SYNTHETIC STUDIES ON HETEROCYCLES

ABSTRACT

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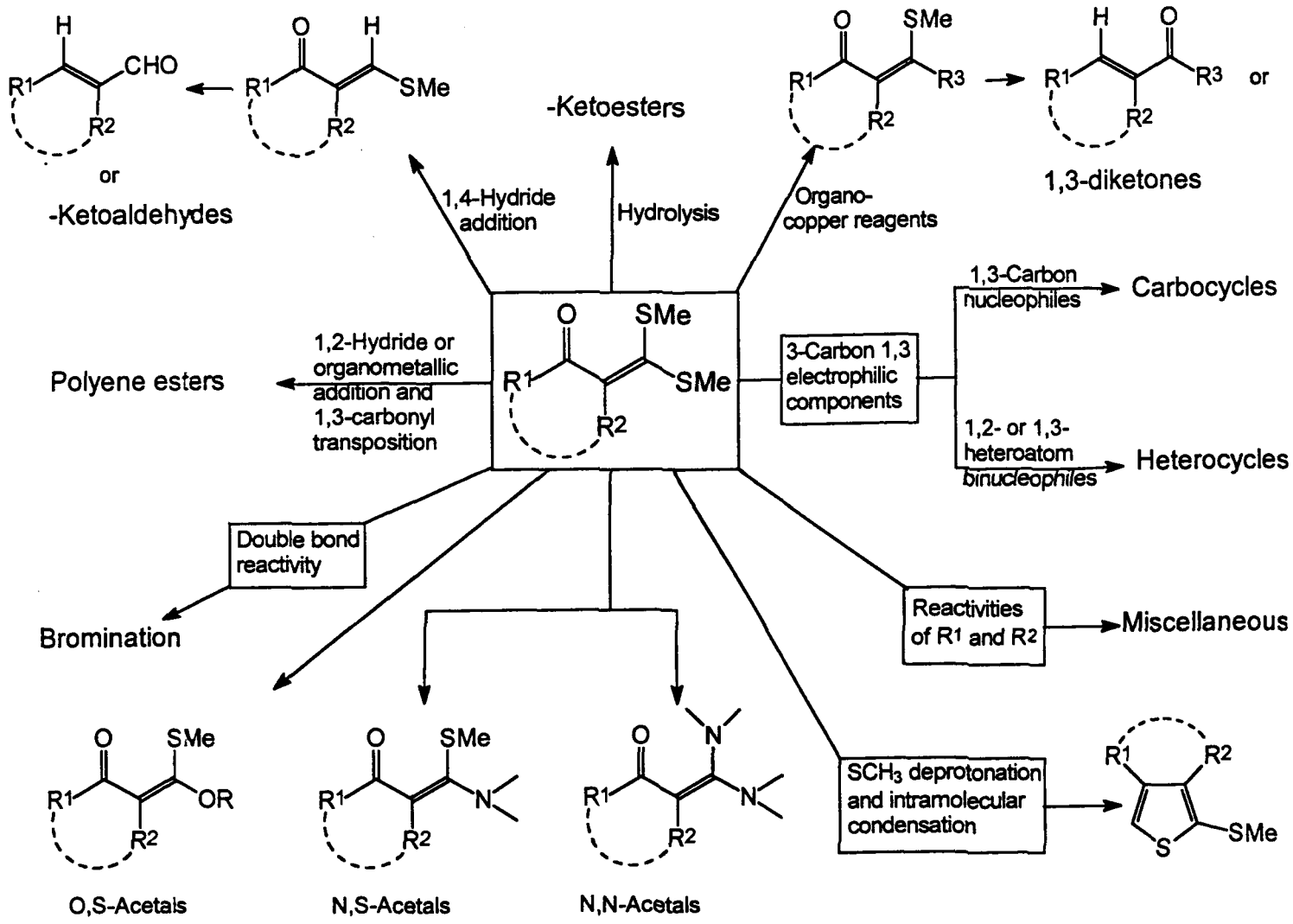
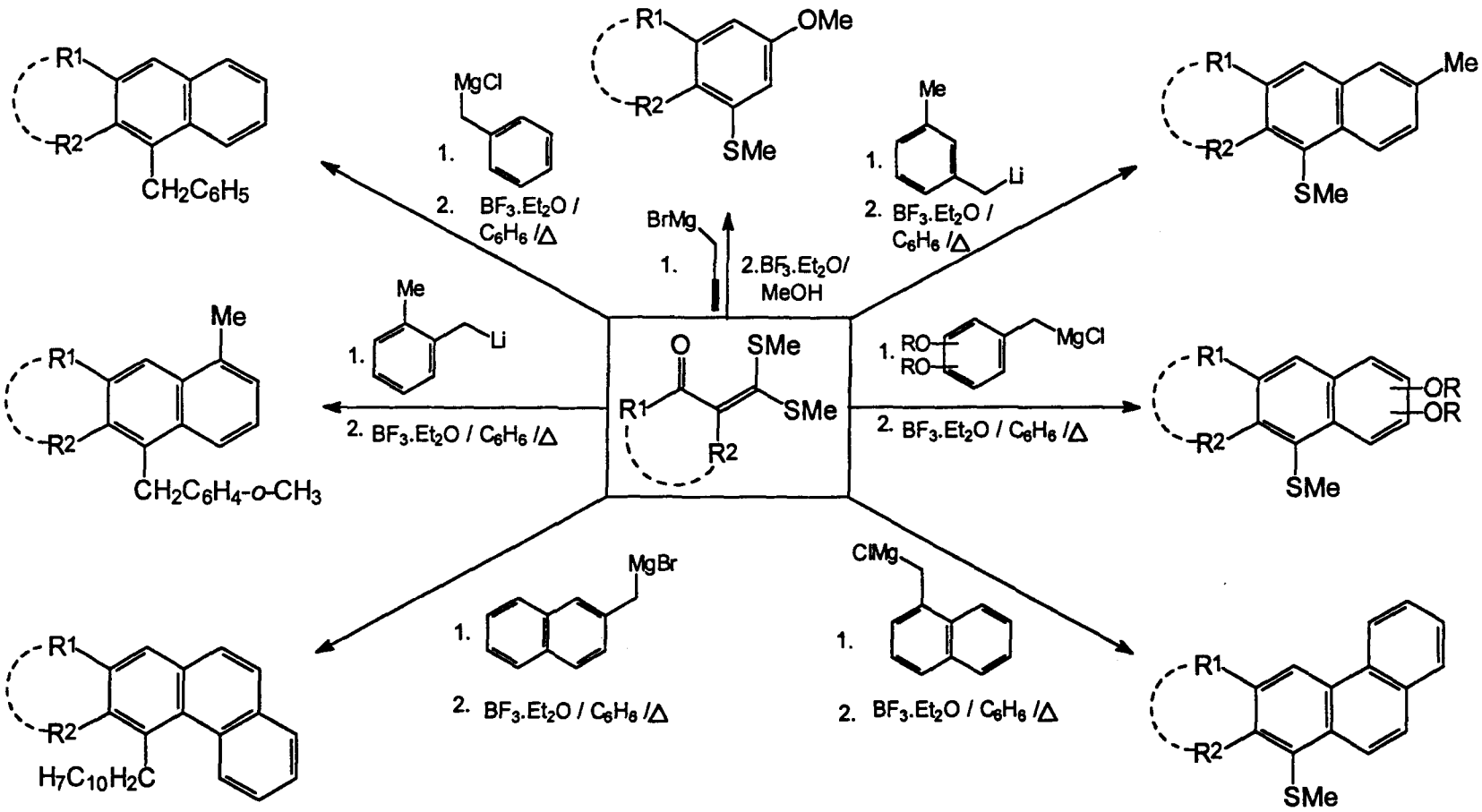
Heterocyclic compounds[1] are very widely distributed in nature and are essential to life; they play a vital role in the metabolism of all living cells. There are a vast number of pharmacologically active natural and unnatural heterocyclic compounds, many of which are in regular clinical use. There are also a large number of synthetic heterocyclic compounds with other important practical applications, as dye stuffs, co-polymers, solvents, photographic sensitizers and developers, as antioxidants and many are valuable intermediates in synthesis. Because of all these applications of heterocyclic compounds, there have been continuous efforts for the development of new methods for their synthesis. Heterocyclic units such as indoles, carbazoles and their other hetero atom analogs are of special significance due to their wide spread occurrence in nature and important biological properties. The present investigation deals mainly with the new synthetic strategies for indoles, carbazoles and benzo[*b*]thiophenes. All these new methods are based on a class of intermediates called "α-oxoketene dithioacetals".[2,3] These α-oxoketene dithioacetals, which can be easily prepared from a wide variety of active methylene compounds, have been recognised as useful building blocks in many synthetic operations. Extensive research has been carried out in this laboratory on the synthetic applications of α-oxoketene dithioacetals.[2] The various reactivity profile of these α-oxoketene dithioacetals are outlined in scheme 1. These intermediates have been used as three carbon electrophilic partners in [3+3] aromatic annelation reactions with various allyl anions for the synthesis of a number of carbocycles[4] and benzoheterocycles[5] as shown in the schemes 2 and 3.

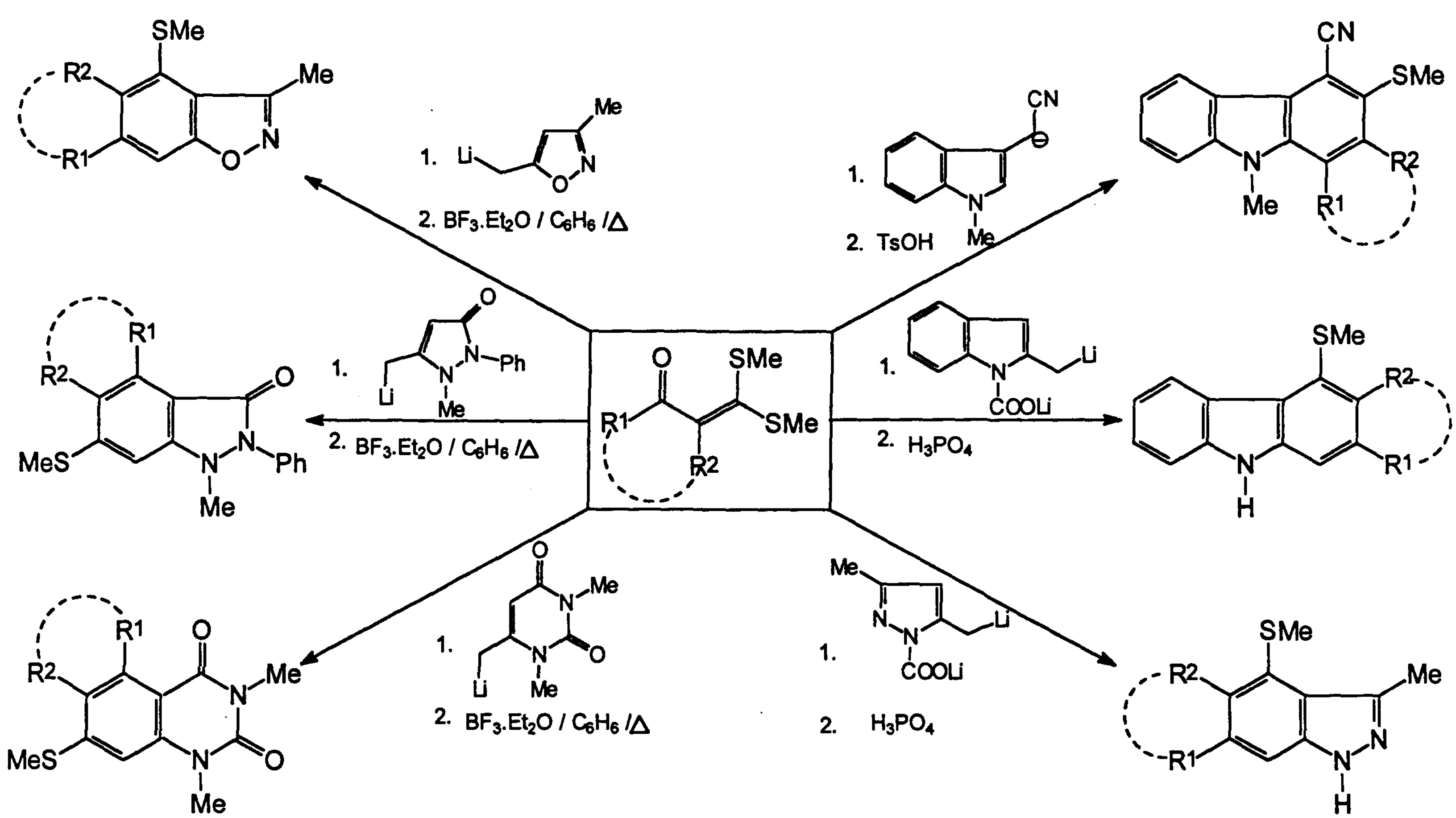
The work described in this thesis has been carried out as part of the study directed towards further synthetic applications of these α-oxoketene dithioacetals.


-Ketoaldehydes
or
-Ketoesters
1,3-diketones
or
1,4-Hydride addition
Hydrolysis
Organo-copper reagents
Polyene esters
1,2-Hydride or organometallic addition and 1,3-carbonyl transposition
3-Carbon 1,3 electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
Double bond reactivity
Bromination
Reactivities of R1 and R2
Miscellaneous
SCH3 deprotonation and intramolecular condensation
O,S-Acetals
N,S-Acetals
N,N-Acetals

Scheme 1


R1
R2
CH2C6H5
MgCl
1.
2. BF3.Et2O / C6H6 /Δ
R1
R2
OMe
SMe
Me
1.
Li
2. BF3.Et2O / C6H6 /Δ
R1
R2
Me
SMe
BrMg
1.
2.BF3.Et2O/ MeOH
Me
1.
Li
2. BF3.Et2O / C6H6 /Δ
R1
R2
Me
CH2C6H4-o-CH3
O
SMe
R1
SMe
R2
1. RO RO
MgCl
2. BF3.Et2O / C6H6 /Δ
R1
R2
OR
OR
SMe
MgBr
1.
2. BF3.Et2O / C6H6 /Δ
R1
R2
H7C10H2C
ClMg
1.
2. BF3.Et2O / C6H6 /Δ
R1
R2
SMe

Scheme 2

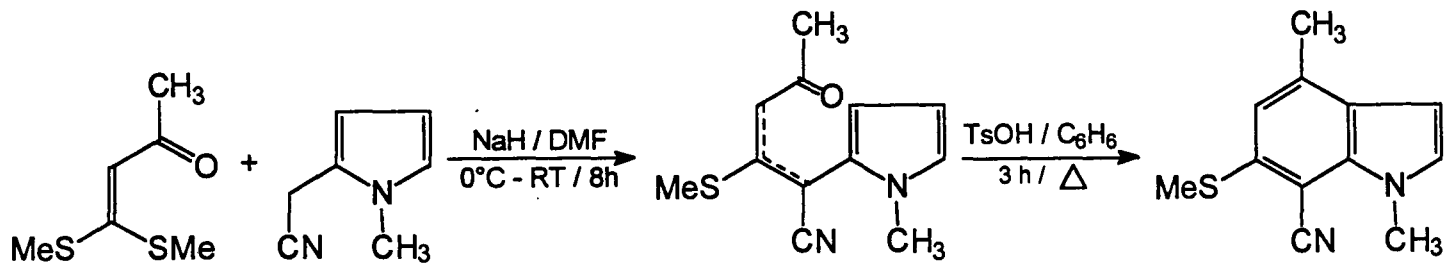

1. 2. BF3.Et2O / C6H6 /Δ
1. 2. TsOH
1. 2. H3PO4
1. 2. BF3.Et2O / C6H6 /Δ
1. 2. BF3.Et2O / C6H6 /Δ
1. 2. H3PO4

Scheme 3

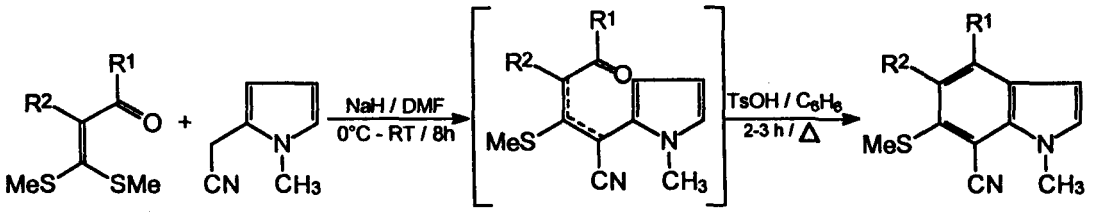
A NEW GENERAL REGIOCONTROLLED SYNTHESIS OF HIGHLY SUBSTITUTED AND CONDENSED INDOLES VIA HETEROAROMATIC ANNELATION.

Indole and its derivatives have attracted considerable attention due to their importance as building blocks for many therapeutically useful materials and wide ranging potential biological properties.[6-8] In view of the importance of this class of compounds in natural product chemistry and pharmacology, we became interested to extend the heteroaromatic annelation methodology developed in our laboratory for the synthesis of indoles. We have used 1-methylpyrrole-2-acetonitrile **2** as 3-carbon nucleophilic partner in [3+3]annelation reaction with various α-oxoketene dithioacetals to afford the corresponding indole derivatives.

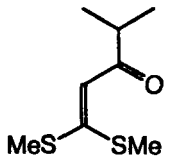
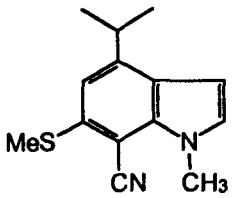
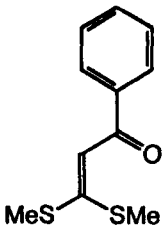
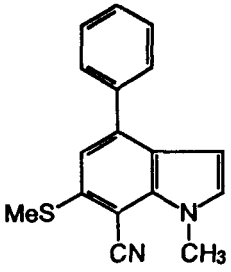
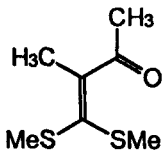
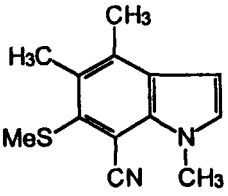
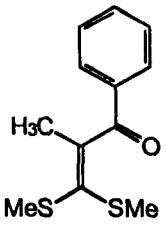
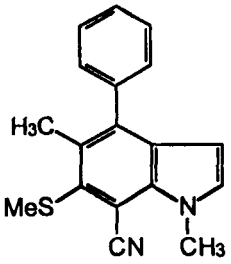
In a typical experiment, 1-methylpyrrole-2-acetonitrile **2** was reacted with α-oxoketene dithioacetal **1a** in the presence of NaH in DMF at ice-cold temperature to afford the corresponding 1,4-addition-elimination product **3a** in near quantitative yield (Scheme 4). This intermediate underwent cycloaromatization when treated with *p*-toluene sulfonic acid in refluxing benzene to yield 7-cyano-1,4-dimethyl-6-(methylthio)indole **4a** in 86% yield. Similarly the corresponding 4-isopropyl, 4-phenyl, 4,5-dimethyl, 4-phenyl-5-methyl, 4-dimethoxymethylindoles **4b-f** were obtained by reacting the corresponding oxoketene dithioacetals **1b-f** with **2** under the described reaction conditions (Schemes 5 and 6). The strategy was successfully extended to 4,5-annelated indoles as shown in the schemes 7 and 8. An interesting example in this series is the synthesis of optically active indole **11** by reacting α-oxoketene dithioacetal **10** derived from estrone methyl ether with **2** under similar reaction conditions (Scheme 9). This methodology is also useful for the synthesis of 6-methoxy- and 6-aminoindoles as shown in the schemes 10 and 11. Thus


CH3
O
MeS
SMe
1a
+
N
CN
CH3
2
NaH / DMF
0°C - RT / 8h
CH3
O
MeS
N
CN
CH3
3a
TsOH / C6H6
3 h / Δ
CH3
MeS
N
CN
CH3
4a

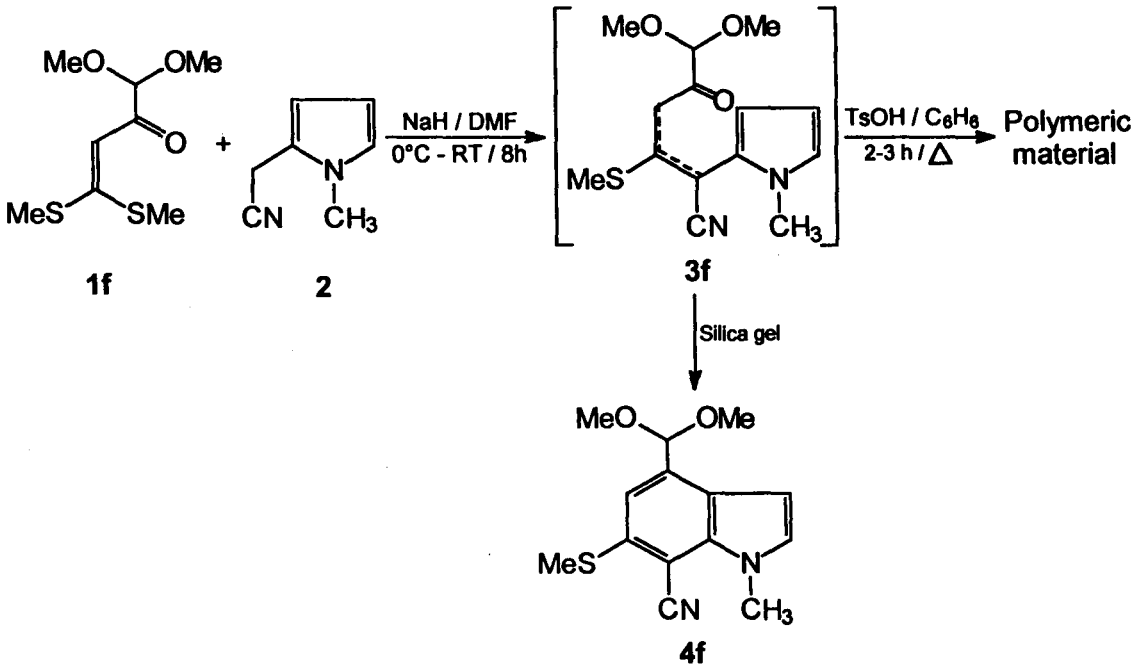
Scheme 4



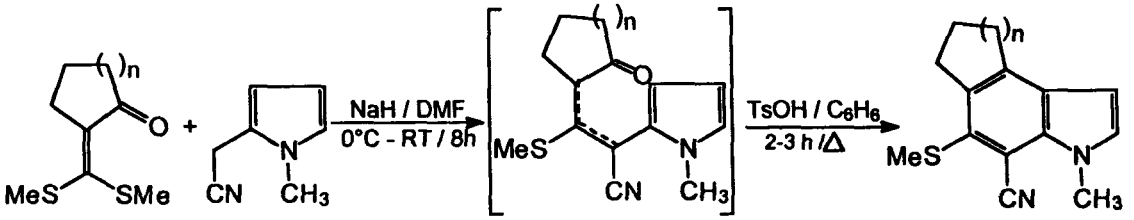
1 2 3 4

S,S-Acetal	Indole	Yield %
 **1b**	 **4b**	72
 **1c**	 **4c**	85
 **1d**	 **4d**	88
 **1e**	 **4e**	76

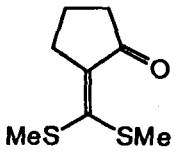
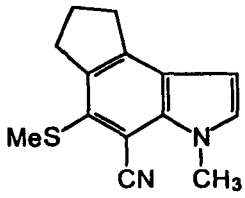
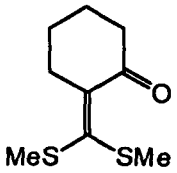
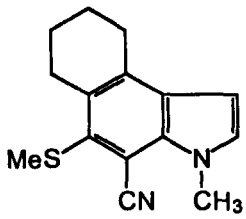
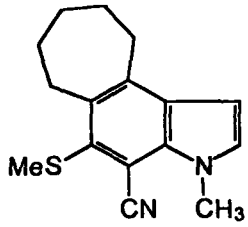
Scheme 5


MeO
OMe
O
MeS
SMe
1f
+
N
CN
CH3
2
NaH / DMF
0°C - RT / 8h
MeO
OMe
O
MeS
N
CN
CH3
3f
TsOH / C6H6
2-3 h / Δ
Polymeric material
Silica gel
MeO
OMe
MeS
N
CN
CH3
4f

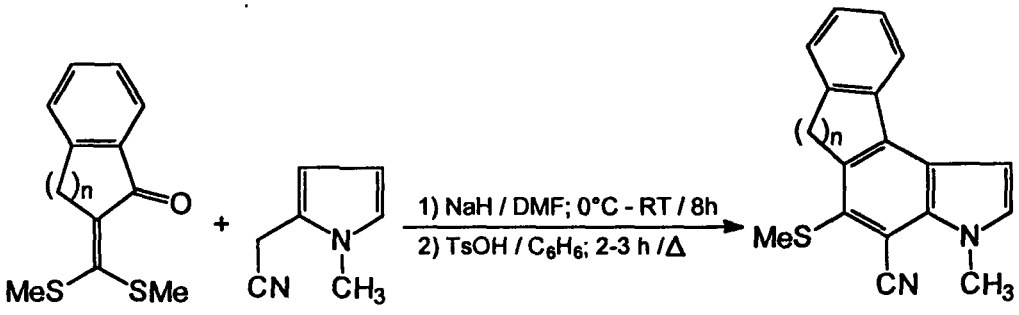
Scheme 6



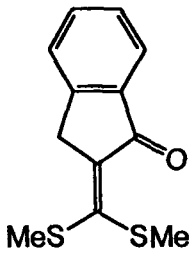
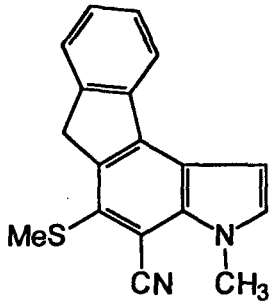
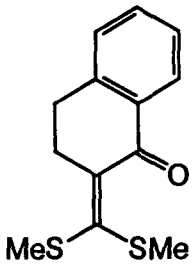
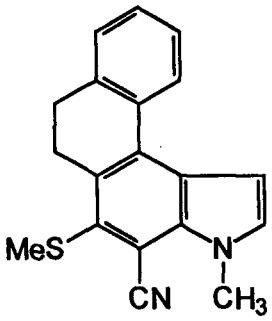
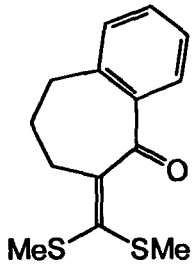
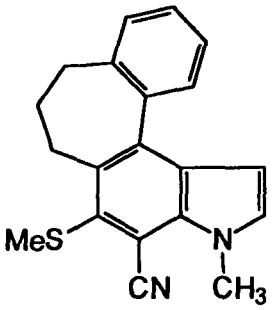
5 2 6 7

S,S-Acetal	Indole	Yield
		74
5a	7a	
		68
5b	7b	
		78
5c	7c	

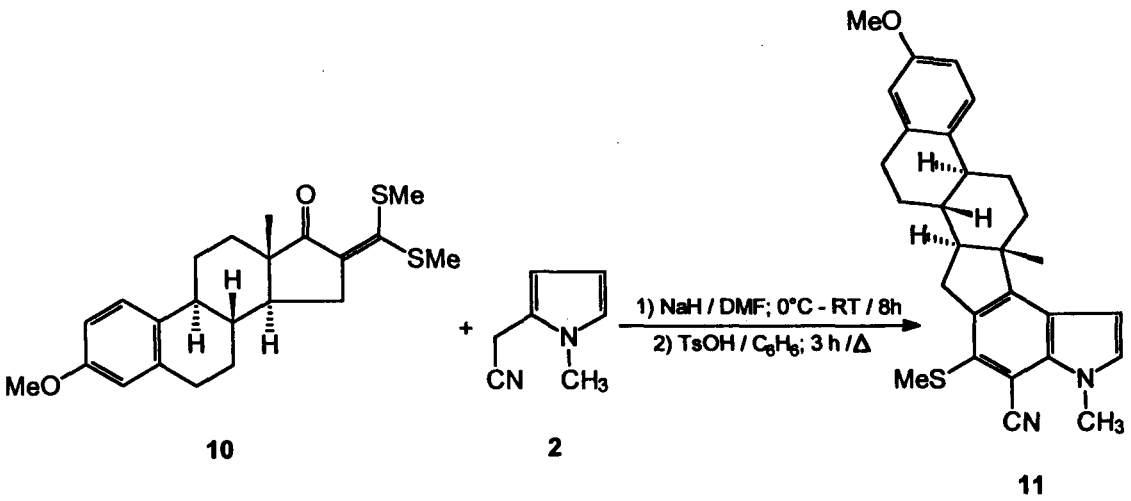
Scheme 7



8 **2** **9**

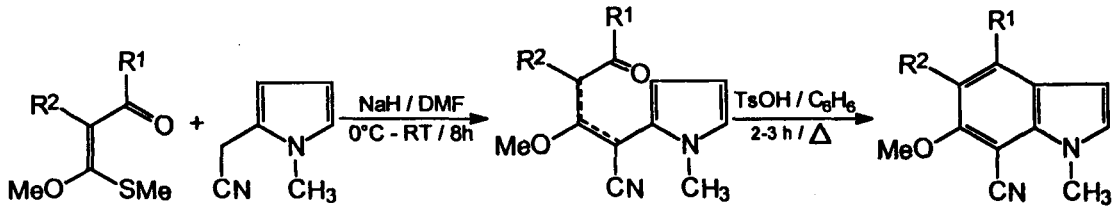
S,S-Acetal	Indole	Yield
 **8a**	 **9a**	82
 **8b**	 **9b**	66
 **8c**	 **9c**	72

Scheme 8

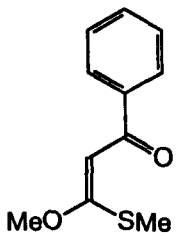
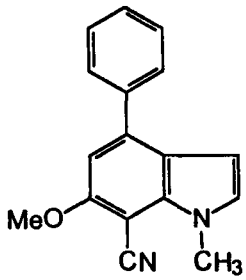
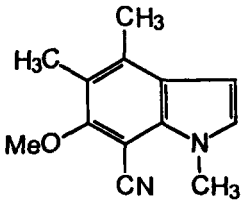


10 2 11

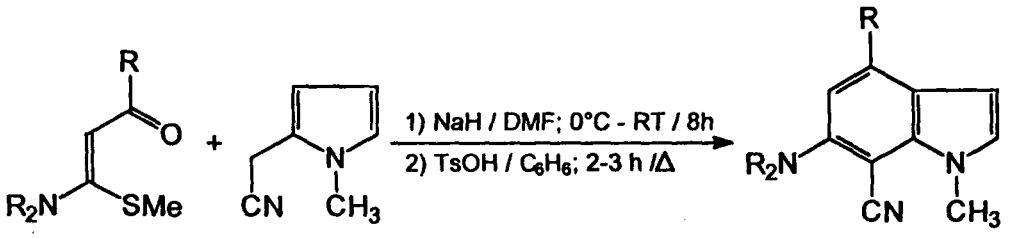
Scheme 9



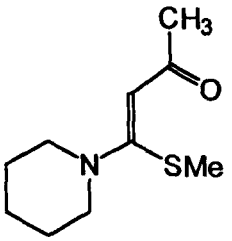
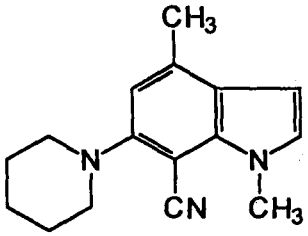
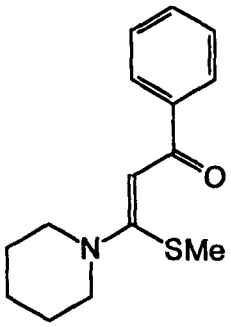
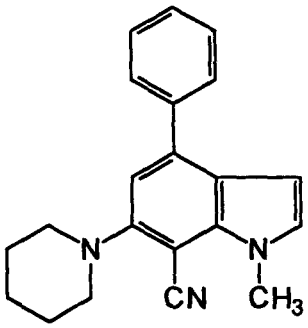
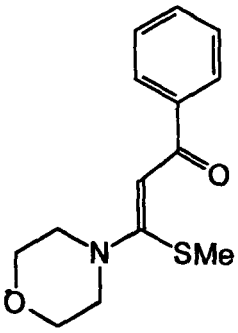
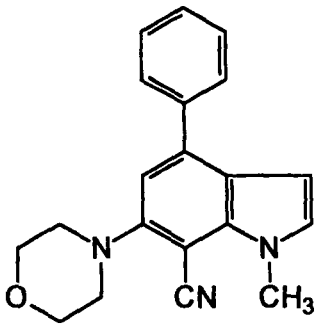
12 2 13 14

O,S-Acetal	Indole	Yield
		80
12a	14a	
		86
12b	14b	

Scheme 10



15 **2** **16**

N,S-Acetal	Indole	Yield
 **15a**	 **16a**	65
 **15b**	 **16b**	70
 **15c**	 **16c**	73

Scheme 11

oxoketene O,S-acetals and S,N-acetals were reacted with **2** to obtain the corresponding indoles **14a-b** and **16a-c** respectively.

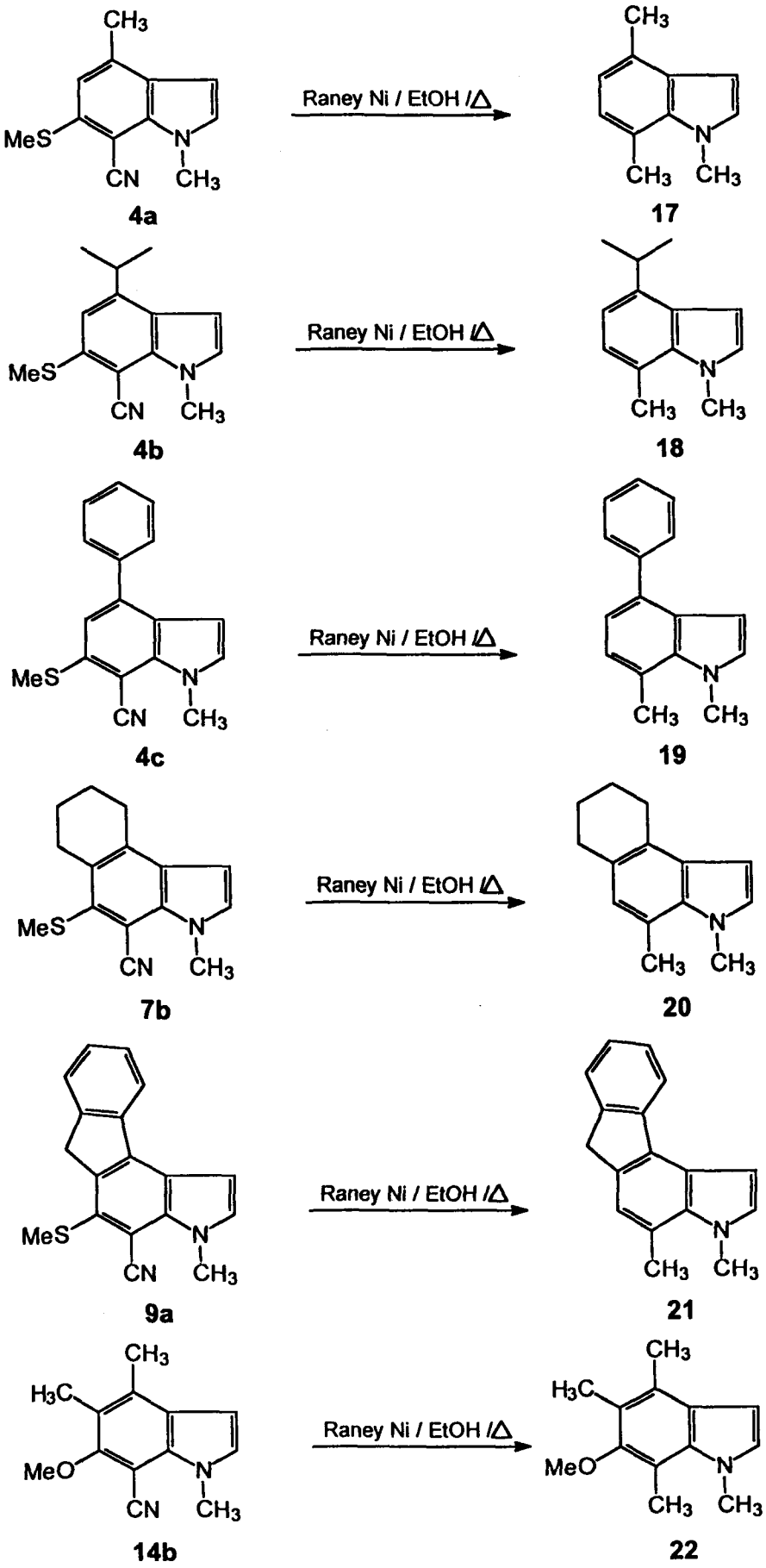
Some of the newly synthesised indoles were subjects to Raney nickel desulfurization in refluxing ethanol (Scheme 12). However the cyano group was also reduced along with dethiomethylation to afford the corresponding 7-methylindoles.

To further explore the scope of the reaction to obtain highly functionalised indole derivatives, doubly activated ketene dithioacetals **23** and **26** derived from acetylacetone and diethylmalonate respectively were reacted with **2** to obtain the corresponding indoles as shown in the schemes **13** and **14**.

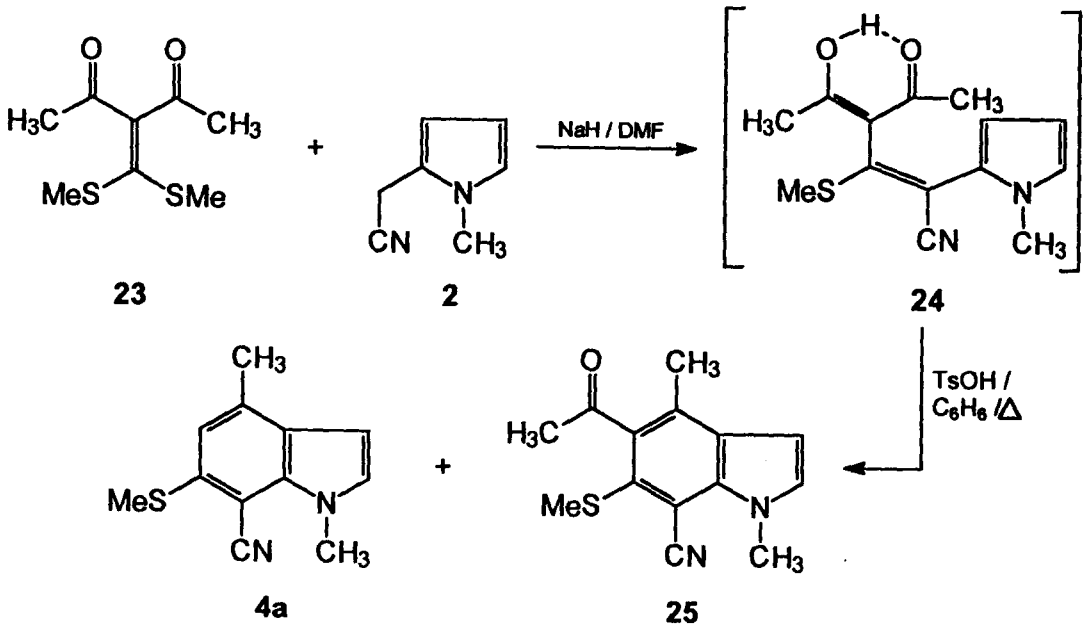
In conclusion, we have developed a new general route for the synthesis of indoles having control on the substituents at 4,5,6 and 7-positions using heteroaromatic annelation methodology.

REACTION OF THIOPHENE-2-ACETONITRILE WITH α-OXO-KETENE S,S- AND N,S-ACETALS: A NEW EFFICIENT SYNTHESIS OF SUBSTITUTED AND CONDENSED BENZO[B]THIOPHENES

Benzo[*b*]thiophene and its derivatives are found to exist in coal tar, in various crude petroleum oils and in shale oil.[9] This class of compounds have attracted considerable interest as potential biologically active agents and as bioisoesters of indoles.[10] In continuation of our interest in the chemistry of α-oxoketene dithioacetals we have described, in the previous chapter, the utilisation of 1-methylpyrrole-2-acetonitrile as allyl anion precursor to afford indoles. We further considered of interest to extend these studies to the thiophene-2-acetonitrile to develop a methodology for the synthesis of benzo[*b*]thiophenes.

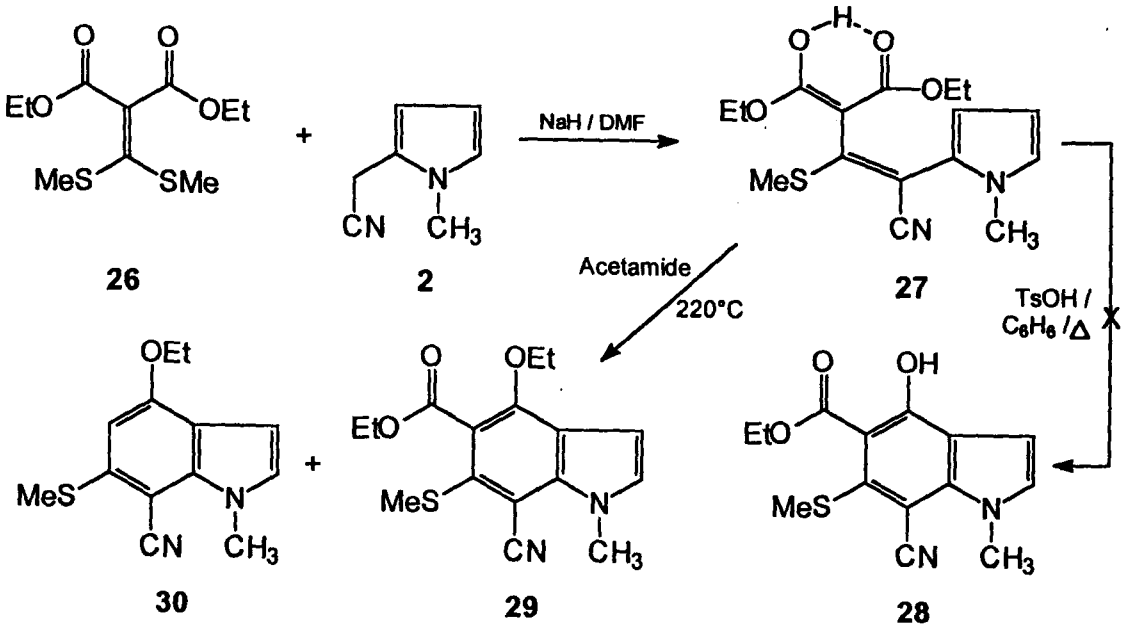

CH3
MeS
N
CN
CH3
Raney Ni / EtOH /Δ
4a
17
4b
18
4c
19
7b
20
9a
21
H3C
MeO
14b
22

Scheme 12



23 2 24 4a 25

Scheme 13



26 2 27 30 29 28

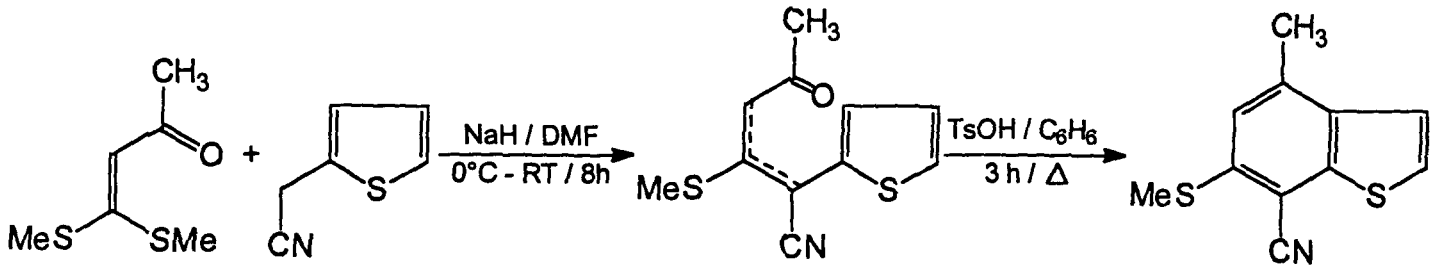
Scheme 14

Thus various α-oxoketene dithiocetals were reacted with thiophene-2-acetonitrile in the presence of NaH in DMF to afford the corresponding 1,4-addition-elimination products which were subsequently cycloaromatized to the corresponding benzo[*b*]thiophenes by treating with *p*-toluene sulfonic acid in refluxing benzene (Schemes 15-19). The reaction was further extended for for the synthesis of 6-aminobenzo[*b*]thiophenes (Scheme 20) by reacting α-oxoketene S,N-acetals with **32** under the described reaction conditions.

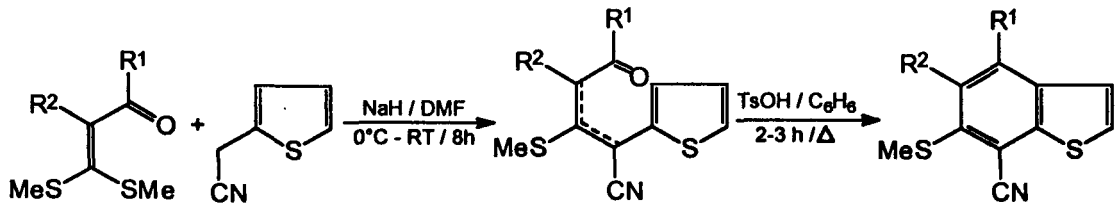
In conclusion, a facile method for the synthesis of benzo[*b*]thiophenes has been developed. The method is so versatile and a large number of benzo[*b*]thiophenes and their condensed variants can be prepared by reacting thiophene-2-acetonitrile with a wide variety of functionalised oxoketene S,S-, O,S-, and N,S-acetals though only a selected number of S,S- and N,S-acetals have been reacted in the present study.

ATTEMPTS TO TRANSFORM OXINDOLE INTO INDOLE DERIVATIVES: REACTION OF 3-BIS(METHYLTHIO)METHYLENE-2,3-DIHYDRO-2-OXO-1-METHYLINDOLE WITH GRIGNARD REAGENTS.

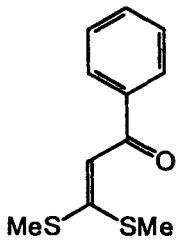
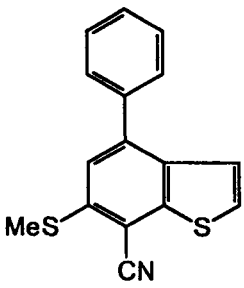
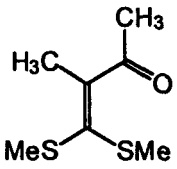
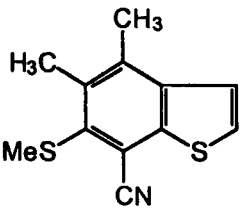
The importance of indoles is reflected in the numerous methods devised for its synthesis.[6] Particularly 2- and 2,3-substituted indoles gained importance due to the fact that they are precursors for various carbazole alkaloids and their analogs.[11] These 2- and 2,3-disubstituted indoles are generally synthesised by intramolecular ring closure of monosubstituted or *ortho*-disubstituted benzene precursors where the substituents in the 2 and 3-positions are installed in the ring closure sequence.[12] An alternative approach is the functionalization of preconstructed indole nucleus.[13] In the present investigation we have made an attempt to transform easily accessible oxindole into indole derivatives *via* its


CH3
O
MeS
SMe
31a
+
S
CN
32
NaH / DMF
0°C - RT / 8h
CH3
O
MeS
S
CN
33a
TsOH / C6H6
3 h / Δ
CH3
MeS
S
CN
34a

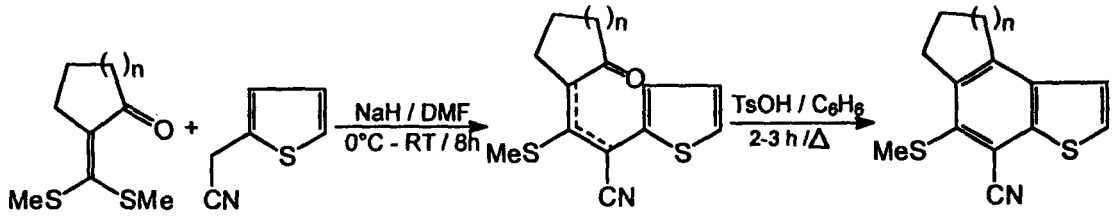
Scheme 15



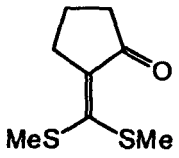
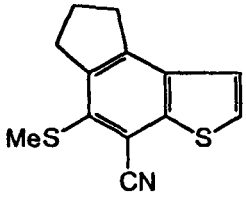
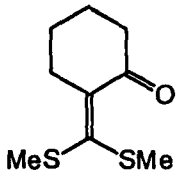
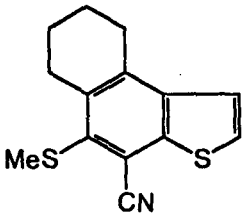
31 32 33 34

S,S-Acetal	Benzo[b]thiophene	Yield
 **31b**	 **34b**	72
 **31c**	 **34c**	64

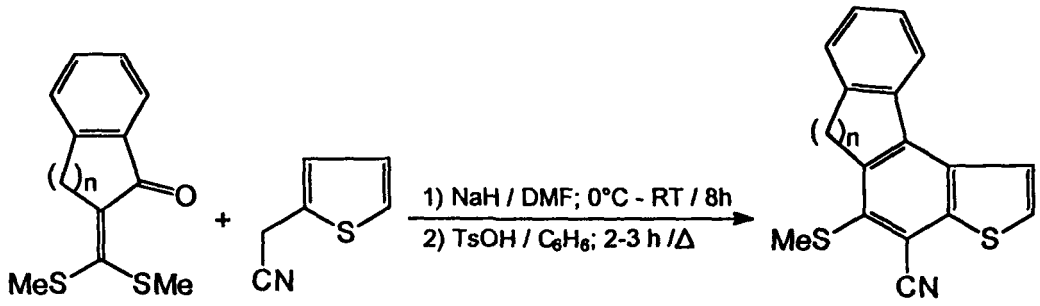
Scheme 16



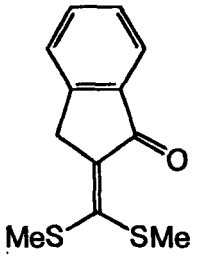
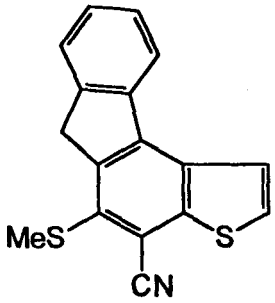
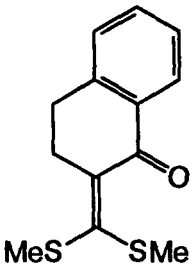
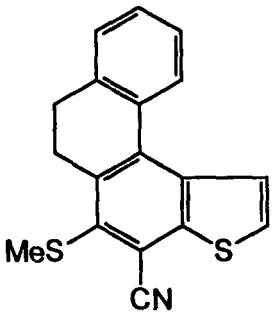
55 32 36 37

S,S-Acetal	Benzo[b]thiophene	Yield
 **35a**	 **37a**	66
 **35b**	 **37b**	60

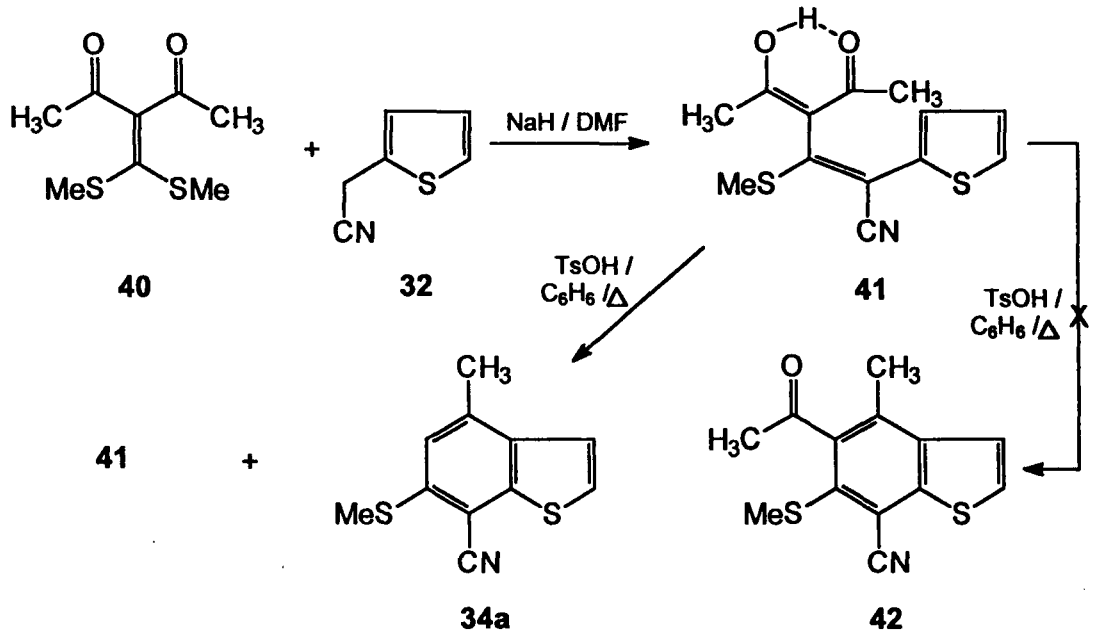
Scheme 17



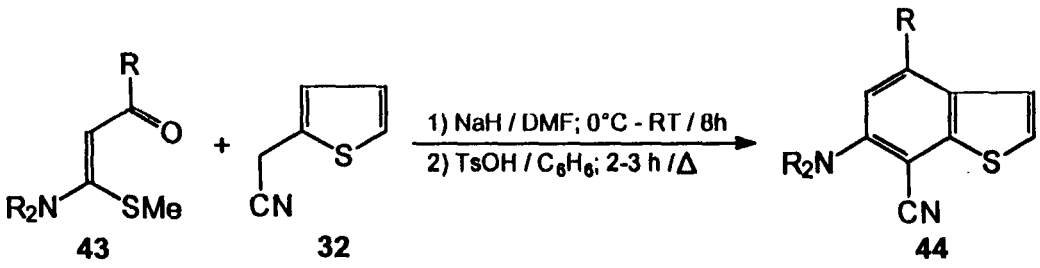
38 **32** **39**

S,S-Acetal	Benzo[b]thiophene	Yield
 **38a**	 **39a**	56
 **38b**	 **39b**	62

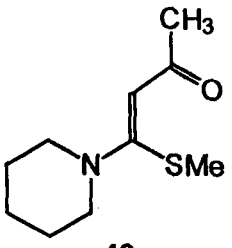
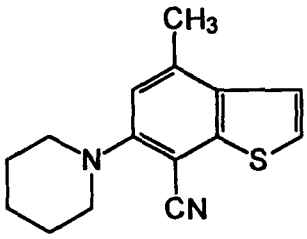
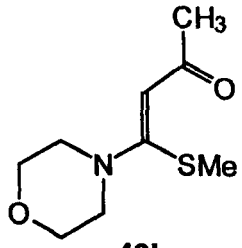
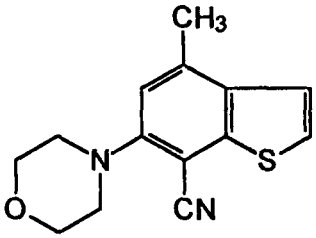
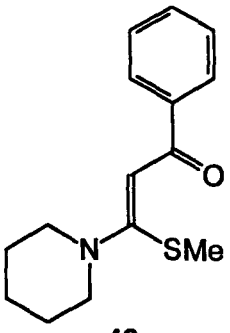
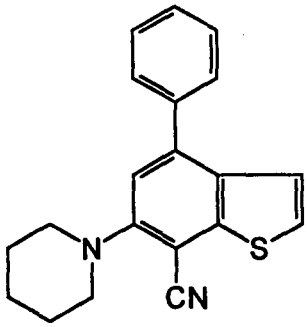
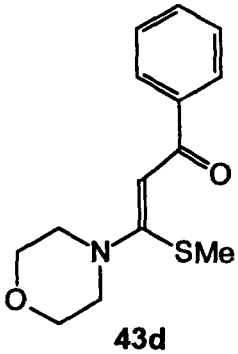
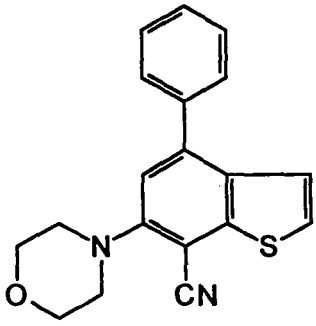
Scheme 18



Scheme 19



43 32 44

N,S-Acetal	Benzo[b]thiophene	Yield
 43a	 44a	65
 43b	 44b	56
 43c	 44c	70
 43d	 44d	73

Scheme 20

corresponding ketene dithioacetal **46**.[14] There are only a few methods reported in the literature for the transformation of oxindole into indole derivatives.[15] Most of them involve lithium aluminium hydride reduction of oxindole and its 3-substituted derivatives or treatment with $POCl_3$ to afford 3-substituted indoles. To our knowledge there is no unambiguous report in the literature for the conversion of oxindole to 2-substituted or 2,3-disubstituted indoles. In the present study we have reacted various Grignard reagents with ketene dithioacetal derived from oxindole with a view to developing a method for 2-substituted indoles as well as carbazoles.

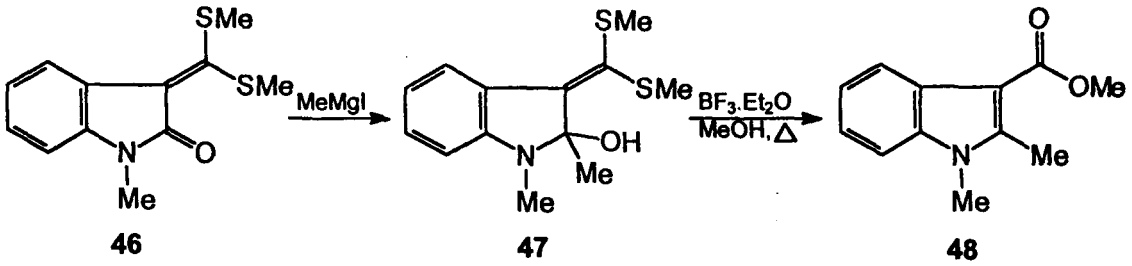
3-Bismethylthio-2,3-dihydro-1-methyl-2-oxoindole **46** was first reacted with MeMgI and the intermediate adduct obtained was directly treated with $BF_3.Et_2O$ in refluxing methanol to get the corresponding methyl 1,2-dimethylindole-3-carboxylate **48** (Scheme 21).

The reaction of higher alkyl Grignard reactions like ethylmagnesium bromide, *n*-propyl magnesium bromide and *n*-butyl magnesium bromide with **46** resulted in the formation of a mixture of products from which no well defined compounds could be isolated (Scheme 22).

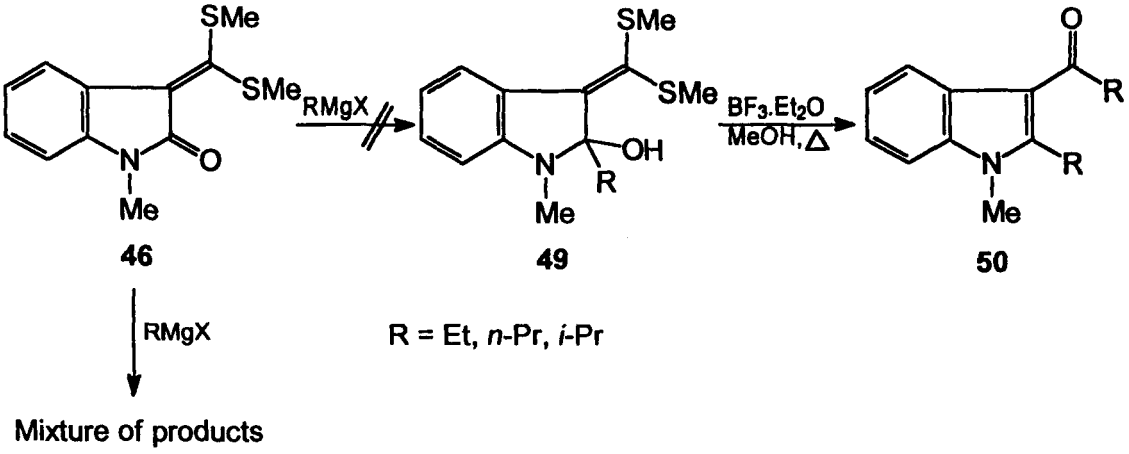
Interestingly isopropyl magnesium bromide reacted with **46** in 1,2-fashion and afforded after mathanolysis the corresponding methyl 2-isopropyl-1-methylindole-3-carboxylate **52**(Scheme 23).

When **46** was reacted with allyl and methylallyl Grignard reagents they underwent smooth 1,2-addition and yielded the corresponding carbazoles **55** when treated with $BF_3.Et_2O$ in refluxing benzene (Scheme 24).

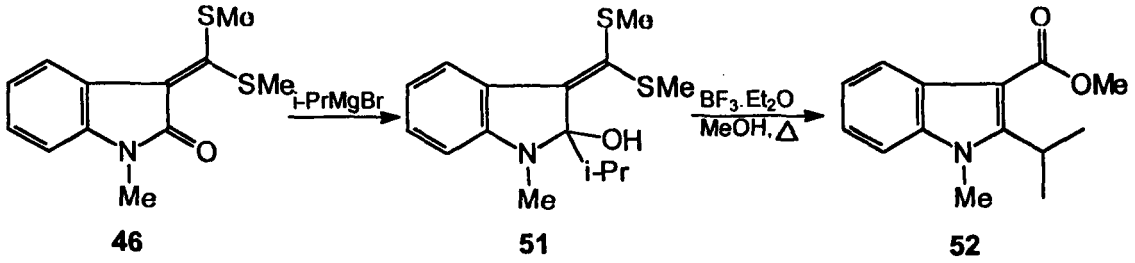
The reaction of benzyl and phenyl Grignard reagents resulted in the formation of 1,4-addition products as shown in the schemes 25 and 26.



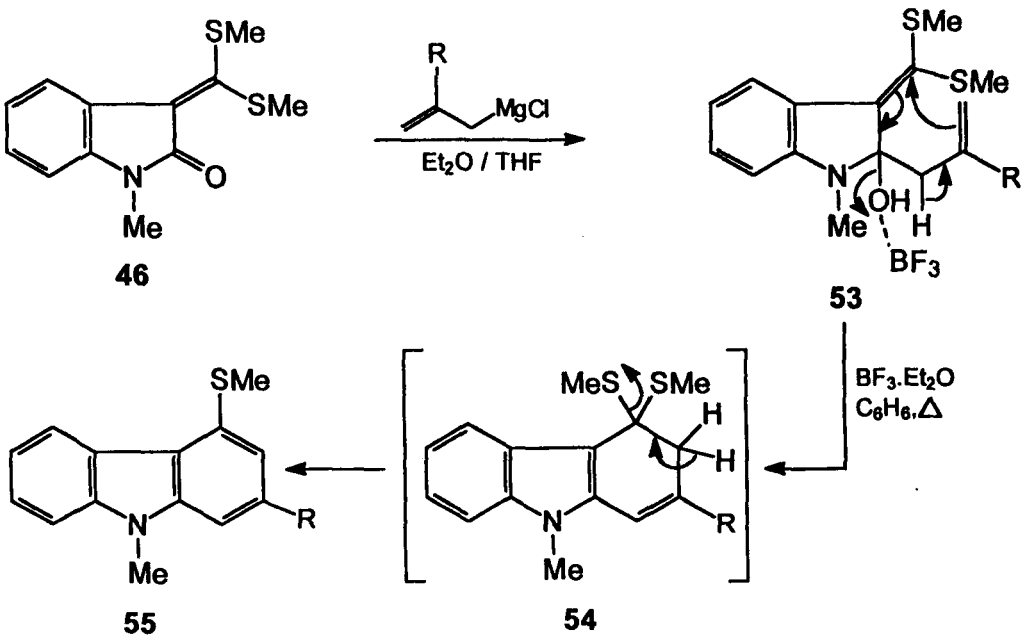
Scheme 21



Scheme 22



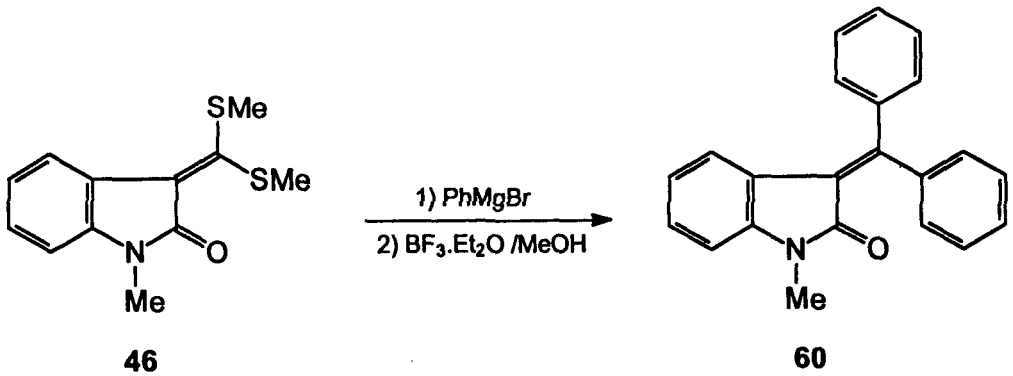
Scheme 23



46 53 54 55

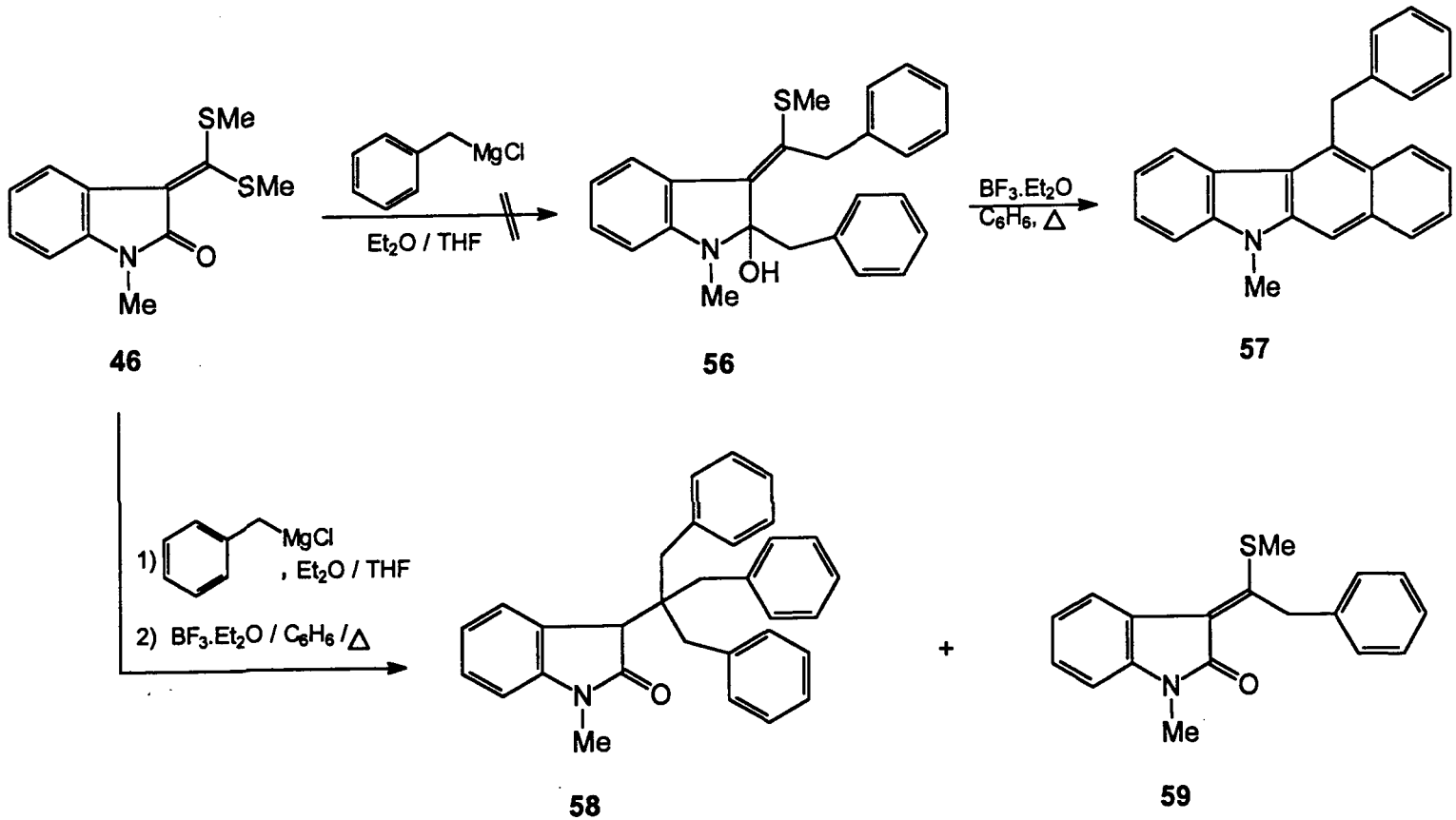
R = H, CH_3

Scheme 24



46 60

Scheme 26



46 56 57

58 59

Scheme 25

In conclusion, the further exploration of 3-bis(methylthio)methylene-1-methyloxindole to the corresponding indole derivatives have resulted in a mixed results. Well defined indole derivatives were obtained only when the Grignard reagents, like MeMgI and *i*-PrMgBr, add in exclusive 1,2-fashion to **46**. The other higher alkyl Grignard reagents which are known to add in sequential 1,4-followed by 1,2-fashion yielded only mixture of products. However, the corresponding benzyl and phenyl Grignard reagents gave only 1,4-addition products possibly due to the steric factors. Allyl Grignard reagents smoothly added to **46** in 1,2-fashion and yielded the corresponding carbazoles after cycloaromatization. To our knowledge this is the first report where the reaction of nucleophiles with 2-oxo function of oxindole has been exploited for the synthesis of carbazoles.

REFERENCES

1. Eicher,T.; Hauptmann, S. *The Chemistry of Hetrocycles* Thieme, Stuttgart, **1995.**
2. Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron* **1990**, *46*, 5423.
3. Dieter, R.K. *Tetrahedron* **1986**, *42*, 3029.
4. Junjappa, H.; Ila, H. *Phosphorus, Sulfur and Silicon* **1994**, *95-96*, 35.
5. (a) Balu, M.P.; Pooranchand, D.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1988**, *29*, 501. (b) Reddy, K.R.; Roy, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1995**, *51*, 10941. (c) Satyanarayana, J.; Reddy, K.R.; Ila, H. Junjappa, H. *Tetrahedron Lett.* **1992**, *33*, 6173. (d) Patra, P.K.; Suresh, J.R.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1997**, *38*, 3119. (e) Syam Kumar, U.K.; Patra, P.K.; Ila, H.; Junjappa. H. *Tetrahedron Lett.* **1998**, *39*, 2029.
6. Sundberg, R.J. *Indoles* Academic Press, San Diego, **1996.**
7. Saxton, J.E. (Ed.), *The Chemistry of Heterocyclic Compounds-Indoles*, Wiley Interscience, New York, Vol. 25, Part 4, **1983.**
8. Sundberg, R.J. *The Chemistry of Indoles*, Academic Press, New York, **1970.**
9. (a) Iddon, B.; Scrowston, R.M. *in Advances in Heterocyclic Chemistry* Katritzky, A.R.; Boulton, A.J. (Eds.), Academic Press, New York, **1970**, Vol. 11, pp 177. (b) Scrowston, R.M. in *Advances in Heterocyclic Chemistry* Katritzky, A.R. (Ed.), Academic Press, New York, **1981**, Vol. 29, pp 171.
10. (a) Campaigne, E.; Knapp, D.R.; Neiss, E.S.; Bosin, T.R. *Adv. Drug. Res.* **1970**, *5*,1. (b) Bosin, T.R.; Campaigne, E. *Adv. Drug. Res.* **1977**, *11*, 191.

11. (a) Manske, R.H.F. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 1-16, **1950-1977**. (b) Rodrigo, R.G.A. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 17-20, **1979-1981**. (c) Brossi, A. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 21-45, **1983-1994**.

12. (a) Saxton, J.E. (Ed.), *The Chemistry of Heterocyclic Compounds-Indoles*, Wiley Interscience, New York, Vol. 25, Part 4, **1983**.
(b) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1.
(c) Hegedus, L.S. *Angew. Chem. Int. Ed. Eng.***1988**, *27*, 1113.
(d) Alvarez, M.; Salas, M.; Joule, J.A. *Heterocycles* **1991**, *32*, 1391.
(e) Gribble, G.W. *Contemporary Organic Synthesis* **1994**, *1*, 145.

13. (a) Sundberg, R.J. in *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R.; Rees, C.W.; Bird, C.W.; Cheeseman, G.W.H. (Eds.), Pergamon Press, Oxford, **1984**, Vol. 4.
(b) Mohanakrishnan, A.K.; Srinivasan, P.C. *Ind. J. Chem.* **1996**, *35B*, 838. (c) Labadie, S.S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250.
(d) Palmisano, G.; Santagostino, M. *Synlett* **1993**, 771. (e) Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. *Heterocycles* **1993**, *36*, 941.
(f) Kondo, Y.; Takazawa, N.; Yoshida, A.; Sakamoto, T.; *J. Chem. Soc. Perkin Trans. 1* **1995**, 1207.
(g) Gharpure, M.; Stoller, A.; Bellamy, F.; Firnace, G.; Snieckus, V. *Synthesis* **1991**, 1079.
(h) Katritzky, A.R.; Akutagawa, K. *Tetrahedron Lett.***1985**, 26, 5935.

14. (a) Teshigawara, T.; Kobayashi, G.; Matsuda, Y. Japan 15543 (1967); *Chem. Abstr.* **1968**, *69*, 2869p.
(b) Kobayashi, G.; Furukawa, S.; Matsuda, Y. *Yakugaku Zasshi* **1966**, *86*, 1152; *Chem .Abstr.* **1967**, *67*, 3031e.

15. (a) Julian, P.L.; Printy, H.C. *J. Am. Chem. Soc.* **1949**, *71*, 3206.

(b) Hudson, C.B.; Robertson, A.V. *Aust. J. Chem.* **1967**, *20*, 1699.

(c) Plieninger, H.; Werst, G. *Angew. Chem.* **1958**, *70*, 272.

(d) Sirowej, H.; Khan, S.A.; Plieninger, H. *Synthesis,* **1972**, 84.

(e) Harley-Mason, J.; Leeney, T.J. *Proc. Chem. Soc.* **1964**, 368.

(f) Powers, J.C. *J. Org. Chem.* **1966**, *31*, 2627.

(g) Kubo, A.; Nakai, T. *Synthesis* **1980**, 365.

(h) Seshadri, S.; Sardessai, M.; Betrabet, A.M. *Indian J. Chem.* **1969**, *7*, 662. (i) Behringer, H.; Weissauer, H. *Chem Ber.* **1952**, *85*, 743.

SYNTHETIC STUDIES ON HETEROCYCLES

By

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NEHU

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FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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SHILLONG - 793 022

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CERTIFICATE

This is to certify that the work described in this thesis has been carried out by **Mr. J.R. Suresh** under my supervision in the Department of Chemistry, North-Eastern Hill University, Shillong and it has not been submitted for any other degree or diploma in this or any other University.

H. Junjappa
Supervisor

TO

MY MOTHER

AND

MEMORIES OF

MY FATHER

AND

GRAND MOTHER

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Shillong
August, 1998. J.R.SURESH.

PREFACE

Heterocyclic compounds are very widely distributed in nature and are essential to life; they play a vital role in the metabolism of all living cells. There are a vast number of pharmacologically active natural and unnatural heterocyclic compounds, many of which are in regular clinical use. There are also a large number of synthetic heterocyclic compounds with other important practical applications, as dye stuffs, co-polymers, solvents, photographic sensitizers and developers, as antioxidants and many are valuable intermediates in synthesis. Because of all these applications of heterocyclic compounds, there have been continuous efforts for the development of new methods for their synthesis. Heterocyclic units such as indoles, carbazoles and their other hetero atom analogs are of special significance due to their wide spread occurrence in nature and important biological properties. The present investigation deals mainly with the new synthetic strategies for indoles, carbazoles and benzo[*b*]thiophenes. All these new methods are based on a class of intermediates called "α-oxoketene dithioacetals". These α-oxoketene dithioacetals, which can be easily prepared from a wide variety of active methylene compounds, have been extensively explored in this laboratory for the development of new methods for the synthesis of a variety of heterocyclic and carboyclic compounds. The work described in this thesis has been carried out as a part of this ongoing research programme.

The thesis consists of four chapters. The first chapter gives a brief introduction to α-oxoketene dithioacetals. The general reactivity profile of α-oxoketene dithioacetals and some of their transformations recently reported from this laboratory are discussed in this chapter.

The second chapter describes the synthesis of highly substituted and condensed indoles by the reaction of 1-methylpyrrole-2-acetonitrile with α-oxoketene dithioacetals in the presence of base followed by acid catalysed cyclization of the resulting intermediates.

A new regiocontrolled synthesis of substituted and condensed benzo[*b*]thiophenes by the reaction of thiophene-2-acetonitrile with α-oxoketene dithioacetals is described in the third chapter.

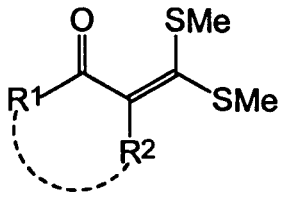
In the fourth chapter, reactions of various Grignard reagents with 3-bis(methylthio)methylene-2,3-dihydro-1-methyl-2-oxoindole for the synthesis of indole derivatives and carbazoles are described.

CONTENTS

CHAPTER I

α-OXOKETENE DITHIOACETALS: A BRIEF INTRODUCTION

The α-oxoketene dithioacetals of the general formula **1** are among the simplest synthetic intermediates in organic synthesis. They have been recognised as useful building blocks in many synthetic operations.[1] These class of compounds can be conveniently prepared[2-10] by reacting any active methylene compound with base and carbon disulfide followed by alkylation. Various bases and reaction conditions have been employed depending on the nature of the active methylene compound.



1

The first synthesis of α-oxoketene dithioacetals was reported by Kelber and co-workers[11-13] in 1910. Much of the earlier work on α-oxoketene dithioacetals was confined to their preparation and properties while little attention was paid for their synthetic utility. Later Thuillier and co-workers[2-5] prepared these compounds in high yields in one pot reaction by reacting the active methylene ketones with carbon disulfide in the presence of sodium amylate followed by alkylation. Subsequently these reaction conditions have been greatly improved using different bases and reaction conditions.[6-10] A large number of α-oxoketene dithioacetals have now been reported and their chemistry has been reviewed by Dieter[1b] in 1986 and by Junjappa and Ila[1a] in 1990.

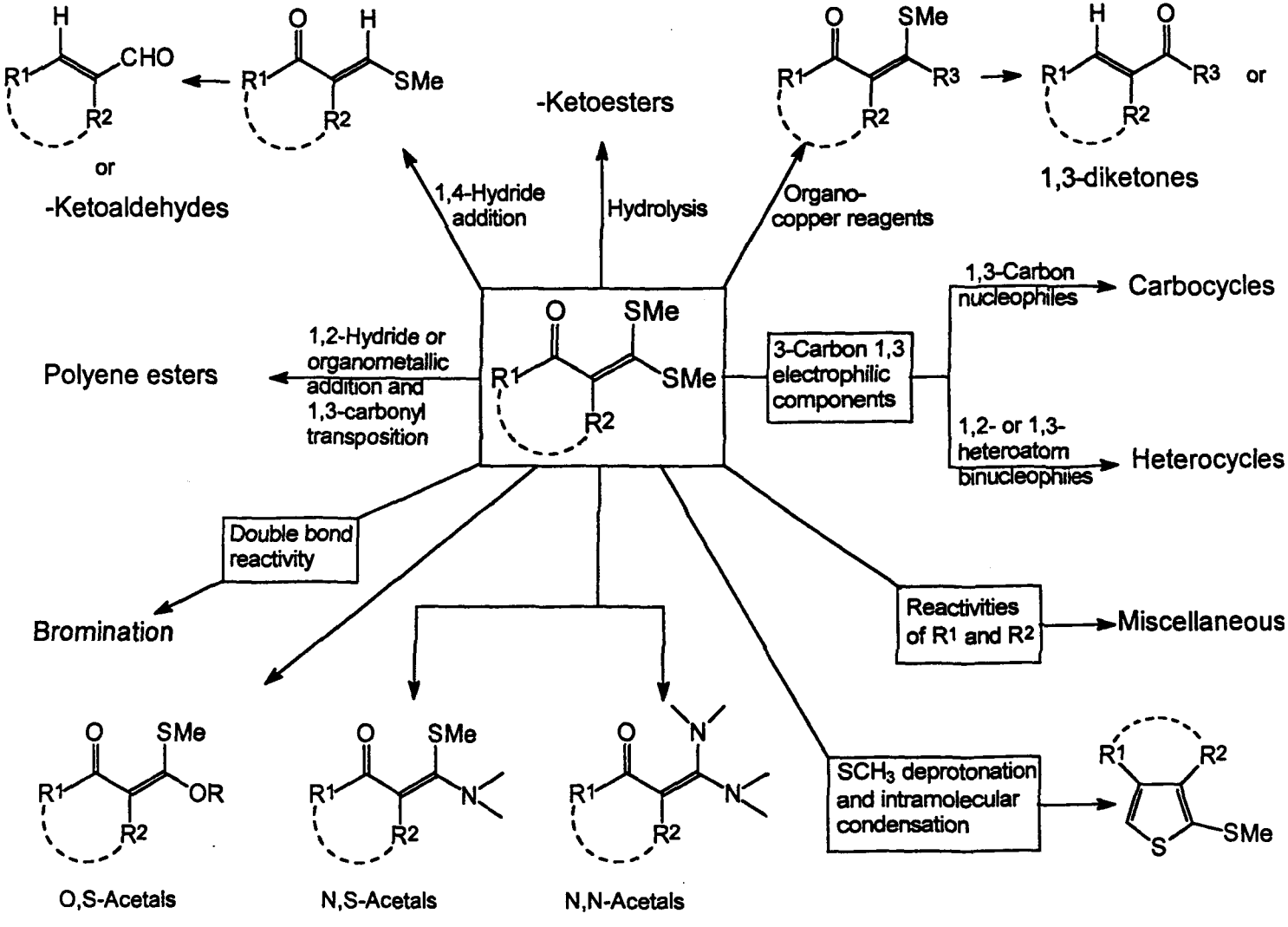
The α-oxoketene dithioacetals generally exhibit well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stored indefinitely without decomposition. However, the corresponding α-oxoketene O,O-acetals are moisture sensitive and undergo hydrolysis under mild conditions. The α-oxoketene dithioacetals can be considered as masked β-ketoesters in which the ester functionality is protected as a ketene dithioacetal. Alternatively it may be viewed as α,β-unsaturated ketones containing a highly functionalised β-carbon. They are versatile 3-carbon fragments with 1,3-electrophilic centres of differing electrophilicity. These intermediates possess considerable potential in the stereo- and regioselective construction of bonds either by a 1,2-nucleophilic addition to carbonyl group or 1,4-conjugate addition to the β-carbon of the enone system. Also the α-oxoketene dithioacetals are the primary precursors for the corresponding O,S- N,S- and N,N-acetals. The preparation of O,S-acetals is accomplished through the displacement by oxygen nucleophiles of the sulfonium salts of the corresponding S,S-acetals.[14,15] The N,S-acetals can be prepared by the displacement of one of the thiomethyl group by suitable amines in refluxing ethanol[16,17] or by the reaction of lithioanilines with S,S-acetals.[18] The α-

oxoketene N,N-acetals can be prepared in high yields by displacing both the thiomethyl groups by amines in refluxing acetic acid.[17,19] All these α-oxoketene acetals have been extensively used in this laboratory for the synthesis of both heterocyclic and carbocyclic compounds.[1]

In Scheme 1, various reactivity profiles of α-oxoketene dithioacetals of general formula **1** have been outlined. Hydrides and organometallic reagents give 1,2-addition products typical of carbonyl function reactivity.[20-24] These additions can be directed in a 1,4-manner by suitably manipulating the reagent and reaction conditions.[24,25] Further transformations after the initial 1,2- or 1,4-additions are also reported.[20-25] The enolate ion formed by the deprotonation (when R^1 = alkyl) can undergo condensation with aldehydes to give α-enoylketene dithioacetals.[26,27] An allylic anion formation has been reported when R^2 is a methyl group, leading to rearranged products.[28]

Also deprotonation on the thiomethyl group followed by intramolecular aldol type condensation to thiophene is also reported.[29,30] The reactivity of the mercaptal double bond is also exploited with electrophiles. The dithioacetals **1** (R^2 = H) can undergo bromination at α-position with N-bromosuccinimide.[31] Thus it is apparent that the α-oxoketene dithioacetals of general formula **1** constitute an important class of synthons with reactive electrophilic and nucleophilic centres distributed in various centres of its skeleton permitting reactions of great synthetic importance. Some of the selected transformations reported from this laboratory are briefly described as follows.

The carbonyl group of α-oxoketene dithioacetals has been reported to undergo sodium borohydride reduction in 1,2-fashion to give the corresponding carbinol acetals **2** (Scheme 2). These carbinol acetals are shown to undergo smooth methanolysis in the presence of boron trifluoride-etherate to afford α,β-unsaturated methyl esters **3** in high yields.[23] The overall transformation can be


-Ketoaldehydes
-Ketoesters
1,3-diketones
or
1,4-Hydride addition
Hydrolysis
Organo-copper reagents
Polyene esters
1,2-Hydride or organometallic addition and 1,3-carbonyl transposition
3-Carbon 1,3 electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
Double bond reactivity
Bromination
Reactivities of R1 and R2
Miscellaneous
SCH3 deprotonation and intramolecular condensation
O,S-Acetals
N,S-Acetals
N,N-Acetals

Scheme 1

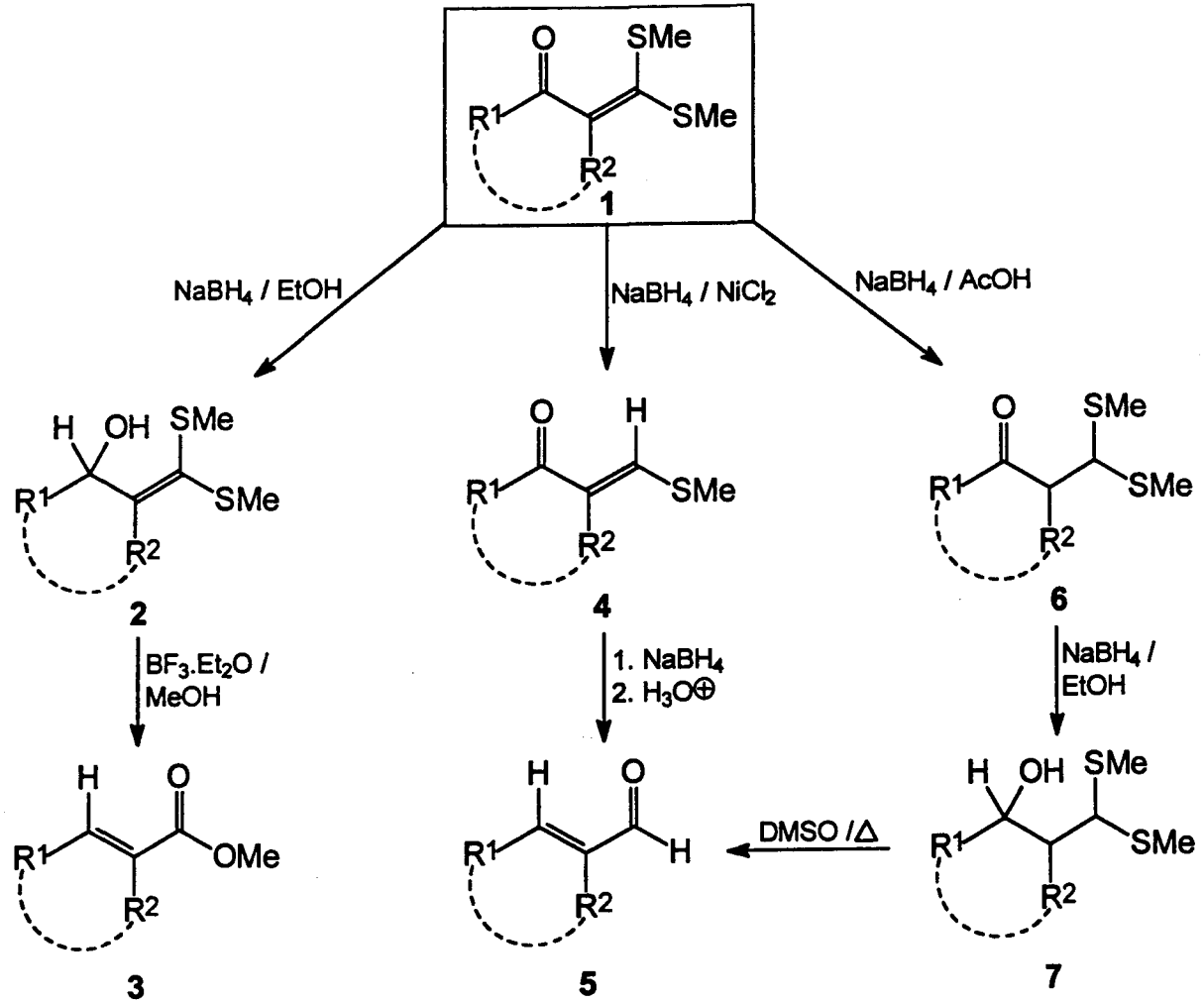
viewed as homologation of active methylene ketones at the α-position involving a 1,3-carbonyl transposition.

The α-oxoketene dithioacetals are shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthioalkenyl ketones **4**.[32] The α-oxoketene dithioacetals were also shown to undergo conjugate 1,4-reduction in highly regio- and chemoselective manner with sodium borohydride in acetic acid to afford the corresponding β-oxodithioesters **6**.[33] These intermediates are hydrolysed to the α,β-unsaturated aldehydes **5**[32,34] (Scheme 2).

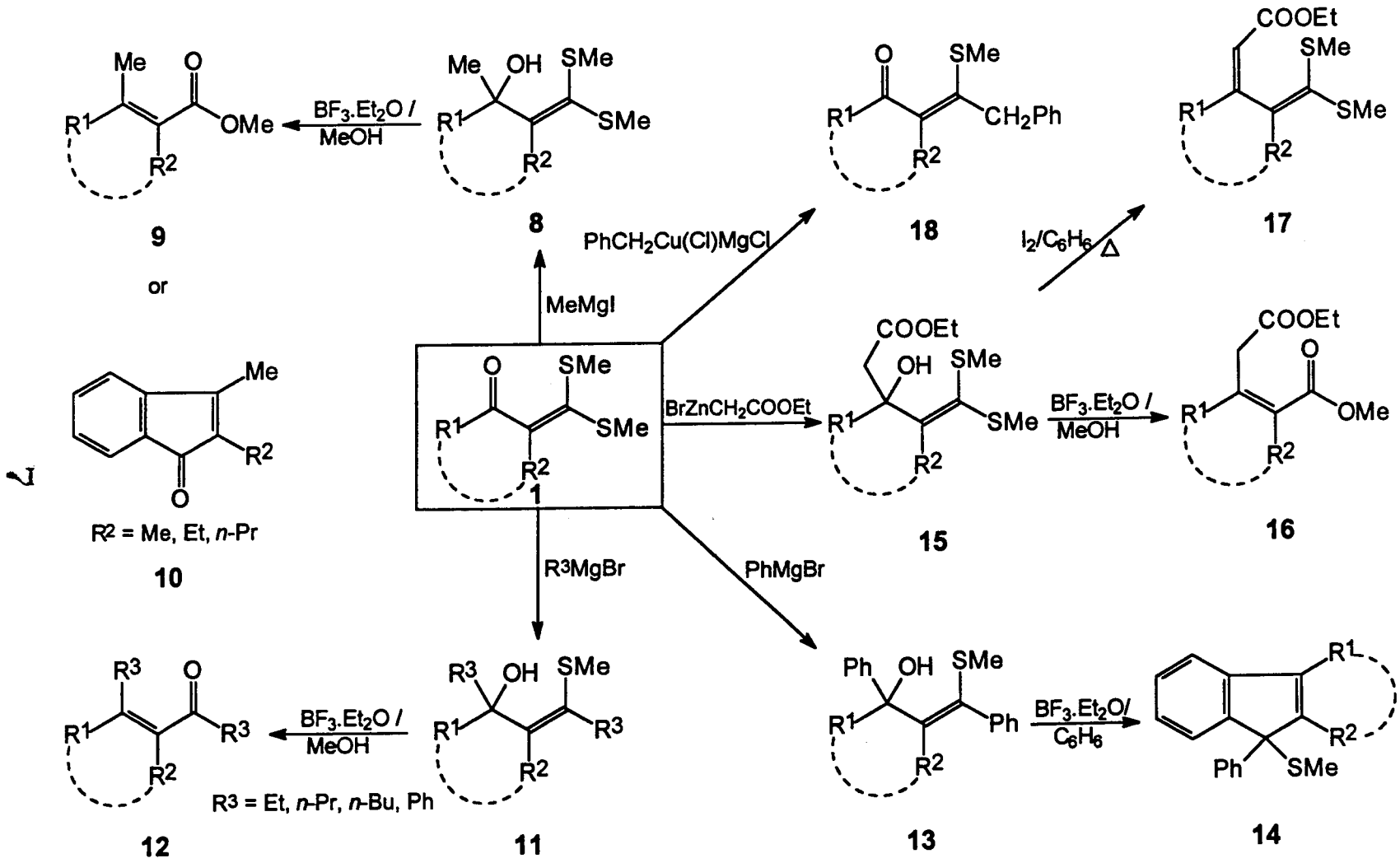
Methyl magnesium iodide was shown to react with α-oxoketene dithioacetals to afford the carbinol acetals **8** by 1,2-addition in good yields (Scheme 3).[24] The $BF_3.Et_2O$ assisted methanolysis of these carbinol acetals afford the corresponding β-methyl-α,β-unsaturated esters **9** as exclusive E stereoisomers. The corresponding α,β-unsaturated thiol esters could also be obtained under hydrolytic conditions. The carbinol acetals derived from α-alkyl oxoketene dithioacetals of higher homologues of acetophenone, on the other hand, yielded the corresponding 2-alkyl-3-methylindenones **10** under identical solvolytic conditions.[24]

The course of addition of higher alkyl Grignard reagents (R = Et, *n*-Pr, *n*-Bu) and phenyl magnesium bromide to α-oxoketene dithioacetals followed a sequential 1,4- and 1,2-addition pattern to afford carbinols **11** which are shown to afford α,β-unsaturated ketones **12** after subsequent methanolysis in the presence of $BF_3.Et_2O$.[24] However, when the carbinols **13** obtained by the reaction of phenyl magnesium bromide with α-oxoketene dithioacetals were treated with BF_3-Et_2O in benzene, they underwent cyclization to afford the corresponding 1-methylthio-1-phenylindenes **14** in good yields.[35]

The 1,2-addition of ethylbromozinc acetate (Reformatzky reagent) to α-oxoketene dithioacetals to yield the corresponding carbinol acetals **15** has been


O
SMe
SMe
R1
R2
1
NaBH4 / EtOH
NaBH4 / NiCl2
NaBH4 / AcOH
H
OH
SMe
SMe
R1
R2
2
O
H
SMe
R1
R2
4
O
SMe
SMe
R1
R2
6
BF3.Et2O /
MeOH
1. NaBH4
2. H3O⊕
NaBH4 /
EtOH
H
O
OMe
R1
R2
3
H
O
H
R1
R2
5
DMSO /Δ
H
OH
SMe
SMe
R1
R2
7

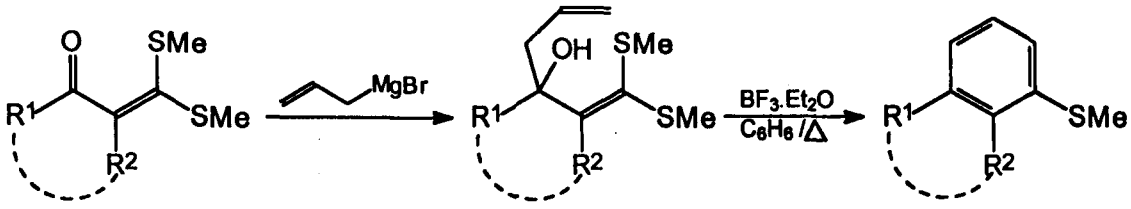
Scheme 2


Me
O
OMe
R1
R2
BF3.Et2O /
MeOH
Me
OH
SMe
SMe
9
or
8
MeMgI
PhCH2Cu(Cl)MgCl
18
I2/C6H6
Δ
17
COOEt
SMe
CH2Ph
Me
R2
O
10
R2 = Me, Et, n-Pr
1
BrZnCH2COOEt
15
16
COOEt
OH
OMe
R3MgBr
PhMgBr
R3
12
11
13
14
Ph
R3 = Et, n-Pr, n-Bu, Ph

Scheme 3

reported.[36] These carbinol acetals were found to undergo $BF_3.Et_2O$-assisted methanolysis to afford propene dicarboxylates **16** while iodine catalysed dehydration of **15** afforded the corresponding diene esters **17**. Benzyl organocopper reagents were shown to undergo chemo- and stereoselective conjugate addition to α-oxoketene dithioacetals to give β-methylthio-β-benzyl-α,β-unsaturated ketones **18**.[37,38]

In continuation of these studies on new C-C bond forming reactions by addition of carbon nucleophiles to α-oxoketene dithioacetals, it was shown that allyl magnesium bromide reacts with **1** to afford carbinol acetals **19** exclusively in excellent yields[39] (Scheme 4). The carbinol acetals **19** thus obtained underwent facile cycloaromatization in the presence of $BF_3.Et_2O$ in refluxing benzene to afford methylthio substituted aromatics **20** instead of observed solvolytic transformation.[39]



1 **19** **20**

Scheme 4

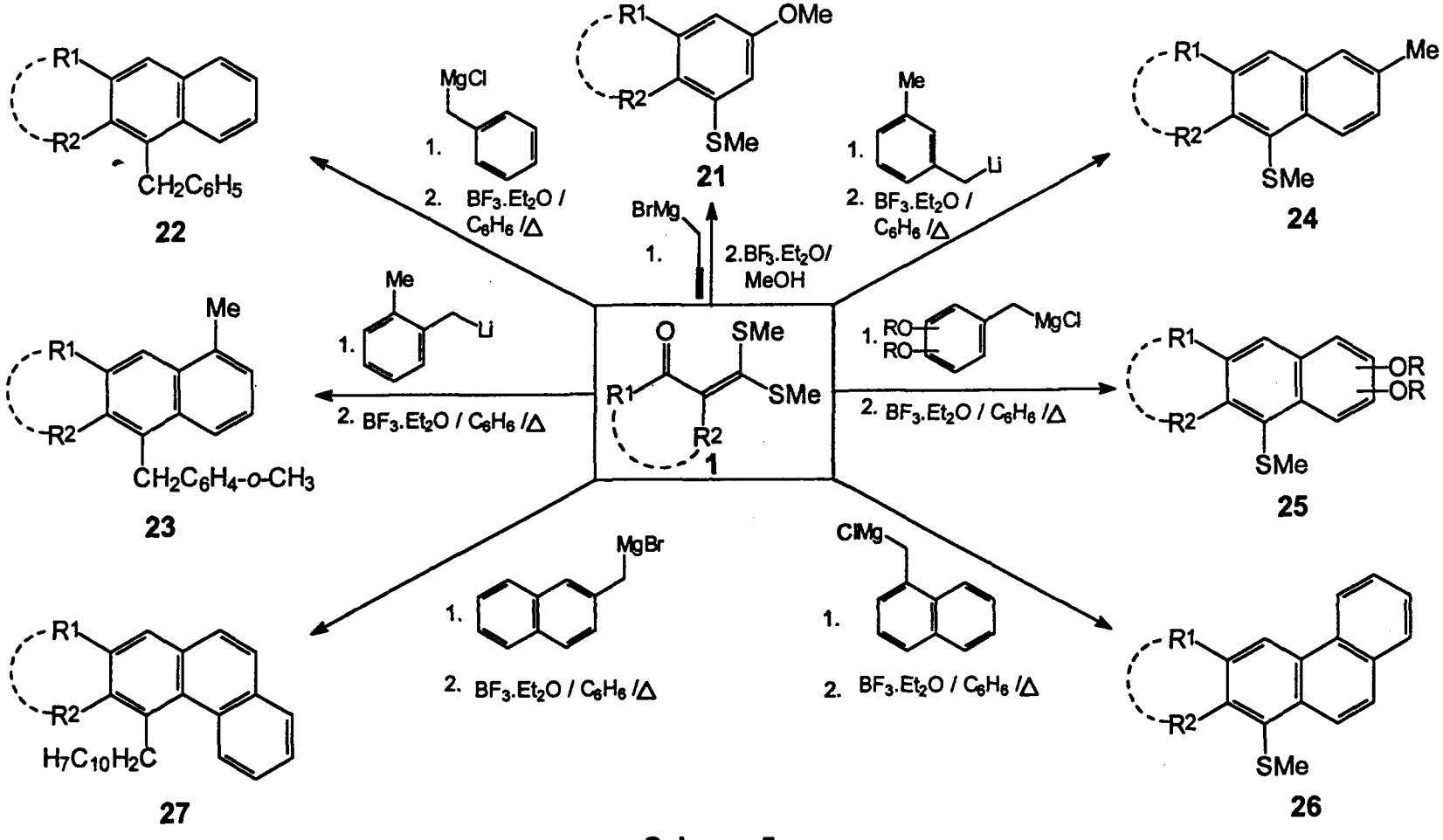
Thus, a new [3+3] aromatic annelation methodology *via* α-oxoketene dithioacetals was discovered in our laboratory and this protocol has emerged as an area of great synthetic potential.[40] This new method of aromatic annelation has been extensively investigated to establish its general applicability through the use of a large number of allyl anions as precursors of 1,3-binucleophiles and a wide variety of α-oxoketene dithioacetals as precursors of 1,3-electrophilic open chain

fragments. Some of the important synthetic outcome of this aromatic annelation methodology is outlined in scheme 5. This method is shown to be extremely versatile when extended to methylallyl magnesium chloride, crotyl magnesium bromide and propargyl magnesium bromide[41] to afford substituted benzannelated products **21**.

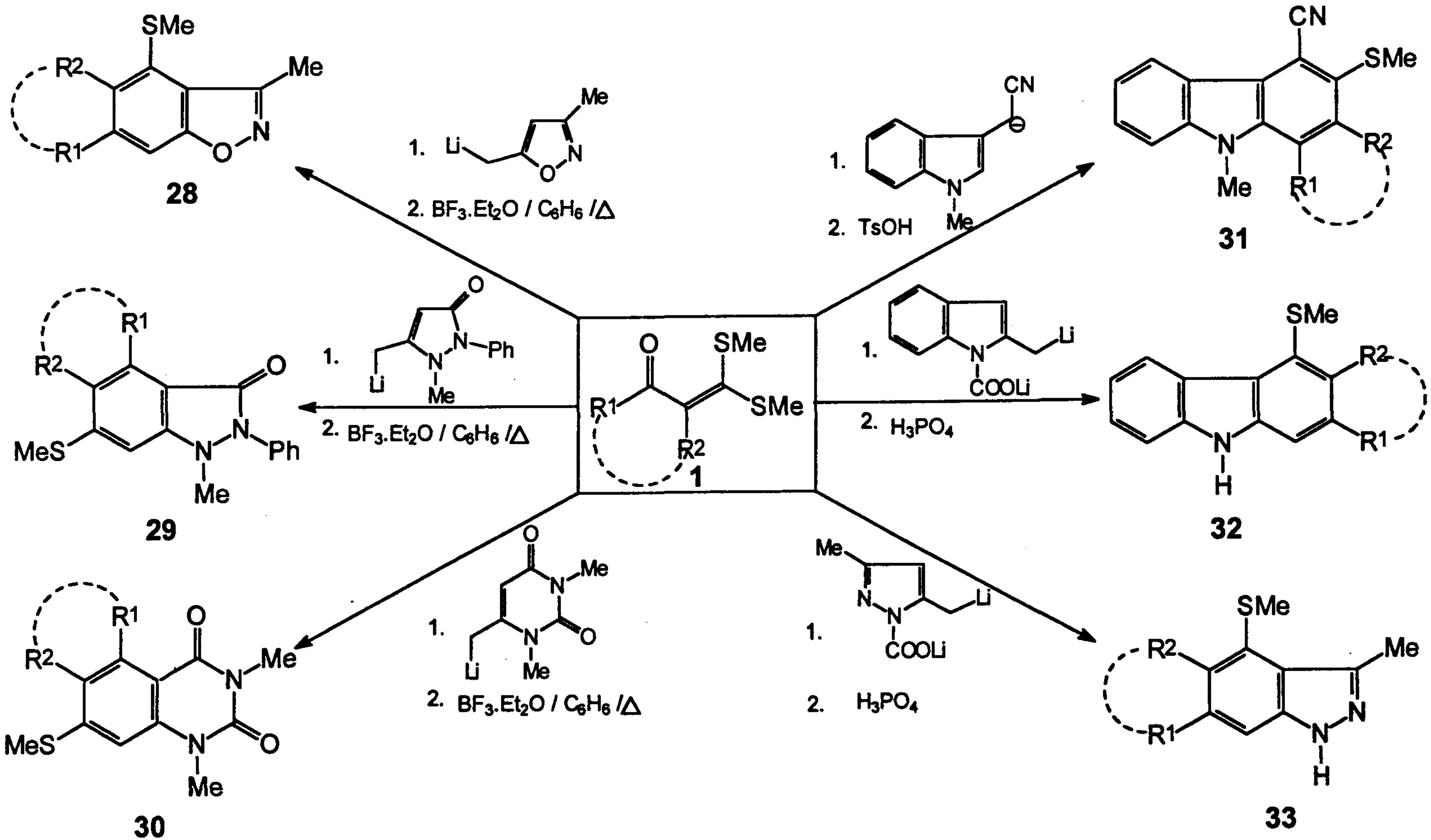
Subsequently, this method of aromatic annelation was extended to naphthannelation.[42] This transformation was achieved by reacting benzyl magnesium chloride with α-oxoketene dithioacetals to afford the intermediate carbinols which on treatment with BF_3-Et_2O yielded the corresponding naphthalene derivatives **22** through benzene ring participation.[42] Similarly *o*-xylyl lithium, *m*-xylyl lithium[43] and methoxy substituted benzyl magnesium chlorides[44] were reacted with α-oxoketene dithioacetals followed by $BF_3.Et_2O$-assisted cyclization to afford the corresponding substituted naphthalenes **23**, **24** and **25**.

The reaction was also extended to α- and β-methylnaphthyl Grignard reagents to react with various α-oxoketene dithioacetals to afford after cycloaromatization, the corresponding phenanthrenes **26**, **27** and polycondensed aromatic compounds.[45]

This aromatic annelation methodology was not only applicable for the synthesis of condensed aromatics but has also been found to be highly successful for the construction of aromatic ring over the preconstructed heterocyclic molecules, providing a new synthetic dimension to the entire chemistry of benzoheterocyclic compounds and their condensed variants. Some of the successful results are depicted in scheme 6. Thus 5-lithiomethyl-3-methylisoxazole, 3-lithiomethyl-2-methyl-1-phenyl-5-pyrazolone, 6-lithiomethyl-1,3-dimethylpyrimidine-2,4-dione were reacted with α-oxoketene dithioacetals to afford the corresponding benzisoxazoles **28**,[46] indazolones **29**[47] and quinazolones **30**[48] respectively. This methodology is of considerable synthetic importance due to the fact that a large number of heterocyclic allyl anions can be used to


R1
R2
OMe
SMe
21
MgCl
1.
2. BF3.Et2O / C6H6 /Δ
BrMg
1.
2.BF3.Et2O/ MeOH
Me
Li
1.
2. BF3.Et2O / C6H6 /Δ
CH2C6H5
22
Me
24
Me
CH2C6H4-o-CH3
23
1. BF3.Et2O / C6H6 /Δ
O
SMe
R1
R2
1
1. RO RO MgCl
2. BF3.Et2O / C6H6 /Δ
OR
OR
25
MgBr
1.
2. BF3.Et2O / C6H6 /Δ
ClMg
1.
2. BF3.Et2O / C6H6 /Δ
H7C10H2C
27
26

Scheme 5


1. BF3.Et2O / C6H6 /Δ
2. TsOH
2. BF3.Et2O / C6H6 /Δ
2. H3PO4
2. BF3.Et2O / C6H6 /Δ
2. H3PO4
28
29
30
31
32
33
1

Scheme 6

construct various benzannelated heterocyclic compounds. Recently, expedient synthesis of [*a*]-annelated carbazoles **31**,[49] [*b*]-annelated carbazoles **32**[50] and indazoles **33**[51] have been accomplished by extending this aromatic annelation methodology (Scheme 6).

Benzoheterocycles are generally synthesised by ultimate construction of the heterocyclic component onto preconstructed benzene precursors. But this aromatic annelation methodology involves the construction of the benzene ring onto a preformed heterocycle, which, in a way, is a reversal of the classical approach.

In conclusion, the α-oxoketene dithioacetals have been shown to be a class of versatile intermediates in many synthetic transformations. The success of aromatic and heteroaromatic annelation through oxoketene dithioacetals has been well established as a new general method. Further exploitation of this methodology depends on the generation of the suitably functionalized allyl anions. The versatility of all these transformations as well as further synthetic potential of α-oxoketene dithioacetals are being investigated in our laboratory.

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 it was proposed to exploit them to develop new methods for the synthesis of some benzoheterocycles.

In chapter II a new general synthesis of regioselectively substituted and condensed indoles is described. The anion derived from 1-methylpyrrole-2-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 *p*-toluene sulfonic acid in refluxing benzene to afford the corresponding indoles.

Following similar strategy, highly substituted and condensed benzo[*b*] thiophenes have been synthesised starting from thiophene-2-acetonitrile. The scope and limitations of this approach are presented in chapter III.

In Chapter IV, an attempt has been made to transform oxindole into indole derivatives *via* its corresponding ketene dithioacetal. Various Grignard reagents were reacted with 3-bis(methylthio)methylene-2,3-dihydro-1-methyl-2-oxoindole to yield indole derivatives and carbazoles. Not all the reactions were successful and in some cases unexpected products were obtained. The results of these studies are discussed in chapter IV.

REFERENCES

1. Reviews: (a) Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron* **1990**, *46*, 5423. (b) Dieter, R.K. *Tetrahedron* **1986**, *42*, 3029.
2. Thuillier, A.; Vialle. J. *Bull. Soc. Chim. Fr.* **1959**, 1398.
3. Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1962**, 2187.
4. Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1962**, 2194.
5. Saquet, M.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1966**, 1582.
6. Gompper, R.; Schmidt, R.R.; Kutter, E. *Leibig Ann. Chem.* **1965**, *684*, 37.
7. Corey, E.J.; Chen, R.H.K. *Tetrahedron Lett.* **1973**, 3817.
8. Shahak, I.; Sasson, Y. *Tetrahedron Lett.* **1973**, 4207.
9. Chauhan, S.M.S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1779.
10. Dieter, R.K. *J. Org. Chem.* **1981**, *46*, 5031.
11. Kelber, C. *Chem. Ber.* **1910**, *43*, 1252.
12. Kelber, C.; Schwarz, A. *Chem. Ber.* **1911**, *44*, 1693.
13. Kelber, C.; Schwarz, A. *Chem. ber.* **1912**, *45*, 137.
14. Spitzner, R.; Menzel, M.; Schroth, W. *Synthesis* **1982**, 206.
15. Purkayastha, M.L.; Chandrasekharam, M.; Vishwakarma, J.N.; Ila, H.; Junjappa, H. *Synthesis* **1993**, 245.
16. Gompper, R.; Schaefer, H. *Chem. Ber.* **1967**, *100*, 591.
17. Borrmann, D. in *Houben-Weyl, Methoden der. Organischen. Chemie.* 4th Ed., Muller, E. (Ed.), Vol. VII/4, Georg Thieme Verlag, Stuttgart, **1968**, 421.
18. Singh, O.M.; Junjappa, H.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3561.
19. Thomas, A.; Vishwakarma, J.N.; Ila, H.; Junjappa, H. *Tetrahedron* **1988**, *44*, 1667.
20. Saquet, M.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1966**, 3969.
21. Dieter, R.K.; Jenkitkasemwong, Y. *Tetrahedron Lett.* **1982**, *23*, 3747.

22. Dieter, R.K.; Jenkitkasemwong, Y.; Dieter, J.W. *J. Org. Chem.* **1984**, *49*, 3183.
23. Myrboh, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1983**, *48*, 5327.
24. Singh, G.; Purkayastha, M.L.; Ila, H.; Junjappa, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1289.
25. Dieter, T.K. Silks, L.A.; Fishpaugh, J.R., Kastner, M.E. *J. Am. Chem. Soc.* **1985**, *107*, 4679.
26. Dieter, R.K.; Fishpaugh, J.R.; Silks, L.A. *Tetrahedron Lett.* **1982**, *23*, 3751.
27. Myrboh, B.; Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 50.
28. Apparao, S.; Rahman, A.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1982**, *23*, 971.
29. Marino, J.P.; Kostusyk, J.L. *Tetrahedron Lett.* **1979**, *20*, 2489.
30. Marino, J.P.; Kostusyk, J.L. *Tetrahedron Lett.* **1979**, *20*, 2493.
31. Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 165.
32. Myrboh, B.; Singh, L.W.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 307.
33. Rao, Ch.S.; Chakrasali, R.T.; Ila, H.; Junjappa, H. *Tetrahedron* **1990**, *46*, 2195.
34. Rao, Ch.S.; Chandrasekharam, M.; Patro, B.; Ila, H.; Junjappa, H. *Tetrahedron* **1994**, *50*, 5783.
35. Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1986**, 744.
36. Apparao, S.; Dutta, A.; Ila, H. Junjappa, H. *Synthesis* **1985**, 169.
37. Mehta, B.K.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1995**, *36*, 1925.
38. Mehta, B.K.; Ila, H.; Junjappa, H. Unpublished results.
39. Singh, G.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1984**, *25*, 5095.
40. Junjappa, H.; Ila, H. *Phosphorus, Sulfur and Silicon* **1994**, *95-96*, 35.
41. Gupta, A.K.; Ila, H.; Junjappa, H. Tetrahedron Lett. **1987**, *28*, 1459.
42. Balu, M.P.; Singh, H.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1986**, *27*, 117.

43. Yadav, K.M.; Mahanta, P.K.; Ila, H.; Junjappa, H. *Tetrahedron* **1996**, *52*, 14049.

44. Mehta, B.K.; Ila, H.; Junjappa, H. Unpublished results.

45. Rao, Ch.S.; Balu, M.P.; Ila, H.; Junjappa, H. *Tetrahedron* **1991**, *47*, 3499.

46. Balu, M.P.; Pooranchand, D.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1988**, *29*, 501.

47. Reddy, K.R.; Roy, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1995**, *51*, 10941.

48. Satyanarayana, J.; Reddy, K.R.; Ila, H. Junjappa, H. *Tetrahedron Lett.* **1992**, *33*, 6173.

49. Patra, P.K.; Suresh, J.R.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1997**, *38*, 3119.

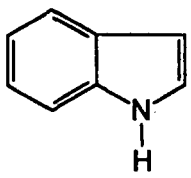
50. Syam Kumar, U.K.; Patra, P.K.; Ila, H.; Junjappa. H. *Tetrahedron Lett.* **1998**, *39*, 2029.

51. Kishore, K.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1998**, *39*, 0000.

CHAPTER II

A NEW GENERAL REGIOCONTROLLED SYNTHESIS OF HIGHLY SUBSTITUTED AND CONDENSED INDOLES VIA HETEROAROMATIC ANNELATION

Indole and its derivatives have been known since long occurring widely in nature both in plants and animals.[1-6] The indole nucleus is an integral part of a large number and wide variety of biologically active natural and unnatural compounds[4-7] and the synthesis and functionalization has been the object of research for over one hundred years.[1-6,8-16]



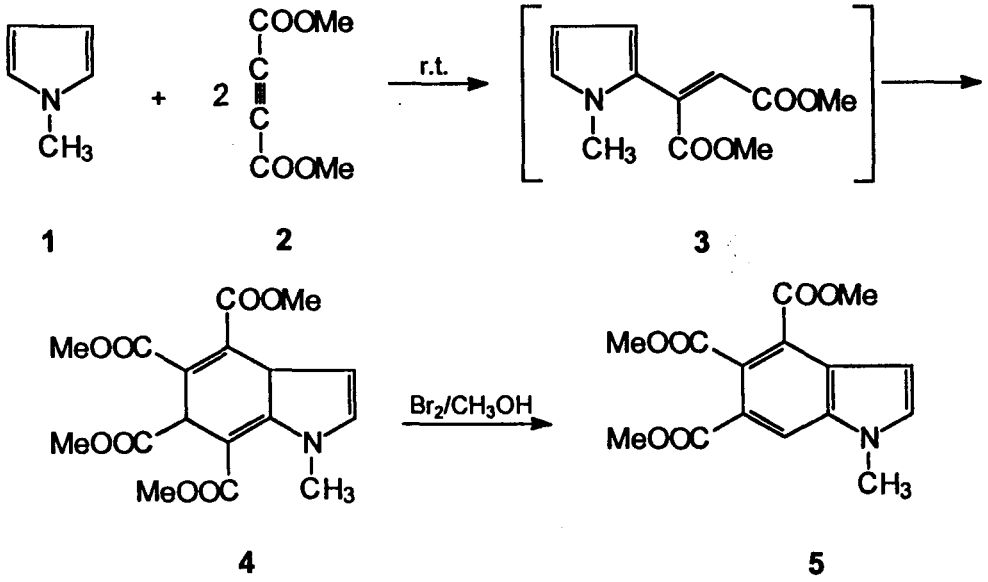
Indole

Indole was first synthesised by Baeyer in 1866.[17] He oxidised indigo to obtain isatin, reduced the isatin to dioxindole and oxindole using zinc dust, and further reduced oxindole to indole by passing its vapour over hot zinc oxide. Ever since a number of synthetic routes to indoles have been reported compared to any other heterocyclic or carbocyclic ring system.

The indole ring system is usually synthesised by constructing a pyrrole ring on to a benzene nucleus by an intramolecular ring closure of either monosubstituted or an *ortho*-disubstituted benzene precursor. Many classical methods such as Fischer, Bischler, Madelung, Reissert, Nenitzescu[11,16,18,19] and recently developed Gassman[20] and transition metals assisted methods[13,21] belong to this category. These methods are useful for the synthesis of indoles functionalized at the 2- and 3-positions which are readily installed in the ring closure sequence; however, the desired substituents at positions 4-7 must be established in the arene precursor. The other important approach involves construction of carbocycle over the pre-constructed pyrrole derivatives,[10,15,16] which in a way, is a reversal of the classical approach. This methodology is of special importance since it offers versatility in the substitution pattern of the carbocycle.

The methods reported for the synthesis of indoles are too many to be included in a brief introduction of this kind and therefore attention is drawn to the reviews for comprehensive coverage on this class of compounds.[1-6,8-16] In the present section, a brief discussion on the synthesis of indoles based on pyrroles is described. There are many approaches utilising this strategy which include (i) Diels-Alder cycloaddition of 2- or 3-vinylpyrroles, and pyrrole-2,3-quino-dimethane or its stable cyclic analogs, (ii) intramolecular electrophilic cyclization of 2- or 3-substituted pyrroles, (iii) palladium catalysed cyclocarbonylation of 2-pyrrolylallyl acetates, (iv) cycloaddition reaction of pyrrole-carbene chromium complex with alkynes and (v) miscellaneous approaches.

The earliest reaction belonging to cycloaddition category was developed by Diels and Adler[22] as described in Scheme 1. 1-Methyl pyrrole **1** was reacted with two equivalents of dimethyl acetylenedicarboxylate **2** to yield the corresponding dihydrotetramethoxyindole **4** *via* the intermediate 2-vinylpyrrole **3**. Aromatization of **4**, accomplished by the action of bromine, was reported to be accompanied by elimination of methoxycarbonyl group to yield 4,5,6-tricarbomethoxyindole **5** in good yield.

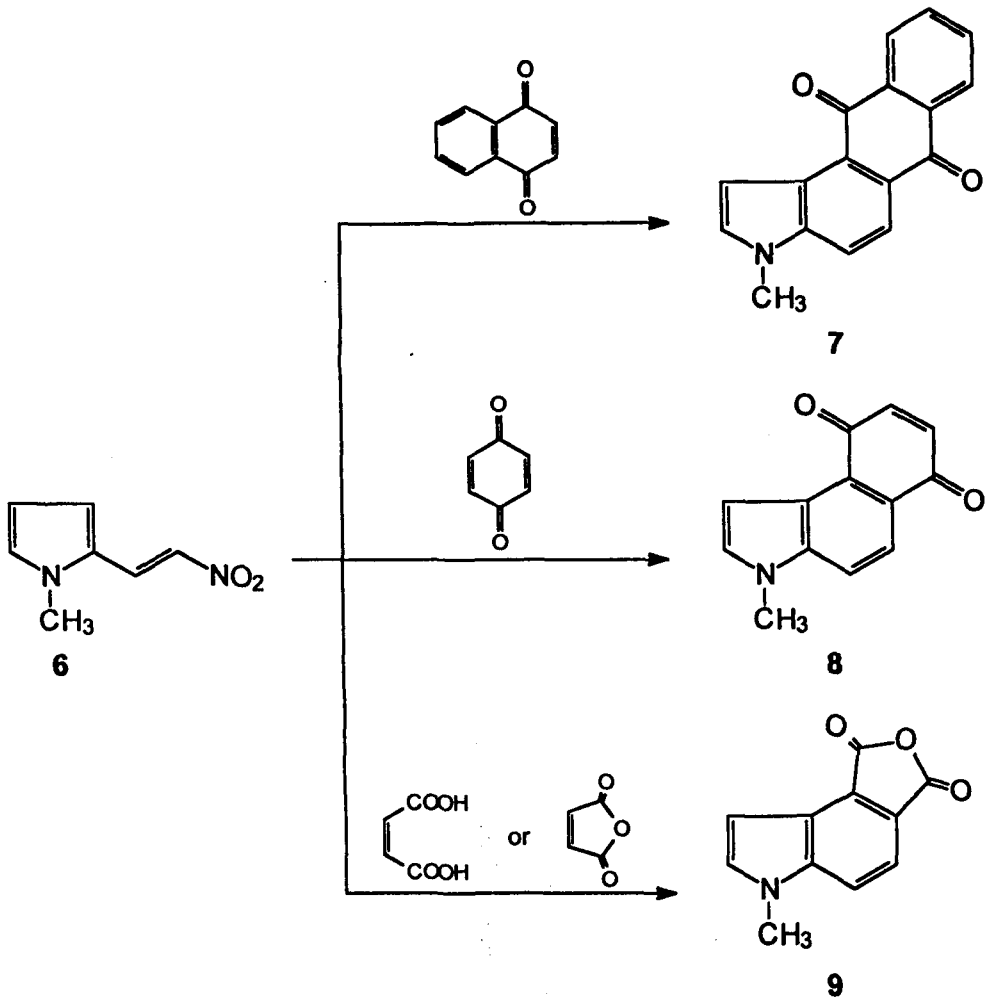


1 **2** **3** **4** **5**

Scheme 1

Hiremath and co-workers[23] reacted 1-methyl-2-nitrovinylpyrrole **6** under Diels-Alder reaction condition with various activated dienophiles to yield the respective indoles **7**, **8** and **9** in good yields (Scheme 2). The nitro group in these reactions was conveniently eliminated to afford the fully aromatized indoles.

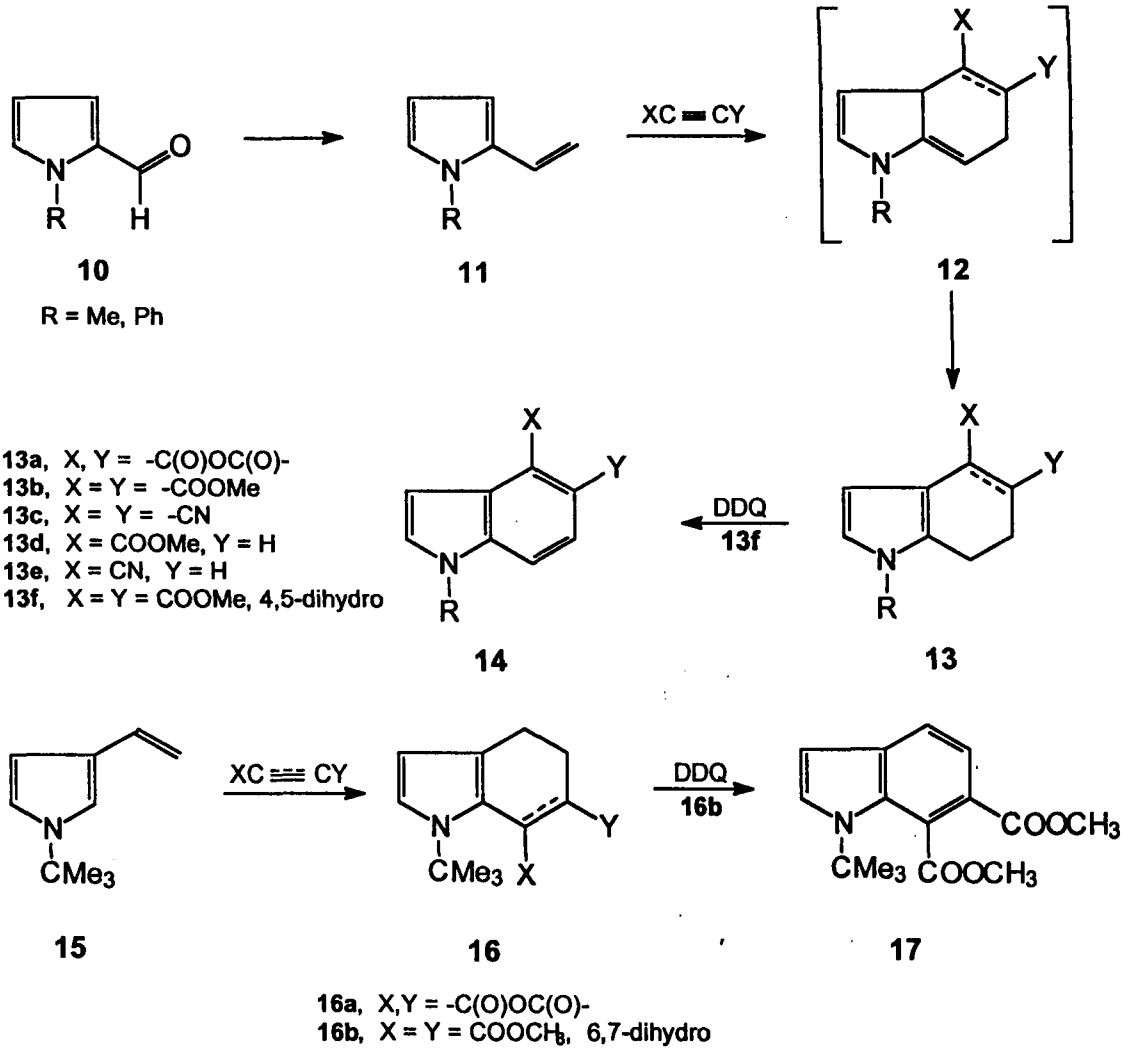
Jones and co-workers[24] prepared 1-methyl- and 1-phenyl-2-vinylpyrroles **11** by subjecting the corresponding aldehydes **10** to Wittig reaction and reacted with various dienophiles to yield the corresponding dihydro- and tetrahydroindoles **13** in 54-91% overall yields (Scheme 3). Also the isomeric dihydro- and tetrahydroindoles **16** were similarly prepared by reacting N-*t*-butyl-



Scheme 2

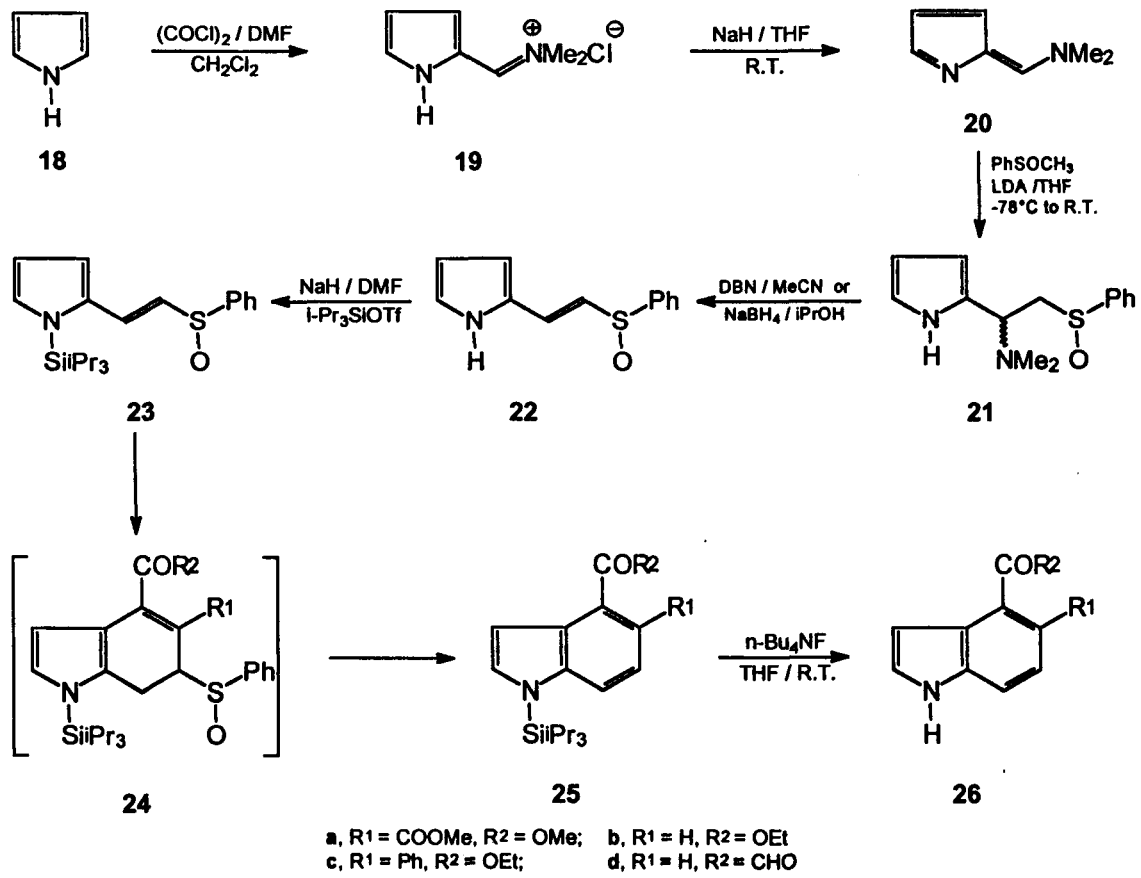
3-vinylpyrrole **15** with dienophiles. The dihydroindoles **13f** and **16b** yielded indoles **14** and **17** when treated with DDQ.

Muchowski and co-workers[25] have utilised 2-vinylpyrrole **23** for the synthesis of 4-acylindoles following [4+2] cycloaddition protocol. The required diene **23** was prepared in five steps from pyrrole as described in Scheme 4. Various dienophiles were then reacted with **23** to afford N-protected indoles **25** which on treatment with tetrabutylammonium fluoride gave the indoles **26** in good yields.



Scheme 3

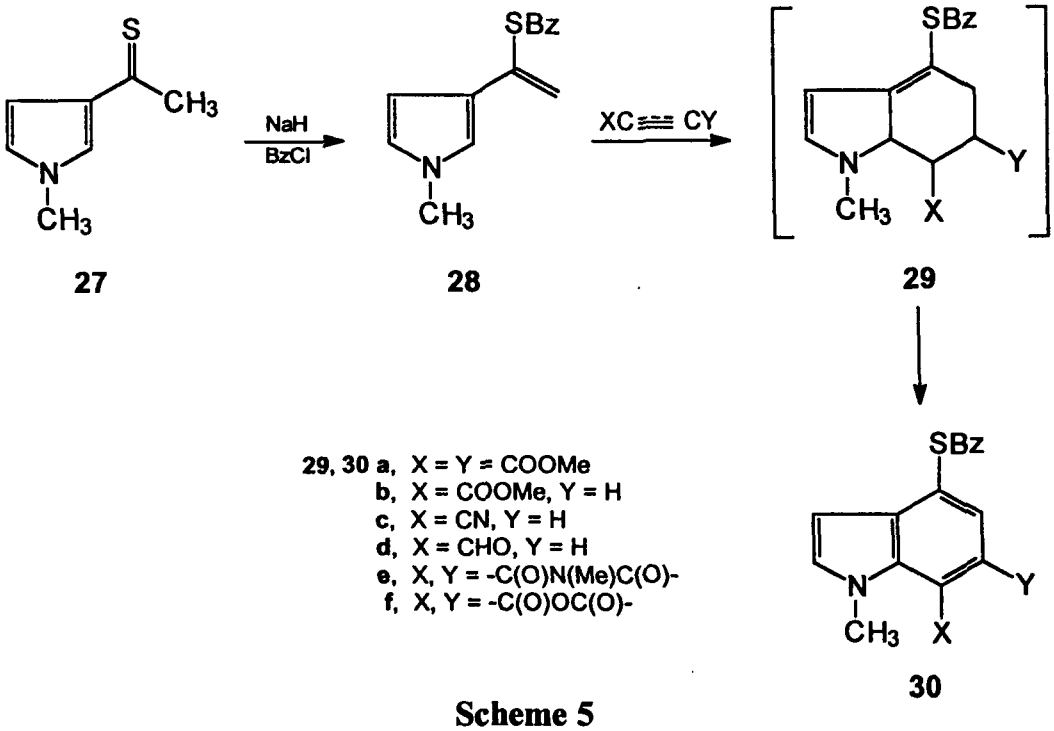
Tobinaga and co-workers[26] have prepared 1-methyl-3-vinylpyrrole **28** by alkylation of the corresponding thioketone **27** and reacted with various dienophiles to yield the corresponding tetrahydroindoles **29** which were directly transformed to the corresponding indoles **30** by treatment with DDQ (Scheme 5). However, when acetylenic esters were used as dienophiles, the corresponding indoles were formed directly.



Scheme 4

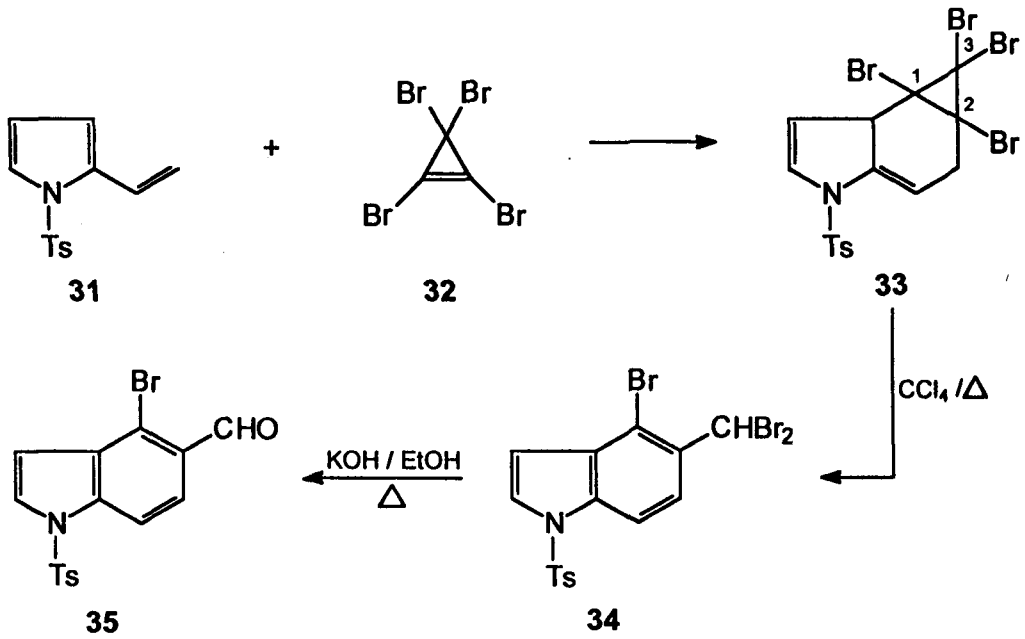
In an another interesting example, Seitz and coworkers[27] have used tetrabromocyclopropene **32** as dienophile in Diels-Alder reaction with 1-tosyl-2-vinylpyrrole **31** to give the functionalized indole **34** by selective cleavage of the C-1/C-3 bond of the intermediate **33**. Compound **34** was converted to the corresponding carbaldehyde by treatment with KOH in ethanol (Scheme 6).

Recently Harman and coworkers[28] have developed an efficient method for the synthesis of 4,5-η^2-β-Os(II)pentaammine-3-vinylpyrrole complexes **37** from the corresponding 1-methylpyrrole complex **36** by an electrophilic addition at C-3 of the pyrrole ring (Scheme 7). Four independent synthetic routes to β-vinylpyrrole complexes are described each introducing different functionality on the pendent double bond. These vinylpyrrole complexes have been shown to



27 28 29 30

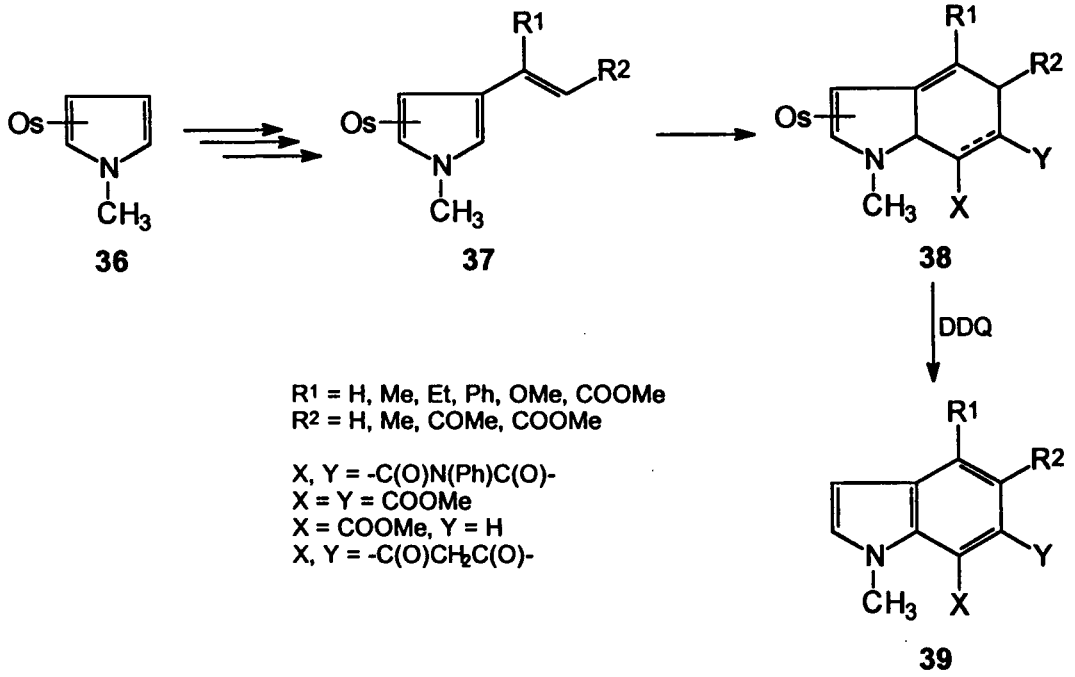
Scheme 5



31 32 33 34 35

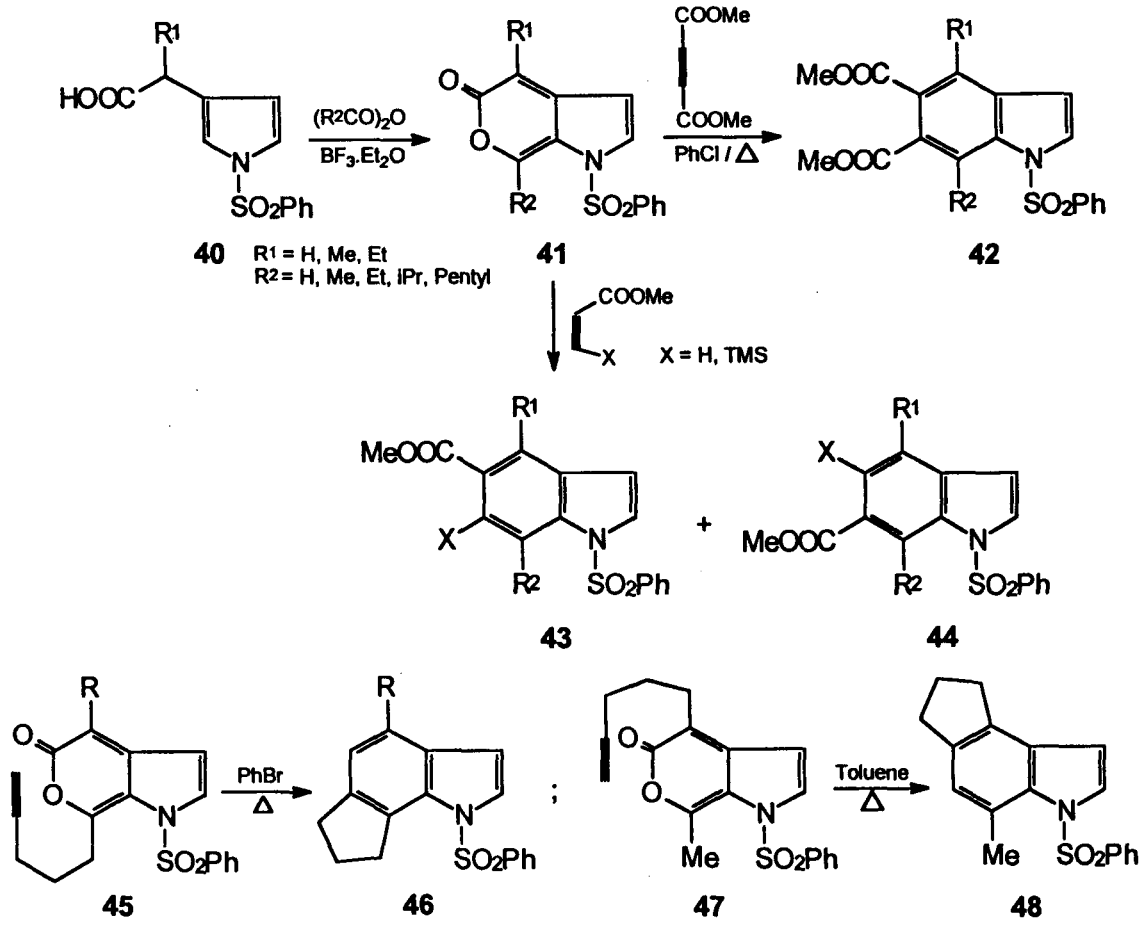
Scheme 6

undergo ready Diels-Alder reaction with suitably activated dienophiles to afford 5,6,7,7a-tetrahydroindole complexes **38**. These tetrahydroindole complexes were then decomplexed and oxidised with DDQ to afford a series of highly functionalized indoles **39**.



Scheme 7

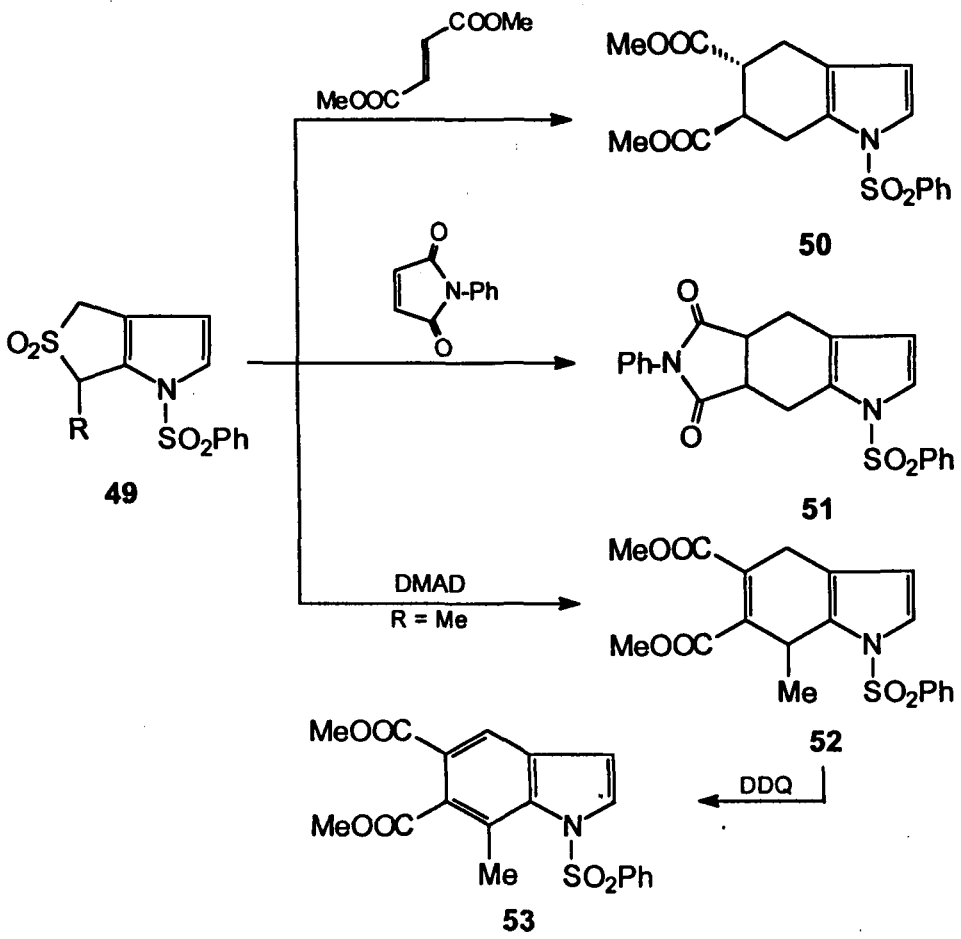
Pyrano[3,4-*b*]pyrrol-5-(1*H*)-one and their derivatives **41** are considered to be stable cyclic analogs of pyrrole-2,3-quinodimethane which are potential Diels-Alder dienes. The intermediates **40** have been successfully prepared by Moody and co-workers[29] and reacted with dimethylacetylene dicarboxylate to yield the corresponding indoles **42** in good yields (Scheme 8). The diene **41** was also reacted with unsymmetrical acetylenic esters to give indoles as a mixture of isomers **43** and **44**. The methodology is quite efficient for the construction of cyclopentaindoles **46** and **48** by intramolecular Diels-Alder reaction as shown in Scheme 8.



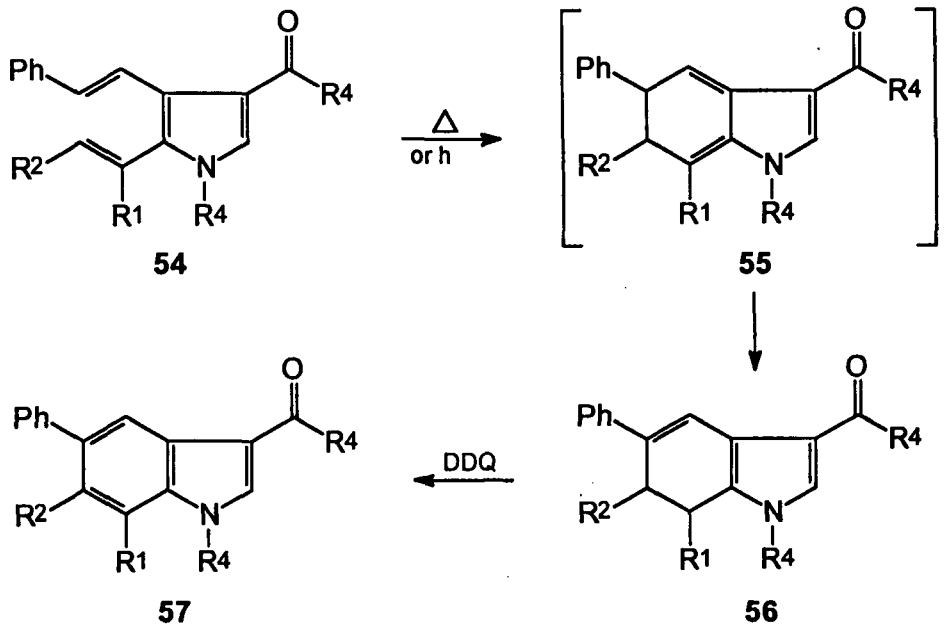
Scheme 8

Chou and Chang[30] have generated pyrrole-2,3-quinodimethane *in situ* by thermolysis of pyrrole-3-sulfolanes **49** and trapped with various dienophiles to yield the corresponding tetrahydro- and dihydroindoles **50-53** as shown in Scheme 9.

Electrocyclization route for the synthesis of indoles has been developed by Leusen and co-workers.[31] The strategy involves thermal or photochemical electrocyclization of 2,3-dialk-1`-enylpyrroles **54** to give the dihydroindoles **56** followed by dehydrogenation using DDQ to yield the corresponding indoles **57** (Scheme 10).



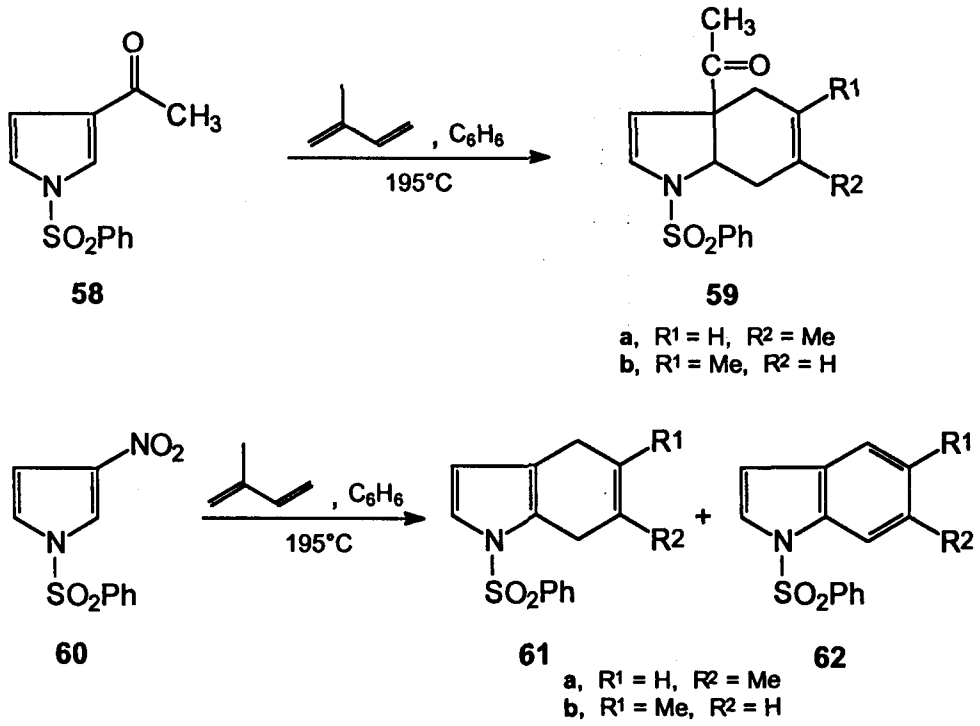
Scheme 9



R^1, R^2 = $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, Me & H
R^3 = Ph, OMe; R^4 = H, Me.

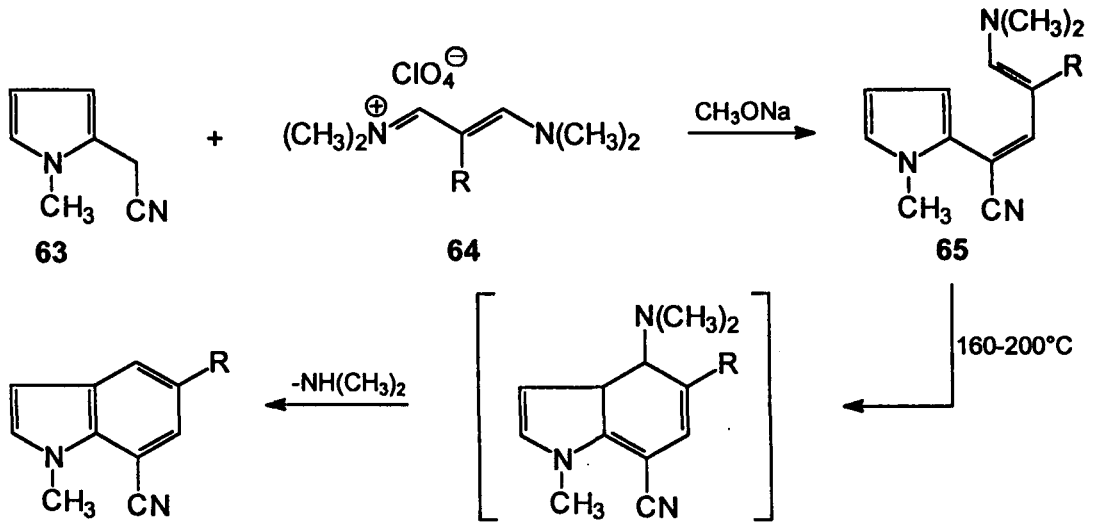
Scheme 10

Wenkert and co-workers[32] have developed a novel Diels-Alder approach for the synthesis of indoles. In this strategy, unlike the above mentioned examples, N-sulfonylpyrrole substituted with electron withdrawing groups at C-3 have been used as dienophiles (Scheme 11). Thus 3-acetyl-1-phenylsulfonyl-pyrrole **58** was reacted with isoprene to afford a 1:1 mixture of the adducts **59a** and **59b** in 51% yield. Similarly, when 1-phenylsulfonyl-3-nitropyrrole **60** was reacted with isoprene, a four-component, 6:2:3:1 mixture of dihydroindoles **61a** and **61b** and indoles **62a** and **62b** in 49% yield. Oxidation of the dihydroindoles **61** with p-quinone gave the corresponding indoles **62** in 91% yield.



Scheme 11

The next approach[33] for the construction of indoles involves thermal cyclization of 5-dimethylamino-2-(1-methyl-2-pyrrolyl)-2,4-pentadienonitriles **65**. The intermediates **65** were prepared by the reaction of 1-methylpyrrole-2-acetonitrile **63** with trimethinimium perchlorates **64** in the presence of sodium methoxide (Scheme 12).

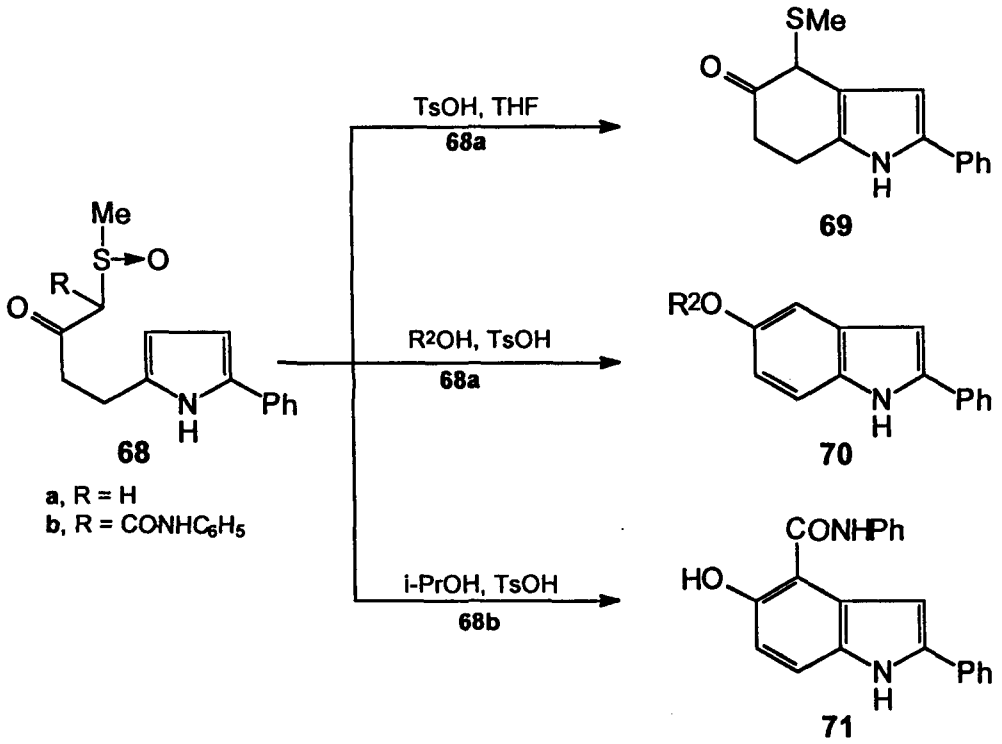


R = H, CH_3, OCH_3, Ph, CH_2Ph

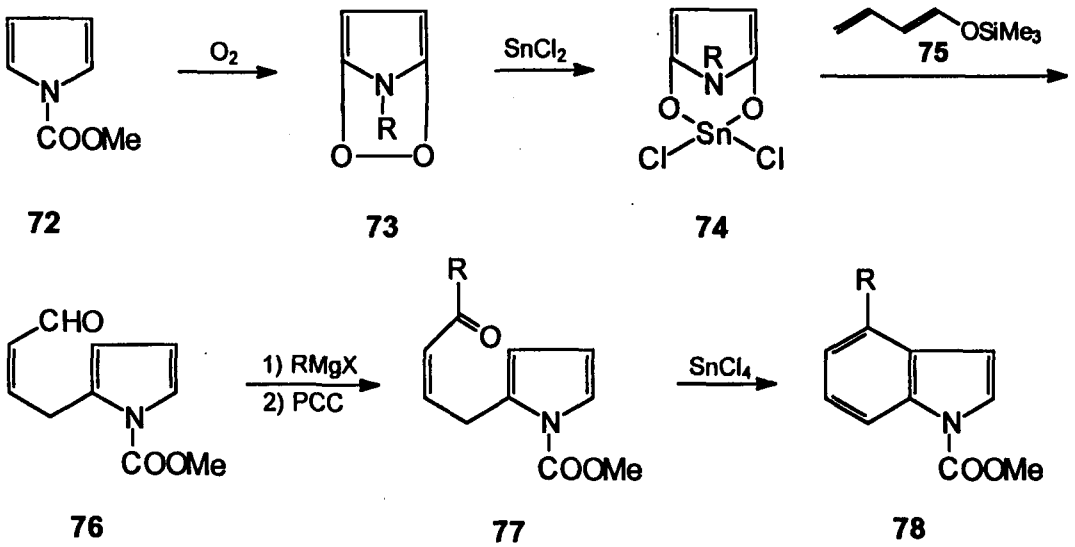
Scheme 12

Yonemitsu and co-workers[34] have reported a facile method for indoles involving acid catalysed cyclization of β-ketosulfoxides **68** as shown in Scheme 13. Two types of compounds, tetrahydroindol-5-one **68** and aromatized compounds **70** & **71** are obtained separately by the choice of the reaction conditions (Scheme 13).

A convenient synthesis of 4-alkylindoles was developed Natsume *et al.*[35] as shown in Scheme 14. N-Methoxycarbonylpyrrole **72** was photooxygenated and endoperoxide **73** thus obtained was condensed with trimethylsilylether **75** by the help of stannous chloride to afford 2-substituted pyrrole derivative **76** which on treatment with stannic chloride afforded 1-methoxycarbonylindole **78** (R=H). The corresponding 4-alkylindoles were synthesized by reacting **76** with Grignard reagents followed by pyridinium chlorochromate oxidation to afford **77** which on acid catalysed cyclization gave the corresponding 4-alkylindoles **78** (Scheme 14).

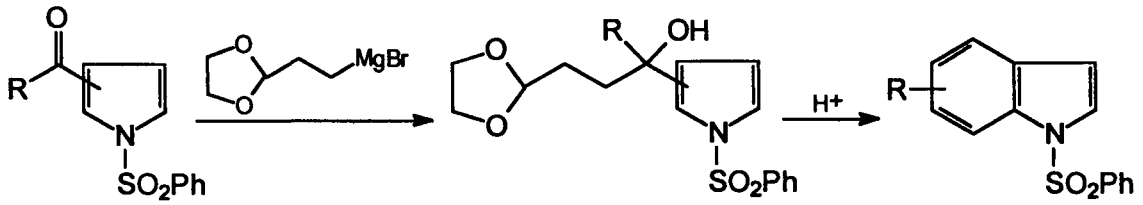


Scheme 13



Scheme 14

Another approach (Natsume *et al.*[36]) to constructions of side chain appropriate for annelation of pyrroles to indoles involves addition of Grignard reagents derived from 2-(2-bromoethyl)dioxolane to 1-sulfonyl 2- or 3-acylpyrrole **79**. Acid catalysed cyclization of the resulting intermediates **80** affords the corresponding 4- or 7-alkylindoles **81** (Scheme 15).



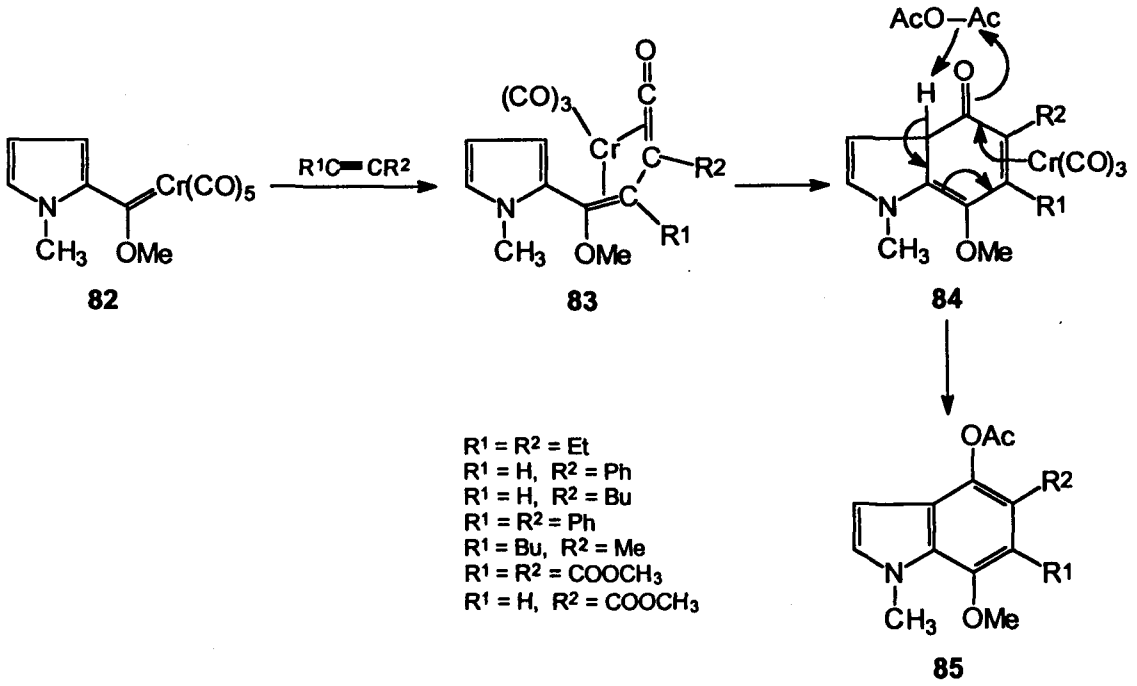
79 **80** **81**

Scheme 15

Natsume and coworkers have throughly exploited the above two strategies (Schemes 14 and 15) for the synthesis of a numbers of different indoles and related natural products.[37]

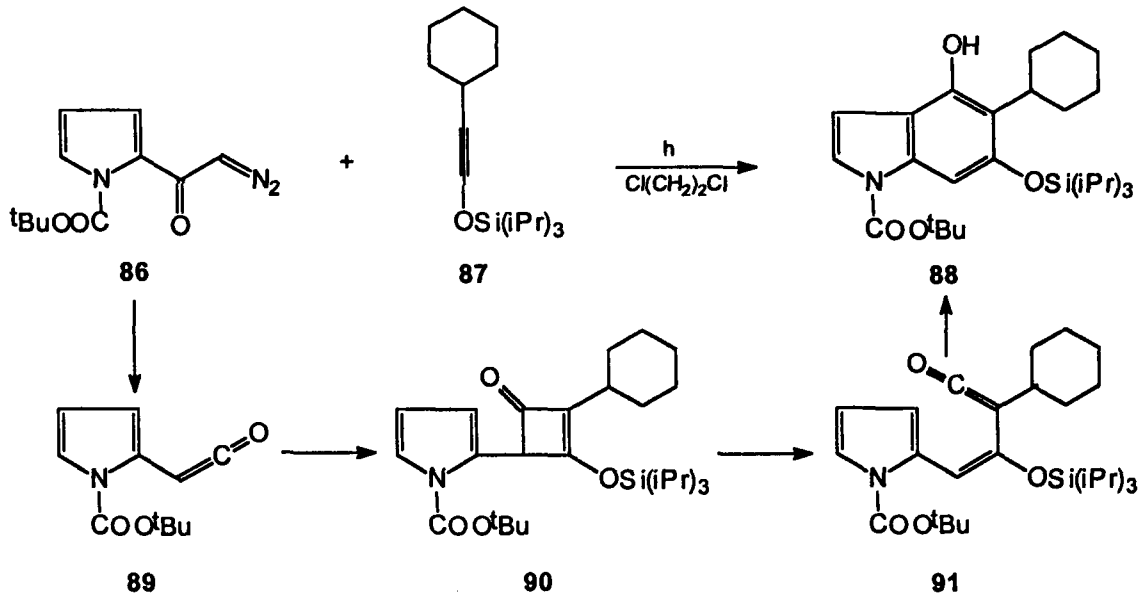
Cycloaddition reaction of pyrrole-carbene chromium complex **82** with alkynes in the presence of acetic anhydride and triethylamine provides another method for the construction of indoles (Scheme 16).[38]

An interesting annulation method for the synthesis of substituted indole **88** has been developed by Danheiser and co-workers[39] as described in Scheme 17. The annulation is achieved by irradiation of a dichloroethane solution of diazoketone **86** and acetylene **87**. Mechanistically the reaction proceeds *via* photochemical Wolff rearrangement of the diazoketone to generate arylketene **89** followed by cascade of three pericyclic reactions (Scheme 17).



82 83 84 85

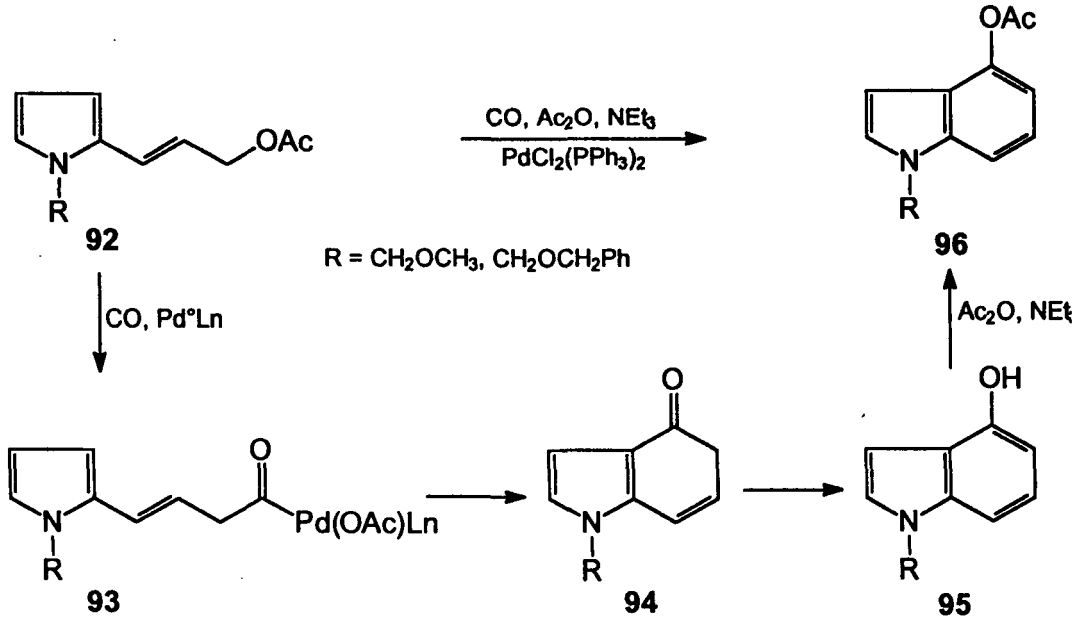
Scheme 16



86 87 88 89 90 91

Scheme 17

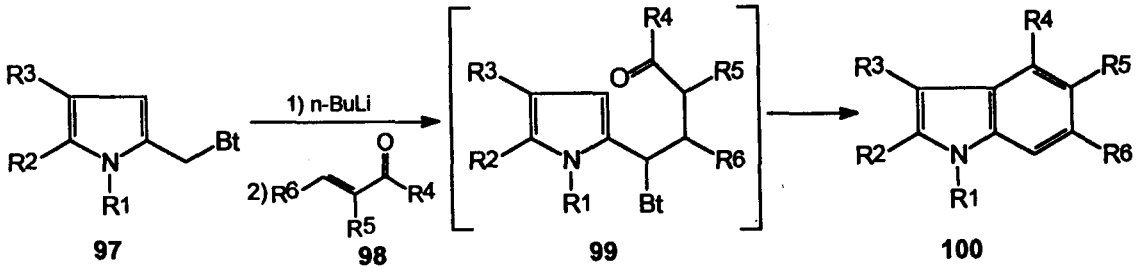
Hidai *etal.*[40] have reported synthesis of 4-acetoxyindoles **96** by cyclocarbonylation of 2-pyrrolylallylacetates **92** in the presence of acetic anhydride, triethylamine and a catalytic amount of $PdCl_2(PPh_3)_2$ at 130-170°C under 50-70 atm. of carbon monoxide (Scheme 18).



Scheme 18

Recently Katritzky and co-workers[41] have developed an efficient method for polysubstituted indoles using substituted 2-(benzotriazol-1-ylmethyl)pyrroles **97**. Compound **97** on lithiation followed by reaction with α,β-unsaturated aldehydes and ketones **98** gave the corresponding addition products **99**. These 1,4-adducts on treatment with acidic resin (Amberlyst 15^R) underwent dehydrobenzotriazolization-cyclodehydration to afford the corresponding indoles **100** in good yields (Scheme 19).

In conclusion, it may be inferred that the use of pyrrole derivatives as a starting precursor for the synthesis of indoles has been well attempted. Two major approaches have been used; (i) Diel-Alder cycloaddition approach and



Bt = 1-Benzotriazolyl; R 1 = H, n-Bu, t-Bu, $(CH_2)_2OMe$, CH_2Ph; R2 = H, Me
R 3 = Me, Ph; R 4 = H, Me, Ph; R 5 = H, Ph; R 6 = H, Et, Ph

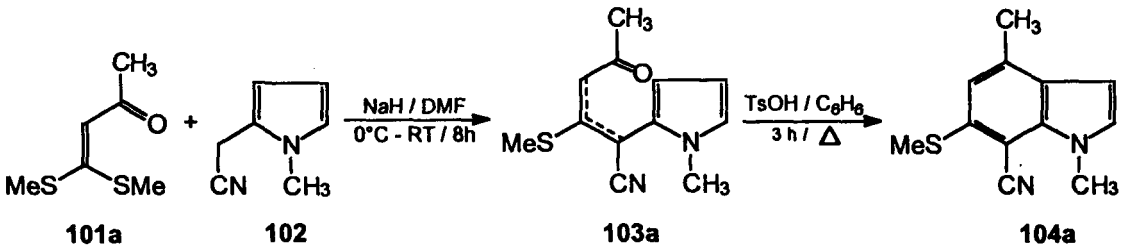
Scheme 19

(ii) intramolecular electrophilic cyclization approach. The first methodology suffers from the difficulties associated with the oxidation of the resulting dihydro- and tetrahydroindoles and also in many cases the dienophiles must be symmetrical in order to control the regiochemistry. In the later methodology, even though the indolization steps appear to be more facile, the preparation of the corresponding starting materials involve multistep processes resulting in overall poor yields. It is therefore necessary to discover efficient methods for the synthesis of this class of compounds. We have made a very successful attempt to develop a facile general route for the synthesis of regiospecifically substituted and annelated indoles. The results are presented in the following section.

RESULTS AND DISCUSSION

A brief review of literature on the synthesis of indoles using pyrrole derivatives as precursor has been described in the preceding section. As a part of the ongoing programme on heteroaromatic annelation protocol developed in our laboratory it was considered of interest to extend this methodology for the *synthesis of indoles by reacting 1-methylpyrrole-2-acetonitrile with various* α-oxoketene dithioacetals under the heteroaromatic annelation protocol. Thus a new general method for the synthesis of indoles has been developed and scope and limitations of this methodology is described as follows.

In a typical experiment, 1-methylpyrrole-2-acetonitrile **102** was reacted with α-oxoketene dithioacetal **101a** derived from acetone in the presence of sodium hydride in dry dimethylformamide at ice cold temperature for 8 hours and the reaction mixture after work-up yielded a product **103a** arising out of addition-elimination sequence of pyrrole-2-acetonitrile anion to **101a** in 1,4-fashion. The yield of this product was quantitative. It was attempted to purify the sample for analysis by passing through silica gel column chromatography and the product was found to under go cyclization to afford 7-cyano-1,4-dimethyl-6-(methylthio)indole **104a**. Thus it was decided to cyclize the intermediate **103a** without purification and characterization. The crude intermediate **103a** when treated with *p*-toluene sulfonic acid in refluxing benzene for 3 hours, the starting



101a **102** **103a** **104a**

Scheme 20

material was completely disappeared and indole **104a** was formed. It was purified by passing through silica gel column using hexane-ethyl acetate (97:3) as eluent to obtain **104a** as colourless crystals (m.p. 110-111°C) in 86% yield. The structure of the compound was established by analytical and spectral data as given below.

IR (KBr): ν_{max} 2200, 1583 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H), 2.58 (s, 3H), 4.10 (s, 3H), 6.47 (d, J=3.2 Hz, 1H), 6.93 (s, 1H), 6.99 (d, J=3.2 Hz, 1H).

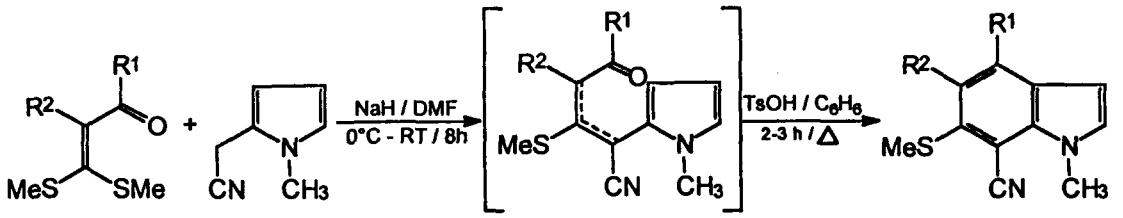
^{13}C NMR (75 MHz): δ 17.94, 19.09, 34.94, 100.35, 116.97, 120.61, 128.28, 130.77, 135.41, 136.35, 137.80.

MS: *m/z* 216 (M^+, 100%).

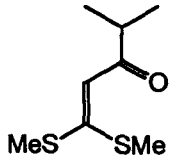
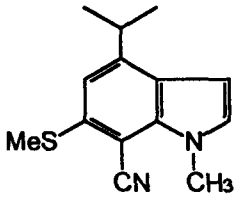
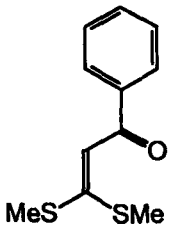
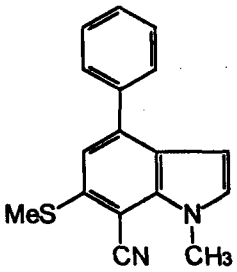
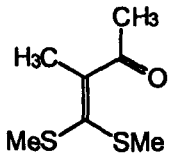
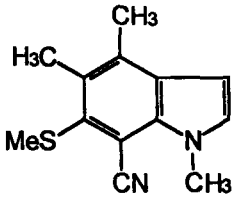
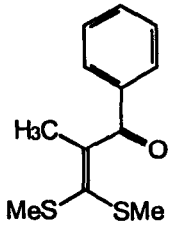
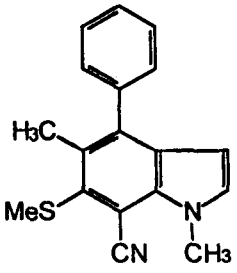
Anal. Calcd. for $C_{12}H_{12}N_2S$ (216.307): C, 66.63; H, 5.59; N, 12.95%. Found: C, 66.92; H, 5.36; N, 13.16%.

Similarly the corresponding 4-isopropyl- (**104b**), 4-phenyl- (**104c**), 4,5-dimethyl- (**104d**), 5-methyl-4-phenyl- (**104e**) indoles were prepared in 72-82% overall yields by reacting **102** with various α-oxoketene dithioacetals **101b-e** derived from isopropyl methyl ketone, acetophenone, ethyl methyl ketone and propiophenone respectively under the described reaction conditions. The structures of all these indoles are fully established by their analytical and spectral data which are given in the experimental section.

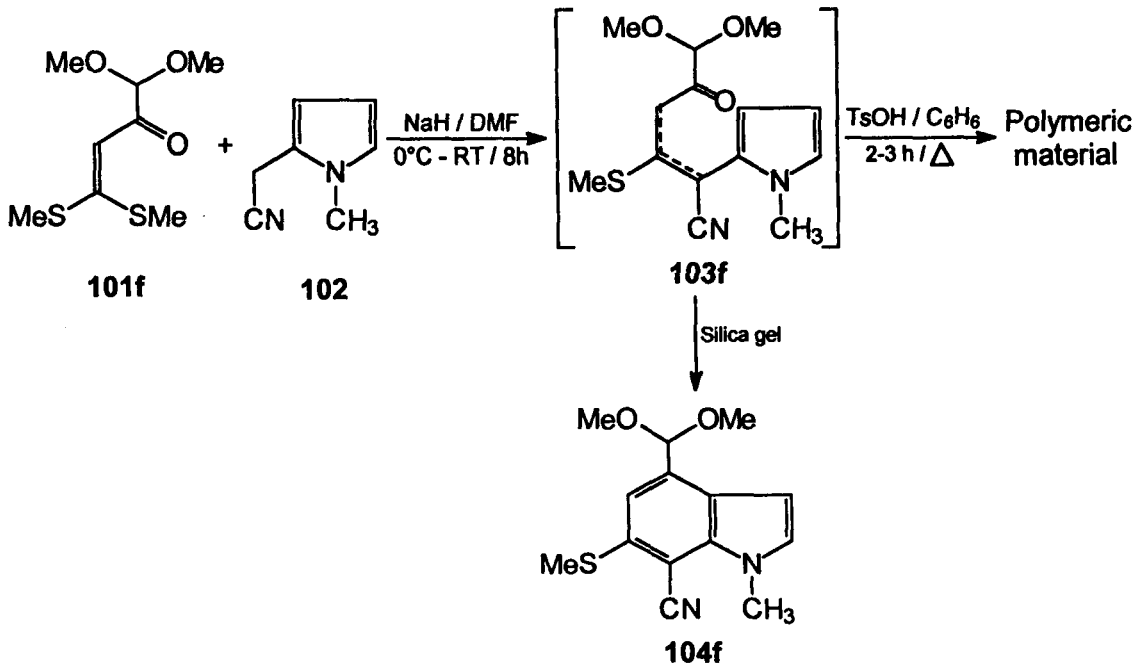
The oxoketene dithioacetal derived from pyruvaldehyde dimethylacetal **101f** was also reacted with **102** to afford the corresponding adduct **103f** which yielded only an insoluble polymeric solid instead of indole **104f** when treated with *p*-toluenesulfonic acid in refluxing benzene. However, the intermediate **103f** underwent facile cyclization when passed through silica gel column to yield the expected indole **104f** in 68% yield. The compound was fully characterized by its spectral and analytical data.



101 102 103 104

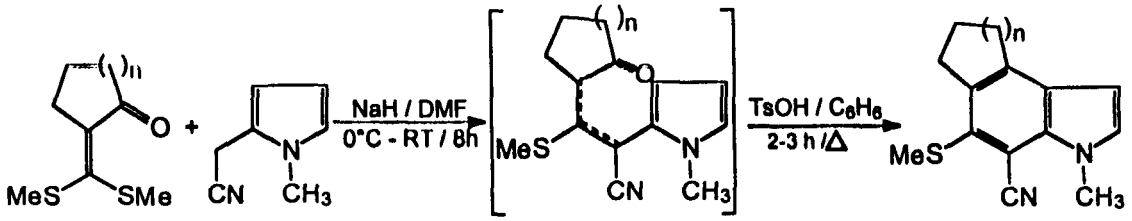
S,S-Acetal	Indole	Yield %
 **101b**	 **104b**	72
 **101c**	 **104c**	85
 **101d**	 **104d**	88
 **101e**	 **104e**	76

Scheme 21

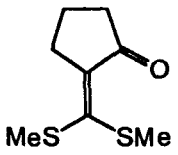
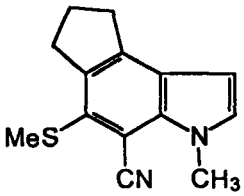
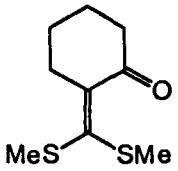
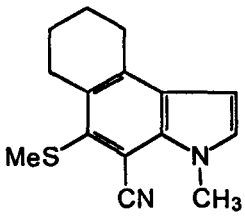
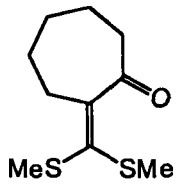
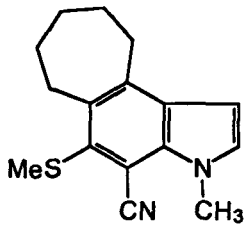


Scheme 22

This facile method was successfully extended for the synthesis of 4,5-annelated indoles **107a-c** by the reaction of **102** with cyclic oxoketene dithioacetals of general formula **105**. The oxoketene dithioacetals derived from cyclopentanone **105a**, cyclohexanone **105b**, and cycloheptanone **105c** were reacted with **102** as described earlier to get the corresponding addition-elimination products **106a-c** in near quantitative yields. The intermediates **106a-c** were then cyclized in the presence of *p*-toluene sulfonic acid in refluxing benzene for 2-3 hours to yield after work up the corresponding 4,5-annelated-7-cyano-1-methyl-6-(methylthio)indoles **107a-c** in 68-78% overall yields. The structures of these compounds were established on the basis of their spectral and analytical data which are presented in the experimental section.

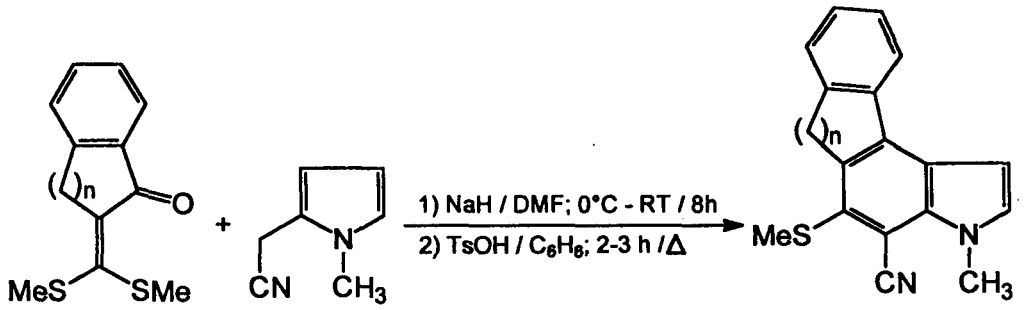


105 102 106 107

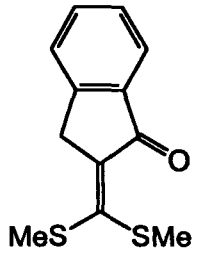
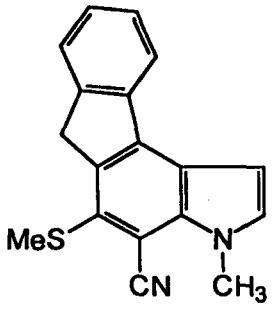
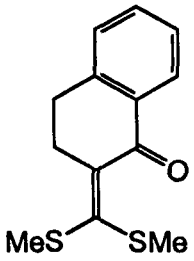
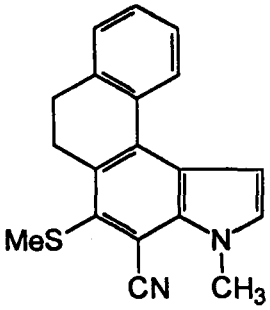
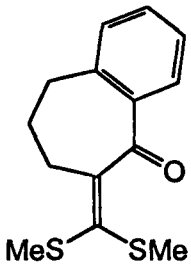
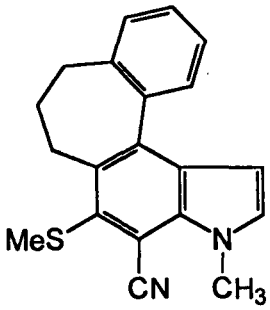
S,S-Acetal	Indole	Yield %
 105a	 107a	74
 105b	 107b	68
 105c	 107c	78

Scheme 23

The reaction was further extended to cyclic ketene dithioacetals derived from 1-indanone **108a**, 1-tetralone **108b** and 1-benzosuberone **108c** to react with pyrrole-2-acetonitrile **102** under aforementioned reaction conditions to afford the corresponding condensed indoles **109a-c** in 66-82% overall yields. The spectra and analytical data of these compounds are in conformity with the assigned structures.

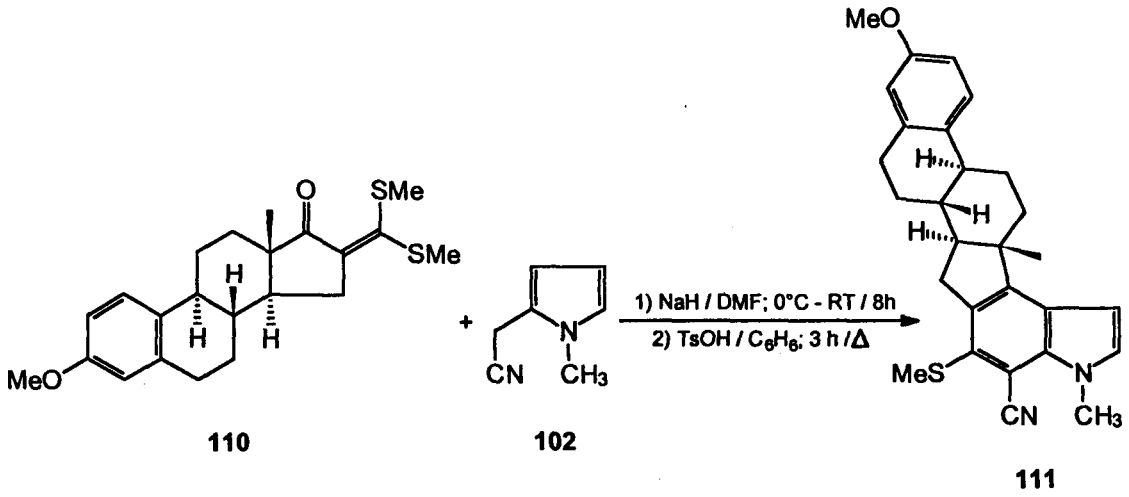


108 **102** **109**

S,S-Acetal	Indole	Yield
 **108a**	 **109a**	82
 **108b**	 **109b**	66
 **108c**	 **109c**	72

Scheme 24

In an another interesting experiment, oxoketene dithioacetal derived from estrone methylether **110** was reacted with pyrrole-2-acetonitrile **102** under similar experimental conditions to afford the corresponding 7-cyano-3-methoxy-1-methyl-6-(methylthio)indolo[17,16-*e*]estra-1,3,5(6)-triene **111** in 74% yield ($[\alpha]^{23}_D$ = +49° (c=0.48, dioxane)). This example demonstrates the efficacy of this method to achieve direct synthesis of optically active indoles which can be called synthetic alkaloids. The oxoketenedithioacetals derived from any optically active methylene ketones should, in principle, yield the optically active indole derivatives.

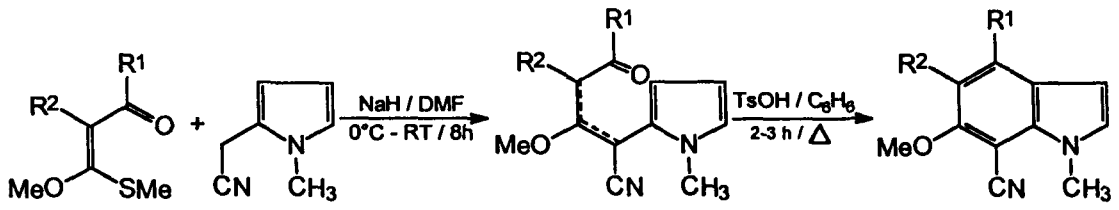


110 **102** **111**

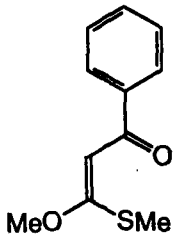
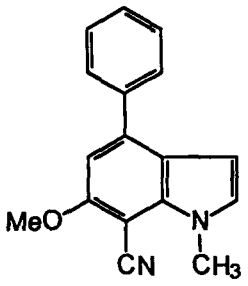
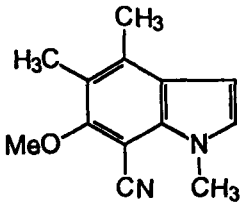
Scheme 25

In the above examples, the indole molecules prepared carry the methylthio group in 6-position. 6-Oxygenated indoles are very important since many indole alkaloids contain this functionality. It was therefore decided to prepare oxoketene-O,S-acetals and react with pyrrole-2-acetonitrile so that the product indoles carry methoxy group in 6-position thus providing an efficient method for the synthesis of 6-methoxyindoles. The required O,S-acetals were prepared by reacting the corresponding methylene ketones with methyl xanthate in the presence of base followed by alkylation according to our earlier reported

method.[50] The O,S-acetal **112a** derived from acetophenone was reacted with **102** as described earlier and the addition-elimination product **113a** was directly cyclized without characterization to yield the corresponding 7-cyano-6-methoxy-1-methyl-4-phenylindole **114a** in 80% yield. Similarly the O,S-acetal derived from ethyl methyl ketone **112b** was reacted with **102** under similar reaction protocol to yield the corresponding 7-cyano-6-methoxy-1,4,5-trimethylindole **114b** in 86% yield. The structure of both **114a** and **114b** were established on the basis of their analytical and spectral data.



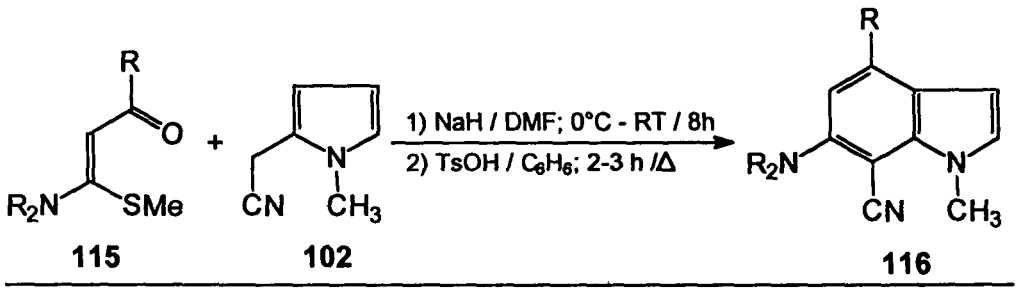
112 **102** **113** **114**

O,S-Acetal	Indole	Yield %
 **112a**	 **114a**	80
 **112b**	 **114b**	86

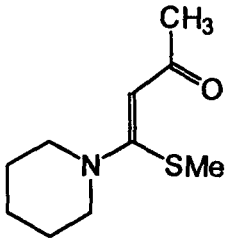
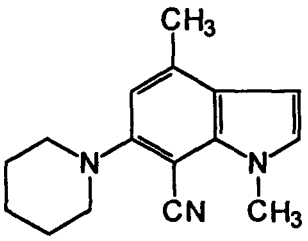
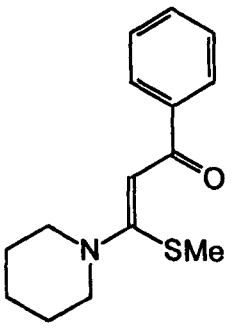
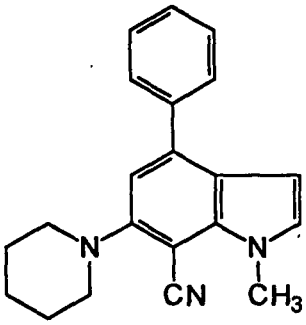
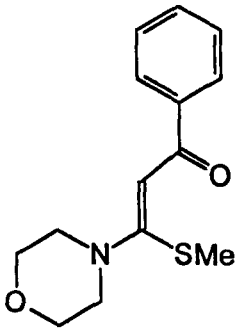
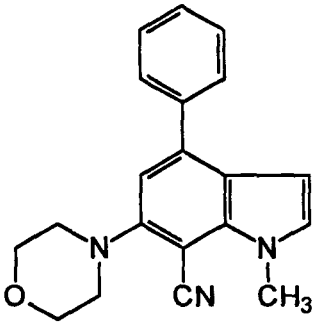
Scheme 26

The method was found to be equally versatile for the synthesis of 6-aminoindoles. Thus the oxoketene-N,S-acetals **115a-c** were reacted with **102** and

cyclized following the earlier reaction protocol to yield the corresponding aminoindoles **116a-c** in 65-73% overall yields.



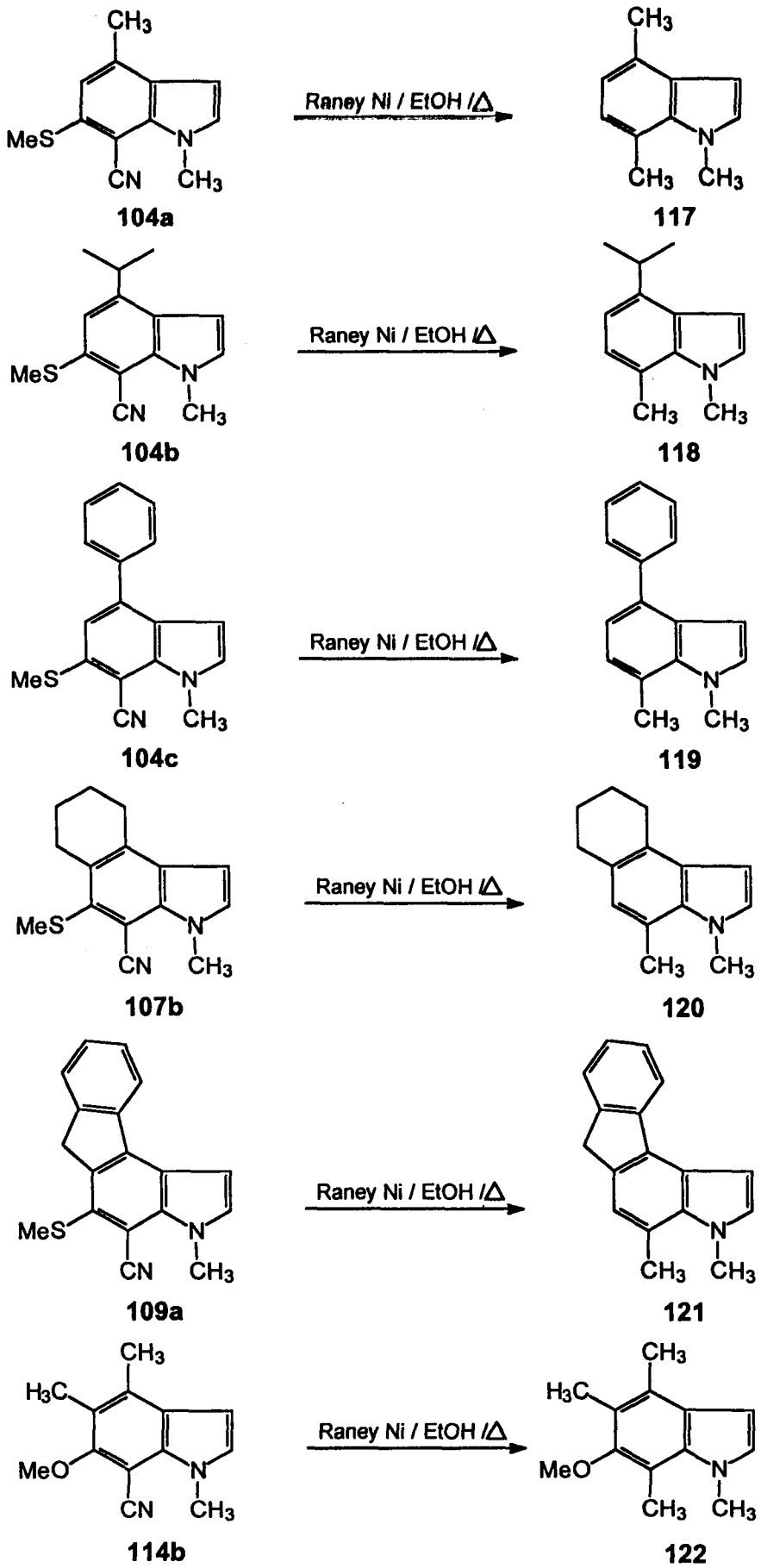
115 **102** **116**

N,S-Acetal	Indole	Yield
 **115a**	 **116a**	65
 **115b**	 **116b**	70
 **115c**	 **116c**	73

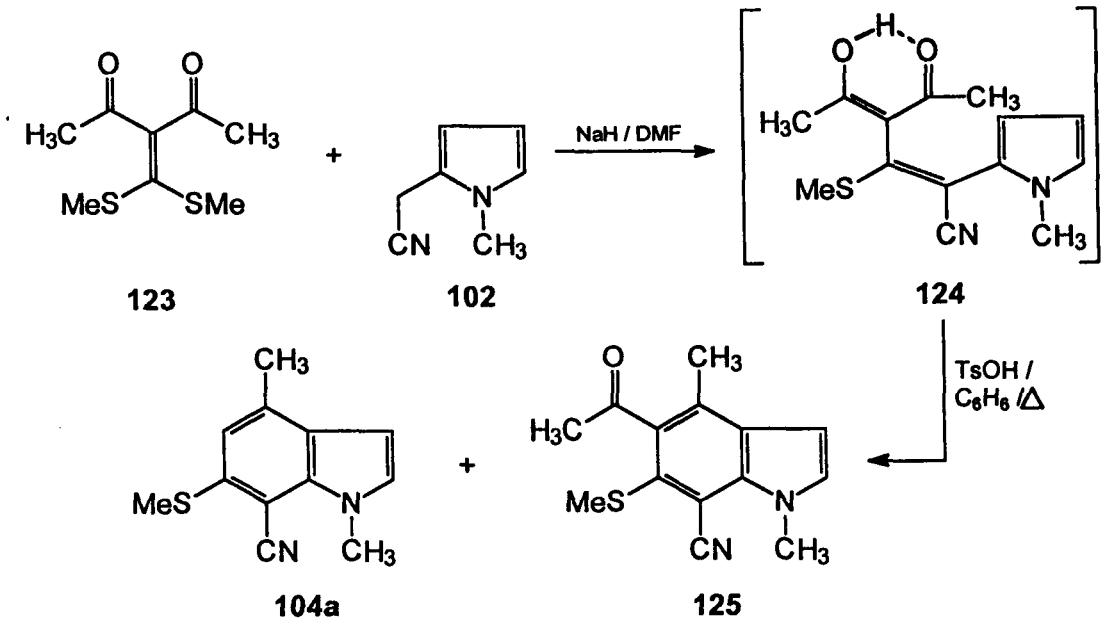
Scheme 27

Some of the newly synthesised indoles **104a-c**, **107b** and **109a** were subjected to Raney nickel desulfurization in ethanol (Scheme 28). However, the cyano group was also reduced concurrently during these reactions to afford the corresponding dethiomethylated 7-methylindoles **117-121** in 85-94% overall yields. The 6-methoxyindole **114b** under RaNi reduction yielded the corresponding 6-methoxy-1,4,5,7-tetramethylindole **122** in 94% yield. The structures **of 117-122** were all established on the basis of their analytical and spectral data which are described in the experimental section. It was necessary to carry Raney Nickel experiments under prolonged heating to complete the reduction of the cyano group to methyl group and to eliminate the methylthio group. When reaction time was reduced to less than 10 hours, the reaction mixture showed several spots in TLC probably due to the products arising through different stages of nitrile group reduction.

All the carbon atoms of the oxoketene-S,S-, O,S-, and -N,S-acetals can carry substituents which will become substituents in the 4, 5 and 6-positions of product indoles. We therefore considered that if we take doubly activated ketene dithioacetals **123** and **126** derived from acetylacetone and diethyl malonate respectively, we expected the product indoles to carry the acetyl- and carbethoxy groups at position 5 (Schemes 29 and 30). Interestingly when **123** was reacted with **102** the addition-elimination product **124** was obtained in near quantitative yield which when cyclized in the presence of *p*-toluene sulfonic acid in refluxing benzene a mixture of two indoles **125** and **104a** were obtained in 54 and 28% yields respectively. Apparently the reaction undergoes deacetylation during cyclization to give 1,4-dimethyl-6-methylthio-7-cyanoindole **104a** in 28% yield which was found to be identical with that obtained by reaction of **101a** with **102**. The structure of **125** which contains 5-acetyl group was fully characterized by its analytical and spectral data which are given in the experimental section.


CH3
MeS
N
CN
CH3
Raney Ni / EtOH /Δ
104a
117
104b
118
104c
119
107b
120
109a
121
H3C
MeO
114b
122

Scheme 28



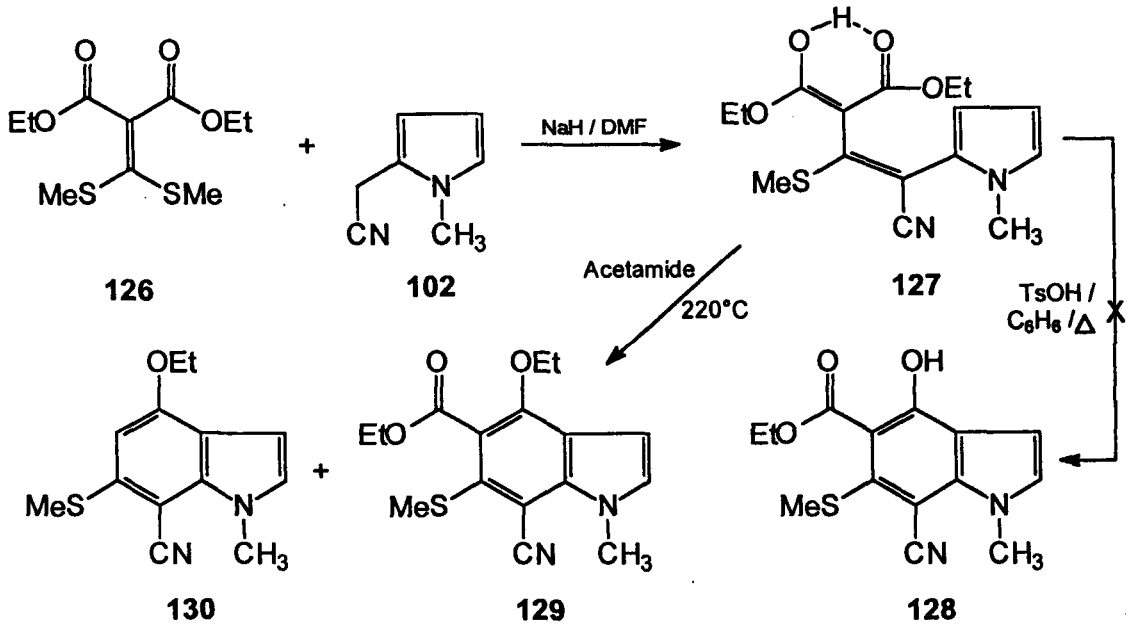
123 102 124

104a 125

Scheme 29

Similarly the oxoketene dithioacetal derived from diethyl malonate **126** reacted with **102** to get the 1,4-adduct **127** which when treated with *p*-toluene sulfonic acid, the expected 4-hydroxy-5-carbethoxyindole **128** was not formed and the unreacted addition-elimination product **127** was recovered. However when **127** was heated using acetamide as the medium at 220°C, cyclization occurred with the elimination of water to afford 5-carbethoxy-4-ethoxyindole **129** along with the decarbethoxylated product **130** in 38 and 28% yields respectively (Scheme 30).

In conclusion, we have developed a new general route for the synthesis of indoles having control on the substituents at 4,5,6 and 7 positions using the heteroaromatic annelation methodology. The method is unequivocally good for the synthesis of 4- and 6-substituted indoles particularly the 6-oxygenated



Scheme 30

derivatives which are precursors of many natural alkaloids. Since the product indoles carry no substituents at 2- and 3-positions, they form an excellent pool of substituted indoles for transforming them to biologically important indole derivatives (tryptophans, tryptamines and indole-3-acetic acids etc.) and the corresponding ß-carbolines through tryptamines. The indoles can also be transformed into carbazoles by extending our heteroaromatic annelation methodology from the corresponding indole-3-acetonitriles.[42] Thus the versatility of this methodology should ensure that the route will enjoy wide applicability for the synthesis of biologically important and naturally occurring indole derivatives.

EXPERIMENTAL

General

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer and the frequencies are expressed in cm^{-1}. ^{1}H NMR (300 MHz), ^{13}C NMR (75.43 MHz) spectra were recorded on Bruker ACF-300 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethyl silane and coupling constants (J) are given in Hertz. Mass spectra were obtained on a Jeol D-300 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

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

Chemicals, Reagents and Solvents

1-Methylpyrrole-2-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. Raney nickel (W2) was prepared according to the reported procedure.[43] The commercial samples of acetone, acetophenone, isopropyl methyl ketone, ethyl methyl ketone, cyclopentanone, cyclohexanone, acetyl acetone, diethyl malonate were purified by simple distillation. Morpholine and piperidine were distilled from sodium hydroxide.

Propiophenone,[44] 1-indanone,[45] 1-tetralone,[46] benzosuberone[47] were prepared according to the reported procedures. Esterone was gifted by Organon Research Centre, Calcutta. Pyruvaldehyde dimethylacetal was purchased from Aldrich and used as supplied. Dimethyl trithiocarbonate[48] and methyl xanthate[49] were prepared by according to the literature procedures. α-Oxoketene-S,S-acetals,[50] -O,S-acetals,[51] and -N,S-acetals[50] were prepared according to the earlier reported procedures and the general procedures are given below.

General procedure for the preparation of α-oxoketene dithioacetals.

To an ice-cold well stirred suspension of sodium *t*-butoxide (0.4 mol) in dry benzene (400 ml) a solution of appropriate methyleneketone (0.2 mol) and carbon disulfide (0,2 mol) in dry benzene was added dropwise and the reaction mixture was allowed to stir for 5-6 hours. Acid free dimethyl sulphate (0.4 mol) was then added dropwise with stirring and cooling and the reaction mixture was further allowed to stir at room temperature for 8-10 hours. The reaction mixture was then poured into water and the aqueous layer was extracted with benzene and the combined benzene extracts was washed thoroughly with water, dried over anhydrous sodium sulphate and the solvent distilled off. Trituration of the oily residue with hexane gave the α-oxoketene dithioacetals as yellow crystalline solids. Liquid dithioacetals were purified by passing through silica gel column using hexane as eluent.

All the α-oxoketene dithioacetals prepared were characterized by comparison of spectral and analytical data with that of the authentic samples.

General procedure for the preparation of α-oxoketene-O,S-acetals.

(i) Preparation of β-oxothionoesters.

To an ice cold stirred suspension of sodium *t*-butoxide (0.2 mol) in *t*-butanol (200 ml) a solution of dimethyl xanthate (0.1 mol) and the appropriate methyleneketone (0.1 mol) in dry benzene was added dropwise and the reaction mixture was stirred for 8-10 hours. It was then poured into water, neutralized with

dilute hydrochloric acid, extracted with benzene and the combined benzene extracts was washed with water, dried over anhydrous sodium sulphate, and the solvent distilled off to give the β-oxothionoesters which were purified by column chromatography over silica gel using hexane as eluent.

(ii) Preparation of α-oxoketene O,S-acetals.

A mixture of β-oxothionoester (0.1 mol) and potassium carbonate (0.2 mol) in dry acetone (150 ml) was refluxed with stirring for two hours and then cooled to room temperature. Methyl iodide (0.1 mol) was then added dropwise with stirring and the reaction mixture was further stirred at room temperature for 5-6 hours (monitored by tlc). Bulk of the solvent was evaporated and then the reaction mixture was treated with ice cold water and extracted with benzene. The benzene layer was washed with water, dried over anhydrous sodium sulphate and the solvent distilled off to get the corresponding O,S-acetals which were purified by column chromatography over silica gel using hexane-ethylacetate as eluent.

General procedure for the preparation of α-oxoketene S,N-acetals.

(i) Preparation of methyl β-oxodithiocarboxylates.

To an ice cold well stirred suspension of sodium *t*-butoxide (0.2 mol) in dry benzene (200 ml), a solution of appropriate methyleneketone (0.1 mol) and dimethyl trithiocarbonate (0.1 mol) in dry benzene was added dropwise and the reaction mixture was allowed to stir for 5-6 hours. It was poured into ice cold water and the aqueous layer was separated, neutralised with dilute hydrochloric acid and extracted with benzene. The combined benzene layers was washed with water, dried over anhydrous sodium sulphate and the solvent distilled off to give the β-oxodithioesters which were pure enough to go for the next step.

(ii) Preparation of β-oxothioamides.

A solution of methyl β-oxodithiocarboxylate and appropriate secondary amine in ethanol was refluxed for 3-4 hours (monitored by tlc). Then the solvent was distilled off and the residue dissolved in benzene, washed with water, dried over anhydrous sodium sulphate, and the solvent distilled off to afford the β-oxothioamides.

(iii) Preparation of oxoketene-N,S-acetals.

A mixture of β-oxothioamide (0.1 mol) and potassium carbonate (0.2 mol) in dry acetone (150 ml) was refluxed with stirring for two hours and then cooled to room temperature. Methyl iodide (0.1 mol) was then added dropwise with stirring and the reaction mixture was further stirred at room temperature for 5-6 hours (monitored by tlc). Bulk of the solvent was evaporated and then the reaction mixture was treated with water and extracted with benzene. The benzene layer was washed with water, dried over anhydrous sodium sulphate and the solvent distilled off to get the α-oxoketene-N,S-acetals which were purified by column chromatography over silica gel using hexane-ethyl acetate as eluent.

General Procedure for the Synthesis of Substituted and Condensed Indoles.

To a stirring suspension of sodium hydride (10 mmol) in dimethylformamide (10 ml) at 0°C, a solution of 1-methyl-pyrrole-2-acetonitrile (5 mmol) in dimethylformamide (5 ml) was added dropwise. After 10 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 sulphate and evaporated to give the crude 1,4-adducts, which 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 2-3 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 sulphate and evaporated to give crude indole which was purified by column chromatography (silica gel) using hexane-ethylacetate (97:3) as eluent. The adduct **103f** was cyclized to the corresponding indole **104f** during column chromatography (silica gel).

7-Cyano-1,4-dimethyl-6-(methylthio)indole (104a):

Colourless crystals; m.p. 110-111°C (chloroform-ether); yield 86%; IR (KBr): ν_{max} 2200, 1583 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H), 2.58 (s, 3H), 4.10 (s, 3H), 6.47 (d, J=3.2 Hz, 1H), 6.93 (s, 1H), 6.99 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 17.94, 19.09, 34.94, 100.35, 116.97, 120.61, 128.28, 130.77, 135.41, 136.35, 137.80; MS: *m/z* 216 (M^+, 100%); Anal. Calcd. for $C_{12}H_{12}N_2S$ (216.307): C, 66.63; H, 5.59; N, 12.95%. Found: C, 66.92; H, 5.36; N, 13.16%.

7-Cyano-4-isopropyl-1-methyl-6-(methylthio)indole (104b):

Light yellow crystals; m.p. 64-65°C (chloroform-ether); yield 72%; IR (KBr): ν_{max} 2965, 2210, 1565 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 1.36 (d, J=7.2 Hz, 6H), 2.60 (s, 3H), 3.36 (septet, J=7.2 Hz, 1H), 4.12 (s, 3H), 6.58 (d, J=3.2 Hz, 1H), 7.03 (d, J=3.2 Hz, 1H), 7.08 (s, 1H); MS: *m/z* 244 (M^+, 100%); Anal. Calcd. for $C_{14}H_{16}N_2S$ (244.36): C, 68.81; H, 6.60; N, 11.46%. Found: C, 69.04; H, 6.47; N, 11.63%.

7-Cyano-1-methyl-6-methylthio-4-phenylindole (104c):

Colourless crystals; m.p. 130-131°C (chloroform-ether); yield 85%; IR (KBr): ν_{max} 2197, 1567 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 4.06 (s, 3H), 6.55 (d, J=3.3 Hz, 1H), 6.98 (d, J=3.3 Hz, 1H), 7.12 (s, 1H), 7.38-7.48 (m, 3H), 7.56-7.60 (m, 2H); ^{13}C NMR (75 MHz): δ 17.72, 35.03, 93.30, 101.42, 116.56, 119.49, 126.53,

128.19, 128.63, 131.79, 136.20, 138.09, 139.13, 139.36; MS: *m/z* 278 (M^+, 100%); Anal. Calcd. for $C_{17}H_{14}N_2S$ (278.378): C, 73.35; H, 5.07; N, 10.06%. Found: C, 73.78; H, 5.34; N, 10.44%.

7-Cyano-6-methylthio-1,4,5-trimethylindole (104d):

Colourless crystals; m.p. 107-108°C (chloroform-ether); yield 88%; IR (KBr): ν_{max} 2214, 1507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.46 (s, 3H), 2.56 (s, 3H), 4.06 (s, 3H), 6.45 (d, J=3.2 Hz, 1H), 7.01 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 17.13, 17.20, 20.11, 34.92, 98.26, 100.12, 117.98, 130.74, 130.93, 131.79, 133.91, 134.31, 134.80; MS: *m/z* 230 (M^+, 100%); Anal. Calcd. for $C_{13}H_{14}N_2S$ (230.334): C, 67.79; H, 6.13; N, 12.16%. Found: C, 67.96; H, 6.20; N, 12.10%.

7-Cyano-1,5-dimethyl-6-methylthio-4-phenylindole (104e):

Colourless crystals; m.p. 123-124°C (chloroform-ether); yield 76%; IR (KBr): ν_{max} 2211, 1506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.47 (s, 3H), 4.13 (s, 3H), 6.09 (d, J=3.2 Hz, 1H), 7.00 (d, J=3.1 Hz, 1H), 7.26-7.29 (m, 2H), 7.38-7.49 (m, 3H); ^{13}C NMR (75 MHz): δ 18.59, 19.97, 34.96, 100.12, 101.59, 117.67, 127.51, 128.30, 129.15, 130.54, 130.76, 132.33, 134.35, 135.07, 139.09, 139.46; MS: *m/z* 292 (M^+, 100%); Anal. Calcd. for $C_{18}H_{16}N_2S$ (292.404): C, 73.94; H, 5.52; N, 9.61%. Found: C, 74.22; H, 5.45; N, 9.78%.

7-Cyano-4-(dimethoxymethyl)-1-methyl-6-(methylthio)indole (104f):

Yellow crystals; m.p. 68-69°C (chloroform-ether); yield 68%; IR (KBr): ν_{max} 2208, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H), 3.35 (s, 6H), 4.11 (s, 3H), 5.68 (s, 1H), 6.68 (d, J=3.1 Hz, 1H), 7.04 (d, J=3.2 Hz, 1H), 7.32 (s, 1H); ^{13}C NMR (75 MHz): δ 17.70, 34.96, 52.79, 94.65, 101.07, 101.44, 116.63, 117.79, 126.16, 131.73, 135.06, 136.20, 137.76; MS: *m/z* 276 (M^+, 47.6%), 245 (100%); Anal. Calcd. for $C_{14}H_{16}N_2O_2S$ (276.358): C, 60.85; H, 5.84; N, 10.14%. Found: C, 60.98; H, 5.96; N, 10.20%.

4-Cyano-3-methyl-5-(methylthio)cyclopenta[e]indole (107a):

Colourless crystals; m.p. 105-106°C (chloroform-ether); yield 74%; IR (KBr): ν_{max} 2924, 2213, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.20 (quintet, J=7.5 Hz, 2H), 2.48 (s, 3H), 3.15 (t, J=7.5 Hz, 4H), 4.13 (s, 3H), 6.37 (d, J=3.1 Hz, 1H), 7.03 (d, J=3.1 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.38, 24.47, 32.54, 33.01, 35.09, 99.84, 117.77, 126.88, 131.16, 132.11, 135.83, 139.17, 141.56; MS: *m/z* 242 (M^+, 100%); Anal. Calcd. for $C_{14}H_{14}N_2S$ (242.345): C, 69.39; H, 5.82; N, 11.56%. Found: C, 69.54; H, 5.89; N, 11.68%.

4-Cyano-3-methyl-5-methylthio-6,7,8,9-tetrahydrobenzo[e]indole (107b):

Colourless crystals; m.p. 98-99°C (chloroform-ether); yield 68%; IR (KBr): ν_{max} 2923, 2214, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (m, 4H), 2.43 (s, 3H), 2.97-3.05 (m, 4H), 4.12 (s, 3H), 6.42 (d, J=3.2 Hz, 1H), 7.01 (d, J=3.1 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.76, 22.10, 23.46, 27.15, 28.11, 34.89, 98.86, 99.46, 117.63, 129.84, 131.51, 131.55, 133.52, 134.79, 135.36; MS: *m/z* 256 (M^+, 100%); Anal. Calcd. for $C_{15}H_{16}N_2S$ (256.371): C, 70.28; H, 6.29; N, 10.93%. Found: C, 70.62; H, 6.40; N, 10.81%.

4-Cyano-3-methyl-5-(methylthio)cyclohepta[e]indole (107c):

Colourless crystals; m.p. 127-128°C (chloroform-ether); yield 78%; IR (KBr): ν_{max} 2907, 2216, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58-1.65 (m, 4H), 1.81-1.84 (m, 2H), 2.37 (s, 3H), 3.00-3.03 (m, 2H), 3.30-3.34 (m, 2H), 4.05 (s, 3H), 6.46 (d, J=3.3 Hz, 1H), 7.01 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.87, 27.01, 27.92,31.43, 31.61, 32.17, 34.86, 98.11, 99.95, 117.91, 130.15, 131.87, 133.21, 134.32, 137.86, 141.71; MS: *m/z* 270 (M^+, 100%); Anal. Calcd. for $C_{16}H_{18}N_2S$ (270.398): C, 71.07; H, 6.71; N, 10.36%. Found: C, 71.42; H, 6.58; N, 10.48%.

4-Cyano-3-methyl-5-(methylthio)indeno[1,2-e]indole (109a):

Light yellow crystals; m.p. 178-179°C (chloroform-ether); yield 82%; IR (KBr): ν_{max} 2208, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.76 (s, 2H), 4.02 (s,

3H), 6.69 (d, J=3.2 Hz, 1H), 7.01 (d, J=3.6 Hz, 1H), 7.28-7.39 (m, 2H), 7.46 (d, J=7.1 Hz, 1H), 7.74 (d, J=6.8 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.45, 35.14, 37.37, 97.03, 99.60, 117.75, 122.36, 123.65, 124.62, 126.83, 127.38, 130.71, 132.61, 136.35, 137.12, 138.39, 140.97, 144.47; MS: *m/z* 290 (M^+, 83%), 243 (100%); Anal. Calcd. for $C_{18}H_{14}N_2S$ (290.389): C, 74.45; H, 4.86; N, 9.65%. Found: C, 74.68; H, 4.78; N, 9.54%.

4-Cyano-6,7-dihydro-3-methyl-5-(methylthio)naphtho[1,2-e]indole (109b):

Light brown crystals; m.p. 173-174°C (chloroform-ether); yield 66%; IR (KBr): ν_{max} 2209, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.79 (t, J=7 Hz, 2H), 3.23 (t, J=7 Hz, 2H), 4.16 (s, 3H), 6.92 (d, J=3.3 Hz, 1H), 7.13 (d, J=3.2 Hz, 1H), 7.30-7.38 (m, 3H), 7.97 (d, J=7 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.00, 26.86, 29.17, 35.31, 99.40, 101.65, 117.84, 126.52, 126.88, 127.40, 127.69, 128.26, 132.86, 132.95, 133.46, 133.61, 134.02, 135.82, 139.51; MS: *m/z* 304 (M^+, 88%), 256 (100%); Anal. Calcd. for $C_{19}H_{16}N_2S$ (304.415): C, 74.97; H, 5.30; N, 9.20 %. Found: C, 75.34; H, 5.42; N, 9.06%.

4-Cyano-3-methyl-5-(methylthio)benzosubereno[e]indole (109c):

Colourless solid; m.p. 150-151°C (chloroform-ether); yield 72%; IR (KBr): ν_{max} 2921, 2213, 1509 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15-2.35 (m, 4H), 2.51 (s, 3H), 2.52-2.58 (m, 1H), 3.63-3.68 (m, 1H), 4.18 (s, 3H), 6.50 (d, J=3.2 Hz, 1H), 7.09 (d, J=3.2 Hz, 1H), 7.28-7.39 (m, 3H), 7.54-7.58 (m, 1H); ^{13}C NMR (75 MHz): δ 21.28, 28.23, 31.08, 33.55, 35.22, 100.04, 101.51, 117.94, 126.11, 128.37, 128.68, 128.92, 129.38, 132.89, 133.60, 134.14, 135.42, 138.20, 38.25, 140.22; MS: *m/z* 318 (M^+, 100%); Anal. Calcd. for $C_{20}H_{18}N_2S$ (318.442): C, 75.44; H, 5.70; N, 8.80%. Found: C, 75.72; H, 5.63; N, 8.89%.

7-Cyano-3-methoxy-1-methyl-6-(methylthio)indolo[17,16-e]estra-1,3,5(6)-triene (111):

Light brown crystals; m.p. 240-241°C (chloroform-ether); yield 74%; $[\alpha]^{23}_{D}$= +49° (c=0.48, dioxane); IR (KBr): ν_{max} 2920, 2211, 1603, 1494 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.10-3.60 (m, 13H), 2.52 (s, 3H), 3.81 (s, 3H), 4.15 (s, 3H), 6.60 (d, J=3.2 Hz, 1H), 6.66-6.84 (m, 2H), 7.10 (d, J=3.2 Hz, 1H), 7.26 (d, J=8 Hz, 1H); MS: *m/z* 442 (M^+, 100%); Anal. Calcd. for $C_{28}H_{30}N_2OS$ (442.624): C, 75.98; H, 6.83; N, 6.33%. Found: C, 76.42; H, 7.04; N, 6.18%.

7-Cyano-6-methoxy-1-methyl-4-phenylindole (114a):

Colourless crystals; m.p. 137-138°C (chloroform-ether); yield 80%; IR (KBr): ν_{max} 2206, 1591 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 4.03 (s, 3H), 4.12 (s, 3H), 6.58 (d, J=3.2 Hz, 1H), 6.84 (s, 1H), 7.00 (d, J=3.2 Hz, 1H), 7.44-7.76 (m, 5H); MS: *m/z* 262 (M^+, 100%); Anal. Calcd. for $C_{17}H_{14}N_2O$ (262.311): C, 77.84; H, 5.38; N, 10.68%. Found: C, 77.58; H, 5.44; N, 10.74%.

7-Cyano-6-methoxy-1,4,5-trimethylindole (114b):

Colourless crystals; m.p. 99-100°C (chloroform-ether); yield 86%; IR (KBr): ν_{max} 2219, 1593 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.48 (s, 3H), 3.96 (s, 3H), 4.08 (s, 3H), 6.50 (d, J=3.2 Hz, 1H), 7.00 (d, J=3.2 Hz, 1H); MS: *m/z* 214 (M^+, 81.2), 199 (100%); Anal. Calcd. for $C_{13}H_{14}N_2O$ (214.267): C, 72.87; H, 6.59; N, 13.07%. Found: C, 73.18; H, 6.50; N, 13.15%.

7-Cyano-1,4-dimethyl-6-piperidinoindole (116a):

Brown viscous liquid; yield 65%; IR (CCl_4): ν_{max} 2936, 2210, 1592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.50-1.58 (m, 2H), 1.72-1.80 (m, 4H), 2.48 (s, 3H), 3.07-3.11 (m, 4H), 3.99 (s, 3H), 6.37 (d, J=3.2 Hz, 1H), 6.62 (s, 1H), 6.85 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.26, 24.20, 26.43, 34.65, 54.49, 86.15, 100.01, 112.04, 118.18, 124.93, 129.68, 135.49, 136.49, 155.68; MS: *m/z* 253 (M^+, 100%); Anal.

Calcd. for $C_{16}H_{19}N_3$ (253.347): C, 75.85; H, 7.56; N, 16.59%. Found: C, 76.32; H, 7.39; N, 16.73%.

7-Cyano-1-methyl-4-phenyl-6-piperidinoindole (116b):

Light yellow crystals; m.p. 130-131°C (chloroform-ether); yield 70%; IR (KBr): ν_{max} 2849, 2203, 1585 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 1.50-2.00 (m, 6H), 3.12-3.32 (m, 4H), 4.14 (s, 3H), 6.57 (d, J=3.2 Hz, 1H), 6.91 (s, 1H), 7.00 (d, J=3.2 Hz, 1H), 7.40-7.74 (m, 5H); MS: *m/z* 315 (M^+, 100%); Anal. Calcd. for $C_{21}H_{21}N_3$ (315.418): C, 79.97; H, 6.71; N, 13.32%. Found: C, 80.48; H, 6.82; N, 13.17%.

7-Cyano-1-methyl-6-morpholino-4-phenylindole (116c):

Light yellow crystals; m.p. 169-170°C (chloroform-ether); yield 73%; IR (KBr): ν_{max} 2934, 2211, 1586 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 3.18-3.34 (m, 4H), 3.88-4.04 (m, 4H), 4.15 (s, 3H), 6.60 (d, J=3.2 Hz, 1H), 6.92 (s, 1H), 7.03 (d. J=3.2 Hz, 1H), 7.42-7.74 (m, 5H); MS: *m/z* 317 (M^+, 100%); Anal. Calcd. for $C_{20}H_{19}N_3O$ (317.39): C, 75.69; H, 6.03; N, 13.24%. Found: C, 75.92; H, 6.16; N, 13.35%.

5-Acetyl-7-cyano-1,4-dimethyl-6-(methylthio)indole (125):

Light brown crystals; m.p. 140-141°C (chloroform-ether); yield 54%; IR (KBr): ν_{max} 2214, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 6H), 2.61 (s, 3H), 4.15 (s, 3H), 6.57 (d, J=3.2 Hz, 1H), 7.17 (d, J=3.3 Hz, 1H); ^{13}C NMR (75 MHz): δ 16.13, 21.58, 33.17, 35.14, 98.85, 101.05, 116.66, 129.12, 130.63, 131.08, 132.99, 134.98, 139.67, 204.96; MS: *m/z* 258 (M^+, 87.5%) 243 (100%); Anal. Calcd. for $C_{14}H_{14}N_2OS$ (258.344): C, 65.09; H, 5.46; N, 10.84%. Found: C, 65.56; H, 5.28; N, 11.08%.

5-Carbethoxy-7-cyano-4-ethoxy-1-methyl-6-(methylthio)indole (129) and

7-Cyano- 4-ethoxy-1-methyl-6- (methylthio)indole (130):

The ketene dithioacetal 126 (10 mmol) was reacted with 102 (10 mmol) following the above mentioned procedure to afford the corresponding 1,4-adduct,

(*ca.* 10 mmol) which was heated with acetamide (10 g) at 220-230°C for 3 hours, in a flask equipped with an air condenser. The warm solution was poured into water, extracted with chloroform, dried over anhydrous sodium sulfate, concentrated and chromatographed by passing through silica gel column using hexane-ethyl acetate (97:3) as eluent to afford indoles 130 and 129.

129: Colourless crystals; m.p. 89-90°C (chloroform-ether); yield 36%; IR (KBr): ν_{max} 2984, 2209, 1729, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7 Hz, 6H), 2.53 (s, 3H), 4.11 (s, 3H), 4.43-4.47 (m, 4H), 6.63 (d, J=3.2 Hz, 1H), 7.07 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 14.62, 15.68, 21.03, 35.29, 61.58, 69.39, 95.18, 100.63, 116.86, 121.15, 124.51, 132.25, 132.73, 138.02, 152.50, 166.77; MS: *m/z* 318 (M^+, 74.2%), 244 (100%); Anal. Calcd. for $C_{16}H_{18}N_2O_3S$ (318.395): C, 60.36; H,5.70; N, 8.80%. Found: C, 60.74; H, 5.82; N, 8.74%.

130: Light brown crystals; m.p. 101-102°C (chloroform-ether); yield 28%; IR (KBr): ν_{max} 2202, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (t, J=7 Hz, 3H), 2.59 (s, 3H), 4.06 (s, 3H), 4.22 (q, J=7 Hz, 2H), 6.54 (s, 1H), 6.55 (d, J=3.2 Hz, 1H), 6.88 (d, J=3.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 14.69, 18.17, 34.93, 64.02, 88.28, 99.33, 102.20, 117.44, 118.96, 129.59, 136.84, 140.06, 166.82; MS: *m/z* 246 (M^+, 100%); Anal. Calcd. for $C_{13}H_{14}N_2OS$ (246.333): C, 63.39; H, 5.75; N, 11.37%. Found: C, 63.68; H, 5.62; N, 11.48%.

General Procedure for Reaction of 104a-c, 107b, 109a and 114b with Raney Nickel.

To a solution of corresponding indole (2.5 mmol) in ethanol (30 ml), was added Raney nickel (W2, 4 times by weight) and the suspension was stirred at 60-70°C for 10-12 hr. (monitored by tlc). The reaction mixture was filtered through sintered funnel and the residue was washed with ethanol. The bulk of the ethanol was distilled off and chloroform was added. The solution was washed with water, dried over anhydrous sodium sulphate and concentrated to give crude products from which

analytically pure compounds were obtained by passing through a small silica gel column using hexane as eluent.

1,4,7-Trimethylindole (117):

Light brown solid; m.p. 64-65°C; yield 85%; IR (KBr): ν_{max} 2922, 1497 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 2.47 (s, 3H), 2.71 (s, 3H), 4.02 (s, 3H), 6.43 (d, J=3.2 Hz, 1H), 6.78 (br.s, 2H), 6.92 (d, J=3.2 Hz, 1H); MS: *m/z* 159 (M^+, 100%); Anal. Calcd. for $C_{11}H_{13}N$ (159.231): C, 82.97; H, 8.23; N, 8.80%. Found: C, 83.34; H, 8.29; N, 8.73%.

1,7-Dimethyl-4-isopropylindole (118):

Light brown solid; m.p. 52-53°C; yield 94%; IR (KBr): ν_{max} 2921, 1497 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 1.25 (d, J=7 Hz, 6H), 2.52 (s, 3H), 3.18 (septet, J=7 Hz, 1H), 3.77 (s, 3H), 6.32 (d, J=3 Hz, 1H), 6.65 (br.s, 3H); MS: *m/z* 187 (M^+, 100%); Anal. Calcd. for $C_{13}H_{17}N$ (187.284): C, 83.37; H, 9.15; N, 7.48%. Found: C, 83.84; H, 9.02; N, 7.66%.

1,7-Dimethyl-4-phenylindole (119):

Colourless crystals; m.p. 69-70°C (chloroform-hexane); yield 88%; IR (KBr): ν_{max} 1595, 1482 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 2.82 (s, 3H), 4.10 (s, 3H), 6.62 (d, J=3.2 Hz, 1H), 6.96-7.08 (m, 3H), 7.32-7.78 (m, 5H); MS: *m/z* 221 (M^+, 100%); Anal. Calcd. for $C_{16}H_{15}N$ (221.302): C, 86.84; H, 6.83; N, 6.33%. Found: C, 86.57; H, 6.95; N, 6.24%.

3,4-Dimethyl-6,7,8,9-tetrahydrobenzo[e]indole (120):

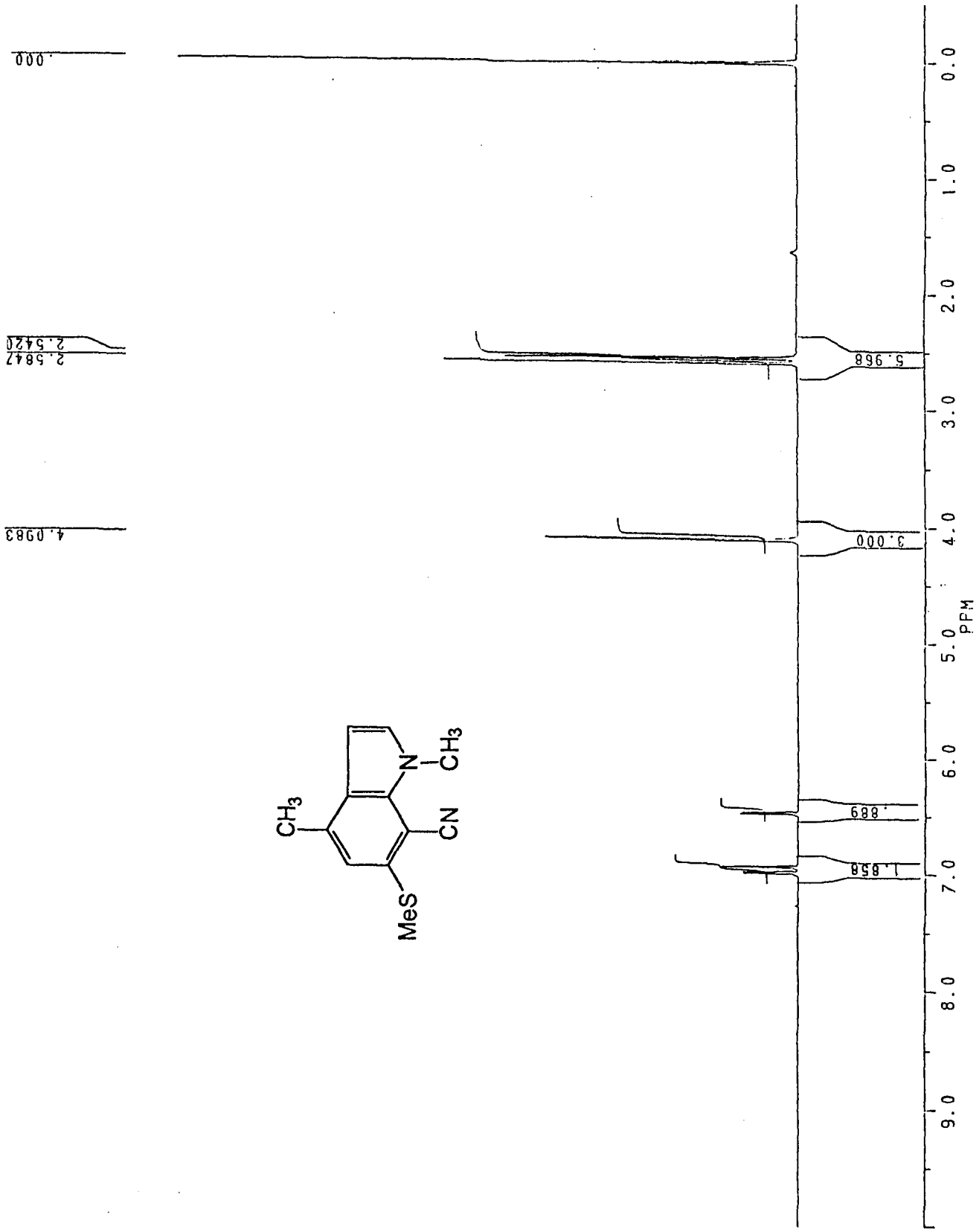
Colourless solid; m.p. 53-54°C; yield 85%; IR (KBr): ν_{max} 2930, 1493 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 1.76-1.96 (m, 4H), 2.68 (s, 3H), 2.70-2.94 (m, 4H), 4.00 (s, 3H), 6.36 (d, J=3.2 Hz, 1H), 6.64 (s, 1H), 6.90 (d, J=3.2 Hz, 1H); MS: *m/z* 199 (M^+, 100%); Anal. Calcd. for $C_{14}H_{17}N$ (199.295): C, 84.37; H, 8.60; N, 7.03%. Found: C, 84.73; H, 8.44; N, 7.14%.

3,4-Dimethylindano[1,2-e]indole (121):

Colourless crystals; m.p. 140-141°C (chloroform-hexane); yield 92%; IR (KBr): ν_{max} 2922, 1599, 1514 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 2.83 (s, 3H), 3.90 (s, 2H), 4.12 (s, 3H), 6.92 (d, J=3.2 Hz, 1H), 7.05-7.64 (m, 5H), 8.00 (d, J=6.8 Hz, 1H); MS: *m/z* 233 (M^+, 100%); Anal. Calcd. for $C_{17}H_{15}N$ (233.313): C, 87.52; H, 6.48; N, 6.00%. Found: C, 87.76; H, 6.57; N, 6.10%.

6-Methoxy-1,4,5,7-tetramethylindole (122):

Colourless crystals; m.p. 103-104°C (chloroform-hexane); yield 94%; IR (KBr): ν_{max} 2934, 1518 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.32 (s, 3H), 2.55 (s, 3H), 3.60 (s, 3H), 3.88 (s, 3H), 6.16 (d, J=3 Hz, 1H), 6.60 (d, J=3 Hz, 1H); MS: *m/z* 203 (M^+, 100%); Anal. Calcd. for $C_{13}H_{17}NO$ (203.283): C, 76.81; H, 8.43; N, 6.89%. Found: C, 77.28; H, 8.29; N, 6.72%.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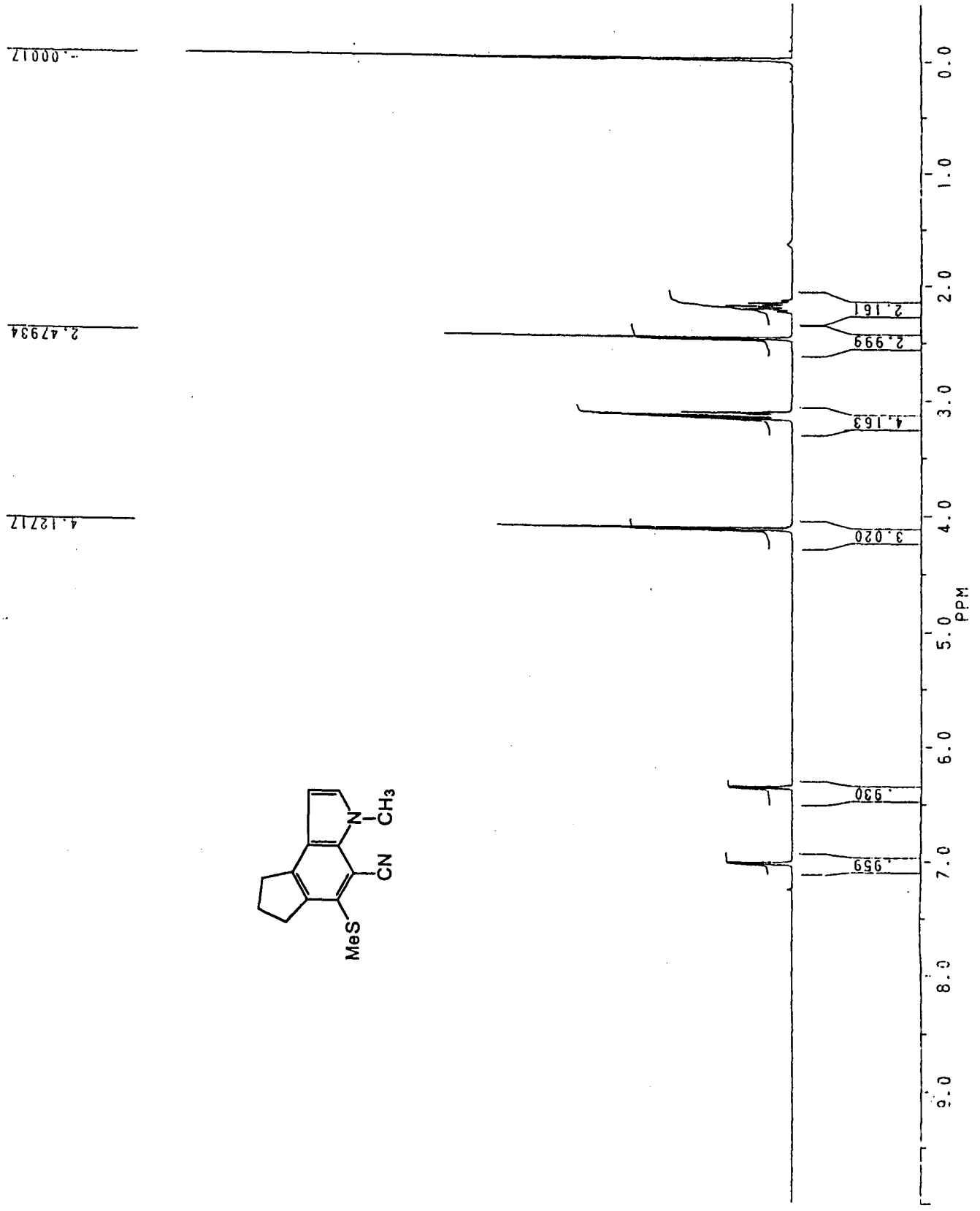
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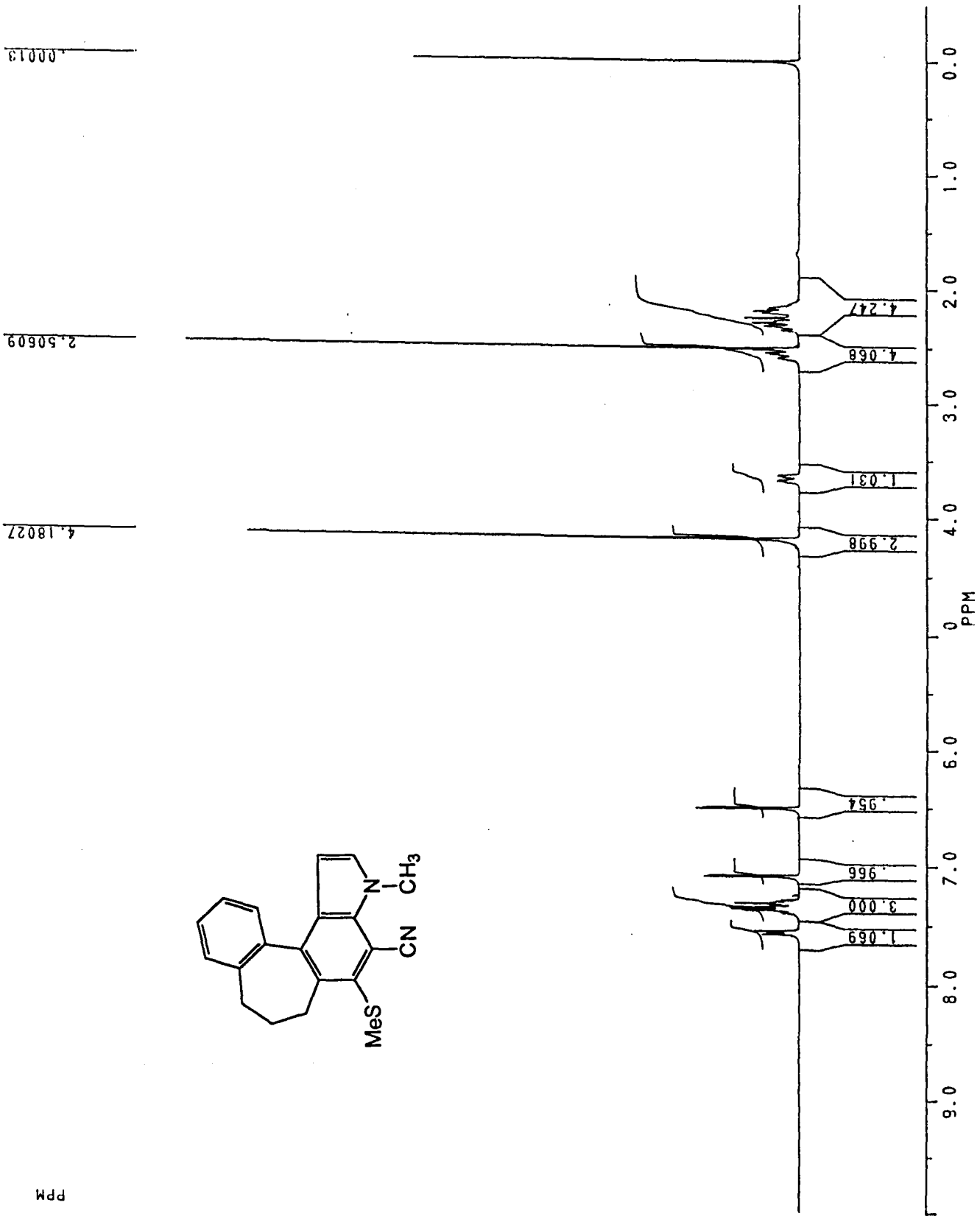
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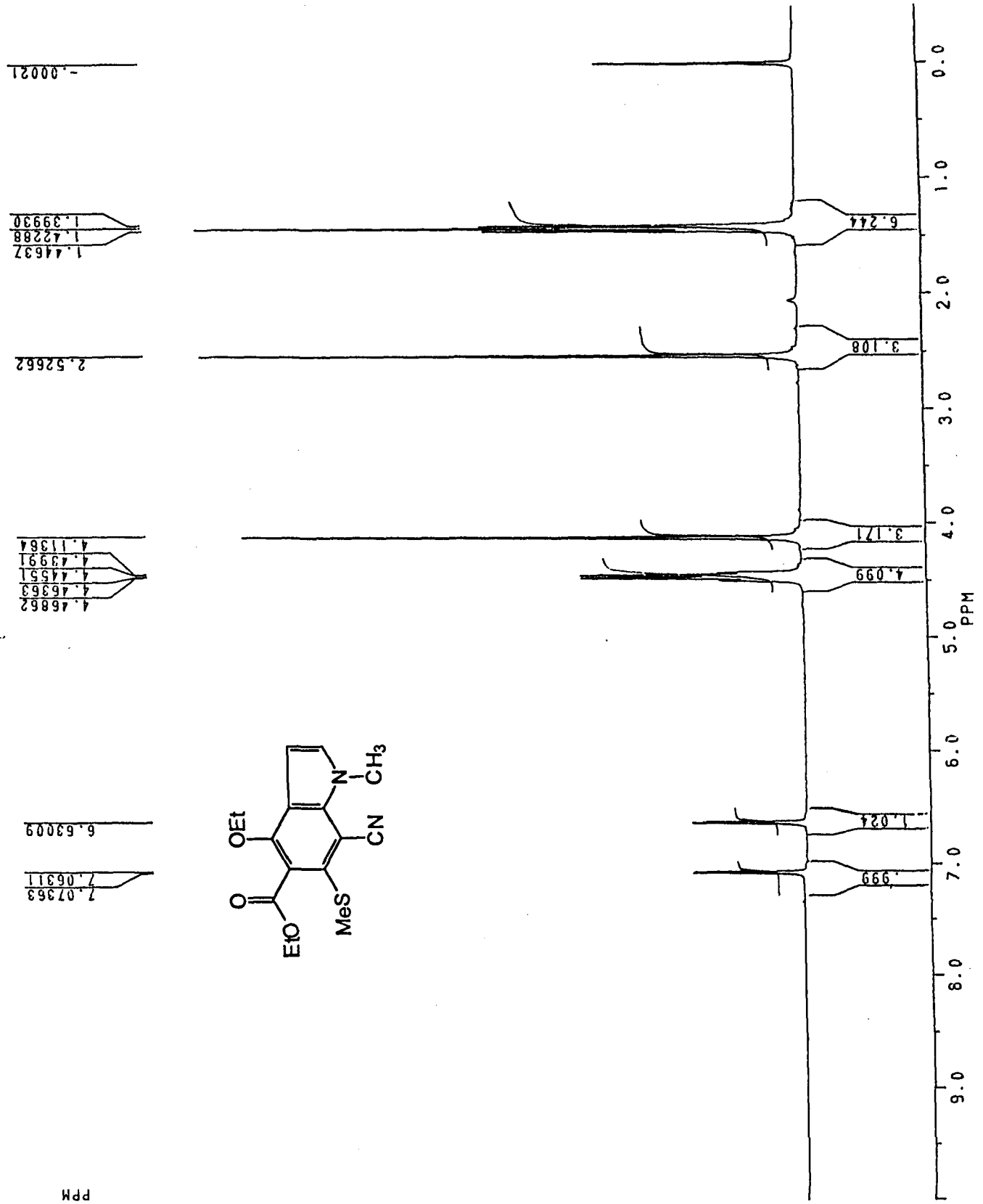
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REFERENCES

1. van Order, R.B.; Lindwall, H.G. *Chem. Rev.* **1942**, *30*, 69.
2. Julian, P.L.; Meyer, E.W.; Printyu, H.C. in *Heterocyclic Compounds*, Elderfield, R.C. (Ed.), Wiley, New York, **1952**, Vol. 3.
3. Sumpter, W.C.; Miller, F.M. *Chem. Heterocycl. Compd.* **1954**, *8*, 1.
4. Sundberg, R.J. *The Chemistry of Indoles*, Academic Press, New York, **1970**.
5. (a) Houlihan, W.J. (Ed.), *The Chemistry of Heterocyclic Compounds-Indoles*, Wiley Interscience, New york, Vol. 25, Part 1, **1972**. (b) Part 2, **1979**. (c) Part 3, **1979**. (d) Saxton, J.E. (Ed.), *The Chemistry of Heterocyclic Compounds-Indoles*, Wiley Interscience, New york, Vol. 25, Part 4, **1983**.
6. Ellis, G.P. in *The Chemistry of Heterocyclic Compounds*, Wiley, Chichester, **1992**, Vol. 47, Part 2.
7. (a) Manske, R.H.F. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 1-16, **1950-1977**. (b) Rodrigo, R.G.A. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 17-20, **1979-1981**. (c) Brossi, A. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 21-45, **1983-1994**.
8. (a) Livingstone, R. in *Rodd's Chemistry of Carbon Compounds*, 2nd Ed., Coffey, S. (Ed.), Elsevier, New York, Vol. IV, Part A, **1973**, 397. (b) Livingstone, R. in *Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*, Ansell, M.F.(Ed.), Elsevier, NewYork, Vol.IV, Part A, **1984**, 401. (c) Joule, J.A. in *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*, Sainsbury (Ed.), Elsevier, New York, Vol. IV, Part A, **1997**.

9. Sundberg, R.J. in *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R.; Rees, C.W.; Bird, C.W.; Cheeseman, G.W.H. (Eds.), Pergamon Press, Oxford, **1984**, Vol. 4, pp 313.

10. Ongoing reviews on indole synthesis: *Pregress in Heterocyclic Chemistry* Suschizky, H.; Scriven, E.F.V. (Eds.) Pergamon Press, Oxford, Vol. 1-7, **1989-95**.

11. Joule, J.A.; Mills, K.; Smith, G. *Heterocyclic Chemistry* 3rd Ed., Chapman and Hall, New York, **1995**. (b) Gilchrist, T.L. *Heterocyclic Chemistry*, 2nd Ed., Wiley, Chichester, **1992**.

12. Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1.

13. Hegedus, L.S. *Angew. Chem. Int. Ed. Eng.***1988**, *27*, 1113.

14. Alvarez, M.; Salas, M.; Joule, J.A. *Heterocycles* **1991**, *32*, 1391.

15. Gribble, G.W. *Contemporary Organic Synthesis* **1994**, *1*, 145.

16. Sundberg, R.J. *Indoles* Academic Press, San Diego, **1996**.

17. (a) Baeyer, A.; Knop, C.A. *Ann.* **1866**, *140*, 1.
(b) Baeyer, A. *Ann.* **1866**, *140*, 295.
(c) Baeyer, A. *Ber.* **1868**, *1*, 17.

18. Robinson, B. *The Fischer Indole Synthesis* John Wiley & Sons, Chichester, New York, **1982**.

19. Allen, Jr, G.R. in *Organic Reactions* John Wiley & Sons, New York, **1973**, Vol. 20, Chapter 3.

20. (a) Gassman, P.G.; van Bergan, T.J.; Gilbert, D.P.; Cue, B.W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495. (b) Gassman, P.G.; Gruetzmad, G.; van Bergan, T.J. *J. Am. Chem. Soc.* **1974**, *96*, 5512.

21. (a) Soderberg, B.C.; Shriver, J.A. *J. Org. Chem.* **1997**, *62*, 5838.
(b) Dong, Y.; Busacca, C.A. *J. Org. Chem.* **1997**, *62*, 6464.
(c) Kondo, Y.; Kogima, S.; Sakamoto,T. *J. Org. Chem.* **1997**, *62*, 6507.
(d) Rieke, R.D.; Hanson, M.V. *Tetrahedron* **1997**, *53*, 1925.

(e) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001 and references cited therein.

22. Diels, O.; Alder, K.; Winckler, H. *Ann.* **1931**, *490*, 267.
23. Hosmane, R.S.; Hiremath, S.P.; Schneller, S.W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2450.
24. Jones, R.A.; Marriott, M.T.P.; Rosenthal, W.P.; Arques, J.S. *J. Org. Chem.* **1980**, *45*, 4515.
25. Muchowski, J.M.; Scheller, M.E. *Tetrahedron Lett.* **1987**, *28*, 3453.
26. Murase, M.; Yoshida, S.; Hosaka, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1991**, *39*, 489.
27. Keil, J.-M.; Kampchen, T.; Seitz, G., *Tetrahedron Lett.* **1990**, *31*, 4581.
28. Hodges, L.M.; Spera, M.L.; Moody, M.W.; Harman, W.D., *J. Am. Chem. Soc.* **1996**, *118*, 7117.
29. (a) Jackson, P.M.; Moody, C.J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2156.

    (b) Jackson, P.M.; Moody, C.J. *Tetrahedron* **1992**, *48*, 7447.
30. Chou, T.-s.; Chang, R.-C., *J. Chem. Soc., Chem. Commun.* **1992**, 549.
31. (a) Moskal, J.; van Stralen, R.; Postma, D.; van Leusen, A.M. *Tetrahedron Lett.* **1986**, *27*, 2173.

    (b) Moskal, J.; van Leusen, A.M. *J. Org. Chem.* **1986**, *51*, 4131.
32. Wenkert, E.; Moeller, P.D.R.; Piettre, S.R. *J. Am. Chem. Soc.* **1988**, *110*, 7188.
33. Zutz, C.; Wagner, R.M.; Lobering, H.-G. *Angew. Chem. internat. Edit.* **1974**, *13*, 737.
34. Oikawa, Y.; Setoyama, O.; Yonemitsu, O. *Heterocycles* **1974**, 21.
35. Natsume, M.; Muratake, H. *Tetrahedron Lett.* **1979**, 3477.
36. Muratake, H.; Natsume, M. *Heterocycles* **1990**, *31*, 683.

37. (a) Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 771.

(b) Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 783.

(c) Muratake, H.; Natsume, M. *Heterocycles* **1990**, *31*, 691.

(d) Muratake, H.; Watanabe, M.; Goto, K.; Natsume, M. *Tetrahedron* **1990**, *46*, 4179.

(e) Okabe, K.; Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 5113.

(f) Fuji, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1992**, *40*, 2338.

(g) Fuji, M.; Muratake, H.; Natsume, M. *Chem.Pharm.Bull.* **1992**, *40*, 2344.

(h) Fuji, M.; Muratake, H.; Akiyama, M.; Natsume, M. *Chem. Pharm. Bull.* **1992**, *40*, 2353.

(i) Utsunomiya, I.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1992**, *40*, 2358.

(j) Muratake, H.; Mikawa, A.; Natsume, M. *Tetrahedron Lett.* **1992**, *33*, 4595.

(k) Muratake, H.; Seino, T.; Natsume, M. *Tetrahedron Lett.* **1993**, *34*, 4815.

(l) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 846.

(m) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, N. *Chem. Pharm. Bull.* **1994**, *42*, 854.

(n) Utsunomiya, I.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1995**, *43*, 37.

38. Yamashita, A.; Scahill, T.A.; Toy, A. *Tetrahedron Lett.* **1985**, *26*, 2969.

39. Danheiser, R.L.; Brisbois, R.G.; Kowalczyk, J.J., Miller, R.F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

40. Iwasaki, M.; Kobayashi, Y.; Li, J. -P.; Matsuzaka, H.; Ishii, Y. Hidai, M. *J. Org. Chem.* **1991**, *56*, 1922.

41. Katritzky, A.R.; Levell, J.R.; Li, J. *Tetrahedron Lett.* **1996**, *37*, 5641.

42. Patra, P.K.; Suresh, J.R.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1997**, *38*, 3119.

43. Vogel's *Text book of Practical Organic Chemistry* 4th Ed., **1978**, pp 303.

44. Reference 42, pp 775.

45. Koo, J. *J. Am. Chem .Soc.* **1953**, *75*, 1891.

46. Olson, C.E.; Bader, A.R. *Organic Synthesis* Coll. Vol. 4, **1963**, 898.

47. Gilmore, Jr., R.C.; Horton, W.J. *J. Am. Chem. Soc.* **1951**, *73*, 1411.

48. Rudorf, W.D. *Synthesis* **1983**, 926.

49. Reference 42, pp 207.

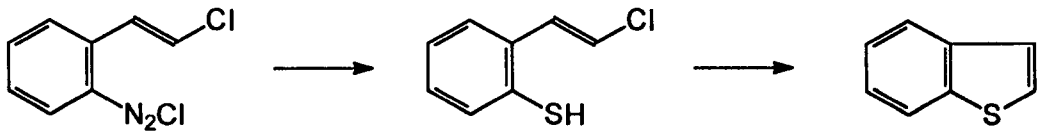
50. Review: Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron* **1990**, *46*, 5423.

51. Purkayastha, M.L.; Chandrasekharam, M.; Vishwakarma, J.N.; Ila, H.; Junjappa, H. *Synthesis* **1993**, 245.

CHAPTER III

REACTION OF THIOPHENE-2-ACETONITRILE WITH α-OXO-KETENE S,S- AND N,S-ACETALS: A NEW EFFICIENT SYNTHESIS OF SUBSTITUTED AND CONDENSED BENZO[B]THIOPHENES

Benzo[*b*]thiophene **1** and its derivatives are found to exist in coal tar, in various crude petroleum oils and in shale oils.[1-3] It was first obtained by Gatterman and Lockhart[4] in 1893 by treating diazotized *o*-amino-*ω*-chlorostyrene **2** with potassium xanthate to afford the corresponding thiophenol **3** which on treatment with potassium hydroxide gave the benzo[*b*]thiophene **1**.



2 **3** **1**

Scheme 1

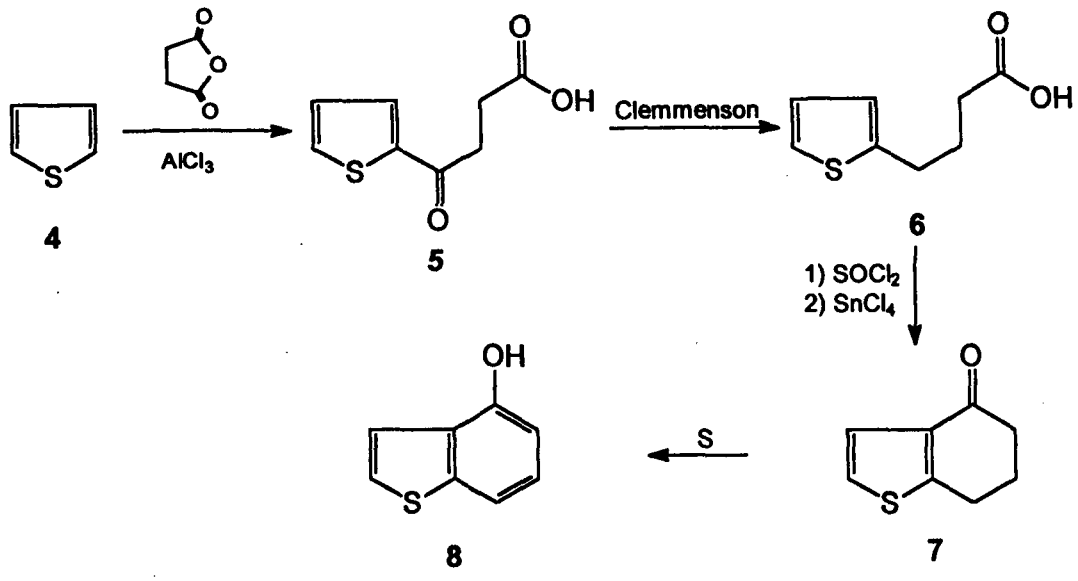
Benzo[*b*]thiophenes have attracted considerable interest as potential biologically active agents and as bioisosters of indoles; for example, numerous benzo[*b*]thiophene analogs of biologically active indole derivatives have proved to be agonists or antagonists of their indole congeners.[5]

A number of benzo[*b*]thiophene synthesis have been reported in the literature[1-3, 6-10] and most of the methods generally involve the functionalization of preconstructed benzene derivatives followed by creation of thiophene ring to afford **1**. This approach generally faced lot of limitations because benzothiophene required two carbon atoms *ortho* to each other in the benzene ring be functionalized to annulate thiophene ring thus creating difficulties to introduce further substitutions. Subsequently, a number of approaches of benzo[*b*]-thiophene synthesis based on thiophene involving the construction of benzene ring were developed.[11-40] Impetus for this approach came from the fact that thiophene itself is also a by product of petroleum and coal industry and its utility is justified using it as a precursor for the synthesis of benzo[*b*]thiophenes. There are many approaches for the benzo[*b*]thiophene synthesis involving thiophene as a precursor. Some of these important method are described in this section.

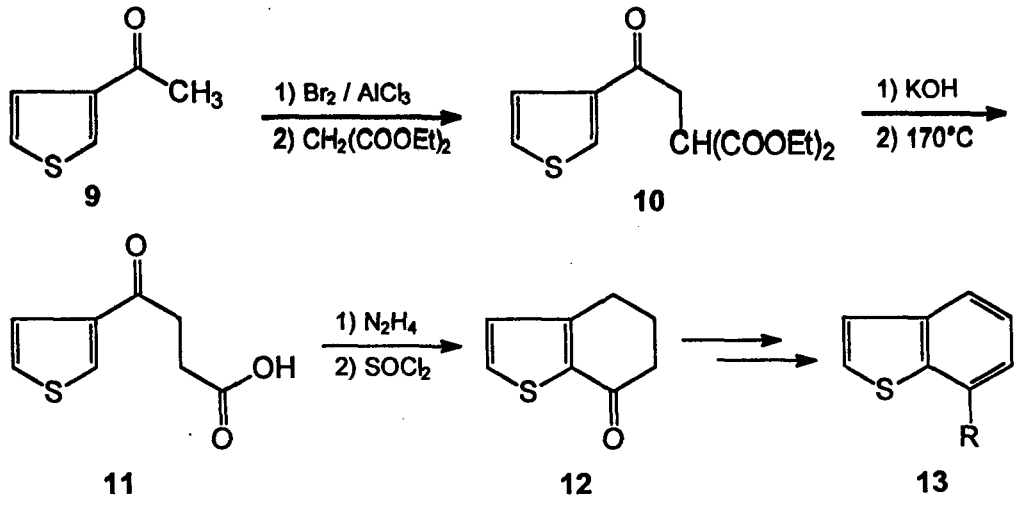
Fischer and co-workers[11] attempted Friedel Crafts reaction between thiophene **4** and succinic anhydride in nitrobenzene to afford a fair yield of β-(α-thenoyl)propionic acid **5**. The ketoacid **5** was then subjected to Clemmenson reduction to afford γ-(α-thienyl)butyric acid **6** which on treatment with thionyl chloride and stannic chloride yielded the corresponding 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene **7** in 90% yield (Scheme 2). Dehydrogenation of the ketone **7** to the 4-hydroxybenzo[*b*]thiophene **8** was accomplished with the help of sulfur.

Mac Dowell and co-workers[12] have developed a method for the synthesis of 7-substituted benzo[*b*]thiophenes. 3-Acetylthiophene **9** was transformed into

7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene **12** as shown in the Scheme 3. Compound **12** on treatment with Grignard reagents followed by dehydrogenation yielded 7-substituted benzothiophenes **13** in good yields.



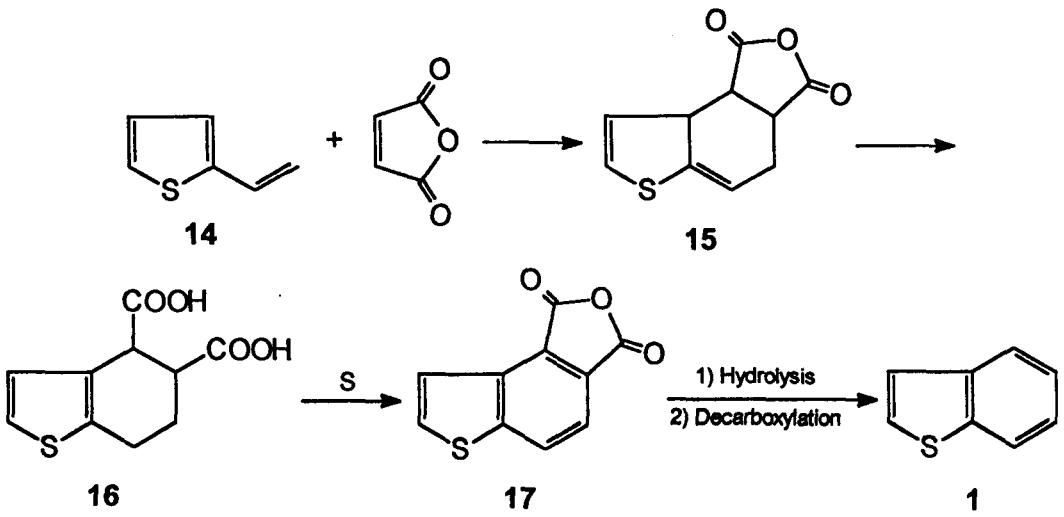
Scheme 2



Scheme 3

Subsequently, tetrahydrobenzo[*b*]thiophene-4-one **7** and -7-one **12** were synthesised by various workers[13-21] by modified and improved procedures and were utilised for the synthesis of various 4,5- and 6,7-substituted and functionalized benzo[*b*]thiophenes.

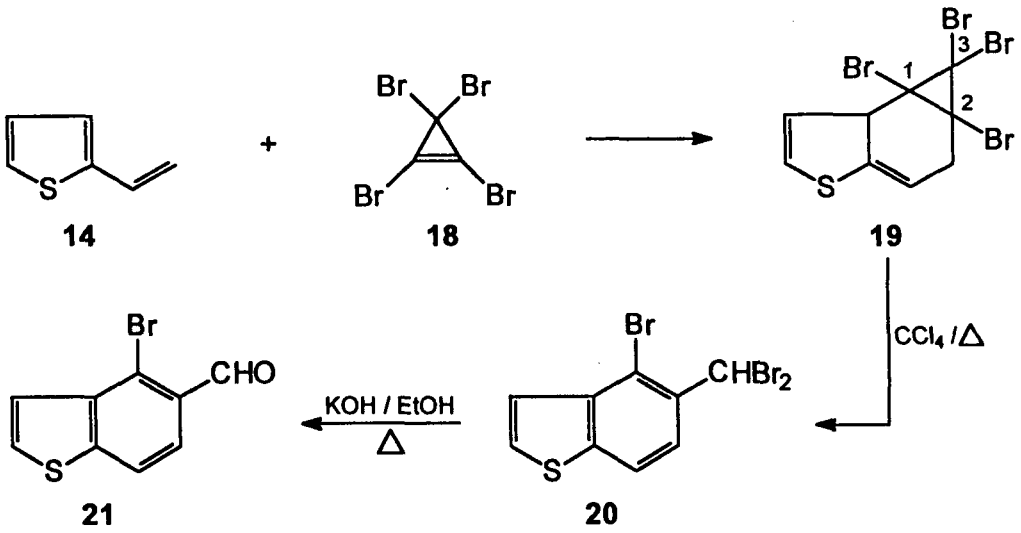
Scully and Brown[22] have synthesised benzo[*b*]thiophene **1** by Diels-Alder cycloaddition approach (Scheme 4). 2-Vinylthiophene **14** was reacted with maleic anhydride in dry benzene on steam bath to obtain the cycloadduct **15** along with some polymeric material. After separating it from polymer the adduct **15** was hydrolysed into dicarboxylic acid **16** and subjected to sulfur dehydrogenation to afford benzo[*b*]thiophene-4,5-dicarboxylic anhydride **17**. Compound **17** on hydrolysis and decarboxylation yielded the desired benzo[*b*]thiophene **1** in over all moderate yields.



Scheme 4

Seitz and co-workers[23] have reacted 2-vinylthiophene **14** with tetrabromocyclopropene **18** to afford the cycloadducts **19** which undergoes cyclopropane ring cleavage selectively at C-1/C-3 to afford functionalized benzothiophene **20**. Compound **20** under hydrolytic condition gave the corresponding 4-bromobenzo[*b*]thiophene-5-carboxaldehyde **21** in 32% yield (Scheme 5).

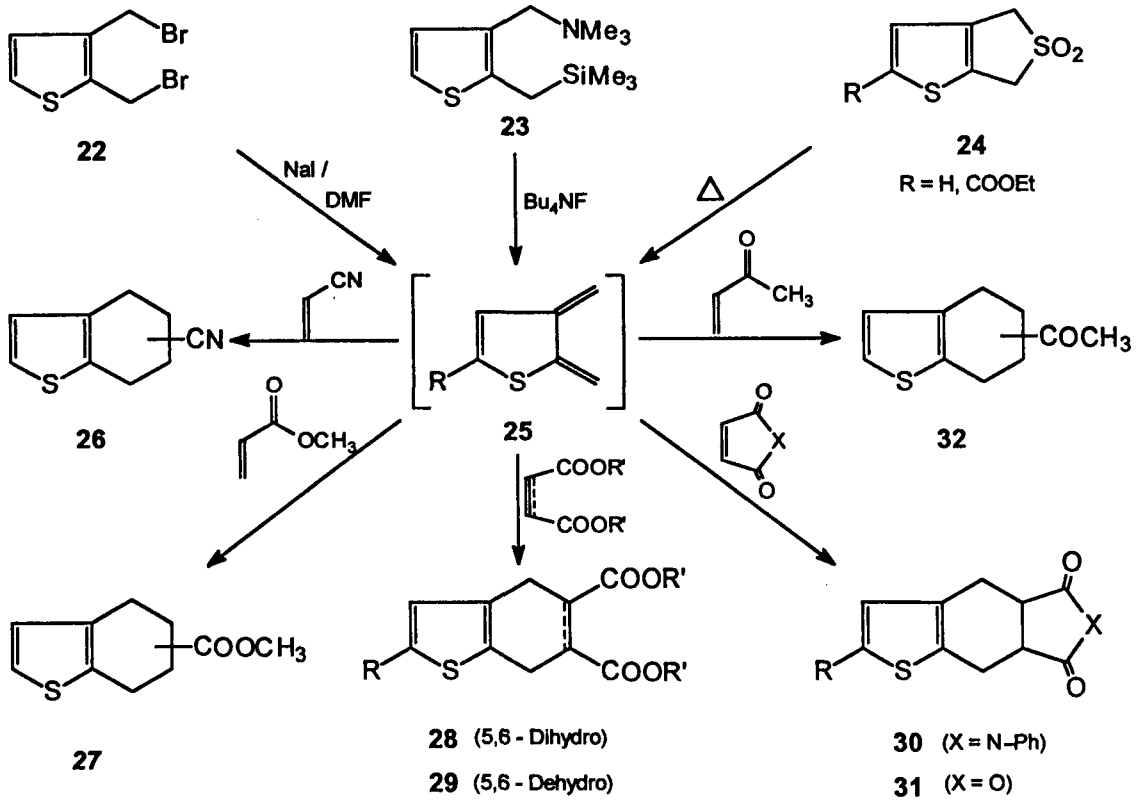
Chadwick and co-workers[24] have developed, for the first time, the synthesis of 2,3-dimethylene-2,3-dihydrothiophene **25** by treatment of



Scheme 5

bisbromide **22** with sodium iodide in dimethyl formamide and trapped as Diels-Alder adducts (Scheme 6). The tetrahydrobenzo[*b*]thiophenes **26** (R=H), **28** and **29** were thus obtained in moderate to good yields. The same quinodimethane **25** was generated alternatively by Leusen and van den Berg[25] by treating 3-(trimethylammonium-methyl)-2-(trimethylsilylmethyl)thiophene iodide **23** with fluoride ion which was then trapped by various dienophiles to afford tetrahydrobenzo[*b*]thiophenes **28, 30** and **31** (R=H). Storr and co-workers[26] have also generated **25** (R=COOMe) by heating 4,6-dihydrothieno[3,4-*b*]thiophene-5,5-dioxide **24** and trapped with various dienophiles to afford the corresponding tetrahydro- and dihydrobenzo[*b*]thiophenes **26, 27, 31** and **32** (Scheme 6).

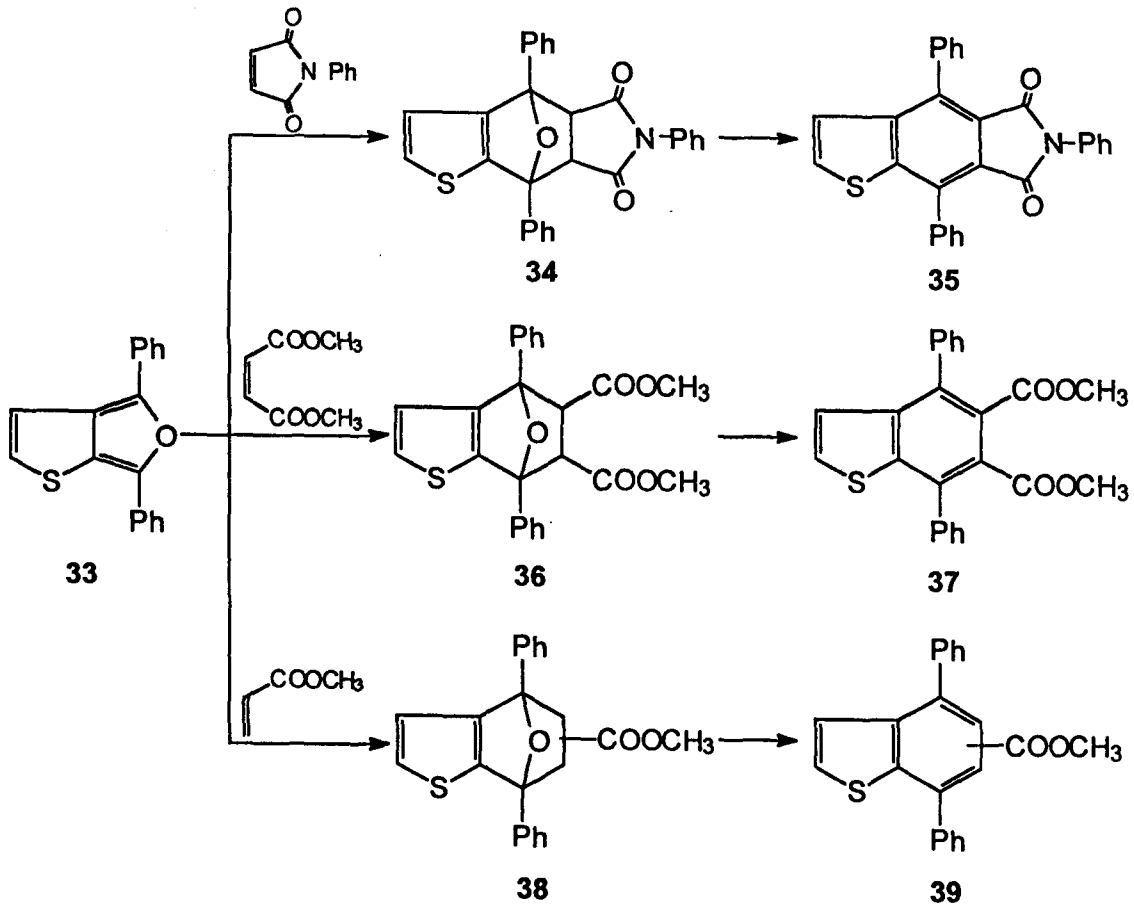
Friedrichsen and co-workers[27] have used 4,6-diphenylthieno[2,3-*c*]furan **33** as a stable cyclic analogue of 2,3-dimethylene-2,3-dihydrothiophene and reacted with various dienophiles to afford the corresponding benzo[*b*]thiophenes **35, 37** and **39** as shown in Scheme 7.



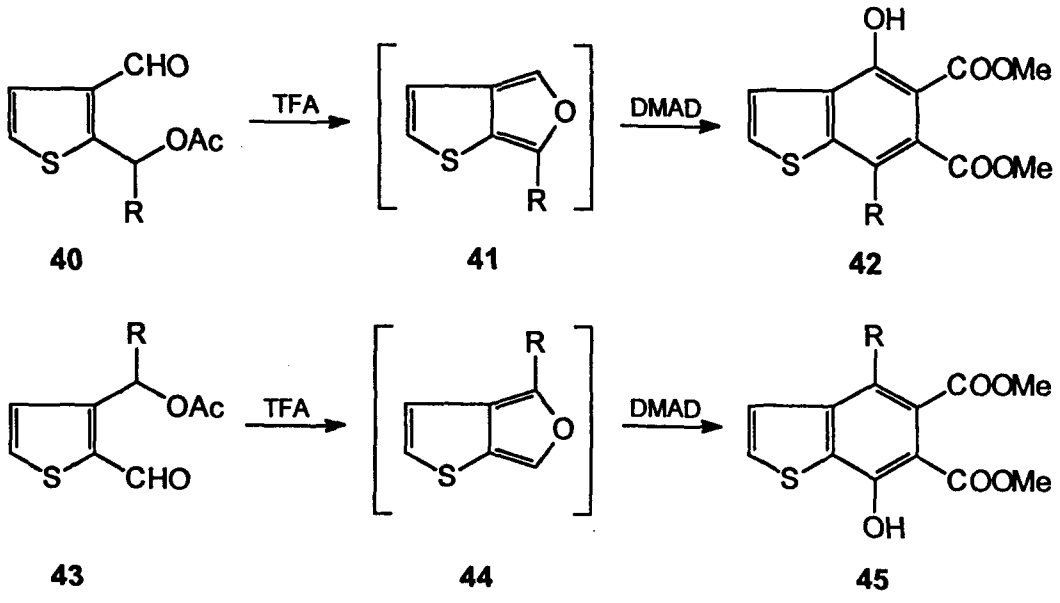
Scheme 6

Iwasaki and co-workers[28] have generated 6-aryl- and 4-arylthieno[2,3-*c*] furans **41** and **44** under acidic conditions from 2-(acetoxybenzyl)thiophene-3-carboxaldehydes and 3-(acetoxy-3,4-dimethoxybenzyl)thiophene-2-carboxaldehyde **40** and **43** respectively which were intercepted *in situ* by dimethyl acetylenedicarboxylate to yield the corresponding benzo[*b*]thiophenes **42** and **45** in good yields (Scheme 8).

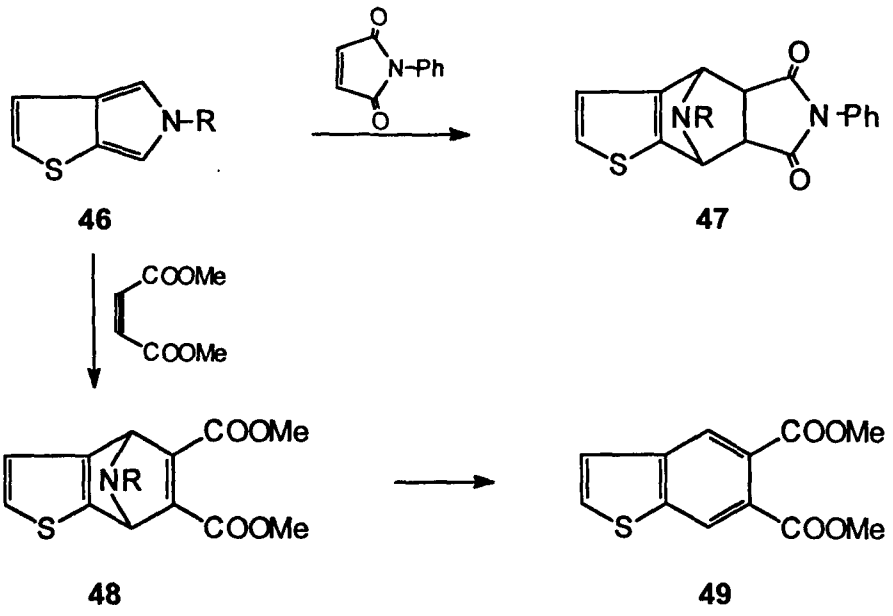
Similarly Sha and Tsou[29] have prepared thieno[2,3-*c*]pyrroles **46** as excellent Diels-Alder dienes to react with N-phenylmaleimide and dimethyl acetylenedicarboxylate to give the corresponding cycloadducts **47** and **48**. Extrusion of imine nitrogen from **48** (R=Me) gave benzothiophene **49** (Scheme 9).



Scheme 7

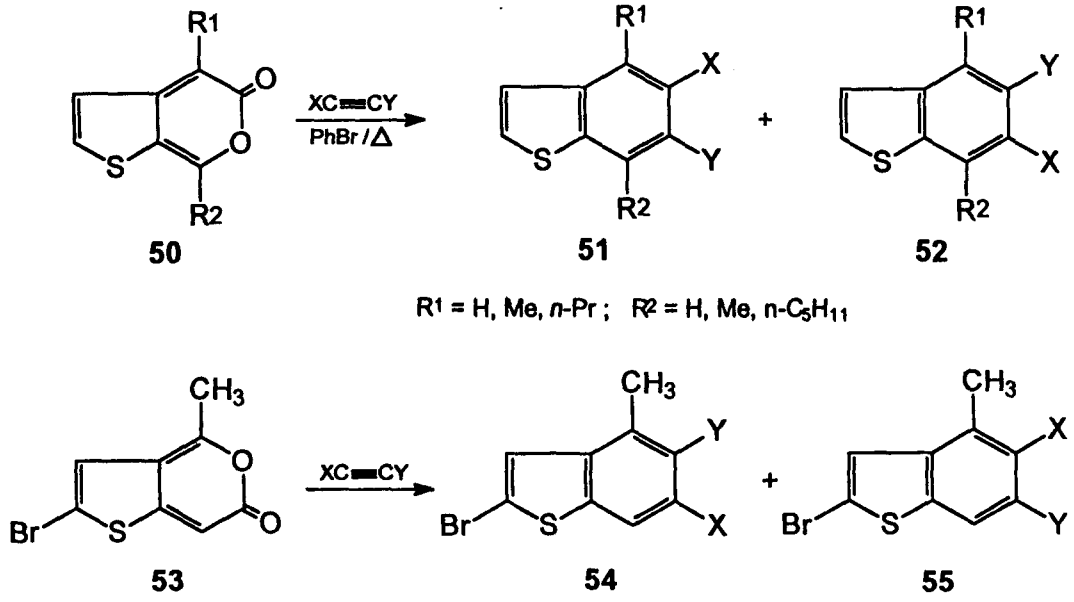


Scheme 8



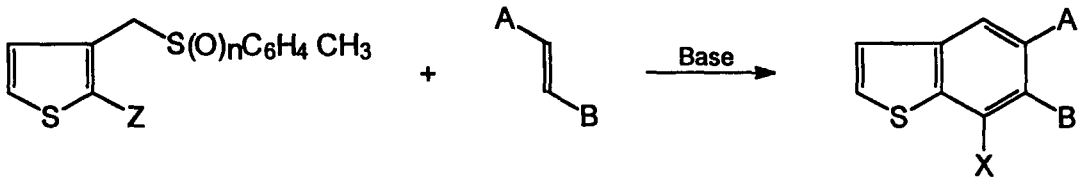
Scheme 9

Moody and co-workers[30] have prepared thieno[2,3-*c*]pyran-3-ones **50** and the isomeric [3,2-*c*]pyranones **53** as stable derivatives of 2,3-dimethylenethiophene. When heated with alkynes they underwent Diels-Alder reaction to give, after loss of carbon dioxide, benzo[b]thiophenes (Scheme 10). With unsymmetrical alkynes, the Diels-Alder reaction exhibited varying degrees of regioselectivity.



Scheme 10

Another approach for benzo[*b*]thiophenes was developed by Leusen and Terpstra[31] involving reaction of 2,3-disubstituted (one electrophilic and one potentially nucleophilic) thiophenes with Michael acceptors followed by intramolecular cyclization. Thus, thiophenes substituted with *p*-toluenesulfonylmethyl and *p*-toluenesulfinylmethyl groups at 3-position and carboxaldehyde, methoxycarbonyl and cyano groups at 2-position **56** were reacted with various Michael acceptors **57** in the presence of base to give the corresponding 5,6-disubstituted and 5,6,7-trisubstituted benzo[*b*]thiophenes **58** in good yields (Scheme 11).



56

Z = CHO, COOMe, CN

57

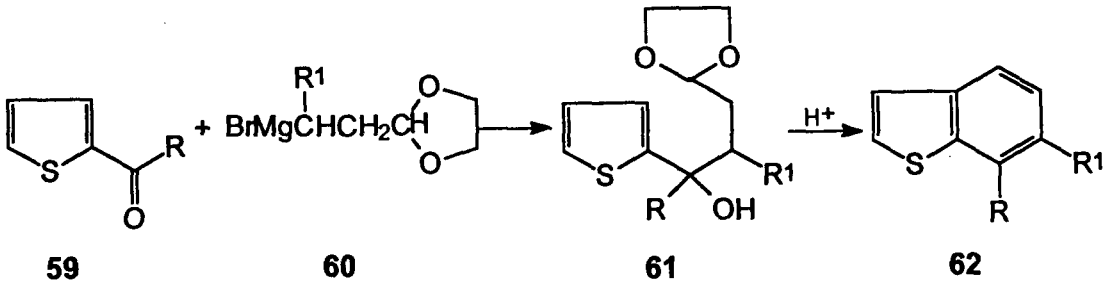
58

A = B = COOH; A = Ph, B = COPh
A = B = COOMe; A = Ph, B = COOMe
A = B = COPh; A = Me, B = COOMe
X = H, OH, NH_2

Scheme 11

Godefroi and Loozen[32] have developed a novel benzo[*b*]thiophene synthesis by annulating aromatic ring over the preconstructed thiophene ring. The Grignard reagents **60** were prepared and reacted with 2-formyl- and 2-acylthiophenes **59** to give the corresponding carbinolacetals **61** in high yields. The intermediates **61** were then treated with 10% refluxing sulfuric acid to afford the corresponding benzothiophenes **62** in 60-70% overall yields (Scheme 12).

Yonemitsu and co-workers[33] have synthesised benzo[*b*]thiophenes by acid catalysed cyclization of β-ketosulfoxides **63** as shown in Scheme 13. Thus when

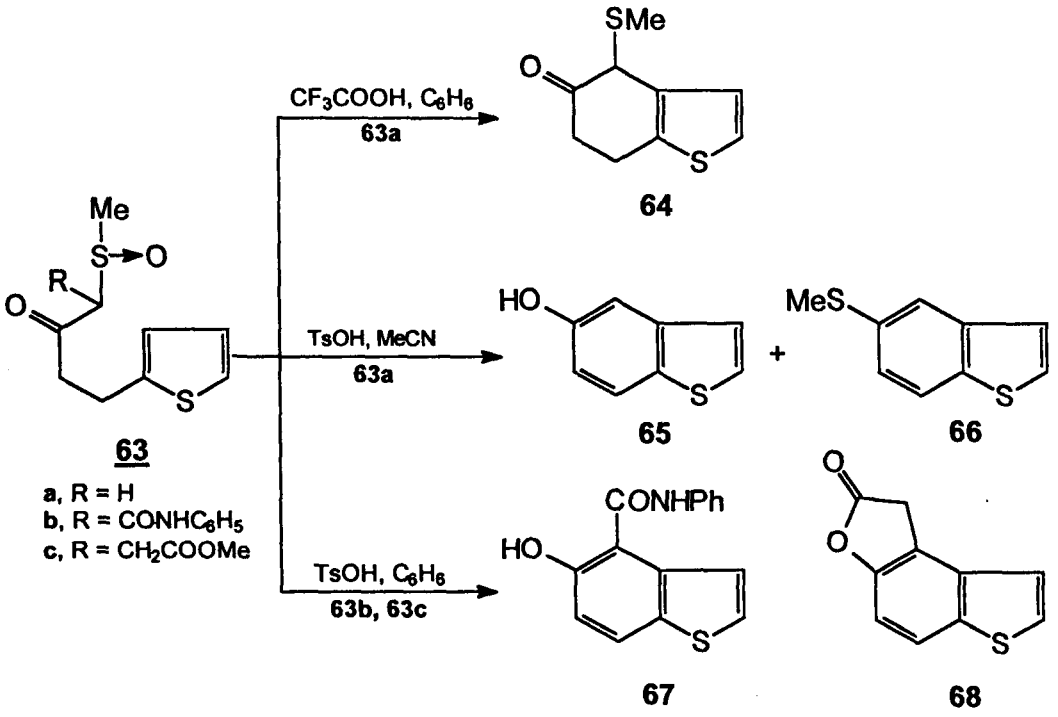


59 60 61 62

R = H, CH_3, C_2H_5, i-C_3H_7, t-C_4H_9, OC_2H_5; R^1 = H, CH_3

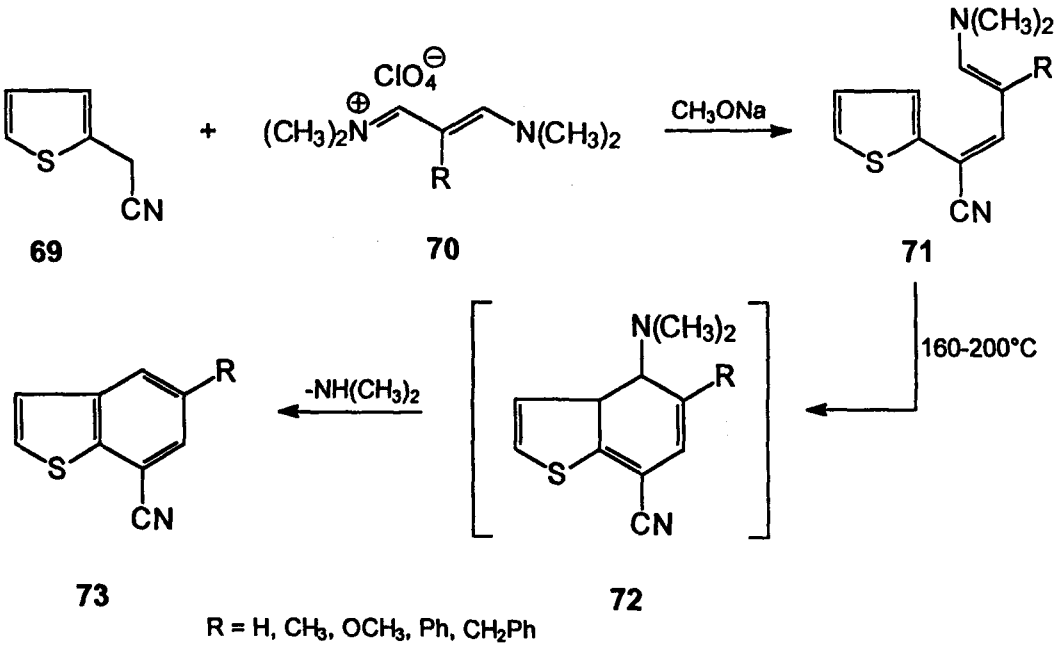
Scheme 12

63a was treated with trifluoroacetic acid in benzene, tetrahydrobenzo[*b*]-thiophene-5-one **64** was formed in 50% yield. Treatment of **63a** with *p*-toluenesulfonic acid in acetonitrile gave a mixture of benzothiophenes **65** and **66** in 56 and 14% yields respectively. The β-ketosulfoxides **63b** and **63c** gave the corresponding benzothiophenes **67** and **68** respectively when treated with *p*-toluenesulfonic acid in benzene.



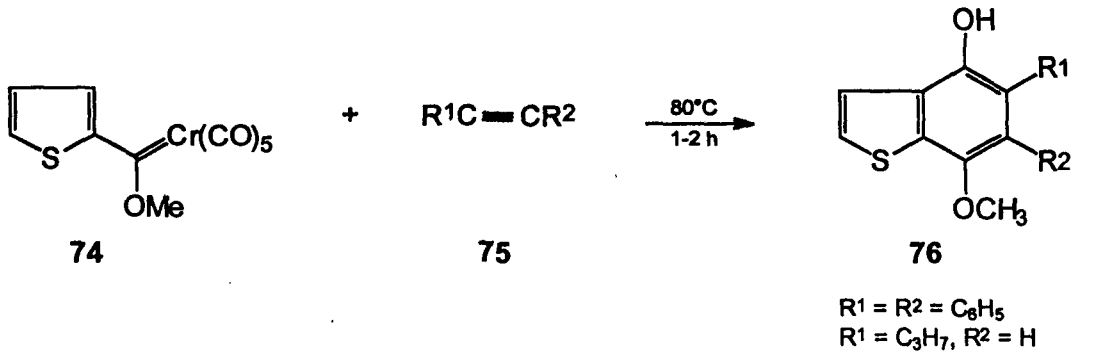
Scheme 13

Thermal cyclization of 5-dimethylamino-2-(2-thienyl)-2,4-pentadienonitriles **71** to the corresponding benzo[*b*]thiophenes **73** has been reported by Jutz and co-workers[34] (Scheme 14). The intermediates **71** were prepared by the reaction of thiophene-2-acetonitrile **69** with trimethinimium perchlorates **70** in the presence of sodium methoxide.



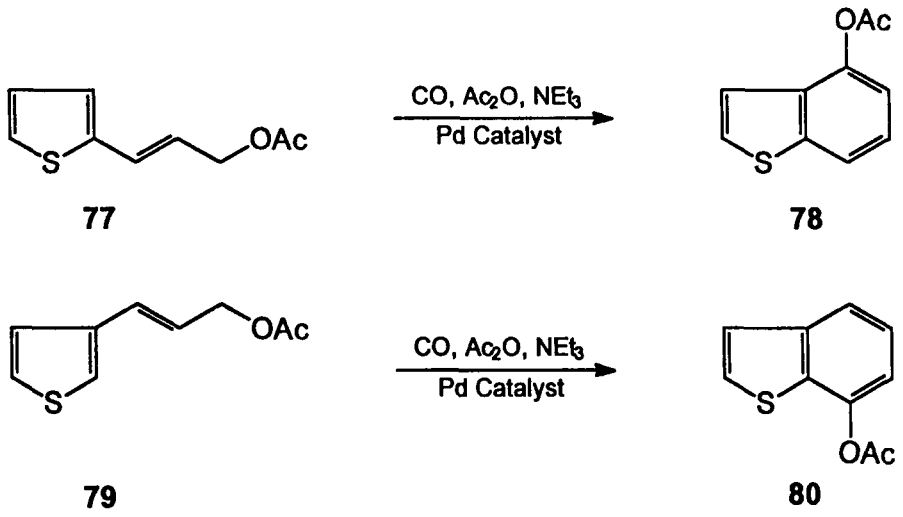
Scheme 14

Dotz and co-workers[35] have reported an interesting method for the synthesis of benzo[*b*]thiophenes **76** involving cycloaddition reaction of thiophene-carbene chromium complex **74** with alkynes **75** (Scheme 15).



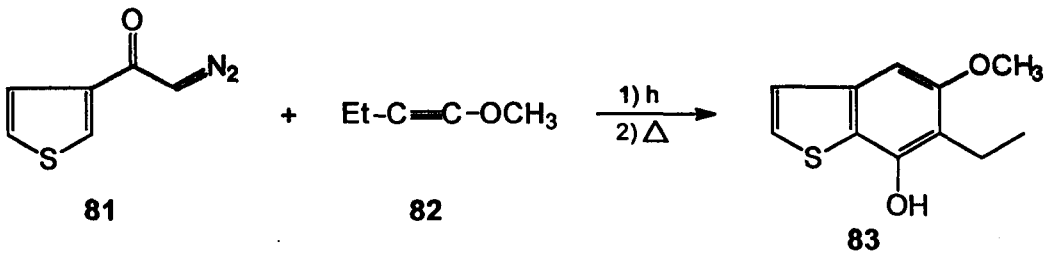
Scheme 15

4-Acetoxy- and 7-acetoxybenzo[*b*]thiophenes **78** and **80** were synthesised in good yields by Hidai and co-workers[36] from 2- and 3-thienyl allylacetates **77** and **79** respectively (Scheme 16). Thus **77** and **79** were cyclocarbonylated in the presence of acetic anhydride, triethylamine and catalytic amount of $PdCl_2(PPh_3)_2$ under carbon monoxide atmosphere to afford the corresponding benzothiophenes **78** and **80**.



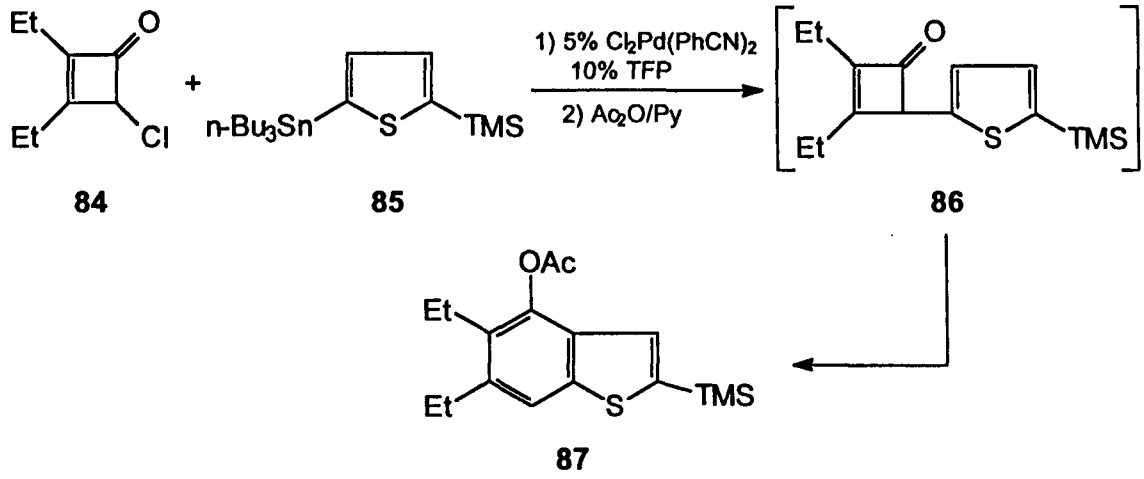
Scheme 16

Danheiser and co-workers[37] have reported an annulation method for the synthesis of benzothiophene which involves irradiation of a dichloromethane solution of diazoketone **81** and acetylene **82** to afford the corresponding substituted benzo[*b*]thiophene **83** (Scheme 17).



Scheme 17

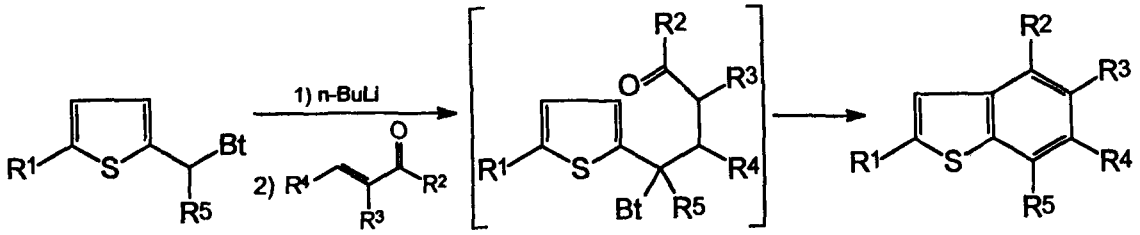
Another annulation approach for benzo[*b*]thiophene has been described by Liebeskind and Wang[38] (Scheme 18). 4-Chloro-2,3-diethyl-2-cyclobutenone **84** underwent palladium catalysed cross coupling with 5-(trimethylsilyl)-2-(tri-*n*-butylstannyl)thiophene **85** and upon thermolysis at 100°C, substituted benzo[*b*]-thiophene **87** was formed in 58% yield.



84 **85** **86** **87**

Scheme 18

Katritzky and co-workers[39] have used 2-(benzotriazol-1-ylmethyl)thiophenes **88** for the synthesis of benzo[*b*]thiophenes as formulated in Scheme 19. These fictionalised thiophenes are 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 catalysed intramolecular cyclization followed by debenzotriazolization-dehydration afforded polysubstituted benzo[*b*]thiophenes **90** in good yields.



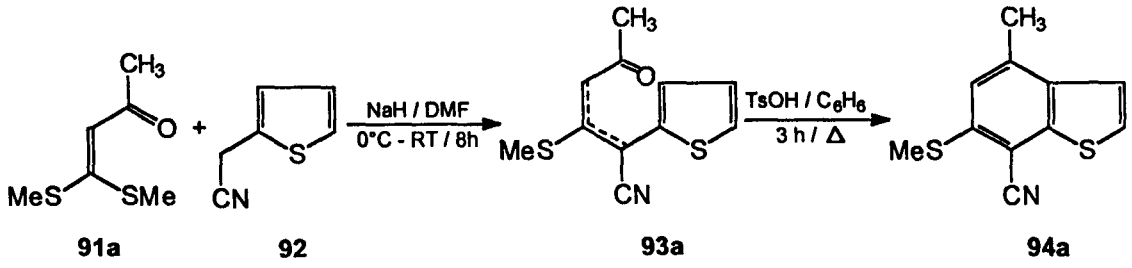
R^1 = H, Me; R^2 = H, Me, Ph; R^3 = H, Me, Ph; R^4 = Et, Ph; R^5 = Me, n-Pr, n-Bu

Scheme 19

RESULTS AND DISCUSSION

In the preceding section we have described a number of methods for the synthesis of benzo[*b*]thiophenes starting from preconstructed thiophene derivatives. Most of the methods fall in the category of cycloaddition reactions to yield dihydro- and tetrahydro benzothiophenes which require dehydrogenation steps to yield the fully aromatic benzo[*b*]thiophenes. Also, in many cases, a mixture of regioisomers were formed when unsymmetrical dienophiles were used. The other condensation methods reported for the synthesis of benzothiophenes possess limited scope of general application for large variety of structural variants. Despite many methods reported on the synthesis of these compounds, the benzo[*b*]thiophene synthesis with regiocontrol on 4,5,6,7-positions will be a method of great synthetic advantage, since many of the preceding methods lack these advantages. In continuation of our interest on the chemistry of α-oxoketene dithioacetals we had earlier described, in chapter II, the utilization of 1-methylpyrrole-2-acetonitrile as allyl anion precursor to afford indoles as a useful protocol of our new general method of heteroaromatic annelation. We further considered of interest to extend these studies to the thiophene-2-acetonitrile to develop a methodology for the synthesis of benzo[*b*]thiophenes. The results of the investigation are described in this section.

In a typical experiment, thiophene-2-acetonitrile **92** and α-oxoketene dithioacetal **91a** derived from acetone were reacted in the presence of sodium hydride in dimethyl formamide at ice-cold temperature to room temperature for 8 hours. The reaction mixture after work up yielded crude addition-elimination product **93a** which was purified by silica gel column chromatography using hexane-ethylacetate (97:3) to yield **93a** as colourless crystals in 88% yield.



Scheme 20

The structure of **93a** was established on the basis of its analytical and spectral data as given below.

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

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

^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.42 (s, 3H), 4.01 (s, 2H), 7.06-7.09 (m, 1H), 7.41-7.46 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.73, 29.46, 49.79, 105.41, 117.47, 126.79, 127.62, 129.67, 135.32, 148.81, 202.08.

MS: *m/z* 237 (M^+, 16%).

Anal. Calcd. for $C_{11}H_{11}NOS_2$ (237.35): C, 55.67; H, 4.67; N, 5.90%. Found: C, 55.28; H, 4.70; N, 5.94%.

This addition-elimination product **93a** was then subjected to cycloaromatization by treating with *p*-toluene sulfonic acid in refluxing benzene for 4 hours. Work-up of the reaction mixture followed by column chromatography using hexane-ethyl acetate (97:3) as eluent afforded 7-cyano-4-methyl-6-(methylthio)benzo[*b*]thiophene **94a** as colourless crystals (m.p. 160-161°C) in 70% yield. The compound was characterised on the basis of its analytical and spectral data as follows.

IR (KBr): ν_{max} 2207, 1560 cm^{-1}.

^1H NMR (300 MHz), $CDCl_3$): δ 2.62 (s, 3H), 2.64 (s, 3H), 7.12 (s, 1H), 7.35 (d, J=7.4 Hz, 1H), 7.47 (d, J= 7.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$); δ 17.00, 20.24, 116.03, 122.27, 124.16, 126.71, 126.77, 137.54, 138.29, 140.63, 143.72.

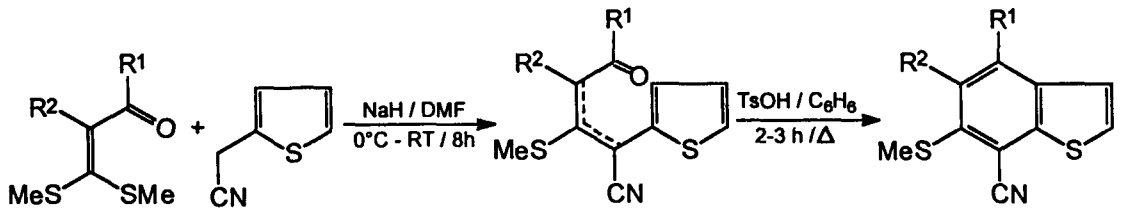
MS: *m/z* 219 (M^+, 100%).

Anal. Calcd. for $C_{11}H_9NS_2$ (219.33): C, 60.24; H, 4.14; N, 6.29%; Found: C, 60.43; H, 4.15; N, 6.26%.

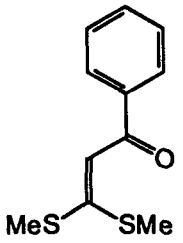
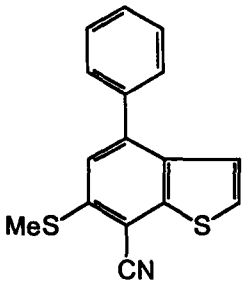
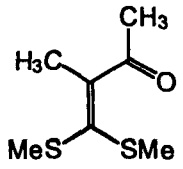
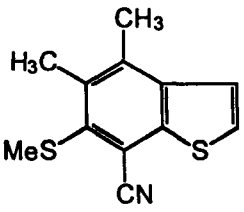
The addition-elimination product was characterised only in this case and in the subsequent reactions the addition-elimination products were generally recognised by tlc spot and the crude adducts were directly subjected to cyclization reactions to afford the corresponding benzo[*b*]thiophenes.

To generalise this reaction, the α-oxoketene dithioacetals selected for the construction of benzo[*b*]thiophenes were so chosen as to demonstrate substitution distribution pattern on 4,5,6 and 7-positions of the benzothiophene. Though cyano group continues to remain at position 7, it is a precursor of carboxylic, amide, ester, methylamine and methyl groups.

The oxoketene dithioacetals **91b** and **91c** derived from acetophenone and ethyl methyl ketone respectively were then reacted with **92** under the described reaction conditions to yield the corresponding 7-cyano-6-methylthio-4-phenylbenzo[*b*]thiophene **94b** and 7-cyano-4,5-dimethyl-6-(methylthio)benzo[*b*]-thiophene **94c** (Scheme 21). The compounds were purified by silica gel column chromatography using hexane-ethylacetate (97:3) as eluent to afford **94b** and **94c** as colourless crystals in 72 and 64% yields respectively. The analytical and spectral data of both the compounds are in accordance with the assigned structure and are recorded in the experimental section.



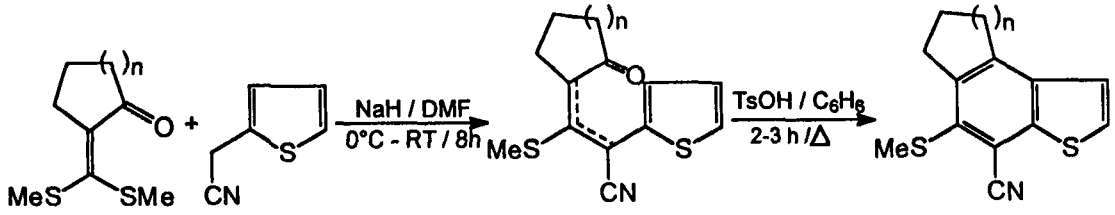
91 **92** **93** **94**

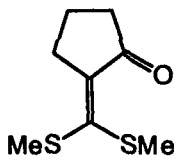
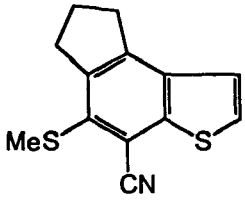
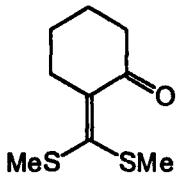
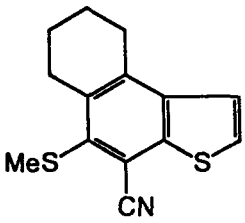
S,S-Acetal	Benzo[b]thiophene	Yield
 **91b**	 **94b**	72
 **91c**	 **94c**	64

Scheme 21

The method was equally useful for the synthesis of 4,5-annelated benzo[*b*]thiophenes. Thus the cyclic α-oxoketene dithioacetal **95a** derived from cyclopentanone was reacted with **92** under aforementioned reaction conditions to afford the corresponding 4-cyano-5-(methylthio)indano[5,4-*b*]thiophene **97a** as colourless crystals (m.p.129-130°C) in 66% yield. The structure of **97a** was confirmed by its spectral and analytical data.

Similarly, oxoketene dithioacetal derived from cyclohexanone **95b** was reacted with **92** under the described reaction conditions to afford the corresponding 6,7,8,9-tetrahydronaphtho[2,1-*b*]thiophene **97b** as colourless crystals obtained in 60% yield. The structure was confirmed by its analytical and spectral data which are described in the experimental section.

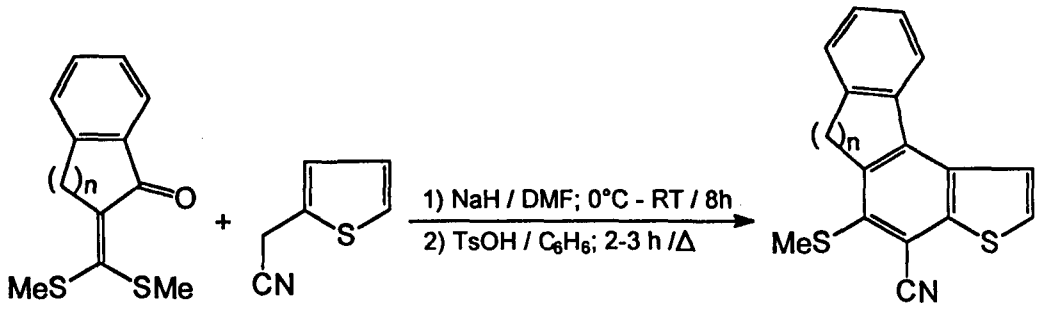


S,S-Acetal	Benzo[b]thiophene	Yield
 **95a**	 **97a**	66
 **95b**	 **97b**	60

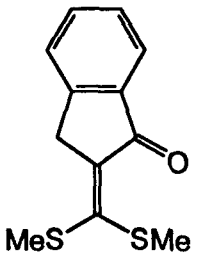
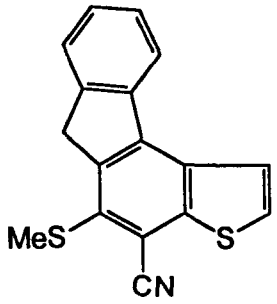
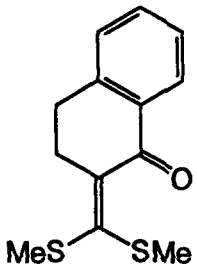
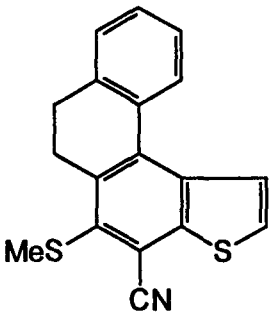
Scheme 22

Further both oxoketene dithioacetals **98a** and **98b** derived from indanone and tetralone respectively were similarly reacted with **92** under the described reaction conditions to afford the corresponding fluoreno[3,4-*b*]thiophene **99a** and

dihydrophenanthreno[3,4-*b*]thiophene **99b** in 56 and 62% yields respectively. The structures of both **99a** and **99b** were established by their spectral and analytical data which are given in the experimental section.

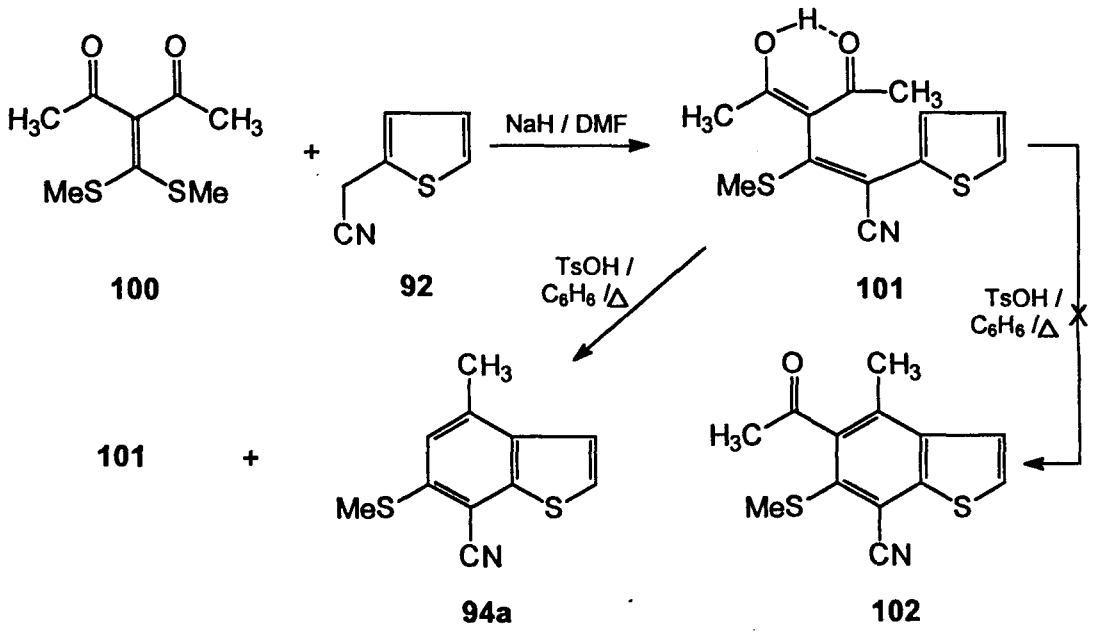


98 **92** **99**

S,S-Acetal	Benzo[b]thiophene	Yield
 **98a**	 **99a**	56
 **98b**	 **99b**	62

Scheme 23

As a typical example, doubly activated ketene dithioacetal **100** derived from acetyl acetone was reacted with **92** in the presence of sodium hydride in dimethyl formamide to afford the corresponding addition-elimination product **101** in near quantitative yield. The crude adduct was then subjected to cycloaromatization by refluxing with *p*-toluene sulfonic acid in benzene. Work-up of the reaction mixture and column chromatography however afforded 7-cyano-4-methyl-6-(methylthio)benzo[*b*]thiophene **94a** in 26% yield, instead of the expected 5-acetylbenzo[*b*]-thiophene **102**, along with uncyclized adduct **101** in 48% yield. The compound thus isolated was found to be identical with that obtained by reaction of **92** with **91a**. Apparently one of the acetyl group is eliminated during the cyclization step. When the pure adduct **101** obtained from column was again treated with *p*-toluene sulfonic acid in refluxing benzene, the similar result was observed.

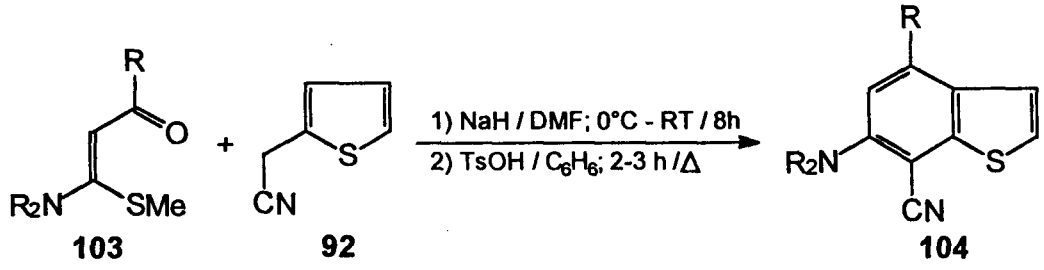


Scheme 24

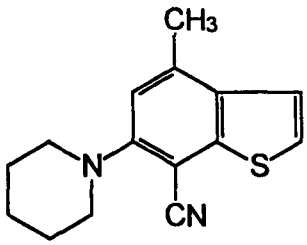
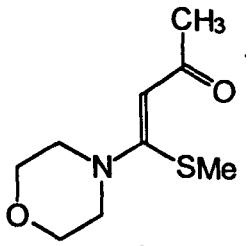
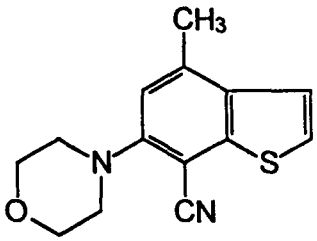
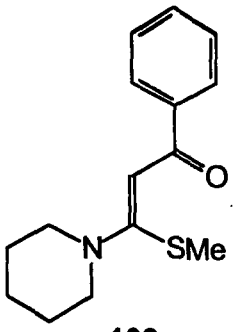
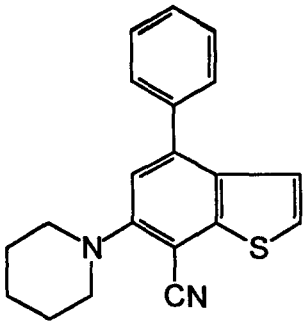
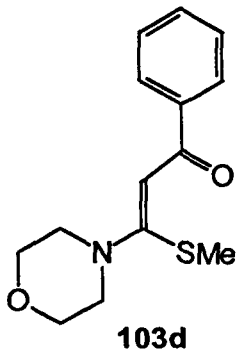
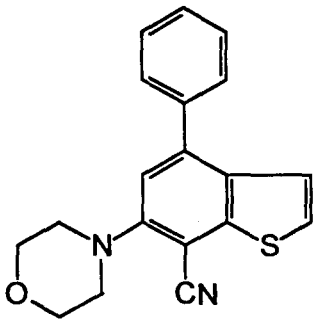
In order to demonstrate the versatility of this benzoannelation methodology, as well as to develop this method for the synthesis of 6-amino-benzo[*b*]thiophenes, the reaction of α-oxoketene-N,S-acetals with thiophene-2-

acetonitrile **92** were examined. Thus S,N-acetal **103a** derived from acetone and piperidine was reacted with **92** under the described reaction conditions to afford the corresponding 7-cyano-4-methyl-6-piperidinobenzo[*b*]- thiophene **104a** in 72% yield. The structure of this compound was established by its analytical and spectral data which are described in the experimental section. Similarly the other oxoketene-N,S-acetals **103b-d** were reacted with **92** to afford the corresponding aminobenzothiophenes in 67-74% overall yields. All these compounds were characterised by spectral and analytical data which are recorded in the experimental section.

In conclusion, it is demonstrated that the thiophene-2-acetonitrile reacts with various ∝-oxoketene S,S and S,N-acetals in the presence of base to yield the corresponding addition-elimination products in excellent yields. The isolation and characterisation of these intermediates was not always necessary and thus the intermediates were directly cyclized in the presence of *p*-toluenesulfonic acid to afford the corresponding benzo[*b*]thiophenes carrying substituents regioselectively at all the four positions of the benzene ring. The method is so versatile and a large number of benzothiophenes and their condensed variants can be prepared by reacting thiophene-2-acetonitrile with a wide variety of functionalized oxoketene S,S-, O,S, and N,S-acetals though only a selected number of S,S- and S,N-acetals have been selected in the present study. Despite many methods described in the literature, most of them appear to suffer from limitation of one or the other making them less practical for general synthetic applications. The present method, therefore, is more versatile with easy to operate and less complicated experimental conditions with good yields of benzothiophene formation. In addition to these advantages, the method offers further scope to introduce substituents in the thiophene ring through appropriate electrophilic substitutions to yield potentially biologically important isoesters of the corresponding indole derivatives.



103 **92** **104**

N,S-Acetal	Benzo[b]thiophene	Yield
 **103a**	 **104a**	72
 **103b**	 **104b**	67
 **103c**	 **104c**	70
 **103d**	 **104d**	74

Scheme 25

EXPERIMENTAL

General

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer and the frequencies are expressed in cm^{-1}. ^1H NMR (300 MHz), ^{13}C NMR (75.43 MHz) spectra were recorded on Bruker ACF-300 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethyl silane and coupling constants (J) are given in Hertz. Mass spectra were obtained on a Jeol D-300 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

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

Chemicals, Solvents and Reagents

Thiophene-2-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,[40] 1-indanone,[41] 1-tetralone,[42] were prepared according to the reported procedure. Dimethyl trithiocarbonate[43] was prepared by according to the literature procedure. Oxoketene-

S,S-acetals, and -N,S-acetals[44] 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-2-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 **93a** obtained by the reaction of thiophene-2-acetonitrile **92** and oxoketene dithioacetal **91a** 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.

5-Cyano-4-methylthio-5-(2-thienyl)pent-4-ene-2-one (93a).

Colourless crystals; m.p. 78-79°C (chloroform-ether); Yield 88%; IR (KBr): ν_{max} 2213, 1710, 1549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.42 (s, 3H), 4.01 (s, 2H), 7.06-7.09 (m, 1H), 7.41-7.46 (m, 4H); ^{13}C NMR (75 MHz): δ 15.73, 29.46, 49.79, 105.41, 117.47, 126.79, 127.62, 129.67, 135.32, 148.81, 202.08; MS: *m/z* 237 (M^+, 16%); Anal. Calcd. for $C_{11}H_{11}NOS_2$ (237.35): C, 55.67; H, 4.67; N, 5.90%; Found: C, 55.28; H, 4.70; N, 5.94%.

7-Cyano-4-methyl-6-(methylthio)benzo[*b*]thiophene (94a).

Colourless crystals; m.p. 160-161°C (chloroform-ether); Yield 70%; IR (KBr): ν_{max} 2207, 1560 cm^{-1}; ^1H NMR (300 MHz), $CDCl_3$): δ 2.62 (s, 3H), 2.64 (s, 3H), 7.12 (s, 1H), 7.35 (d, J=7.4 Hz, 1H), 7.47 (d, J= 7.4 Hz, 1H); ^{13}C NMR (75 MHz); δ 17.00, 20.24, 116.03, 122.27, 124.16, 126.71, 126.77, 137.54, 138.29, 140.63, 143.72; MS: *m/z* 219 (M^+, 100%); Anal. Calcd. for $C_{11}H_9NS_2$ (219.33): C, 60.24; H, 4.14; N, 6.29%; Found: C, 60.43; H, 4.15; N, 6.26%.

7-Cyano-6-methylthio-4-phenylbenzo[*b*]thiophene (94b).

Colourless crystals; m.p. 141-142°C (chloroform-ether); Yield 72%; IR (KBr): ν_{max} 2213, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H), 7.28 (s, 1H), 7.36 (d, J=5.5 Hz, 1H), 7.42-7.52 (m, 6H); ^{13}C NMR (75 MHz): δ 16.83, 104.20, 115.84, 123.54, 123.61, 127.00, 128.65, 128.81, 136.09, 138.98, 140.80, 141.90, 144.60; MS: *m/z* 281 (M^+, 100%); Anal. Calcd. for $C_{16}H_{11}NS_2$ (281.40): C, 68.29; H, 3.94; N, 4.98%; Found: C, 68.70; H, 3.87; N, 5.03%.

7-Cyano-4,5-dimethyl-6-(methylthio)benzo[*b*]thiophene (94c).

Colourless crystals; m.p. 115-116°C (chloroform-ether); Yield 64%; IR (KBr): ν_{max} 2209, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.58 (s, 3H), 2.60 (s, 3H), 7.37 (d, J=5.5 Hz, 1H), 7.5 (d, J=5.5Hz, 1H); ^{13}C NMR (75 MHz): δ 17.55, 18.11, 19.96, 110.41, 116.95, 122.77, 127.98, 136.42, 137.03, 139.97,

140.81; Anal. Calcd. for $C_{12}H_{11}NS_2$ (233.36): C, 61.76; H, 4.75; N, 6.00%; Found: C, 61.48; H, 4.76; N, 6.02%.

4-Cyano-5-(methylthio)indano[5,4-*b*]thiophene (97a).

Colourless crystals; m.p. 129-130°C (chloroform-ether); Yield 66%; IR (KBr): ν_{max} 2213, 1549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (pentet, J=7.5 Hz, 2H), 2.54 (s, 3H), 3.15 (t, J=7.5 Hz, 2H), 3.24 (t, J=7.6 Hz, 2H), 7.25 (d, J=5.6 Hz, 1H), 7.53 (d, J=5.6 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.06, 24,39, 33.07, 33.20, 108.62, 116.90, 122.10, 128.57, 134.26, 136.29, 142.78, 143.67, 144.23; MS: *m/z* 245 (M^+, 100%); Anal. Calcd. for $C_{13}H_{11}NS_2$ (245.37): C, 63.64; H, 4.52; N, 5.71%; Found: C, 63.96; H, 4.59; N, 5.67%.

4-Cyano-5-methylthio-6,7,8,9-tetrahydronaphtho[2,1-*b*]thiophene (97b).

Colourless crystals; m.p. 136-137°C (chloroform-ether); Yield 60%; IR (KBr) ν_{max} 2213, 1535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88-1.90 (m, 4H), 2.47 (s, 3H), 3.03-3.07 (m,4H), 7.34 (d, J=5.5 Hz, 1H), 7.52 (d, J=5.5 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.63, 22.06, 22.88, 28.07, 28.31, 110.12, 116.90, 121.88, 128.19, 136.83, 137.60, 137.67, 139.40, 140.39; 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 (99a).

Colourless crystals; m.p. 210-211°C (chloroform-ether); Yield 56%; IR (KBr): ν_{max} 2212, 1531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H), 4.04 (s, 3H), 7.42-7.52 (m, 2H), 7.65 (d, J=7.3 Hz, 1H), 7.73 (d, J=5.5 Hz, 1H), 7.94 (d, J=5.5 Hz, 1H), 8.06 (d, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 19.26, 37.71, 108.48, 116.92, 121.46, 122.85, 125.19, 127.37, 128.28, 129.36, 133.46, 134.16, 139.49, 140.41, 143.46, 144.38, 144.62; MS: *m/z* 293 (M^+, 78.9%); 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 (99b).

Colourless crystals; m.p. 132-133°C (chloroform-ether); Yield 62%; IR (KBr): ν_{max} 2207, 1549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 2.77-2.82 (m, 2H), 3.17-3.22 (m, 2H), 7.34-7.37 (m, 3H), 7.60 (d, J=5.6 Hz, 1H), 7.83 (d, J=5.6 Hz, 1H), 7.83-7.85 (m, 1H); ^{13}C NMR (75 MHz): δ 19.80, 27.15, 28.90, 111.2, 116.87, 124.14, 126.72, 127.82, 128.79, 128.92, 133.46, 135.58, 136.04, 136.44, 139.03, 139.57, 143.28; MS: *m/z* 307 (M^+, 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%.

3-[(2-Cyano-1-methylthio-2-(2-thienyl)]ethenylpentan-2,4-dione (101).

Colourless crystals; m.p. 102-103°C (chloroform-ether); IR (KBr): ν_{max} 3093, 2207, 1656, 1555 cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 6H), 2.29 (s, 3H), 7.13-7.16 (m, 1H), 7.50 (dd, J=5.0, 1, 1H), 7.55 (dd, J=3.8, 1, 1H), 16.77 (s, 1H); 13C NMR (75 MHz): δ 16.30, 23.22, 107.25, 110.29, 117.12, 127.05, 127.95, 129.78, 135.39, 149.73, 191.10; Anal. Calcd. for $C_{13}H_{13}NO_2S_2$ (279.38): C, 55.89; H, 4.69; N, 5.01%. Found: C, 55.52; H, 4.62; N, 5.10%.

7-Cyano-4-methyl-6-piperidinobenzo[*b*]thiophene (104a).

Colourless crystals; m.p. 81-82°C (chloroform-ether); Yield 72%; IR (KBr): ν_{max} 2201, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58-1.64 (m, 2H), 1.75-1.83 (m, 4H), 2.59 (s, 3H), 3.23-3.27(m, 4H), 6.83 (s, 1H), 7.27-7.33 (m,2H); ^{13}C NMR (75 MHz): δ 20.42, 24.12, 26.23, 53.53, 95.67, 116.83, 117.60, 122.05,142.31, 133.65, 138.65, 144.75, 155.59; MS: *m/z* 256 (M^+, 100%); Anal. Calcd. for $C_{15}H_{16}N_2S$ (256.37): C, 70.28; H, 6.29; N, 10.93%; Found: C, 69.91; H, 6.25, N, 10.84%.

7-Cyano-4-methyl-6-morpholinobenzo[*b*]thiophene (104b).

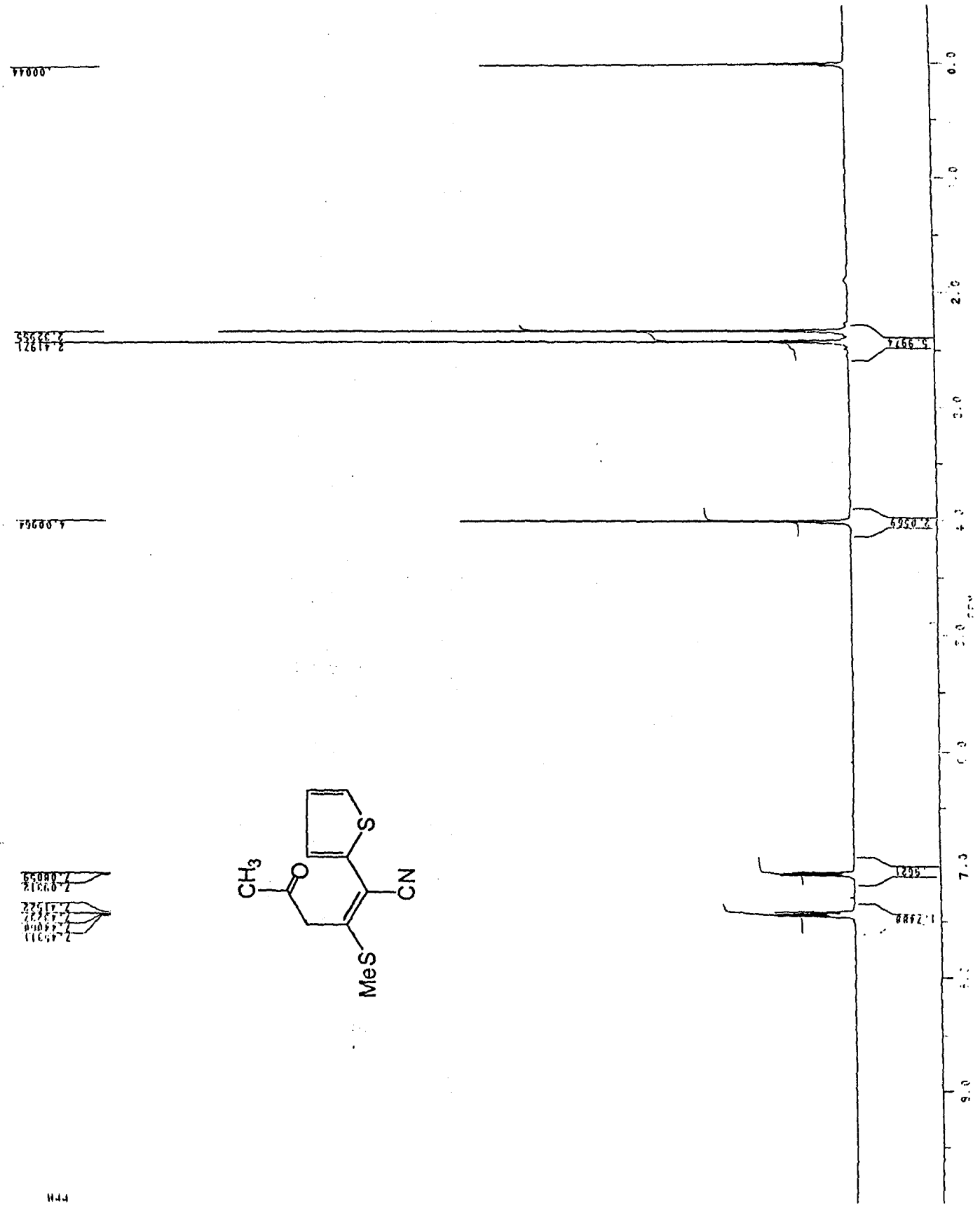
Colourless crystals; m.p. 141-143°C (chloroform-ether); Yield 67%; IR (KBr): ν_{max} 2205, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H), 3.25-3.28 (m, 4H), 3.89-3.93 (m, 4H), 6.85 (s, 1H), 7.30 (d, J=5.5 Hz, 1H), 7.36 (d, J=5.5Hz, 1H); ^{13}C NMR (75 MHz): δ 20.42, 52.22, 66.96, 96.21, 116.40, 117.19, 122.07, 125.02, 134.47, 139.10, 144.31, 154.08; MS: *m/z* 258 (M^+, 71%), 200 (100%); Anal. Calcd. for $C_{14}H_{14}N_2OS$ (258.34): C, 65.09; H, 5.46; N, 10.84%; Found: C, 65.37; H, 5.43; N, 10.77%.

7-Cyano-4-phenyl-6-piperidinobenzo[*b*]thiophene (104c).

Colourless crystals; m.p. 151-152°C (chloroform-ether); Yield 70%; IR (KBr) : ν_{max} 2212, 1565 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$): δ 1.61-1.67 (m, 2H), 1.76-1.81 (m, 4H), 3.28-3.32 (m, 4H), 7.00 (s, 1H), 7.30 (s, 2H), 7.43-7.54 (m, 5H); ^{13}C NMR (75 MHz): δ 24.06, 26.19, 53.53, 97.03, 116.66, 117.40, 123.37, 124.68, 138.33, 128.68, 128.78, 132.30, 139.80, 142.36, 145.41, 155.34; 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%.

7-Cyano-6-morpholino-4-phenylbenzo[*b*]thiophene (104d).

Colourless crystals; m.p. 178-179°C (chloroform-ether); Yield 74%; IR (KBr): ν_{max} 2219, 1564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.32-3.35 (m, 4H), 3.92-3.95 (m. 4H), 7.02 (s, 1H), 7.33-7.39 (m, 2H), 7.48-7.53 (m, 5H); ^{13}C NMR (75 MHz): δ 52.27, 66.98, 97.71, 116.24, 117.03, 123.43, 125.50, 128.53, 128.78, 133.24, 139.55, 142.74, 145.44, 153.96,; MS: *m/z* 320 (M^+, 90.5%), 262 (100%); Anal. Calcd. for $C_{19}H_{16}N_2OS$ (320.41): C, 71.22; H, 5.03; N, 8.74%; Found: C, 71.53; H, 4.98; N, 8.66%.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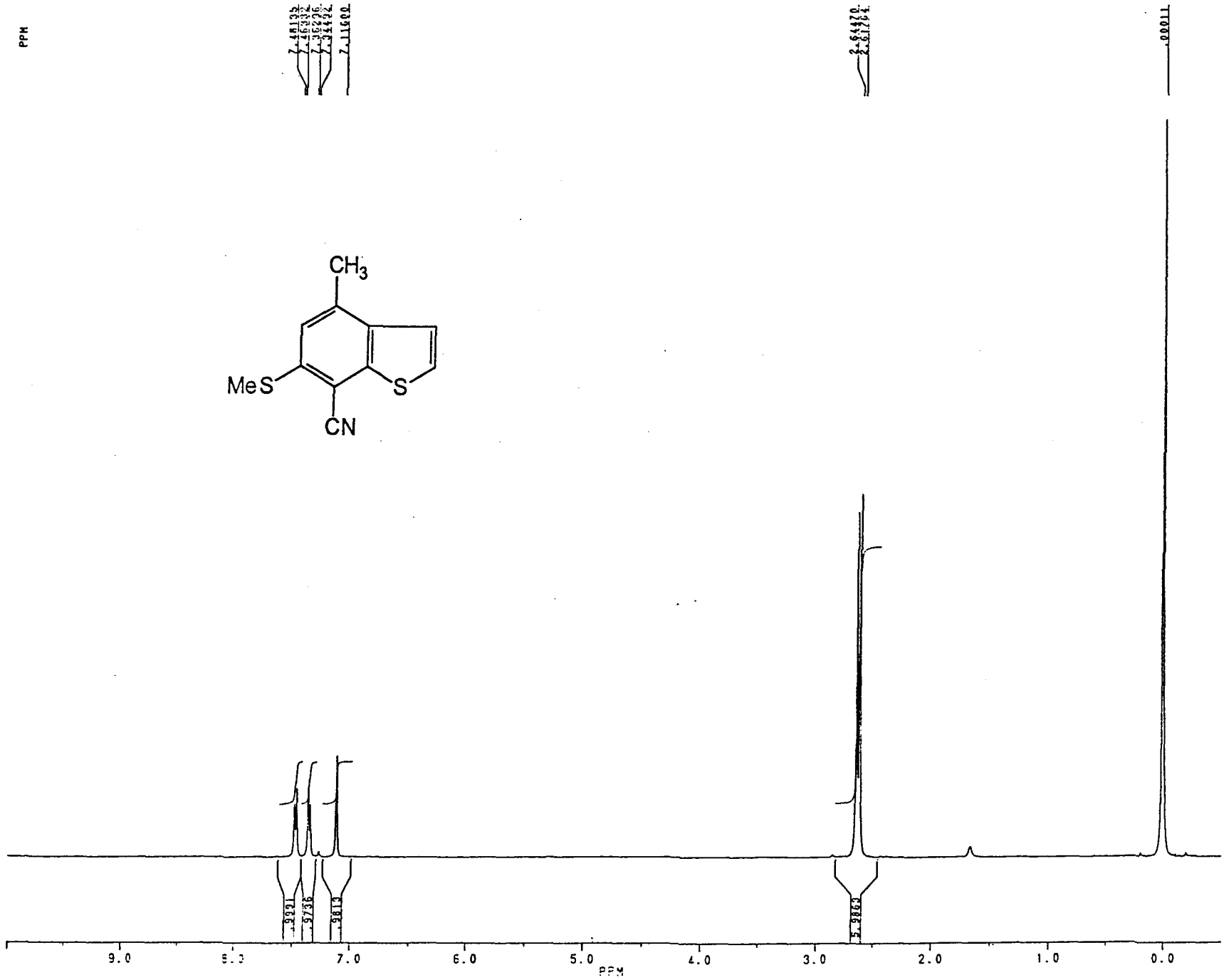
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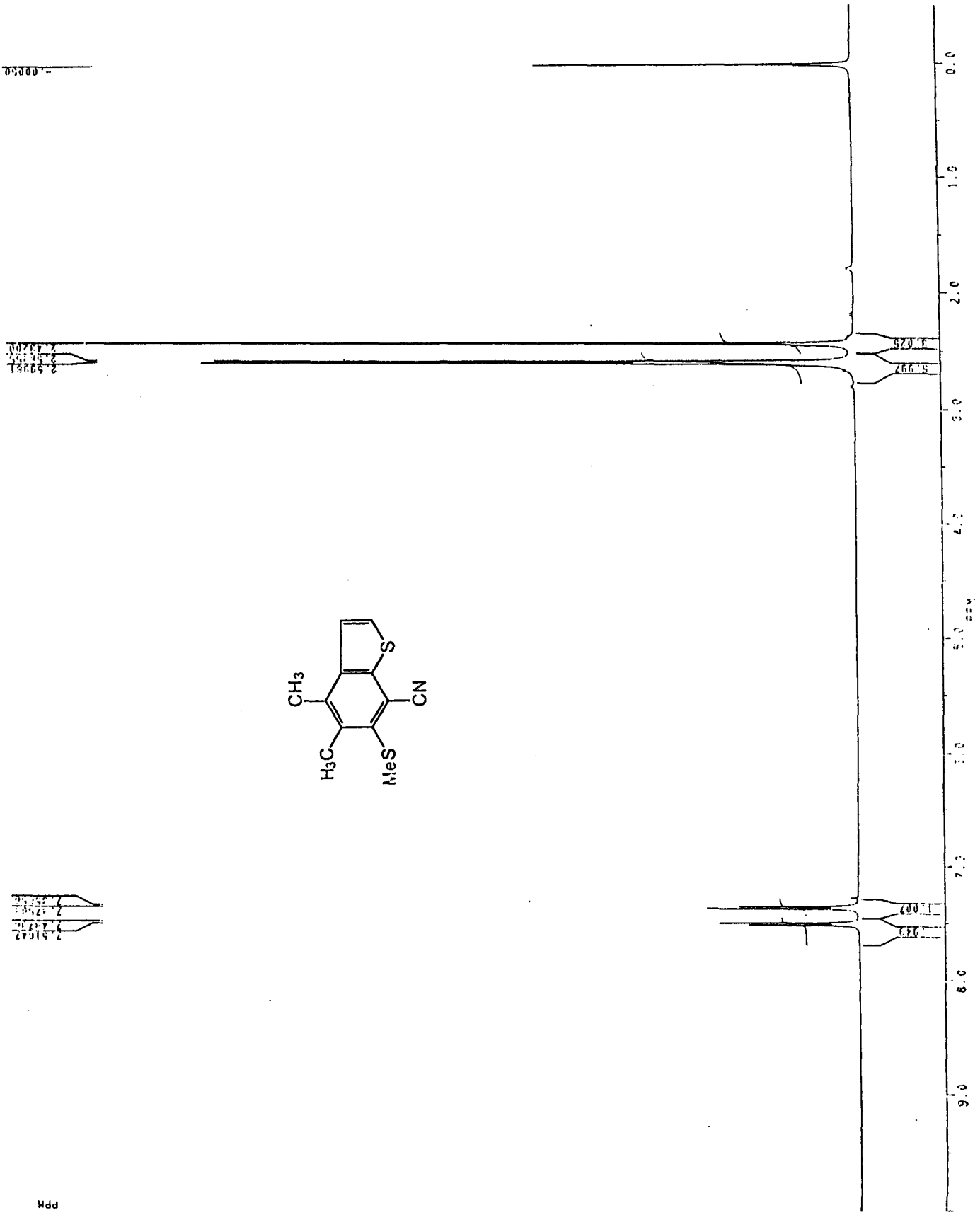
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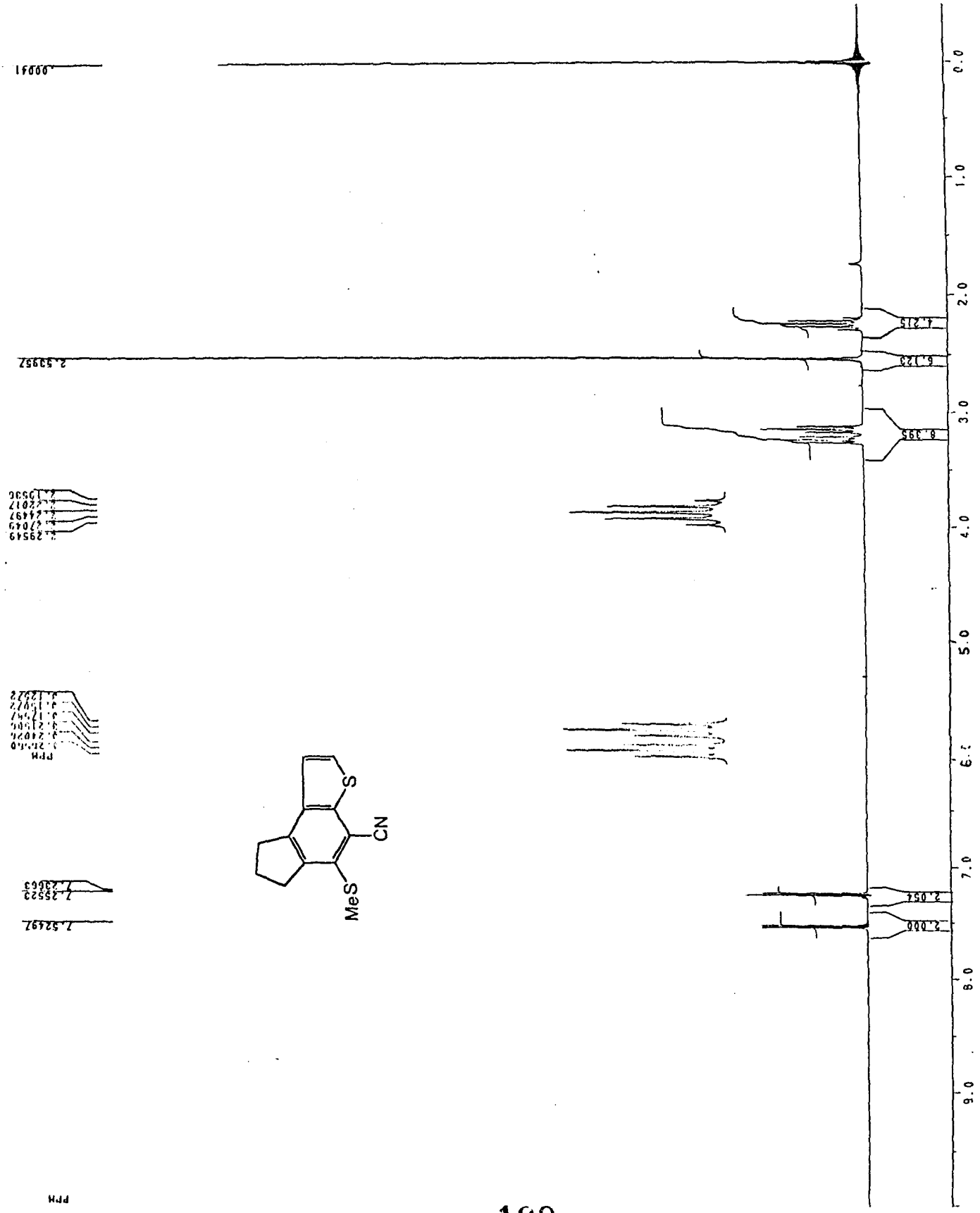
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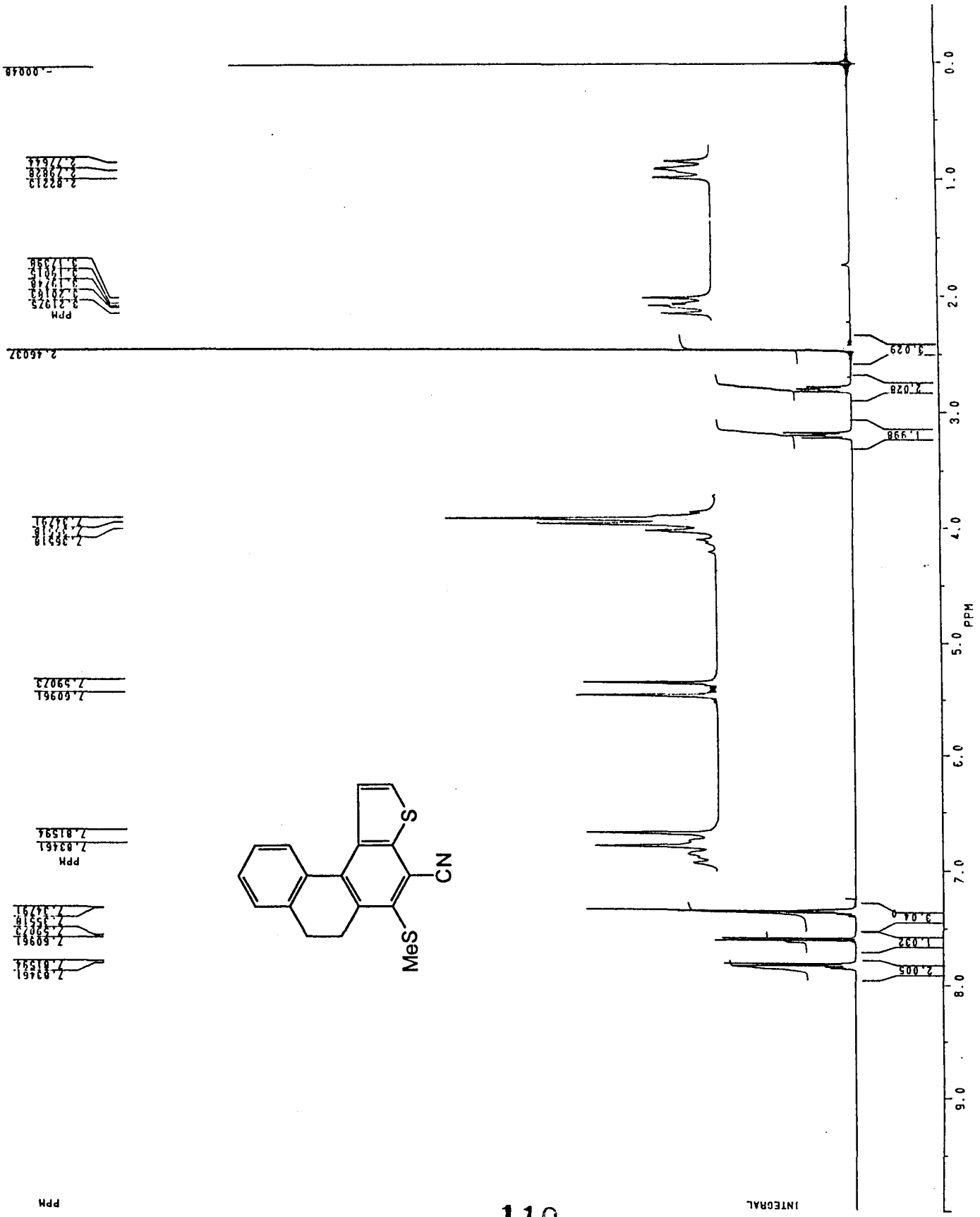
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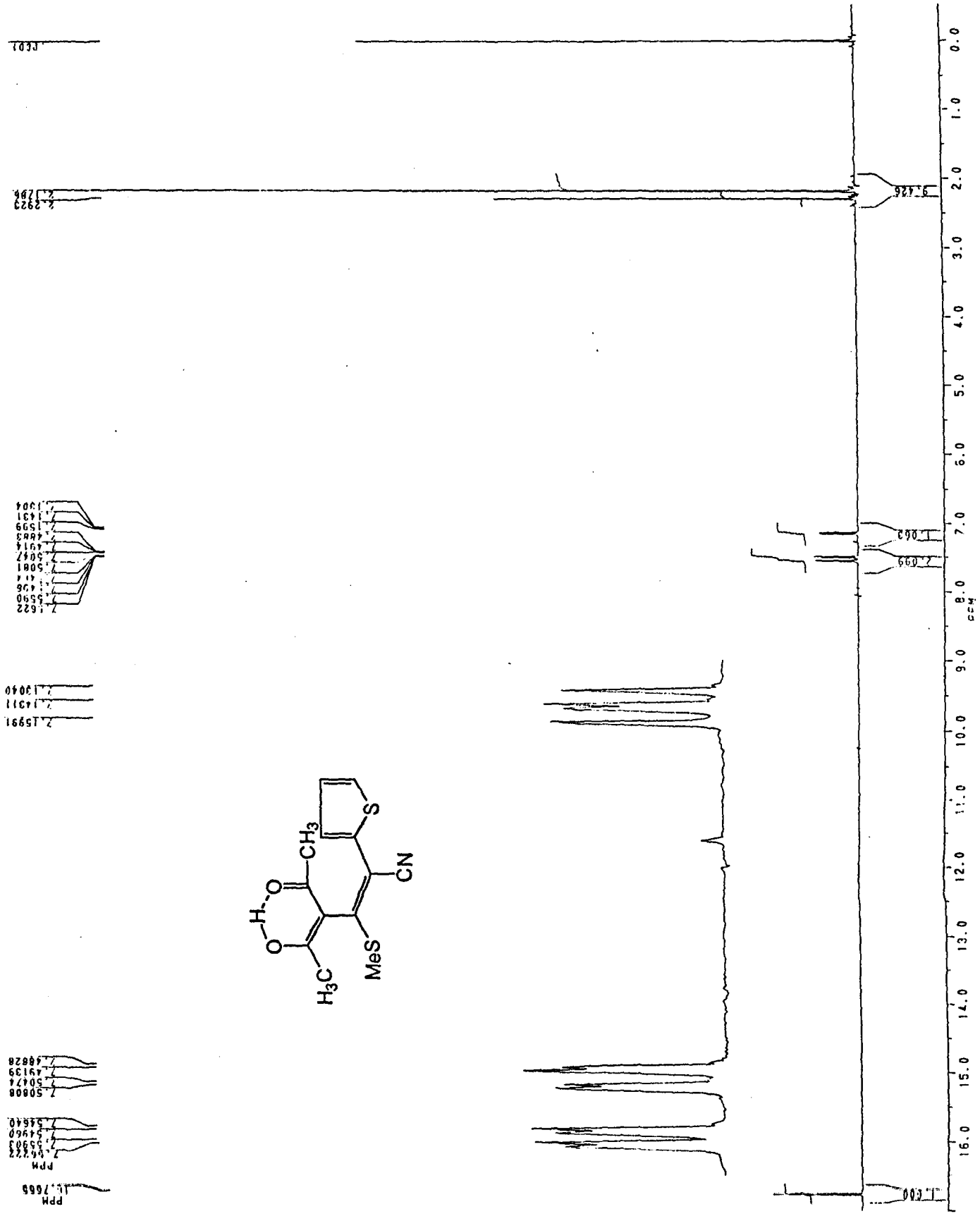
INTEGRAL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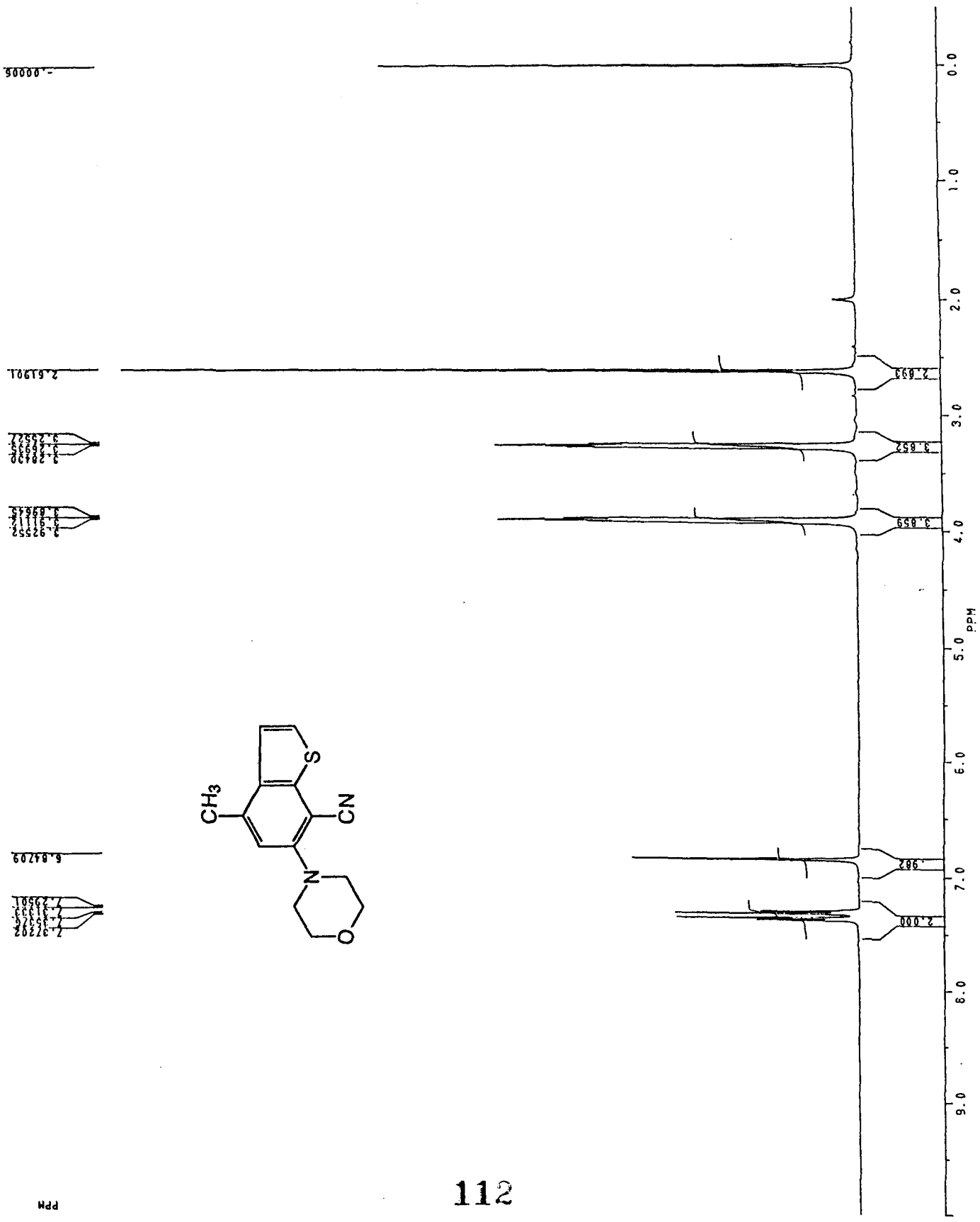
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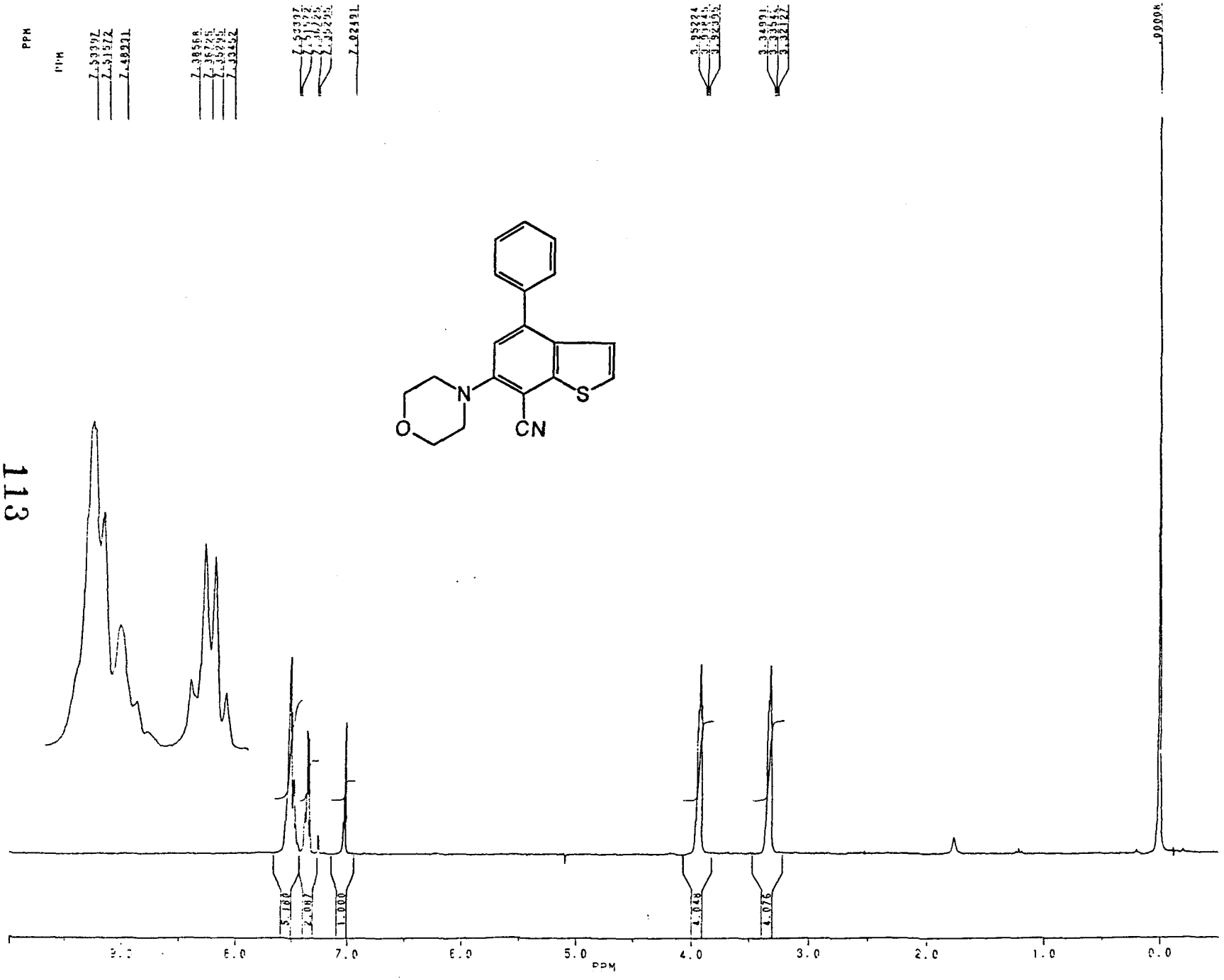
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S
CN
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4.075
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5.0
4.0
3.0
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1.0
0.0
PPM

113

REFERENCES

1. Fukushima, D.K. in *Heterocyclic Compounds* Elderfield, R.C. (Ed.), Wiley, New York, **1951**, Vol. 2, Chapters 4 & 5.
2. Hartough, H.D.; Meisel, S.L. *Chemistry of Heterocyclic Compounds-Compounds with Condensed Thiophene Rings* Weissberger, A. (Ed.), Wiley Interscience, New York, **1954**, Vol. 7.
3. Iddon, B.; Scrowston, R.M. *in Advances in Heterocyclic Chemistry* Katritzky, A.R.; Boulton, A.J. (Eds.), Academic Press, New York, **1970**, Vol. 11, pp 177.
4. Gattermann, L.; Lockhart, A.E. *Ber.* **1893**, *26*, 2808.
5. Campaigne, E.; Knapp, D.R.; Neiss, E.S.; Bosin, T.R. *Adv. Drug. Res.* **1970**, *5*,1. (b) Bosin, T.R.; Campaigne, E. *Adv. Drug. Res.* **1977**, *11*, 191.
6. Iddon, B. *Studies in Organic Chemistry - New Trends in Heterocyclic Chemistry* Elsevier, Amsterdam, **1979**, Vol. 3, pp 250.
7. Scrowston, R.M. in *Advances in Heterocyclic Chemistry* Katritzky, A.R. (Ed.), Academic Press, New York, **1981**, Vol. 29, pp 171.
8. (a) Livingstone, R. *in Rodd's Chemistry of Carbon Compounds* 2nd Ed., Coffey, S. (Ed.), Elsevier, New York, Vol. IV, Part A, **1973**, pp 265. (b) Livingstone, R. in *Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds* Ansell, M.F. (Ed.), Elsevier, New York, Vol. IV, Part A, **1984**, pp 321.
9. Campaigne, E. in *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R.; Rees, C.W.; Bird, C.W.; Cheeseman, G.W.H. (Eds.), Pergamon Press, Oxford, **1984**, Vol. 4, pp 863.
10. Suschizky, H; Scriven, E.F.V. (Eds.), *Progress in Heterocyclic Chemistry* Pergamon Press, Oxford, Vol. 2-7, **1990-1995**.

11. Fieser, L.F.; Kennelly, R.G. *J. Am. Chem. Soc.* **1935**, *57*, 1611.

12. Mac Dowell D.W.H.; Greenwood, T.D. *J. Heterocyclic Chem.* **1965**, *2*, 44.

13. Kitchen, R.; Sandin, R.B. *J. Am. Chem. Soc.* **1945**, *67*, 1645.

14. Kloetzel, M.C.; Little, Jr., J.E.; Frisch, D.M. *J. Org. Chem.* **1953**, *18*, 1511.

15. Cagniant, P.; Merle, G.; Cagniant, D. *Bull. Soc. Chim. Fr.* **1970**, 322.

16. Asprou, C.M.; Brunskill, J.S.A.; Jeffrey, H. J.; De, A. *J. Heterocyclic Chem.* **1980**, *17*, 87.

17. Datta, S.; De, A. *J. Chem. Soc. Perkin Trans. 1* **1989**, 603.

18. Amemiya, Y.; Terada, A.; Wachi, K.; Miyazawa, H.; Hatakeyama, N.; Matsuda, K.; Oshima, T. *J. Med. Chem.* **1989**, *32*, 1265.

19. Samanta, S.S.; Mukherjee, S.; De, A. *J. Chem. Research (S)* **1995**, 429; *(M)* **1995**, 2518.

20. Samanta, S.S.; Mukherjee, S.; De, A. *J. Chem. Research (S)* **1996**, 128; *(M)* **1996**, 0785.

21. Samanta, S.S.; Ghosh, S.C.; De, A. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3673.

22. Scully, J.F.; Brown, E.V. *J. Am. Chem. Soc.* **1953**, *75*, 6329.
See also: Davies, W.; Porter, Q.N. *J. Chem. Soc.* **1957**, 4958.

23. Keil, J.M.; Kampchen, T.; Seitz, G. *Tetrahedron Lett.* **1990**, *31*, 4581.

24. Chadwick, D.J.; Plant, A. *Tetrahedron Lett.* **1987**, *28*, 6085.

25. van Leusen, A.M.; van den Berg, K.J. *Tetrahedron Lett.* **1988**, *29*, 2689.

26. Crew, A.P.A.; Jenkins, G.; Storr, R.C.; Yelland, M. *Tetrahedron Lett.* **1990**, *31*, 1491. See also: Chou, T.-s.; Tsai, C.-Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1287.

27. Schoning, A.; Debaerdemaeker, T.; Zander, M.; Friedrichsen, W. *Chem. Ber.* **1989**, *122*, 1119.

28. Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1635.

29. Sha, C.K.; Tsou, C.P. *J. Org. Chem.* **1990**, *55*, 2446.

30. (a) Jackson, P.M.; Moody, C.J.; Shah, P. *Tetrahedron Lett.* **1988**, *29*, 5817.

(b) Jackson, P.M.; Moody, C.J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2909.

31. (a) van Leusen, A.M.; Terpstra, J.W. *Tetrahedron Lett.* **1981**, *22*, 5097.

(b) Terpstra, J.W.; van Leusen, A.M. *J. Org. Chem.* **1986**, *51*, 230.

32. Loozen, H.J.J.; Godefroi, E.F. *J. Org. Chem.* **1973**, *38*, 1056.

33. Oikawa, Y.; Setoyama, O.; Yonemitsu, O. *Heterocycles* **1974**, 21.

34. Jutz, C.;Wagner, R.M.; Lobering, H.-G. *Angew. Chem. internat. Edit.* **1974**, *13*, 737.

35. Dotz, K.H.; Dittz, R. *Chem. Ber.* **1978**, *111*, 2517.

36. Iwasaki, M.; Li, J.-p.; Kobayashi, Y.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *Tetrahedron Lett.* **1989**, *30*, 95.

37. Danheiser, R.L.; Brisbois, R.G.; Kowalczyk, J.J.; Miller, R.F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

38. Liebeskind, L.S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550.

39. Katritzky, A.R.; Serdyuk, L.; Xie, L.; Ghiviriga, I. *J. Org. Chem.* **1997**, *62*, 6215.

40. Vogel's *Text book of Practical Organic Chemistry* 4th Ed., **1978**, pp 775.

41. Koo, J. *J. Am. Chem .Soc.* **1953**, *75*, 1891.

42. Olson, C.E.; Bader, A.R. *Organic Synthesis* Coll. Vol. 4, **1963**, 898.

43. Rudorf, W.D. *Synthesis* **1983**, 926.

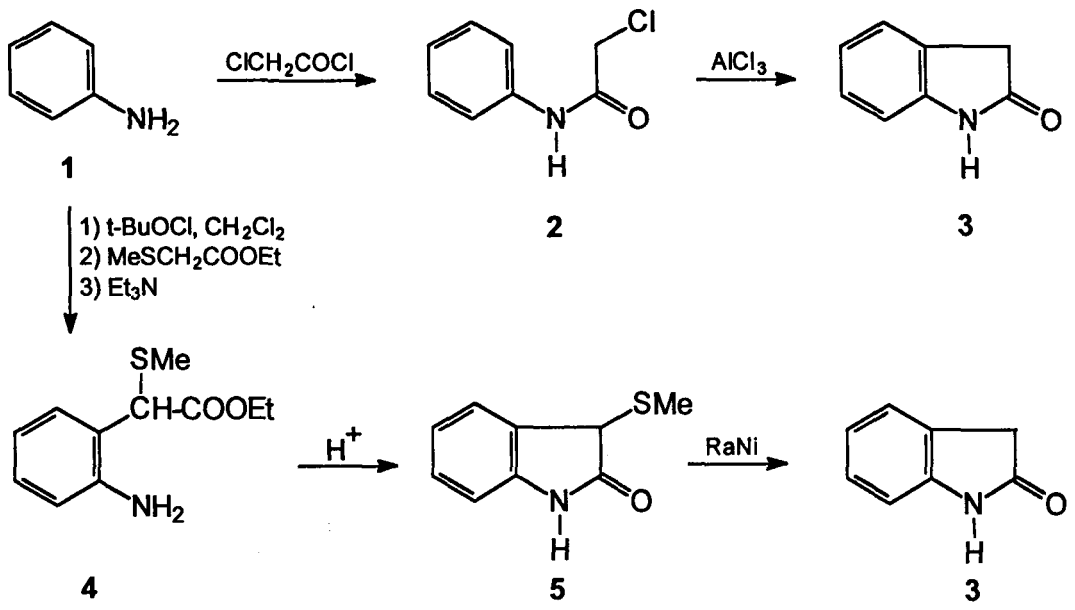
44. Review: Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron* **1990**, *46*, 5423.

CHAPTER IV

ATTEMPTS TO TRANSFORM OXINDOLE INTO INDOLE DERIVATIVES: REACTION OF 3-BIS(METHYLTHIO)METHYLENE-2,3-DIHYDRO-2-OXO-1-METHYLOXINDOLE WITH GRIGNARD REAGENTS.

We have described, in chapter II, the importance of indoles which reflected in the numerous methods devised for their synthesis.[1] Particularly, 2- and 2,3-substituted indoles gained importance due to the fact that they are precursors for various carbazole alkaloids and their analogs.[2-15] These 2- and 2,3-substituted indoles are generally synthesised by intramolecular ring closure of monosubstituted or *ortho*-disubstituted benzene precursors where the substitutions at 2- and 3-positions are installed in the ring closure sequence.[1,16-21] An alternative approach is the functionalization of preconstructed indole nucleus.[22-29]

Oxindole of the formula **3** and its derivatives are generally prepared by subjecting chloroacetanilide under Friedel-Crafts reaction condition[30] and also by Gassman's procedure[31] (**1** → **4** → **5** → **3**) generally in good yields (Scheme 1).[32]

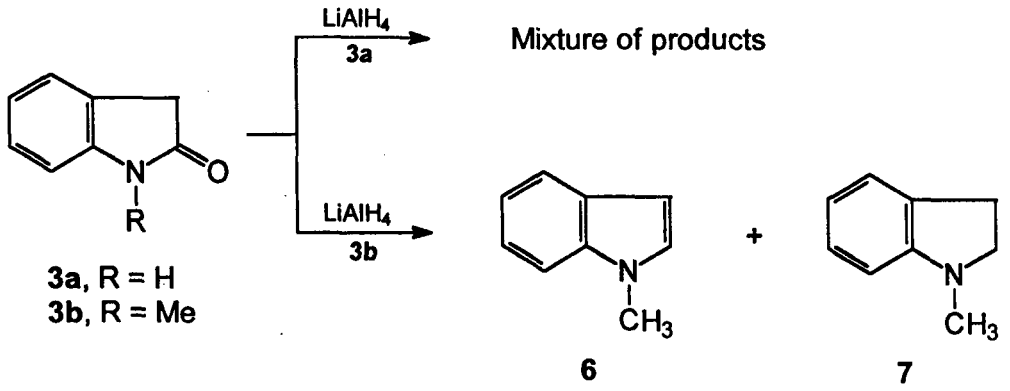


1 2 3 4 5 3

Scheme 1

Attempts are therefore made to transform these easily accessible oxindoles into the corresponding indole derivatives. This approach for the synthesis of indole derivatives appears to be far easier than making from preconstructed indoles since the methods for the synthesis of indoles are not always satisfactory in terms of yields and starting materials. The oxindole and its benzene ring substituted derivatives, which can be made in large quantities, can serve as precursors for many indole derivatives. There are a few attempts reported in the literature to transform oxindoles into indole derivatives. We briefly review some of these methods described in the literature.

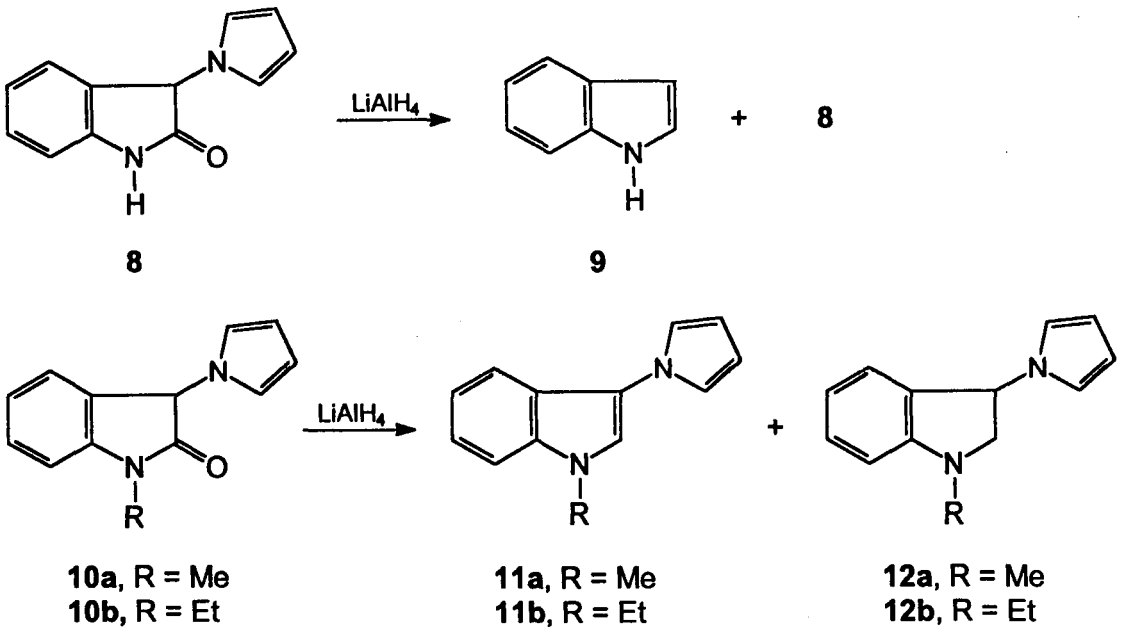
The most important transformation from oxindoles to indoles can be considered the reaction involving metal hydride reduction to afford the corresponding indoles. In an attempt to large scale synthesis of indole, Julian and co-worker[33] have subjected oxindole **3a** to lithium aluminium hydride reduction and found that the reaction was not very satisfactory (Scheme 2). The product analysis of this reduction reaction showed a mixture of products with no well defined single major product. However, when N-methyloxindole **3b** was subjected to lithium aluminium hydride reduction, 1-methylindole **6** was obtained in 61.8% yield along with the corresponding indoline **7** in 12% yield.



Scheme 2

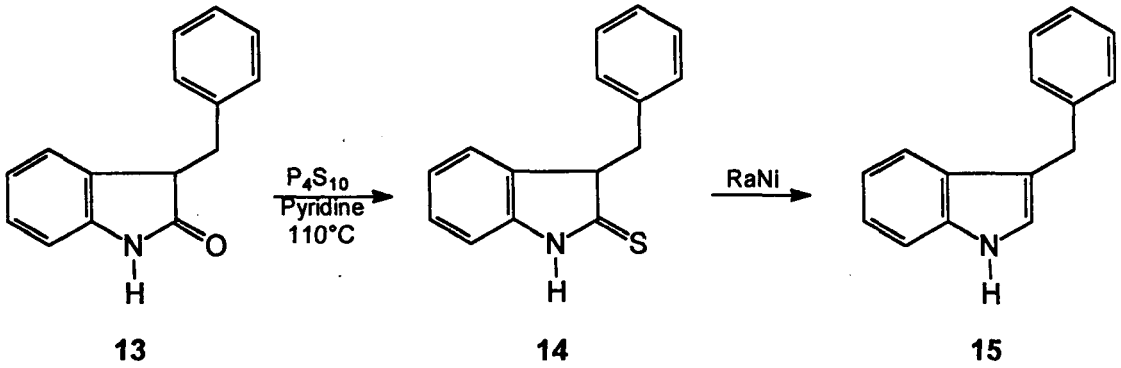
Subsequently Hudson and co-workers[34] have attempted the reduction of 3-(1-pyrrolyl)oxindole **8** using lithium aluminium hydride in refluxing tetrahydrofuran and they obtained simple indole **9** in 29% along with unchanged starting material in 51% yield (Scheme 3). However when N-alkyl substituted analogs **10a** and **10b** were used, the pyrrole ring at 3-position was retained to give a mixture of indole **11** and indoline **12**.

Plieninger and co-workers[35] reacted 3-benzyloxindole **13** with P_4S_{10} to yield the corresponding thio analog of oxindole **14** in good yield which was



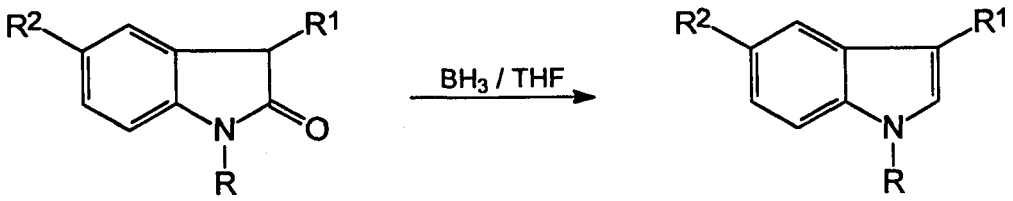
Scheme 3

subjected to Raney nickel reduction in alcohol to afford the corresponding indole derivative **15** in 70% yield (Scheme 4).



Scheme 4

Again Plieninger and co-workers[36] prepared various indole derivatives **17** from the corresponding oxindoles **16** by treating with diborane in tetrahydrofuran (Scheme 5).

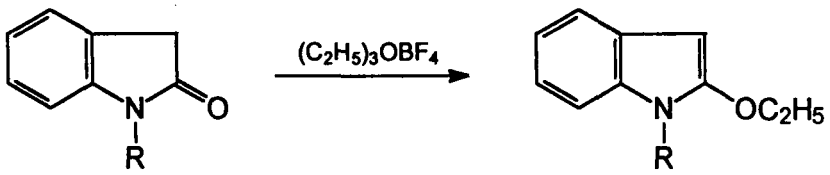


16 **17**

R^1 = H, CH_3; R^2 = H, CH_3, CH_2Ph; R^3 = H, Br, OH, OCH_3

Scheme 5

Harley-Mason and co-worker[37] converted oxindoles **3a** and **3b** into the 2-ethoxyindoles **18a** and **18b** respectively. Thus oxindoles were conveniently alkylated with triethyloxonium fluoborate to yield the corresponding 2-ethoxy-indoles in good yields (Scheme 6).

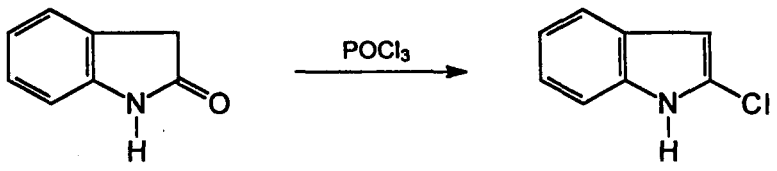


3a, R = H
3b, R = Me

18a, R = H
18b, R = Me

Scheme 6

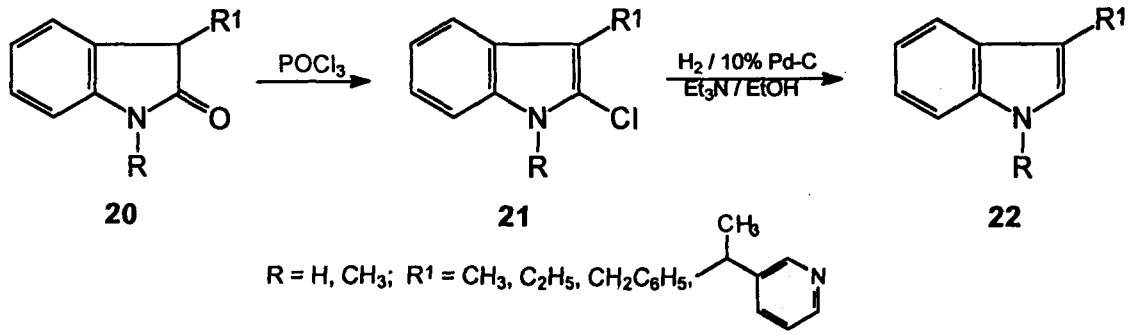
Powers[38] reported the reaction of phosphorous oxychloride with **3a** to get a moderate yield of (18%) 2-chloroindole **19** (Scheme 7).



3a **19**

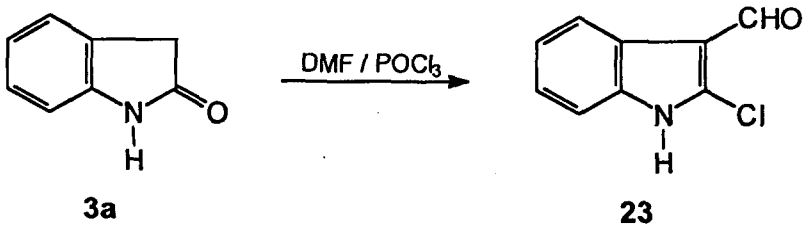
Scheme 7

Subsequently Kubo and co-worker[39] treated 3-substituted oxindoles **20** with phosphorous oxychloride to afford the corresponding 2-chloro-3-substituted indoles **21** in 53-91% overall yields (Scheme 8). All these chloro compounds were dehalogenated in the presence of 10% palladium on carbon to afford the corresponding 3-substituted indoles **22** in very high yields.



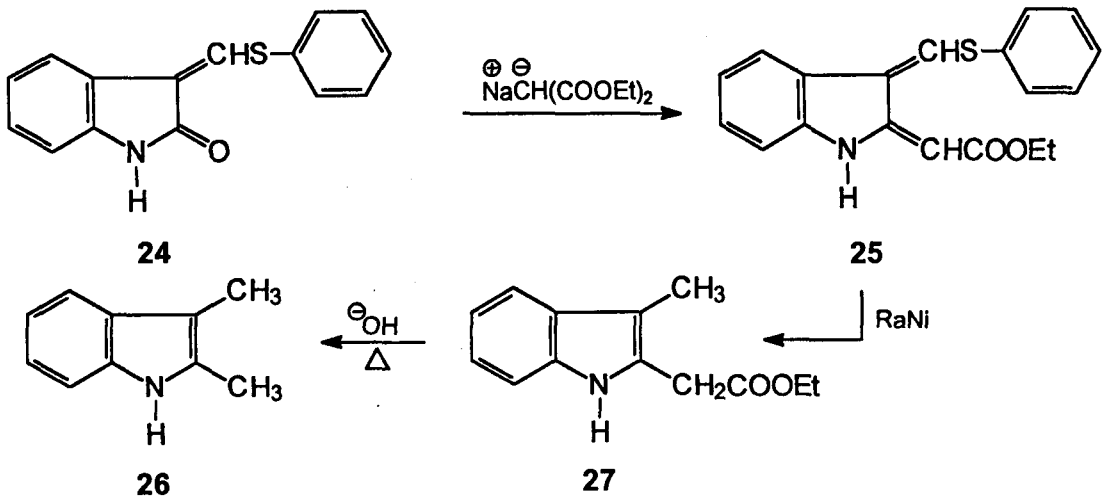
Scheme 8

Seshadri and co-workers[40] treated oxindole **3a** with phosphorous oxychloride in the presence of N,N-dimethylformamide under Vilsmeier-Haack conditions to afford the corresponding 2-chloroindole-3-carboxaldehyde **23** in good yields (Scheme 9).



Scheme 9

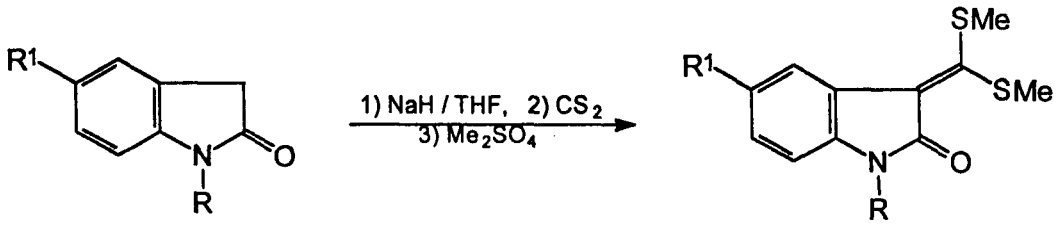
A curious reaction has been reported by Behringer and Weissauer.[41] The thiomethyleneoxindole **24** is said to condense with malonic ester to give **25**. The structure proof is based on the isolation of the picrate of 2,3-dimethylindole after saponification and decarboxylation (Scheme 10).



Scheme 10

Thus there are only a few reports available in the literature for the transformation of oxindole to indole derivatives. These methods are suitable for the synthesis of 3-substituted indoles since oxindole can easily be substituted in the 3-position. To our knowledge there is only one report in the literature (Scheme 10) for the conversion of oxindole to 2-substituted or 2,3-disubstituted indoles. Although the reaction of 2-oxo function of N-protected oxindole with nucleophiles seems to be a useful method for the preparation of 2-substituted indoles, this reaction is limited due to the propensity of oxindole to enolize in the presence of nucleophiles.

Extensive research has been carried out in our laboratory on α-oxoketene dithioacetals and many new reactions were discovered involving their intermediacy and transformation to many useful products.[42] We therefore considered of interest that the α-oxoketene dithioacetal derived from oxindole should be a very useful intermediate for the synthesis of various indole derivatives by subjecting to various reactions developed in our laboratory. The ketene dithioacetal derived from oxindole is already known in the literature, first reported by Kobayashi and co-workers[43] (scheme 11). Thus oxindoles **3a-d** were reacted with carbon disulfide in the presence of sodium hydride in tetrahydrofuran followed by alkylation to afford the corresponding 3-bis(methylthio)methylene-2,3-dihydro-2-oxoindoles **28a-d** respectively in 45-72% overall yields.



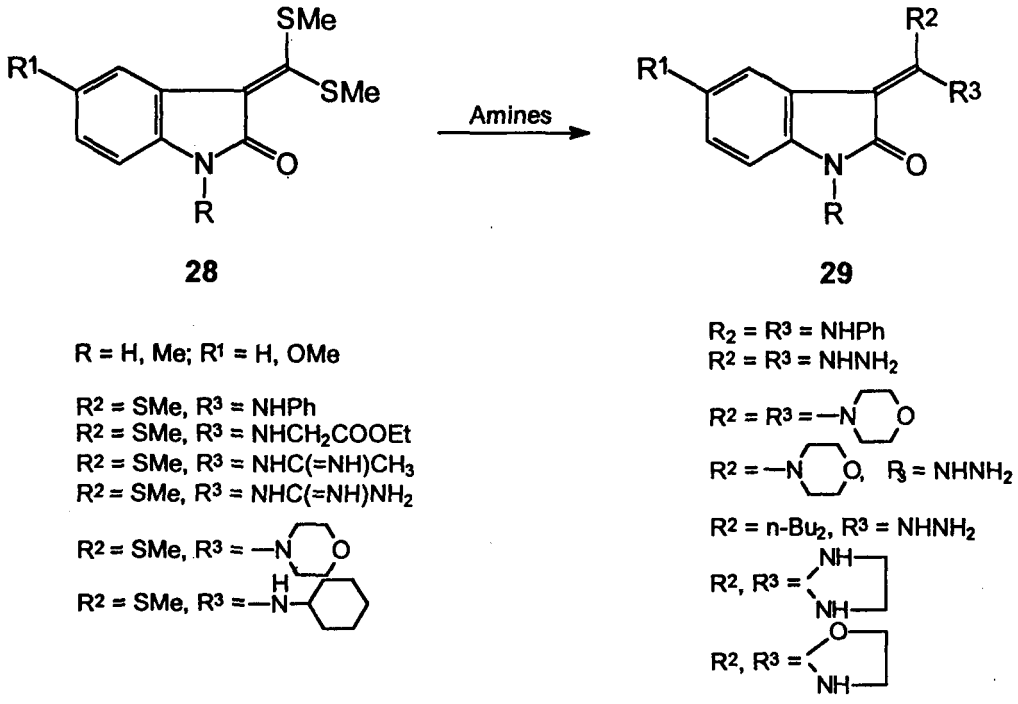
3a, R = R¹ = H
3b, R = Me, R¹ = H
3c, R = H, R¹ = OMe
3d, R = Me, R¹ = OMe

28a, R = R¹ = H
28b, R = Me, R¹ = H
28c, R = H, R¹ = OMe
28d, R = Me, R¹ = OMe

Scheme 11

The same group also synthesised some derivatives of **28** by reacting with amines, carbon nucleophiles, etc. Therefore, before we present our actual work, we would like to discuss the reported reactions of **28**.

The 3-bis(methylthio)methyleneoxindoles **28** have been reacted with a variety of amines to give N,S-acetals involving elimination of one SMe group when one equivalent of the amine was reacted (Scheme 12). Both the SMe groups were replaced when excess of amines were used. Kobayashi and co-workers[43-44] have prepared a large number of these derivatives and found them to be potential antibacterial and antiviral drugs. Interestingly some of the bifunctional amines such as amidines, guanidines and hydrazine hydrate did not cyclize under the reaction conditions described and yielded only open chain products (Scheme 12).



28

R = H, Me; R^1 = H, OMe

R^2 = SMe, R^3 = NHPh
R^2 = SMe, R^3 = $NHCH_2COOEt$
R^2 = SMe, R^3 = $NHC(=NH)CH_3$
R^2 = SMe, R^3 = $NHC(=NH)NH_2$

R^2 = SMe, R^3 =

R^2 = SMe, R^3 =

29

R_2 = R^3 = NHPh
R^2 = R^3 = $NHNH_2$

R^2 = R^3 =

R^2 = , R^3 = $NHNH_2$

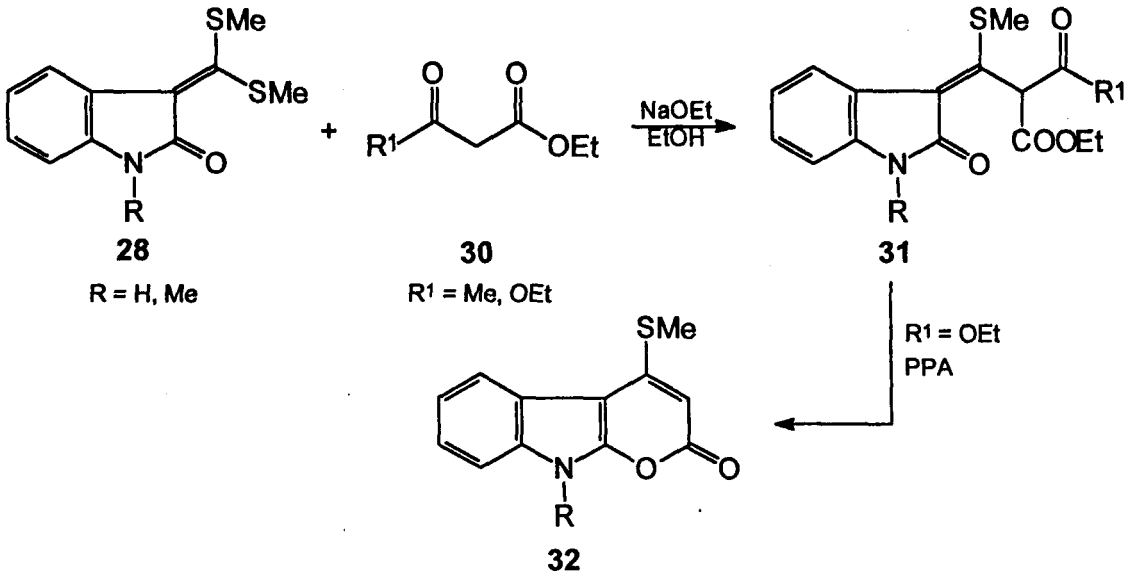
R^2 = n-Bu_2, R^3 = $NHNH_2$

R^2, R^3 =

R^2, R^3 =

Scheme 12

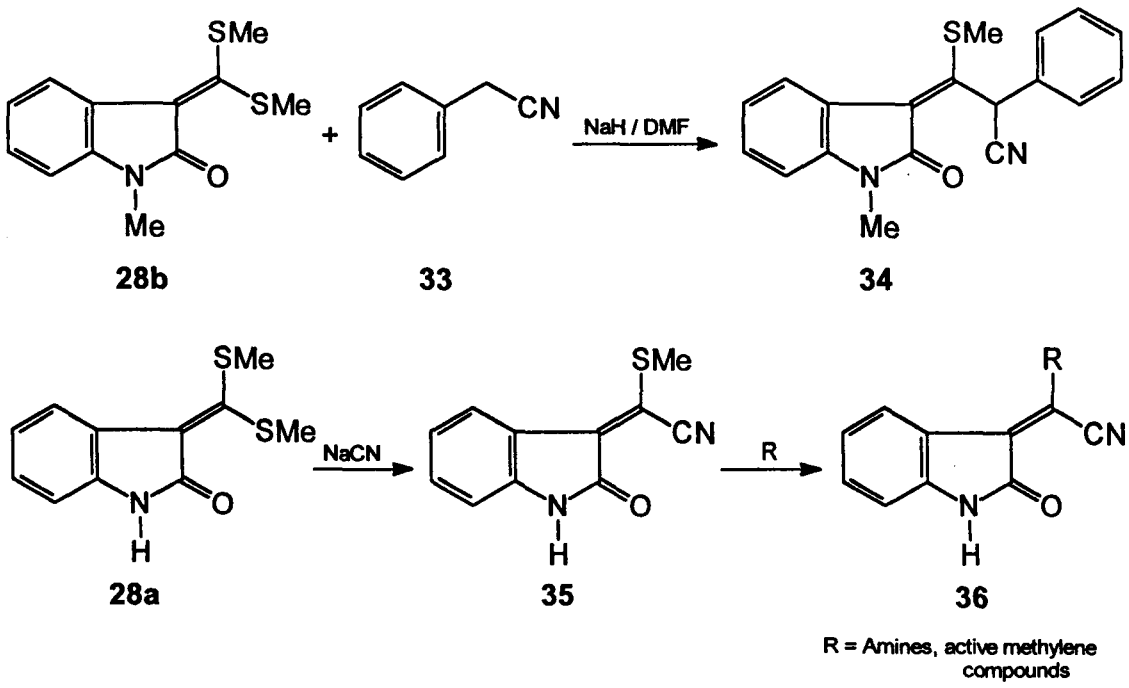
Kobayashi and co-workers also reacted the 3-bis(methylthio)methylene-oxindoles **28** with various carbon nucleophiles. Thus **28** was reacted with ethyl acetoacetate and diethyl malonate in the presence of sodium ethoxide to obtain the corresponding 1,4-addition-elimination products **31** in 50-80% overall yields (Scheme 13).[45] The intermediates obtained by reaction of **28** with diethyl malonate were cyclized in the presence of polyphosphoric acid to afford the corresponding pyranoindoles **32** in 60% overall yield.[46] These pyranoindoles displayed good fungicidal properties.



Scheme 13

The same group have reported the reaction **28b** with phenyl acetonitrile **33** to get the corresponding addition-elimination product **34** in 78% yield.[47] This compound displayed good antiinflamatory activity. Similarly **28a** was reacted

with NaCN to afford the corresponding 3-(cyanomethylthio)methyleneoxindole **35** in good yield.[48] This intermediate was further reacted with various amines and active methylene compounds to displace the second methylthio group (Scheme 14).



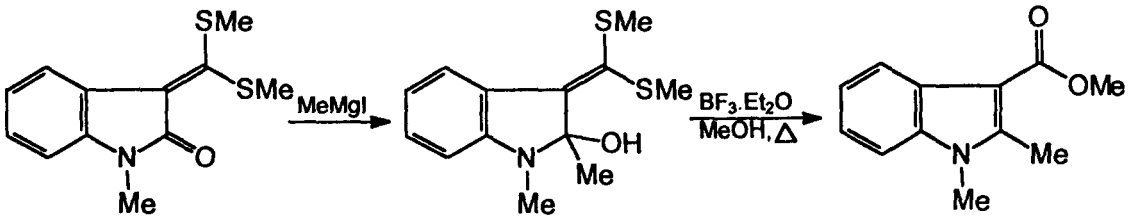
Scheme 14

RESULTS AND DISCUSSION

In the preceding section we have described the chemistry of oxindoles and their derivatives and none of these reports corroborates transformation of **3** into 2,3-substituted or annelated indoles. It seems reactions of oxindole derivatives involving nucleophiles attacking 2-oxocarbon with the elimination of water to afford indole derivatives are rare. It is therefore desirable to examine various reaction conditions and reagents to achieve transformation of oxindole derivatives into useful indole derivatives. We have used 3-bis(methylthio)-methylene-1-methyloxindole **28b** as a potential intermediate for the synthesis of indole derivatives and carbazoles by reacting with various Grignard reagents following the chemistry developed in our laboratory. The results are described as follows.

We have examined the reaction of, to begin with, alkyl Grignard reagents with **28b** and subjected the adducts to alcoholysis so that we can provide a method to transform **28b** into 2-substituted indole 3-carboxylates. Compound **28b** was first reacted with MeMgI in diethyl ether-tetrahydrofuran at 0°C and the intermediate adduct obtained after work-up was directly treated with $BF_3.Et_2O$ in refluxing methanol. The reaction mixture after work-up and column chromatography over silica gel using hexane-ethyl acetate (49:1) as eluent afforded colourless crystals (m.p. 137-138°C) which was characterized as methyl 1,2-dimethylindole-3-carboxylate **38** (Scheme 15). Thus MeMgI reacted with **28b** in 1,2-fashion and underwent $BF_3.Et_2O$-assisted methanolysis to give **38** in 58% yield. The structure was established on the basis of its spectral and analytical data as follows.

IR (KBr): ν_{max} 1685, 1530 cm^{-1}.



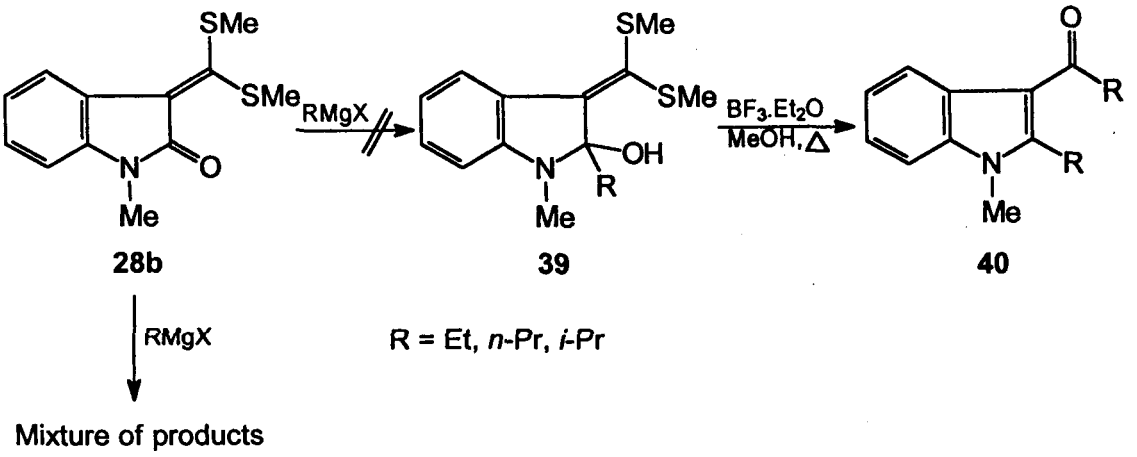
Scheme 15

^{1}H NMR (300 MHz, $CDCl_3$): 2.67 (s, 3H), 3.54 (s, 3H), 3.90 (s, 3H), 7.19-7.21 (m, 3H), 8.06-8.10 (m, 1H).

^{13}C NMR (75 MHz): 11.76, 29.42, 50.62, 103.62, 109.00, 121.31, 121.57, 121.92, 126.46, 136.40, 145.31, 166.51.

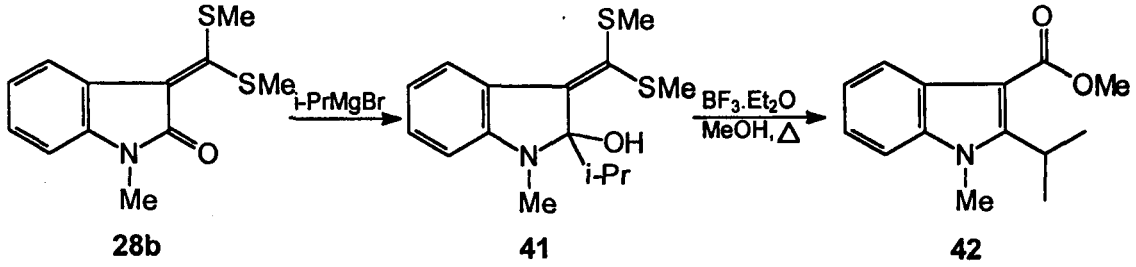
Anal. Calcd. for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89%. Found: C, 70.47; H, 6.56; N, 6.82%.

The reactions of higher alkyl Grignard reagents, ethyl magnesium bromide, *n*-propyl magnesium bromide and *n*-butyl magnesium bromide with **28b** were next investigated. These Grignard reagents are known to undergo sequential 1,4- and 1,2-addition to α-oxoketene dithioacetals.[49] Therefore we expected these Grignard reagents to react with **28b** in sequential 1,4- and 1,2-pattern to afford, after hydrolysis, the corresponding 2-alkyl-2-acylindoles **40** (Scheme 16). Unfortunately when these Grignard reagents were reacted with **28b**, the reaction mixture after work-up, yielded only a mixture of products, from which no well defined compounds could be isolated. Interestingly, when isopropyl magnesium bromide was reacted with **28b**, it underwent smooth 1,2-addition to afford, after $BF_3.Et_2O$-assisted methanolysis, the corresponding methyl 2-isopropyl-1-methylindole-3-carboxylate **42** in 56% yield (Scheme 17). It was purified by silica gel column chromatography using hexane-ethyl acetate (49:1) as eluent to



Scheme 16

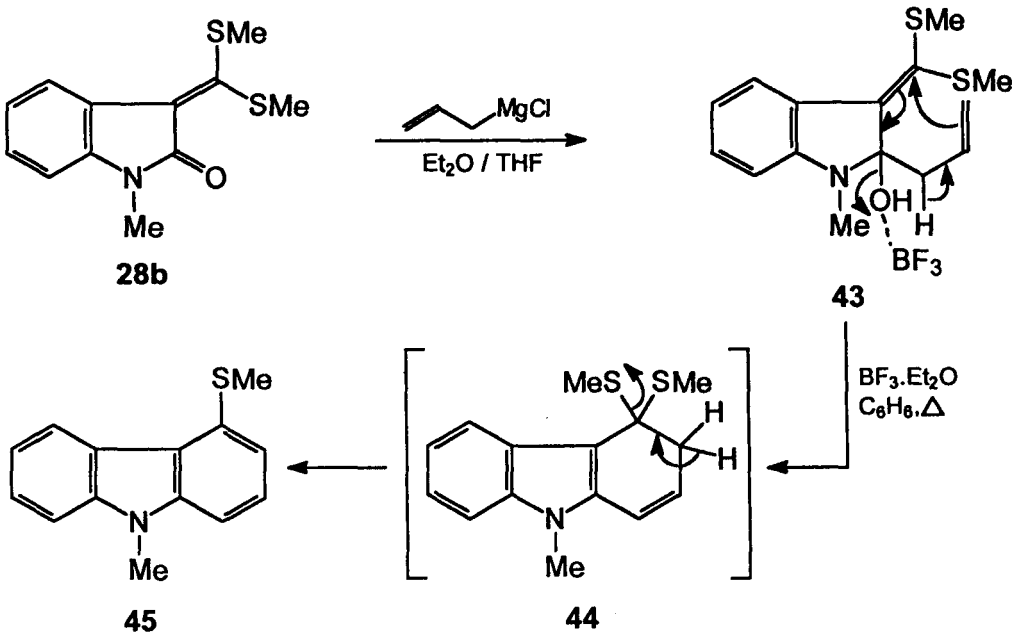
afford **42** as colourless crystals (m.p. 134-123°C). The structure of **42** was fully established on the basis of spectral and analytical data which are given in the experimental section.



Scheme 17

The intermediate **28b** was also reacted with allyl Grignard reagents to explore the possibility of transforming oxindole through **28b** to the corresponding carbazoles. Thus when allyl magnesium chloride was reacted with **28b** it underwent 1,2-addition to yield the intermediate carbinol acetal **43** which was

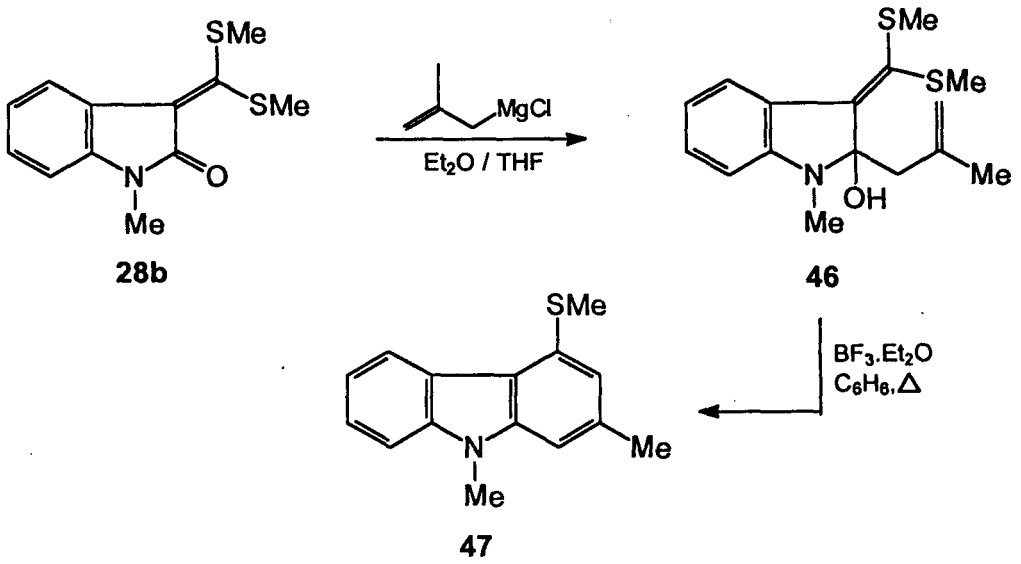
directly treated with $BF_3.Et_2O$ in refluxing benzene to afford the corresponding 9-methyl-4-(methylthio)carbazole **45** in 46% yield (Scheme 18).



Scheme 18

Similarly, methylallyl magnesium chloride was reacted with **28b** under similar reaction conditions to afford the carbinol acetal **46** which was cyclized in the presence of $BF_3.Et_2O$ to afford, after work-up, the corresponding 3,9-dimethyl-4-(methylthio)carbazole **47** in 67% yield (Scheme 19). The spectral and analytical data of both the carbazoles are in conformity with the assigned structure and are recorded in the experimental section.

The reaction of **28b** with benzyl magnesium chloride was next examined with a view to developing a method for benzo[*b*]carbazole **49**. However, when benzylmagnesium chloride was reacted with **28b** followed by treatment with $BF_3.Et_2O$ and work-up, the reaction mixture did not show the formation of **49**



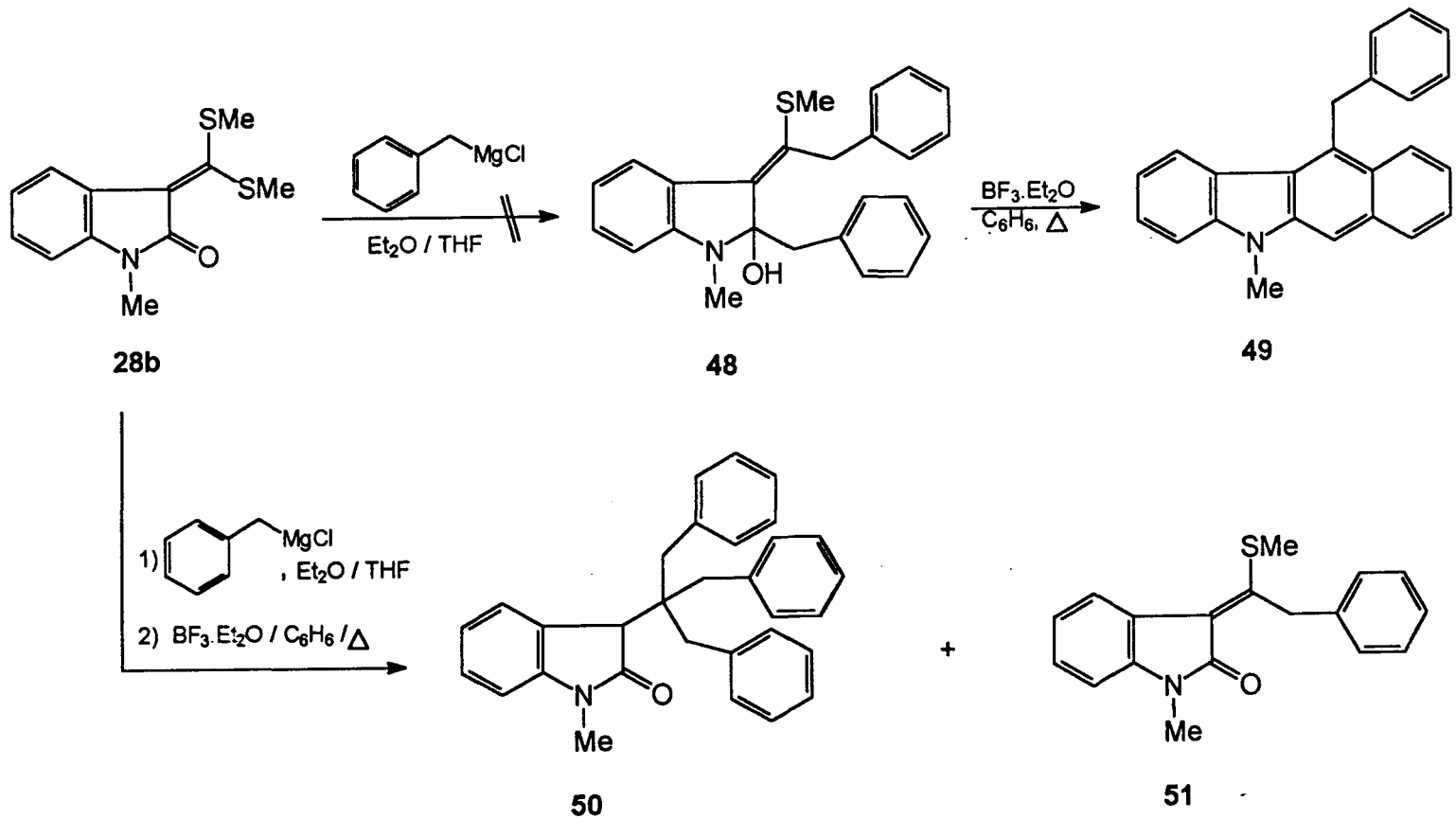
Scheme 19

and the two compounds isolated were characterised as mere 1,4-adducts **50** and **51** formed in 62 and 16% yields respectively (Scheme 20). The structures of both **50** and **51** were established by their spectral and analytical data.

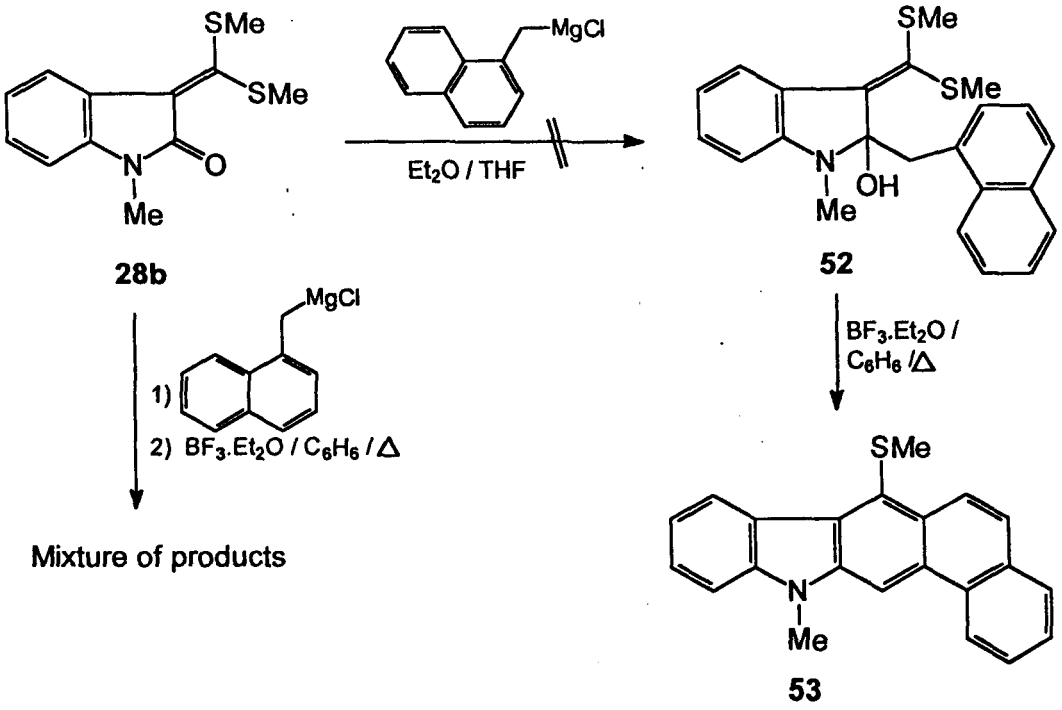
Similarly **28b** failed to react with naphthyl magnesium chloride in the 1,2-addition mode and its expected cyclization to the corresponding naphtho[*b*]carbazole **53** (Scheme 21). The reaction mixture however yielded a mixture of products from which no well defined compound could be isolated.

The phenyl magnesium bromide when reacted with **28b** underwent double 1,4-addition-elimination sequence to afford **54** in 58% yield (Scheme 22). The structure was established by its analytical and spectral data as given in the experimental section.

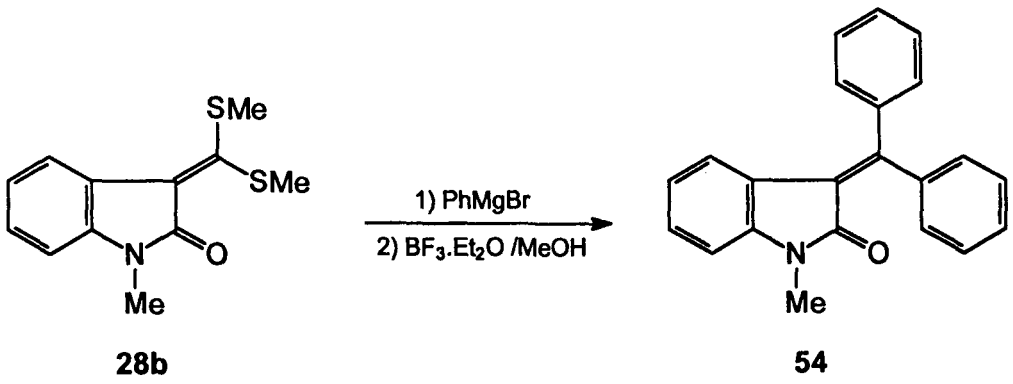
In conclusion, the further exploration of 3-bis(methylthio)methylene-1-methyloxindole to the corresponding indole derivatives have resulted in a mixed results. The amide linkage of the oxindole cleaves in certain cases and resulted in


SMe
SMe
N
O
Me
28b
MgCl
Et2O / THF
SMe
N
OH
Me
48
BF3.Et2O
C6H6, Δ
N
Me
49
1)
MgCl
, Et2O / THF
2) BF3.Et2O / C6H6 /Δ
N
O
Me
50
+
SMe
N
O
Me
51

Scheme 20



Scheme 21



Scheme 22

the formation of undesired product mixture. Well defined indole derivatives have been obtained only when the Grignard reagents, like MeMgI and *i*-PrMgBr, add in exclusive 1,2-fashion to **28b**. The other higher alkyl Grignard reagents which

are known to add in sequential 1,4 followed by 1,2-fashion yielded only mixture of products. However, the corresponding benzyl and phenyl Grignard reagents followed exclusive 1,4-addition mode possibly due to the steric factors and no trace of 1,2-addition products were detected. Allyl Grignard reagents smoothly added to **28b** in 1,2-fashion and yielded the corresponding carbazoles after cycloaromatization. To our knowledge, this is the first report where the reaction of nucleophiles with 2-oxo function of oxindole has been exploited for the synthesis of carbazoles. Thus this route should provide an easy access to carbazole alkaloids by reacting appropriately substituted allyl Grignard reagents with **28b** and its substituted variants.

EXPERIMENTAL

General

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer and the frequencies are expressed in cm^{-1}. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded on Bruker ACF-300 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethyl-silane and coupling constants (J) are given in Hertz. Mass spectra were obtained on a Jeol D-300 mass spectrometer. Elemental analysis were carried out on a Heraeus CHN-O-Rapid analyser.

All the reaction were conducted in oven-dried glassware under dry argon/nitrogen atmosphere. All reactions were monitored by tlc on glass plates coated with silica gel (Acme's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying potassium permanganate (acidic) solution. Column chromatography was carried out using Acme's silica gel (60-120 mesh).

Chemicals, Solvents and Reagents

The commercial samples of methyl iodide, ethyl bromide, *n*-propyl bromide, *i*-propyl bromide, *n*-butyl bromide, allyl chloride, methylallyl chloride and 1-chloromethylnaphthalene were used as supplied. Benzyl chloride and bromobenzene were distilled before use. Magnesium turnings was purchased from Sisco-Chem. Diethyl ether and benzene were dried over sodium wire. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Solvents for column chromatography were used after simple distillation of commercial grades.

3-Bis(methylthio)methylene-2,3-dihydro-1-methyl-2-oxoindole 28b was prepared according to literature procedure[41] and the spectral data are given below.

Yellow crystals; m.p. 83-84°C (chloroform-hexane); lit.[43] m.p. 85-88°C; yield 75%; IR (KBr): ν_{max} 2923, 1670, 1605, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 2.62 (s, 3H), 3.27 (s, 3H), 6.81 (d, J=7.8 Hz, 1H), 7.05 (td, J=7.7, 1.1 Hz, 1H), 8.16 (dd, J=7.8, 1Hz, 1H); ^{13}C NMR (75 MHz): δ 19.17, 19.37, 25.92, 107.55, 121.55, 122.67, 123.35, 123.41, 127.60, 141.55, 158.02, 165.06; Anal. Calcd. for $C_{12}H_{13}NOS_2$ (251.37): C, 57.34; H, 5.21; N, 5.57%. Found: C, 57.53; H, 5.14; N, 5.68%.

General procedure for the reaction of methyl magnesium iodide, ethyl magnesium bromide, *n*-propyl magnesium bromide, *i*-propyl magnesium bromide and *n*-butyl magnesium bromide with 3-bis(methylthio)methylene-2,3-dihydro-1-methyl-2-oxoindole 28b and subsequent methanolysis.

To an ice-cold and stirring suspension of magnesium turnings (15 mmol) and iodine (catalytic amount) in dry diethyl ether (50 ml), a solution of appropriate alkyl halide (12 mmol) in dry ether (20 ml) was added dropwise. The reaction mixture was further stirred for 30 minutes. To the Grignard reagent thus prepared, a solution of **28b** (5 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. The reaction mixture was further stirred for 2 hours and poured into aqueous saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic extracts was washed with water, dried over sodium sulphate and the solvent distilled off. The residue obtained was dissolved in methanol (30 ml) followed by addition of $BF_3.Et_2O$ (2 ml) and refluxed for 3 hours. The reaction mixture was then cooled and poured into saturated aqueous sodium bicarbonate solution, extracted with chloroform, washed with water, dried over sodium sulphate and the solvent distilled off. The crude product obtained was purified by

silica gel column chromatography using hexane-ethyl acetate as eluent. Reaction of methyl and isopropyl Grignard reagents with **28b** afforded the corresponding methyl 2-alkylindole-3-carboxylates **38** and **42** respectively while the other Grignard reagents did not afford any appreciable products.

Methyl 1,2-dimethylindole-3-carboxylate 38.

Colourless crystals; m.p. 137-138°C (chloroform-hexane); yield 58%; IR (KBr): ν_{max} 1685, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H), 3.54 (s, 3H), 3.90 (s, 3H), 7.19-7.21 (m, 3H), 8.06-8.10 (m, 1H); ^{13}C NMR (75 MHz): δ 11.76, 29.42, 50.62, 103.62, 109.00, 121.31, 121.57, 121.92, 126.46, 136.40, 145.31, 166.51; MS: *m/z* 203 (M^+, 100%); Anal. Calcd. for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89%. Found: C, 70.47; H, 6.56; N, 6.82%.

Methyl 1-methyl-2-*i*-propylindole-3-carboxylate 42.

Colourless crystals; m.p. 92-93°C (chloroform-hexane); yield 52%; IR (KBr): ν_{max} 2966, 1690, 1528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (d, J=7.3 Hz, 6H), 3.79 (s, 3H), 3.92 (s, 3H), 4.42 (septet, J=7.3 Hz, 1H), 7.20-7.30 (m, 3H), 8.08-8.12 (m, 1H); ^{13}C NMR (75 MHz): δ 20.16, 25.10, 31.49, 50.68, 102.96, 109.05, 121.68, 121.81, 122.13, 126.64, 136.86, 153.57, 166.44; MS: *m/z* 231 (M^+, 100%); Anal. Calcd. for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06%. Found: C, 73.13; H, 7.32; N, 6.10%.

Procedure for the reaction of allyl magnesium chloride and methylallyl magnesium chloride with 28b.

To an ice-cold and stirring suspension of magnesium turnings (15 mmol) and iodine (catalytic amount) in dry diethyl ether (50 ml), a solution of allyl or methylallyl chloride (12 mmol) in dry ether (20 ml) was added dropwise. The reaction mixture was further stirred for 30 minutes. To the Grignard reagent thus prepared a solution of **28b** (5 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. The reaction mixture was further stirred for 2 hours and poured into

aqueous saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic extracts was washed with water, dried over sodium sulphate and the solvent distilled off. The residue obtained was dissolved in benzene (50 ml) followed by addition of $BF_3.Et_2O$ (2 ml) and refluxed for 3 hours. The reaction mixture was then cooled and poured into saturated aqueous sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic extracts was washed with sodium bicarbonate solution, then with water, dried over sodium sulphate and the solvent distilled off. The crude products thus obtained were purified by silica gel column chromatography using hexane as eluent to afford the carbazoles **45** and **47**.

9-Methyl-4-(methylthio)carbazole 45.

Colourless crystals; m.p. 80-81°C (chloroform-hexane); yield 46%; IR (KBr): ν_{max} 2919, 1579, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 3.63 (s, 3H), 6.98 (d, J=7.5 Hz, 1H), 7.07 (d, J=8 Hz, 1H), 7.22-7.44 (m, 4H), 8.55 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (75 MHz): δ 15.33, 28.88, 105.19, 107.93, 115.54, 118.94, 119.78, 122.62, 123.52, 125.20, 125.56, 133.85, 140.61, 140.83; MS: *m/z* 227 (M^+, 100%); Anal. Calcd. for $C_{14}H_{13}NS$ (227.33): C, 73.97; H, 5.76; N, 6.16%. Found: C, 73.66; H, 5.81; N, 6.25%.

2,9-Dimethyl-4-(methylthio)carbazole 47.

Colourless crystals; m.p. 132-133°C (chloroform-hexane); yield 67%; IR (KBr): ν_{max} 2916, 1593, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.59 (s, 3H), 3.64 (s, 3H), 6.83 (s, 1H), 6.90 (s, 1H), 7.20-7.27 (m, 2H), 7.37-7.42 (m, 1H), 8.49 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz): δ 15.39, 22.19, 28.86, 105.69, 107.84, 117.09, 117.75, 118.87, 122.71, 123.10, 124.71, 133.32, 135.80, 140.70, 141.35; MS: *m/z* 241 (M^+, 100%); Anal. Calcd. for $C_{15}H_{15}NS$ (241.36): C, 74.65; H, 6.26; N, 5.80%. Found: C, 74.91; H, 6.33; N, 5.76%.

Procedure for the reaction of benzyl magnesium chloride with 28b.

To an ice-cold and stirring suspension of magnesium turnings (20 mmol) and iodine (catalytic amount) in dry tetrahydrofuran (100 ml), a solution benzyl chloride (15 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. The reaction mixture was further stirred for 30 minutes. To this Grignard reagent thus prepared a solution of **28b** (5 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. The reaction mixture was further stirred for 2 hours, poured into aqueous saturated solution of ammonium chloride and extracted with benzene. The benzene layer was washed thoroughly with water, dried over sodium sulphate and the solvent distilled off. The residue obtained was dissolved in benzene (50 ml) followed by addition of $BF_3.Et_2O$ (2 ml) and refluxed for 3 hours. The reaction mixture was then cooled and poured into saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic extracts was washed with sodium bicarbonate solution, then with water, dried over sodium sulphate and the solvent distilled off. The residue obtained was adsorbed over silica gel and passed through a silica gel column using hexane-ethyl acetate (19:1) as eluent to afford **50** and **51**.

2,3-Dihydro-1-methyl-2-oxo-3-trisbenzylmethylindole 50.

Colourless crystals; m.p. 160-161°C (chloroform-ether); yield 62%; IR (KBr): ν_{max} 2939, 1703, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.98 (s, 3H), 3.17-3.30 (m, 6H), 3.92 (s, 1H), 6.62 (d, J=7.8 Hz, 1H), 6.87 (td, J=7.6, 0.8 Hz, 1H), 7.10-7.20 (m, 16H), 7.34 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz): δ 25.77, 42.03, 45.29, 50.12, 107.84, 121.63, 125.80, 126.17, 127.07, 127.75, 130.91, 138.09, 144.53, 175.81; MS: *m/z* 431 (M^+, 100%); Anal. Calcd. for $C_{31}H_{29}NO$ (431.58): C, 86.27; H, 6.77; N, 3.25%. Found: C, 85.05; H, 6.59; N, 3.29%.

2,3-Dihydro-1-methyl-3-(1-methylthio-2-phenyl)ethylidene-2-oxoindole 51.

Colourless crystals; m.p. 139-140°C (chloroform-hexane); yield 16%; IR (KBr): ν_{max} 2925, 1629, 1508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.53 (s, 3H), 4.66 (s, 2H), 7.10-7.30 (m, 8H), 8.34-8.37 (m, 1H); ^{13}C NMR (75 MHz): δ 11.43, 29.83, 31.76, 109.51, 114.14, 121.68, 122.01, 122.58, 125.10, 126.50, 128.13, 128.72, 136.83, 137.16, 144.22, 172.14, 186.84; MS: *m/z* 295 (M^+, 100%); Anal. Calcd. for $C_{18}H_{17}NOS$ (295.40): C, 73.19; H, 5.80; N, 4.74%. Found: C, 73.33; H, 5.73; N, 4.92%.

Procedure for the reaction of 1-methylnaphthyl magnesium chloride with 28b.

The procedure is same as that of the reaction of benzyl magnesium chloride with **28b**. The reaction resulted in the formation of a mixture of products and no well defined compound could be isolated from the mixture.

Procedure for the reaction of phenyl magnesium bromide with 28b.

To an ice-cold and stirring suspension of magnesium turnings (20 mmol) and iodine (catalytic amount) in dry tetrahydrofuran (100 ml), a solution bromobenzene (15 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. The reaction mixture was further stirred for 30 minutes. To the Grignard reagent thus prepared a solution of **28b** (5 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. The reaction mixture was further stirred for 2 hours poured into aqueous saturated solution of ammonium chloride and extracted with benzene. The combined organic extracts was washed with water, dried over sodium sulphate and the solvent distilled off. The residue obtained was dissolved in methanol (50 ml) followed by addition of $BF_3.Et_2O$ (2 ml) and refluxed for 3 hours. The reaction mixture was then cooled and poured into saturated aqueous solution of sodium bicarbonate, extracted with chloroform, washed with water, dried over sodium sulphate and the solvent distilled off. The crude product thus

obtained was purified by silica gel column chromatography using hexane-ethyl acetate (97:3) as eluent to afford **54**.

2,3-Dihydro-3-diphenylmethylene-1-methyl-2-oxoindole 54.

Colourless crystals; m.p. 127-128°C (chloroform-hexane); yield 55%; IR (KBr): ν_{max} 2923, 1621, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.56 (s, 3H), 7.00-7.06 (m, 2H), 7.14-7.35 (m, 9H), 7.45 (d, 2H), 8.05 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz): δ 31.14, 109.82 114.49, 121.69, 122.19, 123.15, 127.41, 127.54, 127.89, 128.59, 129.04, 130.58, 130.75, 130.86, 137.14, 140.04, 146.32, 192.76; MS: *m/z* 311 (M^+, 100%); Anal. Calcd. for $C_{22}H_{17}NO$ (311.38): C, 84.86; H, 5.50; N, 4.50%. Found: C, 84.27; H, 5..59; N, 4.45%.

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3.90375
7.19064
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6.963
6.775
6.551
2.000
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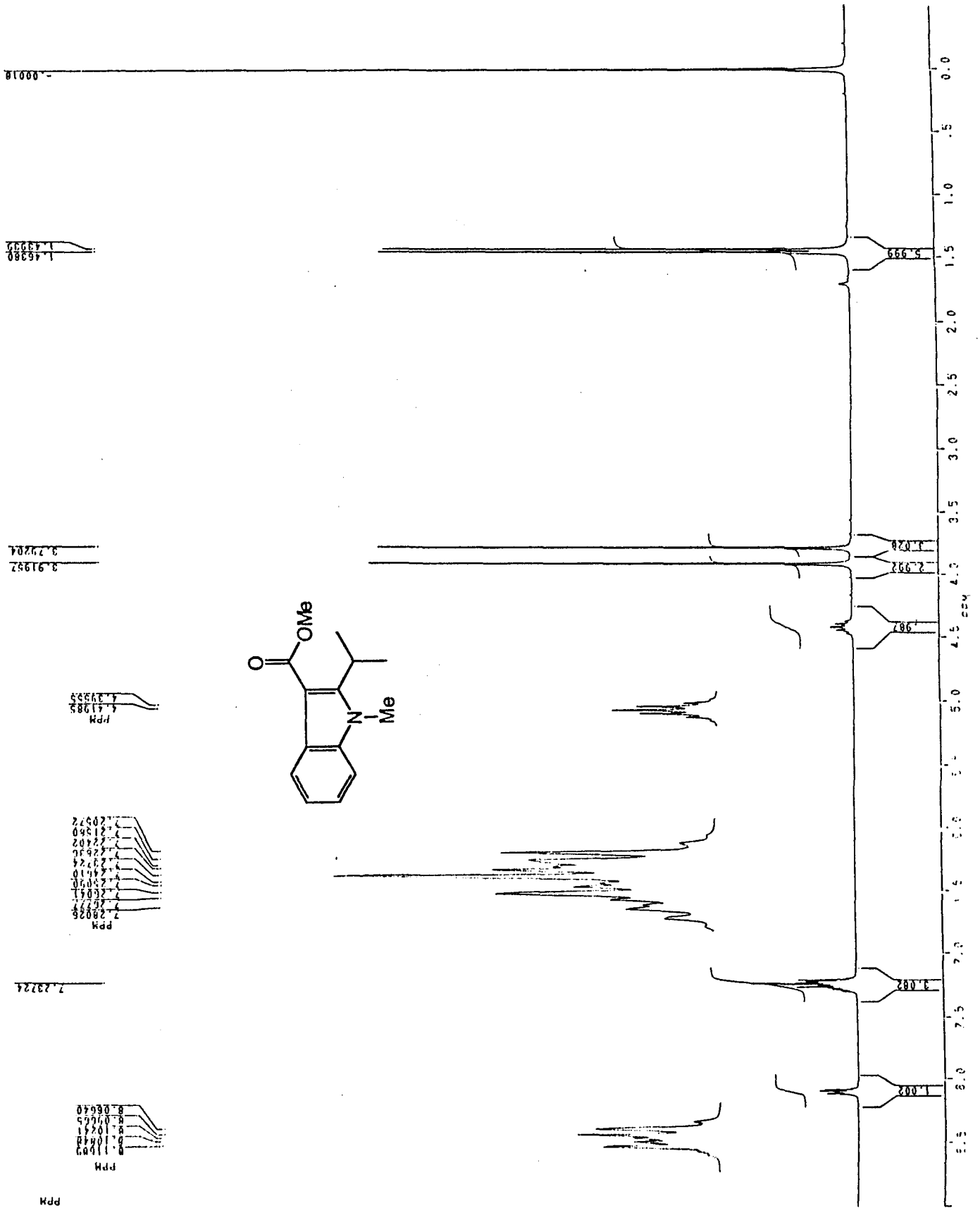
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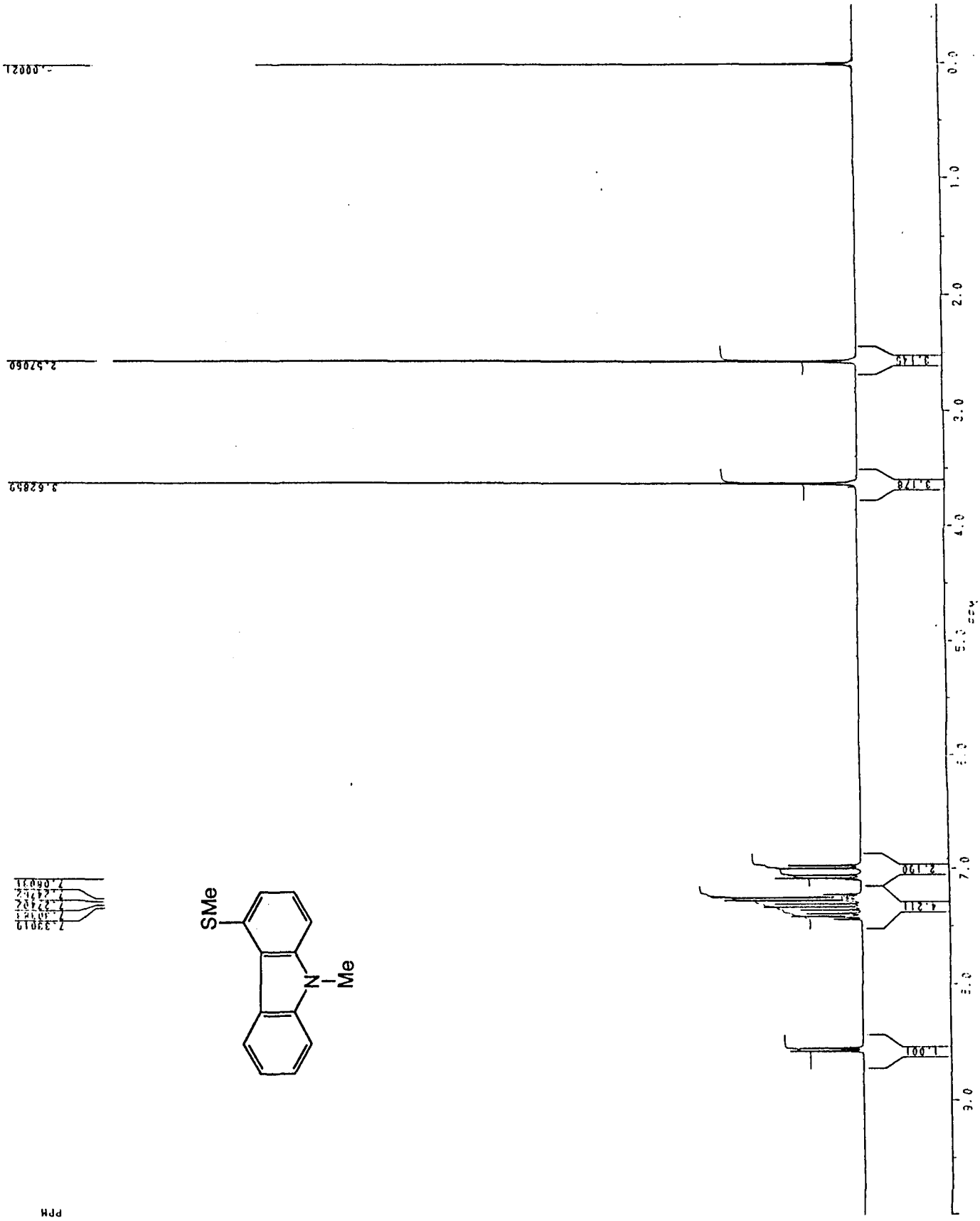
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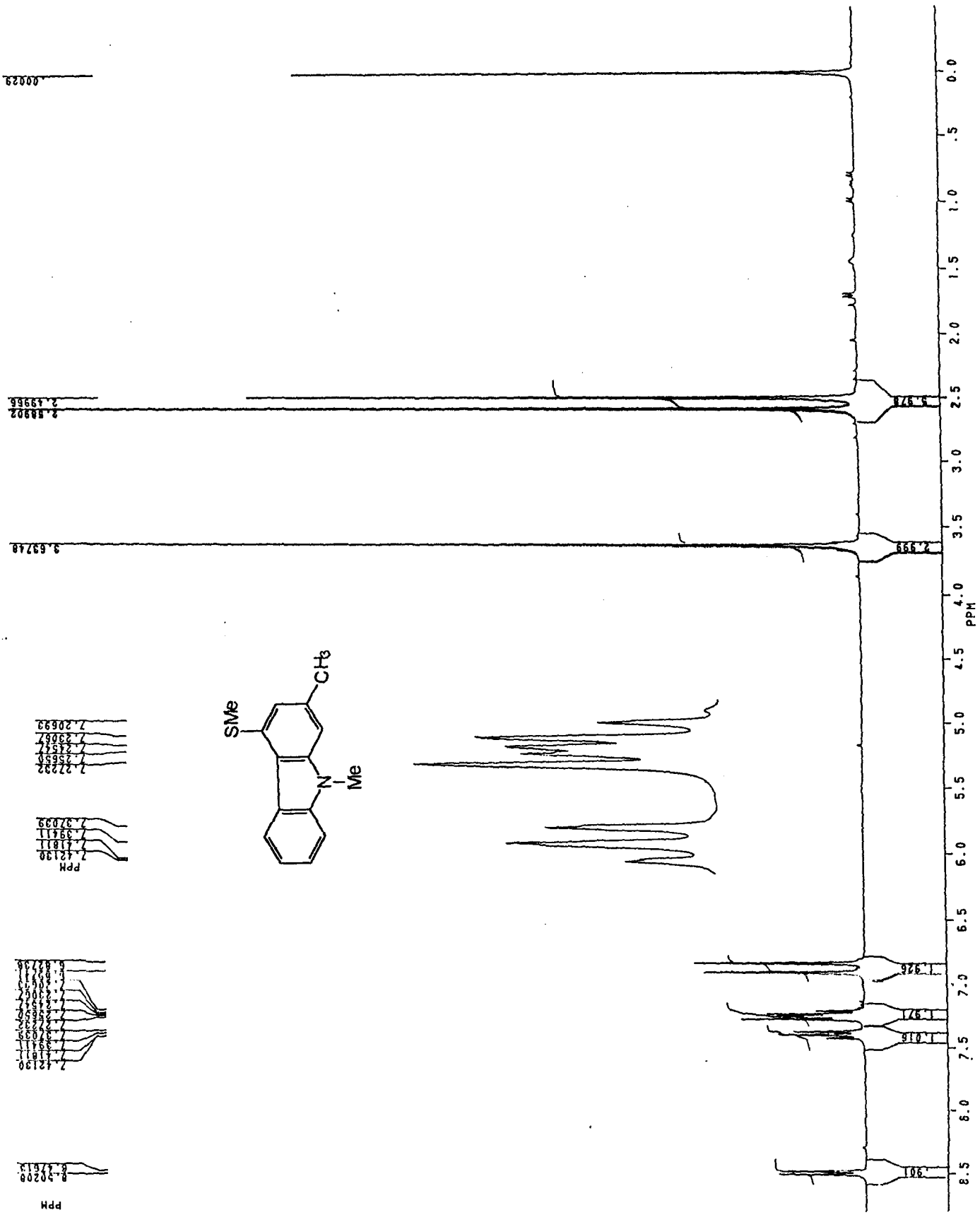
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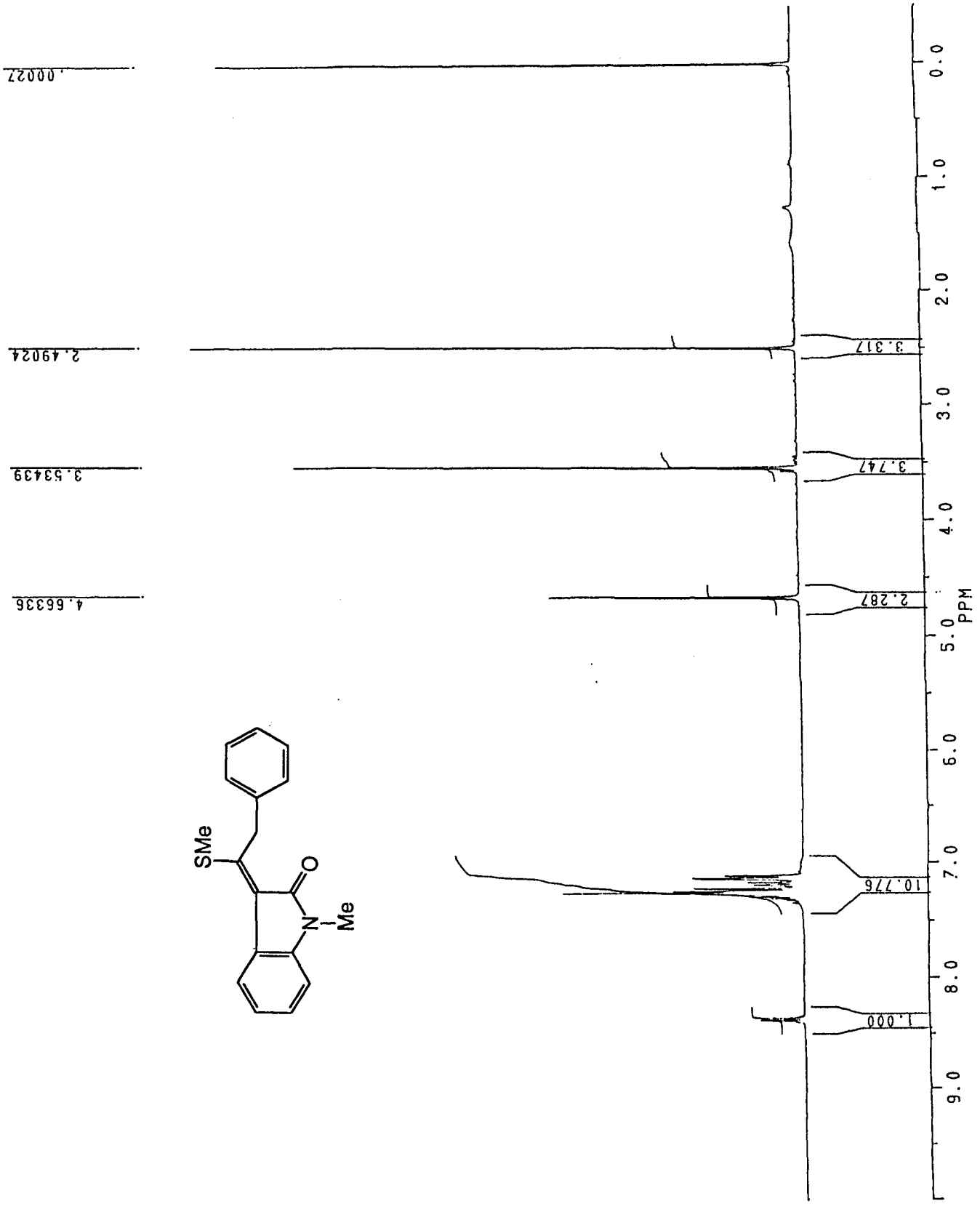
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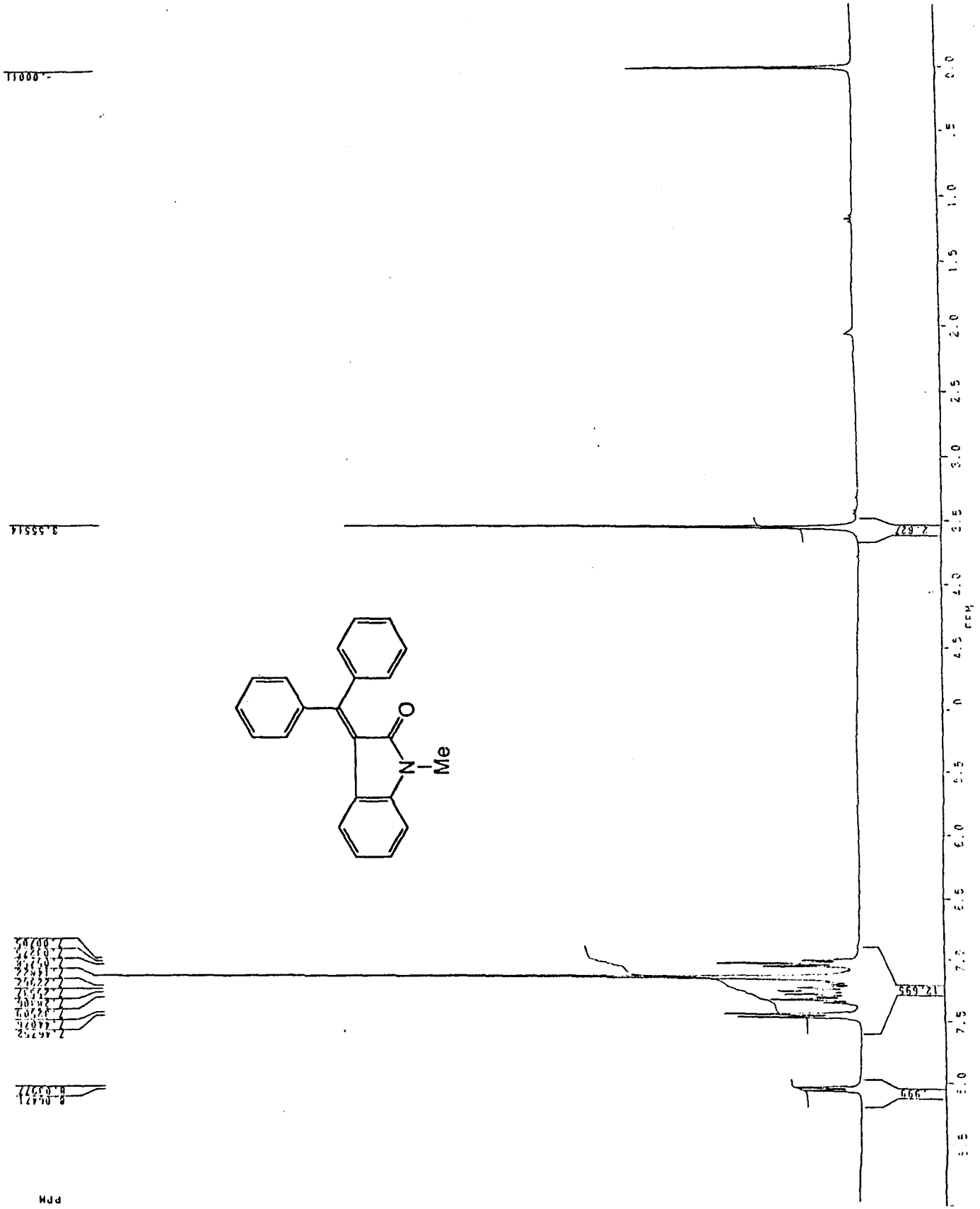
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REFERENCES.

1. Sundberg, R.J. *Indoles* Academic Press, San Diego, **1996**.
2. (a) Manske, R.H.F. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 1-16, **1950-1977**. (b) Rodrigo, R.G.A. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 17-20, **1979-1981**. (c) Brossi, A. (Ed.) *The Alkaloids* Academic Press, New York, Vol. 21-45, **1983-1994**.
3. Syam Kumar, U.K.; Patra, P.K.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1998**, *39*, 2029.
4. Rao, M.V.B.; Satyanarayana, J.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1995**, *36*, 3385.
5. Jeevanandam, A.; Srinivasan, P.C. *J. Chem Soc., Perkin Trans. 1* **1995**, 2663.
6. Mohanakrishnan, A.K.; Srinivasan, P.C. *J. Org. Chem.* **1995**, 60, 1939.
7. W.G. Rajeswaran, Srinivasan, P.C. *Ind. J. Chem.* **1994**, *33B*, 368.
8. Mohanakrishnan, A.K.; Srinivasan, P.C. *Tetrahedron Lett.* **1993**, *34*, 1343.
9. Elango, S.; Srinivasan, P.C. *Tetrahedron Lett.* **1993**, *34*, 1347.
10. Gribble, G.W.; Keavy, D.J.; Davis, D.A.; Saulnier, M.G.; Pelcman, B.; Barden, T.C.; Sibi, M.P.; Oslon, E.R.; BelBruno, J.J. *J. Org. Chem.* **1992**, *57*, 5878.
11. Mali, R.S.; Jagtap, P.G. *Tetrahdron Lett.* **1992**, *33*, 1655.
12. Martin, T.; Moody, C.J. *J. Chem .Soc. Perkin Trans. 1* **1988**, 235.
13. Martin, T.; Moody, C.J. *J. Chem .Soc. Perkin Trans. 1* **1988**, 240.
14. Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215.
15. Saroja, B.; Srinivasan, P.C. *Tetrahedron Lett.* **1984**, *25*, 5429.

16. Saxton, J.E. (Ed.), *The Chemistry of Heterocyclic Compounds-Indoles*, Wiley Interscience, New York, Vol. 25, Part 4, **1983**.

17. Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1.

18. Hegedus, L.S. *Angew. Chem. Int. Ed. Eng.***1988**, *27*, 1113.

19. Alvarez, M.; Salas, M.; Joule, J.A. *Heterocycles* **1991**, *32*, 1391.

20. Gribble, G.W. *Contemporary Organic Synthesis* **1994**, *1*, 145.

21. (a) Soderberg, B.C.; Shriver, J.A. *J. Org. Chem.* **1997**, *62*, 5838.
(b) Dong, Y.; Busacca, C.A. *J. Org. Chem.* **1997**, *62*, 6464.
(c) Kondo, Y.; Kogima, S.; Sakamoto,T. *J. Org. Chem.* **1997**, *62*, 6507.
(d) Rieke, R.D.; Hanson, M.V. *Tetrahedron* **1997**, *53*, 1925.
(e) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001 and references cited therein.

22. Sundberg, R.J. in *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R.; Rees, C.W.; Bird, C.W.; Cheeseman, G.W.H. (Eds.), Pergamon Press, Oxford, **1984**, Vol. 4.

23. Mohanakrishnan, A.K.; Srinivasan, P.C. *Ind. J. Chem.* **1996**, *35B*, 838.

24. Labadie, S.S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250.

25. Palmisano, G.; Santagostino, M. *Synlett* **1993**, 771.

26. Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. *Heterocycles* **1993**, *36*, 941.

27. Kondo, Y.; Takazawa, N.; Yoshida, A.; Sakamoto, T.; *J. Chem. Soc. Perkin Trans. 1* **1995**, 1207.

28. Gharpure, M.; Stoller, A.; Bellamy, F.; Firnace, G.; Snieckus, V. *Synthesis* **1991**, 1079.

29. Katritzky, A.R.; Akutagawa, K. *Tetrahedron Lett.***1985**, 26, 5935.

30. (a) Stolle, R. *J. Pr. Chem.* **1930**, *128*, 1.
(b) Abramovitch, A.; Hey, D.H. *J. Chem. Soc.* **1954**, 1697.

31. (a) Gassman, P.G.; van Bergen, T.J. *J. Am. Chem. Soc.* **1973**, *95*, 2718.
(b) Gassman, P.G.; van Bergen, T.J.; Gruetmacher, G. *J. Am. Chem. Soc.* **1973**, *95*, 6508.
(c) Gassman, P.G.; van Bergen, T.J. *J. Am. Chem. Soc.* **1974**, *96*, 5508.
32. For the synthesis and reactions of oxindoles: Sundberg, R.J. *The Chemistry of Indoles* Academic Press, New york, **1970**.
33. Julian, P.L.; Printy, H.C. *J. Am. Chem. Soc.* **1949**, *71*, 3206.
34. Hudson, C.B.; Robertson, A.V. *Aust. J. Chem.* **1967**, *20*, 1699.
35. Plieninger, H.; Werst, G. *Angew. Chem.* **1958**, *70*, 272.
36. Sirowej, H.; Khan, S.A.; Plieninger, H. *Synthesis,* **1972**, 84.
37. Harley-Mason, J.; Leeney, T.J. *Proc. Chem. Soc.* **1964**, 368.
38. Powers, J.C. *J. Org. Chem.* **1966**, *31*, 2627.
39. Kubo, A.; Nakai, T. *Synthesis* **1980**, 365.
40. Seshadri, S.; Sardessai, M.; Betrabet, A.M. *Indian J. Chem.* **1969**, *7*, 662.
41. Behringer, H.; Weissauer, H. *Chem Ber.* **1952**, *85*, 743.
42. Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron* **1990**, 46, 5423.
43. (a) Teshigawara, T.; Kobayashi, G.; Matsuda, Y. Japan 15543 (1967); *Chem. Abstr.* **1968**, *69*, 2869p.
(b) Kobayashi, G.; Furukawa, S.; Matsuda, Y. *Yakugaku Zasshi* **1966**, *86*, 1152; *Chem .Abstr.* **1967**, *67*, 3031e.
44. Kobayashi, G.; Matsuda, Y.; Teshigawara, T. Japan 6724899 (1967); *Chem. Abstr.* **1968**, *69*, 43798h.
45. Kobayashi, G.; Matsuda, Y. Japan 6824913 (1968); *Chem. Abstr.* **1969**, *70*, 57640h.
46. Kobayashi, G.; Matsuda, Y. Japan 6827601 (1968); *Chem. Abstr.* **1969**, *71*, 22036h.

47. Kobayashi, G.; Matsuda, Y. Japan 7031287 (1970); *Chem. Abstr.* **1971**, *74*, 76327h.

48. Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, Y. *Yakugaku Zasshi* **1973**, *93*, 1520; *Chem Abstr.* **1974**, *80*, 47770t.

49. Singh, G.; Purkayastha, M.L.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1289.