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Digest paper

Baker's yeast as an efficient biocatalyst for regioselective 1,4-conjugate addition of indoles to nitroolefins in aqueous medium

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ABSTRACT

The 1,4-conjugate addition of indoles to nitroolefins was efficiently carried out in aqueous media using baker's yeast as a biocatalyst at room temperature. The merits of the present method are operational simplicity, easy workup, utilization of an inexpensive catalyst, free from hazardous organic solvents and good yields of products. The generality of this method was demonstrated by synthesizing an array of diverse 3-substituted indole derivatives and could be extended for dialkylation of 1,4-bis-(2-nitrovinyl)benzene.

Contents

Organic transformations involving biocatalyst in aqueous media have received great attention from researchers. Biocatalyst has the potential to achieve regio- and stereo-specific conversions under mild conditions, no side reaction products and can accept un-natural compounds as substrates by reducing the use of hazardous reagents and solvents. Although significant progress has been made through the use of isolated enzymes, whole-cell biocatalysts with the ability to regenerate their own respective cofactors are frequently more advantageous.[1] Among biocatalysts, bakers' yeast (*Saccharomyces cerevisiae*) is a renowned catalyst due to its low cost, easy handling and no requirement of assistance of a specialist in microbiology for growth.[2] It has the ability to catalyze functional group conversions[3] and is known to play a vital role in the synthesis of bioactive compounds such as 1,4-dihydropyridines,[4a] 3,4-dihydropyrimidin-2-(1*H*)-ones,[4b] polyhydroquinolines,[4c] benzothiazoles,[4d] 4*H*-pyranes,[4e] 2,3-diaryl-4-thiazolidinones,[4f] 1,4-benzothiazines,[4g] benzimidazoles,[4h] quinoxalines,[4h] isoindolo [2,1-*a*]quinazolines,[4i] bisindolyl alkanes,[4j] and indolyl chromenes.[4j]

Indole nuclei are central building blocks for various biologically active natural products, agrochemicals, and drugs.[5] Indole based framework is a component of complex macromolecules including porphyrins of heme and pigments.[6] Many indole ligands with high affinity for G-protein coupled receptors have been identified.[7] Of these, the 3-substituted indole has privileged status in medicinal chemistry due to its recurring presence among antiviral agents.[8] For instance, **Arbidol** (**1**) is used for the treatment and prophylactic prevention of influenza A and B virus,[9] **Golotimod** (**2**) shows potential immunostimulating, antimicrobial and antineoplastic activities[10] and **Panobinostat** (**3**) is a non-selective histone deacetylase inhibitor developed for the treatment of Acute Myeloid Leukemia[11] (Fig. 1).

The 3-substituted indoles are assessed by Michael addition of indoles to Michael acceptors. Among various types of Michael acceptors, nitroalkenes are undoubtedly the strongest and versatile one, due to their propensity to undergo facile α-alkylation reactions and interconversions to other organic functional groups.[12] Considering the importance of above mentioned transformation, a plethora of catalysts have been developed for this purpose including tetrabutyl ammonium hydrogen sulfate,[13] boric acid,[14] graphite

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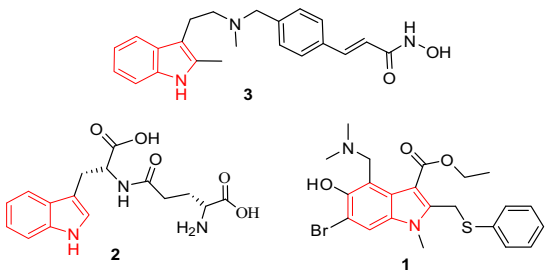


Figure 1. Bioactive compounds containing 3-substituted indole nucleus.

Table 1
Study of catalyst efficiency for the synthesis of 3-substituted indoles[a]

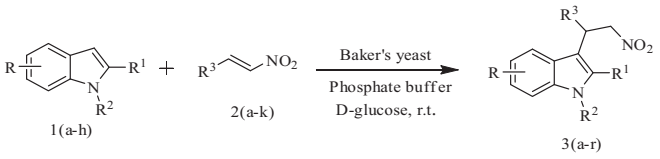
Entry	Amount of catalyst (mg)	Reaction time[b] (h)	Yield[c] (%)
1	100	2.5	72
2	200	2.5	80
3	**300**	2.5	**90**
4	400	2.5	90
5	500	2.5	89

[a] Reaction conditions: indole (1 mmol), β-nitrostyrene (1 mmol), D-glucose, phosphate buffer (pH 7.0, 5 mL) at room temperature.
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

oxide,[15] metal halide hydrates,[16] silanediol,[17] Zn(II)-oxazoline-imidazoline catalyst[18] and HY zeolite.[19] Solvent free,[20] catalyst-free[21] and ultrasound assisted methods[22] are also reported. Very recently Bronsted acid,[23] palladium(II) surfactant combined catalyst[24] and graphite[25] have been used as catalysts for addition of indoles to nitroolefins. Although the synthesis of indole derivatives has been well studied, the area is far from fully explored. The environmental concerns in the entire research community are increasing with increase in pressure to reduce pollutants, especially organic solvents whose recovery is mandated by evermore strict laws. In this context, the synthetic protocols utilizing biomaterial based catalysts in aqueous media are becoming more important due to the growing interest in sustainable chemistry. As a part of our ongoing research program on biocatalysts,[26] herein we report synthetic methodology for the conjugate addition of indoles to nitroolefins in the presence of baker's yeast as catalyst in aqueous medium. To the best of our knowledge, the conjugate addition of indoles to nitroolefins mediated by baker's yeast has not been previously reported.

In the beginning, the reaction between indole (**1a**) and β-nitrostyrene (**2a**) in the presence of baker's yeast was chosen as a standard model reaction to optimize the best experimental conditions (Scheme 1).

The integral role of baker's yeast has been revealed by examining model reaction at different reaction conditions as follows; (I) *Control experiment:* a control reaction was carried out using indole (1 mmol) and β-nitrostyrene (1 mmol) in 5 mL of 0.01 M phosphate buffer (pH = 7) and D-glucose (Scheme 1). The reaction mixture was stirred at room temperature for prolonged time, no product formation was observed by TLC. (II) *With dry yeast:* baker's yeast, D-glucose, indole (1 mmol) and β-nitrostyrene (1 mmol) were taken together in 0.01 M phosphate buffer (5 mL, pH = 7) and stirred for 24 h. After workup and purification, 20% of 3-(2-nitro-1-phenylethyl)-1*H*-indole (**3a**) was obtained. (III) *With fermented yeast:* baker's yeast (300 mg) and D-glucose (500 mg) were taken in 5 mL of 0.01 M phosphate buffer and stirred for 12 h for fermentation of yeast. To the fermented yeast indole (1 mmol) and β-nitrostyrene (1 mmol) were added. Surprisingly the yield of product (**3a**) was increased to 90% after stirring the reaction mixture for 2.5 h. (IV) *With yeast extract:* baker's yeast was stirred in distilled water and supernatant solution thus obtained after centrifugation was used as yeast extract for the model reaction. It was observed that (**3a**) was formed in 20% yield after stirring reaction mixture for 24 h. (V) *With inactive yeast:* by employing inactivated baker's yeast (inactivation of yeast was carried out in boiling water and dead cells obtained after centrifugation were used instead of active baker's yeast) after 24 h, no product formation was observed by TLC.



Scheme 1. Michael addition of indoles to nitroolefins in fermented baker's yeast at room temperature.

Based upon the results obtained in *experiment III*, it was confirmed that the presence of fermented baker's yeast was essential for successful Michael addition of indole to β-nitrostyrene. Table 1 shows the effect of the amount of catalyst on the product yield. The high yield was achieved with 300 mg of baker's yeast and increasing its amount further to 500 mg failed to increase the yield.

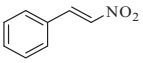
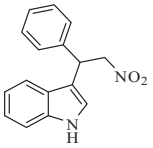
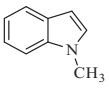
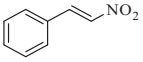
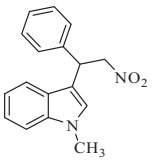
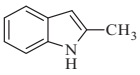
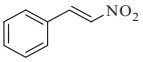
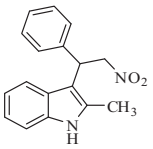
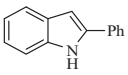
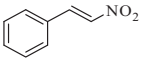
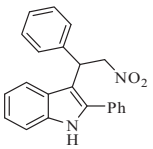
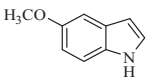
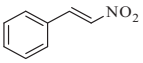
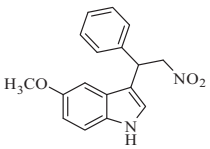
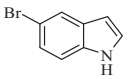
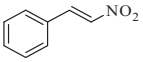
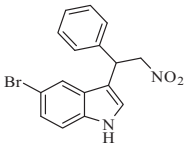
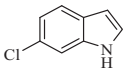
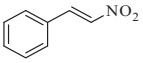
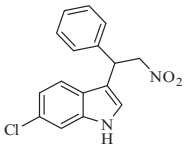
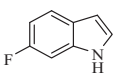
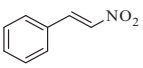
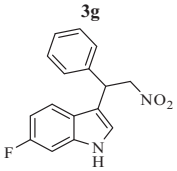
These encouraging results obtained in the preliminary experiments prompted us to explore the generality of this protocol to various other substituted indoles **1**(**a**–**h**) and nitroolefins **2**(**a–k**). As indicated in Table 2 (Scheme 1), all the reactions uniquely occurred at the 3-position of indole ring, indicating that the addition reaction was regioselective and it is remarkable that all products obtained are in the racemic form. The electron rich indole such as 5-methoxy indole alkylated with β-nitrostyrene in a shorter time to obtain the corresponding product, **3e** in good yield (entry 5). However, the electron withdrawing group bearing indoles such as 5-bromo indole, 6-chloro indole and 6-fluro indole require longer reaction time to obtain the desired product (entries 6–8). The reaction of *N*-methyl indole with β-nitrostyrene underwent smoothly to furnish the corresponding Michael adduct, **3b** with excellent yield. This may be due to the presence of electron releasing methyl group which activates the indole ring toward the nucleophilic attack. It was observed that increasing the size of substituent close to the reaction center, nucleophilicity of the indole was depressed which causes yield decrement (entries 3, 4). The reactions of nitroolefins with electron-withdrawing groups (—NO_2, —Cl) on the phenyl ring (entries 11, 12) had a slightly higher reaction rate than the reactions of nitroolefins with electron-donating groups (—OCH_3, —CH_3) on the phenyl ring (entries 9, 10). Similarly, other substituted nitroolefins (entries 13, 14) reacted to deliver the desired products in moderate to good yields. It is important to note that the heteroaromatic nitroolefins also reacted with equal ease to furnish Michael adducts in excellent yields (entries 15, 16). However, the aliphatic nitroalkenes gave products with reduced yields under optimized reaction conditions (entries 17, 18).

Next, we have extended this protocol for dialkylation of 1,4-bis-(2-nitrovinyl)benzene **4**. It underwent Michael addition with indole **1a** in presence of baker's yeast in aqueous medium, to afford the sterically hindered Michael adduct **5** in 82% yield within 3.5 h (Scheme 2).

Baker's yeast produces a variety of enzymes during fermentation.[27,28] Among them, lipase is known to catalyze organic transformations.[4e] It is known that lipases are functional proteins having amino acid residues with varied functionalities at particular locations. These amino acid residues like histidine, serine and aspartate or glutamate are known to form hydrogen bonding with oxygen thereby increasing the electrophilicity of atom attached to

oxygen.[4e,4f] In our case, amino hydrogen of histidine is likely to be responsible for enhancing electrophilicity of nitrostyrene at β-carbon through hydrogen bonding as depicted in Figure 2. Another amino acid residue, aspartic anion[4f] might be responsible for enhancing nucleophilicity at 3-position of indole ring causing its facile addition on the nitrostyrene as depicted in Figure 2. We have also carried out a reaction by employing isolated lipase as a catalyst and obtained 3-(2-nitro-1-phenylethyl)-1*H*-indole (**3a**) with 70% yield. No product formation was observed by employing thermally inactivated baker's yeast, but with active baker's yeast **3a** was obtained in 90% yield. Due to thermal inactivation of baker's yeast lipase is inactivated which results in no product formation. It indicates that, components apart from enzymes present in baker's yeast are not responsible to catalyze the

Table 2
Baker's yeast catalyzed synthesis of 3-substituted indoles[a]

Entry	Indole	Nitroolefin	Reaction time (h)	Product	Yield[b] (%)	Mp (°C)
1	 **1a**	 **2a**	2.5	 **3a**	90	[96–98][19]
2	 **1b**	 **2a**	3.0	 **3b**	89	[94–96][21]
3	 **1c**	 **2a**	3.0	 **3c**	84	[92–94][25]
4	 **1d**	 **2a**	3.0	 **3d**	81	[142–144][21]
5	 **1e**	 **2a**	2.5	 **3e**	91	[116–118][21]
6	 **1f**	 **2a**	3.5	 **3f**	82	[122–124][21]
7	 **1g**	 **2a**	3.5	 **3g**	88	[Pink liquid][19]
8	 **1h**	 **2a**	3.5	 **3h**	86	[Brown liquid][19]

(*continued on next page*)

Table 2 (*continued*)

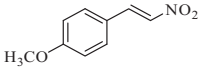
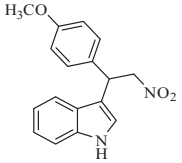
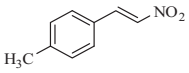
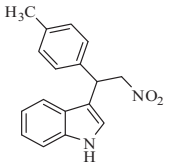
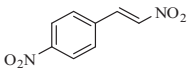
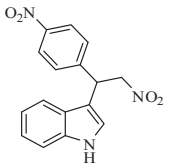
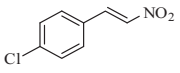
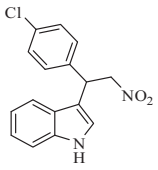
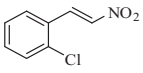
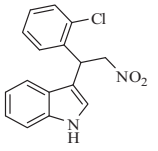
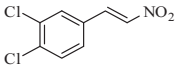
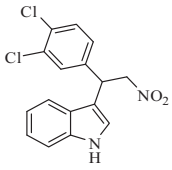
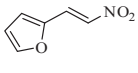
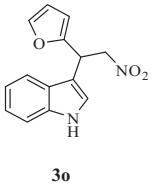
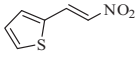
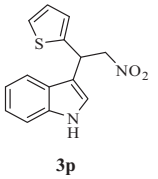
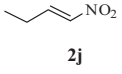
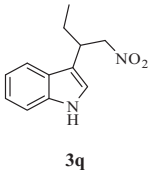
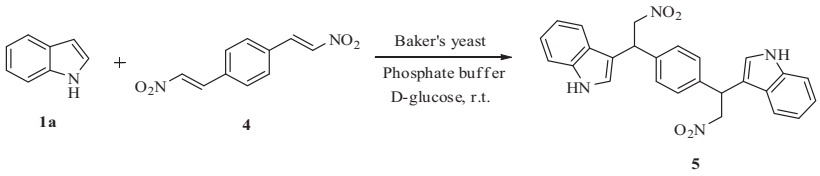
Entry	Indole	Nitroolefin	Reaction time (h)	Product	Yield[b] (%)	Mp (°C)
9	 **1a**	 **2b**	6.0	 **3i**	83	[148–150][25]
10	 **1a**	 **2c**	4.0	 **3j**	86	[Liquid][21]
11	 **1a**	 **2d**	2.0	 **3k**	94	[145–147][21]
12	 **1a**	 **2e**	3.0	 **3l**	89	[104–106][25]
13	 **1a**	 **2f**	3.0	 **3m**	83	[142–144][25]
14	 **1a**	 **2g**	2.5	 **3n**	87	[132–134][19]
15	 **1a**	 **2h**	2.5	 **3o**	85	[68–70][25]
16	 **1a**	 **2i**	4.0	 **3p**	86	[92–94][21]
17	 **1a**	 **2j**	6.0	 **3q**	70	[Liquid] [22]

Table 2 (*continued*)

Entry	Indole	Nitroolefin	Reaction time (h)	Product	Yield[b] (%)	Mp (°C)
18	**1a**	**2k**	6.0	**3r**	74	Liquid

[a] Reaction conditions: indole (1 mmol), nitroolefin (1 mmol), baker's yeast (300 mg), D-glucose (500 mg), phosphate buffer (pH 7.0, 5 mL) at room temperature.
[b] Isolated yield after column chromatography.



1a **4** **5**

Scheme 2. Dialkylation of 1,4-bis-(2-nitrovinyl) benzene in presence of baker's yeast.

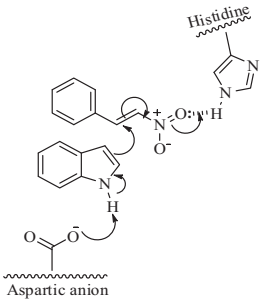


Figure 2. Activation of indole and β-nitrostyrene by baker's yeast for 1,4-conjugate addition.

Michael addition of indole to β-nitrostyrene. Therefore we believe that the enzyme lipase available in baker's yeast is likely to be responsible to accelerate the 1,4-conjugate addition of indoles to nitroolefins.

In conclusion, for the first time we have explored the potential of baker's yeast as a biocatalyst for the synthesis of 3-substituted indoles with simple adoptable procedure. The reactions are remarkably tolerant of substituents at different positions of indolyl rings and benzene ring of nitroolefins. The reactions are carried out in aqueous medium at room temperature so no side product or decomposition product was observed. In terms of green chemistry, the process is of great interest as it avoids the use of corrosive acids, toxic metallic catalysts and organic volatile solvents. Overall, the developed methodology using baker's yeast, turned out to be an environmentally benign one and it is a good contribution for the regioselective 1,4-conjugate addition of indoles to nitroolefins.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.057.

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