

Uncatalyzed Aerial Oxidation of Hantzsch Ester in Different Organic Solvents

XIAOLAN XU[†] and HUAJIAN XU^{*}

School of Chemical Engineering, Hefei University of Technology, Hefei-230009, P.R. China

Tel: (86)(551)2904405; E-mail: hjxu@mail.ustc.edu.cn

The uncatalyzed aerial oxidation of Hantzsch ester in different organic solvents was studied systematically for the first time. The results suggested that the yield of oxidation product was connected with the polarity of solvents at a lower reaction temperature while the yield of oxidation product was connected with the boiling point of solvents under refluxing condition.

Key Words: Hantzsch ester, Oxidation, Solvent, Mechanism.

INTRODUCTION

Hantzsch ester as an NADH model has been extensively used in studies of mechanism and synthesis^{1,2}. Meanwhile, Hantzsch ester and its analogues are important intermediates in the synthesis of pyridine compounds. They are also important constituents of many drugs for the treatment of cardiovascular diseases such as hypertension and angina pectoris³. The oxidative aromatization of them has drawn much attention during the past decades and is of continuing interest. A wide variety of reagents have been used to achieve this purpose including inorganic and organic oxidants⁴. However, these methods were of limited value because of the use of stoichiometric amounts of inorganic or organic oxidants resulting in equal amount of waste, which will cause environmental problems. As a result, the use of clean oxidants such as molecular oxygen is highly desired in order to improve reaction atom efficiency and to render the oxidation process mild and environmentally benign. However, it is accepted that oxygen molecule itself cannot oxidize Hantzsch ester and its analogues effectively and the introduction of catalyst is necessary in previous studies. Towards this end, RuCl₃⁵, silica gel-supported Co/Mn *p*-aminobenzoate⁶, activated carbon⁷, ferric perchlorate in acetic acid⁸, N-hydroxyphthalimide⁹ and 9-phenyl 10-methylacridinium perchlorate¹⁰ have been found to be effective. In present study, it is found that Hantzsch ester can be oxidated easily under oxygen atmosphere without the addition of any catalyst.

[†]Department of Chemistry, Anhui Medical University, Hefei-230032, P.R. China.

EXPERIMENTAL

Initial experiments were concentrated on the selection of solvent for the oxidation of Hantzsch ester **1** as shown in Fig. 1¹¹. Four different solvents were employed. Toluene and *p*-xylene gave very poor conversion. However, acetonitrile and chloroform gave higher isolated yields. From these results, it is concluded that the yield of oxidation product **2** increased with the increase of the polarity of solvents (order of polarity of the four solvents is: acetonitrile > chloroform > toluene > *p*-xylene). In present experiments, it is also found that the solubility of **1** in solvents with lower polarity (toluene and *p*-xylene) was very poor which might lead to the lower yield of **2**.

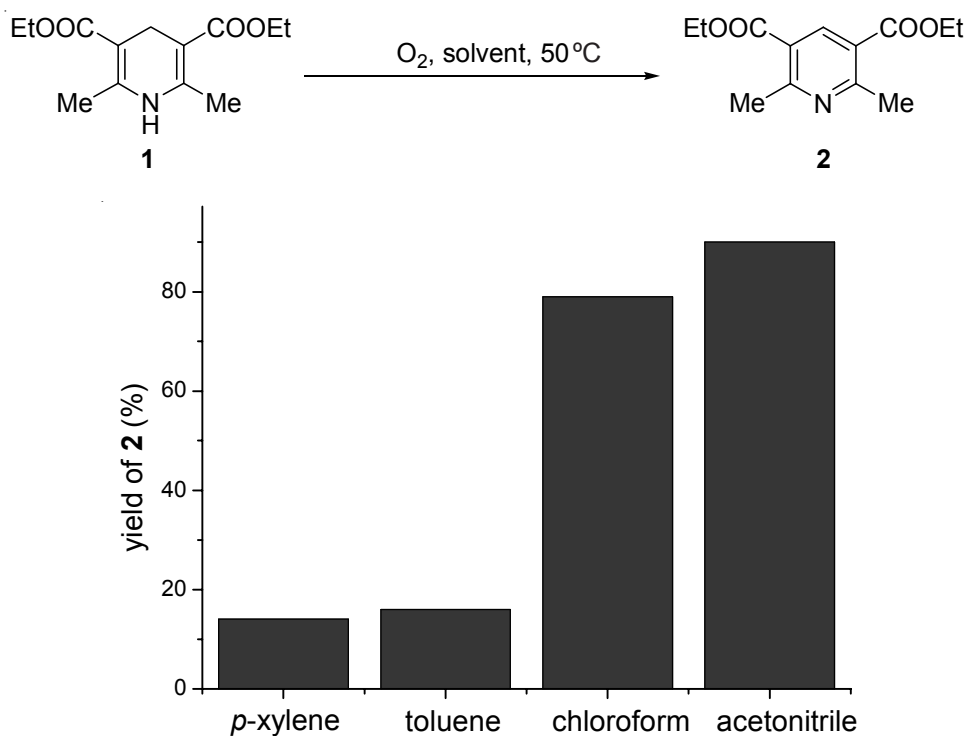


Fig. 1

Here one question arises whether the yield of **2** only connected with the polarity of solvents. For this purpose, we conducted these reactions under refluxing conditions and results were listed in Fig. 2¹². To our surprise, the reaction time was reduced and the yield of **2** increased with the increase of boiling point of solvents (order of boiling point of the four solvents is: *p*-xylene > toluene > acetonitrile > chloroform). Furthermore, the solubility of **1** in solvents with lower polarity (toluene and *p*-xylene) was very good under the current reaction condition.

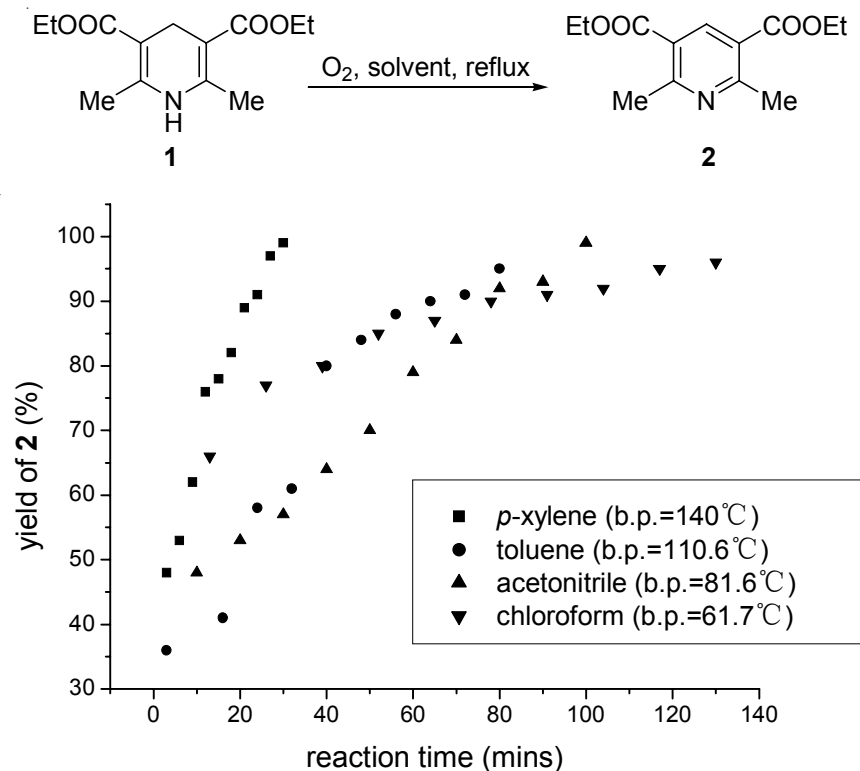
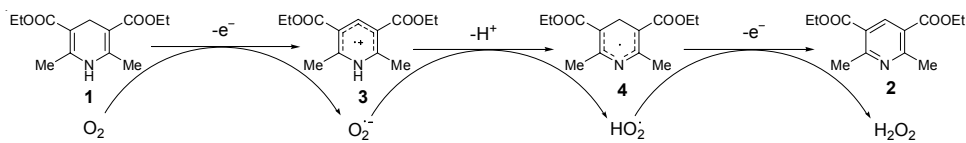


Fig. 2

RESULTS AND DISCUSSION

On the basis of these observations and by reference to the literature¹³, an electron transfer mechanism is proposed for the reaction as shown in **Scheme-I**. Oxygen abstracted an electron from **1** to generate the anion radical of O_2 and cation radical **3**. The fast deprotonation of **3** gave the radical **4**, which reacted with HO_2^\bullet to afford the aromatization product **2** along with the formation of H_2O_2 ¹⁴.



Scheme-I: Proposed mechanism for the oxidation of **1** without any catalyst in oxygen atmosphere

By virtue of this plausible mechanism, all the above experimental observations could be easily explained. At the lower temperature, **1** could be entirely dissolved in solvents with higher polarity so that the efficiency of the whole reaction was

elevated and the higher yield of **2** was obtained. On the other hand, under refluxing condition, the first electron transfer accelerated with increase of boiling point of solvents so that the higher yield of **2** was obtained.

In conclusion, it is reported here that Hantzsch ester can be directly oxidized to the corresponding the substituted pyridine without the addition of any catalyst. It is found that the yield of oxidation product is connected with the polarity of solvents in lower reaction temperature while the yield of oxidation product is connected with the boiling point of solvents under refluxing reaction condition. Study on the analogues of Hantzsch ester under the similar reaction condition is under exploring.

ACKNOWLEDGEMENTS

This research was financially supported by the National Natural Science Foundation of China (No. 20772115) and the Doctoral Special Fund of Hefei University of Technology (No. 2007GDBJ021).

REFERENCES

1. (a) Y.D. Wu, D.K.W. Lai and K.N. Houk, *J. Am. Chem. Soc.*, **117**, 4100 (1995); (b) X.Q. Zhu, J.Y. Zhang and J.P. Cheng, *J. Org. Chem.*, **71**, 7007 (2006); (c) H.J. Xu, D.M. Dai, Y.C. Liu, J. Li, S.W. Luo and Y.D. Wu, *Tetrahedron Lett.*, **46**, 5739 (2005); (d) H. Jiang, Y.C. Liu, G.W. Wang, Y.D. Wu, Q.M. Wang and T.C.W. Mak, *Chin. Chem. Lett.*, **15**, 159 (2004); (e) D.M. Dai, Y.C. Liu, J. Li, P. Wang, X.D. Chen and T.C.W. Mak, *Chin. Chem. Lett.*, **15**, 353 (2004).
2. (a) S.G. Ouellet, J.B. Tuttle and D.W.C. MacMillan, *J. Am. Chem. Soc.*, **127**, 32 (2005); (b) J.B. Tuttle, S.G. Ouellet and D.W.C. MacMillan, *J. Am. Chem. Soc.*, **128**, 12662 (2006); (c) N.J.A. Martin and B. List, *J. Am. Chem. Soc.*, **128**, 13368 (2006); (d) J. Zhou and B. List, *J. Am. Chem. Soc.*, **129**, 7498 (2007); (e) N.J.A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, **129**, 8976 (2007).
3. R. Toniolo, F.D. Narda, G. Bontempelli and F. Ursini, *Bioelectro. Chem.*, **51**, 193 (2000).
4. (a) G. Sabitha, G.S. Reddy, K. Kiran, C.S. Reddy, N. Fatima and J.S. Yadav, *Synthesis*, 1267 (2003); (b) M. Majid, N.E. Masoud, T. Shahram and M. Valiollah, *Bioorg. Med. Chem. Lett.*, **16**, 2026 (2006); (c) M.C. Bagley and M.C. Lubinu, *Synthesis*, 1283 (2006); (d) Z.Y. Chen and W. Zhang, *Chin. Chem. Lett.*, **18**, 1443 (2007).
5. S.H. Mashraqui and M.A. Kamik, *Tetrahedron Lett.*, **39**, 4895 (1998).
6. M.M. Hashemi and Y. Ahmadibeni, *Monatsh. Chem.*, **134**, 411 (2003).
7. N. Nakamichi, Y. Kawashita and M. Hayashi, *Synthesis*, 1015 (2004).
8. M.M. Heravi, F.K. Behbahani, H.A. Oskooie and R.H. Shoar, *Tetrahedron Lett.*, **46**, 2775 (2005).
9. B. Han, Q. Liu, Z. Liu, R. Mu, W. Zhang, Z.L. Liu and W. Yu, *Synlett*, 2333 (2005).
10. X. Fang, Y.C. Liu and C. Li, *J. Org. Chem.*, **72**, 8608 (2007).
11. Typical experimental procedure in lower temperature: A solution of Hantzsch ester **1** (1 mmol) in 1 mL of solvent was stirred under oxygen atmosphere at 50 °C for 1 h. The yield of the substituted pyridine **2** was determined by GC-MS using biphenyl as Internal Standard.
12. Typical experimental procedure in refluxing condition: A solution of Hantzsch ester **1** (1 mmol) and biphenyl (1 mmol) in 1 mL of solvent was stirred under oxygen atmosphere under refluxing for the corresponding time reacted entirely. Ten samples were attracted in each solvent during the whole reaction and the yield of the substituted pyridine **2** was determined by GC-MS using as Biphenyl Internal Standard.
13. J. Zhang, M.Z. Jin, W. Zhang, L. Yang and Z.L. Liu, *Tetrahedron Lett.*, **43**, 9687 (2002).
14. R.D. Mair and A.J. Graupner, *Anal. Chem.*, **36**, 194 (1964).