This article was downloaded by: [Ams/Girona*barri Lib] On: 21 November 2014, At: 04:41 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines by H_2O_2/V_2O_5 at Room Temperature

Jinlong Su $^{\rm a}$, Cai Zhang $^{\rm a}$, Dan Lin $^{\rm a}$, Yiqin Duan $^{\rm a}$, Xiangkai Fu $^{\rm a}$ & Ruizhu Mu $^{\rm a}$

^a College of Chemistry and Chemical Engineering, Southwest University, Chongqing, China Published online: 03 Feb 2010.

To cite this article: Jinlong Su , Cai Zhang , Dan Lin , Yiqin Duan , Xiangkai Fu & Ruizhu Mu (2010) Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines by H_2O_2/V_2O_5 at Room Temperature, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:4, 595-600, DOI: <u>10.1080/00397910903007087</u>

To link to this article: http://dx.doi.org/10.1080/00397910903007087

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms &

Conditions of access and use can be found at <u>http://www.tandfonline.com/page/terms-and-conditions</u>



Synthetic Communications[®], 40: 595–600, 2010 Copyright © Taylor & Francis Group, LLC ISSN: 0039-7911 print/1532-2432 online DOI: 10.1080/00397910903007087

OXIDATIVE AROMATIZATION OF HANTZSCH 1,4-DIHYDROPYRIDINES BY H_2O_2/V_2O_5 AT ROOM TEMPERATURE

Jinlong Su, Cai Zhang, Dan Lin, Yiqin Duan, Xiangkai Fu, and Ruizhu Mu

College of Chemistry and Chemical Engineering, Southwest University, Chongqing, China

A mild and highly efficient synthetic method was developed for the aromatization of 1,4-dihydropyridines employing H_2O_2 and 5 mol% of V_2O_5 . The reactions were carried out in CH₃CN to give pyridine compounds in excellent yields.

Keywords: Aromatization; H2O2; Hantzsch 1,4-dihydropyridines; V2O5

Hantzsch 1,4-dihydropyridine derivatives are usually regarded as a model of the natural reduced nicotinamine adenine dinucleotide (NADH) coenzyme, which plays a vital role in many bioreductions by transferring a hydride ion or an electron to ambient substrates. These compounds possess high pharmacological activity as a class of useful drugs and antioxidants. Therefore, the aromatization of Hantzsch 1,4-dihydropyridines has recently attracted considerable attention from synthetic chemists.

In this context, a wide variety of oxidants have been reported for the aromatization of Hantzsch 1,4-dihydropyridines such as ferric chloride hexahydrate,^[1] manganese dioxde,^[2] I₂/MeOH,^[3] nitrosoglutathione (GSNO),^[4] silica chromate,^[5] Zr(NO₃)₄,^[6] CO(NH₂)₂ · H₂O₂/I₂,^[7] IBX,^[8] ferric perchlorate,^[9] oxone,^[10] Pt (II) complex/hv,^[11] 9-phenyl-10-methylacridinium/O₂/hv,^[12] NHPI/O₂,^[13] KBrO₃/ SnCl₄ · 5H₂O,^[14] vanadium(V) salts under microwave irradiation,^[15] Pd/C/acetic acid,^[16] and 2,6-dicarboxypyridinum.^[17] However, most of these reactions require extended reaction time for completion and give poor yields of the products.

The literature review shows that the combination system of H_2O_2 and V_2O_5 has been used for the oxidation alcohols to their corresponding carbonyl compounds.^[18–20] In continuation of these works, we decided to examine the capability of the H_2O_2/V_2O_5 system for aromatization of Hantzsch 1,4-dihydropyridines.

Reaction conditions were optimized, and the usefulness of this synthetic method was studied by subjecting a variety of Hantzsch 1,4-dihydropyridines to

Received December 22, 2008.

Address correspondence to Ruizhu Mu, College of Chemistry and Chemical Engineering, Southwest University, Chongqing, China. E-mail: muruizhu2008@163.com



the H_2O_2/V_2O_5 system as shown in Scheme 1. The results of this investigation are summarized in Table 1. As shown, all reactions were carried out within 1 h, and the pyridine products were obtained in good to excellent yields. The exact mechanism of this protocol is not clear; however, we think that the aromatization of 1,4-dihydropyridines follows a redox cycle depicted in Scheme 2.

In conclusion, this article described a novel and mild method for the aromatization of Hantzsch 1,4-dihydropyridines using the H_2O_2/V_2O_5 system at room temperature. The cheapness, easy availability of the reagents, mild reaction conditions, and excellent yield of the products are the advantages that make this protocol a useful addition to the existing methodologies.

EXPERIMENTAL

General

All reagents and solvents were purchased from commercial sources and used as received. Hantzsch 1,4-dihydropyridines were synthesized from a combination of ethyl acetoacetate, aldehyde, and ammonium acetate under mild and solvent-free conditions (Hantzsch reaction).^[21] Silica gel (200–300 mesh) for column chromatography was purchased from the Qingdao Marine Chemical Factory in China, and the distillation range of petroleum ether is 60–90°C. Melting points were determined on a Xianke melting-point apparatus and are uncorrected. ¹H NMR spectra were

Hantzsch 1,4-DHPs	Oxidized products	R	Reaction time (h)	Yield ^b (%)
la	2a	Н	1	98
1b	2b	Me	1	94
1c	2c	C_6H_5	1	96
1d	2d	4-Br-C ₆ H ₄	1	98
1e	2e	$4-Cl-C_6H_4$	1	95
1f	2f	4-(MeO)-C ₆ H ₄	1	94
1g	2g	3-(NO ₂)-C ₆ H ₄	1	96
1h	2h	PhCH=CH ₂	1	96
1i	2i	2-Furyl	1	98

Table 1. Aromatization of Hantzsch 1,4-dihydropyridines by H₂O₂/V₂O₅^a

^aAll reactions were carried out at room temperature in CH₃CN.

^bIsolated yields.



recorded on Bruker AV-300 or Varian Mercury Plus 300 spectrometer in CDCl₃, and spectral data are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were determined on a HP 5988A spectrometer by direct inlet at 70 eV. All products were identified by comparison of their ¹H NMR, MS spectra, and/or melting point with those of the authentic samples.

General Procedure for the Aromatization of Hantzsch 1,4-Dihydropyridines with H₂O₂/V₂O₅ System

In a typical reation, a mixture of V_2O_5 (5 mg, 0.027 mmol) and aq. 30% H_2O_2 (2.16 mmol) was prepared. The mixture was stirred at room temperature for 10 min, and then a solution of 1,4-dihydropyridine (0.54 mmol) in CH₃CN (5 mL) was added. The resulting mixture was stirred for 1 h at room temperature. After completion of the reaction (monitored by thin-layer chromatography), the mixture was poured into H_2O (10 mL) and extracted with Et₂O (3 × 10 mL). The combined extracts were dried over anhydrous Na₂SO₄. Evaporation of the solvent under reduced pressure followed by short-column chromatography (silica gel, PE–EtOAc, 6:1 v/v) afforded the pure pyridine product.

Representative Spectral Data

Compound 2a. Colorless solid, mp 69–70°C (lit.^[16] mp 71–72°C); ¹H NMR (300 MHz, CDCl₃): δ 1.42 (t, 6H, J=7.2 Hz), 2.86 (s, 6H), 4.40 (q, 4H, J=7.2 Hz), 8.68 (s, 1H); MS (EI, 70 ev): m/z (%) 251 (39.8, [M]⁺), 206 (100), 195 (19.6), 178 (53.8), 150 (29.0), 106 (21.6).

Compound 2b. Pale yellow oil (lit.^[22] oil); ¹H NMR (300 MHz, CDCl₃): δ 1.27 (t, 6H, J = 6.9 Hz), 2.16 (s, 3H), 2.40 (s, 6H), 4.30 (q, 4H, J = 6.9 Hz); MS (EI, 70 ev): m/z (%) 265 (31.4, [M]⁺), 236 (45.9), 220 (100), 208 (43.2), 192 (25.9), 77 (34.5).

Compound 2c. Colorless solid, mp 60–62°C (lit.^[23] mp 62–63°C); ¹H NMR (300 MHz, CDCl₃): δ 0.85 (t, 6H, J=7.2 Hz), 2.57 (s, 6H), 3.96 (q, 4H, J=7.2 Hz), 7.21 (d, 2H), 7.32 (t, 3H); MS (EI, 70 ev): m/z (%) 327 (71.2, [M]⁺), 282 (48.1), 254 (42.4), 236 (100), 209 (29.4), 139 (33.8).

Compound 2d. Pale yellow solid, mp 53–54°C (lit.^[24] mp 52–54°C); ¹H NMR (300 MHz, CDCl₃): δ 0.95 (t, 6H, J = 7.2 Hz), 2.57 (s, 6H), 4.01 (q, 4H, J = 7.2 Hz), 7.16 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz); MS (EI, 70 ev): m/z (%) 407 (31.3, [M]⁺), 362 (100), 334 (72), 289 (49), 77 (13).

Compund 2e. Pale yellow solid, mp 66–67°C (lit.^[22] mp 65–67°C); ¹H NMR (300 MHz, CDCl₃): δ 0.93 (t, 6H, J = 7.2 Hz), 2.57 (s, 6H), 4.00 (q, 4H, J = 7.2 Hz), 7.16 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz); MS (EI, 70 ev): m/z (%) 361 (100, [M]⁺), 316 (74), 288 (50), 270 (66), 139 (72), 84 (59), 77 (7).

Compound 2f. Colorless solid, mp 50–52°C (lit.^[1] mp 50°C); ¹H NMR (300 MHz, CDCl₃): δ 0.95 (t, 6H, J=7.2 Hz), 2.55 (s, 6H), 3.78 (q, 3H), 4.01 (d, 4H, J=7.2 Hz), 6.86 (d, 2H, J=9.0 Hz), 7.10 (d, 2H, J=9.0 Hz); MS (EI, 70 ev): m/z (%) 357 (100, [M]⁺), 312 (21), 282 (20), 266 (11), 255 (9), 135 (18), 105 (14), 77 (27).

Compound 2g. Pale yellow solid, mp 61–63°C (lit.^[23] mp 61–63°C); ¹H NMR (300 MHz, CDCl₃): δ 0.98 (t, 6H, J = 7.2 Hz), 2.62 (s, 6H), 4.04 (q, 4H, J = 7.2 Hz), 7.57–7.59 (m, 2H), 8.18–8.27 (m, 2H); MS (EI, 70 ev): m/z (%) 372 (48.8, [M]⁺), 355 (29.5), 327 (100), 299 (39.5), 281 (32.5), 139 (23.2).

Compund 2h. Pale yellow solid, mp 163–164°C (lit.^[25] mp 162–163°C); ¹H NMR (300 MHz, CDCl₃): δ 1.27 (t, 6H, J=7.2 Hz), 2.56 (s, 6H), 4.32 (q, 4H, J=7.2 Hz), 6.79 (d, 1H, J=16.5 Hz), 7.10 (d, 2H, J=16.5 Hz), 7.26–7.42 (m, 5H); MS (EI, 70 ev): m/z (%) 353 (78, [M]⁺), 308 (26), 278 (100), 263 (17), 250 (21), 234 (41), 165 (44), 152 (24), 105 (19), 77 (19).

Compund 2i. Yellow oil (lit.^[1] oil); ¹H NMR (300 MHz, CDCl₃): δ 1.15 (t, 6H, J = 7.2 Hz), 2.51 (s, 6H), 4.21 (q, 4H, J = 7.2 Hz), 6.42 (d, 1H, J = 3.3 Hz), 6.54 (d, 1H, J = 3.3 Hz), 7.42 (s, 1H); MS (EI, 70 ev): m/z (%) 317 (71.5, [M]⁺), 272 (52.3), 243 (38.1), 214 (100), 95 (45.3).

ACKNOWLEDGMENT

The authors are grateful to Southwest University of China for financial support.

REFERENCES

- 1. Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Li, W. Ferric chloride hexahydrate: A convenient reagent for the oxidation of Hantzsch 1,4-dihydropyridines. *Synth. Commun.* **2001**, *31*, 2625–2630.
- Bagley, M. C.; Lubinu, M. C. Microwave-assisted oxidative aromatization of Hantzsch 1,4-dihydropyridines using manganese dioxide. *Synthesis* 2006, 1283–1288.
- Yadav, J. S.; Subba Reddy, B. V.; Sabitha, G.; Kiran Kumar Reddy, G. S. Aromatization of Hantzsch 1,4-dihydropyridines with I₂-MeOH. *Synthesis* 2000, 1532–1534.
- Mao, Y. Z.; Jin, M. Z.; Liu, Z. L.; Wu, L. M. Oxidative reactivity of S-nitrosoglutathione with Hantzsch 1,4-dihydropyridine. Org. Lett. 2000, 2, 741–742.
- Zolfigol, M. A.; Salehi, P.; Ghorbani Choghamarani, A.; Safaiee, M.; Shahamirian, M. Silica chromate as a novel oxidizing agent for the oxidation of 1,4-dihydropyridines. *Synth. Commun.* 2007, *37*, 1817–1823.

- Sabitha, G.; Kumar Reddy, G. S. K.; Reddy, C. S.; Fatima, N.; Yadav, J. S. Zr(NO₃)₄: A versatile oxidizing agent for aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines. *Synthesis* 2003, 1267–1271.
- Filipan Litvić, M.; Litvić, M.; Vinković, V. An efficient, metal-free, room temperature aromatization of Hantzsch 1,4-dihydropyridines with urea–hydrogen peroxide adduct, catalyzed by molecular iodine. *Tetrahedron* 2008, 64, 5649–5656.
- Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Baishya, G.; Narsaiah, A. V. Iodoxybenzoic acid (IBX): An efficient and novel oxidizing agent for the aromatization of 1,4-dihydropyridines. *Synthesis* 2006, 451–454.
- 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.
- Liu, Z.; Yu, W.; Yang, L.; Liu, Z. L. A novel oxidation-ring contraction of Hantzsch 1,4-dihydropyridines to polysubstituted furans. *Tetrahedron Lett.* 2007, 48, 5321–5324.
- Zhang, D.; Wu, L. Z.; Zhou, L.; Han, X.; Yang, Q. Z.; Zhang, L. P.; Tung, C. H. Photocatalytic hydrogen production from Hantzsch 1,4-dihydropyridines by platinum(II) terpyridyl complexes in homogeneous solution. J. Am. Chem. Soc. 2004, 126, 3440–3441.
- Fang, X.; Liu, Y. C.; Li, C. 9-Phenyl-10-methylacridinium: A highly efficient and reusable organocatalyst for mild aromatization of 1,4-dihydropyridines by molecular oxygen. *J. Org. Chem.* 2007, 72, 8608–8610.
- Han, B.; Liu, Z.; Liu, Q.; Yang, L.; Liu, Z. L.; Yu, W. An efficient aerobic oxidative aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines. *Tetrahedron* 2006, 62, 2492–2496.
- Zeynizadeh, B.; Dilmaghani, K. A.; Roozijoy, A. Oxidative aromatization of Hantzsch ester 1,4-dihydropyridines by KBrO₃/SnCl₄ · 5H₂O under mild condition. *Synth. Commun.* 2005, 35, 557–562.
- Filipan Litvić, M.; Litvić, M.; Vinković, V. Rapid, efficient, room temperature aromatization of Hantzsch 1,4-dihydropyridines with vanadium(V) salts: Superiority of classical technique versus microwave-promoted reaction. *Tetrahedron* 2008, 64, 10912–10918.
- 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.
- Heravi, M. M.; Bakhtiari, K.; Oskooie, H. A. 2,6-Dicarboxypyridinum chlorochromate: An efficient oxidizing agent for the very fast oxidation of Hantzsch 1,4-dihydropyridines. *Arkivoc* 2007, 13, 190–194.
- Bonchio, M.; Bortolini, O.; Conte, V.; Primon, S. Aerobic oxidation of isopropanol catalysed by peroxovanadium complexes: Mechanistic insights. J. Chem. Soc., Perkin Trans. 2 2001, 763–765.
- Gopinath, R.; Patel, B. K. A catalytic oxidative esterification of aldehydes using V₂O₅-H₂O₂. Org. Lett. 2000, 2, 577–579.
- Li, C.; Zheng, P.; Li, J.; Zhang, H.; Cui, Y.; Shao, Q.; Ji, X.; Zhang, J.; Zhao, P.; Xu, Y. The dual roles of oxodiperoxovanadate both as a nucleophile and an oxidant in the green oxidation of benzyl alcohols or benzyl halides to aldehydes and ketones. *Angew. Chem. Int. Ed.* 2003, *42*, 5063–5066.
- Zolfigol, M. A.; Safaiee, M. Synthesis of 1,4-dihydropyridines under solvent-free conditions. Synlett. 2004, 0827–0828.
- 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.

J. SU ET AL.

- 23. 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.
- Xia, J. J.; Wang, G. W. One-pot synthesis and aromatization of Hantzsch 1,4-dihydropyridines in refluxing water. *Synthesis* 2005, 2379–2383.
- 25. Varma, R. S.; Kumar, D. Manganese triacetate mediated oxidation of Hantzsch 1,4-dihydropyridines to pyridines. *Tetrahedron Lett.* **1999**, *40*, 21–24.