Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3887–3890

Bakers' yeast catalyzed synthesis of polyhydroquinoline derivatives via an unsymmetrical Hantzsch reaction

Atul Kumar* and Ram Awatar Maurya

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

Received 22 January 2007; revised 14 March 2007; accepted 22 March 2007
Available online 25 March 2007

Abstract—Bakers' yeast efficiently catalyzes the unsymmetrical Hantzsch reaction through a four-component coupling of aldehydes, β-ketoesters, dimedone and ammonium acetate to form polyhydroquinoline derivatives in good to excellent yields.
© 2007 Elsevier Ltd. All rights reserved.

In recent years, much attention has been directed towards the synthesis of 1,4-dihydropyridyl compounds due to the wide range of biological activity associated with these compounds.[1] 1,4-Dihydropyridyl compounds are well known as calcium channel modulators. Cardiovascular agents such as nifedipine, nicardipine, amlodipine and other related derivatives are dihydropyridyl compounds, which are effective in treatment of hypertension.[2] 1,4-Dihydropyridine derivatives possess a variety of biological activities such as vasodilator, antitumour, bronchodilator, antiatherosclerotic, geroprotective and hepatoprotective activity.[3] Furthermore, these compounds have been shown to possess diverse medicinal utility such as neuroprotectant, platelet anti-aggregatory activity, cerebral antischaemic activity in the treatment of Alzheimer's disease and chemosensitiser behaviour in tumour therapy.[4] These examples clearly indicate the remarkable potential of novel dihydropyridine derivatives as sources of valuable drug candidates. Oxidation of these compounds to pyridines has also been extensively studied.[5] Thus, the synthesis of this heterocyclic nucleus is of importance.

Numerous methods have been reported for the synthesis of polyhydroquinoline derivatives. The classical method involves three-component coupling of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or by refluxing in alcohol.[6] However, these methods suffer from several drawbacks such as long reaction times, use of a large quantity of volatile organic solvents, low yields and harsh reaction conditions. Therefore, it is necessary to develop an efficient and versatile method for the synthesis of polyhydroquinoline compounds. Recently, several methods have been reported comprising the use of microwaves, ionic liquids, TMSCl–NaI, metal triflates and polymers.[7–21] However, the use of high temperatures, expensive metal precursors, catalysts that are harmful to the environment and longer reaction times limits the use of these methods. Therefore, the search for improved catalysts for the synthesis of polyhydroquinoline derivatives using less hazardous conditions is of prime importance.

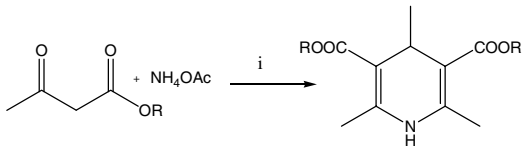
It is well known that bakers' yeast catalyzes the reduction of ketones to optically active alcohols.[22] Reduction of β-ketoesters to β-hydroxy esters provides a representative example.[23] Bakers' yeast has also been successfully used in acyloin type condensations, reduction of carbon–carbon double bonds and oxidative coupling of thiols to disulfides.[24]

More recently, Lee reported the synthesis of dihydropyridyl compounds via Hantzsch reaction using bakers' yeast as the catalyst.[25] Here, the acetaldehyde is generated in situ from fermenting bakers' yeast and is condensed with ethyl acetoacetate and ammonium acetate to form Hantzsch esters (Scheme 1).

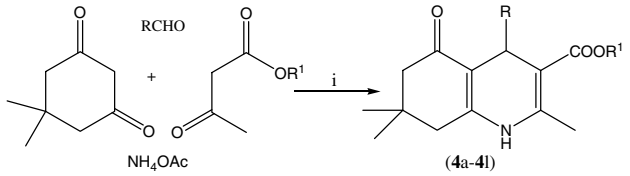
In our ongoing programme, towards the synthesis of polyhydroquinoline derivatives,[26] we decided to add an external aryl aldehyde (other than acetaldehyde) and dimedone to the fermenting yeast conditions (Scheme

Keywords: Bakers' yeast; Hantzsch reaction; Polyhydroquinoline; Multi-component reaction.
* Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405; e-mail: dratulsax@gmail.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.03.130

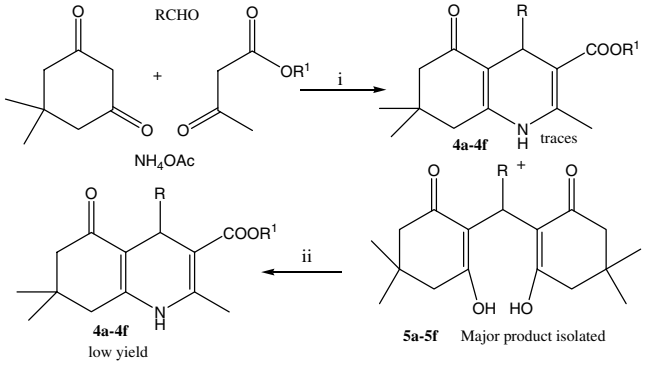


Scheme 1. Reagents and conditions: (i) baker's yeast, D-glucose, phosphate buffer (pH 7.0).



Scheme 2. Reagents and conditions: (i) bakers' yeast, D-glucose, phosphate buffer (pH 7.0), rt, 24 h.

2). Due to the presence of more reactive aryl aldehydes we exclusively obtained the aryl substituted polyhydroquinoline derivatives. Under our reaction conditions no product corresponding to acetaldehyde was generated in situ from fermenting bakers' yeast. The present method provides a versatile approach for the synthesis of aryl substituted polyhydroquinoline derivatives.



Scheme 3. Reagents and conditions: (i) D-glucose, phosphate buffer (pH 7.0), rt, 24 h; (ii) bakers' yeast, D-glucose, phosphate buffer (pH 7.0), ammonium acetate, ethyl acetoacetate, rt, 24 h.

Bakers' yeast (200 mg) and D-glucose (300 mg) were taken in 5 ml phosphate buffer (pH 7.0) and stirred overnight. Dimedone (140 mg, 1 mmol), benzaldehyde (106 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol) and ammonium acetate (75 mg, 1 mmol) were added to the fermenting yeast and the reaction mixture was stirred for a further 24 h, then diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to give a crude product. The pure polyhydroquinoline derivative **4a** was obtained by crystallization from methanol (79% yield).

In order to study the catalytic efficiency of bakers' yeast, we carried out control reactions without bakers' yeast using an identical procedure to that described above (Scheme 3).

Only trace amounts of the desired polyhydroquinolines derivativea **4a–f** were observed on TLC and the major product isolated was a dimedone–aldehyde adduct. We also carried out control reactions with a series of aldehydes **1a–f** and in all cases the dimedone–aldehyde

Table 1. Control reactions:[a] formation of the dimedone–aldehyde adduct

Entry	R	Yield **4a–f**	Yield[b] **5a–f** (%)
1	C_6H_5	Trace	95
2	4-HO–C_6H_4	Trace	94
3	4-HO-3-CH_3O–C_6H_3	Trace	97
4	4-C_2H_5O-3-HO–C_6H_3	Trace	94
5	3-O_2N–C_6H_4	Trace	95
6	2-CH_3O–C_6H_4	Trace	93

[a] D-Glucose (300 mg), phosphate buffer (pH 7.0, 5 ml), aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol), stir, 24 h.
[b] Isolated yields.

Table 2. Synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction catalyzed by bakers' yeast[a]

Entry	R	R^1	Product[b]	Yields[c] (%)	Mp[d] (°C)
1	C_6H_5	C_2H_5	**4a**	79	188–190
2	4-HO–C_6H_4	C_2H_5	**4b**	81	234–235
3	4-HO-3-CH_3O–C_6H_3	C_2H_5	**4c**	72	225–227
4	4-C_2H_5O-3-HO–C_6H_3	C_2H_5	**4d**	73	196–197
5	3-O_2N–C_6H_4	C_2H_5	**4e**	68	177–178
6	2-CH_3O–C_6H_4	C_2H_5	**4f**	67	193–195
7	4-CH_3–C_6H_4	C_2H_5	**4g**	82	261–262
8	$(CH_3)_2N$–C_6H_4	C_2H_5	**4h**	71	222–223
9	4-CH_3–C_6H_4	CH_3	**4i**	75	>270
10	3,4-Cl_2–C_6H_3	CH_3	**4j**	78	198–200
11	3-CH_3O–C_6H_4	*t*-Bu	**4k**	65	190–191
12	C_6H_5	*t*-Bu	**4l**	62	222–223

[a] Reaction conditions: bakers' yeast (200 mg), D-glucose (300 mg), phosphate buffer (pH 7.0, 5 ml), aldehyde (1 mmol), dimedone (1 mmol), β-keto ester (1 mmol) and ammonium acetate (1 mmol), stir, room temperature, 24 h.
[b] Products were characterized by MS, IR, ^1H NMR and ^{13}C NMR spectroscopy.[27]
[c] Isolated yield.
[d] Melting points are uncorrected.

adducts were the major products isolated. The results of this study are shown in Table 1.

We also carried out a reaction in which the bakers' yeast (200 mg) and D-glucose (300 mg) were taken in 5 ml phosphate buffer (pH 7.0) and stirred overnight. Then dimedone–aldehyde adduct (**5a**, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol) and ammonium acetate (75 mg, 1 mmol) were added to the reaction mixture. The reaction was stirred for 24 h leading to polyhydroquinoline derivative **4a**, which was isolated by column chromatography in 24% yield (Scheme 3).

We proceeded to synthesize a series of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction catalyzed by bakers' yeast.[27] Various functionalized aryl aldehydes reacted smoothly to give polyhydroquinoline derivatives in high yields. Hydroxy, methoxy, ethoxy, nitro and chloro substituted aldehydes were tolerated. We also carried out the reaction with other β-keto esters (methyl acetoacetate and *t*-butyl acetoacetate). The results of this study are shown in Table 2.

In conclusion, we have successfully developed an easy, efficient and versatile method for the synthesis of polyhydroquinoline derivatives from the reaction of aldehydes, β-keto esters, dimedone and ammonium acetate 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, environmentally friendly, and high yielding reaction for the synthesis of polyhydroquinolines via unsymmetrical Hantzsch reaction.

Acknowledgement

R.A.M. is thankful to the CSIR, New Delhi for financial support in the form of a junior research fellowship.

Supplementary data

The NMR spectra and details are attached as Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.130.

References and notes

1. (a) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 762–769; (b) Nakayama, H.; Kasoaka, Y. *Heterocycles* **1996**, *42*, 901–909.
2. (a) Buhler, F. R.; Kiowski, W. *J. Hypertens.* **1987**, *5*, S3; (b) Reid, J. L.; Meredith, P. A.; Pasanisi, F. *J. Cardiovasc. Pharmacol.* **1985**, *7*, S18.
3. (a) Godfaid, T.; Miller, R.; Wibo, M. *Pharmacol. Rev.* **1986**, *38*, 321–327; (b) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *7*, 269–289; (c) Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; Schravan, K. *Eur. J. Med. Chem.* **1992**, *27*, 229–235.
4. (a) Klusa, V. *Drugs Future* **1995**, *20*, 135–138; (b) Bretzel, R. G.; Bollen, C. C.; Maester, E.; Federlin, K. F. *Am. J. Kidney. Dis.* **1993**, *21*, 54–63; (c) Bretzel, R. G.; Bollen, C. C.; Maester, E.; Federlin, K. F. *Drugs Future* **1992**, *17*, 465–468; (d) Boer, R.; Gekeler, V. *Drugs Future* **1995**, *20*, 499–509.
5. (a) Zhang, D.; Wu, L. Z.; Zhou, L.; Han, X.; Yang, Q. Z.; Zhang, L. P.; Tung, C. H. *J. Am. Chem. Soc.* **2004**, *126*, 3440–3441; (b) Eynde, J. J. V.; Delfosse, F.; Mayence, A.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 6511–6516; (c) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 5069–5073; (d) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, *46*, 2775–2777; (e) Esfahani, M. N.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Momeni, A. R. *Bioorg. Med. Chem.* **2006**, *14*, 2720–2724.
6. Loev, B.; Snader, K. M. *J. Org. Chem.* **1965**, *30*, 1914–1916.
7. Tu, S.-J.; Zhou, J.-F.; Deng, X.; Cai, P.-J.; Wang, H.; Feng, J.-C. *Chin. J. Org. Chem.* **2001**, *21*, 313–316.
8. Sabita, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129–4131.
9. Ji, S. J.; Jiang, Z. Q.; Lu, J.; Loh, T. P. *Synlett* **2004**, 831–835.
10. Breitenbucher, J. G.; Figliozzi, G. *Tetrahedron Lett.* **2000**, *41*, 4311–4315.
11. Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Tetrahedron* **2004**, *60*, 2311–2326.
12. Wang, L. M.; Sheng, J.; Zhang, L.; Han, J. W.; Fan, Z. Y.; Tian, H.; Qian, C. T. *Tetrahedron* **2005**, *61*, 1539–1543.
13. Ko, S.; Yao, C.-F. *Tetrahedron* **2006**, *62*, 7293–7299.
14. Maheswara, M.; Siddaiah, V.; Damu, G. L. V.; Rao, C. V. *Arkivoc* **2006**, 201–206.
15. (a) Chandrasekhar, S.; Reddy, N. S.; Sultana, S. S.; Narsihmulu, C.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338–345; (b) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732–733; (c) Poulsen, T. B.; Bernardy, L.; Bell, M.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1–5.
16. (a) Rasalkar, M. S.; Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *J. Mol. Catal. A: Chem.* **2005**, *235*, 267–270; (b) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. S. *J. Org. Chem.* **2006**, *71*, 4818–4822.
17. Janey, J. M.; Hsiano, Y.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 390–392.
18. (a) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 827–833; (b) Kotrusz, P.; Toma, S. *Molecules* **2006**, *11*, 197–205.
19. (a) Ramachary, D. B.; Chodari, N. S.; Barbas, C. F., III. *Angew. Chem.* **2003**, *115*, 4365–4369; (b) Kotrusz, P.; Toma, S. *Arkivoc* **2006**, 100–109.
20. Hossein, A. O.; Elham, R.; Majid, M. H. *J. Chem. Res.* **2006**, 246–247.
21. (a) Yadav, J. S.; Kumar, S. P.; Kondaji, G.; Rao, R. S.; Nagaiah, K. *Chem. Lett.* **2004**, *33*, 1168–1169; (b) Mabry, J.; Ganem, B. *Tetrahedron Lett.* **2006**, *47*, 55–56.
22. Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570.
23. Csuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 49–97.
24. (a) Fuganti, C.; Grasselli, P.; Servi, S.; Speafico, F.; Ziroty, C. *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.; Kobavashi, 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.
25. Lee, J. H. *Tetrahedron Lett.* **2005**, *46*, 7329–7330.
26. Kumar, A.; Maurya, R. A. *Tetrahedron* **2007**, *63*, 1952–1956.

27. Data for selected compounds: Compound **4b**: ^{1}H NMR (CD_3OD, 200 MHz) δ: 0.75 (s, 3H), 0.92 (s, 3H), 0.99 (t, $J = 7.1$ Hz, 3H), 1.86–2.31 (m, 7H), 3.82 (d, $J = 7.1$ Hz, 2H), 3.93 (s, 1H), 4.20 (s, 1H), 4.80 (s, 1H), 6.40 (m, 2H), 6.86 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 25.69, 28.34, 31.28, 34.00, 49.52, 58.13, 103.36, 109.54, 113.63, 127.51, 137.61, 143.53, 148.33, 154.42, 166.21, 193.50. IR (KBr, cm^{-1}): 3439, 3280, 3075, 2964, 1679, 1611, 1483. MS (ESI): $m/z = 356$ (M+H). Compound **4k**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 3H), 1.08 (s, 3H), 1.38 (s, 9H), 2.14–2.35 (m, 7H), 3.78 (s, 3H), 4.98 (s, 1H), 5.86 (s, 1H), 6.65 (m, 1H), 6.88 (m, 2H), 7.10 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.73, 26.90, 26.99, 28.10, 31.30, 35.82, 39.42, 49.58, 53.75, 78.55, 105.98, 109.58, 110.06, 112.95, 119.43, 127.32, 141.57, 147.66, 148.31, 157.94, 165.71, 194.57. IR (KBr, cm^{-1}): 3292, 3224, 3087, 2958, 1699, 1605, 1491. MS (ESI): $m/z = 398.0$ (M+H). Anal. Calcd for $C_{24}H_{32}NO_4$: 398.2, Found: 398.0. Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.38; H, 7.76; N, 3.41. Compound **4l**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 3H), 1.07 (s, 3H), 1.37 (s, 9H,), 2.11–2.27 (m, 4H), 2.32 (s, 3H), 4.99 (s, 1H), 6.43 (s, 1H), 7.07 (t, $J = 7.1$ Hz, 1H), 7.18–7.23 (m, 2H), 7.28–7.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.84, 25.92, 26.91, 28.05, 31.36, 35.90, 39.74, 49.53, 78.60, 106.34, 110.60, 124.59, 126.45, 126.85, 141.14, 145.92, 147.29, 165.62, 194.32. IR (KBr, cm^{-1}): 3280, 3216, 3084, 2965, 1678, 1608, 1491. MS (ESI): $m/z = 368$ (M+H). Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.14; H, 7.89; N, 3.72.