CYCLIZATION OF DINITRILES BY HYDROGEN HALIDES. 2.[1] HYDROGEN CHLORIDE AND HYDROGEN IODIDE

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Abstract - The cyclization reaction of the 6-cyanamino-5-cyano-3,4-dihydro-4-methyl-2-pyridone (1) with hydrogen chloride and hydrogen iodide is described. While the reaction with hydrogen chloride is regiospecific leading to the 4-amino-2-chloro-5,6-dihydro-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one (4), hydrogen iodide affords two possible isomers. The 2-amino-4-iodo substituted one (5) is prepared selectively at low temperature whereas higher temperatures lead to the 4-amino-2-iodo substituted compound (6). Reductive deiodination takes place with excess of hydrogen iodide at high temperature but only in position 2.

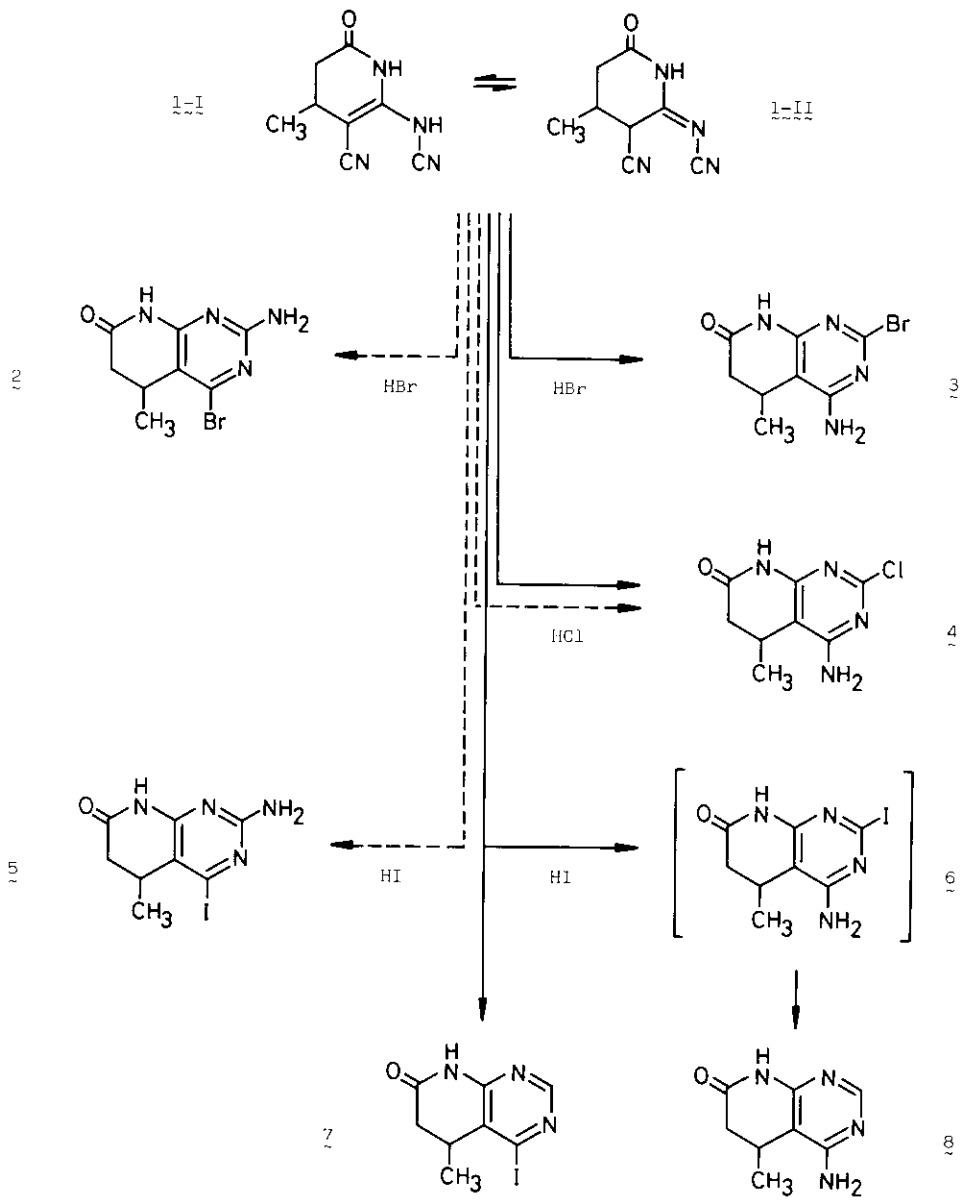
The cyclization reaction of α,ω-dinitriles by addition of hydrogen halides is a useful method for the synthesis of heterocycles,[2] and is known to be regiospecific when one of the cyano groups is bonded to a heteroatom or conjugated with a double bond or an aromatic ring, while the other one is attached to a saturated carbon. In these cases the former will always bear the halogen atom in the cyclized product.[3]

The direction of cyclization of α,ω-dinitriles other than those in the above category has not been predictable. Nevertheless, some interesting works have contributed new information about the influence of the substitution[4,5] or the steric hindrance[6] in the direction of cyclization of some 1-cyanamino-2,2-dicyanoethylenes and 3-cyanamino-2-phenylsulphonylpropenenitriles, but, unfortunately, all the quoted examples have been confined to the use of hydrogen chloride.

Recently, we have reported[1] the selective synthesis of either possible isomers in the cyclization reaction of the 1,3-dinitrile 1[7] by addition of hydrogen bromide. We found that the temperature is, in this case, the determining factor of the direction of cyclization. So, the 2-amino-4-bromo substituted isomer 2 is obtained selectively at low temperature[8], whereas high temperatures afford, also selectively, the 4-amino-2-bromo substituted one 3.

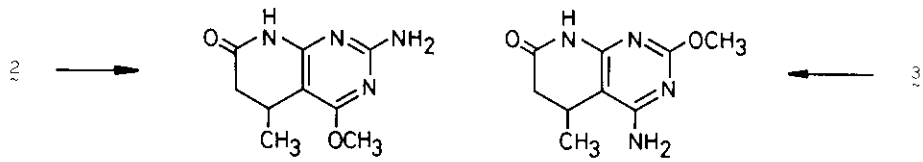
We report here the results obtained in the cyclization reaction of 1 with hydrogen chloride and hydrogen iodide, which have shown a significantly different behaviour in comparison with that with hydrogen bromide (Scheme 1).

Scheme 1


1-I
1-II
HBr
HBr
HCl
HI
HI
2
3
4
5
6
7
8
Low temperature (10-15°C)
High temperature (95-100°C)

When the dicarbonitrile 1 is treated with dry hydrogen chloride using dioxane as the solvent, the 4-amino-2-chloro-5,6-dihydro-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one (4)[9] is always obtained whatever the temperature may be. On changing the solvent to diethyl ether and carrying out the reaction at temperatures below 0°C the same result was obtained even at -40°C. So then, in contrast to hydrogen bromide, the reaction with hydrogen chloride is regiospecific in the range explored (-40 to 100°C), and leads to the 4-amino-2-chloro substituted compound 4, whose structure has been established unequivocally by nucleophilic substitution of the halogen atom by sodium methoxide in refluxing methanol. Physical and spectral data of the product obtained were identical to those of 10, prepared by the same procedure from 3 (Scheme 2).

Scheme 2

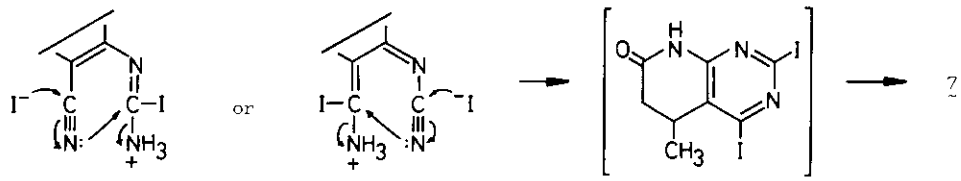


9 10

When the cyclization reaction is carried out using dry hydrogen iodide,[10] the behaviour of 1 recalls that with hydrogen bromide. Thus, the 2-amino-4-iodo substituted isomer 5 is obtained as the main product at low temperature in 88% yield. Its structure has been unequivocally confirmed since the same derivative 9 is available by nucleophilic substitution of the iodine of 5 as well as by substitution of the bromine of 2[1] (Scheme 2). On the contrary, when the reaction is carried out at reflux of dioxane the main products are 8, which has been identified by comparison with an independent sample,[1] and 7 whose formation and structure determination will be discussed later, but no traces of 5 have been detected. 8 seems to proceed through the 4-amino-2-iodo substituted compound 6, which undergoes reductive deiodination by the excess of hydrogen iodide present in the mixture.[11] Fortunately, we were able to isolate 6 in 48% yield from a reaction mixture prepared due to lack of hydrogen iodide at a temperature of 30-35°C.

The treatment of 6 with excess of hydrogen iodide in refluxing dioxane affords the expected deiodinated product 8 in 40% yield. However, all the attempts of reductive deiodination of 5 by the same procedure were unsuccessful, in agreement with the fact that no traces of the 4-deiodinated product, isomer of 8, were found in the cyclization reactions. The different reactivity of iodine in position 2 and 4 can explain the formation of 7 as occurring through the regiospecific deiodination of the 2,4-diiodo substituted compound 11, which may be formed by nucleophilic attack of the nitrile group with loss of ammonia as shown in scheme 3. A very similar cyclization pathway has been reported for the direct formation of condensed 4-chloropyrimidines.[12]

Scheme 3



11

Ultimate confirmation of the structure of 7 was achieved by ^{13}C-nmr. Spectral data of the whole family[13] is presented in table 1.

Table 1. ^{13}C-nmr spectral data.

	C-2	C-4	C-4a	C-5	C-6	C-7	C-8a	CH_3
4 (2-Cl)	156.8	161.9	97.2	23.1	37.4	170.3	156.3	17.7
3 (2-Br)	148.6	161.5	97.6	23.2	37.4	170.3	155.9	17.6
6 (2-I)	126.0	160.5	98.1	23.1	37.4	170.0	154.8	17.5
2 (4-Br)	161.2	150.9	107.7	28.3	37.7	170.8	157.6	18.9
5 (4-I)	160.9	112.2	133.5	32.0	37.7	171.0	155.3	19.0
7 (4-I)	156.4	125.2	132.8	32.8	36.7	170.6	155.0	17.8

This characteristic behaviour of the three hydrogen halides was to be expected due to the noteworthy differences in acidity and polarizability of the acids as well as those in the nucleophilicity of their bases.

Since hydrogen chloride does not effect any cyclization of α,ω-dinitriles with no heteroatom in the internitrile chain,[2] the regiospecific cyclization of 1, together with the reported results on 1-cyanamino-2,2-dicyanoethylenes,[4,5] seems to prove that only cyano groups bonded to heteroatoms (nitrogen or sulfur) are able to polarize the chlorine atom (in HCl) or chloride ion sufficiently to achieve the imidoyl chloride. The reaction proceeds, furthermore, in one specific direction, the halogen atom staying bonded to the carbon between the heteroatoms in the cyclized product.[14]

So, while hydrogen chloride is very sensitive to structural features and it reacts only with one of the cyano groups, hydrogen bromide and hydrogen iodide are so effective that both cyano groups can be attacked. Furthermore, the initially attacked cyano group can evolve in different ways[15] and, therefore, the nature of the cyclization process depends on the experimental conditions.

In addition to the preceding discussion we could not rule out the possibility of any influence of the tautomerism in the cyclization direction. So, in order to refine our approach, we are now preparing compounds like 1-I with N-alkyl substituted cyanamino groups, in which the highly basic N-bonded cyano group of 1-II is not present.

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8. Low temperature and high temperature refers to the ranges 10-15°C and 95-100°C due to the use of dioxane as the solvent.
9. All of the products gave satisfactory elemental and spectral analysis. Selected data:
4 : mp 293-294°C; ir (KBr), 3375, 3310, 3170, 3120, 1690, 1645 cm^{-1}; ^1H-nmr (DMSO-d_6), δ 10.55 (br s, 1H, NHCO), 7.17 (br s, 2H, NH_2), 3.08 (dxq, J_{cb}=6.7 Hz, J_{cd}=6.7 Hz, J_{ca}<1 Hz, 1H, C_5-H_c), 2.75 (dxd, J_{ba}=15.5 Hz, J_{bc}=6.7 Hz, 1H, C_6-H_b), 2.28 (d, J_{ab} = =15.5 Hz, J_{ac}<1 Hz, 1H, C_6-H_a), 0.98 ppm (d, J_{dc}=6.7 Hz, 3H, CH_3); ms, 212 (M^+, 36), 214 (M^++2, 11), 197 (100), 199 (33).
5 : mp 293-294°C; ir (KBr), 3320, 3185, 3105, 1690, 1650 cm^{-1}; ^1H-nmr (DMSO-d_6), δ 10.50 (br s, 1H, NHCO), 6.70 (br s, 2H, NH_2), 2.95 (dxq, J_{cb}=5.4 Hz, J_{cd}=6.8 Hz, J_{ca}<1 Hz, 1H, C_5-H_c), 2.82 (dxd, J_{ba}=13.4 Hz, J_{bc}=5.4 Hz, 1H, C_6-H_b), 2.30 (d, J_{ab} =13.4 Hz, J_{ac}<1 Hz, 1H, C_6-H_a), 1.02 ppm (d, J_{dc}=6.8 Hz, 3H, CH_3); ms, 304 (M^+, 58), 289 (100).
6 : mp 247-248°C; ir (KBr), 3460, 3310, 3200, 3115, 1680, 1625 cm^{-1}; ^1H-nmr (DMSO-d_6), δ 9.87 (br s, 1H, NHCO), 7.03 (br s, 2H, NH_2), 3.07 (dxq, J_{cb}=6.7 Hz, J_{cd}=6.7 Hz, J_{ca}<1 Hz, 1H, C_5-H_c), 2.73 (dxd, J_{ba}=17.3 Hz, J_{bc}=6.7 Hz, 1H, C_6-H_b), 2.23 (d, J_{ab} = =17.3 Hz, J_{ac}<1 Hz, 1H, C_6-H_a), 0.97 ppm (d, J_{dc}=6.7 Hz, 3H, CH_3); ms, 304 (M^+,100).
7 : mp 177-178°C; ir (KBr), 3170, 3110, 1710, 1550, 1545 cm^{-1}; ^1H-nmr (DMSO-d_6), δ 11.08 (br s, 1H, NHCO), 8.33 (s, 1H, C_2-H), 3.13 (dxq, J_{cd}=7.3 Hz, J_{cb}=6.5 Hz, J_{ca}<1 Hz, 1H, C_5-H_c), 2.95 (dxd, J_{ba}=14.7 Hz, J_{bc}=6.5 Hz, 1H, C_6-H_b), 2.41 (d, J_{ab} =14.7 Hz, J_{ac}<1 Hz, 1H, C_6-H_a), 1.08 ppm (d, J_{dc}=7.3 Hz, 3H, CH_3); ms, 289 (M^+, 100).

10. C. J. Hoffmann, Inorg. Synth., 7, 180 (1963).
11. This type of reaction has been observed by others: a) F. Johnson and W. A. Nasutavicus, J. Org. Chem., 28, 1877 (1963); b) D. W. Kaiser, U. S. Patent 2,630,433 (1953); c) C. Broche, J. Prakt. Chem. (2), 50, 97 (1894).
12. C. J. Shishoo, M. B. Devani, V. S. Bhadti, S. Ananthan, and G. V. Ullas, Tetrahedron Lett., 24, 4611 (1983).
13. Recorded in a Varian XL-300 BB apparatus using DMSO-d_6 as the solvent.
14. Unless the other cyano group was strongly activated by donor groups through the double bond.[4]
15. The attack to a cyano group can lead to a nitrilium ion or an imidoyl halide, and then the final cyclized product could be the result of either a nucleophilic attack by the imidoyl halide to the other cyano group, in the first case, or the nucleophilic attack by the free cyano group onto the nitrilium ion or more likely the imonium salt, in the second case. For more information see reference 3, p. 562.

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