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

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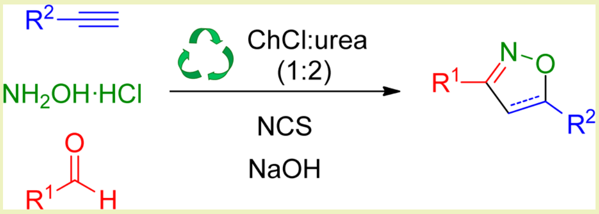
Supporting Information

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 the gram scale without any noticeable problem. Finally, different isoxazoles were easily transformed into β-aminoenones.



KEYWORDS: *Deep eutectic solvent, Metal free, Isoxazoles, Isoxazolines, Recyclable*

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, nontoxicity, 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.

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DES have been used as an 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 the 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 a 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 SECTION

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 min at 75 or 50 °C 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 hydroxylammonium chloride (138 mg, 2 mmol) and sodium hydroxide (80 mg, 2 mmol). The resulting mixture was stirred at 50 °C during 1 h. After that, *N*-chlorosuccinimide (400 mg, 3 mmol) was added to the mixture and it reacted during 3 h at 50 °C. Then, the corresponding alkyne (**2**, 2 mmol) was added and the mixture reacted during 4 h at 50 °C, after this time the reaction was quenched with water and extracted with AcOEt (3 × 5 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 hydroxylammonium chloride (138 mg, 2 mmol) and sodium hydroxide (80 mg, 2 mmol). The resulting mixture was stirred at 50 °C during 1 h. After that *N*-chlorosuccinimide (400 mg, 3 mmol) was added to the mixture and it reacted during 3 h at 50 °C. Then, the corresponding alkene (**4**, 2 mmol) was added and the mixture reacted during 4 h at 50 °C, after this time the reaction was quenched with water and extracted with AcOEt (3 × 5 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**.

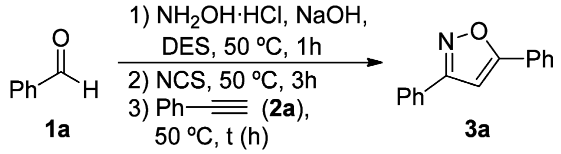
General Procedure for the Formation of *β*-Amino Enones. A solution of isoxazole (**3**, 1 mmol), water (1 mmol), and $Mo(CO)_6$ (0.5 mmol) in acetonitrile (20 mL) was refluxed during 4 h. After this time, 30 mL of hexane was added and the reaction mixture was filtered through Celite. The filtrate was 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**, 1 mmol) in AcChCl:urea 1:2 (1 mL) was added the corresponding alkyne (**2**, 0.5 mmol) and the reaction was stirred at 100 °C during 4 h. After this time, the reaction was quenched with water and extracted with AcOEt (3 × 5 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, hydroxylammonium chloride and solid NaOH were added, which should lead 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).

Table 1. Optimization of the Reaction Conditions for the Multistep 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

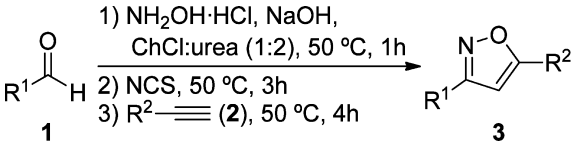
[a] Reaction carried out using compounds **1a** (203 *μ*L, 2 mmol), $NH_2OH{\cdot}HCl$ (138 mg, 2 mmol), NaOH (80 mg, 2 mmol), NCS (400 mg, 3 mmol), and **2a** (110 *μ*L, 2 mmol) in 1 mL of DES. [b] Isolated yield after column chromatography. [c] Reaction carried out using compounds **1a** (2.03 mL, 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 equiv of additive was added. [f] Reaction carried out in the absence of solvent using 2 equiv of additive.

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, and 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 4 h 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 1 M and 10 mL of hexane was added. The resulting mixture was stirred during 30 min 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 the milligram scale.

In order to clarify the role of different components of the solvent, the reaction was performed in THF adding 2 equiv 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$_6$H$_4$	Ph	**3b**	83
3	4-MeC$_6$H$_4$	Ph	**3c**	96
4	2-MeC$_6$H$_4$	Ph	**3d**	81
5	C$_6$H$_{11}$	Ph	**3e**	86
6	2-quinolyl	Ph	**3f**	82
7	2-thienyl	Ph	**3g**	86
8	Ph	3-ClC$_6$H$_4$	**3h**	80
9	Ph	4-MeOC$_6$H$_4$	**3i**	76
10	Ph	2-pyridyl	**3j**	63
11	Ph	C$_6$H$_{11}$	**3k**	84
12	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	**3j**	70

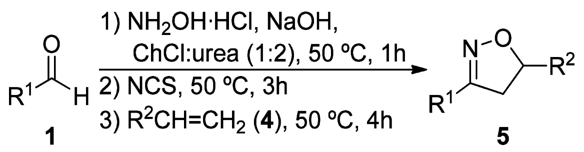
[a]Reaction carried out using compounds **1** (2 mmol), $NH_2OH·HCl$ (138 mg, 2 mmol), NaOH (80 mg, 2 mmol), NCS (400 mg, 3 mmol) and **2** (2 mmol) in 1 mL of ChCl:urea (1:2). [b]Isolated yield after column chromatography.

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 byproducts. The lower DES layer was reused in a second cycle, but the yield decreased from 73 to 32%. The high solubility of initial reagents ($NH_2OH·HCl$, NaOH, NCS), as well as the stoichiometric byproduct 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]

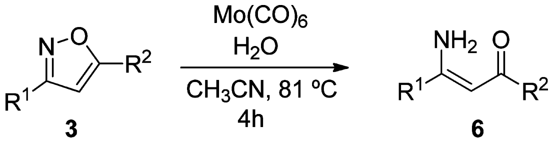


entry	R^1	R^2	isoxazoline	yield (%)[b]
1	Ph	Ph	**5a**	54
2	4-ClC$_6$H$_4$	Ph	**5b**	91
3	4-MeC$_6$H$_4$	Ph	**5c**	51
4	2-Thienyl	Ph	**5d**	79
5	Ph	4-ClC$_6$H$_4$	**5e**	70
6	Ph	2-pyridyl	**5f**	84
7	Ph	C$_6$H$_{13}$	**5g**	74
8	Ph	4-MeOC$_6$H$_4$CH$_2$	**5h**	47
9	4-NO$_2$C$_6$H$_4$	CH$_2$Br	**5i**	42

[a]Reaction carried out using compounds **1** (2 mmol), $NH_2OH·HCl$ (138 mg, 2 mmol), NaOH (80 mg, 2 mmol), NCS (400 mg, 3 mmol), and **4** (2 mmol) in 1 mL 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 equiv of $Mo(CO)_6$ and starting from the previously obtained isoxazoles **3** (Table 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$_6$H$_4$	Ph	**6b**	92
3	Ph	4-MeOC$_6$H$_4$	**6c**	89
4	Ph	C$_6$H$_{13}$	**6d**	55

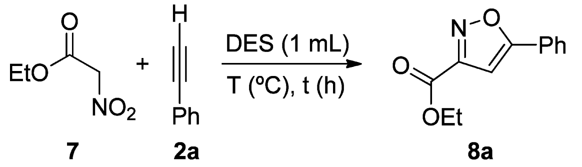
[a]Reaction carried out using compound **3** (1 mmol), H_2O (1 mmol), and $Mo(CO)_6$ (0.5 mmol) in 20 mL of CH_3CN. [b]Isolated yield after column chromatography.

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).

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 24 h. The reaction was tested using 2 equiv of compound 7, obtaining a good yield after only 4 h 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]

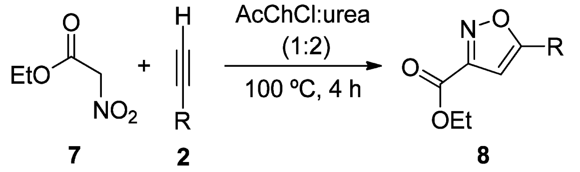


entry	DES (molar ratio)	T (°C)	t (h)	yield (%)[b]
1	ChCl:glycerol (1:2)	50	48	0
2	ChCl:ethylene glycol (1:2)	50	48	0
3	$Ph_3P^+MeBr^-$:glycerol (1:2)	50	48	0
4	AcChCl:urea (1:2)	50	48	42
5	ChCl:urea (1:2)	50	48	35
6	ChCl:urea (1:2)	100	24	40
7	AcChCl:urea (1:2)	100	24	85
8[c]	AcChCl:urea (1:2)	100	4	79 (80)[d]
9		100	24	0

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



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 1 mL 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.

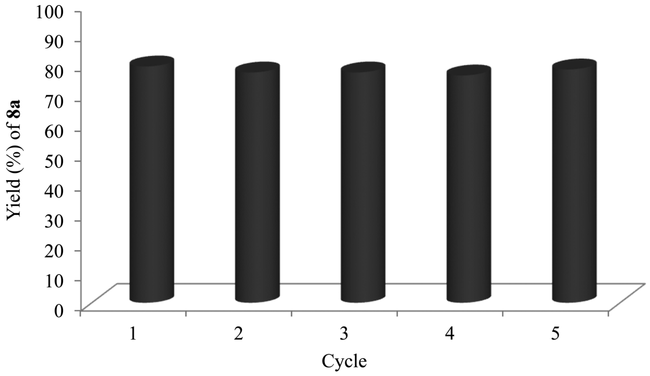
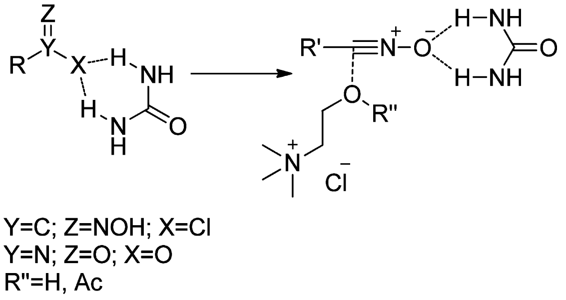


Figure 1. Yields obtained with recycled DES (AcChCl:urea).

Finally, a possible picture of the hypothetic mechanism is described in Scheme 1. In both protocols, only DES containing urea gave a 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.

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 the high obtained yield. This reaction is the first one-pot multistep process described using a highly functionalized

DES as a medium, which is a nontoxic, biodegradable, and green solvent compared to the usual volatile organic compounds (VOC). The reaction could be scaled up to the gram scale with no negative effect, favoring the isolation of product by crystallization. Moreover, the DES could be easily recovered by the addition of a nonprotonated 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b00689.

General information, analytical data for products, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DES, deep eutectic solvent; ChCl, choline chloride; AcChCl, acetyl choline chloride; VOC, volatile organic compounds

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