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# Urea–Zinc Chloride Eutectic Mixture-Mediated One-Pot Synthesis of Imidazoles: Efficient and Ecofriendly Access to Trifenagrel

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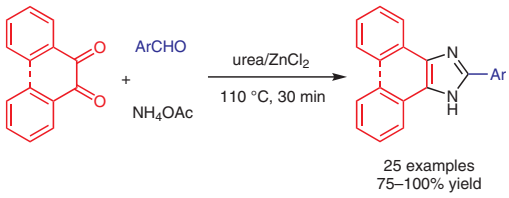


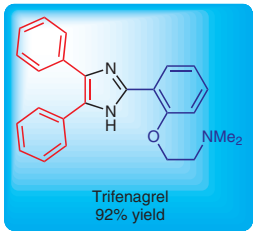


Low cost and easy preparation of the deep eutectic solvent (DES)

Reusabilty of DES up to 4 cycles

Easy reaction setup and workup

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**Abstract** The low-melting mixture urea–$ZnCl_2$ was evaluated as a novel reaction medium for the synthesis of imidazoles. The reaction between a dicarbonyl compound, ammonium acetate, and an aromatic aldehyde is efficiently catalyzed by the eutectic solvent, yielding a wide variety of triaryl-1*H*-imidazoles or 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles in good to excellent yields. In addition, the eutectic solvent was reused in five cycles without loss of its catalytic activity. This protocol was further explored for the synthesis of the drug trifenagrel, giving an excellent yield.

**Key words** imidazoles, deep eutectic solvent, multicomponent reaction, trifenagrel, phenanthroimidazoles

In recent decades, naturally occurring imidazoles and their synthetic derivatives have drawn much interest due to their chemical, physicochemical, and pharmaceutical properties. Several derivatives possess such biological activities as antiallergic,[1] antiinflammatory,[2] antinociceptive,[2] antitumor,[3] antibacterial,[4] antiviral,[5] or analgesic properties,[6] whereas others act as inhibitors of p38 MAP kinase,[7] as glucagon receptors,[8] and as multidrug-resistant modulators.[9] Furthermore, imidazole derivatives have been also used in the preparation of ionic liquids,[10] and their carbenes have found practical use as ligands in coordination chemistry and are versatile catalysts.[11] In addition, the optoelectronic properties of some compounds have prompted their use in materials chemistry for the development of blue-light-emitting materials, fluorescence labeling agents,[12] and chemosensors.[13]

Due to the wide range of applications of substituted imidazoles, numerous and well-established methods for their synthesis can be found in the literature, including the reactions of Van Leusen,[14] Debus,[15] Marckwald,[16] Wallach,[17] and Radziszewski.[18] More recently, the reactions of amidines[19] or *N*-propargylamines[20] with several substrates; the catalytic derivatization of imidazole rings, for example by C–H activation,[21] metal-catalyzed N-arylation,[22] or cross-coupling reactions;[23] and the catalytic formation of imidazole cores[24] have been reported as methods for obtaining this heterocycle. However, the cyclocondensation of 1,2-diketones with amines and aldehydes (the Debus–Radziszewski reaction) in a one-pot multicomponent process remains a versatile, efficient, and economical method that permits the synthesis of a diverse range of substituted derivatives. Therefore, many efforts have been devoted to attaining high yields of pure products by this method in short reaction times by employing various homogeneous and heterogeneous catalysts,[25] solvents,[26] ultrasound,[27] or microwave irradiation.[28]

The introduction of eutectic mixtures in various chemical processes has intensified interest in finding new applications for these versatile solvents. A deep eutectic solvent (DES) is defined as a mixture of two or more components that are capable of self-association through hydrogen-bond interactions, which result a large melting-point depression at a particular composition (the eutectic composition).[29] Depending on its composition, a DES can be classified as one of four types. The first type is formed by combining a metal salt and an organic salt (e.g., $ZnCl_2$ and choline chloride). The second is obtained from a metal salt hydrate and an organic salt (e.g., $CoCl_2{\cdot}6H_2O$ and choline chloride). The third is prepared from a hydrogen-bond donor and an organic salt (e.g., urea and choline chloride). Finally, the fourth type is obtained from a metal chloride and a hydrogen-bond donor (e.g., $ZnCl_2$ and acetamide).[30,31] The eutectic mixture urea–$ZnCl_2$, first reported by Abbott et al.,[31] is a DES of the fourth type, and its lowest freezing temperature ($T_f$ = 9 °C) occurs at a urea–$ZnCl_2$ molar ratio of 3.5:1 (the eutectic composition). Although its physical properties are similar to those of an ionic liquid, only scarce information is

found in the literature regarding its uses, which include the electrodeposition of Zn–Ti alloys,[32] lignin modification,[33] the preparation of bis(indolyl)methanes,[34] and the electrochemical fabrication of nanoporous gold electrodes.[35]

The remarkable importance of imidazoles together with the growing use of DESs in organic synthesis prompted us to develop a sustainable methodology for the synthesis of valuable organic compounds, and here we report the synthesis of imidazole derivatives by employing the urea–$ZnCl_2$ DES as an efficient, ecofriendly, and recyclable reaction medium.

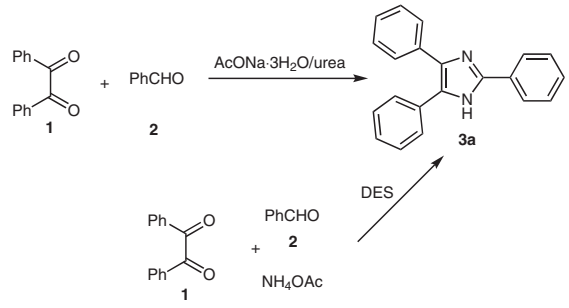
Recently, we reported that the DES formed from sodium acetate trihydrate and urea is an effective source of ammonia for the synthesis of hexahydroacridine-1,8-diones when the reaction is performed at temperatures above 90 °C.[36] With this in mind, we decided to study the Debus–Radziszewski reaction for the preparation of 2,4,5-triaryl-1*H*-imidazoles and, for our initial test reaction, we chose the synthesis of lophine (**3a**; 2,4,5-triphenyl-1*H*-imidazole) from a mixture of benzil (**1**) and benzaldehyde (**2**) in an eutectic mixture of sodium acetate trihydrate and urea (Table 1, entry 1). Under the reaction conditions employed, **3a** was obtained in 91% yield after 90 minutes. Although this result was promising, we decided to evaluate this multicomponent reaction in other eutectic solvents based in choline chloride (ChCl) (entries 2–6). Solvents composed of ChCl and carboxylic acids afforded the product in 78–83% yield, whereas ChCl–glycerol and ChCl–urea mixtures gave poor yields (entries 5 and 6). Interestingly, when the reaction was performed at the same temperature in the urea–$ZnCl_2$ DES, **3a** was obtained in an excellent yield of 99% after 30 minutes (entry 7). A decrease in temperature or the use of $ZnCl_2$ as a catalyst gave lower yields (entries 8–10), and in the absence of the DES, only a 20% yield of the product was obtained (entry 11). Note that other DESs have also been used for the synthesis of lophine (entries 12–15);[37] however, the our method is superior in terms of the reaction time and the yield.

Having optimized the reaction conditions, we evaluated the versatility of the DES in the synthesis of trisubstituted imidazoles from various aromatic aldehydes (Scheme 1).

As can be seen in Scheme 1, compounds **3a–p** were obtained in yields of 75–100%, with *ortho*-substituted aldehydes affording slightly lower yields of compounds **3f**, **3g**, and **3k**, presumably due to steric hindrance. This protocol showed good substrate compatibility for aromatic aldehydes: aldehydes bearing electron-withdrawing groups (chloro, bromo, or nitro) or electron-donating groups (methoxy, hydroxy, dimethylamino, methylenedioxy, and isopropyl) gave the corresponding products in high yields.

Inspired by these results, we then applied this protocol to the synthesis of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles from phenanthrene-9,10-dione (Scheme 1). The fused

**Table 1** Optimization of Reaction Conditions for the Synthesis of Lophine (**3a**) in Deep Eutectic Solvents

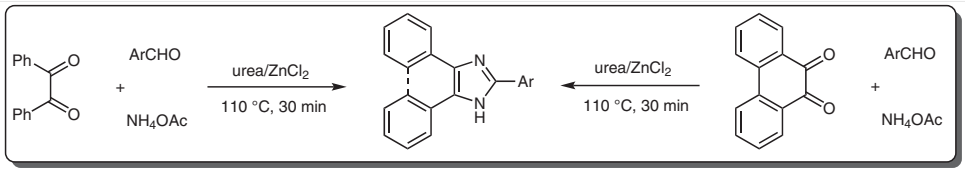


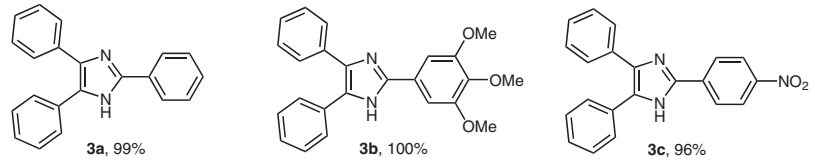

| Entry | DES | Temp (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | NaOAc·$3H_2O$–urea[a] | 100 | 90 | 91[d] |
| 2 | ChCl–malonic acid[b] | 110 | 90 | 83[d] |
| 3 | ChCl–succinic acid[b] | 110 | 90 | 78[d] |
| 4 | ChCl–citric acid[b] | 110 | 90 | 80[d] |
| 5 | ChCl–glycerol[b] | 110 | 90 | 45[d] |
| 6 | ChCl–urea[b] | 110 | 90 | 27[d] |
| 7 | **urea–$ZnCl_2$**[b] | **110** | **30** | **99**[d] |
| 8 | urea–$ZnCl_2$[b] | 60 | 30 | 70[d] |
| 9 | urea–$ZnCl_2$[b] | 80 | 30 | 85[d] |
| 10 | $ZnCl_2$[c] | 110 | 30 | 55[d] |
| 11 | – | 110 | 30 | 20[d] |
| 12 | ChCl–oxalic acid | 110 | 60 | 90[e] |
| 13 | DMU–citric acid | 100 | 25 | 90[e] |
| 14 | ChCl–$ZnCl_2$ | 100 | 60 | 80[e] |
| 15 | ChCl–TsOH in EtOH | 78 | 120 | 95[e] |

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), DES (1.2 g).
[b] Reaction conditions: **1** (1 mmol), **2** (1 mmol), $NH_4OAc$ (2 mmol), DES (0.8 g).
[c] The same amount of $ZnCl_2$ as in entry 7 was used.
[d] Isolated yield.
[e] Reported yield.

imidazoles **3q–y** were obtained in yields of 91–99%, indicating that this method is equally effective for both acyclic and cyclic ketones.

A plausible mechanism for the synthesis of imidazole derivatives is presented in Scheme 2. In the first step, the diamine intermediate **A** is formed by nucleophilic attack of the nitrogen atoms of ammonia, formed from $NH_4OAc$, on the carbonyl group of the aldehyde,[39] which is activated by the DES. Subsequent condensation of diamine **A** with the 1,2-diketone followed by dehydration and rearrangement of the imino intermediate **B** gives the desired product. The action of $ZnCl_2$ (or Zn clusters) presented in the DES[31] as a Lewis acid activates the carbonyl groups, thereby increasing the rate of production of intermediates **A** and **B**.

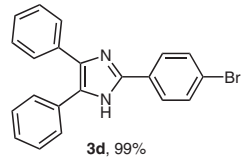


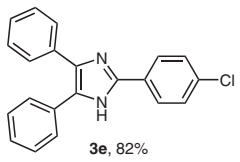



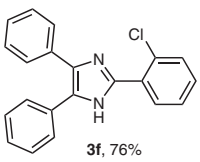


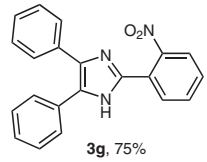


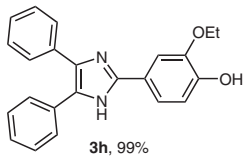


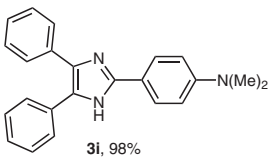



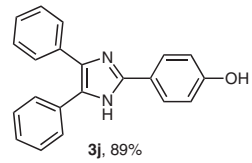



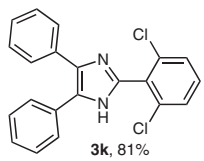



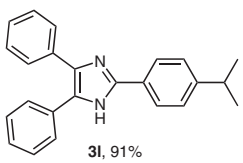



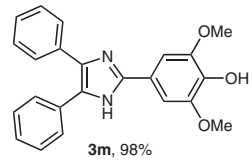



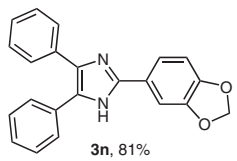



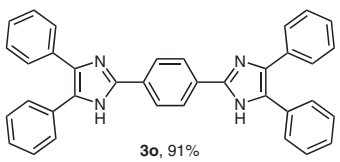



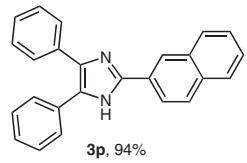



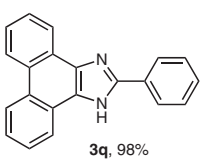



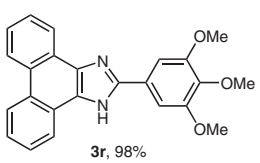



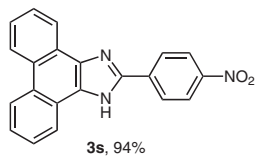



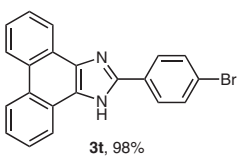



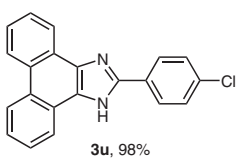



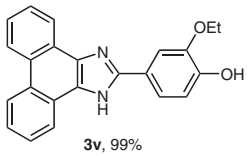



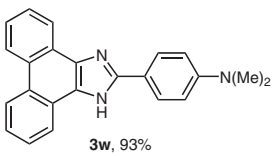



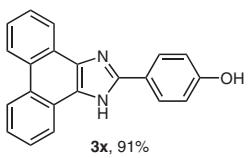



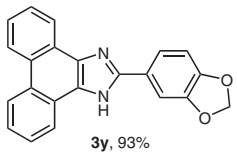



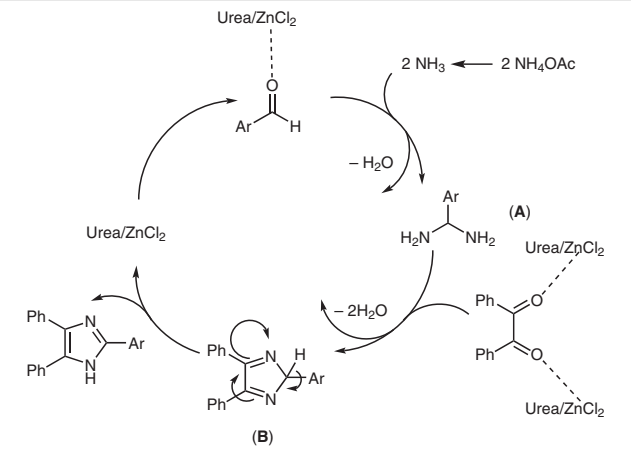




**Scheme 1** Multicomponent syntheses of 2,4,5-triaryl-1*H*-Imidazoles **3a–p** and 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles **3q–y** in the urea–$ZnCl_2$ DES[38]




**Scheme 2** Proposed mechanism for the synthesis of substituted imidazoles by using the urea–$ZnCl_2$ DES

The reusability and recovery of reaction media are important issues, especially when their environmental impact is considered. Therefore, in our next step, we investigated the reusability of the DES in the model reaction and, for this purpose, after completion of the reaction, the mixture was washed with distilled water, and the crude product was separated by filtration. The DES was recovered from the filtrate by lyophilization then recharged with fresh reactants for a subsequent run. This process was repeated four times, giving the target compound in yields of 94, 93, 89, and 84%, respectively. These results show that the DES can be reused in up to five consecutive runs without a significant detrimental effect on its catalytic activity.

To further expand our method toward the synthesis of biologically active compounds, we turned our attention to the synthesis of the drug trifenagrel under our optimized reaction conditions (Scheme 3). Trifenagrel is a potent arachidonate cyclooxygenase inhibitor that reduces platelet aggregation in several animal species, including humans.[40] We began our synthesis by alkylating the phenolic hydroxy group of salicylaldehyde with 1,2-dibromoethane, and then aminating the terminal bromo group with dimethylamine to obtain the desired starting aldehyde; this reacted with benzil and ammonium acetate to give the required drug in 92% yield. These results clearly show that our synthetic method is comparable to or more effective than other reported methods for the synthesis of trifenagrel[28,41] and other imidazoles. Moreover, its operationally simple procedures, combined with its use of a reusable DES as a solvent and catalyst, together with its high yields, short reaction times, and simple and convenient separation and purification processes, make this method economically efficient and environmentally benign.

In summary, we have developed an efficient and mild procedure for the synthesis of 2,4,5-triaryl-1*H*-imidazoles and 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles in the presence of the urea–$ZnCl_2$ DES as an inexpensive, efficient, ecofriendly, and reusable reaction medium. All compounds were obtained in good to excellent yields in short reaction times under mild reaction conditions. In addition, the DES could be easily recycled and reused in at least five consecutive runs without significant loss of its catalytic activity. Further, this methodology was applied in a rapid and high-yielding efficient synthesis of the drug trifenagrel.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610679.

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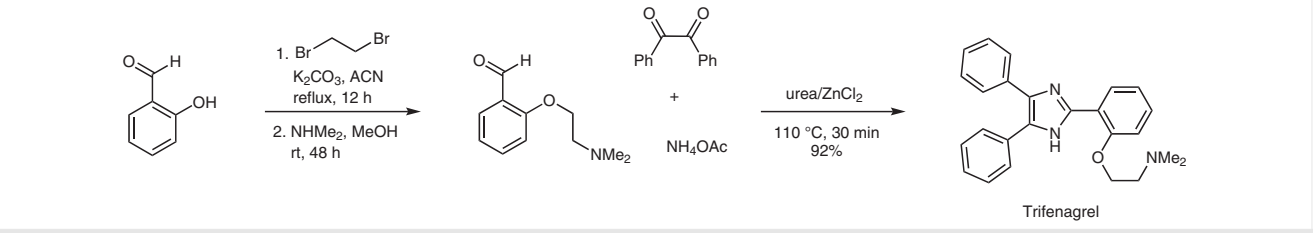


**Scheme 3** Synthesis of trifenagrel in the urea–$ZnCl_2$ DES

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(38) **Imidazoles 3a–y; General Procedure**
Urea–$ZnCl_2$ DES (3.5:1; 0.8 g) was heated to 70 °C to form a clear melt. To this melt was added a mixture of the appropriate dicarbonyl compound (1 mmol), aryl aldehyde (1 mmol), and $NH_4OAc$ (2 mmol), and the mixture was stirred at 110 °C for 30 min. When the reaction was complete (TLC), the reaction was quenched by adding $H_2O$ to the hot mixture, which was then cooled to r.t. The crude solid was collected by filtration then washed with $H_2O$ and EtOH (3 × 2 mL) to afford the pure product.
**2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (3c)**
Yellow solid; yield: 327 mg (96%); mp 235–237 °C (Lit.[42] 237–239 °C). IR (KBr): 3250, 1681, 856 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.9 Hz, 2 H, ArH), 8.10 (d, *J* = 8.7 Hz, 2 H, ArH), 7.58–7.52 (m, 4 H, ArH), 7.40–7.32 (m, 6 H, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 147.4, 143.4, 135.5, 134.9, 129.9, 129.0, 128.7, 127.8, 125.5, 124.3. MS: *m/z* = 341 [$M^+$].
***N*,*N*-Dimethyl-4-(1*H*-phenanthro[9,10-*d*]imidazol-2-yl)aniline (3w)**
Green solid; yield: 313 mg (93%); mp 258–260 °C (Lit.[43] 257 °C). IR (KBr): 3381, 1689, 821 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO): δ = 8.91 (d, *J* = 8.1 Hz, 3 H, ArH), 8.66 (d, *J* = 8.1 Hz, 2 H, ArH), 8.21 (d, *J* = 9.0 Hz, 2 H, ArH), 7.82–7.79 (m, 3 H, ArH), 6.95 (d, *J* = 9.2 Hz, 2 H), 3.06 (s, 6 H, $NMe_2$). $^{13}C$ NMR (100 MHz, DMSO): δ = 154.8, 149.6, 149.0, 146.4, 142.1, 139.5, 133.5, 130.9, 129.6, 128.9, 128.3, 128.0, 127.2, 126.6, 124.8, 124.5, 123.6, 123.0, 122.5, 112.2, 109.2, 108.7, 40.5. MS: *m/z* = 337 [$M^+$].
**{2-[2-(4,5-Diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]-ethyl}dimethylamine (Trifenagrel)**
Light-yellow solid; yield: 352 mg (92%); mp 133–135 °C. FTIR (KBr): 3429, 2922, 1734, 1219, 1039 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO): δ = 8.20 (dd, *J* = 7.8, 1.7 Hz, 1 H, ArH), 7.74 (s, 1 H, ArH), 7.49 (d, *J* = 7.3 Hz, 4 H, ArH), 7.37 (t, *J* = 8.9 Hz, 3 H, ArH), 7.24 (d, *J* = 8.2 Hz, 1 H, ArH), 7.12 (t, *J* = 7.5 Hz, 1 H, ArH), 7.06 (dd, *J* = 9.0, 3.4 Hz, 3 H, ArH), 4.28 (t, *J* = 5.2 Hz, 2 H, $–OCH_2$), 2.64 (t, *J* = 4.8 Hz, 2 H, $–CH_2–N–$), 1.90 (s, 6 H, $NMe_2$). $^{13}C$ NMR (100 MHz, DMSO): δ = 161.2, 155.4, 143.4, 138.6, 130.0, 128.9, 128.4, 127.8, 127.4, 122.2, 120.0, 115.0, 65.9, 57.8, 44.4. MS: *m/z* = 383 [$M^+$].
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