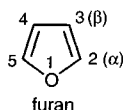
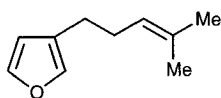


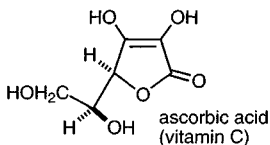
15 Furans: reactions and synthesis



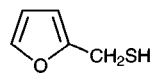
Furans¹ are volatile, fairly stable compounds with pleasant odours. Furan itself is slightly soluble in water. It is readily available, and its commercial importance is mainly due to its role as the precursor of the very widely used solvent tetrahydrofuran (THF). Furan is produced by the gas-phase decarbonylation of furfural (2-formylfuran, furan-2-carboxaldehyde), which in turn is prepared in very large quantities by the action of acids on vegetable residues mainly from the manufacture of porridge oats and cornflakes. Furfural was first prepared in this way as far back as 1831 and its name is derived from *furfur* which is the latin word for bran; in due course, in 1870, the word furan was coined from the same root.



perillene

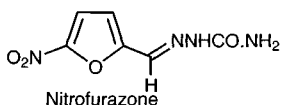


ascorbic acid
(vitamin C)

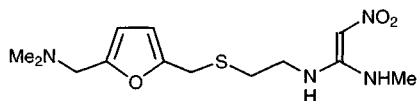


furfuryl thiol

The aromatic furan ring system, though not found in animal metabolism, occurs widely in secondary plant metabolites, especially in terpenoids: perillene is a simple example. Vitamin C, ascorbic acid, is at the oxidation level of a trihydroxyfuran, though it assumes an unsaturated lactone tautomeric form. Though one normally associates thiols with unpleasant odours, furfuryl thiol is present in the aroma of roasted coffee. Some 5-nitrofurfural derivatives are important in medicine, Nitrofurazone, a bactericide, is a simple example. Ranitidine is one of the most commercially successful medicines ever developed; it is used for the treatment of stomach ulcers.



Nitrofurazone



Ranitidine

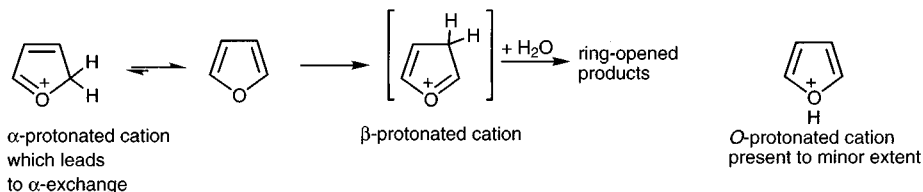
15.1 Reactions with electrophilic reagents

Of the three five-membered systems with one heteroatom considered in this book, furan is the 'least aromatic' and as such has the greatest tendency to react in such a way as to give addition products – this is true in the context of its interaction with the usual electrophilic substitution reagents, considered in this section, as well as in Diels-Alder type processes (section 15.9).

15.1.1 Protonation

Furan and the simple alkyl furans are relatively stable to aqueous mineral acids, though furan is instantly decomposed by concentrated sulfuric acid or by Lewis acids

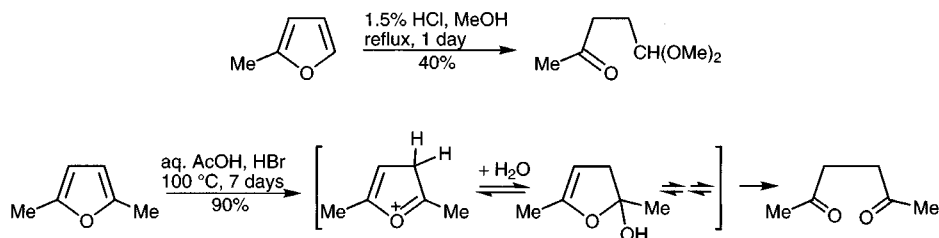
such as aluminium chloride. Furan reacts only slowly with hydrogen chloride either as the concentrated aqueous acid or in a non-hydroxylic organic solvent. Hot dilute aqueous mineral acids cause hydrolytic ring-opening.



No pK_a value is available for O -protonation of furan but it is probably much less basic at oxygen than an aliphatic ether. Acid-catalysed deuteration occurs at an α -position;² 3/4-deuteriofurans are not obtained because, although β -protonation probably occurs, the cation produced is more susceptible to water, leading to hydrolytic ring opening. An estimate of $pK_a -10.0$ was made for the 2-protonation of 2,5-di-*t*-butylfuran which implies a value of about -13 for furan itself.³ An α -protonated cation, stable in solution, is produced on treatment of 2,5-di-*t*-butylfuran with concentrated sulfuric acid.^{3,4}

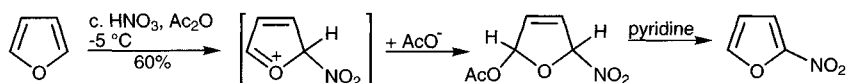
15.1.1.1 Reactions of protonated furans

The hydrolysis (or alcoholysis) of furans involves nucleophilic addition of water (or alcohol) to an initially formed cation, giving rise to open-chain 1,4-dicarbonyl compounds or derivatives thereof. This is in effect the reverse of one of the general methods for the construction of furan rings (section 15.14.1.1). Succindialdehyde cannot be obtained from furan itself, presumably because this dialdehyde is too reactive under conditions for hydrolysis, but some alkylfurans can be converted into 1,4-dicarbonyl products quite efficiently, and this can be viewed as a good method for their synthesis, of cyclopentenones derived from them.⁵ Other routes from furans to 1,4-dicarbonyl compounds are the hydrolysis of 2,5-dialkoxytetrahydrofurans (section 15.1.4) and by various oxidative procedures (section 15.2).



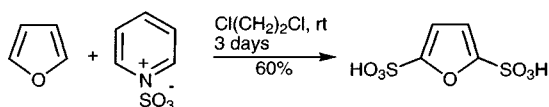
15.1.2 Nitration

Sensitivity precludes the use of concentrated acid nitrating mixtures. Reaction of furan, or substituted furans⁶ with acetyl nitrate produces non-aromatic adducts, in which progress to a substitution product has been interrupted by nucleophilic addition of acetate to the cationic intermediate, usually⁷ at C-5.⁸ Aromatisation, by loss of acetic acid, to give the nitro-substitution product, will take place under solvolytic conditions, but is better effected by treatment with a weak base like pyridine.⁹ Further nitration of 2-nitrofuran gives 2,5-dinitrofuran as the main product.¹⁰



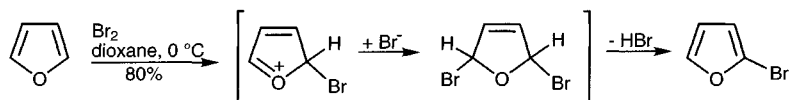
15.1.3 Sulfonation

Furan and its simple alkyl derivatives are decomposed by the usual strong acid reagents, but the pyridine sulfur trioxide complex can be used, disubstitution of furan being observed even at room temperature.¹¹

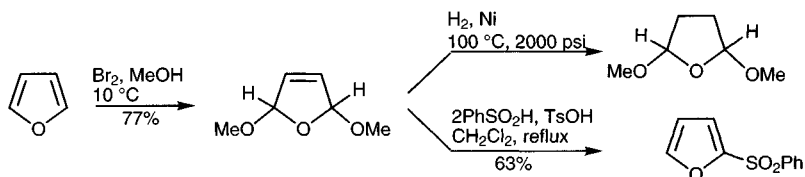


15.1.4 Halogenation

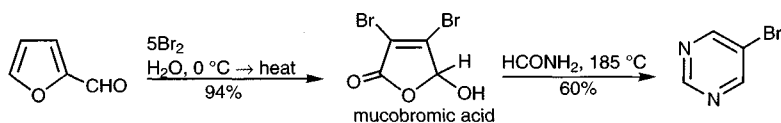
Furan reacts vigorously with chlorine and bromine at room temperature to give polyhalogenated products, but does not react at all with iodine. More controlled conditions can give 2-bromofuran¹² in a process which probably proceeds *via* a 1,4-dibromo-1,4-dihydro-adduct, indeed such species have been observed at low temperature using ¹H NMR spectroscopy.¹³ Reaction with bromine in dimethylformamide at room temperature smoothly produces 2-bromo- or 2,5-dibromofurans.¹⁴



If the bromination is conducted in methanol, trapping of intermediate by C-5 addition of the alcohol then methanolysis of C-2-bromide produces 2,5-dialkoxy-2,5-dihydrofurans, as mixtures of *cis* and *trans* isomers;¹⁵ hydrogenation of these species affords 2,5-dialkoxytetrahydrofurans, extremely useful as 1,4-dicarbonyl synthons – the unsubstituted example is equivalent to succindialdehyde¹⁶ – and heating with benzenethiol or phenyl sulfinic acid in acid gives 2-sulfur-substituted furans.¹⁷ 2,5-Dialkoxy-2,5-dihydrofurans can also be obtained by electrochemical oxidation in alcohol solvents^{15,18} or conveniently by oxidation with magnesium monoperoxyphthalate in methanol¹⁹ (see also Oxidation, section 15.2).

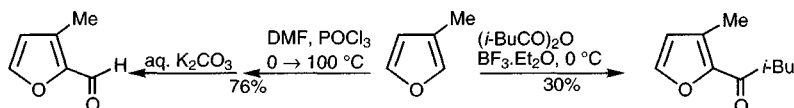


The intrinsically high reactivity of the furan nucleus can be further exemplified by the reaction of furfural with excess halogen to produce ‘mucohalic acids’; incidentally, mucobromic acid reacts with formamide to provide a useful synthesis of 5-bromopyrimidine.²⁰ On the other hand, with control, methyl furoate can be cleanly converted into its 5-mono-bromo- or 4,5-dibromo-derivatives; hydrolysis and decarboxylation of the latter then affording 2,3-dibromofuran;²¹ bromination of 3-furoic acid produces the 5-monobromo-acid.²²



15.1.5 Acylation

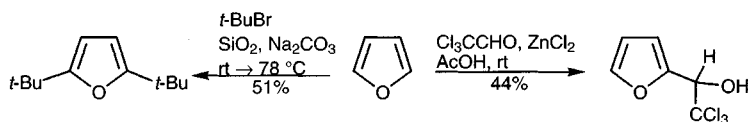
Carboxylic acid anhydrides or halides normally require the presence of Lewis acid (often boron trifluoride) for Friedel-Crafts acylation of furans, though trifluoroacetic anhydride will react alone. The rate of aluminium chloride catalysed acetylation of furan shows the α -position to be 7×10^4 times more reactive than the β -position.²³ 3-Alkylfurans substitute mainly at C-2;²⁴ 2,5-dialkylfurans can be acylated at a β -position, but generally with more difficulty.



Vilsmeier formylation of furans is a good route to formylfurans,²⁵ though the ready availability of furfural as a starting material, and methods involving lithiated furans (section 15.4.1) are important. Formylation of substituted furans follows the rule that the strong tendency for α -substitution overrides other factors, thus both 2-methylfuran²⁶ and methyl furan-3-carboxylate²⁷ give the 5-aldehyde; 3-methylfuran gives mainly the 2-aldehyde.²⁸

15.1.6 Alkylation

Traditional Friedel-Crafts alkylation is not generally practicable in the furan series, partly because of catalyst-caused polymerisation and partly because of polyalkylation. Instances of preparatively useful reactions include: production of 2,5-bis-*t*-butylfuran²⁹ from furan or furoic acid³⁰ and the isopropylation of methyl furoate with double substitution, at 3- and 4-positions.²⁸

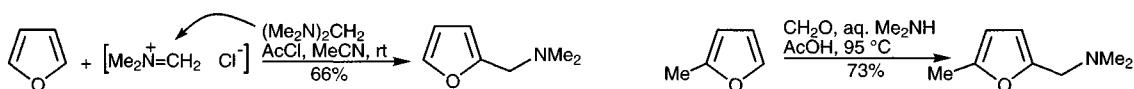


15.1.7 Condensation with aldehydes and ketones

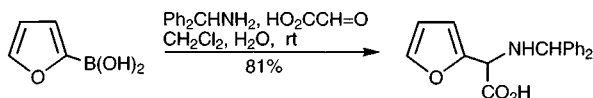
This occurs by acid catalysis, but generally the immediate product, a furfuryl alcohol, reacts further; 2-(3,3,3-trichloro-1-hydroxy)ethylfuran can however be isolated.³¹ A macrocycle can be obtained by condensation with acetone³² via a sequence exactly comparable to that described for pyrrole (section 13.1.7).

15.1.8 Condensation with imines and iminium ions

Early attempts to effect Mannich reactions with furan itself failed, though mono-alkylfurans undergo the reaction normally,³³ but by reaction with preformed iminium salt normal 2-substitution of furan itself occurs at room temperature.³⁴

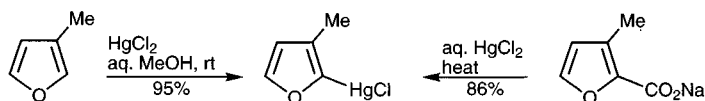


More recently the use of furan boronic acids has allowed Mannich substitutions at both α and β positions, and also incidentally with primary amine components.³⁵



15.1.9 Mercuration

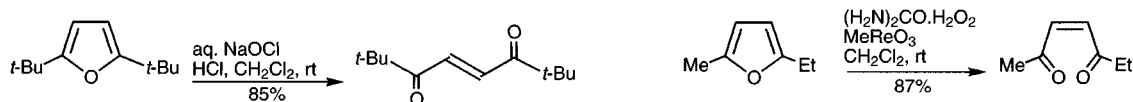
Mercuration takes place very readily with replacement of hydrogen, or carbon dioxide from an acid.³⁶



15.2 Reactions with oxidising agents

The electrochemical or bromine/methanol oxidations of furans to give 2,5-dialkoxy-2,5-dihydrofurans (section 15.1.4), and the cycloaddition of singlet oxygen (section 15.9) are discussed elsewhere. Reaction of furan with lead(IV) carboxylates produces 2,5-diacyloxy-2,5-dihydrofurans in useful yields.³⁷

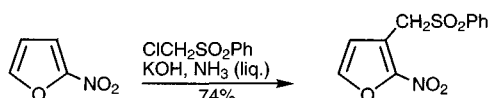
In related chemistry, the ring-opened, Δ^2 -unsaturated 1,4-diones can be obtained in *E*- or *Z*-form using reagents such as bromine in aqueous acetone, *meta*-chloroperbenzoic acid, or sodium hypochlorite; an example is given below.³⁰ Even but-2-en-1,4-dial (malealdehyde) itself, can be produced by oxidation with dimethyldioxirane,³⁸ and urea/hydrogen peroxide adduct, with catalytic methyltrioxorhenium(VII) has been shown to oxidise a range of furans to *cis* enediones.³⁹



Certain oxidants, ruthenium tetroxide for example, completely destroy furan rings; oxidation of a 2-substituted furan leaves just one carbon of the original heterocycle as a carboxylic acid, without disrupting sensitive functionality in the side-chain.⁴⁰

15.3 Reactions with nucleophilic reagents

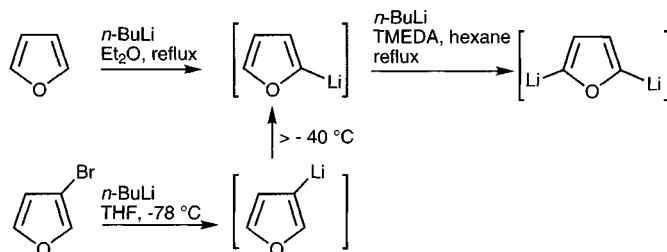
Simple furans do not react with nucleophiles by addition or by substitution. Nitro substituents activate the displacement of halogen, as in benzene chemistry and VNS methodology (section 2.3.3) has also been applied to nitrofurans.⁴¹



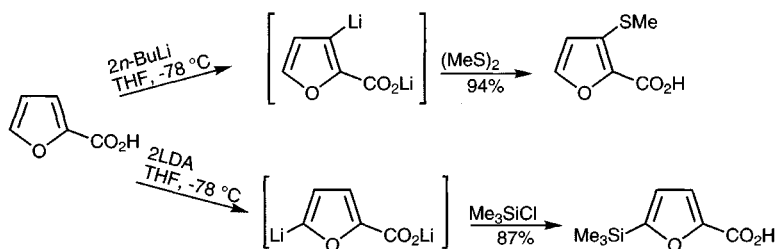
15.4 Reactions with bases

15.4.1 Deprotonation of C-hydrogen

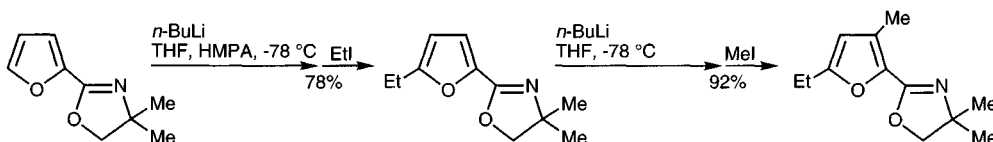
Metallation with alkylolithiums proceeds selectively at an α -position, indeed metallation of furan is one of the earliest examples⁴² of the now familiar practice of aromatic ring-metallation. The preference for α -deprotonation is nicely illustrated by the demonstration that 3-lithiofuran, produced from 3-bromofuran by metal/halogen exchange at -78°C , equilibrates to the more stable 2-lithiofuran if the temperature rises to $> -40^\circ\text{C}$;⁴³ more forcing conditions can bring about 2,5-dilithiation of furan.⁴⁴



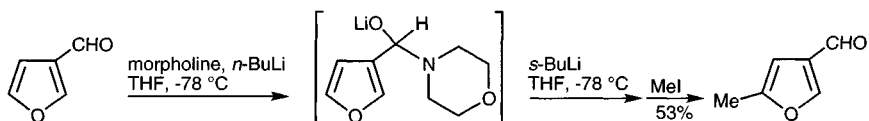
Lithium diisopropylamide can effect C-2-deprotonation of 3-halofurans.⁴⁵ With furoic acid and two equivalents of lithium diisopropylamide, selective formation of the lithium carboxylate/5-lithio compound is found,⁴⁶ whereas *n*-butyllithium, via *ortho*-assistance, produces the lithium carboxylate/3-lithio derivative.⁴⁷



Ortho direction of metallation to C-3 by 2-bis(dimethylamino)phosphate⁴⁸ and 2-oxazoline⁴⁹ groups, and to C-2 by 3-hydroxymethyl⁵⁰ have also been described. 5-Lithiation of furans with non-directing groups at C-2 provides a route to 2,5-disubstituted furans but choice of lithiating conditions can outweigh *ortho* directing effects as illustrated.⁵¹



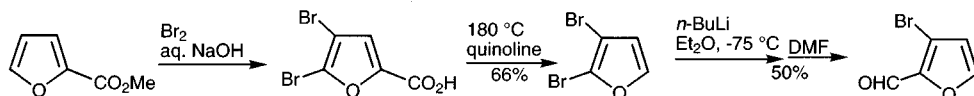
A synthetically useful regioselective 5-lithiation of 3-formylfuran⁵² can be achieved by first adding lithium morpholide to the aldehyde and then lithiation at C-5, resulting finally in 2-substituted 4-formylfurans, as is illustrated below.⁵³



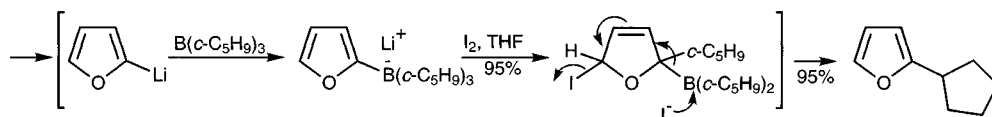
15.5 Reactions of C-metallated furans

15.5.1 Lithium derivatives

Metallation at C-3 can be achieved *via* metal/halogen exchange. The greater stability of a carbanion at an α -position shows up again in a mono-exchange of 2,3-dibromofuran with selective replacement of the α -bromine.^{28,54}



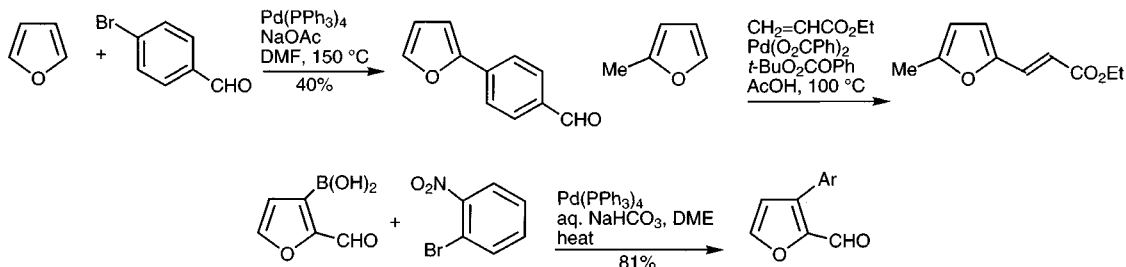
There are many examples of the use of 2- and 3-lithiofurans in reactions with various electrophilic species, such as aldehydes and ketones,^{42,55} and halides.⁵⁶ It has been shown that treatment of 2-lithiofuran with copper(II) chloride leads to 2,2'-bifuran,⁵⁷ and with trialkylboranes to borates, subsequent treatment of which with halogen provides an excellent method for the overall introduction of alkyl groups at the furan α -position.⁵⁸



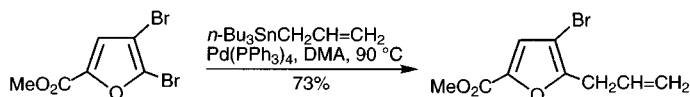
3-Lithiofuran, best obtained⁵⁹ from 3-bromofuran, reacts with bis(trimethylsilyl)-peroxide to provide the trimethylsilyl ether of 3-hydroxyfuran directly.⁶⁰ Oxidation of a 2-boronate ester is a means for the synthesis of butenolides (section 15.13.1).⁶¹ Furan-2- and 3-boronic acids have been made by reaction of the lithiated species with tributylborate in the usual way.⁶²

15.5.2 Palladium-catalysed couplings

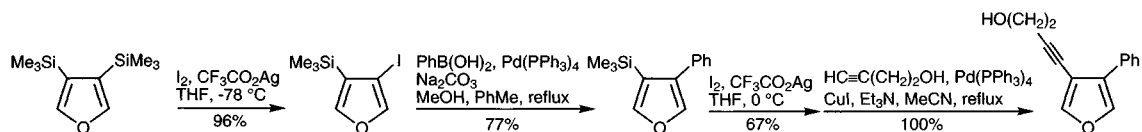
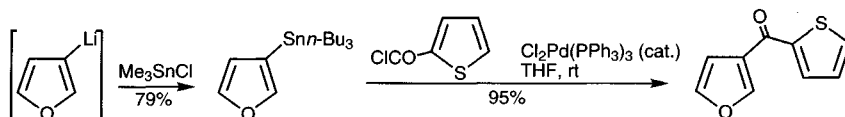
Palladium chemistry has been utilised to introduce aryl groups to a furan α -position⁶³ by substitution of hydrogen, and *via* boronic acids,⁶⁴ and in Heck-type alkenylations, again at C-2,⁶⁵ *via* 'oxidative' type palladation (*cf.* section 2.7.2.1).



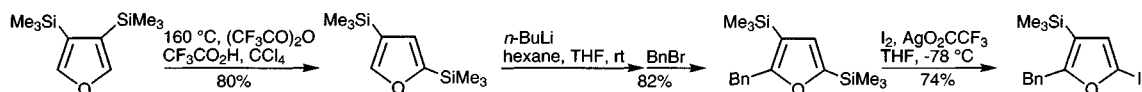
Regioselectivity for 2-bromo over 3-bromo is displayed in palladium(0)-catalysed processes.⁶⁶



Both 3- and 3,4-bis(tri-*n*-butylstannyl)furans and 3,4-bis(tri-*n*-butylsilyl)furans have been studied in detail; manipulation of these provides powerful routes to various 3- and 3,4-disubstituted furans, as illustrated below.⁶⁷



2,3-Bis(trimethylsilyl)furan on vigorous treatment is converted into its 2,4-isomer providing a powerful intermediate for further manipulations.⁶⁸

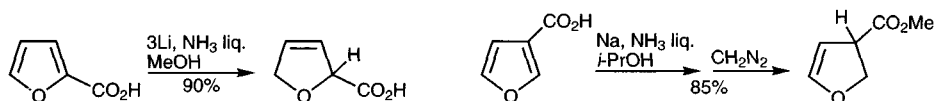


15.6 Reactions with radical reagents

Reactions of furans with radical species (cf. section 2.4.2) as synthetically useful processes have been little developed; arylation⁶⁹ and alkylation⁷⁰ are selective for α -positions. Exposed to dibenzoyl peroxide, furan produces a stereoisomeric mixture of 1,4-addition products.

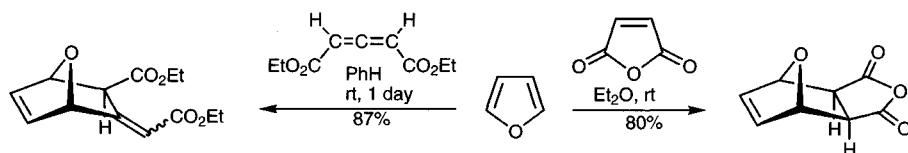
15.7 Reactions with reducing agents

The best way to reduce a furan to a tetrahydrofuran is using Raney nickel catalysis, though ring opening, *via* hydrogenolysis of C–O bonds can be a complication. Most furans are not reduced simply by metal/ammonia combinations, however furoic acids⁷¹ and furoic acid tertiary amides⁷² give dihydro-derivatives.



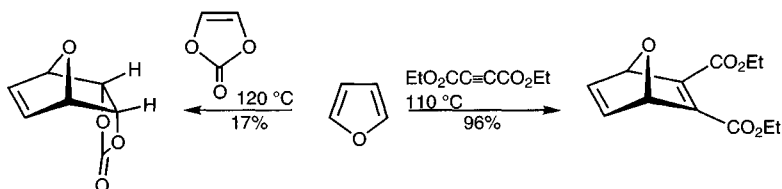
15.9 Electrocyclic reactions (ground state)

The 4 + 2 cycloaddition of furan to reactive dienophiles such as maleic anhydride⁷³ was one of the earliest described examples of the Diels-Alder reaction;⁷⁴ the isolated product is the *exo* isomer⁷⁵ though this has been shown to be the thermodynamic product, the *endo* isomer being the kinetic product and the cycloaddition being easily reversible.⁷⁶



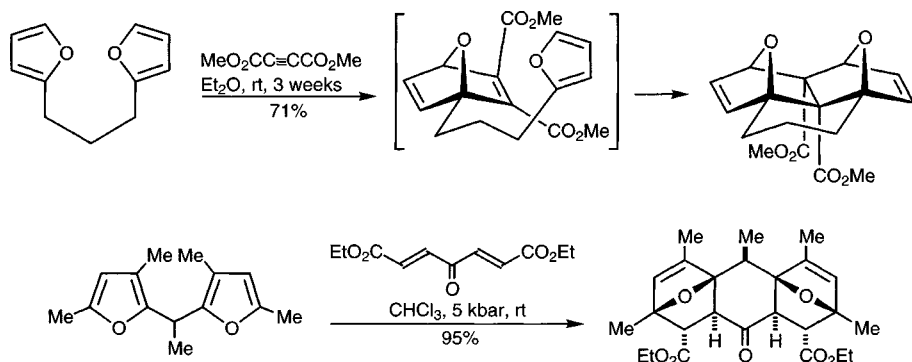
Furan also undergoes cycloadditions with allenes⁷⁷ and even with simpler dienophiles, like acrylonitrile and acrylate (specifically enhanced by the presence of

zinc iodide),⁷⁸ and with maleate and fumarate esters, if the addition is conducted under high pressure.⁷⁹ This device can also be used to increase markedly the reactivity of 2-methoxyfuran and 2-acetoxymethoxyfuran towards dienophiles.⁸⁰ Lewis acid catalysis can also be used to accelerate furan Diels-Alder additions.⁸¹ At higher reaction temperatures alkynes⁸² and even electron-rich alkenes⁸³ will add to furan.

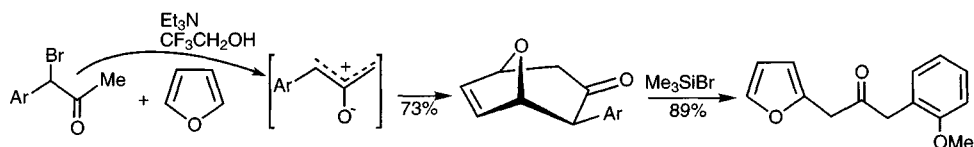


Although, as one would anticipate for the electron-rich component of a normal Diels-Alder pairing, 2-formylfuran is a poor diene, its dimethylhydrazone is a good one, though only ring-opened benzenoid products, derived subsequently from the adducts, are isolated.⁸⁴

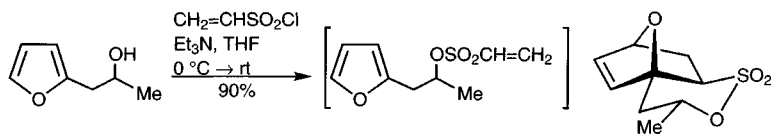
Examples of the exploitation of furan Diels-Alder cycloadditions for the construction of complex systems are many;⁸⁵ two delightful examples are shown below. In the first, the residual dienophilic double bond of the Diels-Alder adduct between one of the two furan rings and dimethyl acetylenedicarboxylate then enters into cycloaddition with the second furan ring.⁸⁶ In the second example, a pentacyclic array related to the skeletons and oxygenation pattern of polypropionate natural products, was assembled from another molecule containing two furan rings and a reaction partner with two dienophilic double bonds.⁸⁷



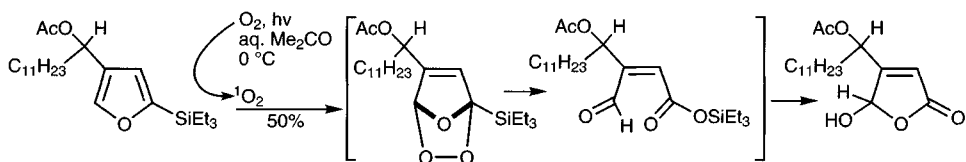
The cycloaddition of 2-oxyallyl cations⁸⁸ is also a process which has been considerably exploited for the synthesis of substituted furans and polycyclic materials.⁸⁹ For example it can be made the means for the introduction of acylmethyl groups at the furan 2-position.⁹⁰



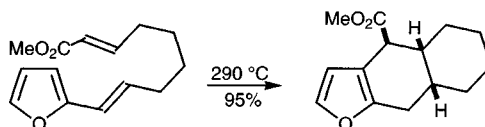
Many examples of furans participating in intramolecular Diels-Alder addition have been described;⁹¹ the example below illustrates the mildness of conditions required in favourable cases.⁹² Even unactivated alkenes will add to furans, in an intramolecular sense.⁹³



Furans also undergo cycloaddition with singlet oxygen.⁹⁴ This has been the basis for several routes to highly oxygenated compounds, for example in syntheses of 5-hydroxy-2(5*H*)-furanones (4-hydroxybut-2-enolides, see section 15.13), a structural unit which occurs in several natural products. Addition to a 3-substituted furan in the presence of a hindered base⁹⁵ or addition⁹⁶ to 2-trialkylsilyl-4-substituted furans⁹⁷ leads through, as shown, to 4-substituted 5-hydroxy-2(5*H*)-furanones. 5-Substituted furfurals also give 5-hydroxy-2(5*H*)-furanones with loss of the aldehyde carbon.⁹⁸ A particularly neat example is the reaction of 2-furoic acid which is converted in quantitative yield, with decarboxylation, into malaldehydic acid (the cyclic hemiacetal of *Z*-4-oxobut-2-enoic acid).⁹⁹

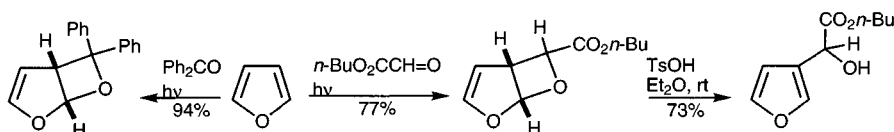


The few examples in which vinylfurans take part as 4- π components¹⁰⁰ in intramolecular cycloadditions include that shown below.¹⁰¹ In simpler, intermolecular cases yields are generally poor and the extraannular mode must compete with the more usual intraannular mode; the inclusion of a bulky group at an α position assists this differentiation.¹⁰²



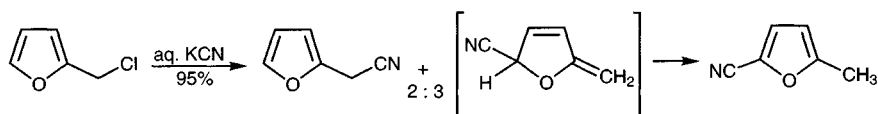
15.10 Photochemical reactions

The cycloaddition of diaryl ketones and some aldehydes across the furan 2,3-double bond proceeds regioselectively to afford oxetanodihydrofurans; proton-catalysed cleavage of the acetal linkage produces 3-substituted furans.¹⁰³

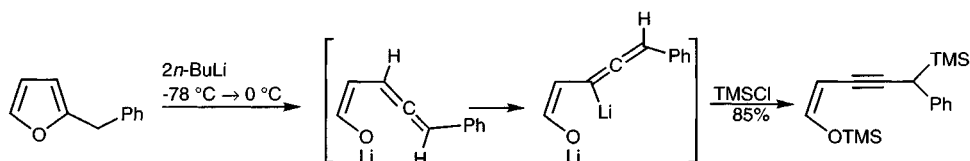


15.11 Furyl-C-X compounds; side-chain properties

The nucleophilic displacement of halide from furyl halides often produces mixtures of products resulting from straightforward displacement on the one hand and displacement with nucleophilic addition to C-5 on the other;¹⁰⁴ the second mode proceeds through a non-aromatic intermediate which then isomerises to aromatic product.

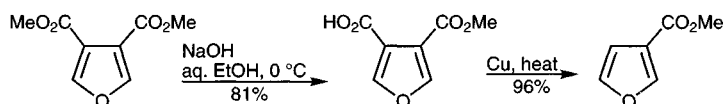


With anion-stabilising groups present it is possible to deprotonate furan α -alkyl groups; these side-chain anions give rise to ring-opened allene-enolates, which in the presence of excess lithiating agent undergo a second lithiation, as demonstrated by their subsequent trapping.¹⁰⁵

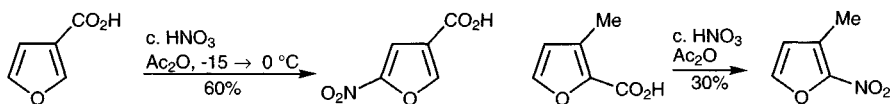


15.12 Furan carboxylic acids and esters

Save for their easy decarboxylation, furan acids (and their esters) are unexceptional. Carbon dioxide is easily lost¹⁰⁶ from either α - or β -acids and presumably involves ring-protonated intermediates and a decarboxylation analogous to that of β -keto-acids, at least in those examples where copper is not utilised.



Nitration of 3-furoic acid takes place normally, and at C-5;¹⁰⁷ α -acids sometimes undergo *ipso*-substitution with decarboxylation,¹⁰⁸ for example 2-furoic acid gives the 5-nitro-derivative, accompanied by some 2,5-dinitrofuran.¹⁰⁹

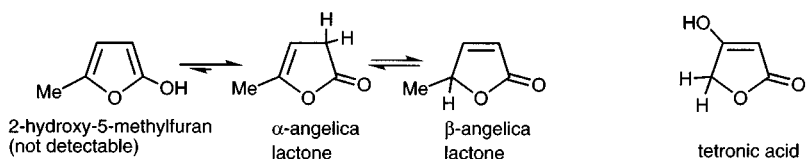


15.13 Oxy- and aminofurans

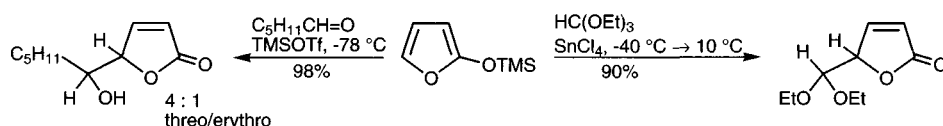
15.13.1 Oxyfurans

2-Hydroxyfurans exist, if at all, at undetectably low concentrations in tautomeric equilibria involving 2(5*H*)-furanone and 2(3*H*)-furanone forms, for example the angelica lactones can be equilibrated *via* treatment with an organic base, the more stable being the β -isomer; the chemistry of 2-oxyfurans, then, is that of unsaturated lactones. Less is known of 3-hydroxyfurans save again that the carbonyl tautomeric form predominates.

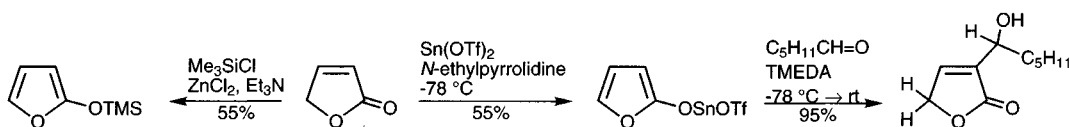
Many natural products¹¹⁰ and natural aroma components¹¹¹ contain 2-furanone units and considerable synthetic work has thereby been engendered.¹¹² In the context of these natural products, the name 'butenolide' is generally employed and compounds are therefore numbered as derivatives of 4-hydroxybutenoic acid and not as a furan, for example a tetronic acid is a 3-hydroxybut-2-enolide.



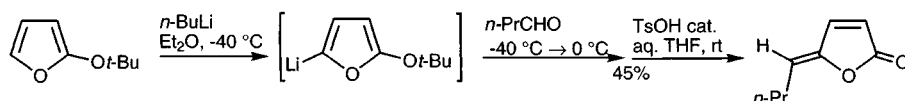
Butenolides can be converted into furans by partial reduction of the lactone, then dehydration.¹¹³



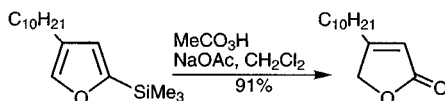
Synthons which have been developed for butenolide construction include 2-trimethylsilyloxyfuran,¹¹⁴ which reacts with electrophiles at (furan) C-5,¹¹⁵ and, complementarily, furans carrying an oxy-tin (or oxy-boron) substituent, which, *via* chelation control, react with electrophiles at C-3.¹¹⁶



2-*t*-Butoxyfuran, available from the reaction of 2-lithiofuran with *t*-butyl perbenzoate,¹¹⁷ can be lithiated at C-5, reaction with a carbonyl component, then hydrolysis with dehydration, furnishing alkylidene-butenolides.¹¹⁸



2-Trimethylsilylfurans are converted into the butenolide by oxidation with peracid.¹¹⁹

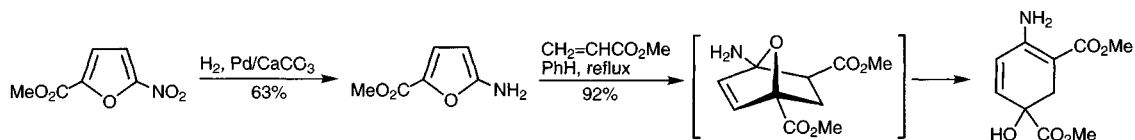


2-Methoxy- and 2-acetoxymfurans are available from 2,5-dimethoxy- and 2,5-diacetoxym-2,5-dihydrofurans (section 15.1.4) *via* acid-catalysed elimination.¹²⁰ They undergo Diels-Alder cycloadditions; the adducts can be further transformed into benzenoid compounds by acid-catalysed opening. 3,4-Dihydroxyfuran is undetectable in tautomeric equilibria between mono-enol and dicarbonyl forms; the dimethyl ether behaves as a normal furan, undergoing easy α -electrophilic substitution, mono- or dilithiation at the α -position(s),¹²¹ and Diels-Alder cycloadditions.¹²² 2,5-Bis(trimethylsilyloxy)furan is synthesised from succinic anhydride; it too undergoes Diels Alder additions readily.¹²³ Both 2- and 3-thiols can be obtained by reaction of lithiated furans with sulfur; in each case the predominant tautomer is the thiol form.¹²⁴

15.13.2 Aminofurans

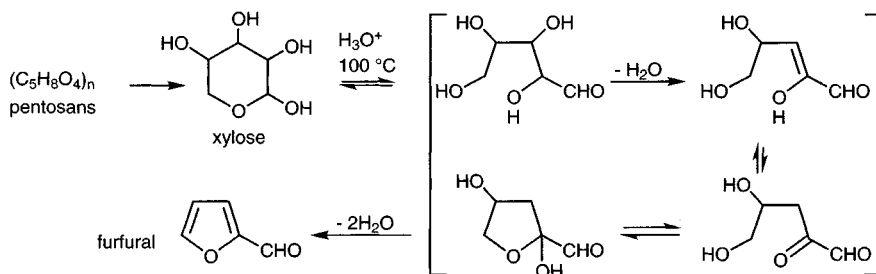
So little has been described of the chemistry of aminofurans that general comment on their reactivity is difficult to make; it seems likely that simple aminofurans are too

unstable to be isolable, though 2-acylaminofurans have been described and so have more heavily substituted aminofurans.¹²⁵ The presence of a 5-ester in conjugation means that methyl 2-aminofuran-5-carboxylate is a relatively stable amino furan; it undergoes Diels-Alder cycloadditions in the usual manner (*cf.* section 15.9).¹²⁶



15.14 Synthesis of furans

Furfural and thence furan, by vapour phase decarbonylation, are available in bulk and represent the starting points for many furan syntheses. The aldehyde is manufactured¹²⁷ from xylose, obtained in turn from pentosans which are polysaccharides extracted from many plants, e.g. corn cobs and rice husks. Acid catalyses the overall loss of three moles of water in very good yield. The precise order of events in the multistep process is not known for certain, however a reasonable sequence¹²⁸ is shown below. Comparable dehydrative ring closure of fructose produces 5-hydroxymethylfurfural.¹²⁹

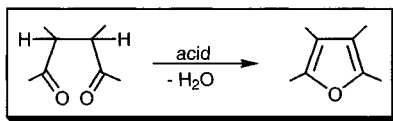


15.14.1 Ring syntheses

Many routes to furans have been described, but the majority are variants on the first general method – the dehydrating ring closure of a 1,4-dicarbonyl substrate.

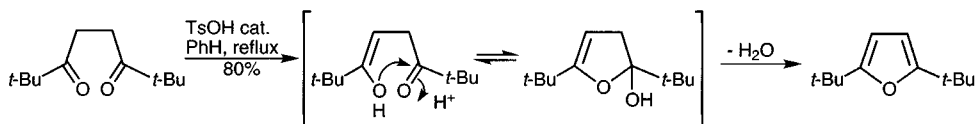
15.14.1.1 From 1,4-dicarbonyl compounds

1,4-Dicarbonyl compounds can be dehydrated, with acids, to form furans.

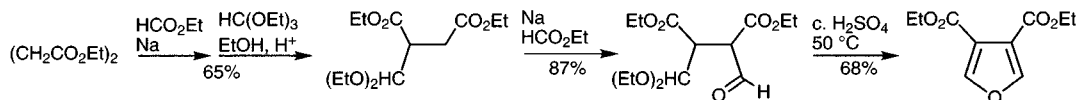


The Paal-Knorr synthesis

The most widely used approach to furans is the cyclising dehydration of 1,4-dicarbonyl compounds, which provide all of the carbon atoms and the oxygen necessary for the nucleus. Usually, non-aqueous acidic conditions¹³⁰ are employed to encourage the loss of water. The process involves addition of the enol oxygen of one carbonyl group to the other carbonyl group, then elimination of water.¹³¹

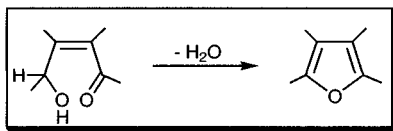


Access to a 1,4-dicarbonyl substrate has been realised in several ways.¹³² Examples include alkylation of imines with 2-alkoxy-allyl halides (equivalents of 2-halo-ketones),¹³³ addition of β -ketoester anions to nitroalkenes, followed by Nef reaction,¹³⁴ and rhodium-catalysed carbonylation of 2-substituted acrolein acetals.¹³⁵ The dialdehyde (as a mono-acetal) necessary for a synthesis of diethyl furan-3,4-dicarboxylate was obtained by two successive Claisen condensations between diethyl succinate and ethyl formate, as shown in the sequence below.¹³⁶

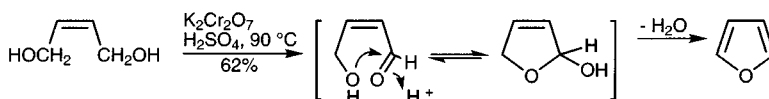


15.14.1.2 From γ -hydroxy- α,β -unsaturated carbonyl compounds

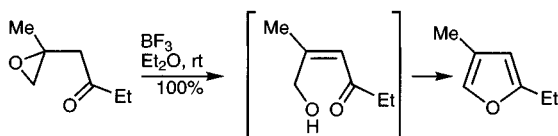
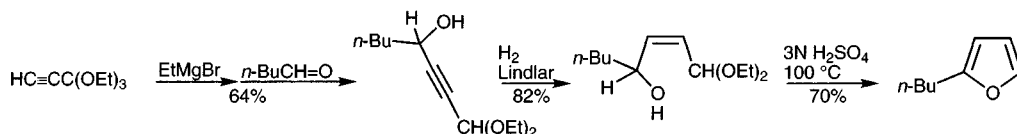
γ -Hydroxy- α,β -unsaturated carbonyl compounds can be dehydrated, using mineral or Lewis acids, to form furans.

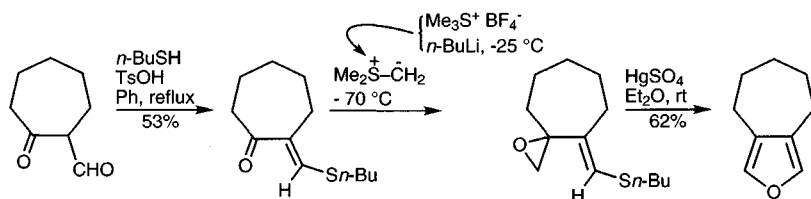


The simplest example here is the oxidation of *cis*-but-2-ene-1,4-diol, which gives furan *via* the hydroxy-aldehyde.¹³⁷



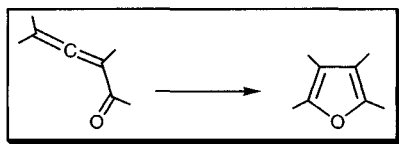
More elaborate 4-hydroxy-enals and -enones have been generated in a variety of ways, for example *via* alkynes¹³⁸ or often *via* epoxides,¹³⁹ it being sometimes unnecessary to isolate the hydroxy-enone,¹⁴⁰ or *via* Hörner-Wadsworth-Emmons condensation of β -ketophosphonates with α -acetoxyketones.¹⁴¹ Acetal¹⁴², thioenol-ether¹⁴³ or terminal alkyne¹⁴⁴ can be employed as surrogate for the carbonyl group. Some of these are exemplified below.



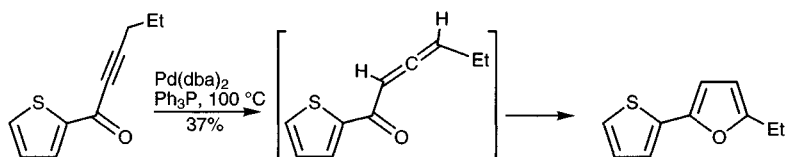


15.14.1.3 From allenyl ketones

Allenyl ketones cyclise to furans with metal ion or metal(0) catalysis.

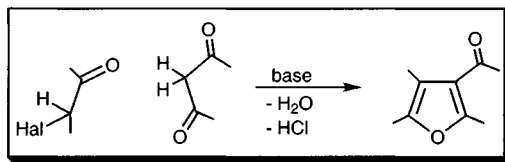


Allenyl ketones presynthesised,¹⁴⁵ or generated *in situ* by acylation of silyl-allenes,¹⁴⁶ or by palladium(0)-catalysed isomerisation of conjugated¹⁴⁷ or non-conjugated¹⁴⁸ alkynyl ketones, can be cyclised to furans. The ring closure has been effected with silver¹⁴² or palladium^{148,149} catalysis; acylation of silylallenes leads to the furan directly.¹⁴² In the presence of water, palladium(II)-catalysed closure of β,γ -alkynyl ketones is believed to proceed *via* the enol, not the allene.¹⁴⁹ 1,2,3-Trienyl-4-ols have also been shown to cyclise to give furans.¹⁵⁰



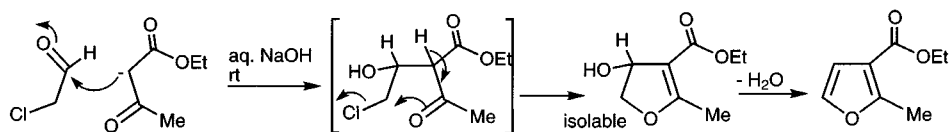
15.14.1.4 From α -halocarbonyl and 1,3-dicarbonyl compounds

α -Halocarbonyl compounds react with 1,3-dicarbonyl compounds in the presence of a base (not ammonia, cf. section 13.18.1.3) to give furans.

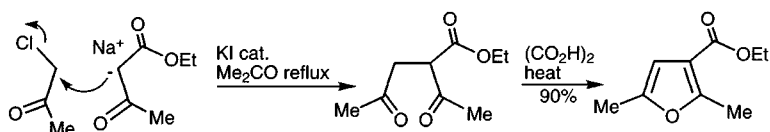


The Feist-Benary Synthesis

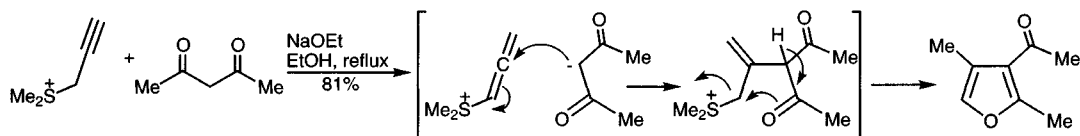
This classical synthesis rests on an initial aldol condensation at the carbonyl carbon of a 2-halocarbonyl component; ring closure is achieved *via* intramolecular displacement of halide by enolate oxygen; intermediates supporting this mechanistic sequence have been isolated in some cases.¹⁵¹



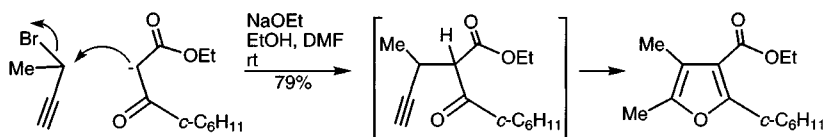
It is important to distinguish this synthesis from the alkylation of a 1,3-dicarbonyl enolate with an 2-haloketone, with displacement of halide, producing a 1,4-dicarbonyl unit for subsequent ring closure;¹⁵² presumably the difference lies in the greater reactivity of the aldehyde group in the Feist-Benary sequence.



The addition of the anion of a 1,3-dicarbonyl compound to an allenyl sulfonium salt, subsequently followed by enolate displacement of dimethylsulfide, produces a furan after isomerisation of the double bond into the ring.¹⁵³

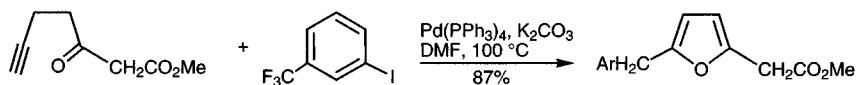


4-Pentynones can be closed to furans using potassium *t*-butoxide¹⁵⁴ or benzyl trimethylammonium methoxide.¹⁵⁵ The base-catalysed 2-alkylation of 1,3-dicarbonyl compounds with propargyl halides, is followed *in situ* by 5-*exo*-dig ring closure.¹⁵⁶

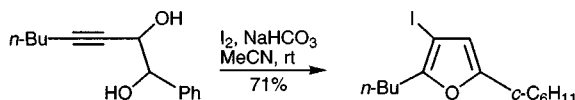


15.14.1.5 Miscellaneous methods

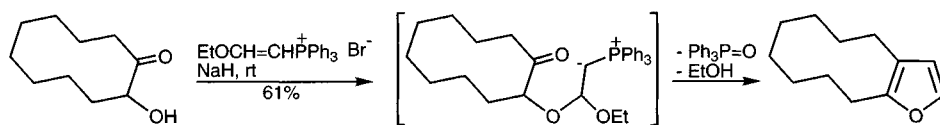
In another use of 4-pentynones, palladium-catalysed arylation leads to *in situ* ring closure and the production of 2,5-disubstituted furans.¹⁵⁷



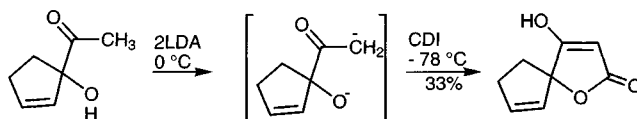
In what is formally a 5-*endo*-dig cyclisation, alk-3-yne-1,2-diols close under the influence of iodine to produce 3-iodofurans.¹⁵⁸



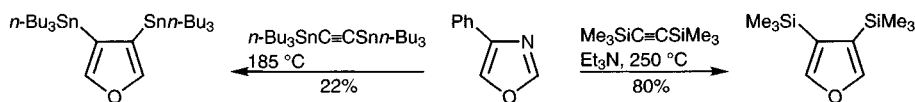
Considerable ingenuity has been exercised in the development of alternative routes to furans. For example, acyloins react with 'acetylene-transfer' reagents,¹⁵⁹ in one of the few furan syntheses which begins with formation of the ether unit; the cyclising step is a Wittig reaction.



Tetronic acids can be constructed using the dianion of an acyloin, this time with the phosgene equivalent, 1,1'-carbonyldiimidazole.¹⁶⁰



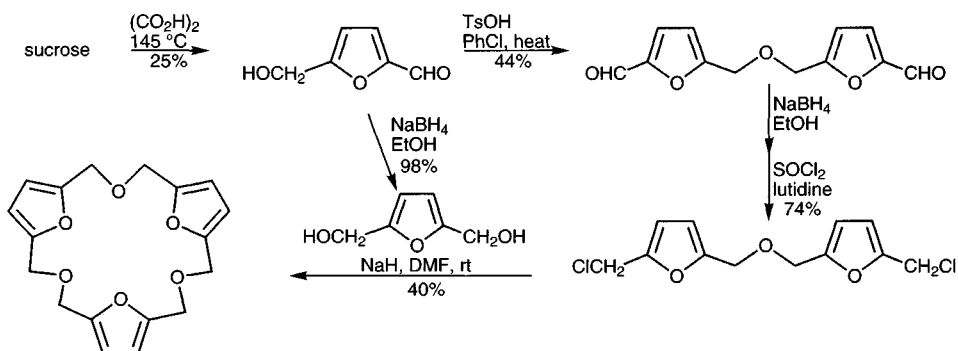
The very useful 3,4-bis(tri-*n*-butylstannyl)-¹⁶¹ and 3,4-bis(trimethylsilyl)furans¹⁶² are available by cycloaddition/cycloreversion steps using 4-phenyloxazole.



15.14.2 Examples of notable syntheses of furans

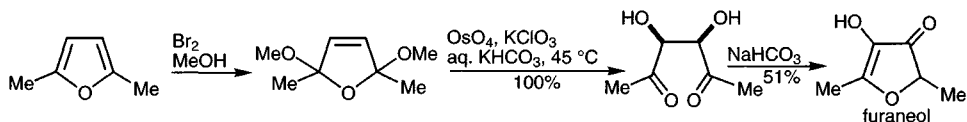
15.14.2.1 Tris(furanyl)-18-crown-6

Tris(furanyl)-18-crown-6 was prepared utilising the reactivity of furfuryl alcohols and chlorides.¹⁶³



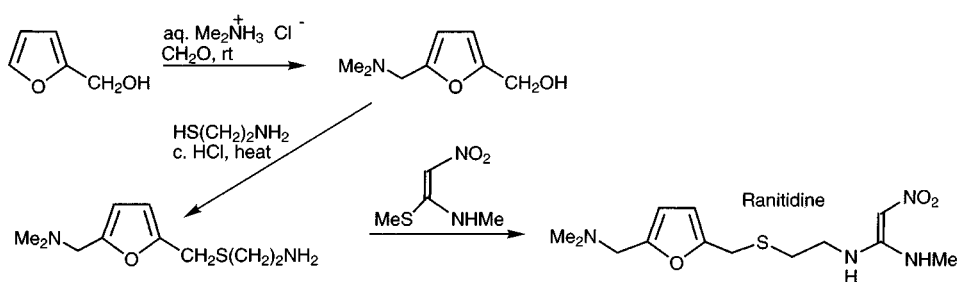
15.14.2.2 Furanol

Furanol is a natural flavour principle, isolated from pineapple and strawberry, and used in the food and beverage industries.¹⁶⁴



15.14.2.3 Ranitidine

Ranitidine has been synthesised from furfuryl alcohol.



Exercises for chapter 15

Straightforward revision exercises (consult chapters 12 and 15)

- Describe three distinctly different reactions of furans which confirm the relatively smaller aromatic resonance stabilisation of furan compared with thiophene and pyrrole (reactions which lead to non-aromatic products).
- At what position does furan undergo lithiation? How could one prepare the alternative lithio isomer?
- With what type of dienophile do furans react most readily?
- What types of product can be obtained from the interaction of furans with singlet oxygen ($^1\text{O}_2$)?
- Do 2-hydroxyfurans exist?
- What is the most common method for the ring synthesis of furans? Write a mechanistic sequence for the ring closing process.
- How could one synthesise 3,4-bis(tri-*n*-butylstannyl)furan?

More advanced exercises

- Hydrolysis of 2-methoxyfuran with aqueous acid produces 4-hydroxybut-2-enoic acid lactone and $\text{MeO}_2\text{C(CH}_2)_2\text{CH=O}$: write sequences involving protonation and reaction with water to rationalise formation of each of these.
- Suggest structures for the products: (i) $\text{C}_{11}\text{H}_8\text{O}_2$ produced by treating 2-phenylfuran with the combination DMF/ POCl_3 then aqueous base; (ii) $\text{C}_9\text{H}_{10}\text{O}_4$ from ethyl furoate/ $\text{Ac}_2\text{O/SnCl}_4$; (iii) $\text{C}_5\text{H}_2\text{N}_2\text{O}_3$ from 3-cyanofuran with $\text{Ac}_2\text{O/HNO}_3$; (iv) $\text{C}_{14}\text{H}_{11}\text{Cl}_3\text{O}_6$ from methyl furoate, $\text{CCl}_3\text{CHO/H}_2\text{SO}_4$.
- Electrochemical oxidation of 5-methylfurfuryl alcohol in methanol solvent afforded $\text{C}_8\text{H}_{14}\text{O}_4$, hydrogenation of which produced $\text{C}_8\text{H}_{16}\text{O}_4$, acid treatment of this gave a cyclic 1,2-dione, $\text{C}_6\text{H}_8\text{O}_2$. What are the structures of these compounds?
- Trace the course of the following synthesis by writing structures for all intermediates: ethyl 2-methylfuran-3-carboxylate with LiAlH_4 , then SOCl_2 , then $\text{LiAlH}_4 \rightarrow \text{C}_6\text{H}_8\text{O}$, treatment of which with Br_2/MeOH , then $\text{H}_2\text{O}/60^\circ\text{C}$, then aq. NaBH_4 gave $\text{C}_6\text{H}_{12}\text{O}_2$.
- Write structures for the products of reacting 2-lithiofuran with (i) cyclohexanone, (ii) $\text{Br(CH}_2)_7\text{Cl}$.
- Suggest structures for the (main) product from the following combinations: (i) 3-methylfuran/DMF/ POCl_3 then aq. NaOH ; (ii) 2,3-dibromofuran/*n*-BuLi then H_2O ; (iii) 3-bromofuran/LDA, then $\text{CH}_2\text{O} \rightarrow \text{C}_5\text{H}_5\text{BrO}_2$; (iv) furfural with $\text{EtOH/H}^+ \rightarrow \text{C}_9\text{H}_{14}\text{O}_3$, then this with BuLi followed by B(OBu)_3 and aqueous

- acid \rightarrow $\text{C}_5\text{H}_5\text{BO}_4$; (v) 3-bromofuran/ $\text{BuLi}/-78^\circ\text{C}$, then $\text{Bu}_3\text{SnCl} \rightarrow \text{C}_{16}\text{H}_{30}\text{OSn}$ and this with $\text{MeCOCl}/\text{PdCl}_2 \rightarrow \text{C}_6\text{H}_6\text{O}_2$.
- Write structures for the products of reaction of (i) furfuryl alcohol with $\text{H}_2\text{C}=\text{C}=\text{CHCN} \rightarrow \text{C}_9\text{H}_9\text{NO}_2$ (ii) 2,5-dimethylfuran with $\text{CH}_2=\text{CHCOMe}/15$ kbar, (iii) furan with 2-chlorocyclopentanone/ $\text{Et}_3\text{N}/\text{LiClO}_4 \rightarrow \text{C}_9\text{H}_{10}\text{O}_2$.
 - (i) How could one prepare 2-trimethylsilyloxyfuran? (ii) What product, $\text{C}_6\text{H}_5\text{NO}_2$, would be formed from this with $\text{ICH}_2\text{CN}/\text{AgOCOCF}_3$?
 - What is the product, $\text{C}_{11}\text{H}_{10}\text{O}_3$, formed from the following sequence: 2-*t*-BuO-furan/*n*-BuLi, then $\text{PhCH}=\text{O}$, then TsOH ?
 - Decide the structures of the furans produced by the ring syntheses summarised as follows: (i) $\text{CH}_2=\text{CHCH}_2\text{MgBr}/\text{EtCH}=\text{O}$ then *m*-CPBA, then $\text{CrO}_3/\text{pyridine}$ then BF_3 ; (ii) $\text{CH}_2=\text{C}(\text{Me})\text{CH}_2\text{MgCl}/\text{HC}(\text{OEt})_3$, then *m*-CPBA, then aq. H^+ ; (iii) $(\text{MeO})_2\text{CHCH}_2\text{COMe}/\text{ClCH}_2\text{CO}_2\text{Me}/\text{NaOMe}$ then heat.
 - For the synthesis of tetronic acid summarised as follows, suggest structures for the intermediates: methylamine was added to dimethyl acetylenedicarboxylate (DMAD) $\rightarrow \text{C}_7\text{H}_{11}\text{NO}_4$, selective reduction with LiAlH_4 then giving $\text{C}_6\text{H}_{11}\text{NO}_3$ which with acid cyclised $\rightarrow \text{C}_5\text{H}_7\text{NO}_2$, aqueous acidic hydrolysis of which produced tetronic acid.

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