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An Ambient Protocol for Polycyclic 1,4-Dihydropyridines Using a Heterogeneous Catalyst

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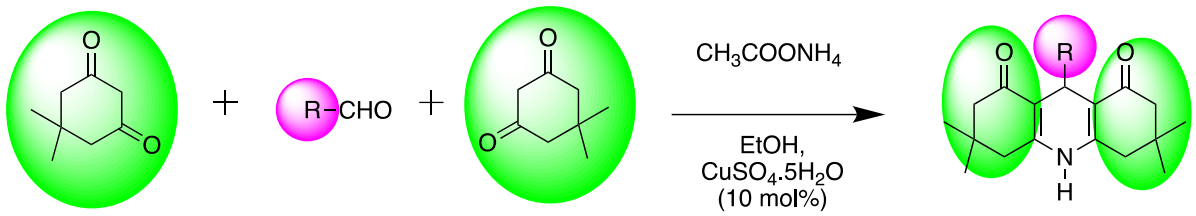
Abstract

Heterogeneous catalysts are chemical catalysts whose physical phase is different from the physical phase of the reactants and products of the chemical reaction being catalyzed. In recent years much interest has been shown in the efficient use of heterogeneous catalysts for the synthesis of biologically relevant heterocycles. In the present investigation, a scaffold of polycyclic 1,4-Dihydropyridines has been synthesized in ambient conditions utilizing the catalytic properties of cupric sulfate pentahydrate. The catalyst was found to be indispensable for carrying out the reaction in ambient conditions. The protocol described herein is benign, convenient, versatile, highly efficient, and free of harmful chemicals. The synthesized compounds were characterized by IR, ^{1}H NMR, LC-Mass spectroscopic techniques, and elemental analysis.



Keywords: 1,4-Dihydropyridines, Dimedone, Cupric sulfate, Heterogeneous Catalyst, Ambient temperature

Introduction

Due to economic and environmental concerns, there has been a growing interest in heterogeneous catalysts in organic synthesis, because they are removable from the reaction media by simple filtration and are reusable. Recently, $CuSO_4.5H_2O$ has been used in the capacity of heterogeneous Lewis acid catalyst for various organic transformations as an inexpensive, available, and safe reagent [1]. The multi-component reaction approach provides a highly valuable and formidable standard in combinatorial synthesis and drug development for the construction of diverse and complex polycyclic and polyfunctionalized heterocyclic compounds [2,3]. The generation of C–C, C–N, C–O, and C–S bonds by multi-component approach exhibits a promising path in synthetic chemistry given the high atom economy and efficiency of single-step one-pot reactions [4-8]. The Hantzsch reaction is one of the easiest and cheapest multi-component reactions [9] used for the synthesis of biologically relevant1,4-DHP derivatives, latter is an important class of heterocyclic compounds because of its umpteen

pharmacological properties ranging from anti-microbial [10], anti-coagulant [11], anti-oxidant [12], anticancer [13], antitubercular[14], cardiovascular [15], antileishmanial and anti-trypanosomal [16] HIV-1 protease inhibitors to antioxidant activities [17]. They have also been reported to possess antidiabetic [18], anti-inflammatory [19], antimicrobial, calcium channel blocker [20], antitumor [21], and antitubercular [22] activities, etc. Various conventional and green protocols have been reported for the synthesis of DHPs using different catalysts such as $AlCl_3 \cdot 6H_2O$ [23], $CeCl_3 \cdot 7H_2O$ [24], Ceric ammonium nitrate [25], Fermenting baker's yeast [26], $HClO_4 \cdot SiO_2$ [27], HY-zeolite [28], Ionic liquids [29], K10-montmorillonite clay [30], Molecular iodine [31], magnetite/chitosan [32], Ni nanoparticles [33], Organocatalysts [34], p-TSA [35], SiO_2 [36], triethylamine [37], TMSCl [38], ZnO [39], Fe-CuZSM-5 [40], microwave irradiation, and Ultrasound [41], etc. by the multi-component approach. However, most of the reported methods suffered many drawbacks such as harsh reaction conditions with high temperatures, the use of expensive and toxic materials, long reaction times, and low yields. The hunt for benign protocols is on and still there, are challenges facing chemists in the synthesis of heterocyclic compounds of medicinal value. To address these synthetic, economic, and safety concerns, we developed an efficient and versatile method for the synthesis of 1,4-DHPs using copper sulfate pentahydrate as a heterogeneous catalyst at ambient temperature [42]. A reaction of dimedone with an aldehyde and aniline, at room temperature, efficiently catalyzed by copper sulfate yielded N-substituted 1,4 DHPs quickly in very high yields. The reaction withstood all the changes concerning the position and nature of substituents in the aldehydic component. In the present work, we tested the versatility of copper sulfate for the Hantzch reaction in presence of ammonium sulfate as a source of nitrogen for the synthesis of a 1,4-DHP nucleus. The results were encouraging and established the copper sulfate pentahydrate as a versatile catalyst for the Hantzch reaction.

Results and Discussion

The product structure 4a-m was characterized by the appearance of N-H stretch between 3100-3200 cm^{-1} in the IR spectra of all these compounds. In the NMR spectra signals in the aromatic region between 6.4-7.5 and 10.96-11.92 ppm due to NH proton and the appearance of two signals of 6H each between 1.11 and 1.15 ppm in the product gave enough evidence for condensation of two molecules of dimedone with one molecule of aldehyde and one of ammonium acetate resulting in the formation of the proposed 1,4-Dihydropyridines.

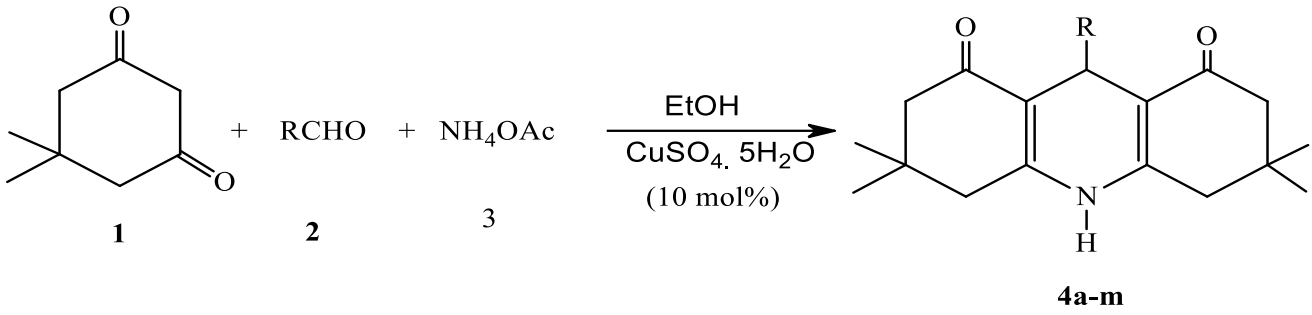
Initially, a mixture of dimedone (5,5-dimethyl-1,3-cyclohexanedione), benzaldehyde, and ammonium acetate in ethanol (5 mL) was stirred at room temperature in presence of 10 mol% of $CuSO_4.5H_2O$ (Scheme 1) to detect its efficiency as a catalyst for Hantzsch reaction. The ammonium sulfate homogenized with the other reactants whereas copper sulfate, as envisaged, did not solubilize and worked well as a heterogeneous catalyst. To our delight, the product formation started immediately and the reaction was complete within 5-6 min (as monitored by TLC plate examination). The reaction mixture was heated to solubilize the product, to recover the insoluble $CuSO_4.5H_2O$, by filtration. Upon cooling, the solid product could be recovered from the filtrate in good yields. The product characterization was done based on spectral data (IR, ^1H NMR, and mass) and elemental analyses.

$CuSO_4.5H_2O$ promotes the reaction as mild lewis acid, apart from its acidity cupric sulfate accelerates the dehydration, thereby facilitating the formation of cyclized 1,4-DHP nucleus. When performed in the absence of $CuSO_4.5H_2O$, the reaction did not take place at room temperature. Hence the presence of the

catalyst was indispensable for ambient synthesis. Having identified the qualitative role of the catalyst we tried to assess the quantitative aspect also. Synthesis of **4a** was carried out with different concentrations of $CuSO_4.5H_2O$.The yields were modest (68%) with 2 mol%, an increase in its concentration to 5 mol%, 10 mol%, and 15 mol% resulted in an increase in the product yield to 87%, 95%, and 96% respectively. Therefore, just 10 mol% of $CuSO_4.5H_2O$ was found sufficient to push the reaction forward in ambient conditions. $CuSO_4.5H_2O$ could be recovered after the reaction and was reused without any significant loss of activity (Table 1).

We then continued to optimize the model process by detecting the efficiency of several classical solvents chosen as the reaction medium for comparison (Table 2). In each case, the substrates were mixed with 10 mol% of $CuSO_4.5H_2O$ and agitated with 5-6 mL of the solvent the polar solvents such as ethanol, and acetonitrile (entry 1, 2) were much better than non-polar solvents (entry 3-6) due to the high solubility of reactants in the former.

Under the optimized reaction conditions next, we investigated the universality of the reaction. Results shown in (Table 3) indicate that aliphatic, aromatic (electron-rich and electron-deficient), and heteroaromatic aldehydes such as thiophene-2-carboxaldehyde and indole aldehyde too worked well exemplifying the generality of the reaction.



Scheme 1. Synthesis of 1,4-DHPs

Experimental

Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a model Perkin-Elmer FTIR-1710 spectrophotometer, ^{1}HNMR on a Bruker Advance Spectrospin 300 instrument (300 MHz) using TMS as an internal standard. Elemental analyses were performed on a Heraeus CHN Rapid Analyser and were in close agreement with calculated data. Mass spectra were recorded on a KC 455 Waters TOF Spectrometer. The purity of the compounds was checked on silica gel-coated aluminum plates (Merck).

Recycling of the Catalyst

After the completion of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 80°C for 1 h, and reused in another reaction. The recycled catalyst was used for five reactions without any appreciable loss in its catalytic activities.

General Synthesis of 4a-m

A mixture of dimedone **1** (2 mmol), aldehyde **2** (1 mmol), and ammonium acetate **3** (2 mmol) in ethanol (5 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC plate examination. After completion of the reaction, the reaction mixture was heated. This solubilized product. Upon cooling, the solid product was recovered from the filtrate in good yields. All products **4a** were recrystallized from ethanol.

Table 1. The percentage yields of 4c during the reuse of the $CuSO_4.5H_2O$ catalyst

Entry	1	2	3	4	5
Yield	96	95.5	95	94.2	93.5

Table 2. Reaction times and yields (%) in $CuSO_4.5H_2O$ catalyzed 1,4-DHP synthesis 4c using different solvents

Entry	Solvent	Time (min)	Yield (%)[a]
1.	C_2H_5OH	6	96
2.	CH_3CN	10	90
3.	Acetone	7	81
4.	Toluene	30	50
5.	CH_2Cl_2	25	54
6.	Cyclohexane	30	39

[a] isolated and un optimized yields.

Table 3. The yield (%) of $CuSO_4.5H_2O$ catalyzed 1,4 DHP synthesis of 4a-m in ethanol

Entry	R	Product	Yield (%)[a]
1.	H[b]	4a	93
2.	CH_3	4b	91
3.	C_6H_5	4c	95
4.	3-$NO_2C_6H_4$	4d	91
5.	4-ClC_6H_4	4e	92
6.	2-HOC_6H_4	4f	91
7.	4-HOC_6H_4	4g	91
8.	3,4-$(OCH_2O)C_6H_3$	4h	90
9.	4-$Me_2NC_6H_4$	4i	91
10.	4-$CH_3OC_6H_4$	4j	90
11.	2-Hydroxynaphthyl	4k	91
12.	3-Indolyl	4l	89
13.	2-Thienyl	4m	90

3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4a:
M.P. >300°C; IR (KBr) cm^{-1}3200,1635,1595,1490; ^1H NMR (300 MHz, $CDCl_3$) ppm 1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 4.12 (s, 2H, C_9H), 11.92 (brs, 1H, NH);Anal. Calc. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12; Found: C, 73.53; H, 7.92; N, 4.86; m/z: 272.8729.

3,3,6,6,9-pentamethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4b:
M.P. 258-260°C; IR (KBr):cm^{-1}3202,1635,1560,1470; ^{1}H NMR (300 MHz, $CDCl_3$) ppm: 1.12 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 1.26(d,3H, CH_3), 2.29-2.50 (m, 8H, CH_2), 4.12 (s, 1H, C_9H),11.89 (brs, 1H, NH);Anal. Calc. for $C_{18}H_{25}NO_2$:C, 75.22; H, 8.77; N, 4.87; Found: C, 75.11; H, 7.96; N, 3.98; m/z:286.7885.

3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4c:
M.P. 272-273°C; IR (KBr) cm^{-1} 3172,1640,1598 1390; ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 5.55 (s, 1H, C_9H), 7.09-7.30 (m, 5H, Ar-H), 11.91 (brs, 1H, NH); Anal. Calc. for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01; Found: C, 78.35; H, 6.89; N, 3.68; m/z: 348.94.

3,3,6,6-tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4d:
M.P. 296-297°C; IR (KBr) cm^{-1}3173, 1598,1510,1420,1390; ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.12 (s, 6H, CH_3), 1.15 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 5.61 (s, 1H, C_9H), 7.43-7.99 (m, 4H, Ar-H), 11.68 (brs, 1H, NH); Anal. Calc. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10; Found: C, 70.53; H, 5.92; N, 6.64; m/z: 394.1893.

9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4e:
M.P. 297-299°C; IR (KBr) cm^{-1} 3187,1630,1550,1470; ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.12 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.28-2.49 (m, 8H, CH_2), 5.31 (s, 1H, C_9H), 6.89-7.23 (m, 4H, Ar-H), 11.90 (brs, 1H, NH); Anal. for $C_{23}H_{26}ClNO_2$: C,71.96; H, 6.83; N, 3.65; Found: C, 71.34; H, 5.48; N, 3.89; m/z: 383.0752.

9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4f:
M.P. 221-222°C; IR (KBr) cm^{-1} 3298, 1640, 1598, 1480,3310; ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 4.68 (s, 1H, OH), 5.32 (s, 1H, C_9H), 6.97-7.46 (m, 4H, Ar-H), 11.91 (brs, 1H, NH); Anal Calc. for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83; Found: C, 75.09; H, 6.68; N, 2.89 m/z: 364.6971.

9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4g:
M.P. 234-336°C; IR (KBr) cm^{-1} 3196,1630,1598,1490, 3320; ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 4.66 (s, 1H, OH), 5.32 (s, 1H, C_9H), 6.93-7.45 (m, 4H, Ar-H), 11.90 (brs, 1H, NH); Anal Calc. for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83; Found: C, 74.63; H, 6.95; N, 2.99 m/z: 364.4991.

9-(benzo[*d*][1,3]dioxol-5-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4h:
M.P. 324-326°C; IR (KBr) cm^{-1} 3186, 1655, 1598, 1420: ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.12 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.28-2.49 (m, 8H, CH_2), 5.32 (s, 1H, C_9H), 5.91 (s, 2H, OCH_2O), 6.73-7.31 (m, 3H, Ar-H), 11.79 (brs, 1H, NH); Anal Calc. for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56; Found: C, 72.87; H, 6.01; N, 2.88 m/z: 394.1040.

9-(4-(dimethylamino)phenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4i:

M.P. 263-265°C; IR (KBr) cm^{-1} 3197,1635, 1568,1370; ^1H NMR (300 MHz, $CDCl_3$) ppm1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 2.85 (s, 6H, NMe_2), 5.32 (s, 1H, C_9H), 6.73-7.44 (m, 4H, Ar-H),11.83 (brs, 1H, NH), Anal Calc. for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14; Found: C, 75.75; H, 8.03; N, 6.72; m/z: 392.2464.

9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4j:

M.P. 298-300°C; IR (KBr) cm^{-1} 3187,1635,1570,1440,1390; ^1H NMR (300 MHz, $CDCl_3$) ppm 1.10 (s, 6H, CH_3), 1.13 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 3.98 (s, 3H, OCH_3), 5.32 (s, 1H, C_9H), 6.83-7.35 (m, 4H, Ar-H), 11.56 (brs, 1H, NH); Anal Calc. for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; Found: C, 75.24; H, 6.84; N, 3.56; m/z: 379.2147.

9-(2-hydroxynaphthalen-1-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4k:

M.P. 243-245°C; IR (KBr) cm^{-1} 3310,3217,1650,1535,1470;^1H NMR (300 MHz, $CDCl_3$) ppm 1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 4.96 (s, 1H, OH), 5.36 (s, 1H, C_9H), 6.94-7.26 (m, 6H, Ar-H), 11.67 (brs, 1H, NH); Anal Calc. for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37; Found: C, 77.63; H, 6.89; N, 3.02; m/z: 414.2147.

9-(1*H*-indol-3-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4l:

M.P. 249-251°C; IR (KBr) cm^{-1} 3210, 1640, 1593,1470; ^1H NMR (300 MHz, $CDCl_3$) ppm 1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 5.36 (s, 1H, C_9H), 6.83-7.31 (m, 5H, Ar-H), 10.96 (brs, 2H, NH); Anal. Calc. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21; Found: C, 77.14; H, 6.94; N, 6.73; m/z: 387.9151.

3,3,6,6-tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione 4m:

M.P. 141-142°C; IR (KBr) cm^{-1} 3186,1598,1460,1387; ^1H NMR (300 MHz, $CDCl_3$) ppm 1.11 (s, 6H, CH_3), 1.14 (s, 6H, CH_3), 2.29-2.50 (m, 8H, CH_2), 5.36 (s, 1H, C_9H), 7.21 (d, J = 4.6 Hz, 1H, thienyl-H), 7.78 (t, 1H, thienyl-H), 8.18 (d, J = 3.0 Hz, 1H, thienyl-H) 11.67 (brs, 1H, NH);Anal. Calc. for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94; Found: C, 70.72; H, 6.96; N, 3.53; m/z: 354.6606.

Conclusion

In our pursuit of developing 'benign by design' protocols, we have developed an eco-friendly methodology for synthesizing polycyclic 1,4-DHPs using $CuSO_4.5H_2O$ as a heterogenous mild lewis acid catalyst. The unprecedented quickness of reaction in ambient conditions has proved the superiority of cheap and easily available $CuSO_4.5H_2O$ over the other Lewis acids (I_2, iron salts, metal triflates, ionic liquids, etc.) reportedly used to catalyze the Hantzsch reaction. The operational simplicity and recyclability of the heterogenous catalyst along with high yields make this procedure adaptable for large-scale production of biologically relevant 1,4-Dihydropyridines. There seems tremendous scope for this heterogeneous catalyst in organic synthesis.

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