Pyrolytic Rearrangement of Oxazolines. Preparation of N-Allyl Amides

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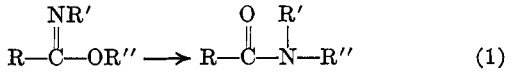
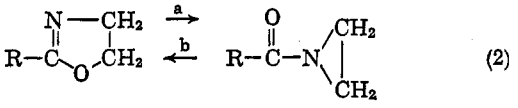
N-Substituted imidates undergo the Chapman rearrangement[1] on heating to yield N,N-disubstituted amides (eq. 1). The successful application of this



(1)

reaction to an oxazoline, a cyclic imidate, would result in a cyclic N,N-disubstituted amide (aziridine) (eq. 2a). This route to an aziridine has not been reported

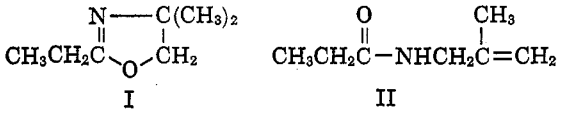


(2)

in the literature. At least two examples of the reverse reaction (eq. 2b) have been reported,[2] namely, the conversion of N-benzoylaziridine to 2-phenyl-2-oxazoline, and the conversion of N-benzoyl-*cis*-cyclohexenimine to *trans*-2-phenyl-4,5-tetramethylene-2-oxazoline. In these instances at least the oxazoline is apparently the more stable isomer.

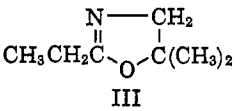
The results of an attempt to bring about reaction 2a are described in this report.

Heating of 2-ethyl-4,4-dimethyl-2-oxazoline (I) at >500° gave a product identified as N-methallylpropionamide (II). This identification was made by analysis, infrared spectroscopy, and by hydrolysis to methallylamine. The N-methallylpropionamide was further characterized by conversion to 2-ethyl-5,5-dimethyl-2-oxazoline (III). N-Acylated allylamines were also obtained by pyrolysis of 2-phenyl-4,4-dimethyl-2-oxazoline and 2,4-dimethyl-2-oxazoline. A temperature of 500–600° is required. Yields of 44–90% were obtained.



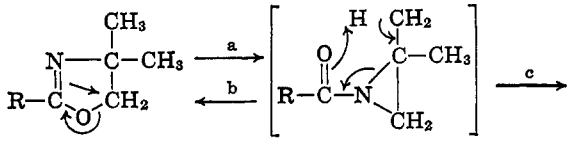
I

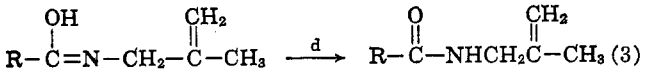
II



III

This rearrangement of oxazolines possibly proceeds *via* the N-acylaziridine as follows.





(3)

(1) R. Royer and D. G. Neilson, *Chem. Rev.*, **61**, 190 (1961).

The isomerization of acylated 2,2-dialkylaziridines to N-acylmethallylamines (eq. 3c,d) was first reported by Fanta[3] and was subsequently extensively investigated by Fanta and others.[4] This reaction proceeds at a temperature much lower than that required for the pyrolytic rearrangement of the oxazolines. It should be noted, however, that 1-acetyl-2-methylaziridine reportedly does not rearrange readily to N-allylacetamide at the reflux temperature nor at higher temperatures under pressure.[3] This is in contrast to the successful rearrangement of 2,4-dimethyl-2-oxazoline to N-allylacetamide.

Experimental[5]

Oxazolines.—The preparation of 2-ethyl-4,4-dimethyl-2-oxazoline and 2-phenyl-4,4-dimethyl-2-oxazoline is described in a previous publication from this laboratory.[6] 2,4-Dimethyl-2-oxazoline was obtained as a colorless liquid, b.p. 111–113.5° (lit.[7] b.p. 116–117°), in a yield of 60% by interaction of acetic acid and 2-amino-1-propanol with azeotropic removal of water.

Pyrolyses. Method A.—The oxazoline was dropped at a fairly steady, manually controlled rate through a vertical 1-in.-diameter Vycor tube filled with glass beads and heated for 12 in. of its length by a furnace. A thermocouple well extended through the center of the tube from the top. Dry nitrogen gas was passed downward through the system throughout a run. The products were collected in a water-cooled receiver and two Dry Ice cooled traps connected in series. The reaction temperatures reported are approximately the maximum attained in the tube, this occurring near the center of the heated zone.

Method B.—The oxazoline was heated in a flask attached to the bottom of the reaction tube described above. Some of the vapors condensed and returned directly to the flask. Materials passing through the tube were deflected to one side, condensed, and returned to the flask by a side tube extending below the surface of the refluxing liquid. Dry nitrogen gas was passed through the system throughout a run. Gases that passed out through the top of the water-cooled condenser were conducted through Dry Ice cooled traps and then were vented. The reaction was continued until the reflux temperature increased to the level desired. The combined overhead and residue mixture was distilled, and the products were suitably identified. The reaction temperatures reported are approximately the maximum attained in the tube, this maximum occurring about 1 in. below the top of the heated zone.

Pyrolysis of 2-Ethyl-4,4-dimethyl-2-oxazoline. N-Methallylpropionamide (II). Method A.—From 344.7 g. of the oxazoline (neut. equiv.[8] 130) passing through the reactor in 6.4 hr. at 540° there was obtained 339 g. of material with neut. equiv. 161. Then 334 g. of this material was again passed through the reactor in 6.2 hr. at 560° to yield 323 g. of material with neut. equiv. 263. Distillation yielded 146 g. of recovered oxazoline I and 135 g. of amide II, b.p. 135–142° (20 mm.), for an oxazoline conversion of 56% and an amide yield of 71%.

Anal. Calcd. for N-methallylpropionamide, $C_7H_{13}NO$: N, 11.01; iodine no., 199.6. Found: N, 11.20; iodine no., 193.8, 193.7.

Method B.—An 85% yield of amide at a 78% conversion of oxazoline was obtained at a reactor temperature of 565°. The reflux temperature increased from 133 to 180° in 6.8 hr.

(2) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895); A. A. Goldberg and W. Kelley, *J. Chem. Soc.*, 1919 (1948); F. Winternitz, M. Mousseron, and R. Dennilauler, *Bull. soc. chim. France*, 382 (1956).

(3) P. E. Fanta, U. S. Patent 2,766,232 (1956); *J. Org. Chem.*, **23**, 72 (1958).

(4) P. B. Talukdar and P. E. Fanta, *ibid.*, **24**, 526 (1959); H. W. Heine, M. E. Felter, and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959); D. V. Kashelikar and P. E. Fanta, *ibid.*, **82**, 4930 (1960); H. W. Heine, *Angew. Chem., Intern. Ed. Engl.*, **1**, 528 (1962); P. E. Fanta, L. J. Pandya, W. R. Groskopf, and H. Juang Su, *J. Org. Chem.*, **28**, 413 (1963).

(5) Boiling and melting points are uncorrected. Melting points were determined with a Fisher-Johns apparatus.

(6) H. L. Wehrmeister, *J. Org. Chem.*, **28**, 2587 (1963).

(7) R. Oda, M. Okano, S. Tokeura, and F. Misumi, *Bull. Chem. Soc. Japan*, **35**, 1219 (1962); *Chem. Abstr.*, **57**, 12454 (1962).

(8) The neutralization equivalents of the oxazolines were determined by potentiometric titration with perchloric acid using acetic acid as a solvent.

Methallylamine.—Hydrolysis of the amide obtained by both methods A and B yielded methallylamine which was identified by the preparation of a picrate, m.p. 204–206° (lit. m.p. 202.5–204.5°,[3] 202–206°[9]), and a phenylthiourea derivative, m.p. 76–77° (lit.[3] m.p. 78–79°), and by benzoylation to N-methallylbenzamide, m.p. 66–67° (lit.[3] m.p. 69.5–70.5°).

2-Ethyl-5,5-dimethyl-2-oxazoline (III).—An 18.5-g. portion of amide product obtained by method B, b.p. 130–135° (20 mm.), was added to 25 ml. of concentrated H_2SO_4 with stirring and cooling (temperature kept at 30–35°) in 15 min. The mixture was then poured onto 200 g. of crushed ice. Sodium hydroxide (40 g.) and water (50 ml.) were added (ice bath cooling), and the mixture was extracted with three 50-ml. portions of ether. Distillation of the dried extract gave 9.0 g. of 2-ethyl-5,5-dimethyl-2-oxazoline, b.p. 139–144° (lit.[3] b.p. 141°).

Anal. Calcd. for $C_7H_{13}NO$: N, 11.01; neut. equiv., 127.2. Found: N, 11.05; neut. equiv., 129.0.

A picrate of this material, m.p. 144–146° (lit.[3] m.p. 147–149°), was shown to differ from the picrate, m.p. 151–154°, of 2-ethyl-4,4-dimethyl-2-oxazoline by mixture melting point (123–128°).

Pyrolysis of 2-Phenyl-4,4-dimethyl-2-oxazoline. N-Methallylbenzamide.—N-Methallylbenzamide, b.p. 113–117° (0.05 mm.), was obtained in a 21% yield (based on oxazoline charged) by pyrolysis of 2-phenyl-4,4-dimethyl-2-oxazoline at 597° using method A.

Pyrolysis of the oxazoline at 559° by method B but at reduced pressure (50 mm.) gave a 79% yield of amide (28% oxazoline conversion), b.p. 136–142° (1 mm.), in 26.5 hr. The reflux temperature rose from 152 to 159.5°. Analysis of the product by gas chromatography indicated a purity of 93.5%.

Anal. Calcd. for N-methallylbenzamide, $C_{11}H_{13}NO$: N, 8.00; iodine no., 144.8. Found: N, 8.09; iodine no., 143.

Similarly prepared material, b.p. 141–143° (1 mm.), was recrystallized from petroleum ether to m.p. 68–69° (lit.[3] m.p. 69.5–70.5°). A mixture melting point with an authentic sample was not depressed.

Pyrolysis of 2,4-Dimethyl-2-oxazoline. N-Allylacetamide.—N-Allylacetamide, b.p. 102–105° (10 mm.), lit.[10] b.p. 113–116° (15 mm.), was obtained in a 44% yield (46% oxazoline conversion by pyrolysis of 2,4-dimethyl-2-oxazoline at 586° using method A.

Anal. Calcd. for N-allylacetamide, C_5H_9NO: N, 14.13; iodine no., 256. Found: N, 14.80; iodine no., 236.

The structure of this impure product was also supported by an infrared spectrum [bands at 3.06 (NH) and at 6.08 μ (C=O)] and by a n.m.r. spectrum [δ 1.97 (CH_3CO), 3.75 (=C-CH_2-N-), 5 (=CH_2), 5.7 (=CH-), and 7.5 (-NH-)]. A slight amount of impurity was also indicated by the presence of small extraneous peaks throughout the n.m.r. spectrum.[11]

(9) R. Adams and T. L. Cairns, *J. Am. Chem. Soc.*, **61**, 2464 (1939).

(10) S. L. Gertler and A. P. Yerington, *U. S. Dep. Agr.*, **ARS-33-14** (1955); *Chem. Abstr.*, **50**, 7111 (1956).

(11) The 60-Mc. n.m.r. analysis and interpretation were supplied by J. L. Holcomb of Varian Associates, Palo Alto, Calif. Deuteriochloroform was used as solvent.

A New Synthesis of α-L-Aspartyl-L-leucine[1]

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The major obstacle to the synthesis of α-aspartyl peptides is the presence of two nonequivalent carboxyl groups. One way of circumventing this difficulty is to utilize a precursor which can be converted under mild conditions to a β-carboxylic acid after formation of the α-peptide bond. The conversion of L-allylglycine (L-2-amino-4-pentenoic acid) to α-aspartyl peptides would afford such a route. As an illustration, α-L-aspartyl-L-leucine has been prepared from *p*-nitrocarbobenzoxy-L-allylglycyl-L-leucine by oxidation with periodate in the presence of catalytic amounts of permanganate.[2] The compound thus prepared is chromatographically pure and is indistinguishable from the product obtained by the condensation of β-benzyl carbobenzoxy-L-aspartate and L-leucine benzyl ester followed by hydrogenolysis.[3]

Coupling reactions with carbobenzoxy- or *p*-nitrocarbobenzoxy-L-allylglycine proceed smoothly either with dicyclohexylcarbodiimide or ethyl chloroformate. The original procedure of Lemieux and Rudloff[2] for the oxidation of unsaturated fatty acids was modified to permit work at higher concentrations. The course of the oxidation can be followed quantitatively by iodimetric titration or qualitatively by the pH rise. The most favorable pH range is between 7 and 9. The rate of oxidation is rapid at 20° in solutions that are 0.1 *M*, 0.025 *M*, and 0.001 *M* with respect to periodate, substrate, and permanganate, respectively. The aspartyl derivatives were isolated either by extraction from the acidified solutions with ethyl acetate or by precipitation from the concentrated aqueous solution after reduction of the excess oxidants with sodium metabisulfite.[4] Yields between 60 and 95% of the theoretical were obtained.

Although the applicability of this approach to other α-aspartyl derivatives has not been studied, certain limitations are inherent in this procedure. Thus, appropriate protective groups are necessary for tyrosine, serine, and threonine. For example, it was found that N-carbobenzoxy-L-tyrosine reacted with permanganate but uptake of oxidant was drastically reduced with O-acetyl-N-carbobenzoxy-L-tyrosine under the conditions used for the oxidation of allylglycine derivatives. However, the carbobenzoxy derivatives of tryptophan, methionine, and cysteine compete with the olefin for oxidant, and peptides containing these amino acids cannot be synthesized directly by the procedure described above.

Experimental[5]

L-Allylglycine was prepared from N-acetyl-DL-allylglycine[6] by the use of hog kidney acylase.[7]

***p*-Nitrocarbobenzoxy-L-allylglycine.**—To 3.8 g. of L-allylglycine in 7.7 ml. of 4 *N* sodium hydroxide at 0° was added with stirring in four portions at 20-min. intervals 8.1 g. of *p*-nitrocarbobenzoxy chloride in 21 ml. of 1,4-dioxane and 10.3 ml. of 4 *N* sodium hydroxide. Stirring was continued for 4 hr. at 0°. The mixture was filtered, the precipitate was discarded, the filtrate was acidified with concentrated hydrochloric acid, and the oil was extracted with ethyl acetate. After washing with water, drying with magnesium sulfate, and evaporating the solvent, the extracts yielded an oil that crystallized from 25 ml. of benzene. After two recrystallizations from benzene, the yield was 6.0 g. (68%), m.p. 81–83°, $[\alpha]^{25}D$ +4.5° (*c* 3.5, dimethyl formamide).

Anal. Calcd. for $C_{18}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.00; H, 4.39; N, 9.82.

(1) Supported in part by a research grant GM 05492 from the National Institutes of Health, Public Health Service.

(2) R. U. Lemieux and E. Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(3) P. M. Bryant, R. H. Moore, P. J. Pimlott, and G. T. Young, *J. Chem. Soc.*, 3868 (1959).

(4) M. Jacobson, M. Beroza, and W. A. Jones, *J. Am. Chem. Soc.*, **83**, 4819 (1961).

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