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ORIGINAL PAPER

Exploring the acidic catalytic role of differently structured deep eutectic solvents in the aza-Michael addition of amines to 2-vinylpiridine

Marco Ballarotto[1,2] · Federico Cappellini[1] · Riccardo Maestri[1] · Tiziana Del Giacco[1] · Pietro Di Profio[3] · Matteo Tiecco[1] · Raimondo Germani[1]

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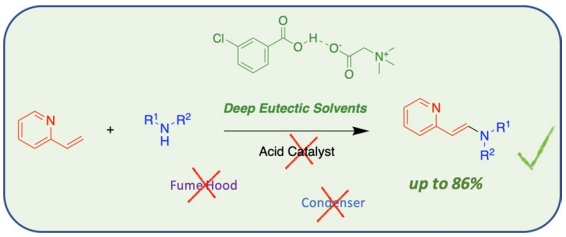
Abstract

The search for innovative and green reaction media is a prominent topic in the recent research in chemistry. Deep Eutectic Solvents (DESs) are currently gaining relevance in this field thanks to their unique properties in terms of their "greenness" as well as in terms of their catalytic properties. In this work we developed an efficient protocol for the conjugate aza-Michael addition of amines to 2-vinylpyridine using 14 differently structured acid DESs as both reaction media and catalysts, so preventing the use of other acid additives. The results are influenced by the acidity of the components of the DESs, showing the best results with weak acids in the DESs components, with isolated yields up to 86%. The aza-Michael reaction is a widely used synthetic route for the C–N bond formation in organic synthesis. In particular, the addition of amines to 2-vinylpyridine is used for the realization of pharmaceutically relevant compounds with anticancer, antiarrhythmic, and analgesic properties. Comparing the results with the ones observed in literature for the same reaction, this procedure revealed to be a convenient and efficient method for this relevant transformation.

Graphic abstract



Keywords Aza-Michael addition · Deep eutectic solvents · Acidity · Green chemistry · Solvent effect

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✉ Matteo Tiecco
matteotiecco@gmail.com

[1] Department of Chemistry, Biology and Biotechnology, University of Perugia, via Elce di Sotto 8, 06123 Perugia, Italy

[2] Department of Pharmaceutical Sciences, University of Perugia, via del Liceo 1, 06123 Perugia, Italy

[3] Department of Pharmacy, University of Chieti-Pescara "G. D'Annunzio", via dei Vestini 31, 66100 Chieti, Italy

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Introduction

Organic solvents and volatile organic compounds (VOCs) play a fundamental role in the chemical industry as they are involved in large amounts in different processes, from chemical transformations to the applications as paints, pharmaceuticals, pesticides, cleaners, inks and so on [1–3]. The easy dispersion of these liquids in the environment, also favoured by their high volatility, represents a severe ecological problem because of their toxicity, reduced biocompatibility, and scarce biodegradability [4, 5]. Moreover, the removal of these pollutants from the environment often requires difficult and expensive procedures [6, 7]. For these reasons, the proper choice of solvents that can have a lower ecological impact has nowadays a relevant role.

In the green chemistry framework, many solvents or approaches have been proposed as alternatives to commonly used organic solvents and VOCs [8–10]; those systems present both advantages and disadvantages but they are still widely used and explored for their favourable green characteristics, such as their non-volatility, their bio-compatibility, the recycle capability and so on [11].

In the recent years Deep Eutectic Solvents (DESs) are gaining importance as ecological green liquids in this topic for their favourable properties [12–14]. DESs are formed by mixing two molecules: a halide "onium" salt (or generally a Hydrogen Bond Acceptor molecule, HBA) with a Hydrogen Bond Donor component (HBD). The network of intra- and inter-molecular weak interactions between them causes the destructuration of the crystal lattice of the components, leading to the formation of a liquid at room temperature [15].

DESs mixtures can be considered as a side-class of Ionic Liquids (ILs), and they share with them many green properties such as the low or absent vapor pressure and recycling capabilities [16]. However, they represent a further step ahead in the development of novel green liquids for different reasons: they are prepared by simply mixing and heating the two solid components at the proper molar ratio; therefore no solvent is needed for their preparation, unlike ILs; DESs can be formed by natural source molecules or primary metabolites (NADESs: NAtural Deep Eutectic Solvents); they are showing a low (or in some cases absent) toxicity as it is emerging from the recent literature [17–19]. The negligible vapor pressure promotes their use for industrial applications thanks to both the scarce diffusion in the air of polluting organic molecules and their economic advantages; in fact the reaction systems do not need any vapor extraction hoods for the reaction solvents. DESs are classified in different types depending on the molecules they are formed by; the high number of possible combinations of the components can lead to differently structured liquids with distinct properties [20, 21]. Used in many different topics (such as separation/extraction agents, in electrochemistry, in biotechnology, etc.), Deep Eutectic Solvents are finding fruitful applications as reaction media for chemical transformation [22]. In this field DESs can play an "innocent" role (if they are only used for the solubilization of the reactants or of the products) or an "active" role if their components can participate in the reaction (i.e. acid catalyst, reactants) and this increases the importance of these liquids [23]. Another advantage of the use of DESs as solvents in chemical transformations is that they permit to work in air with reactions that normally need anhydrous conditions, such as Pd-catalyzed C–H bond activations and polar organometallic chemistry [24, 25]. This is because these liquids can act as water scavengers by incorporation of water molecules it in their H-bond network [26, 27].

Following our research findings in the development of novel green and catalytic reaction media [28–32], in this paper we studied the aza-Michael addition of amines to 2-vinylpyridine as probe acid-catalysed conjugate transformation using a set of 14 different Deep Eutectic Solvents. The solvents acted as both green reaction media as well as acid catalysts as they are formed by different Brønsted or Lewis acids. The aza-Michael reaction is widely used and applied in organic synthesis for the formation of C–N bonds. In particular, the conjugate addition of nitrogen nucleophiles to 2-vinylpyridine can be used to obtain pharmaceutically relevant molecules, e.g. with anticancer, antiarrhythmic, and analgesic properties, and effective chelating molecules for transition metals [33–37].

We developed a protocol that shows good results in terms of yields (up to 86% of isolated products) and reaction times (24 h) when compared to those reported for the same reaction in literature, where volatile organic protic solvents (such as methanol or ethanol) were used at reflux, resulting in yields ranging from 25 to 72% and with reaction times from 24 to 48 h [37, 38]. Moreover, the use of harmful and volatile acids was avoided thanks to the acid properties of the chosen DESs. The results observed underlined the importance of the choice of the proper class of Deep Eutectic Solvents for the reaction.

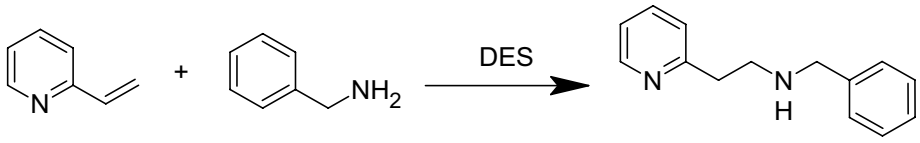
Results and discussion

In this work the aza-Michael conjugate addition of benzylamine to 2-vinylpyridine was studied without any added acid catalyst in different acid Deep Eutectic Solvents. The general reaction scheme is reported in Scheme 1.

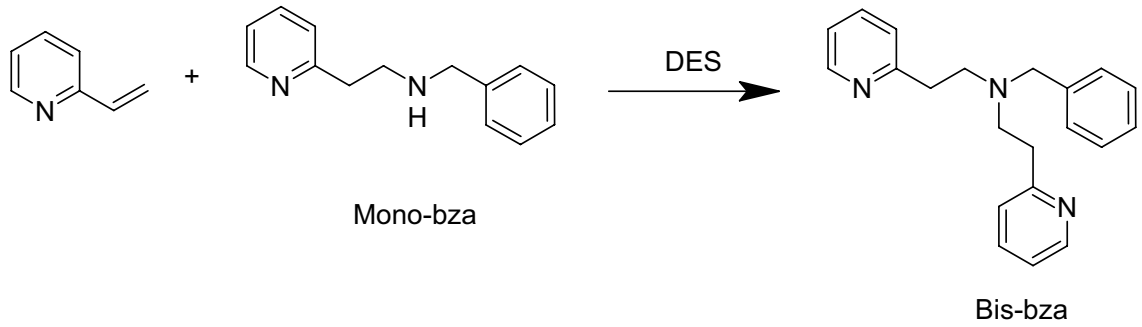
Reaction conditions optimization

The first step of this work was the optimization of the reaction conditions in terms of the temperatures and the reaction times. The DES formed by glycolic acid and trimethylglycine (molar ratio 2/1) was used as a model acidic

Scheme 1



Scheme 2



Mono-bza

Bis-bza

solvent. This liquid demonstrated, in fact, remarkable physico-chemical properties (such as a very low melting point, low viscosity, and low cost of the starting materials) and its NADES nature makes it environmentally friendly and non-toxic, making it a reasonable starting point for our research [39]; its acidity avoided the use of any other acid catalyst.

In all the analysed samples (also with the other DESs in the subsequent sections of this work) beside the main product (Mono-bza) a by-product obtained by addition of Mono-bza to a second molecule of vinylpyridine was observed (Scheme 2), in most cases as traces but in some other with not negligible yields (10–20%; identity confirmed via ^{1}H NMR and MS analyses, see Supporting Information). The optimization of the reaction conditions was made also in order to minimize the formation of this by-product.

The reaction conditions were optimized subsequently (Table 1). Initially, the temperature was analysed performing the reaction at 50 °C (Mono-bza GC yield 38%, entry (1) and 70 °C (Mono-bza GC yield 54%, entry (2); higher temperatures led to polymerization products of 2-vinylpyridine, while lower ones led to very low yields (traces). Moreover, an increment to 10% of Bis-bza GC yield was observed for the sample at 50 °C so the reaction temperature was set at 70 °C. This also permitted to have the possibility of using a larger set of DESs by using the ones with high melting points.

With the temperature set at 70 °C the reaction time was optimized, ranging from 2 h (Mono-bza, GC yield 35%, entry 3) to 72 h (Mono-bza, GC yield 60%, entry 7); in all the samples the Bis-bza yields were low (< 6%). The reaction time was set at 24 h (Mono-bza GC yield 54%, entry 2) as a modest increase of the yield was observed over this reaction time.

Table 1 Optimization of the reaction conditions in the addition of benzylamine to 2-vinylpyridine in glycolic acid/trimethylglycine DES (GLY/TMG molar ratio 2/1)[a]

Entry	Temperature/°C	Time/h	Mono-bza yield /%	Bis-bza yield /%
1	50	24	38	10
2	70	24	54	3
3	70	2	35	6
4	70	4	44	4
5	70	6	52	4
6	70	48	62	5
7	70	72	60	4

[a]Reaction conditions: 2-vinylpyridine (1 mmol), benzylamine (1 mmol), 1 g DES. All the yields are measured by GC

Selection of the media

With the optimized reaction conditions in hand (24 h, 70 °C), we screened a wide array of DESs containing Brønsted or Lewis acids as one of the components and with a melting point inferior to the reaction temperature. Since this reaction needs an acid catalysis, by this way we were able to evaluate the specific activity of the different DESs involved in this study. The results of this screening are reported in Table 2.

The DESs were chosen with a wide range of acidity in their components. Depending on the nature of the molecules forming them, the DESs used can be grouped in different

classes: neutral (choline chloride/urea, entry 1); carboxylic acids/betaine based liquids [39] (entries 2–7); (1*S*)-(+)-camphorsulfonic acid/sulfobetaine based ones [40] (entries 8, 9); *p*-toluenesulfonic acid/ammonium methanesulfonate-based ones [41] (entries 10, 11), and Lewis acid-based ones [42] (entries 12–14). The pK_a value of the acid components of the DESs could not be strictly correlated with the activity of the DESs when their values are close to one another, as observed in recent papers in literature [20, 43]. However, the media chosen in this work display large differences in the pK_a of the HBD components; therefore, this phenomenon could not impact on the observed results. Moreover, the zwitterionic liquids used in this work (entries 2–9) showed advantageous properties related to their low toxicity, as suggested in some recent papers [39, 40].

The results demonstrated that the acidity of the Brønsted acid component plays a crucial role; weaker acids gave the highest yields of Mono-bza (entries 2–6, yields ranging from 50% to > 95%), whereas stronger acids, such as *p*-TSA and (1*S*)-(+)-CSA [32, 40, 41], gave lower yields (entries 8–11, from traces to 33%). Finally, the mixture urea/choline chloride (entry 1) furnished very modest results.

The DES formed by urea and choline chloride (Table 3, entry 1) was used as reference because it was the first eutectic mixture that received a widespread recognition in the field [44]; this liquid lacks any Brønsted or Lewis acidity in its components and, as expected, the yields observed are really low (6%); moreover, a noticeable heterogeneous layer formed on top of the reaction mixture upon the addition 2-vinylpyridine to urea/choline chloride DES suggested difficulties in the solubilisation in the reaction mixture.

Interestingly, best results were obtained by using aromatic carboxylic acids as HBD components: phenylacetic, benzoic, 2-Cl-benzoic and 3-Cl-benzoic acids showed yields of 78%, 75%, > 95%, > 95%, respectively (entries 2, 3, 5, 6); beside their suitable acidic properties, maybe, this could be due to their higher solvating properties towards aromatic compounds. Glycolic Acid based-DESs showed a yield of 50% (entry 4). Oxalic acid/TMG DES (entry 7) is formed by a carboxylic acid but with lower pK_a compared to the previous ones analysed in this work (pK_{a1} = 1.2, pK_{a2} = 4.4); in this case no product was observed. Moreover, after the addition of benzylamine to the eutectic mixture an off-white solid formed at the contact point, which did not dissolve even after prolonged heating; so other solubility problems seem

Table 2 Addition of benzylamine to 2-vinylpyridine in different DES[a]

Entry	Bronsted/lewis acid	Bronsted/lewis base	DES molar ratio (acid/base)	Brønsted acid pK_a	Yield /%	
					Mono-bza	Bis-bza
1	Urea	ChCl	2/1	n.a.[d]	6	Traces
2	Phenylacetic acid	TMG	2/1	4.3	78	6
3	Benzoic acid	TMG	1.5/1	4.2	75	10
4	Glycolic Acid	TMG	2/1	3.8	50	Traces
5	2-Cl-Benzoic acid	TMG	1.5/1	2.9	> 95(70[b],58[b,c])	Traces (42[b,c])
6	3-Cl-Benzoic acid	TMG	1.5/1	3.8	> 95	Traces
7	Oxalic acid	TMG	2/1	1.2, 4.4	Traces	Traces
8	(1*S*)-(+)-CSA	SB3-Cy	1.5/1	1.2	33	Traces
9	(1*S*)-(+)-CSA	SB3-MIM	1.5/1	1.2	15	Traces
10	*p*-TSA	CyMsO	1/1	− 2.8	Traces	Traces
11	*p*-TSA	BnMsO	1/1	− 2.8	Traces	Traces
12	$ZnCl_2$	Acetamide	1/4	n.a	81[b] (56[b,c])	Traces (26[b,c])
13	$SnCl_2$	Acetamide	1/2	n.a	65[b] (26[b,c])	19[b] (74[b,c])
14	$AlCl_3$	Acetamide	1/2	n.a	41[b]	14[b]

ChCl choline chloride, *TMG* trimethylglycine, *SB3-Cy* 3-(cyclohexyldimethylammonio)propane-1-sulfonate, *SB3-MIM* 3-(1-methyl-1*H*-imidazol-3-ium-3-yl)propane-1-sulfonate, *CyMsO* *N*,*N*,*N*-trimethylcyclohexylammonium mesylate, *BnMsO* *N*,*N*,*N*-trimethylbenzylammonium mesylate

[a]Reaction conditions: 2-vinylpyridine (1 mmol), benzylamine (1 mmol), 1 g DES, 70 °C, 24 h. All the yields are measured by GC if not stated otherwise

[b]Isolated yield

[c]2-vinylpyridine:benzylamine molar ratio 2.5:1

[d]pK_a of the protonated form = 0.1. n.a. = not applicable

to add up to the acidity properties. The stronger the acids were present as DESs components, the lower the yields were observed: the (1*S*)-(+)-camphorsulfonic acid-based DESs (HBD pK_a = 1.2) showed quite low yields, irrespective of the sulfobetaines used as eutectic partner (SB3-Cy: 33%; SB3-MIM: 15%, entries 8 and 9, respectively); *p*-toluensulfonic acid-based mixtures (HBD pK_a = − 2.8) gave only traces of the desired product (entries 10 and 11) independently to the ammonium salt used as counterpart.

The Brønsted acidity of the DES can play both roles of catalysing the reaction by activation of the Michael acceptor through protonation of the nitrogen of 2-vinylpyridine and of hampering it via de-activation of the amine in the nucleophile through protonation of the nitrogen atom. The pK_a values of the conjugated acids of the two species are different (9.33 for benzylamine; 4.98 for 2-vinylpyridine [45, 46]), but in the presence of carboxylic acids with pK_a values between 2.9 and 4.3 (most in our set except for oxalic acid), equilibria could occur between the protonated and the deprotonated species. On the other hand, stronger acids lead to a too low amount of the reactive free amine; nevertheless, in the absence of acids 2-vinylpyridine could not be activated towards the nucleophilic attack. Therefore, a proper choice of the DES acidity plays a key role for a successful progress of the reaction, showing the best results with weak acids as part of the mixtures; in Fig. 1 a reaction mechanism based on the acid–base equilibria of the reagents is hypothesized.

In order to explore the acid capability of catalysing the reaction, also Lewis acid-based DESs were used in this work: the selected compounds were $ZnCl_2$, $SnCl_2$, and $AlCl_3$ with acetamide as counterpart (entries 12–14). Even this class of liquids showed good reaction yields, with values ranging from 40 to 80%. These results showed the importance of the acidic character of the liquids, irrespective of their Brønsted or Lewis nature; however, in these reactions a slight increase in the yield of the Bis-bza by-product was also observed.

To further investigate the behaviour of the DESs of both classes and the possibility of driving the reaction towards the double addition by-product Bis-bza, we then repeated the reaction with an excess of 2-vinylpyridine (2.5 equivalents). The chosen reaction media were 2-Cl benzoic acid/betaine, $ZnCl_2$/acetamide, and $SnCl_2$/acetamide, since they gave the best results using equimolar reagents (entries 5, 12, 13). As expected, the molar ratio of the reactants has an impact on the products' yields, with the yield of the Bis-bza increasing up respectively to 42% (entry 5, 2-Cl-benzoic acid/TMG DES), 26% (entry 12, $ZnCl_2$/acetamide DES), and 74% (entry 13, $SnCl_2$/acetamide DES). The values obtained suggested that there is not any peculiar effect of the Lewis acid-based liquids (i.e. coordination of the nitrogen atoms with the ions [47]) that can impact on the yields; but that the molar excess of 2-vinylpyridine can provoke an increase of the yield of the bis-adduct irrespective of the DES acidic nature. The yield of 2-Cl-benzoic/TMG liquid (42%, entry 5) is in fact higher than the one of $ZnCl_2$/acetamide liquid (26%, entry 12), therefore suggesting that even if a coordination or chelation process could be present, the effects on the yields observed could be driven much more by the molar ratio of the reagents.

The obtained Bis-bza by-product could be useful as chelating agent as the three branches can easily fold and coordinate transition metals [37]. In Fig. 2 are reported ^{1}H-^{1}H NOESY ($CDCl_3$) interactions to prove this possibility, where NOE signals are present between methylene groups of the branch derived from 2-vinylpyridine and all the other

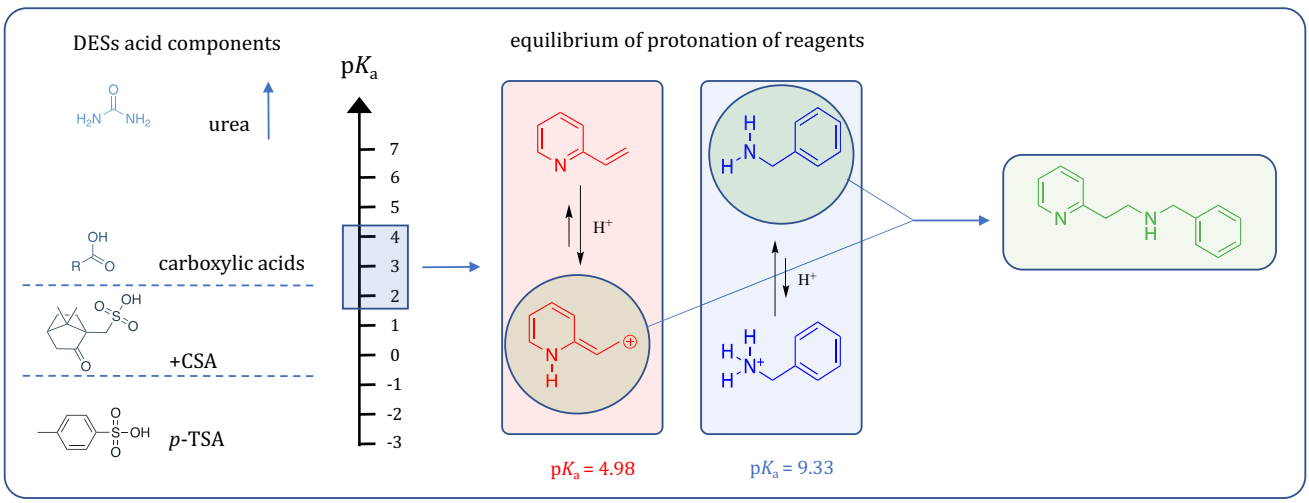


Fig. 1 Suggested reaction mechanism based on acid/base equilibria of the reagents

functional groups of the molecule, so indicating a possible folding of the structure (the full spectrum is reported in ESI). Probably the π–π interactions that can occur between the aromatic branches could favour this conformation.

Scope and limitations with other amines

We then explored the scope of our approach with other amines (i.e., aniline, 2-phenylethan-1-amine, and morpholine) by using the best-performing DESs presenting either Lewis and Brønsted acidity: 2-Cl-benzoic acid/TMG, $ZnCl_2$/acetamide, and $SnCl_2$/acetamide (Scheme 3, Table 3). The three amines were chosen to have a set of differently structured nucleophiles to be compared with the benzylamine, namely an aromatic amine (aniline), a primary aliphatic acyclic amine (2-phenylethan-1-amine), and a secondary aliphatic cyclic amine (morpholine).

In most cases, the yields range from good to excellent (61% to 87% of isolated product yields) except for entries 7–9 ($SnCl_2$/acetamide eutectic mixture). When an aromatic amine was employed (entries 1, 4, 7), the yields of mono-addition product (73%, 71%, and 61% of isolated product yields, respectively) were not influenced by the DESs structures, with the 2-Cl benzoic acid/TMG (entry 1) showing a small amount of double addition product (6%). An increase in the length of the carbon chain spacer between the amine and the aromatic ring (2-phenylethan-1-amine) led to a slight decrease in the yields (entries 2, 5, 8 with 69%, 66% and 46% of isolated product yields, respectively). Noticeably, the yield of the double addition product increased only with the 2-Cl benzoic acid/TMG DES (entry 2, 13%). On the other hand, by using the cyclic amine morpholine as nucleophile

Table 3 Aza-Michael addition of different nucleophiles to 2-vinylpyridine[a]

Entry	Reaction medium	R^1	R^2	Yield /%	
				Mono-product	Bis- product
1	2-Cl benzoic acid/TMG[b]	Ph	H	73	6
2		CH_2CH_2Ph	H	69	13
3		Morpholine		87	–
4	$ZnCl_2$/acetamide [c]	Ph	H	71	Traces
5		CH_2CH_2Ph	H	66	Traces
6		Morpholine		86	–
7	$SnCl_2$/acetamide [d]	Ph	H	61	Traces
8		CH_2CH_2Ph	H	46	Traces
9		Morpholine		86	–

[a]Reaction conditions: 2-vinylpyridine (1 mmol), nucleophile (1 mmol), 1 g DES, 70 °C, 24 h. All the yields are of isolated products

[b]2-Cl benzoic acid/TMG 1.5/1

[c]$ZnCl_2$/acetamide ¼

[d]$SnCl_2$/acetamide 1/2

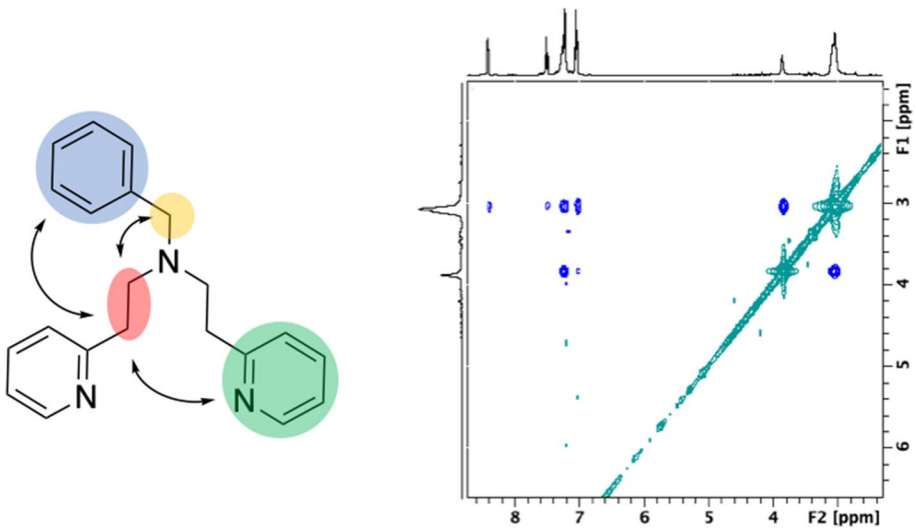
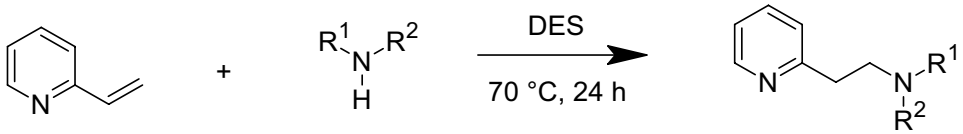


Fig. 2 ^1H-^1H NOESY interactions observed in the Bis-bza compound in $CDCl_3$

Scheme 3



(entries 3, 6, 9) similar yields were obtained in all reaction media: 87%, 86%, and 86%, respectively.

These results demonstrated that the nature of the amine did not strongly affect the reaction yields that they still remain excellent in most of the experiments.

Conclusion

In conclusion, we explored the use of differently structured acid Deep Eutectic Solvents and their catalytic role in the aza-Michael addition between 2-vinylpyridine and amines.

Thanks to their different acid capabilities, the wide set of used green liquids helped to define the best reaction solvents that showed excellent yields (between 85 and 95% in different experiments with different liquids). The acidity of the components of the media (in the case of Brønsted acids) played in fact a key-role in determining yields that are relevant only with weak acid molecules such as the class of carboxylic acids/trimethylglycine DESs; 2-Cl-benzoic and 3-Cl-benzoic acids as counterpart of the trimethylglycine in the liquids gave the best results, as they showed over 95% of GC yields (70% of isolated product). The use of Lewis acids as DESs components ($ZnCl_2$, $SnCl_2$, and $AlCl_3$ with acetamide) led to excellent yields as well. The use of other differently structured amines as nucleophiles (aniline, 2-phenylethan-1-amine, and morpholine) led as well to excellent yields in the best-performing DESs of the set.

Moreover, comparing the results with the ones reported in literature for the same reaction, this protocol showed many advantages: high yields, greenness of the media, absence of harmful acid catalysts, reduced reaction times, possibility to extend the scope with different DESs and nucleophiles.

Experimental

All solvents and reagents were purchased from Sigma-Aldrich, Merck, Fluka and Alfa Aesar and were used without further purifications (purities > 98%). Phenethylamine was purified by Kugelrohr distillation. Agilent 6850 Series II Network Gas Chromatography instrument equipped with DB-35MS column was used for GC analysis. The yields of Mono-bza and Bis-bza were calculated using dibenzylether as internal standard for the GC analysis adding specific amounts of it before the extraction procedures. The response factors (γ) were determined by a calibration curve and their values are 0.804 and 1.111, respectively. ^{1}H NMR and ^{13}C NMR spectra were measured at 25 °C with a Bruker Avance III HD 400 MHz instrument and the spectra were calibrated on the solvent residual peak. ^{1}H-^{1}H NOESY experiment was conducted in $CDCl_3$ solution with a 2048 × 512 sized FID, 16 scans, D8 = 0.8 s. LC and MS analysis were performed on an Agilent 6500 Series Quadrupole Time-of-Flight LC/MS (Q-TOF) system. The UV–Vis detector was set to read at 254 nm. Thin Layer Chromatography (TLC) was performed on fluorescent dye-coated silica gel 60 supported on aluminium sheets; flash column chromatography was performed on silica gel 60.

DES preparation

The DESs were prepared by mixing the two weighed components in a vial and heating the sample under magnetic stirring at 70 °C for the proper time (spanning from 20 to 60 min approximately) until homogeneous liquids were formed. The non-commercial components of the Brønsted acid-containing DESs were prepared as previously reported [40, 41]. Choline chloride/urea DES was prepared according to the literature [44]. The $ZnCl_2$/acetamide and the $SnCl_2$/acetamide DESs were prepared following the same procedure reported in literature [48].

General experimental procedure

1 g of DES was weighted into a vial (or prepared by weighting its components directly into a vial); the nucleophile was then added with a syringe. The mixture was homogenized by heating and mixing, then 2-vinylpyridine was then added with a syringe. The mixture was put in an oil bath under magnetic stirring for the proper time. Subsequently, a basic water solution was added (NaOH 10%) and the water phase was extracted with ethyl acetate (3 × 10 cm^3); the organic phases were collected, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The products were purified by flash column chromatography using the solvents reported in the product characterization and in Electronic Supplementary Material Sections.

Products purification and characterization

All the ^{1}H NMR, ^{13}C NMR, and LC–MS spectra and the purification procedures are reported in Electronic Supplementary Material.

N-[2-(2-Pyridyl)ethyl]benzylamine (Mono-bza, entries 1/14) [37], *N*,*N*-*bis*[2-(2-pyridyl)ethyl]benzylamine (Bis-bza, entries 1/14) [49], *N*-[2-(2-pyridyl)ethyl]aniline (Mono-an, Table 3, entries 1, 4, 7) [50], *N*,*N*-bis[2-(2-pyridyl)ethyl]-aniline (Bis-an, Table 3, entries 1, 4, 7) [51], *N*,*N*-*bis*[2-(2-pyridyl)ethyl]phenethylamine (Bis-ph, Table 3, entries 2, 5, 8) [52], and *N*-[2-(2-pyridyl)ethyl]morpholine (Mono-mor, Table 3, entries 3, 6, 9) [53] showed spectral data identical to the literature (see Supplementary Material).

***N*-[2-(2-Pyridyl)ethyl]phenethylamine (Mono-ph, $C_{15}H_{18}N_2$, Table 3, entries 2, 5, 8)** Flash chromatography eluent: ethyl acetate:methanol:Et_3N 49:50:1. A yellow oil was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (m, 1H, Pyr-H6), 7.62

(m, 1H, Pyr-H4), 7.34 (t, 2H, Phe-H_{ortho}), 7.27 (m, 3H, Pyr-H3 and Phe-H_{meta}), 7.15 (m, 2H, Pyr-H5 and Phe-H_{para}), 4.12 (brs, 1H, H–N), 3.15 (t, 2H, N–CH_2–CH_2–Phe), 3.05 (m, 4H, N–CH_2–CH_2–Pyr), 2.91 (t, 2H, N–CH_2–CH_2–Phe) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 159.90$ (Pyr-C2), 149.18 (Pyr-C6), 139.60 (Phe-C_{ipso}), 136.42 (Pyr-C4), 128.75 (Phe-C_{meta}), 128.48 (Phe-C_{ortho}), 126.21 (Phe-C_{para}), 123.27 (Pyr-C3), 121.30 (Pyr-C5), 50.58 (N–CH_2–CH_2–Phe), 48.72 (N–CH_2–CH_2–Pyr), 37.39 (Pyr-CH_2), 35.73 (Phe-CH_2) ppm; MS: *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}N_2$ 227.15428, found 227.15502; purity (by LC): 83%.

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