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Synergetic effects of naturally sourced metal oxides in organic synthesis: a greener approach for the synthesis of pyrano[2,3-c]pyrazoles and pyrazolyl-4*H*-chromenes

Sachin K. Shinde[1] · Megha U. Patil[1] · Shashikant A. Damate[1] · Suresh S. Patil[1]

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Abstract A clean and more economic protocol for the synthesis of pyrano[2,3-c]pyrazoles and pyrazolyl-4*H*-chromenes has been carried out using bael fruit ash (BFA) as a non-conventional natural catalyst in aqueous condition at ambient temperature. The catalyst was obtained from renewable resources by simple thermal treatment to dry rind of *Aegle marmelos* (Bael) fruit and formation of its active phase was confirmed by AAS, DSC-TGA, XRD, FT-IR, and SEM techniques. The BFA catalyst was found to be a green, highly active, easily biodegradable, and recyclable without loss of activity after the fifth run. The methodology provides an alternative platform to the conventional catalyzed process.

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✉ Suresh S. Patil
sanyujapatil@yahoo.com

[1] Synthetic Research Laboratory, PG Department of Chemistry, PDVP College, Affiliated to Shivaji University, Kolhapur, Tasgaon, Dist-Sangli, MS 416312, India

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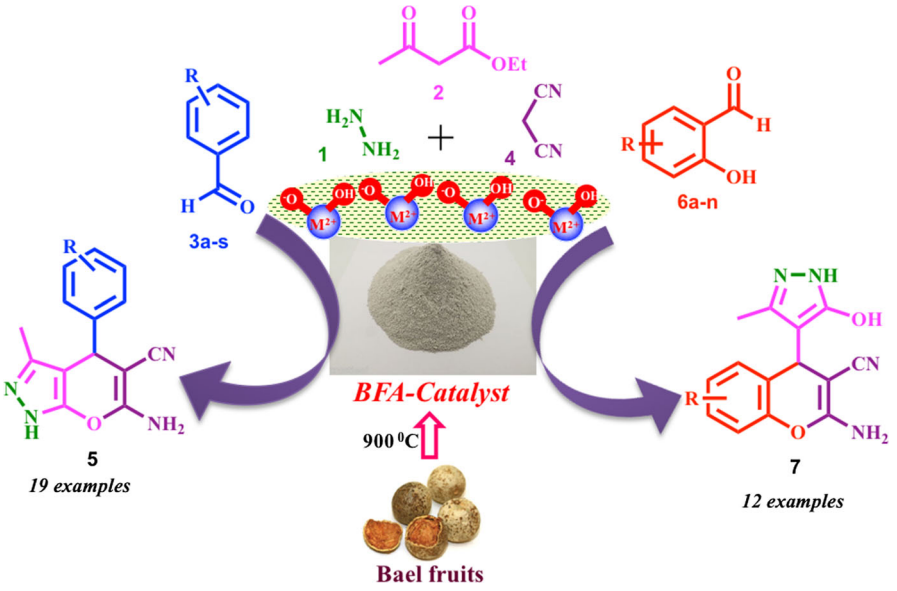
Graphical Abstract



Keywords Pyrano[2,3-c]pyrazoles · Pyrazolyl-4*H*-chromenes · Multi-component reactions · Natural catalyst · Aqueous medium · Green chemistry

Introduction

The development of green and efficient chemical processes or methodologies such as reaction in aqueous media, multi-component reactions (MCR) and reusable catalysts-performed reactions for the synthesis of biologically active compounds is one of the major challenges for chemists. These advantages comply with the principles of green chemistry in terms of simplicity and synthetic efficiency over conventional chemical reactions [1–3]. Functionalized pyrano[2,3-c]pyrazoles are an important class of N-heterocycles because the core fragment is constituted by a great variety of natural products and biologically active compounds. The synthesis of pyrano[2,3-c]pyrazole and their derivatives have attracted much attention from organic chemists due to their many pharmacological properties including anticancer [4], antimicrobial [5], anti-inflammatory [6], insecticidal, and molluscicidal activities [7], and are potential inhibitors of human Chk1 kinase [8].

A review of the literature revealed that Junek and Aigner first established the synthesis of pyrano[2,3-c]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine [9]. Wamhoff et al. [10] synthesized various 6-amino-5-cyano-4-aryl-4*H*-pyrazolo[3,4-b]pyrans by the reaction of arylidienemalononitrile with 3-methyl-pyrazoline-5-ones or by the condensation of 4-arylidienepyrazoline-5-one with malononitrile. Sharanin et al. [11] have

developed a three-component reaction between pyrazolone, an aldehyde and malononitrile in ethanol using triethylamine as the catalyst. Shestopalov et al. [12] reported the synthesis of pyranopyrazoles via three-component condensation of N-methylpiperidone, pyrazolin-5-one and malononitrile by a chemical as well as an electrochemical method. Peng et al. [13] have reported a flash synthesis of 4*H*-pyrano[2,3-c]pyrazoles in aqueous media under combined microwave and ultrasound irradiation. More recently, the highly functionalized pyrano[2,3-c]pyrazoles were reported using a variety of reagents, such as a piperidine [14], glycine [15], L-proline [16], imidazole [17], heteropolyacid [18], per-6-amino-β-cyclodextrin [19], nanosized magnesium oxide [20], ionic liquid (IL) [21], silica-bonded *n*-propylpiperazine sodium *n*-propionate [22], silica-bonded n-propyltriethylene-tetramine [23], silica-grafted *n*-propyl-imidazolium hydrogen sulfate [(Sipim)HSO_4] [24], silica-bonded *n*-propylimidazolium chloride [(Sipim)Cl] [25] and Mg/Al hydrotalcite [26], bovine serum albumin (BSA) [27], *Citrus limon* (lemon juice) [28], IL-[DMDBSI]2HSO_4 [29], and magnetized water [30].

Surprisingly, only one method has been reported for the synthesis of 4-pyrazolyl-4*H*-chromenes by a four-component reaction of hydrazine hydrate, ethyl acetoacetate, 2-hydroxybenzaldehyde and malononitrile in water [31]. This method is only compatible with salicylaldehydes. However, despite the potential utility of the methods published so far, they exhibit varying degrees of success as well as limitations such as harsh reaction conditions, cost of the catalyst, long reaction times, lack of catalyst recovery, and tedious reaction work-ups.

Performing organic reactions in water has attracted much attention over the past decades due to its numerous advantages such as being considerably safe, non-toxic, environmentally friendly, and cheap [32–34]. Nowadays, biosynthetic processes involving bio-based catalysts have received much attention as viable alternatives for the development of green protocols for organic transformations [35–39]. In this regard, naturally sourced catalysts as part of the chemical process offer excellent alternatives to chemically generated catalysts in being more environmentally friendly technologies due to their ease of biodegradability, ability to act as catalysts, low toxicity, and non-flammable properties. Again, due to their high natural abundance, their production is potentially less expensive.

Therefore, the aim of the present work is to explore the synthetic utility of naturally sourced catalysts in organic transformations. A plant, *Aegle marmelos* (Linn.) Correa ex Roxb, belongs to the family Rutaceae, is locally known as bael in India, and known from pre-historic timed [40]. The bael tree has its origin in the Eastern Ghats and Central India, and is also found in tropical and subtropical regions of the world. Every part of the bael tree such as the fruit, seed, bark, leaf and root has medicinal [41], therapeutic and traditionallimportance [42]. Physico-chemical studies have revealed that bael fruit is rich in mineral and vitamin contents [43, 44].

In view of the above, and as a part of our on-going research on the development of natural catalysts for organic transformations [45–48], to the best of our knowledge we report here for first time a naturally sourced, relatively mild, less expensive, non-toxic, non-corrosive, and bio-degradable catalyst (BFA) for one-pot four-component synthesis of pyrano[2,3-c]pyrazoles and 4-pyrazolyl-4*H*-chromenes

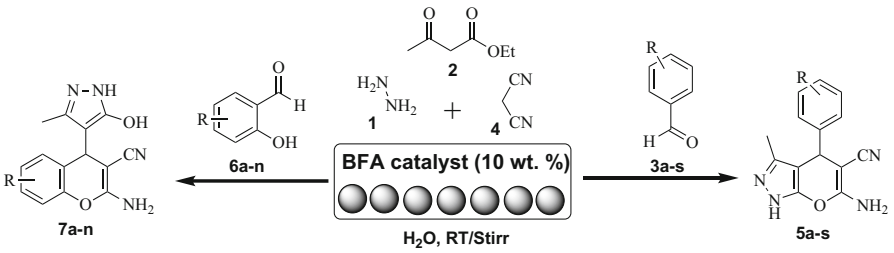
under aqueous conditions at ambient temperature (Scheme 1). A very simple protocol was followed in the reaction process. This strategy also provides a high yield and good recyclability of the catalyst.

Experimental

All chemicals were of reagent grade and procured from Sigma-Aldrich, and were used without any further purification. Analytical thin-layer chromatography (TLC) was carried out on precoated Merck silica gel 60 F_{254} aluminum plates. Melting points were recorded on a DBK programmable melting point apparatus and are uncorrected. IR spectra were obtained using potassium bromide pellets ona Bruker ALPHA FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds were recorded on a Bruker AC (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer using $CDCl_3$ and DMSO as solvent. Chemical shifts (δ) are expressed in parts per million (ppm) values with tetramethylsilane as the internal reference and coupling constants are expressed in hertz (Hz). Mass spectra were recorded on a Shimadzu QP2010 GCMS with an ion source temperature of 280 °C. The pH of aqueous solutions of BFA were measured using a pH meter (Pro-Lab 3000 laboratory pH meter). A SHIMADZU AA-7000 atomic absorption spectrophotometer (AAS) was used for elemental analysis by the flame emission method. Thermal gravimetric analysis (TGA) curves were obtained using a TA SDT Q600 V20.9 Build 20 instrument in the presence of static air at a linear heating rate of 10 °C min^{-1} from 25 to 1000 °C. XRD was taken using a Brucker D_2 Phaser. It was obtained in reflection mode with Cu Kα radiation (λ = 1.5418 Å) at 30 kV, 10 mA, a scan speed of 1.0 ° $min,^{-1}$ and a scan range of 10°–90°. The data was analyzed in the 2θ/° range from 2° to 70° with the scanning step of 0.5 per s. A JEOL (Tokyo, Japan) JSM-5200 scanning electron microscope was used for SEM analysis.

Synthesis of pyrano[2,3-c]pyrazoles (5)

In a 25-mL round-bottom flask, a mixture of hydrazine hydrate **1** (1 mmol), ethyl aceto acetate **2** (1 mmol), aldehydes **3a–s** (1 mmol) and, molanonitrile **4** (1 mmol)



Scheme 1 BFA-catalyzed synthesis of functionalized pyrano[2,3-c]pyrazoles and 4-pyrazolyl-4*H*-chromenes

was stirred at room temperature using the BFA catalyst 10 wt% in water (2 mL) for certain time periods as indicated in Table 2 (see "Results and discussion"). The reaction was monitored by TLC (ethyl acetate: hexane 1:9) and after elusion the Merck silica gel 60 F_{254} aluminium plates were visualized under UV light. After completion of the reaction, the reaction mixture was subjected to solvent extraction using ethyl acetate (4 × 10 mL). The combined organic phase was washed with water and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a crude product. The pure products were obtained in good yields by recrystallization from 96% ethyl alcohol without any use of further purification. The physical and spectroscopic data are consistent with the proposed structure and in harmony with the literature values [14–30]. Eight newly synthesized compounds were ascertained on the basis of FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques.

Synthesis of 4-pyrazolyl-4*H*-chromene (7)

In a 25-mL round-bottom flask, a mixture of hydrazine hydrate **1** (1 mmol), ethyl aceto acetate **2** (1 mmol), salicylaldehydes **6a–n** (1 mmol) and molanonitrile **4** (1 mmol) was stirred at room temperature using the BFA catalyst 10 wt% in water (2 mL) for certain time periods as indicated in Table 3 (see "Results and discussion"). The reaction was monitored by TLC (ethyl acetate: hexane 1:9) and after elusion the Merck silica gel 60 F_{254} aluminium plates were visualized under UV light. After completion of the reaction, the appropriate work-up from the method above was used.

Analytical and spectral data of unreported compounds

*6-Amino-4-[4-(diethoxymethyl)phenyl]-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5j**)*

Pale yellow solid; MP (°C): 284–286; IR (KBr): 3498, 3390, 3106, 2961, 2183, 1648, 1618, 1510, 1302, 1100, 758 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-*d6*) δ_H: 1.11 (t, 6H CH_3), 1.76 (s, 3H, CH_3) 3.50 (m, 4H, CH_2), 4.58 (s, 1H, CH), 5.43 (s, 1H, CH), 6.88 (s, 2H, NH_2), 7.14 (d, 2H, J = 7.5 Hz, Ar–H), 7.32 (d, 2H, J = 7.5 Hz, Ar–H), 12.10 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-*d6*) δ_C: 9.81, 15.20, 36.01, 57.08 60.88, 97.60, 100.97, 120.86, 126.63, 127.24, 128.37, 130.02, 135.68, 137.76, 144.42, 154.77, 160.93 ppm; MS/EI m/z: 354.1 (M^+).

*6-Amino-4-(3-ethoxy-4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5l**)*

Yellow solid; MP (°C): 192–194; IR (KBr): 3568, 3465, 3390, 3000, 2946, 2177, 1654, 1615, 1536, 1406, 1130 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-*d6*) δ_H: 0.96 (t, 3H, J = 6.5 Hz, CH_3) 1.94 (s, 3H, CH_3), 3.65 (q, 3H, J = 6.5 Hz, CH_2), 5.49 (s, 1H, CH), 6.62 (s, 2H, NH_2), 6.72 (d, 1H, J = 2.1 Hz, Ar–H), 6.88 (d, 1H,

$J = 8.2$ Hz, Ar–H), 7.16 (dd, 1H, $J = 8.2$, 2.1 Hz, Ar–H), 9.43 (bs, 1H, OH), 12.14 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-*d6*) δ_C: 9.90, 14.80, 29.64, 35.84, 57.71, 63.93, 97.97, 113.11, 115.57, 119.88,135.41, 145.58, 146.43, 154.80, 160.73, 169.71 ppm; MS/EI m/z: 312.1 (M^+).

*6-Amino-4-(3-bromo-4-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5n**)*

Brown solid; MP (°C): 224–226; IR (KBr): 3458, 3310, 3084, 2938, 2195, 1644, 1618, 1510, 1483, 1170 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-*d6*) δ_H:1.79 (s, 3H, CH_3), 4.67 (s, 1H, CH), 6.97 (s, 2H, NH_2), 7.21 (dd, 1H, $J = 8.5$ Hz, Ar–H), 7.32 (dd, 1H, $J = 8.5$, 2.3 Hz, Ar–H), 7.48 (d, 1H, $J = 2.3$ Hz, Ar–H), 12.17 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-*d6*) δ_C: 9.82, 35.15, 56.44, 97.01, 115.81, 117.68, 120.68, 128.95, 132.18, 135.89, 142.76, 155.49, 158.72, 161.03 ppm; MS/EI m/z: 348.0 (M^+).

*6-Amino-4-(2-bromo-5-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5q**)*

Yellow solid; MP (°C): 251–253; IR (KBr): 3464, 3326, 3104, 2942, 2184, 1654, 1608, 1505, 1443, 1158 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-*d6*) δ_H:1.77 (s, 3H, CH_3), 5.04 (s, 1H, CH), 7.02 (s, 2H, NH_2), 7.06 (d, 1H, $J = 2.1$ Hz, Ar–H), 7.11 (dd, 1H, $J = 8.2$, 2.1 Hz, Ar–H), 7.63 (d, 1H, $J = 8.2$ Hz, Ar–H), 12.28 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-*d6*) δ_C: 9.72, 36.27, 55.26, 96.37, 116.33, 117.55, 120.28, 134.56, 135.61, 144.99, 154.91, 160.15, 161.42, 163.40 ppm; MS/EI m/z: 348.0 (M^+).

*4,4′-(Thiophene-2,5-diyl)bis(6-amino-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) **14***

Brown solid; MP (°C): Above 310; IR (KBr): 3589, 3354, 3245, 2922, 2139, 1640, 1558, 1503, 1289, 973 cm^{-1}. ^{1}H NMR (300 MHz, excess DMSO-*d6*) δ_H: 1.72 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 4.55 (s, 1H, CH), 4.57 (s, 1H, CH), 6.85 (s, 1H, Ar–H), 6.96 (s, 1H, Ar–H), 7.09 (s, 4H, NH_2), 12.11 (s, 2H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-*d6*) δ_C: 9.73(2C), 11.01(2C), 35.96(2C), 57.14(2C), 97.77(2C), 120.86(2C), 126.70(2C), 126.69(2C), 135.65(2C), 142.80(2C), 154.72(2C), 160.90(2C) ppm; MS/EI m/z: 432.1 (M^+).

*2-Amino-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-8-methoxy-4H-chromene-3-carbonitrile (**7h**)*

White solid; MP (°C): IR (KBr): 3422, 3365, 2919, 2198, 1665, 1611, 1525, 1402, 1332, 1250 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d6*) δ_H: 1.94 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.58 (s, 1H, CH), 6.68 (s, 2H, NH_2), 6.94 (d, 1H, $J = 3.6$ Hz, Ar–H), 7.13 (dd, 1H,$J = 8$, 0.8 Hz, Ar–H), 7.28 (t, 1H,$J = 8$ Hz Ar–H), 10.11 (br s, 1H, NH), 10.88 (br s, 1H, OH)ppm; ^{13}C NMR (75 MHz, DMSO-*d6*) δ_C: 162.84, 160.10,

146.74, 137.91, 136.52, 124.34, 123.95, 120.11, 118.37, 110.11, 105.02, 55.92, 54.95, 28.83, 9.94 ppm; MS/EI m/z: 299.11 (M^+).

*2-Amino-8-bromo-6-chloro-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromene-3-carbonitrile (**7m**)*

White solid; MP (°C): 244–246; IR (KBr): 3455, 3333, 2917, 2190, 1658, 1609, 1520, 1412, 1402, 825 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d6*) δ_H: 2.04 (s, 3H, CH_3), 4.65 (s, 1H, NH_2), 6.90 (s, 2H), 7.00 (s, 1H Ar–H), 7.61 (s, 1H, Ar–H), 9.78 (br s, 1H, NH), 11. 31 (bs, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-*d6*) δ_C: 159.51, 159.14, 144.68, 136.67, 130.41, 128.00, 127.91, 127.15, 120.22, 109.98, 104.33, 55.17, 29.43, 9.84 ppm; MS/EI m/z: 379.97 (M^+).

*3-Amino-1-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-1H-benzo[f]chromene-2-carbonitrile (**7n**)*

White solid, MP (°C): 232–234; IR (KBr): 3441, 3294, 3169, 2182, 1661, 1584, 1405, 1224, 1085, 807 cm^{-1}; ^1H NMR (300 MHz, DMSO-*d6*) δ_H: 1.87 (s, 3H CH_3), 5.05 (s, 1H, CH), 6.75 (s, 2H, NH_2), 7.21 (d, 1H, $J = 8.8$ Hz), 7.49–7.38 (m, 2H, Ar–H),7.88 (d, 1H, $J = 7.6$ Hz, Ar–H), 7.92 (d, 1H, $J = 8.4$ Hz, Ar–H), 10.01 (br s, 1H, NH), 11.27 (br s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-*d6*) δ_C: 159.65, 158.2, 146.44, 130.68, 130.53, 128.80, 128.45, 126.88, 124.75, 123.38, 120.96, 116.57, 115.17, 105.29, 56.40, 26.73, 9.71 ppm; MS/EI m/z: 319.11 (M^+).

Results and discussion

Preparation and characterization of the catalyst

Collected dry fruits of *Aegle marmelos* (Fig. 1a) were authenticated by the Department of Botany. The rind of the dried fruits were (5.0 g) manually broken into small pieces (Fig. 1b) and used for ashing. In each case, the small pieces of the fruits were taken in a cleaned silica crucible and burned in open air, which resulted in fine soft ash (3.2 g). This ash was named as the BFA catalyst (Fig. 1c). The alkalinity of BFA in water was measured and was found to be strongly alkaline with pH 12.8.

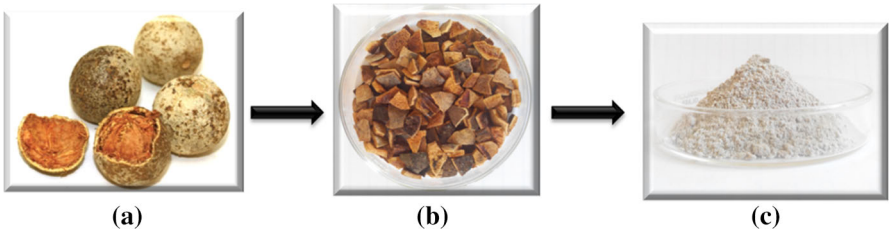


Fig. 1 **a** Dry bael fruit, **b** pieces of bael fruit, **c** ash of bael fruit (BFA catalyst)

AAS is a very common and reliable technique for detecting metals and metalloids in environmental samples. Therefore, the presence of elements in BFA was determined by flame AAS using a hot filtration test. Results shows that BFA contains major content of K (30.5%) along with Ca (13.9%), Mg (2.82%)), Na (2%), P (2.4%), S (0.41%)), Cl (0.08)), B (0.09%), with small amounts of transition metals like Mn (0.042%), Fe (0.345%), Cu (0.012%), and Zn (0.05%).

Thermal stability of the prepared catalyst was investigated by using a DSC-TGA thermal analyser. The TGA result (Fig. 2) shows the temperatures at which the BFA decomposed when heated in a controlled environment to avoid any misleading oxidation reactions at a given temperature rate. The temperature ranged from 0 to 1000 °C depicting the decomposition of ash. Three distinct stages of weight loss were observed. In the first step, minor weight loss at temperatures below 89.90 °C was 2.246% occurred due to the loss of adsorbed moisture. Another weight loss occurred in the second step between 89.90 and 278.56 °C and was 8.188%, reflecting the decomposition of organic compounds such as carotenoids, alkaloids, pectins, tannins, flavonoids, terpenoids and chlorides. In the third step, the 9.187% weight loss between temperature range of 626.61–746.66 °C was due to the decomposition of metal carbonates. Finally, 65.957% weight of residue remaining after the temperature of 985.05 °C was due to metal oxides and silica.

The phase composition of the BFA catalyst is evident from X-ray diffraction analysis (Fig. 3). The XRD patterns of PBF displayed very broad peaks at $2\theta = 11.08°$, 14.10°, 16.00°, 17.09°, 17.70°, 19.43°, and 20.56° suggesting the

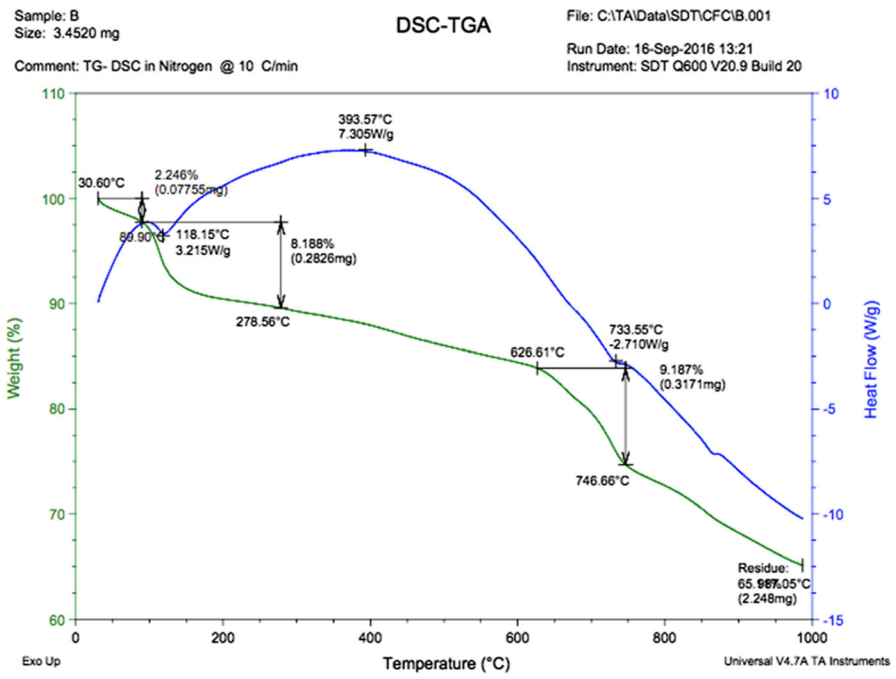


Fig. 2 DSC-TGA curves of the BFA catalyst

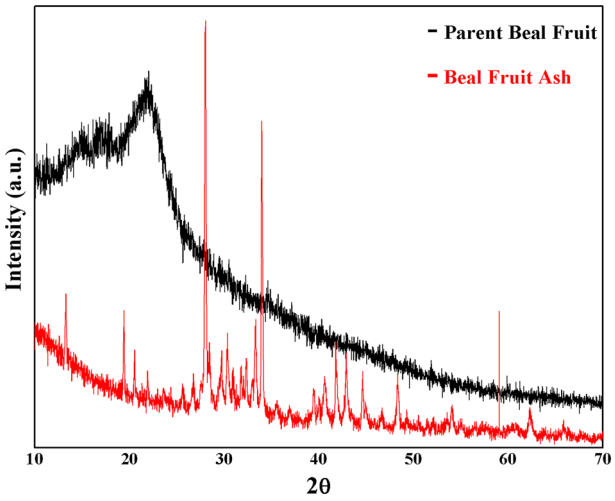


Fig. 3 X-ray diffraction patterns of parent beal fruit (**a**) and BFA catalyst (**b**)

amorphous nature of these materials. After the thermal treatment, the peaks at $2\theta = 28.05°$, $28.46°$, $29.78°$, $40.62°$, $44.65°$, $48.38°$, $59.08°$ and $65.89°$ corresponded to the characteristic patterns of the metal carbonates. The peaks appearing at $2\theta = 32.34°$, $33.37°$, $33.99°$,$41.80°$, $42.92°$, $53.57°$, $62.32°$ were characteristic of metal oxides. Metal hydroxides was also observed at $2\theta = 13.31°$, $19.43°$, $20.56°$ and $21.94°$. Therefore, this active phase of the catalyst was utilized for the conversion of the reactant into the product.

In the FT-IR spectrum of BFA (Fig. 4), the observation of absorption bands at 698, 870, 1458, 2516 cm^{-1} are the characteristic peaks of carbonates, and the weak absorption that occurred around 1795 cm^{-1} corresponds to C=O from carbonate. Also the observation of a weak stretching broad band at 3155 cm^{-1} due to the small

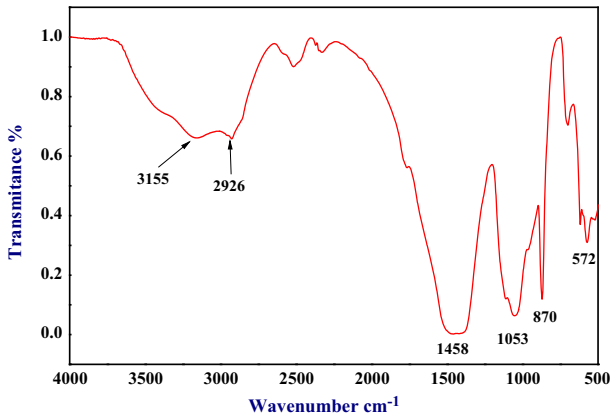


Fig. 4 FT-IR spectra of Bthe FA catalyst

concentration of the OH group in the spectrum of BFA supports the formation of metal hydroxides due to the absorption of moisture from the environment.

The shape and surface morphology of the BFA catalyst was studied by scanning electron microscopy (SEM). Figure 5 clearly shows that the SEM images of the BFA catalyst illustrate the porous nature of the prepared catalyst which provides a smooth and soft surface area for catalyzing the reaction.

Catalytic performance

The catalyst is sourced from the thermal treatment of the rind of dry bael fruit, which is a tree of Indian origin and known from pre-historic timexs. At the outset of the protocol, our goal was to identify the catalytic activity of the BFA catalyst for the synthesis pyrano[2,3-c]pyrazole derivatives, and we defined the following criteria: a green solvent system, a low catalyst loading, relatively low reaction temperature, and good reaction yield in a short reaction time. With these goals in mind, the reaction conditions were optimized using hydrazine hydrate **1** (1 mmol), ethyl acetoacetate **2** (1 mmol), 4-chlorobenzaldehyde **3b** (1 mmol), and malononitrile **4** (1 mmol) as model reactants reacting under different amounts of catalyst and solvents at ambient temperature. The observed results are summarized in Table 1. At first, the model reaction was examined under solvent-free conditions and in water (2 mL) without any catalyst. It was found that the desired product, **5b**, was not observed on the TLC plate even after 2 h of stirring (Table 1, entries 6–7). As the reaction requires a catalyst, the model reaction was performed using the BFA catalyst by varying the catalytic amounts (2, 5, 10, 15, and 20 wt%) in water (2 mL) and under solvent-free conditions. It was found that when increasing the amount of the catalyst from 2 to 5 and 10 wt% in water, the yield also increased (Table 1, entries 1–3). A further increase in the catalyst amount (above 10 wt%) surprisingly reduced the yield (Table 1, entries 4–5), when the reaction was performed in 2 mL

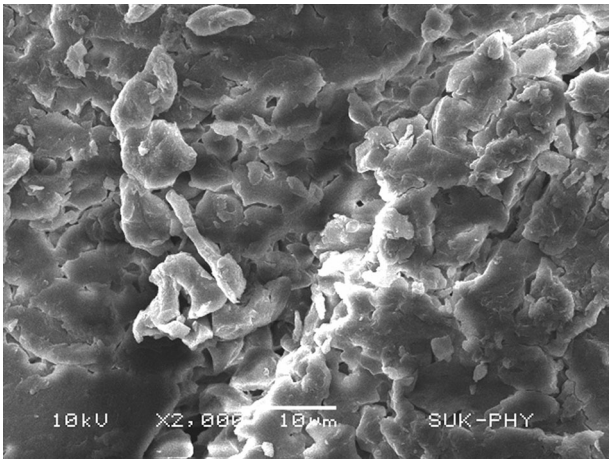


Fig. 5 SEM images of the BFA catalyst

Table 1 Optimization of reaction conditions on the reaction of **1**, **2**, **3b** and **4**[a]

Entry	Catalyst (wt%)	Solvent (2 mL)	Time (min)	Yield (%)[b]
1	BFA (2)	Water	120	42
2	BFA (5)	Water	120	70
3	BFA (10)	Water	10	93
4	BFA (15)	Water	30	90
5	BFA (20)	Water	30	86
6	–	–	120	Nr[c]
7	–	Water	120	Nr[c]
8	BFA (10)	EtOH	30	82
9	BFA (10)	CH_3CN	30	54
10	BFA (10)	CH_2Cl_2	60	48
11	BFA (10)	Toluene	60	30

[a]Reaction conditions: hydrazine hydrate **1** (1 mmol), ethyl acetoacetate **2** (1 mmol), 4-chlorobenzaldehydes **3b** (1 mmol), malononitrile **4** (1 mmol), catalyst (wt%), and solvent (2 mL) at room temperature

[b]Isolated yield

[c]No reaction

water. Therefore, 10 wt% of BFA catalyst in 2 mL water is sufficient to remarkably enhance the reactivity of the reactants (1 mmol each), and the corresponding product **5b** was obtained in 93% yield within 10 min (Table 1, entry 3).

We immediately undertook a study to examine the effect of thermal treatment on the activity of the catalyst: a dried PBF powder was tested for the model reaction, and the reaction did not proceed even at a prolonged reaction time in water and solvent-free conditions (Table 1, entry 7). Optimization was carried out with variation of the reaction medium. The preceding reaction was also examined in different conventional organic solvents like EtOH, CH_3CN, CH_2Cl_2, and toluene and afforded low to moderate yields (Table 1, entries 8–11). Thus, the best yield, cleanest reaction, and most facile work-up was achieved employing 10 wt% of BFA in water (2 mL) at room temperature.

Therefore, to compare the catalytic activity of the BFA catalyst, the model reaction was performed under optimized reaction conditions in the presence of analytical grade alkali metal carbonates and metal oxides (Table 2, entries 1–8). The result shows only trace amounts of the product were observed on TLC after 2 h. (Table 1, entries 1 and 7), indicating that a synergetic effect of all alkali metal carbonates and oxides along with transition metals (Mn, Fe, Cu and Zn ions) in BFA provides a better catalytic activity for this transformation (Table 2, entry 8).

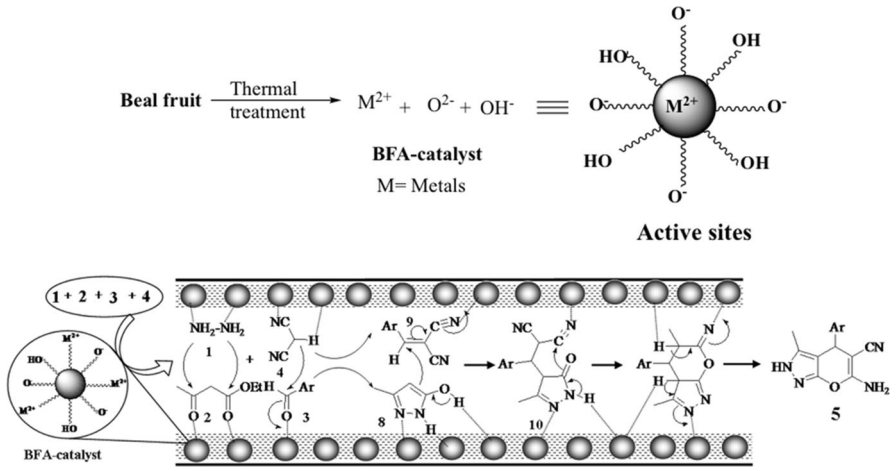
The dramatic acceleration of this reaction by the catalytic activity of BFA is currently not well understood. Although we did not investigate the reaction mechanism, a probable mechanistic rationale portraying the sequence of events for this condensation reaction over BFA catalyst system is schematically shown by a conceptual picture (Scheme 2). The BFA catalyst containing the mixture of metal carbonates and oxides is soluble to some extent in water which was confirmed by

Table 2 Comparison of catalytic efficiency of alkali metal carbonates and oxides with BFA on the reaction of **1**, **2**, **3b** and **4**[a]

Entry	Catalyst	Time (min)	Yield (%)[b]
1	K_2CO_3	120	58
2	Na_2CO_3	120	54
3	$CaCO_3$	120	42
4	$MgCO_3$	120	48
5	CaO	120	64
6	MgO	120	62
7	ZnO	120	60
8	BFA	10	93

[a]Reaction conditions: hydrazine hydrate **1** (1 mmol), ethyl acetoacetate **2** (1 mmol), 4-chlorobenzaldehydes **3b** (1 mmol), malononitrile **4** (1 mmol), catalyst (10 wt%), and water (2 mL) at room temperature

[b]Isolated yield



Scheme 2 Conceptual picture of pyrano[2,3-c]pyrazoles formation

conducting a hot filtration test, and detectable metals by dissolution were analyzed by AAS. The report reveals very high oxide contents of K, Ca, Mg, and Na with small amounts of Mn, Fe, Cu and Zn. The dissolution reaction of metal oxides having active M^{2+}, oxide and hydroxides provides a number of Lewis basic sites (O^{2-} and OH) along with Lewis acid sites (M^{2+}) for the activation of reactants to forward the reactions in the proper direction. In this reaction, the first is the formation of pyrazolone **8** intermediate by reaction between **1** and **2**, and arylidenemalononitriles **9** by the Knoevenagel condensation between **3** and **4** on the active sites of the catalytic surface. Intermediates **8** and **9** undergo subsequent Michael addition to afford **10** which on intramolecular cyclization yields the targeted pyrano[2,3-c]pyrazoles **5**.

Next, we investigated the 100% reusability of the BFA catalyst. The reusability of a catalyst is an important benefit for the scale-up the practical and industrial applications. After complication of the reaction **5b**, the product was extracted with ethyl acetate from the reaction mixture. After extraction, it comes in the aqueous phase and isolates the product from the reaction mass. The remaining aqueous suspension was regenerated as the catalyst by concentring the excess of water. The recovered catalyst was tested for its activity in further subsequent runs. The results obtained in our experiment confirmed that the BFA catalyst could be reused for up to five run cycles with only negligible loss of activity (Fig. 6).

Under the preceding optimized conditions, the scope and limitations of this new MCR protocol were next investigated using a variety of structurally different aromatic aldehydes **3a**–**s**, and the results are summarized in Table 3. Gratifyingly, we found that the BFA-catalyzed four-component reaction worked well for a wide range of aromatic aldehydes carrying electron-donating and electron-withdrawing substituents on the aromatic aldehydes and providex easy access to pyrano[2,3-c]pyrazoles **5a**–**s** in good to excellent yields. Notably, the reactions were clean and all the products were easily extracted with ethyl acetate.

Next, the scope of this four-component reaction was achieved through a pseudo-eight-component reaction with two equivalents of each of the building blocks, i.e., hydrazine hydrate **1**, ethylacetoacetate **2**, molanonitrile **4** and one equivalent of dialdehyde such as terephthalaldehyde **11** and thiophene-2,5-dicarbaldehyde **12** in the presence of 30 wt% BFA in water (2 mL) affording the sterically hindered product4,4′-(1,4-phenylene)bis(6-amino-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) **13** and 4,4′-(thiophene-2,5-diyl)bis(6-amino-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) **14** with up to 90% yield in 25 min (Scheme 3). This reaction can be considered as two four-component reactions occurring simultaneously. The reaction could not be controlled at the level of a single four-component reaction. This new protocol clearly demonstrates that BFA is an excellent catalyst for this one-pot pseudo-eight-component reaction in water.

A few derivatives of 4-pyrazolyl-4*H*-chromenes **7** have been reported in just one publication [31]. Therefore, there is an urgent need to increase the scope of the

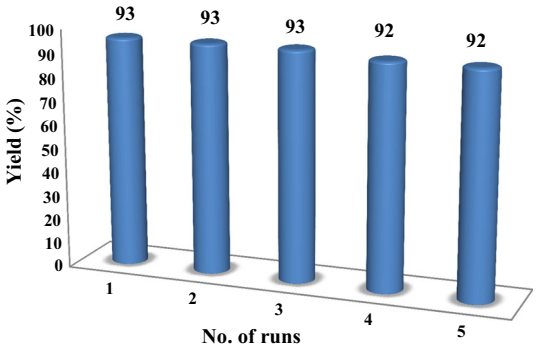


Fig. 6 Recyclability of the catalyst

Table 3 Synthesis of pyrano[2,3-c]pyrazoles **5a–s** using BFA-catalyst[a]

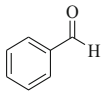
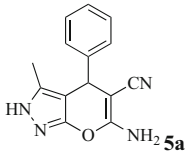
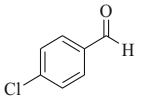
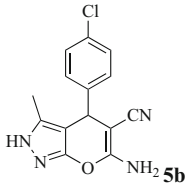
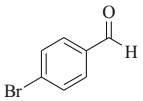
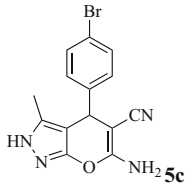
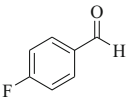
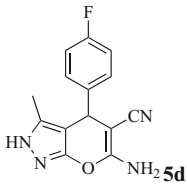
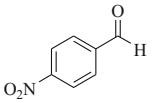
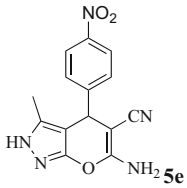
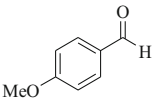
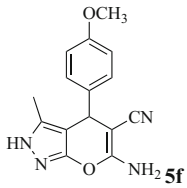
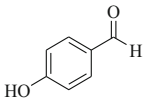
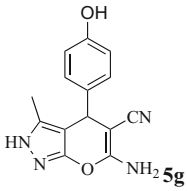
Entry	Aldehydes **(3)**	Product **(5)**	Time (min)	Yield (%)[b]	Mp. (^{0}C) (Lit.) [Ref.]
1	 **3a**	 **5a**	15	92	244–245 (245–246) [13]
2	 **3b**	 **5b**	5	93	234–236 (234–235) [13]
3	 **3c**	 **5c**	10	92	180–182 (180–183) [19]
4	 **3d**	 **5d**	12	90	168–170 (170–171) [19]
5	 **3e**	 **5e**	8	94	262–254 (251–252) [19]
6	 **3f**	 **5f**	10	92	210–212 (212–213) [19]
7	 **3g**	 **5g**	15	88	224–226 (223–224) [19]

Table 3 continued

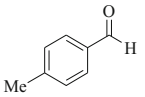
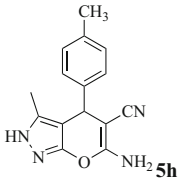
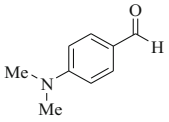
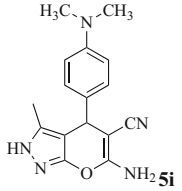
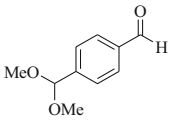
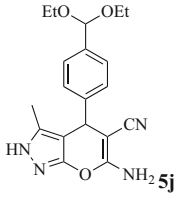
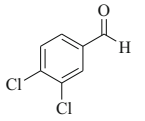
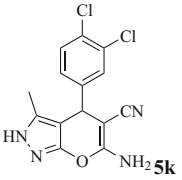
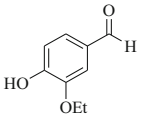
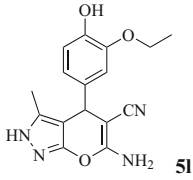
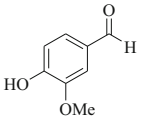
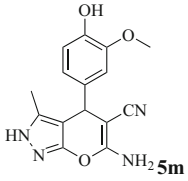
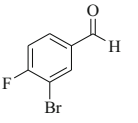
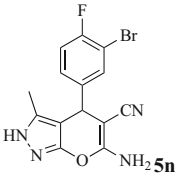
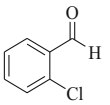
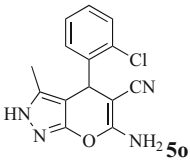
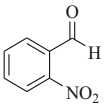
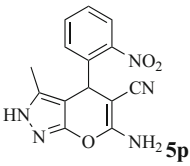
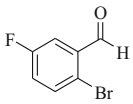
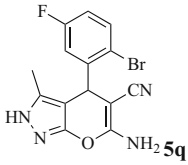
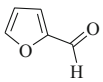
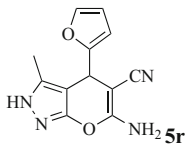
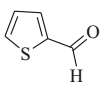
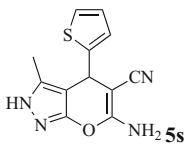
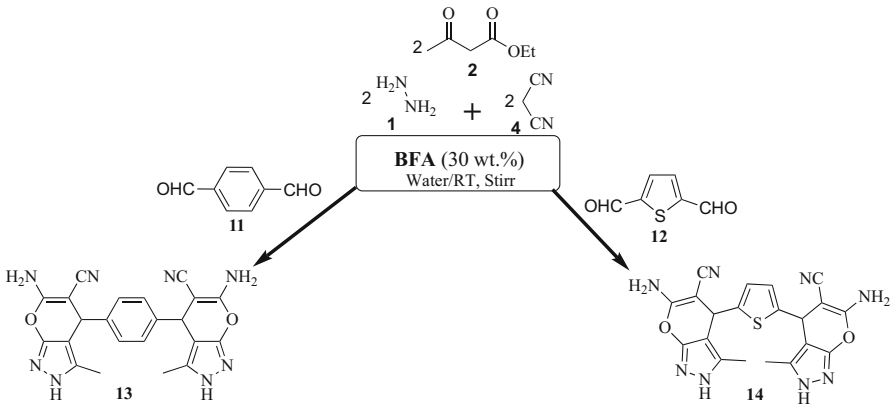
Entry	Aldehydes **(3)**	Product **(5)**	Time (min)	Yield (%)[b]	Mp. (^{0}C) (Lit.) [Ref.]
8	 **3h**	 **5h**	20	90	174–176 (175–176) [19]
9	 **3i**	 **5i**	30	86	162–164 (162–165) [19]
10	 **3j**	 **5j**	20	90	284–286 [New]
11	 **3k**	 **5k**	14	94	154–156 (156–158) [19]
12	 **3l**	 **5l**	10	92	192–194 [New]
13	 **3m**	 **5m**	10	92	232–234 (233–235) [13]
14	 **3n**	 **5n**	12	92	224–226 [New]

Table 3 continued

Entry	Aldehydes **(3)**	Product **(5)**	Time (min)	Yield (%)[b]	Mp. (^{0}C) (Lit.) [Ref.]
15	 **3o**	 **5o**	8	94	246–248 (245–246) [13]
16	 **3p**	 **5p**	10	92	220–222 (220–223) [16]
17	 **3q**	 **5q**	10	94	251–253 [New]
18	 **3r**	 **5r**	25	86	174–176 (175–177) [19]
19	 **3s**	 **5s**	30	90	190–192 (190–191) [19]

[a]Reaction conditions: hydrazine hydrate **1** (1 mmol); ethyl acetoacetate **2** (1 mmol); 2-hydroxyaldehydes **6a–s** (1 mmol); malononitrile **4** (1 mmol); BFA (10 wt%); water (2 mL); room temperature

[b]Isolated yield



Scheme 3 One-pot pseudo-eight-component reaction in water

substrate. To recognize the efficiency and scope of the proposed method for the synthesis 4-pyrazolyl-4*H*-chromenes **7** via one-pot, four MCRs of hydrazine hydrate **1**, ethyl acetoacetate **2**, and malononitrile **4** was reacted with salicylaldehydes **6** in the presence of 10 wt5% BFA catalyst in water at ambient temperature. The results are incorporated in Table 4, which indicate that various aromatic aldehydes possessing electron-donating as well as electron-withdrawing substituent on their aromatic rings afforded the desired 4-pyrazolyl-4*H*-chromenes **7** in higher yields within short reaction times.

Compares the efficiency of our method for the synthesis of pyrano[2,3-c]pyrazoles with other reported works (Table 5). Each of these methods has its own advantages, but some of them suffer from disadvantages such as very poor yield, long reaction time, use of organic solvents and the employment of expensive catalysts, none from natural sources. So the present method furnishes a naturally sourced catalyst, a green reaction medium, with a shorter reaction time, while a small quantity of this inexpensive and readily available catalyst is sufficient to obtain good yieldx of the expected product.

Conclusion

In the present research, we have developed a green, highly efficient and eco-friendly protocol for one-pot four-component synthesis of pyrano[2,3-c]pyrazoles and 4-pyrazolyl-4*H*-chromenes using BFA as a non-conventional catalyst under aqueous medium at ambient temperature. The advantages of the reported method the use of

Table 4 Synthesis of 4-pyrazolyl-4*H*-chromenes **7** (**a**–**n**) using BFA-catalyst[a]

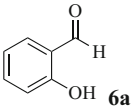
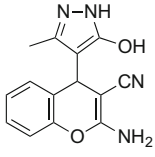
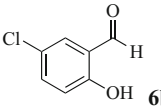
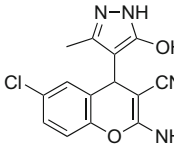
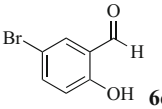
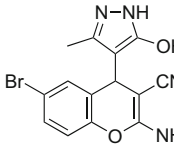
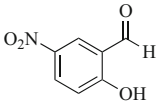
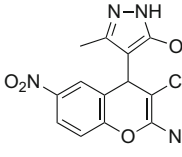
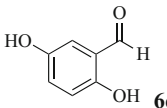
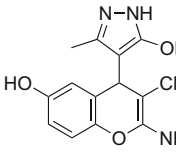
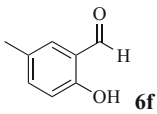
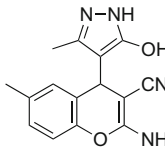
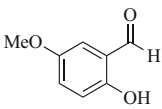
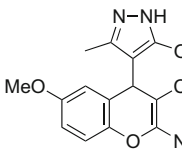
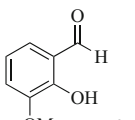
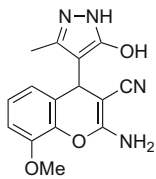
Entry	Salicyaldehydes **(6)**	Product **(7)**	Time (min)	Yield (%)[b]
1	 **6a**	 **7a**	15	86
2	 **6b**	 **7b**	5	94
3	 **6c**	 **7c**	5	90
4	 **6d**	 **7d**	5	92
5	 **6e**	 **7e**	10	92
6	 **6f**	 **7f**	15	90
7	 **6g**	 **7g**	10	92
8	 **6h**	 **7h**	5	90

Table 4 continued

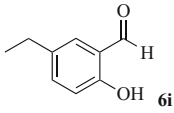
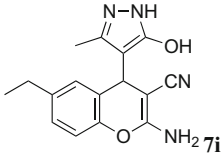
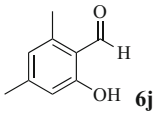
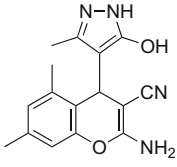
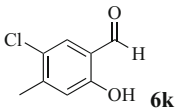
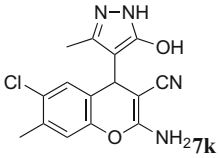
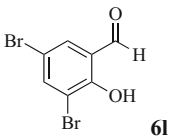
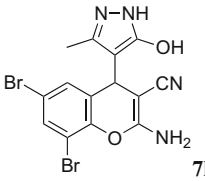
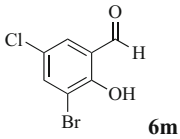
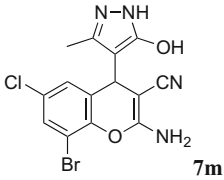
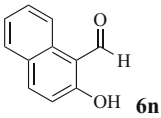
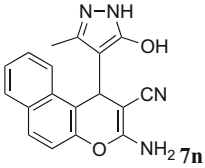
Entry	Salicyaldehydes **(6)**	Product **(7)**	Time (min)	Yield (%)[b]
9	 **6i**	 **7i**	15	84
10	 **6j**	 **7j**	10	86
11	 **6k**	 **7k**	15	90
12	 **6l**	 **7l**	10	92
13	 **6m**	 **7m**	10	94
14	 **6n**	 **7n**	15	90

Table 5 Screening of some reported catalysts with the present protocol for the synthesis of **4b**

Entry	Catalyst	Reaction condition	Time (min)	Yield (%)	References
1	Piperidine (5 mol%)	Water, r.t.	5–10	89	[14]
2	Glycine (2 mol%)	Water, r.t.	5–20	89	[15]
3	L-proline (10 mol%)	Water, reflux	10	94	[16]
4	Imidazole (50 mol%)	Water, 80 °C	20	90	[17]
5	Per-6-ABCD (0.8 mol%)	Solvent-free, r.t.	01	> 99	[19]
6	Nano MgO (50 mg)	Acetonitrile, r.t.	05	97	[20]
7	Ionic liquid (25 mol%)	Solvent-free, r.t.	30	85	[21]
8	Mg/Al hydrotalcite (0.1 g)	Ethanol, r.t.	240	86	[26]
9	BSA (60 mg)	Water–ethanol (7:3), r.t.	120	88	[27]
10	Lemon Juice (1 mL)	Water–ethanol (9:1), 90 °C	45	94	[28]
11	[DMDBSI]·$2HSO_4$ (10%)	Water, 60 °C	12	90	[29]
12	Magnetized water (4 mL)	25 °C	20	92	[30]
13	BFA (10 wt%)	Water, r.t.	5	93	This work

na atural catalyst obtained from renewable resources having a high catalytic activity in water, short reaction time, excellent yields, and simple work-up, and an easy separation of products. Utilization of a natural material as a source of a catalyst not only provides an opportunity to catalyze organic reactions but also addx value to the waste generated. Thus, this catalyst is a better and more practical alternative for green processes.

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