CHEMISTRY LETTERS, pp. 1005-1008, 1974. Published by the Chemical Society of Japan

MECHANISM FOR THE FORMATION OF α-AMINONITRILES: INTERMEDIACY OF AN IMINE OR A CYANOHYDRIN

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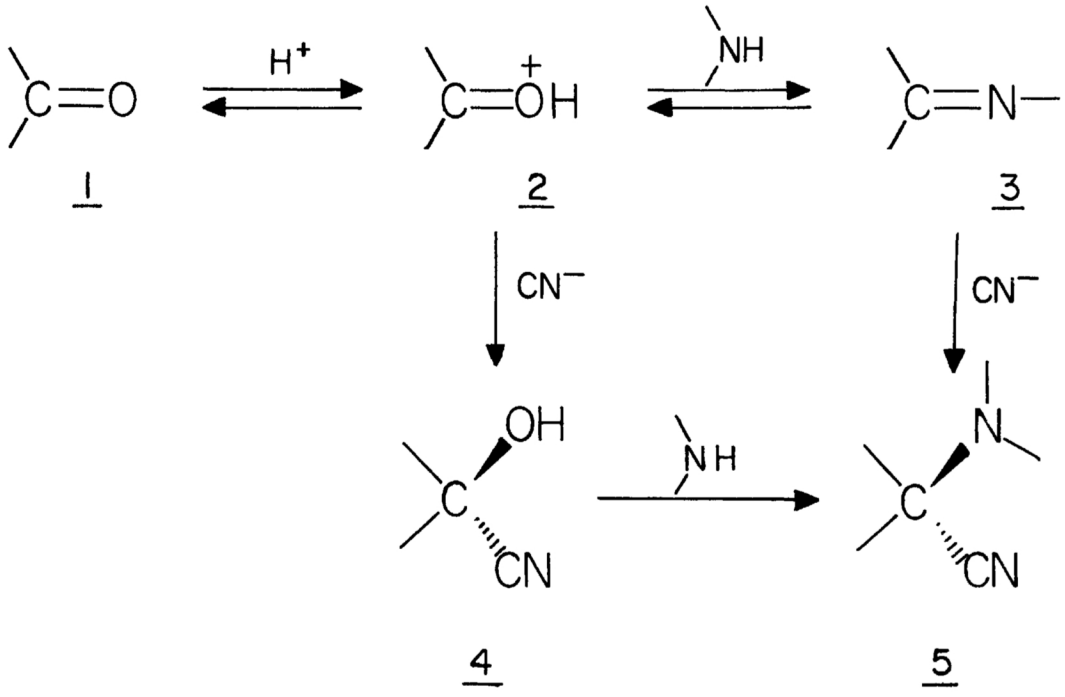
The reaction of benzaldehyde, 2-aminobenzenecarbothioamide, potassium cyanide, and acetic acid yields tetrahydroquinazolinethione 7 and/or α-aminonitrile 11 under different conditions. These results are used to support the intermediacy of an imine 3 or its immonium ion in the formation of α-aminonitriles 5.

One of the simplest and most convenient methods[1,2] for the formation of α-aminonitriles involves the reaction of a carbonyl compound, an amine, and alkali cyanide in the presence of an acid, usually acetic acid. Despite their usefulness as synthetic intermediates[2-7] for an almost endless variety of products, the mechanism for their formation is not fully understood. However, two mechanisms proceeding through the intermediacy of an imine, or a cyanohydrin have been proposed.[2,3] This is shown in Scheme I.



1 2 3 4 5

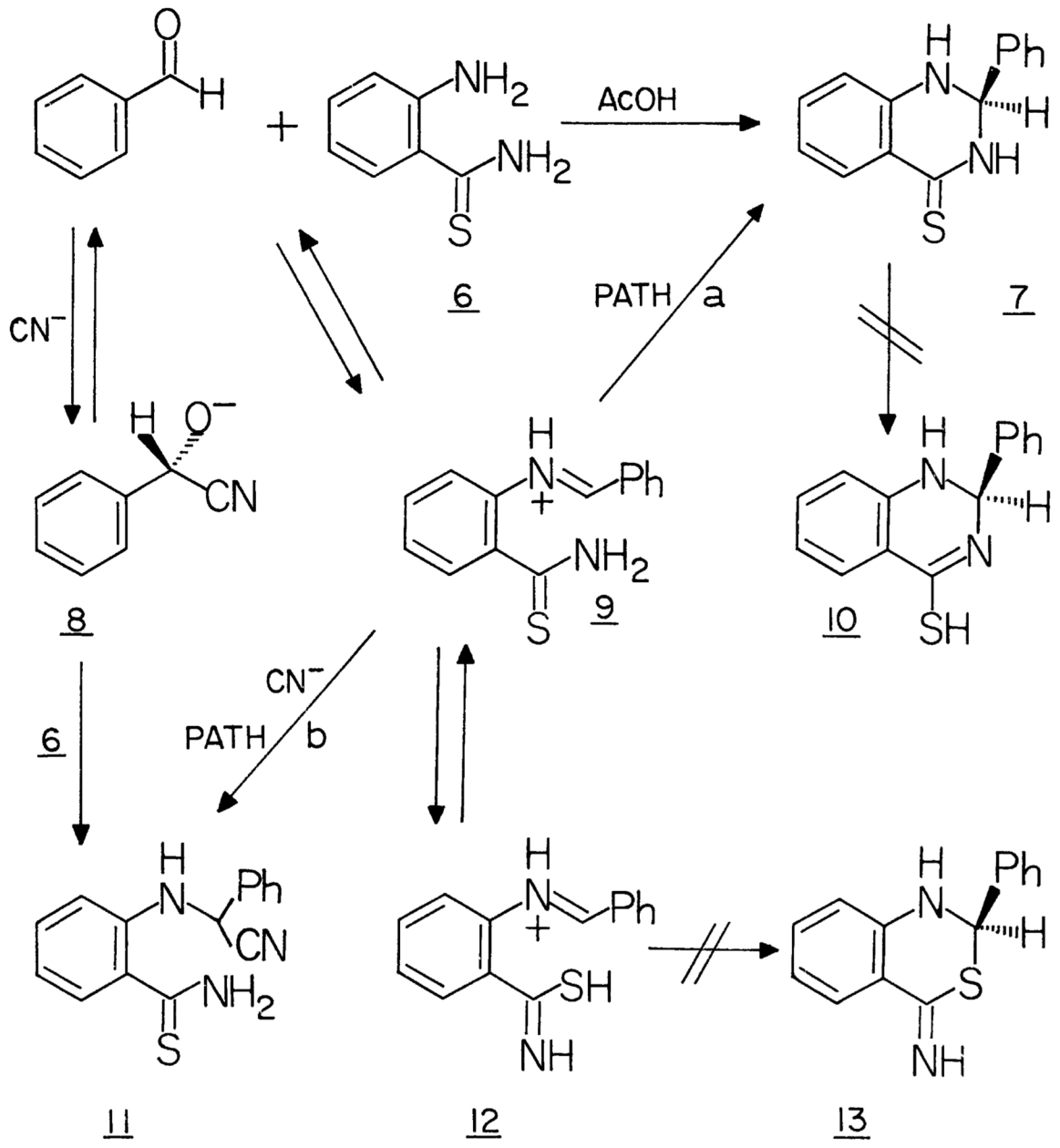
Scheme 1

Recently Ogata and Kawasaki[8] have favored the mechanism involving imine intermediate 3 on the basis of the faster rate of formation of α-cyanobenzylaniline from the reaction of benzylideneaniline and hydrogen cyanide, than from mandelonitrile and aniline. We report evidence which further supports the intermediacy of imine 3 (or its immonium ion) in the formation of α-aminonitriles 5.

If the imine 3 (or its immonium ion) is indeed the true intermediate, the presence of a resident powerful nucleophile, favorably situated in 3, should compete for intramolecular attack at the azomethinyl carbon with that of intermolecular attack of the cyanide ion. A molecule which satisfies this structural requirement ought to be accessible using 2-aminobenzenecarbothioamide (thioanthranilamide) (6), whose amino group would serve the role of an amine in the formation of α-aminonitrile, and the thiocarbamoyl group could act as the internal built-in nucleophile.

The reaction of equivalent amounts of benzaldehyde, carbothioamide 6, acetic acid, and potassium cyanide in methanol gave only one product, mp 178-179°C, whose ir ($CHCl_3$) was clear in the nitrile region (2200-2250 cm^{-1}). It is assigned tetrahydroquinazoline-4-thione structure 7 on the basis of its elemental, ir and nmr analyses, and is presumably formed by an intramolecular attack of thiocarbamoyl group in the immonium ion intermediate 9 (Scheme 2, path a). The lack of formation of any α-aminonitrile 11 under these conditions would argue against the cyanohydrin intermediate 8 and favor the intermediacy of immonium ion 9 in Scheme 2. It is significant that when the reaction was carried out using 20 and 30 mole equivalents of potassium cyanide and acetic acid respectively, the α-aminonitrile 11, mp 140-141°C, was obtained in 90% yield along with about 5% of quinazolinethione 7. The elemental and spectral analyses (ir, nmr) for 11 were consistent with its structure. Interestingly, when 10 and 15 mole equivalents of cyanide ion and acetic acid respectively were used, we obtained 30% 11 and 45% 7. These observations must mean that under the swamping effect of cyanide ion path b in Scheme 2 involving attack of cyanide ion at the immonium carbon in 9 occurs almost exclusively, whereas both paths a and b become important at about half the concentration of cyanide ion, compared to that of swamping cyanide ion concentration. As expected from Scheme 2, quinazolinethione 7 was also obtained from the acetic acid catalyzed reaction of benzaldehyde and thioamide 6 (in the absence of cyanide ion).

In principle, the intramolecular attack of the ambident mucleophilic thiocarbamoyl group onto the immonium linkage in 9 could occur in two ways. The reaction from the nitrogen, or the sulfur end of the thio carbamoyl group would produce quinazolinethione 7, or the heterocyclic imine 13. Further, quinazolinethione 7 could tautomerize to dihydroquinazolinethiol 10. A clear distinction between these alternatives was provided by the 60 MHz-nmr spectrum in DMSO-d_6. The methinyl proton only in 7 would be expected to be split by two adjacent N-H protons. Indeed, this proton appears as a three line signal at δ5.79, and is reduced to a one line signal on D_2O addition. Furthermore,



Scheme 2

the appearance of a doublet at δ10.50 (J 3.2 Hz), ascribable to the rather acidic proton of -C(=S)-NH-, implies the presence of a neighboring proton, consistent only with structure 7.

It is pertinent to point out that cyanohydrins are known[9] to react with amines to afford α-aminonitriles. Since substitution of hydroxyl group in a cyanohydrin by an amine via SN_1 and/or SN_2 process seems unlikely, it would appear that under the basic conditions of reaction medium the amine first decomposes the cyanohydrin to the free carbonyl compound. Its subsequent reaction with amine and cyanide ion then affords the α-aminonitrile. Such an argument is supported by the

known base catalyzed decomposition of cyanohydrins.[10]

Financial support from the Edward G. Schlieder Educational Foundation is greatfully acknowledged. We thank Mr. Gordon G. Boudreaux, Southern Regional Research Laboratory, United States Department of Agriculture for nmr spectra.

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(Received May 13, 1974)