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An efficient synthesis of imidazo[1,2-a]azine using nanocrystalline alumina powder

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Abstract

Nanocrystalline alumina powder has been synthesized using solution combustion method. The obtained nanocrystalline alumina powder was used as an efficient catalyst for the synthesis of imidazo[1,2-a]azine derivatives from one-pot three component reaction of benzaldehyde, 2-aminoazine and trimethylsilylcyanide under ultrasonic irradiation and refluxing condition. Reusability of catalyst and short reaction time as well as high yields are the advantages of this procedure.

Keywords: *Multi component reaction, Nanocrystalline alumina powder, Imidazo[1, 2-a] azine*

1. Introduction

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as an effective method to generate molecular diversity [1–2]. They offer significant advantages over conventional linear step syntheses by way of reducing time, saving money, energy and raw-materials thus resulting in both economical and environmental benefits. MCRs have great contribution toward convergent synthesis of complex and important biologically active molecules from readily available starting materials, and have emerged as powerful tools for drug discovery [3]. Recently many reports have been published based on the application of MCRs to develop novel, drug-like scaffolds [4]. Considering the importance of MCRs, the development of new and efficient routs for the synthesis of such heterocycles is of great importance [5].

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Several biological and pharmaceutical properties have been discovered for imidazo[1,2-a]azine derivatives [6]. Classically these compounds can be obtained from two component reaction of α-haloketones and 2-aminoazines [7]. For example 2-Arylimidazo [1, 2-a]pyrimidines were synthesized from reaction of α-Bromo-4-chloroacetophenone and 2-aminopyrimidine in the presence of sodium bicarbonate in ionic liquid. Although this procedure gave the desired products in good to excellent yields but the application of excessive amount of sodium bicarbonate and ionic liquid is one of the disadvantages of this procedure [8]. Being only a two-component condensation, this reaction is less suitable for the generation of a large ensemble of compounds.

In recent years many procedures for synthesis of imidazo[1,2-a]azine have been developed [9]. Synthesis of 3-amino-2-arylimidazo[1,2-a]pyridines, 3-amino- 2-arylimidazo[1,2-a]pyrazines, and 3-amino-2-arylimidazo[1,2-a]pyrimidines by heating a mixture of a 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine, a benzaldehyde, and imidazoline- 2,4,5-trione under solvent-free conditions has been disclosed [10]. Synthesis of imidazo[1,2-a]azine derivatives from reaction of isocyanide, aldehydes and 2-aminoazines has been reported in literature [9]. Various catalyst have been used for synthesis of imidazo[1,2-a]azines such as *p*-toluenesulfonic acid and [11] ammonium chloride [12].Unfortunately some of isocyanide-based multi-component reactions led to products in low yields or require long times or complicated work up procedure [13]. Imidazo[1,2-a]azine derivatives can be achieved from three-component reaction of an 2-aminoazine, aldehydes, and trimethylsilylcyanide under microwave irradiation using $Sc(OTf)_3$ as catalyst [14]. Despite the novelty of this procedure, low yields and expensive catalysts are drawbacks of this procedure. Recently ionic liquids have been used in synthesis of imidazo[1,2-a]azines [14]. Although this procedure led to high yield, but the application of relatively large amount of ionic liquids was one of the disadvantages of this method. Concerning the importance of these compounds and lack of efficient methods for synthesis of imidazo[1,2-a]azine, developing new methods for synthesis is of great interest.The application of ultrasonic irradiation in reactions using heterogeneous catalyst is a promising technique. Some advantages of ultrasound procedure are short reaction times, mild reaction conditions, formation of purer products and waste minimization. Ultrasonic irradiation can also be used to influence selectivity and yields of reactions [15]. Recently a great interest in the synthesis of nanocrystalline metal oxides due to enhanced sinter ability, mechanical [16], electrical [17], and chemical properties [18] can be seen. Various methods such as milling, sol-gel co-precipitation [19] and solution combustion [20], have been used to produce oxides nanopowder. Alumina nanopowder is one of the famous oxides with wide range of applications such as catalyst and catalytic supports. The most useful properties of this alumina provide catalyst supports which have high surface area and are well defined porosity. These properties result primarily from the nano-scale crystalline character of the alumina.

Various chemical methods such as spray pyrolysis [21], precipitation [22], sol-gel [23] and hydrothermal [24] have been employed to synthesize ultrafine Al2O3 powders.Among the available chemical processes, self-sustaining solution combustion synthesis is a convenient process, simple experimental and time saving device [25]. Solution combustion synthesis process involves an aqueous mixture containing suitable metal salts which are the precursors of the final desired oxide and a proper sacrificial organic fuel which acts as reagent reducer. Generally, hydrate nitrates are preferred to other salts because of their good solubility in water which allows them to obtain a highly homogeneous solution. The homogeneous solution is moved to a heating system to complete the reaction. Both chamber furnace and microwave can be used as the heating sources. In general, a good fuel should not react violently nor produce toxic gases, and must act as a complexing agent for metal cations. Suitable fuels are citric acid, glycine, urea, some amino acids such as serine and

asparagine, ammonium acetate or mixture of them. Urea because of its relatively low price, availability in commercially grade and safety is the most convenient fuel can be used in the combustion processes. However, combination of urea and ammonium acetate in an optimum ratio can be suitable for obtaining crystalline nanosize alumina with less agglomeration [26]. In this case, the optimum concentration of fuel was reported to be 0.75 urea and 0.25 ammonium acetate [26].Using a mixture of urea and ammonium acetate as fuel, the reactions between (and) aluminum nitrate urea and ammonium acetate are shown in equations (1) and (2) respectively:

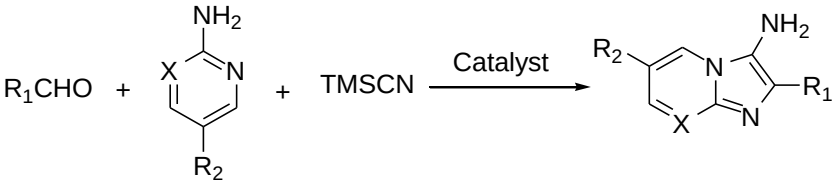
$$2\ Al(NO_3)_3.9H_2O + 5\ CO(NH_2)_2 \longrightarrow Al_2O_3 + 5\ CO_2 + 8N_2 + 28\ H_2O$$

Equation 1.

$$2\ Al(NO_3)_3.9H_2O + 2.73\ CH_3CO_2NH_4 \longrightarrow Al_2O_3 + 5.46\ CO_2 + 4.36\ N_2 + 27.55\ H_2O$$

Equation 2.

Herein we report the synthesis of nanocrystalline alumina powder using self-sustaining solution combustion and its catalytic property in the synthesis of imidazo[1,2-a]azine derivatives from one pot reaction of benzaldehydes, 2-aminoazine and trimethylsilylcyanide under refluxing and ultrasonic irradiation (Scheme1).



Sch.1.

2. Materials and methods

Aldehyde, 2-aminoazine, trimethylsilylcyanide and solvents were obtained from Merck Company and used as received.Aluminum nitrate, urea and ammonium acetate were purchased from Aldrich. Melting points were measured using Barnstead Electro thermal. Yields are based on GC/mass analysis using Agilent 6890 GC system Hp-5 capillary 30m×530µm×1.5µm nominal. Ultrasound cleaner bath was Wiseclear (Seol, Korea), with a frequency of 40 kHz, nominal power of 770W. The amount of ultrasonic energy dissipated in the reactor was estimated 200 W, using the calorimetric method. The temperature of the water bath is controlled by the addition or removal of water.

2.1. Synthesis of nanocrystalline alumina powder

Aluminum nitrate (10 g), urea (3.0 g) and ammonium acetate (1.0 g) were dissolved in 50 ml deionized water. The obtained solution was heated on hotplate (80-90 ̊C) until the excess water was removed and a highly viscous precursor gel was gained. The gel like solution was moved to a furnace and heated at 400^{o}C.Then the obtained powder was calcined in a chamber furnace at 700^{o}C.

2.2. Synthesis of imidazo[1,2-a]azine under refluxing condition: General Procedure

To a mixture of benzaldehydes (1 mmol), 2-aminoazine (1 mmol) and trimethylsilylcyanide (1 mmol) catalytic amount of nanocrystalline alumina powder (0.5 mg) was added and the mixture was refluxed in EtOH (10 mL) for proper reaction time. The progress of the reaction was monitored by TLC. At the end of reaction the catalyst was separated by centrifuge. To obtain pure product the solid residue was recrystallized from ethyl acetate.

All products were synthesized and characterized by comparing their physical and spectral data with authentic samples [6].

2.3. Synthesis of imidazo[1,2-a]azine under ultrasonic irradiation: General Procedure

Catalytic amount of nanocrystalline alumina powder (0.5 mg) were added to the mixture of aldehyde (1 mmol) 2-aminoazine (1 mmol) and trimethylsilylcyanide (1 mmol) in EtOH. The mixture was irradiated in water bath of the ultrasonic apparatus at room temperature for appropriate reaction time. As the ultrasonic apparatus show the temperature automatically so the temperature was controlled and fixed at room temperature by addition or removal of water in the bath in the case of any elevation of temperature. The reaction was monitored by TLC and after completion of the reaction, to obtain pure products the solid residue was recrystallized from ethyl acetate. All products were synthesized and characterized by comparing their physical and spectral data with authentic samples [6].

3. Results and discussion

The result of the solution combustion method was fine and white color powder with a foamy and easily crumbling structure. The crystallinity and phase identification of the powder were performed on a Philips Xpert Xray diffractometer using Cu Kα as the radiation source and Ni as the filter (Figure 1).

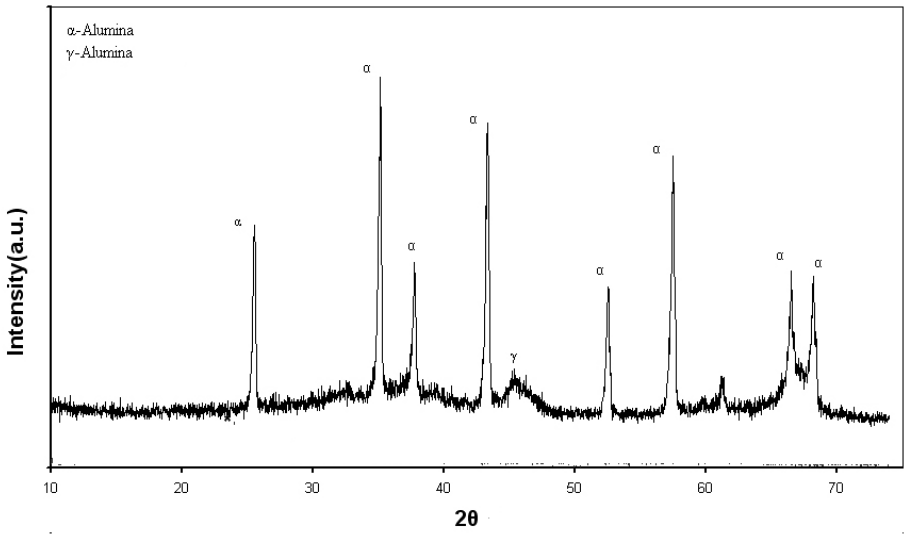


Fig.1. XRD patterns of nanocrystalline alumina powder.

As can be seen from figure 1, after heat treating at 600°C for 1 hour the sample is well crystallized and the crystalline phases are α and ß-alumina. The peak broadening method was used to calculate the average crystallite size of the powder. The full width at half maximum (FWHM) of the peak was measured from figure 1 and the average crystallite sizes were estimated using the equation of Scherrer [27]:

$$D = \frac{0.9\lambda}{(\cos\theta)\sqrt{B^2 - b^2}}$$

Equation 3.

Where D is the crystallite size, λ the wavelength of the radiation, θ the Bragg's angle and B and b are the FWHMs observed for the sample and standard, respectively. Silicon powder with a mean particle diameter of 25 mm was used to measure the instrumental peak broadening.Using equation 3 and figure 1, the average crystallite size of the powder was calculated at 60 nm. Particle size analysis results, made by a Mastersizer 2000 laser particle size analyzer, can be seen in Figure 2. Figure 2 shows a normal particle size distribution with the mean size of 15 μm.

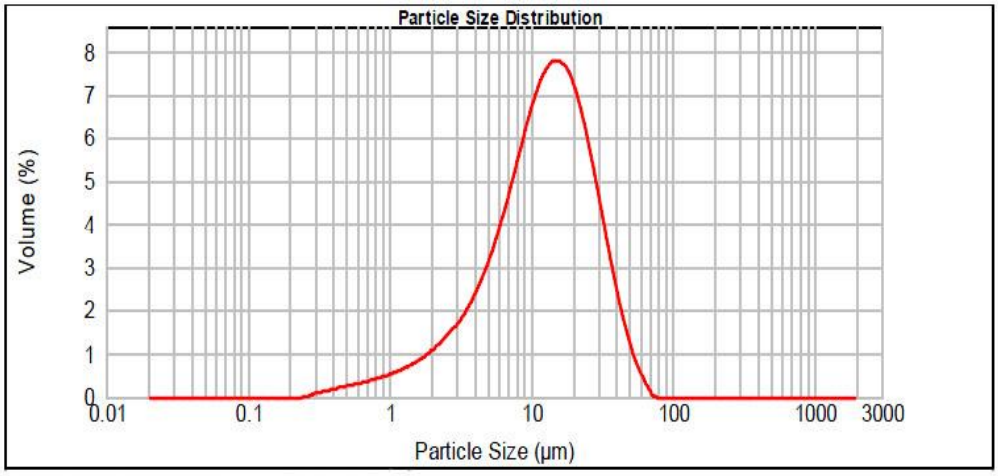


Fig.2. Particle size distribution of nanocrystalline alumina powder.

Morphology of the powder was determined by a LEO 1455VP scanning electron microscope (Figure 3). It can be seen that the particles have flake like morphology, that's why those are brittle and easy crumbling powders.

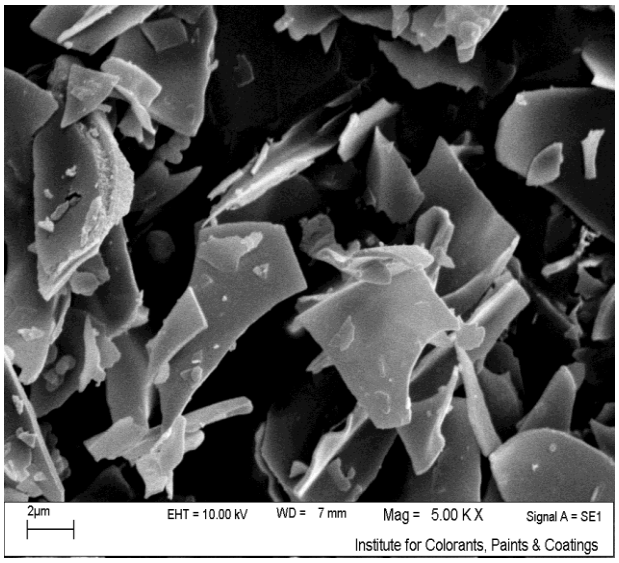


Fig.3. SEM image of nanocrystalline alumina powder

In Table 1 the results of synthesis of imidazo[1,2-a]azine in the presence of nanocrystalline alumina powder under ultrasonic irradiation and refluxing condition have been summarized. As it is shown this table in both conditions, the benzaldehyde with electron withdrawing groups led to products with higher yields and benzaldehydes with electron donating groups gave the corresponding products with slightly lower yields. It has been clear in this table that the yields of reaction in both conditions are relatively similar but under ultrasonic irradiation the reaction times and temperatures are lower than those of refluxing condition.

Table 1. Synthesis of imidazo[1,2-a]azine using 5 mg nanocrystalline alumina powder under ultrasonid irradiation and refluxing condition.

Entry	R	R'	X	Time (min)		Yield %[a]		mp.(found)	mp.(r.f.) [6]
				R*	U*	R	U		
1	4-NO_2Ph	H	N	80	50	81	81	213-215	215-218
2	4-OMe Ph	H	N	90	50	70	71	211-215	212-214
3	Ph	Br	CH	80	40	82	85	213	230
4	3-NO_2Ph	Me	CH	60	30	85	88	221-224	220-223
5	4-ClPh	Me	CH	60	30	85	86	250	248-250
6	4-Me Ph	Me	CH	60	30	85	85	230-232	230

[a]Yields refer to isolated products. *R: Refluxing Condition at 100 °C. *U: Ultrasonic irradiation at 25°C.

It is presumed that the efficiency of using ultrasound irradiation is due to the cavitation phenomena. An ultrasonic wave is a pressure wave with alternate compressions and rarefactions which is able to break the intermolecular forces maintaining the cohesion of the liquid and produces a cavity in the rarefaction section of the wave. The chemical and physical effects of ultrasound derive primarily from acoustic cavitation which includes formation, growth and collapse of the cavity [28, 29]. Bubble collapse in liquids results in an enormous concentration of energy from the conversion of kinetic energy of liquid motion into heating of the contents of the bubble. The high local temperatures and pressures produced by cavitation lead to a diverse set of applications of ultrasound such as accelerating the rate of the reaction, changing the reaction pathway, enhancing

chemical reactivity and important uses in synthetic organic compounds [30]. To optimize the reaction condition, the synthesis of 2-(4-nitro-phenyl)-imidazo[1,2-a]pyrimidine-3-ylamine was selected as model reaction.

To investigate the effect of catalyst amounts on the yields of reactions, the model reaction has been carried out in the presence of various amounts of catalysts (0.1, 0.3, 0.5, 0.7, 0.1 mg) under ultrasonic irradiation. The results have been shown in Table 2. The results show that the optimum amount of catalyst was 0.5 mg.

Table 2. The results of using various amounts of nanocrystalline alumina powder on the yields of 2-(4-nitro-phenyl)-imidazo[1,2-a]pyrimidine-3-ylamine under ultrasonic irradiation at 25°C.

Entry	Catalyst amount (mg)	Yield(%)[a]
1	0.1	69
2	0.3	75
3	0.5	81
4	0.7	80
5	0.1	80

[a]Yields refer to isolated products.

To compare the efficiency of nanocrystalline alumina powder with other catalysts, the model reaction was performed in the presence of same amount of various catalysts under ultrasonic irradiation. The results are summarized in Table 3.

Table 3. The comparison of efficiency of 5 mg of various catalysts for synthesis ofimidazo[1,2-a]azine derivatives under ultrasonic irradiation at 25°C.

Catalyst	Time (min)	Yield%[a]
Nanocrystalline alumina powder	80	81
Alumina	100	72
Silica sulforic acid	150	71
***p*-toloen sulforic acid**	150	75
Sulfamic acid	1500	73
$H_4[SiMo_{12}O_{40}]$	120	65
$H_4PMo_9O_{34}$	120	65

[a]Yields refer to isolated products.

As it is shown in this table nanocrystalline alumina powder is more effective than other used catalysts. At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with diethylether and subjected to a second run of the reaction process. The comparison of efficiency of this catalyst in the synthesis of imidazo[1,2-a]azine derivatives after three times is shown in Table 4. As shown in this table, the reduction in the yields, using reused catalyst is slight.

Table 4. The reusability of nanocrystalline alumina powder in the synthesis ofimidazo[1,2-a]azine derivatives under ultrasonic irradiation at 25°C after three times.

Entry	R	R'	X	Yield %[a] Run		
				First	Second	Third
1	4-NO_2Ph	H	N	81	80	78
2	4-OMe Ph	H	N	71	69	68
3	Ph	Br	CH	85	82	80
4	3-NO_2Ph	Me	CH	88	88	85
5	4-ClPh	Me	CH	86	86	85
6	4-Me Ph	Me	CH	85	85	83

[a]Yields refer to isolated products.

4. Conclusion

In summary, nanocrystalline alumina powder was synthesized using self-sustaining solution combustion method. The synthesized nanocrystalline alumina powder was successfully used for the synthesis of imidazo[1,2-a]azine from the one-pot three component reaction of benzaldehydes, 2-aminoazine and trimethylsilylcyanide under ultrasonic irradiation and refluxing condition. The reasonable reaction times, very good yields, simple workup procedure, and environmentally friendly conditions are main merits of this method.

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