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EXECUTIVE SUMMARY OF THE THESIS

Synthesis and applications of deep eutectic solvents as media for nucleophilic substitutions

LAUREA MAGISTRALE IN CHEMICAL ENGINEERING - INGEGNERIA CHIMICA

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1. Introduction to DESs

The use of solvents occupies a strategic place in chemistry [2]. In order to meet different criteria like biodegradability, non-toxicity, availability and recyclability a new type of medium has been studied in recent years: the deep eutectic solvents [5]. A DES is a fluid generally composed of two or three cheap and safe components that are capable of self-association, usually through hydrogen bond interactions, to form a eutectic mixture with a melting point lower than that of each individual component. These are solutions prepared by mixing two or more individual compounds (with a hydrogen bond donor and a hydrogen bond acceptor) at a precise molar ratio until a homogeneous phase is formed [3]. They are generally liquid at temperatures below 100°C. Although DESs show different chemical properties with respect to ILs, on the other hand they share the same physical features, in particular the potential as tunable solvents that can be customized to a particular type of chemistry [4]. Deep eutectic solvents show low vapor pressure, nonflammability and wide liquid range with several advantages over traditional ILs like straight preparation and easy availability from inexpensive components. The grey line in the follow-

ing figure (Fig 1) shows the growing interested poured into DESs research.

One of the most wide-spread components used for the formation of these DESs is choline chloride (ChCl). Others examples of possible DESs solvents are reported in the table below.

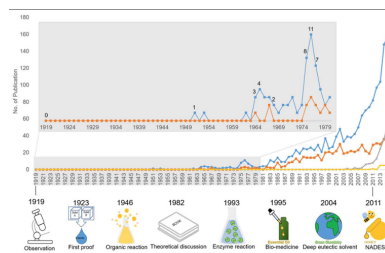


Figure 1: Number of publications since 1950.

	HBA	HBD	molar ratio
DES1	ChCl	Urea	1:2
DES2	ChOAc	Urea	1:2
DES3	Betaine	Urea	1:3
DES4	ChCl	Glycolic acid	1:2
DES5	ChOAc	Glycolic Acid	1:2

Table 1: Table of common DESs.

2. Discussion and results

All the thesis work has been focused on the synthesis and applications of deep eutectic as solvents in a different type of reactions. Given their great potential in terms of sustainability and easy preparation, DESs are seen as the green media alternative to a series of conventional processes nowadays conducted with toxic solvents [1]. One of these applications is the nucleophilic substitution, a reaction pathway that has been the main topic of the first part of my research work. It is a class of reactions where an electron rich species, known as nucleophile, replaces a functional group inside another electron deficient molecule, called electrophile. Particularly, the object of my study has been the synthesis of azides under different conditions with DES solvents, trying to understand the possible interactions between reactants and this new class of compounds.

2.1. Model reaction

In the first reaction was studied the nucleophilic substitution between benzylbromide and sodium azide; -Br shows good capability as leaving group and, at the same time sodium azide exhibits strong nucleophilic behavior (Fig 2).

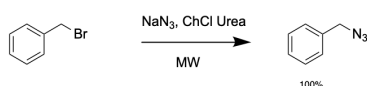


Figure 2: Model reaction

This reaction path was performed in a choline chloride – urea (1 : 2) DES solvent. The choice of this type of solvent is strongly related to its high level of polarity; this is a property which

must be carefully evaluated before designing a reaction, especially organic reactions since it can affect the solubility of the reactants and change the activation energy drastically. Analyzing these data (Table 2), temperature represents the most influencing factor for the reaction, which reaches the ideal value of conversion and yield at 60°C for a time equal to 60 min. From now on, these will be the usual conditions adopted during the reaction, performed by irradiation by means of a microwave reactor.

T [°C]	time [min]	Yield
100	15	41
60	30	86
60	45	51
60	60	100
50	60	35
50	30	87.4

Table 2: Different operating conditions of the model reaction.

2.2. Formation of azides using different electrophiles

In order to prove the efficiency of the DESs solvents to carry out nucleophilic substitutions, the first part of the research work has been focused on keeping sodium azide as reactant, showing strong nucleophilic properties and allowing the choice of several electrophiles to work with. For this reason, different types of molecules were considered. The reaction was tried starting from 1-(bromomethyl)-4-nitrobenzene (Fig 3). The process was conducted by means of a microwave, maintaining a temperature of 60°C for 60 min. The product was then extracted using dichloromethane, dried with sodium sulphate and concentrated under reduced pressure. The final product was characterized by 1H-NMR after being dissolved in deuterated chloroform, with a yield equal to 91.21 percent.

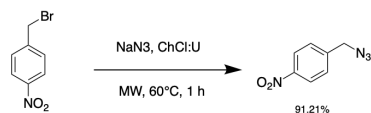


Figure 3: Synthesis of azide starting from 1-(bromomethyl)-4-nitrobenzene

The nucleophilic substitution was tested also starting from aliphatic compounds, to understand the reaction's behavior without the benzene ring. The reactants chosen were 1-bromooctane, 1-iodoheptane and 1-iodobutane using sodium azide as nucleophile (Fig 4). The yields obtained were respectively equal to 100, 50 and 100 percent.

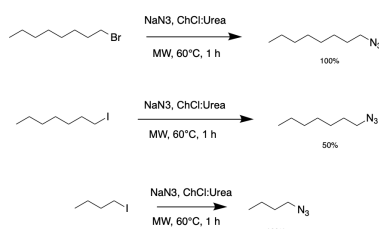


Figure 4: Nucleophilic substitutions on aliphatic molecules

The reaction was performed changing the functional group inside the electrophile, dealing with chloride substituents. As known, -Cl atom exhibits a lower ability as leaving group inside a molecule with respect to -Br. This was confirmed by the results of the $^1\text{H-NMR}$ characterization, with a final yield equal to 44 percent (Fig 5).

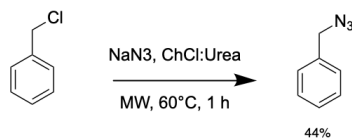


Figure 5: Nucleophilic substitutions on chloride substituted reactants

In contrast to benzene ring, pyridine more efficiently supports several nucleophilic substitutions. The main reason for this is the relatively lower electron density of the carbon atoms of the ring. Moreover, this type of reaction could be still enhanced by modifying the pyridine with bromine, chlorine fragments that

then become the leaving group. The two reactants used, 2-(chloromethyl)pyridine and 4-(chloromethyl)pyridine, have been treated as the previous cases. The yields obtained by these experiments are 82.3 and 78.3 percent respectively (Fig 6).

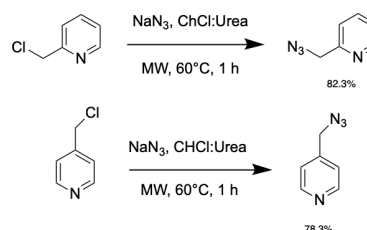


Figure 6: Nucleophilic substitutions on pyridines

2.3. Substitutions on benzyl bromide using different nucleophiles

In the previous section, it was proved with a series of reactions how the use of sodium azide (as nucleophile) with different reactants can lead to very good yields for the reaction studied. As the data show, sodium azide exhibits a strong nucleophilic nature and it can carry out the reaction even in presence of a weak electrophile. On the other hand, to complete the characterization of DESs application, it is necessary to understand the behavior of the considered process also varying the nucleophilic unit. For this reason, in the following chapter the attention will be focused on different classes of nucleophiles, keeping as electrophilic compound the same of the model reaction (benzyl bromide).

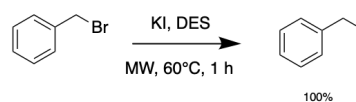


Figure 7: Formation of benzyl iodide

As part of the experiments, the nucleophilic substitution was carried out using iodide as nucleophile (KI, Fig 7). The lone pair of electrons on this larger, less basic atom interact less tightly with the protons of the solvent molecules; for this reason, -I is better able to break free from its solvent cage compared to smaller and more basic anions like fluoride or bromide. In other words, the electron density of this Nu can be more eas-

ily given to another molecule. The reaction was made in two different solvents, ChCl - urea and choline acetate - glycolic acid, with a quantitative yield in both cases. Another class of reaction taken into consideration is the nucleophile substitution of aromatic and aliphatic components with primary amines to get as product secondary amines.

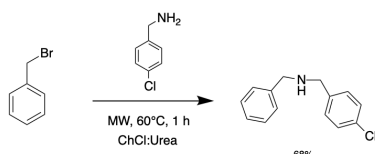


Figure 8: Formation of secondary amine

Generally, amines can work as good nucleophiles, even if this is not the case since the lone pair of electrons of nitrogen are stabilized by the benzene ring: however, the reaction is performed by using reactants which act as strong electrophiles such as benzyl bromide (Fig 8). The choice of molecules containing bromide group is warranted by the fact that, being weak basic halides, they are capable of stabilizing the negative charge so becoming favorable leaving groups.

In order to get tertiary amines, two other reactants were used as nucleophiles: piperidine and morpholine (Fig 9). The presence of the lone pair of electrons on the nitrogen atom gives these molecules a high degree of nucleophilicity, even if the oxygen atom of the morpholine acts as electro-withdrawing group. The effect of oxygen on the electrodensity of the ring is not significant, because the yields for the two performed reactions are both quantitative, as shown by the characterization made by means of GC-MS analysis.

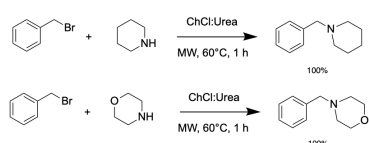


Figure 9: Nucleophilic substitutions using piperidine and morpholine as Nu

The formation of tertiary amines has been investigated not only in choline chloride-based DES; other solvents, and reactants, were tried

to study the behavior of the reaction and the relative yield. The two mixtures prepared for the experiments are: choline acetate and glycolic acid, betaine and urea. The first solution exhibits physical features similar to ChCl and urea, while for the use of the second one a constant heating and stirring was needed to set up the vial and the reaction in the microwave. The yields of the reactions performed in betaine and urea were good and equal to 88, 60 and 100 percent (Fig 10).

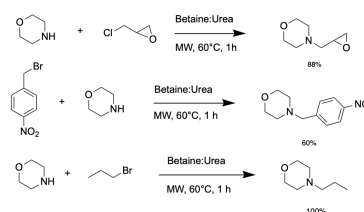


Figure 10: Synthesis of tertiary amines in betaine - urea DES

2.4. Recycling of deep eutectic solvents

The application of deep eutectic solvents as solvent/catalyst for a series of different reactions has demonstrated the great potential DESs have in terms of sustainability and efficacy. Their use as media for nucleophilic substitutions and oxidations foresees a possible scale up inside industries, with the opportunity to avoid the handling of toxic components and the improvement of treatment/disposal technologies. Moreover, as verified by the experiment's data (Fig 11), the activity of a DES solvent for a generic reaction does not show a worsening trend if employed in a cycle of synthesis in series. In fact, the benchmark synthesis of benzyl azide was performed starting from benzyl bromide and sodium azide in choline chloride - urea DES, for three consecutive times, trying to recover for each reaction the amount of solvent used in the previous step. Even if the procedure were stopped after the third recycle, due to complications related to the tools used for the extraction, the characterization of each final product made by GC-MS analysis shows great results in terms of yield. This means not only the possibility of a multiple reuse of DES solvents, but also the opportunity of saving water from the extraction procedure to enhance the phase separation.

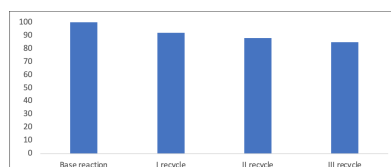


Figure 11: Yields for the recycles of DES

2.5. Industrial applications of DESs

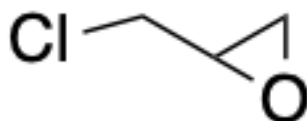


Figure 12: Epichlorohydrin molecule

Epichlorohydrin is an organochlorine compound and an epoxide (Fig 12). It's a highly reactive electrophilic compound, used together with piperidine to perform nucleophilic substitution and formation of a tertiary ammine. It is traditionally manufactured from allyl chloride with the addition of hypochlorous acid, which form two isomeric alcohols. The use of epichlorohydrin is crucial for the production of synthetic glycerol, mainly used in pharmaceutical and biotech applications where the required standards are high. The proposed reaction has been performed involving ECH and piperidine with the usual conditions in ChCl:Urea DES (Fig 13); after being extracted by means of DCM, the organic phase was dried with sodium sulphate and then characterized by GC-MS analysis.

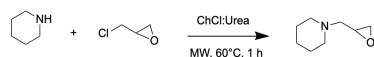


Figure 13: Synthesis using epichlorohydrin as nucleophile

2.6. Oxidations in DESs

Another pathway of reactions studied is the one regarding oxidations; 4-fluorobenzaldehyde was used as starting material and dissolved in a DES solvent (Figure 14). After the reaction was completed, the procedure followed consisted of extraction of the organic phase with ethyl acetate, drying with sodium sulphate and concentration of the solution under reduced pressure. The final

product was then dissolved in deuterated chloroform and characterized by $^1\text{H-NMR}$ analysis.

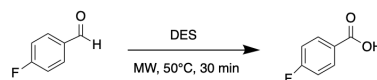


Figure 14: Oxidation of 4-fluorobenzaldehyde

The results obtained by the analysis were very good in terms of yield, for each of the four DESs used to carry out the reaction (Table 3).

DES used	Yield
ChCl - Urea	75
ChOAc - Urea	100
ChCl - glycolic acid	75
ChOAc - glycolic acid	92

Table 3: Different operating conditions of the model reaction.

3. Conclusions

The aim of the research was to highlight the properties of deep eutectic solvents and their possible industrial applications as alternative media to perform a series of different reactions. The most important solvents studied, choline chloride – based DESs, have been used to explore a precise class of reactions, the nucleophilic substitution. The model reaction performed, using benzyl bromide and sodium azide, showed very good results in terms of yield so paving the way to several reactions where other electrophiles and nucleophiles were used. Following the model case, the reaction was performed starting from substituted benzyl bromide, aliphatic electrophiles, benzyl chloride and pyridines. The main result obtained was the possibility of reaching a good yield regardless the strength of the different leaving groups contained by the electrophile compound. In the second part of the study, very reactive atom groups in reactants like potassium iodide, primary amines, piperidine and morpholine triggered a good response by the solvent, in which the substitution of benzyl bromide has been always favored in ChCl and urea.

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POLITECNICO DI MILANO

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Master of Science in Chemical Engineering

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**SYNTHESIS AND APPLICATIONS OF DEEP
EUTECTIC SOLVENTS AS MEDIA FOR
NUCLEOPHILIC SUBSTITUTIONS**

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Academic year: 2020-2021

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EXECUTIVE SUMMARY

The use of solvents occupies a strategic place in chemistry. In order to meet different criteria like biodegradability, non-toxicity, availability and recyclability a new type of medium has been studied in recent years: the deep eutectic solvents. A DES is a fluid generally composed of two or three cheap and safe components that are capable of self-association, usually through hydrogen bond interactions, to form a eutectic mixture with a melting point lower than that of each individual component. These are solutions prepared by mixing two or more individual compounds (with a hydrogen bond donor and a hydrogen bond acceptor) at a precise molar ratio until a homogeneous phase is formed. They are generally liquid at temperatures below 100°C.

These solutions are very easy to prepare and exhibits physico-chemical properties similar to the traditional used ionic liquids, while being much cheaper and environmentally friendlier. Owing to these remarkable advantages, DESs are now of great interests in many fields of research; in this review, it is reported the possible applications and contributions of deep eutectic solvents in very common reaction pathways, such as nucleophilic substitutions and oxidations. In the first case, the experiments performed are focused on the use of different reactants, to test different conditions in which the new type of solvent should work. Starting from a model reaction based on benzyl bromide and sodium azide, the optimal conditions are reproduced as first experiment of the research to verify the efficacy of choline chloride – based DESs. Then a series of different compounds are used both as nucleophile and electrophile to change the conditions of the process and understand which response the solvent can give in terms of yield. The investigation done inside this work considers not only different class of molecules (aliphatic and aromatic) but also the presence of a variety of functional groups, which can modify the dynamics of the substitution.

Of great importance are the studied substitutions of molecules like piperidine and morpholine together with epichlorohydrin. These are processes used at an industrial scale to produce intermediate compounds for the synthesis of very common pharmaceuticals like haloperidol, benproperine and metopimazine. The possible use of green solvents such as DESs inside this context would mean a unique opportunity to meet all the necessary criteria to make a process feasible and sustainable, avoiding the contact with toxic and hazardous substances. Moreover, as demonstrated in the study, a single reaction can be performed different times using the same amount of DES solvent, which can be recycled and reused without losing efficacy in terms of yield.

1.INTRODUCTION

1.1 THE FUTURE OF SOLVENTS

The sustainability of a chemical process strongly relies on the solvent used: in fact, solvents are ubiquitous in chemistry and are adopted in large amount for a variety of products, including paints, coatings, adhesives, as raw materials for product synthesis and for equipment cleaning [1]. A solvent is the common medium used to carry out organic reactions because of the easy control of mass and heat transfer, stabilization of transition states and fast modification of reactivity. In order to avoid the most common drawbacks of organic solvents, new types of media have been studied in the recent years; despite some promising features, they still show some considerable disadvantages. Water, for example, has strong limitations as regards solubility of catalysts and organic reagents and its purification could be difficult and expensive. Even fluorinated solvents have been proposed as a possible alternative but they are not so attractive due to their higher prices and persistence in the atmosphere. Moreover, high costs of equipment and complementary properties of certain components have been a limiting factor for supercritical fluids [2] and biomass-derived solvents [3].

Ionic liquids (ILs) have been considered as the best possible alternative to organic solvents: made up of an organic cation and a weak nucleophilic and coordinating anion, they show low vapor pressure, nonflammability, stability at temperatures higher than 200°C, possible fine tuning properties and catalytic activity [4]. Despite these advantages, the drawbacks are still so important that they can't be obviated: price, water stability, need of using organic solvents at the end of reactions, toxicity and poor degradability. For these reasons, the chemical society has evaluated a new medium, starting from the beginning of this century, to get rid of VOC (volatile organic solvents): the eutectic mixtures [5]. The interest drawn from this new field of study is verified by the number of publications issued in the most recent years, as the following image (Figure 1) shows reporting in grey line the exponential growth in DES studies.

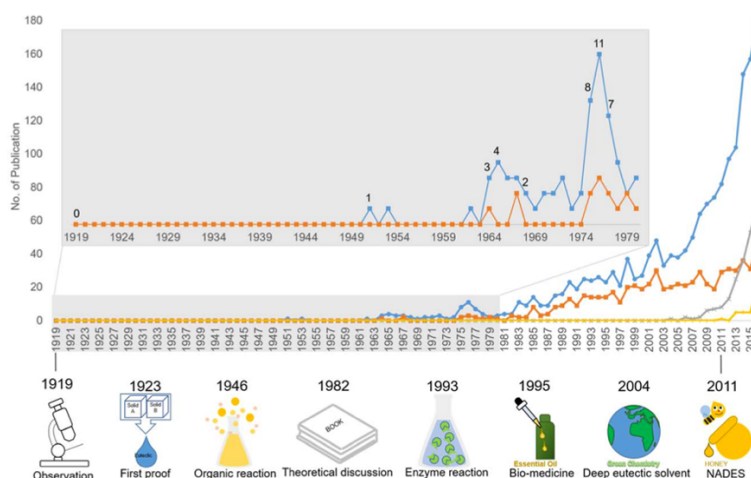


Figure 1 Number of publications on key topics since 1950

1.2 DEFINITION OF DEEP EUTECTIC SOLVENTS

DESs are systems formed from a eutectic mixture of Lewis or Brønsted acids and bases which can contain a variety of anionic or cationic species. They are usually obtained from the mixing of a quaternary ammonium salt with a metal salt or hydrogen bond donor (HBD) and, thanks to a low lattice energy, they deviate from ideal mixtures, resulting in a significant depression of the freezing point. This type of solvent is just one of those ion-dominated systems found very useful in a variety of applications and has emerged as a promising alternative to the use of ionic liquids (ILs).

Although DESs show different chemical properties with respect to ILs, on the other hand they share the same physical features, in particular the potential as tunable solvents that can be customized to a particular type of chemistry. Deep eutectic solvents show low vapor pressure, nonflammability and wide liquid range with several advantages over traditional ILs like straight preparation and easy availability from inexpensive components.

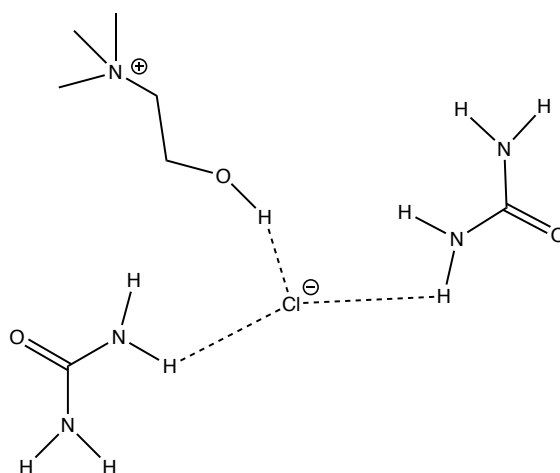


Figure 2 Structure of choline chloride – urea

The depression of the melting point of the mixture with respect to those of the individual components is due to the charge delocalization between the halide ion and the hydrogen-donor [6]; this is considered the key physical driving force for the formation of DESs, with studies which supported this assertion spectroscopically. One of the most wide-spread components used for the formation of these DESs is choline chloride (ChCl). ChCl is a very cheap, biodegradable and non-toxic quaternary ammonium salt which can be either extracted from biomass or readily synthesized from fossil reserves (million metric tons) through a very high atom economy process. In combination with safe hydrogen bond donors, such as urea, renewable carboxylic acids or renewable polyols, ChCl is capable of forming a DES. An

example is the mixture of choline chloride- urea, 1:2 equivalents, also known as reline (Figure 2).

The drastic change in the melting point can be immediately seen inside this structure: with choline chloride and urea having a melting point, respectively, at 302°C and 133°C, the mixing of the two solid components creates a homogeneous liquid phase at the temperature of 80°C. The possibility of having a liquid mixture at room temperature is due to the depression of the melting point at 12°C, where the difference of temperature measured is not only the one between the real eutectic point and the individual components' melting points but also the difference between real and ideal eutectic points. A diagram of select binary combinations of choline chloride with various HBDs is shown in the following image, illustrating the melting points of the constituents compared to the one of the formed eutectics (Figure 3).

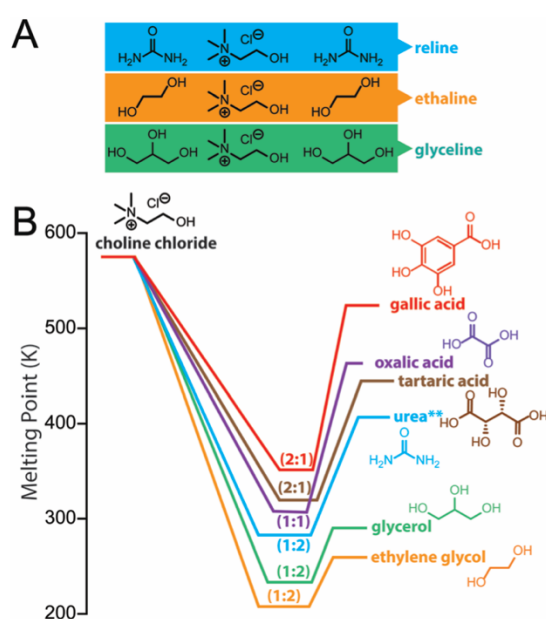
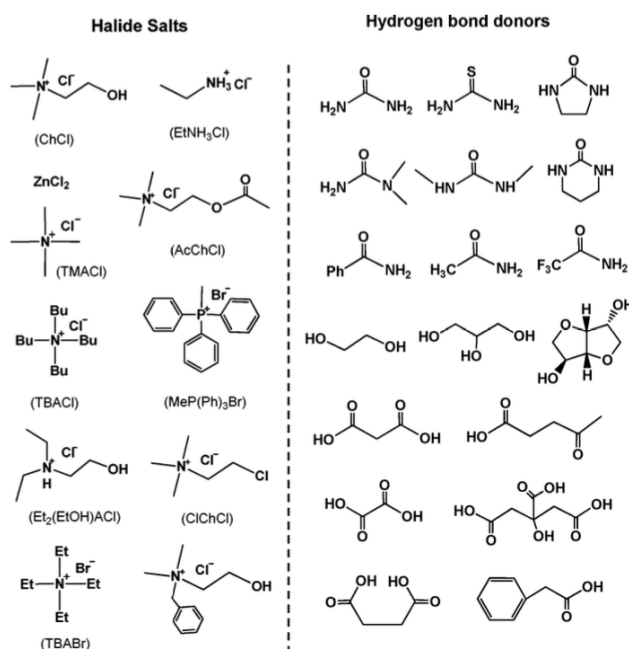


Figure 3 Phase diagram of the eutectic mixture

Although most of DES are made from ChCl as anion, they cannot be considered as ionic liquids because they are not entirely composed by ionic species and they can also be obtained from non-ionic species. Comparing this new type of media to ILs, it is immediately clear the easy preparation of DESs, simply mixing two cheap components and so by-passing all problems related to purification and disposal. In most cases, a DES is obtained by mixing a quaternary ammonium salt with metal salts or a hydrogen bond donor (HBD) that has the ability to form a complex with the halide anion of the quaternary ammonium salt; DESs formed starting from urea are attractive since they exhibit similar physico-chemical properties to traditional imidazolium based ILs and so can replace them in many applications. What makes these solvents even more interesting is the fact that they have been proven biodegradable and compatible with enzymes, with a 100% atom economy and the possibility of a feasible scale-up. Moreover, DESs are promising for the design of catalytic processes, the preparation of new materials and structures, dissolution of valuable substrates and in the field of electrochemistry. The increasing interest poured in these solvents is due to the possibility of

being tailorable solvents: task-specific eutectic with different physicochemical properties such as freezing point, viscosity, conductivity and pH, can be prepared (Scheme 1).



Scheme 1 Typical structures of halide salts and HBD used in DES systems

1.3 CLASSIFICATION OF DESs

Deep eutectic solvents can be described by the following formula, Cat(+) X(-) zY where Cat is in principle an ammonium, phosphonium or sulfonium cation, and X is a Lewis base, generally a halide anion. The complex is formed between X and either a Lewis or Brønsted acid (z is the number of molecules that interacts with the anion). Most of the studies are being focused on quaternary ammonium and imidazolium cations, considering more practical systems such as choline chloride. DESs strongly depend on the nature of the complexing agent and several types can be encountered (Table 1):

type	general formula	terms
type I	$\text{Cat}^+ \text{X}^- z\text{MCl}_z$	$\text{M} = \text{Zn},^{1,5,6} \text{Sn},^7 \text{Fe}, \text{Al},^8 \text{Ga},^9 \text{In}^{10}$
type II	$\text{Cat}^+ \text{X}^- z\text{MCl}_z \cdot y\text{H}_2\text{O}$	$\text{M} = \text{Cr},^{11} \text{Co}, \text{Cu}, \text{Ni}, \text{Fe}$
type III	$\text{Cat}^+ \text{X}^- z\text{RZ}$	$\text{Z} = \text{CONH}_2,^{12} \text{COOH},^{13} \text{OH}^{14}$
type IV	$\text{MCl}_x + \text{RZ} = \text{MCl}_{x-1}^+ \cdot \text{RZ} + \text{MCl}_{x+1}^-$	$\text{M} = \text{Al}, \text{Zn}$ and $\text{Z} = \text{CONH}_2, \text{OH}$

Table 1 General type of classification of DESs

DESs from type I can be considered as very similar to metal halide/imidazolium salts systems; they also include less common ionic liquids, for example made up of iron(II) chloride.

However, the scope of deep eutectic solvents can be used by using hydrated metal halides and choline chloride (type II DES): they are considered more attractive for the industrial scale use thanks to their relatively low cost and air/moisture insensitivity of many hydrated metal salts. Type III eutectics are obtained from choline chloride and hydrogen bond donors, interesting for their ability to solvate a wide range of transition metal species, including chlorides and oxides [7]. The wide range of HBDs under study means that deep eutectic solvents are a highly adaptable class of solvents: several DESs are formed using amides, carboxylic acids and alcohols, simply to prepare and unreactive with water. They are highly versatile, with numerous applications like the removal of glycerol from biodiesel, processing of metal oxides, and the synthesis of cellulose derivatives. Inorganic cations generally do not form eutectic mixture with low melting points, due to their high charge density; however, recent studies have shown how some systems could be melted at temperatures lower than 150°C [8]. Abbot et al. have studied a series of transition metals that can be incorporated into ambient temperature eutectics, and these have now been termed type IV DES; for instance, zinc chloride can form eutectics with urea, acetamide, ethylene glycol and 1,6-hexanediol.

The building block of the previous cited DESs, quaternary ammonium cation chloride, is nontoxic and has a comparatively low cost when compared with imidazolium and pyridinium. It is classified as provitamin in Europe and is produced on megatonne scale as animal feed supplement starting from HCl, ethylene oxide and trimethylamine with negligible ancillary wastes.

1.4 PROPERTIES OF DESs

DESs are solvents easy to prepare. There are two possible methods and the most common is by heating and mixing the individual components at a specific temperature and with a precise molar ratio, providing a continuous stirring of the mixture. This process lasts until a homogeneous liquid phase is formed; alternatively, the grinding method consists in mixing two components and grinding them in a mortar, until a homogenous liquid is formed. It is pivotal the absence of other solvents or reactions during this preparation step, implying that it is no further necessity of downstream purification and contributing to their promise as economically alternatives to organic solvents and ionic liquids.

DESs are viscous and clear liquids: the wide range of possible components that can be used for the preparation of eutectics make this type of solvents perfectly tunable for any kind of application [9], with the possibility to optimize every single property of the mixture that is forming. The immense number of HBD and HBA species would mean a great effort to find systems suitable and “optimal” for any situation, implying an endless series of experiments to be completed. For these reasons, the scientific community has decided to develop

predictive models for the formation of deep eutectics which are so considered as inexpensive green media.

1.4.1 Freezing point (T_f)

As mentioned, DESs are formed by mixing two solids capable of generating a new liquid thanks to the creation of hydrogen bonds: the new phase, as it occurs with ChCl and urea, is characterized by a freezing point lower than that of individual components. For all DESs studied the freezing temperature is below 150°C, with particular attention to those with T_f lower than 50°C since they can be used as inexpensive and safe solvents in many applications. Although a broad range of amides has been used to produce DESs with a freezing point lower than 100°C, it should be said that the number of eutectics liquid at room temperature is still very limited. Among them urea is capable of forming a liquid DES at room temperature due to its stronger ability to form hydrogen bond interactions with choline chloride; the choice of HBD is thus a critical point, with carboxylic acids and sugar-derived polyols as possible HBDs to form room temperature liquid eutectics.

Another factor affecting the freezing point of these mixtures is the nature of the organic salts (e.g. ammonium or phosphonium): for example, when urea is used and mixed with different ammonium salts in a molar ratio of 2 : 1 (urea : salt), the obtained DES exhibit very different freezing points ranging from -38°C to 113°C (Figure 4). The anion of choline-derived salts also impacts the freezing point: in combination with urea, it decreases in the order $F > NO_3 > Cl > BF_4$. Moreover, the organic salt/HBD has also a significant impact on the freezing point: for example, when ChCl was mixed with urea in a molar ratio of 1 : 1 and 1 : 2, the resulting DESs exhibited a freezing point >50 °C and 12°C, respectively. Although these components have been deeply studied, no clear correlation between the freezing point of DESs and the melting points of the pure components has been established.






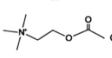



Organic salts Cation	Hydrogen bond donor (X ⁻) (HBD)	Salt : HBD (molar ratio)	T_f /°C
	F ⁻ Urea	1 : 2	1
	BF ₄ ⁻ Urea	1 : 2	67
	NO ₃ ⁻ Urea	1 : 2	4
	Cl ⁻ Urea	1 : 2	-38
	Br ⁻ Urea	1 : 2	113
	Cl ⁻ Urea	1 : 2	-14
	Cl ⁻ Urea	1 : 2	-33
	Cl ⁻ Urea	1 : 2	15
	Br ⁻ Urea	1 : 2	55

Figure 4 List of urea - based DESs

1.4.2 Density

As regards solvents, density is one of the most important properties. The following table (Table 2) shows the density data of common DESs, which are obtained by means of a gravity meter. Most of eutectics exhibit higher density with respect to water: for example, type IV DESs such as zinc chloride – HBD have densities higher than 1.3 g/cm³. Studies have related this difference to a particular molecular organization or packing of the mixture. Other DESs have a higher density than single HBDs: this phenomenon could be explained by means of the hole theory. In fact, deep eutectic solvents are composed of holes or empty vacancies, and during the mixture formation the average hole radius is decreased, resulting on a slight increase of the density [10]. The organic salt/HBD molar ratio has also a direct effect on density, where the addition of ChCl to glycerol, for example, leads to a decrease of the density, which may be explained in terms of free volume. Finally, it could be used the Rackett equation to predict the density behavior as function of the temperature, with an error around 1.9 %.

Salts	HBD	Salt : HBD (mol : mol)	Density (ρ , g cm ⁻³)	Ref.
EtNH ₃ Cl	CF ₃ CONH ₂	1 : 1.5	1.273	23
EtNH ₃ Cl	Acetamide	1 : 1.5	1.041	23
EtNH ₃ Cl	Urea	1 : 1.5	1.140	23
ChCl	CF ₃ CONH ₂	1 : 2	1.342	23
AcChCl	Urea	1 : 2	1.206	23
ChCl	Urea	1 : 2	1.25	23,24
ZnCl ₂	Urea	1 : 3.5	1.63	12
ZnCl ₂	Acetamide	1 : 4	1.36	12
ZnCl ₂	EG	1 : 4	1.45	12
ZnCl ₂	Hexanediol	1 : 3	1.38	12
ChCl	Glycerol	1 : 2	1.18	25,27
ChCl	Glycerol	1 : 3	1.20	25
ChCl	Glycerol	1 : 1	1.16	26
ChCl	Glycerol	1 : 3	1.20	26
ChCl	EG ^b	1 : 2	1.12	25,26
ChCl	EG	1 : 3	1.12	25,26
ChCl	Malonic acid	1 : 2	1.25	24
Et ₂ (EtOH)NCl ^a	Glycerol	1 : 2	1.17	26
Et ₂ (EtOH)NCl ^a	Glycerol	1 : 3	1.21	26
Et ₂ (EtOH)NCl ^a	Glycerol	1 : 4	1.22	26
Et ₂ (EtOH)NCl ^a	EG	1 : 2	1.10	26
Et ₂ (EtOH)NCl ^a	EG	1 : 3	1.10	26
Et ₂ (EtOH)NCl ^a	EG	1 : 4	1.10	26
Me(Ph) ₃ PBr ^c	Glycerol	1 : 2	1.31	26
Me(Ph) ₃ PBr ^c	Glycerol	1 : 3	1.30	26
Me(Ph) ₃ PBr ^c	Glycerol	1 : 4	1.30	26
Me(Ph) ₃ PBr ^c	EG	1 : 3	1.25	26
Me(Ph) ₃ PBr ^c	EG	1 : 4	1.23	26
Me(Ph) ₃ PBr ^c	EG	1 : 6	1.22	26

^a Et₂(EtOH)NCl: *N,N*-diethylenethanol ammonium chloride. ^b EG is ethylene glycol. ^c Me(Ph)₃PBr: methyltriphenylphosphonium bromide.

Table 2 Densities of common DESs at 25 °C

1.4.3 Viscosity

In order to be adopted at an industrial scale, viscosity is a problem that needs to be addressed. Except for ChCl – EG (ethylene glycol), most of eutectics have relatively high viscosities (>100

cP) at room temperature. This property is often related to the extended hydrogen bond network which is established between the components of a solvent, resulting in a lower mobility of free spaces inside the DES. Other factors that contribute to the high viscosity are the large ion size and the very small void volume, electrostatic and Van Der Waals interactions. Since they are considered one of the most attractive green media, the choice of low viscosity DESs is highly desirable: hence, the use of the hole theory can be used to design this type of solvents, for example exploiting small cations or fluorinated hydrogen bond donors [11]. As the following table shows (Table 3), the viscosity of ChCl-based DESs is closely dependent on the nature of HBD. For instance, ChCl/EG (1 : 4) DES exhibits the lowest viscosity (19 cP at 20 °C). In contrast, use of derived sugars (e.g. xylitol, sorbitol) or carboxylic acids (e.g., malonic acid) as HBDs led to DESs exhibiting high viscosities (e.g., 12 730 cP at 20 °C for ChCl/sorbitol) due to the presence of a more robust 3D intermolecular hydrogen-bond network.

Organic Salts	HBD	Salt : HBD molar ratio	Viscosities (cP)	Ref.
ChCl	Urea	1 : 2	750 (25 °C)	24
ChCl	Urea	1 : 2	169 (40 °C)	23
ChCl	EG	1 : 2	36 (20 °C)	25
ChCl	EG	1 : 2	37 (25 °C)	24
ChCl	EG	1 : 3	19 (20 °C)	25
ChCl	EG	1 : 4	19 (20 °C)	25
ChCl	Glucose	1 : 1	34 400 (50 °C)	19
ChCl	Glycerol	1 : 2	376 (20 °C)	25
ChCl	Glycerol	1 : 2	259 (25 °C)	24
ChCl	Glycerol	1 : 3	450 (20 °C)	25
ChCl	Glycerol	1 : 4	503 (20 °C)	25
ChCl	1,4-Butanediol	1 : 3	140 (20 °C)	25
ChCl	1,4-Butanediol	1 : 4	88 (20 °C)	25
ChCl	CF ₃ CONH ₂	1 : 2	77 (40 °C)	23
ChCl	Imidazole	3 : 7	15 (70 °C)	18
ChCl	ZnCl ₂	1 : 2	85 000 (25 °C)	29
ChCl	Xylitol	1 : 1	5230 (30 °C)	19
ChCl	Sorbitol	1 : 1	12 730 (30 °C)	19
ChCl	Malonic acid	1 : 2	1124 (25 °C)	24
ZnCl ₂	Urea	1 : 3.5	11 340 (25 °C)	25
Bu ₄ NBr	Imidazole	3 : 7	810 (20 °C)	18
EtNH ₃ Cl	CF ₃ CONH ₂	1 : 1.5	256 (40 °C)	23
EtNH ₃ Cl	Acetamide	1 : 1.5	64 (40 °C)	23
EtNH ₃ Cl	Urea	1 : 1.5	128 (40 °C)	23
AcChCl	Urea	1 : 2	2214 (40 °C)	23
Bu ₄ NBr	Imidazole	3 : 7	810 (20 °C)	18

Table 3 Viscosities of selected DESs at different temperatures

1.4.4 Polarity

A solvent polarity is generally measured by its polarity scale, which is the electronic transition energy of a probe dye; this property is related to intermolecular attractions and it is pivotal for the understanding of the ability to dissolve solutes. Although eutectics are deeply investigated as potential green media, there is not enough material to date as regards their polarity; the polarity scale of a solvent, Et, can be evaluated by means of UV-vis technology and using Reichardt's Dye 30 and can be calculated according to the formula (1).

$$ET(30)(\text{kcal mol}^{-1}) = h_{CU} \max_{NA} = (2.8591 \times 10^3) U_{\max}(\text{cm}^{-1}) = 28591/l_{\max} \quad (1)$$

Results have shown that ChCl/glycerol based DES exhibit a similar level of polarity of ionic liquids.

1.4.5 Ionic conductivity

Since they are viscous solvents, most of DESs are characterized by a low value of ionic conductivity (lower than 2 mS/cm at room temperature). It increases significantly as the temperature increases due to a decrease in DES viscosity. For this reason, to predict the value of conductivity an Arrhenius-like equation can be adopted; the organic salt/HBD molar ratio strongly influences the conductivity [12], as well as viscosity, which can be increased by increasing the ChCl content [13]. For instance, when the molar fraction of choline chloride is increased up to 25%, the conductivity of ChCl-glycerol DES is 0.85 mS/cm; at higher concentrations, these types of eutectics exhibit a viscosity (<400 cP) and conductivity (> 1 mS/cm) comparable to those of ionic liquids.

1.4.6 Acidity or alkalinity

As stated before, being composed of Lewis or Brønsted acids and bases, in deep eutectic solvents is fundamental to understand the value of pH, which varies depending on the relative acidity or alkalinity of the anionic and cationic species that are present in each composition. To predict the behavior of DESs as regards their acidity is pivotal also from an industrial perspective, because the pH value of a solvent dramatically influences the choice of a material employed within a generic process. The Hammett function has been widely used to evaluate the acidity or basicity of nonaqueous solvents by determining the ionization ratio inside a system: for a basic solution, the Hammett function measures the tendency to capture protons and it can be defined by the following equation (2):

$$H_{-} = pK(HI) + \log([I^{-}]/[HI]) \quad (2)$$

where $pK(HI)$ is the thermodynamic ionization constant of the indicator in water, $[I^{-}]$ and $[HI]$ represent the molar concentrations of anionic and neutral forms of the indicator, respectively. A solvent with large value of this function has a strong level of basicity: the H_{-} indicator of the ChCl/urea (1:2) DES is 10.86, suggesting that this mixture is weakly basic [14], even if this value slightly decreases to 10.65 when the system contains 1-3 % of water (due to a partial solvation of basic sites). Since the aforementioned type of DESs show low alkalinity, it can be used to absorb acid gas such as CO_2 ; in the presence of 1 atm of CO_2 the H_{-} value of choline chloride/urea decreases to 6.25. Moreover, bubbling N_2 inside the DES the initial value of the

Hammett function was recovered, suggested that the acidity or basicity of DESs can be easily switched reversibly by bubbling CO₂ or N₂.

Of course, also the chemical nature of hydrogen bond donors and the temperature are determining factors on the pH of DES systems [15], with different behaviors and responses to changes of these conditions as the following figure shows (Figure 5).

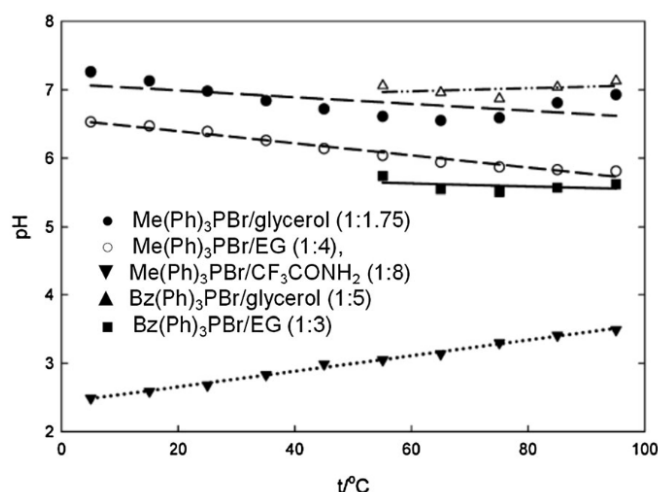


Figure 5 pH of selected phosphonium-based DESs

1.4.7 Surface tension

To date, studies related to surface tension have been scarce: among the reported data, surface tensions of ChCl/malonic acid (1 : 1) and ChCl/phenylacetic acid (1 : 2) DESs were about 65.68 and 41.86 mN/m. This property is expected to follow a similar trend to viscosity because it depends on the intermolecular interactions that govern the formation of DESs; in fact, the surface tensions of some ChCl/glycerol DESs showed a linear correlation with temperature [16]. Moreover, it decreases as ChCl concentration increases due to the disruption of the extensive hydrogen bond network of glycerol (as previously discussed for viscosity).

1.4.8 Renewability and toxicity

Even though DESs cannot be considered as perfectly green media, their use, alternatively to ionic liquids, could bring several benefits to the economy of the process and to the

environment. DESs are in principle inherently nontoxic because they are composed by benign components: however, type I, II and IV eutectics may contain metal salts with a small value of toxicity which is significantly lower with respect to the one of the aqueous mineral acids that they seek to replace. Matthijs et al. have carried out a study on the environmental impact of DESs based on choline chloride and ethylene glycol in electroplating applications. Both components are nonharmful to the environment, and they are both biodegradable (so making biodegradable also the final solution). Hence, the main environmental impact was found to be the presence of heavy metals in the solution and products formed during the electrolysis due to an incomplete current efficiency at the cathode and anode reactions.

1.5 APPLICATIONS OF DESs

The key advantages of DESs with respect to other solvents like ILs is that DESs have lower costs and are much easier to produce in large scale batches, promoting the scale-up of DES processes to an industrial level. However, the scaling up of a new technology like this is very difficult and it takes years to convince a company that it is worthy challenge. The most important operational steps for an industrial implementation include the scaleup from bench to a pilot plant, from pilot plant to full scale process and the optimization of the process itself.

Although they are a rather young technology, deep eutectic solvents have been applied to a wide range of research topics at a lab scale, with still few pilot scale plants being developed. From lubrication of steel to an alternative electrolyte of water, or organic solvent for the study of electronically conducting polymers [17]. They have been used also as devices to detect analytes such as lithium and sodium ions and in the DES-assisted synthesis of carbon electrodes for capacitors. The main application of eutectics to date is related to metal finishing, even if the number of studies investigating DESs as synthesis media is strongly increased in the recent years.

1.5.1 Metal processing applications

The electrofinishing industry works with aqueous systems due to the high solubility of electrolytes and metals salts in water, resulting in highly conducting solutions; nevertheless, this type of technology shows some drawbacks, since in water the deposition of some metals is limited by poor current efficiencies or hydrogen embrittlement of the substrate. Other limitations are present because of the curbs imposed by nations regarding the use of aqueous Cr and the toxicity of Co and Ni plating sector. The main use of DESs is now related to incorporation of metal ions in solution for metal deposition, metal dissolution or metal processing; the key advantages brought by adopting DESs are high solubility of metal salts, absence of water and high conductivity compared to nonaqueous solvents. While the

preparation of eutectics is a lot easier than the one of ILs, there still are a number of EU and TSB funded projects which are studying the scale up and commercialization of DESs in this field [18].

Research involving metal processes is divided into three different topics: metal electrodeposition, metal electropolishing and metal extraction/processing of metal oxides. Nowadays, the electroplating industry works with acidic or basic solutions, rarely with organic solvents [19]; Zn, Ni, Cr, Co, Cu, Ag are all materials successfully plated by means of brighteners and additives. The main issue of this type of process is the high capital investment and running costs. In principle, electroplating solutions should be low cost, nonflammable, with a high solubility of metal salts, high rates of mass transport and low ohmic losses with a high degree of stability.

One of the main advantages of DESs is the possibility to increase the potential of metal deposition thanks to their ability to dissolve metal oxides and hydroxides. In fact, passivation is often a problem for aqueous solution due to non-soluble oxides/hydroxides which deposit on the surface of the electrode, limiting the coating with the targeted metal. For these reasons, deep eutectics can provide a suitable solution in this industrial environment, with thicker metal films that can be more easily deposited in DESs solutions.

Metal polishing processes consist of a controlled dissolution of a metal surface in order to reduce the roughness of the surface and so increase reflectivity: it's a procedure that increases also corrosion resistance and lubricity in engines, overcoming a major cause of failures. The current procedures adopted in metal electropolishing show significant drawbacks: the solutions are corrosive and toxic and the process is characterized by gas evolution, associated with low current efficiency. The use of eutectics could bring several advantages to this type of process; for instance, gas evolution at the anode/solution interface would be negligible and so current efficiencies could be higher. Compared to the actual acid solutions, DESs are noncorrosive and benign.

Finally, also the dissolution of metal oxides is crucial to a series of processes such as metal winning, corrosion remediation and catalyst preparation. Treating large amount of metal materials means at the same time the necessity to deal to an enormous quantity of aqueous waste, with the treatment of byproducts which are energetically and chemically intensive. In recent years, there have been studies investigating how to rethink and promote a different kind of waste treatment, finding in the use of DESs a possible solution. For example, there is a project called RECONIF which is analyzing the use of certain types of DES to extract nickel from different waste streams, including filter cakes and battery waste. Type III DESs have been shown to dissolve a range of metal oxides with ligands such as urea, thiourea, and oxalate being well-known complexants for a variety of metals.

1.5.2 Separations in DESs

As mixture composed by ionic species, DESs have also interesting properties for high CO₂ dissolution; this, in combination with green features of DESs, shows the strong potential of this new type of solvents for a variety of chemical processes like separation and purification of gas, chemical fixation of CO₂ and catalysis. Research groups have focused their attention on the ChCl and urea system, taking into account changes in temperature and pressure. These studies exhibit how solubility strongly depends on three factors: CO₂ pressure, temperature and the ChCl/urea molar ratio [20], with maximum solubility value obtained at a ratio equal to 1:2. Being capable of donating or accepting electrons or protons to form hydrogen bonds also confer to solvents important dissolution properties, with a series of different substances which could be dissolved, including inorganic salts, aromatic acids and amino acids.

It is fundamental the ability of DESs to dissolve metal oxides: this new possibility means the creation of a green strategy for the separation and recycling of metal materials, a key point in electrochemistry. Even if this still remains poorly explored due to the lack of data, the following table shows the solubility of three different oxides in three DESs (Table 4).

DESs	Solubility (mol L ⁻¹)		
	CuO	Fe ₃ O ₄	ZnO
ChCl/malonic acid	0.246	0.071	0.554
ChCl/oxalic acid	0.071	0.341	0.491
ChCl/phenylpropionic acid	0.473	0.014	> 0.491

Table 4 Solubility of ZnO, CuO and Fe₃O₄ in three DESs at 50°C

Recently there have been studies also on the dissolution of organic macromolecules in DESs: several poorly soluble drugs were investigated including benzoic acid, griseofulvin, danazol, itraconazole and AMG517. For example, the solubility of AMG517 in pure water was lower than 0.0001 mg/mL vs 0.01 mg/mL and 0.4727 mg/mL in pure ChCl/urea and ChCl/malonic acid, respectively. In the case of aqueous solutions of DESs, solubility of drugs was enhanced as compared to neat water; for these reasons, DESs are now emerging as promising media for oral dosing of rats during the early pharmacokinetic investigations. Moreover, deep eutectics have shown the possibility to be anhydrous solvents for nucleic acids, thanks to secondary structures which could be broken upon heating of DESs.

1.5.3 Catalysis and Biocatalysis

It was previously stated the importance of choosing the best solvent in a chemical process for a variety of reasons, without mentioning how this choice strongly influences the interaction between reactants and catalysts. In fact, the solvent not only affects the contact between molecules and catalysts but also work-up procedures, recycling or disposal strategies. Studies have exhibited how ILs used as solvents are suitable to stabilization of nanoparticles, immobilization of homogeneous catalysts and the catalytic conversion of raw materials, even if the ecological and economical footprint of these processes remain still unacceptable for industrial applications. Hence, DESs have been proposed as the safe and cheap media to develop this catalysis-related function. One example is the electrophilic substitution of 1-aminoanthra-9,10-quinone derivatives in ChCl-urea (1 : 2) system [21]: as compared to the traditional organic solvents, like methanol or chloroform, the reaction rate was greatly improved and some groups attributed this to the basic nature of the solvent mixture. Dibrominated products are obtained with a yield ranging from 84 to 95 % at 80°C (Figure 6).

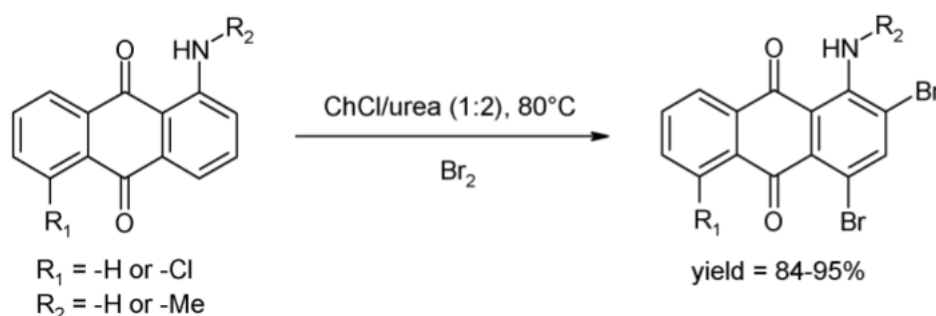


Figure 6 electrophilic substitution of 1-aminoanthra-9,10-quinone derivatives in ChCl-urea (1:2) system

Biocatalysis is a branch of organic chemistry that uses enzymes or similar microbes as catalysts to facilitate reactions such as epoxidations, transesterifications, and C–C bond formation. The use of DESs for biotransformations has not been accurately investigated because strong HBD like urea are known to denature proteins [22]. However, in 2008, Kazlauskas and co-workers studied the first examples of biocatalysis in DESs, analyzing the activity of enzymes in the transesterification of ethyl valerate with butanol. Even if they were poorly soluble in an aqueous solution of ChCl and urea, enzymes were found to be stable in ChCl/urea DESs. The explanation to this phenomenon was ascribed to the hydrogen bond network of deep eutectic solvent that lowered the chemical reactivity of the components towards enzymes. Finally, the activity of enzymes in selected DESs was established to be similar to that observed in toluene, without significant losses in the process efficiency.

1.5.4 Organic Synthesis

The use of green solvents is of great interests and aims at reducing the presence of toxic chemicals: in fact, compared to conventional organic solvents, DESs show low melting points, low volatility, and thus are often non-flammable. Different types of reaction were tested: redox, esterification, condensation, cyclisation and multicomponent with good excellent results. For example, a research group reported the multicomponent synthesis of biologically active dihydropyrimidinone (DHPM) in acidic DESs [23]. The main goal of this experiment is to by-pass the use of Brønsted and Lewis acids which dramatically impact the sustainability of this reaction. DHPM is synthesized from urea, aldehyde and beta-ketoesters, exploiting the use of urea not only as reactant but also as DES component (Figure 7).

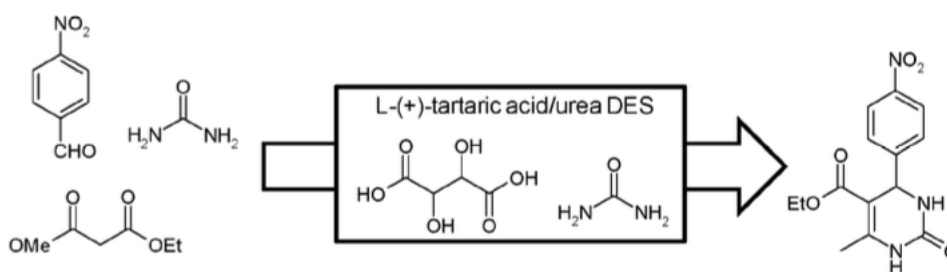


Figure 7 Production of DHPM in DES

Due to an increasing demand of renewable sources, lignocellulosic has gained significant attention as possible alternative to fossil fuels; in this context, a catalytic method to convert cellulose into gluconic acid has been developed in DES, employing FeCl₃ as catalyst in the oxidation step. The process could be applied at industrial scale thanks to the precipitation of products: the use of deep eutectics as reaction media is fundamental to overcome the reuse of FeCl₃. Different DES have been prepared by mixing with FeCl₃ several HBDs obtaining solvents with low viscosity, high conductivity and a relatively high degree of acidity, pivotal to promote the first step of the reaction (hydrolysis of cellulose into monomeric glucose). The optimal conditions were found with a combination of FeCl₃ and ethylene glycol as DES at 120°C, with a final yield equal to 52.7%. Despite DES have low freezing points, high temperatures were required in order to increase selectivity.

2. DISCUSSION AND RESULTS

2.1 RESULTS

All the thesis work has been focused on the synthesis and applications of deep eutectic as solvents in a different type of reactions. Given their great potential in terms of sustainability and easy preparation, DESs are seen as the green media alternative to a series of conventional processes nowadays conducted with toxic solvents. One of these applications is the nucleophilic substitution, a reaction pathway that has been the main topic of the first part of my research work. It is a class of reactions where an electron rich species, known as nucleophile, replaces a functional group inside another electron deficient molecule, called electrophile. Particularly, the object of my study has been the synthesis of azides under different conditions with DES solvents, trying to understand the possible interactions between reactants and this new class of compounds.

2.2 PREPARATION OF DESs

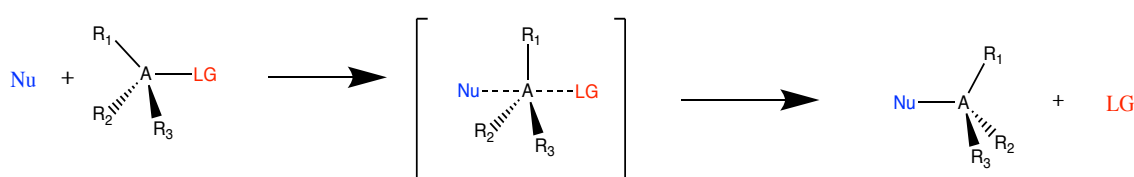
Every deep eutectic solvent used in the experiments is obtained by mixing the two individual components with a continuous stirring (30 min) maintained at the desired temperature (80°C). The hydrogen bond donor and the hydrogen bond acceptor have been mixed according to the molar ratio reported in literature, getting in most cases a transparent liquid phase. Whenever the obtained solution was more viscous, a surplus of heating was applied to ease the preparation and the application of DES solvent inside the reaction (this is the case of betaine and urea). The prepared DESs was cooled and used without any purification, keeping the vessel containing the solution at room temperature. The main solvents used for the experiments are the reported in the table below (Table 5).

DES	HBA	HBD	molar ratio
1	choline chloride	urea	1:2
2	choline chloride	glycolic acid	1:2
3	choline acetate	urea	1:2
4	choline acetate	glycolic acid	1:2
5	betaine	urea	1:3

Table 5 DESs used for the reactions

2.3 MECHANISM OF THE NUCLEOPHILIC SUBSTITUTION

The nucleophilic substitution is the reaction of an electron pair donor (the nucleophile, Nu) with an electron pair acceptor (the electrophile); in order for this process to take place, a sp^3 -hybridized electrophile must have a leaving group (X) able to create the space for the attack of the negatively charged species. There are two different types of mechanism by which the SN (nucleophilic substitution) can take place: S_N1 and S_N2 . The first one consists of a reaction between a single reactant and the solvent, that acts as both the second reactant and catalyst. Instead, bimolecular nucleophilic substitution (S_N2) constitutes one of the most common organic reactions, in chemistry and biology. The nucleophile (Nu) attacks the central atom of a molecule (electrophile) and simultaneously a leaving group (LG) is displaced (Scheme 2).

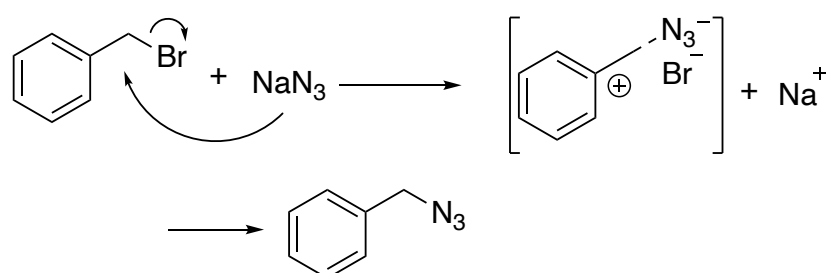


Scheme 2 General mechanism of bimolecular nucleophilic substitution

Halide anions are often used both as nucleophiles and/or leaving groups in studies on S_N2 reactions: fluoride is the best nucleophile, while iodide the best leaving group. Studies have found that nucleophilicity strongly depends on the electron donor capability of the nucleophile (energy and shape of the X np atomic orbital), and the leaving group ability is derived directly from carbon-leaving group (LG) bond strength.

2.4 MODEL REACTION – SODIUM AZIDE AS NUCLEOPHILE

In the first reaction was studied the nucleophilic substitution between benzylbromide and sodium azide; -Br shows good capability as leaving group and, at the same time sodium azide exhibits strong nucleophilic behavior (Scheme 3).



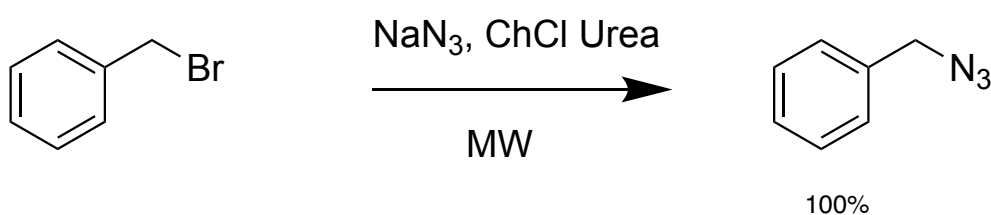
Scheme 3 Synthesis of benzyl azide

This reaction path was performed in a choline chloride – urea (1 : 2) DES solvent. The choice of this type of solvent is strongly related to its high level of polarity; this is a property which must be carefully evaluated before designing a reaction, especially organic reactions since it can affect the solubility of the reactants and change the activation energy drastically. Solvent effects have large influence on the reactivity and mechanisms of nucleophilic substitution reactions, particularly true for ionic systems. For S_N1 mechanism a polar solvent stabilizes transition state and carbocation intermediate, while in a S_N2 substitution a polar solvent is needed to dissolve the nucleophile and to bind the cation, so freeing the nucleophile itself. Solvent molecules form “shells” around reactants and dramatically influence their reactivity.

Most DESs solvents show a good value of polarity, which is crucial for the stabilization of charge separation in the transition state and so in the rate enhancement of the nucleophilic substitution. To test the ability of a deep eutectic solvent as green medium for this kind of reaction, it was taken into consideration choline chloride – urea (1 : 2) as model. The choice of this particular compound has been validated also from the perspective of thermodynamic stability, since ChCl:Urea shows a small percentage of lost mass with a temperature increase. This feature is crucial for the experiments made in the thesis, avoiding a significant dissolution of the solvent due to high values of temperatures.

The choline chloride and urea based DES exhibits one of the lowest percentage of mass loss; for this reason, it was decided to perform the nucleophilic substitution of benzylbromide and sodium azide in ChCl:U considering a range of temperature going from 50 to 100°C, with a mass loss varying from 0.3 to 3.06 %.

It can be seen how the synthesis of benzylazide displays a strange behavior under a thermodynamic perspective (Table 1): time and temperature are strictly dependent from each other, with small yield values with respect to the highest and lowest temperature set for the reaction (50 and 100 °C) but with a completely different amount of time (15 – 60 min). Analyzing these data, temperature represents the most influencing factor for the reaction, which reaches the ideal value of conversion and yield at 60°C for a time equal to 60 min. From now on, these will be the usual conditions adopted during the reaction, performed by irradiation by means of a microwave reactor.



Scheme 4 Model reaction performed

Temperature [°C]	Time [min]	Yield [%]
100	15	41
60	30	86
60	45	51
60	60	100
50	60	35
50	30	87.4

Table 6 Different operating conditions of the reaction

The two phases which the final solution was made of (DES and product) have been separated by means of a separatory funnel, adding at every step a small quantity of water to ease the separation process.

The organic phase has been extracted from the solution using dichloromethane, dried with sodium sulphate and was then concentrated under reduced pressure. The crude product was recovered and the yields were evaluated using ¹H-NMR and GC-MS analyses (Figure 8-9).

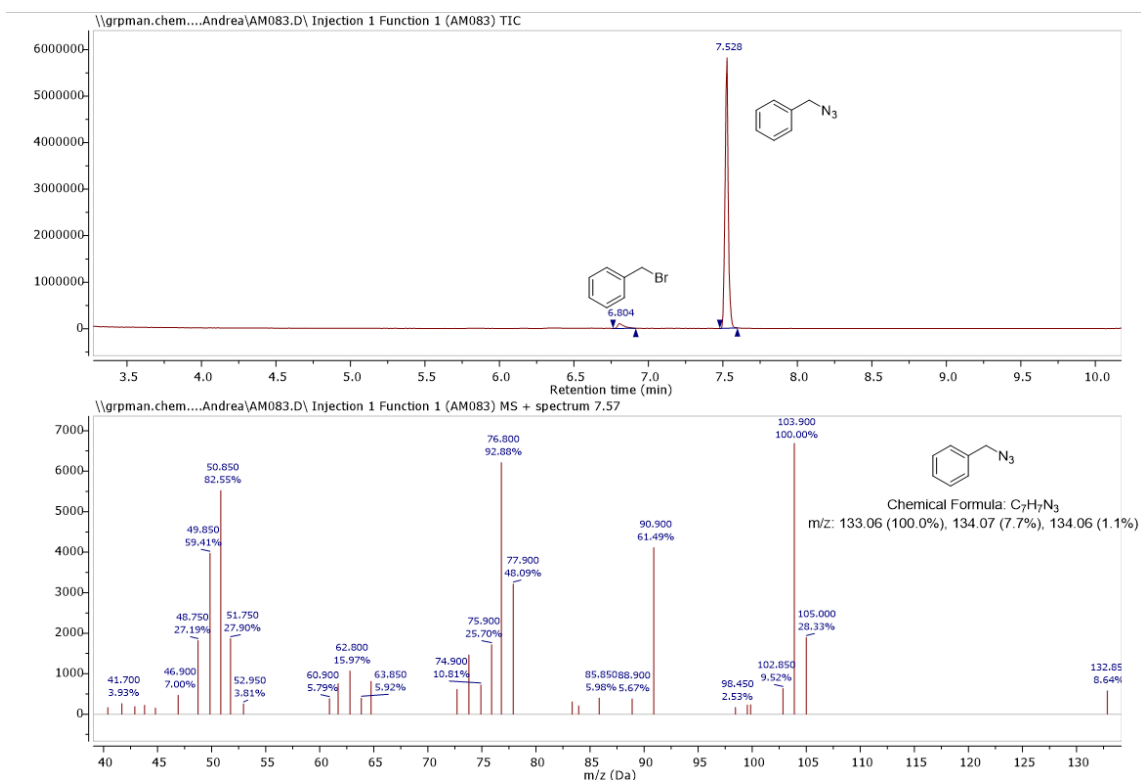


Figure 8 Example of GC-MS spectrum of the model reaction

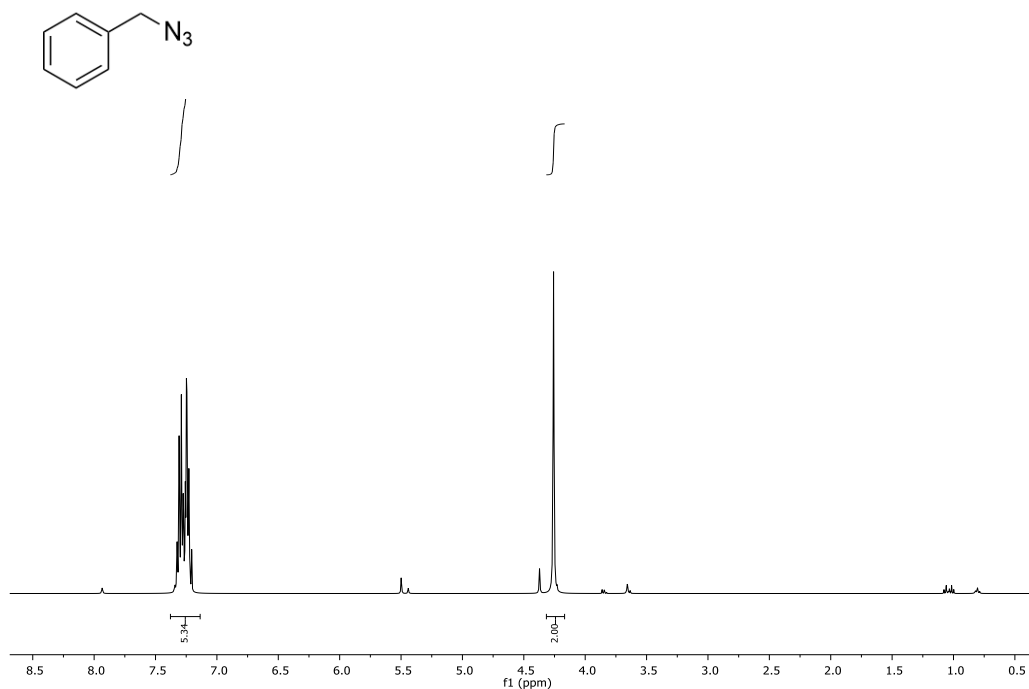
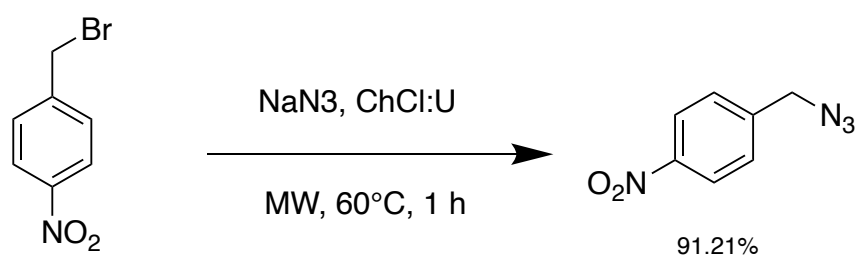


Figure 9 Example of the H-NMR spectrum of the model reaction

2.5 FORMATION OF AZIDES USING DIFFERENT ELECTROPHILIC COMPOUNDS

In order to prove the efficiency of the DESs solvents to carry out nucleophilic substitutions, the first part of the research work has been focused on keeping sodium azide as reactant, showing strong nucleophilic properties and allowing the choice of several electrophiles to work with. For this reason, different types of molecules were considered.

2.5.1 1-(bromomethyl)-4-nitrobenzene



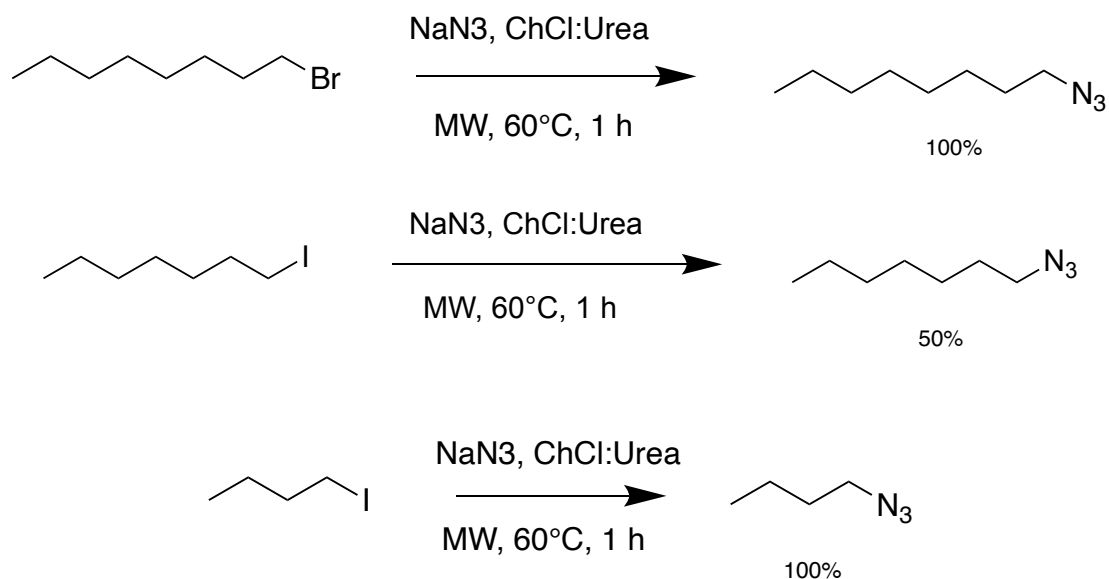
Scheme 5 Synthesis of azide starting from 1-(bromomethyl)-4-nitrobenzene

The same reaction was tried starting from 1-(bromomethyl)-4-nitrobenzene (Scheme 5). The process was conducted by means of a microwave, maintaining a temperature of 60°C for 60 min. The product was then extracted using dichloromethane, dried with sodium sulphate and concentrated under reduced pressure.

The final product was characterized by $^1\text{H-NMR}$ after being dissolved in deuterated chloroform, with a yield equal to 91.21 %.

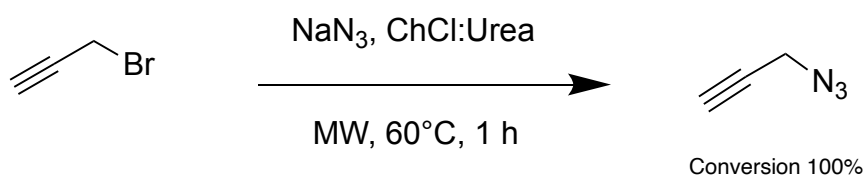
2.5.2 Aliphatic electrophiles

The nucleophilic substitution was tested also starting from aliphatic compounds, to understand the reaction's behavior without the benzene ring. The reactants chosen were 1-bromooctane, 1-iodoheptane and 1-iodobutane using sodium azide as nucleophile (Scheme 6). The yields obtained were respectively equal to 100%, 50% and 100%.



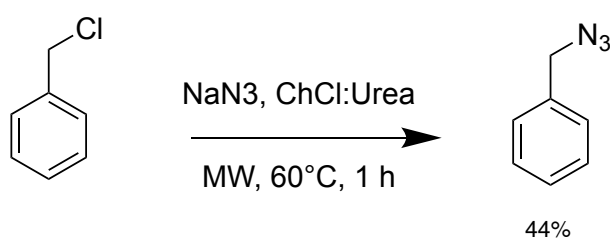
Scheme 6 Nucleophilic substitution on aliphatic compounds

The same reaction was applied to aliphatic reactants like 3-bromoprop-1-yne (Scheme 7). Even if, after the extraction of the organic phase in dichloromethane, drying and characterization by $^1\text{H-NMR}$ the obtained conversion was quantitative, the correspondent yield was instead very low, due to the high volatility of the product. So it has been decided to follow another path of reactions changing the leaving group (Scheme 8).



Scheme 7 Synthesis of 3-azidoprop-1-yne

2.5.3 Electrophiles with chloride substituents

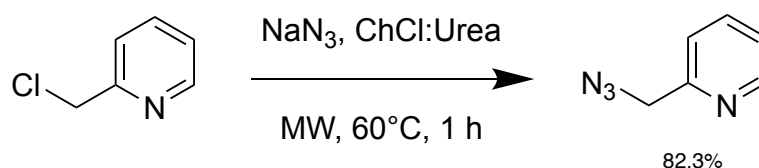


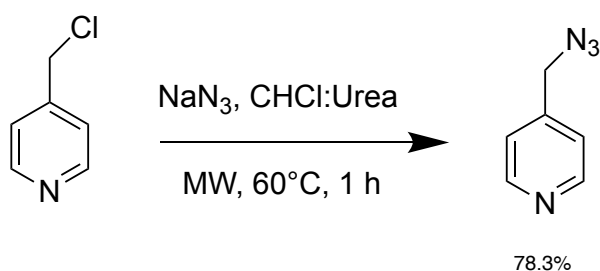
Scheme 8 Reaction involving -Cl as leaving group

As known, -Cl atom exhibits a lower ability as leaving group inside a molecule with respect to -Br. This was confirmed by the results of the $^1\text{H-NMR}$ characterization, with a final yield equal to 44 %.

2.5.4 Nucleophilic substitutions on chloromethyl pyridines

In contrast to benzene ring, pyridine more efficiently supports several nucleophilic substitutions. The main reason for this is the relatively lower electron density of the carbon atoms of the ring. Moreover, this type of reaction could be still enhanced by modifying the pyridine with bromine, chlorine fragments that then become the leaving group. This is what it is done in the research, where a nucleophilic substitution was applied on pyridines in the presence of -Cl attached to a primary carbon atom (Scheme 9).



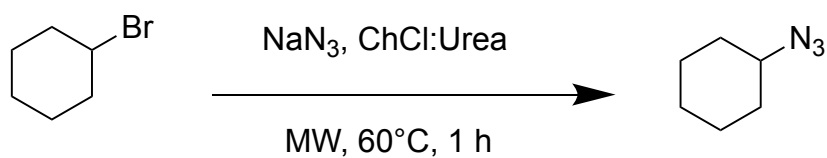


Scheme 9 Nucleophilic substitutions on pyridines with chloride groups

The two reactants used, 2-(chloromethyl)pyridine and 4-(chloromethyl)pyridine, have been treated as the previous cases. After being extracted with DCM, the organic phase was dried using sodium sulphate, concentrated under reduced pressure and characterized by $^1\text{H-NMR}$ analysis. The yields obtained by these experiments are 82.3 and 78.3 %, respectively.

2.5.5 Bromocyclohexane as electrophile

The DES used, choline chloride – urea, was tested in the synthesis of secondary azides, employing as starting material bromocyclohexane and sodium azide (Scheme 10). The operating conditions were the same of the previous procedures. After being treated, the final product has been characterized by GC-MS analysis, showing very low yield whit choline-based DES.



Scheme 10 Synthesis of secondary azide azidocyclohexane

To improve the yield of the reaction performed in choline chloride – urea, the operating conditions were changed, setting the desired time to 3 hours. However, even in this case no good results were obtained after the analysis.

2.6 SUBSTITUTION ON BENZYL BROMIDE USING DIFFERENT NUCLEOPHILES

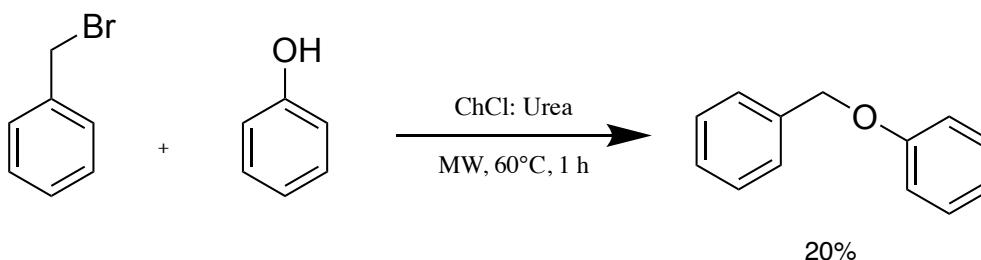
In the previous section, it was proved with a series of reactions how the use of sodium azide (as nucleophile) with different reactants can lead to very good yields for the reaction studied. As the data show, sodium azide exhibits a strong nucleophilic nature and it can carry out the reaction even in presence of a weak electrophile. On the other hand, to complete the characterization of DESs application, it is necessary to understand the behavior of the considered process also varying the nucleophilic unit. For this reason, in the following chapter the attention will be focused on different classes of nucleophiles, keeping as electrophilic compound the same of the model reaction (benzyl bromide).

These procedures led to new classes of molecules like ethers, secondary/tertiary amines and iodides, which were treated with the same separation process conducted for the previous reactions and characterized by $^1\text{H-NMR}$ analysis (Table 7).

Substituent	Yield
Ethers	0
(4-chlorophenyl)methanamine	68
Piperidine	100
Morpholine	100
Potassium iodide	100

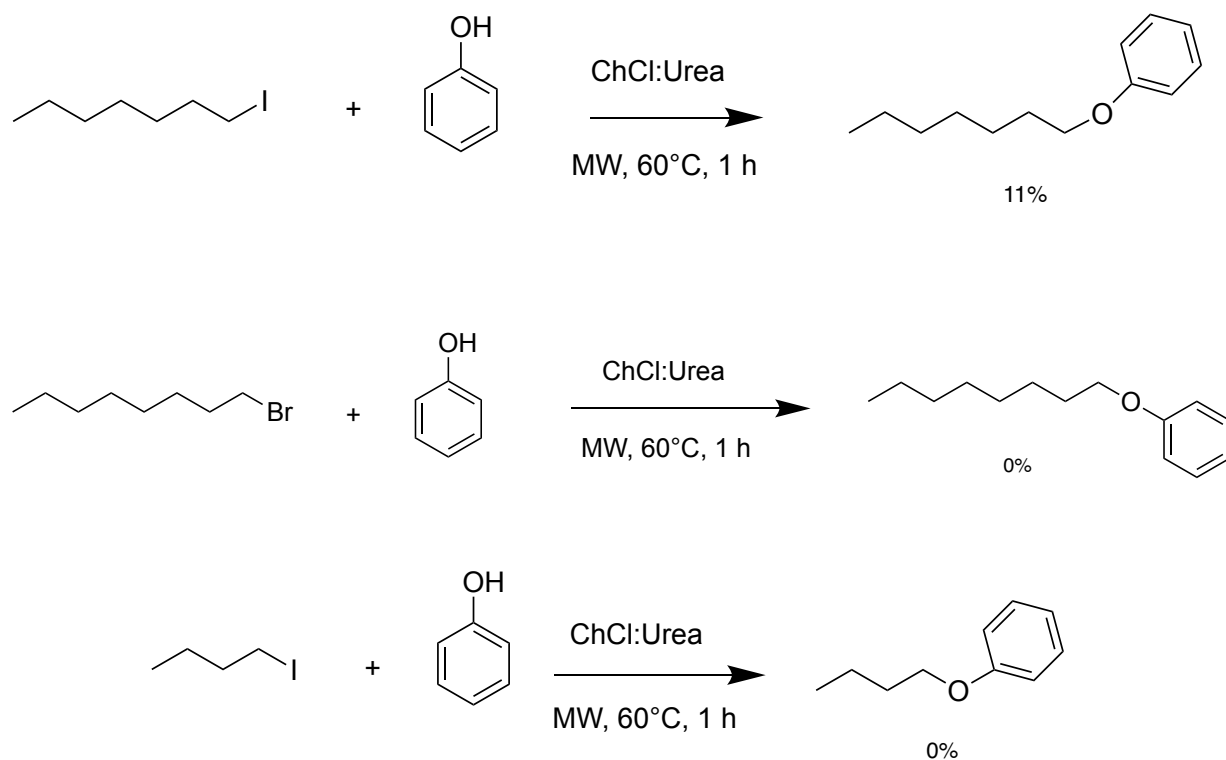
Table 7 Summary of nucleophilic substitutions on benzyl bromide

2.6.1 Phenol



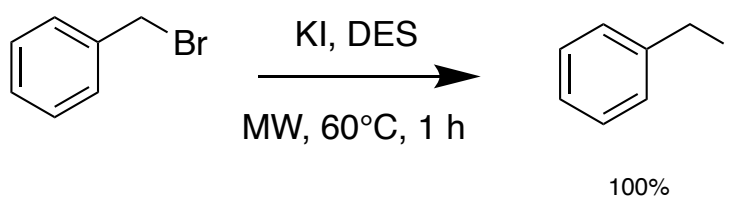
Scheme 11 Synthesis of (benzyloxy)benzene

Another path of reactions followed is the synthesis of ethers (Scheme 11-12). The procedure adopted is the same for the synthesis of azides: the extraction is done using dichloromethane, with the organic phase dried, concentrated and characterized by $^1\text{H-NMR}$ analysis. However, the yield obtained is not very good (20%), because to improve the reaction's mechanism there is the need to add a base to the reactants. The same results were derived starting from 1-bromooctane, 1-iodoheptane and 1-iodobutane (together with phenol), with yields equal to 0%.



Scheme 12 Synthesis using phenol as nucleophile of (heptyloxy)benzene, (octyloxy)benzene and butoxybenzene

2.6.2 Formation of benzyl iodide using different DESs



Scheme 13 Formation of benzyl iodide

As part of the experiments, the nucleophilic substitution was carried out using iodide as nucleophile (KI, Scheme 13). The lone pair of electrons on this larger, less basic atom interact less tightly with the protons of the solvent molecules; for this reason, I^- is better able to break free from its solvent cage compared to smaller and more basic anions like fluoride or bromide. In other words, the electron density of this Nu can be more easily given to another molecule. The reaction was made in two different DES solvents, with the following yields (Table 8).

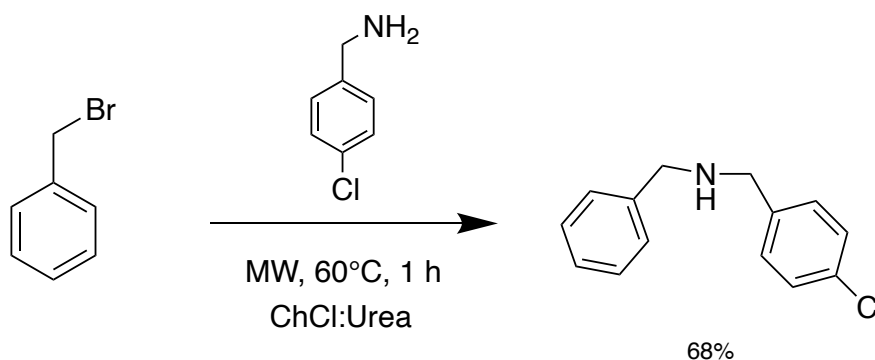
HBA	HBD	Yield
choline chloride	Urea	100
choline acetate	Glycolic acid	100

Table 8 Different DESs used for nucleophilic substitution of benzyl bromide with potassium iodide

2.6.3 (4-chlorophenyl)methanamine

Another class of reaction taken into consideration is the nucleophile substitution of aromatic and aliphatic components with primary amines to get as product secondary amines. Generally, amines can work as good nucleophiles, even if this is not the case since the lone pair of electrons of nitrogen are stabilized by the benzene ring: however, the reaction is performed by using reactants which act as strong electrophiles such as benzyl bromide (Scheme 14). The choice of molecules containing bromide group is warranted by the fact that, being weak basic halides, they are capable of stabilizing the negative charge so becoming favorable leaving groups.

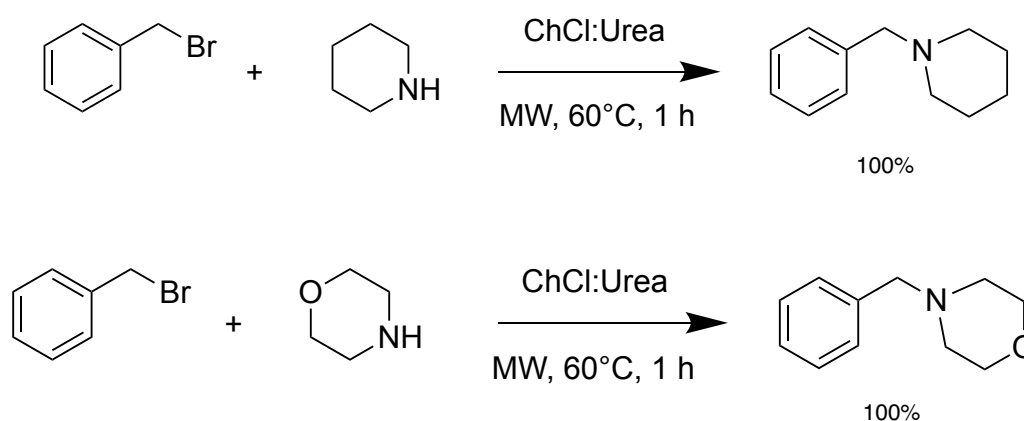
The nucleophilic substitution done, following the usual operating conditions and procedure, is reported in the following scheme. The yield obtained is good (68%).



Scheme 14 Formation of secondary amine

2.6.4 Piperidine and morpholine - synthesis of tertiary amines

In order to get tertiary amines, two other reactants were used as nucleophiles: piperidine and morpholine (Scheme 15). The presence of the lone pair of electrons on the nitrogen atom gives these molecules a high degree of nucleophilicity, even if the oxygen atom of the morpholine acts as electro-withdrawing group. The effect of oxygen on the electrodensity of the ring is not significant, because the yields for the two performed reactions are both quantitative (100%), as shown by the characterization made by means of GC-MS analysis.



Scheme 15 Nucleophilic substitution using piperidine and morpholine as nucleophiles

2.7 RECYCLING OF DEEP EUTECTIC SOLVENTS

The application of deep eutectic solvents as solvent/catalyst for a series of different reactions has demonstrated the great potential DESs have in terms of sustainability and efficacy. Their use as media for nucleophilic substitutions and oxidations foresees a possible scale up inside industries, with the opportunity to avoid the handling of toxic components and the improvement of treatment/disposal technologies. Moreover, as verified by the experiment's data (Figure 8), the activity of a DES solvent for a generic reaction does not show a worsening trend if employed in a cycle of synthesis in series. In fact, the benchmark synthesis of benzyl azide was performed starting from benzyl bromide and sodium azide in choline chloride – urea DES, for three consecutive times, trying to recover for each reaction the amount of solvent used in the previous step.

Even if the procedure were stopped after the third recycle, due to complications related to the tools used for the extraction, the characterization of each final product made by GC-MS analysis shows great results in terms of yield. This means not only the possibility of a multiple reuse of DES solvents, but also the opportunity of saving water from the extraction procedure to enhance the phase separation.

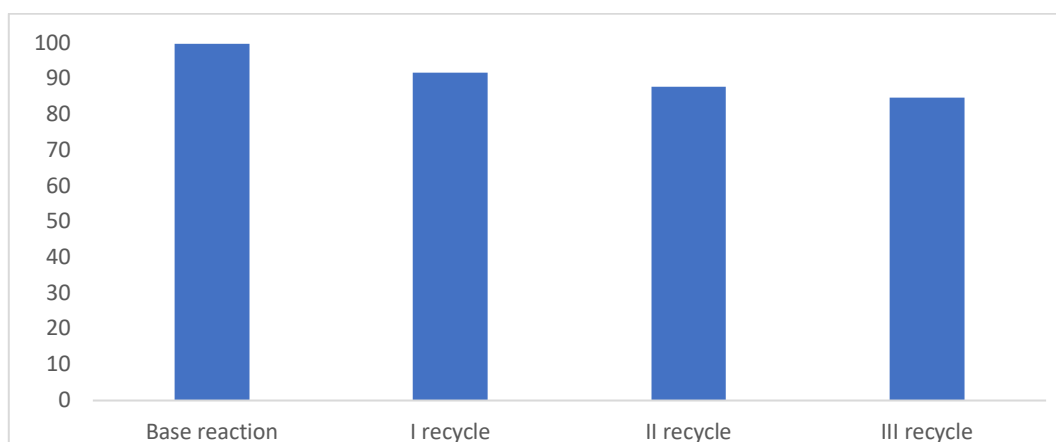


Figure 10 Yields for the recycle of DES

2.8 GENERAL BEHAVIOR OF DESs AS MEDIA FOR NUCLEOPHILIC SUBSTITUTIONS

Taking into consideration the aforementioned results, carrying out a nucleophilic substitution using DESs relies on a series of different factors, including both the nucleophile and the electrophile. The initial part of the experiments was focused on the use of the strongest nucleophile considered (sodium azide) and one of the most reactive electrophile unit (benzyl bromide) to prove the capability of the DESs as solvent in the optimal conditions. The quantitative yield obtained by this model reaction shows the possibility to exploit choline chloride – based DESs, which then have been used considering different reactants. Together with sodium azide, compounds containing good leaving groups like iodide or bromide showed high yields for the substitution, making molecules like 1-(bromomethyl)-4-nitrobenzene, 1-bromooctane, 1-iodobutane very good electrophiles. Choosing a less reactive leaving group, for example chloride, the results were not so satisfactory as the reaction with benzyl chloride verified. However, with the addition inside the benzene ring of a nitrogen atom, the electrodensity of a specific molecule could be decreased, with a pair of lone electrons ready to be donated: this is what happened considering as reactants pyridines. On the other hand, changing the nucleophile of the reaction brought to very different results: weak nucleophiles like phenol are not capable of completing the substitution and needs the presence of a base. Contrarily, reactants such as potassium iodide, piperidine, morpholine and 4-(chlorophenyl)methanamine give strong results thanks to the presence of lone pair of electrons that can be given to the electrophilic unit. The following table aims at summarizing all these considerations, with molecules reported according to a decreasing scale of nucleophilicity/electrophilicity (Table 9).

In some particular case, where the reaction is performed in the presence of a weak nucleophile as well as a weak electrophile, it may undergo a competitive substitution due to the presence of the chloride group inside the ChCl – urea solvent. In order to avoid this, the use of a different DES not containing the leaving group is suggested, for example betaine and urea.

The research work studied the application of deep eutectic solvents not only as solvents but also catalysts. In fact, choline chloride and choline acetate – based DESs have been used together with an electrophile, in this case benzyl bromide, to see if they can act as both solvent and nucleophile.

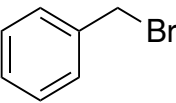

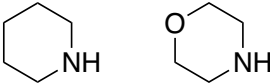
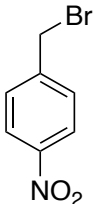
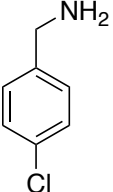
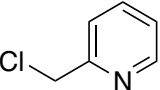
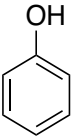
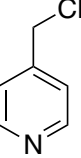
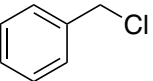
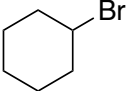
Nucleophile	Electrophile
NaN_3	
KI	
	
	
	
	
	

Table 9 List of nucleophiles and electrophiles according to their strength

2.9 INDUSTRIAL APPLICATIONS OF DESs

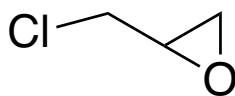
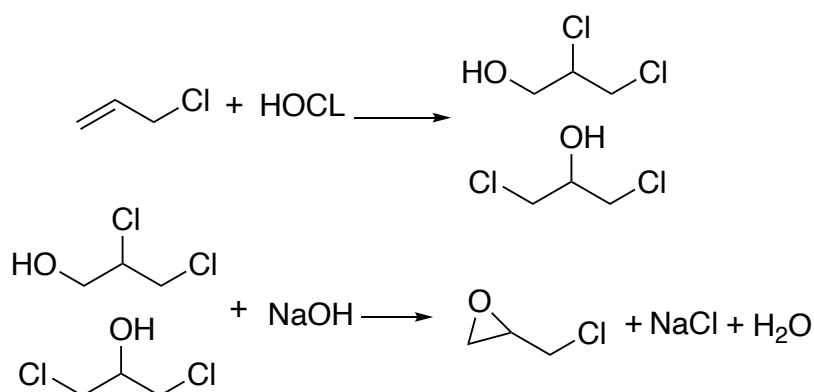


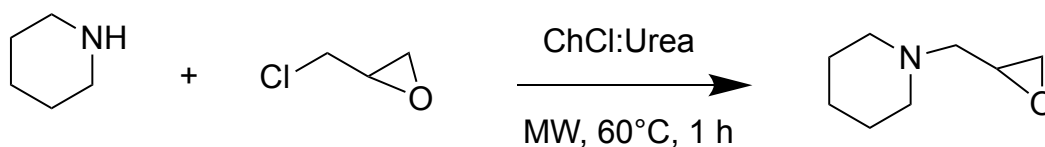
Figure 11 Epichlorohydrin molecule

Epichlorohydrin is an organochlorine compound and an epoxide (Figure 9). It's a highly reactive electrophilic compound, used together with piperidine to perform nucleophilic substitution and formation of a tertiary amine. It is traditionally manufactured from allyl chloride with the addition of hypochlorous acid, which form two isomeric alcohols. In a second step, the mixture is treated with a base to give the epoxide (Scheme 16).



Scheme 16 Production of epichlorohydrin

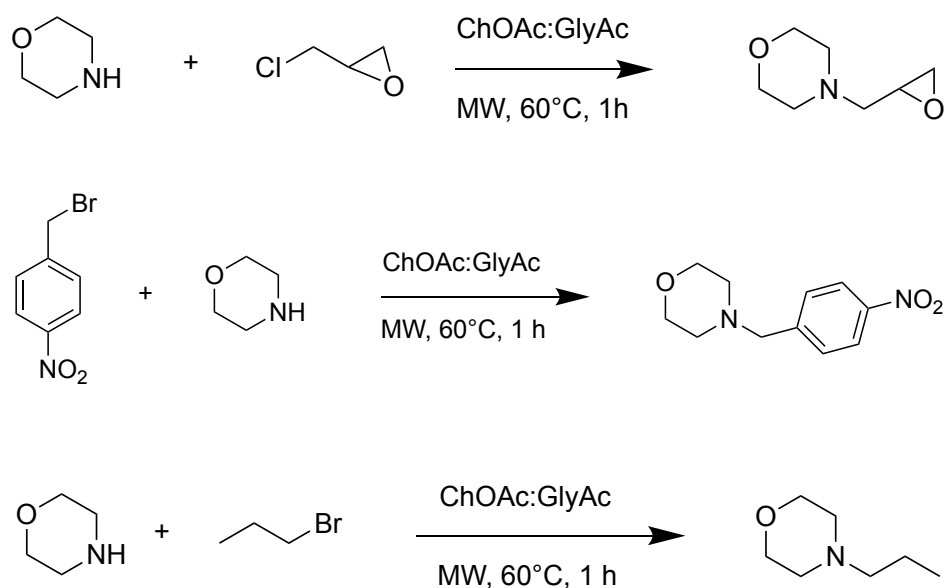
The use of epichlorohydrin is crucial for the production of synthetic glycerol, mainly used in pharmaceutical and biotech applications where the required standards are high. The proposed reaction has been performed involving ECH and piperidine with the usual conditions in ChCl:Urea DES (Scheme 17); after being extracted by means of DCM, the organic phase was dried with sodium sulphate and then characterized by GC-MS analysis.



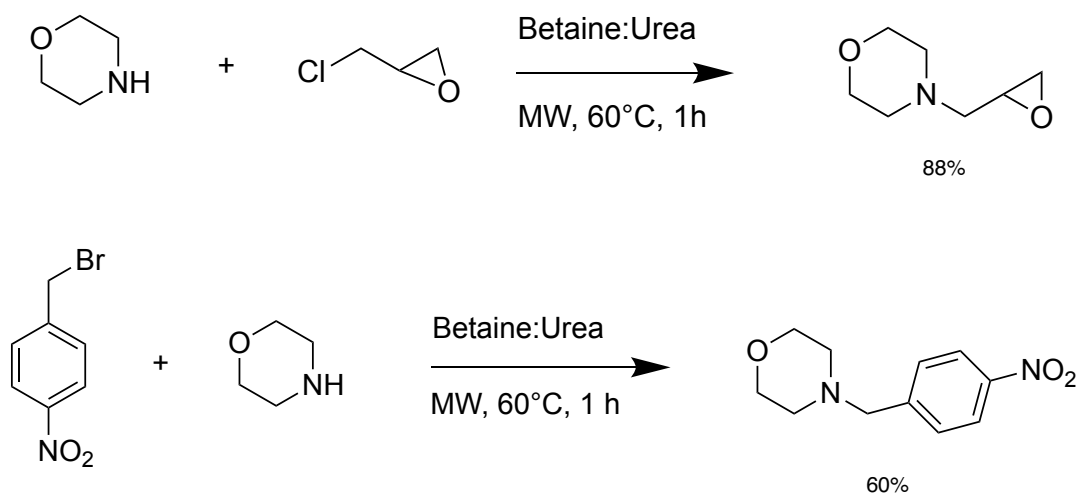
Scheme 17 Synthesis of 1-(oxiran-2-ylmethyl)piperidine

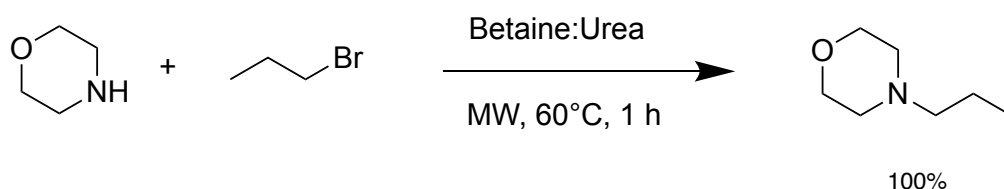
2.9.1 Use of morpholine as electrophile for the synthesis of tertiary amines

The formation of tertiary amines has been investigated not only in choline chloride-based DES; other solvents were tried to study the behavior of the reaction and the relative yield. The two mixtures prepared for the experiment are: choline acetate and glycolic acid, betaine and urea. The first solution exhibits physical features similar to ChCl and urea, while for the use of the second one a constant heating and stirring was needed to set up the vial and the reaction in the microwave. The following schemes (18-19) summarize the results obtained, with very good yield values, after the product solution was treated according to the usual procedure.



Scheme 18 Synthesis of tertiary amines in choline acetate – glycolic acid DES





Scheme 19 Synthesis of tertiary amines in betaine – urea DESs

The yields of the reactions performed in betaine and urea were good and equal to 88%, 60% and 100%.

2.9.2 Production of pharmaceutical molecules

The importance of these good results obtained with morpholine in betaine – urea goes further the lab scale, since this procedure could be in principle applied to the syntheses of several tertiary amines which constitutes common pharmaceutical compounds. Deep eutectic solvents might be used as media to produce for example haloperidol and benproperine, respectively a medicine employed to treat schizophrenia and a cough suppressant. Another molecule that can be synthesized is metopimazine, an antiemetic of the phenothiazine group which is used to treat nausea and vomiting (Figure 10).

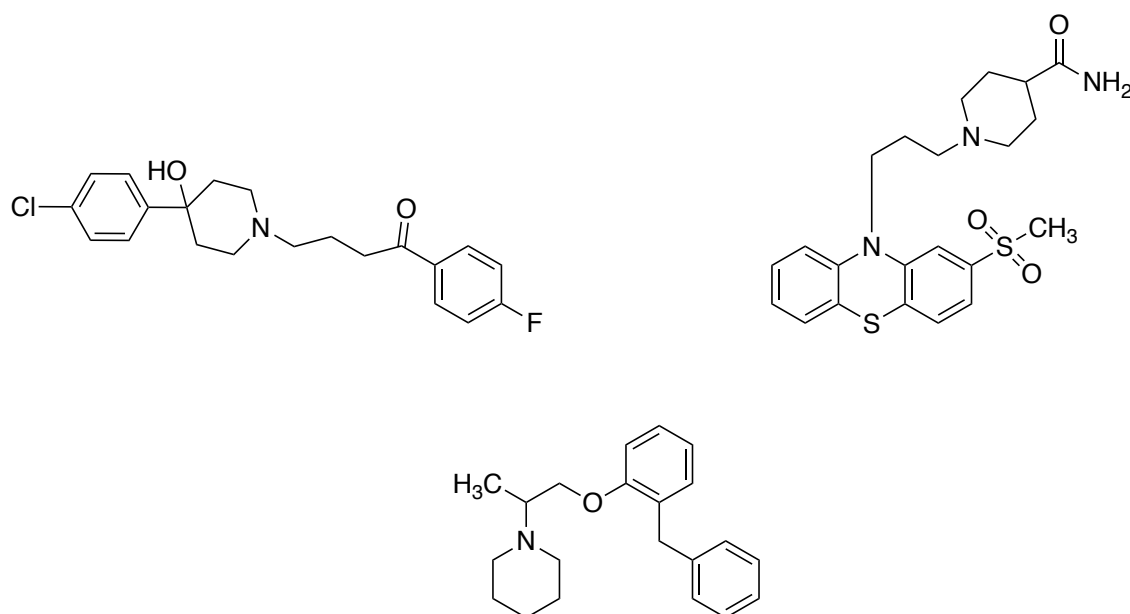
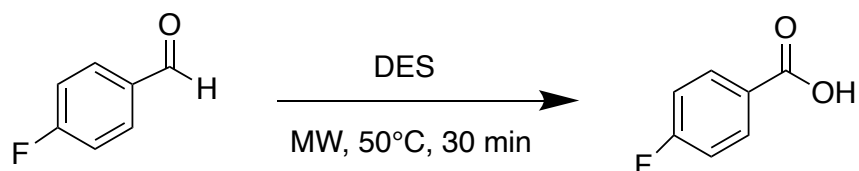


Figure 12 Tertiary amines used as pharmaceutical compounds

2.10 Oxidations in deep eutectic solvents

Another course of reactions studied is the one regarding oxidations; 4-fluorobenzaldehyde was used as starting material and dissolved in a DES solvent (Scheme 20). After the reaction was completed, the procedure followed consisted of extraction of the organic phase with ethyl acetate, drying with sodium sulphate and concentration of the solution under reduced pressure. The final product was then dissolved in deuterated chloroform and characterized by $^1\text{H-NMR}$ analysis.



Scheme 20 Oxidation of 4-fluorobenzaldehyde

The results obtained by the analysis were very good in terms of yield, for each of the four DESs used to carry out the reaction (Table 10); this exhibits a high capability of a DES to oxidize an aromatic compound acting both as solvent and catalyst.

DES used	Yield
ChCl - Urea	75
ChOAc -Urea	100
ChCl - glycolic acid	75
ChOAc - glycolic acid	92

Table 10 Yields obtained in the oxidation process for each DES

3. CONCLUSIONS

3.1 FINAL COMMENTS AND FUTURE TRENDS

The aim of the research was to highlight the properties of deep eutectic solvents and their possible applications as alternative media to perform a series of different reactions. The first part of the experiments was focused on the preparation of DESs, which has resulted much easier if compared to the preparation of common solvents used in industrial application (such as ionic liquids). The eutectic point has been reached by mixing the two starting individual components at a specific molar ratio and by then stirring them at a constant temperature (80°C) for the desired time (30 min). The most important solvents studied, choline chloride – based DESs, have been used to explore a precise class of reactions, in order to understand the behavior of this new type of media: the nucleophilic substitution. The model reaction performed, using benzyl bromide and sodium azide, showed very good results in terms of yield so paving the way to several reactions where other electrophiles and nucleophiles were used. To completely characterize the features of deep eutectic solvents it has been necessary to test molecules with different nucleophilic and electrophilic strength.

Following the model case, the reaction was performed starting from substituted benzyl bromide, aliphatic electrophiles, benzyl chloride and pyridines. The main result obtained was the possibility of reaching a good yield regardless the strength of the different leaving groups contained by the electrophile compound. Bromide, chloride and iodide led to the completion of the substitution in presence of a strong nucleophile such as sodium azide.

In the second part of the study, very reactive atom groups in reactants like potassium iodide, primary amines, piperidine and morpholine triggered a good response by the solvent, in which the substitution of benzyl bromide has been always favored in ChCl and urea. These results would be still more promising if the substitution was applied to molecules like epichlorohydrin for the formation of intermediate compounds in pharmaceutical processes. One of the main goals of future research will be the possible scale up of these procedures to the industrial scale, which would mean a significant step towards economic and environmental sustainability. Employing DESs as alternative to conventional liquids, such as ILs, would strongly reduce the toxicity of the chemical components used and would let the producer start a recycle of the solvent, saving time and economic resources.

4. SYNTHETIC PROCEDURES

4.1 GENERAL INFORMATION

4.1.1 DES preparation

DES were prepared according to one of the most common procedures reported in the literature. The preparation of a generic DES involved the combination of a HBA (hydrogen bond acceptor) with a HBD (hydrogen bond donor), according to the molar ratio reported in the following table. These mixtures were stirred for 30 min until a homogeneous and transparent solution was formed. The prepared DES were cooled and used without any purification.

DES	HBA	HBD	molar ratio
1	choline chloride	urea	1:2
2	choline chloride	glycolic acid	1:2
3	choline acetate	urea	1:2
4	choline acetate	glycolic acid	1:2
5	betaine	urea	1:3

Table 11 DESs used for the experiments

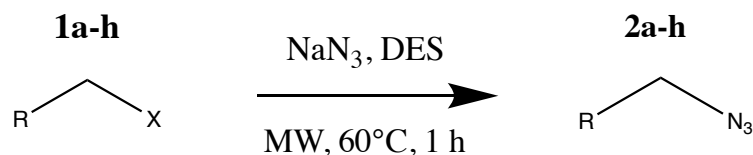
4.1.2 NMR spectroscopy

All products were characterized by ¹H-NMR spectroscopy. The ¹H NMR spectra were recorded on a Bruker ARS 400 spectrometer (¹H NMR, 400 MHz). The spectra were registered at room temperature, otherwise indicated, in deuterated solvents, with chloroform-d used as the internal standard. ¹H NMR spectra are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signals), coupling constant and number of protons.

4.1.3 GC-MS

GC-MS analyses were performed using an Agilent HP-6890 gas-chromatograph equipped with a 5973 mass detector, and an Agilent HP-5MS column (30 m x 0.25 mm, 0.25 μm film thickness) with the following temperature program: 60°C (1min) - 6°C/min - 150°C (1min) - 12°C/min - 280°C (5min); carrier gas, He; constant flow 1mL/min; split ratio, 1/30; *rt* given in minutes.

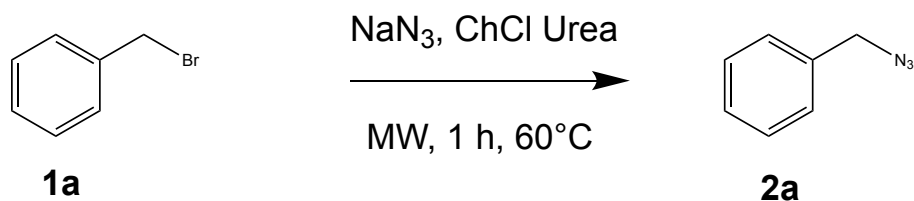
4.2 GENERAL PROCEDURE FOR THE SYNTHESIS OF AZIDES IN DESs (2a-h)



- 1a** R=-Ph; X=-Br
- 1b** R=-4NO₂Ph; X=-Br
- 1c** R=-Ph; X=-Cl
- 1d** R=-2Py; X=-Cl
- 1e** R=-4Py; X=-Cl
- 1f** R=-(CH₂)₆CH₃; X=-Br
- 1g** R=-(CH₂)₅CH₃; X=-I
- 1h** R=-(CH₂)CH₃; X=-I
- 2a** R=-Ph
- 2b** R=-4NO₂Ph
- 2c** R=-Ph
- 2d** R=-2Py
- 2e** R=-4Py
- 2f** R=-(CH₂)₆CH₃
- 2g** R=-(CH₂)₅CH₃
- 2h** R=-(CH₂)CH₃

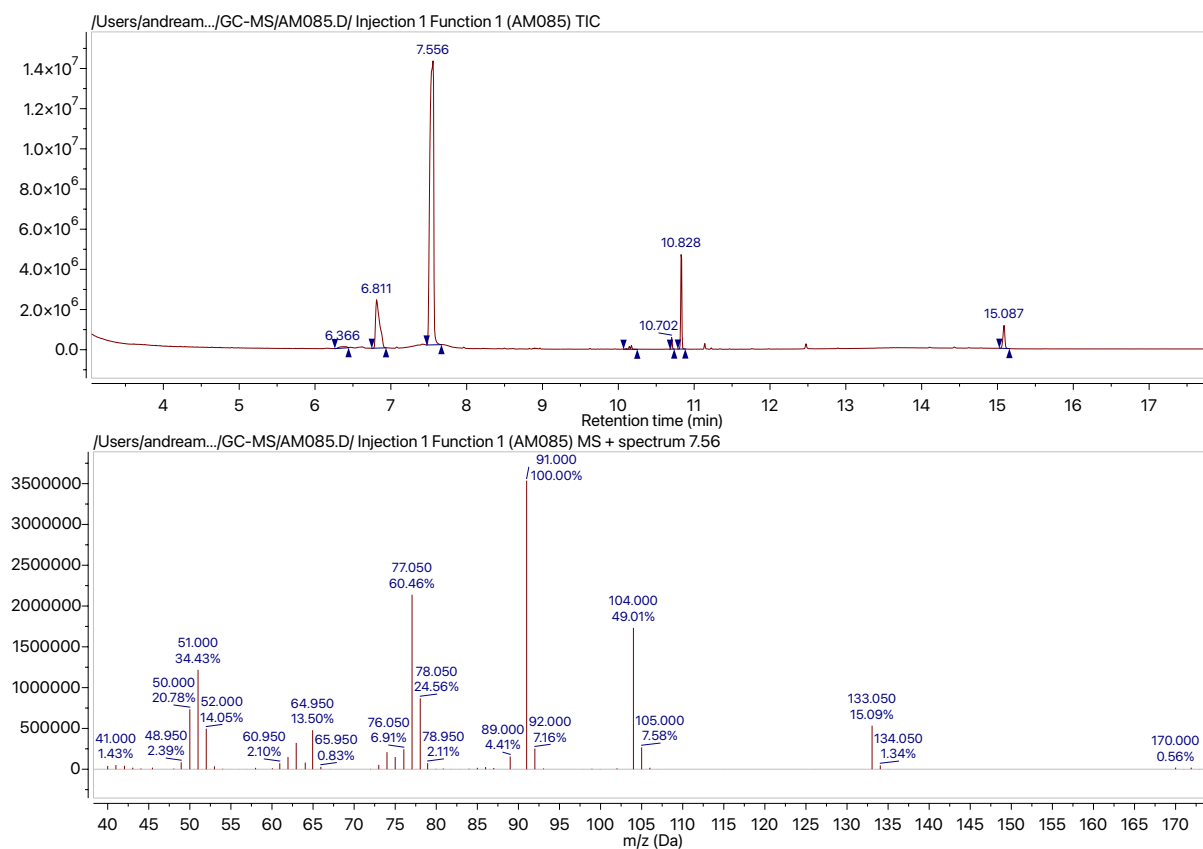
The selected compound **1**, bearing the X (X = Cl, Br, I) group (100 mg, 1 equivalent), was dissolved in 800 mg of DES1 (ChCl - Urea); sodium azide (2 equivalents) was then added to the solution. The reaction was performed under irradiation, by means of a BIOTAGE® Initiator 2.5 microwave, at 60°C for 1 hour. The organic product was extracted using DCM. The combined organic phases were dried over Na₂SO₄. The organic phase was then concentrated under vacuum to obtain the crude product. It was dissolved in a proper solvent for analysis to study the reaction performance.

4.2.1 (Azidomethyl)benzene (2a)

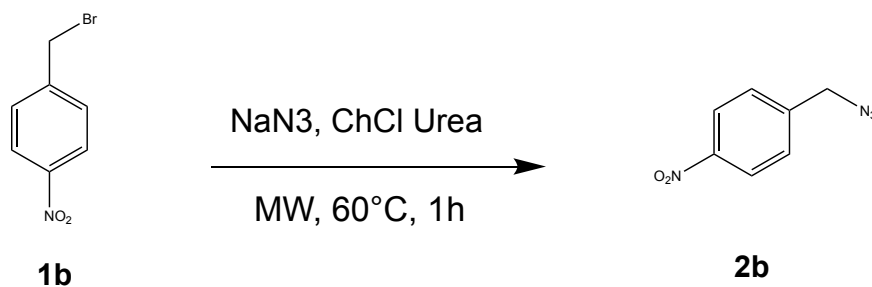


The reaction was checked by GC-MS analysis. The spectrum is in agreement with literature data.

m/z 133.06 (100%), 134.07 (7.7%), 134.06 (1.1%)



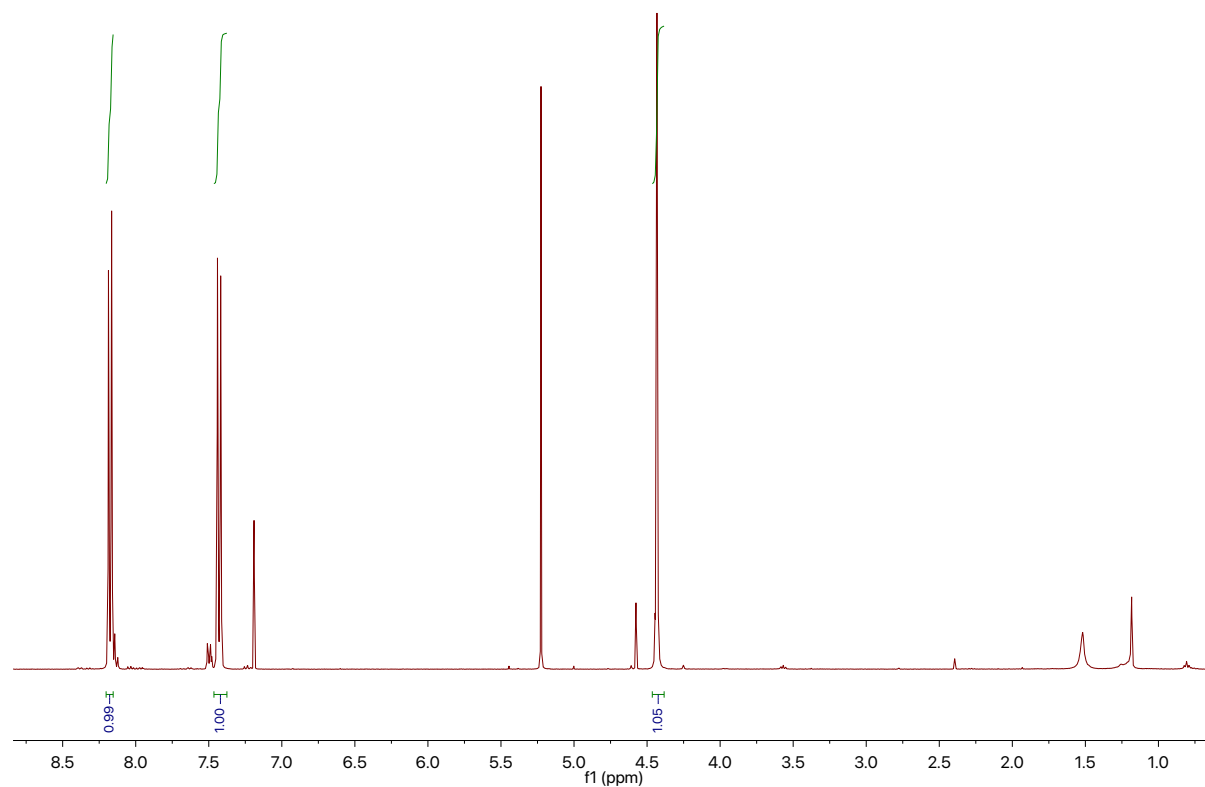
4.2.2 1-(azidomethyl)-4-nitrobenzene (2b)



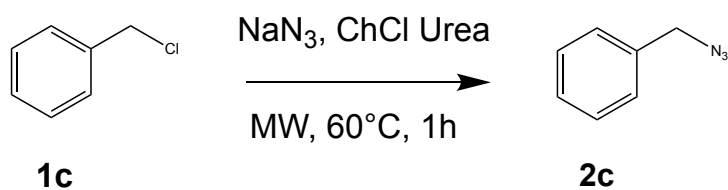
The reaction was checked by $^1\text{H-NMR}$ analysis.

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.22 (d, $J = 8.7$ Hz, 2H, $H_3; H_5$), 7.50 (d, $J = 8.7$ Hz, 2H, $H_2; H_6$), 4.51 (s, 2H, H_1).

The spectrum is in agreement with literature data.

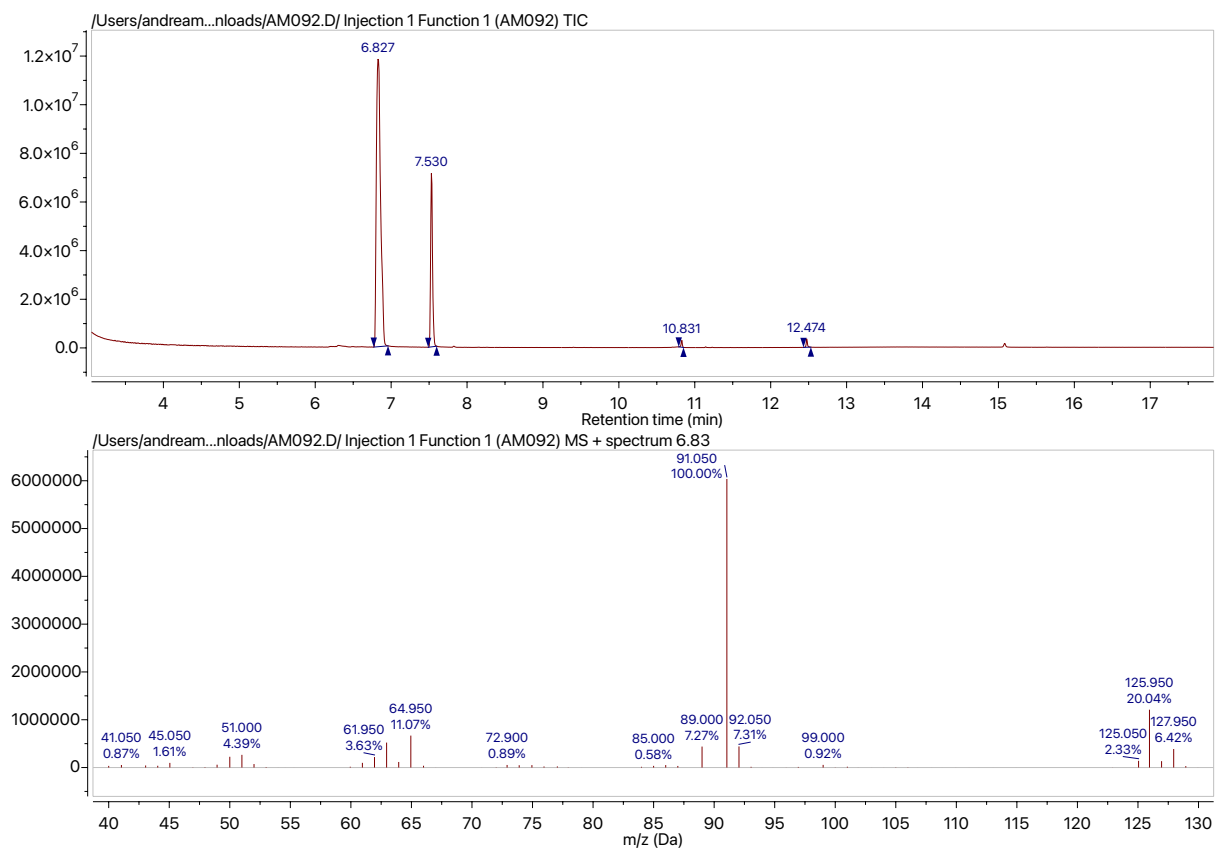


4.2.3 (azidomethyl)benzene (2c)

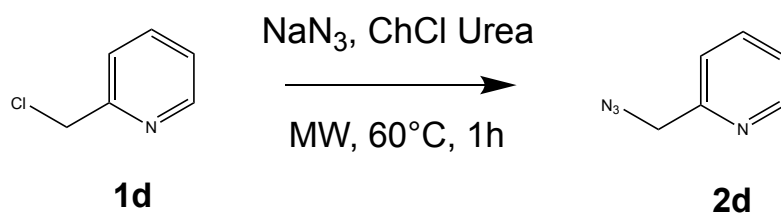


The reaction was checked by GC-MS analysis. The spectrum is in agreement with literature data.

m/z 133.06 (100%), 134.07 (7.7%), 134.06 (1.1%)



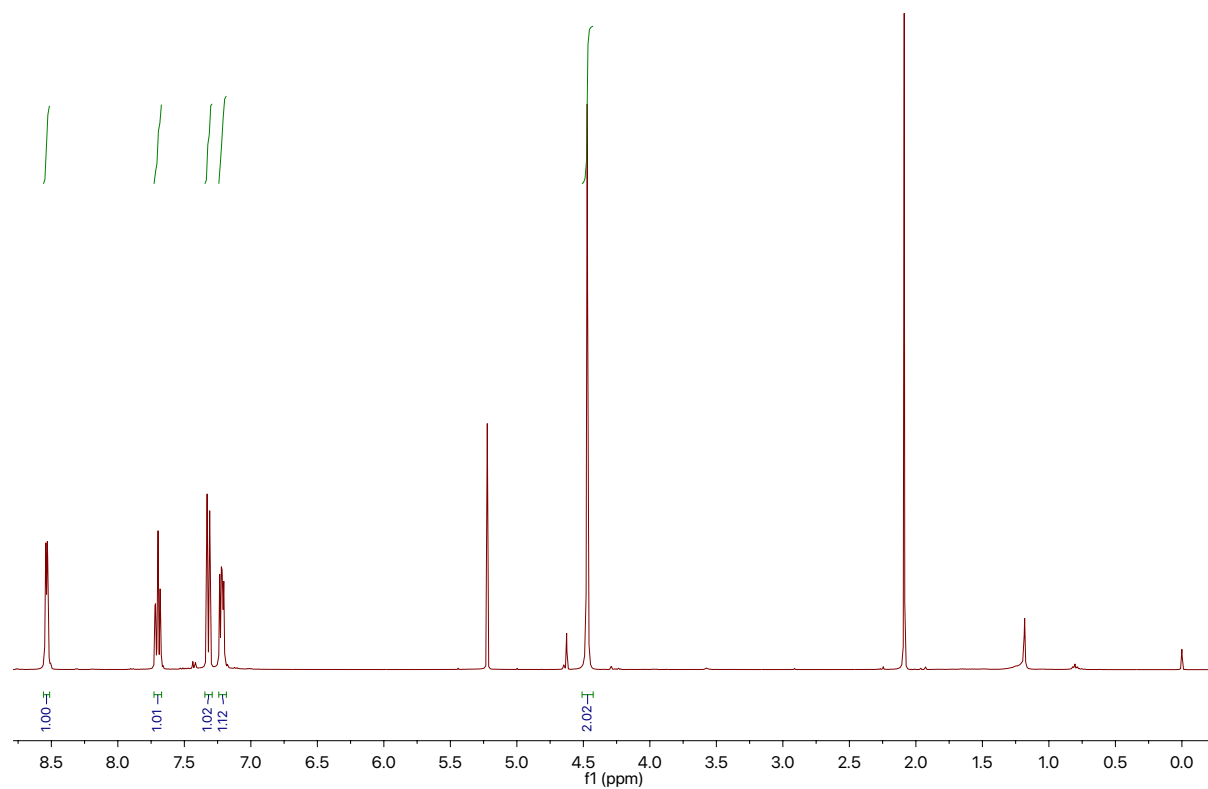
4.2.4 2-(azidomethyl)pyridine (2d)



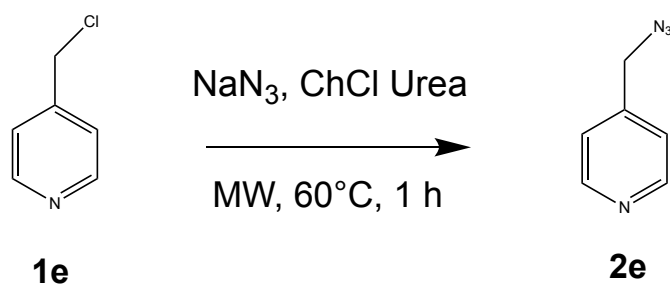
The reaction was checked by means of $^1\text{H-NMR}$ analysis.

The spectrum is in agreement with literature data.

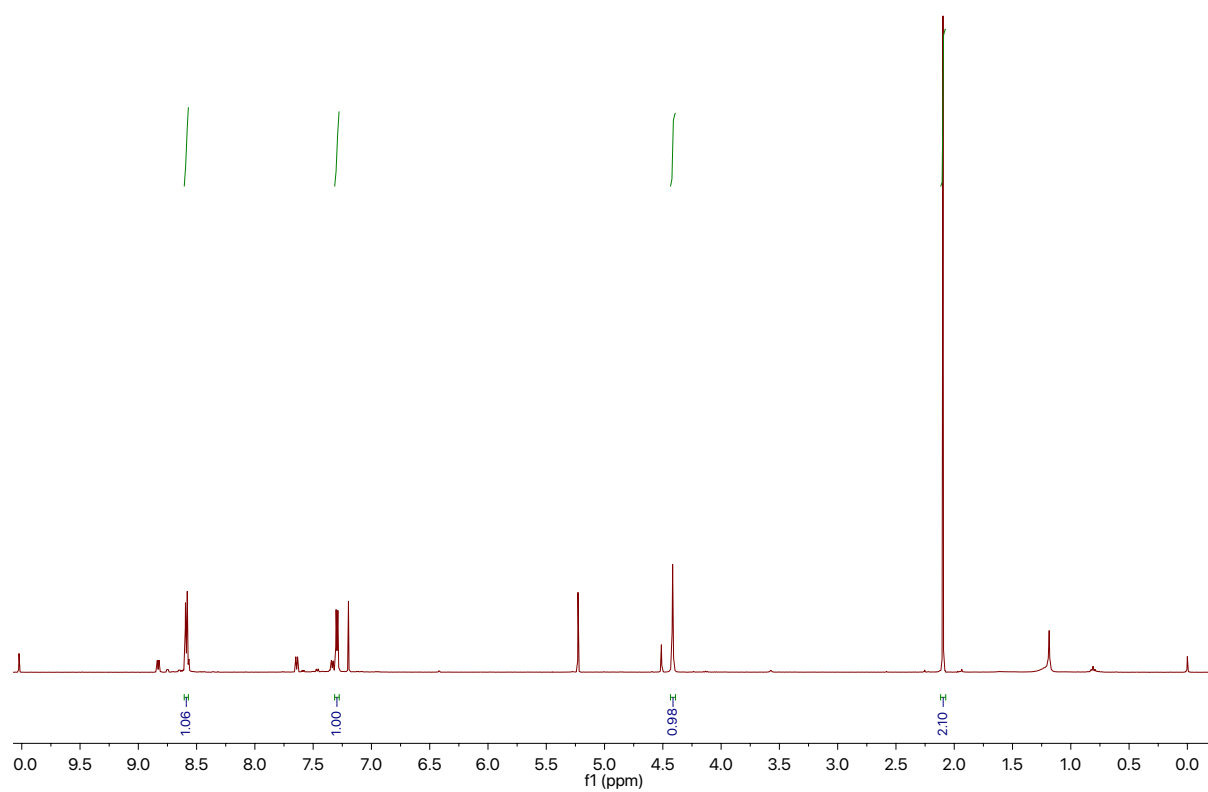
m/z 134.06 (100%), 135.06 (8%)



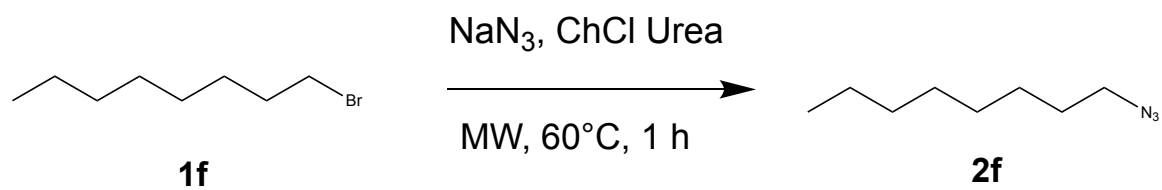
4.2.5 4-(azidomethyl)pyridine (**2e**)



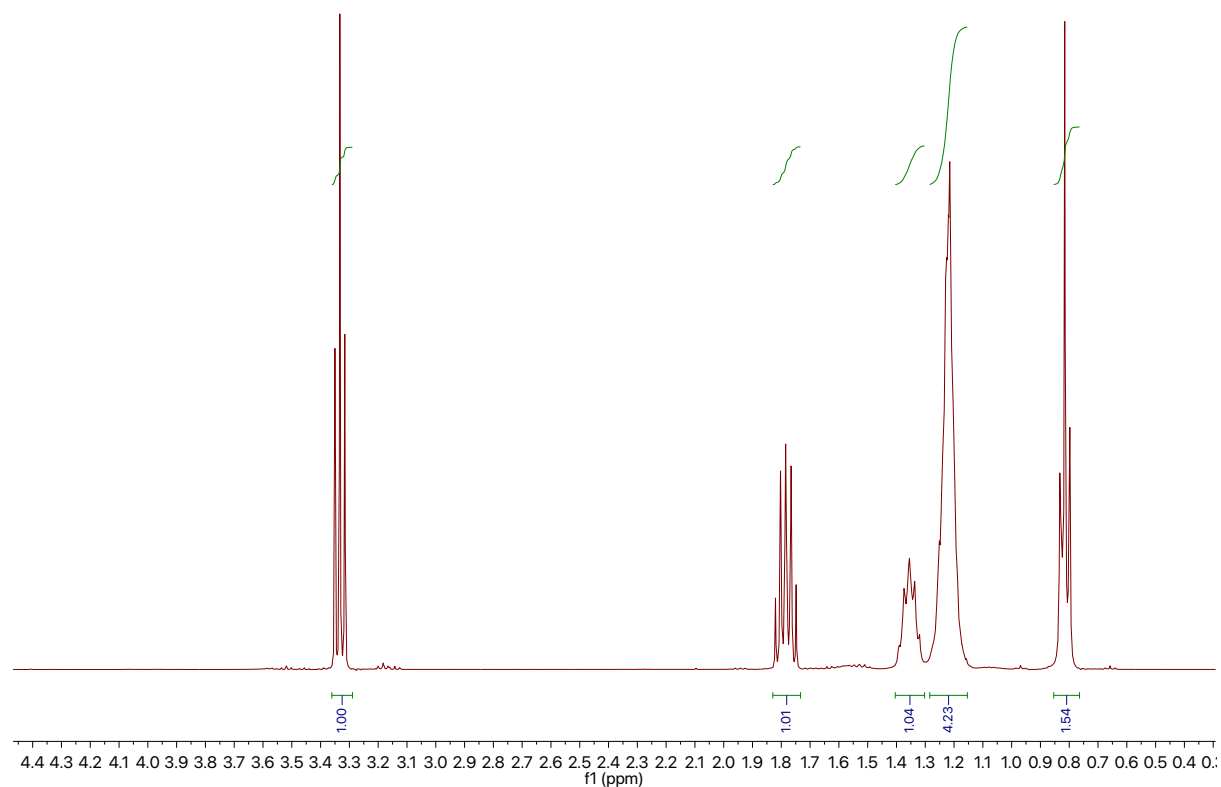
The reaction was checked by $^1\text{H-NMR}$ analysis. The spectrum is in agreement with literature data.



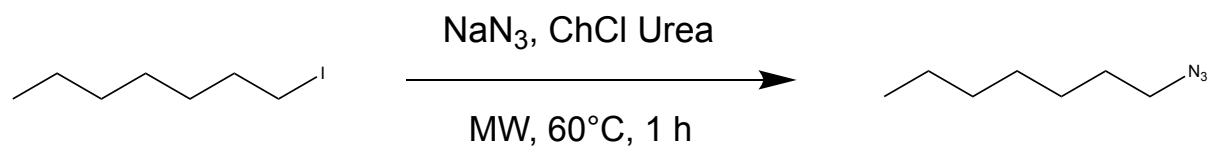
4.2.6 1-azidoctane (2f)



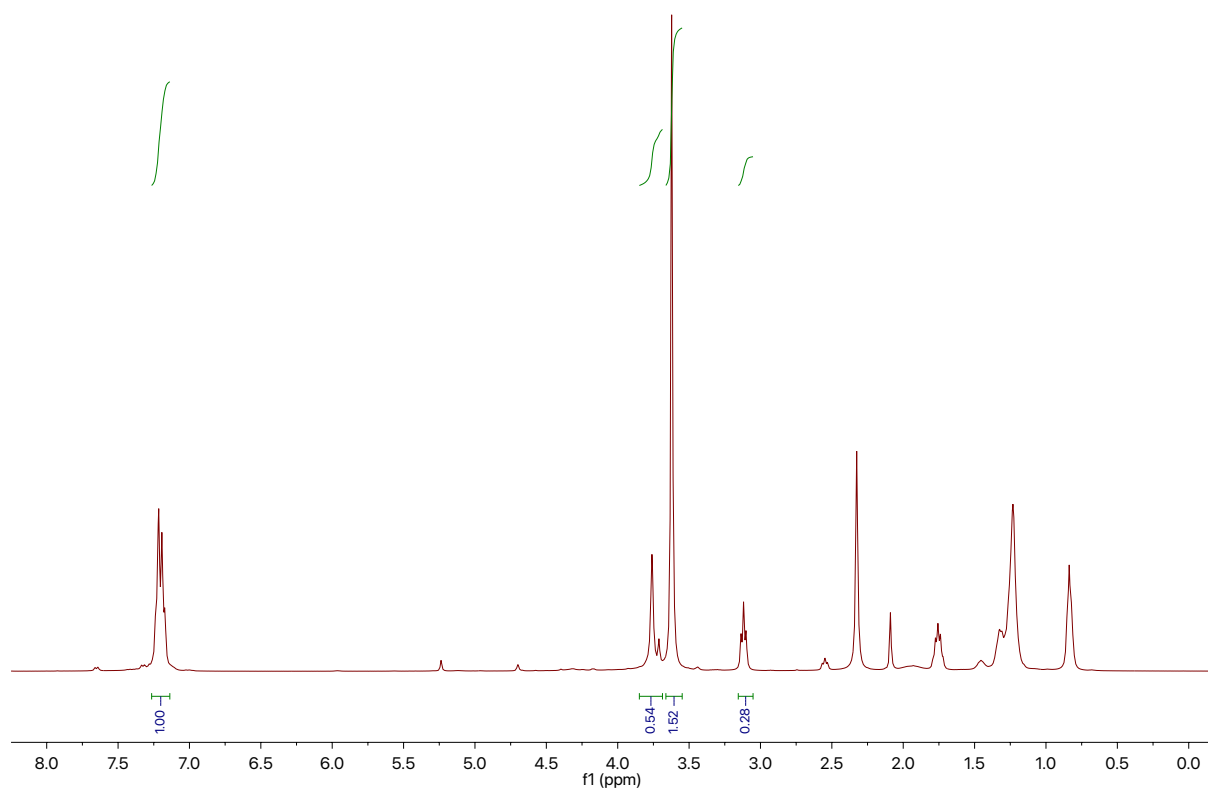
The reaction was checked by $^1\text{H-NMR}$ analysis. The spectrum is in agreement with literature data.



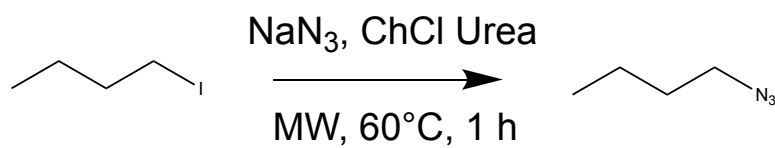
4.2.7 1-azidoheptane (2g)



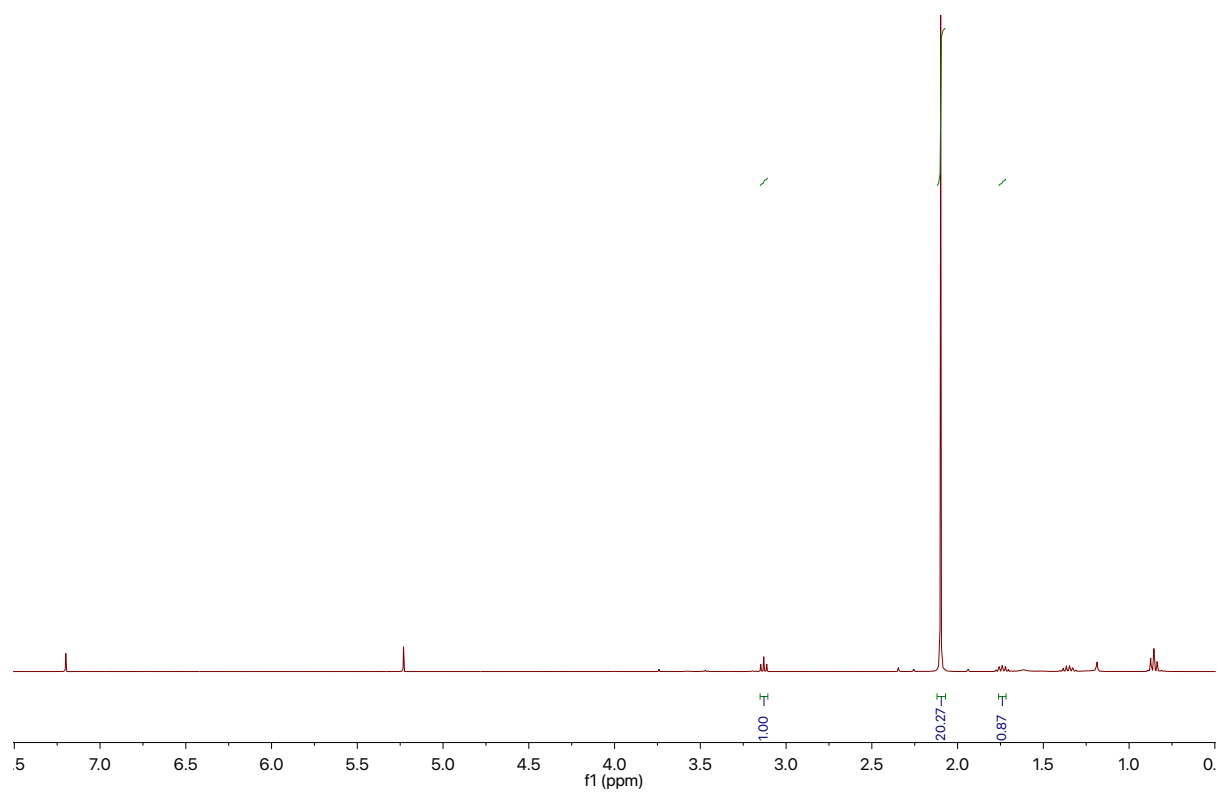
The reaction was checked by $^1\text{H-NMR}$ analysis. The spectrum is in agreement with literature data and the yield obtained is equal to 50%.



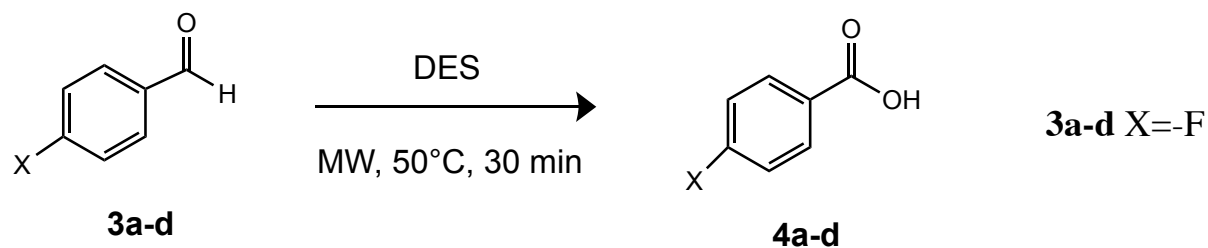
4.2.8 1-azidobutane (2h)



The reaction was checked by $^1\text{H-NMR}$ analysis. The spectrum is in agreement with literature data.

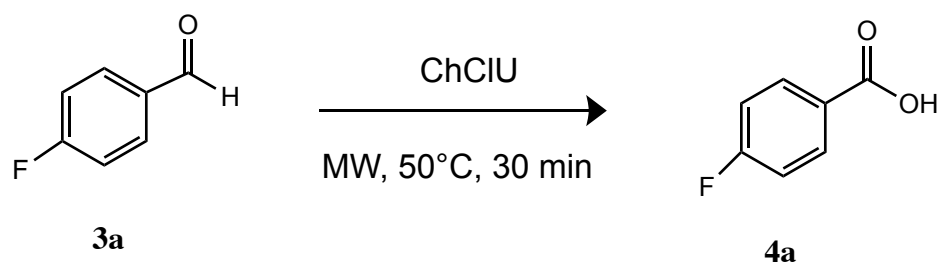


4.3 GENERAL PROCEDURE FOR OXIDATIONS IN DESs (3a-d)

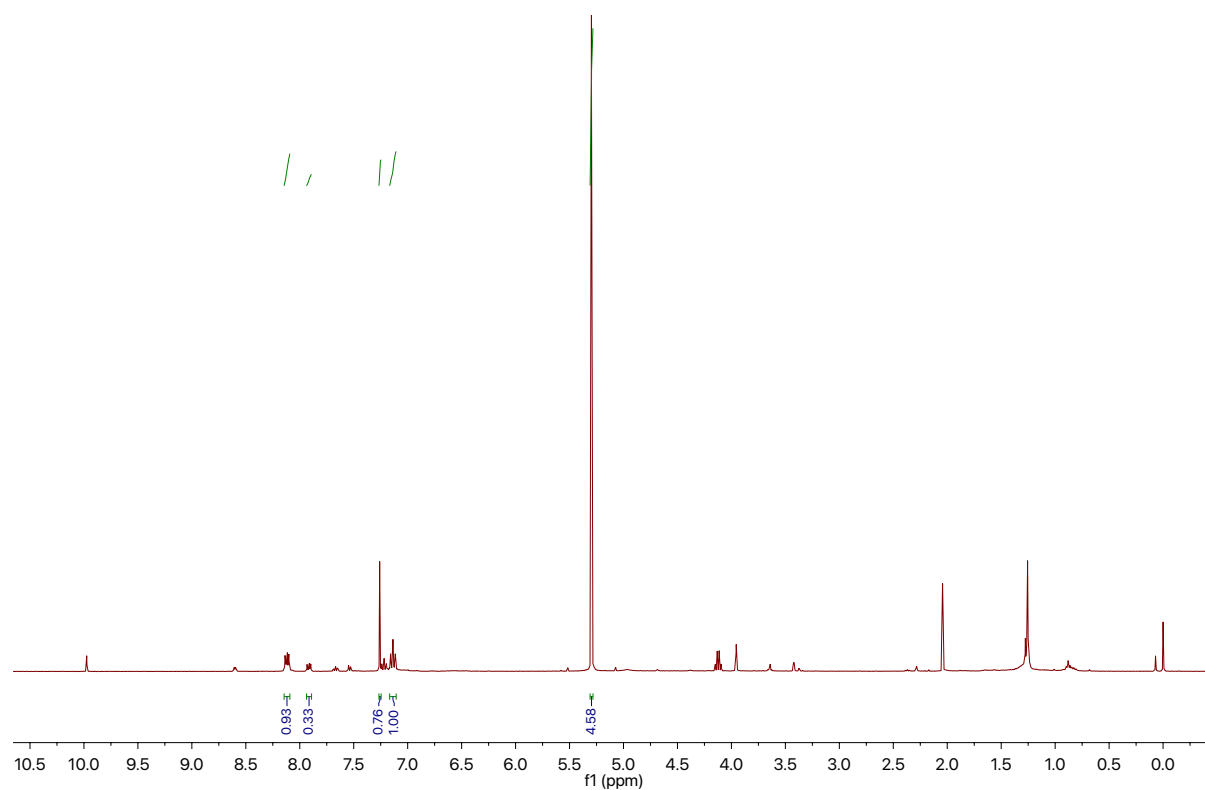


The selected compound **3**, bearing X (= F, Br) group (20 mg, 1 equivalent), was dissolved in 320 mg of DES1, DES2, DES3 and DES4. The reaction vessel was irradiated with MW using a BIOTAGE® Initiator 2.5 microwave and maintained at the indicated temperature for the desired time. At the end of the reaction, the mixture was extracted with dichloromethane and the combined organic phases were dried over Na₂SO₄. The organic phase was then concentrated under reduced pressure to remove the solvent. The resulting crude mixture was dissolved in CDCl₃ for ¹H-NMR analysis.

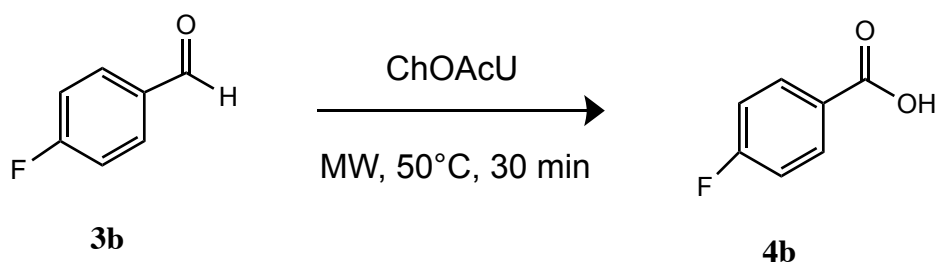
4.3.1 4-fluorobenzoic acid in choline chloride - urea (3a)



The reaction was checked by $^1\text{H-NMR}$ analysis. The spectrum is in agreement with literature data.

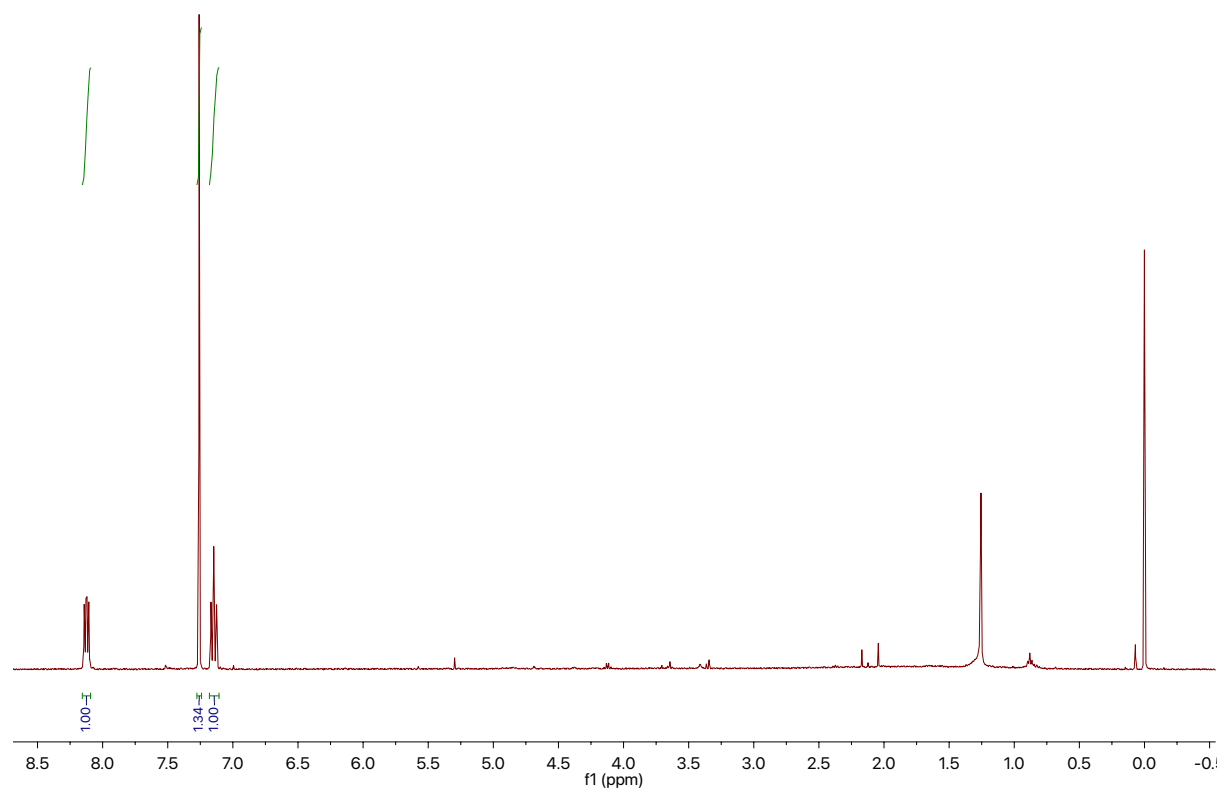


4.3.2 4-fluorobenzoic acid in choline acetate - urea (3b)

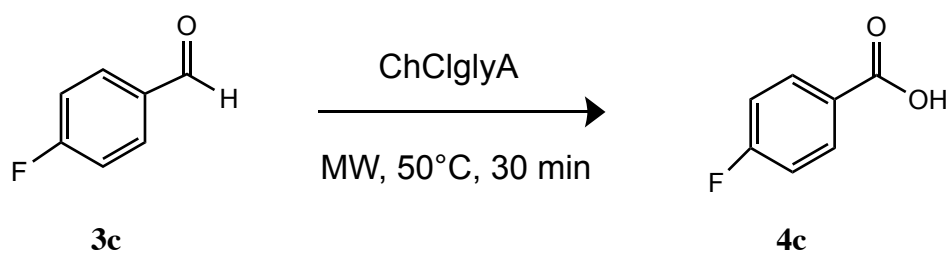


The reaction was checked by $^1\text{H-NMR}$ analysis.

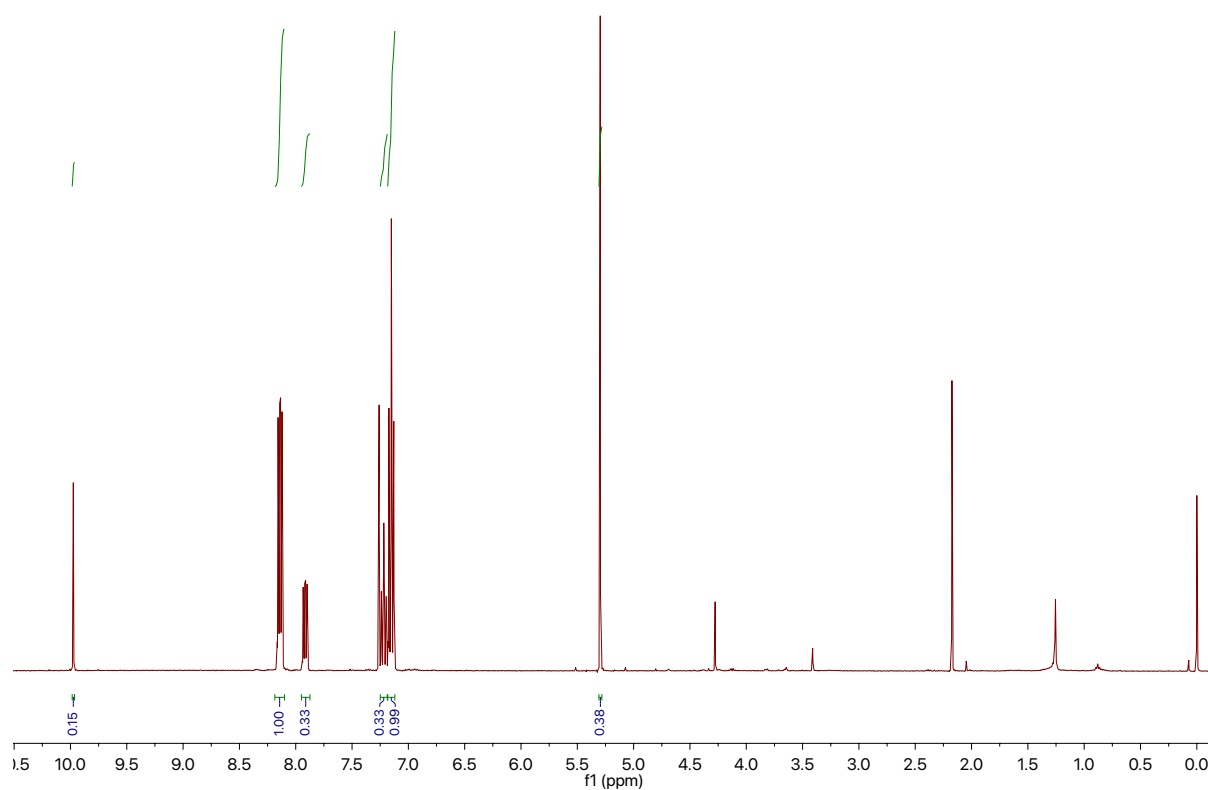
The spectrum is in agreement with literature data.



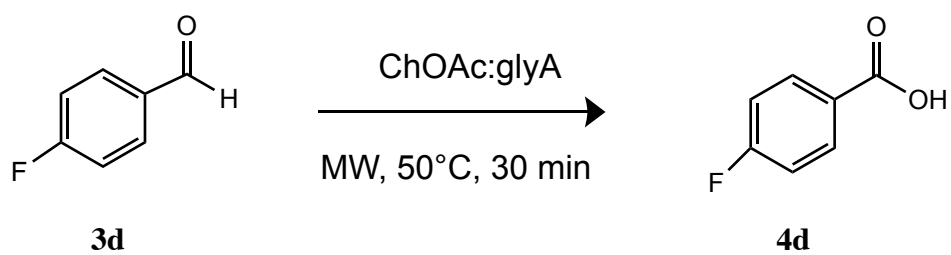
4.3.3 4-fluorobenzoic acid in choline chloride – glycolic acid (3c)



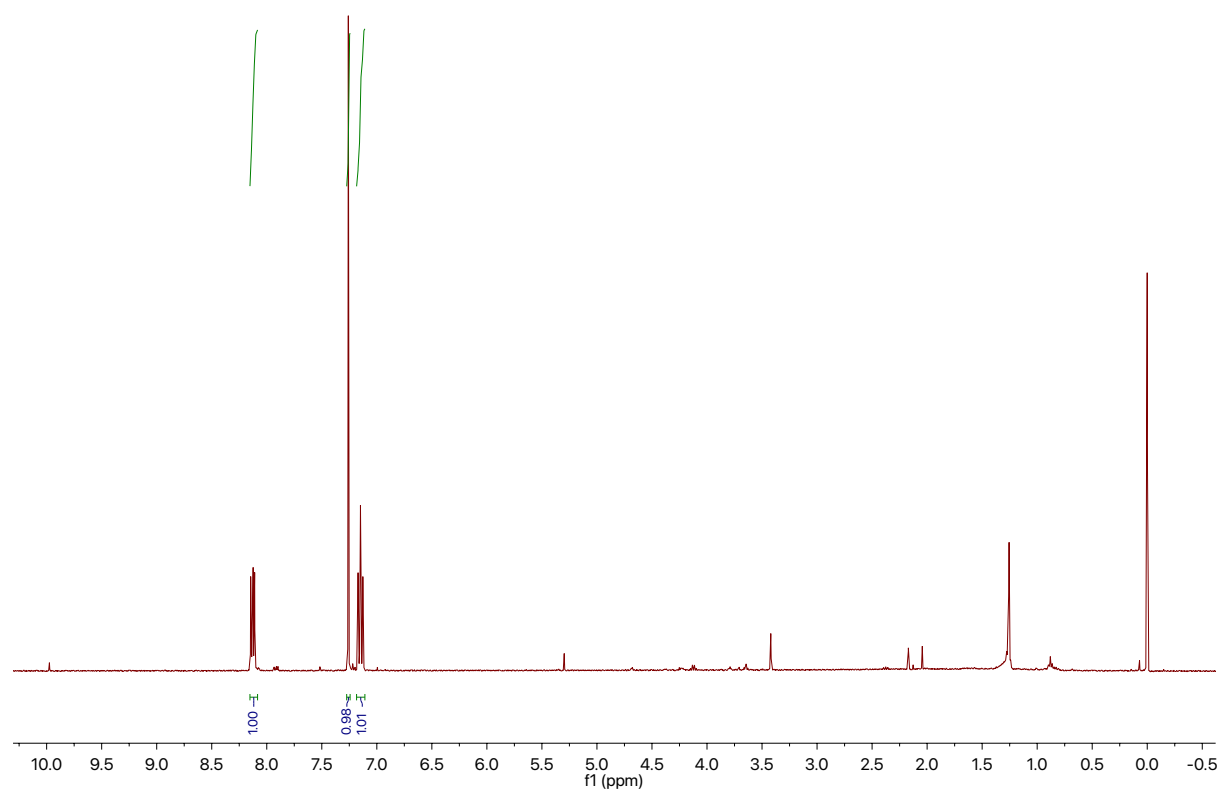
The reaction was checked by means of $^1\text{H-NMR}$ analysis. The spectrum is in agreement with literature data.



4.3.4 4-fluorobenzoic acid in choline acetate – glycolic acid (3d)



The reaction was checked by $^1\text{H-NMR}$ analysis. The spectrum is in agreement with literature data.



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