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Saccharomyces cerevisiae catalyzed one-pot three component synthesis of 2,3-diaryl-4-thiazolidinones

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ABSTRACT

Saccharomyces cerevisiae (baker's yeast) catalyzed one-pot three component cyclocondensation of aryl aldehydes, amines, and thioglycolic acid in organic medium leading to 2,3-diaryl 4-thiazolidinones has been carried out for the first time.

4-Thiazolidinones are the structural units of biological and medicinal importance.[1] Some of the thiazolidiones are found to possess interesting biological activities, such as anticancer,[2] anti-HIV,[3] antimalarial,[4] tuberculostatic,[5] antihistaminic,[6] anticonvulsunt,[7] antibacterial[8], and antiarrythmic.[9] In view of the biological/pharmacological significance of 4-thiazolidinones considerable synthetic efforts have been made to construct this class of heterocycles.[10]

Several synthetic protocols for 4-thiazolidinones are reported in the literature. One-pot three component cyclocondensation of carbonyl compounds, amines, and mercaptoacetic acid or its derivatives has been widely used as a synthetic route for the 4-thiazolidinones. The above mentioned cyclocondensation can be either run in one-pot or in two steps with prolonged heating in toluene or benzene.[11]

There are reports for accelerating the above cyclocondensation using catalysts like *N,N′*-dicyclohexylcarbodiimide (DCC),[12] *O*-(benzotriazol-yl)-*N,N,N′,N′*-tetramethyluronium hexafluoro phosphate (HBTU),[13] ferrite,[14] $ZnCl_2$,[15] sodium sulfate,[16] [bmim][PF_6][17], and activated fly ash.[18] The use of microwave heating,[19] solid phase,[20] and polymer supported[21] systems to run the cyclocondensation leading to 2,3-disubstitiuted 4-thiazolidinones have also been reported. However, the use of above mentioned protocols has certain limitations, such as harsh reaction conditions, prolonged heating, simultaneous removal of water by Dean and Stark distillation system or by incorporating desiccant, and need of inert and dry atmosphere to accelerate the cyclocondensation.

While the DCC mediated route has been found to be better the separation of the byproduct, *N,N′*-dicyclohexyl urea is tedious. Therefore, the design of a new method which circumvents these difficulties is needed.

Whole cell biocatalysis with baker's yeast (*Saccharomyces cerevisae*) is gaining prime importance in synthetic organic chemistry[22,23] as yeast catalyzes variety of organic transformations. Baker's yeast is easily available, cheap and has the ability to accelerate the transformations under mild reaction conditions.[24,25]

Cyclocondensation using biocatalysts has not been explored. Lipases and baker's yeast have the ability to catalyze the cyclocondensations leading to bioactive heterocycles, such as benzimidazoles,[26] dihydropyridines,[27] dihydropyrimidines,[28] polyhydroquinolines,[29] benzothiazoles,[30] benzotriazoles,[31] and quinoxaline.[32] but the role of biocatalysts in the formation of 4-thiazolidinones has not been investigated.

In view of the useful applications of 4-thiazolidinones and in continuation of our earlier interest in biocatalysis[33] leading to biodynamic heterocycles and 4-thiazolidinones,[34,35] we thought it is worthwhile to use biocatalyst, baker's yeast in the cyclocondensation to accelerate the one-pot three component synthesis of 4-thiazolidinones.

In this Letter we wish to report a three-component one-pot cyclocondensation of aryl aldehydes, amines, and thioglycolic acid leading to 4-thiazolidinones employing baker's yeast as a whole cell biocatalyst at an ambient temperature in an organic medium.

To optimize the reaction conditions, the condensation of anisaldehyde, aniline, and thioglycolic acid was considered as the model reaction.

Baker's yeast displays better catalytic behavior in aqueous medium.[22,23] However organic substrates are not soluble/compat-

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ible with water. Therefore, the cyclocondensation has been carried out in organic medium using baker's yeast.

Initially when the model reaction was run in ethanol the desired product was not formed, however the intermediate, imine (Schiff base) was isolated. This indicates that the ethanol does not favor further cyclization of the Schiff base to 4-thiazolidinone (**4b**).

When the model reaction was allowed to run in tetrahydrofuran (THF) it was found that the cyclocondensation has taken place leading to 4-thiazolidinone in 40 h at room temperature. The cyclocondensations catalyzed by DCC[13] in THF leading to high yields thiazolidinones have been reported.

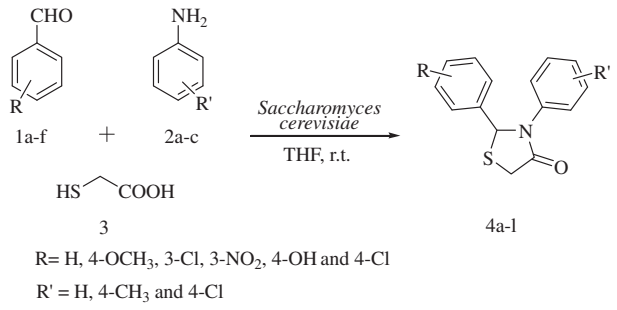
After having these results an effort was made to carry out the reaction in two steps. In the first step the condensation of anisaldehyde and aniline was carried using baker's yeast in THF to obtain better yield of the imines. Then in the second step the isolated imine was condensed with thioglycolic acid using baker's yeast in THF to form, 4-thiazolidinone. From this result it is clear that the baker's yeast is able to catalyze the formation of the intermediate, imine as well as the subsequent cyclization of imine and thioglycolic acid in THF without a loss in activity leading to 4-thiazolidinone.

The model reaction was performed by varying the amount of baker's yeast from 1 to 3 g per 10 mmol of the reactants. It was observed that when 2 g of baker's yeast was used, the condensation was found to be complete within 40 h yielding 62% of 4-thiazolidinone.

With these optimized reaction conditions diverse set of aldehydes and amines were cyclocondensed with thioglycolic acid to afford a variety of 2,3-disubstituted-4-thiazolidinones (Scheme 1, Table 1).[36,37] Aryl aldehydes bearing electron withdrawing and donating functionalities smoothly undergo cyclocondensation to respective 4-thiazolidinones with good to moderate yields.

To assess the catalytic efficiency of baker's yeast, one-pot three component condensation of 4-anisaldehyde, aniline, and thioglycolic acid was performed in tetrahydrofuran without baker's yeast as a blank reaction at room temperature. It was noticed that there was neither formation of imines nor 4-thiazolidinone. A model reaction was also performed using inactivated (heat treated) baker's yeast as a catalyst where we found that there was no formation of the product. It reveals that the role of baker's yeast is crucial for the cyclocondensation.

We believe that the enzyme lipase available in baker's yeast might be responsible for accelerating the formation of imines as well as cyclondensed products, 4-thiazolidinones. Therefore, we have carried a model reaction employing isolated lipase, *Candida antarctica* lipase B in THF. The formation of imine took place but the cyclocondensation of imine with thioglycolic acid was found to be slower and the final product was obtained in 10% yield. This indicates that lipase catalyzes both steps but the rate of cyclocondensation is slower. In our case yeast lipase accelerated the rate of imine formation and cyclocondensation.

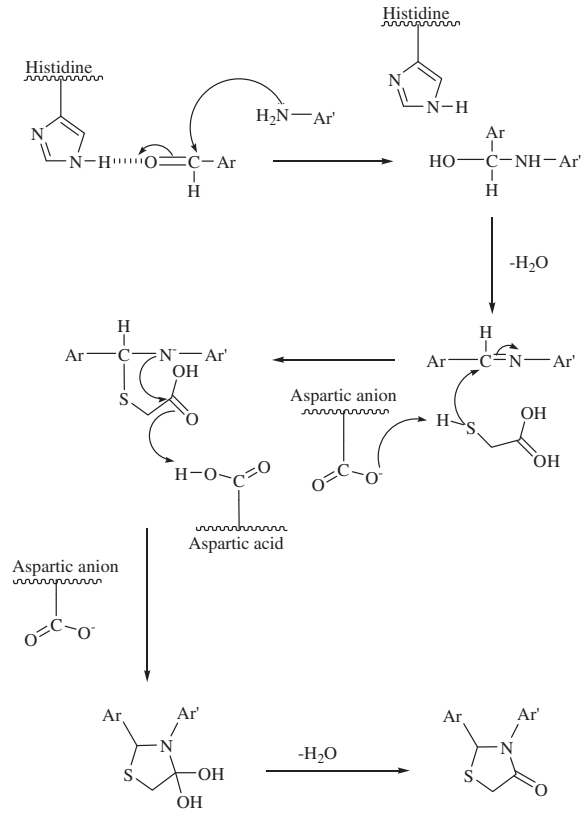


Scheme 1. Baker's yeast catalyzed one-pot three component synthesis of 4-thiazolidinones.

Table 1
Baker's yeast catalyzed synthesis of 4-thiazolidinones in tetrahydrofuran.[a]

Entry	R	R′	Product	Yield[b] (%)
1	H	H	**4a**	60
2	4-OCH_3	H	**4b**	62
3	4-Cl	H	**4c**	69
4	H	4-CH_3	**4d**	65
5	3-Cl	4-CH_3	**4e**	53
6	4-Cl	4-CH_3	**4f**	71
7	3-NO_2	4-CH_3	**4g**	66
8	H	4-Cl	**4h**	58
9	4-OCH_3	4-Cl	**4i**	55
10	4-OH	4-Cl	**4j**	51
11	4-Cl	4-Cl	**4k**	72
12	4-OH	4-CH_3	**4l**	68

[a] Reaction conditions: aryl aldehyde (10 mmol), aryl amine (10 mmol), thioglycolic acid (10 mmol), and baker's yeast (2 g) in THF (40 mL) stir, 40 h r.t.
[b] Isolated yields.



Scheme 2. Plausible mechanism for the formation of 4-thiazolidinone.

It is known that lipases are functional proteins having amino acid residues with varied functionalities at particular locations.

The amino acid residues like histidine, serine, and aspartic acid might be participating in this condensation. Amino hydrogen of histidine may be responsible for enhancing electrophilic character of aldehydic carbon forming hydrogen bonding with carbonyl oxygen, thereby accelerating the rate of addition of amines to aldehydes. Another amino acid residue, aspartic anion may be responsible for enhancing nucleophilicity of mercapto group of thioglycolic acid causing its facile addition on the imino intermediate generated in situ. These factors are probably responsible for the cyclocondensation at room temperature in successive steps forming the desired 4-thiazolidinones (Scheme 2).

In summary we have reported for the first time the use of a biocatalyst for the synthesis of 2,3-disubstituted 4-thiazolidinones. Baker's yeast employed for the cyclocondensation is very cheap and easily available making the protocol cost-effective and ecofriendly.

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References and notes

1. Verma, A.; Saraf, S. *Eur. J. Med. Chem.* **2008**, *43*, 897–905.
2. Hongyu, Z.; Wu, S.; Zhai, S.; Liu, A.; Sun, Y.; Li, R.; Zhang, Y.; Ekins, S.; Swaan, P. W.; Fang, B.; Zhangand, B.; Yan, B. *J. Med. Chem.* **2008**, *51*, 1242–1251.
3. (a) Barreca, M. L.; Balzsarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Höltje, H. D.; Höltje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zapalla, M. *J. Med. Chem.* **2002**, *45*, 5410–5413; (b) Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zapallà, M. *Antivir. Res.* **2004**, *63*, 79–84; (c) Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 3134–3142.
4. Solomon, V. R.; Haq, W.; Srivastava, K.; Puri, S. K.; Katti, S. B. *J. Med. Chem.* **2007**, *50*, 394–398.
5. Kucukguzel, G. C.; Shchullek, J. R.; Kaocatepe, A.; De Clercq, E.; Sahinv, F.; Gulluce, M. *Eur. J. Med. Chem.* **2006**, *41*, 353–359.
6. Diurno, M. V.; Mazzoni, O.; Calignano, P. E.; Giorodano, F.; Bolognese, A. *J. Med. Chem.* **1992**, *35*, 2910–2912.
7. (a) Archana; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2002**, *37*, 873–882; (b) Dwivedi, C.; Gupta, S. S.; Parmar, S. S. *J. Med. Chem.* **1972**, *15*, 553–554.
8. Desai, K. G.; Desai, K. R. *J. Sulfur Chemistry* **2006**, *27*, 315–328.
9. Jackson, C. M.; Blass, B.; Coburn, K.; Djandjighian, L.; Fadayel, G.; Fluxe, A. J.; Hodson, S. J.; Janusz, J. M.; Murawsky, M.; Ridgeway, J. M.; White, R. E.; Wu, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 282–284.
10. Cunico, W.; Gomes, C. R. B.; Vellasco, W. T., Jr. *Mini Rev. Org. Chem.* **2008**, *5*, 336–344.
11. (a) Belardi, P. G.; Simonoi, D.; Moroder, F.; Manferdini, S.; Muchhi, L.; Vecchia, F. D. *J. Heterocyl. Chem.* **1982**, *19*, 557–560; (b) Holmes, C. P.; Chinn, J. P.; Look, C. G.; Gorden, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328–7333.
12. Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619–7624.
13. Rawal, R. K.; Srivastava, T.; Haq, W.; Katti, S. B. *J. Chem. Res.* **2004**, *5*, 368–369.
14. Sadashivaa, C. T.; Narendra, J. N.; Chandraa, S.; Kavithaa, C. V.; Thimmegowdab, A.; Subhashc, M. N.; Rangappaa, K. S. *Eur. J. Med. Chem.* **2009**, *44*, 4848–4854.
15. Srivastava, S. K.; Srivastava, S. L. *J. Ind. Chem. Soc.* **2002**, *77*, 104.
16. Kumar, R. C.; Kumar, D. *J. Ind. Chem. Soc.* **2002**, *77*, 492.
17. (a) Yadav, A. K.; Kumar, M.; Yadav, T.; Jain, R. *Tetrahedron Lett.* **2009**, *50*, 5031–5034; (b) Zhang, X.; Li, X.; Li, D.; Qu, G.; Wang, J.; Loiseau, P. M.; Fan, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6280–6283.
18. Kanagarajana, V.; Thanusua, J.; Gopalakrishnana, M. *Green Chem. Lett. Rev.* **2009**, *2*, 161–167.
19. Gududuru, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. *Synlett* **2004**, 2357–2358.
20. Holmes, C. P. WO 96/ 00148, 1996.
21. Stephanie, E.; Justus, A.; Hodges, J. C.; Wilson, M. W. *Biotech. Bioeng.* **2000**, *61*, 17–22.
22. Csuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 49–97.
23. Servi, S. *Synthesis* **1990**, 1–25.
24. Stewart, J. D. *Curr. Opin. Biotechnol.* **2000**, *11*, 363–368.
25. de SouzaPereira, R. *Crit Rev. Biotechnol.* **1998**, *18*, 25–83.
26. Renard, G.; Lerner, D. A. *New J. Chem.* **2007**, *31*, 1417–1420.
27. Lee, J. H. *Tetrahedron Lett.* **2005**, *46*, 7329–7330.
28. Kumar, A.; Maurya, R. A. *Tetrahedron Lett.* **2007**, *48*, 4569–4571.
29. Kumar, A.; Maurya, R. A. *Tetrahedron Lett.* **2007**, *48*, 3887–3890.
30. Csaba, P.; Majdic, C.; Tosa, M.; Misca, R.; Irimie, F. D. *Roum. Biotechnol. Lett.* **2001**, *6*, 325–330.
31. Baik, W.; Park, T. H.; Kim, B. H.; Jun, Y. M. *J. Org. Chem.* **1995**, *60*, 5683–5685.
32. Baez, M. V.; Robinsohn, A. E.; Legaspi, M. J.; Hedrera, M. E.; Fernandez, B. M. *J. Planar Chromatogr.* **2003**, *16*, 28–31.
33. Pratap, U. R.; Mali, J. R.; Jawale, D. V.; Mane, R. A. *Tetrahedron Lett.* **2009**, *50*, 1352–1354.
34. Mali, J. R.; Pratap, U. R.; Netankar, P. D.; Mane, R. A. *Tetrahedron Lett.* **2009**, *50*, 5025–5027.
35. Lingampalle, D. L.; Jawale, D. V.; Waghmare, R. A.; Mane, R. A. *Syn. Commun.* **2010**, *40*, 2397–2401.
36. *General procedure for the synthesis of 2, 3-diaryl 4-thiazolidinones* (**4a**–**l**): To the stirred solution of aryl aldehyde (10 mmol), aryl amine (10 mmol), and thioglycolic acid (10 mmol) in THF (40 mL), active dry baker's yeast (2 g) was added and the resulting mixture was again stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography using ethyl acetate: hexane as a solvent system. After 40 h of stirring the reaction mass was filtered through the bed of Celite to remove the yeast. The filtrate was concentrated under reduced pressure and the crude products obtained were crystallized from ethanol.
37. *Spectral data for the representative compounds* (**4b**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H), 3.84–4.01 (dd, 2H), 5.06 (s, 1H), 6.78 (d, 2H), 7.12 (d. 2H), 7.16–7.30 (m, 5H). DART MS (ES^+) *m*/*z*: 286 (M^+). (**4c**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83–4.06 (dd, 2H), 6.06 (s, 1H), 7.10–7.49 (m, 9H). DART MS (ES^+) *m*/*z*: 290 (M^+), 292 (M^++2). (**4e**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (s, 3H), 3.83–4.02 (dd, 2H), 5.99 (s, 1H), 7.01–7.29 (m, 8H). DART MS (ES^+) *m*/*z*: 304 (M^+), 306 (M^++2).