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Note

One step selective 5′-*O*-allylation of thymidine using microwave or ultrasound activation

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Abstract—An improved procedures for the synthesis of 5′-*O*-allylthymidine via one step selective allylation of thymidine using either ultrasound or microwave activation is described.

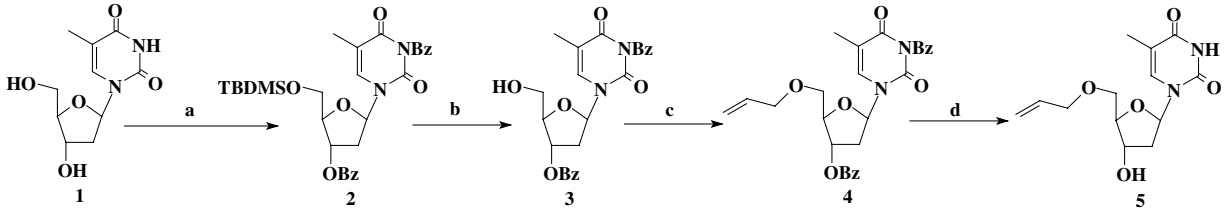
Keywords: Selective allylation; Thymidine; Nucleoside; Ultrasound; Microwave

We recently described the homodimerization of a 3′-*C*-allyl derivative of thymidine.[1] As part of this programme, we became interested in the preparation of 5′-*O*-allylthymidine. According to classical methods, 5′-*O*-substituted deoxynucleosides are obtained in several steps starting from the corresponding deoxynucleosides.[2] The first step involves protection of the 5′ primary hydroxyl group using selective silylation (TBDMS or TBDPS) or tritylation. In a second step, the 3′-hydroxyl group is protected and the 5′ protecting group then removed in order to introduce the desired modification.

In our hands, 5′-*O*-allylthymidine was prepared as follows (Scheme 1). Thymidine **1** and *tert*-butyldimethylsilyl chloride[3] in dry pyridine were stirred overnight, then benzoyl chloride and 4-dimethylaminopyridine (DMAP) were added and the reaction mixture was stirred for 28 h. The silylated group was then removed by treatment with carbon tetrabromide[4] in dry methanol to afford **3**, which was then converted into **4** by *O*-allylation of the C-5′ hydroxyl group with NaH and allyl bromide in DMF. Deacylation of **4,** carried out in methanolic ammonia at room temperature, gave **5**.

Thymidine was thus converted in four steps to 5′-*O*-allylthymidine in 42.4% overall yield.

To minimize the steps and maximize the overall efficiency of our strategy, we decided to examine the direct allylation of thymidine without prior protection (Scheme 2).



Scheme 1. Reagents and conditions: (a) (1) TBDMSCl (1.05 equiv), dry pyridine, overnight; (2) BzCl (6 equiv), DMAP (1.5 equiv), 28 h; (b) CBr_4 (0.1 equiv), dry MeOH, reflux, 1.5 h; (c) (1) NaH (1.2 equiv), dry DMF, 30 min, (2) $BrCH_2CH{=}CH_2$ (2 equiv), 1 h; (d) NH_3/MeOH (7 M), rt, 2 days.

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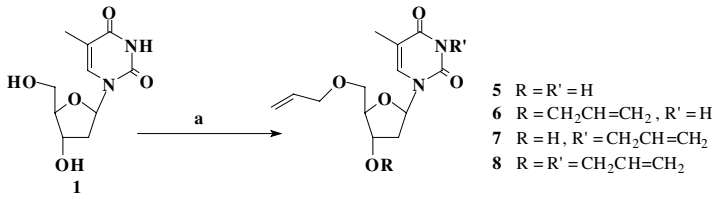

Scheme 2. Reagents and conditions: (a) (1) NaH (1.15 equiv), dry DMF;))) or MW (100 W); (2) $BrCH_2CH{=}CH_2$ (1.2 equiv),))) or MW (100 W).

Table 1. Selected results of direct 5′-*O*-allylation of **1**: influence of the activation method

Entry	Activation[a]	Reaction time first step/second step	**5**[b] (%)	**6**[b] (%)	**7**[b] (%)	**8**[b] (%)
1	Classical stirring	30 min/4 h	75	10	5	5
2	Ultrasound	30 min/4 h	93	—	—	—
3	Microwave	2 min/2 min	97	—	—	—

[a] Conditions: (1) first step: NaH (1.15 equiv), dry DMF, activation; (2) second step: $BrCH_2CH{=}CH_2$ (1.2 equiv), activation.
[b] Yield after purification.

Selected results of direct 5′-*O*-allylation of thymidine are summarized in Table 1. Our initial studies, which traditionally used NaH and allyl bromide in DMF at room temperature, resulted in the formation of **5** together with 3′,5′-bis(allylated) thymidine **6**, 3,5′-bis(allylated) thymidine **7** and 3,3′,5′-tris(allylated) thymidine **8** (Table 1, entry 1). The effect of various activation modes was studied. Using ultrasonication,[5] the reaction gave 5′-*O*-allylthymidine (**5**) in 93% yield without secondary product (Table 1, entry 2). The best result was obtained with microwave activation (Table 1, entry 3). The product was obtained in quantitative yield with a dramatic decrease in reaction times (4 min). It displayed physical characteristics strictly identical to those of **5** obtained according to the classical method in Scheme 1.

1. Experimental

1.1. General methods and equipments

Microwave irradiation was performed in a monomode reactor (MicroSYNTH from Milestone) with focused waves ($T = 40\,°C$, $P = 100$ W). Sonication was performed in a LEO-80 ultrasonic cleaner with a frequency of 46 kHz and a power of 30 W. Analytical TLC was performed on E. Merck aluminium precoated Silica Gel 60 F_{254} sheets, with detection by UV and also by spraying with H_2SO_4 (6 N) and heating to 200 °C. Silica Gel (E. Merck Kieselgel 60, 15–40 μm) was used for flash chromatography. ^1H NMR spectra were recorded using a Bruker DPX-400 spectrometer for solutions in $CDCl_3$ or CD_3OD with tetramethylsilane as internal standard. The chemical shifts are given in ppm and coupling constants are in Hertz. Elemental analyses were carried out by the Microanalytical Service of the University Pierre et Marie Curie (Paris VI). Optical rotation was measured with a Jasco (DIP-370) polarimeter in a 1 dm quartz cell at 22 °C.

1.2. Di-*N*-3,*O*-3′-benzoyl-5′-*O*-*tert*-butyldimethylsilyl-thymidine (2)

To a soln of thymidine (1.5 g, 6.19 mmol) in dry pyridine (25 mL) was added 1.05 equiv of TBDMSCl (0.980 g, 6.50 mmol) and the reaction was stirred at room temperature overnight. DMAP (1.13 g, 9.28 mmol) and benzoyl chloride (4.21 mL, 37.14 mmol) were then added. After 28 h stirring at room temperature, the mixture was diluted with $CHCl_3$, neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3×20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed. The residue was purified by chromatography over silica gel (toluene–EtOAc) to give **2** as a foam (2.897 g, 83%); R_f 0.55 (4:1, toluene–EtOAc); ^1H NMR ($CDCl_3$): *thymine* 7.72 (q, 1-H, J_{H_6,CH_3} 1.0 Hz, H-6), 1.98 (d, 3H, CH_3); *dRib*: 6.49 (dd, 1-H, $J_{1',2'a}$ 5.2 Hz, $J_{1',2'b}$ 9.3 Hz, H-1′), 5.52 (m, 1-H, H-3′), 4.28 (m, 1-H, H-4′), 4.04 (dd, 1-H, $J_{5'a,5'b}$ 11.4, $J_{5'a,4'}$ 2.0 Hz, H-5′$_a$), 4.02 (dd, 1-H, $J_{5'b,5'a}$ 11.4 Hz, $J_{5'b,4'}$ 2.0 Hz, H-5′$_b$), 2.42 (ddd, 1-H, $J_{2'a,3'}$ 3.6 Hz, $J_{2'a,1'}$ 5.2 Hz, $J_{2'b,2'a}$ 13.8 Hz, H-2′$_a$), 2.09 (ddd, 1-H, $J_{2'b,1'}$ 9.3 Hz, $J_{2'b,3'}$ 6.1 Hz, H-2′$_b$); *protecting groups*: 0.20 (s, 6H, CH_3-Si), 0.99 (s, 9H, CH_3, *t*-Bu), 7.17–8.02 (m, 10H, H-Ar).

1.3. Di-*N*-3,*O*-3′-benzoylthymidine (3)

To a soln of **2** (1.746 g, 3.096 mmol) in dry MeOH (25 mL) was added CBr_4 (0.105 g, 0.310 mmol).The reaction mixture was heated at reflux for 1.5 h. The solvent was then removed and the crude residue purified on a silica gel column ($CHCl_3$–EtOH) yielding **3** as a foam (1.226 g, 88%); R_f 0.47 (95:5, $CHCl_3$–EtOH);

^{1}H NMR (CD_3OD): *thymine* 8.09 (q, 1-H, J_{H_6,CH_3} 0.8 Hz, H-6), 1.96 (d, 3H, CH_3); *dRib*: 6.39 (dd, 1-H, $J_{1',2'a}$ 6.4 Hz, $J_{1',2'b}$ 7.9 Hz, H-1′), 5.59 (dt, 1-H, $J_{2'a,3'}$ 2.7 Hz, $J_{2'b,3'}$ 5.4 Hz, $J_{4',3'}$ 2.7 Hz, H-3′), 4.26 (q, 1-H, J 2.7 Hz, H-4′), 3.93 (dd, 1-H $J_{5'b,5'a}$ 12.1 Hz, $J_{5'b,4'}$ 2.7 Hz, H-5′$_b$), 3.90 (dd, 1-H, $J_{5'a,4'}$ 2.7 Hz, H-5′$_a$), 2.59 (ddd, 1-H, $J_{2'a,2'b}$ 14.3 Hz, H-2′$_a$), 2.55 (ddd, 1-H, $J_{2'b,3'}$ 5.4 Hz, H-2′$_b$). *Benzoyl groups*: 7.48–8.04 (m, 10 H, H-Ar).

1.4. Di-*N*-3,*O*-3′-benzoyl-5′-*O*-allylthymidine (4)

To a soln of **3** (1.267 g, 2.81 mmol) in dry DMF, was added NaH (60%, 135 mg, 3.378 mmol) and the mixture was stirred for 30 min under Ar. Allyl bromide (487 μL, 5.62 mmol) was then added to the mixture and stirring was continued for 1 h. The reaction mixture was evaporated and after usual work up, the residue was purified on a silica gel column to give **4** as a viscous oil (0.963 g, 70%); R_f 0.50 (95:5, $CHCl_3$–EtOH); ^{1}H NMR ($CDCl_3$, δ): *thymine* 7.85 (q, 1-H, J_{H_6,CH_3} 1.0 Hz, H-6), 1.66 (d, 3H, CH_3); *dRib*: 6.51 (dd, 1-H, $J_{1',2'a}$ 5.4 Hz, $J_{1',2'b}$ 8.7 Hz, H-1′), 5.65 (dt, 1-H, $J_{2'a,3'}$ 1.6Hz, $J_{2'b,3'}$ 6.6 Hz, $J_{4',3'}$ 1.6 Hz, H-3′), 4.80 (dd, 1-H $J_{5'b,5'a}$ 12.2 Hz, $J_{5'b,4'}$ 3.0 Hz, H-5′$_b$), 4.68 (dd, 1-H, $J_{5'a,4'}$ 3.5 Hz, H-5′$_a$), 4.54 (m, 1-H, H-4′), 2.72 (ddd, 1-H, $J_{2'a,2'b}$ 14.0 Hz, H-2′$_a$), 2.20 (ddd, 1-H, H-2′$_b$); *allyl group*: 5.86 (ddt, 1-H, $J_{\beta,\gamma}$ 10.3 Hz, $J_{\beta,\gamma'}$ 17.2 Hz, $J_{\beta,\alpha}$ 5.9 Hz, H-β), 5.25 (dd, 1-H, $J_{\gamma,\gamma'}$ 1.3 Hz, H-γ′), 5.13 (dd, 1-H, H-γ), 4.54 (m, 2H, H-α). *Benzoyl groups*: 7.48–8.05 (m, 10 H, H-Ar).

1.5. 5′-*O*-Allylthymidine (5)

Compound **4** (0.705 g, 1.438 mmol) was dissolved in MeOH (10 mL) and a soln of ammonia in MeOH (7 M, 20 mL) was added. After 2 days at room temperature, the soln was evaporated and the crude product was purified using preparative TLC (9:1, CH_2Cl_2–EtOH) yielding **5** as a white solid (0.336 mg, 83%); $[\alpha]_D^{25}$ +27.96 (*c* 0.8, EtOH); mp 97 °C; R_f 0.45 (9:1, $CHCl_3$–EtOH); ^{1}H NMR (CD_3OD): *thymine* 7.85 (q, 1-H, J_{H_6,CH_3} 1.0 Hz, H-6), 1.91 (d, 3H, CH_3); *dRib*: 6.30 (t, 1-H, $J_{1',2'}$ 6.8 Hz, H-1′), 4.39 (dt, 1-H, $J_{3',4'}$ 3.5 Hz, $J_{2'a,3'}$ 3.5 Hz,, $J_{2'b,3'}$ 6.4 Hz, H-3′), 3.91 (q, 1-H, $J_{4',5'}$ 3.5 Hz, H-4′), 3.80 (dd, 1-H $J_{5'b,5'a}$ 12.0 Hz, H-5′$_b$), 3.72 (dd, 1-H, H-5′$_a$), 2.27 (ddd, 1-H, $J_{2'a,2'b}$ 13.7 Hz, H-2′$_b$), 2.20 (ddd, 1-H, H-2′$_a$); *allyl group*: 5.86 (ddt, 1-H, $J_{\beta,\gamma}$ 10.4 Hz, $J_{\beta,\gamma'}$ 17 Hz, $J_{\beta,\alpha}$ 5.6 Hz, H-β), 5.16 (dq, 1-H, H-γ′), 5.12 (dq, 1-H, H-γ), 4.51 (dt, 2H, $J_{\alpha,\beta}$ 5.6 Hz, $J_{\alpha,\gamma}$ 1.4 Hz, H-α). Anal. Calcd for $C_{13}H_{18}O_5N_2$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.36; H, 6.39; N, 9.87.

1.6. 5′-*O*-Allylthymidine (5) via direct allylation

To a soln of thymidine (300 mg, 1.24 mmol) in dry DMF (10 mL) was added NaH (60%, 57 mg, 1.425 mmol) and the mixture was stirred and irradiated (first step, see Table 1) under argon. Allyl bromide (0.129 mL, 1.49 mmol) was then added and the reaction mixture was stirred and irradiated (second step, see Table 1). After removal of the solvent, the syrup was purified on a silica gel column yielding **5** as a white solid (yields in Table 1). This product displayed physical characteristics strictly identical to those of **5** obtained according to the four steps sequence in Scheme 1.

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