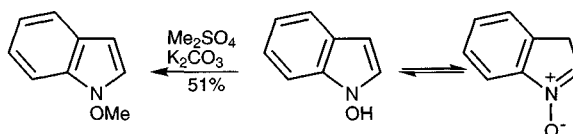
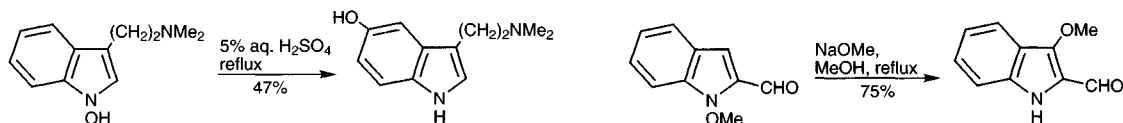


17.14.4 1-Hydroxyindole²¹³

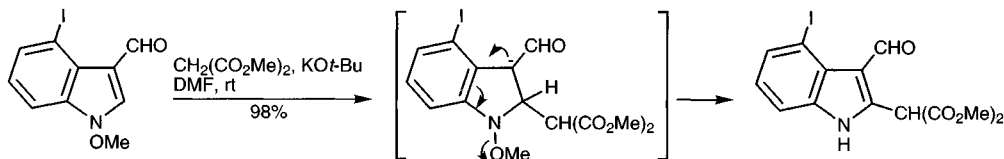
1-Hydroxyindole can be prepared in solution, but attempted purification leads to dimerisation *via* its nitron tautomer, however *O*-alkyl derivatives can be formed easily and are stable.²¹⁴



1-Hydroxy- and 1-alkoxyindoles are being developed for various synthetic purposes; for example lithiation of 1-methoxyindole takes place at C-2 and thus substituents can be introduced. More importantly, various nucleophilic substitutions, with departure of the 1-substituent take place. One of the reactions below shows the introduction of a hydroxy group onto the indole 5-position by an acid-catalysed reaction of a 1-hydroxyindole.²¹⁵ 1-Methoxy groups allow nucleophilic attack on the heterocyclic ring, as illustrated by the second example.²¹⁶

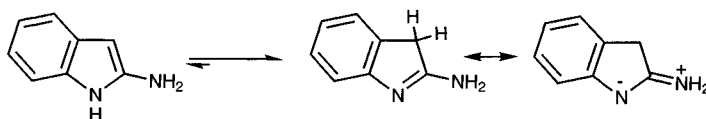


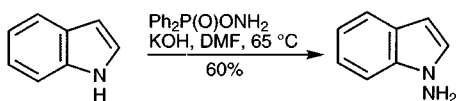
Cine-nucleophilic substitution of methoxy in 1-methoxy-3-formylindole produces the 2-substituted product.²¹⁷



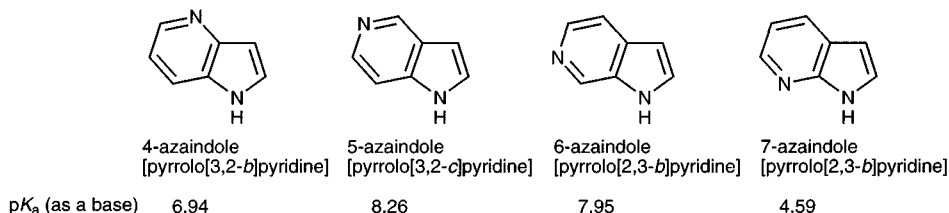
17.15 Aminoindoles

2-Aminoindole exists mainly as the *3H*-tautomer, presumably because of the energy advantage conveyed by amidine-type resonance. 3-Aminoindole is very unstable, and easily autoxidised²¹⁸ however its acetamide is stable (section 17.1.2). 1-Aminoindoles can be prepared by direct amination of the indolyl anion.²¹⁹

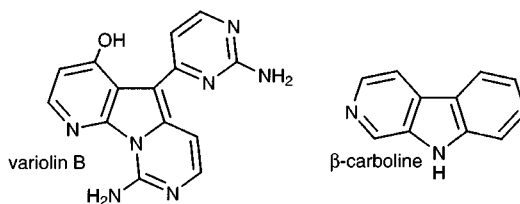




17.16 Azaindoles²²⁰



The (mono)-azaindoles, or more correctly pyrrolopyridines, where a carbon of the six-membered ring has been replaced by nitrogen, are of theoretical interest as prototypes of bicyclic systems comprising an electron-rich ring fused to an electron-poor ring. The simple systems do not occur in nature, but polycyclic compounds, such as the variolins have been isolated from sponges. Simple azaindoles have been isolated from coal tar and the oxidative degradation of carboline alkaloids. They have elicited significant interest in medicinal chemistry as isosteres of indoles, particularly as components of azatryptamine analogues and even as di-deazapurines.



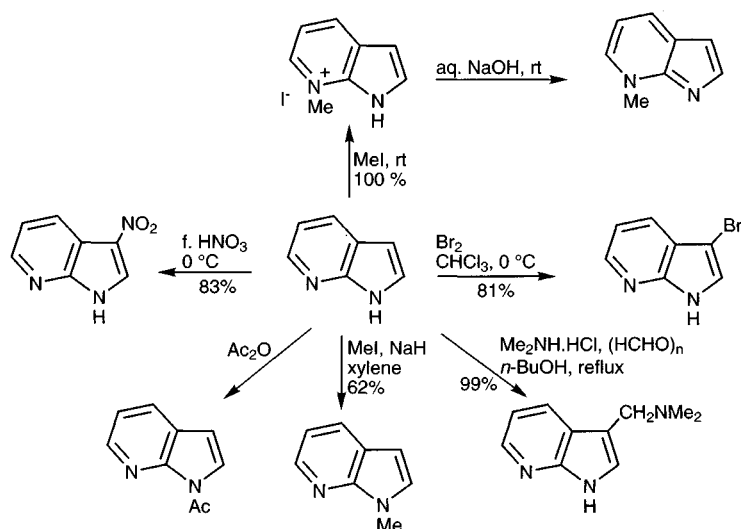
Azaindoles show the typical reactivity of both component systems but to a reduced and varying degree, with reduced electron density in the five-membered ring and increased electron density in the six-membered ring.

The differential pK_a s for protonation on the pyridine nitrogen, of the four parent systems, demonstrate the degree of push-pull interaction between the two rings. For example, the pK_a s of 5- and 7-azaindoles reflect, but to a greater degree, the pK_a s of 4-aminopyridine (9.1) and 2-aminopyridine (7.2) respectively and are partly explained by the more favourable γ -interaction between the donating and accepting groups in the former. This differential reactivity is exaggerated in mildly acidic solutions such as are used in Mannich reactions, where the 5-azaindole is present predominantly in protonated form while the 7-azaindole is mainly present in the form of its free base.



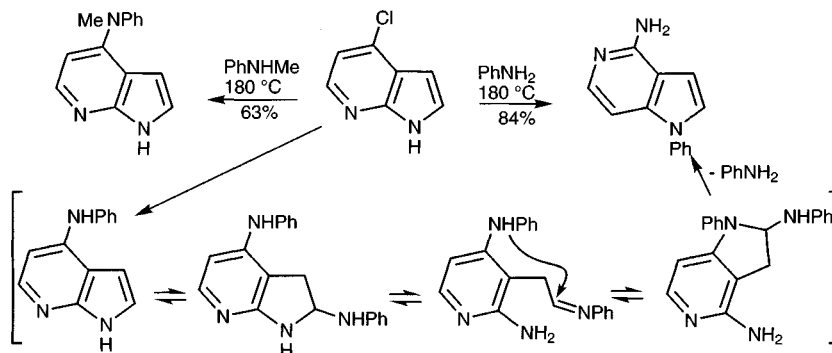
17.16.1 Electrophilic substitution

Reactions with electrophilic reagents takes place with substitution at C-3 or by addition at the pyridine nitrogen. All the azaindoles are much more stable to acid than indole (*cf.* section 17.1.1) no doubt due to the diversion of protonation onto the pyridine nitrogen, but the reactivity towards electrophiles at C-3 is only slightly lower than that of indoles. Bromination and nitration occur cleanly in all four parent systems²²¹ and are more controllable than in the case of indole. Mannich and Vilsmeier reactions can be carried out in some cases, but when the latter fails, 3-aldehydes can be prepared by reaction with hexamine, possibly via the anion of the azaindole. Alkylation under neutral conditions results in quaternisation on the pyridine nitrogen and reaction with sodium salts allows *N*-1-alkylation. Acylation under mild conditions also occurs at N-1. The scheme below summarises these reactions for the most widely studied system – 7-azaindole.



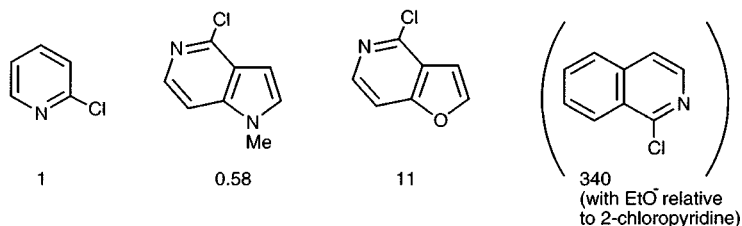
17.16.2 Nucleophilic substitution

Only a few examples of nucleophilic substitution have been reported – displacement of halogen α and γ to the pyridine nitrogen can be carried out under vigorous conditions or long reaction times. No Chichibabin substitutions have been reported. Reaction of 4-chloro-7-azaindole with a secondary amine results in normal substitution of the halogen but reaction with primary amines gives 5-azaindole rearrangement products by the sequence shown below.²²²

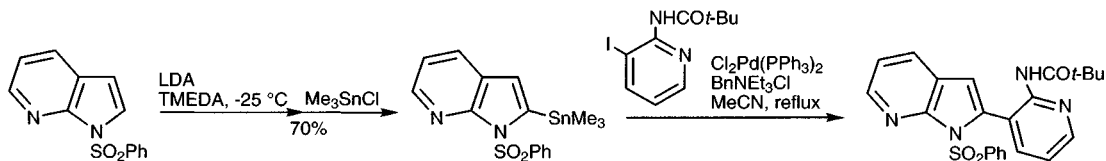


The reactivity of 4-chloro-1-methyl-5-azaindole, for which data is available, towards nucleophilic substitution of chlorine by piperidine²²³ can be usefully compared with that of some related systems: it is significantly less reactive than the most closely related bicyclic systems, probably due to increased electron density in the six-membered ring resulting from donation from N-1.

Relative rates for nucleophilic displacement with piperidine
in $\text{MeO}(\text{CH}_2)_2\text{OH}$ at 100°C ²²⁴



1-Phenylsulfonyl-7-azaindole is lithiated at C-2 by lithium diisopropylamide; subsequent reactions of the lithiated azaindole are normal; that shown is the formation of a stannane and its subsequent coupling.²²⁵



17.17 Synthesis of indoles

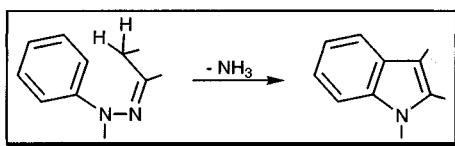
17.17.1 Ring synthesis

Indoles are usually prepared from non-heterocyclic precursors by cyclisation reactions on suitably substituted benzenes; they can also be prepared from pyrroles by construction of the homocyclic aromatic ring, and from indolines by dehydrogenation.

Because of the importance of indoles in natural products synthesis and pharmaceutical chemistry, many new routes to indoles and improvements of older reactions have been developed since the last edition of this book. This section discusses the most important methods now available, often those which have been used most frequently and are the most adaptable.²²⁶

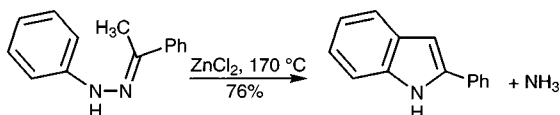
17.17.1.1 From phenylhydrazones of aldehydes and ketones

Still the most widely used route, the Fischer synthesis consists of heating an arylhydrazone, usually with acid, sometimes in an inert solvent; ammonia is lost and an indole formed.



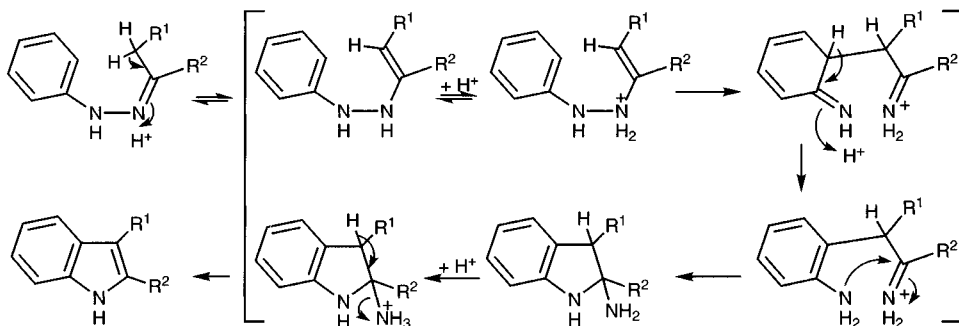
The Fischer synthesis

The Fischer synthesis,²²⁷ first discovered in 1883, involves the acid- or Lewis acid-catalysed rearrangement of a phenylhydrazone with the elimination of ammonia. The preparation of 2-phenylindole illustrates the process in its simplest form.²²⁸

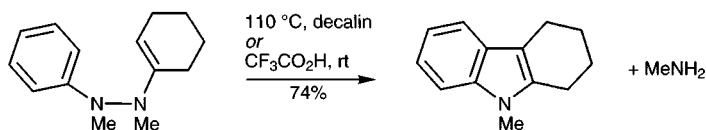


In many instances the reaction can be carried out simply by heating together the aldehyde or ketone and phenylhydrazine in acetic acid;²²⁹ the formation of the phenylhydrazone and its subsequent rearrangement take place without the necessity for isolation of the phenylhydrazone. Toluenesulfonic acid, cation exchange resins, and phosphorus trichloride have each been recommended for efficient cyclisations, sometimes even at or below room temperature.²³⁰ Electron-releasing substituents on the benzene ring increase the rate of Fischer cyclisation whereas electron-withdrawing substituents slow the process down,²³¹ though even phenylhydrazones carrying nitro-groups can be indolised satisfactorily with appropriate choice of acid and conditions, for example a two-phase mixture of toluene and phosphoric acid,²³² or boron trifluoride in acetic acid.²³³ Electron-withdrawing substituents *meta* to the nitrogen give rise to roughly equal amounts of 4- and 6-substituted indoles; electron-releasing groups similarly oriented produce mainly the 6-substituted indole.¹⁶⁵

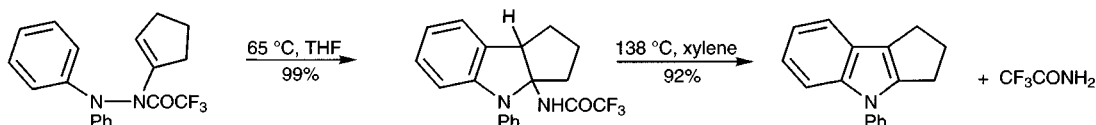
The full mechanistic details of the multi-step Fischer sequence are still not completely sure, but there is considerable evidence that the sequence shown below operates, for example labelling studies proved the loss of the β -nitrogen as ammonia, and in some cases intermediates have been detected by ^{13}C and ^{15}N NMR spectroscopy.²³⁴ The most important step – the one in which a carbon–carbon bond is made – is electrocyclic in character and analogous to the Claisen rearrangement of phenyl allyl ethers.



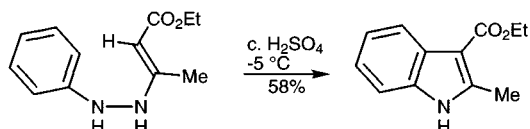
Support for this sequence also comes from the observation that in many cases indolisation can be achieved thermally, at a temperature as low as 110 °C, in the special case of preformed ene-hydrazines, i.e. in which the first step of the normal sequence – acid-catalysed tautomerisation of imine to enamine – has already been accomplished.²³⁵ The reaction does however still occur more rapidly in the presence of acid and this is interpreted as protonation of the β -nitrogen, as shown, facilitating the electrocyclic step.



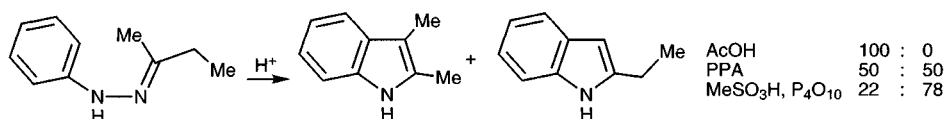
Fischer cyclisations can be achieved thermally, but generally much higher temperatures are required and proton transfer from solvent (typically a glycol) may be involved. However, using preformed *N*-trifluoroacetyl ene-hydrazines allows thermal cyclisation at temperatures as low as 65 °C.²³⁶ As the example below shows, in the case of derivatives of cyclopentanones, the 2-aminoindoline intermediates can be isolated at lower temperatures; subsequent elimination of trifluoroacetamide is easy and efficient.



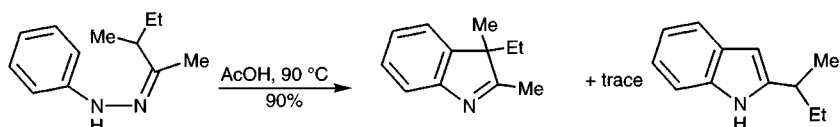
An extreme case of acid catalysis is the indolisation of phenylhydrazones of β -dicarbonyl compounds in concentrated sulfuric acid;²³⁷ in milder acid, only pyrazolones are produced from the interaction of β -keto-esters with hydrazines (section 22.13.1.1).



An aspect of the Fischer reaction which is of considerable practical importance is the ratio of the two possible indoles formed from unsymmetrical ketones; in many instances mixtures result because ene-hydrazine formation occurs in both directions. It appears that strongly acidic conditions favour the least substituted ene-hydrazine.²³⁸

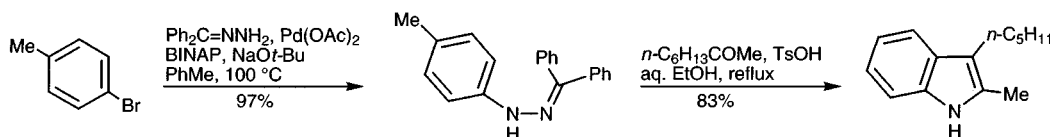


Indolenines (3*H*-indoles) are formed efficiently on Fischer cyclisation of the phenylhydrazones of branched ketones; note, again, the use of a weaker acid medium to promote formation of the more substituted ene-hydrazine required for indolenine formation.²³⁹ In another example, addition of sodium acetate to the acetic acid reaction medium promoted indolenine formation from the phenylhydrazone of 1-decalone.²⁴⁰



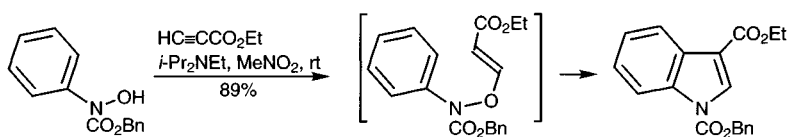
An important extension to the Fischer synthesis is the preparation of arylhydrazines by palladium-catalysed coupling of benzophenone hydrazone with aryl halides – this allows the convenient preparation of a much wider range of

arylhazines than the classical method involving the reduction of diazonium salts. The benzophenone arylhydrazone can be hydrolysed to the hydrazine, but even more conveniently used directly in the Fischer cyclisation where exchange occurs with the ketone. The whole process, from arylhalide to indole, can be carried out in one pot without isolation of any intermediates.²⁴¹



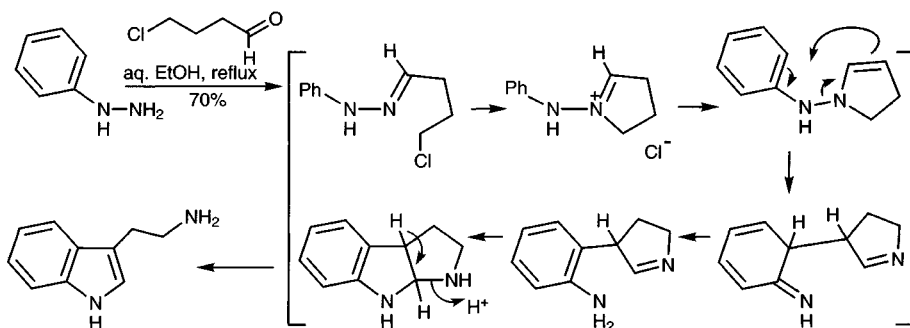
Another way of making arylhydrazines is the electrophilic amination of electron-rich arenes with an azodicarboxylate.¹⁵

Transformations which are mechanistically analogous to the Fischer, and also produce indoles, use phenylhydroxylamines instead of phenylhydrazines, as shown below.²⁴²



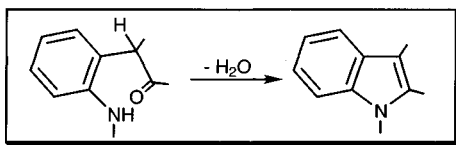
The Grandberg synthesis

An exceptionally useful adaptation is the Grandberg synthesis of tryptamines from 4-halobutanals, or more often in practice their acetals,²⁴³ in which the nitrogen usually lost during the Fischer process is incorporated as the nitrogen of the aminoethyl side-chain.²⁴⁴



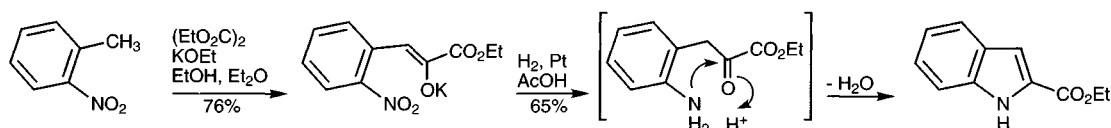
17.17.1.2 From *ortho*-(2-oxoalkyl)anilines

Cyclisation of *ortho*-(2-oxoalkyl)anilines by simple intramolecular condensation with loss of water, occurs spontaneously. Several new ways of generating the intermediate amino-ketone have been developed; the prototype was the Reissert synthesis.

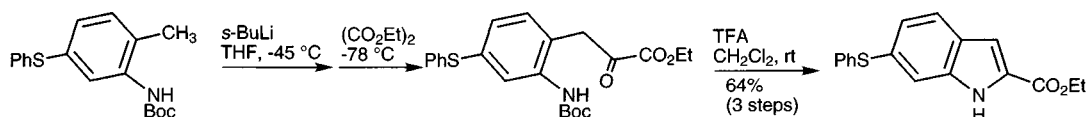


The Reissert synthesis

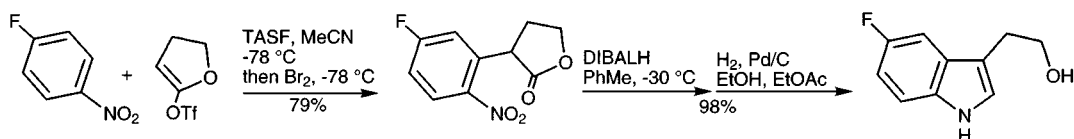
In the classical Reissert synthesis the acidity of a methyl group *ortho* to nitro on a benzene ring is the means for condensation with oxalate; the nitro group is then reduced to amino.²⁴⁵



In a development, the nitrogen is already at the oxidation level of amine, but carries a *t*-butoxycarbonyl group to assist the methyl (alkyl) lithiation, reaction with oxalate as in the classical sequence and removal of the *N*-substituent with acid at the end, again leads to an indole-2-ester.²⁴⁶ The synthesis of 2-unsubstituted indoles is achieved by reaction of the *N,C*-dilithiated species with dimethylformamide.²⁴⁷

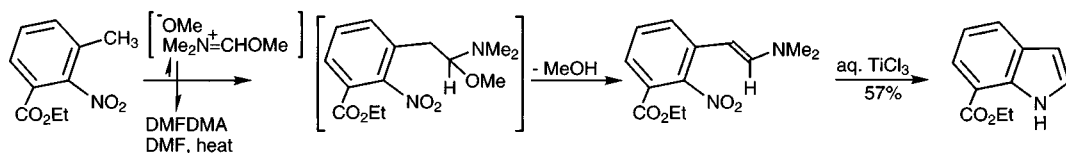


In another variant, aromatic nitro compounds can be made to condense²⁴⁸ with silyl enol ethers using tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF); a non-aromatic nitronate intermediate is oxidised up with bromine, without isolation, to provide a 2-(*ortho*-nitroaryl)ketone and thence an indole after nitro group reduction.²⁴⁹

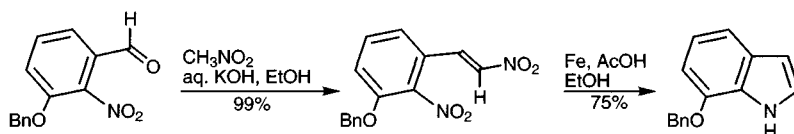


Leimgruber-Batcho synthesis

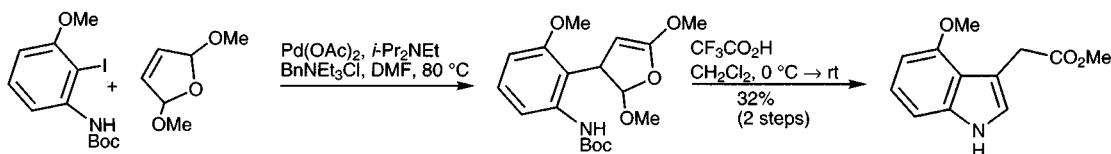
The Leimgruber-Batcho synthesis²⁵⁰ is one of the most widely used new variations which also depends on the acidity of methyl groups *ortho* to aromatic nitro (or at α or γ positions on a pyridine²⁵¹) to allow introduction of the future indole α -carbon as an enamine. Condensation with hot dimethylformamide dimethyl acetal (DMFDMA) (no added base being necessary) leads to an enamine; subsequent reduction of the nitro group, usually in acid conditions, leads directly to the heteroring-unsubstituted indole. Mechanistically this, at first sight extraordinary, process is believed to involve ionisation of the reagent producing methoxide (which deprotonates the aromatic methyl) and an electrophilic component, $\text{MeOCH}=\text{N}^+\text{Me}_2$, which combines with the deprotonated aromatic. Both tris(piperidin-1-yl)methane and bis(dimethylamino)-*t*-butoxymethane are said to function even better than the commercially available DMFDMA.²⁵² A variety of benzene substituents are tolerated and the approach has been utilised for syntheses of, amongst others, 4- and 7-indole-carboxylic esters.²⁵³



A Leimbruger-Batcho-type amino-enamine intermediate is likely to be involved on reduction of the base-catalysed condensation product of an *ortho*-nitro arylaldehydes with nitromethane.²⁵⁴ Reduction, traditionally with metal/acid combinations, but now with reagents such as palladium/carbon with ammonium formate and formic acid,²⁵⁵ iron with acetic acid and silica gel,²⁵⁶ or titanium(III) chloride,²⁵⁷ gives the indole. The arylacetaldehyde precursors can also be generated by Heck reactions on vinylidene carbonate.²⁵⁸

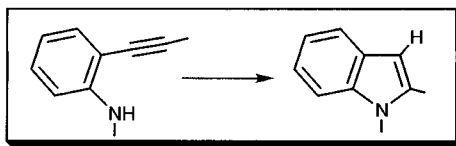


Coupling reactions using *ortho*-haloanilines have been widely used; in these instances no reductive step is required though the carbonyl unit is sometimes incorporated in masked form, such as a 2-ethoxyvinylboronate, requiring deprotection.²⁵⁹

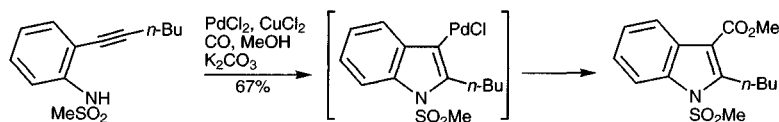
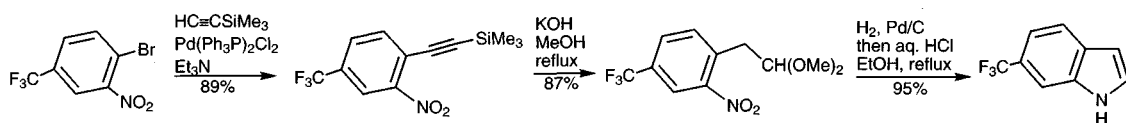


17.17.1.3 From *ortho*-alkynylarylamines

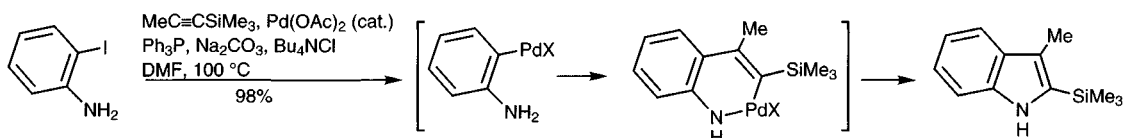
Cyclisation of *ortho*-alkynylarylamines can be achieved in various ways; palladium-catalysed couplings provide the starting alkynylanilines.



Palladium-catalysed coupling methodology now allows easy access to arenes with an alkynyl substituent *ortho* to nitrogen, from *ortho*-iodo- and -bromonitrobenzenes,²⁶⁰ or *ortho*-iodo- and -bromo-*N*-acyl (or *N*-sulfonyl) arylamines,²⁶¹ or even by coupling acetylenes with 2-iodoaniline itself.²⁶² Conversion of *ortho* alkynyl-nitrobenzenes and -arylamines into indoles has been achieved in various ways. The former react with alkoxides *via* addition to the triple bond and form nitro-acetals, nitro group reduction then acetal hydrolysis bring ring closure. Direct cyclisation of *ortho*-alkynylanilines can be effected simply by treatment with tetrabutylammonium fluoride.²⁶³ Alternatively, palladium or copper salts can be utilised, and in the former cases the organopalladium intermediate can be either protonolysed, or trapped out with consequent insertion of a substituent at the indole β -position.²⁶⁴

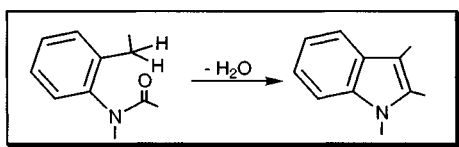


Disubstituted acetylenes can also be utilised in a palladium-catalysed cyclisation of *ortho* haloanilides; the larger group (or hydroxyl-containing group) finishes at C-2.²⁶⁵



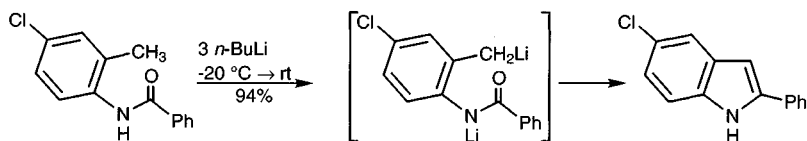
17.17.1.4 From *ortho*-toluidides

Base-catalysed cyclo-condensation of an *ortho*-alkylanilide gives an indole.

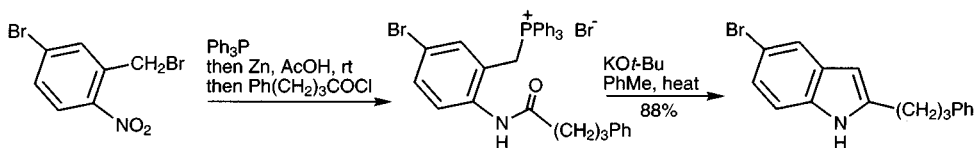


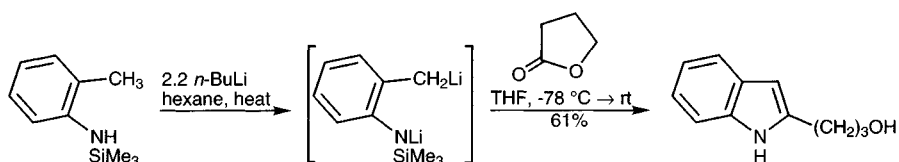
The Madelung synthesis

In its original form, this route employed very harsh conditions (typically²⁶⁶ sodium amide or potassium *t*-butoxide at 250–350 °C) to effect base-catalysed intramolecular condensation between an unactivated aromatic methyl and an *ortho* acylamino-substituent, and was consequently limited to situations having no other sensitive groups. With the advent of the widespread use of alkylolithiums as bases, these cyclocondensations can now be brought about under much milder conditions.²⁶⁷

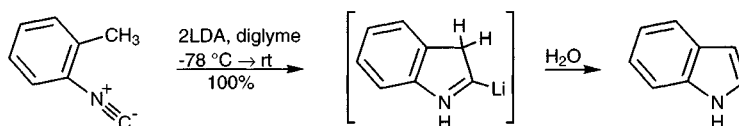


Modifications in which the benzylic hydrogens are acidified also allow the use of mild conditions; one example is the generation of a phosphonium ylide and then an intramolecular Wittig-like reaction, involving the amide carbonyl;²⁶⁸ another variant uses a benzylsilane.²⁶⁹ The use of an amino-silane permits reaction at both nitrogen and benzylic carbon to take place in one pot.²⁷⁰



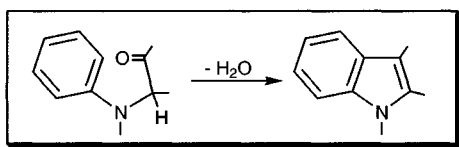


Finally, in this category there must be included cyclisations of the benzylic anions derived from *ortho*-isocyanatotoluenes; the scheme shows the synthesis in its simplest form. However, the synthesis is very flexible, for example the initial benzylic anion can be alkylated with halides or epoxides, before the ring closure thus providing 3-substituted indoles and additionally, the final *N*-lithioindole can be *N*-alkylated by adding a suitable electrophile before work up.²⁷¹



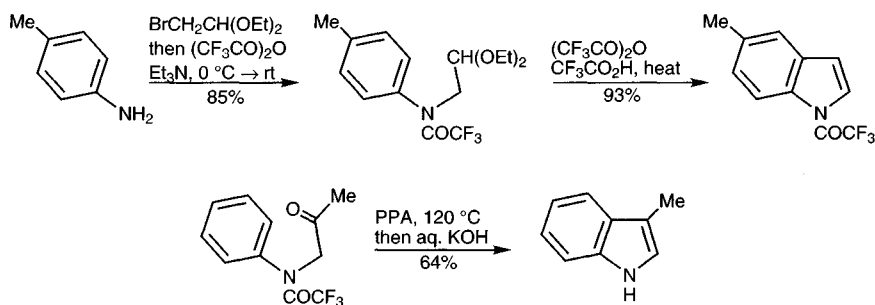
17.17.1.5 From α -arylamino carbonyl compounds

An α -arylamino ketone is cyclised by electrophilic attack onto the aromatic ring.



The Bischler synthesis

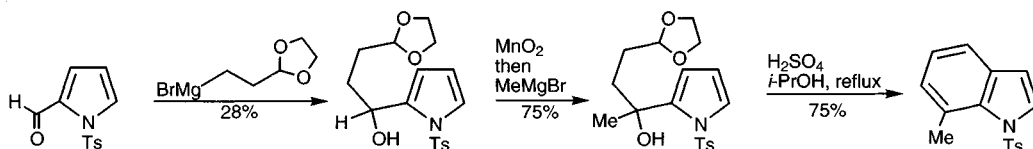
In the original method, the Bischler synthesis, harsh acidic treatment of α -arylamino ketones (produced from the 2-halo ketone and an arylamine) was used to bring about electrophilic cyclisation onto the aromatic ring; these conditions often resulted in mixtures of products *via* rearrangements.²⁷² It is now known that *N*-acylated- α -arylamino ketones can be cyclised under much more controlled conditions, and in contrast to early work, this approach to indoles can even be used to produce hetero-ring-unsubstituted indoles.²⁷³



17.17.1.6 From pyrroles (see also section 13.9)

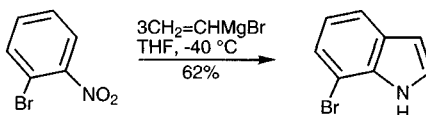
Several unrelated strategies have been utilised for the fusion of a benzene ring onto a pyrrole to generate an indole;²⁷⁴ most follow a route in which a pyrrole, carrying a

four-carbon side-chain at the α -carbon, is cyclised *via* an electrophilic attack at the adjacent pyrrole β -position; one of these is shown.²⁷⁵ Another route involves the electrocycisation of 2,3-divinylpyrroles.²⁷⁶

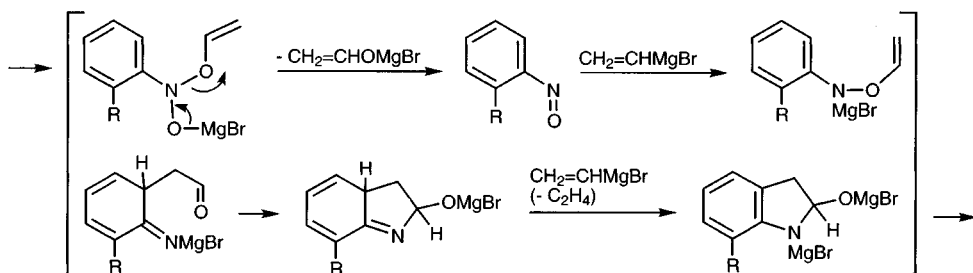


17.17.1.7 From *ortho*-substituted nitroarenes

Bartoli synthesis



In the extraordinary, but nonetheless efficient and extremely practically simple process now known as the Bartoli synthesis, *ortho*-substituted nitrobenzenes treated with three mol equivalents of vinylmagnesium bromide give 7-substituted indoles. The process works best when the 7-substituent is large²⁷⁷ and it is thought that initial attack by the vinyl Grignard is at the nitro group oxygen with subsequent elimination of magnesium enolate producing the nitroso equivalent of the original – it seems likely that this step is encouraged by non-planarity of the nitro group and the aromatic system forced on the molecule by the large *ortho* substituent. A second mol equivalent of vinyl Grignard then adds, again to oxygen generating an intermediate which undergoes a 3,3-sigmatropic rearrangement, much like that involved in the Fischer sequence, and finally hetero ring closure.²⁷⁸

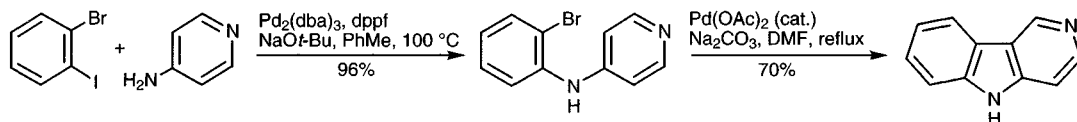


17.17.1.8 From *N*-arylenamines

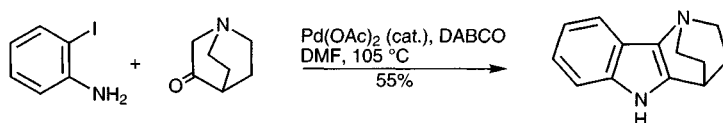
It is not clear whether the palladium-mediated cyclisations of anilino-acrylates and related systems²⁷⁹ operate via a Heck sequence or *via* an electrophilic palladation of the enamine.



A related palladium-catalysed cyclisation can be used to prepare carbazoles or carbolines (illustrated below) from mono- or dihalo diarylamines.²⁸⁰ The starting materials for these are also readily prepared by palladium-catalysed reactions.

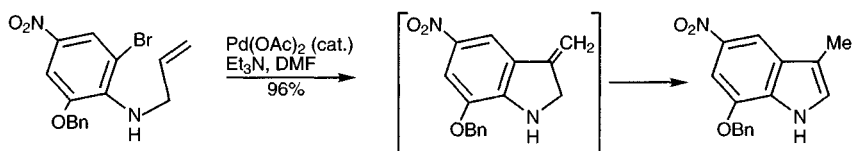


In an important development, simple α -methylene ketones (cyclic ketones work much better than acyclic ketones) and *ortho*-iodoarylamines react under palladium catalysis to give indoles directly. The use of dimethylformamide as solvent and diazabicyclooctane (DABCO) as the base are crucial to the success of the route. Mechanistically, the sequence certainly proceeds through the enamine. As well as being conceptually and practically simple, this method tolerates functional groups which would be sensitive to the acid of the traditional Fischer sequence.²⁸¹

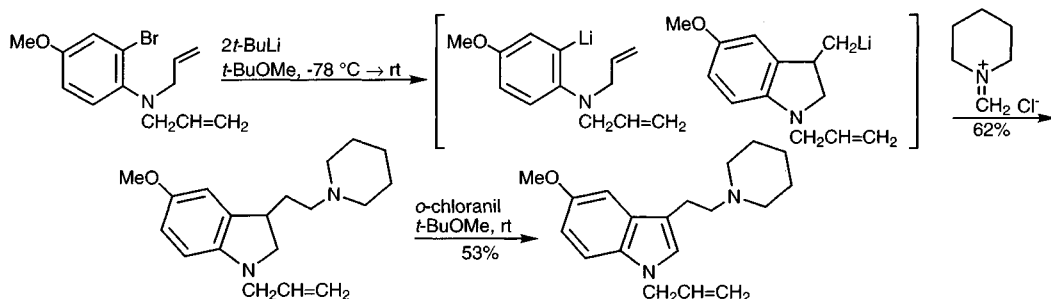


17.17.1.9 From *N*-allyl *ortho*-halo arylamines

N-Allyl *ortho*-haloarylamines can be cyclised under a variety of conditions to give either indoles or indolines, the latter being convertible into indoles by dehydrogenation or elimination of hydrogen halide from a suitable intermediate.²⁸² An intramolecular Heck reaction gives the indole directly via migration of an initially formed exocyclic double bond into the heterocyclic ring; the *exo* isomer is isolable if silver salts are added to the reaction mixture.²⁸³



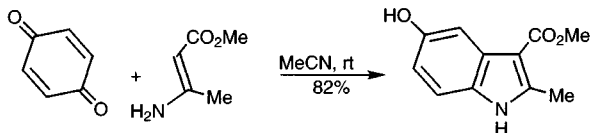
The aryllithiums derived from *N,N*-diallylarylamines with an *ortho* halogen by exchange with an alkyl lithium cyclise by addition to an allyl group double bond generating a primary alkyl lithium which can be trapped with electrophiles finally producing indolines.²⁸⁴



17.17.1.10 From enamines and *p*-quinones

The Nenitzescu synthesis

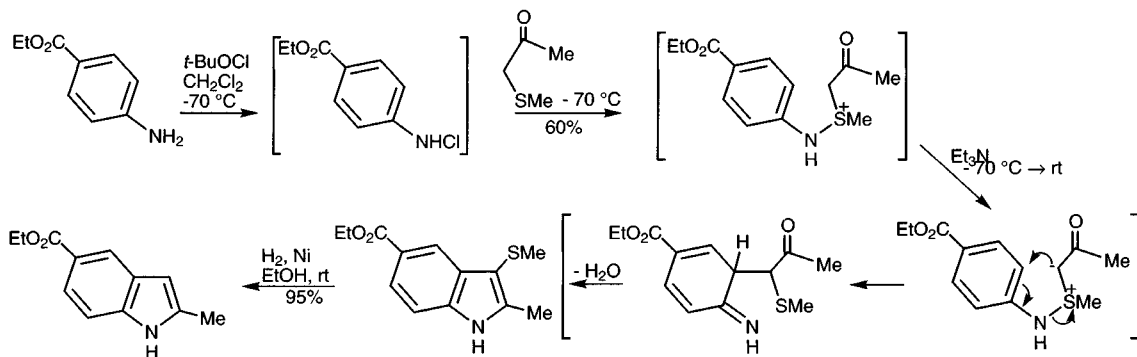
The Nenitzescu synthesis²⁸⁵ is another process about which some of the mechanistic details remain unclear,²⁸⁶ but which can be used for the efficient synthesis of certain 5-hydroxyindoles.²⁸⁷



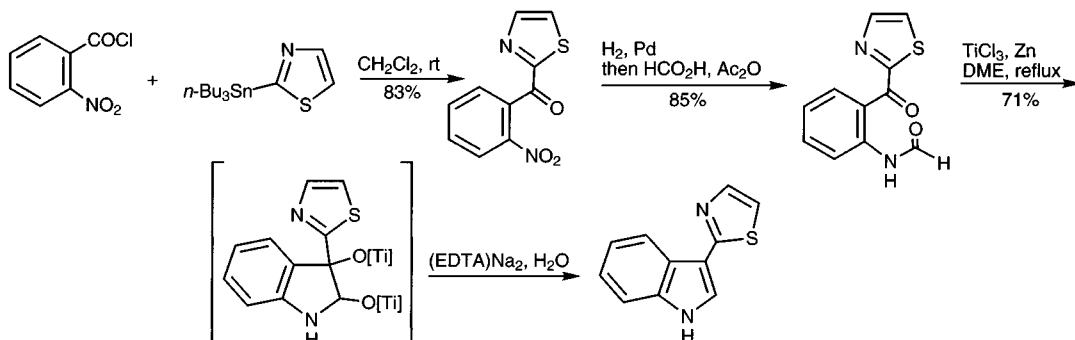
17.17.1.11 From arylamines

The Gassman synthesis

The Gassman synthesis²⁸⁸ produces sulfur-substituted indoles, but these can easily be hydrogenolysed if required.

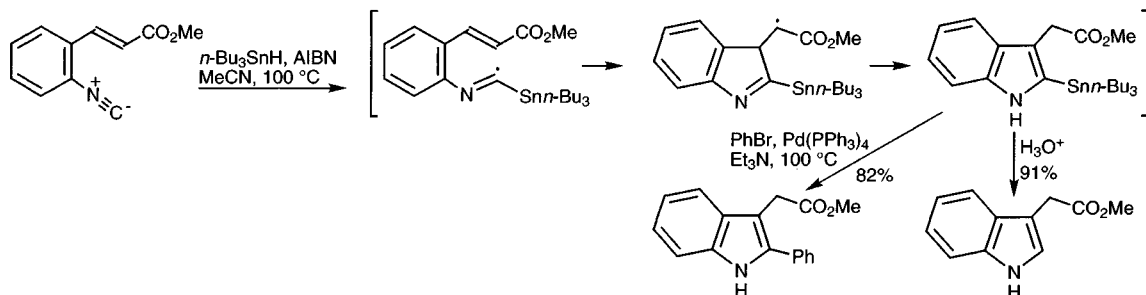
17.17.1.12 From *ortho*-acyl anilidesThe Fürstner synthesis²⁸⁹

This flexible synthesis depends on the reductive cyclisation of *ortho*-acylanilides with low valent titanium – the conditions used for the McMurray coupling of ketones. In the example below, the cyclisation precursor was built up via the acylation of trimethylstannylthiazole.²⁹⁰



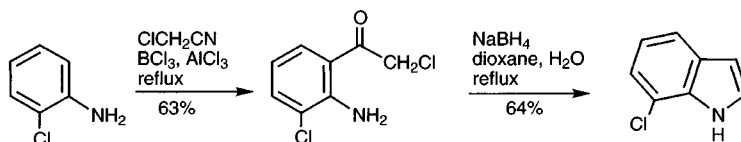
17.17.1.13 From *ortho*-isocyano styrenes The Fukuyama synthesis²⁹¹

ortho-Isocyano styrenes, which are readily prepared by dehydration of the corresponding formamides, undergo tin-promoted radical cyclisation to give unstable 2-stannylindoles, which can either be hydrolysed to afford the corresponding 2-unsubstituted indole, or used without isolation for coupling with aryl halides using palladium(0)-catalysis, as illustrated below.²⁹²



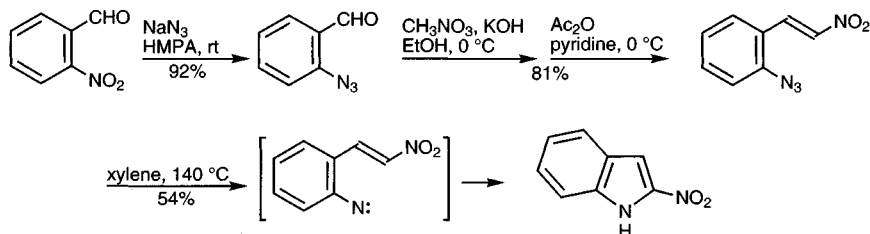
17.17.1.14 From *ortho*-chloroacetyl arylamines Sugasawa synthesis

Arylamines, without protection of the nitrogen, undergo Friedel-Crafts acylation regioselectively *ortho* to the nitrogen using nitriles and boron trifluoride. Thus, using chloroacetonitrile produces (*ortho*-chloroacetyl)arylamines in which ring closure to give an indole takes place after reduction of the ketone to the alcohol oxidation level.²⁹³

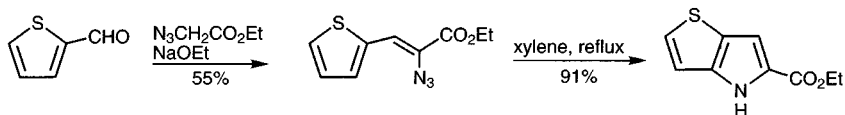


17.17.1.15 By cyclisation of nitrenes

Thermolysis of *ortho*-azidostyrenes gives nitrenes which insert into the side chain to form indoles.²⁹⁴ Similar nitrenes have been generated by reaction of nitro compounds with trialkyl phosphites. The azide thermolysis method can be used to prepare 2-nitroindoles, which are not available by other methods.²⁹⁵

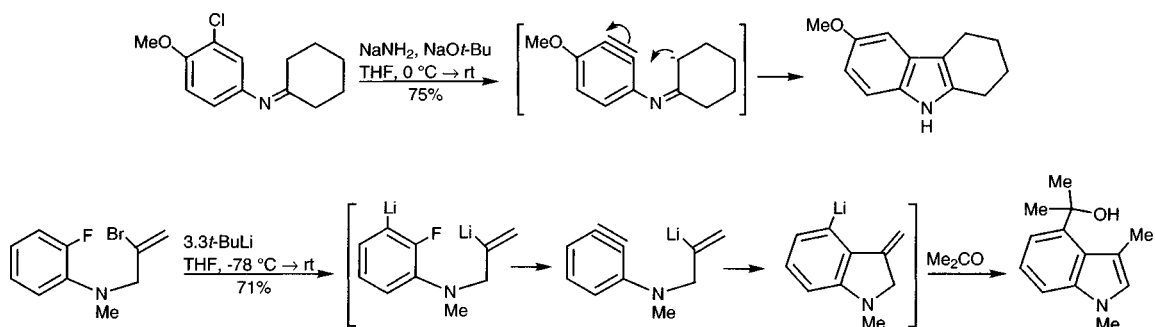


In a complementary sense, thermolysis of β -azidostyrenes also gives indoles but here the intermediate may be an azirine;²⁹⁶ this method is particularly useful for the fusion of a pyrrole ring onto rings other than a benzene ring, as illustrated below.²⁹⁷



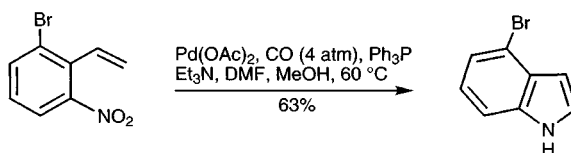
17.17.1.16 Cyclisation onto arynes

Indoles can be prepared by intramolecular addition of iminates²⁹⁸ or vinylolithiums²⁹⁹ to arynes. In the latter case the intermediate aryllithium can be trapped with electrophiles to give 4-substituted indoles.



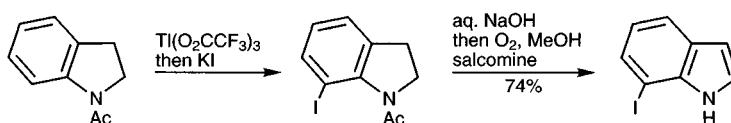
17.17.1.17 From *ortho*-nitro styrenes

ortho-Nitrostyrenes are readily available by a number of routes – (1) reaction of an (*ortho*-bromomethyl)nitroarene with a phosphine then Wittig condensation with an aldehyde, (2) Wittig reaction employing an (*ortho*-nitro)araldehyde as the carbonyl component, (3) base-catalysed condensation of a methyl group *ortho* to an aromatic nitro group with an aldehyde, and (4) *ortho* nitration of a styrene. In a palladium-catalysed process, the mechanism of which remains obscure, very efficient ring closure to indoles takes place in one pot, but clearly not by one step.³⁰⁰



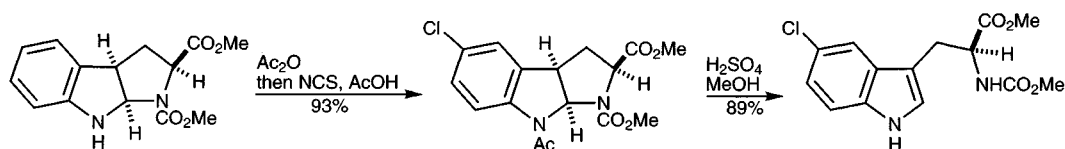
17.17.1.18 From indolines

Indolines are useful intermediates for the synthesis of indoles with substituents in the carbocyclic ring. In electrophilic substitutions, they behave like anilines; the example shows *N*-acetylindoline undergoing regioselective 7-halogenation. Indolines can be obtained easily from indoles by reduction (see section 17.8) and can be cleanly oxidised back to indoles using a variety of methods, including oxygen with cobalt catalysis (salcomine),³⁰¹ hypochlorite/dimethylsulfide,³⁰² Mn(III),³⁰³ and Au(III) compounds.³⁰⁴

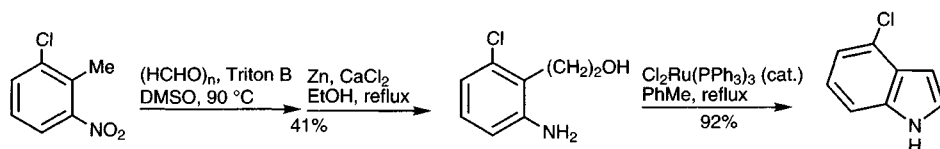


An attractive variant is to utilise certain products of reversible addition to 3*H*-indolium cations, such as the indole bisulfite adduct (section 17.1.1), or where there has been an intramolecular nucleophilic addition: such compounds, though they are

indolines, are still at the oxidation level of indoles, needing only mild acid treatment to regenerate the aromatic system.³⁰⁵

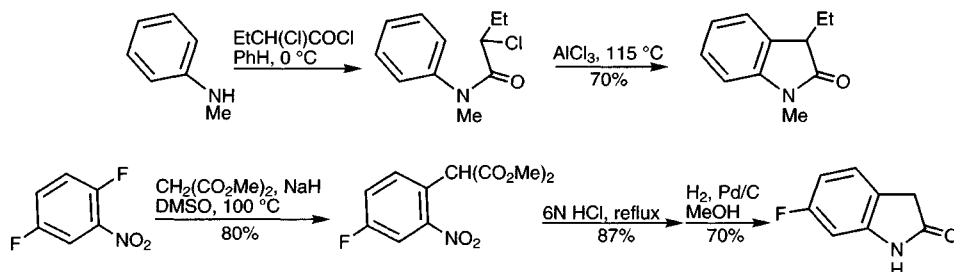


Methods involving ruthenium-catalysed condensations of arylamines with alcohols may prove to be useful for the large scale production of indoles. The mechanism involves hydride transfer giving aldehyde intermediates. The process can be carried out intramolecularly as shown³⁰⁶ or intermolecularly, for example by the reaction of aniline with triethanolamine.³⁰⁷

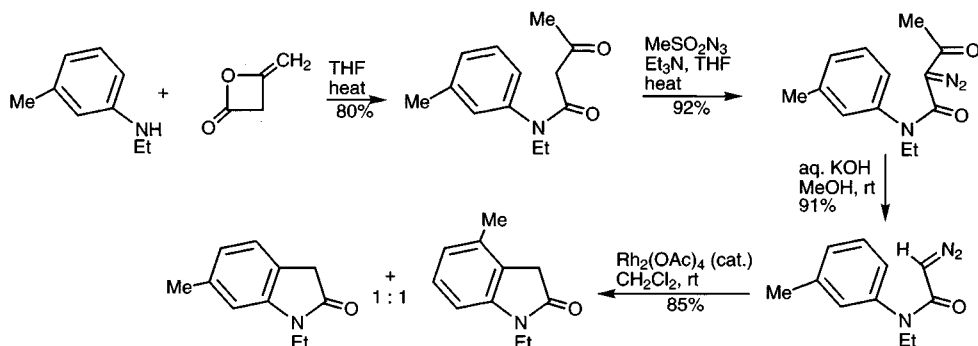


17.17.2 Synthesis of oxindoles

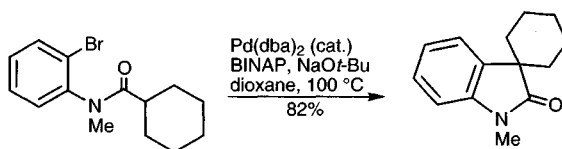
The main synthesis of oxindoles is simple and direct and involves an intramolecular Friedel-Crafts alkylation reaction as the cyclising step.³⁰⁸ Also straightforward in concept is the displacement of halogen from an *ortho* halonitroarene with malonate, this leading to an oxindole after decarboxylation and reduction of the nitro group with spontaneous lactamisation.¹⁹³



A less orthodox route to oxindoles depends on the intramolecular insertion of a rhodium carbenoid into an adjacent aromatic C–H bond.³⁰⁹

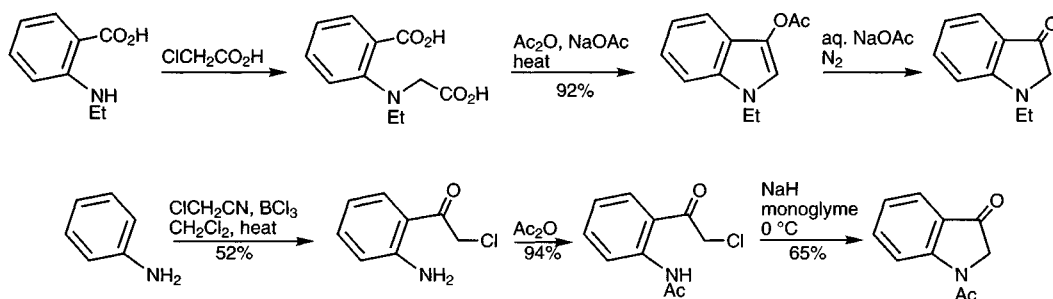


Oxindoles can also be prepared by palladium-catalysed enolate cyclisation of *ortho* halo anilides.³¹⁰



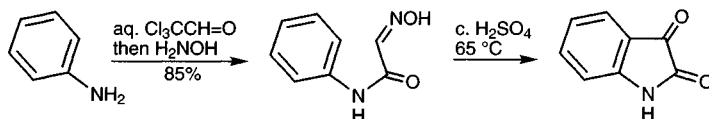
17.17.3 Synthesis of indoxyls

Indoxyls are normally prepared from anthranilic acids *via* alkylation with a haloacetic acid followed by a cyclising Perkin condensation.³¹¹ It is also possible to directly chloroacetylate an aniline, *ortho* to the nitrogen.³¹²



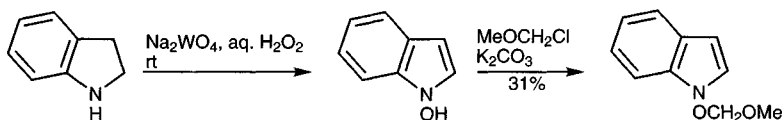
17.17.4 Synthesis of isatins

Isatins are readily prepared *via* the reaction of an aniline with chloral, the resulting product converted into an oxime, and this cyclised in strong acid.³¹³



17.17.5 Synthesis of 1-hydroxyindoles

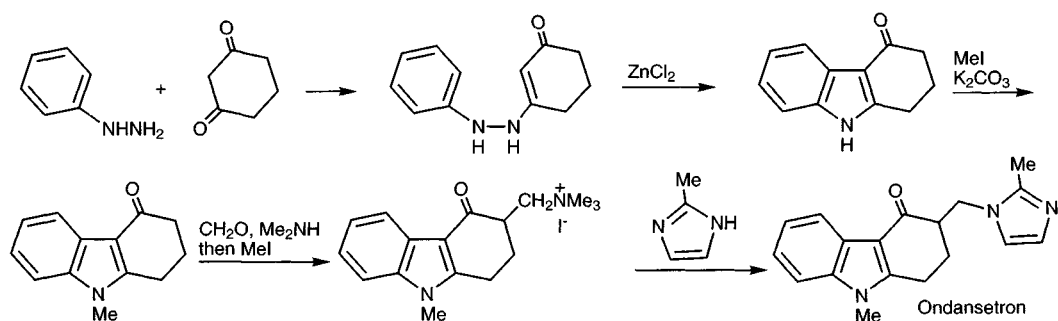
The oxidation of indolines with sodium tungstate/hydrogen peroxide both aromatises and also oxidises the nitrogen, resulting in 1-hydroxyindoles.¹⁰⁶ 1-Hydroxyindoles can also be obtained *via* partial reduction of the nitro group of Leimgruber-Batcho intermediate nitro-enamines (section 17.17.1.2) with zinc then cyclisation.³¹⁴



17.17.6 Examples of notable indole syntheses

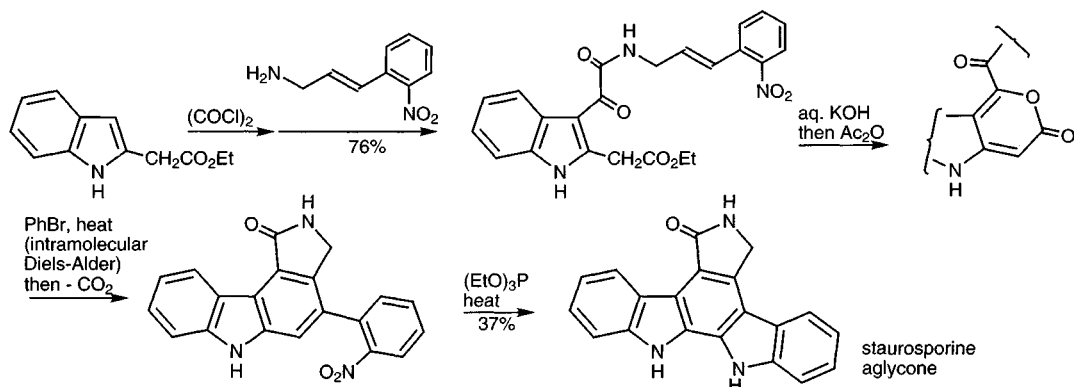
17.17.6.1 Ondansetron

Ondansetron is a selective, 5-hydroxytryptamine antagonist, used to prevent vomiting during cancer chemotherapy and radiotherapy.



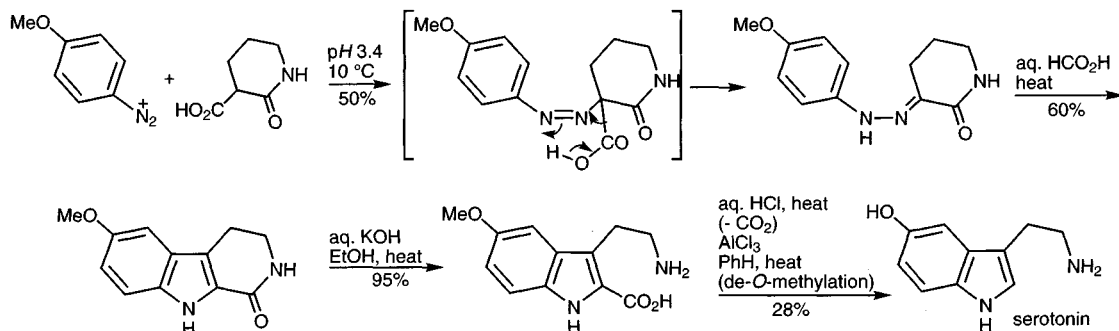
17.17.6.2 Staurosporine aglycone³¹⁵

Staurosporine and related molecules are under active investigation as potential antitumour agents. The synthesis illustrates several aspects of heterocyclic chemistry, including a 2-pyrone acting as a diene in an intramolecular Diels-Alder reaction, and the use of nitrene insertion for the formation of 5-membered nitrogen rings.



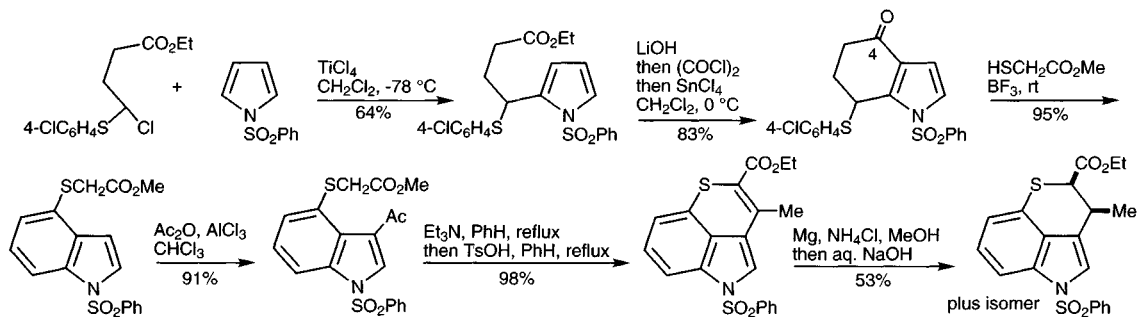
17.17.6.3 Serotonin

Serotonin has been synthesised by several routes; the method shown³¹⁶ relies on a Fischer indole synthesis, the requisite phenylhydrazone being constructed by a process known as the Japp-Klingemann reaction in which the enol of a 1,3-dicarbonyl compound is reacted with an aryldiazonium salt, with subsequent cleavage of the 1,3-dicarbonyl unit.



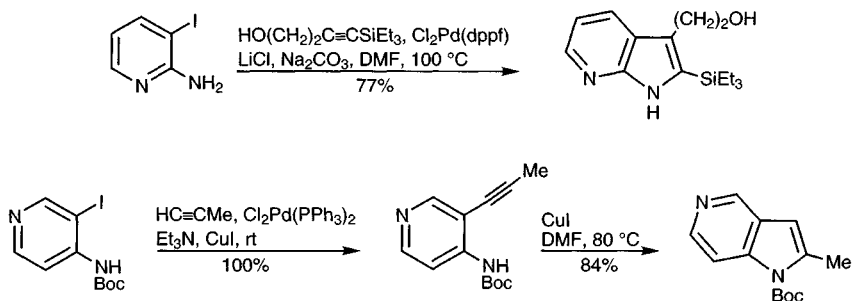
17.17.6.4 *Chuangxinmycin*³¹⁷

This synthesis uses the approach of starting from a pyrrole: the cyclic ketone intermediate is in general a useful intermediate for the synthesis of 4-substituted indoles – in this case a sulfur substituent – it is already at the aromatic oxidation level needing only the loss of the 4-chlorophenylthiol.

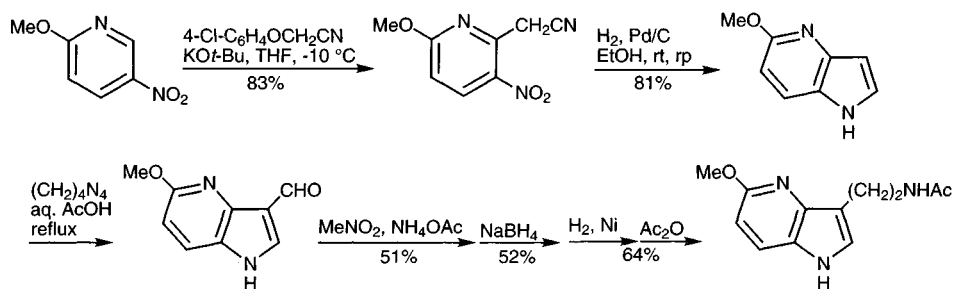


17.17.7 Synthesis of azaindoles (see also section 5.5.1)

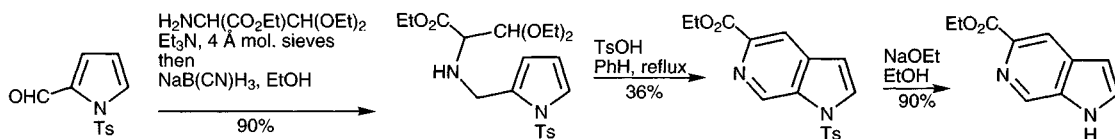
Most syntheses of azaindoles start from pyridines and parallel the standard indole syntheses discussed above. However, the Fischer reaction using pyridylhydrazones is much less consistent and useful than for phenylhydrazones; the Madelung reaction is also not as useful. The most successful methods involve palladium-catalysed coupling of acetylenes with amino halopyridines either as one-³¹⁸ or two-step³¹⁹ processes. The starting amino halopyridines are generally available via directed metallations.



Syntheses utilising nitropyridines by Leimgruber-Batcho processes work well³²⁰ but can be limited by the availabilities of the starting nitropyridines – the sequence below shows the assembly of the ring closure precursor using a VNS (section 2.3.3) sequence.³²¹



Synthesis from pyrroles is useful in particular cases.^{320,322}



Exercises for chapter 17

Straightforward revision exercises (consult chapters 16 and 17)

- What is the pK_a of indole as a base and where does it protonate? What is the pK_a of indole as an acid?
- At what position is electrophilic substitution of indole fastest? Cite two examples.
- What are the structures of the intermediates and final product in the following sequence: indole with $(\text{COCl})_2 \rightarrow \text{C}_{10}\text{H}_6\text{ClNO}_2$ then this with ammonia $\rightarrow \text{C}_{10}\text{H}_8\text{N}_2\text{O}_2$ then this with $\text{LiAlH}_4 \rightarrow \text{C}_{10}\text{H}_{12}\text{N}_2$? Explain the last transformation in mechanistic terms.
- How could one prepare from indole: (i) 3-formylindole, (ii) 3-(2-nitroethyl)indole, (iii) 3-dimethylaminomethylindole, (iv) 1-methylindole.
- At what position does strong base deprotonate an *N*-substituted indole? Name two groups which can be used to block the 1-position for such deprotonations and which could be removed later. How would these blocking groups be introduced onto the indole nitrogen?
- What is the mechanism of the conversion of 3-dimethylaminomethylindole into 3-cyanomethylindole on reaction with NaCN ?
- Which phenylhydrazones would be required for the Fischer indole synthesis of (i) 3-methylindole; (ii) 1,2,3,4-tetrahydrocarbazole; (iii) 2-ethyl-3-methylindole; (iv) 3-ethyl-2-phenylindole?
- How could one convert 2-bromoaniline into 2-phenylindole (more than one step is required)?
- What are the advantages of using an indoline (a 2,3-dihydroindole) as an intermediate for the synthesis of indoles?

More advanced exercises

- Indole reacts with a mixture of *N*-methyl-2-piperidone and POCl_3 , followed by NaOH work-up to give $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$. What is its structure?
- Suggest a structure for the tetracyclic product, $\text{C}_{18}\text{H}_{19}\text{NO}$, formed when 3-methylindole is treated with 2-hydroxy-3,5-dimethylbenzyl chloride.
- When indole dimer (section 17.1.9) is subjected to acid treatment in the presence of indole, 'indole trimer', $\text{C}_{24}\text{H}_{21}\text{N}_3$, is produced. Suggest a structure for the 'trimer' (hint: consider which of the two reactants would be most easily protonated, and at which atom).
- Starting from indole, and using a common intermediate, how could one prepare (i) indol-3-ylacetic acid and (ii) tryptamine?
- What would be the products from the reactions of 5-bromo-3-iodo-1-phenylsulfonylindole with (i) $\text{PhB}(\text{OH})_2/\text{Pd}(\text{PPh}_3)_4/\text{aq. Na}_2\text{CO}_3$; (ii) ethyl acrylate/ $\text{Pd}(\text{OAc})_2/\text{Ph}_3\text{P}/\text{Et}_3\text{N}$?

6. Deduce a structure, and write out the mechanism for the conversion of 2-formylindole into a tricyclic compound, $C_{11}H_9N$, on treatment with a combination of NaH and $Ph_3P^+CH=CH_2 Br^-$.
7. When 3-ethyl-3-methyl-3*H*-indole is treated with acid, two products, each isomeric with the starting material, are formed – deduce their structures and explain the formation of two products.
8. Suggest a structure for the salt $C_{15}H_{13}N_2^+ Br^-$ formed by the following sequence: 2-(2-pyridyl)indole reacted first with *n*-BuLi then $PhSO_2Cl$ ($\rightarrow C_{19}H_{14}N_2O_2S$), then this sequentially with *t*-BuLi at $-100^\circ C$ then ethylene oxide ($\rightarrow C_{21}H_{18}N_2O_3S$), aq. NaOH ($\rightarrow C_{15}H_{14}N_2O$), and this, finally reacted with PBr_3 .
9. What are the products formed in the following sequence: indole/*n*-BuLi, then I_2 , then LDA, then $PhSO_2Cl \rightarrow C_{14}H_{10}INO_2S$, then this with LDA, then $I_2 \rightarrow C_{14}H_9I_2NO_2S$?
10. When indol-3-yl- CH_2OH is heated with acid, di(indol-3-yl)methane is formed: suggest a mechanism for this transformation.
11. What product, $C_{10}H_{11}NO$, would be obtained from refluxing a mixture of phenylhydrazine and 2,3-dihydrofuran in acetic acid?
12. Draw structures for the azaindoles resulting from treatment of 2-methyl-3-nitro- and 4-methyl-3-nitropyridines, respectively, with $(EtO_2C)_2/EtONa$, followed by $H_2/Pd-C$. Both products have the molecular formula $C_{10}H_{10}N_2O_2$.
13. Heating DMFDMA with the following aromatic compounds led to condensation products; subsequent reduction with the reagent shown gave indoles. Draw the structures of the condensation products and the indoles: (i) 2,6-dinitrotoluene then $TiCl_3$ gave $C_8H_8N_2$; (ii) 2-benzyloxy-6-nitrotoluene then H_2/Pt gave $C_{15}H_{13}NO$; (iii) 4-methoxy-2-nitrotoluene then H_2/Pd gave C_9H_9NO ; (iv) 2,3-dinitro-1,4-dimethylbenzene then H_2/Pd gave $C_{10}H_8N_2$.

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