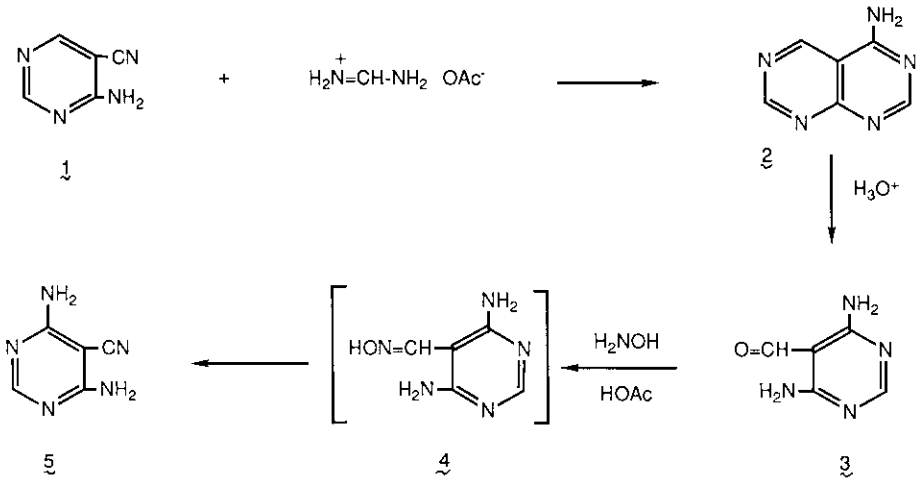
A NOVEL "RING-SWITCHING" AMINATION: CONVERSION OF 4-AMINO-5-CYANOPYRIMIDINE TO 4,6-DIAMINO-5-CYANOPYRIMIDINE

Edward C. Taylor*, Wendell A. Ehrhart, Clive O.S. Tomlin, and Jang B. Rampal
Department of Chemistry, Princeton University, Princeton, New Jersey 08544, U.S.A.

Abstract - 4-Amino-5-cyanopyrimidine is "aminated" to 4,6-diamino-5-cyanopyrimidine by a ring-switching process involving ring closure with formamidine acetate to 4-aminopyrimido(4,5-d)pyrimidine, acidic hydrolysis to 4,6-diaminopyrimidine-5-carboxaldehyde, conversion of the latter to its oxime and dehydration.

Acid-catalyzed addition of water (covalent hydration) across the 3,4-imine bond in certain 4-unsubstituted pyrimidines and in a variety of 4-unsubstituted condensed pyrimidines (pteridines, quinazolines, pyrimido(4,5-d)pyrimidines) is a well-established phenomenon[1]. Acid-catalyzed hydration has been shown to be the first step in the cleavage of the 4-unsubstituted pyrimidine ring in these latter systems to give o-aminoaldehydes[2,3]. We describe in this brief note a novel synthetic exploitation of this ring cleavage reaction by means of which 4-amino-5-cyanopyrimidine (1) is converted into 4,6-diamino-5-cyanopyrimidine (5). This unusual transformation, which involves what appears to be the introduction of an amino group at the 6-position of the substrate is accomplished by the sequence of reactions outlined in the Scheme. Reaction of 1 with formamidine acetate gives 4-aminopyrimido(4,5-d)pyrimidine (2)[4], which gives 4,6-diaminopyrimidine-5-carboxaldehyde (3) upon acidic cleavage of the 4-unsubstituted pyrimidine ring. The aldehyde 3 is then converted directly to 4,6-diamino-5-cyanopyrimidine (5) by reaction with hydroxylamine hydrochloride in acetic acid containing anhydrous sodium acetate. The o-aminonitrile functionality initially present in 1 has formed the pyrimidine ring of the product, while the original pyrimidine ring has become the o-aminonitrile functionality in the product 5. By means of this "ring-switching" reaction, 4-amino-5-cyanopyrimidine should be readily converted into a series of 2-substituted 4,6-diamino-5-cyanopyrimidines with apparent introduction of both the 6-amino group and the 2-substituent into the precursor 1[5].



Scheme

EXPERIMENTAL

4,6-Diaminopyrimidine-5-carboxaldehyde (3): A mixture of 0.50 g of 4-aminopyrimido(4,5-d)-pyrimidine (prepared from 4-amino-5-cyanopyrimidine by reaction with formamidine acetate as previously described[4]) and 15 ml of 0.5 N HCl was heated under reflux for 2 h. The resulting clear solution was cooled and basified by the addition of solid NaOH. The precipitate which separated was collected by filtration, washed with water and dried to give 0.33 g (72%) of 3 as a white microcrystalline powder, mp 253°C (dec.); ir (KBr) 3400, 3340, 3160, 1665, 1630 cm^{-1}; ^1H nmr (DMSO-d_6) δ 7.79 (br s, 4 H), 7.95 (s, 1 H), 10.15 (s, 1 H). Anal. Calcd for $C_5H_6N_4O$: C, 43.46; H, 4.39; N, 40.56. Found: C, 43.72; H, 4.60; N, 40.52.

4,6-Diaminopyrimidine-5-carboxaldehyde Oxime (4): A mixture of 0.20 g (1.45 mmol) of 4,6-diamino-pyrimidine-5-carboxaldehyde, 0.14 g (1.50 mmol) of hydroxylamine hydrochloride, 0.11 g (1.35 mmol) of sodium acetate and 9 ml of water was heated under reflux for 1 h. The resulting suspension was cooled to r.t., filtered and the collected solid washed well with water followed by ethanol. Crystallization from ethanol gave 0.15 g (69%) of 4, mp 283°C (dec.); ir (KBr) 3430, 3380, 3210, 1632 cm^{-1}; ^1H nmr (DMSO-d_6) δ 6.98 (br s, 4 H), 7.83 (s, 1 H), 8.52 (s, 1 H), 10.94 (s, 1 H). Anal. Calcd for $C_5H_7N_5O$: C, 39.20; H, 4.62; N, 45.73. Found: C, 39.02; H, 4.55; N, 45.47.

4,6-Diamino-5-cyanopyrimidine (5): Method A. A mixture of 0.072 g of 4,6-diaminopyrimidine-5-carboxaldehyde oxime (4) and 5 ml of acetic anhydride was heated under reflux for 14 h, and then cooled and evaporated under reduced pressure. Recrystallization of the residual solid from water gave 0.05 g (88%) of 5 as a colorless solid, mp 345°C (dec.); ir (KBr) 3440, 3400, 3340, 3160, 2210, 1665 cm^{-1}; ^1H nmr (DMSO-d_6) δ 7.15 (br s, 4 H), 7.95 (s, 1 H); uv λ_{max}^{EtOH} nm (log e)

226 (4.60), 276 (3.62).

Method B. A mixture of 0.50 g (3.3 mmol) of 4,6-diaminopyrimidine-5-carboxaldehyde, 0.31 g (4.5 mmol) of hydroxylamine hydrochloride and 0.43 g (5.2 mmol) of anhydrous sodium acetate in 25 ml of glacial acetic acid was heated under reflux overnight and filtered hot. The filtrate was cooled and the colorless needles which separated were collected by filtration and recrystallized from water to give 0.16 g (63%) of 5, identical in every respect with the material prepared by Method A. Anal. Calcd for $C_5H_5N_5$: C, 44.43; H, 3.74; N, 51.83. Found: C, 44.46; H, 3.78; N, 51.90.

REFERENCES AND NOTES

1. See A. Albert, Adv. Heterocycl. Chem., 1976, 20, 117, for a review of covalent hydration.
2. T.J. Delia, J. Org. Chem., 1984, 49, 2065.
3. G. Evens and P. Caluwe, J. Org. Chem., 1975, 40, 1438.
4. (a) E.C. Taylor, R.J. Knopf, R.F. Meyer, A. Holmes, and M.L. Hoefle, J. Amer. Chem. Soc., 1960, 82, 5711 (b) E.C. Taylor and W.A. Ehrhart, J. Amer. Chem. Soc., 1960, 82, 3138.
5. For the conversion of o-aminonitriles such as 1 to annulated 4-aminopyrimidnes with a variety of 2-substituents, see E.C. Taylor and A. McKillop, "The Chemistry of Enaminonitriles and o-Aminonitriles", Interscience, N.Y., 1970.

Received, 24th September, 1985