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Nano-ovalbumin: a green biocatalyst for biomimetic synthesis of tetrahydrodipyrazolo pyridines in water

Naeimeh Salehi[1] · Bi Bi Fatemeh Mirjalili[1]

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Abstract

In this investigation, a simple and new protocol was used to prepare large quantities of purified nano-ovalbumin from egg white. Nano-ovalbumin, as a retrievable and metal-free biocatalyst, was characterized by FT-IR, FESEM, XRD, MALDI-TOF and TGA/DTA. This biocatalyst displayed a high activity for green and efficient synthesis of tetrahydrodipyrazolo pyridines via multi-component reaction of ethyl acetoacetate, hydrazine, aldehyde and ammonium acetate in water. This new bio-catalyzed process could serve as a valuable synthetic alternative for such multi-component reactions in terms of economic aspects and biocompatibility of conditions.

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✉ Bi Bi Fatemeh Mirjalili
fmirjalili@yazd.ac.ir

[1] Department of Chemistry, College of Science, Yazd University, P.O. Box 89195-741, Yazd, Islamic Republic of Iran

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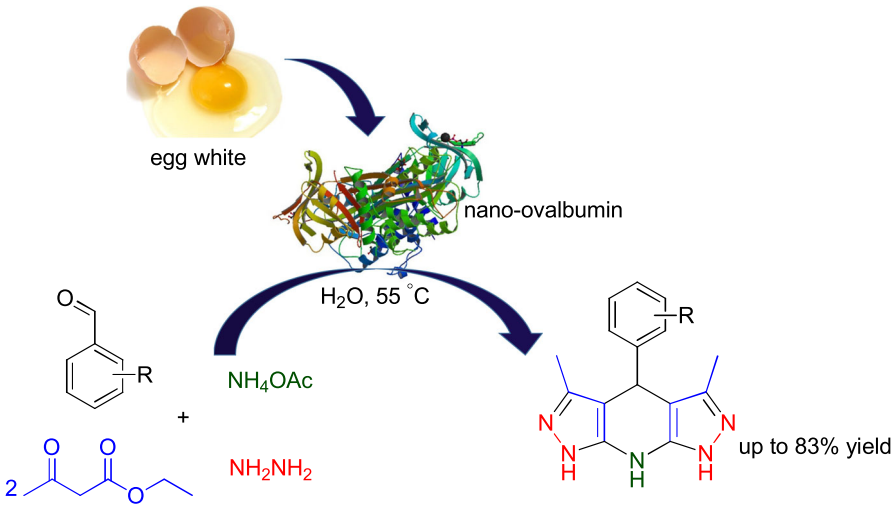
Graphical abstract



Keywords Nano-ovalbumin · Biocatalyst · Egg white · Tetrahydrodipyrazolo pyridine · Multi-component reaction

Introduction

In recent decades, discovery of creative ways to decrease environmental pollution has been the aim of many organic chemists. The use of water as an abundantly available and green solvent for organic reactions is one of the finest choices for the problem of solvent toxicity and disposal. It is presumed that water accelerates the organic reactions by a number of factors, including by the hydrophobic effect as well as hydrogen bonding between water molecules and reactants [1]. Additionally, the catalysis of reactions by biocatalysts can be another adaptable idea to decrease environmental pollution. Biocatalysts are more advantageous than conventional catalysts in many ways, including low toxicity, abundant availability, high specificity and efficiency, metal-free nature and simple reaction conditions [2].

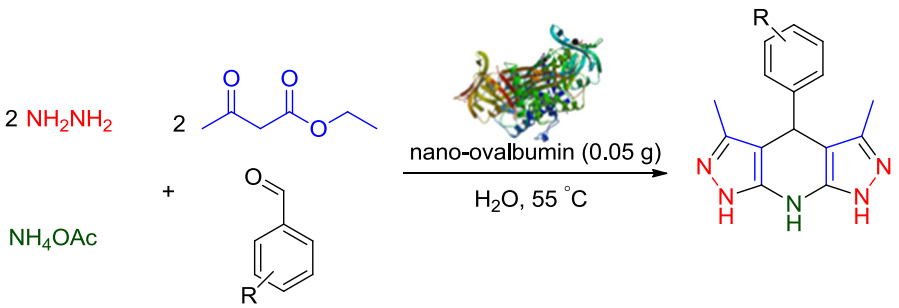
Egg white has 9.7–12% protein, and its main protein is ovalbumin (54% of egg-white proteins). Ovalbumin is a globular, biocompatible and nontoxic phosphoglyco protein. Having a molecular weight of 44.5 kDa, this protein contains 385 residues of amino acids with an isoelectric point (pI) of 4.5 [3]. Many purification procedures have been reported for egg-white proteins such as gel permeation and anion exchange chromatography [4], Q Sepharose fast flow column [5] and salting out precipitation using ammonium sulfate and sodium sulfate at a specific salt concentration, pH and temperature [6]. In this work, we have reported a new, simple and rapid protocol using acetic acid and sodium chloride to separate ovalbumin from egg white in nanometer size.

Although albumin, similar to enzymes, does not have a specific catalytic site, bovine serum albumin (BSA) and human serum albumin (HSA) have recently emerged as promiscuous biocatalysts to accelerate some organic reactions such as the Kemp elimination [7], Morita–Baylis–Hillman (MBH) reaction [8], aldol reaction [9], Henry reaction [10], thio-Michael addition [11], Gewald condensation [12] and Biginelli reaction [13]. A strong affinity to bind organic molecules by reversible non-covalent complexation in its hydrophobic pockets could be responsible for the protein catalytic activity [14].

Pyrazolopyridines are well-known as unique scaffolds in organic and medicinal chemistry owing to the broad spectrum of their biological and pharmacological activities, including antiviral [15], antitumor [16], hypoglycemic [17], anti-inflammatory [18], anxiolytic [19], anti-*Leishmania* [20], antiherpetic [21], antiallergic [22] and protein kinase inhibitors [23]. Literature survey reveals that there are only a few methods to synthesize tetrahydrodipyrazolo pyridines via multi-component reaction (MCR) of ethyl acetoacetate, hydrazine, aldehyde and ammonium acetate. Previously, *p*-TSA [24], nano-$CuCr_2O_4$ [25], nano-$CdZr_4(PO_4)_6$ [26], Fe_3O_4/KCC1/IL/HPW [27], $FeNi_3$–ILs MNPs [28] and nano-Fe_3O_4@SiO_2–SO_3H [29] were used as catalysts for this process. Despite the remarkable achievements, biocompatible synthesis of these potent pyridines using an inexpensive, easily available and metal-free catalyst is still in demand.

MCRs as flexible reactions have been utilized for the rapid synthesis of a variety of biologically active compounds [30]. The synthesis of tetrahydrodipyrazolo pyridines via MCRs offers significant advantages in terms of purity, selectivity, atom economy, simplicity, energy consumption reduction and low waste production [31].

Inspired by these results and in pursuit of our previous research in developing green methods to synthesize useful heterocycles [32], in the current study, we have reported a biocompatible protocol to synthesize tetrahydrodipyrazolo pyridines using nano-ovalbumin in water (Scheme 1).



Scheme 1 Synthesis of tetrahydrodipyrazolo pyridines in the presence of nano-ovalbumin

Experimental

General

Fourier transform infrared (FT-IR) spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) nuclear magnetic resonance (NMR) instrument was used to record the ^{1}H-NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected. Matrix assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF) measurement was performed by the Applied Biosystems (AB) Model 4800 MALDI-TOF/TOF mass spectrometer. Field emission scanning electron microscopy (FESEM) was obtained on a Mira 3-XMU. The X-ray diffraction (XRD) pattern was obtained by a Philips Xpert MPD diffractometer (Cu Kα, radiation, k = 0.154056 nm). Thermal gravimetric analysis (TGA) was conducted using STA 504 instrument. Elemental analysis (C, H, N) was performed using a Vario EL analyzer. The products were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and a comparison of their physical properties with those reported in the literature.

Preparation of nano-ovalbumin

In a beaker containing 33 g of egg white, 50 mL of water, 9 mL of concentrated acetic acid and 3 g of NaCl were added and mixed to appear as a bulky solid. The obtained solid was filtered, washed with water and purified by acetone and then water. Nano-ovalbumin as a white solid (4.5 g) was dried at room temperature and stored in a refrigerator.

General procedure for synthesis of tetrahydrodipyrazolo pyridines

In a 25-mL round-bottom flask, a mixture of hydrazine hydrate 50–60% (0.15 mL) and ethyl acetoacetate (2.0 mmol, 0.26 mL) in water (3 mL) was stirred at room temperature. Then, aldehyde (1.0 mmol), ammonium acetate (4.0 mmol, 0.308 g) and nano-ovalbumin (0.05 g) were added to it and stirred at 55 °C. The progress of reaction was monitored by thin-layer chromatography (TLC; hexane-to-EtOAc, 70:30). The reaction mixture was cooled after completion, diluted by cold water, filtered off and washed with cold water and then acetone. To separate the catalyst from the solid product, it was washed with dimethylformamide (3 mL). By adding water to the residue, tetrahydrodipyrazolo pyridine appeared as a pure solid product.

Characterization and spectral data for new compounds

3-(3,5-Dimethyl-1,4,7,8-tetrahydrodipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)phenol (5e) Cream solid, m.p. 220–222 °C. FT-IR (ATR) $\bar{\upsilon}$ (cm^{-1}): 3447, 3318, 1585, 1478, 1453, 1257, 750. ^{1}H NMR (400 MHz, DMSO-d$_6$)/δ ppm: 11.32 (s, NH, 3H), 9.11 (s, OH, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.57 (s, 1H), 6.53 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.74 (s, 1H), 2.07 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d$_6$)/δ ppm:

161.58, 157.41, 145.32, 140.29, 128.98, 118.71, 115.05, 112.84, 104.73, 33.04, 10.86. Anal. calcd. for $C_{17}H_{117}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.23; H, 6.33; N, 15.25.

4-(3,5-Dimethyl-1,4,7,8-tetrahydrodipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)benzene-1,3-diol (5l) Reddish-brown solid, m.p. 208–210 °C. FT-IR (ATR) $\bar{\upsilon}$ (cm^{-1}): 3496, 3220, 1597, 1527, 1469, 1249, 1112, 726. ^{1}H NMR (400 MHz, DMSO-d_6)/δ ppm: 11.30 (s, NH, 3H), 8.63 (s, OH, 1H), 8.52 (s, OH, 1H), 6.56 (d, J = 8 Hz, 1H), 6.55 (s, 1H), 6.35 (d, J = 8 Hz, 1H), 4.67 (s, 1H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6)/δ ppm: 161.59, 144.97, 143.43, 140.21, 134.55, 118.56, 115.61, 115.32, 105.18, 32.36, 10.86. Anal. calcd. for $C_{17}H_{16}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.34; H, 5.95; N, 14.45.

2-(3,5-Dimethyl-1,4,7,8-tetrahydrodipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)-6-methoxyphenol (5n) White solid, m.p. 240–242 °C. FT-IR (ATR) $\bar{\upsilon}$ (cm^{-1}): 3431, 3339, 1589, 1575, 1477, 1271, 1139, 773. ^{1}H NMR (400 MHz, DMSO-d_6)/δ ppm: 11.44 (s, NH, 3H), 8.66 (s, OH, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.62 (t, J = 7.6 Hz, 1H), 5.10 (s, 1H), 3.75 (s,3H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6)/δ ppm: 161.93, 147.31, 143.18, 140.46, 131.45, 121.99, 118.23, 109.52, 104.62, 56.17, 31.17, 11.07. Anal. calcd. for $C_{17}H_{16}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.11; H, 6.32; N, 13.68.

Results and discussion

As Fig. 1 illustrates, nano-ovalbumin as a biocatalyst was prepared by a novel, simple and low-cost method from egg white in two steps (Fig. 1). Firstly, NaCl was added to a mixture of fresh egg white, water and concentrated acetic acid and was then mixed to obtain a bulky solid. In the next step, the resulting solid was purified as a white solid by acetone and then water at room temperature. The obtained nano-ovalbumin was characterized by FT-IR, MALDI-TOF, FESEM, XRD and TGA/differential thermal analysis (TGA/DTA).

The FT-IR spectrum of nano-ovalbumin exhibited a broad band at 3200–3500 cm^{-1} corresponding to stretching vibration of NH and OH (Fig. 2). Two bands at 1622 and 1532 cm^{-1} correspond to the C=O and C–N stretching vibrations, respectively. The signal at 1073 cm^{-1} is assigned to P–O stretching

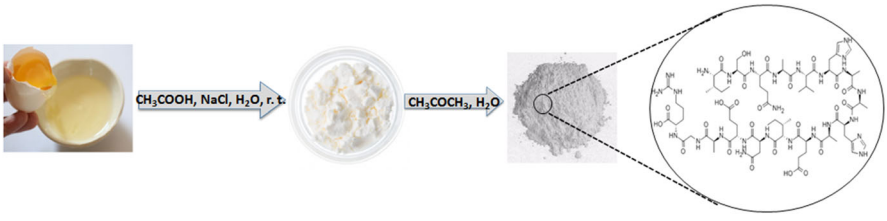


Fig. 1 Preparation of nano-ovalbumin

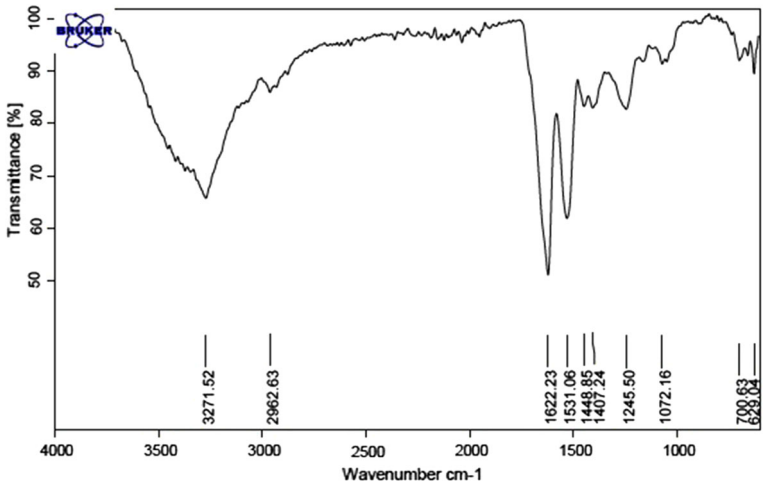


Fig. 2 FT-IR (ATR) spectra of nano-ovalbumin

vibration. Therefore, the FT-IR spectrum of obtained nano-ovalbumin is similar to the previously reported one [33].

The particles size of nano-ovalbumin was investigated by FESEM. This image indicates that the nanoparticle dimensions are approximately 60 nm on average (Fig. 3).

Figure 4 depicts the XRD pattern of nano-ovalbumin in a range of 10°–80°. A broad peak observed at 2θ = 20°–50° describes an amorphous structure for nano-ovalbumin, being in accordance with the previously reported pattern [34].

The purity and molecular weight of nano-ovalbumin were determined by MALDI-TOF/TOF tandem mass spectrometry through a single peak at 44.7 kDa (m/z) (Fig. 5), being in agreement with the literature [3].

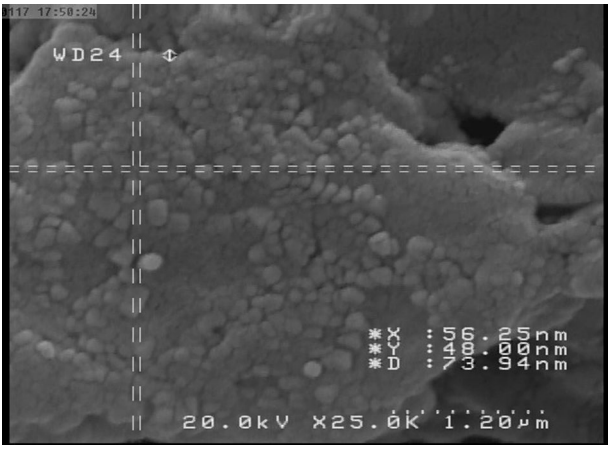


Fig. 3 FESEM image of nano-ovalbumin

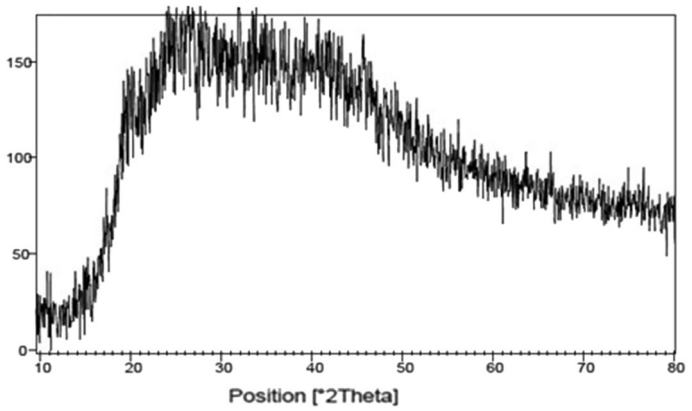


Fig. 4 XRD pattern of nano-ovalbumin

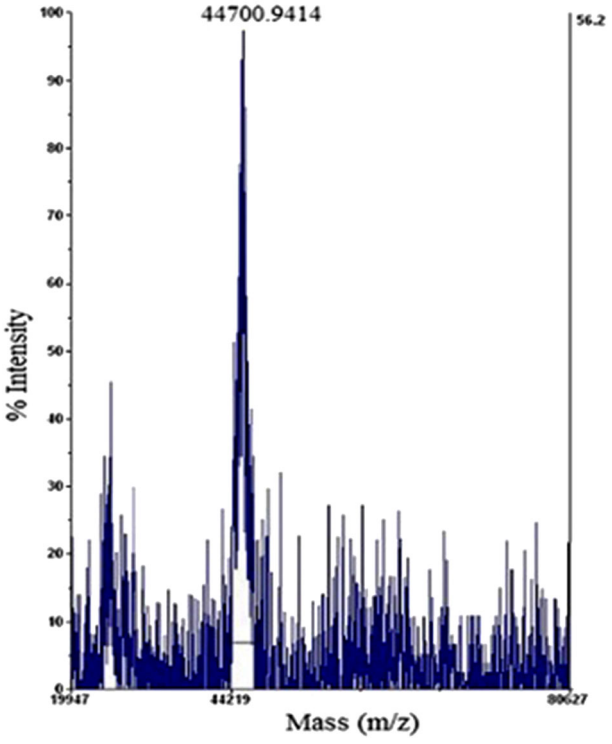


Fig. 5 MALDI-TOF/TOF mass spectrum of nano-ovalbumin (0.016 g of ovalbumin was dissolved in 0.5 mL of 7.0 M aqueous solution of guanidinium chloride)

Figure 6 presents the TGA results of ovalbumin in the temperature range of 45–817 °C. A slight weight loss was assigned to removal of moisture from the catalyst (endothermic effect at 50–110 °C, 1% weight loss). The main weight loss

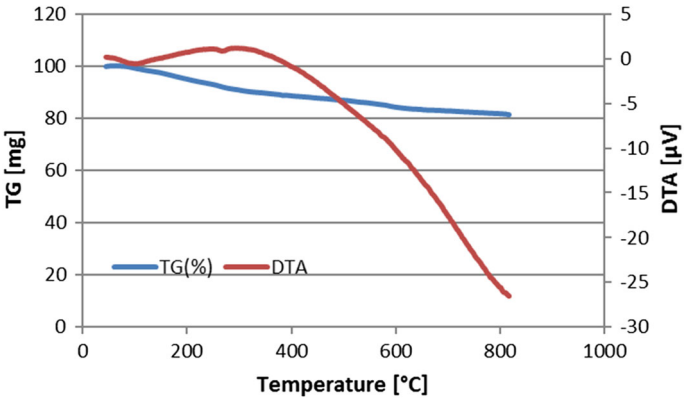


Fig. 6 Thermal gravimetric analysis (TGA/DTA) pattern of nano-ovalbumin

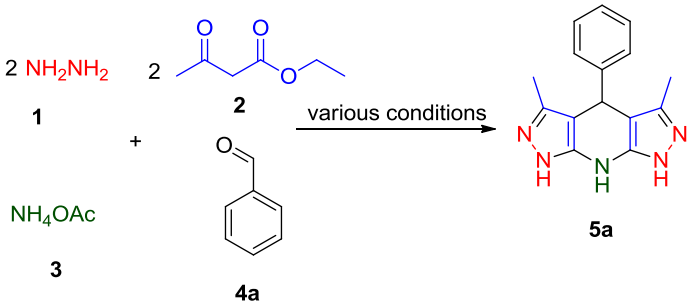
(19%) at the temperature range of 110–817 °C is due to protein degradation. The char yield of the catalyst at 817 °C is 81.44%. Therefore, it was found that nano-ovalbumin is appropriate to promote organic reactions at temperatures below 100 °C.

Following the successful characterization, the catalytic activity of nano-ovalbumin was investigated by synthesizing biologically active tetrahydrodipyrazolo pyridines. To optimize the reaction conditions, the effect of several parameters such as catalyst amount, temperature, time reaction and solvent was studied in the MCR between hydrazine hydrate, ethyl acetoacetate, benzaldehyde and ammonium acetate (Table 1). The reaction medium is one of the most important factors in biomimetic reactions owing to its effects on biocatalyst activity. Based on the solvent screening results, water showed an 85% yield after 1 h, whereas the other solvents such as EtOH, MeOH, CH_3CN, H_2O/EtOH and solvent-free conditions showed lower yields. The effect of the nano-ovalbumin amount on the reaction was then examined. It was observed that increasing the amount of the catalyst to 0.05 g caused the high yield of product (85%). Meanwhile, the higher used amounts of the catalyst did not increase the reaction yield. The reaction was also sensitive to temperature. In conclusion, the best condition of reaction was obtained using 0.05 g of nano-ovalbumin in water at 55 °C after 45 min (Table 1, entry 16).

To extend the scope of this biomethodology, we investigated various aldehydes containing either electron-withdrawing or electron-donating functional groups under optimal conditions. As the results in Table 2 show, all these reactions occurred smoothly affording high yields without forming any side products.

To evaluate the stability and level of biocatalyst reusability once the mentioned model reaction was completed, nano-ovalbumin was conveniently and efficiently recovered from the reaction mixture by filtration, washed with water, acetone and then DMF, dried and reused for subsequent reactions. It was observed that the recovered biocatalyst could be used at least four times without significant loss of activity (Fig. 7).

Table 1 Optimization of the reaction conditions for the synthesis of **5a**



Entry	Solvent	Conditions (°C)	Catalyst[a] (g)	Time (min)	Yield[b] (%)
1	H_2O	65	0.05	30	85
2	EtOH	65	0.05	30	58
3	H_2O-to-EtOH (1:1)	65	0.05	30	63
4	MeOH	65	0.05	30	56
5	CH_3CN	65	0.05	30	38
6	–	65	0.05	30	29
7	H_2O	65	–	30	18
8	H_2O	65	0.02	30	68
9	H_2O	65	0.03	30	75
10	H_2O	65	0.04	30	82
11	H_2O	65	0.06	30	84
12	H_2O	25	0.05	45	23
13	H_2O	35	0.05	45	48
14	H_2O	45	0.05	45	84
15	**H_2O**	**55**	**0.05**	**45**	**93**
16	H_2O	65	0.05	45	90

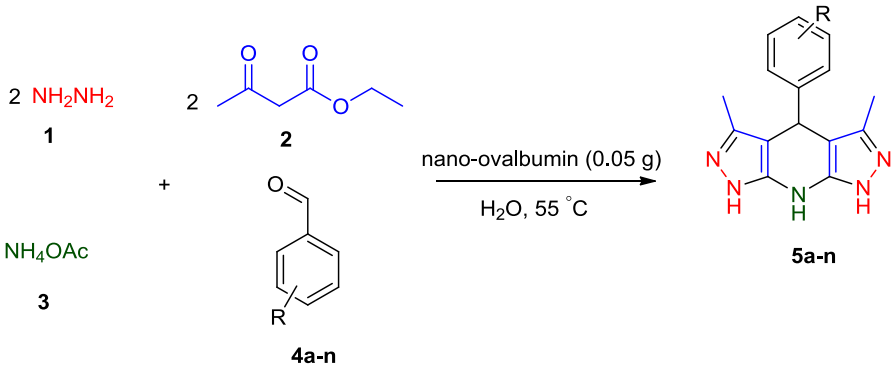
The molar ratio of hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), benzaldehyde (1 mmol) and ammonium acetate (4 mmol) is equal to 2:2:1:4

[a]Nano-ovalbumin

[b]Isolated yields

The study of literature on other albumins such as BSA and HSA revealed that the catalytic activity of albumins was due to acidic and basic properties of the side-chain amino and carboxylic acid groups in some amino acid residues such as Arg, Lys, His, Asp and Glu [38]. However, we measured the pH value of nano-ovalbumin solution in guanidinium chloride (7 M) at 3.75. Scheme 2 presents a proposed mechanism to synthesize tetrahydrodipyrazolo pyridine derivatives using nano-ovalbumin as a biocatalyst. Initially, hydrazine attacked the nano-ovalbumin-activated carbonyl group of ethyl acetoacetate. Subsequently, through removing one water molecule and intramolecular nucleophilic attack by another NH_2 group of hydrazine to the next carbonyl group of ethyl acetoacetate and loss of EtOH,

Table 2 Synthesis of tetrahydrodipyrazolo pyridine derivatives (**5a**–**n**) in the presence of nano-ovalbumin in water



Entry	R	Product	Time (min)	Yield[a] (%)	M.P. (°C)	Lit. M.P. (°C) [Ref.]
1	H	**5a**	45	93	244–246	240–242 [35]
2	2-Cl	**5b**	55	88	170–172	164–165 [36]
3	3-NO_2	**5c**	35	91	282–284	286–288 [35]
4	3-Br	**5d**	50	83	248–250	245–247 [37]
5	3-OH	**5e**	60	84	220–222	–
6	4-Me	**5f**	45	87	241–243	244–246 [35]
7	4-OH	**5g**	45	94	268–270	268–270 [35]
8	4-OMe	**5h**	50	86	188–190	185–187 [35]
9	4-NO_2	**5i**	30	95	288–290	> 300 °C [35]
10	4-F	**5j**	35	95	262–264	258–260 [35]
11	4-Cl	**5k**	35	94	256–258	254–256 [35]
12	3,4-$(OH)_2$	**5l**	50	94	208–210	–
13	3-OMe-4-OH	**5m**	40	95	258–260	262–264 [35]
14	3-OMe-2-OH	**5n**	45	92	240–242	–

Reaction conditions: hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), benzaldehyde (1 mmol) and ammonium acetate (4 mmol), water (3 mL) and nano-ovalbumin (0.05 g), 55 °C

[a]Isolated yields

pyrazolone A is prepared and converted to B via tautomerization. In the next step, the Knoevenagel condensation between activated aldehyde by nano-ovalbumin and B leads to the intermediate C which takes part in Michael reaction with the second pyrazolone ring to give intermediate D. Finally, nucleophilic attack of ammonia on intermediate D in the presence of nano-ovalbumin followed by intramolecular cyclization, and tautomerization gives the final product 5.

To indicate the capability of the present method and efficiency of our catalyst in comparison with the reported methods to prepare tetrahydrodipyrazolo pyridines, we compared our results with other methods in the literature for the model reaction (Table 3). This comparison clearly explains that our method can be one of the best ones from green chemistry and simplicity of protocol viewpoints.

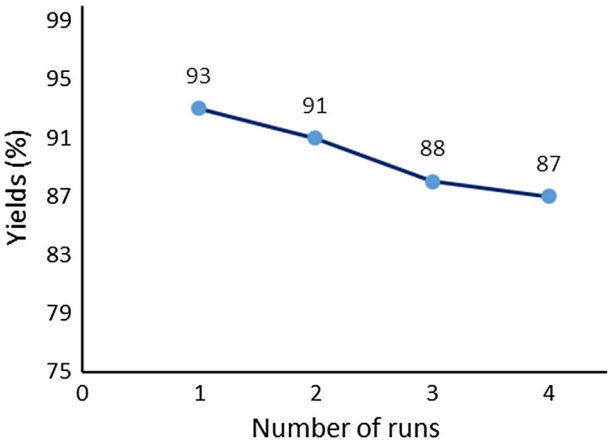
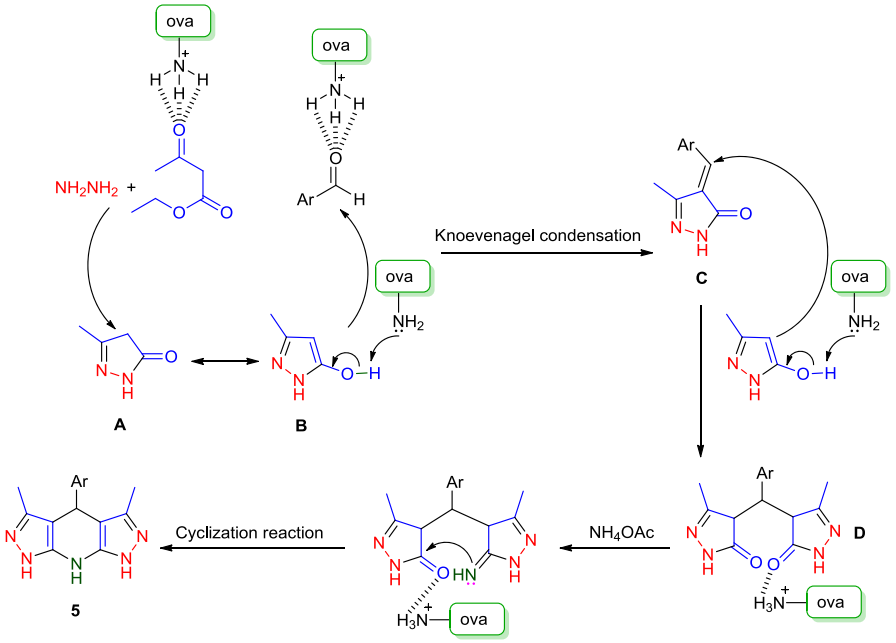


Fig. 7 Catalyst recycling experiments



Scheme 2 Plausible mechanism for synthesis of tetrahydrodipyrazolo pyridine derivatives in the presence of nano-ovalbumin

Conclusion

In summary, we have introduced an eco-friendly protocol to synthesize tetrahydrodipyrazolo pyridines using ovalbumin as an environmentally benign biocatalyst whose attractive features are as follows: (1) separation of large quantities of purified

Table 3 Catalytic performances of nano-ovalbumin versus other catalysts for synthesis of **5a**

Entry	Catalyst	Conditions	Time (min)/yield[a] (%) [Ref.]
1	Nano-$CuCr_2O_4$ (4 mol%)	EtOH/25 °C	50/90 [25]
2	Fe_3O_4/KCC1/IL/HPWMNPs (0.0001 mg)	H_2O/r.t.	30/96 [27]
3	Nano-$CdZr_4(PO_4)_6$ (0.6 mol%)	EtOH/reflux	43/88 [26]
4	$FeNi_3$-ILs MNPs (0.002 g)	EtOH/reflux	48/86 [28]
5	Nano-Fe_3O_4@SiO_2-SO_3H (0.004 g)	EtOH/MW	20/90 [29]
6	**Nano-ovalbumin (0.05 g)**	**H_2O/55 °C**	**45/93 [this work]**

[a]Isolated yields

nano-ovalbumin from egg white by a simple method, (2) the metal-free nature of biocatalyst, (3) reusability of the biocatalyst, (4) use of water as a green solvent, (5) mild reaction conditions and less pollution and (6) excellent yields and purities of products. Moreover, this is the first report of synthesizing biologically interesting tetrahydrodipyrazolo pyridines using a biocatalyst that could be a valuable synthetic alternative for such four-component reactions in biotechnological processes.

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