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Deep eutectic solvent for multi-component reactions: a highly efficient and reusable acidic catalyst for synthesis of 2,4,5-triaryl-1*H*-imidazoles

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Abstract Efficient synthesis of 2,4,5-trisubstituted imidazoles has been achieved by three-component cyclocondensation of benzil or benzoin, an aldehyde, and ammonium acetate by use of an acidic catalyst. The catalyst is a deep eutectic mixture of choline chloride and oxalic acid that is non-toxic and biodegradable. Crucial advantages of this process are high yields, shorter reaction times, easy work-up, purification of products by non-chromatographic methods, and reusability of the catalyst.

Keywords 2,4,5-Trisubstituted imidazoles · Multi-component reactions · Choline chloride · Deep eutectic solvent · Oxalic acid

Introduction

The imidazole nucleus is a fertile source of biologically important molecules. Compounds containing the imidazole group have many pharmacological properties and are important in biochemical processes. They are well known as inhibitors of P38MAP kinase, and act as fungicides, herbicides, anti-inflammatory agents, antithrombotic agents, plant-growth regulators, and therapeutic agents. They are also used in photography as photosensitive compounds. Some substituted triarylimidazoles are selective antagonists of the glucagons receptor and inhibitors of IL-1 biosynthesis [1]. Radziszewski and Jaap [2, 3] proposed the first synthesis of the

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imidazole core in 1882, starting from 1,2-dicarbonyl compounds, aldehydes, and ammonia to obtain 2,4,5-triphenylimidazole. Several methods are used for synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles; these entail use of such catalysts as $ZrCl_4$ [4], zeolite HY and silica gel [5], $NaHSO_3$ [6], sulfanilic acid [7], iodine [8], ceric ammonium nitrate [9], oxalic acid [10], ionic liquids [11], acetic acid with microwave irradiation [12], and polymeric catalysts [13]. Each of these methods has its own merits, but some suffer from such limitations as poor yield, long reaction time, difficult work-up, and effluent pollution [1]. Development of a new mild method which overcomes these disadvantages is, therefore, still a challenge for organic chemists.

One of our objectives is to introduce a new cost-effective catalyst for synthesis of 2,4,5-trisubstituted imidazoles in high yields under mild condition. In an attempt to achieve this, we have investigated the catalytic activity of deep eutectic solvent (DES) for multi-component synthesis of 2,4,5-trisubstituted imidazoles. Multicomponent reactions (MCRs) have attracted much interest, and are highly important in modern organic synthesis and medicinal chemistry, because these one-pot processes involving three or more components have high atom economy and are highly selective [14, 15]. MCRs have made a large contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery [16, 17]. DESs are simple ionic mixtures of quaternary ammonium salts, for example choline chloride, with either hydrogen bond donors, for example urea and glycerol, or with Lewis acids, for example zinc chloride. The ability to form a hydrogen bond with the halide ion leads to a eutectic combination, because these hydrogen-bonding interactions lead to depression in freezing point. Thus formation of the eutectic is more energetically favored relative to the lattice energies of the pure constituents [18, 19]. DESs derived from choline chloride are biodegradable, non-toxic, insensitive to moisture, recyclable, and cost-effective [18].

We report here the one-pot synthesis of 2,4,5-trisubstituted imidazoles using a DES of choline chloride and oxalic acid as a novel catalyst (Fig. 1). We examined a wide variety of aromatic aldehydes with a variety of substituents to establish the importance of this catalyst in this reaction.

Experimental

Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were recorded with a Varian 3100 FT-IR spectrometer. CHN analysis was performed with an Exeter Analytical Model CE-400 CHN Analyzer. ^{1}H NMR spectra were recorded with a Bruker DRX-400 Avance spectrometer at 298 K, with DMSO-d_6 as solvent. All the products are known compounds [8, 10, 20–22], and were characterized by use of IR and NMR spectral data and comparison of their melting points with literature data.

Preparation of catalyst

The DES catalyst was prepared in accordance with the literature [23]. Choline chloride (10 g, 71.4 mmol) and oxalic acid (6.5 g, 71.4 mmol) were heated with stirring at 100 °C until a homogeneous colorless liquid was obtained. The DES formed (16.5 g, 100 %) was cooled and used in reactions without any purification (Fig. 2). This liquid can be characterized on the basis of such physical properties as freezing point, viscosity, and conductivity [23]. The freezing point of this DES, taken as the temperature at which the first solid began to form, was 34 °C. FTIR data for the liquid were (cm^{-1}): 3361, 2962, 1751, 1479.

General procedure for preparation of **2a–h**

A mixture of aldehyde (1 mmol), benzil or benzoin (1 mmol), ammonium acetate (5 mmol), and the DES (0.5 ml), as catalyst, was stirred in a 20-ml glass tube at 110 °C for 60 min. After completion of the reaction, appropriate amounts of distilled water were added and the mixture was stirred for 10 min. The residue was

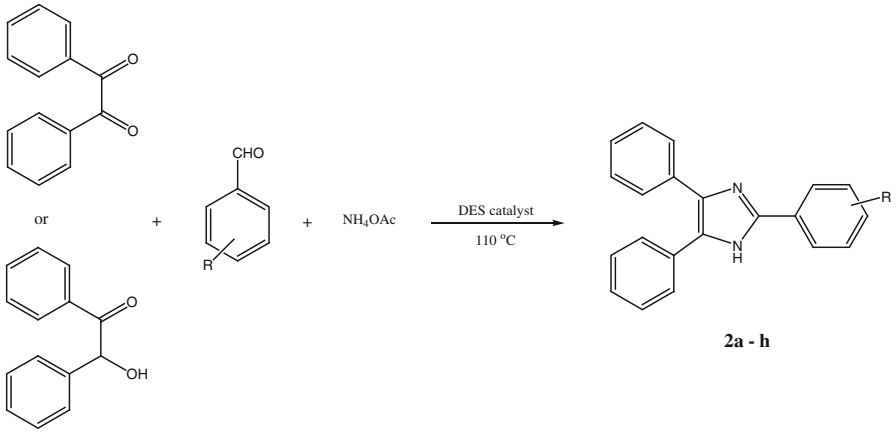

Fig. 1 Deep eutectic solvent catalyzed synthesis of 2,4,5-trisubstituted imidazole

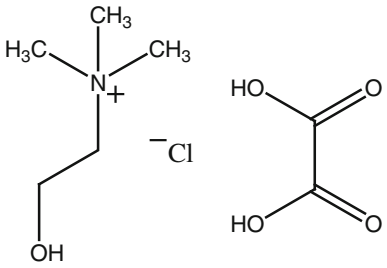

Fig. 2 Deep eutectic solvent of choline chloride and oxalic acid

then isolated by filtration, washed with cold water, and crystallized from hot ethanol to afford the pure product.

Spectral data

*2,4,5-Triphenyl-1H-imidazole (**2a**)*

Color: white; Mp 273–275 °C; FTIR (KBr, cm^{-1}): 3451, 3034, 2962, 1601, 1490; ^1H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H), 8.09 (d, $J = 7.7$ Hz, 2H), 7.56–7.22 (m, 13H); Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.18; H, 5.49; N, 9.33.

*2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (**2b**)*

Color: white; Mp 264–266 °C; FTIR (KBr, cm^{-1}): 3080, 1597, 1485; ^1H NMR (400 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.11 (d, $J = 8.4$ Hz, 2H), 7.56–7.23 (m, 12H); Anal. Calcd for $C_{21}H_{15}N_2Cl$: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.20; H, 4.61; N, 8.41.

*2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (**2c**)*

Color: white; Mp 230–233 °C; FTIR (KBr, cm^{-1}): 3425, 3029, 2956, 1610, 1495, 1249; ^1H NMR (400 MHz, DMSO-d_6): δ 12.50 (s, 1H), 8.03 (d, $J = 8.5$ Hz, 2H), 7.50–7.05 (m, 12H), 3.82 (s, 3H); Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.90; H, 5.51; N, 8.63.

*2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole (**2d**)*

Color: orange; Mp 238–240 °C; FTIR (KBr, cm^{-1}): 3400, 3088, 2928, 1597, 1515; ^1H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 8.08 (d, $J = 7.1$ Hz, 2H), 7.65–7.30 (m, 12H); Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.84; H, 4.47; N, 12.39.

*2-(4-(Dimethylamino)phenyl)-4,5-diphenyl-1H-imidazole (**2e**)*

Color: white; Mp 260–262 °C; FTIR (KBr, cm^{-1}): 3455, 3060, 2933, 1616, 1507; ^1H NMR (400 MHz, DMSO-d_6): δ 12.85 (s, 1H), 8.08 (d, $J = 7.1$ Hz, 2H), 7.65–7.10 (m, 12H), 2.8 (s, 6H); Anal. Calcd for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.45; H, 6.15; N, 12.41.

*2-(4-Isopropylphenyl)-4,5-diphenyl-1H-imidazole (**2f**)*

Color: white; Mp 255–257 °C; FTIR (KBr, cm^{-1}): 3030, 2960, 1605, 1490; ^1H NMR (400 MHz, DMSO-d_6): δ 12.60 (s, 1H), 8.01 (d, $J = 7.1$ Hz, 2H), 7.65–7.10 (m, 12H), 2.96 (sep, $J = 6.5$, 1H), 1.26 (d, $J = 6.5$, 6H); Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.21; H, 6.59; N, 8.20.

*2-(2-Chlorophenyl)-4,5-diphenyl-1H-imidazole (**2g**)*

Color: white; Mp 196–198 °C; FTIR (KBr, cm^{-1}): 3450, 3064, 1593, 1479; ^1H NMR (400 MHz, DMSO-d_6): δ 12.50 (s, 1H), 8.53 (s, 1H), 7.65–7.28 (m, 13H); Anal. Calcd for $C_{21}H_{15}N_2Cl$: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.33; H, 4.55; N, 8.50.

*2-(3-Nitrophenyl)-4,5-diphenyl-1H-imidazole (**2h**)*

Color: yellow; Mp 301–302 °C; FTIR (KBr, cm^{-1}): 3400, 3056, 1601, 1522; ^1H NMR (400 MHz, DMSO-d_6): δ 13.12 (s, 1H), 8.90 (s, 1H), 8.56 (d, $J = 7.4$ Hz, 1H), 8.21 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.56–7.30 (m, 10H); Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.84; H, 4.47; N, 12.39.

Results and discussion

The efficiency of this reaction is mainly affected by amount of catalyst, temperature, and reaction time. To determine the best conditions, we initially investigated condensation of benzil (1 mmol), 4-chlorobenzaldehyde (1 mmol), and ammonium acetate (5 mmol) in the presence of the DES catalyst (0.2 ml) at room temperature. Even after 24 h, however, only a trace of product was obtained. When the reaction temperature was increased to 70 °C the desired product, i.e. **2b**, was obtained in 30 % yield. When the reaction temperature was again increased, to 130 °C, reaction time decreased but the yield was still not very high (Table 1, entry 4). Hence, it was thought worthwhile to perform the reaction in the presence of a larger amount of the catalyst. As indicated in Table 1, the maximum yield (95 %) was obtained when the reaction was performed with 0.5 ml DES catalyst at 110 °C. A further increase of the amount of catalyst did not affect the yield (entry 9, Table 1).

After optimizing the conditions, we used this catalyst for synthesis of trisubstituted imidazoles from different aromatic aldehydes with a wide range of substituents to establish the catalytic importance of the DES in this reaction. The

Table 1 Optimization of one-pot synthesis of trisubstituted imidazoles by DES catalyst

Entry	DES catalyst (ml)	*T* (°C)	Time (h)	Yield (%)
1	0.2	rt	24	Trace
2	0.2	70	3	30
3	0.2	90	1	45
4	0.2	110	1	50
5	0.2	130	1	50
6	0.3	110	1	65
7	0.4	110	1	80
8	0.5	110	1	95
9	0.6	110	1	95

Benzil (1 mmol), 4-chlorobenzaldehyde (1 mmol), and ammonium acetate (5 mmol)

Table 2 Synthesis of 2,4,5-triaryl-1*H*-imidazoles (**2a–h**) by use of the DES catalyst (0.5 ml)

Product[a]	R	Yield (%)[b]		Mp (°C)	
		Benzil	Benzoin	Found	Reported
2a	4-H	90	90	273–275	272–274 [8]
2b	4-Cl	95	90	264–266	262–264 [8]
2c	4-OCH_3	85	80	230–233	228–231 [8]
2d	4-NO_2	85	80	238–240	239–242 [20]
2e	4-$N(CH_3)_2$	90	80	260–262	259–260 [10]
2f	4-$CH(CH_3)_2$	85	80	255–257	253–255 [21]
2g	2-Cl	90	85	196–198	197–199 [21]
2h	3-NO_2	85	80	301–302	>300 [22]

[a] All the isolated products were characterized on the basis of their physical properties, IR and ^{1}H NMR spectroscopic analysis, and direct comparison with authentic materials

[b] Reaction time (1 h)

Table 3 Reusability of the DES catalyst for synthesis of **2b**

Entry	Time (h)	Yield[a] (%)
1	1	95
2	1	95
3	1	93
4	1	87

[a] Isolated yields

Table 4 Comparison of results using the DES catalyst with literature results

Entry	Catalyst	Conditions	Time (min)	Yield (%)
1	$ZrCl_4$	CH_3CN, RT	600	93 [4]
2	Zeolite HY and silica gel	Microwave irradiation	6	85 [5]
3	$NaHSO_3$	Ethanol/water, 80 °C	30	90 [6]
4	Sulfanilic acid	Ethanol/water, 80 °C	50	95 [7]
5	Iodine	Ethanol, 75 °C	28	98 [8]
6	Ceric ammonium nitrate	Ethanol/water, 65 °C	50	95 [9]
7	Oxalic acid	Ethanol/water, 80 °C	60	90 [10]
8	Polymeric catalyst	Solvent free, 110 °C	60	90 [13]
9	Choline chloride and oxalic acid	Solvent free, 110 °C	60	90 [this work]

corresponding results are given in Table 2. Also, direct use of benzoin, rather than benzil, resulted in a synthesis which was much more environmentally benign but of almost equal efficiency. As indicated in Table 2, when benzoin was used instead of benzil, the yield of the reaction decreased slightly.

In the next step, we investigated the reusability of the DES catalyst. For this purpose, the catalyst was used for synthesis of product **2b**. When the reaction

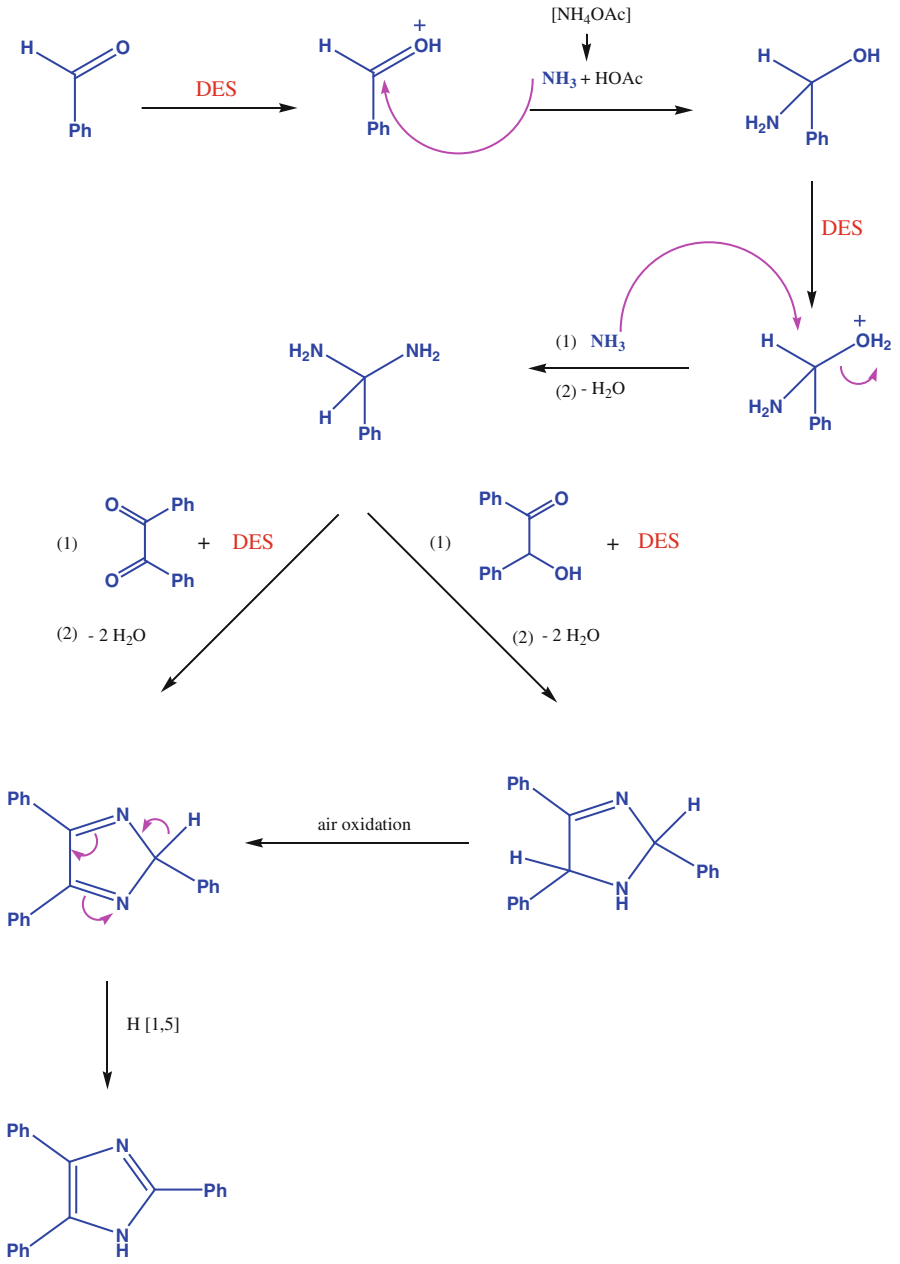

Fig. 3 Possible mechanism of synthesis of trisubstituted imidazoles by use of the DES catalyst

was completed, the mixture was washed with distilled water and the crude product was separated by simple filtration. The DES catalyst was recovered from the filtrate by removing the aqueous layer by distillation under vacuum. The

recycled catalyst was used consecutively in subsequent reactions; the results are given in Table 3.

Finally, the efficiency of the DES catalyst was compared with that of other catalysts reported elsewhere for synthesis of 2,4,5-triphenyl-1*H*-imidazole by one-pot, three-component condensation of 2-chlorobenzaldehyde, benzil, and ammonium acetate. The data listed in Table 4 show that the DES is a suitable catalyst for this reaction.

A possible mechanism of the DES-catalyzed synthesis of trisubstituted imidazoles is depicted in Fig. 3 [13, 18].

In summary, in this paper we report a convenient and efficient process for one-pot synthesis of trisubstituted imidazoles by three-component coupling of benzil or benzoin, aldehydes, and ammonium acetate using a DES catalyst. The reaction profile is very clean and no by-products are formed. All the synthesized imidazoles were characterized on the basis of elemental analysis and spectral studies. We believe this procedure enables convenient, economic, and user-friendly synthesis of trisubstituted imidazoles of biological and medicinal importance.

Conclusion

We report an efficient and environmentally friendly approach for synthesis of biologically active trisubstituted imidazoles by condensation of benzil or benzoin, a variety of aromatic aldehydes, and ammonium acetate using a deep eutectic mixture of choline chloride and oxalic acid as catalyst. High yields, easy work-up, purification of compounds by a non-chromatographic method (crystallization only), and reusability of the catalyst are crucial advantages of this method.

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