Synthesis of Pyrazole Nucleosides Using Acylketene Dithioacetal Derivatives

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Synopsis. Several nucleosides bearing pyazole ring as the base moiety were synthesized by the reaction of D-ribofuranosylhydrazine or 2-deoxy-D-ribosuranosylhydrazine with easily available acylketene ditioacetal derivatives.

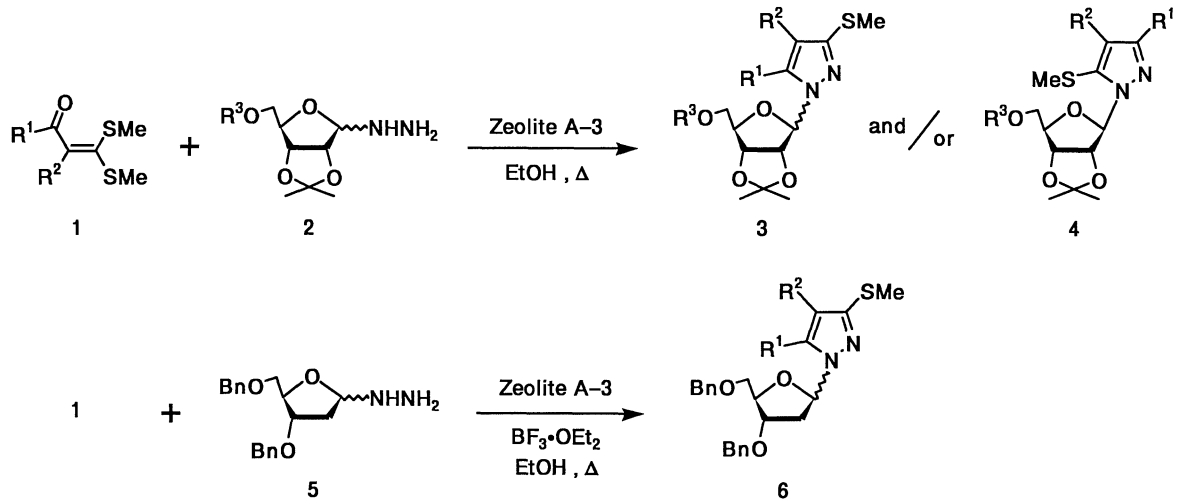
In a part of our study directed toward the synthesis of pharmaceutically important compounds,[1] we found that several kinds of pyrazole nucleosides could be easily synthesized by the reaction of ketene dithioacetals de rived from cyanoacetamide or malononitrile with pro tected D-ribofuranosylhydrazine.[2] In this paper the work was extended to acylketene dithioacetal derivatives as ketene dithioacetals and to protected 2-deoxy-D-ribofuranosylhydrazine as a sugar moiety. The acylketene dithioacetal derivatives could be easily synthesized by the reaction of the corresponding ketones and carbon disulfide followed by methylation. The protected 2-deoxy-D-ribofuranosylhydrazine could be synthesized by the reaction of protected 2-deoxy-D-ribose with hydrazine.

This report presents a simple synthetic method for 5-substituted or 4,5-disubstituted 3-(methylthio)pyrazole nucleosides. The nucleosides obtained by this method are β-anomer or a mixture of α- and β-anomers, which can be separated by usual preparative TLC on silica gel.

Results and Discussion

The reaction of 3,3-bis(methylthio)-1-phenyl-2-propen-1-one (**1a**) with 2,3-*O*-isopropylidene-D-ribofuranosylhydrazine **2a′(H)** gave an expected nucleoside **3a″(H)** as only β-form. However **1a** reacted with 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosylhydrazine **2a′(T)** to afford the corresponding nucleoside **3a″(T)** in 77% yield (α/β=51/26). The steric hindrance of bulky trityl group seems to have effect on the increase of the α-anomer. In the reaction of 4,4-bis(methylthio)-3-buten-2-one (**1b**) with **2a′(H)**, 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-methyl-3-(methylthio)pyrazole **3b″** and its regioisomer **4b″** were isolated in 13% and 22% yields, respectively. The reaction of 2-[bis(methylthio)methylene]-cyclohexanone (**1c**) with **2a′(H)** gave 1-(2,3-*O*-isopropylidene-D-ribofuranosyl)-3-methylthio-4,5,6,7-tetrahydro-1*H*-indazole **3c″** as β-form.

Further, the present reaction was extended to the synthesis of 2-deoxy-D-ribonucleosides. 3,5-Di-*O*-benzyl-2-deoxy-D-ribofuranosylhydrazine (**5**) was prepared by the reaction of 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranose with hydrazine. Its ^{1}H NMR observation shows that **5** comprises an equilibrium mixture of the hydrazone form **5a** and the hydrazino form **5b**, in which the former predominates (ca. 90%). This result is the same as in the



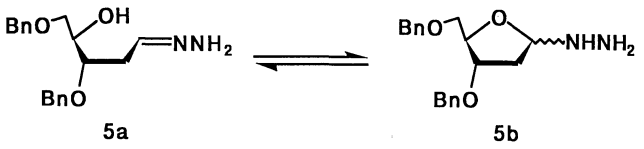
1 2 3 4 5 6

a : R^1 = Ph ; R^2 = H
b : R^1 = Me ; R^2 = H
c : R^1, R^2 = -$(CH_2)_4$-

a′(H) : R^3 = H
a′(T) : R^3 = Tr

a″(H) : R^1 = Ph ; R^2 = H ; R^3 = H
a″(T) : R^1 = Ph ; R^2 = H ; R^3 = Tr
b″ : R^1 = Me ; R^2 = H ; R^3 = H
c″ : R^1, R^2 = -$(CH_2)_4$- ; R^3 = H

Scheme 1.



Scheme 2.

Table 1. Isolated Yields of Pyrazole Nucleosides

Compd	R^1	R^2	R^3	Yield[a]/%
3a′(H)	Ph	H	H	25(10)
3a′(T)	Ph	H	Tr	77(51)
3b′	Me	H	H	13(0)
3c′	$-(CH_2)_4-$		H	15(0)
4b′	Me	H	H	22(0)
6a	Ph	H	—	30(12)
6b	Me	H	—	38(10)

a) The value in the parenthesis shows the yield of α-anomer.

case of 2,3-*O*-isopropylidene-D-ribofuranosylhydrazine.[3]

The reaction of **1a** with **5** in the presence of boron trifluoride etherate gave 1-(3,5-di-*O*-benzyl-2-deoxy-D-ribofuranosyl)-3-methylthio-5-phenylpyrazole **6a** in 30% yield. Thus obtained **6a** was a mixture of α- and β-anomers, which could be separated easily by low-pressure chromatography (α-anomer 12%; β-anomer 18%). Several nucleosides prepared by this procedure are summarized in Table 1.

The structures of α- and β-anomers of **3** were determined on the basis of a difference of chemical shift values for the two methyl protons of the isopropylidene moiety in the ^{1}H NMR.[4] Regioisomers, **3b″** and **4b″** could be differentiated by the splitting pattern of $^3J_{C-H}$ of the ^{13}C NMR[5] [**3b″**: quartet splitting (C-3 and C-4), doublet splitting (C-5); **4b″**: singlet splitting (C-3), quartet splitting (C-4), multiplet splitting (C-5)]. The structures of α- and β-anomers for **6** were tentatively assigned by the characteristic splitting pattern of **1′-H**[6] (dd, $J_{1',2'_A}$=8.0 Hz, $J_{1',2'_B}$=4.0 Hz for the α-anomer; t, $J_{1',2'_A}=J_{1',2'_B}$=5.5 Hz for the β-anomer).

The deblocking of **3** and **6** could be easily carried out in the usual way (stir at r.t. with AcOH for **3**; Ac_2O/BF_3, followed by NH_3–MeOH for **6**).

Experimental

Microanalysis was performed with a Perkin–Elmer elemental 240 analyser at the Chemical Analysis Center of Chiba University. IR, MS, UV, and ^{1}H NMR spectra were measured with Hitachi 215, RMU 6MC, EPS-3T, JOEL MH-100, and JMN-GX-270 spectrometers, respectively. Optical rotation was measured on a JASCO-DIP-370 polarimeter. Wakogel C-200 was used for low-pressure liquid chromatography and Wakogel B-5F was used for TLC. 3,3-Bis(methylthio)-1-phenyl-2-propen-1-one (**1a**),[7] 4,4-bis(methylthio)-3-buten-2-one (**1b**),[8] and 2-[bis(methylthio)methylene]cyclohexanone (**1c**),[9] were prepared according to the literature. 2,3-*O*-Isopropylidene-D-ribofuranosylhydrazine **2a′(H)** was prepared by our previous method.[2]

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosylhydrazine 2a′(T). 2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose was prepared according to the literature,[10] and then allowed to react with anhydrous hydrazine by the same method for the preparation of **2a′(H)** (R^3=H). The colorless crystals thus obtained (mp. 59—60 °C in sealed tube) were used without purification in the next step.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-3-methylthio-5-phenylpyrazole 3a″(H). A mixture of **2a′(H)** (0.57 g, 3 mmol), dry ethanol (5 ml), Zeolite A-3 (400 mg), and **1a** (224 mg, 1 mmol) was refluxed under stirring for 3 d. The reaction mixture was filtered through Celite and then the filtrate was evaporated to give an oil, which was purified by TLC on silica gel (eluent: $CHCl_3$–MeOH, 9:1) to form colorless crystals **3a″(H)** (91 mg, 25%), mp 84—85 °C; IR (KBr) 3220 (OH), 3020 (Ph), and 2980, 2920 cm^{-1} (CH); ^{1}H NMR ($CDCl_3$) δ=1.36 (s, 3H, Me), 1.49 (s, 3H, Me), 2.55 (s, 3H, SMe), 3.77, 3.98 (AB pattern, J_{gem}=14 Hz, $J_{4',5'}$=7 Hz, 2H, CH_2OH), 4.49 (s, 1H, OH), 5.06 (dd, $J_{4',5'}$=7 Hz, $J_{3',4'}$=2 Hz, 1H, 4′-H), 5.26 (dd, $J_{2',3'}$=3 Hz, $J_{1',2'}$=2 Hz, 1H, 2′-H), 5.70 (dd, $J_{2',3'}$=3 Hz, $J_{3',4'}$=2 Hz, 1H, 3′-H), 5.90 (d, $J_{1',2'}$=2 Hz, 1H, 1′-H), 6.22 (s, 1H, 4-H), and 7.26—7.50 (m, 5H, Ph); MS *m/z* 362 (M$^+$); UV (99% EtOH) 208 (ε 27000) and 242 nm (21000); $[\alpha]_D$ −126° (*c* 0.55, EtOH); Found: C, 59.6; H, 6.14; N, 7.66%. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.6; H, 6.12; N, 7.73%.

Compounds **3b″** and **3c″** were prepared from **1b** and **1c** by the same method as above.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-5-methyl-3-(methylthio)pyrazole 3b″. Syrup; IR (neat) 3280 (OH) and 2990, 2860 cm^{-1} (CH); ^{1}H NMR ($CDCl_3$) δ=1.37 (s, 3H, Me), 1.60 (s, 3H, Me), 2.31 (s, 3H, Me), 2.48 (s, 3H, SMe), 3.66, 3.88 (AB pattern, J_{gem}=13 Hz, $J_{4',5'}$=7 Hz, 2H, CH_2OH), 4.52 (s, 1H, OH), 5.10 (m, 2H, 2′-H and 4′-H), 5.82 (m, 2H, 1′-H and 3′-H), and 5.94 (s, 1H, 4-H); MS *m/z* 300 (M$^+$); UV (99% EtOH) 210 (ε 7000), 230 (6460), and 250 nm (sh, 3420); $[\alpha]_D$ −52° (*c* 0.07, EtOH); Found: C, 51.6; H, 6.72; N, 9.30%. Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.9; H, 6.71; N, 9.32%.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-3-(methylthio)-4,5,6,7-tetrahydro-1*H*-indazole 3c″. Syrup; IR (neat) 3250 (OH) and 2960, 2920, 2840 cm^{-1} (CH); ^{1}H NMR ($CDCl_3$) δ=1.36 (s, 3H, Me), 1.59 (s, 3H, Me), 1.78 (m, 4H, CH_2×2), 2.33 (s, 3H, SMe), 2.50 (m, 4H, CH_2×2), 3.73, 3.94 (AB pattern, J_{gem}=12 Hz, $J_{4',5'}$=8 Hz, 2H, CH_2OH), 4.52 (s, 1H, OH), 5.10 (m, 2H, 2′-H and 4′-H), 5.75 (d, $J_{1',2'}$=2 Hz, 1H, 1′-H), and 6.16 (m, 1H, 3′-H); MS *m/z* 340 (M$^+$); UV (99% EtOH) 242 (3900), and 309 nm (7200); $[\alpha]_D$ −21° (*c* 0.12, EtOH); Found: C, 56.0; H, 7.10; N, 8.17%. Calcd for $C_{16}H_{24}N_2O_4S$: C, 56.4; H, 7.11; N, 8.23%.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-3-methyl-5-(methylthio)pyrazole 4b″. Syrup; IR (neat) 3280 (OH) and 2980, 2840, 2710 cm^{-1} (CH); ^{1}H NMR ($CDCl_3$) δ=1.36 (s, 3H, Me), 1.62 (s, 3H, Me), 2.24 (s, 3H, Me), 2.40 (s, 3H, SMe), 3.69, 3.92 (AB pattern, J_{gem}=13 Hz, $J_{4',5'}$=7 Hz, 2H, CH_2OH), 4.53 (s, 1H, OH), 5.05 (m, 2H, 2′-H and 4′-H), 6.15 (m, 2H, 1′-H and 3′-H), and 6.25 (s, 1H, 4-H); MS *m/z* 300 (M$^+$); UV (99% EtOH) 207 (ε 5620), 238 (sh, 5420), and 260 nm (6250); $[\alpha]_D$ −85° (*c* 1.24, EtOH); Found: C, 51.6; H, 6.72; N, 9.30%. Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.9; H, 6.71; N, 9.32%.

3,5-Di-*O*-benzyl-2-deoxy-D-ribofuranosylhydrazine 5. A mixture of methyl 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranoside[11] (5.1 g, 16 mmol) and 80% aqueous acetic acid (50 ml) was refluxed for 15 min. The reaction mixture was evaporated to give an oil, which was purified by column chromatography on silica gel (eluent: AcOEt–hexane, 1:2) to afford colorless crystals (3.19 g, 66%). 3,5-Di-*O*-benzyl-2-deoxy-D-ribofuranose obtained thus (0.63 g, 2 mmol), dry methanol (3 ml), and anhydrous hydrazine (0.64 ml, 20 mmol) was stirred for 17 h at room temperature. The solvent was removed under reduced

pressure. The residue was evaporated with dry methanol (4 ml×4) and then under vacuum pump (133.3 Pa) below 50 °C to remove excess hydrazine. A pale yellow syrup was used without purification for next step.

1-(3,5-Di-*O*-benzyl-2-deoxy-D-ribofuranosyl)-3-methylthio-5-phenylpyrazole 6a. A mixture of **5** (2 mmol), dry ethanol (5 ml), Zeolite A-3 (400 mg), **1a** (449 mg, 2 mmol), and boron trifluoride etherate (0.3 ml, 2 mmol) was refluxed for 18 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to give a light brown oil, which was purified by TLC on silica gel (eluent: AcOH–hexane, 1:4): A lower band gave α-anomer (113 mg, 12%) and an upper band gave β-anomer (170 mg, 18%); MS *m/z* 487 $(M+1)^+$; Found: C, 71.8; H, 6.10; N, 5.70%. Calcd for $C_{29}H_{30}N_2O_3S$: C, 71.6; H, 6.17; N, 5.76%.

α-Anomer: IR (neat) 3050, 3020 (Ph) and 2900, 2850 cm^{-1} (CH); ^1H NMR ($CDCl_3$) δ=2.4 (s, 3H, SMe), 3.1 (m, 2H, 2'-H), 3.6 (m, 2H, 5'-H), 4.3—4.4 (m, 2H, 3'-H and 4'-H), 4.6 (bs, 4H, CH_2Ph×2), 6.0 (dd, $J_{1',2'A}$=8.0, $J_{1',2'B}$=4.0 Hz, 1H, 1'-H), 6.2 (s, 1H, 4-H), 7.2 (bs, 10H, CH_2Ph×2), and 7.3—7.4 (m, 5H, 5-Ph); UV (99% EtOH) 208 (ε 36000) and 248 nm (16000); $[\alpha]_D$ +81° (*c* 0.93, EtOH).

β-Anomer: IR (neat) 3050, 3020 (Ph) and 2920, 2850 cm^{-1} (CH); ^1H NMR ($CDCl_3$) δ=2.3, 3.1 (m, 2H, 2'-H), 2.4 (s, 3H, SMe), 3.6 (m, 2H, 5'-H), 4.3 (m, 1H, 3'-H), 4.4 (m, 1H, 4'-H), 4.5—4.6 (m, 4H, CH_2Ph×2), 6.0 (t, $J_{1',2'A}$=$J_{1',2'B}$=5.5 Hz, 1H, 1'-H), 6.2 (s, 1H, 4-H), 7.2—7.3 (m, 10H, CH_2Ph×2), and 7.4—7.5 (m, 5H, 5-Ph); UV (99% EtOH) 211 (ε 22600) and 245 nm (12500); $[\alpha]_D$−70° (*c* 0.06, EtOH).

Compound **6b** was prepared from **1b** by the same method as above.

1-(3,5-Di-*O*-benzyl-2-deoxy-D-ribofuranosyl)-5-methyl-3-(methylthio)pyrazole 6b. Purification by TLC on silica gel (eluent: AcOEt–hexane, 1:4); α-anomer (66 mg, 14%) in a lower band; β-anomer (114 mg, 24%) in an upper band. Found: C, 67.8; H, 6.53; N, 6.70%. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.9; H, 6.60; N, 6.60%.

α-Anomer: IR (neat) 3050, 3020, (Ph) and 2900, 2850 cm^{-1} (CH); ^1H NMR ($CDCl_3$) δ=2.3 (s, 3H, 5-Me), 2.4 (s, 3H, SMe), 2.4, 3.1 (m, 2H, 2'-H), 3.6 (m, 2H, 5'-H), 4.3 (m, 1H, 3'-H), 4.4 (m, 1H, 4'-H), 4.5—4.6 (m, 4H, CH_2Ph×2), 5.9 (s, 1H, 4-H), 6.0 (dd, $J_{1',2'A}$=8.0, $J_{1',2'B}$=4.0 Hz, 1H, 1'-H), and 7.3—7.4 (bs, 10H, CH_2Ph×2); UV (99% EtOH) 211 (ε 8100), 235 (2300), and 248 nm (sh, 2100); MS 424 (M^+); $[\alpha]_D$+54° (*c* 0.08, EtOH).

β-Anomer: IR (neat) 3050, 3020, (Ph) and 2920, 2850 cm^{-1} (CH); ^1H NMR ($CDCl_3$) δ=2.2 (s, 3H, 5-Me), 2.4 (s, 3H, SMe), 2.4, 3.0 (m, 2H, 2'-H), 3.6 (m, 2H, 5'-H), 4.3 (m, 1H, 3'-H), 4.4 (m, 1H, 4'-H), 4.5—4.6 (m, 4H, CH_2Ph×2), 6.1 (s, 1H, 4-H), 6.3 (t, $J_{1',2'A}$=$J_{1',2'B}$=6.3 Hz, 1H, 1'-H), and 7.3—7.4 (bs, 10H, CH_2Ph×2); UV (99% EtOH) 211 (ε 18400), 229 (4500), and 247 nm (2100); MS 424 (M^+); $[\alpha]_D$−3.7° (*c* 0.10, EtOH).

1-(β-D-Ribofuranosyl)-3-methylthio-5-phenylpyrazole. A mixture of **3a″(H)** (26.5 mg, 0.07 mmol) and 10% acetic acid (1 ml) was stirred under refluxing for 4 h. The reaction mixture was evaporated under reduced pressure and then purified by TLC on silica gel using AcOEt as eluent to give a colorless oil (21 mg, 93%); IR (neat) 3500—3200 (OH) 3020 (Ph), and 2840 cm^{-1} (CH); ^1H NMR ($CDCl_3$–CCl_4) δ=2.3 (s, 3H, SMe), 3.2—4.2 (br, 3H, OH×3), 3.68 (m, 2H, CH_2OH), 4.2 (m, 1H, 4'-H), 4.4 (m, 1H, 2'-H), 4.8 (m, 1H, 3'-H), 5.6 (d, $J_{1',2'}$=4 Hz, 1H, 1'-H), 6.0 (s, 1H, 4-H), and 7.2 (s, 5H, Ph); MS 332 (M^+); UV(99% EtOH) 209 (ε 18600) and 243 nm (16600); $[\alpha]_D$−97.4° (*c* 0.09, EtOH); Found: C, 55.8; H, 5.56; N, 8.72%. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.63; N, 8.69%.

1-(2-Deoxy-β-D-ribofuranosyl)-3-methylthio-5-phenylpyrazole. The reported procedure[12] was modified as follows: Boron trifluoride etherate (0.05 ml, 0.4 mmol) was added to a stirred solution of **6a** (β-isomer, 94.4 mg, 0.2 mmol) in acetic anhydride (3 ml). The resulting solution was kept at room temperature for 16 h and then evaporated in vacuo. The residue was subjected to TLC on silica gel (eluent: AcOEt–hexane, 1:1) to give 1-(3,5-di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl)-3-methylthio-5-phenylpyrazole as a colorless syrup, which was then stirred with methanolic ammonia (saturated at 0 °C, 10 ml) in a closed flask at room temperature for 16 h and then evaporated. The usual work-up by TLC on silica gel gave a colorless oil (32 mg, 53%); IR (neat) 3300—3400 (OH), 3020 (Ph), and 2900—2850 cm^{-1} (CH); ^1H NMR ($CDCl_3$) δ=2.0 (m, 2H, 2'-H), 2.4 (s, 3H, SMe), 3.6—6.0 (m, 5H, 1',3',5'-H), 6,2 (s, 1H, 4-H), and 7.1 (m, 5H, Ph); MS 306 (M^+); Found: C, 58.8; H, 5.90; N, 9.04%. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.8; H, 5.91; N, 9.14%.

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