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Regioselective Ribosylation of 6,7-Dichloroimidazo[4,5-*b*]quinolin-2-one

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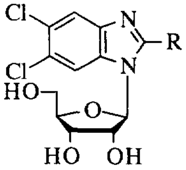
Key words: regioselective ribosylation, imidazo[4,5-*b*]quinolin-2-one, nucleoside analog

Abstract: Regioselective ribosylation conditions were established which gave both 6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**4**) and 6,7-dichloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5**), respectively, in high yield from 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**). The distributions of the sites of ribosylation under a variety of conditions are discussed. Copyright © 1996 Elsevier Science Ltd

Recently, a series of polyhalogenated benzimidazole ribonucleosides (**1**) have been prepared[1] and found to possess potent activity against human cytomegalovirus (HCMV). The lead compound, 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB), is more active than ganciclovir and foscarnet against HCMV infections in cell culture studies. To further study the behavior of certain structurally related analogs and derivatives of these benzimidazole ribonucleosides in a dimensionally stretched-out manner and the spatial limitation of the targeted macromolecules (enzymes), a series of 6,7-dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolines (**2**) and 6,7-dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]quinolines (**3**), with several different substituents at the 2-positions, were required as dimensional probes[2] of **1**.



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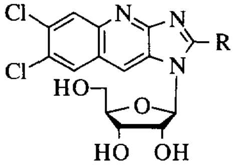

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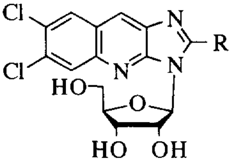

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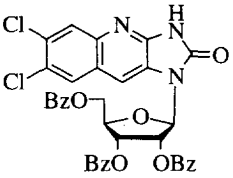
R = Cl
R = SCH_2Ph
R = H

It was established that 6,7-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**4**) and 6,7-dichloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5**) were the key intermediates in a retrosynthetic analysis involving a convergent approach for the synthesis of **2** and **3** with labile substituents at the 2-positions. To synthesize both **4** and **5** in practical quantities from 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one[3] (**6**), the development of regioselective ribosylation conditions were required.



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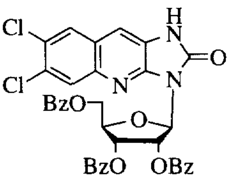

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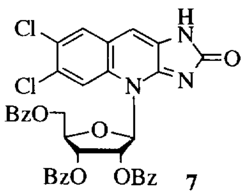

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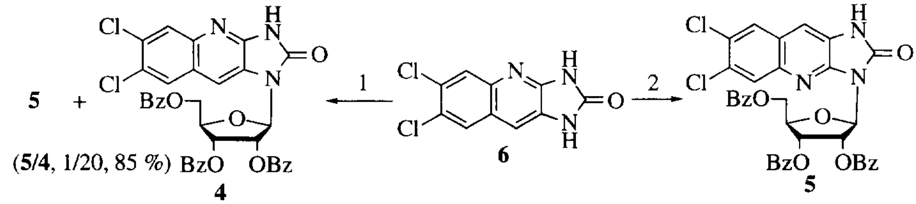
A literature search revealed that while glycosylation of imidazo[4,5-*b*]quinolin-2-ones or the imidazo[4,5-*b*]quinolines, *per se*, was unknown, ribosylation of the structurally related imidazo[4,5-*b*]pyridines was well documented[4] in the literature. Especially interesting was the use of the modified Hilbert-Johnson method[5] for the ribosylation of imidazo[4,5-*b*]pyridine derivatives.[4b,4c] When imidazo[4,5-*b*]pyridine was condensed with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (TAR) in acetonitrile catalyzed by $SnCl_4$, the N3-riboside was isolated[4b] as the sole product in a 57 % yield. However, a mixture of N3-, N4- and N1-isomers were obtained when the silylated imidazo[4,5-*b*]pyridine was condensed with TAR in acetonitrile catalyzed by $SnCl_4$. Moreover, the N3-isomer was obtained as the major product under the thermodynamic conditions and the N4-isomer was found to be the major product under kinetic conditions.[4b] Only in one case[4d] was the N1-riboside regioselectively obtained and that was when the silylated imidazo[4,5-*b*]pyridine 4-oxide was condensed with TAR catalyzed by $SnCl_4$. These studies on the imidazo[4,5-*b*]pyridines revealed that the site of ribosylation was influenced by reaction conditions and suggested that the site of ribosylation could also be directed for the imidazo[4,5-*b*]quinolines under the appropriate reaction conditions.

The condensation of 6,7-dichloroimidazo[4,5-*b*]quinolin-2-one (**6**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (TBAR), catalyzed by $SnCl_4$ in acetonitrile at 50 °C for 4 hours, gave 6,7-dichloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]quinolin-2-one (**5**)[8a] in 88 % yield as the only product. This regioselectivity is in agreement with that reported[4b] for imidazo[4,5-*b*]pyridine.



Reagents: 1. a). BSA, $ClCH_2CH_2Cl/CH_3CN$ (3/1), r.t. b). TBAR, TMSOTf, $ClCH_2CH_2Cl/CH_3CN$ (3/4), 70 °C
2. TBAR, $SnCl_4$, CH_3CN, 50 °C

Compound **6** was silylated[6] and condensed with TBAR, catalyzed by $SnCl_4$, to give a mixture of protected N1-riboside (**4**)[8a] and N3-riboside (**5**)[8b]. However, The N1-isomer (**4**) was found to be the major product (Table, entries 1,2,3,4) in this case and this is different from that reported for imidazo[4,5-*b*]pyridine[4b] using the silylated Hilbert-Johnson method.[5] This prompted us to use different temperatures and solvent systems to study the effect of these conditions on the distribution of the sites of ribosylation. Generally, a more polar solvent system, e.g. acetonitrile or $ClCH_2CH_2Cl/CH_3CN$ (3/4), gave higher ratios of **4**/**5** (Table, entries 1 and 4), while under higher temperatures, slightly higher yields were obtained (Table, entries 1 and 2).

When trimethylsilyl trifluoromethanesulfonate (TMSOTf)[7] was used as the Lewis acid instead of $SnCl_4$, in the silylated Hilbert-Johnson ribosylation, a dramatic increase in the formation of **4** was observed. A regioselective ribosylation was achieved to give a 20/1 ratio of **4**/**5** in a combined 85 % yield (Table, entry 5) when the reaction was catalyzed by TMSOTf in $ClCH_2CH_2Cl/CH_3CN$ (3/4) at 70 °C for one hour. When the polarity of the solvent system was decreased ($ClCH_2CH_2Cl/CH_3CN$; 3/1), a decrease of regioselectivity was observed (Table, entry 6). However, when acetonitrile was used as the solvent, a mixture of **4** and **5** in a ratio of 4.2/1 was obtained in a combined 76 % yield (Table, entry 8). This low regioselectivity is presumably due to the incomplete silylation in acetonitrile.[6] It was found that a high temperature was also required for the ribosylation when TMSOTf was used as the Lewis acid since at room temperature, the ribosylation is very slow. At 50 °C, in $ClCH_2CH_2Cl/CH_3CN$ (3/4) for 5 hours (Table, entry 7), a high regioselectivity was also obtained but the yield was lower than that observed at 70 °C. It is apparent that the type of Lewis acid, solvent and temperature are all important for the regioselective synthesis of the N1-riboside (**4**).

Table: Ribosylation of Silylated **6** with TBAR

Entry	Lewis Acid[a]	$ClCH_2CH_2Cl/CH_3CN$	temperature	time(h)	**4/5**[b]	Yield(%)[c]
1	$SnCl_4$	3/4	70 °C	1	2.1/1	65
2	$SnCl_4$	3/1	70 °C	1	1.8/1	75
3	$SnCl_4$	3/1	r.t.	6	1.5/1	61
4	$SnCl_4$	0/1	r.t.	6	2.0/1	60
5	TMSOTf	3/4	70 °C	1	20/1[d]	85
6	TMSOTf	3/1	70 °C	1	5.2/1	86
7	TMSOTf	3/4	50 °C	5	17/1	68
8	TMSOTf	0/1	70 °C	1	4.2/1	76

a. Two equivalencies of a Lewis acid were used in all cases. b. Ratios determined from HPLC analysis.
c. Combined yield of **4** and **5** isolated from flash chromatography. d. Ratio from isolated products.

When the silylated Hilbert-Johnson ribosylation was conducted under low temperature (Table, entries 3, 4, 7), the ribosylation proceeded at a slower speed and the N4-riboside (**7**) was observed very shortly after the addition of the Lewis acids. However, both **4** and **5** (for entries 3, 4) or **4** (for entry 7) began to appear shortly after the formation of **7**. With a continuation of the reactions, the amount of **4** and **5** continued to increase while the amount of **7** was maintained at a relatively constant level until gradually disappearing towards the end of the reactions. A small amount of **7**[8c] was isolated by quenching the ribosylations a short time after the addition of the Lewis acids. When treated with BSA and then TMSOTf at 70 °C in $ClCH_2CH_2Cl/CH_3CN$ (3/4), **7** was converted to **4** and **5** in a ratio of 15/1 in a combined 82 % yield. When **7** was treated with $SnCl_4$ under the same conditions, **4** and **5** was obtained in a ratio of 4.7/1 in a combined 86 % yield. This would suggest that **7** is a kinetic product and **4** and **5** are the thermodynamic products under the silylated Hilbert-Johnson conditions.[9]

In conclusion, ribosylation conditions were established under which both the protected N3-riboside (**5**) and N1-riboside (**4**) were synthesized regioselectively in high yield from the same substrate. The N4-riboside (**7**) was also isolated and found to be the kinetic product in the silylated Hilbert-Johnson ribosylation. The mechanism for the almost exclusive generation of the N1-riboside (**4**) under the silylated Hilbert-Johnson method catalyzed by TMSOTf is now under further investigation in our laboratory.

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6. Compound **6** was silylated by *N,O*-bis(trimethylsilyl)acetamide (BSA). It was found that when either acetonitrile or 1,2-dichloroethane was used alone as a solvent, a homogeneous solution cannot be generated when **6** was silylated with BSA. However, **6** was silylated by BSA (2eq) in a mixture of 1,2-dichloroethane/acetonitrile (3/1) at room temperature for one hour to give a clear solution. Most silylations of **6** were conducted under these conditions. A more polar solvent system for the subsequent ribosylation was obtained by the addition of more acetonitrile after the silylation. When acetonitrile was used as the only solvent, **6** was treated with BSA (2eq) at room temperature for one hour and the suspension was then used for the subsequent ribosylation.

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8. a). Compound **4**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 12.32 (bs, 1H, N1-H), 8.08-7.40 (m, 15H, benzoyl H), 8.05 (s, 1H,), 8.01 (s, 1H), 7.66 (s, 1H), 6.37 (d, J=5.49 Hz, 1H, H1'), 6.25 (t, J=6 Hz, 1H), 6.11 (t, J=6 Hz, 1H), 4.88-4.69 (m, 3H, H4', 2xH5'); *Anal.* Calcd for $C_{36}H_{25}O_8N_3Cl_2$: C, 61.89; H, 3.58; N, 6.02; Found: C, 61.94; H, 3.74; N, 5.94. b). Compound **5**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.86 (bs, 1H, -NH-), 8.06-7.06 (m, 18H, aromatic H), 6.73 (dd, J=2.93, 6.01 Hz, 1H, H2'), 6.59 (q, J=6.6 Hz, 1H, H3'), 6.43 (d, J=2.9 Hz, 1H, H1'), 4.84 (dd, 1H, H5'), 4.78-4.69 (m, 2H, H4' and H5'); *Anal.* Calcd for $C_{36}H_{25}O_8N_3Cl_2$: C, 61.89; H, 3.58; N, 6.02; Found: C, 61.65; H, 3.77; N, 5.80.

   c). Compound **7**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 11.22 (bs, 1H), 8.55 (s, 1H), 8.25 (s, 1H), 8.00-7.44 (m, 16H), 7.15 (s, 1H), 6.68 (m, 1H), 6.46 (t, J=7.5 Hz, 1H), 4.85 (m, 1H), 4.78 (m, 1H), 4.66 (m, 1H); *Anal.* Calcd for $C_{36}H_{25}O_8N_3Cl_2$: C, 61.89; H, 3.58; N, 6.02; Found: C, 61.62; H, 3.70; N, 5.87. Both **4** and **5** were deprotected by ammonia in methanol and **7** was deprotected by NaOMe in methanol. The deprotected nucleosides were used for the structure determinations. The sites of ribosylation were determined by long-range ^{1}H-^{13}C selective decoupling experiments and ^{1}H-nOe experiments. The β-configurations were determined by ^{1}H-nOe experiments. For example, three-bond couplings were observed for compound **4** between H1'-C$_2$ and H1'-C9a which confirmed that the ribosyl moiety was attached at N1. ^{1}H-nOe was observed for compound **4** between H1'and H4' which confirmed the β-configurations.

9. For a similar transglycosylation of imidazo[4,5-*b*]pyridine, see reference 4b.

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