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FULL PAPER

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# Choline chloride-urea deep eutectic solvent as an efficient media for the synthesis of propargylamines via organocuprate intermediate

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A facile method for the synthesis of various propargylamines derivatives with different structural parts has been reported. The reaction has consisted of one-pot coupling between aldehydes, secondary amines and terminal alkynes using CuCl as a catalyst and choline chloride/urea DES as a cheap and biocompatible reaction media. The procedure is free of using toxic solvents and used CuCl as an available, inexpensive and non-toxic catalyst. Using this methodology, 15 different propargylamine derivatives were successfully synthesized at 60 °C in 15 hr, mostly in good yields.

**KEYWORDS**

choline, DES, green, Organocopper, Propargylamine

## 1 | INTRODUCTION

In the recent years, propargylamine scaffolds have been widely considered due to their enormous utilities in synthetic organic chemistry and pharmaceuticals.[1,2] They have been used not only as key synthetic intermediates for biologically active compounds,[3,4] but also as useful precursors and versatile building blocks for the synthesis of various nitrogen containing heterocyclic compounds.[5–7] According to the recent studies, some propargylamine derivatives have been used for the treatment of neurological disorders such as Parkinson's and Alzheimer's.[8] In Scheme 1, some propargylamine-containing structures were showed, which they have been used as monoamine oxidase inhibitors (MAOI) for Alzheimer's treatment.[9]

Due to the significance of these compounds, several synthetic methodologies have been developed by chemists.[10] Among various reports, three-component reaction between aldehydes, alkynes, and amines (briefly named as $A^3$-coupling) have been the most popular and efficient method for this synthesis.[11–15] The importance of the one-pot $A^3$-coupling is related to the use of mild and environmental friendly conditions, no moisture-sensitivity, avoiding toxic reagents and high atom economy.[16,17] Via this methodology, both homogeneous and heterogeneous catalysts have been employed in several studies. For example, various transition metal catalytic systems such as copper,[18,19] gold,[20] silver,[21] indium,[22] iron,[23] iridium,[24] zinc,[25] nickel[26] and cobalt[27] have been used for the C-H activation of terminal alkynes and performing the reaction. Among these catalysts, copper salts are more useful candidates due to their availabilities, low-cost, low-toxicities and high-reactivity.[28] However, the most of the presented methodologies suffers from some disadvantages such as using toxic solvents, employing expensive and non-reusable catalysts and performing the reaction at high temperature.[29–31] Therefore, it is highly desirable to develop new efficient, environmental friendly and green synthetic methodologies for the synthesis of propargylamines using $A^3$-coupling reaction. Decreasing environmental pollutions and employing a secure, non-toxic and biodegradable solvent is necessary for a green process.[32,33] Recently, toxic and volatile organic solvents have been substituted by ionic liquids to decrease their environmental issues. However, despite all desirable properties of ionic liquids such as negligible vapor pressure, non-flammability,

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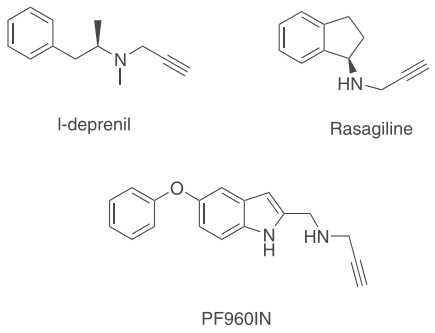



**SCHEME 1** Propargylamine moiety containing drugs

thermal stability and recyclability, their uses have been restricted by various disadvantages and limitations such as high cost and difficult preparation.[34,35] Deep eutectic solvents (DESs) are a new generation of ionic liquids, which introduced by Abbott et al. (2003).[36] DESs are more promising alternatives of ionic liquids due to their low costs and the employing biodegradable, renewable and available starting materials.[37,38] After the first report on this class of compounds, several studies have been reported on the synthesis and applications of DESs in various fields like chemical synthesis, biochemistry, separation, adsorption processes and pharmacy.[39–44] Therefore, in continuation of the previous efforts of our research group in the development of synthetic methodologies using DESs,[45–47] the use of these useful media for the preparation of propargylamines using $A^3$-coupling reaction has been considered. In this study, CuCl in choline chloride/urea DES has been used as a green and efficient media for the synthesis of propargylamines derivatives. The details of experiments and the results will be discussed in the next sections.

## 2 | EXPERIMENTAL

All chemical compounds have purchased from Sigma-Aldrich and Merck companies and used without further purification. Thin layer chromatography was employed to monitor the progress of the reactions using n-hexane-ethyl acetate (3:1 ratio) as eluent. IR spectra were recorded on KBr disks using JASCO FT-IR spectrophotometers in the range of 400 to 4,000 $cm^{-1}$. $^1$HNMR (400 MHz, $CDCl_3$) and $^{13}$CNMR (100 MHz, $CDCl_3$) spectra were recorded on Bruker Ultra shield spectrometer. $^1$H and $^{13}$C chemical shifts were referenced to TMS as an internal standard. Mass spectra were recorded using AB SCIEX 3200 QTRAP instrument (USA) with ESI TURBO ionization source.

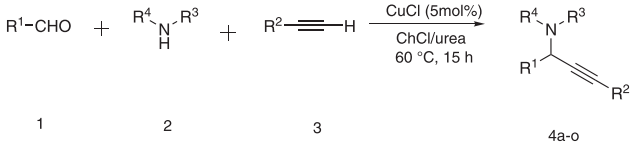
### 2.1 | Preparation of deep eutectic solvents-catalyst mixtures

Choline chloride based DESs and their mixtures with catalyst were prepared by combination of ChCl with other components like $CuCl_2.2H_2O$, $FeCl_3.6H_2O$, $SnCl_2.2H_2O$, $ZnCl_2.2H_2O$, $NiCl_2.6H_2O$, urea and ascorbic acid in accordance with the methodologies described in the literature.[48–51] For example (for the final media), ChCl (0.28 g), urea (0.24 g) and CuCl (0.005 g) were simply mixed, heated and stirred at 80 °C for 1 hr to obtain a clear green liquid. The successful syntheses of these DESs were confirmed by comparing their IR spectra with the related reports.

### 2.2 | General procedure for preparation of propargylamines

In a round-bottom flask, ChCl/urea/CuCl (1 ml), aldehyde (1 mmol), amine (1.2 mmol) and alkyne (1.2 mmol) were mixed. The reaction mixture has been stirred for 15 hr at 60 °C (Scheme 2). The progress of the reaction was monitored by TLC (eluent phase: 3:1 ratio of n-hexane: EtOAc). After the completion of the reaction, the mixture was cooled to room temperature and diluted with EtOAc and $H_2O$. Next, triphasic mixture was obtained which includes organic phase, aqueous phase and CuCl between two other phases. The organic phase was separated and dried over $MgSO_4$ and it was concentrated by using a rotary evaporator. The residue was purified by thin-layer chromatography on 20 × 20 $cm^2$ silica gel plate to afford the pure product. The aqueous phase containing DES was separated and dried under vacuum. Finally, it was reused for the next cycle. However, during the work-up step, CuCl was not completely recycled and after recyclization, the desired amount of CuCl was added to the ChCl/urea mixture.

The structures of all products were confirmed by comparing their physical properties and spectral data with the reported values. The spectral data for all products were listed below and all of the original spectra were shown in supporting information.




**SCHEME 2** The general reaction for the synthesis of propargylamine derivatives

**DES** (Choline chloride.2urea): mp = 12–14 °C; IR (KBr, $cm^{-1}$) 3200–3,400 (s), 2,150 (w), 1,645 (s), 1,440 (s), 1,330 (m), 1,160 (m), 1,080 (m), 958 (m), 868 (w), 784 (m), 580 $cm^{-1}$ (s).

**4a: 4-(1,3-diaromaticprop-2-yn-1-yl) morpholine:** yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.55 (m, 4H, $CH_2$-N), 3.65 (m, 4H, $CH_2$-O), 4.71 (s, 1H, CH-N), 7.27 (m, 6H, $CH_{aromatic}$), 7.43 (m, 2H, $CH_{aromatic}$), 7.55 (d, J = 7.4 Hz, 2H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 49.9 (CH-N), 62.0 ($CH_2$-N), 67.2 ($CH_2$-O), 85.0 (acetylenic carbon), 88.5 (acetylenic carbon), 123.0, 127.8, 128.3, 128.3, 128.3, 128.6, 131.8, 137.8 (all for aromatic rings) ppm.

**4b: 4-(1-(4-chloroaromatic)-3-aromaticprop-2-yn-1-yl) morpholine:** yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.63 (m, 4H, $CH_2$-N), 3.75 (m, 4H, $CH_2$-O), 4.78 (s, 1H, CH-N), 7.36 (m, 5H, $CH_{aromatic}$), 7.53 (m, 2H, $CH_{aromatic}$), 7.6 (d, J = 8.3 Hz, 2H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 48.8 (CH-N), 60.3 ($CH_2$-N), 66.1 ($CH_2$-O), 83.3 (acetylenic carbon), 87.9 (acetylenic carbon), 121.7, 127.3, 127.4, 127.4, 128.9, 130.8, 132.6, 135.4 (all for aromatic rings) ppm.

**4c: 4-(1-(3-methoxyaromatic)-3-aromaticprop-2-yn-1-yl) morpholine:** yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.64 (m, 4H, $CH_2$-N), 3.55 (m, 4H, $CH_2$-O), 3.85 (s, 3H, $OCH_3$), 4.77 (s, 1H, CH-N), 6.86 (d, J = 7.9 Hz, 1H, $CH_{aromatic}$), 7.29 (m, 6H, $CH_{aromatic}$), 7.51 (m, 2H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 49.9 (CH-N), 55.3 (OMe), 62.0 ($CH_2$-N), 67.2 ($CH_2$-O), 85.0 (acetylenic carbon), 88.4 (acetylenic carbon), 113.1, 114.3, 121.0, 122.9, 128.3, 128.3, 129.2, 131.8, 139.4, 159.6 (all for aromatic rings) ppm.

**4d: 4-(1-(naphthalen-2-yl)-3-aromaticprop-2-yn-1-yl) morpholine:** yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.71 (m, 4H, $CH_2$-N), 3.78 (m, 4H, $CH_2$-O), 4.98 (s, 1H, CH-N), 7.38 (m, 3H, $CH_{aromatic}$), 7.51 (m, 2H, $CH_{aromatic}$), 7.59 (m, 2H, $CH_{aromatic}$), 7.78 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H, $CH_{aromatic}$), 7.88 (m, 3H, $CH_{aromatic}$), 8.12 (s, 1H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 50.1 (CH-N), 62.2 ($CH_2$-N), 67.2 ($CH_2$-O), 85.0 (acetylenic carbon), 88.8 (acetylenic carbon), 123.0, 126.1, 126.1, 126.5, 127.6, 127.6, 128.0, 128.1, 128.3, 128.4, 131.9, 133.1, 135.4 (all for aromatic rings) ppm.

**4e: 4-(3-aromatic-1-(thiophen-2-yl) prop-2-yn-1-yl) morpholine:** yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.72 (m, 4H, $CH_2$-N), 3.79 (4H, m, $CH_2$-O), 5.03 (s, 1H, CH-N), 7.00 (m, 1H, $CH_{aromatic}$), 7.33 (m, 5H, $CH_{aromatic}$), 7.55 (m, 2H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 49.7 (CH-N), 57.8 ($CH_2$-N), 67.1 ($CH_2$-O), 84.3 (acetylenic carbon), 87.6 (acetylenic carbon), 122.7, 125.8, 126.3, 126.4, 128.4, 128.4, 131.9, 142.8 (all for aromatic rings) ppm.

**4f: 4-bromo-2-(1-morpholino-3-aromaticprop-2-yn-1-yl) phenol:** yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.81 (m, 4H, $CH_2$-N), 3.83 (m, 4H, $CH_2$-O), 5.12 (s, 1H, CH-N), 6.92 (m, 2H, $CH_{aromatic}$), 7.40 (m, 3H, $CH_{aromatic}$), 7.59 (m, 3H, $CH_{aromatic}$), 10.81 (s, 1H, OH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 49.2 (CH-N), 60.7 ($CH_2$-N), 66.9 ($CH_2$-O), 81.6 (acetylenic carbon), 90.4 (acetylenic carbon), 116.5, 119.5, 120.6, 122.3, 128.5, 128.8, 129.8, 131.9, 157.0 (all for aromatic rings) ppm.

**4g: methyl 4-(1-morpholino-3-aromaticprop-2-yn-1-yl) benzoate:** white solid, m.p: 171-173 °C, IR (KBr, $cm^{-1}$): 2925, 1,718, 1,383, 1,107, 887, 742. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.65 (m, 4H, $CH_2$-N), 3.77 (m, 4H, $CH_2$-O), 3.95 (s, 3H, OMe), 4.86 (s, 1H, CH-N), 7.37 (m, 3H, $CH_{aromatic}$), 7.55 (m, 2H, $CH_{aromatic}$), 7.75 (d, J = 8.3 Hz, 2H, $CH_{aromatic}$), 8.07 (d, J = 8.3 Hz, 2H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 49.8 (CH-N), 52.2 (OMe), 61.8 ($CH_2$-N), 67.1 ($CH_2$-O), 84.1 (acetylenic carbon), 89.1 (acetylenic carbon), 122.7, 128.4, 128.5, 128.5, 129.6, 129.7, 131.8, 143.0 (all for aromatic rings), 166.9 (C=O ester) ppm. ESI-MS (m/z): 336 $[M]^+$, 263, 249, 219, 165, 149, 143, 121.

**4h: 4-(1-aromaticpent-1-yn-3-yl) morpholine:** pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.4 Hz, 3H, $CH_3$(connected to $CH_2$)), 1.67 (m, 2H, $CH_2$ (connected to Me)), 2.50 (m, 2H, $CH_2$-N), 2.67 (m, 2H, $CH_2$-N), 3.34 (t, J = 7.4 Hz, 1H, CH-N), 3.69 (m, 4H, $CH_2$-O), 7.22 (m, 3H, $CH_{aromatic}$), 7.36 (m, 2H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 11.2 ($CH_3$ (connected to $CH_2$)), 26.1 ($CH_2$ (connected to Me)), 49.7 (CH-N), 59.8 ($CH_2$-N), 67.1 ($CH_2$-O), 86.2 (acetylenic carbon), 87.0 (acetylenic carbon), 123.2, 128.0, 128.2, 131.7 (all for aromatic rings) ppm.

**4i: 4-(1-aromatichex-1-yn-3-yl) morpholine:** pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.2 Hz, 3H, $CH_3$ (connected to $CH_2$)), 1.76 (m, 2H, $CH_2$ (connected to Me)), 2.06 (m, 2H, $CH_2$(between $CH_2$ and CH-N), 2.59 (m, 2H, $CH_2$-N), 2.77 (m, 2H, $CH_2$-N), 3.43 (t, J = 7.4 Hz, 1H, CH-N), 3.78 (m, 4H, $CH_2$-O), 7.38 (m, 5H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 11.2 ($CH_3$ (connected to $CH_2$)), 14.2 ($CH_2$ (connected to Me)), 26.1($CH_2$(between $CH_2$ and CH-N), 59.8 ($CH_2$-N), 60.4 (CH-N), 67.2 ($CH_2$-O), 86.2 (acetylenic carbon), 87.0 (acetylenic carbon), 123.2, 128.0, 128.2, 131.7 ppm.

**4j: 4-(1-(4-(tert-butyl) aromatic)-4-methylpent-1-yn-3-yl) morpholine:** pale yellow oil. IR (KBr, $cm^{-1}$): 2960, 1,385, 1,113, 787. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.6 Hz, 3H, $CH_3$ (connected to CH)), 1.12 (d, J = 6.6 Hz, 3H, $CH_3$(connected to CH)), 1.33 (s, 9H, t-Bu group), 1.92 (m, 1H, CH (*i*-Pr group)), 2.53 (m, 2H, $CH_2$-N), 2.72 (m, 2H, $CH_2$-N), 3.03 (d, J = 9.5 Hz, 1H, CH-N), 3.76 (m, 4H, $CH_2$-O), 7.34 (d, J = 8.6 Hz, 2H, $CH_{aromatic}$), 7.40 (d, J = 8.6 Hz, 2H, $CH_{aromatic}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 19.8 ($CH_3$(connected to CH)), 20.3 ($CH_3$(connected to CH)), 29.8 (CH (*i*-Pr group)), 31.2 (3Me for t-Bu group), 34.7 (C of t-Bu group), 50.0 (CH-N), 65.2 ($CH_2$-N), 67.2 ($CH_2$-O), 85.97 (acetylenic carbon), 86.6 (acetylenic carbon),

120.4, 125.2, 131.4, 151.1 (all for aromatic rings) ppm. ESI-MS (m/z): 300 $[M]^+$, 263, 214, 213, 164, 157, 149, 129, 114.

**4k: 4-(3-(4-(tert-butyl) phenyl)-1-(3-methoxyphenyl) prop-2-yn-1-yl) morpholine:** yellow oil. IR (KBr, $cm^{-1}$): 2960, 2,224, 1,385, 1,115, 835, 704. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H, t-Bu group), 2.67 (m, 4H, $CH_2$-N), 3.77 (m, 4H, $CH_2$-O), 3.85 (s, 3H, OMe), 4.79 (s, 1H, CH-N), 6.87 (d, J = 7.3 Hz, 1H, $CH_{aromatic}$), 7.29 (m, 3H, $CH_{aromatic}$), 7.38 (d, J = 8.4 Hz, 2H, $CH_{aromatic}$), 7.48 (d, J = 8.4 Hz, 2H, $CH_{aromatic}$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 31.2 (3Me for t-Bu group), 34.8 (C of t-Bu group), 49.9 (CH-N), 55.3 (OMe), 61.9 ($CH_2$-N), 67.2 ($CH_2$-O), 84.3 (acetylenic carbon), 88.5 (acetylenic carbon), 113.1, 114.3, 112.0, 121.0, 125.3, 129.2, 131.6, 139.6, 151.5, 159.6 (all for aromatic rings) ppm. ESI-MS (m/z): 364 $[M]^+$, 278, 277, 262, 247.

**4l: 4-(3-(4-(tert-butyl) phenyl)-1-(thiophen-2-yl) prop-2-yn-1-yl) morpholine:** yellow oil. IR (KBr, $cm^{-1}$): 2960, 1,385, 1,265, 1,117. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H, t-Bu group), 2.70 (m, 4H, $CH_2$-N), 3.78 (m, 4H, $CH_2$-O), 5.02 (s, 1H, CH-N), 6.99 (m, 1H, $CH_{aromatic}$), 7.26 (m, 1H, $CH_{aromatic}$), 7.31 (m, 1H, $CH_{aromatic}$), 7.38 (d, J = 8.4 Hz, 2H, $CH_{aromatic}$), 7.48 (d, J = 8.4 Hz, 2H, $CH_{aromatic}$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 31.2 (3Me for t-Bu group), 34.8 (C of t-Bu group), 49.6 (CH-N), 57.8 ($CH_2$-N), 67.1 ($CH_2$-O), 83.5 (acetylenic carbon), 87.7 (acetylenic carbon), 119.6, 125.3, 125.8, 126.3, 126.4, 131.6, 142.9, 151.7 (all for aromatic rings) ppm. ESI-MS (m/z): 339 $[M]^+$, 255, 252, 238, 223, 143.

**4m: 4-(3-(4-(tert-butyl) phenyl)-1-(naphthalen-1-yl)prop-2-yn-1-yl) morpholine:** yellow oil. IR (KBr, $cm^{-1}$): 2960, 2,220, 1,606, 1,477, 1,385, 1,267, 1,115, 829, 586. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9H, t-Bu group), 2.73 (m, 4H, $CH_2$-N), 3.70 (m, 4H, $CH_2$-O), 5.46 (s, 1H, CH-N), 7.40 (d, J = 8.6 Hz, 2H, $CH_{aromatic}$), 7.47 (d, J = 8.1 Hz, 1H, $CH_{aromatic}$), 7.51 (d, J = 8.6 Hz, 2H, $CH_{aromatic}$), 7.57 (m, 2H, $CH_{aromatic}$), 7.85 (d, J = 8.1 Hz, 1H, $CH_{aromatic}$), 7.90 (d, J = 7.8 Hz, 1H, $CH_{aromatic}$), 7.95 (d, J = 7.0 Hz, 1H, $CH_{aromatic}$), 8.41 (d, J = 8.3 Hz, 1H, $CH_{aromatic}$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 31.2 (3Me for t-Bu group), 34.8 (C of t-Bu group), 49.8 (CH-N), 60.1 ($CH_2$-N), 67.2 ($CH_2$-O), 84.2 (acetylenic carbon), 89.1 (acetylenic carbon), 120.0, 124.8, 124.8, 125.3, 125.7, 125.9, 127.1, 128.5, 128.8, 131.5, 131.7, 133.3, 134.0, 151.5 (all for aromatic rings) ppm. ESI-MS (m/z): 382 $[M]^+$, 338, 297, 282, 256, 219, 165, 149, 143, 121.

**4n: 2-(3-(4-(tert-butyl) phenyl)-1-morpholinoprop-2-yn-1-yl)-4-chlorophenol:** yellow oil. IR (KBr, $cm^{-1}$): 2960, 2,218, 1,604, 1,279, 1,115, 835, 762. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9H, t-Bu group), 2.80 (m, 4H, $CH_2$-N), 3.82 (m, 4H, $CH_2$-O), 5.11 (s, 1H, CH-N), 6.81 (d, J = 8.6 Hz, 1H, $CH_{aromatic}$), 7.21 (dd, J = 8.6 Hz, J = 2.6 Hz, 1H, $CH_{aromatic}$), 7.43 (d, J = 8.6 Hz, 2H, $CH_{aromatic}$), 7.52 (d, J = 8.6 Hz, 2H, $CH_{aromatic}$), 7.56 (m, 1H, $CH_{aromatic}$), 10.59 (bs, 1H, OH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 31.2 (3Me for t-Bu group), 34.9 (C of t-Bu group), 48.6 (CH-N), 60.4 ($CH_2$-N), 66.8 ($CH_2$-O), 79.9 (acetylenic carbon), 91.1 (acetylenic carbon), 117.8, 118.9, 122.2, 124.2, 125.5, 128.7, 129.6, 131.7, 152.4, 155.7 (all for aromatic rings) ppm. ESI-MS (m/z): 384 $[M]^+$, 300, 299, 298, 297, 282, 267, 219, 165, 149, 143, 121.

**4o: 1-(1,3-diphenylprop-2-yn-1-yl)pyrrolidine:** yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.91 (m, 4H, $CH_2$ (connected to -$CH_2$N)), 2.94 (m, 4H, $CH_2$-N), 5.23 (s, 1H, CH-N), 7.38 (m, 6H, $CH_{aromatic}$), 7.54 (m, 2H, $CH_{aromatic}$), 7.70 (d, J = 8.6 Hz, 2H, CH $_{aromatic}$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 23.6 ($CH_2$ (connected to -$CH_2$N)), 50.0 (CH-N), 59.0 ($CH_2$-N), 85.3 (acetylenic carbon), 88.0 (acetylenic carbon), 123.0, 128.1, 128.4, 128.5, 128.5, 128.7, 131.9, 137.3 (all for aromatic rings) ppm.

## 3 | RESULTS AND DISCUSSION

By considering the importance of green chemistry, the development of environmental friendly synthetic methods using green solvents is essential. Therefore, the use of various deep eutectic solvents (based on ChCl) for the preparation of propargylamines has been investigated in this study. First, a three-component reaction between benzaldehyde, morpholine and phenylacetylene was selected as a model reaction to optimize the values of various parameters and obtain the best conditions (solvent, catalyst amount, temperature and time). The results of these optimization processes were listed in Table 1. Surely, the reaction was not preceded without using any catalyst or reaction media. To obtain the best green reaction media under Lewis acid condition, various reported DESs, formed from choline chloride and a different Lewis acid such as $CuCl_2$, $ZnCl_2$, $SnCl_2$, $FeCl_3$ and $NiCl_2$ were employed (entries 1–5) at 60 °C in 24 h.[48–51] Among these DESs, ChCl/$CuCl_2$ has shown the highest yield but not high enough. Therefore, it was also decided to try the other Cu (I) and Cu (II) salts as a catalyst of this reaction. Based on the recent studies, Cu (I) could be a better alternative than Cu (II) for employing as the catalyst reaction. Therefore, it was focused on these salts at the next step. However, any report related to the formation of DES from ChCl and Cu (I) salts has not been found. Therefore, the mixture of Cu (I) salts and ChCl/urea DES was considered as a reaction media. The selection of ChCl/urea DES was based on its availability, low price, biocompatibility and good solubility of transition metal salt (according to the reports) in this DES. Moreover,

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

| Entry | Reaction media | Metal salt (mol%) | Temp (°C) | Time (hr) | Yield (%)[b] |
|---|---|---|---|---|---|
| Optimization of the reaction media (based on various DESs) | | | | | |
| 1 | ChCl/$CuCl_2$ (1:2) DES | - | 60 | 24 | 50 |
| 2 | ChCl/$ZnCl_2$ (1:2) DES | - | 60 | 24 | trace |
| 3 | ChCl/$SnCl_2$ (1:2) DES | - | 60 | 24 | - |
| 4 | ChCl/$FeCl_3$ (1:2) DES | - | 60 | 24 | - |
| 5 | ChCl/$NiCl_2$ (1:2) DES | - | 60 | 24 | - |
| **6** | **CuCl in ChCl/Urea (1:2) DES** | **5** | **60** | **24** | **60** |
| 7 | CuI in ChCl/Urea (1:2) DES | 5 | 60 | 24 | 52 |
| 8 | $CuSO_4$ in ChCl/Urea (1:2) DES | 5 | 60 | 24 | 25 |
| 9 | $CuCl_2$ in ChCl/Urea (1:2) DES | 5 | 60 | 24 | 37 |
| 10 | ChCl/urea (1:2) DES | - | 60 | 24 | - |
| 11 | CuCl in ChCl/Ascorbic acid (4:1) DES | 5 | 60 | 24 | 65 |
| 12 | CuCl in water | 5 | 60 | 24 | 24 |
| 13 | CuCl in Ethanol | 5 | 60 | 24 | 39 |
| 14 | CuCl in $H_2O$:Ethanol (1:1) | 5 | 60 | 24 | 32 |
| Optimization of the reaction temperature and time | | | | | |
| **15** | **CuCl in ChCl/Urea (1:2) DES** | **5** | **60** | **15** | **75** |
| 16 | CuCl in ChCl/Urea (1:2) DES | 5 | 60 | 10 | 60 |
| 17 | CuCl in ChCl/Urea (1:2) DES | 5 | 40 | 15 | 27 |
| 18 | CuCl in ChCl/Urea (1:2) DES | 5 | 50 | 15 | 35 |
| 19 | CuCl in ChCl/Urea (1:2) DES | 5 | 70 | 15 | 51 |
| 20 | CuCl in ChCl/Urea (1:2) DES | 5 | 80 | 15 | 53 |
| 21 | CuCl in ChCl/Urea (1:2) DES | 5 | 100 | 15 | 35 |
| Optimization of the catalyst's amount | | | | | |
| 22 | CuCl in ChCl/Urea (1:2) DES | 1 | 60 | 15 | 51 |
| 23 | CuCl in ChCl/Urea (1:2) DES | 3 | 60 | 15 | 66 |
| 24 | CuCl in ChCl/Urea (1:2) DES | 10 | 60 | 15 | 70 |
| 25 | CuCl in ChCl/Urea (1:2) DES | 15 | 60 | 15 | 70 |

[a]The model reaction: benzaldehyde (1 mmol), morpholine (1.2 mmol) and phenylacetylene (1.2 mmol) in 1 ml DES or solvent.
[b]Isolated yield.

ChCl/urea DES is well known as green media and the basicity of urea beside the Lewis acid salt, provide a dual acid–base rule for the produced media. In the entries 6–9, different Cu (I) and Cu (II) salts were employed in combination with ChCl/urea DES to obtain the most appropriate copper salt for this reaction. According to these entries, the most efficiency was devoted to the implementation of CuCl as catalyst in ChCl/urea DES (yield = 60%) and CuCl was chosen as a final catalyst of the reaction. It should be noticed that by using only ChCl/urea DES and without using Lewis acid, the reaction was not performed at all (entry 10). To use another DES, in attendant with CuCl, ChCl/Ascorbic acid DES was used as an appropriate DES (entry 11, based on the reported studies). In this reaction, 65% yield was obtained that was comparable with the use of ChCl/urea DES. However, because of the oxidation, destruction and leaching of ascorbic acid during the reaction,[52] the purification of the product was harder and the recycling of this DES was impossible. Therefore, this DES was ignored in the next parts of this study. This reaction was also investigated using CuCl in traditional green solvents such as $H_2O$, Ethanol and $H_2O$: Ethanol (1:1) mixture (entries 12–14) to compare their results with the employed DES. Under the same reaction conditions, these solvent showed much less efficiencies (yields between 24–39%) versus ChCl/urea DES for the model reaction and they have been ignored. After the selection of CuCl in ChCl/urea DES as a reaction

**TABLE 2** The prepared propargylamine derivatives, based on the presented reaction in scheme 1 [a]

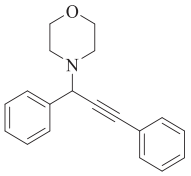
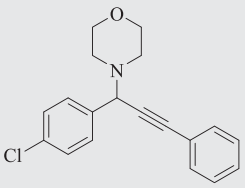
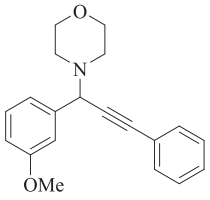
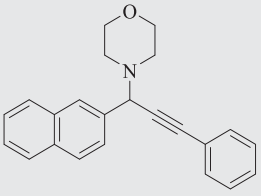
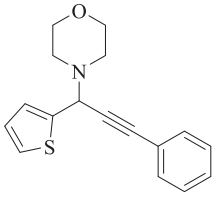
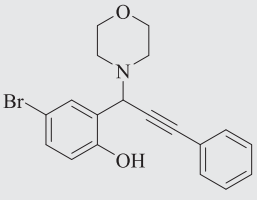
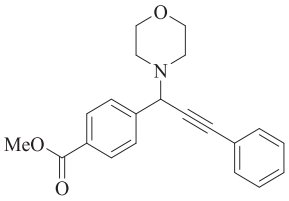
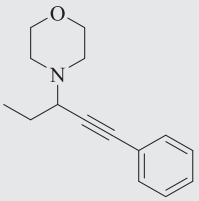
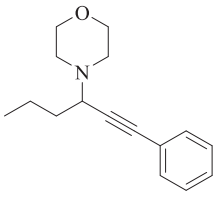
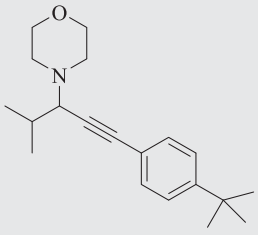
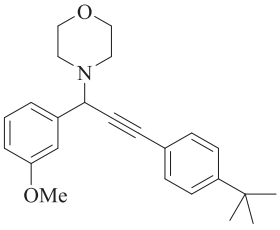
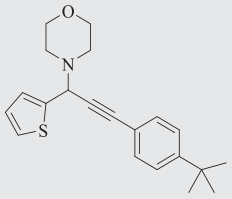
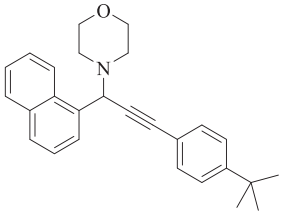
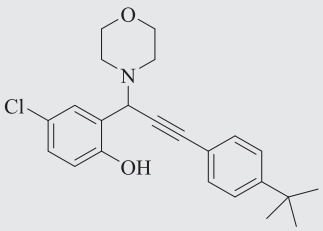
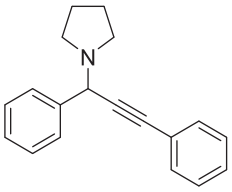
| Structure | $R^1$ | $R^2$ | Amine | Product | Yield(%)[b] | [Ref] |
|---|---|---|---|---|---|---|
| **4a** | Phenyl- | Phenyl- | morpholine |  | 75 | [53] |
| **4b** | 4-chloro-$C_6H_4$- | Phenyl- | morpholine |  | 73 | [54] |
| **4c** | 3-methoxy-$C_6H_4$- | Phenyl- | morpholine |  | 81 | [55] |
| **4d** | 2-naphtyl- | Phenyl- | morpholine |  | 85 | [56] |
| **4e** | 2-thiophenyl- | Phenyl- | morpholine |  | 91 | [57] |
| **4f** | 5-bromo-2-hydroxy-$C_6H_4$- | Phenyl- | morpholine |  | 65 | [57] |

**TABLE 2** (Continued)

| Structure | $R^1$ | $R^2$ | Amine | Product | Yield(%)[b] | [Ref] |
|---|---|---|---|---|---|---|
| **4 g** | 4-$CO_2$Me-$C_6H_4$- | Phenyl- | morpholine |  | 89 | - |
| **4 h** | Propyl- | henyl- | morpholine |  | 38 | [56] |
| **4i** | butyl- | Phenyl- | morpholine |  | 42 | [58] |
| **4j** | isobutyl- | *ert*-butyl-$C_6H_4$- | morpholine |  | 52 | - |
| **4 k** | 3-methoxy-$C_6H_4$- | *tert*-butyl-$C_6H_4$- | morpholine |  | 90 | - |
| **4 l** | 2-thiophenyl- | *tert*-butyl-$C_6H_4$- | morpholine | | 85 | - |

(Continues)

**TABLE 2** (Continued)

| Structure | $R^1$ | $R^2$ | Amine | Product | Yield(%)[b] | [Ref] |
|---|---|---|---|---|---|---|
| | | | |  | | |
| **4 m** | 1-naphtyl- | *tert*-butyl-$C_6H_4$- | morpholine |  | 90 | - |
| **4n** | 5-chloro-2-hydroxy-$C_6H_4$- | *tert*-butyl-$C_6H_4$- | morpholine |  | 54 | - |
| **4O** | Phenyl- | Phenyl- | pyrrolidine |  | 83 | [59] |

[a]Rwaction conditions: mixture of aldehyde derivatives (1 mmol), amine (1.2 mmol), phenylacetylene derivatives (1.2 mmol), ChCl/urea (1 ml), CuCl (5 mol%), 60 °C, 15 hr; [b] Isolated yield.

medium (entry 10), the reaction's time was optimized. After the monitoring of the reaction, it was observed that by the increase of the reaction's time to 24 h, the amounts of unknown by-products were increased and the yield was decreased. Therefore, the less values for the reaction's time were examined and two new experiments in 15 and 10 hr were performed (entries 15 and 16, comparing with entry 10). According to these values, 15 hr (entry 15) showed the highest yield and this time was chosen as the best time for this reaction. Moreover, it was tried to use the other reaction temperatures (40, 50, 70, 80, 100 °C) to obtain the best temperature for the reaction (entries 17–21, comparing with entry 15). The results indicated that increasing temperature has wrecking effect on the yield of product because of the formation of various by-products and decreasing the temperature make the reaction much slower. Therefore, 60 °C (entry 15) was selected as the best temperature for this reaction. At the final optimization step, the catalyst amount was optimized and in addition to using 5 mol% of the catalyst (entry 15); 1, 3, 10 and 15 mol% of catalysts were used at the optimized conditions (entries 22–25). By the increase of the amount of catalyst from 1 to 5 mol%, the yield was increased and by more increase to 10 and 15 mol%, the

yield has not been changed. Therefore, 5 mol% (entry 15) is the optimized value of the employed catalyst for this reaction.

After the optimization of the reaction conditions, to show the efficiency of the introduced reaction and determine the effects of various substituents on the yield of the reaction, in addition to the model reaction, 15 different reactions were performed and the results were shown in Table 2. In these experiments, phenylacetylene and (4-tert butyl phenyl) acetylene were used as alkyne sources, in combination with various aliphatic and aromatic aldehydes. The yields were in the range of 38–52% for aliphatic aldehyde, 54–65% for salicylaldehyde and 73–91% for the other aromatic aldehydes. Unfortunately, the reaction did not produce the desired product when acyclic amines (such as dibutylamine, dicycloheylamine and dihexylamine) were used. The yields for the reactions of aliphatic aldehydes (propanal, butanal and 2-methyl propanal) were low, maybe because of the lower boiling points of these aldehydes, as the temperature used may exceed their boiling points.[60] The yields for the reactions involving salicylaldehyde derivatives (5-bromo and 5-chloro) were low because of the possible formation of benzofuran derivatives.[61] Among aromatic aldehydes, the derivatives with electron donor groups showed higher yields than the other aldehydes and the highest yields were belong to the reactions involving thiophen carbaldehyde.

To complete this work, the recoverability of ChCl-urea in the model reaction using the optimized conditions was examined and the results were shown in Figure 1. After each run, the eutectic solvent (ChCl-urea) was isolated from the product and reused in the next run. As shown in this figure, ChCl-urea could be reused at least three runs with 30% loss of its activity.

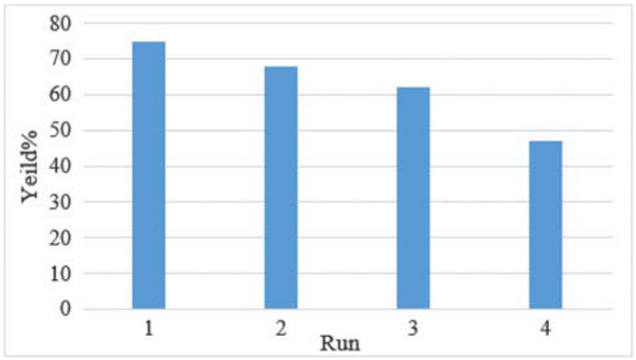



**FIGURE 1** The result of the experiments related to the reusability of the DES

The main outcome of this research is the successful synthesis of propargylamines under green conditions and using available and inexpensive catalysts. Due to the applicability of this protocol for this synthesis, it has been compared with the previous related reports. The results of this comparison were presented in Table 3 and the advantages of this work are using DESs instead of toxic and volatile organic solvents and employing inexpensive and available metal salts instead of expensive catalysts with time-consuming methods. Moreover, using little mass value of catalyst in reaction under relatively low temperature condition is another advantage of this research.

**TABLE 3** Comparisons of ChCl-urea/CuCl with other recent reports of reaction condition for the synthesis of propargylamine

| Entry | Catalyst | reaction conditions | Time (hr) | Catalyst amount | Yield (%) | [Ref] |
|---|---|---|---|---|---|---|
| **1** | Zn $(OAC)_2.2H_2O$ | toluene/reflux | 14–17 | 10% | 68–98 | [56] |
| **2** | $[Cu(N_2S_2)]Cl$@Y-zeolite | DCE/70 °C | 12–20 | 10% | 78–91 | [62] |
| **3** | MCM-TSCuI | toluene/80 °C | 4–10 | 10% | 81–93 | [63] |
| **4** | ZnS nano | $CH_3CN$/reflux | 4–6 | 10% | 89–94 | [64] |
| **5** | CuBr | toluene/MW/100 °C | 0.42 | 20% | 42–94 | [65] |
| **6** | CuBr | $[Bmim]PF_6$ | 3.5–6.5 | 30% | 81–89 | [66] |
| **7** | $SiO_2$-NHC-CuI | Solventless/r.t | 24 | 20% | 43–96 | [67] |
| **8** | Cu $(OTf)_2$ | Ball-milling/25 Hz | 0.17–0.5 | 10% | 90–99 | [68] |
| **9** | CuI | Neat/MW/100 °C | 0.42 | 20% | 21–82 | [69] |
| **10** | Au-NPs-$Fe_3O_4$-rGO | DMSO/90 °C | 6 | 25 mg | 89–97 | [70] |
| **11** | Ag@HNT-T | $H_2O$/100 W/r.t | 0.25–0.67 | 25 mg | 80–94 | [71] |
| **12** | CuI | PEG/100 °C | 12 | 10% | 85–94 | [72] |
| **13** | CuBr | toluene/25 °C | 36 | 20% | 68–96 | [73] |
| **14** | **CuCl** | **ChCl-urea/60 °C** | **15** | **5%** | **36–91** | **This work** |

## 4 | CONCLUSION

In summary, using ChCl/urea DES as a substitution for toxic and volatile organic solvents and CuCl as a catalyst, a green and applicable methodology for the synthesis propargylamine derivatives was presented. The employed media and catalyst were non-expensive, biocompatible and the used methodology and work-up process were easy. 15 different derivatives with various structural parts were prepared mostly in good yields. Using aromatic aldehydes give higher yield than aliphatic ones. The smaller yields were due to the lower boiling point of the employed aliphatic aldehydes and formation of benzofuran byproduct in the use of salicylaldehyde derivatives. Moreover, aromatic aldehydes with electron-donor substituents showed higher yields because of the easier formation of iminium salts using these aldehydes.

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## SUPPLEMENTARY DATA

Supplementary data associated (IR, Mass and NMR spectra) with this article can be found, in the online version, at DOI:

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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