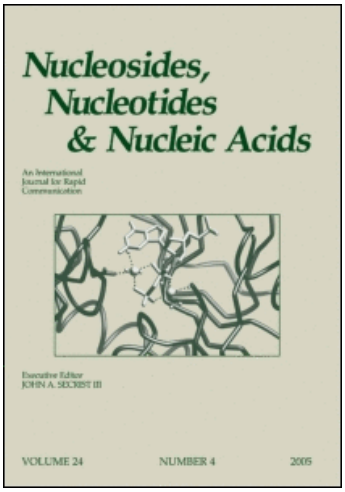


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Supported Synthesis and Functionnalization of 2''-Deoxyuridine by Suzuki-Miyaura Cross-Coupling

Saïd El Kazzouli[a]; Sabine Berteina-Raboin[a]; Luigi A. Agrofoglio[a]
[a] Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, Orléans, France

To cite this Article Kazzouli, Saïd El , Berteina-Raboin, Sabine and Agrofoglio, Luigi A.(2007) 'Supported Synthesis and Functionnalization of 2''-Deoxyuridine by Suzuki-Miyaura Cross-Coupling', Nucleosides, Nucleotides and Nucleic Acids, 26: 10, 1395 — 1398
To link to this Article: DOI: 10.1080/15257770701534170
URL: http://dx.doi.org/10.1080/15257770701534170

Nucleosides, Nucleotides, and Nucleic Acids, 26:1395–1398, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701534170

Taylor & Francis
Taylor & Francis Group

SUPPORTED SYNTHESIS AND FUNCTIONNALIZATION OF 2′-DEOXYURIDINE BY SUZUKI-MIYAURA CROSS-COUPLING

Saïd El Kazzouli, Sabine Berteina-Raboin, and Luigi A. Agrofoglio □
Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, Orléans, France

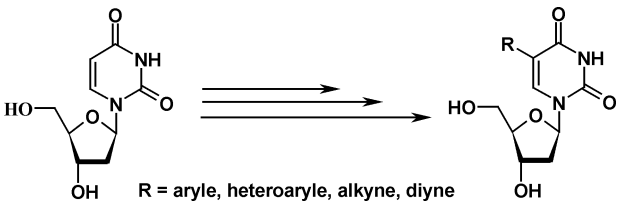
□ *The synthesis and modification of 2′-deoxyuridine has been realized under Suzuki-Miyaura palladium-catalyzed cross-coupling conditions. Using $Pd(PPh_3)_4$ and Na_2CO_3, 5-iodo-2′-deoxyuridine bound to solid support is coupled with various boronic acids to give 5-(hetero)aryl-2′-deoxyuridine. $Pd(PPh_3)_4$ palladium catalyzed was found to be superior to $Pd(OAc)_2$ and (NHC)Pd(allyl)Cl for Suzuki-Miyaura palladium-catalyzed reactions.*

Keywords Polystyrene; solid phase; Pd(0) cross-coupling; Suzuki-Miyaura; nucleosides

INTRODUCTION

The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis from hundreds of academic and pharmaceutical laboratories. One useful approach, recently reviewed by our group, has involved the use of palladium-catalyzed insertion and cross-coupling reactions (Heck, Stille, Sonogashira, Tsuji-Trost, etc.), which have gained recognition due to their broad scope. Another approach that has developed rapidly in recent years involves the synthesis of small organic molecule libraries by a parallel solid-phase strategy. Except for the very well-known solid phase oligonucleotide synthesis, this powerful technology has tardy been applied to mono nucleoside chemistry. Thus, as part of our drug discovery program, we describe here the successful application and optimization of palladium-assisted routes to pyrimidine nucleosides bound to polystyrene resins. We have focused on the optimization of the Suzuki-type reactions; the presented methods exhibit a significant improvement and facilitate the synthetic procedure with respect to purification and yields (determined after filtration over silica gel).

Address correspondence to Luigi A. Agrofoglio, Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France. E-mail: luigi.agrofoglio@univ-orleans.fr

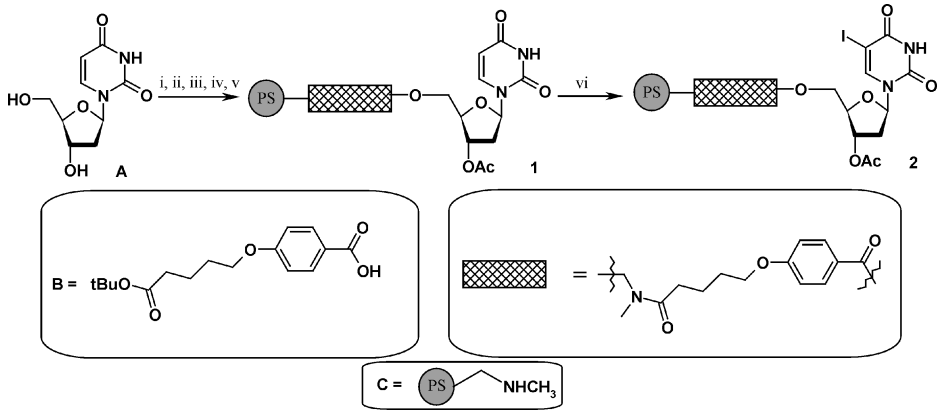


SCHEME 1 General approach to C5-substituted carbanucleoside via solid-phase synthesis and Pd(o) chemistry.

RESULTS AND DISCUSSION

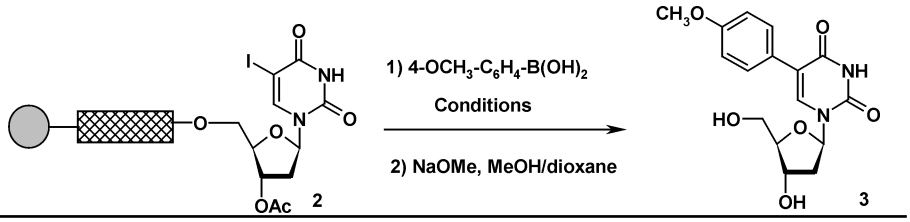
Recently, we reported a new and useful approach for nucleoside synthesis and modification by combination of solid-phase synthesis and palladium mediated cross-coupling reaction.[1] As part of our continuing efforts to develop this drug discovery program, we were interested herein in the use of Suzuki-Miyaura[2] palladium cross-coupling reaction on 2′-deoxyuridine as a route to new nucleoside (Scheme 1).

In our previous paper, we have reported the C-5-substitution on 5-iodo-2′-deoxyuridine bound to polystyrene resin[3] using Heck, Stille and Sonogashira palladium catalyzed reaction.[1] We described also that the standard Suzuki-Miyaura cross coupling conditions gave the desired compounds in very low conversion (<15%). For this reason, we decided to study the scope and limitation of this reaction types using different experimental conditions. We first prepared 5-iodo-2′-deoxyuridine bound to polystyrene resin,[1] Scheme 2.



SCHEME 2 Conditions : i) **B** (1 equiv.), $Me_2C{=}C(NMe_2)Cl$ (1.1 equiv.), CH_2Cl_2, 3 hours; then **A** (1 equiv.), NEt_3 (1.5 equiv.), pyridine (10 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 21 hours; ii) Ac_2O, pyridine, 4 hours; iii) TFA/CH_2Cl_2 (5/95), 15 hours; iv) NEt_3 (1.1 equiv.), O-(1H-benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyl uronium tetrafluoroborate (1.1 equiv.), *N*-hydroxybenzotriazole (0.5 equiv.), dioxane, 5 hours, then resin **C** (0.25 equiv.), NEt_3 (2.5 equiv.), DMAP (0.25 equiv.), dioxane, 60 hours; v) Ac_2O, pyridine, 18 hours; vi) I_2/CAN, dioxane/CH_3CN.

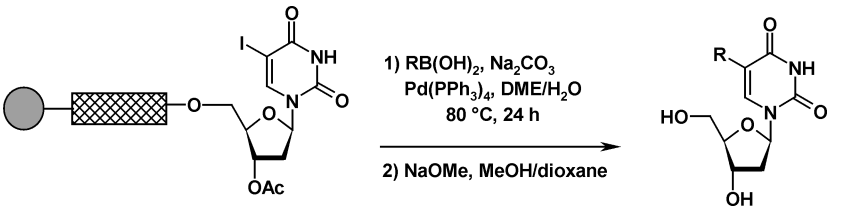
TABLE 1 Optimization of Suzuki-Miyaura cross-coupling reactions



Entry	Condition	Conversion (%)
1	$RB(OH)_2$ (4 equiv.), K_2CO_3 (9 equiv.), $Pd(OAc)_2$ (0.1 equiv.), dioxane/H_2O, 80°C	<15
2	$RB(OH)_2$ (8 equiv.), K_2CO_3 (9 equiv.), $Pd(OAc)_2$ (0.1 equiv.), dioxane/H_2O, 80°C	<20
3	$RB(OH)_2$ (4 equiv.), NaO^tBu (0.1 equiv.), Cs_2CO_3 (1.5 equiv.), (NHC)Pd(allyl)Cl (0.1 equiv.), 80°C	<10
4	$RB(OH)_2$ (4 equiv.), Na_2CO_3 (9 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), DME/H_2O, 80°C	100

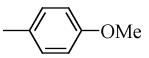
We set out to investigate the feasibility of Suzuki-Miyaura cross coupling on 5-iodo-2′-deoxyuridine bound to polystyrene resin **2** using the $Pd(OAc)_2$ (0.1 equiv.), K_2CO_3 (9 equiv.) and a excess of 4-methoxyphenylboronic acid (4–8 equiv.), unfortunately, the desired product **3** was obtained with low conversion (<20%). We observed a mixture of **1** and a large amount of starting 2′-deoxyuridine. We then turned our attention to apply the very well-known Nolan Palladium-catalyzed conditions.[5] Thus, using (NHC)Pd(allyl)Cl (0.1 equiv.), Cs_2CO_3 (1.5 equiv.), NaO^tBu (0.1 equiv.) and 4 equivalents of 4-methoxyphenylboronic acid at 80°C, we obtained less than 10% conversion. Finally, we founded that the optimum conditions using $Pd(PPh_3)_4$ as catalyst. When the reaction conducted with 4-methoxyphenylboronic acid (4 equiv.), Na_2CO_3 (9 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.) in a mixture of DME/H_2O at 80°C, occurred, the compound **3** were quantitatively converted (Scheme 2, Table 1).

Encouraged by these promising results, we prepared various 5-(hetero)arylated derivatives under the optimized Suzuki-Miyaura cross coupling conditions (Scheme 3). All desired products were obtained in 27–35% of yields (after five steps). It's noteworthy that all the conversion rates of



SCHEME 3 Optimized Suzuki-Miyaura cross-coupling conditions.

TABLE 2 Suzuki-Miyaura cross-coupling

Entry	R	Product	Conversion (%)[a]	Yield (%)[b]
1		**3**	100	27
2		**4**	100	35
3		**5**	100	30
4		**6**	100	32

[a]Conversions were calculated from ^{1}H MNR of crude product after cleavage.
[b]Yields (after 5 steps).

these reactions were totals, thus, the reported yields are those calculated after a simple washing of crude product with acetone (Table 2). Typically, the resin-bounded (170 mg, 0.08 mmol) was suspended in clean DME (2 mL) containing 330 μL of H_2O. Na_2CO_3 (9 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.) were successively added prior to the addition of 4 equiv. of the boronic acid derivatives. The suspension was strirred at 80°C and then cooled to room temperature and filered through a fritted glass funnel. Standard cleavage of the resin followed by flash column chromatography of the crude resin afforded desired nucleosides.

In summary we have for a first time found the optimum conditions for a new Suzuki-Miyaura palladium-catalyzed reaction on 5-iodo-2′-deoxyuridine bound to solid support using $Pd(PPh_3)_4$, Na_2CO_3 and various boronic acids. Under these conditions, various compounds were prepared with good yield and excellent purity.

REFERENCES

1. Aucagne, V.; Berteina-Raboin, S.; Guenot, P.; Agrofoglio, L.A. *J. Comb. Chem.* **2004**, 6, 717.
2. For recent article on Suzuki-Miyaura see: a) Agrofoglio, L.A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, 103, 1875; b) Western, E.C.; Daft, J.R.; Johnson, E.M., II; Gannett, P.M.; Shaughnessy, K.H. *J. Org. Chem.* **2003**, 68, 6767.
3. For article on aminomethylated resin see: a) El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2003**, 44, 6265; b) El Kazzouli, S.; Berthault, A.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Lett. Org. Chem.* **2005**, 2, 184.
4. Viciu, M.S.; Germaneau, R.F.; Navarro-Fernandez, O.; Stevens, E.D.; Nolan, S.P. *Organometallics* **2002**, 21, 5470.
5. a) Glaser, C. *Ber.* **1869**, 2, 422; b) Glaser, C. *Ann.* **1870**, 137, 154; c) Eglington, G. *Chem. Ind.* **1956**, 737.