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Cross-coupling of propargylated arabinogalactan with 2-bromothiophene

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ABSTRACT

Novel pharmacologically prospective derivatives of arabinogalactan (a polysaccharide from larch wood) containing acetylenic and thiophene moieties have been obtained in up to 90% yield by cross-coupling of propargylic ethers of arabinogalactan with 2-bromothiophene. The reaction proceeds in the presence of the catalytic system $Pd(Ph_3P)_4$/CuBr/LiBr and piperidine in DMSO at 80–85 °C. An advantageous feature of the synthesis is that it requires 5–25 times lesser catalytic loading than in common Sonogashira protocols thus making the reaction particularly beneficial to synthesize pharmaceutically-oriented polysaccharides.

1. Introduction

Arabino-3,6-galactan (AG) is a natural highly-branched polysaccharide from larch constituted of galactose and arabinose units. The amount of AG that could be obtained from 1% of larch trees each year in the United States is 4.6 million metric tonnes. The Swiss company Lonza Inc. has a production capacity for 3.7 million metric tonnes (dry weight) of AG (López-Franco, Higuera-Ciapara, Goycoolea, & Wang, 2009). Its excellent pharmaceutically attractive properties such as membranotropic, immunomodulating, anticancer, prebiotic and hepatoprotective activity in combination with water solubility, low toxicity and commercial availability make this polysaccharide highly prospective source of diverse substances and materials for medicine and pharmaceutics (Ganenko et al., 2015; Kolesnikova, Karpova, Vlasov, Sukhov, & Trofimov, 2015; López-Franco et al., 2009; Papkina et al., 2015; Pawar et al., 2011; Shurygina et al., 2011; Sukhov et al., 2007; Trofimov et al., 2003). New possibilities for the synthesis of biologically important derivatives of this polysaccharide appeared after recent elaboration of the expedient method for it propargylation (Grishchenko et al., 2013; Trofimov, Parshina, & Grishchenko, 2011).

At the other hand, different thiophene derivatives are extensively used in medicine as antibiotics (cefalotin, cefaloridine, cefoxitin, temocillin and ticarcillin), antihypertensive agents (arotinolol, eprosartan, temocapril, tiamenidine), chemotherapeutic (leukemia) medication (teniposide), analgesic (sufentanil), diuretics (asocemide and tienilic acid), anticonvulsant (tiagabine), anti-inflammatory remedies (suprofen and tiaprofenic acid), anticoagulant (tioclomarol), antihistaminic (thenalidine), anthelmintics (pyrantel and thenium closilate) (Kleemann, Engel, Kutscher, & Reichert, 2001), platelet aggregation inhibitor (clopidogrel), atypical antipsychotic drug (olanzapine), selective estrogen receptor modulator (raloxifene, osteoporosis and brest cancer) (Baumann, Baxendale, Ley, & Nikbin, 2011).

The thiophene ring is ubiquitous in nature and many examples relate to plants and foods (Majumdar & Mondal, 2011). More than 150 thiophene-type natural products comprising one, two, or three thiophene rings and side chains with a variable number of double or triple bonds have been characterized from Asteraceae (different species of *Tagetes*, *Helianthus*, *Echinops*, *Ambrosia*, *Eclipta*, *Helenium*, *Buphthalmum* and so on) (Christensen & Lam, 1991; Konovalov, 2014; Margl, Eisenreich, Adam, Bacher, & Zenk, 2001). Many naturally occurring and synthetic acetylene-containing thiophenes have been found to possess UV-mediated antimicrobial activity. Thiophenic compounds having 1-alkynyl groups linked to a thiophene 2-position have exhibited photoactive antibiotic, antiviral and cytotoxic activities (Majumdar & Mondal, 2011).

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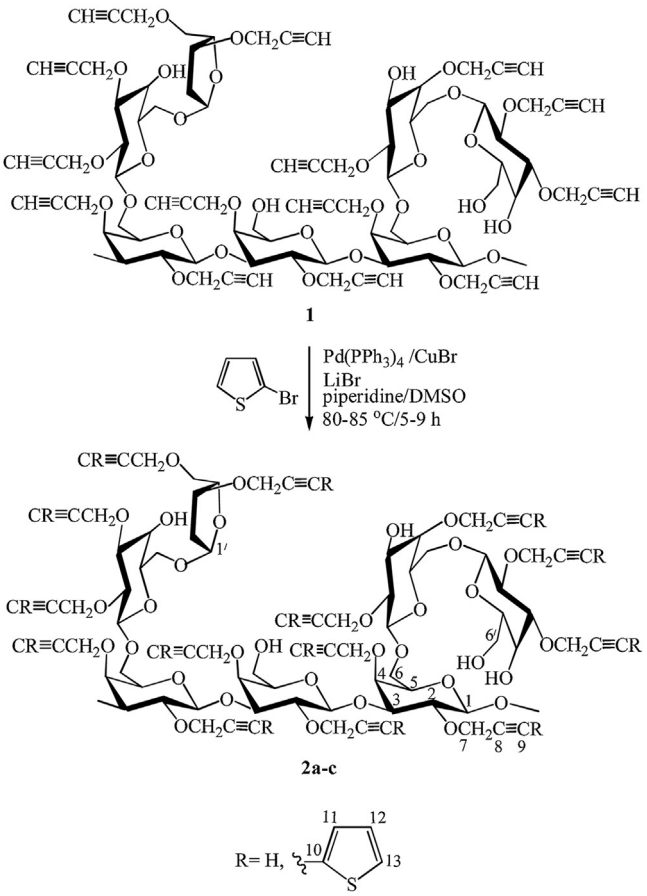
Table 1
Conditions and results of Sonogashira coupling of propargylated AG (DS 2.0–2.2, 2.1 mmol of monosaccharide units) with 2-bromothiophene.

2-Bromothiophene (mmol)	Piperidine (mmol)	Time (h)	Product		
			Sample	DS[a]	Yield (%)
15.5	33.0	5	**2a**	1.6 (1.6[b])	90
15.5	33.0	9	**2b**	1.4 (1.5[b])	88
11.0	33.0	5	**2c**	0.6	89
11.0	20.0	5	**3a**	0.5	87
11.0	10.0	5	**3b**	0.8	88

[a] DS determined by elemental analysis.
[b] DS determined by quantitative ^{13}C NMR.

Owing to the importance of alkynylated thiophenes in the nature and medicinal chemistry, the linking of thiophene ring with new bioactive natural products bearing terminal alkynes would be desirable. An important potential advantage of conjugates formed is that in this case, the therapeutic action of acetylenic thiophene derivatives as antimicrobial, antiviral and cytotoxic agents may be strengthen due to immunomodulating, membranotropic and antimetastatic properties of AG (López-Franco et al., 2009; Pawar et al., 2011). To support this inference, amphotericin B-AG conjugates, prepared by reductive amination of oxidized AG, can be mentioned. These conjugates show in vitro and in vivo the same antifungal activity and are about 20 times less toxic than free amphotericin B in mice (Ickowicz et al., 2014).

The aim of this work was to study the cross-coupling of propargylated AG (Grishchenko et al., 2013; Trofimov et al., 2011) with 2-bromothiophene using the Sonogashira reaction and thereby to build-in the thiophene-acetylene moiety into the macromolecule of this polysaccharide. Previously, the Sonogashira reaction has been successfully implemented to propargylated cyclodextrins, the second partner being iodophenol derivatives of mannose (Ortega-Caballero, Giménez-Martínez, & Vargas-Berenguel, 2003). Later, a carbohydrate functionalized with thiophene-acetylenic moiety has been synthesized by a Sonogashira protocol from propargylated mannose and diiodotetrathiophene (Schmid, Mena-Osteritz, Kopyshev, & Bäuerle, 2009). Likewise, similar carbohydrate acetylene-thiophene derivatives were synthesized from tetraacetylpropargyl mannoside or galactoside and iodinated oligothiophenes, which reveal specific binding with the model lectin Concanavalin A (Schmid, Mishra, & Bäuerle, 2011).



Scheme 1. Sonogashira coupling of propargylated AG with 2-bromothiophene.

2. Material and methods

2.1. Materials and measurements

AG was functionalized by propargylic groups (DS 2.0–2.2, the weight-average molecular mass 18 kDa) following a previously described protocol (Grishchenko et al., 2013) using a biphasic mixture of solubilized AG in an aqueous basic solution and propargyl bromide in toluene. AG was extracted from *Larix sibirica* (Babkin, Kolzunova, Medvedeva, Malkov, & Ostroukhova, 2005). AG is highly branched polysaccharide composed of galactose and arabinose units in a 6:1 ratio. $Pd(PPh_3)_4$ was prepared according to the published procedures (Brandsma, Vasilevsky, & Verkruijsse, 1998). 2-Bromothiophene, PPh_3, piperidine, CuBr, LiBr, DMSO are commercially available. All chemical reagents and solvents used were of analytical grade.

The ^{1}H, ^{13}C NMR spectra were recorded on a Bruker DPX 400 (400.13 and 100.61 MHz, respectively) in DMSO-d_6 (concentration was 10%) at a temperature of 25 °C. Chemical shifts were calibrated to the carbon resonances of the solvent (DMSO-d_6 δ_H = 2.5, δ_C = 39.5). 90° Pulses and an antigate sequence were the proton decoupler switched off during the pulse delay. The pulse delays were 5.0 s and the number of scans ranged from 15,000 to 20,000 for ^{13}C NMR spectra. IR (KBr) spectra were run on a Bruker Vertex 70 instrument. The elemental analysis (EA) (C, H) was performed with a Flash EA Analyzer, while the S content was determined by titration of sulfate ions, formed in the course of sample burning.

The weight-average molecular mass was determined by means of gel permeation chromatography (GPC) with Sephadex G-100 column (24 × 350 mm). Dextran standards (20, 40, 70, 2000 kDa) and D-galactose were used to calibrate the column. DMSO was used as eluent. Content of propargylated AG and 3-(2-Thienyl)propynyl AG in fractions was determined by phenol-sulfuric acid method (Dubois, Gilles, Hamilton, Rebers, & Smith, 1956).

2.2. Preparation of 3-(2-Thienyl)propynyl derivative of AG (sample **2a**)

To a stirred degassed solution of propargylated AG (**1**, DS 2.2, 0.47 g, 2.1 mmol of monosaccharide units) in DMSO (4.5 mL)