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A Novel One-Step Synthesis of Thioquinazoline Glycosides and Pyrazolopyrimidine Glycoside Analogs[1]

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The reaction of glycosyl isothiocyanates (**1a**, **b**, **c**) with anthranilic acid gave corresponding glycosyl thioquinazolines (**3a**, **b**, **c**) in the presence of zinc chloride in excellent yields. The reaction performed in the absence of zinc chloride afforded the intermediate glycosyl thioureides (**2a**, **b**) along with the cyclized compounds.

However, similar treatment of **1a** with 2-amino-3-carboethoxypyridine did not give the corresponding glycosyl pyridopyrimidine (**5a**), but glycosyl thioureide (**4a**) was obtained in good yield. Attempted ring closure of **4a** under neutral or acidic conditions failed.

Similar reactions of **1a**, **b**, and **c** with 3-aminopyrazole-4-carboxylic acid in the presence of zinc chloride afforded corresponding pyrazolo[4,3-*e*]pyrimidine glycosides (**6a**, **b** and **c**) in fair yields.

Keywords——glycosyl isothiocyanate; thioquinazoline glycoside; pyrazolo[4,3-*e*]-pyrimidine glycoside; dehydration reaction; zinc chloride

In previous reports,[3] we reported a convenient synthetic method for nucleoside analogs using glycosyl isothiocyanates as starting materials. This paper describes a facile synthetic procedure for thioquinazoline glycosides and pyrazolo[4,3-*e*]pyrimidine glycosides from the reaction of glycosyl isothiocyanates with enaminocarboxylate. Treatment of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**1a**) or 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl isothiocyanate (**1b**) with anthranilic acid in dry xylene under heating at 60—70° for 3 hr, followed by chromatography over silica gel gave the corresponding glycosyl thioureide (**2a** or **b**) and thioquinazoline glycoside (**3a** or **b**) in 1:1 ratio. When the reaction was performed in the presence of zinc chloride at 110° for 4 hr, the ratio changed to 3:8. Furthermore, on extending the reaction time to 7—10 hr, the cyclized compound (**3a** or **b**) was the sole product. In the case of the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl isothiocyanate (**1c**) with anthranilic acid, ribofuranosyl thioureide (**2c**) was not isolated and thioquinazoline riboside (**3c**) was obtained in a fair yield.

The infrared (IR) spectra of these products (**2a**, **b** and **3a**, **b**, **c**) showed NH bands at around 3350—3200 cm^{-1} instead of isothiocyanate bands (2000—2100 cm^{-1}). The nuclear magnetic resonance (NMR) spectra of **3a**, **b** and **c** showed a broad singlet peak at δ 10.60—10.82 which was assigned to the NH proton. The physical data for these products are summarized in Table I. It can be concluded that the presence of zinc chloride in the reaction mixture was effective in promoting a dehydration reaction to afford thioquinazoline glycosides.

Similar treatments of **1a**, **b** and **c** with 3-aminopyrazole-4-carboxylic acid in the presence of zinc chloride gave the corresponding pyrazolo[4,3-*e*]pyrimidine glycoside analogs (**6a**, **b** and **c**) in excellent yields (Table II). However, treatment of **1a** with 2-amino-3-carboethoxypyridine gave N-(3-carbethoxypyrid-2-yl)-N'-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thioureide (**4a**) in good yield and **5a** was not obtained. The NMR spectrum of **4a** showed a quartet

1) Previous paper: H. Takahashi, N. Nimura, and H. Ogura, *Chem. Pharm. Bull.* (Tokyo), **27**, 1137 (1979); This constitutes Part XXVIII in a series entitled "Studies on Heterocyclic Compounds."
2) Location: *5-9-1 Shirokane, Minato-ku, Tokyo 108, Japan.*
3) H. Ogura, H. Takahashi, K. Takeda, and N. Nishimura, *Nucleic Acids Res.*, **S2**, 7 (1976); H. Ogura and H. Takahashi, *Heterocycles*, **6**, 1633; **8**, 125 (1977); H. Ogura, H. Takahashi, and E. Kudo, *J. Carbohydr. Nucleosides Nucleotides*, **5**, 329 (1978).

Table I. N-Glycosyl-N′-(*o*-carboxyphenyl) thioureide (**2a, b**) and N-Glycosyl-2-thioquinazolin-4-one (**3a, b, c**)

Compd. No.	mp (°C)	Yield (%) ($ZnCl_2$)	IR ν_{max}^{KBr} cm^{-1})	NMR (δ, $CDCl_3$) heterocyclic moiety	Analysis (%) Calcd.	Found
					$C_{22}H_{26}N_2O_{11}S$	
2a	175—176	20(0)	3200, 1740, 1690, 1610, 750	7.00—8.20 (4H, m, Ph), 8.90 (1H, d, J=8.0 Hz, 1-NH), 11.08 (1H, bs, NH)	C 50.19	50.32
					H 4.98	4.95
					N 5.32	5.50
					(M^+–H_2O, *m/e* 508)	
					$C_{22}H_{24}N_2O_{10}S$	
3a	150—153	70(95)	3300, 1740, 1600, 760, 740	6.78—8.10 (4H, m, Ph), 10.61 (1H, bs, NH)	C 51.97	51.75
					H 4.76	4.90
					N 5.51	5.73
					(M^+, *m/e* 508)	
					$C_{20}H_{24}N_2O_9S$	
2b	183—184 (dec.)	40(0)	3250, 1740, 1600, 750	7.08—8.30 (4H, m, Ph), 2.38 (3H, s, Me)	C 51.28	51.38
					H 5.16	5.24
					N 5.98	5.72
					(M^+, *m/e* 468)	
					$C_{19}H_{20}N_2O_8S$	
3b	123—124	52(87)	3250, 1740, 1700, 1600, 1590, 1750	7.10—8.30 (4H, m, Ph), 10.18 (1H, bs, NH)	C 52.30	52.48
					H 4.62	4.65
					N 6.42	6.54
					(M^+, *m/e* 436)	
					$C_{34}H_{26}N_2O_8S$	
3c	188—189	80(97)	3200, 1710, 1690, 1630, 1530, 750	10.82 (1H, bs, NH)	C 65.59	65.83
					H 4.21	4.50
					N 4.50	4.48

Table II. 3-Glycosylpyrazolo[4,3-*e*]-4-thiopyrimidin-6-one (**6a, b, c**)

Compd No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	NMR (δ, $CDCl_3$) heterocyclic moiety	Analysis (%) Calcd.	Found
					$C_{19}H_{22}N_4O_{10}S$	
6a	136—137	93	3500, 3300, 1740, 1540, 1510, 1220, 1050	8.28 (1H, d, J=4.0 Hz, 7-H), 9.00 (1H, bs, NH), 9.88 (1H, bs, NH)	C 45.78	45.90
					H 4.45	4.26
					N 11.24	11.19
					(M^+, *m/e* 498)	
					$C_{16}H_{18}N_4O_8S$	
6b	Syrup[a)]	82	3250, 3300, 1740, 1540, 1210, 1050	8.32 (1H, d, J=4.0 Hz, 7-H), 9.15 (1H, bs, NH), 9.50 (1H, bs, NH)	C 45.07	45.32
					H 4.26	4.28
					N 13.14	13.20
					(M^+, *m/e* 426)	
					$C_{31}H_{24}N_4O_8S$	
6c	Syrup[b)]	87	3500, 3250, 1710, 1590, 1580, 690	9.05 (1H, bs, NH), 9.45 (1H, bs, NH)	C 60.78	60.95
					H 3.95	4.08
					N 9.15	9.27

a) TLC (silica gel) *Rf* 0.55 (benzene/acetone=4: 1).
b) TLC (silica gel) *Rf* 0.75 (benzene/acetone=4: 1).

peak at δ 4.40 and a triplet peak at δ 1.40 due to the ethyl group. The NH signal at the anomeric position appeared at δ 12.50 as a doublet. Another NH signal was observed at δ 11.62 as a broad singlet. Both signals disappeared on addition of D_2O. The mass spectrum of **4a** showed *m/e* 555 (M^+). Attempts to cause ring closure of **4a** under neutral or acidic conditions failed, and the starting material was recovered.

Debenzoylation of **3c** with methanolic ammonia gave the free thioquinazoline riboside (**7c**) in 77% yield. The mass pattern of **7c** is shown in Fig. 1. In the mass spectrum, the molecular ion was observed at *m/e* 310 (1.5%) and the loss of H_2O produced *m/e* 292 (3%). Direct cleavage of the glycosidic bond produced *m/e* 178 (base+1) (100%), *m/e* 179 (base+2) (38%) and *m/e* 133 (sugar moiety) (4%); such phenomena are common in mass spectra of nucleosides.[4]

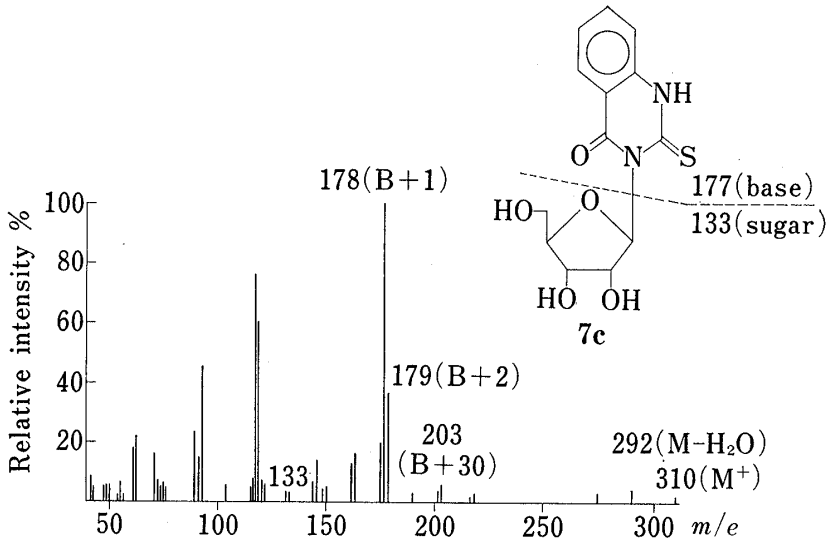

Fig. 1

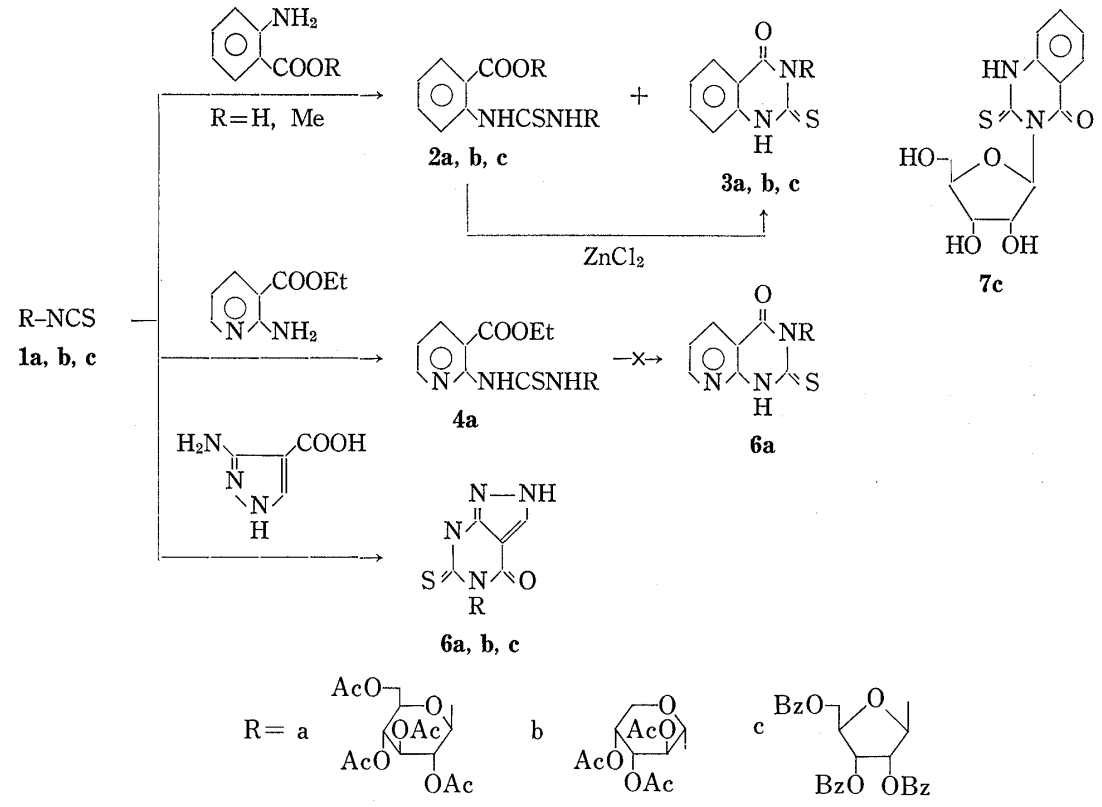

Chart 1

4) K. Bieman and J.A. McCloskey, *J. Am. Chem. Soc.*, **84**, 2005 (1962); J.J. Dolhun and J.L. Wiebers, *Org. Mass Spectrometry*, **3**, 669 (1970).

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-2 spectrometer and NMR spectra on a Varian T-60 spectrometer. Tetramethylsilane was used as an internal reference. Mass spectra were determined with a JMS-D-100 spectrometer using a direct inlet system at 75 eV.

N-Glycosyl-N′-(*o*-carboxyphenyl)thioureide (2a, b, c) and N-Glycosyl-2-thioquinazolin-4-one (3a, b)——a) A mixture of **1a** (390 mg, 0.001 mol) and anthranilic acid (137 mg, 0.001 mol) in dry xylene (20 ml) was heated on a water bath (at 60—70°) for 1.5 hr and allowed to stand at room temperature. After collection of the separated crystals by filtration, these were recrystallized from MeOH to give N-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-N′-(*o*-carboxyphenyl)thioureide (**2a**) as colorless needles (370 mg, 70%). To the filtrate was added dry xylene (30 ml), and the mixture was further heated at 110° for 4 hr. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with $CHCl_3$–acetone. The eluate from $CHCl_3$–acetone (19: 1) was crystallized from *n*-hexane–ether (1: 1) to give 3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)thioquinazolin-4-one (**3a**) as fine colorless needles (100 mg, 20%).

b) A mixture of **1b** (319 mg, 0.001 mol) and anthranilic acid methyl ester (167 mg, 0.001 mol) in dry benzene (15 ml) was refluxed for 20 hr and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel with benzene–acetone (19: 1) to give **3b** (230 mg, 52%). Further, elution with benzene–acetone (17: 3) gave **2b** (190 mg, 40%). Both crystals were recrystallized from benzene to give **6b** and **3b** as fine colorless needles.

c) A mixture of **1c** (503 mg, 0.001 mol) and anthranilic acid (137 mg, 0.001 mol) in dry xylene (20 ml) was refluxed for 17 hr. The reaction solution was treated as described in a), then 3-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-2-thioquinazolin-4-one (**3c**) was isolated (498 mg, 80%) and recrystallized from MeOH to give **3c** as colorless needles.

d) A mixture of **1a, b, c** (0.001 mol), anthranilic acid (137 mg, 0.001 mol) and $ZnCl_2$ (20—50 mg) in dry xylene (20 ml) was refluxed for 3 hr and the reaction mixture was treated as described in a).

N-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-N′-(3-carboethoxypyrid-2-yl)thioureide (4a)——A mixture of **1a** (389 mg, 0.001 mol) and 2-amino-3-carboethoxypyridine (166 mg, 0.001 mol) in MeCN (20 ml) was refluxed for 10 hr and allowed to stand at room temperature. Crystals that separated were collected by filtration and recrystallized from benzene to give 525 mg (95%) of **4a** as fine colorless needles. mp 267—268°. *Anal.* Calcd. for $C_{23}H_{29}N_3O_{11}S$: C, 49.73; H, 5.25; N, 7.56. Found: C, 49.68; H, 5.25; N, 7.31. MS *m/e*: 555 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1740 (ester), 1690, 1230, 1050. NMR ($CDCl_3$) δ: 1.40 (3H, t, $CH_2C\underline{H}_3$), 4.40 (2H, q, $C\underline{H}_2CH_3$), 11.62 (1H, bs, NH), 12.50 (1H, d, J=8.0 Hz, 1-NH), 8.35 (3H, m, pyridine ring).

Attempted Cyclization of 4a——a) A solution of **4a** (530 mg, 0.001 mol) in dry xylene (30 ml) was refluxed for 50 hr. The solvent was removed under reduced pressure to leave the starting material.

b) A solution of **4a** (525 mg, 0.001 mol) in PPA (10 ml) (prepared form H_3PO_4 (3 ml) and P_2O_5 (3 g)) was heated at 100° for 6 hr. After cooling, the reaction mixture was poured into ice-water, the separated crystals were collected by filtration and the starting material was recovered.

3-Glycosylpyrazolo[4,3-*e*]-2-thiopyrimidin-4-one (6a, b, c) (Table II)——A mixture of **1a, b** or **c** (0.001 mol) and 3-aminopyrazole-4-carboxylic acid (127 mg, 0.001 mol) in dry xylene (20 ml) in the presence of $ZnCl_2$ (40—50 mg) was refluxed for 2—3 hr. After removal of the solvent the residue was crystallized from benzene to yield **6a, b** or **c** as fine colorless needles.

3-(*β*-D-Ribofuranosyl)-1,2,3,4-tetrahydro-2-thioquinazolin-4-one (7c)——In 10 ml of MeOH saturated with NH_3 was dissolved **3c** (600 mg, 0.002 mol) with ice cooling. The reaction mixture was stirred for 3 hr under the same conditions, then the solvent was evaporated off under reduced pressure below 45°. The residue was crystallized from EtOH to give 230 mg (77%) of **7c** as fine colorless needles. mp 188—189°. IR ν_{max}^{KBr} cm^{-1}: 3450, 1700, 1620, 1030, 750. *Anal.* Calcd. for $C_{13}H_{14}N_2O_5S$: C, 50.32; H, 4.55; N, 9.03. Found: C, 50.56; H, 4.83; N, 8.95.