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SYNTHESIS OF FUNCTIONALIZED 5-NITROURACIL DERIVATIVES INVOLVING ELECTRON TRANSFER COUPLING REACTIONS

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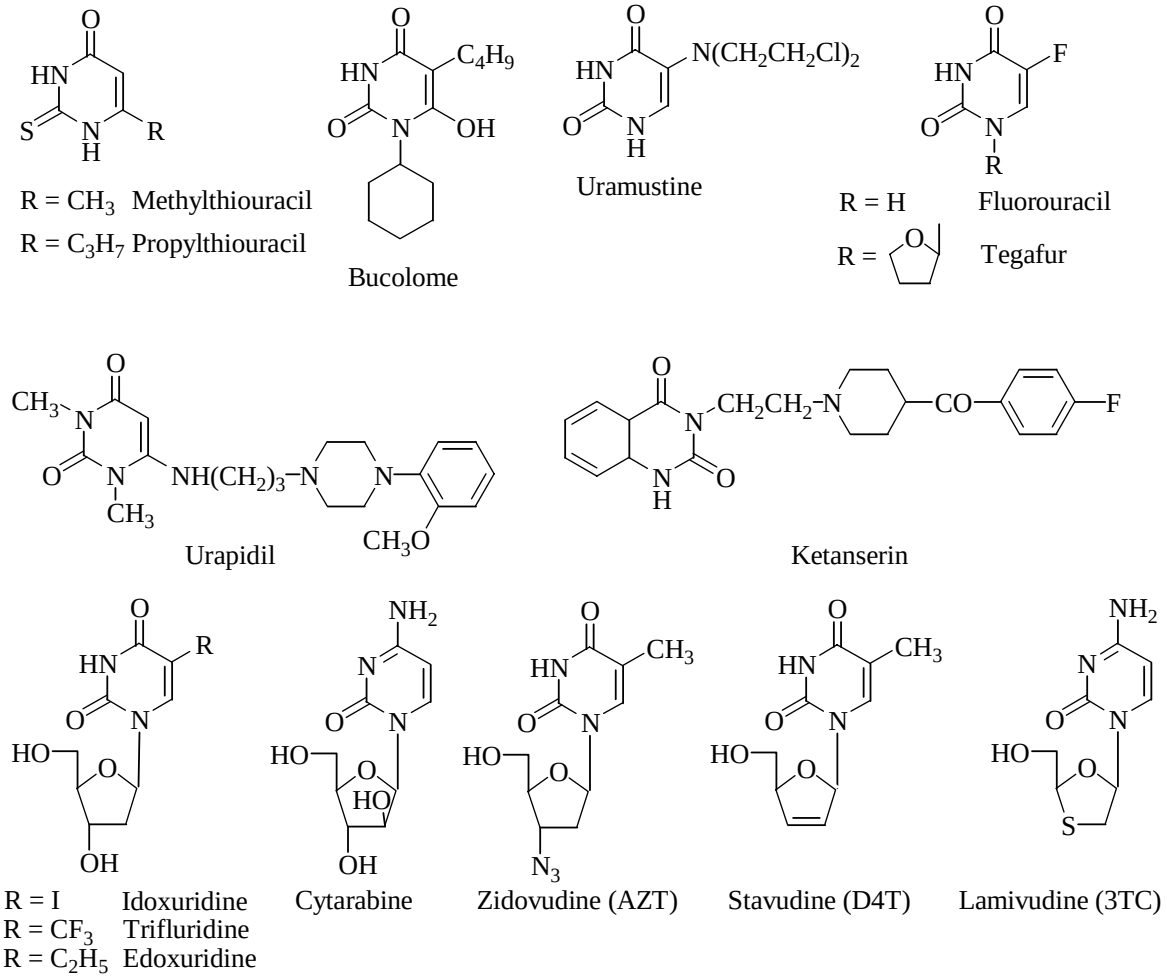
Abstract - The tetrabutylammonium salts of 1,3-dialkyl-6-methyl-5-nitrouracils reacted with reductive alkylating agents, *p*-nitrobenzyl chloride and 2,2-dinitropropane, by electron transfer coupling reactions to yield new potentially active and highly functionalized uracil derivatives.

Uracils have represented a class of coumpounds that continually attract organic chemists, biochemists, medicinal chemists and photobiologists.[1] Several uracil derivatives have been developed as drugs (Scheme 1). Thus, methylthiouracil and propylthiouracil are thyroid inhibitors,[2] bucolome is an anti-inflammatory,[3] uramustine (uracil mustard), fluorouracil and its masked compounds are anticancer agents,[4] and urapidil and ketanserine are used as antihypertensives.[5] Uracil nucleosides, the uridines and their derivatives play a decisive role as biologically and pharmacologically active principles. For example, idoxuridine, trifluridine and edoxuridine[6] show antiviral activity as an antimetabolite of thymidine, cytarabine is used for clinical treatment of leukemia,[7] and the recently developed zidovudine (AZT),[8] stavudine (D4T),[9] and lamivudine (3TC)[10] have been applied successfully as reverse transcriptase inhibitors in AIDS treatment. With the objective of discovering new antiviral agents, several research groups have made contributions to the development of acyclic analogs of pyrimidine nucleosides.[11] As part of our program directed toward study of electron transfer reactions to synthesize new biologically active compounds,[12] we investigated the reactivity of various uracil nitronate anions

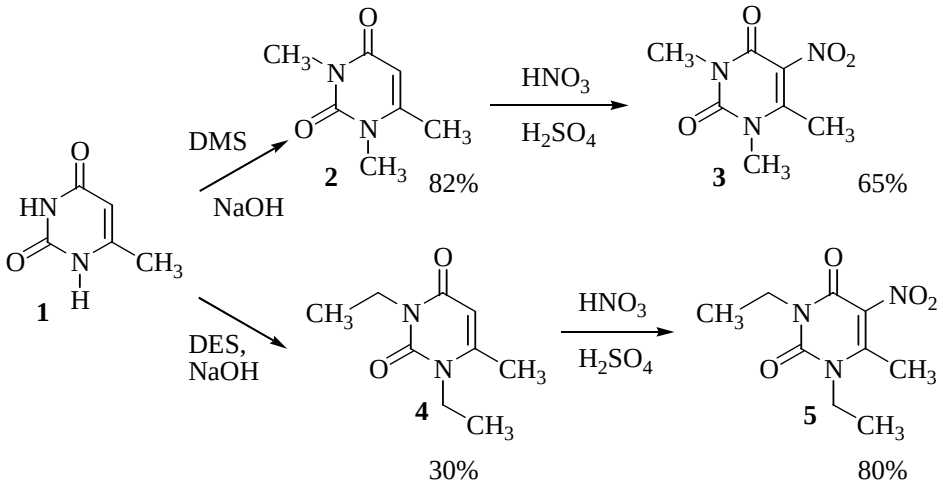
with reductive alkylating agents such as *p*-nitrobenzyl chloride or 2,2-dinitropropane in order to determine the influence of the steric hindrance of the substituents in position 1 and position 6 on the electron transfer cross-coupling reactions and to prepare original functionalized 5-nitrouracil derivatives.

Scheme 1



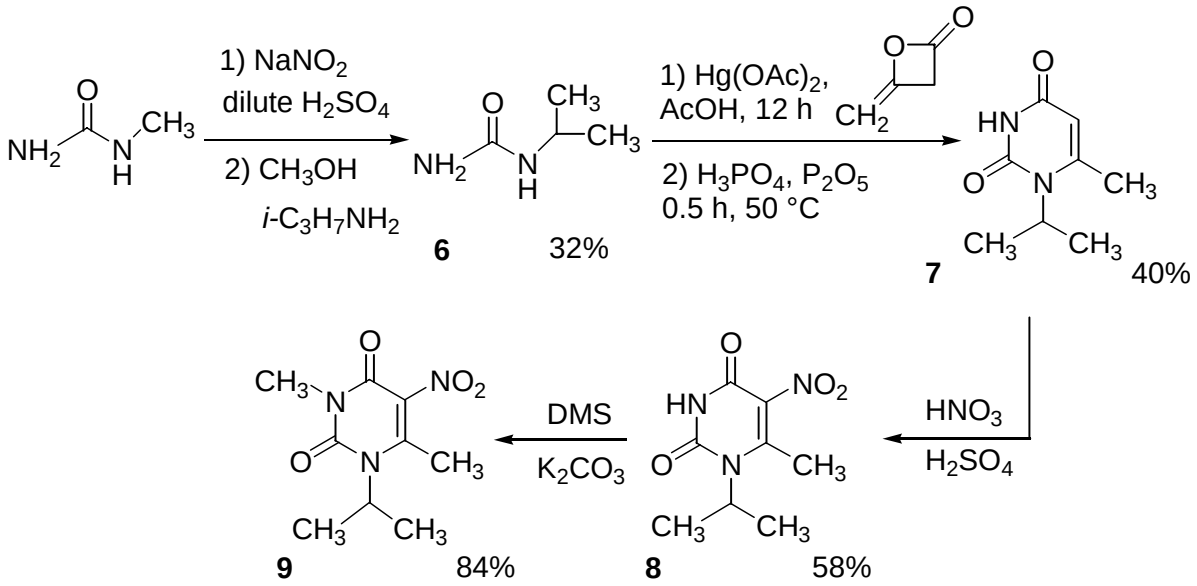
1,3,6-Trimethyl-5-nitrouracil (**3**) and 1,3-diethyl-6-methyl-5-nitrouracil (**5**) were prepared in two steps by classical direct alkylation[13, 14] and nitration[15] respectively in 65 and 80% yields (Scheme 2).

Scheme 2



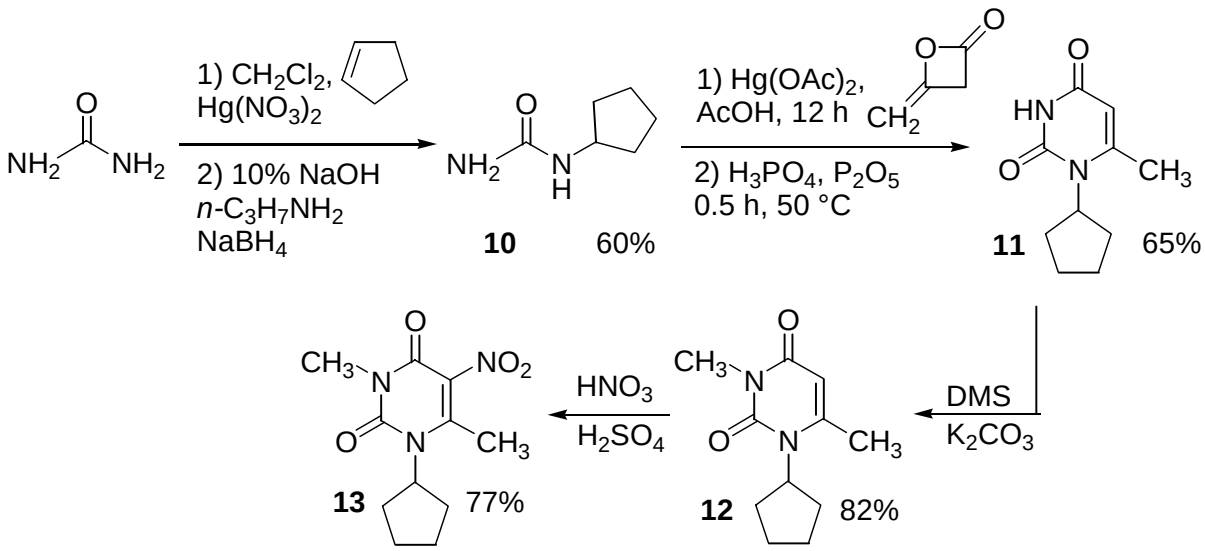
1-Substituted 6-methyluracils (**7**) and (**11**) were obtained by condensation of monosubstituted ureas (**6**) and (**10**) with diketene followed by a ring closure similar to that used by Senda in 1972.[16] In the present study, it was possible to isolate and identify the intermediate 3-substituted 1-acetoacetylureas but, heating without isolating such an intermediate was advisable. Nitration with HNO_3-H_2SO_4 at 0 °C and *N*-alkylation gave derivative (**9**) in good yield (Scheme 3).

Scheme 3



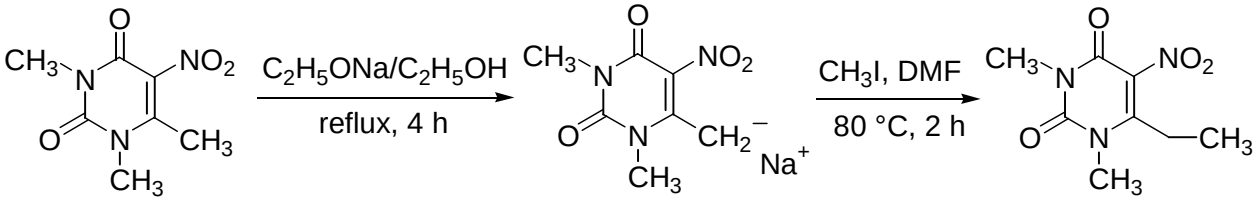
In order to optimize the synthesis of cyclopentyl derivative (**13**), we have realized the *N*-alkylation before nitration on 5-position. This modification resulted in an increase in the yield of **13** from 35 to 77% (Scheme 4).

Scheme 4



The sodium salt of 1,3,6-trimethyl-5-nitrouracil was used as a starting material: it was easily prepared by reacting **3** with sodium ethoxide in refluxing ethanol, as reported previously.[17] This salt reacted with methyl iodide in dry DMF at 80 °C as described by Hirota[17] to give **14** as shown in Scheme 5.

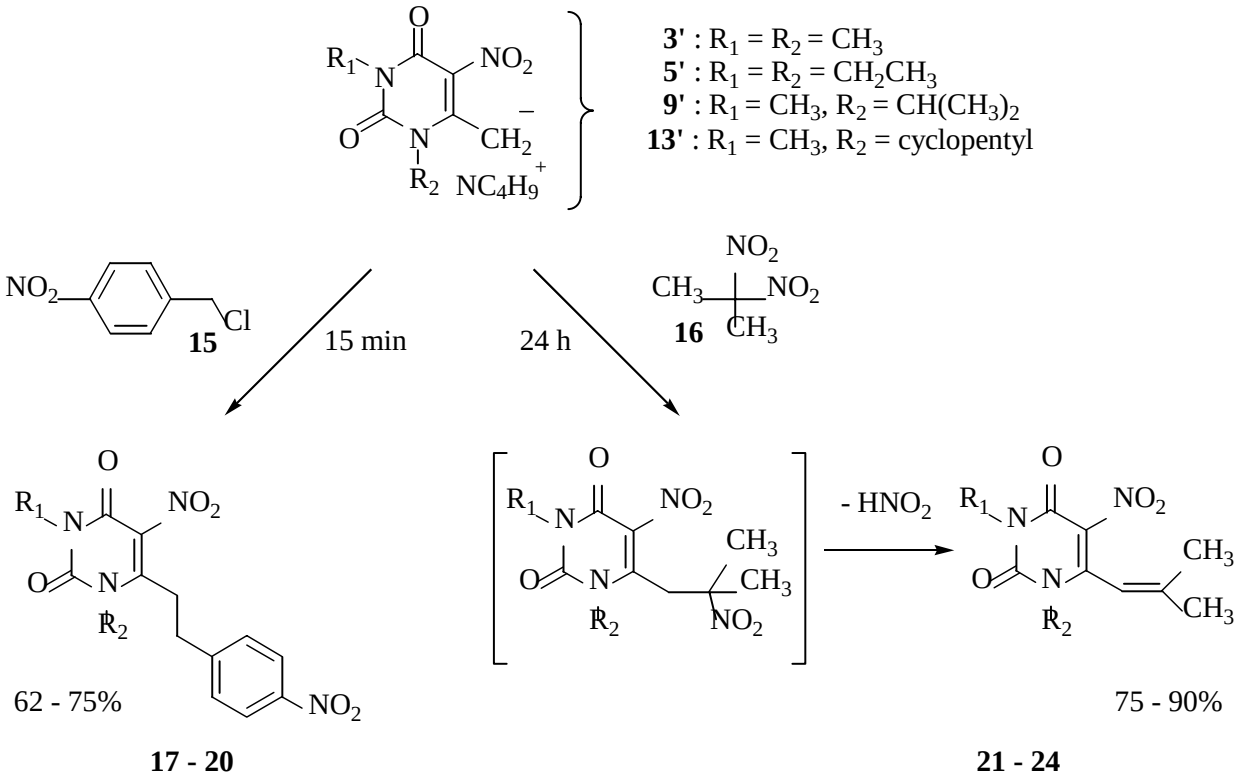
Scheme 5



3 **14** 63%

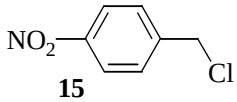
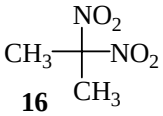
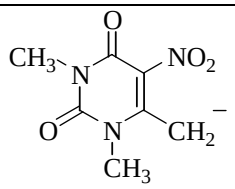
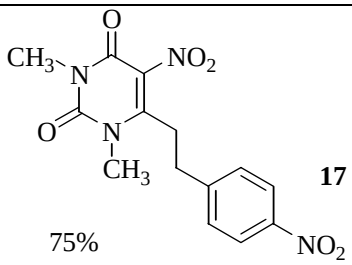
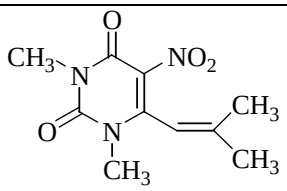
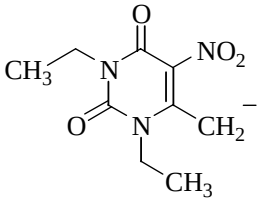
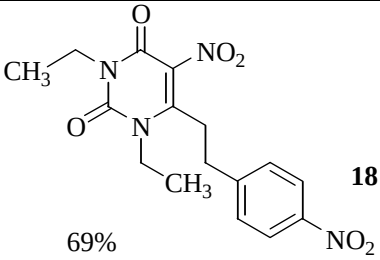
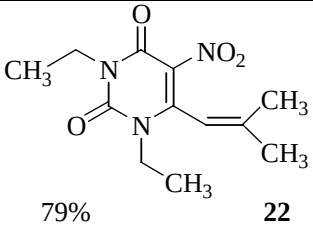
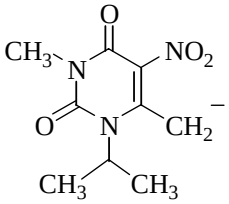
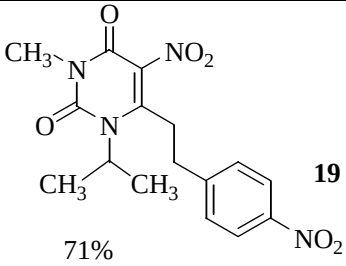
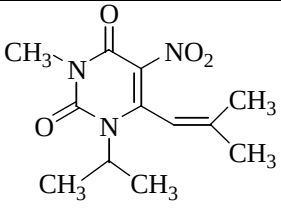
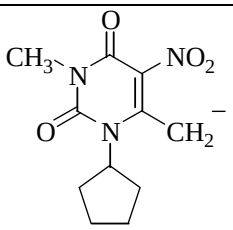
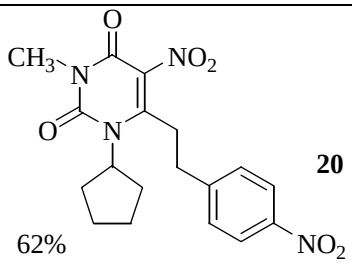
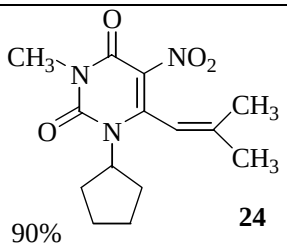
Uracil nitronate anions (**3'**, **5'**, **9'** and **13'**) were prepared *in situ* from the 1,3-disubstituted 5-nitro-6-methyluracils by treatment with tetrabutylammonium hydroxide solution in methanol. These anions were treated under nitrogen and photostimulation with *p*-nitrobenzyl chloride (**15**) or 2,2-dinitropropane (**16**).

Scheme 6



By using 2.2 equivalents of primary anion (**3'**, **5'**, **9'** or **13'**) during appropriate time, the reactions with *p*-nitrobenzyl chloride (**15)** gave only the *C*-alkylation products (**17-20**) while with 2,2-dinitropropane (**16)** we obtained only the ethylenic derivatives (**21-24**) in good yields as shown in Scheme 6 and indicated in the Table. The single electron transfer mechanism was confirmed in the reaction of **3'** with **15** by depression of reaction rate[18] by addition of classical inhibitors[19] (2,2,6,6-tetramethyl-1-piperidinyloxy or TEMPO, cupric chloride, bubbling dioxygen, performing the reaction in the dark). The alkenes (**21-24**) were classically formed by electron transfer *C*-alkylation and base-promoted nitrous acid elimination from the *C*-alkylation product.

Table

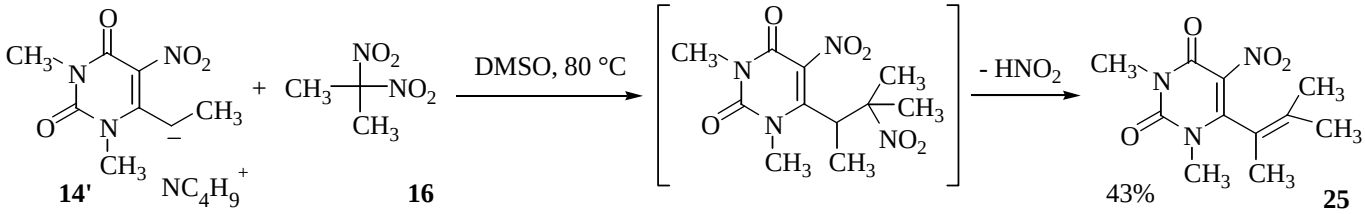
Uracil anion	Final product with  **15**	Final product with  **16**
 **3'**	 **17** 75%	 88% **21**
 **5'**	 **18** 69%	 79% **22**
 **9'**	 **19** 71%	 **23** 75%
 **13'**	 **20** 62%	 **24** 90%

Conditions : All reactions were carried out in DMSO under nitrogen and irradiation with fluorescent lamp (150 W) by using 2.2 equiv. of uracil anion and 1 equiv. of **15** or **16**. Product as per cent of theorical yield relative to the electrophile as pure isolated product.

Contrary to precedent result with **3'**, the secondary nitronate anion (**14')** did not react at room temperature with **15** in DMSO or DMF. When the reaction was conducted at 50 °C, we observed only recovered **15** and untractable tarry matters. However with **16**, the expected ethylenic derivative (**25**) was obtained in 43% yield under more drastic experimental conditions (DMSO at 80 °C), as shown in Scheme 7. The lower *C*-alkylation yield may be explained by a possible steric hindrance. Norris and co-workers have already tested the steric limits of the $S_{RN}1$ reactions of *p*-nitrobenzyl derivatives.[20] At a certain steric bulk

of the anion and the intermediate radical, addition was hindered and other reactions (as reduction) predominated. The $S_{RN}1$ reactions between nitroimidazole anions and halonitro compounds were also influenced by steric hindrance.[21]

Scheme 7



In conclusion, we have shown that there is few influence of the nature of the substituent in position 1 on the reactivity of the anions formed from 1,3-dialkyl-6-methyl-5-nitrouracils in the electron transfer cross-coupling reactions with *p*-nitrobenzyl chloride and 2,2-dinitropropane. Simplicity, generality and high yields make this methodology based on electron transfer reactions a useful synthetic way for the preparation of new potentially active and highly functionalized uracil derivatives. However, using the same strategy with secondary anions for the preparation of highly 6-substituted derivatives is limited in success.

ACKNOWLEDGEMENTS

This work has been supported by the Centre National de la Recherche Scientifique and the Universities of Aix-Marseille. M. D. Crozet thanks the Ministry of National Education for a student research fellowship. We express our thanks to M. Noailly for ^{1}H and ^{13}C NMR spectra recording.

EXPERIMENTAL

Melting points were determined on Büchi melting point B-540 apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3 and of the INP-ENSCT (Toulouse, France). Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker ARX 200 spectrometer. The ^{1}H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvent peak: $CDCl_3$ (76.9 ppm). Solvents were dried by conventional methods. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particule size 0.063-0.200 mm, 70-230 mesh ASTM). TLC were performed on 5 cm x 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate solvent.

1,3,6-Trimethyluracil,[13] 1,3,6-trimethyl-5-nitrouracil,[15] 1,3-diethyl-6-methyluracil,[14] isopropylurea,[22] cyclopentylurea,[23] 1-cyclopentyl-6-methyluracil,[16] 1-cyclopentyl-3,6-dimethyluracil,[16] 6-ethyl-1,3-dimethyl-5-nitrouracil, [17] and 2,2-dinitropropane[24] were obtained as previously described.

1,3-Diethyl-6-methyl-5-nitrouracil (5)

To a solution of 1,3-diethyl-6-methyluracil (**4**) (4.2 g, 23 mmol) in concd sulfuric acid (20 mL), fuming nitric acid (7 mL) was added dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, poured into cold ice (100 mL) and extracted with dichloromethane (3 x 30 mL). Purification by chromatography on silica gel eluting with chloroform-acetone (7:3) and recrystallization from ethanol gave 4.19 g (80%) of yellow solid. **5**, mp 97 °C, ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H); 1.35 (t, *J* = 7.1 Hz, 3H); 2.42 (s, 3H); 4.02 (q, *J* = 7.1 Hz, 2H); 4.04 (q, *J* = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 12.62; 13.95; 15.48; 37.74; 41.38; 148.28; 148.60; 154.66. Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.58; H, 5.79; N, 18.51.

1-Isopropyl-6-methyluracil (7)

A mixture of diketene (5.5 g, 65 mmol), isopropylurea (**6**) (4.66 g, 45.6 mmol) and mercury (II) acetate (1 g, 3 mmol) in acetic acid (40 mL) was allowed to stand overnight. After removal of the solvent under reduced pressure, phosphoric acid (20 g, 20.4 mmol) and phosphorus pentoxide (20 g, 70.4 mmol) were added successively to the residue. The mixture was heated at 50 °C for 30 min, poured into cold water (100 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The solvent was dried on magnesium sulfate and removed under vacuum. Purification by chromatography on silica gel eluting with dichloromethane-ether (6:4) and recrystallization from ethanol gave 3.1 g (40%) of white solid. **7**, mp 165 °C, ^{1}H NMR ($CDCl_3$) δ 1.46 (d, *J* = 6.8 Hz, 6H); 2.25 (s, 3H); 4.41 (m, 1H); 5.43 (s, 1H); 11.00 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.90; 18.71; 47.93; 99.68; 149.40; 152.60; 161.36. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.09; H, 7.17; N, 16.63.

1-Isopropyl-6-methyl-5-nitrouracil (8)

To a solution of 1-isopropyl-6-methyluracil (**7)** (2.5 g, 15 mmol) in concd sulfuric acid (7.5 mL), fuming nitric acid (5 mL) was added dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and poured into cold ice. After filtration, the crude product was recrystallized from ethanol to give 1.85 g (58%) of yellow solid. **8**, mp 295 °C, ^{1}H NMR ($CDCl_3$) δ 2.48 (d, *J* = 6.7 Hz, 6H); 3.36 (s, 3H); 5.45 (m, 1H); 12.95 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.05; 19.37; 51.11; 128.46; 148.59; 151.51; 155.29. Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.07 ; H, 5.20 ; N, 19.71. Found: C, 45.09 ; H, 5.18 ; N, 20.27.

1-Isopropyl-3,6-dimethyl-5-nitrouracil (9)

To a solution of 1-isopropyl-6-methyl-5-nitrouracil (**8**) (1.5 g, 7 mmol) in acetone (50 mL), potassium carbonate (5.8 g, 42 mmol) was added. Then dimethyl sulfate (1.3 g, 10.3 mmol) was added dropwise. The reaction mixture was refluxed for 3 h, and filtered. The crude product was purified by recrystallization from ethanol to give 1.35 g (84%) of yellow solid. **9**, mp 172 °C, ^{1}H NMR ($CDCl_3$) δ 1.60 (d, *J* = 6.8 Hz, 6H); 2.38 (s, 3H); 3.34 (s, 3H); 4.47 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 16.20; 19.84;

28.21; 52.67; 148.36; 149.14; 155.09. Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.54; H, 5.77; N, 18.53.

1-Cyclopentyl-3,6-dimethyl-5-nitrouracil (13)

To a solution of 1-cyclopentyl-3,6-dimethyluracil (**12**) (2.4 g, 12 mmol) in concd sulfuric acid (7 mL), fuming nitric acid (3 mL) was added dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and poured into cold ice. After filtration, the crude product was recrystallized from ethanol to give 2.2 g (77%) of yellow solid. **13**, mp 170 °C, ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2H); 1.90 (m, 4H); 2.20 (m, 2H); 2.40 (s, 3H); 3.35 (s, 3H); 4.51 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 16.66; 25.75; 29.25; 28.30; 60.26; 148.83; 155.06. Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.05; H, 5.96; N, 16.49.

General procedure for the reaction of **3, 5, 9, 13** with *p*-nitrobenzyl chloride (**15)** and 2,2-dinitropropane (**16)**.

To a solution of 1.0 M tetrabutylammonium hydroxide (1.8 g, 2.2 mmol) in methanol, 1,3-dialkyl-6-methyl-5-nitrouracil (**3, 5, 9, 13**) (2.2 mmol) was added. After stirring for 30 min, the solvent was evaporated under reduced pressure. The resulting crude product and *p*-nitrobenzyl chloride (0.17 mg, 1 mmol) or 2,2-dinitropropane (0.13 g, 1 mmol) were dissolved in dry DMSO (5 mL). The reaction mixture was stirred at rt for 15 min (in the case of *p*-nitrobenzyl chloride) or 24 h (in the case of 2,2-dinitropropane) under nitrogen and irradiation with a 150 W lamp. The reaction was quenched with addition of water (50 mL). After neutralization by 10% acetic acid, the mixture was extracted with ethyl acetate (3 x 30 mL). The organic extracts were dried over magnesium sulfate and evaporated under reduced pressure. Purification by chromatography on silica column eluting with dichloromethane-ether (6:4) (purification A) or chloroform-ether (9:1) (purification B) and recrystallization from ethanol gave the required products.

1,3-Dimethyl-5-nitro-6-[2-(4-nitrophenyl)ethyl]uracil (17)

Yellow solid,[18] 75% yield (purification A), mp 194 °C, ^{1}H NMR ($CDCl_3$) δ 3.02 (m, 4H); 3.24 (s, 3H); 3.51 (s, 3H); 7.62 and 8.24 (2d, A_2B_2, J = 8.1 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 26.65; 28.36; 30.38; 30.61; 121.80; 127.95; 144.64; 145.39; 148.31; 150.12; 155.21. Anal. Calcd for $C_{14}H_{14}N_4O_6$: C, 50.30; H, 4.22; N, 16.76. Found: C, 50.38; H, 4.15; N, 16.79.

1,3-Diethyl-5-nitro-6-[2-(4-nitrophenyl)ethyl]uracil (18)

Yellow solid, 69% yield (purification A), mp 150 °C, ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H); 1.39 (t, J = 7.1 Hz, 3H); 3.03 (m, 4H); 4.06 (q, J = 7.1 Hz, 2H); 4.11 (q, J = 7.1 Hz, 2H); 7.41 and 8.21 (2d, A_2B_2, J = 8.7 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 12.40; 14.34; 30.25; 34.03; 37.76; 41.11; 124.09; 129.06; 129.87; 145.09; 147.05; 149.22; 150.14; 154.53. Anal. Calcd for $C_{16}H_{18}N_4O_6$: C, 53.02; H, 5.01; N, 15.47. Found: C, 53.02; H, 4.97; N, 15.45.

1-Isopropyl-3-methyl-5-nitro-6-[2-(4-nitrophenyl)ethyl]uracil (19)

Yellow solid, 71% yield (purification B), mp 186 °C, ^{1}H NMR ($CDCl_3$) δ 1.60 (d, *J* = 6.8 Hz, 3H); 1.68 (d, *J* = 6.8 Hz, 3H); 3.05 (m, 4H); 3.33 (s, 3H); 4.46 (m, 1H); 7.42 and 8.16 (2d, A_2B_2, *J* = 8.8 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 20.13; 30.61; 33.67; 52.84; 124.02; 129.13; 145.75; 146.75; 148.97; 149.95; 155.03. Anal. Calcd for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 5.01; N, 15.46. Found: C, 52.98; H, 4.99; N, 15.42.

1-Cyclopentyl-3-methyl-5-nitro-6-[2-(4-nitrophenyl)ethyl]uracil (20)

Yellow solid, 62% yield (purification A), mp 180 °C, ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 2H); 1.94 (m, 2H); 2.10 (m, 2H); 2.30 (m, 2H); 3.03 (m, 4H); 3.38 (s, 3H); 4.49 (m, 1H); 7.38 and 8.20 (2d, A_2B_2, *J* = 8.0 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 25.96; 28.55; 29.85; 31.24; 33.98; 60.52; 124.39; 129.19; 145.59; 147.35; 148.94; 150.09; 155.03. Anal. Calcd for $C_{18}H_{20}N_4O_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.66; H, 5.15; N, 14.38.

1,3-Dimethyl-6-(2-methylpropenyl)-5-nitrouracil (21)

Yellow solid,[18] 88% yield (purification A), mp 142 °C, ^{1}H NMR ($CDCl_3$) δ 1.72 (d, *J* = 1.5 Hz, 3H); 1.94 (d, *J* = 1.5 Hz, 3H); 3.39 (s, 3H); 3.41 (s, 3H); 5.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.39; 25.38; 28.76; 33.29; 111.75; 147.59; 148.51; 150.33; 155.18. Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.18; H, 5.50; N, 17.51.

1,3-Diethyl-6-(2-methylpropenyl)-5-nitrouracil (22)

Yellow solid, 79% yield (purification A), mp 127 °C, ^{1}H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H); 1.27 (t, *J* = 7.1 Hz, 3H); 1.74 (d, *J* = 1.5 Hz, 3H); 1.94 (d, *J* = 1.5 Hz, 3H); 3.92 (q, *J* = 7.1 Hz, 2H); 4.05 (q, *J* = 7.1, 2H); 5.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 12.56; 13.77; 20.56; 25.41; 37.63; 41.87; 111.20; 129.85; 147.32; 147.96; 149.40; 154.86. Anal. Calcd for $C_{12}H_{12}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.66; H, 6.40; N, 15.84.

1-Isopropyl-3-methyl-6-(2-methylpropenyl)-5-nitrouracil (23)

Pale yellow solid, 75% yield (purification B), mp 150 °C, ^{1}H NMR ($CDCl_3$) δ 1.49 (d, *J* = 6.8 Hz, 3H); 1.53 (d, *J* = 6.8 Hz, 3H); 1.74 (d, *J* = 1.4 Hz, 3H); 1.93 (d, *J* = 1.4 Hz, 3H); 3.36 (s, 3H); 4.53 (m, 1H); 5.80 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 19.78; 20.44; 25.24; 28.18; 53.68; 111.75; 146.86; 147.99; 149.20; 155.24. Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.87; H, 6.45; N, 15.69.

1-Cyclopentyl-3-methyl-6-(2-methylpropenyl)-5-nitrouracil (24)

Pale yellow solid, 90% yield (purification A), mp 154 °C, ^{1}H NMR ($CDCl_3$) δ 1.56 (m, 2H); 1.72 (s, 3H); 1.80 (m, 2H); 1.92 (s, 3H); 2.00 (m, 2H); 2.20 (m, 2H); 3.36 (s, 3H); 4.59 (m, 1H); 5.80 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.44; 25.38; 25.75; 26.88; 28.30; 29.28; 61.25; 111.95; 146.95; 148.60; 148.97; 155.24. Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.36; H, 6.58; N, 14.39.

1,3-Dimethyl-6-(1,2-dimethylpropenyl)-5-nitrouracil (25)

The described procedure was followed, except that the reaction mixture was stirred at 80 °C. Purification by chromatography on silica column eluting with dichloromethane-ether (9:1) and recrystallization from ethanol gave 0.11 g (43%) of yellow solid. **25**, mp 161 °C, ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 3H); 1.80 (m, 3H); 1.92 (m, 3H); 3.33 (s, 3H); 3.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 20.39; 23.87; 25.38; 28.76; 33.29; 147.59; 148.51; 149.27; 150.33; 155.18. Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.36; H, 5.99; N, 16.43.

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