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Triethylammonium acetate ionic liquid assisted one-pot synthesis of dihydropyrimidinones and evaluation of their antioxidant and antibacterial activities

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Abstract A mild and efficient catalytic method has been developed to synthesize 3,4-dihydropyrimidinones in high yield by one-pot three component Biginelli condensation in the presence of triethylammonium acetate (TEAA) which acts as catalyst/reaction medium. Further, we have studied the antioxidant and antibacterial activities of these synthesized 3,4-dihydropyrimidinones. All the synthesized compounds reveal the significant antioxidant properties, these properties have been studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and cupric reducing antioxidant capacity (CUPRAC) assays. In addition, to this, these compounds also show the good antibacterial activity against four human pathogenic bacteria.

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1. Introduction

In recent years, environmentally friendly chemical synthesis has been gaining substantial attention both in academia and industrial research (Anastas and Warner, 1998; Clark and Macquarie, 2002). In this context, surrogation of toxic and volatile organic solvents as reaction media with environmentally acceptable alternatives such as water, ionic liquids (ILs) is an area of tremendous importance in modern organic synthesis (Breslow, 1991; Grieco, 1998; Sheldon, 2001; Wasserscheid and Keim, 2000; Welton, 1999). ILs completely

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consist of weakly coordinating ions i.e., organic cation and inorganic/organic anion possessing desirable properties, and are liquids at or close to room temperature (Attri et al., 2010a,b, 2011a). An interesting aspect is that ILs do not influence the physicochemical properties of mixtures. ILs are emerging as more promising solvents in various fields such as organic synthesis, catalysis, materials science, electrochemistry and separation technology (Attri et al., 2010a,b, 2011a,b,c; Attri and Pal, 2010; Attri and Venkatesu, 2011; Karbalaei-Heidari et al., 2013; Parmar et al., 2013a,b; Verma et al., 2008). Notwithstanding the unique advantages of ILs as reaction media and catalysts, currently they have not been extensively implemented in industries (Attri and Pal, 2010; Grieco, 1998; Sheldon, 2001; Verma et al., 2008; Wasserscheid and Keim, 2000; Wang et al., 2006; Weng et al., 2006). The issues related to the less usage of ILs are most probably high cost, the difficulty in separation or recycling and the paucity of data with regard to their toxicity and biodegradability etc.

3,4-Dihydropyrimidinones, known as Biginelli compounds are highly important heterocyclic units in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties, including anti-viral, anti-tumor, anti-bacterial and anti-inflammatory activities (Kappe, 2000a,b; Kappe and Falsone, 1998). Furthermore, these compounds have emerged as calcium channel blockers, anti-hypertensive agents and α -1a-adrenergic antagonists. Also, several alkaloids containing dihydropyrimidine nucleus isolated from marine sources have been found to possess interesting biological activities (Atwal et al., 1990, 1991). Owing to the wide range of pharmacological and biological activities, the synthesis of these compounds has become an important challenge in current years. The Biginelli reaction, first reported in 1893, is a direct and simple approach for the synthesis of 3,4-dihydropyrimidinones by one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea in the presence of strong acid (Biginelli, 1893). However, one serious drawback of this method is the low yield of the products, particularly in case of substituted aromatic and aliphatic aldehydes (Barleunga et al., 1989). This has led to the development of a multistep synthesis of Biginelli compounds that produce higher yields, albeit lacking the simplicity of the one pot synthesis. Thus, the Biginelli reaction involving one step cyclocondensation for the synthesis of dihydropyrimidinones has received renewed interest, and several improved protocols, mainly using Lewis acids as well as protic acids have been developed for accomplishing this reaction (Bigi et al., 1999; Ramalinga et al., 2001; Reddy et al., 2002). Nevertheless, use of toxic organic solvents, expensive catalysts and harsh reaction conditions in these protocols leave scope for further development of new environmentally clean synthesis. Recently, many researchers synthesized the dihydropyrimidinones using ILs (Chen and Peng, 2008; Garima et al., 2010; Peng and Deng, 2001; Sharma et al., 2012; Sajjadifar et al., 2013). Peng and Deng (2001) reported an efficient ionic liquid catalyzed Biginelli reaction using [bmim][BF₄] and [bmim][PF₆] as catalysts under solvent-free conditions. However, ILs especially imidazolium based systems containing PF₆ and BF₄ anions are toxic in nature as they liberate hazardous HF, and their high cost and disposability make their utility limited (Kamal et al., 2005). On the contrary, TEAA is inexpensive, thermally stable, non-toxic and recyclable; so has wide applications as catalysts/reaction medium (Attri and Pal, 2010; Parmar et al., 2013a,b; Verma

et al., 2008; Wang et al., 2006). However, their potential as reaction media and promoter for organic reaction does not appear to be explored much. In order to extend application and show the effectiveness of the simple ammonium ILs, herein we have explained the preparation of 3,4-dihydropyrimidinones using TEAA under solvent free conditions. Further, we have also studied the antioxidant and antibacterial activities.

2. Experimental

2.1. General procedure

Quercetin, Gallic acid, Neocuprine, 1,1-di-phenyl-2-picrylhydrazyl (DPPH), copper (II) chloride tryptone soya agar were procured from Sigma Aldrich. Glacial acetic acid, hydrochloric acid, hexane, methanol, tris buffer and sodium acetate were procured from Merck India Ltd., and ready-made Nutrient agar and broth was purchased from Hi-Media Lab, New Delhi. Bacterial culture *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 3160), *Pseudomonas aeruginosa* (MTCC 2581) and *Klebsiella pneumoniae* (MTCC 7028) were procured from the microbial type culture collection and gene bank, Institute of Microbial Technology, Chandigarh. All the reagents used were of AR grade. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. ¹H (400 MHz) and ¹³C NMR (75 MHz) spectra were recorded on a Jeol 400 NMR spectrometer in CDCl₃ (with TMS for ¹H and chloroform-*d* for ¹³C as internal references) unless otherwise stated. Mass spectra were recorded on a Hybrid Quadrupole-TOF LC\MS\MS mass spectrometer (Q. Star XL). The reactions were monitored by Thin Layer chromatography (TLC) using aluminum sheets with silica gel 60 F₂₅₄ (Merck).

2.2. Synthesis of triethyl ammonium acetate (TEAA)

The synthesis of IL was carried out in a 250 mL round-bottomed flask, which was immersed in a water-bath and fitted with a reflux condenser. Acetic acid (1 mol) was dropped into the triethyl amine (1 mol) at 70 °C for 1 h. The reaction mixture was then heated at 80 °C with stirring for 2 h to ensure that the reaction had proceeded to completion. The reaction mixture was further dried at 80 °C until the weight of the residue remained constant. The sample was analyzed by Karl Fisher titration, which revealed very low levels of water (below 70 ppm). The yield of TEAA was found to be 98 %. ¹H NMR (CDCl₃): δ (ppm) 0.78 (t, 9H), 1.47 (s, 3H), 2.58 (m, 6H), 11.00 (s, 1H).

2.3. General procedure for the preparation of 3,4-dihydropyrimidinones

In a typical experimental procedure, a mixture of three components was added in a round bottom flask containing aldehyde (1 mmol), urea (1.6 mmol), β -dicarbonyl compound (1 mmol) and TEAA (2 mL) and stirred thoroughly for 45 min at 70 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, dichloromethane (5 mL \times 3) was added and the reaction mixture was washed with saturated

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