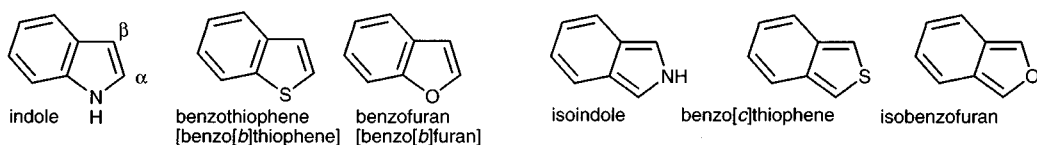
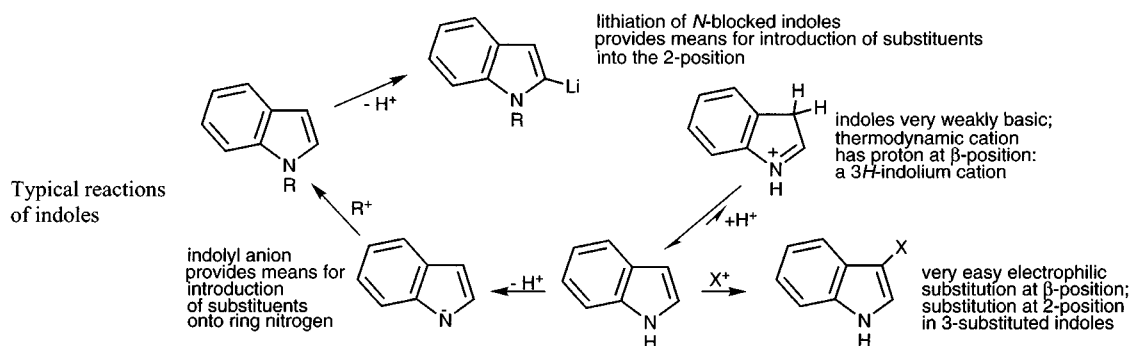


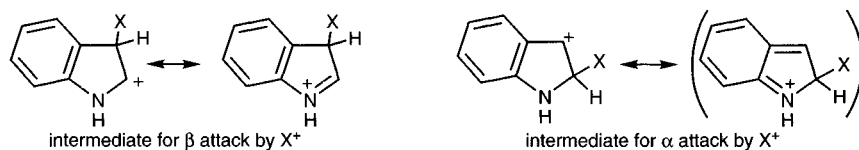
16 Typical reactivity of indoles, benzo[*b*]thiophenes, benzo[*b*]furans, isoindoles, benzo[*c*]thiophenes and isobenzofurans



The fusion of a benzene ring to the 2,3-positions of a pyrrole generates one of the most important heterocyclic ring systems – indole. This chapter develops a description of the chemistry of indole, then discusses modifications necessary to rationalise the chemistry of the benzo[*b*]furan and benzo[*b*]thiophene analogues. Finally, the trio of heterocycles in which the benzene ring is fused at the five-membered ring 3,4-positions are considered.

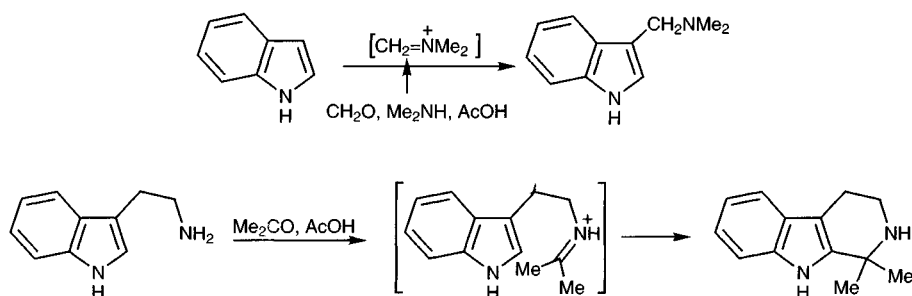


The chemistry of indole is dominated by its very easy electrophilic substitution. Of the two rings, the heterocyclic ring is very electron-rich, by comparison with a benzene ring, so attack by electrophiles always takes place in the five-membered ring, except in special circumstances. Of the three positions on the heterocyclic ring, attack at nitrogen would destroy the aromaticity of the five-membered ring, and produce a localised cation; both of the remaining positions can be attacked by electrophiles, leading to *C*-substituted products, but the β -position is preferred by a considerable margin. This contrasts with the regiochemistry shown by pyrrole but again can be well rationalised by a consideration of the Wheland intermediates for the two alternative sites of attack.

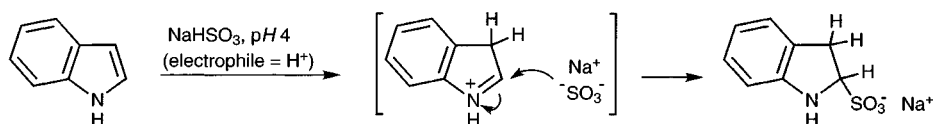


The intermediate for attack at C-2 is stabilised – it is a benzylic cation – but it cannot derive assistance from the nitrogen without disrupting the benzenoid resonance (resonance contributor, which makes a limited contribution, shown in parenthesis). The more stable intermediate from attack at C-3, has charge located adjacent to nitrogen and able to derive the very considerable stabilisation attendant upon interaction with its lone pair of electrons.

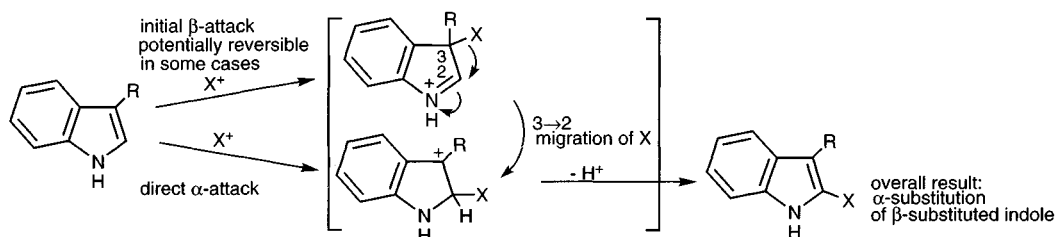
The facility with which indoles undergo substitution, and the possibility for substitution at C-2 can both be illustrated using Mannich reactions – the electrophilic species in such reactions ($C=N^+R_2$) is generally considered to be a ‘weak’ electrophile, yet substitution occurs easily under mild conditions.



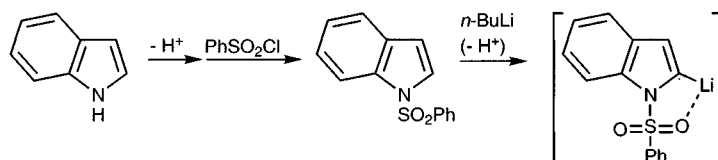
There is a strong preference for attack at C-3, even when that position carries a substituent, and this is nicely shown by examples in which there is the possibility for nucleophilic trapping of the Wheland intermediate: the reaction of indole with sodium hydrogen sulfite is a simple example.



2-Electrophilic substitution of 3-substituted indoles could proceed in three ways: (i) initial attack at a 3-position followed by 1,2-migration to the 2-position; (ii) initial attack at the 3-position followed by reversal (when possible), then (iii); or (iii) direct attack at the 2-position. It has been definitely demonstrated, in the case of some irreversible substitutions, that the migration route operates, but equally it has been demonstrated that direct attack at an α position can occur.

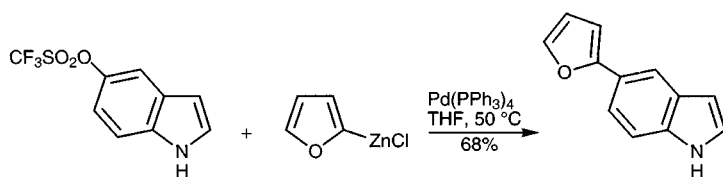


Indoles react with strong bases losing the *N*-hydrogen and forming indolyl anions. When the counterion is an alkali metal these salts have considerable ionic character and react with electrophiles at the nitrogen, affording a practical route for *N*-alkylation (or acylation) of indole nitrogen. Indolyl anions are used, for example, for the synthesis of indoles carrying *N*-blocking substituents. From *N*-blocked indoles, deprotonation (lithiation) can be effected at C-2, often with the additional chelating assistance of the *N*-substituent, though this last is not essential, for even *N*-methylindole lithiates at C-2, where the acidifying effect of the electronegative hetero atom is felt most strongly.



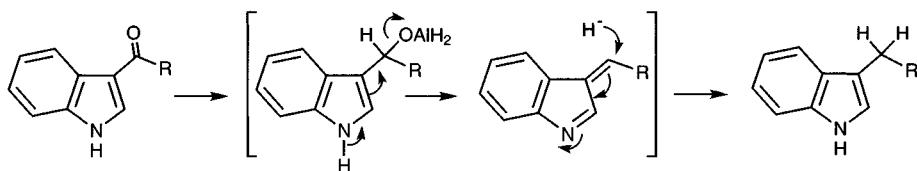
The reactivity of *N*-magnesioidindoles, which result from displacement of the active *N*-hydrogen with a Grignard reagent, or the analogous zinc derivatives, are rather different from that of the sodium, potassium and lithium salts. The greater covalent character of the *N*-metal bond means that electrophiles tend to react at C-3, rather than at nitrogen.

As in all heterocyclic chemistry, the advent of palladium(0)-catalysed processes (see section 2.7 for a detailed discussion) has revolutionised the manipulation of indoles, benzothiophenes and benzofurans: the example below is typical.



The ready electron availability in the heterocyclic ring means that indoles are rather easily (auto)oxidised in the five-membered ring. Reductions can be made selective for either ring: in acid solution, dissolving metals attack the hetero ring, and the benzenoid ring can be selectively reduced by Birch reduction.

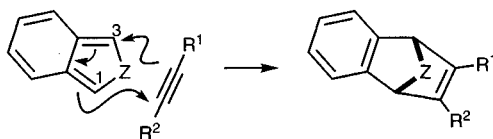
Apart from commenting that substituents on the homocyclic ring of indoles are 'normal', i.e. behave as they would on simpler benzene compounds, the last major aspect of note is the reactivity of indoles which carry leaving groups at benzylic positions, especially C-3, on the heterocyclic ring. Such compounds undergo displacement processes extremely easily, encouraged by stabilisation of positive charge by the nitrogen or, alternatively, in basic conditions, by loss of the indole hydrogen. This last occurs in lithium aluminium hydride reduction of 3-acylindoles which produces 3-alkylindoles. In a sense, 3-ketones behave like vinylogous amides, and reduction intermediates are able to lose oxygen to give species which, on addition of a second hydride, produce the indolyl anion of the 3-alkylindole, converted into the indole during aqueous work up.



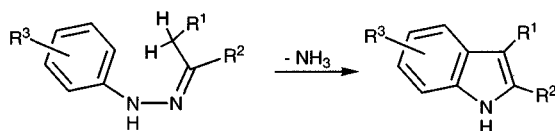
In comparison with indoles, benzo[*b*]furans and benzo[*b*]thiophenes have been studied much less fully, however similarities and some differences have been noted. Each system undergoes electrophilic substitution but the 3-regioselectivity is much lower than for indole, even to the extent that some attack takes place in the benzene ring of benz[*b*]thiophene and that 2-substitution is favoured for benzo[*b*]furan. These changes are consequent upon the much poorer electron donating ability of oxygen and sulfur – the nitrogen of indole is able to make a much bigger contribution to stabilising intermediates, particularly, as was shown above, for β -attack, and consequently to have a larger influence on regioselectivity. In the case of benzo[*b*]furan, it appears that simple benzylic resonance stabilisation in an intermediate from 2-attack outweighs the assistance that oxygen might provide to stabilise an adjacent positive charge.

Oxygen and sulfur systems undergo lithiation at their 2-positions, consistent with the behaviour of furans, thiophenes, and of *N*-blocked pyrroles and indoles.

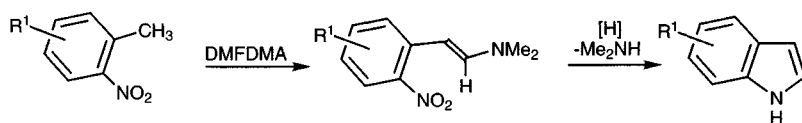
The chemical behaviour of isoindole, benzo[*c*]thiophene and isobenzofuran is dominated by their lack of a 'complete' benzene ring: these three heterocycles undergo cycloaddition processes across the 1,3-positions with great facility, because the products do now have a regular benzene ring. Often, no attempt is made to isolate these heterocycles but they are simply generated in the presence of the dienophile with which it is desired that they react. As a result of this strong tendency, few of the classical electrophilic and nucleophilic processes have been much studied.



There has probably been more work carried out on the synthesis of indoles than on any other single heterocyclic system and consequently many routes are available; ring syntheses of benzo[*b*]thiophenes, benzo[*b*]furans have been much less studied. It is surprising that the Fischer indole synthesis, now more than a hundred years old, is still widely used – an arylhydrazone is heated with an acid, a multi-step sequence ensues, ammonia is lost and an indole is formed.



As an illustration of a recently developed and efficient route, 2,3-unsubstituted indoles are obtained from an *ortho*-nitrotoluene by heating with dimethylformamide dimethylacetal generating an enamine which, after reduction of the nitro group, closes with loss of dimethylamine generating the aromatic heterocycle.



Both benzo[*b*]thiophenes and benzo[*b*]furans can be obtained from the thiophenol or phenol respectively, by *S*-/*O*-alkylation with bromoacetaldehyde acetal and then acid-catalysed ring closure involving intramolecular electrophilic attack on the ring.

