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Synthesis of 3,5-Disubstituted Isoxazoles and Isoxazolines in Deep Eutectic Solvents

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ABSTRACT: The synthesis of different 3,5-disubstituted isoxazoles and related isoxazolines using choline chloride:urea as deep eutectic solvent (DES) in a one-pot three step reaction has been accomplished successfully. The use of highly nucleophilic functionalized DES did not affect the process where highly electrophilic reagents or intermediates are involved. The presence of DES showed to be essential since the reaction in absence of this media did not proceed. The DES media could be reused up to five times without a detrimental effect on the yield of the reaction. To exemplify the synthetic potential of this methodology, the reaction was scaled up to gram scale without any noticeable problem. Finally, different isoxazoles were easily transformed into β-aminoenones.

INTRODUCTION

Isoxazoles and related 4,5-dihydroisoxazoles, are a valuable and well established[1-4] class of heterocyclic compounds[5] with broad applications,[6-7] including pharmaceutical and agricultural activities.[8-11]

Numerous synthetic approaches for the construction of the isoxazole and 4,5-dihydroisoxazole framework have been reported. There are two main methodologies: The first approach involves the condensation of hydroxylamine with 1,3-dicarbonyl compounds, or their three-carbon 1,3-electrophilic variants, such as α,β-unsaturated ketones, enamino ketones, β-alkylthioenones and ynones. The second one is the 1,3-dipolar cycloaddition reaction between alkynes or alkenes with nitrile oxides, generated in situ from aldoximes or nitroalkanes.[12-23] In turn, these heterocycles can be transformed into β-functionalizes carbonylic compounds,[24] by cleavage of the labile N-O heterocyclic bond.

Different metallic derivatives have been used to perform the regioselective cycloaddition reaction, including aluminum,[25] magtrieve (CrO_2),[26-27] cobalt[28] and copper[29-36] complexes, $AgBF_4$,[37] $SnPh_4$,[38] triscetylpyridiniumtetrakis(oxodiperoxotungsto) phosphate,[39] gold compounds[40] and $Pb(OAc)_2$.[41] Conversely, in the case of cyclopentadienyl ruthenium derivatives,[42] the regioselective formation of the related 4,5-disubstituted heterocycles was observed. It should be pointed out that for many applications the use of toxic transition metals is undesirable, if not prohibited. Therefore, there is a clear necessity for metal-free protocols. This green approach has been conducted by different oxidative reagents such as oxone,[43-44] iodine,[45-47] iodobenzene trifluoroacetate,[48] iodobenzene diacetate,[49-51] *tert*-butyl hypoiodite[52] or chloramine-

T.[53] However, these new protocols have several inconveniencies such as stability, price and manipulation of reagents. The importance of the used solvent has been recently addressed by the use of aqueous biphasic protocols,[54-55] ionic liquid,[56] and aqueous polyethylene glycol.[57]

Within the framework of green chemistry, solvents occupy a strategic place. To be qualified as a green medium, the components of this solvent have to meet different criteria such as availability, non-toxicity, biodegradability, recyclability, inflammability, renewability and low price, among others. Deep eutectic solvents[58-61] (DES) are an environmentally benign alternative to hazardous (organic) solvents and, in many cases, might replace them. DESs are liquid systems formed from a eutectic mixture of solid Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species.[62] These two components are capable of self-association, often through a strong bond interaction, to form an eutectic mixture with a melting point lower[63-66] than that of each individual component. The typical green characteristic properties of a solvent, such as conductivity, viscosity, vapor pressure and thermal stability can be fine-tuned by the appropriate choosing of the mixture components, with the large-scale preparation being feasible.

The applications of DES in organic synthesis have notable advantages. As most of the components are soluble in water, addition of water to the reaction mixture dissolves the reaction medium, and the organic products either form a separate layer or precipitate. Moreover, the solvent and the catalyst may be recycled by the adequate quenching of the reaction.

DES have been used as ideal medium in biocatalyzed,[67] organocatalyzed[68] reactions, as well as in reactions using homogeneous[69] and heterogeneous[70] catalysts. Although there are several misconceptions about their uses in Organic Synthesis due to the high reactivity of intermediate, this kind of eutectic mixture has a promising future.

Herein we report an experimentally and environmentally convenient one-pot three-component process for the regioselective synthesis of 3,5-disubstituted isoxazoles and the related 3,5-disubstituted-4,5-dihydroisoxazoles from aldehydes and alkynes or alkenes using choline chloride (ChCl):urea as biorenewable DES. The protocol permitted the simple use of highly reactive reagents, such as NCS, even the presence of highly electrophilic intermediate, such as imidoil chlorides.

EXPERIMENTAL

General Procedure for the DES preparation. A mixture of choline chloride (6.98 g, 50 mmol) or acetylcholine chloride (9.08 g, 50 mmol) and urea (6.00 g, 100 mmol) was added in a round bottom flask under inert atmosphere. The mixture was stirred during 60 minutes at 75 or 50 ºC for ChCl:urea or AcChCl:urea, respectively, obtaining the corresponding DES.

General Procedure for the formation of 3,5-disubstituted isoxazoles. To a stirred solution of the corresponding aldehyde (**1**, 2 mmol) in ChCl:urea 1:2 (1 mL) were added hydroxylamine (138 mg, 2 mmol) and sodium hydroxide (80 mg, 2 mmol). The resulting mixture was stirred at 50 ºC during one hour. After that, *N*-chlorosuccinimide (400 mg, 3 mmol) was added to the mixture and it reacted during three hours at 50ºC. Then, the corresponding alkyne (**2**, 2 mmol) was added and the mixture reacted during four hours at 50ºC, after this time the reaction was quenched with water and extracted with AcOEt (3x5 mL). The organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. The product was usually purified by column chromatography on silica gel (hexane/ethyl acetate) to give the corresponding products **3**.

General Procedure for the formation of 3,5-disubstituted-4,5-dihydroisoxazoles. To a stirred solution of the corresponding aldehyde (**1**, 2 mmol) in ChCl:urea 1:2 (1 mL) were added hydroxylamine (138 mg, 2 mmol) and sodium hydroxide (80 mg, 2 mmol). The resulting mixture was stirred at 50 ºC during one hour. After that *N*-chlorosuccinimide (400 mg, 3 mmol) was added to the mixture and it reacted during three hours at 50ºC. Then, the corresponding alkene (**4**, 2 mmol) was added and the mixture reacted during four hours at 50ºC, after this time the reaction was quenched with water and extracted with AcOEt (3x5 mL). The organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. The product was usually purified by column chromatography on silica gel (hexane/ethyl acetate) to give the corresponding products **5**.

General Procedure for the formation of β-amino enones. A solution of isoxazole (**3**, 1 mmol), water (1 mmol), and $Mo(CO)_6$ (0.5 mmol) in acetonitrile (20 mL) was refluxed during 4h. After this time, 30 mL of hexane was added and the reaction mixture was filtered through Celite. The filtrate was concentrated and the residue was purified by column chromatrography on silica gel (hexane/ethyl acetate) to give the corresponding products **6**.

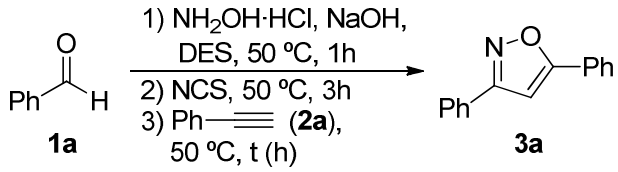
General Procedure for the formation of 3,5-disubstituted isoxazoles. To a stirred solution of ethyl 2-nitroacetate (**7a**, 1mmol) in AcChCl:urea 1:2 (1 mL) was added the corresponding alkyne (**2**, 0.5 mmol) and the reaction was stirred at 100ºC during 4h. After this time, the reaction was quenched with water and extracted with AcOEt (3x5 mL). The organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. The product was purified by chromatography on silica gel (hexane/ethyl acetate) to give the corresponding products **8**.

RESULTS AND DISCUSSION

To start our study we decided to examine the three step one pot synthesis of 3,5-disubstituted isoxazoles using benzaldehyde (**1a**) and phenylacetylene (**2a**) as the starting materials. After dissolving reagents in DES, hydroxylamine and solid NaOH were added, which should led to the formation of the corresponding oxime. Then NCS was added to the basic reaction mixture, which should result in formation of hydroxyiminoyl chloride, which should enter the reaction with present phenylacetylene (Table 1). Initially, the effect of DES in the reaction was examined (entries 1-6). In first place, the reaction was performed in the deep eutectic solvent formed by ChCl:glycerol and although the yield was not satisfactory, it proved that the concept may work (entry 1). Then, other DESs were examined as medium for the reaction, finding that DES containing urea gave better results. The mixture ChCl:urea (1:2) reached the best yield (entry 6).

It should be pointed out that this renewable solvent is a good medium for different reactions including the deprotonation of aromatic hydroxylammonium chloride with solid sodium hydroxide, condensation of amine derivative with benzaldehyde, chlorination of the formed oxime with *N*-chlorosuccinimide to give the corresponding hydroximinoyl chloride, which is stable enough into the highly functionalized medium, to permit the final [3+2] cycloaddition by slow HCl elimination. Then, the reaction time was evaluated for the last cycloaddition step (entries 6-9), finding that after 4h the increase of the yield was marginal. The reaction was scaled up to grams using 10 mL of DES (entry 9, footnote c), and after completion of the reaction 10 mL of NaOH 1M and 10 mL of hexane was added. The resulting mixture was stirred during 30 minutes and after that, the obtained solid was filtrated obtaining the corresponding pure product with good yield. This purification protocol is easier and greener than that employed in mg scale.

Table 1. Optimization of the Reaction Conditions for the Multi-Step Approach.[a]



entry	DES (molar ratio)	t (h)	yield (%)[b]
1	ChCl:glycerol (1:2)	8	20
2	ChCl:trifluoroacetamide (1:2.5)	8	0
3	ChCl:ethylene glycol (1:2)	8	0
4	$Ph_3P^+MeBr^-$:glycerol (1:2)	8	0
5	AcChCl:urea (1:2)	8	40
6	ChCl:urea (1:2)	8	71
7	ChCl:urea (1:2)	1	46
8	ChCl:urea (1:2)	2	64
9	ChCl:urea (1:2)	4	73 (70)[c]
10[d]	THF	8	4
11[d]	THF (urea)[e]	8	13
12[d]	THF (ChCl)[e]	8	11

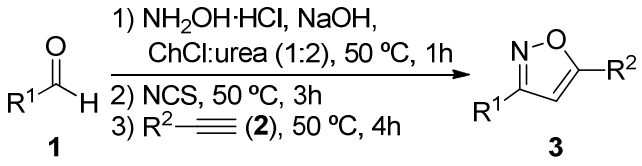
13	Urea[f]	8	34
14	ChCl[f]	8	15

[a]Reaction carried out using compounds **1a** (203 µL, 2mmol), $NH_2OH \cdot HCl$ (138 mg, 2 mmol), NaOH (80 mg, 2 mmol), NCS (400 mg, 3 mmol) and **2a** (110 µL, 2 mmol) in 1mL of DES. [b]Isolated yield after column chromatography. [c]Reaction carried out using compounds **1a** (2.03 mL, 20 mmol), $NH_2OH \cdot HCl$ (1,38 g, 20 mmol), NaOH (800 mg, 20 mmol), NCS (4g, 30 mmol) and **2a** (2.2 mL, 20 mmol) in 10 mL of DES. [d]Reaction performed using 1 mL of THF. [e] 2 Equivalents of additive was added. [f]Reaction carried out in absence of solvent using 2 equivalents of additive.

In order to clarify the role of different components of the solvent, the reaction was performed in THF adding 2 equivalents of urea or choline chloride (Table 1, entries 10-12), obtaining slightly better results using additives. When the reaction was repeated in absence of solvent but in the presence of the aforementioned additives (Table 1, entries 13-14), the best result was obtained in the presence of urea. These facts highlight the beneficial role of urea in the reaction mechanism, probably by stabilizing the ionic intermediates through hydrogen bonds.

With the best conditions in hand, the scope of the reaction was evaluated (Table 2). The reaction gave excellent results for substituted benzaldehydes independently of the nature of the substituent on the aromatic ring of the aldehyde (entries 1-3) as well as of the relative position (compare entries 3 and 4). The reaction was tested using aliphatic (entry 5) and heterocyclic (entries 6 and 7) aldehydes obtaining good yields.

Table 2. Preparation of Isoxazoles[a]



entry	R^1	R^2	Isoxazole	yield (%)[b]
1	Ph	Ph	**3a**	73
2	4-ClC_6H_4	Ph	**3b**	83
3	4-MeC_6H_4	Ph	**3c**	96
4	2-MeC_6H_4	Ph	**3d**	81
5	C_6H_{11}	Ph	**3e**	86
6	2-Quinolyl	Ph	**3f**	82
7	2-Thienyl	Ph	**3g**	86
8	Ph	3-ClC_6H_4	**3h**	80
9	Ph	4-$MeOC_6H_4$	**3i**	76
10	Ph	2-Pyridyl	**3j**	63
11	Ph	C_6H_{11}	**3k**	84
12	4-MeC_6H_4	4-$MeOC_6H_4$	**3j**	70

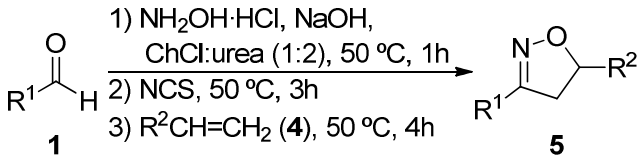
[a]Reaction carried out using compounds **1** (2mmol), $NH_2OH{\cdot}HCl$ (138 mg, 2 mmol), NaOH (80 mg, 2 mmol), NCS (400 mg, 3 mmol) and **2**(2 mmol) in 1mL of ChCl:urea (1:2). [b]Isolated yield after column chromatography.

The reaction was also accomplished with different substituted ethynylbenzenes, using electron-donating substituents as well as electron-withdrawing groups obtaining good yields (entries 8 and 9). Heterocyclic (entry 10) and aliphatic (entry 11) alkynes were also tested reaching the previous results. The combination of substituted aldehydes and alkynes was not problematic obtaining the corresponding product with a similar good yield (entry 12).

The recycling of ChCl:urea medium was evaluated once the compound **3a** was obtained. The simple decantation of DES mixture with toluene permitted the partial isolation of all organic products and by-products. The lower DES layer was reused in a second cycle, but the yield decreased from 73 to 32%. The high solubility of initial reagents ($NH_2OH{\cdot}HCl$, NaOH, NCS), as well as the stoichiometric by-product formed (H_2O and succinimide) presented in the second cycle might modify the initial DES structure, decreasing the initial beneficial solvent effect.

Once the study of this reaction was finished, a similar process was performed but using alkenes[71] (Table 3). The yields were similar to the previously obtained with alkynes allowing either the use of aromatic (entry 1-3) and heterocyclic (entry 4) aldehydes or the use of aromatic (entry 5), heterocyclic (entry 6) and aliphatic (entries 7 and 8) alkenes. The combination of aromatic aldehydes and aliphatic alkenes gave the corresponding product with moderate yield (entries 9).

Table 3. Preparation of Isoxazolines[a]

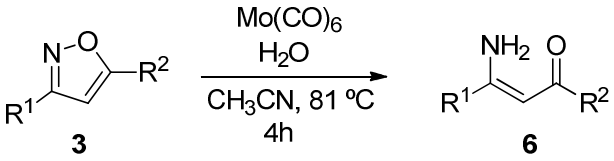


entry	R^1	R^2	Isoxazoline	yield (%)[b]
1	Ph	Ph	**5a**	54
2	4-ClC_6H_4	Ph	**5b**	91
3	4-MeC_6H_4	Ph	**5c**	51
4	2-Thienyl	Ph	**5d**	79
5	Ph	4-ClC_6H_4	**5e**	70
6	Ph	2-Pyridyl	**5f**	84
7	Ph	C_6H_{13}	**5g**	74
8	Ph	4-$MeOC_6H_4CH_2$	**5h**	47
9	4-$NO_2C_6H_4$	CH_2Br	**5i**	42

[a]Reaction carried out using compounds **1** (2mmol), $NH_2OH·HCl$ (138 mg, 2 mmol), NaOH (80 mg, 2 mmol), NCS (400 mg, 3 mmol) and **4** (2 mmol) in 1mL of DES. [b]Isolated yield after column chromatography.

Once the scope of the reaction was studied, a ring opening reaction[72-79] was carried out using 0.5 equivalents of $Mo(CO)_6$ and starting from the previously obtained isoxazoles **3** (Table 4). The reaction took place with good yields when the substituents of the isoxazole were aromatic, independently of the electronic nature of the substituents in these rings (entries 1-3). However, when the reaction was performed with aliphatic substituents, the yield decreased (entry 4).

Table 4. Synthesis of β-amino enones[a]



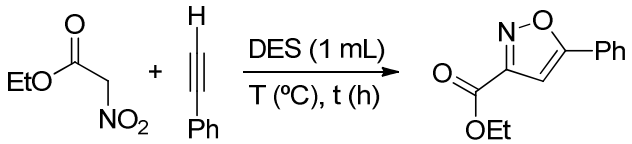
entry	R^1	R^2	β-amino enones	yield (%)[b]
1	Ph	Ph	**6a**	90
2	4-ClC_6H_4	Ph	**6b**	92
3	Ph	4-$MeOC_6H_4$	**6c**	89
4	Ph	C_6H_{13}	**6d**	55

[a]Reaction carried out using compound **3** (1 mmol), H_2O (1 mmol), $Mo(CO)_6$ (0.5 mmol) in 20 mL of CH_3CN. [b]Isolated yield after column chromatography.

Our next goal was to examine if similar dipolar cycloaddition would go also with activated nitroalkenes. So, the simple approach for the synthesis of ethyl 5-substituted isoxazole-3-carboxylates by reaction of the corresponding nitrocompounds using a DES was tested (Table 5).

Ethyl 2-nitroacetate (**7**) and phenylacetylene (**2a**) were selected as the model for the optimization of the reaction conditions. Initially, the effect of different DES was examined (entries 1-5). The reaction was performed in some of the previously tested DES, only those containing urea gave the expected product **8a**. With these results in hand, the reaction was repeated increasing the temperature (entries 6 and 7) observing that in acetyl choline chloride (AcChCl):urea the reaction took place in good yield after 24h. The reaction was tested using 2 equivalents of compound **7**, obtaining a good yield after only 4h of reaction (entry 8), with the yield not being improved by an increase in the reaction time. To prove the beneficial effect of the DES media the reaction was repeated in absence of solvent, under the best reaction conditions, and the starting material was recovered unchanged (entry 9).

Table 5. Optimization of the Reaction Conditions[a]



7 **2a** **8a**

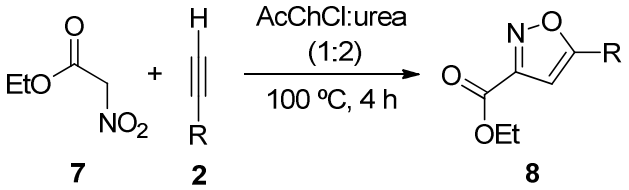
entry	DES (molar ratio)	T (ºC)	t (h)	yield (%)[b]
1	ChCl:glycerol (1:2)	50	48	0
2	ChCl:ethylene glycol (1:2)	50	48	0
3	$Ph_3P^+MeBr^-$:glycerol (1:2)	50	48	0
4	AcChCl:urea (1:2)	50	48	42

5	ChCl:urea (1:2)	50	48	35
6	ChCl:urea (1:2)	100	24	40
7	AcChCl:urea (1:2)	100	24	85
8[c]	AcChCl:urea (1:2)	100	4	79 (80)[d]
9	-	100	24	0

[a]Reaction carried out using compounds **7** (0.5 mmol) and **2a** (0.5 mmol) in 1mL of DES. [b]Isolated yield after column chromatography. [c]Reaction carried out using compounds **7** (1 mmol) and **2a** (0.5 mmol) in 1mL of AcChCl:urea. [d]After 8h of reaction.

Once the optimization was performed and with the best conditions in hands, the scope of the reaction was evaluated using AcChCl:urea (1:2) at 100 ºC (Table 6). The reaction gave excellent results with different substituted ethynylbenzenes **2** independently of the relative position or the electron nature of the substituent. However, the reaction with the related aliphatic alkyne gave the expected product **8e** with a slight decrease in the yield (entry 5).

Table 6. Preparation of Isoxazoles[a]



7 **2** **8**

entry	R	Isoxazole	yield (%)[b]
1	Ph	**8a**	79
2	3-ClC_6H_4	**8b**	91
3	3-MeC_6H_4	**8c**	85
4	4-$MeOC_6H_4$	**8d**	78
5	C_6H_{13}	**8e**	63

[a]Reaction carried out using compounds **7** (1 mmol) and **2** (0.5 mmol) in 1mL of DES. [b]Isolated yield after column chromatography.

Once the positive effect of the DES on the reaction was proved, the recycling of the media was evaluated. After performing the reaction and generating compound **8a** in AcChCl:urea the product was isolated by extraction with toluene and the DES media was reused for the next process (Figure 1). The DES solvent could be reused five times obtaining similar yields to the freshly prepared one.

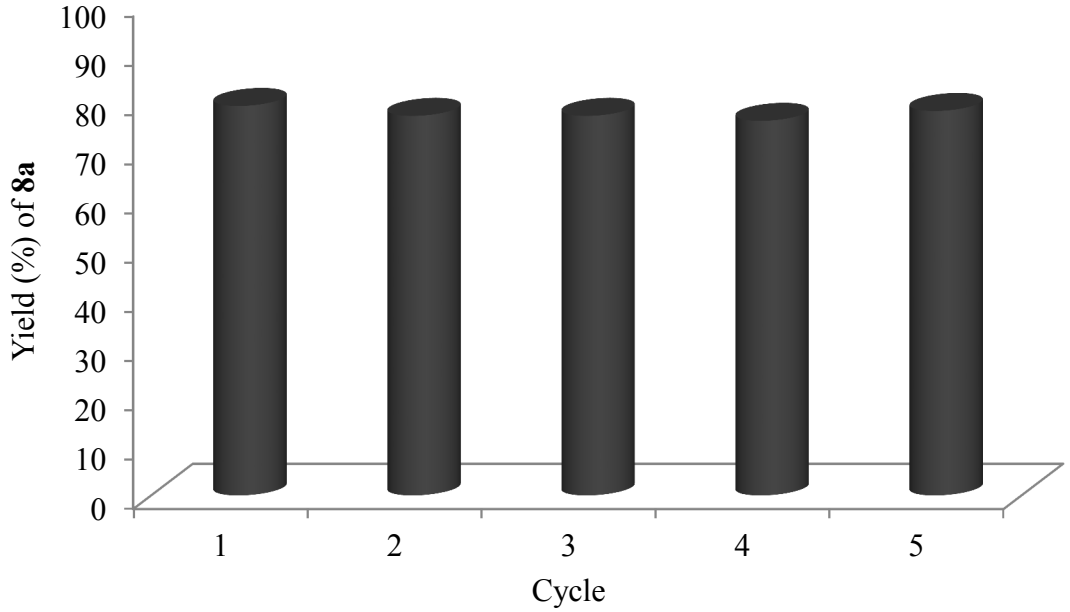
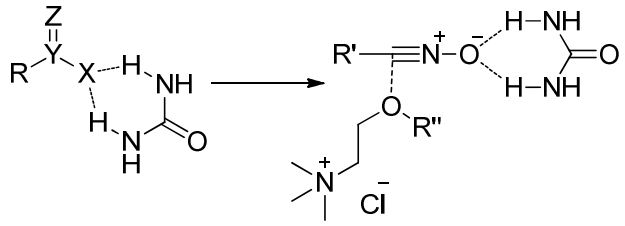


Figure1. Yields obtained with recycled DES (AcChCl:urea).

Finally, a possible picture of the hypothetic mechanism is described in Scheme 1. In both protocols, only DES containing urea gave product in a reasonable yield. This fact might be due to the high hydrogen-bond donating character of this component. In the first approach, we believe that urea favors the release of chloride from the imidoyl chloride. In fact, this interaction is the responsible for the formation of DES. In the second approach, a similar interaction would favor the nitro-tautomerization. Finally, the nitrile oxide intermediate formed in both cases could be stabilized by both component of DES, through hydrogen bonding with urea and through electronic interaction with the choline derivative.



Y=C; Z=NOH; X=Cl
Y=N; Z=O; X=O
R"=H, Ac

Scheme 1. Possible mechanism pathway.

CONCLUSIONS

In conclusion, we have demonstrated that the appropriate DES is a good solvent to perform the one-pot three step reaction to obtain isoxazoles and isoxazolines under mild reaction conditions, using highly reactive reagents and through excellent electrophiles, with the different nucleophilic functionalities of the DES media not interfering in the reaction process and not affecting into the high obtained yield. This reaction is the first one-pot multistep process described using a highly functionalized DES as medium, which is a non-toxic, biodegradable and green solvent compared to usual Volatile Organic Compounds (VOC). The reaction could be scaled up to gram scale with no negative effect, favouring the isolation of product by crystallization. Moreover, the DES could be easily recovered by the addition of a non-protonated and a polar solvent to solve the product, recycling the DES up to five times, by simple decantation, without any decrease in the reaction yields.

ASSOCIATED CONTENT

Supporting Information. General information, analytical data for products and NMR spectra of products.

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ABBREVIATIONS

DES, Deep Eutectic Solvent; ChCl, choline chloride; AcChCl, Acetyl choline chloride; VOC, Volatile Organic Compounds.

REFERENCES

(1) Padwa, A. Intermolecular 1,3-Dipolar Cycloadditions. *In Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 4, ch. 4.9, pp. 1069-1105.

(2) Sutharchanadevi, M.; Murugan, R. Isoxazoles. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; vol. 4, ch. 3.03, pp. 221-234.

(3) Wakefield, B. J. Isoxazoles. In *Science of Synthesis*, Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 2002; vol. 11, ch. 9, pp. 229-288.

(4) Pinho e Melo, T. M. V. D. Recent Advances on the Synthesis and Reactivity of Isoxazoles. *Curr. Org. Chem.* **2005**, *9*, 925-958.

(5) Kotyatkina, A. I.; Zhabinsky, V. N.;Khripach, V. A. 1,3-Dipolar cycloaddition reactions of nitrile oxides in the synthesis of natural compounds and their analogues. *Russ. Chem. Rev.* **2001**, *70,* 641-653.

(6) Lopopolo, G.; Fiorella, F.; de Candia, M.; Nicolotti, O.; Martel, S.; Carrupt, P.-A.; Altomare, C. Biarylmethoxy isonipecotanilides as potent and selective inhibitors of blood coagulation factor Xa. *Eur. J. Pharm. Sci.* **2011**, *42*, 180-191.

(7) Levent, S.; Çalişkan, B.; Çiftçi, M.; Özkan, Y.; Yenicesu, I.; Ünver, H.; Banoglu, E. Pyrazole derivatives as inhibitors of arachidonic acid-induced platelet aggregation. *Eur. J. Med. Chem.,* **2013**, *64*, 42-53.

(8) Castellano, S.; Kuck, D.; Viviano, M.;Yoo, J.; López-Vallejo, F.; Conti, P.; Tamborini, L.; Pinto, A.; Medina-Franco, J. L.; Sbardella, G. Synthesis and Biochemical Evalution of Δ^2-Isoxazoline Derivatives as DNA Methyltransferase 1 Inhibitors. *J. Med. Chem.* **2011**, *54*, 7663-7677.

(9) Ruthu, M.; Pradeepkumar, Y.; Chetty, C. M.; Prasanthi, G.; Reddy, V. J. S. Pharmacological Activities of Isoxazole Derivatives. *J. Global Trend Pharm. Sci.* **2011**, *2*, 55-62.

(10) Kumar, K. A.; Jayaroopa, P. Isoxazoles: Molecules with Potential Medicinal Properties. *Int. J. Pharm. Chem. Biol. Sci.* **2013**, *3*, 294-304.

(11) Dong, K.-Y.; Qin, H.-T.; Bao, X.-X.; Liu, F.; Zhu, C. Oxime-Mediated Facile Access to 5-Methylisoxazoles and Applications in the Synthesis of Valdecoxib and Oxacillin. *Org. Lett.* **2014**, *16*, 5266-5268.

(12) Sugiyama,T. Cerium in organic reactions: Construction of 2-isoxazoline ring mediated by ammonium cerium nitrate. *Appl. Organomet. Chem.* **1995**, *9*, 399-411.

(13) Basel, Y.; Hassner, A. An Improved Method for Preparation of Nitrile Oxides from Nitroalkanes for In Situ Dipolar Cycloadditions. *Synthesis* **1997**, *3*, 309-312.

(14) Giacomelli, G.; De Luca, L.; Porcheddu, A. A method for generating nitrile oxides from nitroalkanes: a microwave assisted route for isoxazoles. *Tetrahedron* **2003**, *59*, 5437-5440.

(15) Cecchi, L.; De Sarlo, F.; Machetti, F. Isoxazoline derivatives from activated primary nitrocompounds and tertiary diamies. *Tetrahedron Lett.* **2005**, *46*, 7877-7879.

(16) Cecchi, L.; De Sarlo, F.; Faggi, C.; Machetti, F. 1,2,5-Oxadiazole (Furazan) Derivatives from Benzoylnitromethane and Dipolarophiles in the Presence of DABCO: Structure and Intermediates. *Eur. J. Org. Chem.* **2006**, 3016-3020.

(17) Cecchi, L.; De Sarlo, F.; Machetti, F. 1,4-Diazabicyclo[2.2.2]octane (DABCO) as an Efficient Reagent for the Synthesis of Isoxazole Derivatives from Primary Nitro Compounds and Dipolarophiles: The Role of the Base. *Eur. J. Org. Chem.* **2006**, 4852-4860.

(18) Machetti, F.; Cecchi, L.; Trogu, E.; De Sarlo, F. Isoxazoles and Isoxazolines by 1,3-Dipolar Cycloaddition: Base-Catalysed Condensation of Primary Nitro Compounds with Dipolarophiles. *Eur. J. Org. Chem.* **2007**, 4352-4359.

(19) Cecchi, L.; De Sarlo, F.; Machetti, F. Synthesis of 4,5-Dihydroisoxazoles by Condensation of Primary Nitro Compounds with Alkenes by Using a Copper/Base Catalytic System. *Chem. Eur. J.* **2008**, *14*, 7903-7912.

(20) Burkhard, J. A.; Tchitchanov, B. H.; Carreira, E. M. Eine Reaktionskaskade zur Gewinnung von Isoxazolen durch einfache basenvermittelte Umlagerung substituierter Oxetane. *Angew. Chem. Int. Ed.* **2011**, *123*, 5491-5494.

(21) Itoh, K.-I.; Aoyama, T.; Satoh, H.; Fujii, Y.; Sakamaki, H.; Takido,T. Application fo silica gel-supported polyphosporic acid (PPA/SiO_2) as reusable solid acid catalyst to the synthesis of 3-benzoylisoxazoles and isoxazolines. *Tetrahedron Lett.* **2011**, *52*, 6892-6895.

(22) Trogu, E.; Vinattieri, C.; De Sarlo, F.; Machetti, F. Acid-Base-Catalysed Condensation Reaction in Water: Isoxazolines and Isoxazoles from Nitroacetates and Dipolarophiles. *Chem. Eur. J.* **2012**, *18*, 2081-2093.

(23) Mohammed, S.; Vishwakarma, R. A.; Bharate, S. B. Metal-free DBU promoted regioselective synthesis of isoxazoles and isoxazolines. *RSC Adv.* **2015**, *5*, 3470-3473.

(24) Raghava, B.; Parameshwarappa, G.; Acharya, A.; Swaroop, T. R.; Rangappa, K. S.; Ila, H. Cyclocondensation of Hydroxylamine with 1,3-Bis(het)arylmonothio 1,3-Diketones and 1,3-Bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 3,5-Bis(het)arylisoxazoles with Complementary Regioselectivity. *Eur. J. Org. Chem,* **2014**, 1882-1892.

(25) Jackowski, O.; Lecourt, T.; Micouin, L. Direct Synthesis of Polysubstituted Aluminoisoxazoles and Pyrazoles by Metalative Cyclization. *Org. Lett.* **2011**, *13*, 5664-5667.

(26) Bhosale, S.; Kurhade, S.; Prasad, U. V.; Palle, V. P.; Bhuniya, D. Efficient synthesis of isoxazoles and isoxazolines from aldoximes using Magtrevite (CrO_2). *Tetrahedron Lett.* **2009**, *50*, 3948-3951.

(27) Bhosale, S.; Kurhade, S.;Vyas, S.; Palle, V. P.; Bhuniya, D. Magtrevite (CrO_2) and MnO_2 mediated oxidation of aldoximes: studing the reaction course. *Tetrahedron* **2010**, *66*, 9582-9588.

(28) Wei, X.; Fang, J.; Hu, Y.; Hu, H. A convenient preparation of 3,5-diarylisoxazoles. *Synthesis* **1992**, *12*, 1205-1206.

(29) Hansen, T. V.; Wu, P.; Fokin, V. V. One-Pot copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles. *J. Org. Chem.* **2005**, *70*, 7761-7764.

(30) Koufaki, M.; Fotopoulou, T.; Heropoulos, G. A. Synergistic effect of dual-frequency ultrasound irradiation in the one-pot synthesis of 3,5-disubstituted isoxazoles. *Ultrason. Sonochem.* **2014**, *21*, 35-39.

(31) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharples, K. B.; Fokin, V. V. Copper(I)-Catalyzed ¨Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127*, 210-216.

(32) Willy, B.; Frank, W.; Rominger, F.; Müller, T. J. J. One-pot-three-component synthesis, structure and redox properties of ferrocenyl isoxazoles. *J. Organomet. Chem.* **2009**, *694*, 942-949.

(33) Vieira, A. A.; Bryk, F. R.; Conte, G.; Bortoluzzi, A. J.; Gallardo, H. 1,3-Dipolar cycloaddition reaction applied to synthesis of new unsymmetric liquid crystal compounds-based isoxazoles. *Tetrahedron Lett.* **2009**, *50*, 905-908.

(34) Bharate, S. B.; Padala, A. K.; Dar, B. A.; Yadav, R. R.; Singh, B.; Vishwakarma, R. A. Montmorillonite cly Cu(II) catalyzed domino one-pot multicomponent synthesis of 3,5-disubstituted isoxazoles. *Tetrahedron Lett.* **2013**, *54*, 3558-3561.

(35) Kovács, S.; Novák, Z. Copper on iron promoted one-pot synthesis of β-aminoenones and 3,5-disubstituted pyrazoles. *Tetrahedron* **2013**, *69*, 8987-8993.

(36) Chanda, K.; Rej, S.; Huang, M. H. Investigation of facet effects on the catalytic activity of Cu_2O nanocrystals for efficient regioselective synthesis of 3,5-disubstituted isoxazoles. *Nanoscale* **2013**, *5*, 12494-12501.

(37) Ueda, M.; Ikeda, Y.; Sato, A.; Ito, Y.; Kakiuchi, M.; Shono, H.; Miyoshi, T.; Naito, T.; Miyata, O. Silver-catalyzed synthesis of disubstituted isoxazoles by cyclization of alkynyl oxime ethers. *Tetrahedron* **2011**, *67*, 4612-4615.

(38) Moriya, O.; Urata, Y.; Endo, T. Dehydrochlorination of Hydroximic Acid Chlorides by the Use of Organotin Compounds: An Application for Synthesis of Isoxazolines and Isoxazoles. *J. Chem. Soc., Chem. Commun.* **1991**, 17-18.

(39) Ballistreri, F. P.; Chiacchio, U.; Rescifina, A.; Tomaselli, G.; Toscano, R. M. Conversion of Oximes to Carbonyl Compounds by Triscetylpyridinium Tetrakis(oxodiperoxotungsto) Phosphate (PCWP)-mediated Oxidation with Hydrogen Peroxide. *Molecules* **2008**, *13*, 1230-1237.

(40) Kung, K. K.-Y.; Lo, V. K.-Y.; Ko, H.-M.; Li, G.-L.;Chan, P.-Y.;Leung, K.-C.; Zhou, Z.; Wang, M.-Z.; Che, C.-M.; Wong, M.-K. Cyclometallated Gold(III) Complexes as Effective Catalysts for Synthesis of Propargylic Amines, Chiral Allenes and Isoxazoles. *Adv. Synth. Catal.* **2013**, *355*, 2055-2070.

(41) Sharma, T. C.; Rojindar, S.; Berge, D. D.; Kale, A. V. Les tetraacetate oxidation of chalcone oximes. *Indian J. Chem. B* **1986**, *25B*, 437.

(42) Grecian, S.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles. *Angew. Chem. Int. Ed.* **2008**, *47*, 8285-8287.

(43) Yoshimura, A.; Middleton, K. R.;Todora, A. D.; Kastern, B. J.; Koski,S. R.; Maskaev, A. V.; Zhdankin, V. V. Hypervalent Iodine Catalyzed Generation of Nitrile Oxides from Oximes and their Cycloaddition with Alkenes or Alkynes. *Org. Lett.* **2013**, *15*, 4010-4013.

(44) Han, L.; Zhang, B.; Zhu, M.; Yan, J. An environmentally benign synthesis of isoxazolines and isoxazoles mediated by potassium chloride in water. *Tetrahedron Lett.* **2014**, *55*, 2308-2311.

(45) Ingle, A. V.;Doshi, A. G.;Raut, A. W.; Kadu, N. S. Synthesis of 3,5-disubstituted isoxazolines and isoxazoles. *Orient. J. Chem.* **2011**, *27*, 1815-1818.

(46) Akbar, s.; Srinivasan, K. A Tndem Strategy for the Synthesis of 1*H*-Benzo[*g*]indazoles and Naphto[2,1-*d*]isoxazoles from *o*-Alkynylarene Chalcones. Eur. *J. Org. Chem.* **2013**, 1663-1666.

(47) Harigae, R.; Moriyama, K.; Togo, H. Prepration of 3,5-Disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines, and Hydroxylamine. *J. Org. Chem.* **2014**, *79*, 2049-2058.

(48) Jawalckar, A. M.; Reubsaet, E.; Rutjes, F. P. J. T.; van Delft, F. L. Synthesis of isoxazoles by hypervalent iodine-induced cycloaddition of nitrile oxides to alkynes. *Chem. Commun.* **2011**, *47*, 3198-3200.

(49) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.;Aulakh, V. S.; Ciufolini, M. A. Oxidation of Oximes to Nitrile Oxides with Hypervalent Iodine Reagents. *Org. Lett.* **2009**, *11*, 1539-1542.

(50) Sanders, B. C.; Friscourt, F.; Ledin, P. A.; Mbua, N. E.; Arumugam, S.; Guo, J.; Boltje, T. J.; Popik, V. V.; Boons, G.-J. Metal-Free Sequential [3+2]-Dipolar Cycloadditions using Cyclooctynes and 1,3-Dipoles of Different Reactivity. *J. Am. Chem. Soc.* **2011**, *133*, 949-957.

(51) Gonçalves, R. S. B.; Santos, M. D.; Bernadat, G.; Bonnet-Delpon, D.;Crousse, B. A one-pot synthesis of 3-trifluoromethyl-2-isoxazolines from trifluoromethyl aldoxime. *Beilstein J. Org. Chem.* **2013**, ***9***, 2387-2394.

(52) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. Generation of Nitrile Oxides from Oximes Using *t*-BuOI and Their Cycloaddition. *Org. Lett.* **2011**, *13*, 2966-2969.

(53) Koufaki, M.; Fotopoulou, T.; Kapetanou, M.; Heropoulos, G. A.; Gonos, E. S.; Chondrogianni, N. Microwave-assisted synthesis of 3,5-disubstituted isoxazoles and evaluation of their anti-ageing activity. *Eur. J. Med. Chem.* **2014**, *83*, 508-515.

(54) Kozikowski, A. P.; Adamczyk, M. Methods for the Stereoselective Cis Cyanohydroxylation and Carboxyhydroxylation of Olefins. *J. Org. Chem.* **1983***, 48*, 366-372.

(55) Koyama, Y.; Yonekawa, M.; Takata, T. New Click Chemistry: Click Polymerization via 1,3-Dipolar Addition of Homo-ditopic Aromatic Nitrile Oxides Formed In Situ. *Chem. Lett.* **2008**, *37*, 918-919.

(56) Valizadeh, H.; Amiri, M.; Gholipur, H. Efficient and Convenient Method for the Synthesis of Isoxazoles in Ionic Liquid. *J. Heterocyclic Chem.* **2009***, 46,* 108-110.

(57) Chary, R. G.; Reddy, G. R.; Ganesh, Y. S. S.; Prasad, K. V.; Raghunadh, A.; Krishna, T.; Mukherjee, S.; Pal, M. Effect of Aqueous Polyethylene Glycol on 1,3-Dipolar Cycloaddition of

Benzoylnitromethane/Ethyl 2-Nitroacetate with Dipolarophiles: Green synthesis of Isoxazoles and Isoxazolines. *Adv. Synth. Catal.* **2014**, *356*, 160-164.

(58) Abbott, A. P.; Harris, R. C.; Ryder, K. S.; D'Agostino, C.; Gladden, L. F.; Mantle, M. D. Glycerol eutectics as sustainable solvent systems. *Green Chem.* **2011**, *13*, 82-90.

(59) Zhang, Q.; Vigier, K. D. O.; Royer, S.; Jérôme, F. Deep eutectic solvents: syntheses, properties and applications. *Chem. Soc. Rev.* **2012**, *41*, 7108-7146.

(60) Dai, Y.; van Spronsen, J.; Witkamp, G.-J.; Verpoorte, R.; Choi, Y. H. Natural deep eutectic solvents as new potential media for green technology. *Anal. Chim. Acta* **2013**, *766*, 61-68.

(61) Tang, B.; Row, K. H. Recent development in deep eutectic solvents in chemical science. *Monatsh Chem.* **2013**, *144*, 1427-1454.

(62) Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep Eutectic solvents (DESs) and Their Applications. *Chem. Rev.* **2014**, *114*, 11060-11082.

(63) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. *Chem. Commun.* **2003**, 70-71.

(64) Kareem, M. A.; Mjalli, F. S.; Hashim, M. A.; AlNashel, I. M. Phosphonium-Based Ionic Liquids Analogues and Their Physical Properties. *J. Chem. Eng. Data* **2010**, *55*, 4632-4637.

(65) Ruβ, C.; König, B. Low melting mixtures in organic synthesis – an alternative to ionic liquids?. *Green Chem.* **2012**, *14*, 2969-2982.

(66) Francisco, M.; van den Bruinhorst, A.; Kroon, M. C. Low-Transition-Temperature Mixtures (LTTMs): A New Generation of Designer Solvents. *Angew. Chem. Int. Ed.* **2013**, *52*, 3074-3085.

(67) Maugeri, Z.; Domínguez de María, P. Whole-Cell Biocatalysis in Deep-Eutectic-Solvents/Aqueous Mixtures. *ChemCatChem.* **2014**, *6*, 1535-1537.

(68) Müller, C. R.; Meiners, I.; Domínguez de María, P. Highly enantioselective tandem enzyme–organocatalyst crossed aldol reactions with acetaldehyde in deep-eutectic-solvents. *RSC Adv.* **2014**, *4*, 46097-46101.

(69) Gu, L.; Huang, W.; Tang, S.; Tian, S.; Zhang, X. A novel deep eutectic solvent for biodiesel preparation using a homogeneous base catalyst. *Chem. Eng. J.* **2015**, *259*, 647-652.

(70) Lu, J.; Li, W.-T.; Ma, E.-Q.; Mo, L.-P.; Zhang, Z.-H. Superparamagnetic $CuFeO_2$ Nanoparticles in Deep Eutectic Solvent: an Efficient and Recyclable Catalytic System for the Synthesis of Imidazo[1,2-*a*]pyridines. *ChemCatChem* ***2014,*** 6*,* 2854-2859.

(71) Han, L.; Zhang, B.; Xiang, C.; Yan, J. One-Pot synthesis of Isoxazolines from Aldehydes Catalyzed by Iodobenzene. *Synthesis* **2014**, *46*, 503-509.

(72) Kashima, C.; Tobe, S.; Sugiyama, N.; Yamamoto, M. The Alkylation of 3,5-Dimethylisoxazole. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 310-313.

(73) Kashima, C. A New Conversion of 3,5-Disubstituted Isoxazoles to α,β-Unsaturated Ketones. *J. Org. Chem.* **1975**, *40*, 526-527.

(74) Curran, D. P. Reduction of Δ^2-Isoxazolines. 3. Raney-Nickel Catalyzed formation of *β*-Hydroxy Ketones. *J. Am. Chem. Soc.* **1983**, *105*, 5826-5833.

(75) Nitta, M.; Kobayashi, T. Metal-carbonyl-Induced Reaction of Isoxazoles. Ring Cleavage and Reduction by Hexacarbonylmolybdenum, Pentacarbonyliron, or Nonacarbonyldi-iron. *J. Chem. Soc., Perkin Trans.* **1985**, *1*, 1401-1406.

(76) Li, C.-S.; Lacasse, E. Synthesi of pyran-4-ones from isoxazoles. *Tetrahedron Lett.* **2002**, *43*, 3565-3568.

(77) Saxena, R.; Singh, V.; Batra, S. Studies on the catalytic hydrogenation of Baylis-Hillman derivatives of substituted isoxazolecarbaldehydes. Unusual retention of isoxazole ring during Pd-C-promoted hydrogenation of Baylis-Hillman adducts. *Tetrahedron* **2004**, *60*, 10311-10320.

(78) Sviridov, S. I.; Vasil'ev, A. A.; Shorshnev, S. V. Straightforward transformation of isoxazoles into pyrazoles: renewed and improved. *Tetrahedron* **2007**, *63*, 12195-12201.

(79) Zhu, L.; Wang, G.; Guo, Q.; Xu, Z.; Zhang, D., Wang, R. Copper-Catalyzed Intramolecular Oxytrifluoromethylthiolation of Unactivated Alkenes. *Org. Lett.* **2014**, *16*, 5390-5393.

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Synthesis of 3,5-Disubstituted Isoxazoles and Isoxazolines in Deep Eutectic Solvents

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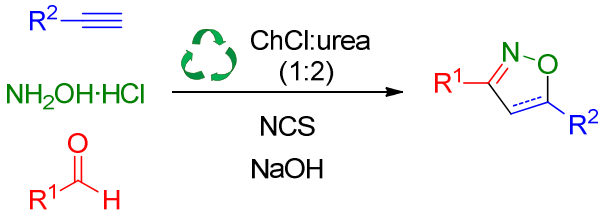

The synthesis of different 3,5-disubstituted isoxazoles and related isoxazolines using choline chloride:urea as deep eutectic solvent (DES) in a one-pot three step reaction has been accomplished successfully.