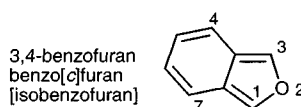
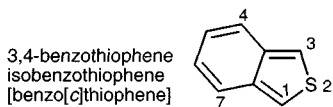
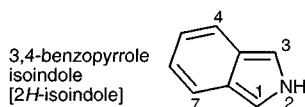
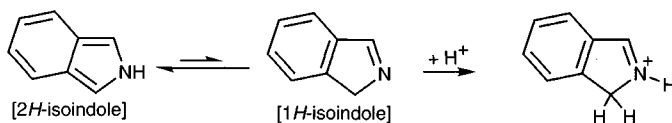


19 Isoindoles, benzo[*c*]thiophenes and isobenzofurans: reactions and synthesis



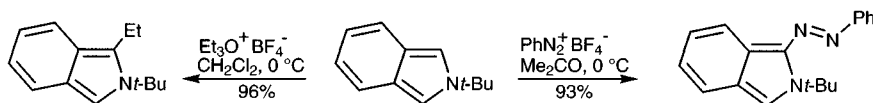
Isoindole,¹ benzo[*c*]thiophene² and isobenzofuran³ are much less stable than their isomers, indole, and benzo[*b*]thiophene and benzo[*b*]furan. This is undoubtedly associated with their lower aromaticity which can be appreciated qualitatively by noting that in these [*c*]-systems the six-membered ring is not a complete benzenoid unit. Of the three unsubstituted heterocycles, benzo[*c*]thiophene is the most stable – it survives as a solid for a few days at -30°C – but most chemistry has been carried out with substituted derivatives. The instability manifests itself in a strong tendency to add reagents so as to generate products which do have a complete benzene ring, in particular these heterocycles are susceptible to cycloaddition of dienophiles. In this context, then, it is not surprising that for isoindole, for which an alternative tautomer (1*H*-isoindole, sometimes called ‘isoindolenine’) is possible, which does have a complete benzenoid unit, an appreciable percentage of that alternative exists in equilibrium.⁴ Indeed, some isoindoles exist largely as the tautomer with a C–N double bond – 1,3,4,7-tetramethylisoindole is an example⁵ – but 1-phenylisoindole favours the 2-*H*-tautomer to the extent of 91%.⁶ Substituents on the benzenoid ring can also influence both the stability of the isoindole and the position of tautomeric equilibrium, for example 4,5,6,7-tetrabromoisindole is a stable crystalline solid which exists wholly as the 2*H*-tautomer;⁷ a pivaloyl substituent at C-5, though remote from the sensitive heterocyclic ring, can also stabilise an isoindole.⁸ The position of such tautomeric equilibria can be altered by changing solvent – solvents such as dimethylsulfoxide tend to favour the *N*-hydrogen tautomer, where protic solvents like alcohols favour the imine tautomer.



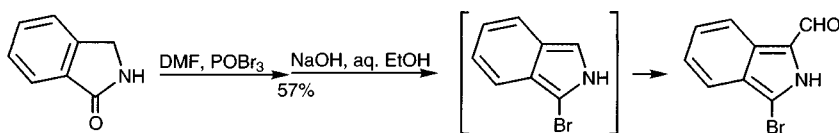
19.1 Reactions with electrophilic reagents

Isoindoles protonate to generate only one cation;⁵ this electrophilic addition of protons sets the pattern for substitution in these systems, but there are relatively few clear cut examples, no doubt partly because of the instability of less substituted isoindoles, isobenzofurans and benzo[*c*]thiophenes. Detritiation studies showed the intrinsic reactivity of 2-methylisoindole in this electrophilic substitution to be 10^4 greater than that of 1-methylindole.⁹

2-*t*-Butylisoindole is much more stable than the unsubstituted heterocycle or other 2-substituted isoindoles, thus its reactions can be used as a measure of intrinsic reactivity, set aside from instability: even weak electrophiles such as aryldiazonium ions attack it and it undergoes alkylation, in each case at the hetero ring 1-position.¹⁰



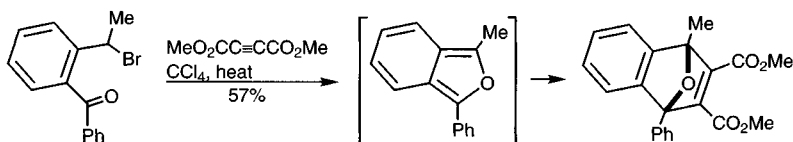
An interesting example of electrophilic substitution is the conversion of phthalimidine (2,3-dihydro-1*H*-isoindol-1-one) into 1-bromo-3-formylisoindole under Vilsmeier conditions (formation of 1-bromo-2*H*-isoindole must be the first step).¹¹ Mannich condensation of 2-methyl-1-phenylisoindole is another straightforward example.¹²



19.2 Electrocyclic reactions

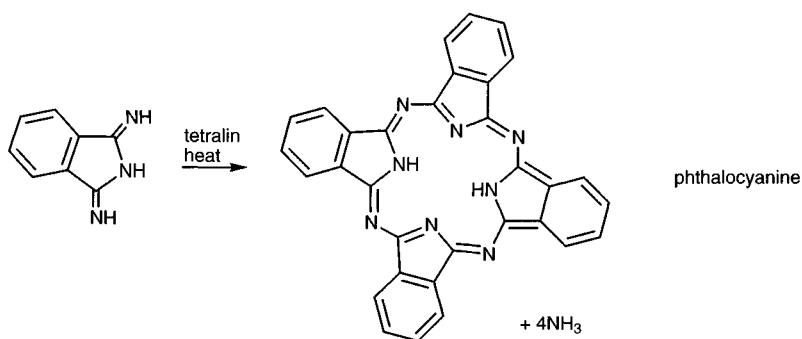
Each of the three systems has a strong tendency for cycloaddition with dienophiles across the 1- and 3-positions, thereby gaining the stabilising contribution of a complete benzene ring, isobenzofuran itself, for example, reacts instantly at 0 °C with maleic anhydride.¹³ Isobenzofuran has been dubbed 'the most reactive isolable diene'. More typically, the synthesis of one of these non-isolable, or extremely reactive systems is immediately followed by a trapping with a dienophile, so that discussion of synthesis must inevitably involve discussion of their cycloaddition chemistry.

Reactions of 1,3-diphenylisobenzofuran which is much more stable, are typical: it undergoes Diels-Alder cycloaddition with diethyl acetylenedicarboxylate¹⁴ and adds singlet oxygen,¹⁵ indeed this commercially available isobenzofuran is often used as a trapping reagent for transient alkenes and alkynes. Less stable isobenzofurans are traditionally generated and reacted *in situ*: 1-methyl-3-phenylisobenzofuran is typical.¹⁶ More modern methods for the production of isobenzofurans in solution have allowed detailed study of the rates of various substituted derivatives with *N*-methylmaleimide.¹⁷ Diels-Alder additions are also known for benzo[c]thiophene^{18,19} and isoindoles.⁴



19.3 Phthalocyanines²⁰

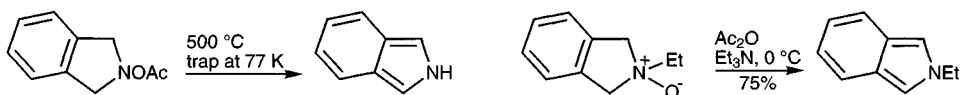
The phthalocyanine macrocyclic system, formally derived from four isoindoles, is the basis for many blue dyestuffs. Metal derivatives have a cation complexed at the centre, much as the iron atom in haem. Phthalocyanine can be produced by the reductive cyclisation of 2-cyanobenzamide or, in a route which makes its relationship to isoindole more obvious, by the combination of four molecules of 1,3-diiminoisoindoline with the elimination of ammonia.²¹



19.4 Synthesis of isoindoles, benzo[*c*]thiophenes, and isobenzofurans

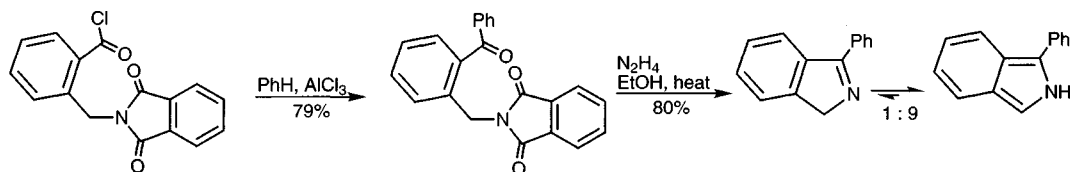
19.4.1 Isoindoles

Isoindoles can be produced by eliminations from *N*-substituted isoindolines (1,3-dihydroisoindoles), themselves readily produced by the reaction of a nitrogen nucleophile and a 1,2-bis(bromomethyl)benzene:²² examples are the pyrolytic elimination of the elements of methyl hydrogen carbonate from the cyclic hydroxylamine carbonate,⁴ or, at a much lower temperature, of benzyl alcohol from an *N*-hydroxyisoindoline benzyl ether,²³ or of methanesulfonic acid from a corresponding mesylate.²⁴

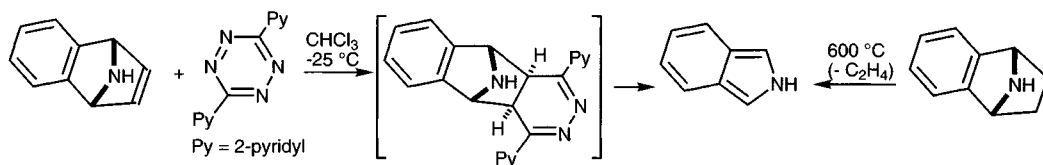


N-substituted isoindoles, too, have generally been made from an isoindoline by elimination processes, thus *N*-oxides can be made to lose water by pyrolysis²⁵ or better, by treatment with acetic anhydride.²⁶

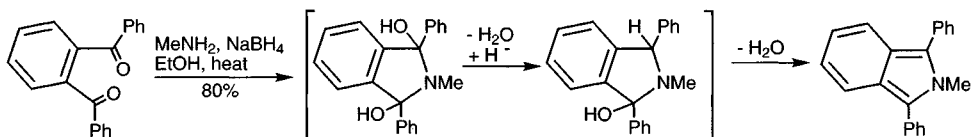
A synthesis of 1-phenylisoindole represents a classical approach to the construction of a heterocycle: a precursor is assembled in which there is an amino group (initially protected in the form of a phthalimide) five atoms away from a carbonyl group with which it must interact and form a cyclic imine.⁶



More recently developed routes involve cycloreversions as final steps;²⁷ each of the starting materials shown below is available from the cycloadduct (cf. section 13.9) of benzyne and 1-methoxycarbonylpyrrole.

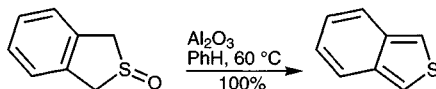


1,3-Diarylisoidoles can be constructed from 1,2-diaroylbenzenes by reaction with an amine and a reducing agent.²⁸

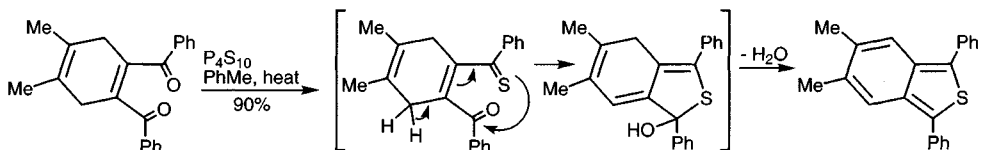


19.4.2 Benzo[*c*]thiophenes

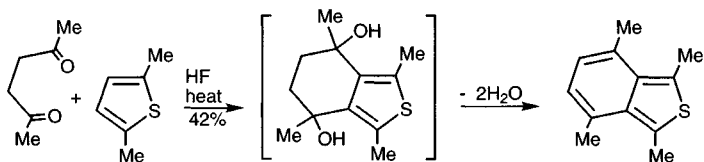
Elimination from dihydrobenzo[*c*]thiophene *S*-oxides has been successfully applied, as for isoindoles, for the preparation of benzo[*c*]thiophenes, including the parent compound.^{19,29}



In a neat manipulation of oxidation levels, the reaction of a 1,4-dihydro-1,2-diaroylbenzenes, such as are available from Diels-Alder addition of buta-1,3-dienes with 1,2-diaroylalkynes, with a sulfur source, produces benzo[*c*]thiophenes;³⁰ note that no reductant is required as would be necessary if a 1,2-aroylbenzene were utilised. These same Diels-Alder adducts react with primary amines to give 2-substituted isoindoles.

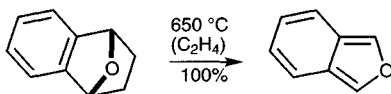


It is comparatively rare for the construction of a benzanellated heterocycle to involve formation of the benzene ring last, however benzo[*c*]thiophenes can be made by this strategy, utilising a double Friedel-Crafts type alkylation of a 2,5-disubstituted (to prevent attack at α -positions) thiophene with a 1,4-diketone.³¹



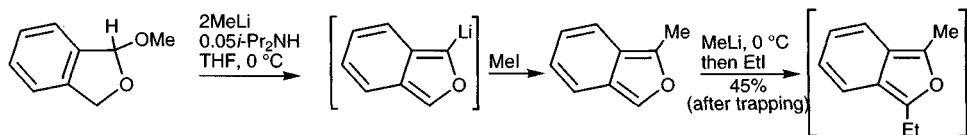
19.4.3 Isobenzofurans

Isobenzofuran can be isolated by trapping on a cold finger, following thermolysis of a suitable precursor such as 1,4-epoxy-1,2,3,4-tetrahydronaphthalene,^{13,32} but although isolable, for trapping experiments it can be conveniently produced by either acid or base-catalysed elimination of methanol from 1-methoxyphthalan in the presence of the intended dienophile.³³

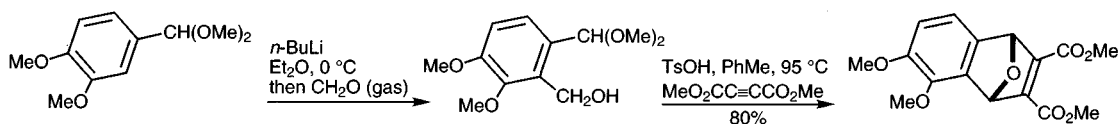


1-Methoxyphthalan is obtained by partial oxidation of 1,2-bis(hydroxymethyl)-benzene with hypochlorite in methanol; treatment with lithium diisopropylamide

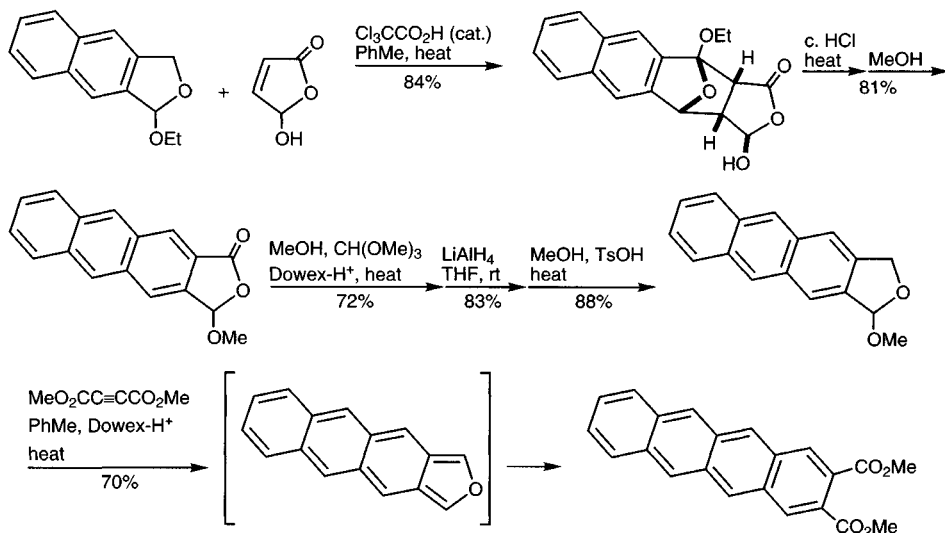
gives isobenzofuran.³⁴ Conditions have been defined whereby this elimination can be run in such a way as to allow immediate ring lithiation; this species then can be further reacted.³⁵



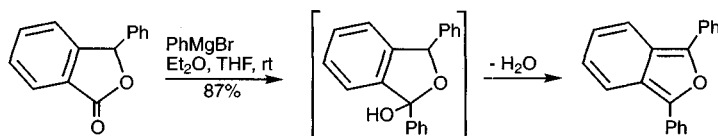
This same oxidation level situation – a disubstituted benzene with aldehyde (ketone) *ortho* to carbinol ready for cyclisation and dehydration to an isobenzofuran – can be achieved in alternative ways: phthalaldehyde can be mono-acetalised, then the remaining aldehyde reduced,³⁶ or lithiation technology can be utilised, as shown below.³⁷



A spectacular demonstration of this approach is provided by the ‘stretched’ isobenzofuran synthesis shown below.³⁸ Note that the first cycloaddition is with a dienophile able to provide the *ortho* related carbinol/aldehyde arrangement ready for the formation of another furan ring.



Most of the stable isobenzofurans are 1,3-diaryl substituted, and are deep yellow. Such compounds are available *via* the partial reduction, and dehydrating cyclisation of 1,2-diaroylbenzenes.³⁹ Both 1-mono- and 1,3-disubstituted isobenzofurans are available from phthalides by Grignard addition then elimination of water.⁴⁰



Exercises for chapter 19

Straightforward revision exercises (consult chapters 16 and 19)

- The [c]-fused heterocycles considered in this chapter are much less stable than the [b]-fused isomers - why?
- What factors favour 1*H*-isoindoles over 2-*H*-isoindoles?
- What is the most characteristic reactivity of the [c]-fused heterocycles considered in this chapter? Give three examples of this typical reactivity.
- Describe one method each for the ring synthesis of isoindoles, benzo[c]thiophenes, and isobenzofurans.

More advanced exercises

- Deduce structures for the compounds formed at each stage in the following sequences: (i) 1,2-bis(bromomethyl)-4-pivaloylbenzene with $\text{H}_2\text{NCH}_2\text{C}\equiv\text{CH}/\text{Et}_3\text{N} \rightarrow \text{C}_{16}\text{H}_{19}\text{NO}$ which was then heated at 500°C producing $\text{C}_{13}\text{H}_{15}\text{NO}$, which was trapped with *N*-phenylmaleimide $\rightarrow \text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_3$ (what is the mechanism of the high temperature reaction?); (ii) phthalaldehyde reacted, in sequence, with 2 x NaHSO_3 , then MeNH_2 , then 2 x $\text{KCN} \rightarrow \text{C}_{10}\text{H}_8\text{N}_2$; (iii) benzoic acid *N,N*-diethylamide with *n*-BuLi then $\text{PhCH}=\text{O}$ then acid $\rightarrow \text{C}_{14}\text{H}_{10}\text{O}_2$ then this with PhMgBr then acid $\rightarrow \text{C}_{20}\text{H}_{14}\text{O}$ and finally this with $\text{O}_2/\text{methylene blue}/h\nu/-50^\circ\text{C} \rightarrow \text{C}_{20}\text{H}_{14}\text{O}_3$; (iv) phthalaldehyde with $\text{HO}(\text{CH}_2)_2\text{OH}/\text{CuSO}_4 \rightarrow \text{C}_{10}\text{H}_{10}\text{O}_3$ then this with NaBH_4 followed by TsOH with $\text{MeO}_2\text{CC}\equiv\text{CCO}_2\text{Me}$ in hot toluene $\rightarrow \text{C}_{14}\text{H}_{12}\text{O}_5$; (v) benzo[c]thiophene with maleic anhydride then hot NaOH then acid $\rightarrow \text{C}_{12}\text{H}_8\text{O}_4$.

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