Tetrahedron Letters 53 (2012) 253–255

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 6-aryl-2′-deoxyuridine nucleosides via a Liebeskind cross-coupling methodology

Martin Kögler, Steven De Jonghe, Piet Herdewijn *

Laboratory of Medicinal Chemistry, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 7 October 2011
Revised 3 November 2011
Accepted 8 November 2011
Available online 15 November 2011

Keywords:
6-Substituted 2′-deoxyuridine nucleoside analogues
Liebeskind cross-coupling reaction
Copper thiophene carboxylate

ABSTRACT

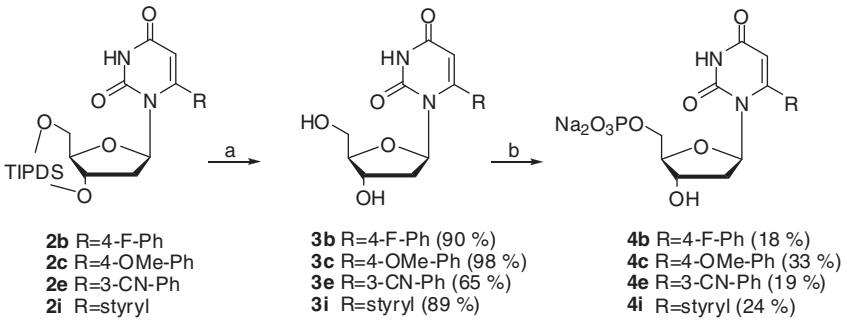
Hitherto, the synthesis of 6-substituted 2′-deoxyuridine nucleoside analogues via Pd-catalyzed Suzuki cross-coupling reaction was hampered by the instability of the TIPDS-protected precursor 6-iodo-2′-deoxyuridine **1** in alkaline media due to cleavage of the glycosidic bond. Herein, the successful application of the Liebeskind reaction under base-free conditions is reported. This method comprises of the stoichiometric use of copper thiophene carboxylate (CuTC) as co-reagent at slightly elevated temperatures. Fluoride-mediated desilylation and Yoshikawa-phosphorylation afforded the nucleotide analogues **4b–c**, **4e**, and **4i**.

Nucleoside analogues constitute an important class of organic molecules with interesting biological profiles.[1] In the past decades, substitution at position 5 of the uracil moiety in 2′-deoxyuridine nucleosides has been proven a validated strategy for the development of drugs used for the treatment of cancer and viral infections.[2] Aryl and heteroaryl groups are usually introduced via a Suzuki–Miyaura cross-coupling reaction[3] using arylboronic acids or via a Stille coupling using arylstannanes.[4] The Suzuki–Miyaura cross-coupling reaction has become the method of choice as a large number of non-toxic, structurally diverse (hetero)arylboronic acids is commercially available. It also allows carrying out the reaction in the presence of H_2O, which is favorable in terms of environmental impact. On the other hand, position 6 of the uracil base in nucleosides remained largely unexplored in medicinal chemistry programs and relatively few derivatives have been reported in the literature. This might partly be due to the difficulties encountered during the preparation of these compounds. Hitherto, gaining entry to these derivatives required multistep reaction sequences and their further development was hampered by low overall yields and the reduced chemical stability compared with their C-5 congeners. Two recent papers elaborate on new synthetic methodologies for the preparation of 6-aryl-uridines. Shih and Chien prepared a series of 6-aryl uridines using palladium(II)acetate as catalyst, triphenylphosphine as ligand and sodium carbonate as a base.[5] On the other hand, Nencka et al. reported the synthesis of 6-aryl-5′-*O*-TBDMS-2′,3′-*O*-isopropylideneuridine nucleosides under standard, as well as ligand-free, Suzuki–Miyaura conditions.[6] Recently, a number of cross-coupling reactions with protected and unprotected uracil derivatives at position 6 have been reported in the literature.[7,8] In detail, Čerňová et al. described the regioselective C–H arylation at C-6 of protected uracils in the presence of a Pd-catalyst and CuI.[8] However, the reported yields were frequently low to moderate and mixtures of the two regioisomers (C-5 and C-6-substituted products) were obtained. Furthermore, this approach would require the inclusion of additional steps (deprotection, silylation, glycosylation) which makes it less attractive in medicinal chemistry programs. To the best of our knowledge, 6-(hetero)aryl-2′-deoxy-uridines are not known in the literature. As part of an ongoing drug discovery program toward the identification of novel mycobacterial thymidylate synthase inhibitors,[9] we were in need of an efficient process to get access to 6-aryl-2′-deoxy-uridines. In this letter, we describe their synthesis via a base-free Liebeskind methodology.

In order to get access to 6-aryl-2′-deoxyuridine derivatives, 6-iodo-2′-deoxyuridine derivative **1** was considered as an ideal key intermediate. It was prepared according to a literature protocol from 2′-deoxyuridine by protection of both hydroxyls as a 1,1,3,3-tetraisopropoxydisiloxanylidene (TIPS) group, followed by iodination at position 6.[10] Classical Suzuki–Miyaura coupling of **1** with a number of substituted phenylboronic acids was envisioned. However, for the synthesis of the corresponding 2′-deoxyuridine congeners, all attempts in which classical conditions (various Pd-catalysts, such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or $PdCl_2$(dppf), boronic acids or their pinacol esters, and aqueous base) were employed, failed. These results highlight a particular instability of compound **1** in alkaline media, which predominantly led to deglycosylation. It is noteworthy that the attempted fluoride-mediated desilylation

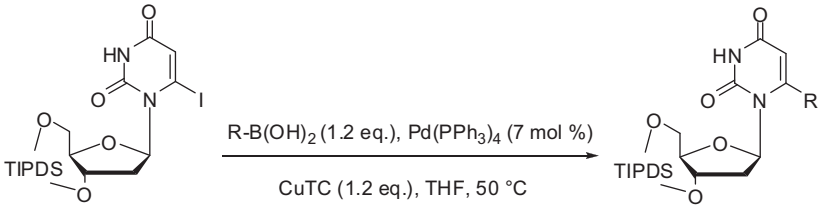
* Corresponding author. Tel.: +32 16 337387; fax: +32 16 337340.
E-mail address: Piet.Herdewijn@rega.kuleuven.be (P. Herdewijn).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.11.036

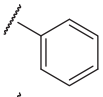
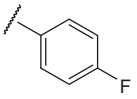
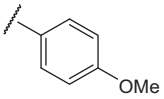
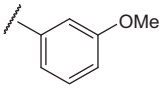
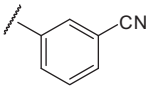
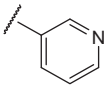
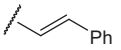
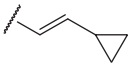


Scheme 1. Reagents and conditions: (a) TBAF, THF, rt; (b) $POCl_3$, proton sponge, $PO(OMe)_3$, 0 °C.

Table 1
Liebeskind cross-coupling reaction of **1** with various boronic acids or their esters



1 **2a-j**

Entry	Compound	R	Yield (%)
1	**2a**		79
2	**2b**		84
3	**2c**		64
4	**2d**		72
5	**2e**		66
6	**2f**		0
7	**2g**		0
8	**2h**		33[a]
9	**2i**		76
10[b]	**2j**		0[c]

[a] An unseparable 5:1 mixture of **2h**:**1** was obtained.
[b] Boronic acid pinacol ester used.
[c] Complex reaction mixture.

of compound **1** (TBAF/THF or NH_4F/MeOH) resulted in the formation of 6-iodouracil along with other degradation products and that no unprotected 6-iodo-2′-deoxyuridine could be obtained. Consequently, alternative Suzuki conditions were sought. Using a suspension of a base (e.g., K_2CO_3 or K_3PO_4) in an organic solvent, such as toluene or DMF, was equally unsuccessful. Furthermore, temperatures above 70 °C and long reaction times (>24 h) also appeared to have a detrimental effect on the stability of **1**.

This major stumbling block has been overcome by switching to an alternative base-free Suzuki coupling methodology developed by Liebeskind and co-workers.[11] This method comprises the stoichiometric use of copper thiophene carboxylate (CuTC), acting as a Cu(I)-cocatalyst, and allows to run reactions under nonbasic conditions even at room temperature. Although the original Liebeskind methodology[12] uses thioalkyl groups as leaving groups, we applied the methodology on aryliodide **1** as substrate. Using standard Liesbeskind reaction conditions (1.2 equiv of boronic acid or ester, 1.2 equiv of CuTC and 7 mol % of $Pd(PPh_3)_4$ in dry THF at 50 °C) the TIPDS-protected 6-substituted nucleoside derivatives were obtained in moderate to good yields (60–80%).

This method works well with substituted phenylboronic acids (compounds **2a**–**e**), as well as with (*E*)-(2-phenylvinyl)-boronic acid (compound **2i**). Fluoride-mediated desilylation[10] (TBAF/THF) of compounds **2b–e** and **2i** furnished the desired nucleosides **3a–e** and **3i** (Scheme 1).[13]

This is the first time a series of 6-aryl-2′-deoxy-nucleosides has been prepared in an efficient way. In order to broaden the applicability of this method, it was envisioned to introduce also a number of heteroaryl groups at position 6 of the uracil base. It turned out, however, that heterocyclic boronic acids are much less reactive under these reaction conditions. In the case of 3-pyridylboronic acid **2f** and 2-furylboronic acid **2g**, no conversion was observed after 48 h at 50 °C. When 2-thiopheneboronic acid was employed, an unseparable 5:1 mixture (as determined by ^{1}H NMR) of the desired 2-thienyl derivative **2h** and unreacted **1** was obtained after 24 h, albeit in low yield. Prolonged reaction times (up to 3 days at 50 °C) had no measurable improvement on this ratio. Similarly, performing the reaction with the pinacol ester of (*E*)-2-cyclopropylvinylboronic acid gave only a low yield of the desired derivative **2j** containing substantial amounts of impurities. The results are summarized in Table 1. These 6-aryl nucleoside analogues were made as part of a project toward the identification of inhibitors of a novel flavin-dependent thymidylate synthase from *Mycobacterium tuberculosis*, called ThyX. It has been shown that the presence of a 5′-phosphate moiety is required for ThyX-inhibition.[9] Therefore, nucleosides **3b–c**, **3e**, and **3i** have been selected for phosphorylation of the primary hydroxyl group under standard Yoshikawa-conditions[14] ($POCl_3$/proton sponge/$PO(OMe)_3$/0 °C) and evaluated in a biochemical assay as potential inhibitors of mycobacterial ThyX. At a concentration of 50 μM, none of the tested nucleotides showed significant ThyX-inhibition.

Herein, the application of the base-free Liebeskind cross-coupling methodology for the synthesis of 6-substituted 2′-deoxyuridine nucleosides is described. Position 6 of the uracil moiety has been largely unexplored in medicinal chemistry programs and 6-aryl-2′-deoxyuridine analogues are not known in the literature. Therefore, the Liebeskind methodology, as presented here, shows great promise to introduce structural variation at position 6 of different nucleosides and to study its effect on the biological activity. This methodology works well with simple substituted phenylboronic acids. Unfortunately, the corresponding heteroaryl derivatives could not be obtained and further optimization is required in order to find a versatile method for the synthesis of this class of organic molecules.

Acknowledgment

Martin Kögler is deeply indebted to the IWT Vlaanderen for providing a PhD-scholarship.

References and notes

1. (a) De Clercq, E. *Nat. Rev. Drug Discovery* **2002**, *1*, 13–25; (b) De Clercq, E. *Med. Res. Rev.* **2003**, *23*, 253–274; (c) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115–133.
2. (a) Lehman, N. L. *Expert Opin. Investig. Drugs* **2002**, *11*, 1775–1787; (b) Kumar, R. *Curr. Med. Chem.* **2004**, *11*, 2749–2766.
3. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
4. (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998; (b) Wigerinck, P.; Kerremans, L.; Claes, P.; Snoeck, R.; Maudgal, P.; De Clerq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, *36*, 538–543.
5. Shih, Y.-C.; Chien, T.-C. *Tetrahedron* **2011**, *67*, 3915–3923.
6. Nencka, R.; Sinnaeve, D.; Karalic, I.; Martins, J. C.; Van Calenbergh, S. *Org. Biomol. Chem.* **2010**, *8*, 5234–5246.
7. Bardagí, J. I.; Rossi, R. A. *J. Org. Chem.* **2008**, *73*, 4491–4495.
8. Černová, M.; Černa, I.; Pohl, R.; Hocek, M. *J. Org. Chem.* **2011**, *76*, 5309–5319.
9. Kögler, M.; Vanderhoydonck, B.; De Jonghe, S.; Rozenski, J.; Van Belle, K.; Herman, J.; Louat, T.; Parchina, A.; Sibley, C.; Lescrinier, E.; Herdewijn, P. *J. Med. Chem.* **2011**, *54*, 4847–4862.
10. Tanaka, H.; Hayakawa, H.; Iijima, S.; Haraguchi, K.; Miyasaka, T. *Tetrahedron* **1985**, *41*, 861–866.
11. Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149–2152.
12. Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91–93.
13. *Representative example: Synthesis of 6-(4-fluorophenyl)-2′-deoxyuridine* **3b**: Compound **1** (419 mg, 0.7 mmol), $Pd(PPh_3)_4$ (49 mg, 0.042 mmol), CuTC (147 mg, 0.77 mmol), and 4-fluorophenylboronic acid (118 mg, 0.84 mmol) were flushed with Ar and subsequently suspended in dry THF (8 ml) under an Ar atmosphere. The reaction mixture was stirred at 50 °C for 24 h and then allowed to cool to room temperature. The solvent was evaporated, and the residue was taken up in EtOAc (30 ml), and the organic layer was washed with satd $NaHCO_3$ (2 × 20 ml) and brine (1 × 20 ml), dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (0.5% EtOH in CH_2Cl_2) to yield the TIPDS-protected intermediate **2b** (332 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (br s, 1H, NH), 7.43 (br s, 2H, ArH), 7.18 (t, 2H, *J* = 8.6 Hz, ArH), 5.55 (s, 1H, H-5), 5.51 (dd, 1H, *J* = 9.5, 3.1 Hz, H-1′), 4.97 (m, 1H, H-3′), 4.08–3.92 (m, 2H, H-5′), 3.67 (m, 1H, H-4′), 2.94–2.83 (m, 1H, H-2′), 2.24–2.10 (m, 1H, H-2′), 1.15–0.96 (m, 28H, 4 × *i*-propyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.98 (d, J_{CF} = 251 Hz), 162.19, 155.93, 149.76, 130.24 (d, J_{CF} = 8.3 Hz), 129.33 (d, J_{CF} = 3.8 Hz), 116.47 (d, J_{CF} = 22.5 Hz), 104.08, 86.50, 86.24, 73.76, 64.23, 39.79, (17.69, 17.57, 17.50, 17.47, 17.29, 17.12: 8 C), 13.42, 13.36, 12.83, 12.71. MS (ESI) calcd for $C_{27}H_{41}FN_2O_6Si_2$ 587.24 (M+Na$^+$), 1151.49 (2 M+Na$^+$); found 587.12, 1151.62.
To a solution of intermediate **2b** (332 mg, 0.588 mmol) in dry THF (12 ml) was added TBAF (1 M in THF, 1.18 ml, 1.18 mmol), and the reaction mixture was stirred at room temperature for 45 min. The solvent was evaporated, and the residue was purified by silica gel column chromatography (7–8% EtOH in CH_2Cl_2), which yielded compound **3b** (171 mg, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$–MeOD = 5:2) δ 7.48 (s, 2H, ArH), 7.22 (t, 2H, *J* = 8.1 Hz, ArH), 5.65 (t, 1H, *J* = 7.2 Hz, H-1′), 5.60 (s, 1H, H-5), 4.57 (m, 1H, H-3′), 3.87–3.70 (m, 3H, H-4′ and H-5′), 3.06–2.93 (m, 1H, H-2′), 2.03–1.92 (m, 1H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$–MeOD = 5:2) δ 163.77 (d, J_{CF} = 252 Hz), 163.12, 155.95, 151.04, 129.81 (d, J_{CF} = 9.1 Hz), 128.91 (d, J_{CF} = 3.8 Hz), 116.20 (d, J_{CF} = 21.9 Hz), 104.20, 88.23, 87.56, 70.99, 62.31, 37.59. MS (ESI) calcd for $C_{15}H_{15}FN_2O_5$ 345.09 (M+Na$^+$), 667.18 (2 M+Na$^+$); found 345.0, 666.85. HRMS (ESI) calcd for $C_{15}H_{15}FN_2O_5$ 345.0857 (M+Na$^+$); found 345.0867.
Synthesis of 6-(4-fluorophenyl)-2′-deoxyuridine-5′-monophosphate **4b**: To a solution of compound **3b** (127.6 mg, 0.396 mmol) and proton sponge (132 mg, 0.61 mmol) in 2.1 ml of $(MeO)_3P{=}O$ was added $POCl_3$ (56 μl, 0.61 mmol) in one portion at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was poured into ice/H_2O and brought to pH 8–9 with 1 M NaOH, then the volatiles were removed in vacuo. The residue was purified by silica gel column chromatography (2-propanol/NH_4OH/H_2O = 85:10:5→75:15:10) followed by RP-HPLC (30 mM aq TEAB/CH_3CN = 90:10→85:15, 16 ml/min). Next, the phosphates were subjected to ion exchange (Dowex 50 WX-8, Na$^+$) and lyophilized, yielding title compound **4b** (32 mg, 18%) as a white solid. ^{1}H NMR (500 MHz, D_2O) δ 7.52 (br s, 2H, ArH), 7.29 (m, 2H, ArH), 5.75 (dd, 1H, *J* = 8.8, 4.4 Hz, H-1′), 5.74 (s, 1H, H-5), 4.53 (m, 1H, H-3′), 4.01–3.95 (m, 1H, H-5′), 3.92–3.86 (m, 1H, H-5′), 3.85–3.78 (m, 1H, H-4′), 2.96–2.89 (m, 1H, H-2′), 2.10–2.01 (m, 1H, H-2′). ^{13}C NMR (125 MHz, D_2O) δ 165.17, 163.34 (d, 1C J_{CF} = 247.5 Hz), 156.92, 151.13 129.93 (d, 2C, J_{CF} = 8.8 Hz), 128.19, 115.73 (d, 2C, J_{CF} = 22.5 Hz), 103.36, 86.80, 84.87 (d, 1C, J_{CP} = 7.5 Hz), 70.65, 63.60 (d, 1C, J_{CP} = 3.8 Hz), 35.99. ^{31}P NMR (121 MHz, D_2O) δ 3.91. HRMS (ESI) calcd for $C_{15}H_{16}FN_2O_8P$ 401.0555 (M−H$^+$); found 401.0543.
14. Yoshikawa, M.; Kato, T.; Takenish, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3505–3508.