Tetrahedron Letters No. 45, pp 4435 - 4438. 0040-4039/78/1101-4435$02.00/0

TRAPPING OF A 4,5-DIDEHYDROPYRIMIDINE WITH FURAN

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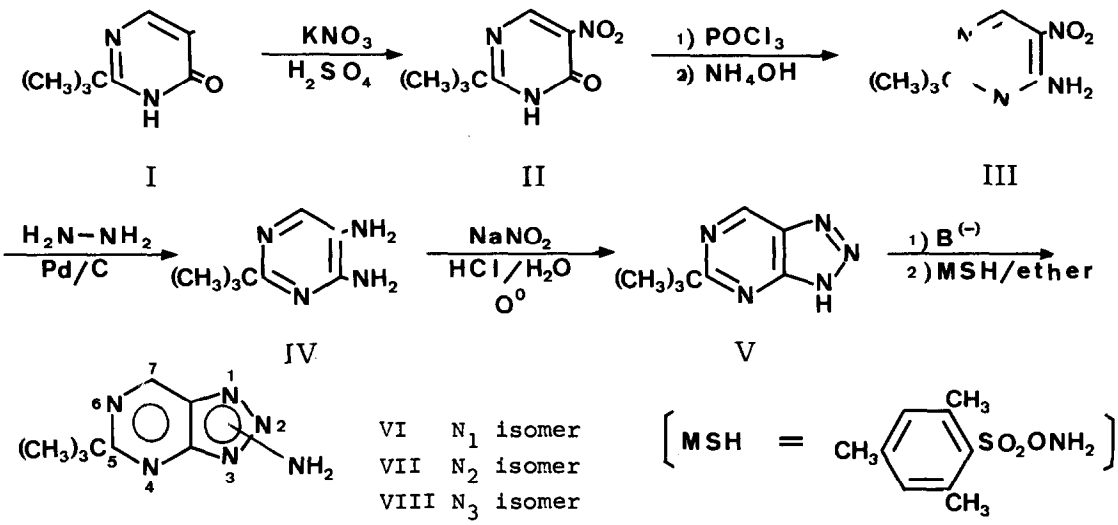
A number of reactions involving pyrimidine derivatives, namely, (a) the amination of 4-substituted 5-bromopyrimidines[1,2], 4-halogeno-6-phenylpyrimidines[3], and 4-halogeno-2,6-diphenylpyrimidines[4] with potassium amide in liquid ammonia, (b) the displacement of the halogen atom in 5-bromopyrimidine, 5-chloropyrimidine[5], 5-bromo-4-hydroxypyrimidine, and 5-bromo-3,4-dihydro-3-methyl-4-pyrimidinone[6] by strong secondary amines, (c) the formation of 4,4'- and 4,5'-dipyrimidinyles by halogen-metal interchange between 5-bromo-2,4-dimethoxypyrimidine or 5-bromo-2,4-bismethylthio-pyrimidine and n-butyllithium[7], have been interpreted in terms of an elimination-addition mechanism occurring either alone or in competition with other mechanisms of nucleophilic aromatic substitution (i.e. normal and abnormal addition-elimination, ANRORC mechanism[8]). Although the intermediacy of 4,5-didehydropyrimidines has been substantiated in some cases[3,5], to our knowledge, such arynes have never been trapped by dienes in a Diels-Alder reaction. An attempt, based on the decomposition of a pyrimidine-5-diazonium-4-carboxylate, has failed[6]. Therefore, we have had recourse to the method developed by Campbell and Rees[9], which has been successfully applied to the generation of 3,4-didehydro-pyridine[10] and -quinoline[10a] (but to a much less extent to 2,3-didehydro-pyridine and -quinoline[10a]), and 3,6-diphenyl-4,5-didehydropyridazine[11].

Synthesis of 1- and 3-amino-5-t-butyl-v-triazolo[4,5-d]pyrimidines (VI and VIII).

Expecting that a t-butyl group in the 5-position would improve the solubility in the common organic solvents, and inhibit any undesirable amination of the nitrogen atoms 4 and 6[12] during the last step of the synthesis, we have chosen the compounds VI and VIII as potential precursors of the hetaryne

IX. They have been prepared according to the following scheme:



2-t-Butyl-4-hydroxypyrimidine (I)[13] was nitrated, at 110-120°, in a mixture of concentrated sulfuric acid and potassium nitrate (92% yield). The 5-nitro derivative II (m.p. 211-212°) was converted to 2-t-butyl-4-chloro-5-nitropyrimidine by refluxing phosphorus oxychloride. Since the chloro compound was very reactive, it was used immediately. Adding the crude material to a concentrated ammonia solution gave 4-amino-2-t-butyl-5-nitropyrimidine (III) (m.p. 130-130.5°) in 91% over-all yield for the two steps. Reduction of the nitro group was carried out in ethanol using hydrazine hydrate and palladium on carbon (5%) as catalyst, and afforded 4,5-diamino-2-t-butylpyrimidine (IV) (m.p. 162-163.5°) almost quantitatively[14]. Treatment of the diamine IV with nitrous acid led to 5-t-butyl-v-triazolo[4,5-d]pyrimidine (V) (m.p. 189-191°) (92.5% yield). The latter was aminated with O-mesitylsulfonylhydroxylamine (MSH)[15] either via the sodium salt obtained by adding sodium hydride to an ethereal solution of the triazolopyrimidine V or via the potassium salt prepared by neutralizing an alcoholic solution of V with potassium hydroxide. There was obtained a mixture of products which were separated by column chromatography (silica ; ether-chloroform 1:1 followed by ether). After a small amount of the starting material V, the first component to be eluted was 1- or 3-amino-5-t-butyl-v-triazolo[4,5-d]pyrimidine (VI or VIII) (ca. 50%). The second component was the 2-amino isomer VII (ca. 5%), and the third the 3- or 1-amino derivative VIII or VI (10 to 30%). N.m.r. and mass data support the proposed structures. Chemical support came from the oxidation reaction (vide infra)[16].

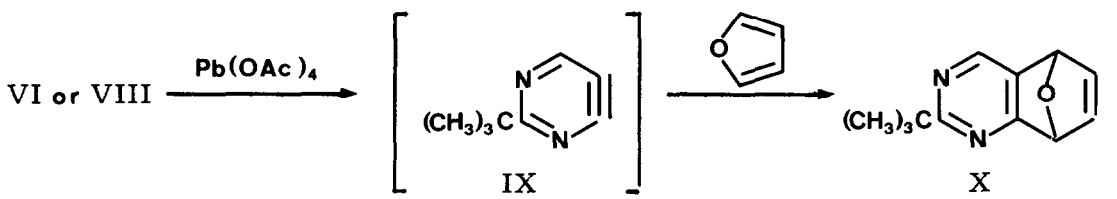
^{1}H N.m.r. spectra

Compounds	H_7	NH_2	$C(CH_3)_3$		
V	9.68 (1H) s	-	1.63 (9H) s		
VI or VIII	9.43 (1H) s	6.01 (2H) b	1.46 (9H) s		
VII	9.36 (1H) s	7.71 (2H) b	1.46 (9H) s		
VIII or VI	9.37 (1H) s	6.50 (2H) b	1.43 (9H) s		
	H_4	H_6 + H_7	H_8 or H_5	H_5 or H_8	$C(CH_3)_3$
X	8.30 (1H) s	7.06 (2H) m	5.85 (1H) d (J=1 Hz)	5.60 (1H) d (J=1 Hz)	1.38 (9H) s

Solutions in $CDCl_3$. Chemical shifts are expressed in ppm downfield from internal TMS. Number of protons in parentheses. s = singlet, b = broad signal, d = doublet, m = multiplet.

Oxidation of 1- and 3-amino-5-t-butyl-v-triazolo[4,5-d]pyrimidines (VI and VIII)

The two isomers VI and VIII were independently oxidized with lead tetra-acetate, in dichloromethane, at room temperature, in the presence of excess furan. Gas evolution occurred immediately. In both cases, the compound X (m.p. 91.5-92°)[17] was isolated by preparative thin-layer chromatography (silica ; ether). Its structure was established spectroscopically (found: $M^{+\cdot}$ 202.1102 $C_{12}H_{14}N_2O$ requires M 202.1106. N.m.r. spectrum, see table[18]).



The formation of 2-t-butyl-5,8-epoxy-5,8-dihydroquinazoline (X), in fairly good yields (ca. 50% from each isomer), may be regarded as a positive test for the 4,5-didehydropyrimidine intermediates.

Acknowledgments. We thank the I.R.S.I.A. for a research studentship to D.C. We also thank Dr. G. Jacques (Continental Pharma, S.A.) for the n.m.r. spectral determinations.

References and footnotes

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(Received in UK 4 August 1978)