OXAZOLES IN ORGANIC SYNTHESIS: SOME OBSERVATIONS ON THE USE OF 5-ALKOXYOXAZOLES IN THE DIELS-ALDER PROCESS

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The preparation and Diels-Alder reactivity of 5-ethoxy-2-carboethoxyoxazole and its derivatives have been examined. As a consequence of this investigation, a simple procedure for the preparation of 5-ethoxyoxazole has been discovered.

In the 1900's Kondrat'eva demonstrated that oxazoles could undergo the Diels-Alder reaction to provide substituted pyridines.[2] These not fully aromatic heterocycles thus serve as azabutadiene components for the 4+2 cycloaddition process.[3] Oxazoles have found extensive application in the synthesis of pyridoxine[4] and most recently in the synthesis of the antitumor agent ellipticine.[5]

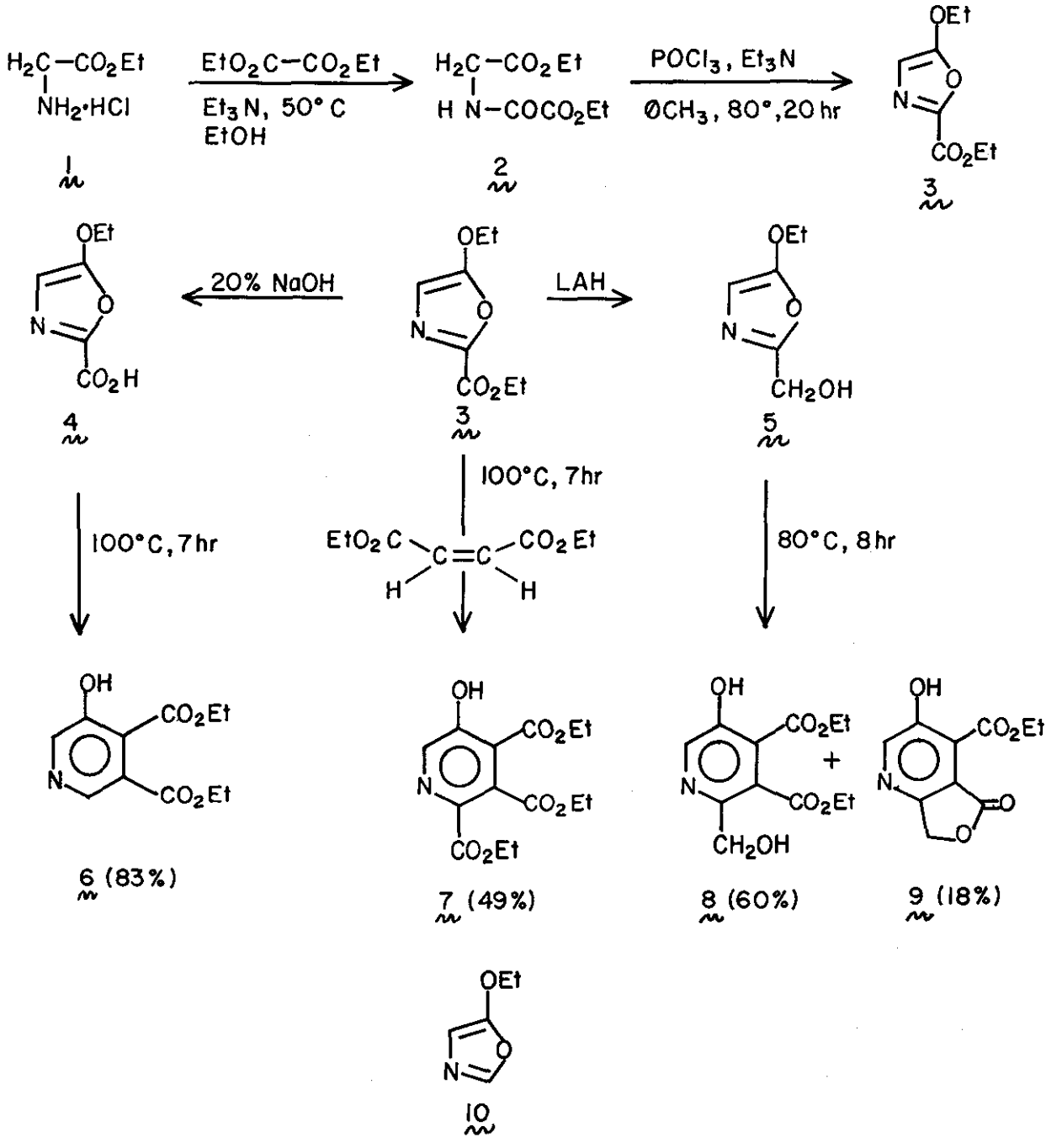
In examining the use of these heterocycles for the preparation of other target structures, we have prepared the previously unknown 5-ethoxy-2-carboethoxyoxazole (3) and its derivatives 4 and 5. Compound 3 was obtained in 58% yield as a semisolid by the phosphorous oxychloride cyclodehydration of ethyl N-ethoxalylglycinate (prepared by heating ethyl glycinate hydrochloride with diethyl oxalate and triethylamine in ethanol at 50°C for 20 hr).[6] Hydrolysis

of 3 to acid 4 (mp 96-98°C, decomp) was accomplished with 20% aqueous sodium hydroxide. Treatment of 3 with lithium aluminum hydride in ether (0° → 25°C) afforded alcohol 5.

The Diels-Alder capacity of these three oxazole derivatives was examined with diethyl maleate as the test dienophile. While all three compounds underwent cycloaddition without solvent in Kimax culture tubes under the conditions presented in the accompanying scheme to provide pyridines 6-9 [compound 6 was purified by bulb-to-bulb distillation (160-170°C oven temperature, 1 mm); compounds 7-9 were purified by silica gel chromatography with CH_2Cl_2-Et_2O-MeOH (10:10:0.1) as eluent], it was surprising to find that the acid 4 reacted at a rate roughly comparable to that of the more electron rich oxazole 5 to afford the decarboxylated pyridine 6.

While previous reported studies with related carboxy bearing oxazoles do not provide sufficient information to define the stage at which decarboxylation takes place, our observations of the relative reactivities of 3, 4 and 5 clearly seemed to indicate that CO_2 loss must occur prior to cycloaddition rather than after formation of the pyridine ring.

The solid acid 4 was thus heated in a sealed tube without solvent at 100°C for 30 min. ^1H nmr analysis of the resulting liquid revealed that 5-ethoxyoxazole (10) had formed in near quantitative yield. Further reaction of 10 with diethyl maleate generated 6 in amounts comparable to that obtained from direct reaction of 4 with this dienophile.[7]


H2C–CO2Et
NH2·HCl
1
EtO2C–CO2Et
Et3N, 50° C
EtOH
H2C–CO2Et
H N–COCO2Et
2
POCl3, Et3N
ØCH3, 80°, 20 hr
OEt
N
O
CO2Et
3
20% NaOH
CO2H
4
LAH
CH2OH
5
100°C, 7hr
EtO2C
CO2Et
H
H
100°C, 7hr
80°C, 8hr
OH
6 (83%)
7 (49%)
8 (60%)
+
9 (18%)
10

These studies thus reveal that published routes to the pyridoxines through 5-alkoxyoxazolecarboxylic acids actually proceed through the 5-alkoxyoxazoles. This finding does, moreover, serve to define an alternative method for the preparation of 2-unsubstituted-5-alkoxyoxazoles, compounds which have been prepared previously only through a rather troublesome and low yield procedure involving the dehydration of N-formyl derivatives of α-aminoacid esters.[8]

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References and Footnotes

1. On leave from Showa College of Pharmaceutical Sciences, Setagaya-ku, Tokyo 154, Japan.
2. G. Ya. Kondrat'eva, Khim. Nauk i Prom. 1957, 2, 666; Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk, 1962, 525.
3. For recent reviews of oxazole chemistry, see R. Lakhan and B. Ternai, "Advances in Heterocyclic Chemistry", ed. by A. R. Katritzky and A. J. Boulton, Vol. 17, Academic Press, New York, 1974, pp 99-211, and I. J. Turchi and M.J.S. Dewar, Chem. Rev., 1975, 75, 389.
4. R. A. Firestone, E. E. Harris, and W. Reuter, Tetrahedron, 1967, 23, 943; P. F. Muhlradt, Y. Marino, and E. E. Snell, J. Med. Chem., 1967, 10, 341.
5. A. P. Kozikowski and N. M. Hasan, J. Org. Chem., 1977, 42, 2039.

6. I. Maeda, M. Takehara, K. Togo, S. Asai and R. Yosida, Bull. Chem. Soc. Jap. 1969, 42, 1435.

7. All compounds reported had spectroscopic properties consistent with their assigned structures.

8. For an efficient synthesis of a 5-ethoxycarbonyloxy-oxazole, see M. Murakami and M. Iwanami, Bull. Chem. Soc. Jap. 1968, 41, 726.

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