SYNTHESIS OF 5-ALKYL SUBSTITUTED URACIL DERIVATIVES FROM BARBITURIC ACID

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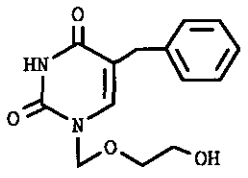
Abstract - A new two step synthesis of 5-alkyluracil derivatives from barbituric acids is described. Regioselective mono O-mesylation of barbituric acids, followed by desulfonylation under reductive conditions, afforded uracils in high overall yield. The reductive desulfonylation step is also discussed.

5-Alkyluracil derivatives are useful intermediates in the synthesis of antiviral uridines.[1] Having been interested in the synthesis of the potent inhibitor of uridine phosphorylase, 5-benzylacyclouridine (BAU, 1),[2] we sought a new conversion from the inexpensive and easily available 5-alkylbarbituric acid derivatives (2) to the valuable 5-alkyluracils (4) through a straightforward two step deoxygenative process. In spite of the massive literature[3] available, the synthesis of 5-substituted uracil derivatives usually requires multistep synthetic sequences.[4] To our knowledge, approaches starting from barbituric acid have received only very limited attention.[5,6] In fact, the exclusive formation of mono O-derivatives of barbituric acid has been seldom observed,[7] a complex reaction mixture being instead often obtained. We now wish to report our results on the reaction of the unprotected barbiturate anion toward sulfonyl halides, and on the previously unreported reductive desulfonylation of 3a-d to the desired uracil derivatives (4) (Scheme 1).



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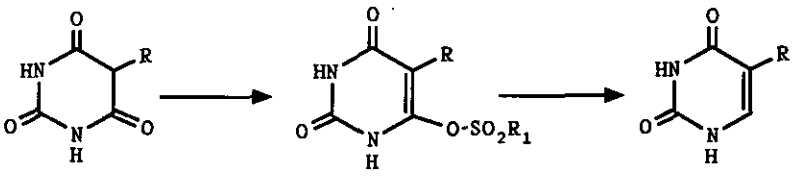
Scheme 1

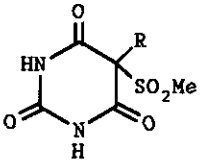


2a, R= CH_2Ph
2b, R= Et
2c, R= H

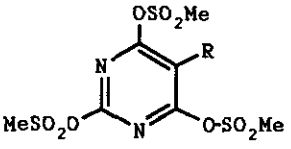
3a, R = CH_2Ph, R_1= Me
3b, R = Et, R_1= Me
3c, R = H, R_1= Me
3d, R = CH_2Ph, R_1=p-MePh

4a, R= CH_2Ph
4b, R= Et
4c, R= H

When a solution of methanesulfonyl chloride (1.1 mol equiv., DMF) was dropped into a suspension of the triethylammonium salt of **2a**[8] (2% w/v in DMF, room temperature, 30 min, 0.3 equiv. Et_3N), a new product was isolated as a white-off solid in 78% yield. On the basis of its analytical data,[9] its structure was assigned to **3a**. The reaction mixture contained minor amounts of other sulfonylated products (9% and 4% by hplc monitoring), together with some unreacted starting material (~4%). On the basis of their nmr, and mass spectra, they were assigned to **5a** and **6a** respectively.[10]



5a, R= CH_2Ph



6a, R= CH_2Ph

The relative ratios of **3a**, **5a** and **6a** were found to be dependent from the reaction conditions. The parameters mainly affecting the regioselectivity resulted the nature of the solvent, the substrate concentration, and the presence of an added base. A decrease in solvent polarizability (from DMF to MeCN and CH_2Cl_2) resulted in an increase of both **5a** and **6a** up to 33 and 14% (hplc monitoring) respectively.[11] High substrate concentration (10% w/v) also gave unfavorable results (38% of **5a**). Addition of 0.3 equiv. of base proved to be necessary for the completition of the reaction. Aromatic and sterically hindered bases (pyridine and diisopropylethylamine) gave high regioselectivity (till 97/3 of **3a** vs. **5a**). Different 5-alkyl substituents proved to have small effects on the outcome

of the reaction. In fact, no significant differences in term of yield and regioselectivity (hplc monitoring) were observed on the readily available 5-ethyl substituted derivative (2b).[12] Compound 3b was isolated (same conditions) in 65% yield. Nevertheless the absence of a substituent in 5 position dramatically affected the outcome of the reaction. Mesylation of the commercially available unsubstituted barbituric acid (2c) afforded the desired 3c only in moderate yield (35%). Following the above protocol, the 6-tosyl derivative (3d)[9] was also uneventfully obtained in 65% yield, while attempts to synthesize the trifluoromethansulfonate analog of 3a failed.

Attempted palladium-catalyzed reductions of both 3a and 3d under homogeneous catalysis conditions,[13] in the presence of Bu_3SnH or triethylammonium formate, failed. No trace of 4a was observed. Complex reaction mixtures were obtained in the former case, while with triethylammonium formate a rapid reaction took place, affording mainly barbituric acid (2a). On the other hand a palladium-based reaction involving the unprotected 5-iodouracil has been recently reported,[14] indicating that this somewhat unexpected failure is not related with the unprotected nucleus itself. The problem was overcome by the use of heterogeneous catalysis. In fact, under restricted experimental conditions, the use of Pd/C as a catalyst allowed to obtain a smooth reaction on 3a, but not on 3d, (H_2O/EtOH 9/1, 1 atm. H_2, 5% by weight of Pd/C 10%, 1 equiv. Et_3N, room temperature, 6 h) to yield 4a[15] in 85% unoptimized yield (63% overall yield based on 2a). Notably 3a behaved toward the heterogeneous Pd/C reduction, differently from the homogeneous counterpart, as a plain aromatic mesylate.[16] Reduction of 3b and 3c required somewhat more drastic conditions. Carrying out the reduction at moderate H_2 pressure (methanol, 10 atm., 24 h, room temperature), the desired 4b[15] and 4c[15] were obtained in 60 and 50% yield respectively.

In summary a new practical synthetic route from barbituric acids to uracil derivatives has been disclosed. Further work is still in progress in order to perform manipulations on the methansulfonyl group in 6 position of mesylates (3).

ACKNOWLEDGEMENT

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9. Physical data for sulfonates (3a-d): 3a: amorphous solid, mp 182-184 °C; ir (nujol mull, ν, cm^{-1}): 3300, 1740, 1670; uv (dioxane, λ_{max}, nm): 260; ^1H nmr (200 MHz, DMSO-d_6, δ, ppm): 3.63 (2H, s), 3.70 (3H, s), 6.90-7.40 (5H, m), 11.44 (1H, s), 11,90 (1H, br s); ms (EI, m/z): 296, 218, 217; 3b: amorphous solid, mp 218-219 °C; ir (nujol mull, ν, cm^{-1}): 3200, 1720, 1650; uv (dioxane, λ_{max} nm): 263; ^1H nmr (200 MHz, DMSO-d_6, δ, ppm): 0.97 (3H, t, J= 7.3 Hz), 2.24 (2H, q, J= 7.3 Hz), 3.66 (3H, s), 11.35 (1H, s), 11.74 (1H, br s); mass (EI, m/z): 234, 155; 3c: amorphous solid, mp 190 °C (decomp.); ir (nujol mull) ν,

cm^{-1}: 3200, 1720 (br), 1650 (br); uv (dioxane, λ_{max}, nm): 254; ^1H nmr (200 MHz, DMSO-d_6, δ, ppm): 3.63 (3H, s), 5.50 (1H, br s), 11.31 (1H, s), 12.02 (1H, br s); **3d**: white crystals, mp 198-200 °C; ir (Nujol mull, ν, cm^{-1}): 3400, 1700, 1640; uv (dioxane, λ_{max}, nm): 264; ^1H nmr (200 MHz, DMSO-d_6, δ, ppm): 2.44 (3H, s), 3.15 (2H, s), 6.96-7.01 (2H, m), 7.11-7.19 (3H, m), 7.51-7.54 (2H, m), 7.93-7.97 (2H, m), 11.41, (1H, s), 11.88 (1H, br s); mass (EI, m/z): 372, 217.

10. Selected physical data for **5a** and **6a**: **5a**: amorphous solid, ir (nujol mull, ν, cm^{-1}): 3200, 1770, 1740, 1705; ^1H nmr (200 MHz, DMSO-d_6, δ, ppm): 3.38 (3H, s), 3.71 (2H, s), 7.10-7.30 (5H, m), 12.16 (2H, s). The chemical shift of the quaternary carbon in 5 position in ^{13}C nmr (77.55 ppm), together with the equivalence of the carbonyl carbons in 4 and 6 (163.2 ppm) was also consistent with the structure (**5a**); mass (EI, m/z): 296, 218, 217. **6a**: ^1H nmr (200 MHz, DMSO-d_6, δ, ppm): 3.78 (6H, s), 3.79 (3H, s), 3.90 (2H, s), 7.20-7.30 (5H, m); ms (EI, m/z): 452, 373, 295, 217.

11. As sulfonyl sulfur may be regarded as a relatively "hard" reagent, preferential formation of **3a** vs. **5a** is in accord with previous findings (see for instance, A. R. Katritzky, M. Karelson, and P. A. Harris, Heterocycles, 1991, 32, 329, 335). The higher regioselectivity observed in high polarizability solvents accounts for the presence of a more "naked" anion.

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14. V. Farina and S. I. Hauk, Synlett., 1991, 157.

15. Physical data for **4a**: white crystals, mp 292-293 °C; ir (Nujol mull, ν, cm^{-1}): 3200, 1750, 1680; uv (dioxane, λ_{max}, nm): 265; ^1H nmr (200 MHz, DMSO-d_6, δ, ppm): 3.50 (2H, s), 7.18-7.32 (6H, m), 10.71 (1H, s), 11.08 (1H, s); ms (EI, m/z): 202; compounds (**4a-b**) were identical to authentic samples prepared according known methodologies.[2,6] **4c** was identical to authentic commercial sample.

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