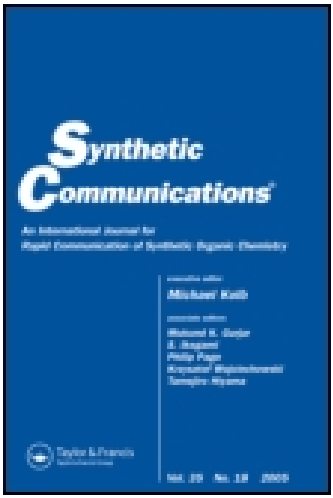

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A SHORT SYNTHESIS OF 1-VINYLURACIL AND 1-VINYLTHYMINE

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Abstract: 1-Vinyluracil and 1-vinylthymine, monomers for nucleic acid bases attached functional polymers, were synthesized for the first time from uracil and thymine in 3 steps in 54% and 50% overall yields using the Mitsunobu reactions of **2a** and **2b** with 2-chloroethanol as a key step.

Considerable interest has developed during the last two decades in the preparation of functional polymers that have nucleic acid bases attached. Biomimetric studies on the interaction between purine and pyrimidine families in such polymers may offer insight into the properties and interactions within nucleic acid molecules provided the physiological and chemical properties of natural polynucleotides can be approximated by the incorporation of nucleic acid base into simple synthetic polymer backbones of known structure and composition.[1] Most of the polymers prepared for this purpose have been derived from molecules which contained vinyl, methacrylate, acrylate or another appropriate group at the

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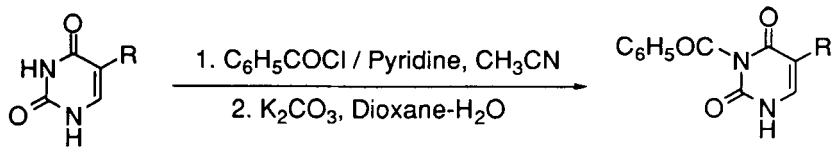
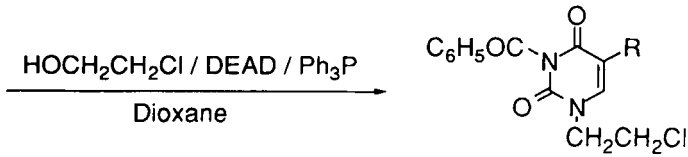
1N-position of pyrimidine bases or the 9N-position of purine bases.[2] The preparation of 1-vinyluracil **4a** and 1-vinylthymine **4b** is usually accomplished via dehydrochlorination of 1-(2-chloroethyl)uracil and 1-(2-chloroethyl)thymine which are the chlorination products of 1-(2-hydroxyethyl) uracil and 1-(2-hydroxyethyl)thymine.[3] Unfortunately, it is not trivial to synthesize the hydroxyethyl derivatives of uracil and thymine. Direct alkylation of uracil **1a** and thymine **1b** with ethylene carbonate to give 1-(2-hydroxyethyl) uracil and 1-(2-hydroxyethyl)thymine is accompanied by the predominant disubstitution.[3a] To avoid disubstitution, bis(o-trimethylsilyl)uracil and bis(o-trimethylsilyl)thymine have been used to react with 2-bromoethyl acetate followed by acid hydrolysis.[4] Extra steps are involved in such a scheme, and extensive reaction times (10 days) are required for alkylation alone. In 1985, a different approach was developed by Takemoto and coworkers who prepared 1-(2-bromoethyl)uracil from acrylonitrile and ethanolamine in 5 steps.[5] Not only does this procedure involve a long reaction sequence, it is not applicable to the preparation of thymine derivatives. It has been reported that 3-benzoyluracil **2a** and 3-benzoylthymine **2b** can react with secondary alcohols under Mitsunobu conditions to incorporate a cyclopentyl group into the 1-position of a pyrimidine ring.[6] Our success in achieving Mitsunobu coupling of **2a** and **2b** with primary alcohols led us to develop an efficient synthesis of 1-vinyluracil **4a** and 1-vinylthymine **4b** from uracil and thymine in only 3 steps.

3-Benzoyluracil **2a** and 3-benzoylthymine **2b** were readily prepared from uracil **1a** and thymine **1b** via intermediates 1,3-dibenzoyluracil and 1,3-dibenzoyl thymine in an overall yield of 88% and 90%.[7] Reaction of **2a** and **2b** with 2-chloroethanol under Mitsunobu conditions gave 3-benzoyl-1-(2-chloroethyl)uracil **3a** and 3-benzoyl-1-(2-chloroethyl)thymine **3b** in 75% and 80% isolated yield, respectively. Treatment of **3a** and **3b** with sodium methoxide accomplished both dehydrochlorination and removal of protecting benzoyl group to generate 1-vinyluracil **4a** (82%) and 1-vinylthymine **4b** (70%).

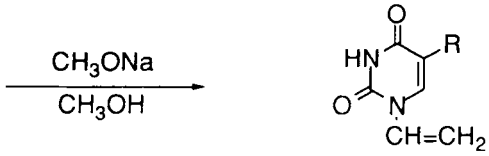


1a R=H
1b R=CH_3

2a R=H
2b R=CH_3



3a R=H
3b R=CH_3



4a R=H
4b R=CH_3

Experimental

Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer using $CDCl_3$ as solvent (unless otherwise indicated) and TMS as internal standard. Mass spectra were obtained on Finnigan 3300 or VG 7070E mass spectrometers.

3-Benzoyluracil, 2a, and 3-benzoylthymine, 2b

The large scale preparation of **2a** and **2b** was accomplished with a slight modification of the two-step acylation-hydrolysis sequence developed by Reese

and coworkers.[7] To a suspension of uracil **1a** (11.21 g, 0.1 mol) or thymine **1b** (12.6 g, 0.1 mol) and pyridine (64.7 ml, 0.8 mol) in acetonitrile (160 ml) was slowly added benzoyl chloride (46.4 ml, 0.4 mol). The reaction mixture was stirred at room temperature for 2 days. The solution was evaporated to dryness and the residue was taken up in dioxane-H_2O (300 ml, 1:1). Potassium carbonate (20.8 g, 0.15 mol) was added and the suspension was stirred at room temperature overnight. The solution was neutralized with 1N HCl to pH~3 and the precipitate was collected and recrystallized from EtOH to give **2a** and **2b** as colorless needles. **2a**: Yield 88%; m.p. 149-150°C, (lit. 148-149°C)[7]; ^{1}H NMR (DMSO-d_6) δ 5.73 (d, J = 7.7 Hz, 1H), 7.56-7.64 (m, 3H), 7.76 (t, J = 7.4 Hz, 1H), 7.93 (d, J = 7.3 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 100.35, 129.75, 130.41, 131.45, 135.71, 143.51, 150.30, 163.26, 170.26; MS (EI) *m/z* (rel int) 216 (M^+, 2.4), 188 (17.5), 105 (100.0), 77 (64.3), 51 (20.9). **2b**: Yield 90%; m.p. 150-151°C, (lit. 150-152°C)[7]; ^{1}H NMR (DMSO-d_6) δ 1.82 (s, 3H), 7.53-7.63 (m, 3H), 7.77 (t, J = 7.4 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 11.69, 107.92, 129.46, 130.21, 131.42, 135.32, 138.77, 149.98, 163.57, 170.15; MS (EI) m/z (rel int) 230 (M^+, 1.9), 202 (4.3), 126 (18.1), 105 (100.0), 77 (71.9), 51 (22.9).

3-Benzoyl-1-(2-chloroethyl)uracil, 3a, and 3-benzoyl-1-(2-chloroethyl)thymine, 3b.

To a mixture of **2a** (2.16 g, 10 mmol) or **2b** (2.30 g, 10 mmol), 2-chloroethanol (1.34 ml, 20 mmol) and triphenylphosphine (5.24 g, 20 mmol) in dry dioxane (50 ml) was added diethylazodicarboxylate (DEAD, 3.3 ml, 20 mmol) in dioxane (20 ml) dropwise at 0°C under argon. The suspension was stirred at room temperature overnight to yield a clear solution. The solution was evaporated to

dryness and the residue was purified by flash chromatography using 5% acetone-CH_2Cl_2 as eluent. **3a**: 75%; m.p. 162-163°C; ^{1}H NMR (DMSO-d_6) δ 3.91 (t, J = 6.0 Hz, 2H), 4.12 (t, J = 6.0 Hz, 2H), 5.89 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 2H), 7.78 (t, J = 8.1 Hz, 1H), 7.93-7.99 (m, 3H); ^{13}C NMR δ 42.02, 49.41, 100.63, 129.68, 130.42, 131.21, 135.72, 147.13, 149.74, 162.46, 169.71; MS (CI) *m/z* (rel int) 279 (M+1, 100); HRMS calcd for $C_{13}H_{12}ClN_2O_3$ 279.0537 found 279.0537. **3b**: 80%; m.p. 130-131°C; ^{1}H NMR δ 1.95 (s, 3H), 3.79 (t, J = 5.5 Hz, 2H), 4.03 (t, J = 5.5 Hz, 2H), 7.19 (s, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.90 (d, J =7.7 Hz, 2H); ^{13}C NMR δ 12.25, 41.75, 50.78, 110.30, 129.13, 130.33, 131.45, 135.03, 140.99, 149.62, 162.72, 168.77; MS (CI) *m/z* (rel int) 293 (M+1, 100); HRMS calcd for $C_{14}H_{14}ClN_2O_3$ 293.0694 found 293.0693.

1-Vinyluracil, 4a, and 1-vinylthymine, 4b.

To a solution of **3a** (2.79 g, 10 mmol) or **3b** (2.93 g, 10 mmol) in dry dioxane (100 ml) was slowly added 0.5M sodium methoxide in methanol (40 ml, 20 mmol) at 0°C. The mixture was stirred at room temperature overnight. The solution was neutralized with 10% acetic acid and evaporated to dryness. The residue was purified by flash chromatography using 2% acetone-CH_2Cl_2 as eluent. **4a**: 82%; m.p. 180-181°C, (lit. 180-181.5°C)[3a]; ^{1}H NMR (D_2O, dioxane) δ 4.89 (dd, J = 1.7, 7.2 Hz, 1H), 5.10 (dd, J = 1.7, 14.2 Hz, 1H), 5.72 (d, J = 7.6 Hz, 1H), 6.97 (dd, J = 8.9, 7.0 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H); ^{13}C NMR (D_2O, dioxane) δ 103.21, 103. 26, 131.89, 140.82, 158.47, 176.89; MS (CI) *m/z* (rel int) 139 (M+1, 100), 156 (M+18, 25). **4b**: 70%; m.p. 205-206°C, (lit. 205-207°C)[3a]; ^{1}H NMR δ 2.00 (s, 3H), 4.91 (dd, J = 2.1, 6.9 Hz, 1H), 5.05 (dd, J =

2.1, 14.1, 1H), 7.17 (dd, J = 9.0, 15.9 Hz, 1H), 7.35 (s, 1H), 8.64 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.94, 99.87, 110.80, 129.31, 135.16, 149.57, 163.88; MS (CI) *m/z* (rel int) 153 (M+1, 100).

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