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THE SYNTHESIS OF SUBSTITUTED INDOLES VIA ARENE CHROMIUM TRICARBONYL COMPLEXES

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ABSTRACT

The review is divided into two parts. In the first, the use of chromium tricarbonyl complexes of dihydropyridines and benzo-fused heterocycles in organic synthesis is discussed, while in the second, the synthesis of carbocyclic-ring, carbon-substituted indoles is surveyed.

The main part of this thesis describes the preparation of tricarbonyl-(η^6-N-protected-indole)chromium(0) complexes and their application to the synthesis of 4- and 7- substituted indoles. The key step in these syntheses is the regioselective lithiation of N-protected indole complexes, the regiochemistry of which is determined by the nature of the N-protection. Thus, a sterically demanding N-protecting group, the tri-isopropylsilyl group, led to predominately 4-lithiation, while less sterically demanding groups led to predominately 7-lithiation.

The subsequent reaction of the lithiated indole complexes with electrophiles afforded good yields of the substituted indole complexes. The cleavage of these complexes gave excellent yields of the corresponding substituted indoles.

The future prospects for these reactions are also discussed.

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- and finally to my family for their support.

ABBREVIATIONS

Apart from the usual, common chemical abbreviations, the following, more specialised abbreviations were used in this thesis:

DMF	-	dimethylformamide;
DMSO	-	dimethylsulphoxide;
HMPA	-	hexamethylphosphoric triamide;
TBAF	-	tetra-n-butylammonium fluoride;
THF	-	tetrahydrofuran;
TMEDA	-	tetramethylethylenediamine.

All temperatures quoted are measured in degrees centigrade ($^{\circ}C$) and the word complex is taken to mean a tricarbonyl-(η^6-arene) chromium complex, unless otherwise stated.

REVIEW

SYNTHETIC APPLICATIONS OF CHROMIUM TRICARBONYL COMPLEXES OF DIHYDROPYRIDINES AND BENZO-FUSED HETEROCYCLES

A Introduction

In the past 25 years many stable π-arene chromium tricarbonyl complexes have been prepared.[1] The chemical and physical properties of these compounds have been extensively studied,[1] but it is only more recently that their application to the field of organic synthesis has been investigated.[1,2] This work has, in the main, concentrated on the application of carbocyclic arene complexes, with the use of the non-carbocyclic complexes receiving scant attention. It is intended to review here the use of non-carbocyclic chromium tricarbonyl complexes in organic synthesis.

The methods for preparing non-carbocyclic arene complexes are, for the most part, similar to those used to prepare their carbocyclic analogues; that is, by direct thermal displacement of other ligands from a neutral chromium tricarbonyl species such as chromium hexacarbonyl, trisacetonitriletricarbonylchromium or trisammoniatricarbonylchromium. Reaction conditions depend on the nature of the arene being complexed and on the nature of the ligand undergoing displacement, but reaction temperatures of between 25° and 160° are required. Yields of the complexes are usually good once the reaction conditions have been optimised. For example, indole reacts with chromium hexacarbonyl in refluxing dibutylether to give the indole complex in 80% yield.[3]

Cleavage of the arene complex to generate the free arene is achieved in excellent yields and under mild conditions by either the use of mild oxidising agents, such as irradiation/oxygen[4] or iodine,[5] or by the thermal exchange of the π-arene ligand for other ligands such as pyridine.[6]

The coordination of a chromium tricarbonyl group to an arene results in changes in the reactivity of the arene which are well documented for carbocyclic arenes.[1,2] Although the most important effect is the withdrawal of electron density from the arene ring, other effects are also present, resulting in the changes in reactivity outlined below:

(a) side chain (benzyl) cations and anions are stabilised;

(b) the arene ring protons are enhanced in acidity;

(c) the steric effect of the chromium tricarbonyl group directs attack on the complex exo to the chromium;

(d) nucleophilic aromatic addition and substitution of the complexed arene is enhanced.

B Electronic effects of the chromium tricarbonyl group

There is some controversy about the mechanism by which the chromium tricarbonyl group withdraws electron density from the complexed arene.

Recent theoretical work[7] prompted by the regiochemistry of nucleophilic addition to substituted benzene complexes[2]

suggested that electron withdrawal is the result of the greater overlap of the π-molecular orbitals of the arene with orbitals on the chromium tricarbonyl group than the corresponding overlap of orbitals on the chromium tricarbonyl group with the arene π^*-molecular orbitals. This results in greater back-bonding from the arene π-molecular orbitals to the chromium tricarbonyl group than donation from chromium tricarbonyl to the arene π^*-molecular orbitals, thus producing the overall electron withdrawal from the ring.

However, earlier work[8] based upon experimental results suggested that complexation by chromium tricarbonyl decreases the nett σ-electron density with little effect on the π-electron density. This is surprising since it is usually assumed that the π-electrons of an arene participate in the coordination with a metal and the contribution of the σ-framework in the total bonding is negligible.

The apparent discrepancies between these results, together with the observations that the theoretical treatment neglects the effects of complexation on the σ-framework, while the earlier work fails to explain the nucleophilic addition to arene complexes, suggests that a full explanation of the effects of complexation will have to await a more rigorous theoretical treatment.

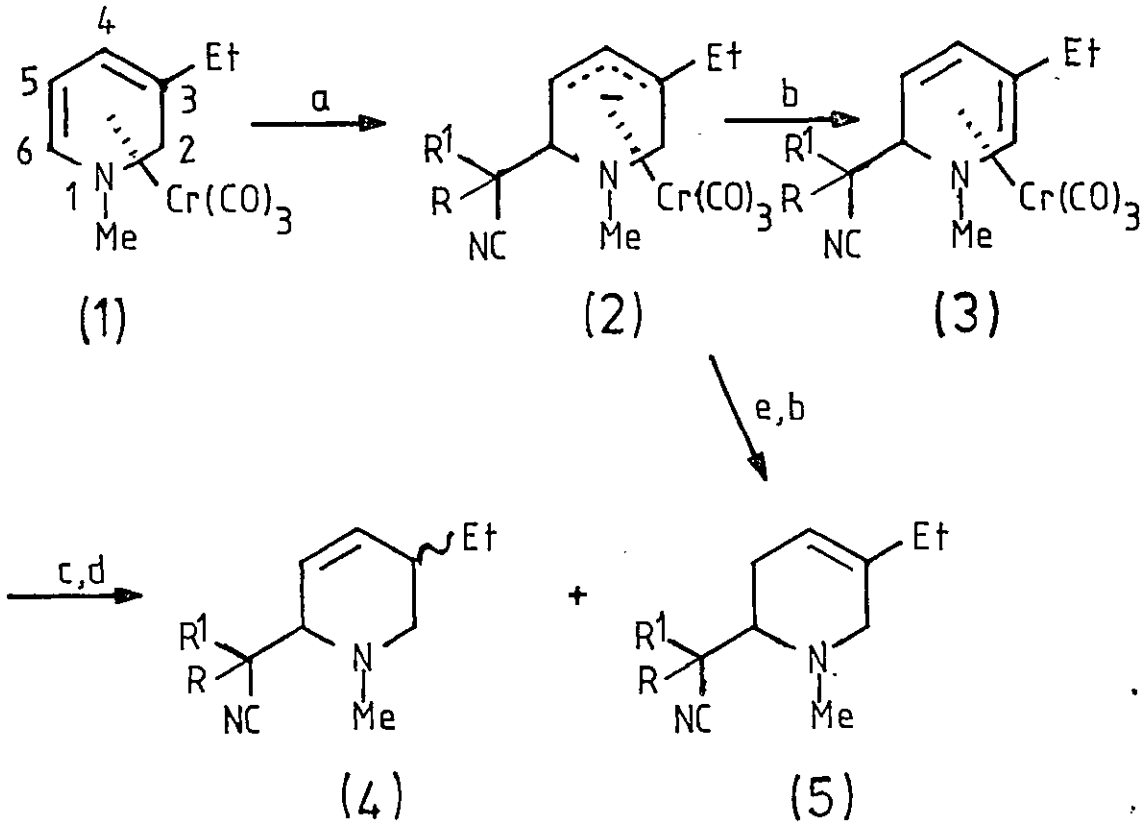
C Dihydropyridine complexes

The 1,2-dihydropyridine complex (1), prepared from 1,2-dihydro-3-ethyl-1-methylpyridine and trisacetonitriletricarbonylchromium, although not strictly an arene π-complex as the nitrogen is a chelating ligand, has been used as a means of stabilising and modifying the chemistry of the unstable 1,2-dihydropyridine system to the extent that regiospecific nucleophilic addition to 6-position of the complex becomes feasible (Scheme 1).

Treatment of the 1,2-dihydropyridine complex (1) with lithioisobutyronitrile (R^1,R=Me) gave, after treatment with one equivalent of iodine, the complex (3; R^1,R=Me) in 54% yield.[9] This resulted from nucleophilic addition to the 6-position followed by hydride loss from C_2 of the anionic intermediate (2; R^1,R=Me). Decomplexation of (3; R^1,R=Me) with pyridine and subsequent sodium borohydride reduction gave a mixture of the tetrahydropyridines (4; R^1,R=Me; 34%) and (5; R^1,R=Me; 8%).

Treatment of the intermediate (2; R^1,R=Me) with trifluoroacetic acid and subsequent oxidation with an excess of iodine afforded a more efficient route to the 1,2,5,6-tetrahydropyridine (5; R^1,R=Me) (67% yield). Similarly, the reaction of the 1,2-dihydropyridine complex (1) with lithiopropionitrile (R^1=H,R=Me) and lithioacetonitrile (R^1,R=H) gave good yields

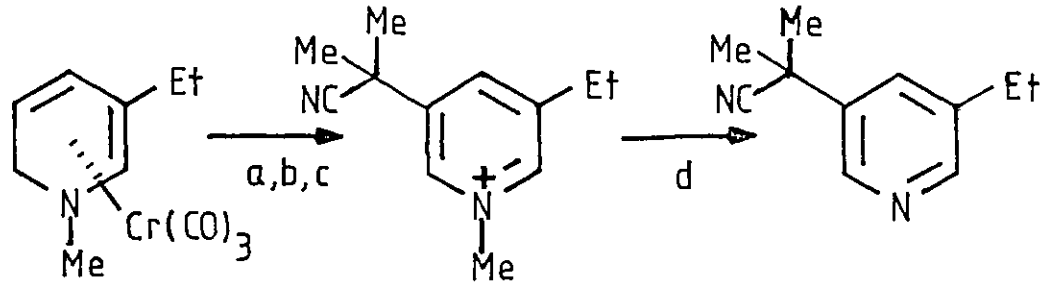
of the 1,2,5,6-tetrahydropyridines (5; R^1=H,R=Me and R^1, R=H respectively).



(a)LiC(R)(R^1)CN,THF,-78°; (b)I_2; (c)pyridine; (d)$NaBH_4$; (e)CF_3COOH.

(Scheme 1)

The reaction of the 1,6-dihydropyridine complex[10] (6), isolated as a by-product from the complexation of 1,2-dihydro-3-ethyl-1-methylpyridine or from the thermal isomerisation of the 1,2-dihydropyridine complex (1)[11], with lithioisobutyronitrile gave, after treatment with iodine and an excess of silver nitrate, the pyridinium salt (7)[9]. Demethylation of this salt with triphenylphosphine in acetonitrile afforded the 3,5-disubstituted pyridine (8) (Scheme 2).

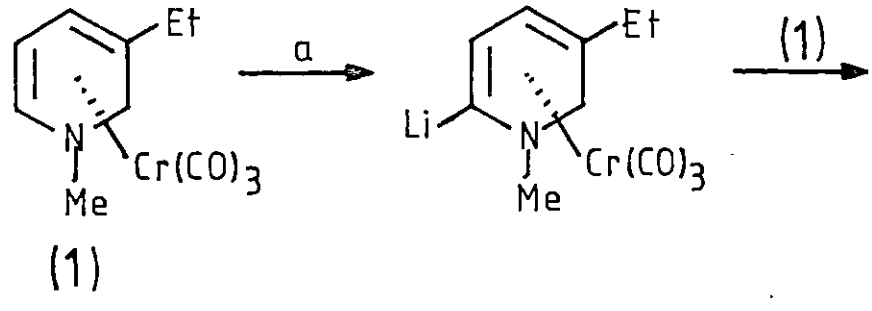


(6) (7) (8)

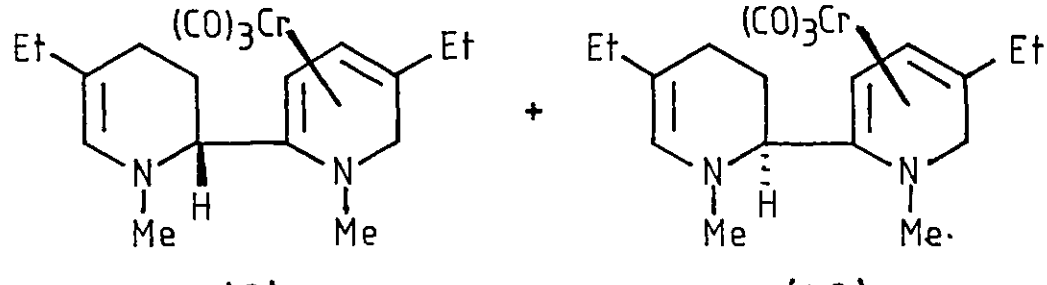
(a)$LiC(Me)_2CN$,THF,-78°; (b)I_2; (c)$AgNO_3$; (d)Ph_3P,MeCN,Δ.

(Scheme 2)

The reaction of the 1,2-dihydropyridine complex (1) with methyllithium at -78° gave, after work-up, a mixture of dimeric compounds (9,32%), (10,27%) and (11,25%),[12] presumably via 6-lithiation of complex (1) and nucleophilic addition of this carbanion to the 6-position of another molecule of complex (1) (Scheme 3).

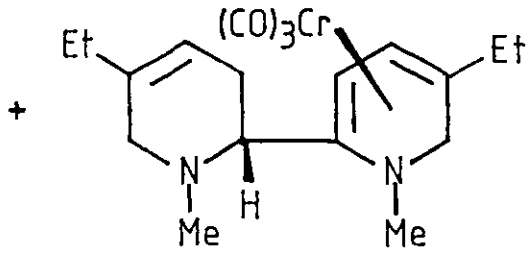


(1)



(9) (10)

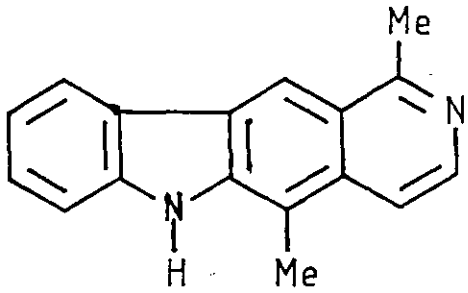
a) MeLi, THF, -78°



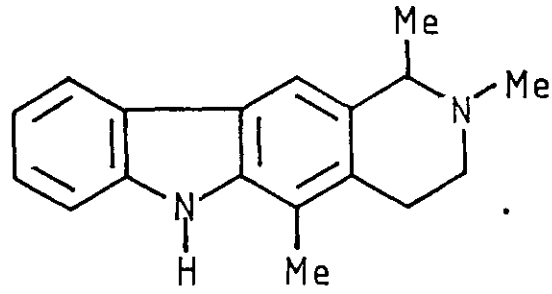
(11)

(Scheme 3)

A synthesis of the indole alkaloids olivacine (12) and guatambuine (13) utilising the chemistry of 1,2-dihydropyridine complexes has been reported.[13]



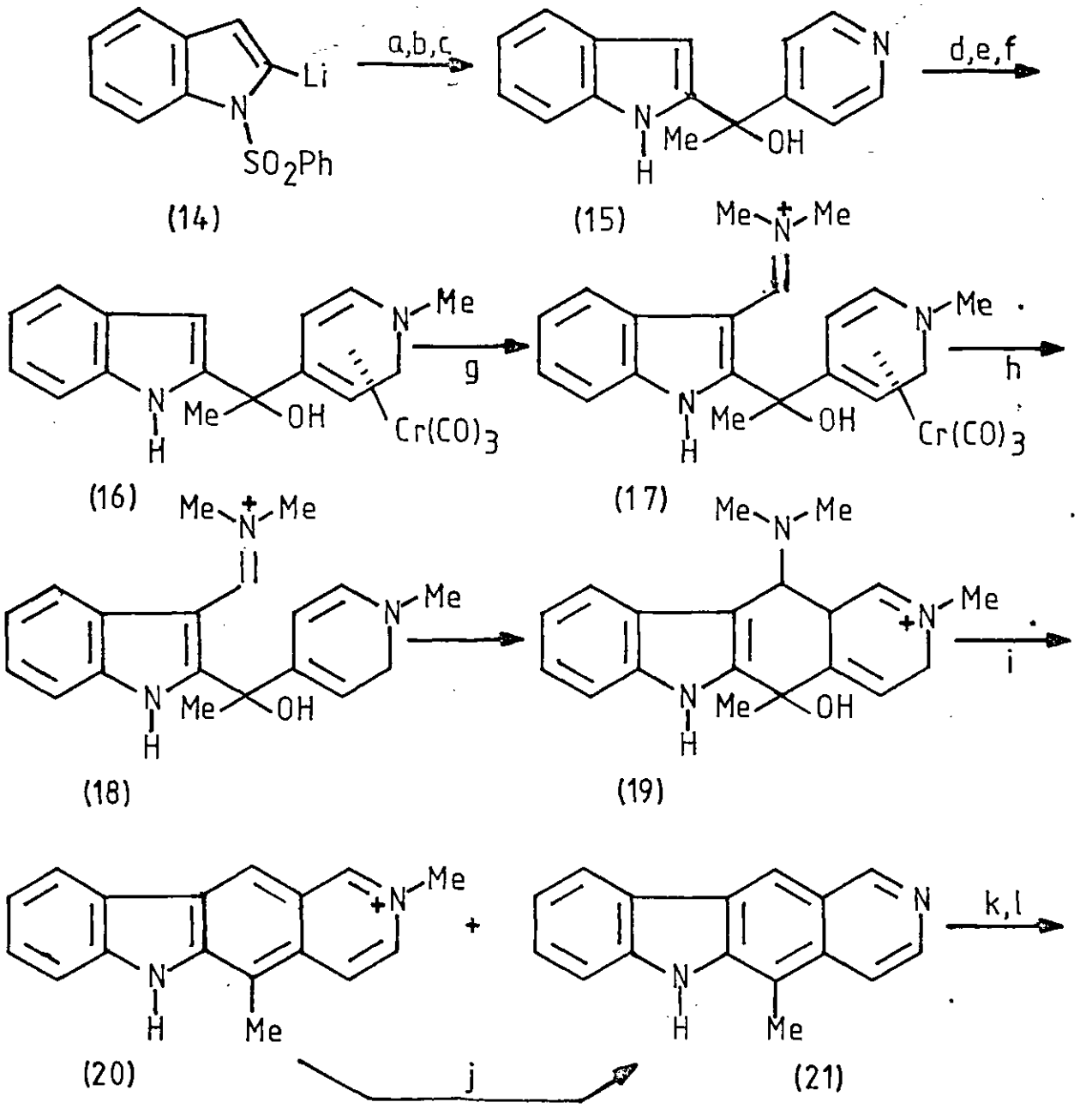
(12)



(13)

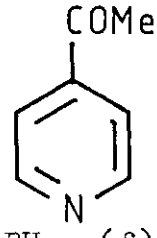
The reaction of 1-phenylsulphonyl-2-lithioindole,(14) with 4-acetylpyridine and subsequent hydrolysis of the nitrogen-protecting group gave the 2-substituted indole (15) (Scheme 4). Quarternisation with methyl iodide followed by sodium borohydride reduction and complexation with trisacetonitrile-tricarbonylchromium gave the 1,2-dihydropyridine complex (16). Reaction of this complex (16) with Vilsmeier's salt gave an intermediate (17) which, on decomplexation with pyridine, gave a mixture of products (18 and 19). Dehydrogenation of this crude mixture with palladium on charcoal gave a mixture of the pyridinium salt (20,60% from 16) and the

pyridine (21, 10% from 16). The demethylation of the pyridinium salt (20) with triphenylphosphine in HMPA or DMF and subsequent treatment with methyllithium followed by iodine oxidation gave olivacine (12) in 54% overall yield. Quarternisation of olivacine (12) with methyl iodide and sodium borohydride reduction gave (±)-guatambuine (13).



(14) (15) (16) (17) (18) (19) (20) (21)



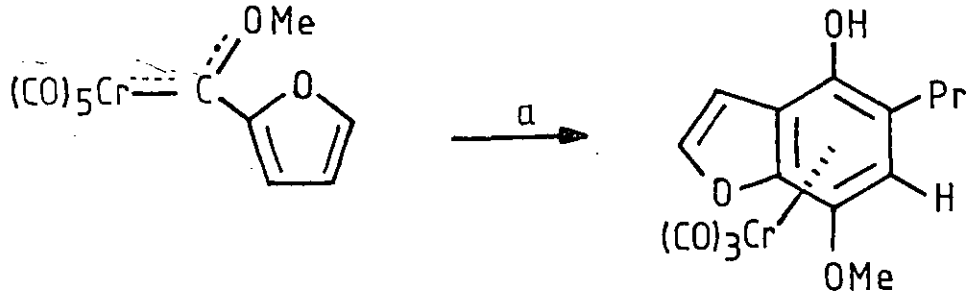


(a) ; (b)H^+; (c)NaOH,H_2O,MeOH; (d)MeI; (e)$NaBH_4$; (f)$(MeCN)_3Cr(CO)_3$;(g)$POCl_3$,DMF; (h)pyridine; (i)Pd/C,300°; (j)Ph_3P, HMPA or DMF; (k)MeLi; (l)I_2.

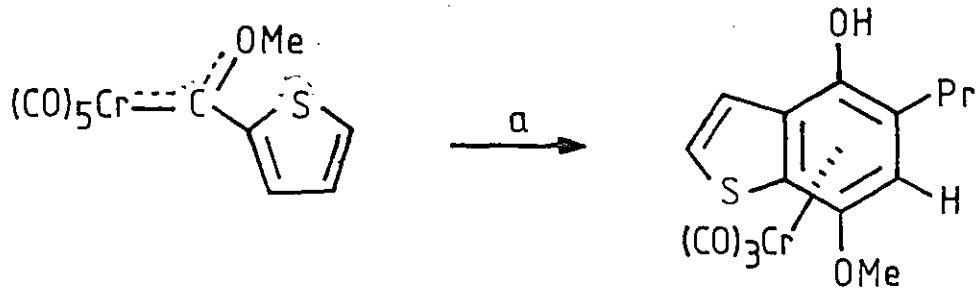
(Scheme 4)

D Benzofuran and benzothiophene complexes

Pentacarbonylchromium complexes with aromatic carbene ligands react with acetylenes in a stereoselective fashion via incorporation of a carbon monoxide ligand, to give substituted benzo-fused aromatic (including benzofuran and benzothiophene) chromiumtricarbonyl complexes (Scheme5). For example, pentacarbonyl-(2-furanyl(methoxy)carbene)chromium(0) (22) and pentacarbonyl-(2-thiophenyl(methoxy)carbene)chromium(0) (24) reacted with pent-1-yne in dibutylether to give the substituted benzofuran (23) and benzothiophene (25) complexes respectively.[14]



(22) (23)



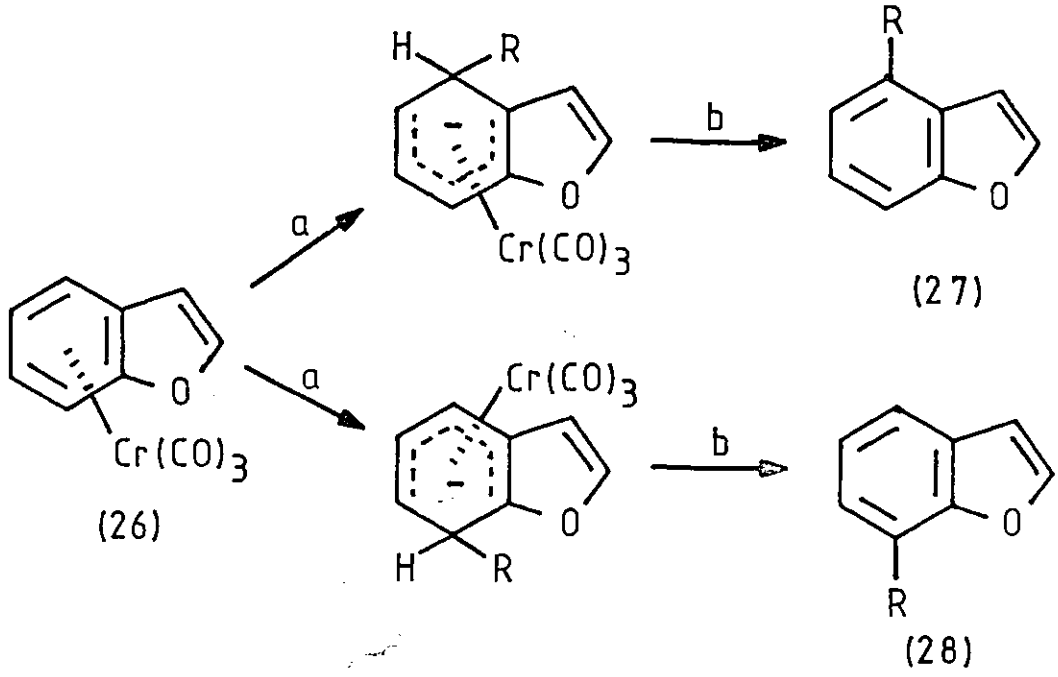
(24) (25)

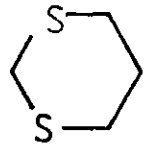
(a)$PrC\equiv CH, Bu_2O, \Delta$.

(Scheme 5)

The construction of the benzo-fused aromatic skeleton is thought to occur in the coordination sphere of the metal, possibly after substitution of a carbon monoxide ligand by the alkyne.[15]

The benzofuran complex (26) reacted with carbanions to give, after oxidation of the intermediates, a mixture of 4-(27) and 7-(28) substituted benzofurans,[16] with the former predominant.



R=CMe_2CN, 

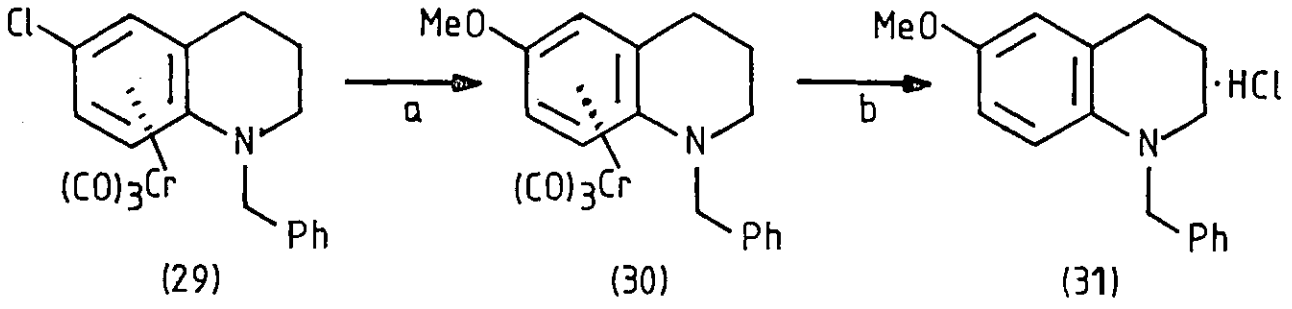
a) LiR, THF, -78°; b) I_2.

E Tetrahydroquinoline and indoline complexes

The enhanced nucleophilic aromatic substitution of chloride from chloroarene complexes by methoxide is well known[6] and has been used to prepare N-protected-methoxy-tetrahydroquinoline and N-protected-methoxyindoline complexes.[17]

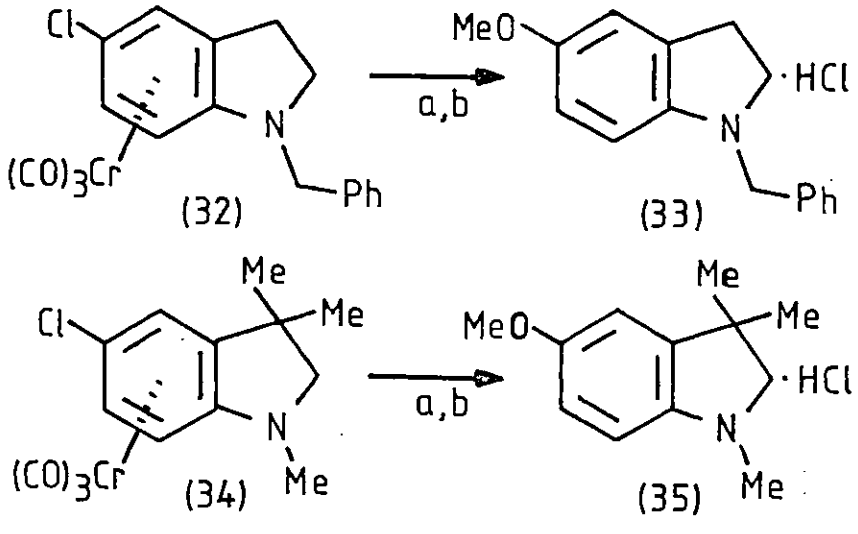
Treatment of 1-benzyl-6-chloro-1,2,3,4-tetrahydroquinoline complex (29) with an excess of potassium methoxide in the presence of 18-crown-6 at 70° gave the 6-methoxy substituted complex (30) in 91% yield. Decomplexation with iodine afforded

1-benzyl-6-methoxy-1,2,3,4-tetrahydroquinoline(31), isolated as the hydrochloride salt, in almost quantitative yield.



(a)KOMe,18-crown-6; (b)I_2,THF,HCl,H_2O.

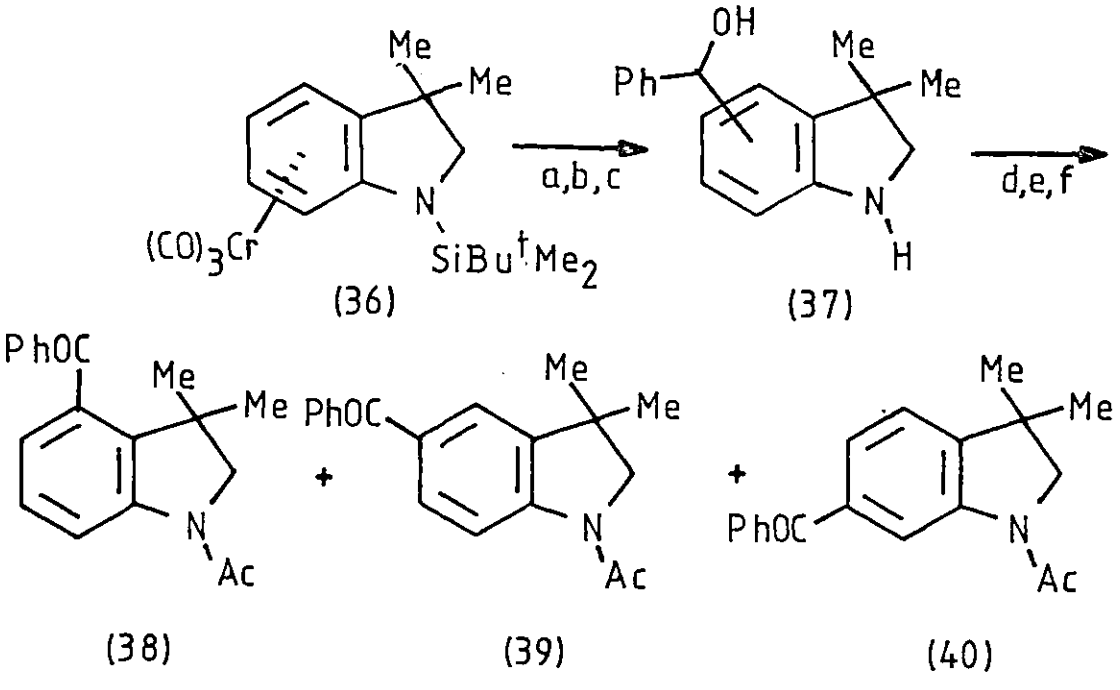
Similarly, 1-benzyl-5-chloroindoline (32) and 1,3,3-trimethyl-5-chloroindoline (34) complexes gave the 1-benzyl-5-methoxyindoline (33) and 1,3,3-trimethyl-5-methoxyindoline (35). hydrochlorides in excellent yields.



(a)KOMe,18-crown-6; (b)I_2,THF,HCl,H_2O.

The lithiation of 1-(t-butyldimethylsilyl)-3,3-dimethylindoline complex (36) with n-butyllithium in TMEDA/THF at low temperatures followed by reaction with benzaldehyde and subsequent

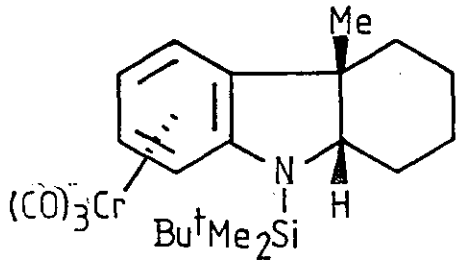
decomplexation and desilylation with iodine and acid, afforded a mixture of the 4-,5- and 6-phenyl(hydroxy)methyl-3,3-dimethylindolines (37) (Scheme 6). This mixture was converted to the 4-(38), 5-(39) and 6-(40) benzoyl-1-acetyl-3,3-dimethylindolines, which were present in the ratios of 27:19:54 respectively.[18]



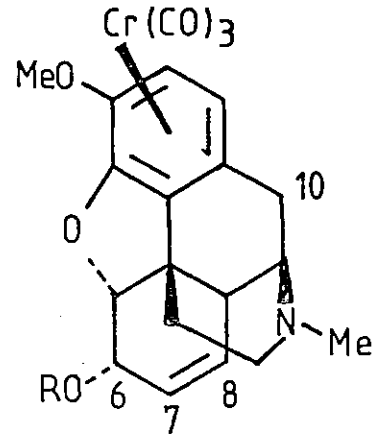
(a)n-BuLi,THF,TMEDA,-60°; (b)PhCHO,H^+; (c)I_2,THF,HCl,H_2O camphorsulphonic acid; (d)Ac_2O,pyridine; (e)KOH,MeOH; (f)Jones' reagent.

(Scheme 6)

This reaction was repeated using acetaldehyde and also with the tricyclic indoline complex (41). In all examples the 6-substituted product was the predominant isomer, and the overall yield of the 4-,5- and 6- substituted products was 50-60%.



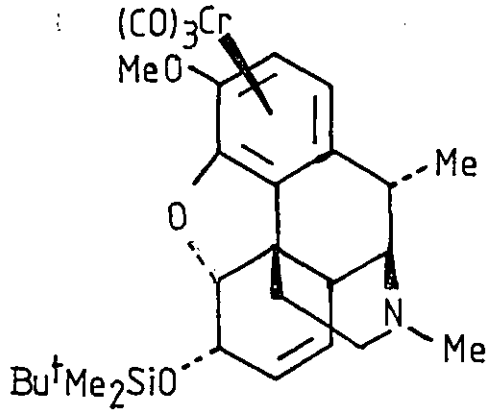
(41)



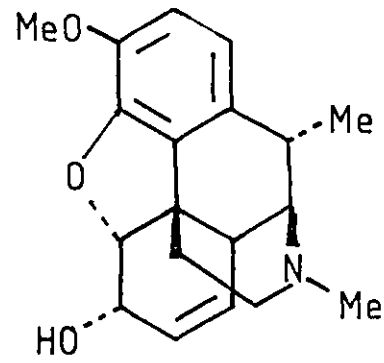
(42)

The chromium tricarbonyl complex of codeine has been prepared [19] and has been found to consist of one steroisomer only, that with the chromium tricarbonyl group attached to the β-face of the aromatic ring (as 42, R=H). Complexation to the α-face is hindered by steric interaction between the carbonyl ligands and C_6, C_7 and C_8.

The O-(t-butyldimethylsilyl)-codeine complex (42, R=Si.Bu^{t}Me$_2$) was stereospecifically alkylated with sodium hexamethyldisilazide and methyl iodide to give the 10(S)-methylcodeine complex (43) in 37% yield, *via* attack *exo* to the chromium tricarbonyl group. Decomplexation with refluxing pyridine and desilylation with tetrabutylammonium fluoride (TBAF) gave 10(S)-methylcodeine (44) in excellent yield.

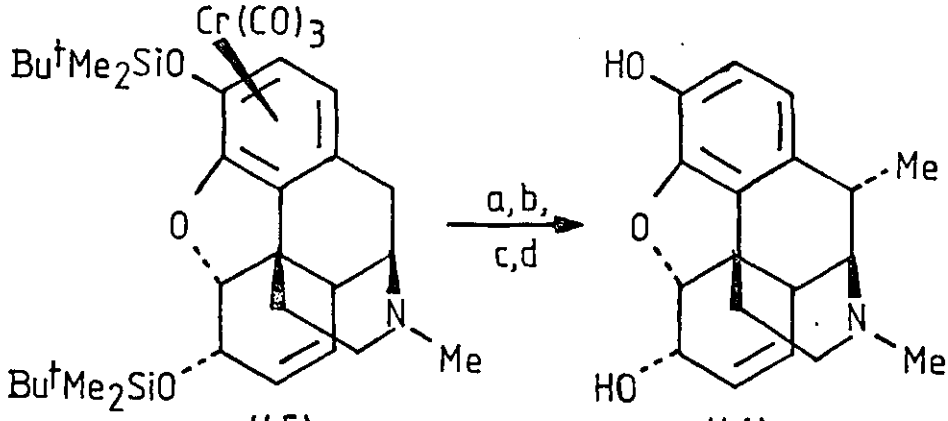


(43)



(44)

The O,O'-bis(t-butyldimethylsilyl) morphine complex (45) was similarly alkylated to give 10(S)-methylmorphine (46).



(45) (46)

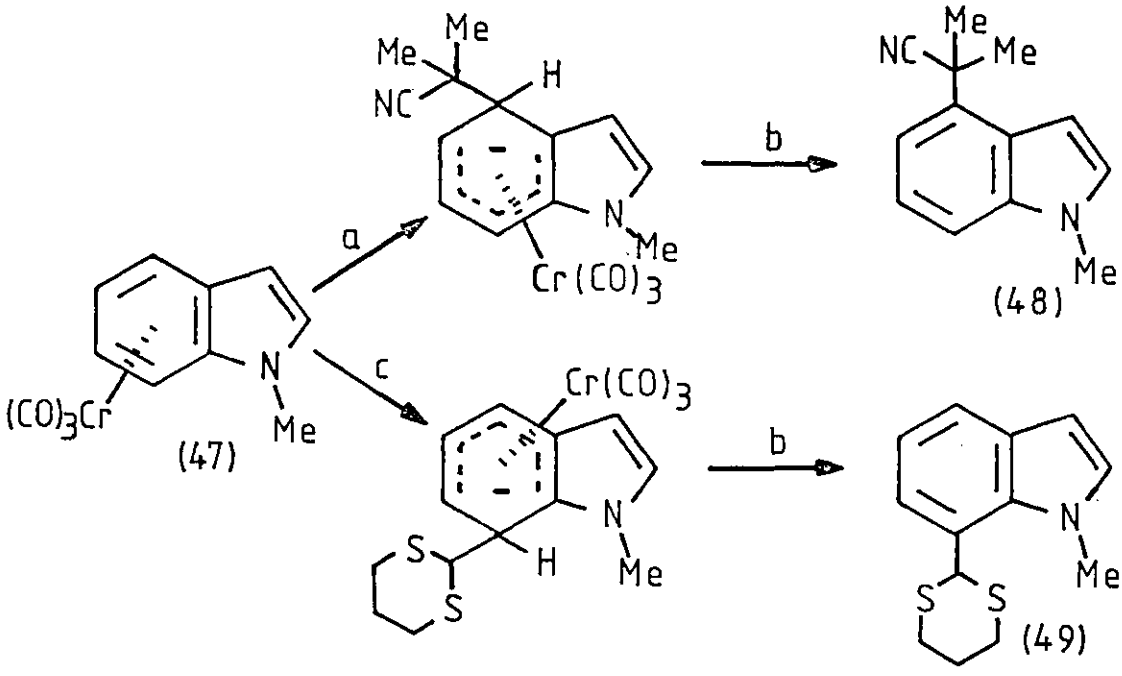
(a)$NaN(SiMe_3)_2$, THF; (b)MeI; (c)pyridine, Δ; (d)TBAF, THF.

G Indole Complexes

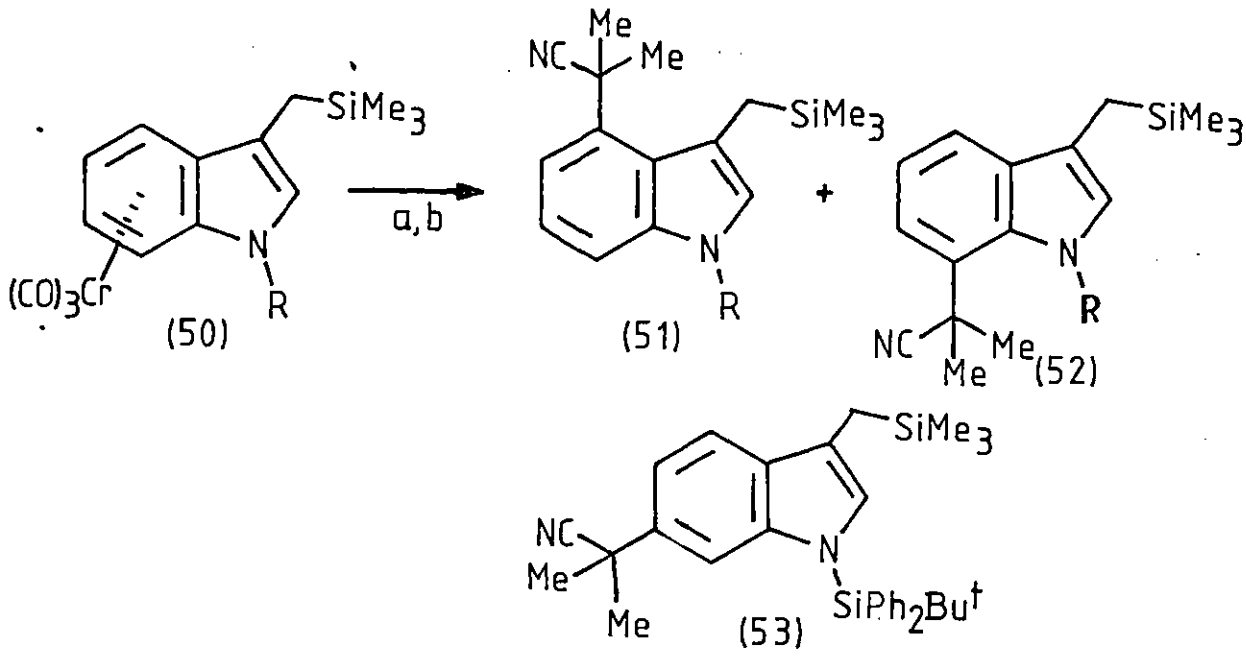
The reaction of 1-methylindole complex (47) with carbanions gave anionic intermediates which, on oxidation with iodine, afforded either the 4- or the 7- substituted indoles.[20] The regiochemistry of the nucleophilic attack was dependent on the nucleophile; with lithioisobutyronitrile addition to C_4 (48) was preferred while with 2-lithio-1,3-dithian addition to C_7 (49) was predominant. This is an experimental

observation for which there is, at present, no satisfactory explanation.

Semmelhack has examined the nucleophilic addition of carbanions to indole complexes in more detail[16] and has found that addition to C_4 was generally preferred over addition to C_7, the only exception to this being the reaction with 2-lithio-1,3-dithian. The ratio of 4-substituted to 7-substituted indoles ranged from 14:86 for 2-lithio-1,3-dithian to 99:1 for lithioisobutyric acid t-butylester. The introduction of a bulky alkyl substituent at C_3 (50, R=Me) directed the nucleophilic addition predominately to C_7 (52, R=Me), while a bulky nitrogen protecting group such as t-butyldiphenylsilyl (50, R=Ph_2Bu^tSi) again favoured C_4 addition (51, R=PH_2Bu^tSi), with only a trace of what was tentatively assigned as the product arising from addition to C_6 (53).



a) $LiCMe_2CN$; b) I_2; c) 2-lithio-1,3-dithian.



a) $LiCMe_2CN$, THF; b) I_2.

H. Conclusion

The use of non-carbocyclic chromium tricarbonyl complexes in organic synthesis has received little attention until very recently, however the relative ease with which substituents can now be introduced into certain, previously inaccessible, positions of heterocyclic systems suggests that these compounds will have a significant role to play in the development of new, efficient syntheses of complex molecules.

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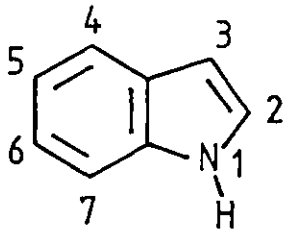
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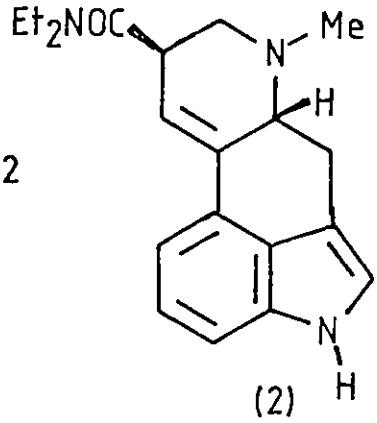
THE SYNTHESIS OF CARBOCYCLIC-RING, CARBON-SUBSTITUTED INDOLES

A Introduction

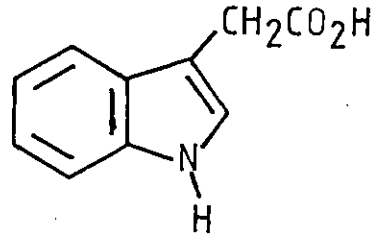
The indole nucleus (1) is widespread in nature occurring in a range of alkaloids and other biogenic compounds.[1] A number of these compounds possess useful or interesting properties, such as the infamous hallucinogen, lysergic acid diethylamide (LSD) (2) and the plant-growth regulating hormone indole-3-acetic acid (3).



(1)



(2)



(3)

The synthesis of indoles with a range of substituents in all possible positions of the skeleton is therefore desirable in order to investigate their structure-activity relationships.

Introduction of substituents into the pyrrolic ring of indole is straight forward.[2] The 3-position of indole is the most reactive site towards electrophilic substitution. N-substituted products are obtained by electrophilic attack on a localised N-anion in a polar solvent. Finally, 2-substituted products can be obtained by electrophilic attack on 2-lithioindoles, generally obtained by the action of alkyllithiums on N-protected indoles.[3]

The direct introduction of substituents into the carbocyclic ring of indole is more difficult, usually resulting in poor yields or complex mixtures.[2] This problem is usually overcome by the preparation of substituted indoles from non-indolic starting materials and most frequently from a reaction in which the pyrrole ring is built on to an already substituted benzene ring. The more established indole syntheses have been extensively reviewed[2] and might be generally described as inefficient as they produce mixtures of products, except in a few favourable cases, or require blocking groups in certain ring positions to direct the regiochemistry. Only the more recent developments of these methods will be discussed in this review.

Since the ergot alkaloids exhibit a range of pharmacological properties and are of some medicinal importance, the syntheses of 4- substituted indoles and their elaboration to ergot-type compounds have recently been reviewed.[4]

The material covered in this review will be discussed in the following manner:

(a) syntheses based on a substituted benzene ring, with a clear division made between the older classical methods and more recent strategies;

(b) syntheses based on a pyrrole ring;

(c) syntheses based on other ring systems;

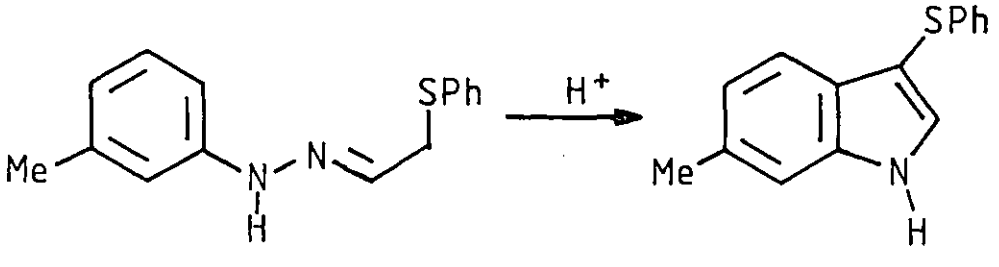
(d) methods of directly substituting the carbocylic ring.

B Syntheses based on a substituted benzene ring

(i) Classical methods

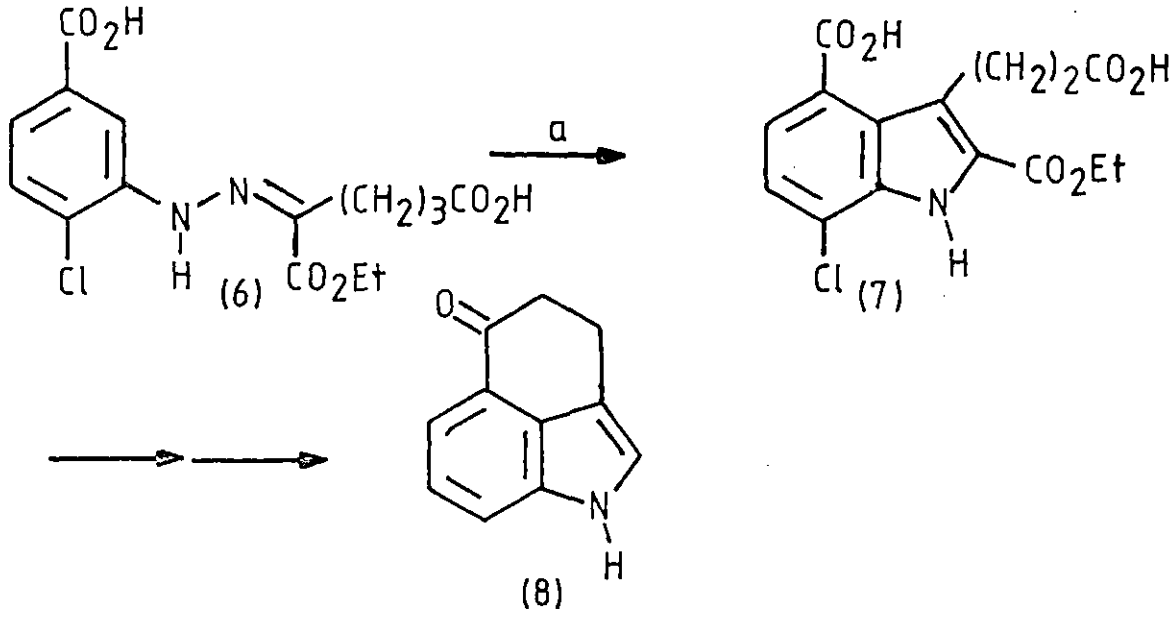
(1) The Fischer indole synthesis

The Fischer indole synthesis is one of the oldest and most widely used methods of preparing indoles and involves the cyclisation of a substituted phenylhydrazone under a variety of conditions.[2] However, unsymmetrically substituted phenyl rings give a mixture of isomeric indoles[2] so a number of modifications have been reported. For example, the cyclisation of meta-substituted phenylhydrazones usually gives a mixture of 4 and 6 substituted indoles[2] but the cyclisation of the m-methylphenylhydrazone (4) gave the 6-methylindole (5) only.[5] Desulphurisation of the product was possible using Raney-nickel.



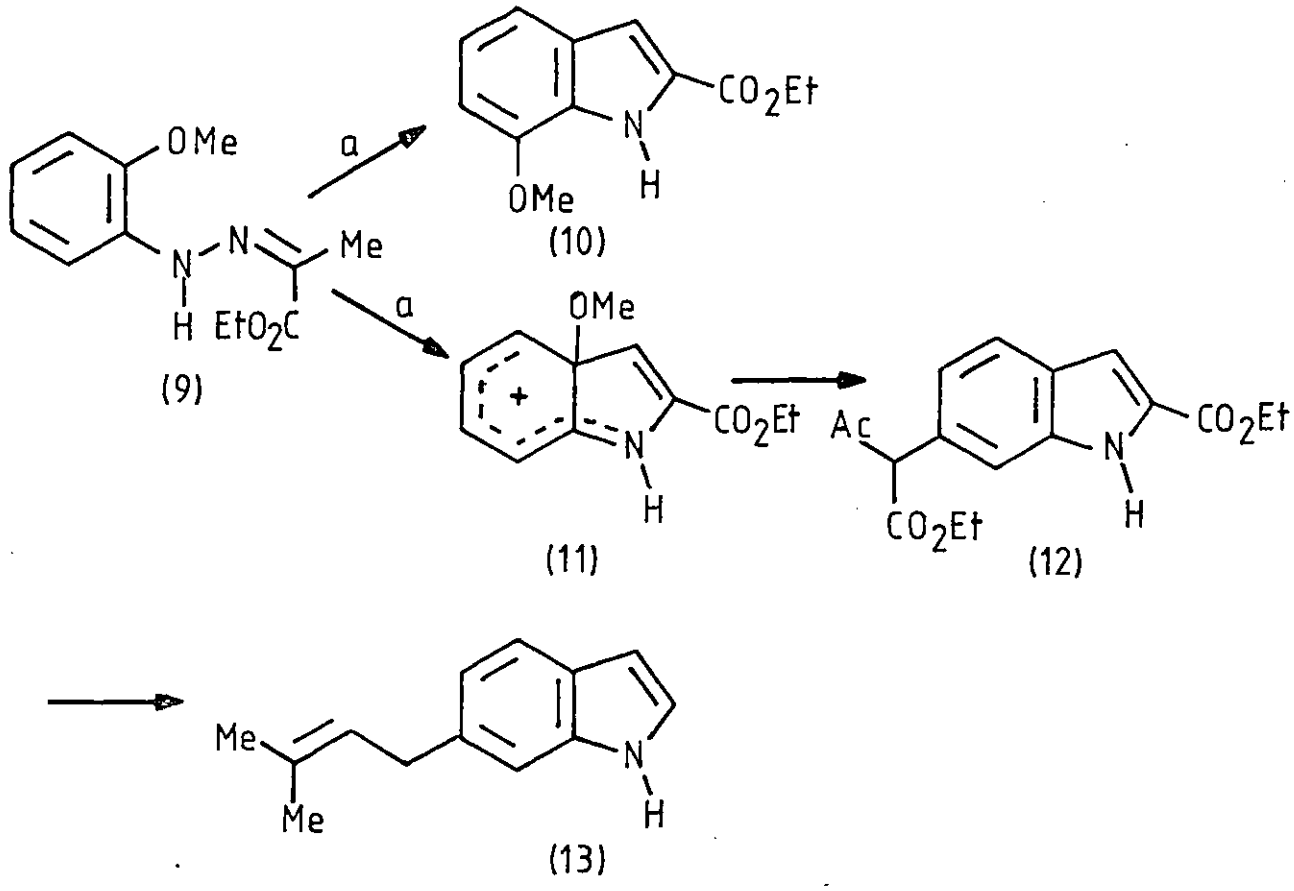
(4) (5)

The Fischer indole cyclisation of the hydrazone (6), containing a blocking chlorine atom to direct the cyclisation gave the substituted indole (7) which was an intermediate in a synthesis of Uhle's ketone (8).[6]



(a) BF_3·AcOH, AcOH, Δ.

Treatment of the o-methoxyphenylhydrazone (9) with p-toluene-sulphonic acid and an excess of ethylacetoacetate gave the expected 7-methoxyindole (10, 18%) and the 6-substituted indole (12) in 56% yield.[7] The major product arose by attack of the enolisable dicarbonyl compound on the intermediate (11), itself formed by an abnormal Fischer reaction (Scheme 1). The 6-substituted indole (12) was elaborated to a range of more interesting 6-substituted indoles including 6-(3',3'-dimethylallyl)-indole (13), a simple alkaloid.[8]



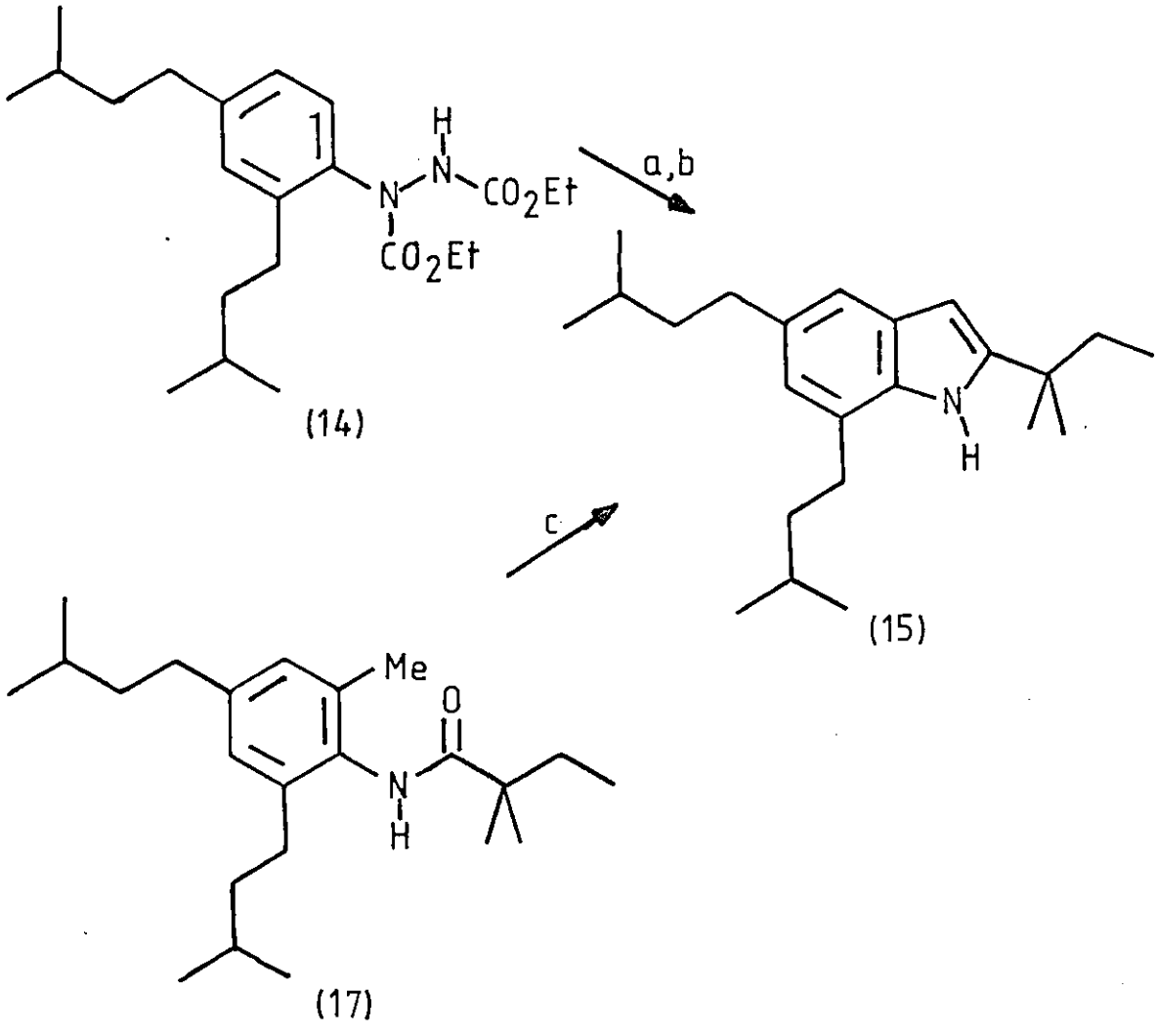
(a) p-$MeC_6H_4SO_3H$, $AcCH_2CO_2Et$, PhH, Δ.

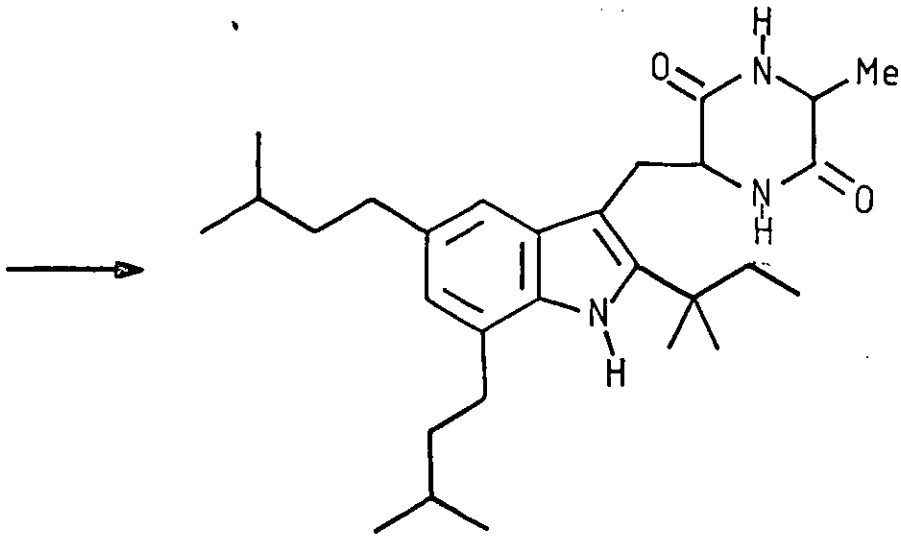
(Scheme 1)

The cyclisation of phenylhydrazones over an alumina catalyst at temperatures of 300 - 400° is claimed to give higher yields of indoles on an industrial scale, and with a greater tolerance

for simple substituents than under the normal Fischer reaction conditions.[9]

The synthesis of the trisubstituted indole (15), a key intermediate in the synthesis of (dl)-hydroechinuline (16), was achieved in poor yield by the alkaline hydrolysis of the 2,4-diisoamylphenylhydrazine (14) followed by a Fischer indole synthesis with 3,3-dimethylpentan-2-one and polyphosphoric acid[10] (Scheme 2) or, more efficiently, by a Madelung reaction of the substituted toluene (17) with potassium t-butoxide.





(16)

(a)base hydrolysis; (b)$MeCOCMe_2CH_2Me$, polyphosphoric acid; (c)$KOBu^t$.

(Scheme 2)

Despite the poor regiocontrol and low yields often experienced in the Fischer indole synthesis it remains one of the most widely used methods of constructing the indole skeleton primarily because of the simple reaction conditions required.

(2) The Bischler indole synthesis

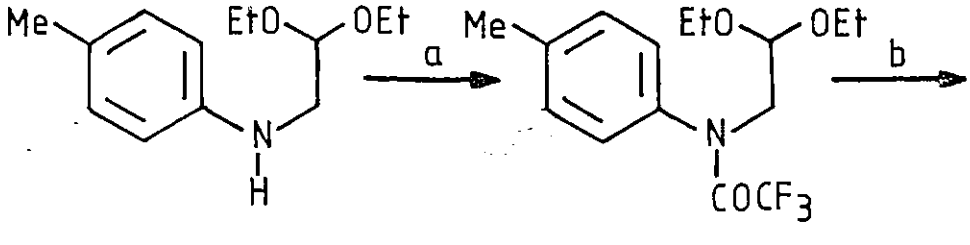
The cyclisation of α-anilinoketones under protic or Lewis acid conditions is known as the Bischler indole synthesis.[2]

Although the mechanism of this reaction has been studied in depth[2] the mixtures of products that often result from this

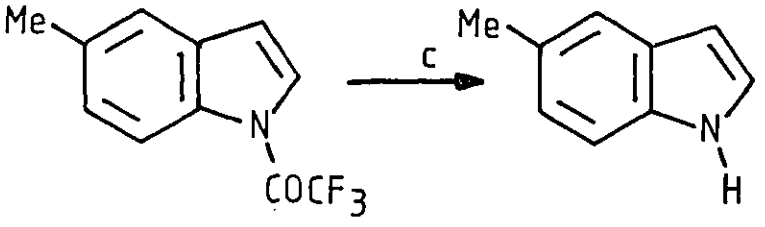
reaction has meant that it has found little use in preparative chemistry.

A range of di- or tri-methyl-2-arylindoles have been prepared in good yield by the cyclisation of substituted α-anilino-ketones in the presence of an acid catalyst.[11]

In an extension of the Bischler reaction it has been found that 1-(trifluoroacetyl)-indoles are produced in high yield from the cyclisation of N-trifluoroacetyl-α-anilinoacetals[12] (Scheme 3). Treatment of the p-methyl-α-anilinoacetal (18) with trifluoroacetic anhydride yielded the N-trifluoroacetyl compound (19) which on treatment with boiling trifluoroacetic acid containing trifluoroacetic anhydride afforded 1-(trifluoro-acetyl)-5-methylindole (20). Hydrolysis of the trifluoro-acetyl group with potassium hydroxide gave 5-methylindole (21) in 86% overall yield.



(18) (19)



(20) (21)

(a)$(CF_3CO)_2O$,Et_3N; (b)CF_3COOH,$(CF_3CO)_2O$,Δ; (c)KOH,MeOH.

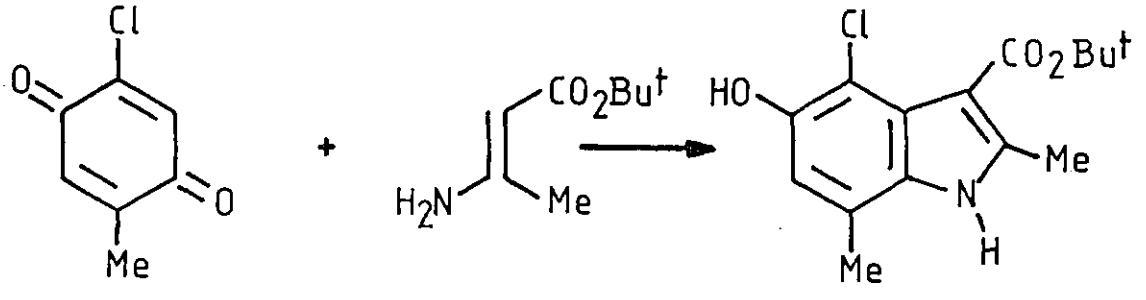
(Scheme 3)

Cyclisation of the m-methyl-N-trifluoroacetyl- α-anilinoacetal proceeded via the two possible paths to give a mixture of 4- and 6-methylindoles in 9% and 77% overall yields respectively. At present, though only simple indoles without electron-withdrawing substituents have been prepared, this one-pot procedure constitutes an efficient method for the preparation of some simple alkyl or alkoxy indoles.

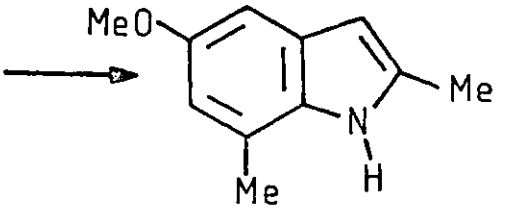
(3) The Nenitzescu indole synthesis

The reaction of the aminocrotonate (23) with the substituted benzoquinone (22) in a Nenitzescu indole synthesis[2] afforded the 7-substituted indole (24) via initial condensation of the enamine onto the position ortho to chlorine. Subsequent

reactions on the indole (24) gave 2,7-dimethyl-5-methoxyindole [13] (25).



(22) (23) (24)



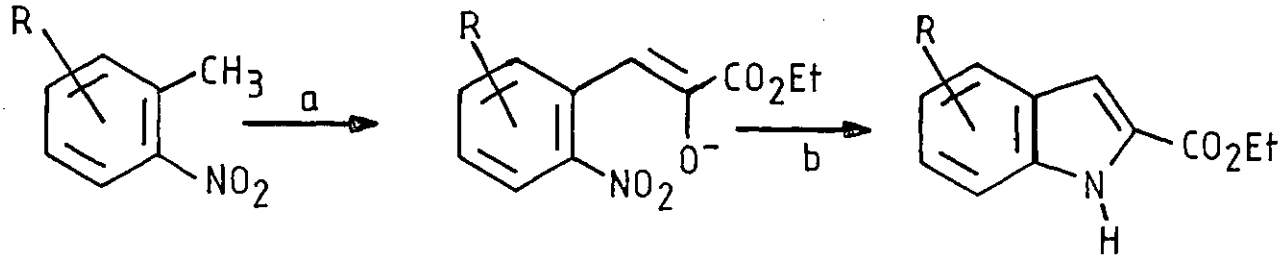
(25)

Substituted benzoquinones generally condense with β-amino-crotonates in the two possible ways leading to a mixture of products; the example above is a directed condensation giving only one product. The Nenitzescu reaction requires the α-position of the aminocrotonate to be substituted and consequently 2-substituted products are obtained. Overall it is an efficient route to 5-hydroxy-2-substituted indoles.

(4) The Reissert and Related Indole Syntheses

The reduction of an o-nitrobenzylketone generates an o-amino-benzylketone which can cyclise and dehydrate, in situ, to give an indole. This is an efficient strategy for the preparation

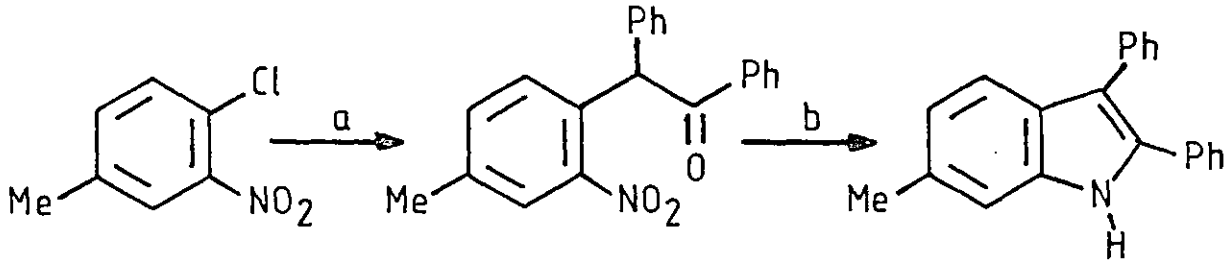
of indoles substituted in the carbocyclic ring as there is only one possible mode of ring closure. The Reissert indole synthesis, in which a substituted o-nitrotoluene (26) is condensed with an oxalate ester and then reductively cyclised to a substituted indole-2-carboxylic acidderivative (27), is a well documented example of this general procedure.[2]



(26) (27)

(a)base, $EtOCOCO_2Et$; (b)Catalyst/H_2.

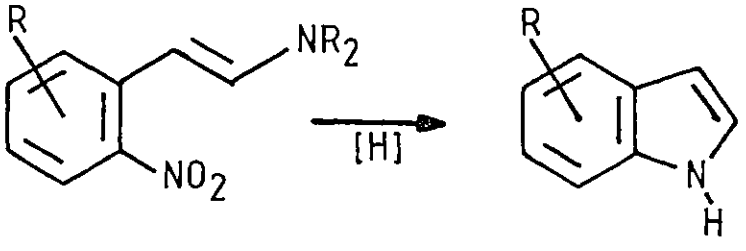
A recent modification of this procedure has been used to prepare 2,3-diphenylindoles.[14] Reaction in DMSO of 3-nitro-4-chlorotoluene (28) with deoxybenzoin enolate resulted in the displacement of chloride to give the substituted o-nitrobenzylketone (29) which, on reduction, gave 2,3-diphenyl-6-methylindole (30) in 83% yield.



(28) (29) (30)

(a)PhCH·COPh, DMSO; (b)Pd/C, H_2 or Fe/AcOH.

Although the Reissert reaction has found little use in preparative chemistry, the recent related synthesis of indoles (32) by the reductive cyclisation of o-nitro- β-dialkylaminostyrenes (31) has found widespread application in the syntheses of substituted indoles and will be discussed later in this review (Page 49).

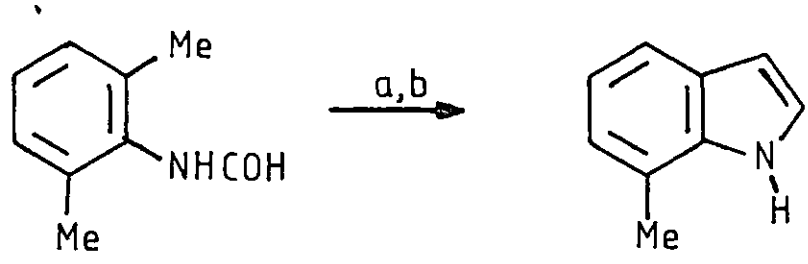


(31) (32)

(5) The Madelung indole synthesis

The Madelung reaction[2] involves the cyclisation of N-acyl-o-alkylanilines under strongly basic conditions at elevated temperatures.

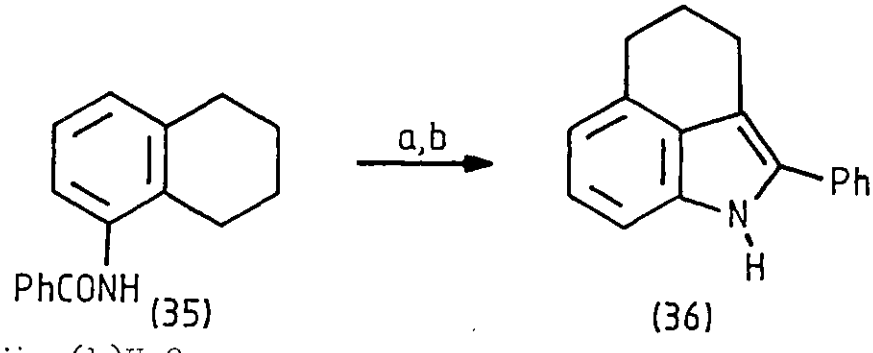
In its traditional form, the conditions are such that it is limited to the preparation of simple alkylindoles, as with the synthesis of 7-methylindole (34) in 50% yield[15] from the reaction of 2,6-dimethylformanilide (33) with potassium ethoxide at 350°.



(33) (34)

(a)KOEt, 350°; (b)H_2O.

A recent modification of the Madelung reaction used butyl-lithium at room temperature to effect the cyclisation of N-benzoyl-1-amino-5,6,7,8-tetrahydronaphthalene (35) to the 2-phenylindole derivative (36) in 41% yield.[16]



(35) (36)

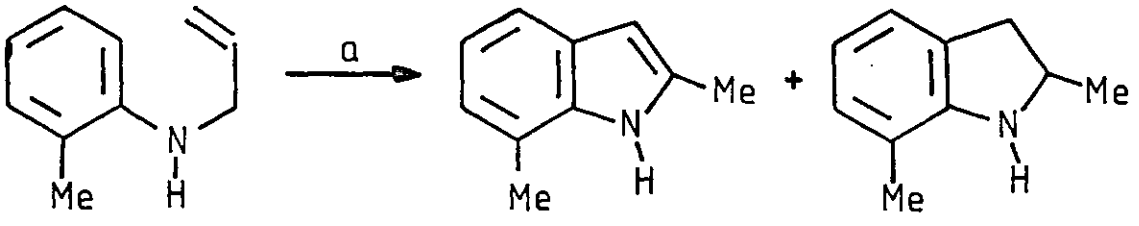
(a)n-BuLi; (b)H_2O.

(ii) Newer strategies towards substituted indoles

(1) From rearrangement reactions

Several modern approaches towards the construction of the indole nucleus depend, as does the Fischer indole synthesis, on a rearrangement reaction to construct the pyrrole ring.

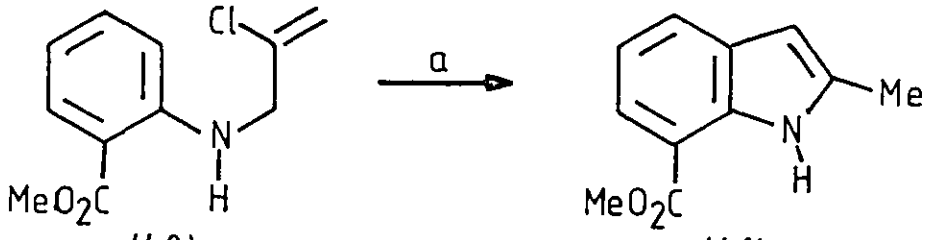
The acid catalysed thermal rearrangement of N-allyl-o-toluidine (37) gave, in fair yield, a mixture of 2,7-dimethylindole (38) and 2,7-dimethylindoline (39).[17] The latter was readily dehydrogenated to the indole (38). As the yields of indole are poor and because of the severe reaction conditions necessary for the rearrangement, this particular method has found little preparative use.



(37) (38) (39)

(a)H^+, Δ.

In a similar reaction, substituted N-(2-chloroallyl)anilines rearranged to substituted 2-methylindoles in good yields.[18] For example, 2-methyl-7-methoxycarbonylindole (41) was produced in 75% yield from the rearrangement of the substituted aniline (40).



(40) (41)

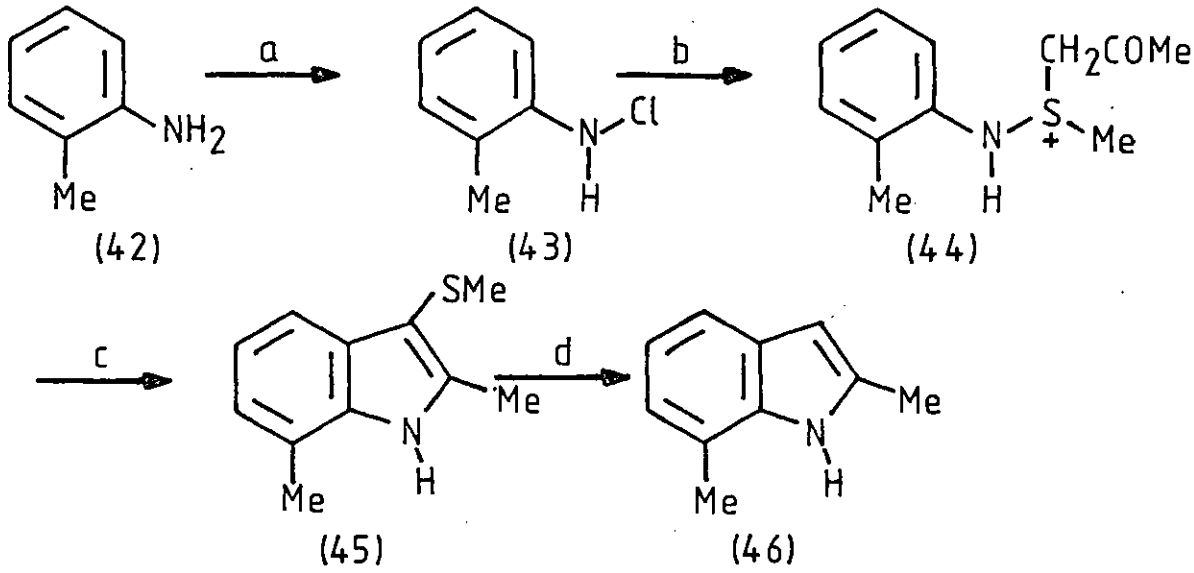
(a)polyphosphoric acid, Δ or BF_3·MeOH, Δ.

This reaction is confined to the synthesis of simple 2-methyindoles.

Another method for the preparation of indoles, due to Gassman *et al*, is outlined below (Scheme 4). Reaction of the substituted *N*-chloroaniline (43), obtained from *o*-toluidine (42), with 1-methylthiopropan-2-one gave the azasulphonium salt (44) which, on treatment with base, rearranged to the substituted 2-methyl-3-methylthioindole (45). Desulphurisation with Raney-nickel afforded 2,7-dimethylindole (46) in 53% overall yield.[19]

The use of 1-methythioacetaldehyde in place of 1-methylthiopropan-2-one gave indoles unsubstituted in the 2-position but in lower overall yields. Since the reaction involves an *N* to *ortho* rearrangement, *meta* substituted anilines afford a mixture of 4- and 6-substituted indoles.

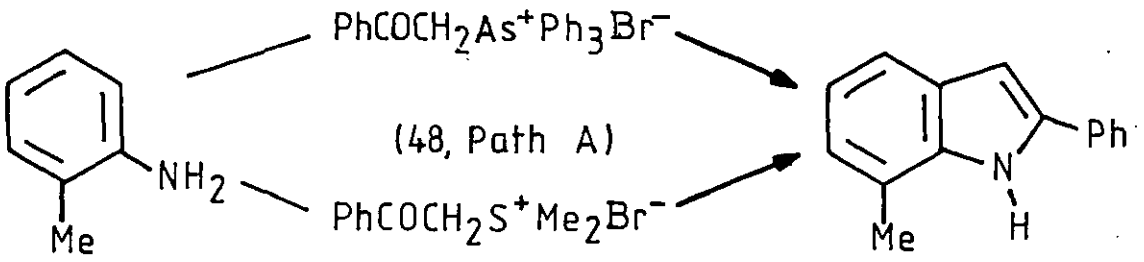
This reaction is similar to the Fischer indole synthesis but has a couple of advantages in that the starting substituted anilines are more readily available than substituted phenylhydrazines and that the reaction conditions are milder.



(a)$Bu^tOCl, CH_2Cl_2, -65^o$; (b)$MeSCH_2COMe$; (c)Et_3N; (d)Raney-nickel.

(Scheme 4)

Reaction of o-toluidine (47) with phenacyltriphenylarsonium-bromide (48) in refluxing N,N-dimethylaniline afforded 2-phenyl-7-methylindole (49) in 63% yield[20] (Path A) and on treatment with phenacyldimethylsulphonium bromide (50) in refluxing N,N-diethylaniline gave the same indole (49) in 72% yield[21] (Path B).

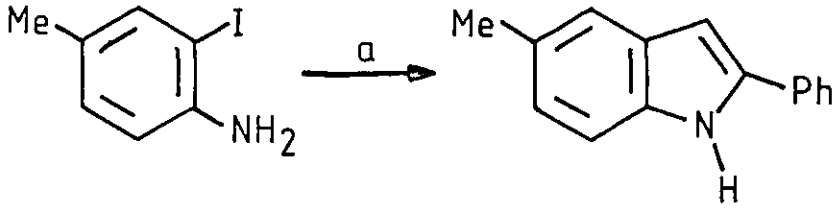


(47) (50, Path B) (49)

These, almost identical reactions, have only been used for the preparation of a few simple 2-phenylindoles. Further applications will have to await a more extensive study of the scope of these reactions.

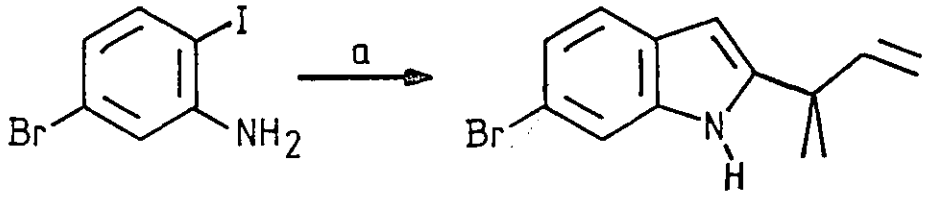
(2) From o-haloanilines

The reaction of substituted o-iodoanilines with cuprous acetylides afford good yields of the substituted indoles.[22] For example, the reaction of o-iodo- p-methylaniline (51) with cuprous phenylacetylide gives a 90% yield of 2-phenyl-5-methylindole (52). This reaction is limited to the synthesis of 2-substituted indoles and has been used to prepare, in quantitative yield from 2-iodo-5-bromoaniline (53), 2-(1', 1'-dimethylallyl)-6-bromoindole (54), an intermediate in the synthesis of neoechinulin [23] (55).

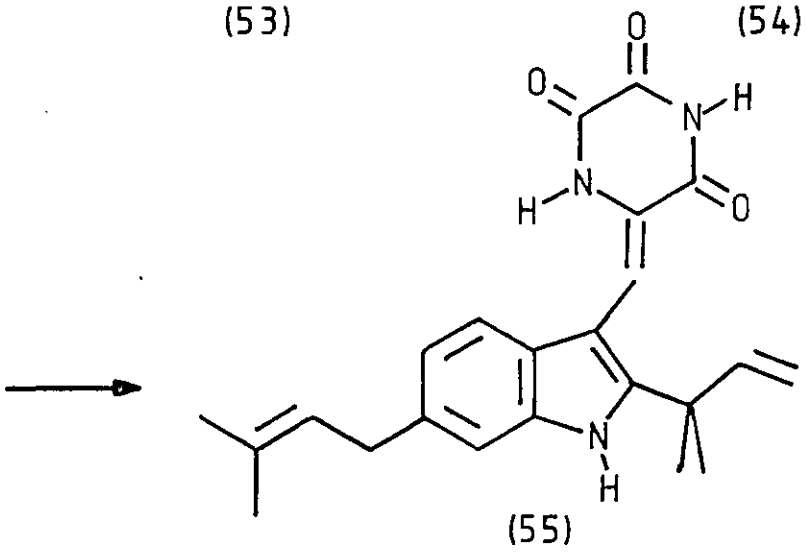


(51) (52)

(a)PhC≡CCu, DMF, Δ.



(53) (54)

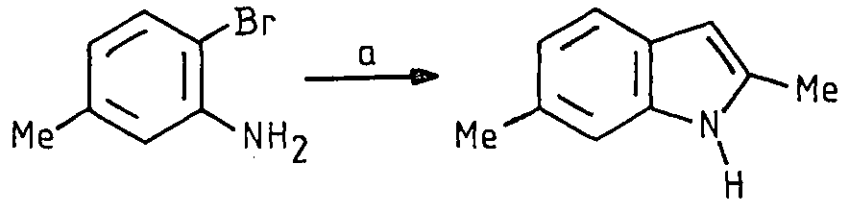


(55)

(a)$H_2C{=}CHCMe_2C{\equiv}CCu$, DMF, Δ.

In a related reaction, 2-substituted indoles were prepared in good yields from the treatment of substituted o-haloanilines with ketone enolates under irradiation.[24] For example, the

reaction of 2-bromo-5-methylaniline (56) with acetone potassium enolate afforded an 82% yield of 2,6-dimethylindole (57).



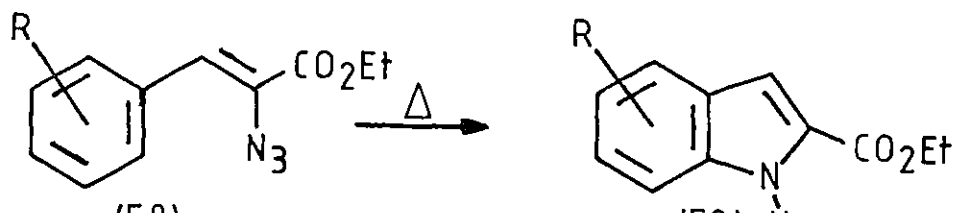
(56) (57)

(a) $K^+ CH_2=C(O^-)Me$, liq.NH_3, hν.

As with the previous indole synthesis, this method is restricted to the preparation of 2-alkylindoles.

(3) From azides and azirines

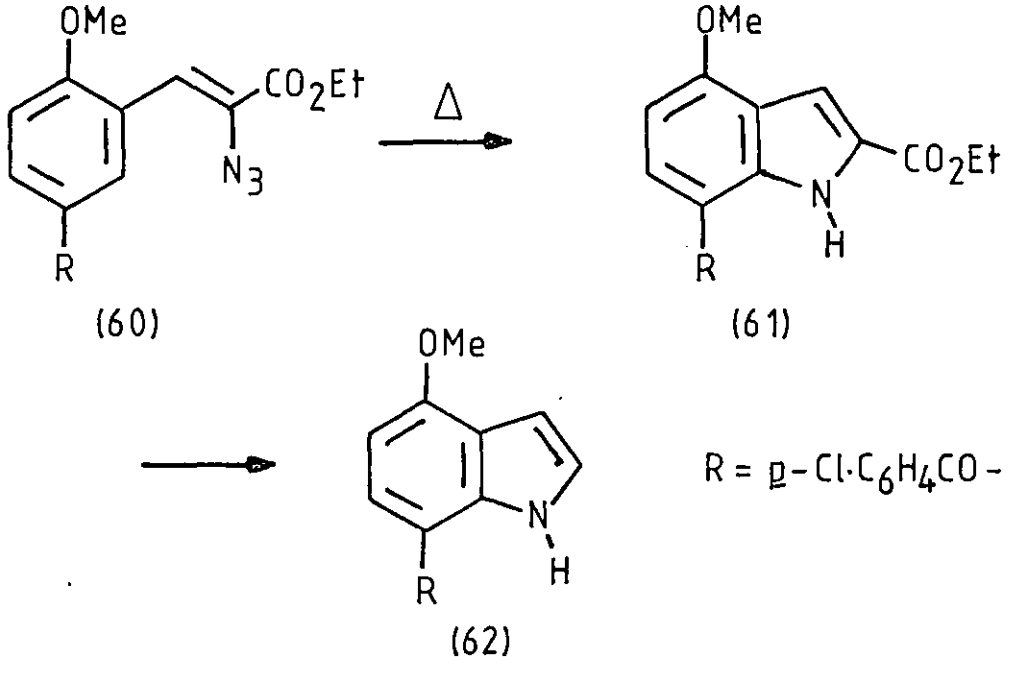
The thermolysis of ortho and para substituted α-azidocinnamates (58) in boiling xylene gave excellent (90-95%) yields of the substituted 2-ethoxycarbonylindoles[25] (59); however, meta substituted α-azidocinnamates afforded a mixture of 5-and 7-substituted indoles.



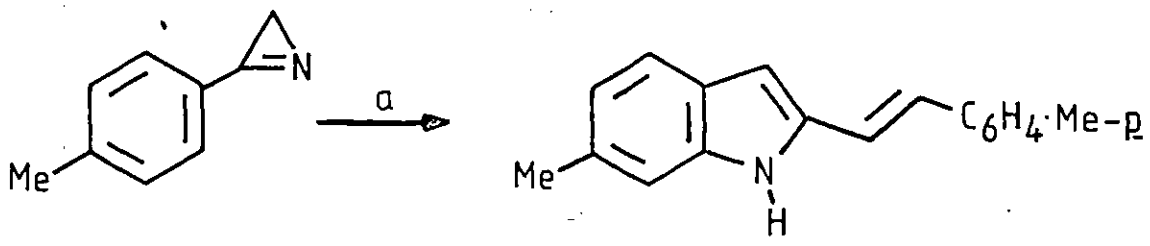
(58) (59)

This reaction is limited to the synthesis of indole-2-carboxylates and if the 2-position is required unsubstituted

additional hydrolysis and decarboxylation steps are required, as in the recent preparation of 6- and 7-acylindoles.[26,27] In the preparation of 7-acylindoles,[27] one ortho position of the substituted α-azidocinnamate was blocked with a methoxy group (as 60) directing the cyclisation to give the 7-acylindole (61). Subsequent hydrolysis and decarboxylation steps gave 4-methoxy-7-(p-chlorobenzoyl)indole (62).



Certain transition metal compounds react with substituted 2-arylazirines (63) to give variable yields of the substituted 2-styrylindoles[28] (64). This reaction has found little application as it requires further study to extend its scope beyond that of the preparation of 2-styrylindoles.

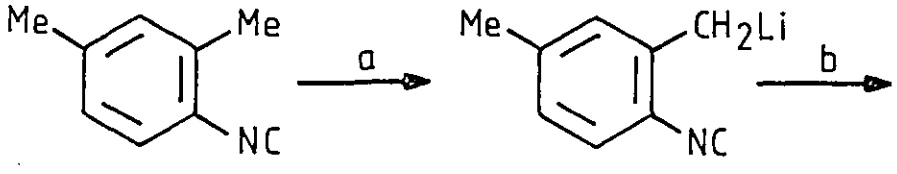


(63) (64)

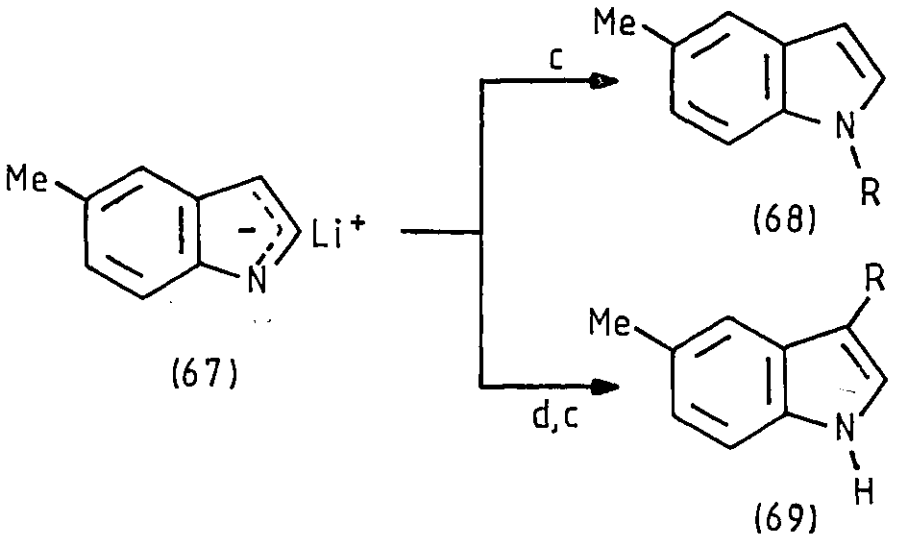
(a)[$Co_2(CO)_8$,PhH; or /$Rh(CO)_2Cl$/$_2$,PhH; or /$(Ph_3P)_2Rh(CO)Cl$/, PhH.

(4) From Isocyanides (Scheme 5)

The action of lithium diisopropylamide on o, p-dimethylphenyl-isocyanide (65) at -78° generated the α-lithiomethylanion (66) which on warming to room temperature cyclised to 5-methyl-lithioindole (67). Reaction of this anion with alkylhalides gave 1-alkyl-5-methylindoles (68) in good overall yields, while treatment with magnesium iodide prior to the alkylation afforded 3-alkyl-5-methylindoles[29] (69), also in good yields.



(65) (66)



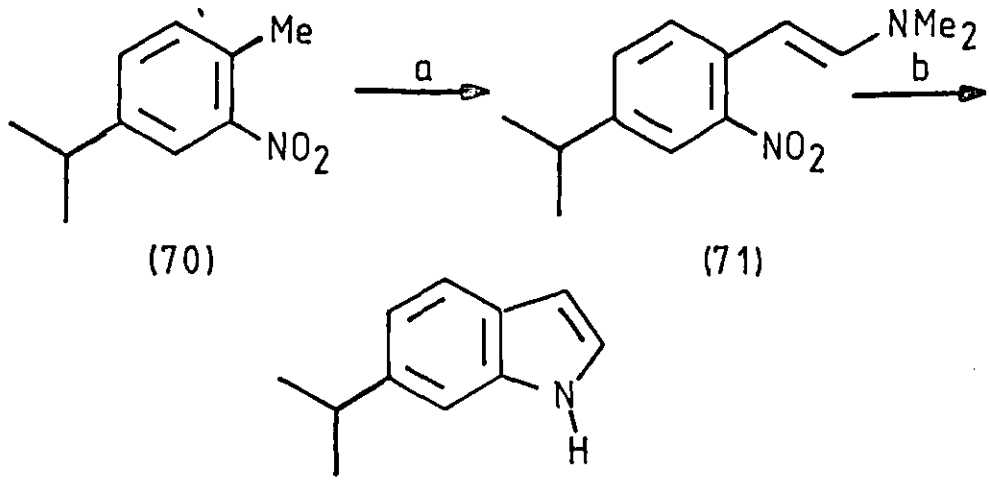
(a)LiN($\underline{i}$-C_3H_7)$_2$,-78°,diglyme; (b)-78° → Room Temp; (c)RX; (d)MgI_2.

(Scheme 5)

This is an efficient, mild route to substituted indoles that does not produce isomeric mixtures of products, but which is limited by the fact that disubstituted phenylisocyanides are not readily available compounds.

(5) From $\underline{o}$-nitrotoluenes

In a strategy patented by Batcho and Leimgruber, the condensation of substituted $\underline{o}$-nitrotoluenes (as 70) with dimethylformamide dialkylacetals gave the corresponding β-dimethylamino-$\underline{o}$-nitrostyrenes (as 71) which on reductive cyclisation afforded the substituted indoles (as 72) in variable overall yields.[30] For example, 6-isopropylindole (72) was prepared in 43% overall yield from $\underline{o}$-nitro-$\underline{p}$-isopropyltoluene (70).



(70) (71) (72)

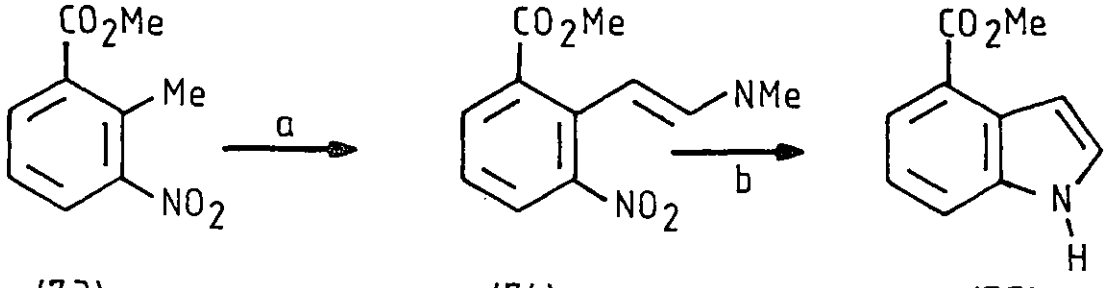
(a)$Me_2NCH(OMe)_2$,DMF,Δ ; (b)Pd/C,H_2; or Raney-nickel or Fe,AcOH.

As the reductive cyclisation involves the reaction of two ortho substituents, there is only one possible product. This strategy tolerates a broad range of functional groups of widely differing electronic character, and it constitutes an efficient method for the preparation of a range of simple indoles from readily available starting materials.

More recently, this strategy has formed the basis of a number of syntheses of 4-substituted indoles,[31-38] particularly those which serve as intermediates in the synthesis of ergot alkaloids.

Condensation of 2-methyl-3-nitrobenzoic acid methylester (73) with dimethylformamide dimethylacetal gave the enamine (74) which reductively cyclised to give 4-methoxycarbonylindole (75) in 63%,[32] 66%[33] or 74%[34] overall yields depending on the

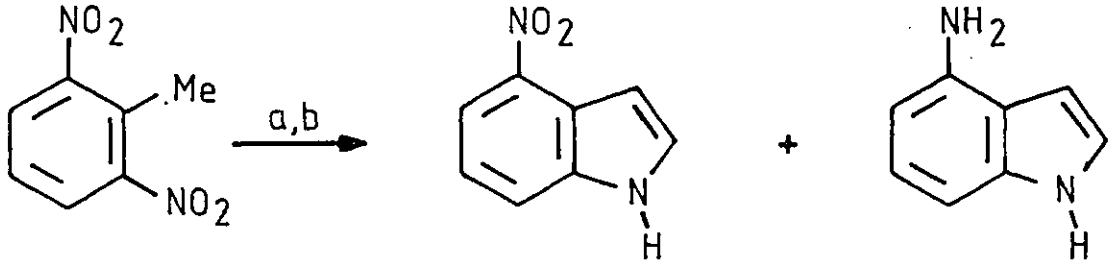
reaction conditions used. This indole (75) was readily converted to 4-formylindole and other ergot alkaloid precursors.[32,33]



(73) (74) (75)

(a)$Me_2NCH(OMe)_2$, DMF, Δ ; (b)Fe, AcOH; or Pd/C, H_2; or $TiCl_3$.

Similarly, o, o-dinitrotoluene (76) gave 4-nitroindole (77) or 4-aminoindole (78) depending on the conditions of the cyclisation step.[35]

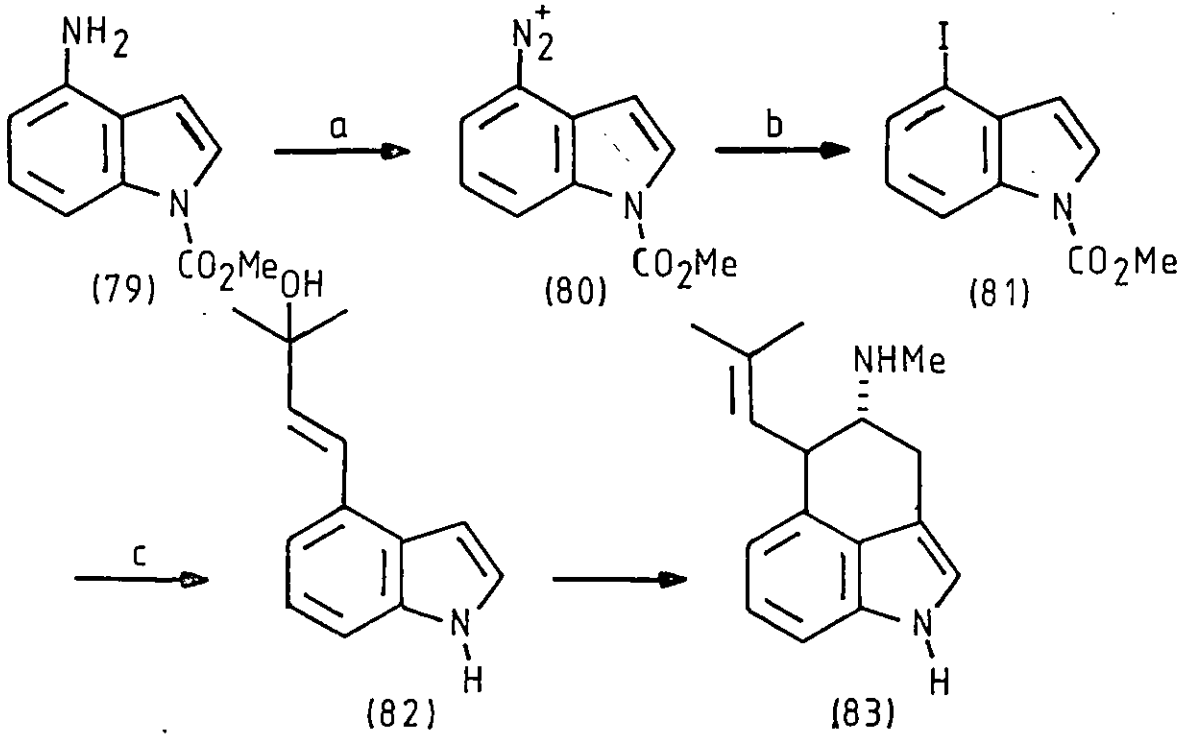


(76) (77) (78)

(a)$Me_2NCH(OMe)_2$, DMF, Δ ; (b)$TiCl_3$.

Diazotisation of 1-methoxycarbonyl-4-aminoindole (79), prepared from 4-nitroindole in 88% yield, gave the diazonium salt (80) which on treatment with potassium iodide gave a 76% yield of 1-methoxycarbonyl-4-iodoindole[36] (81). The palladium catalysed reaction of this iodoindole (81) with 3-methyl-3-hydroxybut-1-ene

afforded 4-(3'-hydroxy-3'-methylbut-1'-enyl)indole (82), an intermediate in a synthesis of (±)-6,7-secoagroclavine (83), in 47% yield (Scheme 6).

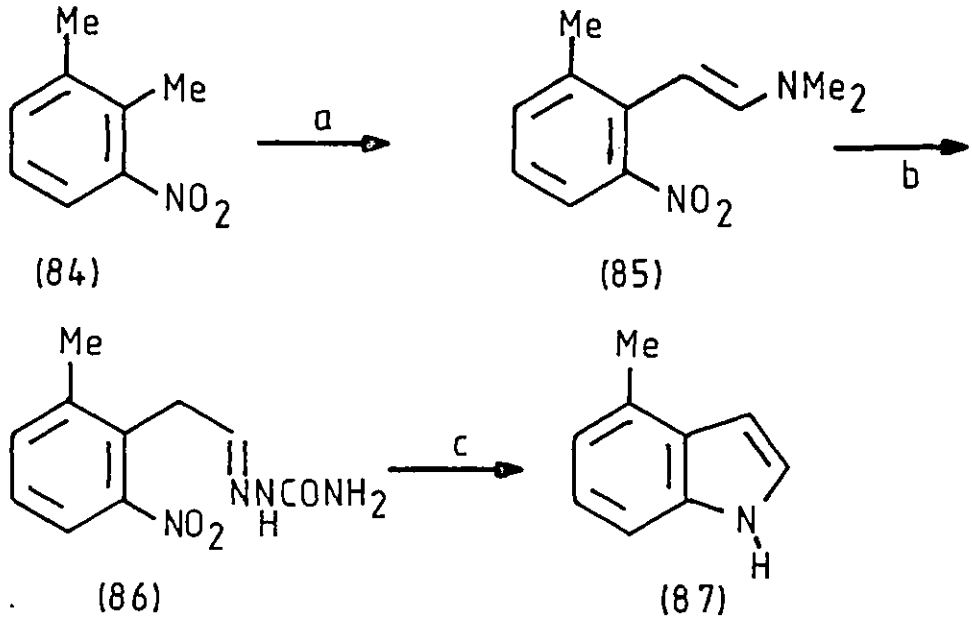


(a)$NaNO_2$,HCl,H_2O; (b)KI; (c)$Pd(OAc)_2$,PPh_3,NEt_3,CH_3CN,3-methyl-3-hydroxy-but-1-ene.

(Scheme 6)

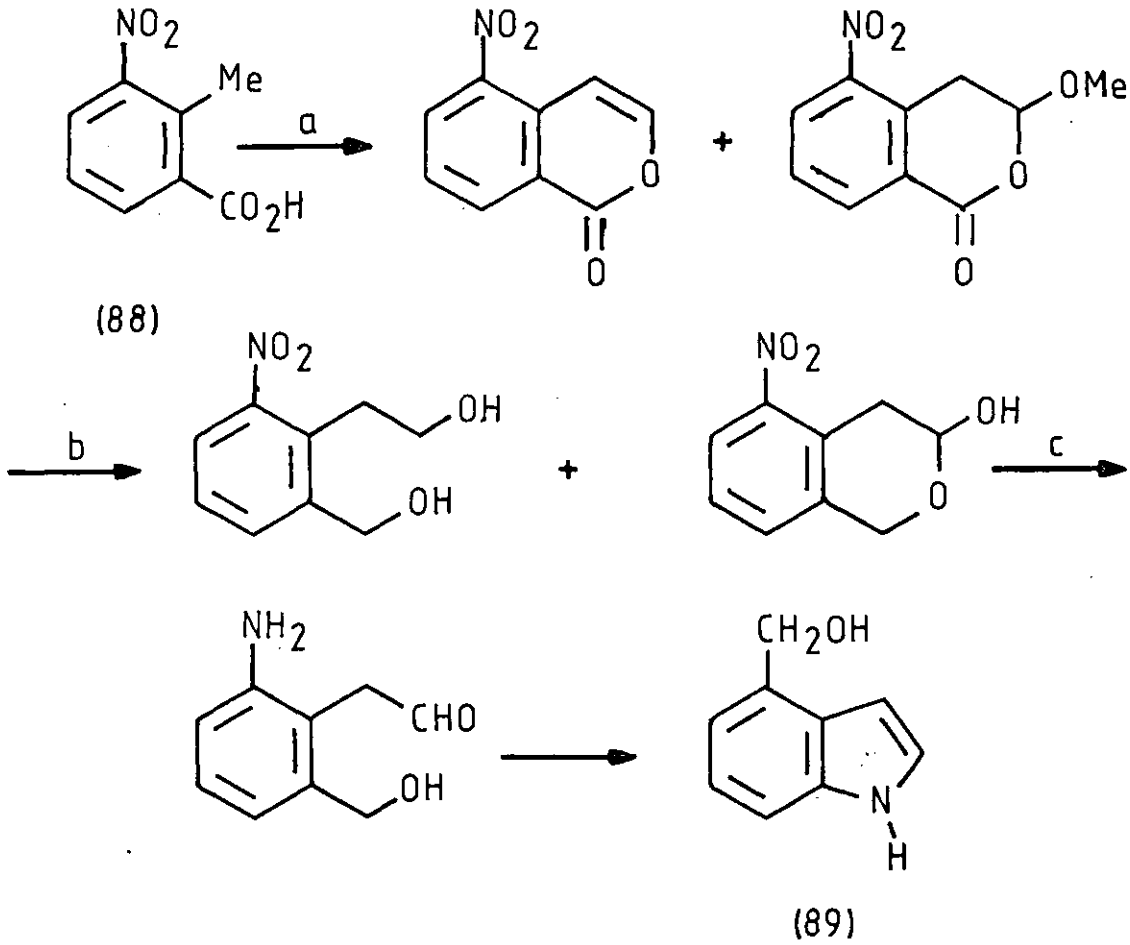
A recent improvement in the preparation of 4-substituted indoles from substituted o-nitrotoluenes has been reported by Kruse,[37] and is illustrated here by the synthesis of 4-methylindole. The use of tris-(N,N-dimethylamino)methane to prepare

the substituted β-dimethylamino-o-nitrostyrene (85) from the substituted o-nitrotoluene (84) permitted lower temperatures and shorter reaction times than those required for dimethylformamide acetals. Also, reduction of the semi-carbazone (86), prepared *in situ* from the enamine (85), improved the yields of the substituted indole (87).



(a)$(Me_2N)_3CH$, DMF, Δ; (b)$H_2NNHCONH_2HCl$, HCl, H_2O; (c)Pd/C, H_2.

A one-pot synthesis of 4-(hydroxymethyl)indole (89) from 2-methyl-3-nitrobenzoic acid (88) has recently been reported.[38] The sequential treatment of 2-methyl-3-nitrobenzoic acid with dimethylformamide dimethylacetal, lithium aluminiumhydride and titanium trichloride gave, at best, a 30% yield of 4-(hydroxymethyl)indole *via* the intermediates indicated (Scheme 7).



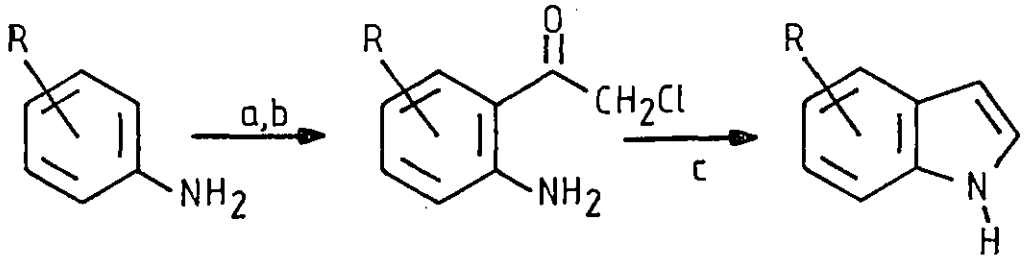
(a)$Me_2NCH(OMe)_2$, DMF, Δ; (b)$LiAlH_4$, THF; (c)$TiCl_3$, NH_4OAc, H_2O, MeOH.

(Scheme 7)

These syntheses are specifically 4-substituted indole syntheses, although the improvement in the general method reported by Kruse[37] could be applied to give higher yields of other substituted indoles.

(6) From the ortho α-chloroacetylation of anilines

The reaction of a substituted aniline (90) with chloroacetonitrile and boron trichloride in the presence of an additional Lewis acid gave substituted o-amino- α-chloroacetophenones (91). Reductive cyclisation of these intermediates (91) with sodium borohydride in refluxing dioxan afforded the substituted indoles (92) in good overall yields.[39]



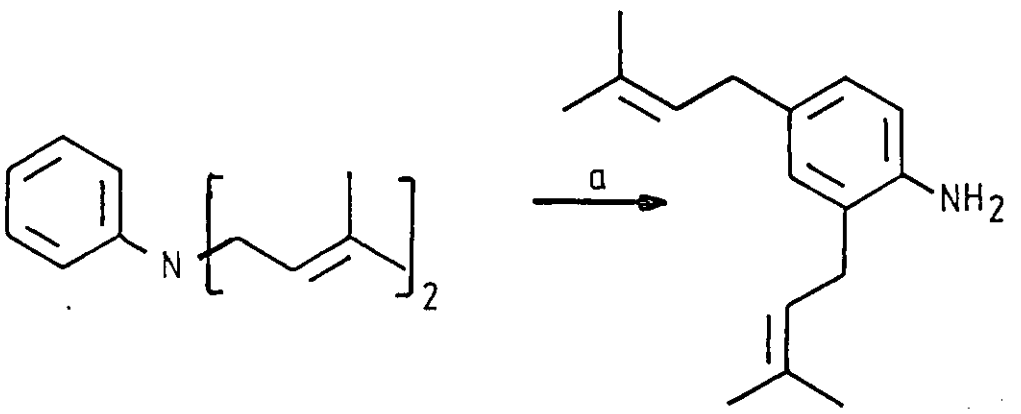
(90) (91) (92)

(a)$ClCH_2CN$, BCl_3, ($TiCl_4$ or $AlCl_3$), PhH, Δ; (b)H^+; (c)$NaBH_4$, dioxan, Δ.

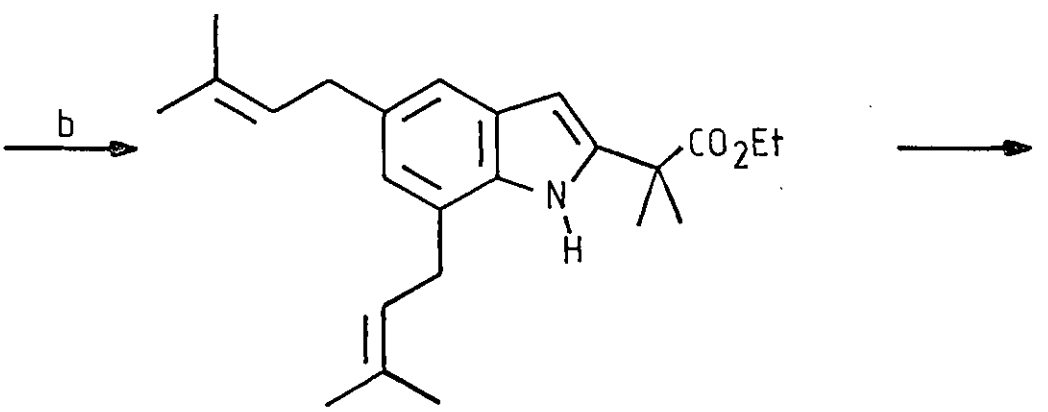
This strategy is an efficient method for the preparation of simple indoles from readily available substituted anilines. However, meta-substituted anilines are ortho-chloroacetylated in the two possible unsymmetrical positions, giving an isomeric mixture of products. In principle, this strategy involves an ortho-substitution of an aniline and is thus similar to that of Gassman.[19] However, this method affords a higher yielding route to 2-unsubstituted indoles using readily available reagents.

(7) From miscellaneous reactions

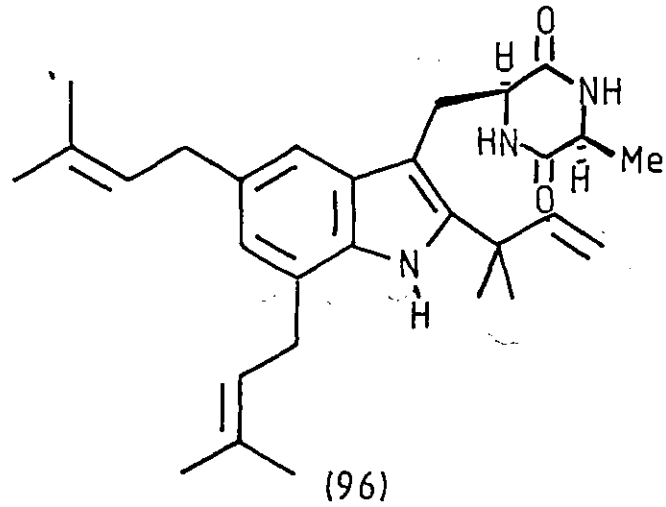
In the synthesis of echinulin[40] (96), the prenylated aniline (94), prepared by Lewis-acid catalysed rearrangement of N,N -di(3',3'-dimethylallyl)aniline (93), was condensed with ethyl-4-bromo-2,2-dimethylacetoacetate to give the tri-substituted indole (95) in poor yield.



(93) (94)



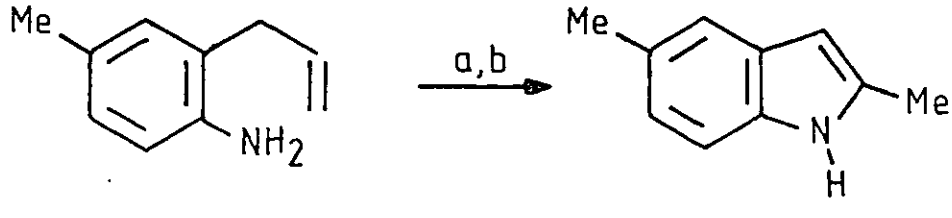
(95)



(96)

(a)$ZnCl_2$, Δ; (b)$BrCH_2COCMe_2CO_2Et$.

The reaction of a substituted o-allylaniline with a stoichiometric amount of a palladium (II) species and triethylamine afforded a good yield of the substituted 2-methylindole,[41] as with the reaction of p-methyl-o-allylaniline (97) to give 2,5-dimethylindole (98) in 76% yield. This is a mild, high yielding strategy that is however limited to the preparation of 2-methylindoles.



(97) (98)

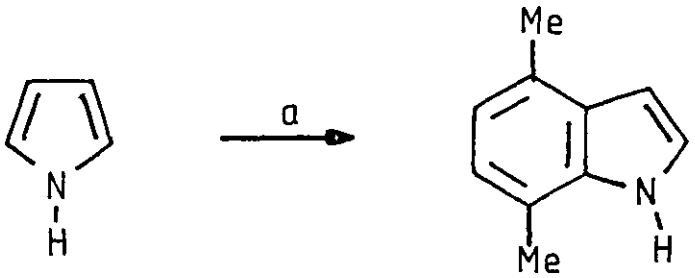
(a)$PdCl_2(CH_3CN)_2$, THF; (b)Et_3N.

C Syntheses based on the pyrrole ring

In contrast to the many indole syntheses that utilise substituted benzene rings as starting materials and fuse on the pyrrole ring in subsequent steps, there are few syntheses which start with a pyrrole and then build on the carbocyclic ring.

(1) From a condensation reaction

A simple example of this strategy is the preparation of 4, 7-dimethylindole (100) in 28% yield from the condensation of pyrrole (99) with hexane-2,5-dione.[42]



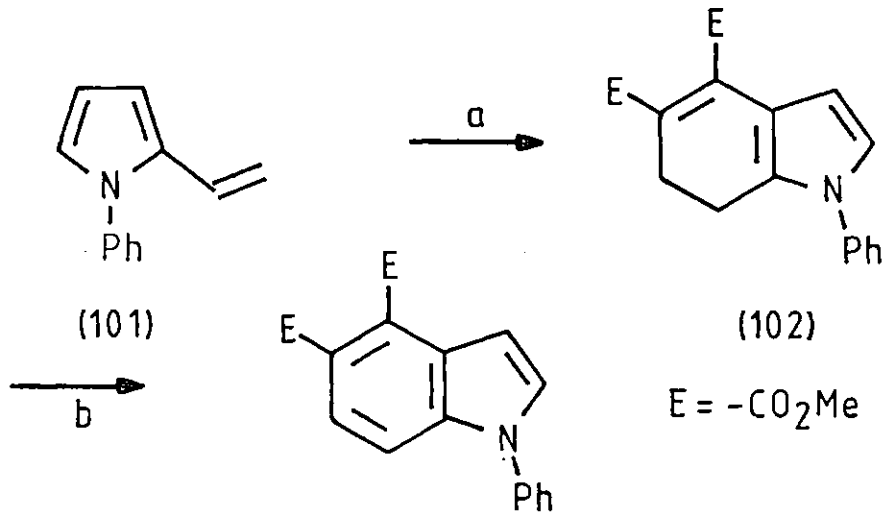
(99) (100)

(a) $MeCOCH_2CH_2COMe$, $Zn(OAc)_2$, AcOH, Δ.

This is a low yielding method applicable only to the condensation of a few symmetric diketones with pyrroles.

(2) From a cycloaddition reaction

The cycloaddition reaction of 1-phenyl-2-vinylpyrrole (101) with dimethylacetylenedicarboxylate gave the 6,7-dihydroindole (102) which, on aromatisation with 2,3-dichloro-5,6-dicyanoquinone (DDQ), afforded dimethyl 1-phenylindole-4,5-dicarboxylate (103) in 50% overall yield.[43]

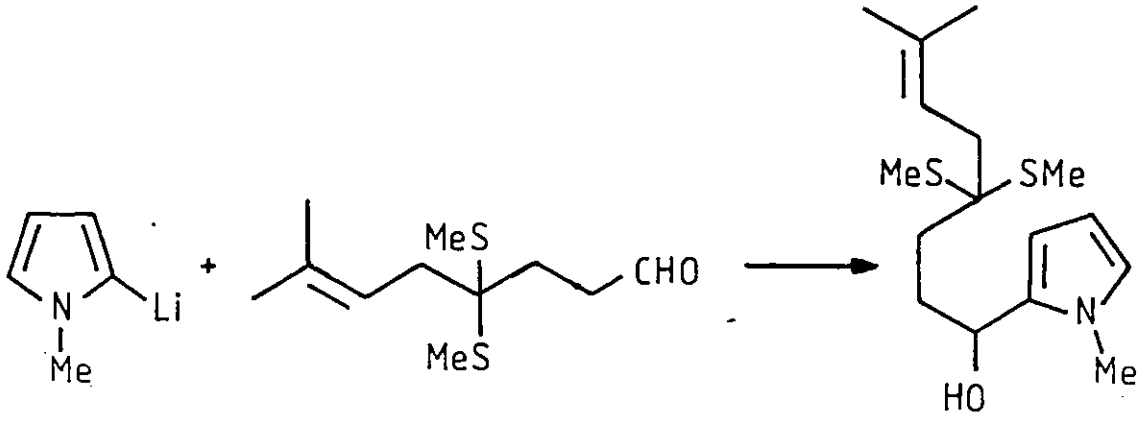


(a)$MeO_2CC{\equiv}CCO_2Me$, $CHCl_3$, Δ; (b)DDQ, PhH, Δ.

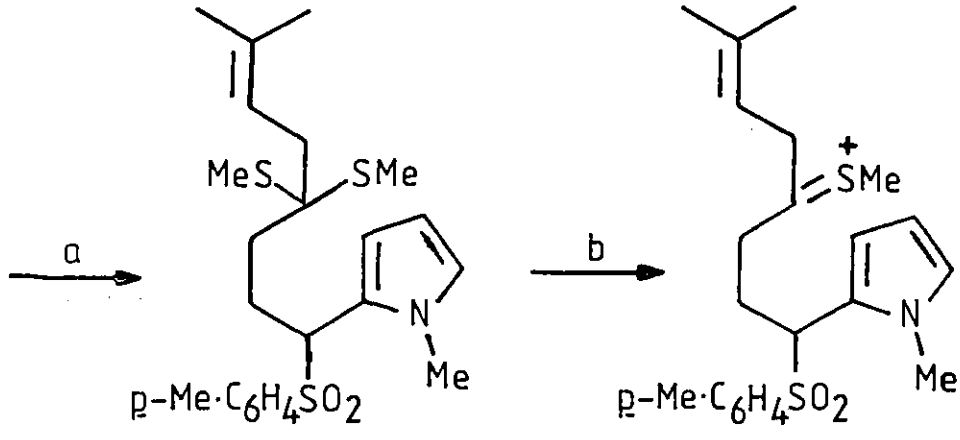
This is a rather elegant preparation of 4,5 or 6,7 (with a 3-vinylpyrrole) indoledicarboxylates which is, at present, limited to the synthesis of 1-alkyl or aryl indoles.

(3) From the cyclisation of thionium ions

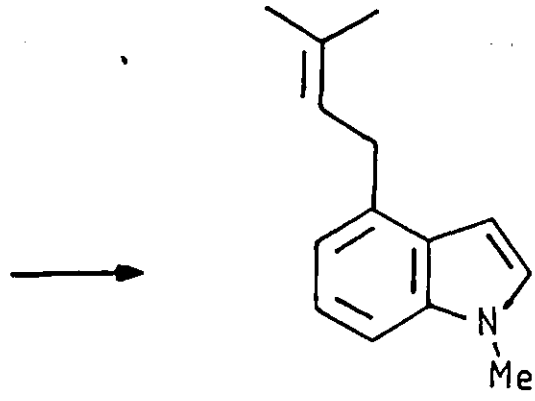
The cyclisation of thionium ions with electron-rich aromatic systems has been used to construct several fused-ring systems including the indole nucleus [44] (Scheme 8). The reaction of 1-methyl-2-lithiopyrrole (104) with the aldehyde (105) gave the 2-substituted pyrrole (106) which, on treatment with one equivalent of p-toluenesulphinic acid afforded the sulphone (107). Reaction of this sulphone with p-toluenesulphinic acid in refluxing acetonitrile yielded 1-methyl-4-(3',3'-dimethylallyl)indole (109) via cyclisation of the intermediate thionium ion (108).



(104) (105) (106)



(107) (108)



(109)

(a) p-$MeC_6H_4SO_2H$, MeCN, Room temp.; (b) p-$MeC_6H_4SO_2H$, MeCN, Δ.

(Scheme 8)

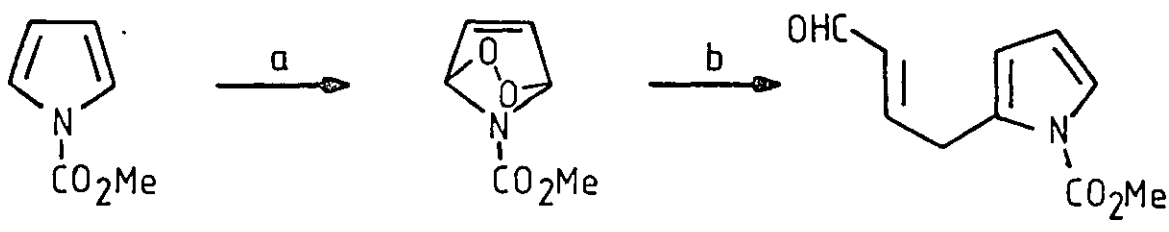
At present, this elegant strategy is limited to the synthesis of 1-methyl-4-alkylindoles and further work is required in order to extend its scope.

(4) From the photooxygenation of pyrrole

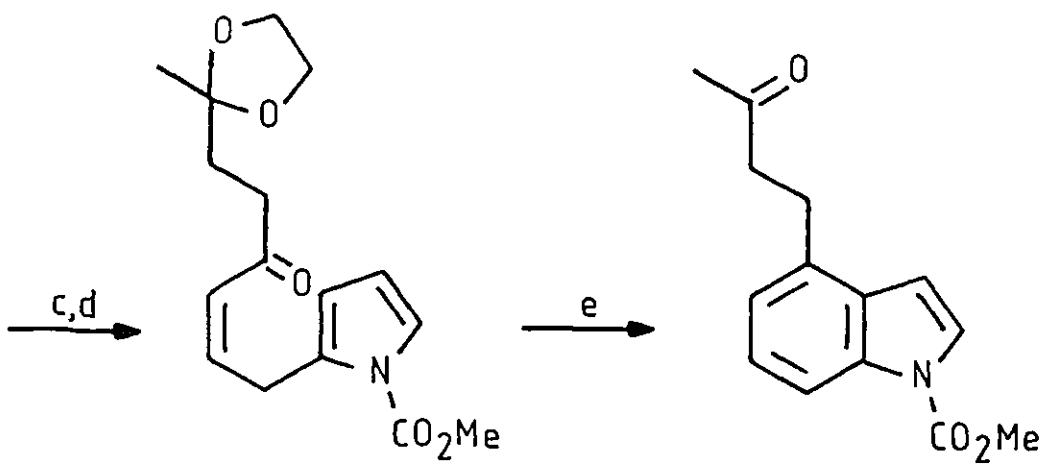
An efficient route to 4-substituted indoles from the photooxygenation of a pyrrole has been reported by Natsume et al[45] (Scheme 9). Photooxygenation of 1-methoxycarbonylpyrrole (110) with singlet oxygen gave the endoperoxide (111) which, in the presence of stannous chloride, reacted with nucleophiles to give 2-substituted pyrroles. For example, reaction of the endoperoxide with 1-trimethylsiloxy-1,3-butadiene afforded a 62% yield of the 2-substituted pyrrole (112). Treatment of

this unsaturated aldehyde (112) with Grignard reagents followed by pyridinium chlorochromate oxidation gave the unsaturated ketones in good yields; in particular, the unsaturated ketone (113) was prepared in 63% yield. Cyclisation of the ketone (113) with stannic chloride also cleaved the acetonide group to give the 4-substituted indole (114) in 52% yield.

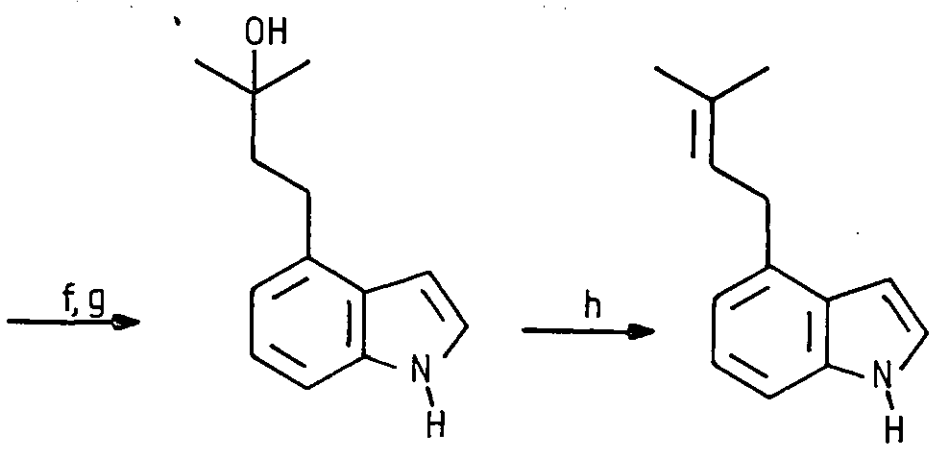
Subsequent alkaline hydrolysis of the methoxycarbonyl group followed by treatment with methylmagnesium iodide gave the alcohol (115) in 78% overall yield. Dehydration with p-toluenesulphonic acid and purification of the resulting mixture through its crystalline picrate afforded, in 40% yield, 4-(3',3'-dimethylallyl)indole (116).



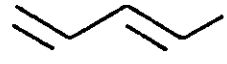
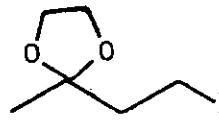
(110) (111) (112)



(113) (114)



(115) (116)

(a) $^1O_2$; (b) $SnCl_2$, ; (c) 

(d) $C_5H_5N^+ClCrO_3^-$; (e) $SnCl_4$, CH_2Cl_2; (f) KOH, MeOH, H_2O; (g) MeMgI
(h) p-$MeC_6H_4SO_3H$, PhH, Δ.

(Scheme 9)

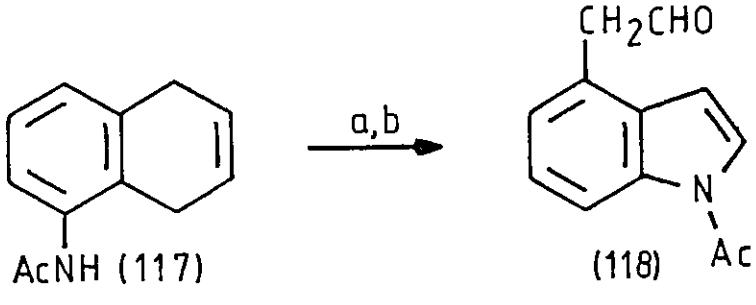
This is an efficient synthesis of a range of 4-substituted indoles based on readily available starting materials and reagents, that should be amenable to multigram-scale preparations. Using this basic strategy it should be possible to synthesise indoles substituted in positions other than C_4, although this has not, at present, been reported and further work in this field has concentrated on the elaboration of the 4-substituted indoles to ergot alkaloids.[46]

D Syntheses based on other ring systems

Several novel approaches to substituted indoles involve the "rearrangement" of other substituted carbocyclic or heterocyclic ring systems to the indole nucleus. These approaches have, at present, been applied solely to the preparation of 4-substituted indoles.

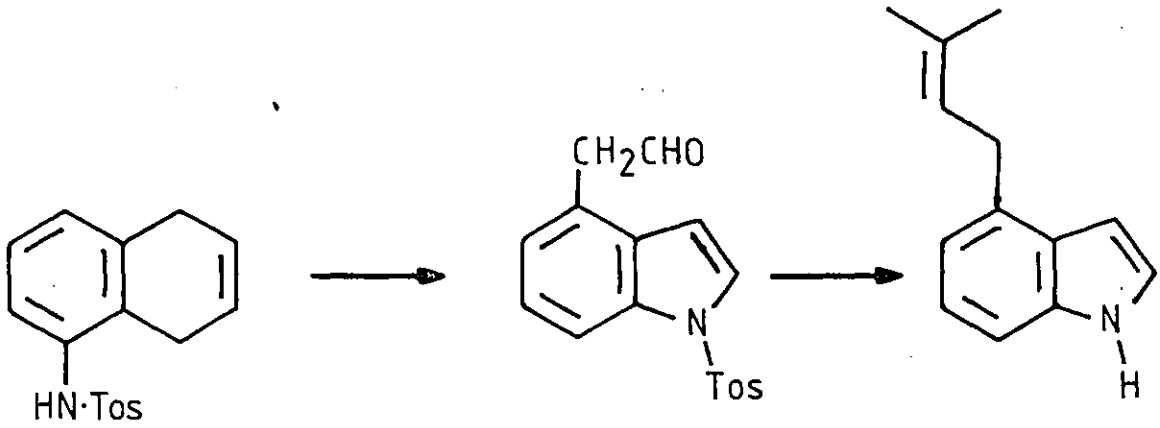
(1) From dihydronaphthalenes

In the earliest of these methods, reported by Plieninger[47] in 1956, the ozonolysis of 1-acetamido-5,8-dihydronaphthalene (117), prepared by reduction and acetylation of 1-aminonaphthalene, followed by reductive work-up afforded 1-acetylindole-4-acetaldehyde (118), isolated as its semi-carbazone.



(a)O_3; (b)Pd/C,H_2.

Under similar reaction conditions 1-(tosyl)amino-5,8-dihydronaphthalene (119) gave the more stable 1-tosylindole-4-acetaldehyde[48] (120), an intermediate in a synthesis of 4-(3',3'-dimethyallyl)indole (121).



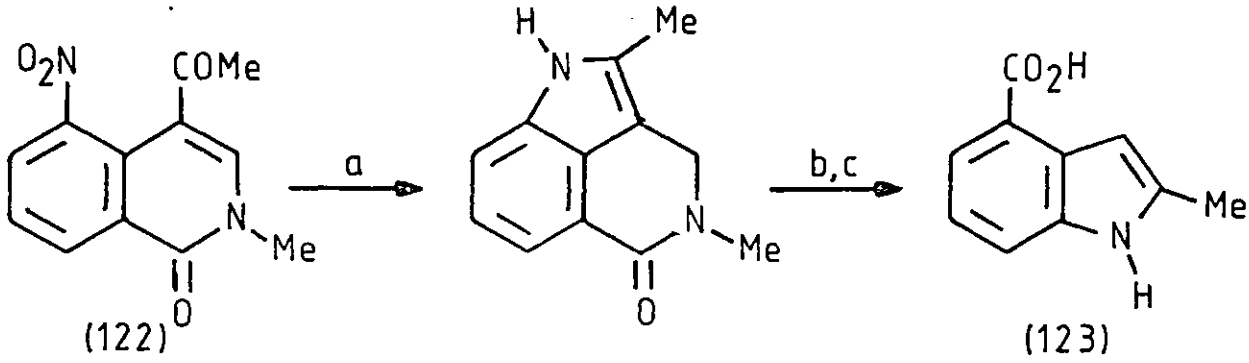
(119) (120) (121)

Tos = p-Me·$C_6H_4SO_2$ -

This is an elegant and efficient method of preparing 4-substituted indoles which are capable of elaboration to a range of ergot precursors.

(2) From nitroisocarbostyrils

The hydrogenation of 2-methyl-4-acetyl-5-nitroisocarbostyril (122) followed by treatment with a strong base gave 2-methyl-indole-4-carboxylic acid (123) in 46% yield.[49]



(122) (123)

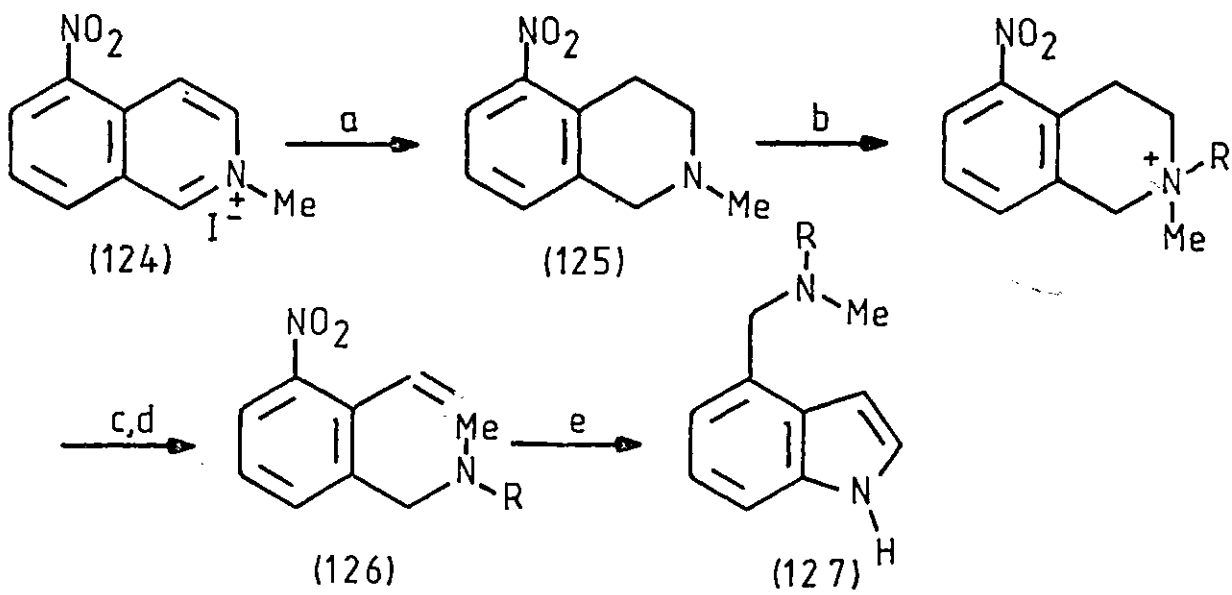
(a)Pd/C,H_2; (b)KOH,DMSO: (c)H^+.

This scheme provides a concise route to 2-substituted indole-4-carboxylic acids but, to date, no further investigations extending the scope of this reaction have been published.

(3) From nitroisoquinolinium salts

Since 5-nitroisocarbostyrils are prepared by the oxidation of 5-nitroisoquinolinium salts,[49] it is not surprising that a couple of syntheses of 4-substituted indoles from 5-nitroisoquinolinium salts have been reported.[50,51]

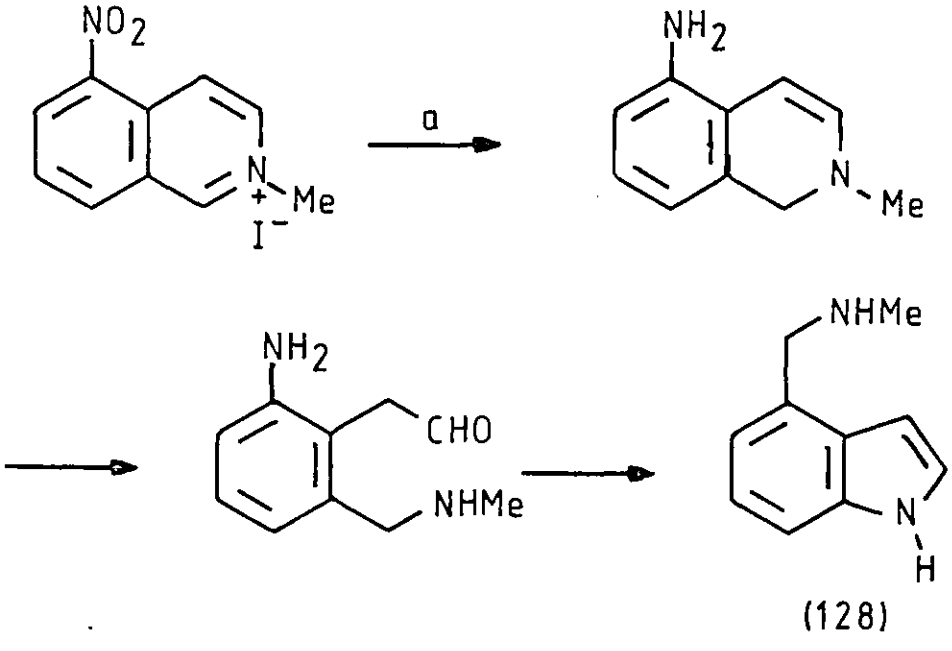
In the first of these reports by Somei,[50] 2-methyl-5-nitroisoquinolinium iodide (124) was reduced with sodium borohydride to the 1,2,3,4-tetrahydroisoquinoline (125). Quarternisation with an alkylhalide followed by Hofmann degradation with butyllithium gave the o-nitrostyrene (126) in variable yields. Refluxing triethylphosphite cyclised the o-nitrostyrenes to the substituted indoles (127) in moderate yields (Scheme 10).



(a)$NaBH_4$; (b)RX; (c)n-BuLi; (d)H_2O; (e)$(EtO)_3P, \Delta$.

(Scheme 10)

Recently this strategy has been improved to give a one-step synthesis of 4-(N-methylaminomethyl)indole (128) in 20% yield[51] from the reaction of 2-methyl-5-nitroisoquinolinium iodide with aqueous titanium trichloride, which presumably proceeds via the intermediates indicated (Scheme 11).



(128)

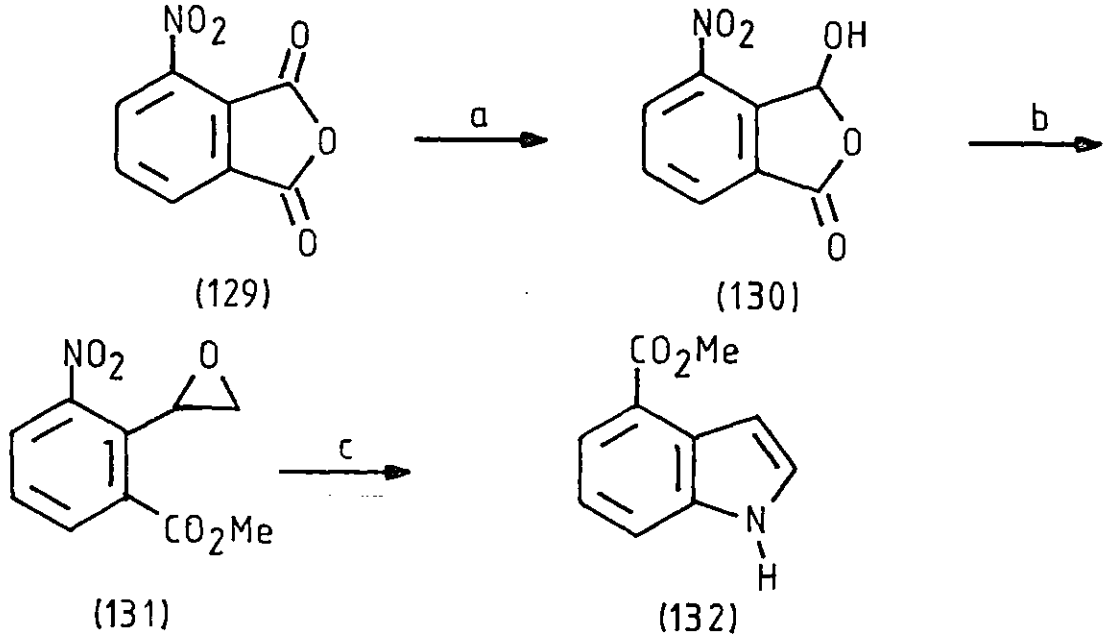
(a)$TiCl_3$,H_2O.

(Scheme 11)

Further improvements to this method have led to the multigram isolation of 4-(N-acetyl-N-methylaminomethyl) indole in 24% yield[52]. This is clearly an expedient synthesis of a 4-substituted indole which is capable of elaboration to a range of more complex indoles.[52]

(4) From nitrophthalic anhydride

The reduction of 3-nitrophthalic anhydride (129) with sodium borohydride gave 3-hydroxy-4-nitrophthalide (130) which, on treatment with excess diazomethane, afforded the o-nitrostyrene oxide (131) in 86% yield from (130). Reduction of the nitro-group followed by epoxide ring opening gave 4-methoxycarbonyl-indole (132) in 62% yield.[53]



(a)$NaBH_4$,THF; or (i)$(NH_4)_2CO_3$,Δ; (ii)$NaBH_4$,MeOH; (iii)HCl,H_2O; (b)CH_2N_2; (c)PtO_2,H_2,MeOH.

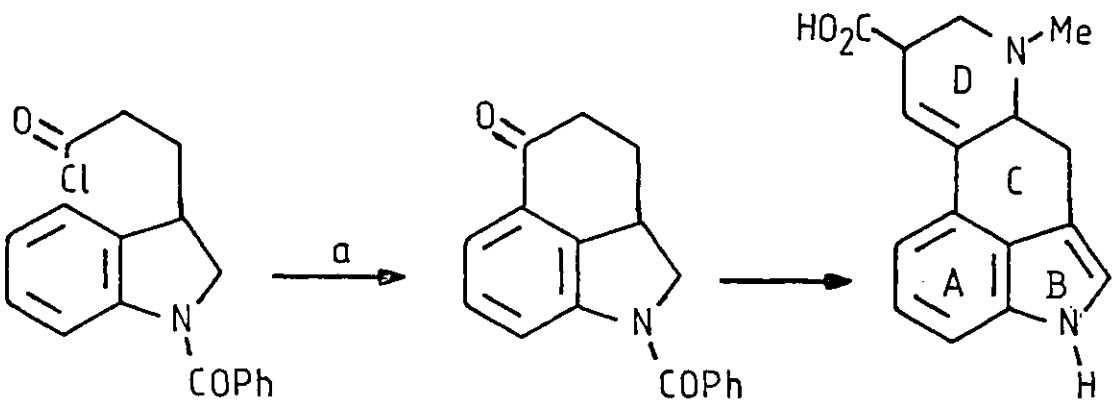
This is a concise synthesis of 4-methoxycarbonylindole but is not as suited to multigram preparation as the other syntheses of this compound already discussed.

E Methods of directly substituting the carbocyclic ring

(i) Approaches to 3,4 linked indole derivatives

Several approaches to the direct 4-functionalisation of 3-substituted indole derivatives have been reported, primarily as steps towards the construction of the C ring of lysergic acid (135).

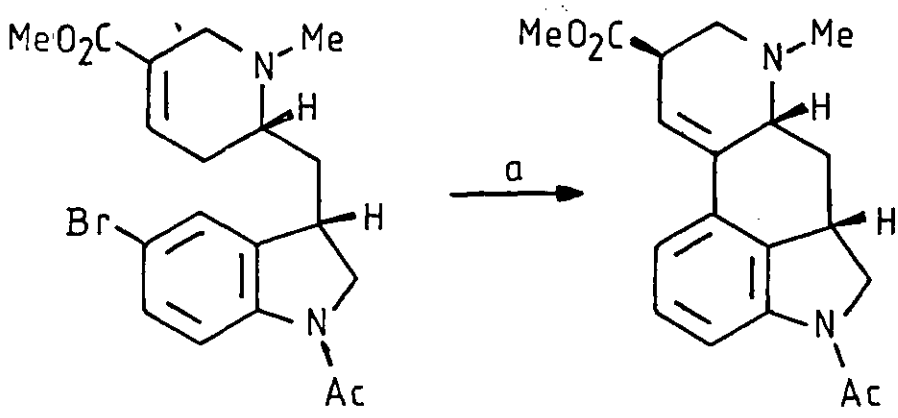
Woodward used an intramolecular Friedel-Crafts reaction of the dihydroindole acidchloride (133), and hence avoided competing intramolecular acylation at C_2, to give the tricyclic ketone (134) in 77% yield.[54] This ketone was a key intermediate in his synthesis of racemic lysergic acid (135).



(133) (134) (135)

(a) $AlCl_3$.

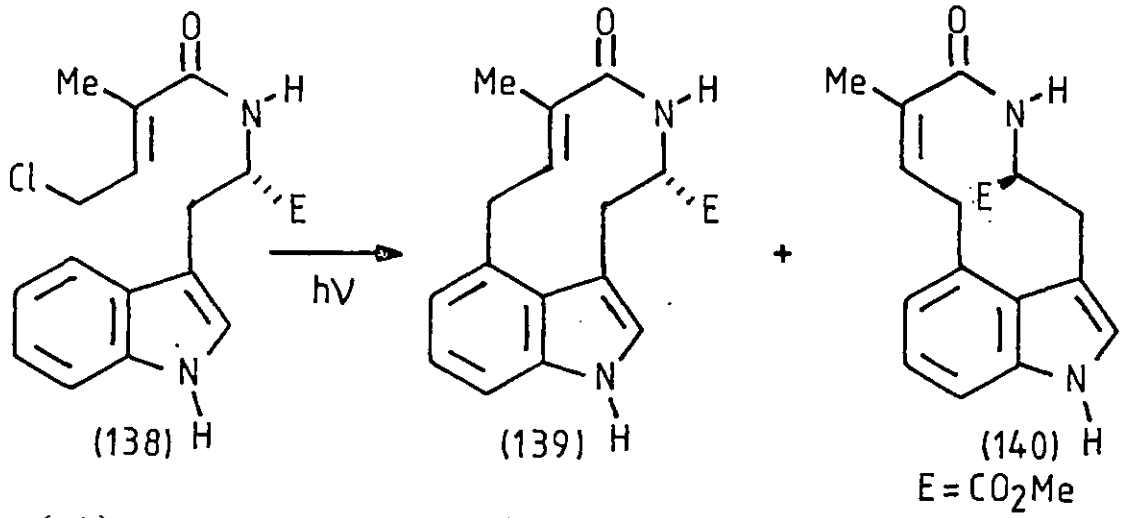
Treatment of the tetrahydropyridine (136) with sodium amide in liquid ammonia gave the lysergic acid precursor (137) in 15% yield via addition of a carbanion to an aryne.[55]



(136) (137)

(a)$NaNH_2$, liq.NH_3.

The photocyclisation of the L-tryptophan ester (138) gave the lactams (139) and (140) in yields of 33% and 19% respectively.[56]



(138) (139) (140)

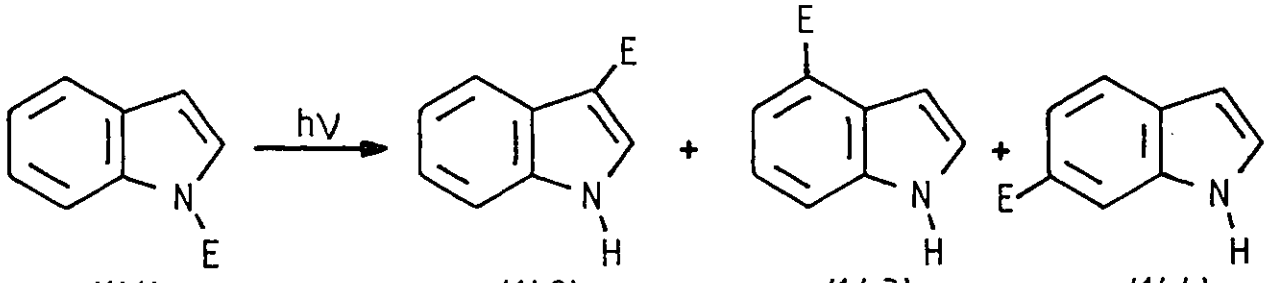
(ii) Other substituted indoles

There are few methods currently available for the direct introduction of a substituent into the carbocyclic ring of indole; and in general they tend to be low yielding or too specialised to find widespread application.

(1) Via a photochemical rearrangement

The photochemical rearrangement of 1-substituted indoles gave a mixture of 3-, 4-and 6-substituted indoles.[57]

For example, the irradiation of 1-ethoxycarbonylindole (141) afforded a mixture of 3-(142,47%), 4-(143,9%) and 6-(144,23%) ethoxycarbonylindoles. With 1,3-disubstituted indoles, rearrangement to the 3-position was blocked and consequently the 6-substituted indoles were the major products.

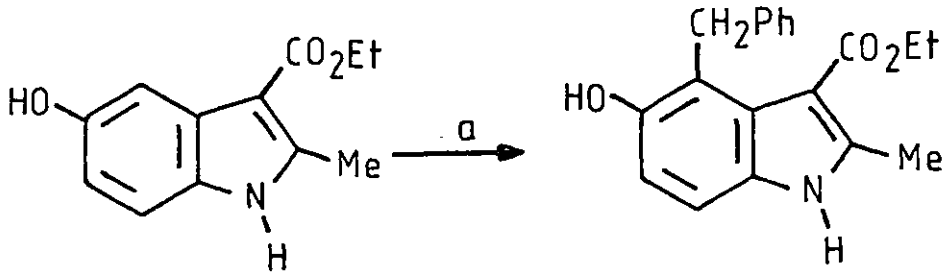


(141) (142) (143) (144)

E = CO_2Et

(2) Via directed Grignards

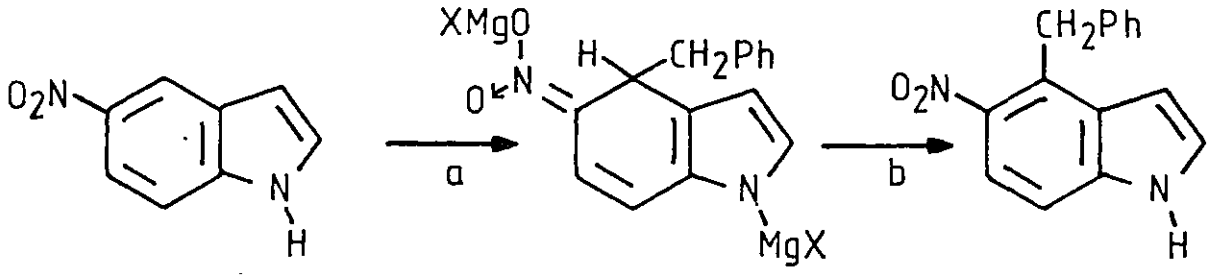
The reaction of benzylchloride and dilute sodium hydroxide solution with the 5-hydroxyindole (145), on heating, is claimed[58] to give a 42% yield of the 4-benzylindole (146).



(145) (146)

(a)$PhCH_2Cl$,NaOH,H_2O,xylene, Δ .

The conjugate addition of an alkyl Grignard to 5-nitroindole followed by oxidation of the intermediate o-alkylnitronate adduct (148) gave good yields of 4-alkylindoles[59]; for example 4-benzyl-5-nitroindole (149) was obtained in 68% yield from 5-nitroindole (147).



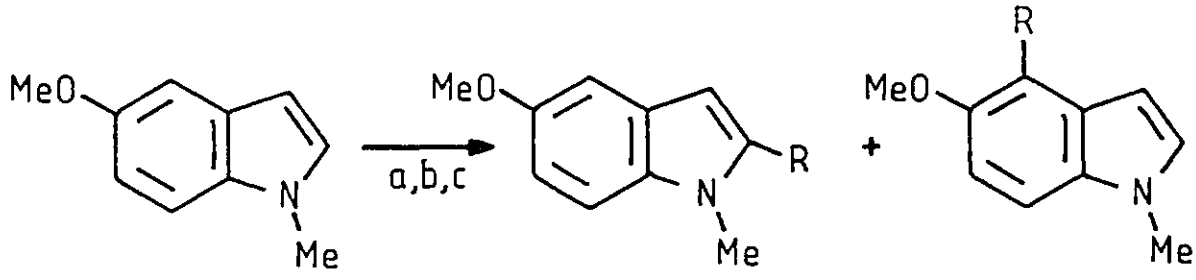
(147) (148) (149)

(a)$PhCH_2MgX$; (b)$KMnO_4$,H_2O,Me_2CO.

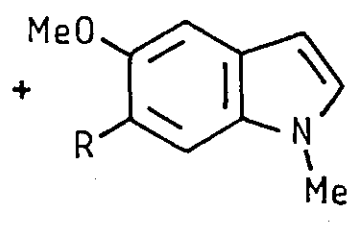
This is an interesting, high yielding synthesis of 4-alkylindoles. However, 5-nitroindole is itself as difficult to prepare as simple 4-alkylindoles are by other indirect methods.

(3) Via a directed lithiation

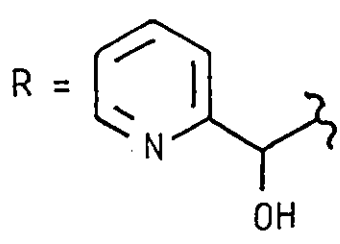
It is well established that 1-protected indoles can be lithiated at C_2[3], and recently the effect of a 5-methoxy group on the selectivity of the lithiation was investigated.[60] The lithiation of 1-methyl-5-methoxyindole (150) with n-butyllithium was non-selective, giving, after reaction with pyridine-2-carboxaldehyde, the 2-(151), 4-(152) and 6-(153) substituted indoles in the ratios of 4:5:1 respectively.

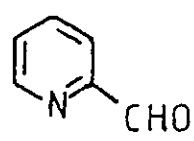


(150) (151) (152)



(153)



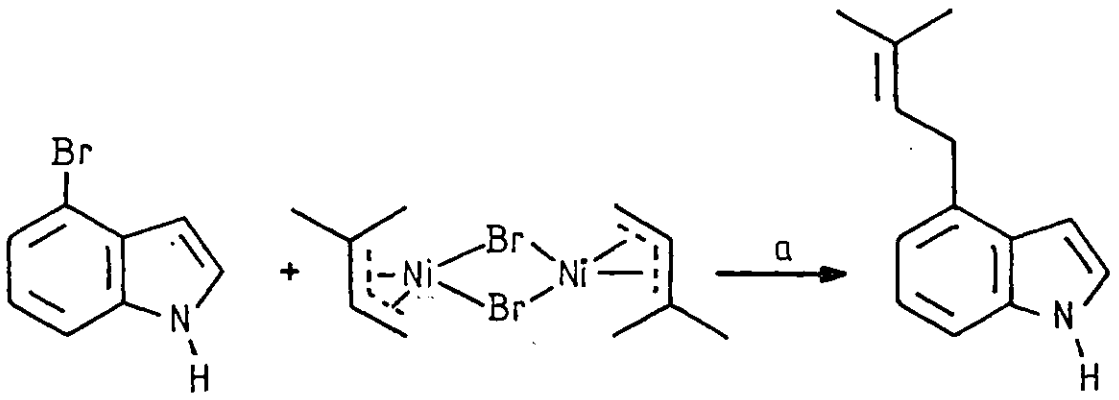
(a) n-BuLi, Et_2O, Δ; (b) 

; (c) H^+.

(4) From haloindoles

Halo-substituted indoles can be regiospecifically alkylated with organometallic reagents, as with the palladium catalysed reaction of a 4-iodoindole and 3-methyl-3-hydroxybut-1-ene discussed previously (Page 51).

The reaction of π-(3',3'-dimethylallyl)nickel bromide (155) with 4-, 5- or 6-bromoindoles gave the 4-, 5- or 6-(3',3'-dimethylallyl)indoles in good yields;[61] for example, 4-(3',3'-dimethyallyl)indole (156) was obtained in 67% yield from 4-bromoindole (154).



(154) (155) (156)

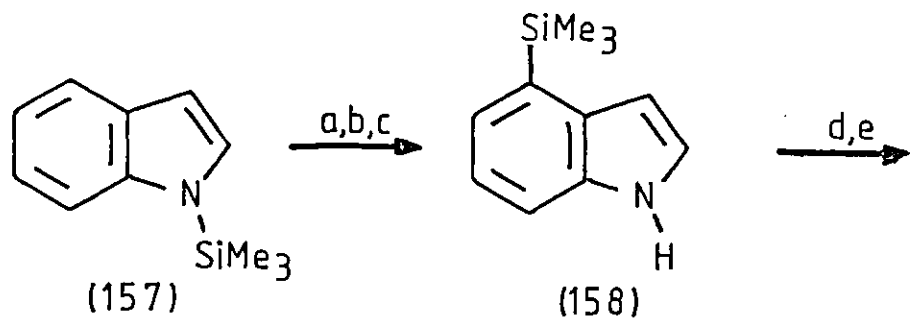
(a) DMF, Δ.

This reaction was also used to introduce the 6-(3',3'-dimethyl-allyl)-group in the synthesis of neochinulin.[23]

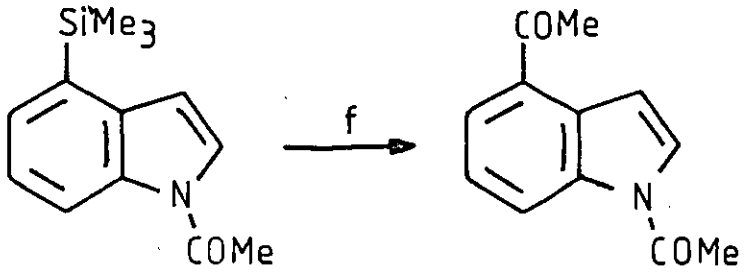
The major disadvantage of this strategy is that already-substituted indoles are required as starting materials, the regioselective preparation of which is not routine.

(5) Via a directed electrophilic substitution

A new method for the synthesis of 4-substituted indoles via a directed electrophilic substitution has been reported.[62] The lithium reduction of 1-trimethylsilyl-indole (157) in the presence of chlorotrimethylsilane followed by in situ oxidation with p-benzoquinone and treatment with aqueous methanol gave 4-trimethylsilyl-indole (158) in 52% overall yield. Treatment of this indole (158) with sodium hydride and acetylchloride afforded 1-acetyl -4- trimethylsilyl-indole (159) which reacted with acetylchloride and aluminium trichloride to give 1,4-diacetylindole (160), via electrophilic substitution of the trimethylsilyl group, in 91% overall yield (Scheme 12).



(157) (158)



(159) (160)

(a)Li,THF,Me_3SiCl; (b) p-benzoquinone,CH_2Cl_2; (c)MeOH,H_2O; (d)NaH,THF; (e)MeCOCl; (f)MeCOCl,$AlCl_3$,CH_2Cl_2.

(Scheme 12)

This is an elegant, multigram synthesis of 4-substituted indoles from inexpensive, readily available starting materials that requires further investigation to discover the scope of the electrophilic substitution reaction.

(6) Via Chromium tricarbonyl complexes

Another procedure that achieves direct functionalisation of the indole skeleton is the nucleophilic addition of carbanions to N-protected-indole chromium tricarbonyl complexes followed by oxidation of the anionic intermediates. This strategy, which affords good yields of 4-(or 7-) substituted indoles, has already been discussed in the previous review (Page 22).

F Conclusion

Over the past few years great advances have been made in the synthesis of indoles substituted in the carbocyclic ring. It is now possible to prepare indoles substituted with a variety of groups, by a range of concise strategies. This is especially true for the synthesis of 4-substituted indoles which have been in demand as precursors in ergot alkaloid syntheses.

Of all the strategies, the method of Batcho and Leimgruber[30] is perhaps the most general method for the synthesis of simple indoles as it tolerates a wide variety of functional groups and does not give isomeric mixtures of products. For more complex 4-substituted indoles, the strategies of Plieninger[47,48], Somei[51] and Natsume[45], in which the substituted indole ring is constructed from other ring systems, are the most general and direct.

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RESULTS AND DISCUSSION

A. Introduction

The considerable biological activity of some of the more elaborate substituted indoles has stimulated considerable synthetic interest in these compounds, especially in recent years (see review).

Of all the methods for preparing carbocyclic-ring substituted indoles, the strategy which has received the least attention is the direct introduction of substituents into preformed indole ring systems (see review). This strategy represents a great challenge in the synthesis of substituted indoles as it, more than any other approach, has potential for the concise and efficient synthesis of indoles substituted with more elaborate substituents.

It was decided, during the course of studies directed towards the preparation of substituted indoles *via* chromium tricarbonyl complexes, to investigate the selectivity of proton abstraction from *N*-protected indole complexes and the subsequent reaction with electrophiles. It was already well established that the complexation of a $Cr(CO)_3$ group to an aromatic ring enhanced the acidity of the arene-ring protons[1] rendering them labile to the action of strong bases.

This approach towards the preparation of substituted indoles affords several advantages over the nucleophilic addition of carbanions to indole complexes[2,3] (discussed in the review). One advantage is that the substituted indole is obtained as a $Cr(CO)_3$ complex which, in itself, affords several advantages:

(a) the $Cr(CO)_3$ complexes are coloured and are usually crystalline making it easier to isolate and purify the product;

(b) there is the opportunity to perform other $Cr(CO)_3$ mediated reactions on the product;

(c) the $Cr(CO)_3$ complexes, although oxygen sensitive in solution, are usually air stable solids and are frequently more stable than the free arene.

Also, it was reasoned that a wider range of electrophiles would react with the lithioindole $Cr(CO)_3$ species than the range of carbanions which could add to indole complexes. This last advantage was important since it was hoped to develop a strategy with which it would be possible to synthesise a wide range of substituted indoles.

For the initial approaches it was decided to use 1-methylindole $Cr(CO)_3$ complex, the simple N-protected indole complex which Kozikowski et al[2] used in their study of the regioselective addition of carbanions to indole complexes.

It is intended to discuss the preparation and cleavage of the complexes, processes that must be optimised before any other reactions of these complexes can be investigated, before the main part of the work is presented. This will be organised in the following manner, based upon the starting indole complex and hence the substituted indole obtained:

(a) Preparation of 2-substituted 1-methylindoles;

(b) Preparation of 7-substituted 1-methylindoles;

(c) Preparation of 7-substituted 1-methoxymethylindoles;

(d) Preparation of 4-substituted indoles.

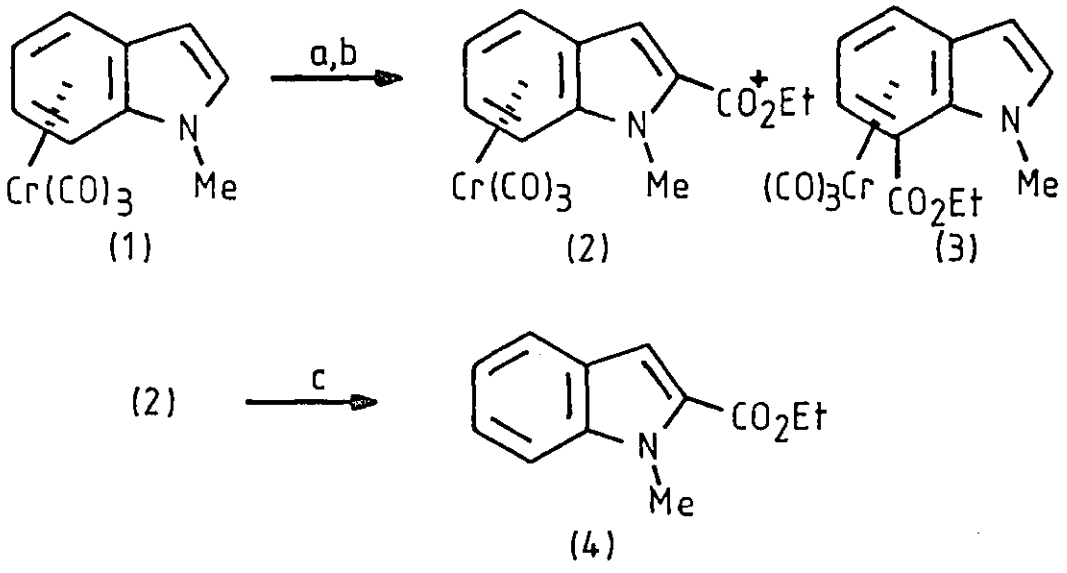
B. Preparation and cleavage of the indole complexes

The indole complexes were prepared by the direct thermal displacement of carbon monoxide ligands from chromium hexacarbonyl by refluxing in a mixture of di-n-butylether and THF[4] in a Strohmeier apparatus. Since this method gave excellent (ca. 80-90%) yields of the complexes on a reasonable scale (up to 2.0-3.5g depending on the complex) it was considered unnecessary to use a more active $Cr(CO)_3$ transferring species, such as trisacetonitrile-tricarbonylchromium[5] or trisammoniatricarbonylchromium[6], to prepare the complexes. The Strohmeier apparatus[7] allowed the $Cr(CO)_6$ which sublimed out of solution to be returned to the reaction flask by the condensing solvent vapours, thus avoiding the need to continually return the $Cr(CO)_6$ via mechanical means.

Decomplexation of the indole complexes was most efficiently realised via irradiation[8] of dilute solutions of the complex in THF or acetonitrile in air, or less efficiently, via the thermal exchange of pyridine ligands for the arene ligand on $Cr(CO)_3$[9]. The advantage of the latter method was that the valuable $Cr(CO)_3$ group could be recovered as $(pyridine)_3Cr(CO)_3$ and re-used, in conjunction with a Lewis acid, to prepare other arene complexes[10]. However, since this method was only applicable to indoles with thermally stable functional groups and because of the negligible amounts of $(pyridine)_3Cr(CO)_3$ recovered, it was abandoned in favour of the photolytic cleavage.

C. Preparation of 2-substituted 1-methylindoles

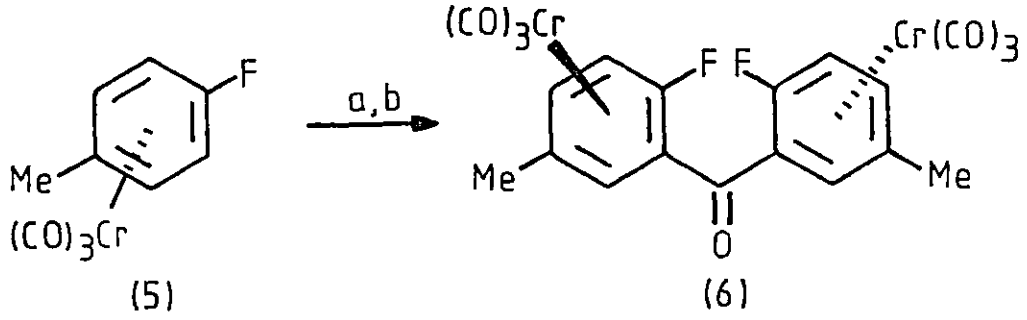
As mentioned previously, 1-methylindole complex(1) was used in the initial lithiation studies. Treatment of this complex (1) with one equivalent of n-butyllithium in THF and an excess of TMEDA at -78° followed by reaction with ethylchloroformate gave a product which was later identified as 2-ethoxycarbonyl-1-methylindole complex (2), in 78% yield. Repeating this reaction in the absence of TMEDA led to lower yields of the 2-substituted product (2, 27%) and the recovery of starting material (50%), suggesting that the lithiation requires TMEDA to break up the aggregates of butyllithium and to promote its reactivity[11]. This is in contrast to the observations of Rausch et al[1], who found that far from promoting the lithiation of benzene $Cr(CO)_3$ complex, TMEDA actually retarded it[1]. Photochemical decomplexation of the 2-substituted complex (2) gave a 93% yield of the 2-ethoxycarbonyl-1-methylindole (4).



(a) n-BuLi, TMEDA, THF, -78°; (b) $ClCO_2Et$; (c) $h\gamma$, THF or MeCN, air.

This reaction, on its own, has little synthetic potential since uncomplexed N-protected indoles are also lithiated at C_2[12,13], although this requires higher temperatures (-20° to 36°) and under the reaction conditions employed to lithiate 1-methylindole complex, the free arene, 1-methylindole, was unaffected.

The use of ethylchloroformate as a quenching reagent was found to give a fairly clean reaction which is in contrast to a recent observation that the lithiation of the fluorobenzene complex (5) with an excess of t-butyllithium and subsequent reaction with methylchloroformate gave a 60% yield of the benzophenone bis-complex[14] (6). While products of this nature were not searched for in the reaction of 1-methylindole complex with n-butyllithium and ethylchloroformate, or indeed in subsequent reactions which employed a chloroformate quench, and so their presence cannot be rigorously excluded, they could only have been present, if at all, in trace amounts and certainly nothing like the 60% yield obtained by Sandilands et al[14].

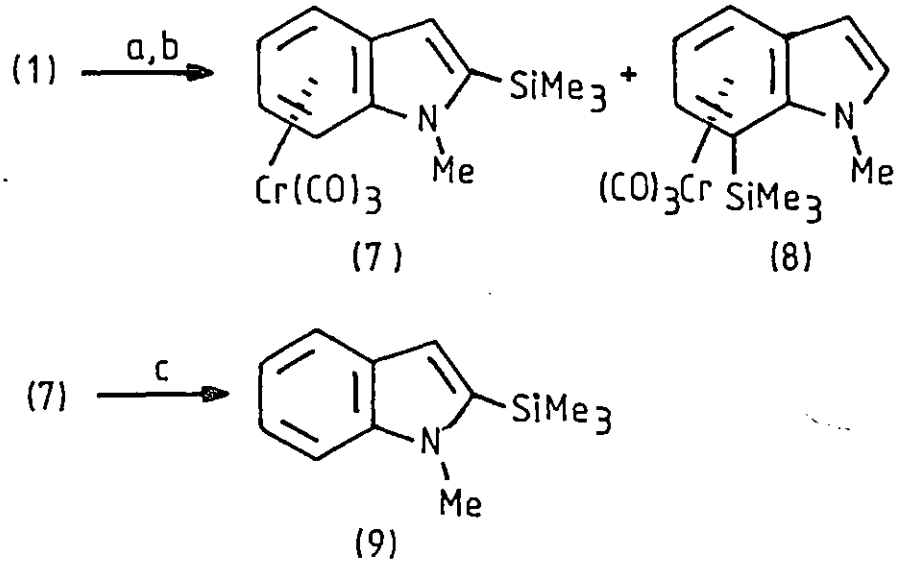


(5) (6)

(a) t-BuLi, Et_2O, -78°; (b) $ClCO_2Me$.

Reaction of 1-methylindole complex (1) with n-butyllithium followed by quenching with chlorotrimethylsilane gave an 83% yield of trimethylsilylated complexes. The major component, isolated from

the mixture by careful crystallisation in 60% overall yield, was identified as 1-methyl-2-trimethylsilylindole complex (7) by photochemical decomplexation to give the indole (9, 95%) which was identical (tlc, ir, ^{1}H nmr and mass spectrum) to authentic 1-methyl-2-trimethylsilylindole prepared by quenching 2-lithio-1-methylindole[12] with chlorotrimethysilane. The minor component (8), which was present in 15-20% yield was recognised as probably having arisen from 7-lithiation and attempts were made to increase the ratio of C_7:C_2 lithiation by altering the reaction conditions. However, under a range of conditions, different temperatures and different bases, the ratio of C_7:C_2 lithiation, as measured by the reaction with chlorotrimethylsilane never rose above 1:3 (Table 1).



(a) n-BuLi, THF, TMEDA, -78°; (b) $ClSiMe_3$; (c) hγ, THF, air.

Lithiation of 1-methylindole complex

alkyllithium	temperature	approximate ratio of C_7 : C_2 products [a]
n-BuLi	-23^{o}	- [b]
n-BuLi	-50^{o}	1 : 5
n-BuLi	-78^{o}	1 : 4
n-BuLi	-100^{o}	1 : 3
t-BuLi	-78^{o}	1 : 3

(a) determined by ^{1}H nmr of the mixture of trimethylsilylated indoles;

(b) extensive decomposition of the lithiospecies was observed.

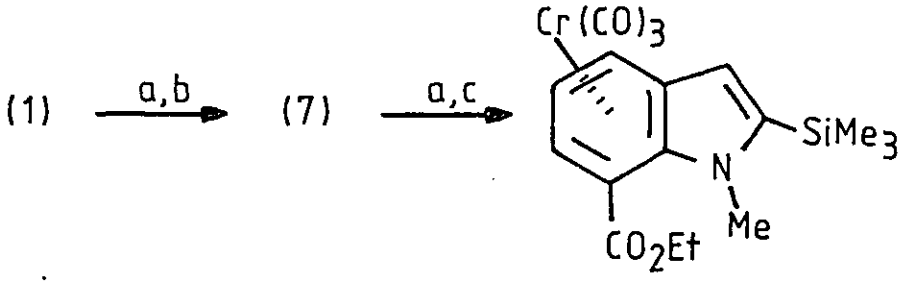
(Table 1)

Closer investigation of the mother-liquors of the reaction mixture which yielded 2-ethoxycarbonyl-1-methylindole complex (2), revealed the presence of another isomer presumably, by analogy to the reaction yielding 2- and 7- trimethylsilyl-1-methylindole complexes, the 7-ethoxycarbonyl-1-methylindole complex (3).

As the 7-substituted-1-methylindoles were never obtained pure, no definite structural assignments could be made and the tentative assignments are based on the results of later work.

D. Preparation of 7-substituted 1-methylindoles

Having determined the initial site of lithiation for 1-methylindole complex (1), it was decided to determine the second site of deprotonation using the trimethylsilyl group, a relatively easy group to remove from an aromatic system[15], to block the 2-position. Thus, 1-methyl-2-trimethylsilyl-indole complex (7), generated *in situ*, was reacted with another equivalent of *n*-butyllithium and quenched with ethylchloroformate giving, after liquid chromatography and crystallisation, a 67% yield of 7-ethoxycarbonyl-1-methyl-2-trimethylsilylindole complex (10).



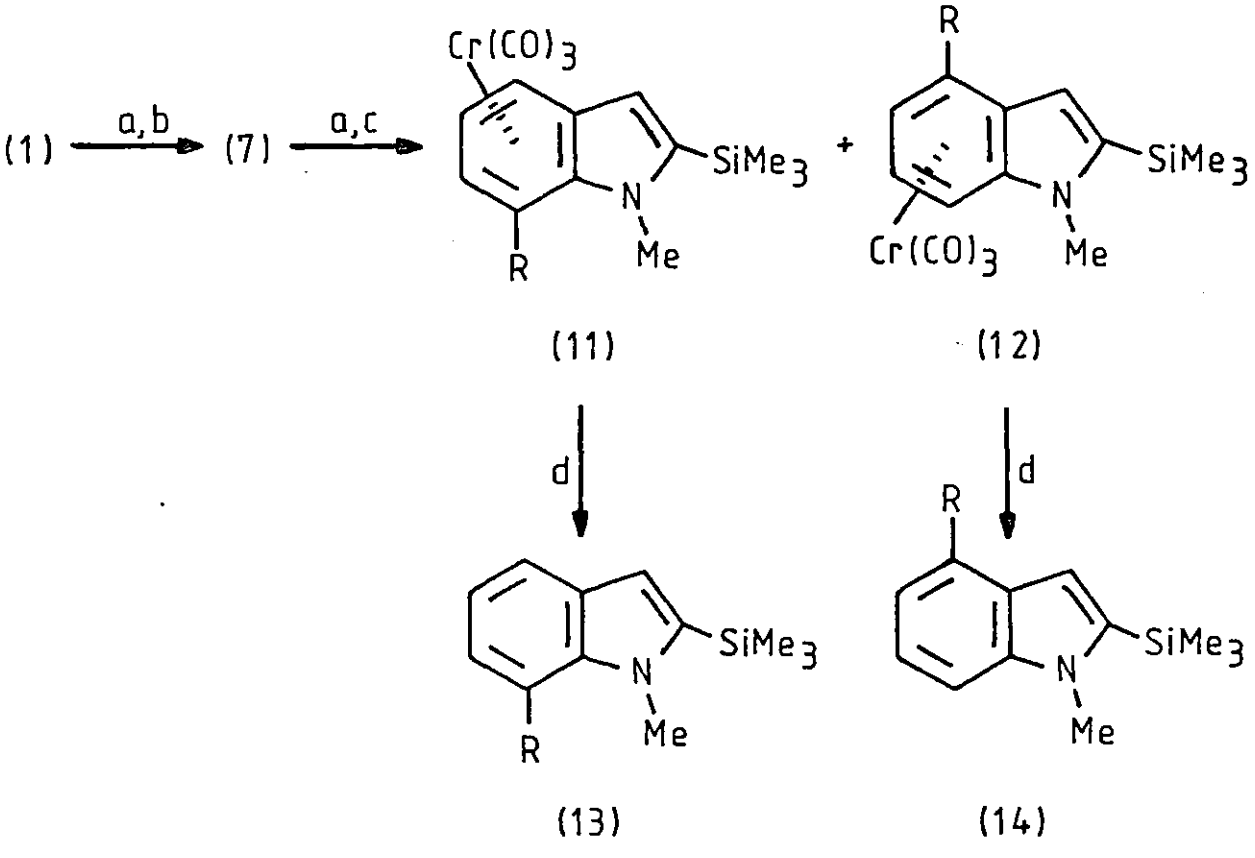
(10)

(a) *n*-BuLi, THF, TMEDA, -78°, (b) $ClSiMe_3$; (c) $ClCO_2Et$.

The ^1H nmr of complex (10) showed a clear vicinal ABC splitting pattern for the carbocyclic ring protons (δ4.8 - 6.6) suggesting 4- or 7- substitution, while the *N*-methyl group (δ 3.9) showed a clear downfield shift relative to the chemical shift of the 1-methyl-2-trimethylsilylindole complex (7, δ 3.7) inferring 7-substitution. However, without authentic samples which would be both difficult and time-consuming to prepare, the discrimination between 4- and 7- substituted products could not be made with

complete confidence. Therefore, an X-Ray crystallographic analysis was undertaken (figure 1) which showed that the major product was indeed the 7-substituted complex (10).

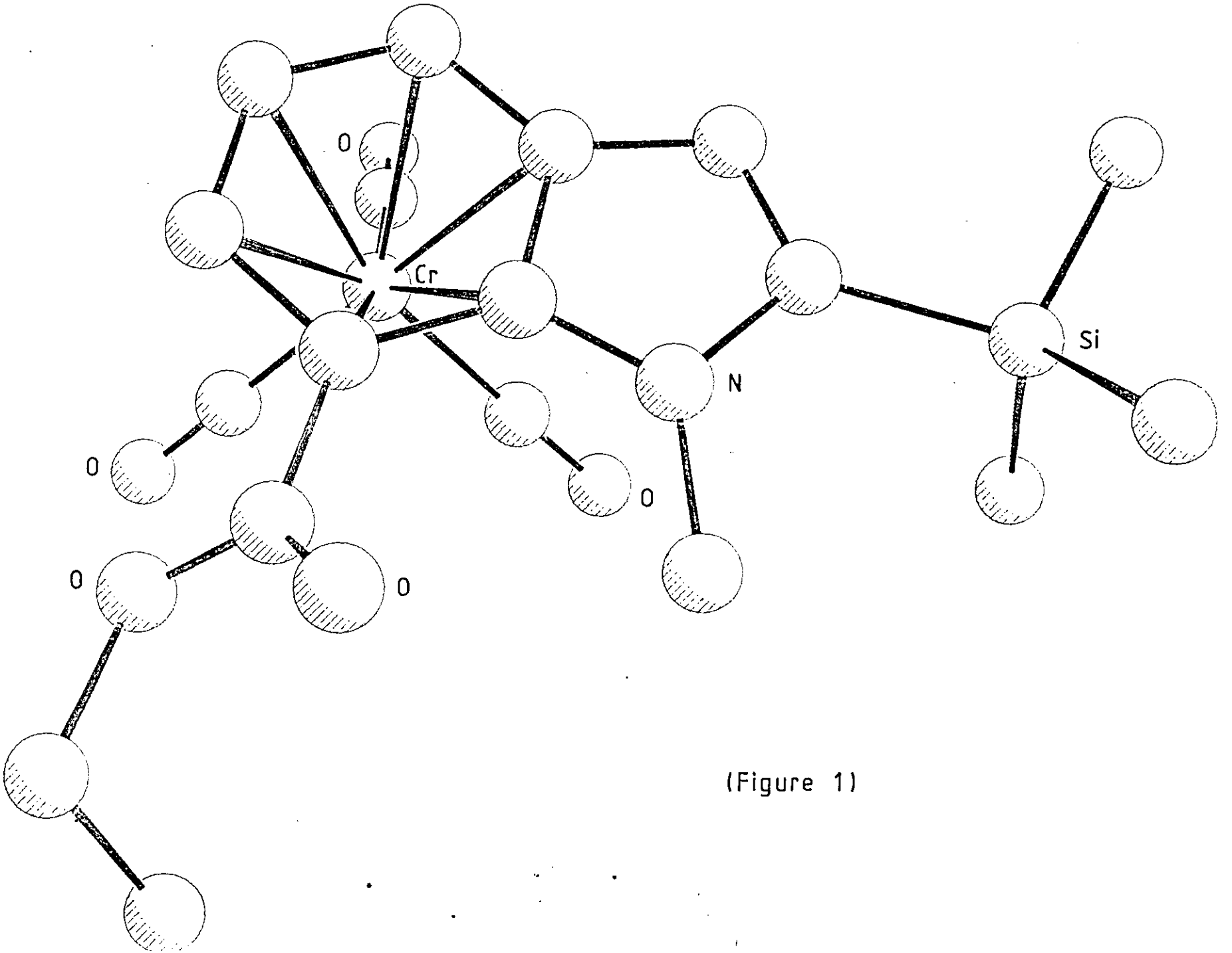
With the structure of the major product established, it was decided to examine the scope of the reaction of the lithioindole complex with a range of electrophiles to give 7-substituted indole complexes (11) (Scheme 1).



(a) n-BuLi, THF, TMEDA, -78°; (b) $ClSiMe_3$; (c) Electrophile, (H^+); (d) $h\gamma$, THF or MeCN, air.

(Scheme 1)

During the course of these reactions (Table 2) it was found that the reaction with methyl iodide (run 2) gave an inseparable mixture of isomeric products (11 and 12, R=Me) which were present, by ^1H nmr,



(Figure 1)

in the ratio of, ca. 5:1. Photochemical decomplexation of this mixture and careful chromatography afforded 2 fractions, pure 1,7-dimethyl-2-trimethylsilylindole (13, R=Me) and a mixture of the 7-methylated compound (13,R=Me) and an isomer. This unknown compound which was present in ca. 13% of the mixture was shown to be the 1,4-dimethyl-2-trimethylsilylindole (14, R=Me) by its high resolution ^{1}H nmr. The absorptions due to the minor component were well separated from those of the 7-substituted indole, and in particular the signal due to H_3 (δ 6.3) showed a small (ca. 0.8Hz) coupling to H_7 (δ 7.55). This long range coupling between H_3 and H_7 is well documented [16], and combined with the vicinal ABC splitting pattern observed for the carbocyclic ring protons (δ 7.0-76) of the minor component, confirmed the assignment of the structure as (14,R=Me).

The synthesis of 7-substituted 1-methyl-2-trimethysilylindoles

Run	Electrophile	Product (R=)	Indole Complex(11) Yield[a]/%	Free Indole (13) Yield[b]/%
1	$ClCO_2Et$	CO_2Et	67	90
2	MeI	Me	64[c]	-
3	PhCHO	C·H·OH·Ph	63	89
4	CH_2=CHCHO	C·H·OH·CH=CH_2	60	92
5	PhSCl	SPh	51	85
6	Me_2C=$CHCH_2Br$	CH_2CH=CMe_2	43	77

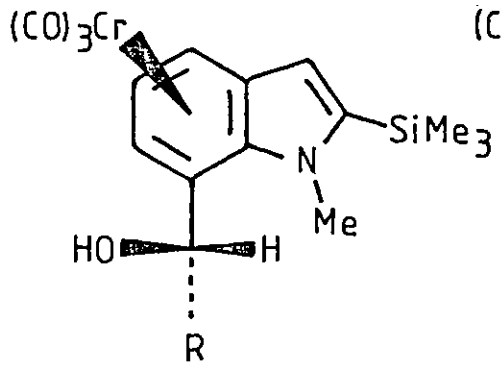
(a) pure complex;
(b) from complex;
(c) mixture of 4 and 7 isomers.

(Table 2)

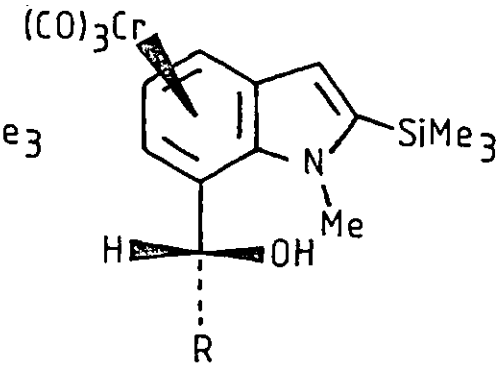
The crude complex isolated from the other reactions (Table 2) was found, by ^{1}H nmr, to contain an impurity in approximately the same

percentage as the methylation (run 2) but in these reactions chromatography and crystallisation gave the pure 7-substituted complexes (11). The impurity was assumed, by analogy with the methylation, to be the 4-substituted indole (12) but as these complexes were never obtained pure and as other areas of work were showing promise, this was never verified.

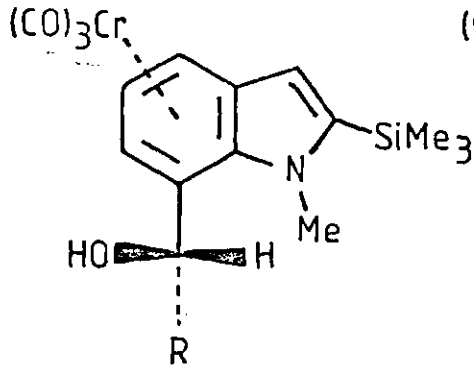
Reaction of the lithio-species with the 2 aldehydes (runs 3 and 4) afforded a mixture of diastereomeric products (15, 16, 17 and 18) due to the creation of an asymmetric centre and to the fact that indole complexes are chiral.



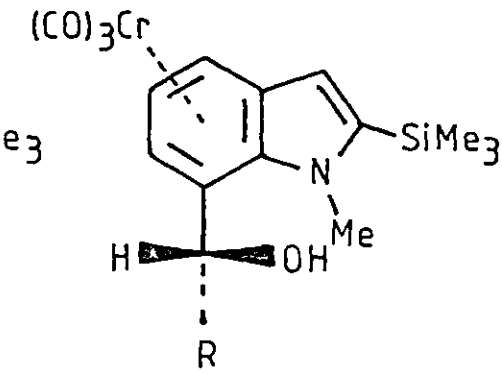
(15)



(16)



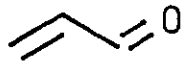
(17)



(18)

R = Ph, $CH{=}CH_2$

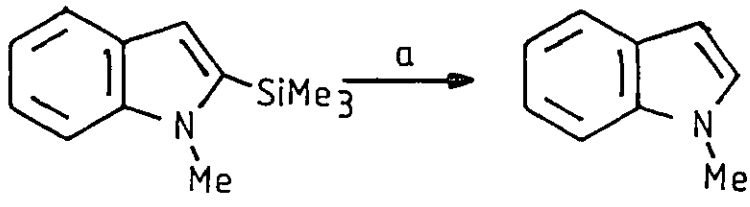
The 2 diastereomeric pairs (15 and 16) and (17 and 18) show different ^{1}H nmr signals for the OH and N-Me groups due to the different environments created by the asymmetric centre, and are present in almost equal quantities showing that there is little or no stereoselection in this reaction. The reaction with acrolein (19) (run 4) also showed exclusive 1,2-addition to the carbonyl group.



(19)

Photolytic cleavage of the 7-substituted complexes (11) afforded excellent yields (Table 2) of the corresponding indoles (13).

In order to demonstrate the potential for the synthesis of 1,7-disubstituted indoles it was necessary to show that the 2-trimethylsilyl group could be readily removed. Thus,



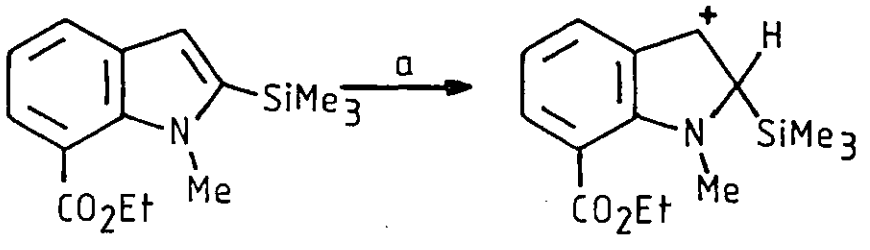
(9) (20)

(a) CF_3CO_2H, H_2O, CCl_4.

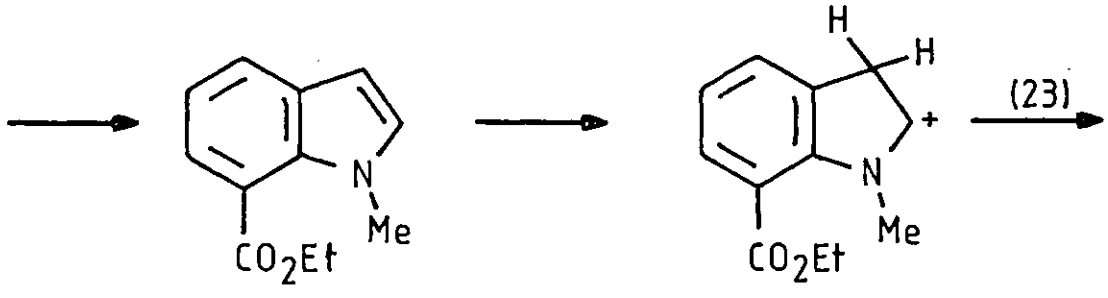
aromatic desilylation of 1-methyl-2-trimethylsilylindole (9) with aqueous trifluoroacetic acid[15] in a 2 phase system gave 1-methylindole (20) in 80 % yield. The use of carbon tetrachloride as co-solvent

allowed the reaction to be followed by ^{1}H nmr.

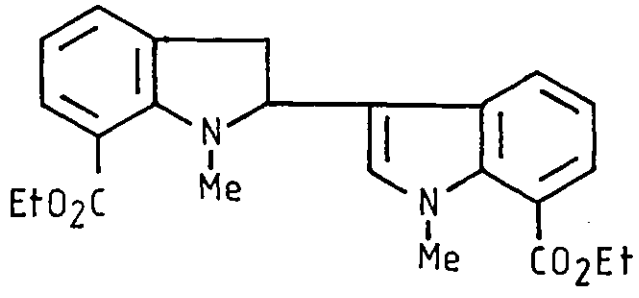
The desilylation of the 7-ethoxycarbonyl substituted indole (21) (Scheme 2) required a more strongly acidic medium, presumably because 2-protonation to give the intermediate (22) is retarded by the electron withdrawing nature of the ethoxycarbonyl group. As a direct consequence of this, other, side reactions took place lowering the yield of the desilylated product (23) to 53%. In particular, 3-protonation of 7-ethoxycarbonyl-1-methylindole (23) to give the intermediate (24) was facile, occurring to a significant degree before all the starting material had been desilylated. This protonated intermediate (24) reacted with another molecule of 7-ethoxycarbonyl-1-methylindole (23) to give the bis-indole (25) which was identified on the basis of its ^{1}H nmr, 2 overlapping O-ethyl absorptions and 2 N-methyl absorptions, one at the normal N-methylindole chemical shift (δ 3.85) and the other to higher field (δ 2.8), together with the ample literature precedent for the acidic dimerisation of indoles [17].



(21) (22)



(23) (24)



(25)

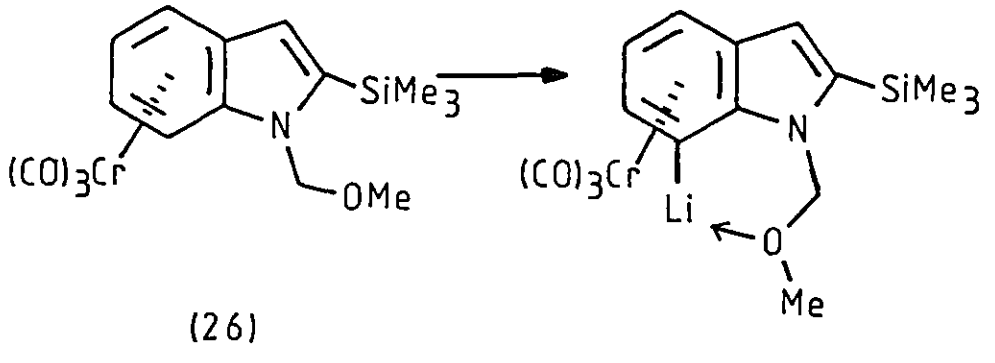
(a) CF_3CO_2H, H_2O, CCl_4.

(Scheme 2)

This strategy afforded a wide range of 7-substituted 1-methyl-2-trimethylsilylindoles in good yield from 1-methylindole and has the potential to give fair to good overall yields of the 7-substituted indoles by aromatic desilylation. For example, 7-ethoxycarbonyl-1-methyl-2-trimethylsilylindole was obtained in 53% overall yield and desilylation gave 7-ethoxycarbonyl-1-methylindole in 28% overall yield from 1-methylindole.

E. Preparation of 7-substituted 1-methoxymethylindoles

Since the lithiation of 1-methyl-2-trimethylsilylindole complex produced a mixture of 4- and 7- lithiated intermediates (see previous section), it was decided to use the methoxymethyl group as N-protection. It was hoped that the well known chelating properties of this group[18] would favour attack at C_7 to the exclusion of attack at C_4 in the second lithiation step (Scheme 3), and consequently afford a more efficient route to 7-substituted indoles.

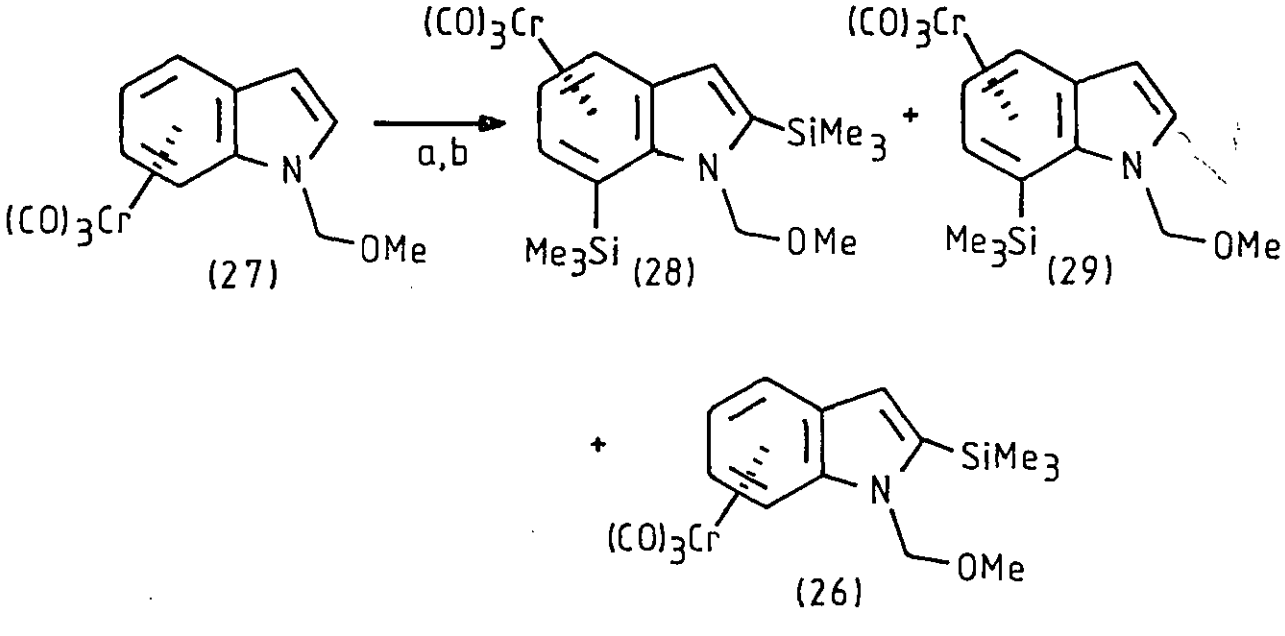


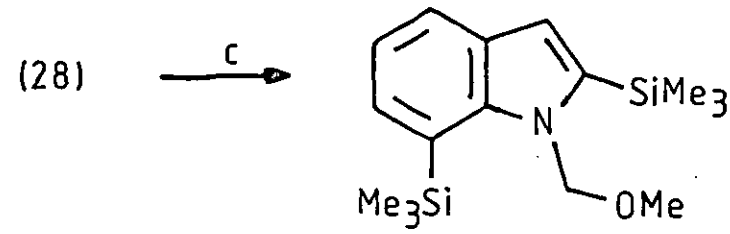
(26)

(Scheme 3)

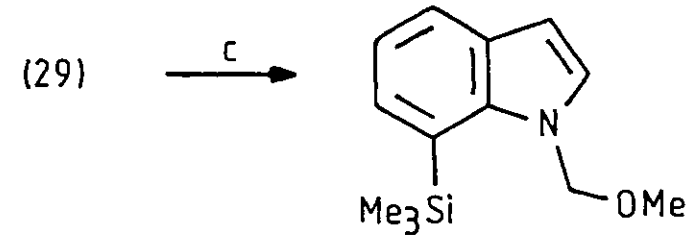
Complexation of 1-methoxymethylindole[13] with chromium hexacarbonyl in a refluxing mixture of di-n-butylether and THF gave a 91% yield of the corresponding complex (27). Lithiation of this complex (27) (Scheme 4) with 1.2 equivalents of n-butyllithium in THF and TMEDA at -78^{o} followed by reaction with chlorotrimethylsilane was expected to give the 2-trimethylsilylated complex (26). However, after chromatography the reaction was found to have given 2 distinct products, the former, a crystalline solid was tentatively identified on the basis of its ^{1}H nmr as the 2,7-di(trimethylsilyl)-1-methoxymethylindole complex (28, 17%), while the latter, a semi-crystalline oil was shown to consist of a mixture of products, again by ^{1}H nmr. Crystallisation of this mixture gave a single product which was tentatively identified as 1-methoxymethyl-7-trimethysilylindole complex (29) while the other, minor component was identified as 1-methoxymethyl-2-trimethylsilylindole complex (26).

The assignments of the complexes (28 and 29) were confirmed by nuclear Overhauser effect[19] (nOe) difference spectra of the decomplexed indoles (30 and 31 respectively).





(30)

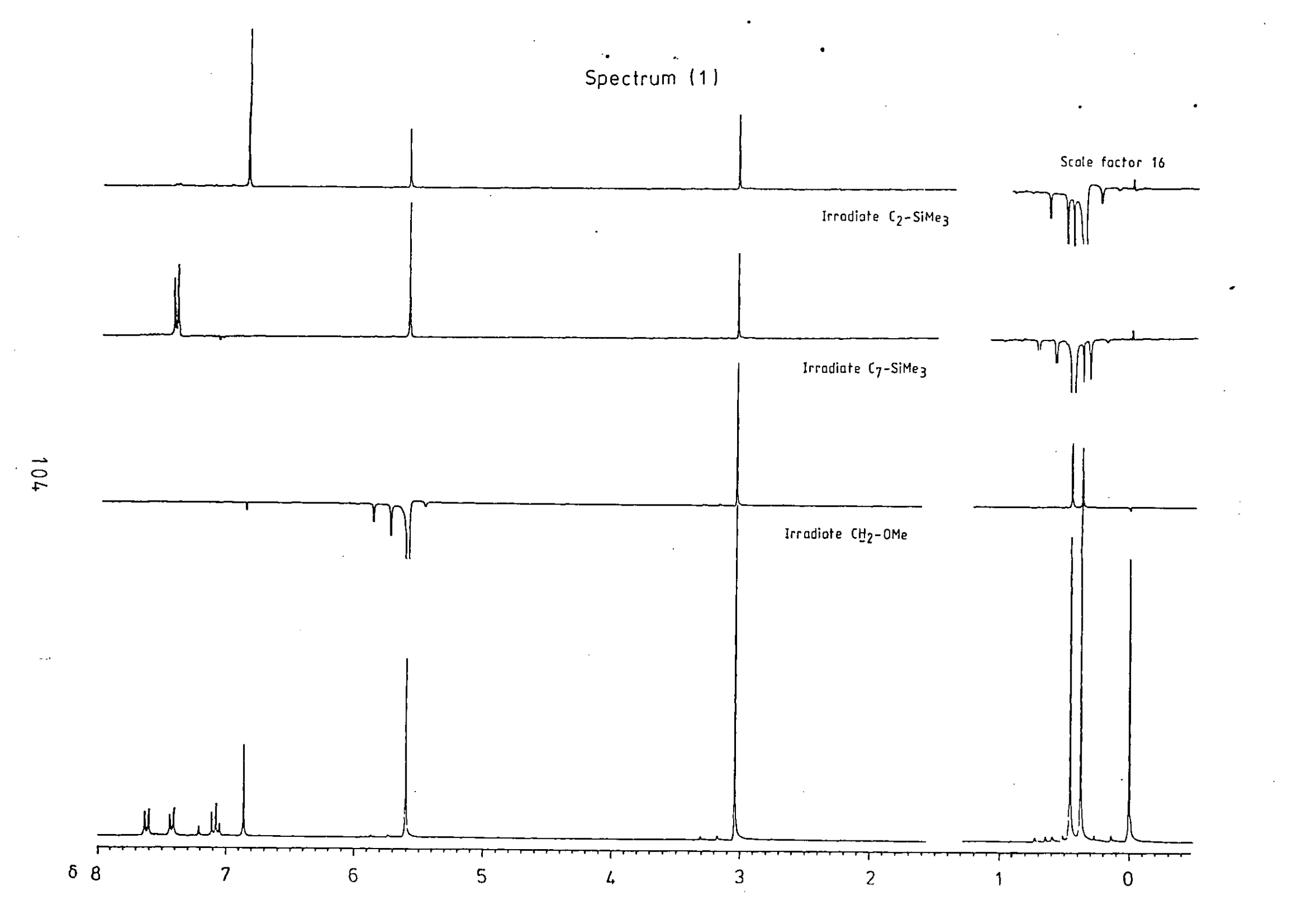


(31)

(a) n-BuLi, THF, TMEDA, -78^{o}; (b) $ClSiMe_3$;(c) $h\gamma$, MeCN, air.

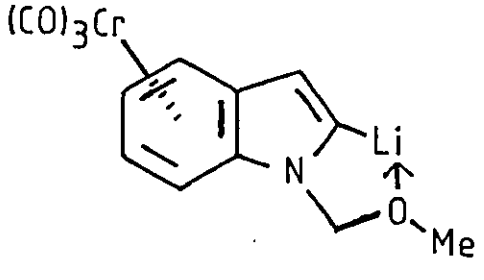
(Scheme 4)

Spectrum (1) shows the results obtained from nOe experiments on 2,7-di(trimethylsilyl)-1-methoxymethylindole (30). Apart from the normal high field ^1H nmr, plotted with a scaling factor, spectrum (1) shows the nOe difference spectra obtained from the irradiation of the resonances at δ 5.60, 0.46 and 0.38 ($C\underline{H}_2$-OMe, C_7-$Si\underline{Me}_3$ and C_2-$Si\underline{Me}_3$ respectively). Irradiation of the resonance at δ 0.46 (C_7-$Si\underline{Me}_3$) produced a large effect on H_6 (δ 7.42, 16%) with smaller effects on the $C\underline{H}_2$-OMe and CH_2-$O\underline{Me}$ signals, while irradiation of the resonance at δ 0.38 (C_2-$Si\underline{Me}_3$) showed a large effect on H_3 (δ 6.87, 11%) with again smaller effects on $C\underline{H}_2$-OMe and CH_2-$O\underline{Me}$. These results confirmed that structure was (30), as was previously

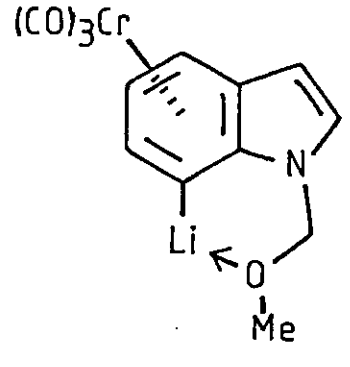

Spectrum (1)
Scale factor 16
Irradiate C_2-$SiMe_3$
Irradiate C_7-$SiMe_3$
Irradiate CH_2-OMe
δ 8
7
6
5
4
3
2
1
0

proposed. Spectrum (2) shows the results obtained from the nOe experiments on 1-methoxymethyl-7-trimethylsilylindole (31). Irradiation of the resonance at δ 5.57 ($C\underline{H}_2$-OMe) produced a significant effect on H_2 (δ 7.20, 9%) with smaller effects on CH_2-$\underline{OMe}$ (δ 3.16) and $SiMe_3$ (δ 0.46), while irradiation of the resonance at δ 0.46 ($SiMe_3$) showed a large effect on H_6 (δ 7.44, 15%) with less significant effects on $C\underline{H}_2$-OMe and CH_2-$\underline{OMe}$. These results confirmed that the structure was (31), as was also previously proposed. It is interesting to note that the nOes induced in $SiMe_3$ and H_2, from the irradiation of the $C\underline{H}_2$-OMe resonance, <u>themselves</u> induce secondary nOes in their neighbours H_6 and H_3 respectively, which consequently appear as negative effects. Smaller and therefore less pronounced secondary nOes are also observable on spectrum (1).

With the structures unambiguously assigned, the reaction can be discussed in greater depth. The major products from this reaction (78%) were the 7- (29) and 2- (26) trimethylsilyl complexes which were present in the ratio of <u>ca.</u> 4:1 respectively. Thus, changing the <u>N</u>-protecting group from <u>N</u>-methyl to <u>N</u>-methoxymethyl has altered the regioselectivity of the initial lithiation from predominately C_2 to predominately C_7. This is best explained by examining the chelated intermediates for C_2- (32) and C_7-(33) lithiation. Chelation <u>via</u> a 5-membered ring on to the 2-lithiated product (32) is obviously more

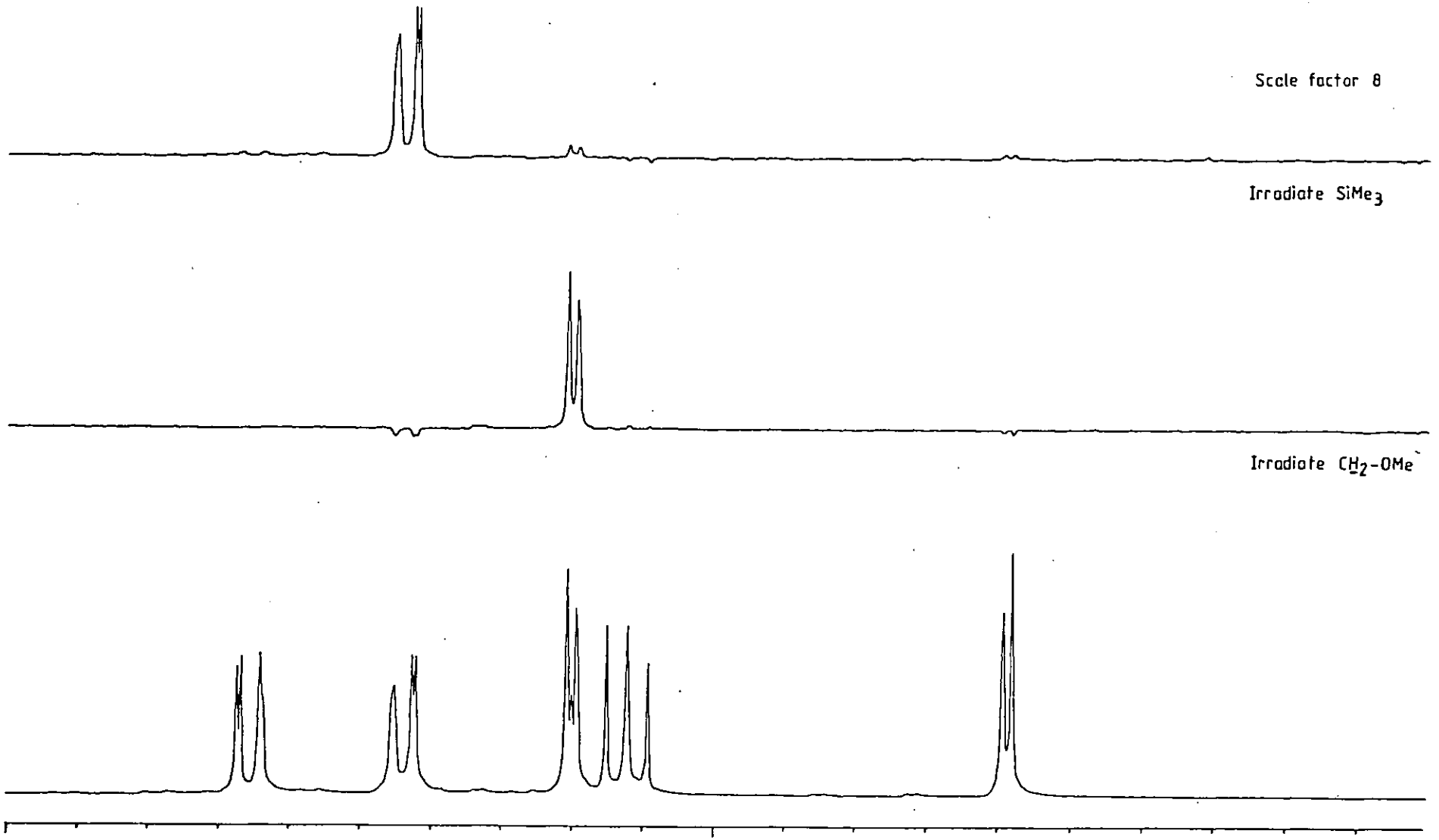


(32)



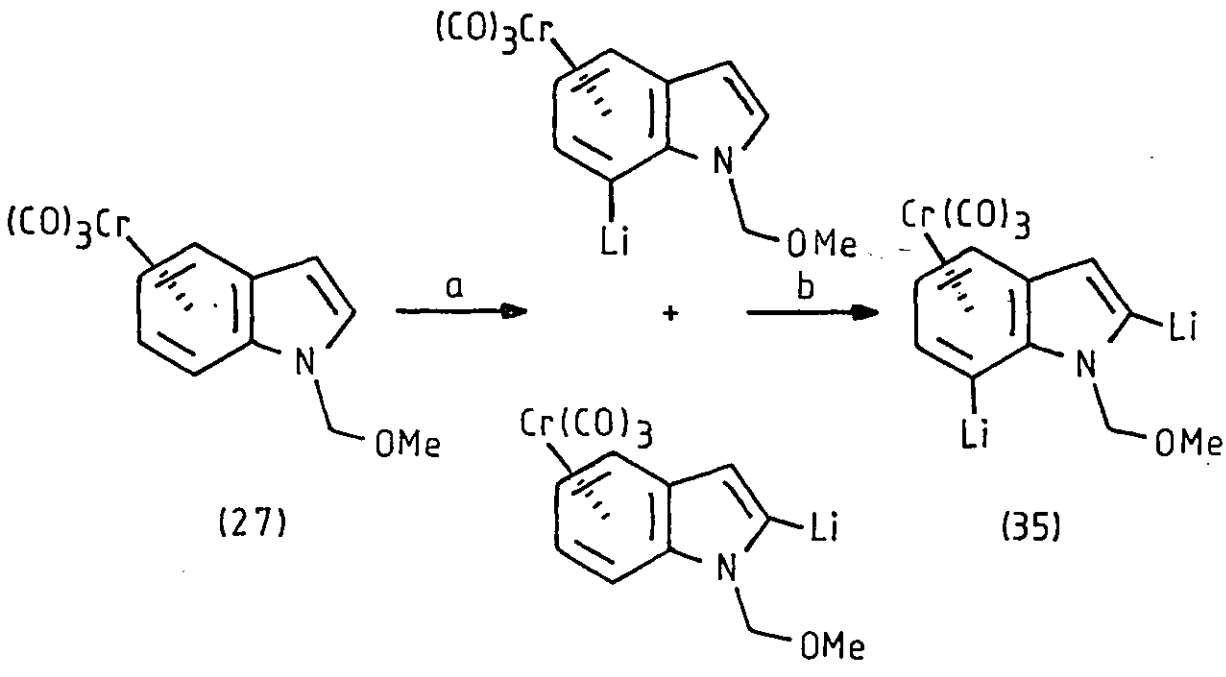
(33)

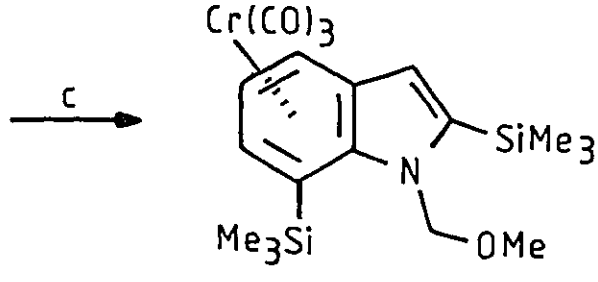
Spectrum (2)



strained and consequently less favourable than chelation *via* a 6-membered ring on to the 7-lithiated product (33). As *N*-methoxymethylindole is known to lithiate exclusively at C_2[13], complexation with $Cr(CO)_3$ has altered the regioselectivity of attack to give predominately the 7-lithiated indole complex (33).

The formation of the 2,7-di(trimethylsilyl)-indole complex (28) can be explained by the initial formation of the mono (2- or 7-) lithiated complexes (34)(Scheme 5) which can be further deprotonated by the excess of base present (1.2 equivalents) to give the 2,7-dilithiated species (35). Reaction of this with chlorotrimethylsilane gives the disilylated product (28). To test this theory,





(28)

(a) n-BuLi, THF, TMEDA, -78^{o}; (b) excess n-BuLi; (c) $ClSiMe_3$.

(Scheme 5)

1-methoxymethylindole complex (27) was treated with 2 equivalents of n-butyllithium followed by reaction with chlorotrimethylsilane to give an 80% yield of the 2,7-disilylated complex (28) and a 16% yield of the monosilylated complexes (26 and 29).

In order to minimise the yield of the disilylated complex (28) and hence increase the yield of the monosilylated complexes (29 and 26), the lithiation of 1-methoxymethylindole complex was repeated under the same conditions as before, using an exact equivalent of n-butyllithium which was added over a period of 5 minutes. Subsequent reaction with chlorotrimethylsilane gave a 90% yield of the monosilylated complexes (26 and 29) and a 9% yield of the disilylated complex (28).

With the aim of improving the C_7 : C_2 lithiation ratio and perhaps realising exclusive 7- lithiation, the reaction of 1-methoxymethylindole complex with n-butyllithium was performed under a range of different conditions (Table 3).

Lithiation of 1-methoxymethylindole complex

Run	Solvent	Temperature	Yield[a]/%	Ratio of C_7 : C_2 Lithiation[b]
1	THF/TMEDA	-46^{o}	90	3 : 1
2	THF/TMEDA	-78^{o}	90	4 : 1
3	THF	-78^{o}	94	4 : 1
4	THF	-98^{o}	98	5 : 1

(a) Yield of monosilylated complexes (26 and 29);

(b) As measured by reaction with chlorotrimethylsilane and decomplexation to give a mixture of 2- and 7- trimethylsilylindoles.

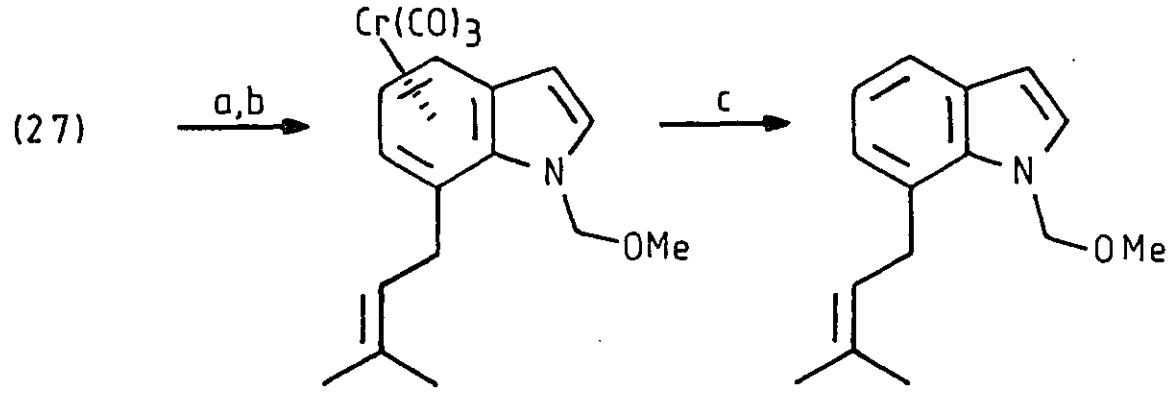
(Table 3)

As can be seen (Table 3), though the ratio of C_7:C_2 lithiation was temperature dependent the effect is not marked and exclusive 7-lithiation was not possible. It is interesting to note that, in contrast to the lithiation of 1-methylindole complex, the lithiation of 1-methoxymethylindole complex did not require TMEDA to increase the reactivity of the alkyllithium, presumably because the chelating ability of the methoxymethyl group led to an easier deprotonation.

Lithiation with n-butyllithium at -98^{o} (run 3) followed by quenching with chlorotrimethylsilane gave an almost quantitative yield (98%) of the mixture of monosilylated complexes (26 and 29) from which, after careful crystallisation, a yield of 66% pure 1-methoxymethyl-7-trimethylsilylindole was obtained.

In order to show that this route is as general as that based on 1-methylindole complex, and to discover whether chromatographic separation of more elaborate 2- and 7- substituted 1-methoxymethylindole

complexes was possible, the lithiation step was followed by reaction with 3,3-dimethylallyl bromide. Chromatographic separation was indeed feasible, giving a 49% yield of pure 7-(3',3'-dimethylallyl)-1-methoxymethylindole complex (36).



(36) (37)

(a) n-BuLi, THF, -78°; (b) $Me_2C{=}CHCH_2Br$; (c) hγ , MeCN, air.

Photolytic cleavage of the methoxymethylindole complexes was accomplished as readily as before, giving almost quantitative yields of the free indole. For example, the 7-(3',3'-dimethylallyl)-indole (37) was obtained from its complex in 93% yield.

Various attempts were made to remove the methoxymethyl group from N-methoxymethylindole with the aim of extending this strategy to the preparation of 7-substituted indoles without any N-protection. However, as was discovered by Sundberg *et al*[13] the deprotection of 1-methoxymethylindole under mild conditions is not trivial. Under both protic and Lewis acid conditions 1-methoxymethylindole polymerised to give undetermined products, while the action of a good nucleophile (LiSMe in HMPA[20]) on 1-methoxymethylindole complex only served to cleave the complex,possibly *via* the thermal exchange of HMPA ligands for the arene ligand on the $Cr(CO)_3$ group.

This strategy for the preparation of 7-substituted indoles affords

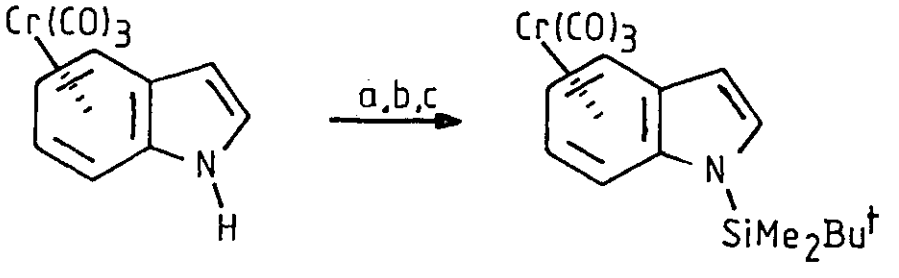
a more concise and higher yielding route than that based on 1-methylindole complex. For example, 1-methoxymethyl-7-trimethylsilylindole was prepared in 45% overall yield in 4 steps from indole. However, both these approaches to 7-substituted indoles are at present restricted to N-protected indoles.

F. Preparation of 4- substituted indoles

As 4- substituted indoles have considerable biological properties it was decided to try to adapt the chemistry of N-protected indole complexes to the preparation of these compounds.

Since the lithiation of 1-methyl-2-trimethylsilylindole complex and subsequent reaction with methyl iodide gave a mixture of 4- and 7- substituted indoles with the latter predominating, it was reasoned that a bulky N-protecting group would sterically hinder lithiation at C_2 and C_7, and consequently favour attack at C_4.

As the t-butyldimethylsilyl group is a sterically demanding group that had been used with some success for the N-protection of indoline $Cr(CO)_3$ complexes[21] (page 19) and because it was readily removed, it was decided to prepare 1-t-butyldimethylsilylindole complex (39). Treatment of the indole complex[22] (38) with potasssium hydride in THF followed by reaction with t-butyldimethylsilylchloride and work-up with a THF/aqueous pH=7 buffer solution, to prevent the desilylation of the protected complex (39) by hydroxide ion produced by the aqueous quenching of the excess potassium hydride, afforded an 83% yield of the 1-t-butyldimethylsilylindole complex (39).

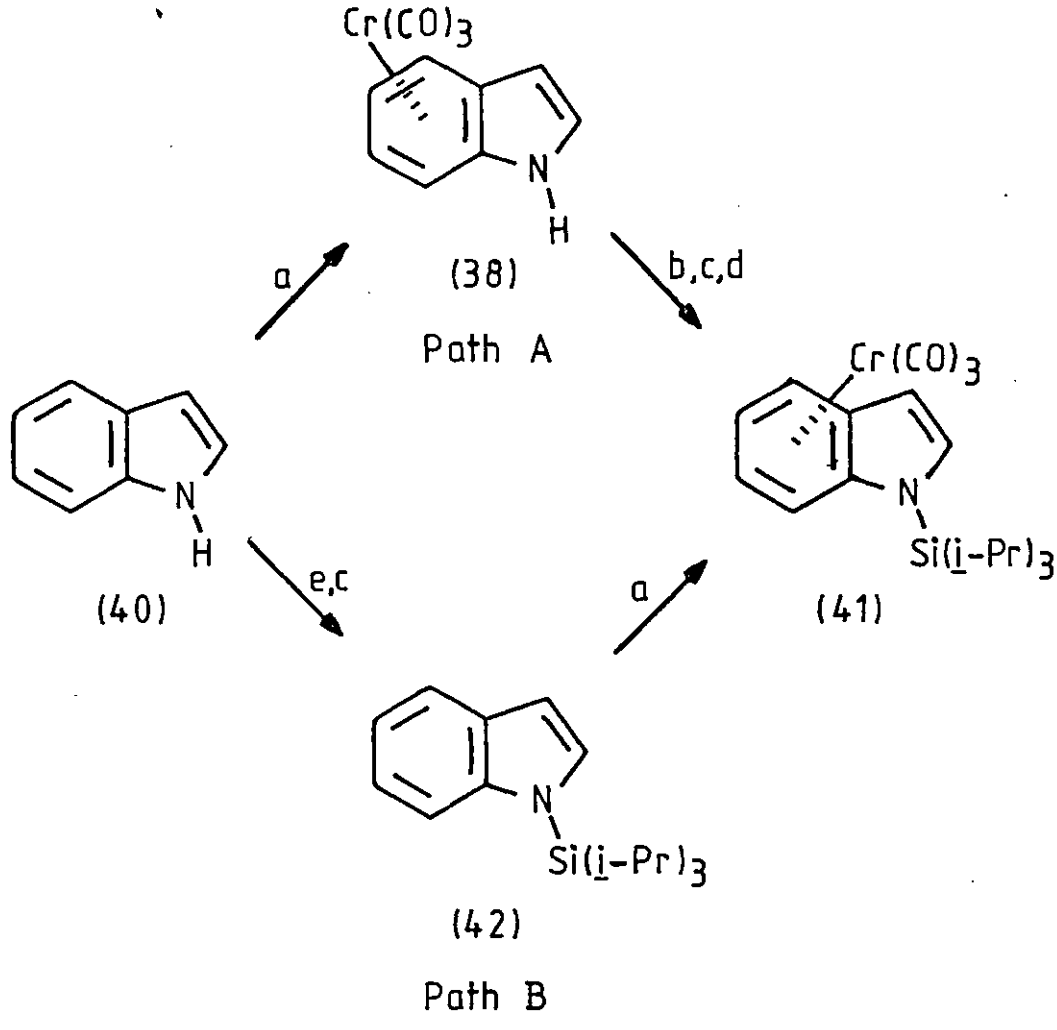


(38) (39)

(a) KH, THF; (b) Me_2Bu^tSiCl; (c) THF, H_2O, pH=7 buffer.

Lithiation of this protected complex (39) with t-butyllithium in THF and TMEDA under a range of reaction conditions followed by reaction with ethylchloroformate gave only low yields of a mixture of undetermined products. The bulk of the t-butyldimethylsilyl protecting group lies principally in the t-butyl group and in order to provide a more spatially complete protection, other N-protecting groups were sought. A report[23] on the relative rates of desilylation of various silyl ethers showed that the tri-isopropylsilyl ethers were more stable to acid, base and fluoride hydrolysis than the corresponding t-butyldimethylsilyl ethers and were more stable to base hydrolysis than t-butyldiphenylsilyl ethers, which suggested that an N-tri-isopropylsilyl protecting group would indeed render a more complete protection. Another important advantage of the tri-isopropylsilyl protecting group is that the corresponding silylchloride is easily prepared on a large scale from readily available, cheap reagents[24].

Thus, 1-tri-isopropylsilylindole complex (41) was initially prepared in 77% overall yield from indole (40) (Scheme 6, Path A) in a fashion analogous to that by which the 1-t-butyldimethylsilylindole complex (39) was prepared. Alternatively, a more convenient preparation of this complex (41) involved the intial N-tri-isopropylsilylation of indole (40) with n-butyllithium and tri-isopropylsilylchloride (Scheme 6, Path B) after the fashion of Sundberg et al[13] to give the N-protected indole (42) which was then reacted with $Cr(CO)_6$ to give the desired complex (41) in 85% overall yield. Purification of the N-protected indole (42) proved difficult, attempts at the distillation of the crude product gave at best a 54% yield of distillate, until it was discovered that the crude product (42), produced in quantitative yield, gave almost the same yield of complex (41) as the distilled material.



(a) $Cr(CO)_6$, n-Bu_2O, THF, Δ ; (b) KH, THF;

(c) $(i\text{-}Pr)_3SiCl$; (d) THF, H_2O, pH=7 buffer; (e) n-BuLi, THF.

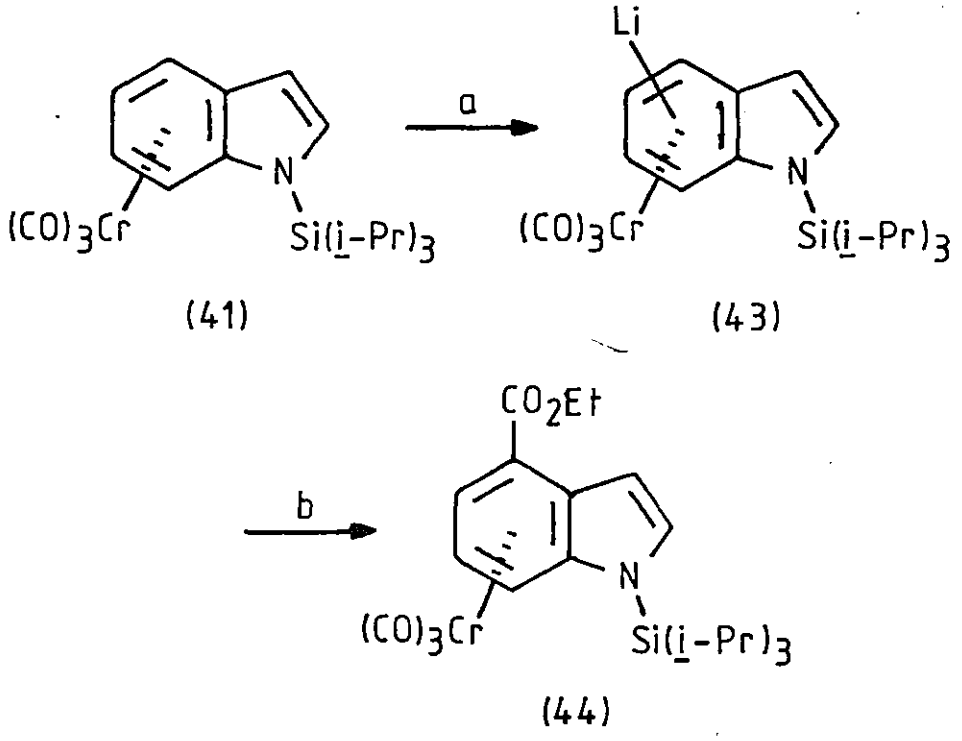
(Scheme 6)

The second route (Scheme 6, Path B) was the preferred route to the complex (41) as it was the higher yielding path and the intermediate (42) could be made and stored in large quantities, while the other intermediate, the indole complex (38), could only be made on a relatively small scale (ca. 3g) and was unstable and so had to be used almost immediately.

Lithiation of the 1-tri-isopropylsilylindole complex (41) required 2 equivalents of n-butyllithium in THF and TMEDA at -78^{o} for 3 hours. The absence of TMEDA, less than 2 equivalents of

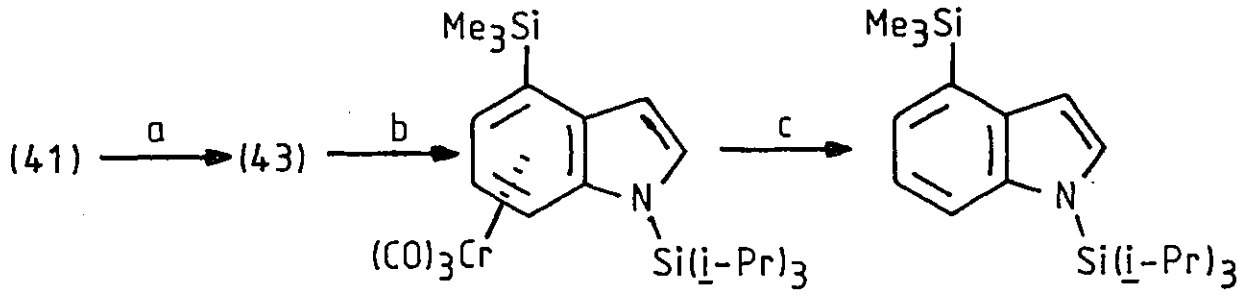
base or a significantly shorter reaction time all decreased the extent of lithiation, as measured by the subsequent reaction with ethylchloroformate.

Reaction of the lithiated complex (43) with ethylchloroformate gave a red oil which on crystallisation afforded a single product (60%). The ^{1}H nmr of this complex showed that H_2 (δ 7.35) and H_3 (δ 7.0) were still present and that the protons of the carbocyclic ring (δ 5.05 - 6.4) showed a vicinal ABC splitting pattern, suggesting 4- or 7- substitution. The downfield shift of H_3 (0.5ppm) relative to the starting material (41), and the fine coupling (ca. 0.8 Hz) between H_3 and the furthest downfield carbocyclic-ring proton, indicated that the product was 4-ethoxycarbonyl-1-tri-isopropylsilylindole complex (44).



(a) n-BuLi, THF, TMEDA, -78°; (b) $ClCO_2Et$.

In order to confirm that the predominant site of deprotonation was indeed C_4, the lithiated complex (43) was reacted with chlorotrimethylsilane to give, after crystallisation, a 56% yield of a complex, the ^1H nmr of which suggested it was the 4-trimethylsilyl complex (45). The 4-substitution was confirmed by an nOe difference



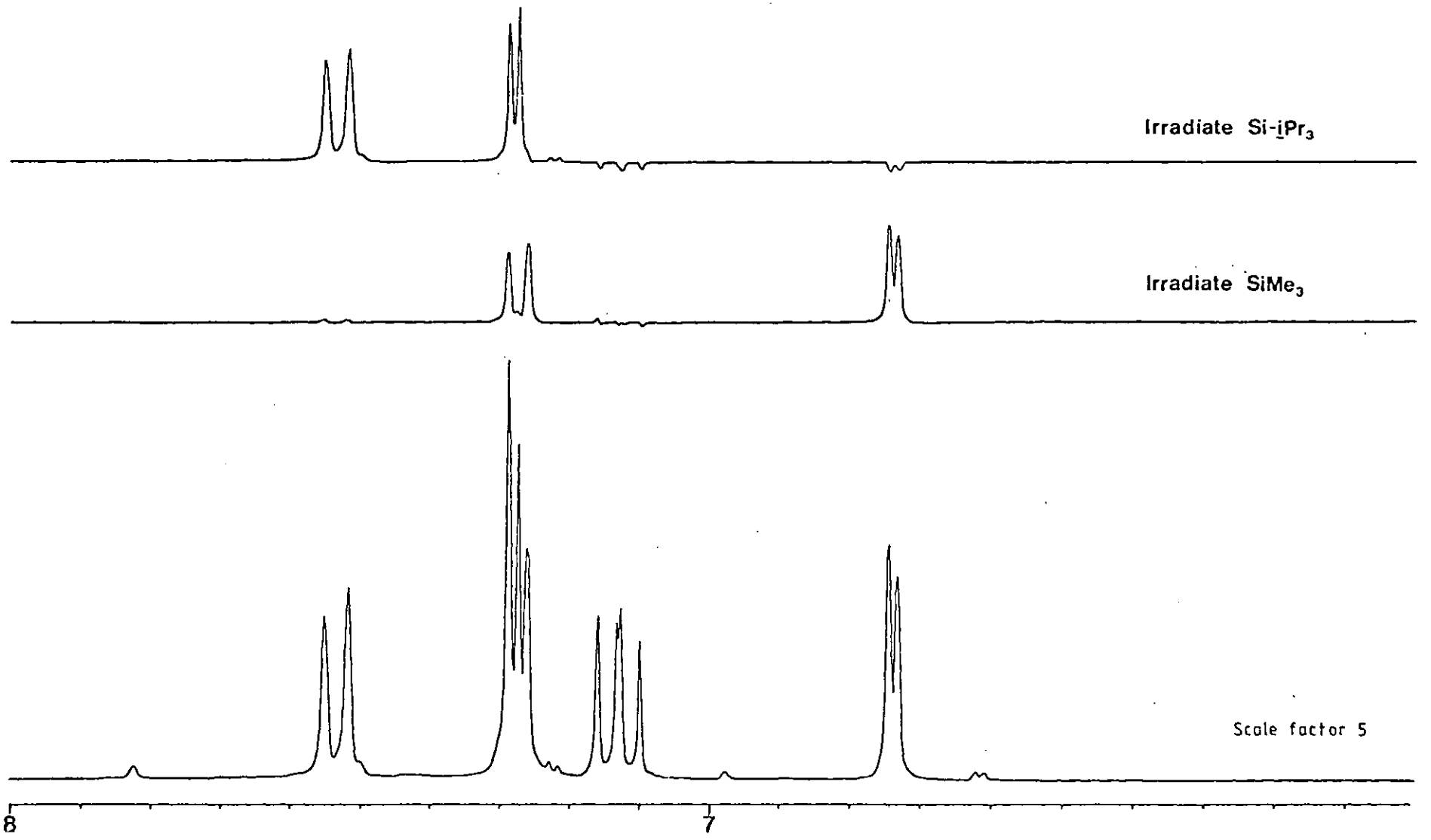
(45) (46)

(a) n-BuLi, THF, TMEDA, -78°; (b) $ClSiMe_3$; (c) hγ, MeCN or THF, air.

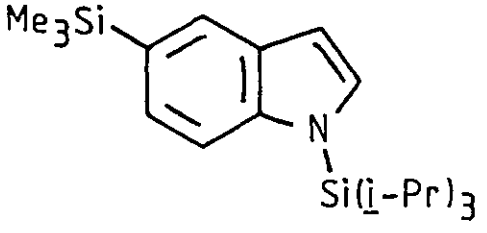
spectrum of the free indole (46), obtained in a 93% yield from photolytic cleavage of the complex (45). Thus, as spectrum (3) shows, irradiation of the protons of the tri-isopropylsilyl group produced a large effect on 2 protons, H_7 (δ 7.54, 12%) and H_2 (δ 7.27, 9%), while irradiation of the protons of the trimethylsilyl group also produced a large effect on 2 protons, H_5 (δ 7.27, 7%) and H_3 (δ 6.75, 7%). These results unambiguously established that the major product of the reaction was 4-substituted. Small secondary nOes (see page 105) were observed for H_6 and H_3, due to the nOes induced in H_7 and H_2 respectively by the irradiation of the tri-isopropylsilyl group.

The mother liquors from the crystallisation of the 4-substituted complexes (44 and 45) were shown by ^1H nmr to be a mixture of isomers,

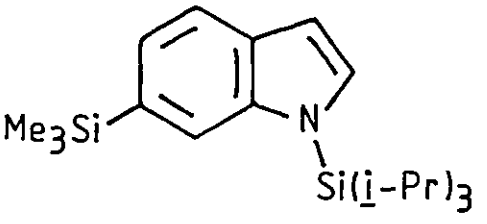
Spectrum (3)



with the 4-substituted complexes predominating. A high resolution ^1H nmr of the decomplexed mother-liquors from the crystallisation of the 4-trimethylsilyl indole complex (45) showed the presence of the 4-silylated compound (46) together with smaller amounts of 2 other isomers which were tentatively assigned as the 5- (47) and 6- (48) trimethylsilyl indoles. Consequently, the tri-isopropylsilyl protecting group has indeed prevented lithiation at C_2 or C_7.

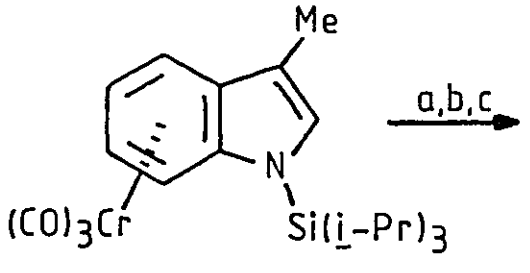


(47)

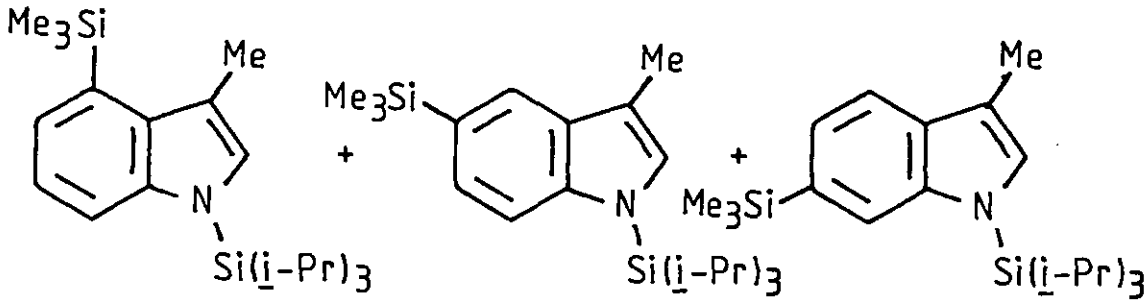


(48)

The assignments of the minor components (47 and 48) were corroborated by the fact that the lithiation of 3-methyl-1-tri-isopropylsilylindole complex (49) (Scheme 7) followed by reaction with chlorotrimethylsilane yielded a mixture of 4- (50), 5- (51) and 6- (52) trimethylsilylated products, as shown by the nOe assignments of the decomplexed products[25].



(49)



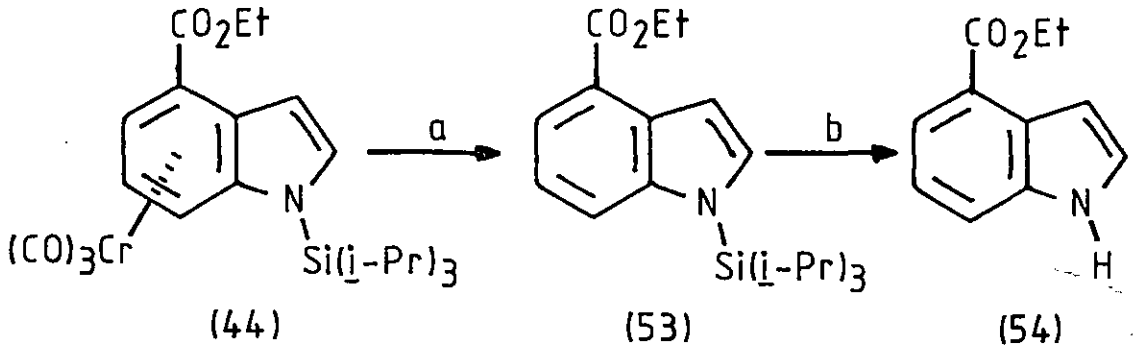
(50) (51) (52)

(a) n-BuLi, THF, TMEDA, -78°; (b) $ClSiMe_3$; (c) $h\gamma$, MeCN, air.

Scheme 7

The mixture of 4- (46), 5- (47) and 6- (48) trimethylsilyl indoles were present in the ratios of ca. 2.6:1:1. Thus, reaction of 1-tri-isopropylsilylindole complex with n-butyllithium followed by quenching with chlorotrimethylsilane was estimated to give ca. 70% of the 4-trimethylsilyl indole complex (45) with ca. 8% of each of the 5 and 6 isomers.

Photolytic cleavage of the 4-ethoxycarbonylindole complex (44) gave the free indole (53) which was deprotected almost instantaneously with tetra-n-butylammonium fluoride (TBAF) in THF[23] to give 4-ethoxycarbonylindole (54) in 84% overall yield. In contrast, when the 4-trimethylsilylindole (46) (Scheme 8) was treated with TBAF under the same conditions, the reaction was extremely slow and gave, after several days at room temperature, a mixture of products by tlc. The more ready deprotection of the 4-ethoxycarbonylindole (53) is probably due to the fact that the electron-withdrawing nature of the ethoxycarbonyl group

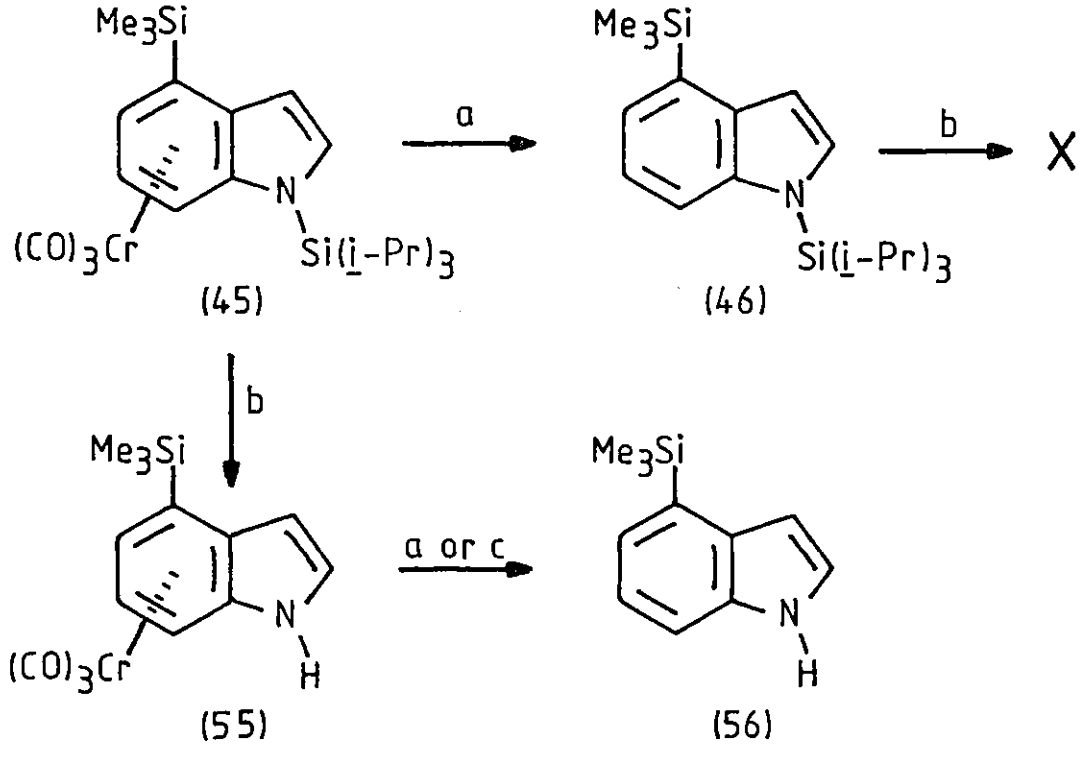


(44) (53) (54)

(a) hγ, THF, air; (b) TBAF, THF, 0°.

stabilises the negative charge produced by the fluoride desilylation.

Since complexation of an arene to $Cr(CO)_3$ is known to reduce the electron density in the ring (see review), the deprotection was performed on the corresponding 4-trimethylsilylindole complex (45). In this case, the reaction was almost instantaneous and the deprotected indole complex (55) was decomplexed by the action of refluxing pyridine to give 4-trimethylsilylindole (56) in 86% overall yield.



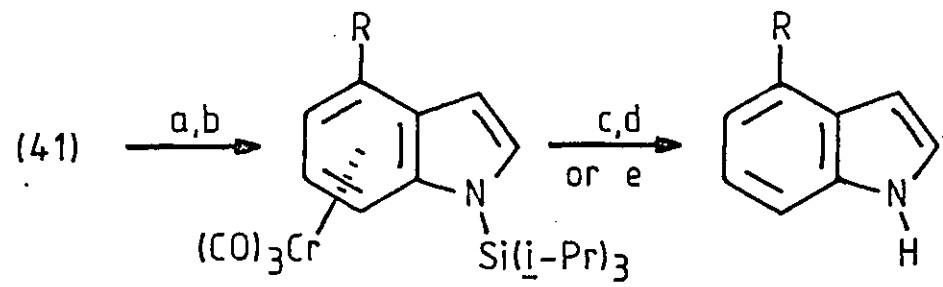
(45) (46) (55) (56)

(a) $h\gamma$, THF or MeCN, air; (b) TBAF, THF, 0^{o}; (c) pyridine, Δ .

(Scheme 8)

As the silicon-carbon bond is much more stable than the silicon-nitrogen bond[26], cleavage of the 4-trimethylsilyl group by fluoride was not expected and indeed, under the reaction conditions previously described, none was observed.

The lithiation-quench procedure was repeated with a series of electrophiles (Scheme 9) and the products (57) were isolated in fair to good yields (Table 4). Desilylation of these complexes (57) was accomplished by treatment with TBAF in THF and the decomplexation was effected by either light and oxygen or the action of refluxing pyridine to give the 4-substitued indoles (58) in excellent overall yields.



(57) (58)

(a) n-BuLi, THF, TMEDA, -78^{o}; (b) Electrophile;
(c) TBAF, THF, 0^{o}; (d) $h\gamma$, MeCN or THF, air;
(e) Pyridine, Δ .

(Scheme 9)

Synthesis of 4-substituted indoles

Run	Electrophile	Product (R=)	Complex (57) Yield[a]/%	Free Indole (58) Yield[b]/%
1	$ClCO_2Et$	CO_2Et	60	84
2	$ClSiMe_3$	$SiMe_3$	56	86
3	$ClCO_2Me$	CO_2Me	59	81
4	MeI	Me	–[c]	–
5	PhSCl	SPh	–[d]	26[e]
6	$Me_2C{=}CHCH_2Br$	$CH_2CH{=}CMe_2$	36	95

(a) isolated yield;
(b) yield from complex;
(c) an inseparable mixture of starting material and product was obtained;
(d) complex was too unstable to isolate;
(e) overall yield.

(Table 4)

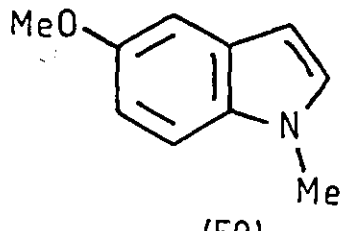
The reaction with methyl iodide (run 4) gave, by ^1H nmr, a ca. 45% yield of 4-substituted complex (57, R=Me) but unfortunately this was inseparable from the starting material and the 5 and 6 isomeric products.

The crude product arising from reaction with benzenesulphenyl chloride (run 5) was unstable to attempts to induce it to crystallise so was desilylated and decomplexed directly to give a 26% overall yield of 4-phenylthioindole (58, R=SPh). A high resolution ^1H nmr of this material shows that it was almost completely composed of the 4-substituted indole. Thus, the resonance at δ 6.55 (H_3) shows fine coupling to H_2, H_7 and NH, as shown by decoupling experiments.

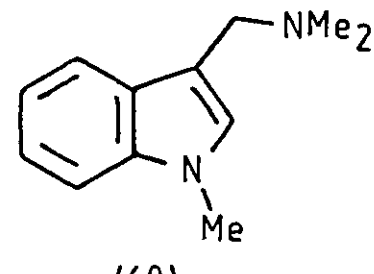
Reaction with 3,3-dimethylallyl bromide (run 6) gave, by ^1H nmr, a ca. 50% yield of the 4-substituted indole (57, R= $CH_2CH{=}CMe_2$), of which 36% could be separated from the 5- and 6- substituted isomeric

products and the starting material by careful crystallisation of the initial fractions from liquid chromatography. Desilylation and decomplexation gave 4-(3',3'-dimethylally)-indole (58, R=$CH_2CH{=}CMe_2$) in 95% overall yield. This completes a synthesis of 4-(3',3'-dimethylallyl)-indole in 28% overall yield from indole, a higher yielding route to this compound from readily available starting materials than any other strategy previously discussed (see review).

In an attempt to obtain exclusive 4-lithiation it was decided to investigate the lithiation of a suitably protected indole complex that could chelate and thus stabilise a 4-lithio species. Lithiation of free indoles containing groups that could chelate a 4-lithio species has already been shown to give either mixtures of products or exclusive 2-lithiation. For example, as discussed earlier (page 73), 5-methoxy-1-methylindole (59) was lithiated in the 2, 4 and 6 positions in the ratios of 4:5:1[27] respectively, while 3-dimethylaminomethyl-1-methylindole (60) was lithiated exclusively at C_2, as measured by the subsequent reaction with D_2O[28].



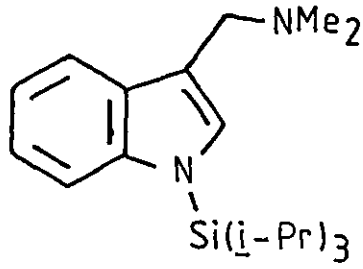
(59)



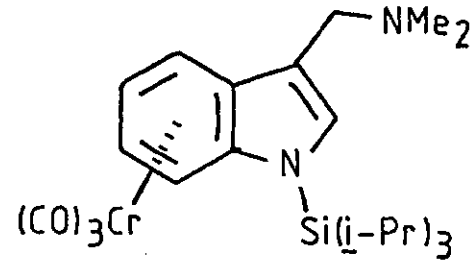
(60)

Since 3-dimethylaminomethylindole (gramine) is more readily prepared than 5-methoxyindole, it was decided to investigate the lithiation of the N-protected gramine complex (62). Thus, gramine was N-tri-isopropylsilylated in the usual manner to give an almost quantitative yield of the protected gramine (61). However, complexation of the crude, or the distilled material (61) under the normal conditions gave an intractable tar without any trace of the

π-complex (62), possibly because the electron-rich tertiary nitrogen of gramine could act as a competing σ-ligand for the chromium carbonyl group.



(61)



(62)

Since complexation of the protected gramine (61) under different reaction conditions failed to give more than a trace of the complex (62), for which there was only mass spectral evidence, this approach was abandoned due to lack of time.

G. Conclusion and future prospects

The general strategy of lithiating N-protected indole complexes and the subsequent reaction with electrophiles has been shown to be a general, expedient and high yielding route to 4- and 7- substituted indoles.

The advantages and drawbacks common to both the approaches to 4- and 7- substituted indoles will be discussed before more specific remarks concerning each approach are made.

(1) General comments

The main advantage of this general strategy is that it affords a concise and high yielding route to 4- or 7- substituted indoles depending on the N-protection used. This strategy is an example of the direct substitution of indole (see review), and as such, is a route to a wider range of substituted indoles than those mentioned previously since the key step is a regioselective lithiation. Once this is realised, the subsequent reactions are, as far as can be determined by this initial investigation, typical of the wide range of reactions of organolithium compounds[29].

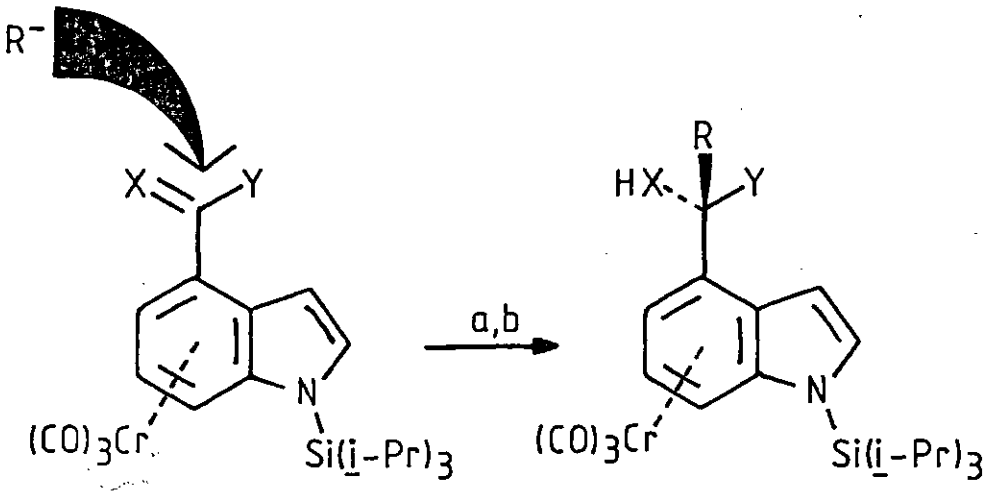
The drawbacks are for the most part, those that result from the properties of the chromium hexacarbonyl that is used to form the complexes. It is an expensive reagent (£89.60 per 100g)[30]. It requires elevated reaction temperatures (ca.150°) for complexation, although the use of more active $Cr(CO)_3$ transferring species such as trisacetonitriletricarbonylchromium or trisammoniatricarbonylchromium could enable milder reaction conditions to be used. Optimum yields of indole complexes are obtained through the use of rigorously oxygen-free conditions and a Strohmeier apparatus (page 87). Even then, it is not possible to complex all indoles due to either the severe

conditions or to the fact that other functional groups on some indoles can interfere with the π-complexation.

These properties of chromium hexacarbonyl could feasibly restrict the use of indole $Cr(CO)_3$ complexes to the synthesis of the more elaborate and otherwise inaccessible substituted indoles, as with those based on natural products since the more simple indoles are more economically prepared by either a range of ring syntheses (see review) or by the elaboration of simple already-substituted indoles.

Although the chromatographic separation of simple 4- or 7-substituted indole complexes, as with those prepared in this study, was not always realised, it is envisaged that the chromatographic separation of indoles substituted with more elaborate substituents would be more practicable.

As was mentioned previously (page 85), this lithiation-quench procedure has several distinct advantages over the nucleophilic addition of carbanions to indole complexes. The main advantage is that the products are obtained as their $Cr(CO)_3$ complexes enabling further $Cr(CO)_3$ mediated reactions to be performed, whereas in the nucleophilic addition approach the products are obtained *via* an oxidation, thereby cleaving the complex and discarding the valuable $Cr(CO)_3$ moiety. In particular, a further $Cr(CO)_3$ mediated reaction that could be envisaged is the nucleophilic addition to a complexed double bond species (as Scheme 10). This would be directed *exo* to the $Cr(CO)_3$ group and thus provides a potential route for the asymmetric synthesis of substituted indoles based on the ergot alkaloids.



X, Y = any other atom or group

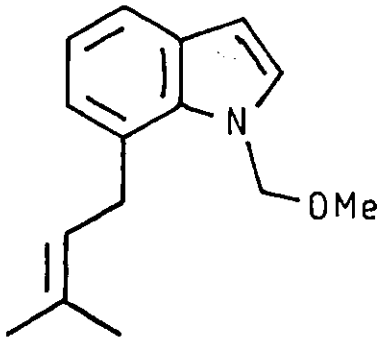
(a) R^-; (b) H^+.

(Scheme 10)

2. Approaches to 7- substituted indoles

Using this strategy it is possible to prepare 7- substituted N-protected indoles in good overall yields from indole; for example 7-(3',3'-dimethylallyl)-1-methoxymethylindole (37) was prepared in 34% overall yield. As a route to 7- substituted indoles, the approach from 1-methoxymethylindole complex is on the whole more efficient than that from 1-methylindole complex as it does not involve the protection and deprotection of the 2-position.

At present, it is not possible to prepare 7- substituted indoles without any N-protection, although the use of a more readily removable methylene-oxy N-protecting group like the β-trimethylsilylethoxymethyl group (63)[31] should make this objective feasible.



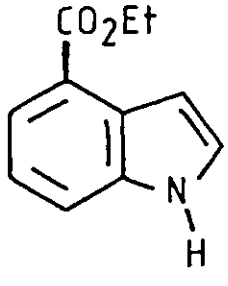
(37)



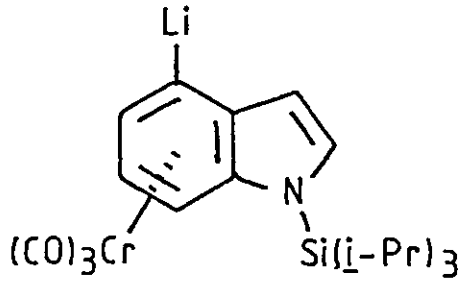
(63)

3. Approaches to 4- substituted indoles

This strategy has led to the concise synthesis of 4- substituted indoles in good overall yield from indole. For example, 4-ethoxy-carbonylindole (54) was prepared in 43% overall yield from indole.



(54)



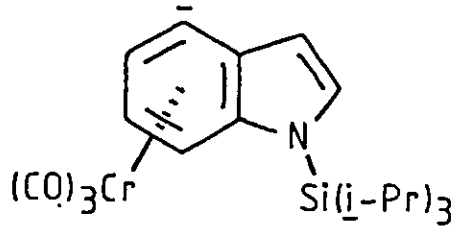
(64)

The greatest potential of this strategy is in the synthesis of the more elaborate ergot-type structures and it is possible to envisage the construction of the skeleton of some ergot alkaloids *via* a rapid and convergent synthesis (see page 129).

In order to extend the scope of this strategy an area that requires initial investigation is the moderation of the reactivity of the

organolithium intermediate (64) to enable reaction with a wider range of electrophiles to take place. One of the ways of accomplishing this is *via* a trans-metallation reaction, for example the formation of an organocopper species from an organolithium.

Cuprates are generally less basic than the corresponding organolithiums and their range of reactions complements those of organolithiums[32]. Since it is desirable to react all the valuable complex anion (65) with an electrophile, a mixed cuprate which is compatible with the reaction conditions required for the lithiation step would have to be used. One of the few mixed cuprates that is compatible with THF solvent and gives good yields of products is the mixed homocuprate (66)[33].



(65)

$[R'SO_2CH_2CuR]^- Li^+$

R' = Me, Ph;

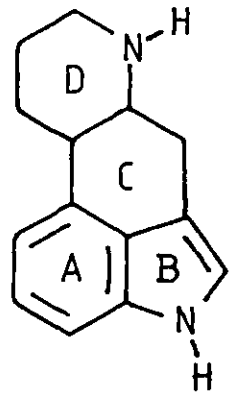
R = transferable group.

(66)

Other trans-metallation reactions to give, for example organozinc and organomagnesium compounds are also feasible and might further add to the range of reactions possible for the complex anion (65).

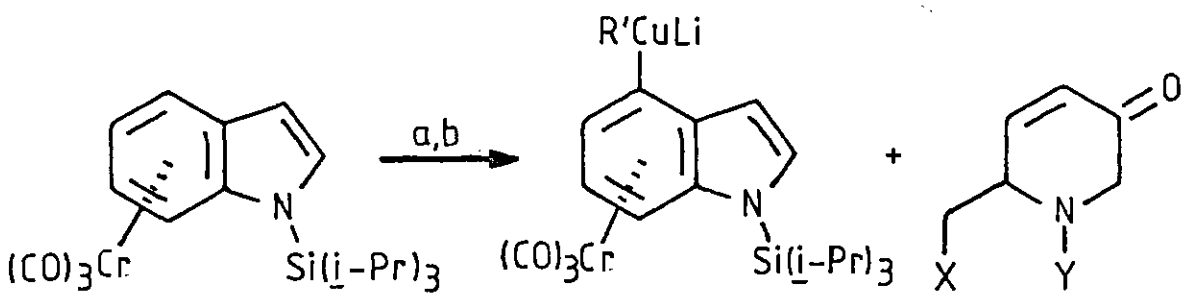
An example of the potential envisaged for the organocopper compound (68) is the convergent synthesis of the skeleton of the ergoline ring system (67) (Scheme 11). The mixed cuprate (68) would react *via* a 1,4-addition to the unsaturated ketone of the reduced pyridine

equivalent (69) to give, after work-up, the 4-substituted indole

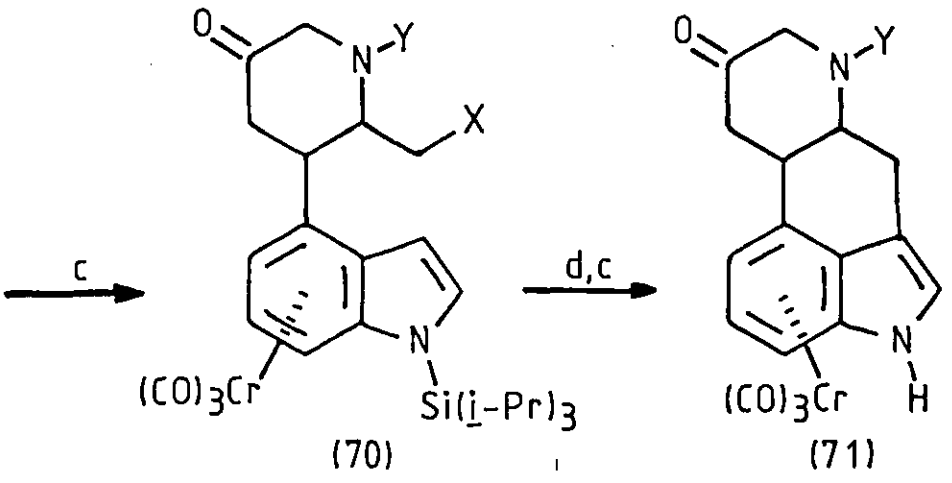


(67)

complex (70). Treatment of this complex (70) with fluoride could also lead to concomitant closure of the 'C' ring *via* an intramolecular nucleophilic displacement to give the complexed ergoline skeleton (71), obtained in 3 steps from the protected indole complex (41).



(41) (68) (69)



R' = non-transferable ligand of the mixed homocuprate;
X = a leaving group;
Y = a group to stabilise the reduced pyridine equivalent
(a) n-BuLi, THF, TMEDA, -78^{0}; (b) R'Cu; (c) H_2O; (d) F^-

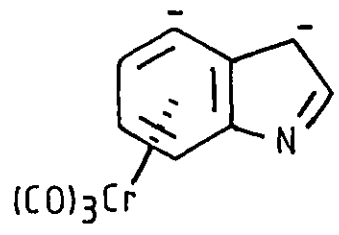
(Scheme 11)

As this scheme is so attractive by virtue of the ease with which the ergoline ring system can be constructed, a considerable time and effort expended in the search for a suitable enone (69) can be justified.

With this approach to the ergot-type compounds, the major problem is no longer the 4-substitution of indole, described in the following manner in a review by Kozikowski[34], "the direct introduction of a carbon unit as an electrophile into the 4-position of indole is, of course, difficult to achieve", but rather the preparation of suitable electrophiles with which the 4-anionic species (65) can react.

The ability to regioselectively lithiate the 4-position of indole, together with the normal electron-rich character of the 3-position, which could possibly be enhanced *via* desilylation of a protected complex, suggests that the 1-tri-isopropylsilylindole

complex could act as a 3,4-dianion equivalent (as 72), thus providing a new methodology for the construction of the "C" ring of the ergoline ring system which could prove to be a powerful synthetic tool in subsequent syntheses of ergot-type compounds.



(72)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 298 grating spectrometer. ^1H nmr were routinely recorded at 60 MHz on Varian T-60 or EM-360A spectrometers or at 250 MHz on a Brucker WH-250 FT spectrometer with tetramethylsilane as an internal standard. Apparent J values and multiplicities are quoted, and the following abbreviations are used; s (singlet), d (doublet), t (triplet), q (quartet), h (heptet), m (multiplet) and b (broad).

Solvents were purified as follows: petroleum ether-redistilled, dried if necessary by distillation from phosphorous pentoxide and stored over sodium wire; dichloromethane-distilled; acetonitrile-distilled, dried if necessary by distillation from calcium hydride or phosphorous pentoxide; di-n-butylether-distilled from sodium; diethyl-ether and THF - dried if necessary by distillation from sodium-potassium-benzophenone ketyl; ethanol, methanol, pyridine and carbon tetrachloride-AnalaR reagents; TMEDA - stored over sodium wire. Petrol refers to the petroleum ether fraction of bp 40-60^o unless otherwise stated.

Silica gel type 60H was used for liquid chromatography, analytical tlc was performed on precoated GF-254 silica plates and preparative tlc (prep. tlc) was carried out on plates coated with silica GF-254 unless otherwise stated.

Reactions involving chromium tricarbonyl complexes or alkyllithiums were carried out under an atmosphere of dry, oxygen-free nitrogen.

Organic solutions were routinely dried over anhydrous magnesium sulphate and solutions that contained an appreciable amount of THF were predried by shaking with saturated brine. Solvents were routinely removed at reduced pressure on a Büchi rotary evaporator.

Microanalyses and mass spectra were carried out by the respective laboratories at Imperial College.

General Procedure for the thermal complexation of indoles

A mixture of the indole (1.1 equivalents) and chromium hexacarbonyl (1.0 equivalent) in a mixture of di-n-butylether (80ml) and THF[4] (5ml) was thoroughly deoxygenated and was heated under reflux in a Strohmeier apparatus[7] for 15 hours. After cooling, the resulting orange solution was filtered through celite with THF and was concentrated to ca. 10ml. On standing, a first crop of complex crystallised out of this solution and a second crop was obtained by the addition of petrol. The complex was filtered off and was thoroughly washed with petrol. The complexes produced by this method were dried in vacuo and were used without further purification.

General Procedure for the photolytic cleavage[8] of the indole complexes

A dilute solution of the complex in THF or acetonitrile (ca. 300mg per 150ml) was irradiated with a 300W tungsten lamp in air until tlc indicated that the reaction had gone to completion. Removal of the solvent and chromatography gave the free indole.

Procedure for the decomplexation of indole complexes via the action of refluxing pyridine[9]

A solution of complex in pyridine (ca. 100mg per ml) was deoxygenated and was heated under reflux, under a nitrogen atmosphere, for 2 hours. Removal of the excess pyridine and chromatography gave the free indole and $(pyridine)_3Cr(CO)_3$.

1-Methylindole[35]

Potassium (13.0g, 0.33mol) was added to liquid ammonia (500ml) which contained a trace of anhydrous ferric chloride and the mixture was left to react under a nitrogen atmosphere (1 hour). Indole (35.1g,0.3mol) in THF (100ml) was added and was allowed to react for 1 hour before an excess of methyliodide (55g) in THF (50ml) was added. After 30 minutes, the reaction was cautiously quenched with wet THF

(20ml) before water (200ml) was added. The ammonia was allowed to evaporate overnight and the reaction mixture was extracted with dichloromethane (3x100ml). The organic layers were combined and acidified (pH=5) with dilute hydrochloric acid and were washed with water (3x50ml). The aqueous phases were neutralised and were extracted with dichloromethane (2x50ml) and the combined organic phases were combined, dried and concentrated. Distillation from calcium hydride afforded 1-methylindole (36.7g, 93%) as a clear oil, bp 78-80° @ 2 mmHg (Lit.,[36] 78-9° @ 2 mmHg).

Tricarbonyl-(η^6-1-methylindole)chromium(0) (1)

The complexation of 1-methylindole (2.16g, 16.5 mmol) and chromium hexacarbonyl (3.36g, 15 mmol) was carried out as previously described to give the title compound (1) (3.54g, 88%) as yellow needles, mp 131-2° (dec.) (from ether-THF-petrol); γ_{max} ($CHCl_3$) 1955, 1865, 1555, 1455, 1300, 1130 and 630cm^{-1}; δ ($COCl_3$) 3.65 (3 H, s, N-Me), 5.05 (1 H, t, J=6Hz), 5.35 (1 H, t, J=6Hz), 6.0 (1 H, d, J=6Hz, H_4), 6.2-6.4 (2 H, m, H_3 and H_7) and 7.05 (1 H, d, J=3Hz, H_2); m/e 267(M^+), 211, 183 and 131(100%) (Found: C, 54.07; H, 3.35; N, 5.26. $C_{12}H_qCrNO_3$ requires C, 53.94; H, 3.39; N, 5.24%).

Lithiation of 1-methylindole complex (1) and reaction with ethylchloroformate

To a solution of 1-methylindole complex (534 mg, 2 mmol) in THF (60 ml) and TMEDA (2ml) at -78° was added n-butyllithium (2 mmol). After 1 hour, an excess of ethylchloroformate (2 ml) in THF (10 ml) was added and was allowed to react at -78° (1 hour) before being allowed to warm to room temperature. Dilute hydrochloric acid (10 ml of 1M soln.) was added and the organic layer was washed with water (2x25ml). The aqueous layers were extracted with ether (2x25ml) and the combined organic phases were dried and concentrated to give a red oil. Chromatography (petrol-ether ; 50:50) gave a red oil which was crystallised

with petrol to give tricarbonyl-(η^6-2-ethoxycarbonyl-1-methylindole)-chromium(0) (2) (530 mg, 78%) as red crystals, mp 124° (from petrol-ether or petrol-di-isopropylether); ν_{max} ($CDCl_3$) 1960, 1885, 1710 and 1145cm^{-1}; δ ($CDCl_3$) 1.4 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 3.9 (3 H, s, N-Me), 4.35 (2 H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 5.15 (1 H, t, J=7Hz, H_5), 5.55 (1 H, t, J=7Hz, H_6), 6.0 (1 H, d, J=7Hz, H_4), 6.35 (1 H, d, J=7Hz, H_7) and 7.2 (1 H, s, H_3); m/e 339(M^+), 255(100%) and 203 (Found: C, 52.89; H, 3.89; N, 4.06. $C_{15}H_{13}CrNO_5$ requires C, 53.10; H, 3.86; N, 4.13%).

2-Ethoxycarbonyl-1-methylindole (4)

Photochemical decomplexation of the complex (2) (530 mg, 1.56 mmol) in acetonitrile in the manner described previously, gave the title compound (4) (295 mg, 93%) as a clear oil which solidified on standing. Prep. tlc (developing solvent, petrol(30-40)-ether; 70:30) and crystallisation from petrol(30-40) at -78° gave analytically pure material as white crystals, mp 61-61.5°; ν_{max} ($CDCl_3$) 2980, 1705, 1520, 1400, 1245, 1230, 1170, 1150, 1135 and 1085cm^{-1}; δ ($CDCl_3$) 1.4 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 4.05 (3 H, s, N-Me), 4.4 (2 H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$) and 7.0-7.8 (5 H, m, H_3-H_7); m/e 203(M^+, 100%), 188, 175 and 158 (Found: C, 70.70; H, 6.45; N, 6.75. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%).

Lithiation of 1-methylindole complex and reaction with chlorotrimethylsilane

The complex (1) (534 mg, 2 mmol) was lithiated as before, and chlorotrimethylsilane (228 mg, 2.1 mmol) in THF (5 ml) was added and allowed to react at -78° (1 hour) before being warmed to room temperature. Work-up as before, and chromatography (petrol-ether; 80:20 to 60:40) gave an orange oil (563 mg, 83%) which was crystallised with petrol-ether to give tricarbonyl-(η^6-1-methyl-2-trimethylsilyl-indole)-chromium(0) (7) (410 mg, 60%) as bright orange prisms, mp 105°

(from petrol-ether); γ_{max} ($CDCl_3$) 1950, 1860, 1455, 1255, 1210, 1120, 1070, 835 and 625 cm^{-1}; δ ($CDCl_3$) 0.35 (9 H, s, $SiMe_3$), 3.7 (3 H, s, N-Me), 5.0 (1 H, t, J=6Hz, H_5), 5.45 (1 H, t, J=6Hz, H_6), 5.95 (1 H, d, J=6Hz, H_4), 6.35 (1 H, d, J=6Hz, H_7) and 6.5 (1 H, s, H_3); m/e 339(M^+), 269, 255(100%), 203 and 188 (Found: C, 53.33; H, 5.02; N, 4.13. $C_{15}H_{17}CrNO_3Si$ requires C, 53.08; H, 5.05; N, 4.13%).

1-Methyl-2-trimethylsilylindole (9)

A solution of 1-methylindole (3.28g, 25 mmol) in ether (50 ml) was added to n-butyllithium (30 mmol) in ether (50 ml) and the mixture was heated under reflux[12] for 8 hours. After cooling to 0°, a solution of chlorotrimethylsilane (3.26g, 30 mmol) in ether (25 ml) was slowly added and allowed to react at 0° (30 minutes) before water (10 ml) was added. The organic layer was washed with water (2x50 ml) and the aqueous phases were extracted with ether (2x25 ml). The combined organic phases were dried and concentrated to give an orange oil, distillation of which gave the title compound (9) (3.61g, 71%) as a clear liquid, bp 80-5° @ 0.06 mmHg; γ_{max} (film) 2960, 1350, 1250, 1070, 840, 750 and 625 cm^{-1}; δ (CCl_4) 0.35 (9 H, s, $SiMe_3$), 3.7 (3 H, s, N-Me), 6.55 (1 H, s, H_3) and 6.8-7.6 (4 H, m, H_4-H_7); m/e 203(M^+) and 188(100%) (Found: C, 70.72; H, 8.67; N, 6.94. $C_{12}H_{17}NSi$ requires C, 70.88; H, 8.43; N, 6.89%).

Photochemical cleavage of 1-methyl-2-trimethysilylindole complex (7)

Photochemical decomplexation of the complex (7) (264 mg, 0.78 mmol) in acetonitrile in the usual manner afforded 1-methyl-2-trimethylsilyl-indole (9) (150 mg, 95%) as a clear oil which was identical (tlc, ir, ^1H nmr and mass spectrum) to the authentic material prepared above.

Lithiation of 1-methylindole complex under different conditions

The lithiation of 1-methylindole complex (534 mg, 2 mmol) was carried out in the manner previously described and under the conditions

outlined in Table 1 (Page 91). The reaction was quenched with chlorotrimethysilane and the usual work-up and chromatography (petrol-ether) gave the mixture of trimethylsilylated complexes (7 and 8). Photochemical decomplexation of these compounds gave a mixture of the free indoles, the composition of which was determined by integration of the relevant signals in the ^1H nmr.

General Procedure for the preparation of 7-substituted 1-methyl-2-trimethylsilylindole complexes (11)

To a solution of 1-methylindole complex (801 mg, 3 mmol) in THF (100 ml) and TMEDA (2 ml) at -78° was added n-butyllithium (3 mmol). After 1 hour, chlorotrimethylsilane (358 mg,3.3 mmol) was added and allowed to react at -78° (1 hour) before n-butyllithium (3.5 mmol) was added. After 1 hour at -78°, a solution of the dry, redistilled electrophile in THF (10 ml) was added and was allowed to react at -78° (30 minutes) before warming to room temperature. Dilute hydrochloric acid (10 ml of 1M soln.) was added and the organic layer was washed with water (3x50 ml). The aqueous layers were extracted with ether (3x25ml) and the organic phases were combined, dried and concentrated. Chromatography (eluant was a gradient of petrol-ether) gave the products described below.

Tricarbonyl-(η^6-7-ethoxycarbonyl-1-methyl-2-trimethysilylindole) chromium(0) (10)

The reaction was performed, as described above, with ethylchloroformate (400 mg, 3.7 mmol). Chromatography (petrol-ether; 100:0 to 85:15) gave a red oil which was crystallised with petrol to give the title complex (10) (825 mg, 67%) as red crystals. Recrystallisation from di-isopropylether-petrol gave analytically pure, X-Ray crystallographic material as red needles, mp 107°; γ_{max} ($CDCl_3$) 1960, 1885, 1710, 1245, 1190, 1130, 1100, 835 and 615 cm^{-1}; δ ($CDCl_3$) 0.35 (9 H, s, $SiMe_3$),

1.45 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 3.85 (3 H, s, N-Me), 4.45 (2 H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.95 (1 H, t, J=6Hz, H_5), 6.05 (1 H, d, J=6Hz), 6.5 (1 H, d, J=6Hz) and 6.55 (1 H, s, H_3); m/e 411(M^+), 355, 327(100%), 312, 275, 255, 230 and 214 (Found: C, 52.76; H, 5.16; N, 3.42. $C_{18}H_{21}CrNO_5Si$ requires C, 52.54; H, 5.14; N, 3.40%). Crystal data: Crystals of (10) $C_{18}C_{21}CrNO_5Si$ are orthorhombic, a = 23.694(6), b = 17.616(5), c = 9.683(2) Å, U = 4042 Å^3; spacegroup Pbcn, Z = 8. Of the 2080 independent reflections ($\theta \leq 50^o$) measured on a diffractometer using Cu-$K\alpha$ radiation, 560 were classified as unobserved. The structure was solved by the heavy atom method and refined anisotropically to give a current R = 0.051.

7-Ethoxycarbonyl-1-methyl-2-trimethylsilylindole (13,R=CO_2Et)

Photolytic cleavage of the complex (10) (800 mg, 1.95 mmol) gave the title compound (13, R=CO_2Et) (482 mg, 90%) as a clear oil, prep. tlc of which (petrol (30-40)-ether; 50:50) gave analytically pure material; ν_{max} ($CHCl_3$) 2950, 1700, 1440, 1360, 1340, 1300, 1200, 1100, 1070, 875 and 680 cm^{-1}; δ ($CDCl_3$) 0.4 (9 H, s, $SiMe_3$), 1.4 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 3.9 (3 H, s, N-Me), 4.4 (2 H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 6.75 (1 H, s, H_3), 7.05 (1 H, t, J=7Hz, H_5) and 7.5-7.8 (2 H, m, H_4 and H_6); m/e 275 (M^+, 100%), 260, 230 and 214 (Found: C, 65.48; H, 7.77; N, 5.05. $C_{15}H_{21}NO_2Si$ requires C, 65.41; H, 7.68; N, 5.09%).

1,7-Dimethyl-2-trimethylsilylindole (13,R=Me)

The general procedure was carried out with an excess of methyl iodide (3.0g). The usual work-up and chromatography (petrol-ether; 90:10 to 70:30) gave, by ^{1}H nmr, a mixture of 7- and 4- methylated products in the ratio of ca. 5:1. Photochemical decomplexation of this mixture and careful chromatography (petrol-ether; 100:0 to 95:5) gave a sample of pure 1,7-dimethyl-2-trimethylsilylindole (13, R=Me) as fine white needles, mp 109-110^o (from petrol at -78^o), prep. tlc of

which (petrol (30-40)-ether; 95:5) gave analytically pure material; γ_{max} ($CHCl_3$) 2950, 1450, 1305, 1110, 865, 835 and 660 cm^{-1}; δ ($CDCl_3$) 0.4 (9 H, s, $SiMe_3$), 2.75 (3 H, s, Me), 4.1 (3 H, s, N-Me), 6.6 (1 H, s, H_3) and 6.8-7.5 (3 H, m, H_4-H_6); m/e 217 (M^+) and 202(100%) (Found: C, 71.74; H, 8.85; N, 6.40. $C_{13}H_{19}NSi$ requires C, 71.83; H, 8.81; N, 6.44%).

Tricarbonyl-(η^6-1-methyl-7-(phenylhydroxymethyl)-2-trimethylsilylindole)-chromium(0) (11, R=CHOHPh)

The usual procedure was carried out with benzaldehyde (400 mg, 3.77 mmol). The usual work-up and chromatography (petrol-ether; 85:15 to 70:30) gave the title complex (840 mg, 63%) as orange prisms, mp 149°(dec.) (from petrol-ether); γ_{max} ($CDCl_3$) 3580, 1950, 1860, 1445, 1240, 1100, 1065, 830 and 620 cm^{-1}; δ ($CDCl_3$) 0.4 (9 H, d, $SiMe_3$), 3.55 and 3.75 (1 H, d, J=4Hz, disappears on addition of D_2O, OH), 3.8 and 4.1 (3 H, s, N-Me), 4.8-5.8 (2 H, m, H_5 and H_6), 6.2-6.7 (3 H, m, simplifies on addition of D_2O, H_3, H_4 and CHOHPh) and 7.2-7.6 (5 H, m, Ph); m/e 445 (M^+), 429, 361, 345, 309 and 293(100%) (Found: C, 59.22; H, 5.17; N, 3.14. $C_{22}H_{23}CrNO_4Si$ requires C, 59.31; H, 5.20; N, 3.14%).

1-Methyl-7-(phenylhydroxymethyl)-2-trimethylsilylindole (13, R=CHOHPh).

Photolytic cleavage of the complex (11, R=CHOHPh) (300 mg, 0.67 mmol) in THF gave the title compound (185 mg, 89%) as white crystals, mp 110° (from petrol at -78°), prep. tlc (petrol (30-40)-ether; 90:10) of which gave analytically pure material; γ_{max} ($CDCl_3$) 3600, 2960, 1445, 1310, 1250, 1075, 810 and 645 cm^{-1}; δ ($CDCl_3$) 0.35 (9 H, s, $SiMe_3$), 2.6 (1 H, d, J=5Hz, OH), 3.9 (3 H, s, N-Me), 6.4 (1 H, d, J=5Hz, CHOHPh), 6.65 (1 H, s, H_3) and 6.8.7.6 (8 H, m H_4-H_6 and Ph); m/e 309 (M^+, 100%) and 292 (Found: C, 73.50; H, 7.53; N, 4.37. $C_{19}H_{23}NOSi$ requires C, 73.74; H, 7.49; N, 4.53%).

Tricarbonyl-(η^6-7-(1'-hydroxyprop-2'-enyl)-1-methyl-2-trimethylsilyl-indole)chromium(0) (11, R=CHOHCH=CH_2).

The general procedure, described previously, was performed with acrolein (207 mg, 3.7 mmol). Chromatography (petrol-ether; 85:15 to 60:40) and crystallisation with petrol afforded the title complex (11, R=CHOHCH=CH_2) (710 mg, 60%) as orange crystals, mp 155° (dec.) (from petrol-ether); ν_{max} ($CDCl_3$) 3580, 2970, 1950, 1860, 1445, 1405, 1380, 1295, 1250, 1100, 1070, 980, 830 and 620 cm^{-1}; δ ($CDCl_3$) 0.35 (9 H, s, $SiMe_3$), 2.2-2.3 (1 H, m, disappears on addition of D_2O, OH), 3.85 and 4.05 (3 H, s, N-Me), 4.8-6.5 (7 H, m, H_4-H_6 and CHOHCH=CH_2) and 6.45 (1 H, s, H_3); m/e 395(M^+), 389, 339, 323, 311 (100%), 295, 259 and 243 (Found: C, 54.50; H, 5.29; N, 3.52. $C_{18}H_{21}CrNO_4Si$ requires C, 54.67; H, 5.35; N, 3.54%).

7-(1'-hydroxyprop-2'-enyl)-1-methyl-2-trimethylsilylindole (13, R=CHOHCH=CH_2)

Photolytic cleavage of the complex (11, R=CHOHCH=CH_2) (200 mg, 0.5 mmol) in THF gave the title compound as a clear unstable oil, (120 mg, 92%), prep. tlc (petrol-ether; 90:10) of which gave analytically pure material; ν_{max} ($CDCl_3$) 3590, 2960, 1445, 1400, 1300, 1060, 980, 810 and 660 cm^{-1}; δ ($CDCl_3$) 0.4 (9 H, s, $SiMe_3$), 2.05 (1 H, d, J=6Hz, OH), 4.15 (3 H, s, N-Me), 5.2-7.6 (7 H, m, H_4-H_6 and CHOHCH=CH_2) and 6.65 (1 H, s, H_3); m/e 259 (M^+) (Found: C, 69.76; H, 8.35; N, 5.24. $C_{15}H_{21}NOSi$ requires C, 69.45; H, 8.16; N, 5.40%).

Benzenesulphenyl chloride

Benzenesulphenyl chloride was prepared according to the method of Lecher and Holschneider[37], bp 72° @ 8 mmHg (Lit.[37], 73-5° (corr.) @ 9 mmHg).

Tricarbonyl-(η^6-1-methyl-7-phenylthio-2-trimethylsilylindole) chromium(0) (11, R=SPh)

The general procedure was performed with benzenesulphenyl chloride (520 mg, 3.6 mmol). Chromatography (petrol-ether; 90:10 to 70:30) gave the title complex (11, R=SPh) (680 mg, 51%) as golden-yellow crystals, mp 135-40° (dec.) (from petrol-ether); γ_{max} ($CDCl_3$) 1950, 1880, 1250, 1090, 830 and 615 cm^{-1}; δ ($CDCl_3$) 0.35 (9 H, s, $SiMe_3$), 4.0 (3 H, s, N-Me), 5.05 (1 H, m, H_5), 5.5 (1 H, m, H_6), 6.4 (1 H, m, H_4), 6.5 (1 H, s, H_3) and 7.1-7.4 (5 H, bs, Ph); m/e 447 (M^+), 363 and 311 (100%) (Found: C, 56.27; H, 4.65; N, 3.08; S, 7.50. $C_{21}H_{21}CrNO_3SSi$ requires C, 56.36; H, 4.73; N, 3.13; S, 7.16%).

1-methyl-7-phenylthio-2-trimethylsilylindole (13, R=SPh)

Photochemical decomplexation of the complex (11, R=SPh) (320 mg, 0.72 mmol) in THF gave the title compound (190 mg, 85%) as a clear oil which was crystallised from petrol (30-40) at -78° to give white crystals, mp 104.5-6°, prep. tlc (petrol(30-40)-ether; 90:10) of which gave analytically pure material; γ_{max} ($CDCl_3$) 3060, 2950, 1580, 1440, 1305, 1105, 1070, 830, 805 and 635 cm^{-1}; δ ($CDCl_3$) 0.35 (9 H, s, $SiMe_3$), 4.1 (3 H, s, N-Me), 6.7 (1 H, s, H_3) and 6.8-7.8 (8 H, m H_4-H_6 and Ph); m/e 311 (M^+, 100%) and 296 (Found: C, 69.47; H, 7.08; N, 4.33. $C_{18}H_{21}NSSi$ requires C, 69.40; H, 6.79; N, 4.50%).

3-Methylbut-2-enyl bromide (3,3-dimethyallyl bromide)

The title compound was prepared by the method of Staudinger et al[38]. A solution of hydrogen bromide in glacial acetic acid (32.4 ml of 45% w/v soln., 0.18 mol) was added dropwise to isoprene (20 ml, 0.2 mol) cooled to 0°. After the addition was complete, the reaction mixture was stirred for 30 minutes and was then poured into cold sodium hydroxide solution (300 ml of 2M soln.) The product

settled out as a lower layer and this, and dichloromethane extracts of the aqueous phase (3x25 ml) were washed with water (2x25 ml), dried and concentrated to give an orange oil (21.0g). Distillation gave 3-methylbut-2-enyl bromide (18.4g, 69%) as a clear liquid, bp 52-5° @ 45 mmHg (Lit.[38], 26-33° @ 12 mmHg).

Tricarbonyl-(η^6-1-methyl-7-(3'-methylbut-2'-enyl)-2-trimethylsilylindole)chromium(0) (11, R=$CH_2CH{=}CMe_2$)

The general procedure was carried out with 3-methylbut-2-enyl bromide (1.19g, 8 mmol). Chromatography (petrol-ether; 90:10 to 70:30) gave the title complex (11, R=$CH_2CH{=}CMe_2$) (530 mg, 43%) as bright orange crystals, mp 119-20°, (from petrol-ether); γ_{max} ($COCl_3$) 1940, 1850, 1440, 1250, 1100, 830 and 620 cm^{-1}; δ ($COCl_3$) 0.35 (9 H, s, $SiMe_3$), 1.8 (6 H, bs, $CH_2CH{=}C\underline{Me}_2$), 3.5-3.8 (2 H, m, $C\underline{H}_2CH{=}CMe_2$), 3.9 (3 H, s, N-Me), 5.0-5.5 (3 H, m, H_5, H_6 and CH_2-$C\underline{H}{=}CMe_2$), 6.15 (1 H, dd, J=6,2 Hz, H_4) and 6.4 (1 H, s, H_3); m/e 407 (M^+), 351, 328, 323 (100%) and 271 (Found: C, 59.07; H, 6.25; N, 3.38. $C_{20}H_{25}CrNO_3Si$ requires C, 58.95; H, 6.18; N, 3.44%).

1-Methyl-7-(3'-methylbut-2'-enyl)-2-trimethylsilylindole (13, R=$CH_2CH{=}CMe_2$)

Photolytic cleavage of the complex (11, R=$CH_2CH{=}CMe_2$) (200 mg, 0.49 mmol) in THF gave the title compound (102 mg, 77%) as a white crystalline solid, mp 106.5-107° (from petrol (30-40) at -78°), prep. tlc (petrol (30-40)-ether; 95:5) of which gave analytically pure material; γ_{max} ($CHCl_3$) 2960, 2920, 1440, 1305, 1110, 1070, 870, 840 and 660 cm^{-1}; δ ($COCl_3$) 0.35 (9 H, s, $SiMe_3$), 1.7 (6 H, bs, $CH_2CH{=}C\underline{Me}_2$), 3.75 (2 H, d, J=7Hz, $C\underline{H}_2CH{=}CMe_2$), 4.05 (3 H, s, N-Me), 5.3 (1 H, bs, $CH_2C\underline{H}{=}CMe_2$), 6.55 (1 H, s, H_3) and 6.8-7.6 (3 H, m, H_4-H_6); m/e 271 (M^+, 100%), 256, 216 and 198 (Found: C, 74.95; H, 9.05; N, 5.12. $C_{17}H_{25}NSi$ requires C, 75.21; H, 9.28; N, 5.16%).

Desilylation of 1-methyl-2-trimethylsilylindole (9)

To a solution of 1-methyl-2-trimethylsilylindole (1.40 g, 6.9 mmol) in carbon tetrachloride (10 ml) at 0^{o} was added a mixture (also at 0^{o}) of trifluoroacetic acid (4.0 g) and water (8.0 g) and the resulting 2-phase mixture was stirred vigorously. The reaction was followed by ^{1}H nmr and was judged to be complete after 2.5 hours. Water (10 ml) was added and the reaction mixture was neutralised with sodium bicarbonate. The aqueous layer was extracted with dichloromethane (2x10 ml) and the combined organic phases were washed with sodium bicarbonate solution (10 ml of 5% w/v soln.) and water (10 ml) before being dried and concentrated to an orange oil. Filtration through silica (type 60H) with petrol gave 1-methylindole (724 mg, 80%) as a clear oil which was identical (tlc, ^{1}H nmr and ir) with the authentic material previously prepared.

Desilylation of 7-ethoxycarbonyl-1-methyl-2-trimethylsilylindole (13, R=CO_2Et)

To a solution of 7-ethoxycarbonyl-1-methyl-2-trimethylsilylindole (623 mg, 2.27 mmol) in carbon tetrachloride (10 ml) at room temperature was added trifluoroacetic acid (3.0 g) and water (1.5 g) and the resulting 2-phase system was stirred vigorously. The reaction was followed by ^{1}H nmr and was stopped after 2 hours. A similar work-up to before and chromatography (petrol-ether; 100:0 to 85:15) gave 2 fractions:

(a) 7-ethoxycarbonyl-1-methylindole (23) (244 mg, 53%) as a clear oil, prep. tlc (petrol (30-40)-ether; 50:50) of which gave analytically pure material; ν_{max} ($CDCl_3$) 1700, 1320, 1260, 1220, 1200, 1135 and 1105 cm^{-1}; δ ($CDCl_3$) 1.4 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 3.85 (3 H, s, N-Me), 4.4 (2 H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 6.55 (1 H, d, J=3Hz, H_3), 7.0 (1 H, d, J=3Hz, H_2), 7.1 (1 H, t, J=7Hz, H_5) and 7.6-7.9 (2 H, m, H_4 and H_6); m/e

203 (M^+, 100%), 175, 174, 158 and 156 (Found: C, 70.63; H, 6.47; N, 6.70. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%).

(b) 7-ethoxycarbonyl-2-(7'-ethoxycarbonyl-1'-methylindolyl)-1-methyl-2,3-dihydroindole (25) (43 mg, 9%) as an orange oil, γ_{max} 1700, 1450, 1365, 1200, 1130 and 1095 cm^{-1}; δ ($CDCl_3$) 1.4 (6 H, qd, 2 overlapping $CO_2CH_2\underline{CH_3}$), 2.8 (3 H, s, saturated N-Me), 3.0-3.6 (2 H, m, $\underline{CH_2}CH$-Ind.), 3.85 (3 H, s, Indolic N-Me), 4.4 (4 H, m, 2 overlapping $CO_2\underline{CH_2}CH_3$), 6.7 (1 H, t, J=7Hz, $CH_2\underline{CH}$-Ind.) and 7.0-8.0 (7 H, m, Indolic H_2 and Ar.); m/e 406 (M^+) and 404 (100%) (Found: M^+ = 406.1881. $C_{24}H_{26}N_2O_4$ requires M^+ = 406.1892).

1-Methoxymethylindole

1-Methoxymethylindole was prepared in 85% yield by the method of Sundberg et al[13] to give a colourless oil, bp 88-93° @ 0.5 mmHg (Lit.[13], 69-71° @ 0.1 mmHg); γ_{max} (film) 2920, 1605, 1505, 1455, 1385, 1305, 1225, 1180, 1095, 910 and 740 cm^{-1}; δ ($CDCl_3$) 3.15 (3 H, s, OMe), 5.3 (2 H, s, $\underline{CH_2}$-OMe), 6.5 (1 H, d, J=3Hz, H_3) and 7.0-7.8 (5 H, m, H_2 and H_4-H_7); m/e 161 (M^+) and 130 (100%).

Tricarbonyl-(η^6-1-methoxymethylindole)chromium(0) (27)

Complexation of 1-methoxymethylindole (403 mg, 2.5 mmol) with chromium hexacarbonyl (500 mg, 2.27 mmol) in the usual manner afforded the title complex (27) (610 mg, 90% yield) as yellow prisms, mp 153-5° (dec.) (from THF-ether-petrol) which were almost completely insoluble in any of the common nmr solvents; γ_{max} ($CHCl_3$) 1955, 1870, 1440, 1295, 1120, 1095, 660 and 625 cm^{-1}; m/e 297 (M^+), 266, 241, 213, 183, 161 and 130 (100%) (Found: C, 52.63; H, 3.69; N, 4.74. $C_{13}H_{11}CrNO_4$ requires C, 52.53; H, 3.73; N, 4.71%).

Tricarbonyl-(η^6-2,7-di(trimethylsilyl)-1-methoxymethylindole) chromium(0) (28)

n-Butyllithium (8 mmol) was added to a solution of 1-methoxymethylindole complex (1.188 g, 4 mmol) in THF (150 ml) and TMEDA (2 ml) at -78°. After 1.5 hours, chlorotrimethylsilane (1.09 g, 10 mmol) in THF (10 ml) was added and was allowed to react at -78° (30 minutes) before being warmed to room temperature. Ether (100 ml) was added and the reaction mixture was washed with dilute hydrochloric acid (20 ml of 1 M soln.) and water (3x100 ml). The aqueous layers were extracted with ether (2x50 ml) and the combined organic phases were dried and concentrated. Chromatography (petrol-ether; 90:10 to 70:30) gave the title complex (1.447 g, 82%) as orange crystals, mp 136-9° (from THF-ether-petrol); γ_{max} ($CDCl_3$) 1950, 1870, 1375, 1250, 1200, 1160, 1110, 1080, 830 and 625 cm^{-1}; δ ($CDCl_3$) 0.35 (9 H, s, C_2-$SiMe_3$), 0.6 (9 H, s, C_7-$SiMe_3$), 3.2 (3 H, s, OMe), 4.85 (1 H, t, J=6Hz, H_5), 5.4 (2 H, q, J=11 Hz, CH_2OMe), 5.55 (1 H, d, J=6Hz, H_6), 6.5 (1 H, d, J=6Hz, H_4) and 6.6 (1 H, s, H_3); m/e 441 (M^+), 385, 357, 342 and 327 (100%) (Found: C, 51.53; H, 6.15; N, 3.17. $C_{19}H_{27}CrNO_4Si_2$ requires C, 51.68; H, 6.16; N, 3.17%).

2,7-Di(trimethylsilyl)-1-methoxymethylindole (30)

Photochemical cleavage of the complex (28) (370 mg, 0.84 mmol) in acetonitrile gave the title compound (245 mg, 96%) as white crystals, mp 57-8° (from petrol (30-40) at -78°), prep. tlc of which gave analytically pure material; γ_{max} ($CDCl_3$) 2940, 2900, 1380, 1290, 1250, 1200, 1160, 1080, 1045, 825 and 640 cm^{-1}; δ (250 MHz, $CDCl_3$) 0.38 (9 H, s, C_2-$SiMe_3$), 0.46 (9 H, s, C_7-$SiMe_3$), 3.04 (3 H, s, OMe), 5.60 (2 H, s, CH_2OMe), 6.87 (1 H, s, H_3), 7.07 (1 H, t, J=7Hz, H_5), 7.42 (1 H, dd, J=11, 1.5 Hz, H_6) and 7.62 (1 H, dd, J=11, 1.5 Hz, H_4); m/e 305 (M^+, 100%), 275, 260, 230, 215, 200 and 185 (Found: C, 63.11; H, 8.99; N, 4.68. $C_{16}H_{27}NOSi_2$ requires C, 62.89; H, 8.91; N, 4.58%).

Tricarbonyl-(η^6-1-methoxymethyl-7-trimethylsilylindole)chromium(0) (29)

n-Butyllithium (2 mmol) was added to a solution of 1-methoxymethylindole complex (594 mg, 2 mmol) in THF (80 ml) at -98° over a period of 5 minutes and was allowed to react at -98°. After 1.25 hours, a solution of freshly distilled chlorotrimethylsilane (543 mg, 5 mmol) in THF (10 ml) was added and was allowed to react at -98° (15 minutes) before being warmed to room temperature. Dilute hydrochloric acid (5 ml of 1M soln.) was added and the organic layer was washed with water (3x50 ml). The aqueous layers were extracted with ether (2x50 ml) and the organic phases were combined, dried and concentrated. Chromatography (petrol-ether; 90:10 to 60:40) gave a mixture of the 2- (26) and 7- (29) trimethysilylated complexes (722 mg, 98%). Crystallisation of this mixture with THF-ether-petrol gave the title complex (487 mg, 66% overall yield) as orange crystals, mp 121-2° (from THF-ether-petrol); ν_{max} ($CHCl_3$) 1955, 1875, 1135, 1110, 1040, 840, 660 and 625 cm^{-1}; δ ($CDCl_3$) 0.45 (9 H, s, $SiMe_3$), 3.25 (3 H, s, OMe), 4.9 (1 H, t, J=6Hz, H_5), 5.35 (2 H, q, J=12Hz, CH_2OMe), 5.45 (1 H, d, J=6Hz, H_6), 6.35 (1 H, d, J=3Hz, H_3), 6.45 (1 H, d, J=6Hz, H_4) and 7.15 (1 H, d, J=3Hz, H_2); m/e 369 (M^+), 338, 313, 285, 270 and 255 (100%) (Found: C, 51.97; H, 5.15; N, 3.77. $C_{16}H_{19}CrNO_4Si$ requires C, 52.02; H, 5.18; N, 3.79%).

1-Methoxymethyl-7-trimethylsilylindole (31)

Photolytic decomplexation of the complex (29) (400 mg, 1.08 mmol) in acetonitrile gave the title compound (225 mg, 89%) as a clear oil, prep. tlc (petrol-ether; 85:15) of which gave analytically pure material; ν_{max} ($CDCl_3$) 2940, 2900, 1520, 1410, 1375, 1300, 1250, 1210, 1185, 1090, 830 and 640 cm^{-1}; δ (250 MHz, $CDCl_3$) 0.46 (9 H, s, $SiMe_3$), 3.16 (3 H, s, OMe), 5.57 (2 H, s, CH_2OMe), 6.6 (1 H, d, J=3Hz, H_3), 7.12 (1 H, t, J=6Hz, H_5), 7.2 (1 H, d, J=3Hz, H_2), 7.44 (1 H, dd, J=10, 1.5 Hz, H_6) and 7.66 (1 H, dd, J=10, 1.5 Hz, H_4); m/e 233 (M^+), 218, 203, 188 and

144 (100%) (Found: C, 66.71; H, 8.27; N, 5.88. $C_{13}H_{19}NOSi$ requires C, 66.90; H, 8.21; N, 6.00%).

Lithiation of 1-methoxymethylindole complex under different conditions

The lithiation of 1-methoxymethylindole complex (27) with one equivalent of n-butyllithium was performed as described previously and under the conditions outlined in Table 3 (Page 109). The reaction was quenched with chlorotrimethylsilane, and the usual work-up and chromatography (petrol-ether) gave the mixture of the 2- (26) and 7- (29) trimethylsilylated complexes. Photochemical decomplexation of these complexes gave a mixture of the free indoles, the composition of which was determined by the integration of the relevant signals in the ^1H nmr.

Tricarbonyl-(η^6-1-methoxymethyl-7-(3'-methylbut-2'-enyl)indole chromium(0) (36)

To a solution of 1-methoxymethylindole complex (1.188 g, 4 mmol) in THF (150 ml) at -78^o was added n-butyllithium (4 mmol). After 1 hour, a solution of 3-methylbut-2-enyl bromide (894 mg, 6 mmol) in THF (10 ml) was added and was allowed to react at -78^o(30 minutes) before being warmed to room temperature. Water (10 ml) and ether (50 ml) were added and the organic layer was washed with water (2x50 ml). The aqueous layers were extracted with ether (2x50ml) and the organic layers were combined, dried and concentrated. Chromatography (petrol-ether; 95:5 to 60:40) gave the title complex (36) (720 mg, 49%) as bright yellow crystals, mp 102.5-103^o (from THF-ether-petrol); γ_{max} ($CDCl_3$) 2910, 1945, 1860, 1290, 1180, 1110 and 615 cm^{-1}; δ ($CDCl_3$) 1.75 (6 H, s, $CH_2CH{=}C\underline{Me}_2$), 3.25 (3 H, s, OMe), 3.7 and 3.95 (2 H, d, J=7Hz, $C\underline{H}_2CH{=}CMe_2$), 5.0-5.7 (5 H, m, H_5, H_6, $CH_2C\underline{H}{=}CMe_2$ and $C\underline{H}_2OMe$), 6.1 (1 H, dd, J=6,1 Hz, H_4), 6.35 (1 H, d, J=3Hz, H_3) and 7.15 (1 H, d, J=3Hz, H_2); m/e 365 (M^+), 309, 281 and 249 (100%) (Found: C, 59.32;

H, 5.25; N, 3.96. $C_{18}H_{19}CrNO_4$ requires C, 59.18; H, 5.24; N, 3.83%).

1-Methoxymethyl-7-(3'-methylbut-2'-enyl)indole (37)

Photochemical decomplexation of the complex (36) (440 mg, 1.2 mmol) in acetonitrile gave the title compound (37) (251 mg, 91%) as a clear oil, prep. tlc (petrol-ether; 55:45) of which gave analytically pure material; ν_{max} ($CDCl_3$) 2930, 1440, 1420, 1370, 1300, 1210, 1180, 1115, 1085 and 635 cm^{-1}; δ ($CDCl_3$) 1.75 (6 H, s, $CH_2CH=CMe_2$), 3.2 (3 H, s, OMe), 3.8 (2 H, d, J=6Hz, $CH_2CH=CMe_2$), 5.35 (1 H, t, J=6Hz, $CH_2CH=CMe_2$), 5.45 (2 H, s, CH_2OMe), 6.5 (1 H, d, J=3Hz, H_3) and 7.0-7.7 (4 H, m, H_2 and H_4-H_6); m/e 229 (M^+), 197, 182 (100%) and 154 (Found: C, 78.33; H, 8.30; N, 6.10. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35; N, 6.11%).

Tricarbonyl-(η^6-indole)chromium(0)[22] (38)

The complexation of indole (2.16 g, 18.5 mmol) with chromium hexacarbonyl (3.70 g, 16.8 mmol) under the usual conditions gave the title compound (38) (3.61 g, 85%) as yellow crystals which did not have a clear melting point, but which darkened at ca. 95°.

Tricarbonyl-(η^6-1-t-butyldimethylsilylindole)chromium(0) (39)

To a suspension of potassium hydride (440 mg, 11 mmol) (washed free of oil with dry petrol (3x25 ml)) in THF (40 ml) was added a solution of indole complex (38) (2.0 g, 7.9 mmol) in THF (60 ml). After the evolution of hydrogen had ceased (ca. 15 minutes), a solution of t-butyldimethylsilylchloride (1.21 g, 8 mmol) in THF (10 ml) was added. Tlc (dichloromethane) indicated that the reaction was complete within 5 minutes and the excess potassium hydride was quenched with a mixture of aqueous pH=7 buffer solution and THF (20:80,25 ml). The organic layer was washed with buffer solution (25 ml) and water (3x25 ml). The aqueous layers were extracted with ether (2x25 ml)

and the organic phases were combined, dried and concentrated to ca. 10 ml. Crystallisation with the aid of petrol afforded the title complex (39) (2.41 g, 83%) as bright yellow crystals, mp 143° (dec.) (from ether-petrol); γ_{max} (ether) 1945, 1870, 1020, 665 and 625 cm^{-1}; δ ($CDCl_3$) 0.55 (3 H, s, SiMeMeBu^t), 0.75 (3 H, s, SiMeMeBu^t), 0.95 (9 H, s, $SiMe_2Bu^t$), 4.9-5.4 (2 H, m, H_5 and H_6), 6.0-6.3 (2 H, m, H_4 and H_7), 6.35 (1 H, d, J=4Hz, H_3) and 7.15 (1 H, d, J=4Hz, H_2); m/e 367 (M^+), 311, 283 (100%), 231 and 227 (Found: C, 55.53; H, 5.75; N, 3.80. $C_{17}H_2CrNO_3Si$ requires C, 55.57; H, 5.76; N, 3.81%).

Tri-isopropylsilylchloride[24]

Tri-isopropylsilane, prepared in 70% yield by the method of Namektin et al[39], (85.5 g, 0.54 mol) and anhydrous copper(II) chloride (160.1 g, 1.19 mol) were heated at reflux in dry acetonitrile for 16 hours. After cooling, the reaction mixture was extracted with dry petrol (4x150 ml). Concentration and distillation gave tri-isopropylsilylchloride (83.97 g,81%) as a clear liquid, bp 68-70° @ 7 mmHg (Lit., 88-92° @ 18 mmHg[24]; 82-5° @ 15 mmHg[40]).

Preparation of tricarbonyl-(η^6-1-tri-isopropylsilylindole)chromium(0) (41) via the indole complex (38)

Using a similar procedure to that described for the preparation of complex (39), indole complex (38) (2.10 g,8.3 mmol) was reacted with potassium hydride (530 mg, 13.3 mmol) and tri-isopropylsilylchloride (1.93 g, 10 mmol). A similar work-up to before and crystallisation with the aid of petrol gave tricarbonyl-(η^6-1-tri-isopropylsilylindole) chromium(0) (41) (3.05 g, 90%) as bright yellow cystals, mp 138-40° (from di-isopropylether-ether-petrol); γ_{max}($CHCl_3$) 2950, 2870, 1955, 1860, 1430, 1270, 1140, 1105, 880 and 630 cm^{-1}; δ(250 MHz, $CDCl_3$) 1.2 (18 H, d, $Si(CHMe_2)_3$), 1.7 (3 H, m, $Si(CHMe_2)_3$), 5.15 (1 H, t, J=6Hz), 5.3 (1 H, t, J=6Hz), 6.25 (2 H, d, J=6Hz, H_4 and H_7), 6.45 (1 H, d,

J=4Hz, H_3) and 7.3 (1 H, d, J=4Hz, H_2); m/e 409 (M^+), 325, 273 and 230 (100%) (Found: C, 58.85; H, 6.69; N, 3.43. $C_{20}H_{27}CrNO_3Si$ requires C, 58.65; H, 6.65; N, 3.42%).

1-Tri-isopropylsilylindole (42)

n-Butyllithium (30 mmol) was added to a solution of indole (2.93 g, 25 mmol) in THF (70 ml) at -20°. After 1 hour, a solution of tri-isopropylsilylchloride (5.78 g, 30 mmol) in THF (20 ml) was added and was allowed to react at -20° (1 hour) before being warmed to room temperature. The solution was concentrated to ca. 30 ml and was washed with water (2x50 ml). The aqueous layers were extracted with ether (2x25 ml) and the organic phases were combined, dried and concentrated. Distillation of this compound (bp 140° @ 0.2 mmHg) led to an excessive loss of product (54% yield). Traces of solvent and other volatile impurities were removed from the crude product by heating (ca. 60°) under vacuum for 15 hours to give the title compound (6.85 g, 100%), identical (ir and ^1H nmr) to the distilled material, as a red oil, prep. tlc (petrol (30-40)-ether; 95:5) of which gave analytically pure material; ν_{max} ($CHCl_3$) 2940, 2870, 1520, 1450, 1270, 1140, 1015, 885, 740, 690 and 660 cm^{-1}; δ ($CDCl_3$) 1.1 (18 H, d, J=8Hz, $Si(CH\underline{Me}_2)_3$), 1.4-2.0 (3 H, m, $Si(C\underline{H}Me_2)_3$), 7.55 (1 H, d, J=3Hz, H_3) and 6.95-7.7 (5 H, m, H_2 and H_4-H_7); m/e 273 (M^+), 230 (100%), 202, 188, 174 and 160 (Found: C, 74.36; H, 10.05; N, 5.15. $C_{17}H_{27}NSi$ requires C, 74.66; H, 9.95; N, 5.12%).

Complexation of 1-tri-isopropylsilylindole

The reaction of distilled 1-tri-isopropylsilylindole (42) (683 mg, 2.5 mmol) and chromium hexacarbonyl (500 mg, 2.27 mmol) under the usual conditions afforded 1-tri-isopropylsilylindole complex (41) (809 mg, 87%) and reaction of the crude 1-tri-isopropylsilylindole (1.49 g, 5.46 mmol) with chromium hexacarbonyl (1.0 g, 4.55 mmol) gave

the same complex (41) (1.58 g, 85%) as bright yellow crystals, mp 137-9° (dec.) (from ether-petrol), with the same spectral properties as those reported previously (Found: C, 58.91; H, 6.62; N, 3.40. Calc. for $C_{20}H_{27}CrNO_3Si$ C, 58.65; H, 6.65; N, 3.42%).

General procedure for the preparation of 4-substituted 1-tri-isopropylsilylindole complexes (57)

n-Butyllithium (4 mmol) was added to a solution of 1-tri-isopropylsilylindole complex (41) (818 mg, 2 mmol) in THF (70 ml) and TMEDA (1 ml) at -78°. After 3 hours, a solution of dry, redistilled electrophile in THF (10 ml) was added and was allowed to react at -78° (15 minutes) before being warmed to room temperature. Aqueous ammonium chloride solution (10 ml of 15% w/v soln.) was added and the organic layer was washed with water (3x25 ml). The aqueous layers were extracted with ether (2x25 ml) and the organic phases were combined, dried and concentrated. Chromatography (eluant was a gradient of petrol-dichloromethane) gave the crude isomeric mixture of products. Crystallisation of this mixture with petrol gave the 4-substituted complex (57).

Tricarbonyl-(η^6-4-ethoxycarbonyl-1-tri-isopropylsilylindole) chromium(0) (44)

Complex (41) (409 mg, 1 mmol) was lithiated as described above and was reacted with an excess of ethylchloroformate (2 ml). The usual work-up and chromatography (petrol-dichloromethane; 80:20 to 50:50) and crystallisation gave the title complex (289 mg, 60%) as orange-red crystals, mp 134-6° (from THF-ether-petrol); ν_{max} ($CDCl_3$) 2950, 2870, 1960, 1880, 1705, 1280, 1150, 1090 and 1010 cm^{-1}; δ ($CDCl_3$) 1.0-2.0 (21 H, m, Si(i-Pr)$_3$), 1.5 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 4.4 (2 H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 5.05 (1 H, t, J=6Hz, H_6), 5.95 (1 H, d, J=6Hz, H_5), 6.4 (1 H, d, J=6Hz, H_7), 7.0 (1 H, d, J=3Hz, H_3) and 7.35 (1 H, d, J=3Hz, H_2); m/e 481 (M^+), 397 (100%), 345, 326 and

302 (Found: C, 57.41; H, 6.49; N, 2.89. $C_{23}H_{31}CrNO_5Si$ requires C, 57.36; H, 6.49; N, 2.91%).

4-Ethoxycarbonyl-1-tri-isopropylsilylindole (53)

Photolytic cleavage of the complex (44) (250 mg, 0.52 mmol) in THF gave the title compound (150 mg, 84%) as a clear oil, prep. tlc (petrol(30-40)-ether; 50:50) of which gave analytically pure material; ν_{max} ($CDCl_3$) 2940, 2870, 1690, 1440, 1280, 1150, 1095 and 1015 cm^{-1}; δ (250 MHz, $CDCl_3$) 1.15 (18 H, d, J=7Hz, $Si(CH\underline{Me}_2)_3$), 1.47 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH}_3$), 1.72 (3 H, h, $Si(\underline{CH}Me_2)_3$), 4.46 (2 H, q, J=7Hz, $CO_2\underline{CH}_2CH_3$), 7.2 (1 H, t, J=6Hz, H_6), 7.33 (1 H, dd, J=3, 0.8 Hz, H_3), 7.4 (1 H, d, J=3Hz, H_2), 7.71 (1 H, dt, J=7, 0.8 Hz, H_7) and 7.93 (1 H, dd, J=7,0.8 Hz, H_5); m/e 345 (M^+), 302 (100%), 274 and 256 (Found: C, 69.47; H, 9.04; N, 4.24. $C_{20}H_{31}NO_2Si$ requires C, 69.52; H, 9.04; N, 4.05%).

4-Ethoxycarbonylindole (54)

To a solution of 4-ethoxycarbonyl-1-tri-isopropylsilylindole (53) (110 mg, 0.32 mmol) in THF (5 ml) at 0° was added TBAF (0.7 ml of a 1 M soln., 0.7 mmol). Tlc indicated that reaction was complete within 5 minutes. Dichloromethane (10 ml) was added and the reaction mixture was washed with water (3x10 ml). The aqueous layers were extracted with dichloromethane (10 ml) and the organic phases were combined, dried and concentrated. Chromatography (petrol-dichloromethane) afforded 4-ethoxycarbonylindole (60 mg, 100%) as white crystals, mp 70-1° (from ethanol-petrol) (Lit.[41], 70-1°); ν_{max} ($CDCl_3$) 3480, 1700, 1340, 1270, 1180, 1145 and 1070 cm^{-1}; δ ($CDCl_3$) 1.45 (3 H, t, J=7Hz, $CO_2CH_2\underline{CH}_3$), 4.4 (2 H, q, J=7Hz, $CO_2\underline{CH}_2CH_3$), 7.0-8.0 (5 H, m, H_2, H_3 and H_5-H_7) and 8.2-8.8 (1 H, bs, NH); m/e 189 (M^+, 100%), 174, 161 and 144.

Tricarbonyl-(η^6-1-tri-isopropylsilyl-4-trimethysilylindole) chromium(0) (45)

1-Tri-isopropylsilylindole complex (41) (818 mg, 2 mmol) was lithiated using the usual procedure and was reacted with chlorotrimethylsilane (500 mg, 4.6 mmol) to give, after work-up, chromatography (petrol-dichloromethane; 90:10 to 70:30) and crystallisation, the title complex (45) (540 mg, 56%) as orange crystals, mp 145° (dec.) (from ether-petrol); γ_{max} ($CHCl_3$) 2950, 2870, 1950, 1865, 1370, 1135, 840 and 625 cm^{-1}; δ ($CDCl_3$) 0.45 (9 H, s, $SiMe_3$), 1.0-2.0 (21 H, m, Si(i-Pr)$_3$), 4.8-5.3 (2 H, m, H_5 and H_6), 6.4 (2 H, m, H_3 and H_7) and 7.35 (1 H, d, J=4Hz, H_2); m/e 481 (M^+), 425, 397, 345 (100%), 302 and 238 (Found: C, 57.63; H, 7.36; N, 2.92. $C_{23}H_{35}CrNO_3Si_2$ requires C, 57.34; H, 7.32; N, 2.91%).

1-Tri-isopropylsilyl-4-trimethylsilylindole (46)

Photochemical decomplexation of the complex (45) (260 mg, 0.54 mmol) in THF gave the title compound (46) (173 mg, 93%) as a colourless oil, prep. tlc (petrol (30-40)-ether; 95:5) of which gave analytically pure material; γ_{max} ($CDCl_3$) 2920, 2870, 1395, 1275, 1145, 1020 and 830 cm^{-1}; δ (250 MHz, $CDCl_3$) 0.4 (9 H, s, $SiMe_3$), 1.15 (18 H, d, J=7Hz, Si($CHMe_2$)$_3$), 1.7 (3 H, m, Si($CHMe_2$)$_3$), 6.75 (1 H, dd, J=3,0.8 Hz, H_3), 7.13 (1 H, t, J=6Hz, H_6), 7.25-7.3 (2 H, m, H_2 and H_5) and 7.54 (1 H, dt, J=6,0.8 Hz, H_7); m/e 345 (M^+, 100%), 330 and 302 (Found: C, 69.21; H, 10.15; N, 3.89. $C_{20}H_{35}NSi_2$ requires C, 69.49; H, 10.21; N, 4.05%).

4-Trimethylsilylindole (56)

To a solution of complex (45) (300 mg, 0.62 mmol) in THF (5 ml) at 0° was added TBAF (1.2 ml of a 1M soln., 1.2 mmol). Tlc indicated that reaction was complete within 10 minutes. Dichloromethane (20 ml) was added and the reaction mixture was washed with water (3x10 ml). The aqueous layers were extracted with dichloromethane (10 ml) and

the organic phases were combined, dried and concentrated. Decomplexation with pyridine followed by chromatography (petrol-ether; 90:10 to 50:50) gave the title compound (56) (101 mg, 86%) as white crystals, mp 65-6° (from petrol) which was not depressed on mixing with a sample of 4-trimethylsilyl indole prepared via an alternative route[42]. Prep. tlc and crystallisation (from petrol(30-40) at -78°) of this compound afforded analytically pure material; ν_{max} ($CDCl_3$) 3490, 1395, 1345, 1260, 1155, 1140, 1100, 835 and 640 cm^{-1}; δ (250 MHz, $CDCl_3$) 0.4 (9 H, 3, $SiMe_3$), 6.68 (1 H, bs, H_3), 7.15-7.3 (3 H, m, H_2, H_5 and H_6), 7.4 (1 H, d, J=6Hz, H_7) and 8.1-8.2 (1 H, bs, NH); m/e 189 (M^+) and 174 (100%) (Found: C, 69.78; H, 8.01; N, 7.36. $C_{11}H_{15}NSi$ requires C, 69.78; H, 7.99; N, 7.40%).

Tricarbonyl-(η^6-4-methoxycarbonyl-1-tri-isopropylsilylindole) chromium(0) (57, R=CO_2Me)

Complex (41) was lithiated by the usual procedure and was reacted with methychloroformate (500 mg, 5.3 mmol). The usual work-up and chromatography (petrol-dichloromethane; 85:15 to 70:30) gave a red oil (760 mg) which was crystallised with petrol-ether to give the title complex (550 mg, 59%) as red crystals, mp 100-1° (from petrol-ether); ν_{max} ($CDCl_3$) 2940, 2870, 1960, 1880, 1710, 1420, 1285, 1190, 1150, 1095 and 1015 cm^{-1}; δ ($CDCl_3$) 1.0-2.0 (21 H, m, Si(i-Pr)$_3$), 4.0 (3 H, s, CO_2Me), 5.1 (1 H, t, J=6Hz, H_6), 6.0 (1 H, d, J=6Hz, H_5), 6.5 (1 H, d, J=6Hz, H_7), 7.1 (1 H, d, J=3Hz) and 7.45(1 H, d, J=3Hz); m/e 467 (M^+), 411, 383(100%), 331 and 288 (Found: C, 56.74; H, 6.33; N, 2.96. $C_{22}H_{29}CrNO_5Si$ requires C, 56.51; H, 6.25; N, 3.00%).

4-Methoxycarbonylindole (58, R=CO_2Me)

Desilylation of the complex (57, R=CO_2Me) (280 mg, 0.6 mmol) in THF (5 ml) with TBAF (1.2 ml of 1M soln., 1.2 mmol) under the usual conditions followed by decomplexation with refluxing pyridine and chromatography (petrol-dichloromethane; 100:0 to 0:100) afforded

4-methoxycarbonylindole (58,R=CO_2Me) (85 mg, 81%) as white crystals, mp 68-9° (from methanol-petrol) (Lit. [41, 43, 64°, 67-9°]); γ_{max} ($CDCl_3$) 3470, 1700, 1430, 1335, 1270, 1190, 1140 and 1070 cm^{-1}; δ ($CDCl_3$) 3.9 (3 H, s, CO_2Me), 7.0-8.0 (5 H, m, H_2, H_3 and H_5-H_7) and 8.3-9.0 (1 H, bs, NH); m/e 175 (M^+), 144(100%) and 116.

4-Phenythioindole (58, R=SPh)

1-Tri-isopropylsilylindole complex (41) (1.636 g, 4 mmol) was lithiated by the conditions described previously and was reacted with benzenesulphenyl chloride (1.20 g, 8.3 mmol). The usual work-up and chromatography (petrol (60-80)-dichloromethane; 90:10 to 70:30) gave an orange oil (1.55 g) which was unstable and could not be induced to crystallise. Desilylation of this material in THF (15 ml) with TBAF (5 ml of 1 M soln., 5 mmol) followed by photochemical decomplexation and chromatography (petrol-ether; 85:15 to 70:30) gave the title compound (58,R=SPh) (230 mg, 26%) as a yellow oil, prep. tlc (petrol (30-40)-ether; 50:50) of which gave analytically pure material; γ_{max} ($CDCl_3$) 3480, 1580, 1410, 1330, 1190, 1135, 1100, 1070, 1030, 850 and 640 cm^{-1}; δ (250 MHz, $CDCl_3$) 6.54 (1 H, m, H_3), 7.1-7.3 (8 H, m, H_2, H_5, H_6 and Ph), 7.35 (1 H, dt, J=7, 0.8Hz, H_7) and 8.1-8.3 (1 H, bs, NH); m/e 225 (M^+, 100%) (Found: C, 74.52; H, 4.97; N, 6.18. $C_{14}H_{11}NS$ requires C, 74.63; H, 4.92; N, 6.22%).

Tricarbonyl-(η^6-4-(3'-methylbut-2'-enyl)-1-tri-isopropylsilylindole) chromium(0) (57,R=$CH_2CH{=}CMe_2$)

1-Tri-isopropylsilylindole complex (41) (1.636 g, 4 mmol) was lithiated, as previously, and was reacted with 3-methylbut-2-enyl bromide (2.40 g, 16 mmol). The usual work-up, chromatography (petrol (60-80)-dichloromethane; 95:5 to 80:20) and crystallisation of the first fractions gave the title complex (689 mg, 36%) as orange crystals, mp 112-113.5° (from ether-petrol); γ_{max} ($CDCl_3$) 2930, 2880, 1945, 1860, 1445, 1420, 1270, 1145, 1105 and 1010 cm^{-1}; δ ($CDCl_3$) 1.0-2.0 (21 H, m,

Si(i-Pr)$_3$), 1.8 (6 H, s, $CH_2CH=CMe_2$), 3.6 (2 H, bd, J=8Hz, $CH_2CH=CMe_2$), 4.9-5.4 (3 H, m, H_5, H_6 and $CH_2CH=CMe_2$), 6.1 (1 H, d, J=6Hz, H_7), 6.45 (1 H, d, J=4Hz, H_3) and 7.25 (1 H, d, J=4Hz, H_2); m/e 477(M^+), 461, 393 and 341(100%) (Found: C, 63.19; H, 7.44; N, 2.94. $C_{25}H_{35}CrNO_3Si$ requires C, 62.87; H, 7.39; N, 2.93%).

4-(3'-Methylbut-2'-enyl)indole (58, R = $CH_2CH=CMe_2$)

The complex (57, R = $CH_2CH=CMe_2$) (240 mg, 0.5 mmol) was desilylated with TBAF (0.8 ml of 1M soln., 0.8 mmol) and the product was photochemically decomplexed in acetonitrile to give, after purification by prep. tlc (petrol(30-40)-ether; 70:30), the title compound (88 mg, 95%) as a clear oil which had the same spectral properties (^{1}H nmr and ir) as those reported by Plieninger et al[44]; γ_{max} (CCl_4) 3490, 2980, 2910, 2880, 1500, 1430, 1405, 1335, 1145, 1100, 1075, 900 and 715 cm^{-1}; δ (CCl_4) 1.7 (6 H, s, $CH_2CH=CMe_2$), 3.55 (2 H, d, J=7Hz, $CH_2CH=CMe_2$), 5.35 (1 H, m, $CH_2CH=CMe_2$), 6.4 (1 H, m, H_3), 6.6-7.1 (4 H, m, H_2 and H_5-H_7) and 7.2-7.6 (1 H, bs, NH); m/e 185 (M^+), 170, 155, 154, 143, 130 and 117.

3-(Dimethylaminomethyl)indole (gramine)

3-(Dimethylaminomethyl)indole was prepared in 97% yield by the method of Snyder et al[45] and was dried in a vacuum oven at 60° to give material with mp 126-8° (Lit.[45] 127-8°).

3-(Dimethylaminomethyl)-1-tri-isopropylsilylindole (61)

3-(Dimethylaminomethyl)indole (871 mg, 5 mmol) was N-tri-isopropylsilylated using the same procedure as that described for indole (Page 152) to give the title compound (61) (1.63 g, 99%) as an orange oil, prep. tlc (alumina F-254 (Type E); developing solvent, petrol-ether; 50:50) of which gave analytically pure material; γ_{max} ($CDCl_3$) 2930, 2870, 1445, 1305, 1135, 1015, 850 and 640 cm^{-1}; δ ($CDCl_3$) 1.0-2.0 (21 H, m, Si(i-Pr)$_3$), 2.25 (6 H, s, NMe_2), 3.6 (2 H, s,

$C\underline{H}_2NMe_2$) and 7.8–7.8 (5 H, m, H_2 and H_4–H_7); *m/e* 330(M^+) and 286(100%) (Found: C, 72.46; H, 10.46; N, 8.62. $C_{20}H_{34}N_2Si$ requires C, 72.66; H, 10.37; N, 8.47%).

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