

A Joint Action of Deep Eutectic Solvents and Ultrasound to Promote Diels–Alder Reaction in a Sustainable Way

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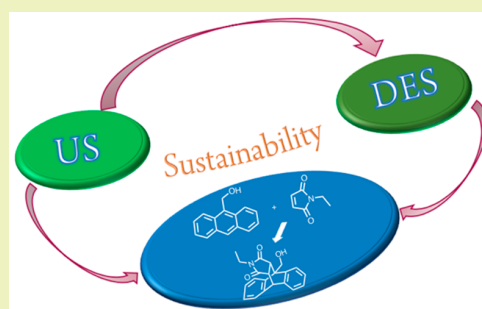
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ABSTRACT: The need to reduce environmental impact of chemical processes has induced a surge of attention in the choice of solvent and methodologies to carry them out. In this context, we studied the Diels–Alder reaction using *N*-ethylmaleimide as dienophile and changing the nature of the diene in deep eutectic solvents (DES) under both conventional heating and ultrasonic activation. DES obtained by the combination of different hydrogen bond acceptors and donors allowed assessing the role played by solvent nature. DES proved suitable solvent media for the target reaction, allowing higher yields and faster reactions compared to conventional organic solvents. The trend of yields, both in silent and under ultrasound irradiation, was rationalized considering solvent viscosity and structural organization. In particular, thanks to a combined approach of resonance light scattering (RLS) and ¹H NMR investigation, a relationship between performance of the reaction and thickness and strength of the hydrogen bond network of the solvent was identified. Moreover, DES could be recycled up to eight times without any loss in yield. Using ultrasonic activation in combination with DES proved beneficial providing good yields in drastically reduced reaction times. From the standpoint of Green Chemistry, the combined use of ultrasound and DES allowed reducing energy consumption by more than 99% compared with silent reactions and proved beneficial for the scalability of the process.

KEYWORDS: Deep eutectic solvents, Diels–Alder reaction, Ultrasound irradiation, solvent effect, recyclability



INTRODUCTION

The urgent demand of new protocols able to reduce the impact of industrial activities on the environment makes sustainability one of the main goals in chemistry research.¹ Pursuing important targets like an increase in selectivity and a decrease in energy consumption and waste production, as well as use of low toxicity materials, plays a significant role in planning of synthetic methodologies.

Although the above considerations represent key points in the area of synthetic chemistry, they assume an added value if processes of industrial relevance, like the Diels–Alder reaction (DAR),² are taken in consideration. Since its discovery,³ this reaction has been used to obtain six-membered rings with high diastereo- and regioselectivity. From the sustainability point of view, the power of DAR stands on its atom-economical character that offers the possibility of obtaining also complex structures with minimal waste, fulfilling the requirements to scale up a chemical process, i.e. robustness, operational simplicity, and safety.^{4–6} This justifies its use for manufacturing of pharmaceutical and agrochemical ingredients or flavors and fragrances on industrial plants.²

From a mechanistic point of view, its pathway is well understood in conventional solvents.^{7–9} It proceeds in a single step through a cyclic transition state and consequently can be used for evaluating solvent effects. For this reason, it has been

performed in water¹⁰ and fluoruous solvents,¹¹ as well as ionic liquids (ILs)^{12,13} and ionic liquid mixtures.¹⁴

In the context of planning more environmentally friendly synthetic strategies, also the solvent choice represents an important concern. On this subject, the replacement of conventional organic solvents, which pose risks to the environment in terms of inherent toxicity as well as emission and accumulation of volatile organic compounds (VOC),¹⁵ represents one of the main issues of chemistry literature. Consequently, a large body of work is focused on the use of alternative solvents.¹⁶ These include water,¹⁷ supercritical fluids,¹⁸ ionic liquids (ILs),¹⁹ and deep eutectic solvents (DES).^{20,21}

Among these, DES are a new class of solvents. First introduced by Abbott, they represent a burgeoning field with application in different areas of chemical research^{21–23} from organic synthesis and catalysis²⁴ to fuel desulfurization,²⁵ extraction of bioactive natural products,²⁵ and separation

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methods.²⁶ DES are mixtures of two or more compounds characterized by a lower melting point than any of the individual components. These latter comprise, in general, hydrogen bond acceptors (HBA) like quaternary ammonium salts and hydrogen bond donors (HBD) like amides, carboxylic acids, or carbohydrates.²⁷ Similarly to ILs, DES have negligible vapor pressure and flammability and are formed thanks to the occurrence of intra- and intermolecular hydrogen bonds between the components.²⁸ Moreover, they are often composed of readily available, nontoxic components derived from renewable resources.²⁹ All these considerations make DES new promising replacements of conventional organic solvents.²¹

Along these premises, in the framework of our interest in studying the use of alternative reaction media in organic synthesis,^{30–33} we undertook the investigation of a DAR in DES, under both conventional thermal activation and ultrasound irradiation. In particular, we chose to study the DAR between different dienes like 9-anthracenemethanol, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene (**1a–c**), and *N*-ethylmaleimide (**2**) (Scheme 1).

Our investigation was performed bearing in mind two main goals. First, we were interested in searching new experimental

conditions able to meet sustainability criteria, with the aim to make greener a process that has important repercussions from an applicative point of view and consequently on the environment. Furthermore, taking into consideration the above premises on the mechanism of DAR, we would like to gain insights about the effect that solvents of new generations, like DES, are able to exert on this reaction. This aims to understand if DES behave as conventional solvents or rather their action is mainly determined by the organized network of the hydrogen bond between HBA and HBD. To date, only a few reports have been reported about the study of DAR in “smart” solvents.^{20,34–36}

The target reaction was studied in DES obtained by the combination of different HBA and HBD (Scheme 1). The combinations employed allowed assessing the solvent effect as a function of their different natures. Furthermore, for a useful comparison with conventional solvents, the DAR was also carried out in hexane, methanol, and water.

Special attention was devoted to energy waste associated with the process, performing the reaction also under ultrasound irradiation. Ultrasound (US) constitutes a non-conventional mean of promoting a wide range of reactions.³⁷ US is especially attractive in the context of Green Chemistry because it can enable significant reductions in reaction times and temperatures, owing to the high and localized energy generated by the cavitation phenomenon.^{38,39} US can be suitably coupled with low vapor pressure and viscous solvents like ILs since these conditions lead to stronger cavitation effects.⁴⁰ In this context, some previous reports shed light on the significant enhancement of the ultrasonic effect in ILs with a high degree of structural organization.^{41,42} Since DES possess similar physical properties,²³ they can be, in principle, suitably used in conjunction with US.

Data collected clearly evidence the beneficial effect exerted by DES on the target reaction. Under the same experimental conditions, these unconventional solvents allowed obtaining higher yields than the ones determined in conventional solvents. The solvent structure proved important in determining the outcome of the reaction, and with the support of resonance light scattering (RLS) and NMR investigations, we were able to identify the relationship working between yield and features of hydrogen bond networks of DES.

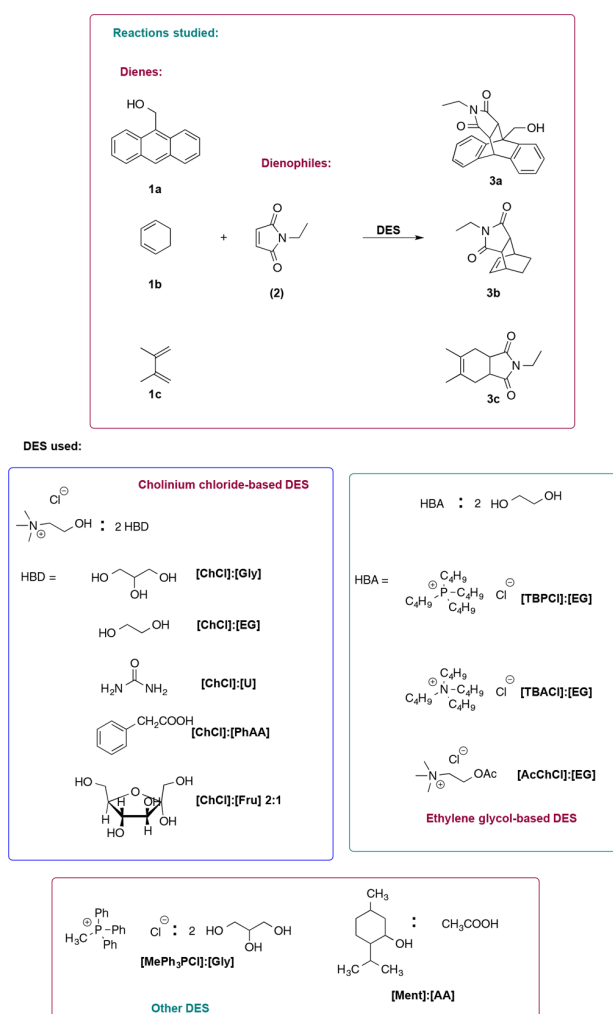
The use of DES really allowed for improving the greenness of DAR. First, under mechanical stirring, the solvent can be reused at least eight times without loss in terms of yield. Furthermore, the combined action of DES and US significantly decreases the energetic demand of this reaction. Indeed, a drop in the reaction time from 24 h to 70 min was detected, obtaining good yields.

EXPERIMENTAL SECTION

Materials. Commercially available 9-anthracenemethanol, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene, *N*-ethylmaleimide, cholinium chloride, acetylcholinium chloride, tetrabutylammonium chloride, tetrabutylphosphonium chloride, methyltriphenylphosphonium chloride, (\pm) menthol, glycerol, ethylene glycol, acetic acid, phenylacetic acid, and urea were used without further purification.

General Procedure for Preparation of DES. A suitable amount of each DES component was weighed in a round-bottomed flask. The resulting mixture was stirred and heated at 80 °C for 30 min. The liquid obtained was dried under reduced pressure at 70 °C for 1 h and kept in a desiccator over calcium chloride. All DES were liquid at the reaction temperature.

Scheme 1. Reactions Studied and DES Used



General Procedure for DAR under Silent Conditions. In a screw-capped vial, 0.96 mmol of diene and 1.15 mmol *N*-ethylmaleimide were dissolved in 1 g of DES. The resulting mixture was kept at 40 °C for 24 h under stirring, and then, 1 mL of water was added and extracted with ethyl acetate (3 × 1 mL). Solvent removal from the combined organic phases afforded a yellow residue which was purified by flash chromatography on silica using petroleum ether:ethyl acetate 10:1 (v:v) and 2:1 (v:v) as eluting mixtures.

To recycle DES, the relevant phase left after the extraction was dried under reduced pressure at 60 °C for 1 h, and then, fresh reactants were added. Recycling of DES was performed until a loss in mass higher than 10% of DES was detected.

General Procedure for DAR under US Irradiation. US-promoted reactions were carried out by placing the reaction vessel under an ultrasonic probe equipped with a 0.5 cm diameter horn. The nominal output power was 70 W, and the operating frequency was 25 kHz. Reactions were performed at 40 °C applying sonication for a suitable time in 5 s ON and 20 s OFF cycles. For a typical reaction, 200 mg (9.6 mmol) of diene and 11.5 mmol of *N*-ethylmaleimide were dissolved in 10 g of DES. Reactions were monitored by TLC, and the workup was performed as described for silent reactions.

General Procedure for E_{NR} and π^* Values Determination. A suitable amount of a solution of Nile Red or *N,N*-dimethyl-*p*-nitroaniline in acetone was added in a screw-capped vial, and the solvent was removed by evaporation. Then, 500 μ L of DES were added. Upon complete dissolution of the probe in DES, the solution obtained was injected in a quartz cuvette (optical pathway 0.2 cm) and thermostated at 298 K. The concentration of the probe was 2×10^{-4} M. The UV-vis spectra of these solutions were recorded, and E_{NR} and π^* parameters were calculated as previously reported.⁴³

NMR Measurements. ¹H NMR spectra were collected with a 300 MHz spectrometer. In NMR measurements, the appropriate volume of DES was placed in a 5 mm NMR tube. A steam coaxial capillary tube loaded with [D₆]DMSO was used for the external lock of the NMR magnetic field/frequency, and its signal was used as the ¹H NMR external reference at 2.56 ppm. ¹H NMR spectra at different temperatures were recorded after DES had been thermostated for 20 min.

RLS Measurements. RLS measurements were carried out with a spectrofluorometer employing a synchronous scanning mode in which the emission and excitation monochromators were preset to identical wavelengths. The RLS spectrum was recorded from 300 to 700 nm, with both excitation and emission slit widths set at 3.0 nm. In all cases, spectra were recorded using pure DES.

RESULTS AND DISCUSSION

Optimization of Experimental Conditions. First, we tried to determine the best experimental conditions to perform DAR in DES. To this aim, we took into consideration [TBPCl]:[EG] (1:2) as the reference solvent, and using a diene/dienophile ratio equal to 1/1.2, we carried out the reaction in the temperature range of 20–40 °C. As the probe substrate, we used 9-anthracenemethanol (**1a**), and in all cases, we monitored the composition of the mixture by TLC, choosing 24 h as a suitable reaction time. Data collected are reported in Table 1.

We immediately observed that the first rise in temperature, going from 20 to 30 °C, induced a corresponding increase in yield (Table 1, entries 1 and 2). A lower variation was observed performing the reaction at 40 °C (Table 1, entries 2 and 4), and that was used as the reaction temperature.

We also paid attention to the diene/dienophile ratio, testing different ratios ranging from 1/1 up to 1/1.5 (Table 1, entries 3–7). To our surprise, we noted that as a consequence of the systematic increase in dienophile concentration the yield first increased from 30% to 69% (Table 1, entries 3 and 4), then decreased to 58% (Table 1, entries 4 and 7). With the above

Table 1. Operating Conditions and Yields for Silent DAR between 9-Anthracenemethanol (1a**) and *N*-Ethylmaleimide (**2**) in [TBPCl]:[EG]^a**

Entry	<i>T</i> (°C)	(1a)/(2) mole ratio	Yield (%) ^b
1	20	1/1.2	53
2	30	1/1.2	65
3	40	1/1	30
4	40	1/1.2	69
5	40	1/1.25	58
6	40	1/1.35	57
7	40	1/1.50	58

^aReaction time = 24 h. ^bIsolated yields, reproducible within 2%.

results in mind, we performed the reaction at 40 °C for 24 h and using a diene/dienophile equal to 1/1.2.

Solvent Effect. After optimization of the experimental conditions, we carried out the reaction in different DES and conventional solvents (Table 2). The majority of DES have the same component ratio (1:2). Consequently, we indicate the ratio only when it is different.

Table 2. Yields for Silent DAR between 9-Anthracenemethanol (1a**) and *N*-Ethylmaleimide (**2**) at 40 °C as a Function of Solvent Nature,^a Together with Polarity (E_{NR}), Polarizability (π^*), and Viscosity (η) of Solvents Used**

Entry	Solvent	Yield (%) ^b	E_{NR} (kcal/mol)	π^*	η (cP) ^c
1	[TBPCl]:[EG]	69	213.6	1.00	
2	[MePh ₃ PCl]:[Gly]	94	206.9	1.00	
3	[TBACl]:[EG]	73	214.3	1.01	76.4 ⁴⁴
4	[ChCl]:[EG]	96	211.9	1.03	31 ⁴⁵
5	[ChCl]:[Gly]	75	209.5	1.11	104 ⁴⁵
6	[ChCl]:[U]	86	210.4	1.17	161 ⁴⁵
7	[ChCl]:[PhAA]	^c	201.2	1.00	
8	[ChCl]:[Fru] (2:1)	23			3920 ⁴⁶
9	[AcChCl]:[EG]	83	213.4	1.06	
10	[Ment]:[AA] (1:1)	83	219.0	0.53	4.5 ⁴⁷
11	Hexane	^d	59.0 ⁴³	−0.08 ⁴⁸	0.258 ⁴⁹
12	MeOH	43	52.0 ⁴³	0.60 ⁴⁸	0.431 ⁵⁰
13	H ₂ O	56	48.2 ⁴³	1.09 ⁴⁸	0.653 ⁵¹

^aReaction time = 24 h. ^bIsolated yields, reproducible within 2%. ^cProduct was not isolated from the reaction mixture. ^dProduct formation was not detected. ^eValues reported at 40 °C.

In all cases, **3a** was the only product observed, except for the case of [TBPCl]:[EG], in which we detected the formation of traces of byproducts, which we were not able to isolate and identify. Yields go from 23% in [ChCl]:[Fru] up to 96% in [ChCl]:[EG] that proves the best solvent for the studied reaction. In all cases, as a consequence of the whole recovery of the unreacted substrate, yield and conversion values were equal.

The reaction was also performed in [ChCl]:[PhAA] (1:2). However, in this case, notwithstanding the presence of a significant amount of product, as accounted for by TLC analysis, we were not able to isolate the product from the reaction mixture. Indeed, after the liquid–liquid extraction, we always obtained a mixture rich in DES components. This is

probably due to the hydrophobicity of the solvent,^{52,53} and this is the reason why we decided to avoid the use of this DES.

For a useful comparison, the reaction was also studied in conventional solvents, like hexane, methanol, and water (Table 2, entries 11–13), spanning a wide range of polarity. Furthermore, water is considered an excellent solvent for DAR, and in the literature, a clear distinction between “at water” and “on water” is made for this reaction to highlight the difference between the case in which the reaction is performed with gentle or vigorous stirring, proceeding in a biphasic system or emulsion.^{54–58}

The comparison among data collected in DES and the ones obtained in conventional solvents demonstrates that DES are suitable solvents for the target reaction. Indeed, with the only exception of yield collected in [ChCl]:[Fru] (2:1), in all the other cases, values obtained in DES are better than the ones obtained in conventional solvents. Moreover, also in our experimental conditions, the well-known accelerating effect of a DAR reaction in water^{59,60} was observed, according to the higher yield obtained in water than in MeOH (Table 2, entries 12 and 13).

DAR feels the solvent effect in DES, and both changes in HBD (Table 2, entries 4–8) or HBA (Table 2, entries 1, 3, 4, and 9) induce changes in yield. The above variations were more significant in dependence of the HBD nature than HBA nature. In the first case, considering [ChCl]-based DES, going from [Fru] to [EG], the yield increases from 23% up to 96%. On the other hand, considering [EG]-based DES and going from [TBPCI] to [ChCl], an increase in yield from 69% up to 96% was observed. The very low yield obtained in [ChCl]:[Fru] (2:1) can be ascribed to the high viscosity of this solvent (Table 2, entry 8).

A good yield was also collected in [Ment]:[AA] (Table 2, entry 10). On the other hand, the result collected in [MePh₃PCI]:[Gly] is comparable to the one obtained in [ChCl]:[EG].

Previous investigations performed on the DAR in an ILs solution demonstrated that the IL amount on the reaction mixture significantly affects the outcome of the process.¹³ To verify if this effect operated also in our case, we took into consideration the composition of the reaction mixture. The DES mole numbers range from 2.4 up to 3.8 mmol; however, yield values do not change systematically with mixture composition. Specifically, comparable yields were collected in [TBACl]:[EG] and [TBPCI]:[EG], having similar compositions (2.4 mmol), but different yields were obtained in [ChCl]:[EG] and [ChCl]:[Gly], notwithstanding the similar compositions (3.8 mmol).

In light of the above results, we considered the frequently claimed effect of solvent viscosity on the outcome of DAR,¹³ and we tried to correlate viscosities with yields. Viscosity values were previously reported for some of DES used in this work (Table 2 and Figure 1).

The above attempt gave a nonmonotonic trend. Indeed, upon increasing the solvent viscosity, the yield first dropped then increased, indicating that viscosity alone does not account unequivocally for the observed trend.

With the above results in mind, we analyzed data collected as a function of solvent polarity. To this aim, we gained information about solvent polarity (E_{NR}) and polarizability (π^*), through the use of solvatochromic probes Nile Red and *N,N*-dimethyl-4-nitroaniline (Table 2).

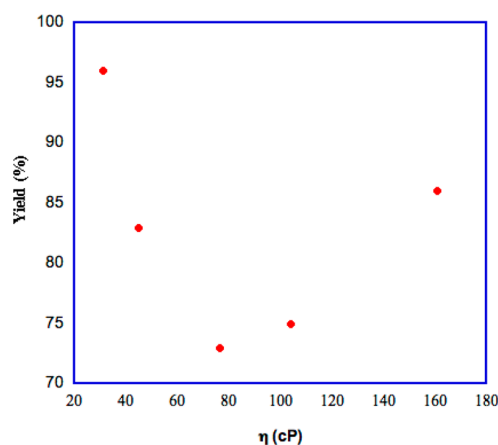


Figure 1. Trend of yield values for DAR between 9-anthracenemethanol (1a) and *N*-ethylmaleimide (2) at 40 °C, as a function of DES viscosity.

Here, π^* values range from 0.53 up to 1.17. However, the majority of DES used in this work show similar values. Our finding perfectly matches the one previously reported by Marrucho et al.,⁶¹ indicating that DES dipolarity and polarizability do not account for changes in yield.

Differently, E_{NR} values change in a wider range, going from 201.2 up to 219.0 kJ/mol. However, only taking into consideration [EG]-based DES and with the exception of [TBPCI]:[EG], we observed that yield increases in parallel with solvent polarity (Table 2, entries 1, 3, 4, and 9), perfectly recalling a trend already detected in conventional solvents.⁶²

A different way to analyze data collected is taking a look to the HBD or HBA nature of DES and considering how this factor influences the solvent structure. Similarly to ILs, DES feature a distinctive nanoscale heterogeneity, with segregated domains,^{30,32,33,63,64} and changes in solvent structure as a function of component natures could represent a key point to understand the reaction outcome in these solvent media.

To this aim, considering [ChCl]-based DES, yields change along the following trend: [EG] > [U] > [Gly] > [Fru]. Analogously, considering [EG]-based solvents, yields decrease as [ChCl] > [AcChCl] > [TBACl] > [TBPCI]. In both cases, the trend obtained indicates that decreasing the size of DES components induces a corresponding increase in yield. Probably, components of a smaller size give rise to a more compact solvent structure that favors the outcome of the reaction.

The above hypothesis could also explain the significant increase in yield detected on going from [TBPCI]:[EG] to [MePh₃PCI]:[Gly] (Table 2, entries 1 and 2), and with the necessary precautions due to the different nature of the HBD, it is reasonable to assume that the presence of phenyl groups in [MePh₃PCI]:[Gly] gives rise to a more organized solvent structure, with respect to the one featuring [TBPCI], as a consequence of the occurrence of π - π interactions. This higher structural organization could be the reason for the significantly higher yield value obtained in the first DES.

To have a further support to the above hypothesis, we set out to gain information about solvent structure and strength of the hydrogen bond network. We first recorded RLS spectra for the pure DES used. RLS is a scattering technique able to detect the presence of aggregates in solution, allowing one to have insights on their size. Indeed, RLS intensities (I_{RLS}) are

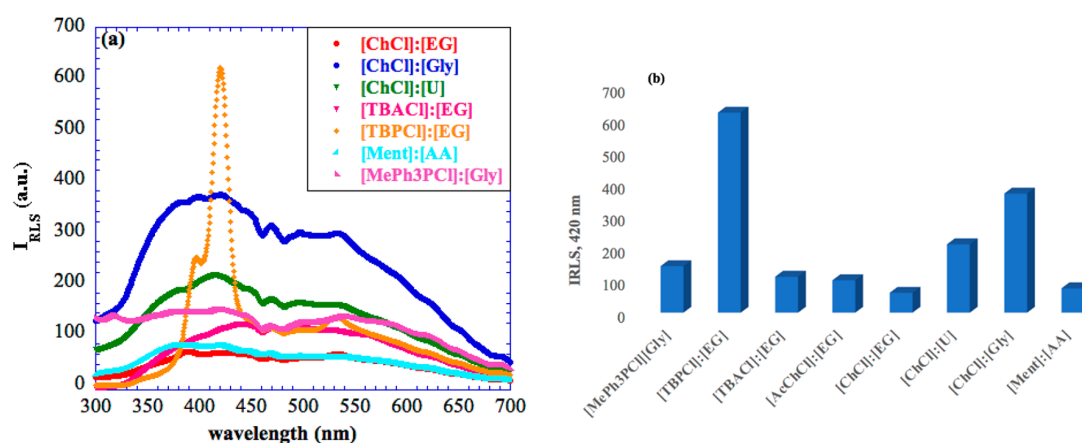


Figure 2. (a) RLS spectra for DES used as reaction media. (b) I_{RLS} at 420 nm as a function of DES nature.

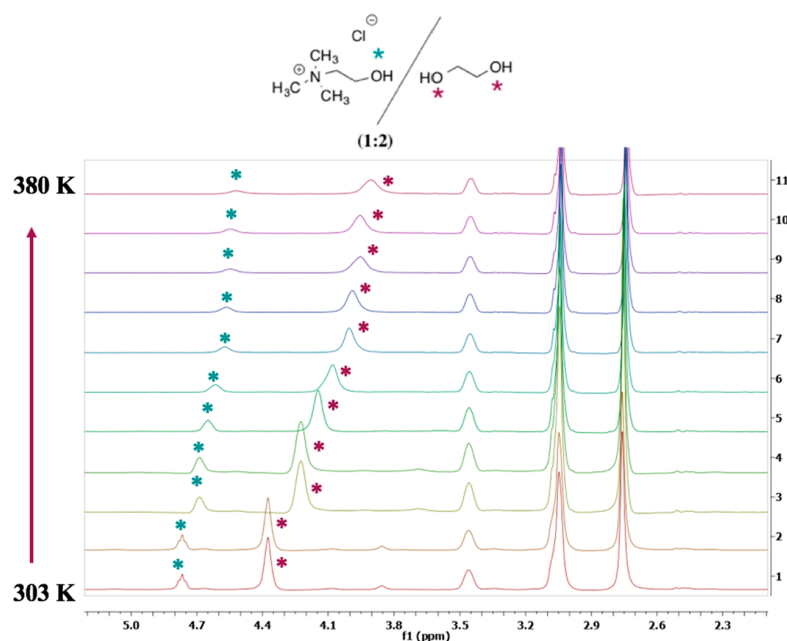


Figure 3. ^1H NMR spectra of pure $[\text{ChCl}]:[\text{EG}]$ as a function of the temperature (303–380 K).

proportional to the square of the aggregates volume.^{65,66} We successfully used this technique to have information about the structural organization of ILs^{31,41} but also to have a better understanding of ionic liquid gels formation.^{33,67}

RLS spectra obtained for DES used as solvent media are reported in Figure 2 together with I_{RLS} values measured at 420 nm.

Analysis of data reported in Figure 2 points out that the size of the aggregates, featuring pure DES, depends on both the HBD and HBA natures. In particular, taking in consideration [EG]-based DES, I_{RLS} decreases according to the following trend: $[\text{TBPCl}] > [\text{TBACl}] > [\text{AcChCl}] > [\text{ChCl}]$. On the other hand, considering [ChCl]-based DES, the above parameter changes along the order: $[\text{Gly}] > [\text{U}] > [\text{EG}]$. In both cases, trends allow for explaining the increase in yield values, indicating that better performance of DAr is detected in solvents featured by the presence of smaller aggregates and probably by a thicker network.

Analogous considerations can be drawn comparing results corresponding to $[\text{MePh}_3\text{PCl}]:[\text{Gly}]$ and $[\text{TBPCl}]:[\text{EG}]$ as well as the ones corresponding to $[\text{ChCl}]:[\text{EG}]$ and $[\text{Ment}]:[\text{AA}]$. In the first case a higher yield corresponds to the presence of smaller aggregates, while in the second case comparable yields were obtained in the presence of aggregates of similar size. We also performed RLS investigation as a function of the temperature (303–333 K), to deepen the information about the solvent structure. We took into account $[\text{ChCl}]:[\text{EG}]$ and $[\text{TBPCl}]:[\text{EG}]$, showing the lowest and the highest I_{RLS} at 303 K (Figure S1). Temperature differently affected DES behavior, as superimposable spectra were obtained in the case of $[\text{ChCl}]:[\text{EG}]$, while in the case of $[\text{TBPCl}]:[\text{EG}]$ a more significant variation in I_{RLS} was detected, accounting for a more flexible network.

With the above premises in mind, we also performed an ^1H NMR investigation on pure DES, in the temperature range of 303–380 K. For a useful comparison, we analyzed also the behavior of pure EG and Gly (Figures 3 and S2).

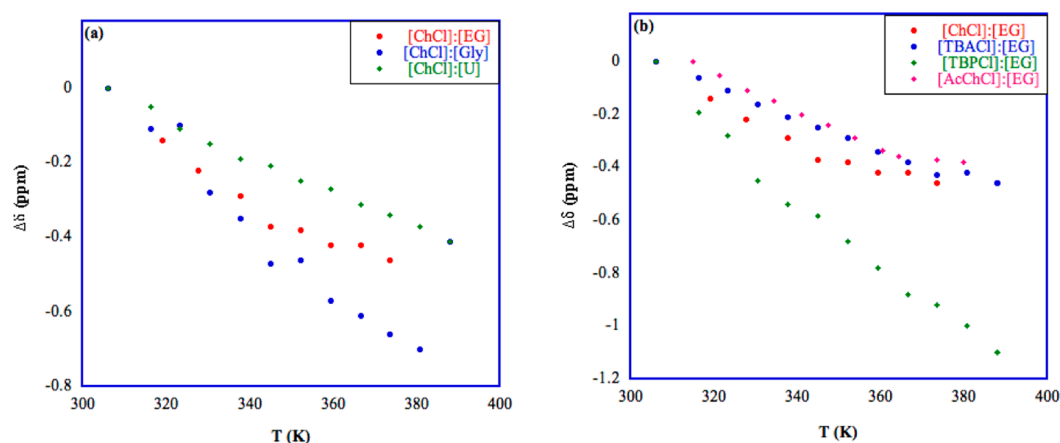


Figure 4. Changes in chemical shift ($\Delta\delta$) as a function of the temperature for (a) [ChCl]-based DES and (b) [EG]-based DES.

In general, heating the eutectic mixtures induced a shielding effect of the signals corresponding to the OH and NH_2 groups of HBD and in the case of [ChCl]-based DES of the hydroxyl group of the cholinium cation. It is worth noting that, for the cholinium cation, comparable changes in chemical shifts were observed independently from the HBD nature. Differently, variations detected for hydroxyl groups of [EG] or [Gly] were different as a function of the HBA nature and were more significant in the pure components than in the corresponding eutectic mixtures.

The temperature increases also caused an enlargement of the above signals and for [Gly] and [Gly]-based DES, also a partial coalescence.

The observed shielding effect can be ascribed to the breaking of the DES hydrogen bond network. Consequently, the comparison among shielding effects, detected for different DES, could give a qualitative indication of the resilience of the network, as more significant variations could be related to the occurrence of less strong interactions.

Taking into consideration the above premises, for all affected signals, we calculated $\Delta\delta$ values as the difference between chemical shifts at a given temperature and the ones measured at 380 K (Figure 4 and Figure S3).

For [ChCl]-based DES, the trend of $\Delta\delta$ as a function of the temperature evidences the largest shift for [ChCl]:[Gly] and the lowest for [ChCl]:[U], indicating the occurrence of feebler interactions in the first case than in the second case. Our result perfectly agrees with data previously reported by Page et al. that, on the grounds of quantum mechanical molecular dynamics simulations, evidenced differences in the nanostructures of the above DES showing different conformational flexibilities.⁶⁸ The above trend supports our hypothesis about the favorable effect that a thicker network exerts on the outcome of the DAr. Indeed, higher yields were obtained using solvent systems where stronger hydrogen bond interactions occurred ([ChCl]:[U] and [ChCl]:[EG]). This picture perfectly agrees with the one recently reported by Tiecco et al. about the interconnection between the structural organization of chiral DES and their activity as reaction media.⁶⁹

Analogous conclusions can be drawn considering [EG]-based DES. Indeed, $\Delta\delta$ values change along the order [TBPCl] > [ChCl] ~ [AcChCl] ~ [TBACl], with the more flexible network giving the lower yield in DA product. These findings also agree with data collected performing RLS

investigations at variable temperatures, accounting for more significant changes in the network featured by the occurrence of feebler interactions (see above).

A further support to all of the above considerations comes from the analysis of ^1H NMR spectra corresponding to [MePh₃PCl]:[Gly]. Indeed, in this case, the $\Delta\delta$ value was comparable to the one calculated for [ChCl]:[EG] as well as yield values. Interestingly, in the above case, the temperature increase caused a corresponding increase in signals resolution that proved more significant for signals corresponding to protons of phenyl rings at approximately 6.5 ppm.

The only exception to the above trends is represented by [Ment]:[AA] which, notwithstanding changes in chemical shift, were comparable to the ones calculated for [TBPCl]:[EG], a significantly higher yield was obtained.

On the whole, data collected indicate that different factors, like viscosity, polarity, and solvent structure simultaneously act on the reaction outcome and results likely arise from the sum of such effects. However, the contribution due to the solvent structure seems to be predominant. This picture recalls what we observed studying the same reaction in of ILs.¹⁴ In that case, we found that reactivity was mainly influenced by variations in the structural organization and viscosity of solvent medium. Analogously, in this case, we can infer that a more organized solvent network can favor the outcome of a reaction that, like DAr, proceeds through a concerted mechanism and is featured by an ordered transition state. This hypothesis is further confirmed by the effect exerted by the substrate structure (see later), and it is reminiscent of the influence that structured solvents, like aromatic ionic liquids,⁷⁰ are able to exert on the outcome of organic reactions.³³

Effect of the Substrate. After gaining information about solvent effect, we performed the reaction using different dienes. Besides 9-anthracenemethanol (**1a**), we also used 1,3-cyclohexadiene (**1b**) and 1,3-dimethylbutadiene (**1c**). The dienes chosen show different flexibility, going along the order of **1a** < **1b** < **1c**. This factor could play a pivotal role in affecting the reactivity in organized reaction media such as DES.

Reactivities of both **1b** and **1c**, in the presence of *N*-ethylmaleimide (**2**), have been previously studied in organic solvents having different polarities and water.⁶² In both cases, a significant increase in the rate of the reaction was observed going from organic solvents to water, as a consequence of the hydrophobic effect. Furthermore, in organic solvents, the

second-order rate constant increased with solvent polarity, and in general, the reaction was faster for **1c** than for **1b**.⁶²

With the above premises in mind, we performed the reactions in water, MeOH, and [ChCl]:[EG] (Figure 5 and Table S1).

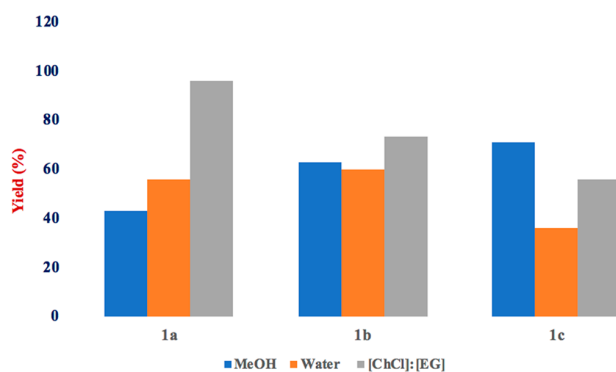


Figure 5. Yield values for DAR among different dienes (**1a–c**) and *N*-ethylmaleimide (**2**) at 40 °C and 24 h as a function of solvent nature.

In conventional solvents, different trends were obtained as a function of the diene nature. Indeed, beside the already discussed activating effect of water in the case of **1a**, comparable yields in water and MeOH were collected for **1b**, whereas in the case of **1c** a better result was obtained in MeOH solution.

In general, in a water solution, yield increases in parallel with substrate hydrophobicity, according to previous reports in the literature.⁶² On the other hand, in methanol, the yield increases along the order of **1a** < **1b** < **1c**.

With the only exception of **1c**, going from conventional solvents to DES, we detected an increase in yield value. Interestingly, in DES solutions, yield values increase with lower substrate flexibility (**1c** < **1b** < **1a**). Probably, a more rigid and organized diene better fits the confined cavities of the DES structure and, going toward the transition state, takes advantage from its thick network.

From the standpoint of Green Chemistry, it is desirable to recycle the reaction system to reduce the discharge of materials in the environment, and this aspect is presently of great interest.⁷¹ To address this issue, we chose [ChCl]:[EG] as the solvent system, and we attempted its reuse. After the first reaction, 1 mL of water was added to the reaction mixture that was washed with ethyl acetate (3 × 1 mL). We chose this solvent on the grounds of the holistic approach proposed by Clark et al. that includes ethyl acetate among recommended solvents.⁷²

Then, the resulting DES phase was dried under reduced pressure at 60 °C for 1 h, and a fresh batch of reactants was added. This procedure was repeated as long as a loss in mass of the solvent lower than 10% was detected (Figure 6 and Table S2).

The plot reported in Figure 6 shows that DES could be used up to eight times without any significant loss in yield and with a modest decrease in yield in the tenth cycle. All of the above results highlight that DES are suitable solvents for the DAR, under silent conditions, not only in terms of yield but also in terms of solvent reuse.

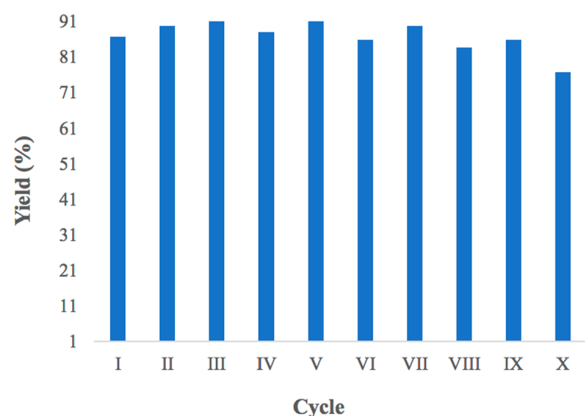


Figure 6. Yields obtained by recycling [ChCl]:[EG] in DAR between 9-antracemethanol (**1**) and *N*-ethylmaleimide (**2**) at 40 °C for 24 h.

Reactivity under Sonochemical Conditions. The last point to be addressed was the possibility of performing the DAR in DES under US irradiation. In terms of sustainability of a chemical process, US-assisted organic synthesis has gained significant attention in green and sustainable chemistry,^{73–75} as the use of US not only improves the reaction efficiency and enhances the reaction rate but in most cases also minimizes side reactions.^{42,76} These effects have been detected not only in conventional organic solvents but also in ILs solution.^{77,78}

Notwithstanding the surge of interest in the use of DES in organic synthesis, currently only a few papers have had as the main subject the study of the combined action of DES and US irradiation.^{79–83} This could prove fruitful for a reaction of industrial interest like DAR.

To this aim, we first performed the reaction using a microtip. This allowed us to carry out the reaction employing the same solvent/reactant ratios used in silent conditions. To find the best operating conditions, we selected [ChCl]:[EG] as a model solvent.

We used a pulsed mode of irradiation to avoid overheating of the reaction mixture. The yields obtained are reported in Table 3 and Table S3 and are displayed in Figure 7.

The first attempt was performed using an output power of 70 W and monitoring the reaction by TLC until the disappearance of the substrate. We obtained 85% yield after 70 min of sonication (Table 3, entry 1). Notably, sonication allowed for having a good yield in a significantly lower reaction time than the one used under silent conditions. Since at the

Table 3. Optimization of Reaction Conditions under US Irradiation for DAR between 9-Antracemethanol (**1a**) and *N*-Ethylmaleimide (**2**) in [ChCl]:[EG] Solution

Entry	Output power (W)	Time (min)	Yield (%) ^a
1	70	70	85 ^b
2	70	15	71 ^c
3	70	30	83 ^c
4	70	70	85 ^c
5	40	70	77 ^c
6	75	70	80 ^c
7	^d	1440	96

^aIsolated yields, reproducible within 2%. ^bExperiment performed using a microtip. ^cExperiment performed using an ultrasonic horn. ^dReaction performed under silent conditions.

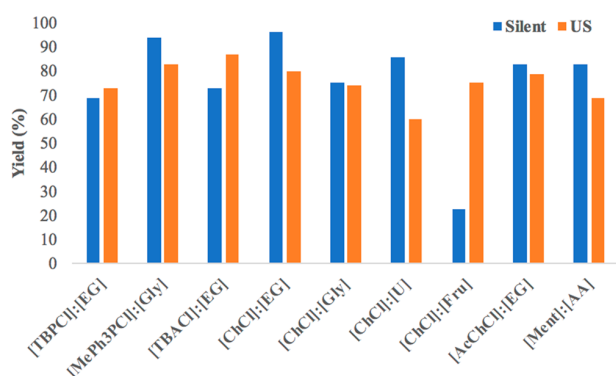


Figure 7. Comparison among yields obtained under silent and US irradiation (reaction time: 24 h and 70 min for silent and ultrasound irradiation, respectively) for DAR between 9-antracemethanol (1a) and *N*-ethylmaleimide (2).

end of the reaction we observed a light yellowing of the reaction mixture, we verified the DES stability to US, recording ¹H NMR spectra before and after the irradiation (Figure S4). However, we did not observe evidence accounting for the occurrence of degradation processes.

Encouraged by the above result, we performed the US-promoted DAR by placing the reaction mixture under an ultrasonic horn. Notably, in this case, we applied sonication to a reaction mixture containing a larger amount of reactants (200 mg) than the one used under silent conditions or with the microtip (20 mg). We used this system to search for the optimal reaction time and output power.

As reported in Table 3 (entries 2–4), the highest yield was obtained after 70 min. Further sonication did not improve the yield significantly. Then, we evaluated the effect of output power finding an optimal value at 70 W (entries 4–6), and we applied these conditions to carry out the reaction in the other DES.

In general, sonication allowed us to obtain good yields in a much shorter time than under silent conditions (70 min and 24 h for sonochemical and silent reactions, respectively). A closer look at the yields displayed in Figure 7 shows that the application of US appears most beneficial when [ChCl]:[Fru] and [TBACl]:[EG] are used as the solvents, in which cases the marked reduction in time is associated with a significant improvement in yield (73% and 87%, and 23 and 75% under silent and sonochemical conditions, [TBACl]:[EG] and [ChCl]:[Fru], respectively).

In some cases, namely, [TBPCl]:[EG], [ChCl]:[Gly], and [AcChCl]:[EG], the yields are comparable to those obtained under silent conditions, but the rate of the process is still drastically improved. Finally, in the case of [MePh₃PCl]:[Gly] and [Ment]:[AA], the application of US appears detrimental and accounted for the drop in yield.

Under US irradiation, we looked again for correlation between yield and solvent viscosity. Indeed, it is well known that the phenomenon of acoustic cavitation, which is responsible for energy transfer in US promoted processes, is affected by this parameter. In particular, when sonication occurs in more viscous liquids, more energy is required to form a cavitation bubble. However, once it is formed, the bubble collapses more violently allowing a more efficient energy transfer and, in principle, higher rate enhancements compared with silent conditions.³⁸

Examining the results obtained shows that the trend of yields cannot be directly related to solvent viscosity. Indeed, we obtained a nonmonotonic trend in which the yield first increased with solvent viscosity, then decreased (Figure S5). The above result indicates the concomitant action of different factors determining performance of the process under sonochemical conditions. This result is reminiscent of what we observed studying a related reaction in ILs, namely, the Cu(I)-catalyzed azide–alkyne cycloaddition under sonochemical conditions.⁴¹ In that case, we explained this result considering that US can induce a localized perturbation on the nanostructure of the solvent in close proximity of the bubble, where the reaction most likely occurs. As above stated, the DES features also a distinctive structural organization, and for this reason, we propose that a similar effect can be operative.

On the other hand, the relevance of the solvent structure in determining the outcome of the reaction is confirmed also under sonochemical conditions. Indeed, according to data collected under silent conditions, both for [EG]- and [ChCl]-based DES, higher yields were obtained in solvent systems featured by the occurrence of smaller aggregates and stronger hydrogen-bonded networks. Probably, in the above solvents, the formation of cavitation bubbles is more difficult, but the implosion proves more energetically efficient.

The principles of Green Chemistry emphasize the minimization of the energy consumed in a given process. To address this issue, we calculated the amount of energy required per mass of materials processed that includes reactants and solvent. A detailed description of the calculation procedure is reported in the SI. Considering that for the reactions carried out under conventional heating we used a 420 W heater and that sonochemical reactions were performed using a ultrasonic horn with an output power of 70 W, we calculated a net energy consumption of 35,094 kJ/g for silent reactions and 28.4 kJ/g for US-assisted reactions, respectively. This results in a 99% of energy saved. All these observations strongly suggest that the combined use of DES and US irradiation is an efficient and energy saving methodology for important synthetic processes like DAR.

CONCLUSIONS

Sustainable development is one of the keywords in different industrial sectors. This explains the surge of interest in chemistry research aimed at identifying the suitable combination of experimental factors that could allow limiting the impact of a given process on the environment.

In this context, we investigated a process of industrial value, like DAR, in DES. Data collected show that these solvents are particularly convenient for this type of reaction. Indeed, they allow obtaining higher yields than the one obtained in conventional organic solvents under the same experimental conditions. Data collected show that the activating effect of DES can be ascribed to a combined action of viscosity, polarity, and structure of solvent used. As far as the last factor is concerned, the combined approach of ¹H NMR and RLS investigation allows stating that better performance is detected in DES featured by thicker and stronger networks.

From the standpoint of Green Chemistry, our system perfectly addresses guidelines of the holistic approach presented by Clark et al.⁷² Indeed, the reaction proceeds at relatively low temperature, in solvents of low environmental impact and, with only few exceptions, affords yields higher than

70%. Furthermore, thanks to the high solubilizing ability of DES, the reaction was performed using a relatively low amount of solvent, and this contributes to a decrease in the amount of discharged materials at the end of the process. In addition, we were able to reuse the DES up to eight times without any loss in yield and using a modest amount of an environmentally friendly extracting organic solvent. Moreover, under silent conditions, [ChCl]:[Gly] was found to be the best solvent.

Notably, DES proved to be suitable solvents for the sonochemically promoted reaction, allowing drastic reduction of reaction time and more than 99% of energy saved without a drop in yield. Finally, the combined use of DES and US allowed us to process an amount of materials 10 times higher than under silent conditions.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.0c00193>.

Yield values for DAR among different dienes (1a–c) and N-ethylmaleimide (2). Yields obtained in different reuses of [ChCl]:[EG] as reaction media for DAR. Yields under US irradiation for DAR between 9-antracemethanol (1a) and N-ethylmaleimide (2). RLS spectra as a function of temperature for [ChCl]:[EG] and [TBACl]:[EG]. ¹H NMR spectra of EG, Gly, and pure DES as a function of temperature. Changes in chemical shift ($\Delta\delta$) as a function of temperature for [Ment]:[AA], [MePh₃PCl]:[Gly], [EG], and [Gly]. ¹H NMR spectra of [ChCl]:[EG] before and after US irradiation. ¹H NMR spectra of the DAR products. (PDF)

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Notes

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