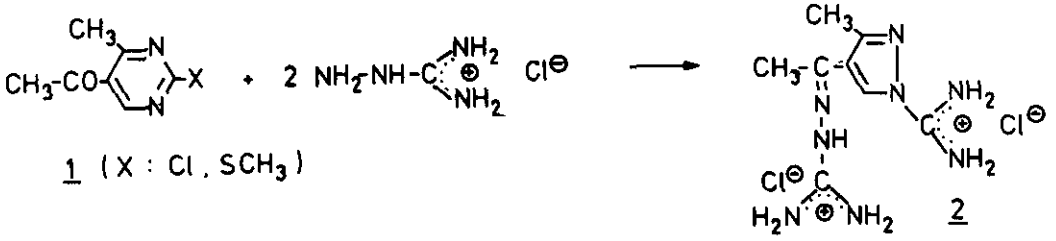
CONVERSION OF PYRIMIDINES INTO AMIDINOPYRAZOLE BY ACTION OF AMINOGUANIDINE HYDROCHLORIDE

Gabriel Menichi, Jaouad Naciri, Bruno Kokel and Michel Hubert-Habart

Institut Curie, 11, rue Pierre et Marie Curie, 75231 Paris Cédex 05, FRANCE

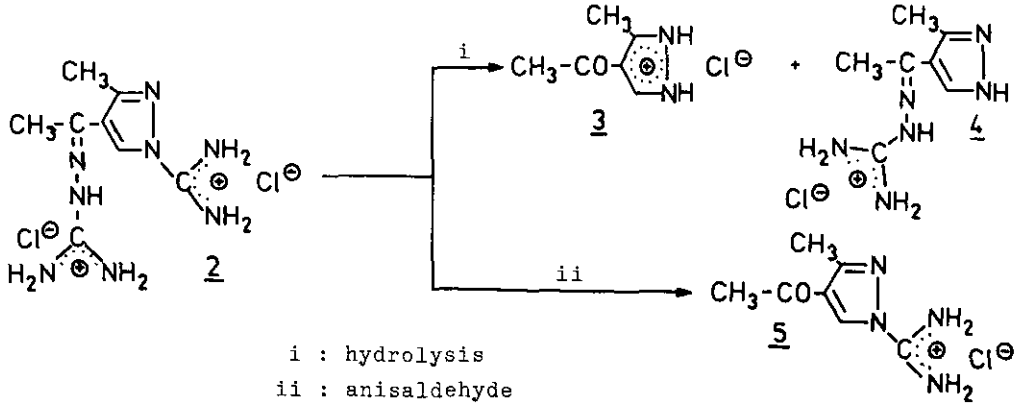
Abstract - Aminoguanidine hydrochloride reacts with pyrimidines of type 1 giving the unexpected 1-amidino-3-methyl-4-pyrazolyl methyl ketone amidinohydrazone dihydrochloride 2.

Some aminoguanidine derivatives exhibit good antitumor activities.[1] In an attempt to prepare new amidinohydrazones of 5-acetylpyrimidines,[2] we found an unexpected ring contraction of the pyrimidine into the pyrazole. Thus, we wish to report that aminoguanidine hydrochloride reacts with pyrimidines 1 in acidic methanolic solution (pH < 1), leading to the substituted pyrazole 2 with a very good yield.



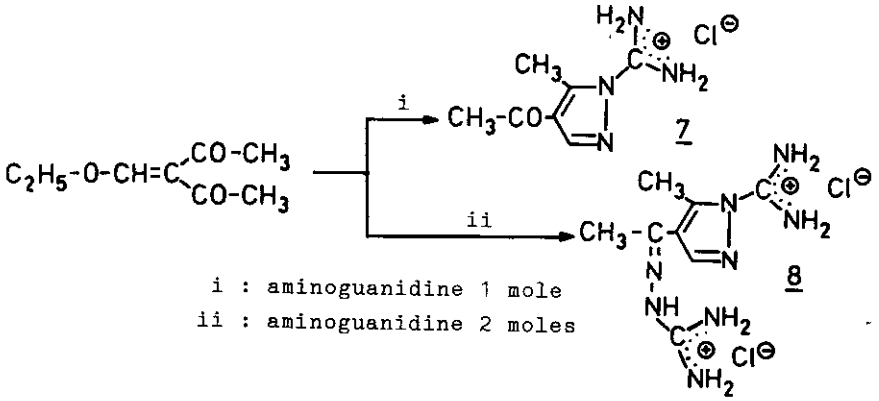
1 (X : Cl, SCH_3)

The pyrazolic structure of 2 was established on the basis of its elemental analysis, mass and nmr spectra, and chemical behavior. So while hydrolysis of 2 leads to a mixture of the known 4-acetyl-3-methylpyrazole 3,[3] and its amidinohydrazone 4, action of anisaldehyde in acidic methanolic solution allows formation of 4-acetyl-1-amidino-3-methylpyrazole hydrochloride 5.



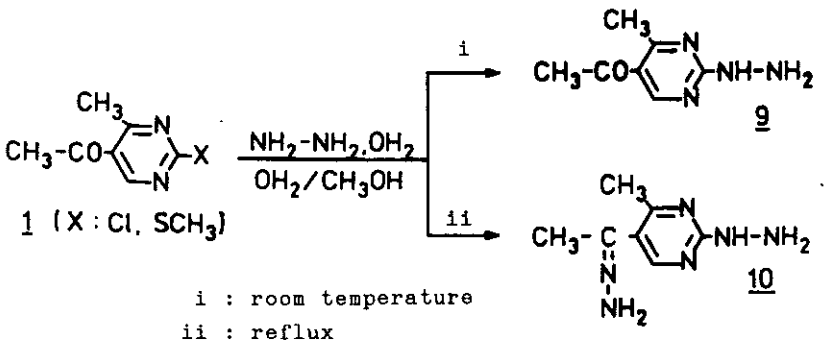
i : hydrolysis
ii : anisaldehyde

Pyrazoles 2 and 5 were shown to be isomers of pyrazoles 7 and 8 respectively, which were prepared from ethoxymethyleneacetylacetone 6 and aminoguanidine hydrochloride :



The amidino group position on the pyrazole ring of 7 and 8 rests on the fact that phenylhydrazine in a similar way reacts with 6 to form exclusively, 4-acetyl-5-methyl-1-phenylpyrazole.[4] As expected hydrolysis of 8 leads also to the mixture of 3 and 4. The latter is easily obtained by condensing one molecule of aminoguanidine hydrochloride on pyrazole 3.

Ring contraction of pyrimidines into pyrazoles caused by the action of hydrazine on pyrimidine is a well documented reaction.[5] However, (1) to our knowledge such a transformation in acidic medium and in particular by means of aminoguanidine hydrochloride, has so far never been reported, and (2) in contrast we found that pyrimidines 1 react with hydrazine hydrate itself without transformation of the pyrimidine ring, leading exclusively to the hydrazine 9 and hydrazino-hydrazone 10.



We believe then, according to these facts, that the above preparation of pyrazole 2, should not be considered as a mere extension of the classical transformation of pyrimidines into pyrazoles by means of substituted hydrazines.

EXPERIMENTAL

Spectral data are shown as follows : ^{1}H-nmr (δ, DMSO-d_6). s = singlet, br = broad, ex = exchangeable by D_2O. ms (electron impact), m/e (relative intensity).

Isomers 2 and 8 :

2 : 1-amidino-3-methyl-4-pyrazolyl methylketone amidinohydrazone dihydrochloride ($C_8H_{14}N_8$, 2HCl)
A methanolic solution of 0.9 g (0.005 M) of pyrimidine 1 (X = S-CH_3) is added to a cold solution of aminoguanidine hydrochloride prepared from 3.26 g (0.024 M) aminoguanidine hydrogencarbonate, 4.14 ml (0.05 M) of concentrated hydrochloric acid and 6ml of water. The mixture is kept under reflux for 4 hours then concentrated under vacuum. The white precipitate is collected and crystallized from methanol yielding in the first crop 0.75 g (52 %) of product 2 . mp > 270°C, nmr : 10.5 (br, 4, ex), 9.6 (s, 1, 5-CH), 7.87 (br, 3, ex), 3.45 (br, 2, ex), 2.55 and 2.40 (2s, 3 each, CH_3) ; ms : 222(27), 207(4), 180(100), 165(90).

Analysis of 2 for $C_8H_{14}N_8$, 2HCl = 295.17

Calc. :	C 32.55	H 5.46	N 37.96	Cl 24.02
Found :	32.33	5.55	38.06	24.09

Additional 30% of the pure pyrazole 2 is isolated by concentration and cooling of the residual methanolic solution.

8 : 1-amino-5-methyl-4-pyrazolyl methylketone amidinohydrazone dihydrochloride ($C_8H_{14}N_8$, 2HCl).
To a methanolic solution of 1.56 g (0.01 M) of ethoxymethyleneacetylacetone 6 stirred at - 15°C, a cooled solution of 3.3 g (0.024 M) of aminoguanidine hydrogencarbonate and 4.1 ml (0.05 M) of concentrated hydrochloric acid in 6 ml of water is added dropwise. Then the mixture is stirred at room temperature for 24 hours. A white precipitate separates slowly. This is collected and washed with a few milliliters of methanol and dried under vacuum. Yield : 1.1 g (35 %). By further concentration of the mother liquor one can collect additional crops of the pure product 8 ; nmr : 10.4 (br, 4, ex), 8.4 (s, 1, 3-CH), 7.85 (br, 3, ex), 3.5 (br, 2, ex), 2.7 and 2.4 (2s, 3 each, CH_3) ; ms : 222 (2.3), 207 (0.4), 180 (90), 165 (100).

Analysis of 8 for $C_8H_{14}N_8$, 2HCl, 0.88 H_2O = 311.02

Calc. :	C 30.89	H 5.75	O 4.52	N 36.02	Cl 22.79
Found :	31.03	5.84		35.92	22.58

Isomers 5 and 7 :

5 : 4-acetyl-1-amidino-3-methylpyrazole hydrochloride ($C_7H_{10}N_4O$, HCl)

A solution of 2g (0.0068 M) of compound 2, 1.45 ml (0.012 M) of paraanisaldehyde, 2 ml (0.024 M), of concentrated hydrochloric acid in 30 ml of water and 100 ml of ethanol is refluxed for 14 hours then evaporated to dryness. After dissolution of the residue in methanol, cooling and addition of ether one can collect a dense precipitate of recovered starting material 2 and 0.24 g of compound 3. Further addition of ether in the filtrate and cooling at - 15°C during 14 hours gives 0.34 g (25 %) of microcrystals of compound 5, mp > 260 ; nmr : 9.9 (s, 1, 5-CH), 9.75 (br, 3, ex), 3.5 (br, 1, ex), 2.45 (s, 6, 2 CH_3) ; ms : 166 (1.5), 124 (100), 109 (100).

Analysis of 5 for $C_7H_{10}N_4O$, HCl = 202.64

Calc. :	C 41.48	H 5.47	N 27.64	O 7.89	Cl 17.49
Found :	41.13	5.60	27.36	8.04	17.79.

7 : 4-acetyl-1-amidino-5-methylpyrazole hydrochloride ($C_7H_{10}N_4O$, HCl)

A solution of 1.36 g (0.01 M) of aminoguanidine hydrogencarbonate, in 2.4 ml of water and 1.7 ml (0.02 M) of concentrated hydrochloric acid is added dropwise to a cooled (- 15°C) methanolic solution of 1.56 g (0.01 M) of ethoxymethyleneacetylacetone 6, then the mixture is stirred 3 hours at room temperature. The solvent is evaporated at low temperature and the residue is neutralized by HCO_3Na, then extracted with ethylacetate. The evaporation of the organic layer followed by acidification with hydrochloric acid in ethanol of the solid, subsequent precipitation with ether and trituration with boiling methanol gives 0.470 g (23 %) of product 7 ; nmr : 10.1 (br, 3, ex), 8.5 (s, 1, 3-CH), 3.6 (br, 1, ex), 2.8 and 2.55 (2s, 3 each, CH_3) ; ms : 166 (7.5), 124 (50), 109 (100).

Analysis of 7 for $C_7H_{10}N_4O$, HCl, 1/4 H_2O = 207.14

Calc. :	C 40.59	H 5.60	N 27.05	O 9.65	Cl 17.11
Found :	40.90	5.42	26.71	9.75	17.19

Compound 3 : 4-acetyl-3-methyl pyrazole hydrochloride ($C_6H_8ON_2$, HCl)

This compound is obtained as a by-product during the preparation of 5 and is separated from the recovered starting material 2 by sublimation. Yield : 0.24 g (12 %) ; nmr : 11.6 (br, 2, ex), 8.25 (s, 1, 5-CH), 2.45 and 2.35 (2s, 3 each, CH_3) ; ms : 124 (33), 109 (100).

Analysis of 3 for $C_6H_8N_2O$, HCl = 160.60

Calc. :	C 44.87	H 5.64	O 9.96	N 17.44	Cl 22.07
Found :	45.14	5.58	9.54	17.55	22.19

Compound 3 may also be found with a very low yield during the alkaline (by sodium hydroxide) or

the acidic (by hydrochloric acid) hydrolysis of compound 2 (see below).

Compound 4 : 3-methyl-4-pyrazolyl methylketone amidinohydrazone dihydrochloride ($C_7H_{12}N_6$, HCl). Refluxing during 16 hours of an aqueous solution of 2g (0.0068 M) of compound 2 in 30 ml (0.36 M) of hydrochloric acid and extraction with ethylacetate and ether gives two layers. The aqueous one yields, after evaporation and crystallization, 1 g (68 %) of compound 4 ; F > 260°C ; nmr : 11.35 (s, 1, ex), 8.3 (s, 1, 5-CH), 7.7 and 6.72 (2br, 5, ex), 2.50 and 2.35 (2s, 3 each, CH_3); ms : 180 (67), 165 (100).

Analysis of 4 for $C_7H_{12}N_6$, HCl = 216.67

Calc. :	C 38.80	H 6.05	N 38.79	Cl 16.36
Found :	38.67	6.06	38.80	16.40

The organic layer gives a very small amount of compound 3.

By refluxing of 2 g of compound 2 in an ethanolic solution of 2 g of sodium hydroxide during 24 hours, then acidification with hydrochloric acid and work up as in the case previously described, one collects a very small quantity of 3 and 70 % of compound 4.

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