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Bovine Serum Albumin catalyzed one-pot, three-component synthesis of dihydropyrano[2,3-c]pyrazole derivatives in aqueous ethanol

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Abstract

Bovine serum albumin (BSA) catalyzed synthesis of dihydropyrano[2,3-c]pyrazole derivatives via one pot, three component reaction of aldehyde/ketone or isatin, malononitrile and 3-methyl-1*H*-pyrazol-5 (4*H*)-one in H_2O-EtOH (7:3) at ambient temperature was developed in this work. The catalyst was found to work efficiently for aldehydes, ketones and isatins to give the corresponding dihydropyrano[2,3-*c*] pyrazole and spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives in high yields. The BSA showed a broad range of catalytic promiscuity towards various aldehydes, aromatic/aliphatic ketones and substituted isatins. Use of environmentally benign protocol, reusability of the catalyst, free from hazardous solvent, excellent yields, easy work up and no byproducts formation make BSA an attractive candidate for expanding its applications as biocatalyst.

Keywords: Biocatalysis, Dihydropyanopyrazole, Bovine serum albumin, 3-Methyl-1*H*-pyrazol-5(4*H*)-one.

Introduction

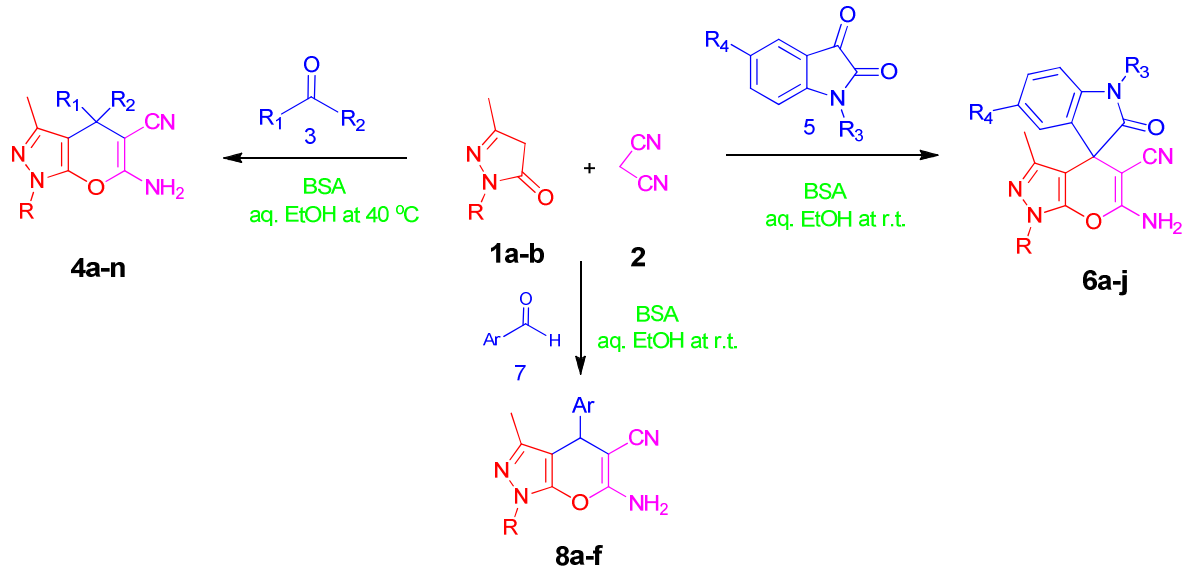
Dihydropyrano[2,3-c]pyrazole is a promising class of heterocyclic compounds and a structural unit of a variety of therapeutic agents.[1]The synthesis of dihydropyrano[2,3-c]pyrazole derivatives is receiving great attention among synthetic chemists due to their diverse bioactivity profiles with various medicinal activities which include potential inhibitor of human Chk1 kinase,[2a] anti-inflammatory,[2b] anticancer,[3a] analgesic,[3b] molluscicidal[4] and antimicrobial.[5] Because of the abovementioned important properties of pyranopyrazoles, development of new methods for the synthesis of this heterocyclic moiety has gained huge significance and demanding task in organic synthesis. Generally, it is synthesized by multicomponent reaction of aldehyde/ketones, malononitrile, ethyl acetoacetate, and hydrazine hydrate in the presence of environmentally noncompatible base catalysts.[6-9] Recently, some environment-friendly catalysts such as L-proline,[10] γ-alumina,[11] and per-6-amino-cyclodextrin,[12]Amberlyst A21,[13] piperidine,[14a] meglumine,[14b] cocamidopropyl betaine (CAPB),[15a] cetyltrimethylammonium chloride (CTACl),[15b] molecular sieves, (MS 4Å)[16a] and saccharose[16b] were also used to achieve this transformation. Their diverse biological, pharmacological properties and high cost necessitates search for economically efficient and environmentally benign synthetic methodology for the preparation of these heterocyclic compounds.

Biocatalysis is a green chemistry approach to chemical transformations because of its high selectivity, mild reaction conditions, low energy requirements and few by-products[17-20]. The biocatalytic promiscuity provides a new tool for extending the applications of enzymes in organic synthesis.[21] Hence, search for exploring the new possible biocatalyst to achieve

environmental friendly reaction continues that avoids use of hazardous organic solvents, toxic metals, and other harsh reaction conditions and producing different types of chemical and biological substance with higher yields.[22] Since few decades, several examples to exploit the biocatalysts, like lipase,[23a] DNA,[23b] whole cell[23c] and laccase[23d] for catalyzing organic synthesis have been set up bearing high catalytic activity and simple operation. It is important to increase the promiscuity of enzyme and develop cost effective as well as green protocol for the synthesis of dihydropyrano[2,3-c]pyrazole compounds. The literature states that Bovine Serum Albumin (BSA) was an efficient biocatalyst in many organic reactions, which includes aerobic oxidative coupling of thiols into disulphides,[24] nitro-aldol addition,[25] Gewald reaction,[26] Stereoselective thio-Michael addition to chalcones,[27] Knoevenagel condensation between diethylmalonate with aldehydes,[28] and Biginelli reaction[29] for the synthesis of valuable compounds. The BSA or "Fraction V" is the most abundant, low cost serum albumin protein derived from cows. It binds several organic molecules due to presence of hydrophobic binding sites and basic characters have attracted features.[30-31] Recently Bora *et al*.[32] have reported biocatalytic route for the synthesis of dihydropyrano[2,3-*c*]pyrazoles from aldehydes and ketones using Lipase from *Aspergillus niger*. However, there is a scope left to explore better biocatalyst. Therefore, it is obvious to search new biocatalysts with ecofriendly protocol, atom economy and broad substrate range. In general, the ketones are less reactive than aldehydes and less explored, hence ketone based dihydropyrano[2,3-*c*]pyrazole synthesis was investigated.

In continuation of our work on protein isolation[33] and biomimetic heterocycles synthesis,[34] recently we developed an efficient method for the synthesis of dihydropyrano[2,3-c]pyrazoles and spirooxindoles by β-cyclodextrin in ethanol-water mixture.[35] Herein, we envisioned the highly efficient and environmentally benign protocol for the synthesis of

dihydropyrano[2,3-c]pyrazoles and spiro[indoline-3,4'-pyrano[2,3-*c*] pyrazole] derived from aldehydes, ketones and isatins respectively by using BSA at ambient temperature as a biocatalyst (Scheme 1).



Scheme 1 Synthesis of dihydropyrano[2,3-c]pyrazoles and spiro[indoline-3,4'-pyrano[2,3-c]pyrazoles in aqueous ethanol

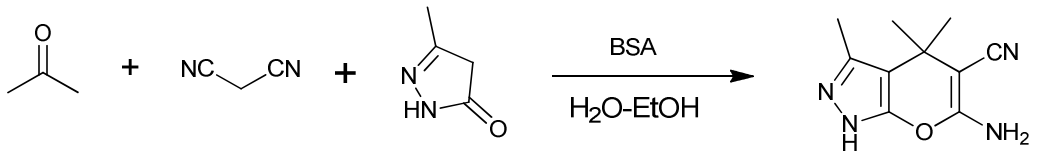
Results and Discussion:

Screening of enzymes:

The different commercially available enzymes were selected to screen their role as a catalyst in the synthesis of dihydropyrano[2,3-*c*]pyrazole compounds. We choose the equimolar mixture of acetone, malononitrile and pyrazolone. Acetone (2 mmol), malononitrile (2 mmol) were mixed together in round bottom flask containing mixture of water and ethanol (7:3) and stirred vigorously for 10 min to make homogeneous solution. Then pyrazolone (2 mmol) and BSA (60 mg) were added to it. Reaction was carried out at temperature (40 °C) with continuous stirring for 1 h. The transformation of product was monitored by thin layer chromatography

(TLC). The product obtained was solid and insoluble in water. So, the reaction mixture was diluted with 10 mL water and separated by filtration. Different enzymes were used to catalyze synthesis of **4a** and results were summarized in Table 1.

Table 1 Screening of the catalytic activities of different enzymes[a]



Entry	Enzyme	Yield[b] (%)
1	No catalyst	20
2	Lipase from *Candida rugosa*	13
3	Lipase from Porcine pancreas	35
4	Trypsin from Bovine	57
5	Trypsin from Porcine Pancreas	30
6	Papain	40
7	Diastase α-Amylase	25
8	Bovine Serum Albumin	94

[a] Reaction conditions: Acetone (2 mmol), malononitrile (2 mmol), pyrazolone (2 mmol), BSA(60 mg) and H_2O-EtOH (7:3, 10 ml) at 40 ^oC for 1 h, [b]Isolated yield.

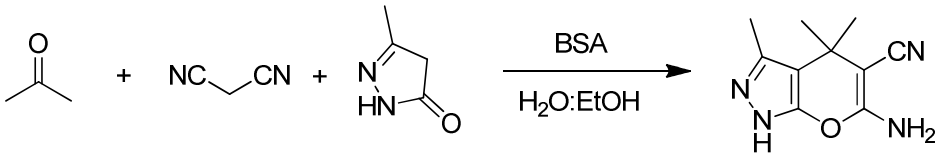
When Lipase from *Candida rugosa* used as a catalyst, only 13% yield was obtained in 1h while Lipase from Porcine pancreas gave 35% yield. We also used some digestive enzymes like trypsin from bovine, surprisingly 57% yield was found but in case of trypsin from Porcine

pancreas, the yield was decreased (30%). When Papain was used 40% product formation observed while Diastase α-Amylase gave lower yield (25%). If no catalyst added, only 20% yield was detected. When BSA was used, the yield increased dramatically to 94% probably bringing catalysis due to rich diversity of amino acids present on surface of BSA.[36]

Optimization of solvent

The reaction medium plays an important role in enzyme catalyzed reactions owing to its effects on enzyme activity as well as substrate solubility.[37a] The effects of different solvents having different polarities on the model reaction were investigated. The results in Table 2 exhibit diverse effects of different solvent on activity of BSA in the reaction. Independently water showed ~39% yield after 1 h whereas rest of the solvents such as ethanol, methanol, acetonitrile, THF, DMF showed trace yields. However, it was observed that the mixture of water and ethanol at different ratios enhances the yield of reaction. The best result was obtained by using mixture of water and ethanol (7:3) with highest yield of 94 %. Therefore, the BSA in water and ethanol mixture (7:3) was used to carry out further reactions.

Table 2 Optimization of solvent [a]



Entry	Solvent	Yield[b] (%)
1	Water	39
2	Ethanol	Trace

3	Methanol	Trace
4	Acetonitrile	Trace
5	THF	Trace
6	DMF	Trace
7	H_2O : EtOH (1:1)	Trace
8	H_2O : EtOH (9:1)	43
9	H_2O : EtOH (8:2)	50
10	H_2O : EtOH (7:3)	94

[a] Reaction conditions: Acetone (2 mmol), malononitrile (2 mmol), pyrazolone (2 mmol), BSA(60 mg) and H_2O-EtOH (7:3, 10 mL), Reaction Time: 1 h at 40 ^{0}C, [b]Isolated yield.

Effect of catalyst loading:

In order to optimize the catalyst loading of BSA, the model reaction was performed with varied quantity of BSA as 20 to 70 mg per mmol of substrate (Figure 1) while rest of the reaction conditions was kept same. It was observed that increase in enzyme concentration up to 60 mg, increased the yield of reaction, however, no significant improvement in the yield of reaction observed further. The best yield 94% was obtained with 60 mg BSA per 2 mmol of substrate in 1 h of duration.

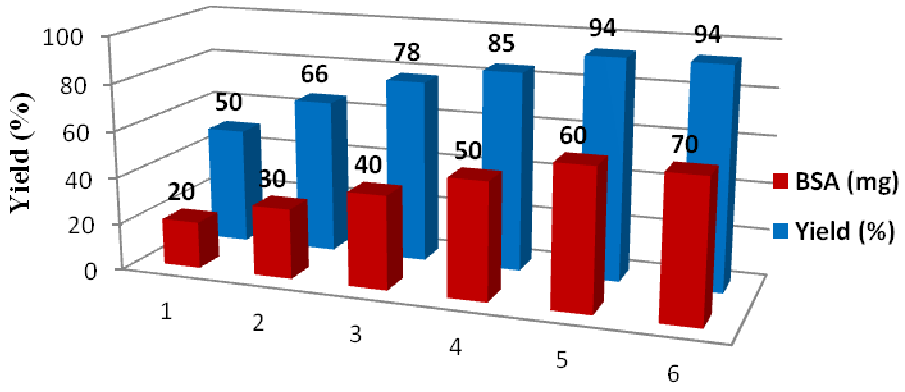


Figure 1. Study of the amount of catalyst on reaction yields

Effect of temperature:

Temperature is an important factor in every biocatalytic reactions. When the reaction temperature was increased, the collision between enzyme and substrate molecules might have accelerated to form enzyme-substrate complexes resulting in improved reaction rate.[38] In the present study, the reaction temperature was changed from 20 to 50 °C to investigate its effect. The results shown in Fig. 2 indicated that the yield was greatly improved by raising the temperature from 20 to 30 °C, and reached to highest of 94% at 40 °C in one hour duration, further increase in the temperature up to 50 °C resulted in same yield.

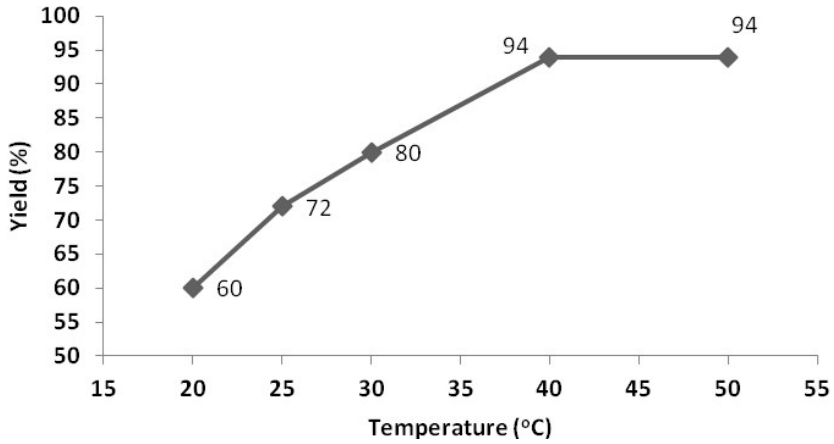


Figure 2. Study of the effect of temperature on reaction yields

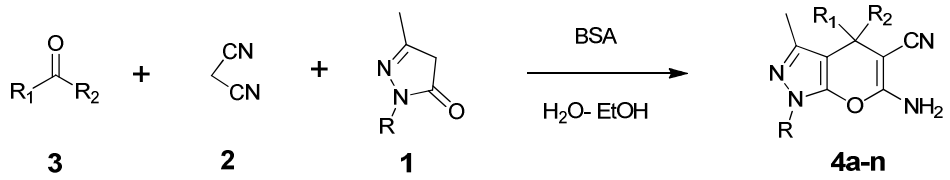
Substrate Scope:

Having set optimized parameters, the substrate scope for BSA-catalyzed dihydropyrano[2,3-*c*]pyrazole was investigated by varying the nature of ketones. As shown in Table 3, the BSA-catalyzed reaction proceeded smoothly with aliphatic, cyclic and aromatic ketones. The chain length of ketone has shown great influence on the reaction time. In the case of acetone (Entry 1, Table 3), compound **4a** was obtained with excellent yield of 94% in one hour, while when 2-butanone was used as ketone under the same condition, a slightly decreased yield 90% was observed (Entry 2, Table 3) in 15 h. When ethyl acetoacetate and methyl acetoacetate (Entries 3-4, Table 3) was used as ketone, 94 % and 95 % yields in 12 h and 15 h respectively were obtained for compound **4c** and **4d**. This indicates that BSA was chemo selectively reacts with ketone carbonyl in the presence of ester carbonyl group. Furthermore, the ring size of cyclic ketones might be exerting an obvious influence. For example, the yield of cyclohexanone, malononitrile and pyrazolone after 21 h came up to 80% (Entry 5, Table 3). But, when cyclopentanone was used as a substrate, the yield dramatically increased to 86% (Entry 6, Table 3) in only 10 h. This phenomenon might be ascribed to the higher internal ring strain. When the methodology was tested to aromatic ketones (Entries 7-12, Table 3) having electron donating and electron withdrawing substituents, reaction time for complete conversion to products were found to be higher with good yields than previously reported method.[32]

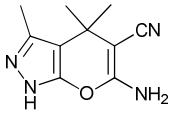
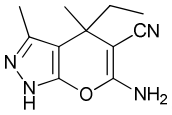
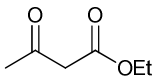
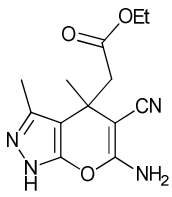
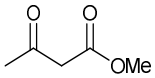
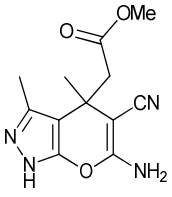
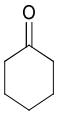
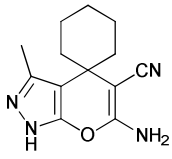
The efficiency of protocol in multigram scale was established by using equimolar (100 mmol) acetone, malononitrile and pyrazolone. Acetone (100 mmol, 5.8 g), malononitrile (100 mmol, 6.6 g) were mixed together in round bottom flask containing mixture of water and ethanol 200 mL (7:3) and stirred vigorously for 10 min to make a homogeneous solution. Then

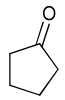
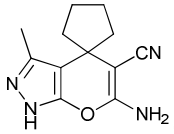
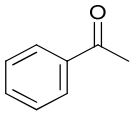
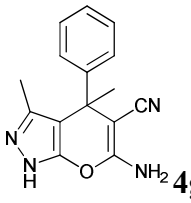
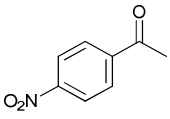
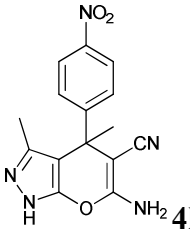
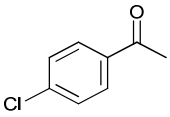
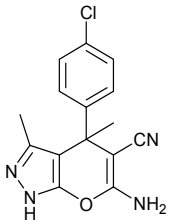
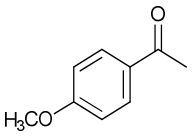
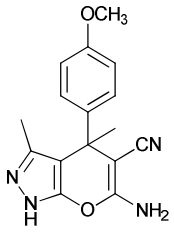
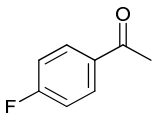
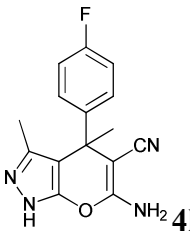
pyrazolone (100 mmol, 9.8 g) and BSA (3 g) were added to it and stirred at 40 °C for 1 h. The reaction promptly proceeded to afford **4a** in 95 % yields (19.4 g).

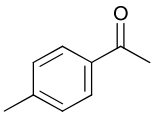
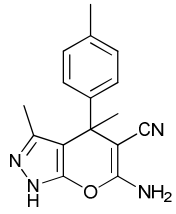
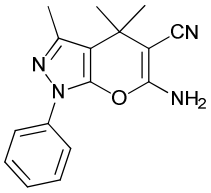
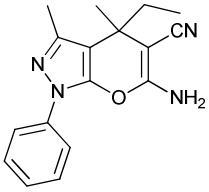
Table 3 Synthesis of dihydropyrano[2,3-c] pyrazoles from ketones



3 **2** **1** **4a-n**

Entry	Ketone	Product	Time (h)	Yield (%)	M.P. (°C)[Lit.] Found	M.P. (°C)[Lit.] Reported
1		 **4a**	1	94	174-176	176-177[14b]
2		 **4b**	15	90	164-166	--
3		 **4c**	12	94	204-206	--
4		 **4d**	15	95	200-202	--
5		 **4e**	21	80	146-148	147-148[14b]

6		 **4f**	10	86	164-166	164-165[14b]
7		 **4g**	30	94	175-176	174-175[32]
8		 **4h**	36	86	210-212	220-221[14b]
9		 **4i**	24	95	182-184	181-182[13]
10		 **4j**	48	76	193-194	194-195[13]
11		 **4k**	36	83	208-210	--

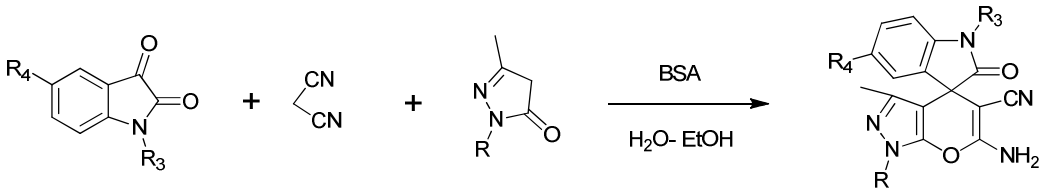
12		 **4l**	48	86	182-183	183-184[13]
13		 **4m**	24	72	140-142	--
14		 **4n**	24	85	158-160	--

[a] Reaction conditions: Ketone (2 mmol), malononitrile (2 mmol), pyrazolone (2 mmol), BSA (60 mg) and H_2O-EtOH (7:3, 10 mL) at 40 °C, [b]Isolated yield.

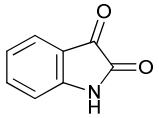
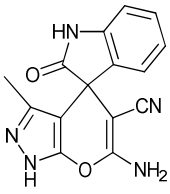
Isatin is an important molecule for designing potential pharmacological agents, and its derivatives have shown a broad range of bioactivity and involved in synthesis of various heterocyclic compounds.[39] Spiro compounds are naturally occurring compounds present in many pharmacological agent and natural alkaloids.[40] The indole nucleus show antibacterial and antifungal activities and it is important heterocyclic agent present in diverse types of medicinal agents and natural products.[41] These interesting properties promoted us to widen the applicability of this procedure with isatins. To explore the scope, we used isatin as a ketone substrate to react with malononitrile, and 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1a**) under previously optimized conditions. Interestingly, the reactions with isatin proceed speedily at room temperature to spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] with excellent yields (Table 4). The reactions for isatin, 5-chloroisatin and 5-bromoisatin (Entries 1-3, Table 4) were completed in 15 minutes

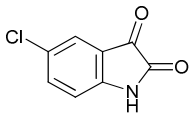
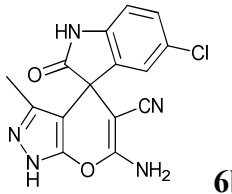
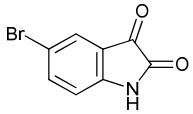
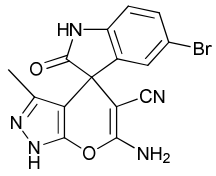
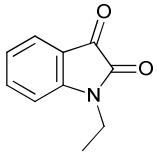
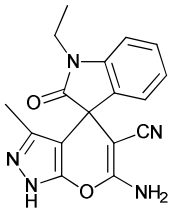
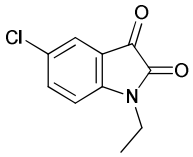
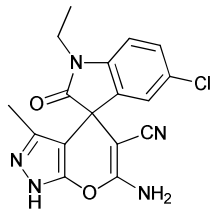
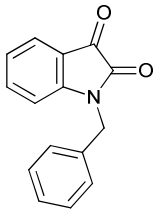
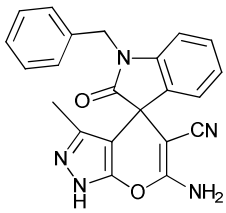
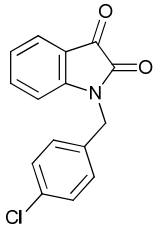
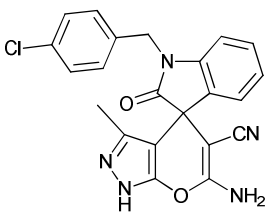
where as N-alkyl isatins (Entries 4-7, Table 4) required slightly longer reaction time. Overall, reactions with isatin resulted in excellent yields with 35 minutes except 5-bromoisatin resulted in somewhat lower yields 84%. However, when the four component one pot reaction was attempted by using acetone, malononitrile, hydrazine and ethyl acetoacetate, the reaction was completed in longer reaction time with lower yields. In order to explore substrate scope, the carbonyl compounds, malononitrile and 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**1b**) were reacted in aqueous ethanol medium to give the products **4m-n** and **6h-j** in good yields. X-ray studies and molecular structure of pyranopyrazole (**4c** and **6e**) revealed that it exists in the crystal phase as a 2H, instead of 1H tautomer as shown in Figure S1 and S2 (See Supporting information), which is in congruence with the literature reports on pyranopyrazoles.[43]

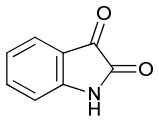
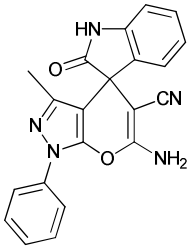
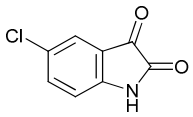
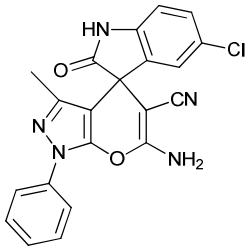
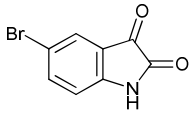
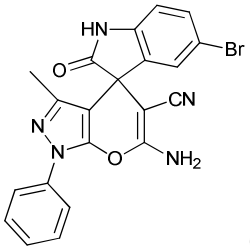
Table 4 Synthesis of spiro[indoline-3,4-pyrano[2, 3-c]pyrazole] derivatives from Isatins



5 **2** **1** **6a-j**

Sr. No.	Isatin	Product	Time (min)	Yield (%)	M.P. Found	M.P. Reference
1		 **6a**	15	94	284-286	286-287[14b]

2		 **6b**	15	98	296-298	298-299[14b]
3		 **6c**	15	84	278-280	283-284[14b]
4		 **6d**	30	90	284-286	284-286[35]
5		 **6e**	35	93	267-268	--
6		 **6f**	20	94	274-276	276-278[35]
7		 **6g**	25	97	274-276	--

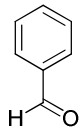
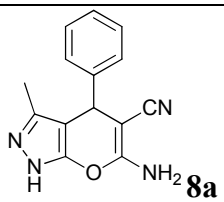
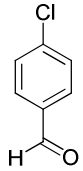
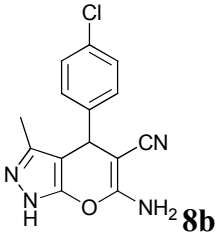
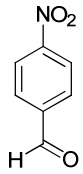
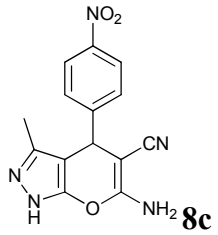
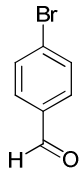
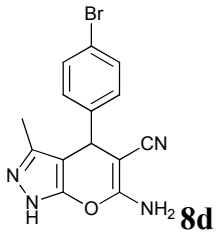
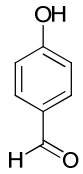
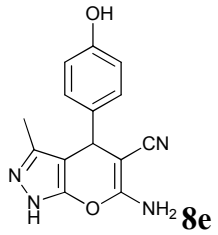
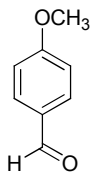
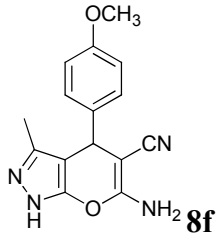
8		 **6h**	30	98	226-228	228-230[37b]
9		 **6i**	30	93	230-232	232-234[37c]
10		 **6j**	35	89	230-232	232-234[37c]

[a] Reaction conditions: Isatin (2 mmol), malononitrile (2 mmol), pyrazolone (2 mmol), BSA(60 mg) and H_2O-EtOH (7:3, 10 mL) at rt., [b]Isolated yield.

Inspired from the above initial success, we generalized the applicability of this method for the synthesis of dihydropyrano[2,3-*c*]pyrazoles from various aromatic aldehydes. Interestingly, a variety of aromatic aldehydes including electron withdrawing and donating abilities participated well in this reaction and brought good to excellent yield (Table 5).

Table 5 Synthesis of dihydropyrano[2,3-*c*]pyrazoles from aldehydes

Sr. No.	**Aldehyde**	**Product**	**Time (h)**	**Yield (%)**	**M.P.**	
					Found	**Reference**

1		 **8a**	1.5	94	244-246	244-246[35]
2		 **8b**	2	88	236-238	234-236[35]
3		 **8c**	2.5	82	246-248	248-250[35]
4		 **8d**	2	95	178-180	178-180[35]
5		 **8e**	2	97	218-220	223-224[35]
6		 **8f**	3	94	210-212	210-212[35]

[a] Reaction conditions: Aldehyde (2 mmol), malononitrile (2 mmol), pyrazolone (2 mmol), BSA (60 mg) and H_2O-EtOH (7:3, 10 mL) at rt, [b]Isolated yield.

Test of recyclability:

The enzyme BSA remains in aqueous medium after the reaction. This aqueous medium was reused to recycle for three runs while the product isolated was good enough with potential to make it cost effective as shown in Figure 3. Slight decrease in the yield of product was observed in the first, second and third reaction runs (92%, 88% and 82% respectively).

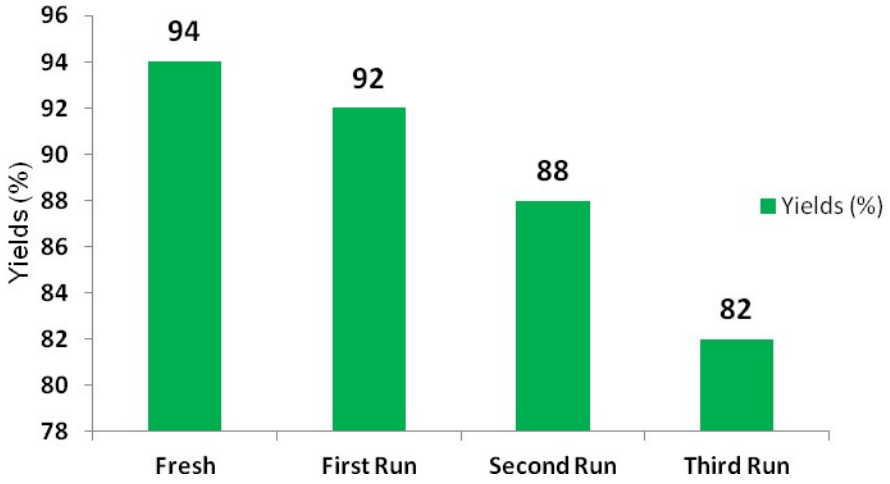
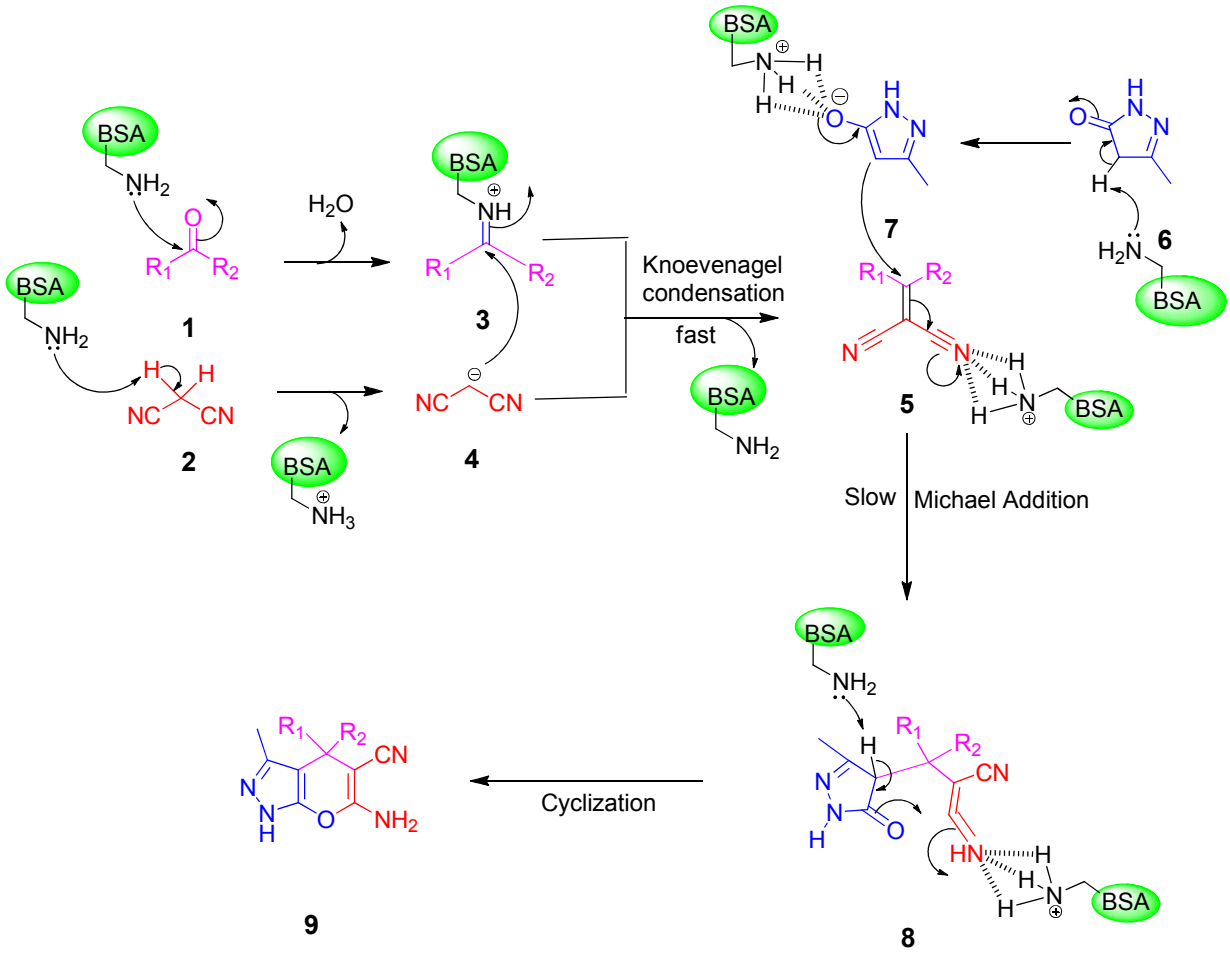


Figure 3 Recycle studies of BSA and its effect on yield.

Plausible Mechanism:

On the basis of the above results and previous studies, a plausible mechanism is proposed for the synthesis of dihydroprano[2,3-*c*]pyrazole from ketones. According to the literature reports,[40] the catalytic activity of BSA is based on the basic character of the amino groups present in the side chain of some amino acid residues, especially the lysine residue. It is proposed that firstly, the lysine's amine attacks on the carbonyl group of a ketone leading to the formation of iminium ion **3**. At same time, the removal of proton from malononitrile by the free basic amino group of BSA forms a carbanion which is subsequently condensed with iminium ion to

give α, β-unsaturated nitrile **5**. This step is known as Knoevenagel condensation. Then activated 3-methyl-1*H*-pyrazol-5(4*H*)-one **7** and α, β-unsaturated nitrile **5** reacts with each other through Michael addition to form **8** which undergoes cyclization to the desired product **9** as shown in Scheme 2.



Scheme 2 Plausible mechanism for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives in the presence of BSA in aqueous ethanol medium.

Conclusion

In conclusion, we described simple, efficient and biocatalytic route for the synthesis of various dihydropyrano[2,3-*c*] pyrazoles and spiro[indoline-3,4'-pyrano[2,3-*c*] pyrazoles using inexpensive BSA. The advantages of this protocol include good to high yields, operational simplicity, simple filtration and needing no metal catalyst or activation, and no extraction or separation by column chromatography is necessary. Overall approach towards the green chemistry and the use of BSA as biocatalyst in reaction is of practical significance in expanding its applications in biocatalysts.

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