Formation of Isoxazolecarboxylic Acids from α, β-Unsaturated α-Nitroesters[1]

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We wish to report the synthesis of new members of isoxazolecarboxylic acids. When treated with *n*-butylamine (2.0 g.) in ligroin at room temperature overnight, diethyl α-nitroglutaconate[2] (I) (1.0 g.) produced 3, 5-bis(*n*-butylcarbamoyl) - 4 - (*n*-butylcarbamoylmethyl)-isoxazole (III) (crude product 0.6 g.). We have found that the cyclization is generally applicable to the synthesis of 4-substituted isoxazole-3, 5-dicarboxylic acids. Thus, 4-phenyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole (VI) (crude product 0.22 g.) and 4-methyl-3, 5-bis (*n*-butylcarbamoyl)isoxazole (IX) have been obtained from ethyl α-nitrocinnamate[3] (V) (1.0 g.) and ethyl α-nitrocrotonate[4] (VIII) by refluxing with *n*-butylamine in absolute ethanol for three hours, respectively (Tables I and II).

By mild alkaline hydrolysis with 10% sodium hydroxide in 50% aqueous ethanol at about 60°C for two hours, III (1.12 g.) and VI (1.0 g.) were converted into isoxazole-3, 5-dicarboxylic-4-acetic acid (IV) (crude product 0.56 g.) and 4-phenylisoxazole-3, 5-dicarboxylic acid (VII) (crude product 0.45 g.), respectively (Table I).

Drastic alkaline hydrolysis of VI by refluxing with 28% potassium hydroxide in 50% aqueous ethanol resulted in the formation of phenylacetic acid and oxalic acid, the fact indicating that the above-mentioned cyclization forms a 4-substituted isoxazole-3, 5-dicarboxylic acid derivative.

It seems reasonable to suggest that the initial step involves base-catalyzed cleavage of α, β-unsaturated α-nitroester to liberate nitroacetic ester moiety which may be in equilibrium

1) Presented in part at the Division of Organic Chemistry of the Annual Meeting of the Chemical Society of Japan, Kyoto, April 2, 1959.

2) Prepared by the condensation of sodium salt of ethyl formylacetate with ethyl nitroacetate in the presence of diethylamine or *n*-butylamine; b. p. 125~130°C/0.2 mmHg.

3) Prepared by the method of A. Dornow and H. Menzel, [*Ann.*, **580**, 43 (1952)]. They obtained carbethoxy-diethylcarbamoyl-4-phenylisoxazoline *N*-oxide by refluxing an ethanol solution of diethylamine and diethylamine salt of ethyl 1,3-dinitro-2,3-diphenylbutyrate which was prepared from ethyl α-nitrocinnamate and phenylnitromethane. This result is closely related to the method reported in the present paper, whereby, however, isoxazole derivatives are obtained.

4) Prepared from ethyl α-nitro-β-acetoxybutyrate by heating with anhydrous sodium carbonate in dry benzene by a variation of the method of H. B. Hass, A. G. Susie and R. L. Heider, (*J. Org. Chem.*, **15**, 8 (1950)).

TABLE I. 4-SUBSTITUTED 3,5-BIS(*n*-BUTYLCARBAMOYL)ISOXAZOLES AND ISOXAZOLE-3,5-DICARBOXYLIC ACIDS

Compounds	M.p. °C	Formula	Analyses Calcd. C,%	H,%	N,%	Found C,%	H,%	N,%	Neutralization equivalent Calcd.	Found
III	179~179.5[a]	$C_{19}H_{32}O_4N_4$	59.97	8.48	14.73	60.41	8.22	15.15	—	—
VI	160~162[a]	$C_{19}H_{25}O_3N_3$	66.45	7.34	12.24	66.86	6.90	12.55	—	—
IX	84~ 86[b]	$C_{14}H_{23}O_3N_3$	59.76	8.24	14.94	60.32	7.95	15.18	—	—
IV	108~110 (hydrate)[c]	$C_7H_5O_7N$	39.08	2.34	6.51	39.02	2.42	6.57	71.7	72.3
VII	183~183.5[d] (decomp.)	$C_{11}H_7O_5N$	56.66	3.03	6.01	56.87	2.97	6.08	116.6	115.7

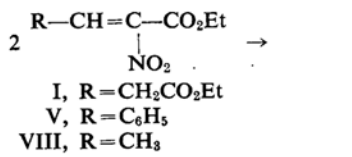
a) Recrystallized from ethanol.
b) Recrystallized from ligroin.
c) Recrystallized from dioxane-chloroform; the anhydrous sample melted at 177~178°C (decomp.).
d) Recrystallized from a mixture of dioxane and ethylenedichloride-ligroin.

TABLE II. ABSORPTION SPECTRA OF 4-SUBSTITUTED 3,5-BIS(*n*-BUTYLCARBAMOYL)ISOXAZOLES

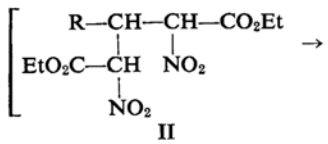
Compounds	U.V. absorption λ_{max}, mμ (ε)	Infrared absorption γ_{max}^{Nujol}, cm^{-1}		
III	245 (10500)[a]	3299 (NH),	1682 (CO),	1537 (secondary, non-cyclic amide)
VI	—[b]	3338,	1678,	1535
IX	246 (10100)[c]	3290,	1664,	1555

a) Methanol solution.
b) No characteristic maximum in the range of 220~340 mμ.
c) Ethanol solution.

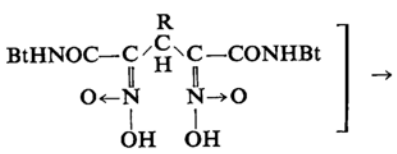
with the original unsaturated nitroester, followed by the addition of the former to the latter to give a key intermediate II, which may cyclize by elimination of water and nitrous acid to form isoxazole derivatives, as outlined in the following scheme:



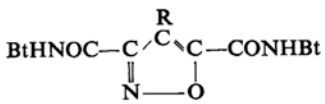
I, R=CH_2CO_2Et
V, R=C_6H_5
VIII, R=CH_3



II



Bt=*n*-Butyl



III, R=$CH_2CONHBt$
VI, R=C_6H_5
IX, R=CH_3

The validity of the above mechanism has been supported by the experimental observation that, if ethyl nitroacetate is added to the above-mentioned reaction system as an external source of nitroacetate moiety, the yield of isoxazole derivative is significantly increased. As a typical result: When a mixture of ethyl α-nitrocinnamate (5.0 g.) and ethyl nitroacetate (3.0 g.) was caused to react with *n*-butylamine (10 g.) under similar conditions, VI (crude product 4.7 g.) was obtained in a 60% yield.

Further studies on the related reactions are in progress.

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