

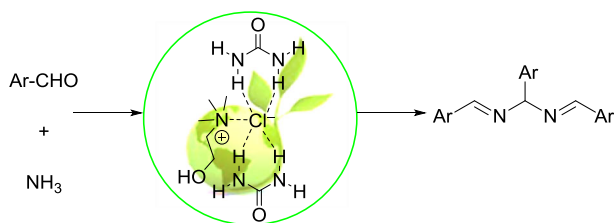
# Deep eutectic solvent catalyzed eco-friendly synthesis of imines and hydrobenzamides

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**Abstract** The urea–choline chloride-based deep eutectic solvent was found to be an efficient catalyst and reaction media for the additive-free synthesis of imines (Schiff bases) and hydrobenzamides by the reaction of aldehydes with amines and ammonia in good to high yields. Outstanding features of this protocol were the general and atom-economical reaction, absence of external catalysts and additives, simple workup, and availability and recycling of urea–choline chloride as a green solvent.

**Graphical abstract**



**Keywords** Deep eutectic solvent · Green chemistry · Schiff bases · Hydrobenzamides · Urea–choline chloride

## Introduction

As a new stream in organic synthesis, deep eutectic solvents (DESs) have attracted much attention as advanced ionic liquids. They are ideal systems of solvents due to their sustainable and appropriate reaction have to be compared to

hazardous organic solvents. Deep eutectic solvents are mixtures that are exclusively composed of cations and anions, and have low melting point, negligible vapor pressure, and fabulous thermal and chemical stability. Deep eutectic solvents have allocated a great deal of concern in green chemistry due to their comfortable availability, absence of purification problems, reusability, and biodegradability [1–8].

The synthesis of nitrogen containing compounds in the moderate and safe reaction media without additive and catalyst, which is characterized by eco-friendly degradation, plays an important role in organic synthesis as well as medicinal chemistry [9–12]. The condensation reaction of primary amines with active carbonyl compounds in the presence of acid catalyst was first reported by Hugo Schiff in 1864, and the products are often referred to as Schiff bases or imines [13].

The promising applications of imines and their derivatives as key intermediates in the synthesis of various novel nitrogen heterocyclic compounds and alkaloids that have shown considerable biological actions, have attracted a great deal of attention in contemporary organic and medicinal chemistry [14–16]. Furthermore, they found tremendous applications as antibiotics, antifungal drugs, antiviral drugs, anthelmintics, and essential pharmaceutical compounds [17, 18].

The condensation reaction of ammonia or equivalents with carbonyl compounds produces *N,N'*-bis(arylmethylene)arylmethanes called hydrobenzamides [19]. Due to the unique arrangement of nitrogen atoms with unsaturated bonds in the hydrobenzamide derivatives, they have been recognized as excellent synthetic nitrogen key intermediates for the synthesis of a variety of biologically active nitrogen heterocyclic compounds [20–23]. Because of the widespread applications of hydrobenzamides, great efforts have been made to the synthesis of this pivotal intermediate

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in the most affordable way using different solvents and catalysts [24–35]. Although some of these procedures are so influential and proper in small scale, developing a clean and efficient way for the synthesis of this versatile intermediate, which is not burdened by environmental and safety problems as encountered for large-scale preparations, is most desirable.

## Results and discussion

In conjunction with our interest in developing an efficient and a green procedure for organic reactions in DESs [36–41] herein we report the straightforward and mild preparation of *N,N'*-bis(arylmethylidene)arylmethane diamines and imines from the reaction of aromatic aldehydes with ammonia and a variety of amines in choline chloride-based deep eutectic solvent under the safe and eco-friendly conditions.

In the model reaction, the synthesis of hydrobenzamides was studied with the reaction of ammonia (3.2 mmol) and benzaldehyde (3 mmol) in urea–choline chloride as the solvent (0.5 cm<sup>3</sup>). The desired product was obtained with an isolated yield of 85 % after 2 h at 60 °C. To develop an environmentally benign procedure, foul smelling and toxic ammonia was replaced with HMDS as a green source of ammonia in this protocol. However, a low yield was obtained while the reaction was performed with aldehyde (3 mmol) and HMDS (3 mmol) in DES (0.5 cm<sup>3</sup>) at 60 °C in 2 h which afforded the corresponding product **3a** in 45 % isolated yield. Furthermore, it was observed that the

same mixture at room temperature for 5 h produced the corresponding products in very low yield (28 %).

Under above reaction condition, to elaborate the scope and generality of this DES, various aromatic and heterocyclic aldehydes were examined and the details of the result are summarized in Table 1. Aromatic aldehydes bearing electron-donating as well as electron-withdrawing groups undergo condensation with ammonia to afford hydrobenzamides **3** in moderate to good yields. Aromatic aldehydes, such as benzaldehyde, 3-nitrobenzaldehyde, 4-bromobenzaldehyde, 4-chlorobenzaldehyde, and 4-methoxybenzaldehyde proved to be effective substrates and produced hydrobenzamides **3** in good to excellent yields (58–85 %). Furfural as a heteroaryl aldehyde reacted efficiently with ammonia to result in the related hydrobenzamides **3d** in good yields (Table 1, entry 4). However, aliphatic aldehydes did not participate in the reaction.

Based on this remarkable efficiency of DES as green reaction media, and to study the scope of this green protocol, we next extended our study to various aromatic and aliphatic amines for the preparation of imines and the results are listed in Table 2. Under optimized reaction condition, it was observed that simple mixing of aldehyde (1 mmol), aniline (1 mmol) in DES (0.2 cm<sup>3</sup>) at 60 °C for 2 h gives product **5a** in 95 % isolated yield. A range of functionalized aromatic and aliphatic aldehydes as well as various aromatic and aliphatic amines were employed for the preparation of imines. These results show that the reaction is general with respect to starting material and nature of aldehyde or amine which has little effect on the yields and reaction times.

**Table 1** Synthesis of *N,N'*-bis(arylmethylidene)arylmethane diamines in DES

Entry	Ar	Product	Yield/%	M.p./°C	
				Found	Reported
1	Ph	<b>3a</b>	85	98–100	104–105 [33]
2	4-Cl–C <sub>6</sub> H <sub>4</sub>	<b>3b</b>	68	86–88	88–90 [33]
3	3-MeO–C <sub>6</sub> H <sub>4</sub>	<b>3c</b>	72	126–127	128–129 [34]
4	2-Furanyl	<b>3d</b>	58	114–116	116 [35]
5	3-NO <sub>2</sub> –C <sub>6</sub> H <sub>4</sub>	<b>3e</b>	68	180–182	178 [31]
6	4-(MeOCO)–C <sub>6</sub> H <sub>4</sub>	<b>3f</b>	62	136–138	140–142 [33]
7	4-Br–C <sub>6</sub> H <sub>4</sub>	<b>3h</b>	76	120–121	120 [33]
8	4-MeO–C <sub>6</sub> H <sub>4</sub>	<b>3i</b>	74	128–129	127 [30]

**Table 2** Synthesis of imines in DES

$\text{ArCHO} + \text{RNH}_2 \xrightarrow[60\text{ }^\circ\text{C, 1-4 h}]{\text{Urea-CHCl (0.2 cm}^3\text{)}} \text{Ar}-\text{CH}=\text{N}^-\text{R}$ <div style="display: flex; justify-content: space-around; width: 100%;"> <span><b>1</b>      <b>4</b></span> <span><b>5</b></span> </div>						
Entry	R	Ar	Product	Yield/% <sup>a</sup>	M.p./°C	
					Found	Reported
1	Ph	Ph	<b>5a</b>	95	52–54	52–54 [21]
2		4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>5b</b>	95	62–63	62–64 [21]
3		4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>5c</b>	74	61–62	63 [22]
4		2,4-(MeO) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	<b>5d</b>	72	64–65	65 [21]
5		4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>5e</b>	75	88–89	89–90 [23]
6	PhCH <sub>2</sub>	3- <i>i</i> -Pr-C <sub>6</sub> H <sub>4</sub>	<b>5f</b>	81	Oil	Oil [25]
7		3-Br-C <sub>6</sub> H <sub>4</sub>	<b>5g</b>	95	Oil	Oil [25]
8		4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>5h</b>	82	41–42	41 [23]
9		3-Br-C <sub>6</sub> H <sub>4</sub>	<b>5i</b>	80	37–38	38 [23]
10		4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>5j</b>	78	55–57	56 [21]
11	3-Cl-C <sub>6</sub> H <sub>4</sub>	Ph	<b>5k</b>	70	Oil	Oil [22]
12		4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>5l</b>	68	54	55–56 [23]
13		3-Cl-C <sub>6</sub> H <sub>4</sub>	<b>5m</b>	80	46–48	47 [20]
14	<i>n</i> -Bu	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>5n</b>	72	66–67	67 [22]
15		3-Br-C <sub>6</sub> H <sub>4</sub>	<b>5o</b>	68	Oil	Oil [24]
16		4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>5p</b>	65	Oil	Oil [24]

<sup>a</sup> Isolated yield

To test the industrial applicability of the procedure, scale-up experiments were done, 4-chlorobenzaldehyde (20 mmol) with aniline (20 mmol) in DES (4 cm<sup>3</sup>) was performed under the above conditions and the *N*-benzylideneaniline in 92 % isolated yield was obtained.

The recycling of DES was examined using the reaction of benzaldehyde and aniline. After the completion of the reaction, water was added to the mixture and shaken vigorously. After simple filtration, the product was purified by recrystallization with ethanol as effectual solvent. The soluble DES in the water was recovered by evaporating the water at 80 °C under vacuum, and it was reused for the next run and recycled again without decreasing the yield.

## Conclusion

In conclusion, a fast and green method for the formation of carbon–nitrogen bond is achieved using DES as a cost-effective and eco-friendly solvent. The proposed reaction proceeds under mild conditions and gives the products in good and quantitative yields between 58 and 95 % with exhaustive eco-friendly procedure. The attractive and

outstanding features of this green synthesis are the use of DES, absence of any external catalyst and additive, short reaction time, simple separation and purification.

## Experimental

All starting materials, reagents, and solvents are commercially available and were used as purchased. All products were confirmed by melting point or boiling point, FT-IR spectroscopy. Water and other extraction solvents were distilled before using. All the reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel with UV light as detecting agent. Melting points and boiling points were recorded on Büchi 535 melting point apparatus. FT-IR spectra were determined on a BrukerVector-22 infrared spectrometer using KBr disks. <sup>1</sup>H NMR spectra were recorded at r.t. on a FT-NMR Bruker UltraShield™ (500 MHz) or Bruker AC 80 MHz instrument in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> as solvent, chemical shifts are expressed in ppm.

Choline chloride–urea deep eutectic solvent was prepared according to the literature [1]. The obtained deep eutectic solvent was used without any further purification.

### General procedure for reaction of aldehydes and ammonia (Table 1)

In a dried test tube, 3.0 mmol aldehyde, 0.4 cm<sup>3</sup> ammonia (3.2 mmol), and 0.5 cm<sup>3</sup> DES were mixed and heated at 60 °C until the reaction was complete. The reaction mixture was then diluted with water and extracted with ethyl acetate. After evaporation of the solvent, the resulting solid or viscous liquid was recrystallized from solvents such as *n*-hexane, ethanol, diethyl ether; in some cases column chromatography (*n*-hexane–ethyl acetate) was applied to give pure products. All compounds were characterized by melting points that were found to be identical with the ones described in literature.

### General procedure for the synthesis of imines in DES (Table 2)

In a dried test tube, 1.0 mmol aldehyde, 1.0 mmol amine, and 0.2 cm<sup>3</sup> DES were added and the mixture was heated at 60 °C until the reaction was completed. After the reaction time, water was added to the mixture, and the residue collected by filtration. The resulting solid was washed with water and was purified by flash column chromatography or recrystallization with ethanol to give pure products. The viscous oil/semi-solid products were extracted with ethyl acetate. All compounds were characterized by melting points that were found to be identical with the ones described in literature.

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