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Water extract of pomegranate ash (WEPA) catalyzed, green and efficient, one-pot multicomponent synthesis of 5-aminopyrazole-4-carbonitrile

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In this work, we have described one pot multicomponent synthetic approach for 5-aminopyrazole-4-carbonitrile synthesis by using WEPA (Water Extract of Pomegranate Ash) as an organo catalyst. A series of substituted derivatives of product have been synthesized using this easy and efficient catalyst as a green organic solvent. The reaction involves condensation of malononitrile, benzaldehyde and phenylhydrazine generating one-pot pyrazole product. The synthetic route of this work involves green solvent and less hazardous reactions. The advantages of this protocol are short reaction periods, high yield of products, safe and easy procedures and operational simplicity.

Keywords: Pyrazole, WEPA (Water extract of pomegranate ash), Green organic solvent, Knoevenagel condensation, Green chemistry

In the epoch of organic chemistry several methods had been derived for organic synthesis, out of this Multicomponent Reactions (MCR) are universally accepted for the organic reactions. Multicomponent reactions (MCR's) plays significant role in synthetic organic chemistry in which condensation of three or more components in a single step, producing final product with maximum yield and no any by-product[1]. MCR's have many significant advantages such as their time ability and reaction step economy due to the simultaneous formation of two or more bond resulting overall in a better chemical yield than a corresponding multistep synthesis[2]. Pyrazoles are five-membered heterocycles that constitute a class of compound particularly useful in organic synthesis the molecular formula $C_3H_4N_2$[3]. Nowadays, pyrazole derivatives, as biomolecules, have attracted more attention due to their interesting pharmacological properties[4].This substituted pyrazole shows numerous applications and variety of biological activities in drug and medicinal chemistry. Among the useful properties of pyrazoles such as, antimalarial[5], angiotensin converting enzyme[6], antifungal[7], estrogen receptive[8], antioxidant[9], antidiabetic[10], and anticancer[11]. Lonazolac (anti-inflammatory) and Fezolamine (Anti-depressant) are the drug molecules having Pyrazole system[12] (Fig. 1).

The widespread and important applications of these Pyrazole derivatives in organic synthesis, medicinal chemistry, and drug discovery, so we decided to synthesis these pyrazole derivatives in greener way using WEPA (Water extract of Pomegranate Ash) as a catalyst. In the last few years, several methods have been reported for the synthesis of 5-aminopyrazole -4-carbonitrile using various catalysts like Mg-Fe hydrotalcite[13], $NiFe_2O_4$[14], $DMF/POCl_3$[15]. These reported protocols have some advantages but at some point they show disadvantages like expensive catalyst, hazardous catalyst, longer reaction time, lack of product yield, *etc*. But all these drawbacks can be overcome by using WEPA as a green catalyst. In the last decade, bio waste catalysts are used as a possible alternative for organic synthesis[16,17]. The WEPA catalyst containing mixtures of metal oxide and carbonates is soluble to some extent in water which provides the number of Lewis basic sites (O^{2-} and OH^-) with Lewis acid sites

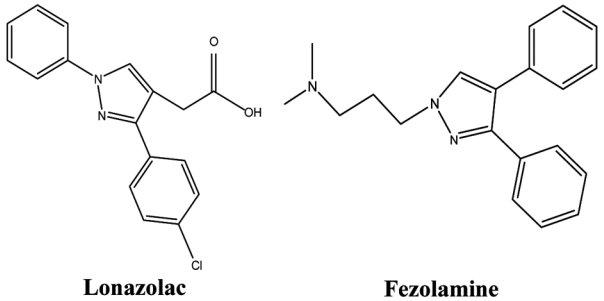


Fig. 1 — Some drug molecules possessing pyrazole skeleton

(M^{2+}) for activation of reactant to carry forward the reactants in the proper direction.

Experimental Section

Materials and Methods

All the chemicals were obtained from Spectrochem and used without further purification. All reactions were performed in a borosil round bottom flask, volume 25 mL. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F_{254} Merck (20 × 20 cm). TLC plates were visualized by exposing to UV light. The melting points of the synthesized compounds were determined on digital melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded with JEOL 400 MHz NMR instrument. Chemical shifts for protons are reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS) and are referenced to the residual proton in the NMR solvent (DMSO-d_6).

Preparation of catalyst

During this work, pomegranate fruit peels were obtained from the waste of local fruit market and the ash of pomegranate peel was obtained by thermal treatment in muffle furnace. Initially, all attached dust and impurities were removed by washing several times with tap water (Fig. 2a) and then left in open air for 3 h. Later, they were transferred to the oven at 100°C for drying. Then dried peels (around 10 g) were manually broken into small pieces (Fig. 2b**)** then converted to peels powder, which were treated at heating rate of 5°C/min in muffle furnace between 800°C and 1000°C and this temperature was maintained for 1 h. After thermal treatment, most of the organic materials were burnt out (Fig. 2c) and got transformed into the mortar pestle and grinding soft ash obtained (Fig. 2d). The resulting ash (about 0.5 g) was dissolved in 50 mL distilled water and stirred for 2 h for proper dissolution of ash to get pure basic mixture (Fig. 2e), then the resultant solution was filtered by Whatman filter paper no. 41(Fig. 2f). The clear solution obtained was designated WEPA catalyst (Fig. 2g) and *p*H checked by *p*H paper and *p*H meter. it was found to be around 12 to14 in range, which indicated the extracted solution to be strongly basic in nature (Fig. 2h) and directly utilized for the synthesis of 5-aminopyrazole-4-carbonitrile derivatives.

Structural analysis

The X-ray diffractograms (XRD) were used to study the structural properties of the prepared WEPA catalyst. The XRD pattern of the prepared WEPA catalyst is shown in Fig. 3. The synthesized WEPA catalyst has a polycrystalline character with a combination of metal oxides and carbonates, as seen in the Fig. 3. The main peak at 28.32° along with minor peaks at 32.34°, 40.51° and 45.11° corresponds to K_2O phase (JCPDS Reference No. 77-2176). The appearance of peaks at 2θ values of 19.35°, 26.89° and 66.34° (JCPDS Reference No. 17-0912) is related to CaO. The presence of the calcium carbonate phase was confirmed by the observations of peaks at 2θ values 26.69°, 33.92° and 50.15° (JCPDS Reference No. 17-0763). The peaks at 11.18° and 22.50° have

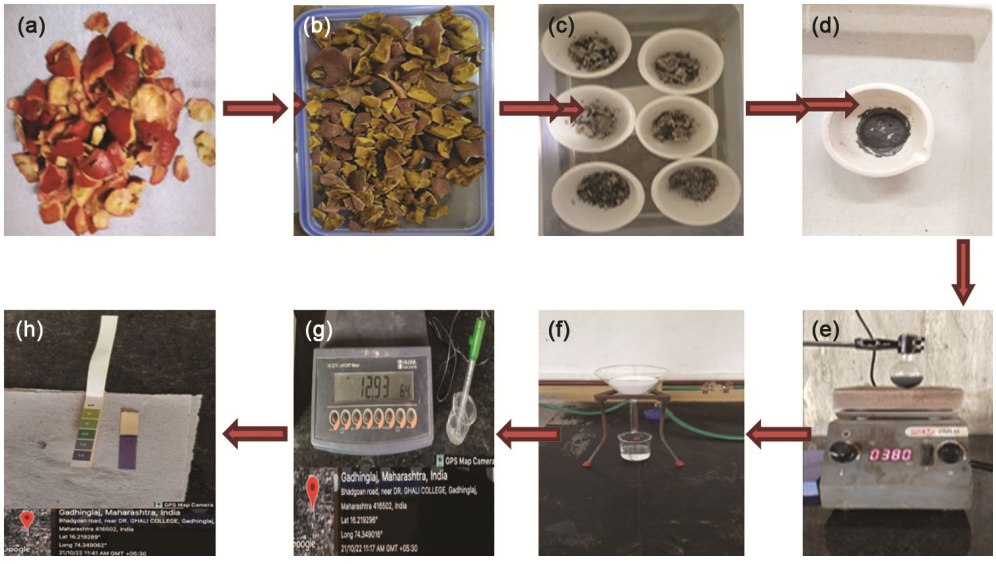


Fig. 2 — Preparation of catalyst

been attributed to elemental chlorine. The existence of peaks at 12.76° and 25.46° belong to the Na_2O and MgO compounds, respectively [A, B].

Surface morphology

The surface morphology of the prepared WEPA catalyst was studied using a scanning electron microscope (SEM). Fig. 4a-d shows the surface micrographs of the WEPA catalyst at different magnification levels. From the figure, it is observed that small spherical-shaped granules (~ 4-5 µm size) are agglomerated to each other to form larger grains. Additionally, the surface texture exhibits pores between the grains. The prepared WEPA catalyst with a smaller particle size offers a greater surface area for catalyzing reactions.

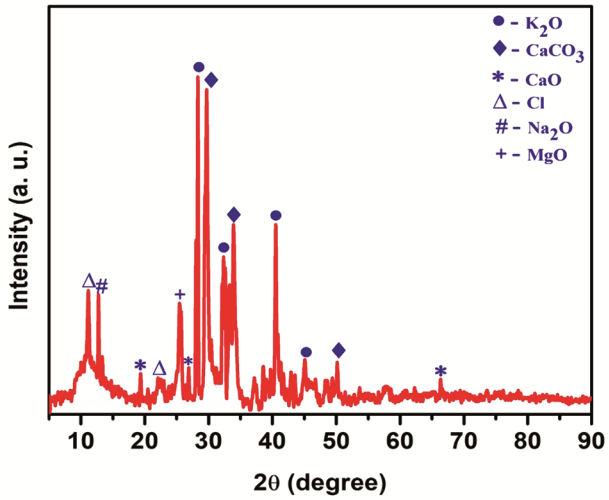


Fig. 3 — XRD pattern of the prepared WEPA catalyst

General experimental procedures for 5-aminopyrazole-4-carbontrile derivatives

10 mL 50%v/v solution of ethanol and distilled water was taken in a 25 mL round bottom flask. Malononitrile (1 mmol) was added to this solution, followed by addition of 1 mL of WEPA (water extract of pomegranate ash) in it and stirring was initiated *via* a magnetic stirrer. 1 mmol benzaldehyde (substituted) was added to the stirring solution and stirring was continued for about 2-3 min, till a light precipitate appeared. After this, 1 mmol phenyl hydrazine was added to this solution and a dense precipitate appeared, stirring was continued till the completion of reaction (Table 1). The entire reaction was carried out at RT and completion of reaction was monitored by TLC. The product was filtered off, washed with water and naturally air dried. The synthesis of the required compounds was confirmed and substantiated by ^{1}H and ^{13}C NMR, *etc*.

Spectral analysis of synthesized compound

5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (Table 2, Entry1)

Pale yellow solid. Yield 92%. m.p.158-160°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, 2H), 7.39

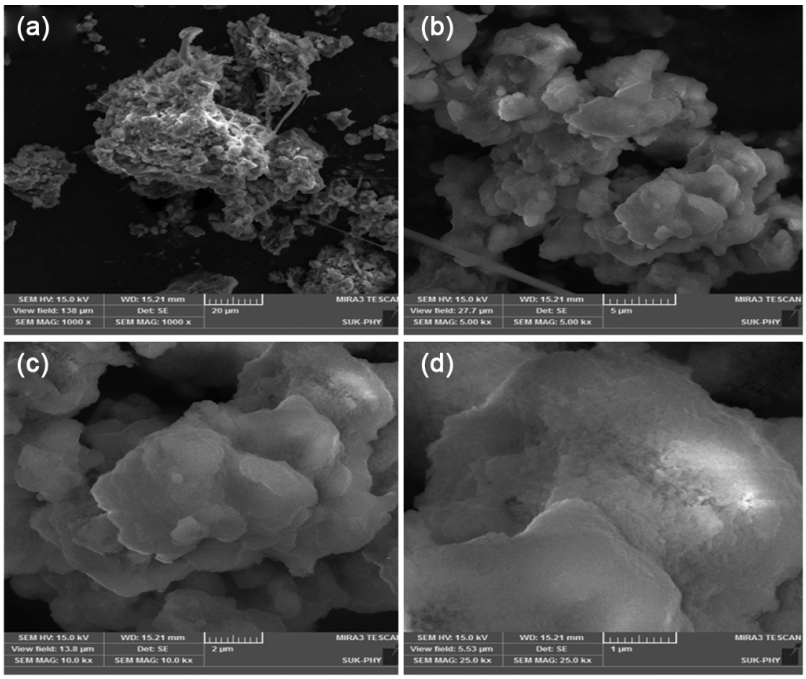
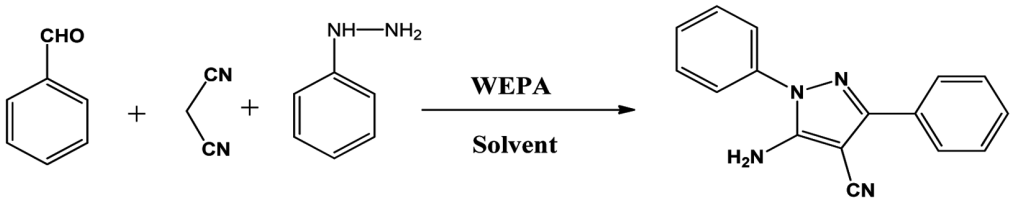


Fig. 4 — SEM images of WEPA catalyst

Table 1 — Optimization of the reaction conditions using amount of WEPA and with different solvents



R = H , Cl , Br , NO_3, OH

Entry	Catalyst	Solvent (10 mL)	Time (min)	Yield (%)[a]
01	–	–	180	–
02	–	EtOH	180	–
03	–	H_2O	180	–
04	WEPA (1.0 mL).	EtOH	60	65
05	WEPA (1.0 mL).	H_2O	30	70
06	WEPA (1.0 mL).	THF	60	58
07	WEPA (1.0 mL).	DCM	60	52
08	WEPA (1.0 mL).	CH_3CN	60	61
09	WEPA (0.5 mL)	EtOH: H_2O (1:1)	30	75
10	WEPA (0.8 mL)	EtOH: H_2O (1:1)	30	84
11	WEPA (1.0 mL)	EtOH: H_2O (1:1)	30	92
12	WEPA (1.5 mL)	EtOH: H_2O (1:1)	30	91
13	WEPA (2.0 mL)	EtOH: H_2O (1:1)	30	90

Reaction conditions: Benzaldehyde (1mmol), malononitrile (1 mmol), phenyl hydrazine (1 mmol) at RT.
[a] Isolated yield.

(t, 2H),7.10 (t, 1H), 7.36 (d, 2H), 7.27 (t, 2H), 6.90 (t, 1H), 10.29 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.9, 137.0, 136.4, 129.6, 129.2, 128.4, 126.1, 119.3, 112.6, 40.7, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5.

Results and Discussion

Optimization of reaction conditions

For the optimization of reaction condition for optimal loading of catalyst and identification of suitable solvent, we investigated our study by choosing benzaldehyde, phenylhydrazine and malononitrile as model substrate. We carried out this model reaction at RT in the presence of four different solvents and then with varying amount of catalyst loading. The results are summarized in Table 1.

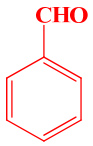
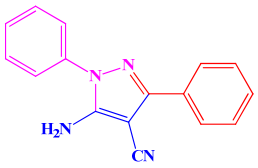
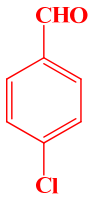
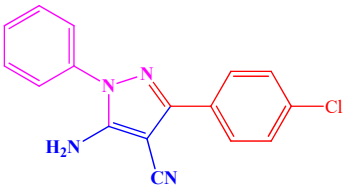
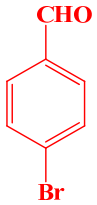
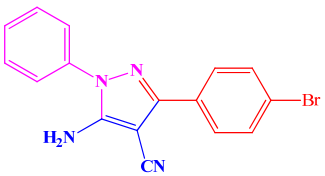
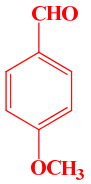
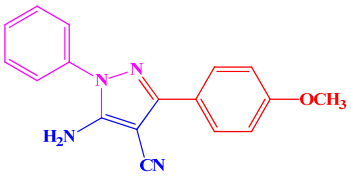
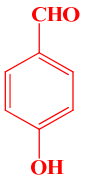
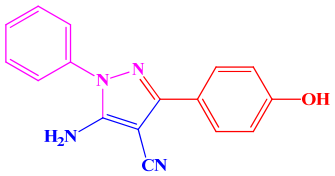
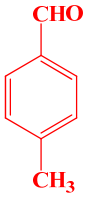
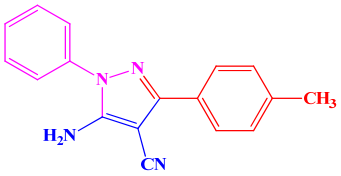
At first, the model reaction was examined under solvent-free conditions and in the water (5 mL) and in ethanol (5 mL) without any catalyst. It was found that the desired product was not observed on the TLC plate even after 3 h of stirring which indicated that catalyst plays crucial role to carry the reaction (Table 1, entries 1, 2, 3). The model reaction was performed using WEPA catalyst by varying the catalytic amount of catalyst from 0.5 mL to 2.0 mL in EtOH:H_2O (1:1) system. It was observed that when we increased the catalyst amount from 0.5 to 0.8 and 1.0 mL in EtOH: H_2O (1:1) system, the product yield also increased (Table 1, entries 9, 10, 11). Further increase in catalyst amount above 1 mL slightly reduced the yield (Table 1, entries 12, 13).

Optimization of reaction also carried for different solvents such as H_2O, EtOH, THF, DCM, CH_3CN. The results show that moderate yield obtained for desired product (Table 1, entries 4-8). The results of optimization studies shows that 1.0 mL WEPA with 3 mL EtOH:H_2O (1:1) system as solvent was found to be the best condition to carry the present protocol in terms of yield and reaction time. Utilizing a variety of substrate aryl aldehydes with WEPA as catalyst to synthesize various 5-aminopyrazole-4-carbonitrile derivatives demonstrated the versatility of the methodology (Table 2).

Mechanism of formation of compounds

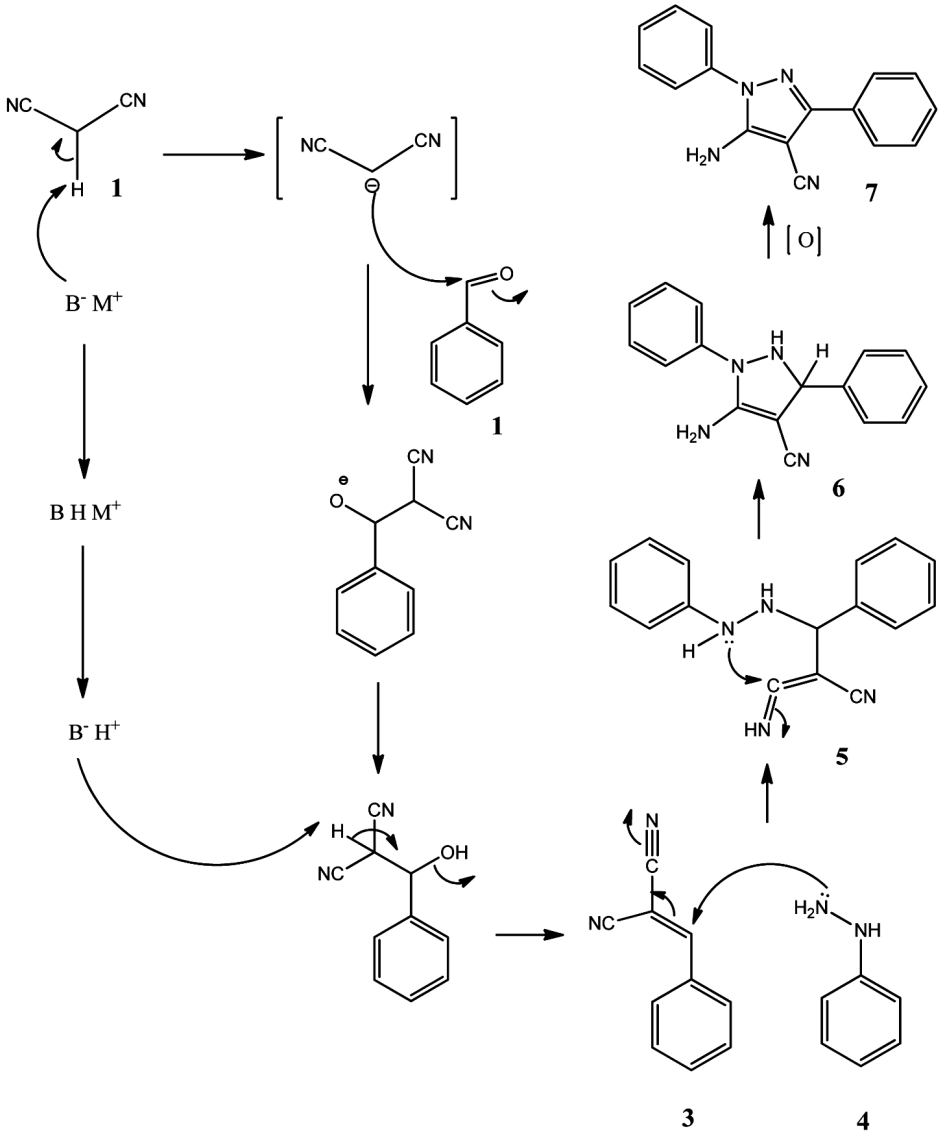
The WEPA-catalyst containing the mixture of metal oxides, metal hydroxide and carbonates *i.e.* B^- M^+ which are soluble to some extent in water

Table 2 — Synthesis of various 5-Aminopyrazole-4-carbonitrile derivatives using WEPA as catalyst

Entry	Aryl Aldehyde	Product	Yield(%)[a]	Time (min)	Observed m.p. (°C)
1			92	30	158-160
2			90	35	128-130
3			92	30	152-155
4			91	25	162-164
5			90	30	189-192
6			93	30	118-120

Reaction conditions: Benzaldehyde (1mmol), malononitrile (1 mmol), phenyl hydrazine (1 mmol) and WEPA (1 mL) at RT.
[a] Isolated yield.

which 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. On the basis of our work and previous reports we have suggested a possible mechanistic route for synthesis of target molecules. The plausible mechanism manifests that, at first the reaction stirred with WEPA and malononitrile so malononitrile is activated by Lewis basic site along with Lewis acid site and generates a nucleophile *via* abstraction of a proton from malononitrile **1**. Thereafter, addition of benzaldehyde takes place and generated malononitrile nucleophile attacks benzaldehyde **2** and undergoes Knoevenagel condensation *via* eliminating water molecule to afford the target 2-benzylidene-malononitrile **3**. After that, the added phenyl- hydrazine **4** reacts with 2-benzylidene-malononitrile **3** to form 3-imino-2-[phenyl-(N-phenyl-hydrazino)-methyl]-acrylonitrile **5**. 3-Imino-2-[phenyl-(N-phenyl-hydrazino)-methyl]-acrylonitrile **5** undergoes intramolecular cyclization to yield 5-amino-1, 3-diphenyl-2,3-dihy-dro-1*H*-pyrazole-4-carbonitrile **6** which then undergoes aerobic oxidation, yielding 5-amino-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile **7** (Scheme 1).



Scheme 1 — Plausible mechanism for the synthesis of 5-aminopyrazole-4-carbonitrile

Conclusion

It is concluded that WEPA was found to be an effective catalyst for the synthesis of 5-amino-pyrazole-4-carbonitrile and its derivatives at RT conditions. Use of WEPA-catalyst obtained from renewable bio-waste, mild reaction conditions and simple work-up without involvement of any hazardous material qualifies this method as an environmentally benign approach for this condensation. Use of bio-waste-derived catalyst and good-to-excellent yields in shortest reaction time has been demonstrated in the present work. The prepared catalysts were characterized with SEM showing that the strong basic sites in double layers and coordinative unsaturated O^{2-} ion acting as basic sites in the WEPA may be responsible for their catalytic activity. This process has several advantages over the other reported methodologies such as a non-toxic, reusable catalyst, convenience of use and cost-effectiveness.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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