Formation of Benzofuro[2,3-*c*]tetrahydropyran-3,4-dione 4-Oximes from 4-Substituted 5-Hydroxymethyl-3-methoxycarbonyl-2-isoxazoline 2-Oxides[1)]

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4-Substituted 5-hydroxymethyl-3-methoxycarbonyl-2-isoxazoline 2-oxides (1) reacted with an excess of titanium tetrachloride in dichloromethane to yield a new type of functionalized heterocycle, benzofuro[2,3-*c*]tetrahydropyran-3,4-dione 4-oximes (2). The structure of the 7-chloro derivative (2a) was determined by single crystal X-ray analysis and a mechanism is proposed for the formation of 2 from 1.

Keywords 2-isoxazoline 2-oxide; titanium tetrachloride; X-ray analysis; benzofuro[2,3-*c*]tetrahydropyran

2-Isoxazolines have recently become useful intermediates in organic synthesis.[2)] They undergo a variety of reactions including reductive ring opening, oxidative ring rupture, acid- and base-induced transformations, and photolytic conversions. In contrast, very few examples of synthetically useful reactions of isoxazoline 2-oxides have been reported, although they should have synthetic potential as reactive cyclic nitronic esters.[3)] As a continuation of our studies[4)] of the reaction of isoxazoline 2-oxides with Lewis acids, we have reported the novel ring transformation of 5-hydroxymethyl-2-isoxazoline 2-oxide methanesulfonates to 5,6-dihydro-4*H*-1,2-oxazines.[5)] The above finding aroused our interest in the reactivity of the 5-hydroxymethyl-2-isoxazoline 2-oxides (**1**)[5,6)] themselves. In this paper, we wish to report a novel formation of functionalized benzofuro[2,3-*c*]tetrahydropyrans by the reaction of **1** with titanium tetrachloride.

When 4-*p*-chlorophenyl-5-hydroxymethyl-3-methoxycarbonyl-2-isoxazoline 2-oxide (**1a**)[5,6)] was allowed to react with a four-fold excess of titanium tetrachloride in dichloromethane at 40 °C, the expected 5,6-dihydro-4*H*-1,2-oxazine was not obtained, but 7-chlorobenzofuro[2,3-*c*]tetrahydropyran-3,4-dione 4-oxime (**2a**) was isolated in a yield of 39% from a complex reaction mixture. The structure of **2a** was confirmed by single crystal X-ray analysis. A perspective drawing of the molecule of **2a** is illustrated in Fig. 1. The molecule consists of a benzofuro[2,3-*c*]tetrahydropyran ring with an oxime group which is *syn* to the benzofuran moiety, so that the molecule has the *E* configuration. Other isoxazoline 2-oxides (**1b**: $R_1 = Br$ and **1c**: $R_1 = CH_3$) reacted analogously to give the corresponding benzofuro[2,3-*c*]tetrahydropyrans (**2b** and **2c**) in reasonable yields. Treatment of **2c** with ethyl iodide afforded the alkylated derivative (**3c**) (Chart 1).

Formation of **2** can be postulated to occur *via* opening

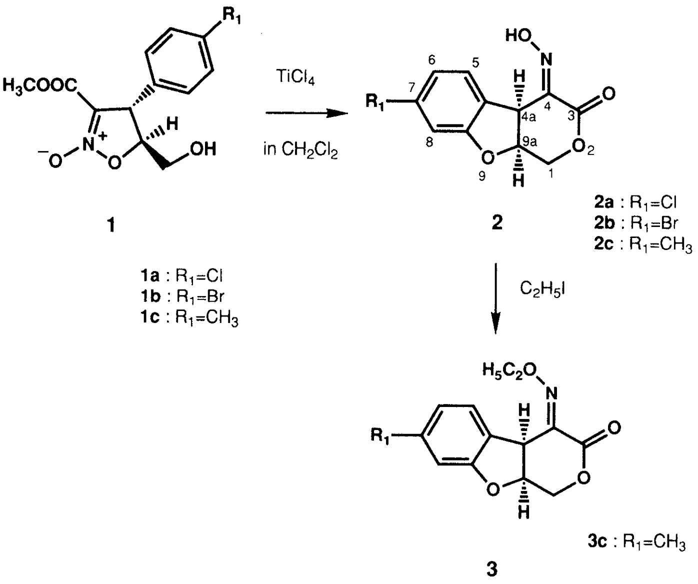

Chart 1

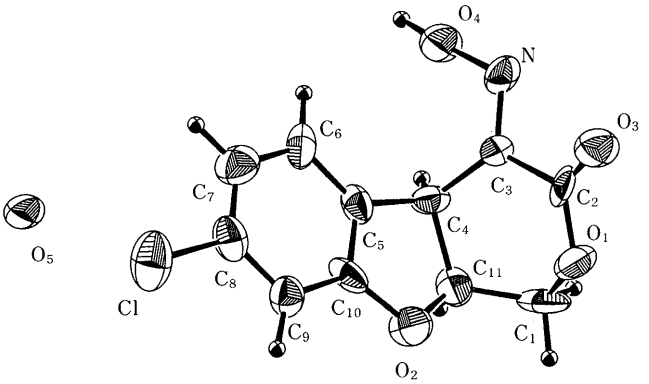

Fig. 1. Molecular Structure of Compound **2a** with the Numbering Scheme Used in the Crystallographic Analysis

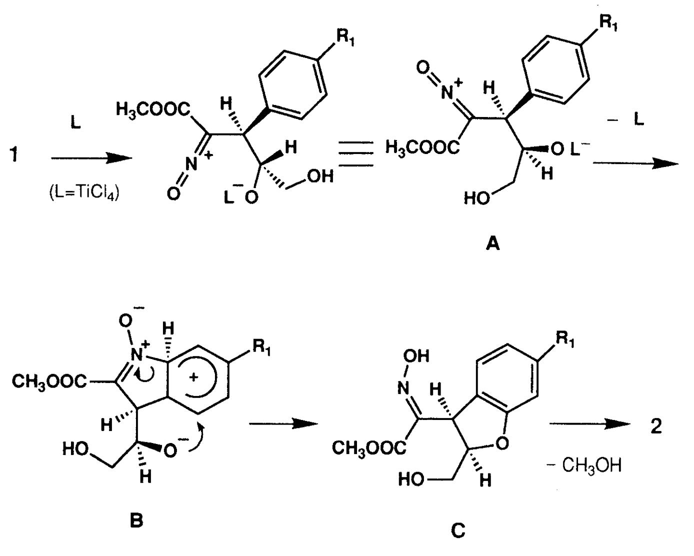

Chart 2

of the isoxazoline ring by an electrophilic attack of titanium tetrachloride to give the nitrosonium ion intermediate (A).$^{7)}$ The subsequent formation of the 3*H*-indole 1-oxide intermediate (B) results from electrophilic attack of the nitrogen atom of the nitrosonium species in A at the *ortho* position on the phenyl ring in **1**. Then, nucleophilic attack of negatively charged oxygen at the site *meta* to the substituent R_1 in B causes formation of the furan ring and subsequent cleavage of the C–N bond gives intermediate (C), which finally cyclizes to benzofuro[2,3-*c*]tetrahydropyran (**2**) (Chart 2).

Further detailed studies are in progress.

Experimental

Reaction of 4-Substituted 5-Hydroxymethyl-3-methoxycarbonyl-2-isoxazoline 2-Oxides (1) with Titanium Tetrachloride A stirred solution of **1** (1.0 mmol) in 20 ml of CH_2Cl_2 was treated with $TiCl_4$ (4.0 mmol) with ice-cooling, and stirring was continued at 40 °C overnight. The reaction was quenched with 10% aqueous Na_2CO_3 and the mixture was extracted with CH_2Cl_2 followed by column chromatography of the extract on silica gel with hexane–ethyl acetate (1 : 3) as an eluent to afford the corresponding 7-substituted benzofuro[2,3-*c*]tetrahydropyran-3,4-dione 4-oximes (**2**).

2a: Yield 39%, mp 215—219 °C (ethyl acetate–hexane). IR ν^{KBr} cm^{-1}: 3325 (N–OH), 1740 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 4.68 (2H, m, H-1), 5.27 (1H, d, $J_{4a,9a}=8.5$ Hz, H-4a), 5.36 (1H, m, H-9a), 6.93 (1H, d, $J_{5,6}=8.0$ Hz, H-5), 6.99 (1H, s, H-8), 7.25 (1H, d, $J_{5,6}=8.0$ Hz, H-6), 13.20 (1H, br s, N–OH). MS *m/z*: 253 (M^+). *Anal.* Calcd for $C_{11}H_8ClNO_4$: C, 52.09; H, 3.18; N, 5.52. Found: C, 51.84; H, 3.10; N, 5.40. No other products were isolated.

2b: Yield 47%, mp 223—227 °C (ethyl acetate–hexane). IR ν^{KBr} cm^{-1}: 3350 (N–OH), 1740 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 4.67 (2H, m, H-1), 5.25 (1H, d, $J_{4a,9a}=9.5$ Hz, H-4a), 5.35 (1H, m, H-9a), 7.06 (1H, d, $J_{5,6}=8.0$ Hz, H-5), 7.12 (1H, s, H-8), 7.19 (1H, d, $J_{5,6}=8.0$ Hz, H-6), 13.21 (1H, br s, N–OH). MS *m/z*: 296 (M^+). *Anal.* Calcd for $C_{11}H_8BrNO_4$: C, 44.32; H, 2.71; N, 4.70. Found: C, 43.47; H, 2.70; N, 4.57.

2c: Yield 53%, mp 235—241 °C (ethyl acetate–hexane). IR ν^{KBr} cm^{-1}: 3350 (N–OH), 1740 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.25 (3H, s, CH_3), 4.64 (2H, m, H-1), 5.22 (1H, d, $J_{4a,9a}=9.0$ Hz, H-4a), 5.26 (1H, m, H-9a), 6.66 (1H, s, H-8), 6.67 (1H, d, $J_{5,6}=8.0$ Hz, H-5), 7.12 (1H, d, $J_{5,6}=8.0$ Hz, H-6), 13.06 (1H, br s, N–OH). MS *m/z*: 233 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.53; H, 4.74; N, 5.88.

4-Ethoxyimino-7-methylbenzofuro[2,3-*c*]tetrahydropyran-3-one (3c) After addition of 300 mg of **2c** (1.3 mmol) and 2.1 ml of iodoethane to a solution of 0.76 g of KOH in 8 ml of MeOH, the mixture was heated at 80 °C overnight, then poured into ice-water and extracted with ether. Column chromatography of the extract on silica gel with hexane–ethyl acetate (1 : 1) as an eluent afforded **3c**. Yield 46%, mp 236—245 °C (ethanol). IR ν^{KBr} cm^{-1}: 1740 (C=O). ^{1}H-NMR (DMSO) δ: 1.44 (3H, t, $OCH_2C\underline{H}_3$), 2.99 (3H, s, CH_3), 4.41 (1H, d, $J_{1,1'}=1.4$ Hz, H-1), 4.49 (2H, q, $OC\underline{H}_2CH_3$), 4.76 (1H, d, $J_{1,1'}=1.4$ Hz, H-1′), 5.11 (1H, m, H-9a), 5.21 (1H, d, $J_{4a,9a}=9.0$ Hz, H-4a), 6.65 (1H, s, H-8), 6.91 (1H, d, $J_{5,6}=8.0$ Hz, H-5), 7.14 (1H, d, $J_{5,6}=8.0$ Hz, H-6). MS *m/z*: 261 (M^+). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.11; H, 5.75; N, 5.19.

X-Ray Analysis of 7-Chlorobenzofuro[2,3-*c*]tetrahydropyran-3,4-dione 4-Oxime (2a) A crystal with dimensions of approximetely 0.3 × 0.3 × 0.3 mm was mounted on a Rigaku AFC-5R diffractometer, and the cell parameters and the intensity data were measured with graphite-monochromated CuK_α ($\lambda=1.54179$ Å) radiation at 23 °C. The crystal data are: $C_{11}H_8ClNO_4$, M.W. = 253.64, monoclinic, space group $P2_1/a$ from systematic absences in the reflection data, $Z=4$. Unit cell dimensions, $a=11.59(1)$ Å, $b=8.074(4)$ Å, $c=13.52(1)$ Å, $\beta=107.10(7)°$, $V=1210(3)$ Å^3. $D_{\mathrm{cal}}=1.480\ \mathrm{g\,cm^{-3}}$, μ (CuK_α) = 29.72 cm^{-1}. Of the total of 2501 reflections up to the 2θ range of 141.0° (unique reflections: 2386), only 492 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.$^{8)}$ The parameters of non-hydrogen atoms were refined by the full-matrix least-squares method with anisotropic temperature factors. The hydrogen atoms were located from a difference Fourier synthesis, and refined with isotropic temperature factors. The final *R* value was 0.068 including all eight hydrogen atoms. The positional parameters and the torsional angles are listed in Tables I and II.

TABLE I. The Positional Parameters and Equivalent Isotropic Thermal Parameters of **2a** with Their Estimated Standard Deviations in Parentheses

Atom	*x*	*y*	*z*	B_{eq} (Å^2)
Cl	0.8638 (4)	0.1092 (6)	0.6549 (3)	9.8 (3)
O_1	0.809 (1)	0.529 (1)	0.1653 (8)	6.7 (7)
O_2	0.973 (1)	0.398 (1)	0.3581 (8)	7.3 (7)
O_3	0.618 (1)	0.446 (1)	0.105 (1)	6.9 (6)
O_4	0.7357 (8)	−0.025 (1)	0.1133 (7)	6.7 (5)
O_5	0.4410 (8)	0.230 (1)	0.9671 (6)	6.6 (5)
N	0.692 (1)	0.135 (2)	0.0972 (9)	5.4 (7)
C_1	0.934 (2)	0.489 (3)	0.186 (1)	8 (1)
C_2	0.721 (2)	0.417 (2)	0.138 (1)	5 (1)
C_3	0.774 (2)	0.236 (2)	0.150 (1)	4 (1)
C_4	0.893 (2)	0.192 (2)	0.277 (1)	5 (1)
C_5	0.880 (1)	0.147 (2)	0.329 (1)	5 (1)
C_6	0.830 (2)	0.008 (2)	0.356 (1)	6 (1)
C_7	0.823 (1)	−0.001 (2)	0.458 (2)	7 (1)
C_8	0.871 (2)	0.121 (3)	0.529 (1)	6 (1)
C_9	0.924 (1)	0.260 (2)	0.500 (1)	6 (1)
C_{10}	0.925 (1)	0.266 (3)	0.399 (1)	6 (1)
C_{11}	0.974 (1)	0.344 (3)	0.258 (1)	8 (1)

TABLE II. Bond Lengths (Å) and Torsional Angles (°) for the Molecule of **2a** with Their Estimated Standard Deviations in Parentheses

A–X–Y–B	Bond length X–Y	Torsional angle along X–Y
O_2–C_{11}–C_4–C_3	1.55 (2)	103 (2)
O_2–C_{11}–C_4–C_5	1.55 (2)	−17 (2)
C_1–C_{11}–C_4–C_3	1.55 (2)	13 (2)
C_1–C_{11}–C_4–C_5	1.55 (2)	133 (2)
C_1–O_1–C_2–C_3	1.32 (2)	−11 (2)
C_2–O_1–C_1–C_{11}	1.44 (2)	47 (2)
O_4–N–C_3–C_4	1.28 (2)	−6 (2)

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