



Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Target *cum* flexibility: simple access to benzofuran conjugated sugar and nucleoside derivatives

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ARTICLE INFO

Article history:

Received 11 September 2012

Revised 19 January 2013

Accepted 21 January 2013

Available online xxx

Keywords:

Benzofuran
Carbohydrates
Nucleoside
Palladium
Cyclization

ABSTRACT

The [Pd]-catalyzed domino process comprising of the coupling of alkynes and *o*-iodophenol and the subsequent cyclization leading to benzofurans has been successfully applied on the sugar and nucleoside derived alkynes.

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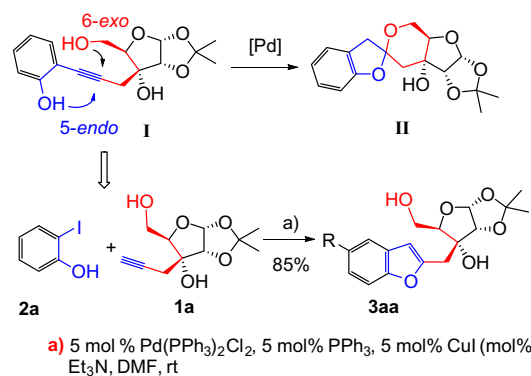
Benzofuran is a promising structural unit with widespread occurrence in natural and medicinally important compounds.^{1,2} Among the various methods available for the construction of the benzofuran unit, the coupling-*cum*-cyclization of *o*-iodophenols with alkynes in particular (both being catalyzed by various metal complexes)^{1,3} has been evolved as a mild method of choice with tolerance for various functional groups. In this letter, we describe the application of Pd-mediated coupling-*cum*-cycloisomerization of simple sugar and nucleoside derived alkynes with various *o*-iodophenols resulting in the synthesis of sugar-benzofuran and nucleoside-benzofuran conjugates.⁴

Our initial interest in this regard was on the synthesis of alkynol I and its [Pd]-mediated cycloisomerization⁵ for constructing the spirobicyclic unit II which is present in natural products such as lysidicins and aquilarinoside A.⁶ However, the Sonogashira coupling of the alkynol **1a** with *o*-iodophenol (**2a**)⁷ proceeded smoothly and provided exclusively the benzofuran derivative **3aa** in 85% yield. The structure of **3aa** was confirmed with the help of spectral and analytical data.⁸ For example, in the ¹H NMR spectrum of **3aa**, the characteristic C(3)-H of the benzofuran ring is present at 6.63 ppm as a singlet and the 2H of the methylene unit appeared as doublets at 2.86 and 3.15 ppm with a large geminal coupling (15.1 Hz). As expected, the C(3) of the benzofuran ring resonated at up field (103.5 ppm, d) and the methylene unit attached to the C(2) appeared at 35.5 ppm. Although the outcome was not the desired one, the simplicity of this domino process has attracted our attention because of the two-component coupling in nature. We

have intended to explore the potential of the coupling *cum* cyclization reaction in the synthesis of sugar- and nucleoside-conjugated benzofuran derivatives.

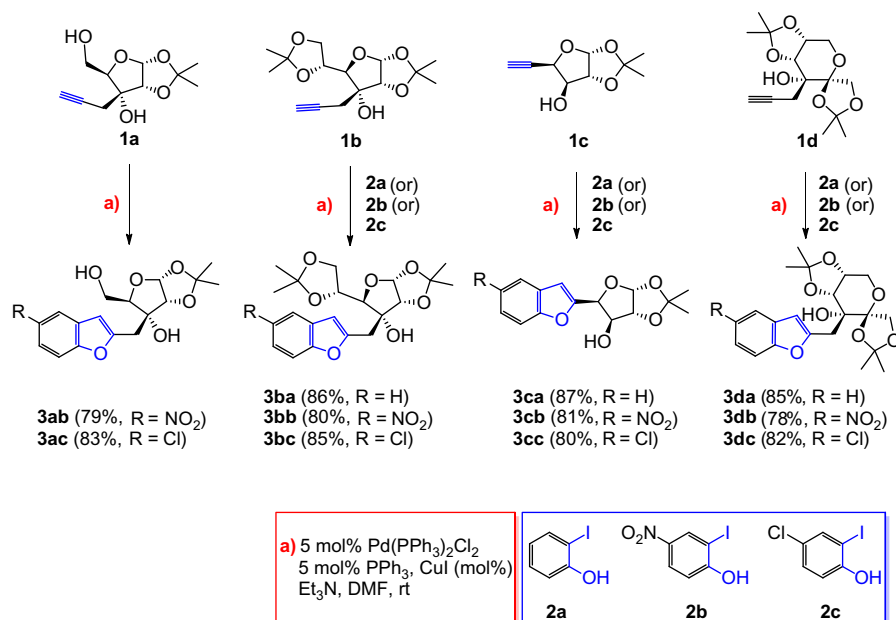
Scheme 2 shows the scope of this reaction on four sugar templates **1a–1d** employing three representative iodophenols **2a–2c**. The reactions were facile with all the four alkynes employed and gave the corresponding sugar-benzofuran conjugates in very good yields.

Having established the [Pd]-catalyzed benzofuran synthesis on simple sugar derivatives, we next focussed on the feasibility of this reaction with unprotected C(3) C-propargylated nucleosides. The modification of the sugar unit in the nucleosides is one of the

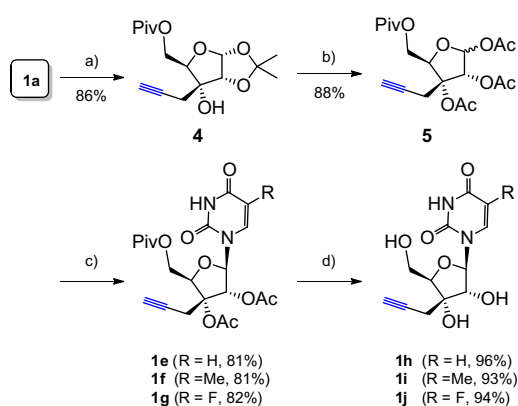
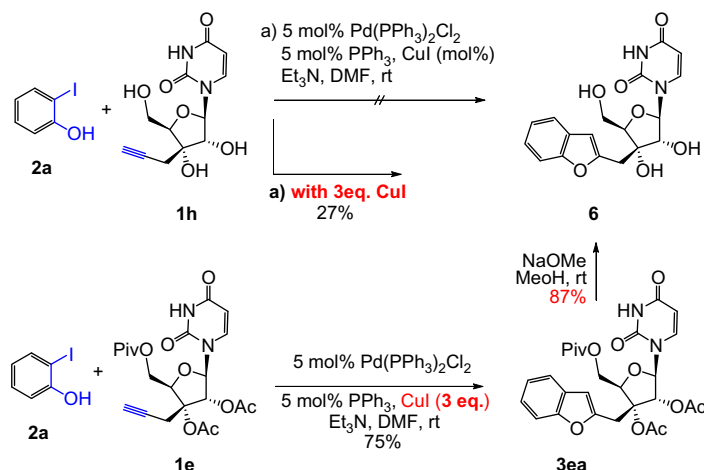


Scheme 1. The intended cycloisomerization and the synthesis of sugar-benzofuran conjugates.

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Scheme 2. Scope of [Pd]-catalyzed benzofurannulation of sugar derivatives.

Scheme 3. Reagents and conditions: (a) PivCl, DMAP, CH₂Cl₂, rt, 6 h; (b) (i) 60% AcOH, reflux, 2 h; (ii) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt, 1 h; (c) uracil/5-fluorouracil/thymine *N,O*-bis(trimethylsilyl)-acetamide (BSA), TMSOTf, CH₃CN, 50 °C, 2 h; (d) NaOMe, MeOH, rt, 20 min.

Scheme 4. The substrate and reaction optimization for the synthesis of benzofuran-conjugated nucleosides.

promising approaches for the derivation of new antiviral agents.⁹ Our initial intention was to carry out this benzofurannulation reaction on free nucleosides **1h–1j**, thereby making a provision of substrate flexibility at the final stage and provide an easy access to synthesize a collection of C(3)-modified nucleosides (Scheme 2).¹⁰

The synthesis of the alkynyl nucleosides **1h–1i** started with the selective protection of C(5)-OH of alkynol **1a** as its pivaloate **4** by using pivaloyl chloride in the presence of triethyl amine in dichloromethane. The hydrolysis of the acetone group followed by peracetylation of the intermediate lactol gave an anomeric mixture of C(3)-paraglyl ribose derivatives **5**. The N-glycosidation of the anomeric mixture **5** was carried out under modified Vorbrüggen conditions¹¹ employing uracil, thymine, and 5-fluorouracil to afford the protected nucleosides **1e–1g**, respectively. The anomeric configuration of the protected nucleosides **1e–1g** was established with the help of spectral data analysis. In general, anomeric-H in compounds **1e–1g** appeared with a characteristic large $J_{1,2}$ coupling constant (7.6–7.9 Hz). Quite interestingly, in the case of **1g**,¹² the anomeric-H appeared as a doublet of doublet at 6.19 (d, $J_{(H,F)} = 1.5, 7.8$) where it was a doublet in the case of compounds

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