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Dimethylurea/citric acid as a highly efficient deep eutectic solvent for the multi-component reactions

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Abstract. Dimethylurea/citric acid deep eutectic solvent was used as a dual catalyst and a green reaction medium for the efficient synthesis of *bis*(indolyl)methanes, quinolines and aryl-4, 5-diphenyl-1H-imidazoles. Ease of recovery and reusability of DES with high activity makes this method efficient and eco-friendly.

Keywords. Deep eutectic; citric acid; dimethylurea; *bis*(indolyl)methane; quinoline; aryl-4, 5-diphenyl-1*H*-imidazole.

1. Introduction

Solvents play an essential role in chemical processes serving to put reactants into contact by dissolution and also affecting rates of the reactions. Solvents are also used in the later stages of a reaction for extraction and purification of the products.

Organic solvents are extensively used in organic synthesis and for this reason they are a matter of much concern due to characteristics such as high flammability, volatility, hazardness, and toxicity. Thus the search for environmentally benign substitutes for organic solvents has recently gained more attention in view of the increasing importance of Green Chemistry.

Room-temperature ionic liquids (ILs) are potential green alternatives to organic solvents[1] for extractions,[2] chemical reactions[3] and biotransformations.[4] Ionic liquids are non-volatile, thermally stable and their solvation properties vary by changing the cation and anion. However, most ILs have the disadvantage of high cost for large-scale production and some of them are environmentally unsafe. Moreover, the preparation of ILs often requires the use of organic solvents, and heat supply,[5] and cost can be high.

Another new versatile reaction medium has emerged, known as deep eutectic solvents (DESs). Abbott *et al*.[6,7] pioneered the development of these solvents which are low-melting liquids derived from the mixture of a solid organic salt and a suitable organic complexant, typically a hydrogen-bond donating species such as a polyol or urea derivatives.

DESs exhibit similar physico-chemical properties to the traditionally used ionic liquids, while being much cheaper and environmentally friendlier. Relative to conventional ILs, DESs have significant advantages, such as being easier and cheaper to prepare, non-reactive with water and many are biodegradable, but still exhibit chemical stability, non-flammability and conductivity.[8,9]

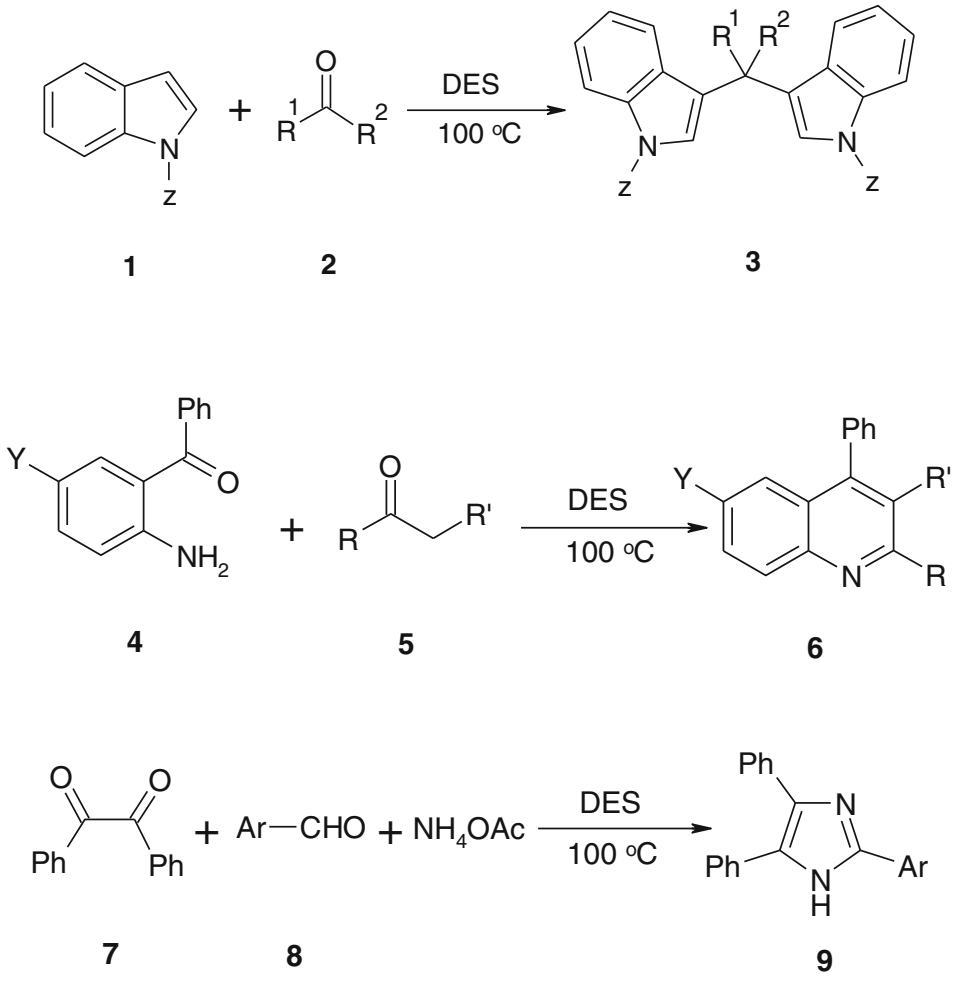
In recent years DES were used in synthetic organic chemistry due to their ability to serve as catalysts as well as solvents.[10–12]

In this investigation a new method for the synthesis of *bis*(indolyl)methanes, quinolines and aryl-4, 5-diphenyl-1*H*-imidazole in the presence of dimethylurea/citric acid deep eutectic solvent (DES) as an efficient, low cost and homogeneous catalytic medium will be described (scheme 1).

2. Experimental

All chemicals were purchased from Merck chemical company and were used without further purification. All products are known and were identified by comparison of their spectral data and physical properties with those of the authentic samples. Melting points were obtained in open capillary tubes and were measured on an Electrothermal-9100 and 9200 apparatus. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300-DRX Avance instrument at 300 and 75 MHz.

*For correspondence



Scheme 1. Synthesis of bis(indolyl)methane, quinoline and imidazole derivatives in presence of DES.

2.1 *Preparation of deep eutectic solvent*

The deep eutectic solvent (DES) was prepared as follows: a mixure of dimethylurea/citric acid with 6:4 ratio was heated at 100°C in air with stirring until a clear colourless liquid was obtained. Then the mixture was used.

2.2 *General procedure for the preparation of bis(indolyl)methanes*

A mixture of an aldehyde **1** (1 mmol), indole derivative **2** (2 mmol) and 1 g of DES was heated at 100°C for a period of time as indicated in table 1. The reactions were followed by thin-layer chromatography (TLC). After completion of the reaction, 10 mL of water was added to the mixture and the resulting precipitate was filtered off. The product was recrystalyzed from ethanol and the filtered solution was evaporated to recover the DES.

2.3 *General procedure for the preparation of quinolines*

2-Amino aryl ketone **4** (1 mmol) was added to 1.1 mmol ketone **5** and were reacted in the same conditions for the preparation of *bis*(indolyl)methanes.

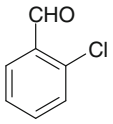
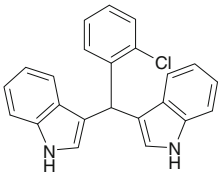
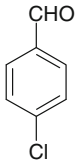
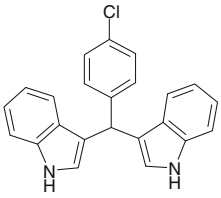
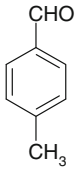
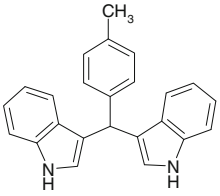
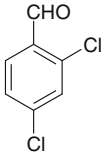
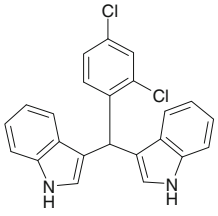
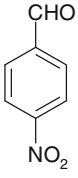
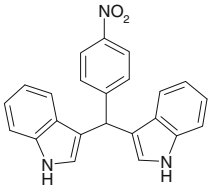
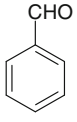
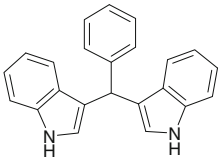
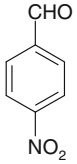
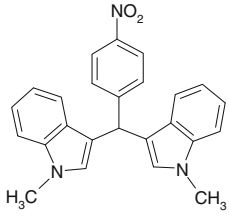
2.4 *General procedure for the preparation of aryl-4, 5-diphenyl-1H-imidazole*

Benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (3 mmol) were reacted in the same conditions for the preparation of *bis*(indolyl)methanes.

2.5 *Spectral data*

2.5a *3, 3′-Bis-indolyl phenylmethane (table 1, entry 6):*[13] ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92 (s, 1H), 6.60 (d, J = 15 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 7.20

Table 1. Synthesis of *bis*(indolyl)methanes in dimethylurea/citric acid DES.

Entry	Aldehyde	Product	Time (min)	Yield (%)	Mp (observed)	Mp (reported)	Ref.
1			2	86	74–76	70–71	[17]
2			2	95	77–79	76–77	[17]
3			4	90	97–99	93–94	[17]
4			4	96	102–105	103–106	[14]
5			4	85	224–226	220–223	[18]
6			2	90	127–130	125–127	[14]
7			6	88	210–211	215–217	[13]

(d, J = 7.9 Hz, 2H, Ar–H), 7.23–7.28 (m, 1H, Ar–H), 7.29–7.35 (m, 3H, Ar–H), 7.36–7.40 (m, 3H, Ar–H), 7.42 (d, J = 79 Hz, 2H, Ar–H), 7.82 (s, 2H, N–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.1, 111.1, 119.2, 119.7, 121.0, 121.9, 123.8, 126.1, 127.1, 128.2, 128.8, 136.6, 144.1.

2.5b *3, 3′-Bis-(N-methylindolyl)-(4-nitro phenyl-methane) (table 1, entry 7)*:[14] ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.79 (6H, s, $2CH_3$), 6.10 (1H, s), 6.68 (2H, s), 7.14 (2H, t, J = 7.3 Hz), 7.34 (2H, t, J = 7.7 Hz), 7.45 (4H, m), 7.61 (2H, d, J = 8.5 Hz), 8.23 (2H, d, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ

(ppm) 32.8, 40.2, 109.4, 116.7, 119.1, 119.7, 121.9, 123.6, 127.1, 128.4, 129.5, 137.5, 146.5, 152.4.

2.5c *Ethyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (table 2, entry 1)*:[15] ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.95 (3H, t, J = 7.2 Hz, CH_3), 2.77 (3H, s, CH_3), 4.06 (2H, q, J = 7.2 Hz, CH_2), 7.33 (1H, d, J = 2 Hz, arom), 7.35 (1H, d, J = 3.6 Hz, arom), 7.49 (2H, d, J = 2.4 Hz, arom), 7.50 (1H, s, arom), 7.54 (1H, d, J = 2.4 Hz, arom), 7.65 (1H, dd, J = 8.8 Hz, J = 2.4 Hz, arom), 8.01 (1H, d, J = 8.8 Hz, arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.6, 23.7, 61.4, 125.2, 125.9, 128.2, 128.4, 128.7, 129.3, 130.5, 131.1, 132.3, 135.0, 145.4, 146.1, 155.0, 168.1.

2.5d *Ethyl-2-methyl-4-phenylquinoline-3-carboxylate (table 2, entry 2)*:[15] ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.95 (3H, t, J = 7.2 Hz, CH_3), 2.79 (3H, s, CH_3), 4.06 (2H, q, J = 7.2 Hz, CH_2), 7.36 (1H, d, J = 2.0 Hz, arom), 7.37 (1H, d, J = 4.0 Hz, arom), 7.43 (1H, t, J = 8.0 Hz, arom), 7.47 (2H, d, J = 2.0 Hz, arom), 7.48 (1H, d, J = 1.6 Hz, arom), 7.58 (1H, d, J = 8.0 Hz, arom), 7.72 (1H, d, J = 6.8 Hz, arom), 8.08 (1H, d, J = 8.4 Hz, arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.6, 23.8, 61.3, 125.1, 126.4, 126.5, 127.4, 128.2, 128.4, 128.8, 129.3, 130.2, 135.7, 146.2, 147.7, 154.6, 168.4.

2.5e *2-(4-Chloro-phenyl)-4, 5-diphenyl-1H-imidazole (table 3, entry 2)*:[16] ^{1}H NMR (300 MHz, DMSO-d_6)δ (ppm): 7.21–7.48 (10H, m), 7.54 (2H, d, J = 8.5 Hz), 8.09 (2H, d, J = 8.5 Hz), 12.76 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6)δ (ppm): 126.5, 126.8, 127.0, 127.8, 128.1, 128.4, 128.6, 128.7, 129.1, 130.8, 132.7, 134.9, 137.2, 144.3.

2.5f *2-(3-Nitro-phenyl)-4, 5-diphenyl-1H-imidazole (table 3, entry 5)*:[16] ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.21–7.57 (10H, m), 7.77 (1H, t, J = 8.0 Hz), 8.18-8.22 (1H, m), 8.50 (1H, d, J = 8.0 Hz),

Table 2. Synthesis of quinolines in dimethylurea/citric acid DES.

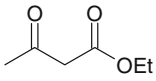
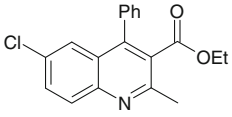
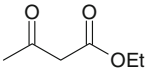
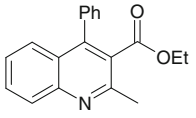
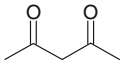
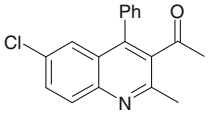
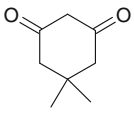
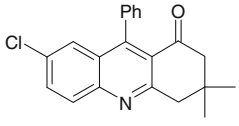
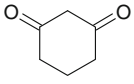
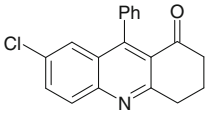
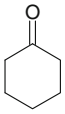
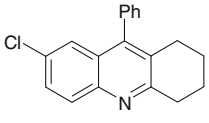
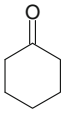
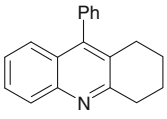
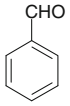
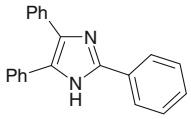
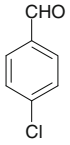
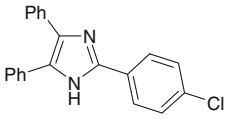
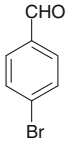
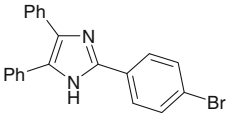
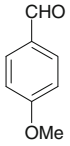
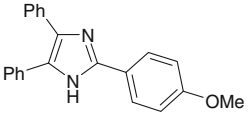
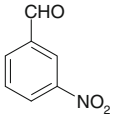
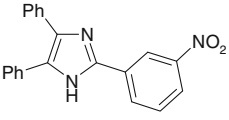
Entry	Carbonyl	Product	Time (min)	Yield (%)	Mp (observed)	Mp (reported)	Ref.
1			10	92	102–104	106–107	20
2			15	90	96–98	100–101	20
3			25	88	145–147	150–151	21
4			15	93	202–205	208–210	20
5			15	90	180–183	185–186	21
6			30	90	160–162	164–165	21
7			25	85	151–153	156–157	21

Table 3. Synthesis of aryl-4, 5-diphenyl-1*H*-imidazole in dimethylurea/citric acid DES.

Entry	Aldehyde	Product	Time (min)	Yield (%)	Mp (observed)	Mp (reported)	Ref.
1			25	90	275–278	280–281	22
2			30	92	260–265	263–265	22
3			30	88	260–262	264–266	16
4			50	86	228–230	230–232	22
5			30	92	290–295	301–302	16

8.95 (1H, m), 13.08 (1H, s).^{13}C NMR (75 MHz, DMSO-d_6)δ (ppm): 119.3, 122.5, 126.7, 127.1, 128.2, 128.4, 128.6, 129.1, 130.4, 130.6, 131.1, 131.8, 134.7, 137.6, 143.3, 147.0, 148.3.

3. Results and discussion

Initially, we chose indole (2 mmol) and benzaldehyde (1 mmol) as standard starting materials to establish the best conditions for the reaction.

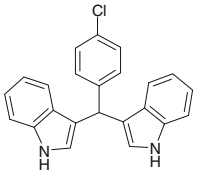
Best results were obtained with (6:4) dimethylurea/citric acid DES at 100°C.

After setting up the optimized reaction conditions, the reaction of a series of carbonyl compounds with indole were investigated. In order to show the general applicability of this method, various aldehydes were efficiently reacted with two equivalents of indole derivatives in the same conditions. As shown in table 1 yields are good to excellent in most cases.

After successfully synthesizing a series of *bis*(indolyl)methanes, we turned our attention towards the synthesis of quinoline derivatives in the presence of dimethylurea/citric acid (6:4) DES under similar reaction conditions.

As shown in table 2, this method is equally effective for both cyclic and acyclic ketones. This reaction is very clean and free from side reactions such as self-condensation of ketones, which is normally observed under basic conditions.

Table 4. Reaction of indole with carbonyl compounds in the presence of different catalysts.

Product	Catalyst	Conditions	Solvent	Time (min)	Yield (%)	Ref.
	$Fe(HSO_4)_3$	R.T.	CH_2Cl_2	30	80	23
	[BTBAC]Cl-$FeCl_3$[1]	60°C	Solvent-free	15	95	24
	[bnmim][HSO_4]	Microwave	Solvent-free	6	95	25
	–	100°C	Dimethylurea/citric acid	2	95	–

[1]Benzyl tributylammonium chloride

Table 5. Reaction of ethylacetoacetate with 2-amino-5-chloro benzophenone in the presence of different catalysts.

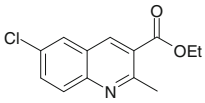
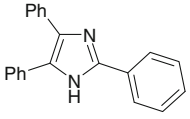
Product	Catalyst	Conditions	Solvent	Time (min)	Yield (%)	Ref.
	Cellulose sulphuric acid	100°C	Solvent-free	15	92	19
	I_2	60°C	Solvent-free	120	80	15
	Dodecylphosphonic acid	90°C	Solvent-free	20	96	26
	–	100°C	Dimethylurea/citric acid	10	92	–

Table 6. Reaction of benzil with benzaldehyde in the presence of different catalysts.

Product	Catalyst	Conditions	Solvent	Time (min)	Yield (%)	Ref.
	–	110°C	PEG-400	90	88	21
	poly(AMPS-co-AA)[1]	110°C	Solvent-free	25	92	22
	$H_2SO_4.SiO_2$	110°C	Solvent-free	50	90	27
	–	100°C	Dimethylurea/citric acid	25	90	–

[1]Poly acrylamido-2-methyl-1-propane sulphonic acid-acrylic acid

In the next step, dimethylurea/citric acid (6:4) DES was used for the synthesis of 2-aryl-4, 5-diphenyl-1*H*-imidazole derivatives under similar reaction conditions. The results are summarized in table 3.

In order to show the merit of dimethylurea/citric acid DES catalytic system in comparison with the other catalytic systems used for the similar reactions, some of the results have been given in tables 4, 5 and 6. As it is evident from the results, the present method is very efficient for the synthesis of *bis*(indolyl) methanes and quinolines.

3.1 *Recyclability of deep eutectic solvent*

The deep eutectic solvent medium was recycled and re-used up to three times. Reaction of 4-nitro benzaldehyde with N-methyl indole was selected as the model reaction. Deep eutectic solvent that recycled from the previous run was re-used for the next run without further purification. Only a slight decrease in yields was observed as shown in table 7. This indicates the fact that DES reserves its activity even after three runs.

Table 7. The reaction of 4-nitro benzaldehyde with N-methyl indole in DES.

Entry	Cycle	Time (min)	Yield (%)
1	1st run	6	88
2	2nd run	6	86
3	3rd run	6	86

4. Conclusion

In conclusion, we have developed an environmentally friendly, and practical procedure for the synthesis of *bis*(indolyl)methane, quinoline and aryl-4, 5-diphenyl-1*H*-imidazole derivatives in the presence of a deep eutectic solvent and readily available starting materials in high yields. This method offers several advantages including using of a green DES instead of organic solvents, high yields, short reaction times, and a simple work-up procedure, and reusability of DES.

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