New, Efficient Approach for the Ligand-Free Suzuki–Miyaura Reaction of 5-Iodo-2′-deoxyuridine in Water

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Abstract: A series of 5-aryl-2′-deoxyuridines was prepared, using ligandless Suzuki–Miyaura cross-coupling reactions in neat water, starting from 5-iodo-2′-deoxyuridine as totally deprotected starting material. This ligand-free process gave good to high isolated yields within short reaction times and with low loadings of palladium.

Key words: Suzuki–Miyaura reaction, ligandless, nucleosides, green chemistry

Nucleoside analogues have attracted much attention due to their potential biological activities as antiviral and antitumoral agents and their use as building blocks for oligonucleotides with promising therapeutic and diagnostic applications. *C*-Aryl-substituted nucleosides are an important class of nucleoside analogues which have received considerable attention in recent years (e.g., compound **1**,[1a] d4T analogue **2**[1b,c] and benzo[*c*]furan derivative **3**;[1d–k] Figure 1). Very recently, compounds with a *C*-aryl group in the aglycone part have been used as a biosensor for the detection of uridine-related protein targets,[2] and as fluorescent probes for the study of electron transfer in DNA.[3–16]

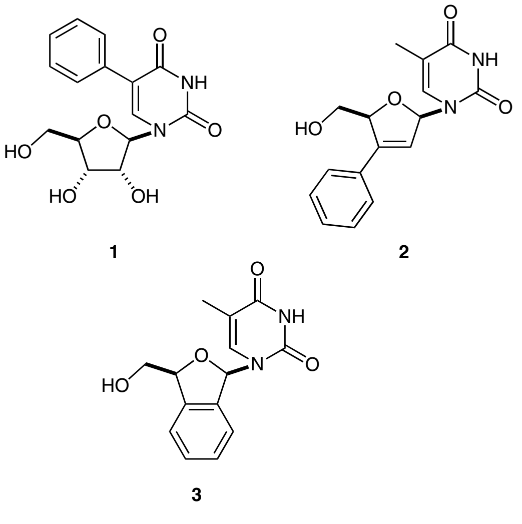

Figure 1 Nucleoside analogues **1**–**3** having an aryl group

The synthesis of 5-aryluridines and the corresponding 2′-deoxyuridines was usually readily achieved by the palladium-catalyzed Suzuki–Miyaura[10,17,18] or Stille reaction in organic solvents, starting from protected 5-halouridines and 2′-deoxyuridine, respectively.[9,12,14,19–29] In regard to the development of green chemistry, academic and industrial research has permitted the establishment of a catalytic Suzuki–Miyaura protocol based on atom economy, less hazardous chemical syntheses, and safer solvents and auxiliaries. In this respect, the Suzuki–Miyaura reaction has been developed with or without ligand in safe, economical and environmentally benign aqueous media such as a cosolvent mixture in water[30,31] or neat water.[32] Recently, aqueous-phase Suzuki–Miyaura reactions of unprotected 5-halo-2′-deoxyuridines with boronic acids have been developed either in water/various organic cosolvent mixtures[3,5–8,11,13–16,33–40] or, to a lesser extent, in sole water.[2,41,42] In order to prepare 5-aryl-2′-deoxynucleoside derivatives, our group developed an efficient, sustainable protocol starting from the corresponding iodo analogue in neat water in the presence of a low loading of catalyst [Na_2PdCl_4 (0.1 mol%) and sodium triphenylphosphine trisulfonate (TPPTS, 0.25 mol%)].[41] It is notable that this strategy permitted the target nucleoside analogues to be obtained without any protection/deprotection steps. In order to have a ‘greener’ protocol, atom-economy should be examined and unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible because each step requires additional reagents and can generate waste. Here, we report on an efficient extension of this work in order to establish whether the presence of the ligand influences the reaction results.

For this purpose, 5-iodo-2′-deoxyuridine (**4**) and phenylboronic acid were engaged in Suzuki–Miyaura cross-coupling reactions with different amounts of palladium (0.01–0.5 mol%) either in the presence or absence of TPPTS (2.5 equiv/Pd) at 100 °C (Table 1). In the present work, the reaction time was determined by monitoring the reaction until full conversion of the starting material was observed. Our results clearly show that the presence of TPPTS in the mixture is not necessary at 100 °C. Whatever the amount of palladium (0.01–0.5 mol%), the absence of TPPTS had no inhibiting effect on the reaction course. In our hands, no significant differences in reaction time and/or yields were observed with 0.5 mol%, 0.1 mol% and 0.05 mol% of palladium(II). Indeed, using those catalytic conditions (Table 1, entries 1–6), the desired cross-coupling products were obtained in very good yields (79–86%) within 30 minutes maximum. Upon dramatically decreasing the amount of palladium, the expect-

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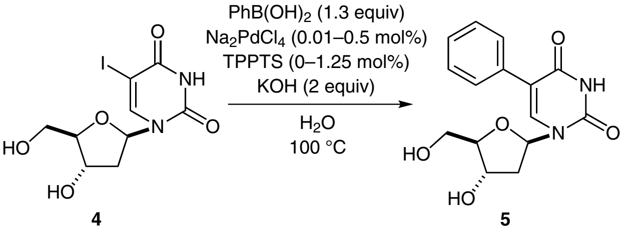
ed increase in reaction times was observed, but 5-phenyl-2′-deoxyuridine (**5**) was still obtained after 24 hours in good yield even with only 0.01 mol% of palladium (Table 1, entries 9 and 10). These encouraging preliminary experiments (Table 1, entries 4 and 6) led us to define two ligand-free methods in order to (i) establish different optimized reaction conditions (variation of the nature of the boronic acids having different electronic and steric demands, and the time) and (ii) have a large and coherent library of nucleoside analogues.

Table 1 Coupling of 5-Iodo-2′-deoxyuridine (**4**) and Phenylboronic Acid with or without Ligand (TPPTS)



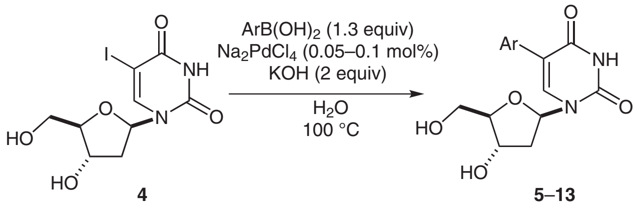
Entry	Na_2PdCl_4 (mol%)	Time (h)	Yield[a] (%)
1	0.5	0.25	79[b]
2	0.5	0.08	82[c]
3	0.1	0.25	80[b]
4	0.1	0.25	80[c]
5	0.05	0.50	84[b]
6	0.05	0.50	86[c]
7	0.02	4	73[b]
8	0.02	4	72[c]
9	0.01	24	60[b]
10	0.01	24	58[c]

[a] Isolated yields.
[b] In the presence of TPPTS (2.5 equiv/Pd).
[c] Without TPPTS.

All reactions were performed using 5-iodo-2′-deoxyuridine (**4**, 0.28 mmol), an arylboronic acid (1.3 equiv) and potassium hydroxide (2 equiv) at 100 °C with degassing of neat water (18.2 MΩ) prior to use. Coupling products were all isolated from the crude reaction mixtures by flash chromatography on C18-phase silica gel.

Using various boronic acids (Table 2), the reaction times and yields in the presence of Na_2PdCl_4 (0.1 mol%) were often shorter and higher, respectively, than those observed in the presence of a lower loading of Na_2PdCl_4 (0.05 mol%) (Table 2, entries 3–18). Arylboronic acids with an electron-donating substituent in the *para* position delivered the cross-coupling products, **6** and **7**, in good yields either with 0.1 mol% or with 0.05 mol% Na_2PdCl_4 (Table 2, entries 3–6). When comparing with compound **5**, the presence of a methyl group in the *para* position of the aromatic ring does not change the reaction result much, since compound **6** was isolated in a similar range of yield and time (Table 2, entries 1–4). On the contrary, when a heteroatom is directly bound to the arylboronic acid in the *para* position, an extended reaction time was needed to reach completion (Table 2, entries 5 and 6). Due to less nucleophilic properties, reactions using arylboronic acids with electron-withdrawing groups, particularly with nitrile and formaldehyde groups, were less efficient (Table 2, entries 7–12). In our hands, no hydrolysis was detected with our basic reaction conditions (Table 2, entries 7–10). Among the reactions of arylboronic acids with an electron-withdrawing group, product **10** is an exception and was obtained in a 69% yield in 30 minutes when 0.1 mol% of palladium was used (Table 2, entry 11). Its formation was slowed in the presence of only 0.05 mol% of palladium as a reaction time of 24 hours was necessary to reach a full conversion of starting material (Table 2, entry 12), compared to five hours for compounds **8** and **9** (Table 2, entries 8 and 10).

Table 2 Variation of the Nature of the Boronic Acid for the Ligand-Free Suzuki–Miyaura Coupling of 5-Iodo-2′-deoxyuridine (**4**)



Entry	Ar	Product	Time (h)	Yield[a] (%)
1	Ph	**5**	0.25	80[b]
2			0.50	86[c]
3	4- MeC_6H_4	**6**	0.50	79[b]
4			2	80[c]
5	4-$MeOC_6H_4$	**7**	7	64[b]
6			24	57[c]
7	4-NCC_6H_4	**8**	1	39[b]
8			5	13[c]
9	4-$HC(O)C_6H_4$	**9**	6	17[b]
10			5	13[c]
11	4-AcC_6H_4	**10**	0.5	69[b]
12			24	49[c]
13	2- MeC_6H_4	**11**	24	22[b]
14			24	19[c]
15	2-$MeOC_6H_4$	**12**	24	23[b]
16			24	18[c]
17	2-Naph	**13**	2	80[b]
18			24	70[c]

[a] Isolated yields.
[b] In the presence of Na_2PdCl_4 (0.1 mol%).
[c] In the presence of Na_2PdCl_4 (0.05 mol%).

The sterically demanding 2-methyl- and 2-methoxyphenylboronic acid proved to be difficult substrates for the Suzuki–Miyaura cross-coupling reaction of nucleosides even under ‘standard’ conditions. Both methods permitted isolation of the product in modest yields (Table 2, entries 13–16); however, this time, no matter what the atom directly bound to the aromatic part of the boronic acid (methyl or methoxy group), no difference in the length of the reaction time was observed. Steric restrictions may take over from electronic effects in these cases. Once again, an exception has to be mentioned as 2-naphthylboronic acid reacted with 5-iodo-2′-deoxyuridine (**4**) in the presence of 0.1 mol% of Na_2PdCl_4 to give compound **13** in a very good yield (80%) within two hours (Table 2, entry 17). The use of 0.05 mol% of Na_2PdCl_4 gave the corresponding nucleoside analogue **13** in 70% yield, with an extended reaction time (Table 2, entry 18). Our group was the first to describe this compound[41] and, at that time, our optimized reaction catalyst was Na_2PdCl_4 (0.1 mol%)–TPPTS (0.25 mol%). Under these previous conditions, a reaction time of five hours was necessary to observe a full conversion of 5-iodo-2′-deoxyuridine (**4**) and compound **13** was isolated in 77% yield.

It is important to note that, using our current reaction conditions, we have never observed any loss of the aglycone moiety of compounds **5**–**13**.

In summary, a simple and efficient procedure for the Suzuki–Miyaura cross-coupling reaction of 5-iodo-2′-deoxyuridine (**4**) in neat water has been developed using a ligandless palladium catalyst. The ligand was not necessary even with very low loadings of palladium (0.05 mol% Na_2PdCl_4). Our new reaction conditions allowed us to obtain 5-arylated nucleoside derivatives with substituents with various steric and electronic demands in yields which are at least equal to those previously reported reactions using organic solvents or a mixture of water/organic solvents in the presence of higher loadings of palladium and expensive ligands. To the best of our knowledge, this is the first time in nucleoside chemistry that the Suzuki–Miyaura reaction has been used under such green and economical conditions.

Reagents were purchased from either Acros or Sigma Aldrich, depending on availability. All solvents were purchased from Carlo Erba. All reactions were monitored by TLC [Merck Kieselgel $60F_{254}$ aluminum sheets, detection by UV light and/or with H_2SO_4 in EtOH (9:1, v/v)] and by HPLC [Shimadzu; column: Grace Prevail C18; mobile phase: H_2O–MeOH, 1:1; detectors: SPD-M20A photo diode array detector (Shimadzu), LCMS-2020 mass spectrometer (Shimadzu) and ELSD-LTII detector (Shimadzu)].

5-Aryl-2′-deoxyuridines 5–13; General Procedure

Under nitrogen atmosphere, 5-iodo-2′-deoxyuridine (**4**; 100 mg, 0.28 mmol, 1 equiv), KOH (31 mg, 0.56 mmol, 2 equiv) and the arylboronic acid (0.37 mmol, 1.3 equiv) were placed in a 25 mL flask. Nitrogen-flushed solutions of Na_2PdCl_4 in H_2O (1 mL, 0.28 μmol, 0.1 mol%) and H_2O (1 mL) were added. The mixture was then heated to 100 °C. Conversion was followed by HPLC. After complete conversion, the mixture was cooled to r.t. and concentrated under reduced pressure. The crude residue was purified by flash chromatography on C18 silica gel (H_2O–MeOH, 95:5 to 5:95) to afford the target 5-arylated nucleoside **5**–**13**. All the synthesized compounds have been reported in the literature and were characterized by comparing the corresponding spectroscopic data.[41]

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