SYNTHESIS OF 1-(β-D-GLUCOPYRANOSYL) PYRIMIDIN-2(1*H*)-ONES FROM 2-CHLOROPYRIMIDINES

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Abstract: Tetra-*O*-acetyl derivatives **10-12** of the title compounds are easily obtained by hydrolysis of 2-chloropyrimidines **1-3** followed by coupling of the resultant pyrimidin-2(1*H*)-ones **4-6** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide under basic conditions (method A) or treatment of **1-3** with potassium trimethylsilanolate followed by coupling of the resultant 2-(trimethylsilyloxy)pyrimidines, without isolation, with β-D-glucose pentaacetate in the presence of tin tetrachloride (method B).

Introduction

Synthesis of non-natural nucleosides is an intense field of study. Diverse compounds composed of different heterocyclic bases and sugar moieties are being prepared as potential antivirial and antineoplastic drugs or useful models in molecular biological research. The many synthetic methods currently available have been reviewed (1,2). In particular, substituted oxopyrimidines have been invariably popular substrates for the preparation of nucleosides (3,4).

Chloropyrimidines have not been considered previously because they are normally obtained from the corresponding oxopyrimidines (5). Recently, however, we have reported highly efficient synthesis of 2-chloro-4(6)-heteroarylpyrimidines such as **1-3** (Scheme 1) by the reaction of a 2-chloropyrimidine with a heteroaryllithium reagent followed by oxidation of the resultant dihydropyrimidine intermediate (6). 4(6)-Alkylpyrimidine derivatives are also synthesized efficiently by this approach (7). As a result, a large number of 2-chloropyrimidines containing diverse substituents at the position 4 and/or 6 have become available. In this paper we examined two synthetic routes to 1-(β-D-glucopyranosyl)pyrimidin-2(1*H*)-ones from substituted 2-chloropyrimidines.

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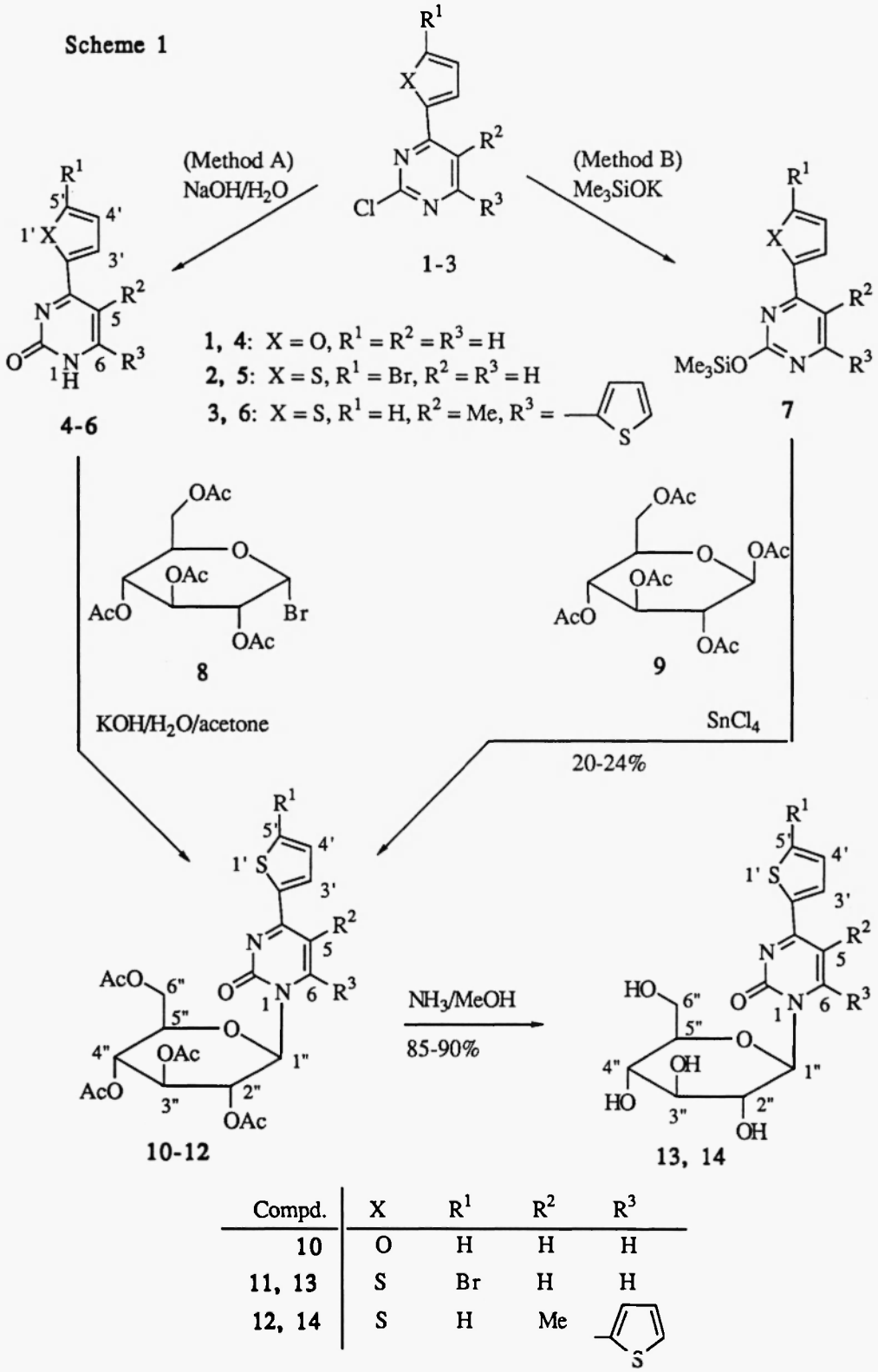
Scheme 1



Compd.	X	R^1	R^2	R^3
10	O	H	H	H
11, 13	S	Br	H	H
12, 14	S	H	Me	

Results and Discussion

In method A, substituted 2-chloropyrimidines **1-3** were hydrolyzed to the corresponding pyrimidinones **4-6** which were isolated and purified. A subsequent coupling of **4-6** with a tetraacetylglucopyranosyl bromide **8** furnished tetraacetyl-substituted glucosides **10-12** in an overall yield ranging from 34% to 37%. Two selected acetyl derivatives **11** and **12** were efficiently hydrolyzed to the respective nucleosides **13** and **14.** All reactions were conducted under conditions reported to be optimized for similar transformations (1,5).

Silylation of a pyrimidinone followed by a Lewis acid-catalyzed reaction of the resultant silyloxypyrimidine with a peracetyl sugar derivative is a popular synthetic route to nucleosides (2). With 2-chloropyrimidines as starting materials this methodology would involve three independent steps, namely hydrolysis, silylation and coupling. In this work, in order to simplify this procedure, the chlorine atom in **1-3** was substituted by the reaction with potassium trimethylsilanolate and the resultant silyloxy derivatives **7**, without isolation, were allowed to react with glucose pentaacetate **9** in the presence of tin tetrachloride to furnish acetylated nucleosides **10-12** directly (method B). Although the yields of **10-12** under optimized conditions were modest, at best, this one-pot procedure is experimentaly simple. Morever, glucose pentaacetate **9** is several times less expensive than the the glucose bromide derivative **8** required in method A. Other sugar derivatives are priced in a similar way.

All three pairs of products **10-12** obtained under anionic (method A) and cationic conditions (method B) gave identical values of specific rotations within the experimental error. They are β-anomers as determined by a coupling constant of 8.4-9.6 Hz between sugar protons *H*1' and *H*2' in the NMR spectra. A much smaller coupling constant is obseved for α-anomers (2,3). The examination of the proton NMR spectra of crude products **10-12** revealed that α-anomers were not present in the mixtures obtained by either method. All products **10-14** are *N*-glucosides, rather than *O*-glucosides, because these compounds are stable under basic and acidic conditions. For steric reasons it was assumed that compounds **10, 11** and **13** are *N*1-substituted pyrimidines (there is no regiochemistry problem for **12** and **14**). This assumption was confirmed by proton NOE studies in conjunction with conformational analysis. In all three cases the irradiation of *H*1 of the sugar (δ 5.93±0.34) gave a strong NOE signal for *H*6 of the pyrimidine (δ 6.86±0.30). These results strongly suggest that a substantial fraction of the molecules of **10, 11** and **13** is in the *syn* orientation of the sugar and pyrimidinone moieties (shown).

Results of the molecular modeling of **11** and **13** by using a PCmodel program (8) are fully consistent with the NOE studies. The conformational analysis gave two low-energy conformations, *syn* and *anti*, in both of which the plane at the pyrimidine ring bisects the sugar moiety. According to the computations the energy minimized (8) pairs of conformers for **11** and **13** (*syn* and *anti*) differ in energy by less than 1 kcal/mol, the anti conformer being slightly more stable. The calculated distance between *H*6 and *H*1' in the *syn* stereochemistry of **11** and **13** is 2.33 Å and 2.29 Å, respectively. In summary,(i) the calculated low energy difference between

the conformers *syn* and *anti*, resulting in a substantial population of the *syn*-conformers, and (ii) the calculated short distance between *H*1'and *H*6 in the *syn*-conformers are fully consistent with the observed *H*1'-*H*6 NOE enhancements.

Experimental Section

M.ps. (pyrex capillary) are not corrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were obtained at 25 °C in $CDCl_3$ or DMSO-d_6 solution with TMS as an internal standard. NOE and decoupling experiments were conducted for chemical shift assignments of protons. The specific rotations (sodium D line) were determined on samples weighing between 15-20 mg and are significant to approximately ±5%. Chloropyrimidines **1-3** were synthesized as reported previously (6) and all remaining reagents were obtained from Aldrich.

Synthesis of Nucleosides 10-12: Method A. A mixture of 2-chloropyrimidine **1-3** (10 mmol), aqueous solution of NaOH (1M, 50 mL) and a catalytic amount of hydrogen peroxide was heated under reflux for 20 h, then cooled and acidified with aqueous acetic acid (5%) to pH 5. The resultant precipitate of **4-6** was filtered, washed with dichloromethane, and then crystallized from glacial acetic acid.

4-(2'-Furyl)pyrimidin-2(1*H*)-one (4): yield 46%; mp 230-234 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (m, H-4'), 7.26 (d , J = 5.1 Hz, H-5), 7.47 (m, H-5'), 8.21 (m, H-3'), 8.48 (d, J = 5.1 Hz, H-6), 11.8 (bs, exchangeable with D_2O, NH). Anal. Calcd for $C_8H_6N_2O_2$: C, 59.25; H, 3.70 ; N, 17.28. Found: C, 58.92 ; H, 3.73; N, 17.42.

4-(5'-Bromo-2'-thienyl)pyrimidin-2(1*H*)-one (5): yield 48 %; mp > 300 °C; ^{1}H NMR (DMSO-d_6): δ 6.94 (d, J = 6.4 Hz , H-5), 7.39 (d , J = 3.6 Hz , H-4'), 7.91 (d, J = 3.6 Hz, H-3'), 7.98(d, J = 6.4 Hz, H-6), 11.85 (bs, exchangeable with D_2O, NH). Anal. Calcd for $C_8H_5N_2OS$: C, 37.37; H, 1.96; N, 10.90. Found: C, 37.38; H, 1.87; N, 10.50.

5-Methyl-4,6-di(2'-thienyl)pyrimidin-2(1*H*)-one (6): yield 46 %; mp 250-253 °C; ^{1}H NMR (DMSO-d_6): δ 2.55 (s, Me), 7.27 (m, H-4'), 7.72 (m, H-5'), 7.85 (m, H-3'), 11.70 (bs, exchangeable with D_2O, NH). Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.93; H, 3.64 ; N, 10.21. Found: C, 56.78; H, 3.55; N, 10.03.

A solution of **4-6** (10 mmol) and KOH (0.56 g, 10 mmol) in water (6 mL) was treated with a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**8**, 4.5 g, 11 mmol) in acetone (30 mL). The mixture was stirred at 23 °C for 10 h, filtered and the solution concentrated on a rotatory evaporator. Products **10-12** were obtained by silica gel chromatography eluting with hexanes/ether/chloroform (1:2:2) followed by crystallization from ethanol.

1-(2",3",4",6"-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(2'-furyl)pyrimidin-2(1*H*)-one (10): yield 75 % (35% from **1**); mp 140-142 °C; $[\alpha]^{26}$ +45.3° (*c* = 2 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.02, 2.05, 2.07

and 2.09 (4s, 3H each, Ac), 3.98 (m, H-5"), 4.13 and 4.29 (2m, 1H each, H-6'), 5.15 (m, H-4"), 5.19 (m, H-2"), 5.44 (m, H-3"), 6.18 (d, J = 9.6 Hz, H-1"), 6.56 (d, J = 6.8 Hz, H-5), 6.96 (m, H-4'), 7.51 (m, H-3'), 7.72 (d, J = 6.8 Hz, H-6), 8.19 (m, H-5'); ^{13}C NMR, ($CDCl_3$): δ 20.4, 20.5, 20.6, 20.7, 61.7, 68.0, 70.5, 72.7, 75.2, 81.4, 102.4, 108.9, 125.3, 142.3, 144.7, 146.2, 155.4, 167.1, 169.5, 169.9, 170.4; FAB-MS: m/z 493 (M^++1). Anal. Calcd for $C_{22}H_{24}N_2O_{11}$•1/2H_2O: C, 52.69; H, 4.99 ; N, 5.58. Found : C, 52.83 ; H, 4.87; N, 5.26.

1-(2",3",4",6"-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(5'-bromo-2'-thienyl)pyrimidin-2(1*H*)-one (11): yield 78 % (34% from **1**) ; mp 250-53 °C; $[\alpha]^D$ +23.0° (*c* = 2 mg/mL, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 1.90, 1.97, 2.01 and 2.03 (4s, 3H each, Ac), 4.09 (m, H-6"), 4.35 (m, H-5"), 5.25 (m, H-4"), 5.46 and 5.58 (2m, H-2"), 6.28 (d, J = 8.8 Hz, H-1"), 7.17 (d, J = 7.2 Hz, H-5), 7.44 (d, J = 4.0Hz, H-3'), 8.05 (d, J = 4.0 Hz, H-4'), 8.50 (d, J = 7.2 Hz, H-6); ^{13}C NMR (DMSO-d_6): δ 20.0, 20.1, 20.3, 20.4, 61.9, 67.5, 70.4, 71.7, 73.0, 80.2, 99.9, 120.7, 132.6, 133.1, 142.8, 146.0, 153.8, 164.7, 169.1, 169.3, 169.4, 169.9; FAB-MS: m/z 589 (M^++1). Anal. Calcd for $C_{22}H_{23}BrN_2O_{10}S$•1/2H_2O: C, 44.30; H, 4.06 ; N, 4.69. Found: C, 44.35 ; H, 4.06; N, 5.02.

1-(2",3",4",6"-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-methyl-4,6-di(2'-thienyl)pyrimidin-2(1*H*)-one (12): yield 75 % (37% from 1) ; mp 195-97 °C; $[\alpha]^D$ -29.5°, *c* = 1.5 mg/mL, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 1.84, 1.99, 2.01 and 2.04 (4s, 3H each, Ac), 2.71 (s, Me), 4.13 (m, H-6"), 4.30 (m, H-5"), 5.04 (m, H-4"), 5.18 (m, H-2"), 5.61 (m, H-3"), 6.36 (d, J = 8.4 Hz, H-1"), 7.31 (m, H-4'), 7.85 (m, H-3'), 7.93 (m, H-5'); ^{13}C NMR (DMSO-d_6): δ 17.2, 20.3, 20.4, 20.5, 61.5, 68.1, 70.3, 71.5, 72.4, 93.8, 117.4, 128.6, 131.4, 131.7, 141.4, 159.7, 161.1, 169.2, 169.4, 169.6, 170.0. Anal. Calcd for $C_{27}H_{28}N_2O_{10}S_2$: C, 53.63; H, 4.67; N, 4.64. Found: C, 53.61 ; H, 4.64; N, 4.60.

Synthesis of Nucleosides 10-12: Method B. A solution of **1-3** (10 mmol) and potassium trimethylsilanolate (0.13 g, 10 mmol) in anhydrous acetonitrile (25 mL) under a nitrogen atmosphere was stirred at 23 °C for 12 h and then heated under reflux for an additional 48 h. The mixture was treated with a solution of β-D-glucose pentaacetate (**9**, 4.3 g , 11 mmol) in anhydrous acetonitrile (20 mL) and anhydrous tin tetrachloride (0.9 mL , 8 mmol), stirred for 4-6 h, and then poured into a solution of sodium bicarbonate (100 mL). Extraction with chloroform (3x50 mL) was followed by a standard workup and purification of the resultant products as described above. The respective yields for **10-12** were 21%, 20%, 24%.

Deacetylation of 11 and 12. A saturated solution of ammonia in methanol (15 mL) was added to a solution of **11** or **12** (1 mmol) in methanol (10 mL) and the resultant mixture was stirred at 23 °C for 12 h. Concentration on a rotatory evaporator was followed by silica gel chromatography eluting with chloroform/methanol (14:1). Products **13** and **14** were additionally crystallized from methanol.

4-(5'-Bromo-2'-thienyl)-1-(β-D-glucopyranosyl)pyrimidin-2(1*H*)-one (13): yield 85%; mp 198-200 °C; $[\alpha]^D$ +45.6° (*c* = 2 mg/mL, MeOH); ^{1}H NMR (DMSO-d_6): δ 3.20-3.75 (4m, 6H, sugar protons), 4.58 (t, J = 6 Hz, 1H, exchangeable with D_2O, OH), 5.11 (d, J = 6 Hz, 1H, exchangeable with D_2O, OH), 5.25 (d, J = 4 Hz,1H, exchangeable with D_2O, OH) , 5.33 (d, J = 6 Hz,1H, exchangeable with D_2O, OH), 5.59 (d, J = 9.2 Hz,

H1"), 7.07 (d, J = 7 Hz, H5), 7.41 (d, J = 4 Hz, H4'), 7.97 (d, J = 4 Hz, H3'), 8.23 (d, J = 7 Hz, H6); ^{13}C NMR (DMSO-d_6): δ 60.9, 69.6, 71.8, 76.9, 80.2, 83. 8, 99.4, 120.2, 132.5, 143.2, 146.2, 154.6, 164.1, 171.5. Anal. Calcd for $C_{14}H_{15}BrN_2O_6S \bullet 1/2H_2O$: C, 39.34; H, 3.74 ; N, 6.55. Found : C, 39.89 ; H, 3.67; N, 6.46.

1-(β-D-Glucopyranosyl)-5-methyl-4,6-di(2'-thienyl)pyrimidin-2(1*H*)-one (14): yield 90 %; mp 190-193 °C; $[\alpha]^D$ -52.4°, (*c* = 2 mg/mL, MeOH); ^{1}H NMR (DMSO-d_6): δ 2.68 (s, Me), 3.20-3.65 (3m, 6H, sugar protons), 4.47, 4.99, 5.12 and 5.44 (4 bs, 1H each, exchangeable with D_2O, OH), 5.75 (d, J = 8Hz, H-1"), 7.27 (m, H-4'), 7.80 and 7.85 (2m, 2H each, H-3' and H-5'); ^{13}C NMR (DMSO-d_6): δ 17.1, 60.3, 69.4, 72.5, 77.0, 77.7, 97.3 ,116.5, 128.2, 128.5, 131.0, 131.3, 141.9, 160.6, 160.8. Anal. Calcd for $C_{19}H_{20}N_2O_6S_2 \bullet H_2O$: C, 50.22; H, 4.84 ; N, 6.16. Found: C, 50.61; H, 4.76; N, 6.42.

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