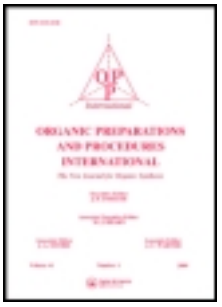

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THE PREPARATION OF 1-ALLYLURACIL. N(1)-ALKYLATION OF N(3)-PROTECTED URACIL DERIVATIVES

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THE PREPARATION OF 1-ALLYLURACIL. *N*(1)-ALKYLATION OF *N*(3)-PROTECTED URACIL DERIVATIVES

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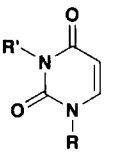
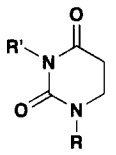
Acyclic and carbocyclic analogs of nucleosides have received a great deal of attention in recent years due to their potential use as antiviral and anticancer agents.[1] *N*-Allylated uracils are also known to possess significant biological activity.[2,3] Monoalkylation of uracil or thymine is most often not regioselective, *N*(1),*N*(3)-dialkylated products usually accompanying *N*(1)- or *N*(3)-monoalkyl derivatives.[4] Therefore the selective *N*(1)-alkylation of pyrimidine bases is of utmost importance. Since we required *N*(1)-allyluracil (**1**) for further synthetic elaboration, a high yield, inexpensive and selective method for its preparation was desired.

Allylation of uracil, thymine and cytosine with triallyl phosphite gave low yield of *N*(1)-allyl derivatives,[5] while the use of allyl bromide in basic solution led to a mixture of *N*(1)- and *N*(3)-monoallyl- and diallyl derivatives in low yield.[3,6] Pd(0)-catalyzed allylation of a thymine derivative with allyl acetate resulted in formation of *N*(1)-allyl and *N*(1),*N*(3)-diallyl derivative.[7] Regioselectivity of allylation was solvent and catalyst dependent.[8] Alkylation of 4-methylthio-5-fluoropyrimidin-2-one gave 65% yield of 1-allyl-5-fluorouracil.[9] 1-Allyluracil (**1**) was obtained by direct alkylation of uracil in 47% yield along with the 1,3-diallyl compound which could be removed by recrystallization.[10] With a bulky alkylating agent such as the adamantane derivative, regioselective *N*(1)-alkylation has been achieved under phase-transfer catalysis.[11] Selective *N*(3)-alkylation of *N*(1)-protected uracil has also been described.[12] When we attempted to alkylate uracil with allyl bromide-potassium carbonate in DMF solution[6] 1-allyluracil (**1**) could be isolated, albeit in low yield. The present communication describes an effective procedure for the selective *N*(1)-alkylation of uracil.



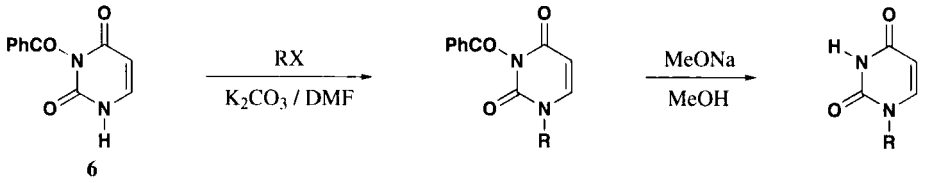
1 R =  , R' = H
2 R = R' = $C_6H_5CH_2$
3 R = H, R' = $CH_2C_6H_5$
4 R = $PhCH_2$, R' = H
5 R = R' = PhCO
6 R = H, R' = PhCO
7 R =  , R' = PhCO
8 R = Et, R' = PhCO
9 R = Et, R' = H
10 R = cyclopentyl, R' = PhCO
11 R = cyclopentyl, R' = H



12 R = R' = $PhCH_2$
13 R = $PhCH_2$, R' = H
14 R = H, R' = $PhCH_2$

N(3)-Protected uracil was considered for achieving selective *N*(1)-allylation. For this purpose, 3-benzyluracil (**3**) appeared to be an attractive substrate, as deprotection step following allylation would not require base or acid as catalyst. However, attempted benzylation of the *N*(3) in uracil failed. Reductive debenzylation of 1,3-dibenzyluracil[13] (**2**) in the presence of Pd(C) catalyst[14] gave a complicated mixture in spite of careful and extensive drying of the solvent and the catalyst. In addition the deprotection was accompanied by hydrogenation of the 5,6-double bond of **2**. Reaction of compound **2** with ammonium formate in methanol in the presence of Pd(C) catalyst gave a mixture of 3-benzyluracil (**3**) and 5,6-dihydro-1,3-dibenzyluracil (**12**) in varying proportions, depending on the method used for drying reagents and the solvent. The expected compound **3** was isolated in 28-43% yield and the dihydroderivative **12** in 39-50% yield. When the proportion of catalyst to substrate was increased to 2:1 by weight, the reaction mixture consisted of **3**, **12** and **13** in ratio 7:2:1. Compound **12** was isolated in each run despite the careful removal of traces of moisture. Therefore we checked the sensitivity of the reaction toward water. When three equivalents of H_2O were added in methanol, a complicated mixture containing the large proportion of the unreacted starting material was obtained. This mixture could be partially separated by chromatography. The presence of partially debenzylated and dihydro compounds was evidenced from the careful analysis of the ^1H NMR spectra; it showed signals characteristic for each component and the following compounds were identified: the substrate **2** (60%, δ 5.14 and 4.92), **3**[14] (5.0 %, δ 5.76 and 5.12), **4**[13] (0.5%, δ 4.70), **12**[15] (32%, δ 5.02), **13**[16] (0.5%, δ 4.62) and **14**[17] (1.5%, δ 4.90).

These difficulties prompted us to turn attention to 3-benzoyluracil (**6**). The reaction of uracil with benzoyl chloride in acetonitrile-pyridine mixture gives 1,3-dibenzoyluracil (**5**). Only the protective group at *N*(1) was removed under mild basic conditions,[18] a result which allows the selective alkylation of *N*(1) in 3-benzoyluracil (**6**).



6

R = allyl, ethyl, cyclopentyl

Alkylation of **6** with allyl bromide in DMF solution in the presence of potassium carbonate gave 3-benzoyl-1-allyluracil (**7**) in 79% yield. ^1H and ^{13}C NMR spectra of **7** showed all the expected, characteristic signals (see Experimental). Deprotection of **7** to give **1** was achieved by basic hydrolysis with sodium methoxide in methanol. 1-Allyluracil (**1**) showed all spectral data in accordance with literature.[10] A similar procedure was used for alkylation of 3-benzoyluracil with ethyl iodide to afford 1-ethyl-3-benzoyluracil (**8**) (80% yield) which, upon hydrolysis with strong base, gave 1-ethyluracil (**9**) [19] in 75% overall yield. Alkylation of the unprotected uracil with ethyl iodide under similar conditions has been reported to give both *N*(1)-ethyl and *N*(1),*N*(3)-diethyl derivatives.[13]

The alkylation of uracil and thymine with cyclopentanol derivatives under Mitsunobu conditions has been reported to result in *N*(1)- and *O*(2)-alkylation.[20,21] The proportion of the products and the yield changed with substituents on the cyclopentane ring. However, even in the case of the unsubstituted cyclopentanol, *N*- and *O*-alkylated products were formed in the ratio of 3:1.[21] Alkylation of 3-benzoyluracil (**6**) with cyclopentyl bromide gave compound **10** in 86 % yield. This was deprotected to give **11** in 95% yield. In contrast to the alkylation under Mitsunobu conditions, our procedure excludes the formation of *O*(2)-alkylated uracil.

Previously, 1-vinyl derivatives of uracil and thymine were obtained when alkylation was performed with 3-benzoyl protected substrates.[22] 3-Benzoyl derivatives of uracil and thymine also served as substrates in the synthesis of nucleoside analogs under Mitsunobu conditions.[23]

In summary, 3-benzoyluracil is an excellent substrate for the preparation of pure 1-alkylated uracils in high yield. The alkylation is effective in the case of primary and secondary alkyl halides.

EXPERIMENTAL SECTION

IR spectra were obtained as KBr pellets on a FT-IR Bruker IFS 113v Spectrometer. The ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ as solvent on a Varian 300 MHz instrument and the chemical shifts are reported with Me_4Si as an internal standard. The mass spectra were recorded on an AMD-402 mass spectrometer using ionization energy of 70 eV.

General Procedure for *N*(1)-Alkylation of 3-Benzoyluracil (6).- To a solution of **6** (216 mg, 1 mmol) in DMF (5 mL) was added K_2CO_3 (150 mg, 1.09 mmole). To this stirred mixture the alkyl halide (allyl bromide, ethyl iodide, cyclopentyl bromide, 1.2 eq.) was added and the mixture stirred at room temperature under argon for 1 to 4 days (t.l.c. control). The solvent was evaporated under reduced pressure and the residue was dissolved in chloroform or diethyl ether. The solution was

washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave the crude product which was chromatographed on a short SiO_2 column using chloroform as eluent.

1-Allyl-3-benzoyluracil (7) (79% yield): mp 90-93° (H_2O); ^1H NMR: δ 7.92-7.96 (m, 2H), 7.66 (m, 1H), 7.5 (m, 2H), 7.26 (d, J = 7,97 Hz, 1H), 5.87-5.97 (m, 1H), 5.84 (d, J = 7,97 Hz, 1H), 5.31-5.39 (m, 2H), 4.39 (dt, J_1 = 6 Hz, J_2=1,37 Hz, 2H); ^{13}C NMR: δ 168, 162, 149, 143, 135, 131, 130, 129, 120, 102, 50; IR: 3117, 3085, 2984, 2922, 1754,1700, 1661, 1623, 1596 cm^{-1}; *m/z:* 256, 228, 105, 77, 70, 51.

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62, H, 4.72, N, 10.93. Found C, 65.53, H, 4.84, N, 10.86

1-Ethyl-3-benzoyluracil (8) (80% yield): mp 108-110° (heptane); ^1H NMR: δ 7.92-7.96 (m, 2H), 7.63-7.68 (m, 1H), 7.41-7.48 (m, 2H), 7.27 (d, J_1 = 7.98 Hz, 1H), 5.82 (d, J = 8 Hz, 1H), 3.83 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93, H, 4.95, N, 11.47. Found C, 63.70, H, 5.02, N, 11.23

1-Cyclopentyl-3-benzoyluracil (10) (86% yield): mp 142-145° ($CHCl_3$);

^1H NMR: δ 7.96 (m, 2H), 7.66 (m, 1H), 7.54 (m, 2H), 7.33 (d, J=8.24 Hz, 1H,), 5.85 (d, J=8.24 Hz, 1H), 4.9 (m, 1H), 1.59-1.9 (m, 8H); ^{13}C NMR: δ 169, 162, 149, 140, 135, 131, 130, 129, 128, 126, 102, 57,32,32, 31, 24; IR: 3092, 2965, 2896, 1747, 1695, 1658, 1595 cm^{-1}; *m/z:* 284, 256, 189, 105, 77, 28.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59, H, 5.67, N, 9.85. Found C, 67.88, H, 5.67, N, 9.79

General Procedure for Hydrolysis of 1-Alkyl-3-benzoyluracil Derivatives.- To a solution of the substrate (200 mg) in methanol (2 mL) 0.5 M. solution of sodium methoxide in methanol (2 mL) was added and the mixture was stirred at room temperature for 24 h. The solution was neutralized by addition of Dowex 50 in small portions until pH ~ 7 was reached, filtered and evaporated to dryness. The residue was crystallized.

1-Allyluracil (1) (97% yield); mp 103-105° (benzene), *lit.*[3] mp 100-103°; ^1H NMR spectrum was identical with that of original sample and in accordance with the published[3,10] data.

1-Ethyluracil (9) (92% yield); mp 147-149° ($CHCl_3$), *lit.*[19] mp 144-146°; ^1H NMR spectrum in accordance with literature[19] data.

1-Cyclopentyluracil (11) (95% yield); mp. 176-178° (benzene); ^1H and ^{13}C NMR spectra were in accordance with published[21] data; IR: 2998, 2827, 2799, 1774, 1678, 1614 cm^{-1}; *m/z*: 181, 136, 113, 67, 68, 69, 41.

Debenzylation[14] of Compound 2.- Compound **2**[13] (200 mg, 0.68 mmole) was dissolved in 0.4 N solution of ammonium formate (17 mL) in methanol. The catalyst Pd/C (10%, 100 mg) was added and the mixture was refluxed for 6.5 h. The catalyst was filtered off and the filtrate evaporated. The residue was chromatographed on SiO_2 column to give **3** (38 mg, 28% yield) and **12** (100 mg, 50% yield). ^1H NMR spectra of **3** and **12** were in accordance with the published[14,15] data.

Similar debenzylation with 300 mg of the catalyst added gave a mixture of **3**, **12** and **13** in 7:2:1 ratio.

Debenzylation of Compound 2 in the Presence of H_2O (3 eq.).- Compound **2**[13] (200 mg, 0.68

mmole) was dissolved in 0.4 N solution of ammonium formate (17 mL) in dry methanol. The catalyst Pd/C (10%, 100 mg) and H_2O (40 µl) were added and the mixture was refluxed for 6.5 h. The catalyst was filtered off and the filtrate evaporated. The crude reaction product was partially separated on SiO_2 column. The following compounds: **2, 3, 4, 12, 13 and 14** were isolated or their presence was estimated on the basis of the ^1H NMR spectra (see above).

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CONVENIENT *N*-PROTECTION OF L-PYROGLUTAMIC ACID ESTERS†

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(01/17/01)

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Non-genetically coded pyroglutamic acid is an important component of many biological important natural peptides,[1] and *N*-protected-L-pyroglutamic acid esters are important substrates for the synthesis of non-proteinogenic amino acids, natural products, and γ-homologation reactions.[2-5] Direct syntheses of these compounds from pyroglutamic acid esters without significant racemization is an arduous task. Therefore, *N*-benzyloxycarbonyl-L-pyroglutamic acid is consistently prepared by the classical old method of ring cyclization of benzyloxycarbonyl-L-glutamic acid.[6] Furthermore, there is only one example of direct introduction of benzyloxycarbonyl (Z) group at the ring-nitrogen of pyroglutamic acid.[7] However, when attempted in our laboratory, the method proved inadequate with substantial racemization of the product. Additionally, the use of the method fails to introduce *tert*-butoxycarbonyl (*t*-Boc) group directly at the nitrogen of pyroglutamic acid esters. Kikugawa *et al.*[8] reported recently the use of LiHMDS in THF at -78° to prepare Z, *t*-Boc, and other functional groups protected L-pyroglutamic acid esters. However, the method is ineffective on a preparative scale due to complicated reaction conditions, and the use of low temperature. Hence, there is a need to develop methodologies suitable for large-scale synthesis without much difficulty and racemization of the product. A literature survey revealed that, Grieco *et al.*[9] have used molar equivalents of di-*tert*-