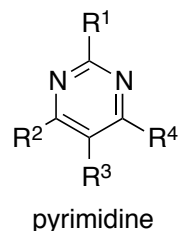
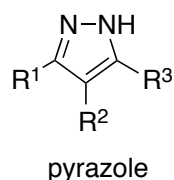
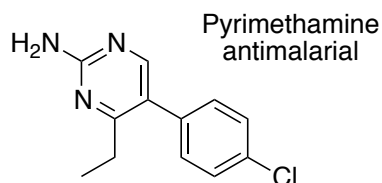
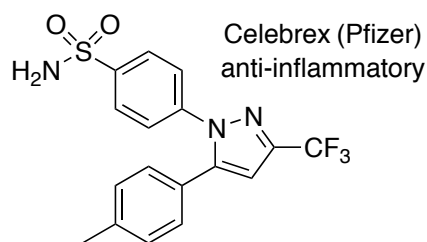


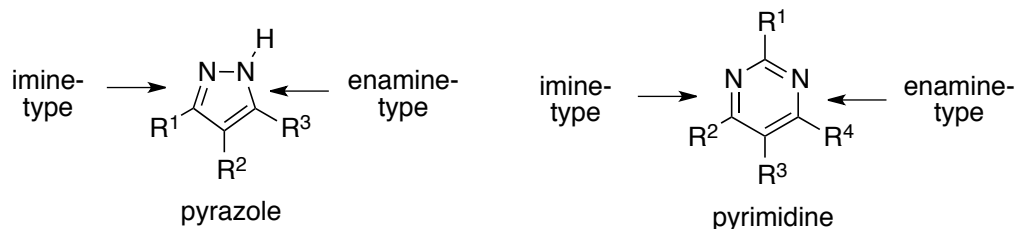
CHEM 330

Topics Discussed on Sept 28

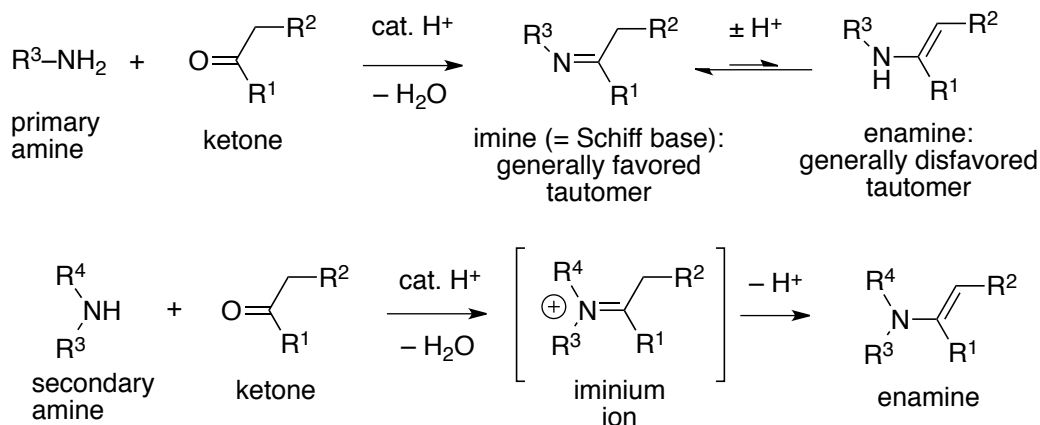
Heterocycles such as pyrazole, pyrimidine, etc., as common subunits of pharmaceuticals



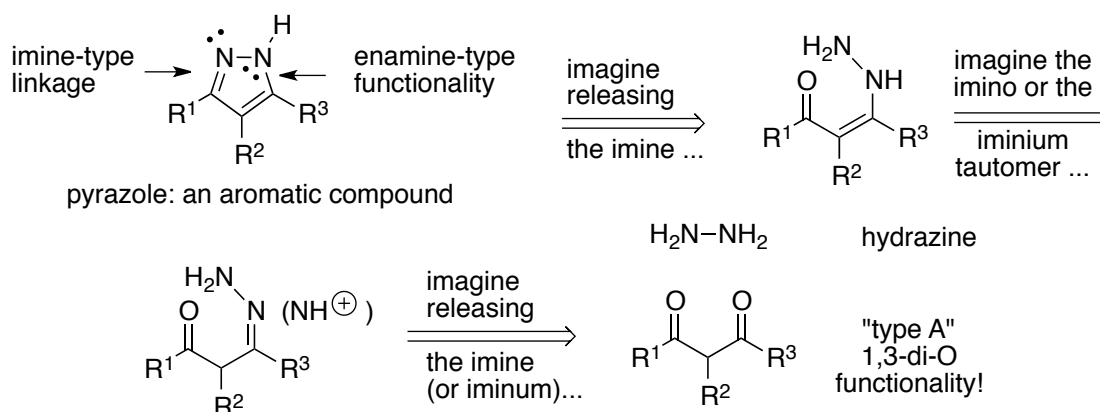
Imine- and enamine-type linkages in nitrogen heterocycles



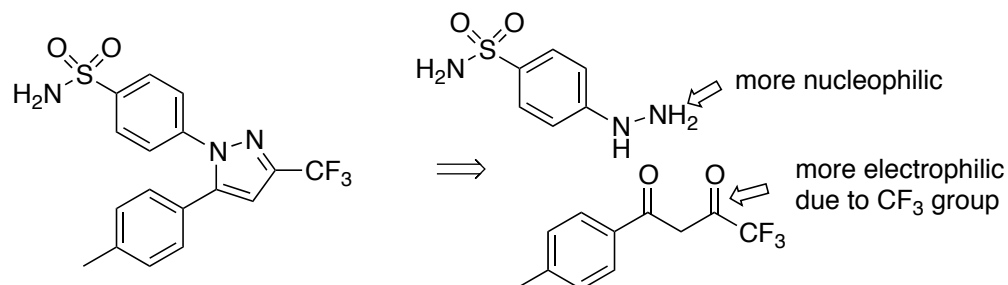
Principle: the construction of heterocyclic systems often involves the formation of imines (=Schiff bases) and / or enamines. These are produced upon the condensation of carbonyl compounds with appropriate amines (see CHEM 203 & CHEM 213 notes):



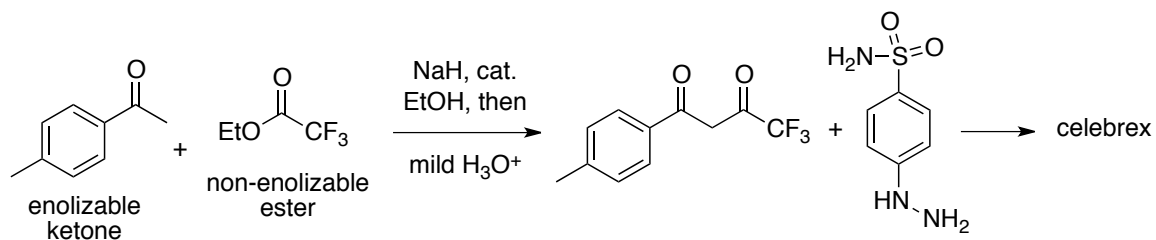
Approach to the synthesis of pyrazoles by reaction of 1,3-dicarbonyls with hydrazine:



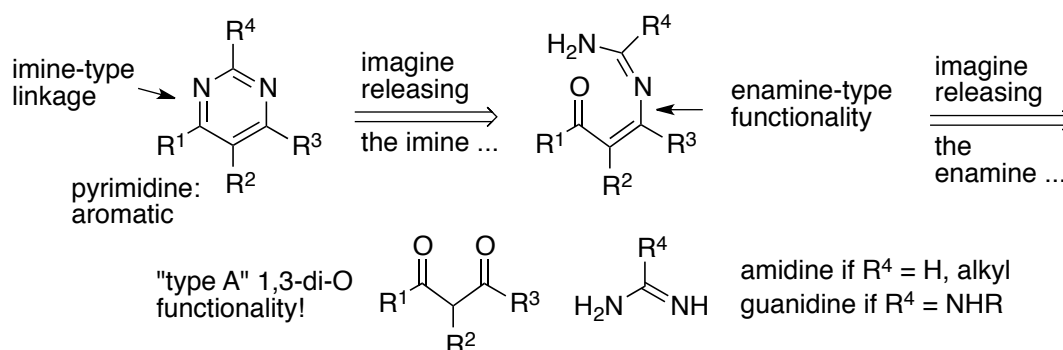
Application of the above logic to the synthesis of Celebrex



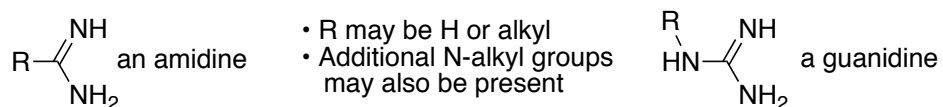
Preparation of diketones of the above type by a cross-Claisen-like reaction taking place under conditions of thermodynamic control:



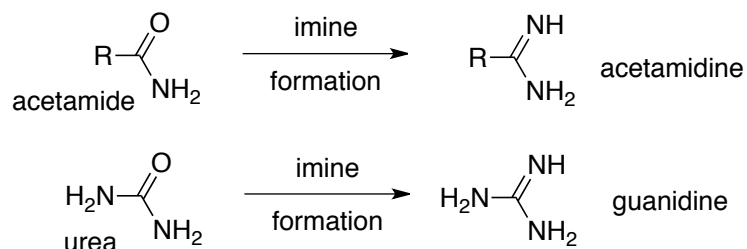
Approach to the synthesis of pyrimidines by reaction of 1,3-dicarbonyls with amidines or guanidines:



Amidines and guanidines: compounds possessing the structures shown below



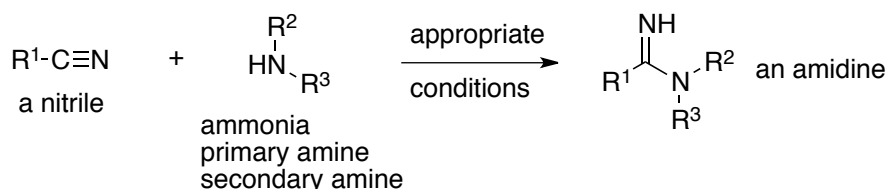
Amidines as *formal* imines of carboxamides; guanidines as formal imines of ureas:



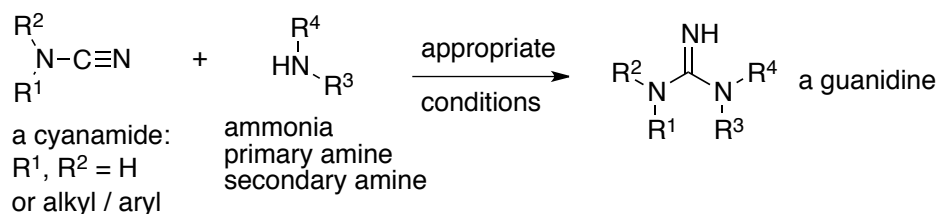
Principle: it is not possible to prepare amidines or guanidines by condensation of amides or ureas of with amines/ NH_3

note: this is because (i) the $\text{C}=\text{O}$ group of amides and ureas is insufficiently electrophilic to react with amines or NH_3 , and (ii) if one forces the issue, other reactions tend to occur.

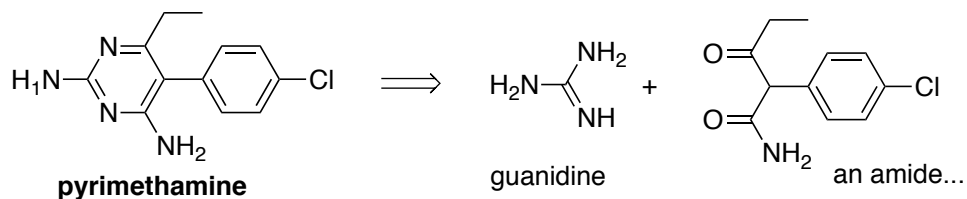
Preparation of amidines by addition of NH_3 or amines to nitriles (under appropriate conditions not covered in CHEM 330):



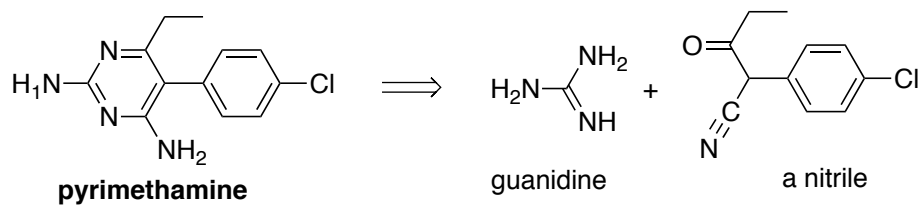
Preparation of guanidines by addition of NH_3 or amines to cyanamides:



Application of the above logic to the synthesis of pyrimethamine

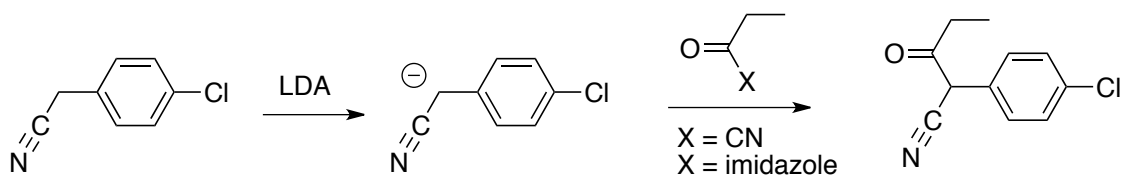


BUT: one cannot make the "imine of an amide," i.e., an amidine, by condensation of amine-type compound with an amide: a nitrile is required instead ...

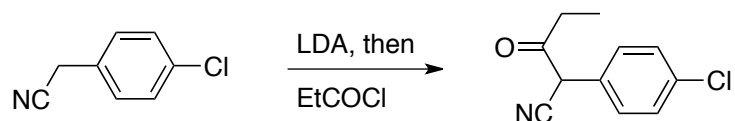


Similarities between the chemistry of nitriles and that of esters

Preparation of ketonitriles of the above type by a cross-Claisen-like reaction taking place under conditions of kinetic control; e.g:



Kinetically controlled cross-Claisen condensations of the type above as exceptional cases in which acid chlorides (instead of acyl cyanides or acyl imidazoles) perform well:



then . . .

