NEW IONIC LIQUIDS IN THE MORITA BAYLIS HILLMAN ADDUCT SYNTHESIS WITH ANTILEISHMANIAL ACTIVITY

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ABSTRACT

Replacing molecular solvents in organic synthesis is one of the twelve principles of green chemistry. Recent studies reported the utilization of Ionic Liquids (ILs) in organic reactions as a sustainable alternative, demonstrating significant improvements in product yields and reaction times. These solvents consist of an organic cation and an organic or inorganic anion, giving them unique physical properties that make them particularly suitable as solvents, especially because of their high polarity, low volatility, and thermal stability [1]. In addition, ILs can also act as catalysts/co-catalysts in organic reactions, reducing reaction times and minimizing by-product formation. Morita-Baylis-Hillman (MBH) reaction is an important method for forming carbon-carbon bonds, and the resulting products, Morita-Baylis-Hillman Adducts (MBHA) possess various biological activities, making this reaction particularly valuable in synthetic and medicinal chemistry [2]. Tertiary amines, such as DABCO, are commonly used to catalyze this reaction [3], however, drawbacks include longer reaction time, low product yields, and catalyst in an equimolar amount, which cannot be recovered after the process [4]. The MBHA-I (methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate), derived from a very reactive substrate, is an important molecule due to antileishmanial activity. The *in vitro* tests performed with the promastigote form of *Leishmania amazonensis* and *Leishmania chagasi,* presented IC_{50} = 46.53 and 27.85µg/mL, respectively [5]. Despite these relevant results, adduct synthesis involves the disadvantage of forming by-products. In this sense, we aim to present the synthesis of four new ionic liquids based on docusate anion, an important surfactant, and to evaluate their effectiveness as solvents for obtaining the adduct MBHA-I. ILs syntheses were obtained from the mixture of equivalent amounts of the sodium docusate with different quaternary ammonium salts (benzalkonium chloride, benzethonium chloride, choline chloride, or ethyl hexadecyl dimethylammonium bromide), in acetone (50%) as the solvent and continuous stirring at room temperature. After 15h of reaction, the solution was extracted with dichloromethane/water and the resulting product was a viscous and limpid liquid. All products were characterized by Nuclear Magnetic Resonance (NMR), Infrared (IR), and Thermogravimetric Analysis (TGA). The MBH reaction was performed in the four ILs with 50 mol% of DABCO as the catalyst. Reaction times ranged from 15 to 24 hours, with product yields varying between 23% and 92%. The IL [Docusate][Bzk] demonstrated the best results, with 15 h of reaction time and 92% of product yield, with no by-products formed. After the reaction, the product was isolated through liquid-liquid extraction, and the IL was recovered, purified on activated charcoal, and reused many times. Furthermore, this method proved superior to the traditional approach, which employs methanol as a solvent. In the latter one, even after 24 hours of reaction, with a stoichiometric amount of DABCO, only trace amounts of the adduct were observed. Thus, the results presented herein indicate that ILs can be successfully used as catalyst/solvent in the MBH reaction, offering an alternative approach that avoids toxic and volatile organic solvents. Additionally, ILs present the advantage of being recoverable and reusable, thereby reducing discarded residues in the environment, and contributing to efficient and sustainable synthetic processes.

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