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An efficient bakers' yeast catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones☆

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Abstract—Bakers' yeast (*Saccharomyces cerevisiae*) efficiently catalyzes the three-component Biginelli reaction of aldehydes, β-keto esters, and urea/thiourea to form 3,4-dihydropyrimidin-2-(1*H*)-ones in good to excellent yields.

Recently, interest in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (Biginelli compounds) and their derivatives has increased tremendously because of their diverse therapeutic and pharmacological properties such as antiviral, antibacterial, antitumour and antihypertensive activities.[1–3] Some have been successfully used as calcium channel blockers, α-1a-antagonists and neuropeptide Y (NPY) antagonists.[4] Several alkaloids which contain the dihydropyrimidine core unit have been isolated from marine sources. Most notable among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors.[5] The Biginelli reaction is considered as an important multi-component reaction for generating compounds with diverse medicinal applications.

The simple and straightforward procedure, reported by Biginelli in 1893, involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions. However, one serious drawback of the Biginelli reaction is the low yields obtained in the case of substituted aromatic and aliphatic aldehydes.[6] This has led to multi-step synthetic strategies that produce somewhat better yields but lack the simplicity of the one-pot, one-step synthesis.[7,8]

Thus, via the Biginelli reaction, the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones has received renewed interest and several improved procedures have recently been reported.[9–23] However, to the best of our knowledge, there is no report on enzyme catalyzed Biginelli reaction.

Bakers' yeast (*Saccharomyces cerevisiae*) is a well known catalyst for the reduction of ketones to optically active alcohols.[24] Reduction of β-ketoesters to β-hydroxy esters provides a representative example.[25] Bakers' yeast has also been successfully used in acyloin type condensations, reduction of carbon–carbon double bonds and oxidative coupling of thiols to disulfides.[26]

Lee[27] reported a multi-component Hantzsch reaction catalyzed by bakers' yeast yielding dihydropyridyl compounds via three-component condensation of an aldehyde, ethyl acetoacetate and ammonium acetate. We were interested to investigate the generality of this method and successfully carried out the four-component unsymmetrical Hantzsch reaction of dimedone, an aldehyde, an acetoacetate ester and ammonium acetate to form polyhydroquinoline derivatives in high yields.[28] Encouraged by these results, we turned our attention towards the Biginelli three-component coupling reaction of an aldehyde, an acetoacetate ester and urea/thiourea under similar reaction conditions. It was interesting to observe that Biginelli compounds could be synthesized in high yields under fermenting yeast conditions.

Bakers' yeast (200 mg) and D-glucose (300 mg) were taken in 5 ml of phosphate buffer (pH 7.0) and stirred overnight. Benzaldehyde (106 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol) and urea (90 mg, 1.5 mmol) were added to the fermenting yeast and the reaction

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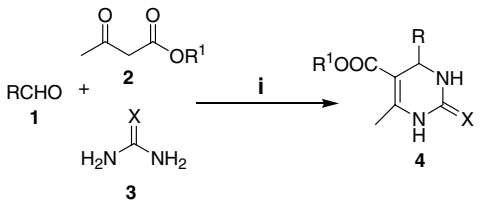


Scheme 1. Reagents and conditions: (i) Bakers' yeast, D-glucose, phosphate buffer (pH 7.0), room temp., 24 h.

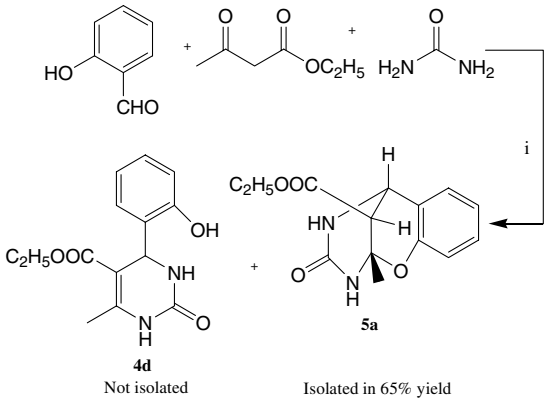
mixture stirred for a further 24 h. Next, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to give a crude product. Pure 3,4-dihydropyrimidin-2-(1*H*)-one derivative **4a** was obtained by crystallization of the crude product from methanol in 84% yield (Scheme 1).

In order to study the catalytic efficiency of bakers' yeast, we carried out a control reaction without yeast using the same reaction protocol as that described above. After work-up, a crude mixture was obtained, which on purification by column chromatography yielded 7% of 3,4-dihydropyrimidin-2-(1*H*)-one derivative **4a**. In another experiment, bakers' yeast, D-glucose, benzaldehyde, ethyl acetoacetate and urea were taken together in 5 ml of phosphate buffer and stirred for 24 h. The reaction mixture, after work-up and purification, yielded **4a** (47%). Thus it was concluded that fermenting bakers' yeast provides a good catalytic medium for efficient coupling of aldehydes, acetoacetate ester and urea/thiourea. It is also clear that adding the three components (aldehyde, acetoacetate ester and urea) in pre-stirred yeast–glucose mixture gives a good yield in comparison to that in which all the components were added simultaneously.

In order to study the generality of this procedure, a series of Biginelli compounds were synthesized. The results are listed in Table 1. Several activated and deactivated aromatic aldehydes afforded high yields of product with high purity. Another important feature of this procedure is the survival of various functional groups such as hydroxy, nitro, methoxy, halides, alkenes etc. Thiourea has been used with similar success to provide the corresponding thio-derivatives of dihydropyrimidinones which are also of interest due to their biological activities.

We observed an interesting reaction in the case of 2-hydroxybenzaldehyde. Reaction of 2-hydroxy benzaldehyde, ethyl acetoacetate and urea (Scheme 2) did not give the expected product **4d**. However, we isolated a compound whose mass was the same as that of the expected product. Based on spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, ESI Mass and elemental analysis), the structure of the compound was deduced as **5a**.[30] Compound **5a** was formed in good yield with high distereoselectivity (90% de) as determined by ^{1}H NMR.

In conclusion, we have successfully developed an efficient and versatile chemo-enzymatic method for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones from the reaction of aldehydes, β-keto esters and urea/thiourea



Scheme 2. Reagents and conditions: (i) Bakers' yeast, D-glucose, Phosphate buffer (pH 7.0), room temp., 24 h.

Table 1. Bakers' yeast mediated synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones[a]

Entry	R	R^1	X	Product[b]	Yield[c]	Mp[d] (°C)
1	C_6H_5	C_2H_5	O	**4a**	84	209–210
2	4-HO–C_6H_4	C_2H_5	O	**4b**	71	235–236
3	1-Naphthyl	C_2H_5	O	**4c**	79	256–258
4	2-HO–C_6H_4	C_2H_5	O	**4d**	Not isolated	—
5	C_6H_5CH=CH	C_2H_5	O	**4e**	73	230–232
6	3-O_2N–C_6H_4	C_2H_5	O	**4f**	69	230–231
7	3-CH_3O–C_6H_4	C_2H_5	O	**4g**	67	205–206
8	4-CH_3–C_6H_4	C_2H_5	O	**4h**	82	204–205
9	$(CH_3)_2NC_6H_4$	C_2H_5	O	**4i**	71	251–252
10	C_6H_5	CH_3	O	**4j**	75	212–213
11	4-HO–C_6H_4	CH_3	O	**4k**	78	245–246
12	4-HO–C_6H_4	C_2H_5	S	**4l**	65	202–203
13	3-CH_3O–C_6H_4	C_2H_5	S	**4m**	62	150–151

[a] Reaction conditions: Bakers' yeast (200 mg), D-glucose (300 mg), phosphate buffer (pH 7.0, 5 ml), aldehyde (1 mmol), β-keto ester (1 mmol) and urea/thiourea (1.5 mmol), room temperature, 24 h.
[b] Products were characterized by MS, IR, ^{1}H NMR and ^{13}C NMR spectroscopies.[29]
[c] Isolated yield.
[d] Melting points are uncorrected.

catalyzed by bakers' yeast at room temperature. The process does not require the use of any volatile organic solvent, harmful metal catalyst and thus, is a simple, easy and environmentally friendly high yielding reaction.

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References and notes

1. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; MaCarthy, J. P.; Zhang, R.; Mereland, S. *J. Med. Chem.* **1995**, *38*, 119–129.
2. Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803–2816.
3. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Mereland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806–811.
4. (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Mereland, S.; Swanson, B. N.; Gougoutas, D. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629–2635; (b) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898–5907.
5. (a) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977–6980; (b) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brosse, C. D.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182–1188.
6. Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *Tetrahedron Lett.* **1989**, *30*, 4573–4576.
7. O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185–1188.
8. (a) Maiti, G.; Kundu, P.; Guin, C. *Tetrahedron Lett.* **2003**, *44*, 2757–2758; (b) Su, W.; Li, J.; Zheng, Z.; Shen, Y. *Tetrahedron Lett.* **2005**, *46*, 6037–6040.
9. Lu, J.; Ma, H. *Synlett* **2000**, 63–64.
10. Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454–3457.
11. Reddy, K. R.; Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Reddy, V. V. N. *Tetrahedron Lett.* **2003**, *44*, 8173–8175.
12. Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett* **2001**, 863–865.
13. Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. *Tetrahedron Lett.* **2001**, *42*, 7873–7875.
14. Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075–9078.
15. Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270–6272.
16. Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305–3308.
17. Ghosh, R.; Maiti, S.; Chakraborty, A. *J. Mol. Catal. A: Chem.* **2004**, *217*, 47–50.
18. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864–3868.
19. Wang, L.; Qian, C.; Tian, H.; Ma, Y. *Synth. Commun.* **2003**, *33*, 1459–1468.
20. Sun, Q.; Wang, Y.; Ge, Z.; Cheng, T.; Li, R. *Synthesis* **2004**, 1047–1051.
21. Lu, J.; Bai, Y. *Synthesis* **2002**, 466–470.
22. Salehi, H.; Guo, Q.-X. *Synth. Commun.* **2004**, *34*, 171–179.
23. Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587–590.
24. Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570.
25. Csuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 49–97.
26. (a) Fuganti, C.; Grasselli, P.; Servi, S.; Spreafico, F.; Zirotty, C.; Casaty, P. *J. Org. Chem.* **1984**, *49*, 4087–4089; (b) Fuganti, C. *Pure Appl. Chem.* **1990**, *62*, 1449–1452; (c) Utaka, M.; Konisi, S.; Tkeda, A. *Tetrahedron Lett.* **1986**, *27*, 4737–4740; (d) Ohta, H.; Kobayashi, N.; Ozaki, K. *J. Org. Chem.* **1989**, *54*, 1802–1804; (e) Rao, K. R.; Kumar, H. M. S. *Bioorg. Med. Chem. Lett.* **1991**, *10*, 507–508.
27. Lee, J. H. *Tetrahedron Lett.* **2005**, *46*, 7329–7330.
28. Kumar, A.; Maurya, R. A. *Tetrahedron Lett.* **2007**, *48*, 3887–3890.
29. Data for selected compounds: Compound **4g**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 1.10 (t, $J = 6.9$ Hz, 3H), 2.27 (s, 3H), 3.74 (s, 3H), 3.97 (q, $J = 6.9$ Hz, 2H), 5.14 (d, $J = 3.0$ Hz, 1H), 6.82–6.86 (m, 3H), 7.23–7.31 (m, 1H), 7.53 (s, 1H), 9.21 (s, 1H). MS (ESI): $m/z = 291$ (M+H). Compound **4k**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 2.25 (s, 3H), 3.54 (s, 3H), 5.01 (s, 1H), 6.66 (d, $J = 8.4$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 7.60 (s, 1H), 9.10 (s, 1H), 9.46 (s, 1H). MS (ESI): $m/z = 263$ (M+H). Compound **4l**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 0.99 (t, $J = 7.0$ Hz, 3H), 2.17 (s, 3H), 3.95 (q, $J = 7.0$ Hz, 2H), 5.12 (d, $J = 3.0$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 9.30 (s, 1H), 9.42 (s, 1H), 10.14 (s, 1H). MS (ESI): $m/z = 293$ (M+H).
30. Compound **5a**: Mp 203–205 °C, ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 1.22 (t, $J = 7.1$ Hz, 3H), 1.76 (s, 3H), 3.26 (d, $J = 2.1$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 4.51 (m, 1H), 6.78 (d, $J = 8.0$ Hz, 1H), 6.92 (m, 1H), 7.18–7.23 (m, 3H), 7.65 (s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 14.37, 24.32, 44.24, 48.05, 60.89, 83.43, 116.91, 120.86, 125.73, 128.97, 129.69, 150.97, 154.95, 168.76. IR (KBr, cm^{-1}): 3238, 3085, 2940, 1747, 1694, 1610, 1589, 1507. MS (ESI): $m/z = 277$ (M+H). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found C, 60.72, H, 5.73, N, 10.02.