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# Synthesis of 6-aryluridines via Suzuki–Miyaura cross-coupling reaction at room temperature under aerobic ligand-free conditions in neat water

Gérald Enderlin, Guillaume Sartori, Gwénaëlle Hervé, Christophe Len\*

Transformations Intégrées de la Matière Renouvelable, UTC-ESCOM, Centre de recherche de Royallieu, BP 20529, 60205 Compiègne, France

#### ARTICLE INFO

### ABSTRACT

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were obtained in moderate to good yields depending on the boronic acid nature. © 2013 Elsevier Ltd. All rights reserved.

A new and efficient ligandless cross-coupling reaction of 6-iodouridine with various boronic acids in the

presence of Na<sub>2</sub>PdCl<sub>4</sub> was performed at room temperature in aerobic water. The target 6-arvl analogues

Research on nucleoside and nucleotide analogues has led to the discovery of very potent drugs against a huge range of diseases as they act as antivirals, antibiotics, or anti-tumorals.<sup>1–3</sup> In addition they have proved to be very efficient tools for diagnostic and examination of biological processes. To have a structure–activity relationship, three main modifications of the canonical nucleosides and nucleotides either on the phosphate part, on the sugar moiety, or on the nucleobase are generally considered. Among the nucleoside analogues, those having *C*-aryl group on the glycone moiety (e.g., d4T analogues  $\mathbf{1}$ ,<sup>4</sup> benzo[*c*]furan derivative  $\mathbf{2}^5$ ) or on the aglycone moiety (e.g., compound  $\mathbf{3}^6$ ) have been particularly studied (Fig. 1).

In particular, the C-5-aryl nucleoside analogues were studied for their potent activities as fluorescent probes,<sup>7-11</sup> as antiviral drugs (e.g., Brivudin, BVDU),<sup>12–14</sup> and for the study of electron-transfer in DNA.<sup>15–17,6,18–20</sup> In the case of C-5 modification, different successful techniques were performed such as photochemical route,<sup>21</sup> C–H activation<sup>22,23</sup> or palladium cross-coupling methodologies,<sup>24</sup> mainly Stille<sup>10,13,25–32</sup> or Suzuki–Miyaura<sup>7,15,16,6,33–40</sup> reactions. Concerning the 6-position, only few examples were reported in the literature.<sup>41–49</sup> In general, the main methodologies have been developed in organic solvent starting from fully protected uridine such as 6-stannyl<sup>42,44</sup> and 6-iodo nucleoside analogues.<sup>43,45–48</sup> In 2011, Shih et al. have also reported the synthesis of 6- and 5-aryluridine via the Suzuki–Miyaura reaction in refluxing toluene or DME starting from fully protected 6- or 5-halouridine with Pd(OAc)<sub>2</sub> as the catalyst, PPh<sub>3</sub> as the ligand, and sodium carbonate as the base.<sup>48</sup> Recently, Nencka et al. described a methodology starting from fully protected vinylphosphonate 6-iodouridine by standard Suzuki-Miyaura cross-coupling with Pd(OAc)<sub>2</sub> and K<sub>3</sub>PO<sub>4</sub> under aerobic and ligandless conditions in a mixture of propanol and water (ratio 1:1).<sup>45</sup> Finally very recently Kögler et al. reported the synthesis of 6arvl-2'-deoxyuridine nucleosides under base free conditions via a Liebeskind cross-coupling methodology which necessitates stoichiometric use of copper thiophene carboxylate as the co-reagent at slightly elevated temperatures (50 °C).<sup>43</sup> Taking advantage of our first reports concerning the synthesis of 5-arvl nucleoside analogues via Suzuki-Miyaura cross-coupling in neat water,<sup>40</sup> development of a new green methodology for the substitution in position six was investigated. The aim of the presented work was to develop green and economic conditions starting from totally deprotected 6-iodouridine (**4**)<sup>47,50,51</sup> for the synthesis of 6-aryl nucleoside analogues having no protection/deprotection steps, no ligand, aerobic conditions in water as sole solvent.

First, application of our general procedure optimized for the synthesis of 5-arylnucleoside analogues was attempted:<sup>40</sup> nucleoside **4** (1.0 equiv), phenylboronic acid (1.3 equiv), Na<sub>2</sub>PdCl<sub>4</sub> (0.1 mol %), and KOH (2.0 equiv) in the presence or not of TPPTS (0.25 mol %) at 100 °C with degassing of neat water (18.2 M). Unfortunately those previously described methods were not transposable to the 6-iodo analogue **4**. It is noteworthy that under these conditions the substitution of KOH by K<sub>3</sub>PO<sub>4</sub> did not permit to obtain the cross-coupling analogue. The instability of the starting material **4** under thermal conditions and alkaline media could be the cause of this non reactivity.<sup>43,45,48,52,53</sup> In order to avoid this phenomenon and to develop greener conditions, room temperature without addition of any ligand has been explored. First,

<sup>\*</sup> Corresponding author. Tel.: +33 344 23 8 828; fax: +33 644 971 591. *E-mail address:* christophe.len@utc.fr (C. Len).

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

variation of the palladium loadings was realized to develop the cross-coupling reaction in water. At 20 °C, the ligandless cross-coupling Suzuki–Miyaura reaction starting from nucleoside analogue **4** was effective with phenylboronic acid (1.3 equiv), Na<sub>2</sub>PdCl<sub>4</sub> (10 mol %), KOH (2.0 equiv) in aerobic water. The target 6-aryl uridine derivative **5** was obtained in 81% yield (Scheme 1).<sup>54</sup> Unfortunately, lower amount of palladium did not furnish the target compound **5** in acceptable yield. Compared with our previous work,<sup>40</sup> the actual amount of palladium (10 mol % vs 0.1 mol %) is due to both lower temperature (rt vs 100 °C) and less reactive starting nucleoside analogue **4**. In the presented work, the time of reaction was determined by monitoring the reaction until full conversion of the starting material was observed.

Different bases, including Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, CsCO<sub>3</sub>, NaOH, KOH, CsF, AcONa, and K<sub>3</sub>PO<sub>4</sub>, were tested with the optimized conditions described above. Interestingly in all cases the yields were moderate to good (60–81%) (Table 1, entries 1–5 and 8) with the exception of CsF and AcONa (Table 1, entries 6 and 7). In those cases, compound **5** was isolated only in respectively, 23% and 10% yields. The best result was obtained when using KOH (Table 1, entry 5). This base permitted both a full conversion in a shorter reaction time (0.5 h vs 1.5–2.0 h) and a higher yield. It is noteworthy that the use of such a strong base did not furnish a detrimental effect on the stability of *C*-6 iodouridine such as deglycosylation or dehalogenation at this temperature (20 °C).

In search of a more efficient catalyst, the next step consisted in examining different palladium sources which are soluble or give colloidal suspensions in water. For this purpose Pd(OAc)<sub>2</sub>, PdI<sub>2</sub>, PdCl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd/C, Na<sub>2</sub>PdCl<sub>4</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(PhCN)<sub>2</sub>, Pd<sub>2</sub>((PhCHCH)<sub>2</sub>CO)<sub>3</sub> were screened by using each time the same amount of catalyst (10 mol %). Even though all the water soluble palladium derivatives promoted the formation of the target nucleoside 5, slight differences were observed in reaction times (0.5-1.5 h) for similar yields (76-80%) (Table 2, entries 1-3, 6, and 8). In our hands, PdI<sub>2</sub>, PdCl<sub>2</sub>, Na<sub>2</sub>PdCl<sub>4</sub> afforded the 6-phenyl analogue **5** in 0.5 h while in the presence of Pd(OAc)<sub>2</sub> and PdCl<sub>2</sub>(PhCN)<sub>2</sub> the reaction was completed in , 1 and 1.5 h, respectively. On the other hand, when water insoluble catalysts such as  $Pd(PPh_3)_4$ , Pd/C,  $PdCl_2(PPh_3)_2$ and  $Pd_2((PhCHCH)_2CO)_3$ were employed, heterogeneous cross-coupling catalysis failed even after longer reaction time (Table 2, entries 4, 5, 7, and 9). Among the palladium sources, Na<sub>2</sub>PdCl<sub>4</sub> (10 mol %) was kept due to its greatest solubility



Scheme 1. Reagents and conditions: (i) PhB(OH)<sub>2</sub> (1.3 equiv), Na<sub>2</sub>PdCl<sub>4</sub> (10 mol %), KOH (2.0 equiv), H<sub>2</sub>O, rt, 81% yield.

#### Table 1

Variation of the nature of the base for the Suzuki–Miyaura cross-coupling starting from 6-iodouridine (4)



Entry	Base	Time (h)	Yield <sup>a</sup> (%)
1	Na <sub>2</sub> CO <sub>3</sub>	1	73
2	K <sub>2</sub> CO <sub>3</sub>	2	60
3	CsCO <sub>3</sub>	2	73
4	NaOH	1	75
5	КОН	0.5	81
6	CsF	2	23
7	AcONa	2	10
8	K <sub>3</sub> PO <sub>4</sub>	1	75

<sup>a</sup> Isolated yield.

Table 2

Variation of the nature of palladium-based species for the Suzuki-Miyaura crosscoupling starting from 6-iodouridine (**4**)



<sup>a</sup> Isolated yield.

in water, fast reaction time, and good yield (Table 2, entry 6). In our hands, the catalytic system cannot be recycled due to the polarity of the target nucleoside analogues.

In order to validate the utility of the method, a series of arylboronic acids with different electronic and steric demands were tested. Application of our optimized conditions using 6-iodouridine (4) as the starting material, Na<sub>2</sub>PdCl<sub>4</sub> (10 mol %) as the catalyst in the presence of KOH (2 equiv) and arylboronic acid (1.3 equiv) in water as the sole solvent was performed at 20 °C without taking care of an inert atmosphere. It is interesting to note that starting from arylboronic acid having either electron-donating (Table 3, entries, 1, 2, 4, and 10) or electron-withdrawing substituents (Table 3, entries 5 and 6) in para position the catalyst system was very efficient. Using our optimized method, the less hydrosoluble 2-naphthylboronic acid furnished the corresponding nucleoside analogue in 84% yield. The presence of a withdrawing group in para position gave similar yield (Table 3, entry 6) with the exception of the methylketone (Table 3, entry 5). To the best of our knowledge, the cross-coupling Suzuki-Miyaura reaction in

#### Table 3

Suzuki-Miyaura cross-coupling starting from various arylboronic acids and 6iodouridine (4)



Entry	Ar	Compound	Time (h)	Yield <sup>a</sup> (%)
1		5	0.5	81 <sup>54</sup>
2	ş	6	1	71
3		7	24	0
4		8	1.5	84
5		9	1.5	61
6		10	1.5	80
7		11	24	0
8	S S	12	4	Traces <sup>b</sup>
9	N	13	24	0
10		14	2	72

<sup>a</sup> Isolated yield.

<sup>b</sup> Complex reaction mixture detected by LC-MS.

position six of uridine analogue using ortho-substituted phenylboronic acid was not reported in the literature. Also application of our methodology to the steric hindered 2-methylphenylboronic acid and 2-formylphenylboronic acid was tested but no cross-coupling reaction was observed (Table 3, entries 3 and 7). The biaryl derivatives 7 and 11 were not obtained even using excess amounts of catalyst and prolonged reaction time. As often mentioned in the literature,40,42,45 the Suzuki-Miyaura reaction using heteroarylboronic acid afforded the target nucleoside analogues in modest yield. In our hands, the use of 2-thienylboronic acid and 4-pyridinylboronic acid as coupling partners did not furnish the target nucleoside (Table 3, entries 8 and 9). Starting from the heteroarylboronic acid, poisoning palladium catalyst would be probably occurred affording a deactivation effect on the rate of the reaction.

A new, simple, and efficient ligand-free procedure for the Suzuki-Miyaura reaction cross-coupling of 6-iodouridine (4) in water at room temperature has been developed using Na<sub>2</sub>PdCl<sub>4</sub> (10 mol %). To the best of our knowledge in nucleoside chemistry, our green and economic conditions having reduced derivatives with no protection/deprotection steps, no ligand, and water as solvent were one of the most efficient procedures.

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# Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/i.tetlet.2013.04.066.

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54. General procedure for 5:  ${}^{51}$  6-iodouridine (50 mg, 0.135 mmol), Na<sub>2</sub>PdCl<sub>4</sub>, 3H<sub>2</sub>O (3.9 mg, 0.013 mmol), phenylboronic acid (25 mg, 0.202 mmol), and KOH (18 mg, 0.270 mmol) were dissolved and stirred in 1 ml of water. The reaction was performed at room temperature during 30 min. Then the solvent was evaporated or lyophilized. The residue was purified on flash reverse phase column chromatography (water/MeOH = 1:0-3:7) to yield 6-phenyluridine (5) (35 mg, 80%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  11.49 (s, 1H, NH), 7.54–7.50 (m, 5H, Ph), 5.51 (s, 1H, H-5), 5.06–5.04 (m, 2H, H-1' and OH), 4.82 (d, 1H, *J* = 6.0 Hz, OH), 4.62–4.57 (m, 2H, OH, and H-2'), 3.40–3.42 (m, 1H, H-5'); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz)  $\delta$  162.1, 156.1, 150.6, 133.1, 130.2 (CH), 128.8 (CH), 128.05 (CH), 103.6 (CH), 93.6 (CH), 84.9 (CH), 70.9 (CH), 69.9 (CH), 62.15 (CH<sub>2</sub>).