Synthesis of Isoxazolecarboxylic Acids from Schiff Bases and Nitroacetate[1]

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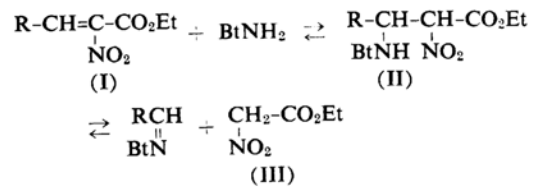
The authors wish to report a new and general method for the synthesis of 4-substituted isoxazole-3, 5-dicarboxylic acids. We have previously reported[2] that dibutylamides of 4-substituted isoxazole-3,5-dicarboxylic acids were obtained when α, β-unsaturated α-nitroesters were treated with *n*-butylamine in an anhydrous solvent, and assumed that the reaction proceeds through a key intermediate IV which is formed by the addition of nitroacetate to α, β-unsaturated α-nitroester. Subsequently, the authors could isolate benzylidene-*n*-butylamine (a Schiff base) from the mother liquor of 4-phenyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole which is obtained from ethyl α-nitrocinnamate by refluxing with *n*-butylamine in absolute ethanol. Therefore, it is suggested that the initial reaction may involve the addition of butylamine to α, β-unsaturated α-nitroester I and the adduct II generates nitroacetate III, which adds to α, β-unsaturated system of I in the presence of a basic catalyst (*n*-butylamine) by the mechanism of the Michael reaction to give the key intermediate IV, as outlined in the following scheme:



1) Presented in part at the Division of Organic Chemistry of the 14th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1961.

2) S. Umezawa and S. Zen, This Bulletin, 33, 1016 (1960).

$$\mathrm{I} + \mathrm{III} \rightarrow \mathrm{EtO_2C\text{-}\underset{\displaystyle NO_2}{\underset{|}{CH}}\text{-}\underset{\displaystyle R}{\underset{|}{CH}}\text{-}CO_2Et}$$

(IV)

As regards the sequel of the path from IV to bis(*n*-butylcarbamoyl) derivatives of isoxazole, the authors had already mentioned in a previous paper[2].

If the above mechanism is valid, one should be able to obtain the derivatives of isoxazole-3, 5-dicarboxylic acid by the reaction of Schiff bases with nitroacetate in the presence of basic catalysts. The expectation has now been realized. When an excess of *n*-butylamine was added to a mixture of Schiff base (1 mol.) and ethyl nitroacetate (2 mol.) in absolute ethanol, an exothermic reaction occurred. After refluxing for several hours, the mixture was concentrated to give a crystalline solid of bis(*n*-butylcarbamoyl) derivative of isoxazole.

The following compounds were prepared by the general procedure: 4-methyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole*; 4-(*n*-propyl)-3, 5-bis(*n*-butylcarbamoyl)isoxazole (V), m. p. 112.5 ~115.5°C; 4-phenyl-3, 5-bis(*n*-butylcarbamoyl)-isoxazole*, 4-(*p*-nitrophenyl)-3, 5-bis(*n*-butylcarbamoyl)isoxazole (VI), m. p. 133~135°C; 4-(*m*-nitrophenyl)-3, 5-bis(*n*-butylcarbamoyl)-isoxazole (VII), m. p. 168~169°C; 4-(*p*-chlorophenyl)-3, 5-bis(*n*-butylcarbamoyl)isoxazole (VIII), m. p. 126~127°C; 4-(2, 4-dichlorophenyl)-3, 5-bis(*n*-butylcarbamoyl) isoxazole (IX), m. p. 139~140.5°C; 4-(*p*-acetamidophenyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (X), m. p. 159~160°C; 4-(*p*-dimethylaminophenyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (XI), m. p. 117~118.5°C.

These derivatives were hydrolyzed with 10% sodium hydroxide in 50% aqueous ethanol at about 60°C to give 4-substituted isoxazole-3, 5-dicarboxylic acids. V, VI, VIII and IX were converted, respectively, to 4-(*n*-propyl)isoxazole-3,5-dicarboxylic acid, m. p. 176~177°C (decomp.), 4-(*p*-nitrophenyl)isoxazole-3, 5-dicarboxylic acid, m. p. 172~174°C (decomp.), 4-(*p*-chlorophenyl)isoxazole-3, 5-dicarboxylic acid, m. p. 187~187.5°C (decomp.), and 4-(2, 4-dichlorophenyl)isoxazole-3, 5-dicarboxylic acid, m. p. 183~186°C (decomp.). The product from X was led to methyl 4-(*p*-aminophenyl)isoxazole-3,5-dicarboxylate, m. p. 163~166°C.

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* Compounds marked with an asterisk were already prepared by another procedure and reported. S. Umezawa, S. Zen, loc. cit.