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The Formation of 4-Substituted-3,5-bismethoxycarbonylisoxazoline N-Oxides *via* O-Alkylation of Nitroacetate with *n*-Alkylhalides[1,2]

This is a report regarding the one-step synthesis of 4-substituted-3,5-bismethoxycarbonylisoxazoline N-oxides (VII) from the O-alkylation reaction of nitroacetate with *n*-alkylhalides in dipolar aprotic solvent.

Kerber, *et al.*[3] have reported the alkylation reaction of nitroparaffins are initiated by ambident nucleophile, *i.e.* the anion of an aliphatic nitro compounds.

Our observation indicates that the alkylation reaction of nitroacetate as well as that of nitroparaffins, also appears to commence with ambident anion. Therefore, the most electronegative atom of nitroacetic ester gives rise to this ambident anion and consequently carbon or oxygen atom can be alkylated as shown in Chart 1. The C-alkylation reaction in dipolar aprotic solvent (such as dimethylacetamide and dimethylformamide) occurred when a reaction of nitroacetate with several kinds of halides except for *n*-alkyl groups to yield the corresponding α-nitroesters (I) in our informations[4,5]; the O-alkylation reaction was resulted from the titled reaction used *n*-alkylhalides to form isoxazoline N-oxides (VII) through one step in preference to C-alkylated product (I). VII might be produced *via* 1,3-dinitroglutarate (V), given from aldehyde[6] (III) and double mole of nitroacetate as reported in our previous paper.[7] When ethyl, *n*-propyl, *n*-butyl, *n*-amyl, *n*-hexyl and *n*-heptadecyl iodides are employed similarly as *n*-alkylhalides, the corresponding VIIa—VIIf could be synthesized respectively (as shown in Table I and II). Typical procedure progresses as follows: 14.9 ml of 1.13N sodium methylate in methanol is added to a solution of 2.62 g (16.8 mmoles) of ethyl iodide and 2.00 g (16.8 mmoles) of methyl nitroacetate in dimethylacetamide (DMA, 40 ml). The reaction mixture is stirred until the solution becomes clear at room

Table I. 4-Alkyl-3,5-bismethoxycarbonylisoxazoline N-Oxides (VII)

Compd.	R^1	R^2	Yield (%)	mp (°C) (Recryst. solvent)	C-Alkylated product (%)
a	CH_3	CH_3	35	63—64 (ethanol–water)	16
b	CH_3	C_2H_5	32[a]	83—84 (ethanol)	20[a]
c	CH_3	n-C_3H_7	39	50—51 (ethanol–water)	14
d	CH_3	n-C_4H_9	39	oily product	17
e	CH_3	n-C_5H_{11}	38	oily product	29
f	CH_3	n-$C_{17}H_{35}$	43	76—77.5 (methanol)	6

a) Sodium salt of nitroacetate was employed.

1) This paper is also taken to be number VIII in the series, "The Synthetic Reactions of Aliphatic Nitro Compounds."
2) This work was presented in part at the 28th Annual Meeting of Chemical Society of Japan, Tokyo, Apr. 1973. Abstracts of presentation, p. 1353, III.
3) R.C. Kerber, G.W. Urry, and N. Kornblum, *J. Am. Chem. Soc.*, **87**, 4520 (1965).
4) Part VII: E. Kaji and S. Zen, *Bull. Chem. Soc. Japan*, **46**, 337 (1973).
5) S. Zen and E. Kaji, *Bull. Chem. Soc. Japan*, **43**, 2277 (1970).
6) Initial O-alkylated product, nitronic ester (II) tends to decompose easily to III and an oxime (IV) (H. Feuer, "The Chemistry of the Nitro and Nitroso Groups Part 1," ed. by Patai, Interscience Publishers, New York, N. Y., 1969, p. 417).
7) S. Zen and M. Koyama, *Bull. Chem. Soc. Japan*, **44**, 2882 (1971): We have reported a synthetic method of 4-substituted-3,5-bis-*n*-butylcarbamoylisoxazole from 1,3-dinitroglutarate (V) with *n*-butylamine and the postulated reaction mechanism therefrom. This result is closely related to the mechanism reported in the present paper.

Table II. Infrared (IR) and Nuclear Magnetic Resonance (NMR) Data of Isoxazoline N-Oxides (VII)

Compd.	IR (KBr) cm^{-1}		NMR δ (60 MHz) in $CDCl_3$			J_{4-5} (Hz)
	ester C=O	C=N	ester CH_3	C_4–H	C_5–H	
a	1760—1735	1615	3.83(s), 3.87(s)	3.67(m)	4.68(d)	3.0
b	1780—1730	1620	3.87(s), 3.90(s)	3.68(m)	4.80(d)	3.0
c	1770—1730	1620	3.80(s), 3.85(s)	3.70(m)	4.77(d)	2.5
d	1760—1730[a]	1630[a]	3.83(s), 3.88(s)	3.67(m)	4.77(d)	2.5
e	1770—1720[a]	1630[a]	3.84(s); 3.88(s)	3.67(m)	4.78(d)	2.5
f	1730, 1700	1640	3.87(s), 3.90(s)	3.67(m)	4.78(d)	3.0

a) Measured in liquid film. s: singlet, d: doublet, m: multiplet

temperature or at 60—70° for 2 hr and 100 g of cold water is added thereto, further extracted with benzene. The benzene layer is washed with water and dried, and then benzene is removed. The resultant syrup can easily be purified by chromatography with silica gel column[8] using *n*-hexane/ethyl acetate (2:1) solvent system. Both an O-alkylated product (major product); VIIa ($R_1=R_2=CH_3$), and a C-alkylated product (minor product); methyl α-nitrobutyrate are obtained in 35% and 16% yield respectively. After recrystallization from ethanol–water, VIIa is collected as colorless needles, mp 63—64°, IR ν_{max}^{KBr}: 1760—1735 (ester C=O), 1615 (C=N) cm^{-1}, NMR δ_{CDCl_3} (60 MHz): 3.67 (1H, m, C_4–H), 3.83 and 3.87 (each 3H, s, ester CH_3), 4.68 (1H, d, C_5–H), $J_{4-5}=3.0$ Hz (*trans*).[9] *Anal.* Calcd. for $C_8H_{11}O_6N$: C, 44.24; H, 5.11; N, 6.45. Found: C, 44.22; H, 5.15; N, 6.44.

Our previous work[7] may support the postulated mechanism shown in Chart 1.

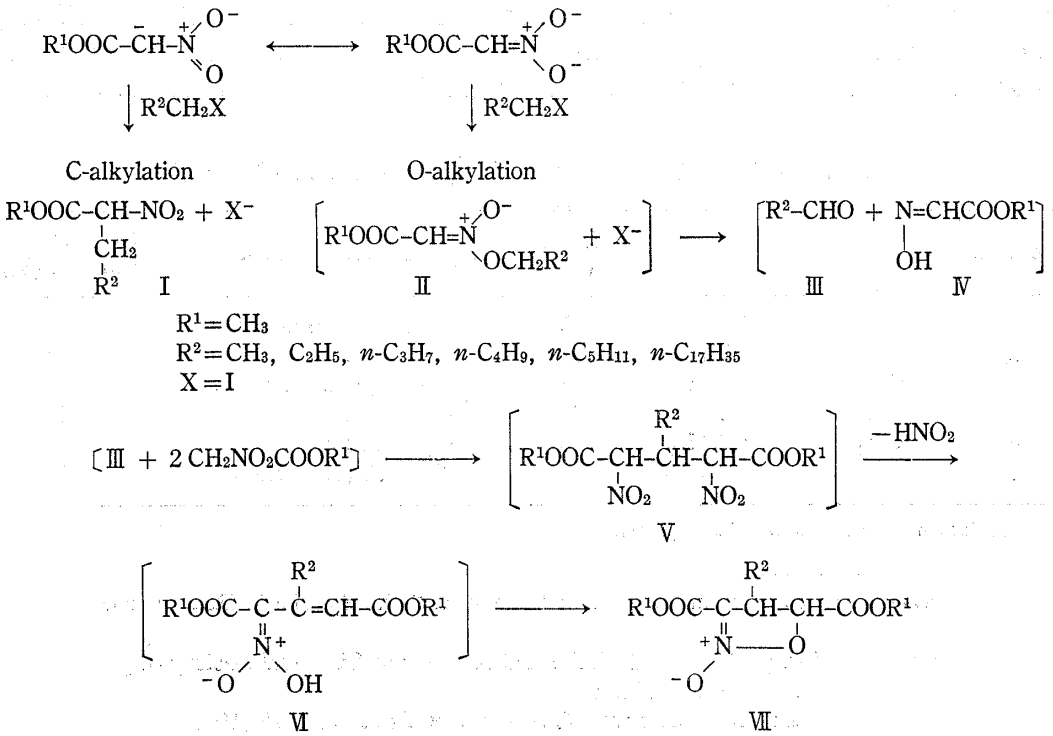

Chart 1

8) 50 g of silica gel (Kanto Chemical Co.), up to 100 mesh, column 2.6×24 cm.

9) The coupling constant (4.4 Hz) of *trans* isomer is much lower than the value (*ca.* 10 Hz) for *cis* by the study of Nielsen on the NMR of *trans* 3,4,5-triphenylisoxazoline N-oxide (*J. Org. Chem.*, **34**, 984 (1969)). The *J*-value for *trans* isomer is also supported by the studies of both Karplus and Iwakura, *et al.* (M. Karplus, *J. Chem. Phys.*, **30**, 13 (1959); Y. Iwakura, K. Uno, Y. Kihara, M. Setsu, and M. Ginnai, *Nippon Kagaku Kaishi*, **1972**, 1452. The value of VIIa agrees with *trans* isomer.

Furthermore, VII gave the diamides (VIII) when heated with *n*-butylamine in alcoholic solution and subsequently dehydrated to yield 4-substituted-3,5-bis-*n*-butylcarbamoylisoxazoles (IX) by refluxing (Chart 2). IXa and IXc could be identified by comparison with the authentic samples.[7,10] The rest reported herein gave satisfactory results in C, H, N analyses and spectroscopic data (Table III).

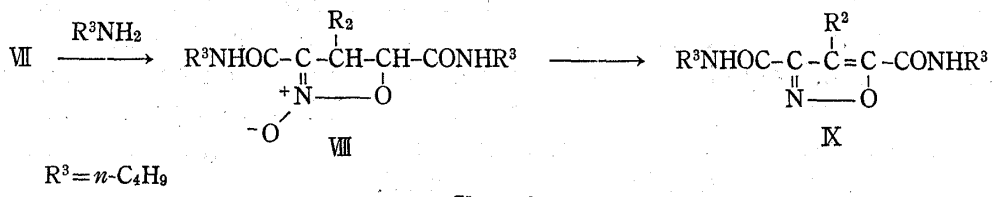

Chart 2

TABLE III. 4-Alkyl-3,5-bis-*n*-butylcarbamoylisoxazoline N-Oxides (VIII) and 4-Alkyl-3,5-bis-*n*-butylcarbamoylisoxazoles (IX)

Compd.	Yield (%)		mp (°C) (Recryst. solvent)	
	VIII	IX	VIII	IX
a	7	56	122.5—123.5 (hexane)	92—93 (acetone–water)
b	14	51	89—90 (hexane)	81—82 (acetone–water)
c	19	60	103—104 (hexane)	114.5—115.5 (acetone–water)
d	11	53	93.5—95 (hexane)	91.5—92.5 (acetone–water)
e	54	49	102.5—103.5 (hexane)	83—85 (acetone–water)
f	—	33	—	75—76 (hexane)

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