Easy Synthesis of 5,6-Disubstituted Acyclouridine Derivatives

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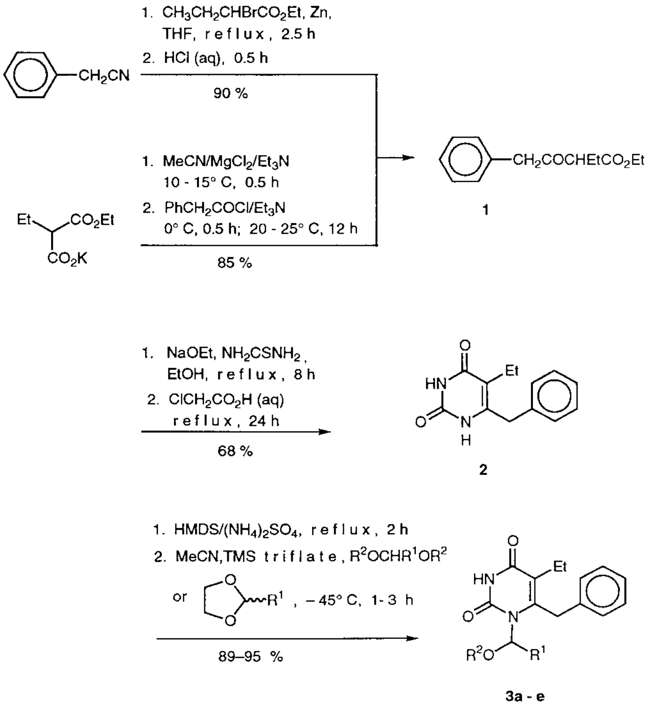
Dedicated to Professor Manfred Regitz on the occasion of his 60th birthday

Ethyl 2-ethyl-3-oxo-4-phenylbutyrate is synthesized in a high yield from the corresponding benzyl cyanide and ethyl 2-bromobutyrate or by reaction of the potassium salt of ethyl 2-ethylmalonate with phenylacetyl chloride. Condensation of the 3-oxo ester with thiourea, desulfurization with chloroacetic acid and finally condensation with acetals or 1,3-dioxolanes using trimethylsilyl triflate (TMS triflate) as a catalyst or with chloromethyl ethyl ether afforded the 5-ethyl-6-benzyl acyclouridine derivatives.

Certain acyclic uridine analogues have recently shown to be highly potent and specific inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT).[1-5] Recently, 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (I-EBU) was chosen as a candidate for clinical trials with AIDS patients because of its very favourable pharmacokinetics and toxicity profile in vivo,[6-8] but the synthesis of the 6-benzyl analogues can be rather tedious,[4,5,9] starting with condensation of the sugar moiety with a 5-substituted uracil,[10,11] if commercially available, followed by lithiation in the 6-position, reaction with benzaldehyde, subsequent reduction of the hydroxy group and eventually deprotection of the sugar moiety. Although the most interesting 5- and 6-substituents of the uracil with respect to HIV-1 inhibition is well established,[4,5,9,11-13] there are still unexplored possibilities in changing the functional groups in the sugar moiety. In the reported synthesis of I-EBU analogues, the lithiation step is an obstacle for introducing a variety of functionalities in the sugar part. We believe it is more convenient to insert the sugar moiety at the *N*-1 position in the last step of the synthesis in order to investigate hitherto unattainable sugar derivatives.

Ethyl 2-ethyl-3-oxo-4-phenylbutyrate (**1**) was prepared using the method of Hannick and Kishi[14] by reaction of benzyl cyanide with zinc and ethyl 2-bromobutyrate, or by using the method of Clay et al.[15] by reaction of phenylacetyl chloride with the potassium salt of ethyl 2-ethylmalonate using an $MeCN/MgCl_2/Et_3N$ system. The so formed 3-oxo ester **1** was converted by reaction with thiourea and sodium in ethanol[16] into a 2-thiouracil which was refluxed with chloroacetic acid overnight to give 6-benzyl-5-ethyluracil (**2**).[17] Silylation[18,19] of the uracil **2** with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) was done prior to condensation with acetals or 1,3-dioxolanes. The condensation reaction with acetals or 1,3-dioxolanes was accomplished by using TMS triflate as a Lewis acid catalyst[19] to give high yields of the desired N^1-substituted nucleosides **3a–e** (Scheme 1).



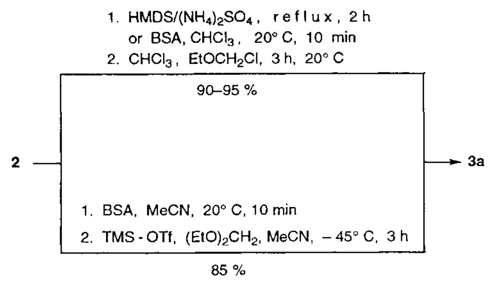
3	a	b	c	d	e
R^1	H	Me	Me	H	Me
R^2	Et	Me	Et	CH_2CH_2OH	CH_2CH_2OH

Scheme 1

In the case of condensation of the nucleobase with acetaldehyde acetal or 2-methyldioxolane racemic mixtures were obtained but no attempts were made to separate the enantiomers. Condensation with ketals gave a complex mixture of compounds and triethoxymethane resulted in N^1-alkylation giving 6-benzyl-1,5-diethyluracil. In order to devise simpler reaction conditions for the last step we prepared **3a** by three other methods (Scheme 2): Silylation in situ of **2** with *N,O*-bis(trimethylsilyl)acetamide (BSA) followed by condensation with diethoxymethane at −45 °C using TMS triflate as catalyst (85 % yield); reaction of silylated **2** with chloromethyl ethyl ether in $CHCl_3$ (90 % yield); and silylation in situ with BSA in $CHCl_3$, followed by reaction with chloromethyl ethyl ether (95 % yield). The structures of **3a–e** were determined by comparison of NMR data of similar structures[9] and by 2D-COSY and nuclear Overhauser effect (NOE) experiments. As an example to determine *N*-3 versus *N*-1 substitution, an NOE experiment was performed on **3c**. Irradiation of the anomeric proton gave an NOE in CH_2Ph (1.3 %) and in CH_3 (6.7 %). Irradiation of CH_2Ph gave an NOE in the anomeric proton (1.0 %) and CH_3 (3.0 %).

NMR spectra were recorded on a Bruker AC-250 FT NMR spectrometer at 250 MHz for ^1H NMR and 62.9 MHz for ^{13}C NMR with TMS as an internal standard. Silica gel (0.040–0.063 mm) and analytical silica gel TLC plates 60 F_{254} were purchased from Merck. THF was distilled from sodium/benzophenone prior to use.

Compounds **2** and **3b, c, e** gave C,H,N analysis ±0.41 %.



Scheme 2

Ethyl 2-Ethyl-3-oxo-4-phenylbutyrate (1):
Method A:

Activated zinc dust (zinc dust washed sequentially with 3 N aq HCl, distilled water, EtOH, Et_2O, and dried in vacuo; 18 g, 275 mmol)[14] was suspended in dry THF (125 mL) at reflux and a few drops of ethyl 2-bromobutyrate were added to initiate the reaction. After the appearance of a green colour (ca. 45 min) phenylacetonitrile (0.53 g, 4.50 mmol) was added in one portion followed by dropwise addition of ethyl 2-bromobutyrate (1.95 g, 10 mmol) over 1 h. The reaction mixture was refluxed for an additional 10 min, diluted with THF (375 mL) and quenched with aq K_2CO_3 (50 %, 54 mL). Rapid stirring for 45 min gave two distinct layers. The THF layer was decanted, the residue washed with THF (2 × 100 mL) and the combined THF fractions were treated with aq HCl (10 %, 50 mL) at r.t. for 45 min. The mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (300 mL) and washed with sat. aq $NaHCO_3$ (200 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give an oily residue, which was used without further purification for the synthesis of compound **2**. Further purification of compound **1** could be achieved by chromatography [silica gel, 200 g; petroleum ether (bp 60–80 °C)/Et_2O, 95 : 5] to give 0.95 g (90 %) of a clear oil.

Method B:

Potassium ethyl 2-ethylmalonate[20] (95 g, 0.48 mol) was dissolved in MeCN (800 mL) under N_2 and cooled to 10 °C. Then Et_3N (52 g, 0.51 mol) was added followed by addition of $MgCl_2$ (54 g, 0.57 mol), and stirring was continued at 20 °C for 2.5 h. The slurry was cooled to 0 °C and phenylacetyl chloride (35 g, 0.21 mol) added dropwise over 20 min, followed by addition of Et_3N (21 g, 0.21 mol). After stirring for an additional 8 h, the mixture was evaporated in vacuo at 20–25 °C and coevaporated with toluene (300 mL) to remove MeCN. Toluene (300 mL) was added followed by cautious addition of aq HCl (12 %, 300 mL) while keeping the temperature below 25 °C. The organic layer was separated, washed with aq HCl (12 %, 2 × 100 mL), sat. aq $NaHCO_3$ (2 × 100 mL), H_2O (2 × 100 mL), and dried (Na_2SO_4). Purification [silica gel, 300 g; petroleum ether (bp 60–80 °C)/Et_2O, 95 : 5] gave compound **1** as a clear oil. Yield: 42 g (85 %).

^1H NMR ($CDCl_3$/TMS): $\delta = 0.85$ (3 H, t, $J = 7.4$ Hz, CH_2CH_3), 1.23 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3), 1.87 (2 H, m, $CHCH_2CH_3$), 3.46 (1 H, t, $J = 7.3$ Hz, CH), 3.81 (2 H, s, CH_2Ph), 4.15 (2 H, q, $J = 7.1$ Hz, OCH_2CH_3), 7.17–7.32 (5 H, m, H_{arom}).

^{13}C NMR ($CDCl_3$/TMS): $\delta = 11.7$ (CH_2CH_3), 14.0 (CH_2CH_3), 21.4 (OCH_2CH_3), 43.7 (CH_2Ph), 59.5 (OCH_2), 61.2 (CH), 127.0, 128.6, 129.5, 133.3 (C_{arom}), 169.5 (C-3), 202.4 (C-1).

6-Benzyl-5-ethyluracil (2):

Sodium (2 g) was dissolved in anhydr. EtOH (45 mL), and thiourea (4.63 g, 60 mmol) and compound **1** (0.94 g, 4.0 mmol) were added to the clear solution. The reaction mixture was refluxed for 6 h, evaporated in vacuo at 40–50 °C until nearly dry, and the residue redissolved in H_2O (40 mL). The 2-thiouracil was precipitated by addition of conc. aq HCl (7 mL) and subsequent acidification to pH 4 with glacial AcOH. The precipitated 2-thiouracil was desulfurized by suspension in 10 % aq chloroacetic acid (100 mL) and subsequent reflux for 24 h. After cooling to r.t. the precipitate was filtered off, washed with cold EtOH and Et_2O and finally dried in vacuo to give compound **2**. Yield: 0.62 g (68 %), white solid: mp 237–238 °C.

^1H NMR (DMSO-d_6/TMS): $\delta = 0.83$ (3 H, t, $J = 7.2$ Hz, CH_2CH_3), 2.25 (2 H, q, $J = 7.1$ Hz, CH_2CH_3), 3.77 (2 H, s, CH_2Ph), 7.25–7.36 (5 H, m, H_{arom}), 10.86 (2 H, br s, 2 NH).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 13.3$ (CH_2CH_3), 17.5 (CH_2CH_3), 34.9 (CH_2Ph), 111.2 (C-5), 126.5, 128.0, 128.4, 136.8 (C_{arom}), 148.64 (C-6), 150.82 (C-2), 164.4 (C-4).

Acyclouridine Derivatives 3a–e; General Procedures:
Method A:

A mixture of compound **2** (0.46 g, 2 mmol), HMDS (10 mL) and $(NH_4)_2SO_4$ (10 mg) was heated under reflux for 2 h. The mixture was concentrated at r.t. under reduced pressure to obtain the silylated base as a pale yellow solid. Anhydr. MeCN (20 mL) was added and the solution was stirred at −45 °C. TMS triflate (0.47 g, 2.1 mmol) was added to the mixture followed by dropwise addition of the appropriate acetal or 1,3-dioxolane (4.0 mmol). The reaction was quenched after 1–3 h and neutralized by addition of sat. aq $NaHCO_3$ at −45 °C, and evaporated in vacuo at r.t. to dryness. The residue was extracted with anhydr. Et_2O (2 × 50 mL) and the ether extracts were evaporated under reduced pressure to give compound **3**. In some cases compound **3** was further purified by preparative TLC ($CHCl_3$).

6-Benzyl-1-ethoxymethyl-5-ethyluracil (**3a**):

Yield: 0.53 g (92 %), white solid: mp 94–96 °C (Lit.[5] 92.5–95 °C).

^1H NMR ($CDCl_3$/TMS): $\delta = 1.06$ (3 H, t, $J = 7.3$ Hz, CH_2CH_3), 1.17 (3 H, t, $J = 7.0$ Hz, OCH_2CH_3), 2.47 (2 H, q, $J = 7.4$ Hz, CH_2CH_3), 3.61 (2 H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.16 (2 H, s, CH_2Ph), 5.12 (s, 2 H, CH_2), 7.11–7.36 (m, 5 H, H_{arom}), 10.13 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$/TMS): $\delta = 13.5$ (CH_2CH_3), 14.8 (OCH_2CH_3), 18.9 (CH_2CH_3), 33.2 (CH_2Ph), 64.7 (OCH_2CH_3), 72.5 (CH_2), 116.7 (C-5), 127.0, 127.1, 129.0, 135.1 (C_{arom}), 148.9 (C-6), 152.0 (C-2), 163.4 (C-4).

6-Benzyl-5-ethyl-1-(1-methoxyethyl)uracil (**3b**):

Yield: 0.51 g (89 %), white solid: mp 137–138 °C.

^1H NMR (DMSO-d_6/TMS): $\delta = 0.83$ (3 H, t, $J = 7.3$ Hz, CH_2CH_3), 1.34 (3 H, d, $J = 6.3$ Hz, $CHCH_3$), 2.20 (2 H, q, $J = 7.3$ Hz, CH_2CH_3), 3.06 (3 H, s, OCH_3), 4.19 (1 H, d, $J = 17.2$, CH_2Ph), 4.31 (1 H, d, $J = 17.2$ Hz, CH_2Ph), 5.90 (1 H, q, $J = 6.0$ Hz, CH), 7.15–7.36 (5 H, m, H_{arom}), 11.33 (1 H, s, NH).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 12.9$ (CH_2CH_3), 18.3 (CH_2CH_3), 20.5 (CH_3), 33.3 (CH_2Ph), 55.7 (OCH_2), 84.7 (CH), 116.0 (C-5), 126.2, 127.3, 128.4, 137.1 (C_{arom}), 148.5 (C-6), 151.1 (C-2), 162.6 (C-4).

6-Benzyl-1-(1-ethoxyethyl)-5-ethyluracil (**3c**):

Yield: 0.54 g (89 %), white solid: mp 118–20 °C.

^1H NMR ($CDCl_3$/TMS): $\delta = 0.93$ (3 H, t, $J = 7.0$ Hz, CH_2CH_3), 0.97 (3 H, t, $J = 7.4$ Hz, OCH_2CH_3), 1.46 (3 H, d, $J = 6.3$ Hz, $CHCH_3$), 2.32 (2 H, q, $J = 7.4$ Hz, CH_2CH_3), 3.31–3.42 (2 H, m, OCH_2CH_3), 4.24 (2 H, d, $J = 16.9$ Hz, CH_2Ph), 4.43 (2 H, d, $J = 16.9$ Hz, CH_2Ph), 6.28 (1 H, q, $J = 6.2$ Hz, CH), 7.07–7.34 (5 H, m, H_{arom}), 9.89 (1 H, s, NH).

^{13}C NMR ($CDCl_3$/TMS): $\delta = 13.1$ (CH_2CH_3), 14.3 (OCH_2CH_3), 18.7 (CH_2Ph), 21.7 ($CHCH_3$), 33.8 (CH_2), 65.0 (OCH_2), 84.1 (CH), 118.0 (C-5), 126.6, 127.2, 128.7, 136.6 (C_{arom}), 149.1 (C-6), 151.9 (C-2), 163.2 (C-4).

6-Benzyl-5-ethyl-1-(2-hydroxyethoxymethyl)uracil (**3d**):

Yield: 0.58 g (95 %), white solid: mp 120–122 °C (Lit.[4] 121–121.5 °C).

^1H NMR (DMSO-d_6/TMS): $\delta = 0.89$ (3 H, t, $J = 7.3$ Hz, CH_2CH_3), 2.31 (2 H, q, $J = 7.3$ Hz, CH_2CH_3), 3.33–3.50 (4 H, m, CH_2CH_2), 4.13 (2 H, s, CH_2Ph), 5.04 (2 H, s, CH_2), 7.16–7.38 (5 H, m, H_{arom}), 11.42 (1 H, s, NH).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 13.4$ (CH_2CH_3), 18.4 (CH_2CH_3), 32.8 (CH_2Ph), 59.8 ($CH_2\mathit{C}H_2OH$), 70.2 ($\mathit{C}H_2CH_2OH$), 72.4 (CH_2), 115.4 (C-5), 126.6, 127.2, 128.8, 136.1 (C_{arom}), 148.3 (C-6), 151.4 (C-2), 162.8 (C-4).

6-Benzyl-5-ethyl-1-[1-(2-hydroxyethoxy)ethyl]uracil (**3e**):

Yield: 0.58 g (91 %), white solid: mp 119–121 °C.

^{1}H NMR (DMSO-d_6/TMS): $\delta = 0.82$ (3 H, t, $J = 7.1$ Hz, $CH_2C\mathit{H}_3$), 1.34 (3 H, d, $J = 6.3$ Hz, $CHC\mathit{H}_3$), 2.18 (2 H, q, $J = 7.1$ Hz, $C\mathit{H}_2CH_3$), 3.27–3.47 (4 H, m, CH_2CH_2), 4.18 (1 H, d, $J = 17.3$ Hz, CH_2Ph), 4.42 (1 H, d, $J = 17.3$ Hz, CH_2Ph), 6.08 (1 H, br s, CH), 7.14–7.35 (5 H, m, H_{arom}), 11.33 (1 H, s, NH).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 12.9$ ($CH_2\mathit{C}H_3$), 18.4 ($\mathit{C}H_2CH_3$), 20.8 ($CH\mathit{C}H_3$), 33.3 (CH_2Ph), 59.5 ($CH_2\mathit{C}H_2OH$), 70.1 ($\mathit{C}H_2CH_2OH$), 83.5 (CH), 116.0 (C-5), 126.2, 127.3, 128.5, 137.3 (C_{arom}), 148.7 (C-6), 151.2 (C-2), 162.7 (C-4).

Method B:

Compound **2** (0.46 g, 2 mmol) was dissolved in a solution of BSA (1.0 g, 5 mmol) in anhydr. MeCN (15 mL) at 20 °C. The mixture was cooled to − 45 °C, TMS triflate (0.44 g, 2 mmol) was added followed by dropwise addition of diethoxymethane (0.47 g, 4 mmol). After 3 h the reaction mixture was worked up as above. Yield: 0.49 g (85 %) of **3a**.

Method C:

Silylated **2** (2 mmol) was obtained as in Method A. A solution of chloromethyl ethyl ether (0.28 g, 3 mmol) in anhydr. $CHCl_3$ (10 mL) was added, the reaction mixture stirred at 20–25 °C for 3 h and worked up as above. Yield: 0.52 g (90 %) of **3a**.

Method D:

Compound **2** (0.46 g, 2 mmol) was dissolved in a solution of BSA (1.0 g, 5 mmol) in anhydr. $CHCl_3$. After 10 min chloromethyl ethyl ether (0.28 g, 3 mmol) was added, the reaction mixture stirred for 3 h and worked up as above. Yield: 0.54 g (94 %) of **3a**.

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