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Article

Synthesis of Tetrahydro-β-carboline Derivatives under Electrochemical Conditions in Deep Eutectic Solvents

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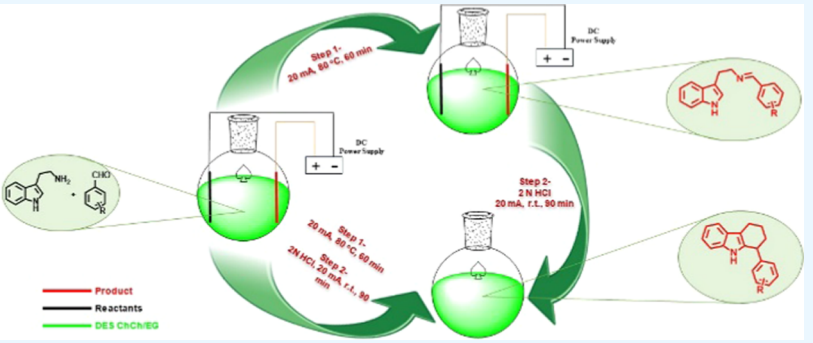

ABSTRACT: In this work, a novel, green, and atom-efficient method for the synthesis of tetrahydro-β-carboline derivatives using electrochemistry (EC) in deep eutectic solvents (DESs) was reported. The EC reaction conditions were optimized to achieve the highest yield. The experimental design was also optimized to perform the reaction in a two-step, one-pot reaction, thereby the time, workup procedure, and solvents needed were all reduced. The new approach achieved our strategy as EC served to decrease the time of reaction, eliminate the use of hazardous catalysts, and lower the energy required for the synthesis of the targeted compounds. On the other side, DESs were used as catalysts, in situ electrolytes, and noninflammable green solvents. The scope of the reaction was investigated using different aromatic aldehydes. Finally, the scalability of the reaction was investigated using a gram-scale reaction that afforded the product in an excellent yield.

1. INTRODUCTION

The β-carboline ring is present in many naturally occurring alkaloids with variable biological activities such as anticancer, antimicrobial, anti-Alzheimer, antimalarial, anti-inflammatory, antihypertensive, analgesic, and vasorelaxant activities.[1−7] There is a wide interest in the development of novel synthetic approaches,[3,8] especially green methods for the preparation of β-carboline derivatives.[9] The green methods used for the synthesis of β-carbolines include the use of microwave[10,11] and ultrasonic irradiation,[12] as well as the use of various types of catalysts including heterogeneous, organometallic,[13,14] inorganic salts,[15] organic,[16,17] natural,[18,19] and enzymatic catalysis.[20] However, most of these methods require hazardous and corrosive reagents, long reaction times, expensive catalysts, or complicated apparatus. This initiates the need for the development of more eco-friendly methods for the synthesis of β-carboline scaffolds.

Throughout the past decade, electrochemistry (EC) has attracted increasing interest as a technique for the synthesis of organic compounds.[21] It provides an atom-efficient approach for performing selective oxidative or reductive reactions using electron flow to perform the rule of heterogeneous catalysts. Thus, EC reduces or eliminates the employment of additional hazardous chemical catalysts and oxidizing or reducing agents, resulting in highly atom-economical reactions. In addition, electrochemical synthesis offers the advantages of the elimination of waste generation, completion of reactions in a short time, and reduction of energy utilization. Accordingly, electrochemical organic synthesis is considered a sustainable and greener synthetic pathway.[22−27]

Deep eutectic solvents (DESs) are a new class of green solvents related to ionic liquids and characterized by significantly lower melting points than the individual components. DESs have received a lot of attention for being used as low-cost solvents and catalysts in the last two decades.[28] Abbott et al. described the preparation of DES for the first time in 2003 by heating choline chloride and urea.[29] As mentioned before, DESs are classified as ionic liquids, but they are more readily prepared by simply mixing and heating two or more components. DESs are formed of H-bond donors

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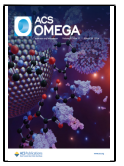

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Scheme 1. General Synthesis of Tetrahydro-β-carboline Derivatives under Electrochemical Conditions

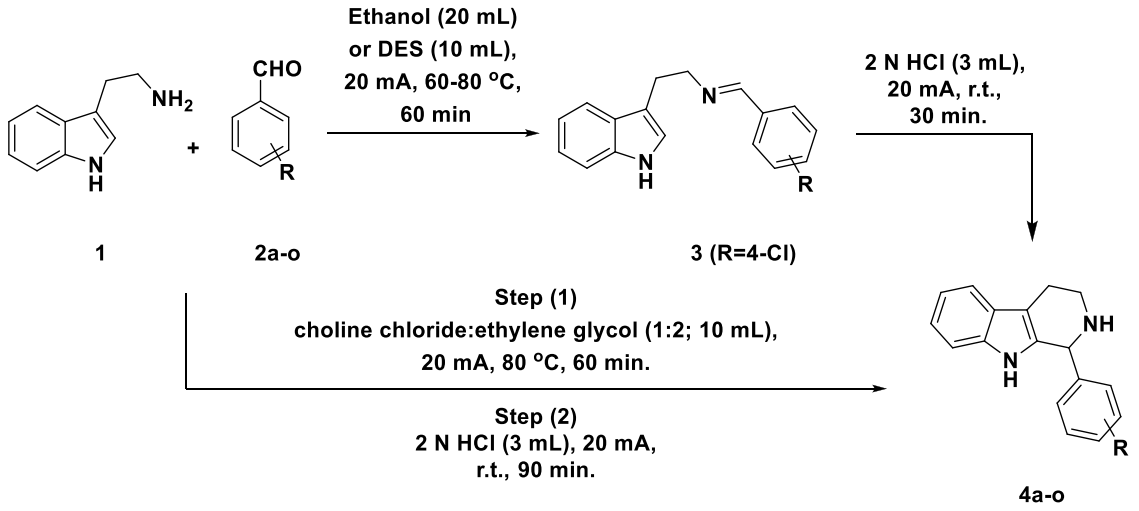
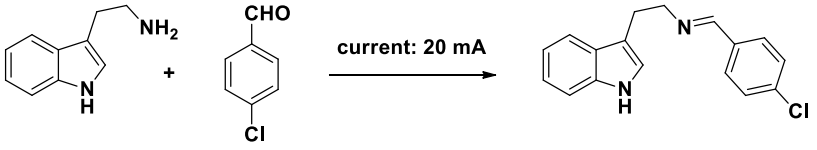


Table 1. Synthesis of *N*-(4-Chlorobenzylidine)-2-(1*H*-indol-3-yl)ethanamine (3) under Electrochemical Conditions in Organic Solvents[a]



entry	solvent	temp (°C)	time (min)	electrolyte	cathode	anode	yield (%)[b]
1	ethanol	60	35	NaBr	graphite	graphite	75%
2	acetonitrile	60	35	$(Bu)_4NPF_6$	graphite	graphite	41%
3	acetic acid	60	35	NaBr	graphite	graphite	oxid.
4	ethanol	60	60	NaBr	graphite	graphite	80%
5	ethanol	R.T.	120	NaBr	graphite	graphite	68%
6	ethanol	60	60	$(Bu)_4NPF_6$	graphite	graphite	62%
7	ethanol	60	60	$NaClO_4$	graphite	graphite	61%
8	ethanol	60	60	NaBr	copper	graphite	70%
9	ethanol	60	60	NaBr	platinum	graphite	57%
10	ethanol	60	60	NaBr	graphite	platinum.	64%

[a]Reaction conditions: **1** (2 mmol), **2a** (2.2 mmol), organic solvents (20 mL), using a constant current of 20 mA. [b]Isolated yield, Oxid.: oxidation of the product.

(HBDs) like urea and H-bond acceptors (HBAs) like choline chloride, which are mixed until they form a homogeneous liquid that can be utilized without further purification. DESs serve as green solvents and catalysts for many organic reactions.[30] DESs are considered green solvents as they are characterized by being biodegradable, noninflammable, biocompatible, thermally stable, nontoxic, and inexpensive. They can be collected and recycled numerous times without significant reduction in their catalytic activity.[26,31−35]

Searching the literature indicated that the β-carboline ring was not prepared earlier using DES or under EC conditions. In this article, we reported the first green synthesis of β-carboline derivatives under electrochemical conditions in DESs in a two-step, one-pot reaction (Scheme 1). The reaction conditions were optimized, and the scope of the reaction was investigated using different aldehydes. A comparison between the conventional methods and the green chemistry methods was performed for each step in this work to prove the efficiency of the developed green methods. Using electrochemistry along with DES achieved the benefits of EC synthesis in reducing the reaction time and eliminating the use of hazardous chemicals as well as the supporting electrolyte.

2. EXPERIMENTAL PART

2.1. General. The melting points were measured using the Stuart SMP10 apparatus and are uncorrected. The IR spectral data were recorded on a Shimadzu IR 435 spectrophotometer, Faculty of Pharmacy, Cairo University, Cairo, Egypt, and the values were expressed in cm^{-1}. The ^1H NMR spectra were carried out on a Bruker 400 MHz (Bruker Corp, Billerica, MA) spectrophotometer, Faculty of Pharmacy, Cairo University, Cairo, Egypt. Tetramethylsilane (TMS) was used as an internal standard. The chemical shifts were recorded in ppm on a δ scale, and coupling constant (J) values were approximated in Hz. ^{13}C NMR spectra were obtained using a Bruker 100 MHz (Bruker Corp, Billerica, MA) spectrophotometer, Faculty of Pharmacy, Cairo University, Cairo, Egypt, using tetramethylsilane (TMS) as the internal standard, and chemical shifts were recorded in ppm on a δ scale. The progress of the reactions

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was monitored by thin-layer chromatography (TLC) using silica gel-coated aluminum sheets Merck 60F 254. The solvent system used was [chloroform: toluene: methanol (4:2:1)]. Zhaoxin RXN-305D direct current power supply was used as a source of electric current in the reactions. The cyclic voltammetric characterizations were performed utilizing the electrochemical workstation PGSTA204 potentiostat/galvanostat (Metrohm Autolab) regulated by NOVA software 1.11.1. The C, H, and N microanalyses were carried out at the regional center of mycology and biotechnology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.

2.2. Preparation of Deep Eutectic Solvents (DESs). Deep eutectic solvents were prepared using the techniques described in the literature.[26,36] The prepared DESs consisted of two main components. Choline chloride, which was constant in all DESs, was mixed with the second component (ethylene glycol, propylene glycol, glycerol, or urea) in a ratio of 1:2 and heated in a water bath at 80 °C. The clear solution obtained was used directly without any modification or purification.

2.3. Synthesis of *N*-(4-Chlorobenzylidine)-2-(1*H*-indole-3-yl)ethanamine (3). *2.3.1. Under Electrochemical Conditions in Organic Solvents.* A mixture of tryptamine **1** (2 mmol), 4-chlorobenzaldehyde **2a** (2.2 mmol), and supporting electrolyte (0.1 M) was dissolved in organic solvents (20 mL) in an undivided cell equipped with the necessary electrodes (Table 1). The reaction was conducted at a constant current (20 mA), different temperatures, different reaction times, and different electrolytes. The results are recorded in Table 1. Thin-layer chromatography was used to monitor the progress of the reaction. The formed product was filtered and recrystallized from ethanol.

2.3.2. Using Conventional Method in DESs. A mixture of tryptamine **1** (2 mmol) and 4-chlorobenzaldehyde **2a** (2.2 mmol) was suspended in the corresponding DES (10 mL). The reaction mixture was heated in a water bath at 80 °C for 150 min (Table 2). Thin-layer chromatography was used to monitor the progress of the reaction. The reaction was poured onto water (20 mL), and the solid formed was filtered and dried. The product was recrystallized from ethanol to yield compound **3**.

Table 2. Synthesis of *N*-(4-Chlorobenzylidine)-2-(1*H*-indol-3-yl)ethanamine (3) in Various DESs[a]

entry	DES components		yield (%)[b]
1	choline chloride	ethylene glycol (1:2)	73
2	choline chloride	propylene glycol (1:2)	61
3	choline chloride	glycerol (1:2)	94
4	choline chloride	urea (1:2)	27

[a]Reaction conditions: **1** (2 mmol), **2a** (2.2 mmol), in DES (10 mL), heated at 80 °C. for 150 min. [b]Isolated yield.

2.3.3. Under Electrochemical Conditions in DESs. A mixture of tryptamine **1** (2 mmol) and 4-chlorobenzaldehyde **2a** (2.2 mmol) was suspended in the corresponding DES (10 mL) in an undivided cell equipped with graphite as both anode and cathode. The reaction was conducted at a constant current (20 mA), a constant temperature (80 °C), and a constant reaction time (60 min), and the results are recorded in Table 3. Thin-layer chromatography was used to monitor the progress of the reaction. The reaction was poured onto water (20 mL), and the solid formed was filtered, dried, and recrystallized from ethanol.

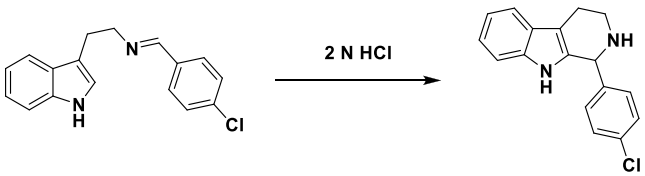
Table 3. Synthesis of *N*-(4-Chlorobenzylidine)-2-(1*H*-indol-3-yl)ethanamine (3) under Electrochemical Conditions in DESs[a]

entry	DES components		yield (%)[b]
1	choline chloride	ethylene glycol (1:2)	94
2	choline chloride	glycerol (1:2)	80
3	choline chloride	propylene glycol (1:2)	84

[a]Reaction conditions: **1** (2 mmol), **2a** (2.2 mmol), in DES (10 mL), heating at 80 °C, for 60 min, using a constant current of 20 mA, Graphite was used as the anode and cathode. [b]Isolated yield.

2.4. Synthesis of 1-(4-Chlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4a). *2.4.1. Under Conventional Conditions in Organic Solvent.* A mixture of Schiff's base **3** (0.35 mmol) and 2 N HCl (3 mL) was dissolved in ethanol (5 mL). The reaction was stirred at room temperature for 4 h. The solid formed was filtered, dried, and recrystallized from ethanol. Compound **4a** was obtained in a 90% yield as shown in entry 1, Table 4.

Table 4. Cyclization of *N*-(4-Chlorobenzylidine)-2-(1*H*-indol-3-yl)ethanamine (3) to Form 1-(4-Chlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4a)[a]



3 4a

entry	method	solvent	current	time	yield (%)[b]
1	conventional stirring	ethanol		4 h	90
2	electrochemical	ethanol	20 mA	20 min	60
3	electrochemical	DES[c]	20 mA	30 min	90

[a]Reaction conditions: compound **3** (0.35 mmol), 3 mL of 2 N HCl, stirring at room temperature. [b]Isolated yield. [c]DES used was choline chloride: ethylene glycol (1:2).

2.4.2. Under Electrochemical Conditions in Organic Solvent or DES. A mixture of Schiff's base **3** (0.35 mmol) and 2 N HCl (3 mL) was dissolved in either ethanol (5 mL) or DES formed of choline chloride/ethylene glycol (1:2; 5 mL). The reaction was stirred at room temperature for 20−30 min in an undivided cell equipped with graphite as both anode and cathode at a constant current of 20 mA. Water (20 mL) was added for washing. The formed precipitate was filtered and recrystallized from ethanol. The results are recorded in entries 2 and 3, Table 4.

2.4.3. Under Electrochemical Conditions in Organic Solvent and DES in a Two-Step, One-Pot Approach. A mixture of tryptamine **1** (2 mmol) and 4-chlorobenzaldehyde **2a** (2.2 mmol) was suspended in ethanol (10 mL) using NaBr as an electrolyte or choline chloride/ethylene glycol (1:2; 10 mL) in an undivided cell equipped with graphite as both anode and cathode. Constant current (20 mA) was used at different temperatures, and the results are reported in Table 5. Then, the reaction was cooled, 2 N HCl (3 mL) was added in the second step, and the reaction was conducted for 60−90 min under different conditions as seen in Table 5. Water (20 mL)

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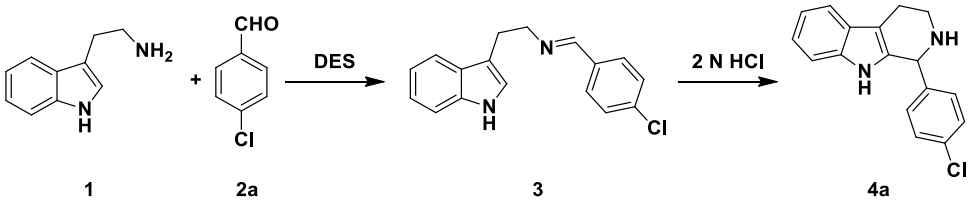
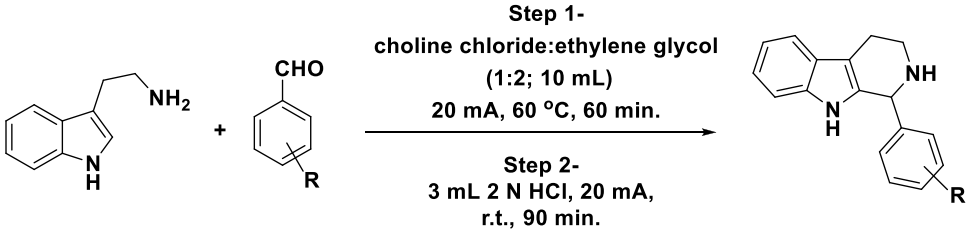
Table 5. Synthesis and Optimization of 1-(4-Chlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole 4a under Electrochemical Conditions in a Two-Step, One-Pot Reaction[a]



		step 1		step 2		
entry	electrolyte/solvent	temp (°C)	time (min)	temp (°C)	time (min)	yield (%)[b]
1	NaBr/ethanol	60	60	60	30	48
2	NaBr/ethanol	60	60	60	60	58
3	choline chloride−ethylene glycol	80	60	80	60	53
4	choline chloride−ethylene glycol	80	60	R.T.	60	75
5	choline chloride−ethylene glycol	80	60	R.T.	30	66
6	choline chloride−ethylene glycol	80	60	R.T.	90	78
7	choline chloride−ethylene glycol	80	60	R.T.	120	71

[a]Reaction conditions: First step: **1** (2 mmol), **2a** (2.2 mmol), in NaBr/ethanol or DES (10 mL), using a constant current of 20 mA, Second step: 2 N HCl (3 mL) was added, a constant current of 20 mA. Graphite was used as an anode and cathode. [b]Isolated yield.

Table 6. Electrochemical Synthesis of Tetrahydro-*β*-carboline Derivatives in DES[a]



compound	R	yield (%)[b]	melting point (°C)	refs
4a	4-Cl	78%	260−261	38
4b	H	41%	251−252	40
4c	4-Br	99.4%	268−270	41
4d	4-F	79%	238−240	38
4e	3-OH	81%	266−268	42
4f	4-CH_3	98%	261−263	41
4g	4-OCH_3	96%	248−250	43
4h	4-benzyloxy	98%	215−216	not reported
4i	3,4-$(OCH_3)_2$	99%	273−275	12
4j	3,4,5-$(OCH_3)_3$	86%	263−265	12
4k	4-$COOCH_3$	30%	217−219	not reported
4l	4-NO_2	85%	247−249	38
4m	2-CF_3	56%	150−153	not reported
4n	4-OH	oxid.	_____	_____
4o	3-OCH_3−4−OH	oxid.	_____	_____

[a]Reaction conditions: First step: **1** (2 mmol), **2a−o** (2.2 mmol), in DES (10 mL), at 80 °C, using a constant current of 20 mA, Second step: 2 N HCL (3 mL) was added, using a constant current of 20 mA. Graphite was used as an anode and cathode. [b]Isolated yield, Oxid.: Oxidation of the product.

was added for washing. After filtration, the residue was recrystallized from ethanol.

2.5. Electrochemical Synthesis of 2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole Derivatives 4b−o in DES in a Two-Step, One-Pot Reaction. A mixture of tryptamine **1** (2 mmol) and aromatic aldehyde **2b−o** (2.2 mmol) was suspended in choline chloride/ethylene glycol (1:2; 10 mL) in an undivided cell equipped with graphite as both anode and cathode. The reaction was performed at a constant current (20 mA), at 80 °C, for 60 min. Then, the reaction was cooled, 2 N HCl (3 mL) was added in the second step, and the electrochemical reaction was performed at room temperature and constant current (20 mA), for 90 min. Water (20 mL) was

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added for washing. After filtration, the precipitate was recrystallized from ethanol. The results are shown in Table 6

2.6. Cyclic Voltammetry Study. All cyclic voltammetric measurements were performed on an electrochemical workstation (Metrohm Autolab PGSTAT204 potentiostat/galvanostat) using NOVA software version 1.11.1. The standard three-electrode configuration was employed: Pt wire was used as the counter electrode, Ag/AgCl was the reference electrode, and pencil graphite electrode (PGE) was the working electrode (HP, 0.9 mm diameter). Two different supporting electrolyte solutions were used: ethanol/0.1 M NaBr and choline chloride/ethylene glycol (1:2). The solvents were degassed by using N_2 for 10 min before measurements, and the experiments were carried out at 80 °C. All of the data are represented in Figures 3−5.

2.7. Scaling Up of Compound 4c. A mixture of tryptamine **1** (6 mmol) and 4-bromobenzaldehyde **2c** (6.6 mmol) was suspended in choline chloride/ethylene glycol (1:2; 10 mL) in an undivided cell equipped with graphite as both anode and cathode. The electrochemical reaction was conducted at a constant current (20 mA) and at 80 °C for 60 min. The reaction was cooled, 2 N HCl (3 mL) was added, and the reaction was conducted at room temperature for 90 min at a constant current of 20 mA. Water (50 mL) was added for washing. After filtration, the precipitate was recrystallized from ethanol. Product **4c** was obtained in a 96.33% yield (1.89 g).

2.8. Spectral Data of the Prepared Compounds. *2.8.1. N-(4-Chlorobenzylidine)-2-(1H-indole-3-yl)-ethanamine (**3**).* IR: 3174 (NH), 1643 (C═N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.03−3.08 (t, 2H, CH_2, J = 6 Hz), 3.85−3.90 (t, 2H, CH_2, J = 6 Hz), 6.95−6.97 (t, 1H, ArH, J = 9 Hz), 7.04−7.09 (t, 1H, ArH, J = 9 Hz), 7.14 (s, 1H, ArH), 7.33−7.36 (d, 1H, ArH, J = 9 Hz), 7.47−7.50 (d, 2H, ArH, J = 9 Hz), 7.56−7.59 (d, 1H, ArH, J = 9 Hz), 7.72−7.75 (d, 2H, ArH, J = 9 Hz), 8.26 (s, 1H, ═CH), 10.78 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 61.4, 111.3, 112.2, 118.1, 118.4, 120.8, 122.8, 127.2, 128.7, 129.4, 135.01, 135.07, 136.1, 159.5 ppm; anal. calculated for $C_{17}H_{15}ClN_2$ (282.77): C, 72.21; H, 5.35; N, 9.91; found: C,72.34; H, 5.59; N, 10.07.

*2.8.2. 1-(4-Chlorophenyl)-2,3,4,9,tetrahydro-1H-pyrido-[3,4-b]indole (**4a**).* IR: 3406 (NH), 3251 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.99−3.15 (m, 2H, CH_2), 3.44−3.47 (t, 2H, CH_2, J = 6.4 Hz), 6.00 (s, 1H, CH), 7.05−7.08 (t, 1H, ArH, J = 6.8 Hz), 7.12−7.16 (t, 1H, ArH, J = 6.8 Hz), 7.30−7.31 (d, 1H, ArH, J = 8.0 Hz), 7.40−7.42 (d, 2H, ArH, J = 8.4 Hz), 7.54−7.56 (d, 1H, ArH, J = 7.6 Hz), 7.59−7.61 (d, 2H, ArH, J = 8.4), 9.23, 9.74 (two s, 1H, NH, D_2O exchangeable), 10.91 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.6, 40.5, 55.3, 107.9, 112.0, 118.7, 119.6, 122.6, 126.0, 128.3, 129.4, 132.3, 133.9, 135.1, 136.9; anal. calculated for $C_{17}H_{15}ClN_2$ (282.77): C, 72.21; H, 5.35; N, 9.91; found: C,72.45; H, 5.62; N, 10.12.

*2.8.3. 1-Phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**4b**).* IR: 3433 (NH), 3217 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.99−3.07 (m, 1H, CH), 3.14−3.21 (m, 1H, CH), 3.39−3.50 (m, 2H, CH_2), 5.92 (s, 1H, CH), 7.03−7.07 (t, 1H, ArH, J = 7.2 Hz), 7.10−7.14 (t, 1H, ArH, J = 7.2 Hz), 7.30−7.32 (d, 1H, ArH, J = 8 Hz), 7.44−7.49 (m, 5H, ArH), 7.52−7.54 (d, 1H, ArH, J = 8.0 Hz), 10.16 (s, 1H, NH, D_2O exchangeable), 10.90 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 55.9, 72.7, 107.9, 112.02, 118.6, 119.4, 122.3, 126.1, 128.9, 129.2, 130.1, 130.4, 135.1, 137.0 ppm; anal. calculated for $C_{17}H_{16}N_2$ (248.32): C, 82.22; H, 6.49; N, 11.28; found: C, 81.98; H, 6.65; N, 11.47.

*2.8.4. 1-(4-Bromophenyl)-2,3,4,9,tetrahydro-1H-pyrido-[3,4-b]indole (**4c**).* IR: 3394 (NH), 3251 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.98−3.05 (m, 1H, CH), 3.11−3.18 (m, 1H, CH), 3.42−3.48 (m, 2H. CH_2), 5.92 (s, 1H, CH), 7.03−7.07 (t, 1H, ArH, J = 8 Hz), 7.11−7.15 (t, 1H, ArH, J = 8 Hz), 7.29−7.31 (d, 1H, ArH, J = 8 Hz), 7.38−7.40 (d, 2H, ArH, J = 8 Hz), 7.52−7.54 (d, 1H, ArH, J = 8 Hz), 7.69−7.71 (d, 2H, ArH, J = 8 Hz), 10.01 (brs, 1H, NH, D_2O exchangeable), 10.87 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.0, 55.41, 55.49, 108.0, 111.9, 118.6, 119.4, 122.3, 123.4, 126.1, 129.0, 132.0, 132.6, 134.9, 136.9 ppm; anal. calculated for $C_{17}H_{15}BrN_2$ (327.22): C, 62.40; H, 4.62; N, 8.56; found: C, 62.63; H, 4.80; N, 8.73.

*2.8.5. 1-(4-Fluorophenyl)-2,3,4,9,tetrahydro-1H-pyrido-[3,4-b]indole (**4d**).* IR: 3387 (NH), 3259 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.00−3.06 (m, 1H, CH), 3.12−3.19 (m, 1H, CH), 3.40−3.51 (m, 2H, CH_2), 5.96 (s, 1H, CH), 7.03−7.07 (t, 1H, ArH, J = 8 Hz), 7.11−7.15 (t, 1H, ArH, J = 8 Hz), 7.29−7.31 (d, 2H, ArH, J = 8 Hz), 7.33−7.35 (d, 2H, ArH, J = 8 Hz), 7.47−7.51 (m, 1H, ArH), 7.53−7.55 (d, 1H, ArH, J = 8 Hz), 9.65, 10.43 (two s, 1H, NH, D_2O exchangeable), 10.89 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 53.5, 55.2, 107.9, 112.0, 115.9, 116.1, 118.6, 119.5, 122.4, 126.1, 128.9, 131.41, 131.44, 132.8, 132.9, 136.9, 162.0, 164.4 ppm; anal. calculated for $C_{17}H_{15}FN_2$ (266.31): C, 76.67: H, 5.68; N, 10.52; found: C, 76.49: H, 5.79; N, 10.61.

*2.8.6. 3-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-phenol (**4e**).* IR: 3400 (OH), 3298 (NH), 3151 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.98−3.05 (m, 1H, CH), 3.08−3.14 (m, 1H, CH), 3.40−3.46 (m, 2H, CH_2), 5.83 (s, 1H, CH), 6.77 (s, 1H, ArH), 6.87−6.91 (m, 2H, ArH), 7.03−7.07 (t, 1H, ArH, J = 8 Hz), 7.11−7.15 (t, 1H, ArH, J = 8 Hz), 7.27−7.32 (m, 2H, ArH), 7.52−7.54 (d, 1H, ArH, J = 8 Hz), 9.33, 10.27 (two s, 1H, NH, D_2O exchangeable), 9.75 (s, 1H, OH, D_2O exchangeable), 10.92 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 40.5, 55.8, 107.7, 112.0, 117.0, 117.1, 118.6, 119.4, 120.8, 122.3, 126.1, 128.9, 130.3, 136.4, 136.9, 158.1 ppm; anal. calculated for $C_{17}H_{16}N_2O$ (264.32): C, 77.25; H, 6.10; N, 10.60; found: C, 77.43; H, 6.26; N, 10.48.

*2.8.7. 1-(p-Tolyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]-indole (**4f**).* IR: 3333 (NH), 3224 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 2.98−3.05 (m, 1H, CH), 3.15−3.19 (m, 1H, CH), 3.48−3.51 (m, 2H, CH_2), 5.86 (s, 1H, CH), 7.02−7.06 (t, 1H, ArH, J = 7.2 Hz), 7.09−7.13 (t, 1H, ArH, J = 7.2 Hz), 7.28−7.33 (m, 5H, ArH), 7.51−7.53 (d, 1H, ArH, J = 8 Hz), 9.59, 10.53 (two s, 1H, NH, D_2O exchangeable), 10.85 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 55.7, 60.7, 72.7, 107.8, 112.0, 118.6, 119.4, 122.3, 126.1, 129.2, 129.7, 130.3, 132.2, 136.9, 139.6 ppm; anal. calculated for $C_{18}H_{18}N_2$ (262.15): C, 82.41; H, 6.92; N, 10.68; Found: C, 82.20; H, 7.14; N, 10.94.

*2.8.8. 1-(4-Methoxyphenyl)-2,3,4,9,tetrahydro-1H-pyrido-[3,4-b]indole (**4g**).* IR: 3421 (NH), 3228 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.98−3.04 (m, 1H, CH), 3.17−3.21 (m, 1H, CH), 3.41−3.45 (m, 2H, CH), 3.79 (s, 3H, CH_3), 5.83 (s,1H, CH), 7.01−7.06 (m, 3H, ArH), 7.09−7.13 (t, 1H, ArH, J = 8 Hz), 7.29−7.31 (d, 1H, ArH, J = 8 Hz), 7.35−7.36 (d, 2H, ArH, J = 8 Hz), 7.50−7.52 (d, 1H, ArH, J = 8 Hz),

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9.72, 10.64 (two brs, 1H, NH, D_2O exchangeable), 10.86 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 53.5, 55.4, 67.3, 107.7, 111.9, 114.4, 118.5, 119.3, 122.2, 126.1, 127.0, 129.4, 131.9, 136.9, 160.6 ppm; anal. calculated for $C_{18}H_{18}N_2O$ (278.35): C, 77.67; H, 6.52; N, 10.06; found: C, 77.94; H, 6.35; N, 10.28.

*2.8.9. 1-(4-(Benzyloxy)phenyl)-2,3,4,9,tetrahydro-1H-pyrido[3,4-b]indole (**4h**).* IR: 3287 (NH), 3255 (NH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.98−3.05 (m, 1H, CH), 3.10−3.18 (m, 1H, CH), 3.39−3.46 (m, 2H, CH_2), 5.17 (s, 2H, CH_2), 5.86 (s, 1H, CH), 7.03−7.07 (t, 1H, ArH, J = 8 Hz), 7.10−7.14 (m, 3H, ArH), 7.29−7.36 (m, 4H, ArH), 7.39−7.44 (m, 2H, ArH), 7.45−7.48 (m, 2H, ArH), 7.52−7.54 (d, 1H, ArH, J = 8 Hz), 9.47, 10.35 (two s, 1H, NH, D_2O exchangeable), 10.87 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 40.4, 55.5, 69.7, 107.8, 111.9, 115.3, 118.6, 119.4, 122.3, 126.1, 127.2, 128.1, 128.3, 128.9, 129.2, 131.8, 136.9, 137.3, 159.7 ppm; anal. calculated for $C_{24}H_{22}N_2O$ (354.44): C, 81.33; H, 6.26; N, 7.90; found: C, 81.07; H, 6.43: N, 8.07.

*2.8.10. 1-(3,4-Dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**4i**).* IR: 3344 (NH), 3318 (NH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.98−3.05 (m, 1H, CH), 3.12−3.19 (m, 1H, CH), 3.41−3.48 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.86 (s, 1H, CH), 6.84−6.86 (d, 1H, ArH, J = 8.4 Hz), 7.03−7.07 (m, 2H, ArH), 7.10−7.14 (t, 1H, ArH, J = 8 Hz), 7.17 (s, 1H, ArH), 7.29−7.31 (d, 1H, ArH, J = 8 Hz), 7.52−7.54 (d, 1H, ArH, J = 7.6 Hz), 9.49, 10.14 (two s, 1H, NH, D_2O exchangeable), 10.86 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 39.5, 40.6, 56.10, 56.13, 107.6, 111.9, 112.0, 113.8, 118.6, 119.4, 122.3, 122.8, 126.1, 127.0, 129.2, 136.9, 149.1, 150.3 ppm; anal. calculated for $C_{19}H_{20}N_2O_2$ (308.15): C, 74.00; H, 6.54; N, 9.08; found: C, 74.24; H, 6.63; N, 9.30.

*2.8.11. 1-(3,4,5-Trimethoxyphenyl)-2,3,4,9,tetrahydro-1H-pyrido[3,4-b]indole (**4j**).* IR: 3653 (NH), 3356 (NH); ^1H NMR (400 MHz, DMSO-d_6): δ 2.98−3.04 (m, 1H, CH), 3.17−3.25 (m, 1H, CH), 3.39−3.44 (m, 1H, CH), 3.53−3.58 (m, 1H, CH), 3.71 (s, 3H, OCH_3), 3.76 (s, 6H, two OCH_3), 5.85 (s, 1H, CH), 6.85 (s, 2H, ArH), 7.03−7.07 (t, 1H, ArH, J = 8 Hz), 7.10−7.14 (t, 1H, ArH, J = 8 Hz), 7.30−7.33 (d, 1H, ArH, J = 8 Hz), 7.52−7.54 (d, 1H, ArH, J = 8 Hz), 9.74, 10.28 (two s, 1H, NH, D_2O exchangeable), 10.84 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 41.4, 56.5, 56.8, 60.4, 107.6, 107.8, 112.0, 118.6, 119.4, 122.3, 126.2, 129.1, 130.3, 137.0, 138.8, 153.4 ppm; anal. calculated for $C_{20}H_{22}N_2O_3$ (338.16): C, 70.99; H, 6.55; N, 8.28; found: C, 71.18; H, 6.48; N, 8.52.

*2.8.12. Methyl 4-(2,3,4,9,tetrahydro-1H-pyrido[3,4-b]-indol-1-yl)benzoate (**4k**).* IR: 3414 (NH), 3224 (NH), 1716 (ester C═O); ^1H NMR (400 MHz, DMSO-d_6): δ 3.00−3.07 (m,1H, CH), 3.17−3.22 (m, 1H, CH), 3.81−3.84 (m, 2H, CH), 3.88 (s, 3H, CH_3), 6.02 (s, 1H, CH), 7.03−7.07 (t, 1H, ArH, J = 8 Hz), 7.10−7.14 (t, 1H, ArH, J = 8 Hz), 7.29−7.31 (d, 1H, ArH, J = 8 Hz), 7.53−7.55 (d, 1H, ArH, J = 8 Hz), 7.61−7.62 (d, 2H, ArH, J = 8 Hz), 8.03−8.05 (d, 2H, ArH, J = 8 Hz), 10.39 (s, 1H, NH, D_2O exchangeable), 10.92 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 53.5, 55.5, 67.3, 108.0, 112.0, 118.6, 119.5, 122.4, 126.1, 128.6, 129.8, 131.02, 131.07, 137.0, 140.1, 166.3 ppm; anal. calculated for $C_{19}H_{18}N_2O_2$ (306.36): C, 74.49; H, 5.92; N, 9.14; found: C, 74.31; H, 6.07; N, 9.40.

*2.8.13. 1-(4-Nitrophenyl)-2,3,4,9,tetrahydro-1H-pyrido-[3,4-b]indole (**4l**).* IR: 3387 (NH), 3278 (NH), 1519, 1350 (NO_2); ^1H NMR (400 MHz, DMSO-d_6): δ 3.04−3.09 (m, 1H, CH), 3.12−3.19 (m, 1H, CH), 3.41−3.48 (m, 2H, CH_2), 6.15 (s, 1H, CH), 7.05−7.09 (t, 1H, ArH, J = 8 Hz), 7.12−7.16 (t, 1H, ArH, J = 8 Hz), 7.30−7.32 (d, 1H, ArH, J = 8 Hz), 7.55−7.57 (d, 1H, ArH, J = 8 Hz), 7.72−7.74 (d, 2H, ArH, J = 8 Hz), 8.34−7.36 (d, 2H, ArH, J = 8 Hz), 9.82, 10.53 (two s, 1H, NH, D_2O exchangeable), 10.93 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 40.7, 55.1, 108.2, 112.0, 118.7, 119.6, 122.6, 124.1, 126.0, 128.1, 132.2, 137.0, 142.0, 148.7 ppm; anal. calculated for $C_{17}H_{15}N_3O_2$ (293.32): C, 69.61; H, 5.15; N, 14.33; found: C, 69.95; H, 5.38; N, 14.58.

*2.8.14. 1-(2-(Trifluoromethyl)phenyl)-2,3,4,9,tetrahydro-1H-pyrido[3,4-b]indole (**4m**).* IR: 3390 (NH), 3305 (NH); ^1H NMR (300 MHz, DMSO-d_6): δ 2.67−2.72 (m, 1H, CH), 2.78−2.87 (m, 1H, CH), 2.93−3.01 (m, 1H, CH), 3.13−3.21 (m, 1H, CH), 3.32 (s, 1H, NH, D_2O exchangeable), 5.43 (s, 1H, CH), 6.94−7.04 (m, 2H, ArH), 7.20−7.23 (d, 1H, ArH, J = 9 Hz), 7.27−7.29 (d, 1H, ArH, J = 6 Hz), 7.43−7.46 (d, 1H, ArH, J = 9 Hz), 7.49−7.58 (m, 2H, ArH), 7.78−7.80 (d, 1H, ArH, J = 6 Hz), 10.32 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.0, 41.6, 52.5, 108.9, 111.1, 117.6, 118.2, 120.7, 125.4, 125.5, 126.6, 127.3, 127.7, 130.8, 132.1, 134.4, 136.1, 141.4 ppm; anal. calculated for $C_{18}H_{15}F_3N_2$ (316.32): C, 68.35; H, 4.78; N, 8.86; found: C, 68.62; H, 5.01; N, 8.98.

3. RESULTS AND DISCUSSION

In 2005, Shen et al. reported a method for the synthesis of tetrahydro-β-carboline derivatives through reacting tryptamine with substituted aldehydes in toluene and trifluoroacetic acid (TFA). The yields obtained were 30−50% after stirring for 48 h.[37] Another approach was reported by Ramu et al. in 2019 who reacted tryptamine and aldehydes in *N*-methyl-2-pyrrolidone (NMP) as a solvent at 140 °C for 24 h.[38] The present work aimed at developing a novel green and sustainable approach that could overcome the problems of long reaction times and the need for hazardous catalysts. Therefore, the reaction was conducted in DESs under electrochemical conditions. The synthesis consisted mainly of two steps as presented in Scheme 1: the formation of Schiff's base and its cyclization into tetrahydro-β-carboline. A study was done to optimize the reaction conditions of each step as presented in the following sections.

3.1. Synthesis of *N*-(4-Chlorobenzylidine)-2-(1*H*-indole-3-yl)ethanamine (3). *3.1.1. Under Electrochemical Conditions in Organic Solvents.* The Schiff's base was obtained by reacting tryptamine and *p*-chlorobenzaldehyde under electrochemical conditions in ethanol, acetonitrile, and acetic acid (Table 1). A careful examination of the ^1H NMR and ^{13}C NMR spectra of the product indicated the presence of two triplet signals at δ 3.03−3.90 ppm corresponding to the aliphatic CH_2CH_2 protons. Their carbon signals appeared at δ 26.6 and 61.4 ppm in the ^{13}C NMR spectrum. The methine proton appeared at δ 8.26 ppm, which confirmed the formation of the Schiff's base.

The effects of varying solvents, time of reaction, temperature, electrolytes, and electrode materials were studied (Table 1). Regarding the type of solvent, it was found that conducting the reaction for 35 min in ethanol afforded compound **3** in a 75% yield (entry 1; Table 1). Upon conducting the reaction in

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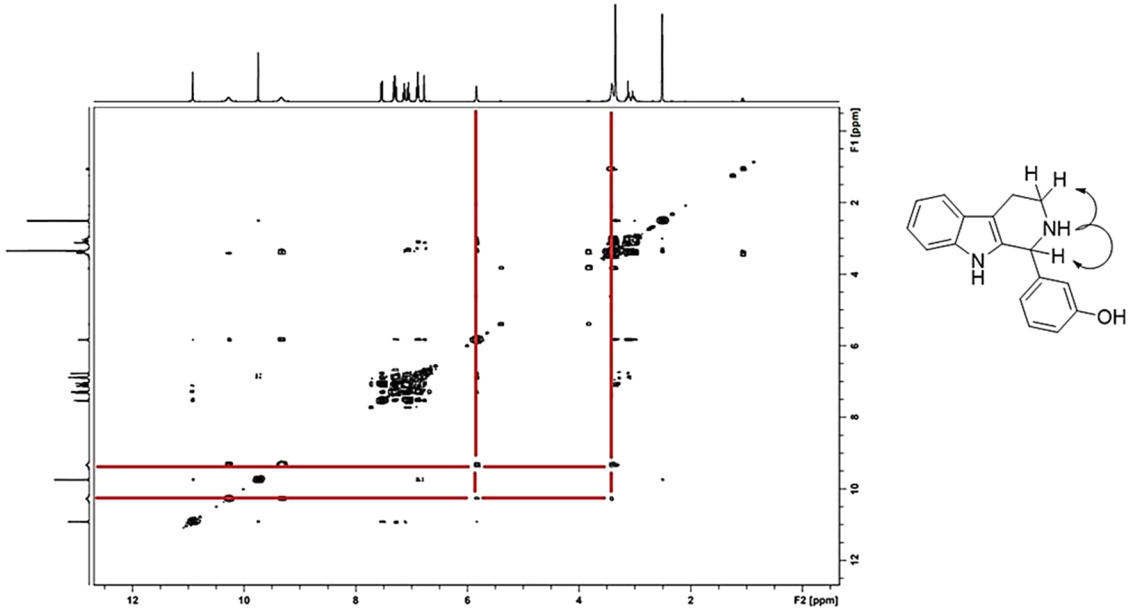

Figure 1. 2D-COSY NMR of compound **4e**.

acetonitrile, the product was obtained in a 41% yield (entry 2; Table 1). The reaction was unsuccessful in acetic acid, probably due to oxidation (entry 3; Table 1). Therefore, ethanol was chosen as the optimum solvent for further study.

Increasing the reaction time from 35 to 60 min (at 60 °C) increased the yield to 80% (entry 4; Table 1). Upon carrying out the reaction at room temperature, compound **3** was obtained with a 68% yield after 120 min (entry 5; Table 1). Thus, the optimum temperature and time were 60 °C for 60 min.

Three types of electrolytes were examined (sodium bromide, tetrabutylammonium hexafluorophosphate, and sodium perchlorate) to give compound **3** in 80, 62, and 61%, respectively (entries 4, 6, and 7; Table 1).

Finally, different types of electrodes were used to study their effects. Graphite and platinum were used as both cathode and anode, while copper was used as a cathode only (entries 4 and 8−10; Table 1). The highest yield was obtained when using graphite as both cathode and anode (entry 4; Table 1).

Based on these trials, the optimum conditions for the reaction were using ethanol as a solvent, sodium bromide as an electrolyte, and carrying out the reaction at 60 °C for 60 min using graphite as the cathode and anode.

3.1.2. Using Conventional Method in DESs. Tryptamine and 4-chlorobenzaldehyde were reacted in different DESs by heating at 80 °C for 150 min. The highest yield was obtained upon using choline chloride/glycerol as DES (94%), while the lowest yield was obtained by using choline chloride/urea (27%), which was excluded from the next trials (Table 2).

3.1.3. Under Electrochemical Conditions in DESs. The product was achieved by reacting tryptamine and 4-chlorobenzaldehyde in DESs at 80 °C for 60 min. Graphite was used as an anode and cathode. The DES mixtures used and the yield observed are presented in Table 3. The reaction was completed in 60 min, and the products were obtained in high yields in all of the DESs examined. The use of electrochemical conditions shortened the reaction time to only 60 min (compared to heating for 150 min in DESs at 80 °C; Table 2). The DESs served as both solvent and electrolyte and eliminated the need for supporting electrolytes owing to the high conductivity of the DESs. Similar results were observed in our previous work.[26,33] The use of DESs increased the yield of the product if compared to the reaction conducted in ethanol under electrochemical conditions (entry 4, Table 1). The optimized conditions were determined to be using choline chloride/ethylene glycol for 60 min at 80 °C with graphite as the anode and cathode.

3.2. Synthesis of 1-(4-Chlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (4a). *3.2.1. Under Conventional Conditions in Organic Solvents.* The cyclization of the Schiff's base derivative **3** into *β*-carboline was achieved by stirring with 2 N HCl at room temperature for 4 h to give compound **4a** (entry 1; Table 4), as previously reported.[39]

3.2.2. Under Electrochemical Conditions in Organic Solvents or DES. The reaction of the Schiff's base derivative **3** and 2 N HCl was investigated under electrochemical conditions, and the results are presented in Table 4. The use of electrochemical conditions shortened the reaction time to 20 min. However, the yield obtained was only 60% (entry 2; Table 4). Conducting the same reaction in DES (choline chloride/ethylene glycol) for 30 min at room temperature afforded the targeted compound in a 90% yield (entry 3; Table 4).

3.2.3. Optimization of Electrochemical Conditions in Organic Solvent or DES in a Two-Step, One-Pot Approach. The one-pot reaction consisted of two steps. The first one was the reaction of tryptamine **1** with 4-chlorobenzaldehyde **2a** for 60 min on heat. Then, the reaction was cooled, and 2 N HCl was added to catalyze the cyclization reaction. The use of ethanol as a solvent gave 48−58% (entries 1 and 2; Table 5). On the other hand, the use of DES enhanced the yield significantly. Optimization of the reaction conditions was done by changing the temperature and time of the reaction in step two as presented in Table 5. Conducting step two at room temperature afforded higher yields of the product (entries 3 and 4; Table 5). Similarly, changing the time of step two to 90 min gave the highest yield of 78% (entries 4−7; Table 5). The optimum condition was conducting the reaction in DES for 60

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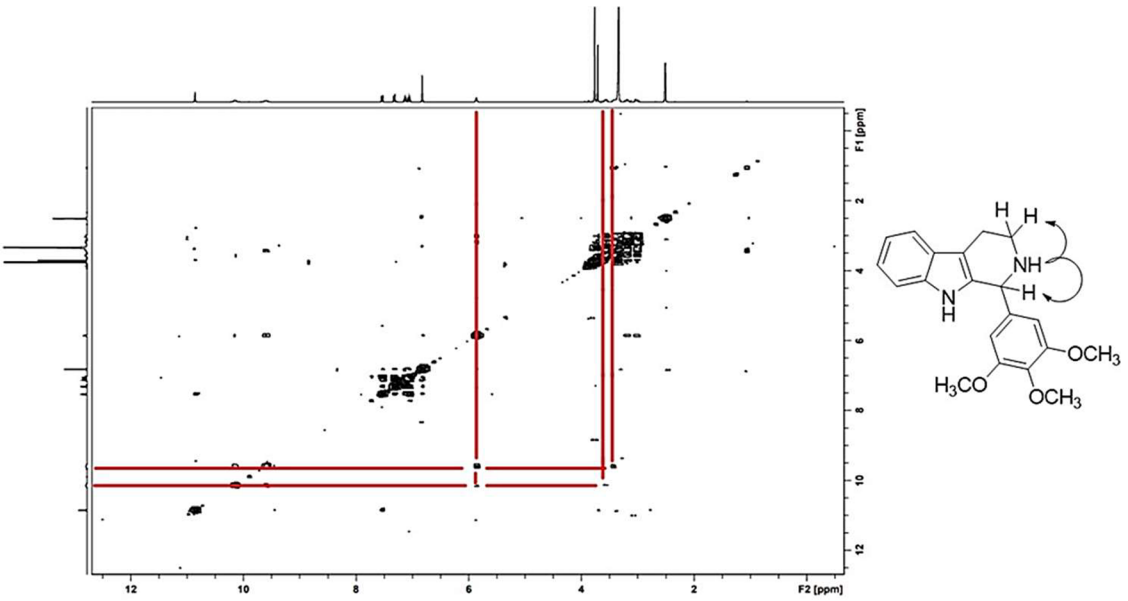

Figure 2. 2D-COSY NMR of compound **4j**.

min at 80 °C and 20 mA current, followed by cooling, addition of 2 N HCl, and applying a 20 mA constant current for 90 min at room temperature.

3.3. Electrochemical Synthesis of 2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole Derivatives 4b−4o in DES in a Two-Step, One-Pot Reaction. Under the optimized conditions discussed above, several aldehydes were used for the synthesis of tetrahydro-*β*-carboline derivatives to investigate the scope of the reaction. By studying the yields obtained in Table 6, it was observed that the substitution of aldehyde at the *para* position with an electron-donating group gave higher yields (compounds **4f, 4g, 4h, 4i**, and **4j**; Table 6) than substitution with electron-withdrawing groups (compounds **4a, 4c**, and **4d**; Table 6). Regarding benzaldehydes substituted with a halogen atom, it was found that the yield of tetrahydro-*β*-carboline product was decreased with increasing the electronegativity of the halogen atom (*F* > Cl > Br) (compounds **4a, 4c**, and **4d**; Table 6). Increasing the number or bulkiness of the electron-donating substituents on benzaldehyde did not affect the yield significantly (compounds **4h, 4i**, and **4j**). The reaction was unsuccessful with *para*-hydroxybenzaldehydes, probably due to their rapid oxidation (**4n** and **4o**), while substitution with the hydroxyl group at the *meta* position led to a low yield of the product (**4e**).

3.4. Scaling Up of Compound 4c. In order to evaluate the scalability of the new two-step, one-pot method, a gram-scale experiment was performed for the synthesis of compound **4c**, using tryptamine **1** and 4-bromobenzaldehyde **2c** as starting compounds. The product **4c** was obtained in an excellent 96.33% after 150 min.

3.5. Spectral Identification of Compounds 4a−4o. The ^{1}H NMR and ^{13}C NMR spectra of the products indicated the presence of multiplate signals at *δ* 2.5−3.88 ppm corresponding to two methylene protons, while the singlet signal appeared at *δ* 5.5−6 ppm corresponding to H-1 proton. The indole NH appeared as an exchangeable singlet signal at *δ* 10−11 ppm. Two broad exchangeable singlet signals appeared at *δ* 9.5−10.5 ppm equivalent to one proton, and both were assigned to the NH proton of the piperidine ring. This was confirmed by applying two-dimensional (2D)-COSY NMR (Figures 1 and 2), which confirmed the correlation of the NH proton with one adjacent CH_2 at position 3 of the ring and with the proton at position 1.

3.6. Green Chemistry Metrics. To ensure the sustainability and productivity of our new approach, the green metrics were calculated for the synthesis of compound **4a** under electrochemical conditions using ethanol and DES (Table 7). The detailed calculations are given in the supplementary file (Tables S1 and S2).

Table 7. Green Chemistry Metrics for the Synthesis of Compound 4a

		calculated values for the synthesis of compound **4a**	
metrics	Ideal value	EC in ethanol	EC in DES
yield	100%	48%	78%
AE	100%	93.78%	93.78%
CE	100%	100%	100%
E-factor	0	73.48	0.39
MI	1	74.48	1.39
mass productivity	100%	1.34%	71.94%
RME	100%	42.85%	98.07%

The atom economy (AE%) calculates the proportion of reagent atoms integrated into the end product. The reaction becomes greener as the AE value increases.[44] The carbon efficiency (CE%) is defined as the proportion of carbon atoms in the reactants that are present in the formed compounds.[44] Almost ideal values were obtained during the synthesis of **4a** by using both ethanol and DES.

The environmental factor (*E*-factor) measures the quantity of waste generated during a chemical process. The *E*-factor of a reaction is the ratio of the total waste mass to product mass. When the synthetic method produces a minimal amount of wastes, the values of *E*-factor will be around zero; consequently, the reaction is greener and more sustainable.[45] Upon comparing the resulting values, the *E*-factor was 73.48 when using ethanol, while it was 0.39 under using DES due to the recyclability of DES as reported before.[26]

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The mass intensity (MI) is defined as the ratio of the stoichiometric reactant mass to the stoichiometric product mass as it considers the reaction yield, solvent and all reagent quantities, and stoichiometry. The ideal value is close to one, which means that the total mass of input is almost equal to the mass of the product. The percentage of the reciprocal of MI is defined as the mass productivity.[44,46] When using ethanol as a solvent, the MI and mass productivity were 74.48 and 1.34%, respectively, while MI was 1.39 and mass productivity was 71.94% when using DES as a solvent.

The reaction mass efficiency (RME%) takes into consideration the chemical yield, atom economy, and stoichiometry. The greater values (near to 100%) imply more efficient reaction conditions with minimal production of wastes.[46] The RME% of the synthesis of **4a** in ethanol was 42.85%, and it was 98.07% when conducting the reaction in DES.

The resulting values showed the superiority of using DESs as a solvent under the electrochemical condition than using ethanol.

3.7. Investigation of the Reaction Mechanism. The mechanism of the synthesis of tetrahydro-*β*-carboline by the Pictet−Spengler reaction involves the initial reaction between tryptamine and aldehyde to form Schiff's base, followed by cyclization to form a *β*-carboline ring. The current reaction mechanism was studied using cyclic voltammetry (Figures 3−5). The results of the cyclic voltammogram in ethanol

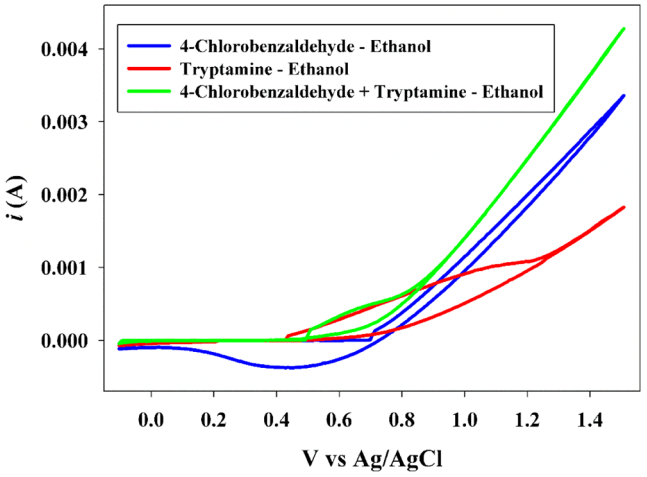

Figure 3. Cyclic voltammogram of 10 mM tryptamine (red curve), 10 mM 4-chlorobenzaldehyde (blue curve), and 10 mM mix of tryptamine and 4-chlorobenzaldehyde (green curve) in ethanol −0.1 M NaBr at PGE surface vs Ag/AgCl at a scan rate of 40 mV/sec.

(Figure 3) showed an irreversible oxidation peak of tryptamine at 0.4 V and an oxidation peak at 0.7 V of 4-chlorobenzaldehyde in the forward direction and a reduction peak at 0.4 V in the backward direction. Based on these data, it was suggested that applying the electric current led to oxidation of aldehyde to form benzoyl cation, which facilitated the attack of the primary amino group to form a Schiff base (Figure 6).

The resulting cyclic voltammetry of the Schiff's base formation in DES (Figure 4) indicated that the oxidation of both tryptamine and 4-chlorobenzaldehyde started around 1 V together with a reduction peak of 4-chlorobenzaldehyde at the backward direction, while the mixture of tryptamine and 4-chlorobenzaldeyhde showed no reduction peak of 4-

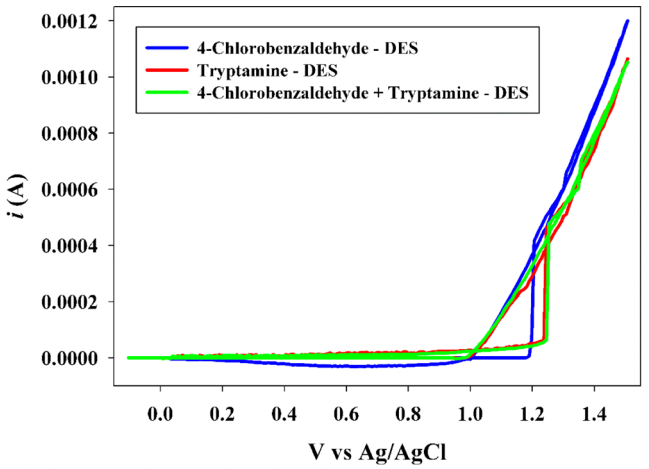

Figure 4. Cyclic voltammogram of 10 mM tryptamine (red curve), 10 mM 4-chlorobenzaldehyde (blue curve), and 10 mM mix of tryptamine and 4-chlorobenzaldehyde (green curve) in DES (choline chloride/ethylene glycol; 1:2) at PGE surface vs Ag/AgCl at a scan rate of 40 mV/sec.

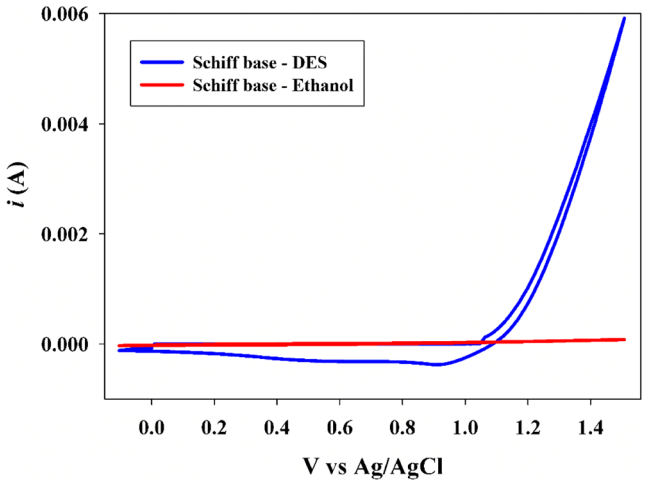

Figure 5. Cyclic voltammogram of 10 mM Schiff base in 2 N HCl in DES (choline chloride/ethylene glycol; 1:2) (blue curve) and 10 mM Schiff base in ethanol −0.1 M NaBr (red curve) at PGE surface vs Ag/AgCl at a scan rate of 40 mV/sec.

chlorobenzaldehyde in the backward direction. This result also suggested that the oxidized form of 4-chlorobenzaldehyde was reacted with tryptamine and accounted for the shorter reaction time needed for completing the reaction in DES compared to ethanol.

The second step of the reaction involved adding HCl as a Bronsted acid that led to protonation of the imine nitrogen atom (Figure 6). This step enhanced the electrophilicity of the imine group of the formed Schiff base as reported earlier.[47] Figure 5 shows the cyclic voltammogram of Schiff base **3** in 2 N HCl in DES (choline chloride/ethylene glycol; 1:2) and in ethanol/NaBr. The results showed an oxidation peak at 1 V in the presence of DES and less oxidation in ethanol. This might be due to oxidation of the indole ring followed by attack on the imine carbon and subsequent cyclization of the ring. The oxidation step accounted for the shorter time of the reaction required for completing the cyclization (90 min versus 4 h in the absence of the EC reaction).

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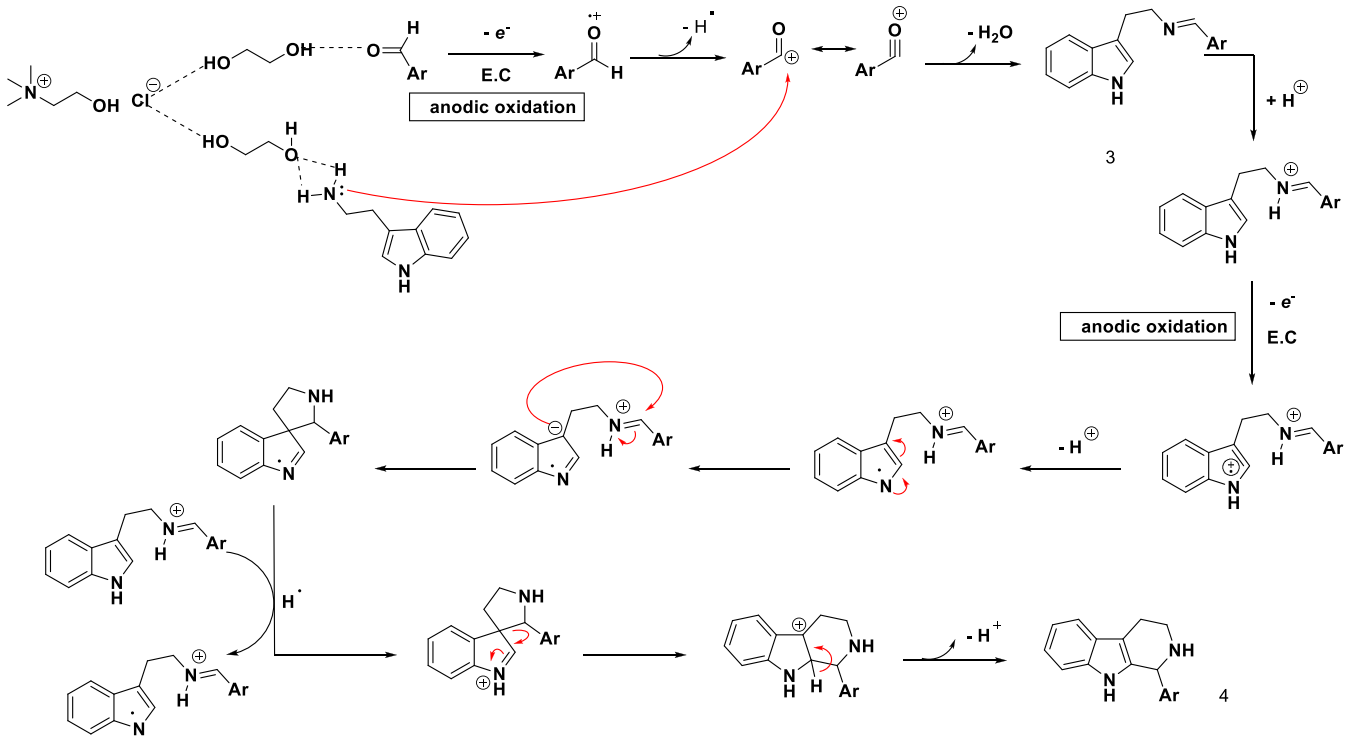

Figure 6. Proposed mechanism for the synthesis of tetrahydro-β-carboline ring under electrochemical conditions in DESs.

The DES catalyzed the formation of Schiff base through activation of the carbonyl group and enhanced the oxidation of the formed Schiff base in comparison with ethanol (Figure 5), which facilitated the cyclization step. The combination of DES and EC conditions exerted a dual catalytic action as evident from the short reaction time and the high yield of the products.

4. CONCLUSIONS

The present work reported a novel method for the synthesis of tetrahydro-β-carboline derivatives that achieved sustainability and fulfilled green chemistry principles. The products were obtained from a one-pot reaction without the need for separation of the intermediate Schiff base. Using EC in DESs saved time and energy, decreased waste generation and workup procedures, eliminated the use of hazardous chemicals and solvents, and led to the formation of pure products in high yields. The reaction method was applied to a large number of aromatic aldehydes, and the scaling-up trial of the reaction afforded excellent yield of the product in a short reaction time. We believe that our strategy can be successfully applied in the field of pharmaceutical and chemical industries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c09790.

Compound **4a** was prepared under electrochemical conditions in either ethanol or DES (Tables S1 and S2) (PDF)

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Notes

The authors declare no competing financial interest.

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