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Choline chloride and urea based deep eutectic solvent promoted synthesis of arylmethylidene-isoxazol-5(4H)-ones

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Abstract : Choline chloride/urea as a deep eutectic solvent is found to be promising solvent under the optimized conditions for the one-pot three component synthesis of arylmethylidene-isoxazol-5(4H)-ones in short span of 15–25 min with an excellent yield of 90-93%.The inexpensive, biodegradable, non-toxic and recyclable nature of choline chloride/urea make this protocol efficient and green.

Keywords : Arylmethylidene-isoxazol-5(4H)-ones, Choline chloride/urea, eco-friendly protocol.

Introduction

The isoxazole scaffold is a privileged structure of many pharmaceutical drugs attracting considerable interest in the field of medicinal chemistry. It has shown wide range of activities such as anti-inflammatory [1], antibacterial [2], anticonvulsant [3], antituberculosis [4], antiviral [5], anticancer [6] and anti protein-tyrosine phosphate 1B inhibitory [7].Many of the marketed drugs which possess isoxazolone ring scaffolds such as drazoxolon **E,** cloxacillin **F**, Dicloxacillin **G**,Zonisamide **H** have potential medicinal values [8-9] **(Figure: 1)**.

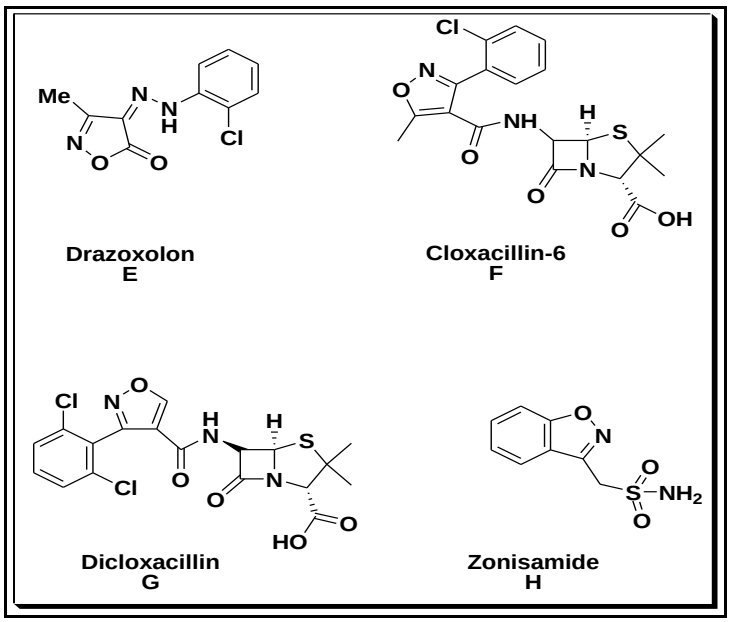


Figure: 1

Over the past few years arylmethylene isoxazol-5(4H)-ones are synthesized by using different catalysts such as DABCO[10], pyridine[11], sodium ascorbate[12], sodium benzoate [13], sodium sulfide [14], sodium silicate [15] tetrabutyl ammonium perchlorate (TBAP) and sodium oxalate or glycine [16].However some of these methods suffer from limitations such as high temperatures,long reaction time, unsatisfactory yields, high catalytic loading and use of hazardous solvents.To overcome these issues, the development of efficient, green, feasible and high yielding protocol for the synthesis of arylmethylene isoxazol-5(4H)-ones remains a valid exercise.Solvents occupy a strategic position within green chemistry outline. To be capable as a green medium, the solvent must have various criteria such as less expensive, easily available, biodegradable, nontoxic and recyclable. Deep eutectic solvents (DES) are green alternative to hazardous solvents and, in many cases, can replace them. DESs systems are prepared from two components of Lewis or Bronsted acids and bases which can contain a variety of anionic and cationic species to form a deep eutectic mixture. These two components are capable of self-association many times through a strong bond interaction, to develop eutectic mixture with a lower melting point than individual component [17-20]. Herein, in continuation of our work towards development of convenient and eco-friendly protocols for various heterocycles [21-26], we report for the first time an environmentally benign and convenient three-component one-pot protocol for the synthesis of 4-arylidene-3-phenylisoxazol-5-ones using choline chloride (ChCl):urea as a bio-renewable DES. Choline chloride : Urea deep eutectic solvent (DES)was prepared according to the literature [20].

Experimental

Chemicals were purchased from SD Fine Chemical Companies. All the products are known and their physical data is confirmed by comparison with those reported in literature. NMR spectra were recorded on a Bruker Advance DPX-250. Mass spectra were recorded on Waters GC-MS spectrophotometer. The progress of the reactions and the purity of the products were observed by TLC on silica-gel.

Typical Procedure for the synthesis of arylmethylidene-isoxazol-5(4H)-ones (4a-g)

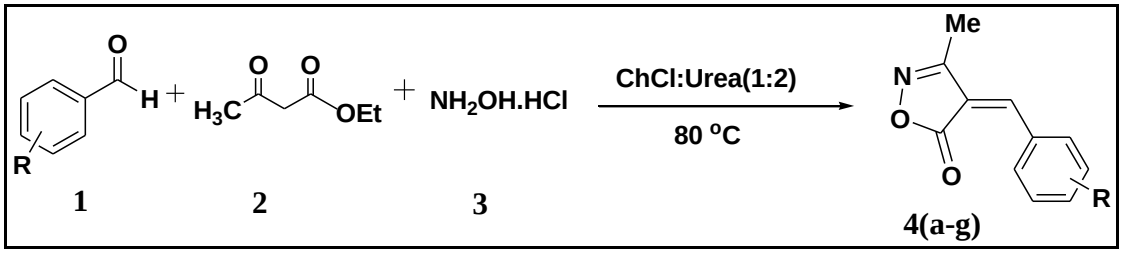
To a stirred solution of ethyl acetoacetate (1mmol), hydroxylamine hydrochloride (1mmol) and 2mL of ChCl:Urea (1:2), aldehyde (1mmol) was added and the mixture was heated at 80 ^{o}C for the appropriate time (Table 4, entry 1-7). After completion of the reaction as indicated by TLC (ethyl acetate-hexane, 2:8),5mL water was added and the obtained solid precipitate was collected by filtration. Then it was recrystallized from EtOH-H_2O (4:1) to afford the pure product.

Spectral data

4-(2-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4a): M.p. 197-199 ^{o}C;^{1}H NMR (DMSO, 400 MHz)/ δ (ppm): 10.58 (bs, 1H); 8.83 (d, 1H), 8.13 (s, 1H), 7.83 (d, 1H), 7.42 (t, 1H), 7.00 (t , 1H), 2.29 (s, 3H), ^{13}C NMR (DMSO, 100MHz) /δ (ppm) 168.16, 161.39, 159.57, 144.64,136.16,132.35, 119.47, 118.85,116.11, 11.16; Mass (m/z)=202.2 (M-1).

Results & Discussion

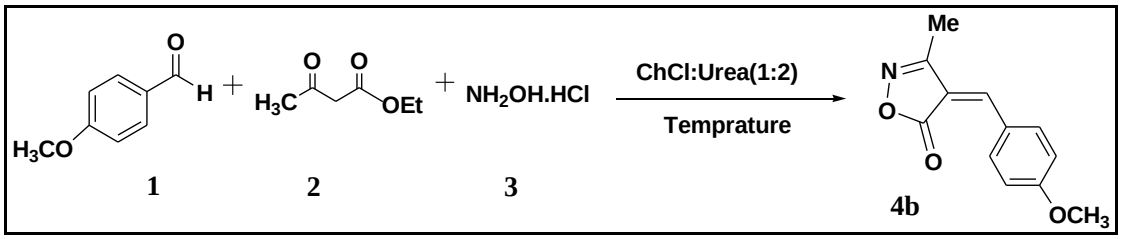
In order to explore the versatility of deep eutectic solvent, we report a new protocol for the synthesis arylmethyledene-isoxazole-5(4H)-ones by using ChCl: urea (1:2) without using any additional additive or catalyst **(Scheme: 1**).



Scheme: 1. ChCl:Urea(1:2) promoted synthesis of arylmethyledene-isoxazole-5(4H)-ones

Optimization of the reaction conditions was carried out by a test reaction using p-methoxy benzaldehyde (1mmol), ethyl acetoacetate (1mmol) and hydroxylamine hydrochloride (1mmol) in 2mL of ChCl: urea (1: 2) (Table 1, entry 1-4). The model reaction was performed by using ChCl: urea (1: 2) as a reaction medium at different temperature. At room temperature less amount of product was observed (Table 1, entry 1). When the temperature of the reaction increased to 70 ^{o}C the product yield also increased (Table1, entry 2).As mentioned in Table 1, the best conditions were determined at 80 ^{o}C temperature with excellent yield of 92% in 15 min (Table 1, entry 3). There was no noteworthy change in the product yield when reaction temperature was increased to 90 ^{o}C (Table 1, entry 4).

Table 1 Optimization under various conditions for the synthesis of arylmethyledene-isoxazole-5(4H)-one in ChCl:Urea



Entry	Deep eutectic Solvent(DES) [a]	Temperature (^{o}C)	Time (min)	Yield (%)[b]
1	Choline chloride: Urea(1:2)	R.T	60	40
2	Choline chloride: Urea(1:2)	70	30	70
3	Choline chloride: Urea(1:2)	80	15	92
4	Choline chloride: Urea(1:2)	90	15	92

[a] 2mL, [b]Isolated yields.

The scope of this reaction was investigated using different substituted aldehydes. It was observed that, aromatic aldehydes having electron releasing functional groups afforded good to high yields of the products (Table 2, entry 1-7).

Table 2 Synthesis of arylmethyledene-isoxazole-5(4H)-ones

Entry	**R**	**P**	**Yield (%)[a]**	**Time (min)**	**M. p (^{o}C)**	
					Observed	**Literature**
1	2-OH	4a	93	25min	197-199	198-201[13]
2	4-CH_3O	4b	92	15min	172-174	175-177[13]
3	H	4c	90	20min	138-140	141-143[13]
4	4-OH	4d	91	20min	212-214	210-211[16]
5	3-OCH_3,4-OH	4e	48	25min	210-212	212-215[13]
6	4-CH_3	4f	94	15min	132-134	135-135[16]
7	C_6H_5CH=CH	4g	93	15min	174-176	171-173[13]

[a]Isolated yields.

Recyclability study for the ChCl: Urea deep eutectic solvent promoted synthesis of arylmethyledene-isoxazole-5(4H)-one was performed for scale up (5mmol) batch of ethyl acetoacetate and 4-OMe benzaldehyde and hydroxyl amine hydrochloride as a model substrate (4b).After reaction completion water was added and the precipitate solid product was filtered off and dried. ChCl: urea was recovered from aqueous filtrate by vacuum evaporation of water at 80 °C, washed with ethyl acetate and was reused for the next similar reaction **(Fig: 1)**. It was observed that ChCl : Urea (1:2) remains in high catalytic activity even after four successive runs.

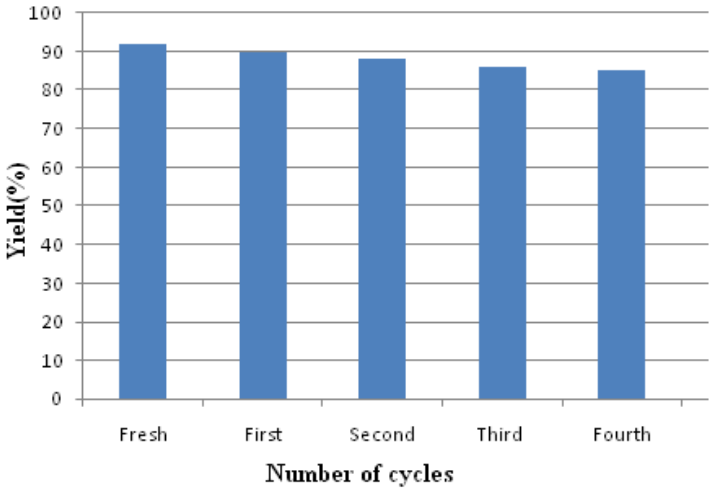


Figure 1.Recyclability study of ChCl: urea for the synthesis of arylmethyledene-isoxazole-5(4H)-ones

Conclusion

A new protocol have been developed for the synthesis of arylmethyledene-isoxazole-5(4H)-ones (**4a-g)** promoted by choline chloride: urea (1: 2) as a deep eutectic solvent. The protocol utilized choline chloride: urea (1: 2) as an efficient reaction medium/catalyst for the synthesis of arylmethyledene-isoxazole-5(4H)-ones (4a-g). Choline chloride: urea DES is less toxic, biodegradable and lower in cost, therefore is better alternative than traditional organic solvents and ionic liquids. Maximum yields, short reaction time, cost effectiveness, easy workup and reusability of the solvent are the merits of this protocol.

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