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Bromination at C-5 of pyrimidine and C-8 of purine nucleosides with 1,3-dibromo-5,5-dimethylhydantoin

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ABSTRACT

Treatment of the protected and unprotected nucleosides with 1,3-dibromo-5,5-dimethylhydantoin in aprotic solvents such as CH_2Cl_2, CH_3CN, or DMF effected smooth bromination of uridine and cytidine derivatives at C-5 of pyrimidine rings as well as adenosine and guanosine derivatives at C-8 of purine rings. Addition of Lewis acids such as trimethylsilyl trifluoromethanesulfonate enhanced the efficiency of bromination.

Halogen-substituted nucleosides and especially uracil derivatives substituted at C-5 and adenine derivatives substituted at C-8 with bromine have been shown to possess interesting synthetic and biological properties.[1,2] The halogenated C-5 pyrimidine and C-8 purine nucleosides are often used in the reactions involving direct displacement with nucleophiles[1,2] and in transition metal catalyzed cross-coupling reactions[3] resulting in the syntheses of a variety of unnatural nucleosides of biological interest and fluorescent probes.[4] A number of 5-substituted uracil derivatives, especially arabinofuranosyl- and 2′-deoxyuridines, have been investigated extensively for the clinical treatment of viral diseases.[5] For instance, the high-yield coupling of 5-iodouracil derivatives with terminal alkynes afforded 5-alkynyluracil nucleosides with antiviral activity[6,7] and such products can be transformed into furanopyrimidine-2-one derivatives which possess potent and selective inhibition of Varicella-Zoster virus.[6,8] Radiolabeled 5-bromo- and 5-iodouracil nucleosides are used in cellular biochemistry.[9]

Halogenated pyrimidine[2] and purine[1] nucleosides have been prepared by direct reaction with halogens and other halogenating agents but some of these methods required vigorous conditions. The 5-bromination of uracil derivatives has been effected with $Br_2/Ac_2O/AcOH$,[2] Br_2/H_2O,[10] *N*-bromosuccinimide (NBS) in DMF[11] or ionic liquids,[12] combination of 3-chloroperoxybenzoic acid/HBr in aprotic solvents,[13] ceric ammonium nitrate (CAN)/LiBr in protic or aprotic solvents,[14] or KBr/Oxone.[15] Bromination of cytidine at C-5 has been accomplished with $Br_2/CCl_4/h\nu$[16] or NBS in DMF[11] or ionic liquids.[12] The 8-bromination of adenine or guanine nucleosides has been typically achieved with Br_2/AcOH/AcONa[17] or NBS/DMF.[11]

The 1,3-dibromo-5,5-dimethylhydantoin (DBDMH or DBH) is a useful reagent for various organic transformations[18–20] including aromatic bromination.[21–25] Enhanced reactivity of DBH toward aromatic bromination in the presence of acids has been noted.[22–24] Furthermore, Lewis acid-catalyzed benzylic bromination with DBH[26] and efficient oxidation of thiols to disulfides with DBH[27,28] have been reported. The combination of DBH/TsOH was also used for α-bromination of aliphatic ketones.[29] Herein, we report an efficient bromination of pyrimidine (at C-5 position) and purine (at C-8 position) nucleosides with 1,3-dibromo-5,5-dimethylhydantoin in aprotic solvents and the effect of Lewis acids.

Treatment of 2′,3′,5′-tri-*O*-acetyluridine **1a** with DBH (1.1 equiv) in CH_2Cl_2 at ambient temperature for 28 h gave protected 5-bromouridine **2a** in 95% yield (Scheme 1; Table 1, entry 1). Although the DBH reagent can deliver two bromonium equivalents, reaction of **1a** with 0.55 equiv of DBH was completed in only 60% yield even after prolonged reaction time (48 h). We found, however, that addition of 0.55 equiv of a Lewis acid such as trimethylsilyl trifluoromethanesulfonate (TMSOTf) significantly enhanced the efficiency of bromination yielding **2a** in 94% yield after only 6 h. (entry 2). Bromination of **1a** at elevated temperature (40 °C) afforded **2a** quantitatively in only 2 h (entry 3), while bromination at lower temperature was incomplete even after 8 h and required 1.1 equiv of DBH for complete conversion (entry 4). Increasing the amount of

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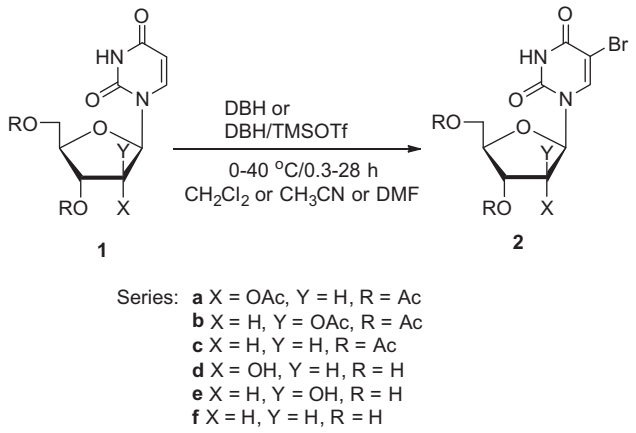


Scheme 1. Bromination of uracil-derived nucleosides **1** with 1,3-dibromo-5,5-dimethylhydantoin (DBH). See Tables 1 and 2 for specific reaction parameters.

TMSOTf to 1.1 equiv had no effect on the rate of reaction (entry 5). Bromination with DBH or the DBH/TMSOTf combination was also effective in polar aprotic solvents such as CH_3CN and DMF (entries 6–9) providing **2a** in shorter reaction times. However, it is noteworthy that bromination in CH_2Cl_2 provides pure **2a** after aqueous workup only and does not require prior evaporation of the solvent from the crude reaction mixture.[30] Moreover, other organic acids such as *p*-toluenesulfonic acid (TsOH) also efficiently catalyzed the bromination (entry 10). Bromination was much less efficient in protic solvents (e.g., MeOH).

The optimized procedure for the 5-bromination of the uracil ring with DBH has general applicability. For example 1-(2,3,5-tri-*O*-acetyl-β,D-arabinofuranosyl)uracil **1b** and 3′,5′-di-*O*-acetyl-2′-deoxyuridine **1c** were efficiently transformed into **2b**[30] and **2c** using this approach (Scheme 1; Table 2, entries 2–6). Furthermore, bromination of the unprotected uridine **1d** using DBH in DMF was completed in only 20 min. producing 5-bromouridine **2d** in 75% crystallized yield (entry 7).[31] DBH also effected efficient bromination of 1-(β,D-arabinofuranosyl)uracil **1e** and the acid sensitive 2′-deoxyuridine **1f** (entries 8 and 9). The 5-bromination of cytidine **3a** and 4-*N*-benzoylcytidine **4a** with DBH in DMF proceeded smoothly as well providing **3b** and **4b**[31] (Fig. 1; Table 3, entries 1 and 2).

The DBH and DBH/TMSOTf combination also effected bromination of purine nucleosides at the 8 position, although reactions usually required higher equivalency of DBH and longer reaction time. Thus, adenosine **5a** and 2′-deoxyadenosine **6a** afforded 8-bromo products **5b** and **6b**, albeit in lower isolated yield when compared to the 5-bromination of pyrimidine nucleosides (Table 3, entries 3 and 4). The 2′,3′,5′-tri-*O*-acetylguanosine **7a** and guanosine **8a** were converted into **7b** and **8b** (entries 5–8). Both reactions appear to be quantitative (TLC). However, protected product **7b** was isolated in 98% yield after aqueous workup, while 8-bromoguanosine **8b** was obtained in approximately 50% yield after crystallization of the crude reaction mixture from H_2O. Treatment of inosine with DBH or DBH/TMSOTf failed to afford 8-bromo product.[32]

Table 1
Effect of various reaction parameters on 5-bromination of 2′,3′,5′-tri-*O*-acetyluridine **1a** with DBH[a]

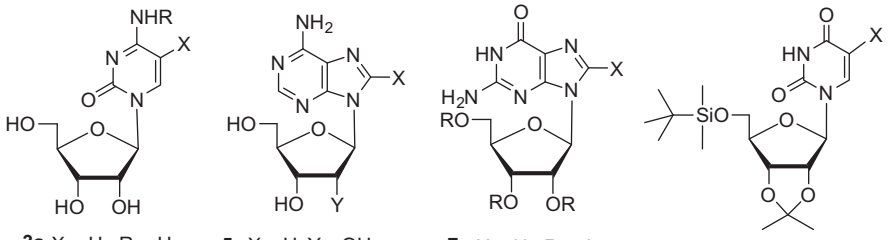
Entry	Solvent	Temp (°C)	DBH (equiv)	TMSOTf (equiv)	Time (h)	Yield[b,c] **2a** (%)
1	CH_2Cl_2	25	1.1	—	28	95
2	CH_2Cl_2	25	0.55	0.55[d]	6	94
3	CH_2Cl_2	40	0.55	0.55	2	98
4	CH_2Cl_2	0	1.1[e]	0.55	3	98
5	CH_2Cl_2	25	0.55	1.10	6	91
6	CH_3CN	25	0.55	—	11	86[f]
7	CH_3CN	25	0.55	0.55	2.5	90
8	DMF	25	0.55	—	0.6	95
9	DMF	25	0.55	0.55	0.3	98
10	CH_2Cl_2	25	0.75	0.75[g]	8	94

[a] Bromination was performed on 0.1 mmol scale of **1a**.
[b] Isolated yield after aqueous work-up.
[c] Purity of the product **2a** was determined by TLC and ^{1}H NMR and was higher than 97% unless otherwise noted.
[d] Reaction without TMSOTf showed 60% conversion to **2a** (TLC) after 48 h and complete conversion after 68 h with purity over 90% (^{1}H NMR).
[e] Reaction with 0.55 equiv of DBH was complete in 65% after 8 h.
[f] With purity over 90%.
[g] TsOH was used instead of TMSOTf.

Table 2
5-Bromination of the uracil-derived nucleosides **1a**–**f**[a]

Entry	Substrate	Product	Solvent	Temp (°C)	DBH (equiv)	TMSOTf (equiv)	Time (h)	Yield[b] (%)
1	**1a**	**2a**	CH_2Cl_2	25	0.55	0.55	6	94[c]
2	**1b**	**2b**	CH_2Cl_2	25	0.55	0.55	10	91[c]
3	**1b**	**2b**	CH_3CN	25	0.55	0.55	2	98[c]
4	**1c**	**2c**	CH_2Cl_2	25	1.10	—	18	72[d]
5	**1c**	**2c**	CH_2Cl_2	25	0.55	0.55	2.5	90[c]
6	**1c**	**2c**	CH_2Cl_2	40	0.55	0.55	0.5	93[c]
7	**1d**	**2d**	DMF	25	0.55	—	0.33	75[e]
8	**1e**	**2e**	DMF	25	0.55	—	1	65[d]
9	**1f**	**2f**	DMF	25	0.55	—	0.75	80[d]

[a] Bromination was performed on 0.25–2.0 mmol scale.
[b] Isolated yield.
[c] After aqueous work-up with purity higher than 97% (^{1}H NMR).
[d] After column chromatography.
[e] After crystallization.



3a X = H, R = H
3b X = Br, R = H
4a X = H, R = Bz
4b X = Br, R = Bz

5a X = H, Y = OH
5b X = Br, Y = OH
6a X = H, Y = H
6b X = Br, Y = H

7a X = H, R = Ac
7b X = Br, R = Ac
8a X = H, R = H
8b X = Br, R = H

9a X = H
9b X = Br

Figure 1. Selected nucleoside precursors (series **a**) and their brominated products (series **b**).

Table 3
Bromination of selected purine and pyrimidine nucleosides at ambient temperature (see Fig. 1 for structures)[a]

Entry	Substrate	Product	Solvent	DBH (equiv)	TMSOTf (equiv)	Time (h)	Yield[b] (%)
1	**3a**	**3b**	DMF	0.55	—	0.5	72[c]
2	**4a**	**4b**	DMF	0.55	—	0.5	74[c,d]
3	**5a**	**5b**	DMF	1.75	—	5	48[c,e]
4	**6a**	**6b**	DMF	1.50	—	3.5	68[c,e]
5	**7a**	**7b**	DMF	0.55	—	2.5	83[c]
6	**7a**	**7b**	CH_3CN	0.55	—	4	98[f]
7	**8a**	**8b**	DMF	0.75[g]	—	2.5	51[h]
8	**8a**	**8b**	DMF	0.60	0.55	0.5	48[h]
9	**9a**	**9b**	DMF	0.55	—	0.5	98[f]

[a] Bromination was performed on 0.5–1 mmol scale.
[b] Isolated yield.
[c] After column chromatography.
[d] Direct crystallization of the crude reaction mixture from MeOH gave **4b** in 46% yield.
[e] Reaction showed formation of the product in approximately 80% yield (TLC).
[f] Isolated yield after aqueous work-up.
[g] Reaction with 0.55 equiv of DBH was completed in 24 h.
[h] After crystallization from water. Bromination was quantitative as judged by TLC.

The bromination with DBH is also compatible with common protecting groups used in nucleoside chemistry. Thus, treatment of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine **9a** with 0.55 equiv of DBH in DMF afforded the corresponding 5-bromo product **9b** in quantitative yield (entry 9).

In summary, we have developed an efficient procedure for the bromination of all RNA nucleobases with 1,3-dibromo-5,5-dimethylhydantoin in polar aprotic solvents at ambient temperature with or without the presence of Lewis acids. The method offers a general and convenient procedure for the synthesis of C-5 pyrimidine and C-8 purine brominated nucleosides and 2′-deoxynucleosides. The protocol is also compatible with common protecting groups used in nucleoside chemistry.

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30. *Typical procedure for the bromination of protected nucleosides*: DBH (161 mg, 0.56 mmol) and TMSOTf (0.1 mL, 125 mg, 0.56 mmol) were added to a stirred solution of **1a** (380 mg, 1.03 mmol) in CH_2Cl_2 (15 mL). The resulting brownish-orange mixture was stirred at room temperature for 6 h or until TLC showed the absence of starting material and formation of less polar product. The reaction mixture was diluted with $CHCl_3$ (35 mL) and was washed with saturated $NaHCO_3/H_2O$ (2 × 100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield **2a** (433 mg, 94%) as a colorless foam with purity over 98% (^{1}H NMR) with data as reported.[14] Compound **2b** had: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3, Ac), 2.07 (s, 3, Ac), 2.09 (s, 3, Ac), 4.12–4.16 (m, 1, H4′), 4.32 (dd, *J* = 3.9, 12.1 Hz, 1, H5″), 4.38 (dd, *J* = 5.8, 12.1 Hz, 1, H5′), 5.04 ('q', *J* = 1.9 Hz, 1, H3′), 5.35 (dd, *J* = 3.7, 4.1 Hz, 1, H2′), 6.22 (d, *J* = 4.1 Hz, 1, H1′), 7.77 (s, 1, H6), 9.33 (br s, 1, NH); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 20.4, 20.6, 20.8 (3×Ac), 62.5 (C5′), 74.4 (C2′), 76.1 (C3′), 80.7 (C4′), 84.4 (C1′), 96.3 (C5), 139.8 (C6), 149.2 (C2), 158.6 (C4), 168.6, 169.6, 170.5 (3×Ac); MS (ESI) *m*/*z* 447 (100, [^{79}Br], MH^-), 449 (98, [^{81}Br], MH^-). The products **2c**,[14] **7b**,[35] and **9b**[37] had physical and spectroscopic properties as reported.

31. Typical procedure for the bromination of unprotected nucleosides: DBH (323 mg, 1.13 mmol) was added to a stirred solution of **1d** (500 mg, 2.05 mmol) in DMF (5 mL). The resulting pale-yellow solution was stirred at room temperature for 20 minutes or until TLC showed absence of starting material and formation of less polar product. Volatiles were evaporated and the residue was coevaporated with MeCN. The resulting pale solid was crystallized from hot acetone to give **2d** (500 mg, 75%) as colorless crystals with data as reported.[14] Compound **4b** had: mp 193–195 °C; UV (MeOH) λ_{max} 252, 335 nm (ε 8900, 13 900), λ_{min} 228, 292 nm (ε 7300, 4200); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.63 (ddd, *J* = 2.1, 4.4, 12.2 Hz, 1, H5″), 3.74–3.82 (m, 1, H5′), 3.90–3.96 (m, 1, H4′), 4.04 ('q', *J* = 5.9 Hz, 1, H3′), 4.07–4.13 (m, 1, H2′), 5.10 (d, *J* = 5.9 Hz, 1, 3′OH), 5.41(t, *J* = 4.6 Hz , 1, 5′OH), 5.57 (d, *J* = 3.9 Hz, 1, 2′OH), 5.7 (d, *J* = 3.6 Hz, 1, H1′), 7.53 (t, *J* = 7.6 Hz, 2H, Bz), 7.62 (t, *J* = 7.3 Hz, 1H, Bz), 8.10–8.24 (br s, 2H, Bz), 8.79 (s, 1, H6), 12.81 (br s, 1, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 59.5 (C5′), 68.6 (C3′), 74.2 (C2′), 84.5 (C4′), 89.7 (C1′), 95.0 (C5), 128.4, 129.4, 132.8, 136.1 (Bz), 142.1 (C6), 147.2 (C4), 154.5 (C2), 177.8 (Bz); MS (ESI) *m*/*z* 426 (100, [^{79}Br], MH^+), 428 (98, [^{81}Br], MH^+). Anal. Calcd for $C_{16}H_{16}BrN_3O_6 \cdot 0.5$ MeOH (442.24): C, 44.81; H, 4.10; N, 9.50. Found: C, 44.62; H, 3.71; N, 9.13. The products **2e**,[33] **2f**,[14] **3b**,[12] **5b**,[34] **6b**,[4] and **8b**[36] had physical and spectroscopic properties as reported.
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