Tetrahedron Letters, Vol.32, No.49, pp 7269-7272, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

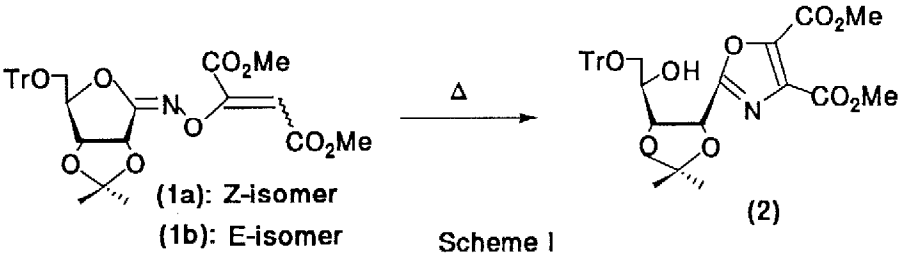
Thermal Rearrangement of Sugar Lactoxime O-Vinyl Ethers

Masataka Yokoyama,* Keiko Sujino, Masakazu Irie, and Hideo Togo
Department of Chemistry, Faculty of Science, Chiba University,
Yayoi-cho, Chiba City 260, Japan

Abstract: The thermal reaction of sugar lactoxime O-vinyl ethers gave the corresponding 1,3-oxazoles bearing sugar moiety (ribose, glucose, mannose, and maltose) *via* a novel rearrangement. The reaction mechanism was briefly discussed.

In our study directed toward the application of sugar lactoxime to organic synthesis,[1] we had occasion to look into the reactions of sugar lactoxime O-vinyl ethers such as D-ribose lactoxime O-vinyl ethers, which was easily prepared by the reaction of D-ribose lactoxime with dimethyl acetylenedicarboxylate (DMAD) in the presence of triethylamine.[2]

In these reactions it was found interestingly that a thermal reaction of (E)-N-(1',2'-dimethoxycarbonylvinyloxy)-2,3-O-isopropylidene-5-O-trityl-D-ribonimido-1,4-lactone **1** gave 1'R, 2'R, 3'R-2-(3'-hydroxy-1',2'-isopropylidenedioxy-4'-trityloxybutyl)-4,5-dimethoxycarbonyl-1,3-oxazole **2** (Scheme I). We now report the unprecedented thermal rearrangement and its reaction mechanism.



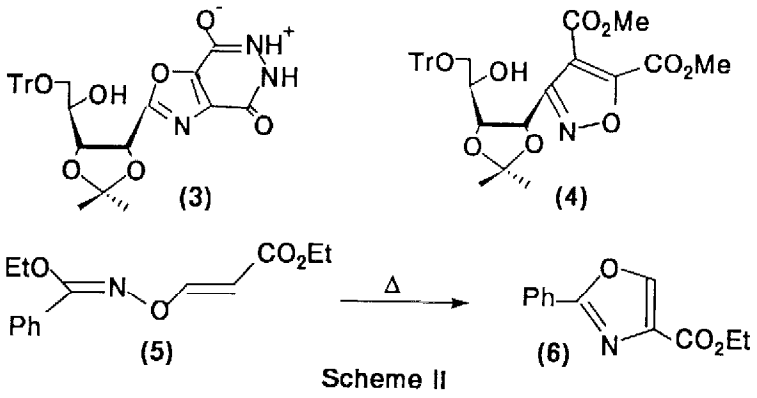
(1a): Z-isomer
(1b): E-isomer

(2)

Scheme I

The Z-isomer (**1a**) of **1** was heated at 200 °C for 2 min under nitrogen (in a sealed tube) to give a brown syrup. Purification by preparative TLC (silica gel B-5F· Et_2O : hexane = 2 : 1) yielded **2** as a colorless oil in 88 % yield. Compound **2** was also prepared from **1a** in refluxing toluene (21 h, 46 %). The E isomer **1b** also afforded **2** (200 °C, 2 min, 70 %).

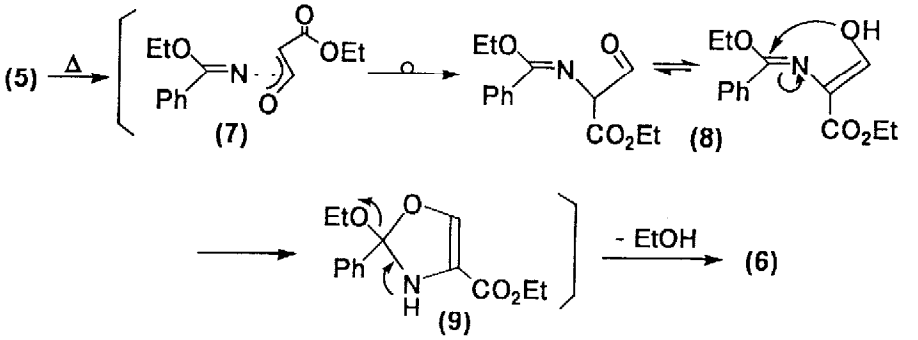
The structure of **2** was established by spectral evidence[3] and the following results: (a) The reaction of **2** with hydrazine gave the corresponding 4,5-dihydroxy-1,3-oxazolo[4,5-d]pyridazine derivative **3**[4]. (b) The NMR data of **2** were different from those of the 1,2-oxazole **4**[5] which was prepared by the reaction of 2,3-O-isopropylidene-5-O-trityl-D-ribose nitrile oxide with DMAD.[1a] (c) The pyrolysis of **4** gave a small amount of **2** together with decomposed materials (225 °C, 1 min).[6] (d) The ^{13}C NMR data of **2** showed signals at 157.0, 136.0, and 142.8 ppm, respectively, the values very close to those of 4-ethoxycarbonyl-2-phenyl-1,3-oxazole **6** [162.36 (C-2), 134.58 (C-4), and 143.6 ppm (C-5)].[7] (e) The thermal reaction of ethyl O-(2'-ethoxycarbonylvinyl)-N-hydroxyiminobenzoate **5**[8] gave 4-ethoxycarbonyl-2-phenyl-1,3-oxazole **6** (170 °C, 1 min, 22 %).



Scheme II

The process 5 to 6 can be considered as follows (Scheme III): Initially the cleavage of N-O bond in 5 gives radical fragments **7**, which then form an intermediate **8** having more stable C-N bond (bond strength: N-O, 53.0 Kcal/mol; C-N, 69.7 Kcal/mol[9]). The species **8** is converted to **6** *via* **9** by intramolecular cyclization followed by elimination of ethanol. The transformation **1** to **2** can be regarded just the same.

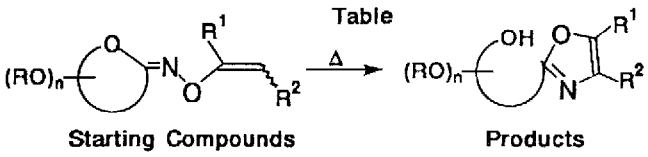
Compound **2** was also prepared by irradiation of **1** (500 W tungsten lamp, 0 °C, in toluene, 17 h, 35 %). This strongly supports the initial N-O bond cleavage shown in Scheme III.[10]



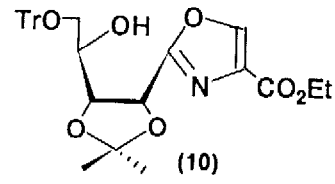
Scheme III

The present reaction was applied to several sugar lactoxime O-vinyl ethers. The result is summarized in Table. The 1,3-oxazole derivatives **11**, **12**, and **13** bearing sugar moiety were synthesized starting from the corresponding sugar lactoxime O-vinyl ether.[11] In the case of **12** and **13**, some epimerization took place at C-2 position of the sugars.

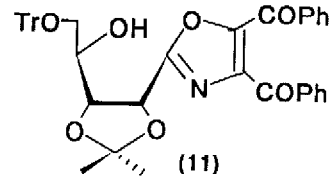
These 1,3-oxazole derivatives are expected to have interesting biological activities because some macrocyclic antibiotics,[7] alkaloids,[12] and hypolimidemic drugs[13] contain substituted 1,3-oxazole ring. The present procedure discloses a new synthetic route to 2-alkyl substituted 1,3-oxazoles from carboxylic acid esters and makes it possible to synthesize various kinds of oxazole derivatives bearing sugar moiety. Further extension of this reaction is underway in our laboratory.



Starting Compounds: Protected Sugar Moiety	R^1/R^2	Reaction Conditions 200 °C (min)	Product	Yield (%)
Ribose	CO_2Me/CO_2Me	2	2	88
Ribose	H/CO_2Et	30	10	19
Ribose	COPh/ COPh	2	11	19
Glucose	CO_2Me/CO_2Me	6	12	64[a]
Mannose	CO_2Me/CO_2Me	6	12	74[b]
Maltose	CO_2Me/CO_2Me	2	13	44[c]

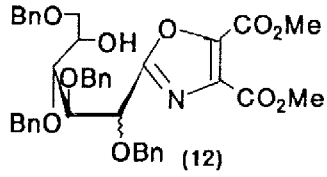


(10)

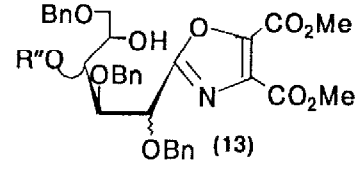


(11)

a) A diastereo-mixture of **12** (1'R : 1'S = 7 : 2); b) A diastereo-mixture of **12** (1'S : 1'R = 3 : 2);
c) A diastereo-mixture of **13** (1'R : 1'S = 13 : 4)



(12)



(13)

R" = O-Benzyl protected D-glucosyl

References

1 (a) Yokoyama, M.; Yamada, N., *Tetrahedron Lett.*, **1989**, 30, 3675.(b) Yokoyama, M.; Yamada, N., Togo, H. *Chem. Lett.*, **1990**, 753.

2 Compound **1** was prepared as follows: A mixture of N-hydroxy-2,3-O-isopropylidene-5-trityl-D-ribonimido-1,4-lactone (223 mg, 0.5mmol), DMAD (0.1 ml, 0.8 mmol), Et_3N (0.07 ml, 0.5 mmol), and dry CH_2Cl_2 (1 ml) was stirred for 2 h at room temperature. Purification by preparative TLC on silica gel (AcOEt : hexane = 2 : 3) gave Z-vinylether **1a** (62 %, colorless needles, mp 149-150 °C) and E-vinyl ether **1b** (23 %, colorless powder, mp 71-72 °C). **1a**: IR (KBr) 3019(Ar,CH), 2970, 2920 (CH), 1720 (CO), 1680 cm^{-1} (C=N), ^1H NMR ($CDCl_3$) δ = 1.34 (3H, s, C-Me), 1.51 (3H, s, C-Me), 2.98 (1H, dd, H-5, J_{gem} = 10.8, $J_{4,5}$ = 1.8 Hz), 3.73 (1H, dd, H-5', J_{gem} = 10.8, $J_{4,5'}$ = 2.8 Hz), 3.69 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 4.56 (1H, bd, H-3, $J_{2,3}$ = 5.9 Hz), 4.78 (1H, m, H-4), 5.36 (1H, d, H-2, $J_{2,3}$ = 5.9 Hz), 6.15 (1H, s, H-2'), 7.22-7.41 (15H, m, Tr). Mass m/e (EI) = 587 (M^+). **1b**: IR (KBr) 3019 (Ar,CH), 2970, 2920 (CH), 1720 (CO), 1680 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ = 1.36 (3H, s, C-Me), 1.49 (3H, s, C-Me), 3.02 (1H, dd, H-5, J_{gem} = 10.7 Hz, $J_{4,5}$ = 1.7 Hz), 3.67

(1H, dd, H-5', J_{gem} = 10.7 Hz, $J_{4,5'}$ = 2.8 Hz), 3.69 (3H, s, CO_2Me), 3.95 (3H, s, CO_2Me), 4.61 (1H, bd, H-3, $J_{2,3}$ = 5.9 Hz), 4.78 (1H, m, H-4), 5.41 (1H, d, H-2, $J_{2,3}$ = 5.9 Hz), 6.01 (1H, s, H-2'), 7.22-7.38 (15H, m, Tr). Mass m/e (EI) = 587 (M^+).

3 IR (KBr) 3400 (OH), 3040 (Ar,CH), 2900 (CH), 1725 cm^{-1} (CO). ^1H NMR ($CDCl_3$) δ = 1.43 (3H, s, C-Me), 1.57 (3H, s,C-Me), 2.42 (1H, d, OH, J = 6.1 Hz), 3.30 (1H, dd, H-4', J_{gem} = 9.7, $J_{3',4'}$ = 3.1 Hz), 3.37 (1H, dd, H-4", J_{gem} = 9.7, $J_{3',4"}$ = 5.1 Hz), 3.58 (1H, m, H-3'), 3.94 (3H, s, O-Me), 3.95 (3H, s, O-Me),4.51 (1H, dd, H-2', $J_{2',3'}$ = 9.2, $J_{1',2'}$ = 6.2 Hz), 5.41 (1H, d, H-1',$J_{1',2'}$ = 6.2 Hz), 7.21-7.44 (15H, m, Tr). Mass m/e (EI) = 587 (M^+).

4 Colorless plates, mp 178 °C (dec); IR (KBr) 3350 (OH), 3270, 3150 (NH, NH^+), 3040 (Ar,CH), 2950 (CH), 1670, 1600 ,1560 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ = 1.44 (3H, s, C-Me), 1.6' '3H, s, C-Me),2.40 (1H, br, OH), 3.31 (1H, dd, H-4', J_{gem} = 9.7, $J_{3',4'}$ =3.3Hz),3.36(1H, dd, H-4", J_{gem} = 9.7, $J_{3',4"}$ = 4.9 Hz), 3.65 (1H, m, H-3'), 4.51 (1H, dd, H-2', $J_{2',3'}$ = 8.7, $J_{1',2'}$ = 6.3 Hz), 5.43 (1H, d, H-1', $J_{1',2'}$ = 6.3 Hz), 7.21-7.42 (15H, m, Tr), 9.94 (1H, s, NH), 12.90 (1H, s, NH^+).

5 Colorless oil; ^1H NMR ($CDCl_3$) δ = 1.42 (3H, s, C-Me),1.49 (3H, s, C-Me), 2.20 (1H, d, OH, J = 5.1 Hz), 3.28 (1H, dd, H-4',J_{gem} = 9.7, $J_{3',4'}$ = 6.0 Hz), 3.33 (1H, dd, H-4", J_{gem} = 9.7, $J_{3',4"}$ = 3.0 Hz), 3.51 (1H, m, H-3'), 3.88 (3H, s, O-Me), 3.99 (3H, s, O-Me), 4.45 (1H, dd, H-2', $J_{2',3'}$ = 9.4, $J_{1',2'}$ = 6.0 Hz), 5.77 (1H, d, H-1', $J_{1',2'}$ = 6.0 Hz), 7.21-7.48 (15H, m, Tr). ^{13}C NMR (125.65 MHz, $CDCl_3$) δ = 25.3, 26.9 (C-Me x 2), 52.7, 53.4 (O-Me x 2), 64.6 (C-4'), 69.2 (C-1'), 72.6 (C-2'), 77.7 (C-3'), 86.9 (C-Ph_3), 110.4 (C-Me_2), 127.1-128.6 (Ph), 143.7 (Ph-ipso), 156.9 (C-3), 160.1 (C-5),160.8, 170.0 (CO x 2).

6 Pyrolysis of the 1,2-oxazoles is known to give the corresponding 1,3-oxazoles; (a) Padwa, A.; Chen, E. *J. Org. Chem.*, **1974**, 39, 1976. (b) Wakefield, B.J.; Wright, A.J. *Adv. Heterocycl. Chem.*, Ed. by Katritzky, A.R.; Boulton, A.J.,Academic Press, New York, Vol. 25,**1979**, pp 184.

7 Connell, R.D.; Tebbe, M.; Helquist, P.; Åkermark, B. *Tetrahedron Lett.*,**1991**, 32, 17.

8 Compound 5 was prepared as follows: Ethyl benzoate was refluxed with Lawesson's reagent in xylene for 15 h to give ethyl thionebenzoate (75 %), which was changed to ethyl N-hydroxyiminobenzoate (NH_2OH·HCl/ AcONa/EtOH, r.t., 17 h, 69 %). The product obtained was converted to 5 in quantitative yield by the same method as described in the preparation of 1.

9 Pauling, L. *The Nature of Chemical Bond*, 3rd Ed., Cornell University Press, New York, **1960**, pp 85.

10 (a) Hasebe, M.; Kogawa, K.; Tsuchiya, T. *Tetrahedron Lett.*, **1984**, 25, 3887. (b) Hasebe, M.; Tsuchiya, T. *ibid.*, **1986**, 27, 3239. (c) *Idem, ibid.*, **1987**, 28, 6207.

11 (E)-N-(1',2'-dimethoxycarbonylvinyloxy)-2,3,4,6-O-tetrabenzyl-D-gluconimido-1,5-lactone, N-(1',2'-dimethoxycarbonylvinyloxy)-2,3,4,6-O-tetrabenzyl-D-mannonimido-1,5-lactone, and N-(1',2'-dimethoxycarbonylvinyloxy)-2,2',3,3',4',6,6'-O-heptabenzyl-D-maltonimido-1,5-lactone were synthesized by the same method as described in preparation of 1.

12 Boyd, G.V. *Comprehensive Heterocyclic Chemistry*, Ed. by Potts,K.T., Oxford, **1984**, Vol. 6, pp 232.

13 (a) Moriya, T.; Takabe, S.; Maeda, S.; Matsumoto, K.; Takashima,K.; Mori,T.; Takeyama, S. *J. Med. Chem.*, **1986**, 29, 333. (b) Moriyama, Y.; Seki,M.; Takabe, S.; Matsumoto, K.; Takashima, K.; Mori, T.; Odawara, A.;Takeyama, S. *ibid.*, **1988**, 31, 1197.

(Received in Japan 23 August 1991)