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Povarov reactions of *exo*-glycals: preparation of C-linked, quinoline analogues

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ABSTRACT

A one-pot approach based upon the Povarov reaction has been efficiently employed with a number of *exo*-glycals and *para*-substituted benzanilines to synthesize novel open-ring, carbohydrate-derived quinolines. The mechanism of this reaction was studied and an explanation for the observed stereoselectivity is proposed. Treatment of the compounds with the Lewis acid, boron trichloride, successfully removes the benzyl ether protecting groups in good yields. Several of the prepared compounds have been screened in the National Cancer Institute's (NCI's) 60 cell line model. Moderate activity was observed for several leukemia cell lines.

1. Introduction

Carbohydrates and glycoconjugates are crucial for the survival of living entities due to their integral involvement in numerous life sustaining processes.[1] As a result of the diversity and functional specialization of carbohydrates, stable and bioavailable sugar-based compounds present themselves as promising platforms for drug design.[2] In fact, saccharide derivatives are recognized as biologically relevant scaffolds that offer a high density of functional groups in addition to numerous chiral centers.[3] Aside from cell-surface interactions, sugars are able to pass through membranes via carbohydrate-specific transport mechanisms and function within cells.[4] Consequently, carbohydrate-derived compounds as well as glycomimetics have been utilized as therapeutics for a wide array of medical conditions.[5]

As is the case with sugars, nitrogen-containing heterocycles, including quinolines, are present in a variety of biologically active molecules and have been applied in several therapeutic areas.[6] For example, fluoroquinolones, such as ciprofloxacin[7] and levofloxacin[8] are used as antibacterial therapies while other quinoline derivatives show promise as antitumor agents.[9] Developments in the area of quinoline chemistry are therefore due, in part, to the pharmacological properties of their derivatives. Consequently, the synthesis of quinolines has been a subject of great importance in the field of organic chemistry.[10] Numerous preparative methods for the formation of substituted quinolines have been developed, and some of the most widely used name reactions include the Camps, Combes, Doebner–Miller, Friedlander, Knorr, Niementowski, Pfitzinger, Pictet–Spengler, Pomeranz–Fritsch, Riehm, and Skraup syntheses.[11]

We became interested in the preparation of sugar-based quinolines because of the biological activity associated with both classes of compounds. The unique structure and glycosidase inhibitory activity of the spironucleoside natural product (+)-hydantocidin[12] **1** and its synthetic glucose analogues[13] **2** and **3** provided additional inspiration to target sugar-based heterocycles (Fig. 1). Furthermore, a recent study focused on the synthesis and evaluation of quinoline-glucose hybrids **4** and **5** also validates the potential application of sugar-derived heterocycles as DNA intercalators.[14] We surmised that C-linked monosaccharide-derived quinolines have the potential to possess antitumor properties as intercalating agents. The incorporation of a carbohydrate group onto the molecule may facilitate delivery of the compound as well as enhance its drug-like properties. We hypothesized that the sugar component of the molecule might also help to stabilize the complex with DNA (via sugar–phosphate backbone interactions), enabling the planar quinoline to insert between the base pairs of DNA. In addition, a carbon–carbon bond linkage between the sugar and quinoline is likely to be more stable toward endogenous enzymes compared to a carbon–oxygen bond found in other reported carbohydrate–quinoline hybrids.[14,15]

Despite the large number of publications covering the synthesis of quinolines, we chose to focus our research around applications of the Povarov reaction. We theorized that a variation of the Povarov reaction would permit access to glycosylidene-linked quinolines.

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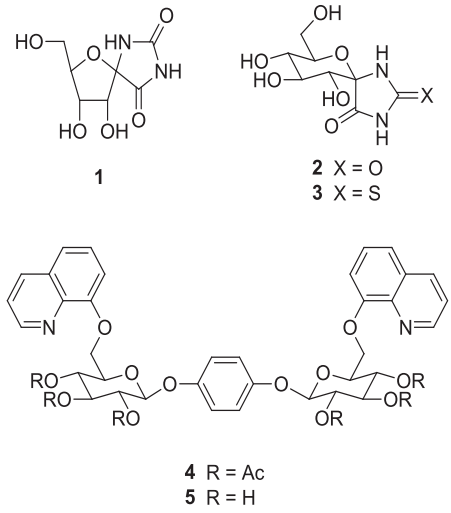
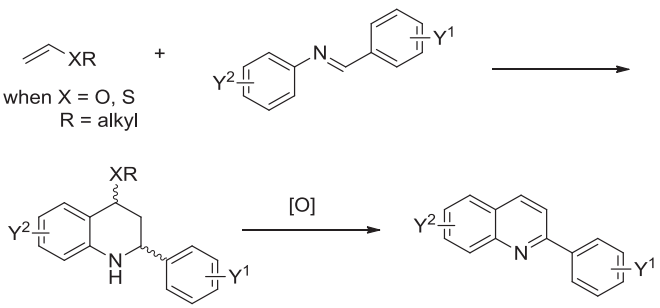


Fig. 1. Carbohydrate-based heterocycles.

Over 40 years ago, Povarov and colleagues described an addition reaction between aromatic Schiff bases (dienes) and activated alkenes (dienophiles) to give tetrahydroquinolines[16] (Scheme 1). In these manuscripts, they also reported that the tetrahydroquinoline products could subsequently be oxidized to the corresponding fully aromatized dihydroquinolines with the elimination of the alkoxy- or alkyl sulfide group. Interest in the Povarov reaction was rekindled in the 1990s, and significant improvements relating to this method's utility have been made. While the mechanism for this reaction has been the subject of debate, the Povarov reaction has now grown into a popular and useful strategy for the preparation of substituted tetrahydroquinolines.[17]



Scheme 1. Generalized Povarov reaction sequence.

Previously we have published our preliminary results surrounding the development of a facile one-pot methodology that was utilized to convert an *exo*-glycal directly into a novel C-linked, glycosylidene-based quinoline.[18] We herein report additional synthetic efforts in this area, namely the application of the reaction methodology to several *exo*-glycals[19] and *para*-substituted benzanilines.[20] These benzaniline precursors were chosen because steric effects of the substituents on reactivity would be minimal and because the product quinolines were desired for subsequent transformations. We also disclose the results of a series of deprotection screening experiments as well as the outcome of the anticancer evaluation of several glucose-derived compounds.

2. Results and discussion

In a previous communication, we reported screening experiments utilizing rare earth metal triflates [$Sc(OTf)_3$, $Yb(OTf)_3$, and $Tb(OTf)_3$] as catalysts for the Povarov reaction between a glucose-based *exo*-glycal and benzaniline.[18] We observed the formation of a 4:1 mixture of spiroanellated tetrahydroquinolines, as well as the oxidized, open-ring product (Scheme 2). The percentage of the open-ring compound present in the reaction mixture was catalyst dependent. For instance, when $Sc(OTf)_3$ was utilized as the catalyst, more than 70% of the reaction mixture consisted of the open-ring product. Lanthanide triflate reaction catalysis, however, produced nearly a 1:1 mixture of open-ring product and spiro tetrahydroquinolines.[21] Nuclear Overhauser effect (NOE) experiments confirmed the stereochemistry of both spiro isomers, **8Major** and **8Minor**, and extensive 1D and 2D NMR experiments were required to determine the structure of the open-ring compound **9a**. For **8Major**, NOEs were observed between the hydrogens attached to the following carbon atoms (for atom labels, see structure in Scheme 2): 2 with both j and a, b with both 3 and 5, and 4 with a. These interactions indicate that the stereochemistry is (*R*) at both carbons 1 and j. For **8Minor**, NOEs were observed between the hydrogens attached to the following carbon atoms: b with both 2 and 4, 3 with a, and 5 with j. The stereochemistry of this isomer is (*S*) at carbon 1 and (*R*) at carbon j. Evidence supporting the formation of open-ring compound **9a** includes the ^{13}C shift of C1 (145.9 ppm) and the coupling constant for the hydrogen attached to C2 (3.1 Hz). The broad ^{13}C resonance of C2 (78.5 ppm) sharpened upon increased temperature, indicating restricted rotation about the C1–C2 bond. NOEs were observed between the hydrogens attached to the following carbon atoms: 2 with both a and b. COSY and NOESY signals, observed between the hydrogen and hydroxyl group attached to C5, also helped to confirm the assignment of **9a**.

A unique aspect of this Povarov addition is the observed facial selectivity and stereocontrol of the reaction. Only two of the four possible glycosylidene-spiroanellated stereoisomers were formed, and the isomers with the (*S*)-configuration at the benzylic carbon j were absent. The regiochemistry of addition to *exo*-glycal **6** to produce the spiroanellated products can be explained on the basis of a non-concerted reaction pathway.[22] According to the two-step process that has been proposed,[23] attack of the imine carbon by the more nucleophilic C2 carbon of the vinyl ether occurs first. This is followed by electrophilic attack of the resulting oxonium ion by the *ortho* carbon of the aniline ring. The observed axial facial preference for addition to **6** leading to the β-substituted methylene group at the anomeric carbon is likely due to the influence of steric effects experienced by the bicyclic component in the equatorial plane.[24] The steric effects may account for the observation that only 20% of the spiro mixture consists of product (**8Minor**) in which the axial substituent from the anomeric carbon is derived from the C2 carbon of the vinyl ether. In addition, we hypothesize that kinetic and or thermodynamic factors involving the formation of a transition state also impact the stereocontrol of the reaction and hence the play a role in the observed spiro product distribution.[25]

During the course of our experiments, we made note of the instability of the spiro isomers. In addition to the presence of open-ring compound **9a** in the reaction mixtures, we also observed the slow, partial conversion of **8Major** and **8Minor** after chromatographic isolation to **9a** at room temperature. We surmise that **9a** is more favorable from the perspective of Gibb's free energy ($\Delta G = \Delta H - T\Delta S$) than its spiro precursors.

We hypothesize that the observed transformation is driven enthalpically by the aromatization of the tetrahydroquinoline to the dihydroquinoline. It is widely accepted that aromatization is an enthalpically favored process, and it confers additional stability to the resulting compound due to the delocalization of the pi electrons within the ring system. Perhaps alkoxy elimination followed by α,β-unsaturated iminium ion formation and single electron transfer leads to the formation of the fully aromatized quinoline (Fig. 2). Aside from enthalpic considerations, **9a** has five additional rotatable bonds, which make an entropic contribution to the overall favorability of the process. The capacity for bond rotation of the