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A novel chemical modification at the 5-position of uridine derivatives

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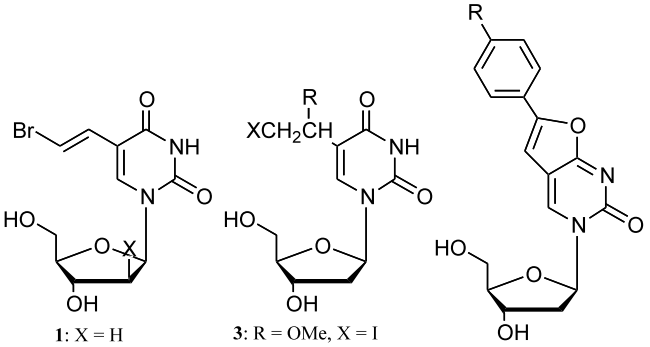
Abstract—A novel chemical modification was achieved at the 5-position of 2′,3′-*O*-isopropylideneuridine (**6**) in a one-pot procedure and a remarkable effect of the base on the progress of the reaction was found.

Various modified nucleosides in the base moiety have become important components of both chemotherapeutic agents, as potential antimetabolites,[1] and synthetic oligonucleotide probes.[2] A broad spectrum of antiviral activity has been described for 5-substituted pyrimidine nucleosides.[1] For example, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU, **1**) and (*E*)-5-(2-bromovinyl)-β-D-arabinofuranosyluracil (sorivudine, **2**) have been found to exhibit potent anti-HSV-1 and/or anti-VZV virus activity.[2] Furthermore, Kumar et al.[3] reported that 5-(1-substituted-2-haloethyl)-2′-deoxyuridine (**3**, **4**) exhibited a broad spectrum of antiviral activity against HSV-1, HSV-2, VZV and EBV. Recently, novel furo-fused pyrimidine nucleosides (**5**) were found to exhibit excellent antiviral activity against VZV.[4]



Although many approaches to the direct introduction of a carbon-unit at the 5-position of uridine have appeared in the literature,[5,6] much more efficient and convenient synthetic methods of 5-substituted uridine derivatives are still of particular interest in terms of new drug development. We describe herein a novel C–C bond formation reaction at the 5-position of uridine derivatives to give the 5-(α-hydroxybenzyl)uridines.

First of all, a mixture of 2′,3′-*O*-isopropylideneuridine (**6**), benzaldehyde (10 equiv.), and KOH (1.0 equiv.) in H_2O was heated for 24 h at 50°C to afford trace quantities of 5-α-hydroxybenzyl-2′,3′-*O*-isopropylideneuridine (**7a**, entry 1 in Table 1) as a diastereo mixture. This coupling reaction of **6** and benzaldehyde proceeded much more smoothly in the presence of a small amount of Aliquat® as a phase transfer catalyst, and **7a** was obtained in 29% yield as a diastereo mixture after chromatographic purification of the crude mixture (entry 2 in Table 1). To explore this coupling reaction, some bases were examined as an additive (Table 1). Although pyridine, a relatively weak base, did not indicate any significant effect on the reaction (entry 3), K_2CO_3, Et_3N, $^iPr_2NEt$ and DMAP gave better yields (69–78%, entries 4–7). Upon employment of a 1,2-ambident tertiary amine, DABCO, the coupling reaction was dramatically improved (93% isolated yield as a diastereo mixture, entry 8).[7,8]

On the basis of the preliminary information, various types of aldehydes were subjected to the present coupling reaction in the presence of 1.0 equiv. of DABCO. Selected results are summarized in Table 2. The reactivity of aldehydes for this reaction was significantly affected by the structure and electronic properties. Electronically neutral and electron-deficient aromatic alde-

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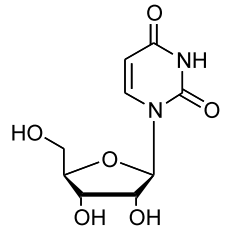
Table 1. Base-catalyzed 5-α-hydroxybenzylation of **6** using various bases



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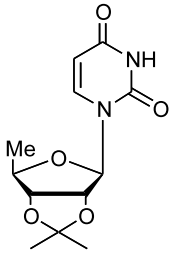

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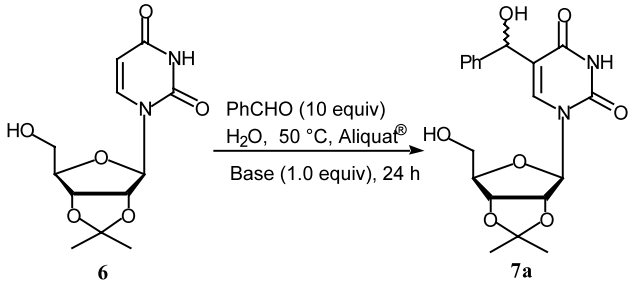
Entry	Base	Yield (%)[a]
1	KOH	Trace[b]
2	KOH	29
3	Pyridine	4
4	K_2CO_3	70
5	Et_3N	79
6	$^iPr_2NEt$	69
7	DMAP	78
8	DABCO	93
9	None	0

[a] Isolated yield.
[b] Without Aliquat®.

hydes (entries 1–5, 9, and 10) could be cleanly and smoothly coupled with the isopropylideneuridine (**6**). For electron-rich aromatic aldehydes (entries 6–8, and 11) and an alkyl aldehyde (entry 12), the desired coupling reaction was less straightforward. Subsequent screening of the reaction conditions revealed that elongation of the reaction time of some electron-rich aromatic aldehydes could be efficiently carried out (entries 6–8, and 11). However, application of the present coupling reaction to butyraldehyde, an alkylaldehyde, did not give any exciting results (entry 12).

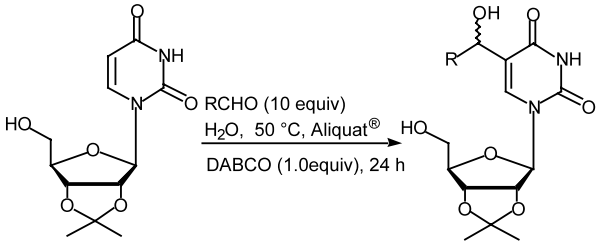
The coupling reaction of uridine (**8**), which possesses no isopropylidene protective group, with benzaldehyde under similar conditions resulted in almost no reaction. Furthermore, the use of 5′-deoxy-2′,3′-*O*-isopropylideneuridine (**9**), which has no hydroxy group at the 5′-position, also led to completely no reaction.



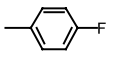
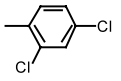
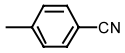
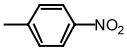
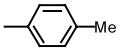
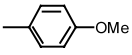
6 **7a**

These facts suggest that the neighboring-group participation of the 5′-hydroxy group of 2′,3′-*O*-isopropylidene-protected ribose significantly facilitates the nucleophilic attack toward the C6-position of the uracil nucleus as shown in our former paper.[9] Taking the above facts into consideration, a plausible reaction sequence for the present coupling reaction is outlined in Scheme 1. An initial nucleophilic attack at the 6-position of the uracil ring by the 5′-hydroxy group that was activated by DABCO could give rise to an adduct **10**

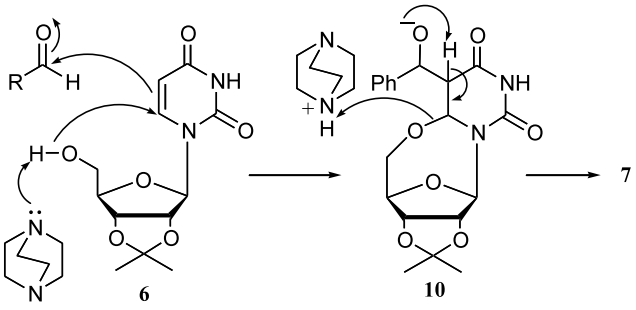
Table 2. DABCO-catalyzed 5-hydroxyalkylation of **6** using various aldehydes



6 **7a-l**

Entry	R	Product	Yield (%)[a]
1	Ph	**7a**	93
2		**7b**	84
3		**7c**	86
4		**7d**	95
5		**7e**	89
6		**7f**	83[b]
7		**7g**	64[c,d]
8		**7h**	47 (87)[e]
9		**7i**	67
10		**7j**	70
11		**7k**	84[f,g]
12	Pr	**7l**	23

[a] Isolated yield. [b] The period of the reaction was extended to 4 days. [c] The period of the reaction was extended to 8 days. [d] 15 equivalents of *o*-anisaldehyde were used. [e] The period of the reaction in parentheses was extended to 3 days. [f] The period of the reaction was extended to 2 days. [g] Because of the lability of 2-furaldehyde, the aldehyde was added in part.



6 **10** **7**

Scheme 1. Plausible reaction mechanism.

and the following ring-opening reaction gives **7**. The present reaction seems like an intramolecular base-catalyzed Baylis–Hillman reaction.[10] Although numerous examples of Baylis–Hillman-type reaction for aldehydes with electron-deficient olefins are reported, a general and intramolecular base-catalyzed procedure for nucleic acids has not been established. Therefore, the present coupling demonstrates sufficient usefulness in nucleic acid chemistry. It discloses a new α-hydroxybenzylation at the 5-position of uridine derivatives under mild conditions.

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7. *Representative procedure*: A mixture of 2′,3′-*O*-isopropylideneuridine (**6**, 100 mg, 0.53 mmol), benzaldehyde (0.36 ml, 5.30 mmol), DABCO (39 mg, 0.53 mmol) and Aliquat® (30 μL) in H_2O (1.1 mL) was stirred under Ar atmosphere at 50°C for 24 h. The resulting mixture was partitioned between AcOEt (10 mL) and H_2O (10 mL) and the organic layer was washed with H_2O (3×10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by flash silica gel column chromatography ($CHCl_3$) to give analytically pure 5-α-hydroxybenzyl-2′,3′-*O*-isopropylideneuridine (**7a**, 127 mg, 93%) as a diastereo-mixture. Mp 98–101°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 and 1.54 (each s, 3H), 2.33 (br, 1H, deuterium exchangeable), 3.67–3.70 (m, 2H), 3.79 (br, 1H, deuterium exchangeable), 4.23–4.24 (m, 1H), 4.80–4.88 (m, 2H), 5.61 (dd, 1H, J=2.9 and 9.7 Hz), 5.78 (d, J=6.4 Hz), 7.18 (s, 6H), 7.33–7.43 (m, 5H), 9.04 (br, 1H, deuterium exchangeable); ^{13}C NMR (100 MHz, CD_3OD): δ 25.2, 27.2, 62.6, 69.2, 80.4, 80.5, 84.1, 84.2, 86.8, 95.2, 114.2, 114.3, 117.5, 126.5, 128.1, 128.6, 140.0, 140.4, 150.0, 163.3; MS (EI): 390 (M^+); HRMS (EI) calcd for $C_{19}H_{22}N_2O_7$: 390.1426. Found: 390.1418. Anal. calcd. for $C_{19}H_{22}N_2O_7 \cdot 1/3H_2O$: C, 57.57; H, 5.76; N, 7.07. Found: C, 57.77; H, 5.89; N, 7.07%.
8. Deprotection of the 5-α-hydroxyalkyl-2′,3′-*O*-isopropylideneuridines (**7**) prepared here was performed in 80% AcOH aqueous solution at 80°C.
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