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Baker's yeast catalyzed one-pot three-component synthesis of polyfunctionalized 4*H*-pyrans

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ABSTRACT

Baker's yeast catalyzed one-pot three-component cyclocondensation of aryl aldehydes, malononitrile, and β-dicarbonyls in organic medium has been carried out to obtain polyfunctionalized 4*H*-pyrans. The reaction has been carried out at room temperature in organic solvent, dimethylacetamide and the products obtained in good to moderate yields with simple work up procedure.

Polyfunctionalised 4*H*-pyrans are the important heterocyclic compounds because of their wide biological and pharmaceutical properties.[1] 4*H*-Pyran is a constituent of some natural products.[2] 4*H*-Pyrans possess potent biological activities like antitumor, antibacterial, antiviral, spasmolytic, and antianaphylactic.[3–9] In addition to this, these compounds are used in the treatment of Alzheimer, Schizophrenia, and Mycolonous diseases.[10] The derivatives of 2-amino 4*H*-pyran are the useful photoactive materials.[11]

Considering the broad spectrum of biological activities of 4*H*-pyrans synthetic chemists have developed numerous protocols for their syntheses including two-step as well as one-pot three-component synthesis, catalyzed by ionic liquids,[12] hexadecyltrimethyl ammonium bromide,[13] Mg/La mixed metal oxides,[14] Cu(II) oxymetasilicate,[15] organic bases,[16] MgO,[4] and rubidinium fluoride.[17] However, these methods often suffer from one or the other kind of drawbacks and most of them give moderate yields even after prolonged reaction time. This has clearly indicated that there is still scope to develop an efficient and ecosustainable method for the synthesis of 4*H*-pyrans.

The use of biocatalysis in organic synthesis has been increasing day by day because of its various advantages. It catalyzes the transformations under mild conditions, with specificities and without side reactions.[18]

Among the biocatalysts used in organic synthesis baker's yeast (*Saccharomyces cerevisiae*)[19] is the most popular due to its easy availability, ease of handling, and versatile nature to catalyze a wide range of organic transformations viz reduction of variety of carbonyl compounds, oxidation of thioethers to sulfoxides, reduction of C=C bond and some of the cyclocondensation reactions.[20]

Biocatalyzed reactions in nonaqueous media become a popular approach and several reviews appeared in the literature.[21] Most of the organic transformations are condensations and cyclocondensations where the removal of water molecule is crucial and also most of the organic substrates are insoluble in water. Hence, the use of aqueous media for these transformations is not advisable. The use of organic solvents overcomes these drawbacks.

Considering the diverse applications of 4*H*-pyrans, limitation with the reported synthetic routes and our earlier interest in biocatalysis,[22] herein we report one-pot three-component synthesis of polyfunctionalised 4*H*-pyrans by cyclocondensing aryl aldehydes, malononitrile, and ethyl acetoacetate or acetyl acetone using active baker's yeast as a whole cell biocatalyst in nonaqueous media.

To find the best experimental conditions we started the investigations by performing one-pot three-component synthesis of 4*H*-pyran by allowing the cyclocondensation of anisaldehyde, (**1a**) malononitrile (**2**), and ethyl acetoacetate (**3a**) using baker's yeast as biocatalyst and this reaction was considered as a model reaction.

To check the effect of solvents the model reaction was separately carried out in various solvents viz. water, ethanol, methanol, dimethylformamide (DMF), and dimethylacetamide (DMAc) under stirring at room temperature. The use of water did not give the desired product, 4*H*-pyran but found to yield an intermediate, 2-(4-methoxybenzylidene) malononitrile (Table 1, entry **1**). When

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Table 1
Effect of solvent on the cyclocondensation of anisaldehyde, malononitrile, and ethyl acetoacetate[a]

Entry	Solvents	Yield (%)[b]
1	Water	n.d.
2	Ethanol	37
3	Methanol	42
4	DMF	51
5	DMAc	62
6	DMAc	n.d.[b]

[a] Reaction conditions: Anisaldehyde (8 mmol), malononitrile (8 mmol), ethyl acetoacetate (8 mmol) in solvent (30 mL), stir, rt 30 h.
[b] Isolated yields, n.d., not detected: Model reaction without baker's yeast.

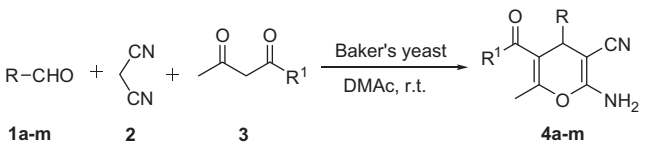
solvents like ethanol, methanol, and DMF were used the condensation was found to occur successfully yielding 4*H*-pyran with moderate yield (Table 1, entry **2–4**).

When the model reaction was run in dimethylacetamide the yield of the product was relatively superior (Table 1, entry **5**). Therefore, the dimethylacetamide was selected as a medium for this transformation. We carried the control experiment to examine the catalytical efficiency of active baker's yeast. The model reaction was performed in the absence of baker's yeast in dimethylacetamide and we noticed that the condensation did not undergo completion and partial conversion of the reactants to intermediate, 2-(4-methoxybenzylidene) malononitrile was recorded (Table 1, entry **6**). This reaction was also run by employing inactivated baker's yeast (inactivation was carried out by boiling yeast in water) as a catalyst but we did not find the formation of the desired product. These results indicate that baker's yeast is necessary to catalyze the reaction.

To generalize this methodology a variety of substituted aryl aldehydes with electron withdrawing and donating functionalities were successfully cyclocondensed with malononitrile and ethyl acetoacetate to yield respective polyfunctionalised 4*H*-pyrans (Scheme 1, Table 2). Heteryl aldehyde, pyridine-3-cabaxaldehyde has also been successfully condensed with malononitrile and ethyl acetoacetate in the presence of baker's yeast to respective pyran with 48% yield (Table 2, entry **9**).

We have also performed the cyclocondensation by subjecting aldehydes, malononitrile, and acetyl acetone in the presence of baker's yeast under the above optimized conditions and obtained the respective 4*H*-pyrans (Table 2, entry **10–13**) with good yields.[25]

To know the reaction sequence the model reaction was carried out in two steps under the optimized reaction conditions. In first step *p*-anisaldehyde was condensed with malononitrile and the intermediate, 2-(4-methoxybenzylidene) malononitrile obtained was subsequently cyclized with ethyl acetoacetate in the second step. The cyclized product was found to be the desired 4*H*-pyran. An attempt was also made to first condense the ethyl acetoacetate with anisaldehyde under the optimized reaction conditions. It was noticed that the condensation did not yield the intermediate, arylidene. Thus it was concluded that the path would have two steps, wherein the aldehyde of the first step undergoes Knoevenagel condensation with malononitrile and the resulting intermediate in situ reacts with ethyl acetoacetate to yield the 4*H*-pyran.



Scheme 1. Baker's yeast catalyzed one-pot three-component synthesis of polyfunctionlized 4*H*-pyrans.

Table 2
Synthesis of polyfunctionalized 4*H*-pyrans catalyzed by baker's yeast in DMAc[a]

Entry	R	R^1	Products[b]	Yields (%)[c]
1	4-$OCH_3C_6H_4$	OEt	**4a**	62
2	C_6H_5	OEt	**4b**	65
3	3-ClC_6H_4	OEt	**4c**	67
4	4-$CH_3C_6H_4$	OEt	**4d**	78
5	4-ClC_6H_4	OEt	**4e**	79
6	4-$NO_2C_6H_4$	OEt	**4f**	83
7	3-$NO_2C_6H_4$	OEt	**4g**	78
8	4-OHC_6H_4	OEt	**4h**	62
9	3-pyridyl	OEt	**4i**	48
10	C_6H_5	CH_3	**4j**	57
11	4-$OCH_3C_6H_4$	CH_3	**4k**	55
12	4-$CH_3C_6H_4$	CH_3	**4l**	67
13	4-FC_6H_4	CH_3	**4m**	76

[a] Reaction conditions: Aryl aldehyde (8 mmol), malononitrile (8 mmol), ethyl acetoacetate (8 mmol) in DMAc (30 mL), stir, rt 30 h.
[b] Products are well characterized by the comparison of their spectral (^{1}H NMR, Mass) and physical data with those reported in literature.[14,4,24]
[c] Isolated yields.

Baker's yeast is a known source of oxidoreductases and lipases.[23] Among these enzymes oxidoreductases have been found to be utilized in organic syntheses. However, the use of lipases produced by baker's yeast has not been explored to undergo Knoevenagel condensation or similar type of condensations. In this route the lipases, produced by baker's yeast might be catalyzing the Knoevenagel condensation of aldehydes and malononitrile to generate intermediates, arylidenyl malononitriles.[26] This probably expedites the Michael addition of 1,3-dicarbonyls on the arylidenyl malononitriles leading to the desired 4*H*-pyrans.

We have developed a novel baker's yeast catalyzed methodology for the cyclocondensation of aryl/heteryl aldehydes, malononitrile, and ethyl acetoacetate/acetyl acetone in an organic solvent, dimethylacetamide. This is one of the extended applications of baker's yeast in organic synthesis. The developed protocol might be useful for the synthesis of new pyran derivatives.

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25. General procedure for the synthesis of 4-substituted-2-amino-3-cyano-4*H*-pyrans (**4a**–**m**): a mixture of aldehydes (8 mmol), malononitrile (8 mmol), and ethyl acetoacetate (8 mmol) was dissolved in DMAc (30 mL). To this stirred solution active dry baker's yeast (2 g) was added. The resulting reaction mass was further stirred at room temperate. The progress of the reaction was monitored by thin layer chromatography using pet ether: ethyl acetate as solvent system. After 30 h, the reaction mass was filtered through the bed of Celite. The filtrate was poured on ice cold water. The obtained solid was filtered and crystallized from ethanol to obtain the pure products (Table 2, **4a**–**m**). *Ethyl(2-amino-3-cyano-6-methyl-4-(4-methoxyphenyl)-4H-pyran)-5-carboxylate* (**4a**) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.05 (q, 2H), 4.38 (s, 2H, NH_2,), 4.47 (s, 1H), 6.77 (d, J = 7.8 Hz, 2H) and 7.06 (d, J = 7.8 Hz, 2H). DART-MS (ESI$^+$, m/z): 315 (M^+). *Ethyl(2-amino-3-cyano-6-methyl-4-(3-chlorophenyl)-4H-pyran)-5-carboxylate* (**4c**) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, 3H), 2.38 (s, 3H), 3.73 (q, 2H), 4.42 (s, 1H), 4.56 (s, 2H) 6.93–7.26 (m, 4H). DART-MS (ESI$^+$, m/z): 319 (M^+), 321 (M^++2). *Ethyl (2-amino-3-cyano-6-methyl-4-(3-pyridyl)-4H-pyran)-5-carboxylate* (**4i**), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24–1.35 (m, 6H), 3.40 (q, 2H), 4.15–4.35 (s, merged 3H), 6.76–8.01 (m, 4H). DART-MS (ESI$^+$, m/z): 256 (M^+). *5-Acetyl-2-amino-4-(4-fluorophenyl)-6-methyl-4H-pyran-3-carbonitrile* (**4m**) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.30 (s, 3H), 3.80 (s, 2H), 4.45 (s, 1H), 6.97–7.13 (m, 4H). DART-MS (ESI$^+$, m/z): 273 (M^+).
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