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Synthesis of a novel oxoxanthenoisoquinoline via a palladium-catalysed cross-coupling reaction; as a fluorophore

Mark P. Prickett, Gurdial Singh * and Hariprasad Vankayalapati

Department of Chemistry, University of Sunderland, Sunderland SR1 3SD, UK

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Abstract

Suzuki cross-coupling of a bromoaromatic anhydride with 2-methoxyboronic acid afforded a novel oxoxanthenoisoquinoline. Subsequent coupling with 2,3,4,6-tetra-*O*-acetyl-D-galactose-1,3-diyl phosphate gave a fluorophore. © 2000 Elsevier Science Ltd. All rights reserved.

The Suzuki cross-coupling reaction of aryl bromides, aryl iodides and pseudohalides, e.g. triflates, is usually catalysed with palladium salts.[1] These reactions generally proceed in good yields for the synthesis of a range of aryl, biphenyl and styryl derivatives.[2] Recently, the groups of Buchwald and Fu reported phosphine-modified palladium-mediated coupling reactions which employ aryl chlorides as substrates.[3] As a direct result of these studies the Suzuki reaction has become the method of choice for synthesis of aryl and hetereoaryl systems.

In parallel with this development there has been a resurgence of interest in the chemistry of carbohydrates and the important roles they play in a large number of biological events has become well-recognised. Alongside this, much effort has been directed towards the detection of saccharides by fluorescent chemosensors.[4] These studies have established that the response which signals an interaction between carbohydrate and a receptor is communicated by changes in fluorescence intensity through chelation.[5] The current generation of saccharide sensors almost exclusively has a common anthracene or polyaromatic hydrocarbon-based fluorophore as the reporting unit, with synthetic modification of the methylene spacers that bind these structures together.

We have recently developed the 1,3-diylphosphate leaving group for the synthesis of saccharides.[6] In order to further extend the scope of this procedure we wished to employ this type of activation for the introduction of fluorophores that were not based upon the anthracene framework.

In this Communication we report on the synthesis of an oxoxanthenoisoquinoline **1** using Suzuki chemistry and its subsequent introduction into a protected sugar. The structural design requirements for a compound such as **1** was based on the premise that we desired the molecule to have an absorption

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* Corresponding author. Tel: +44 191 5153094; fax: +44 191 5153148; e-mail: gurdial.singh@sunderland.ac.uk (G. Singh)

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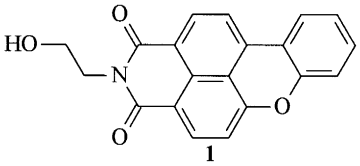
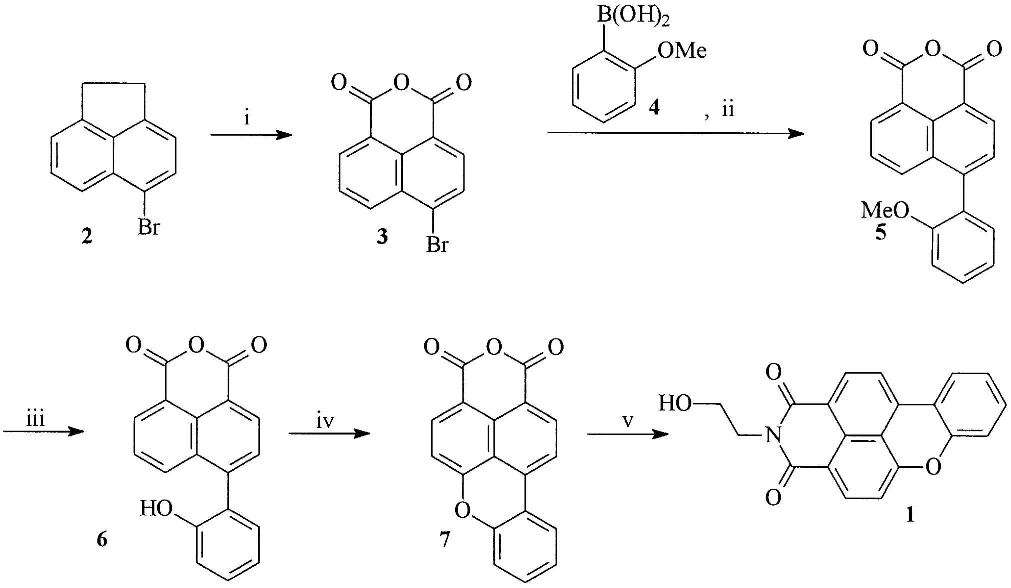
maximum above 400 nm and, in addition, we wished to have a functionality that would not form a strong complex/interaction with Lewis acids, as well as having a nucleophilic arm for easy attachment to the anomeric centre of sugars. These requirements appeared to be fulfilled by the oxoxanthenoisoquinoline **1**.



1

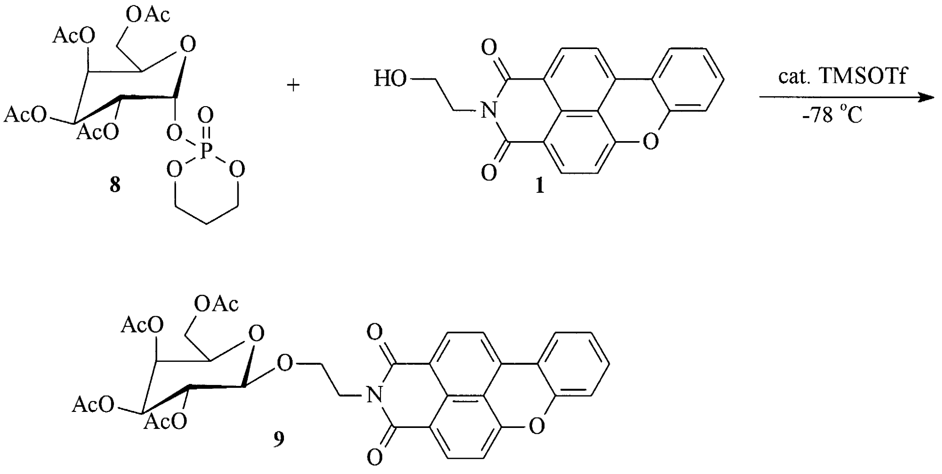
Our starting point for the synthesis of **1** was 4-bromoacenaphthene **2** which is commercially available (Scheme 1). Treatment of **2** with sodium dichromate[7] in 85% acetic acid afforded the bromoanhydride **3** in 80% yield (m.p. 200°C) as a grey crystalline solid. With the anhydride **3** in hand we investigated its elaboration.



Scheme 1. *Reagents and conditions*: (i) $Na_2Cr_2O_7 \cdot 2H_2O$ (6 equiv.), 85% HOAc, Δ, 12 h; (ii) $Pd(OAc)_2$ (3 equiv.), Na_2CO_3, $PhCH_3$, H_2O, Δ, 5 h; (iii) BBr_3, (1.1 equiv.), CH_2Cl_2, 0°C then rt, 2 h; (iv) 5% Pd/C (cat.), Ph_2O, Δ, 12 h; (v) $NH_2CH_2CH_2OH$ (10 equiv.), Δ, 12 h

Initially, we examined the coupling reaction of the bromoanhydride **3** with the boronic acid **4** using hindered palladium(0) phosphines as catalysts and all of these proved to be unsuccessful. Variation of the base employed in these reactions also did not improve the outcome of the reactions. After some experimentation we were able to obtain the desired outcome if we used 3 equivalents of palladium acetate in the reaction and we were able to isolate the cross-coupled product **5** in 50% yield after column chromatography. Removal of the methoxy protecting group of **5** with boron tribromide afforded the phenol **6** in 76% yield. Ring closure to the phenolic anhydride (**6** to **7**) was realised on heating **6** in diphenyl ether in the presence of a catalytic amount of 5% palladium on carbon in a yield of 69%, orange crystals, m.p. 225°C; ν_{max} 3396, 1781 cm^{-1}. Heating the anhydride **7** in ethanolamine resulted in formation of the desired oxoxanthenoisoquinoline **1**, in 77% yield after chromatography. The oxoxanthenoisoquinoline **1** was found to be a highly luminous yellow material, λ_{max} (MeOH) 438, 332, 284, 260 nm.

Having established a successful synthesis of this system we investigated its coupling reaction with a glycosyl donor having an anomeric propane-1,3-diylphosphate as a leaving group. Thus, treatment of **1**[8], with the phosphate **8** in the presence of trimethylsilyl triflate, gave the β-glycoside **9** in 69% yield. The glycoside **9** proved to be a highly yellow fluorescent material that had absorption maxima at 427, 333, 233 nm (Scheme 2).



Scheme 2.

In summary, we have established that Suzuki coupling of the bromoaromatic anhydride can be employed to afford biaryl systems that can be elaborated to afford novel oxoxanthenoisoquinoline which is an excellent fluorophore.

Acknowledgements

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8. Selected data: compound **1**: m.p. 171–173°C, ν_{max} (KBr) 3650, 1731 cm^{-1}; λ_{max} (MeOH) 438 (ε 3540), 332 (ε 2313), 284 (ε 4415), 260 (ε 4670) nm; δ_H (270 MHz, CDCl$_3$), 1.59 (1H, brs), 3.96 (2H, dd, *J*=5.3, 4.3 Hz), 4.43 (2H, app. t, *J*=5.3 Hz), 7.02 (1H, dd, *J*=8.59, 6.6 Hz), 7.11 (1H, d, *J*=6.6 Hz), 7.39 (1H, ddd, *J*=7.9, 7.9, 7.3 Hz), 7.67 (1H, dd, *J*=7.9, 7.3 Hz), 7.74

(1H, d, *J*=7.3 Hz), 8.06 (1H, dd, *J*=8.6, 7.3 Hz), 8.60 (1H, d, *J*=6.6 Hz), 8.65 (1H, d, *J*=7.3 Hz); *m/z* (EI). Found: 332.0923; $C_{20}H_{13}NO_4$ requires: 332.0992. Compound **9**: $[\alpha]_D$ +67.6 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1747; λ_{max} (MeOH) 427 (ε 1147), 333 (ε 7923), 233 (ε 29359) nm; δ_H (270 MHz, $CDCl_3$), 1.97 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.14 (3H, s), 3.92 (1H, dd, *J*=6.6, 6.6 Hz), 4.06–4.14 (4H, m), 4.41 (1H, dd, *J*=5.3, 4.6 Hz), 4.68 (1H, d, *J*=6.6 Hz), 5.01–5.15 (2H, m), 5.38 (1H, s), 5.45 (1H, dd, *J*=3.31, 3.3 Hz), 7.27 (1H, unresolved), 7.73, (1H, d, *J*=7.9 Hz), 7.76 (1H, d, *J*=7.9 Hz), 7.78 (1H, d, *J*=7.9 Hz), 8.20 (1H, d, *J*=7.9 Hz), 8.24 (1H, d, *J*=9.2 Hz), 8.59 (1H, d, *J*=7.3 Hz), 8.62 (1H, d, *J*=7.3 Hz); δ_C (67.8 MHz, $CDCl_3$), 20.54, 20.56, 20.60, 20.64, 61.73, 66.03, 67.19, 68.14, 68.29, 70.85, 70.87, 98.85, 126.93, 126.97, 131.39, 131.58, 134.15, 134.32, 170.08, 170.12, 170.21, 170.28, 170.45, 170.61; *m/z* (CI, NH_3). Found: 679.2149; ($M+NH_4$) $C_{34}H_{35}N_2O_{13}$ requires: 679.2139.