ZnO nanoparticles solid phase acidic catalyst for one-pot synthesis of octahydroquinazolinone derivatives

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The reaction between dimedone, an aromatic aldehyde and urea catalysed by ZnO nanoparticles (ZnO NPs) in refluxing ethanol as a solvent provided a simple and efficient one-pot route for the synthesis of octahydroquinazolinone derivatives in excellent yields.

Keywords: ZnO nanoparticles, dimedone, aromatic aldehyde, urea, solid acid, octahydroquinazolinones

Octahydroquinazolinone derivatives have attracted attention in recent years owing to their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*[1], and also as calcium antagonists[2,3]. Methods employed for their synthesis are variants on the classical one-pot multicomponent Biginelli reaction involving dimedone, aromatic aldehydes and urea[4]. There are very few reports for the synthesis of octahydroquinazolinone derivatives using catalysts[1,4–9] in the extension of the Biginelli reaction, However, many of these procedures are expensive, harmful and are difficult to handle especially on large scale, require longer reaction times, use strongly acidic conditions and give unsatisfactory yields the formation of side products[5]. We have now used ZnO nanoparticles (ZnO NPs) as a solid phase acidic green catalyst which affords excellent yields and in the synthesis of octahydroquinazolinones.

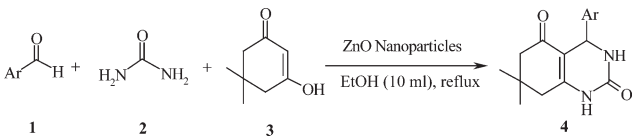
Results and discussion

In continution of our investigations of the application of solid acids in organic synthesis[10–14] we have investigated the synthesis of octahydroquinazolinone derivatives by the three-component condensation of an aromatic aldehyde **1**, urea **2**, and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **3** and in the presence ZnO NPs catalyst (Scheme 1). The best condition for octahydroquinazolinone formation involved the use of (0.009 g) ZnO NPs with 1 mmol reactants and 10mL ethanol at reflux.

The stable catalyst is easily prepared[15] and used for preparation of octahydroquinazolinones. In order to demonstrate the advantageous catalytic activity of ZnO NPs, we compared the reaction using other catalysts at reflux and for 10 min. The results are listed in Table 1 (Table 1). ZnO NPs, a solid acid, is a versatile catalyst that makes the reaction more convenient, more economical and environmentally benign.

In order to determine the optimum quantity of ZnO NPs, the reaction of benzaldehyde, urea and dimedone was carried out at reflux using different quantities of ZnO NPs (Table 2). ZnO NPs of 0.009 g gave an excellent yield in 10 min (Table 2, entry 3).

The above reaction was also examined in various solvents (Table 3).



1 2 3 4

Scheme 1 Synthesis of octahydroquinazolinones by condensation of an aromatic aldehyde, urea and dimedone using ZnO NPs (0.009 g) as catalyst.

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The results indicated that different solvents affected the efficiency of the reaction. Most of these solvents required a longer time and gave moderate yields, and the best results were obtained when ethanol was used as solvent (Table 3, entry 4).

To optimise the temperature in the mentioned reaction, we have carried out a model study with a benzaldehyde, urea and dimedone using 0.009 g of catalyst at various temperatures (Table 4). Table 4 clearly demonstrates that reflux is an effective temperature in terms of reaction time and yield.

Table 1 Evaluation of the activity of different catalysts for the condensation of benzaldehyde, urea and dimedone in ZnO NPs

Entry	Catalyst	Time/h	Yield/%[a]
1	Conc.H_2SO_4	3	85
2	$HClO_4$–SiO_2	6	54
3	Conc.HCl	6.5	35
4	Acid Alumina	6	40
5	VCl_3	2	67–92
6	VB1[b]	0.06	89
7	TMSCl	1.5	95
8	ZnO NPs	0.17	95

[a]Isolated yield.
[b]Thiamine hydrochloride (VB1).

Table 2 Optimisation of the amount of ZnO NPs on the reaction of condensation of 1mmol benzaldehyde, urea and dimedone in ethanol at 10 mL reflux

Entry	Catalyst/g	Time/min	Yield/%[a]
1	0.001	10	65
2	0.007	10	79
3	0.009	10	93
4	0.1	10	95

[a]Isolated yield.

Table 3 Effect of the solvent on the reaction between benzaldehyde, urea and dimedone by (1mmol each) ZnO NPs (0.009 g)

Entry	Solvent	Time/min	Yield/%[a]
1	CH_2Cl_2	45	88
2	H_2O	45	87
3	CH_3CN	45	48
4	EtOH	45	98
5	CH_3COOH	45	32
6	n-Hexane	45	28
7	Solvent-free	100	21

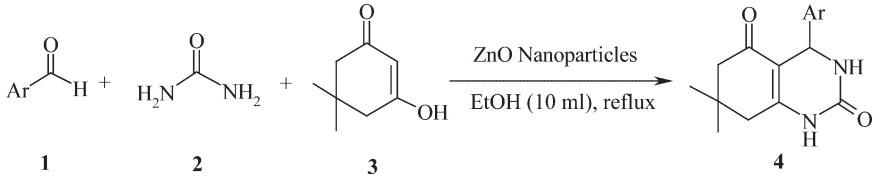
[a]Isolated yield.

Table 4 Optimisation of temperature using EtOH as solvent

Entry	Temperature/°C	Time/min	Yield/%[a]
1	25	240	58
2	60	120	65
3	Reflux	10	95

[a]Isolated yield.

Table 5 Reaction between aromatic aldehyde, urea and dimedone by ZnO NPs (0.009 g) in ethanol at reflux



1 2 3 4

Entry	Ar	Product	Time/min	Yield/%[a]	M.p/°C	
					Found	Reported[2,5,8,9]
1	C^6H_5	**4a**	10	95	292–293	290–291
2	4-ClC^6H_4	**4b**	10	91	>300	>300
3	3-ClC_6H_4	**4c**	10	93	284–285	282–283
4	4-FC_6H_4	**4d**	10	96	135–137	135–136
5	4-OH-3-$OMeC_6H_3$	**4e**	10	94	190–193	191–192
6	953-$NO_2C_6H_4$	**4f**	10	95	298–300	300–301
7	4-$NO_2C_6H_4$	**4g**	10	81	293–294	295–296
8	4-$MeOC_6H_4$	**4h**	10	88	245–247	246–247
9	4-BrC_6H_4	**4i**	10	90	>300	>300
10	4-MeC_6H_4	**4j**	10	89	>300	>300
11	3-$MeOC_6H_4$	**4k**	10	91	245–247	247–248
12	2,4-$Cl_2C_6H_3$	**4l**	10	90	270–271	268–270
13	4-$NMe_2C_6H_4$	**4m**	10	84	231–233	231–232
14	4-OHC_6H_4	**4n**	10	82	299–300	300–302

[a] Yields refer to the pure isolated products.

To study the scope of the reaction, the reaction of a series of aromatic aldehydes, urea and dimedone catalysed by ZnO NPs were examined. The results are shown in Table 5. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave products in excellent yields.

The compounds **4a–n** were characterised by their ^{1}H, ^{13}CNMR, IR and mass spectra.[2,5,8,9].

In conclusion, a series of octahydroquinazolinones have been synthesised efficiently by the condensation of aldehydes **1**, urea **2** and dimedone **3** respectively in the presence of ZnO NPs (0.009 g) in ethanol at reflux conditions. This has shown that this catalyst has advantages such as shorter reaction times, simple work-up, and affords excellent yield. The solid phase acidic catalyst was re-usable for a number of times without appreciable loss of activity. The present method does not involve any hazardous organic solvent. Therefore, this procedure may be classified as green chemistry.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer for solutions in $CDCl_3$ using TMS as an internal standard. The chemicals for this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of ZnO nanocrystals

Aqueous solutions of Zn^{2+} and urea were placed in a flask with vigorous stirring (300 rpm min^{-1}). The molar ratio of Zn^{2+} to urea was about 1:4. In order to inhibit the growth of the ZnO crystallite during the course of precipitation, a certain amount of surfactant sodium dodecyl sulfonate (SDS) was added into reaction system. Then the reaction system was heated to 95% and maintained at that temperature. After stirring for 2h, a semitransparent zinc hydroxide colloid was obtained. The precipitate was then filtered, washed with distilled water and alcohol for three or four hours, dried in air at 80 °C, and finally calcined at 230 °C for 2h to give samples with 10–40 nm particle size.[15]

General procedure

ZnO NPs (0.009 g) was added to a stirred mixture of the aromatic aldehyde (1 mmol), urea (1 mmol) and dimedone (1 mmol) in EtOH (10 mL). The reaction mixture was then stirred for 10 min at reflux. The progress of the reaction was followed by TLC (*n*-hexane:ethyl-acetate). After completion of the reaction, the mixture was filtered to remove the catalyst. After evaporation of the solvent, the crude product was recrystallised from hot ethanol to obtain the pure compound.

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