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

imine-
type
$$R^1$$
 R^3 enamine-
type imine-
type R^2 R^3 enamine-
type R^3 R^4 enamine-
type R^3 pyrazole pyrimidine

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:

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imine-type inhage
$$R^3$$
 enamine-type functionality R^3 enamine-type functionality R^3 imagine releasing the imine ... R^3 imagine the imino or the pyrazole: an aromatic compound R^2 imagine R^3 imagine

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:

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Amidines and guanidines: compounds possessing the structures shown below

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

acetamide
$$\stackrel{O}{NH_2}$$
 $\stackrel{imine}{\xrightarrow{formation}}$ $\stackrel{NH}{R}$ $\stackrel{NH}{\nearrow}$ acetamidine $\stackrel{NH_2}{\nearrow}$ $\stackrel{Imine}{\xrightarrow{formation}}$ $\stackrel{NH}{\nearrow}$ $\stackrel{NH_2}{\nearrow}$ $\stackrel{Imine}{\nearrow}$ $\stackrel{NH_2}{\nearrow}$ $\stackrel{NH_2}{\nearrow}$ $\stackrel{Imine}{\nearrow}$ $\stackrel{NH_2}{\nearrow}$ $\stackrel{NH_2}{\nearrow}$ $\stackrel{NH_2}{\nearrow}$ $\stackrel{NH_2}{\nearrow}$

Principle: it is not possible to prepare amidines or guanidines by condensation of amides or ureas of with amines/NH₃

note: this is because (i) the C=O group of amides and ureas is insufficiently electrophilic to react with amines or NH₃, and (ii) if one forces the issue, other reactions tend to occur.

Preparation of amidines by addition of NH₃ or amines to nitriles (under appropriate conditions not covered in CHEM 330):

Preparation of guanidines by addition of NH₃ 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 ...

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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:

$$CI \qquad LDA \qquad \bigcirc \qquad \qquad X \qquad \qquad O \qquad X \qquad CI \qquad X = CN \qquad X = imidazole \qquad N \qquad X = imidazole \qquad X \qquad$$

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 . . .