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Green, Microwave-Assisted Synthesis of *O*-Perbutyrylated-Alkyl-Glycosides †

Emmanuel Pérez-Escalante [1], Luis Guillermo González-Olivares [1], Araceli Castañeda-Ovando [1], Verónica Salazar-Pereda [1], John F. Trant [2], Mirandeli Bautista-Ávila [3] and Sergio Alatorre-Santamaría [4,*]

[1] Universidad Autónoma del Estado de Hidalgo, Área Académica de Química, Carretera Pachuca-Tulancingo km 4.5, CP 42184 Mineral de la Reforma, Hidalgo, México; emmanuel_perez@uaeh.edu.mx (E.P.-E.); lgonzales@uaeh.edu.mx (L.G.G.-O.); ovandoa@uaeh.edu.mx (A.C.-O.); salazar@uaeh.edu.mx (V.S.-P.)

[2] Department of Chemistry and Biochemistry, University of Windsor, 401 Sunset Ave., Windsor, ON N9B 3P4, Canada; j.trant@uwindsor.ca

[3] Universidad Autónoma del Estado de Hidalgo, Área Académica de Farmacia, Carretera Pachuca-Actopan s/n, CP 42160 San Agustín Tlaxiaca, Hidalgo, México; mirandeli@hotmail.com

[4] Departamento de Biotecnología, Universidad Autónoma Metropolitana, Unidad Iztapalapa, División de Ciencias Biológicas y de la Salud, Av. San Rafael Atlixco 186, AP. 09340 Ciudad de México, México

* Correspondence: salatorre@xanum.uam.mx

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Abstract: Chemical synthesis of carbohydrates is a challenging task. Several protection and deprotection steps of hydroxyl groups are required to ensure regioselective formation of the glycosidic bond. Usually, it is achieved through acylation, where conventional heating is combined with addition of Lewis acids as catalysts. This traditional approach has two drawbacks; it is time consuming and often catalysts are hazardous to the environment. An alternative route relies on application of microwaves and/or other Lewis acids with less or no toxicity. Such combination would reduce reaction times and offer a benign synthetic strategy to obtain peracylated compounds. The current work describes an efficient and environmentally mild synthesis of peracylated glycosides with potential application in enzymatic preparation of carbohydrates. Model compound *O*-perbutyrylated-phenyl-galactose was synthesized using imidazole as catalyst in the microwave-assisted process. The acylation protocol was optimized, and the target sugar was obtained at 50% yield after 1 h. In conclusion, the combination of imidazole and microwaves provides an excellent alternative to swiftly synthesize peracylated glycosides in a benign way.

Keywords: perbutyrylated sugars; imidazole; microwaves; green chemistry

1. Introduction

Traditional carbohydrates synthesis involves multiple protection/deprotection steps, where ester derivatives are the most commonly used protecting groups [1,2]. Carbohydrate esters are obtained via acylation using conventional heating and Lewis acids as catalysts [3]. These protocols often require long reaction times, and the catalysts used may pose health and environmental threats, like in the case of pyridine [4].

Considering the negative environmental impact of the traditional approach, more sustainable protocols for carbohydrate esterification are needed. The benign synthetic route encompasses substitution of hazardous catalysts, such as pyridine with imidazole [5], as well as the use of microwaves under solvent-free conditions [6]. Such a strategy follows the basic principles of green

chemistry, defined as avoidance of the toxic wastes production, and/or preference for chemicals with low toxicity and environmental impact [6].

Although perbutyrylated glycosides have been shown to possess different biopharmaceutical and antitumor properties, they have been hardly investigated as potential peracylated carbohydrate precursors [7,8]. Thus, the present work aimed at developing an efficient and environmentally mild synthesis of peracylated glycosides that can be further used as building blocks in enzymatic preparation of a wide variety of sugars.

2. Methods

2.1. Chemicals and Equipment

All reagents and solvents were at least ACS grade and were used without further purification. Thin layer chromatography (TLC) was performed with SiO_2 plates Kieselgel, UV_{254} and the mobile phase consisted of a mixture of petroleum ether and ethyl acetate (1:0.1), using aqueous sulfuric acid solution (5%) as stain mixture. Nuclear magnetic resonance spectroscopy (NMR) was carried out in $CDCl_3$ using a Bruker Advance 400 Spectrometer.

2.2. Synthesis of O-perbutyrylated-phenyl-galactose at Room Temperature

A total of 100 mg of 1-phenyl-β-D-galactopyranoside (0.39 mmol) and 16 mg of imidazole (0.23 mmol) were dissolved in 4 mL of dried acetonitrile under N_2 atmosphere. Then, 640 µL (3.91 mmol) of butyric anhydride was added and the reaction was maintained for 60 h at room temperature. The product was purified by flash chromatography using a mixture of petroleum ether and ethyl acetate as eluent. The pure compound was characterized by ^{1}H and ^{13}C-NMR.

2.3. Synthesis of O-perbutyrylated-phenyl-galactose by Microwave Heating

A total of 100 mg of 1-phenyl-β-D-galactopyranoside (0.39 mmol) and 83.7 mg of imidazole (1.2 mmol) were transferred to a G30 vessel (Anton Paar). Afterwards, 2 mL of acetonitrile (HPLC grade) and 2 mL of butyric anhydride (12.22 mmol) were added to the reaction tube, and the system was heated in microwaves at 140 °C for 60 min. The product was recovered with CH_2Cl_2 and the organic phase was washed with deionized water, 0.1 M acetates buffer (pH = 5.5), and 1 M $KHCO_3$. The pure product was characterized by ^{1}H and ^{13}C-NMR.

2.4. Characterization of O-perbutyrylated-phenyl-galactose

The product was obtained as pale yellow oil. R_f (petroleum ether:EtOAc; 1:0.1): 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 2H, H9, and H11), 7.06 (t, *J* = 7.4 Hz, 1H, H10), 6.99 (dd, *J* = 8.6 Hz, 0.9 Hz, 2H, H8, and H12), 5.55–5.46 (m, 2H, H6), 5.14 (dd, *J* = 10.5 Hz, 3.4 Hz, 1H, H3), 5.05 (d, *J* = 8.0 Hz, 1H, H1), 4.23 (dd, *J* = 11.1 Hz, 7.0 Hz, 1H, H4), 4.14 (dd, *J* = 11.2 Hz, 6.1 Hz, 1H, H2), 4.10–4.05 (m, 1H, H5), 2.46–2.36 (m, 2H, H16), 2.27 (dt, *J* = 7.3 Hz, 4.4 Hz, 4H, H20, and H28), 2.21 (t, *J* = 7.3 Hz, 2H, H24), 1.69 (dt, *J* = 9.6 Hz, 4.8 Hz, 2H, H27), 1.66–1.55 (m, 6H, H15, H19, and H23), 0.99 (t, *J* = 7.4 Hz, 3H, H26), 0.91 (dt, *J* = 7.5 Hz, 4.5 Hz, 9H, H14, H18, and H22); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.01–172.11 (C13, C17, C21, and C25), 157.13 (C7), 129.65 (C9 and C12), 123.33 (C10), 117.00 (C8, and C12), 99.81 (C1), 71.31 (C3), 70.85 (C5), 68.56 (C2), 66.88 (C4), 61.44 (C6), 36.03 (C16, C20, C24, and C28), 18.78–18.17 (C15, C19, C23, and C27), 13.69 (C14, C18, C22 and C26).

3. Results and Discussion

In order to synthesize *O*-perbutyrylated-phenyl-galactose (Figure 1) in an environmentally benign approach, a methodology described by Tiwari et al. [5] was followed and further optimized to meet green chemistry principles. When the original protocol was followed, in which room temperature was applied, esterification was completed after 60 h. ^{1}H-NMR spectroscopy showed characteristic signals of the product between 0.91 and 2.46 ppm corresponding to the multiplicity of the methyl and methylene groups of the *O*-butyryl chain. Likewise, ^{13}C-NMR spectroscopy showed

the characteristic shifts for carbons in the *O*-butyryl chain: Carbonyl groups were found around 172 ppm, while methyl and methylene group chemical shifts were identified between 13 and 36 ppm, respectively. In these reaction conditions the product was afforded at 33% yield.

With the aim to offer a microwave-assisted method to *O*-perbutyrylated-phenyl-galactose and peracylated sugars in general, the same conditions used previously were tested using microwaves instead of conventional heating. Nonetheless, TLC analysis showed an incomplete consumption of starter material after 1 h of reaction. In fact, the addition of more butyric anhydride and imidazole was needed to complete reaction, extending the process until 2 or 3 h. In order to improve reaction time, the protocol was modified by increasing the concentration of both imidazole (0.3 mmol per hydroxyl group) and butyric anhydride (2 mL; 12.22 mmol). Under these new conditions, a total esterification of *O*-phenyl-galactose was reached in only 1 h and the purified product was obtained at 50% yield.

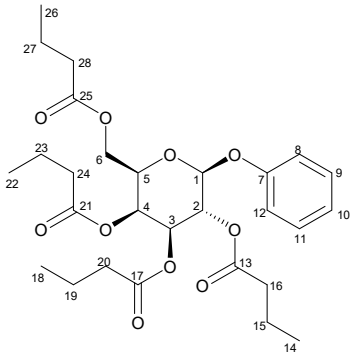

Figure 1. Chemical structure of the target sugar.

4. Conclusions

An efficient and environmentally benign methodology was applied to synthesize *O*-perbutyrylated glycosides using imidazole as a catalyst. Optimization of the reaction conditions involved the combination of imidazole and microwaves, which afforded the best overall yield in a considerably reduced time. Finally, this green synthetic strategy has a great potential to be applied in enzymatic preparations of complex carbohydrates.

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Conflicts of Interest: The authors declare no conflicts of interest.

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