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Cite this: *New J. Chem.*, 2013, **37**, 1989

# Improved microwave-assisted ligand-free Suzuki–Miyaura cross-coupling of 5-iodo-2′-deoxyuridine in pure water†

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Received (in Montpellier, France) 13th February 2013,
Accepted 4th April 2013

DOI: 10.1039/c3nj00174a

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A facile and efficient methodology for direct synthesis of 5-aryl-2′-deoxyuridines was developed through ligand-free Suzuki–Miyaura cross-coupling reactions starting from totally deprotected 5-iodo-2′-deoxyuridine and various boronic acids. Reactions were performed, in pure water, in the presence of very low loading of palladium either by classical thermal heating or with the assistance of microwave irradiation yielding 5-arylated uridine derivatives in moderate to good yields within short reaction times.

## Introduction

Synthetic nucleosides have attracted considerable attention due to their potential biological properties. Various structural modifications of natural nucleosides have been reported and several nucleoside analogues, either in the pyrimidine or the purine series, have been shown to be effective in the development of antiviral, antimetabolic and antibacterial agents.[1] Among modified nucleosides, those having a *C*-aryl group on the glycone part[2,3] (*e.g.* d4T analogue **1**,[2] benzo[*c*]furan derivative **2**[3]) or on the aglycone part[4] (*e.g.* compound **3**[4]) have been particularly studied recently (Fig. 1).

Concerning the modification of the nucleobase, the synthesis of 5-aryl derivatives of the (2′-deoxy)uridine series involved the palladium-catalyzed Suzuki–Miyaura and Stille reactions in organic solvents starting from a totally protected starting material.[4h–m,5] With regard to the development of green chemistry, aqueous-phase Suzuki–Miyaura reactions of unprotected 5-halo-2′-deoxyuridine have been described in various water–organic co-solvent mixtures[4b,d,g,i,l,o,6] or more recently in sole water.[4a,7] In order to prepare 5-aryl-2′-deoxynucleoside derivatives, our group published efficient sustainable protocols starting from the corresponding iodo-analogue in neat water (18.2 MΩ) under conventional heating.[7a,b] With its high dielectric constant, water is potentially a very useful solvent for microwave-mediated synthesis.[8] Indeed, microwave heating has been widely recognized as an efficient synthetic tool and its benefits have been well-documented.[8,9] Many reactions are known to result in higher yield and/or shorter reaction times under microwave heating compared with the conventional one. Using this alternative technology, Suzuki–Miyaura cross-coupling reaction has been much documented in the literature.[10] To the best of our knowledge, there are only few reports on using microwave irradiation as a heating source for the introduction of an aromatic moiety on the heterocyclic part of nucleosides.[7f,11] Based on our preliminary work on various uridine analogues obtention,[7a,b] we now report a novel and efficient ligandless Suzuki–Miyaura cross coupling for the synthesis of 5-aryl-2′-deoxyuridine derivatives with the assistance of microwave irradiation.

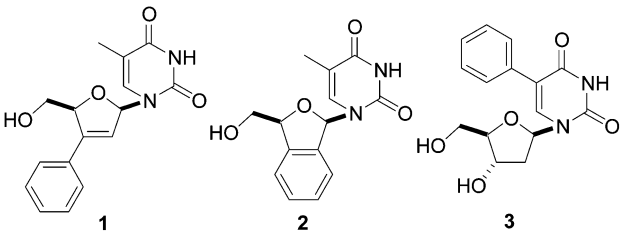


**Fig. 1** Nucleoside analogues **1–3** having an aryl group.

## Results and discussion

For this purpose, 5-iodo-2′-deoxyuridine (**4**) and phenylboronic acid were engaged in Suzuki–Miyaura cross-coupling reactions

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3nj00174a

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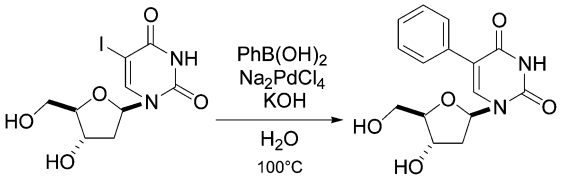
**Table 1** Four optimized reaction conditions for the ligandless Suzuki–Miyaura coupling starting from 5-iodo-2′-deoxyuridine




4 5

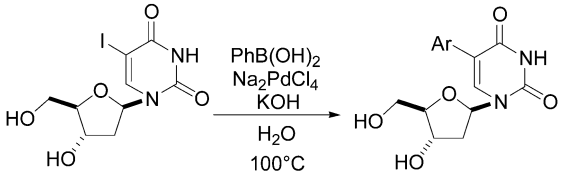
| Entry | $Na_2PdCl_4$ (mol%) | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | 0.1 | 0.08[b] (0.25)[c] | 85[b] (80)[c] |
| 2 | 0.05 | 0.25[d] (0.50)[e] | 82[d] (86)[e] |

[a] Isolated yields. [b] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [c] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C. [d] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [e] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C.

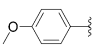
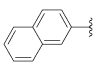
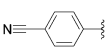
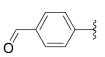
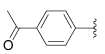
in the presence of a small amount of palladium $Pd^{II}$ (0.1 mol% and 0.05 mol%) in pure water at 100 °C using either thermal heating or microwave irradiation (monowave 850 W) (Table 1). As we have already demonstrated that the presence of a ligand was absolutely not necessary[7b] we made the choice of avoiding it. In the present work, the time of reaction was determined by monitoring the reaction until full conversion of the starting material was observed. When the kinetics was slow, the reaction was stopped after a maximum of twenty-four hours of thermal heating and only one hour of microwave assistance as one of the main features of this tool lies in a drastic decrease of reaction time. With our methods most of the reactions arrived at completion within one hour under microwave activation. After reaction, coupling compounds were all isolated from the crude reaction mixture by flash chromatography on a C18 phase. Our results showed that when using microwave irradiation the desired cross-coupling products could be obtained up to three times faster compared to classical heating (0.08 hours *vs.* 0.25 hours) (Table 1, entry 1). One has to note that considering the reaction efficiency, no fundamental difference was observed between the two ways of heating whatever the amount of palladium $Pd^{II}$ was (0.1–0.05 mol%). Indeed, 5-phenyl-2′-deoxyuridine was still obtained in very good yields.

To probe the scope of the methodology, the influence of both thermal heating and microwave heating assistance on the cross-coupling reactions of 5-iodo-2′-deoxyuridine (**4**) with other boronic acids was examined. For this purpose 4-substituted boronic acids presenting different electronic and/or steric effects were engaged in the presence of, respectively, 0.1 mol% and 0.05 mol% of $Na_2PdCl_4$ as a $Pd^{II}$ source (Table 2). In general, the reaction time and yields in the presence of $Na_2PdCl_4$ (0.1 mol%) were always shorter and higher, respectively, than those observed in the presence of lower loading of $Na_2PdCl_4$ (0.05 mol%) independently of heating. Microwave irradiation assistance allowed us to considerably

**Table 2** Variation of the nature of the *para*-substituted boronic acid for the ligandless Suzuki–Miyaura coupling starting from 5-iodo-2′-deoxyuridine




4 5-11

| Entry | Ar | Products | $Na_2PdCl_4$ (mol%) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  | **5** | 0.1 | 0.08[b] (0.25)[c] | 85[b] (80)[c] |
| 2 | | | 0.05 | 0.25[d] (0.50)[e] | 82[d] (86)[e] |
| 3 |  | **6** | 0.1 | 0.08[b] (0.50)[c] | 79[b] (79)[c] |
| 4 | | | 0.05 | 0.50[d] (2.00)[e] | 79[d] (80)[e] |
| 5 |  | **7** | 0.1 | 1.00[b] (7.00)[c] | 84[b] (64)[c] |
| 6 | | | 0.05 | 1.00[d] (24.00)[e] | 67[d] (57)[e] |
| 7 |  | **8** | 0.1 | 0.50[b] (2.00)[c] | 84[b] (80)[c] |
| 8 | | | 0.05 | 1.00[d,f] (24.00)[e] | 36[d] (70)[e] |
| 9 |  | **9** | 0.1 | 0.25[b] (1.00)[c] | 33[b] (39)[c] |
| 10 | | | 0.05 | 0.50[d] (5.00)[e] | 10[d] (13)[e] |
| 11 |  | **10** | 0.1 | 0.50[b] (6.00)[c] | 66[b] (17)[c] |
| 12 | | | 0.05 | 1.00[d,f] (5.00)[e] | 56[d] (13)[e] |
| 13 |  | **11** | 0.1 | 0.25[b] (0.50)[c] | 78[b] (69)[c] |
| 14 | | | 0.05 | 0.50[d] (24.00)[e] | 57[d] (49)[e] |

[a] Isolated yields. [b] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [c] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C. [d] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [e] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C. [f] Reaction did not go to completion.

shorten the reaction times whatever the palladium loading was (0.05 mol% or 0.1 mol%) with similar or higher yields than those obtained by thermal heating. Considering boronic acids with electron donating group in the *para* position (Table 2, entries 1–8), reaction times can be divided at least by two for the same coupling efficiency.

Indeed the cross-coupling products **5–8** were generally obtained in similar or higher yields. The presence of a methyl group in the *para* position of the aromatic ring did not change the reaction result since compound **6** was obtained in similar yield compared with reference **5** (Table 2, entries 1–4). In the presence of 4-methoxyphenyl boronic acid, extended reaction time was needed to reach completion under both heating conditions (Table 2, entries 5 and 6). Once again the desired product was isolated in better yields when reaction was done under microwave irradiation assistance. The most amazing effect was obtained for this reaction in the presence of 0.05 mol% of palladium since the reaction time was divided by 24 with the yield increasing by 10% (Table 2, entry 6). Starting from the 2-naphthylboronic acid in the presence of $Na_2PdCl_4$ (0.1 mol%), the corresponding cross-coupling product was obtained in a very good yield (80–84%) within 0.5–2.0 hours depending on the heating source (Table 2, entries 7 and 8). The use of $Na_2PdCl_4$ (0.05 mol%)

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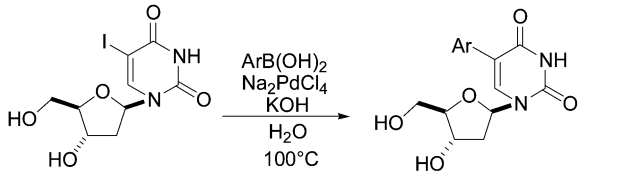
furnished compound **8** in 70% and 36% yields after 24 hours and 1 hour, respectively. It was notable that this time the cross-coupling reaction did not go to completion. Our previous report showed that an extended reaction time could be necessary when lower loading of palladium was used.[7b] The applicability of the optimized reaction conditions to boronic acids with electron-withdrawing groups was then studied (Table 2, entries 9–14). The cyano derivative **9** was obtained in moderate yield (10–40%) whatever the methodology used, but microwave irradiation still permitted us to considerably decrease the reaction times (Table 2, entries 9 and 10). One has to note that no hydrolysis of the cyano function was observed under our aqueous basic conditions. The most remarkable microwave effect was noticed in the case of 5-(4-formylphenyl)-2′-deoxyuridine (**10**). In the presence of 0.1 mol% of $Na_2PdCl_4$, this compound was isolated in 17% yield after 6 hours of reflux when thermal heating was used (Table 2, entry 11) while microwave irradiation assistance allowed us to have a full conversion of the starting material in half an hour and to isolate the target compound **10** in 66% yield (Table 2, entry 11). In the presence of $Na_2PdCl_4$ (0.05 mol%) the yield of compound **10** was low (13%) after 5 hours of thermal heating. One can note that the cross-coupling reaction of 4-formylboronic acid with 5-iodo-2′-deoxyuridine (**4**) was not completed within one hour using microwave irradiation assistance in the presence of 0.05 mol% of palladium. However the desired compound **10** was isolated in 56% yield (Table 2, entry 12). Under microwave irradiation, 4-acetylboronic acid reacted in a similar way *i.e.* increase of the yields (78% *vs.* 69%) and better efficiency of the cross-coupling (Table 2, entry 14) compared to thermal heating. In our hands, no 2′-deoxyuridine was detected during the cross-coupling reaction using those seven boronic acids.

Steric effects were also studied. For this purpose, 2-tolylboronic acid, 2-methoxyphenylboronic acid, 2-formylphenylboronic acid and 2-acetylphenylboronic acid were engaged in Suzuki–Miyaura cross-coupling reactions with 5-iodo-2′-deoxyuridine (**4**) using the previously described methodologies (Table 3). Among those four reagents, three allowed us to obtain the desired cross-coupling compounds in modest yields (Table 3, entries 1–4 and 7). In our hands, microwave irradiation heating conditions did not permit us to have a full conversion in one hour. As already reported by our group, those sterically demanding boronic acids proved to be difficult substrates for the Suzuki–Miyaura cross-coupling reaction under standard conditions.[7b] As observed in Table 2, the use of $Na_2PdCl_4$ (0.1 mol%) permitted us to reduce the reaction times and to increase the yields compared with the use of lower loading of $Na_2PdCl_4$ (0.05 mol%) under thermal as well as microwave heating conditions. Using the alternative technology, both shorter reaction times and higher yields were obtained whatever the palladium loading was (0.05 mol% or 0.1 mol%). Indeed 24 hours were necessary to obtain compounds **12** and **13** in moderate yields (18–23%) when using thermal heating (Table 3, entries 1–4). When the Suzuki cross-couplings were done under microwave irradiation assistance, reactions were not finished within 1 hour (*maximum defined reaction times chosen*), however, compounds **12** and **13** were isolated, respectively, in 30% and 45% yields when using 0.1 mol% of $Pd^{II}$ and in 21% and 23% yields

**Table 3** Variation of the nature of the *ortho* substituted boronic acid for the ligandless Suzuki–Miyaura coupling starting from 5-iodo-2′-deoxyuridine




**4** **12-15**

| Entry | Ar | Products | $Na_2PdCl_4$ (mol%) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  | **12** | 0.1 | 1.00[b,f] (24.00)[c] | 30[b] (22)[c] |
| 2 | | | 0.05 | 1.00[d,f] (24.00)[e] | 21[d] (19)[e] |
| 3 |  | **13** | 0.1 | 1.00[b,f] (24.00)[c] | 45[b] (23)[c] |
| 4 | | | 0.05 | 1.00[d,f] (24.00)[e] | 23[d] (18)[e] |
| 5 |  | **14** | 0.1 | 1.00[b,f] (24.00)[c] | 0[b] (0)[c] |
| 6 | | | 0.05 | 1.00[d,f] (24.00)[e] | 0[d] (0)[e] |
| 7 |  | **15** | 0.1 | 0.50[b] (24.00)[c] | 23[b] (0)[c] |
| 8 | | | 0.05 | 1.00[d,f] (24.00)[e] | 0[d] (0)[e] |

[a] Isolated yields. [b] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [c] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C. [d] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [e] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C. [f] Reaction did not go to completion.

when using 0.05 mol% of $Pd^{II}$ (Table 3, entries 1–4). This improvement of the reaction efficiency was more moderate when we used boronic acids which cumulated both steric effects and electron withdrawing substituents such as 2-acetylphenylboronic acid and 2-formylphenylboronic acid (Table 3, entries 5–8). In general, no cross-coupling product was obtained when reactions were performed with thermal as well as microwave heating for the same amount of palladium $Pd^{II}$ (Table 3, entries 5–8). Only compound **15** could be isolated in 23% yield using $Na_2PdCl_4$ (0.1 mol%) under microwave irradiation for one hour. Using 2-acetylphenylboronic acid and 2-formylphenylboronic acid, the main product was the dehalogenated 2′-deoxyuridine (20 mg, 31%).

In order to expend the array of substrates, 5-iodo-2′-deoxyuridine (**4**) was coupled with a variety of heteroarylboronic acids (Table 4, entries 1–4) and with the (*E*) styrylboronic acid (Table 4, entries 5 and 6). Concerning heteroarylboronic acids, only thiophen-2-boronic acid was reactive enough to give the desired cross-coupling product **16** in a modest yield of 32% in 5 hours when using 0.1 mol% of palladium $Pd^{II}$ under thermal heating (Table 4, entry 1). Furan-2-ylboronic acid was in turn totally nonreactive as only the starting nucleoside and the dehalogenated nucleoside were obtained (Table 4, entries 3 and 4). Once again, microwave irradiation assistance in the presence of $Na_2PdCl_4$ (0.05–0.1 mol%) was beneficial as it allowed us to conduct the Suzuki cross-coupling reactions starting from both the two heteroarylboronic acids and the styrenyl one. In our hands, the target compounds **16–17** were obtained in the presence of

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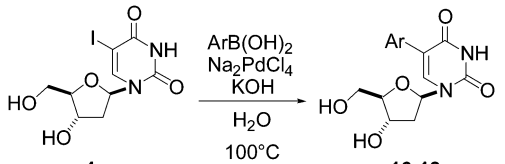
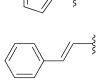
**Table 4** Variation of the nature of the aryl boronic acid for the ligandless Suzuki–Miyaura coupling starting from 5-iodo-2′-deoxyuridine



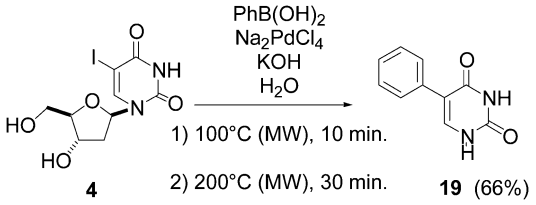

| Entry | Ar | Products | $Na_2PdCl_4$ (mol%) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  | **16** | 0.1 | 1.00[f,b] (6.00)[c] | 40[b] (32)[c] |
| 2 | | | 0.05 | 1.00[d,f] (24.00)[e] | 45[d] (0)[e] |
| 3 |  | **17** | 0.1 | 1.00[b,f] (24.00)[c] | 75[b] (0)[c] |
| 4 | | | 0.05 | 1.00[d,f] (24.00)[e] | 18[d] (0)[e] |
| 5 |  | **18** | 0.1 | 0.5[b] (2.00)[c] | 85[b] (58)[c] |
| 6 | | | 0.05 | 1.00[d] (4.00)[e] | 66[d] (33)[e] |

[a] Isolated yields. [b] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [c] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.1 mol%), KOH (0.56 mmol), water (2 mL), 100 °C. [d] Reaction conditions: 5-iodo-2′deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C, MW irradiation. [e] Reaction conditions: 5-iodo-2′-deoxyuridine (0.28 mmol), arylboronic acid (0.364 mmol), $Na_2PdCl_4$ (0.05 mol%), KOH (0.56 mmol), water (2 mL), 100 °C. [f] Reaction did not go to completion.

$Na_2PdCl_4$ (0.1 mol%) after one hour in 40% and 75% yield, respectively, without a full conversion of the starting material. Our methodology furnished those two target nucleoside analogues in similar yields to those described in the literature but using a lower amount of palladium and without any ligand.[6h,7f] Regarding compound **18**, it was prepared with a full conversion after one hour in 85% yield in the presence of $Na_2PdCl_4$ (0.1 mol%) and in 66% yield in the presence of $Na_2PdCl_4$ (0.05 mol%) (Table 4, entries 7 and 8). Compound **18** has already been described in the literature *via* Heck coupling.[12] To the best of our knowledge, our methodology permitted us, for the first time, to obtain it using Suzuki–Miyaura reaction.

In an attempt to improve reaction efficiency we tested the effect of an increase of temperature (120 °C, 140 °C, 160 °C, 180 °C and 200 °C) on our model reaction (5-iodo-2′-deoxyuridine (**4**) and phenylboronic acid). By increasing the temperature, we gradually observed formation of side-products due to dehalogenation of the starting material and deglycosylation of both the dehalogenated substrate and the cross-coupled product. Moreover it was noticed that at 200 °C only uracil was obtained indicating that at this temperature dehalogenation of the starting material was faster than cross-coupling reaction. This result prompted us to try to deglycosylate our previously isolated cross-coupled product **5**. Compound **19** was then obtained. Starting from 5-iodo-2′-deoxyuridine (**4**), 5-phenyluracil (**19**) was isolated in 66% yield by original ''one-pot, two-step'' synthesis conducted in water as sole solvent (Scheme 1).

Most of the known methodologies for obtaining 5-substituted uracil derivatives started from $N_1$- and $N_3$-protected uracil and were accomplished in organic solvents.[13] Exemplification of this reaction is currently being studied.




**Scheme 1** ''One-pot, two-step'' synthesis of 5-phenyluracil.

## Conclusions

In summary, new, simple and efficient ligandless procedures for Suzuki–Miyaura cross-coupling of 5-iodo-2′-deoxyuridine (**4**) in neat water have been developed using low loading of palladium (0.05–0.1 mol%) in moderate to good yields using either thermal heating or microwave irradiation assistance. Our optimized reaction conditions allowed us to obtain various 5-aryl-2′-deoxyuridine derivatives. The aryl moieties were *para* and *ortho* substituted phenyl rings having electron-donating or -withdrawing substituents and an aromatic heterocyclic core. The reaction time and yields in the presence of $Na_2PdCl_4$ (0.1 mol%) were always shorter and higher than those observed in the presence of lower loading of $Na_2PdCl_4$ (0.05 mol%) under thermal as well as microwave irradiation conditions. In addition, the cross-coupling reactions were more efficient when the microwave irradiation was the heating source. The presented work permitted the synthesis of the sterically hindered and electronically disadvantageous compound **15**, the aromatic heterocyclic derivatives **16–17** and the styrenyl compound **18** in good yields compared with the literature. To the best of our knowledge in the area of nucleoside chemistry, our green and economic conditions having no protection–deprotection steps, no ligand, low loading of palladium, water as sole solvent, thermal and microwave irradiation conditions were the most efficient ones.

## Experimental

All products were purchased either from Acros or Sigma Aldrich depending on their availability. All solvents were purchased from Carlo Erba. All reactions were monitored by TLC (Kieselgel 60F254 MERCK aluminium sheet) with detection by UV light and/or with sulfuric acid in ethanol (90 : 10, v/v) and by HPLC (Shimadzu). The column used is a GRACE Prevail C18. The detectors used are an SPD-M20A photo diode array detector (Shimadzu), an LCMS-2020 mass spectrometer (Shimadzu) and an ELSD-LTII (Shimadzu). The mobile phase is a mixture of water and MeOH (50 : 50). Mass spectrometry analyses were performed on a Shimadzu LCMS-2020 mass spectrometer equipped with an electrospray source (ESCI). $^1H$ and $^{13}C$ NMR spectra were recorded on a 400 MHz Bruker UltraShield 400 MHz/54 mm Ultra long hold. Chemical shifts ($\delta$) are quoted in ppm and are referenced to TMS as an internal standard. Coupling constants ($J$) are quoted in Hz. Melting points are recorded on a Stuart SMP 10 and are uncorrected.

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### Synthesis of 5-aryl-2′-deoxyuridine 5–18

**General procedure for thermal heating.** Under nitrogen atmosphere, 2′-deoxy-5-iodo-uridine (100 mg, 0.28 mmol, 1 equiv.), potassium hydroxide (31 mg, 0.56 mmol, 2 equiv.) and the boronic acid (0.37 mmol, 1.3 equiv.) were placed in a 25 mL flask. Nitrogen flushed solutions of $Na_2PdCl_4$ in water (1 mL, $2.8 \times 10^{-4}$ mmol, 0.1 mol%) and water (1 mL) were added. The mixture was then heated to 100 °C. Conversion is followed by HPLC. After complete conversion, the mixture was cooled down to room temperature and evaporated *in vacuo*. The crude residue was purified by flash-chromatography on C18 silica ($H_2O$ : MeOH 92 : 5 to 5 : 95). The fractions were combined and methanol was removed under reduce pressure. The remaining solution was frozen with liquid nitrogen and lyophilisated.

**General procedure for microwave heating.** 2′-Deoxy-5-iodo-uridine (100 mg, 0.28 mmol, 1 equiv.), potassium hydroxide (31 mg, 0.56 mmol, 2 equiv.) and the boronic acid (0.37 mmol, 1.3 equiv.) were placed in a 10 mL vial. Nitrogen flushed solutions of $Na_2PdCl_4$ in water (1 mL, $2.8 \times 10^{-4}$ mmol, 0.1 mol%) and water (1 mL) were added. The mixture was stirred under microwave irradiation heating (AntonPaar Monowave 300) at 100 °C for the indicated times. The crude residue was purified by flash-chromatography on C18 silica ($H_2O$ : MeOH 92 : 5 to 5 : 95). The fractions were combined and methanol was removed under reduced pressure. The remaining solution was frozen with liquid nitrogen and lyophilisated.

**Procedure for obtention of compound 19.** 2′-Deoxy-5-iodo-uridine (100 mg, 0.28 mmol, 1 equiv.), potassium hydroxide (31 mg, 0.56 mmol, 2 equiv.) and phenylboronic acid (0.37 mmol, 1.3 equiv.) were placed in a 10 mL vial. Nitrogen flushed solutions of $Na_2PdCl_4$ in water (1 mL, $2.8 \times 10^{-4}$ mmol, 0.1 mol%) and water (1 mL) were added. The mixture was stirred under microwave irradiation heating (AntonPaar Monowave 300) at 100 °C for 10 minutes and then at 200 °C for 30 minutes. The crude residue was then diluted in water (20 mL) and pH was adjusted to 5 using acetic acid 95%. Aqueous phase was then extracted with AcOEt (3 × 20 mL). Organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude brown solid was then recrystallized from EtOH to give (**19**).

**5-Phenyl-2′-deoxyuridine (5).** White solid, mp = 187 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.51 (s, 1H), 8.20 (s, 1H), 7.54 (d, 2H, $J$ = 7.2 Hz), 7.38–7.28 (m, 3H), 6.24 (t, 1H, $J$ = 6.4 Hz), 5.26 (d, 1H, $J$ = 4.0 Hz), 5.11 (t, 1H, $J$ = 4.8 Hz), 4.29 (s, 1H), 3.81 (d, 1H, $J$ = 2.8 Hz), 3.64–3.56 (m, 2H), 3.33 (s, 2H), 2.28–2.13 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 161.9, 149.7, 137.9, 133.0, 128.0, 127.8, 127.0, 113.3, 87.3, 84.3, 70.1, 70.0, 60.8, 60.7, (one signal hidden in solvent peaks) MS (ESI): $m/z$ = 305.10 [M + H$^+$], 327.10 [M + Na$^+$], 303.05 [M − H]$^-$.

**5-(4-Tolyl)-2′-deoxyuridine (6).** White solid, mp = 206 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.47 (s, 1H), 8.14 (s, 1H), 7.45 (d, 2H, $J$ = 7.2 Hz), 7.18 (s, 2H), 6.24 (t, 1H, $J$ = 5.2 Hz), 5.28 (s, 1H), 5.11 (s, 1H), 4.29 (s, 1H), 3.81 (d, 1H, $J$ = 2.4 Hz), 3.64–3.56 (m, 2H), 3.34 (s, 2H), 2.31 (s, 3H), 2.25–2.14 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 162.3, 149.9, 137.3, 136.3, 130.2, 128.6, 127.6, 113.3, 83.3, 84.3, 70.1, 60.9, 20.6 (one signal hidden in solvent peaks). MS (ESI): $m/z$ = 341.10 [M + Na$^+$], 317.05 [M − H]$^-$.

**5-(4-Methoxyphenyl)-2′-deoxyuridine (7).** White solid, mp = 186 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.42 (s, 1H), 8.11 (s, 1H), 7.48 (d, 2H, $J$ = 8.8 Hz), 6.92 (d, 2H, $J$ = 8.8 Hz), 6.24 (t, 1H, $J$ = 6.4 Hz), 5.20 (s, 1H), 4.29 (s, 1H), 3.81 (d, 1H, $J$ = 2.8 Hz), 3.76 (s, 3H), 3.60 (qd, 2H, $J$ = 12.0, 2.8 Hz), 3.54 (s, 2H), 2.27–2.12 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 166.5, 155.1, 153.1, 86.9, 84.4, 73.2, 73.1, 73.1, 70.2, 61.1, 48.5, 40.1. MS (ESI): $m/z$ = 357.15 [M + Na$^+$], 333.05 [M − H]$^-$.

**5-(2-Naphthyl)-2′-deoxyuridine (8).** White solid, mp = 205 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.58 (s, 1H), 8.37 (s, 1H), 8.14 (s, 1H), 8.03–8.49 (m, 7H), 6.27 (t, 1H, $J$ = 6.4 Hz), 5.29 (d, 1H, $J$ = 2.0 Hz), 5.19 (s, 1H), 3.81 (d, 1H, $J$ = 2.8 Hz), 4.33 (s, 1H), 3.84 (d, 1H, $J$ = 2.8 Hz), 3.63 (q, 2H, $J$ = 10.4 Hz), 2.34–2.18 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 164.8, 151.9, 140.2, 134.8, 134.2, 131.8, 129.2, 128.7, 128.5, 128.2, 127.3, 127.2, 127.1, 115.9, 89.1, 86.8, 72.0, 62.5, 41.8 (one signal hidden in solvent peaks). MS (ESI): $m/z$ = 377.05 [M + Na$^+$], 353.1 [M − H]$^-$.

**5-(4-Cyanophenyl)-2′-deoxyuridine (9).** White solid, mp > 260 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.58 (s, 1H), 8.37 (s, 1H), 8.14 (s, 1H), 8.03–8.49 (m, 7H), 6.27 (t, 1H, $J$ = 6.4 Hz), 5.29 (d, 1H, $J$ = 2.0 Hz), 5.19 (s, 1H), 3.81 (d, 1H, $J$ = 2.8 Hz), 4.33 (s, 1H), 3.84 (d, 1H, $J$ = 2.8 Hz), 3.63 (q, 2H, $J$ = 10.4 Hz), 2.34–2.18 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 188.1, 161.6, 149.6, 139.7, 138.1, 131.9, 128.2, 111.3, 109.2, 87.4, 84.7, 69.7, 60.6 (1 signal hidden in solvent peaks). MS (ESI): 328 [M − H]$^-$.

**5-(4-Formylphenyl)-2′-deoxyuridine (10).** White solid, mp = 250 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.61 (s, 1H), 10.00 (s, 1H), 8.44 (s, 1H), 7.89 (d, 2H, $J$ = 8.4 Hz), 7.83 (d, 2H, $J$ = 8.0 Hz), 6.23 (t, 1H, $J$ = 6.4 Hz), 5.27 (s, 2H), 4.31 (q, 1H, $J$ = 2.4 Hz), 3.83 (d, 1H, $J$ = 3.2 Hz), 3.64 (qd, 2H, $J$ = 12.0, 2.8 Hz), 3.35 (s, 2H), 2.31–2.16 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 192.5, 162.1, 149.9, 139.3, 139.5, 134.5, 129.3, 128.0, 11.9, 87.5, 84.7, 69.8, 60.7, 40.2. MS (ESI): $m/z$ = 355.15 [M + Na$^+$], 331.05 [M − H]$^-$.

**5-(4-Acetylphenyl)-2′-deoxyuridine (11).** White solid, mp = 249 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.28 (s, 1H), 8.35 (d, 2H, $J$ = 2.0 Hz), 7.83 (d, 2H, $J$ = 8.4 Hz), 7.76 (d, 2H, $J$ = 8.4 Hz), 6.24 (t, 1H, $J$ = 6.4 Hz), 5.39 (s, 2H), 4.32 (s, 1H), 3.82 (d, 1H, $J$ = 2.8 Hz), 3.67–3.60 (m, 2H), 3.34 (s, 2H), 2.58 (s, 3H), 2.27–2.16 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 197.3, 163.3, 150.8, 138.9, 138.8, 134.9, 127.7, 127.6, 112.1, 87.4, 84.6, 69.9, 60.7, 40.2, 26.6. MS (ESI): $m/z$ = 369.15 [M + Na$^+$], 345.05 [M − H]$^-$.

**5-(2-Tolyl)-2′-deoxyuridine (12).** White foam. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 7.79 (s, 1H), 7.21–710 (m, 4H), 6.24 (t, 1H, $J$ = 6.8 Hz), 4.24 (s, 1H), 3.76 (d, 1H, $J$ = 2.8 Hz), 3.51 (t, 3H, $J$ = 12.8 Hz), 2.14–2.08 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 163.4, 151.4, 138.2, 137.0, 133.7, 130.5, 129.6, 127.4, 125.3, 114.6, 87.2, 84.2, 70.3, 61.0, 19.7. MS (ESI): $m/z$ = 341.05 [M + Na$^+$], 317.05 [M − H]$^-$.

**5-(2-Methoxyphenyl)-2′-deoxyuridine (13).** White foam. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.32 (s, 1H), 7.88 (s, 1H), 7.30 (t, 1H, $J$ = 7.6 Hz), 7.22 (dd, 1H, $J$ = 7.2, 0.8 Hz), 7.03 (d, 1H, $J$ = 8.4 Hz),

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6.93 (t, 1H, $J$ = 7.2 Hz), 6.24 (t, 1H, $J$ = 7.2 Hz), 5.08 (s, 2H), 4.23 (s, 1H), 3.78 (d, 1H, $J$ = 2.4 Hz), 3.72 (s, 3H), 3.51 (d, 2H, $J$ = 2.0 Hz), 3.43 (s, 2H), 2.18–2.11 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 162.3, 156.9, 150.5, 138.7, 131.2, 128.8, 122.1, 119.8, 111.2, 111.1, 87.2, 84.0, 70.4, 61.2, 55.3. MS (ESI): $m/z$ = 357.15 $[M + Na^+]$, 333.1 $[M - H]^-$.

**5-(2-Acetylphenyl)-2′-deoxyuridine (15).** White solid, mp > 250 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.26 (s, 1H), 8.49 (d, 1H, $J$ = 5.2 Hz), 8.09 (s, 1H), 7.62–7.55 (m, 2H), 7.12 (t, 1H, $J$ = 6.8 Hz), 4.21 (d, 1H, $J$ = 6.8 Hz), 3.78 (d, 1H, $J$ = 2.4 Hz), 3.72 (s, 3H), 3.51 (d, 2H, $J$ = 2 Hz), 3.43 (s, 2H), 2.08–1.99 (m, 2H), 1.65 (s, 3H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 168.3, 165.5, 156.6, 152, 142.5, 139.9, 101.8, 87.2, 86.7, 84.4, 84.1, 74.1, 70.3, 70.2, 61.3, 61.2. MS (ESI): 369.34 $[M + Na^+]$, 345.35 $[M - H]^-$.

**5-(Thiophen-2-yl)-2′-deoxyuridine (16).** White foam (very hygroscopic). NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.66 (s, 1H), 8.18 (d, 1H, $J$ = 4.8 Hz), 6.11 (t, 1H, $J$ = 6.4 Hz), 5.21 (s, 1H), 5.10 (s, 1H), 4.21 (br s, 1H), 3.75 (d, 1H, $J$ = 2.4 Hz), 3.56 (qd, 2H, $J$ = 10 Hz, $J$ = 2.4 Hz), 2.06–2.04 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 165.6, 163.0, 154.3, 150.2, 142.8, 140.0, 101.2, 86.5, 84.0, 72.2, 69.7, 60.6 (1 signal hidden in solvent peaks). MS (ESI): 333.35 $[M + Na^+]$, 309.35 $[M - H]^-$.

**5-(Furan-2-yl)-2′-deoxyuridine (17).** White foam (very hygroscopic). NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.61 (s, 1H), 8.27 (s, 1H), 7.60 (s, 1H), 6.86 (d, 1H, $J$ = 2.8 Hz), 6.51 (dd, 1H, $J$ = 3.2 Hz), 6.23 (t, 1H, $J$ = 6.4 Hz), 5.30–5.09 (m, 2H), 4.28–4.20 (m, 2H), 2.17–2.14 (m, 2H). MS (ESI): 317.25 $[M + Na^+]$, 293.25 $[M - H]^-$.

**5-(*trans*-β-Styryl)-2′-deoxyuridine (18).** White solid, mp = 145 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.50 (s, 1H), 8.23 (s, 1H), 7.46 (d, 2H, $J$ = 7.2 Hz), 7.41 (d, 1H, $J$ = 16.2 Hz), 7.35 (t, 2H, $J$ = 7.2 Hz), 7.23 (t, 1H, $J$ = 10.8 Hz), 6.89 (d, 1H, $J$ = 16.2 Hz), 6.19 (t, 1H, $J$ = 6.4 Hz), 5.28 (s, 1H), 5.21 (s, 1H), 4.29 (s, 1H), 3.68 (d, 1H, $J$ = 12.8 Hz), 3.62 (d, 1H, $J$ = 10.8 Hz), 2.23–2.12 (m, 2H). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 162.20, 149.49, 138.08, 137.48, 128.69, 127.55, 127.27, 125.96, 121.22, 110.74, 87.42, 84.38, 69.95, 60.97 (one signal hidden in solvent peaks). MS (ESI): 353.35 $[M + Na^+]$, 329.35 $[M - H]^-$.

**5-Phenyluracile (19).** Beige solid (35 mg, 66%) mp > 260 °C. NMR $^1$H (400 MHz, DMSO-$d_6$) $\delta$ = 11.25 (s, 1H), 11.14 (s, 1H), 7.61 (s, 1H), 7.53 (d, 2H, $J$ = 7.2 Hz), 7.35 (t, 2H, $J$ = 7.2 Hz), 7.29 (1H, t, $J$ = 7.2 Hz). NMR $^{13}$C (101 MHz, DMSO-$d_6$) $\delta$ = 163.1, 150.9, 139.7, 133.3, 128.0, 127.9, 126.9, 112.07. MS (ESI): 211.05 $[M + Na^+]$, 187.05 $[M - H]^-$.

## Acknowledgements

GS thanks Dr G. Santini and ESCOM for their financial support. This work was supported in part by regional program of Region Picardie, France.

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