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A green protocol for Erlenmeyer–Plöchl reaction by using iron oxide nanoparticles under ultra sonic irradiation

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1. Introduction

The Erlenmeyer–Plöchl azlactone synthesis is the preparation of azlactones (also called oxazolones) by condensation of aromatic aldehydes with hippuric acid in the presence of acetic anhydride. The azlactones are useful for the synthesis of α -ketos, amino acids and peptides. In literature numbers of methods are reported for the synthesis of azalactones involving the use of sodium acetate [1], anhydrous zinc chloride [2], alumina [3], KPO₄ [4], calcium acetate [5], basic ionic liquid [bmIm]OH [6] are the recent examples. Microwave assisted synthesis of azalactone by Erlenmeyer–Plöchl reaction is also reported [7].

Ultrasonic chemistry has received increasing attention in recent years. The driving force for ultrasound developments in organic synthesis has many facets: The increasing requirement for environmentally clean technology that minimizes the production of waste at source [8]. Ultrasound enhances the rates of reactions particularly those involving free radical intermediates [9]. Sonication allows the use of non-activated and crude reagents as well as an aqueous solvent system; therefore it is friendly and non-toxic. Ultrasound is widely used for improving the traditional reactions that use expensive reagents, strongly acidic conditions, long reaction times, high temperatures, unsatisfactory yields and incompatibility with other functional groups [10].

Continuing our investigations on the application of ultrasound in organic synthesis [11], we wish to report an efficient and

ABSTRACT

Azlactones have been prepared via Erlenmeyer synthesis from aromatic aldehydes and hippuric acid using Fe₂O₃ nanoparticles under ultrasonic irradiation. Short reaction times, easy and quick isolation of the products, and excellent yields are the main advantages of this procedure.

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practical procedure for the synthesis of azlactones with benzaldehydes and hippuric acid in presence of iron oxide nanoparticles under ultrasound irradiation (Scheme 1).

2. Experimental section

2.1. Chemicals and apparatus

All the chemicals were obtained from Merck Company and used as received. A standard magnetic stirrer (Heidolph, model MR3001) was used throughout the work at 500 rpm. X-ray diffraction (XRD) measurements of the catalyst powder were recorded using a Philips PW 1800 diffractometer. The particle size and morphology of the nanocrystalline particle were examined using transmission electron microscope TEM (LEO 912AB). The ultrasound apparatus was cleaning bath Wise clear 770 W (Seoul, Korea). The operating frequency was 40 kHz and the output power was 200 W, estimated calorimetrically [12].

2.2. Preparation of the Fe₂O₃-nanoparticles catalyst

Synthesis of Fe_2O_3 nanoparticles was performed in a 200 cm³ stainless steel batch reactor, particularly planned to endure operational pressure and temperature of 610 atm and 550 °C, respectively (Fig. 1). The reactor was filled with a 0.1 mol dm⁻³ $Fe(NO_3)_2$ ·6H₂O solution to one third of its volume. The reactor was heated at 500 °C for about 2 h. The effects of operational conditions on yield, purity, and size of the metal oxide nanoparticles have been investigated in our previous study [13], accordingly synthesis



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Scheme 1. Synthesis of azlactones in presence of iron oxide nanoparticles under ultrasound irradiation.



Fig. 1. Schematic of high pressure autoclave applied for synthesis of $\ensuremath{\text{Fe}_2\text{O}_3}$ nanoparticles.

of Fe₂O₃ nanoparticles made at optimized condition. Then; it was removed from the furnace and quenched by the cold water. The produced Fe₂O₃ particles underwent numerous washing steps by distilled water with high speed centrifuge procedure. Finally, they were spread on some Petri dishes and dried at ambient condition.

Crystal structure of the prepared Fe_2O_3 nanoparticles was analyzed by using Cu K α radiation (Fig. 2). Size and morphology of







Fig. 3. Transmission electron micrographs of Fe₂O₃ nanoparticles.

the obtained nanoparticles was observed by transmission electron microscopy (Fig. 3).

2.3. General procedure for preparation 4-(4-benzylidene)-2-phenyl-5(4H) oxazolone (**3a**)

A mixture of hippuric acid **1** (1 mmol), benzaldehyde **2a** (1 mmol), acetic anhydride (3 mmol) and iron oxide nanoparticles powder (3 mg) was irradiated in the water bath of an ultrasonic at 25–30 °C for 10 min. After completion of the reaction, the resulting suspension was centrifuged to remove the Fe₂O₃ powder. The filtrate was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO₃ solution and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the crude product, it was recrystallized from ethanol to afford pure product **3a** with 95% yield. All products were known and characterized by comparison of their physical and spectra data with those already reported [5,6].

2.4. Spectroscopic data of selected compounds

4-(4-Benzylidene)-2-phenyl-5(4H)-oxazolone (**3a**). mp. 168–170 °C (lit. mp. 170 °C); ¹H NMR (300 MHz, CDCl₃): 8.22–8.18 (m, 4H), 7.65–7.55 (m, 3H) 7.52–7.45 (m, 3H), 7.26 (s, 1H).

4-(4-Bromobenzylidene)-2-phenyl-5(4H)-oxazolone (**3b**). mp. 204–206 °C (lit. mp. 204 °C); ¹H NMR (300 MHz, CDCl₃): 8.17 (d, J = 7.4 Hz, 2H), 8.06 (d, J = 8.5 Hz, 2H), 7.62 (dd, J = 15.4, 8.1 Hz, 3H), 7.54 (t, J = 7.8 Hz, 2H), 7.15 (s, 1H).

4-(4-Nitrobenzylidene)-2-phenyl-5(4H) oxazolone (**3c**). mp. 240–241 °C (lit. mp. 241 °C); ¹H NMR (300 MHz, CDCl₃): 8.33–8.39 (m, 2H), 8.28–8.34 (m, 2H), 8.20 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.62–7.69 (m, 1H), 7.56 (dd, *J* = 10.7, 4.8 Hz, 2H), 7.20 (s, 1H).

3. Results and discussion

3.1. Reaction mechanism of synthesized nanoparticles

Adschiri et al.'s [13] reported two subsequent key mechanisms for conversion of nitrate salts to the nanoparticle of consequent metal oxides at the supercritical conditions: (1) at high temperature dissociation constant (K_w) of water increases, providing more [OH⁻] ions for metal cations (Fe³⁺) to be hydrolyzed to their hydroxides and through which to the resultant oxides, (2) dielectric constant of water is decreased, and in the same way its solvent power for dissolution of electrolytes declines. As a consequently, at elevated temperature supersaturation for precipitation of metal oxide becomes larger which as a result leads to formation of more nucleation centers, and therefore formation of smaller particles (i.e. nanoparticles) (Eqs. (1)–(3)).

Water dissociation : $H_2 O \rightarrow H^+ + OH^-$ (1)

 $Hydrolysis: Fe^{3+} + 2OH^{-} \rightarrow Fe(OH)_{3}$ (2)

Dehydration :
$$Fe(OH)_3 \rightarrow Fe_2O_3 + H_2O$$
 (3)

It must be regarded that operational condition for synthesis of ferric oxide here, extracted from optimization of the synthesis process of copper oxide nanoparticles which was our prime goal, and thus it was discussed in our previous study [13]. Our prior research had revealed that at supercritical conditions the controlling factors whose variations significantly influence the characteristic of the nanoparticles were: "temperature", "residence time", "initial concentration of relevant metal ions" and eventually its "initial pH". The outcomes of that research were specific operational conditions in which the three target parameters of the study (i.e. purity, yield, and size of the nanoparticles) attain their optimum values. The section started with describing of the procedure of design of experimental array, which was followed by analysis of the responses of the system using Taguchi-ANOVA analysis. Then, complementary experiments were discussed that together with the foregoing statistical methods specify the optimum reaction conditions.

3.2. Reaction mechanism of synthesized azlactones

The use of ultrasound in chemical reactions in solution provides specific activation based on a physical phenomenon: acoustic cavitation. Cavitation is a process in which mechanical activation destroys the attractive forces of molecules in the liquid phase. Applying ultrasound, compression of the liquid is followed by rarefaction (expansion), in which a sudden pressure drop forms small, oscillating bubbles of gaseous substances. These bubbles expand with each cycle of the applied ultrasonic energy until they reach an unstable size; they can then collide and/or violently collapse. It has been estimated and calculated that the pressure within a bubble in water can rise to more than one thousand atmospheres, and the temperature can reach several thousand degrees during a collapse, as heat conduction cannot keep up with the resulting adiabatic heating. As these bubbles are small and rapidly collapse, they can be seen as microreactors that offer the opportunity of speeding up certain reactions and also allow mechanistically novel reactions to take place in an absolutely safe manner [11].

As part of an ongoing program for the construction of natural product-like compounds [14,15], we decided to investigate the possibility of using ultrasonic to accelerate the synthesis of a range of azlactones. Initial study was performed by treatment of 4-meth-oxy benzaldehyde and hippuric acid in acetic anhydride at room temperature under ultrasound irradiation. We observed the formation of the desired product although the yield was not as good as expected (65%). Next, we surveyed the efficiency of iron oxide nanoparticles catalyst for the reaction. The same reaction was carried out in the presence of catalytic amount of iron oxide nanoparticles under ultrasound irradiation at room temperature. The result was dramatically improved when the reaction was performed in the presence of catalytic amount of iron oxide nanoparticles and

Table 1

Synthesis	of	3e	under	different	reaction	conditions.

Entry	Conditions	Catalyst	Time (min)	Yield (%)
1	Stirring rt	Without catalyst	45	11
2	Stirring rt	Fe ₂ O ₃ nanoparticles	30	34
3	Ultrasound-assisted rt	Without catalyst	30	65
4	Ultrasound-assisted rt	Fe ₂ O ₃ nanoparticles	15	97

the reaction time was shortened to 15 min (97% yield). To investigate the role of ultrasonic irradiation in this method, the reactions were carried out in the presence of the same amount of iron oxide nanoparticles under stirring condition at room temperature. The results are summarized in Table 1. It is clear that in the same reaction condition reactions under ultrasonic irradiation led to relatively higher yields and shorter reaction times. Lower yield was obtained with stirring under the same conditions of time and temperature without catalyst (11%). This optimized reaction condition was then applied to a number of reactions where the aldehyde was varied (Table 2). All the reactions proceed to completion at the time indicated in the Table 2 and the yield data are for the isolated products. As shown in Table 2, we can see a series of **2** reacted with **1** to give the corresponding products **3** in good yields.

The reaction mechanism is depicted in Scheme 2, which involves a polar transition state starting from a neutral ground state. Typically, under ultrasonic irradiation ionic reactions are accelerated by physical effects – better mass transport – which is also called "False Sonochemistry". It was suggested that sonication also assists in the breakdown of intermediates and desorption of the products from the surface [16]. The effect of iron oxide nanoparticles can be attributed to the carbonyl complexation by iron cations leading to electrophilic assistance during nucleophilic attack on this group [5].

Finally, the efficacy of the present method for the synthesis of azlactones was compared with other reported procedures (Table 3) [5,6,17,18]. We found that the reaction was efficiently promoted by ultrasound irradiation, and the reaction time was strikingly reduced to 10-15 min from hours (1-6 h) required under the traditional heating conditions in solvent, and the yield was also increased. In comparison of microwave and ultrasound irradiation for the above reaction, we observed that this heterocyclic compound can be prepared under ultrasound irradiation with some improvement in the yield (Table 3).

3.3. Effect of sonication on morphology and size of Fe₂O₃ nanoparticles

Fig. 4 shows the XRD pattern of both Fe_2O_3 before and after sonication. Obviously, neither related peaks were added nor vanished. If relative intensity was considered as a morphology criteria in comparison with reference peaks of haematite iron oxide; then we can confirm the insistence of morphology during sonification process. Moreover, calculation of sizes of the particles from their

 Table 2

 Erlenmever-Plöchl reaction with different aldehvdes.

-					
	Product	х	Time (min)	Yield (%)	Mp (°C) found/reported [15]
	3a	Н	10	95	168–170/170
	3b	4-Br	10	98	204-206/204
	3c	$4-NO_2$	10	98	240-241/241
	3d	$2-NO_2$	15	93	164-165/166
	3e	4-OMe	15	97	164-165/165



Scheme 2. The plausible reaction mechanism for synthesis of azlactones.

Table 3

Comparison of the reported methods for the condensation of benzaldehyde with hippuric acid in different conditions.

Entry	Catalyst	Time	Conditions	Yield (%)
1	Mon. K10	6 h	Reflux	89 [15]
2	Bi(III) salts	1 h	Reflux	75 [15]
3	CaCO ₃	5 min	MW (60-62 °C)	70 [5]
4	Ca(OAc) ₂	5 min	MW (48-50 °C)	97 [5]
5	Ionic liquid [bmIm]OH	10 min	rt	91 [6]
6	ZnO	10 min	rt	90[15]
7	Sm	5 min	MW	92 [16]
8	RuCl ₃	3 min	MW	80 [16]
9	$H_3PW_{12}O_{40}$	3 min	MW	87[16]
10	Fe ₂ O ₃ nanoparticles	10 min	Ultrasound-assisted rt	95



Fig. 4. Comparison of Fe₂O₃ XRD patterns before and after sonification.

XRD peak by the well known Sherrer's [19] formula composes our evidence about the growth or reduction size of nanopartciles. The Sherrer's equation is stated as Eq. (4):

$$d = \frac{k\lambda}{FWHM \times \cos\theta_{\max}} \tag{4}$$

where *k* denotes the shape factor, λ is the X-ray wavelength, (FWHM) shows line broadening at half of the maximum intensity, and θ designates the Bragg angle. In the above formula, "*d*" is the mean size of the crystalline domains, which is normally considered as the size of the nanoparticles [19]. Using the Eq. (4) and Fig. 4 average size of the Fe₂O₃ nanoparticles in fresh and sonificated samples were 11 and 5 nm respectively. Putting the above pieces of evidence in a frame lead to the conclusion that the morphology of particles were unchanged, although, sonication has been shown to reduce the particle size. This result is consistent with other studies [20] and

can be attributed to the high local pressure and temperature produced in the fluid when it is affected by ultrasonic waves cause the breaking of loose links of large nanometric colloids in solution, thus allowing the production of smaller nanoparticles [21].

4. Conclusion

In summary, we have developed an efficient and rapid ultrasonic assisted route for the synthesis of a range of azlactones, which will be applied in different biological assays. Reduction in reaction times, improved yields and suppression of side products make this reaction attractive. The advantages of this method also include good substrate generality and experimental ease.

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