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Synthesis of glucuronic acid derivatives via the efficient and selective removal of a C6 methyl group

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Abstract

This investigation is related to the development of a general strategy for the synthesis of certain glucuronic acid derivatives. In particular, we report exceptionally selective conditions for removing the C6 methyl protecting group by potassium hydroxide without affecting the benzoyl protecting groups on the C2, C3 and C4 hydroxyl groups in high yields (95%–99%). The present method proves to be efficient and environmentally friendly in terms of short reaction time, high yield and the single product.

Keywords: Glucuronic acid; Potassium hydroxide; Selective deprotection

Introduction

Glucuronic acids are ubiquitous in many biological systems and play a vital role in diverse physiological functions. What's more, functionalized glucuronic acid derivatives are used as valuable building blocks in the synthesis of glycoproteins, glycolipids and natural products which have biological function [1-5]. As a result, there are various efforts aiming at developing efficient and mild methods for the synthesis of glucuronic acid derivatives. The synthesis of glucuronic acid is traditionally achieved by the oxidation of the C6 primary alcohol of a monosaccharide to the corresponding C6 carboxylic acid [6]. However, these methods are associated with several limitations such as usage of oxidant, generation of several side products, or unsatisfactory yields.

Recently, Murphy and co-workers reported that glucuronic acid azide **2** can be prepared from azide **1** by saponification of all of the esters and subsequent acetylation for six days [7, 8] (Scheme 1, upper part). Although this method paved the way to prepare glycosides with similar structural features, the disadvantages of the lower yield and the generation of 3,6-lactone as the byproduct due to the longer reaction time are obvious.

By inspecting the structure of compound **2**, several clues were obtained for the optimization of synthetic protocol. For example, it is easy to remove C2, C3 and C4 acetyl protecting groups on glucuronic acid derivative **1** by CH_3ONa/CH_3OH without affecting the C6 methyl ester. Conversely, to obtain a free C6 carboxyl group by removing its methyl protecting group and keep all of the remaining acetyl groups, such as in glycosyl carboxylic acid **2**, is quite difficult. The reason is that the carboxyl group and hydroxyl groups in glucuronic acid tend to be protected or deprotected together. Because glucuronic acid is quite important in the research of multiple disciplines, such as medicinal chemistry, drug metabolism, and natural product chemistry [9-11], it is necessary to find alternative protocol to fulfill the need of selective deprotection.

Herein, we report an efficient method that can selectively remove the C6 methyl group from a glucuronic acid methyl ester without influencing any benzoyl protecting groups (Scheme 1, lower-left part). The resulting carboxyl group is ready to form amides or esters to afford other modified structures or as more complex donors

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