A new method for the synthesis of *N*-phenyl-uracil and -pyrimidine nucleosides

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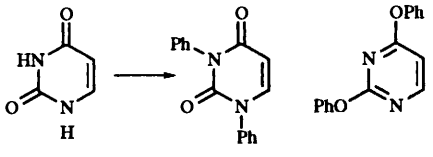
Reaction of uracil or pyrimidine nucleosides with iodobenzene in the presence of cuprous oxide in 2,4,6-trimethylpyridine for 20 h gave N^1,N^3-diphenyluracil **1** or N^3-phenylpyrimidine nucleosides **4**, **7**. The identity of these products were confirmed by comparison of their physical and spectroscopic data with those of 2,4-diphenoxypyrimidine **2** or 4-phenoxypyrimidin-2(1*H*)-one nucleoside **5b**.

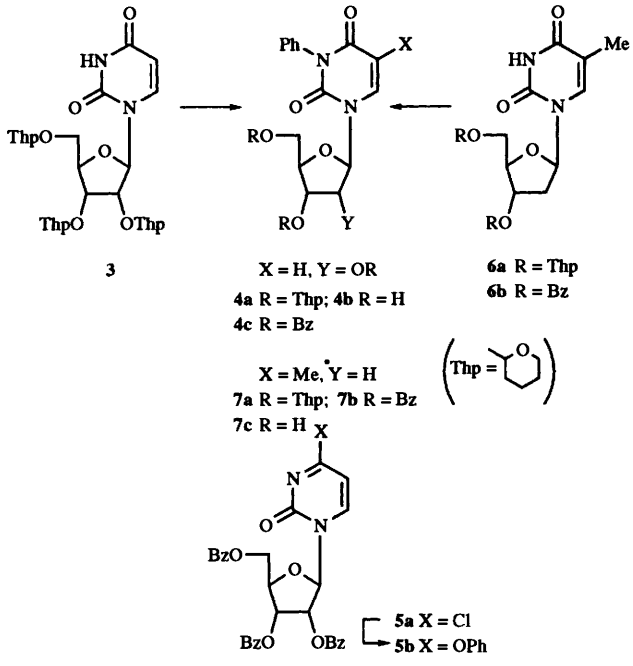
Although *N*-alkylation of nucleosides has been described, *N*-arylation has not, apart from a single report in which 3-phenylpyrimidine-2,4-diones were prepared as pesticides.[2] Since introduction of an aryl group directly onto a nucleobase would constitute an important development in nucleoside chemistry, we have investigated the synthesis of *N*-arylpyrimidine nucleosides. The chemical nature of the NH in uracil being similar to that of phthalimide we chose a method similar to that of the Gabriel synthesis[3,4] for the synthesis of *N*-aryluracil.

Uracil was heated under reflux with iodobenzene in the presence of Cu_2O in 2,4,6-trimethylpyridine (bp 171 °C) for 20 h to give N^1,N^3-diphenyluracil **1** (37%), the IR spectrum of which



1 **2**

showed strong absorption at 1718 cm^{-1}, suggesting the presence of an amido carbonyl group and excluding an *O*-phenyl structure. This was substantiated by comparison of physical and spectroscopic data of the compound with those of 2,4-diphenoxypyrimidine **2** (mp 114 °C[5,6]). The mechanism was explained in terms of *N*H deprotonation by 2,4,6-trimethylpyridine and subsequent nucleophilic attack of iodobenzene by the uracil ion. Attempted application of this method to unprotected uridine was unsuccessful as it was with tri-*O*-benzoyluridine, starting material alone being recovered. However, treatment of 2,3,5-tri-*O*-(tetrahydropyran-2-yl)-uridine **3**[7] gave the N^3-phenyl derivative **4a** (52%) and recovered **3** (16%). These results suggest that the electron-density at N^3 is important for phenylation of uridine derivatives. Deprotection of **4a** with pyridinium toluene-*p*-sulfonate (PPTS) afforded N^3-phenyluridine **4b**, the first *N*-aryl substituted nucleoside. Benzoylation of **4b** gave the tri-*O*-benzoyl derivative **4c** and 4-phenoxypyrimidin-2(1*H*)-one **5b** was prepared from the 4-chloro congener **5a**. The lack of identity between **4c** and **5b** ruled out the *O*-phenyl structure of **4a**. The reactivity towards iodobenzene as a result of the protecting group was reversed in thymidine. Although N^3-phenylation of 3,5-di-*O*-(tetrahydropyran-2-yl)thymidine **6a** gave **7a** in only low yield (7%), 3,5-di-*O*-benzoylthymidine **6b** provided **7b** in improved yield (42%). This difference may be explained as follows. The electron-donating properties of 5-methyl and 2'-methylene make N^3 of thymidine electron-rich, an effect which decreases the acidity of N^3-H and hence makes removal of the proton difficult. Acid treatment of **7a** or alkaline hydrolysis of **7b** gave the N^3-phenylthymidine **7c**.



Since this is the first method to introduce a phenyl group at N^1 and N^3 of uracil or at N^3 of pyrimidine nucleosides, it is likely to be of use in nucleoside chemistry particularly so since it is capable of development.

Experimental

General procedure

A suspension of uracil, **3**, **6a** or **6b** (5.0 mmol) and cuprous oxide (715 mg, 5.0 mmol) in a mixture solution of 2,4,6-trimethylpyridine (10 cm^3) and iodobenzene (2.8 cm^3, 25 mmol) was heated under reflux for 20 h to give a brownish solution. This was diluted with CH_2Cl_2 (200 cm^3) and then filtered. The filtrate was washed with 10% aqueous AcOH 4 times (400 cm^3) and water twice (200 cm^3), dried ($MgSO_4$) and concentrated. The solution was chromatographed on a column of silica gel G (3.0 × 30 cm) to give **1**, **4a**, **7a** or **7b**, respectively, the yields for which are given in Table 1. Deprotection of the nucleoside products gave the *N*-phenylpyrimidine nucleosides **4b**, **7c**.

Selected data for **1**: mp 207–210 °C (Found: C, 72.6; H, 4.6; N, 10.5. $C_{16}H_{12}N_2O_2$ requires C, 72.72; H, 4.58; N, 10.60%); *m/z* 264 (M^+); λ_{max}(MeOH)/nm 216 and 271; δ_H($CDCl_3$) 7.2–7.6 (*ca.* 11 H, m, 6-H, N^1-C_6H_5, N^3-C_6H_5), 5.98 (1 H, d, *J* 8.0, 5-H); ν_{max}/cm^{-1} 3391.16, 3092.17, 1718.73, 1678.22 and 1595.27.

2,4-Diphenoxyuracil **2** was prepared by the known method:[5]

Table 1 Reaction of uracil or pyrimidine nucleosides with iodobenzene in 2,4,6-trimethylcollidine in the presence of Cu_2O.

Nucleosides (or uracil)	Yields: *N*-Phenyl derivatives (%)	Yields: Starting material recovered (%)
Uracil	**1** (37)	—
3	**4a** (52)	16
6a	**7a** (7)	36
6b	**7b** (42)	16

$\delta_H(CDCl_3)$ 8.32 (1 H, d, *J* 5.3, 6-H), 6.9–7.5 (*ca.* 10 H, m, N^1-C_6H_5, N^3-C_6H_5) and 6.54 (1 H, d, *J* 5.3, 5-H).

For **4b**: mp 203–205 °C (Found: C, 55.5; H, 5.1; N, 8.55. $C_{15}H_{16}N_2O_6 \cdot \frac{1}{4}H_2O$ requires C, 55.47; H, 5.12; N, 8.62%); *m/z* 320 (M^+); λ_{max}(MeOH)/nm 218 and 264; δ_H([$^2H_6$]-DMSO) 8.07 (1 H, d, *J* 8.5, 6-H), 7.15–7.5 (5 H, m, N^3-C_6H_5), 5.87 (1 H, d, *J* 8.5, 5-H), 5.78 (1 H, d, *J* 5.2, 1′-H), 5.40 (1 H, br s, 2′-OH), 5.15 (2 H, br s, 3′-OH, 5′-OH), 4.10 (1 H, t, *J* 5.2, 2′-H), 3.99 (1 H, t, *J* 4.7, 3′-H), 3.86 (1 H, m, 4′-H) and 3.62 (2 H, m, 5′-H).

N^3-Phenyl-2′,3′,5′-tri-*O*-benzoyluridine **4c** was prepared by benzoylation of **4b** in 79% yield as a foam; λ_{max}(MeOH)/nm 240 and 258; $\delta_H(CDCl_3)$ 8.10 (1 H, d, *J* 8.1, 6-H), 8.15–7.15 (*ca.* 20 H, complex, N^3-C_6H_5, OCOBz × 3), 6.24 (1 H, d, *J* 4.5, 1′-H), 5.92 (1 H, t, *J* 4.8, 3′-H), 5.87 (1 H, t, *J* 8.2, 2′-H), 5.79 (1 H, d, *J* 8.2, 5-H), 4.86 (1 H, dd, *J* 11.7, 2.0, 5′a-H), 4.73 (1 H, m, 4′-H) and 4.67 (1 H, *J* 11.7, 3.6, 5′b-H).

For **7c**: mp 209–210 °C (Found: C, 59.65; H, 5.7; N, 8.6. $C_{16}H_{18}N_2O_5 \cdot \frac{1}{5}H_2O$ requires C, 59.69; H, 5.76; N, 8.70%); λ_{max}(MeOH)/nm 214 and 267; *m/z* 318 (M^+); δ_H([$^2H_6$]-DMSO) 7.88 (1 H, s, 6-H), 7.2–7.5 (5 H, m, N^3-C_6H_5), 6.19 (1 H, t, *J* 6.8, 1′-H), 5.25 (1 H, d, *J* 4.2, 3′-OH), 5.08 (1 H, t, *J* 5.1, 5′-OH), 4.27 (1 H, m, 3′-H), 3.79 (1 H, q, *J* 3.5, 4′-H), 3.64 (1 H, m, 5′a-H), 3.58 (1 H, m, 5′b-H), 2.51 (3 H, s, CH_3), 2.19 (1 H, m, 2′a-H) and 2.11 (1 H, m, 2′b-H).

4-Phenoxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidin-2(1*H*)-one 5b

Sodium hydride (60% in oil; 800 mg, 20 mmol) was added to a solution of phenol (2.35 g, 25 mmol) in DMF (15 cm^3) and the mixture stirred for 10 min at room temperature. 4-Chloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **5a** (2.85 g, 5.0 mmol) was then added to the mixture which after being stirred for 1 h at room temperature was subjected to work-up. Crystallization of the product from MeOH gave white crystals (2.76 g, 88%), mp 126–132 °C; λ_{max}(MeOH)/nm 232 and 274; $\delta_H(CDCl_3)$ 8.11 (1 H, d, *J* 7.1, 6-H), 7.1–8.0 (*ca.* 20 H, complex, 4-OC_6H_5, OCOBz × 3), 6.43 (1 H, d, *J* 4.7, 1′-H), 6.00 (1 H, d, *J* 7.1, 5-H), 5.91 (1 H, t, *J* 5.3, 3′-H), 5.78 (1 H, t, *J* 5.2, 2′-H), 4.87 (1 H, dd, *J* 11.3, 2.0, 5′a-H), 4.76 (1 H, m, 4′-H) and 4.69 (1 H, dd, *J* 11.3, 4.0, 5′b-H).

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References

1 D. M. Brown, *Basic Principles in Nucleic Acid Chemistry*, ed. P. O. P. Ts'o, Academic Press, New York, 1974, p. 17.
2 S. Ishii, K. Nakayama, K. Yagi, J. Satow, K. Fukuda, K. Itoh, T. Umehara, M. Kudo and T. Nawamaki, Eur. Pat. Appl. EP 438,209 (Cl. C07D239/54), 24 July 1991, JP Appl. 90/8,826, 18 January 1990.
3 S. Gabriel, *Chem. Ber.*, 1887, **20**, 2224.
4 M. Sato and S. Ebine, *Synthesis*, 1981, 472.
5 T. Jojima and S. Tamura, *Agric. Biol. Chem.*, 1966, **30**, 896.
6 D. Ghosh and M. Mukherjee, *J. Org. Chem.*, 1968, **11**, 1237.
7 M. Honjo, T. Maruyama, M. Horikawa, J. Balzarini and E. De Clercq, *Chem. Pharm. Bull.*, 1987, **35**, 3227.

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