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The Photochemical and Thermal Reaction of Ethyl Azidoformate with Cyclohexanone Ethylene Acetal

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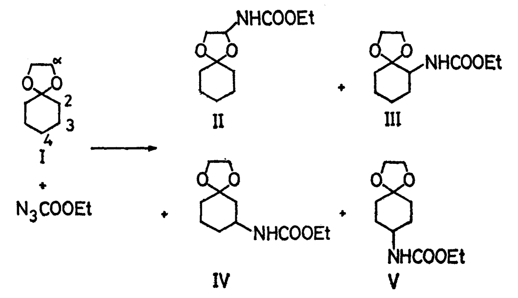
Ethoxycarbonylnitrene reacts regioselectively with cyclic ethers to afford α-C–H insertion products.[1] Radical species and/or oxygen-imine intermediates have been proposed[1,2] as the explanation of the selectivity. In order to obtain further information on this problem, we have examined the reactions of ethoxycarbonylnitrene with cyclohexanone ethylene acetal (I) which has four kinds of methylene groups.

Ethyl azidoformate in I was decomposed photochemically or thermally; the products shown in Scheme 1 were then collected by distillation and preparative gas chromatography (GC). Since the separation of II by preparative GC was not satisfactory, the isomer was isolated by the selective acid hydrolysis of the crude products and by subsequent preparative GC. The regioisomers, III, IV, and V, were identified by comparing them with authentic samples prepared by the acetalization of the corresponding amino ketone. *N*-Ethoxycarbonyl-2-aminocyclohexanone (VI) was obtained by the DMSO-oxidation of 7-ethoxycarbonyl-7-azanorcarane.[3] *N*-Ethoxycarbonyl-3-,[4] and 4-aminocyclohexanone (VIII and X) were prepared by the hydrogenation of ethyl 3- and 4-hydroxycarbanilate, followed by chromic oxidation.



Scheme 1

The reaction conditions and product distributions are summarized in Table 1. The direct photolysis[5] gave a fair amount of V. This may be ascribed to the transition state XIc, arising from the boat-form conformation of an oxygen-imine XI, or simply to the singlet nitrene. Meanwhile, the formation of III and IV can be understood in terms of the intermediacy of the oxygen-imine reaction *via* the two transition states of XIa and XIb. The yield of II increased both in the dilution experiment and, more especially, in the acetophenone-sensitized photolysis. This suggests that a triplet nitrene or a triplet azide attacks the α-methylene of the acetal in a radical sense, producing II *via* a hydrogen abstraction-recombination mechanism. The thermolytic decomposition gave a comparable yield of II, which was, however, absent among the products in the dilution experiment. This may be explained similarly as in the reaction of cyanogen azide with ether.[6] Thus, the acetal oxygen may attack the azide group bimolecularly to form an oxygen-imine intermediate (XI), which may subsequently produce the α-insertion product (II). The dilution

Table 1. Photolysis and thermolysis of ethyl azidoformate in I

Condition	Additive	Yield (%)[a]			
		II	III	IV	V
$h\nu$[b]	——	8.6 (0.17)	24 (0.48)	17 (0.34)	25 (1.0)
	CH_2BrCH_2Br[c]	1.8 (0.95)	1.3 (0.70)	0.46 (0.84)	0.96 (1.0)
	PhCOMe[d]	11.8 (1.4)	3.9 (0.45)	2.7 (0.32)	4.3 (1.0)
Δ[e]	——	9.0 (0.60)	3.2 (0.21)	7.0 (0.45)	7.7 (1.0)
	CH_2BrCH_2Br[c]	trace (0)	5.7 (1.2)	2.3 (0.48)	2.4 (1.0)

a) Determined by GC (Dowfax 9N9 on Neopak 1A, 10%, 3 mm × 2 m, 190°C), with diethyl phthalate as the internal standard. The relative reactivities per methylene are given in parentheses.
b) A solution of ethyl azidoformate (1 mmol) in I (10 m*l*) was placed in a quartz tube and irradiated with a 200 W high-pressure mercury lamp for 40 hr.
c) Dibromoethane (3 m*l*) was added. The products were accompanied by other unidentified by-products.
d) Acetophenone (1 mmol) was added, and the irradiation was effected through a 9% aqueous solution of cupric sulfate (>300 nm) for 50 hr.
e) A mixture of ethyl azidoformate (0.87 mmol) and I (5 m*l*) was heated at 130°C for 3 hr.

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[1] H. Nozaki, S. Fujita, T. Takaya, and R. Noyori, *Tetrahedron*, **23**, 45 (1967).

[2] T. Shingaki, M. Inagaki, N. Torimoto, and M. Takebayashi, *Chem. Lett.*, **1972**, 297.

[3] S. Fujita, T. Hiyama, and H. Nozaki, *Tetrahedron*, **26**, 4347 (1970).

[4] T. Hiyama, H. Taguchi, S. Fujita, and H. Nozaki, This Bulletin, **45**, 1863 (1972).

[5] The direct photolysis of ethyl azidoformate has been reported to generate singlet ethoxycarbonylnitrene mainly, a) D. W. Cornell, R. S. Berry, and W. Lwowski, *J. Amer. Chem. Soc.*, **87**, 3626 (1965). b) W. Lwowski and T. W. Mattingly, Jr., *ibid.*, **87**, 1947 (1965).

[6] "Nitrenes," ed. by W. Lwowski, John Wiley & Sons, New York (1970), p. 342.

Table 2. Physical propertiees of the new compounds

Compound	Mp (°C)[a] [bp (°C/mmHg)]	IR (cm^{-1})[b]	NMR (δ)[c]
II[g]	80—81	3325, 1690, 1550	1.0—1.8 (m+t, 13H), 3.5—4.4 (m+q, 4H), 5.1—5.8 (m, 2H)
III[h]	60—61	3325, 1686, 1540	0.9—2.1 (m+t, 11H), 3.4—4.3 (m+q, 7H), 4.4—4.9 (br d, 1H)
IV[i]	[110—120/0.15]	3325, 1698, 1524[d]	0.9—2.1 (m+11H), 3.6—4.2 (s+q+m, 7H), 5.1—5.5 (br d, 1H)
V[j]	95—96[e]	3350, 1700, 1530	1.1—2.2 (m+t, 11H), 3.3—3.8 (m, 1H), 3.87 (s, 4H), 4.05 (q, 2H), 4.6—5.1 (br d, 1H)
VIII[k]	[140/2][f]	3325, 1705, 1690, 1530[d]	1.0—3.0 (m+t, 11H), 3.4—4.2 (m+q, 3H), 5.8—6.2 (br d, 1H)
X[l]	85—86	3340, 1710, 1685, 1545	0.9—2.6 (m+t, 11H), 3.5—4.4 (m+q, 3H), 4.9—5.6 (br s, 1H)

a) From *n*-hexane. b) KBr. c) Carbon tetrachloride solution. d) Neat. e) From benzene–*n*-hexane.

f) Bath temperature.

g) MS: *m/e* (relative abundance) 229 (M^+, 4), 186 (5), 141 (15), 131 (100), 114 (63), 112 (32), 69 (30), 59 (28), 55 (94). Found: C; 57.4, H; 8.3, N; 6.1%. Calcd for $C_{11}H_{19}NO_4$: C; 57.6, H; 8.4, H; 6.1%.

h) MS: *m/e* (relative abundance) 229 (M^+, 10), 186 (4), 141 (9), 113 (7), 99 (100), 86 (19). Found: C; 57.3, H; 8.4, N; 6.2%. Calcd for $C_{11}H_{19}NO_4$: C; 57.6 H; 8.4, N; 6.1%.

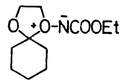
i) MS: *m/e* (relative abundance) 229 (M^+ 10), 186 (83), 141 (100), 129 (21), 113 (26), 99 (60), 86 (87). Found: C; 57.5, H; 8.5, N; 6.0%. Calcd for $C_{11}H_{19}NO_4$: C; 57.6, H; 8.4, N; 6.1%.

j) MS: *m/e* (relative abundance) 229 (M^+, 4), 142 (24), 100 (17), 99 (100), 86 (43), 55 (15). Found: C; 57.5, H; 8.4, N; 6.2%. Calcd for $C_{11}H_{19}NO_4$: C; 57.6, H; 8.4, N; 6.1%.

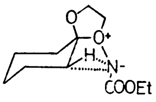
k) MS: *m/e* (relative abundance) 185 (M^+, 9), 156 (57), 128 (79), 115 (52), 114 (46), 96 (84), 56 (98), 43 (100). Found: C; 58.1, H; 8.0, N; 7.8%. Calcd for $C_9H_{15}NO_3$: C; 58.4, H; 8.2, N; 7.6%.

l) MS: *m/e* (relative abundance) 185 (M^+, 2), 156 (3), 128 (36), 96 (100), 90 (92), 84 (32), 56 (69). Found: C; 58.3, H; 8.4, N; 7.6%. Calcd for $C_9H_{15}NO_3$: C; 58.4, H; 8.2, N; 7.6%.

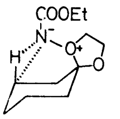
with dibromoethane disfavors the formation of the oxygen-imine (XI) and, consequently, that of II.



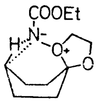
XI



XIa



XIb



XIc

Experimental

Table 2 lists the physical properties of the new compounds.

Photolysis of Ethyl Azidoormate in I. Ethyl azidoformate (2.60 g, 22.6 mmol) and cyclohexanone ethylene acetal (44 m*l*) were irradiated for 20 hr. The recovery of the excess acetal, followed by distillation at 122—143°C/0.18 mmHg, gave a mixture of II, III, IV, and V (0.99 g). The isolation of IV and V was effected by preparative GC (Silicone SE 30, 30%, 6 mm × 1 m, 150°C.)

Isolation of II. A mixture (3.6 g) of the products obtained as has been described above was dissolved in ether (150 m*l*), and the solution was shaken with 10% hydrochloric acid (140 m*l*) for 5 min, washed with water, neutralized with aqueous sodium bicarbonate, and dried over anhydrous sodium sulfate. Concentration and distillation then yielded crude II (0.69 g). The hydrolysis was repeated, and the pure sample was obtained by preparative GC.

Thermolysis of Ethyl Azidoformate in I. A mixture of ethyl azidoformate (1.05 g, 9.1 mmol) and I (5 m*l*) was added, drop by drop (over 40 min), to I (15 m*l*) at 120°C under a nitrogen atmosphere, and thereafter heating was continued for 3 hr. Concentration and distillation gave a mixture of II, III, IV, and V (1.16 g). The separation of each component was effected as has been described above.

N-*Ethoxycarbonyl-3-aminocyclohexanone (VIII).* Ethyl 3-hydroxycarbanilate (10.7 g, 59 mmol), Raney nickel (W-2) (3 g), and ethanol (150 m*l*) were heated at 175—190°C in an autoclave under a hydrogen atmosphere (110 kg/cm^2) for 2 days. The subsequent filtration of the catalyst and evaporation of the solvent yielded VII as a viscous oil (9.8 g, 89%). IR (neat): 3300, 1690, 1540 cm^{-1}. MS: *m/e* 187 (M^+).

A mixture of sodium dichromate dihydrate (6.0 g), concentrated sulfuric acid (5 m*l*), and water (30 m*l*) was added, drop by drop, to a solution of VII (9.8 g) in ether (50 m*l*) at 0°C, and subsequently 20% sulfuric acid (5 m*l*) was added. After stirring for 2 hr, the ether layer was separated, washed with water, and dried (sodium sulfate). Concentration and distillation gave VIII[4] (3.13 g, 32%).

The hydrogenation of ethyl 4-hydroxycarbanilate was performed as has been described above to afford IX in a quantitative yield. IR (Nujol): 3330, 1695, 1540 cm^{-1}. The chromic oxidation of IX, followed by distillation, gave X (27% yield).

Acetalization of VI. A mixture of VI (0.24 g), ethylene glycol (2.0 m*l*), boron trifluoride etherate (0.5 m*l*), and dichloromethane (5 m*l*) was stirred at room temperature for a day. The mixture was then poured into water (100 m*l*), extracted with ether, washed with aqueous sodium bicarbonate, and dried over anhydrous sodium sulfate. Concentration and preparative layer chromatography on silica gel (benzene) gave III (0.113 g, 38%).

The acetalization of VIII and X afforded IV and V in 25 and 44% yields respectively.

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