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Convenient Synthesis of 1-(1,3-Dihydroxy-2-propyl)-4-nitroimidazoles

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The title compounds have been obtained in reaction of 1,4-dinitroimidazoles with 2-amino-1,3-propanedioles in water-methanol solution. 1-(1,3-Dihydroxy-2-propyl)-4-nitroimidazoles were transformed into derivatives that can be used for combinatorial oligomer synthesis.

Key words: nitroimidazoles, 2-amino-1,3-dihydroxypropanediols, *ANRORC* reaction, combinatorial oligomer synthesis

N-Alkylated derivatives of nucleobases, so called acyclic nucleosides, are known as compounds with well established antiviral activity [1–3]. *N*-Alkyl derivatives of nitroimidazoles were used as radiosensitisers in tumour radiotherapy [4–6]. Imidazol-1-yl acetate and diethyl-2-imidazol-1-yl succinate were recently proposed as novel extrinsic ^{1}H NMR probes for the measurement of intracellular pH in erythrocytes [7,8]. The most popular syntheses of *N*-alkylated heterocycles involve substitution of heterocyclic compounds with a suitable alkylating agent [9–11], addition to an activated multiple bond [12–14] or opening of oxirane ring [15,16]. An alternative method is building up a heterocyclic ring on a proper functional group of alkyl derivative [17,18]. When unsymmetrical heterocycles are alkylated, a mixture of regioisomers can be expected. Such mixtures are sometimes very difficult to separation. Recently, we have demonstrated that some *N*-alkylated 4-nitroimidazoles can be obtained in reaction of 1,4-dinitroimidazole and its 2-alkyl derivatives with alkyl compounds having primary amino group. The mechanism of *ANRORC* (*Attack of Nucleophile Ring Opening Ring Closure*) type reaction was proposed [19,20]. The advantage of this method is formation of a 4-nitroimidazole isomer only. 1-(1,3-Dihydroxy-2-propyl)-4-nitroimidazoles were obtained formerly in a multistage reaction of 4-nitroimidazole with *gem*-bromonitroalkanes under $S_{RN}1$ conditions [21].

This paper describes the synthesis of symmetrical 1-(1,3-dihydroxy-2-propyl)-4-nitroimidazoles and their functionalization to phosphoroamidites, suitable for automated synthesis on solid support. We believe, that the flexibility of the pro-

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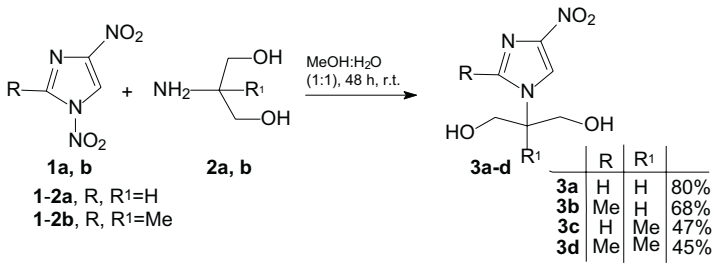
pane-phosphodiester backbone relative to a deoxyribose backbone can change the tertiary structure or shape of oligomers. These changes can be responsible for biological activity, as was proposed before [22,23].

RESULTS AND DISCUSSION

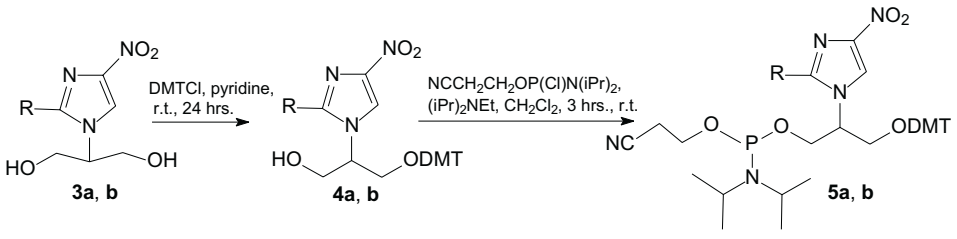
Following addition of an equimolar amount of 2-amino-1,3-dihydroxypropane-diol **2a**, prepared from its oxalate and sodium hydroxide in aqueous solution, to a suspension of 1,4-dinitroimidazole **1a** or 2-methyl-1,4-dinitroimidazole (**1b**) in methanol at room temperature, the mixture gradually clarified within 2–3 hours. After 48 hrs TLC ($MeOH:CHCl_3$, 20:80. v/v) indicated a complete decay of the starting imidazole. Evaporation of the solvents and purification of the residue on silica gel packed column gave product **3a** or **3b** in satisfactory yields (Scheme 1). When 1,4-dinitroimidazole **1a** or **1b** were treated with 2-amino-2-methylpropane-1,3-diol (**2b**), complex mixtures of products were obtained. Besides of the expected products **3c** or **3d**, also denitration products,

Scheme 1



namely 4(5)-nitroimidazole or 2-methyl-4(5)-nitroimidazole, were isolated in approximately 20% yields. The diols **3a** and **3b** were converted into derivatives **5** suitable for automated synthesis on solid support according to reported procedures [25] (Scheme 2).

Scheme 2



EXPERIMENTAL

NMR spectra were recorded at 250 MHz for ^{1}H NMR and 63 MHz for ^{13}C NMR on a Bruker AC-250FT, and at 36.24 MHz on a Jeol FX 90Q spectrometer for ^{31}P NMR; δ-values are in ppm relative to tetramethylsilane as internal standard (^{1}H NMR and ^{13}C NMR) and relative to 85% H_3PO_4 as external standard for ^{31}P NMR; deuterium lock was established on DMSO-d_6 in an internal capillary tube in ^{31}P NMR recordings. Column chromatography was performed on SiO_2 column (230–400 mesh Merck). TLC plates (Merck, silica gel $60F_{254}$) were used for monitoring of the reaction progress. All solvents were of commercial purity, purchased from POCh SA. Gliwice, Poland. 2-Amino-1,3-propanediol, 2-amino-2-methyl-1,3-propanediol, 4,4′-dimethoxytritylchloride (DMTCl), *N*,*N*-diisopropylethylamine and 2-cyanoethyl-*N*,*N*-diisopropylphosphoramidochloridite were purchased from Aldrich. 1,4-Dinitroimidazole and 2-methyl-1,4-dinitroimidazole were obtained according to reported procedure [24].

Reaction of 2-amino-1,3-dihydroxypropane with 1,4-dinitroimidazoles: To the solution of 2-amino-1,3-propanediol oxalate (**2a**) (1.13 g, 4 mmol) in aqueous 0.2 M NaOH solution (40 ml), solution of appropriate 1,4-dinitroimidazole (1.26 g of **1a** or 1.38 g of **1b**, 8 mmol) in methanol (40 ml) was added while stirring. The solution was stirred at room temperature for 48 hrs and then evaporated to dryness under reduced pressure. The residual solid was purified by column chromatography (MeOH/$CHCl_3$, 20:80, v/v). The following compounds were obtained:

1-(1′,3′-Dihydroxy-2′-propyl)-4-nitro-1*H*-imidazole (3a): Yield: 1.20 g (80%); m.p. 114–115°C (MeOH). ^{1}H NMR (DMSO): δ = 3.90 (m, 4H, 2 × CH_2), 4.30 (m, 1H, H-2′), 5.10 (t, 2H, *J* = 5.0 Hz, 2 × OH), 7.85 (d, 1H, *J* = 1.4 Hz, H-2), 8.4 (d, 1H, *J* = 1.4 Hz, H-5). ^{13}C NMR (DMSO): δ = 60.37 (C-1′, C-3′), 62.76 (C-2′), 120.70 (C-5), 137.15 (C-2), 146.78 (C-4). Anal. Calcd. for $C_6H_9N_3O_4$ (187.16): C, 38.51; H, 4.85; N, 22.45. Found: C, 38.30; H, 4.70; N, 22.34.

1-(1′,3′-Dihydroxy-2′-propyl)-2-methyl-4-nitro-1*H*-imidazole (3b): Yield: 0.92 g (68%); m.p. 194–195°C (MeOH). ^{1}H NMR (DMSO): δ = 2.36 (s, 3H, CH_3), 3.66–3.75 (m, 4H, 2 × CH_2), 4.25 (m, 1H, H-2′), 5.05 (t, 2H, *J* = 5.0 Hz, 2 × OH), 8.32 (s, 1H, H-5). ^{13}C NMR (DMSO): δ = 12.93 (CH_3), 60. 64. 60.75 (C-1′, C-3′), 61.15 (C-2′), 119.84 (C-5), 145.77 (C-2), 145.98 (C-4). Anal. Calcd. for $C_7H_{11}N_3O_4$ (201,18): C, 41.79; H, 5.51; N, 20.89. Found: C, 41.46; H, 5.61; N, 20.68.

Reaction of 2-amino-2-methyl-1,3-dihydroxypropane with 1,4-dinitroimidazoles: 2-Amino-1,3-dihydroxy-2-methylpropane **2b** (1.16 g, 11 mmol) in water solution (40 ml) was added at room temperature to nitroimidazole (1.58 g **1a** or 1.72 g **1b**, 10 mmol) in methanol (40 ml) while stirring. After 48 hrs the solvents were evaporated under reduced pressure. The semisolid residue was purified by column chromatography (MeOH/$CHCl_3$, 20:80, v/v). The following compounds were obtained:

1-[(1′,3′-Dihydroxy-2′-methyl)-2′-propyl]-4-nitro-1*H*-imidazole (3c): Yield: 0.94 g (47%); m.p. 156–157°C (MeOH). ^{1}H NMR (DMSO): δ = 1.48 (s, 3H, CH_3), 3.74 (dd, 2H, *J* = 5.4 Hz, 11.4 Hz, CH_2), 3.8 (dd, 2H, *J* = 5.4 Hz, 11.4 Hz, CH_2), 6.18 (t, 2H, *J* = 5.4 Hz, 2 × OH), 7.92 (d, 1H, *J* = 1.5 Hz, H-2), 8.42 (d, 1H, *J* = 1.5 Hz, H-5). ^{13}C NMR (DMSO): δ = 19.71 (CH_3), 65.25 (C-1′, C-3′), 65.29 (C-2′), 121.1 (C-5), 136.75 (C-2), 147.26 (C-4). Anal. Calcd. for $C_7H_{11}N_3O_4$ (201.18): C, 41.79; H, 5.51; N, 20.89. Found: C, 41.70; H, 5.48; N. 20.90.

1-[(1′,3′-Dihydroxy-2′-methyl)-2′-propyl]-2-methyl-4-nitro-1*H*-imidazole (3d): Yield: 0.97 g (45%); m.p. 162–163°C (MeOH). ^{1}H NMR (DMSO): δ = 1.31 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.68–3.90 (m, 6H, 2 × OH, 2 × CH_2), 8.16 (s, 1H, H-5). ^{13}C NMR (DMSO): δ = 14.4 (CH_3), 21.71 (CH_3), 56.72 (C-1′, C-3′), 74.05 (C-2′), 118.99 (C-5), 145.16 (C-2), 154.47 (C-4). Anal. Calcd. for $C_8H_{13}N_3O_4$ (215.21): C, 44.65; H, 6.09; N, 19.53. Found: C, 44.50; H, 5.94; N, 19.46.

1-[[1-*O*-(4,4′-Dimethoxytrityl)-3′-hydroxy]-2′-propyl]-4-nitro-1*H*-imidazole (4a): To the solution of **3a** (0.3 g, 1.61 mmol) in anhydrous pyridine (15 ml) (4,4′-dimethoxytrityl chloride) (0.54 g, 1.61 mmol) was added while stirring. After 24 hr the reaction was terminated by addition of MeOH (2 ml) and the solvent was evaporated under reduced pressure. The residue was redissolved in dichloromethane (20 ml) and washed with a saturated aqueous solution of sodium hydrogen carbonate (2 x 5 ml), dried over sodium sulphate and evaporated to dryness. The product was purified by column chromatography (CH_2Cl_2) to give a pale yellow semisolid. Yield: 0.37 g (48%). ^{1}H NMR ($CDCl_3$): δ = 3.56 (d, 2H, *J* = 5.5 Hz, CH_2), 3.78 (s, 6H, 2 × CH_3O), 3.95 (dd, 1H, *J* = 5.5 Hz, 11.8 Hz, CH_2), 4.02 (dd, 1H, *J* = 6.3 Hz, 11.8 Hz, CH_2) 4.21 (p, 1H, *J* = 5.5 Hz, CH), 6.80 (dd, 4H, *J* = 2.8 Hz, 8.8 Hz, C_6H_4), 7.19 (dd, 4H, *J* = 2.8 Hz, 8.8 Hz, C_6H_4), 7.26–7.33 (m, 5H, Ph), 7.45 (s, 1H, H-2), 7.75 (s, 1H, H-5). ^{13}C NMR ($CDCl_3$): δ = 55.13 (2 ×

CH_3O), 61.25 (CH), 62.21 (CH_2), 62.34 (CH_2), 86.91 (C-Ar_3), 113.25 (C-Ar), 118.81 (C-5), 127.04, 127.66, 127.93, 129.70, 129.73, 129.93, 134.74, (C-Ar), 136.05 (C-2), 143.76 (C-Ar), 147.42 (C-4), 158.61 (C-Ar). Anal. Calcd. for $C_{27}H_{27}N_3O_6$ (489.53): C, 66.25; H, 5.56; N, 8.58; Found: C, 66.22; H, 5.72; N, 8.55.

1-[[1-*O*-(4,4′-Dimethoxytrityl)-3′-hydroxy]-2′-propyl]-2-methyl-4-nitro-1*H*-imidazole (4b): This compound was prepared similarly using following amounts of reagents: **3b** (0.5 g, 2.5 mmol), 4,4′-dimethoxytrityl chloride (0.84 g, 2.5 mmol), pyridine (20 ml). Amorphous pale yellow solid. Yield: 1.0 g (85%). ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3H, CH_3), 3.47 (dd, 1H, *J* = 7.5 Hz, 10.3 Hz, CH_2), 3.53 (dd, 1H, *J* = 4.8 Hz, 10.3 Hz, CH_2), 3.77 (s, 6H, 2 × CH_3O), 3.92 (dd, 1H, *J* = 4.0 Hz, 11.9 Hz, CH_2), 3.98 (dd, 1H, *J* = 7.0 Hz, 11.9 Hz, CH_2), 4.30 (p, 1H, *J* = 4.8 Hz, CH), 6.81 (dd, 4H, *J* = 2.4 Hz, 5.0 Hz, C_6H_4), 7.19–7.28 (m, 9H, Ar), 8.55 (s, 1H, H-5). ^{13}C NMR ($CDCl_3$): δ = 13.41 (CH_3), 55.23 (2 × CH_3O), 59.67 (CH), 62.43 (CH_2), 62.69 (CH_2), 86.95 (CAr_3), 113.29 (C-Ar), 118.01 (C-5), 123.85, 127.11, 127.78, 128.0, 129.81, 129.86, 134.85, 134.95, 136.26, 143.39 (C-Ar),, 145.73 (C-2), 146.19 (C-4), 149.45 (C-Ar), 158.69 (C-Ar). Anal. Calcd. for $C_{28}H_{29}N_3O_6$ (503,56): C, 66.79; H, 5.81; N, 8.34. Found: C, 66.88; H, 5.79; N, 8.47.

General procedure for phosphoramidites (5a), (5b): 1-[[1′-[(2′′-Cyanoethoxy(diisopropylamino)phosphinoxy)]-3′-(4,4′-dimethoxytrityl-oxy)]-2′-propyl]-4-nitro-1*H*-imidazole (5a): Compound **4a** (0.336 g, 0.69 mmol) was dried by co-evaporation with dry MeCN and dissolved in anhydrous and acid free dichloromethane (7.5 ml) under argon atmosphere. Then *N*,*N*-diizopropylethylamine (0.83 ml, 2.98 mmol) was added followed by dropwise addition of 2-cyanoethyl-*N*,*N*-diisopropylethylphosphoramidochloridite (0.27 ml, 1.16 mmol). The reaction mixture was stirred at room temperature for 3 h diluted with dichloromethane (20 ml) and washed with a saturated aqueous solution of sodium hydrogen carbonate (3 × 20 ml) and brine (3 × 20 ml). Organic layer was dried over anhydrous sodium sulphate and evaporated to dryness. The crude product was dissolved in toluene (1 ml) and precipitated from petroleum ether (b.p. 40–60°C, 15 ml) at –30°C. Product was dried over anhydrous calcium chloride in vacuum dessiccator. Yield: 0.36 g (76%) amorphous yellow solid. ^{1}H NMR ($CDCl_3$): δ = 1.11–1.23 (m, 12H, $(CH_3)_2C$), 2.45–2.60 (m, 2H, CH_2CN), 3.40–3.96 (m, 14H, 2 × CH_2, 2 × (CH)N, CH_2O, 2 × OCH_3), 4.40–4.42 (m, 1H, CH), 6.81–7.67 (m, 15H, Ar, H-2, H-5), ^{31}P NMR ($CDCl_3$): δ = 149.35, 150.03 ppm. Anal. Calcd. for $C_{36}H_{44}N_5O_7P$ (689.75): C, 62.69; H, 6.43; N, 10.15. Found: C, 61.94; H, 6.22; N, 10.15.

1-[[1′-[(2′′-Cyanoethoxy(diisopropylamino)phosphinoxy)]-3′-(4,4′-dimethoxytrityloxy)]-2′-propyl]-2-methyl-4-nitro-1*H*-imidazole (5b): Compound was obtained from the following amounts of reagents: **4b** (0.545 g, 1.11 mmol), CH_2Cl_2 (10 ml), *N*,*N*-diizopropylethylamine (1.1 ml) and 2-cyanoethyl-*N*,*N*-diisopropylethylphosphoramido-chloridite (0.35 ml, 1.54 mmol). Reaction conditions, work-up and purification as have been described for **5a**. Yield: 0.61 g (78%). ^{1}H NMR ($CDCl_3$): δ = 1.12–1.31 (m, 12H, $(CH_3)_2C$), 2.20 (s, 3H, CH_3), 2.46–2.60 (m, 2H, CH_2CN), 3.40–4.01 (m, 14H, 2 × CH_2, 2 × (CH)N, 2 × OCH_3, CH_2O), 4.36–4.40 (m, 1H, CH), 6.72–7.65 (m, 14H, Ar, H-5). ^{31}P NMR ($CDCl_3$): δ = 149.43, 150.11 ppm. Anal. Calcd. for $C_{37}H_{46}N_5O_7P$ (703.78): C, 63.15; H, 6.59; N, 9.95. Found: C, 63.66, H, 6.71, N, 10.08.

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