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Novel transformation of 5-cyanouracil derivatives

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Abstract—5-Cyano-1-(dihydroxypropyl)-3-methyluracils were synthesized in the reaction of 1-(4-nitrophenyl)-5-cyano-3-methyluracil with appropriate aminodiols. In the aprotic solvents, the reaction proceeds according to the *ANRORC* type mechanism. In protic solvents the products of Dimroth rearrangement were isolated.

Recently we have demonstrated, that 1,3-disubstituted uracil derivatives possessing an electron-withdrawing group such as a nitro or carbamoyl group at the 5-position can be easily converted into the appropriate 1-(dihydroxypropyl)-5-substituted uracils when reacted with aminodiols.[1] These compounds can be considered as potential building blocks in oligonucleotides synthesis. This reaction occurred by an *ANRORC* mechanism (Attack of Nucleophile, Ring Opening, Ring Closure).[2,3] Investigating the scope and limitations of this transformation on series of uracil derivatives we examined the reaction of 5-cyano-1,3-disubstituted uracils with appropriate functionalized amino compounds. It is known that 5-cyano-3-methyl-1-phenyluracil when treated with primary amines undergoes transformation into 6-amino-3-methyl-1-phenyl-5-(*N*-substituted-iminomethyl)uracil, as a result of a Dimroth type rearrangement.[4,5]

We report here a novel method for the preparation of *N* 1-alkylated 5-cyanouracil derivatives. The crucial influence of a solvent on the direction of this reaction is also considered. The starting 5-cyano-3-methyl-1-(4-nitrophenyl)uracil **1** was prepared according to the method described by Wolfbeis.[6] Condensation of (cyanoacetyl)urea with 4-nitroaniline and triethoxymethane in DMSO solution affords (2*Z*)-*N*-(aminocarbonyl)-2-cyano-3-(4-nitrophenylamino)acrylamide.[7] The acrylamide derivative underwent thermal cyclocondensation in boiling 1,2-dichlorobenzene giving 5-cyano-1-(4-nitrophenyl)uracil.[8] Methylation at *N*3 was carried out in DMSO solution using methyl iodide in the presence of anhydrous potassium carbonate.[9]

When **1** was treated with 1-amino-2-hydroxypropane **2a** in anhydrous ethanol at room temperature the expected product of the Dimroth rearrangement, namely 6-amino-3-methyl-5-(*N*-2-hydroxypropyl)iminomethyl)-1-(4-nitrophenyl)uracil **3** was obtained in 51% yield (Scheme 1).[10]

Application of anhydrous DMF as a solvent changed the course of the reaction. When **1** was reacted with 2 equiv of **2a** at room temperature, the appearance of the characteristic yellow coloured 4-nitroaniline was observed. From the reaction mixture the desired 5-cyano-1-(2-hydroxypropyl)-3-methyluracil **4a** was isolated in 86% yield (Scheme 2, Table 1, entry 1).[11] Under the same conditions **1** was treated with several amino derivatives **2b–e** yielding **4b–e** in satisfactory yields (entries 2–5). The structures of all the synthesized compounds were confirmed by NMR spectroscopy and elemental analyses. The structure of **4c** was also established by X-ray analysis (Fig. 1).[12]

To establish the influence of solvent on the reaction outcome, the reaction of **1** with **2a** was repeated in 2-hydroxypropane and *t*-butanol. In such conditions a mixture of the Dimroth type rearrangement product **3** and *ANRORC* product **4a** was obtained in molar ratios of 3:1 to 4:1, respectively (total yield 90%). The opposite ratio (1:5) of rearrangement/*ANRORC* products was obtained when the reaction was carried out in DMF containing 10% (volume) of water (total yield 96%). This clearly confirms the influence of solvent type on reaction direction. Based on these results we postulate that after

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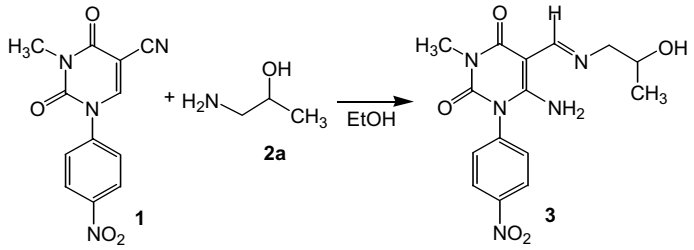
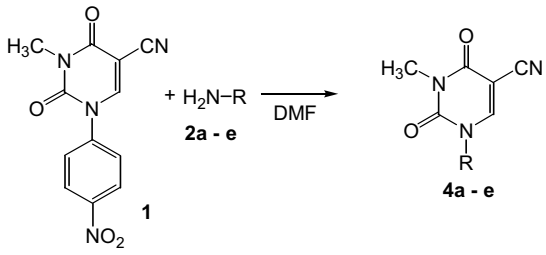
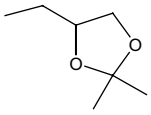


Scheme 1.



Scheme 2.

Table 1. Yields and melting points of 1-(substituted)-5-cyanouracils

Entry	Product	R	Yield (%)	Mp (°C)
1	**4a**	$-CH_2CH(OH)CH_3$	86	108–109
2	**4b**	(*R*,*S*)-$CH_2CH(OH)CH_2OH$	60	150–151
3	**4c**	(*R*)-$CH_2CH(OH)CH_2OH$*	69	147–149
4	**4d**	$-CH(CH_2OH)_2$	64	175–177
5	**4e**		75	168–169

* $[\alpha]_D + 54$ (*c* 1, MeOH).

addition of the nucleophile (amino derivative) to C6 of the uracil ring and ring opening, in protic solvents, addition of a proton to the nitrile nitrogen atom makes the latter more susceptible to attack by the amine nitrogen atom (Scheme 3, path a) and leads to the product of the Dimroth rearrangement. In an aprotic solvent, the attack of the nitrogen atom of the nucleophile occurs on the carbonyl carbon atom giving the *ANRORC* product (Scheme 3, path b). In conclusion a method for the synthesis of 5-cyano-1-hydroxyalkyl or dihydroxyalkyluracil derivatives has been described. These compounds possessing two functional groups (cyano and hydroxyl) may be useful intermediates in the synthesis of other uracil derivatives. They can also be considered as potential building blocks in the synthesis of modified oligonucleotides.

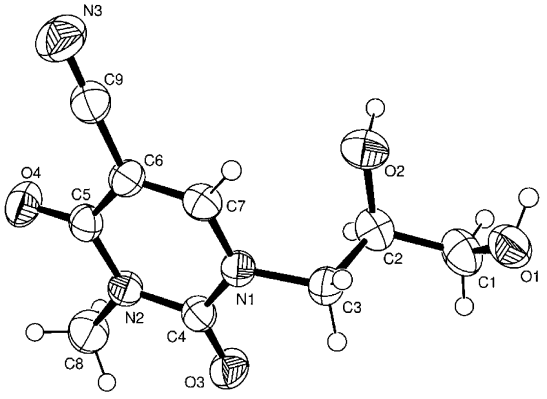
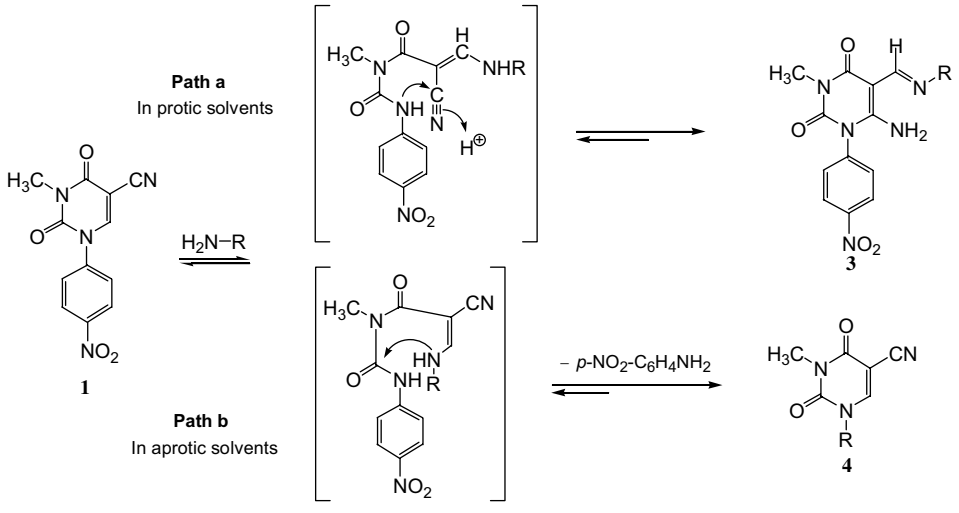


Figure 1. Crystal structure of **4c**. Displacement ellipsoids are drawn at the 50% probability level.



Scheme 3.

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7. (2*Z*)-*N*-(Aminocarbonyl)-2-cyano-3-(4-nitrophenylamino)-acrylamide: To a solution of cyanoacetylurea (5.0 g, 39.4 mmol) in DMSO (50 mL), ethyl orthoformate (6.5 mL, 39.5 mmol) and 4-nitroaniline (6.0 g, 44 mmol) were added. The reaction mixture was stirred in an oil bath at 50–60 °C for 24 h, then poured into aq methanol (MeOH–H_2O, 1:1, 50 mL). The precipitated solid was filtered off and recrystallized from acetic acid. Yield 7.7 g (77%); mp 206–208 °C, ^{1}H NMR (DMSO): δ (ppm) 7.28 (br s, 1H, NH_2), 7.72 (d, 2H, J = 9.3 Hz, Ar), 7.85 (br s, 1H, NH_2), 8.26 (d, 2H, J = 9.3 Hz, Ar), 8.77 (d, 1H, J = 12.9 Hz, =CH), 10.23 (s, 1H, NH), 10.86 (d, 1H, J = 12.9 Hz, NH–Ph). ^{13}C NMR (DMSO): δ (ppm) 115.10, 117.77 (2C), 82.55, 125.12 (2C), 143.04, 145.60, 149.54, 153.93, 164.69.
8. 5-Cyano-1-(4-nitrophenyl)uracil: (2*Z*)-*N*-(Aminocarbonyl)-2-cyano-3-(4-nitrophenylamino)acrylamide (5.0 g, 18.2 mmol) was refluxed in 1,2-dichlorobenzene (120 mL) until TLC (ethyl acetate–*n*-hexane, 1:1 v/v) indicated absence of substrate (approx 3 h). After cooling to room temperature, a precipitate formed. The solid was filtered off, rinsed with *n*-hexane and recrystallized from MeOH. Yield 4.54 g (94%); mp 266–268 °C, ^{1}H NMR (DMSO): δ (ppm) 7.80 (d, 2H, J = 9.0 Hz, Ar), 8.38 (d, 2H, J = 9.0 Hz, Ar), 8.87 (s, 1H, H-6), 12.28 (br s, 1H, NH). ^{13}C NMR (DMSO): δ (ppm) 89.29, 113.99, 124.37, 128.55, 142.93, 147.23, 148.90, 153.83, 160.43.
9. 5-Cyano-3-methyl-1-(4-nitrophenyl)uracil **1**: To a suspension of anhydrous potassium carbonate (0.65 g, 5.0 mmol) in anhydrous DMSO (15 mL), 5-cyano-1-(4-nitrophenyl)uracil was added (1.96 g, 9.2 mmol). The suspension was stirred for 30 min and methyl iodide (0.6 mL, 10 mmol) was added drop wise. After 4 h, TLC (ethyl acetate–*n*-hexane, 1:1 v/v) indicated absence of substrate, the reaction mixture was poured onto crushed ice (60 g) and neutralized with aq 5% HCl. The solid formed was filtered off, washed with water and *n*-hexane. The crude product (1.95 g) was recrystallized from a mixture of MeOH and acetone (1:1). Yield 1.55 g (74%); mp 209–210 °C (lit. mp 201–203 °C),[4] ^{1}H NMR (DMSO): δ (ppm) 3.24 (s, 3H, Me), 7.78 (d, 2H, J = 9.0 Hz, Ar), 8.39 (d, 2H, J = 9.0 Hz, Ar), 8.91 (s, 1H, H-6). ^{13}C NMR (DMSO): δ (ppm) 28.11, 88.57, 113.92, 124.39 (2C), 128.51 (2C), 143.28, 147.27, 149.29, 151.99, 159.59.
10. 6-Amino-3-methyl-5-(*N*-(2-hydroxypropyl)iminomethyl)-1-(4-nitrophenyl)uracil **3** ^{1}H NMR (DMSO): δ (ppm) 1.05 (d, 3H, J = 6.3 Hz, 3′-CH_3), 3.16 (s, 3H, *N*–CH_3), 3.35 (dd, 1H, J = 6.3, 12.3 Hz, H-1′$_a$), 3.43 (dd, 1H, J = 4.8, 12.3 Hz, H-1′$_b$), 3.70–3.78 (m, 1H, H-2′), 4.65 (d, 1H, J = 4.8 Hz, OH), 6.74 (br s, 1H, NH_2), 7.58 (d, 2H, J = 9.0 Hz, Ar), 8.39 (s, 1H, CH=N), 8.41 (d, 2H, J = 9.0 Hz, Ar), 11.19 (br s, 1H, NH_2). ^{13}C NMR (DMSO): δ (ppm) 20.98, 27.09, 64.03, 65.94, 85.67, 125.08 (2C), 131.53 (2C), 140.02, 147.90, 149.88, 154.10, 158.47, 161.80. EIMS (*m*/*z*) = 347 [M^+].
11. Synthesis of 1-alkyl-5-cyano-3-cyanouracils **4a**–**e** (general procedure): To the solution of amine **2a**–**e** (2 mmol) in anhydrous DMF (10 mL), 5-cyano-3-methyl-1-(4-nitrophenyl)uracil **1** was added while stirring. The resulting deep red solution was stirred until the starting uracil had disappeared (3–12 h). The solvent was evaporated under reduced pressure and the residue was purified by chromatography over silica gel using a mixture of ethyl acetate/*n*-hexane (1:1) as eluent. 4-Nitroaniline was eluted first followed by the 1-alkyl-5-cyano-3-methyluracil derivative.
Compound **4a**: 5-Cyano-1-(2-hydroxypropyl)-3-methyluracil ^{1}H NMR (DMSO): δ (ppm) 1.09 (d, 3H, J = 6.0 Hz, CH_3), 3.19 (s, 3H, *N*–CH_3), 3.48 (dd, 1H, J = 13.2 Hz, 9.2 Hz, CH_2–H$_a$), 3.89 – 3.93 (m, 2H, CH_2–H$_b$, H-2′), 5.01 (d, 1H, J = 4.8 Hz, OH), 8.58 (s, 1H, H-6). ^{13}C NMR (DMSO): (ppm) 20.28, 27.93, 56.83, 63.32, 86.11, 114.46, 150.03, 153.67, 159.91. EIMS (*m*/*z*) = 209 [M^+].
Compound **4b**: (*R*,*S*) 5-Cyano-1-(2,3-dihydroxypropyl)-3-methyluracil ^{1}H NMR (DMSO): δ (ppm) 3.19 (s, 3H, *N*–CH_3), 3.29–3.47 (m, 2H, H-3′$_a$, H-3′$_b$), 3.51 (dd, 1H, J = 13.5, 9.3 Hz, H-1′$_a$), 3.67–3.77 (m, 1H, H-2′), 4.10 (dd, 1H, J = 13.5 Hz, 3.3 Hz, H-1′$_b$), 4.76 (t, 1H, J = 5.4 Hz, 3′-OH), 5.09 (d, 1H, J = 5.7 Hz, 2′-OH), 8.57 (s, 1H, H-6). ^{13}C NMR (DMSO): δ (ppm) 28.64, 54.30, 64.16, 68.87, 86.66, 115.18, 150.63, 154.58, 160.60. Anal. Calcd for $C_9H_{11}N_3O_4$ (225.23): %C, 47.99; %H, 4.92; %N, 18.66. Found: %C, 48.05; %H, 5.02; %N, 18.36. EIMS (*m*/*z*) = 225 [M^+].
Compound **4d**: 5-Cyano-1-(1,3-dihydroxy-2-propyl)-3-methyluracil ^{1}H NMR (DMSO): δ (ppm) 3.21 (s, 3H, N–CH_3), 3.59–3.75 (m, 4H, CH_2-1″, CH_2-3′), 4.52–4.60 (m, 1H, H-2′), 4.98 (t, 2H, J = 5.7 Hz, OH-1′, OH-3′), 8.63 (s, 1H, H-6). ^{13}C NMR (DMSO): δ (ppm) 28.15, 58.63 (C-1′, C-3′), 62.03 (C-2′), 86.63, 114.60, 150.46, 151.25, 159.51. Anal. Calcd for $C_9H_{11}N_3O_4$, (M = 225.23): %C, 47.99; %H, 4.92; %N, 18.66. Found: %C, 47.91; %H, 4.73; %N, 18.31.
Compound **4e**: 5-Cyano-1-(2,2-dimethyl-[1,3]dioxolane-4-ylmethyl)-3-methyluracil ^{1}H NMR ($CDCl_3$): δ (ppm) 1.35 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.38 (s, 3H, *N*–CH_3), 3.67–3.80 (m, 2H, H-1′$_a$, H-3′$_a$), 4.15 (dd, 1H, J = 9.0 Hz, 6.9 Hz, H-3′$_b$), 4.23 (dd, 1H, J = 14.1, 2.7 Hz, H-1′$_b$), 4.35–4.44 (m, 1H, H-2′), 7.97 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ (ppm) 24.95, 26.77, 28.76, 52.42, 66.24, 73.22, 89.25, 110.54, 113.23, 150.31, 151.26, 159.27.
12. Crystallographic data for **4c**, has been deposited with Cambridge Crystallographic Data Centre as supplementary publication number **CCDC 240048**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.