Bakers’ yeast: an environment benign catalyst for the one-pot synthesis of indolyl chromenes and bisindolyl alkanes

Nongthombam Geetmani Singh, Ridaphun Nongrum, Chingrishon Kathing, Jims World Star Rani and Rishanlang Nongkhlaw*

Centre for Advanced Studies in Chemistry, North Eastern Hill University, Shillong, India

(Received 13 November 2013; final version received 5 March 2014)

A green protocol for one-pot synthesis of pharmacologically important indolyl chromenes and bis(indolyl)alkanes was achieved using Saccharomyces cerevisiae (commonly known as bakers’ yeast) as catalyst under room temperature stirring condition. This method is relatively simple, efficient, inexpensive, and environment-friendly.

Keywords: bakers’ yeast; indole; chromene; Knoevenagel condensation; Michael addition

1. Introduction

Chromene moiety occupies an integral part in many pharmacologically important alkaloids, anthocyanins (1), tocopherols, flavonoids, etc. Benzopyran (4H-chromene) moieties bearing nitrile substituent have stirred considerable interest among the scientific community working on medicinal drugs (2) due to their diverse applicability as antiviral (3), antiproliferative (4), antimicrobial (5), antitumour (6), mutagenic (7), and sex pheromone (8). Their utilization in the treatment of cancer (9), psoriatic arthritis, rheumatoid, etc., has instigated the biomedical fraternity to carry out detailed research on this class of derivatives.

Bis(indolyl)alkanes are another class of medicinal drugs which serve the purpose of antibiotics (10) and has managed to establish itself as an important cancer chemotherapeutic agent. Various techniques have been reported for its synthesis using Lewis acids (11, 12) and protic acids (13). Researchers are currently engaged in developing biocatalysts and other greener alternatives for the synthesis of bis(indolyl)alkane derivatives. Recently, Z. Xiang et al. have reported the synthesis of bis(indolyl)alkanes using porcine pancreas lipase enzyme (14).

Although 2-amino-4H-chromene derivatives of indole play a crucial role as antioxidants (15), very few people have reported its synthesis from indole, salicylaldehyde, and malononitrile. The reported methods used L-proline (15) / KH2PO4–PEG (16) / InCl3 (17) / Zn(ClO4)2 (18) as catalysts. However, these reported methods were complicated and their reaction times were comparatively long.

Thus, in order to overcome these drawbacks we made use of an environment-friendly biological catalyst, i.e. Saccharomyces cerevisiae (commonly known as bakers’ yeast). Our catalyst, despite being a living microorganism, is non-toxic in nature and has been an important component of bakery industry since time immemorial.

Bakers’ yeast has found application in various organic transformations (Avalani et al.) (19), and reports of ketones being successfully reduced to optically active alcohols have been published in renowned journals (20, 21). Lee et al. reported the use of bakers’ yeast for the synthesis of dihydropyridyl compounds via Hantzsch reaction (22). The catalyst has proved itself useful in oxidative coupling of thiols to disulfides and also in acyloin type condensations (23).

2. Results and discussion

In our approach, we have introduced an environment benign catalyst and avoided the use of external energy source in the form of microwave or external heating. The reaction was successfully carried out under room temperature condition utilizing water, a green solvent as an activator of the catalyst as well as reaction media. Water is an important component for most of the biological reactions occurring in nature, and in our case it assists the fermentation of bakers’ yeast. Bakers’ yeast was initially fermented in phosphate buffer overnight, then salicylaldehyde (or 2-hydroxy-naphthaldehyde), indole, and malononitrile were added and stirred to generate the desired indolyl chromene. The product was formed in 10–18 minutes depending on the substituents on indole and the yield.

*Corresponding author. Email: rhnongkhlaw@gmail.com

© 2014 The Author(s). Published by Taylor & Francis.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.
was found to be satisfactory. The reaction seems to proceed via Knoevenagel type condensation, then cyclisation followed by Michael addition. The schematic representation of the reaction is shown in Scheme 1.

The formation of the desired products 5a−f, 6a−b, and 7a−b was confirmed from IR, 1H-NMR, 13C-NMR, and mass spectra. The mass spectrum of 5a clearly indicated a molecular ion peak at m/z 287 and sodiated peak at m/z 310. A sharp peak at 2188 cm⁻¹ was observed in the IR spectrum of 5a which suggested the presence of nitrile(−CN) group. The 1H-NMR spectrum of 5a exhibited a broad singlet at 89.99 (indole N−H) and another broad singlet at 55.94 due to −NH₂ protons of the chromene ring. Typical peaks at 6160, 149, 59.67, 33.87, etc., corresponding to the carbons of the chromene ring were observed in the 13C-NMR spectrum. When salicylaldehyde was replaced by 2-hydroxynaphthaldehyde, similar kind of chromene derivatives was obtained but with a slightly lower yield in comparison to the salicylaldehyde-associated product. All the reactions (Scheme 1, 2) gave good yield when fermented bakers' yeast was used; however, on the contrary when unfermented bakers' yeast was added to the reaction mixture, reaction time got longer and yield became considerably less.

As far as our literature survey is concerned, we have not come across any report on the synthesis of pyrrole chromene derivatives. So we tested the versatility of our catalyst by replacing indole with pyrrole (Scheme 2) and surprisingly, pyrrole chromene derivatives were obtained (Table 1). Here, considering the fact that very few people have reported on the synthesis of indolyl chromenes and the reported work being very recent in terms of publications, we assumed that the synthesis of pyrrole chromenes may be at the initial stage. In order to confirm the reactivity of pyrrole, we replaced salicylaldehyde with 2-hydroxynaphthaldehyde, but in this case as well, we obtained similar kind of chromene derivative. Hence, we concluded that pyrrole chromene derivatives could be successfully synthesized by our method.

It is observed that in the absence of a catalyst, no product was formed, but when we carried out the same reaction excluding malononitrile, bis(indolyl)alkane derivatives were obtained. The versatility of this method was tested with various aliphatic and

---

Scheme 1. Proposed scheme for the preparation of indolyl chromenes and bis(indolyl)alkanes.

Scheme 2. Proposed scheme for the preparation of pyrrole chromenes.
| Entry | Product | Aldehyde (RCHO) | R₁ | R₂ | R₃ | Melting point (°C) |
|-------|---------|-----------------|----|----|----|-------------------|
|       |         |                 |    |    |    | Reported | Found | Yield (%) | Reaction time (mins) |
| 5a    | ![Image] | CHO             | H  | H  | H  | 190–192 | 193–194 | 93       | 10         |
| 5b    | ![Image] | CH₃             | H  | H  | H  | 186–189 | 187–188 | 92       | 10         |
| 5c    | ![Image] | CHO             | H  | H  | OCH₃| 199–201 | 198–200 | 90       | 12         |
| 5d    | ![Image] | CHO             | H  | H  | H  | –      | 215–217 | 88       | 15         |
| 5e    | ![Image] | CHO             | H  | H  | Br | 160–162 | 164–165 | 87       | 12         |
| 5f    | ![Image] | CHO             | H  | H  | OCH₃| –      | 177–180 | 85       | 15         |
| 6a    | ![Image] | CHO             | H  | CH₃| H  | –      | 184–186 | 91       | 12         |
| Entry | Product | Aldehyde (RCHO) | R₁ | R₂ | R₃ | Melting point (°C) | Yield (%) | Reaction time (mins) |
|-------|---------|----------------|----|----|----|-------------------|-----------|---------------------|
| 6b    | ![6b Product](image) | ![6b Aldehyde](image) | H  | CH₃| H  | 190–191           | 84        | 15                  |
| 7a    | ![7a Product](image) | ![7a Aldehyde](image) | –  | –  | –  | 195–197           | 92        | 12                  |
| 7b    | ![7b Product](image) | ![7b Aldehyde](image) | –  | –  | –  | 204–206           | 89        | 16                  |
| 3a    | ![3a Product](image) | ![3a Aldehyde](image) | H  | H  | H  | 163–165           | 91        | 270                 |
| 3b    | ![3b Product](image) | ![3b Aldehyde](image) | H  | H  | H  | 157–158           | 93        | 270                 |
| 3c    | ![3c Product](image) | ![3c Aldehyde](image) | H  | H  | H  | 124–125           | 98        | 180                 |
| 3d    | ![3d Product](image) | ![3d Aldehyde](image) | H  | H  | H  | 192–195           | 94        | 210                 |
| Entry | Product | Aldehyde (RCHO) | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> | Melting point (°C) | Yield (%) | Reaction time (mins) |
|-------|---------|----------------|-----------|-----------|-----------|-------------------|-----------|--------------------|
| 3e    | ![Image](image1.png) | ![Image](image2.png) | H | H | H | 220–222 | 218–219 | 90 | 210 |
| 3f    | ![Image](image3.png) | ![Image](image4.png) | H | H | H | 100–101 | 102–104 | 94 | 240 |
| 3g    | ![Image](image5.png) | ![Image](image6.png) | H | H | H | 348–349 | >300 | 93 | 240 |
| 3h    | ![Image](image7.png) | ![Image](image8.png) | CH<sub>3</sub> | H | H | 120–123 | 121–122 | 90 | 210 |
| 4a    | ![Image](image9.png) | ![Image](image10.png) | H | CH<sub>3</sub> | H | 123–125 | 126–127 | 86 | 270 |
| 4b    | ![Image](image11.png) | ![Image](image12.png) | H | CH<sub>3</sub> | H | 87–89 | 90–91 | 87 | 300 |
aromatic aldehydes and was successful in synthesizing several bis(indoly)alkane derivatives. However, reaction times for the synthesis of bis(indoly)alkanes were comparatively longer than the indolyl chromene derivatives, i.e., ranging from 3 to 5 h depending on the aldehyde used.

The influence of organic solvents such as ethanol/methanol on the synthesis of 5a and 3c was studied. Fermentation cannot be carried out in the absence of water, but organic solvents can be employed, provided that a small amount of water is present. However in our case, ethanol–water system did not enhance our productivity instead yield of 5a and 3c was reduced to 49% and 42% respectively even after increasing the reaction times.

3. Experimental

The chemicals involved in the synthesis were purchased from Merck and S.D.-Fine and were used without further purification. Purity of the products was confirmed by IR, 1H NMR, 13C NMR, and mass spectra besides melting point data. Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded in KBr pellets on a Perkin Elmer Spectrum 400 FTIR instrument, and the frequencies are expressed in cm⁻¹. 1H and 13C NMR spectra were recorded on a Bruker Avance II-400 spectrometer. Mass spectral data were obtained with a JEOL D-300 (ESI) mass spectrometer. All reactions were monitored by thin layer chromatography (TLC) using precoated aluminum sheets (silica gel 60 F 254 0.2-mm thickness) and developed in an iodine chamber. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

4. Mechanism

Bakers’ yeast tends to produce many enzymes (24) during the fermentation period. Lipase, being one of them, is believed to be the enzyme responsible for enhancing our one-pot transformation process. Lipase (25, 26) is composed of diverse amino acids namely, histidine, serine, aspartic acid, etc. The histidine NH proton has been reported (27) to be responsible for enhancing the electrophilic character of carbonyl carbon of benzaldehyde. After thorough consideration of the above statements, we have proposed a mechanism for the preparation of 5a and is shown in Figure 1.

4.1. Typical procedure for the synthesis of compounds 5a–f, 6a–b, 7a–b

Bakers’ yeast (150 mg), α-glucose (225 mg), and 5 ml of phosphate buffer (pH 7.0) were stirred for 12 h under room temperature condition. Indole/pyrrole (1 mmol), salicylaldehyde /2-hydroxynaphthaldehyde (1 mmol), and malononitrile (1 mmol) were then added to the above mixture and stirring was continued till the completion of reaction (monitored by TLC). On completion, the mixture was diluted with millipore water, extracted with dichloromethane, washed with water (3 × 10 ml) then with brine.

![Figure 1. Proposed mechanism for the synthesis of 5a using Saccharomyces cerevisiae.](image-url)
(10 ml), and finally dried over anhydrous sodium sulfate. The solvent was distilled under reduced pressure and the crude product was triturated with hexane. The product was further purified by column chromatography using ethyl acetate–hexane (4:6) as eluent.

4.2. Typical procedure for the synthesis of compounds 3a–h, 4a–c

Bakers’ yeast (150 mg), D-glucose (225 mg), and 5 ml of phosphate buffer (pH 7.0) were stirred for 12 h under room temperature condition. Indole (1 mmol) and aldehyde (0.5 mmol) were then added to the above mixture and stirring was continued till the completion of reaction (monitored by TLC). On completion, the mixture was diluted with millipore water (3 × 10 ml) then with brine (10 ml), and finally dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The product was further purified by column chromatography using ethyl acetate–hexane (4:6) as eluent.

5. Conclusion

Fermented bakers’ yeast was found to be an ideal catalyst for the synthesis of indolyl chromenes and bis(indolyl)alkanes under environment friendly conditions. The versatility of the catalyst was verified by its ability to catalyse a wide range of indole-derived products. Another important aspect of fermented bakers’ yeast has been observed on the basis of its ability to catalyse the synthesis of pyrrole chromene derivatives. Thus, we have opened up a new possibility for the synthesis of various heterocycles derived from pyrrole using bakers’ yeast as catalyst. Hence, we have developed a simple, efficient, versatile, inexpensive, and green protocol for the synthesis of indolyl chromenes and bis(indolyl)alkanes.

Acknowledgments

The authors would like to thank UGC for financial assistance in the form of fellowship and SAIF-NEHU for analytical assistance.

References

(1) (a) Harborne, J.B. The Flavonoids-Advances in Research; Chapman & Hall: London, 1988; (b) Iacobucci, G.A.; Sweeny, J.G.; Macdonald, S.E. Can. J. Chem. 1968, 46, 3291–3300.
(2) (a) Lewis, L.; Magidson, P. Aust. J. Chem. 1995, 48, 1–26; (b) Polyakov, V.V.; Chem. Nat. Compd. 1999, 1, 21–28.
(3) (a) Sun, W.; Cama, L.J.; Birzin, E.T.; Warrier, S.; Loochi, L.; Mosley, R.; Hammond, M.L.; Rohrer, S.P. Bioorg. Med. Chem. Lett. 2006, 16, 1468–1472. (b) Staculski, A.V.; Berry, N.G.; Low, A.C.L.; Moores, S.L.; Row, E.; Warhurst, D.C.; Adagu, I.S.; Rossignol, J.F. J. Med. Chem. 2006, 49, 1450–1454. (c) Garino, C.; Bibel, F.; Pietrancosta, N.; Laras, Y.; Quelever, G.; Doss, I.; Klein, P.; Bain, J.; Boucher, J.L.; Kraus, J.L. Bioorg. Med. Chem. Lett. 2005, 15, 135–138.
(4) Smith, W.P.; Sollis, L.S.; Howes, D.P.; Cherry, C.P.; Starkey, D.I.; Cobley, N.K. J. Med. Chem. 1998, 41, 787–797.
(5) Dell, C.P.; Smith, C.W. Eur. Pat. Appl. EP 537949, Chem. Abstr. 119, 139102d, 1993.
(6) Mohr, S.J.; Chirigos, M.A.; Fuhrman, F.S.; Pryor, J.W. Cancer Res. 1975, 35, 3750–3754.
(7) Hiramoto, K.; Kasahara, A.; Michishita, K.; Kato, T.; Kikugawa, K. Mutat. Res. 1997, 395, 45–56.
(8) Bianchi, G.; Tava, A. Agri. Biol. Chem. 1981, 57, 2001–2002.
(9) (a) Anderson, D.R.; Hedge, S.; Reinhard, E.; Gomez, L.; Vernier, W.F.; Lee, L.; Liu, S.; Sambandham, A.; Snider, P.A.; Masih, L. Bioorg. Med. Chem. Lett. 2005, 15, 1587–1590.
(10) Sundberg, R.J.; The Chemistry of Indoles; Academic Press: New York, 1970. (b) Safe, S.; Papineni, S.; Chintharlapalli, S. Cancer Lett. 2008, 26 (9), 326–398.
(11) (a) Noland, W.; Venkiteswaran, M.; Richards, C. J. Org. Chem. 1961, 26, 4241–4248. (b) Chatterjee, A.; Manna, S.; Banerji, J.; Pascard, C.; Prange, T.; Shoolery, J. J. Chem. Soc. Perkin Trans. 1980, 1, 553–555; (c) Banerjee, I.; Chatterjee, A.; Manna, S.; Pascard, C.; Prange, T.; Shoolery, J. Heterocycles 1981, 15, 325–329.
(12) Babu, G.; Sridhar, N.; Perumal, P.T. Synth. Commun. 2000, 30, 1609–1614.
(13) Gregorioiuich, B.V.; Liang, K.S.Y.; Gluston, D.M.; MacDonald, S.E. Can. J. Chem. 1968, 46, 3291–3300.
(14) Xiang, Z.; Liu, Z.; Chen, X.; Wu, Qi; Lin, X.-F. Amino Acids. 2013, 45, 937–945.
(15) Shanthi, G.; Perumal, P.T.; Rao, U.; Sehgal, P.K. Indian J. Chem. 2009, 48B, 1319–1323.
(16) Wang, L.; Huang, M.; Zhu, X.; Wan, Y. Appl. Catal. A. 2013, 454, 160–163.
(17) Shanthi, G.; Perumal, P.T. Tetrahedron Lett. 2007, 48, 6785–6789.
(18) Weiliang, C.; Yunfei, C.; Xuan, F.; Xiaohua, L.; Lili, L.; Xiaoming, F. Org. Lett. 2011, 13, 4910–4913.
(19) Aman, R.; Patel, D.S.; Raval, D.K. J. Mol. Cat. B: Enzym. 2013, 90, 70–75.
(20) Sih, C.J.; Chen, C.-S. Angew. Chem. 1984, 23, 570–578.
(21) Csink, R.; Glanzer, B.I. Chem. Rev. 1991, 91, 49–97.
(22) Lee, J.H.; Tetrahedron Lett. 2005, 46, 7329–7330.
(23) (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.

(24) Pratap, U.R.; Jawale, D.V.; Waghmare, R.A.; Lingampalle, D.L.; Mane, R.A. New J. Chem. 2011, 35, 49–51.

(25) Nurminen, T.; Suomalainen, H. Biochem. J. 1970, 118, 759–763.

(26) Pscheidt, B.; Glieder, A. Microb. Cell Fact. 2008, 7, 25.

(27) Pratap, U.R.; Jawale, D.V.; Bhosle, M.R.; Mane, R.A. Tetrahedron Lett. 2011, 52, 1689–1691.