CYCLIZATION OF DINITRILES BY HYDROGEN HALIDES. 1. HYDROGEN BROMIDE.
THE TEMPERATURE AS A NOVEL DETERMINING FACTOR OF THE DIRECTION
OF CYCLIZATION

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Abstract —   A selective synthesis of the 2-amino-4-bromo- and
4-amino-2-bromo-5,6-dihydro-5-methylpyrido[2,3-d]pyrimidin-7(8H)-
ones (2 and 3) by temperature control in the cyclization reaction
of the 6-cyanamino-5-cyano-3,4-dihydro-4-methyl-2-pyridone (1)
with hydrogen bromide is described. The structure of the isomer
obtained in each case is assigned unequivocally.

The cyclization reactions of α,ω-dinitriles under the influence of anhydrous hydro-
gen halides have received a considerable amount of attention because of their wide
applications in the synthesis of heterocycles[1]. The nature of the internitrile chain
determines the direction of cyclization. So, it is known that a nitrile carbon atom
bonded to sulfur, nitrogen or unsaturated carbon will always bear the halogen atom in
the cyclized product[2] (Scheme 1).
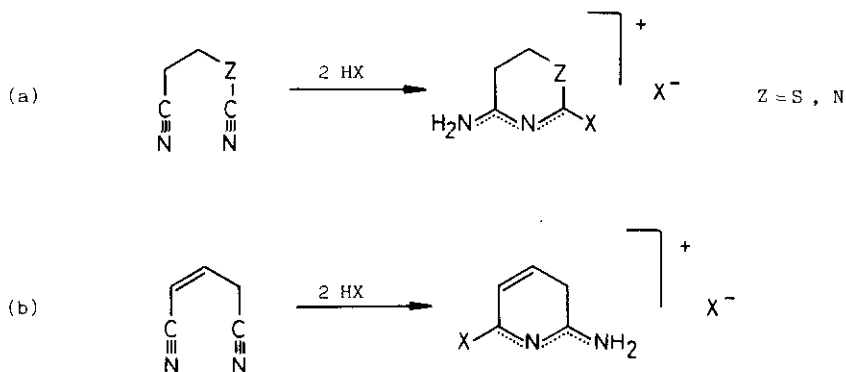
Scheme 1

We have recently reported[3] the synthesis of 6-cyanamino-5-cyano-3,4-dihydro-2-pyridones (1), and their tautomeric equilibrium with the cyanimino form (I ⇌ II), as the first step of a new synthesis of pyrido[2,3-d]pyrimidines that our group has been developing since the last years. The most interesting step of this synthesis is the cyclization of 1 by addition of hydrogen halides to one of the cyano groups. It is worth pointing out that 1 presents a cyano group bonded to nitrogen, the other one being α,β -unsaturated, and this kind of internitrile chain is still almost unknown in the literature[4]. Thus, the direction of this cyclization has not been predictable and it is the subject of our study.

We report here the results obtained in the cyclization of 1 with hydrogen bromide. The reaction is carried out by bubbling a stream of dry hydrogen bromide into a dry dioxane solution of 1 (0.03 mol in 250 ml). The cyclization product precipitates as the hydrobromide which is filtered, washed with dioxane, suspended in methanol and treated with ammonia to give the free base in almost quantitative yield.

Scheme 2
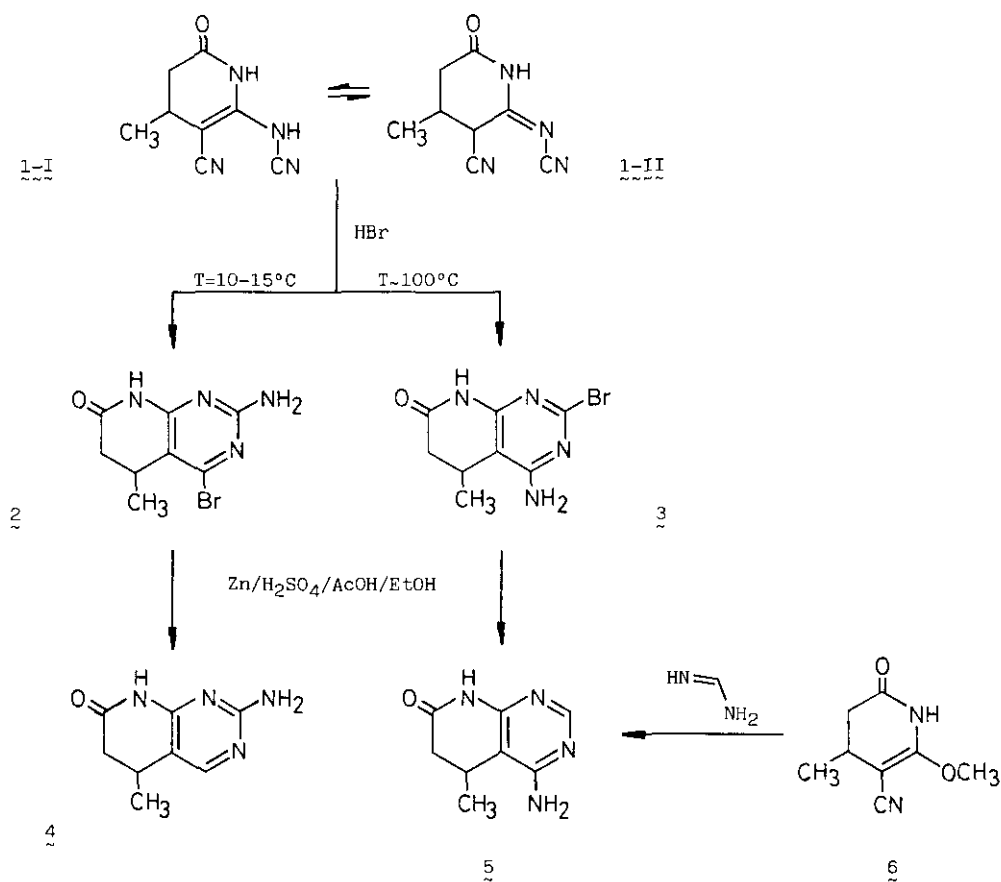
Both of the isomers are obtained as was to be expected from 1-I, whose structure is a mixture of those of (a) and (b), but the really surprising result is the fact that the product obtained depends on the thermic level. So, when the reaction is carried out at 10-15°C, the 2-amino-4-bromo-5,6-dihydro-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one[5] (2) is obtained selectively[6], whereas temperatures of about 100°C afford selectively the 4-amino-2-bromo-substituted isomer (3). Intermediate temperatures lead to mixtures of both isomers which have been analyzed by HPLC[7], showing a direct relationship between the temperature and the composition of the mixture.

In order to determine unequivocally the structure of the isomer obtained in each case, the reaction of 6[8], antecedent of 1, with formamidine acetate was carried out. The ring closure after the nucleophilic substitution of the methoxyl group led to 5, in which the chemical shift of the pyrimidinic proton is 8.62 ppm[9]. This same compound 5 was the one obtained by debromination[10] of the isomer prepared at high temperature whereas the debromination of the other isomer, obtained at low temperature, led to 4, whose pyrimidinic proton appears at 8.06 ppm.

The fact that the temperature decides upon the direction of the cyclization should not be understood as the result of a tautomeric equilibrium shift, assuming a fast enough interconversion rate between the two tautomers (I and II). It would rather seem that the rise in temperature allows to surpass an energy barrier generating a change on the mechanism, either in the sense of which one of the cyano groups undergoes the attack or in which way the initially attacked cyano group evolves[11].

The behaviour of 1 with hydrogen chloride and hydrogen iodide in a wide range of thermic levels must be studied before undertaking any further explanation, and will be reported shortly.

ACKNOWLEDGEMENTS

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2. H. Böhme and H. G. Viehe, 'Adv. Org. Chem.', Vol. 9, part 2, John Wiley & Sons, New York, 1979, p. 552.

3. P. Victory, R. Nomen, O. Colomina, M. Garriga, and A. Crespo, Heterocycles, in press.

4. There are only a few examples of this type of substructure. They are mostly the 1-cyanamino-2,2-dicyanoethylenes with different substituents in the position 1, and their corresponding salts:

a) E. Allenstein and R. Fuchs, <u>Chem. Ber.</u>, <u>101</u>, 1232 (1968).

b) E. Allenstein and R. Fuchs, <u>Chem. Ber.</u>, <u>101</u>, 1244 (1968).

c) H. Kristinsson, <u>J. Chem. Soc. Chem. Commun.</u>, 1974, 350.

d) M. A. Pérez and J. L. Soto, <u>Synthesis</u>, 1981, 955.

Recently has been reported the synthesis of some 3-cyanamino-2-phenylsulphonylprope-nenitriles by M. A. Pérez, J. L. Soto, F. Guzmán, and H. Alcalá, <u>J. Chem. Soc. Perkin Trans. 1</u>, 1985, 87.

There is also a special case with an alkyl substituted cyanamide, by T. Itaya and T. Harada, <u>Tetrahedron Lett.</u>, <u>23</u>, 2203 (1982).

5. All of the products gave satisfactory elemental and spectral analyses. Selected data: 2 : mp 300°C, ir (KBr), 3320, 3185, 3110, 1690, 1655 cm^{-1} ; ^{1}H-nmr (DMSO-d$_6$), δ 10.64 (br s, 1H, NHCO), 6.80 (br s, 2H, NH$_2$), 3.08 (dxq, J_{cb}=6.7 Hz, J_{cd}=6.8 Hz, J_{ca}<1 Hz, 1H, C$_5$-H$_c$), 2.81 (dxd, J_{ba}=15.3 Hz, J_{bc}=6.7 Hz, 1H, C$_6$-H$_b$), 2.31 (d, J_{ab} = 15.3 Hz, J_{ac}<1 Hz, 1H, C$_6$-H$_a$), 1.04 ppm (d, J_{dc}=6.8 Hz, 3H, CH$_3$).

3 : mp 273-275°C, ir (KBr), 3400, 3310, 3180, 3120, 1695, 1640 cm^{-1} ; ^{1}H-nmr (DMSO-d$_6$), δ 10.57 (br s, 1H, NHCO), 7.18 (br s, 2H, NH$_2$), 3.07 (dxq, J_{cb}=6.6 Hz, J_{cd}=6.5 Hz, J_{ca}<1 Hz, 1H, C$_5$-H$_c$), 2.75 (dxd, J_{ba}=16.0 Hz, J_{bc}=6.6 Hz, 1H, C$_6$-H$_b$), 2.28 (d, J_{ab}=16.0 Hz, J_{ac}<1 Hz, 1H, C$_6$-H$_a$), 0.98 ppm (d, J_{dc}=6.5 Hz, 3H, CH$_3$).

6. The mixture has, at least, 90% of that isomer.

7. Chromatographic conditions: Column RP18, 5μ (Resolve Waters); Eluent 0.17 ml/min of CH$_3$CN/H$_2$O (3:7); Temperature, 30°C; Volum injected, 10 μl; UV-Detector at 230 nm; Retention time: 3.44 min (3), 4.87 min (2).

8. P. Victory and J. Diago, <u>Afinidad</u>, <u>35</u>, 161 (1978); <u>Chem. Abstr.</u>, <u>89</u>, 179515j (1978); P. Victory, J. M. Jover, and J. Sempere, <u>Afinidad</u>, <u>38</u>, 491 (1981); <u>Chem. Abstr.</u>, <u>97</u>, 72220x (1982).

9. Recorded in a 90 MHz Brucker HX-90-E apparatus using TFA as the solvent and TMS as internal standard.

10. B. Back, <u>J. Org. Chem.</u>, <u>21</u>, 797 (1956).

11. For information of possible mechanisms see S. Yanagida, M. Okahara, and S. Komori, 'Adv. Org. Chem.', Vol. 9, part 2, John Wiley & Sons, New York, 1979, p. 562.

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