

Tetrahedron Letters

Tetrahedron Letters 46 (2005) 7329-7330

## Synthesis of Hantsch 1,4-dihydropyridines by fermenting bakers' yeast

## Jung Hwan Lee\*

The Albert Einstein College of Medicine, Department of Biochemistry, 1300 Morris Park Avenue, Bronx, NY 10461, USA

Received 14 July 2005; revised 16 August 2005; accepted 25 August 2005

Available online 13 September 2005

Abstract—Hantsch 1,4-dihydropyridines are prepared by fermenting bakers' yeast with alkyl acetoacetate and ammonium acetate. © 2005 Elsevier Ltd. All rights reserved.

Bakers' yeast (Saccharomyces cerevisiae) has been known to reduce carbonyl compounds to optically active secondary alcohols. Reduction of  $\beta$ -keto esters to optically active  $\beta$ -hydroxy esters provide representative examples. Few examples are known for the reduction of carbon–carbon double bonds and acyloin-type condensation with bakers' yeast.

In this communication, a novel and efficient synthesis of Hantsch 1,4-dihydropyridines (1, 2) by fermenting bakers' yeast at ambient temperature is described.

Thus, the reaction of alkyl acetoacetate with  $NH_4OAc$  in the presence of fermenting bakers' yeast results in the formation of Hantsch 1,4-dihydropyridine 1. The reaction was complete in 24 h at room temperature and the product was isolated by usual work-up, in 67–70% yield. Under similar conditions using crotonitrile instead of  $NH_4OAc$ , 3-cyano-1,4-dihydropyridines 2 were obtained in 46–49% yield (Scheme 1).

1,4-Dihydropyridines(DHP) are highly effective calcium antagonists. <sup>5</sup> They act as coenzyme in different dehydrogenases, and they are valuable intermediates in the preparation of alkaloids.

One of the most versatile synthesis of DHP is that due to Hantsch, which uses a dicarbonyl compound or enamine, an aldehyde, and ammonia. A general synthesis approach to the DHP is an aldehyde, acetoacetic ester,

**Scheme 1.** Reagents: (i) bakers' yeast, yeast extract, p-glucose, phosphate buffer (pH 7.0).

and ammonium hydroxide are heated at reflux temperature under acidic conditions.<sup>6</sup> However, the yields of 1,4-DHP obtained by Hantsch method are generally low. Even though a number of modified methods under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, high temperatures, and harsh reaction condition.<sup>7</sup> In recent years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridine owing to their significant biological activity. I now describe an efficient synthesis of DHP derivatives in mild condition using bakers' yeast. In contrast to the techniques used previously, I demonstrate that DHP can be prepared efficiently in water at room temperature under neutral condition without the use of microwave,<sup>8</sup> ionic liquid,<sup>9</sup> high temperature in refluxing solvent,<sup>10</sup> TMSI,<sup>11</sup> metal triflates, <sup>12</sup> and iodine. <sup>13</sup>

Keywords: Hantsch 1,4-dihydropyridine; Bakers' yeast.

<sup>\*</sup>Tel.: +1 718 430 8642; fax: +1 718 430 8565; e-mail: jhlee2000@ hanmail.net

**Scheme 2.** Reagents: (i) bakers' yeast, yeast extract, sucrose, phosphate buffer (pH 7.0).

**Figure 1.** Chemdraw of the proposed reaction pathway of Hantsch type reaction by bakers' yeast.

A typical procedure is described as follows: To a solution of 100 mL of pH 7.0 phosphate buffer, 5.0 g of p-glucose, and 2.0 g of yeast extract, warmed at 35 °C, was added 5.0 g of dry active bakers' yeast and the mixture was stirred at 30 °C for 30 min, after which, acetoacetic ester (1.0 mmol) and ammonium acetate or 3-amino crotonitrile were added. The mixture was shaken at room temperature for 24 h and then extracted with diethyl ether. The organic layer was dried and concentrated in vacuo and the resulting crude products were recrystallized using ether–*n*-hexane to afford pure products 1 and 2 in 46–70% yields. 14

However, (S)- $\beta$ -hydroxyesters are obtained by the bakers' yeast reduction in use of sucrose instead of D-glucose under the same condition (Scheme 2).

The glycolytic pathway from D-glucose to pyruvate is one of the most universal metabolic pathway known. In yeast, glycolysis is supposed to be the main pathway for the catabolism of glucose. According to the classical concept of glycolysis, metabolic acetaldehyde, resulting in the formation of acetoin, should be released from pyruvate in aerobic conditions. <sup>15</sup> It is assumed that this acetaldehyde is involved in this Hantsch-type reaction (Fig. 1).

## Acknowledgements

I wish to thank Dr. Youn Young Lee and Dr. Yang Mo Goo for valuable comments and helpful discussions.

## References and notes

- Sih, C. J.; Chen, C.-S. Angew. Chem., Int. Ed. Engl. 1984, 23, 570.
- 2. Csuk, R.; Glänzer, B. I. Chem. Rev. 1991, 91, 49.
- 3. (a) Kitazume, T.; Ishikawa, N. Chem. Lett. 1983, 237; (b) Utaka, M.; Konishi, S.; Takeda, A. Tetrahedron Lett. 1986, 27, 4737; (c) Ohta, H.; Kobayashi, N.; Ozaki, K. J. Org. Chem. 1989, 54, 1802.
- (a) Fuganti, C.; Grasselli, P.; Servi, S.; Spreafico, F.;
   Zirotti, C. J. Org. Chem. 1984, 49, 4087; (b) Fuganti, C.
   Pure Appl. Chem. 1990, 62, 1449.
- (a) Bossert, F.; Vater, W. Naturwissenschaften 1971, 68, 578; (b) Bossert, F.; Vater, M. Med. Res. Rev. 1989, 9, 291; (c) Nakayama, H.; Kasoaka, Y. Heterocycles 1996, 42, 901.
- 6. Hantsch, A. Justus Liebigs Ann. Chem. 1882, 1, 215.
- (a) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* 1996, 61, 924; (b) Breitenbucher, J. G.; Figliozzi, G. *Tetrahedron Lett.* 2000, 41, 4311; (c) Ohberg, L.; Westman, J. *Synlett* 2001, 1296; (d) Anderson, A. G., Jr.; Berkelhammer, G. *J. Am. Chem. Soc.* 1958, 80, 992; (e) Maquestiau, A.; Maeyence, A.; Eynde, J.-J. V. *Tetrahedron Lett.* 1991, 32, 3839.
- 8. (a) Khadikar, B. M.; Gaikar, V. G.; Chitnavis, A. A. *Tetrahedron Lett.* **1995**, *36*, 8083; (b) Agarwal, A.; Chauhan, P. M. S. *Tetrahedron Lett.* **2005**, *46*, 1345.
- (a) Ji, S.-J.; Jiang, Z.-Q.; Lu, J.; Loh, T.-P. Synlett 2004, 831; (b) Sridhar, R.; Perumal, P. T. Tetrahedron 2005, 61, 2465.
- (a) Singh, H.; Chimni, D. S. S.; Kumar, S. Tetrahedron 1995, 51, 12775; (b) Liang, J.-C.; Yeh, J.-L.; Wang, C.-S.; Liou, S.-F.; Tasi, C.-H.; Chen, I.-J. Bioorg. Med. Chem. 2002, 10, 719; (c) Miri, R.; Niknahad, H.; Vesal, Gh.; Shafiee, A. IL Farmaco 2002, 57, 123; (d) Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S.; Bertoasi, V. J. Org. Chem. 2003, 68, 6172; (e) Dondoni, A.; Massi, A.; Minghini, E.; Bertoasi, V. Tetrahedron 2004, 60, 2311; (f) Tewari, N.; Dwivedi, N.; Tripathi, R. P. Tetrahedron Lett. 2004, 45, 9011; (g) Moseley, J. D. Tetrahedron Lett. 2005, 46, 3179.
- Sabitha, G.; Reddy, G. S. K. K.; Reddy, Ch. S.; Yadav, J. S. *Tetrahedron Lett.* 2003, 44, 4129.
- 12. Wang, L.-M.; Sheng, J.; Zhang, L.; Han, J.-W.; Fan, Z.; Tian, H.; Qian, C.-T. *Tetrahedron* **2005**, *61*, 1539.
- 13. Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 5771–5774.
- 14. Data for selected compounds; 1a: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  0.95 (d, J = 6.49 Hz, 3H), 2.27 (s, 6H), 3.71 (s, 6H), 3.81 (q, J = 6.49 Hz, 1H), 6.04 (br s, 1H); <sup>13</sup>C NMR (80 MHz, CDCl<sub>3</sub>) δ 19.25, 22.22, 28.44, 58.87, 104.35, 144.71, 168.26; IR (KBr) 3320, 1705 cm<sup>-1</sup>; MS m/z 239, 224, 106; mp 155 °C, 67% yield **1b**: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  0.95 (d, J = 6.50 Hz, 3H), 1.29 (t, 6H), 2.26 (s, 6H), 3.75 (q, J = 6.50 Hz, 1H), 4.18 (q, 4H), 5.51 (br s, 1H); <sup>13</sup>C NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  14.28, 19.10, 22.11, 28.40, 58.43, 104.26, 144.66, 167.88; IR (KBr) 3320, 1705 cm<sup>-1</sup>; MS m/z 267, 252, 106; mp 130 °C, 70% yield **2a**:  $^{1}$ H NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  1.29 (d, J = 8.06 Hz, 3H), 2.04 (s, 3H), 3.35 (q, J = 8.06 Hz, 1H), 6.78 (br s, 1H); IR (KBr) 3320, 1705 cm<sup>-1</sup>, 46% yield **2b**: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  0.95 (d, J = 6.48 Hz, 3H), 1.29 (t, 3H), 2.26 (s, 6H), 3.75 (q, J = 6.48 Hz, 1H), 4.18 (q, 2H), 6.47(br s, 1H); IR (KBr) 3320, 1705 cm<sup>-1</sup>, 49% yield.
- Sergienko, E. A.; Jordan, F. Biochemistry 2001, 40, 7369.