Journal of Molecular Liquids 195 (2014) 188–193

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Synergistic effect of ultrasound and deep eutectic solvent choline chloride–urea as versatile catalyst for rapid synthesis of β-functionalized ketonic derivatives

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ARTICLE INFO

Article history:
Received 16 January 2014
Received in revised form 14 February 2014
Accepted 18 February 2014
Available online 11 March 2014

Keywords:
Conjugate addition
α,β-Unsaturated ketones
Choline chloride–urea
Ultrasonication
Ionic liquid catalyst

ABSTRACT

A green protocol for efficient synthesis of β-functionalized ketonic derivatives is achieved with the combination of ultrasound and the deep eutectic solvent (DES) choline chloride–urea [ChCl:urea (1:2)]. Under optimized conditions, nucleophilic attack of active methylene on α,β-unsaturated ketones gives the conjugate addition product in the short span of 40–50 min an excellent yield of 89–95%. The experimental procedure is very simple, easy to set up, solvent free and completely eliminates the use of any toxic metal catalyst. The use of ChCl:urea as a biodegradable, recyclable and reusable catalyst (up to five cycles) further increases the scope of the developed methodology.

1. Introduction

Carbon–carbon bond forming reactions are considered to be of immense importance for the synthesis of complex organic molecules [1–3]. The addition of active methylenes such as ethyl cyanoacetate, malononitrile and nitromethane to α,β-unsaturated ketones results in the synthesis of ketonic nitriles and ketonic nitro derivatives which can be transformed into functionally important hydropyridine derivatives [4–6]. These addition reactions are usually catalyzed by inorganic bases [7–12] and organic bases [13–15], and face the problems of side reactions arising due to auto-condensation, retro-Michael addition and bis-addition. Remarkable efforts have been made by researchers to obtain purer products. Various catalysts have been developed such as transition metal catalyst [16–18], organocatalysts [19], and phase transfer catalyst [20]. However, these reactions are complicated by drawbacks related to the use of expensive catalysts and their efficiency after reuse, high reaction temperature, tedious multi-step synthesis of a catalyst, stability and storage of a catalyst, and use of organic solvents. In order to circumvent this problem, the use of a green approach for conjugate addition has become a challenging area for the organic chemist. Suitable modifications have been brought to this field by the use of eco-friendly catalysts [21–23] and environmentally benign reaction media [24,25]. Clean and green techniques like microwave [26], ultrasound [27], and solvent free conditions [28] are used but there still remains room for further improvement.

Deep eutectics composed of choline chloride and hydrogen bond donors like urea, malonic acid and oxalic acid form eutectics which are liquid at room temperature and are commonly called 'deep eutectic solvents' or 'deep eutectic mixtures' [29,30]. They are completely biodegradable, cheap, and superior to ionic liquids as they are synthesized from readily available raw materials. Thus, in continuation of our work on utilization of choline based deep eutectics for organic synthesis [31–34], we wish to report the conjugate addition of active methylenes to α,β-unsaturated ketones using the environmentally benign catalyst ChCl:urea (1:2) along with use of ultrasound energy. Use of ultrasound for accelerating chemical reactions in ionic liquid is a well documented fact and is well-known to facilitate the reaction by forcing the less volatile substrate to undergo cavitation resulting in a low reaction time [35]. During cavitation, tiny vapor bubbles undergo sequence-formation, growth and collapse. Implosive collapse of bubbles generates short-lived regions with temperatures of roughly 5000 °C, pressures of about 1000 atm as well as heating and cooling rates above 10 billion degrees Celsius per second [36]. The whole process can be considered as a microreactor wherein sound energy is transformed into a useful form of chemical energy, which is to sufficient to activate reactant molecules entering into it and thereby converting them into reactive intermediates [37]. In this

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http://dx.doi.org/10.1016/j.molliq.2014.02.016
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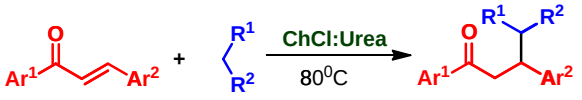


Scheme 1. Synthesis of β-functionalized ketonic derivatives using RTIL ChCl:urea (1:2).

paper we have demonstrated the synergistic effect of ultrasound and the catalytic activity of ChCl:urea (1:2) for carbon–carbon bond forming reactions (Scheme 1).

2. Experimental

All common reagent grade chemicals were procured from SD Fine Chemical Ltd. (Mumbai, India) and were used without further purification. The reactions were monitored by thin layered chromatography using 0.25 mm E-Merck silica gel $60F_{254}$ precoated plates, which were visualized with UV light. ^{1}H spectra were recorded on 400 MHz, 600 MHz and ^{13}C-NMR on a 100 MHz Varian mercury plus spectrometer. Chemical shifts are expressed in δ ppm using TMS as an internal standard. Mass spectral data were obtained with a micromass-Q-TOF (YA105) spectrometer. The synthesis of a deep eutectic mixture has been carried out using a method reported in the literature [31]. It is prepared by mixing choline chloride (100 g, 71 mmol) and urea (86 g, 140 mmol) in a molar ratio of 1:2. The two solids were heated slowly and maintained at 80 °C for 30 min resulting in the formation of eutectic solvent with 100% atom economy. The liquid was allowed to cool till it attains room temperature and was used for synthesis without further purification.

2.1. Ultrasound set up

Ultrasound for sonochemical synthesis is generated with the help of ultrasonic instrument set-up (horn type). The specification and details of the set-up, and processing parameters used during the experiments are:

Make: SONICS, USA	Operating frequency: 20 kHz
Rated output power: 750 W	Diameter of titanium steel tip of horn: 13 mm
Intensity: 2.27×10^6 W/m^2	Surface area of ultrasound irradiating face: 1.32×10^{-4} m^2

2.2. General procedure for synthesis of products (*3a–3l*) by conventional heating

To a mixture of (E)-3-(4-fluorophenyl)-1-(phenyl)prop-2-en-1-one (0.26 g, 1 equiv.) and active methylene (1.2 equiv.), ChCl:urea (1:2) (5 equiv.) was added and the reaction mixture was stirred at 80 °C for an appropriate time. After completion of the reaction as indicated by TLC, ethyl acetate was added to the reaction mass. Evaporation of the organic layer afforded products which were further purified by column chromatography using hexane:ethyl acetate as eluent.

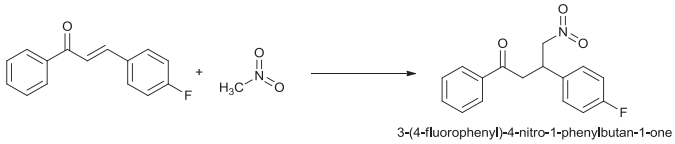
2.3. General procedure for synthesis of products (*3a–3l*) by using ultrasound

To a mixture of (E)-3-(4-fluorophenyl)-1-(phenyl)prop-2-en-1-one (1 equiv.) and active methylene (1.2 equiv.), ChCl:urea (1:2) (5 equiv.) was added. It was placed under sonication using an ultrasonic horn (ACE horn, 22 kHz frequency) at 40% amplitude for an appropriate time with a 5 s on and 5 s off cycle from time t = 0 h. The reaction progress was monitored on thin layer chromatography (TLC). On completion of the reaction as indicated on TLC, ethyl acetate was added to the reaction mass. Evaporation of the organic layer afforded products which were further purified by column chromatography. For recyclability studies, a deep eutectic mixture was given a wash of ethyl acetate and was used for the next batch and recycled again.

2.4. Characterization and spectral data

All the compounds are characterized by mass, FT-IR, ^{1}H and NMR. ^{1}H spectra were recorded on 400 MHz, 600 MHz and ^{13}C-NMR on a 100 MHz Varian Mercury plus spectrometer. Chemical shifts are

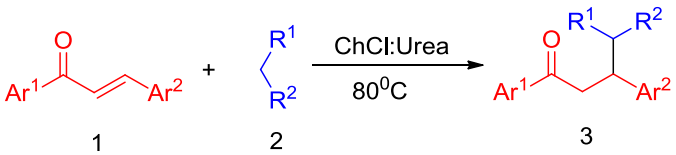
Table 1
Comparison of ChCl:urea with various catalysts in the addition of nitromethane to 4-fluorobenzylideneacetophenone.[a]



Entry	Catalyst	Equiv. of Nitromethane	Solvent	Reaction temp (°C)	Time	Yield[a] (%)	Ref
1	K_2CO_3, 0.2 mmol	5.0	Ethanol	80	10 h	98	[38]
2	Diethylamine, 5 equiv.	5.0	Dry methanol	65	24 h	86	[39]
3	KF/basic alumina	4–8	Dry THF	25	2 h	94	[40]
4	Diethylamine	5.0	Diethylamine	60	6 h	91	[41]
5	SmI_3, 1 equiv.	1.0	Dry THF	60	24 h	88	[42]
6	Rasta resin-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene	1.0	–	60	4 h	80	[43]
7	$[C_4mim][C_2H_5SO_4]$	1.5		80	8 h	69	[25]
8	ChCl:urea, 1 equiv.		Solvent free		2 h	60	
	3 equiv.	1.2	Solvent free		2 h	74	–
	5 equiv.		Solvent free	80	2 h	89	
	7 equiv.		Solvent free		2 h	87	
9	Ultrasonication (US)	1.2	Solvent free	50	60 min	70	–
	ChCl:urea, 5 equiv.		Solvent free	70	50 min	84	
			Solvent free	80	45 min	94	
			Solvent free	90	45 min	94	
10	No catalyst	5.0	No solvent	50	4 h	NR	–
				80	4 h	NR	–

[a] Isolated yield.

Table 2
Michael addition of active methylene compound to chalcones—advantage of ultrasound over conventional heating.[a]



1 2 3

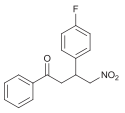
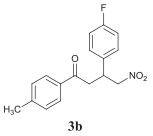
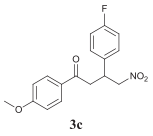
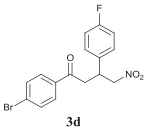
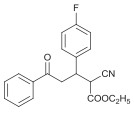
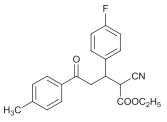
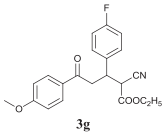
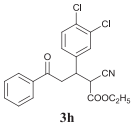
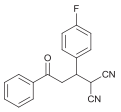
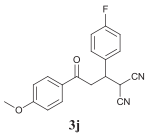
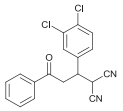
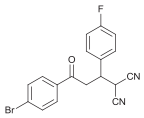
Entry	Ar_1, Ar_2	R_1, R_2	Michael adducts	Conventional heating[b] Time (h), yield (%)	Ultrasonication[c] Time (min), yield (%)[d]
1	Ph, 4-FC_6H_4		 3a	2 h, 90%	40 min, 96%
2	4-$CH_3C_6H_4$, 4-FC_6H_4		 3b	2.5 h, 84%	45 min, 86%
3	4-$OCH_3C_6H_4$, 4-FC_6H_4		 3c	3 h, 82%	45 min, 88%
4	4-BrC_6H_4, 4-FC_6H_4		 3d	2.5 h, 90%	40 min, 92%
5	Ph, 4-FC_6H_4		 3e	4 h, 82%	75 min, 82% $d.e._p = 33.9\%$
6	4-$CH_3C_6H_4$, 4-FC_6H_4		 3f	4 h, 82%	75 min, 82% $d.e._p = 33.9\%$
7	4-$OCH_3C_6H_4$, 4-FC_6H_4		 3g	5 h, 81%	90 min, 80% $d.e._p = 29.0\%$
8	Ph, 3,4-$Cl_2C_6H_3$		 3h	6 h, 80%	95 min, 82% $d.e._p = 30.5\%$
9	Ph, 4-FC_6H_4		 3i	3 h, 89%	45 min, 96%
10	4-$OCH_3C_6H_4$, 4-FC_6H_4		 3j	4 h, 86%	55 min, 89%

Table 2 (*continued*)

Entry	Ar_1, Ar_2	R_1, R_2	Michael adducts	Conventional heating[b] Time (h), yield (%)	Ultrasonication[c] Time (min), yield (%)[d]
11	Ph, 3,4-$Cl_2C_6H_3$		 **3k**	4 h, 89%	55 min, 93%
12	4-BrC_6H_4, 4-FC_6H_4		 **3l**	3.5 h, 91%	45 min, 92%

d.e.$_p$ = diastereomeric excess percentage determined by ^{1}H-NMR analyses.
[a] Reaction conditions: chalcone (1 mmol), active methylene (1 mmol), ChCl:urea (1:2) 5 equiv., temperature 80 °C.
[b] Isolated yield obtained using conventional heating method.
[c] Isolated yield obtained using ultrasound.
[d] All the compounds are characterized by mass, FT-IR and ^{1}H-NMR.

expressed in δ ppm using TMS as an internal standard. Mass spectral data were obtained with a micromass-Q-TOF (YA105) spectrometer.

2.4.1. Product ***3a***

3-(4-Fluorophenyl)-4-nitro-1-phenylbutan-1-one. ^{1}H-NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 3.40 (dd, *J* = 2.43, 4.5, 7.31 Hz, 1H), 3.43 (dd, *J* = 2.43, 4.5, 6.33 Hz, 1H), 4.16–4.26 (br, quintet, *J* = 7.3 Hz, 1H), 4.64 (dd, *J* = 7.8, 8.3 Hz, 1H), 4.80 (dd, *J* = 6.3 Hz, 1H), 6.99 (t, *J* = 8.3 Hz, 2H), 7.25 (dd, *J* = 6.8, 3.4 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 2H) 7.56 (t, *J* = 7.3 Hz, 1H), 7.88 (d, 2H, *J* = 7.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$, Me_4Si); δ = 38.6, 41.5, 79.5, 115.8, 116.0, 128.0, 128.7, 129.1, 129.2, 133.6, 134.8, 134.9, 136.2, 160.5, 163.7, 196.6. IR (neat, cm^{-1}): 2969, 1738, 1681, 1552, 1353, 1216.

2.4.2. Product ***3b***

3-(4-Fluorophenyl)-4-nitro-1-(p-tolyl)butan-1-one. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 1.58 (s, 3H), 3.42 (dd, *J* = 8.2 Hz, 1H), 3.44 (dd, *J* = 6.8 Hz, 1H), 4.20–4.24 (m, 1H), 4.66 (dd, *J* = 20.3 Hz, 1H), 4.82 (dd, *J* = 16.2 Hz, 1H), 6.99–7.05 (m, 2H), 7.23–7.42 (m, 4H), 7.874–7.819 (d, 2H, *J* = 8 Hz). IR (neat, cm^{-1}) 2359, 1682, 1552, 1508, 1384, 1353, 1218. EIMS *m/z* (%) = 318.0 (M^+ + 1), $C_{17}H_{16}FNO_4$ calculated *m/z* 317.31.

2.4.3. Product ***3c***

3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-4-nitrobutan-1-one. ^{1}H-NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 3.31–3.40 (m, *J* = 7.0, 8.2 Hz, 2H), 3.86 (s, 3H), 4.18–4.23 (br, quintet, *J* = 7.2 Hz, 1H), 4.64 (dd, *J* = 8.2, 9.2 Hz, 1H), 4.80 (dd, *J* = 6.2, 7.2 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.00 (t, *J* = 8.2, 2H), 7.25 (dd, *J* = 3.0, 5.1, 13.3 Hz, 2H), 7.89 (d, 2H, *J* = 9.2 Hz, 2H). IR (neat, cm^{-1}): 2960, 1670, 1577, 1260, 1169. EIMS *m/z* (%) = 301.9 (M^+ + 1), $C_{17}H_{16}FNO_3$ calculated *m/z* 301.0.

2.4.4. Product ***3d***

1-(4-Bromophenyl)-3-(4-fluorophenyl)-4-nitrobutan-1-one. ^{1}H-NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 3.34 (dd, *J* = 2.9, 4.4 Hz, 1H), 3.36 (dd, *J* = 2.2, 4.4 Hz, 1H), 4.16–4.21 (br, quintet, 1H), 4.61 (dd, *J* = 6.2 Hz, 1H), 4.75 (dd, *J* = 6.2 Hz, 1H), 6.89–6.95 (t, *J* = 8.7 Hz, 2H), 7.164–7.256 (m, 4H), 7.76–7.79 (d, *J* = 8.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$, Me_4Si); δ = 38.2, 38.3, 40.9, 79.0, 79.2, 79.4, 115.1, 115.3, 115.4, 115.6, 127.7, 128.9, 133.5, 135.0, 135.0, 144.1, 160.0, 163.2, 196.0. IR (neat, cm^{-1}) 2915, 2320, 1668, 1605, 1551, 1509, 1407, 1362. EIMS *m/z* (%) = 367.9 (M^+ + 1). $C_{16}H_{13}BrFNO_3$ calculated *m/z* 366.18.

2.4.5. Product ***3e***

Ethyl 2-cyano-3-(4-fluorophenyl)-5-oxo-5-phenylpentanoate. d.e.$_p$ = 33.9%. *Major isomer*: ^{1}H-NMR (600 MHz, $CDCl_3$, Me_4Si): δ = 1.12 (t, *J* = 7.4 Hz, 3H), 3.50 (dd, *J* = 5.2, 13.3 Hz, 1H), 3.68 (dd, *J* = 4.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 4.13–4.18 (m, *J* = 3.1, 6.2 Hz, 1H), 4.32 (d, *J* = 5.1 Hz, 1H), 6.99–7.59 (m, Ar–H, 7H), 7.95 (d, *J* = 8.2 Hz, 2H). *Minor isomer*: ^{1}H-NMR (600 MHz, $CDCl_3$, Me_4Si): δ = 1.20 (t, *J* = 7.2 Hz, 3H), 3.61 (dd, *J* = 8.2 Hz, 1H), 3.65 (dd, *J* = 5.1, 9.2 Hz), 3.89 (d, *J* = 5.1 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.99–7.59 (m, Ar–H, 7H), 7.92 (d, *J* = 8.2 Hz, 2H). IR (neat, cm^{-1}): 3436, 2953, 2345, 1724, 1692, 1510, 1221, 1038. EIMS *m/z* (%) = 338.1 (M^+ + 1). $C_{20}H_{18}FNO_3$ calculated *m/z* 339.36.

2.4.6. Product ***3f***

Ethyl 2-cyano-3-(4-fluorophenyl)-5-oxo-5-(p-tolyl)pentanoate. d.e.$_p$ = 29.0%. *Major isomer*: ^{1}H-NMR (600 MHz, $CDCl_3$, Me_4Si): δ = 1.13 (t, *J* = 6.3 Hz, 3H), 2.41 (s, 3H), 3.45 (dd, *J* = 5.1 Hz, 1H), 3.66 (d, *J* = 8.9 Hz, 1H), 3.61–3.63 (m, *J* = 7.3 Hz, 8.1 Hz), 4.10 (q, *J* = 7.2 Hz, 2H), 4.32 (d, *J* = 5.1 Hz, 1H), 7.00–7.40 (m, 6H), 7.86 (d, *J* = 8.1 Hz, 2H). *Minor isomer*: ^{1}H-NMR (600 MHz, $CDCl_3$, Me_4Si): δ = 1.21 (t, *J* = 6.3 Hz, 3H), 2.40 (s, 3H), 3.87 (d, *J* = 5.1 Hz, 1H), 3.48 (d, *J* = 5.1 Hz, 1H), 4.12–4.19 (m, 2H), 4.27 (q, *J* = 7.3, 6.8 Hz, 2H), 7.00–7.40 (m, 6H), 7.83 (d, *J* = 8.1 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$, Me_4Si); δ = 13.0, 13.1, 13.2, 20.7, 23.7, 23.9, 24.0, 38.8, 39.7, 39.8, 40.7, 42.9, 43.0, 43.3, 61.9, 62.2, 113.2, 114.6, 114.9, 115.1, 115.4, 126.5, 127.5, 128.7, 128.8, 129.1, 129.2, 129.3, 129.4, 129.5, 133.2, 133.3, 134.0, 134.7, 143.7, 143.9, 159.9, 160.0, 162.8, 163.1, 163.3, 164.5, 195.4, 195.8. IR (neat, cm^{-1}): 2985, 2355, 1674, 1467, 1240, 1065, 1028. EIMS *m/z* (%) = 354.0 (M^+ + 1). $C_{21}H_{20}FNO_3$ calculated *m/z* 353.39.

2.4.7. Product ***3g***

Ethyl 2-cyano-3-(4-fluorophenyl)-5-(4-methoxyphenyl)-5-oxopentanoate. d.e.$_p$ = 30.5%. *Major isomer*: ^{1}H-NMR (600 MHz, $CDCl_3$, Me_4Si): δ = 1.12 (t, *J* = 7.2 Hz, 3H), 3.45 (d, *J* = 5.1 Hz, 1H), 3.86 (s, 3H) 4.09 (q, *J* = 7.2 Hz, 2H), 4.12–4.18 (m, *J* = 6.0, 4.7 Hz, 2H) 4.33 (d, *J* = 5.5 Hz, 1H), 6.913–7.40 (m, ArH, 6H), 7.94 (d, *J* = 9.0 Hz, 2H). *Minor isomer*: δ = 1.20 (t, *J* = 7.2 Hz, 3H), 3.42 (d, *J* = 4.7 Hz, 1H), 3.85 (s, 3H), 3.58 (d, *J* = 7.2 Hz), 3.60–3.63 (m, *J* = 8.0, 09.8 Hz, 2H), 6.91–7.40 (m, ArH, 6H), 7.91 (d, *J* = 8.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$, Me_4Si); δ = 13.9, 39.5, 40.2, 40.2, 41.2, 43.4, 44.1, 55.5, 62.7, 63.0, 113.9, 113.9, 115.6, 113.7, 115.9, 116.0, 129.3, 129.3, 129.5, 129.8, 129.0, 130.4, 134.2, 135.0, 160.6, 160.8, 163.9, 164.0, 164.9, 165.0, 194.8, 195.3. EIMS *m/z* (%) = 370.0 (M^+ + 1). $C_{16}H_{13}BrFNO_3$ calculated *m/z* 369.39.

*2.4.8. Product **3h***

Ethyl 2-cyano-3-(3,4-dichlorophenyl)-5-oxo-5-phenylpentanoate. $d.e._p = 26.7\%$. *Major isomer*: ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 1.18 (t, J = 7.1 Hz, 3H), 3.52 (d, J = 5.2 Hz, 1H), 3.89 (d, J = 5.1 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.31 (d, J = 5.3 Hz, 1H), 4.11–4.16 (m, J = 7.1, 6.5 Hz, 1H), 7.15–7.98 (m, 8H, ArH). *Minor isomer*: δ = 1.24 (t, J = 7.1 Hz, 3H), 3.48 (d, J = 5.2 Hz, 1H), 3.60 (d, J = 7.9 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.31 (d, J = 5.3 Hz, 1H), 4.11–4.16 (m, J = 7.1, 6.5 Hz, 1H), 7.15–7.98 (m, 8H, ArH) IR (neat cm^{-1}) 2923, 2252, 1743, 1683, 1596, 1366, 1251, 1210, 1029. EIMS m/z (%) = 390.1 ($M^+ + 1$). $C_{20}H_{17}Cl_2NO_3$ calculated m/z 390.36.

*2.4.9. Product **3i***

2-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)malononitrile. ^{1}H-NMR (600 MHz, $CDCl_3$, Me_4Si): δ = 3.61 (dd, J = 5.1, 5.2 Hz, 1H), 3.68 (dd, J = 8.2, 9.2 Hz, 1H), 3.95–3.98 (br, quintet, J = 4.1, 5.1 Hz, 1H), 4.62 (d, J = 5.1 Hz, 1H), 7.12 (t, J = 8.2 Hz, 2H), 7.44 (dd, J = 5.1, 6.1 Hz, 2H), 7.50 (t, J = 7.1 Hz, 2H), 7.63 (t, J = 7.2, 2H), 7.96 (d, J = 7.2 Hz, 2H). EIMS m/z (%) = 292 (M^+). IR (neat, cm^{-1}): 3062, 2916, 2256,1676, 1600, 1229, 453. $C_{20}H_{17}Cl_2NO_3$ calculated m/z 292.31.

*2.4.10. Product **3j***

2-(1-(4-Fluorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl) malononitrile. ^{1}H-NMR (600 MHz, $CDCl_3$, Me_4Si): δ = 3.54 (dd, J = 4.1,5.1 Hz, 1H), 3.63 (dd, J = 8.2, 9.3 Hz, 1H), 3.88 (t, 3H), 3.92–3.95 (br, quintet, J = 4.1, 5.1 Hz, 1H), 4.65 (d, J = 5.1 Hz, 1H), 6.66 (d, J = 5.1 Hz, 1H), 6.94 (d, J = 8.2 Hz, 2H), 7.12 (t, J = 5.1 Hz, 2H), 7.44 (dd, J = 3.1, 5.1 Hz, 2H), 7.94 (d, J = 9.2 Hz, 2H). IR (neat, cm^{-1}): 3372, 2913, 2251, 1667, 1600, 1513, 1237. EIMS m/z (%) = 322.0 (M^+). $C_{19}H_{15}FN_2O_2$ calculated m/z 322.33.

*2.4.11. Product **3k***

2-(1-(3,4-Dichlorophenyl)-3-oxo-3-phenylpropyl)malononitrile. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 4.13–4.18 (m, J = 6.6, 8.3 Hz, 2H), 4.65 (d, J = 2.9 Hz, 1H), 5.12 (d, J = 6.6 Hz, 1H), 7.10–7.80 (m, 8H, Ar–H). ^{13}C-NMR (100 MHz, $CDCl_3$, Me_4Si); δ = 40.6, 45.2, 45.3, 48.2, 49.3, 49.4, 51.4, 51.5, 74.5, 115.6, 115.8, 116.1, 124.5, 128.0, 128.2, 128.7, 130.6, 131.2, 133.0, 143.5, 161.3, 161.4, 164.6, 164.7, 203.8. IR (neat, cm^{-1}) 2969.84, 2359.48, 1741.41, 1448.28, 1371.14, 1229.4, 1215.9; EIMS m/z (%) = 344.0 ($M^+ + 1$,100). $C_{18}H_{12}Cl_2N_2O$ calculated m/z 343.1.

*2.4.12. Product **3l***

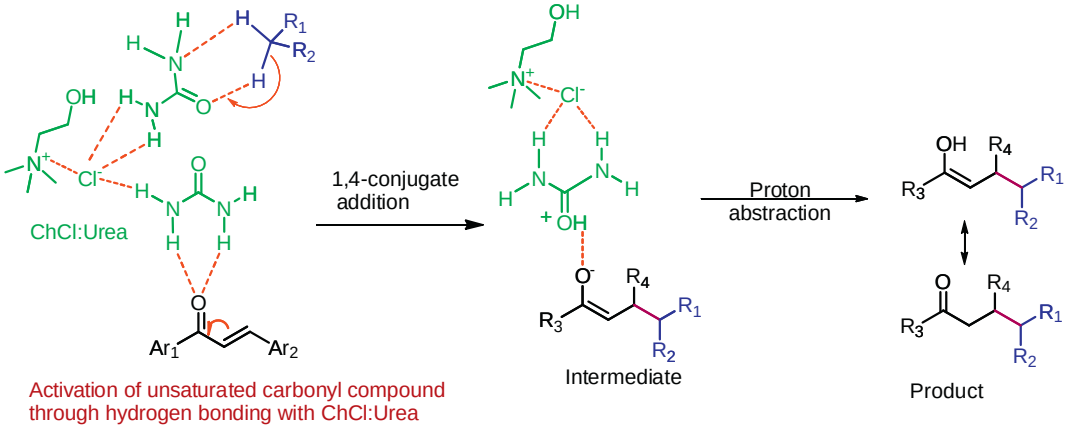
2-(3-(4-Bromophenyl)-1-(4-fluorophenyl)-3-oxopropyl) malononitrile. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 4.13–4.18 (m, J = 6.6, 8.3 Hz, 2H), 4.65 (d, J = 2.9 Hz, 1H), 5.12 (d, J = 6.6 Hz, 1H), 7.10–7.80 (m, 8H, Ar–H). IR (neat cm^{-1}): 3428, 2359, 1644, 1509, 1397, 1226, 1007. EIMS m/z (%) = 371.0 [(M^+,100]. $C_{18}H_{12}BrFN_2O$ calculated m/z 371.20.

3. Results and discussion

In order to optimize the reaction condition, conjugate addition of nitromethane (1.5 mmol) to 4-fluorobenzylideneacetophenone (1 mmol) was taken as a model reaction. The reaction was carried out in varying equivalents of ChCl:urea (1:2) and in different sets of reaction conditions. Among the various tested solvents such as methanol, ethanol, tetrahydrofuran (THF), diethylamine, solvent free conditions, ionic liquid [C_4mim][$C_2H_5SO_4$] and various catalysts (K_2CO_3, KF, SmI_3, $LiNO_3$, diethylamine), the addition was best catalyzed by 5 equiv. of ChCl:urea (1:2) giving a good yield of 89% within 2 h (Table 1).

Further, we carried out the above addition reaction under ultrasonication. It was observed that ultrasonic time and temperature had a great influence on the reaction time. When the reaction temperature was at 50 °C the yield of the product was only 70%; an increase in temperature to 80 °C gave an excellent yield of 92% within a short time of 45 min. However, a further increase in temperature gave a lower yield indicating by-product formation (Table 1, entry 10). Rate of reaction was faster under ultrasound compared to conventional heating. This is attributed to the cavitation phenomena occurring during sonication. Cavitation results in formation and adiabatic collapse of microbubbles resulting in the generation of local hotspots. These hotspots generate high temperature and pressures of several thousand atmospheres which cause the reaction to proceed rapidly.

In order to explore the versatility of the synergistic effect of DES ChCl:urea (1:2) and ultrasound, different substrates were used. Aromatic α,β-unsaturated ketones with different substituents such as $-CH_3$, $-OCH_3$, $-Cl$, $-Br$ and $-F$ were treated with various active methylenes like nitromethane, ethyl cyanoacetate and malononitrile. Addition of nitromethane to α,β-unsaturated ketones gave the desired product in high yields and in short reaction times (Table 2). Electron donating moiety in α,β-unsaturated ketones like methyl (Table 2, entries 2 & 6) and methoxy (Table 2, entries 3, 7 & 10) required longer reaction times to produce comparable yields than those of their simple and electron-withdrawing counterparts. The rate of reaction was found to be slow for ethyl cyanoacetate (70–95 min) as compared to nitromethane (40–45 min) and malononitrile (45–55 min), which is attributed to steric hindrance offered due to bulky substituents and to some extent to their acidities. Conjugate addition of α,β-unsaturated ketones with ethyl cyanoacetate, resulted in diastereomer formation. It is difficult to separate the individual diastereomer as the members of the diastereomeric mixture have very close R_f values (Table 2, entries 5, 6, 7 & 8)



Scheme 2. Mechanistic pathway for conjugate addition reaction catalyzed by ChCl:urea.

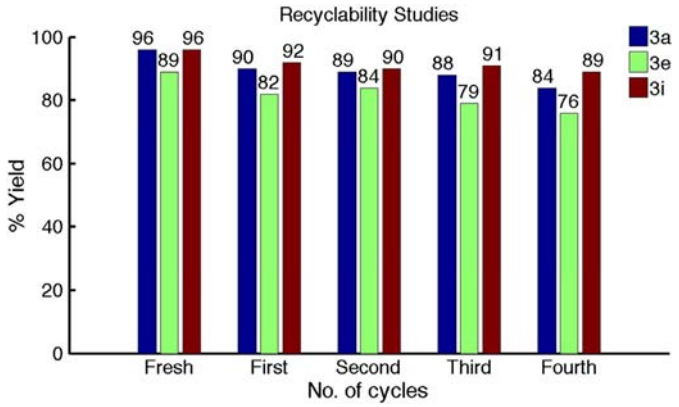


Fig. 1. Recyclability study of ChCl:urea (1:2) for conjugate addition reactions.

[44]. Formation of the diastereomer was very well observed in ^{1}H-NMR (600 MHz) and their diastereomeric ratio was found to be 70:30.

On the basis of results obtained in Table 2, it is observed that ChCl:urea (1:2) proves to be an efficient catalyst for synthesis of β-substituted ketones. Hence, a tentative mechanistic route indicating the important role of the ChCl:urea (1:2) system is demonstrated in Scheme 2. The stronger hydrogen-bonding capabilities of ChCl:urea (1:2) results in an oxyanion intermediate which on further proton abstraction gives the final addition product. The idea of urea in the DES serving as a hydrogen-bond donor has been postulated before by Handy et. al. [45,46].

For large scale operations, the possibility of recycling the catalyst is of great concern. A recyclability study was carried out for products **3a**, **3e** and **3i**. After completion of the reaction as indicated on TLC, ethyl acetate was added. The organic layer was evaporated at a rotary evaporator to afford the desired product. Ionic liquid ChCl:urea (1:2) was given a wash of ethyl acetate and was reused for carrying out a similar reaction. It was also observed that a deep eutectic mixture retains high catalytic activity even after five successive runs (Fig. 1).

4. Conclusion

In summary, the present work represents an expedient and clear-cut protocol for facile synthesis of β-substituted ketonic derivatives using biodegradable eutectic of ChCl:urea (1:2) as a versatile catalyst. The current process is advantageous over conventional methods as it completely avoids strongly basic or acidic conditions, expensive catalysts, and toxic solvents. In regard to synthetic improvements reported till date, this methodology employing eco-friendly ChCl:urea (1:2) as solvent and catalyst demonstrates many advantages such as: re-use of the catalyst, short reaction times, high yields and an easy product isolation step.

Acknowledgements

Authors are thankful to UGC-CAS for providing financial assistance and to the Institute of Chemical Technology, SAIF IIT-Bombay for recording mass spectra and TIFR Mumbai for recording ^{1}H-NMR spectra.

Appendix A. Supplementary data

File contains characterization data of all compounds. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.molliq.2014.02.016.

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