Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supplementary Information

Water gelation abilities of alkylbenzyltriazole-appended 2′- deoxyribonucleosides and ribonucleosides

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Experimental Part

General Information

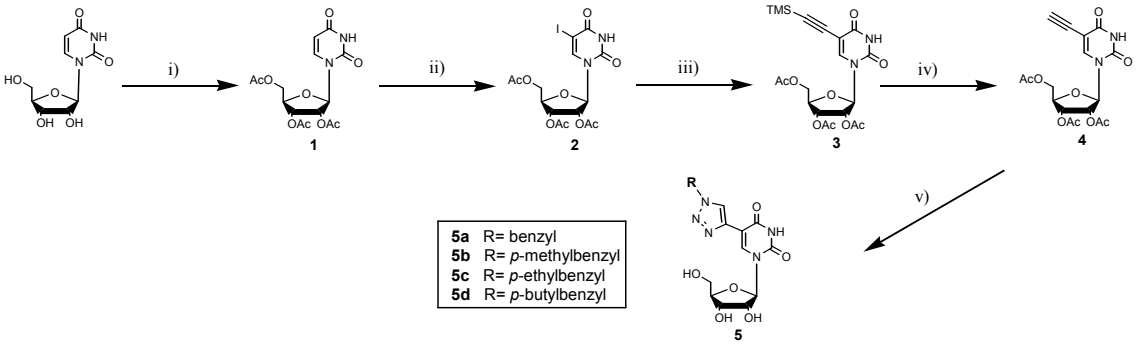
All chemicals were obtained from Aldrich Chemical Company and were used without further purification. Each reaction was executed under an inert atmosphere of dry argon and using glassware that was flame-dried under vacuum. Flash chromatography was performed using silica gel 60 (230–400 mesh; ASTM). Melting points are uncorrected and were obtained using an Electrothermal 1A 9000 series apparatus. FTIR spectra were recorded on a Brucker model FT-IR PS55+ spectrometer. High-resolution FAB^+ mass spectra were obtained using a JEOL JMS-AX505WA (FAB) spectrometer.

^1H and ^{13}C NMR spectra were recorded using a Bruker Aspect 300 NMR spectrometer. Chemical shifts these spectra are reported in parts per million (ppm) downfield relative to the internal standard, tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designed as s, singlet; d, doublet; dd, double doublet; dt, distorted triplet; t, triplet; m, multiplet; and br, broad.
SEM images were obtained using a Philips XL30S FEG SEM analyzer.

Sample Preparations and Tests for Gelation

To avoid evaporation of the liquid components, for most studies we prepared gels in sealed 2ml vial. Weighed quantities of a gelator and a liquid were heated until a solution was obtained. The vials were then kept at room temperature for a certain period; we deemed them to be gels, then the samples were not visually phase-separated, and did not flow perceptibly when the vessels were inverted.

Scheme



Reagents: i) Acetic anhydride, triethylamine, 1,4-dioxane, rt; ii) iodine, Ammonium cerium(IV) nitrate, MeCN, 80^{O}C, 1hr; iii) TMS-acetylene, $Pd(PPh_3)_2Cl_2$, CuI, triethylamine/THF (3:1), 45-50^{O}C; iv) TBAF, THF, rt; v) 1. Alkylbenzylazide, Na-ascorbate, $CuSO_4.5H_2O$, *tert*-BuOH/H_2O (1:1), rt, 2. K_2CO_3, MeOH/H_2O (1:1), rt

Synthesis of the Alkylbenzyltriazole appended uridine

2′, 3′, 5′-*O*-Triacetyluridine (1)

Acetic anhydride (8 mL, 84 mmol) and triethylamine (8 mL) was added to a solution of uridine (2.44 g, 10 mmol) in dry 1, 4-

dioxane (50 mL), and the reaction was allowed to proceed at 25 ^{0}C with stirring for 36 h. Removal of the solvent in vacuo and purification of the product by elution from a silica gel column chromatography using Hex/EtOAc (1:2, v/v) as eluent gave the product **1** (3.70 g, quantitative) as a white solid .

mp 128.3-129.7 ^{0}C

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.01, 2.03, 2.04(3s, 3H, 3H and 3H, 2′, 3′, 5′-OAc), 4.14-4.29(m, 3H, 5′-H, 5′′-H, 4′-H), 5.26-5.29(t, J=5.1Hz, 1H, 3′-H), 5.37-5.42(t, J=4Hz, 1H, 2′-H), 5.67-5.71(t, J=8.1Hz, 1H, 1′-H), 5.83-5.86(d, J=5.4Hz, 1H, 5-H), 7.66-7.69(d, J=8.1Hz, 1H, 6-H), 11.44(br, 1H, CONHCO); HRMS (FAB, m/z) calc.$(M+H)^+$=371.1012, obsvd.$(M+H)^+$=371.1091.

2′, 3′, 5′-*O*-Triacetyl-5-iodouridine (2)

A mixture of **1** (3.3g, 8.91mmol), iodine (1.36g, 5.35mmol), ammonium cerium(IV) nitrate (2.44g, 4.46mmol), and MeCN (142mL) was stirred at 80^{0}C for 1h. Reaction progress was monitored by TLC (Hex: EtOAc=1:1, V/V). Solvent was evaporated, and the residue was partitioned between a cold mixture of EtOAc (120 mL), saturated NaCl/H_2O (100 mL), and 5% $NaHSO_3$/H_2O (125 mL). The aqueous layer was extracted with EtOAc (100 Ml × 2). The combined organic layer was washed carefully with cold 5% $NaHSO_3$/H_2O (125 mL), followed by saturated NaCl/H_2O (150 mL)

and H_2O (150 mL × 2), dried over anhydrous $MgSO_4$, and evaporated. The crude product was purified by column chromatography (Hex:EtOAc=1:1, v/v) to give the product **2** (4.28 g, 97%).

mp 177.8-179.3 ^{0}C

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.01, 2.03, 2.04(3s, 3H, 3H and 3H, 2′, 3′, 5′-OAc), 4.16-4.20(m, 2H, 5′-H), 4.23-4.31(m, 1H, 4′-H), 5.28-5.31(m, 1H, 3′-H), 5.40-5.44(t, *J*=5.4Hz, 2′-H), 5.83-5.84(d, *J*=5.1Hz, 1H, 1′-H), 8.14(s, 1H, 6-H), 11.80(br, 1H, CONHCO); HRMS (FAB, m/z) calc.$(M+H)^+$=496.9978, obsvd.$(M+H)^+$= 497.0057.

2′, 3′, 5′-O-Triacetyl-5-[(trimethylsilyl)ethynyl]-uridine (3)

To a stirred solution of **2** (4.28 g, 8.62 mmol) in anhydrous triethylamine (90 mL) and THF (30 mL) were added TMS-acetylene (1.87 mL, 13.40 mmol), $Pd(PPh_3)_2Cl_2$ (605 mg, 0.86 mmol) and CuI (164 mg, 0.86 mmol). The mixture was stirred for 3h at 45-50°C under a nitrogen atmosphere until TLC monitoring ($CHCl_3$/MeOH, 30:1, v/v) showed complete conversion of the starting material. The reaction mixture was filtered and washed with triethylamine, and the combined filtrate was evaporated to dryness. The crude product was purified by column chromatography (Initial eluent: CH_2Cl_2/MeOH (200:1, v/v),

followed by: CH_2Cl_2/MeOH (100:1, v/v)). The appropriate fractions were combined, and the solvent was removed in vacuo, to give the product **3** (2.64 g, 65%).

mp 81.9-83.4 ^{0}C

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.15 (s, 9H, TMS), 2.01, 2.03, 2.04(3s, 3H, 3H and 3H, 2′, 3′, 5′-OAc) 4.17-4.32(m, 3H, 5′-H, 4′-H), 5.27-5.30(m, 1H, 3′-H), 5.40-5.44(t, *J*=5.4Hz, 1H, 2′-H), 5.86(d, *J*=4.8Hz, 1H, 1′-H), 8.05(s, 1H, 6-H), 11.80(br, 1H, CONHCO); ^{13}C NMR (75 MHz, DMSO-d_6) δ 0.36, 20.60, 20.71, 21.14, 63.15, 70.34, 73.39, 80.44, 87.31, 95.05, 100.44, 101.64, 142.21, 149.36, 160.83, 169.74, 169.86, 170.21; IR (NaCl, cm^{-1}) 758, 846, 1110, 1229, 1373, 1699, 1717, 1749, 2161, 3086; HRMS (FAB, m/z) calc.$(M+H)^+$=467.1486, obsvd.$(M+H)^+$=467.1483.

2′, 3′, 5′-*O*-Triacetyl-5-ethynyl-uridine (4)

To a stirred solution of **3** (2.65 g, 5.69 mmol) in THF (56 mL) were added TBAF (2.40 mL, 1.0 M solution in THF) and stirred at room temperature until TLC monitoring showed complete conversion of the starting material. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (Initial eluent: CH_2Cl_2/MeOH (200:1, v/v), followed by: CH_2Cl_2/MeOH (100:1, v/v)). The appropriate

fractions were combined, and the solvent was removed in vacuo to give the product **4** (2.08g, 93%).

mp 159.2-160.7 ^{0}C

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01, 2.03, 2.04(3s, 3H, 3H and 3H, 2′, 3′, 5′-OAc), 3.19(s, 1H, alkyne H), 4.35-4.37(m, 3H, 5′-H, 4′-H), 5.30-5.31(m, 2H, 3′-H, 2′-H), 6.05-6.06(d, *J*=3.9Hz, 1H, 1′-H), 8.34(s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.23, 20.33, 20.68, 62.70, 69.82, 73.07, 74.19, 80.07, 82.32, 87.29, 99.97, 142.56, 148.96, 160.66, 169.39, 169.47, 169.95; IR (NaCl, cm^{-1}) 755, 899, 1049, 1108, 1227, 1372, 1455, 1506, 1540, 1558, 1627, 1699, 1747, 2161, 3086; HRMS(FAB, m/z) calc.$(M+H)^+$=395.1091, obsvd.$(M+H)^+$=395.1090.

5-[1-(phenylmethyl)-1H-1, 2, 3-triazol-4-yl]-uridine (5a)

To a stirred solution of **4** (394 mg, 1.0 mmol) and an benzylazide (3 mmol, 3 eq.) in *tert*-butanol (8 mL) and water (4 mL) were added $CuSO_4 \cdot 5H_2O$ (12.6 mg, 4 mol%) and sodium ascorbate (50 mg, 20 mol%). The reaction mixture was stirred at room temperature until TLC monitoring showed complete conversion of the starting material (3 days). The reaction mixture was evaporated to dryness, then dissolved in CH_2Cl_2 and was filtered, the filtrate was evaporated to dryness. The residue dissolved in MeOH/H_2O (1:1, v/v, 10ml). To a stirred

solution of benzyltriazole-appeneded uridine was added potassium carbonate (480 mg) and stirred over night at room temperature. The reaction mixture was filtered, solid was dried and then recrystalized with MeOH/H_2O to give the product **5a** (123 mg, 31%).

mp 229.7-231.2 ^{0}C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.51-3.55(m, 2H, 5'-H), 3.77(m, 1H, 4'-H), 3.82(m, 1H, 3'-H), 4.03(m, 1H, 2'-H), 5.53(s, 2H, Ar-CH_2-Ar'), 5.79-5.80(d, J=5.1Hz, 1H, 1'-H), 7.33-7.37(m, 5H, Ar-H), 8.35(s, 1H, 6-H), 8.38(s, 1H, triazole ring H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 52.93, 61.73, 70.53, 74.03, 84.96, 89.01, 105.42, 122.64, 128.24, 128.38, 129.06, 135.79, 136.65, 141.24, 154.35, 166.82; IR(KBr, cm^{-1}) 578, 668, 718, 781, 813, 987, 1052, 1107, 1129, 1164, 1242, 1298, 1332, 1465, 1520, 1544, 1614, 1653, 1701, 1927, 3382; HRMS (FAB, m/z) calc.$(M+H)^+$ =402.1414, obsvd.$(M+H)^+$=402.1415.

5-[1-((*p*-methylphenyl)methyl)-1H-1, 2, 3-triazol-4-yl]-uridine (5b)

To a stirred solution of **4** (394 mg, 1.0 mmol) and *p*-methylbenzylazide (3 mmol, 3 eq.) in *tert*-butanol (8 mL) and water (4 mL) were added $CuSO_4 \cdot 5H_2O$ (12.6 mg, 4 mol%) and sodium ascorbate (50 mg, 20 mol%). The reaction mixture was

stirred at room temperature until TLC monitoring showed complete conversion of the starting material (2-4 days). The reaction mixture was evaporated to dryness, then dissolved in CH_2Cl_2 and was filtered, the filtrate was evaporated to dryness. The residue dissolved in MeOH/H_2O (1:1, v/v, 10ml). To a stirred solution of *p*-methylbenzyltriazole-appeneded uridine was added potassium carbonate (480 mg) and stirred over night at room temperature. The reaction mixture was filtered, solid was dried and then recrystallized with MeOH/H_2O to give the product **5b** (254 mg, 61%).

mp 267.7-269.2 ^{0}C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30(s, 3H, ArCH_3), 3.58-3.66(m, 2H, 5′-H), 3.87-3.89(m, 1H, 4′-H), 3.95-3.98(m, 1H, 3′-H), 4.10-4.13(m, 1H, 2′-H), 5.52(s, 2H, Ar-CH_2-Ar′), 5.92-5.94(d, *J*=6Hz, 1′-H), 7.17-7.24(dd, *J*=5.1Hz, 13.2Hz, 4H, Ar-H), 8.19(s, 1H, triazole ring H), 8.25(s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.98, 52.64, 61.92, 70.46, 74.00, 84.60, 89.50, 105.27, 122.17, 128.23, 129.52, 133.64, 134.95, 137.60, 142.47, 157.27, 170.54; IR (KBr, cm^{-1}) 666, 757, 782, 814, 1054, 1099, 1121, 1163, 1238, 1332, 1462, 1506, 1541, 1590, 1653, 3325; HRMS(FAB, m/z) calc.$(M+H)^+$=416.1570, obsvd.$(M+H)^+$=416.1569.

5-[1-((*p*-ethylphenyl)methyl)-1H-1, 2, 3-triazol-4-yl]-uridine (5c)

To a stirred solution of **4** (394 mg, 1.0 mmol) and *p*-ethylbenzylazide (3 mmol, 3 eq.) in *tert*-butanol (8 mL) and water (4 mL) were added $CuSO_4 \cdot 5H_2O$ (12.6 mg, 4 mol%) and sodium ascorbate (50 mg, 20 mol%). The reaction mixture was stirred at room temperature until TLC monitoring showed complete conversion of the starting material (3 days). The reaction mixture was evaporated to dryness, then dissolved in CH_2Cl_2 and was filtered, the filtrate was evaporated to dryness. The residue dissolved in MeOH/H_2O (1:1, v/v, 10 ml). To a stirred solution of *p*-ethylbenzyltriazole-appeneded uridine was added potassium carbonate (480 mg) and stirred over night at room temperature. The reaction mixture was filtered, solid was dried and then recrystallized with MeOH/H_2O to give the product **5c** (275 mg, 64%).

mp 221.8-223.3 ^{0}C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22-1.27(t, *J*=7.5Hz, 3H), 2.63-2.71(q, 2H, Ar-CH_2-CH_3), 3.64-3.75(m, 2H, 5′-H), 3.96-3.97(m, 1H, 4′-H), 4.07-4.10(m, 1H, 3′-H), 4.20-4.23(m, 1H, 2′-H), 5.65(s, 2H, Ar-CH_2-Ar′), 5.98-6.00(d, *J*=5.4Hz, 1H, 1′-H), 8.44(s, 1H, triazole ring H), 8.40(s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.74, 28.09, 52.78, 61.72, 70.52, 73.96, 84.99,

89.11, 105.46, 109.25, 122.42, 128.28, 128.35, 133.77, 135.83, 141.05, 143.99, 153.95, 166.26; IR (KBr, cm^{-1}) 618, 708, 784, 808, 850, 900, 985, 1052, 1140, 1264, 1328, 1513, 1648, 3150; HRMS (FAB, m/z) calc.$(M+H)^+$=430.1727, obsvd.$(M+H)^+$=430.1728.

5-[1-((*p*-butylphenyl)methyl)-1H-1, 2, 3-triazol-4-yl]-uridine (5d)

To a stirred solution of **4** (394 mg, 1.0 mmol) and *p*-butylbenzylazide (3.0 mmol, 3 eq.) in *tert*-butanol (8 mL) and water (4 mL) were added $CuSO_4 \cdot 5H_2O$ (12.6 mg, 4 mol%) and sodium ascorbate (50 mg, 20 mol%). The reaction mixture was stirred at room temperature until TLC monitoring showed complete conversion of the starting material (3 days). The reaction mixture was evaporated to dryness, then dissolved in CH_2Cl_2 and was filtered, the filtrate was evaporated to dryness. The residue dissolved in MeOH/H_2O (1:1, v/v, 10 ml). To a stirred solution of *p*-butylbenzyltriazole-appeneded triacetyluridine was added potassium carbonate (480 mg) and stirred over night at room temperature. The reaction mixture was filtered, solid was dried and then recrystallized with MeOH/H_2O to give the product **5d** (292 mg, 64%).

mp 242.9-244.4 ^{0}C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83-0.89(*t*, *J*=7.5Hz, CH_3), 1.23-1.30(m, 2H, CH_2), 1.46-1.53(m, 2H, CH_2), 2.49-2.56(t, *J*=7.5Hz, 2H, CH_2), 3.53-3.65(m, 2H, 5'-H), 3.82-3.86(q, *J*=4.2Hz, 1H, 4'-H), 3.92-3.95(m, 1H, 3'-H), 4.07-4.10(t, *J*=5.1Hz, 1H, 2'-H), 5.50(s, 2H, Ar-CH_2-Ar'), 5.88-5.90(d, *J*=5.1Hz, 1'-H), 7.15-7.23(dd, *J*=8.4Hz, 14.7Hz, Ar-H), 8.17(s, 1H, triazole ring H), 8.28(s, 1H, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.71, 21.68, 33.02, 34.44, 52.35, 61.62, 70.17, 73.68, 84.32, 89.21, 104.97, 121.92, 127.88, 128.56, 133.61, 134.72, 142.10, 142.17, 156.70, 169.91; IR(KBr, cm^{-1}) 714, 763, 788, 845, 1057, 1097, 1166, 1237, 1329, 1465, 1503, 1540, 1609, 1649, 2935, 3375; HRMS(FAB, m/z) calc.$(M+H)^+$=458.2040, obsvd. $(M+H)^+$=458.2045.