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A Simple Preparation of N-Protected α-Amino Esters with α,α-Disubstituents from Ethyl Azidoformate and Ketene Silyl Acetals

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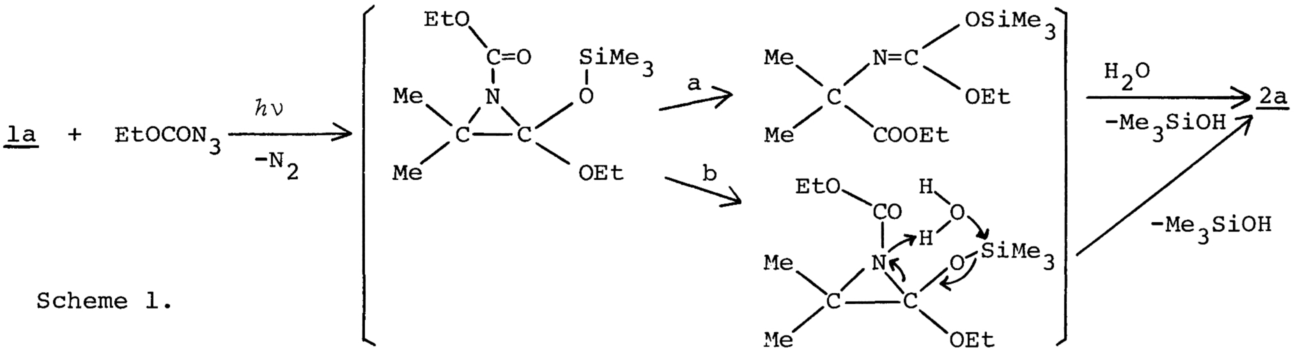
The photolysis of ethyl azidoformate in CH_3CN containing ketene silyl acetals afforded N-ethoxycarbonyl α-amino esters with α,α-disubstituents in one step.

Ethoxycarbonylnitrene (EtOCON) generated from ethyl azidoformate under thermolytic or photolytic conditions is known to perform usually electrophilic insertion and addition reactions. Thus, ethoxycarbonylnitrene has been hardly ever known to insert into the α-C-H bond of the oxycarbonyl group to afford α-amino acid derivatives. The ester can be readily converted to ketene silyl acetal[1)] which is an electron-rich olefin and known to undergo electrophilic addition.[2-4)] We wish to report here our results that ethyl azidoformate reacts with ketene silyl acetals to afford N-protected α-amino esters with α,α-disubstituents in one step. Although a variety of methods to prepare α-amino acid derivatives have been proposed, only a few methods seem to have been applied to the preparation of those with α,α-disubstituents.[5)]

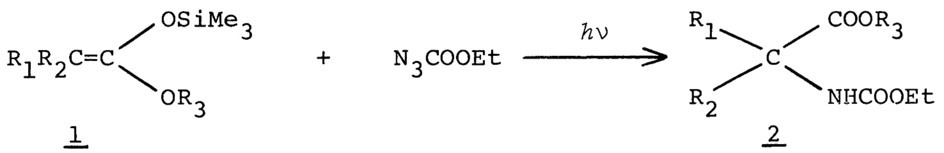
Ethyl azidoformate was first thermolyzed at 120 °C for 3 h in DMF solution containing ketene silyl acetal (1a), but the α-amino ester derivative was not produced and decomposition of 1a resulted instead. Then, photolysis of ethyl azidoformate in CH_3CN containing 1a was investigated and realized the production of the α-amino ester derivative (2a) although the use of a large quantity of the solvent (CH_3CN) led to only ethyl carbamate, a hydrogen abstraction product of ethoxycarbonylnitrene, and recovery of 1a. The typical experimental procedure is as follows. A solution composed of ethyl azidoformate (2 mmol), 1a (5 mmol), and CH_3CN (1 ml) was irradiated with low-pressure mercury lamp until 1 mmol of N_2 gas had been evolved. Then, the reaction mixture was poured into water and extracted with ether. After evaporation of ether, the residue was subjected to silica-gel column chromatography (CCl_4-Et_2O, 1:1) to afford 2a (1.5 mmol). ^1H-NMR, IR, and mass spectra were in accordance with the assigned structure. As for the mechanism of the direct formation of 2a by the photoreaction of ethyl azidoformate with 1a, a pathway proceeding via the aziridine intermediate as shown in Scheme 1 might be operative because Tardella et al proposed a similar reaction sequence for the production of α-amino ketone derivatives by the thermoreaction of ethyl azidoformate with enol silyl ethers[6)] and ketene silyl acetals are known to undergo cycloaddition with chloromethylcarbene to form cyclopropane derivatives.[2,3)] However, the photoreaction of 1a with phenyl azide afforded also the α-amino ester derivative and thus possibility of the other pathway (e.g., b route) than that via the imino intermediate (a route) as proposed by Tardella et al may not be excluded.



Scheme 1.

The results of the photoreaction of several ketene silyl acetals with ethyl azidoformate are shown in Table 1. The ketene silyl acetal functionality seems to be highly nitrenophilic because the functional groups reactive to nitrene such as vinyl, phenyl, or ether are transferred intactly into α-amino ester derivatives (Table 1, 1c-f). The photoreaction of the ketene silyl acetal possessing a vinylic hydrogen (1g) with ethyl azidoformate failed to afford any α-amino ester derivative because of photolability of 1g and gave ethyl carbamate instead.

Table 1. Photoreaction of ethyl azidoformate with ketene silyl acetals



	R_1	R_2	R_3	Yield of 2 / %[a)]
a	Me	Me	Et	75
b	$-(CH_2)_5-$		Et	57
c	Me	Ph	Me	63
d	Me	CH_2Ph	Et	66
e	Me	$CH_2CH=CH_2$	Et	70
f	Me	$CH(Me)OSiMe_3$	Et	45
g	H	n-Bu	Et	0

a) Yield after isolation by silica-gel column chromatography.

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