Scientific paper

Synthesis, Characterization and Application of Various Types of Alumina and nano-γ-alumina Sulfuric Acid for the Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

Abbas Teimouri,[1,*] Hossien Salavati[1] and Alireza Najafi Chermahini[2]

[1] *Department of Chemistry, Payame Noor University, 19395-4697, Tehran, I. R. of Iran*

[2] *Department of Chemistry, Isfahan University of Technology, Isfahan, 841543111, Iran*

* *Corresponding author: E-mail: a_teimouri@pnu.ac.ir, Tel. +98-311-3521804-6, Fax +98-311-3521802*

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Abstract

An efficient and green protocol for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by one-pot reaction of different aromatic carboxylic acids and benzoyl hydrazides using natural alumina, alumina sulfuric acid (ASA), nano-γ-alumina and nano-γ-alumina sulfuric acid (nano-γ-ASA) under microwave irradiation and solvent-free conditions was developed. Short reaction times, mild reaction conditions, easy work-up, and high yields are the main advantages of this methodology. The catalysts could be recovered and reused for the subsequent reactions without any appreciable loss of efficiency.

Keywords: Nano-γ-alumina, nano-γ-alumina sulfuric acid, green synthesis, microwave irradiation, 2,5-disubstituted 1,3,4-oxadiazoles.

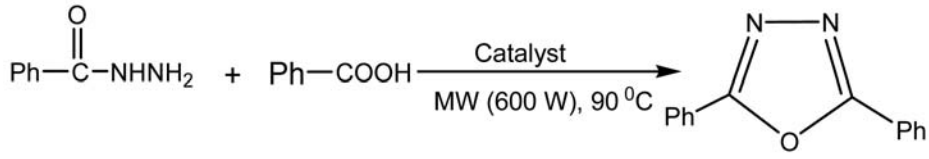
1. Introduction

Organic reactions caused by heterogeneous acid catalysts are very important for chemical processes because of cost-effectiveness, better selectivity and operational simplicity.[1,2] Preparation of 1,3,4-oxadiazoles have particularly attracted interest in the medicinal chemistry, pesticide chemistry and material science.[3] In particular, asymmetrically 2,5-disubstituted 1,3,4-oxadiazoles have received considerable attention because of their pharmaceutical and biological activities.[4] It has been shown that compounds containing these aromatic five-membered heterocycle scan have antifungal,[5] antiinflammatory,[6] antimicrobial,[7] anticonvulsant, muscle relaxant,[8] and hypoglycemic activities.[9]

Several synthetic methods have been reported for the preparation of 1,3,4-oxadiazoles. The common synthetic route used to make these compounds involves cyclization of diacyl hydrazines with a variety of dehydrating reagents,[10–16] oxidation of acyl hydrazones with different oxidizing agents,[17–19] and acylation of tetrazoles.[20]

One-pot synthesis of 1,3,4-oxadiazoles from acid hydrazides using an acid chloride[21] and by carboxylic acids,[22] has also been reported in the literature. Recently, CAN,[23] solid phase,[24–26] and microwave heating,[27,28] have been employed in the synthesis of these interesting compounds.

Although these approaches are satisfactory for the synthesis of 1,3,4-oxadiazoles, they suffer from drawbacks, such as low product yields, harsh reaction conditions, expensive reagents, the need for stoichiometric amounts of catalysts, the formation of a large amount of waste and/or use of toxic organic solvents. Therefore, the development of novel synthetic routes to have access to these molecules is of prime interest and there is still a need to search for better catalysts from viewpoint of handling and economic viability. Furthermore, the performance of chemical reactions under solvent-free condition is one of the best ways to move toward green chemistry.[29–31]



Scheme 1. Catalyzed one-pot reaction of carboxylic acids with benzoyl hydrazide.

In recent years, the use of nano-γ-alumina[32] and heterogeneous solid acid catalysts such as alumina sulfuric acid[33] and nano-γ-alumina sulfuric acid (nano-γ-ASA)[34] has attracted considerable interest in chemistry due to their eco-friendliness, easy preparation in nano-size, reusability and recovery, low cost, and high acid strength. These catalysts are actually sulfuric acid linked to alumina surface via covalent bond without the risks and disadvantages usually associated with sulfuric acid; such as lack of reusability, waste production and scale-up problems. In this report we extend our recent study[35,36] on the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by using one-pot reaction of different carboxylic acids with benzoyl hydrazide in the presence of natural alumina, alumina sulfuric acid, nano-γ-alumina and nano-γ-ASA under microwave irradiation and solvent-free conditions (Scheme 1).

2. Results and Discussion

In an effort to develop an optimal catalytic system, various reaction parameters like catalyst loading and reaction time were studied. The results, listed in Table 1, showed that the conversions were sensitive to the catalyst type. Nano-γ-ASA promoted the reaction more effectively than alumina sulfuric acid (ASA), nano-γ-alumina and neutral alumina, as far as the amount of catalyst and reaction times were concerned (Table 1, entry 3).

Table 1. The effect of the catalyst on the yield of 2,5-diphenyl 1,3,4-oxadiazole.[a]

Entry	Catalyst	Catalyst loading (mg)	Time (min)	Yield (%)[b]
1		–	120	10
2	nano-γ-ASA	10	20	85
3		15	15	96
4		20	15	80
5		25	15	75
6	ASA	10	20	78
7		15	15	85
8		20	15	75
9		25	15	74
10	nano-γ-alumina	10	20	66
11		15	15	70
12		20	15	64
13		25	15	60
14	natural alumina	10	20	58
15		15	15	62
16		20	15	56
17		25	15	52

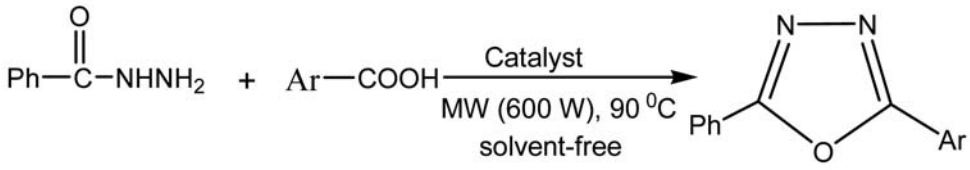
[a] Benzoyl hydrazide (1 mmol), benzoic acid (1 mmol) in the presence of various amounts of catalysts. [b] Isolated yields.

One reason for the increase in the catalytic activity of nano-γ-ASA may be related to the number of available active sites. In order to evaluate the effect of the catalyst particle size on the catalytic activity, the results were compared with those obtained by using ASA. Inferior activity was observed in the presence of ASA or natural alumina (Table 1, entries 7 and 15).

In comparison with the conventional methods, microwave irradiation considerably decreased the reaction times (15–20 min, Table 1) and reactions are cleaner. However, only 10% of the expected product was obtained in the absence of the catalyst (Table 1, entry 1).

The reaction with 10 mg of nano-γ-ASA as catalyst, under similar conditions, required a shorter reaction time and the yield of the product was dramatically increased up to 85% after irradiating the reaction mixture for 20 min. An increase of the amount of nano-γ-ASA from 10 to 15 mg increased the yield of the desired product to 96%. Reaction yields using 10, 15, 20 and 25 mg of ASA as the catalyst were 78%, 85%, 75% and 74%, respectively (Table 1, entries 6–9). For the nano-γ-alumina and natural alumina as the catalyst, when the catalyst content was increased to 25 mg, the product yield decreased to 60% and 52% (Table 1, entries 13 and 17), respectively. It can be concluded that the use of 15 mg of the catalyst was sufficient to promote the reaction, and higher amounts of the catalyst did not increased the yields significantly. The temperature and the MW power were also optimized and the best results were obtained using 15 mg of nano-γ-ASA at 90 °C and microwave power) 600 W(. No increase in yield was observed at higher temperatures, while lowering the temperature below 90 °C reduced the reaction rate. The efficiency of the protocol was further studied in the synthesis of various 1,3,4-oxadiazoles (Table 2). We examined the scope of the reaction using aryl substituted carboxylic acids and various 1,3,4-oxadiazoles bearing Me, MeO, Cl, Br and NO_2 substituents on the aryl ring were prepared in good to excellent yields within a short period of time (Table 2, entries 1–7). Both, electron-rich and electron-poor aryl carboxylic acids afforded the corresponding 1,3,4-oxadiazoles **1a–g** in good to excellent yields. In particular,

Table 2. The solid acid-catalyzed synthesis of 2,5-disubstituted 1,3,4-oxadiazoles under microwave irradiation and solvent-free conditions.[a]



Entry/ Product	Ar	Time (min)/Yield (%)[b]				M.p. (°C) (lit.)[Ref.]
		Natural alumina	nano-γ-alumina	ASA	nano-γ-ASA	
1 (**1a**)	Ph	20/62	20/70	20/85	20/96	134–136 (139–140)[23]
2 (**1b**)	4-$NO_2C_6H_5$	20/60	20/67	20/84	20/92	200–202 (202–204)[23]
3 (**1c**)	3-$NO_2C_6H_5$	20/64	20/68	20/86	20/90	142–144 (147)[27]
4 (**1d**)	4-$CH_3C_6H_5$	20/62	20/72	20/88	20/92	150–152 (145–146)[23]
5 (**1e**)	4-$OCH_3C_6H_5$	20/64	20/70	20/90	20/94	144–146 (149–151)[23]
6 (**1f**)	4-ClC_6H_5	20/62	20/68	20/84	20/90	156–158 (162)[27]
7 (**1g**)	4-BrC_6H_5	20/60	20/67	20/85	20/94	164–166 (167)[27]

[a] Benzoyl hydrazide (1 mmol), aromatic carboxylic acids (1 mmol) in the presence of catalyst.
[b] Isolated yields of products characterized by IR, ^{1}H NMR, and mass spectroscopy.

4-NO_2 substituted derivative **1b** reacted more efficiently than the corresponding 3-substituted regioisomer **1c**, probably because of the steric hindrance of the *meta* substituent (Table 2, entries 2 and 3).

Table 3 compares the efficiency of the present method with the efficiency of other methods in the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. As it is evident from Table 3, nano-γ-ASA showed better efficiency than the other methods. In addition, the reaction times were shorter than in previously reported reactions.

Table 3. Comparison of the efficiency of nano-γ-ASA with other reported catalysts in the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles.[a]

Entry	Condition	Time (min)	Yield (%)[b]	References
1	nano-γ-ASA	15	96	This work
2	Nafion® NR50	25	88	26
3	CAN, solvent-free, rt	20	70	23
4	$KMnO_4$, MW	16	96	27
5	P_2O_5/CH_3CN, rt	10	97	21

[a] Benzoyl hydrazide (1 mmol), benzoic acid (1 mmol) in the presence of catalyst. [b] Isolated yields.

The prepared catalysts were characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR). The obtained XRD patterns of nano-γ-alumina in Figure 1 shows the formation of crystallized alumina. The broad peaks, assigned for nano-γ-alumina, appear at 2θ = 36°, 46° and 67°. The broadening of the XRD peaks revealed the nano-size nature of γ-alumina particles in alumina samples.

The XRD patterns of nano-γ-ASA showed characteristic peaks at 2θ = 31.7°, 34.5°, 36.2° and 56.5° for crystallized structure (Figure 2).

The FT-IR spectra of alumina samples calcined at 550 °C (Figure 3) showed an intense band centered around 3500 cm^{-1} and a broad band at 1640 cm^{-1}, and both were assigned to stretching and bending modes of the absorbed water. The Al–O–Al bending vibrations observed at around 1125 cm^{-1} were due to symmetric and asymmetric bending modes, respectively. The OH torsional mode observed at 800 cm^{-1} overlapped with Al–O stretching vibrations and weak band at 2091 cm^{-1} was assigned to a combination band. Bands observed at 480–650 cm^{-1} were attributed to stretching and bending modes of AlO_6.

The FT-IR spectra of ASA and nano-γ-ASA showed peaks at 605, 889, 1010–1080, and 1120–1230 cm^{-1}, corresponding to asymmetric and symmetric stretching modes of SO_2 and being a good reason for the functionalization of nano-γ-alumina with chlorosulfonic acid. The

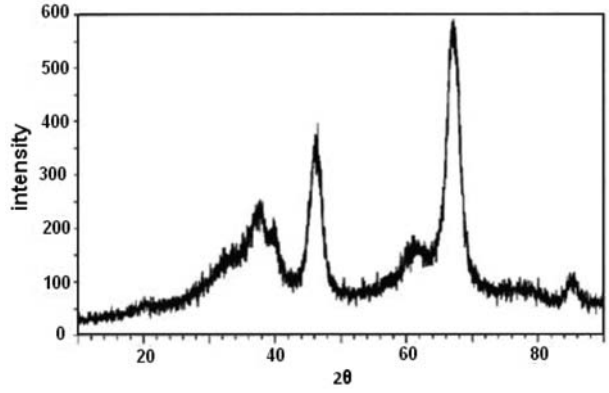


Figure 1. XRD pattern of nano-γ-alumina catalyst.

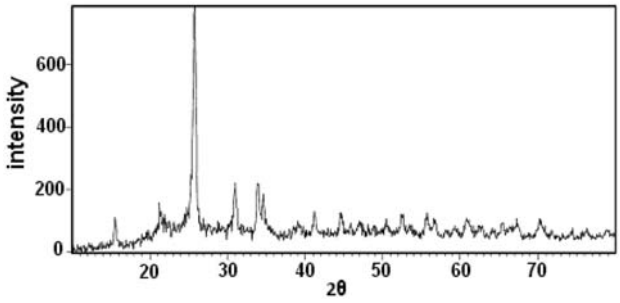


Figure 2. XRD pattern of nano-γ-ASA catalyst.

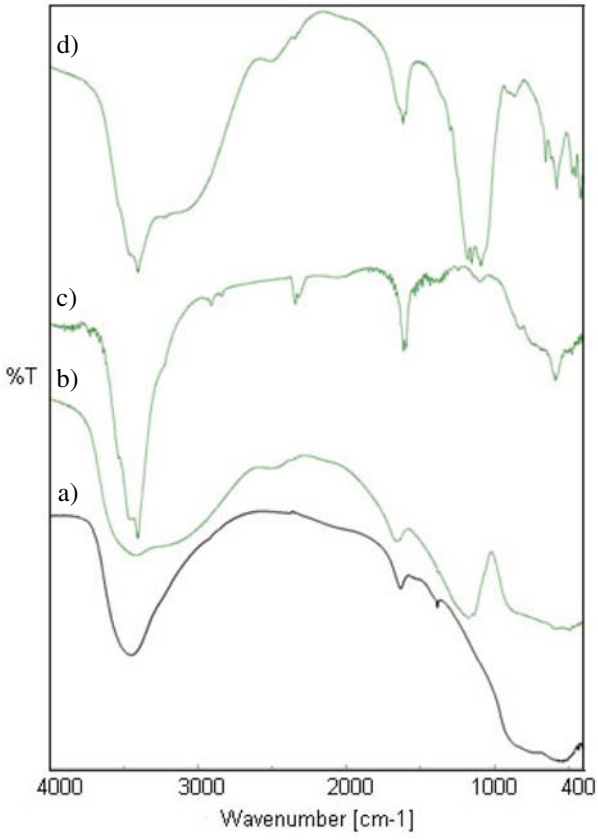


Figure 3. FT-IR spectra of a) alumina b) ASA c) nano-γ-alumina d) nano-γ-ASA catalysts.

spectrum also showed a broad OH stretching absorption around 3000–3700 cm^{-1} (Figure 3).

The morphology of the catalysts was studied with SEM and is presented in Figures 4 and 5. As shown in Figure 4, the nano-γ-alumina powders indicated strong agglomeration of particles with varied spherical sizes; however, Figure 5 showed that the particles were of irregular shape with a wide size distribution. This is quite reasonable because of the varying particle size of commercial neutral alumina, as shown earlier in our previous work.[35]

The proposed mechanism for nano-γ-ASA catalyzed reaction of benzoyl hydrazide and aromatic carboxylic acids are presented in Scheme 2. First, aromatic carboxylic acids were activated with protonation and formation of complex in the presence of the catalyst. Then, the intermediate complex reacted with a benzoyl hydrazide forming 2,5-disubstituted 1,3,4-oxadiazole derivatives.

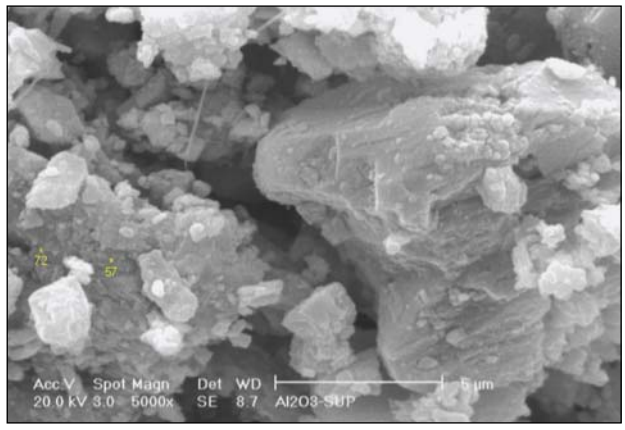


Figure 4. SEM micrograph of nano-γ-alumina catalyst.

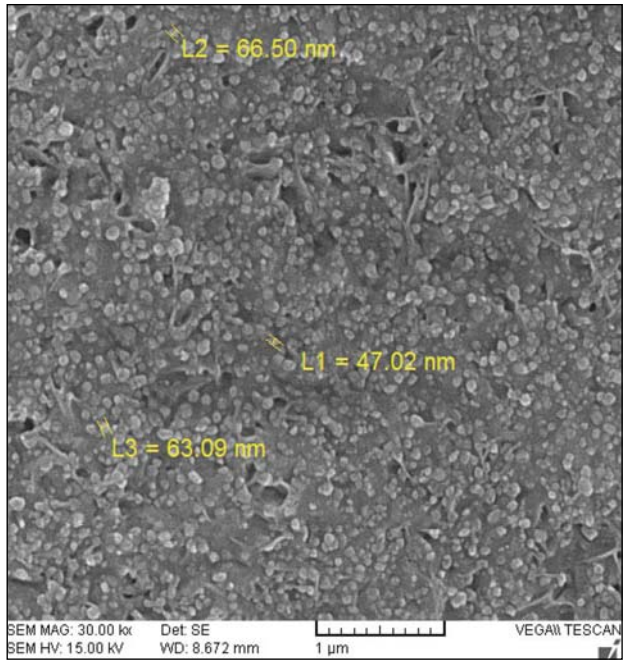
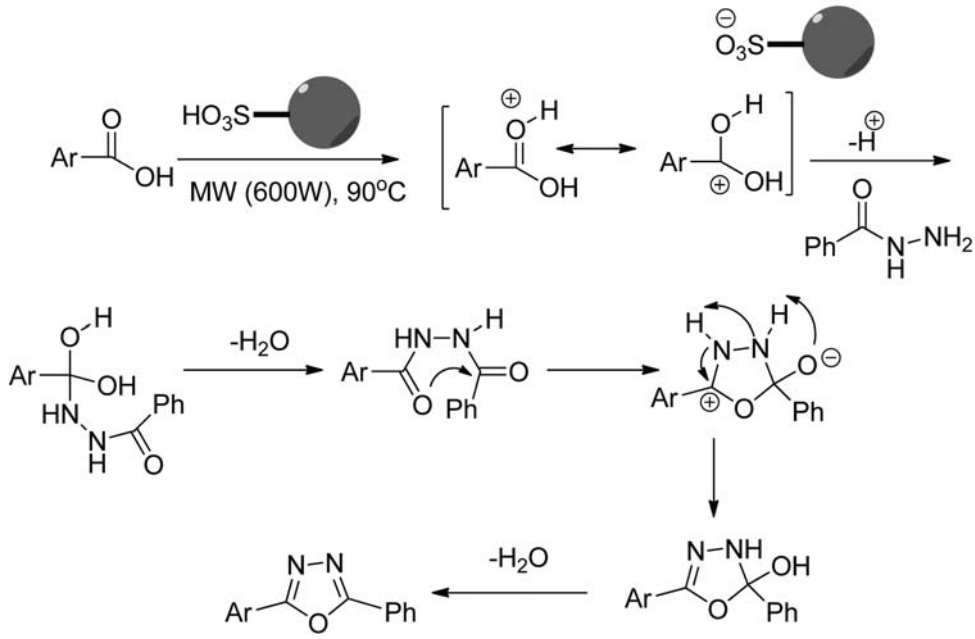


Figure 5. SEM micrograph of nano-γ-ASA catalyst.

According to Figure 6, catalysts were successfully recycled (following washing and activation) with little variation in the yield. The recovery and reusability of the catalyst were investigated in the reaction of benzoyl hydrazide and benzoic acid. After completion of the reaction, the catalyst was filtered and washed three times with 5 ml of acetone, and then several times with doubly distilled water. Finally, the catalyst was dried at 110 °C and used in the next run.



Scheme 2. Proposed mechanism for one-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

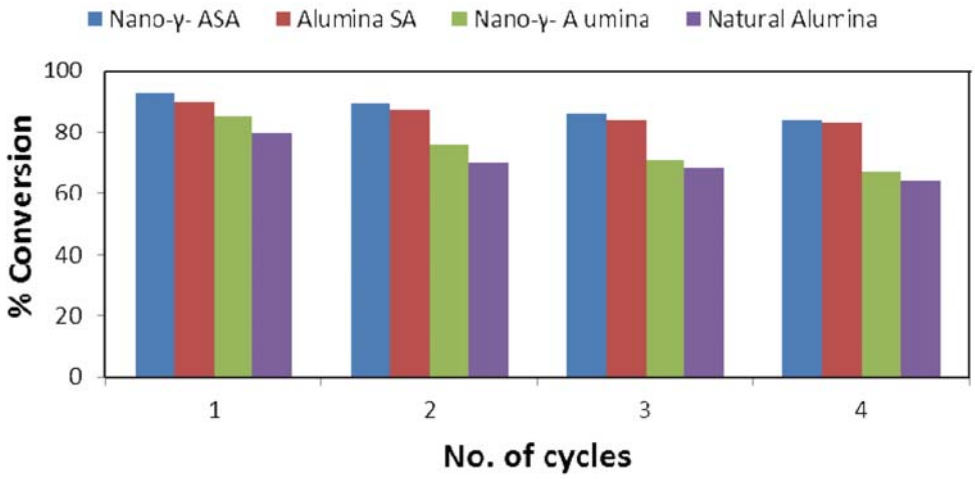


Fig 6. Change of the catalyst activity in the four consecutive runs.

3. Experimental

3. 1. General

All reagents were purchased from Merck and used without further purification. Products were characterized by spectroscopic methods (IR, FTIR, ^{1}H and ^{13}C NMR), elemental analysis (CHN), and melting points. A JASCO FT/IR-680 PLUS spectrometer was used to record IR spectra using KBr pellets. NMR spectra were recorded on a Bruker 400 Ultrashield NMR and DMSO-d_6 was used as a solvent. The reported melting points were determined by open capillary method using a Gallen Kamp melting point apparatus. Mass Spectra were recorded on a Shimadzu Gas Chromatograph Mass Spectrometer GCMS-QP5050A/Q P5000 apparatus. The reactions were performed using a microwave oven with a power of 600 W that had been especially designed for organic synthesis.

3. 2. Preparation of Catalysts

3. 2. 1. Preparation of ASA

The alumina-sulfuric acid was prepared according to the procedure described earlier.[37] A 500 mL suction flask was used and equipped with a constant pressure

dropping funnel containing freshly distilled chlorosulfonic acid (2.75 ml, 41.2 mmol). Flask was further charged with neutral alumina (10 g, 100 mmol) and dried at 120 °C for 2 h by stirring. Chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. The liberated HCl was removed through a $CaCl_2$ drying tube under reduced pressure to a water trap. ASA was kept in this condition for 1 h at room temperature, washed with distilled water several times and ethanol (2 times), and finally dried at 130 °C for 4 h.

3. 2. 2. Synthesis of nano-γ-alumina catalyst

The nano-γ-alumina was prepared by the sol–gel method according to a previously described procedure.[38] In a typical experiment, aluminum nitrate (15.6 g) was added to 400 ml of deionized water. Similarly, the solution of sodium carbonate was prepared by dissolving 7.95 g in 400 ml of deionized water. 200 ml of deionized water was taken in a 2 liter capacity round-bottom flask and vigorously stirred using the magnetic stirrer. Further, sodium carbonate and aluminum nitrate solutions were added to 200 ml of deionized water (from separate burettes) dropwise. The temperature was maintained at 70 °C during the experiment. The pH after precipitation was found to be in the range of 7.5–8.5, and the mixture was stirred for 4 h. The digested precipitates were filtered and re-dispersed again in 2 liter of hot deionized water, filtered and finally, washed with ethanol and after that, with acetone to avoid contamination of žNa' ions. Product was air dried at room temperature and calcined in a furnace at 550 °C for 5 h to produce nano-γ-alumina powders.

3. 2. 3. Synthesis of nano-γ-ASA

In a 500 ml round-bottom flask chlorosulfonic acid (1.35 ml) was added dropwise to the high surface area nano-γ-alumina (5 g) over a period of 30 min at room temperature. The components were mixed by constant stirring for 30 min at ambient temperature to make the nano-γ-ASA a uniform white solid. The liberated HCl was removed through a $CaCl_2$ drying tube under reduced pressure to a water trap. The solid phase obtained was washed with distilled water several times and dried at 130 ° for 4 hours.

3. 3. Characterization

X-ray diffraction pattern was recorded on a diffractometer (Philips X'pert) using Cu Ká radiation (λ = 1.5405 Å). The crystallite size of the crystalline phase was determined from the peak of maximum intensity by using Scherrer formula,[39] using a shape factor (K) of 0.9. The formula was: Crystallite size = K.λ/W.cosθ, where W = W_b-W_s and W_b was the broadened profile width of the experimental sample and W_s was the standard profile width of the reference silicon sample. FT-IR spectra of the catalysts were recorded using FT-IR spectrophotometer in the range of 400–4000 cm^{-1} with a resolution of 4 cm^{-1} by mixing the sample with KBr.

3. 4. The general Procedure for the Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

Reaction mixture of benzoyl hydrazide (1 mmol), aromatic carboxylic acids (1 mmol), and catalyst (15 mg) was subjected to microwave irradiation (600 W) at 90 °C for 15 min. The reaction was monitored with TLC. After the completion of the reaction, EtOAc (2 × 20 mL) was added to the reaction mixture of benzoyl hydrazide (1 mmol) and the catalyst was separated by filtration. The organic solvent was removed under reduced pressure. After purification by chromatography on the silica gel (ethylacetate/n-hexane 20:80), 2,5-disubstituted 1,3,4-oxadiazoles were obtained.

2,5-Diphenyl-1,3,4-oxadiazole (1a)
White solid, mp = 134–136 °C, FTIR (KBr): ν 1610, 1496, 1255, 1095, 834, 730 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23–8.13 (m, 4H), 7.59–7.49 (m, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.58, 131.72, 129.07, 126.93, 123.94 ppm. Anal. Calcd for $C_{14}H_{10}N_2O$ (222.08): C, 75.66; H, 4.54; N, 12.60; Found. C, 75.51; H, 4.43; N, 12.42.

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (1b)
White solid, mp = 200–202 °C, FTIR (KBr): ν 1590, 1466, 1103, 838, 722 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, 2H), 8.30 (d, 2H), 8.25–8.10 (m, 2H), 7.60–7.49 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.55, 162.84, 149.53, 132.33, 129.41, 129.24, 127.79, 127.15, 124.43, 123.31 ppm. Anal. Calcd for $C_{14}H_9N_3O_3$ (267.07): C, 62.92; H, 3.39; N, 15.72; Found: C, 62.64; H, 3.24; N, 15.52.

2-(4-Methylphenyl)-5-phenyl-1,3,4-oxadiazole (1d)
White solid, mp = 150–152 °C, FTIR (KBr): ν 1615, 1467, 1250, 1098, 830, 725 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15–8.03 (m, 2H), 7.98 (d, 2H), 7.51–7.39 (m, 3H), 7.20 (d, 2H), 2.40 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.73, 164.33, 142.26, 131.60, 129.76, 129.03, 126.88, 124.04, 121.16, 21.66 ppm. Anal. Calcd for $C_{15}H_{12}N_2O$ (237.10): C, 76.25; H, 5.12; N, 11.86; Found: C, 76.11; H, 5.06; N, 11.72.

2-[4-(Methoxy) phenyl]-5-phenyl-1,3,4-oxadiazole (1e)
White solid, mp = 144–146 °C, FTIR (KBr): ν 1595, 1486, 1105, 829, 718 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15–7.99 (m, 2H), 8.09 (d, 2H), 7.56–7.48 (m, 3H), 7.01 (d, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.53, 164.12, 162.33, 131.53, 129.02, 128.69, 126.81, 124.05, 116.41, 114.50, 55.46 ppm. Anal. Calcd

for $C_{15}H_{12}N_2O_2$ (252.09): C, 71.42; H, 4.79; N, 11.10; Found: C, 71.24; H, 4.56; N, 10.93.

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (1f)
White solid, mp = 156–158 °C, FTIR (KBr): ν 1611, 1492, 1263, 1097, 834, 728 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.15–8.10 (m, 2H), 8.08 (d, 2H), 7.51–7.40 (m, 5H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.73, 163.77, 137.99, 131.86, 129.48, 129.10, 128.17, 126.95, 123.74, 122.41 ppm. Anal. Calcd for $C_{14}H_9ClN_2O$ (256.04): C, 65.51; H, 3.53; N, 10.91; Found: C, 65.34; H, 3.41; N, 10.93.

4. Conclusions

In summary, we demonstrated an efficient, versatile and convenient method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles through the reaction of different aromatic carboxylic acids with benzoyl hydrazide under microwave irradiation without using of the solvent. A comparison of the catalytic efficiency of natural alumina, ASA, nano-γ-alumina and nano-γ-ASA was made and found that the nano-γ-ASA exhibited the greater activity. This approach is an interesting alternative to the existing methods due to mild reaction conditions, high yields, easy work-up, clean reaction profiles, and low catalyst loading.

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Povzetek

Prispevek poroča o razvoju učinkovite in okolju prijazne metode za sintezo 2,5-disubstituiranih 1,3,4-oksadiazolov z uporabo enostopenjske reakcije med različnimi aromatskimi karboksilnimi kislinami in benzoil hidrazidi v prisotnosti različnih katalizatorjev (Al_2O_3, Al_2O_3–SO_3H, nano-γ-Al_2O_3 in nano-γ-Al_2O_3-SO_3H) in z uporabo mikrovalov ter brez prisotnosti topil. Glavne prednosti metode so mili reakcijski pogoji, kratki reakcijski časi, enostavna izolacija produktov in visoki izkoristki reakcij. Katalizator lahko po reakciji recikliramo in ponovno uporabimo, brez bistvene izgube katalitske učinkovitosti.