SHORT PAPER

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Nucleosides 3[1]: synthesis of novel 1,3,4-oxadiazole nucleosides†

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5-Aryl-1,3,4-oxadiazole-2(3*H*)-thiones are ribosylated by reaction with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose, followed by debenzoylation, to give novel 1,3,4-oxadiazole nucleosides in good yields, one of which reacted with aniline to yield the corresponding 3,4-diaryl-1,2,4-triazole nucleoside.

Keywords: 1,3,4-oxadiazole nucleosides

Considerable interest has been shown in recent years in studying the effects of altering the heterocyclic moiety of a biologically active compound. Since various 5-aryl-1,3,4-oxadiazole-2(3*H*)-thione derivatives have been reported to show significant biological activity, such as antifungal and antibacterial activity.[2–7] Furthermore, modified nucleosides play a very important role in the synthesis of oligonucleotides.[8] The modified oligonucleotides that are modified either in the base, the sugar or the phosphate moiety, have become an area of increased activity due to their potential use as antiviral and antitumor agents.[9] These observations promoted our interest in investigating the ribosylation of 5-aryl-1,3,4-oxadiazole-2(3*H*)-thiones (**1**) in an attempt to synthesise 1,3,4-oxadiazole nucleosides, which so far have not yet been reported in the literature, in continuation of our program[1] for developing new nucleoside derivatives and precursors in the synthesis of modified oligonucleotides.

5-Aryl-1,3,4-oxadiazole-2(3*H*)-thiones (**1**) were prepared by reported methods[10,11] and were ribosylated by using the silyl method,[12] followed by reaction with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**3**) by using trimethylsilyl trifluoromethanesulfonate (TMS triflate). This reaction did not give the *S*-nucleosides, 5-aryl-2-(2,3,5-tribenzoyl-β-D-ribofuranosylmercapto)-1,3,4-oxadiazole (**4**), but the *N*-nucleosides,5-aryl-3-(2,3,5-tribenzoyl-β-ribofuranosyl)-1,3,4-oxadiazole-2(3*H*)-thiones (**5**) in good yield. Thus, it was found that our previously reported 3,4-diphenyl-1,2,4-triazole-5(4*H*)-thiones (**8**) reacted with the ribose derivative **3** through Vorbrüggen coupling[12] to give the *N*-nucleosides[1] (**7**). Compounds **5** were debenzoylated by stirring in methanolic sodium methoxide at room temperature to give the free nucleoside derivatives (**6**). Reaction of **6a** with aniline in dioxane afforded 3,4-diphenyl-1-β-D-ribofuranosyl-1,2,4-triazole-5(4*H*)-thione (**7a**)[1] (Scheme 1).

The chemical structure of the reaction products **5** were established and confirmed on the basis of elemental analysis and spectral data (MS, IR, UV, ^{1}H-NMR and ^{13}C-NMR: see Experimental). The ^{1}H-NMR spectra of **5** showed a doublet at δ 6.70 assigned to the anomeric proton of the ribose moiety with spin-spin coupling constant ($J_{1',2'}$) equal to 2.0 Hz which confirms the β-anomeric configuration. This is in accord with the results for 1-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-1,2-4-triazole derivatives.[1,13] The ^{13}C-NMR spectra of compounds **5** were characterised by a signal at δ 90.08 corresponding to the C-1′ atom in the β-configuration, three signals at δ 162–168 due to the three benzoyl carbons of ribose moiety and signal at δ 178 (weak signal) corresponding to the C–2 (C=S) of oxadiazole which is near to that of 3-methyl-1,3,4-thiadiazole-2(3*H*)-thione (δ C=S 180).[14] The UV spectra **5** indicated that the reaction had led selectively to the formation of *N*-ribofuranosyl derivatives and excluded substitution at the sulfur atom. Thus, the UV spectrum of **5a** or **6a** [$\lambda_{max.}$(EtOH) 290 nm] is close to that of 3-methyl-5-phenyl-1,3,4-oxadiazole-2(3*H*)-thione [$\lambda_{max.}$(EtOH), 295 nm].[15]

Furthermore, the IR spectrum of **5a** showed a characteristic band at 1452 cm^{-1} due to the C=S bond which is close to that in thiadiazole-2(3*H*)-thione[14] (ν_{CS} = 1485 cm^{-1}). Moreover, hydrolysis of **5a** with 5% hydrochloric acid afforded the starting material, 5-phenyl-1,3,4-oxadiazole-2(3*H*)-thione (**1a**) as the sole product; 5-phenyl-1,3,4-oxadiazol-2(3*H*)-one was not detected.

The structure of compounds **7a** was also confirmed by preparation of an authentic sample. Since 3,4-diphenyl-1,2,4-triazole-5(4*H*)-thione (**8**) was ribosylated by reaction with the ribose derivative **3**, followed by debenzoylation by using sodium methoxide in methanol at room temperature to give the nucleoside **7a**.[1]

Experimental

IR spectra were recorded for KBr discs on Testscan Shimadzu FTIR 8000 Series and Bruker IFS 113V spectrophotometers, ^{1}H-NMR and ^{13}C-spectra were recorded on a Bruker 200 MHz and on a Varian Gemini 200 MHz NMR spectrometer using TMS as internal standard; UV spectra were recorded on a Perkin Elmer spectrophotometer Lambda 5; MS spectra were recorded on Varian Mat 711 spectrometer. Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 of Schleicher & Schull and column chromatography on Merck silica gel 60 (particle size 0.063–0.20 mm). Melting points were measured on a Gallenkamp melting point apparatus. Elemental analyses were carried out at Sektion Analytik und Hoechstreinigung, Universität Ulm, Germany.

*5-Aryl-3-(2,3,5-tri-O-benzoyl-β-*D*-ribofuranosyl)-1,3,4-oxadiazole-2(3H)-thione* (**5a–c**): A mixture of **1a–c** (10 mmol each) and dry hexamethyldisilazane (50 ml) was heated under reflux for 10 h with a catalytic amount of ammonium sulfate (50 mg). After the clear solution was cooled, it was evaporated to dryness under anhydrous conditions to give the silylated derivative, which directly was dissolved in 30 ml of dry 1,2-dichloroethane. To this solution was added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **3** (4.80 g, 9.8 mmol) in dry 1,2-dichloroethane (30 ml). The mixture was cooled in ice bath, and a solution of trimethylsilyl trifluoromethanesulfonate (2 ml, 10 mmol) in dry 1,2-dichloroethane (10 ml) was added dropwise. It was stirred at room temperature for 24 h, and then diluted with chloroform (300 ml), washed with a saturated solution of aqueous sodium bicarbonate (100 ml), water (3 × 150 ml) and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with chloroform as eluent to afford a white solid which was crystallised from the proper solvent to yield colourless crystals of the corresponding benzoylated nucleoside derivatives **5a–c**.

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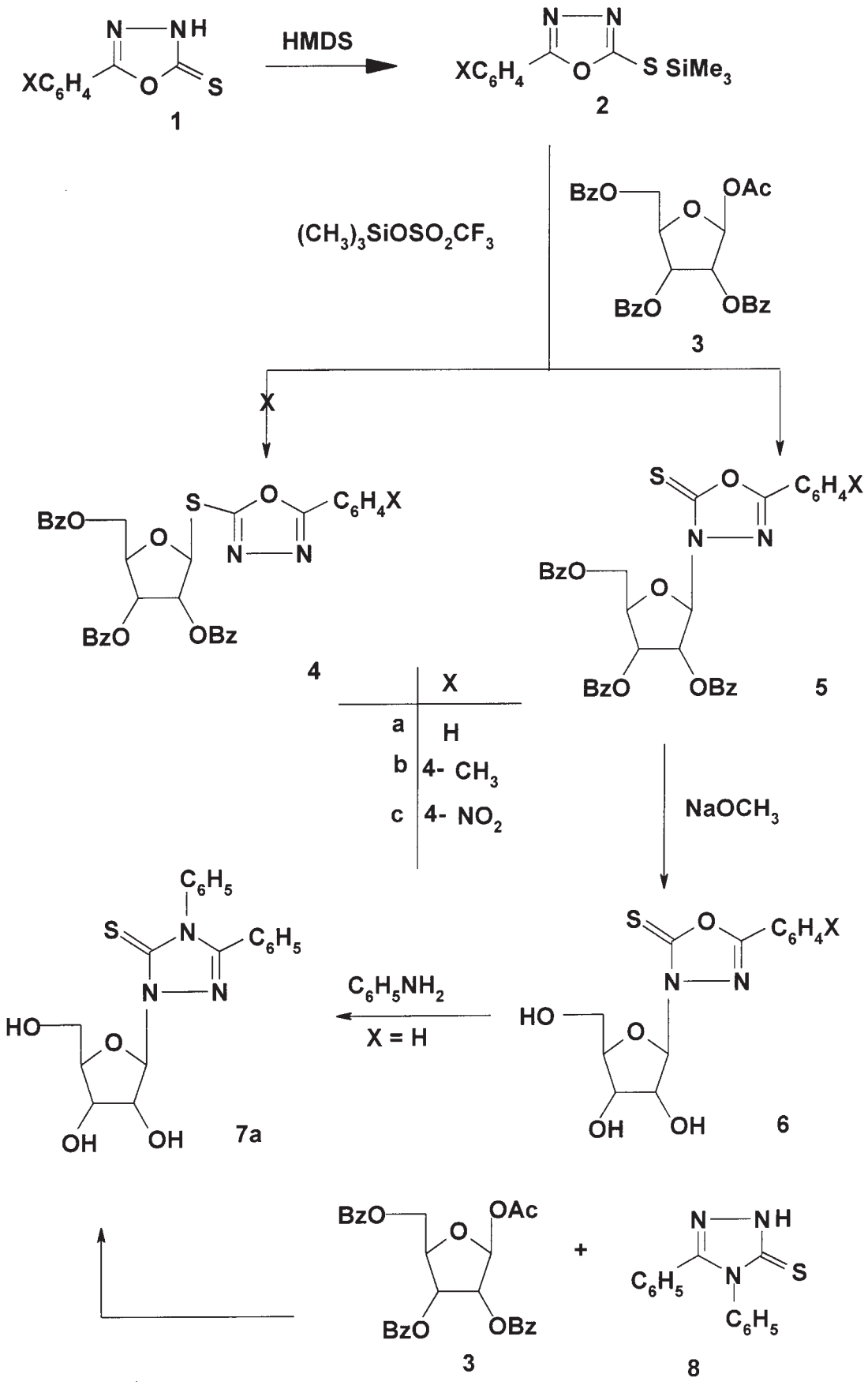
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*


HMDS
1
2
$(CH_3)_3SiOSO_2CF_3$
3
X
4
5
a H
b 4- CH_3
c 4- NO_2
$NaOCH_3$
$C_6H_5NH_2$
X = H
6
7a
3
8

Scheme 1

Compound **5a**: yield 90%; m.p. 164–165°C (EtOH/dioxane, 2:1 v/v); $\lambda_{max.}$(EtOH) 290 nm; ν(cm^{-1}) (KBr) 3438, 2931, 1739, 1729, 1624, 1600, 1583, 1491, 1452(C = S), 1428, 1380, 1361, 1340, 1316, 1265, 1175, 1112; δ_H ($CDCl_3$) 4.62 (m, 1H, 4′-H); 4.85 (m, 2H, 5′ & 5″-H); 6.18 (m, 2H, 3′ & 2′-H), 6.71 (d, 1H, $J_{1',2'}$ = 2.0 Hz, 1′-H,); 7.73 (m, 20H, Ar–H); δ_C ($CDCl_3$) 65, 73, 75, 82, 90, 123, 128–135, 162, 167, 168, 178(CS); *m/z*: 622(7.6%)(M$^+$), 445(100%)(ribose moiety), 177(39%)(M$^+$-ribose moiety); Anal: found: C, 65.85; H, 4.23; N, 4.66. $C_{34}H_{26}N_2O_8S$ requires C, 65.59; H, 4.21; N, 4.50.

Compound **5b**: yield 83%; m.p. 109–111°C (EtOH/dioxane, 2:1 v/v); $\lambda_{max.}$(EtOH) 292nm; ν(cm^{-1}ý) (KBr) 3447, 2972, 1727, 1622, 1602, 1584, 1509, 1492, 1452(C = S), 1410, 1374, 1337, 1315, 1268, 1178, 1109; δ_H($CDCl_3$ý) 2.5 (s, 3H, CH_3), 4.60 (m, 1H, 4′-H), 4.85 (m, 2H, 5′ & 5″-H), 6.20 (m,.1H, 3′ & 2′-H), 6.70 (d, 1H, $J_{1',2'}$ = 2.0Hz, 1′-H,); 7.67 (m, 19H, Ar–H); δ_C($CDCl_3$) 24, 65, 73, 75, 82, 90, 123, 128-135, 162, 166, 168, 178(CS); *m/z*: 636(47%)(M$^+$), 445(100%)(ribose moiety), 191(97%)(M$^+$-ribose moiety); Anal: found C,66.0; H,4.5; N,4.4. $C_{35}H_{28}N_2O_8S$ requires; C,66.03; H,4.43; N,4.40.

Compound **5c**: yield 80%, m.p. 178–180°C (EtOH/dioxane, 2:1 v/v); $\lambda_{max.}$(EtOH) 310 nm; ν(cm^{-1}) (KBr) 3450, 2975, 1729, 1625, 1580, 1510, 1490, 1451(C = S), 1408, 1374, 1338, 1312, 1270, 1178, 1108; δ_H($CDCl_3$) 4.55 (m, 1H, 4′-H) 4.90 (m, 2H, 5′ & 5″-H), 6.07 (m, 1H, 3′-H), 6.24 (m, 1H, 2′-H), 6.70 (d, 1H, $J_{1',2'}$ = 2.2Hz, 1′-H), 7.77 (m, 19H, Ar–H); δ_C($CDCl_3$) 66, 73, 75, 82, 90, 123, 129–135, 162, 166, 168, 177(CS); *m/z*: 667(M$^+$)(35%), 445(100%)(ribose moiety), 222 (90%) (M$^+$-ribose moiety); Anal. Found: C,61.2; H,4.0; N,6.0. $C_{34}H_{25}N_3O_{10}S$ requires C,61.17; H,3.77; N,6.29.

5-Aryl-3-β-D-*ribofuranosyl-1,3,4-oxadiazole-2(3H)-thione* **6a–c**: A mixture of the protected nucleoside **5a–c** (1 mmol each), absolute methanol (20 ml) and sodium methoxide (60 mg, 1.1 mmol) was stirred at room temperature for 48 h. Evaporation of the solvent under vacuum gave a colourless solid, which was dissolved in hot water and neutralised with acetic acid. The precipitate was filtered off and afforded, upon crystallisation from water, the nucleosides **6a–c** as colourless crystals.

Compound **6a**: yield 55%; m.p. 142–144°C; $\lambda_{max.}$(EtOH) 290 nm; ν(cm^{-1}) (KBr) 3544(OH), 2957, 1688, 1640, 1621, 1575, 1494, 1412(C=S), 1363, 1340, 1288, 1259, 1199; δ_H (DMSO-d_6) 3.55 (m, 2H, 5′ & 5″-H), 3.85 (m, 1H, 4′), 4.22 (m, 1H, 3′-H), 4.45 (m, 1H, 2′-H), 4.8 (t, 1H, 5′-OH), 5.15 (d ,1H, 3'-OH), 5.45 (d, 1H, 2′-OH), 6.2 (d, 1H, $J_{1',2'}$=2.0Hz, 1'-H), 7.6 (m, 5H, Ar-H); *m/z*: 310(9.77%)(M$^+$), 179(100%)(M$^+$-ribose), 133(5.6%)(ribose); Anal: found C,50.1; H,4.9; N,8.5. $C_{13}H_{14}N_2O_5S$ requires C,50.32; H,4.55; N,9.03.

Compound **6b**: yield 70%; m.p. 215–216°C; $\lambda_{max.}$(EtOH) 296 nm;ν(cm^{-1}) (KBr) 3499(OH), 2958, 1667, 1624, 1608, 1570, 1509, 1408(C = S), 1355, 1338, 1293, 1273, 1187; δ_H (DMSO-d_6): 2.4 (s, 3H, CH_3), 3.55 (m, 2H, 5′ and 5″-H), 3.95 (m, 1H, 4′-H), 4.25 (m, 1H, 3′-H), 4.45 (m, 1H, 2′-H), 4.6 (t, 1H, 5′-OH), 5.0 (d, 1H, 3′-OH), 5.45 (d, 1H, 2′-OH), 6.05 (d, 1H, $J_{1',2'}$= 2.0Hz, 1′-H,), 7.55 (m, 4H, Ar–H); *m/z*: 324(7.1%)(M$^+$), 193(100%)(M$^+$-ribose), 133(5.8%)(ribose); Anal: found: C,51.91; H,5.07; N,8.73. $C_{14}H_{16}N_2O_5S$ requires C,51.84; H,4.97; N,8.64.

Compound **6c**: yield 50%; m.p. 189–191°C, $\lambda_{max.}$ (EtOH) 335 nm; ν(cm^{-1}) (KBr) 3450(OH), 2960, 1680, 1629, 1610, 1567, 1500, 1415(C = S), 1365, 1330, 1280, 1190; δ_H (DMSO-d_6) 3.55 (m, 2H, 5′ and 5′-H), 3.95 (m, 1H, 4′-H), 4.25 (m, 1H, 3′-H), 4.40 (m, 1H, 2′-H), 4.80 (t, 1H, 5′-OH), 5.15 (d, 1H, 3′-OH), 5.63 (d, 1H, 2′-OH), 6.0 (d, 1H, $J_{1',2'}$ = 2.0 Hz, 1′-H,), 8.0 (m, 4H, Ar-H); *m/z*: 355(10%)(M$^+$ý), 223(90%)(M$^+$-ribose), 133(5.5%)(ribose); Anal. Found: C,43.9; H,3.9; N,11.7. $C_{13}H_{13}N_3O_7S$ requires C,43.94; H,3.69; N,11.83.

Conversion of **6a** *into 3,4-diphenyl-1-β*-D-*ribofuranosyl-1,2,4-triazole-5(1H)-thione* **7a**: A mixture of **6a** (0.31 g, 1 mmol) and freshly distilled aniline (1ml, 1.1mmol) in 30 ml dioxane was heated under reflux for 10 hours (followed by tlc). After cooling the solvent was evaporated, and the residue was crystallized from EtOH/ dioxane (2:1 v/v) to give **7a** as colourless crystals.

Compound **7a**: yield 48%; m.p. 200–201°C (lit.[1] m.p. 202–203°C), ν(cm^{-1}) (KBr) 3550(OH), 1400 and 1165 (CS); δ_H (DMSO-d_6): 3.5 (m, 2H, 5′,5″-H), 3.95 (m, 1H, 4′-H), 4.25 (m, 1H, 3′-H), 4.45 (m, 1H, 2′-H), 4.8 (t, 1H, 5′-OH), 5.25 (d, 1H, 3′-OH), 5.55 (d, 1H, 2′-OH), 6.13 (d, 1H, $J_{1',2'}$ = 2.0 Hz, 1′-H), 7.6 (m, 10H, Ar–H). *m/z*: 385(50%)(M$^+$), 252(100%)(M$^+$-ribose), 133(8%)(ribose); Anal: found C,59.0; H,4.7; N,10.6; S,8.0. $C_{19}H_{19}N_3O_4S$ requires C,59.22; H,4.94; N,10.91; S,8.31.

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