Novel Synthesis of 5-Phenyliodonium Triflate Substituted Uracil Nucleosides

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5-Phenyliodonium triflate substituted uracil nucleosides have been prepared by one step reaction of uracil nucleosides with (diacetoxyiodo)benzene-trifluoromethanesulfonic acid.

In recent years, a variety of hypervalent iodine have been intensively studied.[1] The versatility of these hypervalent organoiodine reagents in organic synthesis has been well documented and recognized.[2,3] Of the different structure types of polyvalent organic iodine species, various kinds of iodonium salts show considerable biological activities such as biocidal, antimicrobial activity of numerous diaryliodonium salts,[4a] thienyliodonium salt,[4b] and iodonium compounds of isoxazole.[4c]

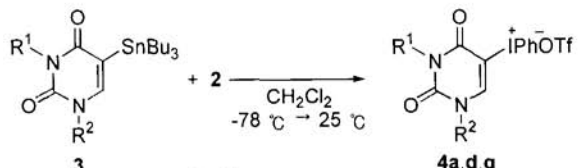
Although a lot of synthetic methods and applications of iodonium salts have been investigated, only two examples for iodonium salts in nucleoside chemistry have been reported in the literature.[5] 5-Substituted pyrimidines constitute a class of biologically important molecules both in terms of their chemotherapeutic activities[6] and synthetic oligonucleotides.[7] In connection of our works on the functionalization at 5-position of pyrimidine nucleosides,[8] we have found that the unsubstituted uracil nucleosides reacted with **1** at low temperature in CH_2Cl_2 to give the corresponding 5-phenyliodonium triflate **4** in excellent yields. This one step procedure shows the high regioselectivity at C-5 position of uracil base over C-6 site.

Recently, Kitamura and his co-workers have prepared biaryl iodonium salts which can be used for the further functionalization of aromatic compounds.[9] Stang and his co-workers also have synthesized alkenyl, alkynyl, aryl, and heteroaryl iodonium salts from the corresponding tributyltin substituted substrates using trivalent iodonium transfer reagent, aryl(cyano)iodonium triflate **2**.[10]

$[PhI(OCOCH_3)_2]$-2TfOH PhI(CN)OTf

1 **2**

At the first attempt, iodonium triflate **4** was able to be prepared by the reaction of 5-tributylstannylated compound **3** with **2** as shown in Scheme 1. 5-Tributylstannylated uracils **3** were synthesized by the known procedure.[11]



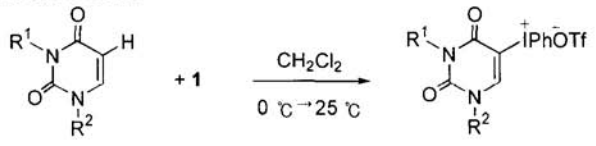
3 **4a,d,g**

4a $R^1=R^2$=Me (87%)
4d R^1=H, R^2=Rib$(OAc)_3$ (68%)
4g R^1=H, $R^2=CH_2O(CH_2)_2OAc$ (51%)

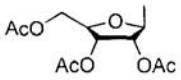
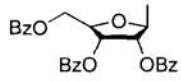
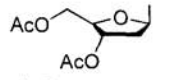
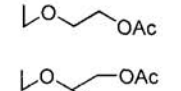
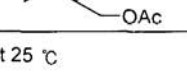
Scheme 1.

The yields are fairly good. But, the synthetic pathway from uracil to iodonium salt **4** needs many reaction steps: uracil **5** → uracil-5-sulfide (-SPh) → uracil-5-tin ($-SnBu_3$) → uracil-5-iodonium salt **4**. Thus, we have developed a new and facile method for the preparation of iodonium species **4** from the unsubstituted uracil nucleosides **5**. This reaction is a simple one-pot procedure; *in situ* preparation of **1** and then the subsequent reaction with uracil nucleosides. It is noteworthy that this new method shows high regioselectivity surprisingly. Only the 5-substitutions occurred in all cases except the unprotected uridine **5i**. The results obtained are summarized in Table 1. Physical properties, spectral data, and high resolution mass spectral data of the new compounds are listed in Reference 12.

Table 1. Synthesis of 5-phenyliodonium triflate substituted uracil nucleosides

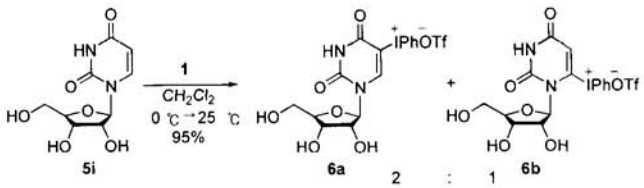


5a-h **4a-h**

Products	R^1	R^2	Time/h [b]	Yield/% [a]
4a	CH_3	CH_3	1	95
4b	$PhCH_2$	$PhCH_2$	3	85
4c	CH_3OCH_2	CH_3OCH_2	3	90
4d	H		2	92
4e	H		3	66
4f	H		3	91
4g	H		1	84
4h	H		2	85

[a] Isolated yields, [b] at 25 °C

The unprotected uridine **5i** reacted with **1** to afford the mixture of the corresponding 5- and 6-iodonium triflate salts. The total yield was very high (95%), but the ratio of the products



Scheme 2.

(**6a**:**6b**) was 2:1 as shown in Scheme 2.[13]

In summary, we have found a novel method for the preparation of 5-phenyliodonium triflate substituted uracil nucleosides. This method is a simple one-pot procedure; *in situ* uracil reacted with the mixture of $PhI(OAc)_2$ and TfOH (**1**) to give **4** regioselectively. Further study on the utility of the iodonium triflate salts for the functionalizations at the 5-position of pyrimidine nucleosides and their biological activities will be reported.

The typical procedure is as follows: To a stirred suspension of $PhI(OAc)_2$ (0.66 g, 2.05 mmol) in CH_2Cl_2 (10 mL), TfOH (0.36 mL, 4.07 mmol) was added slowly at 0 °C with a syringe. The mixture was stirred for 1 h at 25 °C. In the meantime the mixture became a clear yellow solution. The reagent solution was cooled to 0 °C and 1,3-dimethyluracil (0.28 g, 2.0 mmol) was slowly added. The reaction mixture was stirred for 1 h at 25 °C. After evaporation of the solvent, ethyl ether was added to crystallize the residue. The solid was filtered, washed with ethyl ether, and dried in vacuo to afford the product **4a** (0.93 g, 95%). The spectral data are identical with those of **4a** prepared from **3**.

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12 For **4a**: mp 108-110 °C; ^{1}H-NMR (200 MHz, CD_3CN) δ 8.59 (s, 1H), 8.08-7.49 (m, 5H), 3.41 (s, 3H), 3.25(s, 3H); ^{13}C-NMR (50 MHz, CD_3CN) δ 159.5, 156.1, 151.3, 135.8, 133.4, 132.1, 114.4, 86.3, 38.4, 29.9; FAB HR MS m/z 342.9941 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{12}H_{12}O_2N_2I$: 342.9944. **4b**: mp 112-115 °C; ^{1}H-NMR (300 MHz, CD_3CN) δ 8.83 (s, 1H), 8.13-7.49 (m, 5H), 7.38 (s, 5H), 7.26(s, 5H), 5.04 (s, 2H), 5.02 (s, 2H); ^{13}C-NMR (75 MHz, CD_3CN) δ 160.1, 155.7, 151.8, 137.1, 136.6, 136.1, 134.0, 133.2, 130.0, 129.8, 129.6, 129.3, 129.0, 128.9, 115.2, 88.6, 54.9, 47.3; FAB HR MS m/z 495.0543 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{24}H_{20}O_2N_2I$: 495.0564. **4c**: hygroscopic, mp 88-90 °C; ^{1}H-NMR (300 MHz, CD_3CN) δ 8.72 (s, 1H), 8.12-7.50 (m, 5H), 5.26 (s, 2H), 5.16 (s, 2H), 3.38 (s, 3H), 3.29 (s, 3H); ^{13}C-NMR (75 MHz, CD_3CN) δ 160.2, 155.4, 151.9, 136.8, 134.2, 133.2, 114.9, 89.4, 81.9, 75.1, 58.4, 58.1; FAB HR MS m/z 403.0133 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{14}H_{16}O_4N_2I$: 403.0150. **4d**: mp 160-164 °C (dec.), ^{1}H-NMR (200 MHz, CD_3CN) δ 9.94 (br, 1H), 8.58 (s, 1H), 8.10-7.49 (m, 5H), 5.88 (d, 1H), 5.46-5.38 (m, 1H), 5.34-5.30 (m, 1H), 4.37-4.35 (m, 1H), 4.34-4.33 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H); ^{13}C-NMR (50 MHz, CD_3CN) δ 171.8, 170.9, 170.8, 159.7, 153.0, 150.4, 136.9, 134.3, 133.4, 115.1, 90.9, 90.2, 81.6, 74.5, 70.7, 64.1, 20.7, 20.4, 20.3; FAB HR MS m/z 573.0372 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{21}H_{22}O_9N_2I$: 573.0370. **4e**: very hygroscopic; ^{1}H-NMR (200 MHz, CD_3CN) δ 9.87 (br, 1H), 9.01 (s, 1H), 8.08-7.78 (m, 5H), 7.58-7.23 (m, 10H), 6.18-6.14 (d, 1H), 6.03-5.90 (m, 1H), 5.89-5.80 (m, 1H), 4.73-4.68 (m, 3H); FAB HR MS m/z 759.0839 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{36}H_{28}O_9N_2I$: 759.0840. **4f**: mp 114-116 °C (dec.); ^{1}H-NMR (200 MHz, CD_3CN) δ 9.89 (br, 1H), 8.63 (s, 1H), 8.11-7.50 (m, 5H), 6.08-6.05 (m, 1H), 5.22-5.19 (m, 1H), 4.38-4.18 (m, 3H), 2.31-2.53 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H); ^{13}C-NMR (50 MHz, CD_3CN) δ 171.9, 171.6, 161.0, 151.9, 151.2, 136.4, 133.7, 132.8, 115.4, 90.2, 88.4, 84.0, 74.9, 64.6, 38.6, 21.2, 21.1; FAB HR MS m/z 515.0318 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{19}H_{20}O_7N_2I$: 515.0315. **4g**: mp 110-112 °C; ^{1}H-NMR (200 MHz, CD_3CN) δ 9.99 (br, 1H), 8.71 (s, 1H), 8.11-7.48 (m, 5H), 5.19 (s, 2H), 4.13 (t, 2H), 3.76 (t, 2H), 1.97 (s, 3H); ^{13}C-NMR (50 MHz, CD_3CN) δ 171.8, 160.1, 156.6, 151.2, 136.8, 134.2, 133.3, 115.0, 89.7, 79.6, 69.2, 64.1, 21.2; FAB HR MS m/z 431.0102 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{15}H_{16}O_5N_2I$: 431.0104. **4h**: mp 118-120 °C (dec.);^{1}H-NMR (200 MHz, CD_3CN) δ 9.88 (br, 1H), 8.69 (s, 1H), 7.51-8.53 (m, 5H), 5.33(s, 2H), 4.18-4.08 (m, 4H), 3.65-3.62 (m, 1H), 1.96 (s, 6H); FAB HR MS m/z 503.0350 $[M\text{-}CF_3SO_3^-]^+$, calcd. for $C_{18}H_{20}O_7N_2I$: 503.0309.

13 The ratio was determined by ^{1}H-NMR (300 MHz, CD_3CN). For **6a** : δ 9.98 (br, N3), 9.31(s, C6), 5.73-5.69 (m, C1'), **6b** : δ 9.45 (br, N3), 8.59 (s, C5), 5.80-5.78 (m, C1').