CHEMISTRY LETTERS, pp. 183-186, 1979. Published by the Chemical Society of Japan

PREPARATION OF 5-TRIMETHYLSILOXYOXAZOLES FROM 2-OXAZOLIN-5-ONES AND THEIR DIELS-ALDER REACTION: SYNTHESIS OF VITAMIN B_6 DERIVATIVES

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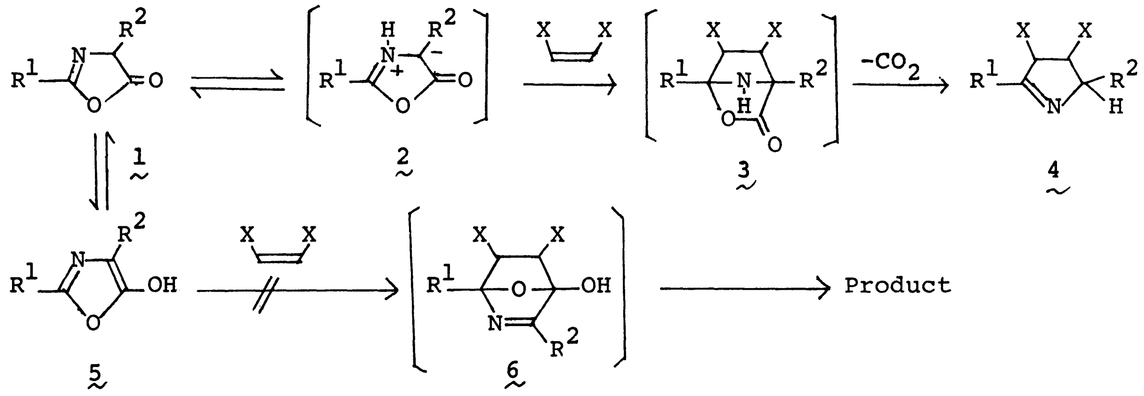
Various 5-trimethylsiloxyoxazoles were synthesized by the silylation of 2-oxazolin-5-ones using chlorotrimethylsilane and triethylamine in high yields. Diels-Alder reaction of the siloxyoxazoles with N-phenylmaleinimide or dimethyl maleate afforded the corresponding substituted pyridines in high yields. This method was applied to the synthesis of Vitamin B_6 derivatives starting from N-formylalanine.

Oxazoles have been known to react as diene components$^{1)}$ of Diels-Alder reaction and were used as intermediates for the synthesis of substituted furans$^{1,2)}$, pyrroles$^{3)}$, and pyridines$^{1,4-6)}$. Especially, 5-alkoxy-4-methyloxazole$^{4)}$ is well known as an important starting material for the synthesis of Vitamin $B_6$$^{1,2)}$.

On the other hand, 2-oxazolin-5-ones (1), which can be easily prepared from acylamino acids in good yields$^{7)}$, have been reported to react with dipolarophile to give 1-pyrroline derivatives (4) through the meso-ionic tautomer (2)$^{8)}$. In this reaction, the Diels-Alder adduct (6) or its decomposition product was not found.



Recently, we found that unsaturated γ-lactones were silylated to give 2-trialkylsiloxyfurans in high yields9). In this connection, we studied the silylation of 2-oxazolin-5-ones (1), which are considered to be aza-analogues of unsaturated γ-lactones, with the expectation that 1 can be fixed to the type of compounds (5)10) which give rise to Diels-Alder reaction. In this paper, we will describe the synthesis of 5-trimethylsiloxyoxazoles and their Diels-Alder reaction.

Silylation of 2-oxazolin-5-ones (1) to 5-trimethylsiloxyoxazoles (8) was easily performed using chlorotrimethylsilane and triethylamine. A typical procedure is as follows (Method A). Triethylamine (1.18 g, 11.64 mmol) and chlorotrimethylsilane (1.27 g, 11.64 mmol) were added to a solution of 4-benzyl-2-methyl-2-oxazolin-5-one (2.00 g, 10.6 mmol) in dry ether (30 ml) at 0 °C under argon atmosphere. The mixture was allowed to warm to room temperature and stirred for 4 h. Triethylammonium chloride was filtered off and the salt was washed with dry ether (30 ml) under argon atmosphere. After evaporation of ether, excess triethylamine and chlorotrimethylsilane, 4-benzyl-2-methyl-5-trimethylsiloxyoxazole was obtained by distillation in 94% yield (2.60 g). This material is sufficiently pure to use for the next step, though it contained a small amount of triethylammonium chloride, which can be removed by redistillation. In a similar manner, 2,4-dimethyl- and 4-isopropyl-2-methyl-5-trimethylsiloxyoxazoles were synthesized.

On the other hand, such 2-oxazolin-5-ones as they have no substituent on position 2 or 4 are unstable and difficult to isolate. In these cases, we obtained the corresponding siloxyoxazoles by the following procedure (Method B). To a 1,2-dimethoxyethane solution (120 ml) of N-formylalanine (4.68 g, 0.04 mol) and triethylamine (16.16 g, 0.16 mol), ethyl chloroformate (4.36 g, 0.04 mol) was added at 0 °C and stirred for 3 h at room temperature. Then chlorotrimethylsilane (9.59 g, 0.09 mol) was added to the mixture at 0 °C and stirred overnight. Triethylammonium chloride was filtered off under argon atmosphere and the filtrate was distilled to give 4-methyl-5-trimethylsiloxyoxazole, 4.98 g (73%).

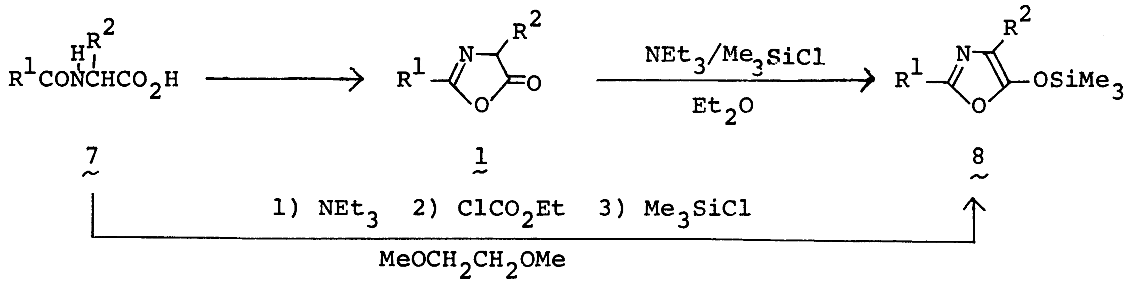
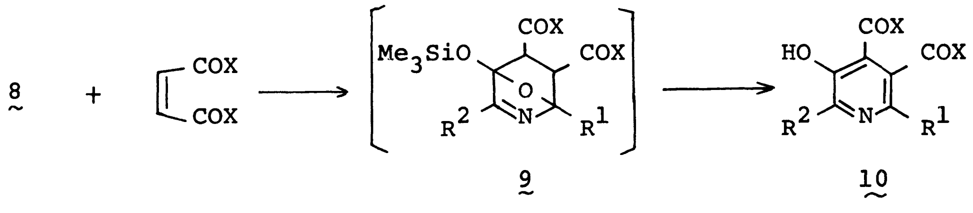


Table 1. Synthesis of 5-Trimethylsiloxyoxazoles

	R^1	R^2	Method$^{a)}$	Bp(°C/mmHg)	Yield(%)
8a	Me	CH_2Ph	A	94-95/4.8×10^{-2}	94$^{b)}$
8b	Me	Me	A	77-79/22	90$^{b)}$
8c	Me	$CHMe_2$	A	96-97/21	92$^{b)}$
8d	Ph	H	B	102/2	67$^{c)}$
8e	H	Me	B	70-71/20	73$^{c)}$

a) See text. b) Based on 2-oxazolin-5-one. c) Based on acylamino acid.

Next, we examined the Diels-Alder reaction of 5-trimethylsiloxyoxazoles with N-phenylmaleinimide or dimethyl maleate. Preliminary experiments showed that the Diels-Alder adducts (9) were unstable to isolate, so without isolation the adducts were decomposed using silica gel. Thus the corresponding pyridine derivatives were obtained in high yields. By this method, Vitamin B_6 derivatives (10d and 10e) were successfully synthesized.



The following experiment provides a typical procedure for the synthesis of substituted pyridines. A mixture of 4-methyl-5-trimethylsiloxyoxazole (342 mg, 2 mmol) and dimethyl maleate (432 mg, 3 mmol) was heated at 140 °C for 4 h under argon atmosphere. Then the mixture was cooled and poured onto silica gel (10 g). After 4 h at room temperature, the decomposition product was eluted with ether from silica gel and was purified by TLC (benzene:acetone=20:1) to give white crystals of dimethyl 5-hydroxy-6-methyl-3,4-pyridinedicarboxylate, 377 mg (83%), mp 139-140 °C (lit.[11]) 138-140 °C).

Table 2. Synthesis of 5-Hydroxy-3,4-pyridinedicarboxylic Acid Derivatives[12)]

Pyridine Deriv.			Dienophile		Solvent	Temp(°C)	Time(h)	Yield(%)	Mp(°C)
	R^1	R^2	X	X					
10a	Me	CH_2Ph	>NPh		Benzene	0-rt	15	87	oil
10b	Me	Me	>NPh		Benzene	0-rt	15	90	203-204(dec)
10c	Me	$CHMe_2$	>NPh		None	0-rt	1	92	101-103.5
10d	H	Me	>NPh		None	0-rt	1	89	190(dec)
10e	H	Me	OMe	OMe	None	140	4	83	139-140

References and notes

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(Received December 4, 1978)