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Synthesis of quinoline-based glycoconjugates: a facile one-pot three-component reaction

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ABSTRACT

A multicomponent one-pot reaction involving propargyl glycosides, methoxy-substituted aromatic aldehydes and aromatic amines using Cu(I) as catalyst is described, which provides an efficient and practical route to synthesize several quinoline-based glycoconjugates in good yield.

1. Introduction

The design and synthesis of novel molecular scaffolds with unique structural and biological properties is an increasingly active area of current chemical research.[1] The importance of glycobiology and subsequently the chemistry of glycoconjugates has gained enormous attention over the past few years owing to the understanding of the role played by these carbohydrates in several biological events.[2–5] These glycoconjugates, which mainly exist as glycolipids or glycoproteins play a unique role in different events such as cell adhesion, cell growth, inflammation, and immune responses.[6] Moreover, several naturally occurring carbohydrates contain a range of more or less complex glycosylated aromatic moieties of plant origin such as arbutin (**1**), sennoside A (**2**), glucofrangulin (**3**) (Fig. 1).[7] Thus, the efficient synthesis of not only simple carbohydrates, but also carbohydrate-containing complex natural products is becoming a more important and challenging field in current synthetic organic chemistry and chemical biology.[8] Moreover, quinoline and its derivatives are also well-known important biological components. Some of the quinoline derivatives such as quinine, chloroquine, and amodiaquine are important for the treatment of malaria. In addition, some of the synthetic quinolines exhibit significant activities in the treatment of many infectious diseases.[9]

In general, multicomponent reactions (MCRs) are an important class of chemical transformations for the efficient synthesis of several natural products and libraries of compounds for the discovery of biological probes and drugs.[10] Therefore, MCR is more ideal for preparing complex structures by a sequence of reactions that assembles several components. Multicomponent reactions such as the Hantzsch[11] and Biginelli[12] reactions are important for synthesis of several heterocycles, while the MCRs of Passerini,[13] Ugi,[14] and Petasis[15] are useful methods for synthesizing amino carboxylic acid derivatives.[16] Thereby, it is desirable to devise novel methods for easy access to heterocyclic derivatives in view of their great potential utility in biological and pharmaceutical studies where the development of multicomponent process would well serve this purpose.

Recently, Doye and co-workers[17] carried out a three-component reaction using the acetylenic moiety as one of the components in synthesizing dihydroisoquinolines. Moreover, Trofimov et al.,[18,19] have also utilized acetylene with an aldehyde and imidazole to carry out a three-component reaction. In addition, a one-pot four-component reaction involving acetylene, a substituted aldehyde, an azide, an aromatic amine, and ammonium acetate in synthesis of phenylquinazolines was carried out by Dabiri et al.[20] Similarly, Gao and Wu[21] synthesized dihydroisoquinolines using acetylene, a substituted aldehyde, an aromatic amine, and benzyl/allyl bromide in a multicomponent reaction involving Mg–Cu as a catalyst. It has also been reported by Nevado and co-workers that cyclopropyl propargylic carboxylates can be used in synthesizing alkylidenecyclopentyl acetates using a gold catalyst.[22] However, Masciadri and co-workers[23] have synthesized quinoline compounds using 2-aminoarylketones with various β-keto derivatives. A detailed study shows that most of the one-pot reaction involves

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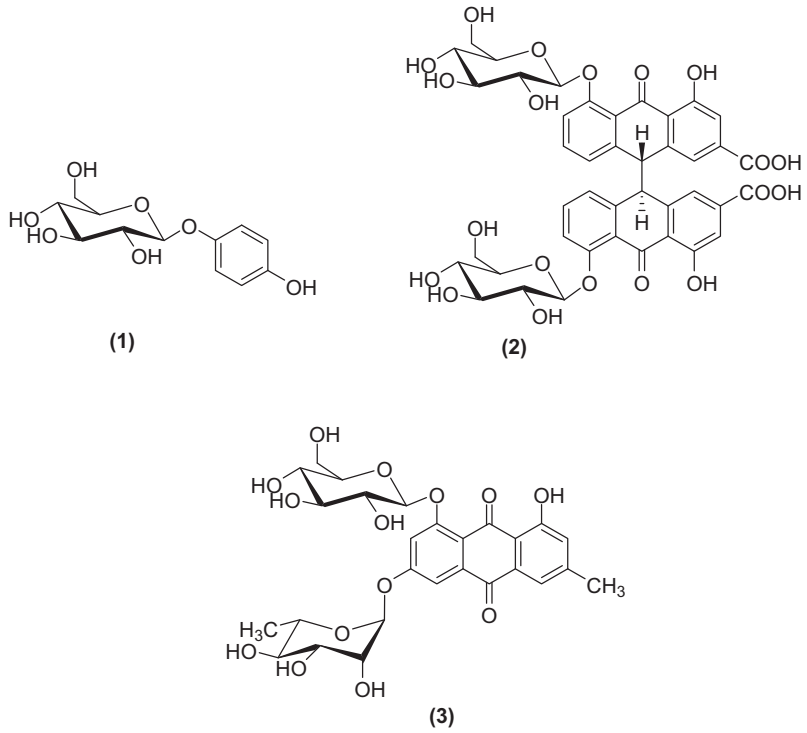

Figure 1. Naturally occurring glycosylated compounds (**1**–**3**).

amine, aldehyde, and acetylene moieties to synthesize quinoline and its derivatives. In the context of our studies in the area of MCRs, we would like to report an efficient approach for the one-pot synthesis of quinoline-coupled saccharide molecules.

2. Results and discussion

As a part of our ongoing project devoted toward the development of interesting heterocyclic-coupled saccharide molecules with varied applications in the field of materials science and medicinal chemistry,[24,25] herein we have explored the possibility of a one-pot multicomponent synthesis of quinoline-coupled saccharide molecules. In this paper we report a new three-component reaction between an aromatic aldehyde, an aromatic amine, and propargyl glycosides that leads to a novel class of quinoline derivatives that possess a substituent at the C-2 position with a benzene moiety and saccharide moiety at the C-4 position.

Initially, to synthesize quinoline-coupled saccharide derivatives, the one-pot three-component reaction was carried out using 3,4-dimethoxybenzaldehyde, aniline and propargyl tetra-*O*-acetyl-β-D-galactopyranoside (**6a**) as a simple model substrate under various reaction conditions. The results are summarized in Table 1. It was found that when the reaction was carried out without any catalyst the expected quinoline-coupled saccharide product was not observed, even after 24 h (Table 1, entry 1). In order to optimize the reaction conditions we examined the reaction using different Brønsted and Lewis acids (Table 1, entries 2–10). Brønsted acids such as HCl and *p*-TSA were not able to catalyze the reaction, even after prolonged reaction times (Table 1 entries 2 and 3). However, the use of Lewis acid catalysts such as $BF_3{\cdot}OEt_2$, $FeCl_3$, $Cu(OAc)_2$, $CuCl_2$, CuI, and CuBr led to low or no product formation (Table 1, entries 4–9). Finally, CuCl was identified as the optimum catalyst, resulting in the formation of **7c** in ~54% yield (Table 1, entry 10). However, carrying out the reaction in the presence of CuCl at room temperature resulted in <5% yield of **7c** even after prolonged reaction time (Table 1, entry 11). Subsequently, optimization by determining the preferred solvent for this reaction was attempted using acetonitrile, DMF, ethanol, and water, all of which showed no superiority over THF (Table 1, entries 12–15). In addition, we also evaluated the amount of CuCl used in this reaction. It was found that when we increase the amount of CuCl catalyst from 10% to 30%, the yield gradually increased. However, the use of 30% CuCl in THF is sufficient enough to push the reaction forward toward the expected quinoline-coupled saccharide compound in moderate yield. However, an additional amount of the catalyst did not improve the yields (Table 1, entries 16–18).

Thus, under optimized reaction conditions a series of quinoline-based glycoconjugates (**7a**–**f**) were synthesized as shown in Scheme 1. In order to evaluate the formation of the expected quinoline-based glycoconjugates, the reaction was carried with propargyl glycosides of D-glucose and D-galactose.[26] A detailed study was performed on the reactivity of different substrates and also on the selectivity of the reaction toward the formation of quinoline-based glycoconjugates. However, formation of propargyl amine varied depending on the aromatic aldehyde/amine used in the course of the reaction. It is therefore important to reveal the selectivity of aromatic aldehydes and amines in this reaction to obtain the expected quinoline-based glycoconjugate as the product. It is interesting to note that the use of alkyl, halogen or unsubstituted aromatic aldehyde and aromatic amine with propargyl glycoside results in a propargyl amine as the major product. A similar observation has been reported in the literature.[27] Since the formation of propargyl amine has been studied exclusively in the literature,[27] we focused on the reaction conditions and substituents favoring the formation of the expected quinoline-based glycoconjugates.

Benzaldehyde and its derivatives **4a**–**b** reacted with aniline **5a** and the propargyl glycoside of D-galactose **6a** to yield quinoline-coupled saccharide compound **7a**–**b** in 34–35% yield. As suggested, the propargyl amine was observed in a higher ratio than the expected quinoline glycoconjugates (**7a**–**b**). Moreover, 3,4-dimethoxybenzaldehyde (**4d**) with aniline (**5a**) and the propargyl glycoside of D-galactose (**6a**), results in satisfactory to good yield of compound **7c**