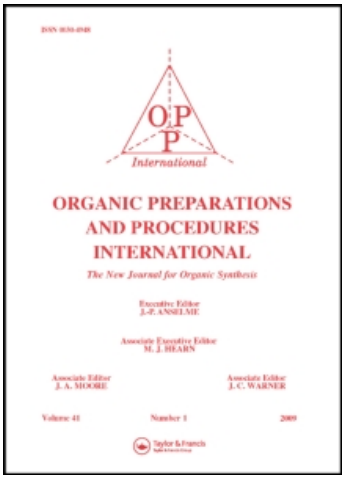


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# FACILE LARGE SCALE SYNTHESIS OF 5-ALKYLURACILS

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# FACILE LARGE SCALE SYNTHESIS OF 5-ALKYLURACILS

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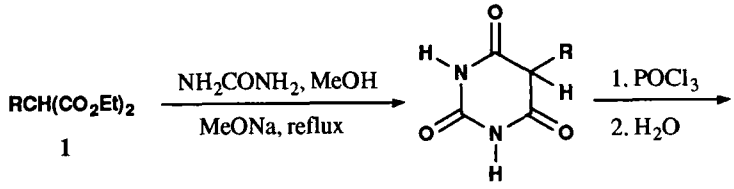
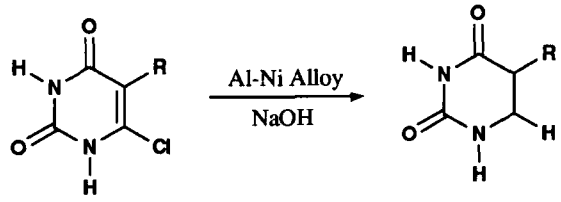
The biological activity of several 5-alkyl-2'-deoxyuridines,[1] and in particular 5-ethyl and 5-*n*-propyl derivatives[2,3] has elicited significant interest in the synthesis of other modified pyrimidine analogues. The most common approach to the preparation of uracils, especially 5-alkyluracils, involved the condensation of appropriate α-formylesters with thiourea (or urea).[4] The products are hydrolyzed with chloroacetic acid to yield desired uracils.[5] This method, however, gives relatively low yields and in its initial stages, requires tedious procedures to obtain appropriate ester (especially in the case of long chain esters). In addition, the preparation of the required α-formyl derivatives sometimes leads to unexpected exothermic reactions. This paper describes a novel approach to the synthesis of 5-alkyluracils *via* barbituric acid derivatives in high overall yields.

The appropriate diethyl alkylmalonates - substrates for 5-alkylbarbituric acids (**2**)- were prepared using general procedure (**1d-f**)[7] or are commercially available (**1a-c**). Treatment of




**1** **2**




**3** **4**

a) R = $C_2H_5$ b) R = *n*-$C_3H_7$ c) R = *i*-$C_3H_7$

d) R = *n*-$C_4H_9$ e) R = *n*-$C_8H_{17}$ f) R = *c*-$C_6H_{11}$

5-alkylbarbituric acids (**2**), obtained by the condensation of diethyl alkyl malonates (**1**) and urea,[6] with $POCl_3$ (in the presence of water) yielded the appropriate 5-alkyl-6-chlorouracils. This one-pot reaction gives in a preliminary stage 2,4,6-trichloro-5-alkylpyrimidines which are then hydrolyzed *in situ* to 5-alkyl-6-chlorouracil. If the hydrolysis was not complete, the basic treatment caused the complete and immediate hydrolysis of 2,4,6-trichloropyrimidines to the 5-alkyl-6-chlorouracils.

In the final step we were able to remove the chlorine atom from the molecule by reduction with Raney nickel in alkaline solution. In a basic solution (aqueous NaOH) the starting material is present as a sodium salt and can be easily dissolved in the reaction medium. Nickel-aluminum alloy is placed in the reaction mixture and Raney nickel is generated *in situ* resulting in reduction of 5-alkyl-6-chlorouracils. This procedure is advantageous in comparison with a typical catalytic reduction; it is a convenient methodology in a small scale synthesis ($H_2$/ 10% Pd/C[3c] or 1% Pd/C[8a]). We also attempted the reduction with sodium borohydride $NaBH_4$; however, this method seems to be useful and efficient only in small scale reductions.

The present procedure provides a very simple and efficient method for the large scale preparation of practically any 5-alkyluracil. Its superiority is particularly obvious at the stage of reductive displacement of chlorine at the 6-position of uracil. The use of nickel-aluminum alloy to generate Raney nickel *in situ* as an alternative to catalytic reductive hydrogenation provides an inexpensive and easy route to the final 5-alkyl derivatives.



## EXPERIMENTAL SECTION

All $^1H$ and $^{13}C$ NMR spectra have been performed on Varian VXR 300MHz spectrometer in DMSO-$d_6$ using TMS as a internal reference. Chemical shifts are reported in $\delta$ scale, in ppm downfield from TMS. Melting points have been determined on Boetius apparatus and are not corrected. Commercially available Merck silica gel plates $HF_{254}$ have been used for TLC chromatography. Elemental analyses were performed on Perkin-Elmer 240 Elemental Analyser. All samples submitted for elemental analysis were recrystallized from water.

**General Procedure for the Preparation of 5-Substituted Barbituric Acids (2).**- In 4L round bottom flask equipped with a mechanical stirrer, a reflux condenser, an addition funnel and a drying tube, sodium methoxide was prepared by portionwise addition of 103.5 g (4.5 g-atoms) of sodium to 2L of dry methanol. After stirring for an additional 30 minutes, after sodium had completely reacted with the methanol, 3 moles of the diethyl alkylmalonate was then added dropwise at room temperature; the reaction mixture was refluxed for 30 minutes and cooled to room temperature. To this mixture, 180.2 g (3 moles) of urea was added at once and the reaction mixture was refluxed for 10 hrs. The solvents (methanol and ethanol) were removed *in vacuo* and the solid residue was dissolved in 2.5L of water. The solution was then treated with conc. hydrochloric acid (to pH 2-3) and the reaction mixture was kept overnight in the refrigerator. The precipitated crude 5-alkylbarbituric acid was collected, washed with 1L of cold water and dried at about 80°. The product was pure by TLC (silica gel, chloroform : methanol = 8:2 v/v) and was used in next step without further purification.

**General Procedure for the Preparation of 5-Alkyl-6-Chlorouracils (3).**- This reaction was carried out in a hood. The round bottom 2L flask equipped with a mechanical stirrer, reflux condenser and an addition funnel was placed 1 mole of 5-alkylbarbituric acid. To the flask water was added (1mL of water per 10 g of barbituric acid). Next $POCl_3$ was added dropwise (2 mL of $POCl_3$ *per* 1 g of 5-alkyl barbituric acid). The temperature of the reaction mixture was slowly raised to 100° with constant stirring and heated on oil bath for 1.5 hr at 100°. After cooling to room temperature, water was added carefully to the reaction mixture to decompose and hydrolyze an excess of $POCl_3$ (about 5 mL water *per* 1 g of 5-alkylbarbituric acid). Upon cooling overnight in the refrigerator, crude 5-alkyl-6-chlorouracil was collected and washed with ethyl ether to remove 5-alkyl-2,4,6-trichloropyrimidine (reaction side-product) until TLC showed its absence. The crude 5-alkyl-6-chlorouracil was dried and used in the next reaction without further purification.

**TABLE 1.** Yields, Melting Points and NMR Spectra of Compounds **2**

| Comp. | Yield (%) | mp (°C) | mp (lit) (°C) | $^1$H NMR (δ)[a] | $^{13}$C NMR (δ) |
|---|---|---|---|---|---|
| **2a** | 82 | 201-202 | 193[b] | 0.81 (3H, t, J = 7.3)<br>1.92 (2H, m)<br>3.50 (1H, t, J = 5.0)<br>11.20 (2H, s) | 10.6, 21.7, 49.1, 151,<br>170.6 |
| **2b** | 95 | 210-211 | 204[c] | 0.82 (3H, t, J = 7.3)<br>1.24 (2H, m)<br>1.85 (2H, m)<br>3.49 (1H, t, J = 5.0)<br>11.17 (2H, s) | 14.1, 19.5, 30.6, 48.1,<br>151.2, 170.9 |
| **2c** | 76 | 216-217 | 214[d] | 0.98 (6H, d, J = 7.0)<br>2.39 (1H, m)<br>3.18 (1H, d, J = 3.5)<br>11.18 (2H, s) | 19.6, 31.8, 54.1, 151.3,<br>170.5 |
| **2d** | 68 | 216-218 | 210[e] | 0.83 (3H, t, J = 7.0)<br>1.22 (4H, m)<br>1.87 (2H, m)<br>3.50 (1H, t, J = 4.5)<br>11.18 (2H, s) | 13.9, 22.2, 28.0, 28.2, 48.1,<br>151.1, 170.8 |
| **2e**[g] | 96 | 199-201 | | 0.83 (3H, t, J = 6.5)<br>1.21 (14H, m)<br>3.50 (1H, m)<br>11.26 (2H, s) | 14.2, 22.3, 28.75, 28.82,<br>28.94, 28.97, 29.1, 31.5,<br>48.1, 151.1, 172.3 |
| **2f** | 45 | 262-264 | 254[f] | 1.25 (11H, m)<br>3.14 (1H, t, J = 4)<br>11.28 (2H, s) | 25.4, 26.0, 29.5, 41.5,<br>54.0, 151.0, 170.1 |

a) Coupling constant J in Hz. b) Ref. 6b, 6e. c) Ref. 6c, 6e. d) Ref. 6d, 6e. e) Ref. 6e. f) Ref. 6f.
g) *Anal.* Calcd for $C_{12}H_{20}N_2O_3$: C, 59.96; H, 8.39; N, 11.66. Found: C, 60.09; H, 8.32; N, 11.55.

**TABLE 2.** Yields, Melting Points and NMR Spectra of Compounds **3**

| Comp. | Yield (%) | mp (°C) | mp (lit) (°C) | $^1$H NMR (δ)[a] | $^{13}$C NMR (δ) |
|---|---|---|---|---|---|
| **3a** | 79 | 227-228 | 215-217[b] | 0.94 (3H, t, J = 7.5)<br>2.31 (2H, q, J = 7.5)<br>11.28 (1H, s)<br>11.78 (1H, s) | 12.8, 18.8, 111.7, 140.8, 149.8, 162.9 |
| **3b**[d] | 81 | 238-240 | | 0.84 (3H, t, J = 7.5)<br>1.38 (2H, sextet, J = 7.5)<br>2.25 (2H, t, J = 7.5)<br>11.28 (1H, s)<br>11.79 (1H, s) | 13.8, 21.2, 27.3, 110.2, 141.3,149.9, 163.1 |
| **3c** | 67 | 256-259 | 243-247[c] | 1.15 (6H, d, J = 7.0)<br>2.99 (1H, septet, J = 7.0)<br>11.19 (1H, s)<br>11.71 (1H, s) | 19.9, 27.4, 114.2, 140.6, 149.8, 162.5 |
| **3d** | 79 | 194-195 | 195-196[c] | 0.85 (3H, t, J = 7.0)<br>1.30 (4H, m)<br>2.27 (2H, t, J = 7.0)<br>11.26(1H, s)<br>11.28 (1H, s) | 14.0, 22.1, 25.0, 30.1, 110.4, 141.2, 149.9, 163.1 |
| **3e**[e] | 75 | 212-214 | | 0.83 (3H, t, J = 6.5)<br>1.21 (14H, m)<br>11.18 (1H, s)<br>11.25 (1H, s) | 14.2, 22.3, 28.2, 28.74, 28.79, 28.92, 29.1, 31.5, 112.3, 141.6, 151.1, 163.5 |
| **3f**[f] | 48 | 281-283 | | 1.21 (11H, m)<br>3.05 (1H, t, J = 4)<br>11.28 (1H, s)<br>11.74 (1H, s) | 25.2, 26.3, 28.9, 41.4, 110.6, 141.0, 150.8, 169.9 |

a) Coupling constant J in Hz. b) Ref. 8a. c) Ref. 3c
d) *Anal.* Calcd. for $C_7H_9N_2O_2Cl$: C, 44.67; H, 4.82; N, 14.89. Found: C, 44.82; H, 4.79; N, 14.80.
e) *Anal.* Calcd. for $C_{12}H_{19}N_2O_2Cl$: C, 55.79; H, 7.42; N, 10.85. Found: C, 55.90; H, 7.36; N, 10.63.
f) *Anal.* Calcd. for $C_{10}H_{13}N_2O_2Cl$: C, 52.62; H, 5.74; N, 12.28. Found: C, 52.81; H, 5.79; N, 12.16.

Removal of the solvent from the ethereal solution containing 5-alkyl-2,4,6-trichloropyrimidine gave a solid residue which was refluxed with sodium ethoxide in ethanol (pH 11-12) for about 30 minutes. Removal of the solvent *in vacuo* gave a residue which was dissolved in water/ethanol and acidified with conc. hydrochloric acid to pH 2-3. The precipitate was collected, washed with cold water, dried and combined with previously obtained title compound 5-alkyl-6-chlorouracil.

**General Procedure of Preparation of 5-Alkyluracils (4).**- In a 4L beaker 200 g (5 moles) of sodium hydroxide and 1 mole of 5-alkyl-6-chlorouracils **3a-f** were dissolved in 1.5L of water. After cooling to room temperature 176 g (1.5 mole) of nickel-aluminum alloy (50% Ni-50% Al) was slowly added with occasional stirring. The reaction mixture was left for about 10-12 hours (overnight). After

**TABLE 3.** Yields, Melting Points and NMR Spectra of Compounds 4

| Comp. | Yield (%) | mp (°C) | mp (lit) (°C) | $^1$H NMR (δ)[a] | $^{13}$C NMR (δ) |
|---|---|---|---|---|---|
| **4a** | 93 | 300-303 | 300-303[b]<br>308-309[c]<br>302-303[d] | 0.98 (3H, t, J = 7.5)<br>2.15 (2H, q, J = 7.5)<br>7.16 (1H, s)<br>10.58 (1H, s)<br>10.96 (1H, s) | 13.4, 19.6, 113.8, 137.3, 151.6, 164.7 |
| **4b** | 93 | 296-299 | 296-298[b] | 0.81 (3H, t, J = 7.3)<br>1.41 (2H, m)<br>2.10 (2H, t, J = 7.3)<br>7.25 (1H, s)<br>10.60 (1H, s)<br>11.05 (1H, s) | 13.7, 21.6, 28.3, 112.1, 138.0, 151.7, 164.8 |
| **4c** | 95 | 284-286 | 286-287[e]<br>283-284[f] | 1.04 (6H, d, J = 7.0)<br>2.68 (1H, septet, J = 7.0)<br>7.05 (1H, s)<br>10.61 (1H, s)<br>10.96(1H, s) | 21.6, 25.3, 118.1, 136.1, 151.4, 162.5 |
| **4d** | 91 | 291-293 | 288-290[e]<br>291-293[b]<br>subl>250[g] | 0.85 (3H, t, J = 7.3)<br>1.23 (4H, m)<br>1.36 (2H, m)<br>2.13 (2H, t, J = 7.3)<br>7.17 (1H, s)<br>10.59 (1H, s)<br>10.96 (1H, s) | 13.9, 21.9, 25.9, 30.6, 112.3, 137.9, 151.6, 164.7 |
| **4e**[h] | 87 | >300 decomp. | | 0.85 (3H, t, J = 6.7)<br>1.22 (14H, m)<br>6.00 (1H, s)<br>11.20 (1H, s)<br>11.27 (1H, s) | 14.2, 22.3, 28.2, 28.7, 28.8, 28.9, 29.0, 31.5, 112.6, 137.9, 151.1, 172.3 |
| **4f**[i] | 72 | >300 | | 1.02 (11H, m)<br>7.14 (1H, s)<br>11.13 (1H, s)<br>11.18 (1H, s) | 24.9, 25.6, 29.1, 41.5, 112.0, 137.9, 151.1, 170.3 |

a) Coupling constant J in Hz. b) Ref. 4a. c) Ref. 8a. d) Ref. 8b. e) Ref. 3c. f) Ref. 8c. g) Ref. 8d.
h) *Anal.* Calcd.for $C_{12}H_{20}N_2O_2$: C, 64.24; H, 8.99; N, 12.49. Found: C, 64.36; H, 8.96; N, 12.42.
i) *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.82; H, 7.27; N, 14.43. Found: C, 61.97; H, 7.22; N, 14.37.

reaction was complete the solid residue was filtered off.[9] The solution was acidified with hydrochloric acid to pH 2-3 and the white precipitate was formed. Reaction mixture was left overnight in refrigerator and the white precipitate was collected, washed with cold water to remove acid and dried at 80°. All crude products were recrystallized from water. The product was pure by TLC (silica gel, chloroform : methanol = 8:2 v/v).

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9. Nickel-aluminum alloy (50%Ni-50%Al) from several chemical companies has been used. The best results, however, were obtained using Fluka or Aldrich products. Reaction has been followed by TLC-silica gel, chloroform:methanol = 8:2 v/v. If the reaction was not completed after 10-12 hours, additional amount of nickel-aluminum alloy has been added to the reaction mixture.

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