A New Method for the Synthesis of Some Pyridazine Nucleosides

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Some pyridazin-6-one nucleosides have been prepared directly without silylation of heterocyclic base using iodine catalyst, a new type Friedel-Crafts catalyst.

Introduction

During the past few decades, a considerable effort has been directed toward the synthesis of modified nucleosides as potential chemotheraputic agents. Therefore, much attention has been given to the synthesis and biological evaluation of pyrimidine, pyridine, pyridazine and related monoheterocyclic nucleosides[1].

Traditionally, the synthesis of these monoheterocyclic nucleosides has been accomplished by the Silyl-Hilbert-Johnson method[2]. Since the Silyl-Hilbert-Johnson reaction involves an attack of a sugar cation on the aromatic heterocyclic ring, one thought that the Silyl-Hilbert-Johnson reaction is a type of Friedel-Crafts reaction[3,4]. Friedel-Crafts catalysts, such as $TiCl_4$ and $SnCl_4$ have been used by Baker[5] and later by Furukawa and Honjo[6] for the synthesis of purine nucleosides. Other Friedel-Crafts catalysts, such as $(CH_3)_3SiSO_3CF_3$, $(CH_3)_3SiClO_4$ and $SnCl_4$ have also been studied by H. Vorbrüggen and his co-workers[3,4] for the synthesis of nucleosides.

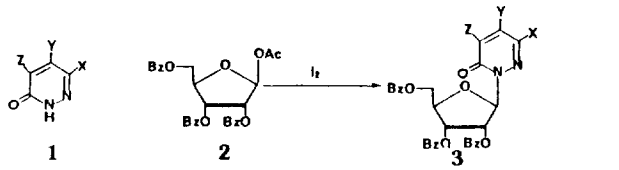
In the priveous reports,[7,8] we have synthesized some pyridazine nucleosides by the Silyl-Hilbert-Johnson method. However, we have always posed some problems, such as the hydrolysis of silylated heterocyclic base, the hygroscopic property of $SnCl_4$ and the difficulty in work-up step. For these reasons, we attempted to develop another type Friedel-Crafts catalyst for the synthesis of pyridazine nucleosides.

In our related report[9], we have synthesized imidazole-2-thione nucleosides from imidazole-2-thione and 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose by the iodine-catalyzed fusion reaction under diminished pressure. Since we thought that the above reaction is a type of Friedel-Crafts reaction, iodine should be possible as a typical Friedel-Crafts catalyst for the synthesis of another type nucleosides. Thus, we attempted to synthesize the pyridazine nucleosides by using iodine.

We now wish to report a efficient one-step procedure for the synthesis of some pyridazine nucleosides.

Results and Discussion

Reactions of the free pyridazine bases (**1a-1d** and **4**) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**2**) and iodine (1 equivalent) in o-dichlorobenzene at 160-170°C for 1-9 hrs under nitrogen gave the corresponding N_1-nucleosides (**3a-3d**) in good yields (61-91%). However, in case of the compound **4**, we obtained the compound **5** as the corresponding O-nucleoside in 37% yield.

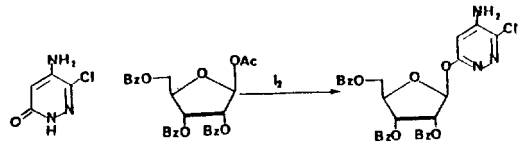


1 2 3

a; X = NO_2, Y = Z = Cl
b; X = Y = Cl, Z = H
c; X = Cl, Y = OEt, Z = H
d; X = Cl, Y = OMe, Z = H

a; X = NO_2, Y = Z = Cl
b; X = Y = Cl, Z = H
c; X = Cl, Y = OEt, Z = H
d; X = Cl, Y = OMe, Z = H

Scheme 1



4 2 5

Scheme 2

During the reaction of the compound **4**, we could detect actually the decomposition of sugar on the TLC plates.

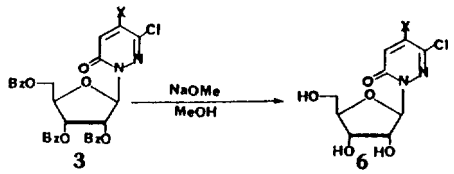
The compound **3a** and **3b** were identical with the previously reported 4,5-dichloro-3-nitro-1-(2,3,5-tri-O-benzoyl-1-β-D-ribofuranosyl)pyridazin-6-one (**3a**) and 3,4-dichloro-1-(2,3,5-tri-O-benzoyl-1-β-D-ribofuranosyl)pyridazin-6-one (**3b**)[8].

Since the compound **3c** is unknown compound, the structure of this compound was assigned by the study of ^{1}H-NMR and UV spectra and on the basis of the elemental analysis (C, H, N).

In addition, removal of the blocking groups from compound **3c** with methanolic sodium methoxide furnished the compound **6a** as the nucleoside in 32% yield.

Because compound **3d** and **5** are also unknown, the structures of these compounds were assigned on the basis of subsequent study. Deblocking reaction of the compound **3d** and **5** with methanolic sodium methoxide gave the previouselly reported 3-chloro-4-methoxy-1-β-D-ribofuranosyl pyridazin-6-one(**6b**) in 73% yield. In case of the compound **5**, however, ^{1}H-NMR and UV spectral data of the product **7** were clearly different from those of the reported 3-chloro-4-amino-1-β-D-ribofuranosyl pyridazin-6-one[8]. Rf value of the compound **7** was also different from that of 3-chloro-4-amino-1-β-D-ribofuranosyl pyridazin-6-one (Rf for the compound

7 = 0.35; for 3-chloro-4-amino-1-β-D-ribofuranosyl pyridazin-6-one = 0.56, solvent = $CHCl_3$/MeOH = 8:2). Therefore, we have compared with the UV spectral data reported for the O-alkylated compound, such as 5-amino-3-methoxypyridazine[11] and 4-amino-1-methylpyridazin-6-one[10]. These observations have unequivocally established the site of the ribosylation for compound **7**.

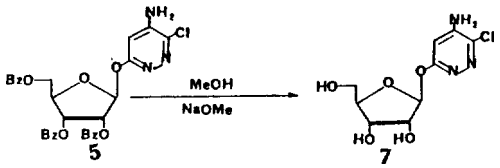


3 **6**

c; X = OEt a; X = OEt
d; X = OMe b; X = OMe

Scheme 3

Furthermore, IR spectral data of the compound **7** were compared with that of 3-chloro-4-amino-1-β-D-ribofuranosyl pyridazin-6-one. In case of the compound **7**, we could not detect the carbonyl peak of the pyridazin-6-one at 1650-1700 cm^{-1}, whereas the carbonyl peak of 3-chloro-4-amino-1-β-D-ribofuranosyl pyridazin-6-one was detected at 1650 cm^{-1}. We also could not detect the carbonyl peak of the compound **5** at the above region.



5 **7**

Scheme 4

The coupling constants between H-1′ and H-2′ of the ribofuranose ring indicated that the β-anomers were formed in all cases (Table I).

We attempted to apply this ribosylation for the synthesis of other pyridazin-6-one nucleosides, such as 3-chloro, 4,5-dichloro and 4-amino-5-chloropyridazin-6-one nucleosides, but we did not obtained the corresponding nucleoside in all cases. We also tried the synthesis of 3-chloro-4-hydroxypyridazin-6-one nucleoside, but we did not separated the product since several spots as the nucleoside were detected on the TLC plates.

In order to extend the reaction to the synthesis of other monoheterocyclic and multicyclic N-nucleosides, the application in the area of the synthesis of other nucleosides are under further investigation in our laboratory.

Experimental

Proton nuclear magnetic resonance(^{1}H-NMR) spectra were obtained on a Varian EM-360 60MHz spectrometer (solution in DMSO-d_6 or $CDCl_3$) with chemical shift values reported in δ units (parts per million) relative to an internal standard (tetramethylsilane). Ultraviolet (UV) absorption spectra were recorded on Hewlett-Packard 8450A UV/Vis spectrophotometer. Melting points were determined with a Thomas Hoover capillary apparatus and are uncorrected. Nucleosides were detected either by an ultraviolet lamp (254 nm) or treatment with sulfuric acid (10%) followed by charring. Analytical thin layer chromatography was performed on glass plates pre-coated silica gel GHLF (250 micron; ANALTECH). Open-bed column chromatography was carried out on silica gel (Kiesel gel 60, 70-230 mesh, Merck) using gravity flow. The column were packed as the powder using the vibrator. Elemental analysis was performed by M-H-W laboratory, Phoenix, AZ. Infrared spectral data were obtained on Perkin-Elmer, IR 281.

General procedure of ribosylation. Mixture of the corresponding pyridazin-6-one (1 equivalent), 1-O-acetyl-

Table 1. ^{1}H-NMR Spectral Data for Certain Pyridazine Nucleosides

Compound No	Solvent (a)	$H_{1'}$ (b)	$J_{1',2'}$ (Hz)	Others (b)
3a	C	6.8(d)	2	8.2-7.2(m, bz, H's) 6.2-5.8(m, $H_{2'}$ + $H_{3'}$) 5.0-4.5(m, $H_{4'}$ + $H_{5'}$)
3b	D	6.7(d)	2	8.2-7.3(m, bz, H's) 6.2-5.9(m, $H_{2'}$ + $H_{3'}$) 5.0-4.53(m, $H_{4'}$ + $H_{5'}$)
3c	D	6.7(d)	2	8.2-7.4(m, bz, H's) 6.55(s, H_5) 6.2-6.0(m, $H_{2'}$ + $H_{3'}$) 5.05-4.6(m, $H_{4'}$ + $H_{5'}$) 4.4-4.05(q. OCH_2) 1.6-1.3(t,-CH_3)
3d	D	6.73(d)	2	8.28-7.4(m, bz, H's) 6.6(s, H_5) 6.3-5.95(m, $H_{2'}$ + $H_{3'}$) 5.1-4.6(m, $H_{4'}$ + $H_{5'}$) 4.0(s, OCH_3)
5	D	6.6(d)	2	8.2-7.3(m, bz, H's) 6.93(bs, NH_2, DE) 6.1-5.86(m, $H_{2'}$ + $H_{3'}$) 5.8(s, H_5) 4.8-4.5(m, $H_{4'}$ + $H_{5'}$)
6a	D	6.13(d)	2	6.43(s, H_5) 5.6-4.5(m, $3OH_{2',3',5'}$, DE) 4.3-3.7(m, $H_{2'}$ + $H_{3'}$ + OCH_2) 3.6-3.3(m, $H_{4'}$ + $H_{5'}$) 1.3(t, -CH_3)
6b	D	6.16(d)	2	6.5(s, H_5) 5.4-4.9(m, $OH_{2'}$ + $OH_{3'}$, DE) 4.83-4.5(t, $OH_{5'}$, DE) 4.4-3.7(m, $H_{2'}$ + $H_{3'}$ + $H_{4'}$) 3.98(s, OCH_3) 3.66-3.4(m $H_{5'}$)
7	D	6.1(d)	2	6.8(bs, NH_2, DE) 5.7(s, H_5) 5.2-4.4(bs, $3OH_{2',3',5'}$, DE) 4.3-3.6(m, $H_{2'}$ + $H_{3'}$ + $H_{4'}$) 3.53-3.46(m, $H_{5'}$)

(a) C = $CDCl_3$ + 1% TMS, D = DMSO-d_6. (b) Abbreviations used: bz = benzoyl, d = doublet, s = singlet, t = triplet, m = multiplet, bs = broad singlet, q = quartet, DE = D_2O exchangable.

Table 2. Ultraviolet Spectral Data for Some Pyridazine Nucleosides: (λ_{max} (ε)

Compound No	Methanol	pH 1	pH 11
3a	275(6480)	------	------
	282(6414)	------	------
	300(4777)	------	------
3b	275(4998)	------	------
	282(4978)	------	------
	306(3624)	------	------
3c	274(7261)	------	------
	281(6636)	------	------
3d	275(3196)	------	------
	282(2944)	------	------
5	275(12445)	------	------
	282(12256)	------	------
6a	252(3017)	253(4152)	253(3732)
	289(1888)	280(2216)	285(sh)
6b	252(1105)	252(3564)	252(3705)
	289(758)	282(2091)	281(2174)
7	282(4692)	281(4545)	284(7242)

2,3,5-tri-O-benzoyl-β-D-ribofuranose (1 equivalent), iodine (1 equivalent) as the catalyst and o-dichlorobenzene as the solvent was stirred at 160-170°C (using the metal alloy bath) for 1-9 hrs under nitrogen. The reaction mixture was cooled to room temperature and applied directly with open-bed Si-Gel column. The reaction solvent and iodine were washed with n-hexane and then the products were eluted with chloroform. Fractions containing the nucleoside were combined and evaporated under reduced pressure.

Compound **3a**; Reaction time 9 hrs. Recrystallization of the crude product from ethanol yielded a light-yellow powder. Yield 76%. mp 99-101°C (lit. (8) 101-102°C)

Compound **3b**; Reaction time 1 hr. Recrystallization from EtOH-EtOAc gave a white needle. Yield 62%. mp 112-113°C (lit. (8) 113-114°C).

Compound **3c**; Reaction time 2 hrs. Recrystallization from EtOH yielded a white needle. Yield 83%. mp 79-81°C. Anal. calcd for $C_{32}H_{27}N_2O_9Cl$; C. 62.09; H. 4.39; N. 4.53: Found; C. 62.24; H, 4.54; N. 4.29.

Compound **3d**; Reaction time 1.5 hrs. White powder. Yield 91%. mp 82-84°C.

Compound **5**; Reaction time 1 hr. Yield 38%. mp 100-101°C. IR(KBr); 3480, 3350, 1730, 1638, 1620, 1585, 1530, 1450 cm^{-1}

Deblocking reaction procedure. Each blocking nucleoside (1 equivalent) was dissolved in methanol. Sodium methoxide (4 equivalents) was added to above solution. The reaction mixture was stirred at room temperature for 4-4.5 hrs. To the reaction mixture, Amberlite IRC-50(H^+ form, 1-2 gm) was added, and then the mixture was stirred at room temperature for an additional 22-24 hrs. The reaction mixture was filtered and washed with hot-MeOH. The combined filterate was evaporated under reduced pressure to give the crude products.

Compound **6a**; The residue was dissolved in EtOAc. The precipitates were filtered and washed with EtOAc. The combined EtOAc layer was evaporated. The resulting residue was triturated with chloroform to give a white powder. Yield 32%. mp 101-102°C.

Compound **6b**; The residue was dissolved in EtOAc. The pricipitates were filtered and washed with EtOAc. The combined EtOAc layer was concentrated to 10 m*l*. Standing gave a white needle. The obtained crystals were triturated with $CHCl_3$, filtered and washed with $CHCl_3$. Yield 73%. mp 115-117°C (lit(8) 116-118°C).

Compound **7**; The residue was crystallized from $CHCl_3$-EtOH, filtered and washed with $CHCl_3$ to give a beige needle. Yield 66%. mp 215-216°C. IR(KBr) 3480, 3460, 1620, 1610, 1560, 1520, 1470, 1450 cm^{-1}

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