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Straightforward Synthesis of Novel Substituted 1,3,4-Thiadiazole Derivatives in Choline Chloride-Based Deep Eutectic Solvent

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ABSTRACT

A one-pot, three-component route for the synthesis of novel 1,3,4-thiadiazole derivatives using a ketene *S*,*S*-acetal, a carbonyl compound and thiocarbohydrazide is described. The main advantages of this approach are high yields, short reaction times, simple reaction conditions and a green reaction medium. The 1,3,4-thiadiazole core has been substituted with biologically active groups such as arylhydrazones, coumarin, isatin, Meldrum's acid and barbituric acid. Structures of the thiadiazoles were elucidated from spectroscopic data.

Amongst heterocyclic compounds, those containing five-membered rings are the most commonly encountered building blocks, with a large number possessing interesting biological activities.[1] Thiadiazoles consist of four isomers; 1,2,3-thiadiazoles, 1,2,4-thiadiazoles, 1,2,5-thiadiazoles, and 1,3,4-thiadiazoles (Fig. 1a), of which 1,3,4-thiadiazoles have seen special interest in recent years demonstrating biological properties including antimicrobial,[2] antiviral,[3] antitubercular,[4] antiparasitic,[5] anticonvulsant,[6] antidepressant, anxiolytic,[7] and anticancer[8] activities. They are also key intermediates in the synthesis of commercially available drugs such as megazol,[9] acetazolamide, and furidiazine (Fig. 1b).[10]

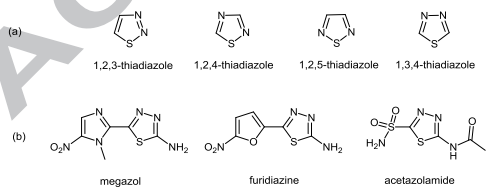

Figure 1. (a) Isomers of thiadiazole. (b) Commercially available 1,3,4-thiadiazole based drugs.

Commonly reported methods for the synthesis of 1,3,4-thiadiazoles include those starting from acylhydrazines, including monoacylhydrazines and *N*,*N*′-diacylhydrazines,[11] or thiosemicarbazides,[12] thiocarbazides,[13] dithiocarbazates,[14] thiohydrazides and bithioureas,[15] as well as the transformation of 1,3,4-oxadiazoles.[16] These methods usually require a sulfuration reagent to introduce the sulfur atom to the ring, a cyclization reagent, or a combination of reagents to form the thiadiazole ring. Additionally, commonly reported methods often suffer from harsh reaction conditions, multi-step procedures, or stoichiometric formation of intractable by-products.[17]

A one-pot or one-step synthesis *via* simple and efficient procedures would be interesting for both laboratory and industrial purposes.[18] Herein, a one-pot approach for the synthesis of novel substituted 1,3,4-thiadiazoles using thiocarbohydrazide, a carbonyl compound and a ketene *S*,*S*-acetal in a deep eutectic solvent (DES) was developed (Scheme 1).

DESs are commonly prepared from a eutectic mixture of Lewis or Brønsted acids and bases, which may contain a variety of anionic or cationic species, and possess a melting point much lower than either of the individual components.[12] Compared to ionic liquids, DESs are generally cheaper to make, are less toxic and are often biodegradable. Thus, DESs can be used as low–cost, safe and efficient solvents.[13]. Herein, the choline chloride and urea based DES (ChCl-urea) was used.

Our investigation started with the one-pot, three-component model reaction of thiocarbohydrazide **1**, Meldrum's acid based ketene-*S*,*S*-acetal **3a** or barbituric acid based ketene-*S*,*S*-acetal **3b** and 4-methoxybenzaldehyde in order to optimize the reaction conditions. First, the effects of various solvents on reaction times and yields were evaluated. Moderate to high yields of **4a** and **5a** were obtained in both protic and aprotic solvents (Table 1, Entries 1-5 and 14-18). Since DESs have many advantages including ready availability, non-toxicity, biodegradability, recyclability, and low price in comparison with organic

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