J. Integr. Sci. Technol. 2023, 11(3), 528 Article

Journal of Integrated
SCIENCE & TECHNOLOGY

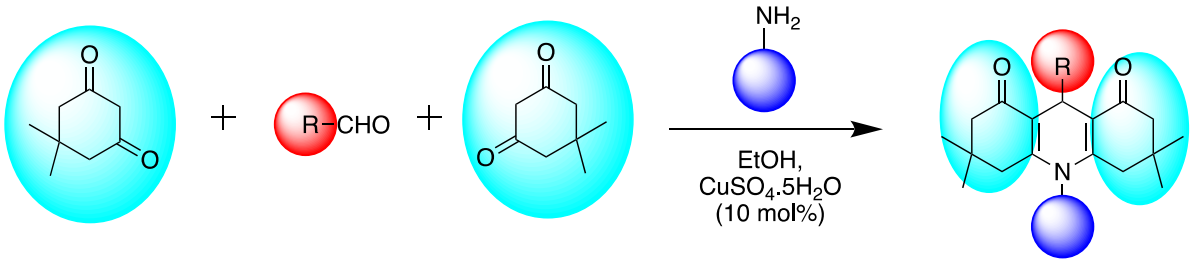
Copper-catalyzed ambient synthesis of functionalized 1,4-Dihydropyridines

Shuchi Kukreja*

Department of Chemistry, Hindu College Sonipat 131001, Haryana, India

Received on: 10-Dec-2022, Accepted and Published on: 05-Feb-2023

ABSTRACT



1,4-Dihydropyridine moiety has received much attention due to the wide spectrum of biological activities associated with it. An array of functionalized 1,4-Dihydropyridines has been synthesized in ambient conditions utilizing the catalytic properties of cupric sulfate pentahydrate. The entire focus of the present work has been to develop a 'benign by design' protocol with short reaction times and a simple reaction procedure. A wide substrate scope, good product yield, use of an eco-friendly solvent, a re-cyclable catalyst, as well as a reaction at ambient temperature are the advantages of this method. The catalyst cupric sulphate pentahydrate is indispensable for carrying out the reaction at room temperature.

Keywords: 1,4-Dihydropyridines, dimedone, cupric sulfate pentahydrate, ambient conditions

INTRODUCTION

1,4-Dihydropyridines (DHP) are much sought-after heterocyclic ring systems by virtue of their importance in synthetic and medicinal chemistry. They show a plethora of significant pharmacological properties and are also analogs of NADH coenzymes. 1,4-DHP derivatives have numerous medicinal applications such as calcium channel blockers for the treatment of cardiovascular diseases[1] including hypertension. They are also used as antidiabetic, anti-tumor,[2] anti-aging,[3] anti-atherosclerotic,[4] bronchodilators,[5] anti-microbial,[6] anti-coagulant,[7] anti-oxidant,[8] anticancer,[10] antileishmanial and anti-trypanosomal[11] agents, HIV-1 protease inhibitors and antioxidants.[12] Since the first report of the synthesis of 1,4-DHP by Hantzch in 1882, this moiety has been a highly active area of research. Umpteen choices of precursors, make 1,4-DHPs privileged scaffolds with a biological activity that can be tuned, in potency and selectivity, to the desired extent to target specific pharmacological effects in diverse therapeutic areas[13-16] That is why the literature is replete with synthetic procedures of 1,4 DHP. A number of conventional and green protocols have been reported for the synthesis of DHPs using various catalysts such as $AlCl_3 \cdot 6H_2O$,[17] $CeCl_3 \cdot 7H_2O$,[18] Ceric ammonium nitrate,[19] Fermenting baker's yeast,[20] $HClO_4 \cdot SiO_2$,[21] HY-zeolite,[22] Ionic liquids,[23] K10-montmorillonite clay,[24] Molecular iodine,[25] magnetite/chitosan,[26] Ni nanoparticles[27] Organocatalysts,[28] p-TSA,[29] SiO_2,[30] triethylamine,[31] TMSC,[32] ZnO,[33] Fe-CuZSM-5,[34] catalyst silica sulfuric acid,[35] Microwave irradiation, and Ultrasound[36] etc. As almost all of the above-mentioned methods have one or the other negative points such as expensive reagents, tedious work-up, moisture sensitivity, and toxic and harsh reaction conditions, thus developing an efficient protocol with a powerful catalyst for the synthesis of 1,4-dihydropyridine is still an active research field.

Catalysis is an important part of green chemistry, and one of the fundamental challenges facing chemists today is the design and application of eco-friendly catalysts.[37-40] Stable and green catalyst is defined as being easily available, highly active, having great selectivity, high stability, efficient recovery, and good recyclability[41] All these qualities are associated with cupric

*Corresponding Author: Dr Shuchi Kukreja
Tel: 7988121605
Email: shuchi.org@gmail.com

Cite as: *J. Integr. Sci. Technol., 2023, 11(3), 528.*
URN:NBN:sciencein.jist.2023.v11.528

 ISSN: 2321-4635
http://pubs.thesciencein.org/jist

sulphate pentahydrate a transition metal catalyst. Copper in its various oxidation states has been used in organic synthesis. Recently, $CuSO_4.5H_2O$ has been used as a Lewis acid catalyst for various organic transformations[42-44] It is an inexpensive, mild, easily available, and extremely safe reagent to be used in chemical reactions. All these desirable characteristics make copper sulfate pentahydrate a suitable catalyst for the synthesis of functionalized 1,4-DHPs. Hence in the present work, the synthesis of the target compounds was taken up via a multicomponent reaction where dimedone as a 1,3-diketone was reacted with an aromatic aldehyde and an aromatic amine in the presence of copper sulfate pentahydrate in a catalytic amount. The results were highly encouraging as the reaction was done at ambient temperature with high product yields and easy work-up. The copper sulfate was recycled with almost no loss of activity.

RESULTS AND DISCUSSION

Initially, a mixture of dimedone (5,5-dimethyl-1,3-cyclohexanedione), benzaldehyde, and aniline in ethanol (5 mL) was stirred at room temperature in presence of 10 mol% of $CuSO_4.5H_2O$ (**Scheme 1**) to study the efficiency of catalyst for Hantzsch reaction. As anticipated, the product formation started immediately and the reaction was complete within 5-10 min (as monitored by TLC plate examination). The reaction mixture was heated to solubilize the product, in order to recover the insoluble $CuSO_4.5H_2O$, by filtration. The filtrate on cooling afforded good yields of pure product. The structure characterization was done on the basis of spectral data (IR, ^{1}H NMR, and mass) and elemental analyses.

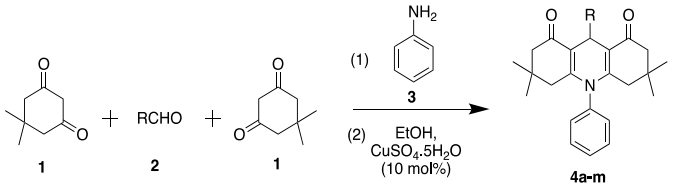
Product formation **4a-m** was confirmed by the spectral data, the appearance of a strong band between 1680-1650 cm^{-1} characteristic of carbonyl in conjugation with the double bond and bands between 1600-1400 cm^{-1} due to aromatic ring skeleton carbon-carbon stretch in the IR spectra of all the target compounds supported the product structure. In the NMR spectra of the compounds **4a-m** appearance of signals in the aromatic region between 6.4-7.5 ppm was further in line with the proposed product structure, further the appearance of two signals of 6H each between 1.11 and 1.15 ppm due to four methyl groups, gave evidence for condensation of two molecules of dimedone with one molecule of aldehyde and one of amine resulting in the formation of the symmetrical 1,4 -DHPs. The elemental analysis data and m/z values also corroborated these results.

$CuSO_4.5H_2O$ promotes the reaction as mild lewis acid, and also accelerates the dehydration, thereby facilitating the product formation. Control reaction in the absence of $CuSO_4.5H_2O$ yielded no product supporting the fact that the presence of the catalyst was indispensable for facilitating the reaction at room temperature.

Having identified the qualitative role of the catalyst assessment of its quantitative aspect was taken up. Synthesis of **4a** was carried out with different concentrations of $CuSO_4.5H_2O$. The yields were modest (68%) with 2 mol%, and an increase in its concentration to 5, 10, 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**). Then the model process was optimized by testing the efficiency of several classical solvents chosen as the reaction medium for comparison (**Table 2**). In each case, the substrates were mixed together with 10 mol% of $CuSO_4.5H_2O$, agitated with 5-6 mL of solvent, as expected, the polar solvents such as ethanol, acetonitrile (entry 1, 2, **Table 2**) were found better than non-polar solvents (entry 4, 6**, Table 2**) due to the high solubility of reactants in the former. When acetone was used (entry 3**, Table 2**) reaction proceeded very fast but the pale solid obtained was contaminated with many by-products probably due to the fast, self-assembling of reagents or some competitive reaction promoted by $CuSO_4.5H_2O$ in acetone. Based on these findings ethanol was chosen as the reaction medium.

Under the optimized reaction conditions next the universality of the reaction was checked. Results shown in (**Table 3**) indicate that aliphatic, aromatic (electron-rich and electron-deficient), and heteroaromatic aldehydes such as thiophene-2-carboxaldehyde (13**, Table 3**) and indole aldehyde(12**, Table 3**) worked well exemplifying the versatility of the reaction.

In nutshell, the presented protocol for the synthesis of 1,4 DHP using $CuSO_4.5H_2O$, a mild Lewis acid for catalyzing the Hantzsch reaction has been very efficient. 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.) used to catalyze the Hantzsch reaction. The operational simplicity along with high yields make this procedure adaptable for large-scale production of biologically relevant 1,4-DHPs.



Scheme 1. Chemical synthesis of 1,4-dihydropyridine derivatives.

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}H NMR, on a Bruker Advance Spectrospin 300 instrument 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).

(1) General Procedure for Synthesis of 4a-m

A mixture of dimedone **1** (2 mmol), benzaldehyde **2** (1 mmol), and aniline **3** (1 mmol) in ethanol (5 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was heated to solubilize the product and the catalyst was separated from the

reaction mixture by simple filtration. Pure products **4a-m** were recrystallized from ethanol.

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.

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 using different solvents

Entry	Solvent	Time (min)	Yield (%)
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 unoptimized 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	92
2.	CH_3	4b	92
3.	C_6H_5	4c	96
4.	3-$NO_2C_6H_4$	4d	90
5.	4-ClC_6H_4	4e	91
6.	2-HOC_6H_4	4f	92
7.	4-HOC_6H_4	4g	92
8.	3,4-(O-CH_2-O) C_6H_3	4h	92
9.	4-$Me_2NC_6H_4$	4i	93
10.	4-$CH_3OC_6H_4$	4j	92
11.	2-Hydroxynaphthyl	4k	90
12.	3-Indolyl	4l	90
13.	2-Thienyl	4m	90

[a]Isolated and unoptimized yields. [b]in 37-41% formaldehyde solution.

3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4a**): M.P.: 254-256℃; IR (KBr) cm^{-1}: 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), 6.97-7.26 (m, 5H, Ar-H); Anal. Calc. for $C_{23}H_{27}NO_2$: C 79.05, H 7.79, N 4.01; found C 78.46, H 7.93, N 3.68; m/z: 349.2042.

3,3,6,6,9-pentamethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4b**): M.P.: 260-261℃; IR (KBr) cm^{-1}: 1635, 1560, 1470; ^1H 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), 6.97-7.26 (m, 5H, Ar-H); Anal. Calc. for $C_{24}H_{29}NO_2$: C 79.30, H 8.04, N 3.85; found C 78.11, H 7.32, N 3.01; m/z: 363.1108.

3,3,6,6-tetramethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4c**): M.P.: 209-210℃; IR (KBr) cm^{-1}: 1640, 1598, 1390; ^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), 5.23 (s, 1H, C_9H), 6.97-7.46 (m, 10H, Ar-H); Anal. Calc. for $C_{29}H_{31}NO_2$: C 81.85, H 7.34, N 3.29; found C 80.31, H 6.79, N 2.93; m/z: 424.6415.

3,3,6,6-tetramethyl-9-(3-nitrophenyl)-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4d**): M.P.: 222-223℃; IR (KBr) cm^{-1}: 1648, 1510, 1420, 1390; ^1H 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), 5.41 (s, 1H, C_9H), 7.09-7.43 (m, 6H, Ar-H), 7.63-7.99 (m, 3H, Ar-H); Anal. Calc. for $C_{29}H_{30}N_2O_4$: C 74.02, H 6.43, N 5.95; found C 73.53, H 5.72, N 5.04; m/z: 470.2206.

9-(4-chlorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4e**): M.P.: 138-140℃; IR (KBr) cm^{-1}: 1630, 1550, 1470; ^1H 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), 7.09-7.53 (m, 9H, Ar-H); Anal. for $C_{29}H_{30}ClNO_2$: C 75.72, H 6.57, N 3.04; found C 74.34, H 5.48, N 2.89; m/z: 458.8914.

9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4f**): M.P.: 220-221℃; IR (KBr) cm^{-1}: 1640, 1598, 1480, 3310; ^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), 4.68 (s, 1H, OH), 5.32 (s, 1H, C_9H), 6.97-7.46 (m, 9H, Ar-H); Anal Calc. for $C_{29}H_{31}NO_3$: C 78.88, H 7.08, N 3.17; found C 77.09, H 6.68, N 2.89; m/z: 441.2304.

9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4g**): M.P.: 210-211℃; IR (KBr) cm^{-1}: 1630, 1598, 1490, 3320; ^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), 4.66 (s, 1H, OH), 5.32 (s, 1H, C_9H), 6.93-7.45 (m, 9H, Ar-H); Anal Calc. for $C_{29}H_{31}NO_3$: C 78.88, H 7.08, N 3.17; found C 79.63, H 6.65, N 2.93; m/z: 440.3412.

9-(benzo[*d*][1,3] dioxol-5-yl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4h**): M.P.: 215-217℃; IR (KBr) cm^{-1}: 1655, 1598, 1420; ^1H 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, 8H, Ar-H); Anal Calc. for $C_{30}H_{31}NO_4$: C 76.73, H 6.65, N 2.98; found C 75.87, H 6.01, N 2.18; m/z: 469.5612.

9-(4-(dimethylamino) phenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4i**): M.P.: 234-235 ℃; IR (KBr) cm^{-1}: 1635, 1568, 1370; ^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), 2.85 (s, 6H, NMe_2), 5.32 (s, 1H, C_9H), 6.73-7.44 (m, 9H, Ar-H); Anal Calc. for $C_{31}H_{36}N_2O_2$: C 79.45, H 7.74, N 5.98; found C 78.75, H 7.03, N 5.12; m/z: 467.8347.

9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4j**): M.P.: 206-208 ℃; IR (KBr) cm^{-1}: 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), 6.89-7.39 (m, 9H, Ar-H);

Anal Calc. for $C_{30}H_{33}NO_3$: C 79.09, H 7.30, N 3.07; found C 78.24, H 6.54, N 2.56; m/z: 455.2387.

9-(2-hydroxynaphthalen-1-yl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4k**): M.P.:198-199 ℃; IR (KBr) cm^{-1}: 3310, 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), 6.86-6.94 (m, 4H, Ar-H), 7.01-7.54 (m, 7H, Ar-H); Anal Calc. for $C_{33}H_{33}NO_3$: C 80.62, H 6.77, N 2.85; found C 79.63, H 5.89, N 2.02; m/z: 490.7986.

9-(1*H*-indol-3-yl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4l**): M.P.: 241-242 ℃; IR (KBr) cm^{-1}: 3210, 1640, 1593, 1430; ^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, 10H, Ar-H), 9.96 (brs, 1H, NH); Anal. Calc. for $C_{31}H_{32}N_2O_2$: C 80.14, H 6.94, N 6.03; found C 79.53, H 6.32, N 5.93; m/z: 463.8629.

3,3,6,6-tetramethyl-10-phenyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**4m**): M.P.: 156-158 ℃; IR (KBr) cm^{-1}: 3212, 1655, 1598, 1460; ^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), 6.97-7.26 (m, 5H, Ar H), 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); Anal. Calc. for $C_{27}H_{29}NO_2S$: C 75.14, H 6.77, N 3.25; found C 74.72, H 5.96, N 2.94; m/z: 430.6238.

CONCLUSION

An environmentally benign protocol for the synthesis of 1,4-DHPs using $CuSO_4.5H_2O$, a mild lewis acid has been developed. The unprecedented quickness of reaction in ambient conditions has proved the superiority of cheap, mild, and easily available $CuSO_4.5H_2O$ over the other lewis acids (I_2, iron salts, metal triflates, ionic liquids, etc.) used to catalyze the Hantzsch reaction. The operational simplicity along with high yields make this procedure adaptable for large-scale production of biologically relevant 1,4-DHPs. There seems enormous scope in organic synthesis for this catalyst.

ACKNOWLEDGMENT

The author S. Kukreja is thankful to UGC for awarding her teacher fellowship and to Prof. M Kidwai under whose guidance she performed these experiments in the green chemistry lab at the Department of Chemistry, University of Delhi. She is also thankful to the Principal, Hindu College, Sonipat for unconditional support.

CONFLICT OF INTEREST STATEMENT

The author does not have any conflict of interest for this work.

REFERENCES

1. J. Reimao, M. Scotti, A. Tempone. Anti-leishmanial and anti-trypanosomal activities of 1,4-dihydropyridines: in vitro evaluation and structure–activity relationship study, *Bioorg. Med. Chem. Lett*. **2010**, 18, 8044–8053.
2. A. Sausins, G. Duburs. Synthesis of 1,4-dihydropyridines by cyclocondensation reactions. *Heterocycles* **1988**, 27, 269–289.
3. A.C. Gaudio, A. Korokovas, Y. Takahata. Quantitative structure-activity relationships for 1,4-dihydropyridine calcium channel antagonists (nifedipine analogues): a quantum chemical/ classical approach. *J. Pharm. Sci*. **1994**, 83, 1110–1115.
4. P.P. Mager, R.A. Coburn, A.J. Solo, D.J. Triggle, H. Rothe. QSAR, diagnostic statistics and molecular modeling of 1,4- dihydropyridine calcium antagonists: a difficult road ahead. *Drug Des. Disc* **1992**, 8, 273–289**.**
5. M.F. Gordeev, D.V. Patel, E.M. Gordon. Approaches to the combinatorial synthesis of heterocycles: a solid-phase synthesis of 1,4-dihydropyridines. *J. Org. Chem***. 1996**, 61, 924–982.
6. R. Kumar, A. Idhayadhulla, A. Abdul Nasser, J. Selvin. Synthesis and anticoagulant activity of a new series of 1,4-dihydropyridine derivatives. *Eur. J. Med. Chem*. **2011**, 46, 804–810.
7. A. Vijesh, A. Isloor, S. Peethambar, K. Shivananda, T. Arulmoli, N. Isloor, Hantzsch reaction: synthesis and characterization of some new 1,4-dihydropyridine derivatives as potent antimicrobial and antioxidant agents. *Eur. J. Med. Chem*. **2011**, 46, 5591–5597.
8. F. Shekari, H. Sadeghpour, K. Javidnia, L. Saso, F. Nazari, O. Firuzi, Cytotoxic and multidrug resistance reversal activities of novel 1,4-dihydropyridines against human cancer cells, *Euro. J. Pharmacol*. **2015**, 746, 233–244
9. M. Khoshneviszadeh, N. Edraki, K. Javidnia, A. Alborzi, B. Pourabbas, J. Mardaneh, et al. Synthesis and biological evaluation of some new 1,4-dihydropyridines containing different ester substitute and diethyl carbamoyl group as anti-tubercular agents. *Bioorg. Med. Chem. Lett*. **2009**, 17, 1579–1586
10. K. Chandra, G. Ramesh. The fourth-generation Calcium channel blocker: cilnidipine, *Indian Heart J***. 2013**, 65, 691–695
11. A. Hilgeroth, H. Lilie, Structure-activity relationships of first bishydroxymethyl substituted cage dimeric 4-Aryl-1,4-dihydropyridines as HIV-1 protease inhibitors. *Eur. J. Med. Chem.*, **2003**, 38(5), 495-499.
12. G. Dıaz-Araya, L. Godoy, L. Naranjo, A. Squella, M. Letelier, L. Nú´ nez-Vergara. Antioxidant effects of 1,4-dihydropyridine and nitroso aryl derivatives on the Feþ3 / Ascorbate-Stimulated lipid peroxidation in rat brain slices, Vasc. *Pharmacol*. **1998**, 31, 385–391
13. G.M. Reddy, M. Shiradkar, A.K. Chakravarthy. Chemical and Pharmacological Significance of 1,4- Dihydropyridines. *Curr. Org. Chem*. **2007**, 11, 847–852.
14. P. Khyaliya, A.P. Devi, S. Kumar, R. Kant, K.L. Ameta. Anti-microbial and anti-tumor studies of newly synthesized 2-(4-morpholinyl)-4,6-diarylpyrimidines using nanosized NiO catalytic framework. *Chem. Biol. Lett.* **2020**, 7 (1), 55–62.
15. P. Chaya, A.A. Cheriyan, S. Shah, et al. Synthesis and medicinal applications of quinoline hybrid heterocycles: a comprehensive review. *J. Mol. Chem*. **2022**, 22 (1), 338–379.
16. E. Carosati, P. Ioan, M. Micucci, F. Broccatelli, G. Cruciani, B.S. Zhorov, A. Chiarini, R. Budriesi. 1,4- Dihydropyridine Scaffold in Medicinal Chemistry, The Story So Far and Perspectives (Part 2): Action in Other Targets and Antitargets. *Curr. Med. Chem*. **2012**, 19, 4306–4323
17. S. Das Sharma, P. Hazarika, D. Konwar. A simple, green and one-pot four-component synthesis of 1,4-dihydropyridines and their aromatization. *Cat. Comm* **2008**, 9, 709–714.
18. G. Sabitha, K. Arundhathi, K. Sudhakar, B. Sastry, J. Yada. $CeCl_3$·7H2O-Catalyzed one-pot synthesis of Hantzsch 1,4-dihydropyridines at room temperature. *Syn. Comm***. 2009**, 39, 2843–2851.
19. S. Ko, C. Yao, Ceric Ammonium Nitrate (CAN) catalyzes the one-pot synthesis of polyhydroquinoline via the Hantzsch reaction. *Tetrahedron*. **2006**, 62, 7293–7299.
20. A. Kumar, R. Maurya. Bakers' yeast catalyzed synthesis of polyhydroquinoline derivatives via an unsymmetrical Hantzsch reaction. *Tetrahedron Lett*. **2007**, 48, 3887–3890.
21. M. Maheswara, V. Siddaiah, Y. Rao, Y. Tzeng, C. Sridhar. A simple and efficient one-pot synthesis of 1,4-dihydropyridines using heterogeneous catalyst under solvent-free conditions. *J. Mol. Catal.* **2006**, 260, 179–180.
22. B. Das, B. Ravikanth, R. Ramu, B. Vittal Rao. An efficient one-pot synthesis of polyhydroquinolines at room temperature using HY-zeolite. *Chem. Pharm. Bull.* **2006**, 54, 1044–1045.
23. S. Ji, T. Loh, Z. Jiang, J. Lu. Facile ionic liquids-promoted one-pot synthesis of Polyhydroquinoline Derivatives under solvent-free conditions. *Synlett***. 2004**, 5, 0831–0835.

24. G. Song, B. Wang, X. Wu, Y. Kang, L. Yang. Montmorillonite K10 clay: an effective solid catalyst for one-pot synthesis of polyhydroquinoline derivatives. *Syn, Comm* **2005,** 35, 2875–2880.
25. S. Ko, M. Sastry, C. Lin, C. Yao. Molecular iodine-catalyzed one-pot synthesis of 4- substituted-1,4-dihydropyridine derivatives via Hantzsch reaction. *Tetrahedron Lett*. **2005**, 46, 5771–5774.
26. A. Maleki, M. Kamalzare. An efficient synthesis of benzodiazepine derivatives via a one-pot, three-component reaction accelerated by a chitosan-supported superparamagnetic iron oxide nanocomposite. *Tetrahedron Lett.* **2014**, 55, 50.
27. G. Sabitha, G. Reddy, C. Reddy, J. Yadav. A novel TMSI-mediated synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature. *Tetrahedron Lett.* **2003**, 44, 4129–4131
28. A. Kumar, R. Maurya. Synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction using organocatalysts. *Tetrahedron.* **2007**, 63 1946–1952.
29. S. Cherkupally, R. Mekala. P-TSA Catalyzed Facile and Efficient Synthesis Of polyhydroquinoline derivatives through Hantzsch multi-component condensation. *Chem. Pharm. Bull*. **2008**, 56,1002–1004
30. R. Dudhe, P. Sharma, P. Verma. Pyrimidine containing furanose derivative having antifungal, antioxidant, and anticancer activity. *Org Med Chem Lett.* **2014**, 4, 3
31. M. Ghandi, N. Zarezadeh. A one-pot four-component reaction providing quinolinebased 1,4-dihydropyridines. *J. Iran. Chem. Soc.* **2015**, 12, 1313–1324.
32. H. Adibi, H. Samimi, M. Beygzadeh, Iron(III) trifluoroacetate and trifluoromethanesulfonate: recyclable Lewis acid catalysts for one-pot synthesis of 3,4-dihydropyrimidinones or their sulfur analogues and 1,4-dihydropyridines via solvent-free Biginelli and Hantzsch condensation protocols. *Catal. Commun*. **2007**, 8, 2119–2124.
33. F. Moghaddam, H. Saeidian, Z. Mirjafary, A. Sadeghi. Rapid and efficient one-pot synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives through the Hantzsch four component condensation by zinc oxide. *J. Iran. Chem. Soc*. **2009**, 6, 317–324.
34. K. Safa, M. Esmaili, M. Allahvirdinesbat. Aqua-mediated one-pot synthesis of Biginelli dihydropyrimidinone/thiones (DHPMs), Hantzsch dihydropyridines (DHPs), and polysubstituted pyridines sonocatalyzed by metal-supported nanocatalysts. *J. Iran. Chem. Soc.* **2015**, 13, 267–277.
35. A. Kailas, A. More, V. Nilesh, A. Gandhare, S. Parvez, B, Ali, B. Naziyanaz, C. Pathan, ,M. Khalid, Al. Mousa. An expeditious one-pot green synthesis of novel bioactive 1, 4-dihydropyridine derivatives at ambient temperature and molecular modeling. *Curr. Res. Green Sustainable Chem.*. **2021**, 4, 100-108.
36. K. Hussain, D. Wadhwa. Highly efficient, one-pot synthesis and oxidation of Hantsch 1,4-dihydropyridines mediated by iodobenzene diacetate (III) using conventional heating, ultrasonic, and Microwave irradiation. Int. *J. Org Chem.* **2014**, 04, 174–181.
37. R.A. Sheldon. Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev*. **2012**, 41, 1437–1451.
38. B.S. Chhikara, R.S. Varma. Nanochemistry and Nanocatalysis Science: Research advances and future perspectives. *J. Mater. Nanosci*. **2019**, 6 (1), 1–6.
39. R.B. NasirBaig, R.S. Varma. Stereo- and regio-selective one-pot synthesis of triazole-based unnatural amino acids and b-amino triazoles. *Chem. Commun*. **2012**, 48, 5853–5855.
40. R.B. NasirBaig, R.S. Varma. Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis. *Chem. Soc. Rev*. **2012**, 41, 1559–1584.
41. S.B. Gawande, P.S. Brancoa, R.S. Varma. Nanocatalysis and prospects of green chemistry. *Chem. Sus. Chem.* **2012**, 5, 65–68.
42. A. T. Khan, H. Lokman, S. Ghosh. Cupric sulfate pentahydrate (CuSO4· 5H2O): a mild and efficient catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols. *Tetrahedron Lett*. **2004**, 45, 7891-7894.
43. B. Akhlaghinia, S. Tavakoli. An efficient method for the protection of alcohols and phenols by using hexamethyldisilazane in the presence of cupric sulfate pentahydrate under neutral reaction conditions. *Synthesis*, **2005,** 11, 1775-1778.
44. M. Gohain, D. Prajapati, & J. S. Sandhu. A novel Cu-catalysed three-component one-pot synthesis of dihydropyrimidin-2 (1H)-ones using microwaves under solvent-free conditions. *Synlett*. **2004**, 02, 0235-0238.