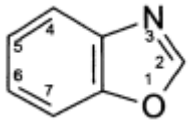
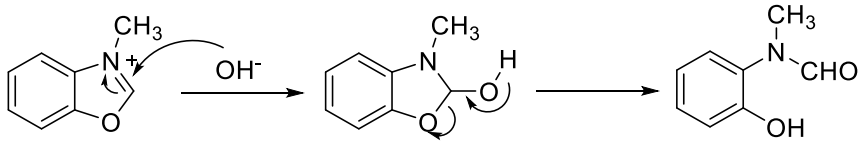
benzoxazole

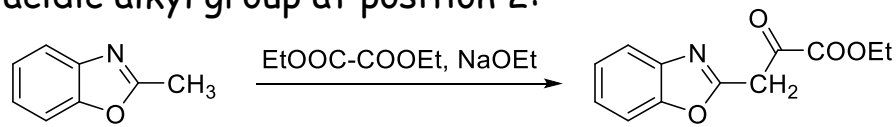


reactivity:

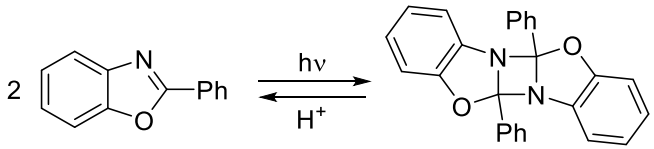
- **salt formation, quaternization:** analogous to oxazoles.
- **nitration:** substitution of the benzene ring at the 5- or 6-position.
- **nucleophiles attack**: at position 2.



- relatively acidic alkyl group at position 2:

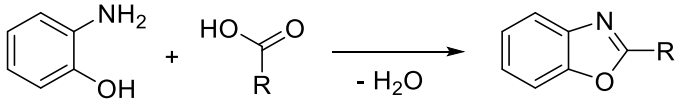


- [2+2] cycloaddition:

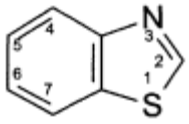


synthesis:

- **cyclocondensation:** of *o*-aminophenol with carboxylic acids or their derivatives.



benzothiazole



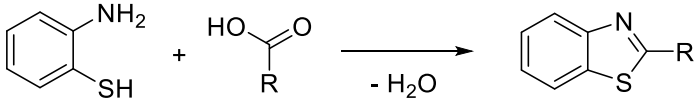
reactivity: benzothiazole is a weaker base than thiazole.

- **metallation**: *n*-BuLi, at position 2.
- **electrophilic substitutions:** only on the benzene ring.

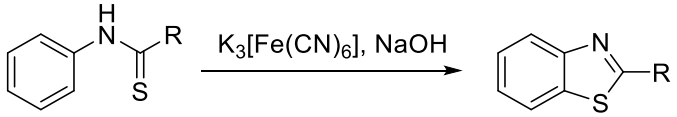
  nitration → mixture of 4-, 5-, 6-, and 7-nitrobenzothiazole.
- **reactions with nucleophilic reagents**: analogous to thiazoles.

synthesis:

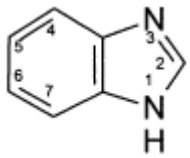
- **cyclocondensation** of *o*-aminothiophenols or their salts with carboxylic acids, their derivatives or with aldehydes.



- **cyclization**:

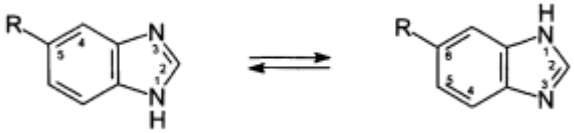


benzimidazole

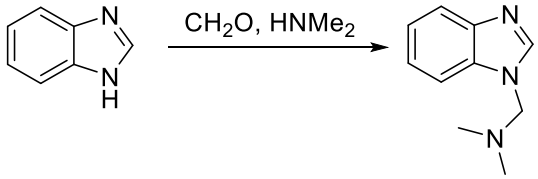


reactivity: benzimidazole is less basic than imidazole, but more NH-acidic.

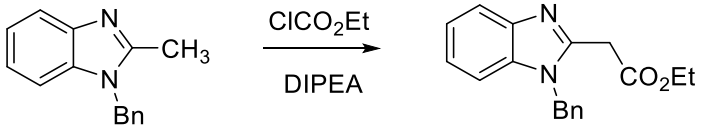
- **tautomerism**:



- **reaction with *n*-BuLi**: Benzimidazoles substituted at position 1 → litiation at position 2.
- **Mannich reaction**:



- **deprotonation of alkyl at position 2**: relatively facile for N-protected benzimidazoles.



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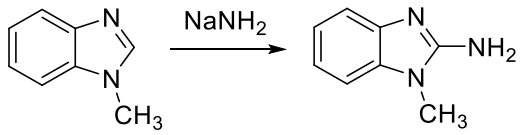
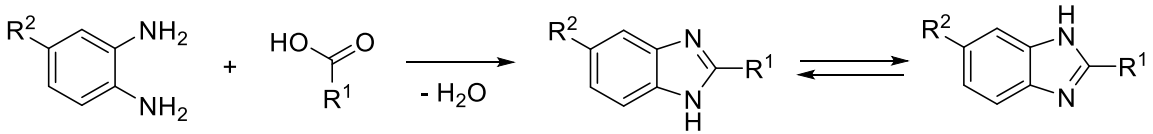
- **electrophilic substitutions**: first at position 5, then at position 6 or 7.

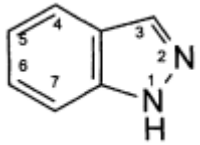
- **reactions with nucleophiles**: attack of position 2 (*e.g.* the Chichibabin reaction).



synthesis:

- **cyclocondensation** of *o*-phenylenediamine or substituted *o*-phenylenediamines with carboxylic acids or their derivatives.



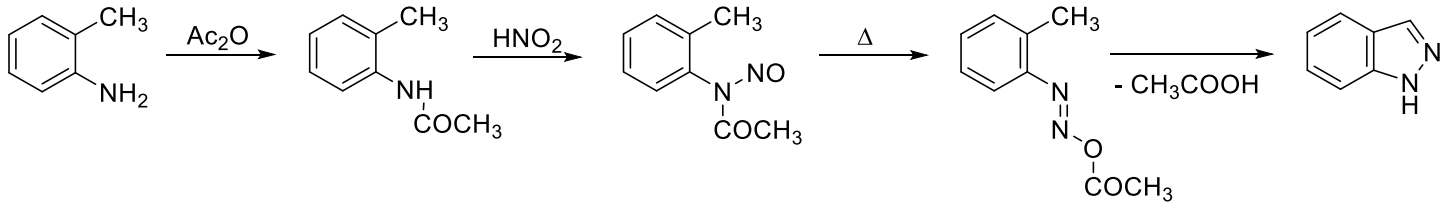
indazole 

reactivity: indazole is less basic than pyrazole but a stronger N-H acid (pK_a = 13.9).

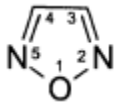
- **reaction with *n*-BuLi**: 1-methylindazole → 1-lithiomethylindazole
  2-methylindazole → 3-lithio-2-methylindazole
- **alkylation**: in the presence of bases proceeds *via* the ambident indazolyl anion
  → mixture of 1- and 2-alkylindazoles
- **halogenation**: preferentially at position 5
- **nitration**: with fuming nitric acid → 5-nitroindazole
- **sulfonation** (with oleum) → indazole-7-sulfonic acid
- **coupling** with diazonium salts: at position 3

synthesis:

- from *o*-substituted anilines:



1,2,5-oxadiazole (furazan)



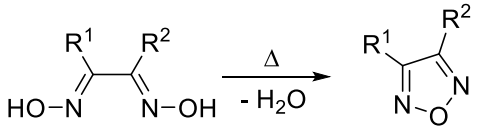
reactivity: ca. 100 times less basic than isoxazole; only slow (if any) reactions with electrophiles.

- quaternization: slow, even with dimethyl sulfate.
- reactions with nucleophiles: do not react at all or only slowly.

find at least one drug with the 1,2,5-oxadiazole motif & its mode of action

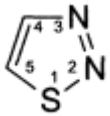
synthesis:

- **cyclodehydration** of dioximes of 1,2-dicarbonyl compounds



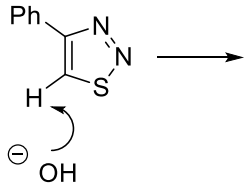
Heterocycles **1984**, 22, 1571.

1,2,3-thiadiazole

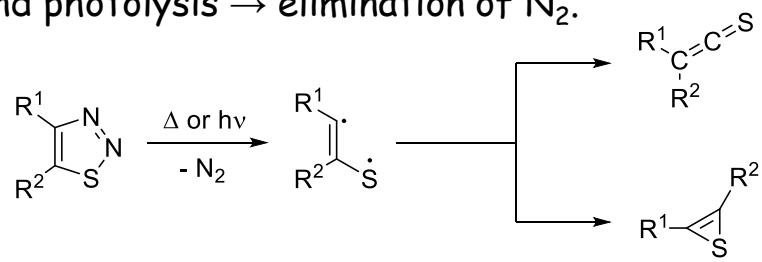


reactivity:

- weak base.
- electrophiles preferentially attack the heteroatoms.
- nucleophiles attack position 5.
- quaternization with dimethyl sulfate → mixture of 2- and 3-methylated isomers
- reaction with nucleophiles → ring-opening.

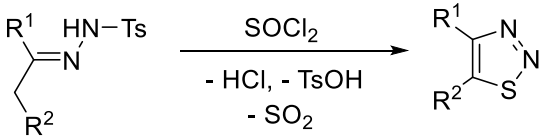


- thermolysis and photolysis → elimination of N_2.



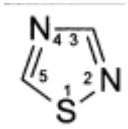
synthesis:

- **Hurd-Mori reaction**: cyclocondensation of tosylhydrazones.



find the mechanism of the Hurd-Mori reaction

1,2,4-thiadiazole

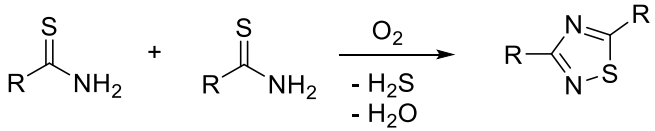


reactivity:

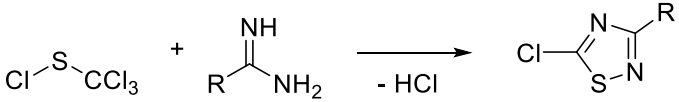
- weak base.
- electrophilic substitution at the C-atoms practically impossible.
- methylation: with CH_3I occurs at N-4, with trimethyloxonium tetrafluoroborate at both Ns.
- reaction with hydroxides → ring-opening.
- reaction with HCl → ring-opening occurs via the 1,2,4-thiadiazolium ion.
- nucleophiles attack the position 5 and/or 3.

synthesis:

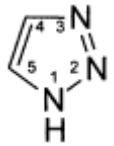
- **oxidation of thioamides**: with H_2O_2 or by the action of $SOCl_2$, SO_2Cl_2 or PCl_5.



- **cyclocondensation of amidines**: with trichloromethylsulfenyl chloride.



1,2,3-triazole

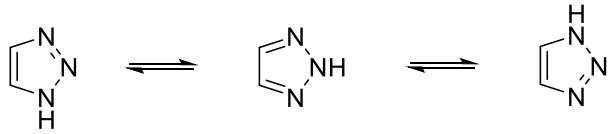


reactivity:

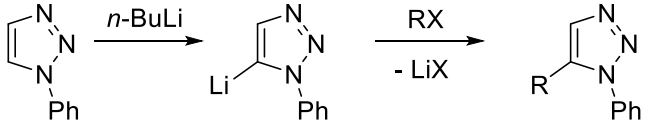
- **acid-base reactions**:
  - 1,2,3-triazole is a weak base, less basic than pyrazole.
  - triazoles unsubstituted on the N-atom are NH-acidic.

    (1,2,3-triazole pK_a value is 9.3; comparable to HCN)

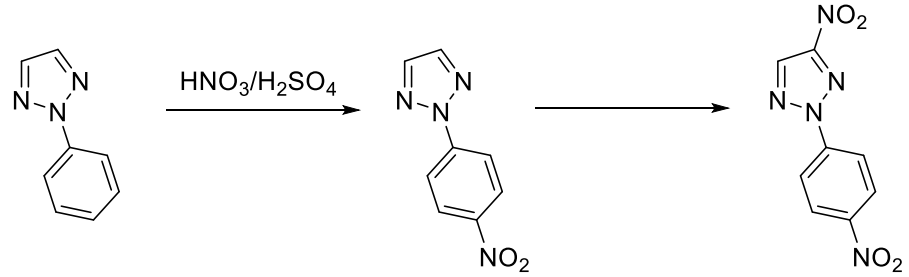
- **tautomerism:**



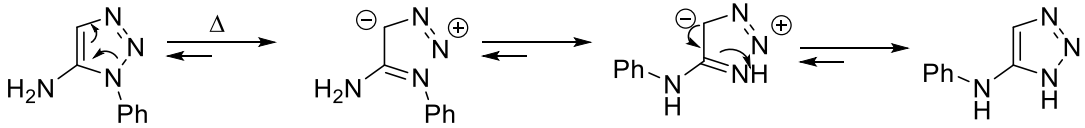
- **metalation:** *N*-substituted 1,2,3-triazoles are metalated by *n*-BuLi at low temperature.



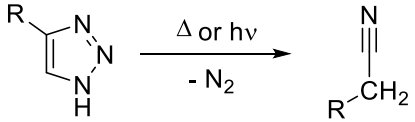
- **reactions with electrophiles:**
  - acetylation, tosylation → usually mixtures of 1- and 2-isomers
  - bromination (Br_2) → 4,5-dibromo-1,2,3-triazole
  - nitration: note: 2-phenyl-1,2,3-triazole undergoes nitration first on the benzene ring and then on the 1,2,3-triazole ring.



  - **Dimroth rearrangement**: with nucleophiles, 1,2,3-triazoles do not react at all or react only slowly with ring opening.

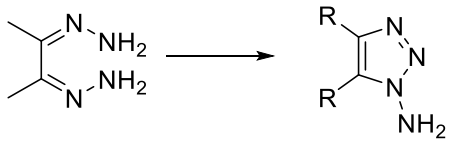


  - **ring cleavage** by pyrolysis or photolysis with loss of nitrogen.

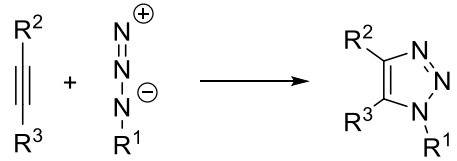


synthesis:

- **oxidation:** of bishydrazones of 1,2-dicarbonyl compounds.

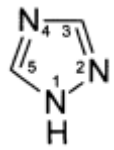


- **dipolar cycloaddition:** azides react with alkynes.



find at least 3 applications of the „click reaction“ in cells

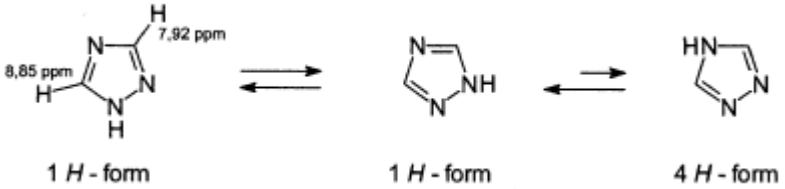
1,2,4-triazole



reactivity:

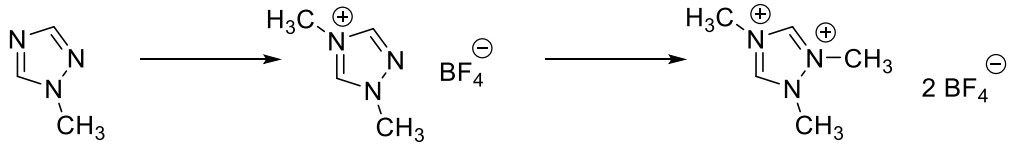
- **acid-base reactions**: 1,2,4-triazole is a weak base; protonation on N4 (pK_a = 2.19); 1,2,4-triazoles unsubstituted on nitrogen are NH-acidic.

- **tautomerism:** two 1*H*-tautomers and one 4*H*-.



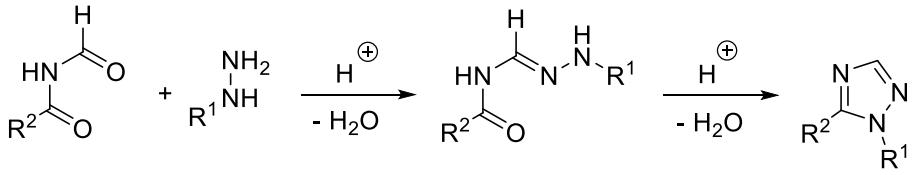
- **reactions with electrophiles:**
  - the N-atoms are preferentially attacked.
  - benzylation, methoxycarbonylation, trimethylsilylation, acylation → mainly 1-substituted compounds.
  - nitration, sulfonation: very slow
  - bromination, chlorination (Br_2 or Cl_2) → (3)5-chloro- or 3(5)-bromo-1,2,4-triazole.

- **quaternization** of 1-methyl-1,2,4-triazole with trimethyloxonium tetrafluoroborate:

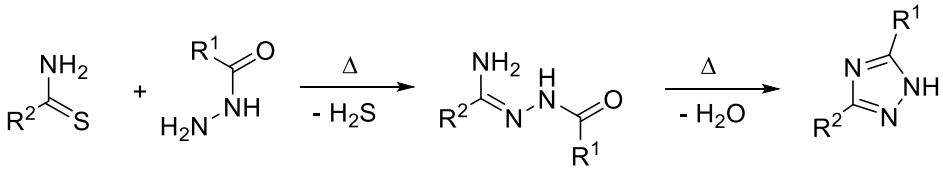


synthesis:

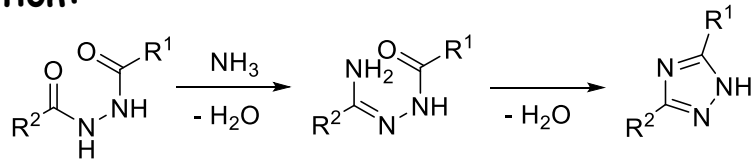
- **Einhorn-Brunner synthesis:** hydrazines condense with diacylamines.



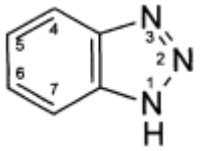
- **Pellizzari synthesis:** acid hydrazides cyclize with acid amides or thioamides.



- **cyclocondensation:**



benzotriazole

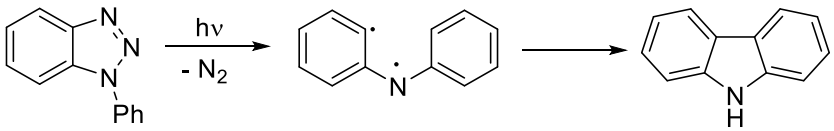


reactivity:

- benzotriazole is a very weak base;
  but a stronger NH-acid than benzimidazole or 1,2,3-triazole (pK_a = 8.2).
- forms complexes with metals → frequently used as a ligand.

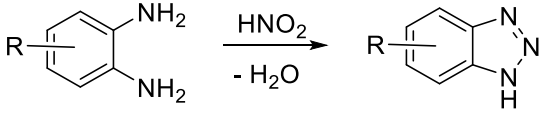
- **alkylation:** → mixtures of 1- and 2-alkylbenzotriazoles.
- **acylation, sulfonation:** occur at N-1.
- **reactions with electrophiles:** only the benzene ring carbon atoms are available.
  chlorination (mixture of concentrated HCl and HNO_3) → 4,5,6,7 tetrachlorobenzotriazole,
  nitration → 4-nitrobenzotriazole)

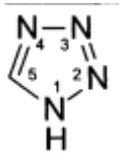
- **Graebe-Ullmann reaction** (dediazoniation of 1-phenylbenzotriazole).



synthesis:

- **cyclocondensation** of *o*-phenylenediamines with sodium nitrite under H^+ conditions.

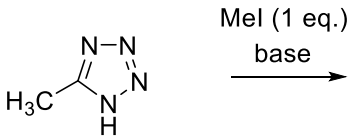


tetrazole 

reactivity:

- **acid-base reactions:**
  - tetrazole is a very weak base; protonation occurs at position 4 (pK_a = -3.0).
  - of all azoles, tetrazole has the strongest NH-acidity (pK_a = 4.9); comparable to acetic acid.

- **tautomerism:** 1*H*-form predominates over the 2*H*-form in solution.



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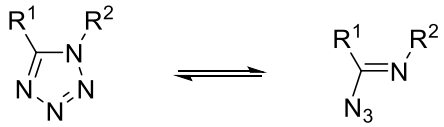
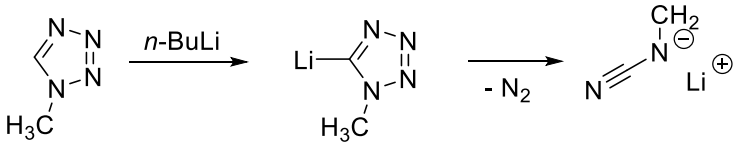
- **ring-chain tautomerism:** 1,5-disubstituted tetrazoles can isomerize to give azidoimines.

J. Am. Chem. Soc. **1998**, *120*, 4723.



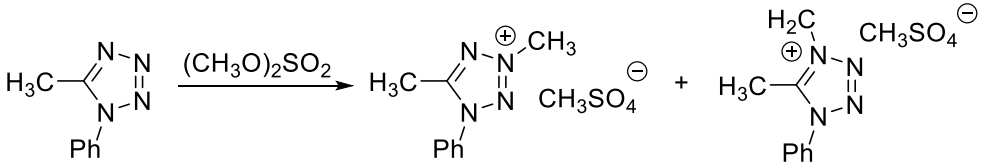
reactivity:

- **metalation:** 1-methyltetrazole is lithiated by *n*-BuLi in THF at -60 °C at position 5.



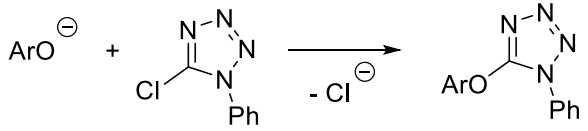
(5-alkyltetrazoles substituted at position 1 undergo metalation of the alkyl substituent as a result of the acceptor action of the tetrazolyl moiety.)

- **reactions with electrophiles:**
  - quaternization → mixture of 1- and 2-methyltetrazole

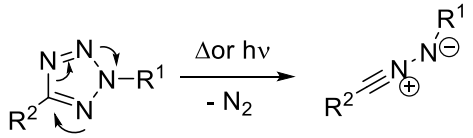


  - acylation (acyl halides) → at position 2 (but the products are not stable)
  - nitration → substitution e.g. of the benzene ring, when available

- **reactions with nucleophiles**: 5-halotetrazoles react with nucleophiles → substitution.

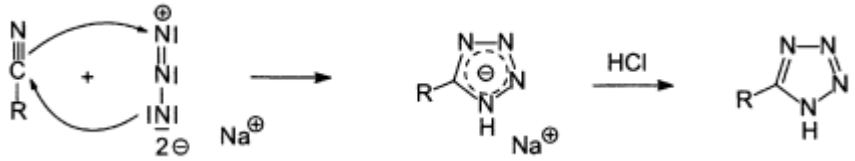


- **thermal of photochemical extrusion of N_2:**

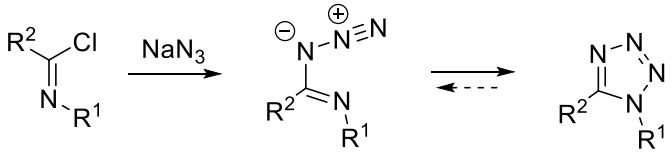


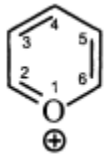
synthesis:

- **[3+2] cycloaddition:** azide + nitriles:

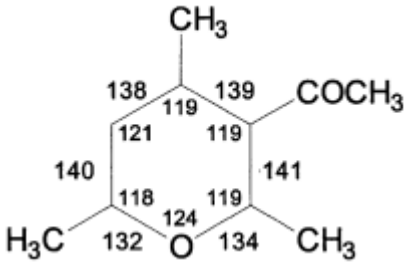


imidoyl halides react with sodium azide:





- planar, slightly distorted hexagon with *C-C* and *C-O* bonds of approximately equal length

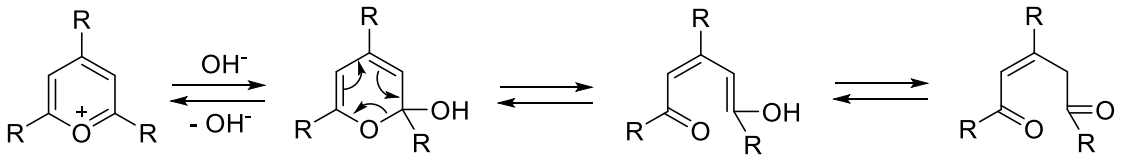


reactivity:

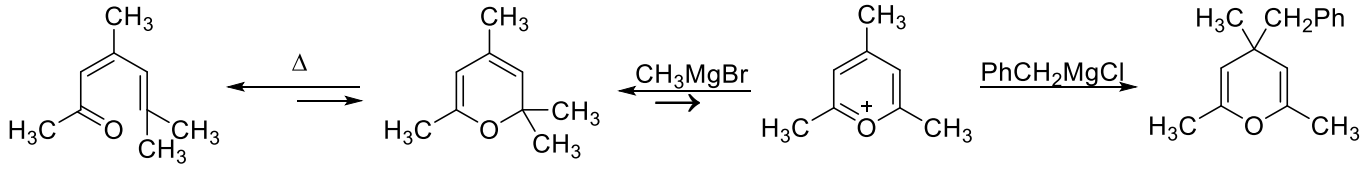
- pyrylium ion is an aromatic system.
- the distribution of the π-electron density can be represented by mesomeric structures.

- typical reactions: attack of nucleophiles onto the positions 2/6 and 4; and subsequent reactions.

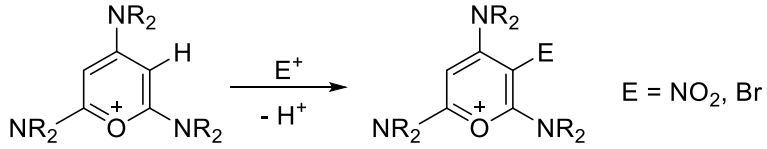
- **reactions with aqueous hydroxides:**



- **reactions with organometallic compounds:** → predominantly form 2*H*-pyrans.
  benzylmagnesium chloride is an exception → 4*H*-pyrans.

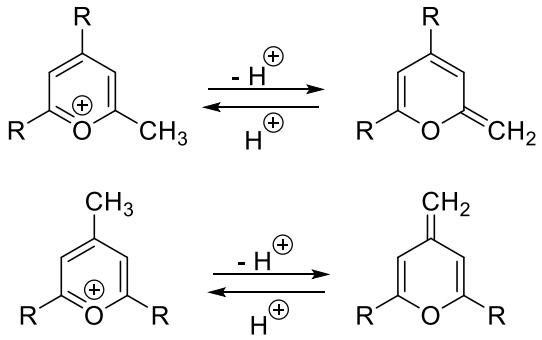


- this reactivity of pyrylium ions can be *reversed* by donor substituents at positions 2, 4 and 6.
- for instance, 2,4,6-tris(dialkylamino)pyrylium ions are stable towards nucleophilic attack, but are easily substituted by electrophiles (e.g. HNO_3/H_2SO_4 or $BrCN/AlCl_3$).

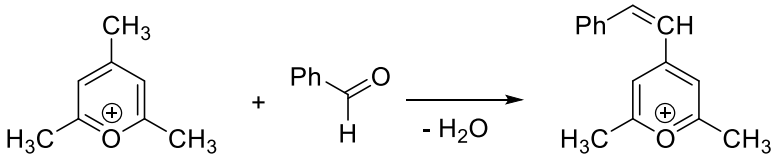


- this behavior may be due to the fact that the donor-substituted pyrylium ion does not possess the structure of cyclic delocalized 6π-systems, but rather that of a localized trimethine cyanine.

- **reactions with nucleophilic reagents**: alkyl groups at positions 2, 4 and 6 display marked CH-acidity. action of bases → deprotonation on CH groups attached to the ring forming 2- or 4-methylenepyrans.



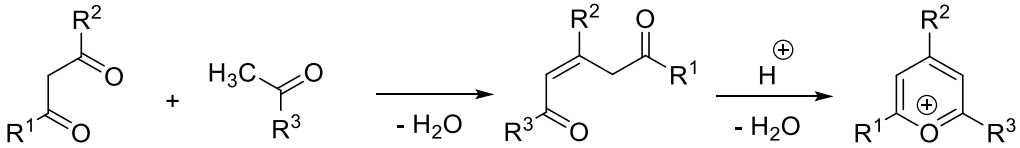
- **aldol condensation:** regioselective



synthesis:

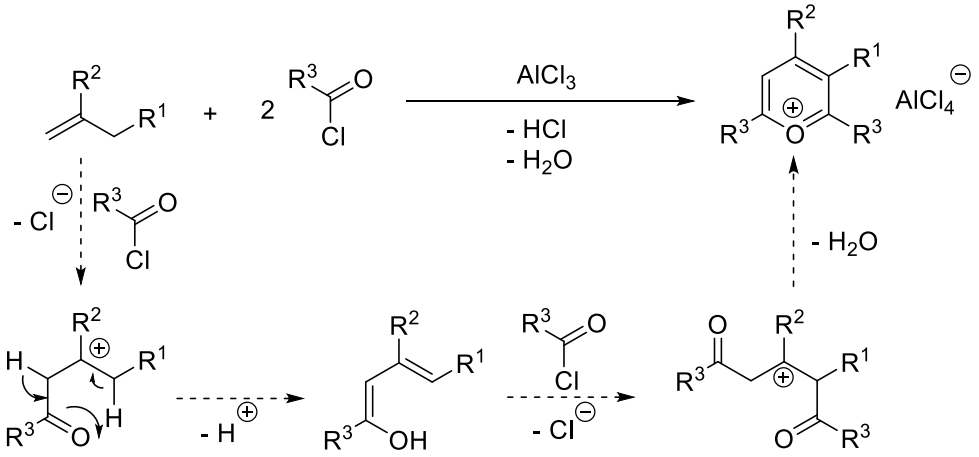
- **condensation:** 1,3-dicarbonyl compounds and aryl methyl ketones in acetic anhydride in the presence of strong acids.

  (chlorovinyl ketones or chlorovinyl immonium salts also condense with aryl methyl ketones.)

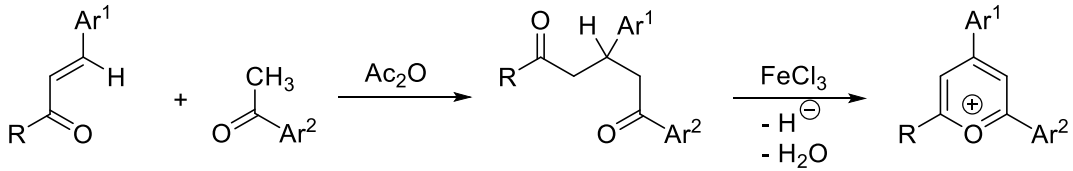


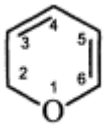
synthesis:

- **Balaban synthesis:** double acylation of propene derivatives with acid chlorides or anhydrides in the presence of Lewis acids, e.g. $AlCl_3$.



- **Dilthey synthesis**: in the presence of a hydride akceptor (e.g. $FeCl_3$) chalcones afford trisubstituted pyrylium salts.

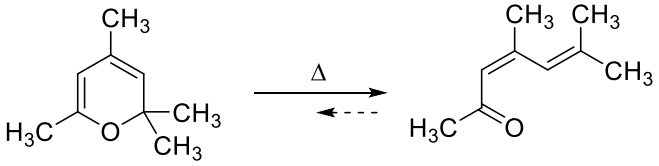




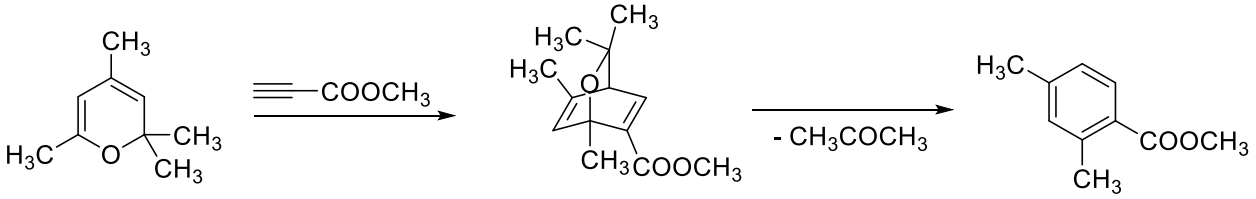
- the parent compound has not yet been isolated; 2,2-disubstituted derivatives have been prepared.

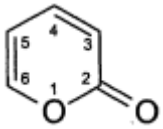
reactivity: 2*H*-pyrans behave like oxacyclohexadienes.

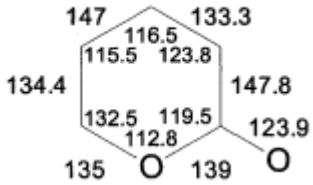
- **thermal ring opening:** process is *reversible* → dienones can be used to prepare 2*H*-pyrans.



- **[4+2] cycloadditions:** with activated double/triple bonds.



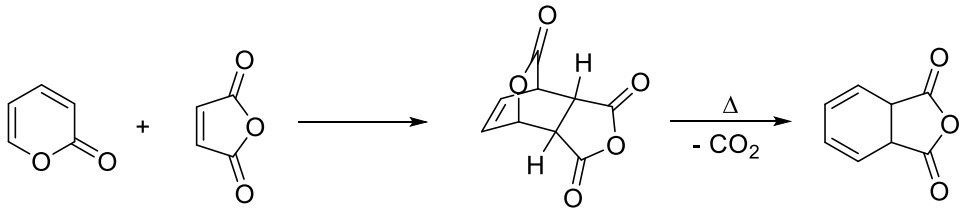




- it possesses the bond parameters of an enol-lactone system with localized *C-C* double and single bonds

reactivity: behaves as 1,3-diene and also as a lactone.

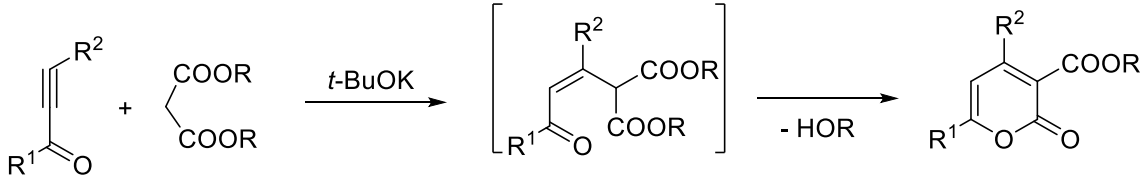
- **Diels-Alder reaction:** with activated alkenes or alkynes.



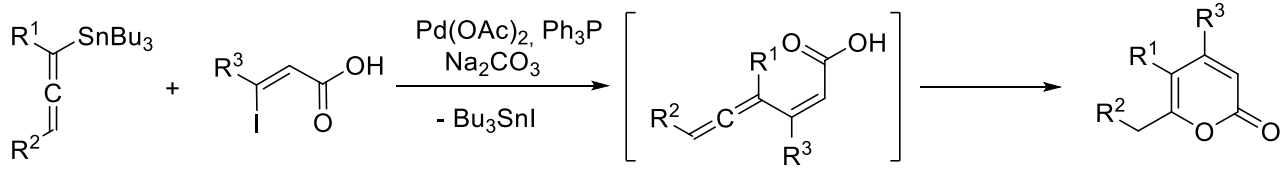
- **reactions with nucleophiles:** attack on the *C*-atom of the carbonyl group.
- **reactions with electrophiles:**
  - bromination → position 3 (higher temp.),
    → trans-5,6-dibromide (lower temp.)

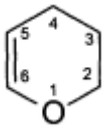
synthesis:

- **base-catalyzed cyclocondensation** of alkynones with malonic esters



- **Pd-catalyzed reaction:** of allenyl stannanes with ß-iodo acrylic acids.



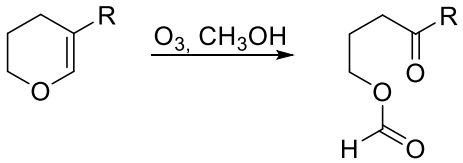


3,4-dihydro-2*H*-pyran

- oxa-analog of cyclohexene derived from 2*H*-pyran.

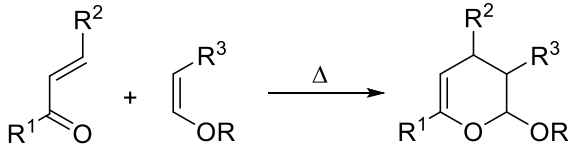
reactivity: reactions of electron-rich double-bonded systems.

- **electrophilic addition**: HX, HOX (X = halogen) or hydroboration.
- **[2+1], [2+2] and [4+2] cycloadditions**
- **nucleophilic additions:** *e.g.* with alcohols or phenols.
- ozonolysis:

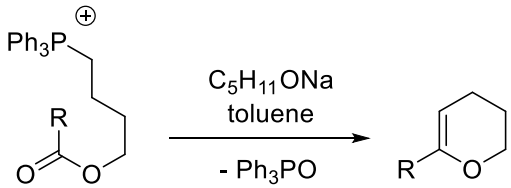


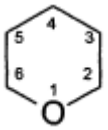
synthesis:

- **[4+2] cycloaddition:** *a,ß*-unsaturated carbonyl compounds + vinyl ethers.



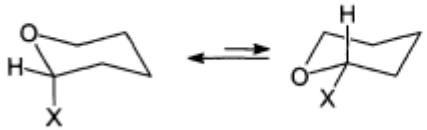
- **intramolecular Wittig reaction:**





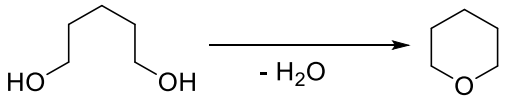
tetrahydropyran

- chair conformation
- electronegative substituents (alkoxy groups, halogens) at position 2(6) prefer to adopt the axial position (**anomeric effect**)



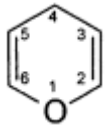
synthesis:

- cyclodehydration of 1,5-diols:



- acid-catalyzed cyclization of 4-hydroxybutyloxiranes
- cyclization of hex-5-en-l-ol with electrophilic halogen reagents

  → 2-substituted tetrahydropyrans

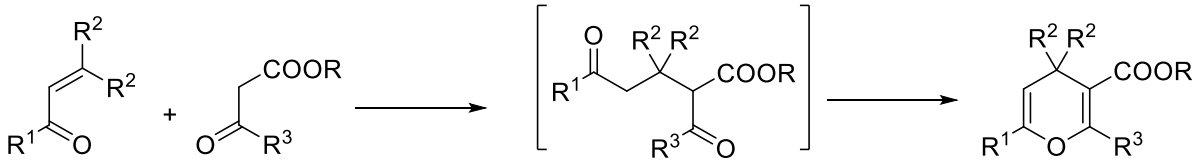


pyran

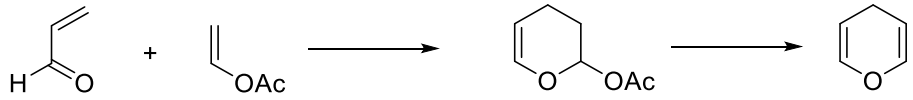
- in contrast to 2*H*-pyran, the parent compound 4*H*-pyran is known and spectroscopically characterized.

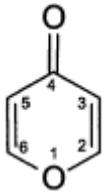
synthesis:

- **cyclocondensation** of ß-disbustituted enone systems with ß-keto esters (*via* 1,5-dicarbonyl compounds):



- **Diels-Alder reaction:**



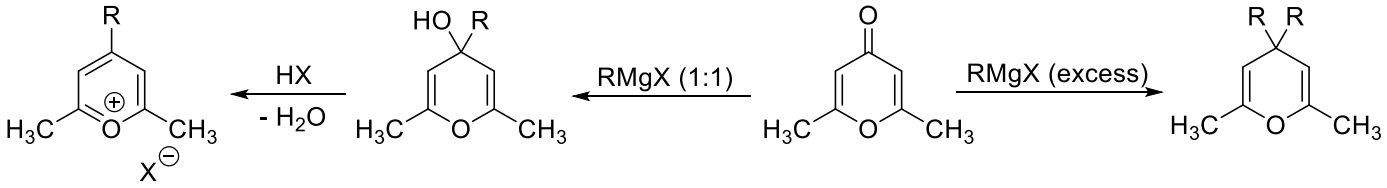


4H-pyran-4-one

- cross-conjugated, localized cycloenone system.

reactivity:

- irradiation → 4*H*-pyran-4-one isomerizes to 2*H*-pyran-2-one.
- *O*-alkylation: with strong electrophiles.
- electrophilic substitution: typically not regioselective.
- nucleophiles attack *C*-2 or *C*-4.
- reaction with Grignard reagents:



synthesis:

- ***γ*-acylation** of 1,3-diketones with carboxylic esters.