

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.

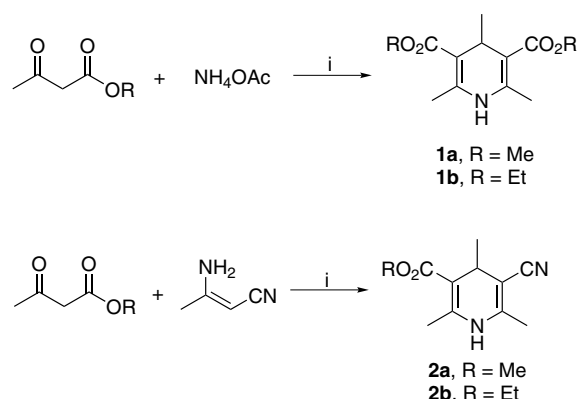
Bakers' yeast (*Saccharomyces cerevisiae*) has been known to reduce carbonyl compounds to optically active secondary alcohols.¹ Reduction of β -keto esters to optically active β -hydroxy esters provide representative examples.² Few examples are known for the reduction of carbon–carbon double bonds³ and acyloin-type condensation⁴ 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.⁵ 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, D-glucose, phosphate buffer (pH 7.0).

and ammonium hydroxide are heated at reflux temperature under acidic conditions.⁶ 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.⁷ 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,⁸ ionic liquid,⁹ high temperature in refluxing solvent,¹⁰ TMSI,¹¹ metal triflates,¹² and iodine.¹³

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

* Tel.: +1 718 430 8642; fax: +1 718 430 8565; e-mail: jhlee2000@hanmail.net

