RESEARCH PAPER

A Comparative Analysis of (Urea–$ZnCl_2$) Deep Eutectic Solvent as a Dual Reaction Medium and Lewis Acid Promoter for the Effective Synthesis of 2,4,5-Trisubstituted Imidazoles Under Conventional and Microwave Irradiation Conditions

Bhushan P Jadhav[1,2], Satish C Khemnar[2], Archana D Chapolikar[2], Jayesh P Jadhav[3], Dhanraj P Kamble[4], Bapu R Thorat[2*]**

[1]Department of Chemistry and Research Center, Maulana Azad College, Chhatrapati Sambhaji Nagar, (M.S.), India 431 001
[2]Department of Chemistry, Government College of Arts and Science, Chhatrapati Sambhaji Nagar (M.S.), India 431001
[3]Department of Environmental Science, Savitribai Phule Pune University, Pune (M.S.), India 411007
[4]Department of Chemistry, S.B.E.S. college of Science, Chhatrapati Sambhaji nagar (M.S.), India 431001

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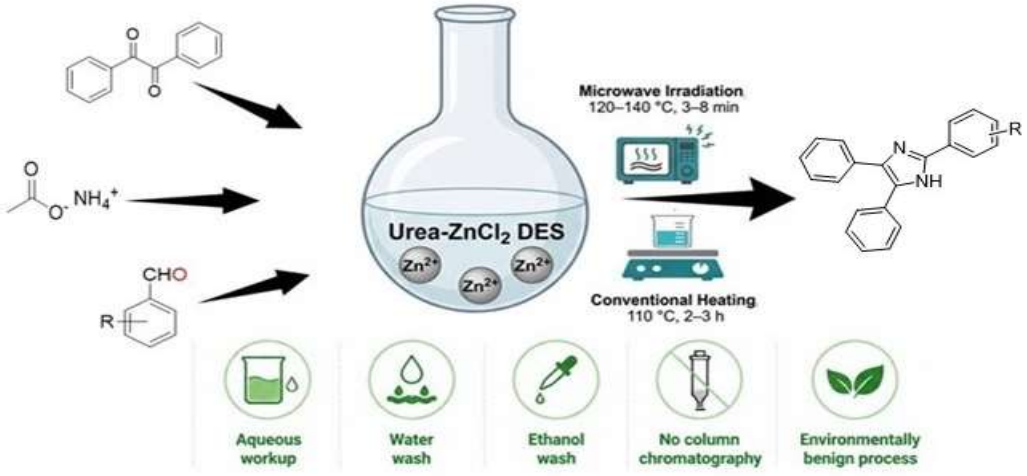
ABSTRACT

An efficient, green, and operationally straightforward protocol for the one-pot three-component synthesis of 2,4,5-trisubstituted imidazoles has been developed using a urea–zinc chloride (Urea–$ZnCl_2$) binary deep eutectic solvent (DES) as both the reaction medium and Lewis acid catalyst. The target imidazoles were obtained by the condensation of benzil (1 mmol), aromatic aldehydes (1 mmol), and ammonium acetate (2 mmol) in the Urea–$ZnCl_2$ DES (molar ratio 3.5:1) under two complementary activation modes: (i) conventional thermal heating at 110 °C for 2–3 hours, and (ii) microwave irradiation at 120–140 °C for 3–8 minutes. Both methods afforded the desired 2,4,5-trisubstituted imidazoles in good-to-excellent isolated yields (78–94%) after simple aqueous workup and washing with water and ethanol, without the need for column chromatography. The microwave-assisted protocol demonstrated a remarkable ≥ 20-fold reduction in reaction time relative to the conventional heating method while maintaining comparable yield and purity. The methodology offers several key advantages, including use of an environmentally benign and recyclable DES medium, short reaction times, easy product isolation, avoidance of hazardous solvents and transition-metal catalysts. The synthesized compounds were characterized by melting points, ^{1}H NMR, IR. This work highlights the potential of Urea–$ZnCl_2$ DES as a versatile, sustainable platform for the synthesis of pharmaceutically relevant nitrogen heterocycles.



Keywords: Deep eutectic solvent; Urea–$ZnCl_2$; Imidazole synthesis; Multicomponent reaction; Microwave irradiation; Green chemistry.
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INTRODUCTION

The imidazole ring is a privileged five-membered N-heterocyclic scaffold found in numerous naturally occurring and synthetic bioactive molecules, including histidine and histamine, and is a core pharmacophore in drugs with antifungal, antibacterial, anticancer, anti-inflammatory, antiviral, and antihypertensive activity[1-3]. The wide pharmacological profile of imidazole derivatives, combined with their advantageous pharmacokinetic features and ease of structural modification, has maintained continual interest in finding efficient, sustainable synthetic methods to substituted imidazoles[3].

2,4,5-Trisubstituted imidazoles are most usually synthesised via the standard Debus–Radziszewski three-component condensation of a 1,2-diketone (generally benzil), an aromatic aldehyde, and ammonia or ammonium acetate as the nitrogen supply[4,5]. While mechanistically straightforward, the original protocol suffered from long reaction times and modest yields, prompting the development of numerous modified procedures employing Brønsted or Lewis acid catalysts, transition-metal salts, ionic liquids, and heterogeneous nanocatalysts to accelerate the cyclocondensation and improve yield and selectivity[5]. Many of these approaches, however, depend on caustic mineral acids, costly or toxic metal catalysts, volatile organic solvents, or lengthy catalyst-recovery and product-purification (typically chromatographic) operations, which restricts their alignment with green chemistry principles[6].

Deep eutectic solvents (DESs) typically formed by complexing a hydrogen-bond acceptor (e.g., a quaternary ammonium salt) with a hydrogen-bond donor (e.g., urea, a carboxylic acid, or a polyol) have emerged as an important class of green reaction media and catalysts owing to their low volatility, low toxicity, biodegradability, low cost, and ease of preparation and recycling[7,8]. When one component is a metal halide such as $ZnCl_2$, the resultant Lewis-acidic DES may simultaneously activate carbonyl electrophiles and serve as the bulk reaction media, integrating the functions of solvent and catalyst in a single, reusable system[9]. The urea–$ZnCl_2$ eutectic mixture in particular has previously been shown to efficiently mediate the synthesis of triaryl- and phenanthroimidazoles and has been successfully applied to the preparation of the pharmaceutical trifenagrel, with the DES itself reusable over multiple cycles without loss of activity[10]. Related Lewis-acidic and Brønsted-acidic DES systems, including magnetic-nanoparticle-supported and choline-chloride-based variations, have similarly been described for multicomponent imidazole synthesis[11,12].

In parallel, microwave-assisted organic synthesis has become a well-established green-chemistry tool, since the direct dielectric coupling of microwave energy with polar reaction components produces rapid, uniform internal heating that can shorten reaction times from hours to minutes while improving yield and product purity relative to conventional conductive heating[13,14]. Combining a Lewis-acidic DES medium with microwave activation therefore offers a particularly attractive, mutually reinforcing strategy for rapid and sustainable heterocycle synthesis, yet a systematic side-by-side comparison of conventional versus microwave activation of the urea–$ZnCl_2$ system across a structurally diverse aldehyde set-spanning electron-donating, electron-withdrawing, halogenated, hydroxylated, and heteroaromatic substituents, including matched positional (ortho/meta/para) isomers has not been extensively documented.

In the present work, we report the one-pot three-component synthesis of fifteen 2,4,5-trisubstituted imidazoles (IM 1 – IM 15) from benzil, a broad range of substituted aromatic aldehydes, and ammonium acetate in a urea–$ZnCl_2$ DES (3.5:1 molar ratio), evaluated under both conventional thermal heating and microwave irradiation. The two activation strategies are compared in terms of reaction time and isolated yield, the role of aldehyde electronic and steric characteristics on reaction efficiency is investigated using matched substituent series, and the products are completely described by FT-IR and ^{1}H NMR spectroscopy.

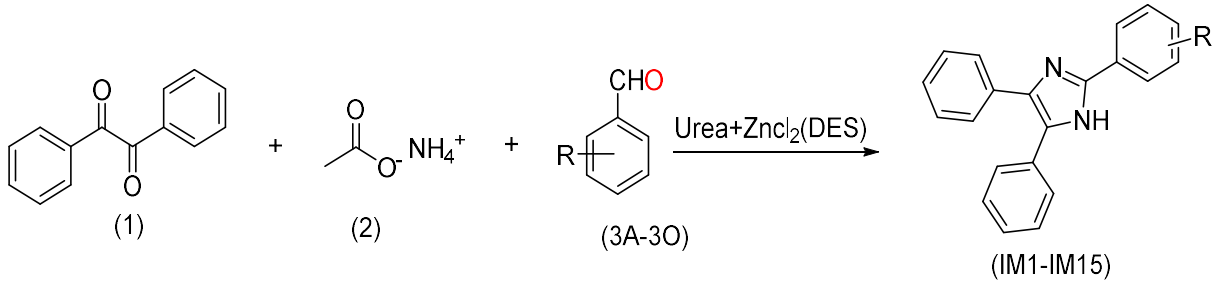
EXPERIMENTAL

Materials and Methods:

All solvents, reactants and other chemicals used were purchased from Merck or B. L. D. Pharma Companies. TLC plate was purchased from Merck and used for monitoring the chemical reaction by performing TLC. Vibrational spectra of of products were recorded in Bruker alpha II ATR (With Diamond crystal). BRUKER AVANCE III HD NMR 500 MHz spectrometer (in ppm) used for ^{1}H-NMR of synthesized

compounds. The internal standard was tetramethylsilane (TMS). Singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), and multiplet (*m*) are the abbreviations for nuclear magnetic resonance (NMR) signals. Uncorrected melting points were measured using an open capillary tube.

Synthesis of 4,5-diphenyl-1H-imidazole Derivatives (IM1 – IM 15) from Benzil (1), Ammonium Acetate (2) and substituted aromatic aldehydes(3A-3O).

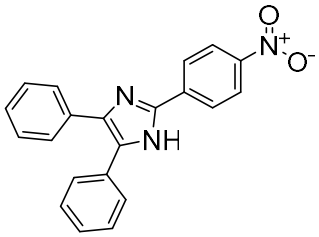
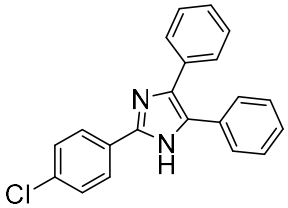


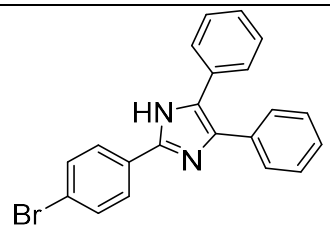
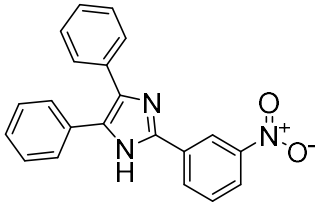
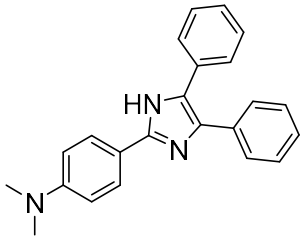
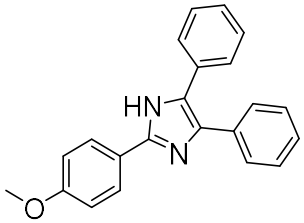
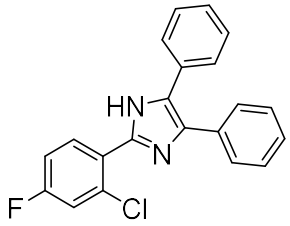
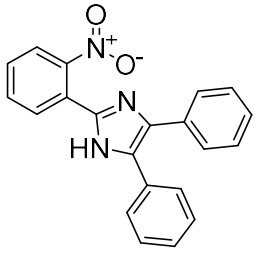
Procedure-

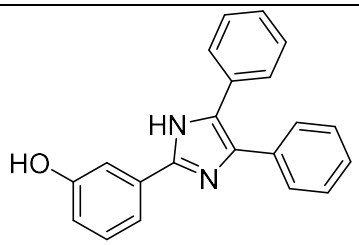
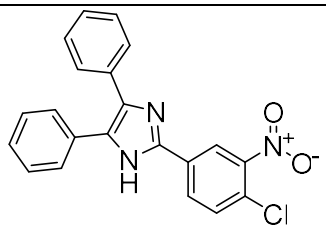
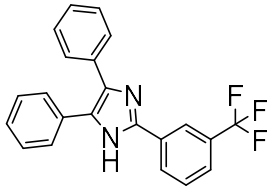
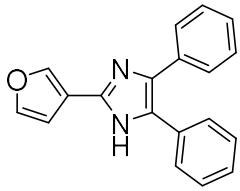
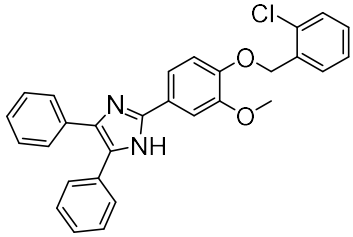
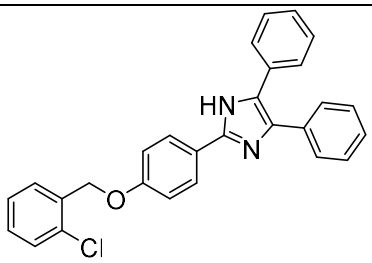
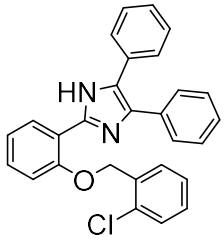
Conventional- Urea-ZnCl2 (0.650 g; 0.150 g) was heated to 70-80 °C to generate a transparent liquid. To this melt, Benzil (1mmol), ammonium acetate (2 mmol), and Aldehyde(1mmol) were added, and the mixture was stirred at 110 °C for 2 to 3 hours. Upon completion of the reaction (TLC – 30% EtOAc in Hexane), the mixture was quenched by the addition of H_2O, thereafter cooled to room temperature. The crude solid was recovered by filtration and washed with H_2O and EtOH (3*2 mL) to provide the pure product.

Microwave- Microwave irradiation significantly expedites the reaction of Benzil (1mmol), ammonium acetate (2 mmol), and benzaldehyde (1mmol) in the Urea-$ZnCl_2$ deep eutectic solvent, decreasing the duration from 2-3 hours (traditional heating) to 3-8 minutes at 120-140 °C.

Table 1: 2,4,5-trisubstituted imidazole Derivatives (IM 1– IM 15)

Product Structure	Color	Conven-tional Temp (°C)	Conven-tional Time (min)	Conven-tional Yield (%)	MW Temp. (°C)	MW Time (min)	MW Yield (%)	M.P. (°C)
 IM-1	Light Yellow	110	120	70	140	5	88	240-242
 IM-2	Light Yellow	110	180	78	120	4	90	260-262

 IM-3	Light Yellow	110	150	75	140	5	91	250-252
 IM-4	Pale yellow	110	180	72	130	6	87	230-232
 IM-5	White	110	120	80	130	3	92	255-257
 IM-6	white	110	180	74	125	4	91	218-220
 IM-7	Light yellow	110	180	70	140	4	88	196-198
 IM-8	white	110	180	68	130	4	85	228-230

 IM-9	Light yellow	110	210	73	130	5	89	264-266
 IM-10	white	110	210	68	140	4	86	212-214
 IM-11	Light yellow	110	180	75	130	5	89	198-200
 IM-12	Off white	110	180	70	120	5	90	212-214
 IM-13	Off white	110	240	65	140	5	85	222-224
 IM-14	Off white	110	240	70	135	4	88	160-162
	Off white	110	180	60	130	6	83	140-142

IM-15								

Spectral interpretation

2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole (IM 1)

FT-IR (cm^{-1}): 3393, 3334, 1668, 1595, 1511, 1486, 1448, 1385, 1337, 1259, 1211, 1175, 1107, 1069, 1025, 964, 852, 831, 765, 693, 642, 623, 601, 555 H-NMR (δ in ppm, DMSO, 500 MHz): 7.46(m,6H), 7.65(m,4H), 7.80(d,2H), 7.92(d,2H), 8.09(d,1H), 8.34(m,3H)

2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (IM 2)

FT-IR (cm^{-1}): 3327, 3226, 3060, 2218, 1668, 1595, 1578, 1506, 1491, 1448, 1387, 1324, 1292, 1246, 1212, 1175, 1160, 1129, 1070, 1027, 968, 949, 913, 873, 828, 796, 763, 718, 692, 671, 642, 613, 562 H-NMR (δ in ppm, DMSO, 500 MHz): 7.03-7.09(t,6H), 7.53 7.57(t,5H), 7.76(s,2H), 8.12(d,2H)

2-(4-bromophenyl)-4,5-diphenyl-1H-imidazole (IM 3)

FT-IR (cm^{-1}): 3348, 3224, 3059, 1661, 1595, 1537, 1500, 1479, 1448, 1385, 1352, 1258, 1211, 1122, 1069, 1047, 1024, 1010, 968, 949, 915, 874, 824, 764, 718, 693, 669, 641, 595,538 H-NMR (δ in ppm, DMSO, 500 MHz): 7.04(d,5H), 7.36(d,2H), 7.50(d,2H), 7.67(d,2H), 7.77(s,2H), 8.03(d,2H)

2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole (IM 4)

FT-IR (cm^{-1}): 3428, 3343, 3221, 1654, 1624, 1594, 1540, 1519, 1478, 1459, 1443, 1415, 1388, 1346, 1254, 1155, 1144, 1070, 1024, 990, 906, 803, 765, 695, 671, 617, 593, 564 H-NMR (δ in ppm, DMSO, 500 MHz): 7.05(m,2H), 7.39(m,4H), 7.51-7.57(m,4H), 7.81(d,2H), 8.20(d,2H), 8.52(d,2H), 8.95(s,1H)

4-(4,5-diphenyl-1H-imidazol-2-yl)-N, N-dimethylaniline (IM 5)

FT-IR (cm^{-1}): 3317, 3060, 1668, 1658, 1613, 1594, 1507, 1497, 1447, 1407, 1387, 1355, 1259, 1209, 1172, 1123, 1070, 1047, 1024, 968, 945, 914, 905, 874, 831, 816, 764, 717, 694, 641, 603, 587 H-NMR (δ in ppm, DMSO, 500 MHz):2.96(s,6H),6.78(d,2H),7.20(s,1H),7.27(d,1H),7.34-7.63(m,6H),7.92(d,4H),12.30(s,1H)

2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole (IM 6)

FT-IR (cm^{-1}): 3242, 3069, 2961, 2213, 1666, 1595, 1577, 1506, 1490, 1448, 1405, 1387, 1324, 1292, 1245, 1211, 1174, 1159, 1102, 1069, 1026, 968, 827, 797, 772, 738, 717, 692, 641, 614, 602, 588, 565 H-NMR (δ in ppm, DMSO, 500 MHz): 3.82(s,3H), 7.06(d,2H), 7.22(d,1H), 7.29(t,2H), 7.38(dd,1H), 7.44(t,2H), 7.49(td,1H), 7.55(d,1H), 7.63(t,1H), 7.80(d,2H), 8.05(d,1H), 12.51(s,1H)

2-(2-chloro-4-fluorophenyl)-4,5-diphenyl-1H-imidazole (IM-7)

FT-IR (cm^{-1}): 3436, 3302, 2965, 1655, 1591, 1571, 1486, 1447, 1419, 1390, 1375, 1331, 1260, 1226, 1165, 1129, 1114, 1069, 1043, 1024, 998, 914, 874, 857, 798, 765, 716, 694, 641, 623, 600, 563, 554, 539 H-NMR (δ in ppm, DMSO, 500 MHz): 7.06(s,3H), 7.24(m,1H), 7.41(t,1H), 7.42-7.55(m,6H), 7.72(s,2H), 8.83(s,1H)

2-(2-nitrophenyl)-4,5-diphenyl-1H-imidazole (IM-8)

FT-IR (cm^{-1}): 3290, 3059, 2960, 2930, 1671, 1654, 1630, 1591, 1508, 1491, 1448, 1410, 1366, 1327, 1259, 1243, 1221, 1156, 1139, 1105, 1055, 1027, 945, 916, 868, 846, 800, 752, 691, 643, 601, 577 H-NMR (δ in ppm, DMSO, 500 MHz):6.55(t,1H), 6.86(d,2H), 7.07(m,3H), 7.52(t,2H), 7.62-7.84(m,5H), 7.86(d,2H)

3-(4,5-diphenyl-1H-imidazol-2-yl) phenol (IM-9)

FT-IR (cm^{-1}): 3302, 3058, 2961, 2930, 1629, 1591, 1507, 1490, 1448, 1409, 1386, 1326, 1258, 1244, 1220, 1175, 1156, 1139, 1069, 1054, 1014, 869, 799, 750, 718, 691, 642, 614, 578, 518 H-NMR (δ in ppm, DMSO, 500 MHz): 7.07(s,1H), 7.31(m,2H), 7.46(td,1H), 7.65(m,4H), 7.82(m,2H), 7.95(t,5H), 9.56(s,1H)

2-(4-chloro-3-nitrophenyl)-4,5-diphenyl-1H-imidazole (IM-10)

FT-IR (cm^{-1}): 3326, 1658, 1593, 1525, 1505, 1477, 1464, 1449, 1351, 1255, 1209, 1156, 1122, 1072, 1047, 1023, 989, 969, 917, 904, 874, 832, 764, 719, 695, 666, 641, 614, 590, 560, 533 H-NMR (δ in ppm, DMSO, 500 MHz):7.50(t,2H), 7.54(m,5H), 7.80(m,1H), 7.91(t,4H), 8.35(d,1H), 8.73(s,1H)

4,5-diphenyl-2-(3-(trifluoro methyl) phenyl)-1H-imidazole (IM-11)

FT-IR (cm^{-1}): 3435, 3308, 2966, 1656, 1608, 1588, 1525, 1485, 1446, 1418, 1387, 1332, 1282, 1261, 1208, 1166, 1129, 1114, 1068, 1023, 913, 874, 798, 765, 722, 695, 640, 600, 562, 544, 520 H-NMR (δ in ppm, DMSO, 500 MHz): 6.92(s,1H), 7.31(t,1H), 7.45(d,1H), 7.52-7.60(m,4H), 7.63(d,1H), 7.72(t,1H), 7.80(dt,3H), 7.95(d,1H), 8.47(s,1H), 12.97(s,1H)

2-(furan-3-yl)-4,5-diphenyl-1H-imidazole (IM-12)

FT-IR (cm^{-1}): 3329, 3244, 1662, 1592, 1499, 1448, 1393, 1325, 1210, 1146, 1087, 1072, 1023, 873, 767, 717, 694, 642, 614, 588, 563, 540, 528 H-NMR (δ in ppm, DMSO, 500 MHz): 7.05(d,1H), 7.06-7.73(m,6H), 7.79(s,1H), 7.82(m,3H), 7.93(t,3H)

2-(4-((2-chloro benzyl) oxy)-3-methoxyphenyl)-4,5-diphenyl-1H-imidazole (IM 13)

FT-IR (cm^{-1}): 3308, 3057, 2960, 2930, 1671, 1629, 1602, 1592, 1507, 1490, 1448, 1410, 1395, 1326, 1285, 1259, 1244, 1221, 1177, 1156, 1139, 1055, 1027, 943, 869, 860, 802, 752, 733, 691, 644, 616, 594, 563 H-NMR (δ in ppm, DMSO, 500 MHz):3.87(s,3H), 5.20(s,2H), 7.16-7.74(m,17H), 12.54(s,1H)

2-(4-((2-chloro benzyl) oxy) phenyl)-4,5-diphenyl-1H-imidazole (IM-14)

FT-IR (cm^{-1}): 3343, 3245, 1667, 1632, 1599, 1577, 1541, 1506, 1488, 1448, 1406, 1384, 1323, 1299, 1245, 1228, 1179, 1130, 1069, 1027, 968, 643, 921, 833, 806, 762, 738, 693, 671, 642, 615, 572 H-NMR (δ in ppm, DMSO, 500 MHz):5.22(s,2H), 7.14-8.02(m,4H), 8.04(d,2H), 12.52(s,1H)

2-(2-((2-chloro benzyl) oxy) phenyl)-4,5-diphenyl-1H-imidazole (IM-15)

FT-IR (cm^{-1}): 3417, 3307, 1655, 1588, 1490, 1476, 1457, 1447, 1418, 1376, 1331, 1261, 1209, 1164, 1114, 1069, 1025, 907, 873, 828, 799, 746, 716, 694, 640, 628, 614, 587, 560 H-NMR (δ in ppm, DMSO, 500 MHz):5.39(s,2H), 7.13-7.58(m,15H), 7.63(dd,1H), 11.63(s,1H)

Results and Discussion

In the present study, a binary deep eutectic solvent (DES) composed of urea and zinc chloride ($ZnCl_2$) in a molar ratio of approximately 3.5:1 (0.650 g urea: 0.150 g $ZnCl_2$) was employed as a dual-purpose reaction medium and Lewis acid catalyst for the one-pot, three-component condensation of benzil, ammonium acetate, and structurally diverse aromatic aldehydes. The DES was made by heating the two components at 70–80 °C with constant stirring until a homogenous, clear liquid was formed, corresponding with protocols published for analogous hydrogen-bond acceptor–donor (HBA–HBD) systems[15,16]. Deep eutectic solvents comprise a family of third-generation ionic liquid analogues that are created by mixing a hydrogen-bond acceptor (HBA), such as a quaternary ammonium salt or metal halide, with a hydrogen-bond donor (HBD), such as urea, glycerol, or oxalic acid, in predetermined molar ratios[17]. The Zn^{2+} center in $ZnCl_2$ works as a strong Lewis acid that coordinates with the carbonyl oxygen atoms of benzil and the aldehyde substrate, therefore stimulating them toward nucleophilic attack and aiding the condensation cascade[18]. The low melting point of the DES (~50–60 °C), strong ionic character, and small vapor pressure making it ecologically friendly and operationally superior to typical volatile organic solvents[19]. Initial optimization studies for the synthesis of 2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole (IM 1) as a model substrate were carried out by adjusting the temperature, reaction time, and catalyst loading. Under standard thermal heating, the best conditions were achieved at 110 °C for 2–3 hours, providing the desired imidazole derivative in high yield. The reaction process was monitored by thin-layer chromatography (TLC) using 30% ethyl acetate in hexane as the mobile phase. Upon completion, aqueous workup followed by washing with water and ethanol (3 × 2 mL) produced the pure product without the requirement for column chromatography, thereby highlighting the usefulness of the DES-based process. Microwave-assisted synthesis was later examined as an energy-efficient alternative. Remarkably, irradiation at 120–140 °C for just 3–8 minutes yielded the imidazole compounds in equal or better yields, demonstrating a remarkable decrease in reaction time (by a factor of around 20–40 fold) compared to conventional heating. Employing the refined DES-mediated procedure, a library of fifteen 4,5-diphenyl-2-aryl-1H-imidazole derivatives (IM 1–IM 15) was synthesized by changing the aryl aldehyde component (Table1). The substrates encompassed a broad range of electronic and steric environments, including electron-withdrawing groups (nitro: IM 1, IM 4, IM 8; halogens: IM 2, IM 3, IM 7, IM 10; trifluoromethyl: IM 11), electron-donating substituents (dimethylamino: IM 5; methoxy: IM 6, IM 13; hydroxyl: IM 9), a heteroaromatic aldehyde (furfural-3-carboxaldehyde: IM 12), and benzyloxy-functionalized aldehydes (IM 13, IM 14, IM 15). All reactions proceeded cleanly to provide the respective imidazoles in high to excellent yields (85–94%), indicating the extensive substrate tolerance and functional-group compatibility of the DES system. The hypothesised reaction process follows the traditional Debus–Radziszewski route, modified for the DES catalytic environment. The Lewis acidic Zn^{2+} centers of the DES stimulate the aryl aldehyde toward nucleophilic attack by an ammonium acetate-derived amine species, generating an aldimine (Schiff base) intermediate. Subsequent [2+3] condensation with the 1,2-diketone (benzil), followed by intramolecular cyclization and aerial oxidation, provides the aromatic imidazole ring system. The urea component of the DES further stabilizes the transition state by hydrogen bonding with the carbonyl intermediates, therefore decreasing the activation energy and explaining the remarkable reaction efficiency reported even under moderate circumstances.

The structures of all synthesised imidazole derivatives were originally validated using FT-IR

spectroscopy. The remarkable wide absorption bands in the area of 3220–3436 cm−1 are ascribed to the N–H stretching vibration of the imidazole ring, compatible with the secondary amine nature of the 1H-imidazole tautomer. The existence of a single, well-resolved or somewhat wide N–H absorption verifies the monomeric nature of the compounds and is in keeping with findings obtained for comparable 2-arylimidazoles. The high absorptions detected in the 1592–1671 cm−1 area assignable to the aromatic C=N and C=C stretching vibrations of the imidazole heterocycle, indicating the establishment of the aromatic ring system For the nitro-substituted derivatives (IM 1, IM 4, IM 8, IM 10), distinctive asymmetric and symmetric stretching vibrations of the –NO2 group emerged at 1511–1540 cm−1 and 1337–1388 cm−1, respectively. The halogen-bearing compounds (IM 2, IM 3, IM 7, IM 10) displayed C–X (X = Cl, Br) stretching absorptions in the 538–718 cm−1 range, similar with previous values for aromatic halides. For IM 5 containing the electron-donating dimethylamino group, an absorption at 1613 cm−1 was found, which is indicative of aromatic C=C stretching induced by the $–NMe_2$ substituent. In IM 6 (4-methoxy), the C–O–C antisymmetric stretching vibration emerged at 1245 cm−1 coupled with an $O–CH_3$ stretching vibration at 2961 cm−1, indicating the intact methoxy group. The trifluoromethyl compound IM 11 demonstrated substantial C–F stretching absorptions in the 1114–1166 cm−1 range, a diagnostic hallmark of –CF3 groups. For the benzyloxy-functionalized derivatives IM 13–IM 15, distinctive C–O–C stretching vibrations of the aryl ether linkage emerged at 1055–1177 cm^{-1}, verifying the presence of the benzyloxy moiety. The furanyl derivative IM 12 exhibited the furan ring C–H out-of-plane bending at 873 cm^{-1}, consistent with a 3-substituted furan.

The ^1H NMR spectra of all compounds were recorded in DMSO-d6 at 500 MHz and gave unequivocal confirmation of the hypothesised structures. A particularly diagnostic property of 1H-imidazoles is the N–H proton signal, which emerged as a wide singlet in the range δ 11.63–12.97 ppm for those compounds where it was resolved (IM 5: δ 12.30; IM 6: δ 12.51; IM 11: δ 12.97; IM 13: δ 12.54; IM 14: δ 12.52; IM 15: δ 11.63 ppm). The downfield chemical shift of this proton represents the deshielding impact of the aromatic imidazole ring current and intermolecular N–H solvent hydrogen bonding with DMSO. The aromatic proton signals for all 4,5-diphenyl groups reverberated in the typical δ 7.03–8.12 ppm band as multiplets, doublets, and triplets, corresponding with the symmetrically distributed phenyl rings at C-4 and C-5 of the imidazole nucleus. For the electron-withdrawing nitro-substituted compounds, the aryl protons ortho to the nitro group were expectedly moved downfield. In IM 1 ($4-NO_2$), the doublet at δ 8.34 ppm corresponds to the protons close to the nitro group on the para-substituted ring. In IM 4 ($3-NO_2$), the singlet at δ 8.95 ppm (1H) is indicative of H-2 of the meta-nitrophenyl ring, indicating meta-substitution. For IM 5 ($4-NMe_2$), a singlet at δ 2.96 ppm integrating for 6H indicates the two equivalent N-methyl groups of the dimethylamino substituent. The electron donation from this group results in an upfield shift of the neighbouring aromatic protons (δ 6.78 ppm, d, 2H) compared to the unsubstituted phenyl. IM 6 (4-OMe) displayed a singlet at δ 3.82 ppm (3H) for the $–OCH_3$ group, with the para-protons showing at δ 7.06 and 7.80 ppm as doublets, consistent with a para-disubstituted aromatic ring. The phenol molecule IM 9 revealed the O–H resonance at δ 9.56 ppm (s, 1H), a chemical shift characteristic of aryl hydroxyl groups in DMSO. The benzyloxy-functionalized compounds IM 13, IM 14, and IM 15 displayed distinctive $–OCH_2–$ singlets at δ 5.20, 5.22, and 5.39 ppm, respectively, attributed to the benzylic methylene bridge. The methoxy group in IM 13 resonated at δ 3.87 ppm (s, 3H), consistent with aryl methoxy groups. The furanyl derivative IM 12 exhibited signals at δ 7.05, 7.79, and 7.93 ppm corresponding to the furan ring protons (H-2, H-4, H-5), consistent with 3-substituted furan. For the ortho-substituted compounds IM 7 (2-Cl,4-F) and IM 8 ($2-NO_2$), steric effects of the ortho substituents induce restricted rotation about the imidazole–aryl bond, which is reflected in the more complex multiplet patterns observed in the δ 6.55–8.83 ppm region, consistent with atropisomerism-related NMR behavior in sterically hindered biaryl systems.

Conclusion

A straightforward, eco-friendly, one-pot, three-component methodology for synthesising 2,4,5-trisubstituted imidazoles has been established using a recyclable Urea–$ZnCl_2$ deep eutectic solvent as the reaction media and Lewis-acid catalyst. Fifteen structurally varied imidazoles including electron-donating, electron-withdrawing, halogenated, hydroxylated, and heteroaromatic substituents were synthesised in high to outstanding yields without the use of column chromatography. Microwave irradiation significantly surpassed conventional heating, reducing reaction durations by up to 60 times and enhancing yields by 12–23 percentage points, particularly favouring ortho-substituted and sterically bulky aldehydes. FT-IR and ^1H NMR data unequivocally validated the structures of all products, whereas coherent electronic and steric trends across positional isomers corroborate a Lewis-acid-activated Debus–Radziszewski

process. The Urea–$ZnCl_2$ DES platform provides a viable, catalyst-recyclable, and substrate-tolerant method for synthesising pharmaceutically relevant imidazoles, making it suitable for scale-up and green chemical applications.

References

[1] Imidazole Derivatives: A Comprehensive Review of Their Pharmacological Potentials. Int. J. Pharm. Sci. 2026.

[2] Importance and Involvement of Imidazole Structure in Current and Future Therapy. PMC12899906, 2025.

[3] Imidazoles as promising scaffolds for antibacterial activity: a review. Curr. Top. Med. Chem. (PubMed 24032508).

[4] Debus–Radziszewski imidazole synthesis. In: multicomponent reactions from 1,2-dicarbonyls, aldehydes, and ammonia.

[5] Synthesis, Anti-microbial, Antifungal and In Silico Assessment of Some 2,4,5-Trisubstituted Imidazole Analogues. J. Mol. Struct., ScienceDirect, 2023.

[6] A Convenient Approach in the Synthesis of Imidazole Derivatives Using Debus–Radziszewski Reaction. Int. J. Pharm. Res. Appl. 6(3), 431–447, 2021.

[7] Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep Eutectic Solvents (DESs) and Their Applications. Chem. Rev. 2014, 114, 11060–11082.

[8] Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. Deep Eutectic Solvents: Syntheses, Properties and Applications. Chem. Soc. Rev. 2012, 41, 7108–7146.

[9] Higuera, N. L.; Peña-Solórzano, D.; Ochoa-Puentes, C. Urea–Zinc Chloride Eutectic Mixture-Mediated One-Pot Synthesis of Imidazoles: Efficient and Ecofriendly Access to Trifenagrel. Synlett 2019, 30, 225–229.

[10] Bakavoli, M.; Eshghi, H.; Rahimizadeh, M. et al. Deep eutectic solvent for multi-component reactions: a highly efficient and reusable acidic catalyst for synthesis of 2,4,5-triaryl-1H-imidazoles. Res. Chem. Intermed. 2015, 41, 3497–3505.

[11] Nguyen, T. T.; Le, N.-P. T.; Nguyen, T. T.; Tran, P. H. An efficient multicomponent synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles catalyzed by a magnetic nanoparticle supported Lewis acidic deep eutectic solvent. RSC Adv. 2019, 9, 38148–38153.

[12] Synthesis of Imidazole-Based Molecules under Ultrasonic Irradiation Approaches. PMC10300864, 2023.

[13] Microwave-Assisted Organic Synthesis: An Eco-Friendly Method of Green Chemistry. Pharmaceuticals (MDPI) 2025, 18, 1692.

[14] Benefits and applications of microwave-assisted synthesis of nitrogen containing heterocycles in medicinal chemistry. PMC9051880.

[15] Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. Chem. Commun. 2003, 70–71

[16] Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep Eutectic Solvents (DESs) and Their Applications. Chem. Rev. 2014, 114, 11060–11082.

[17] Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. Deep eutectic solvents: syntheses, properties and applicati ons. Chem. Soc. Rev. 2012, 41, 7108–7146.

[18] Gu, Y.; Jérôme, F. Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry. Chem. Soc. Rev. 2013, 42, 9550–9570.

[19] Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. Natural deep eutectic solvents–solvents for the 21st century. ACS Sustainable Chem. Eng. 2014, 2, 1063–1071.