Fused *s*-Triazino Heterocycles. III. The Reaction of Methyl *N*-Cyanoacetimidate and 2-Aminopyridine (1)

John T. Shaw, Martha Kuttesch, Steven Funck and Richard C. Allen (2)

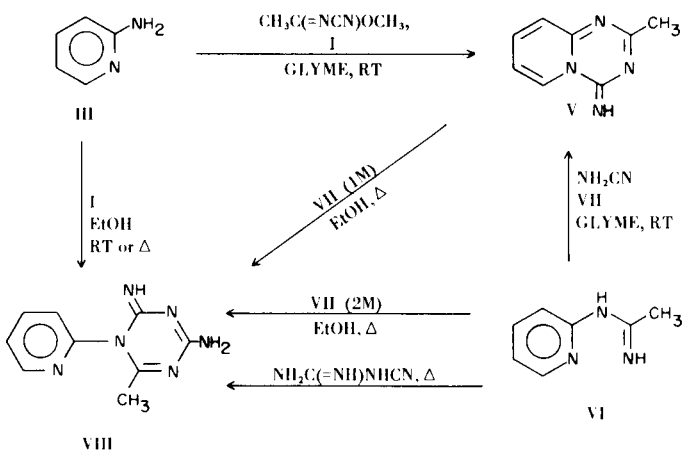
Department of Chemistry, Grove City College, Grove City, PA 16127

Received August 5, 1974

A recent paper (1) described how reacting 2,6-diaminopyridine with methyl *N*-cyanoacetimidate (I) at room temperature in glyme gave *N*-cyano,*N'*(6-amino-2-pyridyl)-acetamidine (II). It was therefore somewhat surprising to find that the analogous reaction of I with 2-aminopyridine (III) under essentially the same reaction conditions did not give the expected *N*-cyano-*N'*-2-pyridylacetamidine (IV) but gave instead 4-imino-2-methyl-4*H*-pyrido[1,2-*a*]-*s*-triazine (V) in 14% yield. Analytical and spectral data to support the structure of V is given in the experimental section. Additional support for the proposed structure of V was afforded by its synthesis from *N*-2-pyridylacetamidine (VI) and cyanamide (VII). At the same time this synthesis ruled out an alternate structure for V, 2-imino-4-methyl-2*H*-pyrido[1,2-*a*]-*s*-triazine.

Changing the reaction solvent from glyme to 95% ethanol altered the course of the reaction completely. An 8% yield of 4-amino-1,2-dihydro-2-imino-6-methyl-1(2-pyridyl)-*s*-triazine (VIII) was obtained and no V; refluxing the reactants raised the yield of VIII to 22%. Proof of the proposed structure for VIII follows from spectral and analytical data given in the experimental section and from three independent syntheses of it: (a) the 140° fusion of *N*-cyanoguanidine and VI, 9.9% yield; (b) the reaction of VI and VII (2 mole) in refluxing 95% ethanol, 59% yield; and (c) the reaction of V and VII (1 mole) in refluxing 95% ethanol. These transformations are outlined in Scheme I.

SCHEME I



The reaction of V and VII in 95% ethanol to give VIII suggests how VIII might be formed by the reaction of I and III in 95% ethanol. Part of III reacts with I to form V (as in the glyme reaction) which in turn reacts rapidly and irreversibly with VII to form the rather insoluble VIII; VII is formed by a side reaction of I with 95% ethanol. Indeed, thin layer chromatography of the reaction mixture in the very early stages of the reaction showed the presence of VII.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas-Hoover melting-point bath and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Infracord Model 137. Nmr spectra were obtained on a Varian EM-360 spectrophotometer using TMS as an internal reference. Analyses were performed by Micro-Analyses Inc., Marshallton, Delaware and Crobaugh Laboratories, Cleveland, Ohio.

Glyme, 1,2-dimethoxyethane was dried over calcium hydride and stored over molecular sieves. 2-Aminopyridine was obtained from Aldrich Chemical Company.

4-Imino-2-methyl-4*H*-pyrido[1,2-*a*]-*s*-triazine (V).

A. From 2-Aminopyridine (III) and Methyl *N*-Cyanoacetimidate (I).

A solution of 4.70 g. (0.05 mole) of III and 9.8 g. (0.1 mole) of freshly distilled I (3) in 5 ml. of glyme was stirred in a stoppered flask at room temperature for 21 hours. The precipitate which formed was filtered and washed with ether: 1.1 g. (14%), m.p. 155-157°. Two recrystallizations from carbon tetrachloride gave a yellow fluffy solid m.p. 164-165°; ir λ (Nujol): 3.05 μ (NH), 5.98 μ (C=N), no significant absorption 4-5 μ; nmr (deuteriochloroform): δ 2.4 (s, 3H, CH_3), δ 6.87 (s, broad, 1H, NH, addition of deuterium oxide removed only this peak), δ 7.02 (m, 1H, aromatic CH), δ 7.3 (m, 1H, aromatic CH), δ 7.85 (m, 1H, aromatic CH) δ 9.12 (m, 1H, aromatic CH); molecular weight, 161 (vapor phase osmometry).

Anal. Calcd. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.05; H, 5.14; N, 34.87.

Carrying out the same reaction in refluxing glyme for 21 hours resulted in total loss of V and the formation of a very small

amount (0.5%) of crude VIII; a considerable amount of intractible gummy material also formed.

B. From *N*-2-Pyridylacetamidine (VI) and Cyanamide (VII).

A stirred solution of 0.55 g. (0.00407 mole) of VI in 0.5 ml. of glyme was treated dropwise at room temperature with a solution of 0.152 g. (0.00361 mole) of VII dissolved in 0.5 ml. of glyme. Ammonia gas was evolved during the 3 hour reaction time and the solid which had formed was collected and washed with ether: 0.29 g. (50%) m.p. 151-154°. Recrystallization from carbon tetrachloride gave a yellow product identical to that prepared in A.

N-2-Pyridylacetamidine (VI).

Difficulty in reproducing the procedure of Bower and Ramage (4) for the preparation of this compound encouraged us to seek an alternative preparation. The following method is patterned after a literature preparation of *N*-(6-amino-2-pyridyl)acetamidine hydrochloride (5).

A suspension of 24.6 g. (0.225 mole) of methyl acetimidate hydrochloride (6) in 100 ml. of absolute ethanol was added to a vigorously stirred solution of 18.8 g. (0.2 mole) of III in 150 ml. of absolute ethanol. The solution was allowed to set for a week at room temperature and then the ethanol was removed at reduced pressure. The residue was treated with 50 ml. of water, made alkaline with 6 *N* sodium hydroxide, extracted with ether and the extracts were dried over anhydrous sodium sulfate. Removal of the ether, followed by distillation of the residue under reduced pressure gave 8.75 g. (32%) b.p. 118-120°/4 mm; the liquid solidified on standing, m.p. 67-69°, Lit. m.p. 67-68° (4).

4-Amino-1,2-dihydro-2-imino-6-methyl-1(2-pyridyl)-*s*-triazine (VIII).

A. From 2-Aminopyridine (III) and Methyl *N*-Cyanoacetimidate (I).

A solution of 4.70 g. (0.05 mole) of III and 4.9 g. (0.05 mole) of I in 10 ml. of 95% ethanol was refluxed for 18 hours; tlc of a sample of the solution removed after 15 minutes of refluxing revealed the presence of cyanamide (silica gel plates; development solvent, ether; a 1% methanolic silver nitrate spray revealed the presence of cyanamide). The white crystals which had formed were collected by filtration and washed with ether: 2.22 g. (22%), m.p. 250-253°. Two recrystallizations from pyridine gave an analytical sample, m.p. 252-253°; ir: λ (Nujol) 3.01, 3.18 μ (NH), 5.99 μ (C=N); nmr (very low solubility in deuterated solvents at room temperature precluded this analysis); molecular weight, 203 (vapor phase osmometry).

Anal. Calcd. for $C_9H_{10}N_6$: C, 53.45; H, 4.98; N, 41.56. Found: C, 53.75; H, 4.90; N, 41.83.

Increasing the ratio, I/III to 2/1 gave about the same yield, 23%.

It is interesting to note that refluxing 0.05 mole of I in 10 ml. of 95% ethanol showed no formation of VII (tlc) after 1 hour of refluxing, but that adding 0.05 mole of pyridine to this solution resulted in identification of VII (tlc) after 15 minutes of reflux. Apparently the reaction is base catalyzed.

B. From *N*-2-Pyridylacetamidine (VI) and Dicyandiamide.

A finely ground mixture of 0.68 g. (0.005 mole) of VI and 0.42 g. (0.005 mole) of dicyandiamide was held at 141 ± 3° for 1.25 hours; ammonia gas evolved during this time. The solid that formed on cooling to room temperature was stirred with 2 ml. of water and filtered: 0.1 g. (9.9%), m.p. 248-252°. Recrystallization from pyridine gave material identical to that prepared in part A.

C. From *N*-2-Pyridylacetamidine (VI) and Cyanamide (VII).

A solution of 0.68 g. (0.005 mole) of VI and 0.42 g. (0.01 mole) of VII in 1 ml. of 95% ethanol was heated on a boiling-water bath for 2 hours. The white crystals (which had begun to form almost immediately on reaching the reflux temperature) were collected: 0.60 g. (59%), m.p. 251-253°, identical to the material prepared in part A.

D. From 4-Imino-2-methyl-4*H*-pyrido[1,2-*a*]-*s*-triazine (V) and Cyanamide (VII).

A solution of 0.12 g. (0.00075 mole) of V and 0.0315 g. (0.00075 mole) of VII in 1 ml. of 95% ethanol was stirred and heated to reflux on a boiling-water bath. Within 5 minutes such a heavy precipitate formed that 1 ml. of 95% ethanol was added to facilitate stirring, and the mixture was refluxed for 1 hour. The solid was collected and weighed 0.11 g. (73%), m.p. 251-253°, identical to the material prepared in part A.

Acknowledgement.

We gratefully acknowledge the donors of the Petroleum Research Fund administered by the ACS for support of this research.

REFERENCES

(1) For another paper in this series see J. T. Shaw, M. E. O'Connor, R. C. Allen, W. M. Westler and B. D. Stefanko, *J. Heterocyclic Chem.*, **11**, 627 (1974).

(2) Taken in part from the Senior Honors Projects of Martha Kuttesch, Steven Funck, and Richard C. Allen.

(3) K. R. Huffman and F. C. Schaefer, *J. Org. Chem.*, **28**, 1816 (1963).

(4) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).

(5) J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, *J. Am. Chem. Soc.*, **69**, 1151 (1947).

(6) A. Pinner, "Die Imidoäther und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, 1892.