

Investigation of Base-free Copper-Catalysed Azide–Alkyne Click Cycloadditions (CuAAc) in Natural Deep Eutectic Solvents as Green and Catalytic Reaction Media

Salvatore V. Giofrè,^{1*} Matteo Tiecco,^{2*} Angelo Ferlazzo,³ Roberto Romeo,¹ Gianluca Ciancaleoni,⁴ Raimondo Germani² and Daniela Iannazzo³

1. Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali, Università di Messina, Viale Annunziata, I-98168 Messina, Italy.
2. Dipartimento di Chimica, Biologia e Biotecnologie, Università di Perugia, via Elce di Sotto 8, I-06123 Perugia, Italy.
3. Dipartimento di Ingegneria, Università of Messina, Contrada Di Dio, I-98166 Messina, Italy
4. Dipartimento di Chimica e Chimica Industriale (DCCI), Università di Pisa, Via Giuseppe Moruzzi, 13, I-56124 Pisa, Italy.

* Corresponding authors

Email addresses: sgiofre@unime.it (Salvatore V. Giofrè); matteotiecco@gmail.com (Matteo Tiecco).

ABSTRACT

The click cycloaddition reaction of azides and alkynes affording 1,2,3-triazoles is a widely used and effective chemical transformation, applied to obtain relevant products in medicine, biology and materials science. In this work, a set of Natural Deep Eutectic Solvents (NADESs) as green and “active” reaction media, has been investigated in the copper-catalysed azide–alkyne cycloaddition reactions (CuAAc). The use of these innovative solvents has shown to improve the reaction effectiveness, giving excellent yields. NADESs proved to be “active” in these transformations for the absence of added bases in all the performed reactions and in several cases, for their reducing capabilities. The reactions outcomes were rationalized by DFT calculations which demonstrated the involvement of H-bonds between DESs and alkynes as well as a stabilization of copper catalytic intermediates. The green experimental conditions, namely the absence of a base, the low

temperatures, the lowering of reagents and the possibility of recycling of the green solvents, outline the great potential of NADESs for CuAAc and in general, for green organic synthesis.

KEYWORDS

Click Chemistry; Copper-catalysed Azide–Alkyne Cycloadditions; Natural Deep Eutectic Solvents; Catalytic Green Solvents; Recycling of Green Solvents; DFT Calculations.

INTRODUCTION

The development of sustainable chemical processes is of prominent importance in response to the increased awareness and concern over the environmental impact of chemical pollutants. The minimizing of environmental impact of solvents in chemicals production still represents a global challenge for their impact on health cost and safety.^{1–3} Solvent represents the main and most abundant component in a chemical transformation. Thus, the substitution of a polluting, toxic and volatile organic liquid with reaction media that possess green advantages is one of the most important options to be considered in order to perform a greener and environmental-friendly chemical process.^{4,5} In this topic, many relevant solutions are emerging from the recent literature to face up the problem of volatile polluting solvents.⁶ Ionic Liquids (ILs) played a relevant role thanks to their non-volatility and to the recycling possibilities.^{7–9} However, ILs revealed to be toxic and easily cumulated in the environment because of their non-easy biodegradability.^{10,11}

Deep Eutectic Solvents (DESs), born as a side-class of ILs, are emerging from the recent literature as an effective solution to these issues. DESs are an innovative class of organic liquids that possess green and catalytic properties. These innovative solvents are finding fruitful applications in many different topics, such as chemical transformations, extraction/preconcentration procedures, nanoparticle synthesis, CO₂ capture, and other applications where they are successfully substituted to the commonly used polluting solvents.^{12–17} DESs can be divided into different sub-classes depending on the molecules forming them; the great number of molecules that can form a DES can lead therefore, to a high number of liquids.^{18–20} However, they can be simply described as mixtures of a Hydrogen Bond Donor (HBD) and a Hydrogen Bond Acceptor (HBA) compounds.²¹ The weak interactions occurring between the counterparts lead to a high decrease in the melting points of the mixtures (an eutectic point at a determined molar ratio) and thus, to the formation of a liquid system. In particular, the interactions occurring between the same species (HBD-HBD and HBA-HBA) and between the different species (HBD-HBA), lead to a difficult lattice regular organization and therefore to liquid

mixtures; this “chaotic” structuration leads to systems with unique properties.²² Structural studies of these liquids are extensively reported in literature because the physical and microscopical properties of these systems deeply affect their uses also in chemical transformations.^{23,24}

DESs possess many green properties: they are non-volatile, easily biodegradable, biocompatible, non-toxic; moreover, they can be easily recovered and recycled and normally are formed by cheap components.^{25–27} A relevant sub-class of DESs is represented by the NADESs (NAatural DESs), liquids formed by natural-source molecules and thus mixtures with increased bioavailability, biodegradability and biocompatibility.^{28,29} Many recent and relevant papers report NADESs as solvents used by some living plants in extremely hot or cold conditions to substitute water for the cellular metabolism processes; this is the reason why these liquids possess a larger liquid window compared to water and they can be useful in extreme conditions in these biological systems.^{30–32}

One of the most important green property of DESs relies on their preparation that can be performed by simply mixing and heating the HBD and the HBA that are often solids. No solvent and no other reactants are needed for their synthesis that afford 100% yield and 100% atom economy. This issue increases their greenness over the other green liquids in a step that is also prior on their use.³³

Over the green properties, DESs can also possess catalytic properties. Recent papers report the acid catalytic behaviour, reducing capabilities and also organocatalytic properties of the reaction media itself.^{34–38} This is because the properties of the liquids reflect on the properties of the molecules forming them; therefore, the properties of these liquids are tuneable.

Structural studies that emerged from the need to rationalize the observed data, shed light on the association constant (or intimacy of HBD-HBA couple) to explain the catalytic behaviour of these liquids. The availability of one of the two components to act in a catalytic role is dependent on the “freedom” of one component from the counterpart in the liquid structure; this effect has an impact on the pKa value of acids, that showed different behaviours when mixed in DESs’ structures.^{34,35,39,40}

In this work, it is reported the use of a set of differently structured NADESs as “active” and green reaction media in copper-catalysed azide–alkyne cycloaddition reactions (CuAAc).

Since it was first introduced by Sharpless^{41,42} and Meldal,⁴³ click chemistry has become a privileged reaction in the chemists' toolbox⁴⁴ and it has shown numerous advantages including easy product recovery, inoffensive by-product formation, modular reaction with wide scope and many inexpensive, readily available starting materials, catalyst, ligands, and so on.⁴⁵ Moreover, 1,2,3-triazoles have found application to a wide variety of research areas, including organic and pharmaceutical chemistry, bioconjugation, drug discovery, polymer, nano- and material sciences.^{44–49} CuAAc click reactions have been explored and analysed in many different green solvents and reaction media, including DESs.⁵⁰ The investigated liquids (choline chloride/glycerol, D-sorbitol/urea and L-carnitine/urea),

used in the presence of a base and of CuI, promoted the cyclization with excellent yields, comparable with those observed using the conventional volatile organic solvents, showing also excellent recycle capabilities.

In this work, a different approach to the CuAAc reaction in DESs is proposed by the use of properly chosen catalytic green NADESs, exploiting their reducing abilities in the absence of any added base. The reducing capabilities of the liquids due to their components are here demonstrated for several of the investigated reactions (50%), where no reagents have been needed to reduce CuSO₄ that is more stable and easier to handle, when compared to its reduced form CuI. In none of the experiments a base (such as triethylamine) was added, as DESs proved to weaken the C-H alkyne bond through their H-bonds network; the green liquids promoted its cleavage, and stabilized copper catalytic intermediates, as demonstrated via DFT studies. Up to date Deep Eutectic Solvents have been used only as acidic catalytic media: the “basic” behaviour due to the involvement of hydrogens in the H-bonds network, represents a novelty in the DESs topic, considering also that the used DESs have acidic components.

The catalytic reducing behaviour of the DESs, the lowering of the number of reagents used, the recycle capabilities of the media, the ease of use of CuSO₄ compared to the reduced CuI and the excellent yields observed, promote this protocol as an efficient green route for this relevant and widely used chemical reaction.

RESULTS AND DISCUSSION

Selection and properties of the NADESs for the reaction

In order to fully explore the role of DES in CuAAc reactions, a set of differently structured NADESs was chosen (Figure 1), and each one for different reasons: urea/choline chloride mixture (**U/ChCl**, molar ratio 2/1, m.p. = 12°C) was used as it represents the most common and widely used DESs for many synthetic applications.⁵¹ L-ascorbic acid/choline chloride (**Asc/ChCl**, molar ratio 1/2, m.p. = 20°C) was selected as the acid component is endowed with reducing capabilities and therefore no ascorbate is needed for the click reaction.⁵² Oxalic acid/choline chloride (**Ox/ChCl**, molar ratio 1/2, m.p. = 30°C) was chosen as it is constituted by another reducing agent, **Ox**, and by the same HBA of **Asc/ChCl**.⁵³ Oxalic acid/trimethylglycine (**Ox/TMG**, molar ratio 2/1, m.p. = 33°C) was used to explore the role of the HBD counterpart of the former liquid and the role of **TMG** as HBA.⁵³ Glycolic acid/trimethylglycine (**GA/TMG**, molar ratio 2/1, m.p. = -36°C) was investigated as it represents a model mixture of the zwitterionic DESs for its favourable physical properties and because it is constituted by the same HBA of other two mixtures in our set.^{54,55}

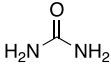
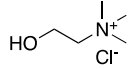
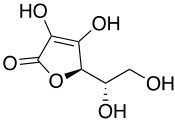
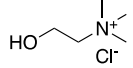
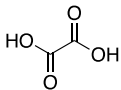
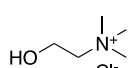
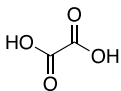
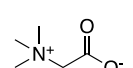
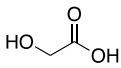
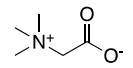
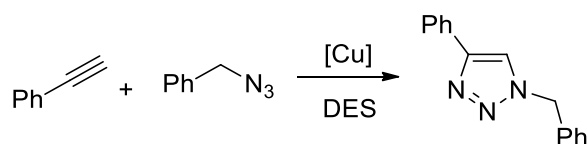
HBD	HBA	Acronym	HBD/HBA molar ratio	melting point, °C
 urea	 choline chloride	U/ChCl	2/1	12°C
 L-ascorbic acid	 choline chloride	Asc/ChCl	1/2	20°C
 oxalic acid	 choline chloride	Ox/ChCl	1/2	30°C
 oxalic acid	 trimethylglycine	Ox/TMG	2/1	33°C
 glycolic acid	 trimethylglycine	GA/TMG	2/1	-36°C

Figure 1. HBD and HBA components, acronyms, composition and melting points of Deep Eutectic Solvents used in this work.

Chemistry

To start this work, the 1,3-dipolar cycloadditions of terminal alkynes with organic azides were investigated, using as a model reaction, the classical cycloaddition of benzyl azide and phenylacetylene. The chemical role of DESs components in the cycloaddition processes was investigated under different experimental conditions (temperature, time, in presence or absence of sacrificial reductants). Because of the network of hydrogen bonds between HBD and HBA molecules, and because of the non-protonation of the HBA species in a DESs, the click reactions analysed in this work were performed in absence on any added base, considering that the hydrogen of the alkyne should be involved in this network. The non-complete transfer of the hydrogen between the species

was demonstrated by studies in literature involving ionic conductivity measures that showed low values compared to the ones of ILs.^{55,56} Therefore, for all the investigated reactions, no base was needed for the reaction effectiveness, as also reported in other studies in different conditions,⁵⁷ thus confirming the green contribution of DESs in CuAAC reactions where a base as co-catalyst is required. A deeper structural investigation about it, is reported in the theoretical calculations section of this paper. Moreover, all the reactions were performed at low temperatures, always below 50 °C, so further highlighting the advantages introduced by these green solvents. The final products were obtained after addition of water to the crude reaction mixture that allows the easy precipitation of the desired triazole without the use of conventional hazardous volatile organic solvents (VOCs) (Table 1).



Scheme 1. Copper-catalysed azide–alkyne cycloadditions (CuAAC).

Table 1. Study of the 1,3-dipolar cycloaddition of benzyl azide and phenylacetylene catalysed by the copper salts in different natural deep eutectic solvents.^a

Entry	Catalyst Mol %	Solvent	Reductant Mol %	Temperature	Time [h]	Yield ^b
1	10, CuSO ₄	GA/TMG	-	r.t.	72	-
2	10, CuSO ₄	GA/TMG	30	r.t.	72	99
3	10, CuSO ₄	GA/TMG	30	r.t.	12	99
4	10, CuSO ₄	GA/TMG	30	r.t.	3	8
5	10, CuSO ₄	GA/TMG	30	50 °C	3	99
6	10, CuSO ₄	Ox/ChCl	-	40 °C	72	95 ^c
7	10, CuSO ₄	Ox/ChCl	30	40 °C	72	95 ^c
8	-	Ox/ChCl	-	40 °C	72	95 ^c
9	10, CuSO ₄	Ox/TMG	-	50 °C	72	95 ^d
10	10, CuSO ₄	Ox/TMG	30	50 °C	72	95 ^d
11	-	Ox/TMG	-	50 °C	72	95 ^d
12	10, CuSO ₄	U/ChCl	-	r.t.	72	57 ^e
13	10, CuSO ₄	U/ChCl	30	r.t.	72	96
14	10, CuSO ₄	U/ChCl	30	r.t.	24	70
15	10, CuSO ₄	Asc/ChCl	-	r.t.	72	97
16	10, CuSO ₄	Asc/ChCl	-	r.t.	24	97
17	10, CuI	GA/TMG	-	r.t.	72	35

^aReactions were performed using 2 g of the corresponding solvent and 1 mmol of both reagents. ^b Yields were calculated by ¹H NMR. ^c1:1.2 ratio (mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole regioisomers). ^d1:1.5 ratio (mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole regioisomers). ^e Phenylethynylcopper (I) ladderane polymer as catalyst.

The initial screening for NADESs was done using **GA/TMG**. As expected, without sodium ascorbate the *in situ* reduction of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ did not occur; therefore, after 72 h only the reagents were found in the reaction mixture (entry 1, Table 1). Conversely, the addition of sodium ascorbate releasing the catalytically reactive Cu(I) ions, led to the 1,4-disubstituted regioisomer with a 99% yield in 12 h, in agreement with the results expected from Sharpless reaction⁴¹ (entry 3, Table 1); shorter reaction times (3 hours, entry 4, Table 1) led to modest yield (8%). The optimized reaction at 50 °C in 3 h led to the 1,4-disubstituted regioisomer with a 99% yield (entry 5, Table 1). It is important to note that the increasing of reaction temperature above 50 °C led to the browning of the reaction mixture due to the degradation of sodium ascorbate. Then, to compare the obtained results, other two DESs were analyzed, **Ox/ChCl** and **Ox/TMG**, based on oxalic acid as HBD, which could act as a reducing agent.⁵⁸ Due to their melting point (30°C for **Ox/ChCl** and 33°C for **Ox/TMG**), the two green solvents were not used at room temperature. Thus, in order to obtain a homogeneous reaction mixture, the experiments were carried out at 40°C and 50 °C respectively. Unexpectedly, the reaction carried out in DES **Ox/ChCl** at 40°C for 72 h led to a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole regioisomers in 1:1.2 ratio (entry 6-8, Table 1), either with and without reducing agents, in according to thermal Huisgen 1,3-dipolar cycloaddition.^{59,60} The same results were obtained using DES **Ox/TMG** at 50°C for 72 h; the performed reaction led to a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole regioisomers in 1:1.5 ratio (entry 9-11, Table 1) either with and without reducing agent. These results can be reasonably attributed to the presence of oxalic acid that acts as a hydrogen bond donor in the formation of DES. Oxalates have been extensively studied as mild reducing agents but also as precipitants and chelating agents.^{61,62} Oxalate ion is a bidentate ligand which forms a five-membered chelate ring when it binds to metals. In particular, metals such as Cu^{2+} and Zn^{2+} can combine with two oxalates, forming a four-coordinate planar square complex.⁶² Based on these considerations, it can be hypothesized that copper is sequestered by DES and the azide-alkyne cycloaddition can follow the Huisgen thermal pathway and not the Cu-catalysed process. It is noteworthy that the classic non-catalysed Huisgen azide-alkyne cycloaddition requires high temperature while in the DESs constituted by oxalic acid, the reaction proceeded under relatively mild conditions at 40-50 °C. These results were also confirmed performing the same reactions without the catalyst CuSO_4 and using the same reaction parameters (entries 8 and 11, Table 1); in all the cases, the formation of a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole regioisomers in the same ratios, was observed.

The DES **U/ChCl** produced particularly interesting results. To investigate the contribution of this DES in the cycloaddition process, the reaction was carried out using only CuSO_4 , in the absence of ascorbate, at r.t.. After 72 h, the formation of the 1,4-disubstituted cycloadduct with a 57% yield was

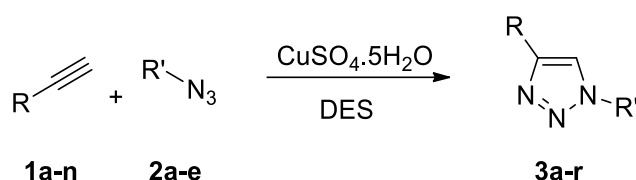
observed (entry 12, Table 1). Surprisingly, the reaction was successful without using the reducing agent, with the formation of a solid yellow insoluble by-product already after 24 h. Therefore, the reaction was further investigated by ^1H and ^{13}C NMR. The analysis of the reaction raw material showed the formation of a small amount of 1,4-diphenylbuta-1,3-diyne similarly to what occurs in Glaser reactions.⁶³ As reported, a phenylethynylcopper (I) ladderane polymer can catalyse the azide-alkyne click chemistry reactions.⁴³ Therefore, it was hypothesized that urea actively participated in the reaction process as ligand⁶¹ by chelating Cu(II) and subsequently, the copper (I) catalyst, required in the click reactions, resulted from the formation of small amounts of polymeric copper (I) pre-catalysts formed in the precursor of Glaser reactions.⁴³ Then, the click chemistry reaction in **U/ChCl** solvent was investigated with the presence of the reducing agent and in these conditions, the reaction led to the formation of the 1,4-disubstituted cycloadduct with a 96% yield. It is noteworthy that in this system we have not observed the formation of the yellow solid, thus assuming that the course of the reaction follows the classical catalytic cycle of the Sharpless reaction (entry 13, Table 1). The reduction of the reaction time led to a decrease in the reaction efficiency (entry 14, Table 1), conversely to what verified with DES **GA/TMG** (entries 1-4, Table 1).

NADESs based on choline chloride and L-ascorbic acid as green solvent in CuAAC was also investigated. This green solvent can be considered an active DES due to the presence of L-ascorbic acid which could act as a reducing agent in copper-catalysed azide-alkyne cycloadditions. Then, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ was added to benzyl azide and phenyl acetylene in the base- and reducing agent-free DES solvent and the mixture was left to react for 72 h at room temperature. As hypothesized, L-ascorbic acid produced the copper (I) catalyst required in the click reactions and the 1,4-disubstituted cycloadduct with a 97% yield was obtained. The decrease in the reaction time was also investigated and a greater efficiency was obtained in 24 h (entries 15 and 16, Table 1); moreover, a further decrease in reaction times or increase in the reaction temperature, led to loss of yield.

To compare the data reported in literature which show the Cu(I)-catalysed 1,3-dipolar cycloaddition azide-alkyne in different environmentally friendly solvents,⁵⁷ we have investigated the catalytic activity of CuI in NADES **GA/TMG** in the base- and reducing agent-free conditions (entry 17, Table 1). The reaction carried out for 72h at room temperature afforded the desired 1,4-disubstituted cycloadduct; the observed low yields (35%) are probably due to the low solubility of the catalyst in the examined DES.

Even if this protocol needed longer reaction times compared to the ones reported in literature with non-catalytic DESs,⁵⁰ the lower temperatures used and the reducing and the basic behaviour of the investigated NADESs (with the same quantitative yields observed) promote this protocol as relevant in CuAAC transformations.

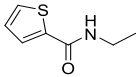
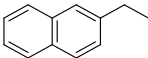

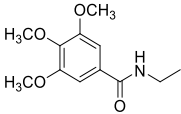
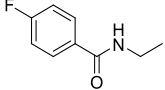
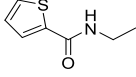
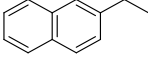
The initial results suggested that NADES **GA/TMG** represents the potentially best green solvent in our set for the investigated CuAAC reactions in base-free conditions. Also, the active DES **Asc/ChCl** showed peculiar characteristics, leading to its use as a green solvent in a non-classical CuAAC base- and reducing agent-free reactions. To extend the scope of this work, our studies were applied to a different azides and terminal alkynes using **GA/TMG** and **Asc/ChCl** as green solvents in the optimized experimental conditions described above. Also, in these entries whenever the products were solids, the water addition to the cooled reaction mixture determined a precipitation of the solid and therefore an easy recover of the product via filtration. In the cases where the products were oils, an extraction with ethyl acetate then a flash chromatography separation with ethyl acetate was performed considering the safety of this solvent when compared to other VOCs.⁶⁴



Scheme 2. Copper-catalysed azide–alkyne cycloadditions (CuAAC) in natural deep eutectic solvents.

Table 2. CuAAC reactions in NADESs^a.

Alkynes	R	Azides	R'	Solvent	Red. Ag. Mol %	Temp.	Time [h]	Product	Yield ^{b,c}
1a	Ph	2a	Bn	GA/TMG	30	50 °C	3	3a	99(96)
1b	CH ₂ CH ₂ OH	2a	Bn	GA/TMG	30	50 °C	3	3b	78(65)
1c	CH ₂ CH ₂ CH ₃	2a	Bn	GA/TMG	30	50 °C	3	3c	94(90)
1d	TMS	2a	Bn	GA/TMG	30	50 °C	3	3d	95(90)
1e		2a	Bn	GA/TMG	30	50 °C	3	3e	95(90)
1f	Cyclopropyl	2a	Bn	GA/TMG	30	50 °C	3	3f	95(92)
1g	<i>t</i> -butyl	2a	Bn	GA/TMG	30	50 °C	3	3g	95(92)
1h	4-NO ₂ -Ph	2a	Bn	GA/TMG	30	50 °C	3	3h	95(90)
1i	4-pentyl-Ph	2a	Bn	GA/TMG	30	50 °C	3	3i	98(95)
1j	4-MeO-Ph	2a	Bn	GA/TMG	30	50 °C	3	3j	98(94)
1k	4-F-Ph	2a	Bn	GA/TMG	30	50 °C	3	3k	98(92)
1l		2a	Bn	GA/TMG	30	50 °C	3	3l	98(91)
1m		2a	Bn	GA/TMG	30	50 °C	3	3m	98(90)

1n		2a	Bn	GA/TMG	30	50 °C	3	3n	98(90)
1a	Ph	2b	Ph	GA/TMG	30	50 °C	3	3o	95(88)
1a	Ph	2c		GA/TMG	30	50 °C	3	3p	92(86)
1a	Ph	2d	CH ₂ CH ₂ OH	GA/TMG	30	50 °C	3	3q	97(88)
1a	Ph	2e	4-MeO-Ph	GA/TMG	30	50 °C	3	3r	96(90)
1a	Ph	2a	Bn	Asc/ChCl	-	r.t.	24	3a	97(94)
1b	CH ₂ CH ₂ OH	2a	Bn	Asc/ChCl	-	r.t.	24	3b	-
1c	CH ₂ CH ₂ CH ₃	2a	Bn	Asc/ChCl	-	r.t.	24	3c	-
1d	TMS	2a	Bn	Asc/ChCl	-	r.t.	24	3d	55(48)
1e		2a	Bn	Asc/ChCl	-	r.t.	24	3e	-
1f	Cyclopropyl	2a	Bn	Asc/ChCl	-	r.t.	24	3f	-
1g	<i>t</i> -butyl	2a	Bn	Asc/ChCl	-	r.t.	24	3g	-
1h	4-NO ₂ -Ph	2a	Bn	Asc/ChCl	-	r.t.	24	3h	94(88)
1i	4-pentyl-Ph	2a	Bn	Asc/ChCl	-	r.t.	24	3i	98(94)
1j	4-MeO-Ph	2a	Bn	Asc/ChCl	-	r.t.	24	3j	87(81)
1k	4-F-Ph	2a	Bn	Asc/ChCl	-	r.t.	24	3k	88(80)
1l		2a	Bn	Asc/ChCl	-	r.t.	24	3l	92(85)
1m		2a	Bn	Asc/ChCl	-	r.t.	24	3m	96(88)
1n		2a	Bn	Asc/ChCl	-	r.t.	24	3n	96(88)
1a	Ph	2b	Ph	Asc/ChCl	-	r.t.	24	3o	91(85)
1a	Ph	2c		Asc/ChCl	-	r.t.	24	3p	75(68)
1a	Ph	2d	CH ₂ CH ₂ OH	Asc/ChCl	-	r.t.	24	3q	75(62)
1a	Ph	2e	4-MeO-Ph	Asc/ChCl	-	r.t.	24	3r	90(84)

^a Reactions were performed using 2 g of the corresponding solvent, CuSO₄·5H₂O 10 Mol% and 1 mmol of both reagents.

^b Yields determined by ¹H NMR. ^c Isolated yields.

The click-chemistry reactions in the investigated two green solvents were carried out using different azides containing aromatic or alkyl residues, **2a-e**, and alkynes linked to a variety of functional groups, **1a-n**. In particular, the acetylene moiety is linked to electron withdrawing or electron donating groups at the aromatic ring (**1h-1k**, Table 2), to alkyl/cycloalkyl (**1c**, **1f** and **1g**, Table 2), cycloalkenyl (**1e**, Table 2), silane (**1d**, Table 2), alkyl/hydroxyl (**1b**, Table 2), amido (**1l-1n**, Table 2) and ether (**1j** and **1l**, Table 2) substituents. All the CuAAC reactions carried out in NADES **GA/TMG**,

in the base-free experimental conditions, afforded for these reactions yields of triazole derivatives from excellent to quantitative, ranging from 78% to 99%. The nature of the substituents and functional groups on the alkynes and azides have proved not to influence the course of the reactions which were carried out for 3 hours at 50°C. Conversely, the CuAAc reactions carried out in active DES **Asc/ChCl**, in the base- and reducing agent-free reaction conditions, were strongly influenced by the nature of the substituents and functional groups on the alkynes. The solvent's ability to solubilize alkyl alkynes was the limiting factor of the process. In many cases the alkyne was completely immiscible with the solvent, resulting in phase separation. This problem was particularly observed with 1-pentyne **1c**, cyclopropyl acetylene **1f**, cyclohexenyl acetylene **1e** and 3,3-dimethyl-1-butyne **1g** (Table 2). However, these results agree with literature data which indicate that some DESs show good efficiency in extracting the aromatic compounds to the detriment of the aliphatic compounds because of their great affinity with aromatics.⁶⁵ Overall, the click chemistry reactions in DES **Asc/ChCl** gave good results only with aromatic alkynes and the nature of the azides have shown to moderately influence the formation of the triazole derivatives (75-97% yield).

DESs recycle

The recycling of green solvents is an important issue in order to increase the sustainability of a chemical process. Thus, we investigated the recycling capabilities of the best tested green solvents in our set. Therefore, the CuAAc optimized reaction between phenyl acetylene and benzyl azide in the two NADES **GA/TMG** and **Asc/ChCl** was used as a model reaction. At the end of each experiment the formed products were obtained by adding water and then filtrating the resulting product as solid. Then the water was removed from DESs *via* vacuum evaporation. The copper remained solubilized in the water-DESs solution, and this is relevant because of the removal of Cu-catalyst from the reaction mixture is often problematic in homogeneous catalysis.⁶⁶

Table 3. Recycling study of the CuAAc reaction in natural deep eutectic solvents **GA/TMG** and **Asc/ChCl**.^a

Entry	Cycle	Solvent	Time [h]	Yield ^b
1	1	GA/TMG	3	99
2	2	GA/TMG	3	99
3	3	GA/TMG	3	90
4	4	GA/TMG	3	68
5	5	GA/TMG	3	10
6	1	Asc/ChCl	24	97
7	2	Asc/ChCl	24	85

^aReactions were performed using 2 g of the corresponding solvent, CuSO₄·5H₂O 10 Mol% and 1 mmol of both reagents, for the **GA/TMG** solvent sodium ascorbate 30 Mol% was added. ^b Yields determined by ¹H NMR.

In the case of **GA/TMG**, the initial reaction and the two subsequent recycling processes proceeded with good yields (entries 1-3, Table 3). A moderate loss of efficiency was found in the fourth cycle and a drastic loss of yield in the fifth cycle (entries 4 and 5, Table 3) as well as a browning of the reaction mixture. In case of **Asc/ChCl**, there is a loss of efficiency accompanied by a strong darkening of the solution already from the second cycle (Table 3). ¹H-NMR spectra of the DESs were performed after each cycle for the two liquids (see supporting information section, figures S37 and S38); the spectra showed the non-degradation of the DESs components, therefore suggesting a leaching of the Copper catalyst.

Theoretical calculations

The possibility of successfully carrying out the reaction in absence of triethylamine (a base commonly used for the development of the click reaction in order to facilitate the C-H bond cleavage in the alkyne)⁶⁷ was furtherly explored via DFT measures. These structural computational studies were carried out to investigate whether and how the active DESs can participate to the reaction *via* deprotonation of the alkyne or participation of the hydrogen in the H-bonds network of the liquids. The two liquids **Asc/ChCl** and **GA/TMG** were investigated in these studies.

The choline chloride/L-ascorbic acid system (**Asc/ChCl**) has been modeled by DFT calculations in the presence and absence of phenylacetylene (**P1**) (PBE-D3/def2-TZVP level, see Computational Details).

In the absence of **P1**, the alcohol groups on both L-ascorbic acid and choline establish hydrogen bonds with the chloride (Figure 2), similarly to what urea does.⁶⁸ The ammonium group of choline is electrostatically attracted by the electron-rich lactonic moiety of L-ascorbic acid.

In the presence of the alkyne, the structure modifies to accommodate **P1** in the weak interaction network (**Asc/ChCl/P1**). The formation Gibbs energy of the adduct is negative with respect to the isolated moieties (-20.5 kcal/mol), ensuring its thermodynamical stability, and a complex network of weak interactions can be observed (Figure 2): the chloride interacts with three hydroxyl groups, one belonging to the choline and two to the L-ascorbic acid. **P1** interacts with the chloride, too, through its terminal CH. The ammonium group of choline is positioned close to the electron-rich part of **P1** and one oxygen of L-ascorbic acid establishes a hydrogen bond with the *ortho* proton of **P1**. Weaker

hydrogen bonds exist between the oxygens of the L-ascorbic acid and the CH of the ammonium moiety.

Noteworthy, the terminal C-H bond of **P1** in the adduct is 1.083 Å, whereas for an isolated P1 the same bond would be 1.070 Å. This lengthening, with the consequent bond weakening, can likely explain the easier abstraction of the terminal proton.

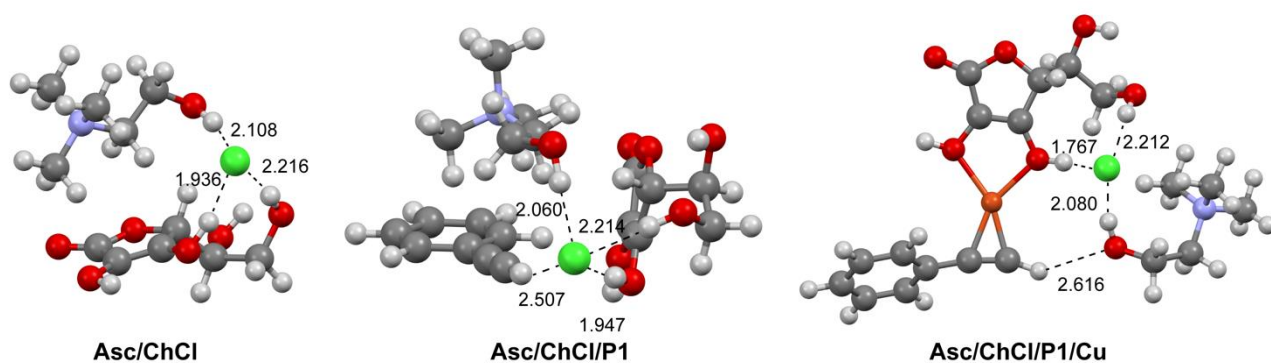


Figure 2. DFT-optimized geometries of the **Asc/ChCl**, **Asc/ChCl/P1** and **Asc/ChCl/P1/Cu** adducts. Relevant distances are expressed in Å.

Upon the reduction of Cu(II) to Cu(I), the latter coordinates the triple bond and the L-ascorbic acid at the same time, stabilizing the complex (**Asc/ChCl/P1/Cu**). Simultaneously, the terminal proton interacts with the oxygen of the choline, again weakening the bond, whereas the chloride is surrounded by alcohol protons. After this intermediate, the reaction can proceed as usual, with proton abstraction, formation of the C-Cu σ bond and reaction with the azide.⁶⁹

A similar investigation was carried out for the **GA/TMG** DES (Figure 3). In the absence of **P1**, the alcohol group of one **GA** and the carboxylic group of the second **GA** interact with the carboxylate moiety of the trimethylglycine. At the same time, the two **GA** units interact each other with an additional, weak hydrogen bond. Introducing the **P1** in the structure (**GA/TMG/P1**), the Gibbs energy is -9.1 kcal/mol. In the optimized geometry, the described arrangement does not change very much, but the terminal proton of **P1** interacts with the available carboxylic group of the **GA**, causing an elongation just slightly smaller than before (1.79 Å). Also, in this case, the solvent can act as a ligand, stabilizing the Cu(I)-alkyne complex (**GA/TMG/P1/Cu**), and as a basic centre, favouring the proton cleavage and the σ -coordination of the copper.

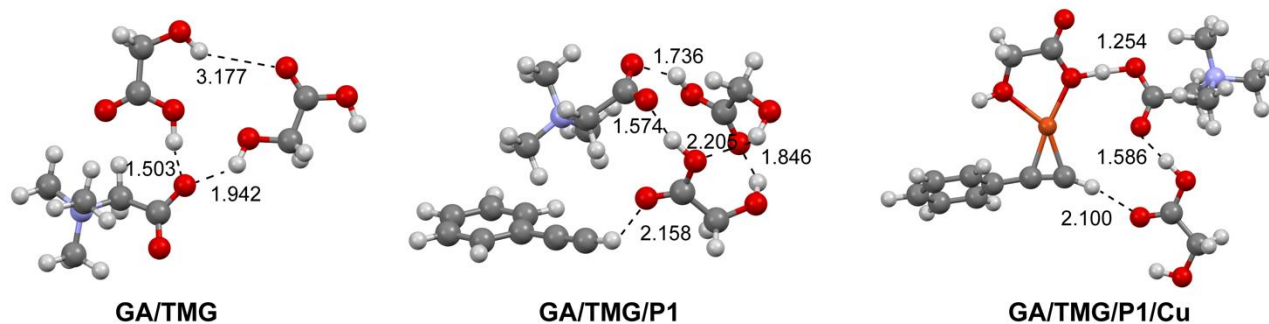


Figure 3. DFT-optimized geometries of the **Asc/ChCl**, **Asc/ChCl/P1** and **Asc/ChCl/P1/Cu** adducts. Relevant distances are expressed in Å.

Notably, also when the same reaction is carried out in standard polar solvents, as acetonitrile for example, the coordination of the solvent is generally invoked to stabilize the Cu(I)-alkyne complex.⁷⁰

CONCLUSIONS

Concluding, in this work we reported the investigation of a set of natural deep eutectic solvents (NADESs) as “active” and green reaction media in the copper-catalysed azide–alkyne cycloaddition reactions (CuAAC). In all the cases, the reactions were carried out in the absence of a base; they did not need high temperatures; they tolerated several functional groups; they did not require an external reducing agent (in the cases of the use of the reducing DESs) and they allowed the recycling of the solvent. As reported, the DES **GA/TMG** represented the best green solvent in our set to obtain 1,2,3-triazoles substituted with different functional groups in good yield. The **Asc/ChCl** DES showed also many advantages and because of its reducing capabilities, avoided the use of any reducing agent in the reaction mixture. In addition, the use of the green solvent **Asc/ChCl** as active DES in a non-classical CuAAC base- and reducing agent-free reaction contribute to the use of active green solvents in catalytic processes with advantages in terms of atom economy. DFT studies showed that the C–H alkyne bond enters in the H-bonds network of the DESs, being elongated and thus giving a rationale for the absence of a catalytic base while, the NADES constituents are able to stabilize the copper intermediates. To the best of our knowledge, this is the first example of this kind of reaction mechanism operated by these active green solvents and it could be relevant for other base-catalysed reaction procedures. The reported results outline the great potential of NADES for CuAAC contributing to the elimination of common organic solvents in organic synthesis and in catalysis.

CONFLICTS OF INTEREST

There are no conflicts to declare.

EXPERIMENTAL

General Information

Solvents and reagents were used as received from commercial sources. The experiments were performed in a glass sealed tube with a magnetic stirrer. NMR spectra (^1H -NMR recorded at 500 MHz, ^{13}C -NMR recorded at 125 MHz) were obtained in CDCl_3 solution on a Varian instrument (Agilent Technologies, Palo Alto, CA, USA), and data are reported in ppm relative to TMS as an internal standard. Benzyl/alkyl and aromatic azides were synthesized according to literature procedures.⁷¹ Isolated yield was determined after addition of water to the crude reaction mixture at room temperature. The water insoluble solid cycloadduct were filtered from the water solutions while the cycloadducts present as oils were extracted with ethyl acetate and (in some cases) purified via flash chromatography with ethyl acetate on silica gel.

Deep Eutectic Solvents Preparation

The DESs were prepared following the procedures reported in previous papers:⁷² the solid components were weighted in a flask at the proper molar ratio and then were mixed and heated at 50°C until a homogeneous liquid was formed in times spanning from 30 mins to 2 hours.

General procedure for the synthesis of 1,2,3-triazole derivatives **3a-r** in deep eutectic solvent

GA/TMG: synthesis of 1-benzyl-4-phenyl-1H-1,2,3-triazole (3a**).** In a glass sealed tube benzyl azide (0.133 g, 1 mmol), phenylacetylene (0.112 mL, 1 mmol), copper sulphate (0.016 g, 10 mol%) and sodium ascorbate (59.4 mg, 30 mol%) in 2 mL of green solvent were added, then it was putted in a oil bath heated at 50 °C. The mixture was stirred for 3 hours. Addition of water (10 mL) to the crude reaction mixture allows the easy separation by filtration of the desired product **3a** with 96% yield as a white powder (0.226 g).

General procedure for the synthesis of 1,2,3-triazole derivatives **3a-r** in deep eutectic solvent

Asc/ChCl: synthesis of 1-benzyl-4-phenyl-1H-1,2,3-triazole (3a**).** In a glass sealed tube benzyl azide (0.133 g, 1 mmol), phenylacetylene (0.112 mL, 1 mmol) and copper sulphate (0.016 g, 10 mol%) in 2 mL of green solvent were added. The mixture was stirred for 24 hours at room temperature. and was extracted with ethyl acetate (3 x 3 mL). Addition of water (10 mL) to the crude

reaction mixture allows the easy separation by filtration of the desired product **3a** with 94% yield as a white powder (0.221 g).

General procedure for the recycling green solvents. The CuAAc optimized reaction between phenyl acetylene and benzyl azide in the two natural deep eutectic solvent GA/TMG and Asc/ChCl was used as a model reaction. After each extraction cycle with ethyl acetate, azide and alkyne were added again to the catalyst system and the reaction mixture was stirred for the required time. This operation was repeated several times (see Table 3).

Computational details: All the structures have been optimized by ORCA 4.1.0⁷³ using the PBE functional in conjunction with a def2-TZVP basis set (grid = 5). The dispersion forces have been taken into account by using the Grimme's correction D3 with BJ damping.^{74,75} The thermodynamic properties have been computed at the same level of theory, showing that all the adducts are true minima of the potential energy surface (no negative vibrational frequencies).

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