

Full Paper

## **N,N'-Ethylene-bis(benzoylacetoinimato) Copper (II), Cu(C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>), a New Reagent for Aromatization of Hantzsch 1,4-Dihydropyridines**

Saeed Dehghanpour \*, Majid M. Heravi \* and Fatemeh Derikvand

Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

\* Authors to whom correspondence should be addressed. E-mails: dehghanpour\_farasha@yahoo.com;  
mmh1331@yahoo.com

Received: 7 January 2007; in revised form: 6 February 2007 / Accepted: 10 February 2007 /

Published: 12 March 2007

---

**Abstract:** A variety of Hantzsch 1,4-dihydropyridines were oxidized to their corresponding pyridines in high yields in the presence of Cu(C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>) in refluxing acetic acid.

**Keywords:** Cu(C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>), Hantzsch 1,4-dihydropyridines, aromatization, oxidation, solid reagents.

---

### **Introduction**

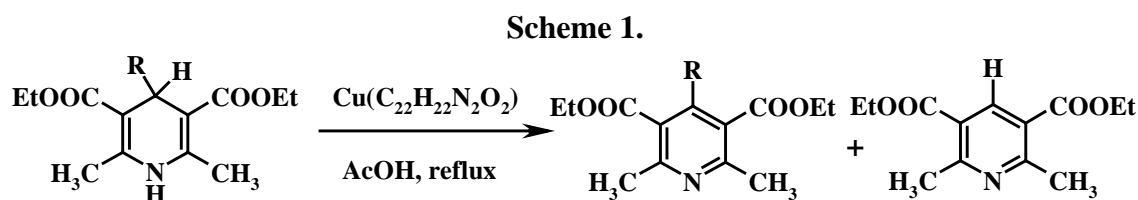
Hantzsch 1,4-dihydropyridines (1,4-DHPs) and their derivatives are an important class of bioactive molecules in the pharmaceutical field [1]. The DHP heterocyclic ring is a common feature of a variety of bioactive compounds including anticonvulsant, antidiabetic, antianxiety, antidepressive, antitumor, analgesic, sedative, vasodilator, bronchodilator, hypnotic and anti-inflammatory agents [2]. DHPs are commercially used as calcium channel blockers for the treatment of cardiovascular diseases, including hypertension [3]. The oxidation of DHPs to the corresponding pyridine derivatives constitutes the principal metabolic pathway in biological systems [4], as well as providing facile access to the corresponding pyridine derivatives, which show antihypoxic and antiischemic activities [5], from the easily available DHPs [6]. Therefore, oxidative aromatization of DHPs has attracted continuing interests of organic and medicinal chemists and a plethora of protocols has been developed [7-9]. Early experiments mostly used strong oxidants, such as HNO<sub>3</sub> [7], KMnO<sub>4</sub> [8], cerium ammonium nitrate

(CAN) [9] or  $I_2$ -MeOH [10]. New more efficient and environmentally benign methods, such as electrochemical oxidation [11] and catalytic aerobic oxidation using  $RuCl_3$  [12], Pd/C [13], activated carbon [14] or  $Fe(ClO_4)_3$  [15] have also been reported.

In recent years considerable emphasis has been placed on diminishing the environmental impact of industrial processes [16] and it is well recognized that solid acid catalysts and reagents can play a significant role in the development of cleaner technologies [17].

Copper(II) complexes of  $N_2O_2$  ligands have generated considerable interest because of their interesting physio-chemical properties, potentially useful in catalytic reaction and biological activities [18]. Recently we have reported the synthesis and structure of N,N'-ethylene-bis(benzoyl-acetoniminato) copper (II),  $Cu(C_{22}H_{22}N_2O_2)$  [19].

Based on our previous studies on the use of solid acid catalysts [20-25] and reagents [26-28] for carrying out organic reactions and our interest in aromatization of Hantzsch 1,4-dihydropyridines [26-29], we have examined the possibility of using  $Cu(C_{22}H_{22}N_2O_2)$  as a novel solid reagent to effect the aromatization of Hantzsch 1,4-dihydropyridines. (Scheme 1)



## Results and Discussion

In order to determine the best reaction conditions, the efficiency of a variety of solvents in the oxidation of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate as a model reaction was studied. First we carried out the model reaction under solvent-free conditions at room temperature. The temperature of the reaction mixture started to rise but the reaction was not complete after 24 h. Then we decided to examine the effect of the solvent on the reaction. As shown in Table 1, the best results in terms of yield and time were obtained in refluxing acetic acid.

**Table 1.** The effect of the solvent on the oxidation of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, in the presence of  $Cu(C_{22}H_{22}N_2O_2)$ .

Solvent	Dichloromethan	Chloroform	Ethanol	Water	Acetonitrile	Acetic acid
	e					
Time (h)	24	24	24	24	24	1
Yield(%) <sup>a</sup>	20	20	25	35	40	90

a) Yields were analyzed by GC.

In order to establish the scope of this novel oxidation protocol, we tested a variety of 1,4-DHPs under the optimized reaction conditions. As shown in Table 2 the presence of both electron donating

and electron withdrawing substituents on the precursors afforded the corresponding pyridines in good to excellent yields. In the presence of excess reagent the corresponding products were obtained in shorter times. (cf. entries 8 and 9, Table 2). As expected, in the case of a 1,4-DHP bearing an isopropyl group in the 4-position, a pyridine derivative resulting from the elimination of isopropyl group was formed. This may be attributed to the stability of the isopropyl cation (Table 2, entry 10).

The oxidizing species in the reaction is the copper(II) complex and it can be reduced to Cu(I) during the reaction. As Cu(I) prefers the tetrahedral structure and we believe it is unstable in its complex form, so, after reduction, the complex will be decomposed. The produced species are soluble in acetic acid and ethanol and could be separated by recrystallization from ethanol or chromatography.

**Table 2.** Oxidation of Hantzsch 1,4-dihydropyridines in the presence of  $\text{Cu}(\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2)$  in refluxing acetic acid.

Entry	R	Time (min)	Yield (%) <sup>a</sup>	m.p (°C)	
				Found <sup>b</sup>	Reported [Ref.]
1	H-	40	89	68-70	69-70[30]
2	Me-	50	88	Oil	Oil[4]
3	Et-	45	90	Oil	Oil[4]
4	Ph	60	90	60-62	61-62[4]
5	4-Me-Ph	55	87	72-73	72-73[11]
6	4-MeO-Ph	50	88	50	50[12]
7	4-Cl-Ph	45	75	64-66	65-66[31]
8	3-NO <sub>2</sub> -Ph	65	80	62-63	61-63[30]
9	3-NO <sub>2</sub> -Ph <sup>c</sup>	40	80	62-63	61-63[30]
10	Isopropyl-	40	85 <sup>d</sup>	68-70	69-70[30]

a) Yields were analyzed by GC.

b) Products exhibited physical properties in accordance with the assigned structures.

c) The reaction was carried out in the presence of 1.2 equivalents of the reagent.

d) The product resulting from the elimination of isopropyl group was formed.

## Conclusions

In summary, we have developed the use of  $\text{Cu}(\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2)$  as an easy to handle, non-corrosive and environmentally benign reagent for the aromatization of Hantzsch 1,4-dihydropyridines. The advantages of the present procedure are simplicity of operation and the good yields of the products.

## Experimental Section

### General

Melting points were measured by using the capillary tube method with an Electrothermal 9200 apparatus. <sup>1</sup>H-NMR spectra were recorded on a Bruker AC-80 MHz spectrometer using TMS as an

internal standard (CDCl<sub>3</sub> solution). IR spectra were recorded using KBr disks on a Bruker Tensor 27FT-IR instrument. GC spectra were recorded on an Agilent 5973 GC instrument. All products were characterized by spectra and physical data. Silica gel 60 for column chromatography was purchased from Merck. The Cu(II) reagent [19] was prepared as follows: the Schiff base *N,N'*-ethylene-bis(benzoyl-acetoniminate) (2 mmol) was dissolved in boiling methanol (20 mL) and mixed with a solution of copper(II) acetate (2 mmol) in the same volume of solvent. The mixture was heated on a water bath for about 3 min and then left to stand overnight. The crystals which had formed were filtered off, washed with methanol and dried. All the dihydropyridines were prepared according to the literature procedure [32], using the appropriate aldehydes, ammonia, and ethyl acetoacetate.

#### *Aromatization of Hantzsch 1,4-dihydropyridines: General procedure*

The Hantzsch 1,4-dihydropyridine (1 mmol) was reacted with Cu(C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>) (1 mmol) in refluxing acetic acid (3 mL). The progress of the reaction was monitored by TLC using 80:20 petroleum ether-ethyl acetate as eluent. After completion of the reaction, diethyl ether (5 mL) was added to the mixture. The solution obtained was washed successively with 5% NaHCO<sub>3</sub> (10 mL) and brine (10 mL) and dried over MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure to yield the crude products. Further purification was achieved by recrystallization from ethanol (in the case of solid products) and flash chromatography. Yields were obtained using GC analysis. All products were known compounds and their physical and spectroscopic data were compared with those of authentic samples [4,11,12,30,31] and found to be identical.

#### **Acknowledgments**

The Authors are thankful for the partial financial assistance from Azzahra University Research Council.

#### **References and Notes**

1. Stout, D. M.; Meyers, A. Recent advances in the chemistry of dihydropyridines. I. *Chem. Rev.* **1982**, *82*, 223-243.
2. Godfraid, T.; Miller, R.; Wibo, M. Calcium antagonism and calcium entry. Blockade. *Pharmacol. Rev.* **1986**, *38*, 321-416.
3. Gaudio, A. C.; Korolkovas, A.; Takahata, Y. Quantitative structure relationships for 1,4-DHP calcium channel, *J. Pharm. Sci.* **1994**, *83*, 1110-1115.
4. Kill, R. J.; Widdowson, D. A. In *Bioorganic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, **1978**; Vol. 4, pp 239-275.
5. Khadilkar, B.; Borkar, S. Silica gel supported ferric nitrate: a convenient oxidizing reagent. *Synth. Commun.* **1998**, *28*, 207-212 and references cited therein.
6. Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. A novel TMSI-mediated synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature. *Tetrahedron Lett.* **2003**, *44*, 4129-4131.

7. Chennot, T.; Eisner, U. A new synthesis of 1,4-dihydropyridines. *J. Chem. Soc., Perkin Trans.1* **1975**, 926-929.
8. Vanden Eynde, J.-J.; D'Orazio, R.; Van Haverbeke, Y. Potassium permanganate, a versatile reagent for the aromatization of Hantzsch 1,4-dihydropyridines. *Tetrahedron* **1994**, *50*, 2479-2484.
9. Pfister, J. R. Rapid, high-yield oxidation of Hantzsch-type 1,4-dihydropyridines with Ceric ammonium-nitrate. *Synthesis* **1990**, 689-690.
10. Yadav, J. S.; Subba Reddy, B. V.; Sabitha, G.; Kiran Kumar Reddy, G. S. Aromatization of Hantzsch 1,4-dihydropyridines with I-2-MeOH. *Synthesis* **2000**, *11*, 1532-1534.
11. Arguello, J.; Nunez-Vergara, L. J.; Sturm, J. C.; Squella, J. A. Voltammetric oxidation of Hantzsch 1,4-dihydropyridines in protic media: substituent effect on positions 3,4,5 of the heterocyclic ring. *Electrochim. Acta* **2004**, *49*, 4849-4856.
12. Mashraqui, S. H.; Karnik, M. A. Catalytic oxidation of Hantzsch 1,4-dihydropyridines by RuCl<sub>3</sub> under oxygen atmosphere. *Tetrahedron Lett.* **1998**, *39*, 4895-4898.
13. Nakamichi, N.; Kawashita, Y.; Hayashi, M. Oxidative aromatization of 1,3,5-trisubstituted pyrazolines and Hantzsch 1,4-dihydropyridines by Pd/C in acetic acid. *Org. Lett.* **2002**, *4*, 3955-3957.
14. Nakamichi, N.; Kawashita, Y.; Hayashi, M. Activated carbon-promoted oxidative aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines using molecular oxygen. *Synthesis* **2004**, 1015-1020.
15. Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. Catalytic aromatization of Hantzsch 1,4-dihydropyridines by ferric perchlorate in acetic acid. *Tetrahedron Lett.* **2005**, *46*, 2775-2777.
16. Smith, K. *Solid Supports and Catalysts in Organic Synthesis*; Ellis Horwood: Chichester, **1992**.
17. Mervartova, K.; Polasek, M.; Calatayud, J. M. Sequential injection analysis (SIA)-chemiluminescence determination of indomethacin using tris[(2,2'-bipyridyl)]ruthenium(III) as reagent and its application to semisolid pharmaceutical dosage forms. *Anal. Chim. Act.* **2007**, *in press*.
18. Bunce, S.; Cross, R. J.; Farrugia, L. J.; Kunchandy, S.; Meason, L. L.; Muir, K. W.; Odonnell, M.; Peacock, R. D.; Stirling D.; Teat, S. J. Chiral Schiff base complexes of copper(II), vanadium(IV) and nickel(II) as oxidation catalysts. X-ray crystal structures of [Cu(R-salpn)(OH<sub>2</sub>)] and [Cu(+/-busalcx)]. *Polyhedron* **1998**, *17*, 4179-4187.
19. Dehghanpour, S.; Mojahed, F.; Farzaneh, F.; Refinement of the crystal structure of N,N'-ethylene-bis(benzoylacetoneiminato) copper(II), Cu(C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>), at 110 K. *Z. Kristallogr. NCS* **2005**, *220*, 587-588.
20. Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. A catalytic method for synthesis of Biginelli-type 3,4-dihydropyrimidin-2 (1H)-one using 12-tungstophosphoric acid. *J. Mol. Catal. A: Chem.* **2005**, *242*, 173-175.
21. Heravi, M. M.; Taheri, Sh.; Bakhtiari, Kh.; Oskooie, H. A. On Water: A practical and efficient synthesis of quinoxaline derivatives catalyzed by CuSO<sub>4</sub>·5H<sub>2</sub>O. *Catal. Commun.* **2006**, *in press*.

22. Heravi, M. M.; Behbahani, F. K.; Bamoharram, F. F.  $H_{14}[NaP_5W_{30}O_{110}]$ : A heteropoly acid catalyzed acetylation of alcohols and phenols in acetic anhydride. *J. Mol. Catal. A: Chem.* **2006**, *253*, 16-19.
23. Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Tavakoli, N. N-oxidation of pyridine carboxylic acids using hydrogen peroxide catalyzed by a green heteropolyacid catalyst: Preyssler's anion,  $[NaP_5W_{30}O_{110}]^{14-}$ . *J. Mol. Catal. A: Chem.* **2006**, *252*, 219-225.
24. Heravi, M. M.; Ranjbar, L.; Derikvand, F.; Bamoharram, F. F.  $H_6P_2W_{18}O_{62}$ : An efficient and reusable catalyst for one-pot synthesis of  $\beta$ -acetamido ketone and esters. *Catal. Commun.* **2007**, *8*, 289-291.
25. Oskooie, H. A.; Heravi, M. M.; Bakhtiari, K.; Zadsirjan, V.; Bamoharram, F. F.  $H_{14}[NaP_5W_{30}O_{110}]$  as an efficient catalyst for the one-pot synthesis of alpha-amino nitriles. *Synlett* **2006**, *11*, 1768-1770.
26. Heravi, M. M.; Dirkwand, F.; Oskooie, H. A.; Ghassemzadeh, M. Aromatization of Hantzsch 1,4-dihydropyridines with Dess-Martin periodinane under classical heating and microwave irradiation in solventless system. *Heterocyclic Commun.* **2005**, *11*, 75-78.
27. Heravi, M. M.; Derikvand, F.; Oskooie, H. A.; Hekmatshoar, R. Zeofen: a user friendly agent for oxidation of the Hantzsch 1,4-dihydropyridines. *J. Chem. Res.* **2006**, 168-169.
28. Heravi, M. M.; Derikvand, F.; Oskooie, H. A.; Hekmatshoar, R. Silica gel-supported bis(trimethylsilyl) chromate: Oxidation of 1,4-dihydropyridines to pyridines. *Synth. Commun.* **2006**, *36*, 77-82.
29. Heravi, M. M.; Moosavi, F. S. S.; Beheshtiha, Y. S.; Ghassemzadeh, M. Manganese dioxide supported onto HZSM-5 zeolite, a versatile reagent for the aromatization of Hantzsch 1,4-dihydropyridines. *Heterocyclic Commun.* **2004** *10*, 415-418.
30. Vanden Eynde, J.-J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. Old reagents, new results - aromatization of hantzsch 1,4-dihydropyridines with manganese-dioxide and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. *Tetrahedron* **1995**, *51*, 6511-6516.
31. Sabitha, G.; Reddy, G. S.; Reddy, C. S.; Fatima, N.; Yadav, J. S.  $Zr(NO_3)_4$ : A versatile oxidizing agent for aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines. *Synthesis* **2003**, *8*, 1267-1271.
32. Hantzsch, A. Condensationprodukte aus Aldehydammoniak und Ketoniartigen Verbindungen. *Ber.* **1881**, *14*, 1637-1638.

*Sample Availability:* Samples of selected compounds (**1-5**, **7**, **8**, **10**) are available from authors.