REACTION OF 2-*tert*-BUTYL-3-PHENYLOXAZIRIDINE WITH ALKYL ISOTHIOCYANATES AND ITS APPLICATION TO GLUCOSYLAMINOHETEROCYCLE SYNTHESIS

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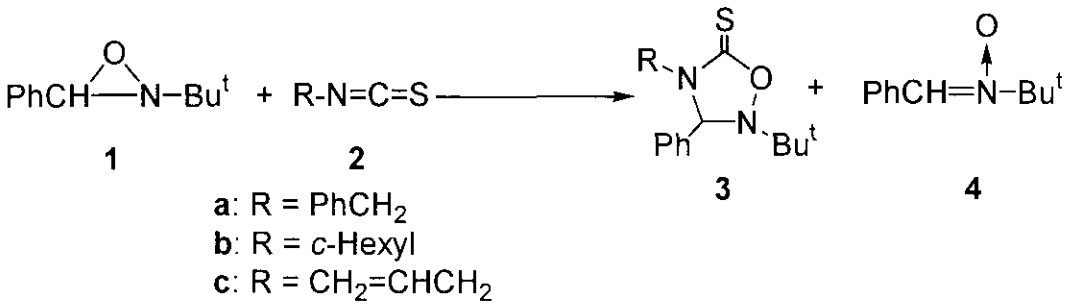
Abstract – 2-*tert*-Butyl-3-phenyloxaziridine was heated with alkyl isothiocyanates to afford 4-alkyl-2-*tert*-butyl-3-phenyl-1,2,4-oxadiazolidine-5-thiones. The reaction mechanism of the ring formation was discussed. This reaction was applicable to synthesis of glucosylaminoheterocycles.

In the preceding paper, we reported the oxidation of sulfides with oxaziridines under high pressure.[1] In the serial studies of oxaziridines, we aimed to the synthesis of novel glucosylaminoheterocycles by the reaction of sugar isothiocyanates with oxaziridines. Sugar isothiocyanates are versatile starting materials for synthesis of sugar derivatives, such as glycosylthioureas,[2] glycosylamino acids,[3] and nucleoside analogues.[4] Among them, glucosylaminoheterocycles are important compounds and some are found in living bodies as pyrimidine or purine nucleosides.[5] Besides, several glucosylaminoheterocycles have biological and pharmaceutical activities.[6]

It has reported that the reactions of oxaziridines with heterocumulenes caused cyclization to give a various kinds of heterocycles.[7-10] However, for the reactions with isothiocyanates, the examples of reaction were limited to phenyl isothiocyanate, and the way of cyclization or product distribution changed with substituents on the oxaziridines and reaction temperature.[8,10] In this paper, we wish to report the reaction of oxaziridines with alkyl isothiocyanates including sugar isothiocyanates.



1 2 3 4

a: R = $PhCH_2$
b: R = *c*-Hexyl
c: R = CH_2=$CHCH_2$

Scheme 1

RESULTS AND DISCUSSION

The reaction of benzyl isothiocyanate with 2-*tert*-butyl-3-phenyloxaziridine (1) was at first carried out. When the mixture of oxaziridine (1) and an excess amount of benzyl isothiocyanate (2a) in toluene was refluxed for 3 h, 4-benzyl-2-*tert*-butyl-3-phenyl-1,2,4-oxadiazolidine-5-thione[11] (3a) as a main product and *N*-*tert*-butyl-α-phenylnitrone[1] (4) were obtained in 58 and 7 % yield, respectively. The products were identified by comparison of

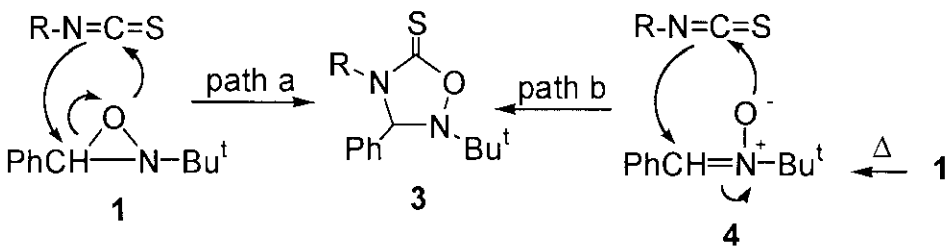
Table 1. Reaction of oxaziridine (1) with isothiocyanates (2).

Isothiocyanate	Reaction Conditions[a]	Time / h	Mole ratio 1:2	Yield[b] / %	
				3	4
2a	A	3	0.8	58	7
2a	B	8	4	42[c]	53
2a	B	3	0.8	54	6
2b	A	10	0.8	26	51
2b	B	9	0.8	43	19
2b	B	6	4	62[c]	44
2c	B	3.5	0.8	24	10
2c	A	3	4	30[c]	73
2c	A	3	0.8	17	38
2d	A	3	3	67[c,d]	53
2e	A	3	3	85[c,e]	65

[a]A:toluene reflux, B: neat 120 °C. [b]Yields were calculated based on 1. [c]Yields were calculated based on 2. [d]**3da**: 50 %, **3db**: 17 %. [e]An inseparable mixture of two products.

their spectral data and melting point with reported ones. Komatsu *et al.* reported that the treatment of oxaziridine (1) with phenyl isothiocyanate gave the mixture of 2-*tert*-butyl-3,4-diphenyl-1,2,4-oxadizolidine-5-thione and -1,2,4-oxadiazolidin-5-one.[8] However, such an oxadiazolidinone was not obtained in the case of the reaction with isothiocyanate (2a). The reactions of other alkyl isothiocyanates with the oxaziridine (1) were carried out and 1,2,4-oxadiazolidinethiones (3) were selectively obtained in the yields shown in Table 1.

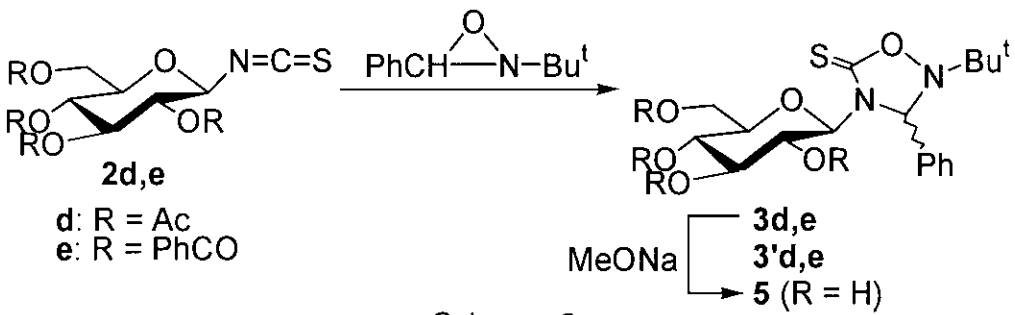
The 1,2,4-oxadiazolidine ring formation is considered to proceed as follows. Because *N*-*tert*-alkyloxaziridines thermally rearrange to nitrones, the 1,2,4-oxadiazolidine-5-thione rings could be formed by 1,3-dipolar cycloaddition of the nitrones to isothiocyanates. However, it was concluded that the reaction of oxaziridines with heterocumulenes did not proceed by way of nitrone formation.[6,8] When the mixture of benzyl isothiocyanate (2a) and *N*-*tert*-butyl-α-phenylnitrone (4) was refluxed in toluene for 8 h, 1,2,4-oxadiazolidine-5-thione (3a) was obtained in 76 % yield. Therefore, it is possible for the reaction of the alkyl isothiocyanates with the oxaziridine to exist two kinds of reaction paths (Scheme 2): the oxadiazolidine rings formed directly with the oxaziridine (path a), and the thermally formed nitrones reacted to isothiocyanates by 1,3-dipolar cycloaddition (path b).



Scheme 2

Since it became clear that oxaziridine (1) reacted with alkyl isothiocyanates to afford 1,2,4-oxadiazolidine-5-thiones (3) selectively, the reactions with glucopyranosyl isothiocyanates were carried out. When the mixture of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**2d**) and an excess amount of oxaziridine (1) in toluene was refluxed for 3 h, two products (**3d** and **3'd**) were isolated from the reaction mixture along with the nitrone (4). The results of elemental analyses showed that the two products were the isomers which formed from equimolecular amount of **1** and **2d**. It is possible that β-glucopyranosyl groups isomerized to α-forms during the reaction. The coupling constants on the C-1 protons of the β-forms (around 10 Hz) is greater than that of the α-forms in the ^{1}H NMR spectrum.

Because the coupling constants on the C-1 protons of the two products were observed in 9.3 and 9.6 Hz, both products had β-glucopyranosyl groups. Therefore, the two isomers were attributed to the stereo isomers of the 1,2,4-oxadiazolidine ring (Scheme 3). In the case of the reaction of 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate (2e), two products (3e and 3'e) were also formed but could not be separated. Assignment of protons on the glucopyranosyl groups in the ^{1}H NMR spectrum was performed with COSY NMR spectrum. Deacetylation of the 3d was carried out with sodium methoxide to afford 2-*tert*-butyl-4-(β-D-glucopyranosyl)-3-phenyloxadiazolidine-5-thione (5) in 44 % yield. During the methanolysis, *N*-*tert*-butylbenzamide was obtained as a by-product, which was formed by elimination of carbonyl sulfide from 5 and subsequent hydrolysis of the produced C=N double bond.



Scheme 3

In conclusion, 2-*tert*-butyl-3-phenyloxaziridine reacted with alkyl isothiocyanates to yield 1,2,4-oxadiazolidine-5-thiones selectively. This reaction was applicable to the synthesis of glucosylaminoheterocycles using glucopyranosyl isothiocyanates.

EXPERIMENTAL

Melting points were determined on a Mettler FP90 microscope plate, and uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Gemini 300 BB spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FTIR-5300 spectrophotometer. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter at 26 °C. MS spectra were taken on a Nippon Denshi DX303 spectrometer.

General procedure for the reaction of 2-*tert*-butyl-3-phenyloxaziridine (1) with alkyl isothiocyanates (2).

A mixture of 2-*tert*-butyl-3-phenyloxaziridine (**1**) and an isothiocyanate (**2**) was heated under the conditions shown in Table 1. When toluene was used as solvent, the solvent was evaporated under reduced pressure. The crude products were chromatographed on silica gel with dichloromethane or dichloromethane:ethyl acetate (10:1) mixture (for **3d**) followed by dichloromethane:acetone:methanol (100:10:2) mixture as an eluent. The product was recrystallized from an appropriate solvent.

2-*tert*-Butyl-3-phenyl-4-phenylmethyloxadiazolidine-5-thione (3a).

mp 102.5-103 °C (dichloromethane-hexane) (lit.,[11] 103-104 °C); IR (KBr) ν 1506, 1456, 1241, 1205, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 3.70 (d, 1H, *J*=14.8 Hz), 5.32 (s, 1H), 5.41 (d, 1H, *J*=14.8 Hz), 7.25-7.30 (m, 4H), 7.35-7.38 (m, 3H), 7.42-7.44 (m, 3H).

2-*tert*-Butyl-4-cyclohexyl-3-phenyloxadiazolidine-5-thione (3b).

mp 147 °C (hexane); IR (KBr) ν 1485, 1454, 1294, 996, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55 (dq, 1H, *J*=3.4 and 12.4 Hz), 0.84-1.00 (m, 1H), 1.20 (s, 9H), 1.13-1.46 (m, 2H), 1.54-1.68 (m, 4H), 1.79-1.89 (m, 1H), 1.92-1.98 (m, 1H), 4.23 (tt, 1H, *J*=12.1 and 3.3 Hz), 5.65 (s, 1H), 7.28-7.31 (m, 2H), 7.37-7.40 (m, 3H); Anal. Calcd for $C_{18}H_{26}N_2OS$: C, 67.87; H, 8.24; N, 8.80. Found: C, 67.89; H, 8.28; N, 8.77.

2-*tert*-Butyl-3-phenyl-4-(2-propen-1-yl)oxadiazolidine-5-thione (3c).

mp 84-85 °C (hexane); IR (KBr) ν 1502, 1310 1238, 932, 774, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 9H), 3.34 (dd, 1H, *J*=8.8 and 15.1 Hz), 4.65 (dd, 1H, *J*=15.1 and 4.7 Hz), 5.20 (d, 1H, *J*=16.2 Hz), 5.31 (d, 1H, *J*=9.9 Hz), 5.58 (s, 1H), 5.69-5.79 (m, 1H), 7.33-7.37 (m, 2H), 7.40-7.44 (m, 3H); Anal. Calcd. For $C_{15}H_{20}N_2OS$: C, 65.18; H, 7.29; N, 10.14. Found: C, 65.34; H, 7.39; N, 10.21.

(+)-2-*tert*-Butyl-3-phenyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-oxadiazolidine-5-thione (3d).

mp 149-150 °C (ethyl acetate-hexane); $[\alpha]_D$ = +47.1° (c=1.0, $CHCl_3$); IR (KBr) ν 1746, 1435, 1370, 1233, 1044, 924 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.92 (s, 3H), 1.96 (s, 3H), 2.01 (s, 3H), 2.10 (s, 3H), 3.62 (dt, 1H, *J*=3.4 and 10.1 Hz, H-5), 3.78 (d, 2H, *J*=4.1 Hz, H-1), 4.62 (dd, 1H, *J*=9.3 and 9.9 Hz, H-2), 5.20 (t, 1H, *J*=9.3 Hz, H-4), 5.30 (t, 1H, *J*=9.3 Hz, H-3), 5.76 (d, 1H, *J*=9.3 Hz, H-1), 5.77 (s, 1H), 7.36-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.37, 20.50, 20.69, 24.80, 28.24, 61.33, 61.86, 67.49, 68.02, 73.63, 73.81, 84.02, 128.04, 128.59, 129.61, 138.33, 169.50, 169.97, 170.41, 170.44, 186.50; Anal. Calcd. for $C_{26}H_{34}N_2O_{10}S$: C, 55.11; H, 6.05; N, 4.95. Found: C, 55.09; H, 6.09; N, 4.86.

(-)-2-*tert*-Butyl-3-phenyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-

oxadiazolidine-5-thione (3'd).

mp 151-152 °C (ethyl acetate-hexane); $[\alpha]_D$ = −7.5° (c=1.0, $CHCl_3$); IR (KBr) ν 1750, 1439, 1370, 1221, 1036, 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 9H), 1.81 (s, 3H), 1.85 (s, 3H), 2.03 (s, 3H), 2.13 (s, 3H), 3.84-3.91 (m, 1H, H-5), 4.09-4.21 (m, 1H, H-6), 4.29-4.37 (m, 2H, H-2 and H-6), 4.98 (t, 1H, *J*=9.9 Hz, H-4), 5.13 (t, 1H, *J*=9.3 Hz, H-3), 5.83 (s, 1H), 5.87 (d, 1H, *J*=9.6 Hz, H-1), 7.32-7.39 (m, 2H), 7.41-7.45 (m, 3H); Anal. Calcd. $C_{26}H_{34}N_2O_{10}S$: C, 55.11; H, 6.05; N, 4.95. Found: C, 55.07; H, 6.02; N, 4.85.

2-*tert*-Butyl-3-phenyl-4-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)oxadiazolidine-5-thione (3e+3'e).

mp 99-104 °C (ethyl acetate-hexane); IR (KBr) ν 1732, 1453, 1265, 1094, 710 cm^{-1}; ^1H NMR ($CDCl_3$) for isomer 3e: δ 1.12 (s, 9H), 3.95 (dd, 1H, *J*=4.9 and 12.1 Hz, H-6), 4.32 (dd, 1H, *J*=2.7 and 12.1 Hz, H-6), 4.29-4.37 (m, 1H, H-5), 4.68 (t, 1H, *J*=9.6 Hz, H-2), 5.59 (t, 1H, *J*=9.9 Hz, H-4), 5.84 (t, 1H, *J*=9.6 Hz, H-3), 5.86 (s, 1H), 6.29 (d, 1H, *J*=9.6 Hz, H-1), 7.04-8.16 (m, 25H); for isomer 3'e: 0.97 (s, 9H), 4.08-4.14 (m, 1H, H-5), 4.51 (dd, 1H, *J*=5.2 and 12.4 Hz, H-6), 4.83 (dd, 1H, *J*=2.5 and 12.4 Hz, H-6), 5.26 (t, 1H, *J*=9.6 Hz, H-4), 5.78 (t, 1H, *J*=9.3 Ha, H-2), 5.91 (t, 1H, *J*=9.3 Hz, H-3), 5.95 (s, 1H), 6.16 (d, 1H, *J*=9.6 Hz, H-1), 7.04-8.16 (m, 25H); Anal. Calcd. for $C_{46}H_{42}N_2O_{10}S$: C, 67.80; H, 5.19; N, 3.44. Found: C, 67.63; H, 5.10; N, 7.37.

Deacetylation of 2-*tert*-butyl-3-phenyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-oxadiazolidine-5-thione (3d).

To a solution of 3d (0.15 mmol) in methanol (15 mL) was added sodium methoxide methanol solution (28 %, 0.02 mL, *ca.* 0.08 mmol). The solution was stirred for 3 h at rt. Amberlyst 15 was added to the solution until the solution became acidic. After removal of the solid with filtration, the filtrate was evaporated and the crude product was chromatographed with dicholromethane:acetone:methanol (10:4:2) mixture as an eluent on silica gel. Deacetylated compound (5, 26.5 mg, 44 %) was obtained along with *N*-*tert*-butylbenzamide (2.7 mg).

2-*tert*-Butyl-4-(β-D-glucopyranosyl)-3-phenyloxadiazolidine-5-thione (5).

oil; ^1H NMR ($CDCl_3$) δ 1.24 (s, 9H), 2.94 (br s, 4H), 3.11 (t, 1H, *J*=9.3 Hz), 3.24 (d, 1H, *J*=9.6 Hz), 3.32 (d, 1H, *J*=10.5 Hz), 3.45 (d, 1H, *J*=10.5 Hz), 3.52 (t, 1H, *J*=9.6 Hz), 3.70 (t, 1H, *J*=8.5 Hz), 5.40 (d, 1H, *J*=9.1 Hz), 5.98 (s, 1H), 7.37-7.43 (m, 5H); FAB MS *m/z* 399 (M^++1), 339(M^++1-O=C=S), 237, 178, 122.

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