Formation of 4-*p*-Bromophenyl-5-hydroxy-3-methoxycarbonyl-5,6-dihydro-4*H*-1,2-oxazine by Means of New Ring Transformation of an Isoxazoline-2-oxide[1)]

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4-*p*-Bromophenyl-5-hydroxymethyl-3-methoxycarbonyl-2-isoxazoline-2-oxide methanesulfonate (1c) reacted with excess titanium tetrabromide in dichloromethane to yield a novel ring transformation product, 4-*p*-bromophenyl-5-hydroxy-3-methoxycarbonyl-5,6-dihydro-4*H*-1,2-oxazine (2). The structural determination of 2 by single-crystal X-ray analysis is reported.

Keywords 2-isoxazoline-2-oxide; 5,6-dihydro-4*H*-1,2-oxazine; ring transformation; X-ray analysis; Lewis acid

In the preceding papers,[1,2)] we have demonstrated that 4-aryl-3,5-bis(methoxycarbonyl)-2-isoxazoline-2-oxides can be readily transformed into benzofuro[3,3*a*—*d*]isoxazole or 3*H*-indole-1-oxide derivatives in the presence of a Lewis acid such as titanium tetrachloride. In this continuing study, we now wish to report a new ring transformation product, 4-*p*-bromophenyl-5-hydroxy-3-methoxycarbonyl-5,6-dihydro-4*H*-1,2-oxazine (**2**), and its structure. Compound **2** was obtained from the reaction of 4-*p*-bromophenyl-5-hydroxymethyl-3-methoxycarbonyl-2-isoxazoline-2-oxide methanesulfonate (**1c**) with titanium tetrabromide.

The methanesulfonate (**1c**) was easily prepared by the reduction[3)] of 3,5-bis(methoxycarbonyl)-4-*p*-bromophenyl-2-isoxazoline-2-oxide (**1a**) with $NaBH_4$ followed by protection of the resulting 5-hydroxymethylisoxazoline-2-oxide (**1b**) with methanesulfonyl chloride. Reaction of **1c** with a four-fold excess of titanium tetrabromide did not yield the expected 3*H*-indole-1-oxide, but did give a novel ring transformation product (**2**) in 40% yield (Chart 1). The structural determination of **2** was accomplished by single-crystal X-ray analysis. A perspective drawing of the molecular structure is illustrated in Fig. 1. It can be seen that the 1,2-oxazine ring adopts approximately a half-chair conformation; the hydroxy group is attached to C(2) in the axial direction and the phenyl group is attached to C(3) in the quasi-equatorial direction with respect to the ring plane, *i.e.* the two substituents exist in a *cis* relation.

A proposed reaction mechanism of this new ring transformation is illustrated in Chart 2. Initially, an electrophilic attack of $TiBr_4$ to **1c** causes the cleavage of the N–O bond to give an intermediate (**3**),[2)] followed by loss of the methanesulfonyl group, and then recyclization gives the 1,2-oxazine-2-oxide (**4**), which is finally deoxygenated to **2** by the action of $TiBr_3$,[4)] probably formed *via* debromination of $TiBr_4$ by an interaction with methanesulfonyl cation.

It should be noted that this novel ring transformation appears to be a potentially useful preparative method of

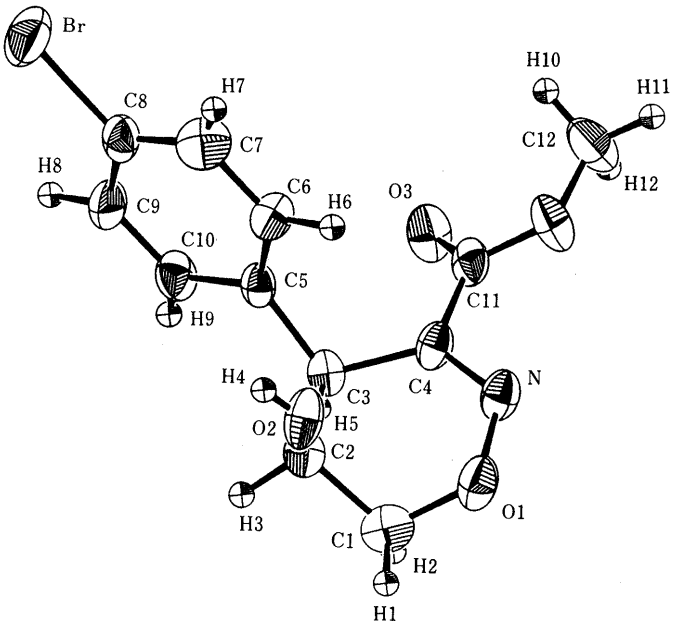
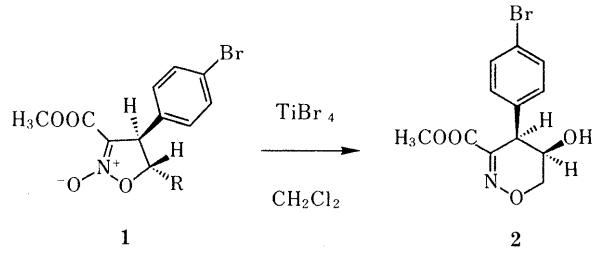


Fig. 1. Molecular Structure of Compound **2**



1a : R=$COOCH_3$
1b : R=CH_2OH
1c : R=$CH_2OSO_2CH_3$

Chart 1

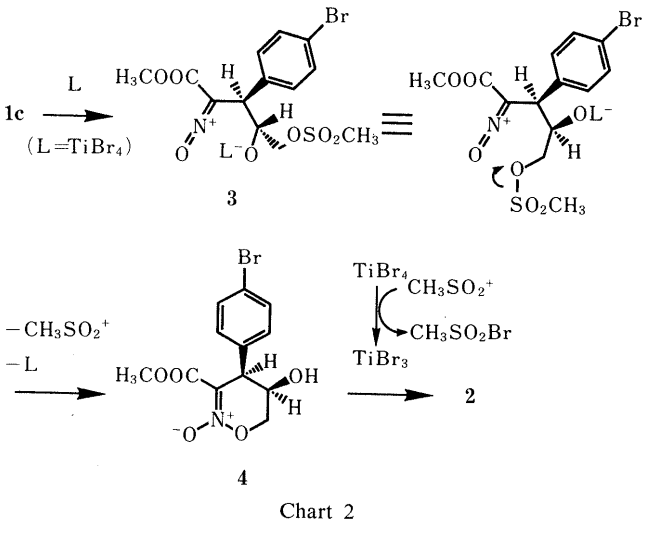


Chart 2

TABLE I. Positional Parameters and Equivalent Isotropic Thermal Parameters with Their Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{eq}
Br	0.31355 (8)	0.1303 (1)	0.48943 (8)	5.23 (5)
O(1)	0.8922 (5)	0.1833 (6)	1.0293 (4)	3.6 (3)
O(2)	0.6701 (5)	0.2907 (7)	0.9399 (5)	3.6 (3)
O(3)	0.8252 (5)	−0.1386 (6)	0.7500 (4)	3.7 (3)
O(4)	0.9827 (5)	0.0168 (6)	0.7526 (4)	3.9 (3)
N	0.9190 (5)	0.1179 (7)	0.9355 (5)	3.1 (3)
C(1)	0.7780 (9)	0.140 (1)	1.0686 (7)	3.4 (4)
C(2)	0.6713 (7)	0.148 (1)	0.9784 (6)	2.9 (4)
C(3)	0.6974 (7)	0.0400 (9)	0.8919 (6)	2.4 (4)
C(4)	0.8338 (7)	0.0508 (8)	0.8740 (6)	2.5 (3)
C(5)	0.6095 (7)	0.0600 (9)	0.7882 (6)	2.4 (3)
C(6)	0.6260 (8)	0.1637 (9)	0.7142 (7)	3.0 (4)
C(7)	0.537 (1)	0.181 (1)	0.6269 (7)	3.9 (5)
C(8)	0.4324 (7)	0.097 (1)	0.6115 (6)	3.0 (4)
C(9)	0.4172 (8)	−0.009 (1)	0.6820 (7)	3.7 (4)
C(10)	0.5047 (8)	−0.029 (1)	0.7687 (7)	3.3 (4)
C(11)	0.8783 (7)	−0.034 (1)	0.7866 (7)	2.9 (4)
C(12)	1.0320 (8)	−0.066 (1)	0.6720 (7)	4.8 (5)

TABLE II. Bond Lengths and Torsional Angles

A–X–Y–B	Bond length (l/Å) X–Y	Torsional angle (ϕ/°)along X–Y
C1–C2–C3–C4	1.53 (1)	−43.7 (9)
N–C4–C3–C2	1.52 (1)	13 (1)
O1–N–C4–C3	1.292 (9)	3 (1)
C1–O1–N–C4	1.383 (8)	17 (1)
N–O1–C1–C2	1.44 (1)	−50.6 (9)
O1–C1–C2–C3	1.51 (1)	64.1 (9)
O1–C1–C2–O2	—	−56.4 (9)
O2–C2–C3–C4	—	72.3 (8)
N–C4–C3–C5	—	136.9 (8)
C1–C2–C3–C5	—	−168.6 (7)
O2–C2–C3–C5	—	−52.6 (9)

monocyclic 5,6-dihydro-4*H*-1,2-oxazines, which are heterocycles of considerable synthetic potential, but for which relatively few synthetic methods are available.[5]

Further studies of the reaction mechanism and the synthetic utility of this ring transformation are in progress.

Experimental

Preparation of 4-*p*-Bromophenyl-5-hydroxymethyl-3-methoxycarbonyl-2-isoxazoline-2-oxide Methanesulfonate (1c) A solution of $NaBH_4$ (1.76 g, 46.5 mmol) and tetrabenzylammonium chloride (1.67 g, 7.3 mmol) in H_2O (90 ml) was added to a stirred solution of **1a**[6] (5.32 g, 14.9 mmol) in 200 ml of CH_2Cl_2, and stirring was continued for 4 h at room temperature. Excess $NaBH_4$ was destroyed by addition of 1 M aqueous HCl (14 ml). The mixture was transferred to a separatory funnel, the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness. The residue was chromatographed on silica gel with hexane–ethyl acetate (1 : 1) as an eluent to afford **1b** (2.87 g, 60%). mp 87.0—90.0 °C (ethyl acetate–hexane). Infrared (IR) ν (KBr) cm^{-1}: 3525 (OH), 1730 (C=O), 1620 (C=N). Proton-nuclear magnetic resonance (^{1}H-NMR) (δ, $CDCl_3$): 3.70 (3H, s, $COOCH_3$), 3.86 (2H, dd, CH_2), 4.56 (1H, q, H-5), 4.66 (1H, d, $J_{4,5}$ = 5.0 Hz, H-4), 7.4—7.6 (5H, m, aromatic protons). Mass spectrum (MS) (m/z): 329 (M^+). *Anal.* Calcd for $C_{12}H_{12}BrNO_5$: C, 43.77; H, 3.68; Br, 23.99; N. 4.26. Found: C, 43.66; H, 3.69; Br, 23.99; N, 4.26.

A stirred solution of **1b** (2.5 g, 7.6 mmol) in 10 ml of pyridine was treated with 1.33 ml of methanesulfonyl chloride with ice-cooling, and stirring was continued overnight at room temperature. The solvent was removed *in vacuo*. The residue was chromatographed on silica gel with hexane–ethyl acetate (1 : 1) as an eluent to afford **1c** (2.71 g, 88%). mp 116.0—119.0 °C (ethyl acetate–hexane). IR ν (KBr) cm^{-1}: 1730 (C=O), 1620 (C=N). ^{1}H-NMR (δ, $CDCl_3$): 3.11 (3H, s, SO_2CH_3), 3.75 (3H, s, $COOCH_3$), 4.43 (2H, d, CH_2), 4.61 (1H, d, H-4), 4.71 (1H, q, $J_{4,5}$ = 4.0 Hz, H-5), 7.1—7.6 (4H, m, aromatic protons). MS m/z: 407 (M^+). *Anal.* Calcd for $C_{13}H_{14}BrNO_7S$: C, 38.32, H, 3.47; Br, 19.39; N, 3.44; S, 7.88. Found: C, 38.31; H, 3.46; Br, 19.41; N, 3.49; S, 7.62.

4-*p*-Bromophenyl-5-hydroxy-3-methoxycarbonyl-5,6-dihydro-4*H*-1,2-oxazine (2) by the Reaction of 1c with $TiBr_4$ A stirred solution of **1c** (728 mg, 2.0 mmol) in 50 ml of CH_2Cl_2 was treated with $TiBr_4$ (2.94 g, 8.0 mmol) with ice-cooling, and stirring was continued at 40 °C overnight. The reaction was quenched with 10% aqueous $NaHCO_3$ and the mixture was extracted with $CHCl_3$ followed by column chromatography of the extract on silica gel with hexane–ethyl acetate (1 : 1) as an eluent to afford **2** (252 mg, 40%). mp 152—154 °C (ethyl acetate–hexane). IR ν (KBr) cm^{-1}: 3350 (OH), 1720 (C=O), 1590 (C=N). ^{1}H-NMR (δ, $CDCl_3$): 3.76 (3H, s, $COOCH_3$), 3.83 (1H, q, H-6), 4.15 (1H, t, H-6′), 4.18 (1H, m, H-5), 4.23 (1H, d, H-4), 7.05, 7.51 (each 2H, d, C_6H_4). ^{13}C-NMR (δ, $CDCl_3$): 42.4 (C-4), 53.0 ($COOCH_3$), 61.9 (C-5), 67.6 (C-6), 149.0 (C=N), 162.8 (C=O). MS m/z: 314 (M^+), *Anal.* Calcd for $C_{12}H_{12}BrNO_4$: C, 45.84; H, 3.85; Br, 25.44; N, 4.46. Found: C, 45.66; H, 3.82; Br, 25.17; N. 4.21. Expected other products were not isolable.

X-Ray Analysis of 2 A crystal with dimensions of approximately 0.6 × 0.6 × 0.3 mm was mounted on a Rigaku AFC-5R diffractometer and the cell parameters and the intensity data were measured with graphite-monochromated Cu$K\alpha$ radiation. Crystal data: 4-*p*-Bromophenyl-5-hydroxy-3-methoxycarbonyl-4,5-dihydro-4*H*-1,2-oxazine, $C_{12}H_{12}BrNO_4$, M.W. = 314.14, monoclinic, space group $P2_1/a$, Z = 4, D_{cal} = 1.655 g cm^{-3}, μ for Cu$K\alpha$ = 32.31 cm^{-1}. a = 10.807(2), b = 9.429(5), c = 12.460(2) Å, β = 96.80(2)°, V = 1260.7(7) Å^3. Of the total of 3232 reflections up to the 2θ range of 55.0°, 3074 were measured as above the 3σ (I) level and were used for the structure determination. Approximate atomic coordinates were obtained by the direct method using MITHRIL[7] and subsequently refined by the full-matrix least-squares method. The final R value was 0.067 including all twelve hydrogen atoms. The torsional angles along with bonds connecting each group are listed in Table II.

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