Novel and Efficient Synthesis of 4-Dimethylamino-2-glycosylaminoquinazolines by Cyclodesulfurization of Glycosyl Thioureas with Dimethylcyanamide

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4-Dimethylamino-2-glycosylaminoquinazoline derivatives were synthesized by cyclodesulfurization of *N*-aryl-*N*′-glycosyl thioureas with dimethylcyanamide in the presence of silver triflate in good yields.

Key words quinazoline; glycosyl thiourea; dimethylcyanamide; silver triflate; cyclodesulfurization

Much attention has been paid to the synthesis of quinazoline derivatives, and in particular to their 2-amino, 4-amino, and 2,4-diamino derivatives, which exhibit biological and pharmaceutical activities.[1)] Particular attention has been focused on 2,4-diamino derivatives, which show bioactivities such as antimalarial effects,[2)] atrial natriuretic peptide receptor modulation,[3)] and dihydrofolate reductase inhibition.[4)] Although several methods for preparing 2,4-diaminoquinazoline derivatives have been reported,[5,6)] there is strong demand for the development of novel and convenient synthetic methods that will facilitate research on novel biological functions. We have been developing a synthetic method based on cyclodesulfurization of various thiocarbonyl compounds by silver salts in carbohydrate chemistry.[7,8)] Glycosyl thioureas have been widely used as important intermediates in synthetic approaches to nucleoside analogues.[9—12)] We have recently found that the cyclodesulfurization of *N*,*N*,*N*′-trisubstituted glycosyl thioureas with silver cyanate gives new types of 1-glycosyl 5-azauracil derivatives as nucleoside analogeus.[13)] We wish to report here a new method for the synthesis of 4-dimethylamino-2-glycosylaminoquinazoline derivatives by cyclodesulfurization of *N*-aryl-*N*′-glycosyl thioureas (**1a**—**c** and **2a**—**c** in Fig. 1) with dimethylcyanamide.

We carried out the cyclodesulfurization of *N*-phenyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (**1a**) first, with 2.6 equivalents of silver triflate (AgOTf) in the presence of excess dimethylcyanamide at 100 °C for 5 h (Chart 1). Neutralization of the resulting crude product with aq. NaOH and subsequent purification by column chromatography on silica gel give 4-dimethylamino-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylamino)-quinazoline (**3a**) in 67% yield. Quinazoline **3a** shows ν_{max} at 1578—1370 cm^{-1}, which is characteristic of the quinazoline ring. The ^{1}H-NMR spectrum of **3a** contains a triplet at 5.68 ppm (H-1′, β-*N*-glycoside), the β-configuration is confirmed by the large vicinal coupling constant ($J_{1',2'}$=9.6 Hz). The ^{13}C-NMR spectrum of **3a** shows at δ 156.96 and 164.91 ppm due to the two carbon atoms (C-2, C-4) of the newly formed quinazoline ring. Novel glycosyl quinazoline derivatives **3b**—**c** and **4a**—**c** were obtained in good yields from glycosyl thioureas **1b**—**c** and **2a**—**c** under the conditions used for **1a** (Chart 1, 2).

A plausible mechanism for the cyclodesulfurization is shown in Chart 3. Glycosyl thiourea and silver triflate initially formed an adduct, which then undergoes attack at the sulfur atom by another silver ion and simultaneous nucleophilic addition of dimethylcyanamide at the imino carbon to afford quinazoline ring with the elimination of Ag_2S.

In conclusion, we have described the cyclodesulfurization of *N*-aryl-*N*′-glycosyl thioureas with dimethylcyanamide in the presence of silver triflate affording 4-dimethylamino-2-glycosylaminoquinazoline derivatives. This synthetic method may facilitate research aimed at the development of 2,4-diaminoquinazoline derivatives with novel biological functions.

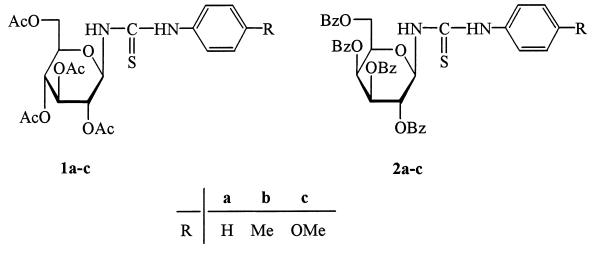

Fig. 1. *N*-Aryl-*N*′-Glycosyl Thioureas

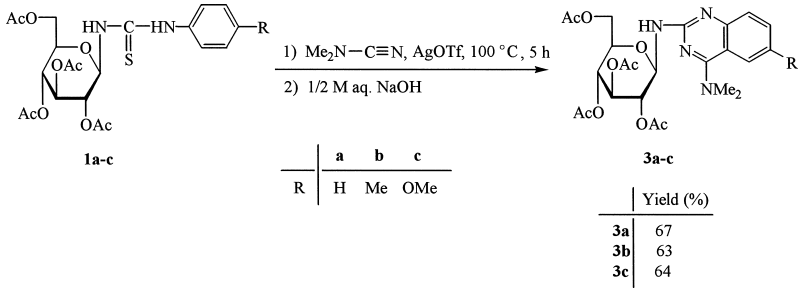

Chart 1. Cyclodesulfurization of *N*-Aryl-*N*′-Glucosyl Thioureas (**1a**—**c**) with Dimethylcyanamide

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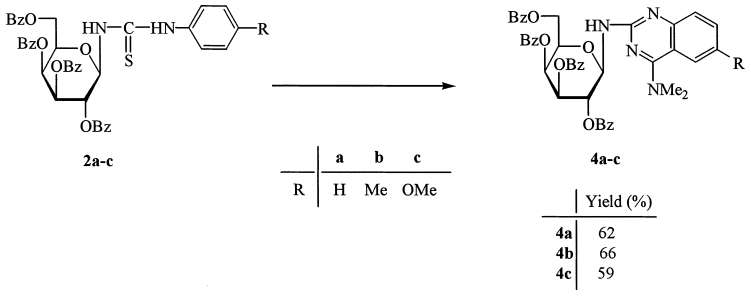

Chart 2. Cyclodesulfurization of *N*-Aryl-*N*′-Galactosyl Thioureas (**2a**—**c**) with Dimethylcyanamide

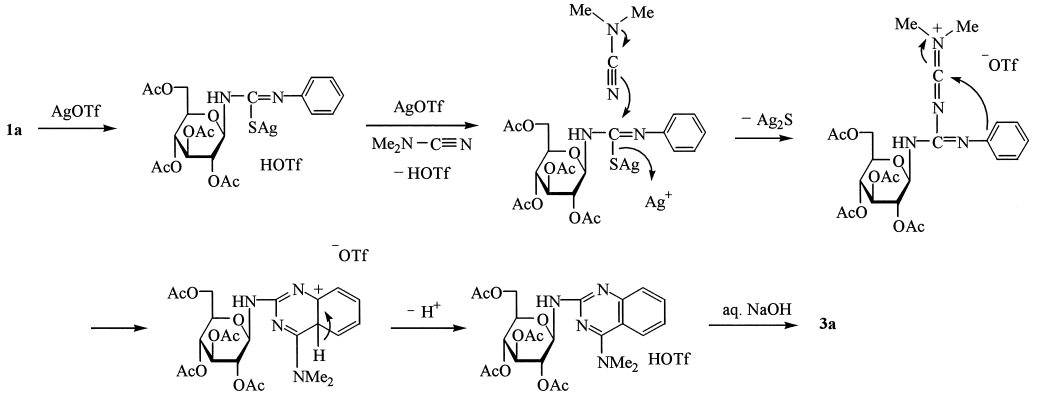

Chart 3. A Plausible Mechanism of Quinazoline Ring Formation

Experimental

Melting points were determined on a Mettler FP90 microscopic plate and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a JASCO FTIR-5300 spectrophotometer on KBr disks. NMR spectra were obtained with a Varian Inova 400 spectrometer, and chemical shifts are reported in parts per million relative to internal tetramethylsilane. TLC was conducted on plates coated with silica gel F_{254} (Merck), and products were detected by UV light or by charring with H_2SO_4. Purification was accomplished by column chromatography on silica gel (Wakogel C-200). Starting *N*-aryl-*N*′-glycosyl thioureas were prepared from the corresponding glycosyl isothiocyanates and arylamines.[14]

General Procedure for the Cyclodesulfurization of *N*-Aryl-*N*′-Glycosyl Thioureas of Dimethylcyanamide To a stirred solution of **1a**—**c** or **2a**—**c** (1 mmol) in dry dimethylcyanamide (3 ml) was added AgOTf (2.6 mmol). The reaction mixture was stirred at 100 °C for 5 h. After cooling the reaction mixture, ethyl acetate, brine, and 0.5 M aq. NaOH (10 ml) were added and silver salts were removed by filtration. The organic layer was separated and washed with water and brine. The washed solution was dried ($MgSO_4$) and concentrated, and the residue was purified by column chromatography on silica gel. The yields, melting points, recrystallization solvents, $[\alpha]_D^{25}$ values, and characterization data are listed below.

4-Dimethylamino-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosylamino)-quinazoline (**3a**): 67%. mp 189—190 °C (hexane–EtOH). $[\alpha]_D^{25}$ −2.0° (*c*=1.32, $CHCl_3$). IR cm^{-1}: 3439, 1757, 1578, 1508, 1370. ^{1}H-NMR ($CDCl_3$) *δ*: 2.02 (3H, s), 2.04 (6H, s), 2.05 (3H, s), 3.29 (6H, s, NMe_2), 3.90 (1H, m, H-5′), 4.11 (1H, dd, *J*=2.4, 12.2 Hz, H-6′), 4.29 (1H, dd, *J*=4.5, 12.5 Hz, H-6′), 5.11 (1H, t, *J*=9.6 Hz), 5.14 (1H, t, *J*=9.9 Hz), 5.41 (1H, t, *J*=9.3 Hz), 5.56 (1H, br d, *J*=10.2 Hz, NH), 5.68 (1H, t, *J*=9.6 Hz, H-1′), 7.1—7.9 (4H, m, Ar). ^{13}C-NMR ($CDCl_3$) *δ*: 20.65 (2C), 20.72, 20.77, 41.76 (2C, NMe_2), 62.15 (C-6′), 68.84, 70.62, 73.01, 73.53, 81.35 (C-1′), 113.13, 121.05, 125.77, 126.27, 132.19, 153.82, 156.96 (C=N), 164.91 (C=N), 169.58, 170.18, 170.49, 170.72. *Anal.* Calcd for $C_{24}H_{30}N_4O_9$: C, 55.59; H, 5.83; N, 10.81. Found: C, 55.63; H, 5.71; N, 10.56.

4-Dimethylamino-6-methyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosylamino)-quinazoline (**3b**): 63%. mp 146—147 °C (^{i}Pr$_2$O–EtOAc). $[\alpha]_D^{25}$ −3.7° (*c*=1.01, $CHCl_3$). IR cm^{-1}: 3430, 1748, 1573, 1520, 1371. ^{1}H-NMR ($CDCl_3$) *δ*: 2.01 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.41 (3H, s, Me), 3.27 (6H, s, NMe_2), 3.90 (1H, m, H-5′), 4.10 (1H, dd, *J*=2.4, 12.3 Hz, H-6′), 4.28 (1H, dd, *J*=4.5, 12.2 Hz, H-6′), 5.11 (1H, t, *J*=9.3 Hz), 5.14 (1H, t, *J*=9.9 Hz), 5.40 (1H, t, *J*=9.3 Hz), 5.58 (1H, br d, *J*=10.1 Hz, NH), 5.66 (1H, t, *J*=9.0 Hz, H-1′), 7.4—7.5 (3H, m, Ar). ^{13}C-NMR ($CDCl_3$) *δ*: 20.69 (2C), 20.78, 20.82, 21.56 (Me), 41.84 (2C, NMe_2), 62.24 (C-6′), 68.90, 70.69, 73.06, 73.64, 81.51 (C-1′), 113.18, 125.14, 126.16, 130.77, 134.30, 152.08, 156.75 (C=N), 165.11 (C=N), 169.91, 170.52, 170.81, 171.07. *Anal.* Calcd for $C_{25}H_{32}N_4O_9$: C, 56.38; H, 6.06; N, 10.52. Found: C, 56.26; H, 5.92; N, 10.30.

4-Dimethylamino-6-methoxy-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosylamino)-quinazoline (**3c**): 64%. mp 112—113 °C (^{i}Pr$_2$O–EtOAc). $[\alpha]_D^{25}$ −10.2° (*c*=1.03, $CHCl_3$). IR cm^{-1}: 3432, 1753, 1580, 1516, 1370. ^{1}H-NMR ($CDCl_3$) *δ*: 2.01 (3H, s), 2.03 (6H, s), 2.05 (3H, s), 3.26 (6H, s, NMe_2), 3.85 (3H, s, OMe), 3.89 (1H, m, H-5′), 4.09 (1H, dd, *J*=2.0, 12.2 Hz, H-6′), 4.28 (1H, dd, *J*=4.4, 12.4 Hz, H-6′), 5.11 (1H, t, *J*=9.2 Hz), 5.13 (1H, t, *J*=9.2 Hz), 5.40 (1H, t, *J*=9.2 Hz), 5.59 (1H, br d, *J*=10.1 Hz, NH), 5.65 (1H, t, *J*=9.2 Hz, H-1′), 7.2—7.5 (3H, m, Ar), ^{13}C-NMR ($CDCl_3$) *δ*: 20.66 (2C), 20.75, 20.79, 41.66 (2C, NMe_2), 55.64 (OMe), 62.11 (C-6′), 68.78, 70.58, 72.94, 73.51, 81.40 (C-1′), 106.17, 113.20, 116.26, 123.02, 127.37, 153.81, 155.83 (C=N), 164.88 (C=N), 169.59, 170.20, 170.50, 170.74. *Anal.* Calcd for $C_{25}H_{32}N_4O_{10}$: C, 54.74; H, 5.88; N, 10.21. Found: C, 54.71; H, 5.67; N, 10.13.

4-Dimethylamino-2-(2′,3′,4′,6′-tetra-*O*-benzoyl-*β*-D-galactopyranosylamino)-quinazoline (**4a**): 62%. mp 110—111 °C (hexane–EtOAc). $[\alpha]_D^{25}$ +97.1° (*c*=1.01, $CHCl_3$). IR cm^{-1}: 3430, 1728, 1572, 1510, 1400. ^{1}H-NMR ($CDCl_3$) *δ*: 3.24 (3H, s, NMe_2), 4.43 (1H, dd, *J*=6.0, 10.8 Hz,), 4.52 (1H, br t, *J*=6.0 Hz, H-5′), 4.59 (1H, dd, *J*=6.4, 10.8 Hz, H-6′), 5.85 (1H, d, *J*=10.0 Hz), 5.88 (1H, dd, *J*=3.2, 10.4 Hz), 5.94 (1H, br d, *J*=*ca.* 10 Hz, NH), 5.99 (1H, t, *J*=9.2 Hz, H-1′), 6.06 (1H, d, *J*=2.8 Hz, H-4′), 7.1—8.1 (24H, m, Ar). ^{13}C-NMR ($CDCl_3$) *δ*: 41.73 (2C, NMe_2), 62.36 (C-1′), 68.71, 69.49, 72.27, 72.37, 82.05 (C-1′), 113.09, 120.96, 125.77, 126.26, 128.3—130.0 (20C, Ar), 132.14, 133.1—133.6 (4C, Ar), 153.80, 157.08 (C=N), 164.80 (C=N), 165.57 (2C), 166.12, 166.44. *Anal.* Calcd for $C_{44}H_{38}N_4O_9$: C, 68.92; H, 5.00; N, 7.31. Found: C, 68.83; H, 4.85; N, 7.23.

4-Dimethylamino-6-methyl-2-(2′,3′,4′,6′-tetra-*O*-benzoyl-*β*-D-galactopyranosylamino)-quinazoline (**4b**): 66%. mp 107—108 °C (hexane–EtOAc). $[\alpha]_D^{25}$ +95.0° (*c*=1.13, $CHCl_3$). IR cm^{-1}: 3430, 1728, 1574, 1514, 1400. ^{1}H-NMR ($CDCl_3$) *δ*: 2.40 (3H, s, Me), 3.21 (6H, s, NMe_2), 4.42 (1H, dd, *J*=6.0, 10.6 Hz, H-6′), 4.52 (1H, br t, *J*=6.0 Hz, H-5′), 4.60 (1H, dd, *J*=6.8, 10.8 Hz, H-6′), 5.85 (3H, m, H-2′, H-3′ and NH), 5.99 (1H, t, *J*=9.2 Hz, H-

1′), 6.06 (1H, d, J=2.0 Hz, H-4′), 7.2—8.1 (23H, m, Ar). ^{13}C-NMR ($CDCl_3$) δ: 21.53 (Me), 41.73 (2C, NMe_2), 62.33 (C-6′), 68.70, 69.49, 72.27, 72.30, 82.10 (C-1′), 112.98, 124.91, 126.02, 128.3—130.0 (20C, Ar), 130.37, 133.0—133.6 (4C, Ar), 133.97, 151.92, 156.62 (C=N), 164.74 (C=N), 165.56 (2C), 166.10, 166.42. *Anal.* Calcd for $C_{45}H_{40}N_4O_9$: C, 69.22; H, 5.16; N, 7.18. Found: C, 69.08; H, 5.18; N, 6.93.

4-Dimethylamino-6-methoxy-2-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-galactopyranosylamino)-quinazoline (**4c**): 59%. mp 109—110 °C. $[\alpha]_D^{25}$ +96.6° (c=1.12, $CHCl_3$). IR cm^{-1}: 3430, 1728, 1562, 1512, 1400. ^{1}H-NMR ($CDCl_3$) δ: 3.21 (6H, s, NMe_2), 3.84 (3H, s, OMe), 4.42 (1H, dd, J=6.0, 10.6 Hz, H-6′), 4.51 (1H, br t, J=6.4 Hz, H-5′), 4.60 (1H, dd, J=6.8, 11.0 Hz, H-6′), 5.87 (3H, m, H-2′, H-3′ and NH), 5.97 (1H, t, J=9.2 Hz, H-1′), 6.06 (1H, d, J=2.0 Hz, H-4′), 7.2—8.1 (23H, m, Ar). ^{13}C-NMR ($CDCl_3$) δ: 41.64 (2C, NMe_2), 55.64 (OMe), 62.33 (C-6′), 68.69, 69.49, 72.26, 72.29, 82.13 (C-1′), 106.04, 113.15, 115.01, 122.80, 127.50, 128.2—129.9 (20C, Ar), 132.9—133.4 (4C, Ar), 153.52, 155.93 (C=N), 164.72 (C=N), 165.40 (2C), 165.94, 166.26. *Anal.* Calcd for $C_{45}H_{40}N_4O_{10}$: C, 67.83; H, 5.06; N, 7.03. Found: C, 67.76; H, 5.09; N, 6.75.

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