BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48 (5), 1675—1676 (1975)

Lactone Carboxylic Acids. IX.⁶⁾ Base-Catalyzed Rearrangement of Ethyl α-Hydroxyaminoaconate Leading to the Formation of Isoxazolines

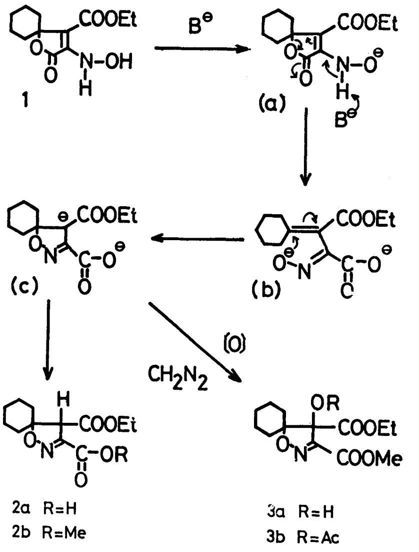
Sigeru Torii, Masasi Ukida, and Hideo Tanaka
Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama 700

(Received December 27, 1974)

Synopsis. The syntheses of 4-ethoxycarbonyl-3-methoxycarbonyl-5,5-pentamethylene-Δ^2-isoxazoline (**2b**) and its 4-hydroxy and 4-acetoxy derivatives (**3a** and **3b**) by the base-catalyzed rearrangement of ethyl γ,γ-pentamethylene-α-hydroxyaminoaconate (**1**) were described.

Several attempts have been made to find the synthetic way in obtaining appropriate Δ^2-isoxazoline-3-carboxylic acids by the reaction of hydroxamic acid with α-ketosuccinic esters,[1] by 1,3-cycloaddition of α-carbonitrile oxides[2] or nitrone esters[3] to olefins, by the condensation of nitroacetic esters,[4] and others.[5] Such compounds are of interest as potential intermediates for the preparation of useful chemicals.[2b,2d,5] We wish to report here a base-catalyzed rearrangement of ethyl γ,γ-pentamethylene-α-hydroxyaminoaconate (**1**)[6] giving the corresponding Δ^2-isoxazolines (**2b, 3a,** and **3b**).

The reaction of ethyl α-hydroxyaminoaconate (**1**) with one equivalent of *n*-butyl lithium in THF at −78 °C afforded the isoxazoline ester **2b** in 84% yield after treating the crude acid **2a** with excess diazomethane and a small amount of **3a** (5.9%). On the other hand, the reaction of two equivalents of *n*-butyl lithium with **1** resulted in **3a** in 63% yield. The hydroxy isoxazoline **3a** could be converted into the corresponding acetate **3b** by the treatment with a mixed solution of acetic anhydride and pyridine. The structures of **2b, 3a,** and **3b** after purifyng by column chromatography are elucidated by PMR, ^{13}C NMR, infrared, and mass spectral analyses together with elemental analyses. The ^{13}C NMR spectra of **2b, 3a,** and **3b** (Fig. 1) provided effective evidences for their structural assignment. The ^{13}C NMR spectrum of **2b** displayed characteristic three bands at δ 149.5 (C=N), 160.7 (carbonyl attached to methoxy group), and 167.0 (carbonyl attached to ethoxy group) and, in addition, the peaks at δ 60.5 (or 61.6) and 93.1 are accounted for the C_4 and C_5 carbon atoms of **2b**. The ^{13}C NMR spectrum of **3a** was almost similar to that of **2b** except for a downfield shift of *ca.* 25 ppm for C_4 of **2b**. The structural relationship between **3a** and **3b** could be assigned reasonably, since the ^{13}C NMR spectrum of **3b** showed two new peaks at δ 21.0 and 164.8 accounted for the acetyl group.



Scheme 1.

A tentative mechanism for the formation of the isoxazolines **2a** and **3a** is outlined in Scheme 1. The mode of the base-catalyzed rearrangement of **1** is assumed to be migration of the electron on nitrogen atom as shown in (**a**) to produce (**b**), which would occur by abstraction of the hydrogen atom attached to the imino group with the

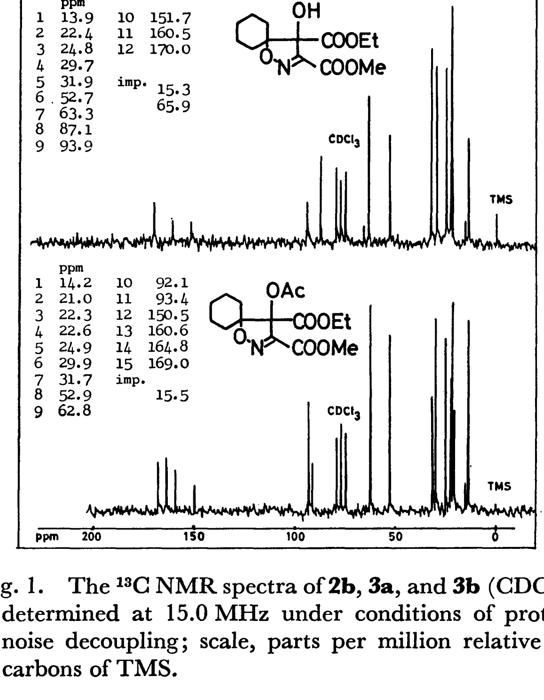


Fig. 1. The ^{13}C NMR spectra of **2b**, **3a**, and **3b** ($CDCl_3$) determined at 15.0 MHz under conditions of proton noise decoupling; scale, parts per million relative to carbons of TMS.

base. The following recyclization of the oxime anion of (**b**) would lead to a dianion (**c**), which is considered to be stable thermodynamically. Thus, the final products formed in this process seem to be similar to those produced in the acid-catalytic acyllactone rearrangement.[7)]

Although the reason of the formation of **3b** is not certain, it seems likely that the formation of **3a** takes place when two equivalents of the base were used, suggesting that the dianion (**c**) may be oxidized with oxygen dissolved in the solvent.[8)]

Experimental

Melting points and boiling points are uncorrected. PMR spectra were recorded on a Hitachi R-24 instrument. ^{13}C NMR spectra were recorded on a JEOL FX-60 instrument. IR spectra were determined with Hitachi EPI-S2, with only major absorptions being cited. Mass spectral analysis was carried out with a Hitachi RMS-4 spectrometer at 70 eV. Wako gel C-200 silica gel was used for elution chromatography. Elemental analysis was performed by Mr. Tsutomu Okamoto of our Laboratory.

Reaction of Ethyl γ,γ-Pentamethylene-α-hydroxyaminoaconate (1) with One Equivalent of n*-Butyl Lithium.* To a stirred solution of **1** (66.0 mg, 0.25 mmol) in THF (0.5 ml), 0.2 ml (0.25 mmol) of 1.3 M *n*-BuLi in ether was added at −78 °C. The reaction mixture was allowed to warm slowly to room temperature during 2 hr and the stirring was continued for additional 2.5 hr. The mixture was poured into ice-cold diluted HCl (0.5 ml) and extracted with $CHCl_3$. The extracts were washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to give 94.5 mg of a yellow oil. Treatment of this oil with an excess amount of diazomethane and subsequent chromatography using *n*-hexane–$ClCH_2CH_2Cl$ gave 56.5 mg (84%) of **2b**: bp 105—107 °C/1.0 mmHg; IR (neat) 1726 (ester C=O), 1590 (C=N) cm^{-1}; PMR (CCl_4) δ 1.28 (t, J=7.0 Hz, 3H, CH_3), 1.20—2.10 (broad s, 10H), 3.69 (s, 1H, H_β), 3.81 (s, 3H, CH_3O), 4.16 (q, J=7.0 Hz, 2H, CH_2O); Mass *m/e* (%) 269 (M^+, 2), 253 (9), 196 (83), 154 (62), 59 (100). Found: C, 57.74; H, 7.06%. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.01%.

From the following elution with $ClCH_2CH_2Cl$ 4.0 mg (5.9%) of **3a** was obtained: bp 117—120 °C/1.0 mmHg; IR (neat) 3475 (OH), 1740 (ester C=O), 1589 (C=N) cm^{-1}; PMR (CCl_4) δ 1.30 (t, J=7.0 Hz, 3H, CH_3), 1.00—2.20 (m, 10H), 3.59 (s, 1H, HO), 3.82 (s, 3H, CH_3O), 4.26 (q, J=7.0 Hz, 2H, CH_2O); Mass *m/e* (%) 212 (28), 127 (52), 99 (100), 81 (97). Found: C, 54.99; H, 7.03%. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71%.

Reaction of 1 with Two Equivalents of n*-Butyl Lithium.* To a stirred solution of **1** (66.0 mg, 0.25 mmol) in THF (1.0 ml), 0.62 ml (0.56 mmol) of 0.9 M *n*-BuLi in ether was added at −78 °C under nitrogen. The reaction mixture was allowed to warm slowly to room temperature for 2 hr and the stirring was continued for additional 2 hr. The reaction mixture was worked up as the standard manner to afford an oil. Treatment of the oil with excess diazomethane gave a yellow oil, whose tlc showed the presence of 2 spots at R_f 0.30 and 0.12 (Merck PF_{254}, benzene–EtOAc: 15/1). The column chromatography using benzene–EtOAc gave 44.8 mg (63.0%) of **3a** and 3.7 mg (3.45%) of an unknown crystal.

Preparation of the Acetate 3b from 3a. A solution of the alcohol **3a** (14.5 mg, 0.051 mmol) in Ac_2O (0.5 ml) and dry pyridine (0.5 ml) was stirred at 65 °C under nitrogen for 12 hr. The solvent was roto-evaporated to give 28.5 mg of a dull reddish material. The crude product was chromatographed using benzene and benzene–EtOAc to give 12.3 mg (74.1%) of **3b**; bp 119.5—122.5 °C/1.0 mmHg; IR (neat) 1756 (ester C=O), 1595 (C=N) cm^{-1}; PMR ($CDCl_3$) δ 1.30 (t, J=7.0 Hz, 3H, CH_3), 0.70—2.30 (broad s, 10H), 2.13 (s, 3H, CH_3CO), 3.85 (s, 3H, CH_3O), 4.28 (q, J=7.0 Hz, 2H, CH_2O); Mass *m/e* (%) 327 (M^+, 0.4), 212 (75), 127 (53), 99 (100), 81 (69). Found: C, 55.04; H, 6.54%. Calcd for $C_{15}H_{21}NO_7$: C, 55.04; H, 6.47%.

From the second elution 3.3 mg (22.8%) of **3a** was recovered.

References

1) G. Adembri and P. Tedeschi, *Boll. Sci. Fac. Chim. Ind. Bologna*, **23**, 203 (1965); *Chem. Abstr.*, **63**, 13234h (1965).

2) a) H. Dahn, B. Favre, and J.-P. Leresche, *Helv. Chim. Acta*, **56**, 457 (1973); b) Y. Kishida, T. Hiraoka, and M. Yoshimoto, Japan **70**, 40892 (1970); *Chem. Abstr.*, **75**, 5880v (1971); c) M. Gattuso, G. Lo Vecchio, and N. Uccella, *Atti Soc. Peloritana Sci. Fis. Mat. Natur.*, **14**, 393 (1968); *Chem. Abstr.*, **74**, 3545v (1971); d) H. H. Hoerhold, Ger. (East) 37461 (1965); *Chem. Abstr.*, **63**, 10062g (1965).

3) a) V. A. Tartakovskii, I. A. Savostýanova, and S. S. Novikov, *Zh. Org. Khim.*, **4**, 240 (1968); *Chem. Abstr.*, **68**, 95738n (1968); b) V. A. Tartakovskii, O. A. Lukýanov, N. I. Shlykova, and S. S. Novikov, *Zh. Org. Khim.*, **3**, 980 (1967); *Chem. Abstr.*, **67**, 100039w (1967).

4) a) Zh. A. Krasnaya, T. S. Stytsenko, E. P. Prokofév, I. P. Yakovlev, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 845 (1974); *Chem. Abstr.*, **81**, 49608r (1974); b) S. Zen and E. Kaji, *Chem. Pharm. Bull.* **22**, 477 (1974); *Chem. Abstr.*, **81**, 63533u (1974); c) Zh. A. Krasnaya, T. S. Stytsenko, E. P. Prokofév, I. P. Yakovlev, and V. F. Kucherov, U.S.S.R. 427,938 (1974); *Chem. Abstr.*, **81**, 77898d (1974); d) E. L. Katelkina, A. S. Sopova, V. V. Perekalin, and B. I. Ionin, *Zh. Org. Khim.*, **10**, 209 (1974); *Chem. Abstr.*, **80**, 108413c (1974); e) L. Kh. Vinograd and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1505 (1970); *Chem. Abstr.*, **74**, 53610h (1971).

5) N. K. Kochetkov and S. D. Sokolov, "Advances in Heterocyclic Chemistry," Vol. II, ed. by A. R. Katrilzky, Academic Press, New York, N. Y. (1963), p. 365.

6) S. Torii, M. Ukida, H. Kano, T. Furuta, and H. Tanaka, This Bulletin, in contribution.

7) F. Korte and K. H. Büchel, "New Methods of Preparative Organic Chemistry," Vol. III, ed. by W. Foerst, Academic Press, New York, N. Y. (1964), p. 199.

8) J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, **33**, 3294 (1968).