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 CH2Cl2, CH3CN, 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.

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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 nucleophiles1,2 and in transition metal catalyzed cross-coupling reactions3 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 activity6,7 and such products can be transformed into furanopyrimidine-2-one derivatives which possess potent and selective inhibition of Varicella-Zoster virus.5,8 Radiolabeled 5-bromo- and 5-iodouracil nucleosides are used in cellular biochemistry.9

Halogenated pyrimidine2 and purine1 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 Br2/CCL4/hv16 or NBS in DMF11 or ionic liquids.12 The 8-bromination of adenine or guanine nucleosides has been typically achieved with Br2/AcOH/AcONa17 or NBS/DMF.11

The 1,3-dibromo-5,5-dimethylhydantoin (DBDMH or DBH) is a useful reagent for various organic transformations18–20 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 DBH26 and efficient oxidation of thiols to disulfides with DBH27,28 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 CH2Cl2 at ambient temperature for 28 h gave protected 5-bromo-uridine 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...
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 CH₃CN and DMF (entries 6–9) providing 2a in shorter reaction times. However, it is noteworthy that bromination in CH₂Cl₂ 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).

Table 2 includes 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 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-arabinofuranosy)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 (Fig. 1; Table 3, entries 1 and 2).

The DBH and DBH/TMSOTf combination also effected bromination of pyrimidine 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 H₂O. Treatment of inosine with DBH or DBH/TMSOTf failed to afford 8-bromo product.²²

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The bromination with DBH is also compatible with common protecting groups used in nucleoside chemistry. Thus, treatment of 5-0-(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 protected nucleosides and 2-ylhydantoin in polar aprotic solvents at ambient temperature with bromination of all RNA nucleobases with 1,3-dibromo-5,5-dimethylhydantoin in quantitative yield (entry 9).

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References and notes

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 1 (380 mg, 1.03 mmol) in CH2Cl2 (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 CHC13 (35 mL) and was washed with saturated NaHCO3/H2O (2 × 100 mL) and brine (100 mL). The organic layer was dried (MgSO4) and concentrated in vacuo to yield 2a (433 mg, 94%) as a colorless foam with purity over 98% (1H NMR) with data as reported. Compound 2b had: 1H NMR (400 MHz, CDCl3) 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 ( "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). 13C NMR
(100 MHz, CDCl₃):  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 (C5), 149.2 (C2), 158.6 (C4), 168.6, 169.6, 170.5 (3 × Ac); MS (ESI) m/z 447 (100, [79Br], MH+), 449 (98, [81Br], MH+). The products 2c, 7b, and 9b 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) λmax 252, 335 nm (ε 8900, 13 900), λmin 228, 292 nm (ε 7300, 4200); 1H NMR (400 MHz, DMSO-d₆) δ 3.63 (ddd, J = 2.1, 4.4, 12.2 Hz, 1, H5'), 3.74–3.82 (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); 13C NMR (100 MHz, DMSO-d₆) δ 59.5 (C5'), 68.6 (C3'), 74.2 (C2'), 84.3 (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, [79Br], MH+), 428 (98, [81Br], MH+). Anal. Calcd for C₁₆H₁₆BrN₃O₆.5 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, 2f, 3b, 4b, and 8b had physical and spectroscopic properties as reported.

32. Unsuccessful attempt of bromination of inosine with NBS in DMF has been reported.11