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Articles

Water mediated and Baker's yeast accelerated novel synthetic protocols for tetrahydrobenzo[a]xanthene-11-ones and pyrazolo[3,4-b]quinolines

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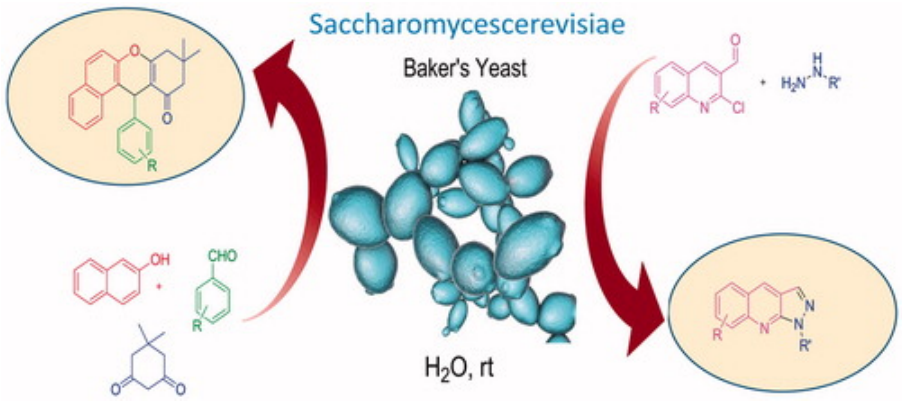
Abstract

Water mediated and baker's yeast catalyzed, efficient synthetic routes have been first time developed for multicomponent cyclocondensations leading to bioactive tetrahydrobenzo[a]xanthene-11-ones (**4a**–**h**) and pyrazolo[3,4-b]quinolines (**7a**–**i**). The developed protocols are conducted at room temperature and gave better to excellent yields of the titled compounds. The biocatalytical resource, activated baker's yeast is readily available, and biodegradable. These protocols are more convenient, scalable, and obey most of the green

ones.

Graphical Abstract



Keywords: Baker's yeast tetrahydrobenzo[a]xanthene-11-ones pyrazolo[3,4-b]quinolines one-pot synthesis multicomponent

Introduction

Oxygen containing fused six membered heterocycles, xanthenes and benzoxanthenes are found to have applications in different fields, *viz*. dyes and pharmaceuticals. Heterocycles with these scaffolds have immense importance in medicinal and pharmaceutical chemistry due to their broad-spectrum therapeutic activities like antibacterial,[1] antiviral,[2] and antiinflammatory.[3] antiplasmodial activity, antagonists for paralyzing the action of zoxazolamine,[4] and photodynamic therapy[5,6] have been displayed by some of the compounds of these heterocyclic series. They are not only valuable synthetic precursors,[7] but are also found to be useful in industries as dyes (leucodyes),[8] in laser technologies,[9] and pH-sensitive fluorescent materials to monitor changes in intracellular pH and for visualization of biomolecules.[2]

Nitrogen containing heterocycles *viz.* pyrazoles and quinolines are also thoroughly explored as therapeutic agents, and some of them displayed promising antibacterial, antihyperglycemic, antimalarial, antituberculosis and anticancer activities.[10-15] Literature reveals that molecules bearing both pyrazole and quinoline rings in their molecular framework are having intensified

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serious threat as most of the present therapeutic agents are receiving microbial resistance. Therefore, a search of new nonmicrobial resistance therapeutic agents is gaining more importance. In this respect recently pyrazoloquinolines are found to be showing promising activity and overcome multidrug resistance problem.[19] They are found to display anticancer activity.[17] Pyrazoloquinolines are found to be useful as potential electroluminescent materials.[18b–d] In view of the notable broad spectrum pharmacological activities of benzoxanthones and fused pyrazoloquinolines, several attempts are made to provide better synthetic protocols for obtaining these derivatives safely and cost effectively.

The classical synthetic route for synthesizing tetrahydrobenzo[a]xanthene-11-onesis by carrying separately one-pot cyclocondensation of β-naphthol, benzaldehydes, and dimedone in the presence of various heterogenous catalysts *viz*. TTAB,[20] [Yb(PFO)$_3$], TPPMS/CBr$_4$,[21] DSIMHS,[22] Zr(HSO$_4$)$_4$,[23] Zr(HSO$_4$)$_4$NP,[24] $H_3PW_{12}O_4$(PWA),[25] BF_3, SiO_2,[26] Fe_3O_4/CS-Ag NP,[27] Fe_3O_4@MCM-41-SO_3H,[28] [DSTMG][CF_3COO] & [DSTMG][CCl_3COO],[29] Fe_3O_4@SiO_3-SO_3H,[30] Nano-$TiCl_4$/SiO_2,[31] Boric acid,[32] calix[n]arenes CX_3/CX_6,[33] [BNBTS],[34] [DDPA][HSO_4],[35] GO or G-SO_3H,[36] Imidazole/isoquinoline,[37] Ce(SO$_4$)$_2$.4H_2O,[38] TiO_2, Al_2O_3, Fe_3O_4 nanoparticles,[39] Fe(III) tetranitrophthalocyanine immobilized on activated carbon,[40] $SiCl_4$/CH_2Cl_2,[41] $NaHSO_4$.SiO_2,[42] Zr-MCM-41,[43] $InCl_3$/P_2O_5,[44] Sr(OTf)$_2$, $ClCH_2CH_2Cl$,[45] *p*-TSA/([bmim]BF_4),[46] MnO_2,[47] and CAN.[48] Microbial irradiation and ultrasonication are also found to be employed for enhancing rate of cyclocondensation leading to xanthenones.[49] All these reported synthetic protocols employed for obtaining xanthenones need nonreadily available, and costly heterogeneous catalysts and most of them are not found to give moderate to good yields, even after longer reaction time.

Several attempts are also found to be performed to develop cost effective synthetic protocols for obtaining pyrazoloquinoline derivatives. There are two classical routes for constructing pyrazoloquinolines. 2-Chloroquinoline-3-carbaldehyde is usually cyclocondensed with hydrazine hydrate or substituted hydrazine hydrates in organic (polyols)/aqueous medium, applying heat or microwave energy.[50] The neat one pot condensation of 2-chloroquinoline-3-carbaldehyde and substituted hydrazines using organic catalyst, *p*-toluene sulfonic acid under microwave energy has also been reported.[51] There are reports [15] to convert quinoline-2-ones for obtaining intermediates, 2-chloroquinoline-3-carbaldehydes. These are then subjected with hydrazine hydrate/phenyl hydrazines under reflux in organic medium to get

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pyrazoloquinolines. Attempts are found to be made to get theses derivatives neatly in one pot using *p*-toluene sulfonic acid as catalyst under microwave.[51] Use of L-proline as a catalyst for carrying one-pot cyclocondenstion of pyrazolones, aldehydes and anilines has also been reported for obtaining pyrazoloquinolines.[15]

The above narrated methods are having one or other kind of lacunae, and there is no report on the use of biocatalysts to accelerate one pot multicomponent syntheses of benzoxanthones and pyrazoloquinolines. Biocatalysts/enzymes are known to catalyze biotransformations. Since last decade of 20th century, they are explored as catalysts for accelerating rates of various organic transformations. [52-57] Usually biocatalysts are isolated enzymes/coenzymes, either in pure or as whole cell crude form. Active baker's yeast is a rich source of library of enzymes, and is employed as whole cell source of biocatalysts in accelerating rates of various organic transformations. Recently our group has reported some cyclocondensations, accelerated by biocatalysts leading to benzothiadiazinones, 2-aryl benzothiazoles, 1,4-benzothiazines, 4*H*-pyrans, 2,3-diaryl-4-thiazolidinones, 5-arylidene-2,4-thiazolidinediones, pyrazolines, and pentasubstituted thiopyridines heterocycles. [52-59] Recently Ebrahimipour et al. [60] have reported L-asparaginase, active enzyme catalyzes the conversion of asparagine to aspartic acid and ammonia.

It seems from above survey that there is dire need of the cost effective and safer synthetic alternatives to synthesize the titled heterocycles, tetrahydrobenzo[a]xanthene-11-ones and pyrazolo[3,4-b]quinolones. In continuation of our earlier interest to perform condensations and cyclocondensations in the presence of pure enzymes or whole cell enzymes, here it has been therefore first time decided to carry these cyclocondensations using respective multicomponents in the presence of whole cell source of biocatalyst, activated Baker's yeast for obtaining the above biodynamic heterocycles rapidly and cost effectively. The attempts are also made to optimize the reaction conditions of these cyclocondensations, carried in presence of baker's yeast.

Results and discussion

Keeping the above mentioned interest in mind, here we have developed baker's yeast catalyzed

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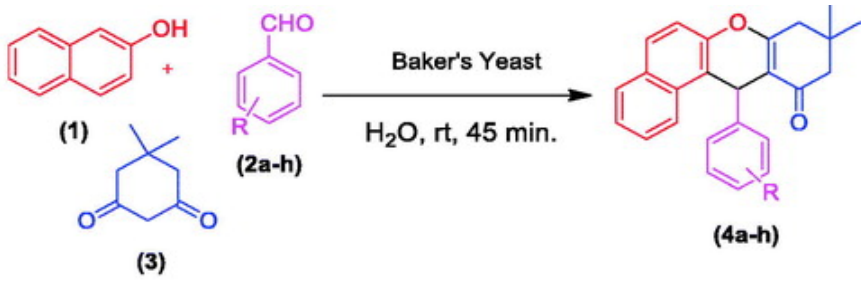
(**3**) (Scheme 1) and (b) cyclocondensation of substituted 2-chloroquinoline-3-carbaldehydes, (**5a**–**i**) and hydrazine hydrate or phenyl hydrazine (**6**) (Scheme 2) by optimizing reaction conditions for obtaining better to excellent yields of the titled tetrahydrobenzo[a]xanthene-11-ones (**4a**–**h**) and pyrazolo[3,4-b]quinolines (**7a**–**i**), respectively.

Scheme 1. Synthesis of tetrahydrobenzo[a]-xanthene-11-ones (**4a**–**h**)

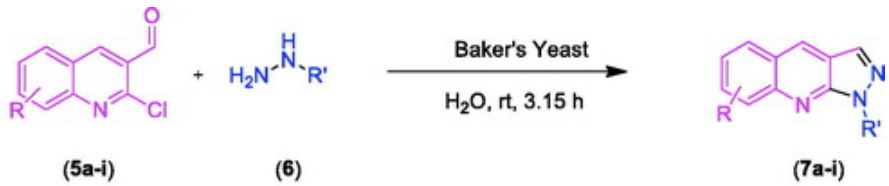


R= 4-Cl, -H, 4-OH, 4-Br, 2-NO_2, 4-OCH_3, 4-CH_3, 4-F

Yields: 79-90 %

Display full size

Scheme 2. Synthesis of pyrazolo[3,4-b]quinolines (**7a**–**i**)



R= -H, 6-CH_3, 7-CH_3, 8-CH_3, 6-Cl, 6-OCH_3

R'= -H, Ph

Yields: 79-90 %

Display full size

To optimize the reaction conditions for the one pot synthesis of tetrahydrobenzo[a]xanthene-11-ones, here we have established suitable optimized reaction conditions by performing separately the multicomponent cyclocondensation of model reaction, *β*-naphthol (**1**), 4-chloro benzaldehyde (**2a**), dimedone (**3**) (Scheme 1) by varying amount of baker's yeast, reaction temperature and media.

It has been observed that in the absence of baker's yeast, the cyclocondensation has not been found to yield respective reaction product even at longer reaction time. It has been also noted that when this model reaction was carried by allowing cyclocondensation of ß-naphthol (3.5

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of activated baker's yeast in water (10 ml) at room temperature gave excellent yield within 45 min. Using these optimized conditions, the other compounds (**4 b–h)** of the series have been synthesized and their physical constants and spectral data are recorded in experimental section.

Similarly, the optimized reaction conditions for carrying cyclocondensation of 2-chloroquinoline-3-carbaldehydes (**5a–i**), and hydrazine hydrate, or phenyl hydrazine (**6**) using Baker's yeast as a source of catalyst have also been established by performing, separately the model reaction varying solvents, amount of Baker's yeast and temperature. It was observed that the model reaction when carried using 2-chloroquinoline-3-carbaldehyde (**5a**), (2.4 mmol), and hydrazine hydrate (7.3 mmol), or phenyl hydrazine (**6**) (7.3 mmol) in the presence of 0.5 gm of activated Baker's yeast at room temperature in water (10 ml) gave better yield of (**7a**) within 3.15 h. Using these optimized conditions, the other derivatives (7a-i) of the series have been synthesized and their physical constants are presented in experimental section.

The titled compounds obtained, using the developed synthetic protocols have been thoroughly characterized using their spectral data viz. mass, proton magnetic resonance (PMR), and carbon-13 nuclear magnetic resonance (CMR). The spectral data are presented in the experimental part and supplementary information.

Here baker's yeast is found to be displaying its role as biocatalysts as it is a whole cell source of many enzymes. After disruption of the yeast, the enzymes having different amino acid residues are becoming readily available for activating reactive functional sites of substrates and reactants. The enzymes having strong nucleophilic and electrophilic active amino acid residues may be participating in the interactions with carbonyl of aldehydes and dimedone enhancing electrophilic character of aldehydes, dimedone and nucleophilic character of *β*-naphthol, and phenyl hydrazine. Amino acid residues like histidine, serine, and aspartate anion present with the enzymes of baker's yeast may be responsible to activate reactants, resulting into acceleration of the rates or cyclocondensations under reference. The plausible mechanism of the cyclocondensation is depicted in Schemes 3(a,b).

Scheme 3. (a) Plausible mechanism for cyclocondensation leading totetrahydrobenzo[a]xanthene-11-ones in the presence of baker's yeast. (b) Plausible mechanism for the synthesis of 1-phenyl-1*H*-pyrazolo[3,4-b]quinolone.

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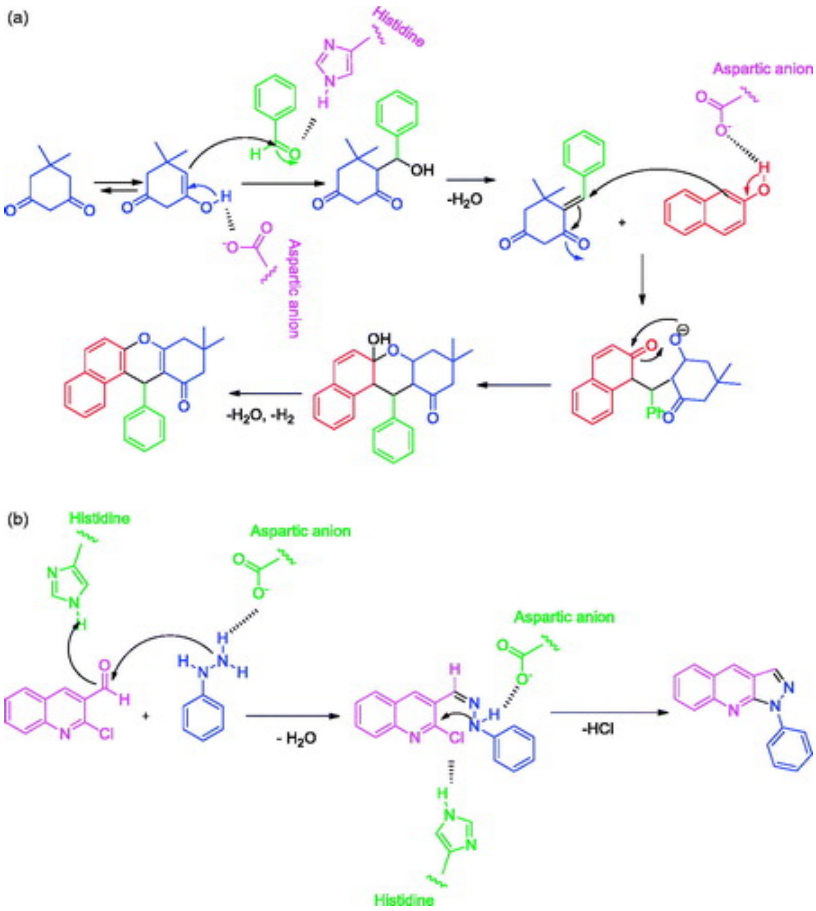

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Conclusion

First time Baker's yeast catalyzed and environmentally accepted one-pot protocols have been developed for obtaining excellent yields of tetrahydrobenzo[a]xanthene-11-ones **(4a–h)** and substituted pyrazolo[3,4-b]quinolines (**7a–i**). These protocols are efficient, more convenient and be performed in aqueous medium at room temperature. The source of biocatalysts need for these cyclocondensations is readily available, and biodegradable. The developed synthetic protocols are rapid, environmentally accepted, convenient, and scalable than those reported in the literature.

Experimental

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local bakery. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance 300 spectrometer operating at 400 MHz using DMSO-d_6 solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm.^{13}C NMR spectra were recorded on Bruker Avance 75 MHz on Jeol. The purity of each compound was checked by TLC using silica-gel, 60 F_{254} aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

General procedure for the synthesis of tetrahydrobenzo[a]xanthene-11-ones (4a–h)

Baker's yeast (0.5 gm) was added to the reaction flask containing 10 ml water. It was then sonicated at 35 KHz at room temperature for 10 min. To this disrupted mass, a mixture of β-naphthol (**1**) (3.5 mmol), benzaldehydes (**2a**–**h**) (3.5 mmol), and dimedone (**3**) (3.5 mmol) was added. The whole reaction mass was then stirred at room temperature. The progress of the reaction was monitored by Thin layer chromatography (TLC). After 45 min stirring, the reaction mass was extracted using ethyl acetate (4 × 10 ml). From the extract, ethyl acetate was removed under vacuum. Thus, obtained crude solid residue was then crystallized using ethanol. Melting points and spectral data of the tetrahydrobenzo[a]xanthene-11-ones **(4a–h)** are in good agreement with those reported in the literature.[20,26]

12-(4-Chlorophenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (4a)

Yield: 89%; m.p.:180–182 °C (Lit: 182–184 °C),[20] ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 0.95 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.25 (s, 2H, CH_2), 2.55 (s, 2H, CH_2), 5.68 (s, 1H, -CH-) and 7.10-7.91 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm) 27.32, 29.49, 32.43, 34.39, 41.60, 51.06, 114.03, 117.23, 123.66, 125.22, 127.31, 128.59, 128.68, 129.29, 130.00, 131.42, 131.72, 132.13, 143.45, 147.94, 164.25, and 197.05. HRMS (m/z) calculated for $C_{25}H_{21}ClO_2$ $(M + H)^+$: 389.1308. Found: 389.1292.

General procedure for the synthesis of substituted pyrazolo[3,4-b]quinolines (7a-i)

Baker's yeast (0.5 gm) was added to the reaction flask, containing 10 ml water. Then it was sonicated at 35 KHz at room temperature for 10 min. To this disrupted mass, a mixture of

mmol), or phenyl hydrazine (**6**) (7.3 mmol) was added. The whole reaction mass was then stirred at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate: pet ether (2:8) as eluent. After stirring for 3.15 h, to this reaction mass, ethyl acetate (10 × 3 ml) was added, and then it was further stirred for 10 min and filtered. From filtrate, ethyl acetate was removed under vacuum, and the obtained crude residue was then crystallized using ethanol. Melting points and spectral data of the substituted pyrazolo[3,4-b]quinolines **(7a, 7 b, 7e, 7f, 7 g, 7i)** are provided and are identical to those reported in the literature.[14,51,61] The other compounds of the series *viz.***7c, 7d** and **7 h** are not reported in the literature. Therefore, their scan spectra and other characteristic data have been reported in the experimental part of supporting information.

8-Methyl-1H-Pyrazolo[3,4-b]quinoline (7 h)

Yield: 86%; m.p.:162-164 °C, ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm) 2.64 (s, 3H, CH_3), 7.46-7.53 (m, 3H, Ar-H), 7.88 (s, 1H, Hb), 8.05 (s, 1H, Ha) and 8.62 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm) 17.26, 126.00, 127.22, 127.94, 130.03, 131.40, 132.82, 135.18, 144.93, and 146.71. HRMS (m/z) calculated for $C_{11}H_9N_3$ $(M + H)^+$: 184.0874. Found: 184.0864.

The physical constant and spectral data HRMS, ^{1}H NMR, and ^{13}C NMR of these compounds, (**4a–h** and **7a–i**) have been provided in supporting information. This material can be found via the "Supplementary Content." section of this article's webpage.

Supplemental material

Supplemental Material

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Acknowledgments

The [illegible] thank [illegible] for [illegible]

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