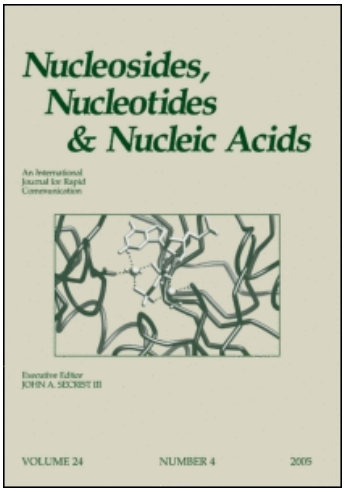

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Nucleosides, IV[1] Synthesis and Properties of 2-Metylthio-Naphthimidazole-Ribonucleoside

Abdullah Hijazi[a]
[a] Dept. of Chemistry, King Saud University, Riyadh, Saudi Arabia

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NUCLEOSIDES, IV[1]

SYNTHESIS AND PROPERTIES OF 2-METYLTHIO-NAPHTHIMIDAZOLE-RIBONUCLEOSIDE

Abdullah Hijazi

Dept. of Chemistry, King Saud University, Riyadh,
Saudi Arabia

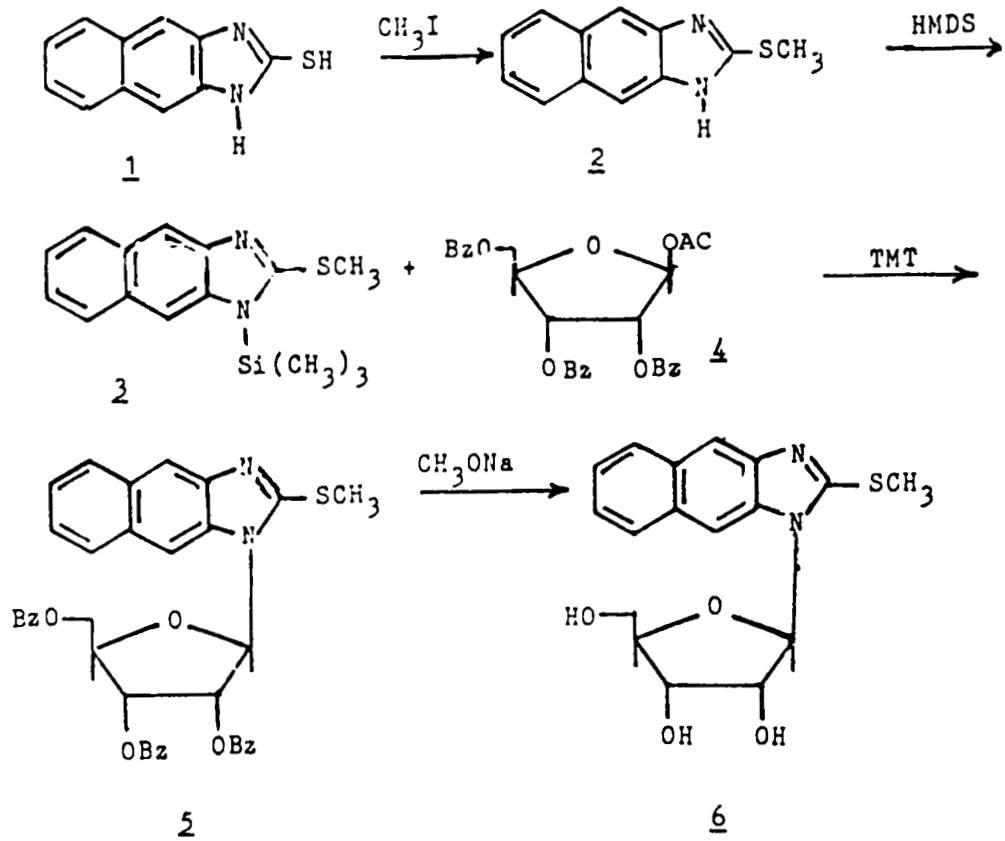
Abstract: The synthesis of 2-Methylthio-1-(β-D-ribofuranosyl) naphthimidazole has been accomplished by condensation of 2-methylthio-1-trimethylsilylnaphthimidazole(3) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose(4) in the presence of trimethylsilyl triflate in 1,2-dichloroethane, followed by subsequent debenzoylation. Structural proofs are based on elementary analysis, UV- and ^{1}H-NMR-spectra.

It is of interest that a 1-substituted benzimidazole-2-thione(1-(β-4-pyridethyl)benzimidazole-2-thione) has been reported[2] to posses the ability to act as a reversible inhibitor of nucleic acid synthesis presumably prior to the formation of inosinic acid in the de novo pathway of purine

biosynthesis. It has also been proposed that it may be acting as an antagonist in the synthesis of vitamin B_{12}.[3] The exact mechanisms for these observations remain unknown. As an extension of the previous investigations with lin-naphth-[2,3-d]imidazole[4], it was desired to ribosylate the 2-methylthionaphth[2,3-d]imidazole system. The structural features of these systems are closely related and reveal therefore some potential significance due to the fact that the lin-naphthimidazole-cobalamine analog[5] has been isolated as a minor vitamin B_{12} component.

The starting material 2-methylthionaphth[2,3-d]imidazole (2) was prepared from 2-mercaptonaphth[2,3-d]imidazole (1)[6], which was synthesized from 2,3-diaminonaphthalene and thiourea at 195^0 and followed by treatment with methyl iodide.

The first attempt to achieve ribosylation of (2), using the fusion method, failed and the expected nucleoside was not isolated. After the first attempt it was decided to examine the new Lewis acid catalyst trimethylsilyl Triflate (TMT). This Lewis acid has recently[7] been used and was described as a highly selective and efficient Friedel-Crafts catalyst for nucleoside formation from silylated heterocycles and preacylated sugars. First 2-methylthionaphth[2,3-d] imidazole(2) was treated with hexamethyldisililazane (HMDS) to form the trimethylsilyl derivative (3) and followed by 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (4) in the presence of (TMT) in 1,2-dichloroethane giving the product 2-



FORMULAS

methylthio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-naphth-[2,3-d]imidazole (5) in 76% yield. Debenzoylation to the free riboside (6) was achieved by Zemplen's method[8] using the purified anomer.

The empirical formulas of the newly synthesized compounds were determined by elementary analyses and the structural formulas were assigned unambiguously from UV-and ^{1}H-NMR spectra. The UV spectra (TAB. 1) are not too informative with regard to fine structural problems but show

Table 1. UV-Absorption Spectra of 2-Methylthionaphth[2,3-d]imidazole Derivatives in MeOH.

Compound	λ_{max} (nm)					log ε				
2-Mercaptonaphth[2,3-d]	217	[237]	272	[300]	316	4.71	4.01	4.79	[3.56]	[4.03]
imidazole(1)				329	343				4.29	4.53
2-Methylthionaphth[2,3-d]	217	252	258.5	[309]	[318]	4.50	4.64	4.73	[3.93]	[4.08]
imidazole (2)				322	332				4.11	4.19
2-Methylthio-1-(2,3,5-	227	253	260	281	[304]	4.84	4.74	4.79	3.74	[3.96]
tri-O-benzoyl-β-D-			317.5	[325]	332			4.14	[4.09]	4.12
ribofuranosyl)naphth-										
[2,3-d]imidazole(5)										
2-Methylthio-1-(β-D-	217	226	253	260	[305]	4.46	4.47	4.72	4.78	3.93
ribofuranosyl)naphth-			319	[325]	333.5			4.11	[4.06]	[4.12]
[2,3-d]imidazole(6)										

a characteristic splitting of the long wavelength band due to the planar and rigid structure of the aglycon.

Constitution and assignment of the configuration of the glycosidic linkage was depicted from the ^{1}H-NMR-spectra taken in $CDCl_3$ and D_6-DMSO respectively (Table 2). As expected[7], the ribosylation in the presence of TMT resulted exclusively in the formation of β-anomer as indicated by an upfield chemical shift of 1'-H. However, this is different from the chemical shift observed in the lower field, which was recognized for α-anomer of similar systems[4,9]. Again this result is in agreement with earlier report for β-anomer on very similar system[4,10] and other ribofuranosides[10-14], that in an anomeric pair the chemical shift of the anomeric 1'-H of the α-D-riboside tends to appear at lower field compared to that of the corresponding β-form. It was noted that in almost all cases, there was a distinct seperation and coupling of the sugar protons, which conclusively proves the assigned constitutions.

Experimental

UV spectra were recorded on a Cary Recording Spectrophotometer, model 118, from Appl. Physics Corp. ^{1}H-NMR spectra were obtained from Bruker WM 250. Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 of Schleicher & Schull, preparative thick layer chromatography on glass plates 40 x 20 cm coated with a 0.2

Table 2. ^{1}H-NMR Spectra of 2-Methylthionaphth[2,3-d]imidazole Derivatives in D_6-DMSO* or $CDCl_3$ (δ-values in ppm).

	2-SH(1) 2-SCH_3(3)	Aromatic Protons	1'-H (1H)	$J_{1',2'}$ (Hz)	Sugar Protons 2'-H (1H)	3'-H (1H)	4'-H (1H)	5'-H (2H)	2'-OH	3'-OH	5'-OH
1*	3.3 s(1)	7.35 dd$^+$(2), 7.55 s(2), 7.91 dd$^+$(2)									
2*	2.96 s(3)	7.49 dd$^+$(2), 8.09 dd$^+$(2), 8.13 s(2)									
5	2.83 s(3)	7.00 - , 8.25 m(21),	6.47 d	7.33	6.20 pt	6.11 dd	4.75 bs	4.91 ddd			
6*	2.78 s(3)	8.30 s(1), 8.05 s(1), 7.91 m(2), 7.38 m(2)	5.76 d	7.33	4.65 dd	4.17 dd	3.98 dd	3.75 m	5.75 d	5.44 d	5.25 t

s = singlet; bs = broad singlet; d = doublet; dd = double doublet (dd$^+$, arised from ^{3}J ortho coupling constant); ddd = doublet of doublet of doublet; pt = pseudotriplet; q = quadruplet; m = multiplet.

( ) number of protons.

cm layer of silica gel PF_{254} of Merck/Darmstadt and column chromatography on Merck silica gel 60(particle size 0.063-0.2 mm). Drying of the substances was achieved in a vacuum desiccator or in a Büchi-TO-50 drying oven under vacuum at room temp. and slightly elevated temp. respectively. Melting points are determined in a Tottoli apparatus and are uncorrected.

2-Mercaptonaphth[2,3-d]imidazole (1). 2,3-Diaminonaphthalene (4.74 g, 0.03 mole) and thiourea (5.20 g, 0.07 mol) were heated at 195°. After 10 min. the crude solid was extracted with 0.5 N sodium hydroxide (700 ml) at 50°C. Treatment with carbon and adjustment of the warm solution to pH 4 with acetic acid, gave the solid thiol. It was recrystallised from ethyl acetate/methanol (20/10) giving, after concentration, colourless crystals (3.50 g, 57%) of m.p. 306-307°C. Lit.[6] m.p. 305°C.

2-Methylthionaphth[2,3-d]imidazole (2). The thiol (1) (3 g, 0.015 mol) was dissolved in 0.5 N potassium hydroxide (200 ml) at 50°C, and the solution was filtered and cooled to 30°C. Methyl iodide (4 ml) was added and the mixture was vigorously shaken for 20 min. The suspension was adjusted to pH 4, by the addition of acetic acid then chilled. The solid precipitate filtered off and recrystallized twice from

ethanol/water (40/15 ml), which upon drying in a vacuum desiccator over P_4O_{10} (2g, 67%) gave crystals of m.p 240-241^{0}C. Lit[6]. m.p. 241^{0}C.

Anal. Calc. for $C_{12}H_{10}N_2S$ (214.3): C, 67.26; H, 4.70; N, 13.07 Found: C, 67.22; H, 4.74; N, 13.03.

2-Methylthio-1-trimethylsilylnaphth[2,3-d]imidazole(3).

A suspension of compound (2) (428.6 mg, 2 mmol) and a few crystals of ammonium sulfate in hexamethyldisilazane (15 ml) was refluxed under anhydrous conditions in an oil bath at 150^{0}C with stirring for 24 h formed a clear solution. The excess of HMDS was distilled off in vacuum to yield compound (3) quantitatively and the residue was used for further reaction.

2-Methylthio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-napth[2,3-d]imidazole(5). To a mixture of the crude material of (3) and 1.99 mmol (1 g.) of 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 18 ml of absol. 1,2-dichloroethane, were added 2,4 ml of 1M trimethylsilyl triflate and stirred for 24 h at 25^0 C. The procedure required routine dilution of the reaction mixture with 1N sodium bicarbonate solution (20 ml) and twice washing with water.

The organic layer was dried over sodium sulfate, and evaporated to dryness. The dry residue was dissolved in CH_2Cl_2 (20 ml) and the solvent was evaporated which yielded a

yellowisch solid foam (1.02 g, 78%). Separation of the pure product was achieved after applying the product twice to silica gel column (33 x 4 cm) chromatography in 1,2-dichloroethane/ethyl acetate (20/1). On evaporation of the main fraction a colourless foam of (5) (0.7 g) was obtained and yielded on recrystallization from ethanol (150 ml) colourless crystals of m.p. 173-4°.

Anal. Calc. for $C_{38}H_{30}N_2O_7S$ (658.7): C, 69.29; H, 4.59; N, 4.25 Found: C, 69.32; H, 4.53 N, 4.21.

2-Methylthio-1-β-D-ribofuranosyl-naphth[2,3-d]imidazole (6).

Compound (5) (0.33 gr, 5 mmol) was added into a methanolic sodium methoxide solution (60 mg sodium in 200 ml of methanol) and then stirred for 4 h at room temp. After addition of water (20 ml) the solution was neutralized with acetic acid and evaporated to dryness. The residue was coevaporated three times with water (10 ml), twice with methanol (20 ml) and then the residue crystallized from water (30 ml) to give colourless crystals (0.148 gr, 85%) of m.p. 137°C.

Anal. Calc. for $C_{17}H_{18}N_2O_4S.\ \frac{1}{2}H_2O$ (355.4): C, 57.45; H, 5.38; N, 7.88 Found: C, 57.45; H, 5.57; N, 7.78.

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REFERENCES

1. Part. III: A. Hijazi, Nucleosides & Nucleotides, 5, 529 (1986).
2. R.A. Bucknall and S.B. Carter, Nature, 213, 1099 (1967).
3. G.R. Revankar and L.B. Townsend, J. Heterocycl. Chem. 5, 477 (1968).
4. A. Hijazi and W. Pfleiderer, Nucleosides & Nucleotides, 3, 549 (1984).
5. W. Friedrich and K. Bernhauer, Angew. Chem. 71, 284 (1959).
6. D.J. Brown, J. Chem. Soc., 1974, (1958).
7. H. Vorbrüggen, K. Krolikiewiez, and B. Bennua, Chem. Ber., 114, 1234, (1981).
8. G. Zemplen, A. Geres and J. Hadacsy, Ber. Dtsch. Chem. Ges. 69, 1827 (1936).
9. Z. Kazimierczuk, R. Stolarski, Li Dudycz and D. Shugar, Nucleosides & Nucleotides, 1(3), 275 (1982).
10. A. Hijazi and W. Pfleiderer, Nucleosides & Nucleotides, 5, 243, (1986).
11. R.U. Lemieux, R.X. Kullnia, H.J. Bernstein and W.G. Schneider, J. Am. Chem. Soc. 80, 6098 (1958).
12. R.U. Lemieux and M. Hoffer, Can. J. Chem., 39, 110 (1961).

13. M.J. Robins and R.K. Robins, J. Am. Chem. Soc., 87, 4934 (1965).

14. T. Nishimura and B. Shimizu, Chem. Pharm. Bull., 13. 803 (1965).

15. I.W. Southon and W. Pfleiderer, Chem. Ber., 111 996 (1978).

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