

Synthesis and Reactions of Potassium Cyanoacetohydroxamate

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The reaction of ethyl cyanoacetate with hydroxylamine gave potassium cyanoacetohydroxamate (I), which cyclised under basic conditions to yield the isoxazolone (IIIa). Reactions of (I) with hydroxylamine and acetylacetone gave α -(hydroxyamidino)acetoacetic acid (II) and the cyanopyridone (IV), respectively. The reaction with benzoyl chloride yielded three products [the *O*-benzoyl derivative (V), the isoxazolone (IIIb), and *NO*-dibenzoylhydroxylamine] in amounts depending on the reaction conditions.

We recently described¹ a convenient synthesis of a cyclic hydroxamic acid from acetylacetone, ethyl cyanoacetate, and hydroxylamine in the presence of an organic base. It was considered that ethyl cyanoacetate and hydroxylamine first reacted to produce cyanoacetohydroxamic acid, which then reacted with acetylacetone.

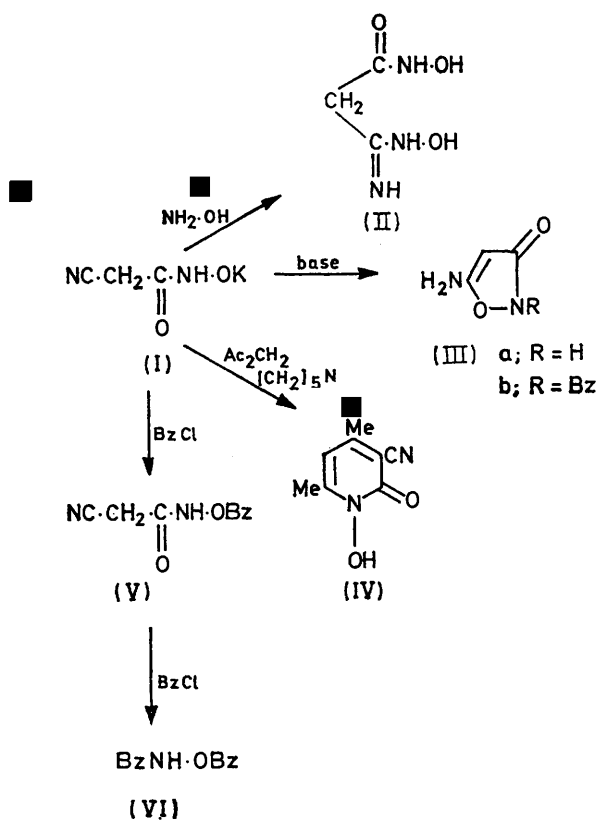
The reaction of hydroxylamine with ethyl cyanoacetate has been the subject of earlier studies.^{2,3} The hydroxyamidino-hydroxamic acid (II) was originally reported as the sole product.² Recent studies³ have, however, shown that this reaction is more complex, and produces 5-aminoisoxazol-3-one (IIIa) and 3-aminoisoxazol-5-one, in addition to (II). Compounds (II) and (IIIa) are derived from the same intermediate, cyanoacetohydroxamic acid.

When we treated ethyl cyanoacetate with an alkaline solution of hydroxylamine in methanol, potassium cyanoacetohydroxamate (I) soon separated. All attempts to isolate the free acid from this salt were unsuccessful.

The salt (I) reacted with methanolic sodium methoxide to yield the isoxazolone (IIIa) and with an equivalent amount of hydroxylamine in alkaline medium to give compound (II). Refluxing an aqueous solution of (I) with acetylacetone and catalytic amounts of piperidine yielded the cyanopyridone (IV). A similar result was obtained when potassium hydroxide was used to catalyse the reaction.

In an attempt to obtain the *O*-benzoyl derivative (V), the potassium salt (I) was treated with benzoyl chloride under Schotten-Baumann conditions. The solid product obtained proved to be 5-amino-2-benzoylisoxazol-3-one

(IIIb). It was believed that under the alkaline conditions used, the salt (I) cyclised prior to benzoylation; in fact compound (I) could be cyclised by treatment



with aqueous sodium hydroxide. We were, however, able to obtain the desired product (V) by conducting the reaction in neutral aqueous medium. In the preparation

¹ F. K. Rafla and M. A. Khan, *J. Chem. Soc. (C)*, 1971, 2044.

² H. Modeen, *Ber.*, 1894, 27, 261.

³ L. Bauer and N. V. Nambury, *J. Org. Chem.*, 1961, 26, 4917.

of (V) dibenzoylhydroxylamine (VI) was isolated in varying amounts. This arose by the reaction of benzoyl chloride with (V); when the latter was treated with an equivalent amount of benzoyl chloride, (VI) was produced in nearly quantitative yield. Under the influence of acylating agents, substituted hydroxamic acids have been reported to undergo similar C-N cleavage.^{4,5}

EXPERIMENTAL

I.r. spectra were run on a Perkin-Elmer 521 spectrophotometer. Known compounds prepared from the salt (I) were identified by comparison (spectra and mixed m.p.s) with authentic samples.³

Potassium Cyanoacetohydroxamate (I).—A solution of potassium hydroxide (28 g, 0.5 mol) in methanol (80 ml) was slowly added to a cold solution of hydroxylamine hydrochloride (17.5 g, 0.25 mol) in methanol (150 ml). The mixture was shaken and left for 15 min. Potassium chloride was filtered off and ethyl cyanoacetate (28 g, 0.25 mol) was added in one portion to the filtrate. The reactants were mixed and the mixture was cooled in ice-water. A white crystalline solid soon separated on scratching the sides of the flask (17 g, 50%); m.p. 112° (decomp). It gave a deep purple colour with iron(III) chloride and decomposed if left in the air; λ_{\max} (KBr) 3215s, br (NH), 2930s, 2960s (CH), 2260s (CN), and 1655s cm^{-1} (CO).

α -(Hydroxyamidino)acetohydroxamic Acid (II).—A solution of the salt (I) (4.1 g, 0.03 mol) in water was treated with aqueous hydroxylamine hydrochloride (2 g in 10 ml) and left overnight. White crystals (2 g, 54%) separated, m.p. 151–152° (lit.,³ 152–153°).

5-Aminoisoxazol-3-one (IIIa).—(i) To sodium methoxide (from 2 g of sodium) in methanol (80 ml), the salt (I) (5.5 g, 0.04 mol) was added. The mixture was left overnight, solvent was removed *in vacuo*, and the gummy residue was dissolved in water, acidified with dilute hydrochloric acid,

and kept at 0° for 2 days. The white solid (2 g, 50%) which separated had m.p. 153°.

(ii) The salt (I) (4 g) was added to sodium hydroxide (1.5 g) in water (25 ml). The mixture was left overnight, acidified with hydrochloric acid, and left at 0°. A white solid (2 g) separated overnight; m.p. 153° (lit.,³ 152–153°).

5-Amino-2-benzoylisoxazol-3-one (IIIb).—The salt (I) (5 g) was added to sodium hydroxide (2 g) in water (80 ml). The solution was stirred with benzoyl chloride (4.5 ml) for 1 h. The solid product (3 g, 40%) was filtered off and washed with water; it formed prisms, m.p. 176° (from ethyl acetate) (lit.,³ 177–179°).

1,2-Dihydro-1-hydroxy-4,6-dimethyl-2-oxopyridine-3-carbonitrile (IV).—A solution of the salt (I) (1.4 g, 0.01 mol) in water (20 ml) was refluxed with acetylacetone (1.0 g, 0.01 mol) in the presence of piperidine (1 ml) for 0.5 h. The mixture was cooled and acidified with acetic acid to give a white crystalline solid (1.4 g, 85%), m.p. 235° (from aqueous methanol) (lit.,¹ 235°). The same result was obtained when potassium hydroxide was used to catalyse the reaction.

N-Benzoyloxycyanoacetamide (V).—A solution of the salt (I) (4.1 g, 0.03 mol) in water (100 ml) was stirred with benzoyl chloride (4.2 g, 0.03 mol) for 15 min, during which time the *O*-benzoyl derivative (2.5 g, 41%) separated. It crystallised from ethyl acetate as needles, m.p. 118°; ν_{\max} (KBr) 3210br (NH), 2263s (CN), 1760s (benzoate), and 1690s cm^{-1} (amide) (Found: C, 58.9; H, 4.1; N, 13.7. $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_3$ requires C, 58.8; H, 4.0; N, 13.7). It gave no colour with iron(III) chloride.

NO-Dibenzoylhydroxylamine (VI).—A suspension of compound (V) (1 g) in water (50 ml) was treated with benzoyl chloride (1 ml) and the mixture was stirred overnight. A white solid (1 g) separated; m.p. 159° (from aqueous methanol) (lit.,⁶ 159°). The same compound was produced by the reaction of (I) with 2 equiv. of benzoyl chloride in aqueous medium.

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⁴ D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 1955, 631.

⁵ P. Namalis, M. J. Rix, and A. A. Sarsfield, *J. Chem. Soc.*, 1965, 6278.

⁶ P. A. S. Smith, 'The Chemistry of Open-Chain Organic Nitrogen Compounds,' vol. II, Benjamin, New York, 1966, p. 76.