

**NEW SYNTHETIC ROUTES TO BIOLOGICALLY IMPORTANT
HETEROCYCLES**

by

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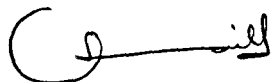
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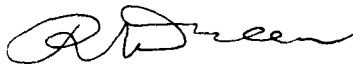
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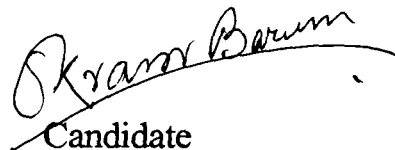
This is being submitted to the North-Eastern Hill University for the degree of Doctor of Philosophy in Chemistry.



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NEHU

..... *to my dear*
Nene (late)

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PREFACE

The importance of heterocycles in natural product chemistry and pharmacology constantly drives the search for new methods for their construction. Heterocyclic units such as indole, carbazole, carbolines, imidazole, benzimidazole, imidazopyridine and their analogues are of special interest in pharmacology, due to their important biological activities. The α -oxoketene dithioacetals are a versatile group of 3-carbon fragment synthons with ambident 1,3-electrophilic centers thus permitting to design various methodologies for the synthesis of both carbocycles and heterocycles. The work described in this thesis highlights the development of new methods for the synthesis of heterocycles of biological interest.

This thesis consists of four chapters. The first chapter gives a general introduction to polarized ketene dithioacetals and some of the recent transformations reported from this laboratory.

The second chapter deals with the synthesis of various substituted pyrido[2,3-*b*]-indoles by reacting with oxindole and various α -oxoketene dithioacetals in two steps. An attempt has been made to extend this new method for the synthesis of a synthetic anxiety agent 4-amino-3-carbethoxy-5,9-dimethylpyrido[2,3-*b*]indole.

The third chapter contains the synthesis of various substituted imidazo[1,2-*a*]-pyridines, which are potent antiviral agents, by a novel oxidative cyclization of N,O-, N,S-, and N,N-acetals using Cu(II)Cl_2 . A novel route for tetracyclic heteroaromatic salts having two bridgehead nitrogen atoms also has been achieved by a facile

cyclodehydration of 3-aryl-2-(2-pyridylamino)imidazo[1,2-*a*]pyridines in the presence of boron trifluoride etherate. Such compounds are potential DNA intercalators.

The fourth chapter contains the synthesis of functionalized and condensed benzo[*b*]thiophenes from thiophene-3-acetonitrile and α -oxoketene S,S-, O,S- and N,S-acetals.

Each chapter is framed with 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 present investigation are cited in the respective chapters.

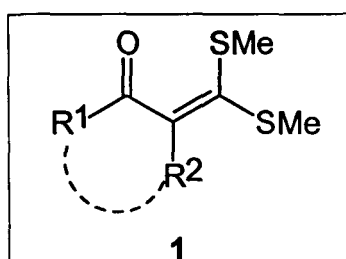
CHAPTER-1

GENERAL INTRODUCTION:

Polarized Ketene Dithioacetals: A Brief Review

The α -oxoketene dithioacetals are a versatile group of 3-carbon synthons with ambident 1,3-electrophilic centers thus permitting to design various methodologies for both carbocyclic and heterocyclic synthesis.

The α -oxoketene dithioacetals¹ of general formula 1, are among the simplest synthetic intermediates in organic synthesis. They can be easily prepared from a wide variety of active methylene compounds and carbon disulfide in the presence of a suitable base followed by alkylation often in one pot reaction in moderate to good yields. They have been recognized as useful building blocks in various synthetic transformations.



The α -oxoketene dithioacetals exhibit well defined physical properties either as crystalline solids or as distillable liquids and can be purified by conventional methods.

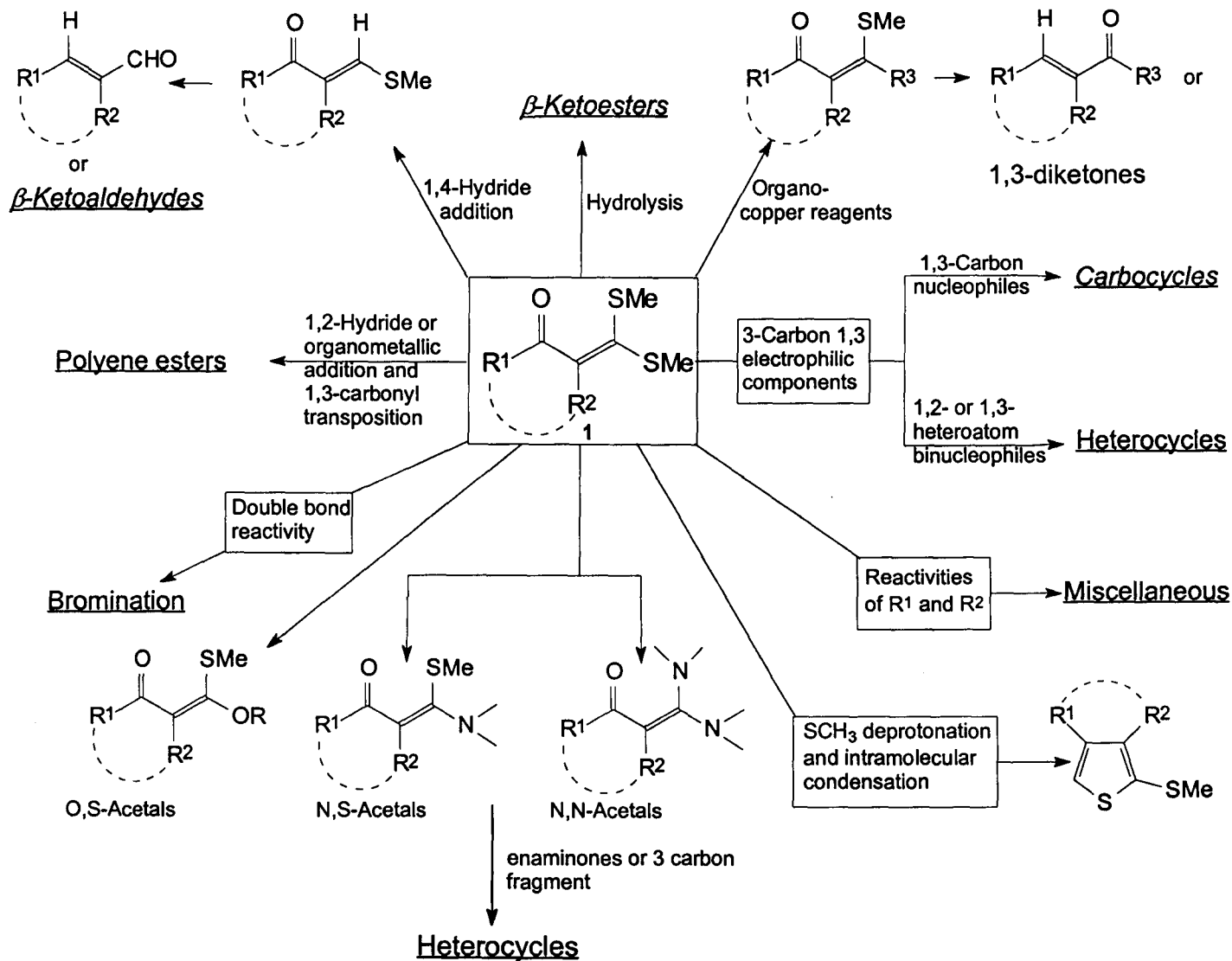
Kelber and co-workers² in 1910 first reported the synthesis of α -oxoketene dithioacetals. However, the chemistry of these intermediates remained unexplored, until Thuillier and co-workers³⁻⁶ prepared these compounds in high yields in one pot reaction by reacting the active methylene ketones with CS_2 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.⁷⁻¹¹

The α -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 functionalised β -carbon. The α -oxoketene dithioacetals have been shown to be excellent three carbon fragments possessing 1,3-electrophilic centers 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 carbon 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. The preparation of O,S-acetals is accomplished through displacement by an oxygen nucleophile of the

sulfonium salt¹² of the corresponding S,S-acetals. The N,S-acetals can be prepared by displacement of one of the thiomethyl groups by a suitable amine in refluxing ethanol^{13,14}.

Scheme-1 outlines various reactivity profiles of α -oxoketene dithioacetals of the general formula 1. Hydrides and organo metallic reagents give 1,2-addition products typical of carbonyl function reactivity¹⁷. These additions can be directed in a 1,4-manner by suitably manipulating the reagents and reaction conditions¹⁷⁻¹⁹. The differential electrophilicity at 1,3-carbon of the oxoketene dithioacetals have been judiciously utilized for the synthesis of both 5- and 6-membered heterocycles by reacting with 1,2- and 1,3-hetero atom binucleophiles respectively. The 1,3-carbon binucleophiles have been similarly used in the synthesis of carbocycles. The enolate anion formed by the deprotonation (when R=alkyl) can undergo condensation with aldehydes to give α -enyl ketene dithioacetals²⁰. The reactivity of the mercapto double bond is also exploited with electrophiles. The α -oxoketene dithioacetals 1 undergo bromination at α -position with N-bromo succinimide²¹. Thus it is apparent that the α -oxoketene dithioacetals 1 constitute an important class of synthon with reactive electrophilic and nucleophilic centres permitting reactions of great synthetic importance. Some of the selected transformations reported from our laboratory are briefly summarized.

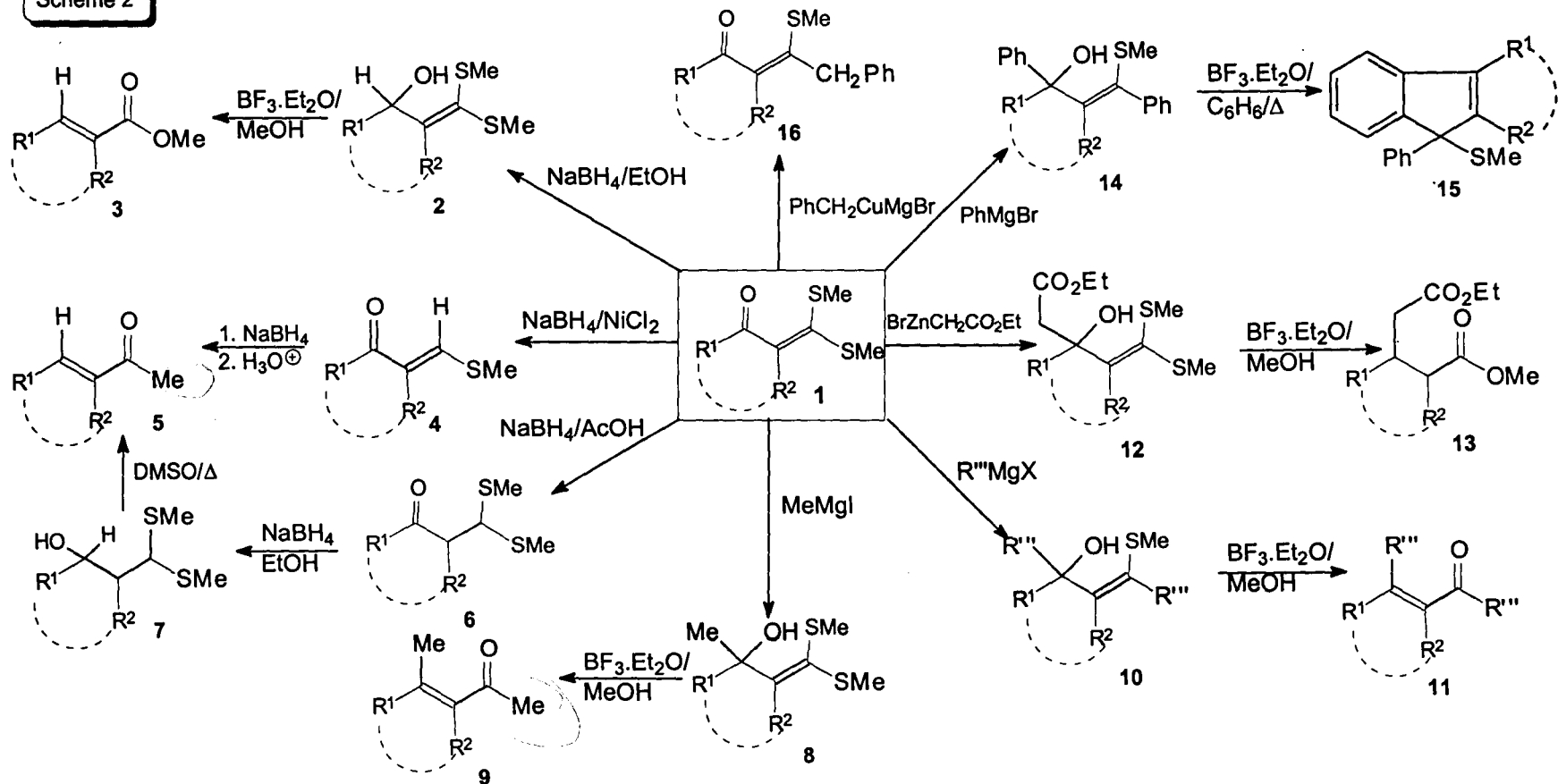
Scheme 1



The α -oxoketene dithioacetals **1** undergo chemoselective 1,2-reduction with sodium borohydride to give the corresponding carbinol acetals **2**. These carbinol acetals are shown to undergo smooth methanolysis in the presence of borontrifluoride-etherate to afford α,β -unsaturated methyl esters **3** in good yields (Scheme-2). The overall transformation can be viewed as homologation of active methyl-ketones at the α -position involving a 1,3-carbonyl transposition. Also the dithioacetals are shown to undergo reduction with $\text{NaBH}_4/\text{NiCl}_2$ to afford the corresponding β -methylthioalkenyl ketones **4**. The α -oxoketene dithioacetals were also shown to undergo conjugate 1,4-reduction in highly regio- and chemoselective manner with sodium borohydride with acetic acid to afford the corresponding β -oxodithioester **6**. These intermediates are hydrolyzed to α,β -unsaturated aldehydes **5**²⁴.

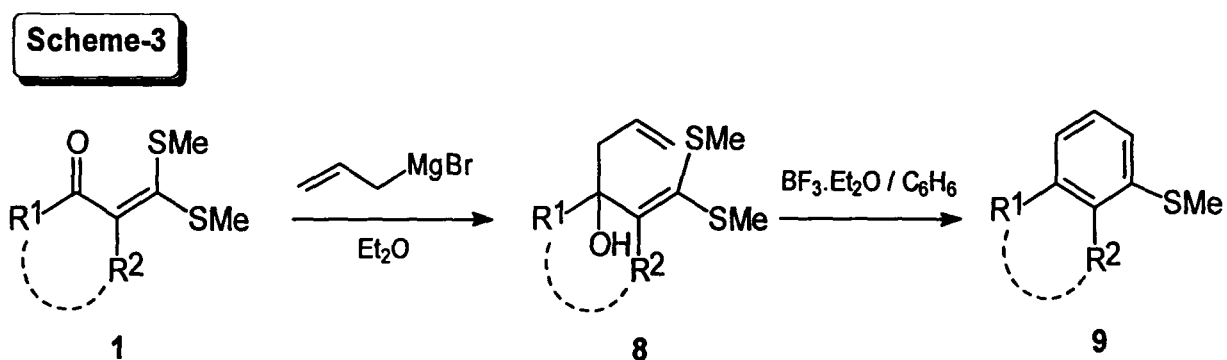
Methylmagnesium iodide was shown to react with α -oxoketene dithioacetals to afford the carbinol acetals **8** by 1,2-addition in good yields. The $\text{BF}_3 \cdot \text{Et}_2\text{O}$ assisted methanolysis of these carbinol acetals afforded the corresponding β -methyl- α,β -unsaturated esters **9** as exclusive *E* stereoisomers. The course of addition of higher alkyl Grignard reagents ($\text{R} = \text{Et}, \text{n-Pr}, \text{n-Bu}$) to α -oxoketene dithioacetals followed a sequential 1,4- and 1,2-addition pattern to afford carbinols **10** which are shown to afford α,β -unsaturated ketones **11** after subsequent hydrolysis in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ¹⁷. The 1,2-addition of ethylbromozinc acetate (Reformatsky reagent) to dithioacetals **1** to give the

Scheme 2



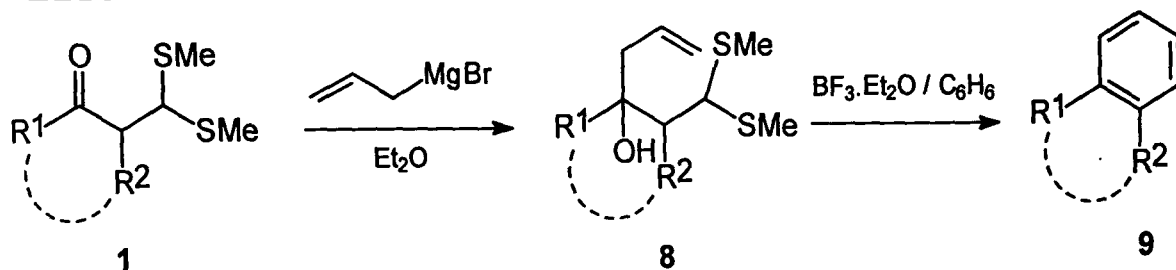
corresponding carbonyl acetals **12** which were found to undergo $\text{BF}_3 \cdot \text{Et}_2\text{O}$ assisted methanolysis to afford propene dicarboxylates **13**²³. The overall transformation is considered as a double 1,3-alkylative carbonyl transposition. Dieter and co-workers have reported the chemo- and stereoselective addition of organo cuprates to dithioacetals **1**^{18,19}. The α -oxoketene dithioacetals have also been extensively explored for the construction of numerous substituted and fused five and six membered heterocycles²⁵⁻³⁵ (Scheme 2).

Aromatic annelation strategy developed from our laboratory has emerged as an area of great synthetic potential. The reaction of allyl magnesium halides with α -oxoketene dithioacetals^{1b} of general formula **1** to afford the corresponding carbinol **8** followed by its acid assisted cyclization to the corresponding aromatic system **9** was discovered in our laboratory in 1984.³⁶



Subsequently it was shown that the β -oxodithioacetals **10** also react with allyl anions to yield the intermediate carbinols **11** which follow acid assisted cyclization to afford the corresponding benzenoids in excellent yields.⁴¹ The general applicability of this methodology has been extensively

Scheme-4



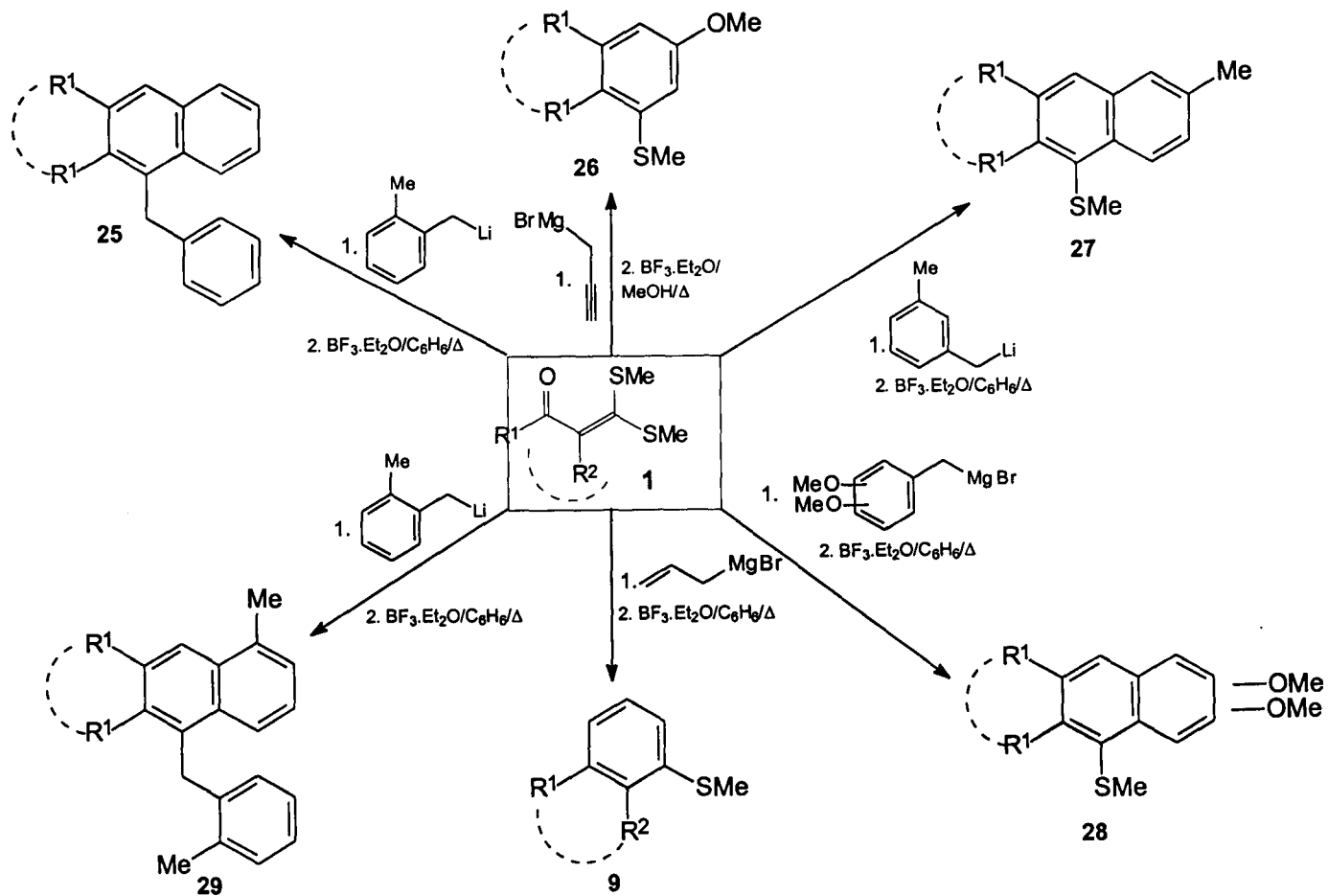
investigated involving application of wide variety of allyl anions and α -oxoketene dithioacetals as open chain precursors to construct regioselectively substituted aromatics in a simple two step sequence.³⁷ Apart from its application to the synthesis of benzenoids, naphthalenes, anthracenes, phenanthrenes and their higher analogs,³⁸⁻⁴² the method has been successfully extended for heteroaromatic annelation providing a new general approach for the construction of aromatic ring over the preconstructed heterocycles.⁴³⁻⁴⁹ This reverse approach for the synthesis of benzoheterocycles is unique with complete regiocontrol of the substituents of the newly formed benzene ring.

The all possible regiocontrol of the newly formed benzene ring is illustrated in schemes 5 and 6 which is self explanatory for the versatility of our heteroaromatic annelation methodology. We have demonstrated the application of this approach for the synthesis of benzisoxazoles,⁴³⁻⁴⁴ quinazolones,⁴⁶ indazolones,⁴⁷ and indoles,⁵¹ etc. This [3+3] aromatic annelation methodology has been extensively investigated to establish its general applicability. This 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, it was extended to methyl allyl magnesium bromide, crotyl magnesium bromide and propargyl magnesium bromide to afford the substituted benzoannulated products.³⁸ Subsequently this method of aromatic

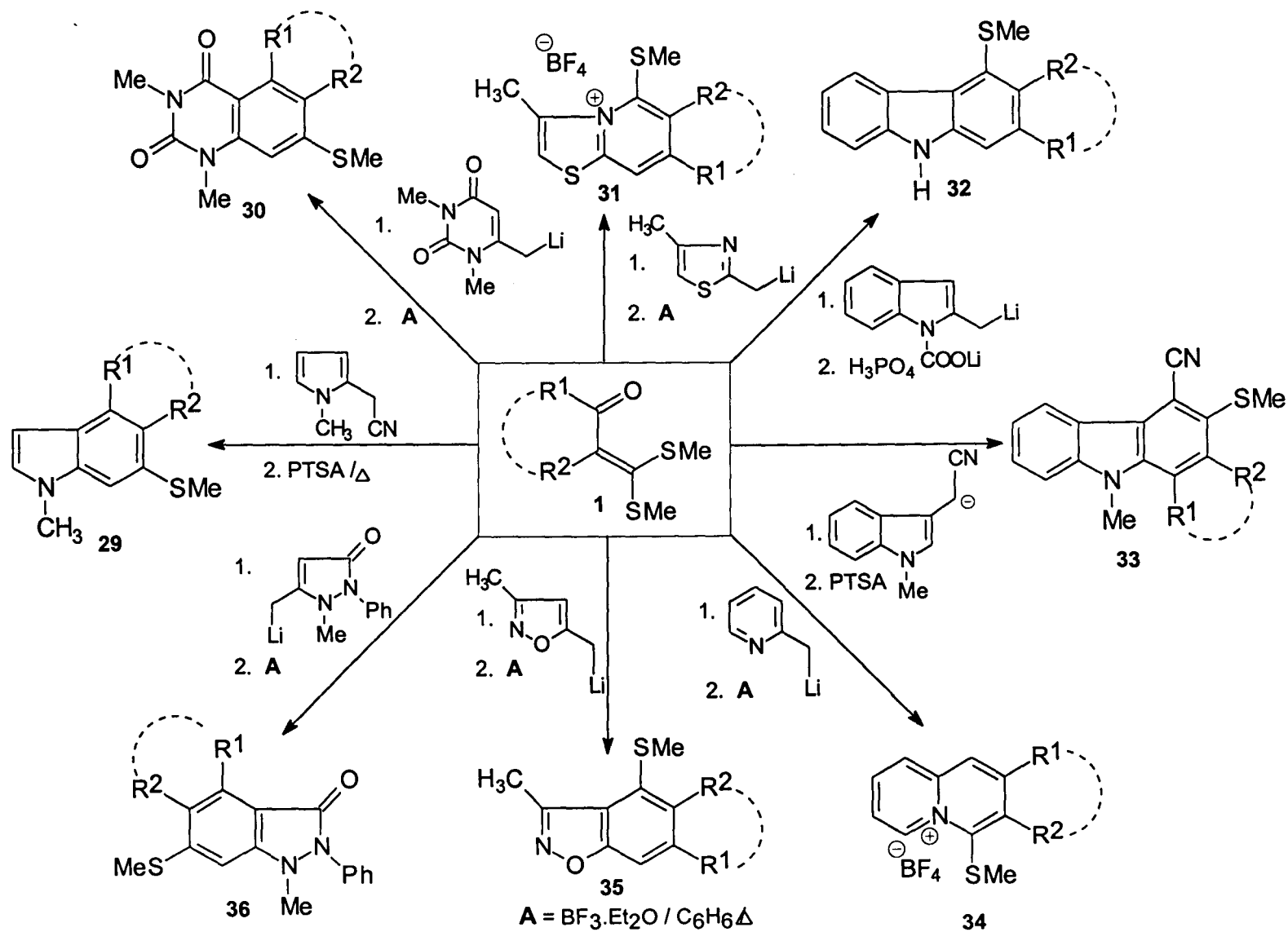
annelation was extended to naphthoannelation, which was achieved by reacting benzyl magnesium chloride with α -oxoketene dithioacetals followed by treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to afford the corresponding naphthalene derivatives through benzene ring participation.³⁹ Similarly *o*-xylyl lithium, *m*-xylyl lithium⁴⁰ and methoxy substituted benzyl magnesium chloride⁴¹ were reacted to afford the corresponding substituted naphthalenes (scheme-5). When α - and β -naphthylmethyl magnesium chloride were reacted with α -oxoketene dithioacetals, it afforded after cycloaromatization, the corresponding phenanthrenes and polycondensed aromatic compounds⁴¹ (scheme-5).

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 -oxoketene dithioacetals yielded the corresponding benzisoxazoles,⁴³ quinazolines,⁴⁵ indazolones⁴⁷ and quinolizinium salts⁴⁸ respectively. Also [a] annelated carbazoles,⁴⁹ [b] annelated carbazoles⁵⁰ and indoles⁵¹ have been achieved by extending this aromatic annelation methodology (scheme-6). Recently a wide variety of biologically important heterocycles containing indole moiety such as carbazoles, [c]annelated carbazoles, pyrazolocarbazoles, β -carboline, δ -carboline and indolo[3,2-*b*]quinolizinium salt etc. (Scheme-7)⁵² has been synthesized in our laboratory through an interesting intermediate 2-bis(methylthio)methylene-1-methyl-3-oxoindole **37** as a three carbon unit. This intermediate was prepared for the first time in our laboratory.⁵² This methodology has been extended to 3-bis(methylthio)methylene-2,3-dihydro-2-

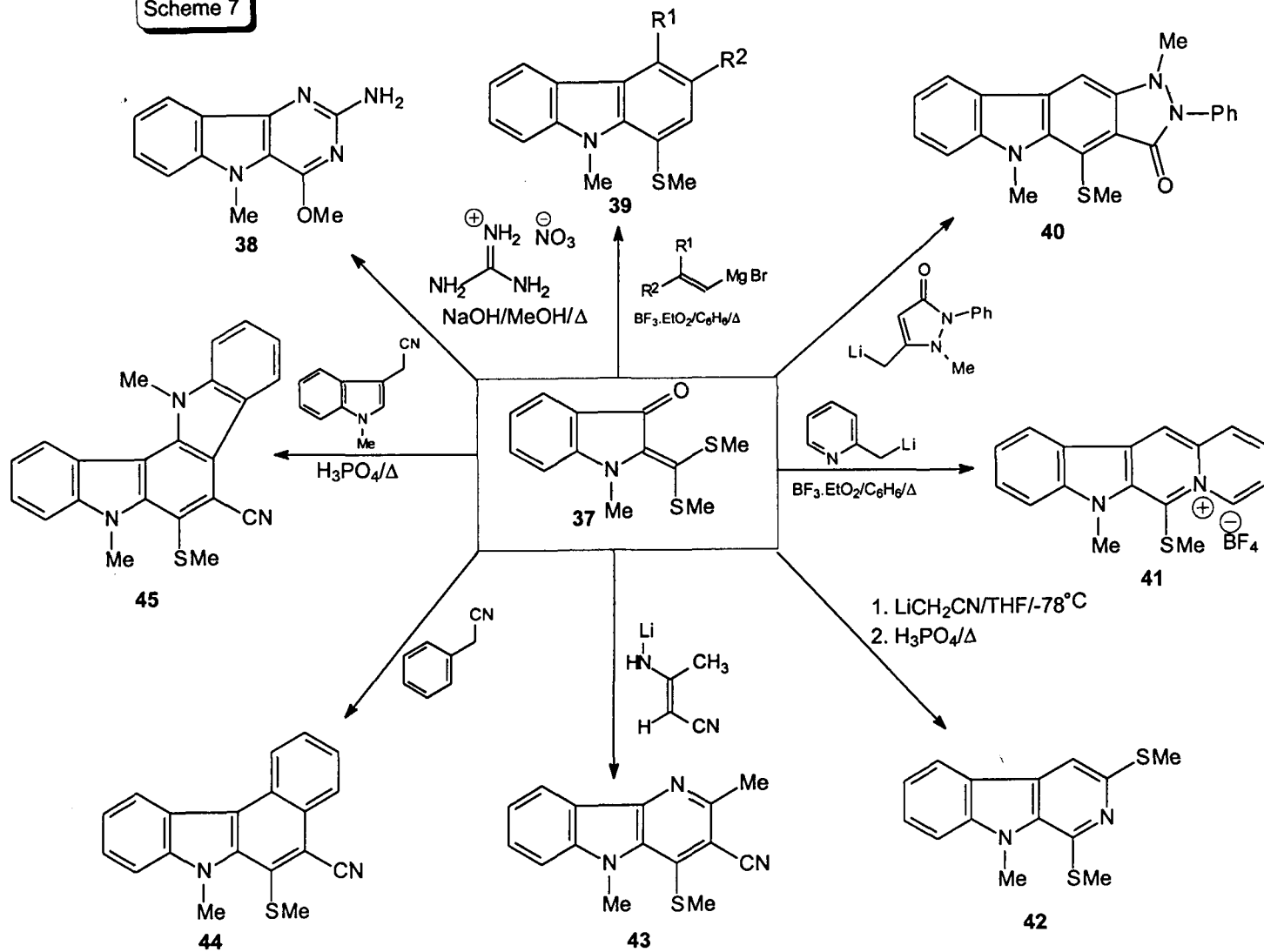
Scheme 5



Scheme 6

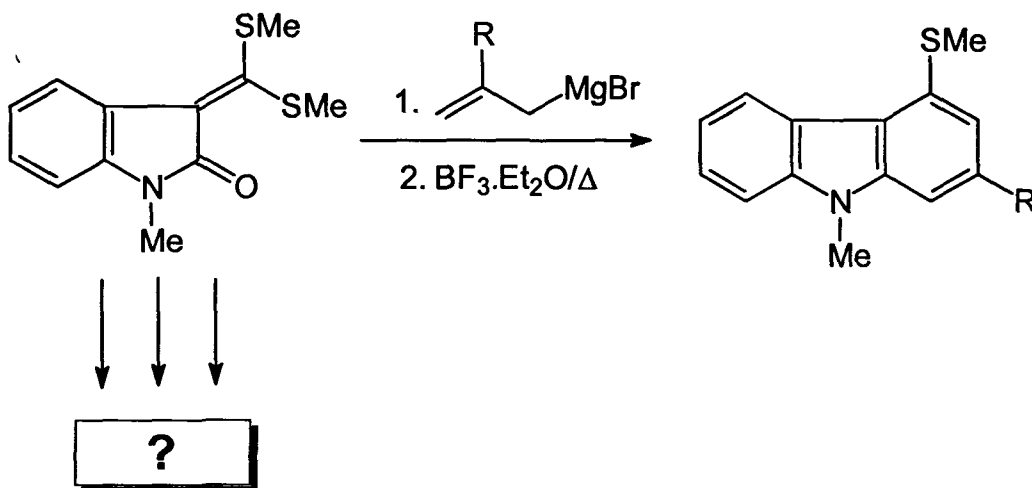


Scheme 7



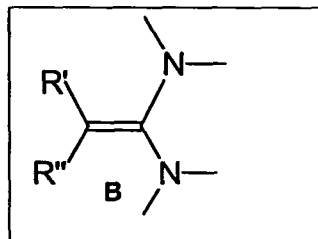
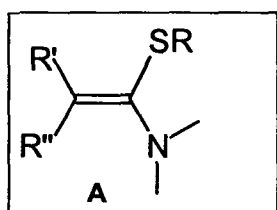
oxo-1-methylindole to achieve annelated indole compounds (scheme-8).⁵³ Most of the work on this intermediate is in progress. Chapter II deals with the synthesis of α -carbolines from α -oxoketene dithioacetals and oxindole.

Scheme 8



Polarized ketene N, S- and N,N-acetals:

The polarized ketene N,S-acetals and N,N-acetals like S,S-acetals are well defined compounds. They can be considered as vinylogous amides if

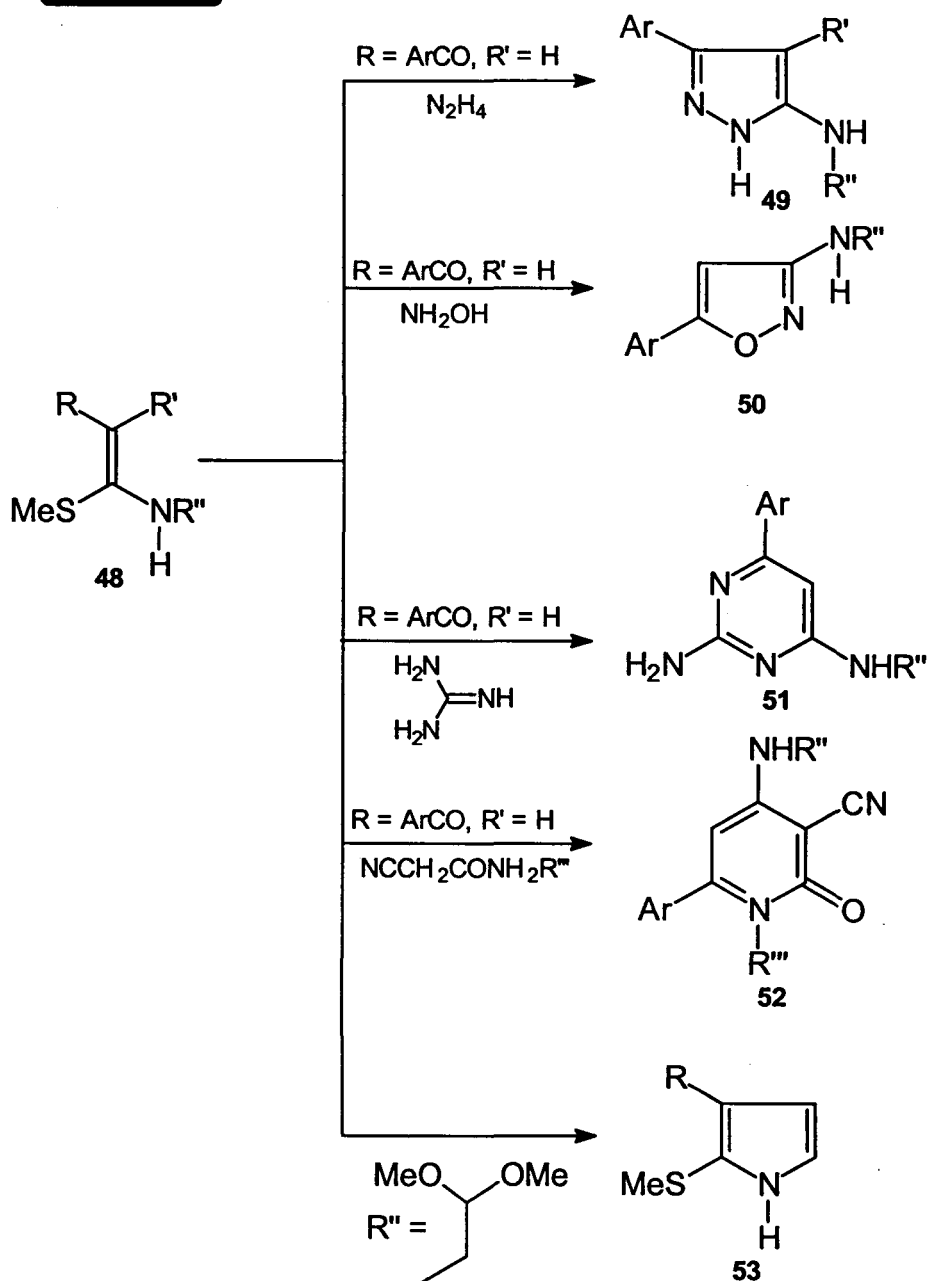


they are derived from ketones and as vinylogous amines if they are derived from other methylene compounds. These N,S-acetals can be prepared by various methods. One of the reported methods is by the reaction of active methylene compounds with alkyl or aryl isothiocyanate in the presence of a

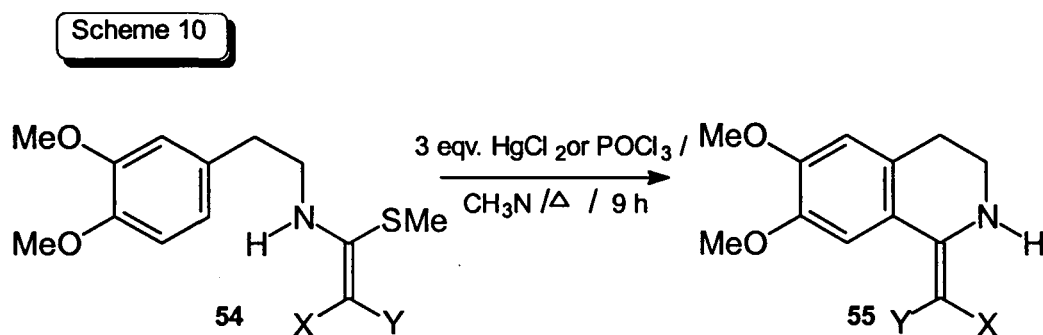
base followed by alkylation. Another efficient method described is the displacement method. The ketene S,S-acetals are known to undergo facile displacement reaction with primary or secondary amines to give the corresponding N,S- and N,N-acetals depending upon the reaction conditions and the stoichiometry of the amine used. In our laboratory also, a new method has been developed for the preparation of ketene N,S-acetals by displacement method using the lithioamino anions. The chemistry of enamines derived from various ketones and primary or secondary amines is well documented. They have been extensively used as synthetic intermediates to react with various electrophiles making use of α -carbon. However, these enaminones are found to be more sensitive to moisture and undergo readily hydrolytic cleavage to the starting materials. On the other hand, the ketene N,S - and N,N-acetals are more stable and exhibit properties identical to enamines. They can undergo a number of reactions with various binucleophiles (Scheme-9)^{16,54-58} followed by intramolecular cyclization with α -oxo functionality. The behaviour of polarized ketene N,S- and N,N-acetals as functionalised enaminones or enamines is manifested in the reaction of **A** and **B** with compounds having activated multiple bonds leading to the synthesis of a wide variety of heterocycles. Few of these transformation for the synthesis of pyrroles **34** via N,S-acetals **32** is shown in scheme-9.⁵⁹ Also synthesis of 2-amino pyrroles starting from ketene S,S-acetals **35** condensed with various amines to give the pyrrole is also shown in Scheme-7.⁵⁶

It is evident that polarized ketene N,S-acetals in addition to their 1,3-electrophilic reactivity, differ from polarized ketene dithioacetals in their enamine reactivity profile providing C-C-N component in the product

Scheme-9



heterocycles. Based on this reactivity a number of reactions have been carried out in our laboratory for the synthesis of wide variety of amino and alkyl heterocycles⁶²⁻⁶⁴ (scheme-9). Recently an efficient general method for the synthesis of novel functionalized heterocyclic enaminones/esters/nitriles derived from tetrahydroisoquinoline has been developed by HgCl_2 (or POCl_3) induced cyclocondensation of newly prepared polarized ketene N,S-acetals from 3,4-dimethoxyphenylethylamine and polarized ketene dithioacetals. (scheme 10).⁶⁵



The work presented in this thesis:

From the above brief review it is evident that the α -oxoketene dithioacetals are versatile intermediates for many organic transformations and potential precursors for the construction of various carbocycles and heterocycles. In the present investigation we have developed new synthetic methods for the synthesis of some of the biologically important heterocycles and their analogs by using α -oxoketene dithioacetals.

In chapter II a new efficient synthesis of substituted and annelated pyrido[2,3-*b*]indoles (α -carbolines) involving conjugate displacement on α -oxoketene

dithioacetals by 1-methyl-2-oxoindole enolate anion and subsequent cyclization of the adducts in the presence of ammonium acetate has been described.

In chapter III an efficient method for the synthesis of biologically important 2,3-functionalized 3-acylimidazo[1,2-*a*]pyridines has been developed *via* an unprecedented CuCl_2 induced oxidative ring closure of N,S-, N,O-, and N,N-acetals. Further cyclodehydration of (2-pyridylamino)imidazo[1,2-*a*]pyridine derivatives yields a novel tetracyclic heteroaromatic salts with two bridgehead nitrogen atoms. The possible mechanism for the CuCl_2 oxidative ring closure is also discussed.

In chapter IV a new general synthesis of regioselectively substituted and condensed benzo[*b*]thiophene is described. The anion derived from thiophene-3-acetonitrile was reacted with various α -oxoketene dithioacetals to give the corresponding 1,4-addition elimination products which were shown to undergo cycloaromatization in the presence of PTSA in refluxing benzene to afford the corresponding benzo[*b*]thiophenes. The scope and limitations of this approach are presented in this chapter.

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CHAPTER - II

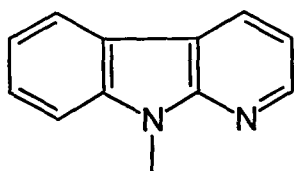
***“A NOVEL AND EFFICIENT METHOD FOR THE SYNTHESIS
OF SUBSTITUTED AND ANNELATED PYRIDO[2,3-b]INDOLES
(α -CARBOLINES)”***

Introduction:

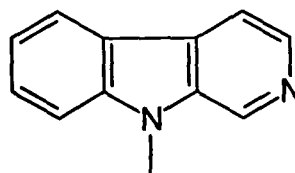
If one of the carbon atoms in the carbazole C ring is replaced by nitrogen, the compounds are called pyrido[*b*]indoles generally known as carbolines. Depending on the position of the nitrogen, it is possible to have four carbolines having nitrogen atom in 1, 2, 3 and 4 positions as depicted in scheme 1. If the nitrogen atom is in 1 position, the compound is generally called pyrido[2,3-*b*]indole (α -carboline)¹ and other carbolines therefore follow successively as pyrido[3,4-*b*]indole (β -carboline)², pyrido[4,3-*b*]indole (γ -carboline)³ and pyrido[3,2-*b*]indole (δ -carbolines)⁴ if the nitrogen atom is in 2, 3 and 4 positions respectively. The chemistry of β - and γ -carbolines has been extensively investigated and literature is reviewed.⁵⁻⁹ It is also to be noted that the number of compounds belonging to β -carboline category is by far the largest compared to other carboline groups described in the literature. The wide occurrence of the β -carboline alkaloid is primarily due to their transformation from the corresponding tryptophans and tryptamines. Similarly the γ -carbolines are likely to have been derived mainly from isotryptamine involving cyclization through indole-3-carbon atom. Accordingly extensive studies on the synthesis of β - and γ -carbolines have been reported in the

literature.¹⁰ On the other hand, synthetic methods for α - and δ -carbolines have not been versatile as the other methods discovered for β - and γ -carbolines.

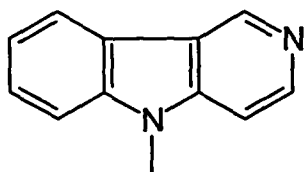
Scheme 1



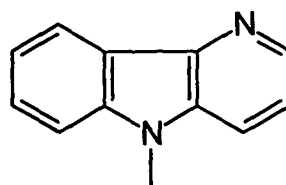
1a: α -Carboline



1b: β -Carboline



1c: γ -Carboline

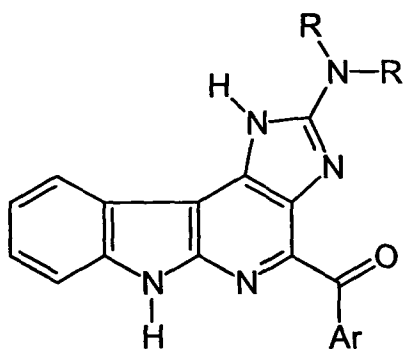


1d: δ -Carboline

It was primarily due to their scant occurrence in nature and their chemistry remained largely unattended. However, recently, a number of natural products containing α -carboline ring system have been isolated, mainly from marine sources and most of them found to possess marked cytotoxic properties. The following are some of the important alkaloids whose structures are described in scheme 2.

1. Grossularine 1 **2a**
2. Grossularine 2 **2b**
3. Didesmethylgrossularine 1 **2c**
4. Cryptotekein **3**
5. Mescengrecin **4**

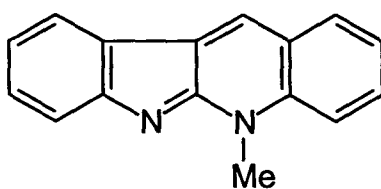
Scheme 2



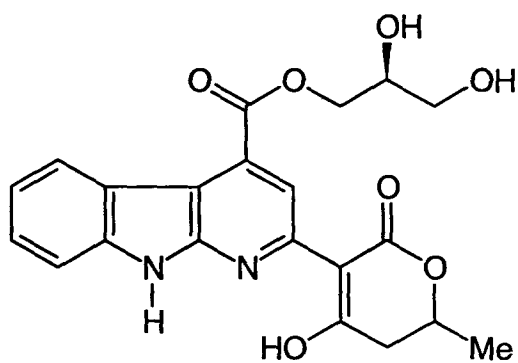
2a: R = CH₃, Ar = 3-indolyl : Grossularine 1

2b: R = CH₃, Ar = 4-hydroxyphenyl : Grossularine 2

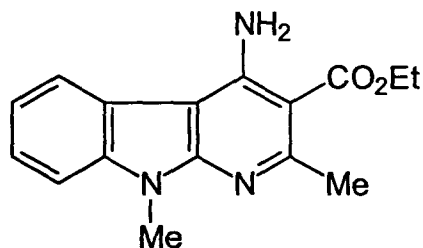
2c: R = H, Ar = 3-indolyl: Didesmethylgrossularine 1



3: Cryptotekien (Neocryptolepin)



4: Mescengricin



5: GABA modulator (anxiolytic agent)

Synthesis of pyrido[2,3-*b*]indole (α -carboline) derivatives has attracted considerable interest due to the recent discoveries of several naturally occurring compounds containing this skeleton. These compounds have displayed a wide range of important biological activities. Grossularine - I and II are the marine alkaloids¹¹ possessing a cyclic guanidine moiety in the form of 2-dimethylaminoimidazole subunit and were isolated in 1984 from the marine tunicate *Dedrodoea grossularia* (Stylidiidae) collected in the coast of Brittany. These compounds, which are the first examples of naturally occurring pyrido[2,3-*b*]indoles (α -carbolines), exhibit marked cytotoxicity toward murine and human tumor. *N,N*-didesmethylgrossularine-1 was isolated from extracts of ascidian *Polycarpa aurata*¹² in 1996 and found to be an antileukemic agent. Mescengricin (isolated from *Streptomyces griseoflavus* in 1997) is found to protect the nervous system against L-glutamate induced excitotoxicity.¹³ Cryptotackiene (also named neocryptolepine) was isolated by two independent groups from *Cryptolepis sanguinolenta*, a shrub indigenous to tropical West Africa, which has been used in folk medicine as an antimalarial agent which displays a strong antiparasitic activity.¹⁴ A few of the synthetic pyrido[2,3-*b*]indole derivatives such as 5 are shown to possess marked biological activity as potential anxiolytic agents.¹⁵

Apparently only a few alkaloids have since been isolated from the natural sources. Significantly small number of this class of compounds appear to have biogenetically derived by some unknown pathway as metabolites in the marine

plants. The first reports on significant biological activity of α -carbolines were described in patents.¹⁶ Interest in their biological activity is increasing in recent years and Isizumi and Katsube have reported¹⁷ the synthesis of 2,3-benzo α -carboline derivatives which has displayed antineoplastic properties. Also cytotoxic activity of 6-chloro, 2 phenyl and 2-pyridylpyrido[2,3-b]indoles (α -carbolines) have been reported. 2,9-Dimethyl-3-carbethoxy-4-aminopyrido [2,3-*b*]indole **5**¹⁰ (scheme 2) a synthetic variant has been marketed as GABA modulator (anxiolytic agent). It is generally observed that their biological activity depends on their physico chemical properties and the substituents. Compounds with small alkyl substituents with Pk values ranging from 7.0 to 7.8 have shown highest biological activity.¹⁸ The mode of biological action of carbolines appears to be their ability to intercalate and complex with DNA.¹⁹ They are also found to be possessing anti-inflammatory and CNS activities.²⁰

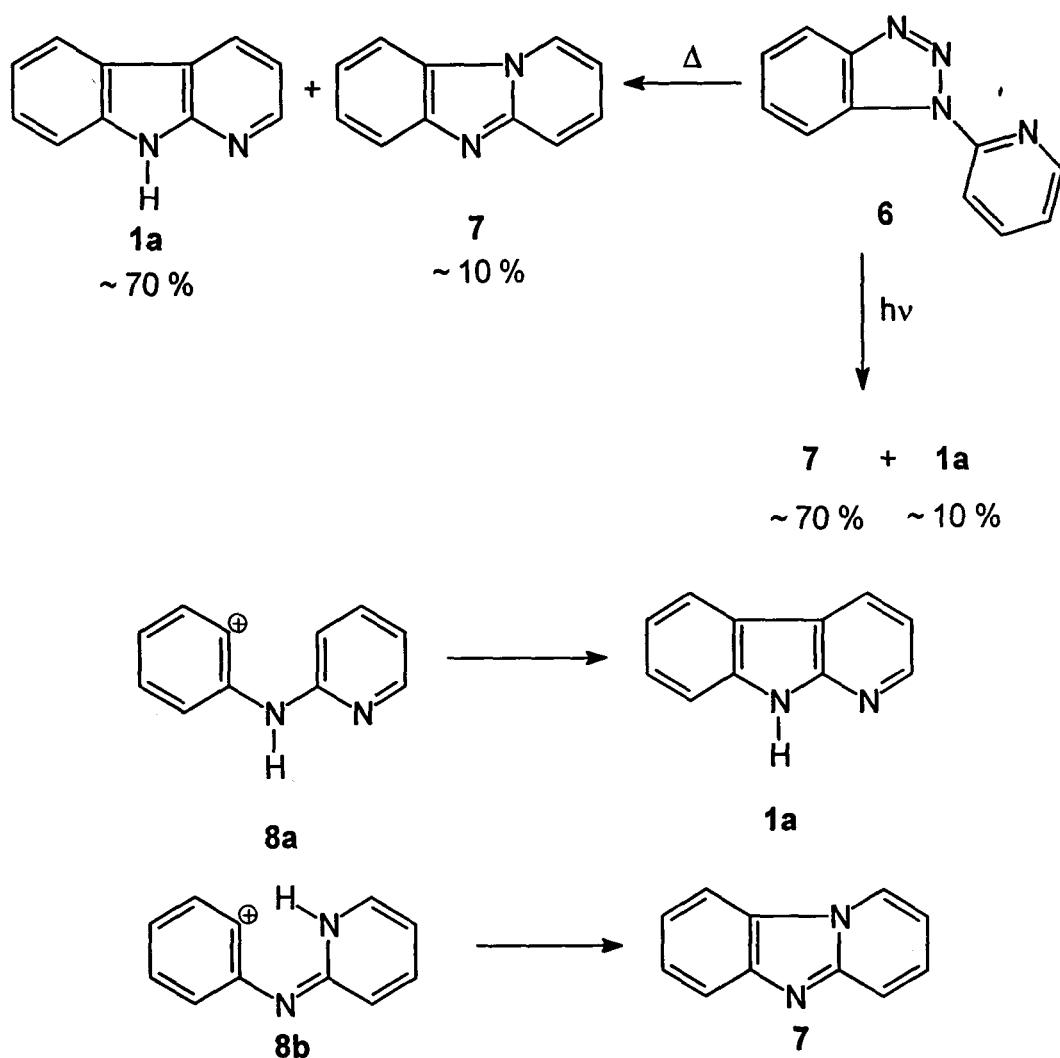
2-Amino carbolines also displayed mutagenic properties.²¹ The carbolines were detected in the pyrolytic product of protein containing food and cigarette smoke and therefore they can constitute mutagenic background of our environment. From this literature it is clear that the not so abundant carbolines appear as rare natural products (scheme 2) as well as in the highly burnt food products.²²

There are several methods of synthesis of pyrido[2,3-*b*]indoles reported in the literature which are reviewed recently.²⁴ We are briefly describing some of these important methods reported for the synthesis of pyrido[2,3-*b*]indoles (α -carbolines.)

Graeb-Ullmann Reaction:

The synthesis of Carbazole from 1-phenylbenzotriazole is called the Graeb-Ullmann reaction. The corresponding N-pyridylbenzotriazole of general structure **6** (scheme 3) also undergo cyclization to yield the corresponding carbolines under acidic or photolytic condition.²⁵ When triazole **6** was heated in the presence of polyphosphoric acid the carboline **1a** was the major product.^{25a} Hubert has reported the formation of carboline in 70 % yield along with 10 % yield of the corresponding pyrido[1,2-*a*]benzimidazole **7** (scheme 3).^{25c} The same reaction under photolytic conditions yielded **1a** only in 5-10% yield while the corresponding **7** were obtained in 70 – 90 % overall yields. Apparently the acid assisted thermal rearrangement of **6** provides the desired carbolines in better yields than the corresponding photolytic decomposition. It appears that in the presence of acid medium the carbon cation **8a** is a major intermediate while the carbon cation **8b** must dominate in the phototransformation to **7**.

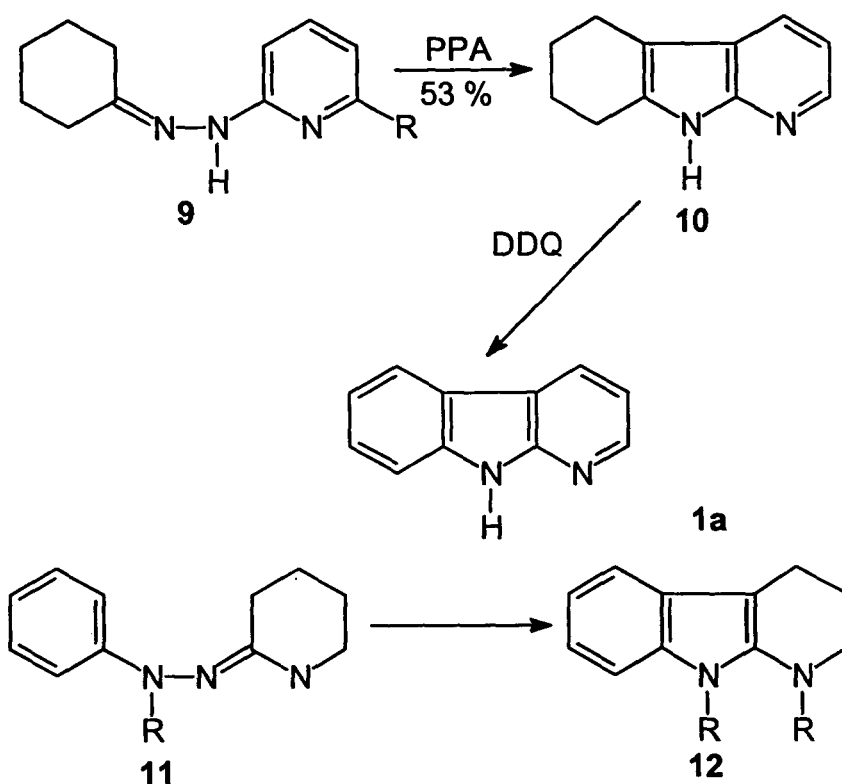
Scheme 3



Carbolines Through Fischer Approach:

The tetrahydropyrido[2,3-*b*]indole **10** (scheme 4) from the corresponding pyridyl hydrazone **9** was obtained in 53% yield using Fischer indole approach in the presence of polyphosphoric acid.²⁶ The method suffers to provide high yield of **10** due to the further inactivation of pyridine ring in the presence of strong acids. The cyclohexanone hydrazone **9** therefore yielded **10** under very severe reactions condition using polyphosphoric acid.

Scheme 4



Other Lewis acid catalysts have also been used to achieve this cyclization. High yields are obtained only when excess of Lewis acids were used. Electron donor substituents in pyridine ring naturally allowed the cyclization to result in high yield of **10** and with electron withdrawing groups under similar reaction condition **10** were obtained in poor yields.^{26c} The tetrahydrocarbolines were conveniently dehydrogenated to **1a** in high yields. The tetrahydrocarboline **12** was similarly obtained from piperidone phenyl hydrazone **11** in moderate yield.

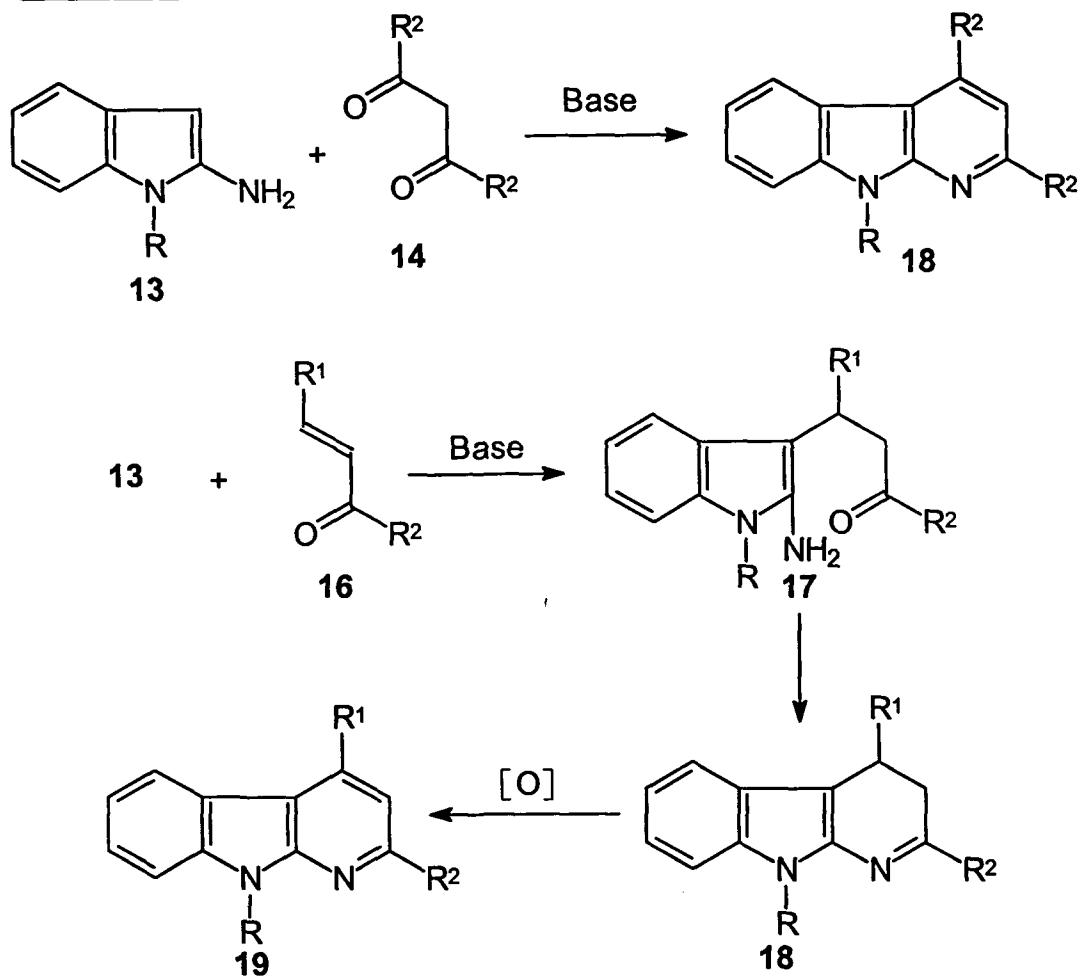
α -Carbolines Based on 2-Amino Indoles:

The synthesis of pyrido[2,3-*b*]indoles (α -carbolines) based on 2-aminoindoles are by far the most direct methods available in the literature. However the method suffers from serious limitations due to instability of the starting 2-aminoindole and also the 1-unsubstituted 2-aminoindole leading cyclization to afford the corresponding pyrimido[1,2-*a*]indoles instead of yielding desired pyrido[2,3-*b*]indole (α -carbolines). The use of a protecting group however also failed to successfully achieve the synthesis of α -carbolines. It was further shown that the synthesis of α -carbolines depends upon the basicity of the medium employed. If the reaction of 2-amino indoles with dicarbonyl compound is carried out at high pH (alkaline alcoholic solution/ Et_3N in isopropyl amine) only the corresponding α -carbolines are formed. It is assumed that the cyclization through carbon occurs due to the resonance stabilized carbanion that follows cyclization to second carbonyl group.

When 2-amino indole was reacted with α,β -unsaturated aldehyde and ketones (scheme 5),²⁷ the reaction yielded the corresponding Michael adduct 17 which underwent cyclization involving an oxidative dehydrogenation to yield corresponding α -carbolines.

The synthesis of pyrido[2,3-*b*]indol-4-one 22a-c were achieved as formulated in scheme 6.²⁷ The 2-amino-1-methylindoles were reacted

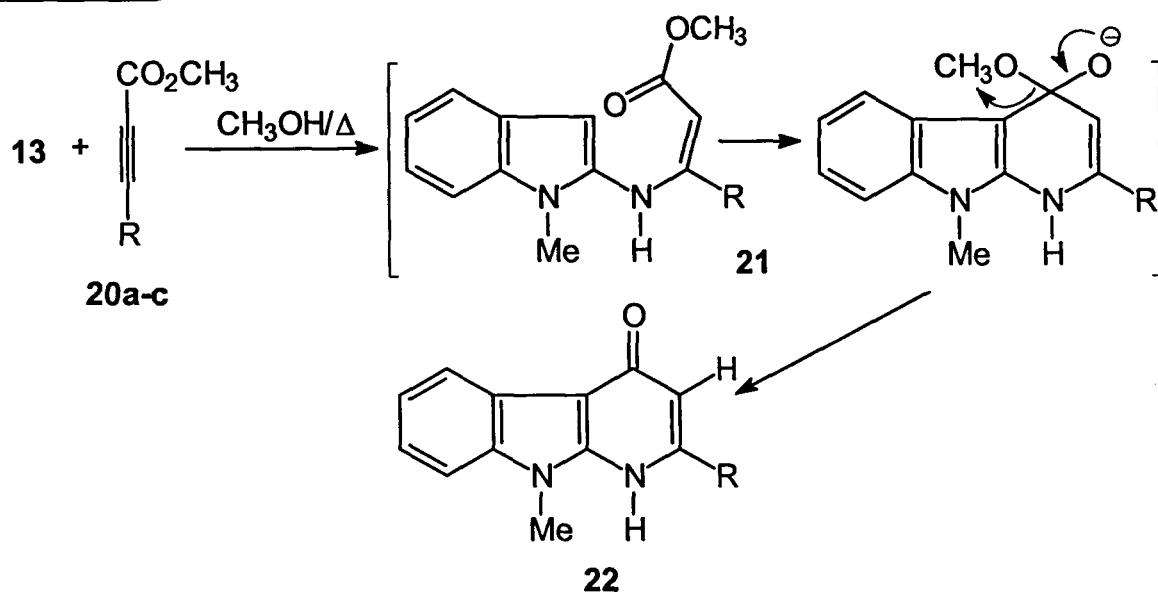
Scheme 5



with acetylenic esters **20a-c** under refluxing condition in the presence of methanol for 5 h to afford the corresponding pyrido[2,3-b]indol-4-ones **22** in overall high yields.

Interestingly, anxiolytic agent **5** was reported as formulated in scheme 7 before it was recognized as a antianxiolytic drug.²⁸ The synthesis involved reaction of 1-benzyl-2-amino-3-cyanotetrahydroindole **23** and α, β unsaturated ester **24** in the presence of PTSA in boiling toluene in the first step to afford the open chain enamine derivative which was cyclized in the presence

Scheme 6



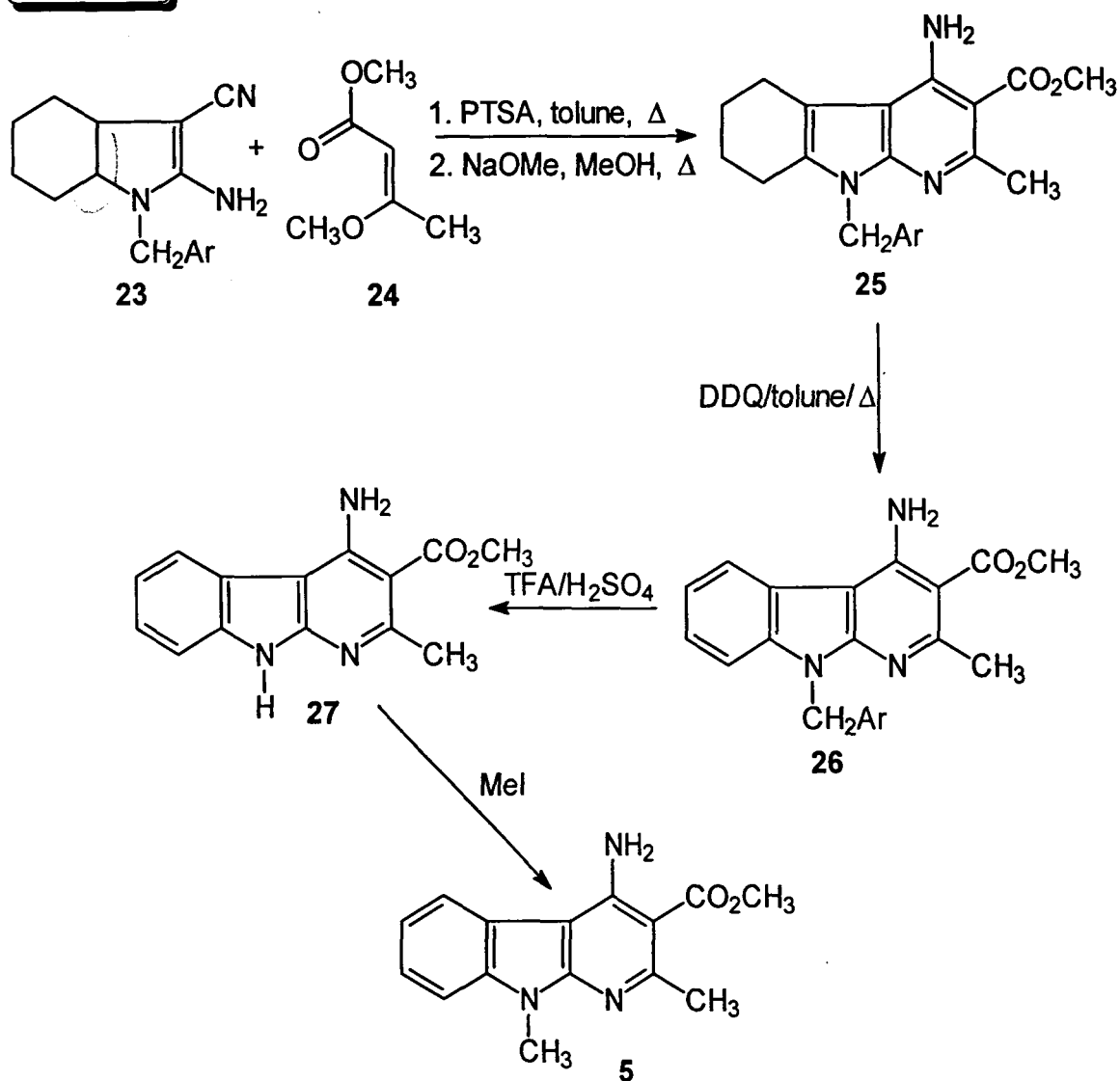
20, 22, 22 a; R = CO_2CH_3
 b; R = C_6H_5
 c; R = CH_3

of MeONa to afford the tetrahydropyrido[2,3-*b*]indole **25**. The tetrahydrocarboline **25** was then dehydrogenated in the presence of DDQ to afford intermediate **26** which on debenzoylation and followed by methylation yielded **5** in good yield.

Pyrido[2,3-*b*]indole via Intramolecular Cycloaddition

Saito and coworkers³⁶ prepared an interesting carbodiimide intermediate **31** in scheme 8 by reacting isocyanate **30** with corresponding Wittig reagent **29**. The carbodiimide intermediate **31** underwent [4+2] intramolecular Diels Alder reaction at 120 °C to afford the corresponding

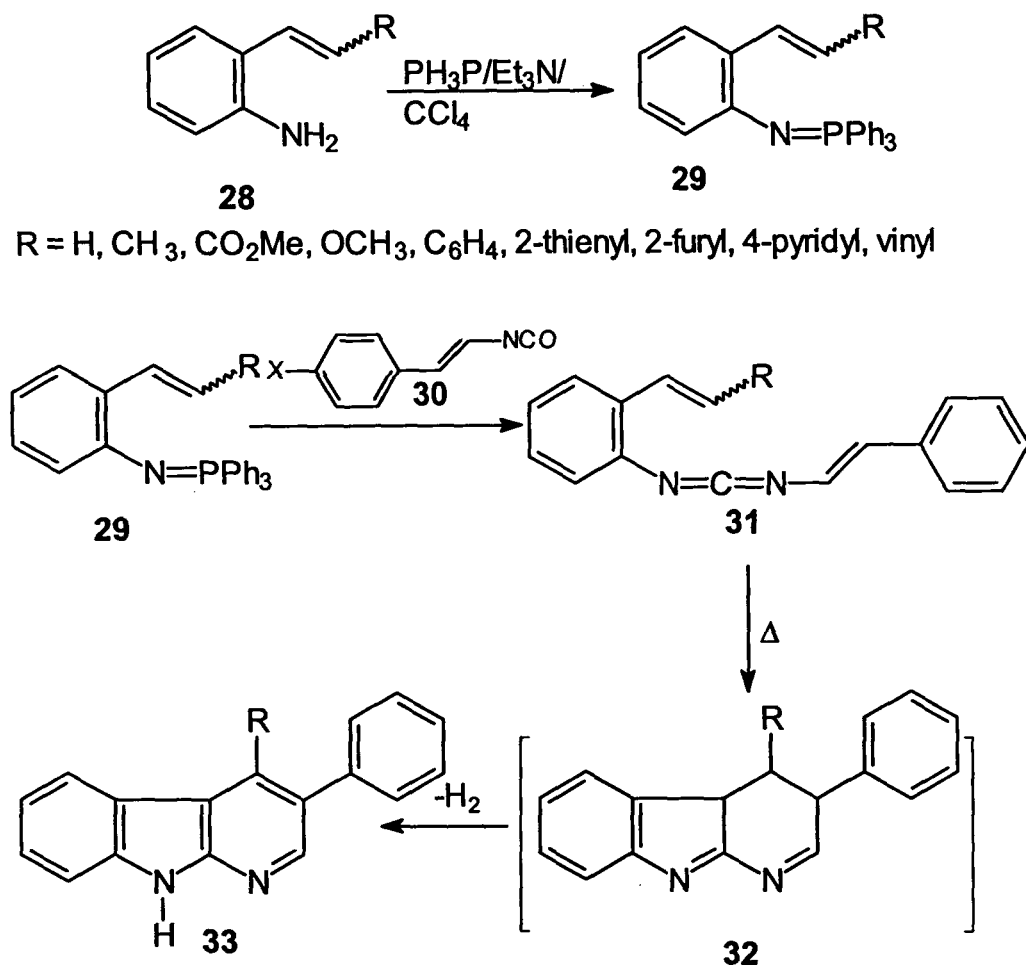
Scheme 7



pyrido[2,3-*b*]indole derivatives **33** via dihydro intermediate **32**. The required Wittig reagent **29** were prepared by reacting the appropriate 2-aminostyrene with a mixture of triphenyl phosphine in CCl_4 and triethylamine at room temperature.

Molina and co-workers³⁷ prepared the iminophosphorane **35** by reacting 2-azido-1-phenylindole-3-carboxaldehyde **34** with triphenyl phosphine and triethylamine. Iminophosphorane **35** was then reacted with nitromethane in

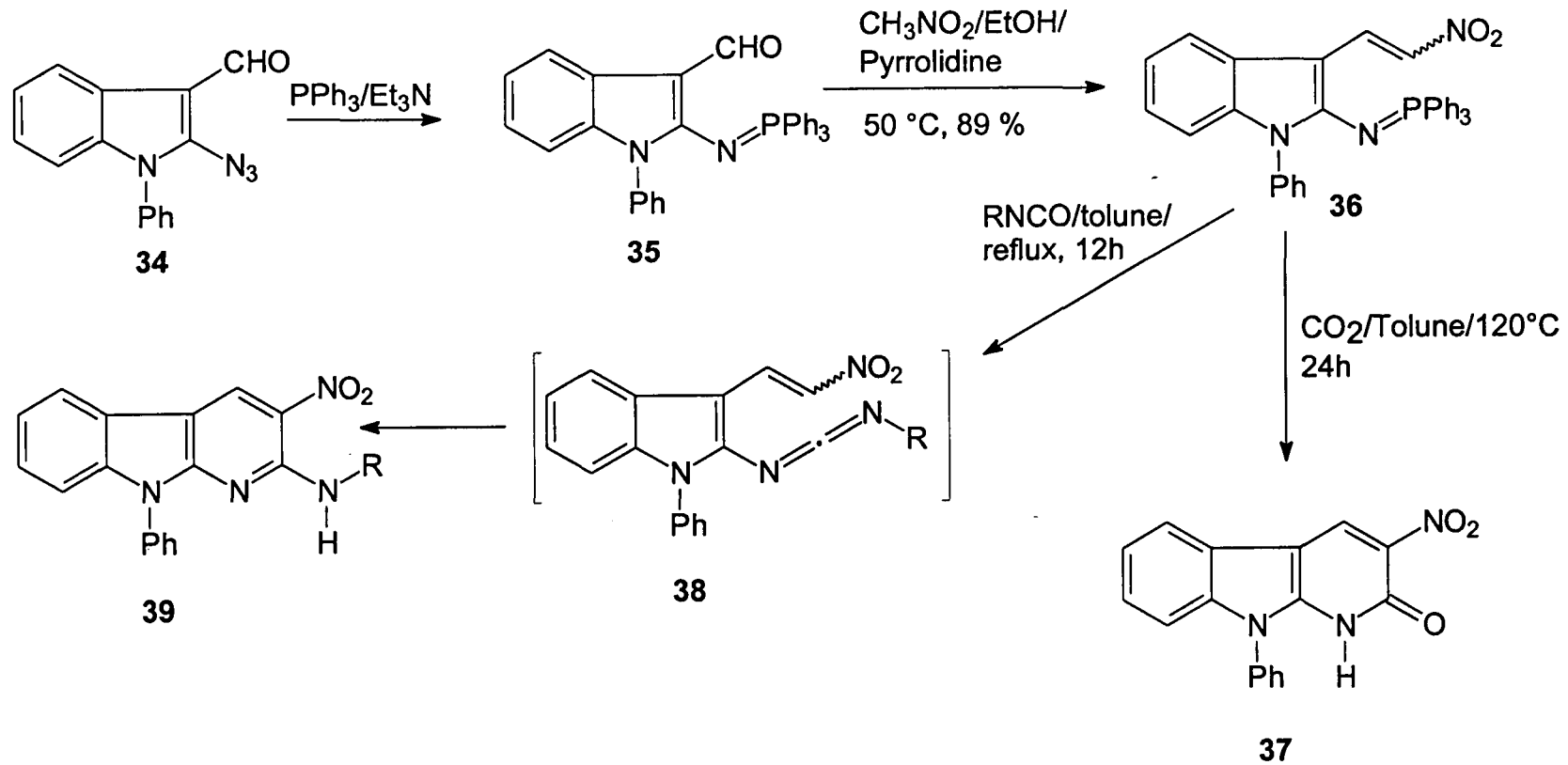
Scheme 8



pyrrolidine to afford the corresponding nitrostyrene 37 in 89 % yield (scheme 9). The phosphorane 36 was reacted with isocyanate in refluxing toluene to afford the corresponding diimide 38 which on heating underwent a tandem intramolecular Diels Alder reaction followed by aromatization to afford 2-amino-9-phenyl-3-nitropyrido[2,3-*b*]indole 39 in excellent yields. A number of substituted carbolines were made by this method.

Hoomert and coworkers³⁸ developed a novel α -carboline synthesis utilizing intramolecular Diels Alder reaction of functionalized pyrazinone 43 by refluxing iodoaniline 41 and dichloropyrazinone 40 in boiling THF in

Scheme 9

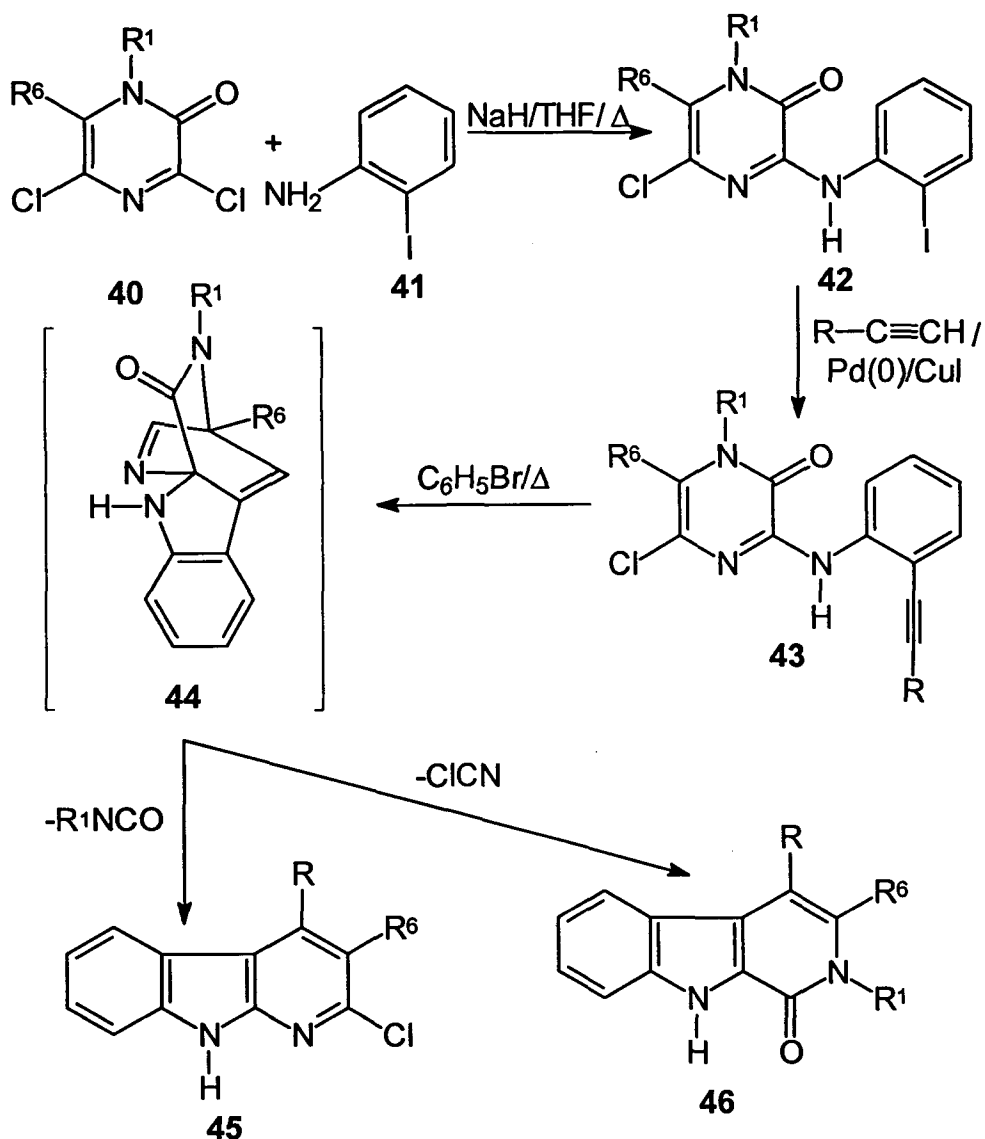


the presence of NaH to afford the corresponding anilino product **42** which was then treated with acetylene to obtain **43**. Compound **43** underwent intramolecular cycloaddition to yield a transient intermediate **44** which with loss of isocyanate afforded the α -carboline **45** (scheme 10).

Dodd and coworkers³⁹ have developed a novel method for efficient synthesis of carboline **46f** (scheme 11) which involves condensation of 1-methyl-2-bromo-indole-3-carboxaldehyde **46b** with 4-(Boc)aminobutyro lactone **46c** to afford the corresponding aldol product **46d** which on treatment with trifluoroacetic acid yielded the corresponding amino compound **46e** followed by Pd assisted coupling to afford the corresponding carboline **46f**.

An intermediate for marine antitumor agent Grossularine **1** was synthesized as formulated in scheme 12 by Achab *et al.*⁴⁰ In their model experiment, they reacted 2,6-dichloropyridine **47** with LDA to introduce an electrophile at 3-position. The trialkylborate and trialkytin were used as electrophiles to afford the corresponding pyridine **48**. Palladium catalyzed cross coupling was then achieved between **48** and orthonitroiodobenzene to afford the corresponding biaryl compound **49** which was then converted to the corresponding α -carboline **50** in 62-68 % overall yields. This model route was then followed up with appropriately substituted 2,6-dichloro-3,4-diaminopyridine. The diamino compound was reacted with dichloromethylene dimethyl ammonium chloride in refluxing chloroform to afford the corresponding imidazolo[4,5-*c*]pyridine **52** in 87 % yield. The intermediate **52**

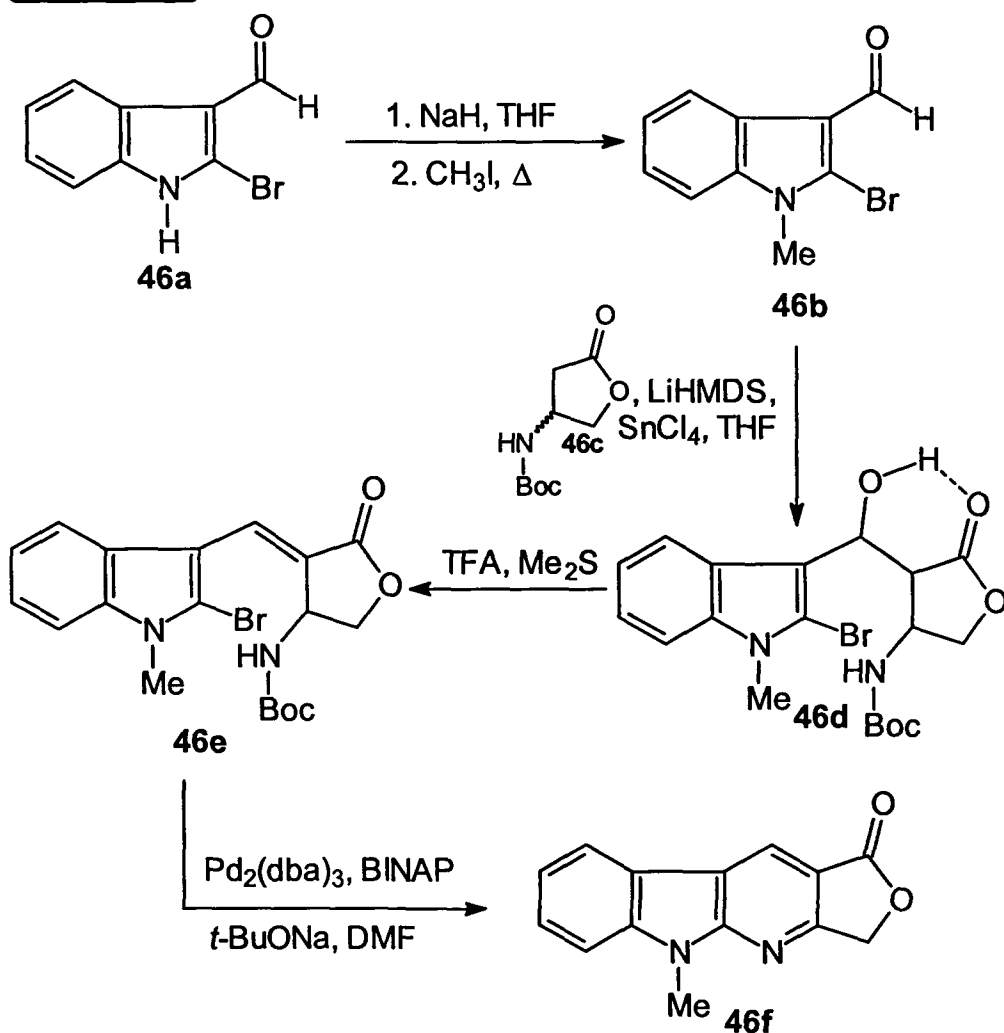
Scheme 10



was then brominated in acetic acid to afford the bromo product **53** which in turn was transformed into an inseparable mixture of two regiomeric SEM derivatives in overall 53% yield. Coupling of **54** with stannate **54b** failed to give **55** in the initial experiments though success was achieved through the use of new catalyst (involving Ag_2O in combination with $Pd^{(0)}$) in refluxing dioxane in 53% yield. Biaryl intermediate **55** on subsequent treatment with

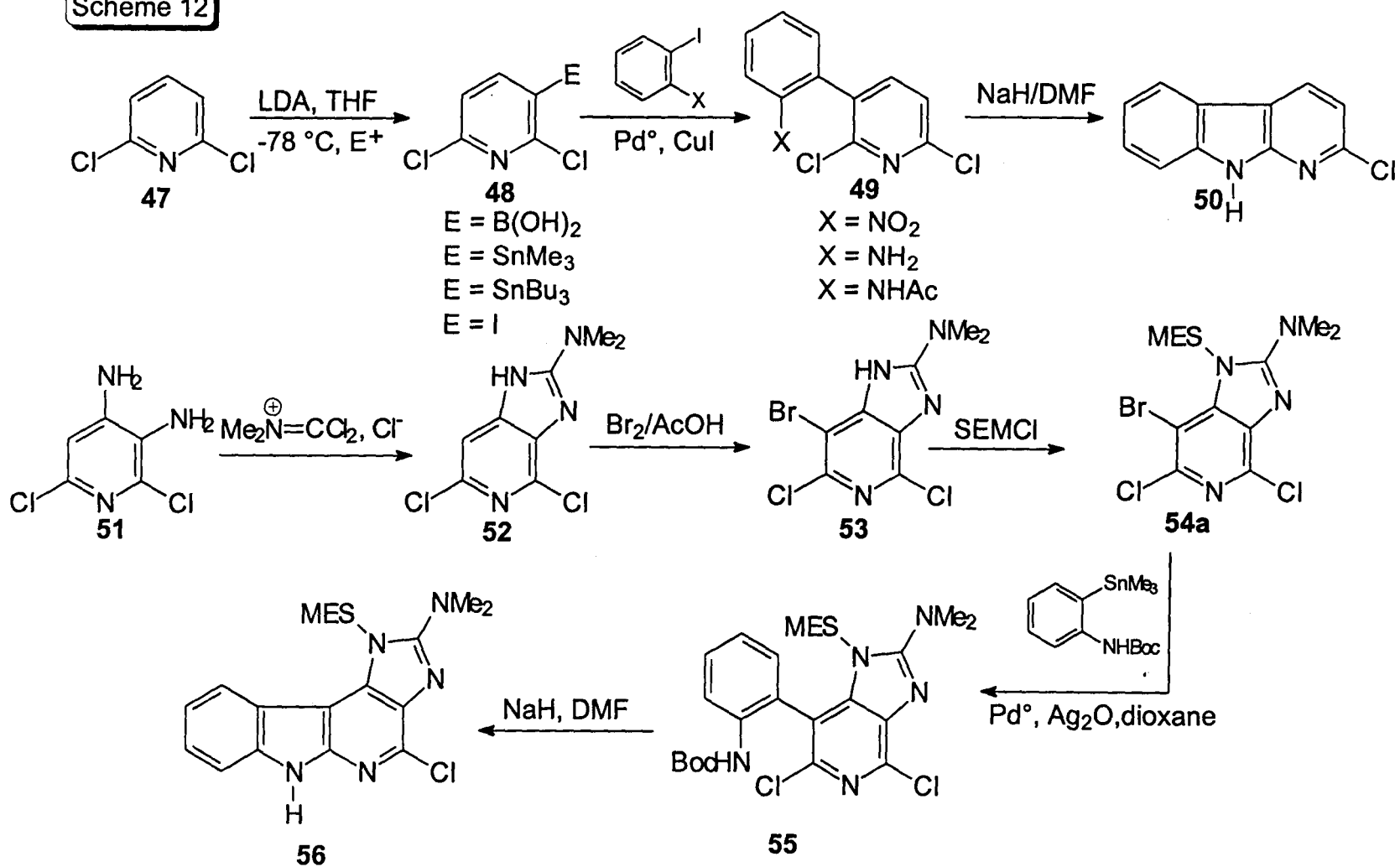
NaH/DMF yielded chloro derivative **56** in 45 % yield which is the intermediate for Grossularins.

Scheme 11



Molina and coworkers^{37c} used N protected 2-chloro-3-acetyl indole **57** as starting material and achieved grossularine ring skeleton **62** as formulated in scheme 13. Thus 2-azidoindole **58** was obtained in 65% yield by treating **57** with NaN₃ in DMSO at 45 °C. It was then treated with Ph₃P in diethyl ether

Scheme 12

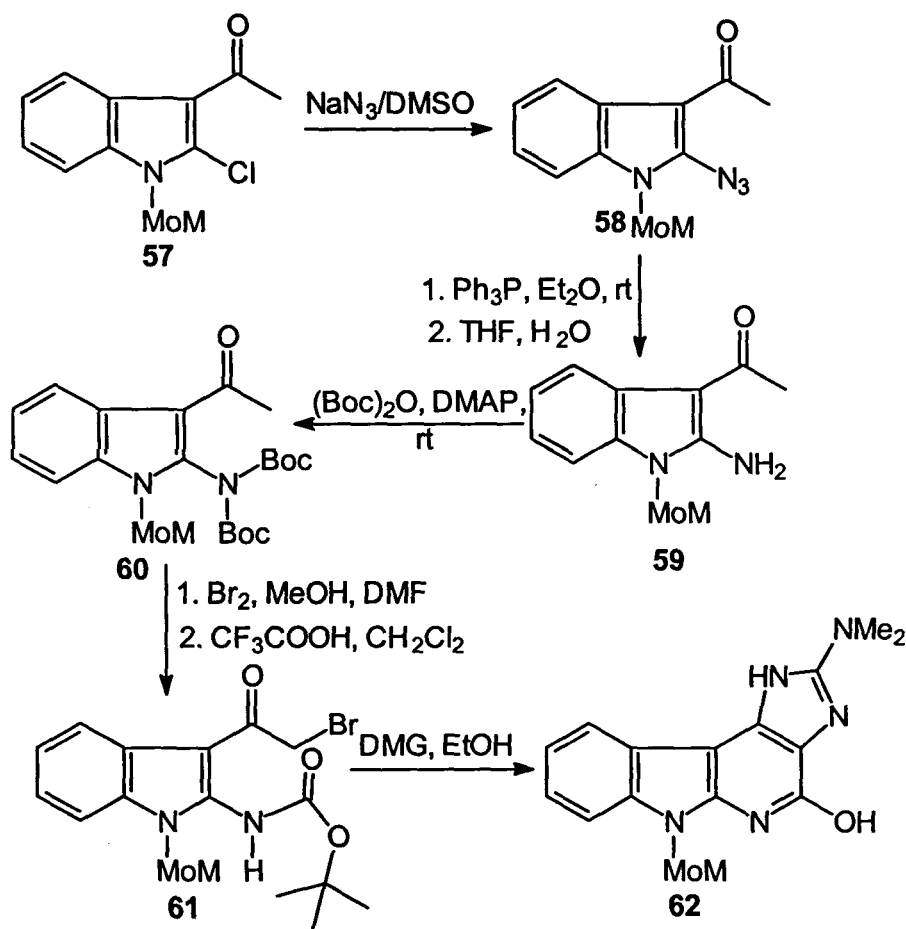


followed by acidification to afford the corresponding 2-aminoindole hydrochloride **59** which was treated with di-terbutyl-dicarbonate $[(\text{Boc})_2\text{O}]$ in the presence of 4-dimethylaminopyridine to afford the corresponding di-ter-butoxy carbonyl amine **60** in good yield. The compound **60** was then brominated and partially deprotected the $\text{N}(\text{Boc})_2$ in the presence of trifluoroacetic acid to afford the corresponding NH t-butoxy carbonyl bromo compound **61** which on treatment with N,N dimethyl guanidine (DMGA) in ethanol to yield **62** which is an intermediate of Grossularines.

Synthesis of Cryptotekien an Alkaloid Containing Carboline Skeleton.

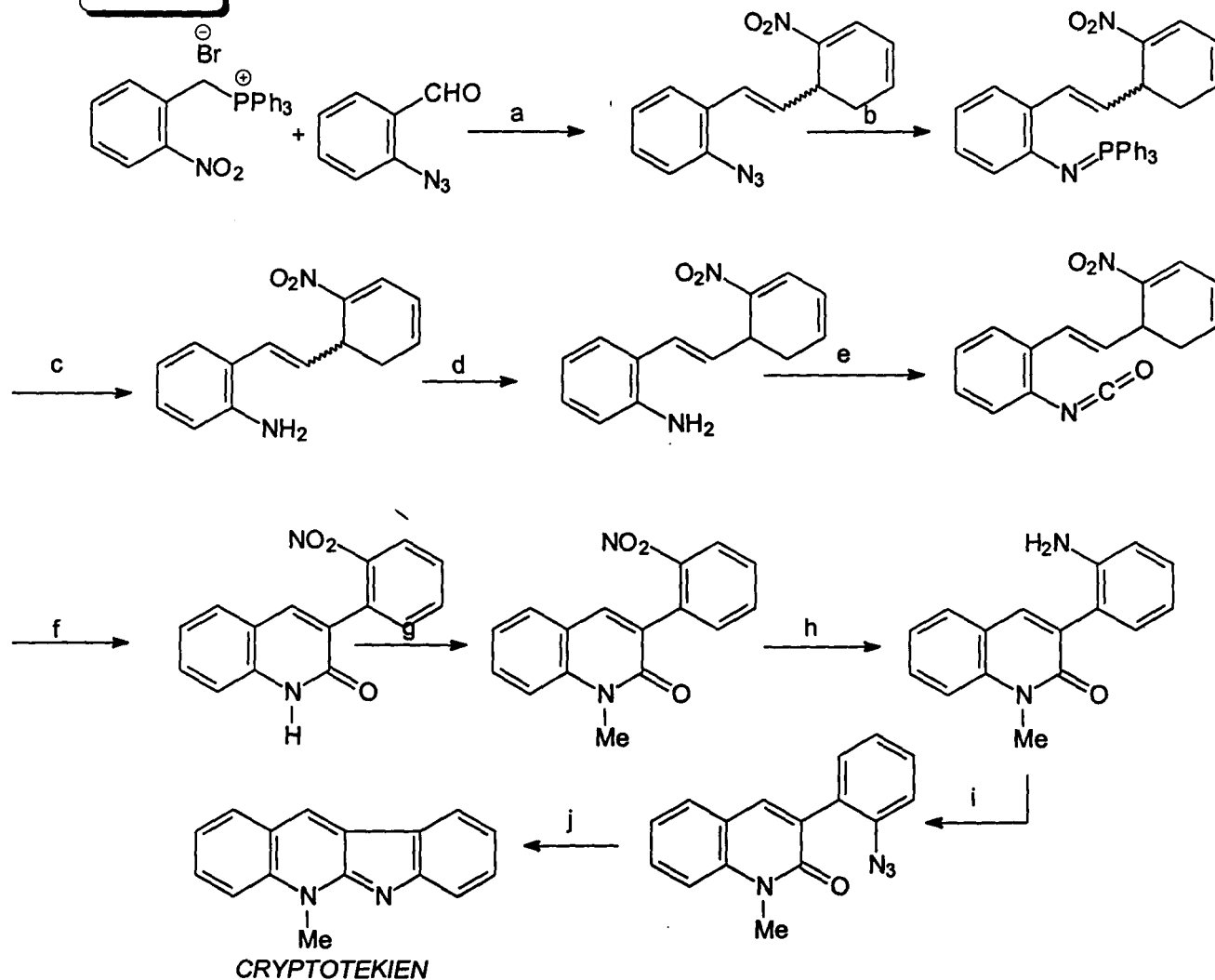
Molina and coworkers⁴¹ have reported the total synthesis of Cryptotekein **74** (scheme 14) an alkaloid containing carboline ring. The alkaloid Cryptotekien was isolated from *Cyptolepus Sanguinolenta* as shrub in tropical west Africa used by local folks as an antimalarial agent. Molina's total synthesis is outlined in scheme 14. Condensation of 2-nitrobenzyl triphenyl phosphonium amide **63** with orthoazidobezaldehyde **64** in the presence of anhydrous K_2CO_3 and catalytical amount of dibenzoantichrome yielded stilbene **65** in 85 % yield as a 4:1 mixture of *Z* and *E* isomers. Compound **65** was then stirred with Ph_3P in dry CH_2Cl_2 to yield the corresponding iminophosphorane **66** in 92 % containing 4:1 *Z:E* isomers. Stilbene **66** was isomerized in the presence of thiophenol and AIBN to afford exclusively *E* isomer **68** in 70 % yield. Treatment with bistrichloromethyl carbonate

Scheme 13



(triphosgene) followed by micro wave cyclization to yield the corresponding quinoline derivative **70** in 80 % yield. Compound **70** on N-methylation, reduction, diazotation and treatment with NaN_3 afforded quinoline-2-one-3-orthoazidophenyl ring **73** in 85% yield. The intermediate **73** underwent cyclization only in the presence of triphenyl phosphine in room temperature and followed by refluxing in nitrobenzene (24 h) yielded the desired Cryptotekien in 13 % yield. However the intermediate **73** on treatment with Ph_3P to get iminophosphorane and then subjected micro wave radiation at 150°C to 180°C for 30 min afforded Cryptotekien in 40 % yield.

Scheme 14



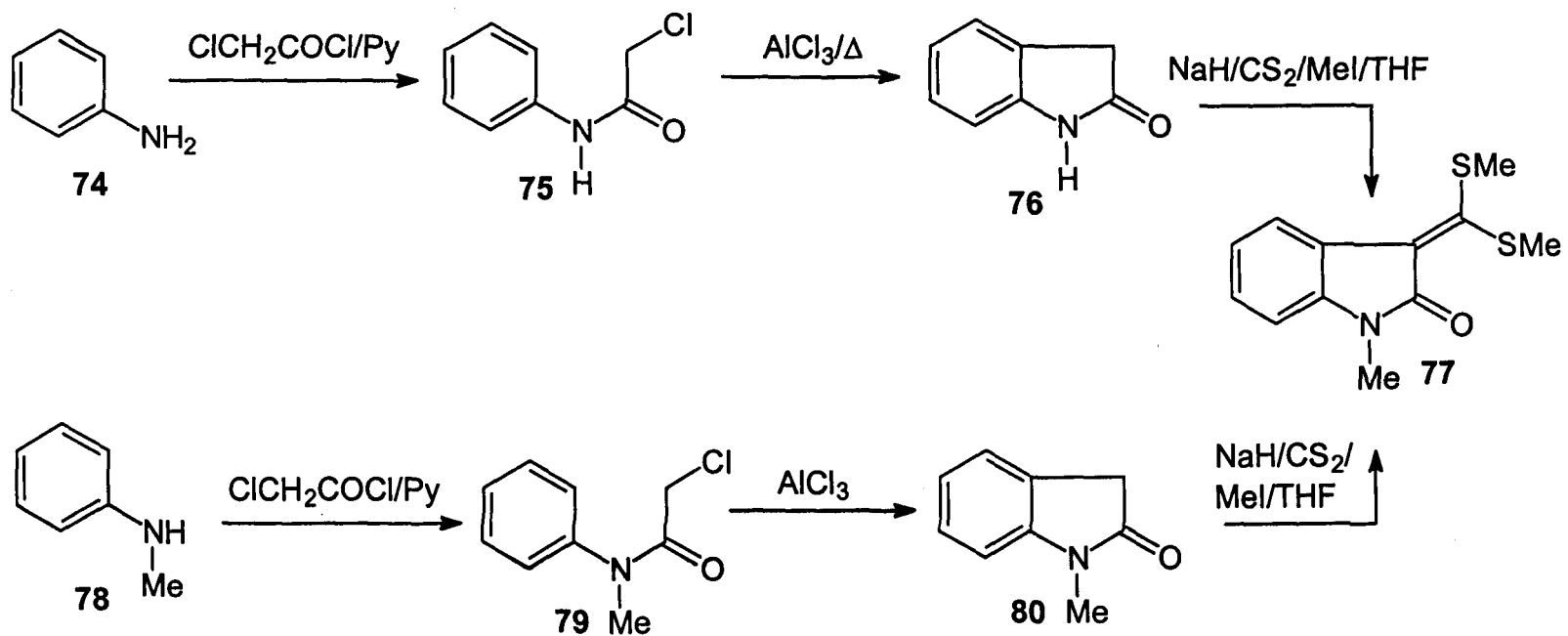
a: K_2CO_3 /Crownether/ CH_2Cl_2 ; b: 1. $Ph_3P/CH_2Cl_2/rt$, 2. $PhSH/AIBN/C_6H_6$; c: $THF/H_2O/rt$; d: $PhSH/AIBN/C_6H_6$
 e: triphosgene/ CH_2Cl_2 ; f: MW/nitrobenzene; g: CH_3I/DMF ; h: $H_2, Pd/C, EtOH$; i: $NaNO_2/H_2SO_4$; j: MW, Me_3P , nitrobenzene

Present Work

From the preceding review on the synthesis of pyrido[2,3-*b*]indoles (α -carbolines) and some important natural products containing α -carboline skeleton, it is apparent that the construction of α -carbolines is not as easy as it should be since the methods reported generally give poor yields or they involve very unstable intermediates as in the case of 2-amino indoles as starting material and inflexibility for substitute introduction. It is therefore necessary that a reasonably good preparatory method for the synthesis of pyrido[2,3-*b*]indoles and possibly applicable to the total synthesis of natural products be developed. With this objective in mind we have investigated and successfully developed an efficient method for the synthesis of pyrido[2,3-*b*]indole. The method consists of simple starting materials involving the preparation of diketone intermediates **84** (scheme 16) either through the reaction of α -oxoketene dithioacetals with *N*-substituted oxindole or through reaction of active methylene ketones with 3-bis(methylthio)methylene-2-oxo-1-methyl indole. The diketones were then treated with ammonium acetate in refluxing acetic acid to yield the corresponding pyrido[2,3-*b*]indoles. The systematic investigation of these studies is presented in this chapter.

The required starting material **77** scheme 15 was reported earlier by Kobayashi and coworkers following the route (**74** \rightarrow **75** \rightarrow **76** \rightarrow **77**) depicted in scheme 15. However we prepared **77** by treating *N*-methyl oxindole in presence of NaH/CS₂ followed by alkylation in one pot reaction in 72 % yield.

Scheme 15



The required oxindole was conveniently prepared in two steps as reported earlier by reacting with chloroacetyl chloride with N-methyl aniline to obtain the corresponding chloroacetanilide **79** in 95 % yield which on Friedel Craft intramolecular alkylated step afforded N-methyloxindole in 55% yield.

In the initial experiment the reaction of acetophenone **81** with N-methyl oxindole mercaptal **77** was carried out in NaH in the presence DMF at 0 °C for 5h and the reaction mixture after work-up yielded the corresponding diketone in 81% yield (scheme 16). It was crystallized as light yellow crystals from hexane/chloroform. The structure of **84a** was fully characterized by analytical and spectral data which are given below.

R_f = 0.4 in benzene

Mp 142 °C

IR (KBr): 1670, 1602, 1563, 1506, 1482 cm⁻¹

¹H NMR (90 MHz, CDCl₃): δ 2.43 (s, 3H, SMe), 3.17 (s, 3H, NCH₃), 5.64 (s, 2H, -CH₂-), 6.65-6.93(m, 5H, ArH), 7.88 – 8.13 (m, 4H, ArH).

Anal. Calcd. for C₂₀H₁₉NO₃S (353.44): C 67.97, H 5.42, N 3.96%

Found C 68.29, H 5.19, N 3.72%.

Alternatively the diketone **84a** was best prepared in 93 % by condensing α-oxoketene dithioacetal **82a** with N-methyl oxindole **80** in the presence of NaH in DMF at 0 °C. In all the other experiments this method was employed since the yields of **84a** through this route were higher than the previous route. The diketone **84a** was then cyclized in the presence of NH₄OAc in refluxing acetic

acid (5 h) to afford after workup the corresponding 2-phenyl-4-methylthio-9-methylpyrido[2,3-*b*]indole **85a** in 79% yield (scheme 16). It was crystallized from hexane/chloroform to afford cream color needles. The structure was established by analytical and spectral data which are given below:

R_f = 0.8 in benzene

Mp 119-120 °C

IR (KBr): 1593, 1554, 1489, 1470 cm⁻¹

¹H NMR (200 MHz, CDCl₃): δ 2.74 (s, 3H, SMe), 4.00 (s, 3H, NCH₃), 7.24-7.29 (m, 1H, ArH), 7.33 (s, 1H, ArH, H-3), 7.39-7.43 (m, 2H, ArH), 7.46 - 7.52 (m, 3H, ArH), 8.12 - 8.15 (m, 2H, ArH), 8.28 (d, 1H, *J* = 7.8 Hz).

¹³C NMR (75.5 MHz, CDCl₃): δ 13.86, 27.60, 96.08, 106.63, 108.50, 111.06, 119.86, 120.56, 123.39, 125.71, 127.25, 128.61, 139.99, 140.17, 145.01, 151.07, 153.50.

MS (m/z, %): 305 (M⁺+1, 31), 304 (M⁺, 100), 303 (M⁺-48, 48)

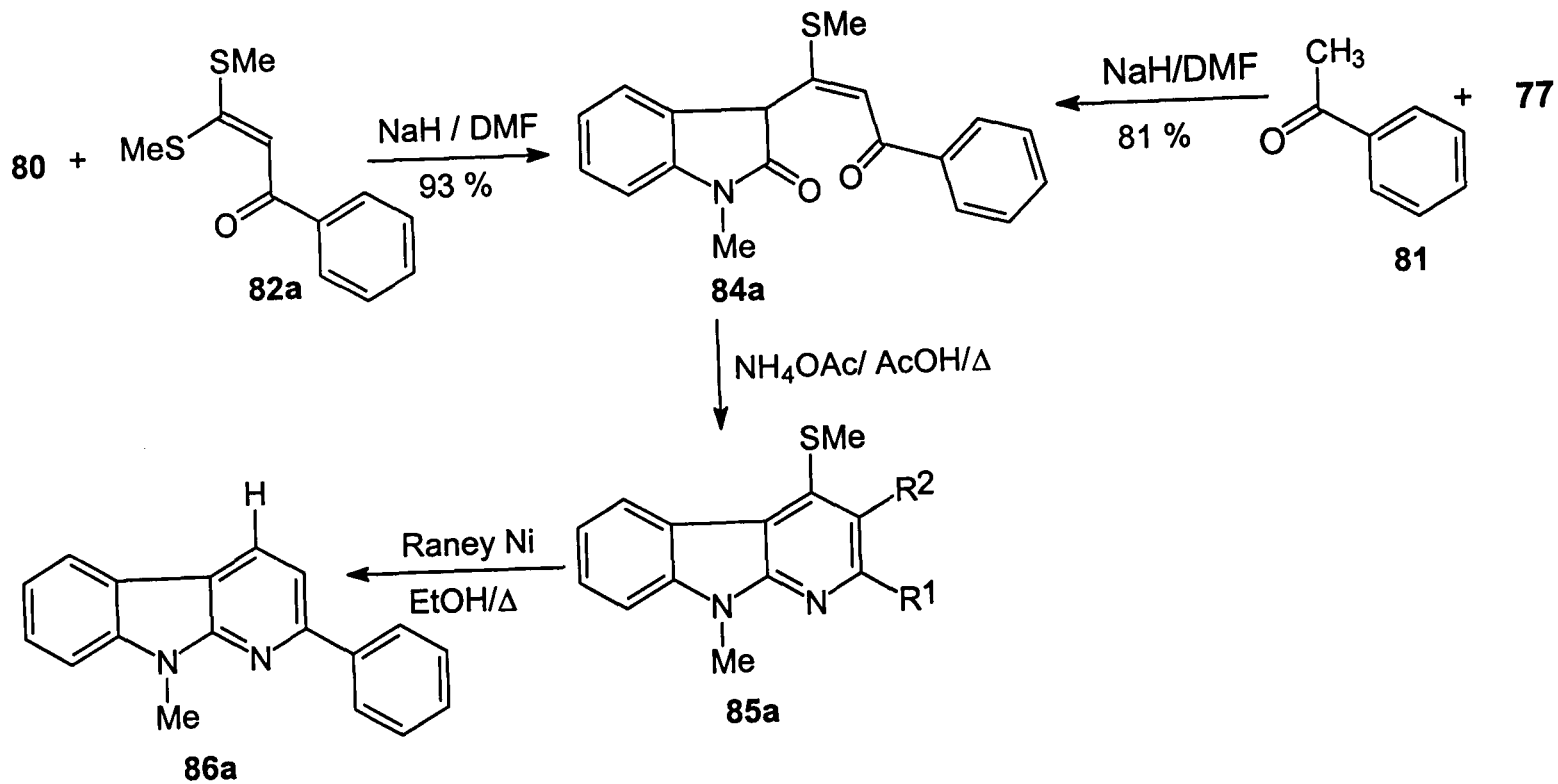
Anal. Calcd. for C₁₉H₁₆N₂S (304.44): C 74.96, H 5.30, N 9.20%

Found C 74.71, H 5.49, N 9.41%.

In subsequent reactions it was not necessary to characterize the diketone **84** since these diketones were obtained in high yields and purity which were carried over directly to the next step.

Similarly, α-oxoketene dithioacetals **82b-f** (scheme 17) were condensed with **80** as described earlier to afford the corresponding diketone **84b-f** in excellent

Scheme 16



yields which were directly treated with ammonium acetate in refluxing acetic acid to afford the corresponding pyrido[2,3-*b*]indoles in 55-79% overall yields. The structures of **85b-f** were fully established by analytical and spectral data. The data are reported in the experimental section. One of the α -carboline **85a** was subjected to dethiomethylation in the presence of Raney Ni in ethanol to afford the corresponding 2-phenyl-9-methylpyrido[2,3-*b*]indole **86** in 82% yield. The structure of **86** was fully characterized by its analytical and spectral data which is given below:

R_f = 0.7 in benzene

Mp 121-122 °C

IR (KBr): 1560, 1485, 1450, 1420 cm⁻¹

¹H NMR (80 MHz, CDCl₃): δ 4.00 (s, 3H, NCH₃), 7.25 (s, 1H, ArH), 7.30 – 7.81 (m, 5H, ArH), 7.92 – 8.23 (m, 3H, ArH), 8.23 (d, 1H, *J* = 4.1 Hz).

MS (m/z, %): 259 (M⁺+1, 21.1), 258 (M⁺, 100), 257 (M⁺-1, 83)

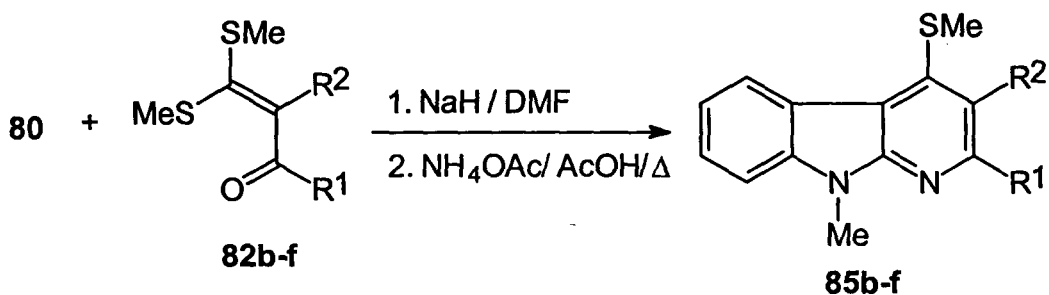
Anal. Calcd. for C₁₈H₁₄N₂ (258.32): C 83.69, H 5.46, N 10.84%

Found C 83.38, H 5.69, N 10.61%.

It should be noted that the method provides one of the shortest high yielding synthesis of pyrido[2,3-*b*]indole analogs with control on substitution pattern in 2, 3 and 4 positions. Entry **85f** proves that both 2 and 3 substituents in the product carboline can be regioselectively placed.

In the next experiment, the scope of this facile method of pyrido[2,3-*b*]indole synthesis was extended to examine the reaction of further variants of α -oxoketene dithioacetals. Thus the reaction of α -oxoketene dithioacetal of isopropyl methyl

Scheme 17



Entry	82, 84, 85	R1	R2	Yield
1	b	4-MeOC ₆ H ₄	H	75
2	c	4-ClC ₆ H ₄	H	74
3	d	4-MeC ₆ H ₄	H	72
4	e	CH ₃	H	61
5	f	CH ₃	CH ₃	60

ketone 82g was reacted with 80 under the described reaction conditions to afford the corresponding diketone 84g which on treatment with ammonium acetate in refluxing acetic acid yielded a mixture of two products containing 55% of the desired as 2-isopropyl-4-methylthio-9-methylpyrido[2,3-*b*]indole 85g. The other fraction with lower R_f value was purified by column chromatography which was eluted as second product and characterized as 2-isopropyl-9-methylpyrido[2,3-*b*]indol-4-one 87g in

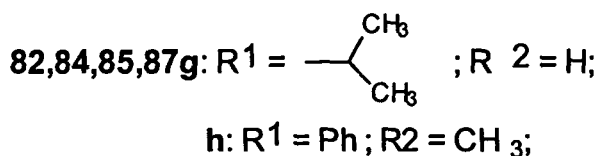
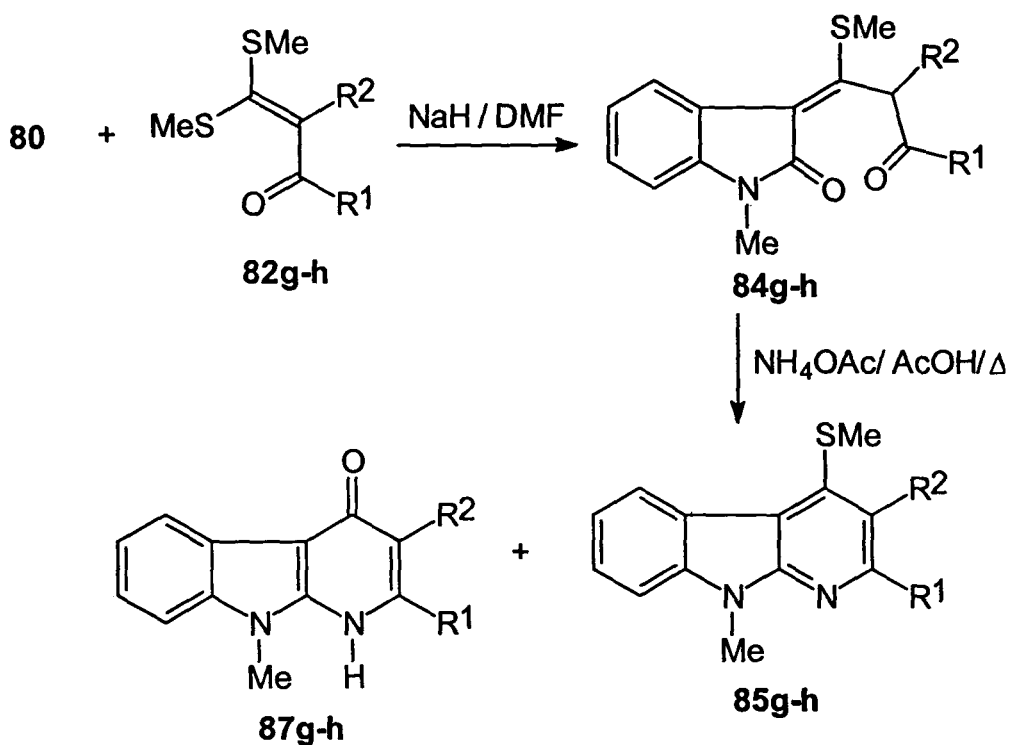
10% yield. The structure of **85g** and **87g** were fully characterized by analytical and spectral data which are given in the experimental section.

Similarly **82h** derived from propiopheone reacted with **80** under the described reaction conditions to yield the diketone **84h** in high yield followed by treatment with ammonium acetate in refluxing acetic acid to afford after workup, a mixture of two products as described above. The fraction with higher R_f was first eluted (hexane/ethyl acetate 9.5: 0.5) over silica gel column, crystallized as light yellow needles. It was characterized as 3,9-dimethyl-4-methylthio-2-phenyl-pyrido[2,3-*b*]indole **85h** (61% yield) and structure was fully established by analytical and spectral data. The second compound obtained from column chromatography was characterized as **87h** in 14% yield. The structure of **85h** and **87h** (scheme 18) were fully confirmed by analytical and spectral data which are presented in the experimental section.

It is to be noted that under the acetic acid ammonium acetate conditions the formation of pyridine ring possibly follows partial hydrolysis to afford **87h** as minor product along with the major products **85h**.

In the next experiment, doubly activated α -oxoketene dithioacetal **82i** was reacted with **80** under the described reaction conditions to afford the corresponding **84i** in 86% yield as light yellow needles from hexane/chloroform and it was characterized by spectral and analytical data which are given in the experimental section. The triketone when heated with ammonium

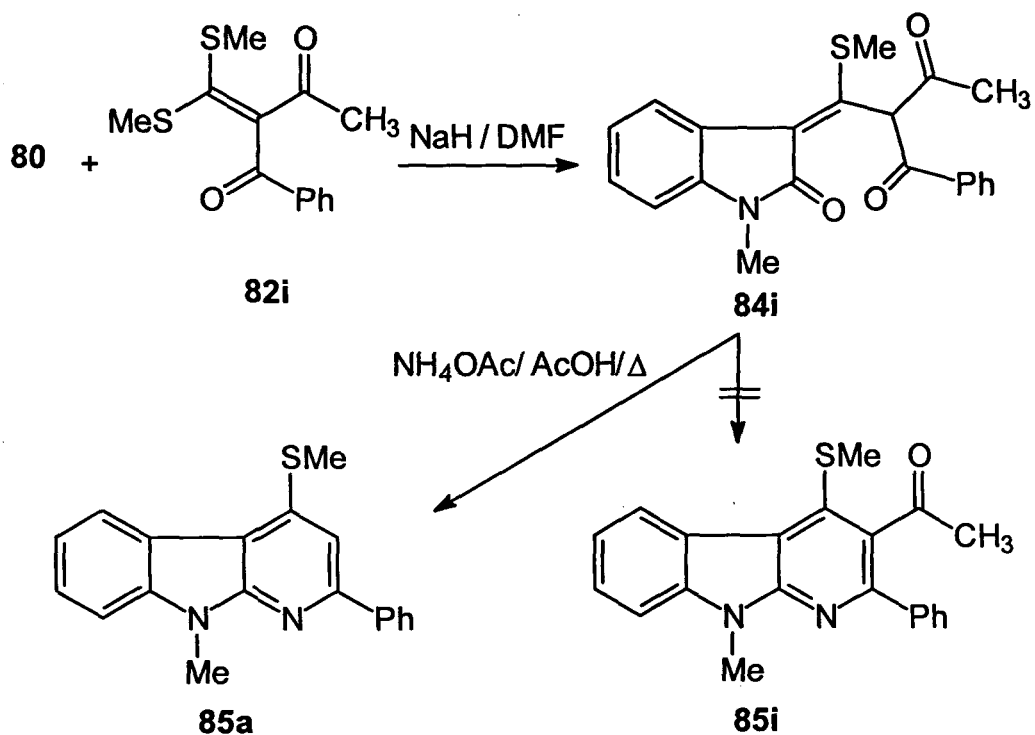
Scheme 18



acetate in refluxing acetic acid, the product isolated did not contain the acetyl group, to afford the corresponding **85i**, however the structure was confirmed as **85a** and found identical with that prepared from acetophenone mercaptal. Both the compounds were found to be identical mmp, superimposable IR spectra **85a** (Scheme 18').

The α -oxoketene dithioacetals from 2-acetylfuran **82j**, 2-acetylthiophene **82k** and 2-acetylpyridine **82l** were reacted with **80** under the

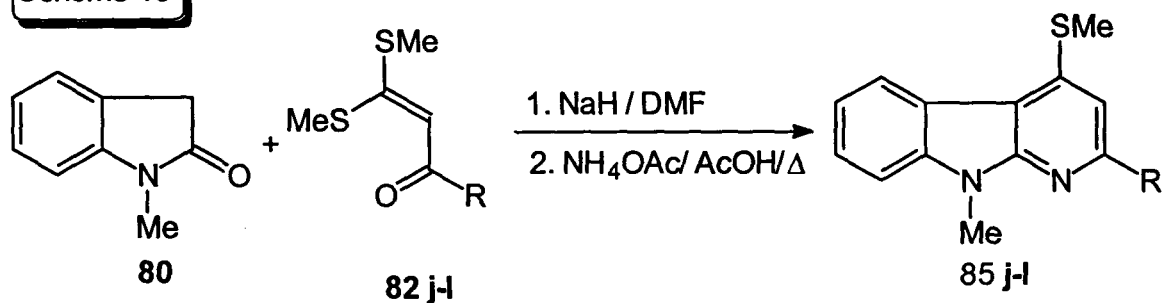
Scheme 18'



described reaction conditions to afford the desired corresponding diketones **84j-l** which on treating with ammonium acetate under refluxing acetic acid yielded the corresponding 2-substituted-9-methyl-4-(methylthio)pyrido[2,3-*b*]indoles **85j-l** in 59-78% overall yields. All the three compounds were characterized by analytical and spectral data which are presented in experimental section.

In the next experiment, attempts were made to apply this method for the synthesis of the antianxiolytic agent containing pyrido[2,3-*b*]indole ring system **5**. The scheme formulating attempted total synthesis is depicted in scheme 20. Thus the α -oxoketenedithioacetal **82m** from ethylacetoacetate reacted with **80** under the described reaction condition to yield the diketone

Scheme 19



82,85	Mercaptal	Product	Yield %
j			78
k			71
l			59

84m in 91% yield. The diketone was fully characterized by its analytical and spectral data which are presented in the experimental section. The diketone **84m** was then heated with ammonium acetate in refluxing acetic acid to afford the corresponding 3-carbethoxy-2,9-dimethyl-4-(methylthio)pyrido[2,3-

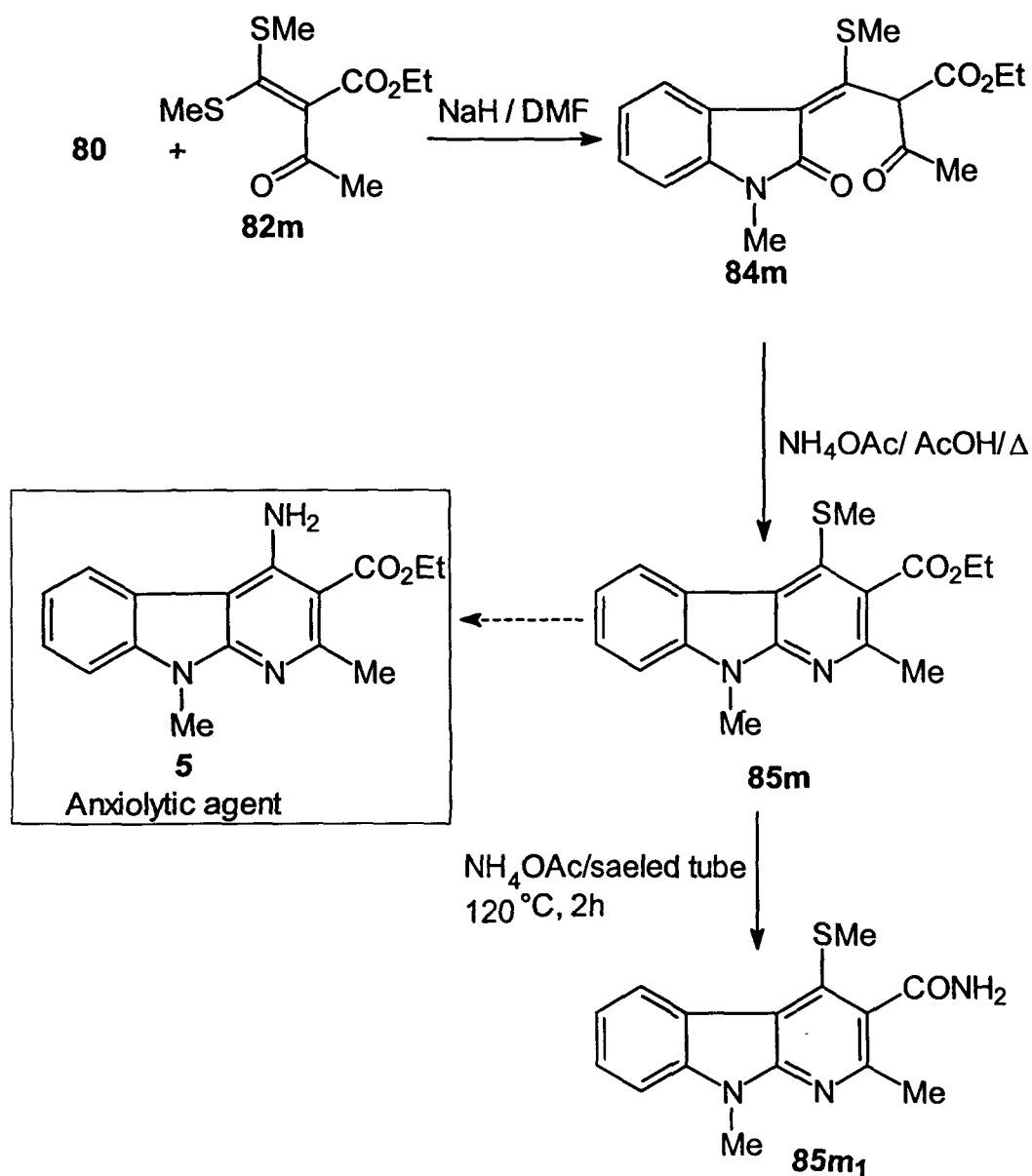
b]indole **85m** in 51% yield and it was confirmed by analytical and spectral data. When **85m** was further heated with ammonium acetate in sealed tube for 2h, the product isolated was characterized as amide **85m₁** in 73% yield and it was confirmed by analytical and spectral data. The experiments to replace methylthio group at 4-position by ammonia under pressure are in progress.

The oxoketene dithioacetal of tetralone **82n** was similarly reacted with **80** to afford the diketone **84n** in 89% yield which after heating with ammonium acetate and acetic acid the reaction mixture after work up yielded corresponding pyrido[2,3-*b*]indole **85n** in 30 % yield (scheme 21). The structure of **85n** was confirmed by its analytical and spectral data which are given in the experimental section.

Under similar reaction condition, the mercaptal derived from 1-benzylsulphonyl-1,2,3,4-tetrahydroquinolin-4-one **82o** also condensed with **80** to afford the corresponding diketone **84o** in 93% yield. The compound **84o** was characterized by its analytical and spectral data described in experimental section.

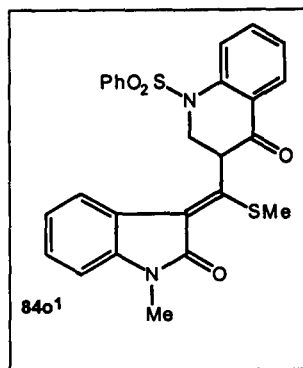
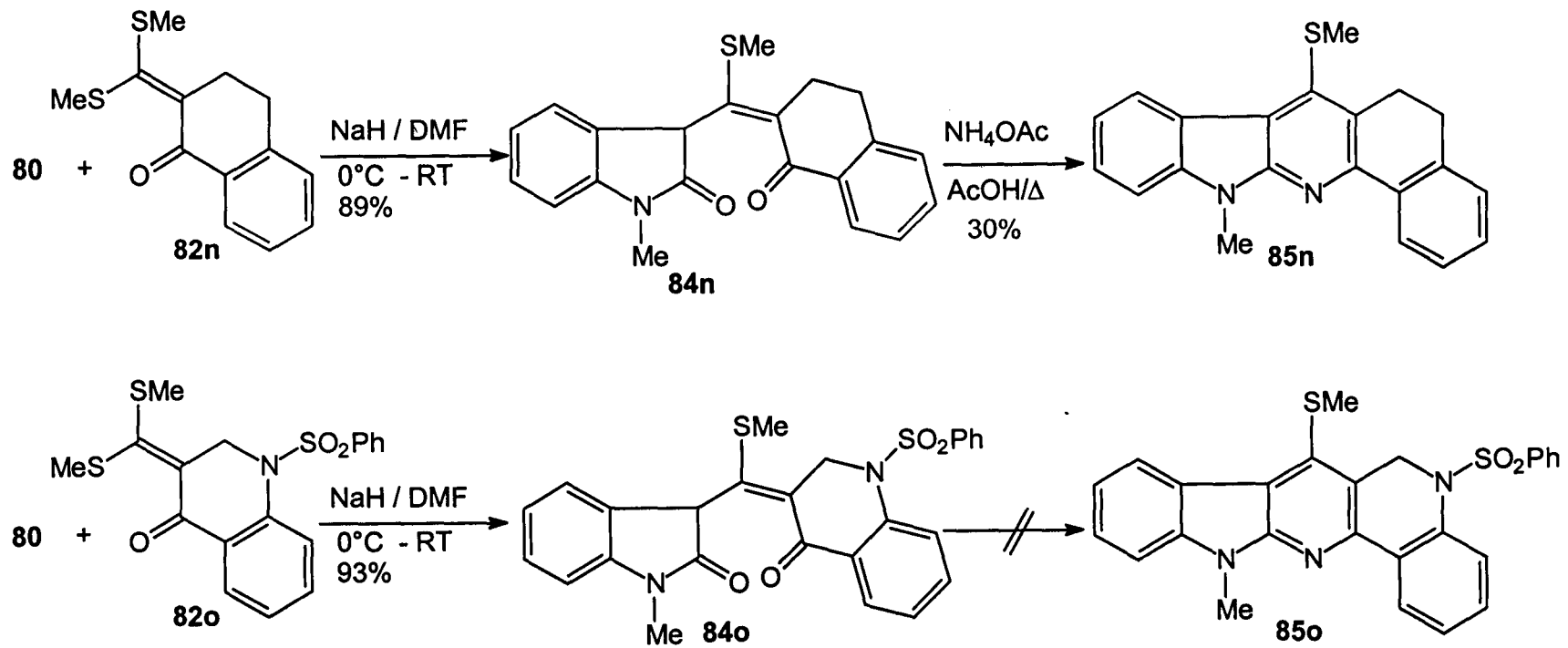
However diketone **84o** failed to cyclized when heated with ammonium acetate in acetic acid. Possibly the reaction failed because of the rigid geometry of **84o₁** which is not favorable for cyclization. Therefore we considered to prepare this intermediate **84o** without SMe group so that the intermediate diketone might follow the favorable geometrical configuration.

Scheme 20



The successful alternative method is described in scheme 22. The desired **82o₂** was prepared as reported earlier from our laboratory⁴² and **82o₂** was then smoothly condensed with **77** to afford the corresponding diketone **84o₂** in 85% yield. The diketone **84o₂** underwent smooth cyclization when heated with ammonium acetate in acetic acid to afford a mixture of two products **88o₁** and **85o₂**. The first fraction was eluted with hexane/ethyl acetate

Scheme 21



9.5: 0.5 over silica gel to get a product characterized as compound **85o₂** in 50 % yield. Mp = 136-137 °C; crystallized as colorless crystals. The structure was confirmed by analytical and spectral data as given below:

IR (KBr): 1593, 1554, 1489, 1470 cm⁻¹

¹H NMR (200 MHz, CDCl₃): δ 3.90 (s, 3H, NCH₃), 5.20 (s, 2H, -CH₂-), 6.80-7.00 (m, 3H, ArH), 7.16-7.29 (m, 3H, ArH), 7.40 – 7.64 (m, 4H, ArH), 7.80 – 7.88 (m, 3H, ArH), 8.32 – 8.40 (m, 1H, ArH).

MS (m/z, %): 426 (M⁺+1, 6.3), 225 (M⁺, 20), 284 (M⁺-31, 100)

Anal. Calcd. for C₂₅H₁₉N₃O₂S (425.51): C 70.57, H 4.50, N 9.88%

Found C 70.31, H 4.75, N 9.63%.

The second fraction with R_f value 0.6 (benzene) was eluted with hexane/ethyl acetate 9:1 and characterized as **88o₁** obtained in 15% yield. The structure was established by analytical and spectral data which are given below:

R_f = 0.6

Mp = 160 °C

IR (KBr): 1598, 1530, 1500, 1450 cm⁻¹

¹H NMR (300 MHz, CDCl₃): δ 4.03 (s, 3H, NCH₃), 7.33-7.39 (m, 1H, ArH), 7.43 (d, 1H, J = 8.1 Hz, ArH), 7.60 (t, 1H, J = 7.5 Hz, ArH), 7.71 (t, 1H, J = 7.3 Hz, ArH), 7.76 – 7.82 (m, 1H, ArH), 8.11 – 8.19 (m, 2H, ArH), 8.71 (m, 1H, ArH), 9.22 (dd, 1H, J = 8.0, 1.3 Hz, ArH), 9.30 (m, 1H, ArH)

^{13}C NMR (75.5 MHz) δ 27.76, 96.08, 109.20, 117.69, 120.23, 120.72, 121.40, 123.79, 126.46, 127.41, 128.15, 129.04, 129.60, 142.05, 146.22, 146.86, 153.06.

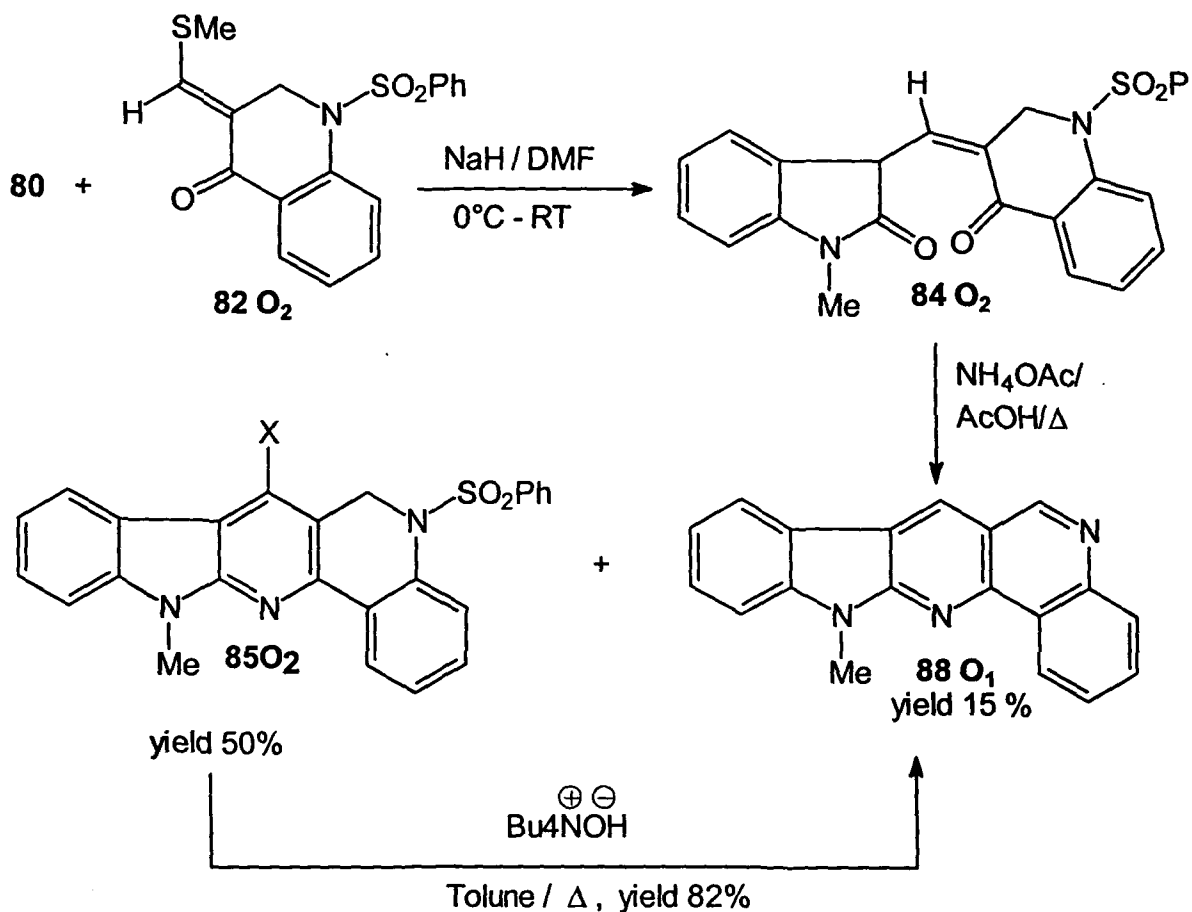
MS (m/z, %): 284 ($M^+ + 1$, 21), 283 (M^+ , 100), 282 ($M^+ - 1$, 65)

Anal Calcd. for $\text{C}_{19}\text{H}_{13}\text{N}_3$ (283.44): C 80.55, H 4.62, N 14.83%

Found C 80.34, H 4.48, N 14.68%

The dihydro compound **85O₂** was transformed into **88O₁** in 82% yield by treatment with base under PTC.

Scheme 22



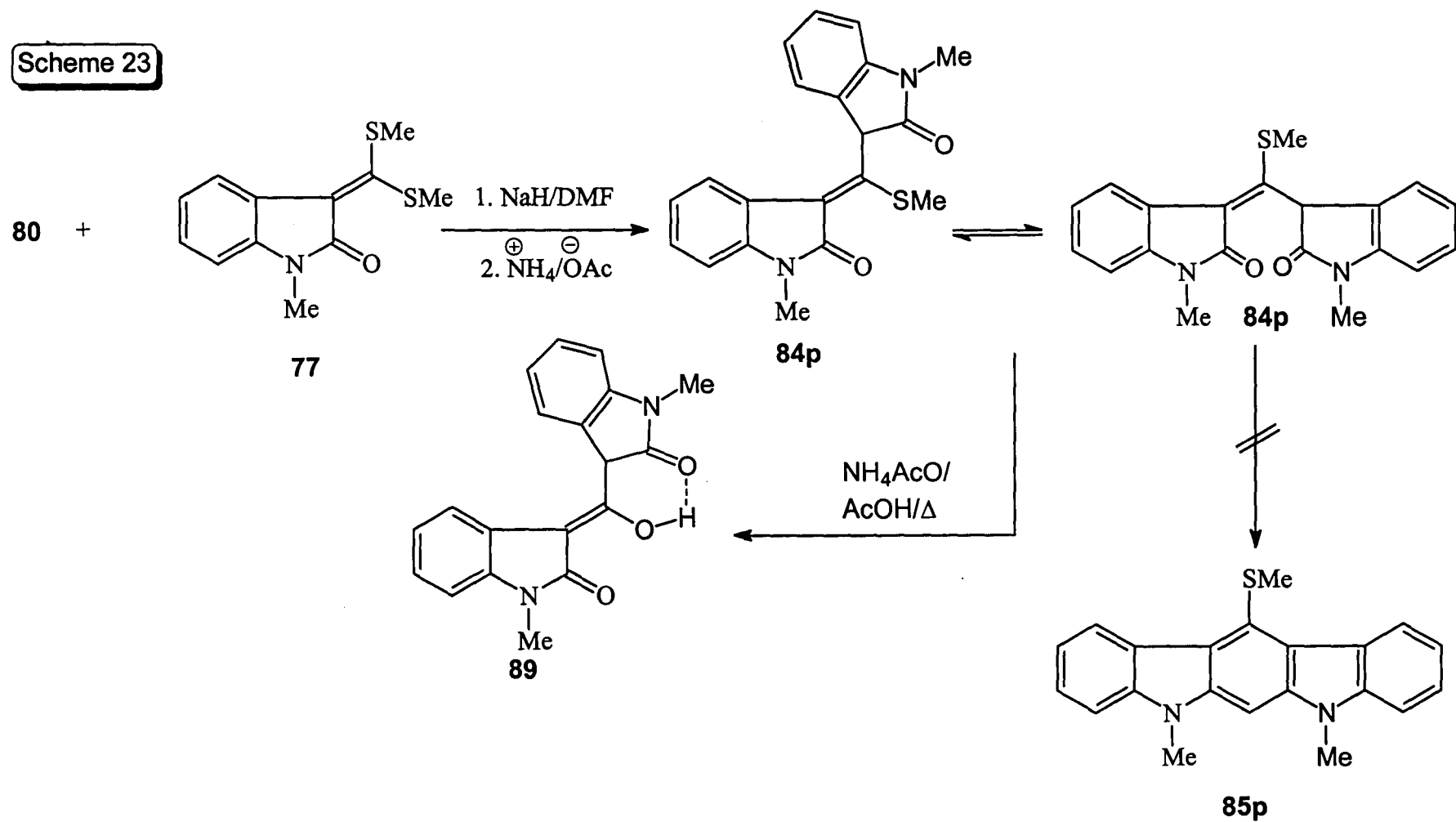
The ketene dithioacetal **77** was reacted with **80** to yield the product **85p** which on treatment with ammonium acetate in refluxing acetic acid afforded a single product which was characterized as the hydrolyzed product **89** in 71% yield.

The analytical and spectral data are presented in the experimental section. The envisaged product **85p** could not be obtained (scheme 23).

Pyrido[2,3-*b*]indoles, generally referred to as α -carbolines have been recently recognized as an important class of bioactive molecules. Many marine alkaloids such as Grossularine **1** and **2**, which are cytotoxic towards tumor cells, belong to this class. There are many other natural products having pyrido[2,3-*b*]indole ring system with various biological activities, described in the introduction of this chapter. The literature methods for the synthesis of these molecule systems are generally not satisfactory due to the difficulties encountered in preparing starting materials and lengthy synthetic operations resulting in poor yields. We have therefore developed an efficient and versatile method for the synthesis of a wide range of substituted and annelated α -carbolines based on simple starting materials. Thus oxindole or its derivatives are conveniently condensed with α -oxoketene dithioacetals to afford the corresponding diketones in high yields. These diketones on treatment with ammonium acetate in acetic acid afforded the corresponding pyrido[2,3-*b*]indoles in high yields. The method is general and flexible with freedom to choose the substituent/substituents on the otherwise less reactive pyridine ring. The synthesis of the anxiolytic agent **5** is attempted through the application of

our method and is described in scheme 20 and it is one step behind the target molecule. **85m** was obtained in good yield which is being investigated for its conversion to target molecule. Efforts are in progress to extend the synthetic application of this method to other biologically important α -carboline.

Scheme 23



EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover (Capillary method) and Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 297 and 983 spectrophotometers and are reported in cm^{-1} . ^1H NMR (300 MHz, 400 MHz and 500 MHz) and ^{13}C NMR (75.5 MHz, 100 MHz and 125 MHz) spectra were recorded on a Bruker-ACF-300 and Jeol-LA-400 and Bruker-AM-500 spectrometers. The chemical shifts (in ppm) and coupling constants (Hz) are reported in the standard fashion with respect to TMS as internal lock. Mass measurements were carried out with JEOL JMS-D-300 and Finnigan Voyager-GC-8000 mass spectrometers. Masses are reported in unit of mass over charge (m/z), the molecular or base peaks and relative intensities are indicated by (M^+) and (%) respectively. Elemental analyses were performed on 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 (160-120 mesh).

CHEMICALS, REAGENTS AND SOLVENTS

Commercially available NaH suspension and glacial acetic acid (SISCO, SPEDTROCHEM) was used. *N,N*-dimethyl formamide (SPECTROCHEM) was purchased bottle grade and dried over calcium hydride, distilled and

stored over molecular sieves (4A). Anhydrous ammonium acetate was purchased from spectrochem. Tetrahydrofuran (THF) was obtained anhydrous by keeping the deperoxidised THF over sodium benzophenone. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Raney Ni (W4) was prepared according to the reported procedure.

STARTING MATERIAL

The commercial sample of aniline, N-methyl aniline, acetone, acetophenone, chloroacetic acid, thionyl chloride, 2-butanone, cyclohexanone, isopropyl methyl ketone, 4-methoxy acetophenone, 4-methyl acetophenone, 4-chloro acetophenone were purified by distillation under reduced pressure before used. 1-Tetralone, propiophenone, N-sulphonyl quinolone were prepared according to the reported procedure. Oxoketene dithioacetals required for the present investigation were prepared according to the earlier reported general procedures which are given below:

General Procedure for Preparation of α -Oxoketene Dithioacetals (82a-n)

:

A mixture of ketone (0.2 mol) and carbon disulfide (0.21 mol) was added dropwise to an ice cold and well stirred suspension of sodium *t*-butoxide (0.4 mol) in dry benzene (200 mL) and the reaction mixture was allowed to stir at ambient temperature for 5-6 h. Acid free dimethyl sulfate

(0.25 mol) was then gradually added at 0C° with constant stirring. After stirring at room temperature for 8-10 h, the reaction mixture was quenched with aqueous saturated ammonium chloride solution (200 ml). The organic layer was separated out and aqueous layer was extracted with benzene (3 x 50 ml) and combined benzene extracts were washed with water (1x 100 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude S,S-acetals in 67-89% yields. Colorless crystals were obtained by crystallization from chloroform-hexane. Formation of all S,S-acetals were confirmed by comparing their mp and NMR, IR data with those of reported data and authentic samples.

Preparation of N-benzenesulphonyl-3-[bis(methylthio)methylene]1,2,3,4-tetrahydro-4-quinolone 82o.

A mixture of N-benzenesulphonyl-1,2,3,4-tetrahydroquinolone 14.3 g (0.05 mol) and carbondisulfide 3ml (0.05 mol) in dry benzene was added to an ice cooled and well stirred suspension of sodium t-butoxide (0.10 mol) in dry benzene (150 ml). The reaction mixture was stirred for 4-5 h and methyl iodide 6.3 ml (2 mol) was then gradually added with cooling and the reaction mixture was further stirred for 6 h. It was then poured into ice cold water (200 ml), extracted with benzene (2X200 ml) and the combined benzene extracts were washed thoroughly with water (3X50 ml), dried over sodium sulphate and evaporated to give only residue which on tituration with hexane/benzene afforded yellow crystalline needles, 78 % yield, mp. $111-112\text{ }^{\circ}\text{C}$.

Synthesis of 3-[Bis(methylthio)methylene]-1,2,3,4-tetrahydro-N-benzene sulphonylquinol-4-one 82o₁ and 3-(methylthio)methylene-N-benzene sulphonylquinol-4-one 82o₂.

To a well stirred solution of 82o₁ 3.91g (0.01 mol) in glacial acetic acid (60 ml), sodium borohydride 1.5 g (0.04 mol) was added slowly (portion wise) in 30 min at 5-10 °C. The reaction mixture was further stirred for another 3 h at room temperature (monitored by tlc) and then poured into ice cold water (100 ml) followed by extraction with chloroform (3X50 ml). The combined chloroform extract were washed with water (3X100 ml), dried over sodium sulfate and concentrated to give a viscous residues, which on column chromatography over silica gel (hexane and ethyl acetate as eluent) gave pure 82o₂

General procedure for the debenzenesulphonylation followed by aromatization of 85o₂. To a solution of 85o₂ (1.3 g, 0.003 mol) in toluene (20 ml), were added a catalytic amount of tetrabutyl ammonium bromide (phase transfer catalyst) and 50 % aqueous NaOH (15 ml). The mixture was heated to reflux for 12 h, cooled, diluted with cold water (100 ml) and extracted with chloroform (3X50 ml) dried over sodium sulphate, concentrated and on tituration with hexane afforded nearly quantitative yields of aromatized product 88o₁ (0.89g, 82 %).

General Procedure for the reaction on N-methyloxindole with α -oxoketene dithioacetal.

To a well stirred solution of NaH (0.04 mol) in dry DMF (10 ml), N-methyloxindole (0.02 mol) dissolved in dry DMF (10 ml) was added dropwise at °C. After keeping for 45 min to 1 h the appropriate α -oxoketene dithioacetal (0.02 mol) was added dropwise to the reaction mixture at 0 °C and kept stirring for further 10-15 h at room temperature. It was then poured into ice cold water and extracted with chloroform (3X100 ml). The combined extract were thoroughly washed with water (3X150 ml), evaporated to give crude product which was crystallized by chlorofom / hexane giving dark yellow needles in quantitative yields.

Some of the diketone adduct formed by the reaction of N-methyloxindole with α -oxoketene dithioacetal are given below:

3-[1-Methylthio-2-(4-methoxybenzoyl)]ethyledene-1-methyl-2-oxoindole (84b):

Yellow crystals; m.p. 132-133 °C (chloroform - hexane); Yield 92 %.

IR (KBr): ν_{\max} 1695, 1670, 1602, 1563, 1506, 1482 cm^{-1} .

^1H NMR (90 MHz, CDCl_3): δ 2.43 (s, 3H, SCH_3), 3.17 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 5.56(s, 2H, $-\text{CH}_2-$), 6.73 – 7.33 (m, 4H, ArH), 7.92 – 8.23 (m, 4H, ArH). Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{NO}_3\text{S}$ (353.44): C, 67.97; H, 5.42; 3.96%. Found: C, 68.29; H, 5.19; N, 3.72.

3-[2-Acetyl-1-methylthio]propyledene-1-methyl-2-oxoindole (84f):

Yellow crystals; m.p. 121 – 122 °C (chloroform – hexane); Yield 90 %.

IR (KBr): ν_{\max} 1710, 1671, 1605, 1587, 1562 cm^{-1} .

^1H NMR (90 MHz, CDCl_3): δ 1.50 (d, 3H, $J = 6.0$ Hz, CH_3), 2.24 (s, 3H, CH_3), 2.45 (s, 3H, SCH_3), 3.24 (s, 3H, NCH_3), 5.90 (d, 1H, $J = 6.2$ Hz), 6.82 – 7.27 (m, 3H, Ar), 8.17 (d, 1H, $J = 6.0$, H-3).

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}_2\text{S}$ (275.37): C, 65.43; H, 6.22; N, 5.09%. Found: C, 65.71; H, 5.97; N, 5.31%

3-[2-Benzoyl-1-methylthio]propylenedene-1-methyl-2-oxindole (84h):

Red crystals; m.p. 142 °C (Chloroform – hexane); Yield 89 %.

IR (KBr): ν_{\max} 1670, 1605, 1585, 1543, 1481 cm^{-1} .

^1H NMR (90 MHz, CDCl_3): δ 1.56 (d, 3H, $J = 6.4$ Hz, CH_3), 2.26 (s, 3H, SCH_3), 3.26 (s, 3H, NCH_3), 6.80 – 7.50 (m, 7H, ArH), 7.93 – 8.12 (m, 3H, ArH).

Anal. Calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_2\text{S}$ (325.43): C, 70.13; H, 5.88; N, 3.96%. Found: C, 70.38; H, 5.61; N, 4.49%.

3-[2-Acetyl-2-benzoyl-1-methylthio]methylenedene-1-methyl-2-oxindole (84i):

Red crystals; m.p. 151 °C (Chloroform – hexane); Yield 86 %.

IR (KBr): ν_{\max} 1710, 1685, 1585, 1543, 1481 cm^{-1} .

^1H NMR (90 MHz, CDCl_3): δ 2.23 (s, 3H, CH_3), 2.26 (s, 3H, SCH_3), 3.34 (s, 3H, NCH_3), 6.32 – 7.47 (m, 7H, ArH), 7.26 – 8.15 (m, 3H, ArH).

Anal. Calcd. for $C_{19}H_{19}NO_3S$ (331.42): C, 70.23; H, 5.45; N, 3.88%. Found: C, 70.33; H, 5.64; N, 4.44%.

3-[(1,2,3,4-Tetrahydro-*N*-benzenesulphonyl-4-quinolone)methylthio]methylene-1-methyl-2-oxoindole (84o):

Yellow crystals; mp. 130 – 131 °C (Chloroform – hexane); Yield 90%.

IR (KBr): ν_{\max} 3450, 1701, 1659 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 2.50 (s, 3H, SCH_3), 3.18 (s, 3H, NCH_3), 4.47 (t, 2H, $J = 8$ Hz, $-\text{CH}_2-$), 6.92 (d, 1H, $J = 8.5$ Hz, ArH), 7.04 (t, 1H, $J = 8.2$ Hz, ArH), 7.22 – 7.34 (m, 3H, ArH), 7.34 – 7.57 (m, 5H, ArH), 7.81-7.82 (m, 2H, ArH), 8.10 (d, 2H, $J = 3.2$ Hz, ArH).

^{13}C NMR (100 MHz, CDCl_3): 15.19, 25.91, 47.95, 51.43, 107.48, 121.89, 122.55, 123.70, 125.52, 125.77, 126.82, 127.90, 128.22, 128.41, 129.39, 133.31, 133.58, 140.26, 142.31, 149.99, 164.32, 188.11.

Anal. Calcd. for $C_{26}H_{22}N_2O_4S_2$ (490.60): C, 63.65; H, 4.52; N, 5.71%. Found: C, 63.84; H, 4.31; N, 5.43%.

3-[Bis(methylthio)methylene]-1,2,3,4-tetrahydro-*N*-benzenesulphonyl-4-quinolone (82o):

Light yellow crystals; mp. 111-112 °C; yield 73 %.

IR (KBR): ν_{\max} 3267, 1620, 1589, 1469, 1345 cm^{-1} .

^1H NMR (90 MHz, CDCl_3): δ 2.29 (s, 3H, SCH_3), 2.47 (s, 3H, SMe), 5.19 (s, 2H, NCH_2), 7.30 – 8.20 (m, 9H, ArH).

MS (m/z , %): 391 (M^+ , 21), 250 ($M^+ - 141$, 100)

Anal. Calcd. for $C_{18}H_{17}NO_3S$ (391.517): C 55.21, H 4.37, N 3.57%

Found C 55.30, H 4.38, N 3.53%.

3-[Bis(methylthio)methyl]-1,2,3,4-tetrahydro-*N*-benzenesulphonyl-4-quinolone (82o₃):

Light yellow crystals (hexane, ether); mp. 80-81 °C; yield 45 %.

IR (KBr): ν_{\max} 2917, 1680, 1596 cm^{-1} .

¹H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H, SCH₃), 2.14 (s, 3H, SMe), 2.65 (dd, 1H, $J = 3.6, 12.9$ Hz, CH), 3.98 (t, 1H, $J = 13.5$ Hz, CH), 4.30 (brs, 1H, CH), 4.63 (dd, 1H, $J = 3.6, 14.7$ Hz, CH), 7.24 (t, 1H, $J = 7.2$ Hz, ArH), 7.45 (t, 2H, $J = 7.5$ Hz, ArH), 7.54-7.56 (m, 2H, ArH), 7.70 (d, 2H, $J = 7.5$ Hz, ArH), 7.83 (d, 1H, $J = 8.0$ Hz, ArH), 7.92 (d, 1H, $J = 7.5$ Hz, ArH).

Anal. Calcd. for $C_{18}H_{19}NO_3S_3$ (393.527): C 54.93, H 4.78, N 3.56%

Found C 54.81, H 4.78, N 3.51%.

3-(Methylthio)methylene-1,2,3,4-tetrahydro-*N*-benzenesulphonyl-4-quinolone (82o₂):

Light yellow crystals (hexane, ether); mp. 164-165 °C; yield 51 %.

IR (KBr): ν_{\max} 2898, 1651, 1596, 1500 cm^{-1} .

¹H NMR (90 MHz, $CDCl_3$): δ 2.51 (s, 3H, SCH₃), 4.63 (s, 2H, NCH₂), 7.30-8.10 (m, 10H, ArH and olefinic H).

MS (m/z , 100 %): 345 (M^+ , 11.9), 204 ($M^+ - 141$, 97.2).

Anal. Calcd. for $C_{17}H_{15}NO_3S$ (345.415): C 59.10, H 4.37, N 4.05%

Found C 58.93, H 4.38, N 4.07%

General Procedure for Ammonium Acetate Induced Cyclization of Diketone Adduct to Pyrido[2,3-*b*]indoles.

To the diketone adduct (0.01 mol) dissolved in glacial acetic acid (25 ml), ammonium acetate (0.03 mol) was added and refluxed for 5 h. The reaction mixture was then brought to room temperature and poured into ice cold water (200 ml), extracted with chloroform (3x75 ml), dried over sodium sulphate, evaporated to give crude product which was purified by column chromatography using hexane/ethylacetate 18:2 as eluent, to yield pure pyrido[2,3-*b*]indoles in excellent yields.

Desulphurization Reaction *via* Raney Ni on 4-Methylthio-2-phenylpyrido[2,3-*b*]indole:

To a solution of 97 (0.001 mol) in ethanol (20 ml) was added Raney Ni (one spoon) and refluxed for 5h, cooled, filtered through sintered funnel (G-3), concentrated to give crude product which was purified by a short column chromatography by hexane as eluent.

2-(4-Methoxyphenyl)-9-methyl-3-methylthiopyrido[2,3-*b*]indole (85b):

White crystals; m.p. 147-148 °C (chloroform - ether); Yield 75 %.

IR (KBr): ν_{\max} 1596, 1534, 1425, 1413 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.58 (s, 3H, SCH_3), 3.79 (s, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 6.95 (d, 2H, $J = 7.5\text{Hz}$, ArH), 7.16 (s, 1H, ArH-3), 7.22-7.30

(m, 2H, Ar H-6 and H-7), 7.41 (t, 1H, $J = 9.1$ Hz, ArH), 8.03 (d, 2H, $J = 7.5$ Hz, ArH), 8.21 (d, 1H, $J = 7.8$ Hz, ArH-5).

^{13}C NMR (75.5 Hz, CDCl_3): δ 13.75, 27.48, 55.27, 105.76, 108.44, 110.39, 113.92, 119.71, 120.60, 123.13, 125.40, 128.39, 132.69, 139.80, 144.86, 150.96, 153.06, 160.20.

MS (m/z , %): 335 ($M^+ + 1$, 87.6), 334 (M^+ , 100), 333 ($M^+ - 1$, 79), 319 ($M^+ - 15$, 37.4).

Anal. calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{OS}$ (334.44): C 71.83, H 5.42; N, 8.38%: Found: C, 72.01; H, 5.19; N, 8.59%.

2-(4-Chlorophenyl)-9-methyl-4-methylthiopyrido[2,3-*b*]indole (85c):

Yellow crystals; m.p. 142-143 °C (chloroform – ether); Yield 74 %.

IR (KBr): ν_{max} 1611, 1601, 1573, 1489, 1463, 1446 cm^{-1}

^1H NMR (200 MHz, CDCl_3): δ 2.75 (s, 3H, SCH_3), 4.00 (s, 3H, NCH_3), 7.33 (s, 1H, ArH-3), 7.47 (d, 2H, $J = 6.6$ Hz, ArH), 7.49-7.52 (m, 3H, ArH), 8.10 (d, 2H, $J = 6.8$ Hz, ArH), 8.31 (d, 1H, $J = 5.2$ Hz, ArH-5).

Anal. calcd for $\text{C}_{19}\text{H}_{15}\text{ClN}_2\text{S}$ (338.86): C 67.35, H 4.46; N, 8.27%: Found: C, 67.06; H, 4.62; N, 8.49%.

9-Methyl -2-(4-methylphenyl)-4-methylthiopyrido[2,3-*b*]indole (85d):

White crystals; m.p. 139-140 °C (chloroform – ether); Yield 76 %.

IR (KBr): ν_{max} 1610, 1557, 1549, 1486 cm^{-1}

^1H NMR (200 MHz, CDCl_3): δ 2.42 (s, 3H, CH_3), 2.74 (s, 3H, SCH_3), 4.00 (s, 3H, NCH_3), 7.24 (s, 1H, ArH-3), 7.32 (d, 2H, $J = 6.0$ Hz, ArH), 7.42-7.52 (m, 3H, ArH), 8.05 (d, 2H, $J = 6.2$ Hz, ArH), 8.30 (d, 1H, $J = 6.0$ Hz, ArH-5).

Anal. calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{S}$ (318.44): C 75.44, H 5.70; N, 8.79%; Found: C, 75.68; H, 5.95; N, 8.58%.

2,9-dimethyl-4-methylthiopyrido[2,3-*b*]indole (85e):

White crystals; m.p. 126-127 °C (chloroform – ether); Yield 61 %.

IR (KBr): ν_{max} 1602, 1584, 1549, 1464 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.66 (s, 3H, SCH_3), 2.69 (s, 3H, CH_3), 3.92 (s, 3H, NCH_3), 6.78 (s, 1H, ArH), 7.26-7.32 (m, 1H, ArH), 7.39-7.50 (m, 2H, ArH), 8.26 (d, 1H, $J = 7.8$ Hz, ArH-5).

^{13}C NMR (75.5 Hz, CDCl_3): δ 13.82, 24.95, 27.75, 108.52, 109.05, 109.89, 119.79, 120.67, 123.08, 125.35, 139.40, 144.99, 150.91, 154.69.

MS (m/z , %): 243 ($\text{M}^+ + 1$, 19), 242 (M^+ , 79), 241 ($\text{M}^+ - 1$, 18).

Anal. calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{S}$ (242.34): C 69.39, H 5.82; N, 11.56%; Found: C, 69.13; H, 6.05; N, 11.79%.

4-Methylthio-2,3,9-trimethylpyrido[2,3-*b*]indole (85f):

Light yellow crystals; m.p. 96-97 °C (chloroform – ether); Yield 60%.

IR (KBr): ν_{max} 1563, 1547, 1489, 1413 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.41 (s, 3H, SCH_3), 2.61 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.91 (s, 3H, NCH_3), 7.25-7.31 (m, 1H, ArH), 7.39 (d, 1H, $J = 7.9$ Hz, ArH), 7.46-7.52 (m, 1H, ArH), 8.72 (d, 1H, $J = 7.9$ Hz, ArH).

^{13}C NMR (75.5 Hz, CDCl_3): δ 16.08, 18.25, 14.45, 27.55, 96.08, 108.52, 115.37, 119.57, 120.48, 123.48, 125.92, 139.99, 140.04, 149.00, 153.88.

MS (m/z, %): 257 ($\text{M}^+ + 1$, 57), 256 (M^+ , 100), 255 ($\text{M}^+ - 1$, 34), 241 ($\text{M}^+ - 15$, 74).

Anal. calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{S}$ (256.66): C 70.28, H 6.29; N, 10.93%; Found: C, 70.43; H, 6.42; N, 10.76%.

2-Isopropyl-9-methyl-4-methylthiopyrido[2,3-*b*]indole (85g):

Yellow crystals; m.p. 86-87 °C (chloroform – ether); Yield 55%.

IR (KBr): ν_{max} 1564, 1533, 1516, 1471 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ 1.39 (d, 6H, $J = 6.9$ Hz, 2CH_3), 2.61 (s, 3H, SCH_3), 3.16-3.19 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.88 (s, 3H, NCH_3), 6.77 (s, 1H, ArH), 7.22- 7.45 (m, 3H, ArH), 8.24 (d, 1H, $J = 7.8$ Hz, ArH).

^{13}C NMR (75.5 Hz, CDCl_3): δ 23.05, 27.48, 31.39, 36.83, 106.42, 108.41, 119.55, 123.00, 125.17, 125.43, 139.49, 144.51, 150.81, 163.86.

MS (m/z, %): 271 ($\text{M}^+ + 1$, 24), 270 (M^+ , 100), 269 ($\text{M}^+ - 1$, 11.7), 223 ($\text{M}^+ - 47$, 53).

Anal. calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{S}$ (270.40): C 71.07, 6.71; N, 10.36%; Found: C, 71.29; H, 6.49; N, 10.55%.

3,9-dimethyl-4-methylthio-2-phenylpyrido[2,3-*b*]indole (85h):

Colorless crystals; m.p. 110-111 °C (chloroform – ether); Yield 59%.

IR (KBr): ν_{\max} 1610, 1591, 1470, 1577 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.50 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.94 (s, 3H, NCH_3), 7.30-7.35 (m, 1H, ArH), 7.41-7.64 (m, 7H, ArH), 8.80 (d, 1H, $J = 7.8$ Hz, ArH).

^{13}C NMR (75.5 Hz, CDCl_3): δ 18.07, 27.73, 29.72, 108.68, 116.35, 119.78, 120.26, 123.98, 125.48, 126.55, 127.80, 128.07, 129.53, 140.79, 142.01, 149.84, 155.63.

MS (m/z, %): 319 ($\text{M}^+ + 1$, 13), 318 (M^+ , 57), 317 ($\text{M}^+ - 1$, 17), 303 ($\text{M}^+ - 15$, 8).

Anal. calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{S}$ (318.44): C 75.44, H, 5.69; N, 8.79%; Found: C, 75.68; H, 5.31; N, 8.98%.

2-(2-Furyl)-9-methyl-4-methylthiopyrido[2,3-*b*]indole (82j):

White crystals; m.p. 151-152 °C (chloroform – ether); Yield 78%.

IR (KBr): ν_{\max} 1613, 1588, 1540, 1485 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.63 (s, 3H, SCH_3), 3.84 (s, 3H, NCH_3), 6.53 (dd, 1H, $J = 3.1, 3.2$ Hz, ArH), 7.25 (d, 1H, $J = 3$ Hz, ArH), 7.22-7.29 (m, 3H, ArH), 7.39-7.44 (m, 1H, ArH), 7.51 (s, 1H, ArH) 8.20 (d, 1H, $J = 6.0$ Hz, ArH).

^{13}C NMR (75.5 Hz, CDCl_3): δ 13.77, 27.54, 96.07, 104.59, 108.37, 108.42, 110.95, 112.06, 119.82, 120.64, 123.15, 125.58, 139.88, 142.82, 145.12, 150.68, 154.53.

MS (m/z, %): 295 ($M^+ + 1$, 40), 294 (M^+ , 100), 293 ($M^+ - 1$, 55), 279 ($M^+ - 13.3$).

Anal. calcd for $C_{17}H_{14}N_2OS$ (225.13): C 69.36, 4.79; N, 9.52%; Found: C, 69.54; H, 4.52; N, 9.37%.

9-Methyl-4-methylthio-2-(2-thienyl)pyrido[2,3-*b*]indole (85k):

White crystals; m.p. 131-132 °C (chloroform – ether); Yield 71%.

IR (KBr): ν_{\max} 1545, 1520, 1480, 1455 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.70 (s, 3H, SCH₃), 3.93 (s, 3H, NCH₃), 7.12 (dd, 1H, $J = 3.9, 1.2$ Hz, ArH), 7.23 (s, 1H, ArH), 7.28-7.31 (m, 1H, ArH), 7.36-7.39 (m, 2H, ArH), 7.44-7.49 (m, 1H, ArH), 7.65 (dd, 1H, $J = 4.0, 1.4$ Hz, ArH), 8.23 (d, 1H, $J = 9.0$ Hz, ArH).

^{13}C NMR (75.5 Hz, CDCl_3): δ 13.84, 27.63, 96.08, 105.06, 108.54, 110.98, 119.94, 120.67, 123.17, 124.35, 125.64, 127.01, 127.86, 139.90, 145.06, 145.85, 148.52.

MS (m/z, %): 311 ($M^+ + 1$, 46), 310 (M^+ , 100), 309 ($M^+ - 1$, 39), 295 ($M^+ - 15$, 35).

Anal. calcd for $C_{17}H_{14}N_2S_2$ (310.45): C 65.77, H, 4.55; N, 9.02%; Found: C, 65.96; H, 4.22; N, 9.26%.

9-Methyl-4-methylthio-2-pyridylpyrido[2,3-*b*]indole (85l):

Yellow crystals; m.p. 151-152 °C (chloroform – ether); Yield 59%.

IR (KBr): ν_{\max} 1604, 1577, 1538, 1465 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.73 (s, 3H, SCH₃), 3.95 (s, 3H, NCH₃), 6.53 (d, 1H, $J = 3.2$ Hz, ArH), 7.25 (d, 1H, $J = 3$ Hz, ArH), 7.22-7.29 (m, 3H,

ArH), 7.89-7.95 (m, 2H, ArH), 8.15-8.19 (m, 1H, ArH) 8.20 (d, 1H, $J = 6.0$ Hz, ArH).

MS (m/z, %): 296 ($M^+ + 1$, 40), 295 (M^+ , 100), 294 ($M^+ - 1$, 57), 279 ($M^+ - 13.3$).

Anal. calcd for $C_{18}H_{15}N_3S$ (305.39): C 70.79, H, 4.95; N, 13.76%: Found: C, 70.55; H, 4.71; N, 13.92%.

3-Carbethoxy-2,9-dimethyl-4-methylthiopyrido[2,3-b]indole (85m):

Yellow crystals; m.p. 97-98 °C (chloroform – ether); Yield 51 %.

IR (KBr): ν_{\max} 1654, 1593, 1575, 1452 cm^{-1}

^1H NMR (80 MHz, CDCl_3): δ 1.21 (t, 3H, $J = 6.0$ Hz, $-\text{CH}_2\text{CH}_3$), 2.15 (s, 3H, CH_3), 2.25 (s, 3H, SCH_3), 3.85 (s, 3H, NCH_3), 4.24 (q, 2H, $J = 6.3$ Hz, $-\text{CH}_2\text{CH}_3$), 6.80-7.2 (m, 3H, ArH), 8.10 (d, 1H, $J = 6.0$ Hz, ArH).

MS (m/z, %): 314 (M^+ , 93), 285 ($M^+ - 29$, 10).

Anal. calcd for $C_{17}H_{18}N_2O_2S$ (314.42): C 64.92, H 5.77; N, 8.91%: Found: C, 64.71; H, 5.96; N, 8.69%.

5,6-Dihydro-12-methylbenzo[*h*]indolo[2,3-*b*]quinoline (85n):

Yellow crystals; m.p. 81-82 °C (chloroform – ether); Yield 30%.

IR (KBr): ν_{\max} 1602, 1536, 1516, 1485, 1462 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 2.45 (s, 3H, SCH_3), 2.99 (t, 2H, $J = 6.9$ Hz, $-\text{CH}_2-$), 3.41 (t, 2H, $J = 6.9$ Hz, $-\text{CH}_2-$), 3.91 (s, 3H, NCH_3), 7.25-7.34 (m, 3H, ArH), 7.38- 7.45 (m, 2H, ArH), 7.50-7.56 (m, 1H, ArH), 8.52 (d, 1H, $J = 7.8$ Hz, ArH), 8.76 (d, 1H, $J = 7.8$ Hz, ArH).

^{13}C NMR (75.5 Hz, CDCl_3): δ 18.28, 25.26, 28.66, 29.68, 108.60, 119.75, 120.62, 123.74, 125.54, 126.42, 126.94, 127.03, 127.45, 128.73, 135.59, 138.55, 139.12, 140.79, 150.54.

MS (m/z, %): 331 ($\text{M}^+ + 1$, 24), 330 (M^+ , 100), 329 ($\text{M}^+ - 1$, 11.7), 315 ($\text{M}^+ - 15$, 35).

Anal. calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{S}$ (330.45): C 76.33, 5.49; N, 8.48%: Found: C, 76.11; H, 5.65; N, 8.21%

5,6-Dihydro-12-methylindolo[2,3-*b*]quinoline (85r):

Red crystals; m.p. 91-92 °C (chloroform – ether); Yield 10%.

IR (KBr): ν_{max} 1601, 1585, 1563, 1449 cm^{-1}

^1H NMR (60 MHz, CDCl_3): δ 1.85-2.11 (m, 4H, $-(\text{CH}_2)_2-$), 2.25 (s, 3H, SCH_3), 3.01-3.23 (m, 4H, $-(\text{CH}_2)_2-$), 3.98 (s, 3H, NCH_3), 7.41-7.62 (m, 3H, ArH), 8.82 (d, 1H, $J = 7.6$ Hz, ArH).

MS (m/z, %): 283 ($\text{M}^+ + 1$, 29), 282 (M^+ , 100), 281 ($\text{M}^+ - 1$, 5), 267 ($\text{M}^+ - 15$, 42).

Anal. calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{S}$ (282.40): C 72.30, H, 6.42; N, 9.92%: Found: C, 72.15; H, 6.67; N, 9.71%.

2-Isopropyl-9-methyl-(1H)pyrido[2,3-*b*]indol-4-one (87g):

White crystals; m.p. 197-198 °C (chloroform-ether); Yield 10%.

IR (KBr): ν_{max} 3400, 1628, 1602, 1536, 1485 cm^{-1}

^1H NMR (300 MHz, CDCl_3): δ 1.45 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.08-3.15 (m, 1H, $-\underline{\text{CH}}(\text{CH}_2)_2$), 3.82 (s, 3H, NCH_3), 6.30 (s, 1H, ArH), 7.28-7.40 (m, 3H, ArH), 8.39 (d, 1H, $J = 6.0$ Hz, ArH), 11.41 (brs, 1H, NH).

MS (m/z, %): 241 ($M^+ + 1$, 17), 240 (M^+ , 100), 239 ($M^+ - 1$, 48), 225 ($M^+ - 15$, 94).

Anal. calcd for $C_{15}H_{16}N_2O$ (240.31): C 74.97, H, 6.71; N, 11.66%: Found: C, 74.68; H, 6.93; N, 11.41%.

2-Phenyl-3,9-dimethyl(1*H*)pyrido[2,3-*b*]indol-4-one (87h):

White crystals; m.p. 193-195 °C (chloroform – ether); Yield 15%.

IR (KBr): ν_{\max} 3450, 1675, 1610, 1540, 1485 cm^{-1}

1H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, CH_3), 3.29 (s, 3H, NCH_3), 7.00-7.26 (m, 3H, ArH), 7.36-7.66 (m, 5H, ArH), 8.00-8.13 (m, 1H, ArH).

MS (m/z, %): 288 (M^+ , 100)

Anal. calcd for $C_{19}H_{16}N_2O$ (288.35): C 79.14, H, 5.59; N, 9.72%: Found: C, 79.14; H, 5.28; N, 9.88%.

3-[(1-Methyl-2-oxoindole)hydroxy]methylene-1-methyl-2-oxoindole (89):

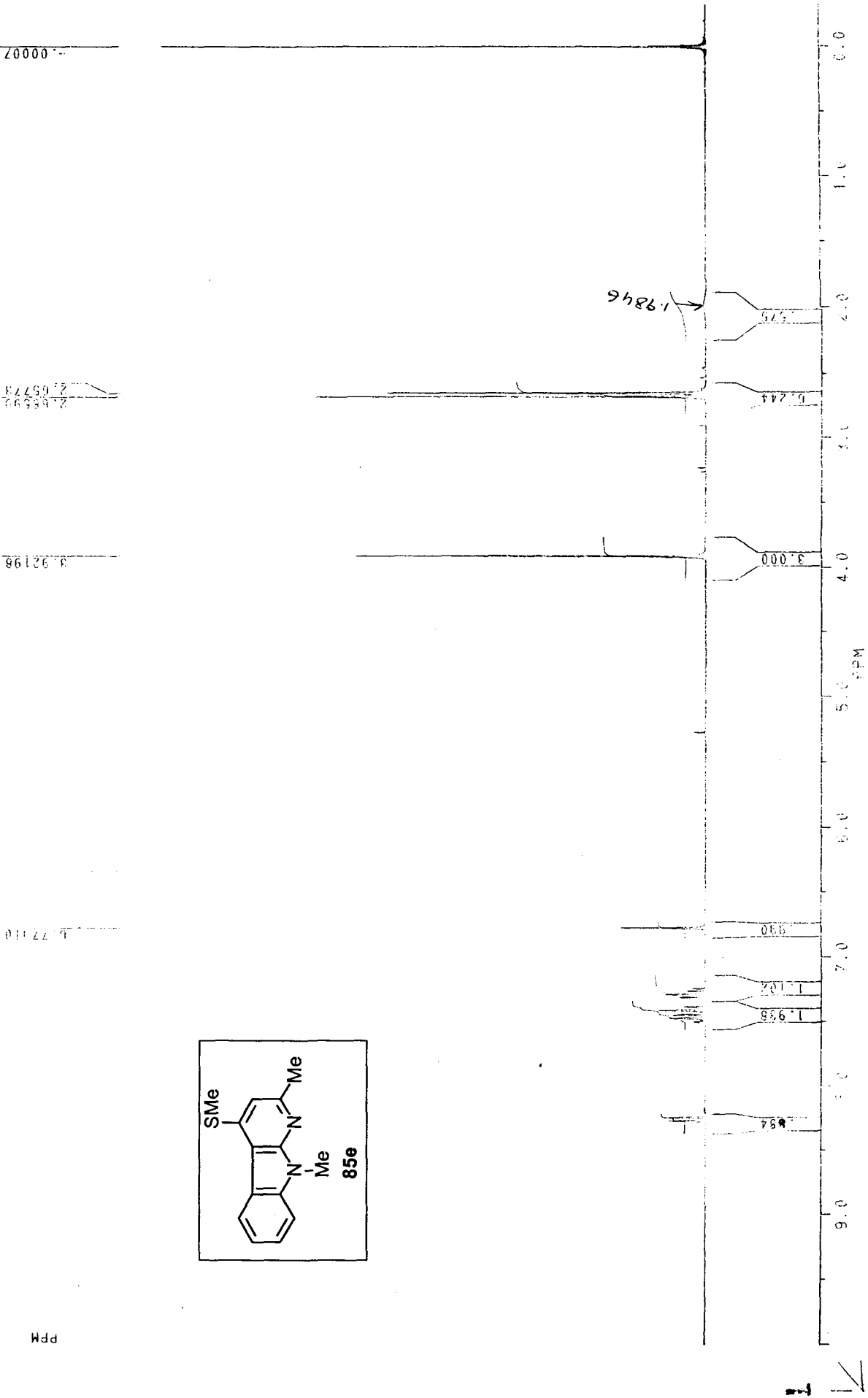
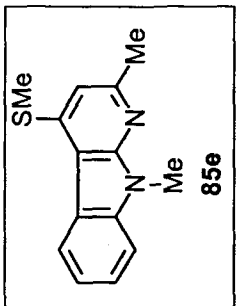
Yellow crystals: m.p. 177 – 178 °C (Chloroform – ether);

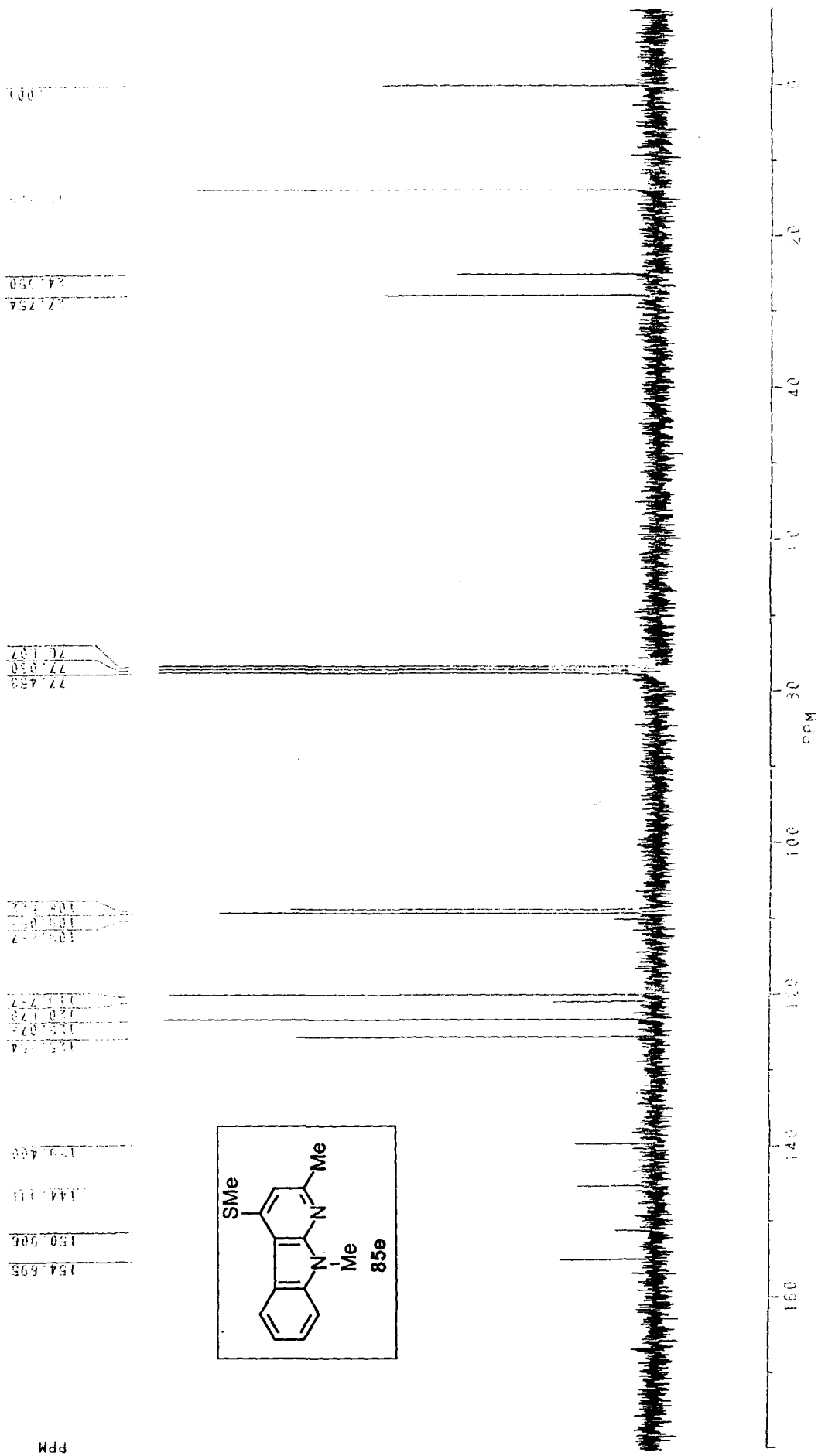
IR (KBr): ν_{\max} 3421, 1758, 1694, 1680, 1586 cm^{-1} .

1H NMR (200 MHz, $CDCl_3$): δ 3.69 (s, 3H, NCH_3), 3.72 (s, 3H, CH_3), 6.02 – 6.14 (m, 3H, ArH), 7.13-7.49 (m, 2H, ArH), 7.51-7.64 (m, 3H, ArH), 8.44 (brs, 1H, OH)

MS (m/z, %) 319 (M^+ , 50), 426 ($M^+ + 1$, 6.3).

Anal. Calcd. for $C_{19}H_{15}N_2O_3$ (319.54): C, 69.54; H, 5.52; N, 8.98%. Found: C, 69.31; H, 5.75; N, 9.13.





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2.67695

3.91371

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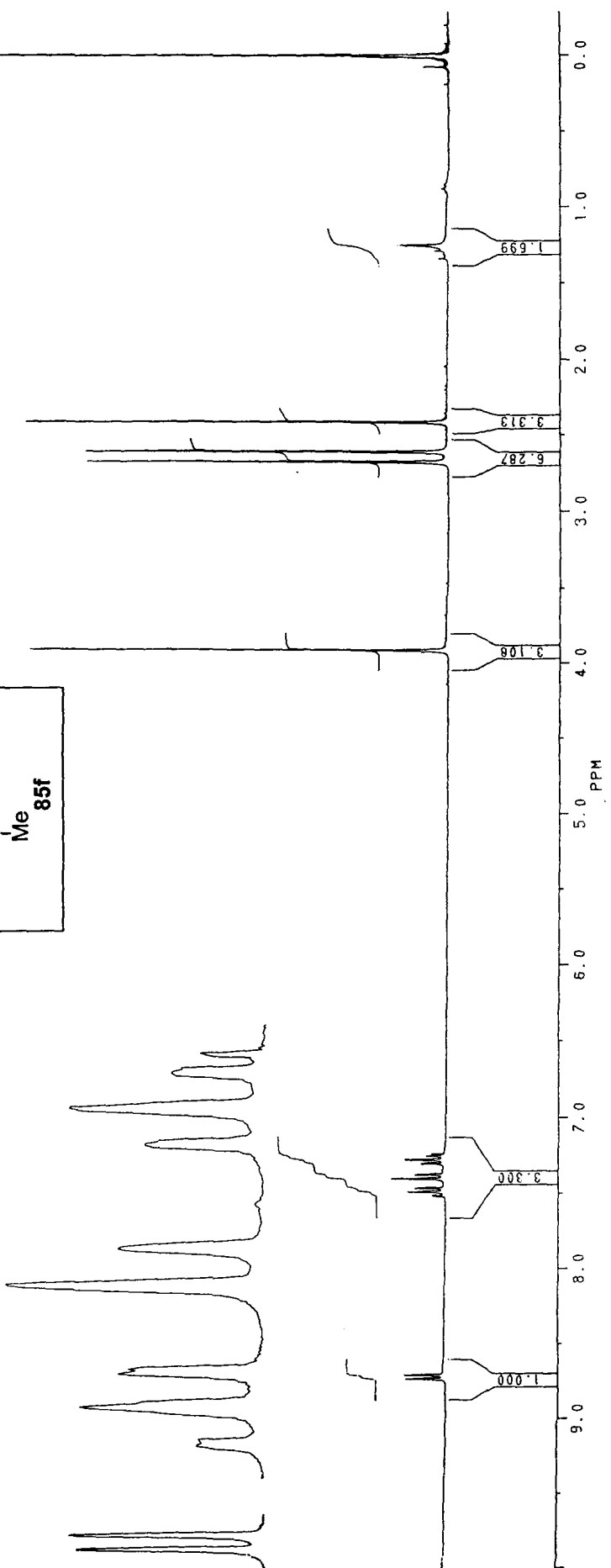
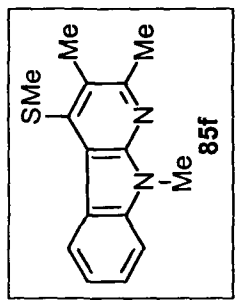
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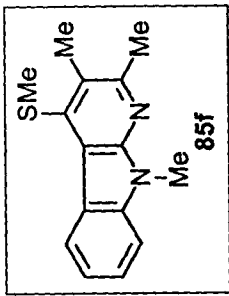
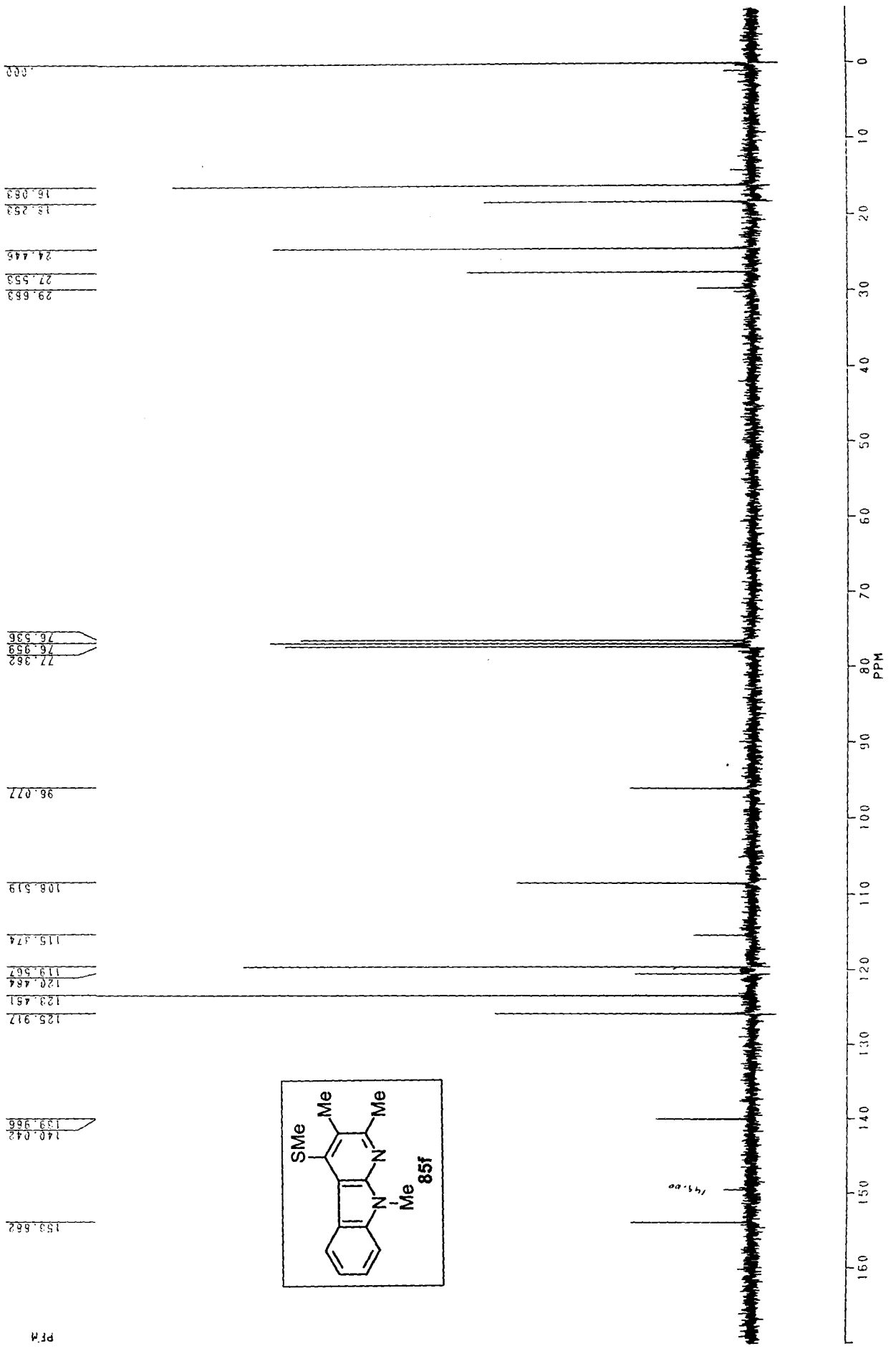
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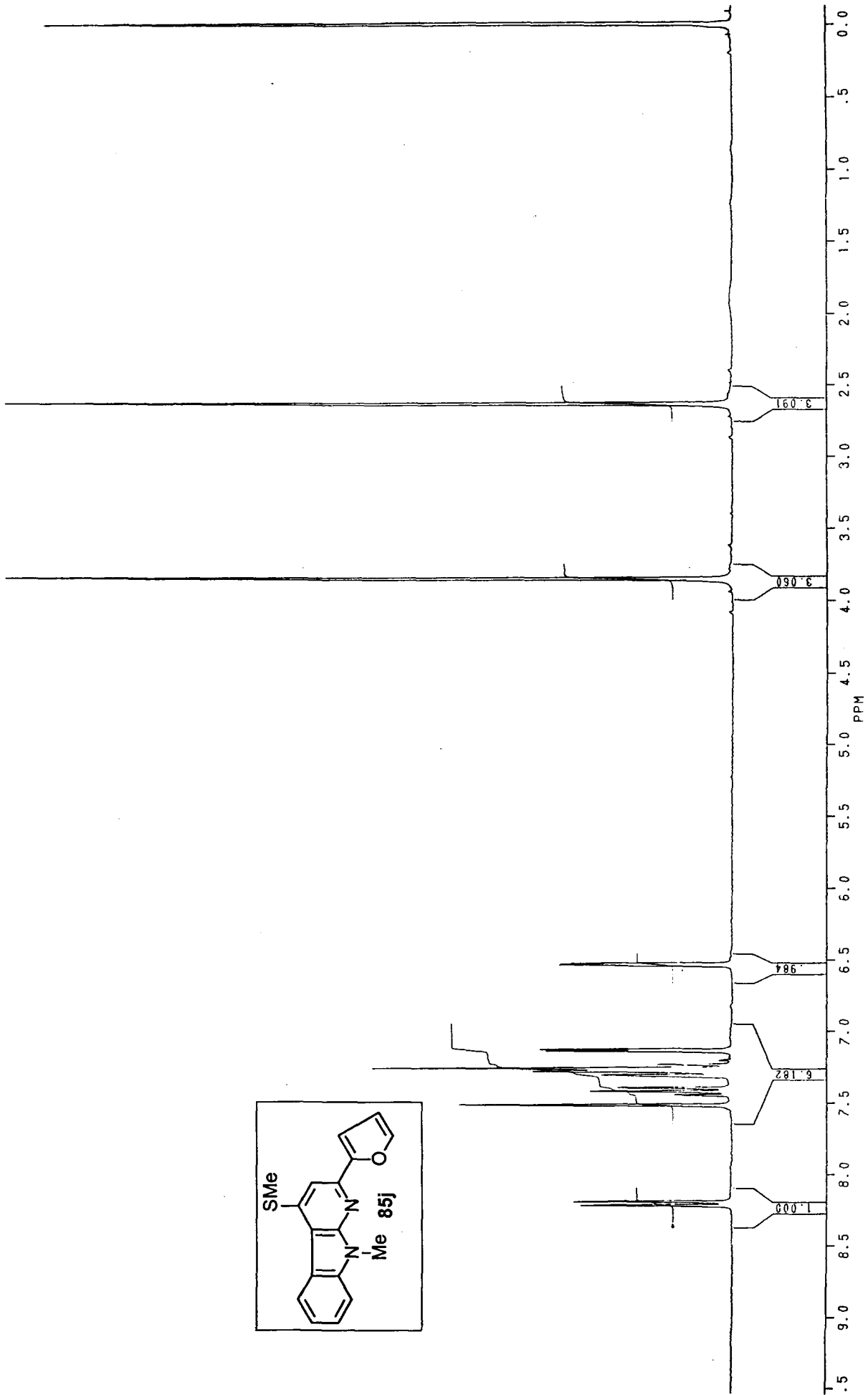
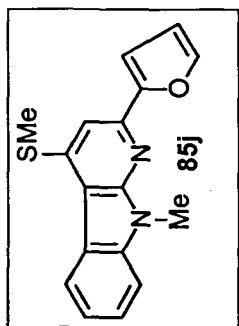
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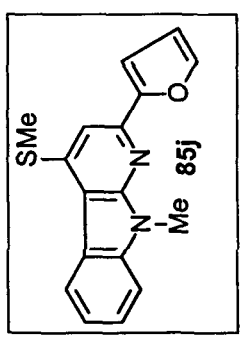
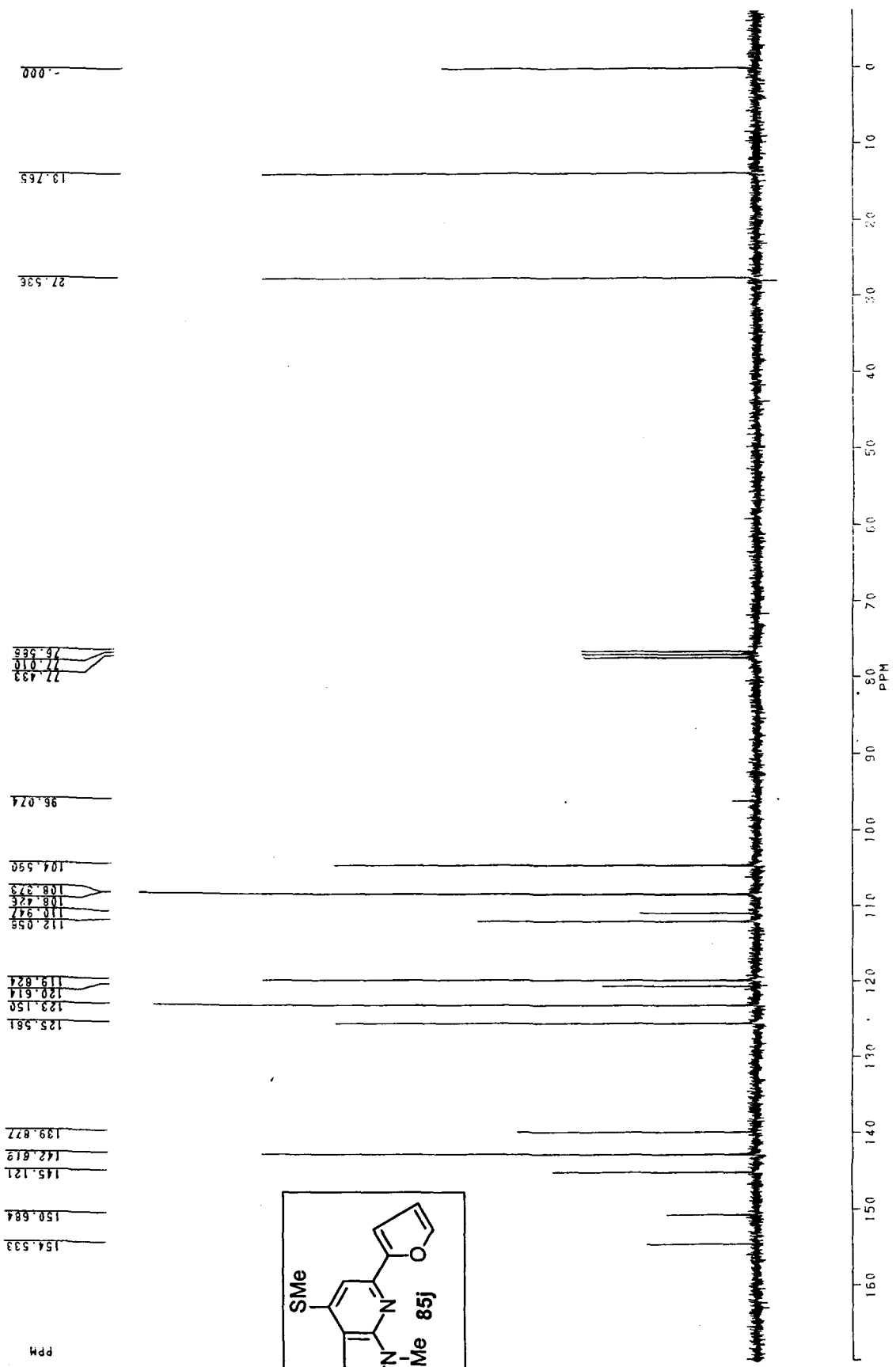
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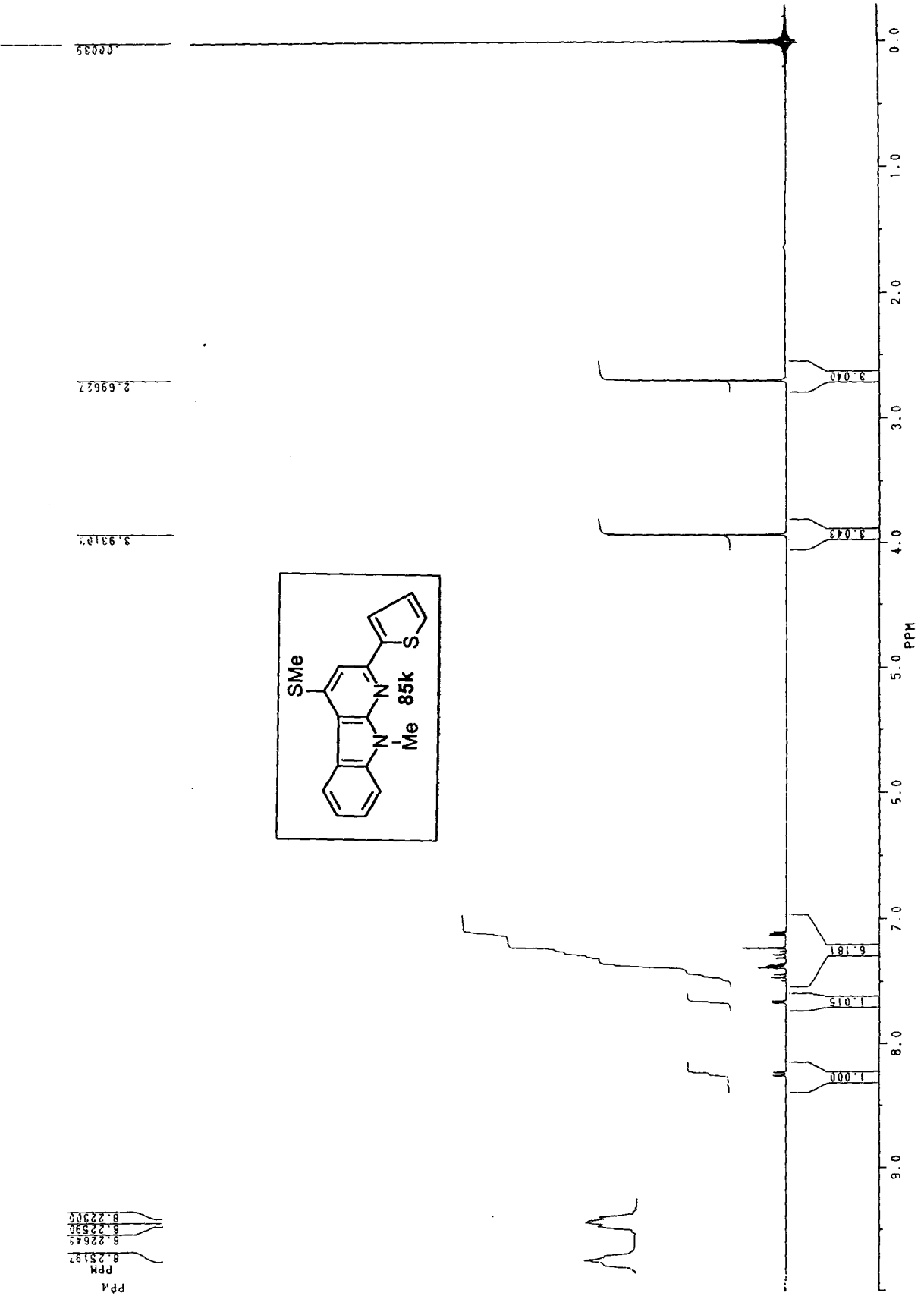
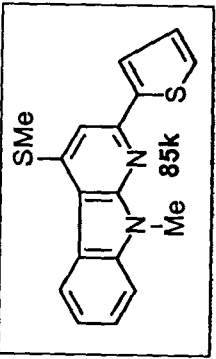




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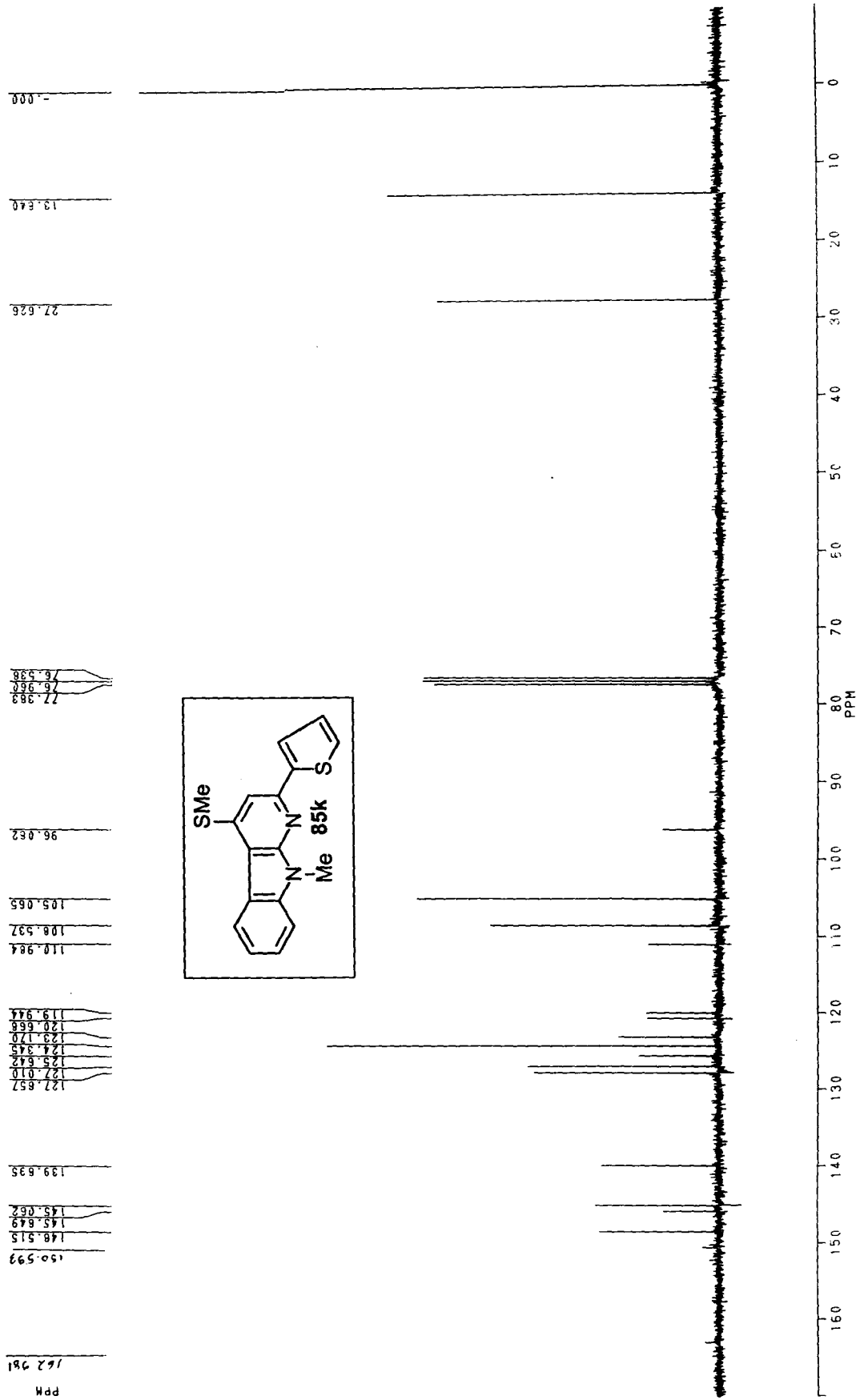
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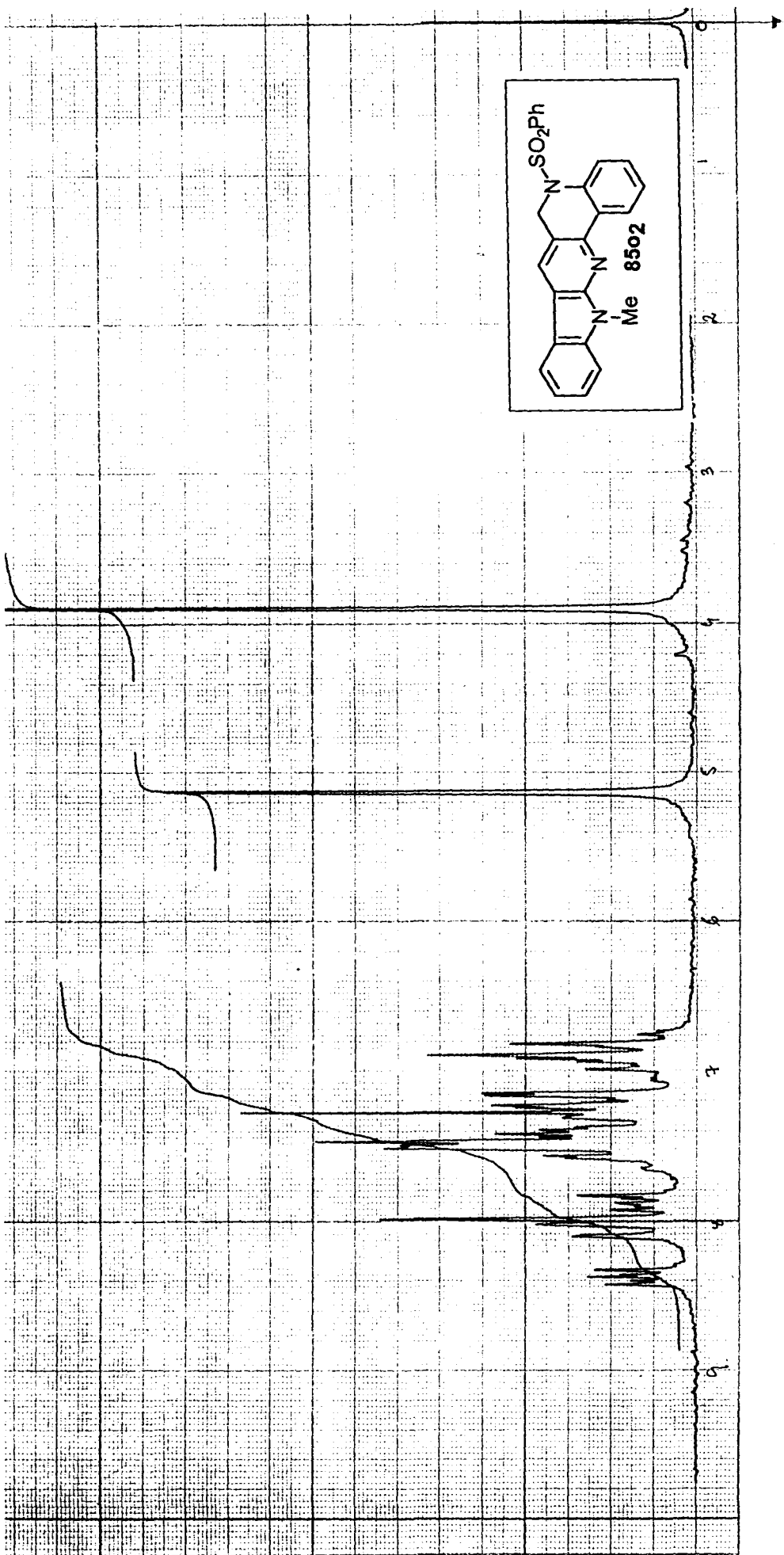
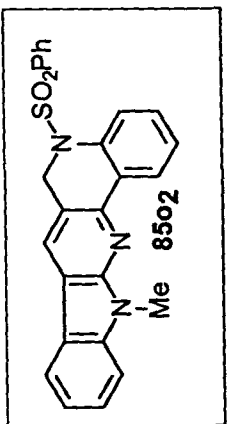
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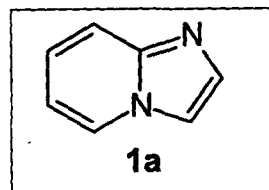
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CHAPTER III

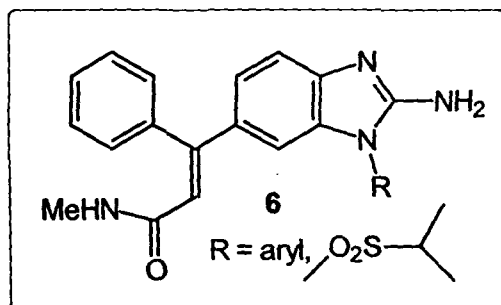
***“A FACILE SYNTHESIS OF 2-METHYLTHIO/ALKOXY/AMINO/
3-ACYLIMIDAZO[1,2-*a*]PYRIDINES: APPLICATION OF CUPRIC
CHLORIDE TO PROMOTE OXIDATIVE RING CLOSURE OF α -
OXOKETENE N,S-, N,O- AND N,N-ACETALS”***

Introduction

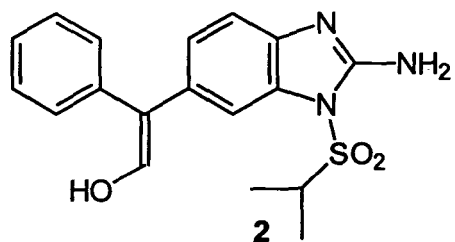
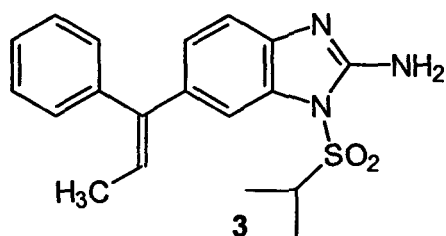
The imidazo[1,2-*a*]pyridine **1a** ring system has recently emerged as the most important skeleton possessing



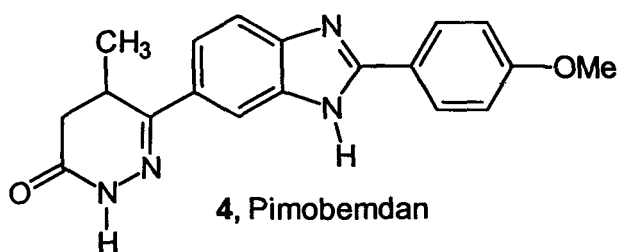
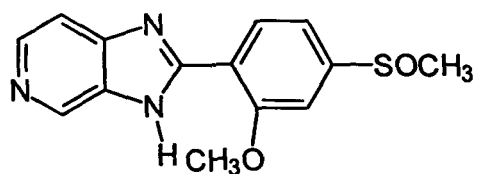
unusual biological properties with excellent bioavailability to treat human rhinovirus infection.¹ Rhinoviruses are a group of 110 categories which are recognized as the most important agents causing common cold in adults and children. The infection of these viruses result in serious tonic condition such as bronchitis, otitis, media, sinusites, emphysema and asthma.² Because of these common and frequently occurring infections, the antiviral activity is an important area of research. There are many strongly active antiviral drugs (scheme 1) which have failed in their *in vivo* activity and therefore they are rejected for any further clinical studies. These molecules Enviroxime **2**,³ Envirodene **3**⁴ and its aza analogues **5**⁵ (scheme 1) have been rejected as clinical candidates because of their high toxicity, unfavorable pharmacology and lack of bioavailability. Effective development of drugs for antiviral treatment has therefore remained elusive and research continues.



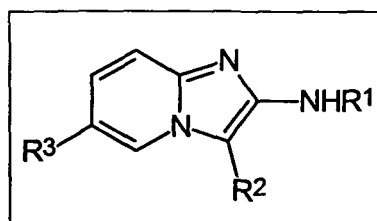
One of the most important developments in recent years is the discovery by

Scheme 1

2
 Enviroxime

3
 Enviradene

Broad spectrum Antiviral Agents


4, Pimobendan

5, Isomazole

Cardiotonic Agents



R1 = H, alkyl

R2 = RSO₂-, RCO-, Alkyl-SCH₂-, Aryl-SCH₂-

R3 = H, Me, Cl, F

Potential Antiviral Agents

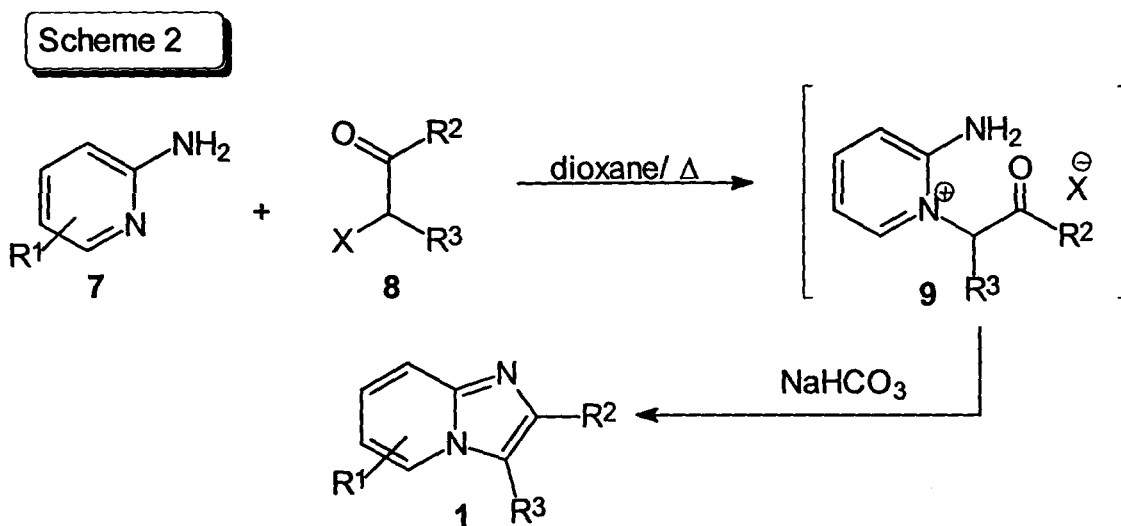
Hamdouchi and coworkers¹¹ that molecules of general formula 6 containing imidazo[1,2-*a*]pyridine ring have displayed pronounced antiviral activity *in vivo* comparable to the strong *in vitro* activities displayed by 2 and 3. The primary reason for the activity of this group of compounds appears to be bioavailability with little or no toxic effect. The chemistry of imidazo[1,2-*a*]pyridines has become important and many efforts are now being initiated to develop facile routes for the synthesis of these compounds.

We have developed a very facile and versatile method for the synthesis of functionalized imidazo[1,2-*a*]pyridines as part of our studies on α -oxoketene N,S-, N,O- and N,N-acetals. We describe in the following section some of the most important methods reported in the literature for the synthesis of imidazo[1,2-*a*]pyridine ring systems so that the new chemistry developed in this investigation for the synthesis of these novel class of compounds will be better appreciated.

A Brief Review on the Methods of Synthesis of Imidazo[1,2-*a*]pyridines

A large number of imidazo[1,2-*a*]pyridines have been reported in the literature generally following the method developed by Chichibabin in 1924. The method involves reaction of 2-aminopyridine 7 with α -halocarbonyl compounds 8 to afford the corresponding imidazo[1,2-*a*]pyridines in high yields (scheme 2)¹⁵. Several variations of this method involving imidazol ring closure are also reported in the literature.

Knolker and coworkers³ reported a new method (scheme 3) involving the construction of pyridine component of the ring over the preconstructed imidazole derivatives. Thus 1-benzylimidazole **10** reacted with dimethyl

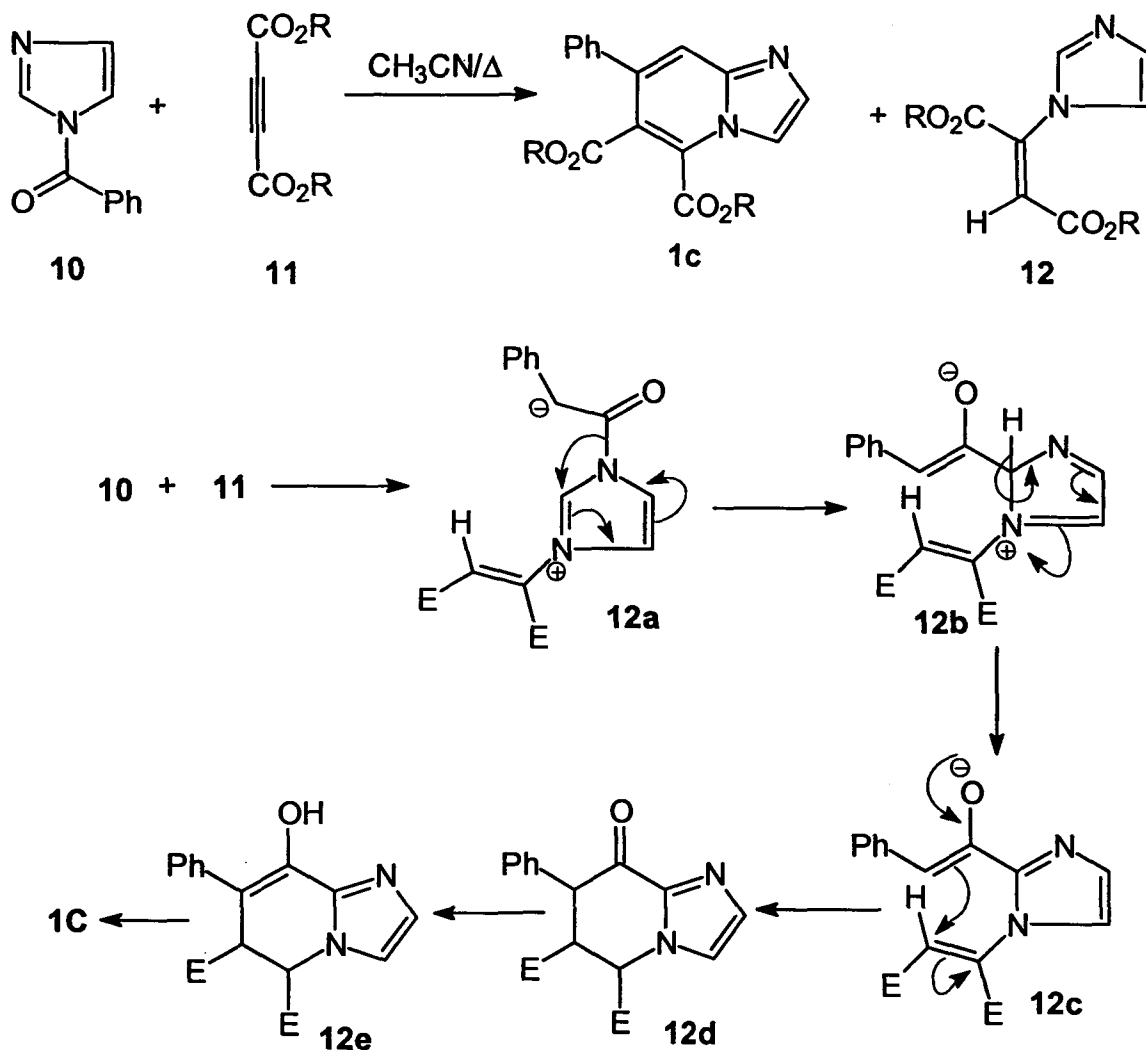


acetylene carboxylate **11** in refluxing acetonitrile to afford the corresponding imidazo[1,2-*a*]pyridines **1c** along with dimethyl imidazolyl fumarate **12** as a byproduct. The authors could get **1c** in 64% yield by manipulating the reaction conditions through slow addition of DMAD to the solution of **10** in dry acetonitrile at 60 °C. The mechanism involves initial electrophilic attack on **11** to yield **12a** which immediately follows 1,2 acyl group migration and proton transfer to afford **12c**. The intermediate **12c** forms C-C new bond through intramolecular attack to give **12d** and then the desired imidazo[1,2-*a*]pyridine **1c**. The authors have reasoned slow addition of DMAD is in confirmation of the mechanism.

Litvinov and coworkers²¹ reported an interesting method for the synthesis of imidazo[1,2-*a*]pyridines (scheme 4) involving *p*-bromophenacylbromide

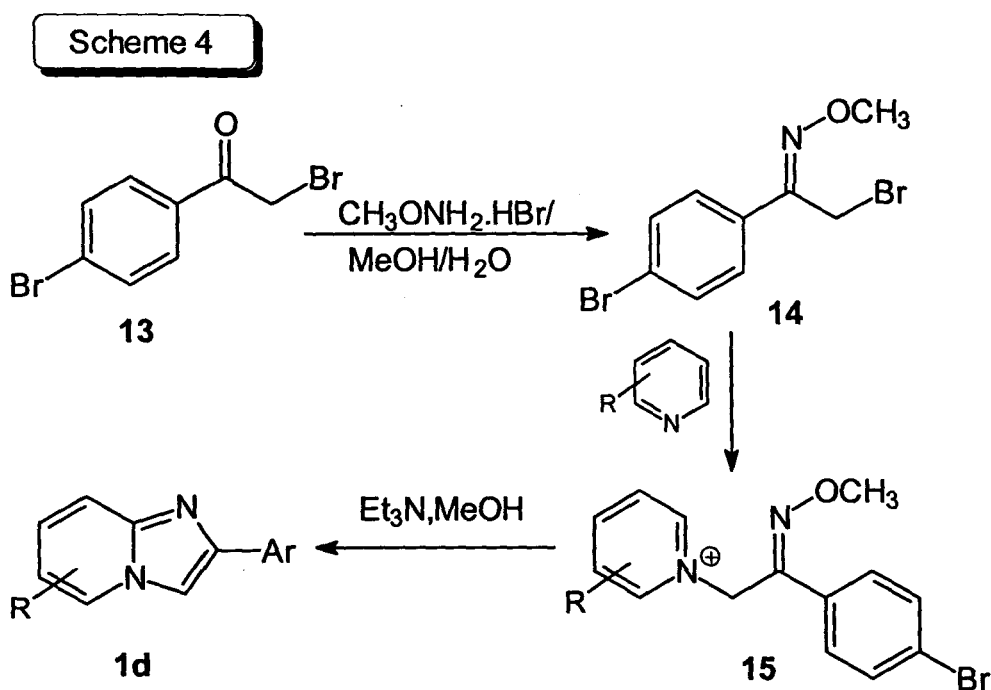
orthomethyloxime **14** with *Z* configuration exclusively which was confirmed by ^1H NMR and ^{13}C NMR spectra. It was then reacted with various pyridine

Scheme 3



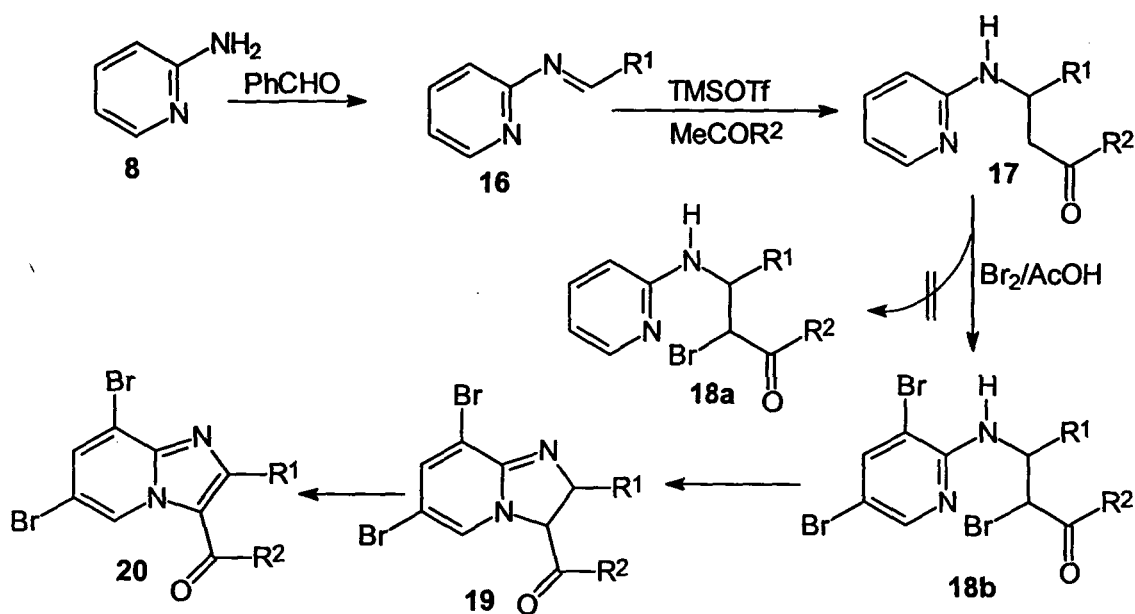
in acetone to form pyridinium salts **15** in excellent yields. Again the configuration of the product oxime was established as *E* configuration by NMR spectroscopy which favors intramolecular attack by nonbonding electrons on the 2-position of the pyridine ring in the presence of triethylamine

followed by elimination of methanol to afford the corresponding imidazo[1,2-*a*]pyridines **1d** in excellent yields. The method is different from that of Chichibabin type in that it does not require 2-aminopyridines since the



nitrogen comes from methyl oxime to form imidazole ring. A novel method for the synthesis of 3-acylimidazo[1,2-*a*]pyridine was reported by Bourguignon and coworkers (scheme 5).²³ The method involves the synthesis of amido ketone **17** which was prepared by addition of enolate anions from ketones to **16**. The compound **17** was brominated with bromine in acetic acid to afford **18b** in 86% yield which spontaneously underwent cyclization to afford unstable dihydro compound **19** which was rapidly transformed into the desired imidazo[1,2-*a*]pyridines **20** (scheme 5).

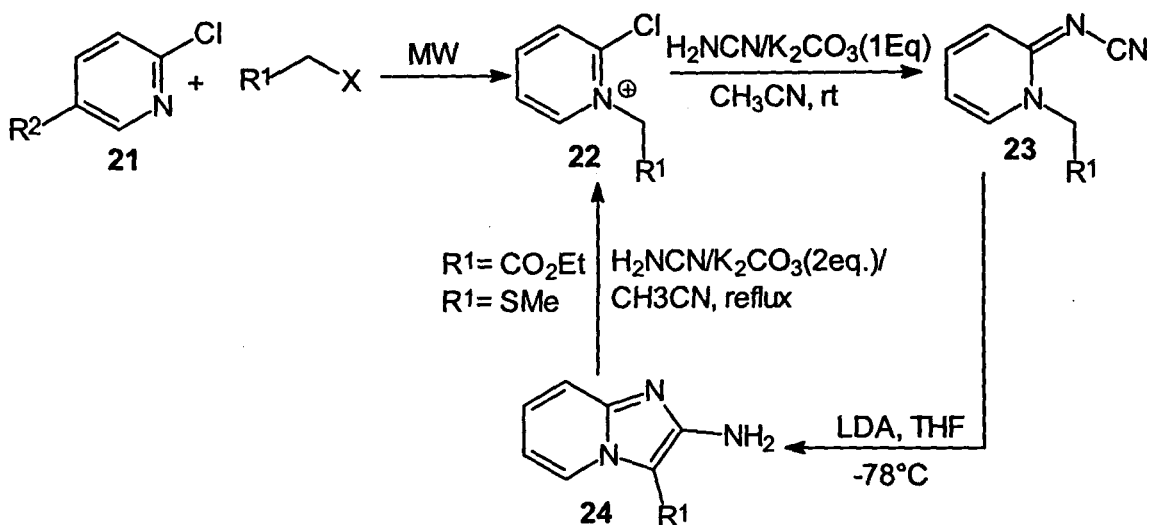
Scheme 5



Builla and coworkers²⁷ have reported a novel method for the synthesis of imidazo[1,2-*a*]pyridines 24 as formulated in scheme 6. The method also avoids the use of 2-aminopyridines which is generally the intermediate of Chichibabin reaction. Thus 2-chloro pyridinium salts 22 were reacted with cyanamide to afford the corresponding 23 followed by base acid cyclization to afford 2-amino-3-substituted imidazo[1,2-*a*]pyridines.

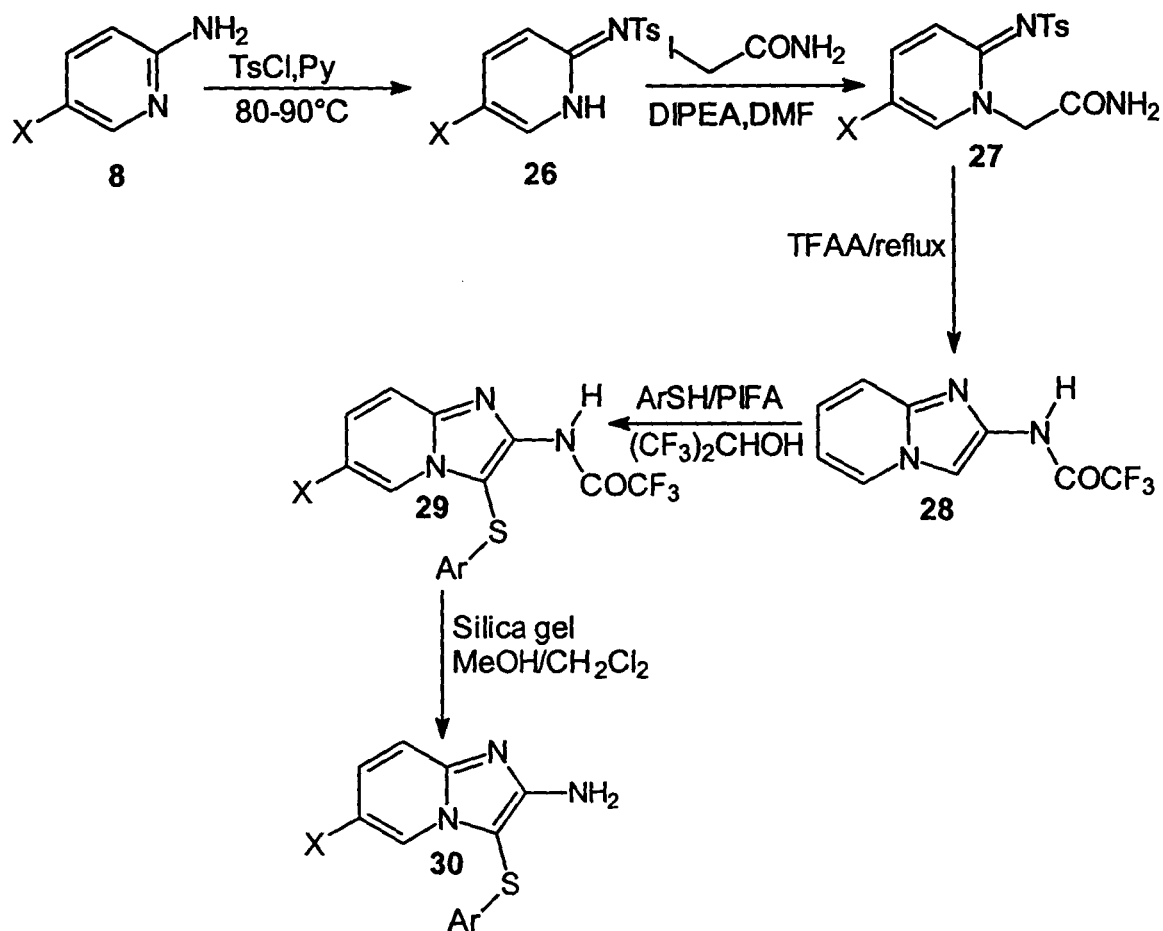
Hamdouchi and coworkers²⁴ have reported a novel method of imidazo[1,2-*a*]pyridines (scheme 7) and their chemoselective phenyl sulphonylation at 3-position in the presence of phenyliodone(III)bis(trifluoroacetate) thus 2-aminopyridine 8 was reacted with *p*-toluene sulphonyl chloride in the presence of pyridine to afford the

Scheme 6



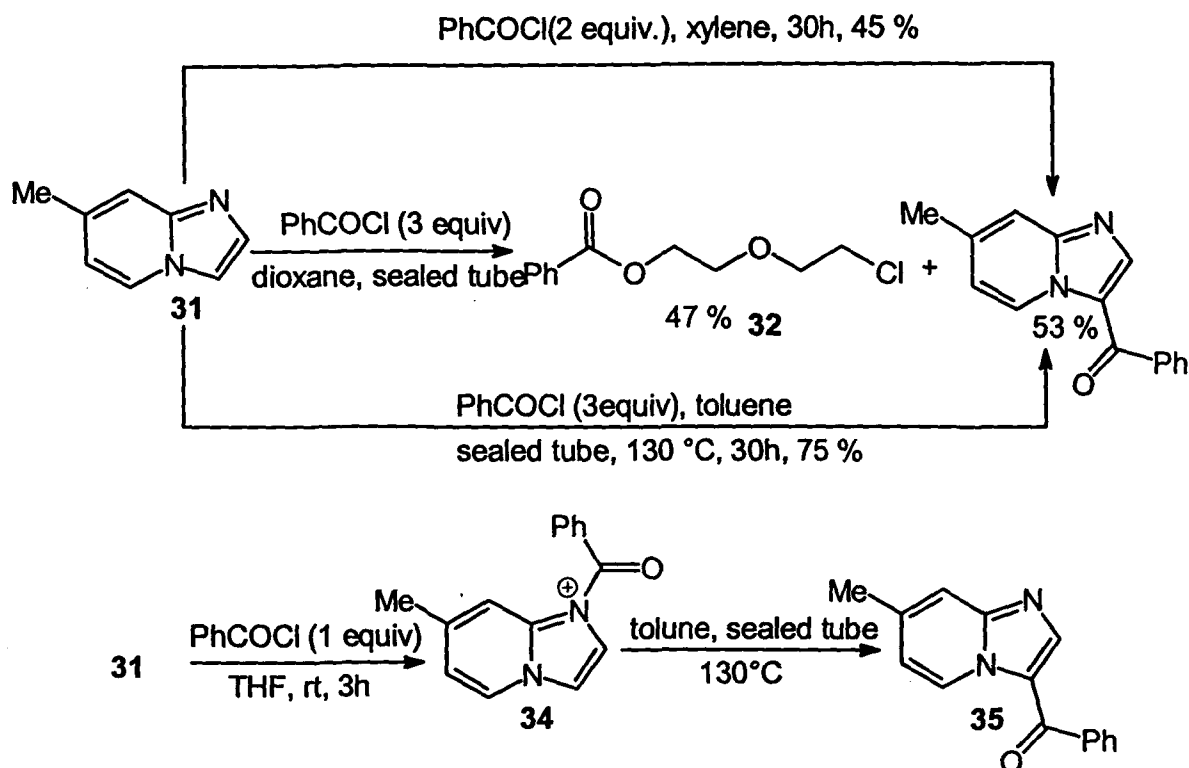
corresponding **26** which was then reacted with iodoacetamide in the presence of diisopropylethylamine in DMF to yield the corresponding carboxamide **27** in good yields. The authors have reported the use of Hunig's base (diisopropylethyl amine) instead of NaH in this reaction yielded **27** in high yields. The carboxamide was then treated with trifluoroacetic anhydride to afford the corresponding 2-trifluoroacetamidoimidazo[1,2-*a*]pyridine **28** in good yields. The sulphonylation was achieved when **28** was first treated with PIFA (phenyliodine (III)bis(trifluoroacetate) in the presence of thiophenol) and dissolved in thiophenol in hexafluoropropanol to afford the sulphenylated product **29**. The trifluoroacetamide was then cleaved to afford the corresponding 2-aminoimidazo[1,2-*a*]pyridine **30** in good yield (scheme7).

Scheme 7



Bourguignon and coworkers²³ have reported regiospecific thermal C-acylation of imidazo[1,2-*a*]pyridines as formulated in scheme 8. They have taken 7-methylimidazo[1,2-*a*]pyridine **31** and reacted with benzoyl chloride to afford the corresponding N -benzoyl imidazo[1,2-*a*]pyridinium ring **34** in high yield which when heated with toluene in sealed tube at 130°C the benzoyl group migrates to C-3 to afford the corresponding 3-benzoylimidazo[1,2-*a*]pyridine **35** in good yield. Compound **35** could also be obtained directly by refluxing **31** with benzoyl chloride (3 or 2 equivalents) in boiling xylene to afford directly **35** in 45 % yield.

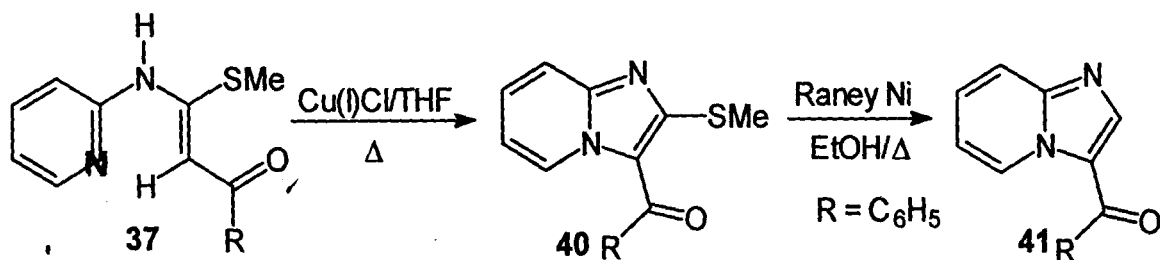
Scheme 8



In our laboratory a new efficient method for the synthesis of 2-methylthio-3-arylimidazo[1,2-*a*]pyridine was developed as formulated in scheme 9.^{26b} Thus the easily accessible S,N-acetals 37 when treated with Cu(I)Cl in dry THF the reaction mixture after workup yielded the corresponding imidazo[1,2-*a*]pyridine 40 in excellent yields. One of these methylthio compounds was subjected to desulphurization to afford the sulphur free imidazo[1,2-*a*]pyridine 41 in good yield (scheme 9).

The S,N-acetals 37 were conveniently prepared by reacting lithiated 2-aminopyridine with α -oxoketene dithioacetals to afford the corresponding S, N-acetals if the reaction is carried out with one equivalent of 2-aminopyridine. The corresponding N,N-acetals 38 were formed when 2-equivalent of

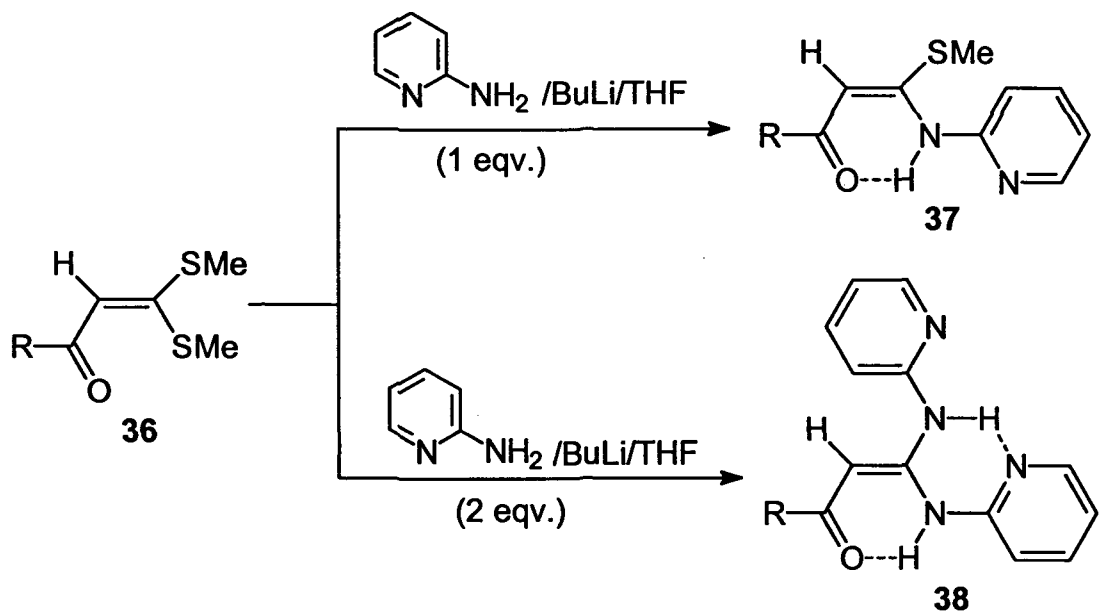
Scheme 9



- 37, 40a:** R = C_6H_5 ; X = SMe
b: R = 4-Cl C_6H_4 ; X = SMe
c: R = 4-MeOC $_6\text{H}_4$; X = SMe
d: R = 4-MeC $_6\text{H}_4$; X = SMe
e: R = 2-thienyl; X = SMe
f: R = 2-furyl; X = SMe

lithiated 2-aminopyridine were reacted with **36** (scheme 10).^{26a} The use of *n*-butyllithium became necessitated since the reaction of 2-aminopyridine **8** was not satisfactory and failed to yield a single product either **37** or **38** under the several attempted conditions in the absence of strong base. The work described however needed further investigation to study the mechanism of the Cu(I)Cl assisted ring closure and scope of the method to diversify the structural variation for its utility to make biological important imidazo[1,2-*a*]pyridines. These investigations have been continued in the present work and the results are presented.

Scheme 10



36 R	37 Yield %	36 R	38 Yield %
a C ₆ H ₅	a 92	a C ₆ H ₅	a 79
b 4-MeC ₆ H ₄	b 90	c 4-MeOC ₆ H ₄	c 68
c 4-MeOC ₆ H ₄	c 93		
d 4-ClC ₆ H ₄	d 90		
e 2-Furyl	e 88		
f 2-Thienyl	f 89		

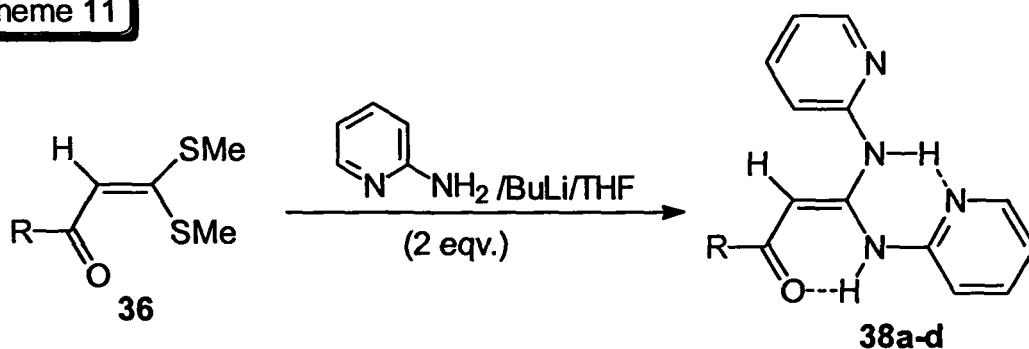
PRESENT WORK

In the preceding brief review we have presented various methods which are recently published on the synthesis of imidazo[1,2-*a*]pyridines. It should be noted the last method developed in this laboratory to make S,N-acetals from less reactive 2-aminopyridine lead to the discovery that high yields of S,N-acetals can be achieved only when lithiated 2-aminopyridine was reacted with α -oxoketene dithioacetals. Reaction could also be controlled to make exclusively S,N-acetals by using one equivalent of lithiated 2-aminopyridine. When two equivalents of lithiated of 2-aminopyridine was used high yields of the corresponding N,N-acetals were formed. It was noted that the use of Cu(I)Cl to achieve the ring closure was not fully investigated since the reactions were not carried out in the inert atmosphere thus it is possible Cu catalyzes the ring closure process in its +2 oxidation state rather than its Cu⁺¹ state. This ambiguity has been fully removed by the experiments in present investigation that the Cu catalyzes the ring closure in its +2 oxidative state and not in its Cu⁺¹ state. All the extended investigation and other related studies are presented.

In addition to N,S,- and N,N-acetals, further experiments were carried out to make N,O- and mixed N,N-acetals from 2-aminopyridines and other amines. In all these experiments *n*-butyllithium was used to metalate the amines and

were then reacted with α -oxoketene S,S-, and N,S-acetals to yield the corresponding N,S-, and N,N-acetals respectively depending on the stoichiometry. However the reaction of lithiated amines failed to displace SMe group when the α -oxoketene dithioacetals derived from aliphatic ketones were used. Thus the method is limited only to the α -oxoketene dithioacetals derived from aromatic ketones.

Scheme 11



36, 38a:	R = C ₆ H ₅	79 %
b:	R = 4-MeC ₆ H ₄	81 %
c:	R = 4-ClC ₆ H ₄	67 %
d:	R = 4-MeOC ₆ H ₄	68 %

Some of the reported N,N-acetals **38a-d** were prepared as formulated in scheme 11 in 68-81% overall yields. The analytical and spectral data were confirmed before their use in the present work. The corresponding N,N-acetals **38a** and **38b** were also prepared by using 2 equivalents of 2-aminopyridine in the presence of *n*-butyllithium as reported earlier. The hitherto unreported N,N-acetals **38c** and **38d** were also prepared following the described method in 67% and 68% yield respectively. The structure of **38c** was established by its analytical and spectral data as presented below.

Light yellow crystals; mp 137-138°C;

IR (KBr) ν_{max} 3417, 1617, 1589, 1213 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 3.90 (s, 3H), 5.60 (s, 1H), 6.90 (m, 1H), 7.40 (d, 2H, $J = 9$ Hz), 7.50-7.75 (m, 2H), 7.95 (d, 2H, $J = 9$ Hz), 8.35 (dd, 1H, $J = 6.9, 1.8$ Hz), 14.56 (brs, 1H);

^{13}C NMR (CDCl_3) δ 46.45, 90.60, 114.50, 118.50, 128.50, 128.59, 137.28, 138.03, 138.35, 146.01, 152.22, 166.58, 184.52. MS m/z (%): 288 (M^+ , 80);

Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_2$: C, 62.39; H, 4.53; N, 9.70. Found: C, 62.45; H, 4.42; N 9.61.

Similarly the N,N-acetal **38d** was obtained in 68% yield and was fully confirmed by its analytical and spectral data as presented in the experimental section.

The synthesis of mixed N,N-acetals **38e** and **38f** were prepared by both methods as depicted in scheme 12. Thus S,N-acetal **37e** which was prepared as reported in the literature was reacted with one equivalent of lithiated 2-aminopyridine at 0 °C and the reaction mixture was raised to reflux temperature of THF. After workup the corresponding mixed N,N-acetal was obtained in 80 % yield and it was purified by filtration over a silica gel short column chromatography and crystallized a light yellow needles from CHCl_3 /hexane mixture. The structure is fully established by its analytical and spectral data as described below.

Yellow crystals; mp 117-118 °C;

. IR (KBr) ν_{\max} 3405, 1605, 1560, 1490 cm^{-1} .

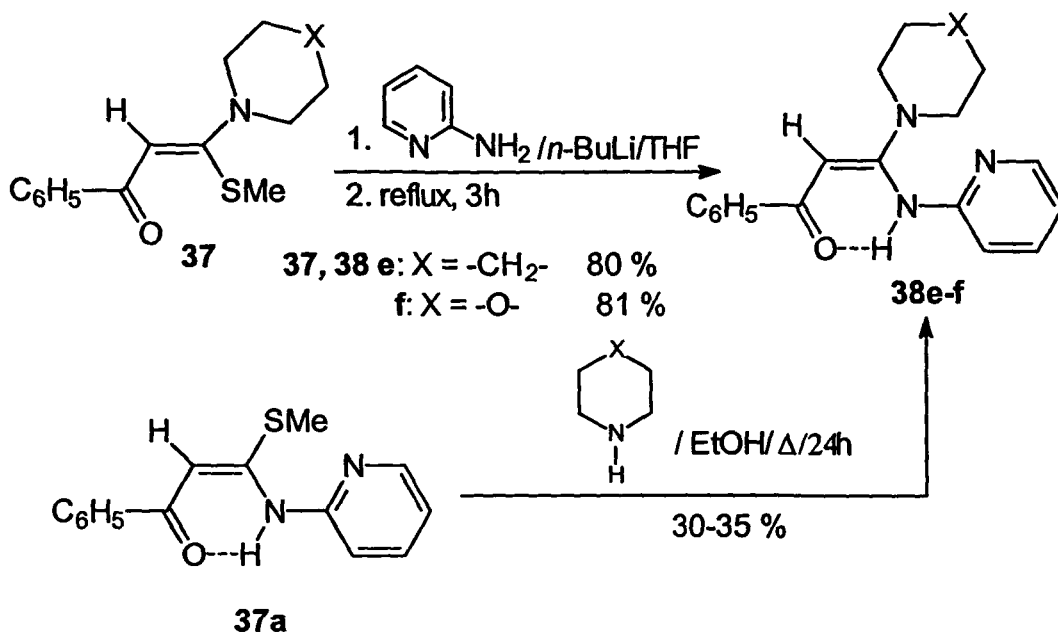
^1H NMR (400 MHz, CDCl_3) δ 1.58-1.60 (m, 2H), 1.73-1.79 (m, 4H), 3.05 (t, 4H, $J = 4.02$ Hz), 5.45 (s, 1H), 7.01-7.03 (m, 1H), 7.13 (d, 1H, $J = 7.8$ Hz), 7.35-7.39 (m, 3H), 7.41 – 7.45 (m, 1H), 7.77 – 7.81 (m, 2H), 8.40 – 8.44 (m, 1H), 12.71 (brs, 1H).

^{13}C NMR (CDCl_3) δ 23.77, 26.78, 55.12, 83.23, 114.98, 119.49, 127.82, 128.21, 130.40, 137.53, 140.77, 147.79, 153.42, 160.13, 189.01

MS m/z (%) 307 (M^+ , 80).

Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$: C, 74.24; H, 6.88; N, 13.67. Found: C, 74.45; H, 6.68; N, 13.88.

Scheme 12



Similarly the N,N-acetal **38f** was obtained in 81 % yield by reacting lithiated 2-aminopyridine with **37f** as described earlier. The product was purified by filtering through a short silica gel column using hexane/ethylacetate 9:1 as

eluent. The product was crystallized from CHCl_3 /hexane as light yellow needles and its structure was confirmed by analytical and spectral data as given in the experimental section.

Alternatively **38e** and **38f** were prepared by treating **37a** with both piperidine and morpholine in refluxing ethanol only in 30% and 35 % yields respectively.

Therefore this method was not subsequently used.

In the next experiments the mixed N,N-acetals **42a** and **42b** were prepared as described in scheme 13. Thus **37a** was reacted with lithiated aniline in THF at room temperature followed by refluxing to afford the corresponding N,N-acetal **42a** in 78 % yield. The compound was purified by crystallization as bright yellow needles from CHCl_3 /hexane mixture and the structure was established by its analytical and spectral data as given below.

Colorless Crystals; mp 123-124 °C;

IR (KBr) ν_{max} 3410, 1658, 1550, 1458 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 5.66 (s, 1H), 6.92 - 6.95 (m, 1H), 7.03 (d, 1H, $J = 8.5$ Hz), 7.25 - 7.39 (m, 7H), 7.43 - 7.46 (m, 2H), 7.67 (dd, 1H, $J = 7.3, 1.5$ Hz), 7.74 (dd, 1H, $J = 4.8, 1.2$ Hz), 8.19 (d, 1H, $J = 5.4$ Hz), 12.19 (brs, 1H), 13.36 (brs, 1H);

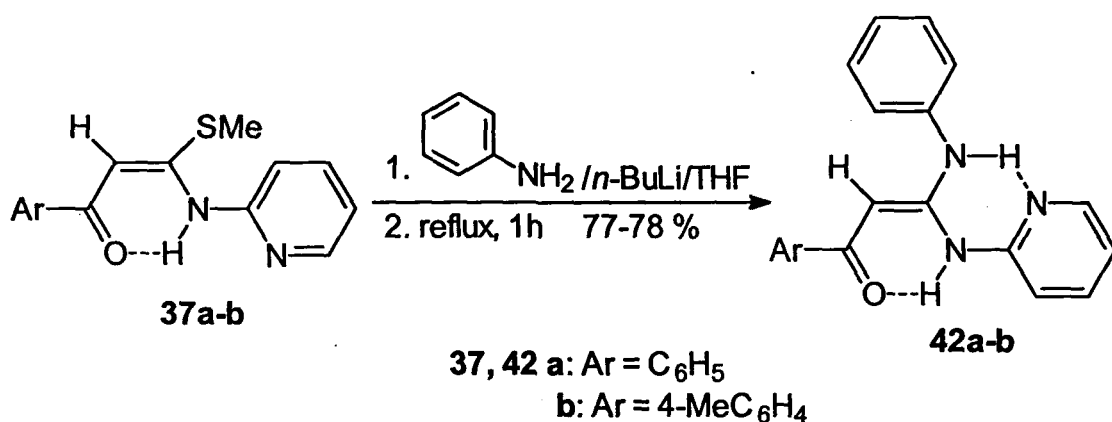
^{13}C NMR (CDCl_3) δ 78.08, 114.18, 117.52, 125.72, 126.31, 126.66, 128.09, 129.46, 130.17, 137.36, 138.61, 140.97, 145.93, 154.79, 159.20, 185.65;

MS m/z (%) 315 (M^+ , 58);

Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17, H, 5.43; N, 13.32. Found: C, 76.33; H, 5.21; N, 13.88.

The N,N-acetal **42b** was similarly prepared by reacting lithiated aniline with **37b** in 77 % yield. It was crystallized as bright yellow needles from $CHCl_3$ /hexane and the structure was fully characterized by its analytical and spectral data as given in the experimental section.

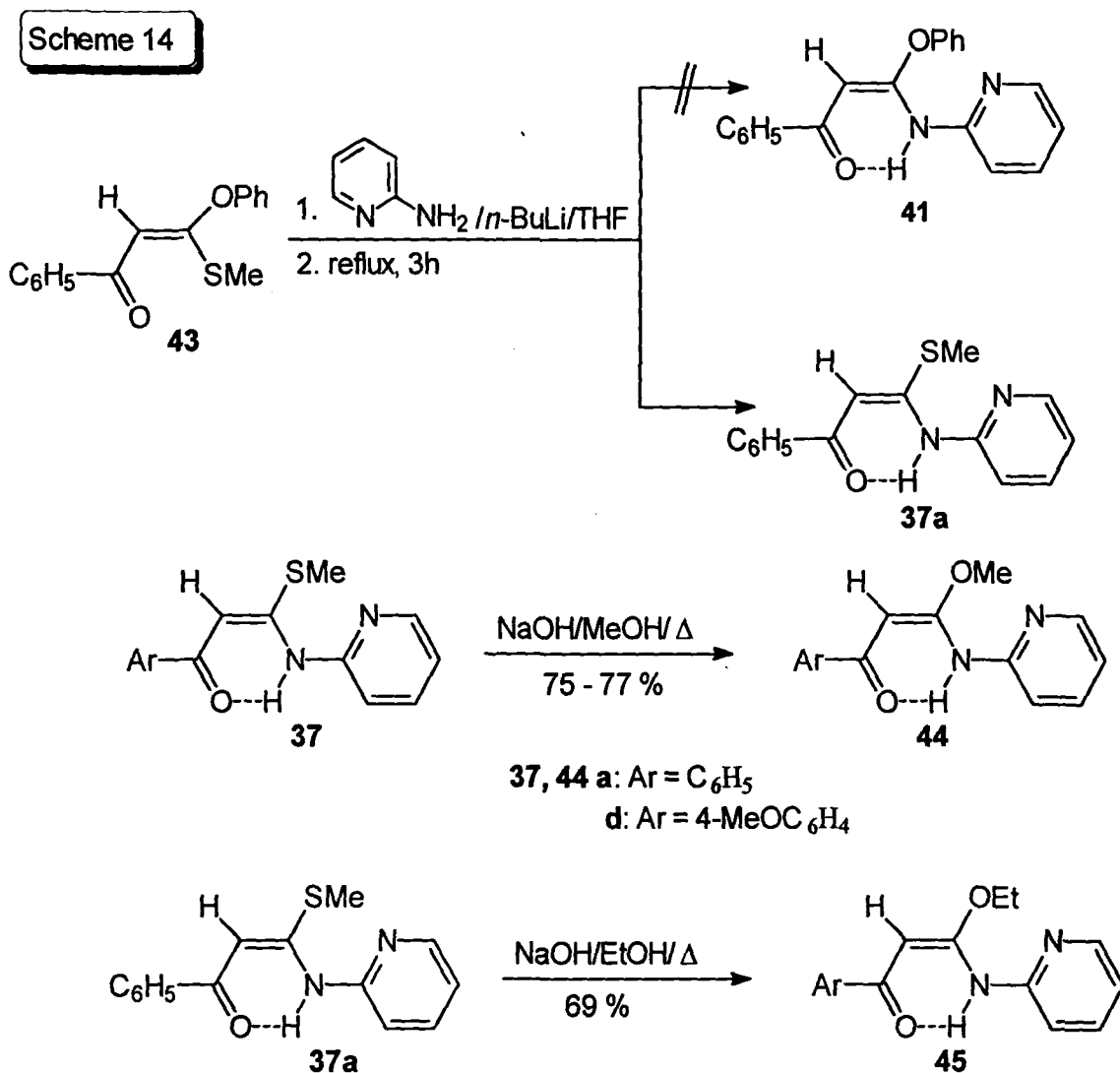
Scheme 13



In the next experiment the α -oxoketene O,S-acetal **43** was reacted with lithiated 2-aminopyridine and after workup the reaction mixture yielded only corresponding S,N-acetal **37a** instead of the expected O,N-acetal **41**, the structure **37a** was fully confirmed with that of reported earlier (mp, mmp, superimposable IR and other spectral data). Interestingly the OPh group is a better leaving group than the SMe.

The corresponding O,N-acetals **44a** and **44d** were then prepared by reacting **37a** with NaOMe in refluxing methanol in 75 % and 77 % yield respectively.

The structure of **44a** and **44d** were confirmed by analytical and spectral data as given in the experimental section. The N,O-acetal **45** was similarly prepared in 69 % yield by reacting with NaOEt in refluxing ethanol.



Cu(II) Chloride Assisted Ring Closure Studies.

In earlier work in our laboratory it was found that $\text{Cu}(\text{I})\text{Cl}$ was the reagent in the new C-N bond formation resulting ring closure of S,N-acetals **37** to afford

the corresponding imidazo[1,2-*a*]pyridines. However we found that the reaction failed to undergo ring closure when the reaction was conducted under the inert atmosphere. This experiment helped to eliminate the possible role played by Cu(I)Cl. Indeed Cu(I)Cl under atmospheric condition was undergoing air oxidation to Cu(II)Cl₂ and catalyzed the reaction to form the observed products. It was then decided to carry out these reactions in the presence of Cu(II)Cl₂ and reaction proceeded smoothly to afford the observed imidazo[1,2-*a*]pyridines further improved. In all the subsequent experiments Cu(II)Cl₂ was used to achieve the desired transformation.

In a typical experiment **37a** and **37d** were reacted with Cu(II)Cl₂ in THF and the reaction mixture was refluxed for 45 min followed by work up to afford the corresponding 2-methylthio-3-arylimidazo[1,2-*a*]pyridines **40a** and **40d** in 93% and 94% yields respectively. 2-Methylthio-3-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine was subjected to desulphurization to afford the sulphur free 3-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine **41d** in good yield (scheme 15). The structure was confirmed by its analytical and spectral data as follows.

Colorless crystals; mp 129-130 °C;

IR (KBr) ν_{\max} 1650, 1585, 1500, 1470 cm⁻¹;

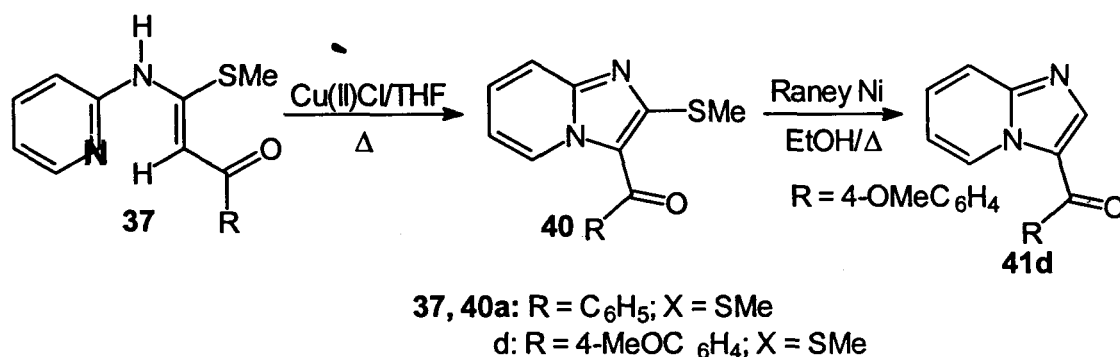
¹H NMR (300 MHz, CDCl₃) δ 7.08 – 7.20 (m, 1H), 7.40-7.50 (m, 1H), 7.54 (d, 2H, *J* = 8.0 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 8.06 – 8.21 (m, 1H), 8.53 (s, 1H), 9.71 – 9.86 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 115.32, 117.84, 128.85, 129.45, 130.15, 130.28, 132.04, 137.57, 138.42, 145.55, 183.37

MS m/z (%) 256 (M^+ , 32), 222 ($\text{M}^+ - 34$, 100).

Anal. Calcd for $\text{C}_{14}\text{H}_9\text{ClN}_2\text{O}$: C, 66.51; H, 3.53; N, 10.91. Found: C, 66.69; H, 3.45; N, 10.82.

Scheme 15



In the next experiment N,N-acetal **38a** was reacted with Cu(II)Cl_2 in THF and the reaction mixture was refluxed for **4h** followed by workup to afford the corresponding 2-(2-aminopyridyl)-3-arylimidazopyridine **46a** in 73 % yield scheme 15. The product was purified by column chromatography (silica gel) using hexane/ethylacetate (8:2) as eluent. The structure was established by its analytical and spectral data as given below.

Colorless crystals; mp 125-126 °C;

IR (KBr) ν_{max} 3350, 1585, 1540, 1490, 1465 cm^{-1} ;

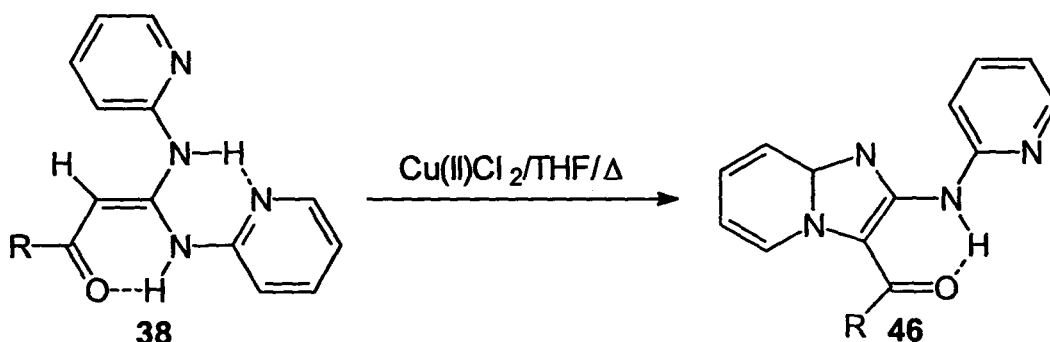
^1H NMR (400 MHz, CDCl_3) δ 6.85 – 6.92 (m, 2H), 7.26 – 7.56 (m, 3H), 7.61–7.69 (m, 5H), 8.16 – 8.19 (m, 1H), 8.20 (brs, 1H), 8.41(d, 1H, $J = 8.0$ Hz), 8.92 (d, 1H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 109.35, 113.03, 115.59, 118.52, 122.17, 127.99, 129.03, 129.48, 130.09, 131.09, 139.85, 140.03, 147.70, 155.66, 182.55;

MS m/z (%) 314 (M^+ , 100);

Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}$: C, 72.59; H, 4.49; N, 17.82. Found: C, 72.71; H, 4.23; N, 17.94.

The other N,N-acetals **38b-d** were similarly cyclized by refluxing with 1 equivalent of Cu(II)Cl_2 in THF to afford the corresponding 2,3-disubstituted imidazo[1,2-*a*]pyridines **46b-d**. All these compounds were purified and characterized by analytical and spectral data which are presented in the experimental section.

Scheme 16



38, 46a: R = C_6H_5 79 %
b: R = 4-Me C_6H_4 81 %
c: R = 4-Cl C_6H_4 67 %
d: R = 4-MeOC $_6\text{H}_4$ 68 %

Cyclization of 2-(2'-Aminopyridyl)-3-arylimidazo[1,2-a]pyridines to Tetracyclic Salts 47.

It was considered of interest to attempt cyclization of 46a (scheme 16) in the presence of Lewis acid to afford the corresponding tetracyclic heterocycles. When 46a was treated with $\text{BF}_3\text{Et}_2\text{O}$ in refluxing benzene, the reaction mixture after workup yielded the cyclized product 47a as a fluoroborate salt in 85 % yield. The crude product was crystallized from acetic acid and the structure was confirmed by its analytical and spectral data as follows.

Yellow crystals; mp 219-229 °C;

IR(KBr) ν_{max} 1650, 1580, 1521, 1460, 1060 cm^{-1} ;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.31 (d, 1H, $J = 7.2$ Hz), 7.41 – 7.42 (m, 1H), 7.51 – 7.53 (m, 1H), 7.75 – 8.00 (m, 5H), 8.11 – 8.22 (m, 2H), 8.34 – 8.45 (m, 2H), 8.56 (d, 1H, $J = 6.5$ Hz);

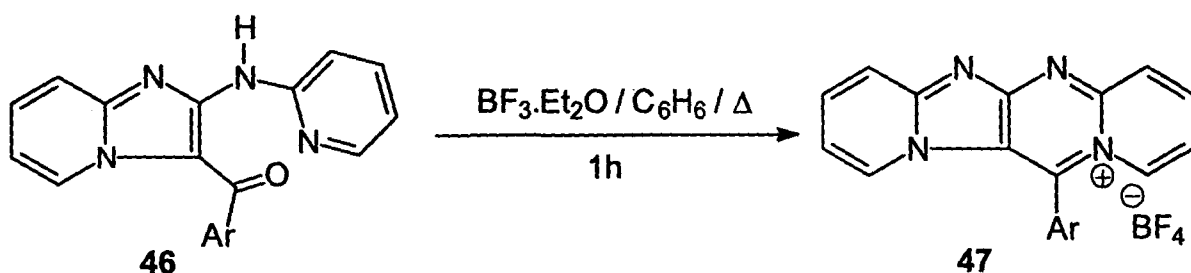
^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 115.70, 118.04, 119.75, 120.21, 124.90, 126.71, 128.82, 129.18, 129.69, 131.78, 133.31, 137.91, 140.27, 140.78, 148.16, 158.87, 159.16;

FAB MS m/z (%) 297 ($\text{M}^+ - \text{BF}_4$, 100).

Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{N}_4\text{BF}_4$: C, 59.41; H, 3.41, N, 14.59. Found: C, 59.67; H, 3.31; N, 14.66.

Similarly **46b** and **46c** underwent cyclization under the described reaction conditions to afford the corresponding tetracyclic heterocycles **47b** in 86 % yield and **47c** also in 86 % yield. Both the compounds were purified and characterized by analytical and spectral data which are described in the experimental section.

Scheme 17



46, 47 a: Ar = C₆H₅ 88 %
b: Ar = 4-MeC₆H₄ 86 %
c: Ar = 4-MeOC₆H₄ 86 %

In the next experiments **42a** and **42b** were cyclized in the presence of Cu(II)Cl₂ under the described reaction conditions to afford the corresponding 2-anilino-3-arylimidazo[1,2-*a*]pyridines **48a** in 71 % and **48b** in 69 % yields (scheme 18). The structure of **48a** was fully established by its analytical and spectral data as follows. The down field shift of NH and infrared band ν_{max} strongly supports the intramolecular hydrogen bonding of the NH proton.

Colorless Crystals; mp 123-124 °C;

IR (KBr) ν_{max} 3410, 1658, 1550, 1458 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 5.66 (s, 1H), 6.92 - 6.95 (m, 1H), 7.03 (d, 1H, *J* = 8.5 Hz), 7.25 - 7.39 (m, 7H), 7.43 - 7.46 (m, 2H), 7.67 (dd, 1H, *J* = 7.3,

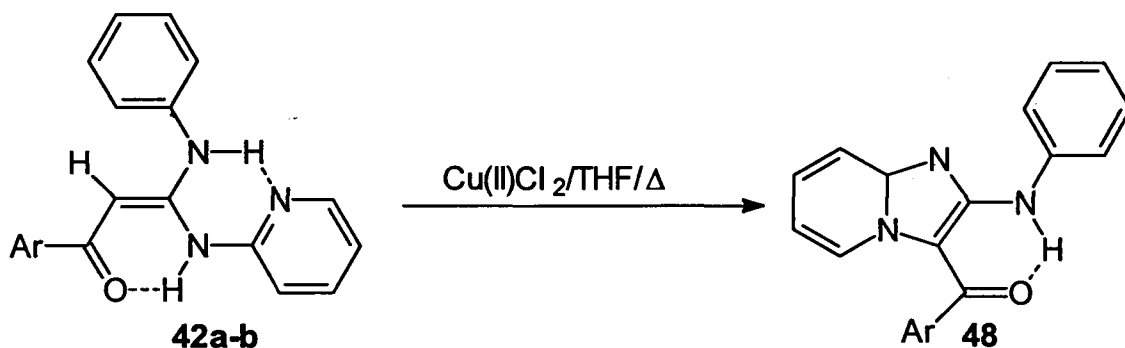
1.5 Hz), 7.74 (dd, 1H, $J = 4.8, 1.2$ Hz), 8.19 (d, 1H, $J = 5.4$ Hz), 12.19 (brs, 1H), 13.36 (brs, 1H);

^{13}C NMR (CDCl_3) δ 78.08, 114.18, 117.52, 125.72, 126.31, 126.66, 128.09, 129.46, 130.17, 137.36, 138.61, 140.97, 145.93, 154.79, 159.20, 185.65;

MS m/z (%) 315 (M^+ , 58);

Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}$: C, 76.17, H, 5.43; N, 13.32. Found: C, 76.33; H, 5.21; N, 13.88.

Scheme 18



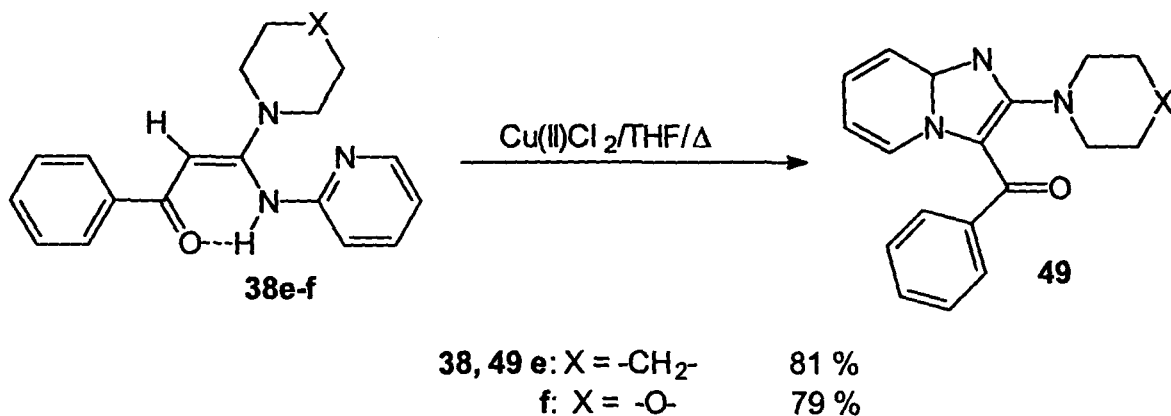
42, 48 a: Ar = C_6H_5 71 %
 b: Ar = 4-Me C_6H_4 69 %

The other 2-anilino-3-(4-methylphenyl)imidazo[1,2-*a*]pyridine **48b** which was prepared as described was also characterized by its analytical and spectral data described in the experimental section.

The S,N-acetals **38e** and **38f** underwent smooth cyclization in refluxing THF in the presence of Cu(II)Cl_2 to afford the corresponding 2-amino-3-arylimidazo[1,2-*a*]pyridine **49e** and **49f** in 81% and 79% yields respectively.

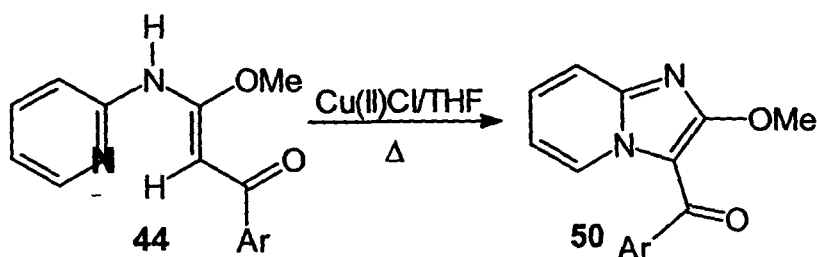
The structures of both **49e** and **49f** were established by analytical and spectral data which are given in the experimental section.

Scheme 19



In the next experiments N,O-acetals **44c** and **44d** were cyclized in the presence of Cu(II)Cl₂ under the described reaction condition to afford the corresponding 3-aryl-2-methoxy-imidazo[1,2-*a*]pyridines **50c** and **50d** in 61% yield 59 % yields. The structure of **50c** and **50d** were fully established by its analytical and spectral data which are presented in the experimental section.

Scheme 20



44, 50c: R = 4-ClC₆H₅
d: R = 4-MeOC₆H₄

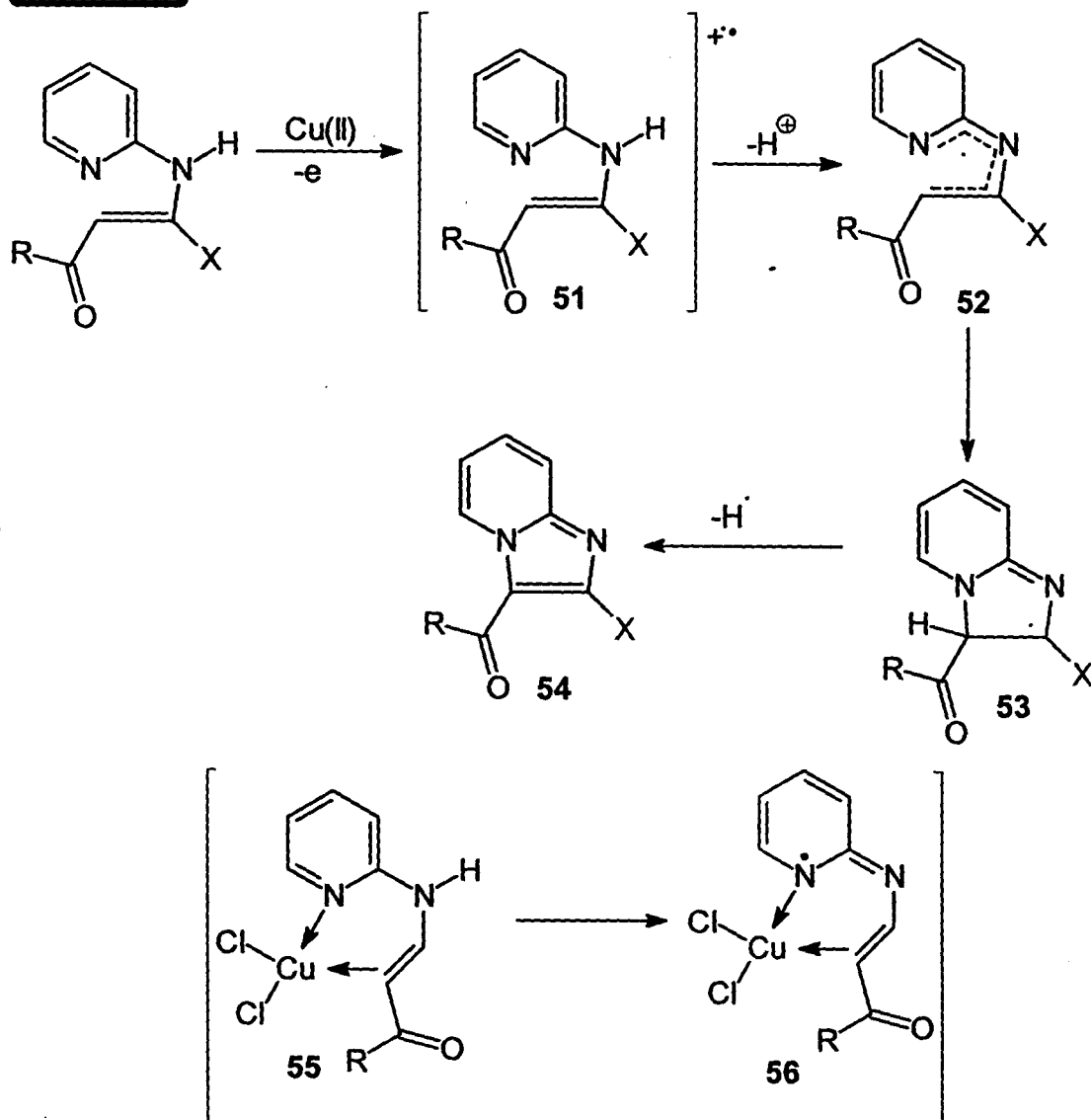
Possible Mechanism for CuCl₂ Oxidative Cyclization

The possible mechanism for the formation of imidazo[1,2-*a*]pyridines from N,S-, N,O- and N,N-acetals is depicted in scheme 22. Cupric chloride induced oxidative abstraction of hydrogen *via* cation radical intermediate **51** may give resonance stabilized aminyl radical **52** which undergoes facile intramolecular addition to the enamine double bond followed by abstraction of a hydrogen radical or proton to give the final product. Alternatively, electron transfer from nitrogen to Cu(II) ion may take place in the coordination sphere of initially formed copper complex of type **55** to give metal-complexed aminyl radical intermediate **56** which on subsequent intramolecular cyclization may afford imidazo[1,2-*a*]pyridines (Scheme 21). Cuprous and cupric salts in the presence of oxygen and pyridine or amines are known to act as useful oxidising systems for cleavage of hydrazides, bishydrazone, *o*-phenylenediamine, and for dimerization of aromatic amines. We are further exploring the mechanism of this novel oxidative cyclization with CuCl₂ and its application for construction of other fused heterocycles.

In conclusion, an efficient method for the synthesis of biologically important 2,3-functionalized imidazo[1,2-*a*]pyridines has been described via an unprecedented CuCl₂ induced oxidative ring closure of novel α -oxoketene N,S-, N,O-, and N,N-acetal intermediates. The methodology allows regiospecific introduction of alkylthio, alkoxy, primary and secondary amino group in 2-position of imidazopyridine ring. These functionalities can further

be elaborated to construct novel fused heterocyclic ring systems. The other advantages include mild reaction conditions and easy accessibility of N,S-, N,N- and N,O-acetals, which can be prepared with large structural variations from various aminoheterocycles, thus broadening the scope of this methodology for the synthesis of diverse class of bridgehead nitrogen heterocycles.

Scheme 21



Experimental Section

Melting points were determined on a Thomas Hoover (Capillary method) and Mel-Temp apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 297 and 983 spectrophotometers and are reported in cm^{-1} . ^1H NMR (300 MHz, 400 MHz and 500 MHz) and ^{13}C NMR (75.5 MHz, 100 MHz and 125 MHz) spectra were recorded on a Bruker-ACF-300 and Jeol-LA-400 and Bruker-AM-500 spectrometers. The chemical shifts (in ppm) and coupling constants (Hz) are reported in the standard fashion with respect to TMS as internal lock. Mass measurements were carried out with JEOL JMS-D-300 and Finnigan Voyager-GC-8000 mass spectrometers. Masses are reported in unit of mass over charge (m/z), the molecular or base peaks and relative intensities are indicated by (M^+) and (%) respectively. Elemental analyses were performed on Heraeus CHN-O-Rapid Analyser. Dry benzene was obtained by washing with concentrated sulfuric acid followed by azeotropic distillation and stored over sodium wire. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was redistilled before use and Cu(II)Cl_2 (AR grade, moisture free) supplied by E-Merck India was used as such.

All the α -oxoketene N,S-(**37a-f**) and N,N-(**38a-d**) acetals were prepared according to our reported²⁶ procedure by reacting 2-(lithioamino)pyridine with corresponding α -oxoketenedithioacetals.

1-(4-Methylphenyl)-3,3-bis-(2-pyridylamino)prop-2-en-1-one (38b):

Light yellow crystals; mp 102 –103 °C;

IR (KBr) 3450, 1640, 1600, 1585, 1545 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 2.35 (s, 3H), 6.79-6.82 (m, 1H), 6.88-6.93 (m, 2H), 7.01 (d, 1H, $J = 8$ Hz), 7.17 (s, 1H), 7.20 (d, 2H, $J = 8.4$ Hz), 7.50-7.58 (m, 2H), 7.85 (d, 2H, $J = 8.4$ Hz), 8.12 – 8.13 (m, 1H), 8.38 – 8.40 (m, 1H), 12.98 (brs, 1H), 14.59 (brs, 1H);

^{13}C NMR (CDCl_3) δ 21.03, 80.42, 113.55, 114.84, 116.97, 118.15, 126.58, 128.49, 137.31, 137.64, 138.13, 140.36, 145.38, 147.91, 151.87, 154.08, 155.40, 180.64;

MS m/z (%) 330 (M^+ , 56).

Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.96; H, 5.28; N, 16.85.

1-(4-Chlorophenyl)-3,3-bis-(2-pyridylamino)prop-2-en-1-one (38c):

Yellow crystals; mp 111-112 °C;

IR (KBr) 3400, 1655, 1610, 1580, 1540 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 6.95-6.98 (m, 1H), 7.01-7.06 (m, 2H), 7.13 (s, 1H), 7.14 (d, 1H, $J = 8.22$ Hz), 7.38 (d, 2H, $J = 8.40$), 7.66 – 7.73 (m, 2H), 7.85 (d, 2H, $J = 8$ Hz), 8.25 (d, 1H, $J = 4.80$ Hz), 8.48 (d, 1H, $J = 4.40$ Hz), 13.12 (brs, 1H), 14.54 (brs, 1H);

^{13}C NMR (CDCl_3) δ 80.73, 114.34, 115.62, 117.70, 118.99, 128.37, 136.53, 137.94, 138.79, 139.24, 145.92, 148.61, 152.22, 154.56, 156.41, 185.82

MS m/z (%) 350 (M^+ , 60).

Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}$: C, 65.05; H, 4.31, N, 15.97. Found: C, 65.25; H, 4.21; N, 15.67.

General Procedure for the Preparation of N,O-Acetals (44c-d). To a stirred solution of methanolic sodium methoxide (prepared from 0.46 g Na metal in 15ml of dry methanol, 15 mmol), the respective N,S-acetal (10 mmol) dissolved in 15 ml of dry methanol was added and the reaction mixture was stirred at room temperature for 10 min, followed by refluxing for 2 h. It was cooled to room temperature, quenched with saturated NH_4Cl solution (100 ml) and extracted with chloroform (2 x 50 ml). The combined extracts were washed with water (100 ml), dried (Na_2SO_4) and evaporated to give the crude N,O-acetals, which were purified by column chromatography over silica gel using hexane / ethylacetate (9:1) as eluent.

1-(4-Chlorophenyl)-3-methoxy-3-(2-pyridylamino)prop-2-en-1-one (44c):

Light yellow crystals; mp 137-138°C;

IR (KBr) 3417, 1617, 1589, 1213;

^1H NMR (400 MHz, CDCl_3) δ 3.90 (s, 3H), 5.60 (s, 1H), 6.90 (m, 1H), 7.40 (d, 2H, $J = 9$ Hz), 7.50-7.75 (m, 2H), 7.95 (d, 2H, $J = 9$ Hz), 8.35 (dd, 1H, $J = 6.9, 1.8$ Hz), 14.56 (brs, 1H);

^{13}C NMR (CDCl_3) δ 46.45, 90.60, 114.50, 118.50, 128.50, 128.59, 137.28, 138.03, 138.35, 146.01, 152.22, 166.58, 184.52.

MS m/z (%): 288 (M^+ , 80);

Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_2$: C, 62.39; H, 4.53; N, 9.70. Found: C, 62.45; H, 4.42; N 9.61.

3-Methoxy-1-(4-methoxyphenyl)-3-(2-pyridylamino)prop-2-en-1-one (44d):

Light yellow crystals; mp 130-131°C;

IR(KBr) 3458, 1627, 1599, 1339 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 3.63 (s, 3H), 3.91 (s, 3H), 5.30 (s, 1H), 6.70 (m, 1H), 7.10-7.50 (m, 4H), 7.80-8.15 (m, 3H), 8.35 (dd, 1H, $J = 6.9, 1.5$ Hz), 14.0 (brs, 1H);

^{13}C NMR (CDCl_3) δ 46.35, 55.83, 87.60, 113.78, 113.94, 119.84, 129.00, 130.59, 131.04, 138.18, 147.81, 151.17, 161.98, 193.09

MS m/z (%) 284 (M^+ , 100).

Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.65; H, 5.60; N, 11.12.

General Procedure for the Preparation of Mixed N,N-Aminals (38e-f, 42a-b). To a stirred solution of aniline (0.91 ml, 10 mmol) in dry THF (20 ml), *n*-butyllithium (15 mmol) was added under nitrogen atmosphere, over a period of 20 min at room temperature (25 °C). The reaction mixture was stirred for 30 min at the same temperature and the lithiation was indicated by the appearance of reddish brown colour. A solution of N,S-acetal (10 mmol) in dry THF (25 ml) was added and the reaction mixture was refluxed for 4 h. It was then brought to room temperature, poured into saturated aq. NH_4Cl (100 ml) solution, and extracted with chloroform (2X50 ml). The combined extracts were washed with water (2X50 ml), dried (Na_2SO_4) and evaporated to give crude products which

were purified by passing through a silica gel column using ethyl acetate / hexane (1:9) as eluent.

1-Phenyl-3-(1-piperidino)-3-(2-pyridylamino)prop-2-en-1-one (38e):

Yellow crystals; mp 117-118 °C;

IR (KBr) 3405, 1605, 1560, 1490 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 1.58-1.60 (m, 2H), 1.73-1.79 (m, 4H), 3.05 (t, 4H, $J = 4.02$ Hz), 5.45 (s, 1H), 7.01-7.03 (m, 1H), 7.13 (d, 1H, $J = 7.8$ Hz), 7.35-7.39 (m, 3H), 7.41 – 7.45 (m, 1H), 7.77 – 7.81 (m, 2H), 8.40 – 8.44 (m, 1H), 12.71 (brs, 1H).

^{13}C NMR (CDCl_3) δ 23.77, 26.78, 55.12, 83.23, 114.98, 119.49, 127.82, 128.21, 130.40, 137.53, 140.77, 147.79, 153.42, 160.13, 189.01.

MS m/z (%) 307 (M^+ , 80).

Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$: C, 74.24; H, 6.88; N, 13.67. Found: C, 74.45; H, 6.68; N, 13.88.

3-(4-Morpholino)-1-phenyl-3-(2-pyridylamino)prop-2-en-1-one (38f):

Light yellow crystals; mp 140 –141 °C;

IR (KBr) 3451, 1619, 1536, 1521, 1490 cm^{-1} ;

^1H NMR (500 MHz, CDCl_3) δ 3.36 - 3.38 (m, 4H), 3.80 - 3.81(m, 4H), 5.56 (s, 1H), 6.91 - 6.94 (m, 1H), 7.10 (d, 1H, $J = 8$ Hz), 7.40-7.46 (m, 3H), 7.60-7.63 (m, 1H), 7.81-7.87 (m, 2H), 8.31-8.33 (m, 1H), 12.62 (brs, 1H).

^{13}C NMR (CDCl_3) δ 48.62, 66.08, 82.53, 114.02, 118.16, 127.01, 128.21, 130.37, 137.96, 140.97, 148.5, 153.78, 160.62, 188.27;

HRMS m/z M^+ calcd for $C_{18}H_{19}O_2N_3$ 309.147, found 309.146.

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.97; H, 5.95; N, 13.75.

3-Anilino-1-phenyl-3-(2-pyridylamino)prop-2-en-1-one (42a):

Colorless Crystals; mp 123-124 °C;

IR (KBr) 3410, 1658, 1550, 1458 cm^{-1} ;

1H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H), 6.92 - 6.95 (m, 1H), 7.03 (d, 1H, J = 8.5 Hz), 7.25 - 7.39 (m, 7H), 7.43 - 7.46 (m, 2H), 7.67 (dd, 1H, J = 7.3, 1.5 Hz), 7.74 (dd, 1H, J = 4.8, 1.2 Hz), 8.19 (d, 1H, J = 5.4 Hz), 12.19 (brs, 1H), 13.36 (brs, 1H);

^{13}C NMR ($CDCl_3$) δ 78.08, 114.18, 117.52, 125.72, 126.31, 126.66, 128.09, 129.46, 130.17, 137.36, 138.61, 140.97, 145.93, 154.79, 159.20, 185.65

MS m/z (%) 315 (M^+ , 58);

Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17, H, 5.43; N, 13.32. Found: C, 76.33; H, 5.21; N, 13.88.

3-Anilino-1-(4-methylphenyl)-3-(2-pyridylamino)prop-2-en-1-one (42b):

Yellow crystals; mp 111- 112 °C;

IR (KBr) 3400, 1654, 1554, 1448, 1404 cm^{-1} ;

1H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 5.66 (s, 1H), 6.90 - 6.96 (m, 1H), 7.02 (d, 1H, J = 8.4 Hz), 7.14 (d, 2H, J = 7.5 Hz), 7.25-7.29 (m, 1H), 7.37 (d, 2H, J = 8 Hz), 7.41 - 7.45 (m, 2H), 7.64 - 7.66 (m, 3H), 8.18 (d, 1H, J = 8Hz), 12.16 (brs, 1H), 13.13 (brs, 1H);

^{13}C NMR (CDCl_3) 21.33, 114.06, 117.36, 125.58, 126.12, 126.61, 128.75, 129.37, 137.39, 138.14, 138.51, 140.37, 145.86, 154.76, 158.96, 185.86;

MS m/z (%): 329 (M^+ , 65).

Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}$: C, 76.57; H, 5.81; N, 12.75. Found: C, 76.44; H, 5.69; N, 12.58.

General Procedure for Oxidative Cyclization of N,S-, N,N- and N,O-Acetals to Imidazo[1,2-*a*]pyridines. To a stirred solution of respective N,S-, N,O- or N,N-acetal (10 mmol) in dry tetrahydrofuran (30 ml), anhydrous Cu(II)Cl_2 (2.02 g, 15 mmol) was added and the reaction mixture was refluxed with stirring for 3-4 h (monitored by TLC). The initial pale green colour of the reaction mixture faded away and after 3 h it gradually turned reddish brown. The reaction mixture after cooling was poured into water (50 ml) and filtered to remove insoluble impurities. The filtrate was extracted with chloroform (2 x 50 ml), the organic layer was washed with water (3 x 50 ml), dried (Na_2SO_4) and evaporated to give crude viscous residue which was passed through silica gel column using hexane / ethylacetate (9:1) as eluent, to afford pure imidazo[1,2-*a*]pyridines in high yields. The analytical and spectral data for the purified compounds are reported below:

3-(4-Chlorobenzoyl)-2-methoxyimidazo[1,2-*a*]pyridine (50c):

Yellow crystals; mp 156°C ;

IR (KBr) 1600, 1559, 1402, 1226 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 3.97 (s, 3H), 7.04 (ddd, 1H, $J = 6.9, 6.6, 1.1$ Hz), 7.39 (d, 2H, $J = 9.0$ Hz), 7.45 – 7.54 (m, 2H), 7.65 (d, 2H, $J = 9.0$ Hz), 9.68 (dt, 1H, $J = 6.6, 1.1$ Hz).

^{13}C NMR (100 MHz, CDCl_3) δ 56.03, 114.11, 115.40, 127.72, 128.95, 129.50, 130.02, 137.18, 137.92, 144.81, 163.26, 182.42.

MS m/z (%) 286 (M^+ , 100); Anal. Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_2\text{Cl}$: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.78; H, 3.79; N, 9.95.

2-Methoxy-3-(4-methoxybenzoyl)imidazo[1,2-*a*]pyridine (50d):

White crystals; mp 109 –110 °C;

IR (KBr) 1605, 1556, 1406 cm^{-1} ;

^1H NMR (300 MHz, CDCl_3) δ 3.88 (s, 3H), 4.01 (s, 3H), 6.95 (d, 2H, $J = 8.1$ Hz), 7.04 (t, 1H, $J = 6.0$ Hz), 7.47 (t, 1H, $J = 8.0$ Hz), 7.55 (d, 1H, $J = 8.4$ Hz), 7.77 (d, 2H, $J = 8.4$ Hz), 9.65 (d, 1H, $J = 6.5$ Hz);

^{13}C NMR (75.5 MHz, CDCl_3) δ 55.31, 56.12, 112.94, 112.98, 114.11, 115.41, 128.90, 129.28, 131.00, 132.02, 144.73, 162.31, 162.89, 183.15.

MS m/z (%) 282 (M^+ , 100).

Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.25; H, 4.89; N, 10.01.

3-Benzoyl-2-(1-piperidino)imidazo[1,2-*a*]pyridine (49e):

Yellow crystals; mp 134-135 °C;

IR (KBr) 1630, 1585, 1539 cm^{-1} ;

^1H NMR (500 MHz, CDCl_3) δ 1.14 – 1.18 (m, 4H), 1.33 – 1.38 (m, 2H), 3.11 – 3.13 (m, 4H), 6.92-6.94 (m, 1H) 7.40 – 7.46 (m, 3H), 7.49 – 7.52 (m, 2H), 7.78(d, 2H, $J = 7.5$ Hz), 9.58 (d, 1H, $J = 5$ Hz).

^{13}C NMR (100 MHz, CDCl_3) δ 24.03, 24.87, 52.55, 109.65, 113.17, 114.88, 128.07, 128.33, 128.92, 129.38, 131.43, 139.87, 146.32, 161.84, 185.03.

HRMS m/z M^+ calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$ 305.152, found 305.1519.

Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$: C, 74.79; H, 6.28; N, 13.77. Found: C, 74.87; H, 6.01; N, 13.91.

3-Benzoyl-2-(4-morpholino)imidazo[1,2-*a*]pyridine (49f):

Yellow crystals; mp 140-141 °C;

IR (KBr) 1599, 1588, 1568, 1462 cm^{-1} ;

^1H NMR (500 MHz, CDCl_3) δ 3.16 (t, 4H, $J = 7.5$ Hz), 3.31 (t, 4H, $J = 7.2$ Hz), 6.98 (dt, 1H, $J = 7.1, 1.5$ Hz), 7.45 – 7.49 (m, 3H), 7.53 – 7.56 (m, 2H), 7.80 – 7.82 (m, 2H), 9.59 (d, 1H, $J = 5.0$ Hz).

^{13}C NMR (100 MHz, CDCl_3) δ 51.50, 65.92, 109.96, 113.68, 115.24, 128.21, 128.47, 128.86, 129.61, 131.82, 139.59, 146.12, 160.86, 184.94;

HRMS m/z M^+ calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$ 307.132, found 307.131.

Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$: C, 70.39; H, 5.58; N, 13.68. Found: C, 70.21; H, 5.42; N, 13.79.

3-Benzoyl-2-(2-pyridylamino)imidazo[1,2-*a*]pyridine (46a):

Colorless crystals; mp 125-126 °C;

IR (KBr) 3350, 1585, 1540, 1490, 1465 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 6.85 – 6.92 (m, 2H), 7.26 – 7.56 (m, 3H), 7.61–7.69 (m, 5H), 8.16 – 8.19 (m, 1H), 8.20 (brs, 1H), 8.41(d, 1H, $J = 8.0$ Hz), 8.92 (d, 1H, $J = 6.0$ Hz);

^{13}C NMR (100 MHz, CDCl_3) δ 109.35, 113.03, 115.59, 118.52, 122.17, 127.99, 129.03, 129.48, 130.09, 131.09, 139.85, 140.03, 147.70, 155.66, 182.55;

MS m/z (%) 314 (M^+ , 100);

Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}$: C, 72.59; H, 4.49; N, 17.82. Found: C, 72.71; H, 4.23; N, 17.94.

3-(4-Methylbenzoyl)-2-(2-pyridylamino)imidazo[1,2-*a*]pyridine (46b):

White crystals; mp 135-136 °C;

IR (KBr) 3300, 1610, 1590, 1565, 1490 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 2.46 (s, 3H), 6.88 (t, 2H, $J = 6.0$ Hz), 7.35 (d, 2H, $J = 7.8$ Hz), 7.44 (t, 1H, $J = 7.8$ Hz), 7.49 – 7.56 (m, 1H), 7.59 (d, 2H, $J = 8$ Hz), 7.65 – 7.70 (m, 1H), 8.19 (brs, 1H), 8.40 (d, 2H, $J = 6.5$ Hz), 8.91 (d, 1H, $J = 6.0$ Hz);

^{13}C NMR (100 MHz, CDCl_3) δ 21.61, 109.46, 112.90, 115.61, 118.62, 122.15, 127.27, 127.99, 129.03, 129.85, 130.04, 137.18, 139.98, 141.65, 147.56, 155.63, 182.81;

MS m/z (%) 328 (M^+ , 100);

Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.29; H, 4.75; N, 17.22.

3-(4-Methoxybenzoyl)-2-(2-pyridylamino)imidazo[1,2-*a*]pyridine (46c):

White crystals; mp 119 –120 °C;

IR (KBr) 3110, 1645, 1590, 1541, 1465 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 3.89 (s, 3H), 6.87 (t, 2H, *J* = 8 Hz), 7.03 (d, 2H, *J* = 7.2 Hz), 7.37 – 7.45 (m, 1H), 7.55(d, 2H, *J* = 4.0 Hz), 7.68 (d, 2H, *J* = 8.5 Hz), 8.18 (d, 1H, *J* = 3.9 Hz), 8.30 (brs, 1H), 8.42 (d, 1H, *J* = 8.0 Hz), 8.90 (d, 1H, *J* = 6.8 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 55.43, 109.54, 112.01, 113.29, 114.60, 115.61, 117.25, 128.10, 129.42, 129.82, 131.82, 137.82, 146.69, 147.99, 152.60, 152.99, 162.49, 182.67; MS *m/z* (%) 344 (M⁺, 100);

Anal. Calcd for C₂₀ H₁₆N₄O₂: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.85; H, 4.45; N, 16.44.

3-(4-Chlorobenzoyl)-2-(2-pyridylamino)imidazo[1,2-*a*]pyridine (46d):

Yellow crystals; mp 121 –122 °C;

IR(KBr) 3125, 1655, 1599, 1555, 1535, 1460 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 6.90 (t, 2H, *J* = 6.3 Hz), 7.27 – 7.50 (m, 1H), 7.56 (d, 2H, *J* = 8.5 Hz), 7.57 –7.59 (m, 1H), 7.64 (d, 2H, *J* = 8.1 Hz), 7.69-7.72 (m, 1H), 8.21 (m, 1H), 8.33 (brs, 1H), 8.40 (d, 1H, *J* = 8.6 Hz), 8.83 (d, 1H, *J* = 6.2 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 109.60, 114.40, 115.56, 117.62, 117.69, 119.91, 128.29, 136.55, 137.90, 138.74, 139.23, 145.94, 148.56, 152.22, 154.46, 156.28, 183.45MS *m/z* (%) 348 (M⁺, 100);

Anal. Calcd for $C_{19}H_{13}ClN_4O$: C, 65.43; H, 3.75; N, 16.06. Found: C, 65.61; H, 3.59; N, 16.21.

2-Anilino-3-benzoylimidazo[1,2-*a*]pyridine (48a):

Yellow crystals; mp 123-124 °C;

IR (KBr) 3120, 1590, 1575 cm^{-1} ;

1H NMR (400 MHz, $CDCl_3$) δ 6.75-6.77 (m, 1H), 6.98 (dt, 1H, $J = 7.0, 1.5$ Hz), 7.25 – 7.32 (m, 2H), 7.36 – 7.40 (m, 1H), 7.49 – 7.52 (m, 1H), 7.53 – 7.62 (m, 7H), 8.10 (brs, 1H), 8.52 (d, 1H, $J = 5.1$ Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.35, 113.03, 115.59, 118.52, 122.17, 127.06, 127.99, 129.03, 129.48, 130.09, 131.09, 139.85, 140.03, 147.70, 155.66, 182.55;

MS m/z (%) 313 (M^+ , 100);

Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.40. Found: C, 76.82; H, 4.92; N, 13.31.

2-Anilino-3-(4-methylbenzoyl)imidazo[1,2-*a*]pyridine (48b):

Yellow crystals; mp 128 –129 °C;

IR (KBr) 3150, 1610, 1580, 1545, 1430, 1415 cm^{-1} ;

1H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 6.73 – 6.77 (m, 1H), 6.97 –7.03 (m, 1H), 7.25 –7.41 (m, 5H), 7.49 – 7.66 (m, 5H), 8.23 (brs, 1H), 8.49 (d, 1H, $J = 5.4$ Hz);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.62, 109.43, 112.89, 115.61, 118.58, 122.13, 127.33, 127.98, 129.16, 129.78, 130.04, 137.15, 139.97, 141.61, 147.54, 155.61, 182.78;

MS m/z (%) 327 (M^+ , 100);

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.21; H, 5.21; N, 12.97.

General Procedure for Raney Nickel Dethiomethylation of 40c to 41. To a stirred solution of 3-aryl-2-methylthioimidazo[1,2-*a*]pyridines (**40c**) (2.5 mmol) in ethanol (25 ml), Raney Nickel (W2, three times by weight) was added and the reaction mixture was refluxed with stirring for 6 h (monitored by TLC). It was then filtered through a sintered glass funnel, washed with ethanol (10 ml) and the filtrate was evaporated under reduced pressure. The residue thus obtained was diluted with chloroform (20 ml), washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to give crude products which were purified by passing through silica gel column using hexane / ethyl acetate (9:1) as eluent.

3-Benzoylimidazo[1,2-*a*]pyridine (41):

Colorless crystals; mp 135 °C;

IR (KBr) 1689, 1597, 1223 cm^{-1}

1H NMR (300 MHz, $CDCl_3$) δ 7.14 (ddd, 1H, $J = 6.9, 6.6, 1.0$ Hz), 7.50-7.60 (m, 4H), 7.70 (m, 2H), 7.79 (dt, 1H, $J = 8.8, 1.1$ Hz), 8.21 (s, 1H), 9.74 (dt, 1H, $J = 6.6, 0.3$ Hz);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 115.13, 117.69, 123.49, 128.50, 128.80, 129.43, 130.16, 132.02, 138.40, 139.21, 145.64, 189.71;

MS m/z (%) 222 (M^+ , 100).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.53; N, 12.60. Found: C, 75.70; H, 4.35; N, 12.50.

3-(4-Chlorobenzoyl)imidazo[1,2-*a*]pyridine (41d):

Colorless crystals; mp 129-130 °C;

IR (KBr) 1650, 1585, 1500, 1470 cm^{-1}

1H NMR (300 MHz, $CDCl_3$) δ 7.08 – 7.20 (m, 1H), 7.40-7.50 (m, 1H), 7.54 (d, 2H, $J = 8.0$ Hz), 7.86 (d, 2H, $J = 8.4$ Hz), 8.06 – 8.21 (m, 1H), 8.53 (s, 1H), 9.71 – 9.86 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 115.32, 117.84, 128.85, 129.45, 130.15, 130.28, 132.04, 137.57, 138.42, 145.55, 183.37;

MS m/z (%) 256 (M^+ , 32), 222 ($M^+ - 34$, 100).

Anal. Calcd for $C_{14}H_9ClN_2O$: C, 66.51; H, 3.53; N, 10.91. Found: C, 66.69; H, 3.45; N, 10.82.

General Procedure for $BF_3 \cdot Et_2O$ Assisted Cyclization of 46a-c to give Salts 47a-c. To a solution of 46 (10 mmol) in dry benzene (30 ml), boron trifluoride etherate (3 ml) was added and the reaction mixture was refluxed with stirring for 1 h. On cooling, the yellow crystalline salt separated was filtered and washed with benzene (2 X 5 ml) and further purified by crystallization from glacial acetic acid.

11-Phenylpyrido[1'',2''-1',2']imidazo[4',5'-d]pyrido[1,2-a]pyrimidinium tetrafluoroborate (47a):

Yellow crystals; mp 219-229 °C;

IR(KBr) 1650, 1580, 1521, 1460, 1060 cm^{-1}

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.31 (d, 1H, $J = 7.2$ Hz), 7.41 – 7.42 (m, 1H), 7.51 – 7.53 (m, 1H), 7.75 – 8.00 (m, 5H), 8.11 – 8.22 (m, 2H), 8.34 – 8.45 (m, 2H), 8.56 (d, 1H, $J = 6.5$ Hz);

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 115.70, 118.04, 119.75, 120.21, 124.90, 126.71, 128.82, 129.18, 129.69, 131.78, 133.31, 137.91, 140.27, 140.78, 148.16, 158.87, 159.16;

FAB MS m/z (%) 297 ($\text{M}^+ - \text{BF}_4$, 100).

Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{N}_4\text{BF}_4$: C, 59.41; H, 3.41, N, 14.59. Found: C, 59.67; H, 3.31; N, 14.66.

11-(4-methylphenyl)pyrido[1'',2''-1',2']imidazo[4',5'-d]pyrido[1,2-a]pyrimidinium tetrafluoroborate (47b):

Yellow Crystals; mp 234 – 135 $^{\circ}\text{C}$;

IR (KBr) 1584, 1519, 1510, 1468, 1065;

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.59 (s, 3H), 7.33 (t, 1H, $J = 6.3$ Hz), 7.51 (d, 1H, $J = 6.0$ Hz), 7.72 – 7.75 (m, 3H), 7.78 (d, 2H, $J = 8.2$ Hz), 8.14 (d, 1H, $J = 8.1$ Hz), 8.20 – 8.23 (m, 1H), 8.37 (m, 1H), 8.45 (d, 1H, $J = 8.4$ Hz), 8.56 (d, 1H, $J = 8$ Hz).

^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 21.43, 115.67, 117.96, 119.62, 120.17, 121.88, 126.62, 128.98, 129.71, 131.72, 131.96, 137.86, 140.55, 140.70, 143.32, 148.10, 158.71, 159.03

FAB MS m/z (%) 311 ($\text{M}^+ - \text{BF}_4$, 100).

Anal. Calcd for $C_{20}H_{15}N_4BF_4$: C, 60.33; H, 3.80; N, 14.07. Found: C, 60.51; H, 3.65; N, 14.22.

11-(4-Chlorophenyl)pyrido[1'',2''-1',2']imidazo[4',5'-d]pyrido[1,2-a]pyridinium tetrafluoroborate (47c):

Yellow Crystals; mp 239-40 °C;

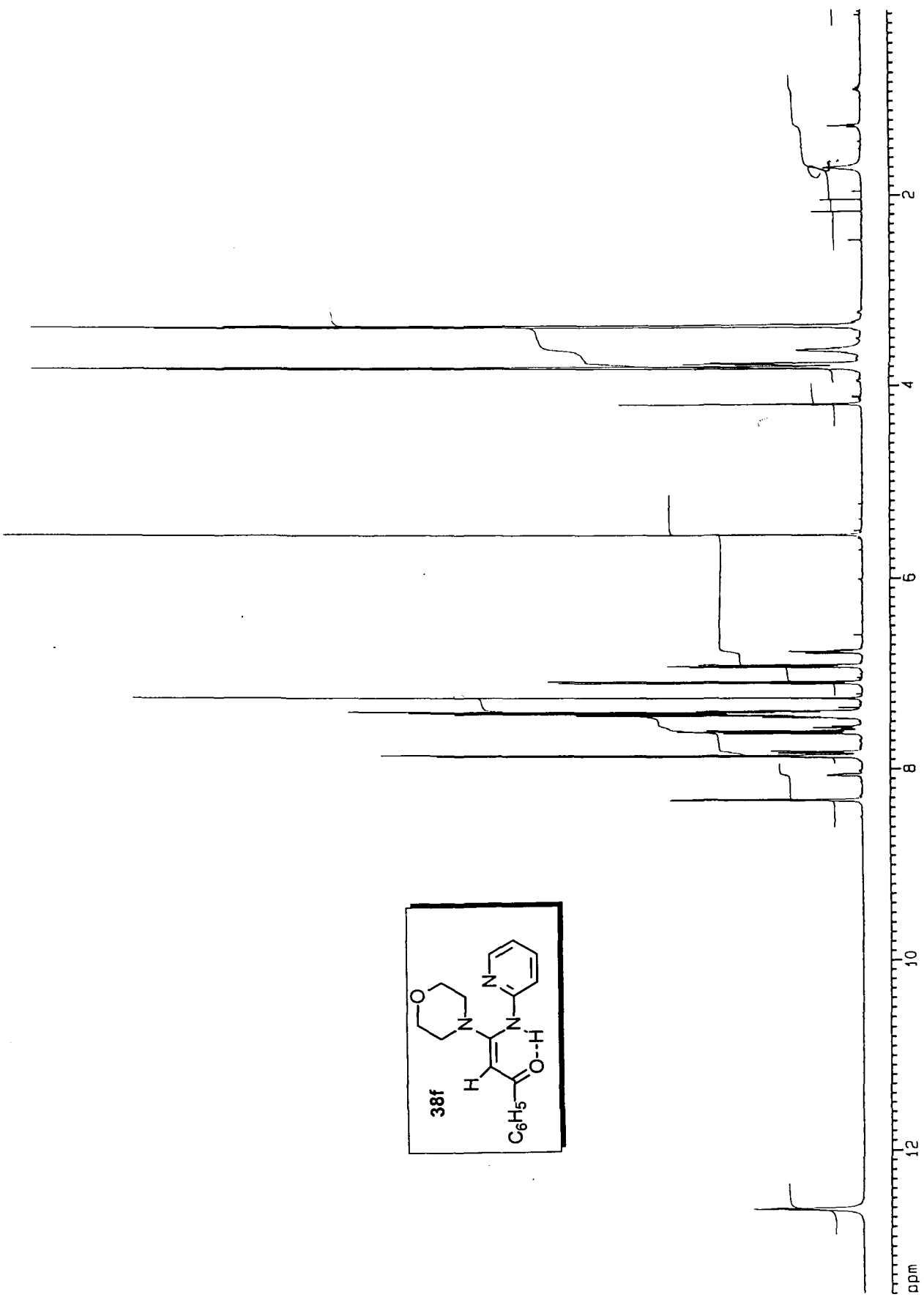
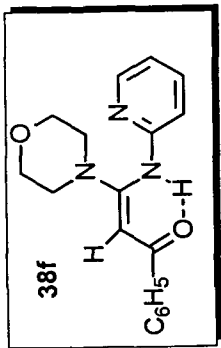
IR(KBr) 1670, 1540, 1521, 1460, 1065 cm^{-1} ;

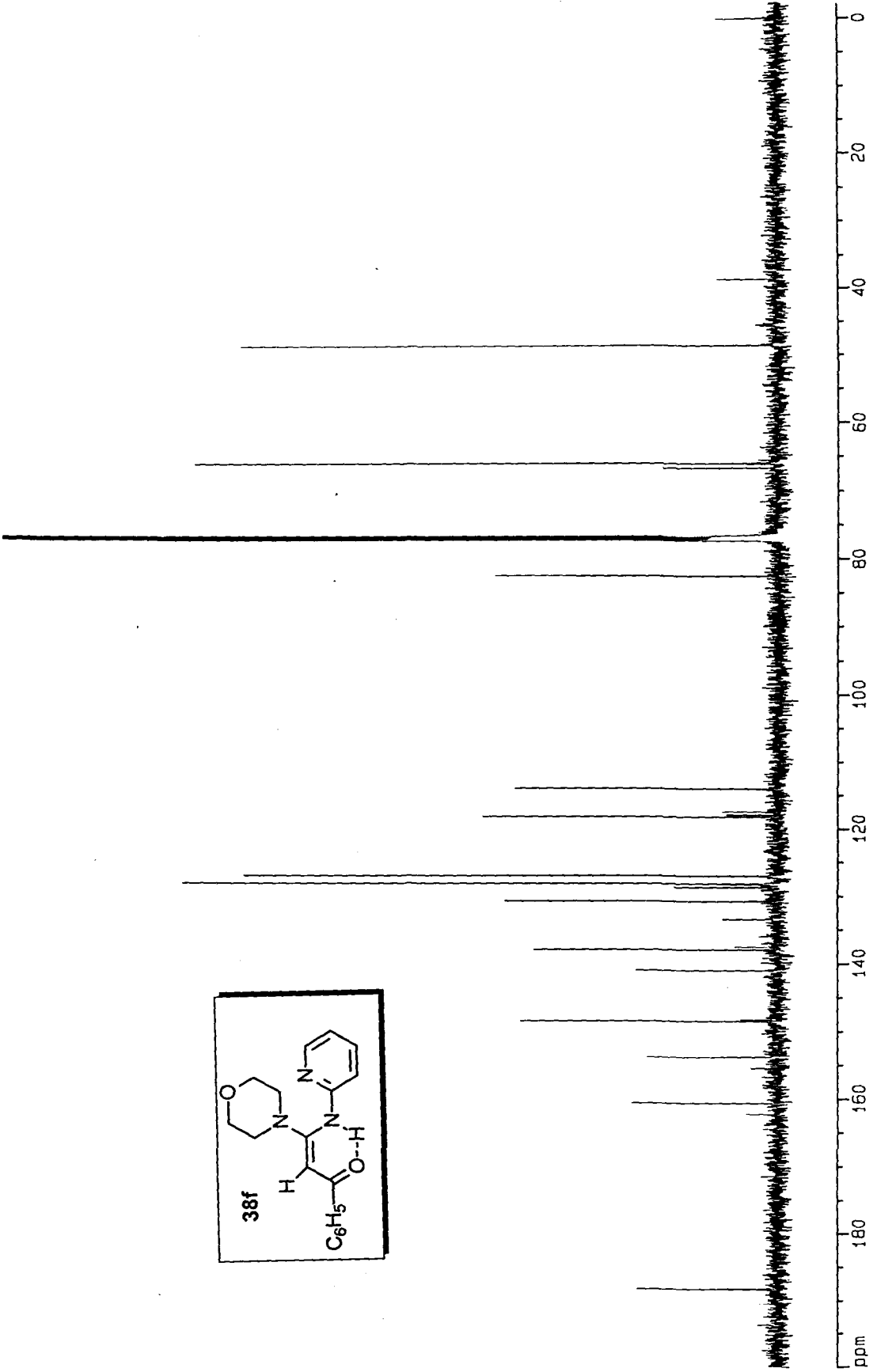
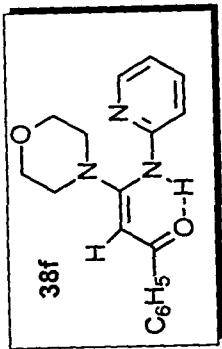
1H NMR (400 MHz, DMSO- d_6) δ 7.27 (t, 1H, $J = 5.4$ Hz), 7.53 (dt, 1H, $J = 6.8$, 1.2 Hz), 7.75 (d, 2H, $J = 8.4$ Hz), 7.82 (d, 2H, $J = 8.5$ Hz), 7.92 – 8.05 (m, 1H), 8.17 – 8.28 (m, 1H), 8.35 (t, 1H, $J = 7.8$ Hz), 8.44 – 8.45 (m, 3H);

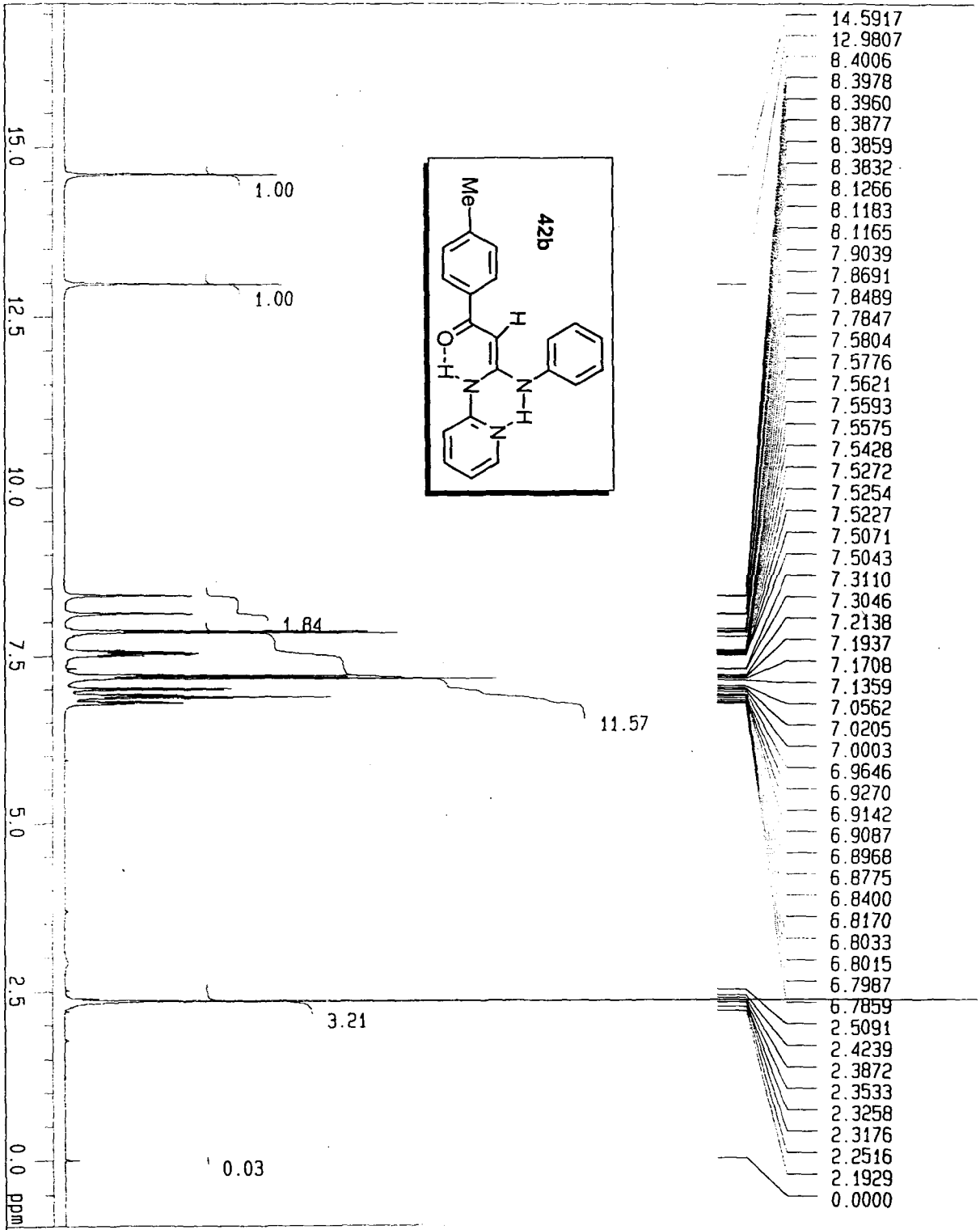
^{13}C NMR (100 MHz, DMSO- d_6) δ 114.70, 117.04, 119.05, 121.21, 124.50, 124.71, 128.62, 128.18, 128.69, 130.51, 132.31, 136.91, 141.26, 141.78, 149.15, 158.47, 159.17

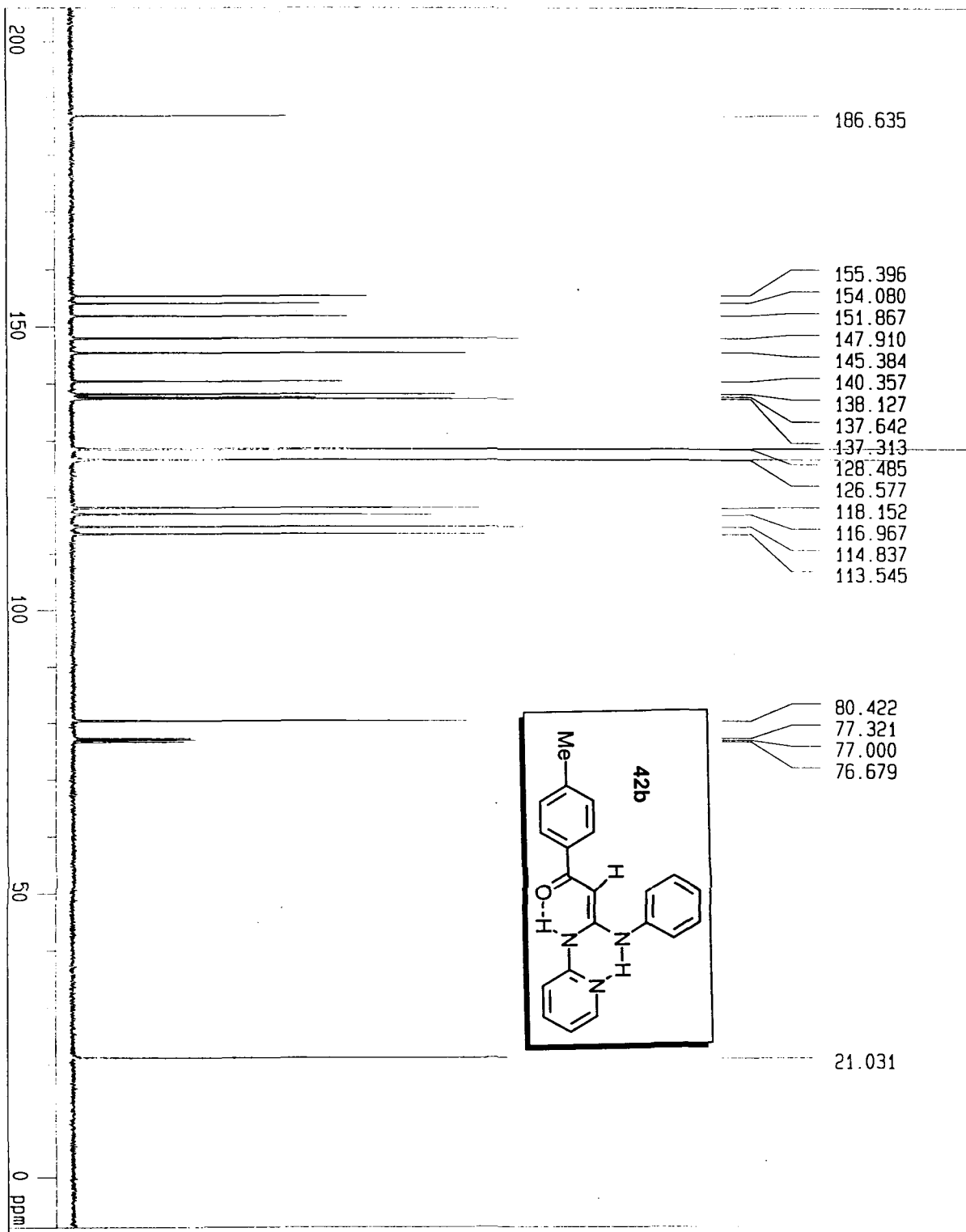
FAB MS m/z (%) 331 ($M^+ - BF_4$, 100).

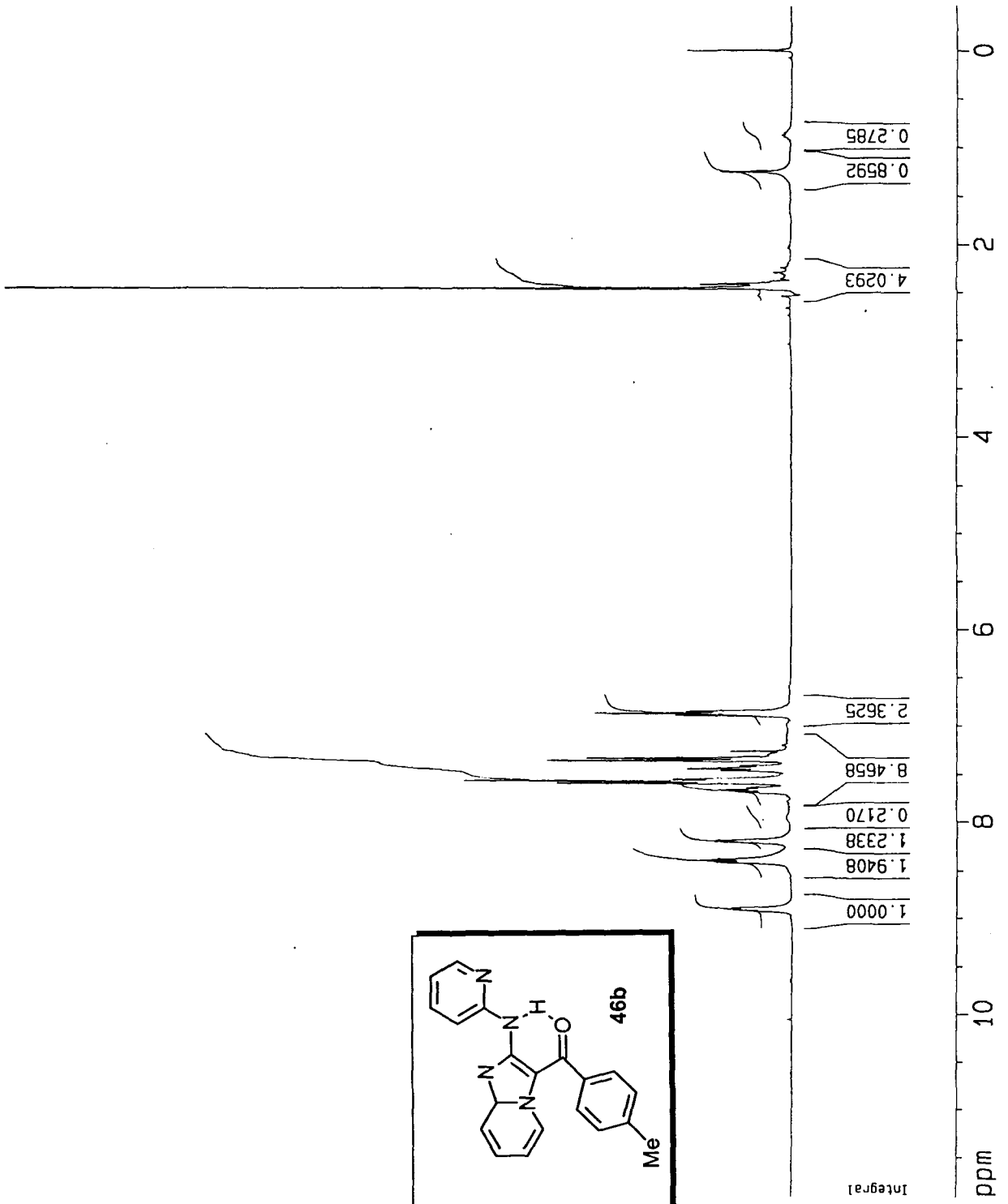
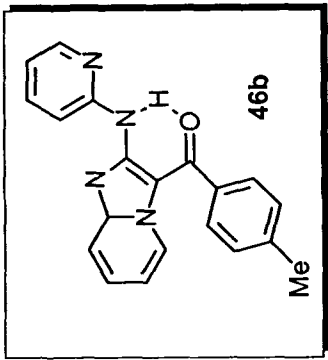
Anal. Calcd for $C_{19}H_{12}ClN_4BF_4$: C, 54.52; H, 2.89, N, 13.38. Found: C, 54.75; H, 2.71; N, 13.56.

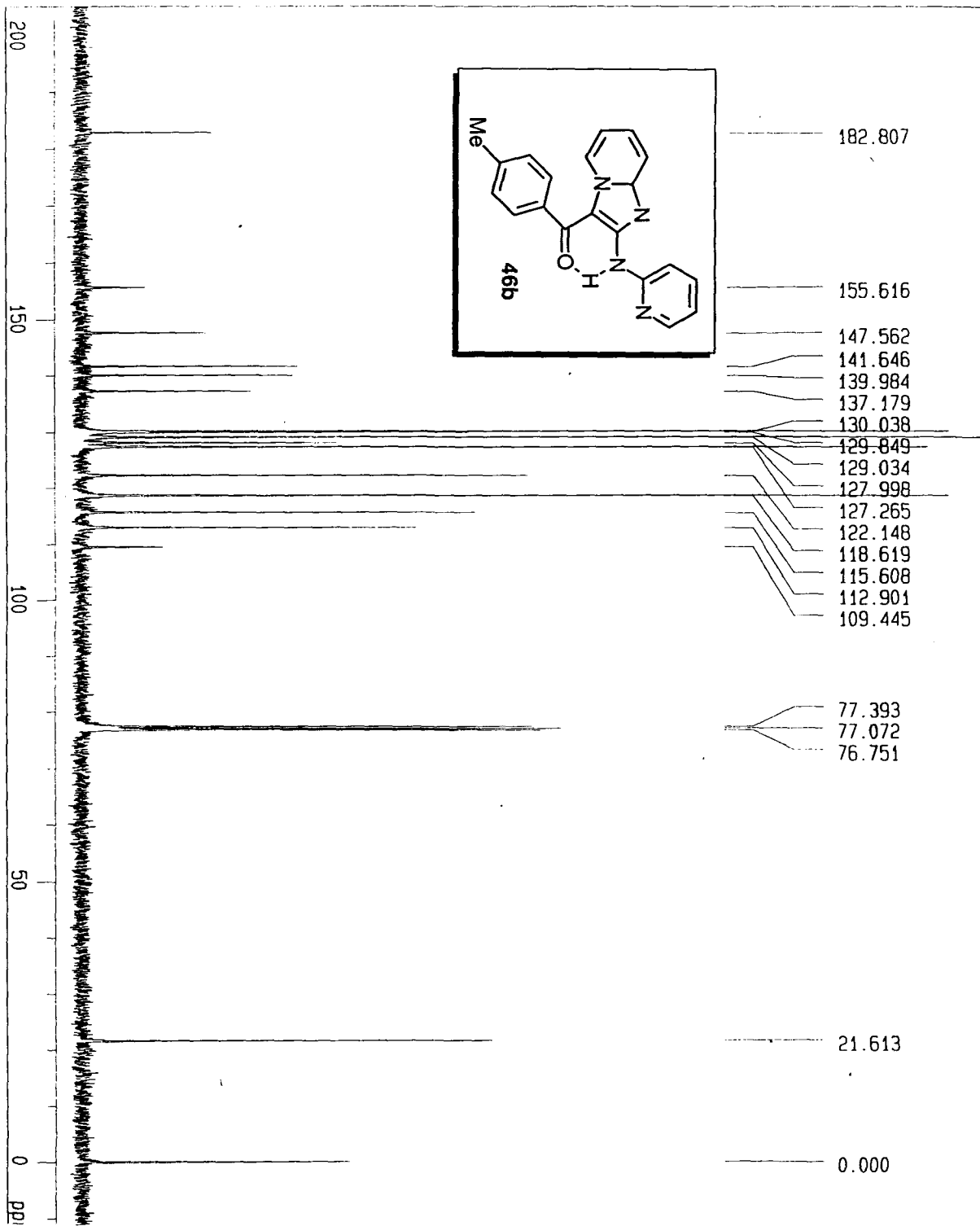












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6
4
2
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Integral

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2.1571

3.1896

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0.1497

0.0417

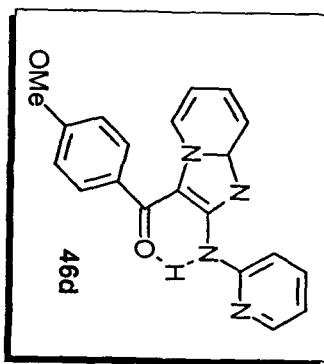
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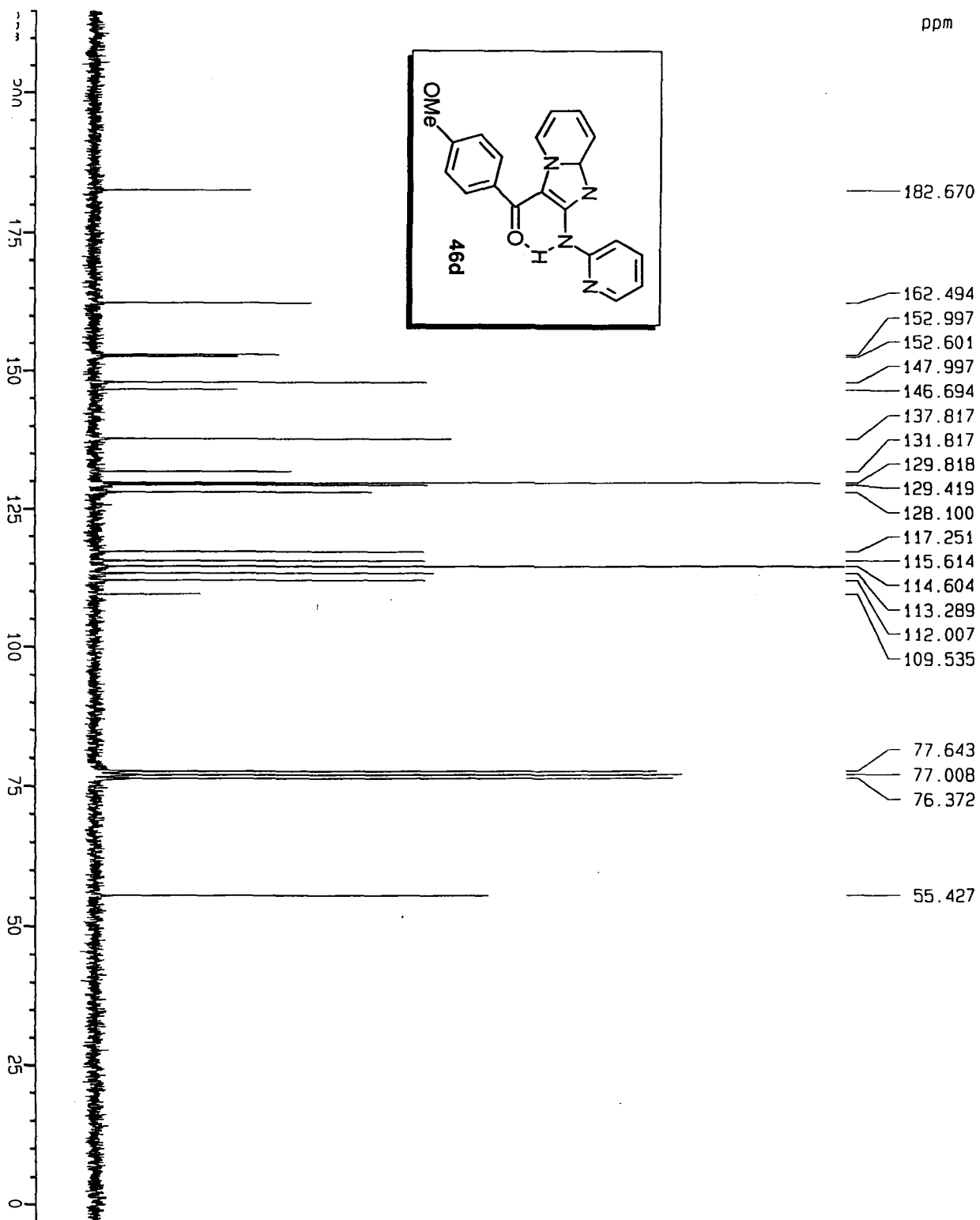
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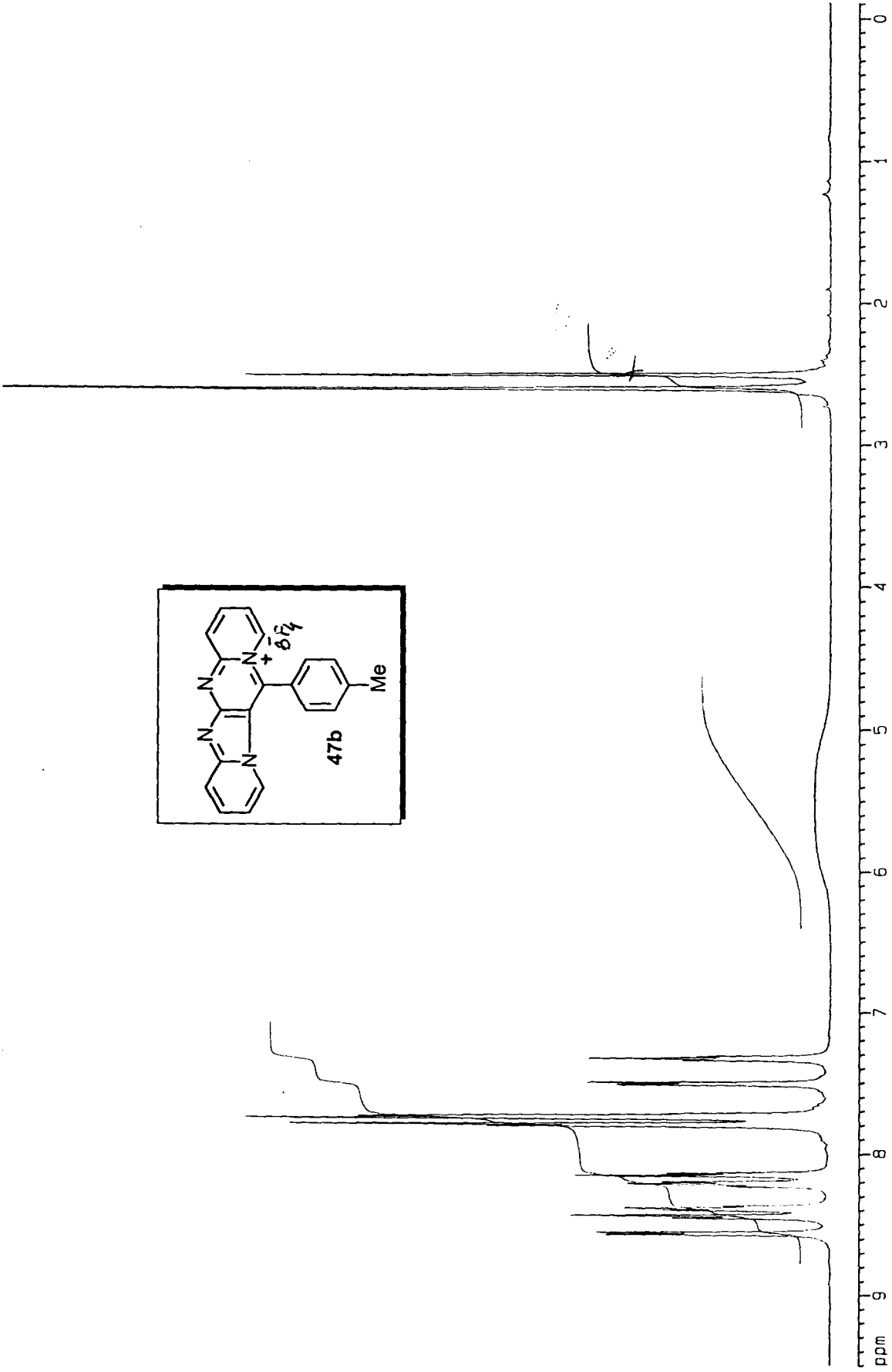
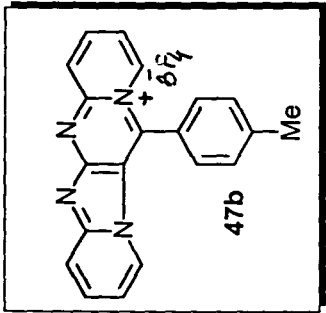
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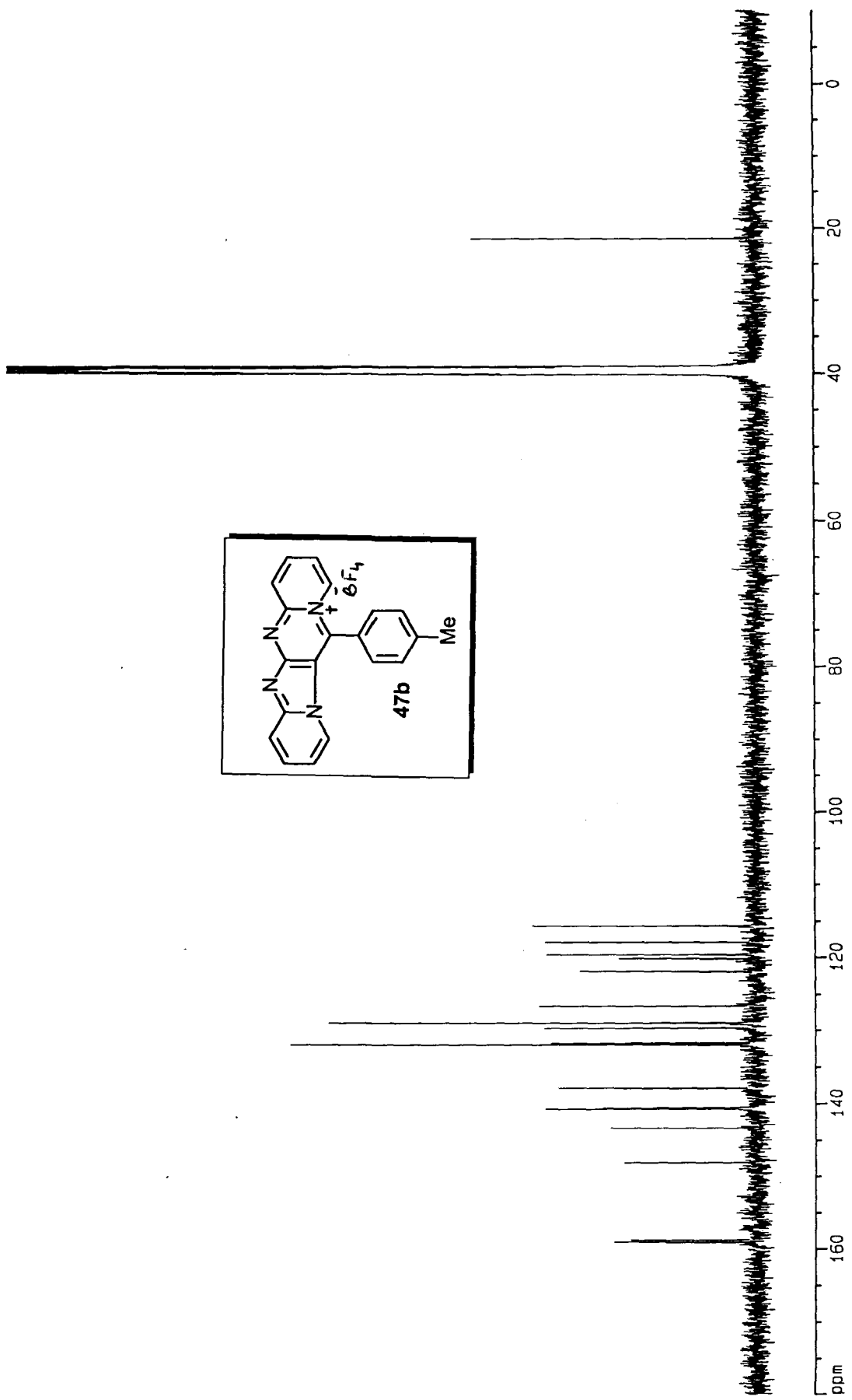
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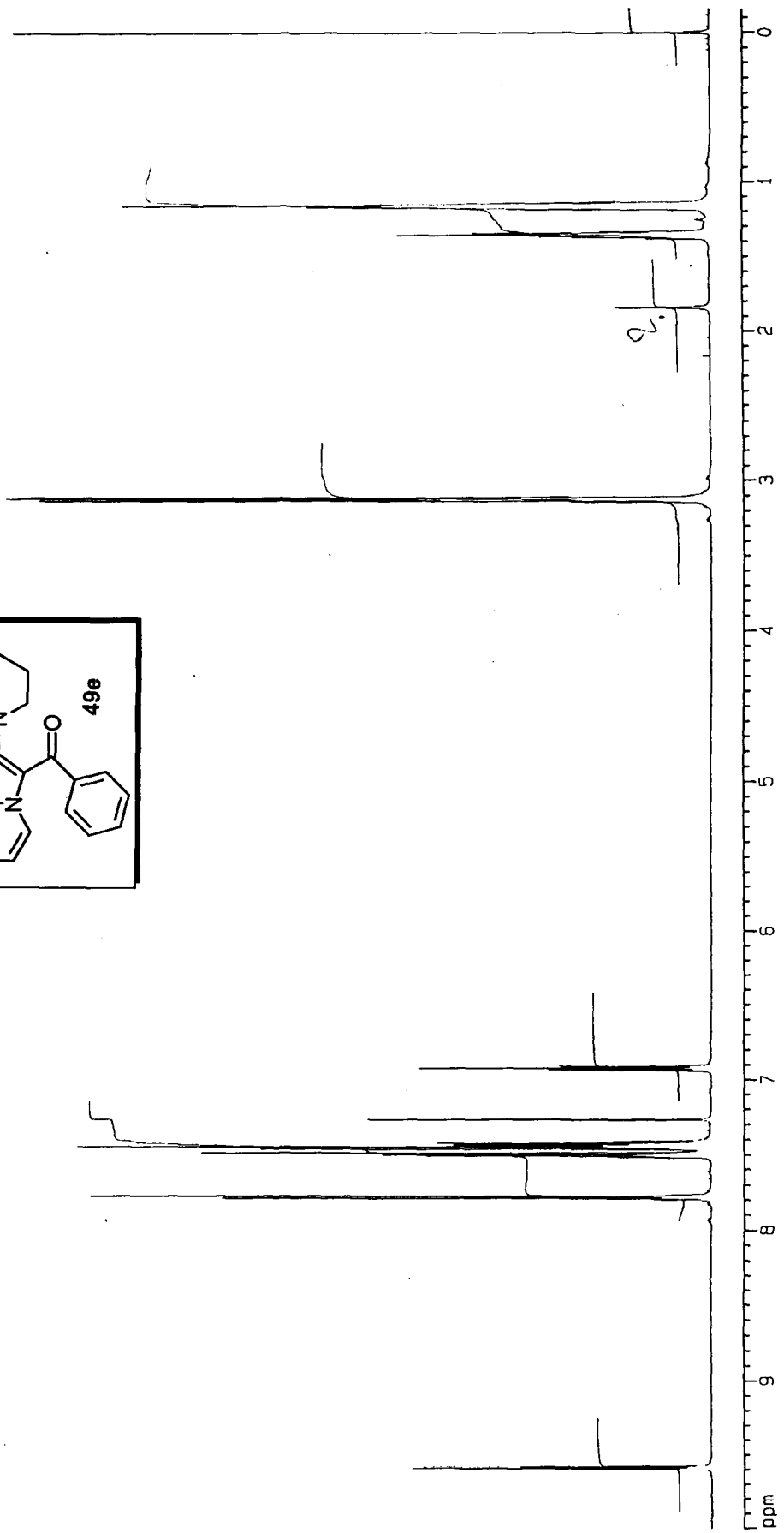
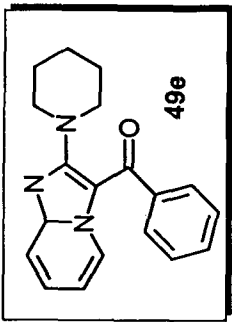
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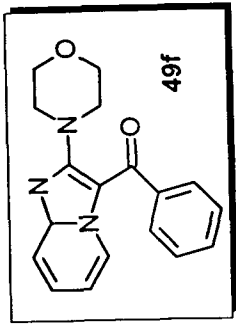
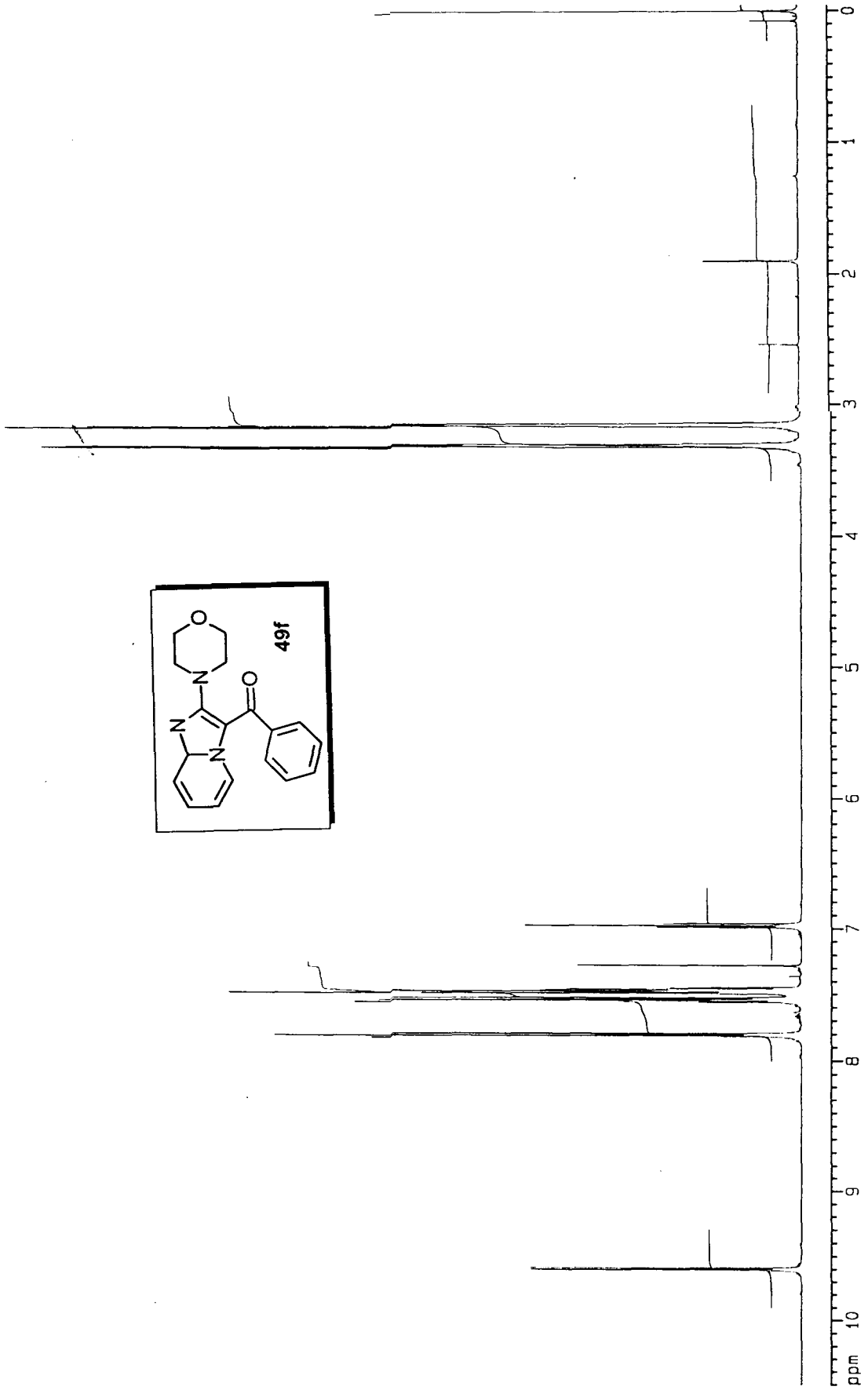


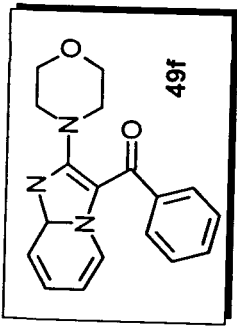
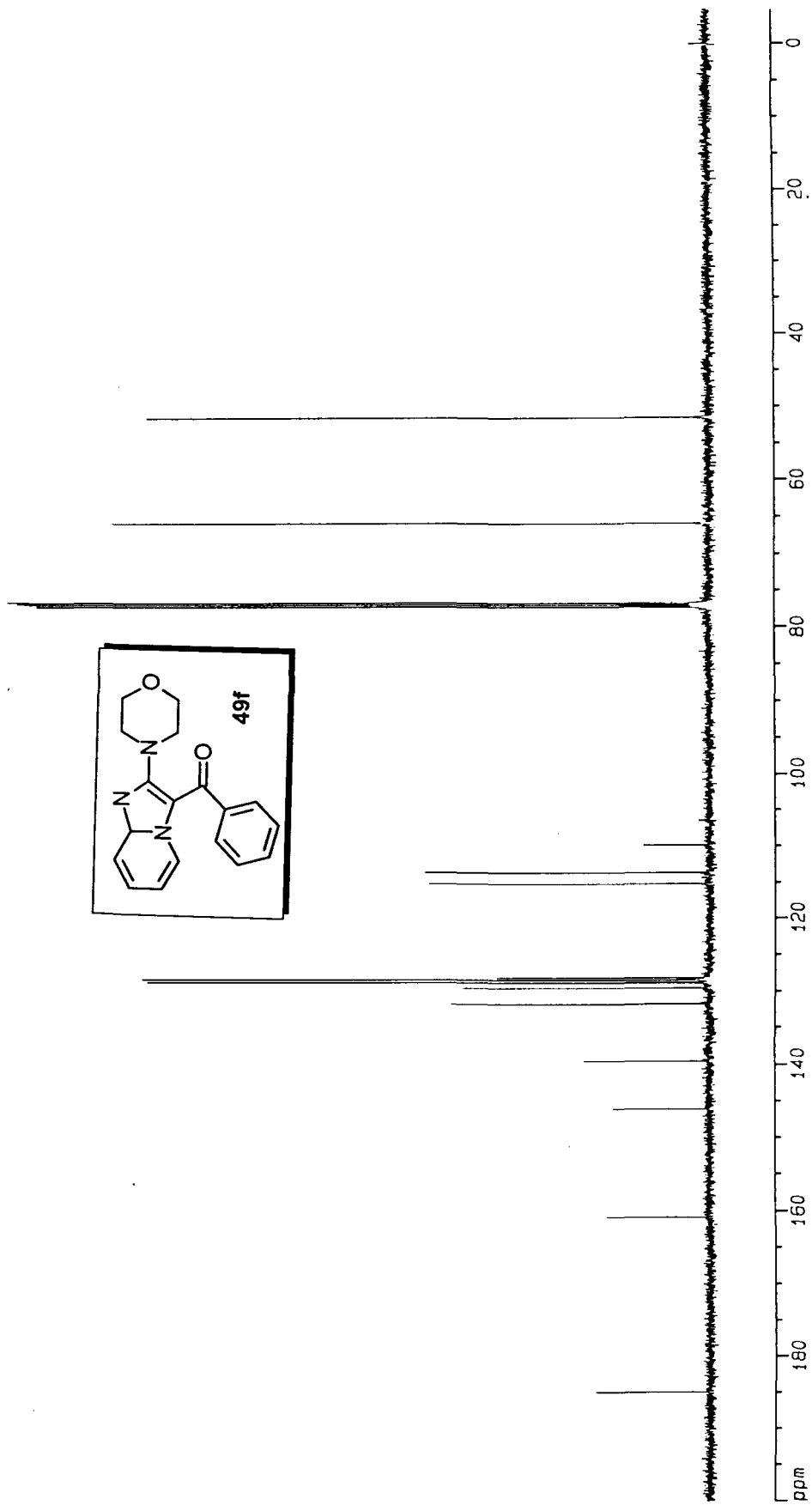


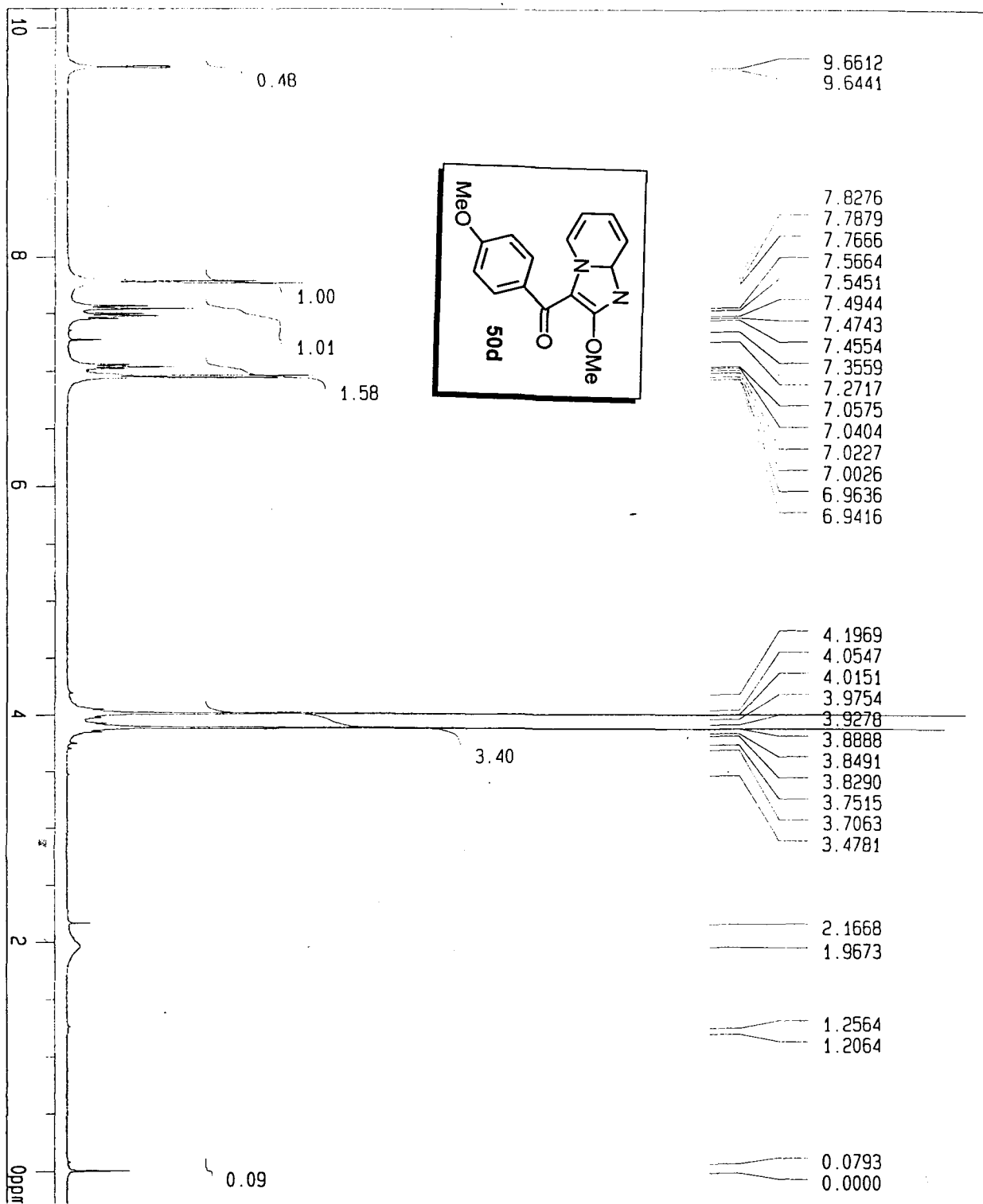


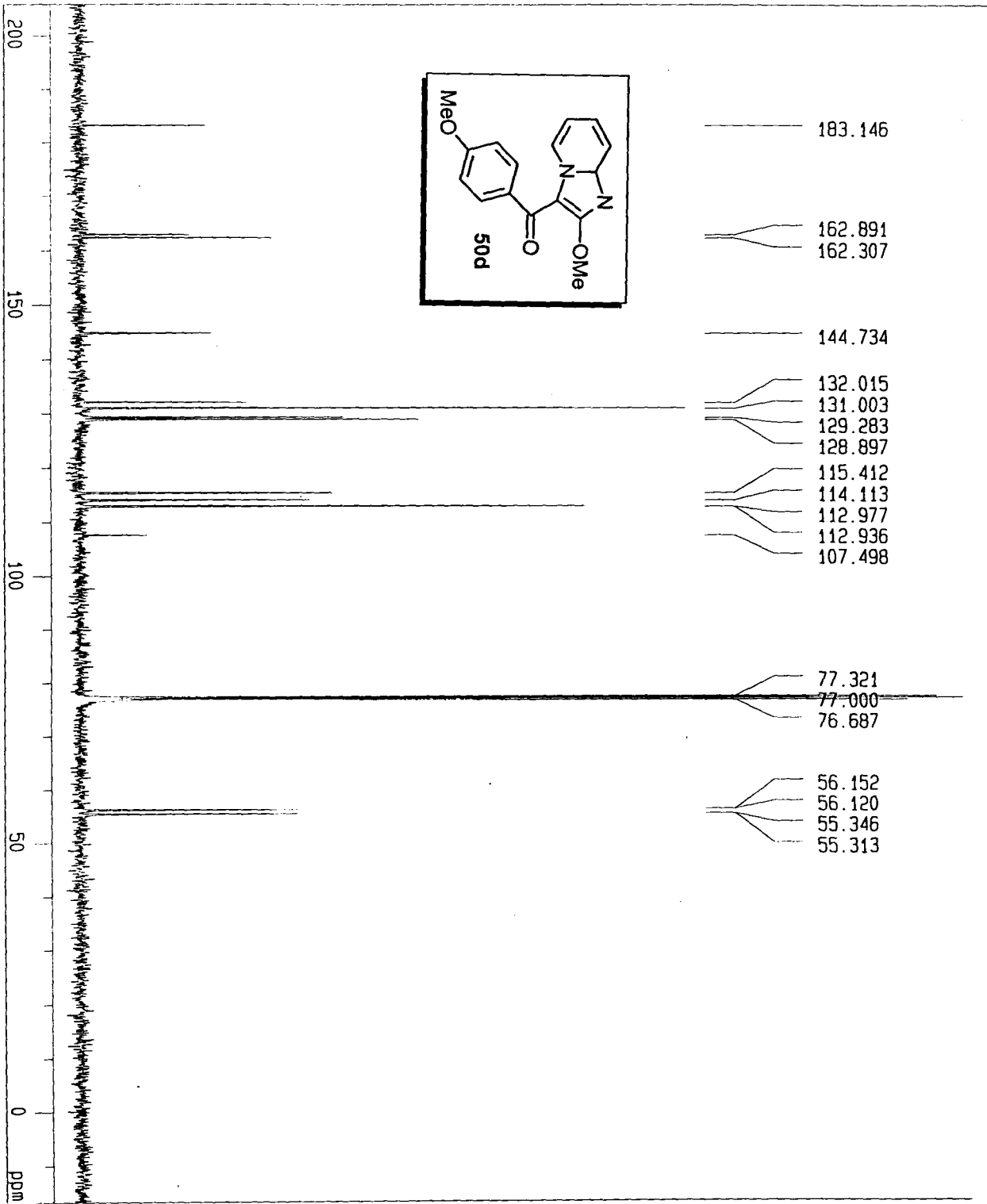












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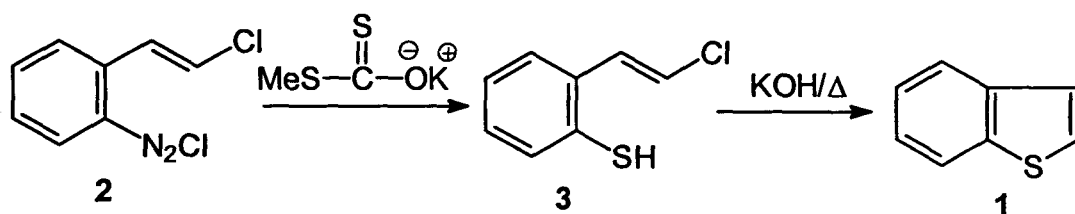
CHAPTER IV

***“A NEW EFFICIENT SYNTHESIS OF SUBSTITUTED
AND CONDENSED BENZO[b]THIOPHENES”***

Benzo[*b*]thiophene **1** and some of its derivatives have been first discovered in coal tar and in various petroleum crude oils.¹⁻³ Its first synthesis was reported by Gatterman and Lockhart⁴ in 1893 by involving diazotization of α -amino- ω -chlorostyrene **2** to the corresponding thiophenol **3** which underwent intramolecular base catalyzed cyclization to yield benzo[*b*]thiophene **1** (scheme 1).

Several benzo[*b*]thiophenes have been recognized as biologically active agents as bioisosters of indoles. Thus a number of benzo[*b*]thiophene analogues of biologically active indole derivatives have proved to be agonists or antagonists of indole derivatives.⁵

Scheme 1



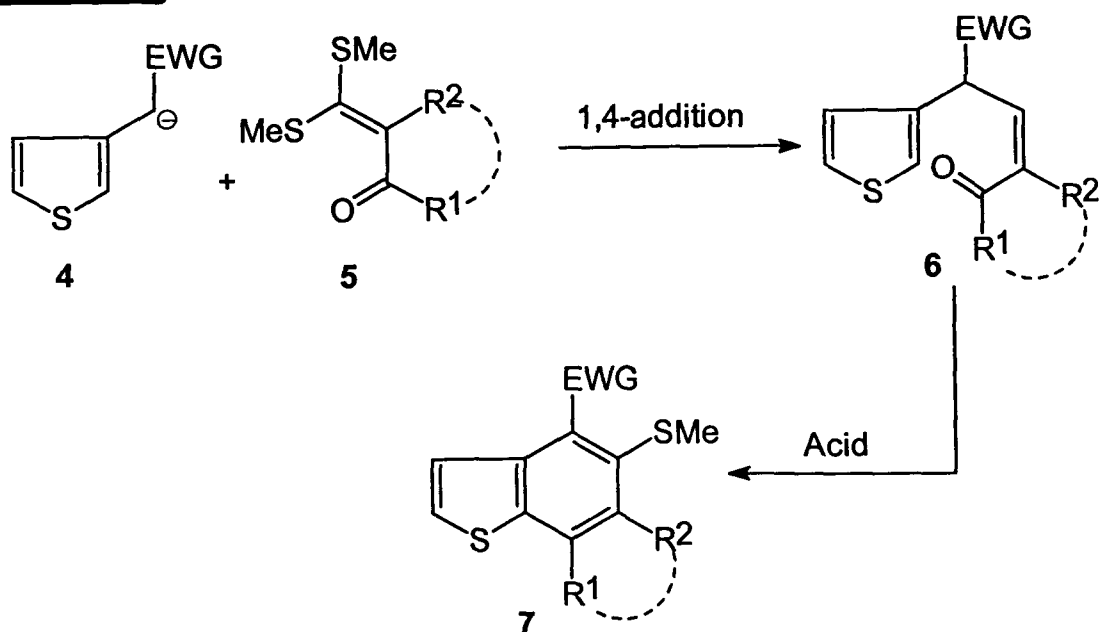
In the last 100 years, many synthetic methods have been developed for the synthesis of benzo[*b*]thiophenes. They can be classified as two major groups as follows.

- 1) Starting from benzene and its derivatives and build thiophene ring to afford the benzo[*b*]thiophenes.

2) Starting from preconstructed thiophene and its derivatives and build the aromatic ring to afford the corresponding benzo[*b*]thiophenes.

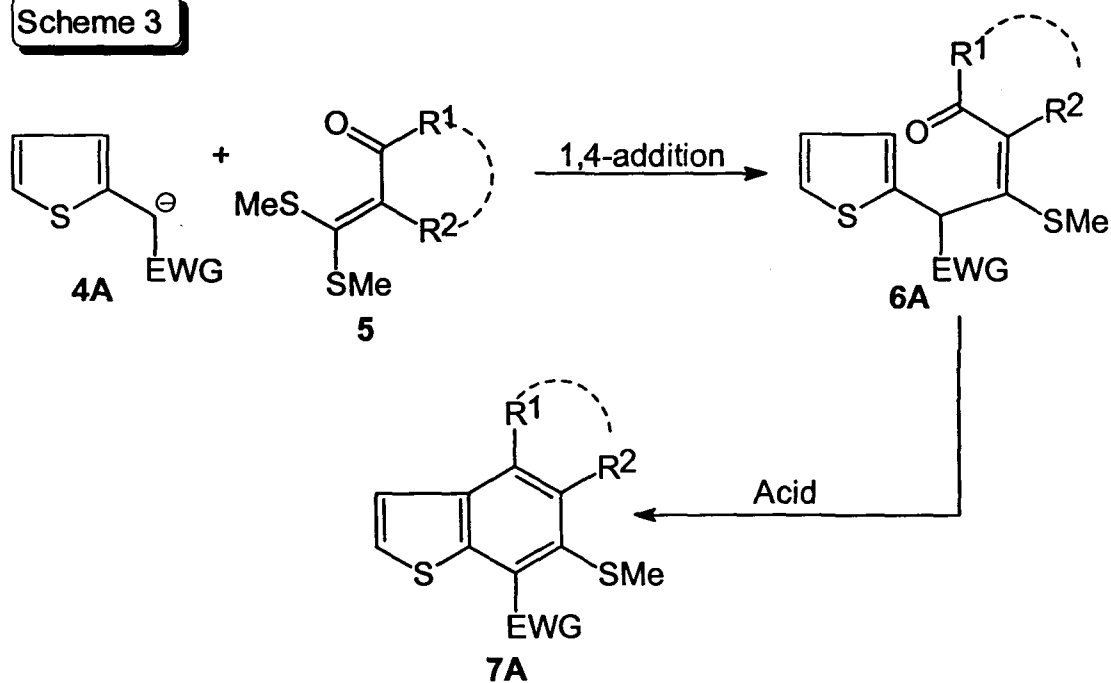
The first method suffers from serious limitations which requires functionalization of benzene ring at two carbon atoms *ortho* to each other and this process is particularly difficult when the product benzo[*b*]thiophene contains substituent/substituents due to problems associated in aromatic orientation.^{3, 6-10} On the other hand, the second approach for the synthesis of benzo[*b*]thiophene based on preconstructed thiophene ring over which appropriately substituted benzene ring could be created. This method is of particular interest because one can manipulate the substituents in newly formed benzene ring by appropriately placing them in open chain precursors. Besides, this approach has further support since the required thiophene is easily available in large quantities from coal products. The advantage of the methodology for the synthesis of benzo[*b*]thiophenes starting from functionalized thiophene derivatives can provide greater regiocontrolled of substituents in the newly formed benzene ring as illustrated in the following four schemes. In scheme 2, the benzo[*b*]thiophene **7** is a possible product when α -oxoketene dithioacetal **5** reacts with thiophene-3-acetonitrile **4** while the corresponding thiophene-2-acetonitrile **4A** when reacted with **5** will yield another regioisomer **7a** exclusively. These possibilities allow us to achieve the synthesis of benzo[*b*]thiophene with full controlled on the substituents. The scheme 2 and 3 illustrates only part of the regiocontrol. The other two

Scheme 2

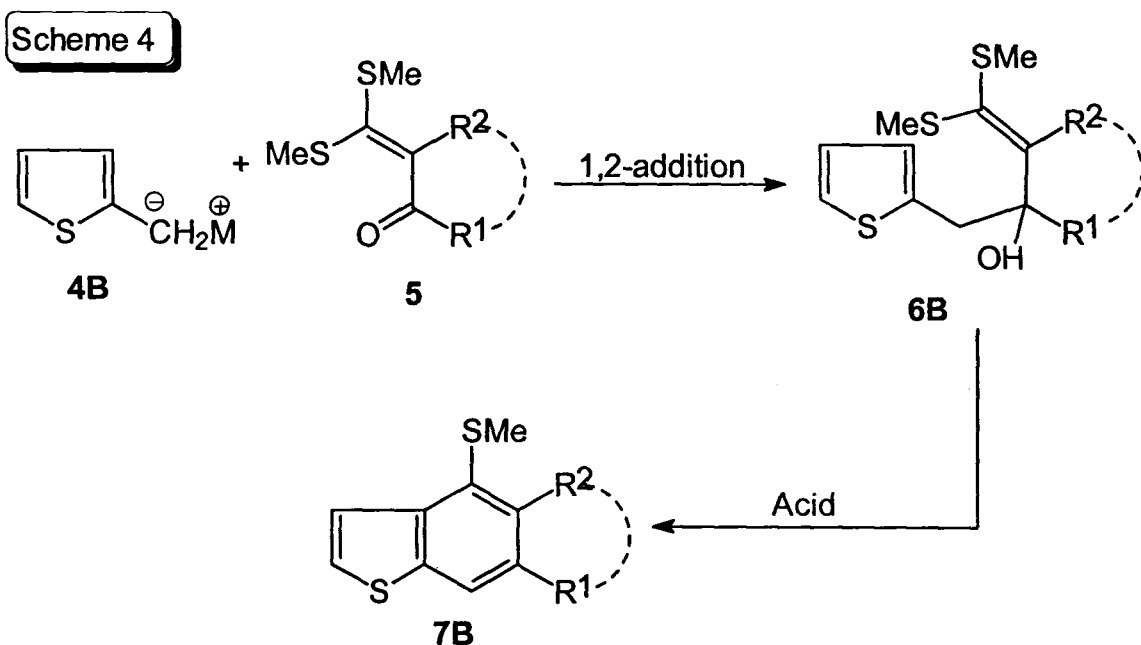


possibilities are described in scheme 4 and 5 where the 2-lithiomethylthiophene will react with 5 in the 1,2-fashion to afford the corresponding carbinol acetal 6 which on acid assisted cyclization should yield benzo[*b*]thiophene with R¹ at 5 and R² at 6 positions. If one consider all the

Scheme 3



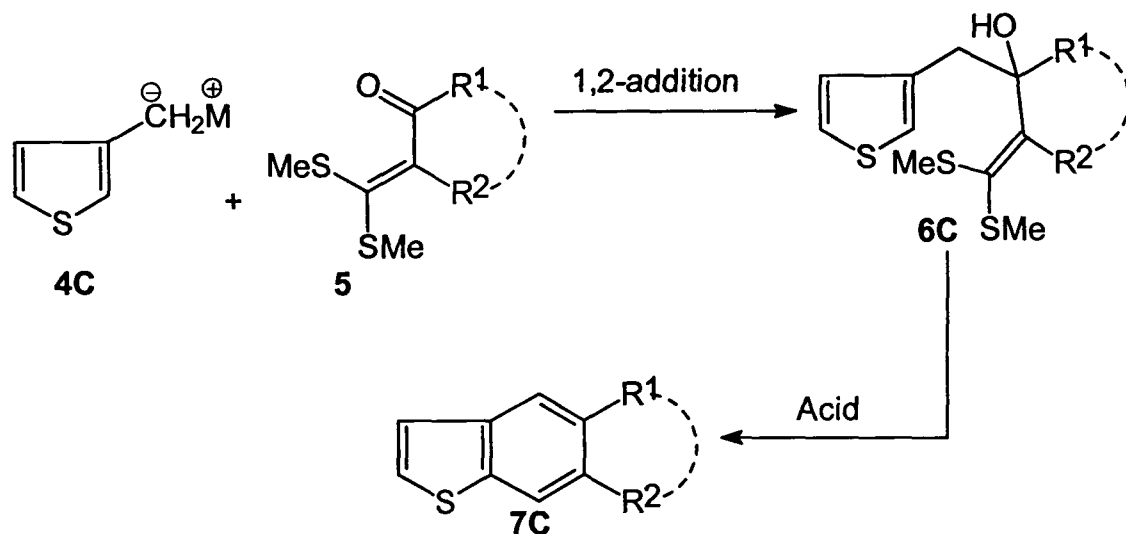
four possibilities of substituents in scheme 2-5, it is clear in scheme 2, R¹ and R² are at 7 and 6 positions respectively and they can be moved on 4 and 5 position in **7A** and 6 and 5 position in **7B** and 5 and 6 position in **7c** is a remarkable regiocontrolled of our methodology heteroaromatic annulation particularly making benzene ring over preconstructed thiophene derivatives. We have already investigated the reaction of thiophene-2-acetonitrile with **5** and confirmed the formation of expected regioisomer **7A** (scheme 3) in unequivocal terms. We have investigated in the present investigation, the



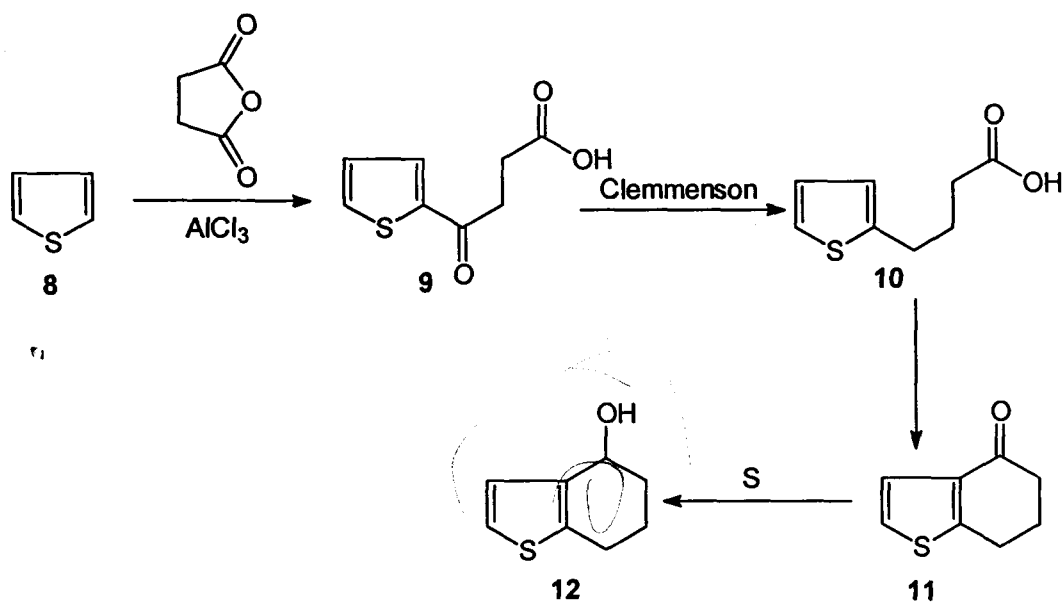
reaction of thiophene-3-acetonitrile with **5** so that regiocontrol can now moved at 7 and 6 positions from 4 and 5 positions in the newly formed benzene rings.

We therefore briefly discuss various literature methods based on construction of benzo[*b*]thiophenes from the preconstructed thiophene derivatives.

Scheme 5

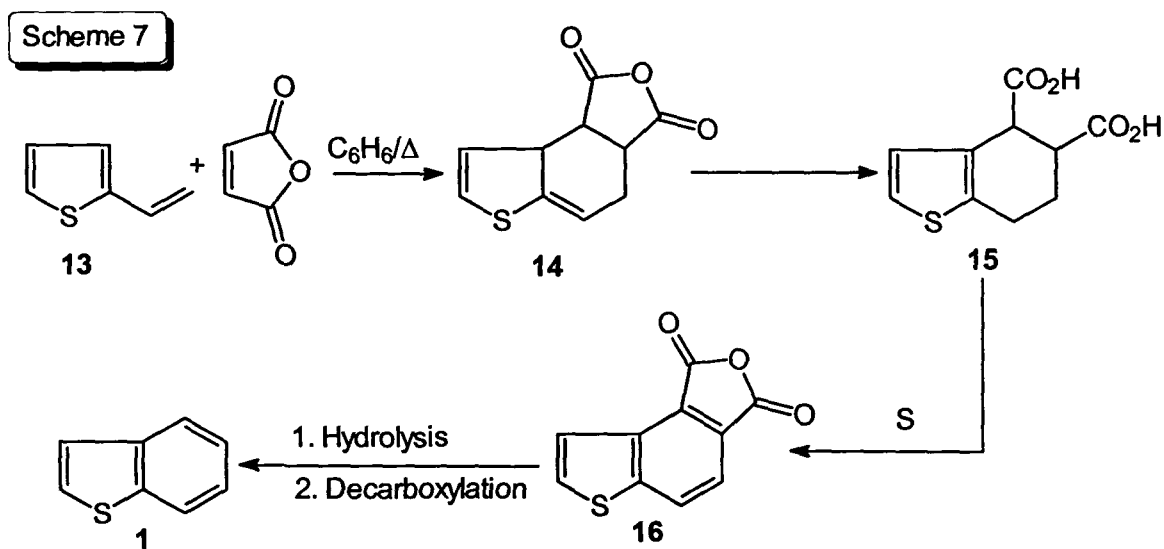


Scheme 6



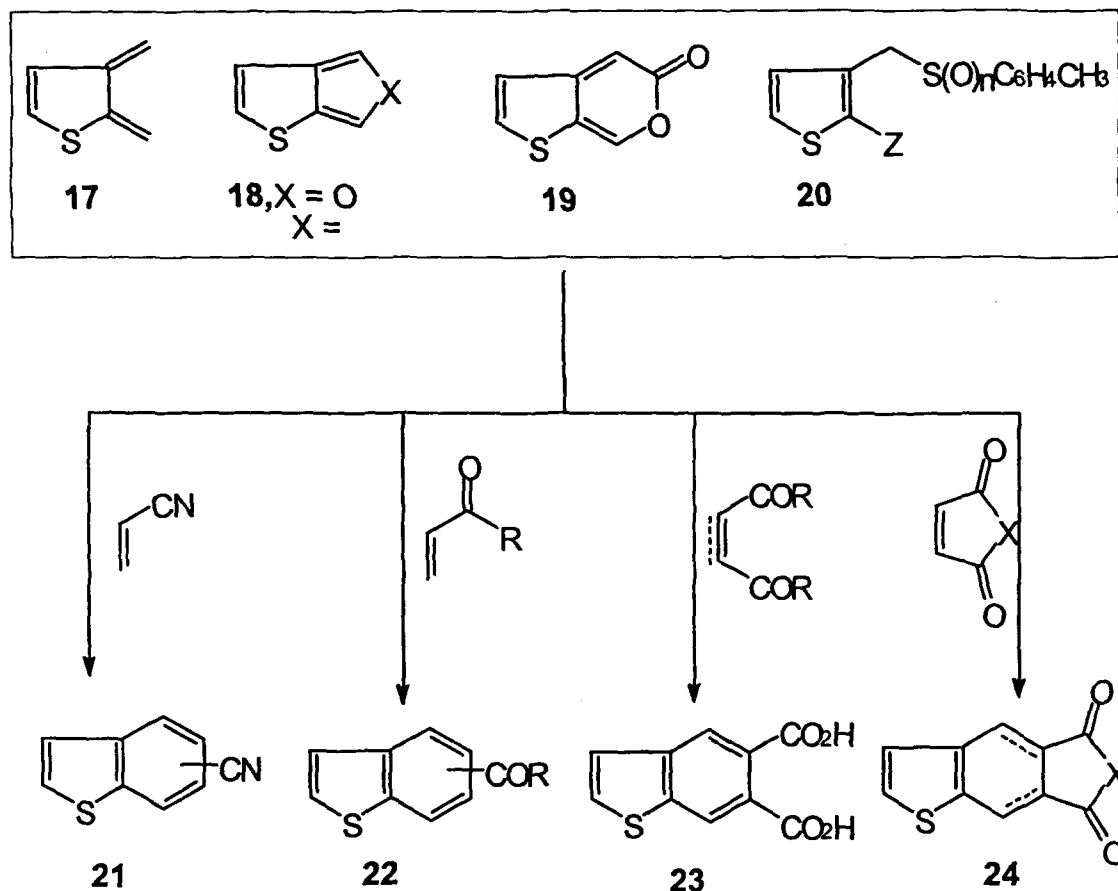
Fieser and co-workers¹¹ reported in 1935 the synthesis of 4-hydroxybenzo[*b*]thiophene 12 as illustrated in scheme 6. Thus on subjecting thiophene 8 with succinic anhydride under Friedel Craft's reaction conditions to afford good yield of β -(α -thienoyl)propionic acid 9 which on Clemmenson

reduction afforded γ -(α -thienyl)butyric acid **10**. The acid **10** was then treated with thionyl chloride and stannic chloride yielded the corresponding 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene **11** in good yield (scheme 6). The tetrahydro compound **11** on sulphur dehydrogenation yielded the corresponding 4-hydroxybenzo[*b*]thiophene **12**. Similarly Mc Dowell and co-workers¹² have developed a method for the synthesis of 7-oxo-tetrahydrobenzo[*b*]thiophene starting from 3-acetylthiophene.



2-Vinyl thiophene **13** (scheme 7) has been used by Scully and Brown¹³ for benzothiophene synthesis by Diels-Alder cycloaddition approach. Thus maleic anhydride and 2-vinylthiophene **13** were refluxed in benzene to afford the corresponding cycloadduct **14** along with some polymeric material. The anhydride was then hydrolyzed to the corresponding tetrahydro dicarboxylic acid **15** which on S dehydrogenation yielding the corresponding anhydride of benzo[*b*]thiophene **16**. The anhydride on further hydrolysis and

Scheme 8

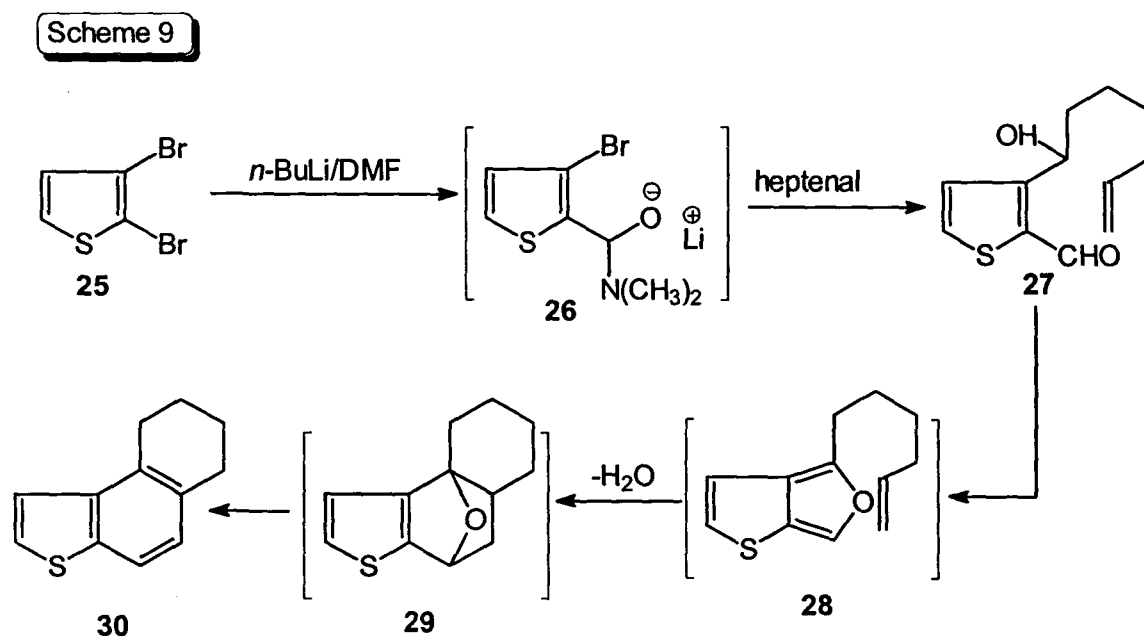


decarboxylation yielded the desired benzo[*b*]thiophene 1 in over all moderate yield. Seitz and co-workers¹⁴ also reacted 2-vinylthiophene 14 with tetrabromocyclopropene to afford the cycloadducts which undergoes cyclopropane ring cleavage selectively at C-1/C-3 to afford functionalized benzothiophene.

There are several methods for the synthesis of benzo[*b*]thiophene systems based on the quinodimethane approach using various functionalized thiophenes 17,¹⁵⁻¹⁶ 18,¹⁷⁻¹⁹ 19,²⁰ 20²¹ etc. (scheme 8). All these dienes and their precursors were reacted with various dienophiles to afford the corresponding

dihydro or tetrahydro benzo[*b*]thiophenes which were subsequently transformed into the corresponding benzo[*b*]thiophenes **21**, **22**, **23** and **24** as illustrated in scheme 8.

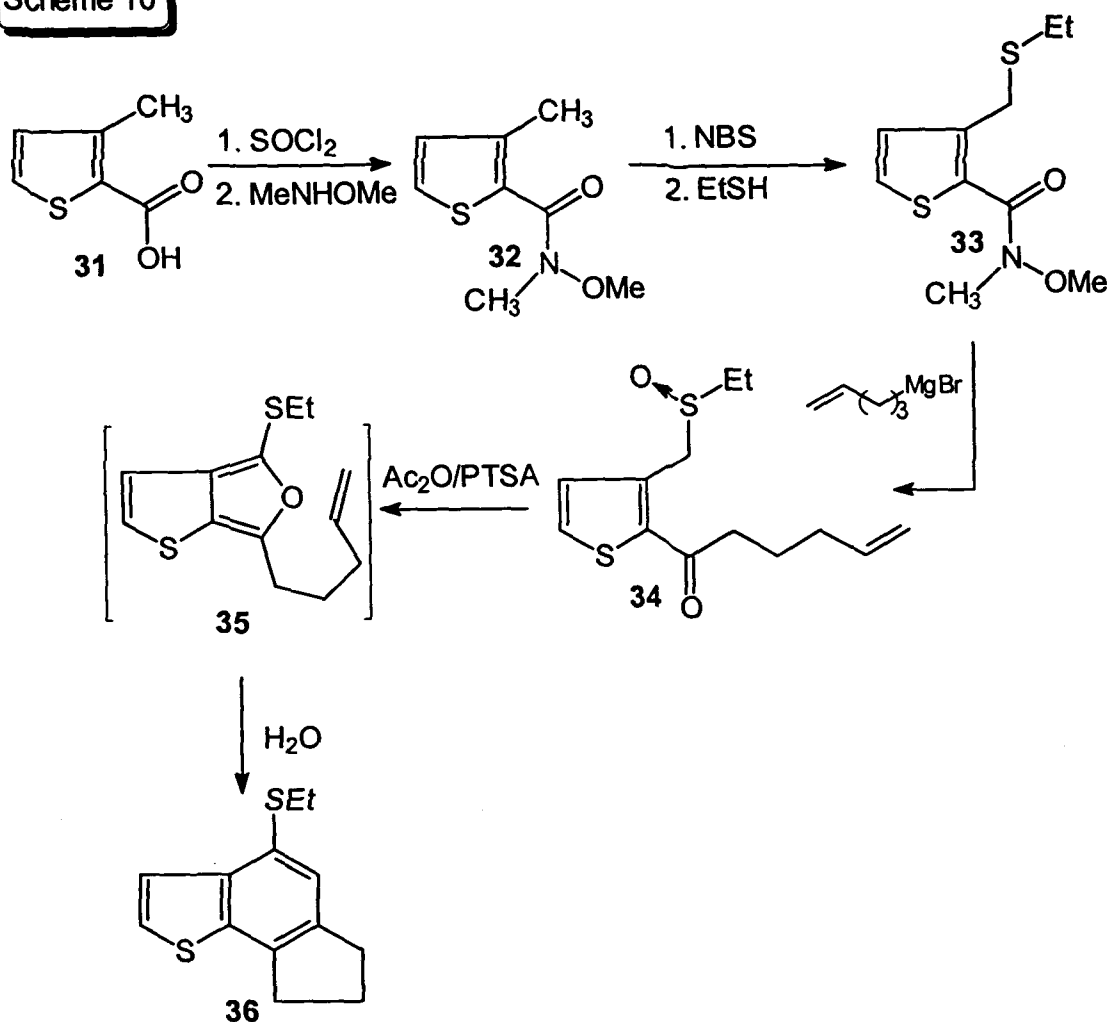
An intramolecular Diels-Alder reaction was designed for the synthesis of annelated benzo[*b*]thiophene **30**.²² Thus 2,3-dibromothiophene **25** was reacted with DMF in the presence of *n*-BuLi to afford the corresponding 2-aldehyde amino acetal **26**. It was then reacted with heptenal to get the



Corresponding tetrahydronaphtho[2,1-*b*]thiophene **30** involving formation of furano thiophene **28** and its cycloadduct **29** followed by elimination of water.

Similarly intramolecular Diels-Alder approach was used for the synthesis of 6,7-cyclopentano-4-(ethylthio)benzo[*b*]thiophene **36** in the recent year (1996).²³ Thus 3-methylthiophene-2-carboxylic acid **31** was converted

Scheme 10

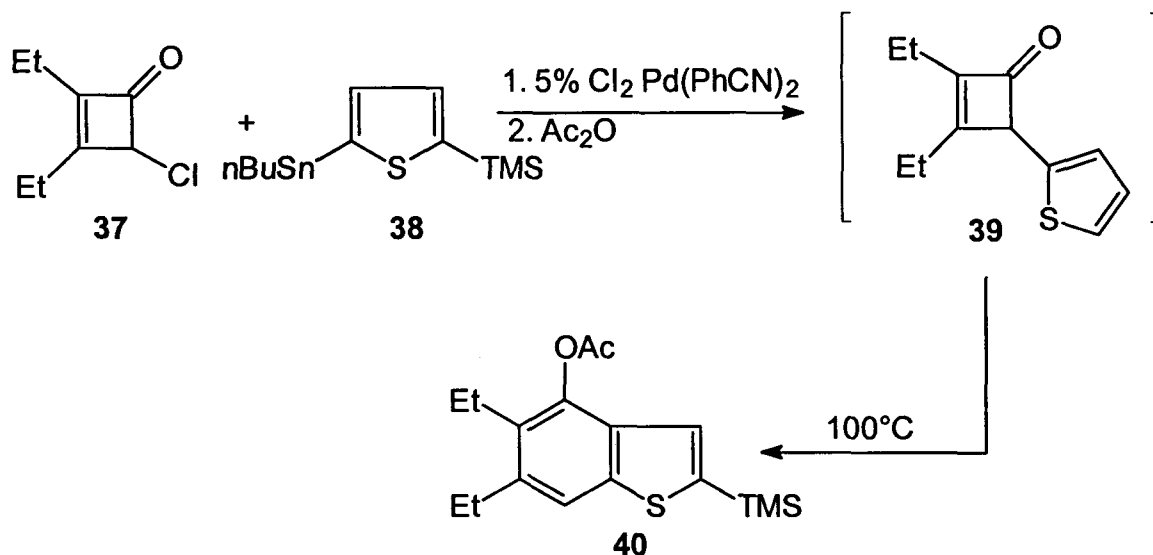


into its amide **32** followed by bromination using *N*-bromo succinimide and reaction with ethanol to afford **33**. 5-Pentylmagnesium bromide was then reacted with amide **33** to get the corresponding ketone **34**. The ketone was then treated with acetic anhydride and PTSA to yield the benzo[*b*]thiophene **36** involving the formation of furan ring cycloaddition and dehydration in one step.

Lebieskind and co-workers³⁰ have described an interesting benzoannulation approach for the synthesis of functionalized

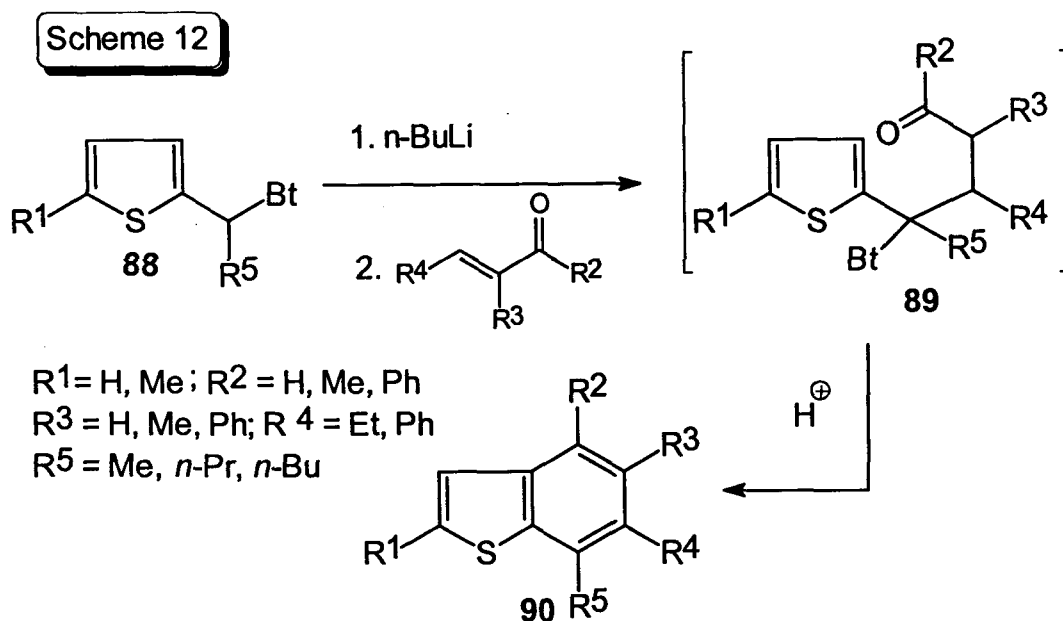
benzo[*b*]thiophene. Thus 4-chloro-2,3-diethyl-2-cyclobutanone **37** underwent palladium catalyzed cross coupling with 5-trimethylsilyl-2-tributylstannylthiophene **38**. The intermediate on thermolysis yielded the corresponding benzo[*b*]thiophene in 58% yield.

Scheme 11



Katritzky and co-workers³¹ have used 2-(benzotriazol-1-ylmethyl)thiophenes **88** for the synthesis of benzo[*b*]thiophenes as formulated in scheme 12. These functionalized thiophenes were easily obtained by condensation of 1-(hydroxymethyl)benzotriazole with thiophenes. Lithiation of these intermediates **88** followed by reaction of the resulting anions to various unsaturated aldehydes and ketones yielded the corresponding 1,4-adducts **89** which on subsequent acid catalyzed intramolecular cyclization

followed by debenzotriazolization-dehydration afforded polysubstituted benzo[*b*]thiophenes **90** in high yields.

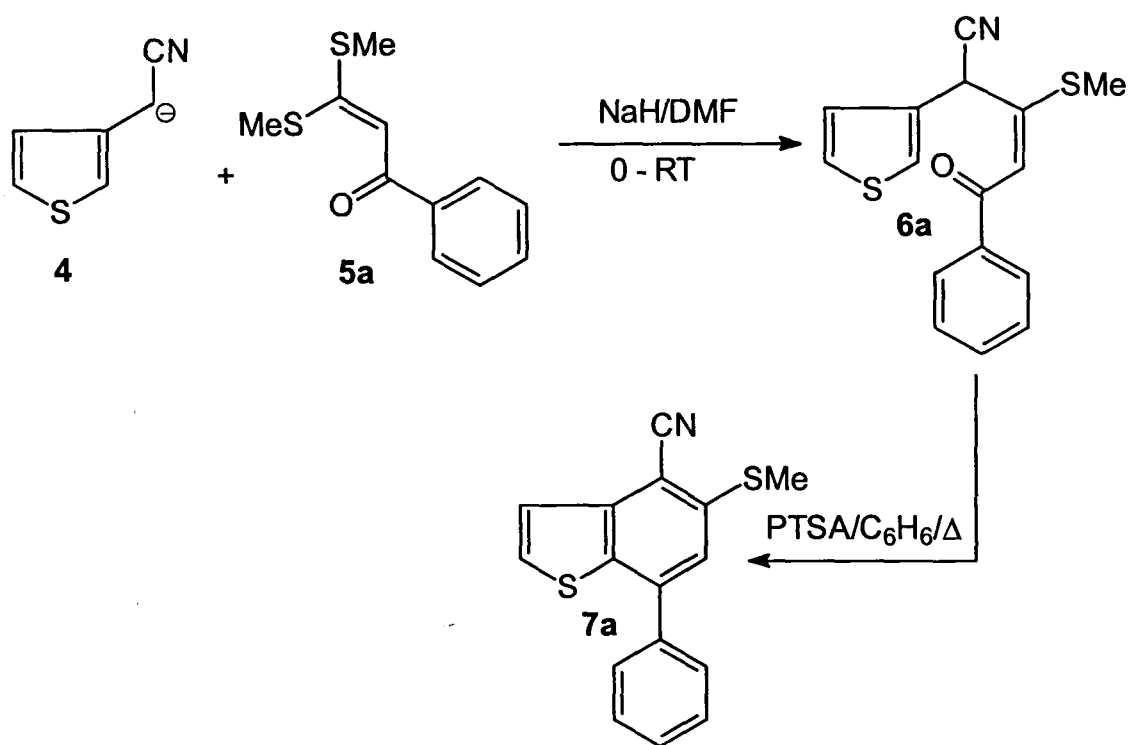


Recently we developed a facile general method for the synthesis of benzo[*b*]thiophenes based on heteroaromatic annulation protocol. There are several possibilities as described in scheme 3 and 4 to generate various allyl anions which can be reacted with α -oxoketene dithioacetals following one of the two possibilities. We have described from our laboratory one such possibilities involving the reaction of thiophene-2-acetonitrile **4A** with α -oxoketene dithioacetals in the presence of NaH and DMF at ambient temperatures to afford the corresponding addition elimination products **6A** in excellent yields. These intermediates were then cyclized by refluxing in the presence of TsOH in benzene to afford the corresponding regioselectively substituted 7-cyanobenzo[*b*]thiophenes **7A** in high yields (scheme 13).

methods do not enjoy preparatory status due to the overall low yields. Also in some cases, particularly the cycloaddition of vinyl thiophenes is reported to yield the regioisomers creating problem of their separation. On the other hand the heteroaromatic annulation methodology developed in our laboratory stands superior to those described in the literature. Particularly in its simplicity less number of steps and high yields of benzo[*b*]thiophenes retaining the regiocontrol of the substituents at 4, 5, 6 and 7 positions. In the present investigation, we considered of interest to examine the reaction of thiophene-3-acetonitrile with various α -oxoketene dithioacetals in order to accomplish the alternative possible regioisomers of benzo[*b*]thiophenes. These new benzo[*b*]thiophenes will carry substituents at 7 and 6 positions along with cyano and methylthio groups at 4 and 5 positions respectively. These reactions have been investigated in the present work and described below.

In a typical experiment thiophene-3-acetonitrile **4** (scheme 14) was reacted with acetophenone mercaptal **5a** in the presence of NaH in DMF at ice cool temperature for 8 h. The reaction mixture after work up yielded the corresponding addition elimination product **6a** in 89 % yield. The structure of **6a** was fully confirmed by its spectral and analytical data to establish the generality of the formation of these intermediates with other α -oxoketene dithioacetals and they were not characterized in subsequent reactions. The analytical and spectral data for **6a** are described below.

Scheme 14



Colourless crystals; m.p. 78-79 °C (chloroform-ether)

IR (KBr): ν_{\max} 2213, 1710, 1549 cm^{-1} .

¹H NMR (300 MHz, CDCl₃): δ 2.42 (s, 3H), 4.01 (s, 2H), 7.06-7.09 (m, 1H), 7.41-7.46 (m, 7H).

Anal. Calcd. for C₁₆H₁₃NOS₂ (299.35): C, 55.67; H, 4.67; N, 5.90%. Found: C, 55.28; H, 4.70; N, 5.94%.

The addition elimination product 6a was then subjected to cycloaromatization by refluxing in benzene in the presence of TsOH. The reaction mixture after work up yielded the crude 4-cyano-5-methylthio-7-phenylbenzo[b]thiophene

7a which was purified by column chromatography using hexane/ethyl acetate as eluent to afford pure **7a** as colourless crystals (m.p. 111-112 °C) in 70% yield. The compound was characterized on the basis of its analytical and spectral data as follows.

IR (KBr): ν_{\max} 2208, 1645, 1558, 1483 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ 2.66 (s, 3H, SCH_3), 7.34 (s, 1H, ArH), 7.47-7.60 (m, 4H, ArH), 7.68-7.71 (m, 3H, ArH).

^{13}C NMR (75 MHz, CDCl_3): δ 17.10, 109.30, 116.40, 122.71, 123.13, 128.16, 129.13, 129.30, 131.52, 136.86, 138.81, 141.22, 142.32.

MS (m/z, %) 281 (M^+ , 100), 233 ($\text{M}^+ - 48$, 27).

Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{NS}_2$ (281.40): C, 68.29; H, 3.94; N, 4.98%; Found: C, 68.70; H, 3.87; N, 5.03%.

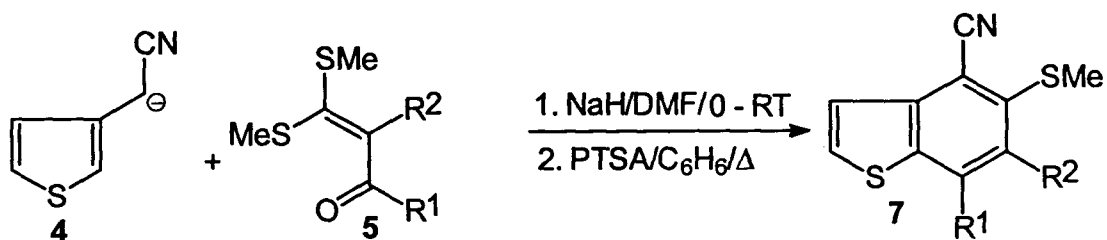
The addition-elimination product was characterized only in this case and in the subsequent reactions. These intermediates were generally recognized by tlc spot and the crude adducts were directly subjected to cyclization reactions to afford the corresponding benzo[*b*]thiophenes.

Also, to generalize this simple methodology the selection of α -oxoketene dithioacetals was carefully done so that the product benzo[*b*]thiophenes will carry appropriate mono and di substituents including the corresponding annelated products. Also the α -oxoketene dithioacetals were suitably modified to yield 5-alkoxy and 5-amino benzo[*b*]thiophenes.

The thiophene-3-acetonitrile **4** was then reacted with α -oxoketene dithioacetals derived from acetone, ethyl methyl ketone, propiophenone and isopropyl methyl ketone under the similar reaction conditions as described earlier to afford the corresponding addition elimination products **6b-e** in excellent yields (scheme 15). These products were subsequently cyclized in the presence of TsOH in refluxing benzene to afford the corresponding benzo[*b*]thiophene **7b-e** in 69-72 % overall yields. All these benzo[*b*]thiophenes were fully characterized by their analytical and spectral data which are in accordance with the assigned structure and are recorded in the experimental section.

The synthesis of 6,7-annulated benzo[*b*]thiophene was next examined. It may be noted that the synthesis of 6,7-cyclopentanobenzo[*b*]thiophene described by Albert Padwa (scheme 10) starting from the not so easily available thiophene-3-methyl-3-carboxylic acid. There are at least four additional steps before the precursor **35** is generated. To highlight the synthesis of 6,7-cyclopentanobenzo[*b*]thiophene **7f** (scheme 16) as against that described by Padwa and co-workers, we have reacted commercially available thiophene-3-acetonitrile with cyclopentanone mercaptal **5f** under the described conditions to afford the addition elimination product in good yield which was pure enough to carry out the next step. The crude **6f** was treated with TsOH to afford the corresponding 6,7-cyclopentanobenzo[*b*]thiophene in 67 % yield. The structure of **7f** was fully confirmed by its analytical and

Scheme 15



Starting Material 5	Product 7	Yield %
<p>5b</p>	<p>7b</p>	78
<p>5c</p>	<p>7c</p>	69
<p>5d</p>	<p>7d</p>	67
<p>5e</p>	<p>7e</p>	63

spectral data as given as below.

Colourless crystals; m.p. 129-130 °C (chloroform-ether); Yield 77%; IR

(KBr): ν_{\max} 2208, 1649, 1562, 1421 cm^{-1} ;

^1H NMR (300 MHz, CDCl_3): δ 2.25 (pentet, 2H, $J=7.5$ Hz), 2.52 (s, 3H, SCH_3), 3.11-3.47 (m, 4H, $-(\text{CH}_2)_2-$), 7.45 (d, 1H, $J=5.6$ Hz), 7.54 (d, 1H, $J=5.6$ Hz);

^{13}C NMR (400 MHz): δ 18.81, 24.06, 33.27, 109.12, 117.11, 122.57, 129.04, 134.04, 135.73, 141.15, 142.35, 143.63;

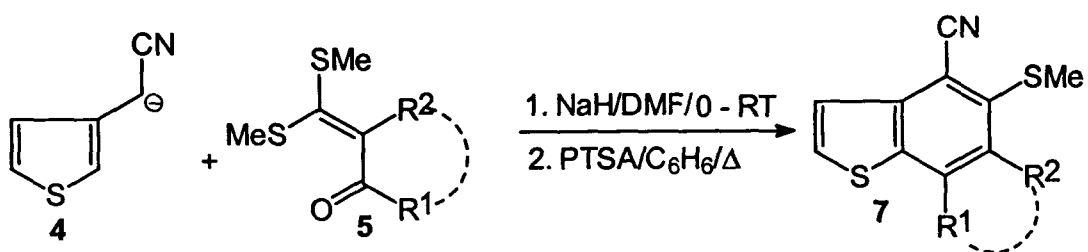
MS: m/z 245 (M^+ , 100%), 230 (M^+-15 , 47);

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{NS}_2$ (245.37): C, 63.64; H, 4.52; N, 5.71%; Found: C, 63.96; H, 4.59; N, 5.67%.

Similarly, various 6,7-annelated benzo[*b*]thiophene **7g**, **7h** and **7i** were obtained in 62-69 % overall yields by following the sequential steps by reacting the corresponding mercaptals derived from cyclohexanone, indanone and tetralone with **4**. The analytical and spectral data **7g-7i** were in conformity with the assigned structures which are described in the experimental section.

In the next experiments the benzo[*b*]thiophene carrying amino and methoxy groups at 5-position were included. Thus the S,N-acetal **5j** was reacted with **4** as described earlier and addition elimination products **6j** which was obtained in about 85 % yield, was directly cyclized in the presence of

Scheme 16

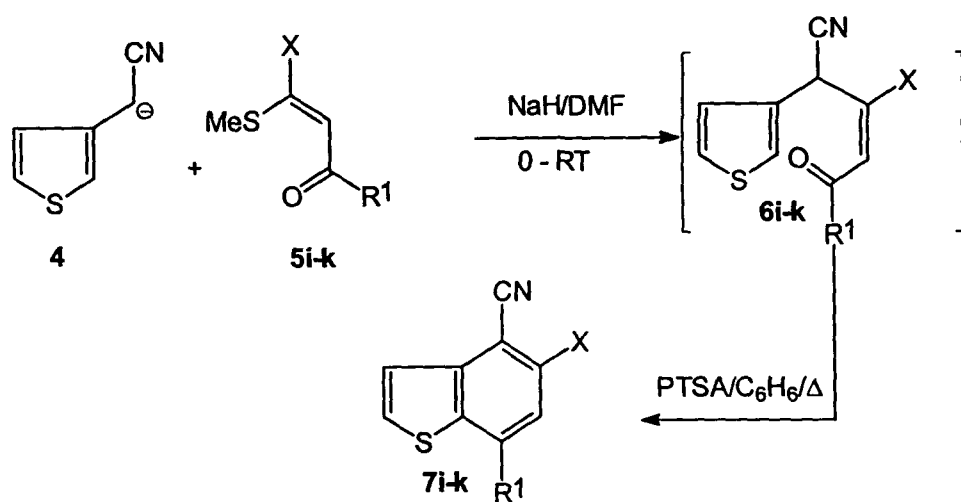


Starting Material 5	Product 7	Yield %
<p>5f</p>	<p>7f</p>	77
<p>5g</p>	<p>7g</p>	65
<p>5h</p>	<p>7h</p>	62
<p>5i</p>	<p>7i</p>	65

TsOH in refluxing benzene then the corresponding 5-piperidine-4-cyano-7-phenylbenzo[*b*]thiophene **7j** was obtained in 74 % yield. The structure of **7j** was confirmed by its analytical and spectral which are given in the experimental section.

Similarly acetone mercaptal was treated with morpholine to obtain the corresponding S,N-acetal **5k** as described earlier which was reacted with **4** under similar reaction conditions to afford the corresponding crude addition elimination product in high yield and was cyclized as described above to yield the corresponding 4-cyano-5-morpholinobenzo[*b*]thiophene (**7k**) in 76 % yield. In the next experiment 5-methoxybenzo[*b*]thiophene was synthesized as typical example. Thus the O,S-acetal **5l** was prepared to our earlier reported method from acetophenone and reacted with **4** under similar reaction conditions to afford after work-up the corresponding addition elimination product **6l** with the elimination of methylthio group. The product was then cyclized as described to afford the corresponding 4-cyano-5-methoxy-7-methylbenzo[*b*]thiophene (**7l**) in 63% yield (scheme 17). The compound **7l** was characterized by spectral and analytical data which are recorded in the experimental section.

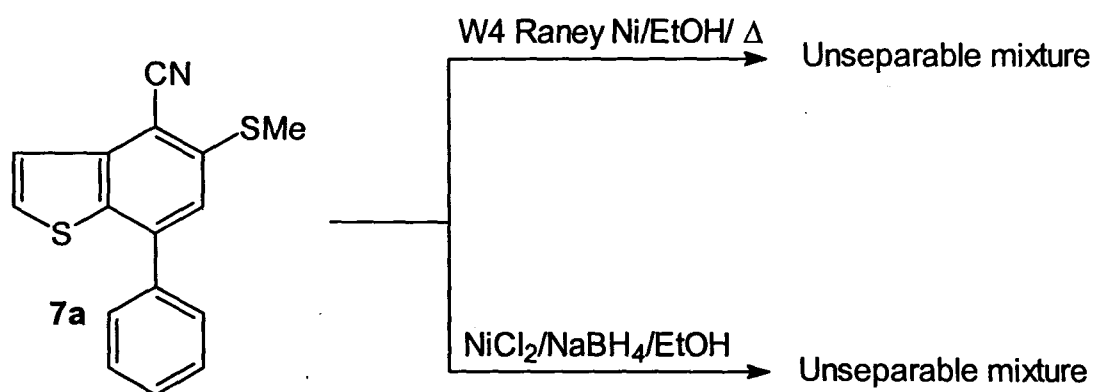
Scheme 17



Starting Material 5	Product 7	Yield %
<p>5j</p>	<p>7j</p>	77
<p>5k</p>	<p>7k</p>	65
<p>5l</p>	<p>7l</p>	62

In the next attempt it was made to achieve the dethiomethylation on **7** with limited success. Thus when **7a** was treated with W4 Raney Ni in ethanol, the reaction mixture did not yield any identifiable product. Similarly, when **7a** was treated with $\text{NiCl}_2/\text{NaBH}_4$ in ethanol also yielded an inseparable product mixture.

Scheme 18

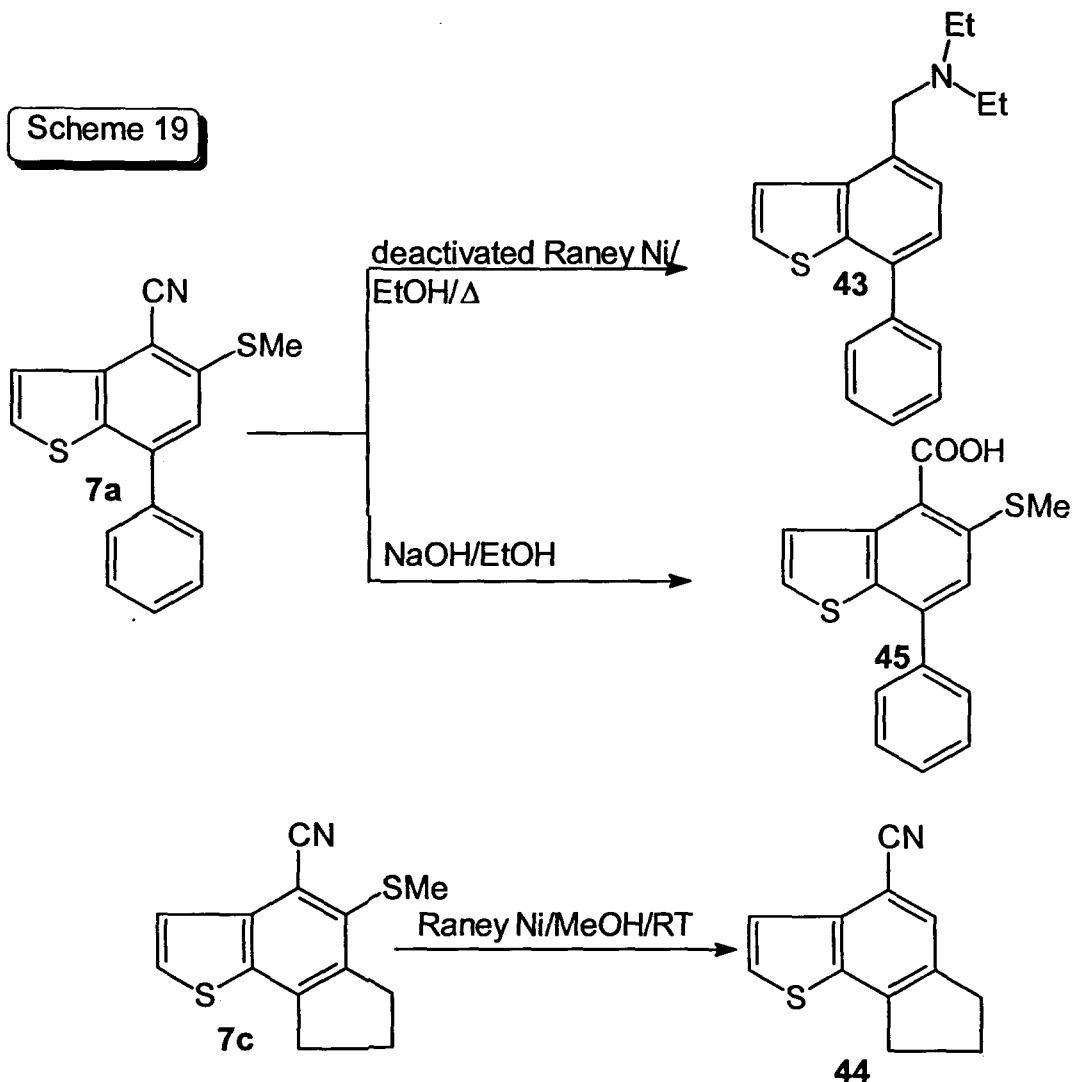


Again attempts were made to achieve selective dethiomethylation by using deactivated Raney Ni. The W4 Raney Ni was deactivated described in the literature by refluxing it in acetone for 2 hours. Only **7a** yielded benzo[*b*]thiophene in 61 % yield involving selective dethiomethylation with simultaneously following reductive alkylation of cyano group to the corresponding N,N-diethylaminomethyl functionality. Compound **43** was fully characterized by analytical and spectral data which are given in the

experimental section. However 7c failed to yield the corresponding dethiomethylated product when it was treated with similar Raney Ni in the presence of refluxing ethanol. On the other hand the product 7e underwent dethiomethylation with the same Raney Ni at room temperature to yield 4-cyano-6,7-cyclopentanobenzo[*b*]thiophene 44 in 55 % yield (scheme 19). It was characterized by its analytical and spectral data which are given in the experimental section. Under similar reaction condition 7a in methanol failed to give any product with well defined structure.

In one of the experiments the cyano group was hydrolyzed with ethanolic NaOH in shield tube and the product after work-up yielded the corresponding 4-carboxylic product in 77 % yield. The product was characterized by its spectral and analytical data which are given in the experimental section. It is to be noted that all the benzo[*b*]thiophenes described in the above schemes failed to undergo dethiomethylation under anyone of methods described in scheme 19.

In conclusion, we have developed a new method for benzo[*b*]thiophene synthesis with regiocontrolled on 4, 5, 6 and 7 positions. Substituents could be introduced at 6 and 7 positions by carrying them through their open chain precursors. Also by reacting with α -oxoketene dithioacetals derived from cycloalkanones, the method can be extended to the synthesis of 6,7-annelated benzo[*b*]thiophenes. The synthesis of 6,7-cyclopentanobenzo[*b*]thiophene



skeleton by our method is superior to the one recently described by Padwa and co-workers (scheme 10). The method is flexible for substituents at 5-position where methylthio group can be replaced by methoxy and amino groups also. However the method suffers some limitations which remain unresolved. It was not possible to knock off methylthio group selectively without effecting the thiophene ring sulphur. We are continuing to develop suitable reagent to remove selectively only the side chain sulphur and the work in this direction is in progress.

EXPERIMENTAL

General

Thiophene-3-acetonitrile was purchased from Aldrich and used as supplied. Commercially available sodium hydride (50% suspension in mineral oil, Spectrochem, Lancaster) was used. N,N-Dimethyl formamide was distilled from calcium hydride prior to use. p-Toluene sulfonic acid was purchased from Loba Chemie and used as such. Dry benzene was obtained by keeping over calcium chloride followed by distillation and again keeping over sodium wire. The commercial samples of acetone, acetophenone, ethyl methyl ketone, cyclopentanone, cyclohexanone, acetyl acetone were purified by simple distillation. Morpholine and piperidine were distilled from sodium hydroxide. Propiophenone, 1-indanone, 1-tetralone, were prepared according to the reported procedure. Dimethyl trithiocarbonate was prepared by according to the literature procedure. Oxoketene-S,S-acetals, and -N,S-acetals were prepared according to the earlier reported procedures and the general procedures are given in the experimental section of Chapter II.

General Procedure for the Synthesis of Substituted and Condensed Benzo[b]thiophenes.

To a stirring suspension of sodium hydride (10 mmol) in dimethyl formamide (10 ml) at 0°C, a solution of thiophene-3-acetonitrile (5 mmol) in dimethyl formamide (5 ml) was added dropwise. After 15 minutes, the appropriate α -oxoketene acetal (5 mmol) in dimethylformamide (10 ml) was

slowly added and the reaction mixture was allowed to warm to room temperature with stirring during 8-10 hours. It was poured into saturated ammonium chloride solution (200 ml) and extracted with chloroform (3x50 ml). The combined organic extracts were washed with water (3x100 ml), dried over anhydrous sodium sulfate and evaporated to give the crude 1,4-adducts. The addition-elimination obtained by the reaction of thiophene-3-acetonitrile and oxoketene dithioacetal was purified by passing through silica gel column using hexane-ethyl acetate (97:3) and characterized by spectral and analytical data and the other 1,4-adducts were used as such for further cyclization.

To a solution of crude 1,4-adduct (ca. 5 mmol) in dry benzene (40 ml), *p*-toluenesulphonic acid (10 mmol) was added and the reaction mixture was refluxed with stirring for 3-4 hours. The solvent was evaporated, the residue was dissolved in chloroform (100 ml), poured into saturated sodium bicarbonate solution (200 ml). The organic layer was separated, washed with water (2x100 ml), dried over anhydrous sodium sulfate and evaporated to give crude benzo[*b*]thiophene which was purified by column chromatography (silica gel) using hexane-ethylacetate (97:3) as eluent.

7-Cyano-4-methyl-6-(methylthio)benzo[*b*]thiophene (7b).

Colourless crystals; m.p. 150-151°C (chloroform-ether); Yield 70%; IR (KBr):

ν_{\max} 2208, 1649, 1562, 1421 cm^{-1} ;

^1H NMR (300 MHz, CDCl_3): δ 2.62 (s, 3H), 2.63 (s, 3H, CH_3), 7.15 (s, 1H, ArH), 7.53 (d, 1H, $J = 6.0$ Hz), 7.65 (d, 1H, $J = 6.1$ Hz);

MS (m/z, %) 219 (M^+ , 100%), 204 ($\text{M}^+ - 15$, 32);

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{NS}_2$ (219.33): C, 60.24; H, 4.14; N, 6.29%; Found: C, 60.43; H, 4.15; N, 6.26%.

7-Cyano-4,5-dimethyl-6-(methylthio)benzo[b]thiophene (7c).

Colourless crystals; m.p. 123-125 °C (chloroform-ether); Yield 64%;

IR (KBr): ν_{max} 2205, 1470, 1440 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3): δ 2.46 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 7.51 (d, 1H, $J = 5.6$ Hz), 7.55 (d, 1H, $J = 5.5$ Hz);

^{13}C NMR (100 MHz): δ 17.56, 19.78, 19.95, 111.19, 117.41, 123.35, 128.94, 135.84, 135.99, 137.63, 139.33, 141.72;

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{NS}_2$ (233.36): C, 61.76; H, 4.75; N, 6.00%; Found: C, 61.48; H, 4.76; N, 6.02%.

4-Cyano-6-methyl-5-(methylthio)-7-phenylbenzo[b]thiophene (7d)

Colourless crystals; m.p. 122-123 °C (chloroform-hexane); Yield 76%:

IR (KBr): ν_{max} 2209, 1535, 1447 cm^{-1}

^1H NMR (400 MHz, CDCl_3): δ 2.47 (s, 3H, CH_3), 2.54 (s, 3H, SMe), 7.32 (d, 1H, $J = 1.6$ Hz), 7.47-7.52 (m, 3H, Ar), 7.54-7.55 (m, 2H, ArH).

^{13}C NMR (100 MHz, CDCl_3): δ 18.82, 19.71, 112.32, 117.12, 122.69, 128.42, 128.91, 130.42, 135.38, 138.21, 139.50, 140.80, 142.24.

MS (m/z, %) 295 (M^+ , 100), 247 (M^+-48 , 69);

Anal. Calcd. for $C_{17}H_{13}NS_2$ (295.42): C, 69.12, H, 4.43, N, 4.74 %; Found: C, 69.35; H, 4.21; N, 4.90 %.

4-Cyano-6-isopropyl-5-(methylthio)benzo[*b*]thiophene (7e)

Yellow crystals; m.p. 56-57 °C (chloroform-ether); Yield 63%.

IR (KBr): ν_{\max} 2208, 1651, 1546 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 1.41 (d, 6H, $J = 6.8$ Hz, $(\text{CH}_3)_2$), 2.64 (s, 3H, SMe), 3.24-3.27 (m, 1H, CH), 7.24 (s, 1H, ArH), 7.47 (d, 1H, $J = 4.8$ Hz, ArH), 7.61 (d, 1H, 5Hz)

^{13}C NMR (100 MHz, CDCl_3): δ 17.23, 22.29, 33.96, 104.36, 116.49, 119.78, 122.64, 122.92, 128.19, 128.48, 130.02, 136.84, 140.93, 141.68, 148.08.

MS (m/z, %) 247 (M^+ , 100), 232 (M^+-15 , 83.4)

Anal. Calcd. for $C_{19}H_{21}NS_2$ (295.44): C, 77.24, H, 7.16, N, 4.74 %; Found: C, 77.01; H, 7.31; N, 4.53 %.

4-Cyano-5-methylthio-6,7,8,9-tetrahydronaphtho[2,1-*b*]thiophene (7g).

Colourless crystals; m.p. 131-132(C (chloroform-ether); Yield 65%;

IR (KBr) ν_{\max} 2205, 1525, 1440 cm^{-1} ;

^1H NMR (300 MHz, CDCl_3): δ 1.91-1.93 (m, 4H, $-(\text{CH}_2)_2-$), 2.48 (s, 3H, SCH₃), 2.93-2.95 (m, 2H, $-\text{CH}_2-$), 3.07-3.08 (m, 2H, $-\text{CH}_2-$), 7.50 (d, 1H, $J=5.6$ Hz), 7.53 (d, 1H, $J=5.5$ Hz).

^{13}C NMR (100 MHz): δ 19.59, 22.04, 23.19, 28.32, 29.07, 110.87, 117.29, 123.03, 128.59, 136.43, 136.73, 137.79, 139.04, 140.77.

MS (m/z, %) 259 (M^+ , 82), 233 (M^+-25 , 100)

Anal. Calcd. for $C_{14}H_{13}NS_2$ (259.40): C, 64.83, H, 5.05, N, 5.40%; Found: C, 65.09; H, 5.02; N, 5.35%.

4-Cyano-5-(methylthio)fluoreno[3,4-*b*]thiophene (7h).

Colourless crystals; m.p. 214-215°C (chloroform-ether); Yield 62%; IR (KBr):

ν_{\max} 2210, 1567, 1470 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H, SMe), 3.92 (s, 2H, $-CH_2-$), 7.38-7.46 (m, 2H, ArH), 7.54 (d, 2H, $J=4.5$ Hz, ArH), 7.63 (d, 1H, $J=5.2$ Hz, ArH), 7.79 (d, 1H, $J=6.0$ Hz, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.07, 37.90, 109.01, 117.31, 122.47, 124.90, 127.28, 128.32, 131.84, 134.17, 138.99, 139.20, 142.52, 142.60, 144.06.

MS (m/z, %) 293 (M^+ , 88.9);

Anal. Calcd. for $C_{17}H_{11}NS_2$ (293.41): C, 69.59; H, 3.78; N, 4.77%; Found: C, 69.21; H, 3.70; N, 4.71%.

4-Cyano-6,7-dihydro-5-(methylthio)phenanthreno[3,4-*b*]thiophene (7i).

Colourless crystals; m.p. 122-123 °C (chloroform-ether); Yield 65%;

IR (KBr): ν_{\max} 2210, 1567, 1470 cm^{-1} ;

1H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H, SMe), 2.84 (t, 2H, $J = 6.8$ Hz, $-CH_2-$), 3.30 (t, 2H, $J = 6.8$ Hz, $-CH_2-$), 7.25-7.45 (m, 3H, ArH), 7.61-7.66 (m, 3H, ArH), 7.61-7.66 (m, 2H, ArH), 8.27(d; 1H, $J = 7.6$ Hz, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.85, 27.15, 28.68, 112.00, 117.36, 123.03, 126.16, 126.90, 128.06, 129.77, 133.13, 134.83, 136.66, 136.95, 138.26, 139.59, 141.52.

MS (m/z, %) 307 (M^+ , 81%), 259 ($M^+ - 48$, 100);

Anal. Calcd. for $C_{18}H_{13}NS_2$ (307.44): C, 70.32; H, 4.26; N, 4.56%; Found: C, 70.53; H, 4.29; N, 4.49%.

4-Cyano-7-phenyl-5-piperidinobenzo[*b*]thiophene (7j).

Colourless crystals; m.p. 141-142 °C (chloroform-ether); Yield 75%;

IR (KBr): ν_{\max} 2212, 1565 cm^{-1} ;

1H NMR (400 MHz, $CDCl_3$): δ 1.62-1.63 (m, 2H, $-CH_2-$), 1.80-1.81 (m, 4H, $-(CH_2)_2-$), 3.30-3.32 (m, 4H, $-N(CH_2)_2-$), 7.00 (s, 1H, ArH), 7.29 (s, 2H, ArH), 7.44-7.51 (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.03, 26.15, 53.47, 96.99, 116.62, 117.33, 123.33, 124.63, 128.27, 128.62, 128.72, 132.27, 139.78, 142.32, 145.38, 155.27.

MS (m/z, %) 318 (M^+ , 100 %);

Anal. Calcd. for $C_{20}H_{18}N_2S$ (318.44): C, 75.44; H, 5.70; N, 8.80%; Found: C, 75.86; H, 5.77; N, 8.73%.

4-Cyano-7-methyl-5-morpholinobenzo[*b*]thiophene (7k).

Colourless crystals; m.p. 91-92 °C (chloroform-ether); Yield 68%;

IR (KBr): ν_{\max} 2201, 1579 cm^{-1} ;

1H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, CH_3), 3.27 (t, 4H, $J = 4.4$ Hz, $-(CH_2)_2-$), 3.91 (t, 4H, $J = 4.4$ Hz, $O(CH_2)_2-$), 6.84 (s, 1H, ArH), 7.30 (d, 1H, $J = 5.2$ Hz, ArH), 7.36 (d, 1H, $J = 5.2$ Hz, ArH).

^{13}C NMR (100 MHz): δ 20.39, 52.27, 66.94, 96.56, 116.36, 116.96, 121.95, 125.09, 134.51, 138.86, 144.49, 154.06.

MS (m/z, %) 258 (M^+ , 100%);

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{OS}$ (258.34): C, 65.09; H, 5.46; N, 10.84%; Found: C, 65.37; H, 5.67, N, 10.61%.

4-Cyano-5-ethyl(diethylamine)-7-phenylbenzo[b]thiophene (43)

Yellow crystals; m.p. 71-72 °C (chloroform-ether); Yield 68%;

IR (KBr): ν_{max} 2900, 1650, 1600, 1550 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3): δ 1.07 (t, 6H, 2XCH_3), 2.61 (q, 4H, $-\text{CH}_2-$), 3.92 (s, 2H, $-\text{CH}_2-$), 7.31-7.50 (m, 6H, ArH), 7.71 (m, 8H, ArH).

MS (m/z, %) 295 (M^+ , 52%), 223 (M^+-72 , 100)

Anal. Calcd. for $\text{C}_{19}\text{H}_{21}\text{NS}$ (295.44): C, 77.24; H, 7.16; N, 4.74%; Found: C, 75.40; H, 7.29, N, 4.56%.

5-Methylthio-7-phenylbenzo[b]thiophene-4-carboxylic acid (45)

Colourless crystals; m.p. 121-122 °C; Yield 77 %;

IR (KBr): ν_{max} 3354, 2226, 1743, 1644 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3): δ 2.49 (s, 3H, SCH_3), 7.32 – 7.34 (m, 2H, ArH), 7.39-7.43 (m, 1H, ArH), 7.46 – 7.50 (m, 2H, ArH), 7.62 – 7.71 (m, 2H, ArH), 7.88 (brs, 1H, OH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{S}_2\text{O}_3$ (316.45): C, 60.75; H, 4.16; Found: C, 60.40; H, 4.29%.

4-Cyanoindano[5,4-*b*]thiophene (44).

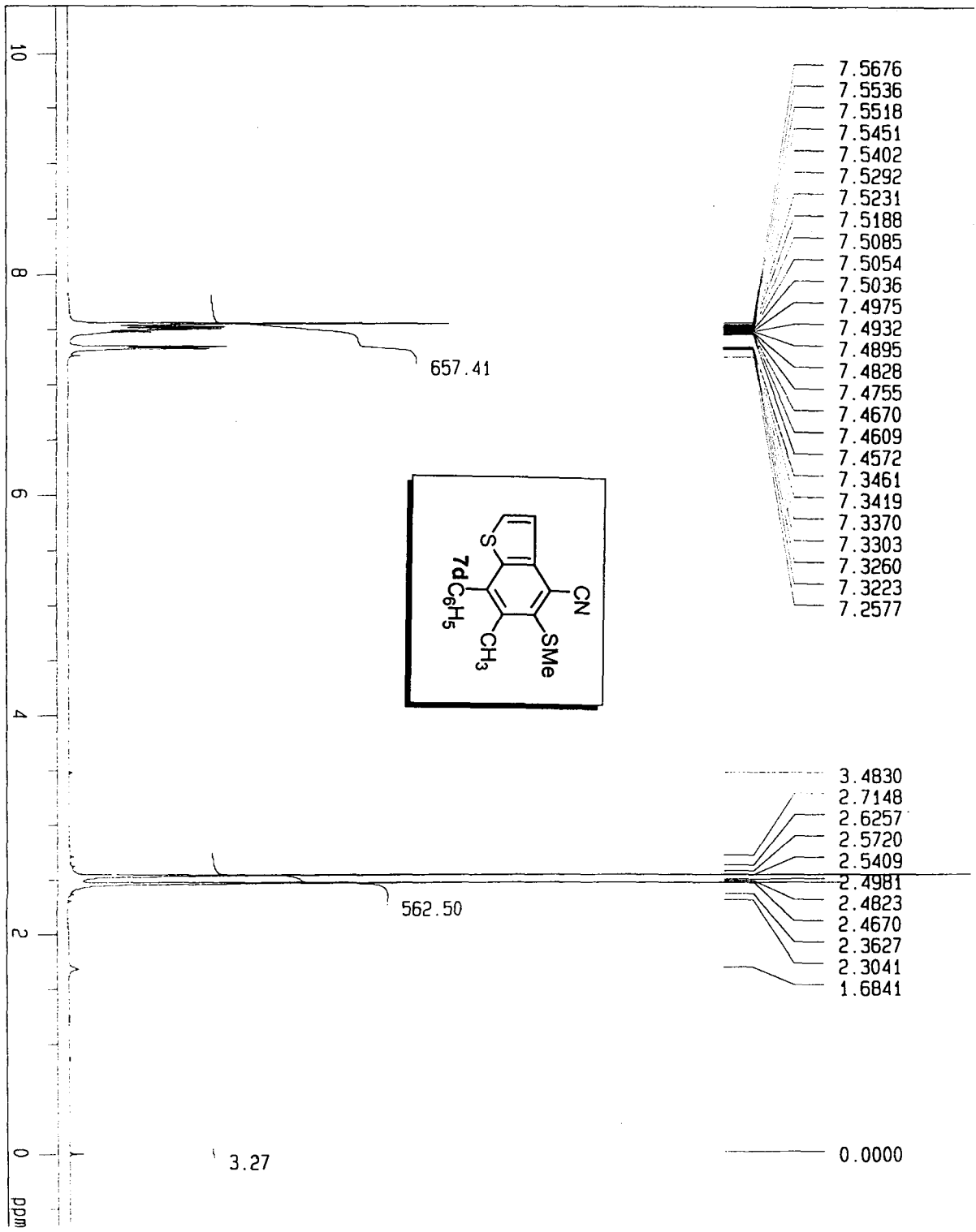
Colourless crystals; m.p. 101-102 °C (chloroform-ether); Yield 55%;

IR (KBr): ν_{\max} 2200, 1579 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3): δ 2.26-2.31 (m, 2H, $-\text{CH}_2-$), 3.08 (m, 4H, $-(\text{CH}_2)_2-$), 7.55-7.75 (m, 3H, ArH).

MS (m/z, %) 199 (M^+ , 100%);

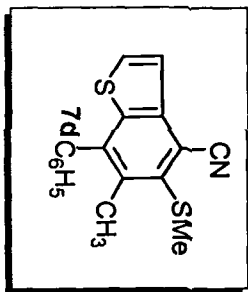
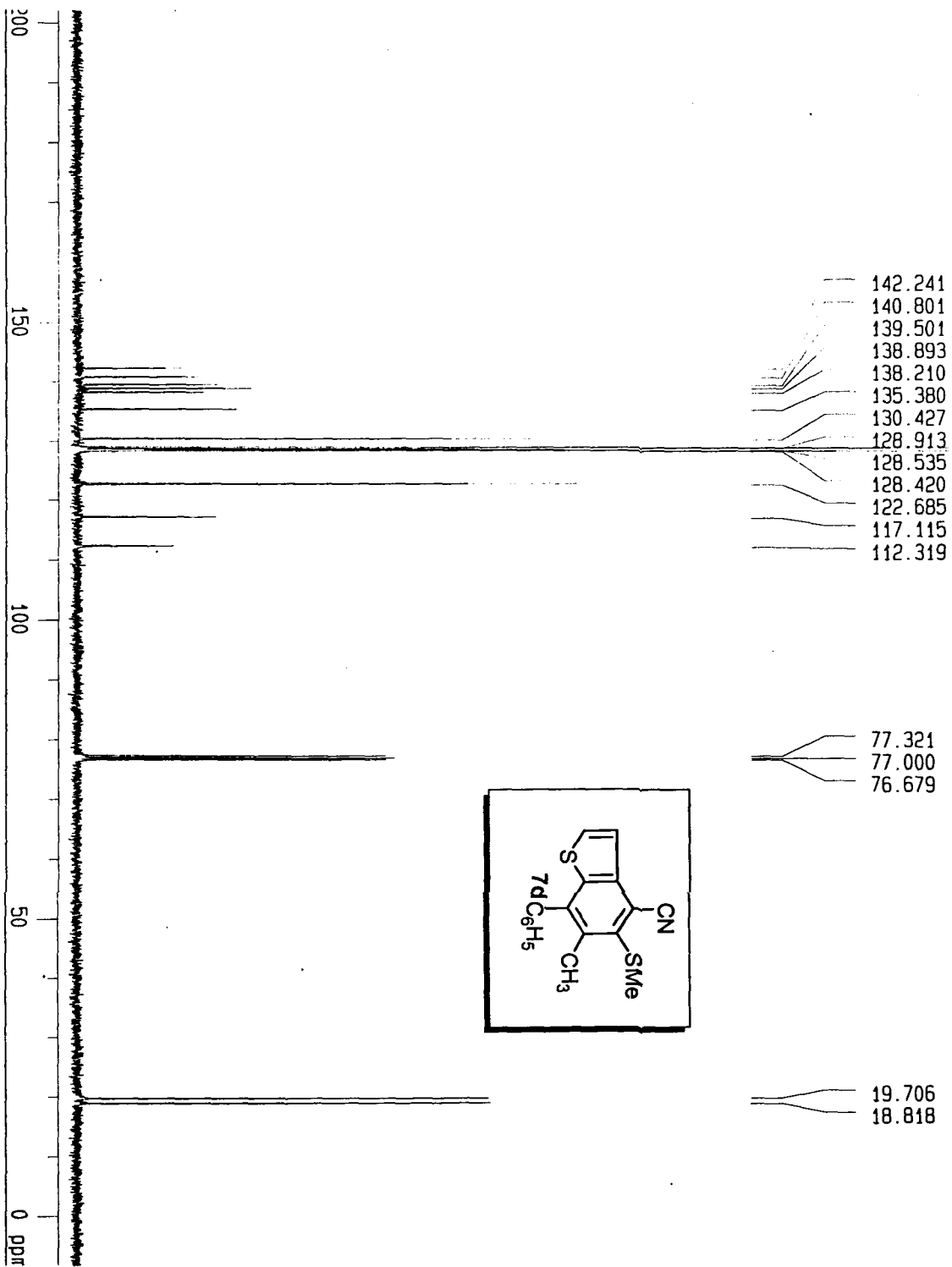
Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{NS}$ (199.34): C, 65.09; H, 5.46; N, 10.84%; Found: C, 65.37; H, 5.67, N, 10.61%.

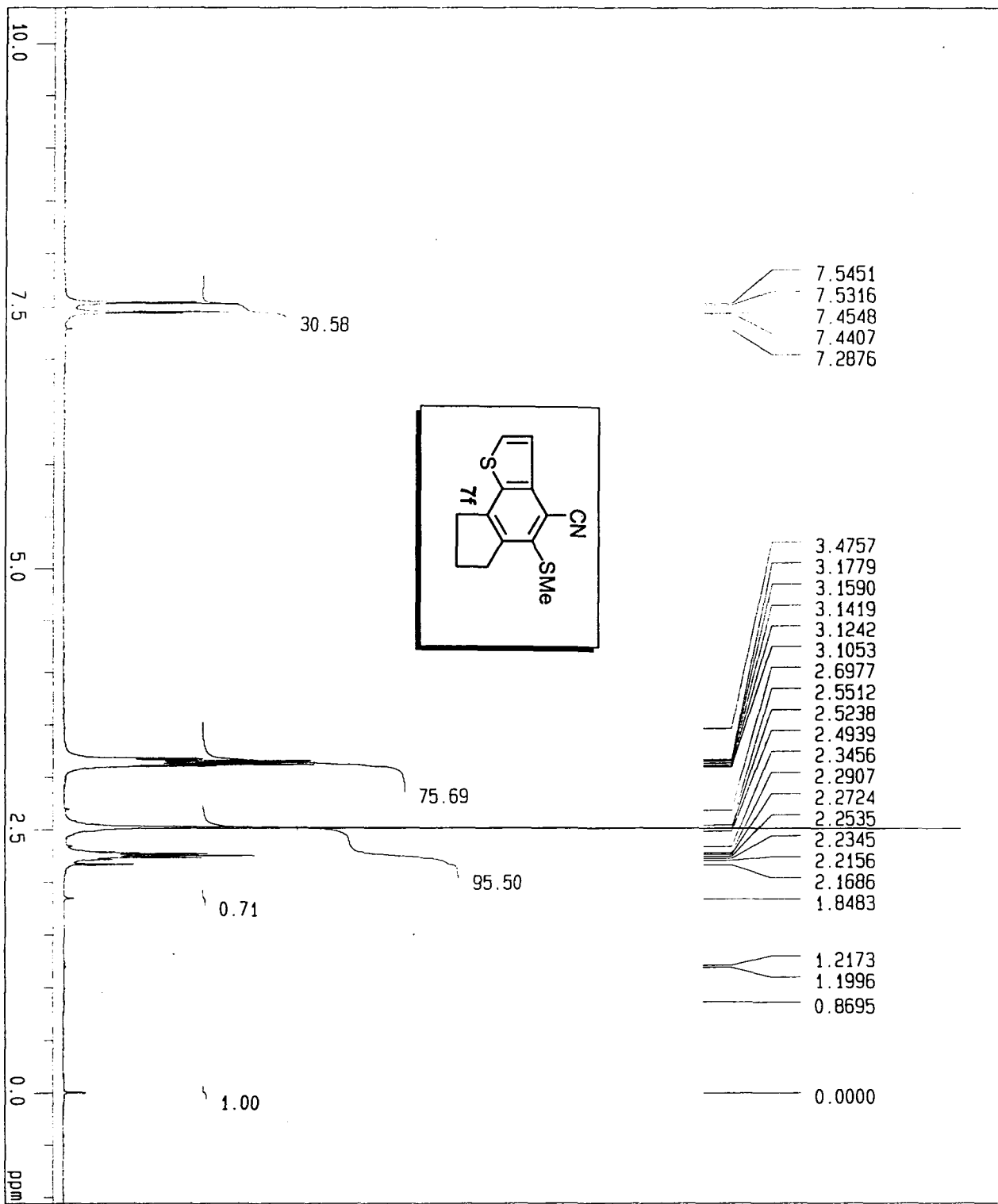


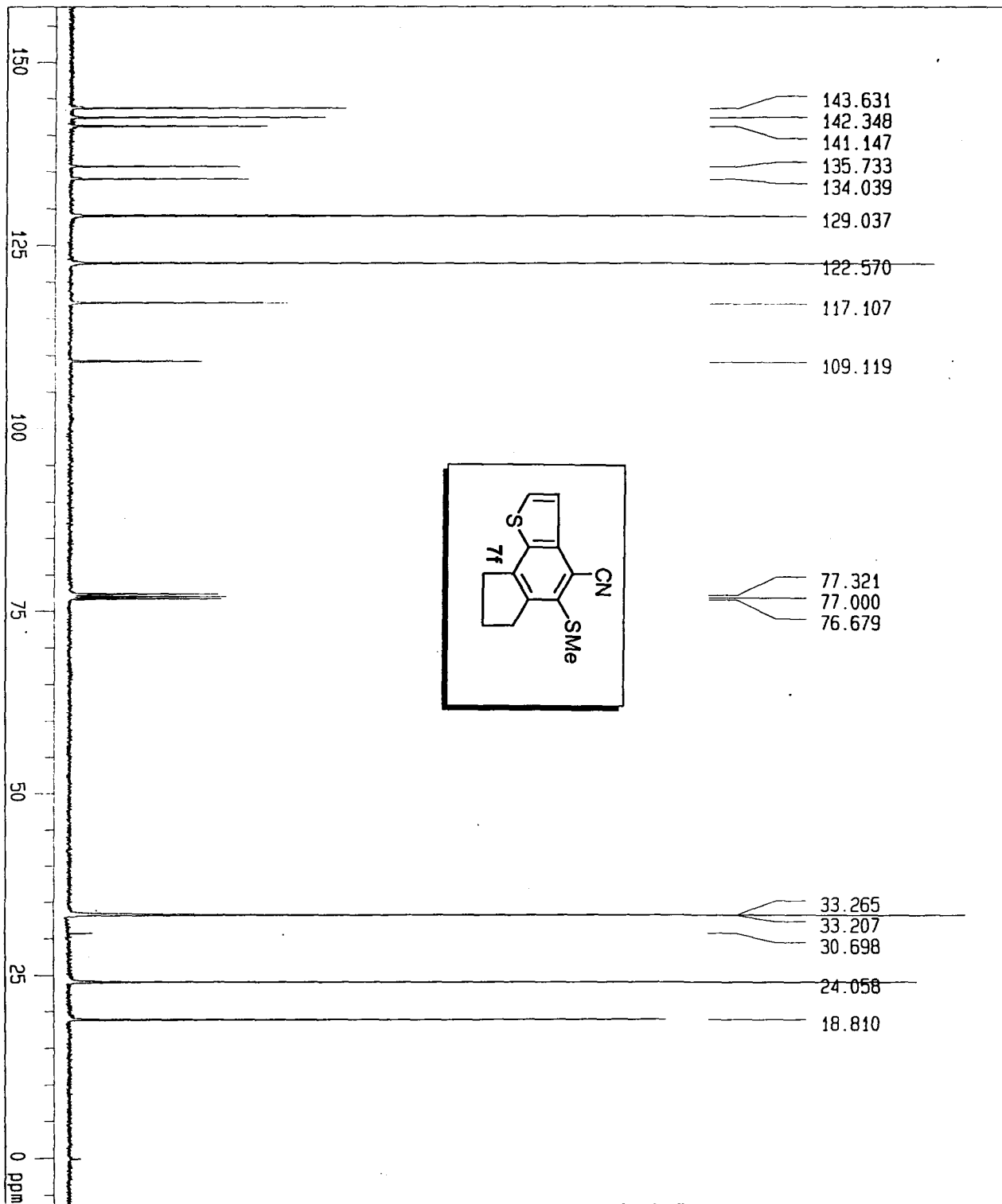
- 7.5676
- 7.5536
- 7.5518
- 7.5451
- 7.5402
- 7.5292
- 7.5231
- 7.5188
- 7.5085
- 7.5054
- 7.5036
- 7.4975
- 7.4932
- 7.4895
- 7.4828
- 7.4755
- 7.4670
- 7.4609
- 7.4572
- 7.3461
- 7.3419
- 7.3370
- 7.3303
- 7.3260
- 7.3223
- 7.2577

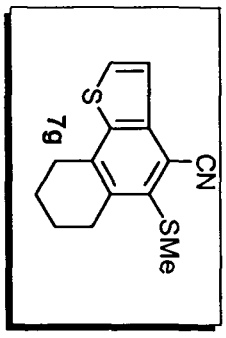
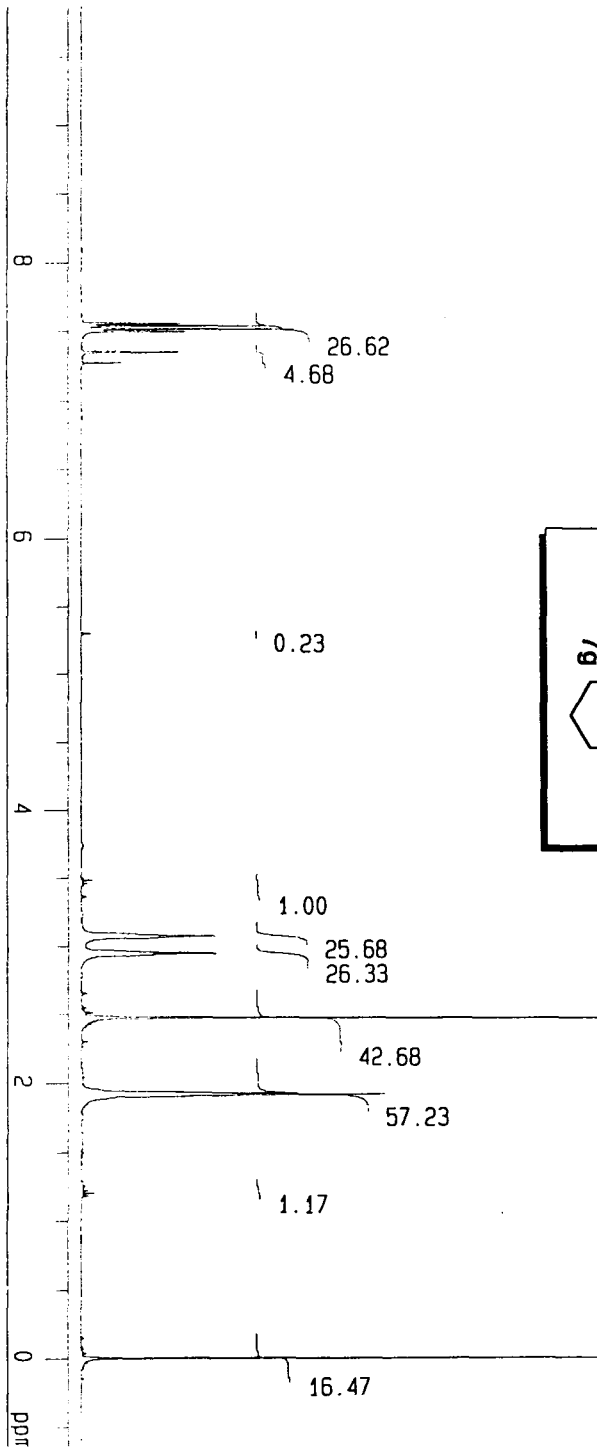
- 3.4830
- 2.7148
- 2.6257
- 2.5720
- 2.5409
- 2.4981
- 2.4823
- 2.4670
- 2.3627
- 2.3041
- 1.6841

0.0000





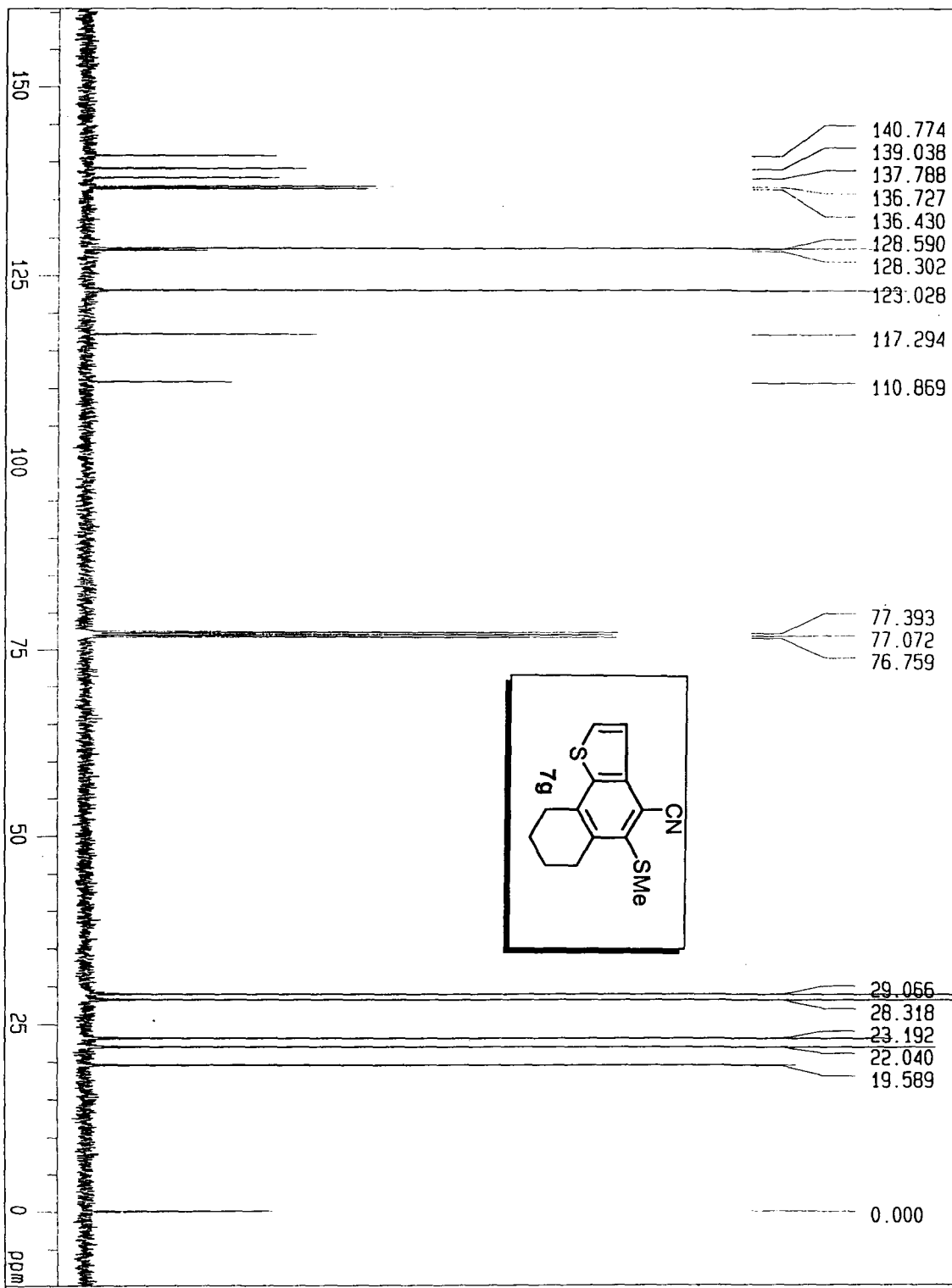


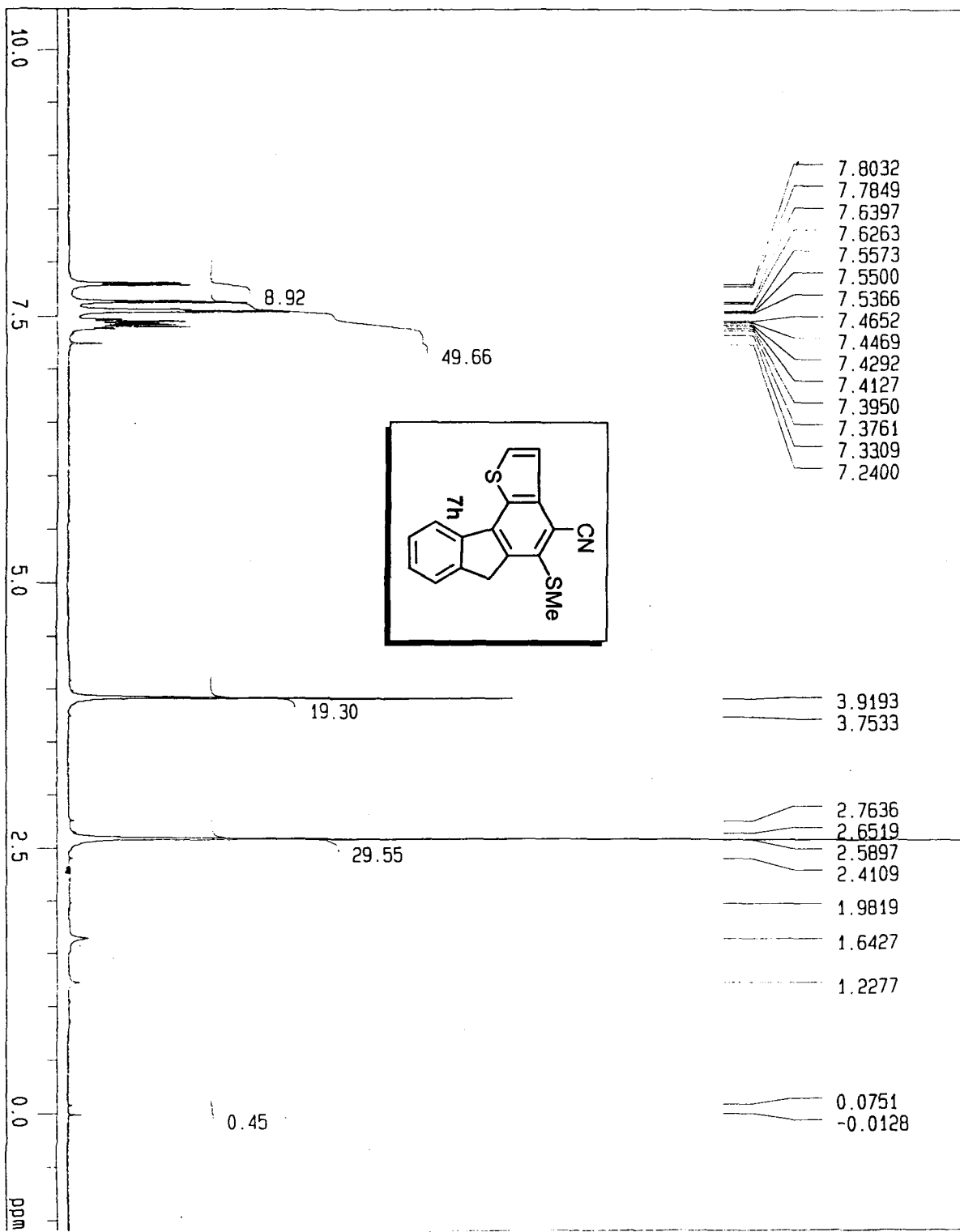


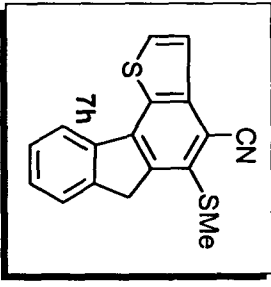
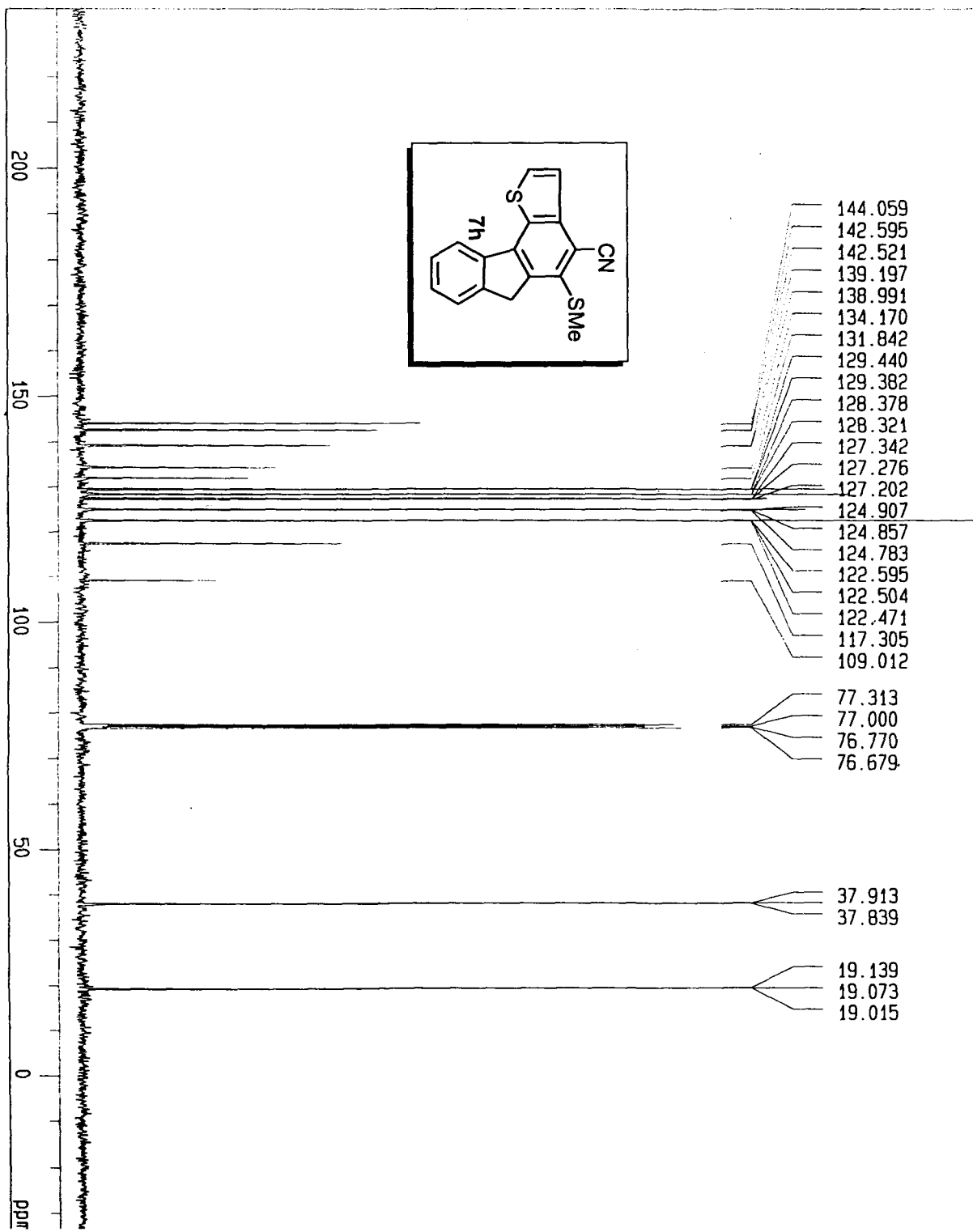
- 7.5493
- 7.5384
- 7.5353
- 7.5121
- 7.5078
- 7.4987
- 7.4938
- 7.3461
- 7.3437
- 7.2644

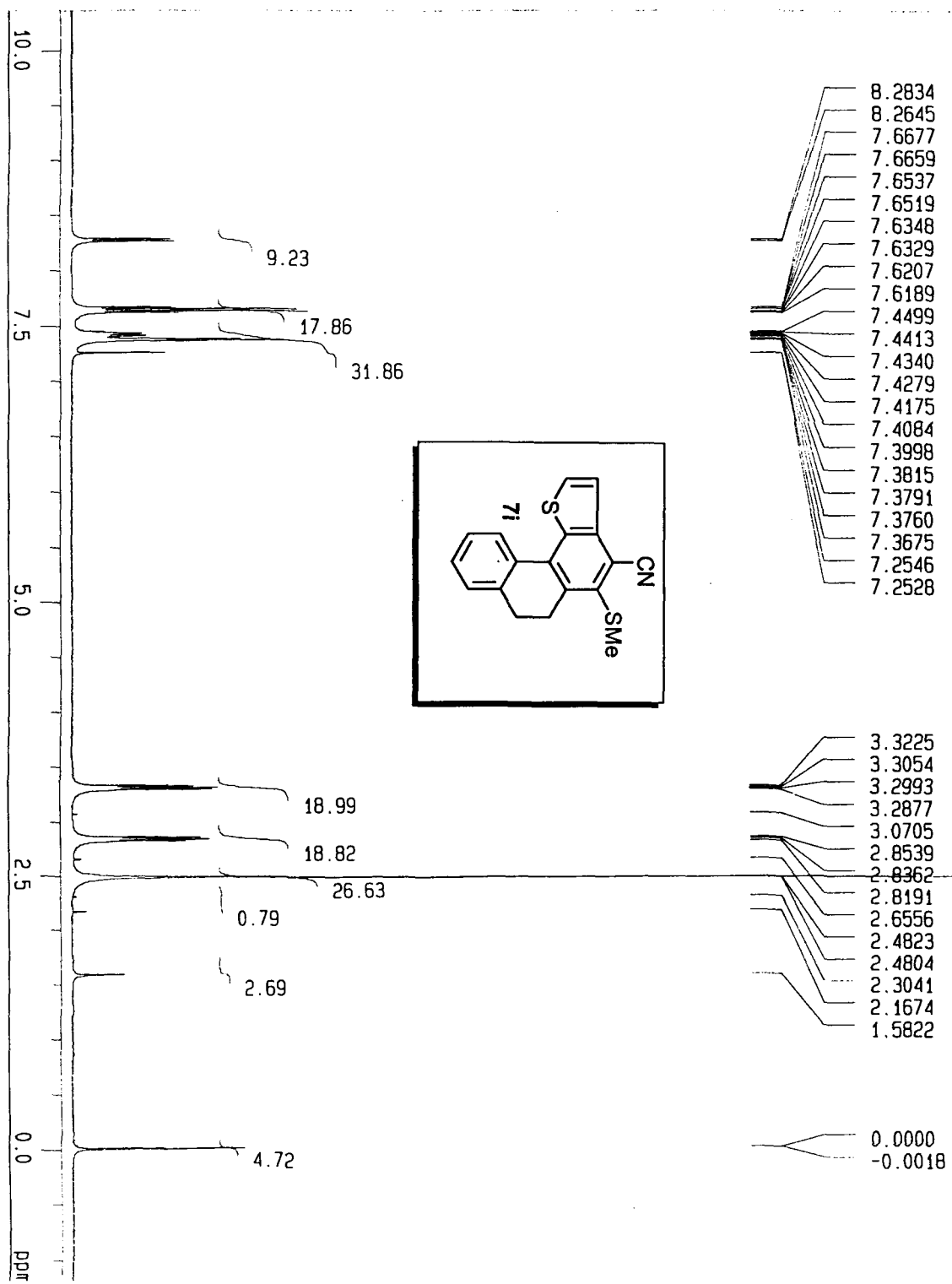
- 5.2941
- 3.7393
- 3.4867
- 3.4647
- 3.3658
- 3.0760
- 2.9485
- 2.9344
- 2.6525
- 2.5494
- 2.5134
- 2.4811
- 2.4786
- 2.4432
- 2.4298
- 2.4170
- 2.3004
- 2.0423
- 1.9380
- 1.9300
- 1.9227
- 1.9142
- 1.9075
- 1.4962
- 1.2576
- 1.2222
- 1.2045
- 1.1868

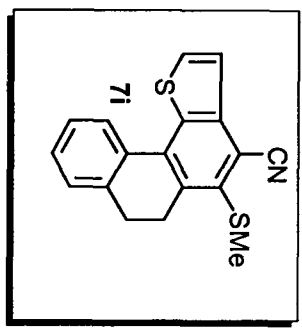
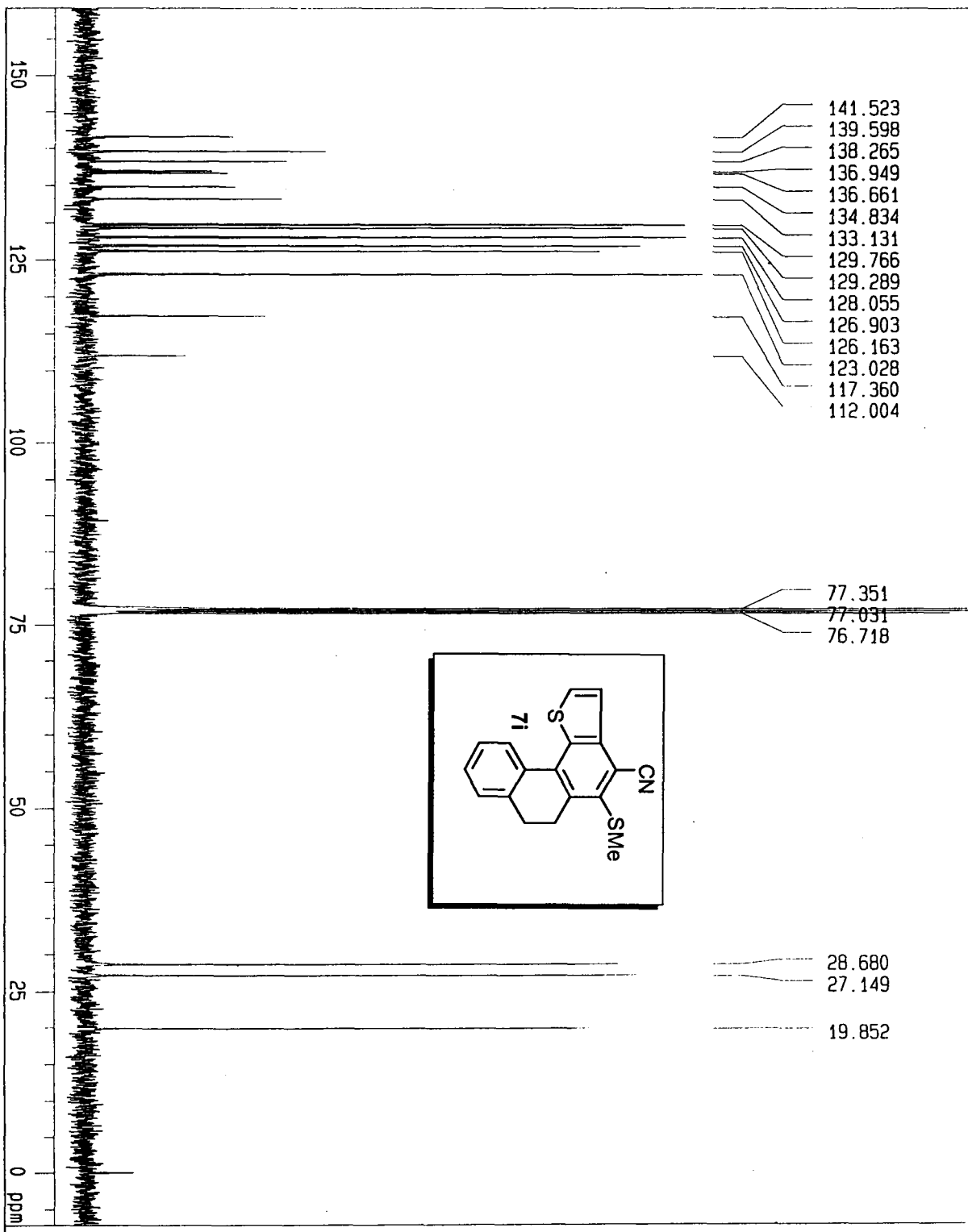
- 0.1464
- 0.0348
- 0.0079
- 0.0000
- 0.0085
- 0.1495

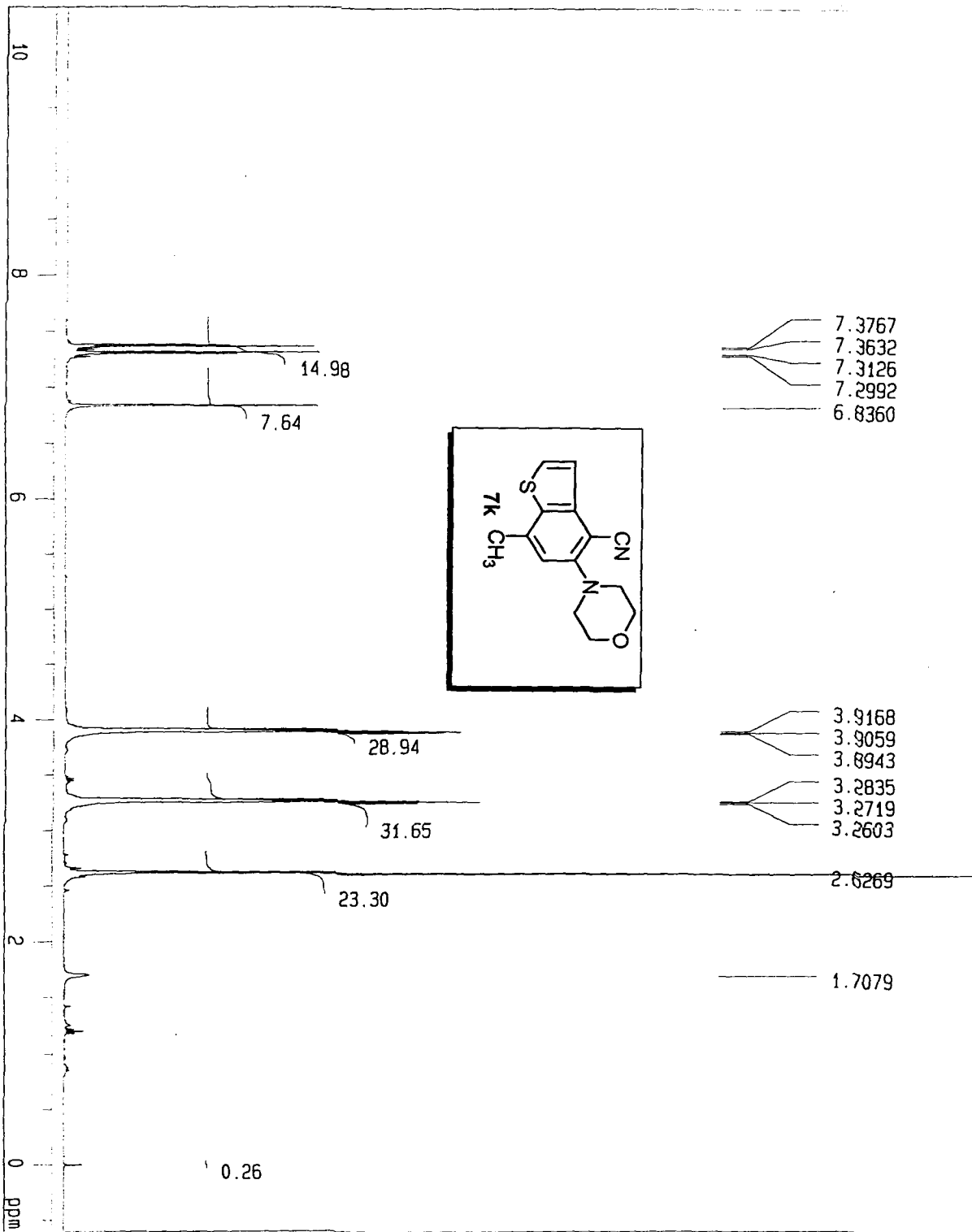


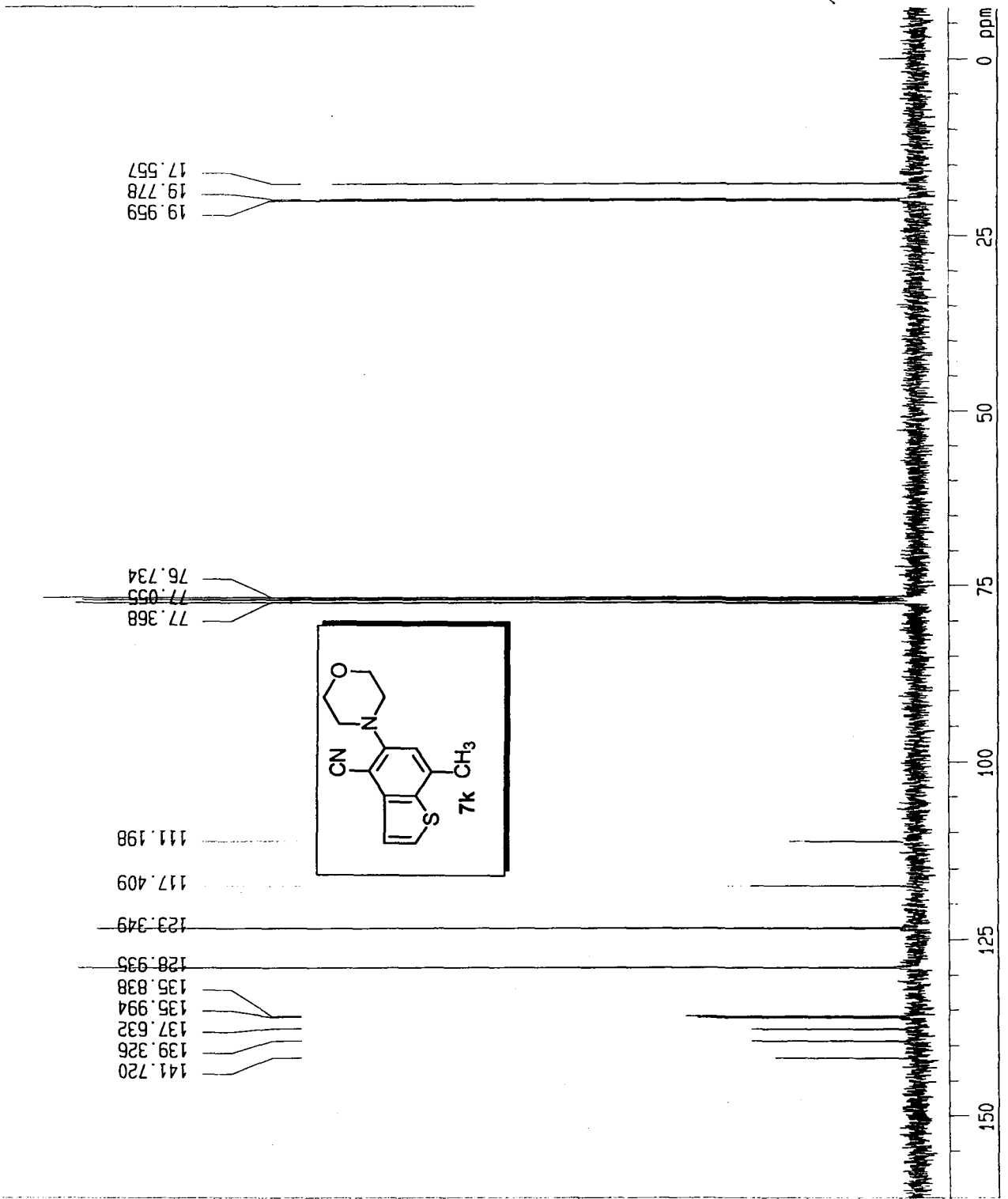












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- An Expeditious Synthesis of Substituted and Annelated Pyrido[2,3-*b*]indoles
Okram Barun, Pranab K. Patra, H. Ila, H. Junjappa *Tetrahedron Letters* **1999**, *40*, 3797-3800
- A Facile Access to 2-Methylthio/Alkoxy/Amino-3-acylimidazo[1,2-*a*]pyridines Based on Cupric Chloride Promoted Oxidative Ring Closure of α -Oxoketene N,S-, N,O-, and N,N-Acetals
Okram Barun, Okram Mukherjee, H. Ila, H. Junjappa *J. Org. Chem.* **2000**, *65*, 1583-1587
- An Efficient General Synthesis of Novel Functionalized Tetrahydroisoquinoline Derived Enamines *via* Polarized Ketene N,S-Acetals
Okram Barun, Pramod K. Mohanta, H. Ila, H. Junjappa *Synlett.* **2000** (in press)
- Formation of Acetaldehyde Enolate from Vinylacetate and its Reaction with Aromatic and Heterocyclic Aldehydes: An efficient Synthesis of Enaldehydes with two Carbon Homologation
Pranab Kumar Mahata, Okram Barun, H. Ila, H. Junjappa *Tetrahedron Letters* **2000** (communicated)
- A New Efficient Synthesis of Substituted and Condensed Benzo[*b*]thiophenes
J. R. Suresh, Okram Barun, H. Ila, H. Junjappa (manuscript under preparation)