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Unveiling the choline chloride–thiourea (1 : 1) DES as a greener medium and reagent for pyrimidinethione synthesis from α,β-unsaturated carbonyl compounds†

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Widespread studies on developing greener organic chemistry techniques were prompted by growing concerns about the health and environmental issues brought on by the effects of organic compounds. Since solvents and catalysts are necessary for many organic reactions, greener solvents and catalysts could remedy this problem. 3,4-Dihydropyrimidine-2(1*H*)-thiones (DHPMs) are an essential class of biomolecules. Several methods for synthesizing DHPMs have been reported. Nevertheless, most of these methods were linked to one or more disadvantages, such as laborious catalyst production, use of expensive catalysts, and severe reaction conditions like longer reaction times, higher temperatures and strong base, and reduced yields. Therefore, a simple, effective, and environmentally friendly protocol for the synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones from α,β-unsaturated carbonyl compounds using the biodegradable, cheap, and easily accessible choline chloride : thiourea (CC : TU) 1 : 1 room temperature deep eutectic solvent (DES) is reported. The pyrimidinethione products were obtained from structurally and electronically diverse α,β-unsaturated carbonyl compounds in good to excellent (45–99%) yields under the optimized reaction conditions. The CC : TU (1 : 1) DES was used for the first time in a synthetic protocol, and it was found to be an augmenting medium and a reactant for the reaction. Hopefully, this paper will open doors to developing new DESs for synthesis. It will also encourage scientists to explore using CC : TU (1 : 1) as a solvent and reactant for several organic transformations involving thiourea.

Introduction

3,4-Dihydropyrimidine-2(1*H*)-thiones (DHPMs) are an interesting class of molecules with considerable interest due to their ease of synthesis[1] and a wide spectrum of pharmacological potentials like antiviral, antitumor, anti-inflammatory, antioxidant, calcium channel blocker and antibacterial activities.[2–4] In particular, 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thione derivatives have been recently proven to exhibit potent cytotoxic activity.[5–8] The structure of a few biologically active molecules with the DHPM core is shown in Fig. 1.

The synthesis of DHPMs was first reported by Biginelli through a three-component, one-pot reaction of a 1,3-dicarbonyl compound, (thio)urea, and an aromatic aldehyde in a protic solvent, with an acidic catalyst, and the reaction was then named after him due to its huge popular acclaim.[9] Since the reaction allows a wide diversification, chemists and medicinal chemists were captivated and developed several methodologies and modifications at all possible positions of the core. The methodologies developed involve the use of NaOH,[3b] protic acid,[10] triphenylphosphine[11] (Scheme 1a and b), K_2CO_3 nanoparticles,[12] ammonium chloride,[13] dicyclohexylcarbodiimide (DCC)[14] (Scheme 1c), ammonium thiocyanate (NH_4SCN),[15] heterogeneous acidic catalysts[16] (Scheme 1d) and strontium pyroarsenate.[17] Other reagents include a Brønsted acid-surfactant catalyst,[18] a SO_3H-containing ionic liquid,[19] organocatalysts,[20] and amino acid-based chiral catalysts.[21] Several urea derivatives have also been explored, such as guanidine[22] and benzimidamide,[23] for the synthesis of pyrimidine derivatives. Some reports have also demonstrated non-Biginelli reactions.[24–26] Despite their useful attributes, many of these methods suffer from some disadvantages such as high cost, use of toxic reagents, slow reaction rate, complex product separation techniques, low yields and limited substrate

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