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Nitrene-promoted α-Alkoxylation of Amides with Silyl Ethers

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Thermolysis of a solution of amides, silyl ethers, and ethyl azidoformate caused the introduction of several alkoxy groups into the positions adjacent to the amide nitrogen.

The introduction of oxygen functionalities into an α-position of amino compounds affords attractive synthetic intermediates; such transformation has been so far performed by using peroxides,1) electrochemical oxidation,2) and metal-catalyzed reactions.3) The previously proposed methods, however, have been limited to the introduction of only some special oxygen functionalities. A nitrene inserts into a C(α)-H bond of ethers and thus constitutes an alternative tool for the preparation of α-oxygenated amino compounds.4) We have recently found that the reaction of a nitrene with a mixture of amides and silyl ethers does not bring about α-amination of the silyl ethers, unlike the reaction with ethers, but α-alkoxylation of the amides. Silyl ethers having the functional groups susceptible to oxidation or metal-catalyzed reaction may also be used.

A solution of 1-(trimethylsilyloxy)pentane (1a) (3 mmol) and ethyl azidoformate (2.5 mmol) in DMF (2j) (5 cm^3) was heated at 120 °C until evolution of nitrogen gas ceased (2 h). Then, DMF was removed in vacuo and purification of the residue by preparative TLC (ether) afforded N-methyl-N-(pentyloxymethyl)formamide (3aj) (1.14 mmol). Also formed were N,N-dimethyl-N'-(ethoxycarbonyl)urea (0.63 mmol) as an insertion product of the nitrene into the formic C-H bond of DMF and ethyl N-pentyloxycarbamate (0.28 mmol) derived from the attack of the nitrene onto an oxygen atom of 1a. Heating 1a in DMF at 120 °C in the absence of ethyl azidoformate did not form 3aj at all. Both the acetophenone-sensitized photoreaction generating the triplet azido or nitrene5) and heating 1a in DMF at 110 °C in the presence of AIBN as a radical initiator were not effective. Thus, a radical pathway via the triplet nitrene may be less possible. A sequence of the attack of singlet nitrene onto the oxygen atom of silyl ethers and migration of the silyl group is presumable because the thermolysis of ethyl azidoformate in 1a afforded ethyl N-pentyloxy-N-trimethylsilylcarbamate, which, in turn, gave 3aj on heating at 120 °C in DMF.

The results of reaction of silyl ethers and amides in the presence of ethyl azidoformate are shown in Table 1.

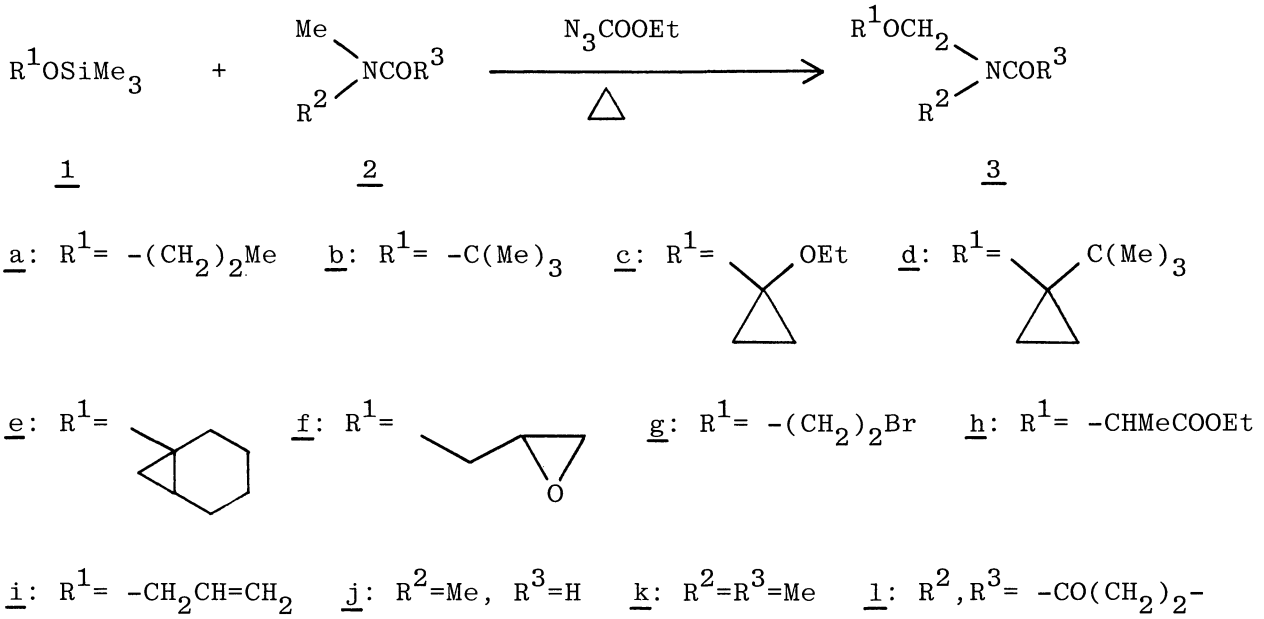

Table 1. α-Alkoxylation of Amides with Silyl Ethers

3	aj	ak	bk	bl	cj	ck	dk	ek	fk	gk	hk	ik
Yield/%[a)]	38	41	51	40	47	54	53	49	45	44	47	22

a) Isolated yields based on silyl ethers.

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