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Practical synthesis of 6-aryluridines via palladium(II) acetate catalyzed Suzuki–Miyaura cross-coupling reaction

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ABSTRACT

Sugar-protected 6-halouridine derivatives underwent Suzuki–Miyaura cross-coupling reactions with arylboronic acids in the presence of palladium(II) acetate as a catalyst, triphenylphosphine as a ligand, and sodium carbonate as a base. This methodology is applicable to both the C5- and C6-position of uridine and provides a direct access for versatile uridine derivatives.

1. Introduction

C-Aryl-substituted uridine derivatives are an important class of pyrimidine nucleoside analogs that have received considerable attention in recent years. 5-Aryluridines have been extensively utilized as fluorescent probes for the studies of electron-transfer in DNA,[1–10] or as biosensors for the detection of uridine-related protein targets.[11] In addition, 5-aryluridines represent a series of dimensional analogs of thymidine[12–19] or flexible ring-split analogs ('fleximers') of purine nucleosides,[20] which have been used as spatial probes to investigate related enzymes or receptors. The synthesis of 5-aryluridines from 5-halouridines was readily achieved by the palladium-catalyzed cross-coupling reactions in which both Suzuki–Miyaura[1–6,11–13,21,22] and Stille[7–10,14–20,22] reactions were applicable.

In contrast, very few examples of 6-aryluridines have been reported in the literature.[23–28] The introduction of aryl substituents at the *C*6-position of uridine was limited to the following two approaches with a restricted scope: (1) photochemical arylation of 6-iodouridines with arenes;[28] (2) Stille coupling reactions of 6-iodouridines with arylstannanes or 6-tributylstannyluridines with aryl halides.[24–27] The synthesis of 6-aryluridine derivatives via the widely-used Suzuki–Miyaura reaction was only very recently reported by Van Calenbergh et al.[23] In an effort to explore the chemical synthesis and biological significance of 6-substituted uridine derivatives, we embarked on an investigation of a general and practical synthesis of 6-aryluridines via the Suzuki–Miyaura reaction.

2. Results and discussion

In the initial trials, 6-halo-1,3-dimethyluracils (**1a**,**b**) were chosen as non-nucleoside models to investigate the C–C bond formation reaction. Using a conventional approach,[29] $Pd(PPh_3)_4$ was selected as the catalyst, and commercially available arylating reagents, including phenylboronic acid (**3a**), phenylboronic acid pinacol ester (**4a**), and tributylphenylstannane (**4b**), along with various bases and solvents, were examined. The survey of reaction conditions showed that both Suzuki–Miyaura and Stille coupling reactions could take place with excellent yields under various conditions (Table 1).

However, our attempts to apply the tested conditions (Table 1) to 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine[30] (**6**) were unsuccessful. In contrast to the model reactions, we speculated that this failure could be attributed to the interaction of the unsubstituted N^3-position with the palladium catalyst or the arylating reagents. To test this hypothesis, a series of N^3-substituted 6-iodouridine derivatives (**10a**,**b** and **11**) were prepared by N^3-alkylation[31,32] of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine (**5**) followed by lithiation-iodination.[27,30,33] The N^3-substituted 6-iodo-uridines **10a**,**b** and **11** were subjected to the optimized condition (entries 1 and 6 in Table 1) and the desired N^3-substituted 6-phenyluridines **12a**,**b** and **13a** were obtained in very good yields (Scheme 1). The results indicated that a protecting group for the reactive N^3-imide is necessary when $Pd(PPh_3)_4$ is used as the catalyst.

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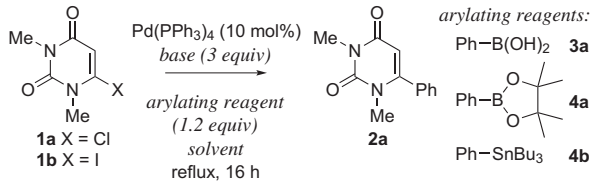
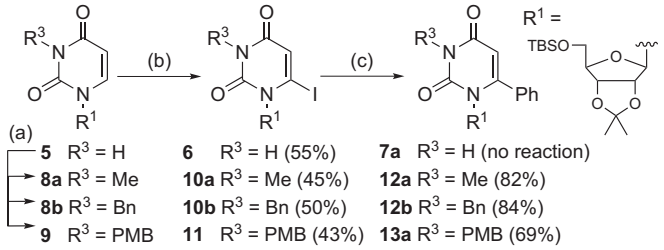
Table 1
Cross-coupling reaction of 6-halo-1,3-dimethyluracils (**1a**,**b**) with arylating reagents (**3a** and **4a**,**b**) using $Pd(PPh_3)_4$ as the catalyst



Entry	Substrate	Base (3 equiv)	Arylating reagent (1.2 equiv)	Solvent[a]	Yield[b] (%)
1	**1a**	2 M Na_2CO_3[c]	**3a**	DME[d]	73
2	**1a**	2 M Na_2CO_3[c]	**4a**	DME[d]	94
3	**1a**	2 M Na_2CO_3[c]	**4b**	DME[d]	86
4	**1a**	DBU	**3a**	DME	59
5	**1a**	DBU	**4a**	DME	59
6	**1b**	2 M Na_2CO_3[c]	**3a**	DME[d]	86
7	**1b**	DBU	**3a**	DME	62
8	**1b**	DBU	**4a**	DME	14

[a] Concentration=0.1 M.
[b] Isolated yield.
[c] 2 M in H_2O.
[d] Approximately DME/H_2O=1:0.15 (v/v).

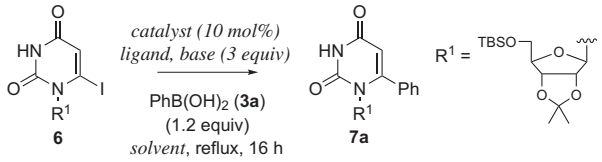


Scheme 1. Reagents and conditions: (a) R^3=Me: MeI, K_2CO_3, DMF, rt, 94%; R^3=Bn: BnBr, K_2CO_3, cat. $^nBu_4NI$, DMF, rt, 84%; R^3=PMB: PMBCl, DBU, CH_3CN, 70 °C, 69%; (b) (i) LDA, THF, −78 °C; (ii) I_2, THF, −78 °C; (c) $Pd(PPh_3)_4$ (10 mol %), $PhB(OH)_2$ (1.2 equiv), 2 M Na_2CO_3 in H_2O (3 equiv), DME, reflux, 16 h.

Meanwhile, our investigation also focused on the direct activation of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine[30] (**6**) for the C–C bond formation reaction. In a continuous screening of palladium catalysts ($Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, Pd_2dba_3), only $Pd(OAc)_2$ and $PdCl_2$ were found to give a minimal yield of the desired product, while $Pd(PPh_3)_4$ was unable to catalyze the coupling reaction. Optimization studies were then performed with various solvents, bases, temperature, boron reagents, and ligands/additives (part of the results was summarized in Table 2). Our investigation revealed that the maximal yield was obtained when the reaction was carried out in toluene with $Pd(OAc)_2$ as the catalyst, PPh_3 as the ligand, and Na_2CO_3 as the base (entry 11 in Table 2). Alternatively, using DME as the solvent, Cs_2CO_3 as the base, or dppf as the ligand, respectively (entries 3, 4, 12, and 14 in Table 2), could provide comparative yields.

The reaction of sugar-protected 6-iodouridine **6** with a variety of arylboronic acids (**3b**–**i**), as shown in Table 3, was examined to explore the scope and generality of the reaction. Under the optimized condition (entry 11 in Table 2), 6-iodouridine **6** could react with most of the arylboronic acids to give the target compounds **7** in good yields except for **3g** and **3i**, which did not give the desired products under all tested conditions (Table 3). It is notable that, although the reactions with 3-thiopheneboronic acid (**3f**) and 3-furanboronic acid (**3h**) proceeded flawlessly under the optimized condition (entries 9–11 in Table 3), their 2-position isomeric congeners (**3e** and **g**) were problematic. Upon changing the solvent from toluene to DME, the reaction with 2-thiopheneboronic acid (**3e**) was

Table 2
Cross-coupling reaction of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine (**6**) with phenylboronic acid (**3a**)



Entry	Catalyst (10 mol %)	Ligand (equiv)	Base (3 equiv)[a]	Solvent[b]	Yield[c] (%)
1	$Pd(PPh_3)_4$	—	Na_2CO_3	DME	0
2	$Pd(OAc)_2$	—	Na_2CO_3	DME	4
3[d]	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	DME	35
4	$Pd(OAc)_2$	PPh_3 (0.2)	Cs_2CO_3	DME	43
5	$Pd(OAc)_2$	PPh_3 (0.2)	K_3PO_4	DME	28
6	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	Dioxane	5
7	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	THF	8
8	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	CH_3CN	0
9	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	DMF	0
10	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	*t*-BuOH	37
11[e]	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	Toluene	82
12	$Pd(OAc)_2$	PPh_3 (0.2)	Cs_2CO_3	Toluene	49
13	$Pd(OAc)_2$	PPh_3 (0.2)	K_3PO_4	Toluene	58
14	$Pd(OAc)_2$	dppf (0.1)[f]	Na_2CO_3	Toluene	62
15	$PdCl_2$	—	Na_2CO_3	DME	5
16	$PdCl_2$	PPh_3 (0.2)	Na_2CO_3	Toluene	11

[a] 2 M in H_2O.
[b] Concentration=0.1 M.
[c] Isolated yield.
[d] Using **4a** (1.2 equiv) as the arylating reagent: 17%.
[e] Using **4a** (1.2 equiv) as the arylating reagent: 0%.
[f] dppf=1,1′-Bis(diphenylphosphino)ferrocene.

improved, while 2-furanboronic acid (**3g**), *p*-nitrophenylboronic acid (**3c**), and *n*-butylboronic acid (**3i**) remained ineffective.

The results prompted us to re-examine the reactivity of these boronic acids (**3c**,**g**, and **i**) with the model reaction. It was found that **3c** and **3i** could react with 6-chloro-1,3-dimethyluracil (**1a**) to afford the desired products under the optimized condition (entries 1–7 in Table 4). This allowed us to apply our successful approach in Scheme 1 to use N^3-(*p*-methoxybenzyl)-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine (**11**) for the coupling reaction with less reactive boronic acids. Thus, N^3-PMB-substituted 6-iodouridine **11** was treated with **3c** and **3i** under the optimized condition to give the corresponding sugar- and N^3-protected 6-substituted uridine derivatives (**13c** and **13i**) (entries 8–14 in Table 4). The results confirmed that the N^3-imide interferes with the coupling reaction and the N^3-protection is required for less reactive reactants.

A product analysis of the reaction mixtures was performed during the optimization studies. Besides the dehalogenated product, another common by-product was identified as *N*-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)malonamide (**15**) on the basis of mass spectrometry and intensive NMR studies. Since 6-halouracil derivatives are very accessible to the nucleophilic aromatic substitution, we rationalized that the hydrolysis of 6-iodouridine **6** under the aqueous alkaline condition first took place to give the corresponding 6-hydroxyuridine derivative (**14**). Subsequently, tautomerization of the 6-hydroxyuridine **14** to the barbiturate nucleoside (**14′**) followed by the ring-opening hydrolysis resulted in the formation of the by-product **15** and further degradation products (Scheme 2).

The hydrolytic degradation appeared to be the competing reaction with the Suzuki–Miyaura cross-coupling reaction. The formation of **15** could only be suppressed when the cross-coupling reaction was effective enough to overcome the hydrolysis, which could account for the low yields of the less reactive boronic acids. In most of the coupling reactions with 6-iodouridine **6**, toluene is a better solvent than DME, due to the fact that water is less miscible with toluene, which decreased the water content in the reaction to