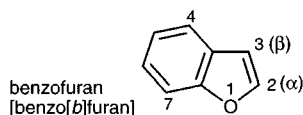
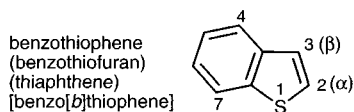
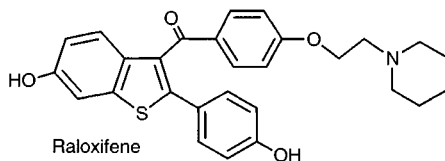
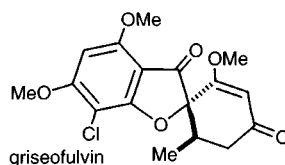
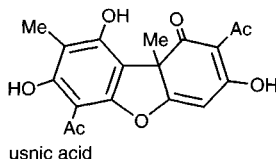
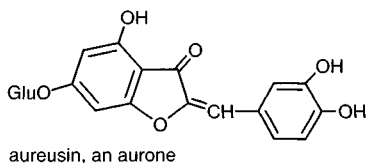


18 Benzo[*b*]thiophenes and benzo[*b*]furans: reactions and synthesis



Benzo[*b*]thiophene¹ and benzo[*b*]furan,² frequently (and in the rest of this chapter) referred to simply as benzothiophene and benzofuran, are the sulfur and oxygen analogues of indole, respectively, but have been much less fully studied. The oxygen system occurs in a range of plant- and microbial-derived natural products, ranging in complexity from 5-methoxybenzofuran, through the orange ‘aurones’, a group of plant pigments isomeric with co-occurring flavones (section 9.2.3.10), usnic acid, a yellow pigment found in many lichens, to griseofulvin, from *Penicillium griseofulvum*, used in medicine as an antifungal agent. Raloxifene shows potential for preventing osteoporosis and reducing the incidence of breast cancer.

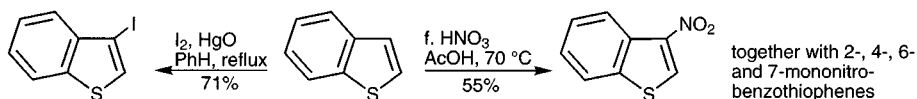


18.1 Reactions with electrophilic reagents

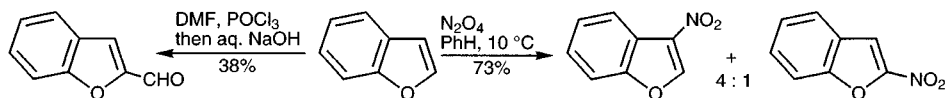
18.1.1 Substitution at carbon

The electrophilic substitution of these systems is much less regioselective than that of indole (effectively complete selectivity for attack at C-3), even to the extent that the hetero-ring positions are only a little more reactive than some of the benzene ring positions. For example, nitration of benzothiophene gives a mixture in which, although more than half the product is the 3-nitro-derivative, 2-nitro-, 4-nitro- 6-nitro- and 7-nitrobenzothiophenes are also all produced, each representing about 10% of the product mixture.³ Measurements of detritiation of 2- and 3-tritiobenzothiophene in trifluoroacetic acid showed rates which were effectively the same for both hetero-ring positions.⁴ Friedel-Crafts alkylation⁵ of benzothiophene gives mixtures in which the 3-isomer predominates over the 2-isomer, however in other substitutions the 3-isomer is said to be the only product – iodination⁶ falls into

this category, as does controlled bromination;⁷ the 2,3-dibromide can be selectively reduced to the 3-monobromo derivative with zinc in acetic acid which must relate to the greater stability of a 2- versus a 3-anion.



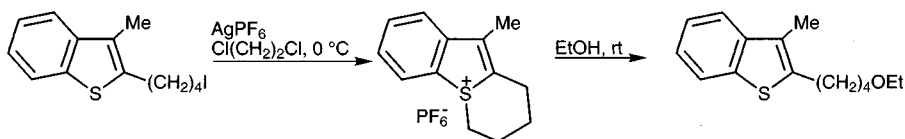
Benzofuran displays a lesser tendency for 3-substitution: formylation of benzofuran reportedly gives only the 2-formyl derivative,⁸ and nitric acid nitration⁹ produces 2-nitrobenzofuran, though in all studies where the isolation of a major product is described, particularly those conducted before the advent of modern analytical techniques, one must be aware that the presence of other minor isomers may have gone undetected; a later study using dinitrogen tetroxide found 3-nitrobenzofuran as a major product together with a smaller percentage of the 2-isomer.¹⁰ Treatment of benzofuran with halogens results in 2,3-addition products,¹¹ with the initial electrophilic attack taking place at C-2; from these addition products, by base-promoted hydrogen halide elimination, 3-monohalo benzofurans can be obtained in high yields.¹² Friedel-Crafts substitution is difficult for hetero-ring unsubstituted benzofurans because typical catalysts tend to cause resinification, but 3-acylations¹³ have been reported using ferric chloride.



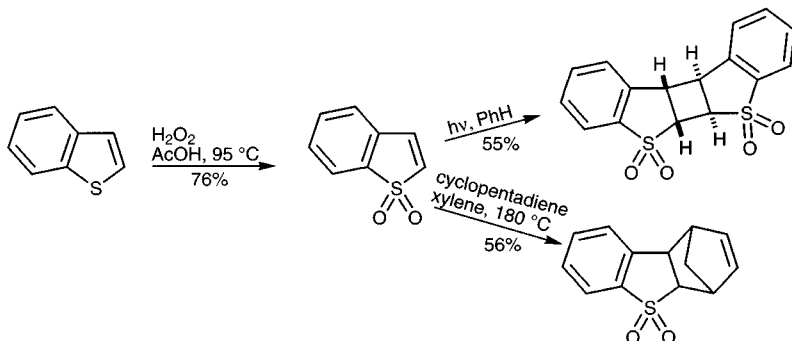
With substituents already present, the pattern of substitution is even more complex: some examples serve to illustrate this. Nitration of 2-bromobenzothiophene results in *ipso* substitution and thus the formation of 2-nitrobenzothiophene whereas 2-chlorobenzothiophene gives the 3-nitro-substitution product;¹⁴ nitration of 3-bromobenzothiophene proceeds in moderate yield to give the 2-nitro derivative.¹⁵ On the other hand 3-carboxy- or 3-acylbenzothiophenes nitrate mainly in the benzene ring.¹⁶ Bromination¹⁷ and Friedel-Crafts substitution¹⁸ of 3-methyl- and 2-methylbenzothiophenes takes place cleanly at the vacant hetero-ring position; similarly 2-bromobenzothiophene undergoes formylation at C-3.¹⁹ 3-Methoxybenzothiophene gives the corresponding 2-aldehyde under Vilsmeier conditions at moderate temperatures but at 95 °C 3-chlorobenzothiophene-2-carboxaldehyde is obtained;²⁰ 6-ethoxybenzothiophene formylates at C-2.²¹

18.1.2 Addition to sulfur in benzothiophenes

Benzothiophenium salts are produced by the reaction of the sulfur heterocycle with more powerful alkylating combinations such as Meerwein salts;²² benzothiophenium salts can themselves act as powerful alkylating agents with fission of the C-S⁺ bond.²³

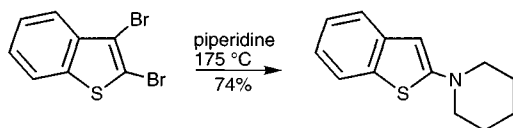


S-Oxidation produces 1,1-dioxides which readily undergo cycloadditions as dienophiles,²⁴ or photodimerisation, the head-to-head dimer (shown) being the major product.²⁵



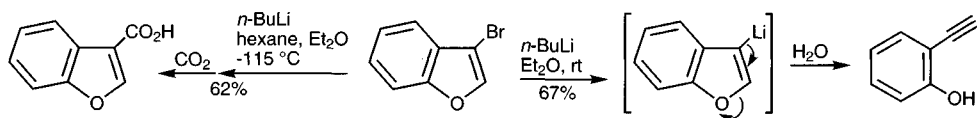
18.2 Reactions with nucleophilic reagents

Halogen at a benzothiophene 2-position is subject to displacement with amine nucleophiles,²⁶ and, surprisingly, rather more easily than halogen at the 3-position, even though an intermediate for 3-attack carries negative charge at C-2, adjacent to the hetero atom. Equally surprising are reactions in which secondary amine anions add to benzothiophene to give 2-dialkylamino-2,3-dihydrobenzothiophenes;²⁷ with irradiation, addition of primary amines gives 3-alkylamino-2,3-dihydrobenzothiophenes.²⁸ *Ipso* displacement²⁹ of bromine from 3-bromo-2-nitrobenzothiophene can sometimes be accompanied by rearranged products.³⁰

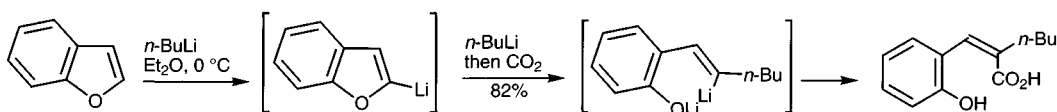


18.3 Reactions with bases; reactions of C-metallated benzo[*b*]thiophenes and benzo[*b*]furans

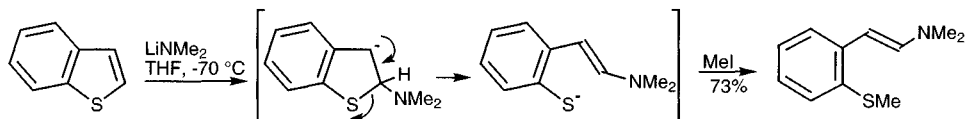
In some of the earliest uses of *n*-butyllithium, 2-lithiobenzofuran was obtained by metal-halogen exchange between the 2-bromo-heterocycle and *n*-butyllithium,³¹ or by deprotonation of benzofuran.³² The generation of 3-metallated benzofurans generally results in fragmentation with the production of 2-hydroxyphenylacetylene at room temperature,^{28,33} though the 3-lithio-derivative can be utilised at very low temperature.³⁴



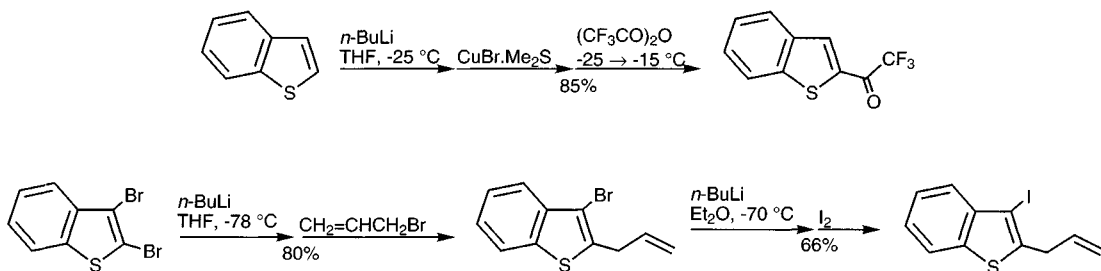
In a sequence which may involve a carbene as intermediate, 2-lithiobenzofuran reacts with aryl- or alkylolithiums with ring opening, as shown.³⁵



Sodium amide causes ring cleavage of benzothiophene to produce 2-ethynylphenylthiol.³⁶ Ring opening in a rather different manner results from exposure of the heterocycle to lithium dimethylamide, followed by trapping with iodomethane, producing an enamine which must result from initial addition at C-2, perhaps by a minor pathway, but one which then leads to ring-opening elimination.³⁷

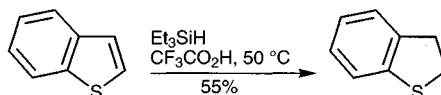


3-Lithiobenzothiophenes can be generated, and reacted with electrophiles, if the temperature is kept low.³⁸ Direct deprotonation of benzothiophenes follows the usual pattern for five-membered heterocycles and takes place adjacent to the heteroatom,³⁹ and in concord with this pattern, metal-halogen exchange processes favour a 2- over a 3-halogen; the sequence below shows how this can be utilised to develop substituted benzothiophenes.⁴⁰ 2-Lithiated reagents can be used to react with electrophiles: for example reaction with *p*-toluenesulfonyl cyanide produces the 2-cyano derivatives.⁴¹ 2-Trialkylstannylbenzofurans⁴² and benzofuran-2-⁴³ and benzothiophene-2-boronic acids⁴⁴ have been used in palladium-catalysed coupling with aromatic halides, in the last case with morphine triflate.



18.4 Reactions with oxidising and reducing agents

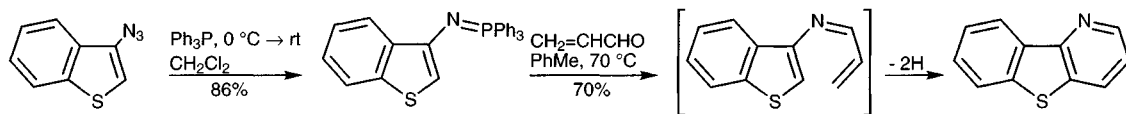
Hydrodesulfurisation of benzothiophenes is conveniently achieved using Raney nickel,⁴⁵ and before the advent of modern spectroscopic methods was utilised in the determination of structure of substituted benzothiophenes by conversion to a recognisable derivative.



Reduction of the hetero-rings of both benzofuran and benzothiophene, notably with retention of the sulfur in the latter case, can be achieved using triethylsilane in acidic solution giving 2,3-dihydro-derivatives.⁴⁶ 2,3-Dihydroxylation of benzofuran and benzothiophene can be achieved using *Pseudomonas putida*;⁴⁷ *S*-oxidation of the sulfur in the latter heterocycle using the same microbiological method has also been reported.⁴⁸

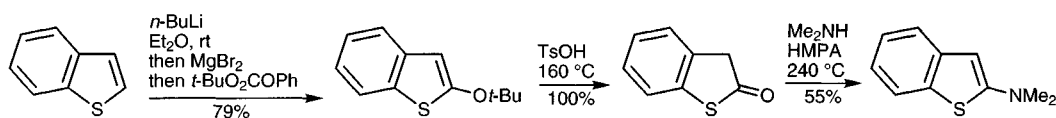
18.5 Electrocyclic reactions

The fusion of a pyridine ring onto benzothiophene can be achieved using either the 2- or 3-azides which after a Staudinger reaction give ylides which undergo aza-Wittig condensations with unsaturated aldehydes, the ensuing electrocyclicisation being followed by spontaneous dehydrogenation.⁴⁹



18.6 Oxy-⁵⁰ and amino-benzothiophenes and -benzofurans

Benzothiophen-2-ones can be conveniently accessed by oxidation of 2-lithiobenzothiophenes.⁵¹ Benzothiophen-2-one will condense at the 3-position with aromatic aldehydes;⁵² benzothiophen-3-one reacts comparably at its 2-position.⁵³



Both benzofuran-2-one, known trivially in the older literature as coumaranone, and best viewed as a lactone, and the isomeric benzofuran-3-one, form ambident anions by deprotonation at a methylene group, the former⁵⁴ requiring a stronger base than the latter.⁵⁵

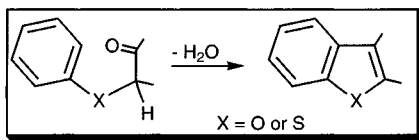
Little is known of simple 2- and 3-amino-derivatives; 2-dialkylaminobenzothiophenes can be obtained by reaction of benzothiophene-2-thiol with secondary amines.⁵¹ In many ways 2-aminobenzothiophene behaves like a normal aromatic amine, but diazotisation leads directly to benzothiophen-2-one.⁵⁶

18.7 Synthesis of benzo[*b*]thiophenes and benzo[*b*]furans

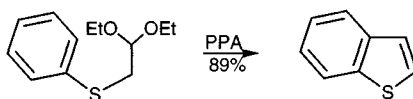
18.7.1 Ring synthesis

18.7.1.1 From 2-arylthio- or 2-aryloxyaldehydes, -ketones or -acids

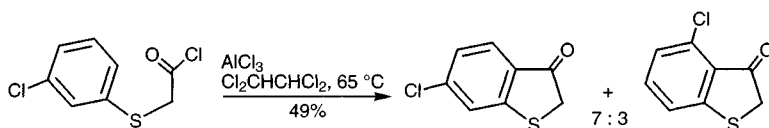
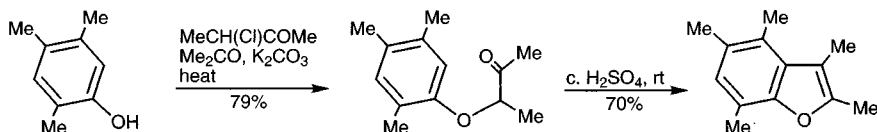
Cyclisation of 2-arylthio- or 2-aryloxyaldehydes, -ketones or -acids *via* intramolecular electrophilic attack on the aromatic ring, with loss of water, creates the heterocyclic ring; this route is the commonest method for benzothiophenes.



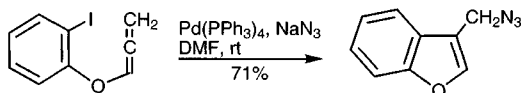
In order to produce hetero-ring unsubstituted benzothiophenes⁵⁷ an arylthioacetaldehyde acetal is generally employed prepared, in turn, from bromoacetaldehyde acetal and the thiophenol. An exactly parallel sequence produces 2,3-unsubstituted benzofurans.⁵⁸



Comparable acid-catalysed ring closures of 2-arylthio-⁵⁹ and 2-aryloxy-⁶⁰ -ketones, and -2-arylthio-⁶¹ and 2-aryloxyacetyl⁶² chlorides lead to 3-substituted heterocycles and 3-oxygenated heterocycles respectively. Attempted formation of 3-ary/benzothiophenes by this route is always accompanied by partial or complete isomerisation to the 2-aryl-heterocycle.⁶³

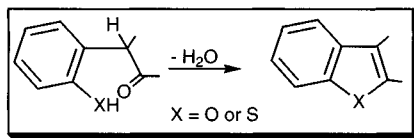


The closure of *O*-allenyl *ortho*-iodophenols using palladium(0) catalysis produces species which can be trapped with azide.⁶⁴

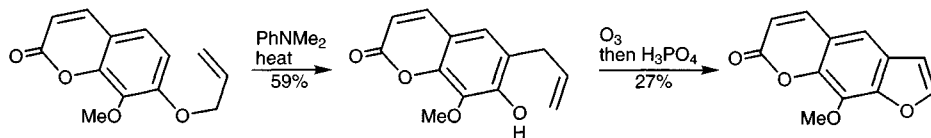


18.7.1.2 From 2-(*ortho*-hydroxy(or thioxy)aryl)-acetaldehydes, -ketones or -acids

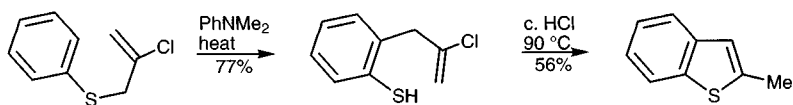
Cyclising dehydration of 2-(*ortho*-hydroxyaryl)-acetaldehydes, -ketones or -acids (and in some cases sulfur analogues) give the heterocycles; this route is important for benzofurans.



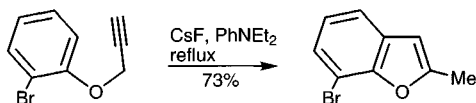
Claisen rearrangement of allyl phenolic ethers, followed by oxidation of the alkene generates *ortho*-hydroxyarylacetaldehydes which close to give benzofurans under acid catalysis.⁶⁵ The formation of 2-substituted benzofurans from 2-(*ortho*-hydroxyaryl)-ketones is also very easy.⁶⁶



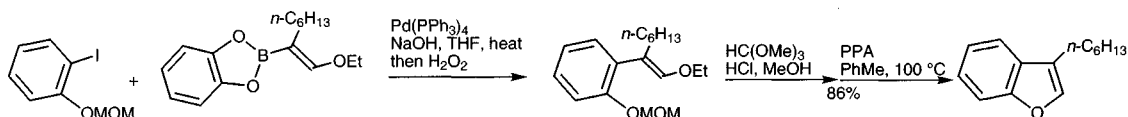
The employment of aryl 2-chloroprop-2-enyl sulfides (or ethers) as thio-Claisen rearrangement substrates neatly eliminates the necessity for an oxidative step thus providing a route to 2-methylbenzothiophenes (-benzofurans).⁶⁷



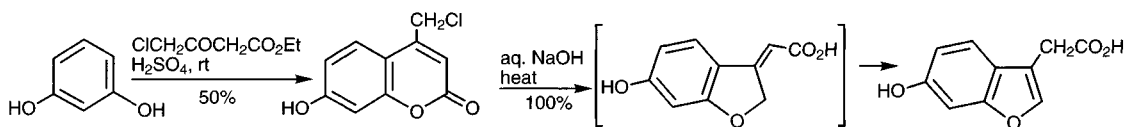
Propargyl aryl ethers undergo a Claisen rearrangement and then ring closure to produce 2-methylbenzofurans.⁶⁸



Another route to compounds of the same oxidation level involves palladium-catalysed coupling of enol ethers.⁶⁹

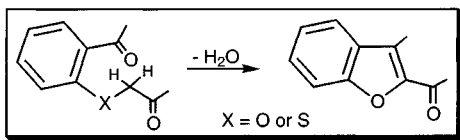


4-Chloromethylcoumarins can be converted into benzofuran-3-acetic acids by exposure to alkali – hydrolysis of the lactone and then reclosure with displacement of chloride by the phenolate leads to the benzofuran.⁷⁰

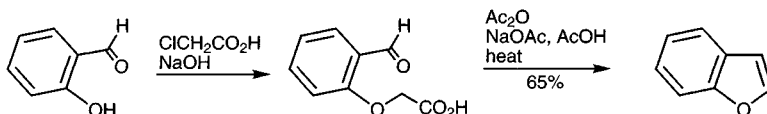


18.7.1.3 From *ortho*-acylaryloxy- or -arylthioacetic acids (esters) (ketones)

Cyclising condensation of *ortho*-acylaryloxy- or -arylthioacetic acids (esters) or ketones gives the bicyclic heterocycles.

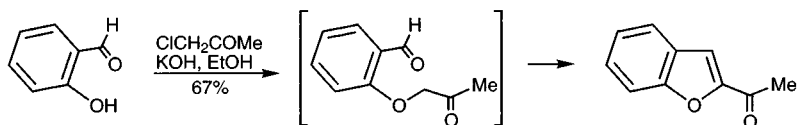


Intramolecular aldol/Perkin type condensation of *ortho*-formylaryloxyacetic acids and arylthioacetic esters produces benzofuran⁷¹ and benzothiophene-2-esters⁷² respectively, as illustrated below. *ortho*-Formyl- or *ortho*-acylaryl benzyl ethers, in which the benzyl group carries an electron-withdrawing substituent, can be comparably closed to produce 2-arylbenzofurans, using potassium fluoride or caesium fluoride on alumina.⁷³

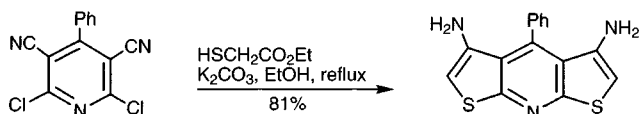




ortho-Hydroxyaryl aldehydes or ketones, by *O*-alkylation with α -haloketones afford substrates which on intramolecular aldol condensation produce 2-acyl benzofurans.⁷⁴

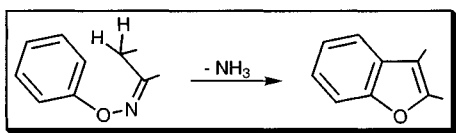


If, instead of an *ortho* carbonyl group, cyclisation is conducted with an *ortho* nitrile, then 3-aminoheterocycles result – the example shows how in appropriately activated situations, both the introduction of the thioacetate and the cyclisation can take place in one pot.⁷⁵

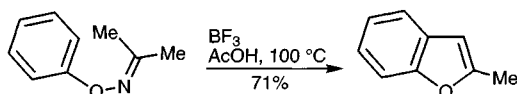


18.7.1.4 From *O*-aryl ketoximes

The electrocyclic rearrangement of *O*-aryl ketoximes produces benzofurans.

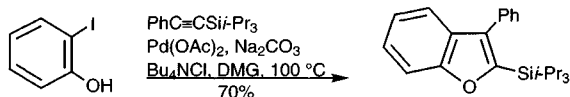
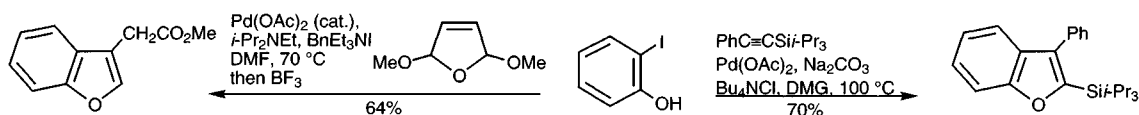


The acid-catalysed rearrangement of *O*-aryl ketoximes,⁷⁶ which produces benzofurans, exactly parallels the rearrangement of phenylhydrazones, which gives indoles – the classical Fischer indole synthesis (section 17.16.1).

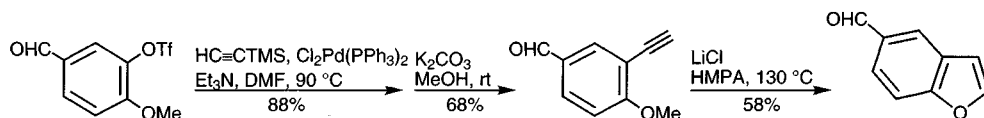


18.7.1.5 From *ortho*-iodophenols

With the advent of palladium(0) catalytic methods, it is now possible to produce the furan ring of a benzofuran by interaction between an *ortho*-iodophenol and an alkyne, the two carbon atoms of the triple bond providing carbons 2 and 3 of the furan ring and the larger substituent of the alkyne ending up at the heterocyclic 2-position.⁷⁷ The sequence has been conducted on solid support.⁷⁸ Coupling with 2,5-dihydro-2,5-dimethoxyfuran leads to methyl benzofuran-3-acetate.⁷⁹

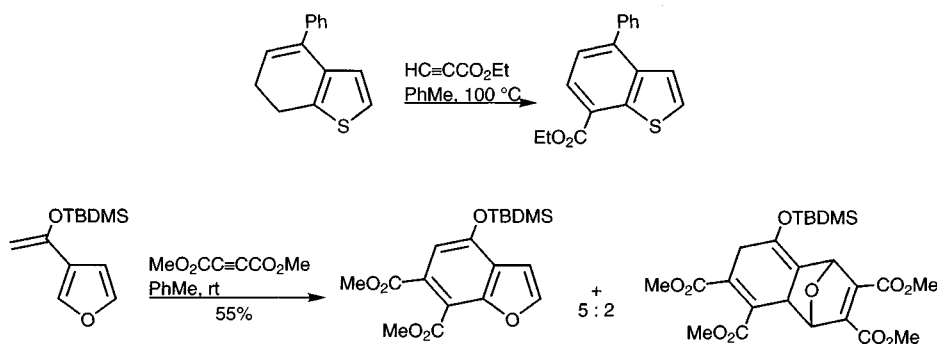


Coupling between alkynes and *ortho*-methoxy triflates produces precursors which cyclise to benzofurans with hot lithium chloride.⁸⁰

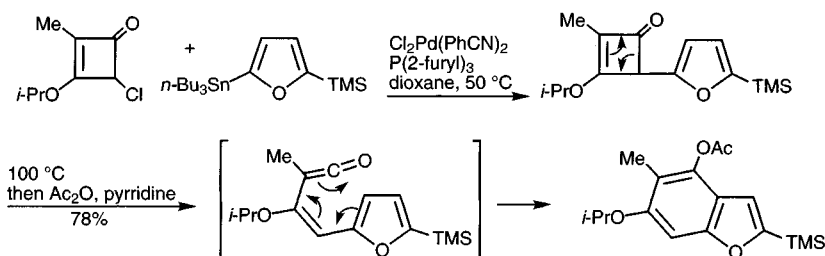


18.7.1.6 Syntheses which involve making the benzene ring

6,7-Dihydrobenzothiophenes react as dienes with alkynes, subsequent retro-Diels-Alder elimination of ethene giving a benzothiophene, as illustrated.⁸¹ In a similar fashion, the silyl enol ether derived from 3-acetylfuran undergoes cycloadditions giving 4-oxygenated benzofurans.⁸²

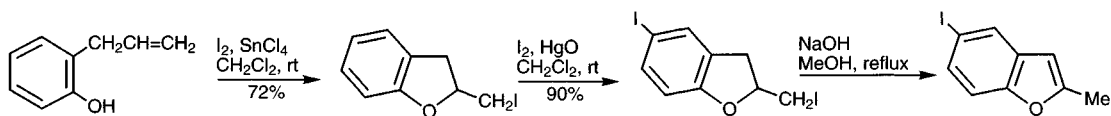


The coupling of furyl and thienyl stannanes to 4-chlorocyclobut-2-enones⁸³ or the addition of furylcerium reagents to cyclobut-3-ene-1,2-dione monoacetals⁸⁴ have been used to synthesise cyclobutenones which on heating ring open to unsaturated ketenes which then undergo an electrocyclic closure producing benzofurans or benzothiophenes with an oxygen substituent at C-4.



18.7.1.7 From partially reduced benzofurans and benzothiophenes

It can be an advantage for the introduction of benzene ring substituents to operate with hetero-ring-reduced derivatives, the aromatic heterocycle being obtained by a final dehydrogenation. 2,3-Dihydrobenzothiophenes can be oxidised up with sulfuryl chloride or *N*-chlorosuccinimide;⁸⁵ 2,3-dichloro-5,6-dicyanobenzoquinone has been employed to dehydrogenate 2,3-dihydrobenzofurans.⁸⁶ In the example below a benzene ring substitution is followed by aromatisation via elimination of hydrogen iodide and isomerisation of the double bond into the aromatic position.⁸⁷



Exercises for chapter 18

Straightforward revision exercises (consult Chapters 16 and 18)

- In the electrophilic substitution of benzothiophene and benzofuran there is less selectivity than for comparable reactions of indole – why?
- What is the principal method for the efficient introduction of substituents to the 2-positions of benzofuran and benzothiophene?
- Beginning from a phenol carrying no substituents *ortho* to the hydroxyl, describe two methods for the synthesis of benzofurans.
- How can salicaldehydes be used for the synthesis of benzofurans?

More advanced exercises

- Suggest structures for the compounds formed at each stage in the following sequence: PhSH with $\text{ClCH}_2\text{COCH}_2\text{CO}_2\text{Et}$ ($\rightarrow \text{C}_{12}\text{H}_{14}\text{SO}_3$), then PPA/heat ($\rightarrow \text{C}_{12}\text{H}_{12}\text{SO}_2$), then NH_3 ($\rightarrow \text{C}_{10}\text{H}_9\text{NSO}$), then LiAlH_4 ($\rightarrow \text{C}_{10}\text{H}_{11}\text{NS}$), then HCO_2H /heat, ($\rightarrow \text{C}_{11}\text{H}_{11}\text{NSO}$) then POCl_3 /heat giving finally a tricyclic substance, $\text{C}_{11}\text{H}_9\text{NS}$.
- Draw structures for the heterocycles formed from the following combinations: (i) $\text{C}_{13}\text{H}_{16}\text{O}$ from 2,4,5-trimethylphenol with 3-chloro-2-butanone then the product with c. H_2SO_4 ; (ii) $\text{C}_{12}\text{H}_8\text{O}_4$ from 7-hydroxy-8-methoxycoumarin with $\text{CH}_2=\text{CHCH}_2\text{Br}/\text{K}_2\text{CO}_3$ then the product heated strongly giving an isomer, then reacted successively with O_3 then H^+ ; (iii) 4-trifluoromethylfluorobenzene with LDA then DMF ($\rightarrow \text{C}_8\text{H}_4\text{F}_4\text{O}$), then with $\text{HSCH}_2\text{CO}_2\text{Me}/\text{NaH}$ giving $\text{C}_{11}\text{H}_7\text{F}_3\text{O}_2\text{S}$; (iv) $\text{C}_9\text{H}_7\text{NO}_3$ from 4-fluoronitrobenzene with $\text{Me}_2\text{C}=\text{NONa}$ then c. HCl /heat.
- Deduce structures for the bi- and tetracyclic heterocycles formed in the following two steps respectively: 4-chlorophenylthioacetic acid with PCl_3 then AlCl_3 ($\rightarrow \text{C}_8\text{H}_5\text{ClOS}$), then this with phenylhydrazine in hot AcOH $\rightarrow \text{C}_{14}\text{H}_8\text{ClNS}$.

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