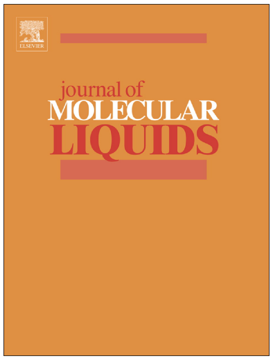

New magnetic-responsive deep eutectic catalyst based on Co2+/choline chloride for the synthesis of tetrahydro-pyrazolopyridines and pyrroles in water

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for the synthesis of tetrahydro-pyrazolopyridines and pyrroles in water

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Abstract: A new magnetic-responsive deep-eutectic (MDE) was detected by screening the components at different mole ratios in the solid-liquid equilibrated mixtures of $CoCl_2.6H_2O$ and choline chloride (ChCl) followed by vacuum evaporation. Among these complexes, the bluish complex $2ChCl.2Ch^+:CoCl_4^{2-}$ (Co4ChDES), given at 1:4 mole ratio of $CoCl_2$:ChCl showed a very deep decrease in mp as well as paramagnetic properties. All complexes were compared by mp, UV-vis, and FT-IR, while the Co4ChDES was finely analyzed by energy-dispersive X-ray spectroscopy (EDX), vibrating sample magnetometery (VSM), and EDS mapping. The positive magnetic response, surface elemental analysis, and characteristic UV-vis absorption wavelengths for Co4ChDES confirmed the presence of magnetic tetrahedral counter ion $CoCl_4^{2-}$ in the structure of this DES. The anionic complex $CoCl_4^{2-}$ which provides magnetically recovering of Co4ChDES in cooperation with the four choline groups are hydrogen bond-acceptor and hydrogen bond-donor components of this DES. The 0.75 mol% and 1.5 mol% of Co4ChDES represented high catalytic performance in the water-based multi-component reactions (MCRs) for the synthesis of substituted tetrahydropyrazolopyridines (THDPPs) and pyrroles under very mild conditions. High efficiency, simple recovery, and reusability are advantages of this non-corrosive liquefy catalyst which makes it a better alternative than that homogenous liquid acid catalysts.

Keywords: Magnetic deep eutectic; Choline chloride; Tetrahedral $CoCl_4^{2-}$; Pyrazolopyridines; substituted pyrroles

Deep eutectic solvents (DESs) are highlight solvents/catalysts in different fields of science and technology [1-8]. While DESs are composed of hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) components, the first DESs are moister-stable Lewis acids prepared from choline chloride (ChCl) and metal halides [9-11]. Recently, various types of DESs have been prepared and used as catalyst or solvent in different organic transformations [12-14]. Despite the polarity and low vapor-pressure advantages of DESs, their recovery and reusability are problematic [15] that could be solved by magnetization either by magnetic supports [12, 14] or entering of the magnetic counter-ions in the structural formula of DESs [16]. Among these magnetization techniques, entering a magnetic counter ion in DES-structure is more considerable due to the difficults associated with the linking of DESs to magnetic supports [14]. We have recently prepared new magnetically separable DESs based on a gemini-surfactant (GS) and tetrachlorometallate anions (MCl_4^{2-}) and used them as catalysts in organic synthesis [16, 17]. Typically, we have prepared the ferromagnetic DES complex $GS^{2+}.CoCl_4^{2-}$ and compared its catalytic activity with the other MCl_4^--complexes in organic synthesis by multi-component reactions (MCRs) [17]. Due to the no formation of magnetic $CoCl_4^{2-}$ in the originally prepared DES of $CoCl_2$:ChCl by Abbott [9, 15, 18], the magnetic behavior, and magnetically recovering of Co^{2+}/choline chloride-based DESs has not been evaluated. Besides, because of growing need to DESs as solvents/catalysts, their recovery issues, biocompatibility of ChCl, and Lewis acidity of $CoCl_2.6H_2O$, the preparation, characterization, and catalytic application of the low-cost, simple, and magnetically separable DESs complexs with tetrahedral counter ion $CoCl_4^{2-}$ from $CoCl_2.6H_2O$ and ChCl is highly desirable.

Tetrahydro-di-pyrazolopyridines (THDPPs) are fused heterocycles, bearing important pharmacophores of 1,4-dihydropyridine (1,4-DHP) [19-21] and pyrazol rings [22]. THDPPs rings instead of 1,3-dicarbonyls, an aldehyde, and ammonium acetate [23-26]. As a result, a variety of catalytic MCRs as modified *pseudo*-six-component reactions have been developed for the synthesis of THDPPs using L-proline [27], carbonaceous acid [28], sulfonic resins [29], nano-$CdZr_4(PO_4)_6$ [30], or nano CeO_2 as catalyst [31]. Design of a more efficient and reusable homogeneous DES catalyst for this MCR synthesis is anticipated.

Poly-substituted pyrroles are another biologically active nitrogenous heterocycles prepared by different tunable MCRs [32-34]. The four-component condensation of aldehydes, 1,3-dicarbonyles, and amines, with nitromethane, is a typical developed [1+1+1+2] strategy for the MCR synthesis of substituted pyrroles in the presence of homogeneous and heterogeneous catalysts [33, 35]. The non-reusable DES of ChCl:malonic acid [36] has been recently used to promote this reaction, while a more efficient magnetically separable DES catalyst for synthesis of pyrroled in water is of interest.

Due to the synergistic advantages of magnetic Co^{2+}/choline chloride-based DES with water-based MCRs and biological activities of THDPPs and pyrroles, design of a reusable and polar magnetically recoverable DES for the upgraded synthesis of these heterocycles has been subjected of this project. Besides, this is the first attempt on the preparation, characterization, and using of a simply prepared cobalt-based liquified magnetic DES in organic synthesis.

2. Experemental

2.1. Materials

All chemicals were purchased from Merck (Darmstadt, Germany), Sigma-Aldrich and used without further purification. The FT-IR spectra of $CoCl_2$/ChCl complexes and products as KBr discs were recorded on a Bruker spectrophotometer. Melting points were determined by a Buchi acetonitrile by Bruker spectrophotometer. The pH of samples was recorded at room temperature by inolab pH 7110. The vibration sample-magnetometry (VSM) for Co4ChDES was monitored by the Lake Shore Cryotronics 7404 at 298 K,whereas its energy dispers X-ray spectroscopy by EDS mapping and EDX were performed with MIRA3TESCAN-XMU, SEM system.

2.2. Preparation of complexes from $CoCl_2.6H_2O$ and ChCl

Various $(CoCl_2)_n/(ChCl)_m$ complexes were prepared by stirring the stoichiometric amounts of white powder of ChCl and pink solid of $CoCl_2.6H_2O$ in different 1:1, 2:1, 1:2, and 1:4 mole ratios. Typically, the blue magnetic DES complexe $CoCl_2$:4ChCl was prepared by stirring of a mixture of $CoCl_2.6H_2O$ (5 mmol) and ChCl (20 mmol) at 100 °C for 1h, washing and hexane, and drying under vacuum to remove the solvent. The obtained DES of $CoCl_2$:4ChCl was named as Co4ChDES.

2.3. Characterization of complexes

The structure of complexes was characterized and confirmed by FT-IR, UV-Vis spectroscopy, pH, EDS mapping, EDX, VSM, and melting point analysis.

2.4. Catalytic experiments

2.4.1. General procedure for the $CoCl_2$:4ChCl-catalyzed synthesis of THDPPs

To a stirring mixture of aldehyde (2.0 mmol), 1,3-dicarbonyl (4.4 mmol), hydrazine (4.4 mmol), and ammonium acetate (3.0 mmol) in water (0.5 mL) was added $CoCl_2$:4ChCl (0.015 mmol) and the mixture was stirred for the given short times at room temperature, until the product was precipitated in water. The solid product was filtered, washed, dried, and isolated in excellent yields. Then the magnetic DES catalyst was recovered from the magnetically isolated aqueous pump. The EDX and VSM analysis of the recovered catalyst was the same as original complex DES. The purity of the precipitated THDPP product was enough to show the expected spectroscopic data for structure confirmation.

2.4.2. Spectroscopic data for the selected THDPP products

2.4.2.1. 3,5-Dimethyl-4-(4-hydroxy-phenyl)-1,4,7,8-tetrahydrodipyrazolo [3,4-b, 4′,3′′-e] pyridine (Entry 3, Table 3): White solid, mp = 267–269 °C (Lit. 267–268 °C) [37]. FT-IR (KBr): 3234 (overlapped NH and OH stretching), 2935 (CH stretching), 1600 (C=N stretching), cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.05 (s, 6H, 2 CH_3), 4.68 (s, 1 H, CH), 6.57 (d, *J* = 8 Hz, 2 H, H_{arom}), 6.89 (d, *J* = 8 Hz, 2 H, ArH), 9.15 (s, OH), 11.52 (s, 3 H, 3 NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.35, 31.76, 104.51, 114.45, 128.25, 133.36, 139.75, 155.05, 161.05 ppm

2.4.2.2. 3,5-Dimethyl-4-(4-methyl-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b, 4′,3′′-e] pyridine (Entry 5, Table 3.): White solid, mp = 244–246 °C (Lit. 244–246 °C) [37]. FT-IR (KBr): 3170 (NH stretching), 2920 (CH stretching), 1610 (C=N stretching), 1520 (C=C aromatic), 1139 (C–N stretching) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.1 (s, 6H, 2 CH_3), 2.20 (s, 3 H, CH_3 (para)), 4.78 (s, 1 H, CH), 6.99–7.00 (m, 4H, H_{arom}), 11.25 (s, 3 H, 3 NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.85, 20.98, 32.85, 104.85, 127.82, 128.83, 134.70, 140.20, 140.75, 161.50 ppm.

2.4.2.3. 3,5-Dimethyl-4-(4-nitro-phenyl)-1,4,7,8-tetrahydrodipyrazolo[3,4-b, 4′,3′′-e] pyridine (Entry 11, Table 3): Cream solid, mp = 333–335 °C (Lit. >300 °C) [37]. FT-IR (KBr): 3250 (NH stretching), 2985 (CH stretching), 1605 (C=N stretching), 1489 (overlapped asymmetrical stretching NO_2 with C=C aromatic), 1352 (NO_2 symmetrical stretching), 753 (out of plane bending C–H, para-substituted) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.1 (s, 6 H, 2 CH_3), ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.70, 33.40, 103.60, 123.40, 129.20, 140.20, 146.1, 152.25, 161.35 ppm.

2.4.3. General procedure for the Co4ChDES -catalyzed synthesis of substituted pyrroles

The $CoCl_2$:4ChCl (0.03 mmol) was added to the mixture of aldehyde (2.0 mmol), ethylacetoacetate (2.0 mmol), aniline derivative (2.0 mmol), and nitromethane (1.0 mL) in distilled water (0.5 mL) and the mixture was stirred at room temperature. After the reaction completion (TLC monitoring), the aqueous phase of the catalyst was isolated by an external magnet and the oily product was extracted with ethyl acetate. The vacuum evaporation of water from the aqueous phase of the magnetic catalyst gave the recovered DES complex and the pure pyrrole product was obtained by removing ethylacetate under reduced pressure.

2.4.4. Spectroscopic data for selected pyrrole products

2.4.4.1. Ethyl 1-(4-chlorophenyl)-2-methyl-4-(p-tolyl)-1H-pyrrole-3-carboxylate (Entry 3, Table 5): White solid, mp = 130-132 °C (Lit. 130-132 °C) [38]. FT-IR (KBr): 2983 (CH stretching), 1667 (C=O stretching) 1434-1554 (C=C aromatic), 1172 (C–N stretching) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (d, *J* = 8.0 Hz, 2 H, H_{arom}), 7.65 (d, *J* = 8.0 Hz, 1 H, H_{arom}), 7.76 (s, 1 H, H_{arom}), 7.70 (d, *J* = 8.0 Hz, 1 H, H_{arom}), 7.50 (*d*, *J* = 8.0 Hz, 4 H, H_{arom}), 3.85(q, *J* = 8.0 Hz, 2 H, CH_2), 2.20 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 1.25 (t, , *J* = 8.0 Hz, 3 H, -CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 180.0, 170.0, 168.0, 164.5, 161.0, 157.5, 152 148.4, 140.0, 137.2, 133.0, 131.5, 128.3, 124.0, 123.0, 120.0, 115.2, 45.5, 36.0, 31.5, 28.0.

2.4.4.2. Ethyl 4-(4-methoxyphenyl)-2methyl-1-phenyl-1H-pyrrole-3-carboxylate (Entry 4, Table 5): White solid, mp = 108-110 °C (Lit. 108-110 °C) [39]. FT-IR (KBr): 2980 (CH stretching), 1695 (C=O stretching) 1449-1500 (C=C aromatic), 1171 (C–N stretching) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10 (s, 1 H, H_{arom}), 7.9 (d, *J* = 8.0 Hz, 2 H, H_{arom}), 7.62 (t, *J* = 8.0 Hz, 1

H, H_{arom}), 3.72 (s, 3 H, -CH_3), 3.35 (q, *J* = 8.0 Hz, 2 H, -CH_2), 1.90 (s, 3 H, -CH_3), 1.25 (t, *J* = 8.0 Hz, 3 H, -CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 179.0, 167.2, 164.0, 160.0, 155.5, 152.0, 149.5, 145.6, 146.0, 141.0, 131.0, 129.5, 128.53, 128.0, 124.5, 123.0, 120.0, 115.7, 44.2, 35.4, 31.0, 27.0.

2.4.4.3. Ethyl 1-(4-chlorophenyl)-2-methyl-4-phenyl-1H-pyrrole-3-carboxylate (Entry 9, Table 5): Yellow solid, mp = 126-128 °C (Lit. 127-129 °C) [39]. FT-IR (KBr): 2916 (CH stretching), 1709 (C=O stretching) 1440-1530 (C=C aromatic), 1139 (C–N stretching) cm^{-1}. ^{1}H NMR(400 MHz, DMSO-d_6): δ = 8.30 (s, 1 H, H_{arom}), 7.85 (d, *J* = 8.0 Hz, 2 H, H_{arom}), 7.6 (t, *J* = 8.0 Hz, 1 H, H_{arom}), 7.45 (d, *J* = 8.0 Hz, 2 H, H_{arom}), 7.35 (d, *J* = 8.0 Hz, 4 H, H_{arom}), 3.74 (q, *J* = 8.0 Hz, 2 H, -CH_2), 2.20 (s, 3 H, -CH_3), 1.15 (t, *J* = 8.0 Hz, 3H, $CH_{3,}$,): ^{13}C NMR (101 MHz, DMSO-d_6) δ = 180.0, 168.5, 166.0, 162.0, 158.0, 153.5, 148.0, 144.4, 136.5, 133.0, 131.0, 127.0, 124.0, 123.0, 120.0, 116.5, 115.6, 46.5, 32.0, 25.0.

3. Results and discussions

Firstly, various $(CoCl_2)_n(ChCl)_m$ complexes were prepared by stirring of a vacuumed mixture of the pink solid $CoCl_2.6H_2O$ and white powder ChCl at controlled stoichiometric ratios of components and 100 °C under solid-liquid equilibrium. Then, the melting points and magnetic responses of these complexes to the NdFeB magnet with magnetic power 3.2 T were evaluated. The physiochemical properties of the as-prepared complexes including formula, color, melting points, and magnetic response to external magnet are summarized in Table 1.

Entry	$ChCl:CoCl_2.6H_2O$ (mol ratio)	Mp (°C)	Chemical composition (Proposed)	Color/physical state/magnetic response
1	1:0	300-302	ChCl	Colorless/solid/negative
2	0:1	724-726	$CoCl_2.6H_2O$	Pink/solid/negative
3	1:1	108-110	$ChCl:CoCl_2$	Blue/solid/negative $^-$
4	1:2	148-150	$ChCl:2CoCl_2$	Blue/solid/negative
5	4:1	72-74	$4ChCl:CoCl_2$ $(2ChCl.2Ch^+:CoCl_4^{2-})$	Blue/liquid[a]/positive
6	2:1	350-352	$2ChCl:CoCl_2$ $(2Ch^+:CoCl_4^{2})^-$	Blue/solid/positive

[a] at>40 °C this amorphos solid was softed and melted at 72-74 °C.

As results show, a deep decrease in the melting point is evident for some complexes formed (entries 3-5) that supports formation of three DES kinds from the same components. The extreme deep decrease is due to the complex formed from ChCl and $CoCl_2.6H_2O$ in a 4:1 molar ratio which cotributes in an exceptional deep eutectic phenomenon (entry 5). Experimenting the complexes by NdFeB magnet with magnetic power 3.2 T resulted magnetic responsivity of the $CoCl_2$:2ChCl and $CoCl_2$:4ChCl complexes (entries 5 and 6), although magnetic properties of the liquify $CoCl_2$:4ChCl was superior than the solid high-melting point complex $CoCl_2$:2ChCl (Fig 1).

Fig 1. Magnetic response of Co4ChDES to NdFeB

of $GS^+.CoCl_4^{2-}$-complex [12], the positive responses of the complexes formed at entries 5 and 6 to NdFeB magnet are attributed to the presence of the magnetic tetrahedral counter ion tetrachlorocobaltate ($CoCl_4^{2-}$) in their structure. The magneticity of Co4ChDES was also evaluated by room temperature VSM analysis at field range -1.5-1.5 T (Fig 2).

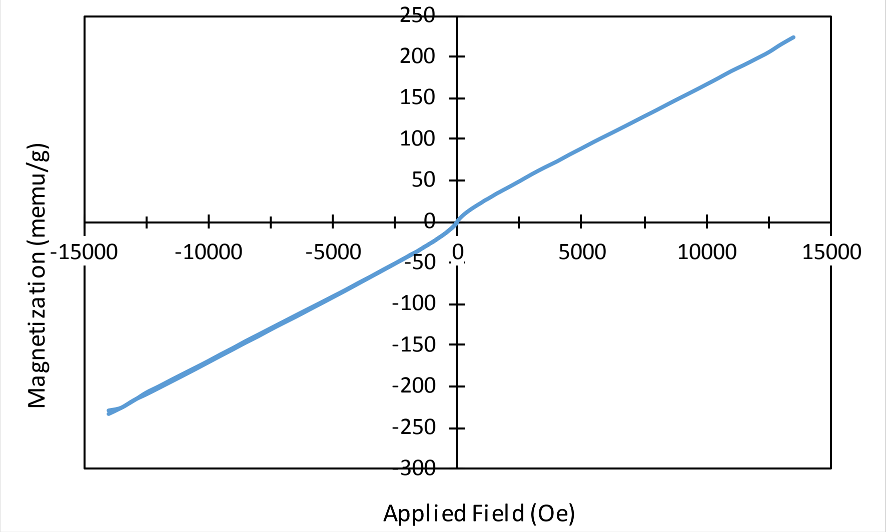
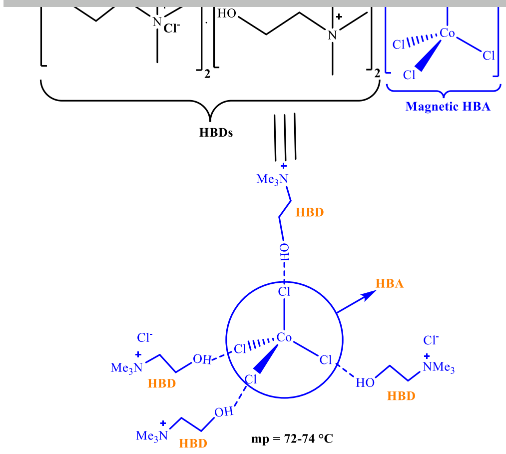


Fig 2. The VSM curve analysis of Co4ChDES

As VSM-curve shows, the complex Co4ChDES is magnetic responsive with paramagnetic properties and magnetic saturation (Ms) = 224 memu/g. This MS-value is higher than gemini sutfactant-cobalt complex $GS^{2+}.CoCl_4^{2-}$ that we prepared previously [16]. The Ms value, positive response to magnetic field, and blue color of Co4ChDES are logical reasons for the presence of the tetrahedral magnetic anionic complex $CoCl_4^{2-}$ in the structure of DES formed at $CoCl_2.4ChCl$ (entry 5, Table 1). The literature data for the magnetic properties of $CoCl_4^{2-}$ in other ionic liquids [40-42] supports our suggestion. Considering the $CoCl_4^{2-}$ as a component of this DES, the following formula for the intermolecular hydrogen bonding interactions of $CoCl_4^{2-}$ as HBA with choline groups as HBD is proposed (Scheme 1).



Scheme 1. The proposed formula for $CoCl_4^{2-}.2Ch^{+}.2ChCl$ abbreviated as Co4ChDES

To determine the element distribution in Co4ChDES complex, the EDS mapping was recorded (Fig. 3).

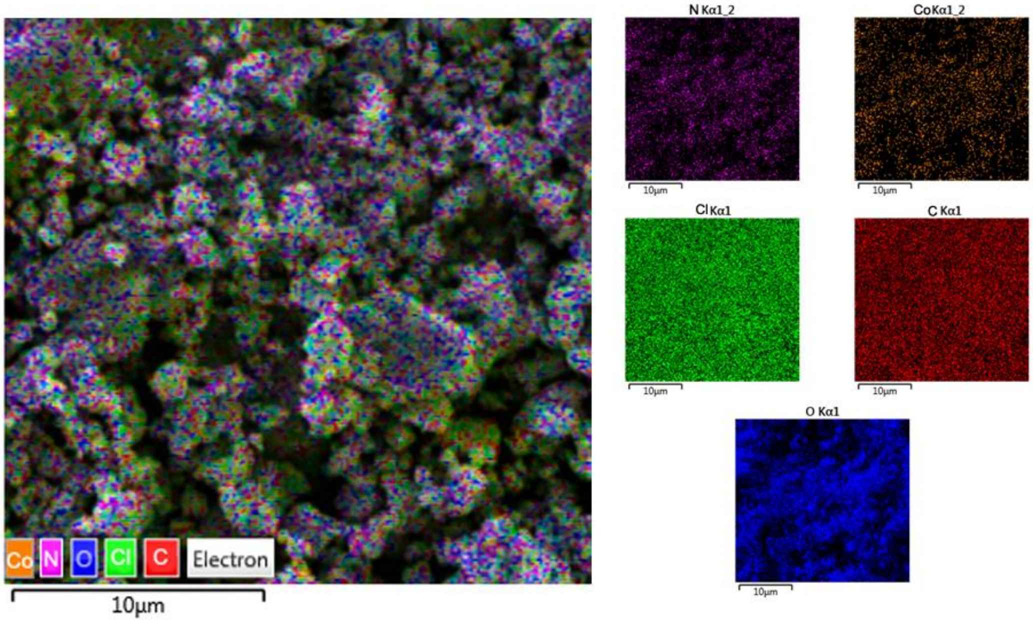
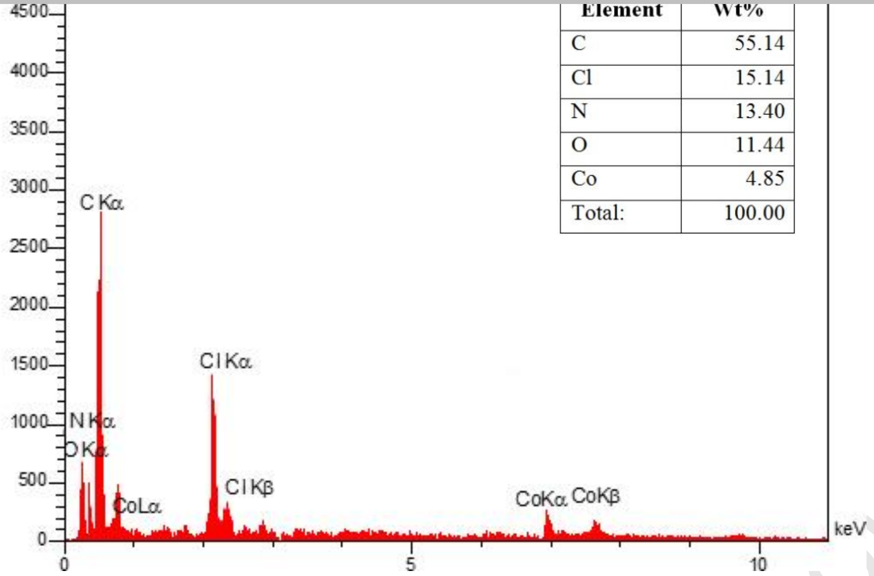


Fig 3. The EDS mapping analysis of Co4ChDES

According to EDS results, the C, N, Cl, and Co have a homogeneous distribution in the surface of Co4ChDES indicating the high uniformity in structure of this complex. Alternatively, chemical composition of Co4ChDES was checked by the EDX analysis and the results show 55.14% C, 13.40% N, 11.44% O, 15.14% Cl, and 4.85% Co, which are compatible with the proposed structural formula of $2ChCl.2Ch^{+}:CoCl_4^{2}$ (Fig 4).



Element	Wt%
C	55.14
Cl	15.14
N	13.40
O	11.44
Co	4.85
Total:	100.00

Fig 4. The EDS analysis of Co4ChDES

Based on the overlaid FT-IR spectra of the as-prepared Co^{2+} complexes, the characteristic absorption bands at 3433 cm^{-1}, 2926 cm^{-1}, 1605 cm^{-1}, 1478 cm^{-1}, and 1100-1300 cm^{-1} are related to the OH stretching, aliphatic CH stretching, CH_2 bending, adsorbed surface water, and C-N/C-O stretchings, respectively. With the similar vibrational modes to other complexes, a large shift for OH stretching from ~3400 cm^{-1} to 3259 cm^{-1} in the spectrum of Co4ChDES is due to the HBD role of cholines OHs in the DES formed that causes shift to the lower adsorption wavenumbers. It is notable that, the broad peaks at 3200 to 3500 and 1632 cm^{-1} in the spectrum of $CoCl_2.6H_2O$ are related to the vibrational modes of surface water [41, 42] (Fig. 5).

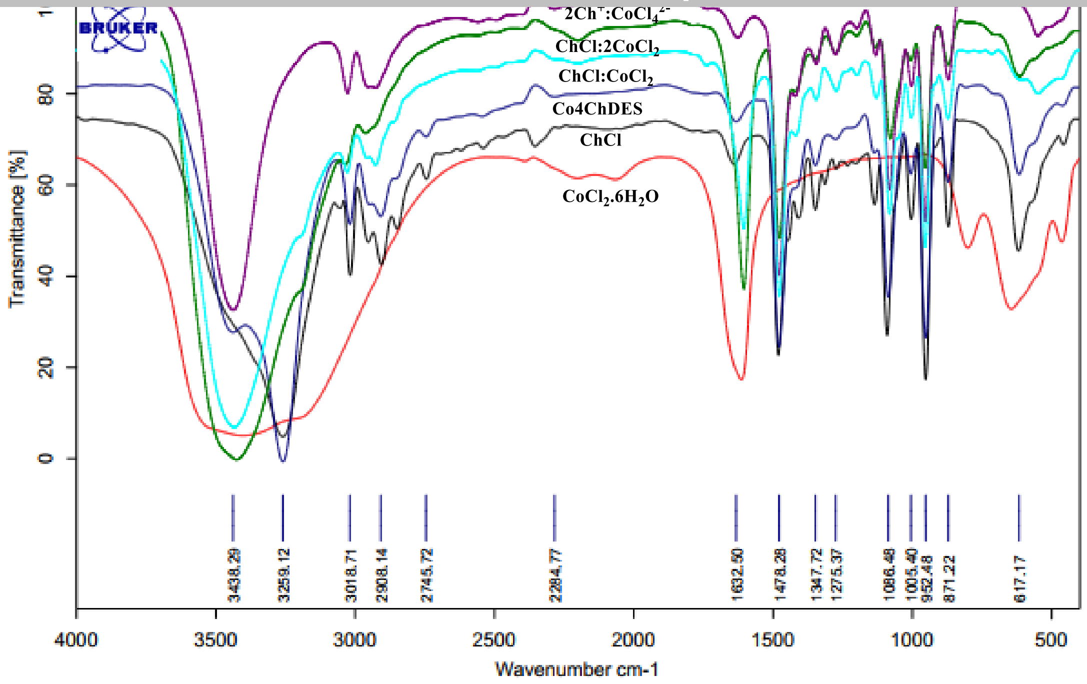
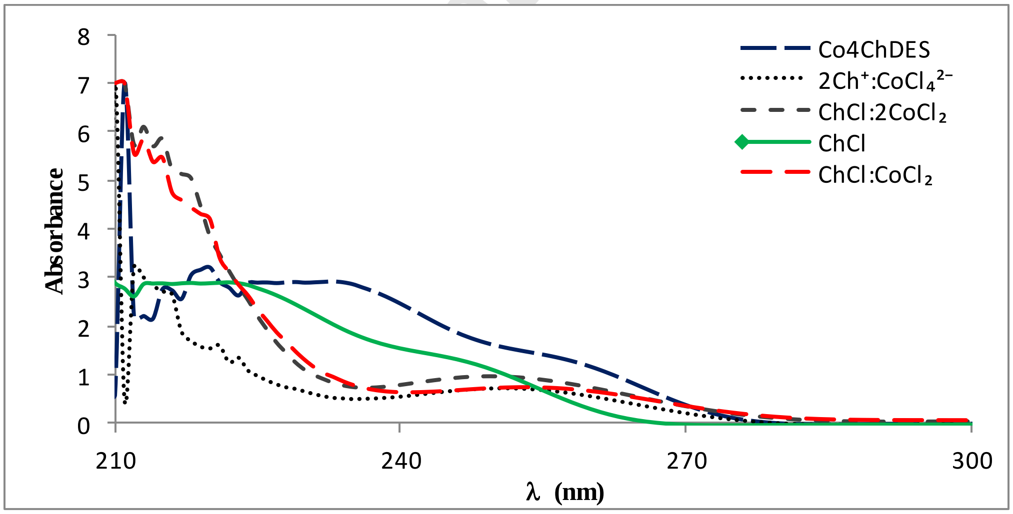


Fig 5. The comparative FT-IR spectra of the $CoCl_2.6H_2O$, ChCl, and the as-prepared complexes

The UV-Vis spectra of ChCl/$CoCl_2$ complexes in acetonitrile were compared in two domains of absorption wavelengths for metal-ligand transitions at 200-300 nm and d-d transitions at 500-800 nm (Fig. 6).



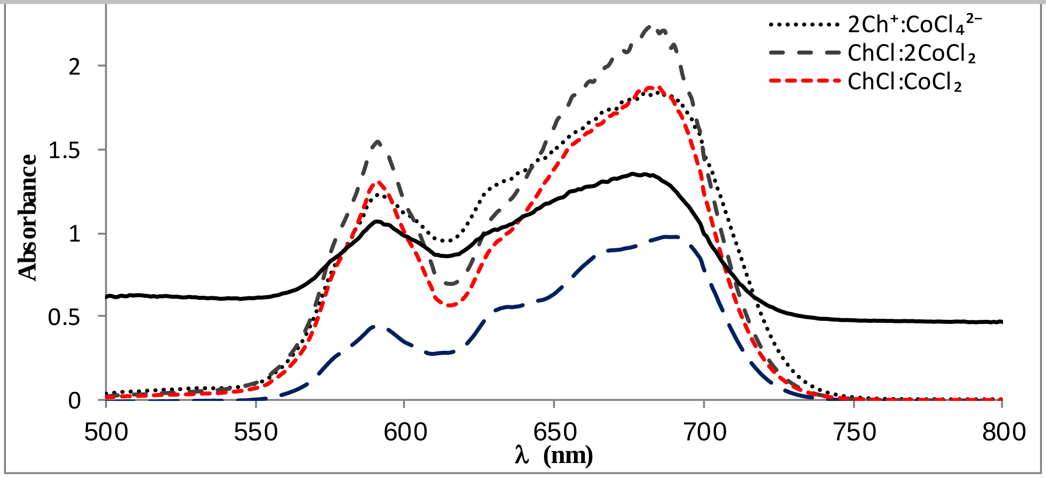


Fig 6. The UV-Vis spectra of ChCl and ChCl/$CoCl_2$-complexes at 200-300 nm and 500-800 nm

Because diverse types of charge-transfer complexes between ChCl and $CoCl_2$, the UV-absorption for metal-ligand transitions of complexes at 200-300 nm region are different, although the variance in absorption bands for d-d transitions of complexes at 500-800 nm are also significant. However, absorbtion wavelengths at 210 nm, 212 nm, 215 nm, 591 nm, and 691 nm confirmed the presence of the tetrahedral bluish complex $CoCl_4^{2-}$, which have been previously detected by UV-Vis absorption as counter ion of ionic liquids. The magnetic anion $CoCl_4^{2-}$ was formed in Co4ChDES by the transfer of two Cl^- from two ChCl molecules into the $CoCl_2$ to give the $CoCl_4^{2-}.2Ch^+.2ChCl$ complex (Co4ChDES). The obvious hypsochromic shift and the minimum absorbance for this DES complex are also attributed to the maximum charge transfer interactions between choline's OH and Co^{2+} in the Co4ChDES. This fact is in agreed with the large shift of choline's OH-stretching to the lower adsorption wavenumbers in the FT-IR spectrum of Co4ChDES (Fig. 5). However, all specra-analytical evidences supports surrounding of anionic complexe $CoCl_4^{2-}$ by choline-grups.

The catalytic efficiencies of the prepared Ch-based magnetized-Lewis acid complexes were furture examined in MCR synthesis of THDPPs. So, factors affecting on the synthesis of 4-nitrophenyl-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4',3'-e]pyridine (THDPP1) by the ethylacetoacetate were optimized (Table 2).

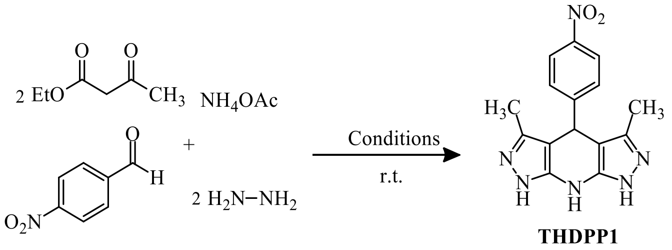


Table 2. Optimization of conditions for the Co^{2+}-complexes-catalyzed synthesis of THDPP1 [a]

Entry	Conditions Catalyst (per 2 mmols of aldehyde)/Solvent (0.5 mL)	Time (min)	Isolated Yield (%)
1	$CoCl_2$ (0.015 mmol)/H_2O	60	18
2	ChCl (0.015 mmol)/H_2O	60	15
3	ChCl:$CoCl_2$ (0.015 mmol)/H_2O	60	17
4	ChCl:2$CoCl_2$ (0.015 mmol)/H_2O	60	20
5	$2Ch^+:CoCl_4^{2-}$ (0.015 mmol)/H_2O	30	76
6	$2Ch^+:CoCl_4^{2-}$ (0.015 mmol)/-	45	69
7	$2Ch^+:CoCl_4^{2-}$ (0.015 mmol)/EtOH	45	45
8	Co4ChDES (0.015 mmol)/H_2O	15	96
9	Co4ChDES (0.02 mmol)/H_2O	30	85
10	Co4ChDES (0.025 mmol)/H_2O	40	76
11	Co4ChDES (0.015 mmol)/EtOH	45	58
12	Co4ChDES (0.015 mmol)/EtOH-H_2O	45	70
13	Co4ChDES (0.015 mmol)/-	60	35

[a] The reaction was performed by 4-nitrobenzaldehyde (2.0 mmol), hydrazine (4.0 mmol), ammonium acetate (3.0 mmol), ethylacetoacetate (4.1 mmol), and catalyst in 0.5 mL solvent at room temperature.

According to the results, the best yield of THDPP1 was obtained using 1.5 mol% of the Co4ChDES for 2 mmol scale reaction in water at room temperature (entry 8), while the other choline/Co^{2+}-based complexes had no similar catalytic effect (entries 3-7). The lower yield and longer time for the model reaction run in EtOH (entry 11) and EtOH/water (entry 12) than water (entry 8) is attributed to the destruction of the tetrahedral complex Co4ChDES by entrance of the tetrahedral complex core, increase the internal pressure, and enhance the contact area of catalyst with the reactants. No color change of catalyst from blue to pink-purple during the reaction in water is an extra evidence for no change of tetrahedral complex Co4ChDES to its hydrated octahedral form. The superiority of Co4ChDES in a very low loading of 0.0075 mmol (0.75 mol%) per 1 mmol of the limited-reactant can be related to the tolerance Lewis acidity of $CoCl_4^{2-}$, DES efficacy for providing the maximum contact between the starting materials, and directing the reaction to a lower energy path. At higher DES-loading, the efficiency was dramatically reduced due to the increase in $CoCl_4^{2-}$ concentration and strong interaction of hydrazine as another HBD with this HBA, which results in the destruction of original Co4ChDES as well as less contribution of hydrazine in synthesis of THDPP1. To confirm this suppose, hydrazine was added to Co4ChDES in an individual experiment, which led to precipitate of components and destruction of DES.

Reusability of the magnetic Co4ChDES was examined in the reaction performed for the synthesis of THDPP1 at 10 mmol scale by reusing the catalyst after each cycle. Thus, after the magnetic separation, the recovered bluish catalyst Co4ChDES was washed with EtOAc and kept under vacuum to remove the solvent. The recovered catalyst was reused in further reaction cycles for the synthesis of THDPP1, while only 5% catalytic activity loss was observed in respect to reaction yield after the sixth reaction run (Fig. 7).

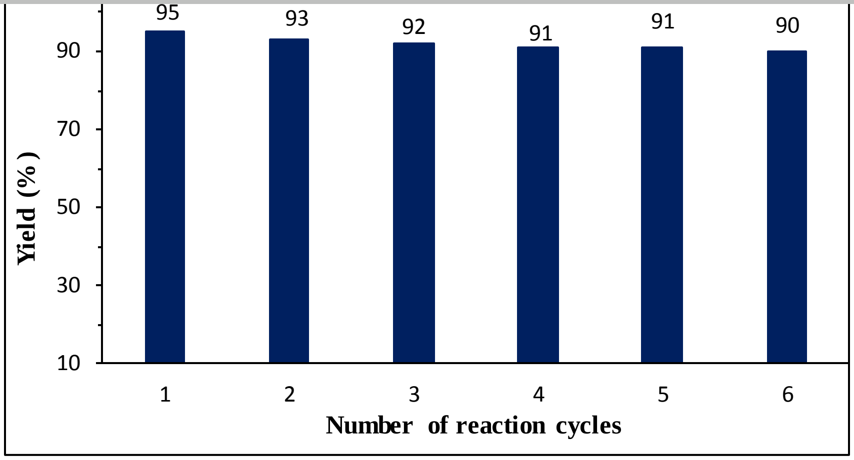
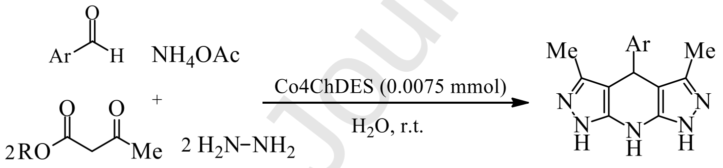


Fig 7. Reusability of Co4ChDES in the synthesis of THDPP1

In terms of pharmaceutic uses of THDPPs, the product contamination with Co^{2+} was studied by ICP analysis of the THDPP1 solution. No detection of Co^{2+} confirmed no leaching of this metal cation from complex Co4ChDES.

Due to the superiority of Co4ChDES in a low loading, the scope of the Co4ChDES-catalyzed synthesis of THDPPs was then demonstrated by the reaction of various ketoesters and aldehydes with hydrazine and NH_4OAc to give the corresponding products (Table 3).

Table 3. The Co4ChDES-catalyzed synthesis of THDPPs in water



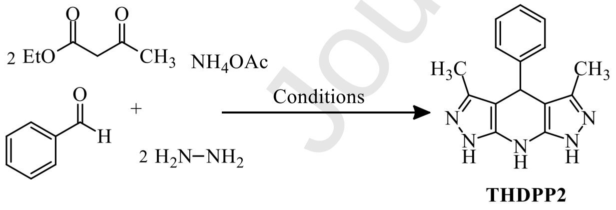
Entry	Ar	R	Time (min)	Yield (%)	Mp (°C) Found/reported [37,44]
1	Ph	Et	15	94	235-237/240-242
2	Ph	Me	10	95	239-241
3	4-OHC_6H_4	Et	20	92	267-269/267-268
4	4-ClC_6H_4	Et	25	94	254-256/254-256
5	4-$CH_3C_6H_4$	Et	18	88	244-246/244-246

7	2-$NO_2C_6H_4$	Et	12	91	185-187/187-188
8	2-$NO_2C_6H_4$	Me	10	93	185-187
9	4-$N(CH_3)_2$	Et	17	97	242-244/240-242
10	4-$N(CH_3)_2$	Me	18	97	242-244
11	4-$NO_2C_6H_4$	Et	10	94	333-335/>300
12	4-$NO_2C_6H_4$	Me	10	95	334-335
13	2-ClC_6H_4	Et	12	86	220-222/164-165
14	4-$CH_3OC_6H_4$	Et	30	82	182-184/185-187
15	4-$CH_3OC_6H_4$	Me	20	90	183-185
16	4-BrC_6H_4	Et	30	78	165-167/165-167

Based on the results, Co4ChDES is an efficient catalyst for a broad scope of substrates to give the pure products with compatible spectroanalytical data with the literature [44], although in all cases methyl acetoacetate reacted faster than ethylacetoacetate (entries 2, 6, 8, 10, 12, 15).

With some autority, this method is comparable with previously reported methods for synthesis of THDPP2 in terms of reaction times, yields, catalyst loading, solvent, and temperature (Table 4).

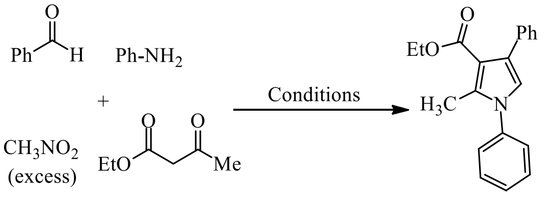
Table 4. The synthesis of THDPP2 in various reported conditions.



Entry	Conditions	Time	Isolated Yield
	Catalyst (mg/1 mmol of starting material)/Solvent/Temp. (℃)	(h)	(%) [Ref]
1	Co4ChDES (0.75 mol%)/H_2O/r.t.	0.25	94 (This work)
2	Nano-$CdZr_4(PO_4)_6$ (0.6 mol%)/EtOH/Reflux	0.66	94 [30]
3	$CuFe_2O_4$@HNTs (5 mg)/EtOH/r.t	0.33	96 [45]
4	-/H_2O:HOAc (3:1)/80 ℃	4	95 [46]

Next, the versatility of the magnetic catalyst Co4ChDES was evaluated in the more problematic water-based synthesis of substituted pyrroles by four-component condensation of ethylacetoacetate, nitromethane, aniline, and benzaldehyde under various conditions (Table 5).

Table 5. Optimization of conditions for pyrroles synthesis using Co4ChDES[a]



Pyrrole1

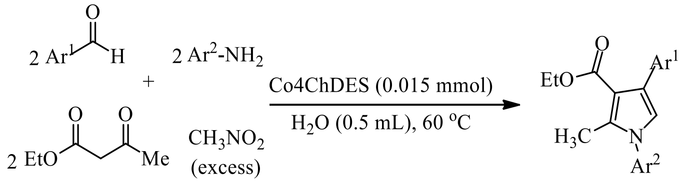
Entry	Conditions Catalyst (per 2 mmols of starting materials) /Solvent/Temp. (°C)	Time (min)	Isolated yield (%)
1	Co4ChDES (0.04 mmol)/-/60	60	52
2	Co4ChDES (0.03 mmol)/-/60	45	75
3	Co4ChDES (0.05 mmol)/H_2O/60	30	28
4	Co4ChDES (0.04 mmol)/H_2O/65	60	67
5	Co4ChDES (0.015 mmol)/H_2O/60	30	78
6	Co4ChDES (0.03 mmol)/H_2O/60	15	96
7	-/H_2O/65	60	21
8	Co4ChDES (0.03 mmol)/H_2O/r.t	240	95
9	Co4ChDES (0.03 mmol)/EtOH/60	70	73
10	Co4ChDES (0.03 mmol)/EtOH-H_2O/60	60	49

[a] The reaction was performed by Benzaldehyde (2.0 mmol), ethylacetoacetate (2.0 mmol), aniline (2.0 mmol), nitromethane (1.0 mL) and catalyst under various conditions.

According to the results, 1.5 mol% of Co4ChDES catalyst, water, and 60 °C were optimized conditions for the best yield of ethyl-1,4-diphenyl-2-methyl-*1H*-pyrrole-3-carboxylate (pyrrole 1) in 1 mmol scale (entry 6). The superiority of reaction run in water (entry 6) than complex Co4ChDES with EtOH and destruction of the active tetrahedral complex Co4ChDES.

Then, these conditions were extended to the other aldehydes and ß-ketoesters. Table 6 shows the generality of the Co4ChDES-catalyzed synthesis of substituted pyrroles that isolated in high yield and purity with the same characteristic data in literature [48].

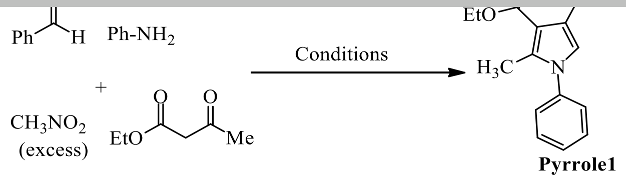
Table 6. The Co4ChDES-catalyzed synthesis of substituted pyrroles



Entry	Ar^1	Ar^2	R	Time (min)	Yield (%)	Mp (°C) Found/reported [Ref.]
1	Ph	Ph-NH_2	OEt	60	94	Oil/Oil [39]
2	Ph	Ph-NH_2	Me	70	92	106-108/106-107 [49]
3	4-$OCH_3C_6H_4$	4-$ClC_6H_4NH_2$	OEt	70	89	130-132/130-132 [38]
4	4-$OCH_3C_6H_4$	Ph-NH_2	OEt	70	91	108-110/108-110 [39]
5	4-$CH_3C_6H_4$	Ph-NH_2	OEt	70	89	120-122/120-122 [39]
6	Ph	4-$BrC_6H_4NH_2$	Me	80	78	140-142/141-143 [49]
7	4-$OCH_3C_6H_4$	4-$CH_3OC_6H_4NH_2$	Me	90	88	136-138/136-137 [49]
8	4-$NO_2C_6H_4$	Ph-NH_2	Me	50	92	Oil/Oil [45]
9	Ph	4-$ClC_6H_4NH_2$	OEt	70	92	126-128/127-129 [39]
10	Ph	Ph-NH_2	OMe	50	95	Oil/Oil [49]

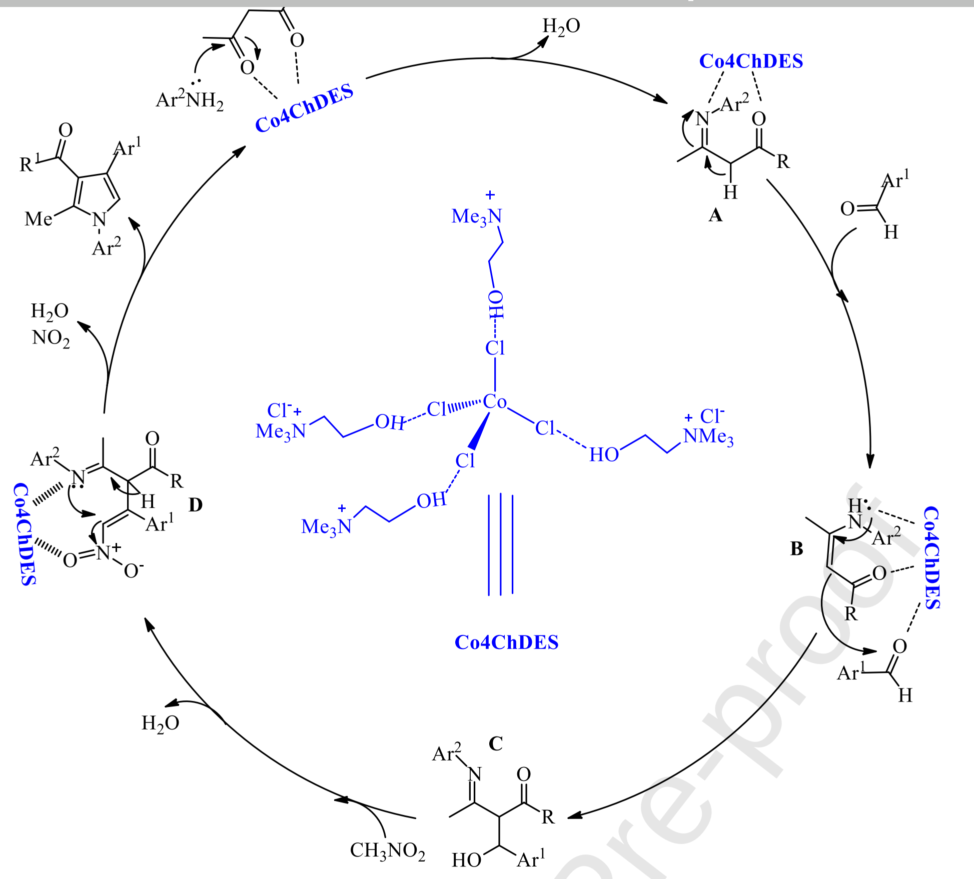
To show the performance of magnetic catalyst Co4ChDES, the synthesis of pyrrole1 in the presence of this catalyst was compared with some previously reported methods (Table 7). This method is superior to others with respect to the catalyst loading, reaction yield, solvent, and reaction time.

Table 7. Performance of Co4ChDES in pyrrole synthesis.



Entry	Conditions Catalyst (mg/1 mmol of starting material)/Solvent/Temp. (℃)	Time (h)	Isolated Yield (%) [Ref]
1	Co4ChDES (1.5 mol%)/H_2O/60 °C	0.25	96 (This work)
2	SBCu@silica-Fe_3O_4 (0.23 mol%)/-/r.t	0.5	93 [39]
3	Cu_2O/Ag (5 mg)/N_2 atmosphere/r.t	15	98 [33]
4	NiO NPs (5 mol%)/N_2 atmosphere/r.t	4	89 [50]
5	Graphite (20 mol%)/CH_3NO_2/Reflux	6	88 [51]

A proposed mechanism for the catalytic roles of Co4ChDES is outlined in Scheme 2. The superior role of this magnetic DES catalyst is the carbonyl activation by complexation with the HBA part of this DES and the help of the catalyst to removing of NO_2 in the last step. Generally, this DES catalyst leads to the reducing of the activation energy and acceleration of the reaction rate. The presence of tetrahedral counter ion $CoCl_4^{2-}$ in the Co4ChDES structure provides easy separation of catalyst by magnet and its reusability.



Scheme 2. The proposed mechanism for Co4ChDES-catalyzed synthesis of substituted pyrroles.

The performed leaching test [52] after 50% progress of the model reaction showed stop of the pyrrol1 synthesis by magnetically removing of the Co4ChDES at half reaction time using an external magnet. This means no leaching of the active species of $CoCl_4^{2-}$ and choline groups as HBA and HBD components in to the reaction mixture.

Conclusion

The separation and reusing of deep eutectics are important challenges. Thus in this work, by screening the mole ratios of $CoCl_2.6H_2O$ and ChCl at 1:1, 2:1, 1:2, and 1:4, a series of complex mixtures were prepared. In the latter case, the best complex deep eutectic (DE) with a deep decrease in melting point was formed, while its paramagnetic properties was confirmed by magnetic responsively and VSM analysis. The magnetic response of this DES is due to the

HBD components of this catalyst. Thus, the $2ChCl.2Ch^{+}:CoCl_4^{2-}$ (Co4ChDES) formula is proposed for this magnetic DE, which was also identified by FT-IR, energy-dispersive X-ray spectroscopy, EDS mapping, and UV-vis analysis. The existence of $CoCl_4^{2-}$ was similarly confirmed by characteristic UV-vis absorption wavelengths. A low-loading of this magnetic DES catalyst showed a superior activity in the rapid synthesis of THDPPs and pyrroles in water, whereas the role of this magnetic DES catalyst is activation of carbonyl groups by complexation with the $CoCl_4^{2-}$ part of this catalyst. Co4ChDES is magnetically recoverable and no significant activity loss and leaching was observed after six consecutive cycles reusing of it in the rapid and efficient synthesis of pyrrole derivatives.

Acknowledgment

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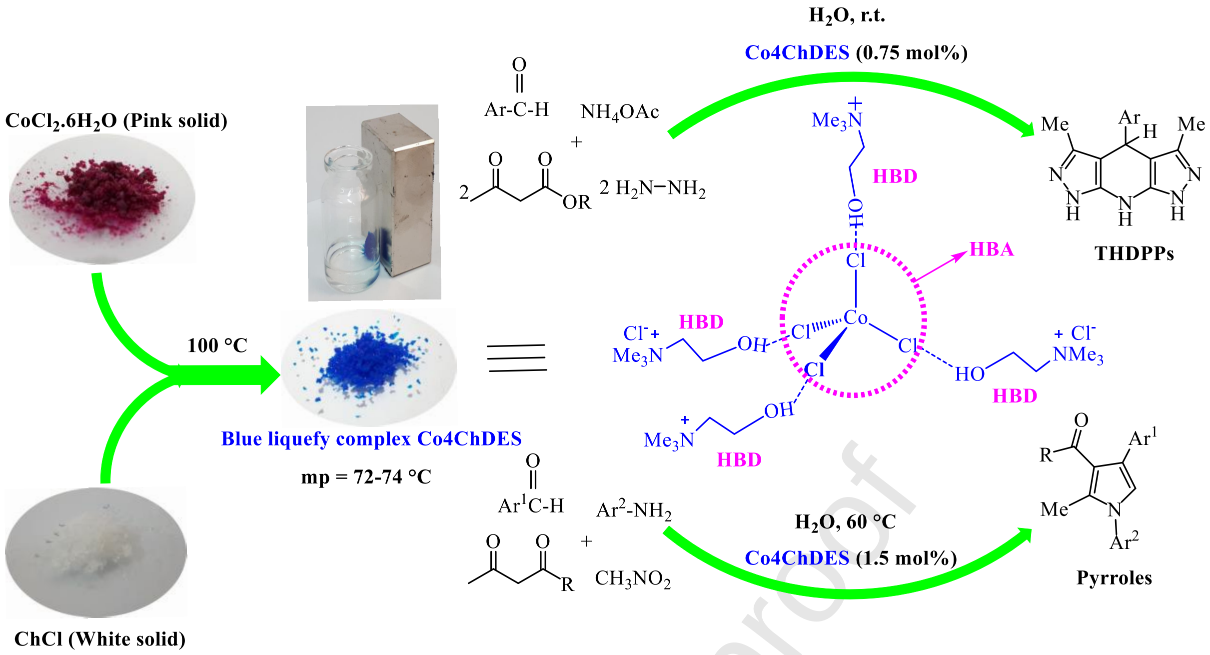
☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:


H2O, r.t.
Co4ChDES (0.75 mol%)
CoCl2.6H2O (Pink solid)
Ar-C-H
NH4OAc
+
2
OR
2 H2N−NH2
Me3N
HBD
Me
Ar
H
Me
N
N
H
N
H
N
H
N
THDPPs
OH
Cl
HBA
100 °C
HBD
Cl-+
Me3N
OH
Cl
Co
Cl
Cl
HO
+ Cl-
NMe3
HBD
OH
Me3N
HBD
Blue liquefy complex Co4ChDES
mp = 72-74 °C
Ar1C-H
Ar2-NH2
+
R
CH3NO2
H2O, 60 °C
Co4ChDES (1.5 mol%)
R
Ar1
Me
N
Ar2
Pyrroles
ChCl (White solid)

- The $CoCl_2.6H_2O$ and choline chloride (ChCl) at 1:4 ratios gives Co4ChDES.
- The magnetic response of Co4ChDES is due to the tetrahedral counter ion $CoCl_4^{2-}$.
- The $CoCl_4^{2-}$ and four choline-OHs are own H-bonding acceptors and donors.
- This magnetic deep eutectic catalyst was structurally confirmed by various methods.
- Co4ChDES is a reusable catalyst for synthesis of *N*-heterocycles in water.