Synthesis of 6-Substituted 1-Alkoxy-5-alkyluracils

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Synthesis of 6-substituted 1-alkoxy-5-alkyluracils **2a-c** have been achieved from readily accessible 2-alkyl-3,3-di(methylthio)acryloyl chlorides **4a,b** in high overall yields. Treatment of **4a,b** with silver cyanate followed by reaction of the resulting isocyanates **5a,b** with an appropriate alkoxyamine afforded *N*-alkoxy-*N'*-[2-alkyl-3,3-di(methylthio)acryloyl]ureas **6a,b** in 85-88% yields. Cyclization of **6a,b** in acetic acid containing methanesulfonic acid followed by oxidation with 3-chloroperoxybenzoic acid gave high yields of 1-alkoxy-5-alkyl-6-(methylsulfonyl)uracils **9a,b**. Nucleophillic addition-elimination reaction of **9a,b** with sodium azide, phenylthiol, or phenylselenol produced 6-azido-1-butoxythymine (**2a**, 98%), 5-ethyl-1-(2-phenoxyethoxy)-6-(phenylthio)uracil (**2b**, 95%), or 5-ethyl-1-(2-phenoxyethoxy)-6-(phenylselenenyl)uracil (**2c**, 91%).

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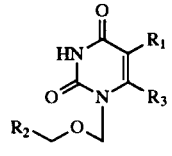
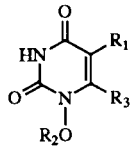
Since the discovery of the acyclic 6-substituted uridine derivative 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (**1a**) as a novel lead for potent and selective reverse transcriptase inhibitors of human immunodeficiency virus type 1 [1], a number of analogs of **1a** have been synthesized to increase its potency. Several of these compounds such as 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (**1b**) [2] and 6-[(3,5-dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyluracil (**1c**) [3] inhibit replication of human immunodeficiency virus type 1 in the nanomolar concentration range. In continuation of our



1

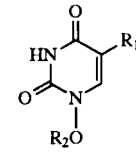
a, R_1 = Me, R_2 = CH_2OH, R_3 = SPh
b, R_1 = *i*-Pr, R_2 = Me, R_3 = CH_2Ph
c, R_1 = *i*-Pr, R_2 = Me, R_3 = SePh (3,5-di-Me)

efforts to develop metabolically stable analogs of **1a** [4,5], 6-substituted 1-alkoxy-5-alkyluracils **2**, we needed a general and efficient synthetic route to **2**. The lithum diisopropylamide lithiation is a simple, general, and regiospecific method for synthesizing various types of 6-substituted



2

uridines and 2'-deoxyuridines and was successfully applied to the synthesis of **1a** and its numerous analogs, **1-3, 6-9.** This method was, however, found not to be applicable to the synthesis of 6-substituted 1-alkyluracil derivatives. For instance, Miyasaka *et al.* [10] and Pontikis *et al.* [11] reported that treatment of 1-butyl-5-ethyluracil and 1-(3-phenyl-2-propenyl)thymine with lithium diisopropylamide in tetrahydrofuran followed by reaction with diphenyl disulfide afforded 1-butyl-5-ethyl-6-(phenylthio)uracil in 7% yield and 1-(3-phenyl-2-propenyl)-6-(phenylthio)-thymine in less than 10% yield, respectively. These results indicate that the 2'-oxygen atom at the N-1 acyclic moiety plays an important role in stabilizing the C-6 lithiated species. On the basis of these results, it is of interest for us to examine the lithium diisopropylamide lithiation of 1-alkoxy-5-alkyluracils which have the 1'-oxygen atom at the N-1 acyclic moiety. But, surprisingly, when 1-alkoxyuracils **3** [4] were treated with lithium diisopropylamide in tetrahydrofuran at -78°, metalation at C-6 did not occur at all, which was confirmed by reactions with dipheny disulfide and deuterium oxide.

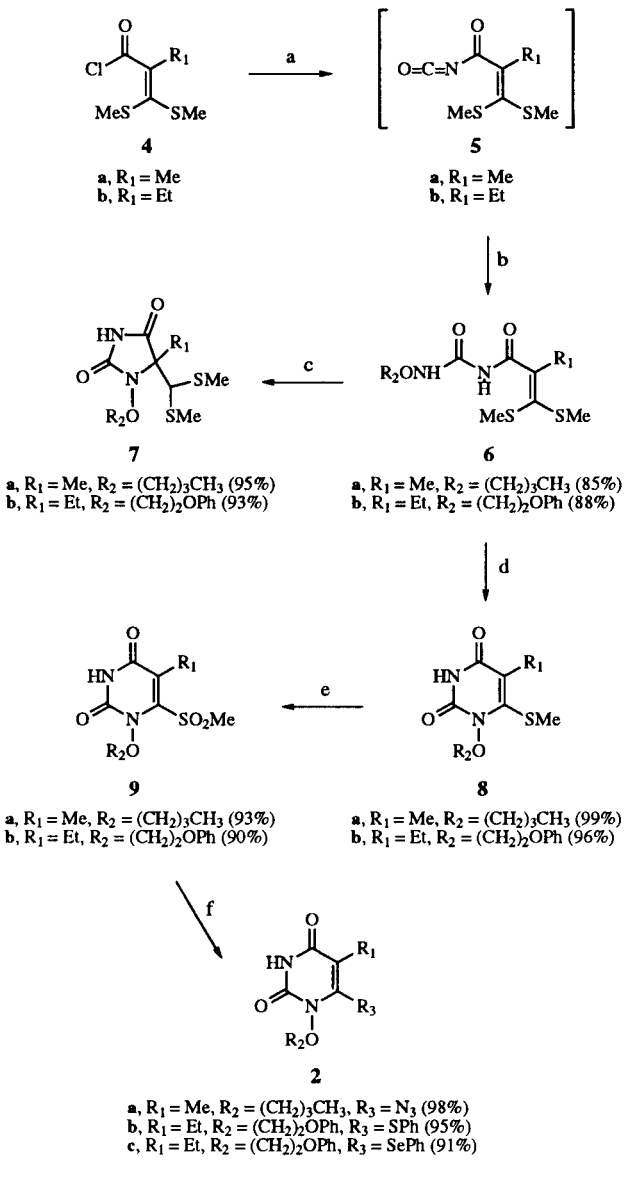


3

R_1 = Et, *i*-Pr
R_2 = Pr, Bu, CH_2CH_2Ph

In a previous communication, we reported a general and convenient approach to the synthesis of 6-substituted 1,5-dialkyluracils from readily accessible ethyl 2-alkyl-3,3-di(methylthio)acrylates, which could overcome the limitation of lithium diisopropylamide lithiation method [12]. This approach involves the coupling reaction of isocyanates derived from ethyl 2-alkyl-3,3-di(methylthio)acrylates with alkyl amines, cyclization of the coupling adducts, oxidation of 6-(methylthio) group, and substitution at the C-6 with nucleophiles. We found that this approach could be extended to the synthesis of 6-substituted 1-alkoxy-5-alkyluracils in high overall yields as shown in Scheme 1.

Scheme 1



[a] AgOCN (1.2 equivalents), toluene, reflux, 0.5 hour; [b] R_2ONH_2 (1.1 equivalents), toluene, room temperature, 1 hour; [c] anhydrous K_2CO_3 (2.0 equivalents), EtOH, reflux, 3 hours; [d] methanesulfonic acid (0.2 equivalent), AcOH, 80°, 1 hour; [e] 3-chloroperoxybenzoic acid (5.0 equivalents), benzene, reflux, 20 minutes; [f] (i) NaN_3 (1.0 equivalent), DMF, room temperature, 0.5 hour (for **2a**), (ii) PhSH (1.1 equivalents), 1*N* NaOH, EtOH, room temperature, 20 minutes (for **2b**), or (iii) PhSeH (1.1 equivalents), 1*N* NaOH, EtOH, room temperature, 20 minutes (for **2c**).

Treatment of 2-alkyl-3,3-di(methylthio)acryloyl chlorides **4a,b** [12] with silver cyanate (1.2 equivalents) in toluene at reflux temperature for 30 minutes followed by reaction of the resulting isocyanates **5a,b** with an appropriate alkoxyamine (1.1 equivalents) at room temperature for 1 hour afforded *N*-alkoxy-*N'*-[2-alkyl-3,3-di(methylthio)acryloyl]ureas **6a,b** in 85-88% yields. Base-induced cyclization of **6a,b** with anhydrous potassium carbonate (2.0 equivalents) in ethanol at reflux tenperature for 3 hours gave 1-alkoxy-5-alkyl-5-[di(methylthio)methyl]hydantoins **7a,b** in excellent yields (93-95%). On the other hand, cyclization of **6a,b** in anhydrous acetic acid containing a catalytic amount of methanesulfonic acid (0.2 equivalent) at 80° for 1 hour afforded 1-alkoxy-5-alkyl-6-(methylthio)uracils **8a,b** in 96-99% yields. It is noteworthy that the five-membered ring compounds **7a,b** or the six-membered ring compounds **8a,b** were exclusively formed under the above-mentioned basic or acidic condition. Compounds **8a,b** were oxidized with excess 3-chloroperoxybenzoic acid (5.0 equivalents) in refluxing benzene for 20 minutes to produce 90-93% yields of 1-alkoxy-5-alkyl-6-(methylsulfonyl)uracils **9a,b**. Finally, nucleophillic addition-elimination reaction of **9a,b** were examined for functionalization at C-6. When compound **9a** was allowed to react with sodium azide (1.0 equivalent) in *N,N*-dimethylformamide at room temperature for 30 minutes, 6-azido-1-butoxythymine (**2a**) was obtained in 98% yield. Reactions of **9b** with phenylthiol (1.1 equivalents) and phenylselenol (1.1 equivalents) in ethanolic sodium hydroxide solution at room temperature for 20 minutes also afforded high yields of 5-ethyl-1-(2-phenoxyethoxy)-6-(phenylthio)uracil (**2b**) and 5-ethyl-1-(2-phenoxyethoxy)-6-(phenylselenenyl)uracil (**2c**), respectively.

In summary, the present study shows that 6-substituted 1-alkoxy-5-alkyluracils can be prepared in high overall yields from readily accessible 2-alkyl-3,3-di(methylthio)-acryloyl chlorides. Employing this approach we developed, synthesis of various 6-substituted 1-alkoxy-5-alkyluracils as potential chemotherapeutic agents for the treatment of human immunodeficiency virus type 1 is currently under way in our laboratory.

EXPERIMENTAL

Melting points were determined on either an Electrothermal F500MA digital or a Mettler FP62 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. The ^1H nmr and ^{13}C nmr spectra were run in deuteriochloroform on a Varian Unity 300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane for ^1H nmr, and deuteriochloroform served as the internal standard at d 77.0 for ^{13}C nmr. The electron impact ms spectra were obtained on a VG Quattro mass spectrometer. The tlc analysis was performed on Merck silica gel 60F-254 glass plates. Medium pressure liquid chromatography was performed using Merck silica gel 60 (230-400 mesh). Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General Procedure for the Preparation of *N*-Alkoxy-*N'*-[2-alkyl-3,3-di(methylthio)acryloyl]ureas **6a,b**.

A mixture of 2-alkyl-3,3-di(methylthio)acryloyl chloride **4a** or **4b** (10.0 mmoles) and silver cyanate (1.80 g, 12.0 mmoles) in anhydrous toluene (20 ml) was heated under reflux for 30 minutes under a nitrogen atmosphere in the dark to generate isocyanate **5a** or **5b** *in situ* and cooled to 0°. To this mixture was

added dropwise butoxyamine or (2-phenoxyethoxy)amine (11.0 mmoles) in anhydrous toluene (10 ml). After stirring at room temperature for 1 hour, the mixture was filtered through a pad of Celite, and the filtrate was again filtered using a millipore filter (0.22 μm). The filtrate was evaporated to dryness, and the residue was purified by medium pressure liquid chromatography on silica gel with ethyl acetate-hexane as eluent and then crystallized from ethyl acetate-hexane.

N-Butoxy-*N'*-[3,3-di(methylthio)-2-methylacryloyl]urea (**6a**).

This compound was prepared from **4a** and butoxyamine in 85% yield, mp 97.4-98.4°; ir (potassium bromide): 3271, 3218, 3120, 1699, 1668, 1494 cm^{-1}; ^1H nmr: δ 0.95 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.43 (m, 2H, $OCH_2CH_2CH_2$), 1.66 (m, 2H, OCH_2CH_2), 2.17 (s, 3H, CH_3), 2.32 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 3.96 (t, J = 6.6 Hz, 2H, OCH_2), 9.33 (br s, 1H, NH), 10.60 (br s, 1H, NH); ^{13}C nmr: δ 13.8, 16.5, 17.7, 19.0, 19.4, 29.9, 76.8, 136.1, 138.8, 154.1, 169.9; ms: m/z 292 (M^+).

Anal. Calcd. for $C_{11}H_{20}N_2O_3S_2$: C, 45.18; H, 6.89; N, 9.58. Found: C, 44.96; H, 6.92; N,9.51.

N-[3,3-Di(methylthio)-2-ethylacryloyl]-*N'*-(2-phenoxyethoxy)-urea (**6b**).

This compound was prepared from **4b** and (2-phenoxyethoxy)amine in 88% yield, mp 122.5-123.9°; ir (potassium bromide): 3305, 3221, 1713, 1666, 1467 cm^{-1}; ^1H nmr: δ 1.06 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.30 (s, 3H, SCH_3), 2.33 (s, 3H, SCH_3), 2.62 (q, J = 7.5 Hz, 2H, CH_2CH_3), 4.24 (m, 2H, OCH_2CH_2OPh), 4.34 (m, 2H, OCH_2CH_2OPh), 6.90-7.04 (m, 3H, Ar H), 7.20-7.35 (m, 2H, Ar H), 9.04 (br s, 1H, NH), 10.85 (br s, 1H, NH); ^{13}C nmr: δ 12.8, 16.4, 17.5, 27.1, 65.8, 75.0, 114.6, 121.1, 129.4, 154.0, 158.4, 169.6; ms: m/z 370 (M^+).

Anal. Calcd. for $C_{16}H_{22}N_2O_4S_2$: C, 51.87; H, 5.99; N, 7.56. Found: C, 51.99; H, 6.05; N, 7.35.

General Procedure for the Preparation of 1-Alkoxy-5-alkyl-5-[di(methylthio)methyl]hydantoins **7a,b**.

A mixture of *N*-Alkoxy-*N'*-[2-alkyl-3,3-di(methylthio)acryloyl]-urea **6a** or **6b** (1.0 mmole) and anhydrous potassium carbonate (0.28 g, 2.0 mmoles) in absolute ethanol (5 ml) was heated under reflux for 3 hours. After cooling, the reaction mixture was concentrated under reduced pressure, dissolved in water (5 ml), acidified with 1*N* hydrochloric acid, and extracted with ethyl acetate (3 x 10 ml). The combined ethyl acetate solution was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The oily residue was purified by medium pressure liquid chromatography on silica gel with ethyl acetate-hexane as eluent.

1-Butoxy-5-[di(methylthio)methyl]-5-methylhydantoin (**7a**).

This compound was prepared from **6a** in 95% yield as a colorless oil; ir (neat) 3219, 3082, 1793, 1732 cm^{-1}; ^1H nmr: δ 0.95 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.44 (m, 2H, $OCH_2CH_2CH_2$), 1.66 (m, 2H, OCH_2CH_2), 2.24 (s, 3H, SCH_3), 2.27 (s, 3H, SCH_3), 3.95 (s, 1H, CH), 4.15 (m, 2H, OCH_2), 9.00 (br s, 1H, NH); ^{13}C nmr: δ 13.9, 16.0, 16.5, 19.0, 19.9, 30.2, 60.9, 72.8, 77.6, 157.0, 172.2; ms: m/z 292 (M^+).

Anal. Calcd. for $C_{11}H_{20}N_2O_3S_2$: C, 45.18; H, 6.89; N, 9.58. Found: C, 44.96; H, 6.93; N, 9.46.

5-[Di(methylthio)methyl]-5-ethyl-1-(2-phenoxyethoxy)-hydantoin (**7b**).

This compound was prepared from **6b** in 93% yield as a colorless oil; ir (neat): 3216, 3074, 1793, 1732 cm^{-1}; ^1H nmr: δ 0.91 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.94 (m, 1H, CH_2CH_3), 2.21 (s, 3H, SCH_3), 2.24 (s, 3H, SCH_3), 2.32 (m, 1H, CH_2CH_3), 3.98 (s, 1H, CH), 4.26 (m, 2H, OCH_2CH_2OPh), 4.51 (m, 2H, OCH_2CH_2OPh), 6.90-7.08 (m, 3H, Ar H), 7.20-7.35 (m, 2H, Ar H), 8.87 (br s, 1H, NH); ^{13}C nmr: δ 8.2, 16.1, 16.3, 26.4, 60.4, 65.4, 75.8, 77.3, 114.7, 121.0, 129.4, 157.6, 158.5, 171.2; ms: m/z 370 (M^+).

Anal. Calcd. for $C_{16}H_{22}N_2O_4S_2$: C, 51.87; H, 5.99; N, 7.56. Found: C, 51.94; H, 6.23; N, 7.33.

General Procedure for the Preparation of 1-Alkoxy-5-alkyl-6-(methylthio)uracils **8a,b**.

A stirred solution of *N*-alkoxy-*N'*-[2-alkyl-3,3-di(methylthio)-acryloyl]urea **6a** or **6b** (2.0 mmoles) and methanesulfonic acid (0.4 mmole) in anhydrous acetic acid (10 ml) was heated at 80° for 1 hour. After cooling, the reaction mixture was evaporated to dryness, and the residue was dissolved in dichloromethane (20 ml). The dichloromethane solution was washed with saturated sodium bicarbonate solution (10 ml) and brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by medium pressure liquid chromatography on silica gel with ethyl acetate-hexane as eluent and then crystallized from ethyl acetate-hexane.

1-Butoxy-6-(methylthio)thymine (**8a**).

This compound was synthesized from **6a** in 99% yield, mp 157.4-157.9°; ir (potassium bromide) : 3153, 3116, 3019, 1726, 1650 cm^{-1}; ^1H nmr: δ 0.98 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.50 (m, 2H, $OCH_2CH_2CH_2$), 1.76 (m, 2H, OCH_2CH_2), 2.15 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 4.21 (t, J = 6.6 Hz, 2H, OCH_2), 9.83 (br s, 1H, NH); ^{13}C nmr: δ 13.5, 13.8, 18.5, 18.9, 29.7, 77.2, 114.3, 147.8, 149.0, 162.0; ms: m/z 244 (M^+).

Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.47. Found: C, 48.89; H, 6.83; N, 11.40.

5-Ethyl-6-(methylthio)-1-(2-phenoxyethoxy)uracil (**8b**).

This compound was prepared from **6b** in 96% yield, mp 134.0-134.5°; ir (potassium bromide): 3432, 3014, 1724, 1654 cm^{-1}; ^1H nmr: δ 1.07 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.56 (s, 3H, SCH_3), 2.64 (q, J = 7.5 Hz, 2H, CH_2CH_3), 4.35 (t, J = 4.2 Hz, 2H, OCH_2CH_2OPh), 4.61 (t, J = 4.2 Hz, 2H, OCH_2CH_2OPh), 6.85-7.02 (m, 3H, Ar H), 7.24-7.34 (m, 2H, Ar H), 9.16 (br s, 1H, NH); ^{13}C nmr: δ 13.9, 18.7, 21.4, 65.2, 75.2, 114.3, 120.1, 121.1, 129.4, 148.0, 148.5, 158.1, 161.4; ms: m/z 322 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.89; H, 5.63; N, 8.69. Found: C, 56.05; H, 5.68; N, 8.54.

General Procedure for the Preparation of 1-Alkoxy-5-alkyl-6-(methylsulfonyl)uracils **9a,b**.

A stirred solution of 1-alkoxy-5-alkyl-6-(methylthio)uracil **8a** or **8b** (2 mmoles) and 3-chloroperoxybenzoic acid (85%, 1.73 g, 10 mmoles) in benzene (10 ml) was heated under reflux for 20 minutes. After cooling, the brownish solution was evaporated to dryness, and the residue was dissolved in ethyl acetate (60 ml). The ethyl acetate solution was successively washed with saturated aqueous sodium bicarbonate solution (15 ml), saturated aqueous sodium thiosufate solution (15 ml) and brine (15 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was crystallized from ethyl acetate-hexane, and

mother liquor was purified by medium pressure liquid chromatography on silica gel with ethyl acetate-hexane as eluent.

1-Butoxy-6-(methylsulfonyl)thymine (**9a**).

This compound was prepared from **8a** in 93% yield, mp 162.7-163.0°; ir (potassium bromide): 3127, 3025, 1737, 1657, 1333, 1153 cm^{-1}; ^1H nmr: δ 0.97 (t, J = 7.5 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.45 (m, 2H, $OCH_2CH_2CH_2$), 1.74 (m, 2H, OCH_2CH_2), 2.35 (s, 3H, CH_3), 3.38 (s, 3H, SO_2CH_3), 4.41 (t, J = 7.1 Hz, 2H, OCH_2), 9.68 (br s, 1H, NH); ^{13}C nmr: δ 10.2, 13.8, 18.8, 29.7, 46.0, 78.6, 115.9, 146.5, 147.3, 162.4; ms: m/z 276 (M^+).

Anal. Calcd. for $C_{10}H_{16}N_2O_5S$: C, 43.47; H, 5.84; N, 10.14. Found: C, 43.63; H, 5.77; N, 10.01.

5-Ethyl-6-(methylsulfonyl)-1-(2-phenoxyethoxy)uracil (**9b**).

This compound was prepared from **8b** in 90% yield, mp 161.0-161.3°; ir (potassium bromide): 3425, 3244, 1728, 1685, 1334, 1151 cm^{-1}; ^1H nmr: δ 1.13 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.92 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.41 (s, 3H, SO_2CH_3), 4.32 (t, J = 4.2 Hz, 2H, OCH_2CH_2OPh), 4.80 (t, J = 4.2 Hz, 2H, OCH_2CH_2OPh), 6.85-7.03 (m, 3H, Ar H), 7.23-7.34 (m, 2H, Ar H), 10.91 (br s, 1H, NH); ^{13}C nmr: δ 14.6, 17.7, 46.4, 65.2, 76.2, 114.4, 121.2, 122.2, 129.4, 146.3, 148.1, 158.2, 161.9; ms: m/z 354 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_2O_6S$: C, 50.84; H, 5.12; N, 7.90. Found: C, 50.98; H, 5.17; N, 7.66.

6-Azido-1-butoxythymine (**2a**).

A suspension of 1-butoxy-6-(methylsulfonyl)thymine **9a** (0.150 g, 0.54 mmole) and sodium azide (0.035 g, 0.54 mmole) in *N,N*-dimethylformamide (3 ml) was stirred at room temperature for 30 minutes, and then the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in water (5 ml) and extracted with ethyl acetate (2 x 15 ml). The ethyl acetate solution was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by medium pressure liquid chromatography on silica gel with ethyl acetate-hexane as eluent and then crystallized from ethyl acetate-hexane to give 0.128 g (98%) of **2a**, mp 113.5-114.0° dec; ir (potassium bromide): 3115, 3091, 2149, 1728, 1677 cm^{-1}; ^1H nmr: δ 0.98 (t, J = 7.5 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.49 (m, 2H, $OCH_2CH_2CH_2$), 1.79 (m, 2H, OCH_2CH_2), 1.92 (s, 3H, CH_3), 4.24 (t, J = 6.9 Hz, 2H, OCH_2), 9.80 (br s, 1H, NH); ^{13}C nmr: δ 9.5, 13.7, 18.8, 29.4, 78.2, 99.0, 143.6, 147.3, 162.7; ms: m/z 239 (M^+).

Anal. Calcd. for $C_9H_{13}N_5O_3$: C, 45.19; H, 5.48; N, 29.27. Found: C, 45.02; H, 5.65; N, 29.24.

General Procedure for the Preparation of 5-Ethyl-1-(2-phenoxyethoxy)-6-(phenylthio)uracil **2b** and -6-(phenylselenenyl)-uracil **2c**.

To a stirred suspension of 5-ethyl-6-(methylsulfonyl)-1-(2-phenoxyethoxy)uracil **9b** (0.35 g, 1 mmole) and phenylthiol (1.1 mmoles) or phenylselenol (1.1 mmoles) in ethanol (2 ml) was added 1*N* sodium hydroxide (1.10 ml) at room temperature under a nitrogen atmosphere. After the mixture was stirred for 20 minutes, 3*N* ethanolic hydrochloric acid (0.37 ml) was added, and the reaction mixture was evaporated to dryness. The residue was purified by medium pressure liquid chromatography on silica gel with ethyl acetate-hexane as eluent and then crystallized from ethyl acetate-hexane.

5-Ethyl-1-(2-phenoxyethoxy)-6-(phenylthio)uracil (**2b**).

This compound was prepared from **9b** and phenylthiol in 95% yield, mp 143.9-144.8°; ir (potassium bromide): 3447, 3162, 3034, 1703, 1673 cm^{-1}; ^1H nmr : δ 1.08 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.72 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.20 (t, J = 4.5 Hz, 2H, OCH_2CH_2OPh), 4.47 (t, J = 4.5 Hz, 2H, OCH_2CH_2OPh), 6.74-7.00 (m, 3H, Ar H), 7.17-7.38 (m, 7H, Ar H), 9.63 (br s, 1H, NH); ^{13}C nmr: δ 13.8, 21.8, 65.2, 75.4, 114.5, 121.1, 122.3, 127.9, 129.4, 129.5, 129.6, 132.1, 146.2, 148.0, 158.2, 161.4; ms: m/z 384 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 62.73; H, 5.21; N, 7.08.

5-Ethyl-1-(2-phenoxyethoxy)-6-(phenylselenenyl)uracil (**2c**).

This compound was prepared from **9b** and phenylselenol in 91% yield, mp 141.0-141.9°; ir (potassium bromide): 3110, 3069, 3003, 1733, 1652 cm^{-1}; ^1H nmr : δ 1.02 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.68 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.26 (t, J = 4.5 Hz, 2H, OCH_2CH_2OPh), 4.53 (t, J = 4.5 Hz, 2H, OCH_2CH_2OPh), 6.80-6.98 (m, 3H, Ar H), 7.17-7.32 (m, 5H, Ar H), 7.46-7.57 (m, 2H, Ar H), 9.64 (br s, 1H, NH); ^{13}C nmr: δ 13.7, 23.5, 65.2, 75.2, 114.5, 121.1, 121.9, 128.4, 129.4, 129.7, 132.6, 144.7, 147.7, 158.2, 161.0; ms: m/z 432 ($M^+ + H$).

Anal. Calcd. for $C_{20}H_{20}N_2O_4Se$: C, 55.69; H, 4.67; N, 6.49. Found: C, 55.54; H, 4.72; N, 6.45.

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