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Diphenhydramine Hydrochloride−CuCl as a New Catalyst for the Synthesis of Tetrahydrocinnolin-5(1*H*)-ones

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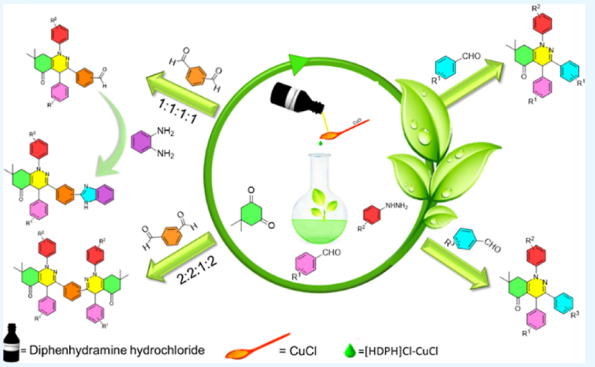
ABSTRACT: The current study deals with the synthesis and characterization of a novel catalyst made from diphenhydramine hydrochloride and CuCl ([HDPH]Cl−CuCl). The prepared catalyst was thoroughly characterized using various techniques, such as ^{1}H NMR, Fourier transform-infrared spectroscopy, differential scanning calorimetry, and thermogravimetric analysis and derivative thermogravimetry. More importantly, the observed hydrogen bond between the components was proven experimentally. The activity of this catalyst was checked in the preparation of some new derivatives of tetrahydrocinnolin-5(1*H*)-ones *via* a multicomponent reaction between dimedone, aromatic aldehydes, and aryl/alkyl hydrazines in ethanol as a green solvent. Also, for the first time, this new homogeneous catalytic system was effectively used for the preparation of unsymmetric tetrahydrocinnolin-5(1*H*)-one derivatives as well as *mono*- and *bis*-tetrahydrocinnolin-5(1*H*)-ones from two different aryl aldehydes and dialdehydes, respectively. The effectiveness of this catalyst was further confirmed by the preparation of compounds containing both tetrahydrocinnolin-5(1*H*)-one and benzimidazole moieties from dialdehydes. The one-pot operation, mild conditions, rapid reaction, and high atom economy, along with the recyclability and reusability of the catalyst, are other notable features of this approach.



INTRODUCTION

Nitrogen-containing heterocyclic compounds, a very important class of heterocycles, are of interest to organic and medicinal chemists because of their occurrence in natural products as well as diverse pharmaceutical and biological activities.[1−3] Notably, cinnolines are one of the vital *N*-containing heterocycles, known for their privileged anti-inflammatory,[4] antibacterial,[4] anticancer,[5] and antimicrobial[6] activities. Also, their derivatives have exhibited remarkable properties in n-channel semiconductors[7] and cell imaging.[8] Accordingly, several protocols have been introduced for the synthesis of cinnolines from different starting materials, including arenediazonium salts,[9] arylsulfonylhydrazones,[10] methylhydrazine,[11] and nitriles.[12] However, introducing a new procedure for the synthesis of cinnoline derivatives using a greener and more sustainable catalyst is highly desirable, and in the present work, we report diphenhydramine hydrochloride−CuCl ([HDPH]-Cl−CuCl) as a new catalyst for the synthesis of tetrahydrocinnolin-5(1*H*)-ones.

Copper catalysts have gained widespread consideration over the past years for the synthesis of many important *N*-heterocyclic compounds due to their low cost, abundance, and low toxicity.[13,14] Among them, CuCl, as one of the most commonly used salts of copper, shows tremendous applications in such organic synthesis.[15−17] Although CuCl is a suitable and valuable Lewis acid catalyst, it suffers from certain shortcomings like moisture and air sensitivity, which limit its practical applications.[18] However, the combination of CuCl with a species capable of hydrogen bonding can stabilize it, providing an excellent opportunity to improve its catalytic purposes.[18−22]

During recent years, multicomponent reactions (MCRs) have gained a great deal of attention in organic and medicinal chemistry owing to the generation of biologically active compounds with significant structural diversity and complex heterocyclic compounds.[23,24] High convergence and atom economy, environmentally favorable processes, mild reaction conditions, simple experimental procedure, and a one-pot character are outstanding advantages of these reactions over the classical stepwise methods.[25−30] Consequently, they provide a more efficient and convenient protocol for synthetic chemistry for the preparation of fine chemicals.

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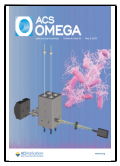
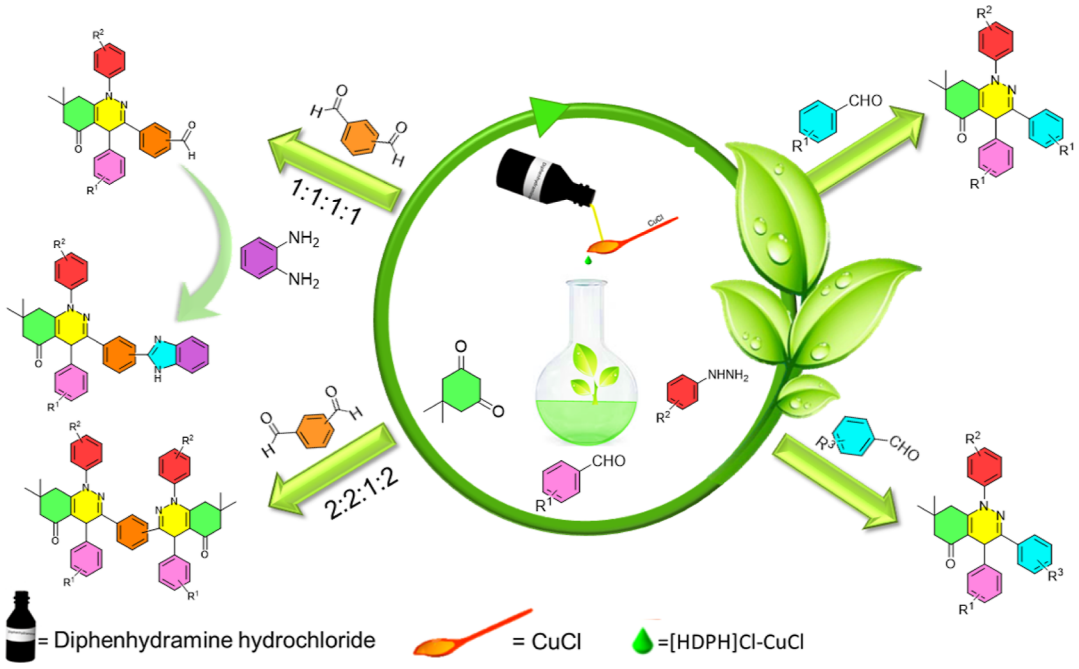


Scheme 1. Synthesis of Tetrahydrocinnolin-5(1*H*)-ones Catalyzed by [HDPH]Cl−CuCl



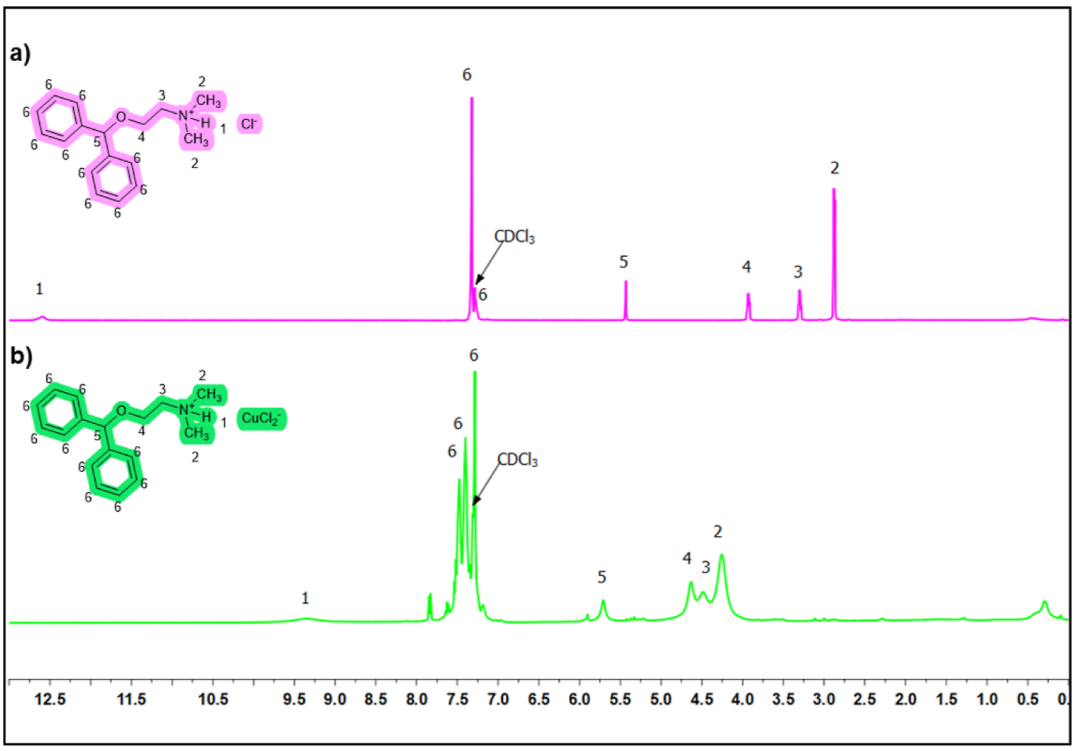


Figure 1. ^{1}HNMR spectra (400 MHz, $CDCl_3$) of: (a) [HDPH]Cl (magenta) and (b) [HDPH]Cl−CuCl (green).

In continuation of our research on synthesizing *N*-containing heterocyclic compounds using effective and reusable catalysts,[31−33] we wish to introduce a novel and convenient protocol for the one-pot domino multicomponent synthesis of symmetric, unsymmetric, as well as *mono*- and *bis*-tetrahydrocinnolin-5(1*H*)-ones *via* the reaction of aromatic aldehydes/dialdehydes, dimedone, and aryl/alkyl hydrazines catalyzed by [HDPH]Cl−CuCl as a new catalyst in the green solvent ethanol (Scheme 1).

RESULTS AND DISCUSSION

Synthesis and Characterization of [HDPH]Cl−CuCl. The desired catalyst was synthesized by mixing diphenhydramine hydrochloride with CuCl in a 1:1 molar ratio, as mentioned in the Experimental Section, and characterized by different techniques as follows.

^{1}H NMR Spectra. The ^{1}H NMR spectra of [HDPH]Cl and [HDPH]Cl−CuCl are shown in Figure 1. The peak attributed to $-N^{+}-H$ in [HDPH]Cl is observed at 12.59 ppm (Figure

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1a), which, after the formation of the catalyst, is up-fielded to 9.37 ppm (Figure 1b). Such a result has already been reported for Lewis acid-ILs. This observation could be attributed to the weaker interaction between $-N^+-H$ and $CuCl_2^-$ compared to $-N^+-H$ and Cl^- and to the higher negative charge distribution on $CuCl_2^-$ than Cl^-.[34] Interestingly, upon formation of the catalyst, the peaks corresponding to the aliphatic moieties are downfielded, especially those of methyl and methylene groups attached to the nitrogen atom. It seems that $CuCl_2^-$ was positioned so that it could interact with the aliphatic hydrogens, decreasing the electron density of these hydrogens and leading to their deshielding. This phenomenon was also observed in the aromatic region; however, the large distance between $CuCl_2^-$ and aromatic moieties caused a slight change in their chemical shifts.

Fourier Transform-Infrared Spectra. The Fourier transform-infrared (FT-IR) spectra of diphenhydramine hydrochloride and [HDPH]Cl−CuCl are presented in Figure 2. The

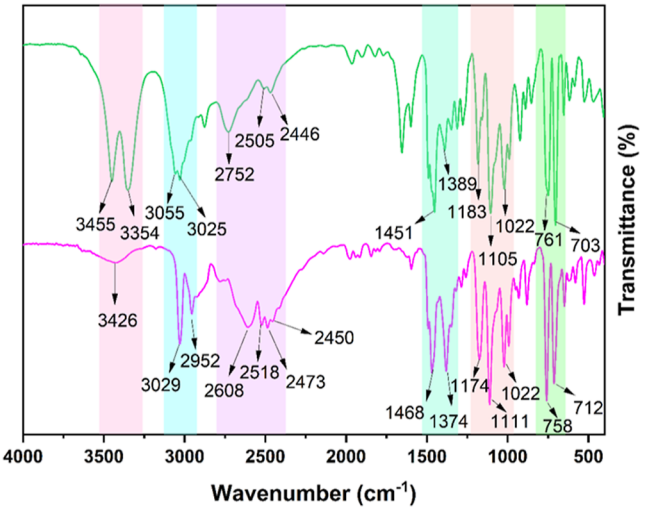

Figure 2. FT-IR spectra of (a) [HDPH]Cl (magenta) and (b) [HDPH]Cl−CuCl (green).

band at about 3354 cm^{-1} corresponds to the (Cu−Cl−)OH groups and physisorbed moisture. The characteristic band at 3029 cm^{-1} (sp^2 C−H) was shifted to higher wave numbers by about 26 cm^{-1}. The bands at 1596 and 1111 cm^{-1} are assigned to aromatic ring skeletal vibrations and C−O−C stretching, respectively.[35] The peak of CH_2 stretching vibration showed a red shift from 1468 to 1451 cm^{-1}, while the peak of CH_3 stretching vibration represented a blue shift from 1374 to 1389 cm^{-1}. Since the interaction between $-N^+-H$ and $CuCl_2^-$ is much weaker than that between $-N^+-H$ and Cl-,[36,37] the peaks related to $-N^+-H$ (2400−2700 cm^{-1}) weakened and showed a blue shift.

Thermal Analysis. To explore the thermal behavior of [HDPH]Cl−CuCl, differential scanning calorimetry (DSC) was used. Upon heating from −60 to 60 °C, the devitrification temperature (T_c) was observed at around −31 °C, and two melting points (T_m) were recorded at around −18 and −5 °C (Figure 3). It is important to note that some designed mixtures, such as ibuprofen:thymol,[38] lidocaine:1,8-octanediol,[39] and methyltriphenylphosphonium bromide:1,8-octanediol,[40] have already been reported with two melting points. The molar ratios on either side of the eutectic composition are a reason for this phenomenon.[39,40] In addition, two melting

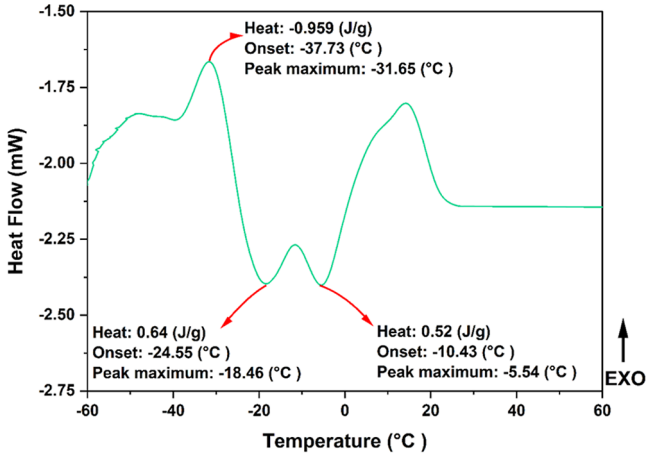

Figure 3. DSC curve of [HDPH]Cl−CuCl.

points for Lewis acid-based-mixtures have also been observed. For instance, in 2005, Liu and co-workers designed a mixture of choline chloride and $ZnCl_2$,[41] representing two melting points at 43 and 85 °C. This mixture had two crystalline structures attributed to the anionic forms of $ZnCl_2$ ($ZnCl_3^-$ and $Zn_2Cl_5^-$). Furthermore, CuCl has two forms, that is, $CuCl_2^-$ and $Cu_2Cl_3^-$, in the designed mixtures, and ILs[18] has been reported. Accordingly, two melting points can be expected for [HDPH]Cl−CuCl.

The thermal stability of the [HDPH]Cl−CuCl was studied using thermogravimetric analysis (TGA; Figure 4). The

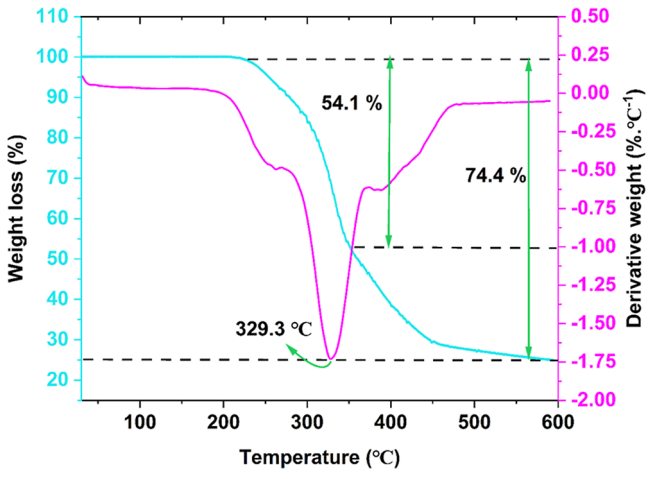

Figure 4. Thermogravimetric analysis and derivative thermogravimetry (TGA/DTG) of [HDPH]Cl−CuCl.

desired catalyst is stable up to 329 °C with $T_{5\%}$ and $T_{10\%}$ at 249.63 and 278.92 °C, respectively. The residual weight at 600 °C (25.57%) corresponds to the inorganic content of chlorocuprate(I) moieties, which is completely comparable with the theoretically calculated amount (25.50%).

Acidity Measurements. One of the essential features of the catalysts is their acidity. In most cases, measuring their pH gives an outlook of their acidity but does not provide enough information about Brønsted and Lewis acid sites. Moreover, specialized measurements, such as temperature-programmed desorption analysis, cannot be used for low melting point materials.[42] Although FT-IR is traditionally used to determine functional groups, it could be applied for the quality

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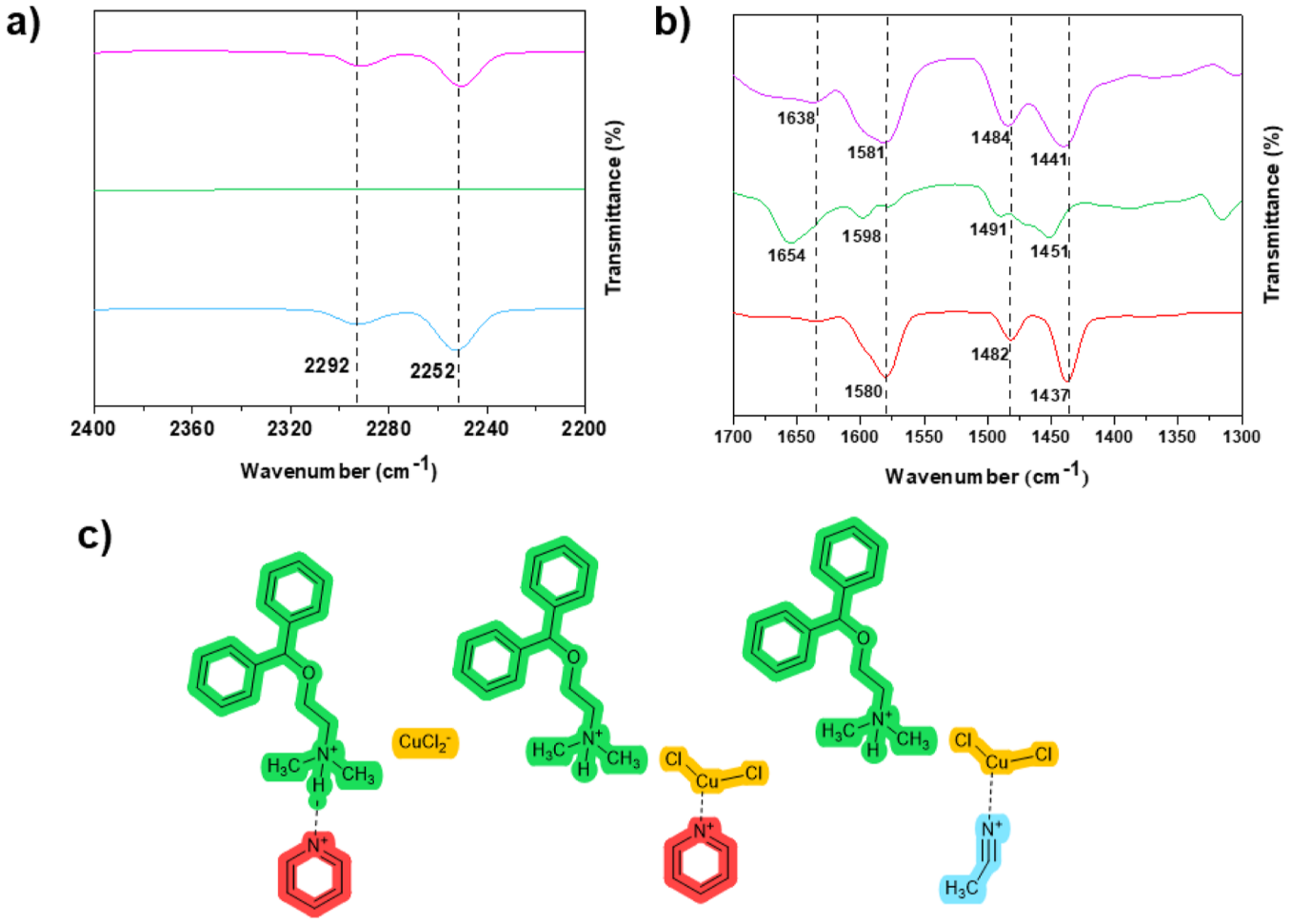

Figure 5. FT-IR spectra of: (a) acetonitrile (blue), [HDPH]Cl−CuCl (green), and [HDPH]Cl−CuCl in acetonitrile (pink). (b) Pyridine (red), [HDPH]Cl−CuCl (green) ,and [HDPH]Cl−CuCl in pyridine (violet). (c) The interaction between the Lewis and Brønsted acid sites with pyridine and acetonitrile.

determination of acid sites. Pyridine FT-IR and acetonitrile FT-IR are two complementary analyses representing excellent data for the Brønsted and Lewis acid sites. For each test, a mixture of [HDPH]Cl−CuCl and probe was prepared[43] and subjected to FT-IR analysis. Figure 5a represents the FT-IR spectrum of acetonitrile-[HDPH]Cl−CuCl. The Lewis acid peak was observed at 2292 cm^{-1}. Several peaks appeared in the case of pyridine FT-IR (Figure 5b). The band centered at 1437 cm^{-1} in pure pyridine was shifted to 1441 cm^{-1} due to the coordination of pyridine groups with the Lewis acid sites. The formation of pyridinium ions ($[PyH]^+$), upon interaction with Brønsted acid sites, also appeared at 1638 cm^{-1}.[44,45] The interactions between the Lewis and Brønsted acid sites with pyridine and acetonitrile are schematically depicted in Figure 5c. The pH measurement was also carried out to confirm the acidity. A solution of [HDPH]Cl−CuCl (1.2×10^{-2} $mol.L^{-1}$) shows a pH value of 5.03, representing a good acidity of the prepared catalyst, which could be utilized for catalyzing organic reactions.

[HDPH]Cl−CuCl Solubility. The solubility of the catalyst is of great importance for its recovery and extraction processes. So, the solubility of the catalyst in water and common organic solvents was studied by dissolving 0.3 mmol of [HDPH]Cl−CuCl in 3 mL of different solvents. As shown in Table 1, [HDPH]Cl−CuCl is utterly soluble in polar aprotic solvents, including acetone, EtOAc, THF, and chloroform; sparingly soluble in polar protic solvents, such as water, methanol, ethanol, and isopropanol; and insoluble in non-polar aprotic solvents like *n*-hexane.

Table 1. Miscibility of [HDPH]Cl−CuCl with Common Solvents[a]

entry	solvent	[HDPH]Cl	CuCl	[HDPH]Cl−CuCl
1	acetone	S	IS	S
2	EtOAc	S	IS	S
3	THF	S	IS	S
4	CH_3Cl	S	IS	S
5	H_2O	S	IS	SS
6	MeOH	S	IS	SS
7	EtOH	S	IS	SS
8	isopropanol	S	IS	SS
9	*n*-hexane	IS	IS	IS

[a]S, soluble; IS, insoluble; SS, sparingly soluble.

Catalytic Activity. *Optimization of the Reaction Conditions.* Because of the aforementioned outstanding properties of the tetrahydrocinnolines, the introduction of an effective, safe, and sustainable procedure for the synthesis of these heterocyclic compounds is very important. In this regard, a new method for the synthesis of tetrahydrocinnolin-5(1*H*)-ones through the reaction of dimedone, aldehydes, and aryl/

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alkyl hydrazines was designed. The reaction between dimedone, 2-chlorobenzaldehyde, and phenylhydrazine was chosen for optimization of the reaction conditions. This reaction was investigated according to the general procedure mentioned in the Experimental Section. At first, the mentioned reaction was investigated without catalyst, using [HDPH]Cl (0.3 mmol) and CuCl (0.3 mmol) in EtOH, and the respective products were gained in 10, 12, and 39% yields, respectively (Table 2, entries 1−3). To further optimize the reaction conditions, various catalysts (Table 2, entries 4−9) were checked, and the best yield of product **4a** (80%) was obtained in the presence of [HDPH]Cl−CuCl (1:1, 0.3 mmol, Table 2, entry 9). In addition, [ChCl]$FeCl_3$ and [ChCl]$ZnCl_2$ were examined in this reaction, and the desired products were obtained in 58 and 46% yields, respectively (Table 2, entries 10, 11). Consequently, [HDPH]Cl−CuCl is more efficient as a catalyst than the choline chloride−Lewis acid combination. Encouraged by this result, further optimization was performed by varying the molar ratios of [HDPH]Cl to CuCl, the solvent, and the catalyst amount. The abovementioned reaction was also performed with 0.3 mmol of 2:1 and 1:2 molar ratios of [HDPH]Cl to CuCl (Table 2, entries 12, 13), and product **4a** was obtained in 40 and 80% yields, respectively. Using other solvents such as $CHCl_3$, *t*-BuOH, EtOAc, and CH_3CN instead of EtOH did not afford satisfactory results (Table 2, entries 14−17). It is also important to note that in the absence of an additional solvent, the product was obtained in 70% yield (Table 2, entries 18). The effect of catalyst loading was also investigated. Increasing the catalyst amount did not improve the yield of **4a**, but a reduction in the product yield was observed with decreasing the catalyst loading (Table 2, entries 19, 20). Consequently, using 0.3 mmol of [HDPH]Cl−CuCl (1:1) in EtOH solvent is the optimized reaction condition, which provided the highest yield of the desired product (Table 2, entry 9).

Table 2. Optimization of the Reaction Conditions for the Model Reaction

entry[a]	catalyst (mmol)	molar ratio	solvent	yield (%)[b]
1	-	-	EtOH	10
2	[HDPH]Cl (0.3)	-	EtOH	12
3	CuCl (0.3)	-	EtOH	39
4	[HDPH]Cl−$CuBr_2$ (0.3)	1:2	EtOH	13
5	[HDPH]Cl−$FeCl_3$ (0.3)	1:1	EtOH	61
6	[HDPH]Cl−$BiCl_3$ (0.3)	1:1	EtOH	30
7	[HDPH]Cl−$InCl_3$ (0.3)	1:1	EtOH	52
8	[HDPH]Cl−$CuCl_2$ (0.3)	1:2	EtOH	64
9	[HDPH]Cl−CuCl (0.3)	1:1	EtOH	80
10	[ChCl]$FeCl_3$	1:1	EtOH	58
11	[ChCl]$ZnCl_2$	1:2	EtOH	46
12	[HDPH]Cl−CuCl (0.3)	2:1	EtOH	40
13	[HDPH]Cl−CuCl (0.3)	1:2	EtOH	80
14	[HDPH]Cl−CuCl (0.3)	1:1	$CHCl_3$	43
15	[HDPH]Cl−CuCl (0.3)	1:1	*t*-BuOH	29
16	[HDPH]Cl−CuCl (0.3)	1:1	EtOAc	25
17	[HDPH]Cl−CuCl (0.3)	1:1	CH_3CN	17
18	[HDPH]Cl−CuCl (0.3)	1:1	-	70
19	[HDPH]Cl−CuCl (0.2)	1:1	EtOH	74
20	[HDPH]Cl−CuCl (0.4)	1:1	EtOH	80
21	[HDPH]Cl−CuCl (0.3)[c]	1:1	EtOH	51
22	[HDPH]Cl−CuCl (0.3)[d]	1:1	EtOH	23

[a]Reaction conditions: a mixture of dimedone **1** (1 mmol), 2-chlorobenzaldehyde **2a** (1 mmol), and catalyst in solvent (3 mL) was stirred for 35 min at room temperature, and then 2-chlorobenzaldehyde **2a** (1 mmol) and phenylhydrazine **3a** (1 mmol) were added to the mixture and stirred for 60 min under reflux conditions. [b]Isolated yield. [c]A mixture of dimedone **1** (1 mmol), 2-chlorobenzaldehyde **2a** (2 mmol), phenylhydrazine **3a** (1 mmol), and the catalyst in the solvent (3 mL) was stirred for 120 min under reflux conditions. [d]The second step was carried out at room temperature.

Synthesis of Tetrahydrocinnolin-5(1H)-one Derivatives. Considering optimal conditions, the scope and applicability of this process were explored for the synthesis of structurally diversified tetrahydrocinnolin-5(1*H*)-ones using a variety of aryl aldehydes and arylhydrazines. As revealed in Scheme 2, the treatment of a series of substituted aromatic aldehydes with either electron-withdrawing groups or electron-donating groups at the *ortho*-, *meta*-, and *para*-positions of the aromatic ring, with dimedone and arylhydrazines in the presence of [HDPH]Cl−CuCl furnished the corresponding symmetric tetrahydrocinnolin-5(1*H*)-one derivatives in 50−90% yields. Moreover, heterocyclic aldehydes, such as pyridine-3-carbaldehyde, participated in the reaction to afford the desired product **4g** in 70% yield.

Also, aliphatic hydrazine, such as methyl hydrazine, took part successfully in this reaction, and the corresponding tetrahydrocinnolin-5(1*H*)-one (**4o**) was obtained in 70% yield. However, the synthesis of tetrahydrocinnolin-5(1*H*)-ones using aliphatic aldehydes, such as 1-heptanal and 3-phenylpropionaldehyde, was unsuccessful.

Encouraged by the obtained promising results in the synthesis of symmetric tetrahydrocinnolin-5(1*H*)-ones, we then tried the synthesis of unsymmetric tetrahydrocinnolin-5(1*H*)-ones with two different aldehydes. Under the optimized conditions, unsymmetric tetrahydrocinnolin-5(1*H*)-ones were obtained by the reactions of 4-*tert*-butyl benzaldehyde and naphthalene-1-carboxaldehyde or 2,4-dichlorobenzaldehyde and pyridine-3-carbaldehyde and/or 4-nitrobenzaldehyde and 3,5-dimethoxy-4-hydroxybenzaldehyde, with dimedone and arylhydrazines in 51, 66, and 60% yields, respectively. As shown in Scheme 3, along with unsymmetric tetrahydrocinnolin-5(1*H*)-ones, little amounts of symmetric derivatives (11−15%) were isolated from the reaction mixture. It is also important to note that in the synthesis of unsymmetric tetrahydrocinnolin-5(1*H*)-ones, the regioselectivity is mainly controlled by the order of addition of aldehyde molecules to the reaction mixture so that the first aldehyde molecule, which reacts with dimedone, enters the 4-position and the second aldehyde molecule, upon reaction with arylhydrazine, enters the 3-position of the tetrahydrocinnolin ring in the final product. The synthesis of symmetric and unsymmetric tetrahydrocinnolin-5(1*H*)-ones *via* a one-pot domino MCR using a green catalyst and solvent can be considered one of the privileged features of this method.

Another outstanding feature of the present procedure lies in the synthesis of *mono*- and *bis*-tetrahydrocinnolin-5(1*H*)-ones from dialdehydes, such as terephthaldialdehyde, isophthaldialdehyde. As revealed in Scheme 4, when dimedone and aldehydes were reacted with terephthaldialdehyde or isophthaldialdehyde and arylhydrazines in a 1:1:1:1 molar ratio under the optimized conditions, the corresponding *mono*-tetrahydrocinnolin-5(1*H*)-ones were obtained as major products in 45−53% yields, along with little amounts of *bis*-products (15−19% yields). Whereas, using the 2:2:1:2 molar ratio of the above-mentioned substrates, the corresponding *bis*-

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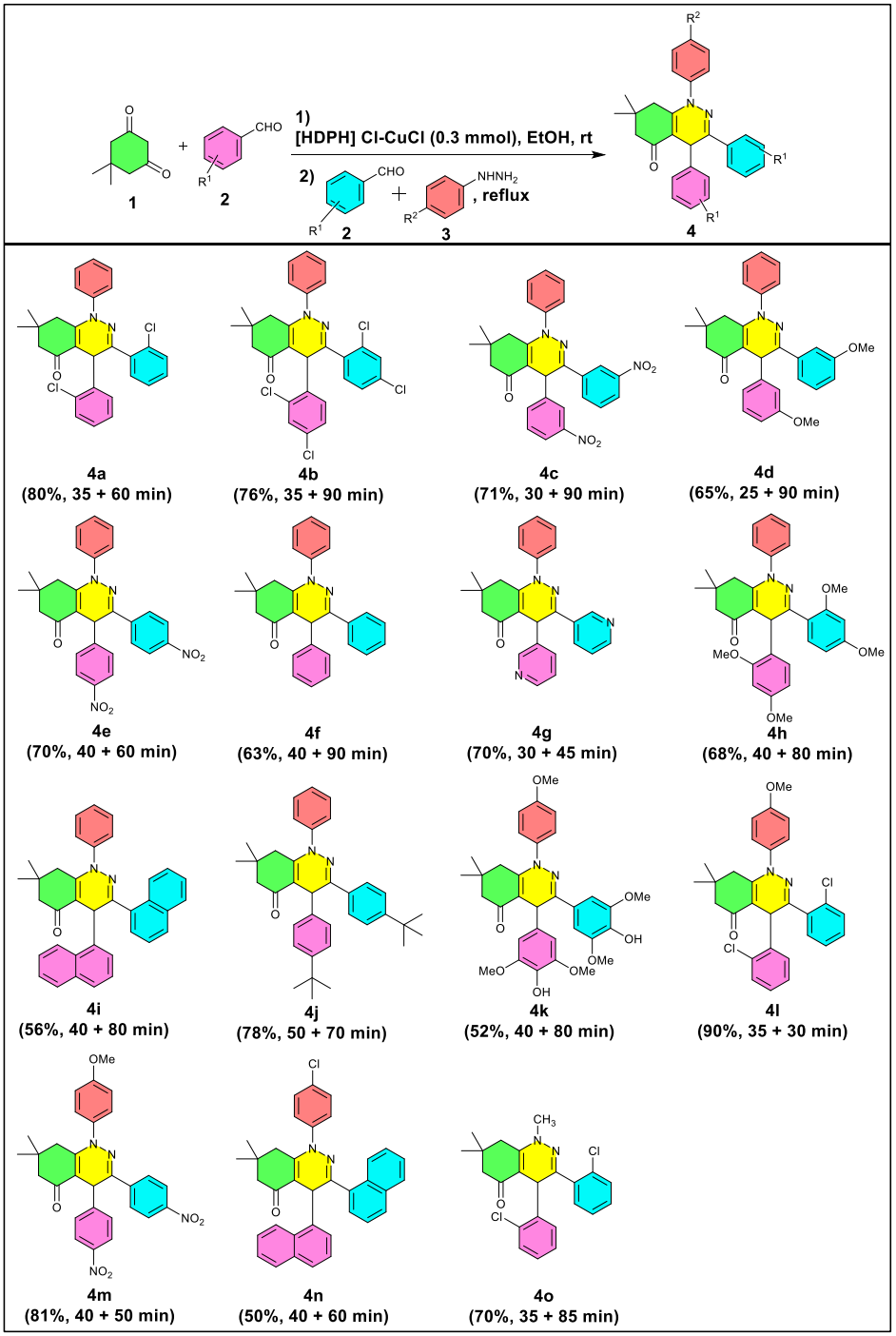
Scheme 2. Synthesis of Symmetric Tetrahydrocinnolin-5(1*H*)-ones Catalyzed by [HDPH]Cl−CuCl



and *mono*-tetrahydrocinnolin-5(1*H*)-ones were formed in 40−45 and 17−19% yields, respectively. It is interesting to point out that in the synthesis of **8e**, the reaction led to a complex mixture from which the desired product **8e** was isolated in 52% yield after chromatography on silica gel.

It is noteworthy that the synthesis of *mono*-tetrahydrocinnolin-5(1*H*)-ones from dialdehydes is practically important and exceedingly desirable since the remaining formyl group can participate in the synthesis of other important organic compounds. To demonstrate such applicability, the reaction of *mono*-tetrahydrocinnolin-5(1*H*)-ones as a new series of aldehydes with *o*-phenylenediamine was checked. As depicted in Scheme 5, these reactions were efficiently carried out in the presence of [HDPH]Cl−CuCl, and the corresponding 1*H*-benzo[*d*]imidazolyl derivatives of tetrahydrocinnolin-5(1*H*)-ones were obtained with excellent selectivity and yields. The selective synthesis of 2-substituted benzimidazoles by condensation of aldehydes with *ortho*-phenylenediamine generally suffers from product selectivity leading to 2-substituted and 1,2-disubstituted benzimidazoles, an aspect that remained unattended till the literature reports[46−49] highlighted and addressed the issue. Thus, the selective synthesis of 2-substituted benzimidazoles achieved in the present work is a notable advantage.

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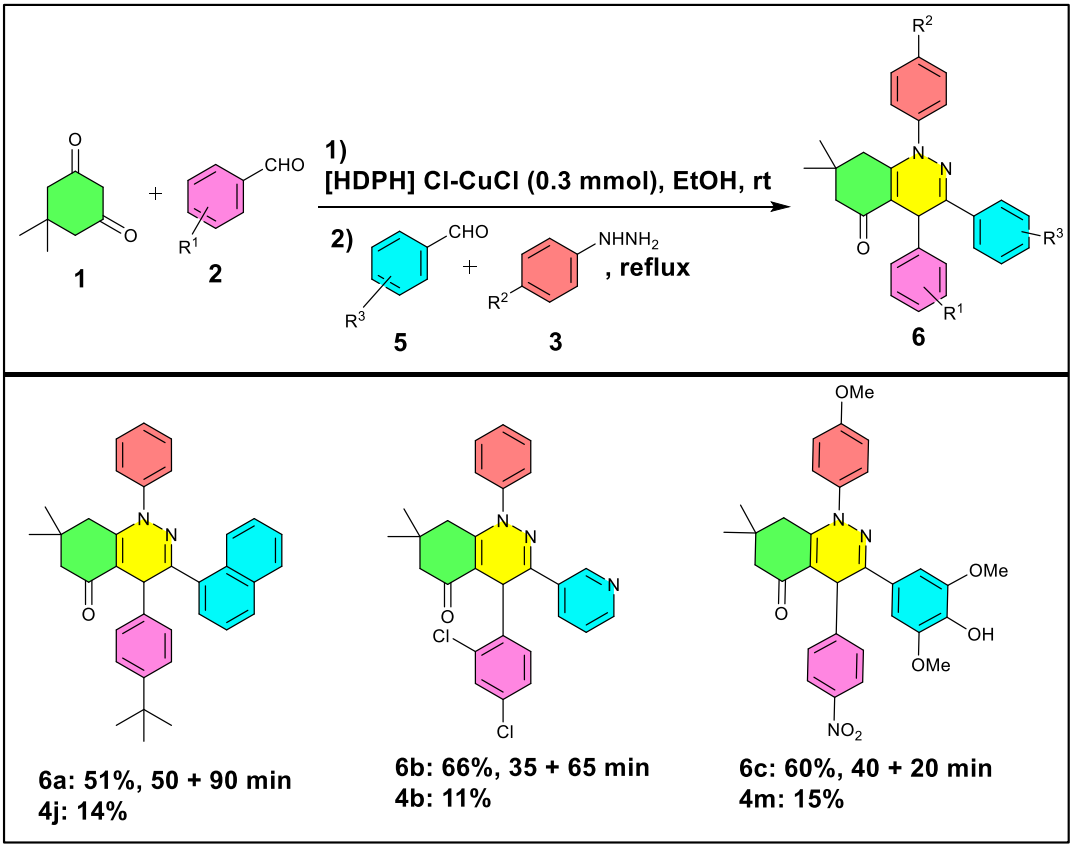
Scheme 3. Synthesis of Unsymmetric Tetrahydrocinnolin-5(1*H*)-ones Catalyzed by [HDPH]Cl−CuCl



Another outstanding feature of the present procedure lies in the gram-scale synthesis of tetrahydrocinnolin-5(1*H*)-ones. In this respect, the model reaction was checked with 10 mmol for each of the starting materials in the presence of [HDPH]Cl−CuCl under the optimized conditions. The corresponding tetrahydrocinnolin-5(1*H*)-one **4a** was produced in 78% yield, which is comparable to the yield obtained by the small-scale experiment. Consequently, this method can be applied to a large-scale operation.

The structures of the products were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analysis. The structure of **4f** was additionally confirmed by X-ray crystallographic analysis (Figure 6; CCDC 2181633).

Catalyst Recycling and Reuse. Recovery and reuse are fundamental aspects for industrial and commercial applications as well as green process considerations. Thus, the reusability of [HDPH]Cl−CuCl was investigated in the tandem multicomponent synthesis of **4a**. At the end of the reaction, the mixture was cooled to ambient temperature, and *n*-hexane was added to form a biphasic solution. The catalyst remains in ethanol in the lower phase, and other components transfer to the *n*-hexane phase. The catalyst was recovered by evaporating ethanol at 70 °C under vacuum and reusing it for the next run. As can be seen (Figure 7a), the catalyst conserved its activity after three consecutive runs. A comparison of the FT-IR (Figure 7b) and ^{1}H NMR (Figure 8) spectra of fresh and recycled catalysts showed no obvious changes in the structure of the catalyst.

As mentioned above, the presence of copper chloride in the structure of the catalyst increases its stability, and thus, its oxidation state is maintained.[18,22] The oxidation state of metals can be checked by Raman spectroscopy. Accordingly, the Raman spectra of the fresh and reused [HDPH]Cl−CuCl were run and depicted in Figure 9. The stretching vibrations of Cu−Cl[50,51] were observed at 250−300 cm^{-1}. The manifestation of a broad band in the range of 250−300 cm^{-1} in the Raman spectra of fresh and recycled catalysts is due to the presence of Cu(I) anionic species and implies that the anion in [HDPH]Cl−CuCl is mainly $CuCl_2^-$, which remains basically unchanged after the reaction.

Green Chemistry Metric Evaluation. To investigate the greenness and sustainability of the present protocol, a series of green metrics,[52−59] such as effective mass yield (EMY), atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency, optimum efficiency (OE), and *E*-factor, for the synthesized compounds were calculated (Supporting Information). The data show that this protocol provides high AE 88.15%−91.95% (for **4a−9d**) and 96.54%−96.73% (for **11a−c**) because only the water molecule is eliminated in this protocol. Also, the calculated EMY, AEf, OE, and CE for the present method measure up to 88.82, 88.99, 94.09, and 92%, respectively. The low *E*-factor indicated the minimum waste formation in this protocol. Based on these data and also using a bio-based solvent (ethanol) and recoverable catalyst, this protocol can be considered a green protocol.

CONCLUSIONS

In conclusion, for the first time, a deep eutectic mixture containing diphenhydramine hydrochloride and CuCl was prepared and used as an effective catalyst for the synthesis of a new series of symmetric and unsymmetric tetrahydrocinnolin-

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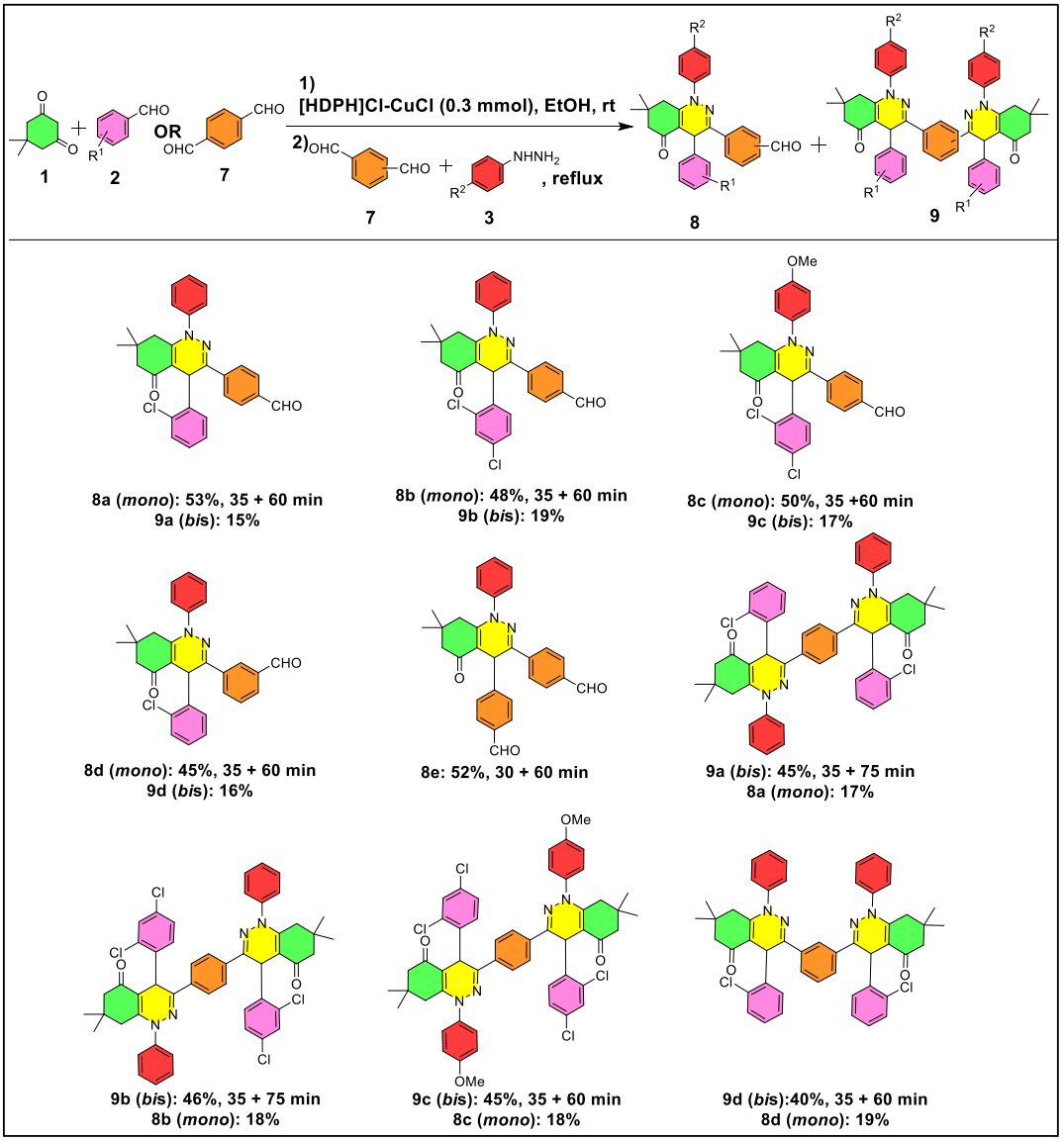
Scheme 4. Synthesis of *Mono*- and *Bis*-tetrahydrocinnolin-5(1*H*)-ones from Dialdehydes Catalyzed by [HDPH]Cl−CuCl



5(1*H*)-ones through the MCR of dimedone, aromatic aldehydes, and aryl/alkyl hydrazines in ethanol as a green solvent. The synthesis of *mono*- and *bis*-tetrahydrocinnolin-5(1*H*)-ones and compounds containing both tetrahydrocinnolin-5(1*H*)-one and benzimidazole moieties from dialdehydes was also achieved using this catalytic system. Moreover, high atom economy, good to high yields, short reaction times, avoiding toxic organic solvents, and catalyst reusability make it an attractive, safe, and green process for the synthesis of these valuable heterocyclic compounds.

EXPERIMENTAL SECTION

General Information. The chemicals were purchased from Fluka and Merck chemical companies. A Stuart Scientific SMP2 apparatus was used to determine the melting points of the synthesized compounds. FT-IR spectra were recorded on a Nicolet Impact 400D spectrophotometer. To identify the structure of the catalyst and products, ^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer using a $CDCl_3$ solvent. Elemental analysis was performed on a LECO, CHNS-932 analyzer. To elucidate the thermal stability of the catalyst, TGA/DTG were evaluated on a Perkin Elmer STA 6000 instrument under nitrogen flow at a uniform heating rate of 10 °C min^{-1} in the range of 30−600 °C. To explore the thermal behavior of [HDPH]Cl−CuCl, DSC was used, which was performed with a TA Instruments model DSC13-Setaram under a nitrogen atmosphere with a scan rate of 10 °C min^{-1} in the range −60 to 60 °C. The Raman spectra of the fresh and reused [HDPH]Cl−CuCl were obtained by using a Renishaw inVia Reflex instrument with a 532 nm argon-ion laser for excitation to check the oxidation state of CuCl.

General Procedure for the Synthesis of Catalysts. To synthesize catalysts, diphenhydramine hydrochloride was mixed with each of the metal chlorides mentioned in Table 3 with appropriate molar ratios. Then, the mixture was heated up to 90 °C with gentle stirring under a nitrogen atmosphere until liquefaction. The mixture was cooled to room temperature and used without any other purification for further studies.

Synthesis of Symmetric and Unsymmetric Tetrahydrocinnolin-5(1*H*)-ones Catalyzed by [HDPH]Cl−CuCl.

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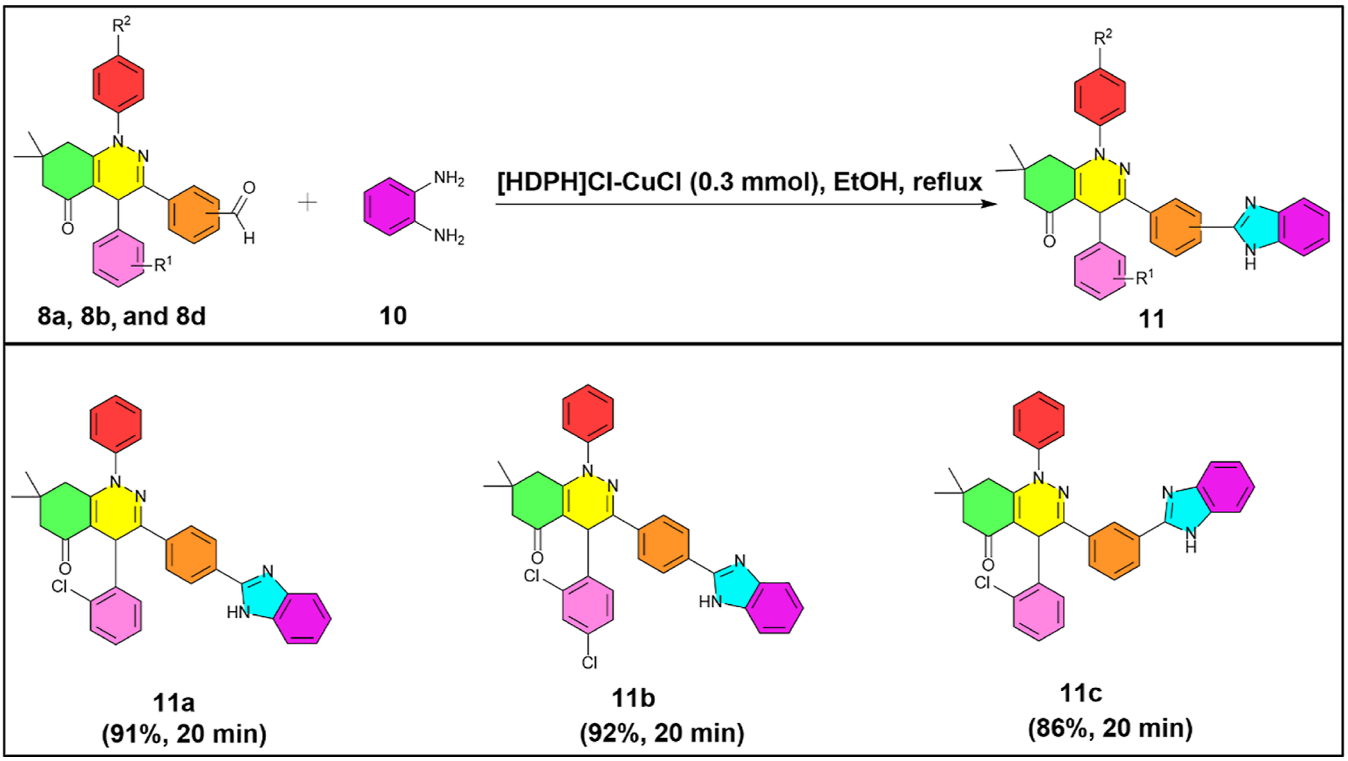
Scheme 5. Synthesis of 1*H*-Benzo[*d*]imidazolyl Derivatives of Tetrahydrocinnolin-5(1*H*)-ones from *Mono*-tetrahydrocinnolin-5(1*H*)-ones Catalyzed by [HDPH]Cl−CuCl



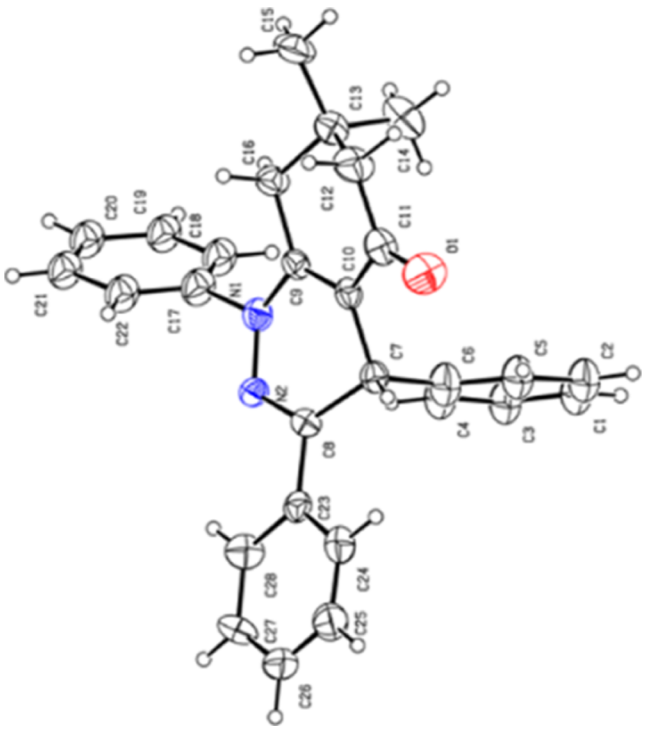


Figure 6. X-ray Crystallography structure of **4f**.

First, a mixture of dimedone **1** (1 mmol), aryl aldehyde **2** (1 mmol), and [HDPH]Cl−CuCl (1:1, 0.3 mmol) in ethanol (3 mL) was stirred for 25−50 min at room temperature. Then, aryl aldehyde **2** or **5** (1 mmol) and arylhydrazine **3** (1 mmol) were added to the mixture and stirred for 20−90 min under reflux conditions. After the consumption of precursors as indicated by thin layer chromatography (TLC) (eluent: *n*-hexane/EtOAc, 5:1), the mixture was cooled to room temperature. Due to the insolubility of the catalyst in *n*-hexane, the crude product was extracted using 15 mL *n*-hexane. Evaporation of the solvent, followed by purification of the crude product by chromatography on silica gel (eluent: *n*-hexane/EtOAc, 5:1) gave the pure product (Schemes 2 and 3).

Synthesis of *Mono* and *Bis*-tetrahydrocinnolin-5(1*H*)-ones from Dialdehydes Catalyzed by [HDPH]Cl−CuCl. For the synthesis of *mono*-derivatives, a mixture of dimedone **1** (1 mmol), aryl aldehyde **2** (1 mmol), and [HDPH]Cl−CuCl (1:1, 0.3 mmol) in ethanol (3 mL) was stirred for 30−35 min at room temperature. Then, dialdehyde **6** (1 mmol) and arylhydrazine **3** (1 mmol) were added to the mixture and stirred for 60 min under reflux conditions. After completion of the reaction, as demonstrated by TLC (eluent: *n*-hexane/EtOAc, 5:1), the purification was carried out as mentioned for the synthesis of tetrahydrocinnolin-5(1*H*)-ones. For the synthesis of *bis*-tetrahydrocinnolin-5(1*H*)-ones, dimedone **1** (1 mmol) reacted with aryl aldehyde **2** (1 mmol) in the presence of [HDPH]Cl−CuCl (1:1, 0.3 mmol) in ethanol (3 mL) for 35 min at room temperature. Then, dialdehyde **6** (0.5 mmol) and arylhydrazine **3** (1 mmol) were added to the mixture and stirred for 60−75 min under reflux conditions. The reaction was checked by TLC (eluent: *n*-hexane/EtOAc, 5:1). The workup was performed according to the procedure above mentioned to provide the desired product (Scheme 4).

Synthesis of 1*H*-Benzo[*d*]imidazolyl Derivatives of Tetrahydrocinnolin-5(1*H*)-one from *Mono*-tetrahydrocinnolin-5(1*H*)-ones. A mixture of *mono*-tetrahydrocinnolin-5(1*H*)-one (1 mmol), 1,2-phenylenediamine (1 mmol), and [HDPH]Cl−CuCl (1:1, 0.3 mmol) in EtOH (3 mL) was stirred under reflux conditions. After spending the starting

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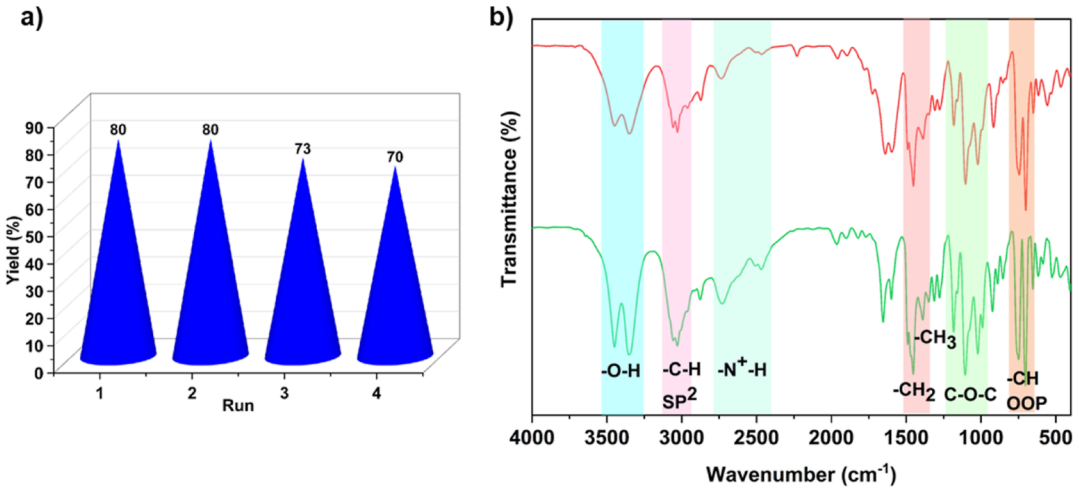

Figure 7. (a) Recovery and reuse of the catalyst for the synthesis of **4a**. (b) FT-IR spectra of fresh (green) and reused (red) [HDPH]Cl−CuCl.

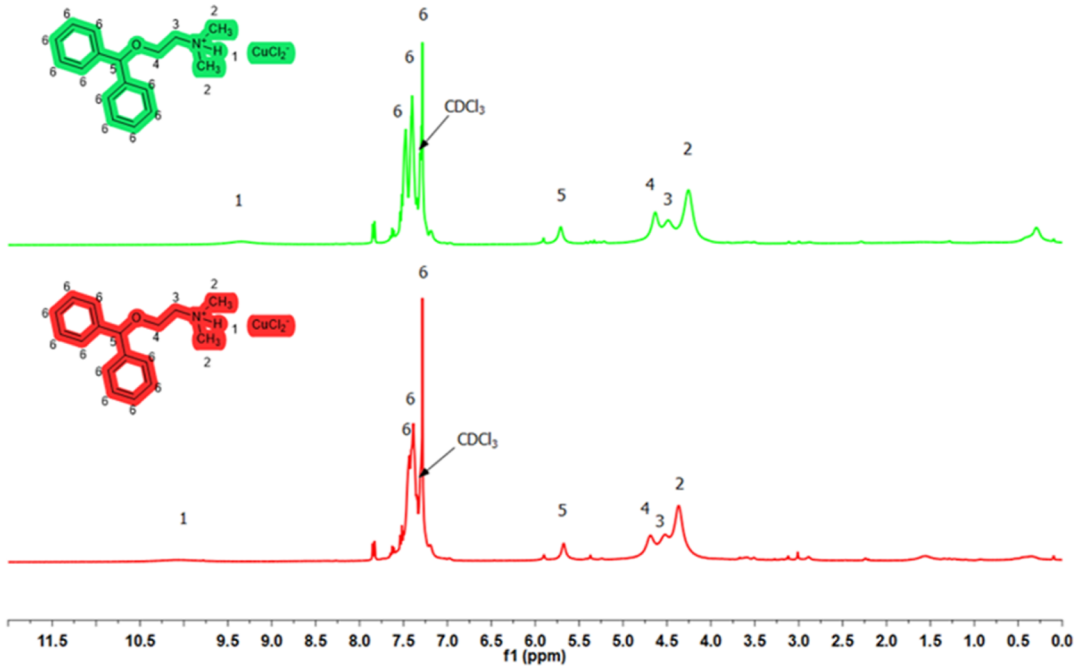

Figure 8. ^{1}H NMR spectra of fresh (green) and reused (red) [HDPH]Cl−CuCl.

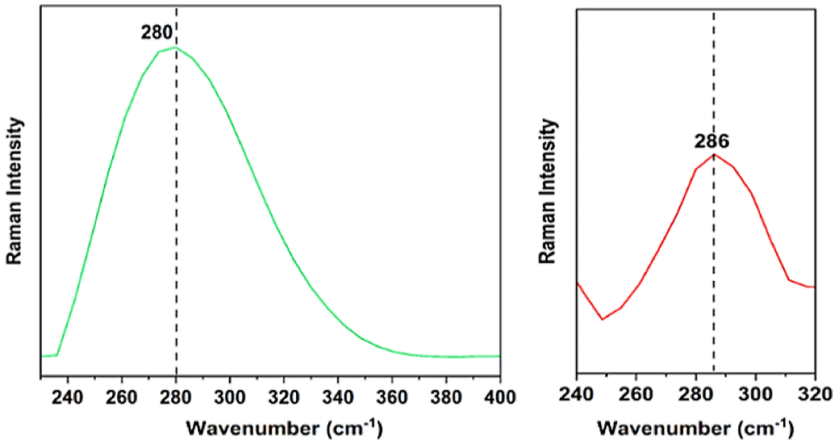

Figure 9. Raman spectra of fresh (green) and reused (red) [HDPH]Cl-CuCl.

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Table 3. State of Different Catalysts

entry	catalyst	ratio	state at room temperature
1	[HDPH]Cl–CuCl	1:1	liquid
2	[HDPH]Cl–CuCl	1:2	liquid
3	[HDPH]Cl–CuCl	2:1	liquid
4	[HDPH]Cl–$CuCl_2$	1:2	liquid
5	[HDPH]Cl–$CuBr_2$	1:2	liquid
6	[HDPH]Cl–$ZnCl_2$	1:2	no clear melt
7	[HDPH]Cl–$FeCl_3$	1:1	liquid
8	[HDPH]Cl–$BiCl_3$	1:1	liquid
9	[HDPH]Cl–$InCl_3$	1:1	liquid
10	[HDPH]Cl–$AlCl_3$	1:1	white solid (no interaction between the solids)

materials as checked by TLC (eluent: *n*-hexane/EtOAc, 5:3), the mixture was cooled to room temperature, and the crude product was extracted with 15 mL *n*-hexane. The solvent was evaporated, and the crude material was purified by chromatography on silica gel (eluent: *n*-hexane/EtOAc, 5:3) to provide the desired pure product (Scheme 5).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06765.

Spectroscopic data of the products, ^{1}H and ^{13}C NMR spectra of the products, X-ray crystallography structure of **4f**, crystal data and structure refinement for **4f**, and bond lengths [Å] and angles [deg] for **4f** (PDF)

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Notes

The authors declare no competing financial interest.

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