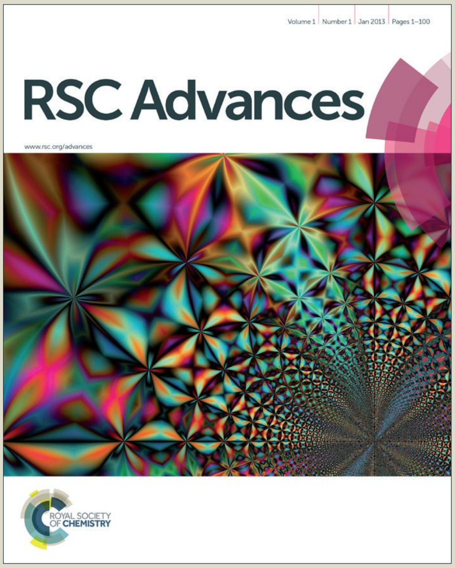
RSC Advances

This article can be cited before page numbers have been issued, to do this please use: M. Tiecco, R. Germani and F. Cardellini, *RSC Adv.*, 2016, DOI: 10.1039/C6RA04721A.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C6RA04721A

Carbon-Carbon bond formation in acid deep eutectic solvent: chalcones synthesis via Claisen-Schmidt reaction

Matteo Tiecco, Raimondo Germani*, Fabio Cardellini

CEMIN, Centre of Excellence on Nanostructured Innovative Materials, Department of Chemistry, Biology and Biotechnology, University of Perugia, via Elce di Sotto 8, I-06123 Perugia, Italy.

*Corresponding author: Raimondo Germani,
Department of Chemistry, Biology and Biotechnology, University of Perugia, via Elce di Sotto 8-I 06123 Perugia, Italy
E-mail: raimondo.germani@unipg.it
Phone: + 39 075 585 5538
Fax: +39 075 585 5560

View Article Online
DOI: 10.1039/C6RA04721A

ABSTRACT

One of the most studied properties of novel organic solvents is represented by their use as media for many chemical reactions. In this field Ionic Liquids (ILs) and more recently Deep Eutectic Solvents (DESs) have been playing significant roles for their smart properties. DESs are increasing their relevance thanks to their low toxicity, and because of their simple and cheap preparation that can be carried out by simply mixing two compounds.

In this work we present the studies of the use of an acid DES obtained from 3-(cyclohexyldimethylammonio)propane-1-sulfonate and (1S)-(+)-10-Camphorsulfonic acid (SB3-Cy / CSA) as reaction media and catalyst for carbon-carbon bond formation reaction via Claisen-Schmidt condensation. This powerful and widely used aldol condensation was performed without the use of any catalysts that are usually needed in this reaction, because of the presence of acid CSA in the DES components. We synthesised sixteen substituted chalcones from benzaldehydes and substituted benzaldehydes in combination with acetophenone and substituted acetophenones as probe reactions.

The advantages of the use of this DES in this relevant reaction are represented by: the green properties of the media and its low toxicity; the absence of harmful acids to catalyse the aldol condensation because of the camphorsulfonic acid composing the DES mixture; the recycling and the re-use of the DES in subsequent reaction cycles; the mild conditions and the excellent conversions and yields observed.

KEYWORDS: C-C bond formation; chalcones; acid DES; sulfobetaine; camphorsulfonic acid.

View Article Online
DOI: 10.1039/C6RA04721A

INTRODUCTION

The design of innovative reaction media and of novel synthetic strategies has increased its relevance in the green chemistry framework, with the goal of obtaining more environmental friendly processes. Novel organic solvents such as ionic liquids (ILs) play a key-role in this field[1-3]. These liquids are formed by organic cations and organic or inorganic anions; they are liquid at temperatures under 100°C, and they have many "green" advantages compared to other typical organic solvents. They have, in fact, low vapour pressure, high thermal stability and low flammability. These properties pushed the researchers to apply these solvents as ecological friendly reaction media[4-7]. Unfortunately the ILs showed low biodegradability and low biocompatibility, and therefore low sustainability[7-10]; the synthesis and purification of these media often requires extensive use of organic solvents[7].

Deep Eutectic Solvents (DESs) represent a step forward on novel green media production, and they are an innovative and promising class of liquids still to be fully described and analysed[11-15]. For their simplicity of preparation, the atom economy, and the low cost of many starting reagents, DESs have gained particularly attention as substitutes of conventional volatile organic solvents and of ILs in many chemical processes[16-21]. A class of DES can be prepared, in fact, simply mixing high-melting point salts (such as ammonium or phosphonium ones) with hydrogen bond donor compounds. The hydrogen-bond interaction that occurs within the donor and the acceptor molecules determines a considerable reduction of the melting point of the mixtures, therefore a liquid system formation, even at room temperature[22]. One of the advantages of the use of the DESs instead of the ILs is represented by their low or absent toxicity, as shown in recent papers[13, 22-25]. DESs have been studied and used in the recent literature as solvents for chemical processes, but also as catalysts[26]. A non-exhaustive list of these reactions is represented by: Knoevenagel condensations[27, 28], Paal-Knorr reaction[29], halogenation reactions[30], N-alkylation of aromatic primary amines[31], synthesis of N-aryl phthalimide derivatives[32], oxidation of alcohols[33], and so on.

Aldol condensation is a powerful and well-known tool for C-C bond formation between two carbonyl derivatives[34, 35]. It has numerous applications in the synthesis of fine chemicals and it can be accomplished both via basic[36] and acid[37, 38] catalysis. The aldol condensation was deeply investigated in ILs, as they can act as reaction media[39, 40] and also as catalysts[41]: this is the case of protic-ILs, a relevant acidic sub-class of these liquids[5]. The Claisen-Schmidt reaction is an important sub-class of aldol condensation involving an aldeide/ketone and a carbonyl compound lacking an alpha-hydrogen. This reaction is generally used for the synthesis of chalcones, an important class of molecules with relevant pharmaceutical properties[42-44]. The syntheses were investigated in ILs reaction media in literature[45]. Dong and co-workers and Qian and co-workers performed the Claisen-Schmidt reactions in acid-ILs media under N_2 atmosphere at 120°C and 140°C respectively[46, 47]. Aldol condensation reaction was carried out even in deep eutectic solvents media in literature, but the DESs used in these works were not able to accomplish both the roles of reaction media and catalysts, calling for the use of other reagents and of other procedures. Müller and co-workers performed aldol reactions with tandem catalysis of enzymes and organocatalysts in DESs[48, 49]. Martínez and colleagues used L-proline as catalyst to achieve an enantioselective intermolecular aldol reaction in D-glucose and racemic malic acid DES[50]. Gotor-Fernández and co-workers performed recently the promiscuous lipase-catalysed aldol reaction in choline chloride / glycerol deep eutectic solvent that led to excellent conversions of the reactants[51].

Moving forward on our characterizations and on our use of novel “greener” solvents[4-6, 52], in this work we report the use of a DES both as reaction media and Brønsted acid catalyst in the synthesis of substituted chalcones via Claisen-Schmidt reaction. This is a probe reaction of C-C bonds formation and it was performed without the use of any other catalysts. 3-(cyclohexyldimethylammonio)propane-1-sulfonate (SB3-Cy) and (1S)-(+)-10-Camphorsulfonic acid (CSA) mixture (hereinafter reported as SB3-Cy / CSA) was chosen in a set of Room Temperature Deep Eutectic Solvents (RTDESs) we recently realized and characterized[22]. This DES was chosen in this set (composed by differently structured sulfobetaines with aliphatic, aromatic and amphiphilic moieties) for many reasons: it is colourless; it has an intermediate viscosity between the set; it has advantages deriving from the cost and the availability of the tertiary amine (SB3-Cy) forming it; the DES from this amine can be easily obtained considering the reactivity of the other aromatic sulfobetaines; it could prevent emulsion formation in the elaboration processes that can occur in the case of amphiphilic sulfobetaines use.

This DES has a catalytic behaviour in the reaction between benzaldehydes and acetophenones due to the acid properties of the CSA composing it. It was prepared by simply mixing the two solid components that have high melting points (198°C for CSA, 116°C for the sulfobetaine), and it is a liquid system even at room temperature (9°C). The low conductivity values observed for this DES in our previous work showed that in the mixture the proton has not been transferred from the acid to the sulfobetaine, therefore it cannot be considered an acid-IL.

There are many “green” advantages in the use of SB3-Cy / CSA DES in this probe reaction: it is an environmental friendly solvent for its properties and for its low toxicity; no harmful acids are needed to catalyse the reaction; the high recyclability of the media was proved on subsequent reaction cycles. SB3-Cy / CSA DES was chosen as model mixture in our set for its properties. We used also SB3-MIM (3-(1-methyl-1*H*-imidazol-3-ium-3-yl)propane-1-sulfonate) / CSA mixture in one of the reactions in order to improve its conversion and yield and to demonstrate the applicability of a specific DES for a specific role[22]. All the reactions studied in this work were performed at the temperature of 90°C and in times spanning from 4 to 16 hours.

EXPERIMENTAL

Materials and Methods

Solvents, *tert*-butylbenzene, (1S)-(+)-10-camphorsulfonic acid, N,N-dimethylcyclohexylamine, 1,3-propanesultone, benzaldehyde and substituted benzaldehydes, acetophenone and substituted acetophenones were purchased of analytical grade from Sigma-Aldrich, Fluka and Alfa Aesar and were used without further purifications.

Melting points were determined on crystallized products on a Barloworld Scientific Stewart SMP3 micro melting point apparatus and are uncorrected. Agilent 6850 Series II Network Gas Chromatography instrument (column DB-35MS l = 30 m, d = 0.32 mm, film = 0.25 mm) was used for GC analysis. ^{1}H-NMR and ^{13}C-NMR spectra were measured at 25°C with a Bruker AVANCE III HD 400 MHz and with a Bruker 200 MHz instruments in D_2O, $CDCl_3$ and acetone-d$_6$ solutions with tetramethylsilane ($(CH_3)_4Si$) as internal standard.

DES preparation

3-(cyclohexyldimethylammonio)propane-1-sulfonate (SB3-Cy) was prepared via reaction of N,N-dimethylcyclohexylamine with 1,3-propanesultone according to previous procedures reported in literature, and the recorded melting point and ^{1}H-NMR spectra agree with the same literature data[22]. The DES was prepared following the procedure reported in the same paper. (1S)-(+)-10-camphorsulfonic acid (CSA) was dried under vacuum over P_2O_5 prior to use. SB3-Cy and CSA, in 1:1.5 molar ratio, were directly weighted in a flask fitted with a stopper. The solid mixture was magnetically stirred and heated at 90°C until a liquid was formed (20-30 minutes).

General synthetic procedure

View Article Online
DOI: 10.1039/C6RA04721A

In a 10 ml round-bottomed flask 10 mmol of (1S)-(+)-10-camphorsulfonic acid (CSA) and 7 mmol of 3-(cyclohexyldimethylammonio)propane-1-sulfonate (SB3-Cy) were introduced (1:1.5 molar ratio). The mixture was heated at 90°C for 20 minutes in a thermostated oil bath under stirring, until a homogeneous liquid was formed. The aldehyde and the ketone (3.3 mmol, 1:1 molar ratio) were added to the mixture. The mixture was stirred at 90°C for the time needed for each reaction; then it was cooled to room temperature. The reaction mixture was quantitatively transferred in a separator funnel and extracted five times with ethyl acetate. The organic phase was dried under Na_2SO_4 and filtered through a fluted filter in a round-bottomed flask. The products were purified with column chromatography with cyclohexane:ethyl acetate mixture as eluent with different elution gradient; a recrystallization was made in some of the reactions performed. Every reaction was repeated twice, in order to determine the conversion via GC and in order to purify the products to determine the isolated product yield.

Conversion determination procedure

The conversions were determined via GC. The reaction mixtures were cooled to room temperature, transferred in a separator funnel, and *tert*-butylbenzene (Sigma-Aldrich, >99%) was added as internal standard. The mixtures were extracted five times with ethyl acetate. The organic phases was dried under Na_2SO_4 and analyzed on GC. The conversion was determined on the benzaldehyde (γ = 1.78) or acetophenone (γ = 1.45) or 3,4-dimethoxybenzaldehyde amounts in different experiments.

Characterization of the chalcones

All the spectra are reported in Supporting Information section.

(1) (2E)-1,3-diphenylprop-2-en-1-one[53]: after chromatographic column the product was recrystallized with H_2O:EtOH 80:20 mixture. A yellow solid was obtained. Yield 64%, m.p. 55-57°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 2H), 7.85 (d, *J* = 15.6 Hz, 1H), 7.71 – 7.50 (m, 6H), 7.45 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.55, 144.85, 138.22, 134.90, 132.81, 130.57, 128.98, 128.65, 128.53, 128.47, 122.10.

(2) (2E)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one[53]: the product was purified via chromatographic column then recrystallized with H_2O:EtOH 80:20 mixture. A yellow solid was obtained. Yield 80%, m.p. 179-180°C, ^1H NMR (400 MHz, Acetone-d_6) δ 8.16 – 8.09 (m, 2H), 7.81 – 7.69 (m, 4H), 7.69 – 7.59 (m, 2H), 7.59 – 7.49 (m, 2H), 6.98 – 6.91 (m, 2H). ^{13}C NMR

View Article Online
DOI: 10.1039/C6RA04721A

(101 MHz, Acetone-d_6) δ 189.02, 159.95, 144.32, 138.60, 132.48, 130.68, 128.57, 128.27, 126.72, 118.80, 115.84, 29.73.

(3) (2E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one[54]: the product was recrystallized with H_2O:EtOH 80:20 mixture. A yellow solid was obtained. Yield 93%, m.p. 163-164°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.3 Hz, 2H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.88 – 7.77 (m, 4H), 7.71 – 7.60 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.62, 148.55, 141.50, 141.05, 137.53, 133.38, 128.95, 128.83, 128.60, 125.71, 124.22.

(4) (2E)-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one[55]: Yield 65%, m.p. 118-120°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 - 8.13 (d, *J* = 16 Hz, 1H), 8.10 - 8.03 (m, 3H), 7.78 - 7.69 (m, 2H), 7.64 – 7.52 (m, 4H), 7.37 – 7.33 (d, *J* = 16 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.48, 148.55, 140.19, 137.41, 133.60, 133.17, 131.33, 130.37, 129.26, 128.80, 128.74, 127.34, 125.01.

(5) (2E)-3-(4-hydroxy-3-methoxyphenyl)-1-phenylprop-2-en-1-one[56]: Yield 76%, m.p. 92-93°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.56 (m, 3H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.28 – 7.19 (m, 1H), 7.15 (s, 1H), 6.98 (m, 1H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.71, 148.34, 146.88, 145.35, 145.32, 145.28, 138.49, 132.59, 128.58, 128.44, 127.45, 123.43, 119.80, 119.76, 114.94, 114.91, 110.08, 110.03, 56.02.

(6) (2E)-3-(2,4-dichlorophenyl)-1-phenylprop-2-en-1-one[57]: Yield 94%, m.p. 127-128°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 15.7 Hz, 1H), 8.04 (m, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.58 (m, 1H), 7.58 – 7.45 (m, 4H), 7.37 – 7.26 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.12, 139.34, 137.77, 136.48, 133.08, 131.86, 130.15, 128.72, 128.50, 127.57, 125.03.

(7) (2E)-3-(2-chloro-5-nitrophenyl)-1-phenylprop-2-en-1-one[58]: Yield 87%, m.p. 142-143°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.25 – 8.13 (m, 2H), 8.12 – 8.05 (m, 2H), 7.72 – 7.62 (m, 3H), 7.61 – 7.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.29, 146.79, 141.71, 137.92, 137.34, 134.83, 133.49, 131.33, 129.23, 128.86, 128.70, 128.05, 126.92, 125.07, 122.82, 122.53.

(8) (2E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one[59]: Yield 51%, m.p. = 61-63°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.98 (m, 2H), 7.81 (m, 1H), 7.68 – 7.39 (m, 6H), 7.02 - 6.91 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.61, 161.69, 144.72, 138.52, 132.56, 130.24, 128.57, 128.42, 127.63, 119.80, 114.43, 55.43.

(9) (2E)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one[53]: the product was recrystallized with H_2O:EtOH 60:40, a yellow solid was obtained. Yield 22%, m.p. 90-91°C. ^1H NMR (400 MHz, $CDCl_3$) δ 12.86 (s, 1H), 7.95 (m, 2H), 7.73 – 7.65 (m, 3H), 7.58 – 7.44 (m, 4H), 7.06 (m, 1H), 6.98 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.74, 163.61, 145.48, 136.43, 134.60, 130.95, 129.68, 129.06, 128.69, 120.12, 120.03, 118.88, 118.65.

View Article Online
DOI: 10.1039/C6RA04721A

(10) (2E)-1-(3-hydroxyphenyl)-3-phenylprop-2-en-1-one[60]**:** The product was recrystallized with H_2O:EtOH 80:20 mixture, a yellow solid was obtained. Yield 93%, m.p. 126-127°C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.71 (s, 1H), 7.68 – 7.47 (m, 4H), 7.41 (m, 4H), 7.18 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 191.25, 156.67, 145.71, 139.36, 134.67, 130.80, 129.95, 128.99, 128.62, 121.91, 121.02, 120.95, 120.71, 115.34.

(11) (2E)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one[61]**:** The product was recrystallized with H_2O:EtOH 80:20; a yellow solid was obtained. Yield 93%, m.p. 102-103°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.83 (m, 1H), 7.72 – 7.52 (m, 3H), 7.44 (m, 3H), 7.08 – 6.94 (m, 2H), 3.98 – 3.89 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 188.72, 163.45, 143.98, 135.09, 131.10, 130.84, 130.46, 130.34, 128.94, 128.57, 128.38, 127.47, 121.89, 113.87, 113.71, 55.51.

(12) (2E)-1-[4-(dimethylamino)phenyl]-3-phenylprop-2-en-1-one[62]**:** The product was recrystallized with H_2O:EtOH 80:20 mixture giving a yellow solid. Yield 80%, m.p. 99-100°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.81 (m, 1H), 7.54 (m, 6H), 7.36 (m, 1H), 6.76 (m, 2H), 3.08 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 190, 150, 146, 138, 132, 130, 129, 128, 128, 117, 112, 40.

(13) (2*E*)-1,3-bis(3,4-dimethoxyphenyl)prop-2-en-1-one[63]**:** The product was recrystallized with H_2O:EtOH 70:30 mixture giving a pale yellow solid. Yield 60%, m.p. 110-112°C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 1H), 7.70 (m, 1H), 7.64 (m, 1H), 7.43 (m, 1H), 7.30 – 7.22 (m, 1H), 7.18 (m, 1H), 6.93 (m, 2H), 4.02 – 3.91 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.67, 153.12, 151.27, 149.24, 149.22, 144.15, 131.56, 128.06, 122.90, 122.87, 119.66, 111.13, 110.83, 110.21, 109.92, 56.09, 56.08, 56.01, 55.99.

(14) (2E,4E)-1,5-diphenylpenta-2,4-dien-1-one[64]**:** An orange solid was obtained. Yield 64%, m.p. 102-103°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.67 - 7.34 (m, 10H), 7.06 - 7.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.49, 144.86, 141.94, 138.24, 136.12, 132.68, 129.25, 128.88, 128.76, 128.61, 128.41, 127.33, 126.97, 125.44.

DES recycling

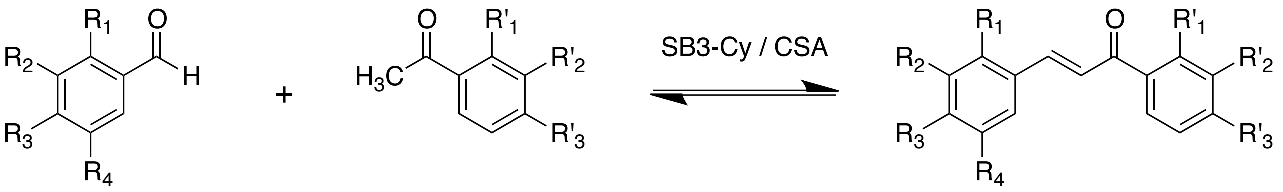
In a 10 ml round-bottomed flask 10 mmol of (1S)-(+)-10-camphorsulfonic acid and 7 mmol of SB3-Cy / CSA mixture (1:1.5 molar ratio) were introduced. The mixture was heated at 90°C for 20 minutes in a thermostated oil bath under stirring until a homogeneous liquid was formed. 2-chloro-5-nitro-benzaldehyde and acetophenone were added to the mixture, 3.3 mmol (1:1 molar ratio). The mixture was maintained at 90°C for 4 h under stirring. The solution was then cooled to room temperature and 2 ml of a mixture of H_2O:EtOH 80:20 were

View Article Online
DOI: 10.1039/C6RA04721A

added. The solid obtained was filtered on a buchner and dried under vacuum. The liquid phase was transferred into a 10 ml round-bottomed flask and dried under vacuum to remove the solvent. The recovered DES was used for another cycle of reaction.

RESULTS AND DISCUSSION

We performed the Claisen-Schmidt reaction between mono- and bi-substituted benzaldehydes and acetophenones in SB3-Cy / CSA DES without any added acid catalyst; the general reaction is reported in Scheme 1.



R_1 = H, NO_2, Cl
R_2 = H, OCH_3
R_3 = H, OH, NO_2, Cl, OCH_3
R_4 = H, NO_2

R'_1 = H, OH
R'_2 = H, OH, OCH_3
R'_3 = H, OCH_3, $N(CH_3)_2$

Scheme 1: Claisen-Schmidt reaction of mono- and bi-substituted benzaldehydes and acetophenones performed in SB3-Cy / CSA Deep Eutectic Solvent.

Reaction conditions optimization

The ratio of the reagents was maintained as 1 in all the reactions analysed, with the aim of minimizing the waste. Preliminary studies on the effect of the temperature on the conversion in the reaction between benzaldehyde and acetophenone showed that in 2h a good and constant conversion was observed at the temperature of 100°C (Table 1).

View Article Online
DOI: 10.1039/C6RA04721A

Table 1: Effect of the temperature on the conversion percentage in the reaction between benzaldehyde and acetophenone after 2h[a].

Temperature, °C	Conversion, %
80	64
90	79
100	86
110	89

[a] Aldehyde : ketone : CSA 1:1:3 molar ratio, 2h, conversion calculated via GC with *tert*-butylbenzene as internal standard.

In order to maintain milder conditions, the effect of the time on the conversion at 90°C was then observed; in 16h the conversion was complete for the benzaldehyde / acetophenone reaction (Table 2), and the time needed was even shorter for the other reactants. So the temperature used in all the experiments was 90°C. This permitted to maintain milder conditions and to obtain complete conversions in good reaction times, spanning from 4 to 16 hours.

Table 2: Effect of the reaction time on the conversion percentage in the reaction between benzaldehyde and acetophenone at 90°C[a].

Time, h	Conversion, %
1	61
2	79
3	89
8	92
16	96

[a] Aldehyde : ketone : CSA 1:1:3 molar ratio, 90°C, conversion calculated via GC with *tert*-Butylbenzene as internal standard.

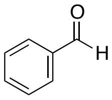
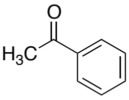
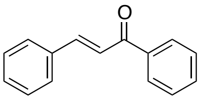
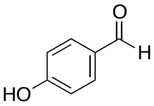
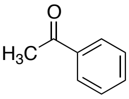
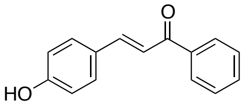
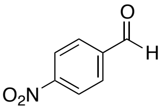
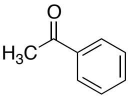
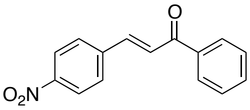
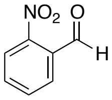
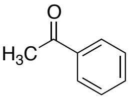
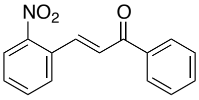
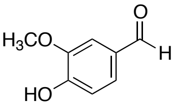
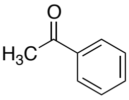
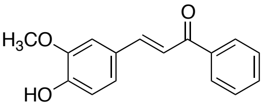
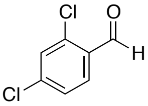
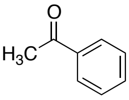
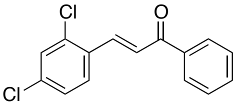
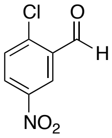
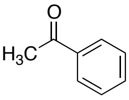
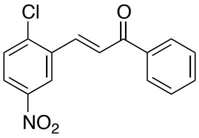
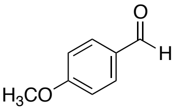
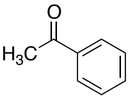
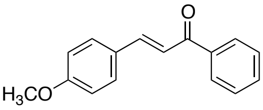
View Article Online
DOI: 10.1039/C6RA04721A

Synthesis of substituted chalcones in DES

In Table 3 and Table 4 the reactions of chalcone synthesis we performed in SB3-Cy / CSA DES are reported. In the tables the reactants and the products, the reaction times, the conversions and isolated product yields (calculated via weight of the product after column chromatography) are shown. In Table 3 the reactions of substituted benzaldehydes with acetophenone are reported.

View Article Online
DOI: 10.1039/C6RA04721A

Table 3: Claisen-Schmidt condensations in SB3-Cy/CSA DES of acetophenone with substituted benzaldehydes [a].

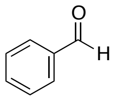
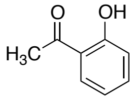
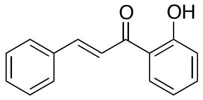
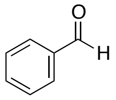
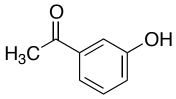
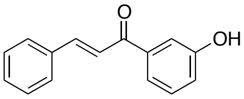
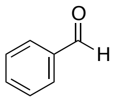
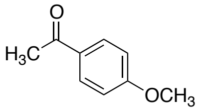
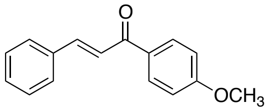
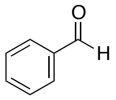
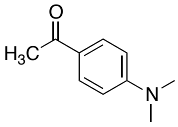
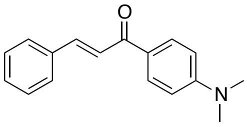
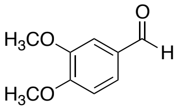
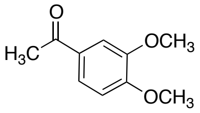
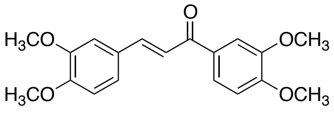
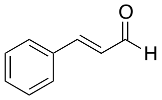
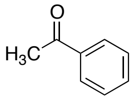
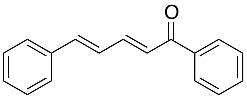
Entry	Aldehyde	Ketone	Chalcone	Time, h	Conversion[b], %	Yield[c], %
1				16	96	67
2				6	93	80
3				16	97	93
4				16	80	65
5				5	94	76
6				16	100	94
7				4	96	87
8				6	96	51

[a] Temperature 90°C, aldehyde : ketone : CSA 1:1:3 molar ratio; [b] conversion calculated via GC with *tert*-butylbenzene as internal standard; [c] yield calculated by weight of isolated product.

View Article Online
DOI: 10.1039/C6RA04721A

In Table 4 the synthesis of chalcones in DES from benzaldehyde and substituted ketones, from 3,4-dimethoxybenzaldehyde and 1-(3,4-dimethoxyphenyl)ethanone and from cinnamic aldehyde with acetophenone are reported.

Table 4: Claisen-Schmidt condensations in SB3-Cy / CSA DES of benzaldehyde with substituted acetophenones, of 3,4-dimethoxybenzaldehyde and 1-(3,4-dimethoxyphenyl)ethanone and of cinnamic aldehyde with acetophenone[a].

Entry	Aldehyde	Ketone	Chalcone	Time, h	Conversion[b], %	Yield[c], %
9				16	90	22
10				6	96	93
11				6	95	93
12				6	90	80
13				16	96	60
14				6	94	64

[a] Temperature 90°C, aldehyde : ketone : CSA 1:1:3 molar ratio; [b] conversion calculated via GC with *tert*-Butylbenzene as internal standard; [c] yield calculated by weight of isolated product.

The conversions observed were excellent for all the products, spanning from 88% to quantitative; *o*-NO_2-benzaldehyde, entry **4**, showed a slightly lower value of conversion of 80%.

The reactions between the aldehydes and the acetophenone (Table 3, entry **1**-**8**) led to the chalcones in good yields of isolated product, spanning from 51% to 98%. The presence of electron withdrawing groups (EWG) on the aromatic ring of the aldehyde (such as Cl and NO_2) led to excellent yields of isolated product (93%, 94%, and 87% for entry **3**, **6** and **7** respectively). In the case of the presence of EDG (electron donating groups), the OH group led to a yield higher than metoxy group (entry **2** and **8**); entry **5** aldehyde (with both OH and OCH_3 groups in the aromatic ring) led to an intermediate yield between the entries **2** and **8**. The steric hindrance of the nitro-group in *ortho* position led to the conversion value of entry **4** aldehyde; this is lower than the one of the *para*-substituted one of entry **3** (97% and 80% respectively); it had impact also on the yields of isolated product (93% and 65% respectively).

In the reaction between the benzaldehyde and substituted ketones (Table 4, entries **9**-**12**), the presence of EDG groups led to excellent conversions (96%, 95%, 90%) and isolated product yields (93%, 93%, 80%) for **10**, **11** and **12** entries. On the contrary, entry **9** reaction showed good conversion (90%) but poor yield (22%); that is because these molecules tend to cyclize through Michael addition between the OH group and the double bond, forming flavones[42].

In the Claisen-Schmidt condensation between a substituted benzaldehyde and a substituted acetophenone (Table 4, entry **13**) excellent conversion was observed (96%). The isolated product yield observed (60%) could be due to the electron donating properties of metoxy-substituents that could slightly decrease the yield of chalcone formation in this reaction.

We extended the reaction set using also an aldehyde that does not have an α-hydrogen, such as cinnamaldehyde (entry **14**); also the reaction of this molecule with acetophenone led to the product with excellent conversion (94%) and good isolated product yield (64%).

The reaction in entry **4** was repeated in another sulfobetaine-based DES: SB3-MIM (3-(1-methyl-1*H*-imidazol-3-ium-3-yl)propane-1-sulfonate) / CSA mixture was chosen as solvent / catalyst. This was made with different aims. The first reason was to increase the conversion and yields observed, because they were the lowest in the set; the second reason was to show the possibility of the use of other DESs mixtures in our set in the same probe reaction[22]. The aromatic imidazolium-based DES was chosen because of the structural similarity with aromatic reagents in the reaction. The conversion values observed were almost the same (81% with SB3-MIM / CSA and 80% with SB3-Cy / CSA) but an increase of the isolated product yields was observed, passing from 65% to 77%. This data could lead to further studies on the use of a specific DES in a set for a specific role.

We also performed an aldol reaction of acetophenone in SB3-Cy / CSA DES in order to evaluate the self-condensation of the ketone in this media. After 48 hours at 90°C the conversion observed was <10%, these data are not reported in any table.

View Article Online
DOI: 10.1039/C6RA04721A

DES recycling

Subsequent reaction cycles were performed in order to estimate the recyclability of SB3-Cy / CSA DES in the Claisen-Schmidt reaction. One of the reactions of the set (2-chloro-5-nitro-benzaldehyde and acetophenone as reactants, entry **7** in Table 1) was performed in subsequent experiments and the capability of re-use of the DES was evaluated via an estimation of the obtained isolated product yields. In Table 5 the isolated product yields in four subsequent reaction cycles are reported.

Table 5: Recycling and reuse of SB3-Cy / CSA DES in 2-chloro-5-nitro-benzaldehyde reaction with acetophenone [a].

Cycle	Yield, %[b]
1	87
2	86
3	87
4	85

[a] Aldehyde : ketone 1:1 molar ratio, 90°C, 4 h; [b] Yield calculated as weight of isolated product after purification, 96% of conversion values observed in all the four reaction cycles.

As it can be easily observed, the DES can be recycled in at least four subsequent reaction cycles without any loss of yields of product obtained. We did not investigate on further reaction cycles because of the constant values observed. This data promotes the “greenness” of this reaction media.

CONCLUSIONS

The Claisen-Schmidt reaction is a powerful tool for C-C bonds formation. We successfully performed this reaction in an acid deep eutectic solvent: SB3-Cy / CSA mixture. We synthesized substituted chalcones combining benzaldehyde and mono- and bi-substituted benzaldehydes with acetophenone and mono- and bi-substituted acetophenones as probe reactions. The reaction media played both the roles of solvent and acid catalyst for this probe reaction, because of the CSA composing it, so no acid (or basic) catalysts were needed.

The advantages of the use of this reaction media were several: it is an environmental friendly solvent for its properties and for its very low toxicity as demonstrated in previous works[22]; it has the advantage of preventing the use of harmful acids (such as H_2SO_4) to catalyse the aldol condensation because of the camphorsulfonic acid composing it. Over four reaction cycles can be performed in it without any loss of activity. It permitted to achieve in mild conditions (90°C, 4 to 16 hours of reaction times) excellent conversions of the reactants (spanning from 88% to quantitative) and very good yields of isolated products after column chromatography.

The work was extended with the use of another sulfobetaine-based DES (SB3-MIM / CSA: 3-(1-methyl-1*H*-imidazol-3-ium-3-yl)propane-1-sulfonate / (1S)-(+)-10-camphorsulfonic acid mixture) in one of the analysed synthesis. This was successfully made in order to improve the conversion and the yield of the reaction and in order to demonstrate the applicability of a specific DES in specific reaction for structural similarities of the reactants and the DES's components and it could lead to further studies on specific liquids for specific reactions.

This study on the Claisen-Schmidt reaction promotes the use of acid Deep Eutectic Solvents in other acid-catalysed reactions as both reaction media and catalysts.

AKNOWLEDGEMENTS

The authors thank the Ministero per l'Università e la Ricerca Scientifica e Tecnologica, MIUR (Rome, Italy) [PRIN "Programmi di Ricerca di Interesse Nazionale" 2010-2011, n. 2010FM738P] for funding.

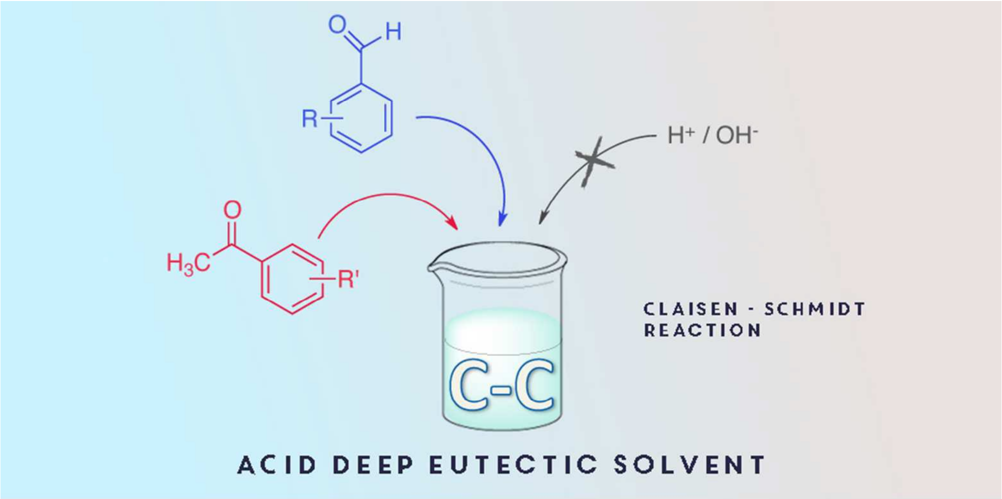
REFERENCES

1. R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792-793.
2. K. R. Seddon, *J. Chem. Technol. Biot.*, 1997, **68**, 351-356.
3. T. Welton, *Chem. Rev.*, 1999, **99**, 2071-2084.
4. L. Brinchi, R. Germani, E. Braccalenti, N. Spreti, M. Tiecco and G. Savelli, *J. Colloid Interf. Sci.*, 2010, **348**, 137-145.
5. F. Cardellini, L. Brinchi, R. Germani and M. Tiecco, *Synthetic Commun.*, 2014, **44**, 3248-3256.
6. V. De Santi, F. Cardellini, L. Brinchi and R. Germani, *Tetrahedron Lett.*, 2012, **53**, 5151-5155.
7. P. Wasserscheid and T. Welton, *Ionic liquids in synthesis*, Wiley Online Library, 2008.
8. B. Jastorff, R. Störmann, J. Ranke, K. Mölter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nüchter and B. Ondruschka, *Green Chem.*, 2003, **5**, 136-142.
9. A. Romero, A. Santos, J. Tojo and A. Rodriguez, *J. Hazard. Mater.*, 2008, **151**, 268-273.
10. D. Zhao, Y. Liao and Z. Zhang, *Clean–soil, air, water*, 2007, **35**, 42-48.

11. A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc.*, 2004, **126**, 9142-9147.
12. D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor and D. J. Ramón, *Eur. J. Org. Chem.*, 2016, **4**, 612-632.
13. F. Cardellini, M. Tiecco, R. Germani, G. Cardinali, L. Corte, L. Roscini and N. Spreti, *RSC Adv.*, 2014, **4**, 55990-56002.
14. L. Gu, W. Huang, S. Tang, S. Tian and X. Zhang, *Chem. Eng. J.*, 2015, **259**, 647-652.
15. A. Paiva, R. Craveiro, I. Aroso, M. Martins, R. L. Reis and A. R. C. Duarte, *ACS Sustain. Chem. Eng.*, 2014, **2**, 1063-1071.
16. N. Azizi and E. Batebi, *Catal. Sci. Tech.*, 2012, **2**, 2445-2448.
17. N. Azizi, E. Batebi, S. Bagherpour and H. Ghafuri, *RSC Adv.*, 2012, **2**, 2289-2293.
18. E. Durand, J. Lecomte, B. Baréa, G. Piombo, E. Dubreucq and P. Villeneuve, *Process Biochem.*, 2012, **47**, 2081-2089.
19. M. a. C. Gutiérrez, F. Rubio and F. del Monte, *Chem. Mater.*, 2010, **22**, 2711-2719.
20. H. G. Liao, Y. X. Jiang, Z. Y. Zhou, S. P. Chen and S. G. Sun, *Angew. Chem.*, 2008, **120**, 9240-9243.
21. C. Ruß and B. König, *Green Chem.*, 2012, **14**, 2969-2982.
22. F. Cardellini, R. Germani, G. Cardinali, L. Corte, L. Roscini, N. Spreti and M. Tiecco, *RSC Adv.*, 2015, **5**, 31772-31786.
23. Y. Dai, J. van Spronsen, G.-J. Witkamp, R. Verpoorte and Y. H. Choi, *Anal. Chim. Acta*, 2013, **766**, 61-68.
24. M. Hayyan, M. A. Hashim, A. Hayyan, M. A. Al-Saadi, I. M. AlNashef, M. E. Mirghani and O. K. Saheed, *Chemosphere*, 2013, **90**, 2193-2195.
25. I. Juneidi, M. Hayyan and O. M. Ali, *Environ. Sci. Pollut. R.*, 2016, 1-12.
26. P. Liu, J.-W. Hao, L.-P. Mo and Z.-H. Zhang, *RSC Adv.*, 2015, **5**, 48675-48704.
27. H. N. Harishkumar, K. M. Mahadevan, H. C. K. Kumar and N. D. Satyanarayan, *Org. Commun.*, 2011, **4**, 9-15.
28. Y. A. Sonawane, S. B. Phadtare, B. N. Borse, A. R. Jagtap and G. S. Shankarling, *Org. Lett.*, 2010, **12**, 1456-1459.
29. S. Handy and K. Lavender, *Tetrahedron Lett.*, 2013, **54**, 4377-4379.
30. S. B. Phadtare and G. S. Shankarling, *Green Chem.*, 2010, **12**, 458-462.
31. B. Singh, H. Lobo and G. Shankarling, *Catal. Lett.*, 2011, **141**, 178-182.
32. H. R. Lobo, B. S. Singh and G. S. Shankarling, *Green Chem. Lett. Rev.*, 2012, **5**, 487-533.
33. Y. Zhang, F. Lü, X. Cao and J. Zhao, *RSC Adv.*, 2014, **4**, 40161-40169.
34. T. D. Machajewski and C. H. Wong, *Angew. Chem. Int. Edit.*, 2000, **39**, 1352-1375.
35. A. T. Nielsen and W. J. Houlihan, *Organic reactions*, 1968.
36. G. W. Cave and C. L. Raston, *Chem. Commun.*, 2000, 2199-2200.
37. L. M. Baigrie, R. A. Cox, H. Slebocka-Tilk, M. Tencer and T. T. Tidwell, *J. Am. Chem. Soc.*, 1985, **107**, 3640-3645.
38. Q. Xu, Z. Yang, D. Yin and F. Zhang, *Catal. Commun.*, 2008, **9**, 1579-1582.
39. L. Q. Kang, Y. Q. Cai, H. Wang and L. H. Li, *Monatsh. Chem.*, 2014, **145**, 337-340.
40. S. R. Sarda, W. N. Jadhav, S. U. Tekale, G. V. Jadhav, B. R. Patil, G. S. Suryawanshi and R. P. Pawar, *Lett. Org. Chem.*, 2009, **6**, 481-484.
41. S. Zhou, L. Liu, B. Wang, M. Ma, F. Xu and R. Sun, *Synthetic Commun.*, 2012, **42**, 1384-1391.
42. H. K. Hsieh, L. T. Tsao, J. P. Wang and C. N. Lin, *J. Pharm. Pharmacol.*, 2000, **52**, 163-171.
43. M. Liu, P. Wilairat and M.-L. Go, *J. Med. Chem.*, 2001, **44**, 4443-4452.
44. L. Svetaz, A. Tapia, S. N. López, R. L. Furlán, E. Petenatti, R. Pioli, G. Schmeda-Hirschmann and S. A. Zacchino, *J. Agr. Food Chem.*, 2004, **52**, 3297-3300.
45. P. Formentín, H. García and A. Leyva, *J. Mol. Catal. A-Chem.*, 2004, **214**, 137-142.

46. F. Dong, C. Jian, F. Zhenghao, G. Kai and L. Zuliang, *Catal. Commun.*, 2008, **9**, 1924-1927.
47. H. Qian, D. Liu and C. Lv, *Ind. Eng. Chem. Res.*, 2010, **50**, 1146-1149.
48. C. R. Müller, I. Meiners and P. D. de María, *RSC Adv.*, 2014, **4**, 46097-46101.
49. C. R. Müller, A. Rosen and P. D. de María, *Sustain. Chem. Process.*, 2015, **3**, 1-8.
50. R. Martínez, L. Berbegal, G. Guillena and D. J. Ramón, *Green Chem.*, 2016, **18**, 1724-1730.
51. D. González‐Martínez, V. Gotor and V. Gotor‐Fernández, *Eur. J. Org. Chem.*, 2016, **8**, 1513-1519.
52. S. R. Cicco, G. M. Farinola, C. Martinelli, F. Naso and M. Tiecco, *Eur. J. Org. Chem.*, 2010, **12**, 2275-2279.
53. C. W. Mai, M. Yaeghoobi, N. Abd-Rahman, Y. B. Kang and M. R. Pichika, *Eur. J. Org. Chem.*, 2014, **77**, 378-387.
54. P. Lin, B. Li, J. Li, H. Wang, X. Bian and X. Wang, *Catal. Lett.*, 2011, **141**, 459-466.
55. A. I. Barros, A. F. Dias and A. M. Silva, *Monatsh. Chem.*, 2007, **138**, 585-594.
56. S. Oh, S. Jang, D. Kim, I.-O. Han and J.-C. Jung, *Arch. Pharm. Res.*, 2006, **29**, 469-475.
57. S. N. López, M. V. Castelli, S. A. Zacchino, J. N. Domínguez, G. Lobo, J. Charris-Charris, J. C. Cortés, J. C. Ribas, C. Devia and A. M. Rodríguez, *Bioorgan. Med. Chem.*, 2001, **9**, 1999-2013.
58. J. Zhang and J. Xu, *Helv. Chim. Acta*, 2013, **96**, 1733-1739.
59. M. Cabrera, M. Simoens, G. Falchi, M. L. Lavaggi, O. E. Piro, E. E. Castellano, A. Vidal, A. Azqueta, A. Monge and A. L. de Cerain, *Bioorgan. Med. Chem.*, 2007, **15**, 3356-3367.
60. R. Karki, P. Thapa, M. J. Kang, T. C. Jeong, J. M. Nam, H.-L. Kim, Y. Na, W.-J. Cho, Y. Kwon and E.-S. Lee, *Bioorgan. Med. Chem.*, 2010, **18**, 3066-3077.
61. S. Kim, S. W. Bae, J. S. Lee and J. Park, *Tetrahedron*, 2009, **65**, 1461-1466.
62. X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 14596-14602.
63. S. Ducki, D. Rennison, M. Woo, A. Kendall, J. F. D. Chabert, A. T. McGown and N. J. Lawrence, *Bioorgan. Med. Chem.*, 2009, **17**, 7698-7710.
64. N. A. Begum, N. Roy, R. A. Laskar and K. Roy, *Med. Chem. Res.*, 2011, **20**, 184-191.

View Article Online
DOI: 10.1039/C6RA04721A



80x39mm (300 x 300 DPI)