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Zhili Zhang [a], Zhijian Cheng [b], Xiaoyan Ma [a], Xiaowei Wang [a] & Junyi Liu [a c]

[a] Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing, China

[b] Department of Chemistry, College of Jiujiang, Jiujiang, China

[c] State Key Laboratory of Natural and Biomimetic Drug, Peking University, Beijing, China

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Facile Alternative Synthesis of 1-Alkyl-5-alkylamino-6-phenethyluracils

Zhili Zhang,[1] Zhijian Cheng,[2] Xiaoyan Ma,[1] Xiaowei Wang,[1] and Junyi Liu[1,3]

[1]Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing, China
[2]Department of Chemistry, College of Jiujiang, Jiujiang, China
[3]State Key Laboratory of Natural and Biomimetic Drug, Peking University, Beijing, China

Abstract: A short alternative synthesis of 1-alkyl-5-alkylamino-6-phenethyluracil is described in 47% overall yield of **1a** via five steps starting from commercially available 6-methyluracil.

Keywords: 1,5-Disubstituted-6-phenethyluracil, heterocycles, synthesis

Pyrimidine and its derivatives are important classes of biologically active heterocyclic compounds. Various 5-alkyl substituted derivatives of uracil have been synthesized for both anticancer and antiviral properties. Notable among them is 6-benzyl-1-(benzyloxymethyl)-5-isopropyluracil (TNK651) (Fig. 1), which is one of the most potent agents effective against HIV-1 reverse transcriptase (HIV-1 RT).[1] Currently, research work in our laboratory has concerned access to 1,5-dialkylsubstituted-6-phenethyluracils I and II (Fig. 1) and their derivatives as potent nonnucleoside HIV-1 RT inhibitors.[2,3] In a previous publication, we described the preparation of 1-alkyl-5-dimethylamino-6-phenethyluracil[2] from 6-methyluracil via six-stage reactions in 34% total yield.

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Address correspondence to Junyi Liu, Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100083, China. E-mail: lilybmu@bjmu.edu.cn

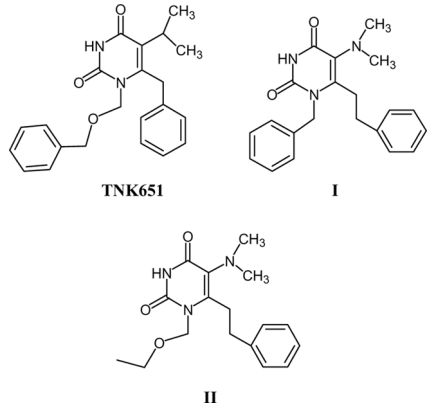
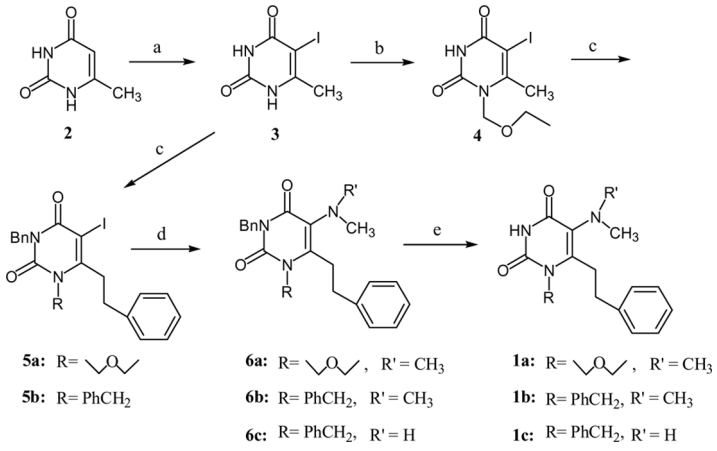


Figure 1. Structures of TNK651, I and II.

However, the both procedures involve six synthetic steps[2] from 6-methyluracil as the starting material and limit a number of other N^5-substituted reactions. Herein, a shorter (five-step), facile, alternative synthesis of the title compounds (Scheme 1) is reported. The total yield of **1a** was 47%, which represents a big improvement in overall yield.

First, we investigated the halogenations of 6-methyluracil (**2**). Initial attempts to get access to the compounds **3** using ICl-MeOH[4,5] failed or led to poor yields. However, treatment of **2** with PbO_2-HOAc-I_2[6] at



Scheme 1. Reagents and conditions: (a) PbO_2, HOAc, I_2, 50°C, 3 h; (b) $ClCH_2OCH_2CH_3$, BSA, CH_3CN, rt; (c) $PhCH_2Br$, NaH, DMF; (d) $(CH_3)_2NH$ or CH_3NH_2; and (e) $HCOONH_4$, Pd/C, MeOH.

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50°C provided the 5-iodo-6-methyluracil **3** in 94% yield after purification by column chromatography. Compound **3** was transformed into 1-ethoxymethyluracil (**4**) via reaction with N,O-bis(trimethylsilyl)acetamide (BSA) and chloromethylethyl ether in CH_3CN. Treatment of **3** or **4** with benzyl bromide and NaH in tetrahydrofuran (THF) gave 1,3-dibenzyl-5-iodo-6-phenethyluracil (**5b**) in 82–85% yield and 1-ethoxymethyl-3-benzyl-5-iodo-6-phenethyluracil (**5a**) in 87% yield. Compound **5a** was transformed into 1-ethoxymethyl-3-benzyl-5-(*N*,*N*-dimethylamino)-6-phenethyluracil (**6a**) via replacement of iodo by dimethylamine under reflux. Compound **5b** was transformed into 1,3-dibenzyl-5-(*N*,*N*-dimethylamino)-6-phenethyluracil (**6b**) and 1,3-dibenzyl-5-(*N*-methylamino)-6-phenethyluracil (**6c**) with the reaction of dimethylamine or methylamine, respectively. Compounds **6a**, **6b**, and **6c** can be smoothly deprotected into title compounds **1a**, **1b**, and **1c** in 53–87% yield using $HCOONH_4$-Pd/C in MeOH under reflux.

All the compounds were characterized by ^1H NMR, mass, and infrared (IR) spectral data, and the final compound **1b** was additionally characterized by ^{13}C NMR.

In conclusion, we have developed a convenient method to synthesize N^5-substituted-6-phenethyluracil. This route is a shorter sequence than the previously published procedure for the compounds **1a**, **1b**, and **1c** and their derivatives, and will have broad application when these kinds of N^5-substituted pyrimidine compounds are explored for therapeutic utilities.

EXPERIMENTAL

Melting points (uncorrected) were determined with an X_4-type apparatus. ^1H and ^{13}C NMR spectra were recorded on a JNM-AL-300 or a Varian Inova-500 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were recorded on a VG-ZAB-HS spectrometer. IR spectra were recorded with Avatar 360 Fourier transform (FT)–IR and are reported in centimeters^{-1}. Silica gel (0.40–0.64 mm) was used for column chromatography.

5-Iodo-6-methyl uracil (3)

PbO_2 (66 mg, 0.28 mmol) was added in portions to the suspension of 6-methyluracil (63 mg, 0.5 mmol) in glacial HOAc (15 mL) while stirring, and then I_2 (70 mg, 0.28 mmol) was added. The reaction mixture was heated to 50°C for 3 h. The PbO_2 was filtered, and then the filtrate was diluted with H_2O (80 mL). The precipitate was isolated, washed with

water and ether, then dried in vacuo to give a solid (118 mg, 94%), mp > 300°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.40 (s, 1H, NH), 11.54 (s, 1H, NH), 2.64 (s, 3H, CH_3). EIMS: $m/z = 257$ $[M + 1]^+$.

1-Ethoxymethyl-5-iodo-6-methyluracil (4)

BSA (0.37 mL, 1.24 mmol) was added to the solution of 5-iodo-6-methyluracil **3** (120 mg, 0.47 mmol) in CH_3CN (15 mL). The solution was stirred at rt for 50 min, then the $ClCH_2OCH_2CH_3$ (45 μL, 0.48 mmol) and LiI (50 mg) were added. The resulting mixture was stirred at rt for 75 min and quenched by addition of $NaHCO_3$. The solution was extracted with EtOAc (3 × 15 mL), and the combined extracts were washed with H_2O and dried over $MgSO_4$. The solvent was removed to give the crude product, which was purified by column chromatograph (EtOAc/petrol. 1:1) to yield the product (110 mg, 73%), mp 163°C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (s, 1H, NH), 5.24 (s, 2H, CH_2), 3.65 (q, $J = 7.2$ Hz, CH_2), 2.51 (s, 3H, CH_3), 1.22 (t, $J = 7.0$ Hz, 3H, CH_3). EIMS: $m/z = 314$ $[M^+]$.

1-Ethoxymethyl-3-benzyl-5-iodo-6-phenethyluracil (5a)

NaH (27 mg, 0.64 mmol, 60% in oil) was added to a solution of 1-ethoxymethyl-5-iodo-6-methyluracil **4** (100 mg, 0.32 mmol) in DMF (10 mL), portionwise under N_2. The mixture was stirred at rt for 1 h, and benzylbromide (1.16 mL, 0.8 mmol) was slowly added. The resulting mixture was stirred for 2–2.5 h, and water (20 mL) was added. After it was concentrated to dryness, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give the crude product, which was chromatographed (EtOAc–petrol. 1:2) to give 137 mg (87%) of **5a**, mp 173–175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, $J = 7.0$ Hz, 3H, CH_3), 2.93–3.04 (m, 4H, CH_2CH_2), 3.63 (q, $J = 7.0$ Hz, 2H, CH_2), 5.32 (s, 2H, CH_2Ph), 5.45 (s, 2H, CH_2O), 7.18–7.25 (m, 10H, 2Ar). EIMS: $m/z = 491$ $[M + 1]^+$.

1,3-Dibenzyl-5-iodo-6-phenethyluracil (5b)

NaH (110 mg, 2.73 mmol, 60% in oil) was added to the solution of 5-iodo-6-methyluracil **3** (200 mg, 0.78 mmol) in dimethylformamide (DMF) under N_2. The reaction mixture was stirred at rt for 1 h, and then benzylbromide (3.6 mL, 2.57 mmol) was added. After reaction for 2 h at rt, the

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mixture was poured into H_2O (25 mL) and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the residue, which was purified by chromatography on silica gel (EtOAc–petrol. = 1:3) to give the solid **5b** (340 mg, 82%), mp 114°C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.81$–293 (m, 4H, CH_2CH_2), 5.16 (s, 2H, CH_2Ph), 5.19 (s, 2H, CH_2Ph), 7.14–7.62 (m, 15H, 3Ph). EIMS: $m/z = 523$ $[M + 1]^+$.

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1-Ethoxymethyl-3-benzyl-5-(*N*,*N*-dimethylamino)-6-phenethyluracil (6a)

The excess $(CH_3)_2NH$ (4 mL) was added to the solution of compound **5a** (500 mg, 1.02 mmol) in THF (1 mL). Then the solution was heated to 60°C for 30–35 h. After the reaction mixture was cooled to rt, H_2O (10 mL) was added and extracted with EtOAc (3×15 mL). The organic layer was washed with H_2O and dried over Na_2SO_4. The solvent was removed to give the product (oil) (380 mg, 90%) after purification by column chromatography (petrol.–EtOAc = 9:1). IR (KBr): 2935, 1705, 1655, 1447, 1095, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 6.9$ Hz, 3H, CH_3), 2.71 (s, 6H, $(CH_3)_2N$), 2.80–2.89 (m, 4H, CH_2CH_2), 3.64 (q, $J = 6.9$ Hz, 2H, CH_2), 5.12 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 7.23–7.45 (m, 10H, 2Ar). ESI-TOF: $m/z = 408.52$ $[M + 1]^+$, 430.53 $[M+Na]^+$.

1,3-Dibenzyl-5-(*N*,*N*-dimethylamino)-6-phenethyluracil (6b)

The general procedure was similar to **6a**. Yield 340 mg (80%), mp 139–141°C.[2] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.71$ (s, 6H, $N(CH_3)_2$), 2.79–3.01 (m, 4H, CH_2CH_2), 5.12 (s, 2H, NCH_2Ph), 5.17 (s, 2H, NCH_2Ph), 7.19–7.54 (m, 15H, 3Ar). EIMS: $m/z = 439$ $[M^+]$.

1,3-Dibenzyl-5-(*N*-methylamino)-6-phenethyluracil (6c)

The procedure was similar to **6a**. Yield 310 mg (76%), mp 146°C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.63$ (s, 3H, CH_3), 2.74–2.97 (m, 4H, CH_2CH_2Ph), 5.01 (s, 2H, CH_2Ph), 5.29 (s, 2H, CH_2Ph), 7.06–7.60 (m, 15H, 3Ar). EIMS: $m/z = 425$ $[M^+]$.

1-Ethoxymethyl-5-(*N*,*N*-dimethylamino)-6-phenethyluracil (1a)

HCO_2NH_4 (200 mg, 3.20 mmol) and 10% Pd/C (160 mg) were added to the solution of compound **6a** (55 mg, 0.11 mmol) in ethanol (12 mL).

The reaction mixture was heated under reflux for 7–7.5 h, then cooled to rt, filtered, and concentrated under reduced pressure to give **7a**, which was purified by column chromatography ($CHCl_3$–MeOH = 95:5) to give 31 mg (87%), mp 142–143°C.[2] IR (KRr): 3024, 1709, 1665, 1460, 1082 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 6.9$ Hz, 3H, CH_3), 2.67 (s, 6H, $N(CH_3)_2$), 2.88–3.16 (m, 4H, CH_2CH_2), 3.62 (q, $J = 6.9$ Hz, 2H, CH_2), 5.21 (s, 2H, CH_2O), 7.19–7.31 (m, 5H, Ph), 8.60 (s, H, N_3-H). ESI-TOF: $m/z = 318.32$ $[M + 1]^+$, 340.35 $[M+Na]^+$.

1-Benzyl-5-(*N*,*N*-dimethylamino)-6-phenethyluracil (1b)

Pd/C (300 mg) and $HCOONH_4$ (270 mg, 4.1 mmol) were added to the solution of compound **6b** (100 mg, 0.22 mmol) in dry MeOH. The mixture was refluxed for 3 days and then cooled to rt. The catalyst was filtered through a celite pad, washed with $CHCl_3$, and concentrated under reduced pressure to give solid **1b**, which was purified by silica column chromatography ($CHCl_3$–MeOH = 9:1). Yield 43 mg (53%), mp 147–148°C.[2] ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.64$ (s, 6H, CH_3), 2.80–2.94 (m, 4H, CH_2CH_2), 5.10 (s, 2H, CH_2Ph), 7.21–7.46 (m, 10H, 2Ph), 10.42 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 31, 33.9, 43.1, 43.5, 124, 126.7, 127.3, 128.2, 128.7, 137.2, 140.7, 150.7, 153.1, 161.8. EIMS: $m/z = 349$ $[M^+]$.

1-Benzyl-5-(*N*-methylamino)-6-phenethyluracil (1c)

The general procedure was similar to **1b**. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.59$ (s, 3H, CH_3), 2.81–2.95 (m, 4H, CH_2CH_2Ph), 3.26 (s, 1H, NH), 5.12 (s, 2H, CH_2Ph), 7.51–7.27 (m, 10H, 2Ar), 9.27 (s, 1H, N_3H). EIMS: $m/z = 336$ $[M + 1]^+$.

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