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Experimental investigation on the correlation between the physicochemical properties and catalytic activity of six DESs in Kabachnik-Fields reaction

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Abstract
Physicochemical properties of six Type IV- Deep eutectic solvents formed from ZrOCl$_2$.8H$_2$O/ CeCl$_3$.7H$_2$O with urea, ethylene glycol & glycerol were compared. The study was performed by correlating the properties of DESs with their activity in Kabachnik-Fields reaction. Among the six DESs, lower density, viscosity, higher acidity & thermal stability were observed for DES 1(Deep eutectic solvent developed from ZrOCl$_2$.8H$_2$O and urea at 1:5 ratio) and is reported as an excellent catalyst and reaction medium for the productive synthesis of α-aminophosphonates within a short period of time. One pot reaction of an aldehyde, dimethyl phosphite and amine (Kabachnik-Fields/ Phospha-Mannich reaction) took place at room temperature to give the corresponding α-aminophosphonates in good yield and the precipitation of these products in to water avoided the regular work up process. Catalyst was recycled up to five times without any loss in its activity.

Keywords
Deep eutectic solvents, Green catalyst and solvent, Phospha-Mannich reaction, α-aminophosphonates

Introduction
Due to the versatile activity, organophosphorous compounds have found extensive applications in industrial, agricultural, and medicinal fields and for transition-metal-catalyzed reactions, phosphine-containing compounds represent the conventional choice of ligands. In recent years, α-aminophosphonates have obtained much attention and are major class of compounds in pharmaceutical chemistry, especially in the field of drug discovery, due to their biological activity and low mammalian toxicity. Because of their effect as enzyme inhibitors, inhibitors of GABA receptors, α-aminophosphonates are very essential in the
development of antibiotics, antitumour agents, antihypertensive, antiviral species, anticlotting agent, antibody production etc.\textsuperscript{7-9} The activities of $\alpha$-aminophosphonates, such as HIV protease,\textsuperscript{10} peptide mimics,\textsuperscript{11} insecticides, herbicide and fungicides\textsuperscript{12} etc. are also reported in the literature. They are phosphorous analogues of the corresponding $\alpha$-aminoacids (bioisosterism), in which the carboxylic group (planar) is replaced by a phosphonic acid (tetrahedral functionality), acting as antagonist of amino acids.\textsuperscript{13} The main synthetic routes for $\alpha$-aminophosphonates are the Kabachnik–Fields reaction (condensation of amines, oxo-compounds and $>$P(O)H species, such as dialkyl phosphites) and the Pudovik reaction of imines and $>$P(O)H reagents (Scheme 1).\textsuperscript{7} The addition of phosphorus-hydrogen bond to electrophilic centers like C=O or C=N is a fascinating topic in synthetic organic chemistry.\textsuperscript{14,15}

\begin{equation}
\begin{array}{c}
\text{R} \quad \text{H} \\
\text{O} \\
\end{array} + \begin{array}{c}
\text{R'} \quad \text{NH}_2 \\
\end{array} \xrightarrow{\text{Kabachnik-Fields}} \begin{array}{c}
\text{H} \\
\text{N} \\
\text{R'} \\
\text{OR''} \\
\end{array} \quad \begin{array}{c}
\text{R} \\
\text{OR'} \\
\end{array} \quad \begin{array}{c}
\text{OR'} \\
\end{array} \xrightarrow{\text{Pudovik}} \begin{array}{c}
\text{R} \\
\text{H} \\
\end{array}
\end{equation}

\textbf{Scheme 1} Common routes towards $\alpha$-aminophosphonate synthesis

Of these, Kabachnik-Fields reaction is the most important pathway because of its one pot three component procedure and was observed when multicomponent processes were rather “exotic birds”.\textsuperscript{16} Three starting materials are involved in the reaction in which all of them are incorporated in the final product structure.

Various systems have been developed for the synthesis of $\alpha$-aminophosphonates like HClO$_4$–SiO$_2$,\textsuperscript{17} LiClO$_4$,\textsuperscript{18} Pentafluorophenylammonium triflate (PFPAT),\textsuperscript{19} Oxalic acid,\textsuperscript{20} Yttria-zirconia based Lewis Acid,\textsuperscript{21} Graphene Oxide,\textsuperscript{22} Choline chloride- 2ZnCl$_2$ ionic liquid,\textsuperscript{23} H$_6$P$_2$W$_{18}$O$_{62}$·14H$_2$O,\textsuperscript{24} etc. However, the drawbacks associated with prior reports such as the demand of solvent, extra reagents, heating, prolonged reaction time, expensive and unstable catalysts, unique apparatus etc. point out the urgency to develop a productive method. Now, there has been a major priority for designing organic reactions using green protocol to make them more environmentally compatible. This displayed the use of ionic liquids over the last few decades. But its high cost and toxicity makes to rethink about an alternate method, which led to the birth of deep eutectic solvents and their different applications in organic synthesis.\textsuperscript{25-28} This is based on all green aspects of sustainable chemical transformations like atom economy, organic solvent free, energy efficiency etc. Deep eutectic solvent is actually a makeover of ionic liquids with additional advantages, but cannot be considered as
conventional ILs, some of its components are uncharged. The name deep eutectic solvent is used to differentiate this system from ionic liquids. The main highlights of DESs are its smooth preparation method; they are formed by mixing two components with gentle heating and the DES are formed with much lower melting point than the individual components. In addition to catalytic activity, DESs can act as reaction media which make the absence of additional volatile organic solvents in the reaction mixture. Solvents are responsible for the heat and mass transfer phenomenon, stabilization of transition state, modification of reactant, etc.

Deep eutectic solvents have been applied in many areas of chemistry including material preparation, extraction & desulfurization of fuels, electrochemistry, photophysical studies, Chromatography, etc. Among them, organic synthesis is the most relevant application. In this work, DESs were introduced to overcome many of the obstacles presented above by the rapid synthesis of α-aminophosphonates. Here, a comparative study was performed between the physicochemical properties of six deep eutectic solvents formed from ZrOCl_2.8H_2O/ CeCl_3.7H_2O with urea, ethylene glycol & glycerol. The properties were correlated with their activity in Kabachnik-Fields reaction for the synthesis of α-aminophosphonates.

**Experimental**

**Preparation of DES**

Preparation and recycling process of all the six deep eutectic solvents were done based on the procedure given in the previous papers.

**General procedure for α-aminophosphonate synthesis**

A mixture of aldehyde (1 mmol), amine (1 mmol), dimethyl phosphite (DMP= 1 mmol) and DES was stirred at room temperature for the time as indicated in Table 2 & 3 (progress was monitored using TLC). After completion of the reaction, sufficient amount of distilled water was added and the α-aminophosphonate precipitated was filtered and analysed by TLC, GCMS, FTIR, ^1^H NMR, ^13^C NMR and melting point measurements.

**Results and discussion**

Recently, six Type IV- Deep eutectic solvents formed from ZrOCl_2.8H_2O/ CeCl_3.7H_2O with urea, ethylene glycol & glycerol) were reported (Table 1, entry 1- 6), their physicochemical
properties were studied and have been reported as an attractive catalyst and suitable reaction medium for Paal-Knorr reaction 35 & Knoevenagel condensation reaction. 36 All synthesized novel DESs existed as liquid DESs at room temperature and were prepared by trial and error method. The depression in freezing point was strongly affected by the HBDs used due to the difference in interaction with the metal chloride hydrate. In addition to this, the different constituents also influenced the physicochemical properties like density, viscosity, acidity, thermal stability etc. of the DESs. The present manuscript includes a comparison between the DESs based on their properties and a correlation between the properties and activity of DESs as catalyst, with a view to better understanding the properties of the DESs.

Higher ratio of urea was needed to obtain a liquid DES at room temperature in both ZrOCl₂·8H₂O and CeCl₃·7H₂O (Metal salt hydrate: urea= 1:5, Table 1, entry 1 & 4) and was lower for both ethylene glycol & glycerol (Metal salt hydrate with ethylene glycol/ glycerol at 1:2, Table 1, entry 2, 3, 5 & 6). The mutual hydrogen bonding abilities of the components depended the optimal ratio of the hydrogen bond acceptor and hydrogen bond donor that formed the eutectic. 37 The depression in freezing point was dependent on the mole ratio of HBD & HBA and the nature of hydrogen bond donor. Various characterisation techniques were performed for all the six deep eutectic solvents; this included DSC analysis, determination of density, viscosity, acidity and thermal stability.

**DSC analysis**

Thermal transitions of the prepared DESs were studied by DSC analysis. Melting point was observed in DES 1 and a discontinuity in the heat flux was observed in DES 2-DES 6, due to glass transition, corresponding to a change in the structure of DESs from glassy state to rubbery state or vice versa. Similar observation (glass transition rather than freezing point for a wide range of ratios) was previously reported in Potassium carbonate-glycerol 38 and Choline Chloride-lactic acid 39 systems and were called Low Transition Temperature Mixtures (LTTM). 38 In the case of CeCl₃·7H₂O based DESs (DES 4-DES 6), this glass transition occurred at a very low temperature (-64, -20 & -18 °C for DES 4, DES 5 & DES 6 compared to 5 & 8 °C for DES 2 & DES 3). The observations are given in table 1.

**Density**

The knowledge about the density of DESs leads to a better understanding of the liquid behaviour and is one of the most important physical properties for a solvent. Densities of
Deep eutectic solvents are comparatively larger (1.49-1.76 g/cm³) than water/other organic solvents. For density, the variation of the six DESs was [Zr: 5U] < [Zr: 2EG] = [Zr: 2Gly] < [Ce: 5U] < [Ce: 2EG] = [Ce: 2G]. Different molecular organization or packing of the DES might be the contributing factor to this notable difference in density and is generally higher than the pure HBDs (density of urea-1.32, ethylene glycol-1.11 & glycerol 1.26 g/cm³ respectively); this may be due to the presence of voids or empty vacancies in DESs like imidazolium-based ILs. Compared to ZrOCl₂·8H₂O (density=1.91 g/cm³) based DESs, CeCl₃·7H₂O (density=3.97 g/cm³) based DESs were found to be more denser. Within the same metal salt, higher density was observed when glycerol was used as hydrogen bond donor (Table 1, entry 3 & 6). The presence of three hydroxyl groups on HBDs in DES 3 & DES 6 was a contributing factor to the increase of density value as shown by the results. This is due to the formation of 3D network of hydrogen bonds through the interactions between glycerol and anions, which resulted in a closely packed structure and an increase in density. Lowest density was observed when urea was paired with ZrOCl₂·8H₂O (Table 1, entry 1). In general, this difference in density of DESs is due to the varying degrees of hydrogen bonds in these systems.

**Table 1** Deep eutectic solvents prepared with their properties

| Entry | DES   | Mole ratio | Abreviation | DSC Analysis (°C) | Density (g/cm³) | Viscosity (η/ (mPa.s) |
|-------|-------|------------|-------------|-------------------|-----------------|-----------------------|
| 1     | Zr: U | 1:5        | DES 1       | T_f= -30          | 1.49            | 52.40                 |
| 2     | Zr: EG| 1:2        | DES 2       | T_g= 5            | 1.57            | 149.50                |
| 3     | Zr: Gly| 1:2      | DES 3       | T_g= 8            | 1.57            | 532.73                |
| 4     | Ce: U | 1:5        | DES 4       | T_g= -64          | 1.64            | 195.39                |
| 5     | Ce: EG| 1:2        | DES 5       | T_g= -20          | 1.76            | 290.40                |
| 6     | Ce: Gly| 1:2     | DES 6       | T_g= -18          | 1.76            | 868.73                |

(ZrOCl₂·8H₂O = Zr, Ce = CeCl₃·7H₂O  U= Urea, EG= Ethylene glycol, Gly= Glycerol)

**Viscosity**

Like density, viscosities of eutectic mixtures were depending upon many factors; this included chemical nature of the pure constituents, interaction between the components, temperature, water content, free volume etc. Higher viscosity is a major issue in DESs compared to molecular solvents, which makes some difficulties in handling, stirring, the

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1 The data were published before in refs. [35] (DES 1 to DES 3) and [36] (DES 4 to DES 6).
ability to transport the mass within the liquid etc. Because of their potential applications as green reaction media, the preparation of DESs with low viscosities is highly advisable. For dynamic viscosity, the tendency of the six DESs was [Zr: 5U] < [Zr: 2EG] < [Ce: 5U] < [Ce: 2EG] < [Zr: 2Gly] < [Ce: 2G]. Similar to density, greater viscosity value was observed for CeCl$_3$.7H$_2$O based DESs compared to ZrOCl$_2$.8H$_2$O based DESs. Abbot et al reported that DES with low viscosity could be obtained by the use of small cations or fluorinated hydrogen-bond donors. Here, Zr$^{4+}$ (ionic radius= 80 pm) is a smaller cation than Ce$^{3+}$ (ionic radius= 102 pm), corresponding DESs formed less viscous and the result is consistent with the previous reports.$^{40}$ The value is based on the extensive hydrogen bonding network between the pure constituents, which resulted in the limited mobility of the free species inside the DES. Highest viscosity was observed when ZrOCl$_2$.8H$_2$O/ CeCl$_3$.7H$_2$O paired with the glycerol HBD (DES 3 & DES 6 (Table 1, entry 2 & 6). The three hydroxyl groups increased the attractive forces between the molecules by hydrogen bonding interaction (presence of a more robust 3D intermolecular hydrogen-bond network) and made the liquid more viscous. Among the six DESs, ZrOCl$_2$.8H$_2$O paired with urea led to low viscous liquids at room temperature (Table 1, entry 1).

**Acidity**

The knowledge of the acidity of DESs is very important for their application in different fields and is the main factor that determines their catalytic activity. The acidic or basic strength of the DESs is strongly dependent on the chemical nature of the HBDs and the metal salt hydrates. Here, the acidity of DESs was determined by FTIR study (using pyridine as probe (Py-IR)) and pH measurement (using pH meter). A peak at 1450 cm$^{-1}$ indicated the Lewis acidity and peak at 1640 cm$^{-1}$ & 1540 cm$^{-1}$ indicated Brønsted acidity, Details are given in previous reports.$^{35}$ & $^{36}$
ZrOCl$_2$.8H$_2$O/ CeCl$_3$.7H$_2$O with urea showed both Brønsted and Lewis acidity and other DESs showed only Brønsted acidity. The variation of Brønsted acidities of the DESs is [Zr: 5U] < [Ce: 2G] < [Ce: 2EG] < [Ce: 5U] < [Zr: 2EG] = [Zr: 2Gly]. Higher bronsted acidity was observed for ZrOCl$_2$.8H$_2$O with urea combination (pH- 2.20) and slightly acidic with ethylene glycol/glycerol (pH- 6.99). But in the case of CeCl$_3$.7H$_2$O, similar Brønsted acidity was observed for all the three DESs (pH of DES 4, DES 5 & DES 6 were 4.71, 4.44 & 4.27 respectively) and were much lower than DES 1; but higher than DES 2 & DES 3. The results are given in Table 2.

### Table 2 Acidity & thermal stability of deep eutectic solvents

| Entry | DES   | Peak for Lewis site (cm$^{-1}$) | Peak for Bronsted site (cm$^{-1}$) | pH     | Complete decomposition takes place at T (°C) |
|-------|-------|---------------------------------|------------------------------------|--------|-------------------------------------------|
| 1     | DES 1 | 1450                            | ~1540                              | 2.20   | 273                                       |
| 2     | DES 2 | -                               | ~1540                              | 6.99   | 118                                       |
| 3     | DES 3 | -                               | ~1540                              | 6.99   | 129                                       |
| 4     | DES 4 | 1450                            | ~1640                              | 4.71   | 275                                       |
| 5     | DES 5 | -                               | ~1640                              | 4.44   | 143                                       |
| 6     | DES 6 | -                               | ~1640                              | 4.27   | 150                                       |

2 The figures were published before in refs. [35] (DES 1 to DES 3) and [36] (DES 4 to DES 6).

3 The data were published before in refs. [35] (DES 1 to DES 3) and [36] (DES 4 to DES 6).
Thermal stability
Similarly, the information about the thermal stability of DESs is very important for their application at higher temperatures and is dependent upon the hydrogen bond donors used. TG curve of six DESs are given below (Figure 2).

**Figure 2** TG curves of DES 1 – DES 6

Hydrogen bond plays an important role on the thermal stability of DESs, it is a type of weak intermolecular force, and could be broken when temperature increases to some extent. Complete decomposition was observed in the case of DES formed from urea and metal salt hydrate (DES 1 & DES 4). But a progressive decomposition with temperature was observed in other DESs. Here, the decomposition is divided into two steps. At first, the decomposition of HBDs with relatively poor thermal stability was observed around 115 °C to 150 °C in DES 2, DES 3, DES 5 & DES 6 ([Zr: 2EG], [Zr: 2Gly], [Ce: 2EG] & [Ce: 2Gly]). The similar observation was reported in the case of ChCl: Urea deep eutectic solvents. Hydrogen bond donors play a vital role in designing more stable deep eutectic solvents. DES with higher

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4 The figures were published before in refs. [35] (DES 1 to DES 3) and [36] (DES 4 to DES 6).
thermal stability could be prepared by selecting suitable HBDs. Higher thermal stability was observed for ZrOCl$_2$.8H$_2$O/ CeCl$_3$.7H$_2$O with urea combination compared to other HBDs.

**Catalytic activity**

To verify the applicability of DESs, Kabachnik-Fields reaction was performed with all the six DESs and the activity was correlated with the physicochemical properties of the six DESs. Initially, a mixture of benzaldehyde (1 mmol), aniline (1 mmol) and dimethyl phosphite (1 mmol) was stirred at room temperature without any solvent and catalyst. The reaction did not progress even after 4 h, which indicated the necessity of a catalyst in this reaction (Table 3, Entry 1). The reaction was performed using 0.2 mmol of DES 1 (ZrOCl$_2$.8H$_2$O: Urea at 1: 5 ratio), 80 % yield was obtained within 15 min (Table 3, Entry 2). The same reaction was repeated by varying the amount of catalyst and time. An outstanding yield (98 %) was obtained within 5 min by using 0.6 mmol of DES 1, after that there was no noticeable improvement in product yield which was the optimum catalytic condition and time needed for the reaction (Table 3, Entry 7). Maintaining this optimum condition, the reaction was repeated using DES 2 - DES 6, but the reaction was sluggish with these DESs (Table 3, Entry 8-12).

**Table 3** Screening & optimisation of catalyst for Kabachnik-Fields reaction

| Entry | DES  | catalyst | Time (min) | Yield (%) |
|-------|------|----------|------------|-----------|
|       |      | (g)      | (mmol)     |           |
| 1     | DES 1 | -        | -          | 4 h       | No reaction |
| 2     | DES 1 | 0.124    | 0.2        | 15        | 80         |
| 3     | DES 1 | 0.248    | 0.4        | 15        | 85         |
| 4     | DES 1 | 0.373    | 0.6        | 15        | 98         |
| 5     | DES 1 | 0.435    | 0.7        | 15        | 98         |
| 6     | DES 1 | 0.497    | 0.8        | 15        | 97         |
| 7     | DES 1 | 0.373    | 0.6        | 5         | 98         |
| 8     | DES 2 | 0.279    | 0.6        | 5         | 60         |
| 9     | DES 3 | 0.303    | 0.6        | 5         | 55         |
| 10    | DES 4 | 0.403    | 0.6        | 5         | 50         |
| 11    | DES 5 | 0.297    | 0.6        | 5         | 40         |
| 12    | DES 6 | 0.331    | 0.6        | 5         | Trace      |
Reaction condition: aldehyde (1 mmol), amine (1 mmol), DMP (1 mmol), RT.

The catalytic activities of DESs are mainly dependent upon their physicochemical properties like density, viscosity, acidity etc. Among the six DESs, quantitative conversion was observed using DES 1 (with lower density, viscosity and higher acidity and thermal stability) and was found to be the most effective catalyst compared to others and solid product was formed instantly by the addition of the catalyst which restricted further stirring.

Two pathways for Kabachnik-Fields reaction was introduced by Cherkasov et al. A) Nucleophilic addition of amine to aldehyde followed by the addition of phosphite to imine. B) The second one involves the formation of α-hydroxyphosphonate by the nucleophilic addition of dialkylphosphite to the carbonyl compound followed by the displacement of hydroxyl group by the amino group (Abramov reaction). Keeping this in mind, benzaldehyde was treated with a) aniline b) dimethylphosphate in the presence of DES 1 in separate experiments to propose a plausible mechanism. Imine formation was observed in the former (GC-MS) and α-hydroxyphosphonate was not observed in the latter (Scheme 2).

**Scheme 2** Pathway for Kabachnik-Fields reaction

In order to establish the result, the reaction was repeated using the aldehydes in Table 3, the outcome was the same. Hence, it was confirmed that the mechanism followed the pathway A (imine forming pathway). Also, the order of addition of reactants did not have any effect in the reaction, like product yield, purity etc. DES 1 & DES 4 were both Brønsted and Lewis acidic; but the other DESs (DES 2, DES 3, DES 5 & DES 6) were only Brønsted acidic; product formation was observed in all the six deep eutectic systems, so the Brønsted acidity may be the activating factor here. This will avoid the problems associated with the deactivation/decomposition of Lewis acid during imine formation. Accordingly, a plausible mechanism is proposed for the DES 1 catalysed Kabachnik-Fields reaction using benzaldehyde & aniline with dimethylphosphite and based on Brønsted acidic condition and is given in Scheme 3.
Initially, DES interacted with the carbonyl group of the benzaldehyde to form an activated complex, followed by the generation of imine through the nucleophilic addition of aniline to the activated complex. In the presence of the catalyst, the carbon of imine was attacked by phosphite and the desired α-aminophosphonate was formed with the regeneration of the catalyst. With these conditions in hand, the attention was focussed to assess the functional group resilience of this reaction with DES 1. For that, various aldehydes, amines and dimethyl phosphite were subjected to a one pot three component reaction catalysed by DES 1. Corresponding α-aminophosphonates were formed in good to excellent yield and the outcome is summarised in Table 4.
Table 4 Synthesis of α-aminophosphonates in DES 1

![Chemical Structure]

| Entry | Aldehyde                  | Amine             | Time (min) | Yield (%) |
|-------|---------------------------|-------------------|------------|-----------|
| 1     | Benzaldehyde              | Aniline           | 5          | 98        |
| 2     | Benzaldehyde              | 3-Chloroaniline   | 5          | 98        |
| 3     | Benzaldehyde              | 4-Bromoaniline    | 5          | 95        |
| 4     | Benzaldehyde              | 4-Methoxyaniline  | 10         | 98        |
| 5     | 4-Chlorobenzaldehyde      | Aniline           | 5          | 96        |
| 6     | 4-Chlorobenzaldehyde      | 3-Chloroaniline   | 5          | 95        |
| 7     | 4-Chlorobenzaldehyde      | 4-Methoxyaniline  | 5          | 95        |
| 8     | 2-Methoxybenzaldehyde     | Aniline           | 10         | 96        |
| 9     | 2-Methoxybenzaldehyde     | 3-Chloroaniline   | 10         | 98        |
| 10    | 2-Methoxybenzaldehyde     | 4-Bromoaniline    | 10         | 95        |
| 11    | 2-Methoxybenzaldehyde     | 4-Methoxyaniline  | 20         | 95        |
| 12    | 4-Methoxybenzaldehyde     | Aniline           | 10         | 98        |
| 13    | 4-Methoxybenzaldehyde     | 3-Chloroaniline   | 5          | 95        |
| 14    | Veratraldehyde            | Aniline           | 5          | 92        |
| 15    | Veratraldehyde            | 3-Chloroaniline   | 10         | 95        |
| 16    | Veratraldehyde            | 4-Bromoaniline    | 10         | 92        |
| 17    | 3,4,5-Trimethoxybenzaldehyde | Aniline         | 10         | 90        |
| 18    | 3,4,5-Trimethoxybenzaldehyde | 3-Chloroaniline | 15         | 92        |
| 19    | 3- Nitrobenzaldehyde      | Aniline           | 25         | 90        |
| 20    | Furfural                  | Aniline           | 10         | 88        |
| 21    | 1-Naphthaldehyde          | Aniline           | 15         | 90        |
| 22    | Cinnamaldehyde            | Aniline           | 20         | 88        |

Reaction condition: aldehyde (1 mmol), amine (1 mmol), DMP (1 mmol) and DES 1 (0.6 mmol), RT
Both electron withdrawing/donating groups on the aromatic aldehyde reacted efficiently with excellent yield. The reaction conditions were very gentle and α-aminophosphonates were formed without the formation of any side products (with all the substrates used, α-hydroxyphosphonates were not formed due to the rapid formation of iminium species). Various aromatic amines reacted neatly with excellent yields.

At first, the reaction was performed by using benzaldehyde/monosubstituted benzaldehydes with aniline/substituted anilines; excellent yields were obtained for all the derivatives (both electron donating and electron withdrawing), the results are tabulated in table 4 (Entry 1-13 & 19). The reaction was repeated by replacing monosubstituted aldehydes with di substituted (Veratraldehyde) & tri substituted aldehyde (3,4,5-Trimethoxybenzaldehyde); higher yields were obtained without any steric effect on the reaction (Table 4, Entry 14-18). The study of catalytic scope was explored by repeating the experiment using heteroaromatic aldehyde (furfural) with aniline, the result was the same (Table 4, Entry 20 & 21). Naphthaldehyde with aniline and dimethyl phosphite reacted well with admirable yield (Table 4, Entry 22). Unsaturated aldehyde, such as cinnamaldehyde underwent the reaction with aniline and dimethyl phosphite under the above condition to produce the corresponding α-aminophosphonates without any polymerisation (Table 4, Entry 23). The reactivity of ketones under similar conditions was also examined. However, in this case, the reactions did not afford the analogous α-aminophosphonates. On the basis of the experimental data, there was no need to use exotic (expensive and environmentally unfriendly) catalysts and organic solvent in this method.

The structures of the synthesised products are given below. Product separation is one of the main advantages of this method, highly soluble DESs can be separated easily by simple water washing of the reaction mixture.
Comparison with previous reports

After the successful utilization of DES 1 as a catalyst for Kabachnik-Fields reaction of various substrates, a comparative study was performed with the reported catalytic systems. In most of the previous reports, the dialkyl phosphite system used was diethyl phosphite. Here,
DES 1 was compared with a few reports using benzaldehyde, aniline and dimethyl phosphite as model substrates. At first, the results were compared with a nano magnetic sulphated zirconia catalyst (Fe₃O₄@ZrO₂/SO₄²⁻) reported by H. Ghafuri et al in 2016. Here, the synthesis of the catalyst was a tedious process (the crucial synthesis of Fe₃O₄ nanoparticles was followed by the synthesis of Fe₃O₄@ZrO₂/SO₄²⁻) and also required higher temperature and time (Table 5, Entry 1) compared to the present catalyst. Similarly, in 2014, M. Nazish et al. reported magnetic-nanoparticle-supported phosphotungstic acid (Fe₃O₄@SiO₂-PTA). Here also, more steps were involved in the catalyst preparation process (three steps were involved here; first, synthesis of Fe₃O₄, then synthesis of silica-coated Fe₃O₄ and finally synthesis of Fe₃O₄@SiO₂-PTA). In addition to this, prolonged reaction time was required for the synthesis of α-aminophosphonates (Table 5, Entry 2).

**Table 5** Comparative study of DES 1 with previous reports for Kabachnik-Fields reaction

| Entry | Catalyst            | Solvent | Time/ Temp (°C) | Yield (%) | Ref. | Reusability |
|-------|---------------------|---------|----------------|-----------|------|-------------|
| 1     | Fe₃O₄@ZrO₂/SO₄²⁻   | -       | 30 min/ 80 °C | 95        | 8    | 5 Runs      |
| 2     | Fe₃O₄@SiO₂-PTA      | -       | 3 h/ RT       | 97        | 15   | 5 Runs      |
| 3     | PFPAT               | Toluene | 60 min/ RT    | 90        | 19   | -           |
| 4     | DTP/SiO₂            | CH₃CN   | 1h/ RT        | 98        | 43   | 6 Runs      |
| 5     | KCAR                | H₂O     | 30 min/ 80 °C | 96        | -    | -           |
| 6     | DHAA-Fe₃O₄          | -       | 2 h/ 40 °C    | 93        | 45   | -           |
| 7     | ZrOCl₂.8H₂O         | -       | 8 h/ RT       | 90        | 46   | -           |
| 8     | DES 1               | -       | 5 min/ RT     | 98        | Present work | 5 Runs |

Reaction condition: benzaldehyde (1 mmol), aniline (1 mmol), DMP (1 mmol)

The study was extended to other catalysts mentioned in Table 5. An organocatalyst, pentafluorophenylammonium triflate (PFPAT) was also used as catalyst in Kabachnik-Fields reaction in 2014. The reaction was completed within 60 min with the use of volatile organic solvent (Toluene). The details are given in table 5 (Table 5, Entry 3). Silica supported dodecatungstophosphoric acid (DTP/SiO₂) was introduced by S. A. R. Mulla et al. in 2014. Here also the reaction was completed after 1h with the use of acetonitrile as solvent (Table 5, Entry 4). A seaweed-derived biopolymer, k-carrageenan (KCAR) was introduced by S.
Rostamnia et al. in 2016. But this method involved long reaction time and higher temperature compared with the present work (Table 5, Entry 5). Another nanocatalyst dehydroascorbic acid capped magnetite nanoparticles (DHAA-Fe₃O₄) was reported. Here also, harsh method of preparation of the nanocatalyst and prolonged reaction time was required (Table 5, Entry 6). Catalytic activity of DES 1 was compared with ZrOCl₂.8H₂O (Table 5, Entry 7). This method required long reaction time (8 h), which indicated the importance of forming DES 1 from ZrOCl₂.8H₂O and urea. DES 1 provided better results in terms of high yield, easy preparation and non-toxic nature of the catalyst, a solvent-free protocol, and the reaction was carried out at room temperature. Among this, easy method of preparation is the main highlight of the present work. In addition to this, the wide substrate applicability was studied by preparing 22 different α-aminophosphonates in the present work.

Recyclability of DES 1
After completion of the reaction, the product was washed with water and filtered off and the catalyst obtained in the water layer was recycled and reused up to 5 runs without any noticeable loss in catalytic activity and the results are summarised in Table 6.

Table 6 Recyclability of DES 1 for Kabachnik-Fields reaction

| No.of cycles | 1   | 2   | 3   | 4   | 5   |
|--------------|-----|-----|-----|-----|-----|
| Yield (%)    | 98  | 95  | 91  | 88  | 85  |

Reaction condition: benzaldehyde (1 mmol), aniline (1 mmol), DMP (1 mmol), RT

Conclusion

The present work outlined the comparison of physicochemical properties of six Type IV-Deep Eutectic Solvents (formed from ZrOCl₂.8H₂O/ CeCl₃.7H₂O with urea, ethylene glycol & glycerol) and a systematic study of catalytic activity of DESs for Kabachnik Fields reaction, which was a simple technique for carbon-phosphorous bond formation. Based on this study, it was concluded that the physicochemical properties of DESs like density, viscosity etc. were closely related to that of conventional ionic liquids (with some additional advantages of lower toxicity, cost effectiveness, convenient synthesis (100 % atom economy) etc. The density and viscosity of CeCl₃.7H₂O based DESs were higher than that of ZrOCl₂.8H₂O based DESs. Higher thermal stability was observed when ZrOCl₂.8H₂O/ CeCl₃.7H₂O was paired with urea compared with ZrOCl₂.8H₂O/ CeCl₃.7H₂O with ethylene
glycol/ glycerol. The properties were strongly dependent upon the selection of HBD & HBA and could be tuned by changing the hydrogen bond donor and hydrogen bond acceptors, which led to the preparation of task specific DES. By this way, DES with lower viscosity could be prepared, which was one of the main issues related with DESs in organic synthesis. Among the six DESs, lower density, viscosity and higher acidity and thermal stability was observed for DES 1 (ZrOCl₂·8H₂O with urea at 1:5 ratio) and was found to be a magnificent catalyst for Kabachnik Fields reaction and could replace many harmful catalysts and volatile solvents. The dominance of this method includes simple procedure, benign reaction conditions, free from organic solvents, broad application scope, cost effectiveness, outstanding yield, easy separation of products and renewability of the catalyst (reusability has been achieved up to 5 runs, without any influence in its activity). In addition to this, the wide substrate scope was scrutinised by synthesising 22 different α-aminophosphonate derivatives in the present work. The products were characterised by TLC, GCMS, ¹H NMR, ¹³CNMR, and melting point measurements (Supporting Information File).

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