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Ultrasound-assisted reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with potassium salt of curcumin under PTC conditions

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Abstract

Reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with potassium salt of curcumin [bis-1,7-(3′-methoxy-4′-hydroxy)phenyl-5-hydroxy-1,4,6-heptatrien-3-one] under either thermal or high pressure conditions affect the labile substrate, curcumin, thus resulting in drastic reduction in the yields of the glucosides. This drawback could be effectively overcome by carrying out the biphasic reaction in the presence of a phase transfer catalyst under the effect of ultrasound. The reaction under the sonochemical conditions was faster and resulted in the increased yield of the glucoside products. The reaction was investigated in detail with a view to optimizing the yield of the glucosides. The detailed study clearly indicated the important role of the nature and quantity of the phase transfer catalyst employed in the reaction. Also, the selectivity with respect to the formation of mono- or di-β-glucosides under both mono- and biphasic reaction conditions was clearly discernable. The study establishes a simple synthetic protocol for the glucoside derivatives of curcumin in high yields and selectivity using ultrasonic waves.

Keywords: Ultrasound; Phase transfer catalyst; Curcumin; Mono- and di-β-glucosides; Selectivity

1. Introduction

Phase transfer catalysis (PTC) technique is extremely useful for carrying out reactions between substances of preferential solubility in different solvent phases. For example, one of the reactants can be an organic compound dissolved in an organic medium and the other one a salt of an alcohol or phenol soluble in the aqueous phase. The catalyst does play a very critical role in these biphasic reactions. Its choice and the careful monitoring of the reaction conditions are essential features that govern the course of the reaction and determine the yields of the products. There are several advantages of the phase transfer catalysis systems over single-phase systems, such as an increased reaction rate, lower reaction temperature, avoiding the need for expensive anhydrous or aprotic solvents and the use of water along with an organic solvent as the reaction medium. Catalysts extensively employed in PTC reactions include quaternary ammonium or phosphate salts or crown ethers/cryptates. Quaternary ammonium salts with their inherent capability to dissolve in both aqueous and organic liquids are the catalysts of choice for most phase transfer applications. The efficiency of phase transfer catalysis is influenced by the bulkiness of the groups attached to the phase transfer catalyst. However, certain reactions studied in two-phase system under PTC conditions being slow would require acceleration and such reactions are usually carried out at higher temperatures. In case of heat-labile substrates this impediment could be overcome by use of ultrasound. Ultrasound accelerated chemical reactions, in fact, are well known and documented in literature [1]. It

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is demonstrated as an alternative energy source for organic reactions normally accomplished by employing higher temperatures. Improved yields and increased selectivity are reported when ultrasound is employed in homogeneous as well as heterogeneous reactions [2]. Effect of ultrasound on PTC reactions has been reported [3–6]. Ultrasound as a technique of synthesis is extensively used in synthesis of organometallics, in enzyme catalyzed reactions and many other synthetic reactions involving reaction mixtures having more heterogeneity in their solubility.

In our studies on curcumin – a natural yellow colorant of turmeric, which is a spice used primarily as a food colorant and also to flavor several foods – study of the synthesis of its glucoside derivative was investigated. Curcumin, is a nutraceutical compound used worldwide for medicinal as well as food purposes [7,8]. It has attracted special attention due to its potent pharmacological activities such as to protect cells from β-amyloid insult in Alzheimer's disease [9] and cancer preventive properties [10]. Biological activities of curcumin chelated to metal ions as well as antioxidant effects of curcumin are also documented in literature [11,12]. However, curcumin is insoluble in water at acidic and neutral pH. Though it is soluble under alkaline conditions, the color of the chromophore changes to deep red and it also undergoes degradation. Its low solubility in aqueous systems is a disadvantage as it renders its use in water based food products difficult. The alkyl and aryl portion of the molecule makes it lipophilic and hence, soluble only in fats and organic media. In order to make it water soluble, it is envisaged that attachment of a polar group or molecule would enhance the hydrophilicity of the molecule. This can be achieved, for example, by making suitable sugar derivatives. Basically, the reaction of Koenigs–Knorr synthesis of glycosides tried under classical condition involves formation of glycosyl halides followed by the glycosyl transfer in the presence of heavy metal salts [13] to get the glycoside. Known methods of preparation of curcumin sugar derivatives employ the reaction of α-D-tetraacetohaloglucose with curcumin under biphasic conditions in the presence of a phase transfer catalyst at higher temperatures but give very low yields [14,15]. Condensation reaction of arylaldehyde with acetyl acetone–B_2O_3 complex also gives curcumin glycoside boron complex [16]. Attempts are also made to synthesize curcumin glucoside by enzymatic means using amyloglucosidase [17] and *Catharanthus roseus* cell cultures by supplying curcumin exogenously [18]. Lower yields, higher temperatures and longer reaction times are the drawbacks of chemical and enzymatic synthetic methods reported.

In the present work, reaction of 2,3,4,6-tetra–*O*-acetyl-α-D-glucopyranosyl bromide with potassium salt of curcumin under biphasic conditions using phase transfer catalysts was studied under the influence of ultrasound for the synthesis of curcumin glucoside, as a new approach to Koenigs–Knorr reaction. The results of synthesis of curcumin glucoside under both mono- and biphasic conditions will be discussed.

2. Method

2.1. Apparatus and materials

All the solvents and reagents employed in the synthesis were of analytical reagent grade. Column chromatography of the compounds was carried out using silica gel (100–200 mesh size). ^{1}H NMR spectra for the compounds were recorded on a Bruker Avance 500 MHz spectrometer using deuterated solvents, $CDCl_3$ and DMSO-d_6. Coupling constants (J values) are given in Hz. Mass spectral analyses of the synthetic compounds were carried out using MS (Waters Q-Tof Ultima) in the ES positive mode. Ultrasound device used for the reaction was Vibracell with a high intensity tapered probe of tip diameter −6.5 mm from Sonics and Materials Inc., Newtown, USA. For the reactions, the ultrasound reactor was set at 25% amplitude and pulse cycle of 25 s (on) and 5 s (off) with frequency of 40 KHz and an output power of 750 W. Thin-layer chromatographic (TLC) analysis was performed on silca gel 60 F_{254} (Merck KgaA, 64271 Darmstadt, Germany) coated on alumina sheet and 3% methanol in chloroform was used as the developing solvent. Isolation of the products was by column chromatography on silica gel (100–200 mesh) with chloroform as the eluent. High performance liquid chromatography of these samples was carried out on reverse phase C-18 column with methanol: water (70:30) containing trifluroacetic acid (0.1%) as the mobile phase at flow rate of 1 ml/ min and monochromatic detection at 423 nm.

2.2. Preparation of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide [19]

To acetic anhydride (145 g, 1.42 mol) cooled to 4 °C, perchloric acid (1 ml) was added drop-wise maintaining the temperature below 4 °C. Glucose (35 g, 0.194 mol) was then added slowly maintaining the temperature between 30 and 40 °C. After cooling the reaction mixture to 20 °C, red phosphorus (10.25 g) was added followed by drop-wise addition of bromine (20 ml) maintaining the temperature below 20 °C. Water (12 ml) was then added over a period of 1 h maintaining temperature below 20 °C. The reaction mixture was stirred for 2 h, and then diluting with dichloromethane (100 ml), filtered through glass wool. The organic layer was washed with cold saturated solution of sodium bicarbonate followed by chilled water. The organic phase was filtered through activated silica gel and the solvent distilled under reduced pressure. The product was crystallized from diethyl ether–hexane (1:2) mixture and stored in an airtight amber colored glass bottle at 4 °C in a refrigerator. [65 g, 81%, m.p. 87 °C, NMR ($CDCl_3$): 2.04 (s, 3H); 2.06 (s, 3H); 2.10 (s, 3H); 2.11 (s, 3H); 4.13(dd, 1H, $J = 1.5$ Hz and $J = 12.5$ Hz); 4.29–4.35 (m, 2H); 4.85(1H, dd, $J = 4$ Hz and $J = 10$ Hz); 5.17 (t, 1H, $J = 9.5$ Hz); 5.56 (t, 1H, $J = 9.5$ Hz); 6.62 (d, 1H, $J = 4$ Hz).