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Pd(II)-Catalyzed Acetoxylation of Uracil *via* Electrophilic Palladation

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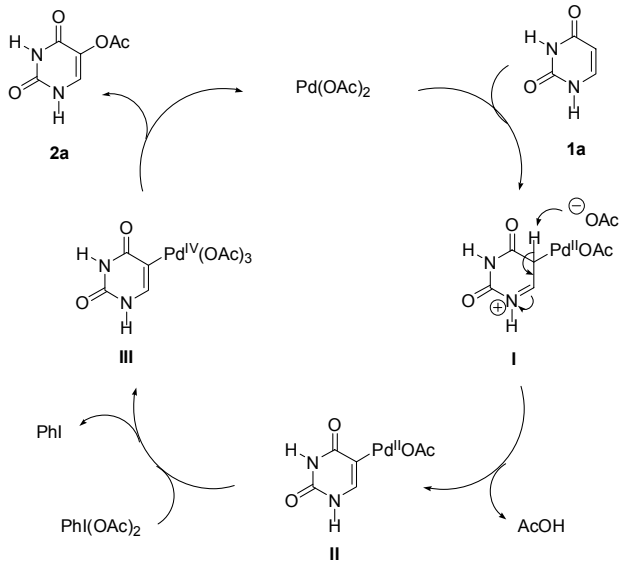
Palladium-catalyzed C-H activation/functionalization reactions are of great utility in organic chemistry because they enable the direct replacement of various C-H bonds with new functionality.[1] Among them a palladium-catalyzed oxidative functionalization of C-H bonds has received much attention. Especially, a Pd-catalyzed acetoxylation or hydroxylation have received a special attention as one of the best oxidative functionalization of C-H bond,[2] and various substrates have been examined in these regards including benzylpyridine,[2a] arylpyridine,[2b,h] benzo[*h*]quinoline,[2c] and acetophenone oxime ether.[2d] Very recently, acetoxylation at the 3-position of indole moiety was published by Suna and co-workers.[3] The nucleophilic nature of the carbon atom at the 5-position of uracil ring is very similar with that of the carbon atom at the 3-position of indole. In addition, 5-hydroxyuracil and related compounds have been known as important oxidative lesions of DNA.[4] Thus, synthesis and applications of these compounds has received much attention.[5] To the best of our knowledge, a palladium-catalyzed oxidative functionalization of uracil has not been reported.[6] Thus we decided to examine the preparation of 5-acetoxyuracil derivatives *via* a Pd(II)-catalyzed direct acetoxylation of uracil moiety.[7]

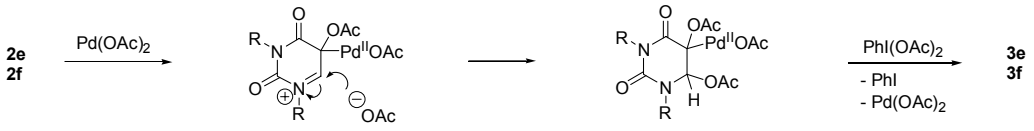
Initially, we examined the reaction of uracil (**1a**) under the conditions of $Pd(OAc)_2$ (10 mol %)/$PhI(OAc)_2$ (2.5 equiv) in AcOH (100 °C, 2 h), and the desired product **2a** was obtained in 68% yield (*vide infra*, conditions B). The reaction proceeded at 60 °C (3 h) more cleanly, and **2a** was obtained in an increased yield (72%, *vide infra*, conditions A). The plausible reaction mechanism is shown in Scheme 1: (i) an electrophilic palladation at the electron-rich 5-position of **1a** to form 5-palladauracil intermediate (**II**) by liberation of acetic acid *via* the intermediate (**I**), (ii) oxidation of (**II**) to (**III**) by phenyliodonium diacetate (PIDA) with liberation of iodobenzene, as Sanford and co-workers already reported,[1,2] and (iii) the final reductive removal of Pd(II) to produce 5-acetoxyuracil (**2a**). The reaction of **1a** and PIDA at 60 °C without a palladium catalyst did not produce any trace amounts of **2a**.[8] The use of $Cu(OAc)_2$, oxone, air, or $K_2S_2O_8$ as an oxidant instead of PIDA were ineffective. The reactions in DMF, CH_3CN, and 1,4-dioxane were also ineffective.



Scheme 1

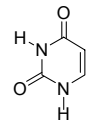
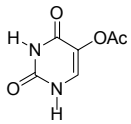
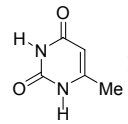
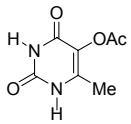
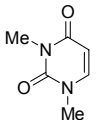
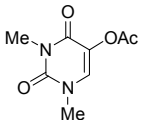
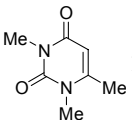
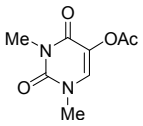
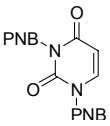
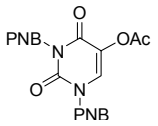
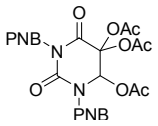
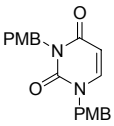
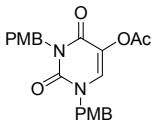
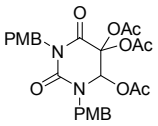
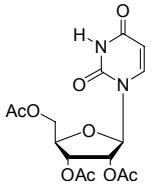
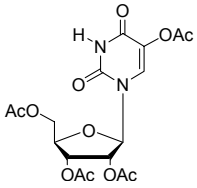
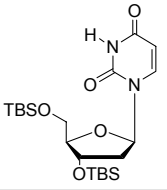
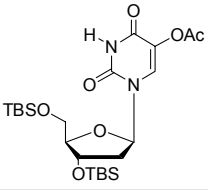
Encouraged by the results, we examined the reactions of various uracil derivatives **1b-h**, and the results are summarized in Table 1. As shown in Table 1, the reactions of 6-methyluracil (**1b**), 1,3-dimethyluracil (**1c**), and 1,3,6-trimethyluracil (**1d**) afforded the corresponding 5-acetoxy derivatives **2b-d** in 56 - 71% isolated yields (entries 2-4). The yields of **2b-d** were somewhat lower (45 - 55%) at 100 °C (conditions B) than those of the conditions A (60 °C) due to increased formation of intractable side products. The reactions of **1e-h**, however, were very sluggish at 60 °C. But we obtained compounds **2e-h** at 100 °C in low to moderate yields (23 - 55%). It is interesting to note that triacetoxy derivatives **3e** and **3f** were formed together in variable yields for the benzyl-substituted uracil derivatives (entries 5 and 6).[3,4a] The plausible mechanism for the formation of triacetoxy compounds are suggested in Scheme 2. We could not isolate the corresponding triacetoxy compounds in appreciable amounts for other entries. In the reaction of **1h**, the yield of **2h** was low and starting material **1h** was recovered in 14%. In addition, we isolated 16% of 5-acetoxyuracil (**2a**) which resulted by the cleavage of *N*-glycoside bond under the acidic conditions.[9] The reaction of 1,3,5-trimethyluracil (**1i**) failed, as expected due to the presence of 5-methyl group. The reaction of methyl 1,3-dimethylorotate (**1j**) also failed completely presumably due to the presence of electron-withdrawing ester group which diminish the nucleophilicity at the C-5 position of uracil ring.

In summary, a palladium-catalyzed electrophilic acetoxylation at the electron-rich 5-position of uracil was examined. The reaction proceeded *via* the electrophilic palladation of Pd(II) at the 5-position of uracil ring, and regeneration of Pd(II) was



Scheme 2

Table 1. Pd(II)-catalyzed 5-acetoxylation of uracil derivatives

Entry	Substrate		Product		Conditions (%)[a]
1		**1a**		**2a**	**A**: 3 h, **2a** (72) **B**: 2 h, **2a** (68)
2		**1b**		**2b**	**A**: 3 h, **2b** (60) **B**: 2 h, **2b** (45)
3		**1c**		**2c**	**A**: 7 h, **2c** (56) **B**: 1 h, **2c** (48)
4		**1d**		**2d**	**A**: 8 h, **2d** (71) **B**: 3 h, **2d** (55)
5[b]		**1e**		**2e**	**A**: 3 h, no reaction **B**: 2 h, **2e** (33) **3e** (23)
				**3e**	
6[c]		**1f**		**2f**	**A**: 3 h, no reaction **B**: 1 h, **2f** (23) **3f** (21)
				**3f**	
7		**1g**		**2g**	**A**: 3 h, no reaction **B**: 3 h, **2g** (55)
8		**1h**		**2h**	**A**: 3 h, no reaction **B**: 5 h, **2h** (25)[d]

[a]Conditions: $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.5 equiv), AcOH, **A**: 60 °C; **B**: 100 °C. [b]PNB is p-nitrobenzyl. [c]PMB is *p*-methoxybenzyl. [d]**1h** (14%) and **2a** (16%) were isolated.

effectively occurred with the aid of PIDA (phenyliodonium diacetate).

Experimental Section

Typical procedure for the synthesis of 5-acetoxyuracil (2a). To a stirred mixture of **1a** (112 mg, 1.0 mmol) and $Pd(OAc)_2$ (22 mg, 0.1 mmol) in AcOH (5 mL) was added $PhI(OAc)_2$ (805 mg, 2.5 mmol) and heated to 60 °C for 3 h. After removal of solvent, the residue was purified by column chromatography ($CHCl_3$/MeOH, 10:1) to afford **2a** (123 mg, 72%) as a white solid. Other compounds were prepared similarly and the spectroscopic data of **2a-h**, **3e**, and **3f** are as follows.

Compound 2a: 72%; white solid, mp 232 - 234 °C (decomp.); IR (KBr) 3194, 1781, 1763, 1709 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.19 (s, 3H), 7.55 (s, 1H), 10.88 (br s, NH), 11.42 (br s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.06, 125.92, 133.33, 150.52, 159.26, 168.55; ESIMS *m/z* 193 (M^++Na). Anal. Calcd For $C_6H_6N_2O_4$: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.47; H, 3.74; N, 16.21.

Compound 2b: 60%; white solid, mp 232 - 234 °C (decomp.); IR (KBr) 3194, 1781, 1763, 1709 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.95 (s, 3H), 2.22 (s, 3H), 10.94 (br s, NH), 11.28 (br s, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 13.08, 19.96, 123.03, 143.38, 150.06, 158.85, 168.40; ESIMS *m/z* 207 (M^++Na). Anal. Calcd For $C_7H_8N_2O_4$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.86; H, 4.42; N, 15.03.

Compound 2c: 56%; white solid, mp 150 - 152 °C; IR (KBr) 1772, 1709, 1677, 1652, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 3.37 (s, 3H), 3.41 (s, 3H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.18, 28.27, 37.03, 126.23, 134.39, 150.67, 158.57, 168.68; ESIMS *m/z* 221 (M^++Na).

Compound 2d: 71%; white solid, mp 146 - 148 °C; IR (KBr) 1771, 1706, 1647, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.19 (s, 3H), 2.33 (s, 3H), 3.36 (s, 3H), 3.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.53, 20.15, 28.34, 31.95, 124.60, 142.99, 151.12, 157.71, 168.66; ESIMS *m/z* 235 (M^++Na).

Compound 2e: 33%; white solid, mp 128 - 130 °C; IR (KBr) 1778, 1716, 1675, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 5.03 (s, 2H), 5.21 (s, 2H), 7.28 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.19, 44.60, 52.14, 123.71, 124.34, 127.21, 128.65, 129.85, 133.51, 141.70, 143.02, 147.51, 147.99, 150.35, 158.12, 168.44; ESIMS *m/z* 462 (M^++Na). Anal. Calcd For $C_{20}H_{16}N_4O_8$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.79; H, 3.62; N, 12.56.

Compound 3e: 23%; white solid, mp 172 - 174 °C; IR (KBr) 1779, 1735, 1521, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.70 (s, 3H), 1.98 (s, 3H), 2.03 (s, 3H), 4.59 (d, *J* = 16.2 Hz, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.95 (d, *J* = 16.2 Hz, 1H), 7.19 (s, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.85, 20.28, 20.40, 42.26, 43.32, 85.10, 85.41, 123.85, 123.89, 128.85, 129.40, 142.04, 143.32, 147.58, 147.75, 155.71, 165.87, 166.77, 167.20, 167.84; ESIMS *m/z* 581 (M^++Na).

Compound 2f: 23%; white solid, mp 56 - 58 °C; IR (KBr) 1778, 1731, 1713, 1674, 1651, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.84 (s, 2H), 5.08 (s, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.08 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.26, 44.68, 51.89, 55.20, 55.30, 113.74, 114.57, 126.47, 126.77, 128.56, 129.94, 130.79, 132.88, 150.62, 158.40, 159.17, 159.87, 168.58; ESIMS *m/z* 433 (M^++Na).

Compound 3f: 21%; white solid, mp 48 - 50 °C; IR (KBr) 1770, 1731, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3H), 1.85 (s, 3H), 2.00 (s, 3H), 3.78 (s, 6H), 4.34 (d, *J* = 15.6 Hz, 1H), 4.69 (s, 2H), 4.97 (d, *J* = 15.6 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.16 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.73, 20.14, 20.39, 42.22, 43.27, 55.25, 55.30, 84.94, 85.51, 113.93, 113.96, 127.98, 128.35, 129.76, 130.06, 155.95, 159.21, 159.29, 166.33, 167.06, 167.57, 167.71; ESIMS *m/z* 551 (M^++Na).

Compound 2g: 55%; white solid, mp 77 - 79 °C; IR (KBr) 3230, 1748, 1715, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.11 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 2.29 (s, 3H), 4.30-4.41 (m, 3H), 5.31-5.33 (m, 2H), 6.06-6.11 (m, 1H), 7.51 (s, 1H), 9.25 (br s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.22, 20.36, 20.47, 20.61, 63.01, 70.06, 72.90, 80.08, 87.23, 127.94, 130.24, 149.21, 157.74, 168.17, 169.54, 169.61, 170.08; ESIMS *m/z* 451 (M^++Na). Anal. Calcd For $C_{17}H_{20}N_2O_{11}$: C, 47.67; H, 4.71; N, 6.54. Found: C, 47.94; H, 4.94; N, 6.29.

Compound 2h: 25%; white solid, mp 106 - 108 °C; IR (KBr) 3188, 1781, 1723, 1697, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.10 (s, 6H), 0.89 (s, 9H), 0.92 (s, 9H), 2.00-2.09 (m, 1H), 2.26 (s, 3H), 2.26-2.35 (m, 1H), 3.75 (dd, *J* = 11.4 and 2.1 Hz, 1H), 3.88-3.95 (m, 2H), 4.37-4.41 (m, 1H), 6.31 (t, *J* = 6.3 Hz, 1H), 7.82 (s, 1H), 8.89 (br s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.59, −4.88, −4.64, 17.97, 18.39, 20.19, 25.71, 25.88, 41.80, 62.79, 71.79, 85.46, 88.01, 127.40, 131.13, 149.16, 158.04, 168.28; ESIMS *m/z* 537 (M^++Na). Anal. Calcd For $C_{23}H_{42}N_2O_7Si_2$: C, 53.67; H, 8.22; N, 5.44. Found: C, 53.82; H, 7.98; N, 5.33.

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8. Although the reaction of **1a** and PIDA at 60 °C without a palladium catalyst did not produce any trace amounts of **2a**, we obtained **2a** in 59% when we run the reaction at 100 °C with only PIDA (2.5 equiv) even in the absence of a palladium catalyst. Thus, there might be acting another mechanism of acetoxylation which is possible with PIDA only. Scrutinizing of reported papers involving the use of PIDA revealed that electron-rich aromatic compounds[10] and enamino esters[11] could be acetoxylated. However, the reactions of **1e-h** and PIDA were very sluggish in the absence of a palladium catalyst even at 100 °C, and the results stated that these compounds are not sufficiently nucleophilic to be acetoxylated with PIDA.
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