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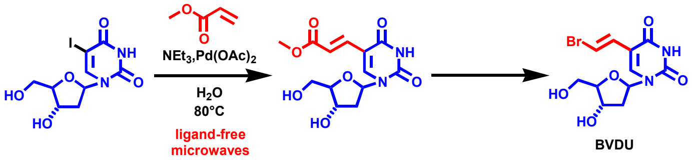

Graphical abstract

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

First ligand-free, microwaves-assisted, Heck cross-coupling reaction in sole water on nucleoside - Application to the synthesis of antiviral BVDU

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

For the first time, palladium catalyzed Heck cross-coupling reaction between 5-iodo-2′-deoxyuridine and various acrylate derivatives was performed using ligand-free conditions and assisted-microwaves in pure water. Those new conditions allowed a totally aqueous access to antiviral BVDU in higher yield than that reported (56 *vs* 31% for three steps).

DNA and RNA have always been a source of inspiration for chemists. Consequently, synthetic nucleosides have attracted considerable attention especially due to their potential biological properties.[1] One of the many modifications which have been made to the structure of regular nucleoside in an attempt to enhance chemotherapeutic potential is the introduction of a *C-C* bond on the pyridine and purine moiety. In this regard, palladium-catalyzed cross-coupling reactions have proven to be convenient and efficient methods.[2] Among all *C-C* coupling reactions, Suzuki-Miyaura has been widely used in the field of nucleoside chemistry either in organic solvents or in aqueous conditions in order to create a sp^2-sp^2 bound.[3] Nevertheless, Heck reaction is certainly the most common method to introduce an alkenyl group on nucleosides. Various methodologies starting from mercuriated nucleosides or halonucleosides have been reported in organic medium such as DMF and dioxan most often in presence of ligand.[4] Even if the Heck cross-couplings in aqueous solvents are well documented,[5] surprisingly only few recent examples of this reaction performed on nucleosides in aqueous conditions have been described.[6,7] To the best of our knowledge there is no example of Heck cross-coupling reaction on nucleoside in pure water. Our recent work on green Suzuki reaction in water led us to explore other *C-C* coupling reactions for the obtention of a larger library.[8] Herein we reported that Heck reaction can be performed in sole water using Pd(II) as catalyst in presence of NEt_3 as base under mild conditions using microwave irradiations. Two sources of hydrosoluble, commercially available and inexpensive palladium Pd(II) have been tested: Na_2PdCl_4 and $Pd(OAc)_2$. Concerning the choice of the base, various possibilities were applicable. In our hands, NEt_3 was chosen for two main reasons: (i) it is a common inexpensive base and (ii) Shaughnessy demonstrated that NEt_3 was able to reduce the Pd(II) precatalyst to the Pd(0) active species.[6] The acrylate pattern has been chosen since its ester moiety can, in theory, be the starting point of various organic functions such as α,β-unsaturated carboxylic acid for the formation of the CVU, an effective tool for ligation in DNA and RNA (Fig. 1)[9] or as bromovinyl group for the formation of the antiviral BVDU (Fig. 1).[10]

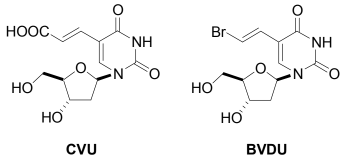
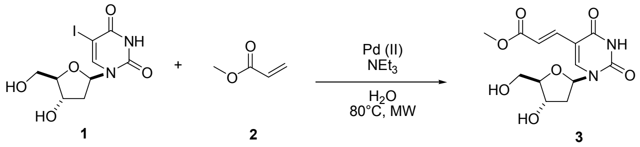


Fig. 1 CVU and BVDU structures.

Initial Heck cross-coupling reaction was performed using deprotected 5-iodo-2′-deoxyuridine (**1**) and methylacrylate (**2**) in presence of Pd(II) and NEt_3 in sole water at 80°C under microwave irradiations in order to isolate compound **3** (Table 1). In accordance with our previous results on Suzuki cross-coupling reactions, ligand-free reaction was studied. In the presented work, the reaction time was determined by HPLC monitoring either until no more conversion of the starting material **1** was observed or within maximum time of one hour. For this methodology different amounts of Pd(II) (1-10 mol%) were tested (Table 1).

Table 1 Ligand-free Heck coupling of 5-iodo-2′-deoxyuridine (**1**) with methylacrylate (**2**) in water as the sole solvent



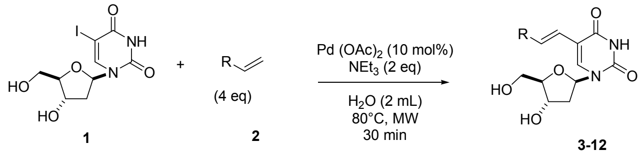
Entry	Pd(II) (mol%)	T(°C)	t (min)	**3** (%)[a]
1	Na_2PdCl_4 (1)	80	60	<5[b]
2	Na_2PdCl_4 (5)	80	60	30[b]
3	Na_2PdCl_4 (5)	100	30	35[b,c]
4	Na_2PdCl_4 (10)	80	60	87
5	$Pd(OAc)_2$ (1)	80	60	<5[b]
6	$Pd(OAc)_2$ (5)	80	60	35[b]
7	$Pd(OAc)_2$ (5)	100	30	43[b,c]
8	$Pd(OAc)_2$ (10)	80	60	90
9	$Pd(OAc)_2$ (10)	80	30	90
10	$Pd(OAc)_2$ (10)	80	15	75[b]

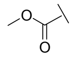
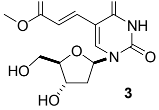
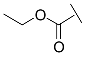
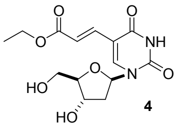
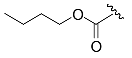
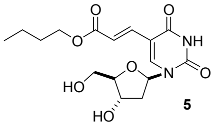
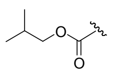
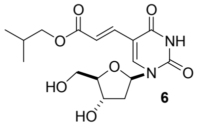
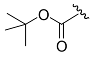
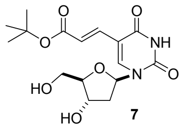
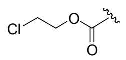
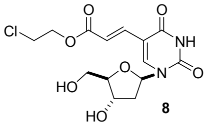
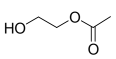
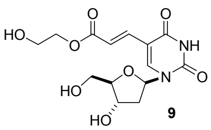
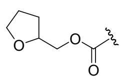
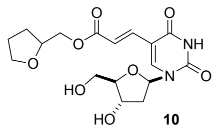
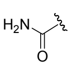
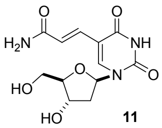
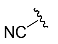
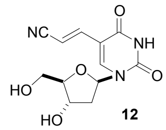
[a]Isolated yields. [b]Full conversion of starting material was not achieved. [c]Presence of 2′-deoxyuridine.

From those experiments one could see that the amount of catalysts and the temperature have an impact on Heck cross-coupling. Na_2PdCl_4 and $Pd(OAc)_2$ were not very efficient when used in low amounts at 80°C (Table 1, entries 1, 2, 5 and 6). In those cases a full conversion of the starting material could not be obtained during the first one hour. An increase of the temperature (100°C *vs* 80°C) led to the apparition of the dehalogenated 2′-deoxyuridine (Table 1, entries 3 and 7). To minimize this side-reaction, one potent option was to raise the amount of palladium (10 mol% *vs* 1-5 mol%) (Table 1, entries 4, 8-10). In those new conditions, $Pd(OAc)_2$ was the best palladium source for this cross-coupling reaction. Indeed full conversion of 5-iodo-2′-deoxyrudine (**1**) was achieved in one hour and cross-coupled product **3** isolated in 90% yield (Table 1, entry 8). A decrease of reaction time was studied (Table 1, entries 9 and 10) and the same efficiency was obtained after 30 minutes of microwaves activation (Table 1, entry 9).

Based on these results, Heck cross-coupling of 5-iodo-2′-deoxyuridine (**1**) with various acrylate derivatives (Table 2) was carried out using the optimized conditions (Table 1, entry 9).

Table 2 Ligand-free Heck coupling of 5-iodo-2′-deoxyuridine (**1**) with acrylate derivatives in sole water



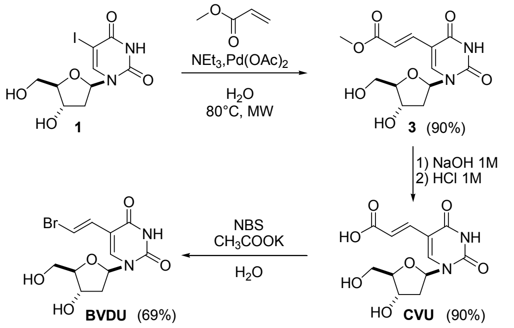
Entry	R	Product	Yield (%)[a]
1		 **3**	90
2		 **4**	90
3		 **5**	45
4		 **6**	45
5		 **7**	45
6		 **8**	40
7		 **9**	45
8		 **10**	35
9		 **11**	60
10		 **12**	51

[a] Isolated yields (see S. I. for purification procedure).

Our method was very efficient with the shortest acrylate chains since it permit to furnish compounds **3** and **4** in 90% yields (Table 2, entries 1 and 2). Butylacrylate and *t*-butylacrylate are known to be less soluble in water compared to methyl- and ethylacrylate. Our method still furnished compounds **5** and **7** in 45% yield even if the starting esters presented lipophilic properties (Table 2, entries 3 and 5). To the best of our knowledge, isobutylacrylate has never been used in Heck cross-coupling reaction on nucleosides. It showed the same low solubility as butyl- and *t*-butylacrylate in water and original product **6** was isolated in 45% yields (Table 2, entry 4). Because the introduction of a heteroatom on the carbonated chain of the acrylate might allow access to more evolved compounds, we undertook to examine the behavior of 2-chloro-, 2-hydroxylethylacrylate and its corresponding cyclic ether in our totally aqueous Heck conditions. The presence of the chlorine or of the oxygen atoms did not seem to change the lipophilic properties of the reactant. Consequently compounds **8**, **9** and **10**, which have also never been described before, were isolated in the same range of yields (Table 2, entries 6-8). In order to modulate the structure, substitution of the ester by amido and cyano groups was studied. By applying our methodology, we could isolate compounds **11** and **12** in respectively 60% and 51% yields.

It has to be noted that traditional organic Heck couplings of the less hindered reactants (methylacrylate and ethylacrylate) have already been reported in the literature.[4g, 11-14] Concerning more hindered and lipophilic acrylates, Shaugnessy and Hocek reported independently the obtention of **5** using aqueous conditions (H_2O/CH_3CN).[6,7] In 2004, Agrofoglio reported the synthesis of **7** using polystyrene-based solid-supports at 100°C in DMA for 24h.[15] Finally cross-coupled products **11** and **12** were briefly described in the literature using refluxing DMF as solvent.[4d, 16] Effectiveness of our method is difficult to compare with reported works as many different reaction parameters such as the nature of the solvent, the presence of ligand, catalyst concentration, temperature ... were different. Yields obtained by the present method are similar to those published when a short chain compounds were used (compounds **3** and **4**) and lower for compounds with higher lipophilicity (compounds 5 and 7). Concerning the cyanovinyl derivative, our methodology is as efficient as the one reported in literature. The acrylamide was obtained in a slightly lower yield. Anyway the use of water as sole solvent, the low amount of palladium (10 mol%), the absence of ligand and the use of an alternative heating source such as microwaves are major advantages in the field of sustainable chemistry.

The first synthesis of BVDU starting from a nucleoside was reported by Walker in 1979.[17] A large scale synthesis of BVDU was since described by De Clercq using compound **3** as key-intermediate. Compound **3** was, at this time, obtained in 70% yield in dioxan starting from 5-iodo-2′-deoxyuridine (**1**) in presence of a large excess of Pd(OAc)$_2$ (47 mol%) and triphenylphosphine (1 eq).[4c, 11] The methylacrylate derivative **3** undertook a basis hydrolysis followed by radical decarboxylation-bromination (Hunsdiecker reaction). This last step was described in different solvents such DMF,[4c, 11] H$_2$O,[17] H$_2$O/THF[18] or more recently ionic liquid.[19] On the basis of our experimental results together with related literature reports, obtention of BVDU *via* CVU is now, for the first time, totally feasible in pure water in absence of other solvent. Indeed, starting from totally deprotected 5-iodo-2′-deoxyuridine (**1**), we were able to obtain BVDU in sole water in three successive steps: free-ligand microwaves-assisted Heck cross-coupling; hydrolysis and Hunsdiecker reaction (Scheme 1). In our hands, BVDU was obtained with a better total yield compared with the literature (56% *vs* 31%[11]).



Scheme 1 Total synthesis of BVDU starting from 5-iodo-2′-deoxyuridine (**1**) in water as the sole solvent.

Conclusions

In conclusion, the first ligand-free Heck cross-coupling of a nucleoside, under microwave irradiations, in pure water has been described starting from 5-iodo-2’-deoxyuridine (**1**). Ten compounds were isolated in modest to very good yields (40%-90%). Furthermore a greener synthesis of CVU and well-known antiviral BVDU have been proposed. Those two compounds were respectively isolated in 80% and 56% yields.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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