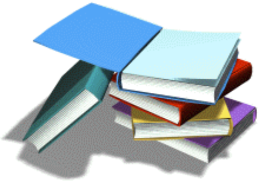
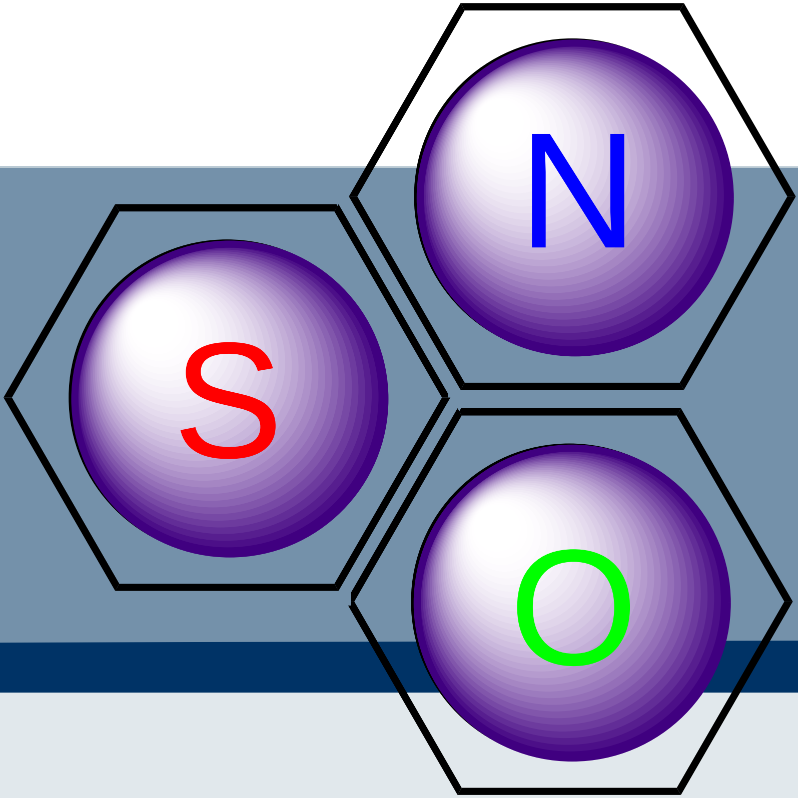
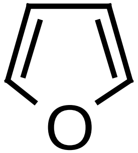


Heterocyclic **Chemistry**

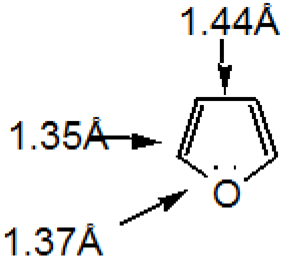


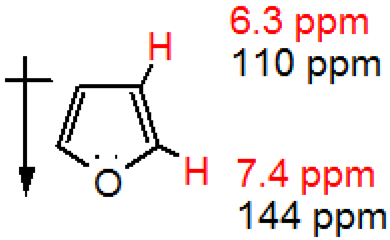
Chapter 8: Furans



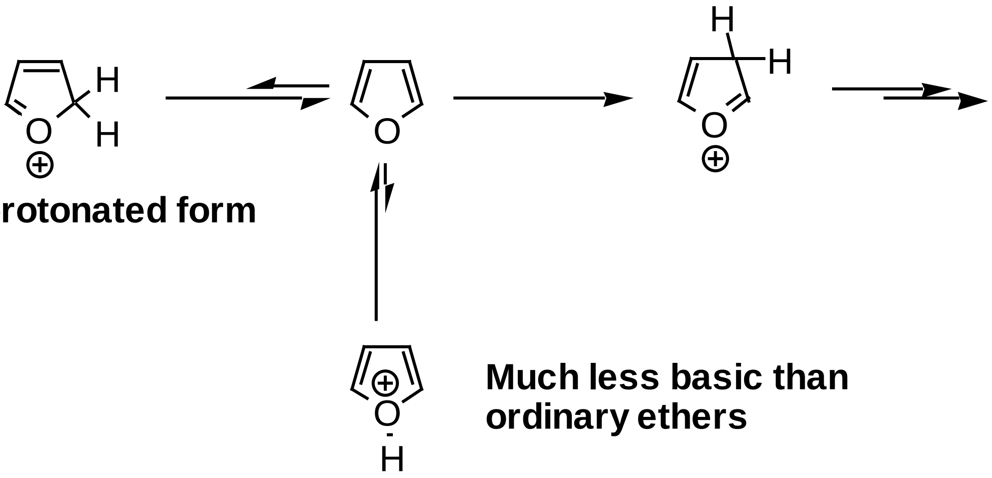
FURAN

The least aromatic 5-membered ring





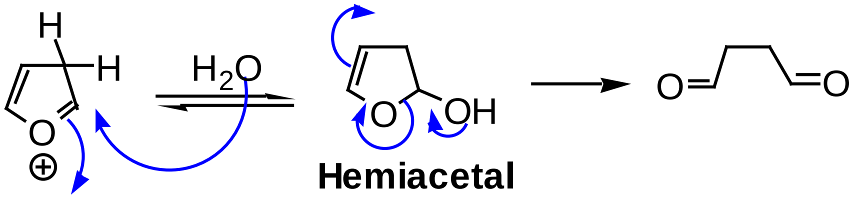
Reaction with electrophiles - Protonation



Ring opening

Major protonated form

Much less basic than ordinary ethers



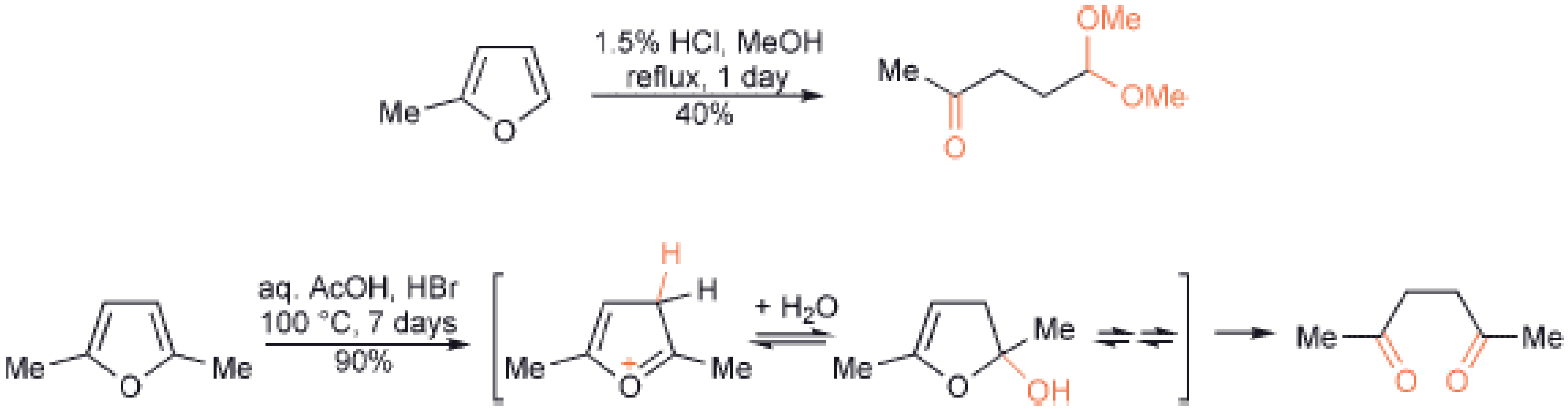
Hemiacetal

Conc. H_2SO_4

Lewis acids (i.e. $AlCl_3$) → **Decomp.**

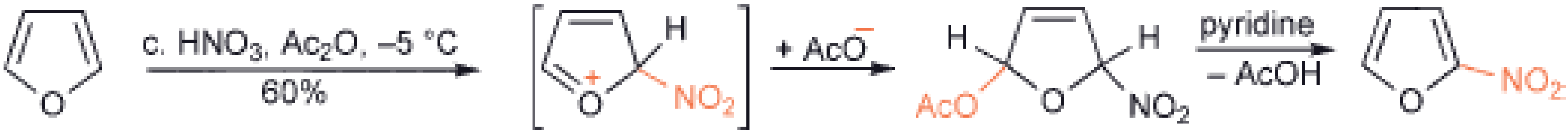
Reactions of Protonated Furans

The hydrolysis (or alcoholysis) of furans involves nucleophilic addition of water (or an alcohol) to an initially formed cation, giving rise to open -chain 1,4-dicarbonyl- compounds or derivatives thereof.



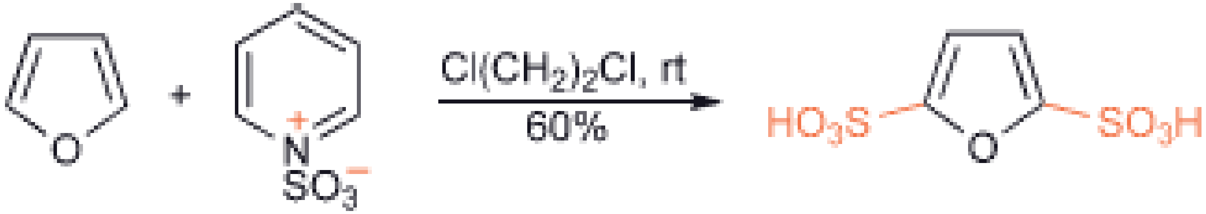
Reaction with electrophiles - Nitration

Cannot use conc. HNO_3 / H_2SO_4. Sensitivity precludes the use of concentrated acid nitrating mixtures.

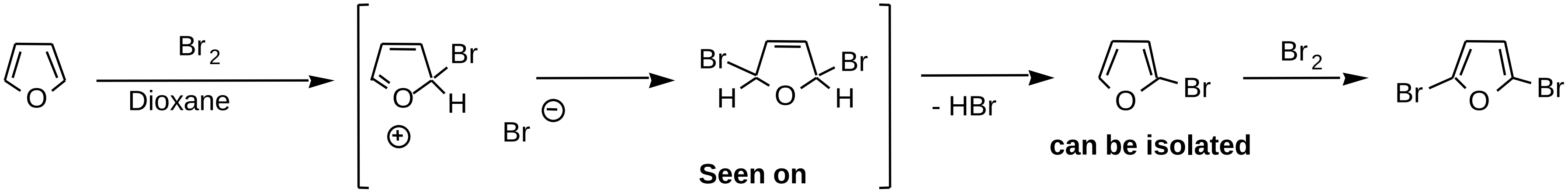


Sulfonation

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 occurring even at room temperature.



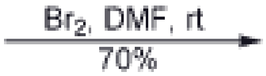
Halogenation



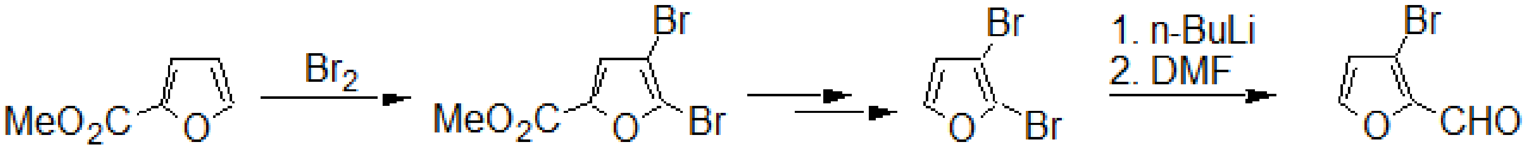
can be isolated

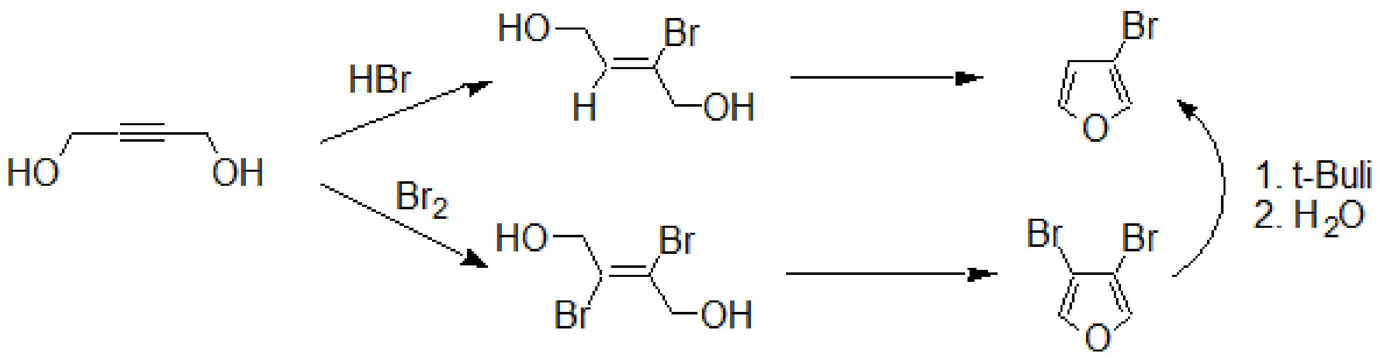
Seen on
low temp NMR

or

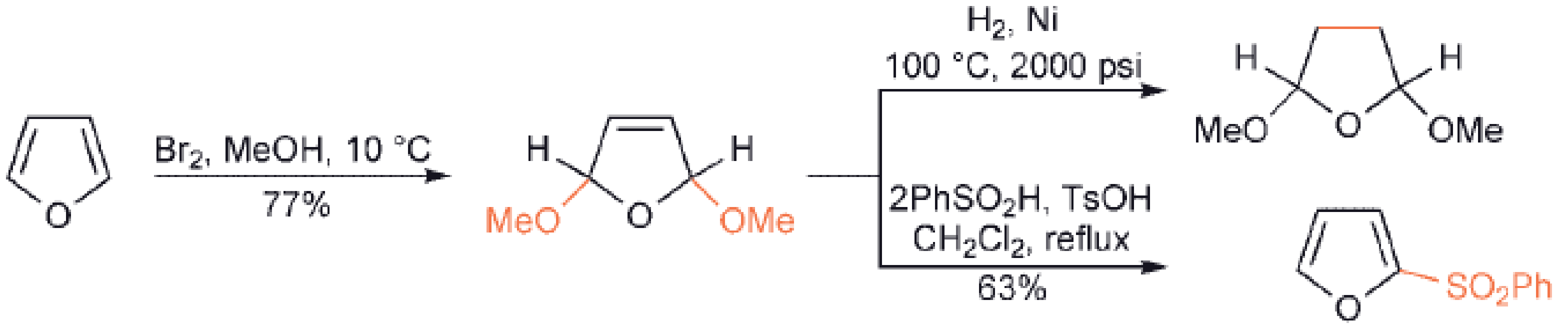


On the other hand, with control, methyl furoate can be cleanly converted into its 5-monobromo or 4,5-dibromo derivatives; hydrolysis and decarboxylation of the latter then affording 2,3-dibromofuran.

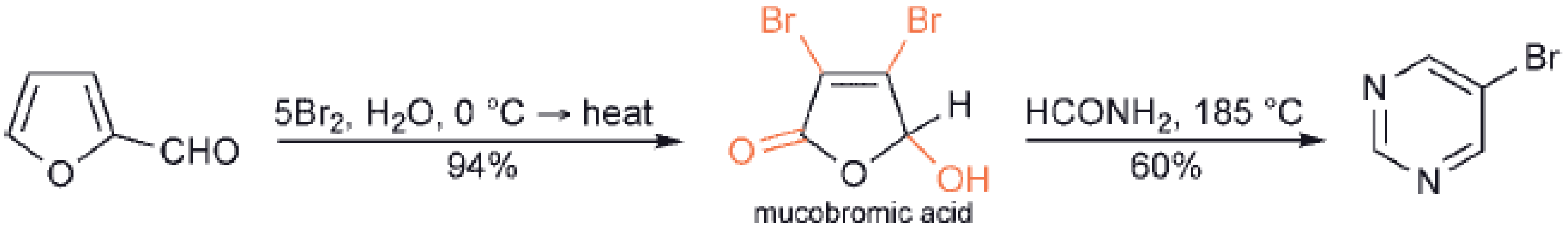



HO
OH
HBr
Br$_2$
HO
Br
H
OH
HO
Br
Br
OH
Br
O
Br
Br
O
1. t-Buli
2. H$_2$O

If the bromination is conducted in an alcohol, trapping of the intermediate by C-5 addition of the alcohol, then alcoholysis of C-2-bromide, produces 2,5-dialkoxy-2,5-dihydrofurans, as mixtures of *cis- and trans*- isomers; hydrogenation of these species affords 2,5-dialkoxy-tetrahydrofurans, extremely useful as 1,4-dicarbonyl synthons – the unsubstituted example is equivalent to succindialdehyde.

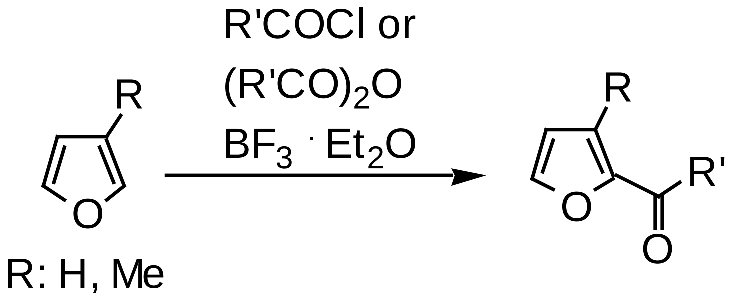


The intrinsically high reactivity of the furan nucleus is further exemplified by the reaction of furfural with excess halogen to produce ‘mucohalic acids’ ; incidentally, mucobromic acid reacts with formamide to provide a useful synthesis of 5 – bromo-pyrimidine.

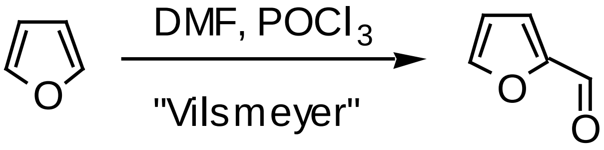


Reaction with electrophiles - Acylation

Carboxylic acid anhydrides or halides normally require the presence of a Lewis acid (often boron trifluoride) for Friedel–Crafts acylation of furans, though trifluoroacetic anhydride will react alone. Aluminium -chloride -catalysed acetylation of furan proceeds 7 × 10^4 times faster at the α-position than at the β-position.



k: $\alpha/\beta = 7 \times 10^4 : 1$

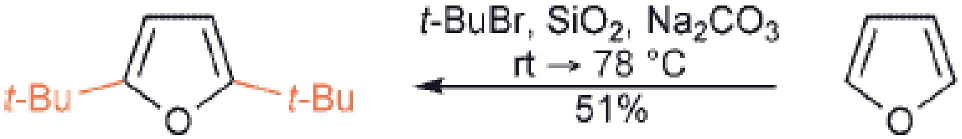


Furfural
Also very readily available
by other routes

Alkylation

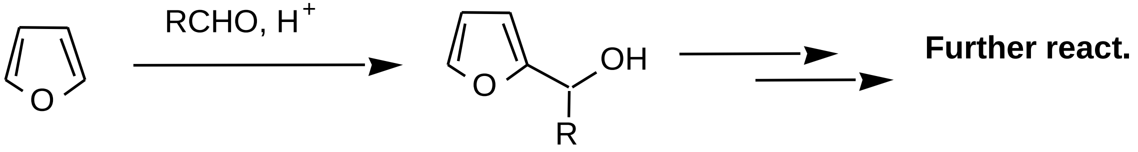
Generally not practical (polyalkylation, polymerisation)

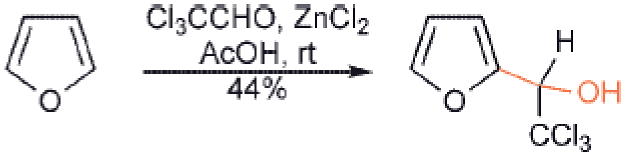
Traditional Friedel–Crafts alkylation is not generally practicable in the furan series, partly because of catalyst - induced polymerisation and partly because of polyalkylation. Instances of preparatively useful reactions include: production of 2,5-di-t-butylfuran from furan or furoic acid and the isopropylation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



Condensation with Aldehydes and Ketones

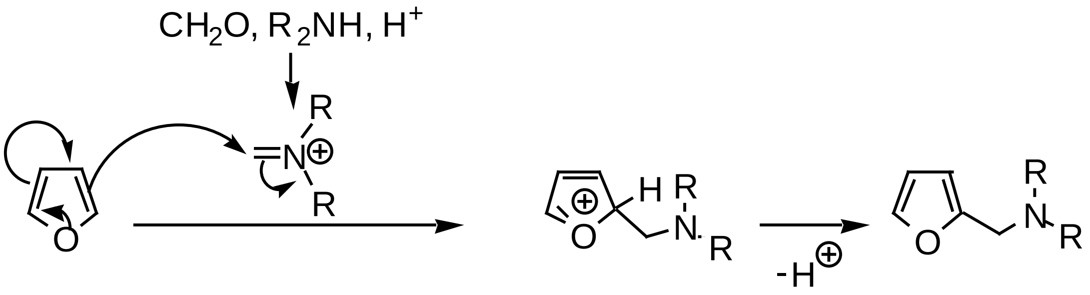
This occurs by acid catalysis, but generally the immediate product, a furfuryl alcohol, reacts further; 2-(2,2,2-trichloro-1-hydroxy)-ethylfuran can, however, be isolated.



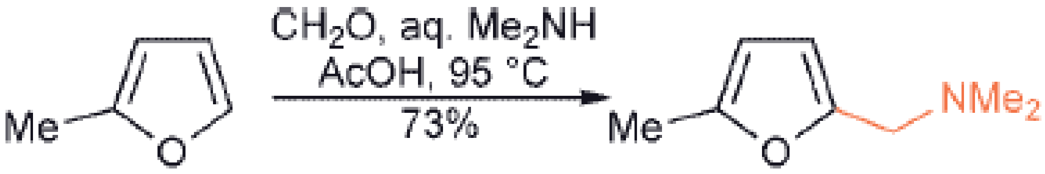


stable

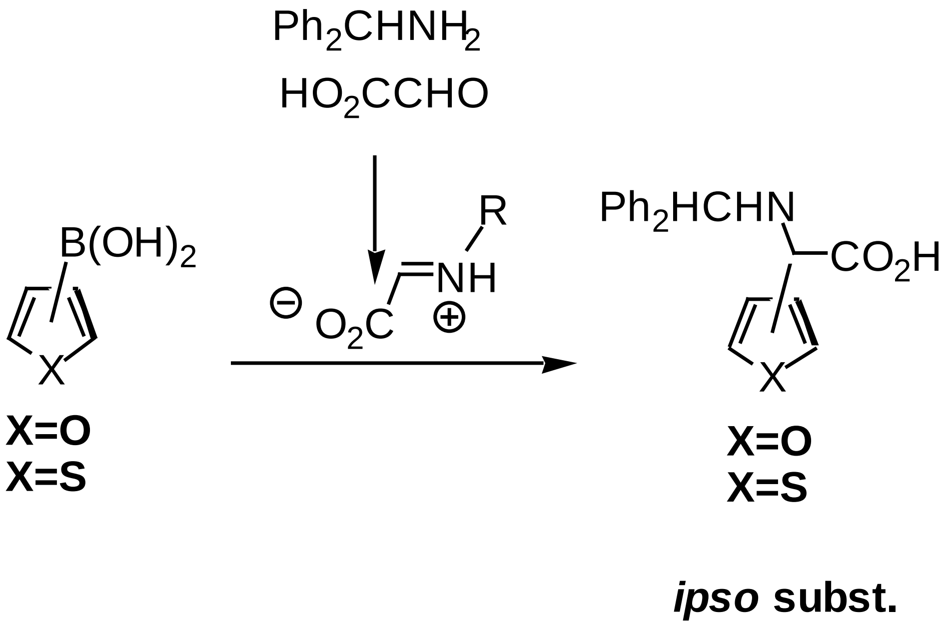
Reaction with electrophiles-Condensation with imines/iminium ions

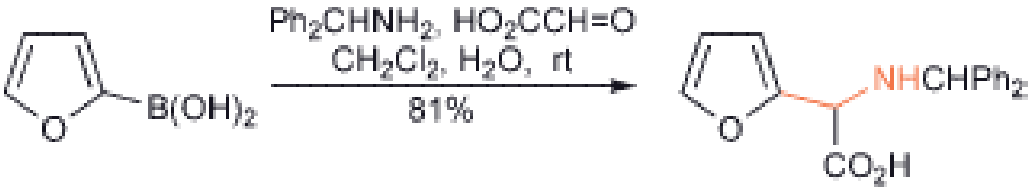


Unsubst furan: iminium ion must be preformed

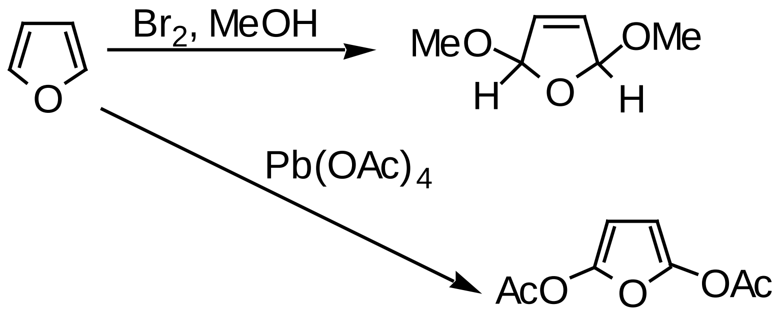


The use of furan boronic acids allows Mannich substitutions at both α- and β- positions, with primary or secondary amine components.

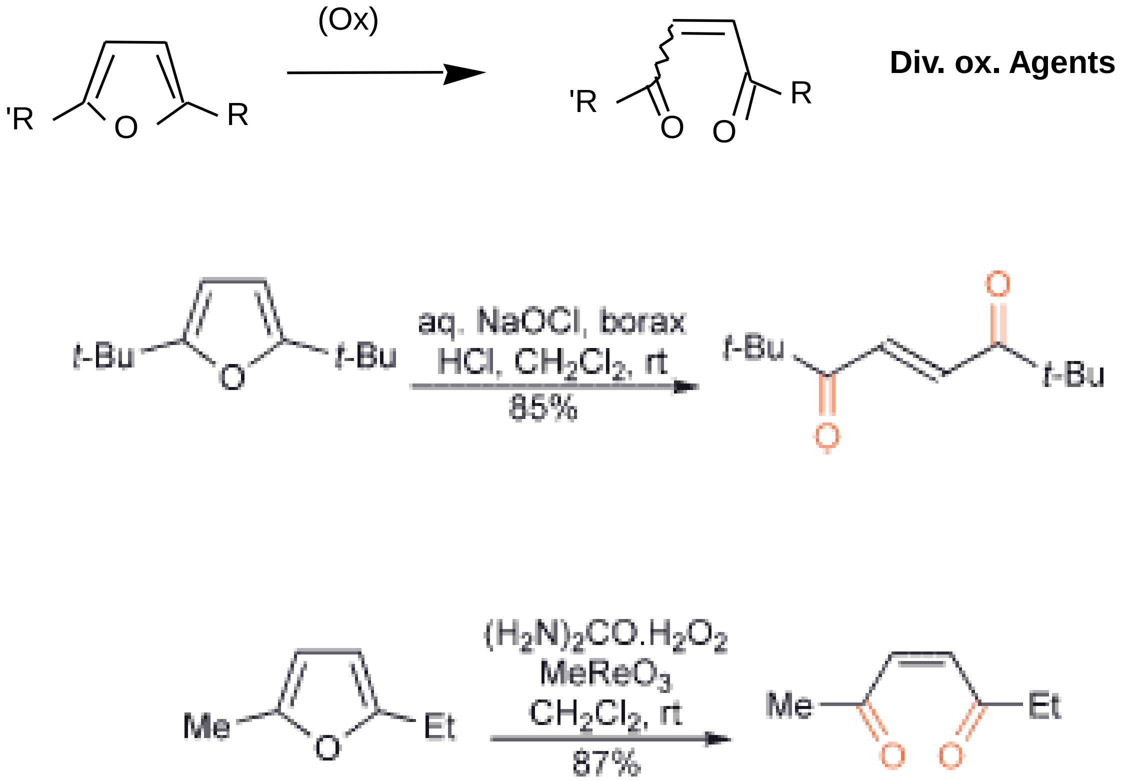




Reaction with oxidating agents



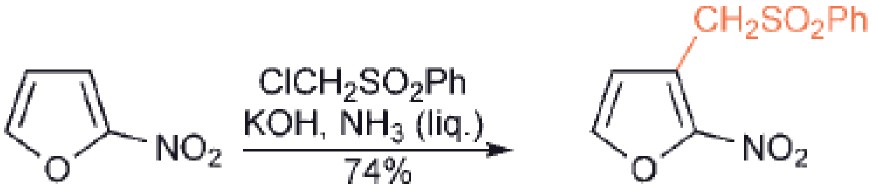
In related chemistry, ring - opened, 2-unsaturated 1,4-diones can be obtained in *E- or Z- form using* reagents such as bromine in aqueous acetone or *meta-chloroperbenzoic acid.*



Div. ox. Agents

Reaction with nucleophiles

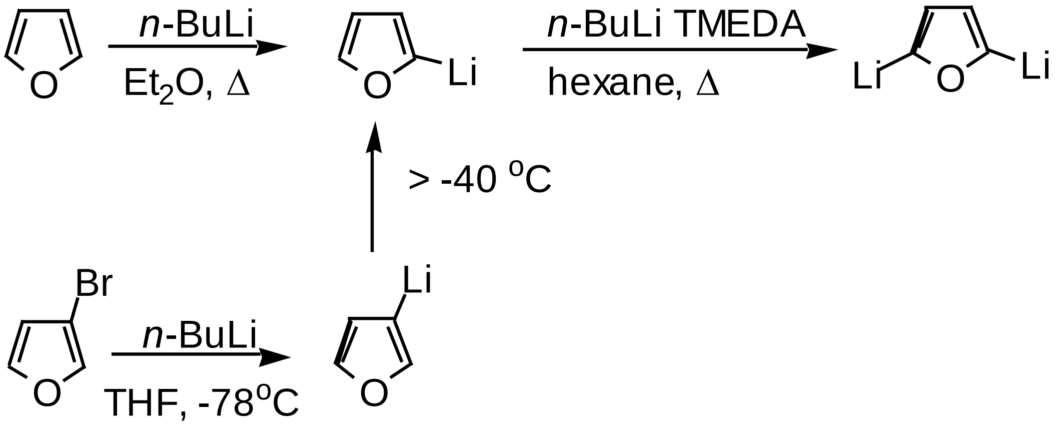
Simple furans do not react with nucleophiles by addition or by substitution. Nitro substituents activate the displacement of halogen, as in benzene chemistry, and VNS methodology can also be applied to nitro - furans.



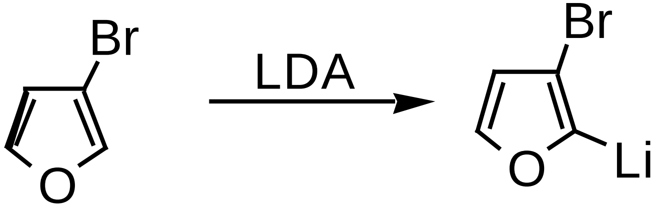
Some ex. on furans activated with -NO_2 group

Metallation and further react.

Metallation with alkyllithiums proceeds selectively at an α - position, indeed lithiation of furan is one of the earliest examples of the now familiar practice of aromatic ring - metallation. The lithiation can be achieved in refluxing ether or indeed at low temperature. More forcing conditions can bring about 2,5-dilithiation of furan. Magnesiation at an α - position can also be achieved at room temperature, with lithium tri-n-butylmagnesate. 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 ° C.

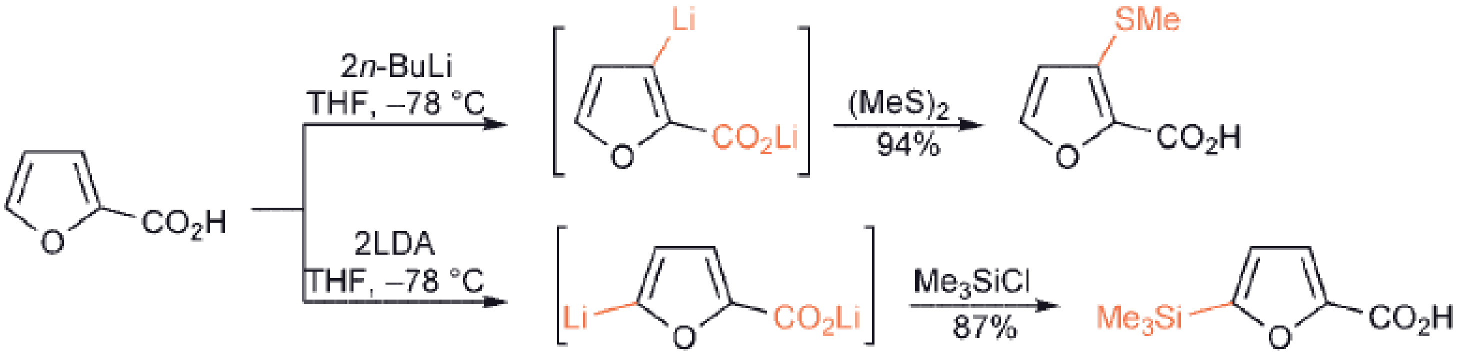


Lithium diisopropylamide can effect C-2-deprotonation of 3-halo furans.



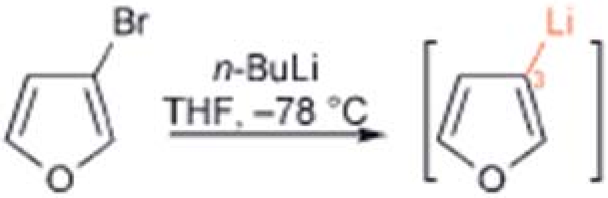
(ODG)

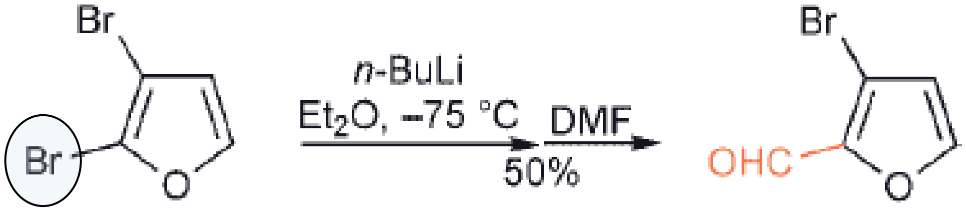
With furoic acid and two equivalents of lithium diisopropylamide, selective formation of the 5-lithio lithium 2-carboxylate takes place, whereas n-butyl-lithium, via ortho-assistance, produces the 3- lithio lithium 2-carboxylate.



Metal – Halogen Exchange

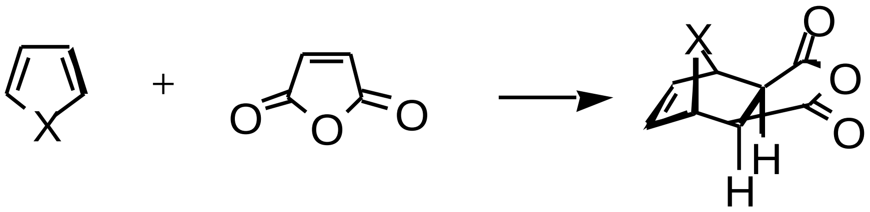
Metallation at C-3 can be achieved via metal–halogen exchange. The greater stability of a carbanion at an α-position shows up again in a mono - exchange of 2,3-dibromofuran with selective replacement of the α - bromine.





Cycloadditions

Furanes as diene - one of the first DA examples
Furan reacts with many dienophiles (alkenes, alkynes, allenes)

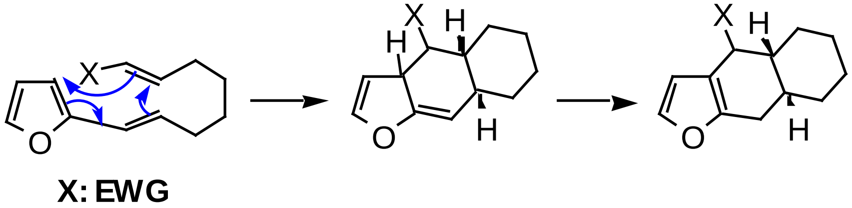


X=O: r.t.; 80%
X=S: 100 °C, 15kbar; 42%

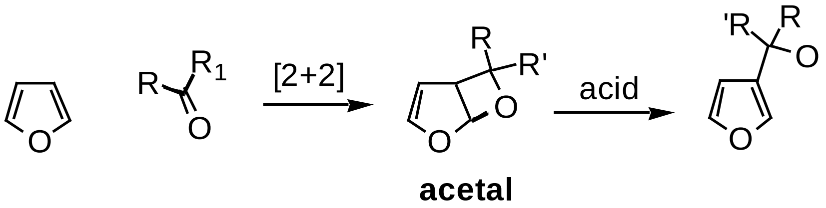
***exo* isolated (termodyn favoured)**
***endo* (kinetic prod.)**

With $^1O_2$

Furan as dienophile (only intramolec. ex)

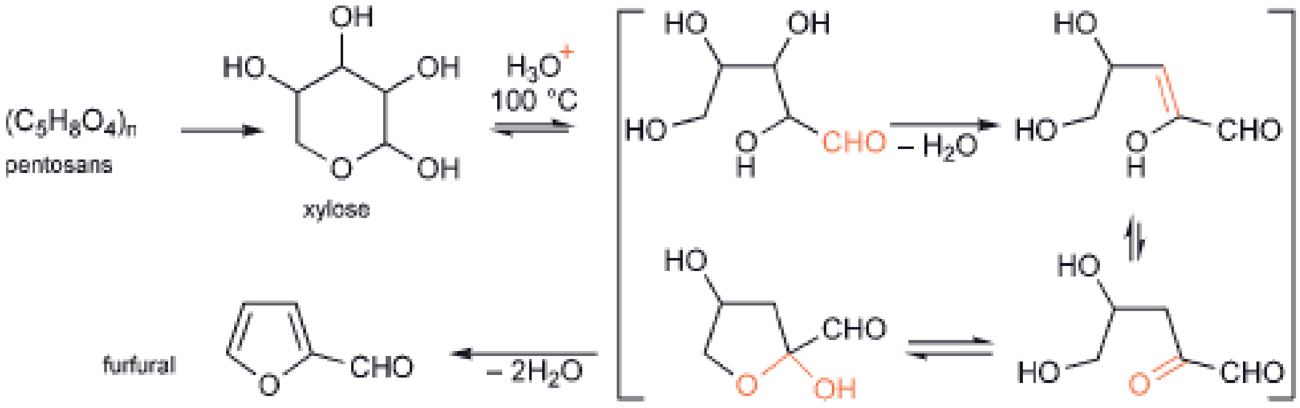


Photochemical cycloaddition



Synthesis of Furans

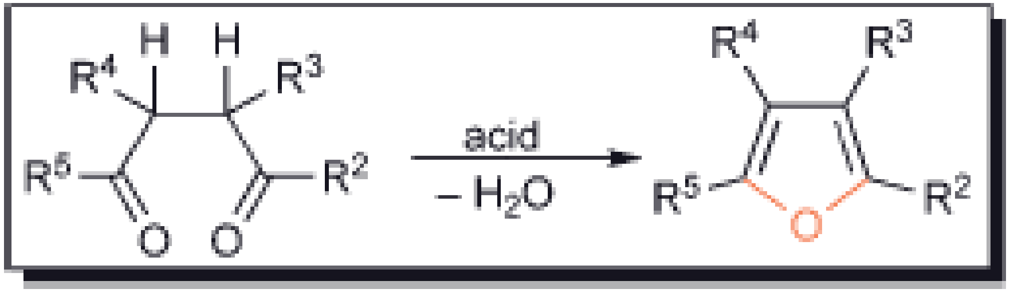
Furfural and thence furan, by vapour-phase decarbonylation, are available in bulk and represent the starting points for many furan syntheses. The aldehyde is manufactured from xylose, obtained in turn from pentosans, which are polysaccharides extracted from many plants, e.g. corn cobs and rice husks. Acid catalyses the overall loss of three mole equivalents of water in very good yield. The precise order of events in the multi - step process is not known for certain, however a reasonable sequence is shown below.



Ring Syntheses

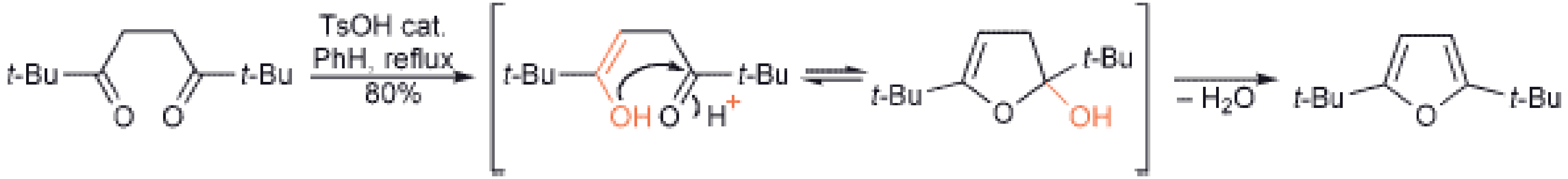
From 1,4-Dicarbonyl Compounds:

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



The Paal–Knorr Synthesis

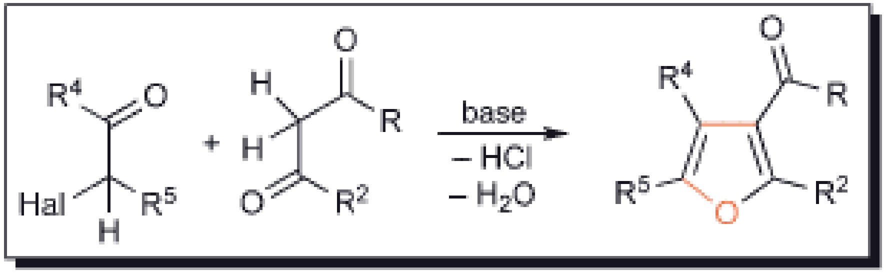
The most widely used approach to furans is the cyclising dehydration of 1,4-dicarbonyl compounds, which provide all of the carbon atoms and the oxygen necessary for the nucleus. Usually, non-aqueous acidic conditions[162] are employed to encourage the loss of water. The process involves addition of the enol oxygen of one carbonyl group to the other carbonyl group, then elimination of water.[163]



Non-aqueous acidic conditions

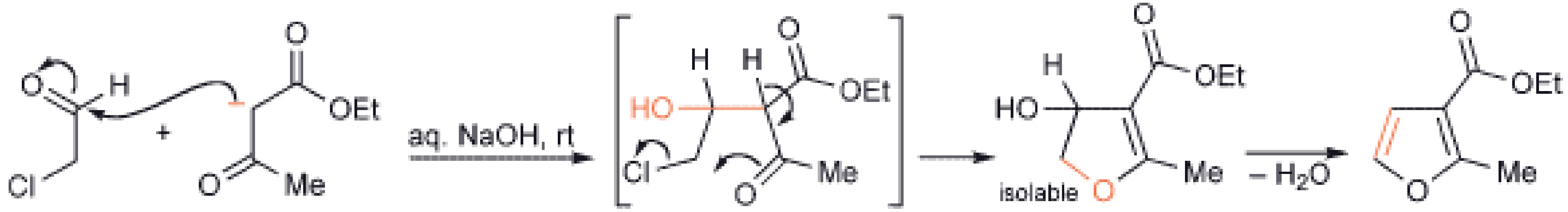
From α-Halo-Carbonyl and 1,3-Dicarbonyl Compounds

α-Halo-carbonyl compounds react with 1,3-dicarbonyl compounds in the presence of a base (not ammonia) to give furans.



The Feist–Benary Synthesis

This classical synthesis rests on an initial aldol condensation at the carbonyl carbon of a 2-halo-carbonyl-component; ring closure is achieved *via* intramolecular displacement of halide by enolate oxygen; intermediates supporting this mechanistic sequence have been isolated in some cases.[169]



From C_4O Compounds

There is a range of furan syntheses that have one aspect in common – the precursor of the aromatic furan has: (i) four carbons, (ii) an oxygen at a terminus and (iii) two degrees of unsaturation located somewhere in the five-atom sequence. Treatment (often acid) of the precursor generates the furan, by a sequence of isomerisations, a ring closure and an elimination (often of water).

The simplest example here is the oxidation of *cis*-but-2-ene-1,4-diol, which gives furan *via* the hydroxy-aldehyde – the two degrees of unsaturation being the carbonyl and carbon–carbon double bonds.[171]