoesters in which the ester functionality is manifested as a ketene dithioacetal moiety. Alternatively, they may be considered as α,β-unsaturated ketones containing a highly functionalized β-carbon. The α-oxoketene dithioacetals have been

shown to be excellent three carbon fragments possessing 1,3-electrophilic centres with differing electrophilic properties. These intermediates possess considerable potential in the stereo- and regioselective construction of bonds either by a 1,2-nucleophilic addition to carbonyl group or 1,4-conjugate addition to the β-carbon of the enone system. They are primary precursors for the corresponding O,S-, N,S- and N,N-acetals.[9]

As a part of systematic study on various reactivity profiles of α-oxoketene dithioacetals,[9] it was shown in our laboratory that these α-oxoketene dithioacetals undergo sodium borohydride reduction in 1,2-fashion to give the corresponding carbinol acetal **2.** These carbinol acetals are shown to undergo smooth methanolysis in the presence of borontrifluoride-etherate to afford α,β-unsaturated methyl esters **5** in good yields[22] (Scheme-1). The overall transformation can be viewed as homologation of active methylene ketones at the α -position involving a 1,3-carbonyl transposition.

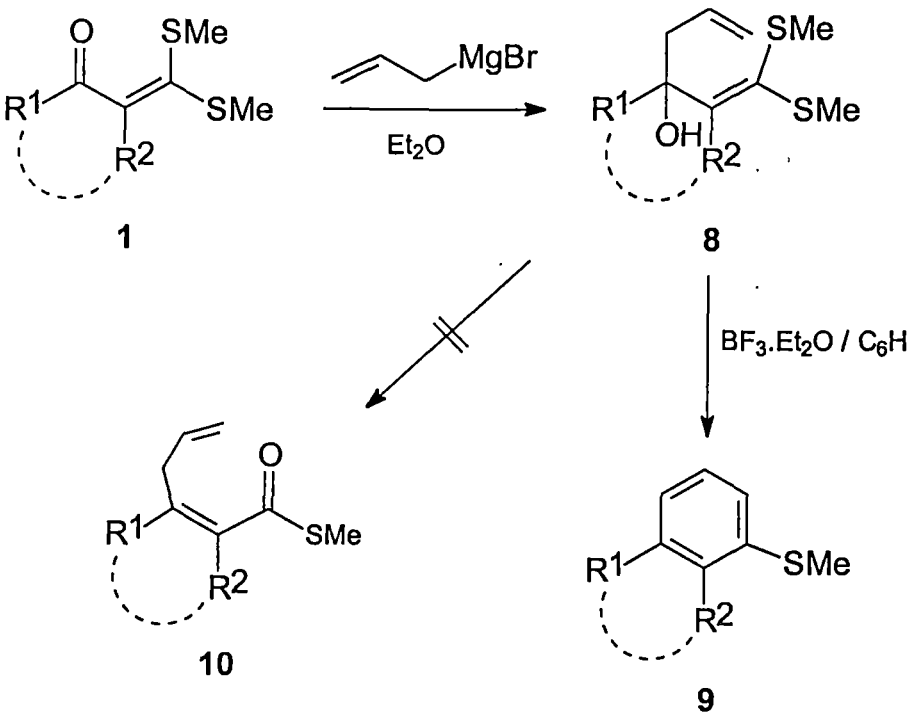
Methylmagnesium iodide was shown to react with α-oxoketene dithioacetals to afford the carbinol acetals **3** by 1,2-addition in good yields (Scheme-1)[23]. The $BF_3.Et_2O$ assisted methanolysis of these carbinol acetals afforded the corresponding β-methyl-α,β-unsaturated esters **6.** The course of addition of higher alkyl Grignard reagents (R = Et, *n*-Pr, *n*-Bu) to α-oxoketene


O
SMe
R1
SMe
R2
1
NaBH4 /
EtOH
MeMgI
R3MgX
R3 = Et, n-Pr, n-Bu
H
SMe
R1
SMe
OH
R2
2
Me
SMe
R1
SMe
OH
R2
3
R3
SMe
R1
R3
OH
R2
4
BF3.Et2O / MeOH
BF3.Et2O / MeOH
BF3.Et2O / MeO
H
O
R1
OMe
R2
5
Me
O
R1
OMe
R2
6
R3
O
R1
R3
R2
7

Scheme 1

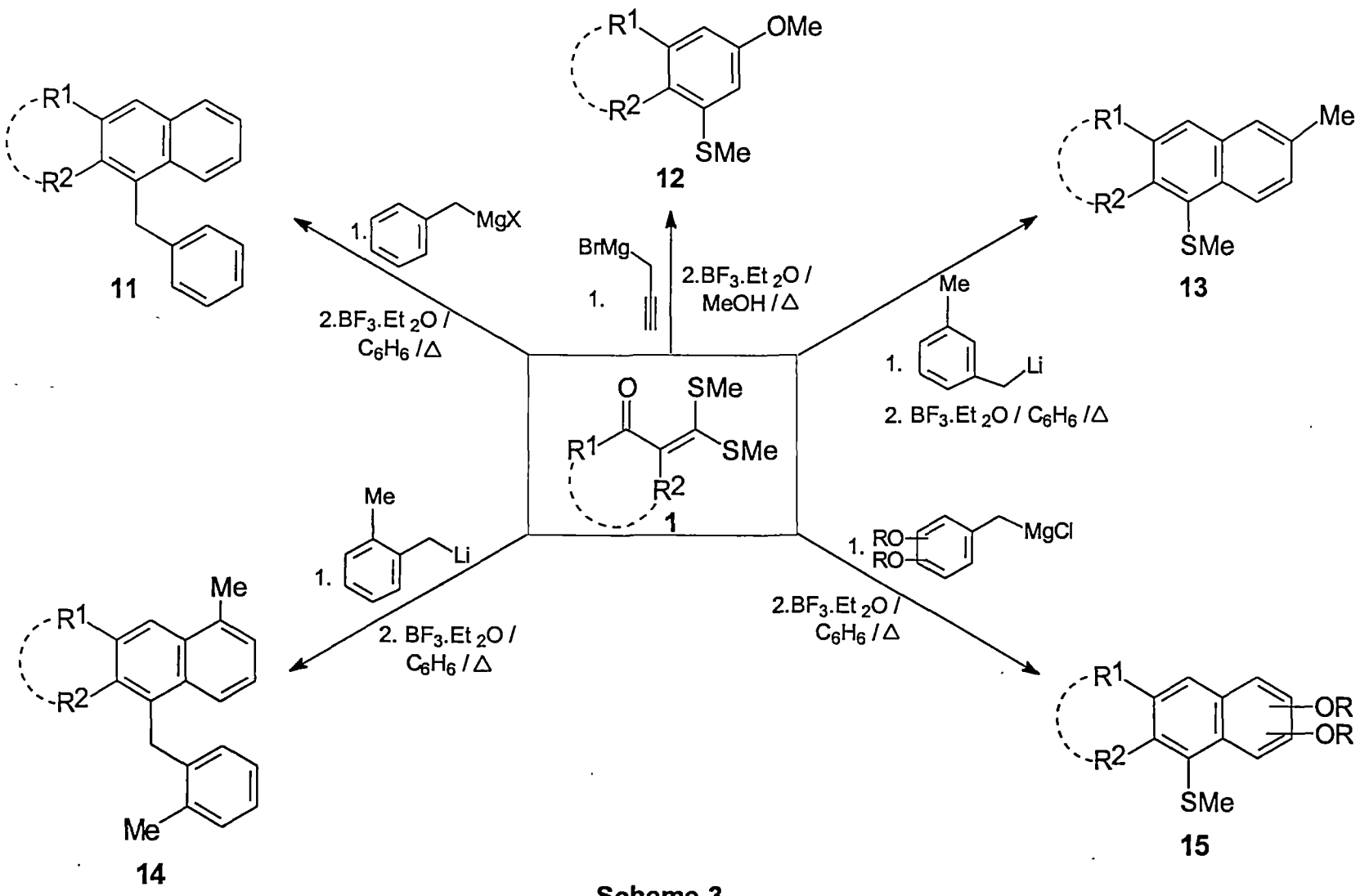
dithioacetals followed a sequential 1,4- and 1,2-addition pattern to afford carbinols **4** which are shown to afford α,β-unsaturated ketones **7** after subsequent hydrolysis in the presence of $BF_3.Et_2O$[23] (Scheme-1).

Allyl magnesium bromide was also reacted with **1** to give the corresponding carbinol acetal **8** in high yields[24]. Interestingly when these carbinol acetals were treated with $BF_3.Et_2O$ in refluxing benzene, they underwent cycloaromatization to afford methylthio substituted aromatics **9** instead of the observed carbonyl transposition (Scheme-2)[24].



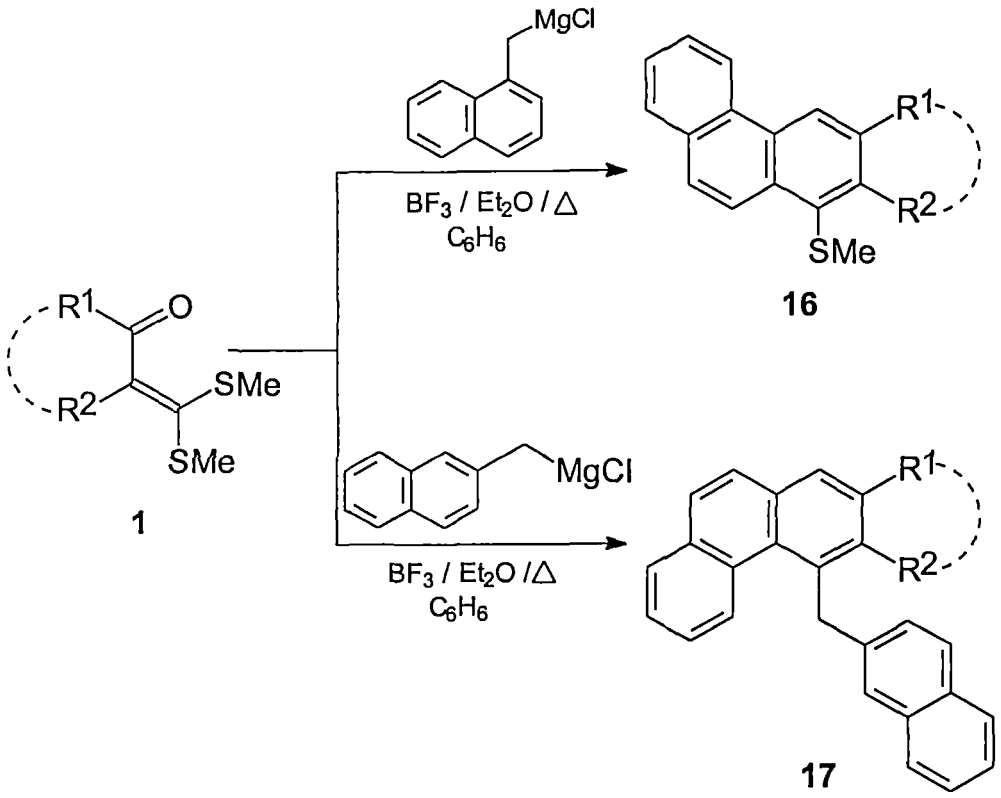
Scheme-2

Thus, a new [3+3] aromatic annelation methodology via α-oxoketene dithioacetals was discovered in our laboratory and this protocol has emerged as an area of great synthetic potential. This new [3+3] aromatic annelation methodology has been extensively investigated to establish its general applicability. The method is a major discovery involving highly functionalized open chain precursors to afford appropriately substituted aromatics in a simple two step sequence. The reaction was found to be general with a large number of α-oxoketene dithioacetals derived from both cyclic, acyclic ketones as well as equally large number of allylic anions making its synthetic scope unlimited. Thus this method was extremely versatile when extended to methyl allyl magnesium bromide, crotyl magnesium bromide and propargyl magnesium bromide to afford the substituted benzoannelated products[8,25]. Subsequently this method of aromatic annelation was extended to naphthoannelation. This transformation was achieved by reacting benzyl magnesium chloride with α-oxoketene dithioacetals to afford the intermediate carbinols which on treatment with $BF_3.Et_2O$ yielded the corresponding naphthalene derivatives through benzene ring participation[26]. Similarly *o*-xylyl lithium, *m*-xylyl lithium[27] and methoxy substituted benzyl magnesium chlorides[28] were reacted with α-oxoketene dithioacetals followed by $BF_3.Et_2O$-assisted cyclization to afford the corresponding substituted naphthalenes (scheme-3).


R1
R2
11
1. MgX
2.BF3.Et2O / C6H6 /Δ
R1
OMe
R2
SMe
12
BrMg
1.
2.BF3.Et2O / MeOH /Δ
R1
Me
R2
SMe
13
Me
1. Li
2. BF3.Et2O / C6H6 /Δ
O
SMe
R1
SMe
R2
1
Me
1. Li
2. BF3.Et2O / C6H6 /Δ
R1
Me
R2
Me
14
1. RO RO MgCl
2.BF3.Et2O / C6H6 /Δ
R1
OR
OR
R2
SMe
15

Scheme-3

When α- and β-naphthylmethylmagnesium halides were reacted with α-oxoketene dithioacetals it afforded after cycloaromatization, the corresponding phenanthrenes and polycondensed aromatic compounds[29] (Scheme-4).



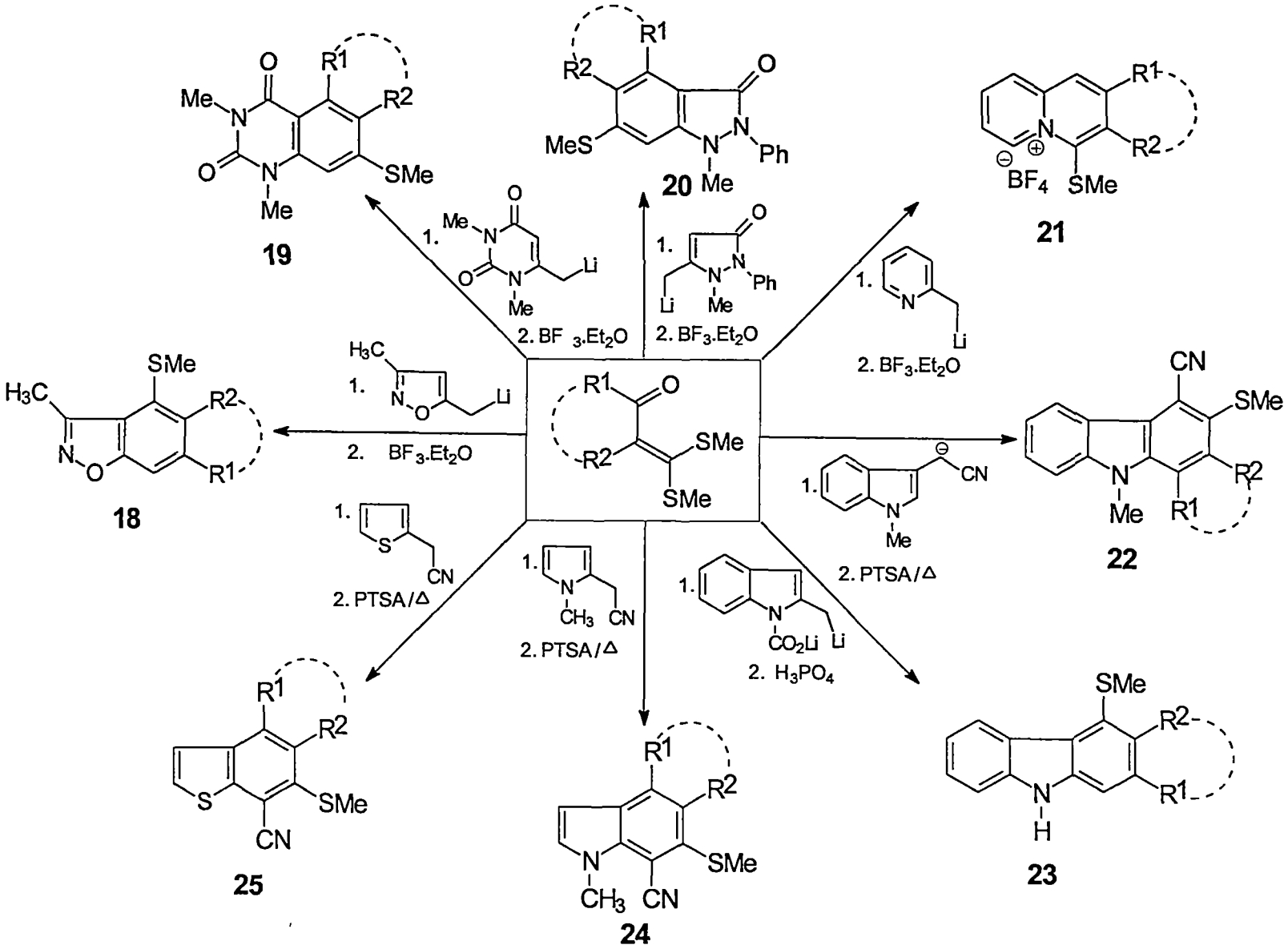
Scheme-4

The versatility of this aromatic annelation methodology was further demonstrated by applying this strategy for the construction of aromatic ring over the preconstructed heterocyclic molecules. Thus the reaction of 5-lithiomethyl-3-methylisoxazole, 6-lithiomethyl-1,3-dimethylpyrimidine, 3-lithiomethyl-2-methyl-1-phenyl-5-pyrazolone and 2-picoline with α-oxo-

ketene dithioacetals yielded the corresponding benzisoxazoles[30], quinazolines[31], indazolones[32] and quinolizinium salts[33] respectively. Recently, [a]annelatedcarbazoles[34], [b]annelated carbazoles[35], indoles[36] and benzothiophenes[37] have been achieved by extending this aromatic annelation methodology (Scheme-5).

The classical synthetic approaches for benzoheterocycles usually involve elaboration of a heterocyclic ring onto an appropriately substituted benzene ring. However, the aromatic annelation strategy of building functionalized benzene ring onto preconstructed heterocycles resulted in the development of new synthetic methodology for target molecules which are otherwise difficult to achieve by classical approaches.

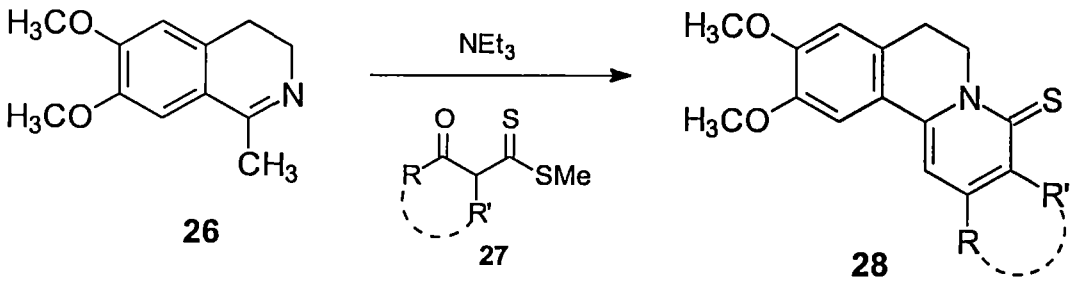
It is apparent from the above examples, that the method of aromatic and heteroaromatic annelation is not only applicable for the synthesis of condensed aromatics but this new strategy has been found to be highly successful for the construction of aromatic ring over the preconstructed heterocyclic molecules providing a new synthetic dimension to the entire chemistry of benzoheterocyclic compounds and their condensed variants.



Scheme - 5

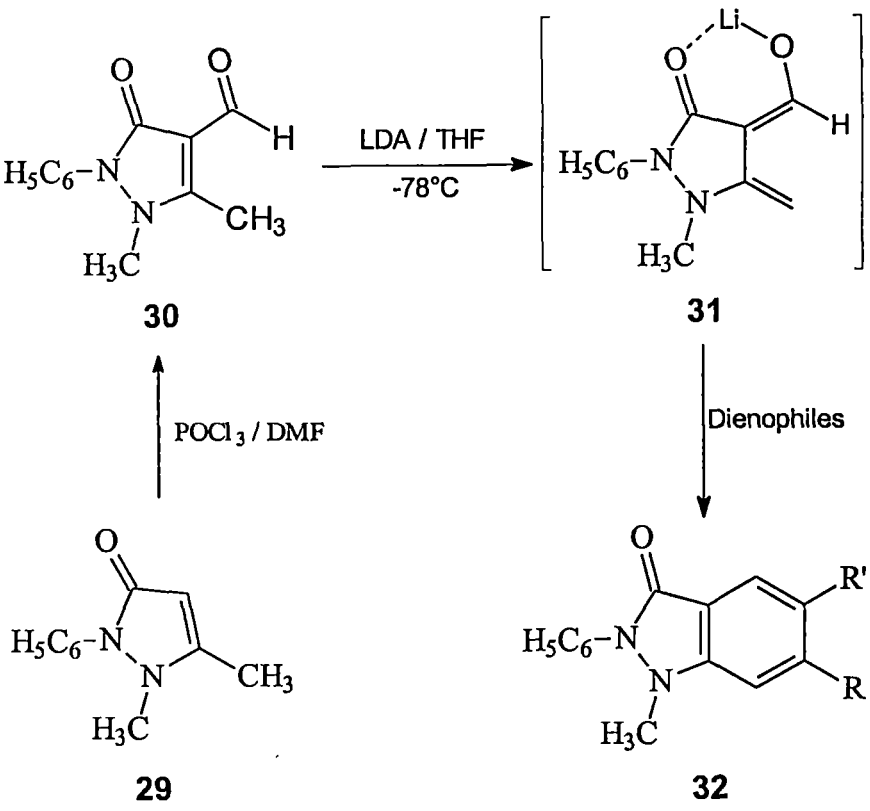
The work presented in this thesis

In the present investigation it was proposed to develop a new efficient method for the synthesis of benzoquinolizines utilizing the heteroaromatic annelation methodology developed in our laboratory. Thus, we have taken 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **26** as the azaallyl component and reacted with various β-oxodithioates **27** to afford benzo[*a*] quinolizines **28** which forms the basic skeleton of various isoquinoline alkaloids. The scope and limitations of this work is discussed in chapter 2 (Scheme-6).



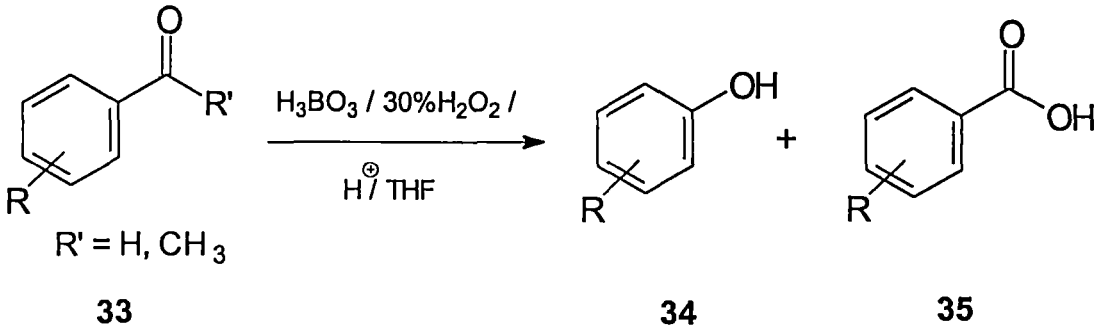
Scheme-6

The third chapter deals with the *in situ* generation of heterocyclic *o*-quinodimethane intermediate **31** from 4-formyl-2,3-dimethyl-1-phenyl pyrazolin-5-one **30** and its reaction with various dienophiles to give a wide range of regiospecifically substituted and condensed indazolones **32** (Scheme-7).



Scheme -7

The fourth chapter deals with the Dakin type oxidation using boric acid and hydrogen peroxide in presence of sulphuric acid for the conversion of aromatic aldehydes and ketones to phenols (Scheme-8).



Scheme-8

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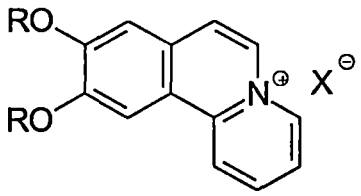
CHAPTER-II

REACTION OF 3,4-DIHYDRO-6,7-DIMETHOXY-1-METHYLISO-QUINOLINE WITH β-OXODITHIOATES: AN EFFICIENT NEW METHOD FOR THE SYNTHESIS OF BENZO[*a*]QUINOLIZINES.

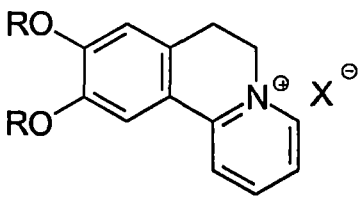
The benzoquinolizines and their corresponding quinolizinium salts occur widely in nature as structural moiety in a large number of isoquinoline alkaloids. Frequent occurrence of benzoquinolizine nucleus in a large number of alkaloids[1,2] have resulted in the generation of large number of products containing this ring system. Also extensive synthetic activity to achieve the synthesis of some of these important alkaloids has generated countless intermediates involving benzoquinolizine structural framework. The basic benzo[*a*]quinolizine ring system is generally associated with either the degradation product or as synthetic intermediates with B and C ring partially or fully reduced. These systems are described in Scheme-1.

Hence these characteristic ring systems are synthetically important for which many methods are reported in the literature[3,4].



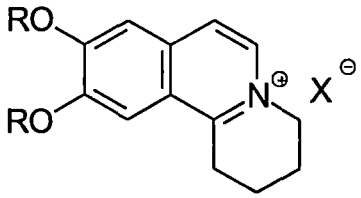
Benzo[*a*]quinolizinium Salt

1a



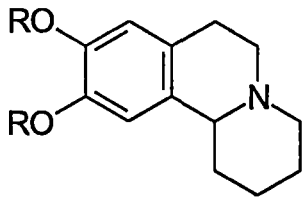
Dihydrobenzo[*a*]quinolizinium Salt

1b



Tetrahydrobenzo[*a*]quinolizinium Salt

1c



Hexahydrobenzo[*a*]quinolizinium Salt

1d

Scheme-1

The most important isoquinoline alkaloids containing this ring system are emetine group of alkaloids which include

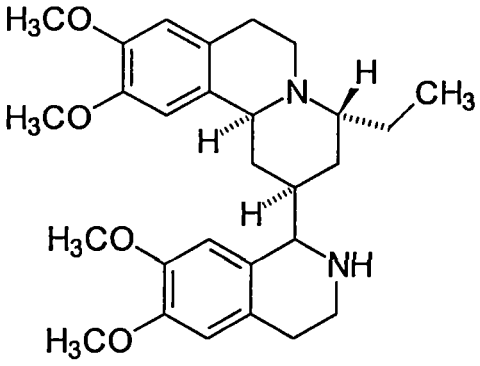
Emetine

Protoemetinol

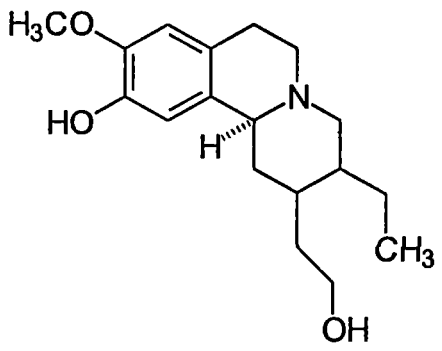
Ankorine

Tubulosine

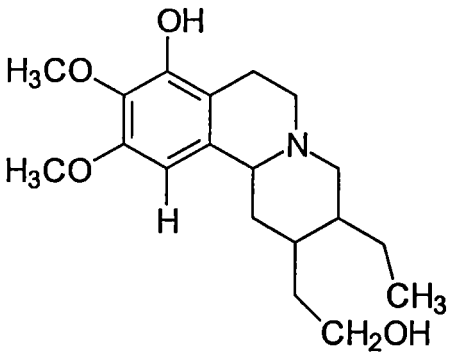
Most of these emetine group of alkaloids generally contain hexahydro B, C ring systems carrying different substituents. Some of their structures are depicted in Scheme-2.



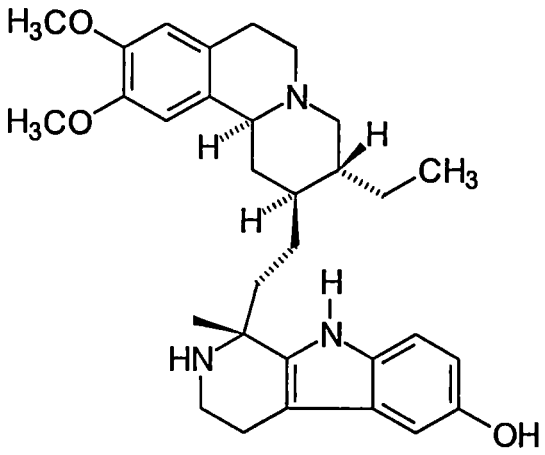
Emetine
2a



10-Demethyl protoemetinol
2b



Ankorine
2c



Tubulosine
2d

Scheme-2

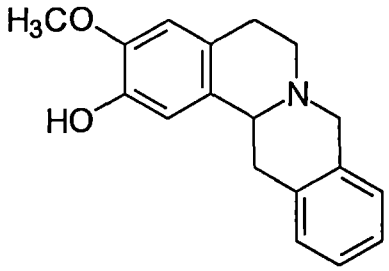
Another group of alkaloids containing this ring system belong to proto-berberine class where over hundred alkaloids have been so far isolated, characterized and many of them have been synthesized. The main structural group of protoberberine class is depicted in Scheme-3. The group constitutes:

1. Bharatamine
2. Xylopinine
3. Palmatine
4. Canadine
5. Dehydroapocavidine
6. Coralydine

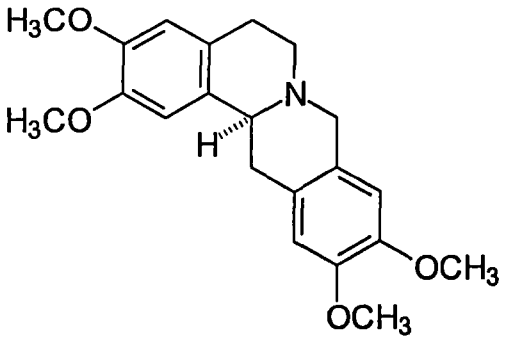
which are a few among many well known berberine alkaloids.

The important biological properties[5,6] of these benzo[*a*]quinolizines has further triggered extensive synthetic activities involving isoquinoline and benzo[*a*]quinolizine chemistry. The methods for constructing isoquinoline ring itself have been extensively reviewed in the literature[7-9].

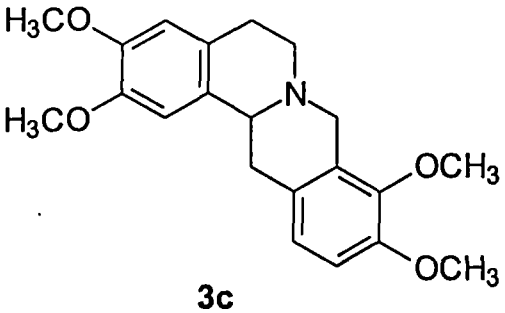
The present work deals with development of new facile method for constructing benzoquinolizine ring system by reacting various β-oxodithioates with 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline in the presence of a mild base like triethylamine. There are several methods reported in the literature for the synthesis of benzo[*a*]quinolizine ring system. The first general method for the synthesis of benzo[*a*]quinolizinium salts[10] involve the quaternization of 2-phenyl pyridine with appropriate halocarbonyl derivatives followed by acid catalyzed cyclization[11,12,13]. These classical methods,



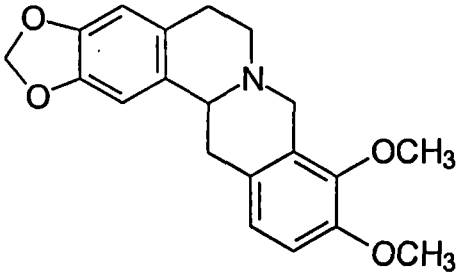
3a
Bharatamine



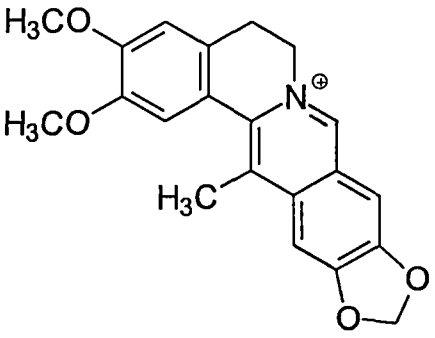
3b
Xylopinine



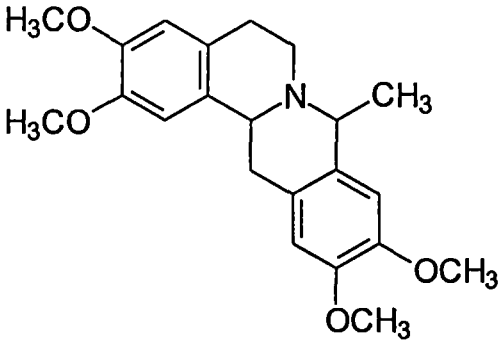
3c
Palmatine



3d
Canadine



3e
Dehydroapocavidine

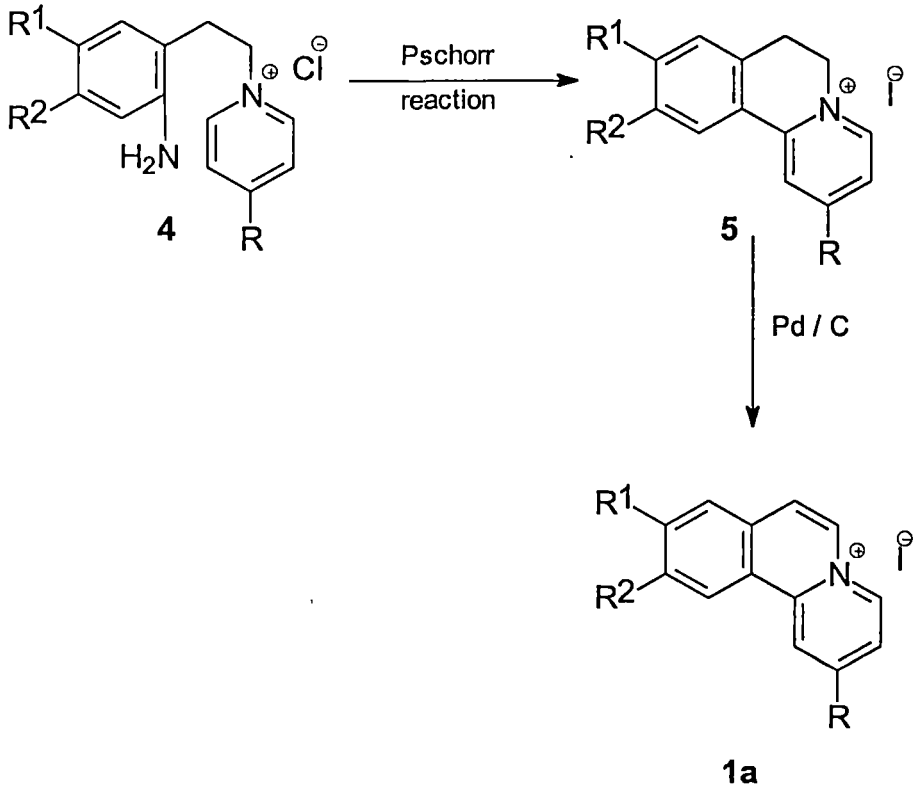


3f
Coralydine

Scheme-3

using 2-phenyl pyridine as main precursors for the synthesis of quinolizinium salts have been reviewed in the literature. Only selected works of synthetic methodologies on quinolizinium systems are reviewed in the following section.

One of the early reports for the synthesis of benzo[*a*]quinolizinium ring system involves 2-aminophenethylpyridinium chloride **4** which was cyclized under Pschorr reaction condition to afford the corresponding 6,7-dihydrobenzo[*a*]quinolizinium iodide **5** in moderate yields[14]. The dihydro compound **5** was dehydrogenated by Palladium on carbon to yield the corresponding benzo[*a*]quinolizinium iodide in good yields (Scheme-4) . A

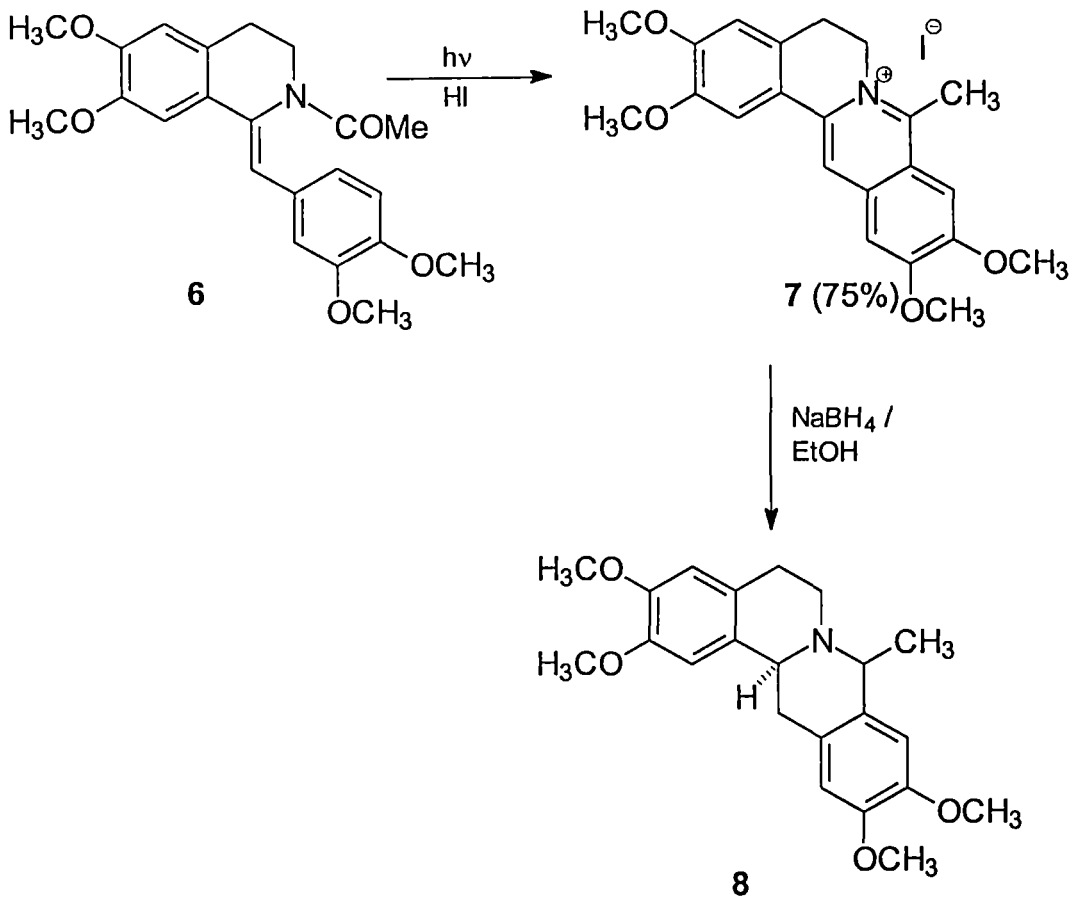


Scheme-4

number of derivatives of this ring system were prepared by this method with substituents on benzene and pyridine rings.

One of the rewarding synthetic methods involving ring closure of isoquinoline derivatives has been the photoassisted ring closure of appropriately substituted isoquinolines[15]. Early efforts of photochemical approach for the synthesis of berberine analogs were reported by Yang and co-workers[16]. Thus irradiation of 2-acetyl-1-(3,4-dimethoxybenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **6** in methanol with equimolar quantities of iodine and hydroiodic acid in an inert atmosphere yielded the corresponding quaternary salt of the cyclized product **7** in 75% yield. The salt **7** on reduction with sodium borohydride in ethanol yielded β-coralydine in quantitative yield. These reactions revealed that photoirradition was essential for cyclization since intermediate **6** failed to cyclize in the absence of radiation (Scheme-5). Interestingly the parallel reactions without any methoxy substituents yielded only 42% of the quaternary salt.

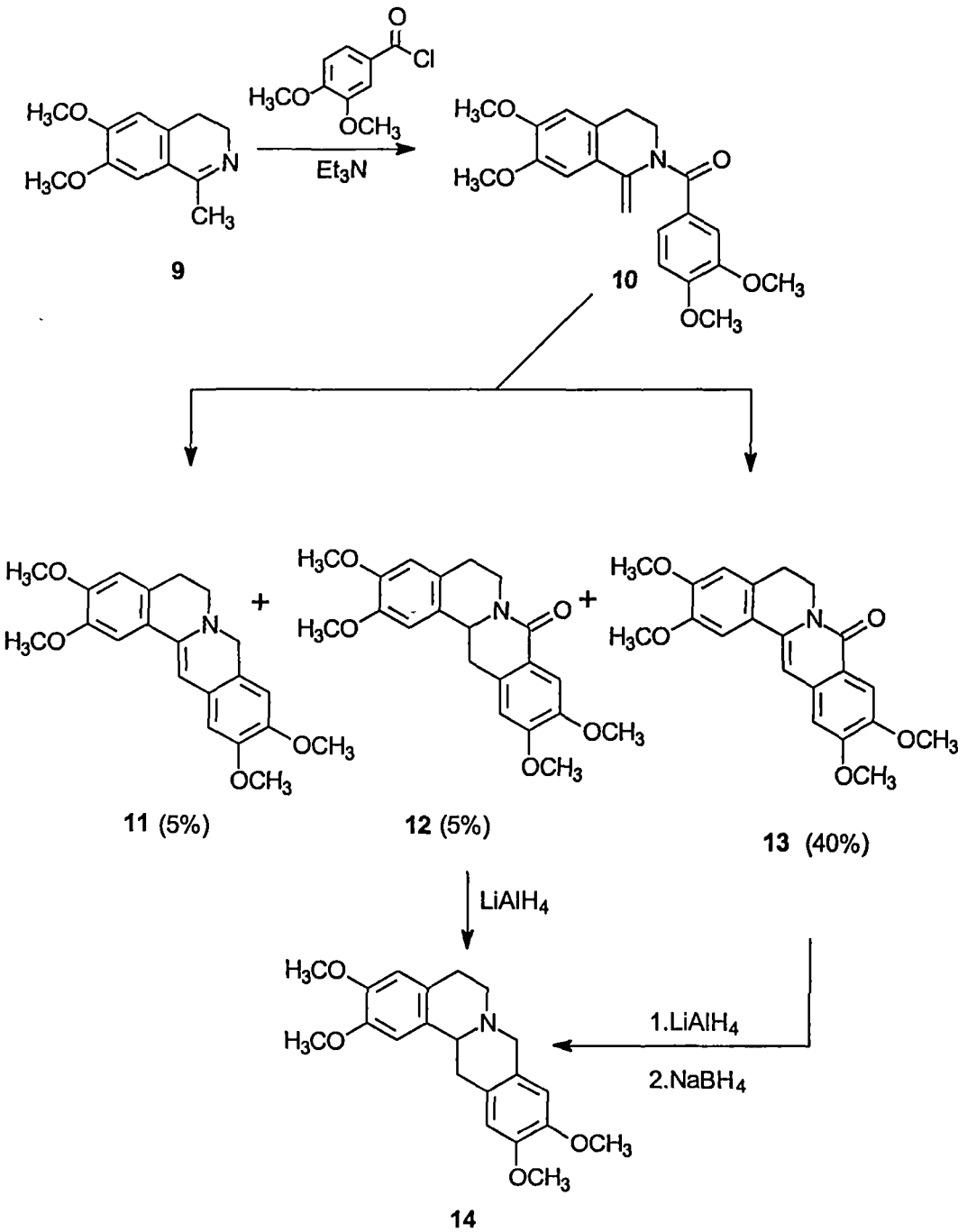
As early as 1970, Ninomiya and co-workers initiated and published a series of papers on photocyclization of enamides[17], which they extended later to photocyclization involving isoquinoline system leading to the synthesis of 8-oxoberbine structures[18]. Easily accessible 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **9** was reacted with 3,4-dimethoxy benzoyl chloride in the



Scheme-5

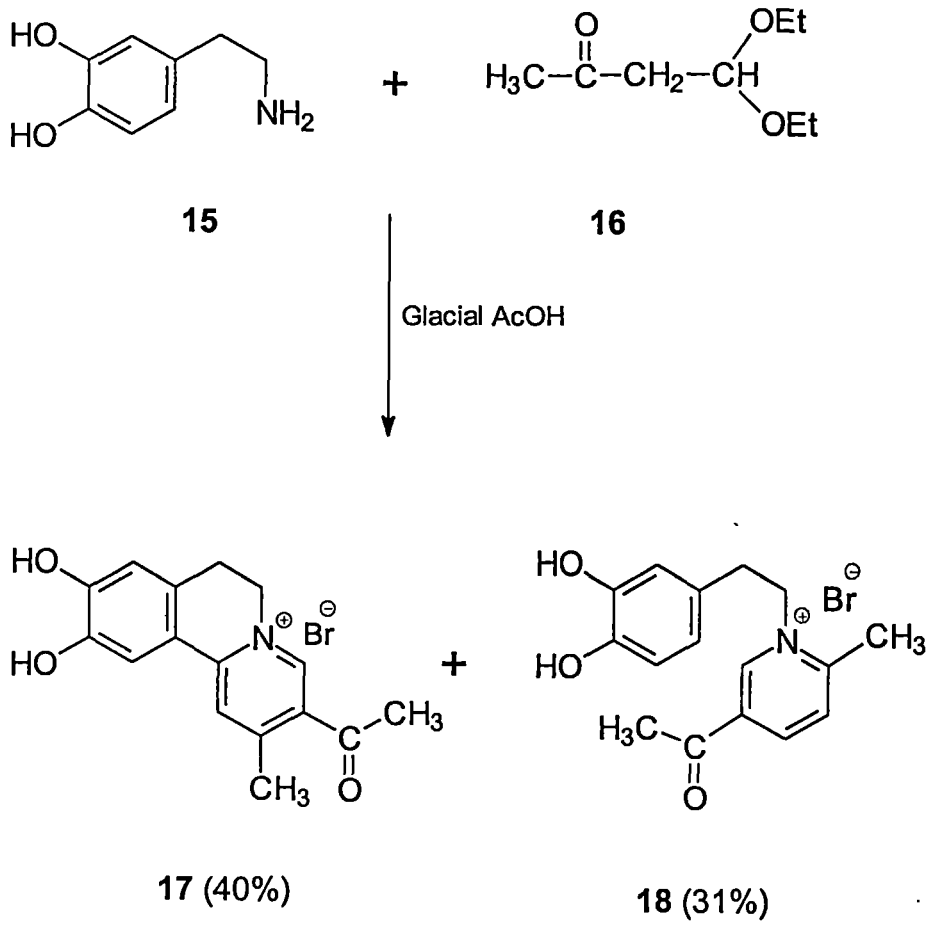
presence of triethylamine to afford the corresponding N- benzoylisoquinoline **10** in quantitative yield. These enamides were irradiated with a low pressure mercury lamp at low temperature for three hours depending on the amount of enamides used. The lactam **12** in 5% and the dehydrolactam **13** in 40% were obtained along with a side product **11** in 5% yield. Reduction of lactam **12** with lithium aluminium hydride yielded the corresponding dl-Xylopinine **14** in

high yields. Reduction of **13** with lithiumaluminiumhydride followed by sodiumborohydride[19] also afforded **14** (Scheme-6).



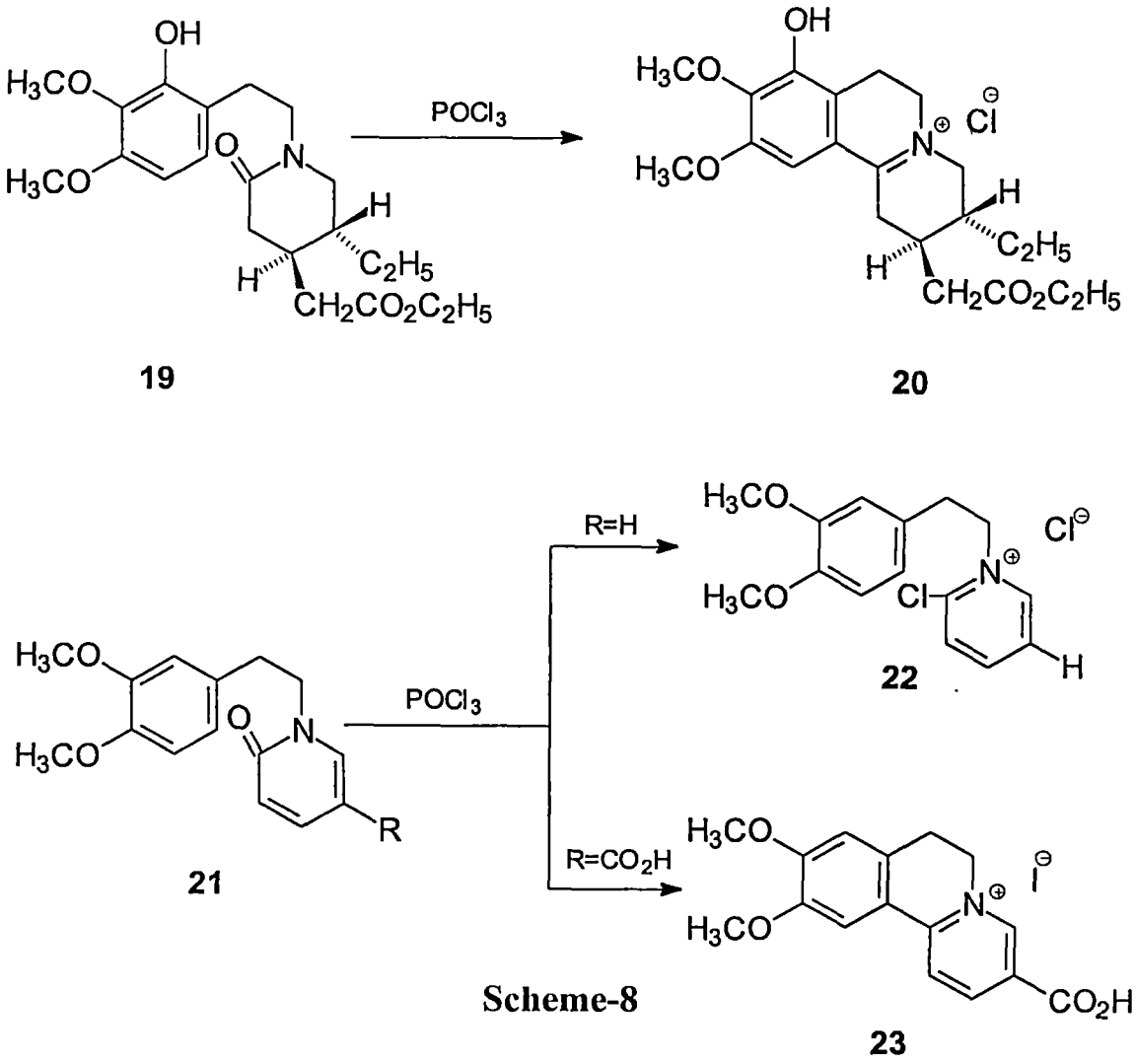
Scheme-6

Teuber and Laudien[20]have reported that 3,4-dihydroxyphenethylamine **15** reacts with two equivalents of acetoacetaldehyde diethyl acetal in glacial acetic acid to afford a mixture of benzo[*a*]quinolizinium salt **17** in 40% yield and the corresponding open chain pyridinium salt **18** in 31% yield (Scheme-7). Treatment of **17** with a number of reagents in the presence of potassium iodide and potassium carbonate in acetone yielded substituted quaternary salts in 23-82% yields[21,22].



Scheme-7

Bischler-Napieralski reaction has been extensively used for the synthesis of benzoquinolizines[23]. Thus N-phenethylpiperidone **19** is easily cyclized using phosphorus oxychloride under Bischler-Napieralski reaction condition to afford the corresponding benzoquinolizidine derivative[24] **20**. This method has been widely used for the synthesis of emetine and its analogs. However N-phenethyl pyridone **21** failed to cyclize to afford the corresponding isoquinoline derivative and instead yielded open chain α-chloropyridine

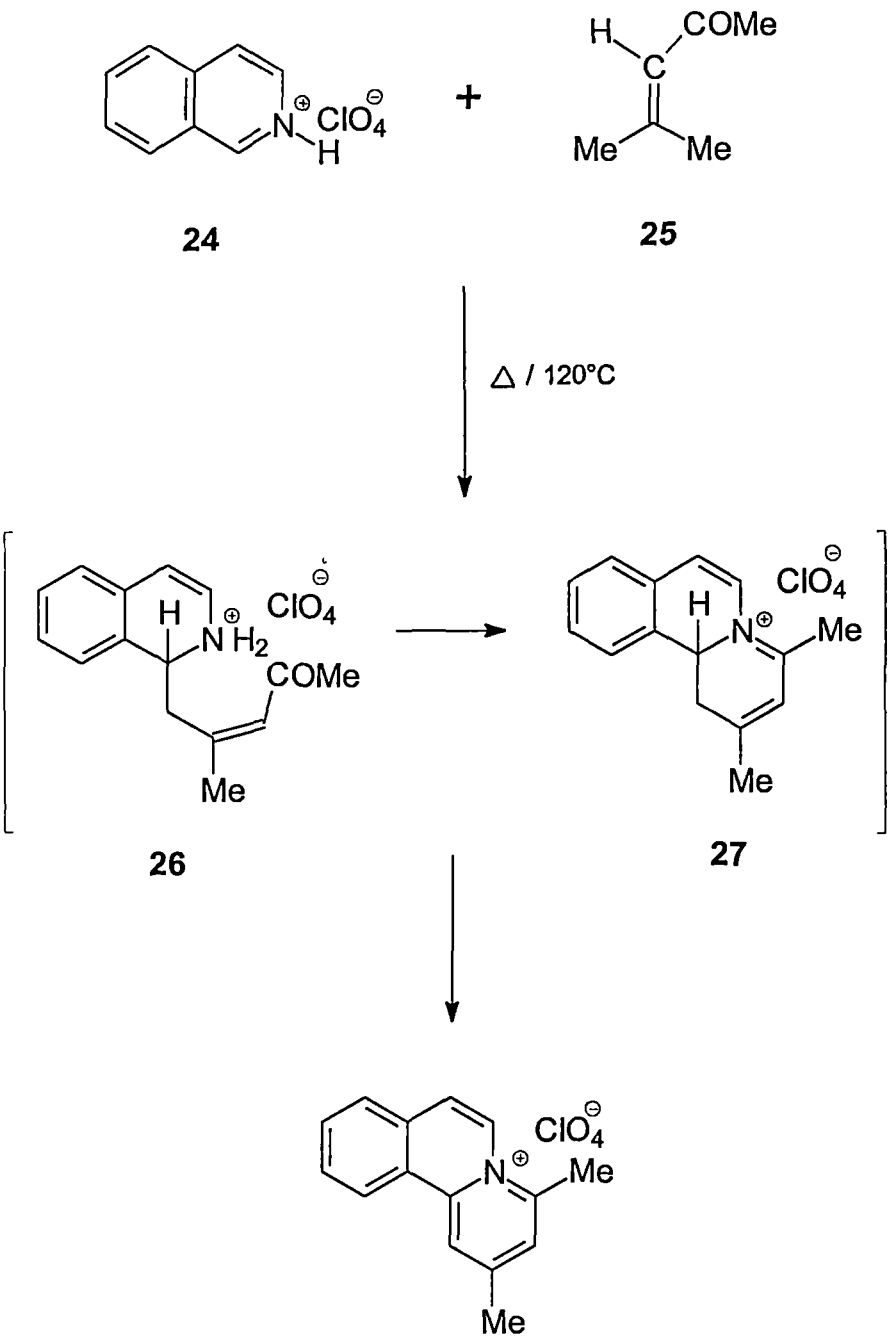


Scheme-8

derivative **22**[25] (Scheme-8). Interestingly, the pyridone underwent smooth cyclization[26] to afford benzoquinolizidine **23** when there was a carboxylic acid group at C-5 carbon atom. Despite the success of Bischler–Napieralski reaction for the synthesis of benzoquinolizidine from N-phenethylimides[27,28], many systems have been reported to fail under those reaction conditions[29].

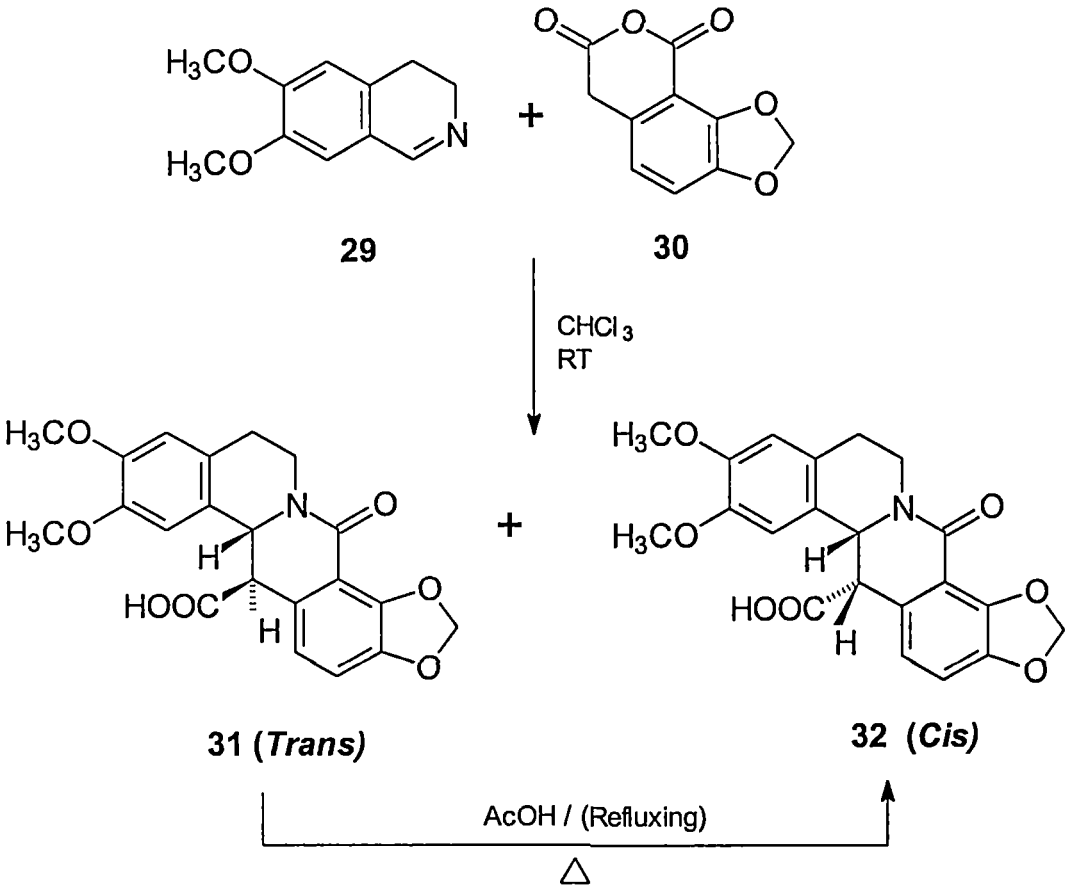
Chapman[30]have reported that mesityl oxide **25** when heated with isoquinolinium perchlorate **24** for several hours at 120°C afforded the corresponding benzo[*a*]quinolizinium salt **28** in 35% yield. The formation is believed to have involved the C-C bond formation from isopropylidine methyl group to the C-1 electrophilic carbon atom of the isoquinolinium ring. The intermediate followed ring closure to afford dihydroquinolizinium perchlorate which rapidly aromatizes to form quinolizinium perchlorate in 35% yield (Scheme-9).

Cushman[31,32]and co-workers have successfully condensed 3,4-dihydro-6,7-dimethoxy isoquinoline **29** with 3,4-methylenedioxyhomophthalic anhydride **30** in chloroform to afford mixture of *cis* and *trans*- 2,3-dimethoxy-8-oxo-9,10-methylenedioxy-13-carboxytetrahydroprotoberberines in moderate



Scheme-9

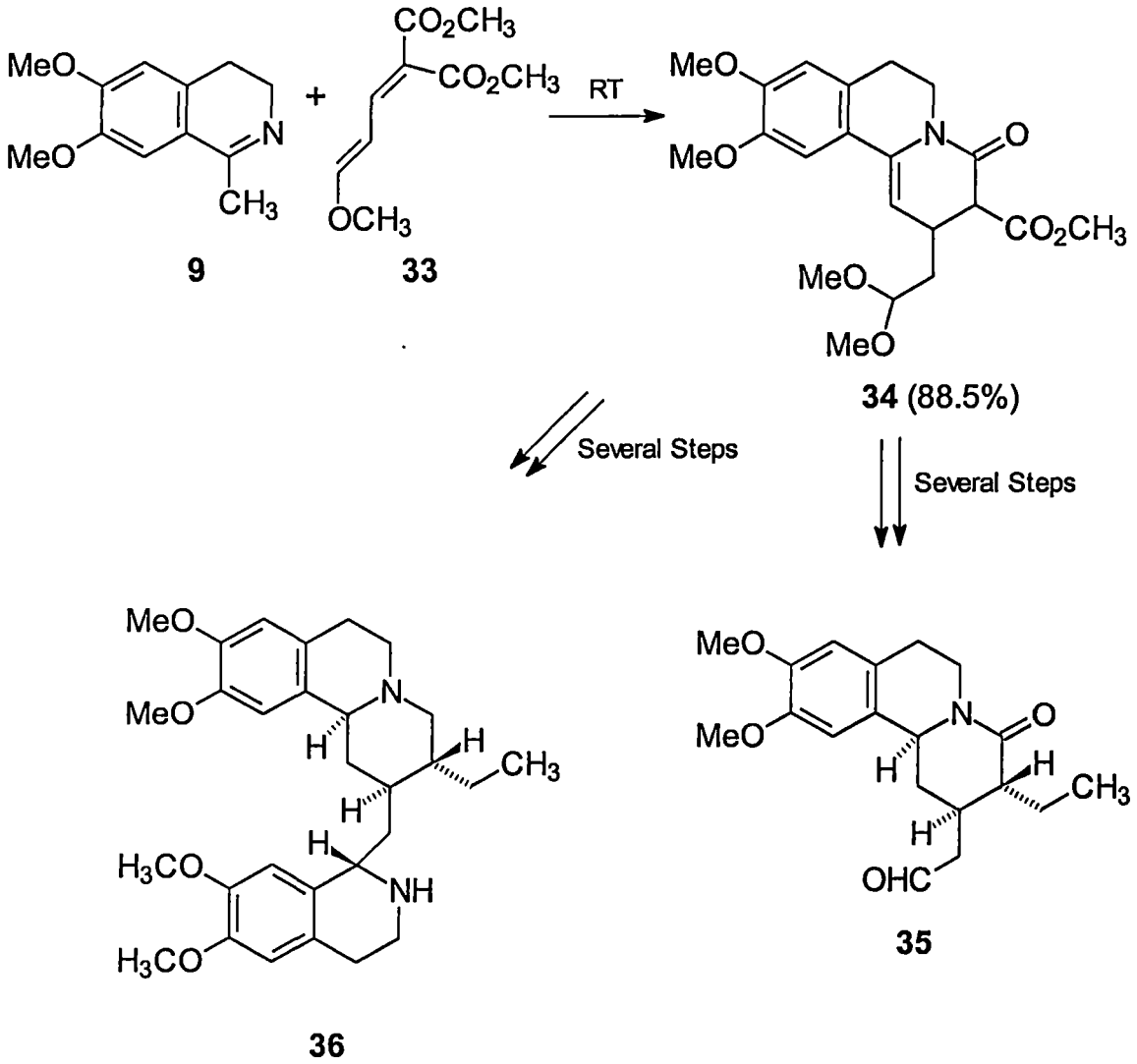
to good yields. Interestingly one of the epimers **31** underwent thermal epimerisation to **32** in refluxing glacial acetic acid (Scheme-10).



Scheme-10

As a part of synthetic strategy for the total synthesis of emetine, Kametani and co-workers[33] reacted 3,4-dihydro-6,7-dimethoxy-1-methyl isoquinoline **9** with dimethyl-3-methoxyallylidenemalonate **33** at room temperature and refluxing sequentially to afford the corresponding 9,10-dimethoxy-3-methoxycarbonyl-2-(β,β-dimethoxyethyl)-2,3,6,7-tetrahydro-benzo[*a*]quinolizine-4-one **34.** The compound **34** is a key intermediate for the

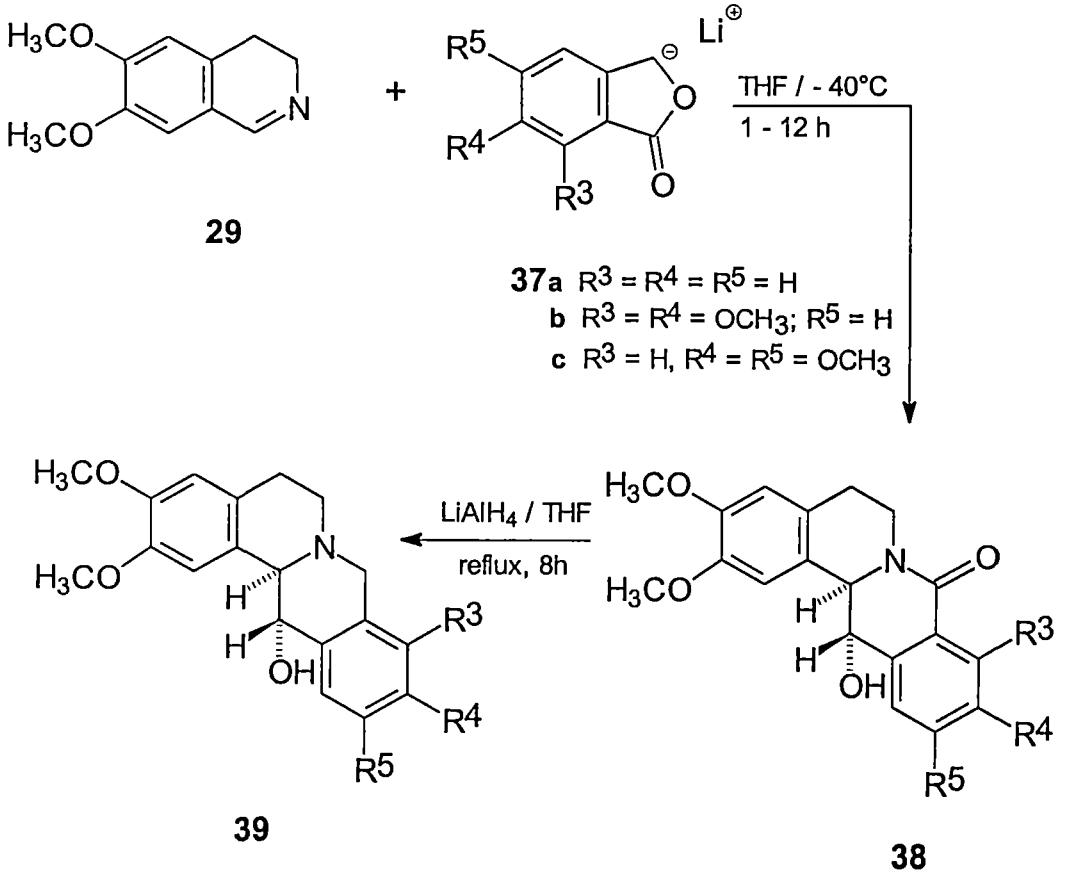
synthesis of emetine and important intermediate **35** encountered in the synthesis of emetine (Scheme11).



Scheme-11

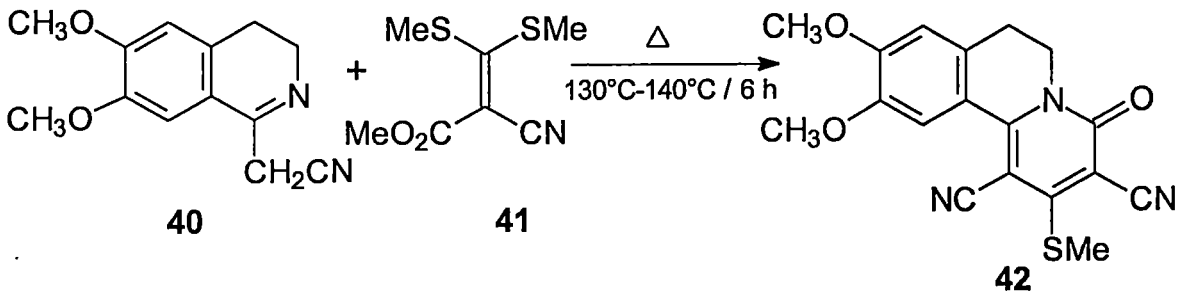
A new synthesis of protoberberine system was reported by Maclean and co-workers[34] where they have reacted lithio derivative of phthalide with 3,4-dihydro-6,7-dimethoxyisoquinoline to afford the corresponding 13-hydroxy-8-

oxo-tetrahydroprotoberberine **38** with trans hydrogen atom at C-13 and C-14 carbon atoms. The amide was subsequently reduced to the corresponding 13-hydroxytetrahydroprotoberberine (Scheme- 12).



Scheme -12

Kobayashi and co-workers[35] condensed 3,4-dihydro-6,7-dimethoxyisoquinoline-1-acetonitrile with cyanoacetate ketene dithioacetal **41** to afford the corresponding 1,3-dicyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (Scheme-13).

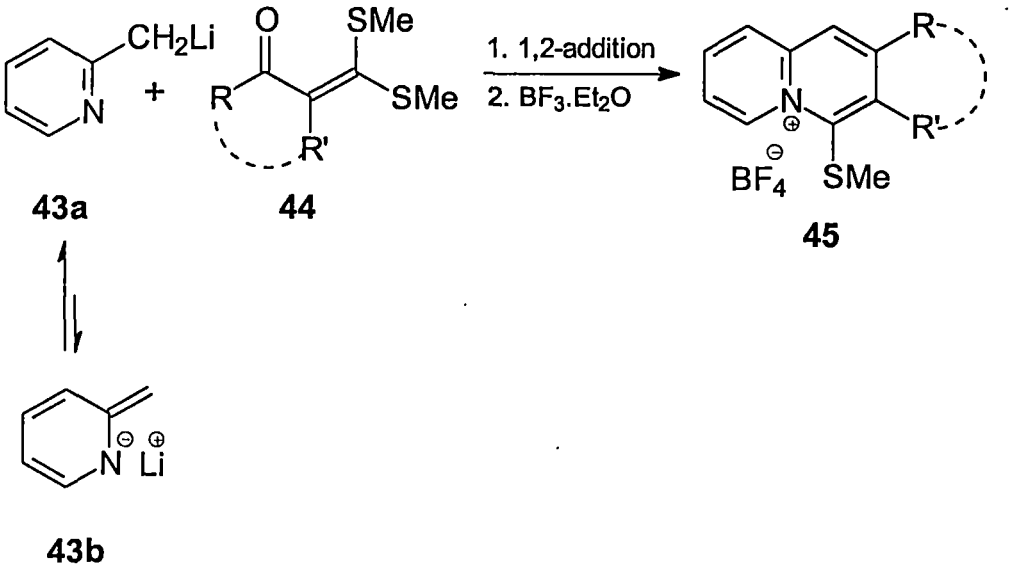


Scheme-13

It should be noted that highly activated 1-methyl group reacts with **41** only under thermal conditions without involving the presence of even mild bases. This reaction is important, though less activated ketene S,S-acetals however, may require use of base to achieve the same transformations. The α-oxoketene dithioacetals failed to react in our laboratory with 1-lithiomethyl-3,4-dihydroisoquinolines and it was considered of interest to initiate systematic investigation on the reactivity of α-oxoketene dithioacetal or their precursors dithioates so that this reaction can be applied to prepare wide structural variants containing quinolizine ring systems. The present chapter deals with this investigation and the results are presented in the following section.

RESULTS AND DISCUSSION

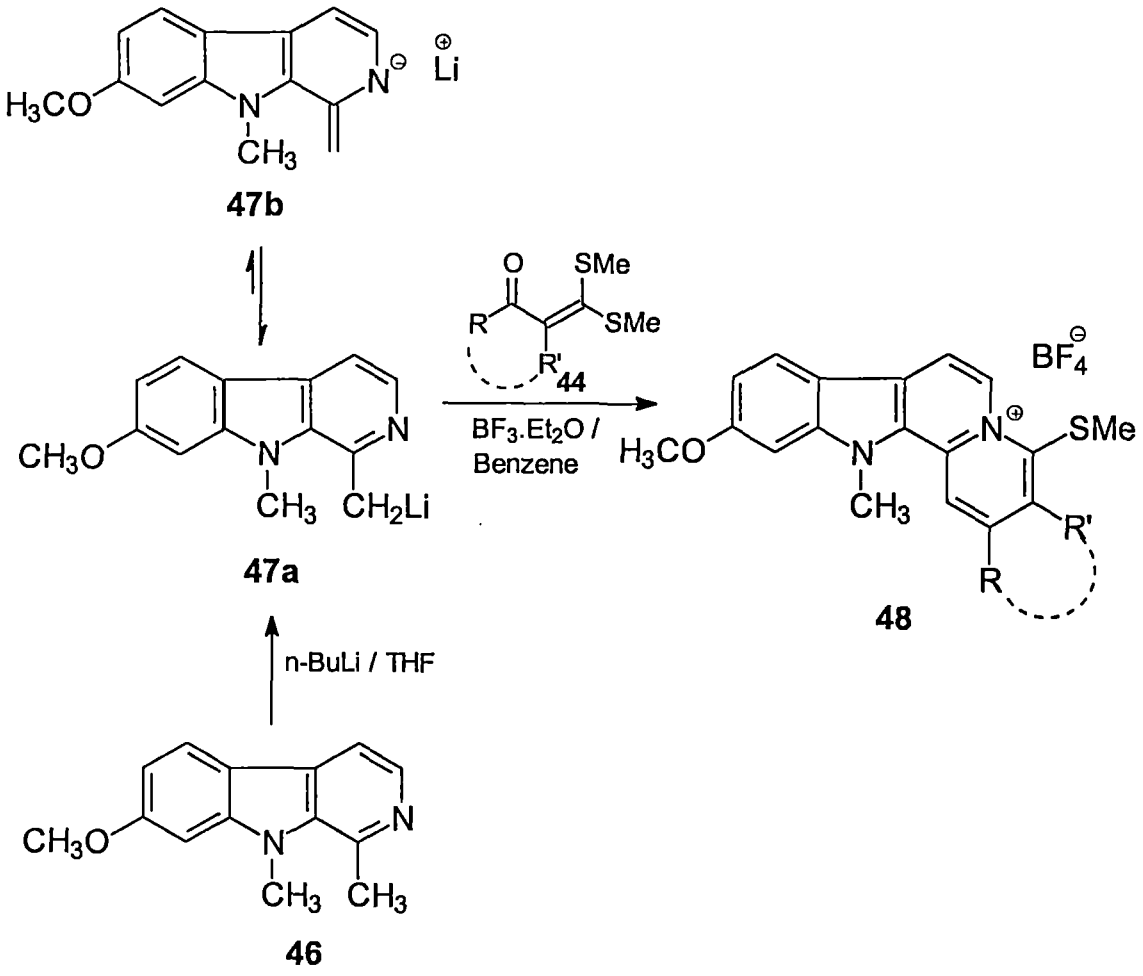
As a part of systematic study on heteroaromatic annelation methodology developed in our laboratory based on the reactivities of azaallyl anions with various α-oxoketene dithioacetals, lithiomethyl pyridine **43a** was reacted with various α-oxoketene dithioacetals to afford the corresponding quinolizinium tetrafluoroborate **45** in excellent yields[36] (Scheme-14). Apparently lithio-



Scheme-14

methyl pyridine anion behaved like a hard nucleophile and reacted with **44** exclusively in 1,2 fashion to afford initially the corresponding carbinol acetals in near quantitative yields which were subsequently cyclized to yield the quinolizinium fluoroborate salts. The intrinsic aromatic character of the lithiomethyl pyridine will resist ring interaction of the lone pair electrons

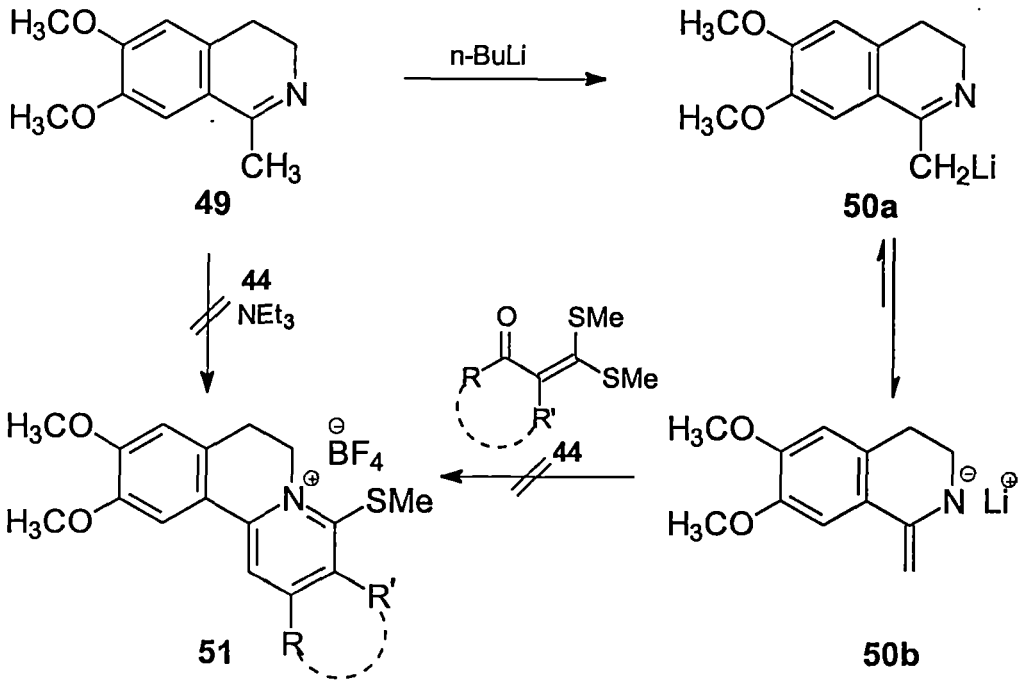
through resonance. It is expected therefore that the charge on methylene side chain is highly localized as it followed the expected charge controlled 1,2 mode. This reaction was similarly extended to lithiomethyl harmine **47a,** which was generated as reported by Woodward and co-workers[37] (Scheme-15)



Scheme-15

and reacted with various α-oxoketene dithioacetals **44** in the 1,2-fashion in the same way as 2-lithiomethyl pyridine The intermediate carbinol acetals were subsequently cyclized in the presence of $BF_3.Et_2O$ to yield the corresponding

quaternary fluoroborate salts **48** in good yields[38]. However when lithiomethyl isoquinoline **50a** generated from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **49** reacted with α-oxoketene dithioacetals **44**, reaction did not proceed and starting material was recovered. It was therefore interesting to note that anion **50a** failed to react with **44** while both lithiomethyl pyridine and lithiomethyl harmine reacted with **44** in a facile manner. The absence of aromaticity of the B-ring appears to have played an important role of increased resonance stabilized *N*-lithio derivative **50b** which obviously will not add in the 1,2-fashion and also not sufficiently basic or sterically compatible to follow the 1,4-addition elimination sequence (Scheme-16). The reaction therefore failed with α-oxoketene dithioacetals compelling to look for



Scheme-16

alternative possibilities. Also when **49** reacted with α-oxoketene dithioacetals **44** in the presence of triethylamine, unreacted starting materials were recovered. It was at this stage of our understanding regarding the behaviour of these anions, we realized that the anion **50b** could perhaps react more easily with β-oxodithioates **52** to yield initially the corresponding thioamides of general formula **53** which will yield the expected product thione **54** (Scheme-17).

We have indeed realized these proposals as depicted in Scheme-17. In a typical experiment the dithioate **52a** (prepared by reacting acetone enolate with 1-(methyldithiocarbonyl)imidazole in 80% yield) was reacted with 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline in the presence of triethylamine in refluxing benzene and the reaction mixture after work up yielded the corresponding 6,7-dihydro-9,10-dimethoxy-2-methyl-4-thionobenzo[*a*]quinolizine in 66% yield. The structure of **54a** was fully established by its analytical and spectral data. The compound was obtained as yellow needles crystallized from chloroform-hexane having melting point 190°-191°C.

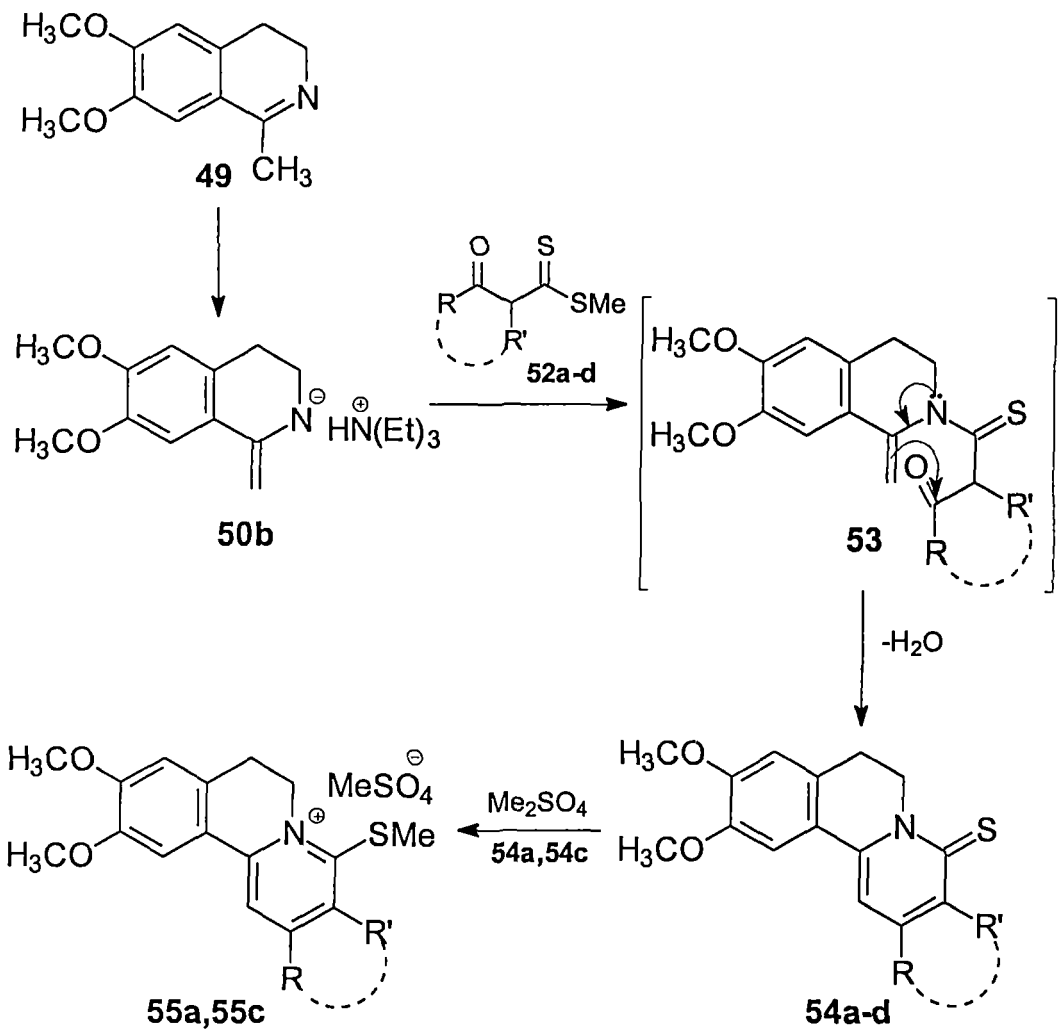
IR (KBr): ν_{max}=1604, 1506, 1229, 1120.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H, CH_3); 2.96 (t, 2H, CH_2); 3.96 (s, 3H, OCH_3); 3.97 (s, 3H, OCH_3); 4.91 (t, 2H, CH_2); 6.78 (s, 1H, ArH); 6.86 (d, 1H, ArH); 7.14 (s, 1H, ArH); 7.56 (d, 1H, ArH).

^{13}C NMR (75.43 MHz, $CDCl_3$): δ =20.92, 27.52, 46.93, 56.14, 56.36, 108.21, 110.21, 112.38, 121.09, 129.46, 133.13, 145.45, 148.65, 151.64, 179.09.

MS: m/z (%) = 287 (M^+ 100), 272 (M^+ -15).

Analytical data for $C_{16}H_{17}NO_2S$ (287): C, 66.96; H, 5.97; N, 4.88%. Found C, 67.01; H, 6.02; N, 5.01%.



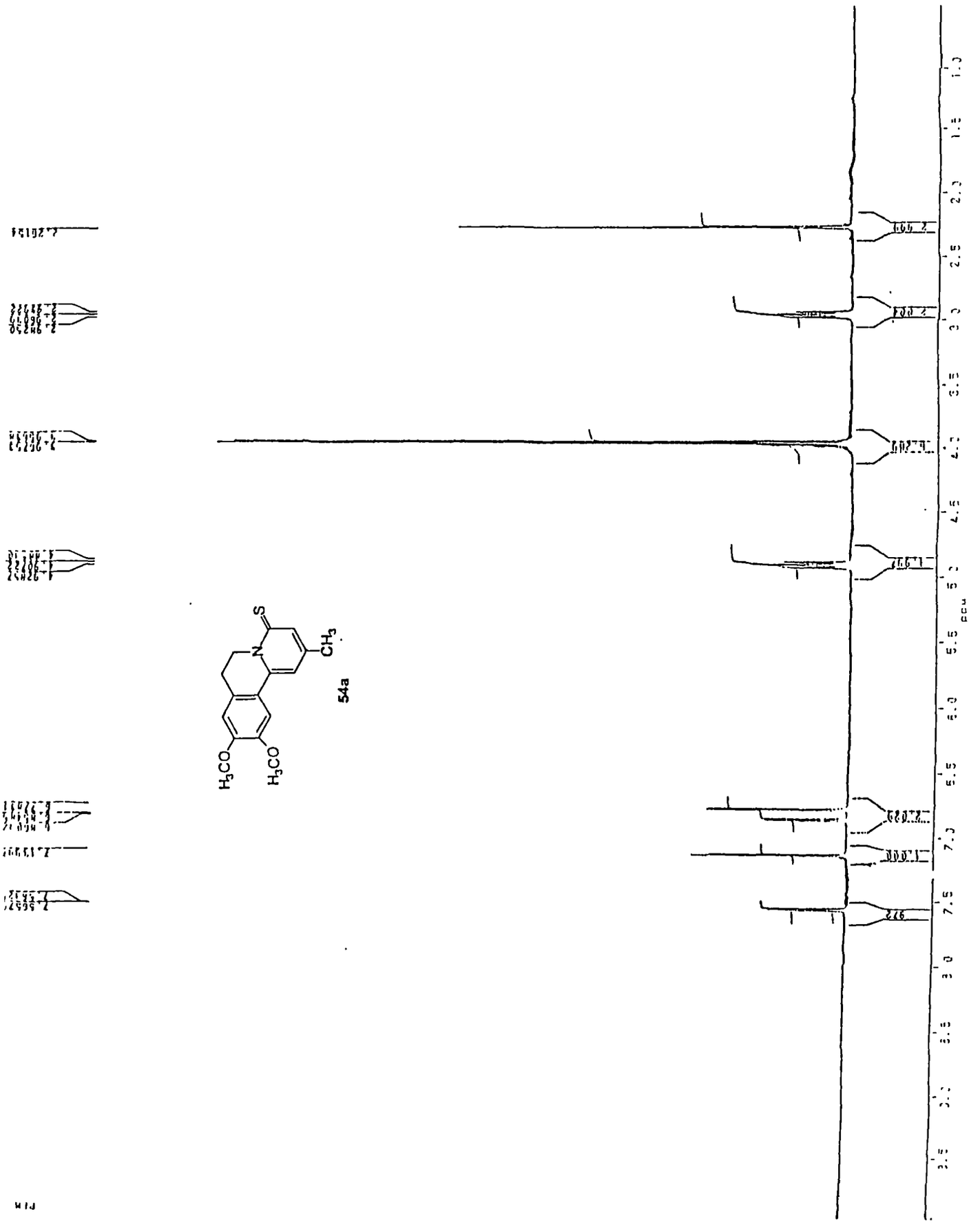
52,53,54,55 a; R = CH_3 ; R' = H

b; R = CH_3 ; R' = CH_3

c; R = C_6H_5; R' = H

d; R = 4-$MeOC_6H_4$; R' = H

Scheme-17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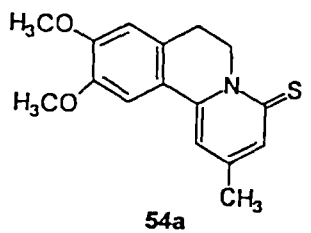
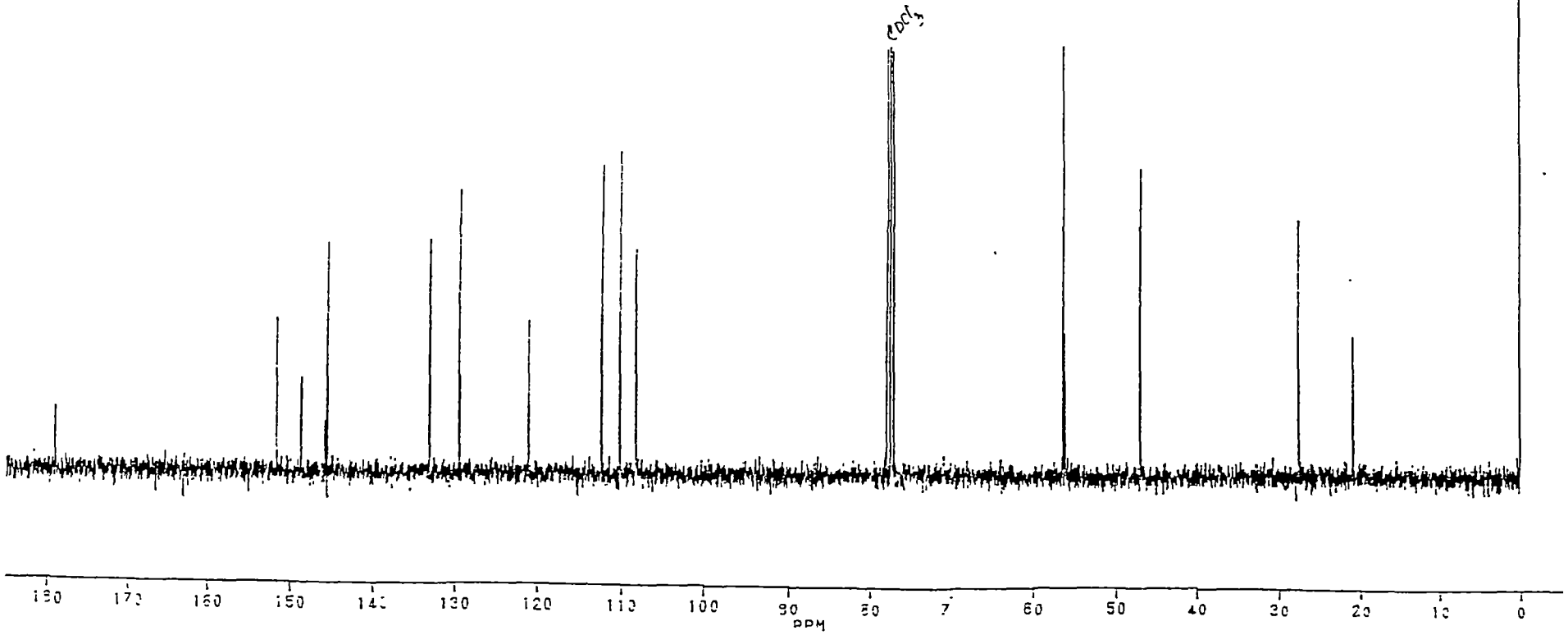
N
CH3
H3CO
H3CO
54a
PPM


H3CO
H3CO
N
S
CH3

54a


CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

The thione **54a** was heated with $(CH_3)_2SO_4$ at 80°C for one hour in dry benzene and the reaction mixture when triturated with dry hexane gave the amorphous quaternary salt 6,7-dihydro-9,10-dimethoxy-2-methyl-4-methylthiobenzo[*a*] quinolizinium salt **55a** in quantitative yield. The structure of **55a** was also confirmed from its analytical and spectral data.

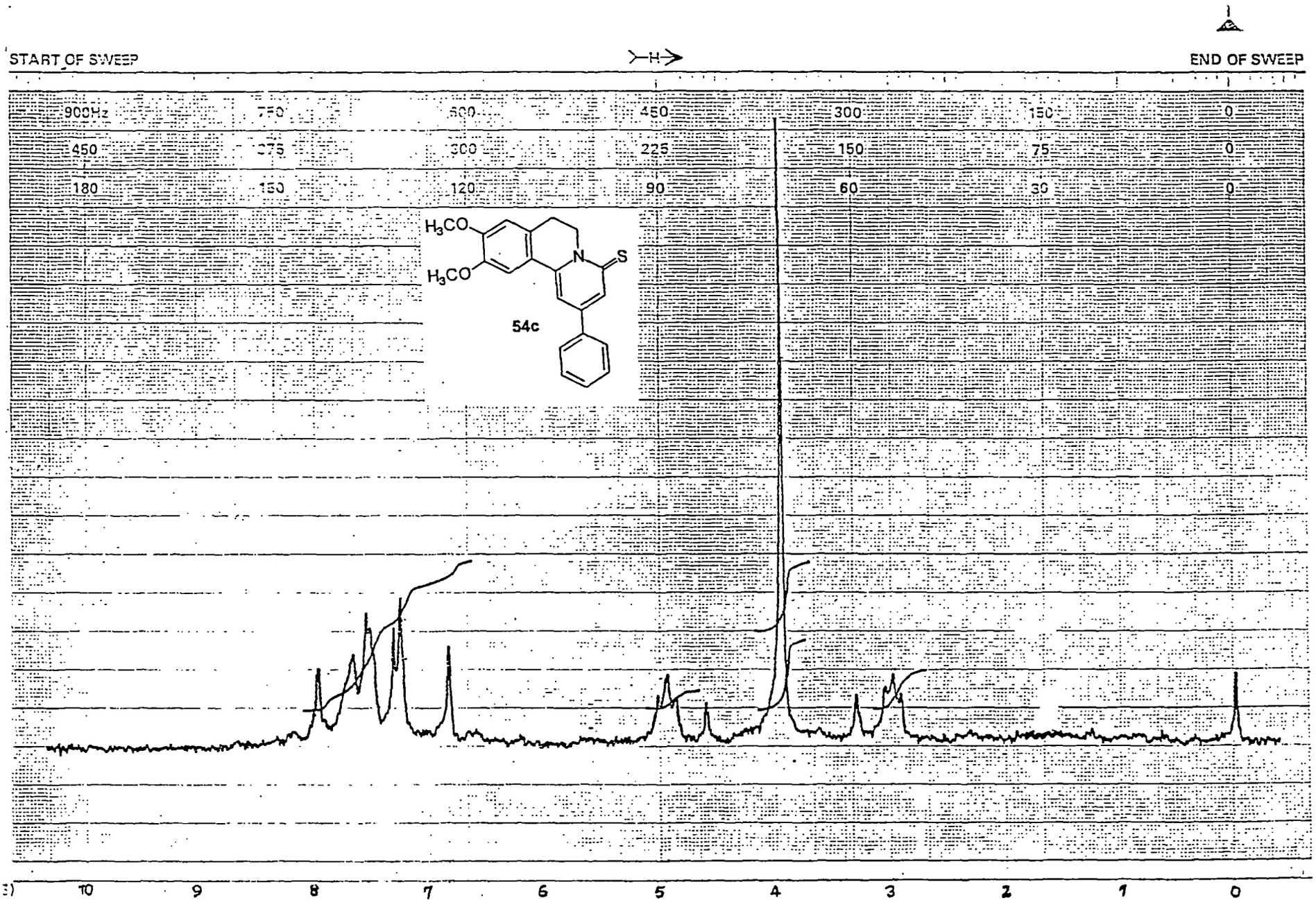
IR (KBr): ν_{max} = 1605, 1541.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.60 (s, 3H, SMe); 2.85 (s, 3H, CH_3); 3.15 (t, 2H, CH_2); 3.40 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 3.97 (s, 3H, OCH_3); 4.60 (t, 2H, CH_2); 7.1 (s, 1H, ArH); 7.55 (d, 1H, ArH); 7.65 (s, 1H, ArH); 8.25 (d, 1H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 20.92, 27.52, 47.5, 52.50, 56.14, 56.36, 108.21, 110.21, 118, 119, 121.09, 129.91, 147.5, 152.5, 155.5, 158.9;

Anal. Calc. for $C_{18}H_{23}NO_6S_2$ (413): C, 52.30; H, 5.57; N,3.39%. Found C, 51.98; H, 5.48; N, 3.34%.

Similarly the β-oxodithioate derived from ethylmethyl ketone was reacted with **50b** under the described reaction conditions to afford the corresponding 2,3-dimethyl-6,7-dihydro-9,10-dimethoxy-4-thionobenzo[*a*]quinolizine in 60% yield. The structure was established from analytical and spectral data. The dithioates derived from acetophenone and p-methoxyacetophenone also reacted with **50b** under similar reaction conditions to afford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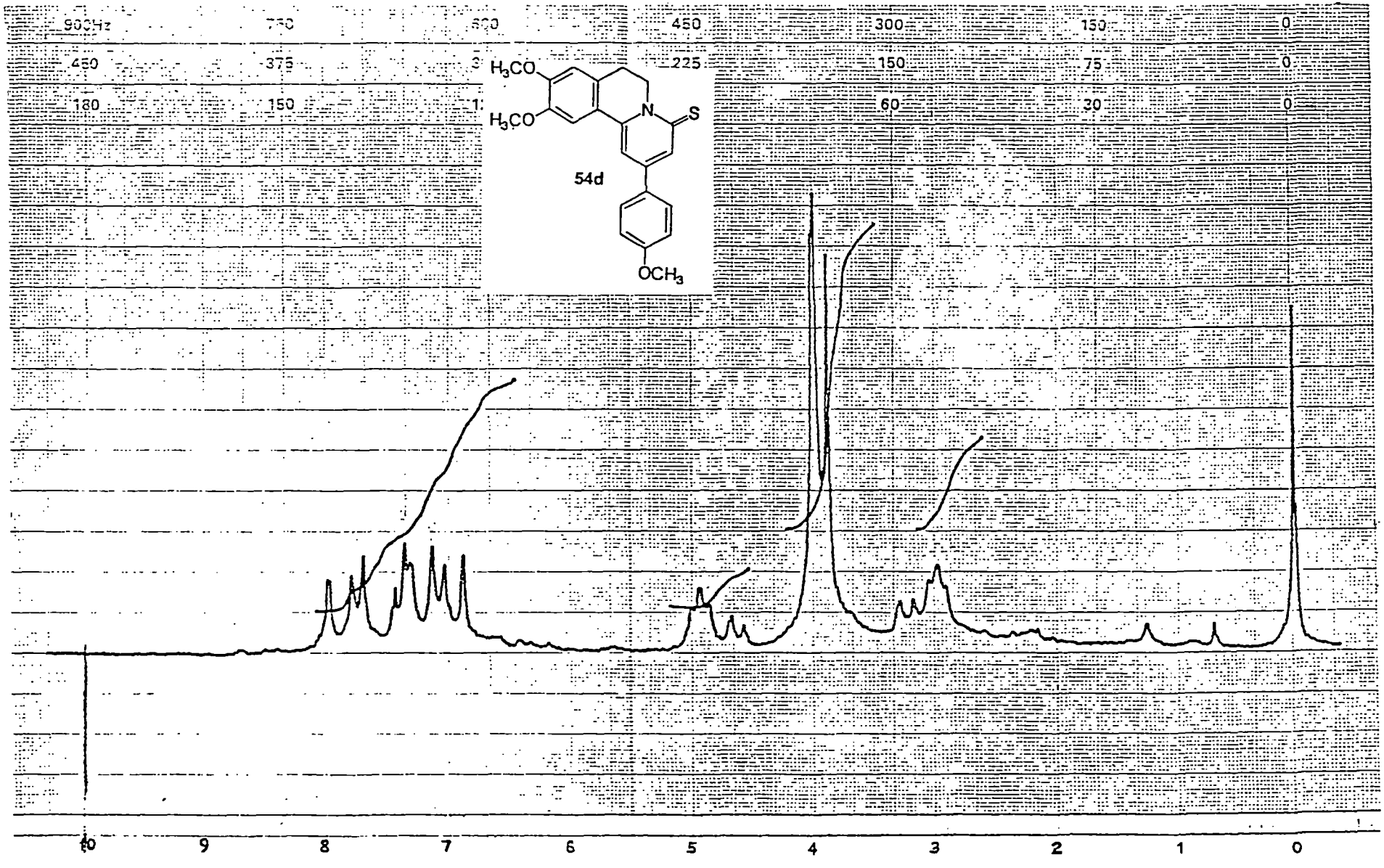
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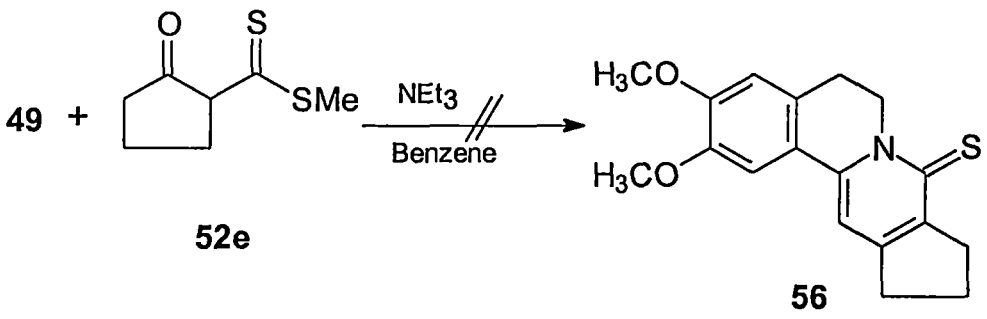
MeO
MeO
SMe
OSO_3CH_3
55c

MeO
MeO
SMe
OSO3CH3
55c

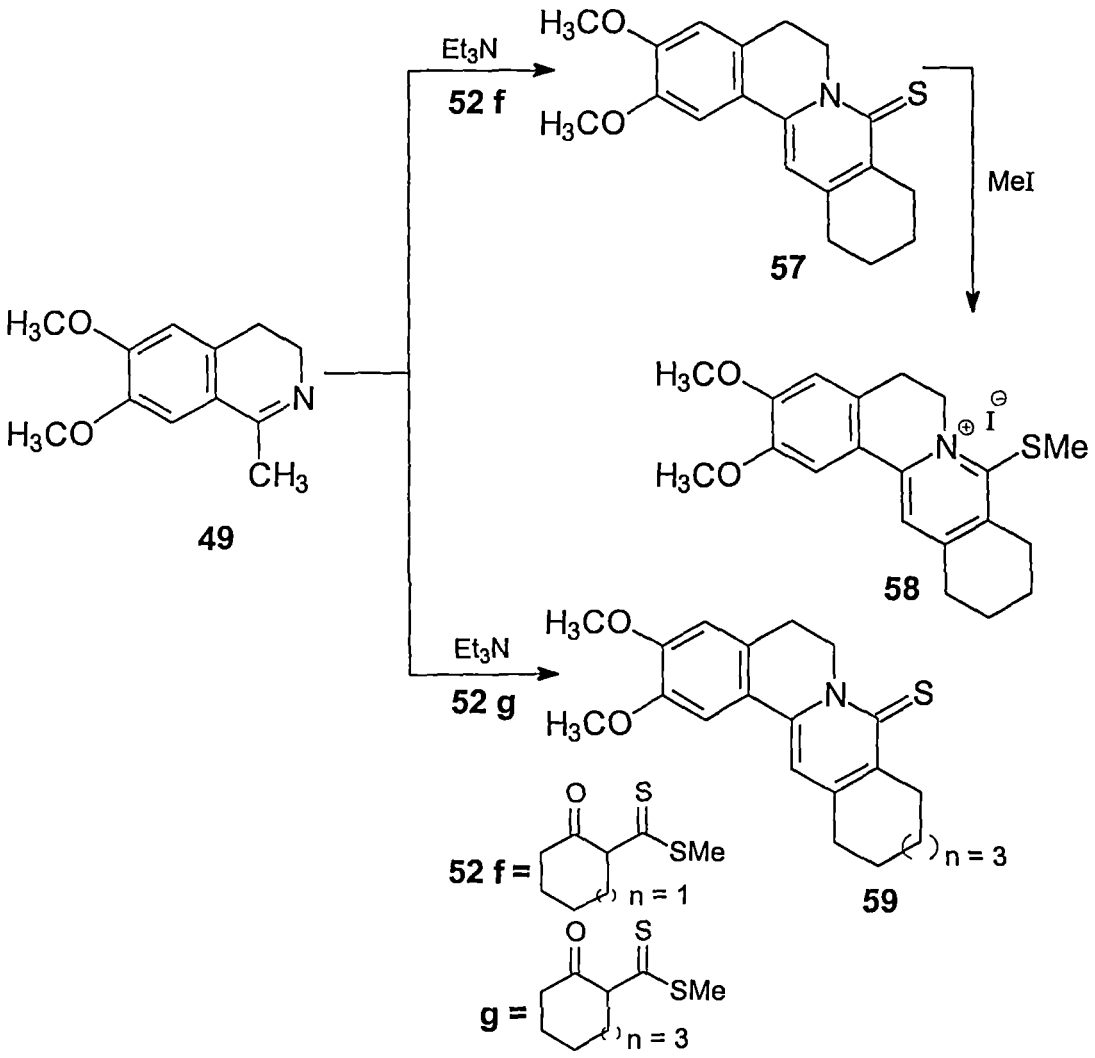
benzo[*a*]quinolizines **54c** and **54d** in 80 and 63 % yield respectively. The structures of these two compounds were fully established by spectral and analytical data (see experimental section). The dithioates derived from cycloalkanones were next examined. The dithioate derived from cyclopentanone **52e** when reacted with **49** under the described reaction conditions, the reaction mixture after several hours did not show any progress and the starting material remained unreacted (tlc) (Scheme 18). However when the dithioate derived from cycylohexanone **52f** was reacted



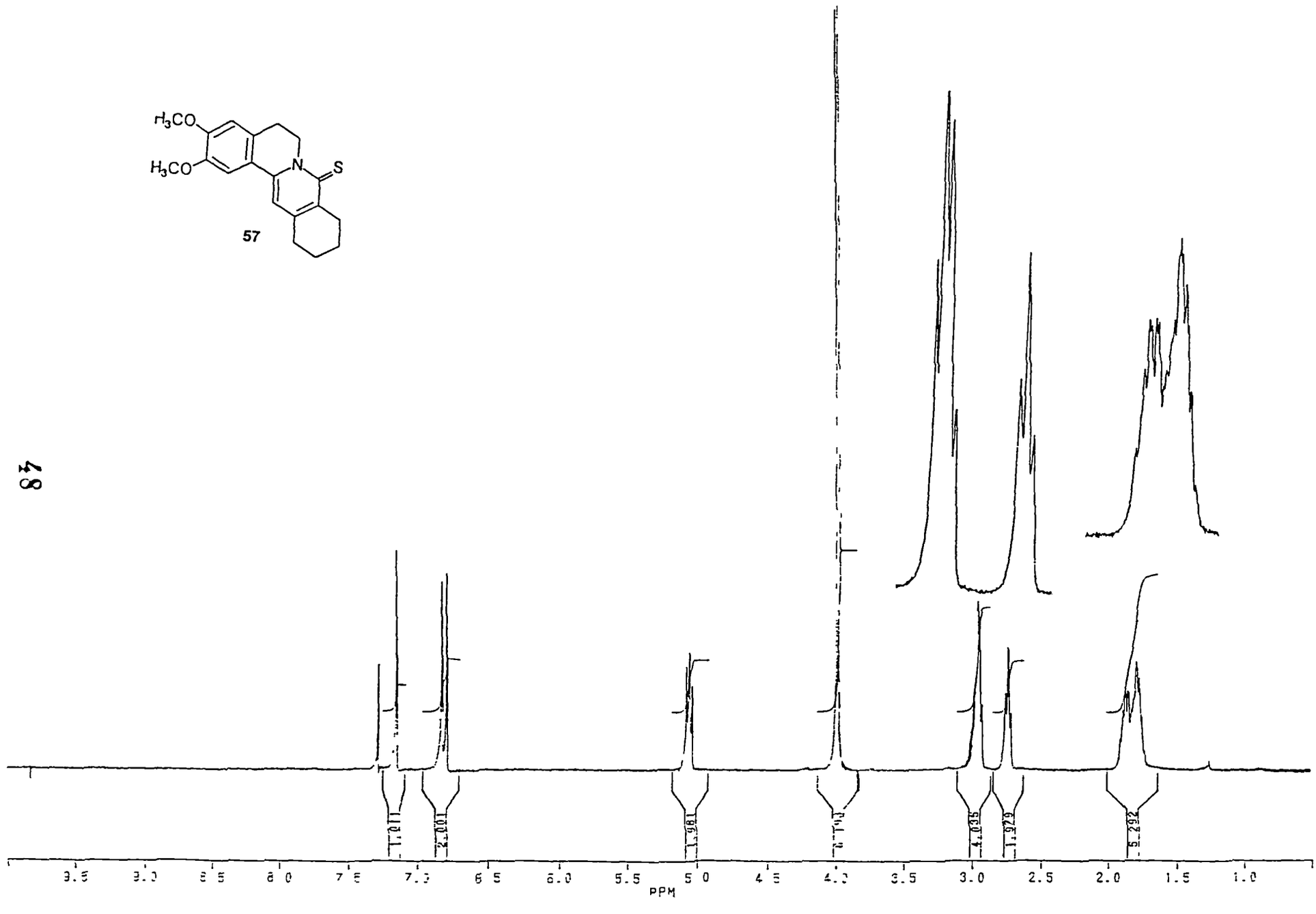
52e **56**

Scheme-18

with **49** under similar reaction conditions it afforded 2,3-dimethoxy-5,6,9,10,11,12-hexahydro-8-thionodibenzo[*a,g*]quinolizine **57** in 70% yield. The structure of **57** was established on the basis of spectral and analytical data (Scheme-19). The compound **57** was obtained as yellow coloured crystals.



Scheme-19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H3CO
N
S
57
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2.001
1.981
6.114
4.035
1.979
5.292
PPM

S
N
H3CO
H3CO
57

IR (KBr): ν_{max} = 3018,1509,1217,1148.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76-1.88 (m, 4H, CH_2); 2.72 (t, 2H, CH_2); 2.95 (q, 4H, CH_2); 3.95 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 5.04 (t, 2H, CH_2); 6.80 (d, 2H, ArH); 7.14 (s, 1H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.75, 23.09, 27.74, 30.31, 30.49, 47.79, 56.12, 108.00, 110.17, 111.46, 121.64, 129.10, 138.00, 142.63, 144.60, 148.59, 151.16, 179.15

MS: (m/z %) = 327 (M^+100), 312 (M^+-15).

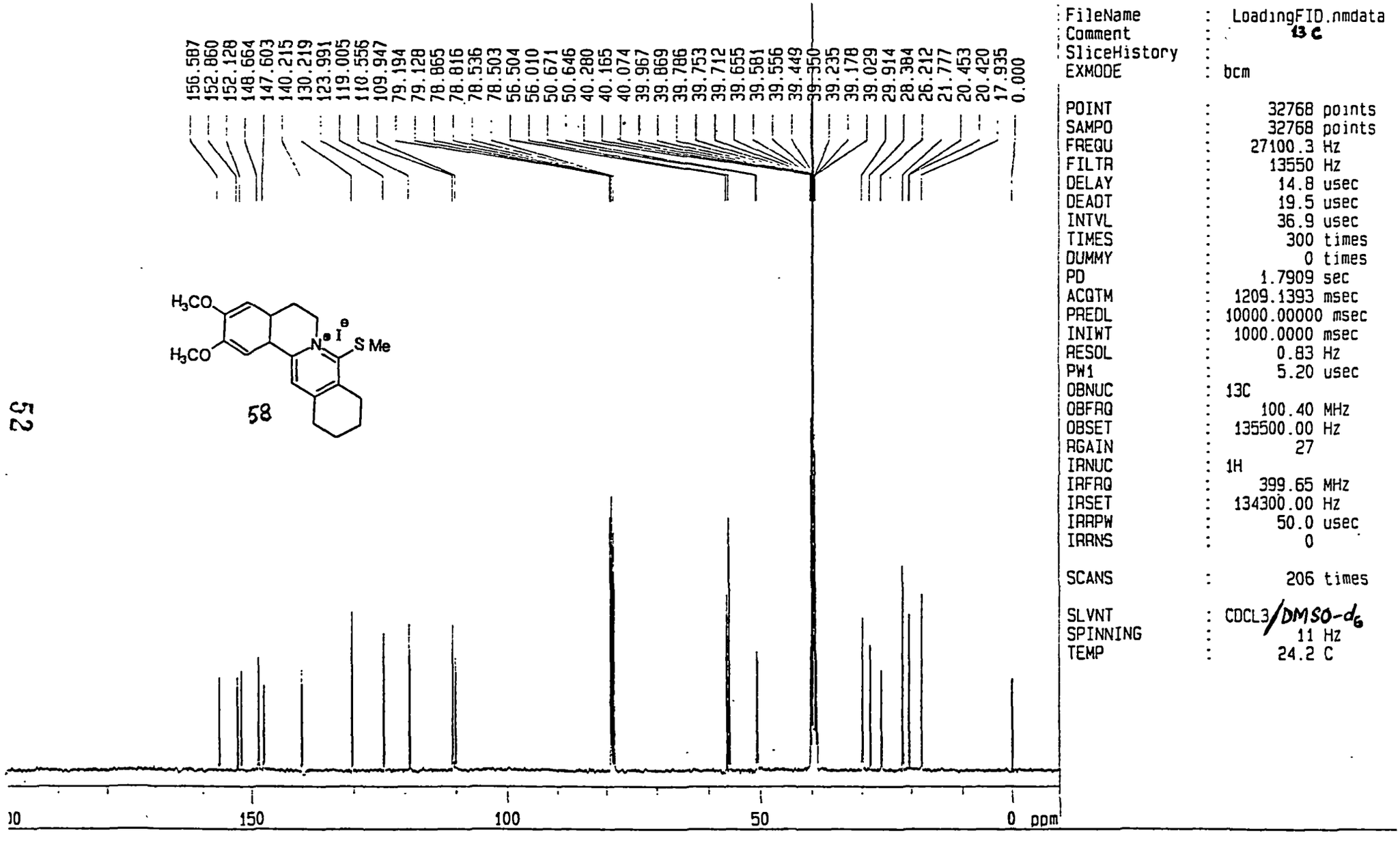
Anal.calc. for $C_{19}H_{21}NO_2S$ (327): C, 69.79; H, 6.47; N, 4.28%. Found C, 69.68; H, 6.47; N, 4.26%.

The thione **57** thus obtained was treated with methyliodide and stirred at room temperature. The reaction mixture was then triturated with dry hexane and filtered to afford the corresponding quaternary salt **58** in quantitative yield. The structure of this salt was fully established on the basis of spectral and analytical data.

IR (KBr): ν_{max} = 2940, 1595, 1545, 1285.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.86-1.90 (m, 4H, CH_2); 2.57 (s, 3H, SCH_3); 3.12 (br s, 4H, CH_2); 3.2 (t, 2H, CH_2); 3.92 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 4.85 (t, 2H, CH_2); 7.10 (s, 1H, ArH); 7.66 (s, 1H, ArH); 8.48 (s, 1H, ArH).

ppm
0
2
4
6
8
10
1.42
3.70
3.42
5.60
5.24
DMSO
6.58
1.88
1.00
0.96
1.00
58
H3CO
H3CO
N
I
SMe



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OBNUC	:	13C
OBFRQ	:	100.40 MHz
OBSET	:	135500.00 Hz
RGAIN	:	27
IRNUC	:	1H
IRFRQ	:	399.65 MHz
IRSET	:	134300.00 Hz
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IRRNS	:	0
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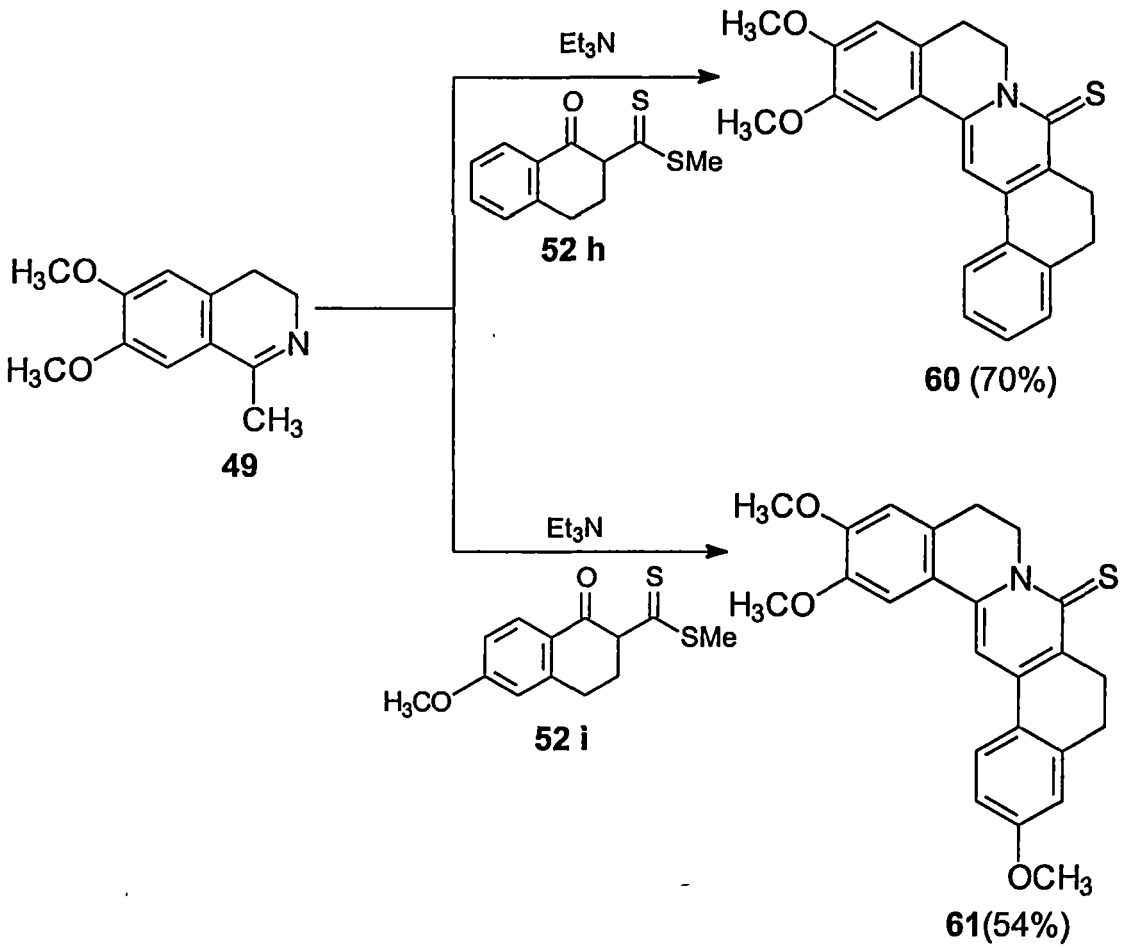
SPINNING	:	11 Hz
TEMP	:	24.2 C

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.00, 20.42, 20.45, 21.78, 26.21, 28.38, 29.91, 50.67, 56.01, 56.50, 109.95, 110.56, 119.01, 124.00, 130.22, 147.60, 148.66, 152.13, 152.86, 156.59.

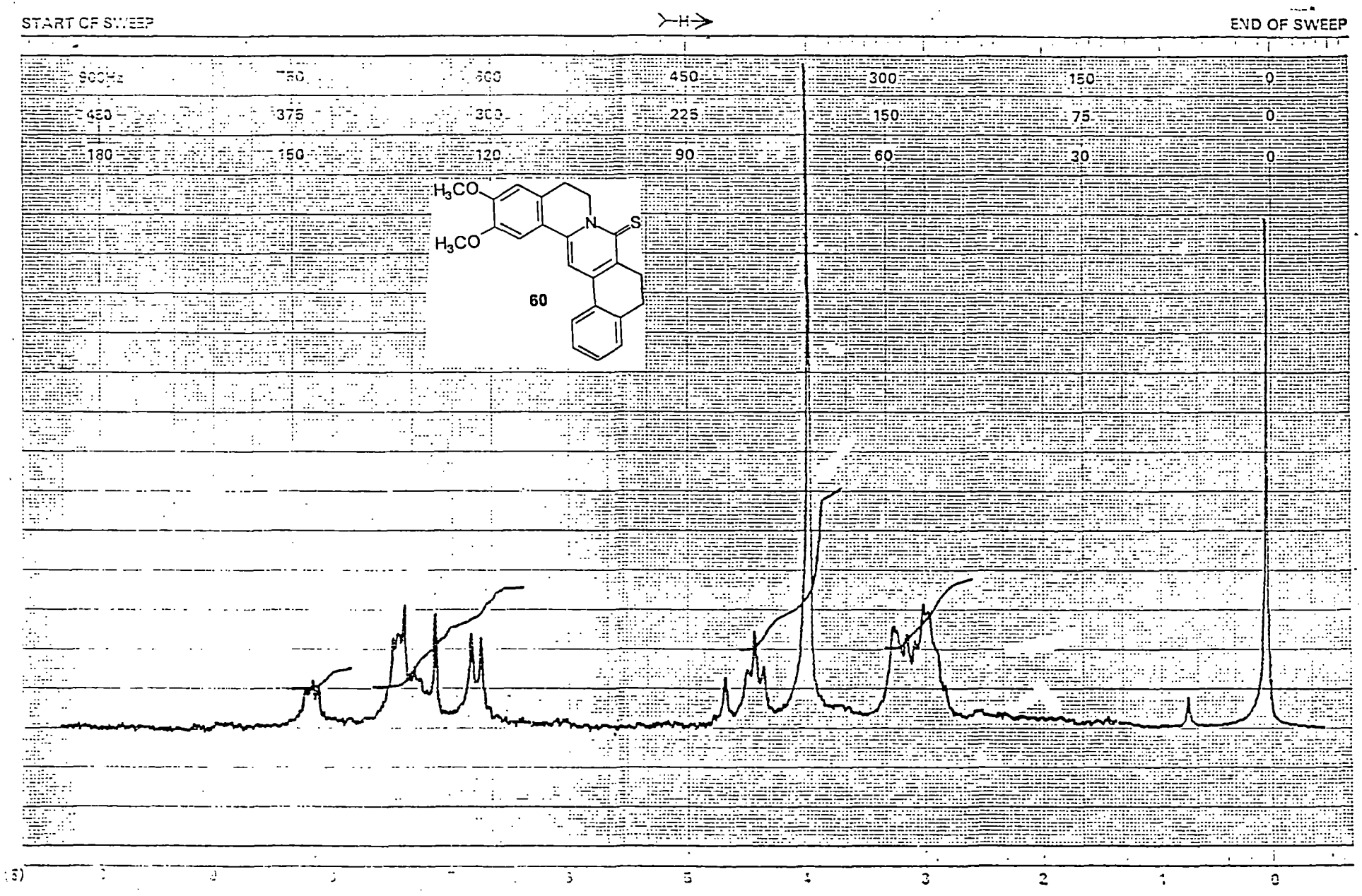
Anal. Calc. for $C_{20}H_{24}NO_2SI$ (469): C, 51.17; H, 5.12, N, 2.98%. Found C, 50.91; H, 5.03; N, 2.54%.

Similarly the dithioate **52g** derived from cyclooctanone also reacted with **49** under the described reaction conditions to afford the corresponding annelated benzo[*a*]quinolizine **59** in 50% yield. The structure was fully established by analytical and spectral data which are described in the experimental section. Both tetralone and 6-methoxy tetralone dithioates, that is; **52h** derived from tetralone and **52i** derived from 6-methoxy tetralone reacted with **49** under similar reaction conditions as described earlier to afford the corresponding annelated benzo[*a*]quinolizines **60** and **61** respectively in 70 and 65 % yields. The compounds thus obtained were fully characterised by their analytical and spectral data as described in the experimental section (Scheme-20).



Scheme-20

The dithioate **52j** derived from N-methyloxindole however failed to react with **49** under identical reaction conditions to yield the expected quinolizine **62** and the unreacted starting materials were recovered back (Scheme-21).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150
120
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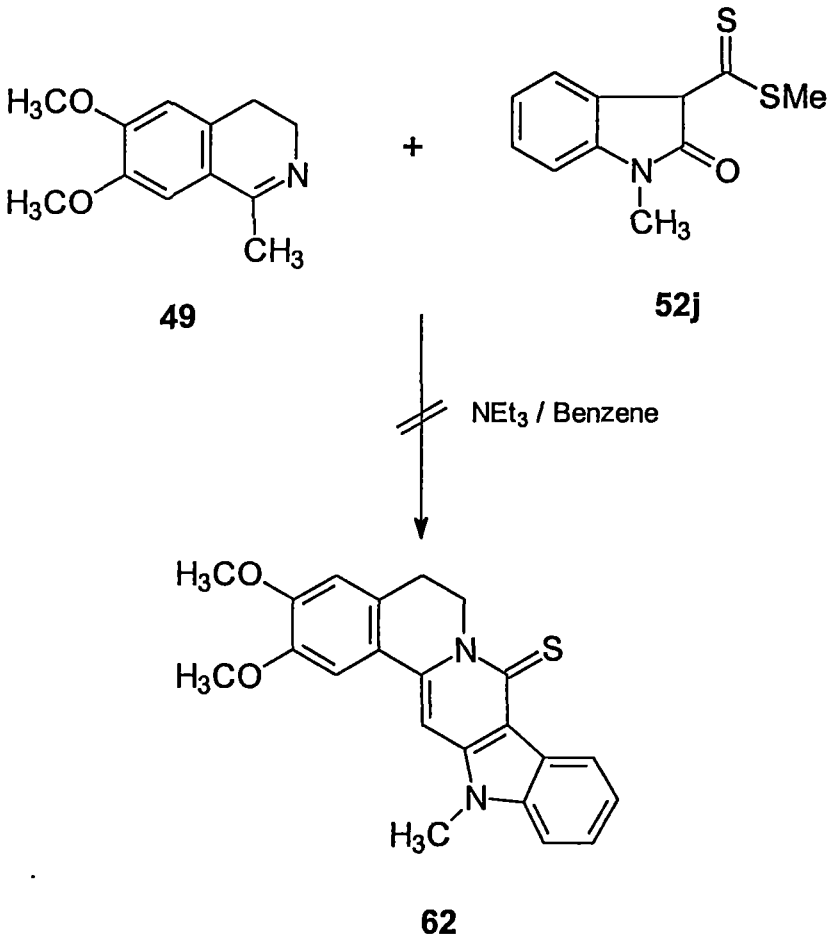
H_3CO
N
S
60
(δ)
6
5
4
3
2
1
0



49 52j 62

Scheme-21

In conclusion, we have developed a new efficient method for the synthesis of benzo[*a*]quinolizines and their corresponding quinolizinium salts by reacting 3,4-dihydro-6,7-dimethoxyisoquinoline with various β-oxodithioates . The method is generally applicable with few exceptions. It is

pertinent to note that the 1-lithiomethyl-3,4-dihydro isoquinoline failed to react with α-oxoketene dithioacetals. Also **49** failed to react with α-oxoketene dithioacetals in the presence of triethylamine. Reasonable explanations have been offered to account for these reactivities. The facile reaction of the dithioate structural unit with enamine nitrogen in the isoquinoline molecules is a useful discovery that can be considered parallel to that of enamide photocyclisation reaction. Further work on these lines is being continued for the synthesis of this type of skeletons, which are closer to many natural products.

EXPERIMENTAL SECTION

General

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer and the frequencies are expressed in cm^{-1}. ^1H NMR (90 MHz) was recorded on Varian EM-390 spectrometer. High resolution ^1H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded on Bruker ACF-300 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethyl silane and coupling constants (J) are given in Hertz (Hz). The following abbreviations are used to describe peak patterns when appropriate: br =broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were obtained on a Jeol D-300 mass spectrometer. Masses are reported in units of mass upon charge (m/z), the molecular and base peaks are indicated by (M^+) and (%) respectively. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were monitored by TLC on glass plates coated with silicagel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying potassium permanganate (acidic) solution. Column chromatography was carried out using ACME's silicagel (60-120 mesh).

Solvents for column chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steam bath.

Chemicals, Reagents and solvents.

Dry benzene was obtained by keeping over calcium chloride followed by distillation and again storing over sodium wire. The commercial samples of acetone, acetophenone, ethyl methyl ketone, cyclopentanone, cyclohexanone, cyclooctanone were purified by simple distillation. 1-tetralone[39], 6-methoxytetralone[40] was prepared according to the reported procedures. β-oxodithioates of the corresponding ketone was prepared according to reported procedures[41-42]. Phenylethylamine, acetyl chloride, $POCl_3$, phosphorous pentoxide were available commercially and used as such.

General procedure for the preparation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline 49:

To an ice cold solution of 3,4-dimethoxy phenethylamine (5mmol) in ether, sodium hydroxide pellets (2g) is added and stirred. To this acetyl chloride (5mmol) is added dropwise. The reaction mixture is allowed to stir for six to eight hours at room temperature followed by work up. About 100 ml of water is poured into the reaction mixture, and then extracted with chloroform. The organic layer is washed with water till it is free from amine, dried and

concentrated when 3,4-dimethoxy phenyl ethyl acetamide is obtained. A solution of 3,4-dimethoxy phenyl ethyl acetamide (3mmol) in dry toluene (75 ml) is added dropwise to P_2O_5 in toluene. When the addition is complete, $POCl_3$ (10 ml) is added dropwise to the reaction mixture. The reaction mixture is refluxed at 110-120°C for 10-12 hours. About 100 ml of water is poured into the reaction mixture and the two layers are separated. The toluene layer is discarded, to the aqueous layer sodium bicarbonate solution is added and extracted with chloroform. The organic layer is washed with water, dried (over Na_2SO_4), concentrated to yield 3,4-dihydro-6,7-dimethoxy-l-methyliso-quinoline, which is crystallized from chloroform-hexane.

Brown solid (chloroform-hexane); yield 70%; mp 105-106°C

IR (KBr): ν_{max} = 2910, 1525 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3); 2.60 (t, 2H, CH_2); 3.61 (t, 2H, CH_2); 3.90 (s, 6H, OCH_3); 6.69 (s, 1H, ArH); 6.99 (s, 1H, ArH).

Anal. Calc. for $C_{12}H_{15}NO_2$ (205): C, 70.24; H, 7.32, N, 6.83%. Found C, 70.82; H, 6.99; N, 6.90%.

General procedure for the preparation of β-oxodithioates using 1-(methyldithiocarbonyl)imidazole iodide with ketones[42].

To a well stirred suspension of NaH (2.4g, 50 mmol; 50% suspension) in dry benzene (25 ml) and DMSO (5 ml) appropriate ketone (10 mmol) is

added and stirred for 10 min. A solution of imidazole dithioate (1.58 g, 10 mmol) in dry benzene is slowly added dropwise and the mixture stirred for a period of four hours at room temperature . After completion of the reaction (TLC), the reaction mixture is poured into ice cold water. The aqueous layer is separated, acidified with 3N HCl and extracted with benzene. The extract is dried with anhydrous Na_2SO_4 and evaporated to give the crude product which is purified by column chromatography using hexane-ethylacetate as eluent.

General procedure for the reaction of 3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline with β-oxodithioates: Synthesis of benzo[*a*]-quinolizines.

A mixture of 3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline (1.03g, 5mmol) and triethylamine (0.7ml, 5mmol) was stirred for half an hour at 80°C. To the reaction mixture, dithioesters of the corresponding ketone (5mmol) was added and refluxed. When the reaction was complete, (monitored by TLC) the reaction mixture was poured into water and extracted with chloroform (3x 25 ml). The combined organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product thus obtained was purified by passing through silica gel column using hexane-ethylacetate as eluent.

6,7-Dihydro-9,10-dimethoxy-2-methyl-4-thionobenzo[*a*]quinolizine 54a:

Yellow crystals (chloroform-hexane); yield 66%; mp 190-191°C

IR (KBr): ν_{max} =2930, 1604, 1506, 1229, 1120 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H, CH_3); 2.96 (t, 2H, CH_2); 3.96 (s, 3H, OCH_3); 3.97 (s, 3H, OCH_3); 4.91(t, 2H, CH_2); 6.78 (s, 1H, ArH); 6.86 (d, 1H, ArH); 7.14 (s, 1H, ArH); 7.56 (d, 1H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.92, 27.52, 46.93 56.14, 56.36, 108.21, 110.21, 112.38, 121.09, 129.46, 133.13, 145.45, 148.65, 151.64, 179.09.

MS: m/z (%) = 287 (M^+ 100), 272 (M^+ - 15).

Anal. Calc. for $C_{16}H_{17}NO_2S$ (287): C, 66.96; H, 5.97; N, 4.88%. Found C, 67.01; H, 6.02; N, 5.01%.

6,7-Dihydro-9,10-dimethoxy-2,3-dimethyl-4-thionobenzo[*a*]quinolizine 54b:

Yellow crystals (chloroform-hexane); yield 60%; mp 186-187°C

IR (KBr): ν_{max} =2930, 1603, 1505, 1278, 1136 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 2.98 (t, 2H, CH_2); 3.95 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 4.89(t, 2H, CH_2); 6.75 (s, 1H, ArH); 6.84 (d, 1H, ArH); 7.04 (s, 1H, ArH).

Anal. calc.for $C_{17}H_{19}NO_2S$ (301): C, 67.77; H, 6.31; N, 4.65%. Found C, 67.72; H, 6.03; N, 4.67%.

6,7-Dihydro-9,10-dimethoxy-2-phenyl-4-thionobenzo[*a*]quinolizine 54c:

Yellow crystals (chloroform-hexane); yield 80%; mp 191-192°C

IR (KBr): ν_{max} = 3008, 1604, 1506, 1133 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 3.00 (t, 2H, CH_2); 4.00 (s, 6H, OCH_3); 4.94 (t, 2H, CH_2); 6.83 (s, 1H, ArH); 7.30 (d, 2H, ArH); 7.41-7.85 (m, 5H, ArH); 7.96 (s,1H, ArH).

MS: m/z (%) = 349 (M^+ 100), 334 (M^+ - 15).

Anal. Calc. for $C_{21}H_{19}NO_2S$ (349): C, 72.27; H, 5.48; N, 4.01%. Found C, 71.99; H, 5.39; N, 4.05%.

6,7-Dihydro-9,10-dimethoxy-2-(4-methoxy)-phenyl-4-thionobenzo [*a*]quinolizine 54d:

Yellow crystals (chloroform-hexane); yield 63%; mp 186-188°C

IR (KBr): ν_{max} = 1601, 1505, 1268 1142 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 3.00 (t, 2H, CH_2); 3.89 (s, 3H, OCH_3); 4.00 (s, 6H, OCH_3); 4.94 (t, 2H, CH_2); 6.89 (s, 1H, ArH); 7.04-7.79 (m, 6H, ArH); 7.98 (s, 1H, ArH).

MS: m/z (%) = 379 (M^+ 100), 364 (M^+ - 15), 346 (M^+ -33).

Anal. Calc. for $C_{22}H_{21}NO_3S$ (379): C, 69.72; H, 5.58; N, 3.69%. Found C, 70.01; H, 5.62; N, 2.99%.

2,3-Dimethoxy-5,6,9,10,11,12-hexahydro-8-thionodibenzo[*a,g*]quinolizine 57:

Yellow crystals (chloroform-hexane); yield 70%; mp 155-156°C

IR (KBr): ν_{max} = 3018, 1509, 1217, 1148 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.76-1.88 (m, 4H, CH_2); 2.72 (t, 2H, CH_2); 2.95 (q, 4H, CH_2); 3.95 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 5.04 (t, 2H, CH_2); 6.80 (d, 2H, ArH); 7.14 (s, 1H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.75, 23.09, 27.74, 30.31, 30.49, 47.79, 56.12, 56.35, 108.00, 110.17, 111.46, 121.64, 129.10, 138.00, 142.63, 144.60, 148.59, 151.16, 179.15.

MS: m/z (%) = 327 (M^+ 100), 312 (M^+ -15).

Anal. Calc. for $C_{19}H_{21}NO_2S$ (327): C, 69.79; H, 6.47; N, 4.28% Found C, 69.68; H, 6.47; N, 4.26%.

2,3-Dimethoxy-5,6,9,10-tetrahydro-4-thionobenzo[*a*]naphtho[*2,1-g*] quinolizine 60:

Yellow crystals (chloroform-hexane); yield 70%; mp 160-162°C

IR (KBr): ν_{max} = 1604, 1506, 1229, 1120 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.85 (t, 2H, CH_2); 2.96 (t, 2H, CH_2); 3.16 (t, 2H, CH_2); 3.91 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3); 4.37 (t, 2H, CH_2); 6.67 (s, 1H, ArH); 6.71 (s, 1H, ArH); 7.29-7.35 (m, 4H, ArH); 8.02 (t, 1H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.02, 29.08, 29.21, 47.37, 56.06, 56.17, 98.06, 102.39, 107.41, 110.21, 119.90, 125.04, 126.30, 126.74, 128.32, 130.11, 135.67, 136.55, 139.55, 148.65, 149.79, 162.12, 179.11.

Anal. Calc. for $C_{23}H_{21}NO_2S$ (375): C, 73.67; H, 5.64; N, 3.74%. Found C, 73.81; H, 5.55; N, 3.85%.

5,6,9,10-Tetrahydro-4-thiono-2,3,12-trimethoxybenzo[a]-naphtho[2,1-g] quinolizine 61:

Yellow crystals (chloroform-hexane); yield 54%; mp 168-170°C

IR (KBr): ν_{max} = 2910, 1604, 1506, 1229 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.95 (t, 2H, CH_2); 3.07 (t, 2H, CH_2); 3.13 (t, 2H, CH_2); 3.93 (s, 3H,OCH_3); 3.95 (s, 3H,OCH_3); 3.97 (s, 3H, OCH_3); 4.13 (t, 2H, CH_2); 6.77 (s, 1H, ArH); 7.07 (s, 1H, ArH); 7.48 (s, 1H, ArH); 7.80 (d, 1H, ArH); 8.40 (d, 1H, ArH).

MS: m/z(%) = 405 (M^+, 23) Anal. Calc. for $C_{24}H_{23}NO_3S$ (405): C, 71.11; H, 5.72; N, 3.46%. Found C, 70.98; H, 5.82; N, 3.75%.

General procedure for the preparation of benzo[*a*]quinolizinium salts: 55a, 55c, 58.

To benzo[*a*]quinolizine (1eqv.), dimethylsulphate or methyliodide (1 eqv.) is added and the reaction mixture is heated for 1h at 80°C in dry benzene. The

corresponding quinolizinium salt separates out which is filtered and washed with hexane to give pure quinolizinium salts.

6,7-Dihydro-9,10-dimethoxy-2-methyl-4-methylthiobenzo[*a*]quinolizinium salt 55a:

Yellow solid; yield 98%; mp 190-191°C

IR (KBr): ν_{max} = 1605, 1541cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 2.60 (s, 3H, SMe); 2.85 (s, 3H, CH_3); 3.15 (t, 2H, CH_2); 3.40 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 3.97 (s, 3H, OCH_3); 4.60 (t, 2H, CH_2); 7.1 (s, 1H, ArH); 7.55 (d, 1H, ArH); 7.65 (s, 1H, ArH); 8.25 (d, 1H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0,20.92, 27.52, 47.5, 52.50, 56.14, 56.36, 108.21, 110.21, 118.00, 119.00, 121.09, 129.91, 147.50, 152.50, 155.50, 158.9.

Anal.Calc. for $C_{18}H_{23}NO_6S_2$ (413): C, 52.30, H, 5.57; N, 3.39%. Found C, 51.98; H, 5.48; N, 3.34%.

6,7-Dihydro-9,10-dimethoxy-2-phenyl-4-methylthiobenzo[*a*]quinolizinium salt 55c:

Yellow solid; yield 98%; mp 210-211°C

IR (KBr): ν_{max} = 2946, 1601, 1222 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3H, SCH_3); 2.96 (t, 2H, CH_2); 3.63 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 4.24 (t, 2H, CH_2); 7.22-7.37 (m, 5H, ArH); 7.71-7.75 (m, 2H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.78, 26.26, 48.51, 54.20, 56.47, 57.03, 109.70, 110.54, 116.39, 118.00, 118.70, 128.33, 129.72, 129.74, 131.66, 134.64, 149.40, 150.04, 153.70, 154.31, 159.84.

Anal. Calc. for $C_{23}H_{25}NO_6S_2$ (475): C, 58.11; H, 5.26; N, 2.95%. Found C, 58.13; H, 5.16; N, 2.98%.

2,3-Dimethoxy-5,6,9,10,11,12-hexahydro-8-methylthiodibenzo[*a*,*g*]quinolizinium salt 58:

Yellow crystals; yield 98%; mp 191-192°C.

IR (KBr): ν_{max} = 2940, 1595, 1545, 1285 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.86-1.90 (m, 4H, CH_2); 2.57 (s, 3H, SCH_3); 3.12 (br s, 4H, CH_2); 3.2 (t, 2H, CH_2); 3.92 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 4.85 (t, 2H, CH_2); 7.10 (s, 1H, ArH); 7.66 (s, 1H, ArH); 8.48 (s, 1H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.00, 20.42, 20.45, 21.78, 26.21, 28.38, 29.91, 50.67, 56.01, 56.50, 109.95, 110.56, 119.01, 124.00, 130.22, 147.60, 148.66, 152.13, 152.86, 156.59.

Anal. Calc. for $C_{20}H_{24}NO_2SI$ (469): C, 51.17; H, 5.12, N, 2.98%. Found C, 50.91; H, 5.03; N, 2.54%.

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CHAPTER III

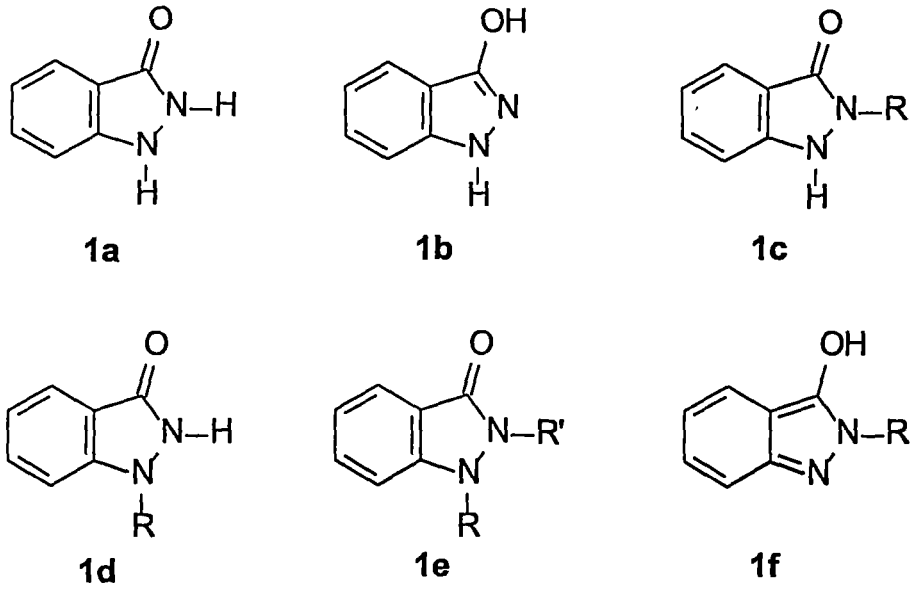
ANIONIC [4+2] CYCLOADDITION REACTIONS OF PYRAZOLIN-5-ONE-3,4-DIENOLATE WITH DIENOPHILES: A NOVEL APPROACH FOR SUBSTITUTED AND FUSED INDAZOLONES.

The indazolones of general formula **1** are generally named in the literature as

1. 1*H*-indazol-3-ol
2. 1,2-dihydro-3*H*-indazol-3-one (Chemical Abstract)
3. Indazolones (Beilstein) or Indazolinones (Chemical Abstract)

The structure may exist either in its enol form **1b** or its lactam form **1a** (Scheme-1). The current chemical abstract name for this compound is 1*H*-indazol-3-one or 3-hydroxy-1*H*-indazole. The unsubstituted indazolols are crystalline solids, melting at temperatures above 200°C with slight

decomposition. They are water soluble and their solubility in non polar solvent is very poor. Indazolols react with aqueous solutions of iron (III) chloride displaying dark brown colour due to 3-hydroxy functionality. The structure of 1*H*-indazol-3-ol i.e. **1a** or **1b** has been the subject of several discussions focussing on its IR-spectrum in KBr where it displays characteristic –NH bands at 3000 and 2700 $cm^{-1}$and another at 1630 cm^{-1} (C=O) (Scheme-1).

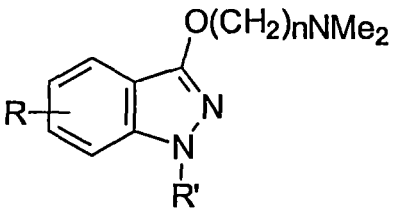


Scheme-1

2-Substituted indazolones of general formula **1c** (Scheme-1) are generally colourless solids and display positive colour test with iron (III) chloride indicating the existence of tautomeric form **1f.** However the carbonyl absorption in these structures appear near 1665 cm^{-1} in KBr analogously to 1,2-disubstitued indazolones. The 1,2 disubstituted indazolones **1e** clearly

exists in their enone form displaying in the IR spectrum a characteristic C=O band at 1600-1670 cm^{-1}. The 1 or 2-substituted or 1,2-disubstituted indazolones are prepared generally by alkylation using alkyl iodide and base where only one of the two N-atoms or both N-atoms are alkylated. However when diazomethane is used, 3-alkoxyindazole is obtained[1]. The mono alkylation is generally controlled by alkylation of N-1 instead of N-2. Therefore it is difficult to prepare 2-alkyl indazolone **1c** by direct alkylation method. These compounds are generally obtained from their acyl derivatives using protection, deprotection approach[2,3,4]. There are very few methods described in the literature for direct synthesis of indazole carrying substituents at 1 and 2-positions.

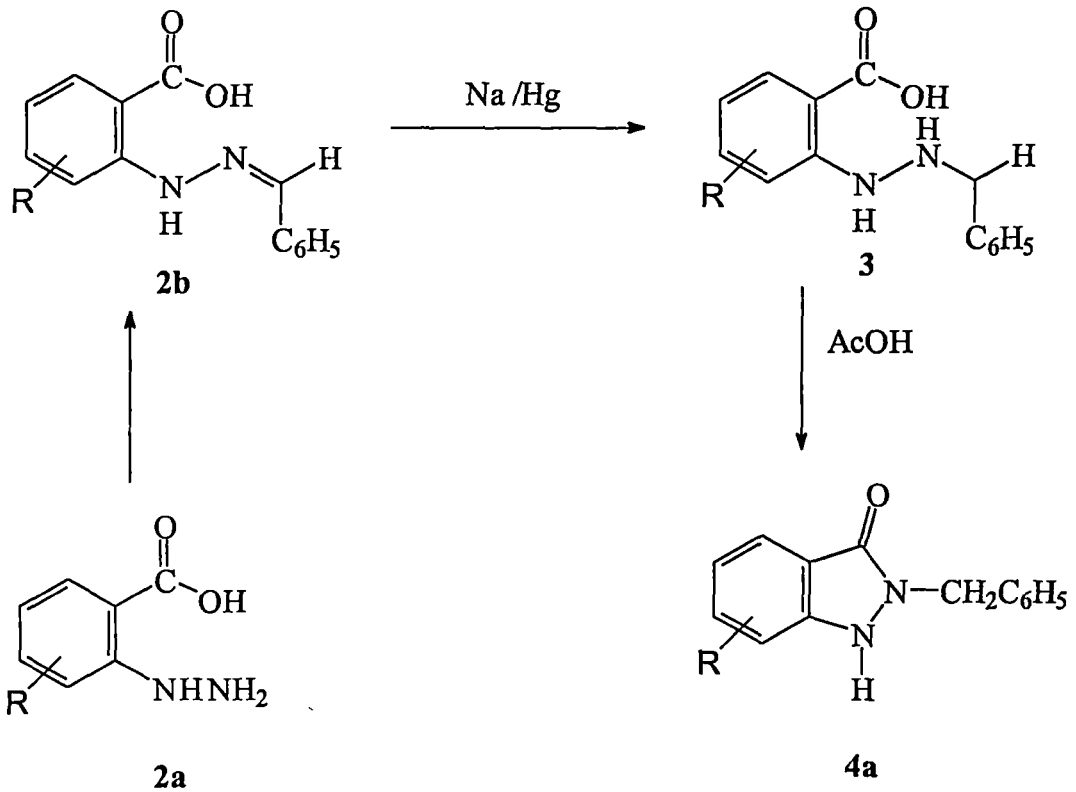
Despite the fact that a large number of aryl pyrazolone derivatives are known for their therapeutic applications, the corresponding indazolones have been little known for their biological importance. One of the reasons for the lack of interest to study their biological properties could be due to absence of appropriate methods for their preparation in the literature. Only few studies on the physiological properties of indazolone derivatives have been reported in the literature. Thus a series of 1,3-disubstituted indazolones **A** have been prepared by novel method (discussed in the following section) and found active as analgesics, anti-inflammatory and anti-spasmodic agents. This is the only study on their biological application described in the literature[5-7].



A R = H, Cl
R' = Alkyl / Aryl
n = 2 or 3

Apparently, indazolone chemistry appears to have not been fully investigated and the whole area suffers from lack of appropriate methods of synthesis. Some of the known methods are briefly reviewed in the following section.

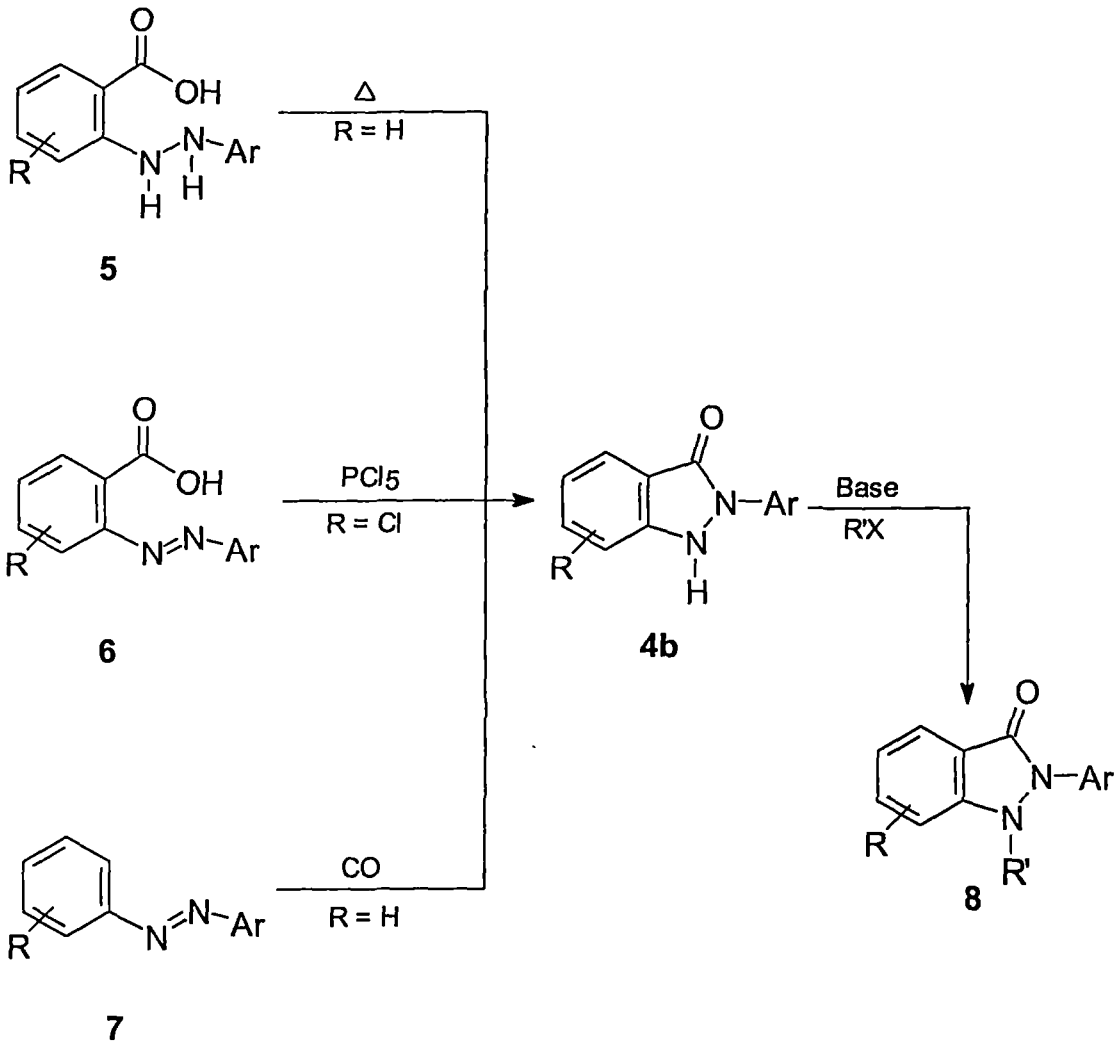
It has been found that there are only two methods described in the literature[8] for the synthesis of 2-alkyl indazolones. In the first method



Scheme-2

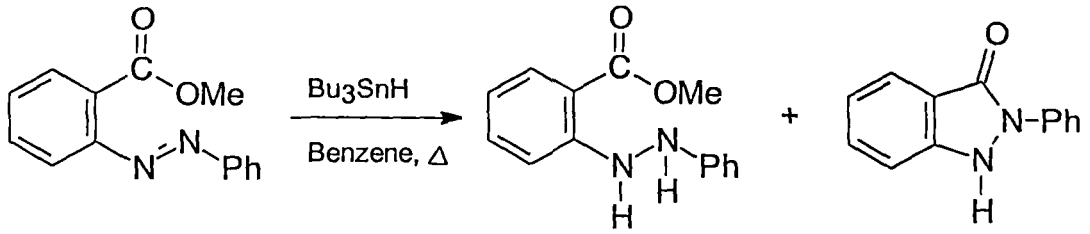
(Scheme-2), hydrazinobenzoic acids **2a** after reaction with aldehydes to afford condensation product **2b** were subjected to sodium amalgam reduction to afford the corresponding N-benzylhydrazinobenzoic acids **3** which were cyclized in acetic acid to the corresponding 2-alkylarylindazolones **4a**.

The second approach for the synthesis of 2-substituted indazolones consists of the saponification of 1-acyl-2-alkylindazolones. However 2-arylindazolones can be prepared as formulated in Scheme-3. The 2-carboxyhydrazobenzenes **5** were cyclized under thermal conditions to give the 2-substituted indazolones **4b**. Also the phenylazobenzoic acid **6** yielded 5-chloro-2-phenylindazolones in moderate yields[9,10]. An efficient synthesis of 2-arylindazolone was reported by Murahasi and Horie[11] in 1956. The easily available azobenzene was reacted with carbon monoxide under pressure in the presence of organo cobalt catalyst. The 2-arylindazolone **4b** thus obtained were alkylated at 1-position to afford the 1-alkyl-2-arylindazolone **8** in good yields (Scheme-3).



Scheme-3

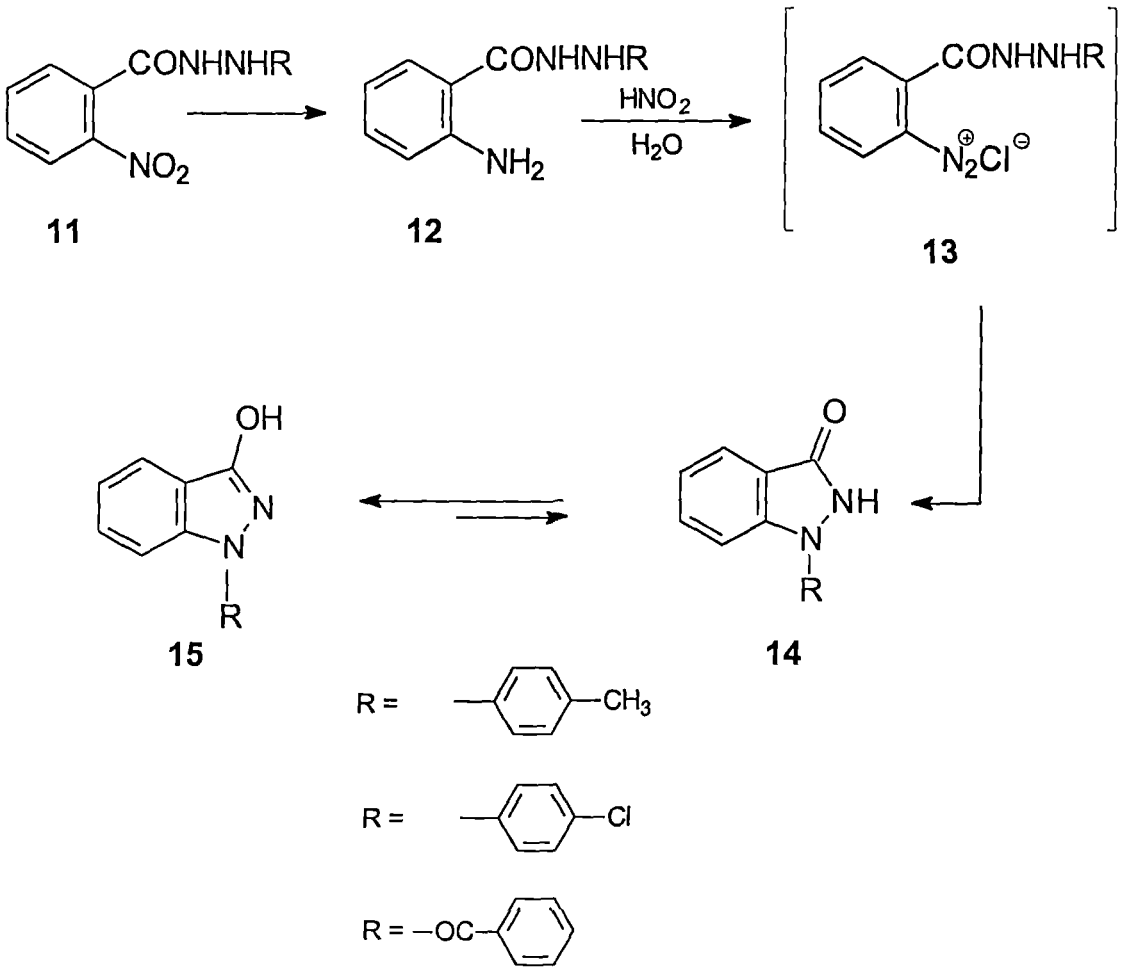
The hydrazo compound **10** were prepared by an Italian group[12] by treating appropriate azoarene **9** with tributyltin hydride which were found to undergo *in situ* cyclization to afford the corresponding indazolones **4b** (Scheme-4).



9 10 4b

Scheme- 4

Kametani and co-workers[13] have examined the reaction of *o*-nitrohydrazides for the synthesis of 1-substituted indazolones. Thus N-(2-nitrobenzoyl)-4-tolylhydrazine was reduced to amino derivative **12** followed

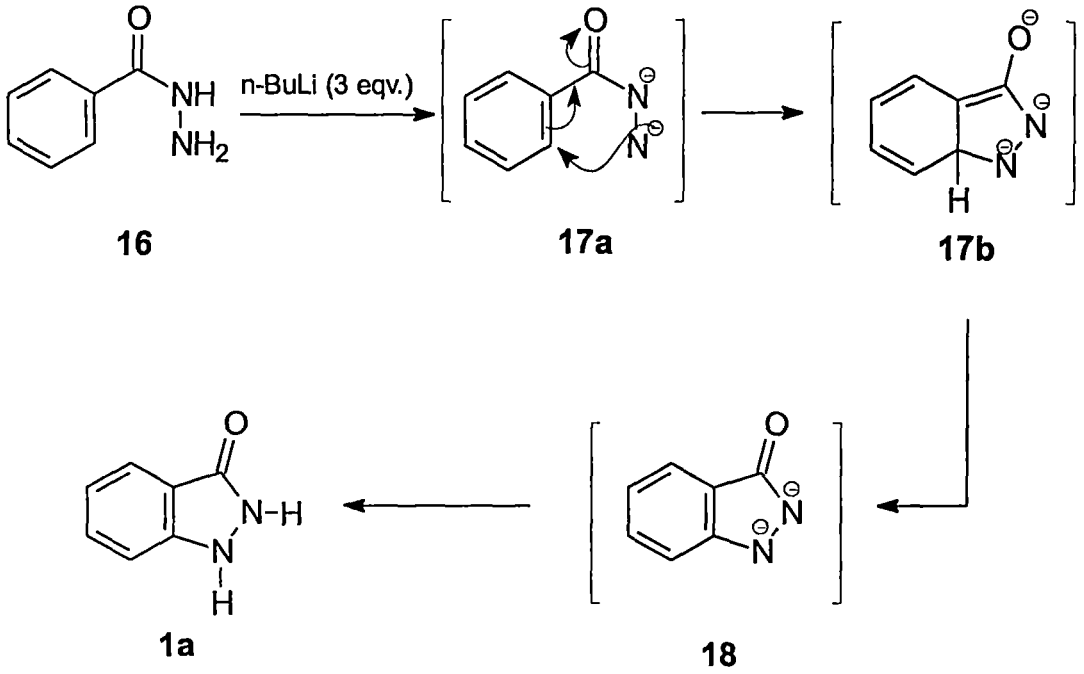


11 12 13 15 14

Scheme-5

by its diazotization to yield the corresponding diazonium chloride. The diazonium chloride underwent intramolecular ring closure with elimination of nitrogen to give 1-arylindazolone **14** in good yields (Scheme-5). This is a novel method for the synthesis of 1-substituted indazolones.

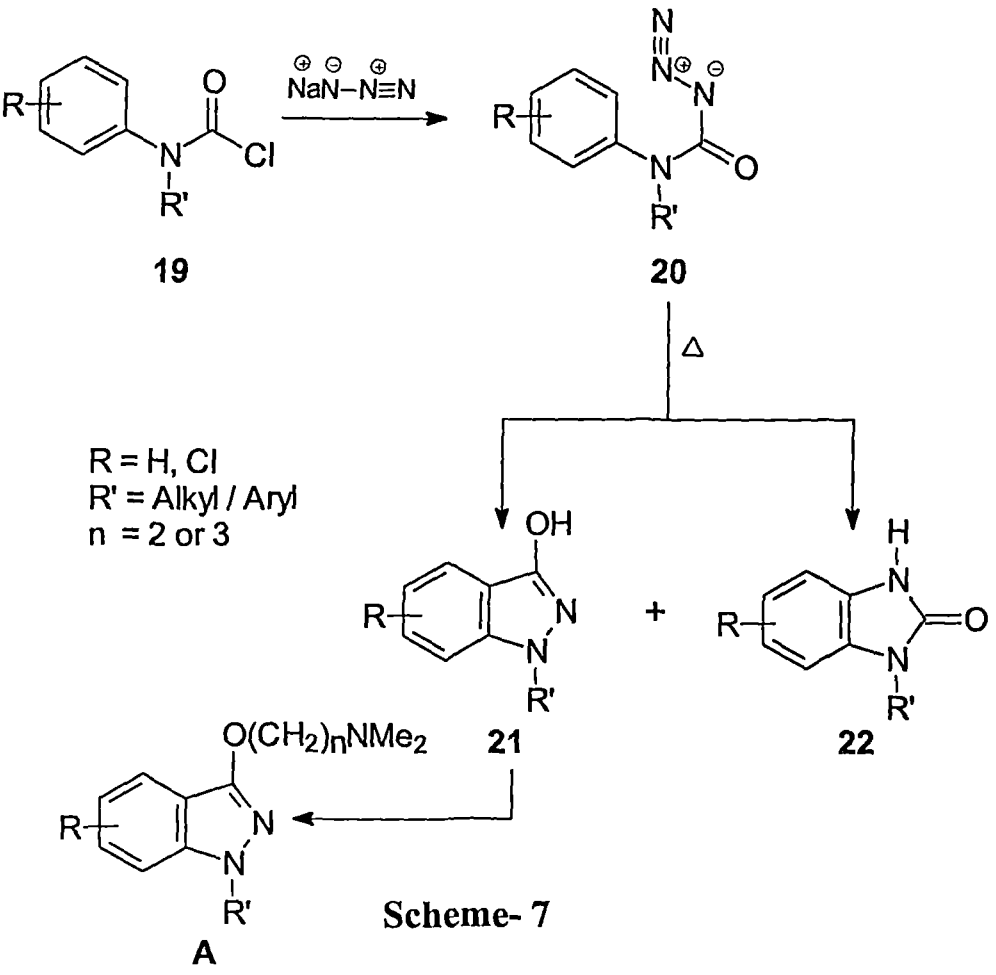
Barton and co-workers[14] have reported that aromatic hydrazides of general formula **16** (Scheme-6) when treated with three equivalents of n-butyllithium yield the corresponding indazolone **1a** in 80% yield. They studied the mechanism of this novel transformation where the dianion **17a** attacked the ring carbon to yield the cyclic intermediate **17b** which, on work up yielded indazolone **1a**.



16 **17a** **17b** **18** **1a**

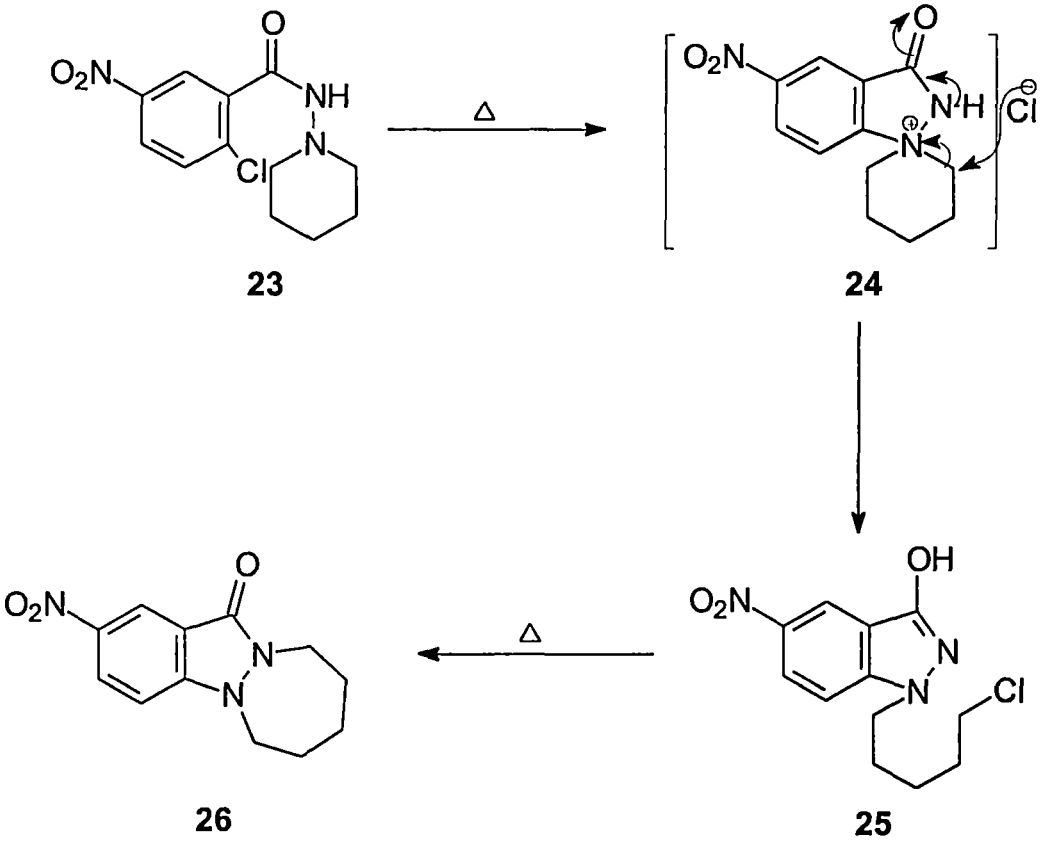
Scheme- 6

Palazzo and co-workers[5] have prepared a series of indazolones by reacting various anilines with phosgene to give the corresponding carbamoyl chloride in very good yields. These carbamoyl chlorides **19** were reacted with sodium azide to yield the corresponding carbamoyl azides **20.** These azides were subjected to thermolysis to give a mixture of indazolones **21** and benzimidazoline-2-ones **22.** The desired indazolones were easily separated from **22** and further transformed into structure **A** for biological evaluation. These compounds of the general structure **A** displayed analgesic, anti-inflammatory activity and also found to be spasmodic agents (Scheme-7).



Scheme- 7

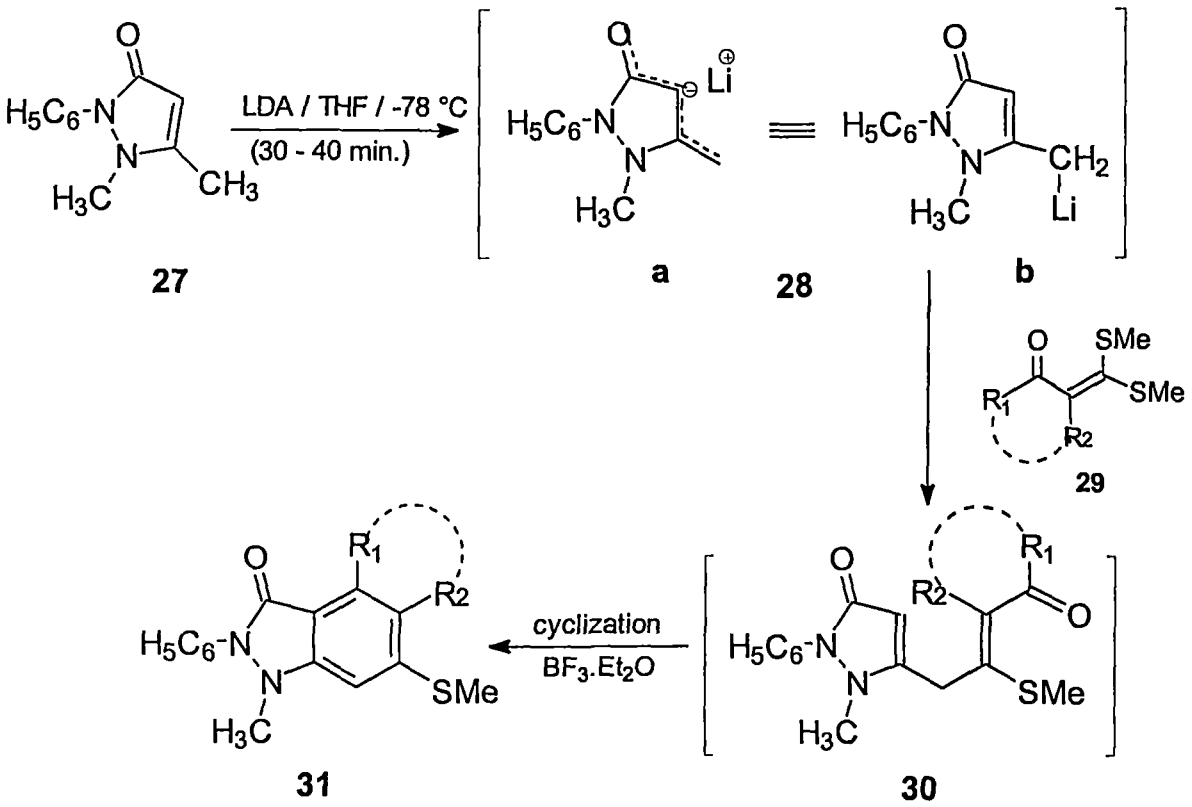
Synthesis of indazole derivatives from N,N-disubstituted 2-halo benzoic hydrazides has been reported by Stud and co-workers[15]. Under thermal conditions these halo substituted hydrazides formed the corresponding betaine **24** *in situ* followed by ring opening by the halide ion to yield the open chain halo compound **25**. The intermediate **25** was cyclized to give 1,2-indazolodiazepine **26** in good yields (Scheme-8).



Scheme- 8

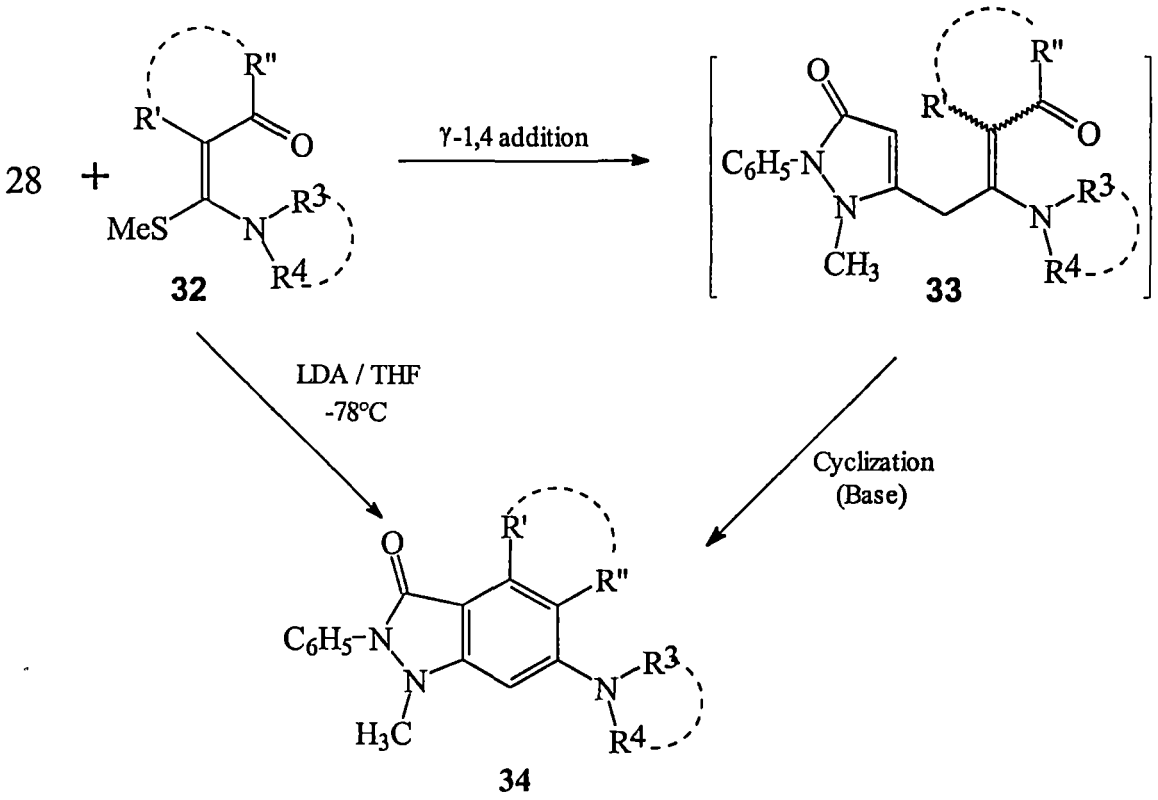
In our laboratory a novel indazolone synthesis[16] was developed as a part of our heteroaromatic annelation protocol. The readily available 2,3-

dimethyl-1-phenyl-5-pyrazolinone **27** (antipyrine) was conveniently deprotonated by treating it with lithium diisopropylamide (LDA) to generate the corresponding 1-phenyl-2-methyl-3-lithiomethyl pyrazolin-5-one **28**. The anion **28** was then reacted with various α-oxoketene dithioacetals[17], to afford the corresponding γ-1,4-addition-elimination products **30** in high yields. The intermediates were then cyclized in $BF_3.Et_2O$ / C_6H_6 to yield 1-methyl-2-phenyl-6-methylthioindazolones **31** in high yields (Scheme-9).



Scheme-9

In a similar reaction sequence the anion was also reacted with α-oxoketene N,S-acetals[18] **32** to yield the corresponding indazolones **34** directly in one pot reaction. The intermediate addition-elimination adducts **33** formed have undergone *in situ* base catalyzed cyclization under the reaction conditions. This is an interesting reaction involving transformation of antipyrine to the corresponding 6-amino indazolones in one pot reaction (Scheme-10).

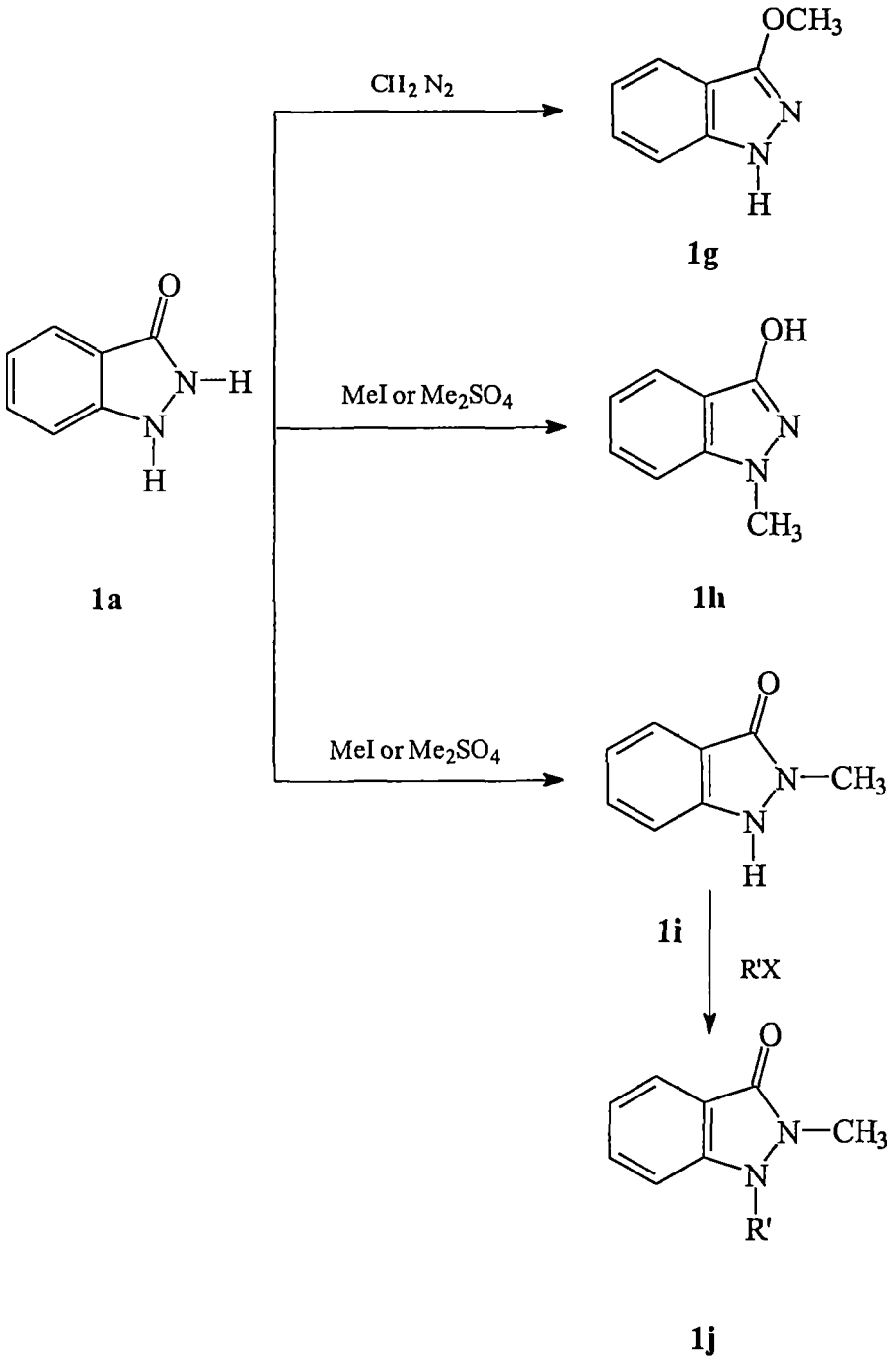


Scheme-10

From the preceding review it is apparent that there are no methods for the direct synthesis of 1,2-disubstituted indazolones. The method developed in our laboratory based on antipyrine anion is the first of its kind to have been used for the synthesis of 1,2-disubstituted indazolones in high yields. Also the method is novel since it adopts the reverse approach of creating aromatic and functionalized aromatic systems over the pre-constructed alkyl pyrazolone derivative. The methods based on pre-constructed pyrazolone appears to provide an easy alternative for the synthesis of a large number of 1,2-disubstituted indazolones for which there are not many methods in the literature.

Attempts have been made to prepare mono- and disubstituted indazolones by directly alkylating pre-constructed 1*H*-indazolone **1a** under different reaction conditions as formulated in Scheme-11. These alkylation reactions have been known to yield a mixture of isomeric products in poor yields.

Apparently there is a great need to further explore the synthesis of substituted indazolones by directly creating aromatic and functionally substituted aromatic rings over the pre-constructed 1,2-disubstituted pyrazolone derivatives. We have already successfully used our aromatic annelation methodology to meet this requirement using 2,3-dimethyl-1-


CH2 N2
OCH3
N
N
H
1g
O
N—H
N
H
1a
MeI or Me2SO4
OH
N
N
CH3
1h
MeI or Me2SO4
O
N—CH3
N
H
1i
R'X
O
N—CH3
N
R'
1j

Scheme-11

phenyl-5-pyrazolinone (antipyrine) as starting material and we further considered of interest to use the same intermediate antipyrine to create more indazolone molecules. In the present work we have developed a new method for the synthesis of indazolones starting from 4-formyl antipyrine *via* *o*-quinodimethane intermediate. The results are discussed in the following section.

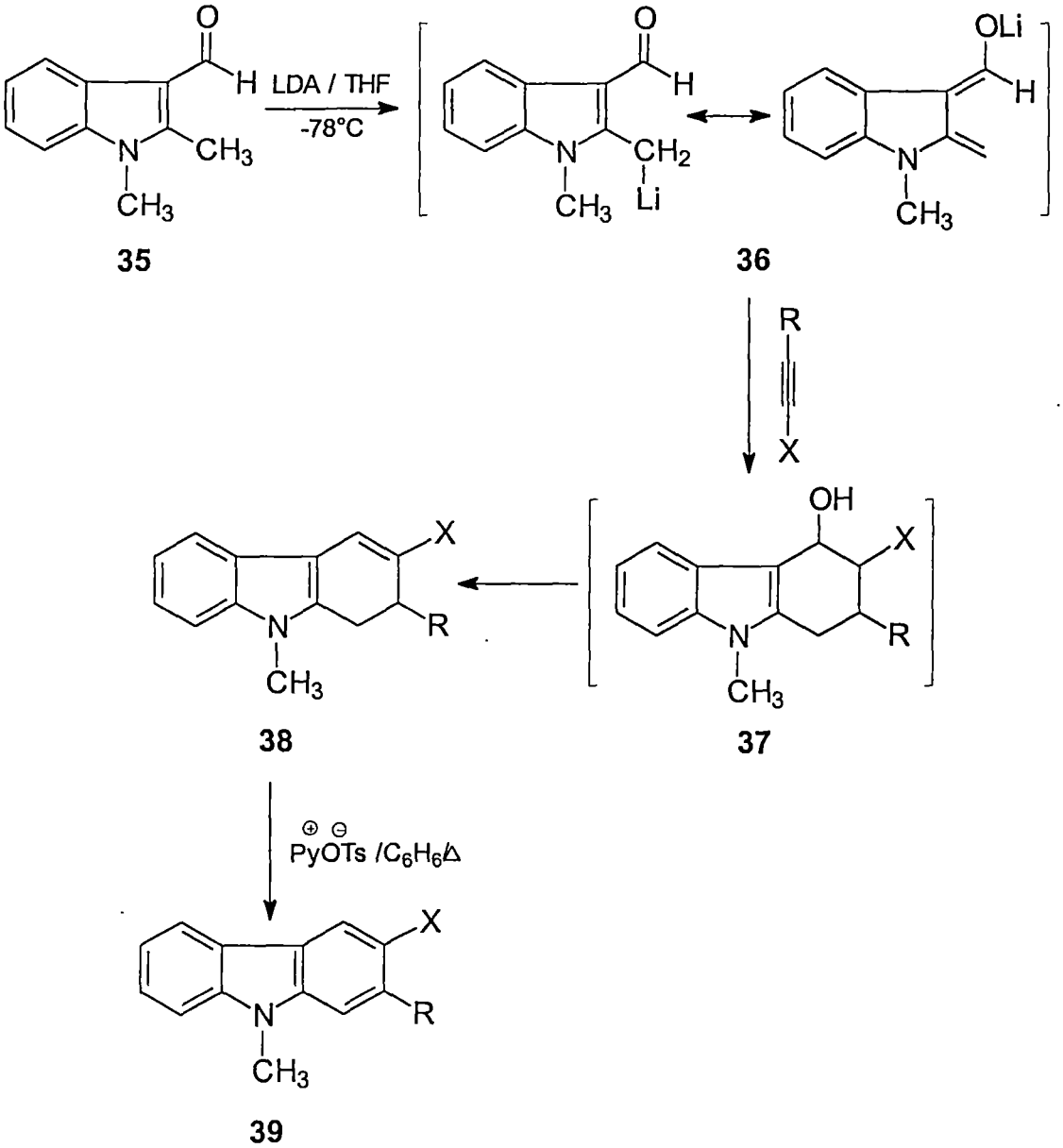
RESULTS AND DISCUSSION

The Diels-Alder [4+2] cycloaddition has been extensively applied in recent years involving highly unstable *o*-quinodimethane (OQDM) structural moiety as 1,3-diene which are trapped by various dienophiles to produce a large number of cycloadducts. The structural parameters required for generation of *ortho*-quinodimethane system have been well defined in the literature[19]. The heterocyclic analogs of *ortho*-quinodimethane (OQDM, *ortho*-xylylene) are of considerable interest both from theoretical point of view and for their potential in organic synthesis[20] as useful dienes which has been elegantly demonstrated in the indole series[21] for the synthesis of several naturally occurring and biologically important indole[22] and carbazole[23] alkaloids. However with the exception of indole-2,3-quinodimethane, the synthetic potential of other heterocyclic analogs remain largely unexplored although several studies involving their methods of generation and trapping have been published in recent years[20]. Most widely used routes to these heterocyclic *o*-

quinodimethanes involve flash vacuum pyrolysis[20,24], 1,4-elimination[20,25,26] of suitable precursors and *via* thermal extrusion of sulfur dioxide from heteroaromatic fused 3-sulfolenes[20,2728,]. Flash pyrolytic 1,4-elimination requires very harsh reaction conditions resulting in the formation of polymeric products thus precluding trapping of *ortho*-quinodimethane intermediates except in most stable cases. However several heterocyclic *ortho*-quinodimethanes have been generated by 1,4-elimination in solution and efficiently trapped by various dienophiles to afford the corresponding adducts in good yields[26]. Similarly heterocyclo- fused 3-sulfolenes have also been shown to be useful precursors for generation and trapping of heterocyclic *ortho*-quinodimethanes[20,27,28] (HQDM). However many of these precursors are not so easily accessible and do not lend themselves readily to structural elaboration thus limiting synthetic scope of these heterocyclic *o*-quinodimethanes especially for regiocontrolled synthesis of substituted heteroaromatic compounds which have many proven applications.

During the course of our continued interest in synthesis of benzoheterocycles *via* heteroaromatic annelation[29,16] we became interested in generation and reactions of anionic heteroaromatic *ortho*-quinodimethanes which are shown to exhibit pronounced enophilic reactivity and high regiocontrol in cycloadditions as a result of increased HOMO energy level (or net atomic charge) and charge controlled orientation of two reactive partners in the transition state[30,31]. It is pertinent to note that neutral HQDM usually

afford mixture of regioisomers on cycloaddition with unsymmetrical dienophiles which limits their synthetic scope for regiocontrolled construction of substituted benzoheterocycles. We have recently reported that enolate derived from 1,2-dimethylindole-3-carboxaldehyde is a useful anionic α-oxy-indolo-2,3-quinodimethane equivalent which undergoes facile cycloaddition with a variety of dienophiles affording wide range of substituted carbazoles

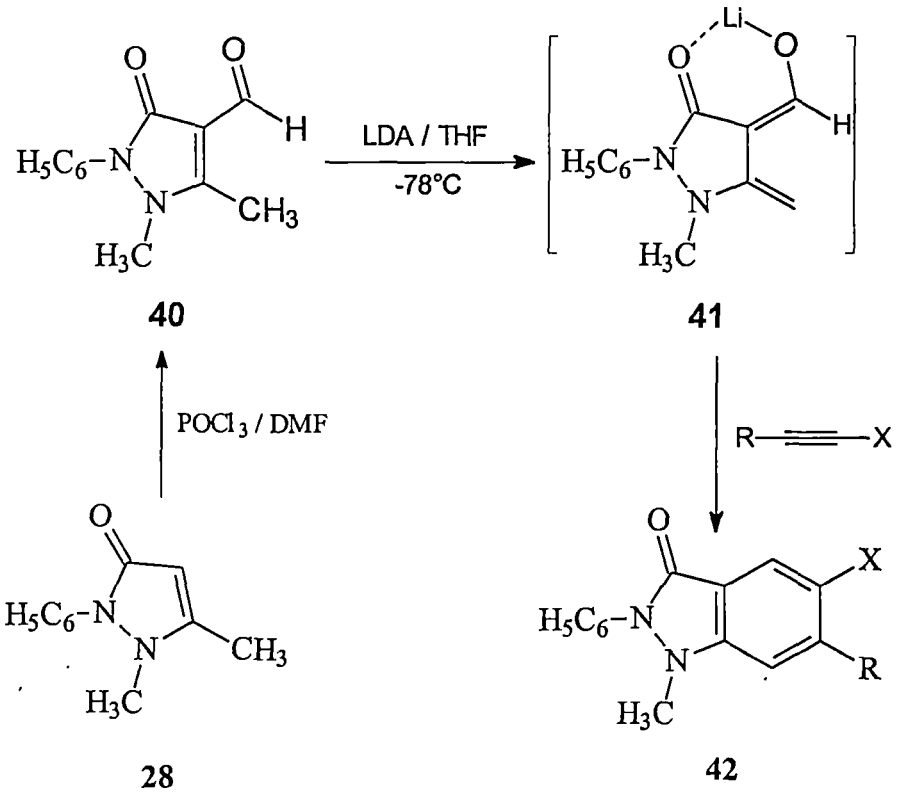


35 36 38 37 39

Scheme-12

under mild conditions with efficient control of regioselectivity[32] (Scheme-12).

We have now demonstrated that pyrazolone dienolate **41** derived from 2,3-dimethyl-1-phenyl-4-formyl-pyrazolin-5-one is an efficient anionic pyrazolone *ortho*-quinodimethane equivalent which undergoes facile regioselective cycloaddition with various dienophiles to afford highly regioselectively substituted indazolones in excellent yields with a total control of the product regioisomers (Scheme-13). These results are described in this section.



40 41 28 42

Scheme-13

The 4-formylantipyrine **40** was prepared by subjecting antipyrine to Vilsmeier-Haack reaction in good yields as reported in the literature[33]. It was then reacted with lithium diisopropylamide at –78°C to form the corresponding hitherto unreported lithioenolate **41** with near colourless to red colour solution which was used as a marker for the anion formation. To this reaction mixture was added dimethyl fumarate in tetrahydrofuran when the red colour was transformed into light yellow colour and the reaction mixture was brought to room temperature and left overnight. After work up a mixture of cycloadduct **44** and **45** were obtained. Consequently the reaction mixture was treated with pyridinium tosylate to give the fully aromatized adduct **45** in 60% yield. The structure was fully confirmed by alternately reacting **41** with dimethylacetylenedicarboxylate so that the fully aromatized adduct **45** was isolated in 72% yield. Both the adducts obtained from these two dienophiles were found identical (mmp) and had superimposable IR. The structure of **45** was fully established by analytical and spectral data (Scheme-14).

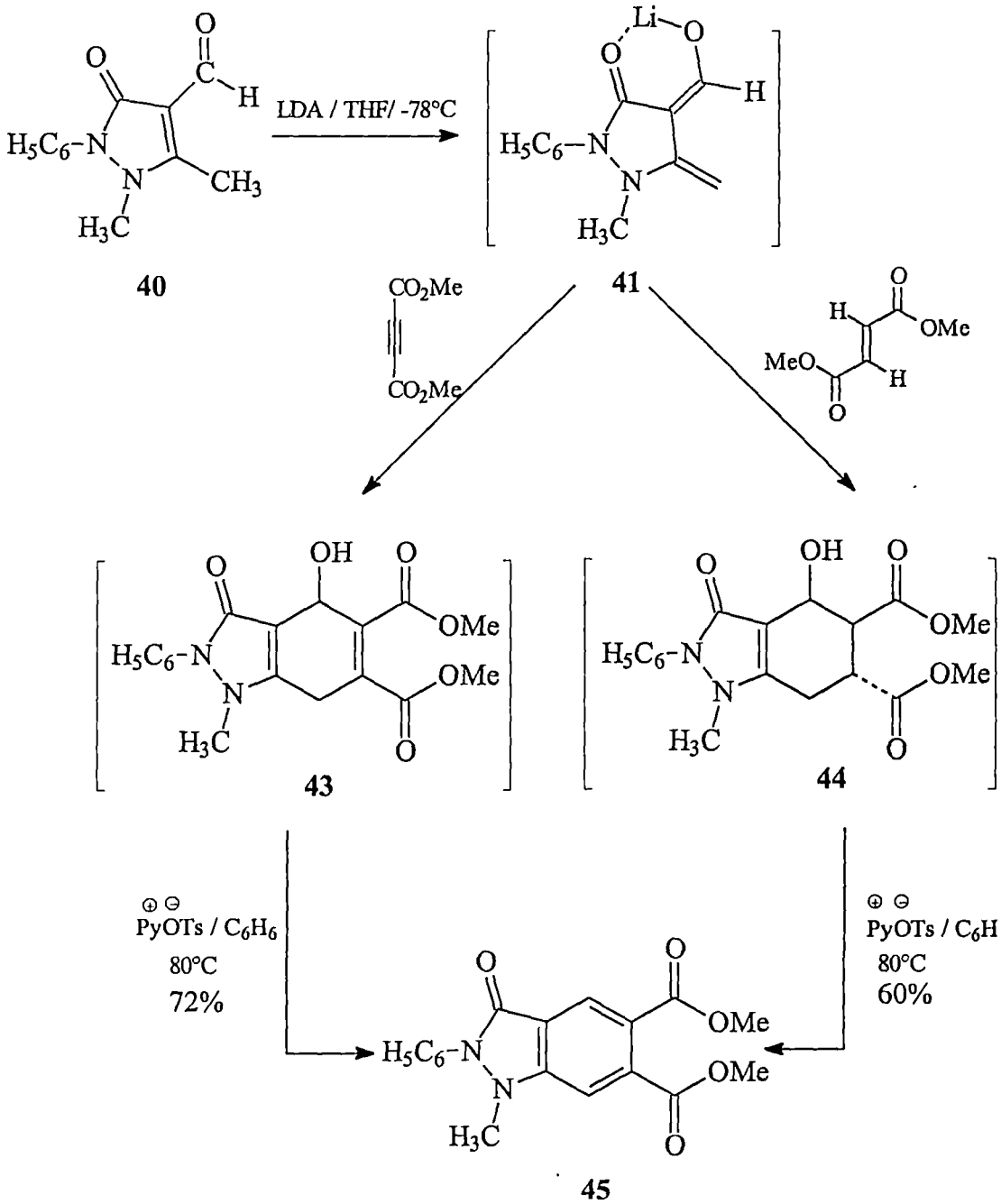
IR (KBr): ν_{max} = 3043, 2948, 1728, 1705, 1678 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): 3.26 (s, 3H, NCH_3); 3.93 (s, 3H, OCH_3); 3.97 (s, 3H, OCH_3); 7.33-7.38 (m, 1H, ArH); 7.47 (s, 1H, ArH); 7.51-7.53 (m, 4H, ArH) 8.47 (s, 1H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.56, 52.70, 53.12, 112.20, 119.31,

124.18, 124.42, 127.25, 127.45, 129.40, 134.23, 138.19, 151.16, 160.71, 166.16, 168.48.

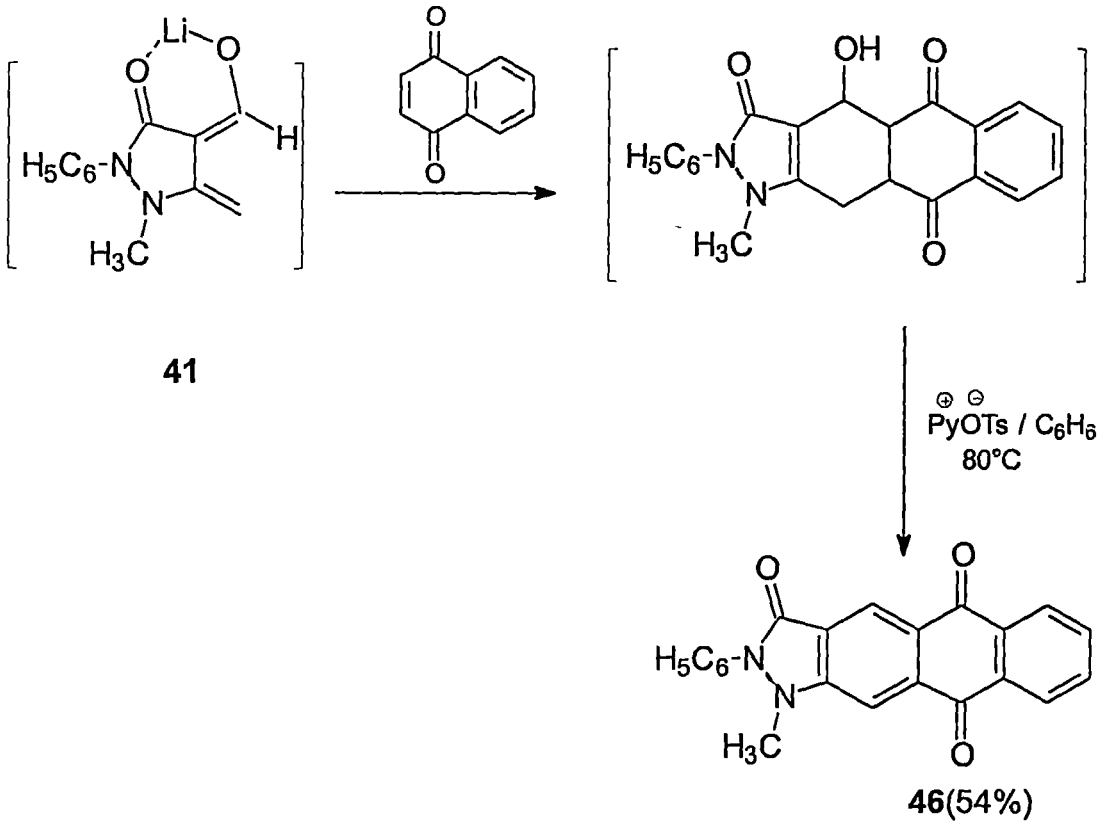
MS: m/z (%) = 340 (M^+, 100), 325 (M^+ -15.0).



Scheme-14

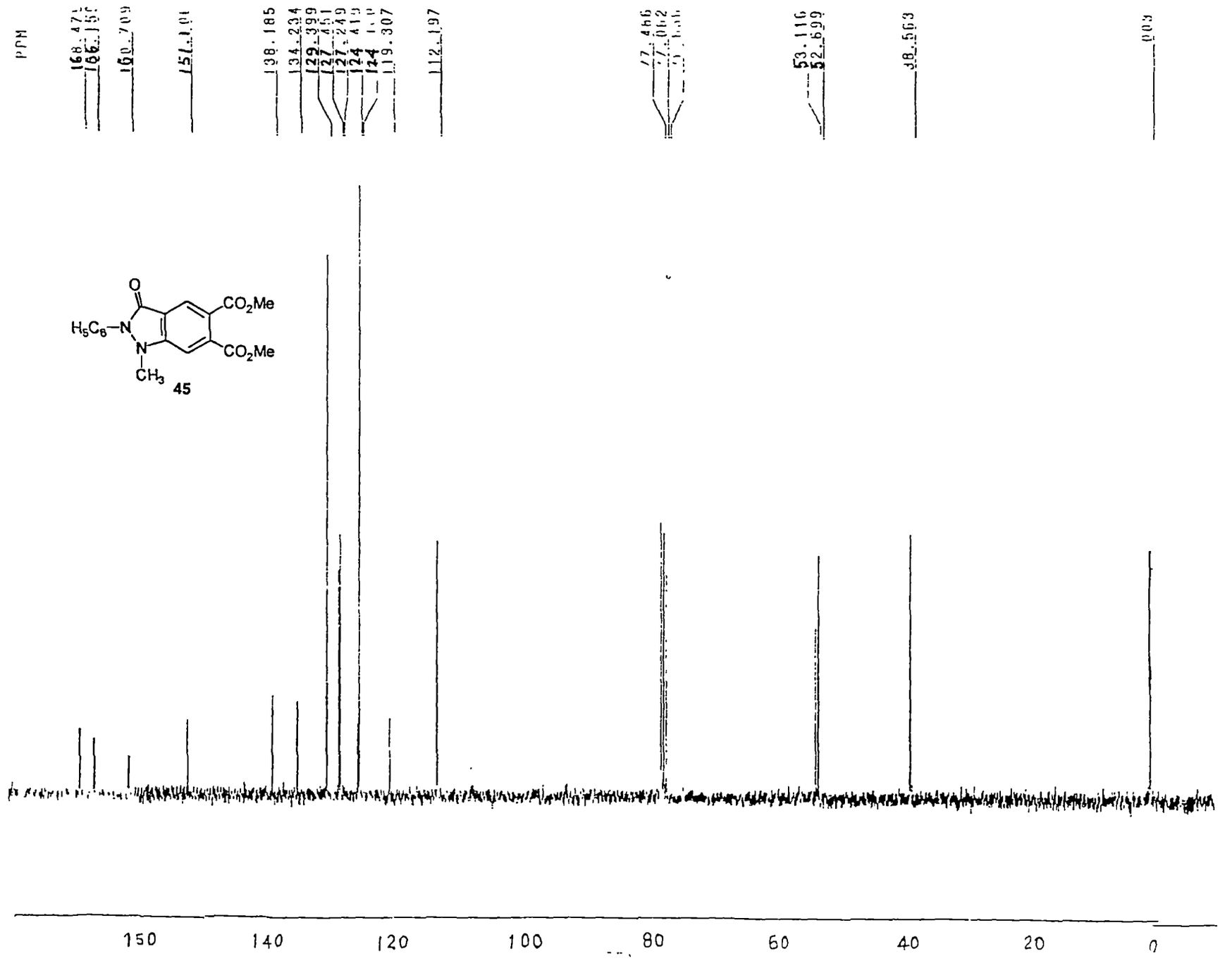
Anal. Calc. for $C_{18}H_{16}N_2O_5$ (340): C, 63.59; H, 4.74 N, 8.24%. Found C, 63.89; H, 4.75; N, 8.23%.

The reaction of cyclic dienophile with **41** was next examined. Thus 3,4-dienolate **41** reacted with naphthoquinone to give the unique indazolo-fused naphthoquinone ring system **46** in 54% yield after subsequent dehydration of the resulting adduct under similar reaction conditions (Scheme-15). Compound **46**, to our knowledge, is the first example of naphtho[*2,3-f*]-indazolone ring system.

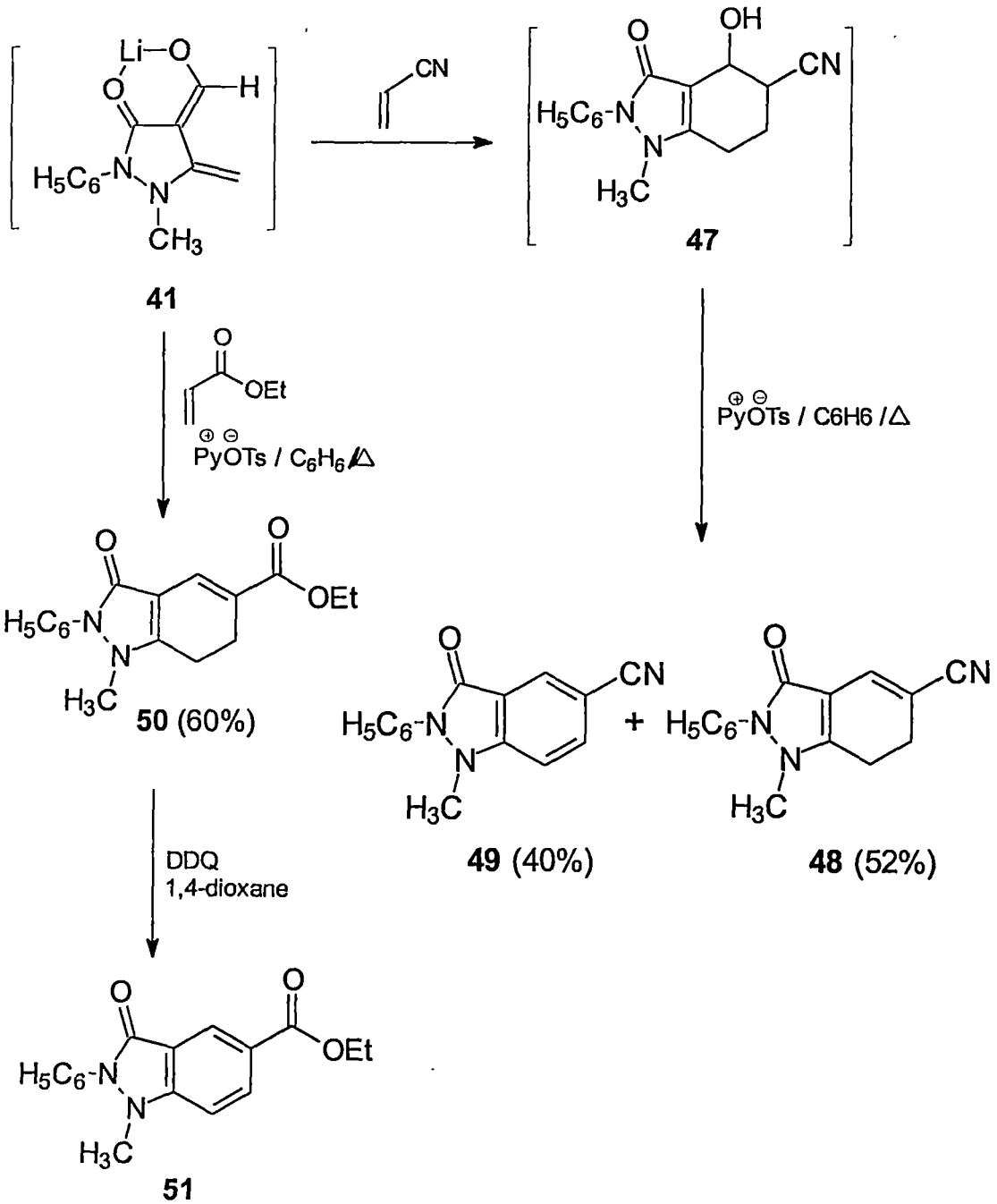


Scheme-15

CO2Me
CO2Me
CH3
45
H5C6
O
N
N
PPM


PPM
168.471
166.155
160.709
151.101
138.185
134.234
129.399
127.451
127.249
124.415
124.
119.307
112.197
77.466
53.116
52.699
48.563
0.0
O
CO2Me
H5C6–N
N
CO2Me
CH3
45
150
140
120
100
80
60
40
20
0

It is already well established that electron rich dienes such as enolate *ortho*-quinodimethane should react with unsymmetrical dienophiles to yield the corresponding cycloadducts through β-carbon so that only one regioisomer is



Scheme-16

formed. To examine this, the dienolate was reacted with ethyl acrylate to give after work up the corresponding 1,2,6,7-tetrahydro-5-ethoxycarbonyl-1-methyl-2-phenyl-3*H*-indazol-3-one **50** in 60% yield. The compound was fully characterized by its analytical and spectral data (Scheme-16).

IR (KBr): ν_{max} = 1691, 1660, 1548, 1204 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, 3H, J = 7.1 Hz, CH_3), 2.78-2.83 (m, 4H, CH_2-CH_2), 3.22 (s, 3H, NCH_3), 4.22 (q, 2H, J = 7.1 Hz, OCH_2), 7.33-7.37 (m, 3H, ArH), 7.45-7.51 (m, 2H, ArH), 7.57 (s, 1H, H-4);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.36, 20.80, 21.95, 34.27, 60.37, 104.73, 119.85, 125.26, 127.59, 128.41, 129.40, 134.36, 155.10, 162.36, 167.12.

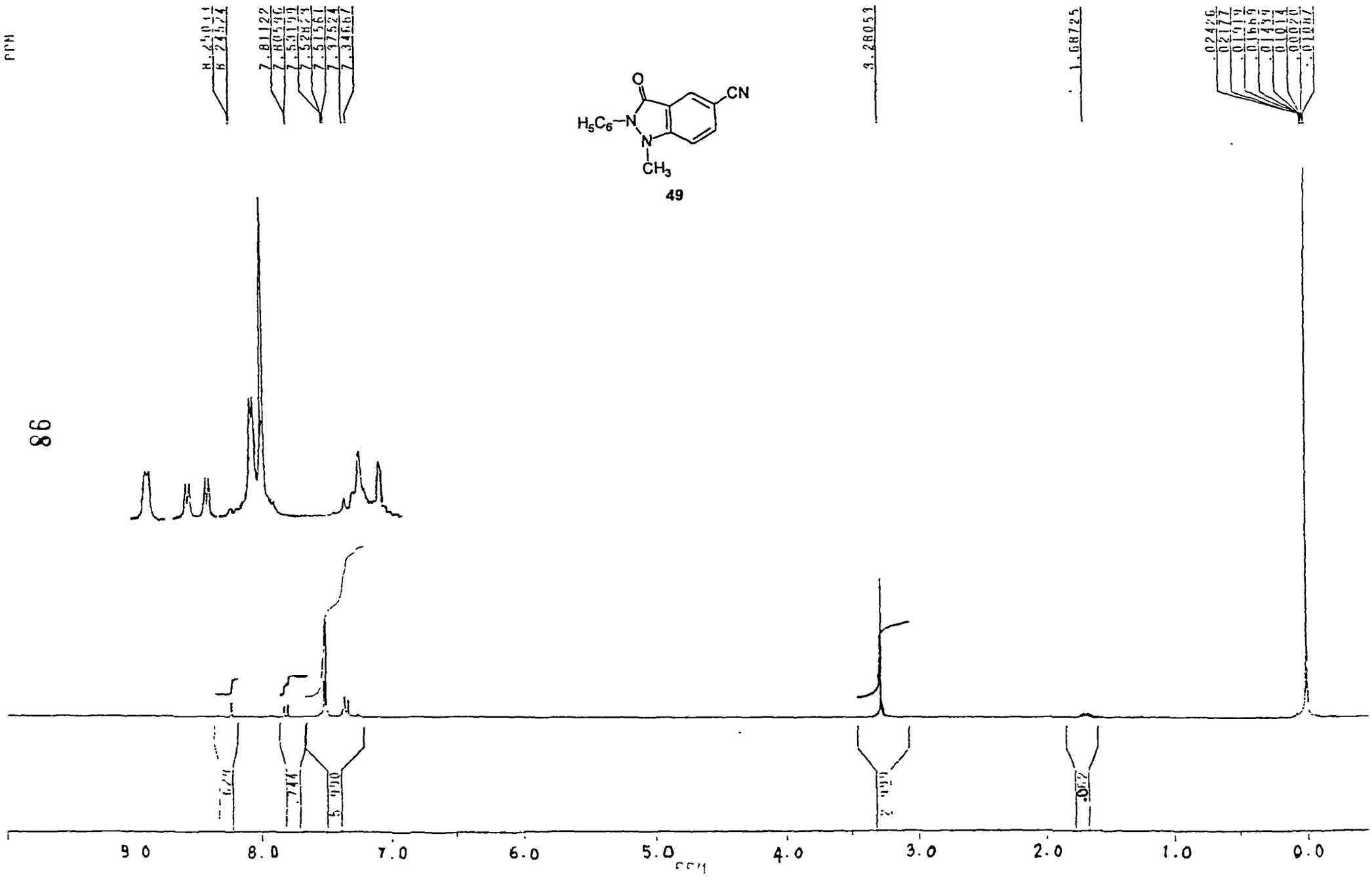
MS: m/z (%) = 298 (M^+, 100).

Anal. calc. for $C_{17}H_{18}N_2O_3$ (298.34): C, 68.44; H, 6.08; N, 9.39%. Found C, 68.73; H, 6.03; N, 9.48%.

The structure of the dihydro compound was further confirmed by transforming it to the fully aromatised indazolone. Thus **50** was treated with DDQ in 1,4-dioxane. After work up, the reaction mixture yielded the corresponding 1,2-dihydro-5-ethoxycarbonyl-1-methyl-2-phenyl-3*H*-indazol-3-one **51** in quantitative yield. Therefore it is fully established that the diene is an excellent precursor for making indazolones with full control of substituents in the benzene ring. This was further confirmed by reacting **41** with acrylonitrile. The adduct after initial work up and treatment with pyridinium tosylate

2.67801
2.70762
2.73421
2.80485
2.83163
2.86171
PPM
7.17374
7.29675
7.32416
7.35726
7.38184
7.40556
7.46821
7.49324
7.51826
PPM
CN
O
N
CH3
48
H5C6
4.129
2.997
.924
5.144
9.0
8.0
7.0
6.0
5.0

161.189
152.506
133.746
129.529
128.170
125.242
120.120
109.320
98.339
77.566
77.142
76.718
34.043
29.647
24.263
20.056
.002
160
140
120
100
80
60
40
20
0
PPM
CN
O
N
CH3
H5C6
48


8.25011
8.24574
7.81122
7.80596
7.53179
7.52823
7.51561
7.37524
7.34667
3.28053
1.68725
0.02426
0.02177
0.01619
0.01669
0.01439
0.01014
0.00920
0.01087
O
CN
H_5C_6–N
N
CH_3
49
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

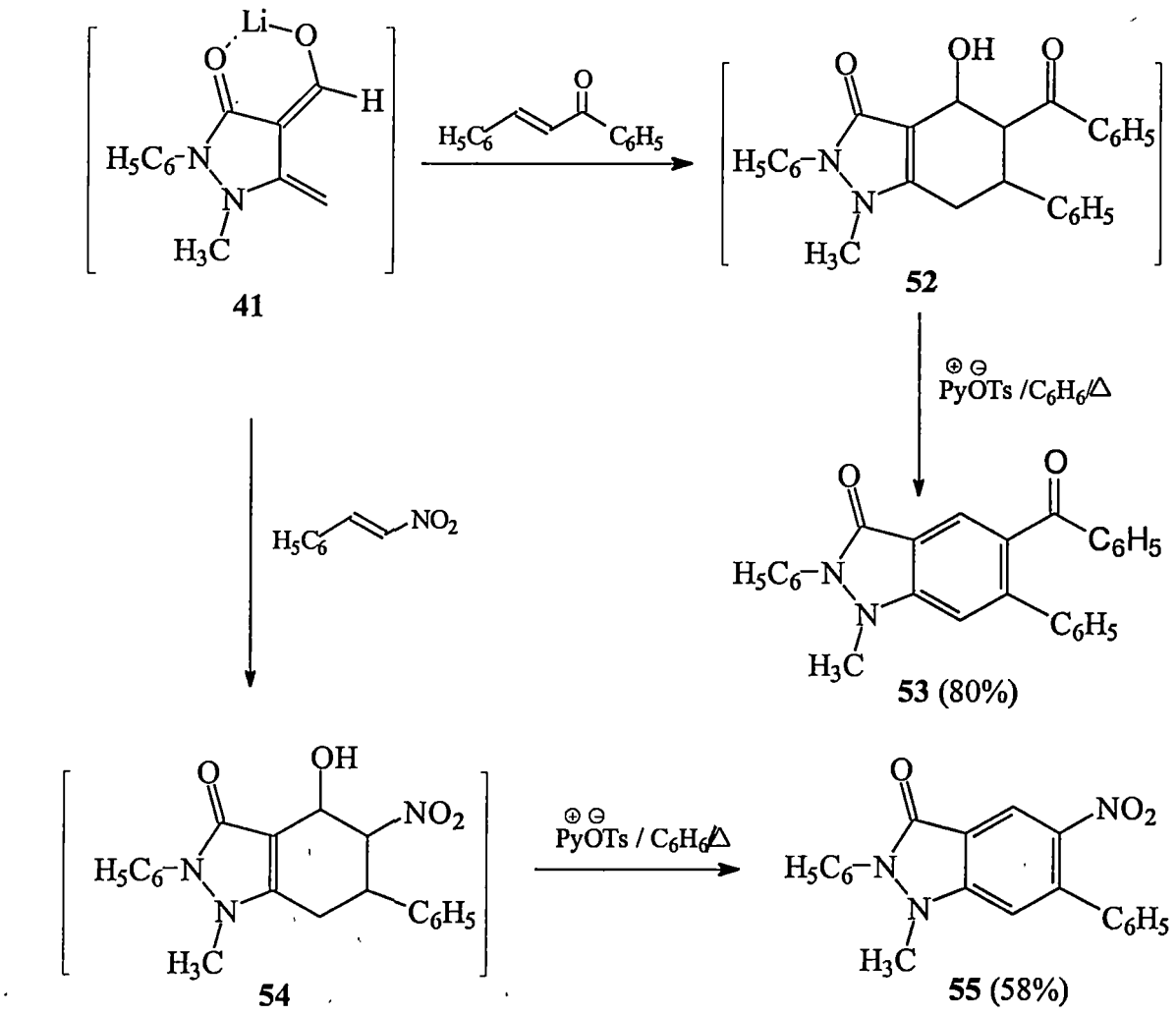
CO2Et
O
N
CH3
H5C6
50
3.09
4.19
2.96
2.000
5.901
PPM

167.116
162.357
155.095
134.362
129.400
128.407
127.590
125.264
119.850
104.734
77.491
77.067
76.643
60.366
44.268
21.949
20.795
14.357
CO2Et
N
CH3
O
H5C6

yielded a mixture of two products (TLC) which were separated by column chromatography. One of them was found to be fully aromatic system **49** which, was obtained in 40% yield and obtained first while separation. The structure of **49** was confirmed by its analytical and spectral data described in the experimental section. The other adduct **48** was characterized as the dihydro indazolone and obtained in 52% yield. Its analytical and spectral data are in conformity as described in the experimental section. These reactions amply demonstrate the regiospecificity of the 3,4-dienolate *ortho*-quinodimethane reactions with unsymmetrical dienophiles (Scheme-16).

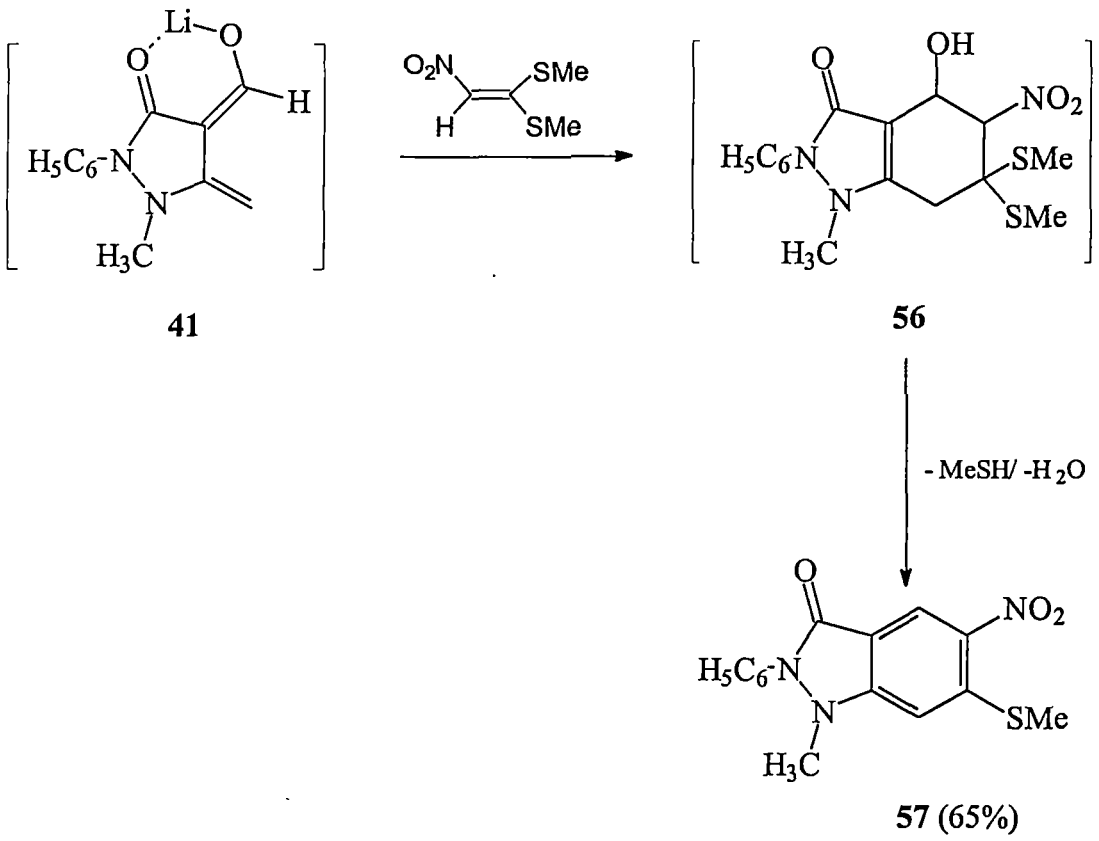
Further reaction of **41** with unsymmetrical dienophile chalcone also yielded only one regioisomer 5-benzoyl-6-phenylindazolones **53** in 80% yield under the described reaction conditions. There was no trace of the other regioisomer detected in the reaction mixture. Similarly, β-nitrostyrene yielded the expected regioisomer 1,2-dihydro-1-methyl-5-nitro-2,6-diphenyl-3*H*-indazol-3-one **55** in 58% yield by treatment with pyridinium tosylate under identical conditions (Scheme-17). The structure of **55** was also confirmed by its analytical and spectral data.

The reaction of **41** with nitroketene dithioacetal was found to be very facile and yielded directly the corresponding 5-nitro-6-methylthio-3*H*-indazol-



Scheme-17

3-one **57** in 65% yield by *in situ* aromatization of the adduct **56** via dehydration and elimination of methyl mercaptan (Scheme-18).

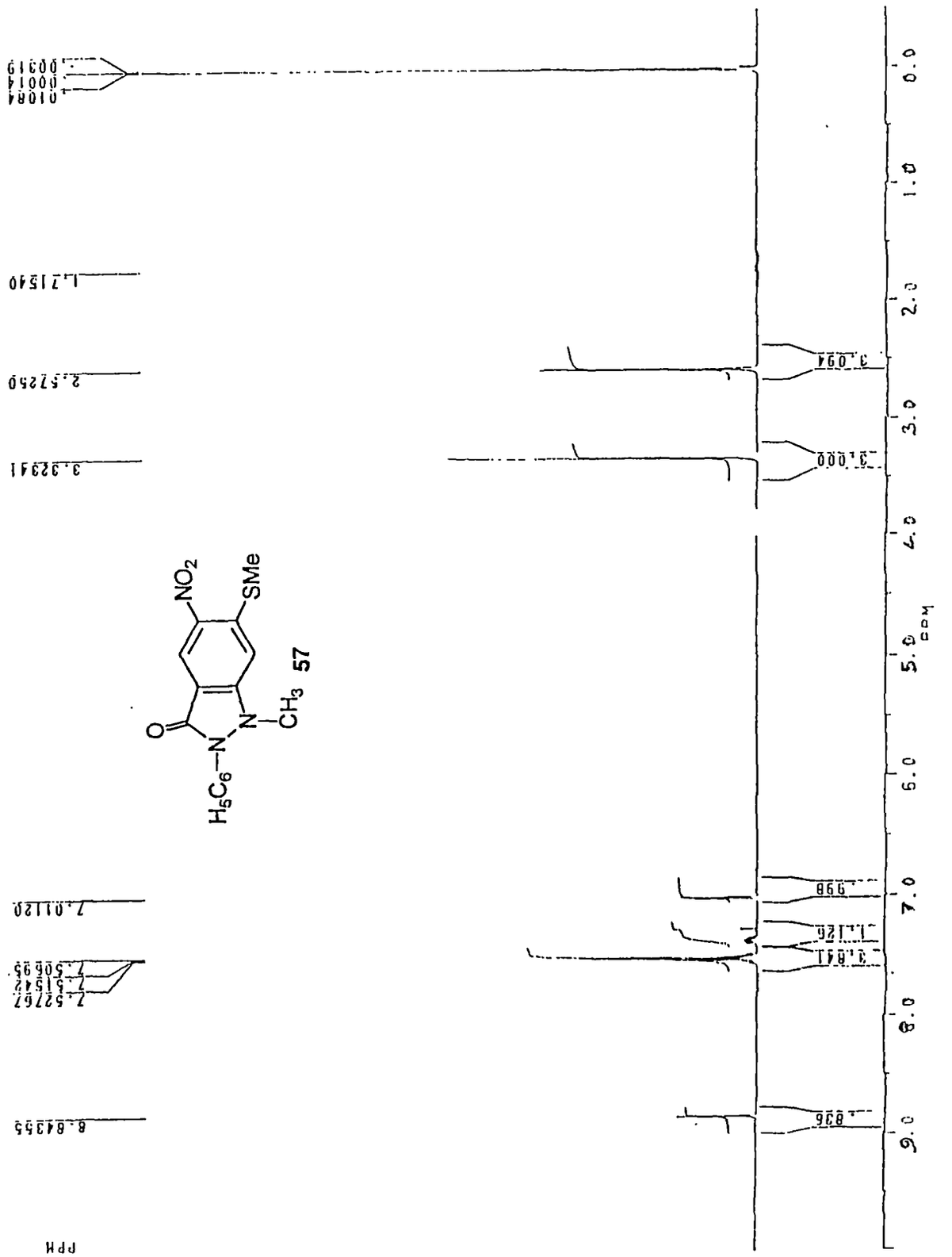


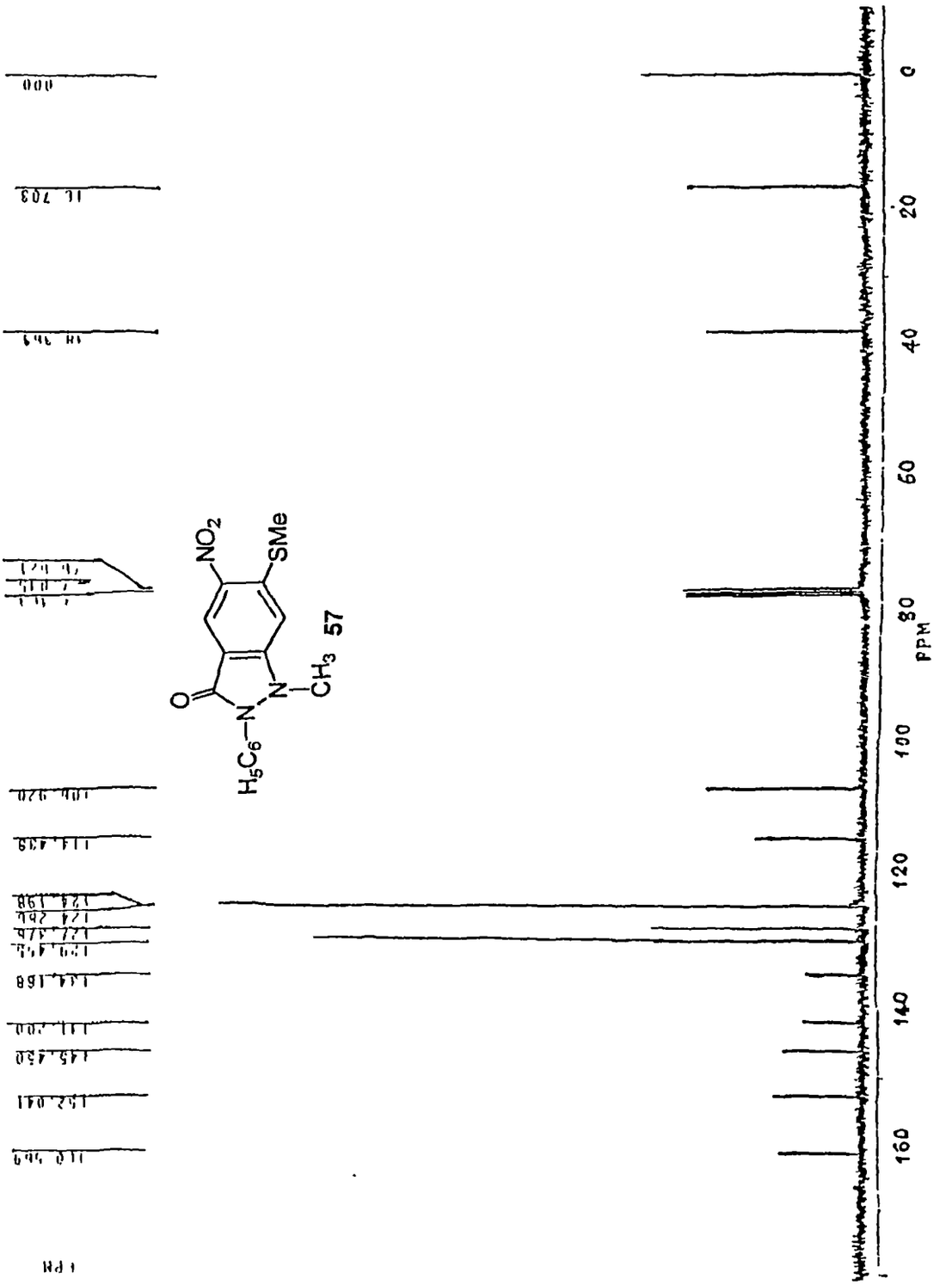
41 **56**

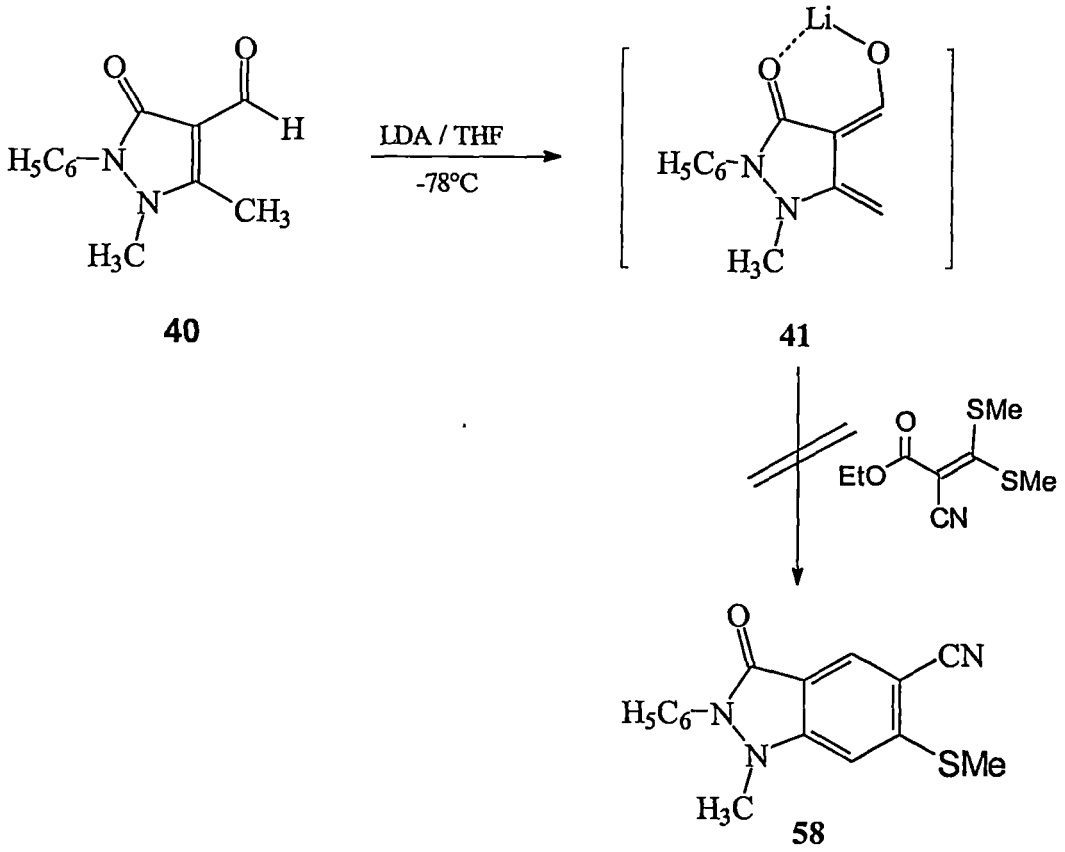
57 (65%)

Scheme-18

After successful cycloaddition reactions of nitroketene dithioacetal with **41**, it was of interest to react ketene dithioacetal derived from cyanoacetate with **41**. However this reaction failed to yield the indazolone **58** probably due to steric reasons (Scheme-19).


NO2
SMe
CH3
57
H5C6
PPM


NO2
SMe
CH3
N
O
N
H5C6
57
PPM
0
20
40
60
80
100
120
140
160



Scheme-19

In conclusion, we have successfully demonstrated the generation of hitherto unreported *o*-quinodimethane from 4-formylantipyrine in excellent yields. The pyrazolin-5-one dienolate **41** has been shown to be an efficient anionic α-oxy heteroaromatic *ortho*-quinodimethane undergoing facile cycloaddition with various dienophiles in highly regiospecific fashion to afford substituted and fused indazolones in good yields. The neutral pyrazole *ortho*-quinodimethane have been generated earlier by dehalogenation of 4,5-

bis(bromomethyl)pyrazole[25] or by thermolysis of pyrazolo- fused 3-sulfolenes[27] followed by their trapping by various dienophiles. However synthetic scope of these reactions has not been much investigated. Further it should be noted that more recently the α-oxybenzo *ortho*-quinodimethane are generated by base catalyzed ring opening of benzocyclobuten-2-ol[34] instead of deprotonation of *o*-tolualdehyde so as to minimize complication due to aldehyde-enolate condensation. However present reactions involving deprotonation of 3-methyl-4-formylpyrazolone **40** to give dienolate **41** were found to be very clean and formation of polymeric and open chain side products was not observed in the reaction mixture. This may be attributed to the stabilization of dienolate due to chelated structure **41** formed by intramolecular interaction between OH and C-5 carbonyl group. The present sequence thus represents an efficient route for assembling indazolone ring system from pyrazole precursors.

EXPERIMENTAL SECTION

General

Melting points were obtained on a "Thomas Hoover" melting point apparatus (capillary method) and are uncorrected. The Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer. ^{1}H NMR (90 MHz) were recorded on Varian EM-390 spectrometer. High resolution ^{1}H NMR (300 MHz), ^{13}C NMR spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either tetramethylsilane as internal lock (for ^{1}H NMR), the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C NMR). The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra (MS) were determined on a Jeol JMS-D 300 mass spectrometer. Masses are reported in units of mass upon charge (m/z), the molecular and base peaks are indicated by (M^{+}) and (%) respectively. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions involving organolithium were performed in an oven dried (120°C) glassware under a positive dry argon / nitrogen atmosphere. Transfer of anhydrous solvents or mixtures were accomplished with oven dried syringe-septum technique. Low temperature reactions were carried in a bath made of

ethyl acetate and liquid nitrogen. Analytical thin layer chromatography (TLC) were performed on glass plates (18 × 4cm) coated with ACME's silicagel containing 13% calcium sulfate as binder and various combinations of ethylacetate-hexane, ethylacetate-benzene, benzene were used as eluents. Visualization of spots was accomplished by exposure to iodine vapour or potassium permanganate (acidic) solution. ACME's silica gel (60-120 mesh) is used for column chromatography, solvents for column chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steam bath.

Chemicals and Reagents.

Diisopropylamine was distilled from potassium hydroxide prior to use. Tetrahydrofuran was obtained anhydrous by distillation after the characteristic blue colour of in situ generated sodium diphenyl ketyl[35] was found to persist. Dry benzene[36a] was obtained by washing with conc. sulphuric acid followed by azeotropic distillation and stored over sodium wire. Pyridinium tosylate was prepared by reported method. n-butyllithium (Aldrich) was used as such. Lithium diisopropylamide (LDA) was prepared according to the literature procedure[37].

Starting materials.

2,3-dimethyl-1-phenylpyrazolin-5-one (Antipyrine) was obtained from Aldrich and used as such. Commercially available dienophiles were either distilled or simply used as such. Naphthaquinone was synthesized from reported literature methods[36b]. The dithioacetals used in the reaction was also prepared by reported methods from our laboratory.

General procedure for the preparation of 4-formyl-2,3-dimethyl-1-phenylpyrazolin-5-one 40:

2,3-dimethyl-1-phenylpyrazolin-5-one (Antipyrine) 9.40g (50 mmol) was taken in 15 ml of dimethylformamide and $POCl_3$ (10.11g, 55 mmol) was added to the reaction mixture at 0°C. The reaction mixture was heated at 70-75°C for 6 to 7 hours. The reaction mixture was poured over crushed ice, then washed with sodium bicarbonate solution and extracted with chloroform. The combined organic layer was washed with water, dried and concentrated when it gave the corresponding 4-formyl-1,5-dimethyl-2-phenyl-pyrazol-3-one in 80% yield, mp 162°C (lit. mp 162°C).

colourless crystals (chloroform-hexane); yield 80%; mp 162°C

IR (KBr): ν_{max} = 1640, 1509 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.56 (s, 3H, CH_3); 3.30 (s, 3H, NCH_3); 7.25-7.65 (m, 5H, ArH); 9.90 (s, 1H, CHO)

General Procedure for Generation of Lithio 1-methyl-2-phenylpyrazolin-5-one-2,3-dienolate 2 and its Cycloaddition with Dienophiles: Synthesis of Indazolones

To a solution of diisopropylamine (2 mL, 14 mmol) in dry tetrahydrofuran (10 mL) under nitrogen atmosphere, was added n-BuLi (6.25 mL, 10 mmol, 1.6 M) at 0°C and the reaction mixture was stirred for 20 min. To the resulting solution of lithium diisopropylamide (LDA) at -78°C, a solution of **40** (1.08 g, 5 mmol) in dry THF (30 mL) was added followed by further stirring for 45 min. To the resulting red coloured solution of dienolate **41**, appropriate dienophile (5 mmol) dissolved in dry THF (15 mL) was added while maintaining the temperature at -78°C. The reaction mixture was then brought to room temperature during 45 min and left overnight with stirring. It was then poured into saturated ammonium chloride solution (150 mL) and extracted with chloroform (3× 50 ml). The combined organic extracts were washed with water, dried (Na_2SO_4) and then concentrated to give crude carbinol adduct which was dissolved in dry benzene (50 mL) followed by addition of pyridinium tosylate (1.5 g, 6 mmol) and further refluxing for 1h. The reaction mixture was poured into water (100 mL) and extracted with chloroform (3 x 50 mL), the combined organic layer was washed with water, dried over sodium sulfate and concentrated. The crude product thus obtained was purified by column chromatography over silica gel using ethyl acetate-hexane (19:1) as eluent.

1,2-Dihydro-5,6-bis(methoxycarbonyl)-1-methyl-2-phenyl-3*H*-indazol-3-one 45:

Colourless crystals; mp 180-181°C (chloroform-hexane); Yield 72%.

IR (KBr): ν_{max} = 3043, 2948, 1728, 1705, 1678, 1621, 1309 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.26 (s, 3H, NCH_3), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.33-7.38 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.51-7.53 (m, 4H, ArH), 8.47 (s, 1H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.56, 52.70, 53.12, 112.20, 119.31, 124.18, 124.42, 127.25, 127.45, 129.40, 134.23, 138.19, 151.61, 160.71, 166.16, 168.48.

MS (m/z, %): 340 (M^+, 100), 325 (37.5).

Anal. calc. for $C_{18}H_{16}N_2O_5$ (340.33): C, 63.53; H, 4.74; N, 8.23%. Found C, 63.81; H, 4.78; N, 8.30%.

1-Methyl-2-phenyl1,2,5,10-tetrahydro-3*H*-naphtho[2,3-f]indazol-3,5,10-trione 46:

Red crystals; mp 240°-241°C (chloroform-hexane); Yield 50%.

IR (KBr): ν_{max} = 1694, 1669, 1589, 1325 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.41 (s, 3H, NCH_3), 7.39-7.42 (m, 1H, ArH), 7.52-7.59 (m, 4H, ArH), 7.83-7.87 (m, 2H, ArH), 8.21 (s, 1H, H-11), 8.37, 8.39 (two d, 2H, J = 8 Hz, H-6 and H-9), 8.96 (s, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.43, 110.77, 122.18, 124.36, 126.29, 127.51, 127.63, 128.37, 129.49, 134.08, 134.73, 152.36, 160.78, 181.51, 182.93.

MS (m/z, %): 354 (M^+, 100).

Anal. calc. for $C_{22}H_{14}N_2O_3$ (354.36): C, 74.57; H, 3.98; N, 7.91%. Found C, 74.34; H, 4.11; N, 7.79%.

5-Cyano-1-methyl-2-phenyl-1,2,6,7-tetrahydro-3*H*-indazol-3-one 48:

Colourless crystals; mp 204-205°C (chloroform-hexane); Yield 52%.

IR (KBr): ν_{max} = 2200, 1669, 1562, 1495 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.67-2.73 (m, 2H, CH_2), 2.80-2.86 (m, 2H, CH_2), 3.23 (s, 3H, NCH_3), 7.17 (s, 1H, H-4), 7.29-7.41 (m, 3H, ArH), 7.46-7.52 (m, 2H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.06, 24.26, 34.04, 98.34, 103.32, 120.12, 125.74, 128.17, 129.53, 133.75, 152.51, 161.19.

MS (m/z, %): 251 (M^+, 100); 222 (M^+ -29).

Anal. calc. for $C_{15}H_{13}N_3O$ (251.29): C, 71.70; H, 5.21; N, 16.72%. Found C, 71.94; H, 5.13; N, 16.80%.

1,2-Dihydro-5-cyano-1-methyl-2-phenyl-3*H*-indazol-3-one 49:

Colourless crystals; mp 196-197°C (chloroform-hexane); Yield 40%.

IR (KBr): ν_{max} = 2185, 1661, 1594, 1482 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28 (s, 3H, NCH_3), 7.36 (d, 1H, J = 8.6 Hz, ArH), 7.49-7.53 (m, 5H, ArH), 7.82 (dd, 1H, J = 8.6, 1.6 Hz, ArH), 8.25 (d, 1H, J = 1.5 Hz, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.36, 112.86, 124.29, 127.40, 129.46, 130.06, 134.05, 135.47, 151.97.

MS: (m/z, %): 249 (M^+, 23.8).

Anal. calc. for $C_{15}H_{11}N_3O$ (249.27): C, 72.28; H, 4.45; N, 16.86%. Found C, 72.09; H, 4.52; N, 16.97%.

5-(Ethoxycarbonyl)-1-methyl-2-phenyl-1,2,6,7-tetrahydro-3*H*-indazol-3-one 50:

Colourless crystals; mp 197-198°C (chloroform-hexane); Yield 60%.

IR (KBr): ν_{max} = 1691, 1660, 1548, 1204 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, 3H, J = 7.1 Hz, CH_3), 2.78-2.83 (m, 4H, CH_2-CH_2), 3.22 (s, 3H, NCH_3), 4.22 (q, 2H, J = 7.1 Hz, OCH_2), 7.33-7.37 (m, 3H, ArH), 7.45-7.51 (m, 2H, ArH), 7.57 (s, 1H, H-4);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.36, 20.80, 21.95, 34.27, 60.37, 104.73, 119.85, 125.26, 127.59, 128.41, 129.40, 134.36, 155.10, 162.36, 167.12.

MS (m/z, %): 298 (M^+, 100); 269 (M^+, -29).

Anal. calc. for $C_{17}H_{18}N_2O_3$ (298.34): C, 68.44; H, 6.08; N, 9.39%. Found C, 68.73; H, 6.03; N, 9.48%.

1,2-Dihydro-5-(ethoxycarbonyl)-1-methyl-2-phenyl-3*H*-indazol-3-one 51:

A solution of 50 (300 mg, 1 mmol) and DDQ (295 mg, 1.3 mmol) in dry dioxane (10 mL) was refluxed with stirring for 2h. The reaction mixture was then cooled, diluted with chloroform (20 mL) and filtered. The filtrate was evaporated to dryness and the residue obtained was purified by passing through silica gel column using hexane-ethyl acetate (19:1) as eluent; colourless crystals; mp 125°-126°C (chloroform-hexane); Yield 90%.

IR (KBr): ν_{max} = 1680 (br), 1626, 1368, 1295 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, 3H, J = 7.1 Hz, CH_3), 3.25 (s, 3H, NCH_3), 4.41 (q, 2H, J = 7.1 Hz, OCH_2), 7.29-7.37 (m, 2H, ArH), 7.48-7.58 (m, 4H, ArH), 8.31 (dd, 1H, J = 8.7, 1.5 Hz, ArH), 8.45 (d, 1H, J = 1.5 Hz, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.37, 38.76, 61.23, 111.78, 118.45, 124.04, 125.34, 126.89, 127.17, 129.32, 133.98, 134.61, 153.35, 161.62, 165.89;

Anal. calc. for $C_{17}H_{16}N_2O_3$ (296.32): C, 68.91; H, 5.44; N, 9.45%. Found: C, 69.14; H, 5.32; N, 9.61%.

1,2-Dihydro-5-benzoyl-2,6-diphenyl-1-methyl-3*H*-indazol-3-one 53:

Light yellow crystals; mp 58-59°C (ether-hexane); Yield 80%.

IR (KBr): ν_{max} = 1658 (br), 1616, 1491, 1315 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.27 (s, 3H, NCH_3), 7.25-7.37 (m, 9H, ArH), 7.45-7.63 (m, 5H, ArH), 7.69-7.74 (m, 2H, ArH), 8.09 (s, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.13, 113.90, 116.94, 123.90, 126.20, 126.79, 128.04, 128.27, 128.46, 128.81, 129.30, 130.01, 133.02, 134.38, 134.74, 137.52, 139.87, 147.13, 151.95, 161.53, 196.94.

MS: (m/z, %): 404 (M^+, 82.4), 389 (19).

Anal. calc. for $C_{27}H_{20}N_2O_2$ (404.47): C, 80.18; H, 4.98; N, 6.93%. Found C, 79.91; H, 5.06; N, 7.02%.

1,2-Dihydro-2,6-diphenyl-1-methyl-5-nitro-3*H*-indazol-3-one 55:

Colourless crystals; mp 196°-197°C (chloroform-hexane); Yield 58%.

IR (KBr): ν_{max} = 1675, 1623, 1522, 1344 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 3.32 (s, 3H, NCH_3), 7.31 (s, 1H, H-7), 7.40-7.75 (m, 10H, ArH), 8.66 (s, 1H, H-4).

MS (m/z, %): 345 (M^+, 100).

Anal. calc. for $C_{20}H_{15}N_3O_3$ (345.36): C, 69.56; H, 4.38; N, 12.17%. Found C, 69.73; H, 4.47; N, 12.09%.

1,2-Dihydro-1-methyl-5-nitro-2-phenyl-6-methylthio-3*H*-indazol-3-one 57:

Light yellow crystals; mp 200-201°C (chloroform-hexane); Yield 65%.

IR (KBr): ν_{max} = 1673, 1615, 1512, 1296 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57 (s, 3H, SCH_3); 3.32 (s, 3H, NCH_3), 7.01 (s, 1H, H-7), 7.33-7.39 (m, 1H, ArH), 7.50-7.53 (m, 4H, ArH), 8.84 (s, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.70, 38.36, 106.92, 114.44, 124.20, 124.29, 127.38, 129.46, 134.19, 141.20, 145.45, 152.04, 160.57.

MS (m/z, %): 315 (M^+, 100), 236 (53).

Anal. calc. for $C_{15}H_{13}N_3O_3S$ (315.35): C, 57.13; H, 4.15; N, 13.33%. Found C, 57.43; H, 4.07; N, 13.50%.

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CHAPTER-IV

REACTION OF AROMATIC ALDEHYDES AND KETONES WITH HYDROGEN PEROXIDE IN THE PRESENCE OF BORIC ACID AND SULPHURIC ACID: AN IMPROVED PROCEDURE FOR DAKIN OXIDATION*.

Reaction of hydrogen peroxide with *ortho-* or *para-* hydroxybenzaldehydes in the presence of sodium or potassium hydroxide leads to the conversion of aldehyde functionality into the corresponding phenolic hydroxyl group (Scheme-1). The reaction is known as Dakin oxidation[1].

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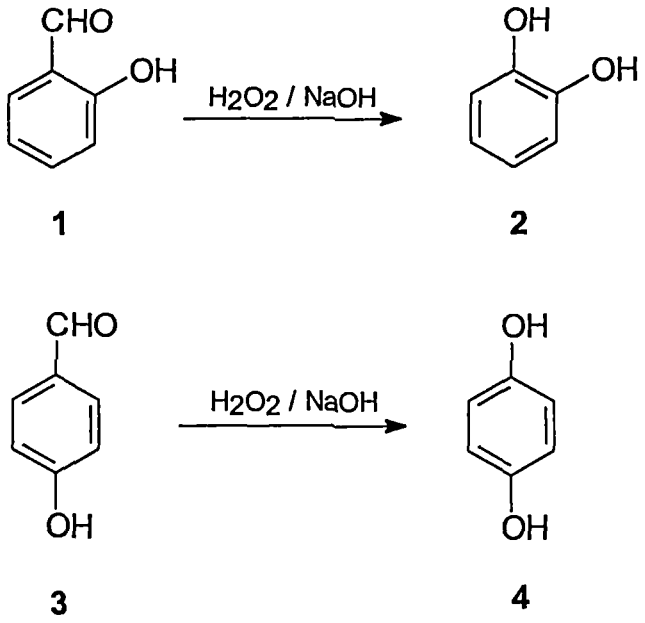
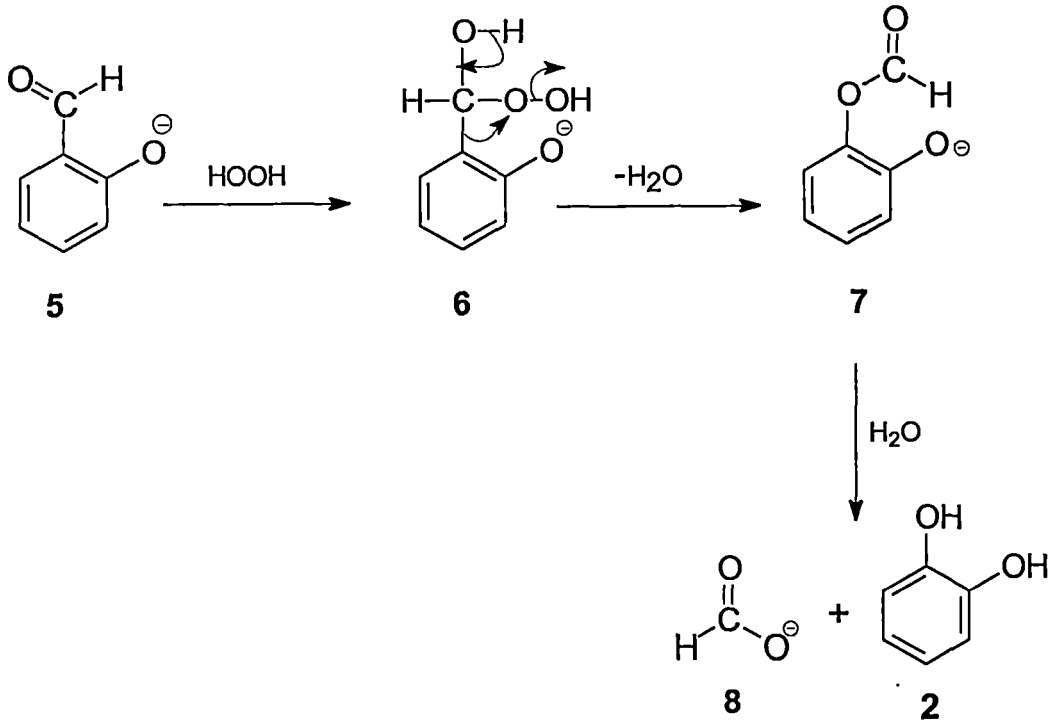
*Amrita Roy, K. R. Reddy, Pramod K. Mohanta, H.Ila, H.Junjappa

Synthetic Commun. **1999**, 29, 0000



Scheme-1

The method has been used extensively since 1909 for transforming aldehyde functional groups to the phenolic group. The mechanism governing the rearrangement has been elucidated as formulated in Scheme-2[2,3]. The hydrogen peroxide anion generated in the presence of sodium hydroxide adds to aldehyde to yield the corresponding peroxy carbinol **6** which follows rearrangement involving aryl group migration to give unstable formate **7** which on hydrolysis yields the corresponding catechol **2**. The method has been subsequently modified to contain all aromatic aldehydes using hydrogen peroxide in the presence of various acids since hydrogen peroxide

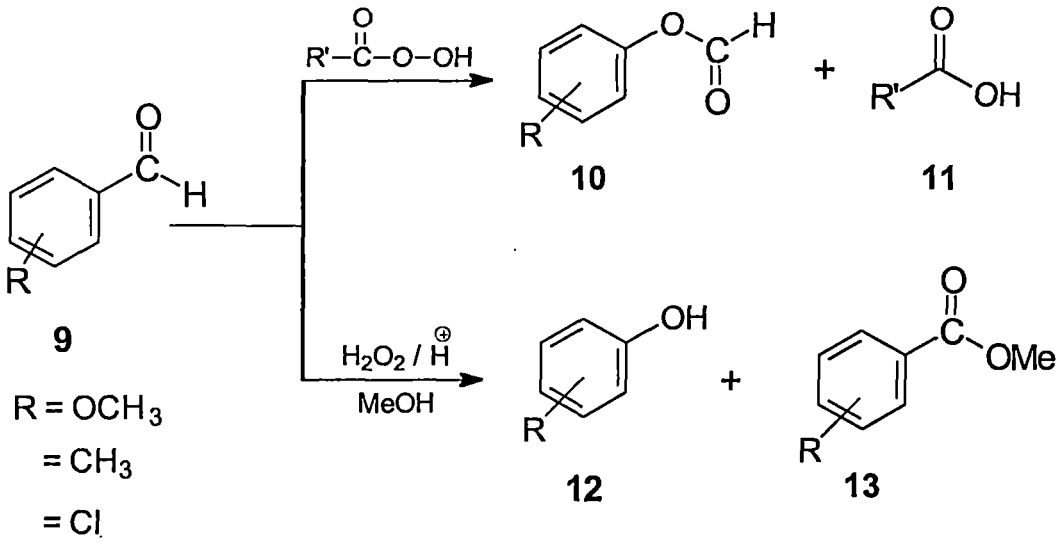


Scheme-2

is quite a weak oxidizing agent and requires specific activation towards functional groups to be transformed. These modifications are important because the Dakin oxidation as described by him in the original papers was confined to *ortho-* and *para-* hydroxybenzaldehydes[4].

Kobayashi and co-workers[5] reported acid-catalyzed conversion of benzaldehydes to phenols in the presence of hydrogen peroxide. The yields of the corresponding phenols were pretty high for those benzaldehydes carrying

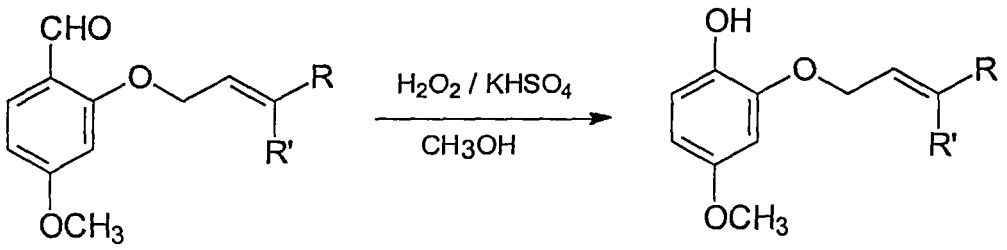
methoxy substituents, though 3-methoxy benzaldehyde gave only the corresponding methylbenzoate. The results showed that under these reaction conditions the transformation of aldehydes to phenols are more selective than



Scheme-3

the peracid oxidation method[6] though the migratory aptitude of aryl groups compared with the hydrogen of the aldehyde were identical with the Baeyer-Villiger oxidation (Scheme-3).

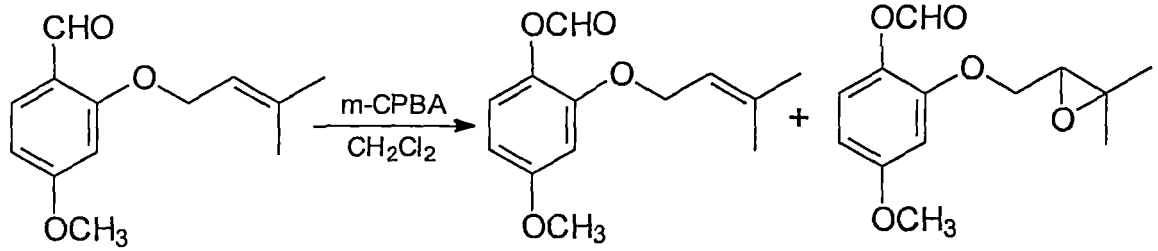
In a typical example (Scheme-4) conversion of 4-methoxy-2-(3-methyl-2-buten-1-yloxy) benzaldehyde **14a** in the presence of H_2O_2 and acidic methanol ($KHSO_4$) yielded the corresponding phenol **15a** in 80% yield.



14 **14 ,15** a R = CH_3 = R' **15**

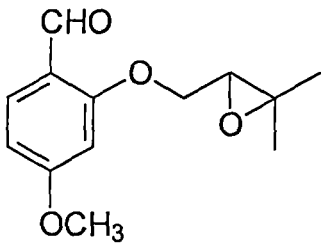
b R = CH_3, R'= H

c R = R' =H



14a **16** (18%) **17**(30%)

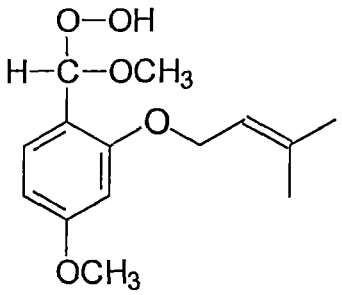
+



18 (40%)

Scheme-4

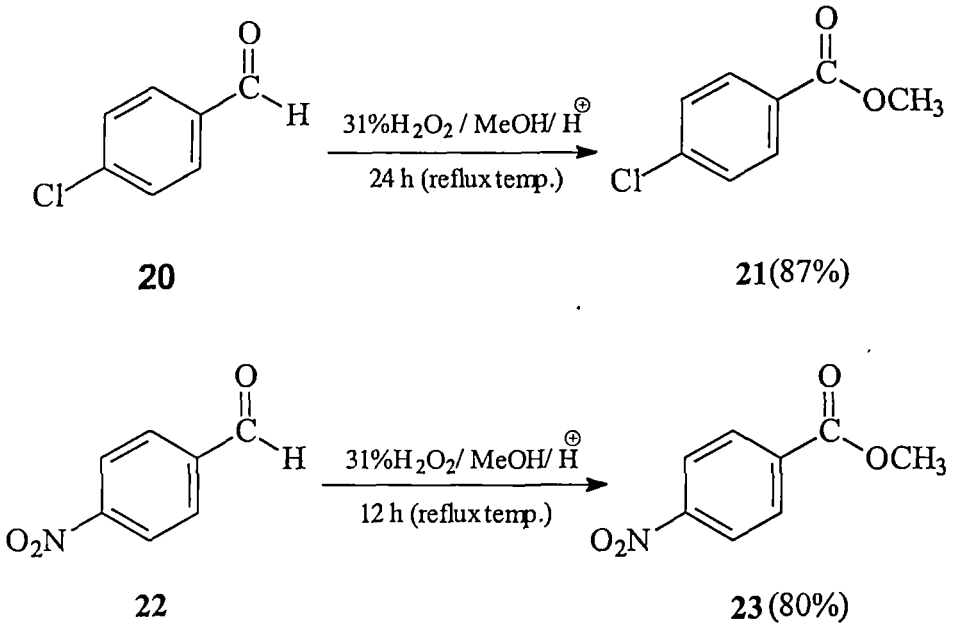
However, **14a** in the presence of m-CPBA gave a mixture of formate **16** and epoxide **17** and epoxy aldehyde **18** in 18%, 30% and 40% yields respectively. A peroxy hemiacetal intermediate **19** is proposed as one of the possible intermediates in overall conversion.



19

Hemiacetal

The reaction with *p*-chloro- (**20**) and *p*-nitrobenzaldehydes (**22**) (Scheme-5) however led to the formation of the corresponding esters **21**and **23** respectively involving hydrogen in preference to aryl migration.

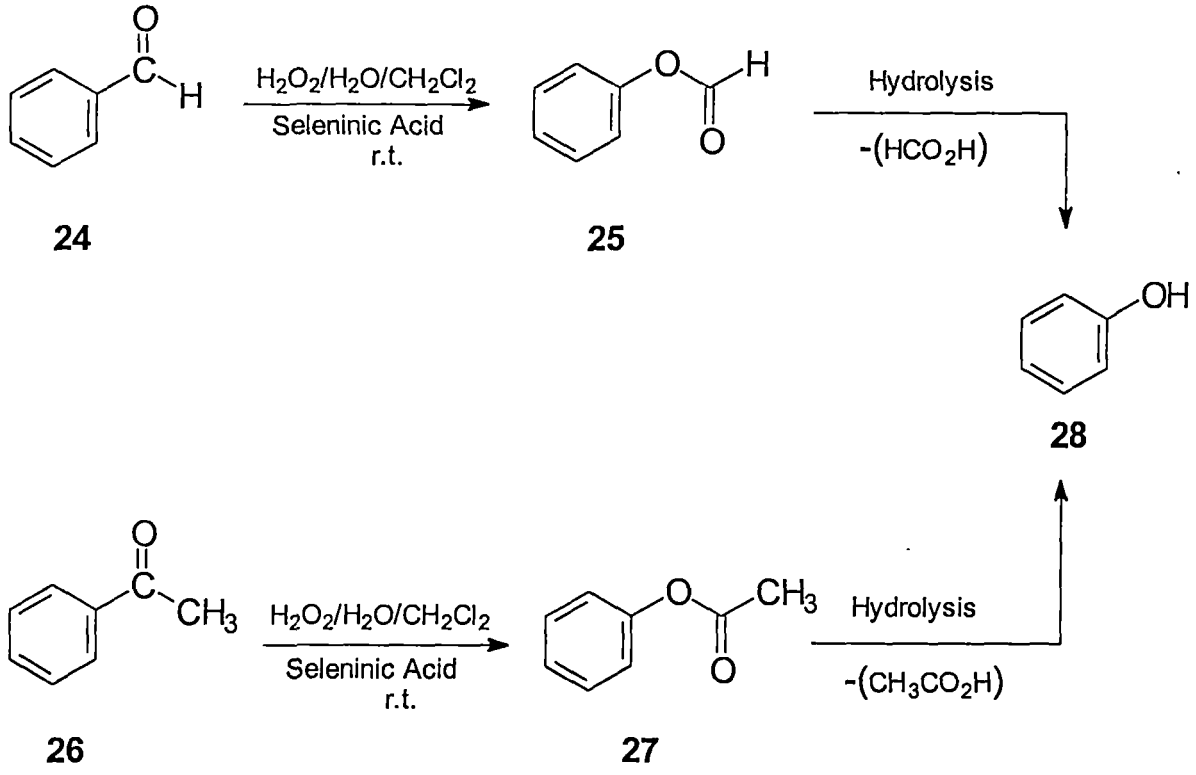


20 **21**(87%)

22 **23** (80%)

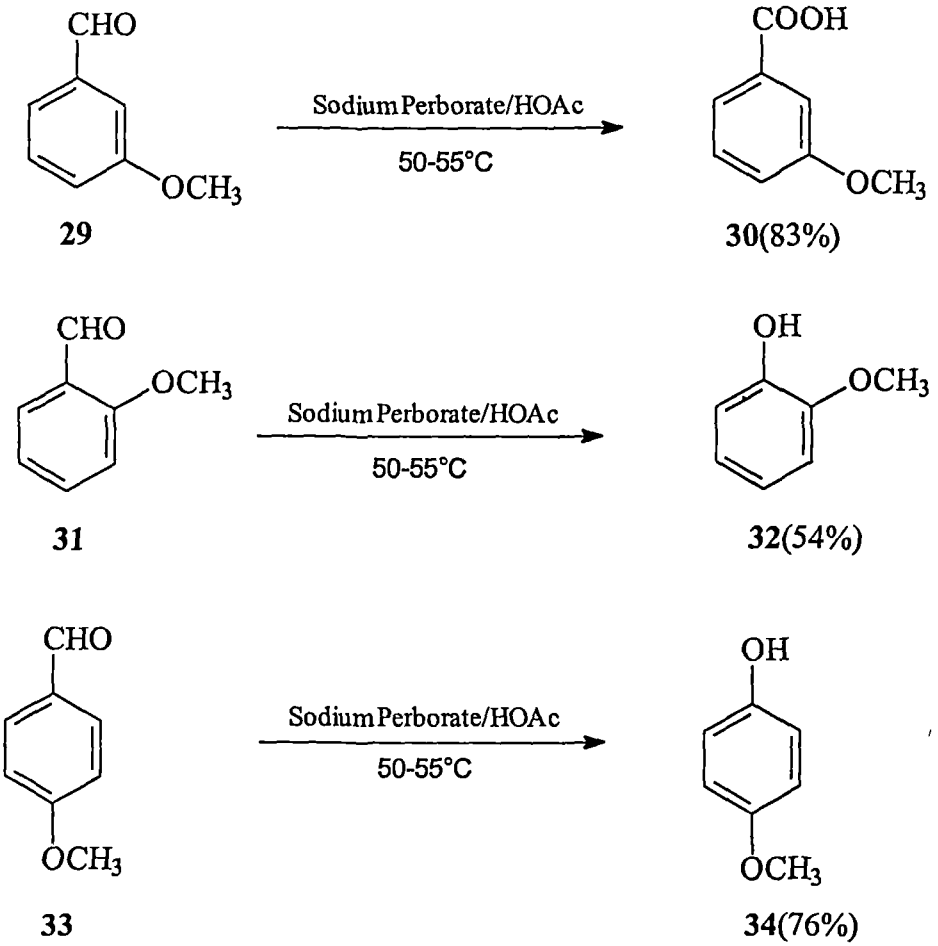
Scheme-5

Syper[7] discovered that aromatic aldehydes could be converted into phenols in the presence of seleninic acids. A series of substituted and polycondensed benzaldehydes were studied by this method utilizing areneseleninic acid activated hydrogen peroxide to oxidize to the corresponding arylformates, which were subsequently hydrolyzed to respective phenols in good yields. The oxidizing species in these reactions has been shown to be organoperoxy seleninic acid[8] formed from seleninic acid and hydrogen peroxide[9,10]. A large number of substituted aldehydes were studied by this method (Scheme-6).



Scheme-6

McKillop and Kemp[11] have reported that sodium perborate in acetic acid is an effective reagent for the oxidation of aromatic aldehydes to carboxylic acids and the reaction proceeds well with aldehydes in which there is an electron-withdrawing group *ortho*, *meta*, or *para* to the aldehyde function. However with electron-donating groups in the *ortho* or *para* position, aldehydes undergo preferential Dakin type oxidation to give the corresponding phenols. Thus, while 3-methoxybenzaldehyde **29** gave



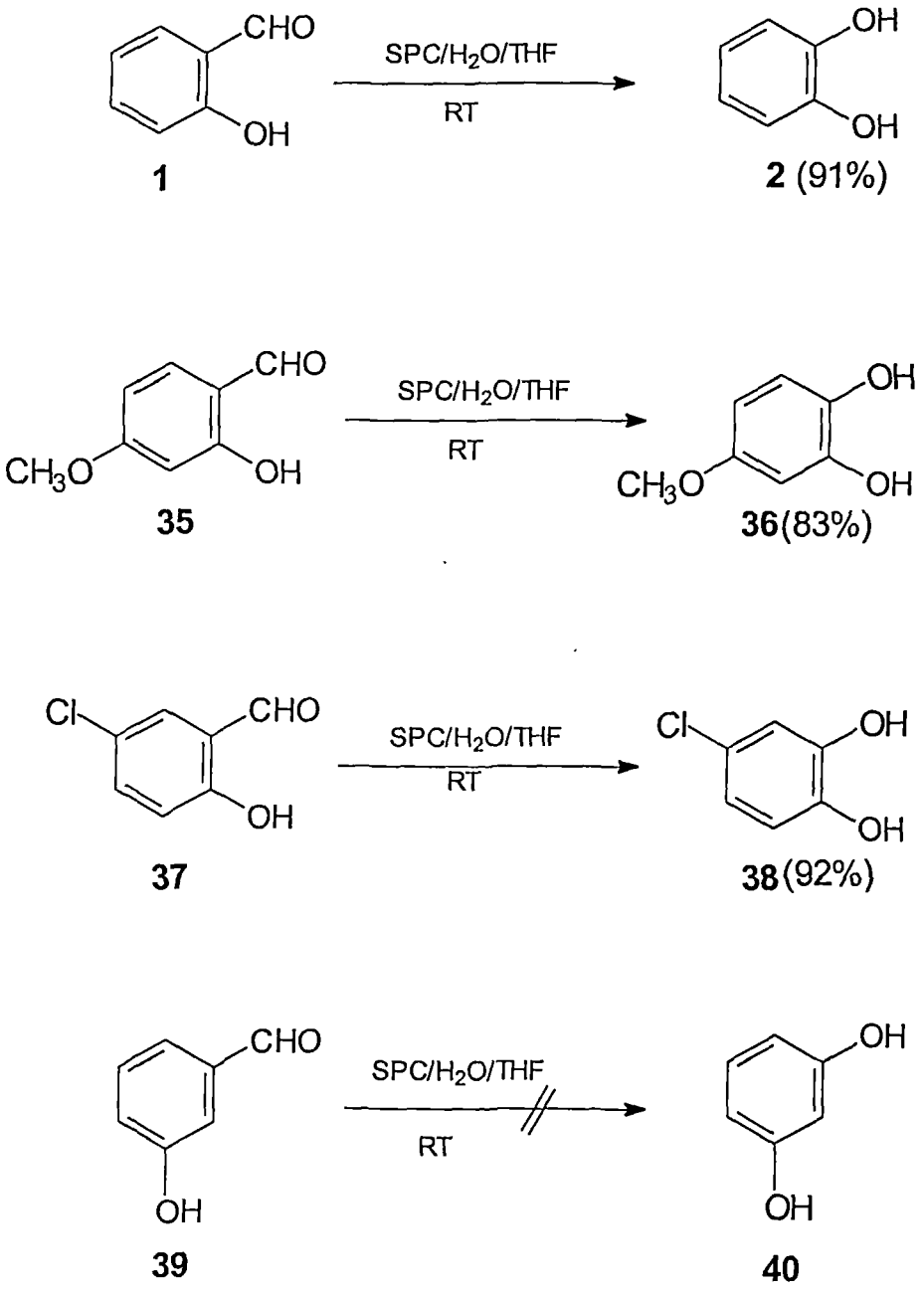
Scheme -7

3-methoxybenzoic acid **30** in 83% yield (Scheme-7) on treatment with sodium perborate in acetic acid at 50-55°C, 2-and 4-methoxybenzaldehydes (**31**and **33**) gave the corresponding 2- and 4-methoxyphenols **32** and **34** respectively in 54% and 76% yields (Scheme 7).

Kabalka and co-workers[12]have examined the reaction of sodium percarbonate (SPC) with various hydroxylated benzaldehydes and observed a facile rearrangement of the aldehyde group transformed into hydroxyl group. Sodium percarbonate (SPC) is a precursor of peroxy ion and is very cheaply available as it is used extensively as a bleaching agent[13] in detergent industry. Thus sodium percarbonate (SPC) in aqueous tetrahydrofuran under sonification has been used for the oxidation of a range of salicylaldehydes. Here again *o*-hydroxybenzaldehyde reacted faster than *p*-hydroxybenzaldehyde. The *m*-hydroxybenzaldehyde however failed to undergo oxidation (Scheme-8).

In the above discussion we have briefly described the reactivity of hydrogenperoxide towards aromatic aldehydes in the presence of base as well as acids. The earlier Dakin oxidation was generally carried out in the presence of base when the rearrangement followed the aryl group migration to yield corresponding catechols from salicylaldehydes. The same rearrangement was

also examined under Baeyer-Villiger in the presence of H_2O_2 and acidic methanolic medium.



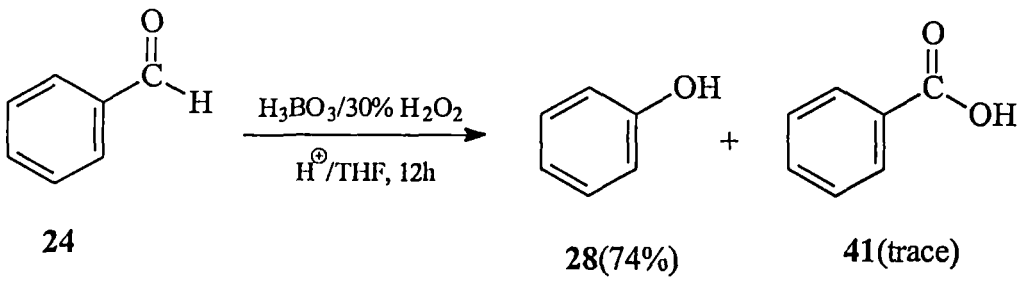
Scheme-8

The conversion of aldehydes to phenols was also quite facile, under these reaction conditions. However the method was limited to aldehydes with electron donating substituents and often the *p*-chloro and *p*-nitrobenzaldehyde yielded benzoic acid rather than phenols. Subsequently Syper discovered that arylseleninic acid is a useful catalyst in the aromatic aldehyde-hydrogenperoxide sequence to yield the corresponding arylformates[14,15] in high yields. The organoperoxy seleninic acid has been shown to be the intermediate in these reactions. Sodium perborate (SPB) and sodium percarbonate (SPC) have also been shown to be versatile hydrogen peroxide activating reagents[16]. On the other hand sodium perborate in acetic acid has been shown to be an excellent agent for the high yield oxidation of aromatic aldehydes to the corresponding benzoic acid, though 2-and 4-methoxybenzaldehyde yielded the corresponding phenols following Dakin oxidation. Shimizu and Ogata[17]have suggested that sodium perborate/acetic acid system involves hydrogen peroxide activated by co-ordination with boric acid as the oxidizing species.

We have in the present investigation shown that 30% H_2O_2 mixed with boric acid in presence of sulphuric acid to yield an activated H_2O_2 system which reacts with various aromatic aldehydes and ketones to yield the corresponding phenols. These results are discussed in the following section.

RESULTS AND DISCUSSION

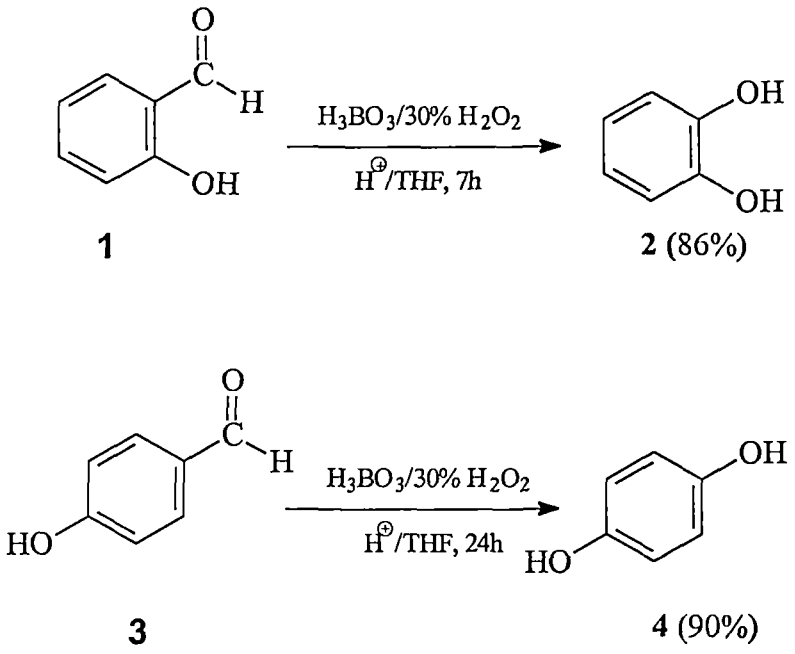
In a typical experiment, when a solution of benzaldehyde **24** (1 eqv.) in tetrahydrofuran was added to a mixture of 30% hydrogen peroxide (2.2 eqv.) and boric acid (5 eqv.) in tetrahydrofuran in the presence of trace of sulphuric acid, the reaction mixture after stirring (12 h) at room temperature followed by work-up yielded phenol **28** (Scheme-9) in 74% yield with a trace of benzoic



24 **28**(74%) **41**(trace)

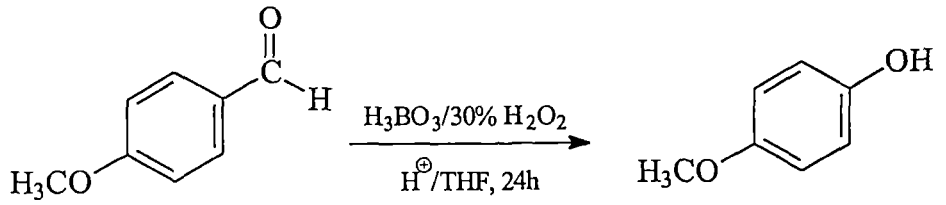
Scheme-9

acid. Similarly the 2- and 4-hydroxybenzaldehydes **1** and **3** were smoothly converted to the corresponding phenols **2** and **4** in 86% and 90% yields (Scheme-10).

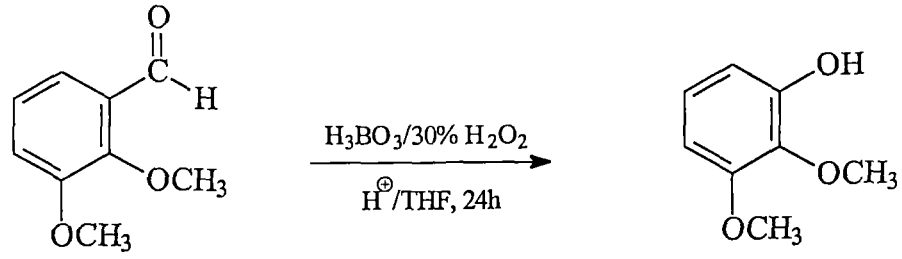


Scheme-10

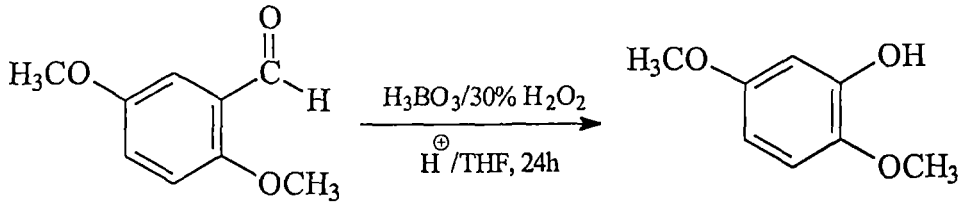
Also 4-methoxy **33**, 2,3-dimethoxy **42**, 2,5-dimethoxy **44** and 3,4-dimethoxy benzaldehydes **46** (Scheme-11) were converted to corresponding phenols **34, 43, 45** and **47** respectively in 70-97% overall yields. Oxidation of 3,4,5-trimethoxybenzaldehyde **48** yielded the corresponding trimethoxyphenol **49** in 60% yield. Similarly 2-allyloxybenzaldehyde **50** and 3,4-methylenedioxy benzaldehyde **52** on oxidation under identical reaction conditions gave the



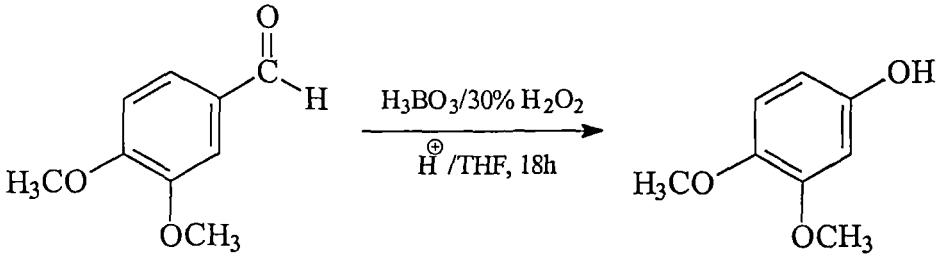
33 **34** (97%)



42 **43** (77%)

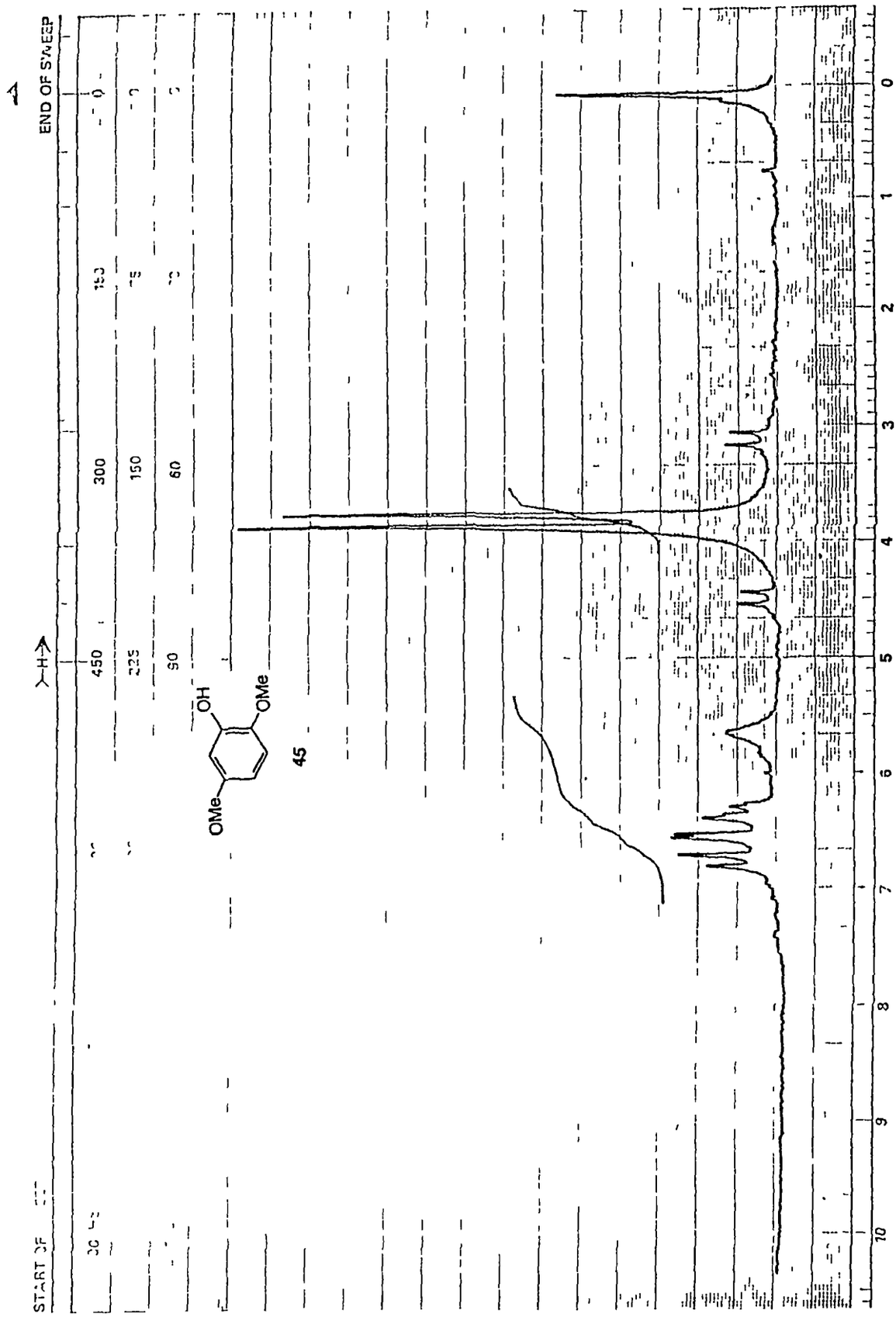


44 **45** (70%)

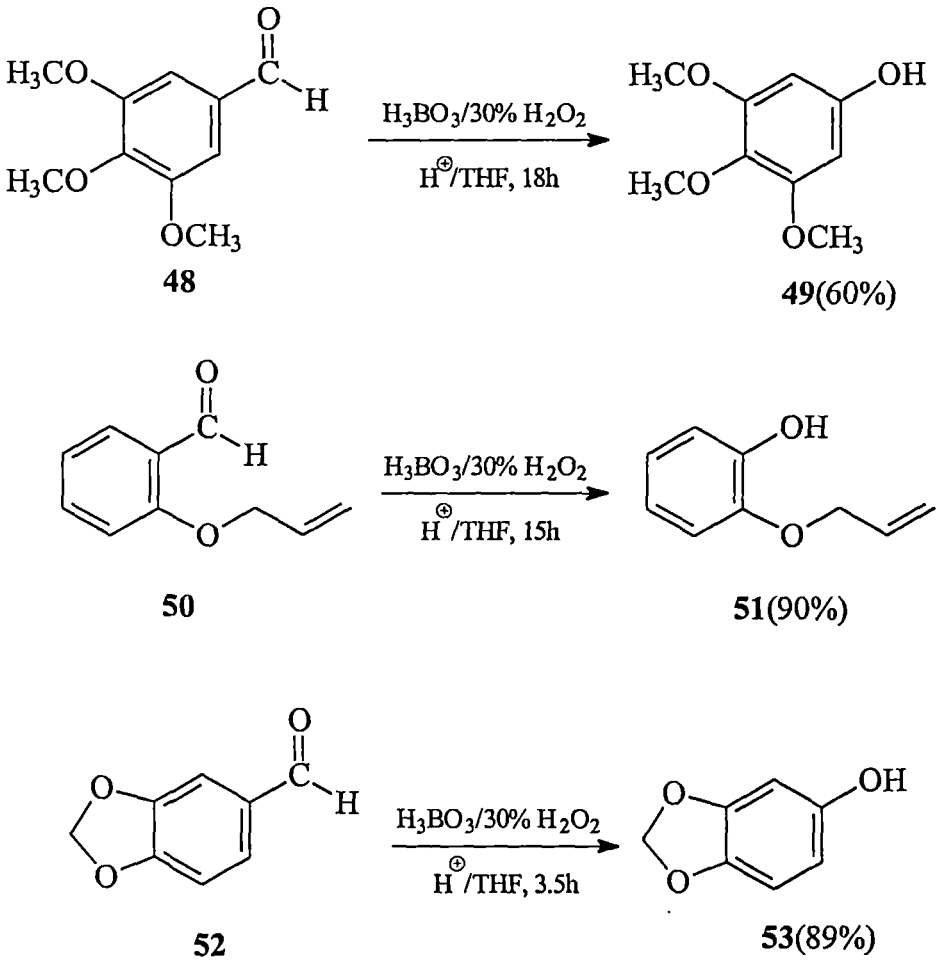


46 **47** (80%)

Scheme-11


END OF SWEEP
OH
OMe
OMe
45

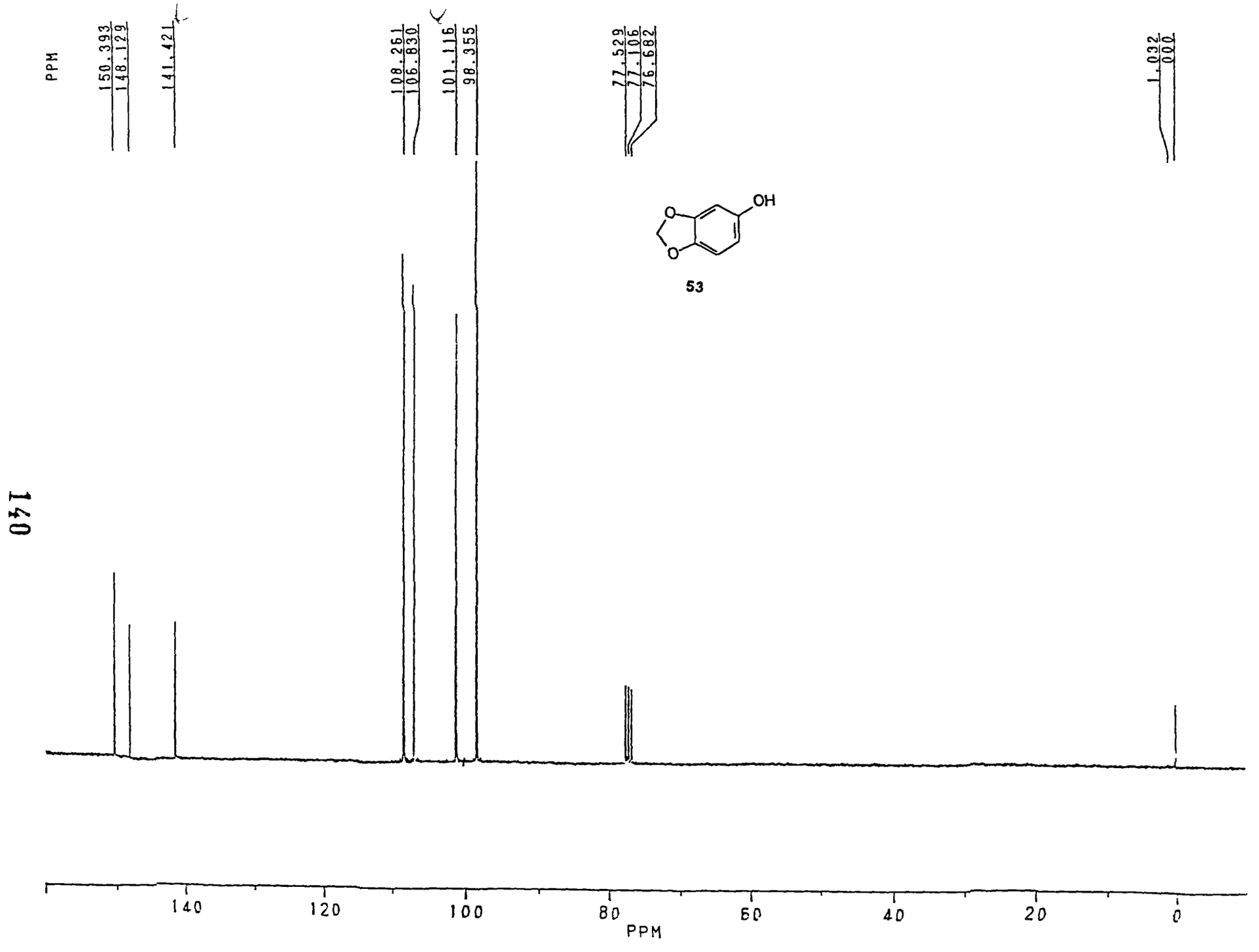
corresponding catechol monoallylether **51** in 90% and sesamol **53** in 89% yields respectively. The allylic side chain of the 2-allyloxybenzaldehyde remained unaffected under the given conditions (Scheme-12).



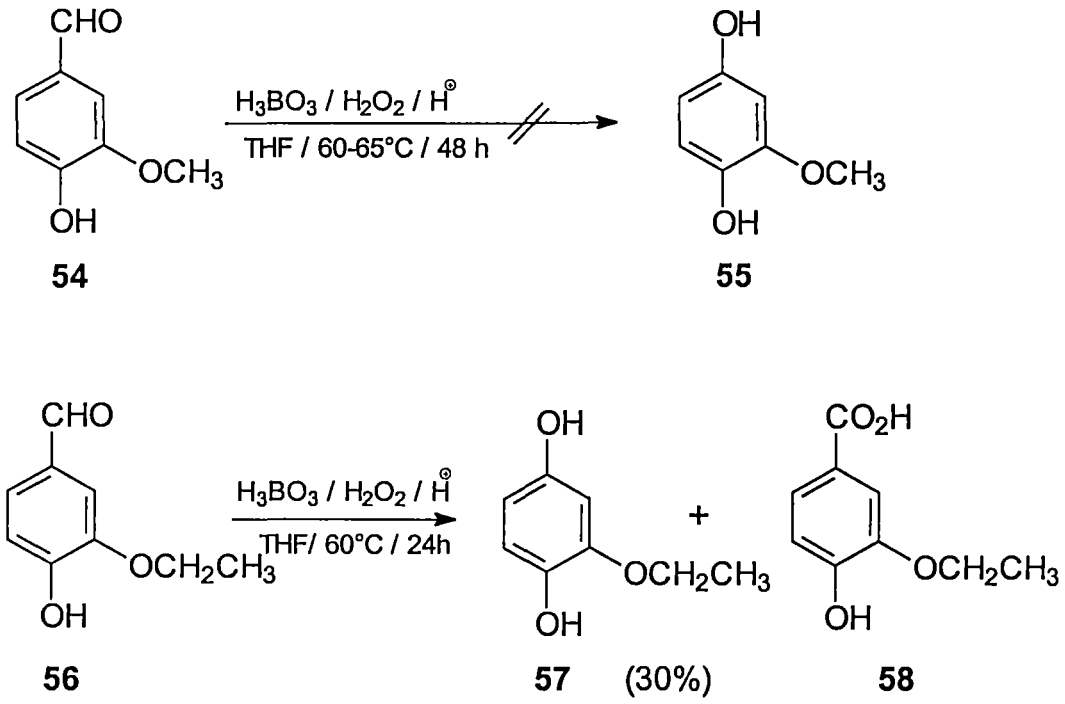
Scheme-12

6.91770
6.91473
6.91206
6.90952
6.82828
6.81354
6.80343
6.79670
6.79060
5.37275
5.36757
5.31527
5.26407
5.25963
5.22921
4.51382
4.51030
4.49550
4.49207
4.169
1.818
2.000
2.123
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
OH
O
51

OH
O
O
53
4.198
6.154
1.999
5.86809
6.26848
6.26020
6.24070
6.23228
6.42116
6.41302
6.63295
6.60521
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0


PPM
150.393
148.129
141.421
108.261
106.830
101.116
98.355
77.529
77.106
76.682
1.032
0.000
OH
O
O
53
140
140
120
100
80
60
40
20
0
PPM

However, Vanillin **54** failed to undergo the observed oxidation even after prolonged (48 h) heating at 60-65°C, while its ethoxy analog **56** yielded only 30% of phenol **57** with a trace of the corresponding benzoic acid **58** (Scheme-13).

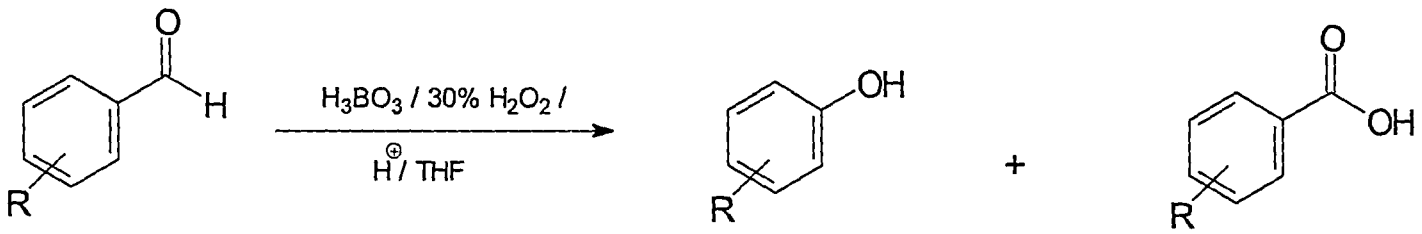


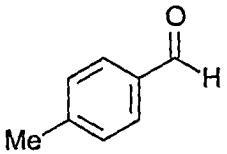
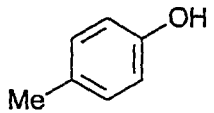
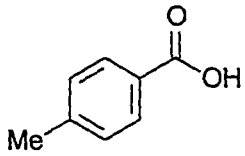
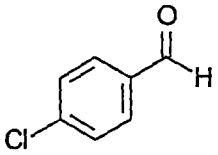
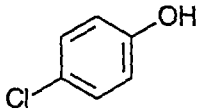
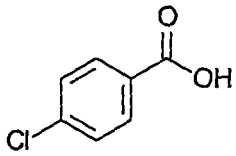
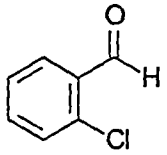
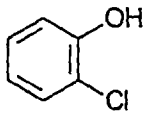
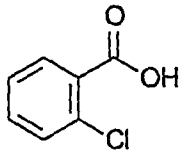
Scheme-13

The superiority of the present system was striking when it was applied to aromatic aldehydes with aryl group of lower migratory aptitude. Thus 4-methyl **59**, 4-chloro **20**, 2-chloro **64** and 4-bromobenzaldehydes **67** yielded the corresponding phenols **60, 62, 65** and **68** respectively in moderate to good

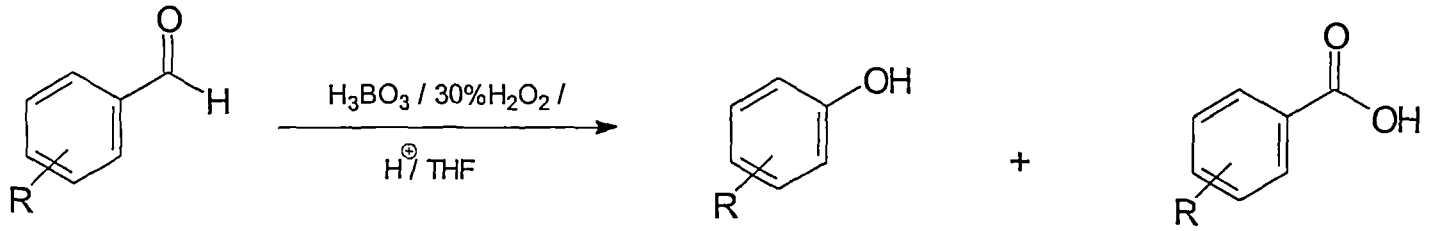
yields along with their respective acids **61, 63, 66** and **69**. Interestingly, 4-nitrobenzaldehyde **22** yielded a surprisingly high yield (70%) of 4-nitrophenol **70**. These yields are highest for Dakin oxidation among all other oxidation systems so far reported. However 2-nitrobenzaldehyde **72** gave only a trace of the corresponding phenol **73** along with 2-nitrobenzoic acid **74**. Thus the present system directs Dakin oxidation more selectively than the peracid oxidation and the migratory aptitude of the aryl groups compared to hydrogen in these aldehydes are not similar to those reported in conventional Baeyer-Villiger oxidations[18] (Scheme-14)

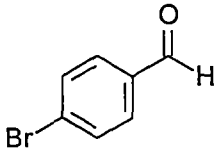
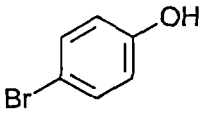
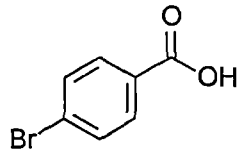
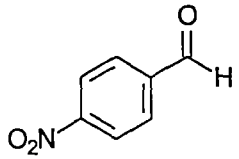
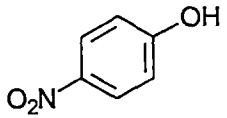
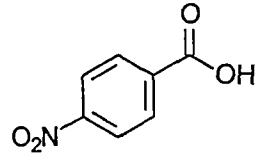
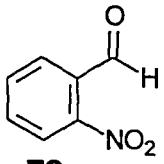
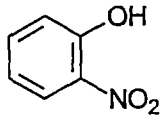
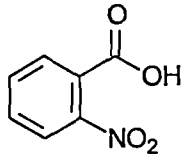
Besides aromatic aldehydes, we have also examined the applicability of this method for the direct oxidation of acetophenones to phenols (Scheme-15). The *o*- and *p*-hydroxyacetophenones are known to get smoothly converted to the corresponding phenols under Dakin reaction conditions using alkaline hydrogen peroxide[4], while *p*-hydroxyacetophenone failed to undergo the observed oxidation with sodium percarbonate system even under sonification[12]. The other *p*-substituted acetophenones (i.e 4-methoxy, 4-methyl, 4-chloro, 4-bromo and 4-phenyl) are reported to furnish *p*-substituted benzoic acid when oxidized with alkaline *t*-butylhydroperoxide[19]. On the other hand, oxidation of acetophenones to aryl formates under areneseleninic acid/H_2O_2 system involves drastic reaction conditions (90%H_2O_2) and requires at least two activating methoxy groups in the aryl ring. Also Baeyer-Villiger



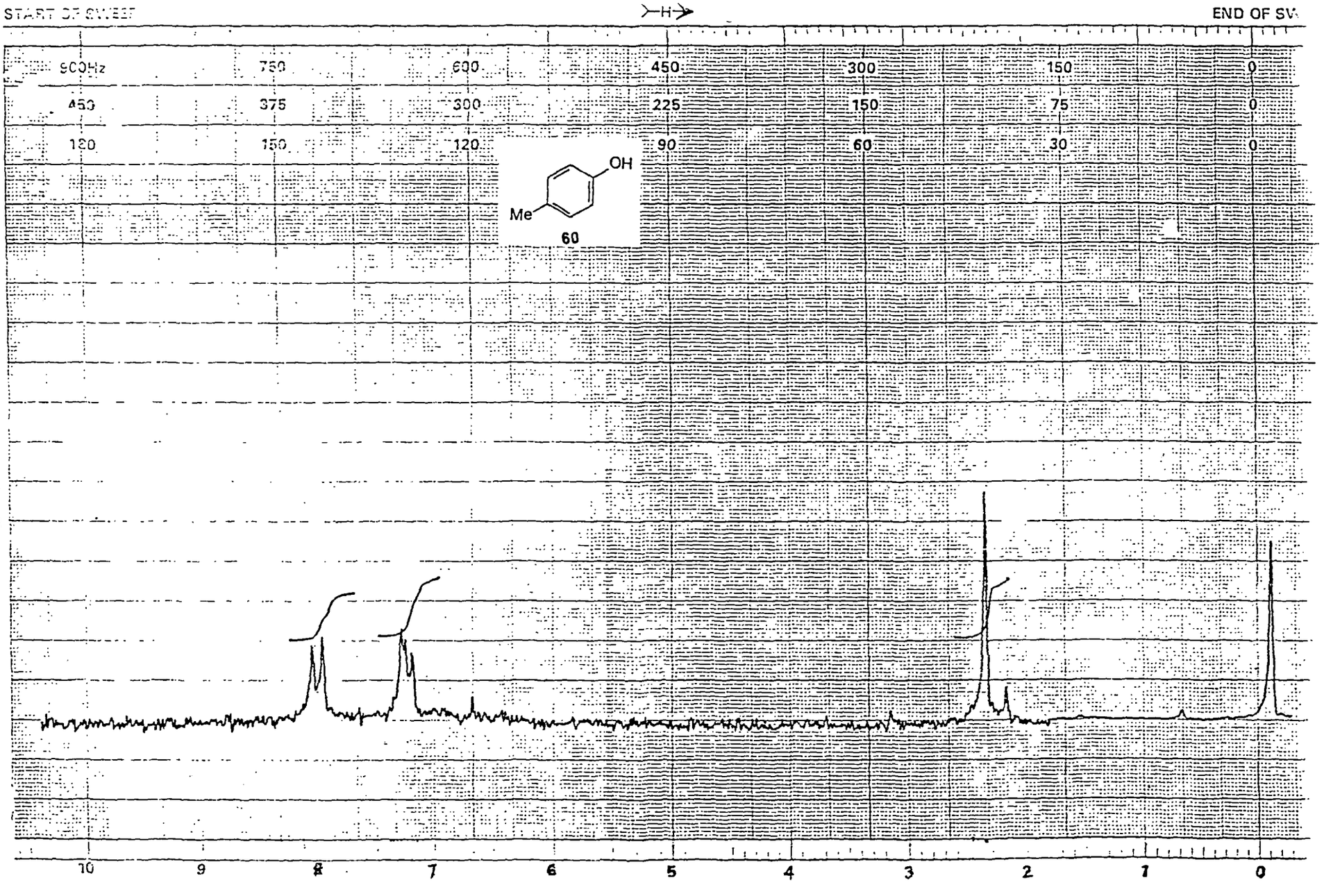
Aldehydes	Reaction Time(h)	Phenol	Acid
 **59**	48	 **60** (50 %)	 **61**(40 %)
 **20**	48	 **62** (60%)	 **63** (30%)
 **64**	19	 **65** (58%)	 **66** (20%)

Scheme-14a

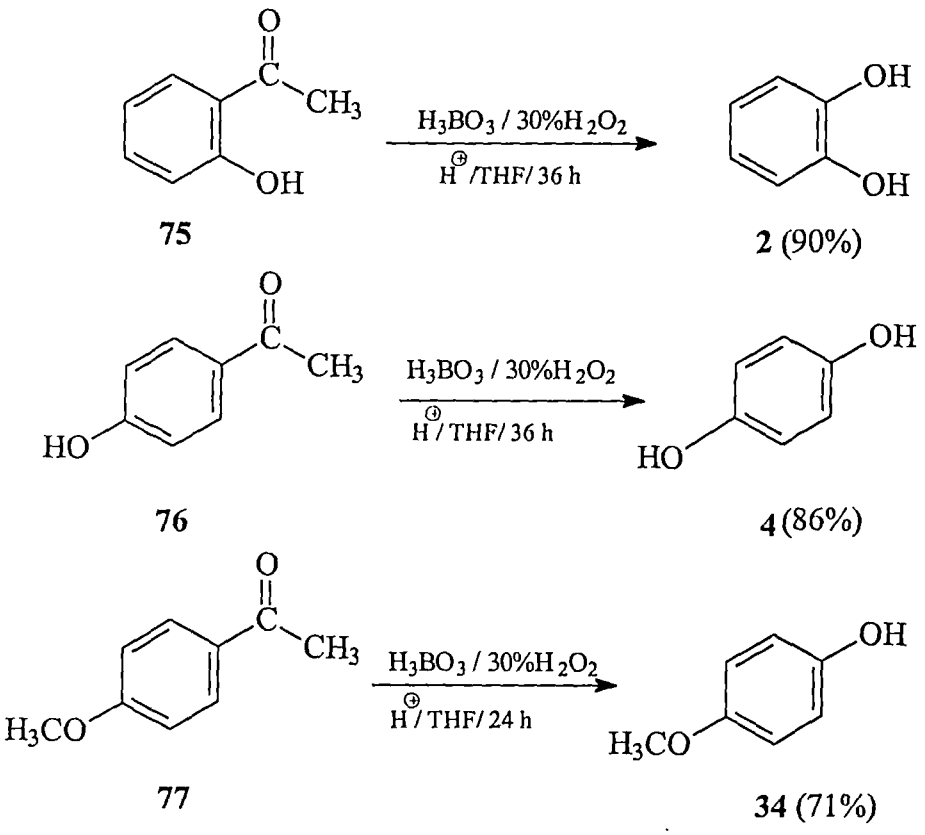


Aldehydes	Reaction Time(h)	Phenol	Acid
 **67**	48	 **68** (60 %)	 **69** (20 %)
 **22**	48	 **70** (70%)	 **71** (28%)
 **72**	50	 **73** (trace)	 **74** (60%)

Scheme-14b

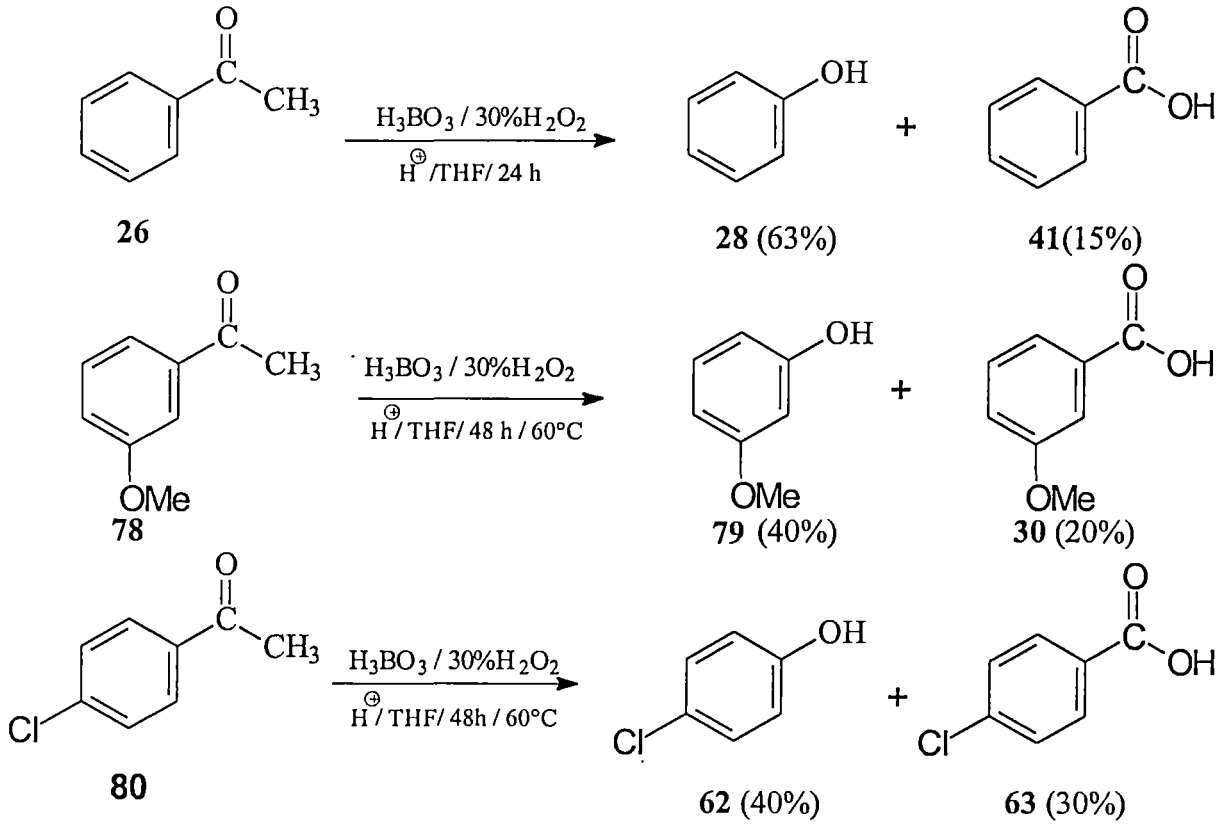

START OF SWEEP
H
END OF SW
900Hz
750
600
450
300
150
0
450
375
300
225
150
75
0
180
150
120
90
60
30
0
OH
Me
60
10
9
8
7
6
5
4
3
2
1
0

oxidation of ketones with sodium perborate in acetic acid gives the corresponding esters[20] and is effective with aromatic ketones which have at least one group of relatively high migratory aptitude. With our system, we have found that 2-hydroxy, 4-hydroxy and 4-methoxyacetophenones (**75-77**) are readily converted to the corresponding phenols **2**, **4** and **34** respectively in excellent yields (Scheme-15).



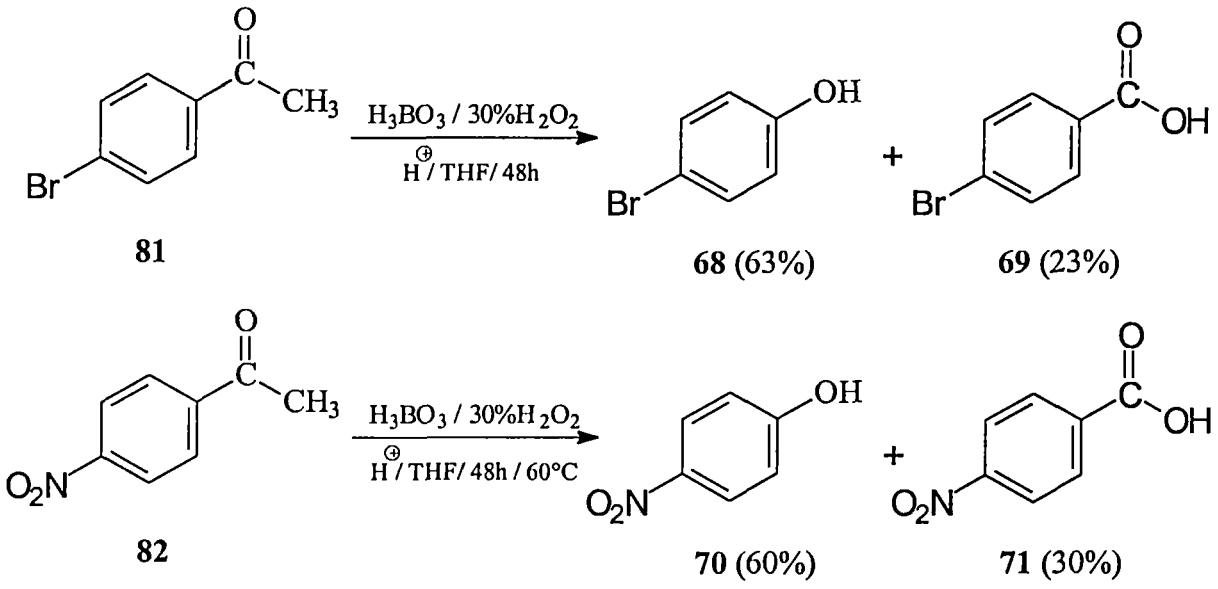
Scheme-15

Thus 2-hydroxyacetophenone **75** gave catechol **2** in 90% yield. Similarly hydroquinone **4** and *p*-methoxyphenol **34** were obtained from the corresponding acetophenones **76** and **77**. Acetophenone **26** and its 3-methoxy **78**, 4-chloro **80**, 4-bromo **81** and 4-nitro **82** derivatives with aryl groups of lower migratory aptitude could also be oxidized to the respective phenols in moderate to good yields along with the corresponding benzoic acids (Scheme-16). Similarly 1-acetylnaphthalene **83** under similar conditions gave the corresponding α-naphthol **84** in 40% yield.



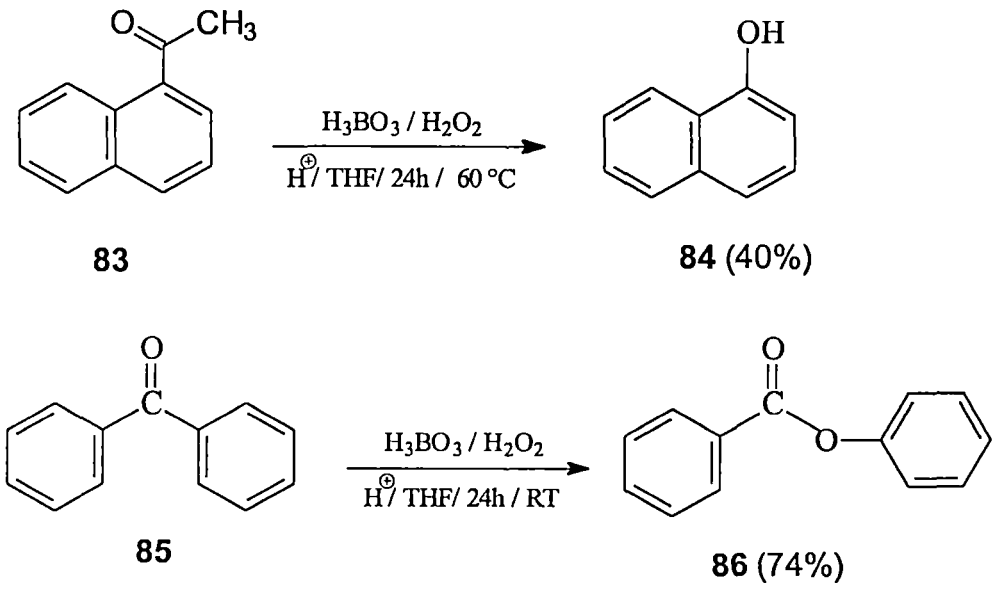
Scheme-16

Scheme-16 contd.



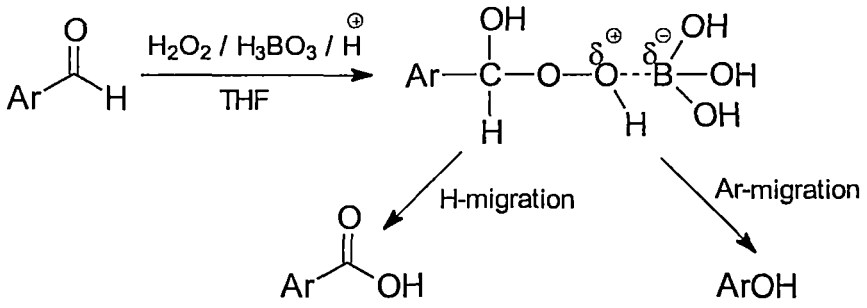
Scheme-16

However when benzophenone **85** was subjected to identical reaction conditions the corresponding phenylbenzoate **86** was obtained in 74 % yield instead of the phenol (Scheme-17).



Scheme-17

The oxidation appears to proceed by intermediacy of highly polarized boric acid co-ordinated H_2O_2-aldehyde adduct which on facile heterolytic cleavage of borate ion and concerted migration of aryl group affords phenol (Scheme-18).



Scheme-18

In summary we have demonstrated the feasibility of H_2O_2-H_3BO_3 oxidizing system for direct conversion of a variety of aromatic aldehydes and acetophenones to the corresponding phenols in higher yields compared to those reported earlier with various Dakin oxidation systems. Of particular importance is the oxidation of substrates having aryl ring with lower migratory aptitude which are incompatible with other oxidizing agents for which (i.e p-nitrobenzaldehyde) to our knowledge, there are no precedence in the literature.

EXPERIMENTAL SECTION

General

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer and the frequencies are expressed in cm^{-1}. ^1H NMR (90 MHz) were recorded on Varian EM-390 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane and coupling constants (J) are given in Hertz (Hz). Elemental analyses were carried out on a Heraeus CHN-O- Rapid analyzer.

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulfate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying potassium permanganate (acidic) solution. Column chromatography was carried out using ACME's silica gel (60-120 mesh).

Chemicals, Reagents and solvents.

Boric acid, 30% hydrogen peroxide were obtained commercially and used as such. Tetrahydrofuran was obtained anhydrous by distillation after the

characteristic blue colour of in situ generated sodium diphenyl ketyl was found to persist.

General Procedure for oxidation of Aromatic Aldehydes and ketones to phenols:

To a stirring mixture of boric acid (3.1 g, 50 mmol) and 30% hydrogen peroxide (2.5 g, 22 mmol) in dry THF (30 mL), conc. H_2SO_4 (1 mL) was added and the reaction mixture was further stirred at room temperature for 0.5h. A solution of benzaldehyde or ketone (10 mmol) in dry THF (10 mL) was added and the reaction mixture was further stirred at room temperature (or 60°C) till the reaction was complete (monitored by TLC). The reaction mixture was filtered and washed with THF, the filtrate was neutralized with aqueous saturated sodium hydrogencarbonate solution (A) and extracted with $CHCl_3$ (3×25 mL). The combined organic extract was washed with water (50 mL), dried over Na_2SO_4 (anhydrous) and was evaporated to give the respective crude phenols which were purified by passing through silicagel column using hexane as eluent. The bicarbonate layer (A) obtained earlier afforded the corresponding acids on acidification with HCl.

All the phenols and aromatic acids were identified by comparison of their physical (m.p.) and spectral data (IR,NMR) with that of authentic samples. Spectral data for few compounds are given below.

2-Hydroxyphenol 2:

Solid; mp 103-104°C (105°C, lit[21b]).

IR (KBr): ν_{max} = 3431, 1616, 1598, 1464.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 5.40 (br s, 1H, OH); 6.9 (m, 5H, ArH).

Anal. Calc. for $C_6H_6O_2$ (110): C, 65.45; H, 5.45%. Found C, 66.01, H, 5.51%.

4-Hydroxyphenol 4:

Dark brown solid; mp 170-171°C (170.5 °C, lit[21c]).

IR (KBr): ν_{max} = 1510, 1464.

1H NMR (90 MHz, $DMSOd_6$): δ = 6.58 (s, 4H, ArH); 8.42 (s, 2H, OH).

Anal. Calc. for $C_6H_6O_2$ (110): C, 65.45; H, 5.45%. Found C, 64.99; H, 5.51%.

4-Methoxyphenol 34:

Solid; mp 56-57°C (58°C, lit[7]).

IR (CCl_4): ν_{max} = 3364, 1507, 1493.

^{1}H NMR (90 MHz, CCl_4): δ = 3.7 (s, 3H, OCH_3); 5.8 (s, 1H, OH); 6.76 (m, 4H, ArH).

Anal. Calc. for $C_7H_8O_2$ (124): C, 67.74; H, 6.45%. Found C, 67.82, H, 6.71%

2,3-Dimethoxyphenol 43:

Liquid (lit[7]).

IR (KBr): ν_{max} = 3400, 1595, 1494, 1478.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.6 (s, 3H, OCH_3); 3.7 (s, 3H, OCH_3); 6.43-7.30 (m, 4H, ArH, OH)

Anal. Calc. for $C_8H_{10}O_3$ (154): C, 62.33; H, 6.49%. Found C, 62.35; H, 6.81%.

3,4 Dimethoxyphenol 47:

Solid; mp 78-80°C (81°C, lit[7]).

IR (KBr): ν_{max} = 1604, 1507, 1428.

^{1}H NMR (90 MHz, CCl_4): δ = 3.91 (s, 6H, OCH_3); 6.9 (d, J = 9 Hz, 2H, ArH); 8.01 (d, J = 9 Hz, 2H, OH ,ArH)

Anal. Calc. for $C_8H_{10}O_3$ (154.17): C, 62.33; H, 6.54%. Found C, 63.01; H, 6.31%.

3,4,5 Trimethoxyphenol 49:

Solid; mp 144-145°C (146-147°C, lit[21d])

IR (KBr): ν_{max} = 3489, 1650, 1606,1225.

^{1}H NMR (90 MHz, CCl_4): δ = 3.76 (s, 3H, OCH_3); 3.94 (s, 6H, OCH_3); 7.31-7.41 (m, 3H, ArH, ArOH)

Anal. Calc. for $C_9H_{12}O_4$ (185.20): C, 58.37; H, 6.53%. Found C, 58.27; H, 6.39%.

2-Allyloxyphenol 51:

Viscous liquid.

IR (CCl_4): ν_{max} = 3478, 1496, 1455

^{1}H NMR (300 MHz, $CDCl_3$); δ = 4.50 (dd, 2H, CH_2); 5.22-5.37 (m, 2H, H_{olef}); 5.93-6.06 (m, 1H, $H_{vinylic}$, OH), 6.79-6.92 (m, 4H, ArH).

Anal. Calc. For $C_9H_{10}O_2$ (150): C, 72.0; H, 6.66; found C, 71.99; H, 6.49%

3,4-Methylenedioxyphenol (sesamol) 53:

Solid, mp 65°C (68°C, lit[7]).

IR (KBr): ν_{max} = 3320, 1496, 1468

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (s, 2H, CH_2); 6.25 (dd, J = 9, 3 Hz, 1H, ArH); 6.41 (d, J = 3Hz, 1H, ArH); 6.41 (s, 1H, OH); 6.62 (d, J = 9Hz, 1H, ArH).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 98.36, 101.12, 106.83, 108.26, 141.42, 148.13, 150.39.

Anal. Calc. for $C_7H_6O_3$ (138): C, 60.87; H, 4.35%. Found C, 61.01; H, 4.29%.

4-Methylphenol 60:

Low melting solid, (36°C,lit [21f]).

IR (KBr): ν_{max} = 3067, 1672, 1607, 1415.

^{1}H NMR (90 MHz, CCl_4): δ = 2.48 (s, 3H, CH_3); 7.30-7.41 (m, 3H, ArH, ArOH),

Anal. Calc. for C_7H_8O (108.14): C, 77.71; H, 7.45%. Found C, 78.02; H, 7.39%.

4-Chlorophenol 62:

Low melting solid

IR (KBr): ν_{max} = 3402, 1588, 1488 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 6.8 (d, *J* = 9 Hz, 2H, ArH); 7.1-7.22 (m, 3H, ArH, OH).

Anal Calc. for C_6H_5OCl (128.45): C, 56.05; H, 3.89%. Found C, 56.09; H, 4.20%.

2-Chlorophenol 65:

Liquid, (lit[21g])

IR (KBr): ν_{max} = 3305, 1567, 1489.

^{1}H NMR (90 MHz, CCl_4): δ = 5.6 (br s, 1H, OH); 6.65-7.45 (m, 4H, ArH).

Anal. Calc. for C6H5Ocl (128.45): C, 56.05; H, 3.89%. Found C, 56.09; H, 4.20%.

4-Nitrophenol 70:

Light yellow solid; mp 112-113°C (114 °C, lit[21i]).

IR (KBr): ν_{max} = 3300, 1587, 1493.

^{1}H NMR (90 MHz, CCl_4): δ = 7.1 (d, *J* = 9Hz, 2H, ArH); 7.37 (s, 1H, OH); 8.33 (d, *J* = 9Hz, 2H, ArH).

Anal. Calc. for $C_7H_8O_2$ (124): C, 67.74, H, 6.45%. Found C, 66.98, H, 6.39%.

Phenylbenzoate 86:

Solid, mp 66-67°C (68°C, lit[21k]).

IR (KBr): ν_{max} = 1690, 1279.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.44- 7.55 (m, 6H, ArH); 7.7-8.10 (m, 4H, ArH).

Anal. Calc. For $C_{13}H_{10}O_2$ (198): C, 78.79; H, 5.05%. Found C, 78.63; H, 5.07%.

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