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RESEARCH ARTICLE

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CuI-catalyzed, one-pot synthesis of 3-aminobenzofurans in deep eutectic solvents

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An environmentally friendly method is presented here for the synthesis of various benzofuran derivatives using CuI catalyst. In this line, a one-pot, 3-component reaction of alkynes, different aldehydes, and amines is employed in choline chloride-ethylene glycol deep eutectic solvent as an available, cheap, and green media. The employed method includes easy workup and good yields. In this work, 12 different benzofuran derivatives have been prepared in 7 h at 80°C.

KEYWORDS
benzofuran, catalyst, choline chloride-ethylene glycol deep eutectic, cyclization, green

1 | INTRODUCTION

Benzofuran skeletons[1] are important heterocyclic compounds because of their biological applications such as antioxidative,[2] anticancer,[3] anti-inflammatory,[4] mutagenic,[5] adenosine antagonist XH-14 inhibition,[6] and 5-lipoxygenase inhibition.[7] These compounds have been found as the important building blocks in synthetic and natural bioactive products.[8] Therefore, several synthetic methods have been developed for these compounds to provide different ways for the global demands. Some of these methods are decarboxylation,[9] cyclization of some ketone derivatives,[10] reaction of 2-chlorophenols with terminal alkynes,[11] the sigmatropic reactions of aromatics,[12] coupling of N-tosylhydrazones and terminal alkynes,[13] and the other methods.[14] In the most of developed methodologies, some issues such as long reaction time, nongenerality, multisteps production (including separation of intermediates), hard condition, and using hazardous reagents have been limited the application of these strategies. Therefore, it is important to present more appropriate methodologies to prepare various benzofurans using available chemicals and easier procedure.

The transition metal-catalyzed reaction of secondary amines, different aldehydes, and terminal alkynes (known as A^3-coupling) is considered in the present work, which normally produces propargyl amines (as we reported recently). Using mild and environmentally friendly conditions, avoiding toxic reagents, no moisture sensitivity, and high atom economy are the advantages of the one-pot A^3-coupling.[15–18] However, in some reports, this reaction was used for the synthesis of different benzofurans.[19] It is predictable that by using ortho-hydroxybenzaldehyde derivatives (instead of simple benzaldehyde without ortho-hydroxy group) in this reaction, after the preparation of aromatic propargyl amines, an intermolecular nucleophilic attack of the ortho-hydroxy group to the Cu-activated triple bond could lead to the ring closure and produce the fused rings. Several researches reported using both homogeneous and heterogeneous catalysts in this method.[20] Transition metal catalytic systems like copper[21,22] and silver[23] salts have been employed in this reaction for both C–H activation (for nucleophilic attack to the iminium salt) and ring closure steps. According to the recent publications, copper salts are better than other choices, and they are available and cheap in addition to their low toxicity and high reactivity.[24] Because of some disadvantages of this reaction that have been reported in many studies, such as using toxic solvents and employing expensive catalysts, it is

necessary to find a more appropriate and environmentally friendly synthetic method to prepare benzofurans using A^3-coupling reaction. In order to decrease environmental pollutions, a green and biodegradable media must be employed to obey principles of the green chemistry.[25] Therefore, volatile and toxic solvents were replaced with ionic liquids (ILs) to decrease the environmental hazards of these techniques. Despite the desirable specifications of common ILs including low flammability, small vapor pressure, thermal stability, and recyclability, using these media was limited by some issues such as high-cost and complex synthetic procedure.[26,27] Instead, their new generation, named as deep eutectic solvents (DESs),[28] solved the most of these problems, in addition to covering the common benefits of ILs.[29] Following the previous works of this group to develop the synthetic methodologies by using DESs[30–33] and a recent report on preparation of benzofuran derivatives,[34] the preparation of benzofuran derivatives has been considered under green media condition in this study.

2 | EXPERIMENTAL

All compounds were purchased from Merck and Sigma-Aldrich companies and they were purified if necessary. The starting materials were purified when necessary. Infared (IR) spectroscopy analyses have been performed using KBr disks and employing JASCO FT-IR spectrophotometers in 400–4000 cm^{-1} region. ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (100 MHz, $CDCl_3$) spectra have been obtained using Bruker Ultra shield instrument.

2.1 | Preparation of various DESs

All DESs (simply or mixed with metal salts) have been prepared by simple mixing of ChCl, urea, or ethylene glycol and other components (such as $CuCl_2.2H_2O$, $FeCl_3.6H_2O$, $SnCl_2.2H_2O$, $ZnCl_2.2H_2O$, $NiCl_2.6H_2O$), as the previous reports.[35–38] For each DES, an appropriate temperature and sufficient mixing time were employed, based on the used ingredients. The prepared DESs were used freshly or up to 1 month after their preparations.

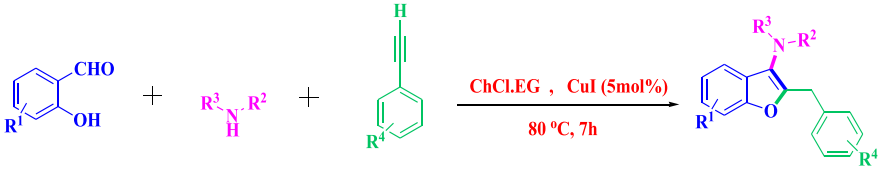
2.2 | The synthesis of benzofurans

Choline chloride (0.14 g, 1 mmol), ethylene glycol (0.12 g, 2 mmol), and CuI (0.01 g, 0.05 mmol) were poured into a flask, on a magnetic heater–stirrer, and heated to 80°C and remained at this temperature for 1 h. Next, 1 mmol of salicylaldehyde, 1.2 mmol of alkyne, and 1.5 mmol of amine were added. The mixture was remained for 7 h at that temperature (Scheme 1). The reaction has been monitored using thin layer chromatography (TLC) (4:1 mixture of *n*-hexane:EtOAc as eluent), then lets it to reach to r.t., and 10-mL EtOAc and 10-mL H_2O were added. After this, the organic layer, consisted of the product, was separated from the other phases and dried using $MgSO_4$. After evaporating the solvent, the product was purified using 20 × 20 cm^2 silica gel TLC. The structures of the reported products were confirmed by comparing their spectral data and physical properties with the recorded data. For new derivatives, in addition to the full spectral analysis, elemental analysis was employed to confirm their structures. All spectral data are listed in the next section. Moreover, all the original spectra are reported in Supporting Information.

2.3 | Physical and spectral data

2.3.1 | 4a: 4-(2-Benzyl-5-bromobenzofuran-3-yl)morpholine

Yellow oil; IR (KBr, cm^{-1}): 3063, 3026, 2971, 2891, 2853, 2752, 2681, 1949, 1803, 1727, 1601, 1448, 1378, 1267, 1201, 1113, 1033, 888, 805, 708; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.06 (m, 4H, CH_2-N), 3.77 (m, 4H, CH_2-O), 4.08 (s, 2H, CH_2 $_{aliphatic}$), 7.19 (m, 7H, CH $_{aromatic}$), 7.71 (d, J = 1.8 Hz, 1H, CH $_{aromatic}$) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 32.36 (CH_2 $_{aliphatic}$), 52.49 (CH_2-N), 67.63 (CH_2-O), 113.14, 115.24, 122.47, 126.36, 126.66, 128.05, 128.28, 128.53, 128.66, 137.74, 151.73, 152.21 (all for aromatic rings) ppm.



SCHEME 1 General reaction for synthesis of benzofuran derivatives

2.3.2 | 4b: 4-(2-Benzyl-5-chlorobenzofuran-3-yl)morpholine

Yellow oil; IR (KBr, cm^{-1}): 3090, 3022, 2918, 2855, 2824, 2752, 2677, 1949, 1865, 1729, 1603, 1449, 1376, 1258, 1206, 1172, 1109, 1064, 806, 712; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.16 (m, 4H, CH_2-N), 3.87 (m, 4H, CH_2-O), 4.18 (s, 2H, CH_2 aliphatic), 7.19 (dd, J_1 = 8.6 Hz, J_2 = 2.1 Hz, 1H, CH aromatic), 7.30 (m, 6H, CH aromatic), 7.66 (d, J = 2.0 Hz, 1H, CH aromatic) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 32.43 (CH_2 aliphatic), 52.50 (CH_2-N), 67.64 (CH_2-O), 112.64, 119.47, 123.67, 126.65, 127.44, 127.74, 128.44, 128.55, 128.65, 128.83, 130.90, 137.77, 151.89 (all for aromatic rings) ppm.

2.3.3 | 4c: 4-(2-Benzylbenzofuran-3-yl) morpholine

Yellow oil; IR (KBr, cm^{-1}): 3055, 3024, 2961, 2851, 2815, 2749, 2678, 1940, 1709, 1602, 1495, 1450, 1380, 1257, 1210, 1111, 1033, 902, 748; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.20 (m, 4H, CH_2-N), 3.87 (m, 4H, CH_2-O), 4.19 (s, 2H, CH_2 aliphatic), 7.23 (m, 3H, CH aromatic), 7.32 (m, 3H, CH aromatic), 7.40 (d, J = 7.40 Hz, 1H, CH aromatic), 7.69 (d, J = 7.0 Hz, 1H, CH aromatic) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.31 (CH_2 aliphatic), 52.57 (CH_2-N), 67.73 (CH_2-O), 111.71, 119.91, 122.10, 123.48, 126.11, 126.48, 128.56, 128.77, 138.20, 140.75, 150.25, 153.52 (all for aromatic rings) ppm.

2.3.4 | 4d: 4-(5-Bromo-2-(4-(tert-butyl) benzyl)benzofuran-3-yl)morpholine

Yellow oil; IR (KBr, cm^{-1}): 3061, 2959, 2926, 2855, 2755, 1903, 1805, 1735, 1607, 1512, 1449, 1366, 1264, 1208, 1114, 1021, 804, 542; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H, CH_3 aliphatic), 3.18 (m, 4H, CH_2-N), 3.88 (m, 4H, CH_2-O), 4.16 (s, 2H, CH_2 aliphatic), 7.26 (m, 4H, CH aromatic), 7.36 (d, J = 11.0 Hz, 1H, CH aromatic), 7.82 (d, J = 2.1 Hz, 1H, CH aromatic) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.38 (CH_3 aliphatic), 31.85 (CH_2 aliphatic), 34.45 (C aliphatic), 52.54 (CH_2-N), 67.65 (CH_2-O), 113.13, 115.21, 122.44, 125.57, 126.31, 128.12, 128.19, 129.10, 134.63, 149.53, 151.95, 152.23 (all for aromatic rings) ppm. Elemental anal. for $C_{23}H_{26}BrNO_2$ (C, 64.49; H, 6.12; Br, 18.65; N, 3.27; O, 7.47); Found: C, 62.47; H, 4.52; N, 2.77.

2.3.5 | 4e: 4-(2-(4-(Tert-butyl)benzyl)-5-chlorobenzofuran-3-yl)morpholine

Yellow oil; IR (KBr, cm^{-1}): 3086, 2960, 2909, 2852, 2752, 2681, 1906, 1805, 1738, 1608, 1512, 1451, 1370, 1263, 1114, 1041, 915, 806, 738, 538; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H, CH_3 aliphatic), 3.18 (m, 4H, CH_2-N), 3.88 (m, 4H, CH_2-O), 4.16 (s, 2H, CH_2 aliphatic), 7.22 (m, 3H, CH aromatic), 7.35 (m, 3H, CH aromatic), 7.66 (d, J = 2.6 Hz, 1H, CH aromatic) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.29 (CH_3 aliphatic), 31.86 (CH_2 aliphatic), 34.48 (C aliphatic), 52.68 (CH_2-N), 67.65 (CH_2-O), 112.62, 119.43, 123.59, 125.57, 127.47, 127.67, 128.19, 128.35, 134.65, 149.52, 151.85, 152.11 (all for aromatic rings) ppm. Elemental anal. for $C_{23}H_{26}ClNO_2$ (C, 71.96; H, 6.83; Cl, 9.23; N, 3.65; O, 8.33); Found: C, 70.77; H, 5.76; N, 3.19.

2.3.6 | 4f: 4-(2-(4-(Tert-butyl)benzyl) benzofuran-3-yl)morpholine

Yellow oil; IR (KBr, cm^{-1}): 3054, 2959, 2901, 2856, 2749, 2681, 1903, 1800, 1730, 1611, 1512, 1453, 1382, 1261, 1207, 1113, 1022, 914, 833, 746; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H, CH_3 aliphatic), 3.22 (m, 4H, CH_2-N), 3.89 (m, 4H, CH_2-O), 4.17 (s, 2H, CH_2 aliphatic), 7.23 (m, 3H, CH aromatic), 7.35 (m, 3H, CH aromatic), 7.41 (d, J = 9.0 Hz, 1H, CH aromatic), 7.70 (d, J = 8.7 Hz, 1H, CH aromatic) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.39 (CH_3 aliphatic), 31.88 (CH_2 aliphatic), 34.36 (C aliphatic), 52.64 (CH_2-N), 67.74 (CH_2-O), 111.71, 119.89, 122.06, 123.42, 125.49, 126.14, 128.21, 135.08, 149.34, 150.47, 153.50 (all for aromatic rings) ppm.

2.3.7 | 4g: 4-(2-Benzyl-7-methoxybenzofuran-3-yl)morpholine

Yellow oil; IR (KBr, cm^{-1}): 3086, 3029, 2957, 2905, 2846, 2755, 2681, 1915, 1728, 1621, 1585, 1491, 1439, 1383, 1335, 1275, 1210, 1114, 1033, 919, 741; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.16 (m, 4H, CH_2-N), 3.85 (m, 4H, CH_2-O), 4.00 (s, 3H, CH_3-O), 4.21 (s, 2H, CH_2 aliphatic), 6.77 (d, J = 8.6 Hz, 1H, CH aromatic), 7.13 (t, J = 7.9 Hz, 1H, CH aromatic), 7.22 (m, 1H, CH aromatic), 7.29 (m, 5H, CH aromatic) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.2 (CH_2 aliphatic), 51.4 (CH_2-N), 54.9 (CH_3-O), 66.6 (CH_2-O), 104.7, 111.3, 112.8, 125.3, 126.8, 127.4, 127.5, 128.0, 137.2, 141.5, 144.4, 149.4 (all for aromatic rings) ppm. Elemental anal. for $C_{20}H_{21}NO_3$ (C, 74.28; H, 6.55; N, 4.33; O, 14.84); Found: C, 73.02; H, 5.99; N, 3.99.

2.3.8 | 4h: 4-(2-(4-(Tert-butyl)benzyl)-7-methoxybenzofuran-3-yl)morpholine

Yellow oil; IR (KBr, cm^{-1}): 3054, 2957, 2905, 2852, 2816, 2752, 2674, 1906, 1693, 1620, 1580, 1491, 1437, 1382, 1275, 1206, 1113, 1074, 1034, 918, 841, 782; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H, CH_3 aliphatic), 3.20 (m, 4H, CH_2-N), 3.88 (m, 4H, CH_2-O), 4.00 (s, 3H, CH_3-O), 4.21 (s, 2H, CH_2 aliphatic), 6.78 (d, J = 7.7 Hz, 1H, CH aromatic), 7.15 (t, J = 7.9 Hz, 1H, CH aromatic), 7.27 (d, J = 8.3 Hz, 2H, CH aromatic), 7.31 (d, J = 7.9 Hz, 1H, CH aromatic), 7.35 (d, J = 8.3 Hz, 2H, CH aromatic) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 (CH_3 aliphatic), 31.7 (CH_2 aliphatic), 34.4 (C aliphatic), 52.5 (CH_2-N), 55.9 (CH_3-O), 67.7 (CH_2-O), 105.7, 112.4, 122.8, 125.4, 127.8, 128.3, 129.0, 135.2, 142.6, 145.5, 149.1, 150.8 (all for aromatic rings) ppm. Elemental anal. for $C_{24}H_{29}NO_3$ (C, 75.96; H, 7.70; N, 3.69; O, 12.65); Found: C, 75.11; H, 7.26; N, 3.22.

2.3.9 | 4i: 1-(2-Benzylbenzofuran-3-yl) piperidine

Yellow oil; IR (KBr, cm^{-1}): 3061, 3025, 2933, 2849, 2820, 2742, 2688, 1941, 1769, 1600, 1494, 1451, 1386, 1331, 1260, 1209, 1108, 1022, 853, 745; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.64 (m, 2H, CH_2 aliphatic), 1.76 (m, 4H, CH_2-N), 3.19 (m, 4H, CH_2-O), 4.21 (s, 2H, CH_2 aliphatic), 7.25 (m, 7H, CH aromatic), 7.39 (d, J = 7.5 Hz,1H, CH aromatic), 7.70 (d, J = 7.3 Hz, 1H, CH aromatic) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.4 (CH_2 [connected to $-CH_2$]), 26.9 (CH_2 [connected to $-CH_2N$]), 32.5 (CH_2 aliphatic), 53.8 (CH_2-N), 111.5, 120.2, 121.8, 123.2, 126.4, 126.7, 128.5, 128.6, 130.2, 138.6, 148.9, 153.5 (all for aromatic rings) ppm.

2.3.10 | 4j: 1-(2-Benzyl-5-chlorobenzofuran-3-yl)piperidine

Yellow oil; IR (KBr, cm^{-1}): 3062, 3028, 2935, 2851, 2807, 2740, 2696, 1945, 1804, 1731, 1601, 1449, 1880, 1256, 1211, 1106, 1020, 965, 860, 803, 710; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.62 (m, 2H, CH_2 aliphatic), 1.73 (m, 4H, CH_2-N), 3.11 (m, 4H, CH_2-O), 4.16 (s, 2H, CH_2 aliphatic), 7.15 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz,1H, CH aromatic), 7.27 (m, 6H, CH aromatic), 7.62 (d, J = 2.0 Hz, 1H, CH aromatic) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4 (CH_2 [connected to $-CH_2$]), 26.7 (CH_2 [connected to $-CH_2N$]), 32.5 (CH_2 aliphatic), 53.6 (CH_2-N), 123.3, 126.4, 127.3, 128.1, 128.6, 130.2, 130.7, 138.1, 150.7, 151.8 (all for aromatic rings) ppm.

2.3.11 | 4k: 1-(2-Benzyl5-bromobenzofuran-3-yl)piperidine

Yellow oil; IR (KBr, cm^{-1}): 3062, 3028, 2935, 2856, 2805, 2740, 2696, 1944, 1803, 1735, 1601, 1493, 1447, 1382, 1267, 1211, 1113, 1019, 860, 801, 708; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.46 (m, 2H, CH_2 aliphatic), 1.62 (m, 4H, CH_2 aliphatic), 3.00 (m, 4H, CH_2-N), 4.05 (s, 2H, CH_2 aliphatic), 7.16 (m, 7H, CH aromatic), 7.67 (d, J = 1.9 Hz, 1H, CH aromatic) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.2 (CH_2 [connected to $-CH_2$]), 26.8 (CH_2 [connected to $-CH_2N$]), 32.5 (CH_2 aliphatic), 53.7 (CH_2-N), 112.9, 114.9, 122.7, 126.0, 128.6, 128.7, 128.8, 129.8, 138.1, 150.5, 152.2 (all for aromatic rings) ppm.

2.3.12 | 4l: 1-(2-(4-(Tert-butyl)benzyl) benzofuran-3-yl)piperidine

Yellow oil; IR (KBr, cm^{-1}): 3058, 3028, 2940, 2858, 2805, 2738, 2663, 1904, 1738, 1628, 1511, 1448, 1381, 1205, 1018, 836, 750; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.36 (S, 9H), 1.65 (m, 4H, CH_2 aliphatic), 1.78 (m, 4H, CH_2 aliphatic), 3.21 (m, 4H, CH_2-N), 4.20 (s, 2H, CH_2 aliphatic), 7.22 (m, 2H, CH aromatic), 7.28 (d, J = 8.2 Hz, 2H, CH aromatic), 7.38 (d, J = 8.2 Hz, 2H, CH aromatic), 7.42 (m, 1H), 7.71 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.4 (CH_2 [connected to $-CH_2$]), 26.9 (CH_2 [connected to $-CH_2N$]), 31.4 (CH_3 aliphatic), 31.9 (CH_2 aliphatic), 34.4 (C aliphatic), 53.8 (CH_2-N), 11.5, 120.1, 121.7, 123.1, 125.4, 126.7, 128.2, 130.1, 135.5, 149.1, 149.2, 153.5 (all for aromatic rings) ppm. Elemental anal. for $C_{24}H_{29}NO$ (C, 82.95; H, 8.41; N, 4.03; O, 4.60); Found: C, 81.23; H, 7.37; N, 3.51.

3 | RESULTS AND DISCUSSION

To find the best media, several choline chloride-based DESs were examined to synthesize benzofuran derivatives. For this purpose, a model reaction including salicylaldehyde, morpholine, and phenylacetylene was design to optimize the reaction conditions, and the results were listed in Table 1. The reaction has not been proceeded in catalyst-free conditions (Entry 1). Then, various DESs, consisting ChCl and some Lewis acids such as $CuCl_2$, $ZnCl_2$, $SnCl_2$, $FeCl_3$, and $NiCl_2$, were used (Entries 2–6) at 80°C in 7 h to gain green reaction media under Lewis's acid condition.[27–30] Among these DESs, ChCl/$CuCl_2$ has demonstrated proper yield as a DES. The yield was not high enough which led to using Cu (I) or Cu (II) salts. It has been reported that Cu (I) is a better choice than Cu (II) in recent researches. Thus, this

TABLE 1 The results of optimization of the reaction conditions for the model reaction[a]

Entry	Reaction media	Catalyst (mol%)	Temp (°C)	Yield (%)[b]
Optimization of the reaction media (based on various DESs)				
1	-	-	80	-
2	ChCl/$CuCl_2$ (1:2) DES	-	80	20
3	ChCl/$ZnCl_2$ (1:2) DES	-	80	Trace
4	ChCl/$SnCl_2$ (1:2) DES	-	80	-
5	ChCl/$FeCl_3$ (1:2) DES	-	80	-
6	ChCl/$NiCl_2$ (1:2) DES	-	80	-
7	CuCl in ChCl/Urea (1:2) DES	5	80	36
8	CuI in ChCl/Urea (1:2) DES	5	80	40
9	CuCl in ChCl/EG (1:2) DES	5	80	55
10	$CuCl_2$ in ChCl/EG (1:2) DES	5	80	42
11	**CuI in ChCl/EG (1:2) DES**	5	**80**	**80**
12	ChCl/EG (1:2) DES	-	80	-
13	EG	-	80	-
14	ChCl	-	80	-
15	CuI in EG	5	80	62
16	CuI in water	5	80	Trace
Optimization of the reaction temperature and time				
17	CuI in ChCl/EG (1:2) DES	5	40	-[c]
18	CuI in ChCl/EG (1:2) DES	5	60	Trace[c]
19	CuI in ChCl/EG (1:2) DES	5	80	75[c]
20	CuI in ChCl/EG (1:2) DES	5	100	61[d]
Optimization of the catalyst's amount				
21	CuI in ChCl/EG (1:2) DES	2.5	80	48
22	CuI in ChCl/EG (1:2) DES	10	80	81
23	CuI in ChCl/EG (1:2) DES	15	80	77

Note: Bold items refers to the final optimized value.

Abbreviation: DES, deep eutectic solvent.

[a]The model reaction: salicylaldehyde (1 mmol), morpholine (1.5 mmol), and phenylacetylene (1.2 mmol) in ChCl/EG (0.5 mL), CuI (5 mol%), 80°C, 7 h.

[b]Isolated yield.

[c]The reaction time was 24 h.

[d]The reaction time was 7 h.

salt was considered as a catalyst of the reaction. In order to prepare a biodegradable low-cost and non-toxic media, combination of choline chloride with ethylene glycol or urea, as hydrogen bond donors, has been considered.

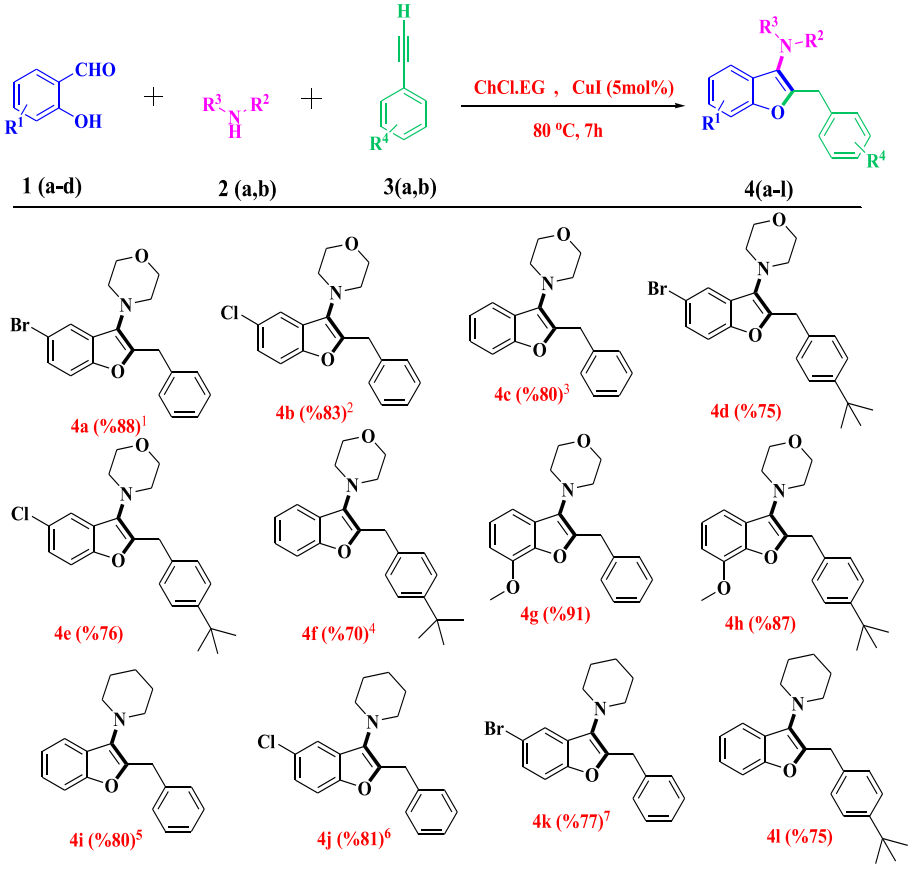
Therefore, the reaction media have been based on the combination of ChCl/urea or ChCl/ethylene glycol DESs with Cu (I) salts. ChCl/urea and ChCl/EG DES were chosen, because they are more available, biocompatible, good soluble of transition metal salt, and have lower price, according to the Entries 7–11. Different Cu (I) and Cu (II) salts have been applied with combination of ChCl/urea or ChCl/EG DES to gain the best reaction media. Results indicate that using CuI as a catalyst in ChCl/EG DES has better efficiency with yield of 80% (Entry 11). Based on the Entries 12–14, the reaction has not been done without application of Lewis acid. Therefore, using ChCl/EG DES with Lewis acid is necessary. H_2O (as a traditional green solvent) was also used to investigate the reaction and compare with using DES (Entry 16). Results of using this solvent under the same condition have indicated less efficiency than application of DESs. Choosing CuI as a catalyst and ChCl/EG DES as a reaction medium (Entry 11) showed the highest yield. So, the best time of reaction is devoted to 7 h (Entry 11), which has showed the highest yield. In order to investigate temperature effects on reaction, the reaction has been done under 40°C, 60°C, and 100°C, and the reported results (Entries 17, 18, and 20) have been

compared with Entry 11. Decreasing temperature causes the reaction would not to proceed and the temperature growth reduces the yield. Therefore, the best reaction temperature was 80°C Entry 11.

Additionally, the other catalyst values (2.5, 10, and 15 mol%) were implemented under the optimal conditions to compare with using 5 mol% of catalyst (Entry 11). The results are demonstrated in Entries 21–23 show that both increasing and decreasing the amount of catalyst (from 5% to 10, 15 and 2.5%) reduces the yield. Therefore, the previous value (5%) is considered as the optimized amount of catalyst.

In order to show the versatility of this method and investigate the possibility of using different substituents, 12 different products were prepared, as they presented in Scheme 2. In addition to phenylacetylene, its 4-*t*-butyl substituted derivative has been used for the reaction with morpholine and pipyridine as amine sources and various salicylaldehydes. The yields of benzofurans were in the range of 70–91%. Salicylaldehydes that contain electron-releasing substituents produced the products in more yields. The most yield was observed in the reactions with 2-hydroxy-3-methoxybenzaldehyde, as aldehyde source. It must be noticed that there was no improvement in the reaction while other amines such as dibutylamine, dihexylamine, benzylamine, and aniline were used as amine source. Additionally, the results show better yield achievement when morpholine was used as amine source than using pipyridine. Existence of electron donor groups like tert-butyl on phenyl acetylene can reduce the reaction yield, approximately.

A plausible mechanism was proposed for this reaction, as it showed in Scheme 3. According to this mechanism, the synthesis of disubstituted benzo furans using CuI follows via the formation of an iminium ion from the reaction between salicylaldehyde and secondary amine, after the elimination of a water molecule. The organometallic intermediate (consisted of C–Cu bond) is produced via activating C–H bond from the reaction of acetylene and CuI. Afterward, Cu–acetylide attacks to iminium ion to produce the amine as another intermediate. Then, oxygen atom attacks as a nucleophile to *sp* carbon and forms a 5-membered ring through an intermolecular reaction. Finally, an isomerization was expected to prepare the desired product. In addition to the role of solvent, the employed DES stabilize highly polar intermediates and transition states because of its ionioc nature. In fact, in the absence of DES, the reaction has been performed slowly. In addition, the hydroxy groups of ethelene glycol



SCHEME 2 The general reaction conditions and produced benzofuran derivatives

SCHEME 3 The plausible proposed mechanism for the reaction

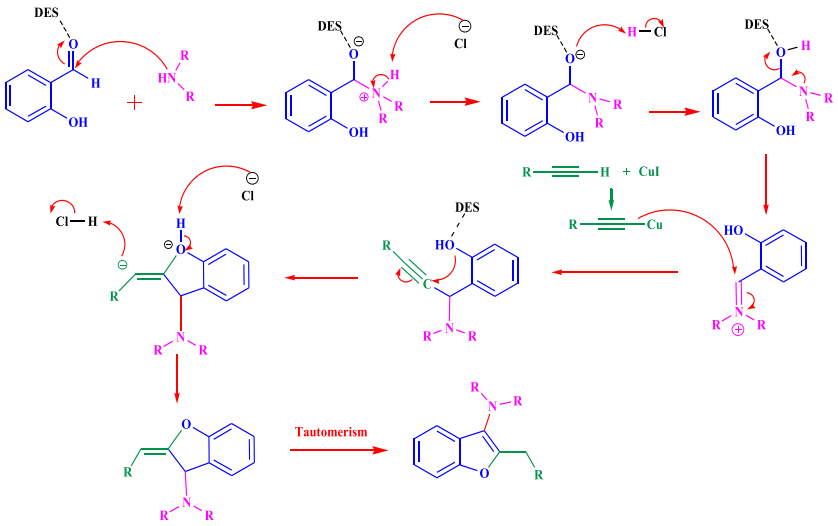


TABLE 2 Comparisons of ChCl-EG/CuI with other recent reports of reaction condition for the synthesis of benzofuran

Entry	Catalyst	Reaction conditions	Time (h)	Catalyst amount	Yield (%)	Ref
1	HS-CuO	Neat/110°C	1.5	4 mg	88–95	Purohit et al.[1]
2	Cu_2ONPs	Neat/K_2CO_3/TBAB/100°C	1.75	20 mol%	79–90	Mahmoodi and Jazayri[21]
3	h-Fe_2O@SiO_2-IL/Ag	H_2O/r.t/ultrasound	0.5	25 mg	88–93	Sadjadi et al.[23]
4	CuI	CH_3CN/reflux	16	30 mol%	40–77	Nguyen and Li[6]
5	CuI	Toluene/110°C	3	20 mol%	46–86	Li et al.[5]
6	CuI	[Bmim]PF_6/80°C	6	10 mol%	52–90	Zhang et al.[22]
7	CuI	ChCl-EG/80°C	7	5 mol%	70–91	This work

make hydrogen bond with all possible ingredients, which could be useful for the better performance. The chloride ion, existed in DES, also could act as a weak base for deprotonation of species, when is needed.

In order to show the applicability of the synthesis method, the results have been compared with the other related studies. The results in Table 2 show that the the presented method has several advantages such as using non-toxic solvents, inexpensive and available catalyst, comparing with the previous reports. Additionally, using little mass amount of catalyst is another advantage of this method.

4 | CONCLUSION

2,3-Disubstituted benzo[*b*]furans have been prepared from a multicomponent reaction between salicylaldehydes, alkynes and amine using CuI as a catalyst and choline chloride/EG DES as a reaction media. An inexpensive, nontoxic, and availability of catalyst, which were used in this study, are known as the advantages of this method. In summary, 12 different derivatives of benzofuran have been prepared during 7-h stirring at 80°C with 70–91% yields.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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