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ARTICLE TYPE

Pseudo five-component process for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives using $ZnAl_2O_4$ nanoparticles in aqueous media

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In the present paper, we report the successful synthesis of zinc aluminate nanoparticles by the co-precipitation method using aqueous ammonia solution as the precipitating agent. $ZnAl_2O_4$ nanoparticles as an efficient catalyst have been used for the preparation of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives by pseudo five component reaction of hydrazine hydrate, ethyl acetoacetate and aldehydes at 60 °C in water. Atom economy, wide range of products, excellent yields in short time and environmentally benign are some of the important features of this protocol.

1. Introduction

The pyrazole ring system is a structural sector of a large number of biologically active compounds. The pyrazole derivatives exhibit important biological properties such as anti-inflammatory and hypnotic activity,[1] antifungal activity against three phytopathogenic fungi, namely *Helminthosporium* species, *Fusariumoxysporum* and *Alternariaalternate,*[2] suppress A549 lung cancer cell growth,[3] nonnucleoside HIV-1 reverse transcriptase inhibitors with enhanced activity versus the P236L mutant,[4] antibacterial,[5] antidepressant.[6] Some other examples of pyrazole derivatives such as celecoxib, SC-558, mefobutazone, and deracoxib have been reported as potent NSAIDs.[7] 4,4-(arylmethylene)bis(1H-pyrazol-5-ols) show excellent antiviral activity against peste des petitsruminantvirus (PPRV).[8] Therefore, the development of simple methods for the synthesis of pyrazoles is an important challenge. Undoubtedly, the synthesis of pyrazole derivatives through multicomponent reactions (MCR) has been paid much attention owing to excellent synthetic efficiency, inherent atom economy, procedural simplicity, and environmental friendliness. Therefore, the designs of novel MCRs for the synthesis of diverse groups of compounds, especially the ones that are biologically active, have commanded vast attention.[9-13] The possibility of accomplishment multicomponent reactions under mild conditions with a heterogeneous catalyst could improve their effectiveness from cost-effective and ecological points of view. Theoretically, nanoscale heterogeneous catalysts should present higher surface areas which are mainly responsible for their catalytic activity. These surface atoms behave as the centers where the chemical reactions could be catalytically activated. These advances have opened the door for the design of new nanocatalysts for particular applications in synthetic chemistry. Recently, nanoparticles as catalyst have emerged as an alternative approach for the development of many significant organic reactions. Ideally, introducing neat processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions has received remarkable attention in recent years.[14-18] Among various inorganic solids, spinel-type mixed oxides(AB_2O_4) are well known for their rich catalytic action. $ZnAl_2O_4$ is generally used as catalytic, ceramic, electronic material and emerging as one of the best wide band gap compound semi-conductor (Eg = 3.8eV) for various optoelectronic applications.[19]

$ZnAl_2O_4$ nanoparticles as a lubricating additive can considerably improve anti-wear and anti-friction performance of lubricant oil and disclose large potential in lubrication.[20] $ZnAl_2O_4$ has a remarkable potential for photocatalytic air purification, particularly for the removal of toxic aromatic compounds.[21] For stoichiometric materials the basicity scale is MgO>ZnO> $MgA1_2O_4$≈ $ZnAl_2O_4$≈$A1_2O_3$. Thus, the basic site distributions on the two normal spinel aluminates $MgA1_2O_4$ and $ZnAl_2O_4$ are apparently very similar to each other.[22]Zinc aluminate ($ZnAl_2O_4$) has been used extensively as a heterogeneous catalyst in many reactions, such as acetylation of amines, alcohols and phenols under solvent-free conditions[23] and synthesis of Xanthene derivatives.[24] They can be recovered easily from the reaction mixture by simple filtration, and reused several times without appreciable loss of activity. In general, there are many methods of preparation of $ZnAl_2O_4$ such as: co-precipitation method,[25] hydrothermal,[26,27] microwave-

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hydrothermal,[28] combustion,[29] and modified sol–gel method.[30] Compared with other techniques, the co-precipitation method is a simple and attractive procedure for preparation of the $ZnAl_2O_4$ nanoparticles.

Recently, pyridine trifluoroacetate or acetic acid,[31] phosphomolybdic acid,[32] Sulfuric acid ([3-(3-silicapropyl) sulfanyl]propyl)ester(SASPSPE),[33] Silica-bonded N-propyltri-ethylenetetramine[34] and Sodium dodecyl sulfate,[35] were reported for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives. Herein we report the use of $ZnAl_2O_4$ nanoparticles as an efficient catalyst for the preparation of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives by the pseudo five component reaction of hydrazine hydrate, ethyl acetoacetate and aldehydes at 60 °C in water (scheme 1).

<Scheme 1>

2. Results and discussion

The catalyst was prepared by the co-precipitation method using aqueous ammonia solution as the precipitating agent $Zn(NO_3)_2.6H_2O$ and $Al(NO_3)_3.9H_2O$ used as starting materials for the synthesis of Zinc aluminate nanoparticles (Figure 1). This method is simple and inexpensive. The XRD patterns for $ZnAl_2O_4$ are shown in Figure 2. Particle size of $ZnAl_2O_4$ nanoparticles was investigated by XRD pattern. The crystallite size diameter (D) of the $ZnAl_2O_4$ nanoparticles has been calculated by Debye–Scherrer equation ($D = K\lambda/\beta\cos\theta$), where FWHM (full-width at half-maximum or half-width) is in radians and Θ is the position of the maximum of diffraction peak, K is the so-called shape factor, which usually takes a value about 0.9, and λ is the X-ray wavelength. The pattern agrees well with the reported pattern for $ZnAl_2O_4$ nanoparticles (JCPDS No.82-1043). The average particle size was estimated by applying the Scherrer formula on the highest intensity peak. An average size of around 21–25 nm was obtained. Figure 3 show FTIR spectrum of nano $ZnAl_2O_4$. The bands at 682 cm^{-1}, 557 cm^{-1} and 495 cm^{-1} were assigned to stretching and bending mode of Al-O. The morphology and particle size of $ZnAl_2O_4$ NPs was investigated by scanning electron microscopy (SEM) as shown in Figure 4. The SEM images show particles with diameters in the range of nanometers.

<Fig.1>

<Fig. 2>

<Fig. 3>

<Fig. 4>

The choice of a suitable reaction medium is of vital importance for successful synthesis. Initially, we had explored and optimized different reaction parameters for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives by the pseudo five component reaction of hydrazine hydrate, ethyl acetoacetate and 4-nitrobenzaldehyde as a model reaction (scheme 2). As given in Table 1, the solvent has a great effect on the acceleration of the reactions. Several reactions were scrutinized using various solvents such as EtOH, CH_3CN, water, and n-propanol.

<Scheme 2>

The best results were obtained at 60 °C in H_2O and found that the reaction gave satisfying results in the presence of $ZnAl_2O_4$ nanoparticles (Table 1). When 2, 4 and 6 mol% of $ZnAl_2O_4$ nanoparticles were used; the yields were 82%, 92% and 92%, respectively. Therefore, 4 mol% of $ZnAl_2O_4$ nanoparticle was appropriate and an excessive amount of catalyst did not increase the yields considerably. Also, the activity and stability of the $ZnAl_2O_4$ nanoparticles in water is in maximum amount compared to other solvents. The model reactions were carried out in the presence of various catalysts such as CaO, ZnO, CuO, Al_2O_3 and ZnS. When the reaction was carried out using ZnS, ZnO NPs and $ZnAl_2O_4$ NPs as the catalyst, the product could be obtained in moderate to good yield. Nanoparticles exhibit good catalytic activity due to their large surface area and active sites which are mainly responsible for their catalytic activity. With these hopeful results in hand, we turned to explore the scope of the reaction using diverse aromatic aldehyde as substrates under the optimized reaction conditions (Table 2). In general the reactions are clean and high-yielding. Several functional groups such as Cl, OH, NO_2, and CH_3 are compatible under the reaction conditions. Interestingly, a variety of aromatic aldehydes including *ortho*, *meta* and *para*-substituted aryl aldehyde participated well in this reaction and gave the corresponding products in good to excellent yield (Table 2). The influence of electron-withdrawing and electron-donating substituents on the aromatic ring of aldehydes upon the reaction yields was investigated. The presence of halogen on the aromatic ring of aldehydes had negligible effect on the reaction results. Aromatic aldehydes having NO_2 group (entries 1 and 2) reacted at faster rate compared with aromatic aldehydes substituted with other groups. Meanwhile, the practicable synthetic efficiency of this reaction was highlighted by the reaction of terephthaldehyde, hydrazine hydrate and ethyl acetoacetate to give **6j**. Therefore, the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ols) is highly flexible, fruitful, simple and versatile from an organic chemistry viewpoint.

<Scheme 3>

<Table 1>

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<Table 2>

All products were well characterized by IR, ^{1}H NMR,^{13}C NMR, and elemental analysis. In the ^{1}H NMR spectra in DMSO-d_6 was shown a singlet around δ= 11.20-11.58 corresponding to NH group and a signal around δ= 3.40-3.70 corresponding to OH group which exchanged with water of DMSO-d_6. Recently, Soleimani and coworkers have developed the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives using pyridine trifluoroacetate or acetic acid[31]. They have reported signal around δ= 3.50-5.50 corresponding to OH and NH groups that are different to our observations.

Meanwhile, short reaction times, excellent yield of products and the use of green catalyst are some of the important features of this protocol.

A plausible mechanism for the preparation of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives using $ZnAl_2O_4$ NPs is shown in Scheme 4.

<Scheme 4>

3. Experimental

3.1. Chemicals and apparatus

All organic materials were purchased commercially from the Sigma–Aldrich and Merck and were used without further purification. All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope. FT-IR spectra were recorded with KBr pellets using a Magna-IR, spectrometer 550 Nicolet. NMR spectra were recorded on a Bruker 400 MHz spectrometer with DMSO as solvent and TMS as internal standard. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company. Microscopic morphology of products was visualized by SEM (MIRA 3 TESCAN).

3.2. Preparation of $ZnAl_2O_4$ nanoparticles

Nano $ZnAl_2O_4$ was prepared according to the procedure reported in the literatures with some modification.[37] The Zn $(NO_3)_2.6H_2O$ aqueous solution (5.94 g (20.0 mmol) in 10 mL) was added to the $Al(NO_3)_3.9H_2O$ aqueous solution (15 g (40.0 mmol) in 10 mL). Then, the appropriate amount of aqueous ammonia solution (28 wt%) was added to the above solution, and the mixture was stirred until complete precipitation occurred at a pH 9.0. The powder was filtered, washed with distilled water, and dried. Then, the solid was treated at 700°C for 4 h to obtain the $ZnAl_2O_4$ nanocrystals.

3.3. General procedure for the preparation of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ols):

A solution of hydrazine hydrate (2.0 mmol, 1.0 g), ethyl acetoacetate (2.0 mmol, 0.26 g), and $ZnAl_2O_4$ nanoparticles (4 mol %) as catalyst in water (5 mL) was stirred. (Hydrazine solutions are hazardous because of their toxic, corrosive, flammable or explosive properties. Hydrazine solutions should always be handled with great care. Avoid inhaling the vapours from hydrazine solutions at all times and whenever possible use a reliable fume hood. Avoid skin contact with hydrazine at all times). After 3 min, aldehyde (1.0 mmol) was added and the mixture stirred at 60 °C for appropriate time. Then it was allowed to cool to room temperature. The formed precipitate was isolated by filtration. The product was dissolved in hot CH_3OH and the catalyst was filtered. After cooling, the crude products were precipitated. The precipitate washed with EtOH to afford the pure product and dried well under vacuum pump. The structures of the products were fully established on the basis of their ^{1}H NMR, ^{13}C NMR and FT-IR spectra.

3.5. Spectral data

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(4-nitrophenyl) methyl)-3-methyl-1H-pyrazol-5-ol (6a) White powder, mp 275–278 °C; IR (KBr) (v_{max}/cm^{-1}): 3392.82, 3104.77, 2931.41, 1600.58, 1515.05, 841.11; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.08 (s, 6H, $2CH_3$), 3.38 (2OH exchanged with water of DMSO-d_6), 4.96 (s, 1H, CH),7.37-8.11 (m, 4H, H-Ar), 11.40 (brs, 2H, 2NH); ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 10.3, 33.0, 103.3, 123.0, 128.8, 140.0, 145.6, 151.7, 160.9; Anal. Calcd For $C_{15}H_{15}N_5O_4$: C, 54.71; H, 4.59; N, 21.27%.Found: C, 54.65; H, 4.62; N, 21.31%. MS, (*m/z*): 330 (M + 1), 241, 232, 217, 135, 97.

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(3-nitrophenyl) methyl)-3-methyl-1H-pyrazol-5-ol (6b) White powder, mp 288–291°C; IR (KBr) (v_{max}/cm^{-1}): 3403.31, 3096.66, 2961.47, 1599.54; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.09 (s, 6H, $2CH_3$), 3.42 (2OH exchanged with water of DMSO-d_6), 4.98 (s, 1H, CH),7.52–8.02 (m, 4H, H-Ar), 11.49 (brs, 2H, 2NH); ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 10.2, 32.5, 103.4, 120.8, 121.9, 129.3, 134.6, 140.1, 145.6, 147.6, 160.9; Anal. Calcd For $C_{15}H_{15}N_5O_4$: C, 54.71;H, 4.59; N, 21.27%.Found: C, 54.62; H, 4.46; N,21.30%. MS, (m/z): 330 (M + 1), 241, 232, 217, 135, 97.

4-((5-hydroxy-3-methyl-1H-pyrazol-4-yl)(phenyl)methyl)-3-methyl-1H-pyrazol-5-ol (6c) white solid,mp206-207 °C; IR (KBr) (v_{max}/cm^{-1}):3532.69, 3315.48, 2924.40, 1602.23;^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.04(s,6H, $2CH_3$), 3.36 (2OH exchanged with water of DMSO-d_6), 4.78 (s,1H, CH),6.93-7.17 (m,5H, H-Ar) 11.37 (brs,2H,2NH);^{13}CNMR (100MHz, DMSO-d_6): δ (ppm) 10.20, 33.0, 103.2, 123.0, 128.6, 140.0, 145.4, 151.2, 160.5. Anal. CalcdFor$C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71 %. Found: C, 63.40; H, 5.69; N, 19.65 %. MS, (m/z): 285 (M + 1), 245, 219, 188, 97.

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(3-hydroxyphenyl) methyl)-3-methyl-1H-pyrazol-5-ol (6d) White powder, mp 209–211°C; IR (KBr) (v_{max}/cm^{-1}): 3321.81, 2924.11, 1602.23, 1521.96, 1481.05; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.049 (s, 6H, $2CH_3$), 3.372 (2OH exchanged with water of DMSO-d_6), 4.69 (s, 1H, CH), 6.48–6.94 (m, 4H, H-Ar), 9.08 (brs,

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1H,OH), 11.34 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.3, 32.5, 104.3, 112.4, 114.5, 118.2, 138.5, 140.1, 144.7, 156.9, 161.1;Anal. Calcd For $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66%. Found: C, 59.96; H, 5.30; N, 18.71%. MS, (m/z): 301 (M + 1), 299, 267, 241, 203, 186, 162, 115.

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(4-cholorophenyl) methyl)-3-methyl-1H-pyrazol-5-ol (6e) white solid, mp 214-216°C;IR (KBr) (v_{max}/cm^{-1}): 3180.94, 2924.39, 1602.60, 1524.39, 1487.38; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.049 (s,6H, 2CH_3), 3.40 (2OHexchanged with water of DMSO-d_6), 4.78 (s, 1H, CH), 7.10–7.24 (m, 4H, H-Ar), 11.51 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm)10.3, 33.3, 103.4, 123.4, 128.7,140.2, 145.8, 151.9, 161.2;Anal. Calcd For $C_{15}H_{15}ClN_4O_2$: C, 56.62; H, 4.74; N, 17.58%. Found: C, 56.49; H, 4.81; N, 17.61%. MS, (m/z): 320 (M + 2), 318 (M^+), 224, 196, 180, 126.

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(*o*-tolyl)methyl)-3-methyl-1H-pyrazol-5-ol (6f) Pale orange solid, mp 278-280 °C; IR (KBr) (v_{max}/cm^{-1}):2923.19, 1602.77, 1529.29, 1484.30, 749.39; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm)1.79(s,6H, 2CH_3),2.11(s,3H, CH_3),3.35 (2OH exchanged with water of DMSO-d_6), 4.93 (s, 1H, CH), 7.04-7.21 (m, 4H, H-Ar), 10.73(brs,2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.85 ,19.60, 31.47, 103.11, 125.51, 126.05, 128.71, 130.33, 135.86, 138.33, 141.86, 160.89; Anal. Calcd For $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78%. Found: C, 64.50; H, 6.11; N, 18.75%. MS, (m/z): 299 (M+1), 241, 203, 160, 115.

4-((5-Hydroxy-3-methyl-1H-pyrazol-4-yl)(*m*-tolyl)methyl)-3-methyl-1H-pyrazol-5-ol (6g)

Pale orange solid, mp245-247 °C; IR (KBr) (v_{max}/cm^{-1}): 3350.54, 2922.97, 1602.64, 1455.93; ^{1}H NMR (400 MHz, DMSO-d_6):δ (ppm) 2.05 (s,6H, 2CH_3),2.18 (s,3H, CH_3),2.75 (2OH exchanged with water of DMSO-d_6), 4.75 (s, 1H, CH), 6.71-7.06 (m, 4H, H-Ar), 11.58 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.82, 21.69, 33.09, 104.80, 125.07, 126.64, 128.13, 128.48, 137.05, 140.45, 143.66, 161.56; Anal. Calcd For $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.785%. Found: C, 64.52; H, 6.10; N, 18.73%. MS, (m/z): 299 (M+1), 241, 203, 160, 115.

4-((2,4-dichlorophenyl)(5-hydroxy-3-methyl-1H-pyrazol-4-yl)methyl)-3-methyl-1H-pyrazol-5-ol (6h) White powder, mp 267–270 °C; IR (KBr) (v_{max}/cm^{-1}): 3411.32, 2927.52, 1606.81, 1529.31, 1466.81; ^{1}H NMR (400 MHz, DMSO-d_6):δ (ppm) 1.93(s,6H, CH_3), 3.36 (2OH exchanged with water of DMSO-d_6), 5.01(s, 1H, CH), 7.32-7.48 (m,3H, H-Ar),11.42 (brs,2H, 2NH);^{13}C NMR (100 MHz, DMSO-d_6):δ (ppm) 10.3, 31.2, 101.9, 126.6, 128.2, 130.9, 132.0, 133.1, 138.6, 140.1,160.4; Anal. CalcdFor$C_{15}H_{14}Cl_2N_4O_2$: C, 51.01; H, 4.00; N, 15.86%. Found: C,51.10; H, 4.02; N, 15.77%. MS, (m/z): 355 (M + 2), 353 (M^+), 278, 255, 241, 219, 202, 175, 158, 112.

4-((2-chlorophenyl)(5-hydroxy-3-methyl-1H-pyrazol-4-yl) methyl)-3-methyl-1H-pyrazol-5-ol (6i) Pale orange solid, mp 265–267 °C; IR (KBr) (v_{max}/cm^{-1}): 3409.36, 2926.67, 1605.31, 1534.23, 1466.52, 753.07; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.916 (s,6H, 2CH_3), 3.341 (2OH exchanged with water of DMSO-d_6), 5.06 (s,1H, CH), 7.19-7.52 (m, 4H, H-Ar), 11.23 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.91, 31.79, 102.87, 126.89, 127.98, 129.51, 131.04,132.72, 139.38, 141.13, 161.14; Anal. Calcd For $C_{15}H_{15}ClN_4O_2$: C, 56.52; H, 4.74; 17.58%. Found: C, 56.59; H, 4.70; N, 17.62%. MS, (m/z): 320 (M + 2), 318 (M^+), 224, 196, 180, 126.

4-((4-(bis(3-methyl-1H-pyrazol-4-yl-5-ol)methyl)phenyl)(3-methyl-1H-pyrazol-4-yl-5ol)methyl)-3-methyl-1H-pyrazole-5-ol (6j) Orange solid, mp 286-288°C;IR (KBr) (v_{max}/cm^{-1}): 3351.22, 3112.39, 1600.70, 1471.53, 833.03; ^{1}H NMR (400 MHz, DMSO-d_6):δ (ppm) 2.04(s,12H, 4CH_3),3.94(4OH exchanged with water of DMSO-d_6), 4.70 (s,2H, 2CH), 6.93 (s, 4H, H-Ar),11.61(brs, 4H, 4NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.84, 32.82, 104.85, 127.34, 140.49, 140.91, 161.56; Anal. Calcd For $C_{24}H_{26}N_8O_4$: C, 58.77; H, 5.34; N, 22.84%. Found: C, 58.72; H, 5.36; N, 22.80%. MS, (m/z): 491 (M+1), 395, 298, 285, 188, 147.

4. Conclusions

In conclusion, we have developed a straightforward and efficient approach to synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivativesby a simple one pot pseudo five component reaction of hydrazine hydrate, ethyl acetoacetate and aldehydes in the present $ZnAl_2O_4$ nanoparticles as catalyst under benign reaction conditions. This green methodology can synthesize new substituted pyrazoles scaffolds. These compounds will provide promising candidates for biological applications and drug discovery. The advantages offered by this method include, short reaction times, a simple procedure, high atom economy, excellent yields, use of no toxic organic solvent in the entire process, no need for chromatographic purification and the employment of a cost-effective catalyst.

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Table 1. Optimization of reaction conditions using different catalysts[a]

Entry	Solvent	Catalyst (mol %)	Time (min)	Yield %[ref]
1	H_2O (80°C)	H_2SO_4 (2)	240	30
2	EtOH (reflux)	H_2SO_4 (2)	300	29
3	EtOH (reflux)	Et_3N (10)	190	38
4	CH_3CN	Et_3N (10)	290	32
5	H_2O (70°C)	Pyridine trifluoroacetate	300	87 [31]
6	n-propanol	ZnS (7)	150	43
7	H_2O (80°C)	CuO(7)	120	38
8	H_2O (reflux)	CaO(10)	150	35
9	H_2O (60 °C)	ZnO(8)	150	51
10	EtOH (reflux)	ZnO (8)	150	45
11	EtOH (reflux)	Al_2O_3 (6)	165	38
12	EtOH (reflux)	$ZnAl_2O_4$ NPs (5)	25	78
13	H_2O (reflux)	ZnO NPs	50	63
14	H_2O (60 °C)	$ZnAl_2O_4$ NPs (2)	14	82
15	**H_2O (60 °C)**	**$ZnAl_2O_4$ NPs (4)**	**14**	**92**
16	H_2O (60 °C)	$ZnAl_2O_4$ NPs (6)	14	92
17	H_2O (80°C)	$ZnAl_2O_4$ NPs (4)	14	91

[a]Reaction conditions: hydrazine hydrate (2 mmol), ethyl acetoacetate(2 mmol) and4-nitrobenzaldehyde (1 mmol)
[b]Isolated yields

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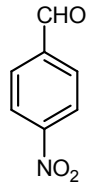
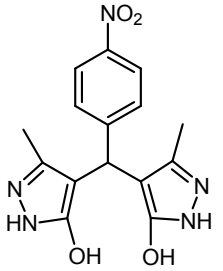
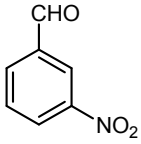
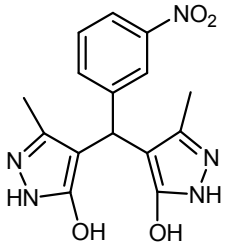
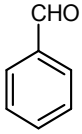
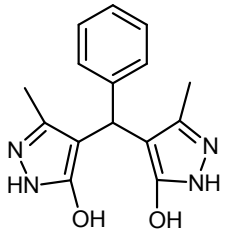
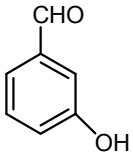
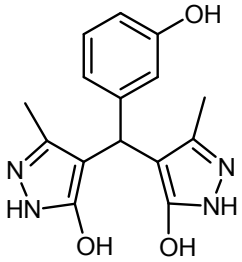
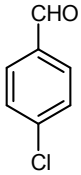
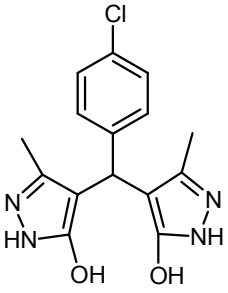
Table 2. Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives using $ZnAl_2O_4$ NPs.

Entry	Aldehyde	Product	Structure (6)	Time (min)	Yield%	M.P °C.[ref]
1		6a		14	92	275-278[31]
2		6b		16	88	288-291 [31]
3		6c		23	87	206-207[36]
4		6d		28	83	209-211 [31]
5		6e		22	88	214-216 [36]

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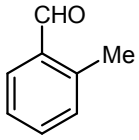
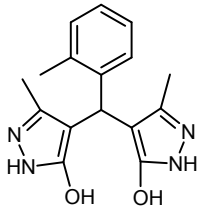
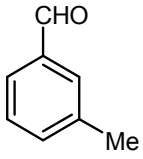
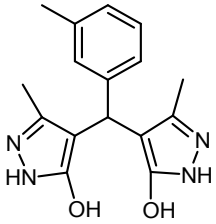
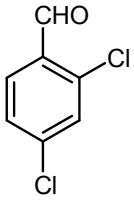
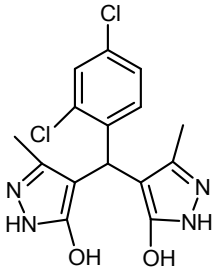
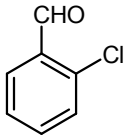
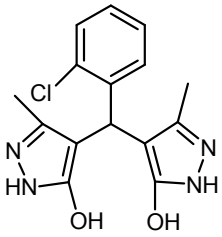
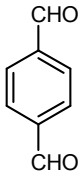
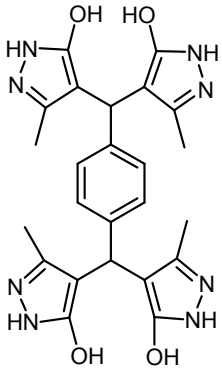
Entry	Aldehyde	product	Structure 6	Time(min)	Yield%	M.P°C[ref]
6		6f		28	83	278-280
7		6g		26	85	245-247
8		6h		24	87	267-270[31]
9		6i		25	84	265-267
10		6j		28	80	286-288

[a]All the reactions were carried out at 60 °C in water

[b] Isolated yields

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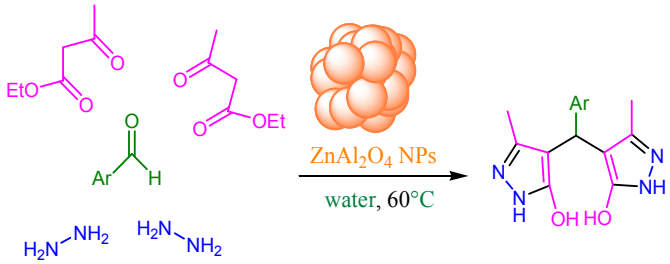

Scheme 1: Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives via $ZnAl_2O_4$ nanoparticles catalyzed multicomponent reactions of hydrazine hydrate, ethyl acetoacetate and aldehydes

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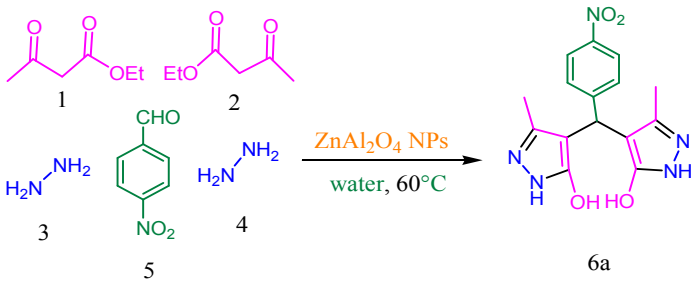

1 2 3 4 5 6a

Scheme 2: The model reaction for the preparation of 4,4'-(arylmethylene)bis(1H-pyrazol-5-ols).

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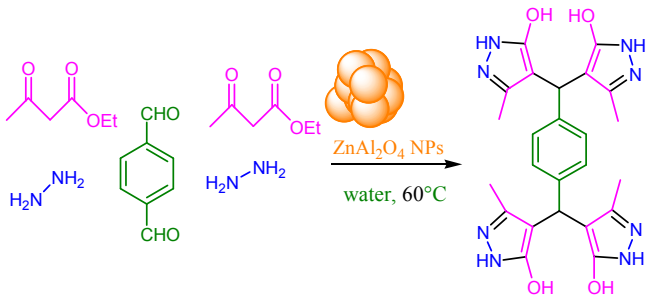

6j

Scheme 3: The reaction of terephthaldehyde,hydrazine hydrate andethyl acetoacetate

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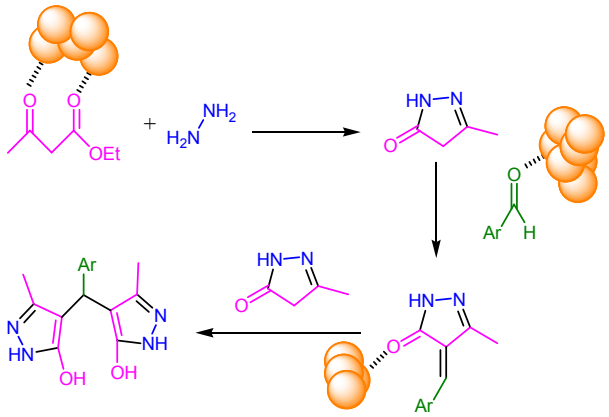

Scheme 4: Proposed reaction pathway for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol)derivatives by $ZnAl_2O_4$ NPs

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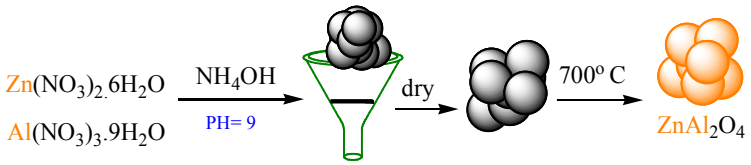

Fig. 1. Flow chart of $ZnAl_2O_4$ nanoparticles preparation procedure

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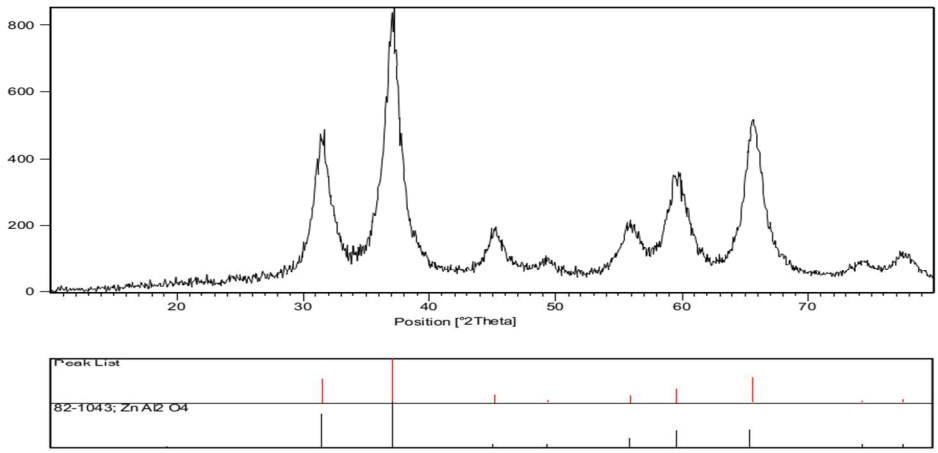

Fig 2. The XRD pattern of $ZnAl_2O_4$ NPs

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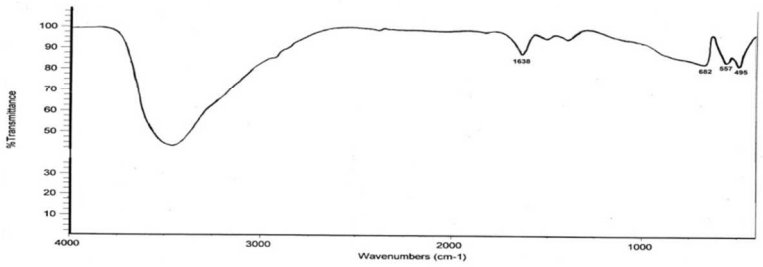

Fig.3. FTIR spectrum of $ZnAl_2O_4$ nanoparticles

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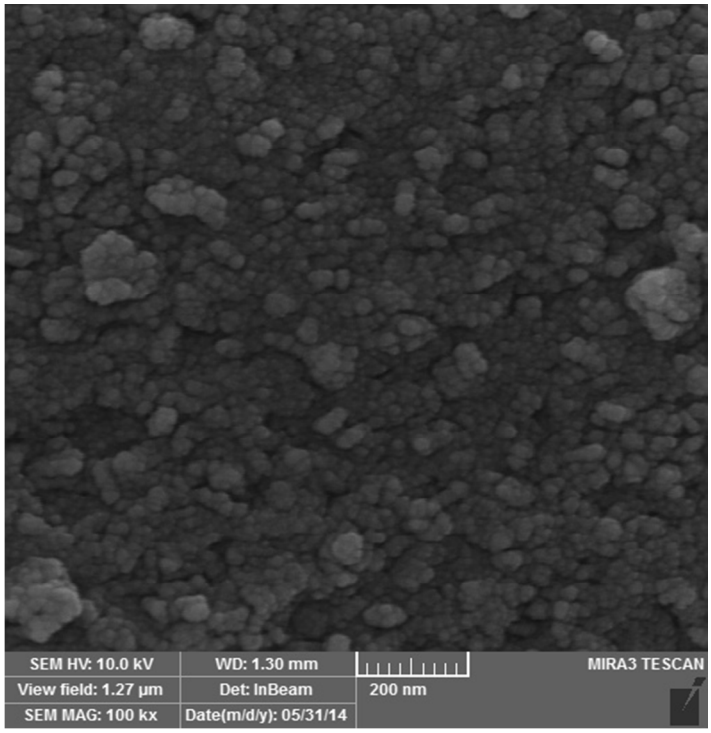

Fig.4.SEM image of $ZnAl_2O_4$ nanoparticles

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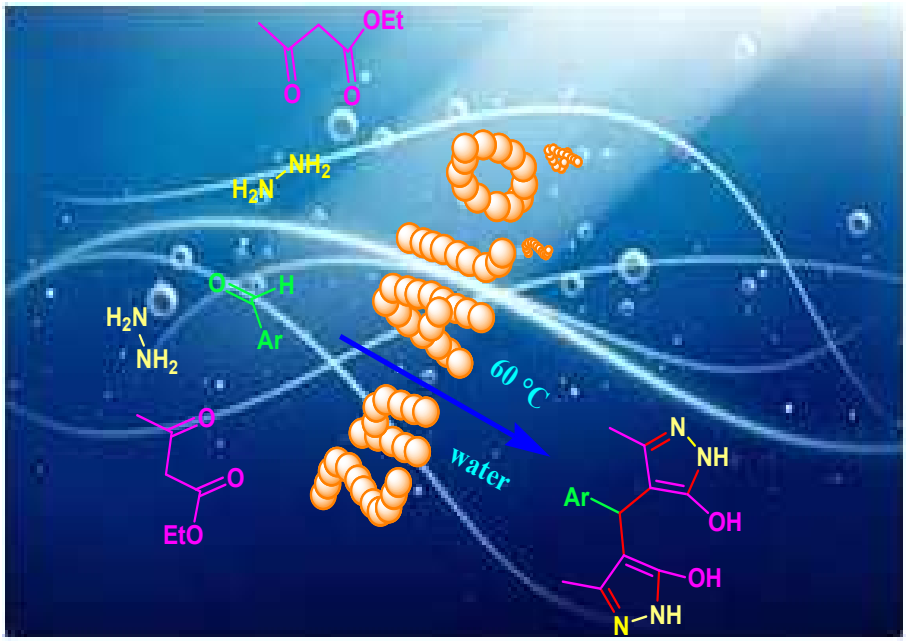
Graphical abstract



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