ACROLEIN AS A SYNTHON FOR PYRIMIDINIC COMPOUNDS. REACTION WITH BENZAMIDINE[1]

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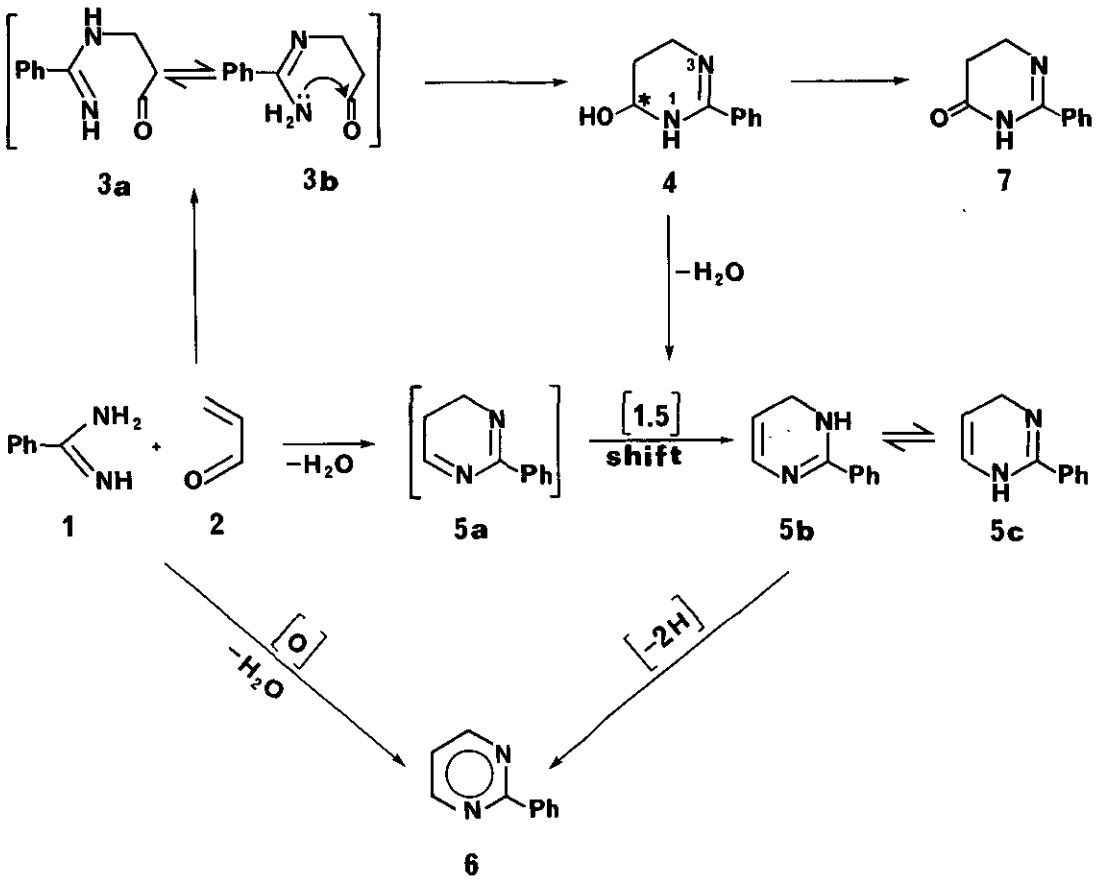
Abstract - Depending on the reaction conditions, acrolein (stabilized by hydroquinone) reacts with benzamidine to give selectively tetrahydropyrimidine (4), dihydropyrimidine (5) and pyrimidine (6) in high yields.

The reaction of amidines with α,β-unsaturated carbonyl compounds is an attractive approach to the synthesis of pyrimidinic ring systems. However, in spite of the substantial progress in the study of this reaction during the last decade[2], all attempts to utilize the parent α,β-unsaturated carbonyl compound, acrolein, failed[3]. Fast polymerization of acrolein in the presence of strong bases probably accounts for this failure. Actually we are facing a problem of at least two concurrent



processes: polymerization and Michael addition to an activated double bond. Therefore, we assumed that upon addition of a stabilizer to acrolein, which could sharply diminish/or stop the polymerization process, the Michael addition would then be permited to proceed. The stabilizer which gave the best results among those tested was hydroquinone.

We report herein that (±)-6-hydroxy-1,4,5,6-tetrahydropyrimidine (4) was prepared by dropwise addition of a solution of acrolein (2)[†] in dry acetone to a stirred solution containing stoichiometric amounts (or a small excess) of free benzamidine (1) in dry acetone at -5°C under an inert gas atmosphere. The white precipitate of analytically pure (4) was filtered after 6 hours. An additional amount of (4) was obtained after 24 h. The total yield was 96%[††], mp 156-158°C.

^{1}H n.m.r. [80 MHz, $CDCl_3$-CD_3OD (10:1), δ, ppm]: 1.85 (2H, m, 5-CH_2), 3.50 (2H, t, J=6.0 Hz, 4-CH_2), 5.07 (H, t, J=3.6 Hz, 6-H), 7.30-7.70 (5H, m, aromat.).

Derivatives of 6-hydroxytetrahydropyrimidine are generally noted for their poor stability and consequently relatively little is known concerning their structural features. The compound (4) was found to be sufficiently stable to permit a complete structural analysis. A single crystal x-ray diffraction study (Figure 1) has confirmed the proposed structure, which contains a carbinolamine (N,O-hemiacetal) moiety and clearly shows that in the solid state, (4) exists in the twist chair conformation, with (pseudo) axial OH and (pseudo) equatorial NH. This is readily explained in terms of the theory of stereoelectronic control, since the lone pairs on both O and N are antiperiplanar to the C-N bond[4]. The crystal structure indicates there to be an intermolecular hydrogen bond between OH and N(sp^2) of neighbouring molecules which is obviously the reason for the poor solubility in apolar solvents.

Boiling of (4) in dimethoxyethane (or acetonitrile, DMF), in the presence of freshly activated molecular sieves (Linde 4Å) allows preparation of the yellow dihydropyrimidine (5) in quantitative yield (tlc), isolated yield 87%.

^{1}H n.m.r. (270 MHz, $CDCl_3$) δ 4.23 (2H, dd, J=1.4 Hz, J=3.0 Hz, CH_2), 4.80 (1H, dt, J=11.6 Hz, J=3.0 Hz, 5-H), 6.31 (1-H, dt, J=11.6 Hz, J=1.4 Hz, 6-H), 7.30-7.70 (5H, m, aromat.). The i.r. and n.m.r. spectroscopic data rule out (5a), but are consistent with the tautomeric structures (5b) and (5c). Comparison of i.r. spectra of dihydropyrimidine (5) recorded in KBr and in different solvents, has clearly shown that in solutions this compound exists in tautomeric equilibrium

[†]Freshly distilled acrolein was stabilized by 0.1-0.5% hydroquinone; commercial acrolein (Merck or Fluka, 0.5% hydroquinone) can be used directly, giving (4) in 80-90% yield.

[††]The yield of (4) is very sensitive to the degree of purity of the starting materials. Satisfactory elemental microanalysis and mass-spectroscopic data were obtained for all compounds recorded here.

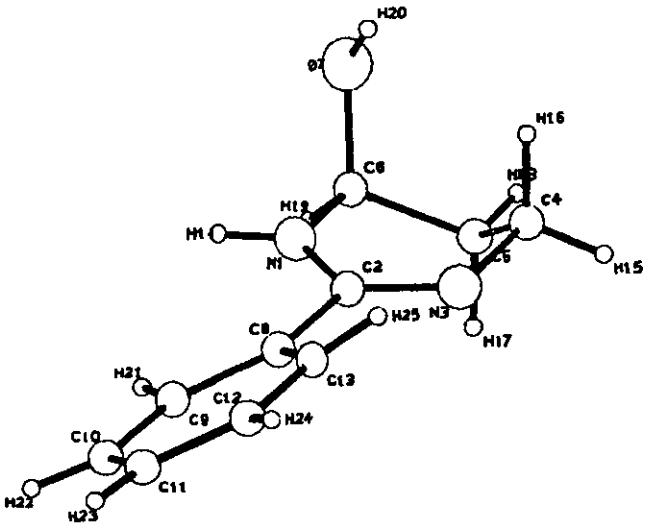


Figure I. The molecular structure of 6-hydroxy-1,4,5,6-tetrahydropyrimidine. Selective bond length: C(2)-N(1) 1.36(3), N(3)-C(2) 1.29(3), C(4)-N(3) 1.46(3), C(6)-C(5) 1.52(4), C(6)-N(1) 1.45(3), C(5)-C(4) 1.52(4), O(7)-C(6) 1.41(3) Å; bond angles: C(6)-N(1)-C(2) 123.5(2), N(3)-C(2)-N(1) 124.7(2), C(8)-C(2)-N(1) 116.3(2), C(8)-C(2)-N(3) 119.0(2), C(4)-N(3)-C(2) 116.0(2), C(5)-C(4)-N(3) 111.5(2), C(6)-C(5)-C(4) 108.7(2), C(5)-C(6)-N(1) 108.0(2), O(7)-C(6)-N(1) 112.2(2), O(7)-C(6)-C(5) 112.4(2)°.

between two forms (5b) and (5c), and that the relative amount of (5c) in the mixture increased with polarity of solvent[5]. Since the characteristic absorptions in the 1600-1700 cm^{-1} region of the i.r. spectra provide an excellent tool for differentiation of tautomers[6], the band at 1638 cm^{-1} in KBr was assigned to the 1,6 (3,4)-dihydropyrimidinic structure (5b), whereas a new band at 1680 cm^{-1} arising in solutions was attributed to the 1,4-dihydrostructure (5c).

Taking into account the factors affecting the possibility of observing tautomerism in dihydropyrimidinic systems, both tautomers were observed in ^{1}H and ^{13}C n.m.r. spectra, measured in specially purified [$^{2}H_{6}$] DMSO[5] or $CDCl_3$[7] solutions. For example, ^{1}H n.m.r. (270 MHz, $CDCl_3$, -60°C, 0.01M δ, ppm):

(5b): 4.25 (CH_2), 5.0 (H-5), 5.14 (NH), 6.43 (H-6).

(5c): 4.32 (CH_2), 4.61 (H-5), 6.24 (NH), 6.16 (H-6).

The kinetic parameters obtained from a synamic n.m.r. investigation are very similar to those reported in our communication[7]. It should be noted that the rate of tautomerism depends on the concentration of a sample, which indicates an intermolecular mechanism of proton transfer[8].

Compound (5) may be prepared from acrolein and benzamidine in benzene under reflux for 12 h, over molecular sieves; however, the yield is lower.

Oxidation of dihydropyrimidine by different oxidizing agents ($KMnO_4$, Ag_2O etc.), gives more than 96% of the corresponding pyrimidine (6). It should be noted that (6) also can be prepared from (4), as well as directly from stabilized acrolein and benzamidine in DMSO[2a]. Upon oxidation of compound (4) with $KMnO_4$ in acetone, 6-oxo-2-phenyl-1,4,5,6-tetrahydropyrimidine, mp 145-146°C[9] was obtained in quantitative yield.

The reactions described in this study provide for the first time, quantitative synthetic routes using acrolein for the preparation of different pyrimidinic compounds. A preliminary investigation has revealed that this approach is also potentially useful in the preparation of the unknown parent 6-hydroxytetrahydro- and dihydropyrimidinic systems. Moreover, this new method might provide a facile route to different pyrimidines and, especially, to the unsubstituted one, which is tedious to prepare, using current techniques.

Crystal Data

Crystals suitable for diffraction experiments were obtained by slow crystallization of (4) from acetone. They are monoclinic, space group $P2_1/C$ with $\underline{a}$ = 10.203(1), $\underline{b}$ = 7.258(3) and $\underline{c}$ = 12.729(4) Å, β = 108.69(1)°, $\underline{V}$ = 897.31 Å^3, $\underline{Z}$ = 4. A total of 1863 independent reflections (one quadrant) were measured using Ni-filtered Cu K_α radiation up to theta-71° on a CAD-4 diffractometer. Intensities were corrected for Lorentz and polarization factors yielding 1772 reflections with $F_o > 3\sigma F_o$. The structure was solved using direct methods and refined to R = 0.067. All hydrogen atoms were found on a difference Fourier map and refined with overall temperature factor. A final difference Fourier map possessed no special features.

ACKNOWLEDGEMENT

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