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Palladium Catalyzed Alkenylation or Alkynylation at C-5 of Uracil Nucleosides Using Novel Phenyliodonium Triflate

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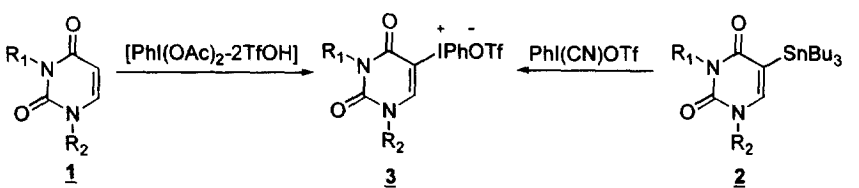
Abstract : A new coupling reaction between novel uracil-5-iodonium triflate and unsaturated stannane or alkenyl boronic acid is described. The reaction is achieved via palladium catalyzed cross-coupling reaction under mild conditions within short reaction time.

Derivation of purine and pyrimidine nucleosides has attracted much attention because of potent antitumor or antiviral activity.[1] Pyrimidine nucleosides substituted at the C-5 position constitute a class of biologically significant molecules.[2] Especially, C-5 alkenyl and alkynyl substituents have shown various antiviral activities.[3,4] Thus, the introduction of unsaturated substituents at C-5 of pyrimidine derivatives has become of considerable interest. Straightforward method for the synthesis of such derivatives is transition metal catalyzed cross-coupling reaction. The most common substrates employed for coupling reaction were 5-mercurated[5], 5-iodo[6,7], 5-triflated uridines[8] which were reacted with unsaturated metal compounds, such as stannane, boron, or aluminum, etc. But, these synthetic methods require high reaction temperature and long reaction time. Thus, we have focused our work on the development of new general method for the C-C bond formation of pyrimidine nucleosides at C-5.

In recent years many trivalent iodonium salts have become readily available and have enjoyed useful synthetic reagents in organic synthesis.[9] They are highly reactive toward various nucleophiles due to powerful leaving ability of iodonium.[10] Also, they undergo palladium catalyzed coupling reaction with many substrates like as Stille type reaction.[11] Hypervalent iodine compounds have advantages which can be used under mild reaction conditions, at room temperature, and in short reaction time. We have developed a new method to prepare iodonium salt substituted at 5-position of uracil nucleoside through two different synthetic pathways.

Scheme 1



1 3 2

The **3** was directly prepared from the uracil derivatives (**1**) by treating **1** with [PhI(OAc)$_2$-2TfOH]. TfOH

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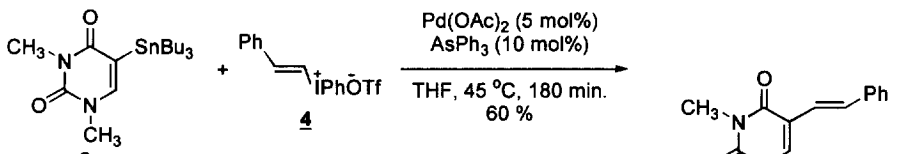
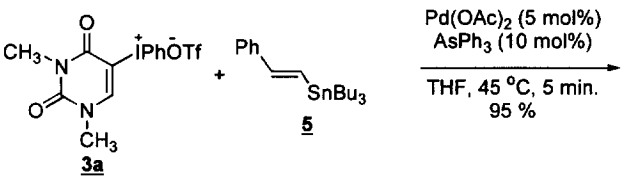
(0.36 ml, 4.07 mmol) was slowly added at 0 °C to the solution of $PhI(OAc)_2$ (2.05 mmol, CH_2Cl_2 : 10 ml) with stirring. The mixture was stirred for 1h at 25 °C, cooled to 0 °C and then 1,3-dimethyluracil (2.0 mmol) was slowly added. The reaction mixture was stirred for 1h at 25 °C, concentrated, and then ethyl ether was added to precipitation. The solid was filtered, washed with ethyl ether, and dried in vacuo to afford the product **3** in good yield. (**3a** : 95 %). We have examined the palladium catalyzed coupling reaction of these iodonium salts with various unsaturated substrates. In the preliminary experiment, the reaction of alkenyliodonium triflate **4**[12] with 5-stannylated uracil **2a** does not proceed at room temperature in the presence of 5 mol% of $Pd(OAc)_2$ and 10 mol% of triphenylarsin as ligand[13,14] in THF. When the reaction was carried out at 45 °C, the reaction proceeded smoothly to provide the cross-coupled products **6** in moderate yield (60 %). But, the undesired reduced product (uracil) was also obtained in significant amount (40 %) as shown in Scheme 2. While, treatment of uracil-5-iodonium triflate **3a** with vinyltin **5** gave the desired coupled product in almost quantitative yield (95 %) within 5 min and the side product was not detected as shown in Scheme 3.

Scheme 2



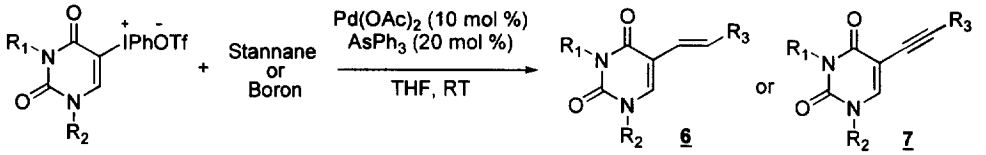
Scheme 3

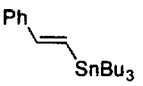
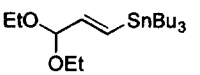
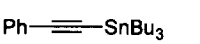
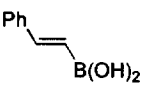
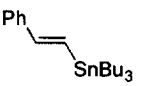
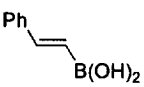
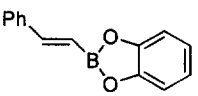
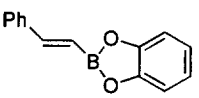


In the coupling reaction of **2a** with **4** or **3a** with **5**, the reaction of Pd inserted catalyst at 5-position of **3a** with **5** appears to be faster than that of Pd inserted catalyst at the vinyl moiety of **4** with **2a**. This efficient reaction can be carried out under mild reaction conditions (25 °C, 5 min).

Initial studies were concentrated on the reaction between **3a** and **5**. The reaction conditions were described in the Table 1. Reaction of **3a** with vinylstannane gave the cross-coupled product in good yield in the presence of 10 mol% of $Pd(OAc)_2$ and 20 mol% of triphenylarsin in THF at room temperature (run 1, 2). The protected uridine **3b** also reacted with vinylstannane to afford the product in 87 % yield (run 5). Alkynylstannane gave coupled product under the same conditions within 30 min (run 3). The reaction were extended to the boron compound. Palladium catalyzed coupling reaction of organoboron was well known by Suzuki and his coworkers.[15] To generalize the suitable substrates, two types of organoboron were used under various conditions. Vinylboronic acid gave the better result than the corresponding boronate ester. Acyclic nucleoside **3c** reacted with vinylboronic acid to afford the corresponding coupled product at 45 °C within 3 h in 61 % yield (run 6). The results obtained are summarized in Table 1.

Table 1. Palladium catalyzed coupling reaction of **3** with organostannanes or borons



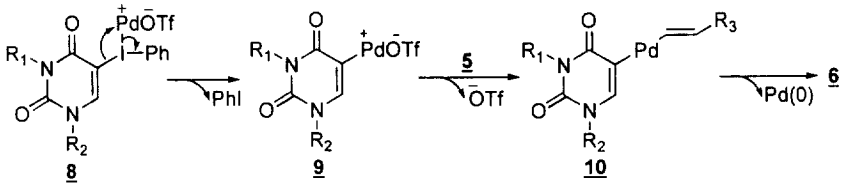
Run	R_1/R_2 (Substrates)	Stannane or Borane	Solvent	Time (h)	Products	Yield (%)[a]
1	Me/Me (**3a**)		THF	0.1	**6a**	95[b]
2	**3a**		THF	2.5	**6b**[e]	76
3	**3a**		THF	0.5	**7a**	57
4	**3a**		THF	3	**6a**	87[c]
5	H/Rib(OBz)$_3$ (**3b**)		THF	3	**6c**	87
6	H/$CH_2O(CH_2)_2OAc$ (**3c**)		THF	3	**6d**	61[c,d]
7	**3a**		DME/H_2O (4/1)	3	**6a**	63[c]
8	**3a**		THF	3	**6a**	65[c]

[a] Isolated yields. [b] $Pd(OAc)_2$ 5 mol %, $AsPh_3$ 10 mol %. [c] 2eq. of K_2CO_3 were added.
[d] Carried out at 45 °C. [e] During the work-up, **6b** quickly converted to aldehyde.

A typical procedure is as follows: To a stirred mixture of uracil-5-iodonium triflate (**3** : 0.5 mmol), $Pd(OAc)_2$ (10 mol %), triphenylarsin (20 mol %) and additives in THF, under argon atmosphere, unsaturated organometal compound (0.55 mmol) was added and stirred. The reaction mixture was filtered through celite. The filtrate was poured into saturated NH_4Cl solution, extracted with EtOAc, concentrated, washed with aqueous NH_4Cl solution, dried over anhydrous $MgSO_4$, followed by flash chromatography (silicagel 230-400 mesh, eluent; hexane/EtOAc) to yield the product **6** or **7**. All the compounds were characterized by NMR, FT-IR, and mass spectroscopy and were in accord with reported data.[6,16]

In considering mechanism, the reaction appears to be initiated by forming an intermediate **8** with **3** and Pd(0), followed by the reductive elimination of iodobenzene and ligand coupling to yield an uracil-5-palladium intermediate **9**. Substitution with **5** by transmetalation (**10**), following by reductive elimination would yield **6** and the catalyst Pd(0) as described in the alkenylation of alkenyl iodonium salt.[17]

Scheme 4



In summary, we have found an efficient method for carbon-carbon bond formation of 5-position of uracil nucleoside using novel substrates, 5-iodonium triflate substituted uracils, by palladium catalyzed cross-coupling with unsaturated tributylstannane or vinylboron compounds under mild conditions in good yields. Further studies on the utility and scope of these iodonium salts will be undertaken.

Acknowledgment

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16. For **6b** : ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60(d, 1H), 7.59 (s, 1H), 7.28 (s, 1H), 7.05 (q, 1H), 3.54 (s, 3H), 3.42 (s, 3H). **7a** :^{1}H-NMR (300 MHz, CD_3CN) δ 7.73 (s, 1H), 7.47-7.35 (m, 5H), 3.33 (s, 3H), 3.25 (s, 3H); FT-IR (KBr, cm^{-1}) 3066, 2940, 2360, 1702, 1648, 1485, 1448.
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