

ZnO Nanoparticles Catalyzed Efficient One-Pot Three-Component Synthesis of 2,3-Disubstituted Quinalolin-4(1*H*)-ones under Solvent-Free Conditions

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ZnO nanoparticles were prepared and applied as a favorable catalyst in three-component one-pot cyclocondensation reaction of isatoic anhydride with amines and aldehydes to afford the corresponding 2,3-disubstituted quinalolin-4(1*H*)-ones in good yields. Reactions occurred under solvent-free conditions in high atom economy.

Keywords: ZnO nanoparticles, Isatoic anhydride, Quinazolinone, Solvent-free

INTRODUCTION

The development of efficient and environmentally benign chemical processes using recyclable catalysts and environmentally benign solvents is one of the major tasks in organic synthesis [1]. Quinazolin-4(1*H*)-ones have been reported to have various biological activities, such as anticancer [2], antidiuretic [3], anticonvulsant [4]. Several methods have been reported for synthesis of quinazolinones. Common synthetic methods for aryl-substituted quinazolinones included cyclization of *o*-acylamino-benzamides [5], amidation of 2-aminobenzonitrile followed by oxidative ring closure [6], solid-phase synthesis of 2-arylamino-substituted quinazolinones [7], preparation from isatoic anhydride [8-14] and Pd-catalyzed heterocyclization of nitroarenes [15]. These procedures have certain limitations such as long reaction time, harsh reaction conditions, and low yields. Herein, we describe the use of ZnO nanoparticles (ZnONPs), as Lewis acid catalyst, for the synthesis of quinazolinone derivatives *via* a one-pot, three- component cyclocondensation reaction of isatoic anhydride with amines

and aldehydes (Scheme 1).

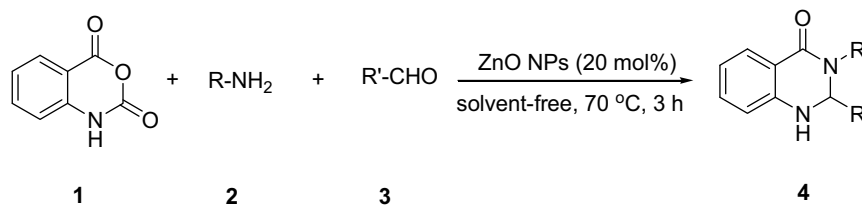
EXPERIMENTAL

All chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Vario EL III CHNOS elemental analyzer and the results agreed favorably with the calculated values. Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ¹H and ¹³C NMR spectra were measured on a Bruker DRX-500 Avance instrument at 500.1 and 125.7 MHz, respectively. Scanning electron microscopy (SEM) images were obtained using a Stereo Scan XL-30 Philips.

General Procedure

A mixture of isatoic anhydride (0.163 g, 1 mmol), amines (1 mmol), benzaldehydes (1 mmol) and ZnO NPs (20 mol-%) was heated at 70 °C for 3 h. After completion of the reaction as indicated by TLC [petroleum ether/EtOAc (4/1)], the reaction mixture was cooled to room temperature. The solid

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Amine 2 R	Aldehyde 3 R'	Product 4	Yield (%) ^a	TON ^b	TOF (h ⁻¹) ^c
Me	Ph	4a	92	4.6	1.5
Et	<i>p</i> -MeOC ₆ H ₄	4b	94	4.7	1.6
Et	<i>m</i> -O ₂ NC ₆ H ₄	4c	97	4.8	1.6
Ph	Ph	4d	88	4.4	1.5
Ph	<i>m</i> -O ₂ NC ₆ H ₄	4e	93	4.6	1.5
Bn	<i>p</i> -ClC ₆ H ₄	4f	92	4.6	1.5
<i>p</i> -MeOC ₆ H ₄ CH ₂	<i>p</i> -MeOC ₆ H ₄	4g	90	4.5	1.5
<i>p</i> -MeOC ₆ H ₄ CH ₂	<i>p</i> -Tolyl	4h	89	4.5	1.5
<i>p</i> -MeOC ₆ H ₄ CH ₂	<i>m</i> -O ₂ NC ₆ H ₄	4i	95	4.8	1.6
<i>p</i> -MeOC ₆ H ₄ CH ₂	<i>p</i> -O ₂ NC ₆ H ₄	4j	96	4.8	1.6

^aThe yields refer to pure isolated products characterized by spectral data. ^bTurnover number (average number of product molecules produced per mole of the catalyst). ^cTurnover frequency (turnover number per time).

Scheme 1

residue was dissolved in hot ethanol and centrifuged to separate the catalyst. The isolated catalyst can be reused without appreciable loss of its catalytic activity. By recrystallization from ethanol, pure products were obtained. Compounds **4a-4e** are known and were characterized by comparison of their spectroscopic and physical data with those reported in the literature [20,21]. The unknown compounds **4f-4j** are properly characterized by their spectroscopic data.

3-Benzyl-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (4f). White powder; yield 0.32 g (92%); m.p.: 122-124 °C; IR (KBr): $\tilde{\nu}$ = 3305, 1630 cm⁻¹; EI-MS: *m/z* = 350 (M⁺ + 2, 6), 348 (M⁺, 16), 257 (56), 237 (93), 214 (11), 180 (14), 120 (13), 106 (31), 91 (100), 65 (16); ¹H NMR (CDCl₃): δ = 3.68 (1H, d, ²J = 15.4 Hz, CH), 4.56 (1H, br s, NH), 5.58 (1H, d, ²J = 15.4 Hz, CH), 5.6 (1H, br s, CH), 6.53 (1H, d, ³J = 8.0 Hz, CH), 6.88 (2H, t, ³J = 7.4 Hz, CH), 7.22 (3H, d, ³J = 8.3 Hz, CH), 7.23-7.34 (6H, m, CH), 8.03 (1H, dd, ³J = 7.7 Hz, ⁴J = 1.2 Hz, CH) ppm; ¹³C NMR (CDCl₃): δ = 47.0 (CH₂),

70.4 (CH), 114.5 (CH), 115.8 (C), 119.5 (CH), 126.6 (C), 127.6 (CH), 128.0 (2CH), 128.6 (2CH), 128.9 (CH), 129.1 (2CH), 133.8 (2CH), 135.2 (CH), 136.6 (C), 137.9 (C), 144.9 (C), 163.1 (C=O) ppm.

3-(4-Methoxybenzyl)-2,3-dihydro-2-(4-methoxyphenyl)quinazolin-4(1H)-one (4g). White powder; yield 0.34 g (90%); m.p.: 159-161 °C; IR (KBr): $\tilde{\nu}$ = 3310, 1626 cm⁻¹; EI-MS: *m/z* = 374 (M⁺, 14), 253 (52), 267 (89), 136 (28), 121 (100); ¹H NMR (CDCl₃): δ = 3.61 (1 H, d, ²J = 15.0 Hz, CH), 3.81 (3H, s, MeO), 3.82 (3H, s, MeO), 4.36 (1H, br s, NH), 5.52 (1H, d, ²J = 15.0 Hz, CH), 5.59 (1H, s, CH), 6.51 (1H, d, ³J = 8.0 Hz, CH), 6.83-6.89 (5H, m, CH), 7.14 (2H, d, ³J = 8.4 Hz, CH), 7.22 (2H, d, ³J = 8.5 Hz, CH), 7.27 (1H, d, ³J = 7.7 Hz, CH), 8.04 (1H, d, ³J = 7.8 Hz, CH) ppm; ¹³C NMR (CDCl₃): δ = 46.1 (CH₂), 55.3 (MeO), 55.4 (MeO), 70.6 (CH), 113.9 (2CH), 114.2 (2CH), 115.9 (C), 119.1 (CH), 128.1 (2CH), 128.8 (CH), 128.9 (C), 129.5 (2CH), 131.5 (C), 133.5 (CH), 145.2 (C), 159.02 (C), 160.4 (C), 163.2 (C=O) ppm.

3-(4-Methoxyphenyl)-2,3-dihydro-2-p-tolylquinazolin-4(1H)-one (4h). White powder; yield 0.32 g (89%); m.p.: 151-153 °C; IR (KBr): $\bar{\nu}$ = 3315, 1625 cm^{-1} ; EI-MS: m/z = 358 (M^+ , 18), 267 (95), 237 (58), 136 (35), 121 (100); ^1H NMR (CDCl_3): δ = 2.34 (3H, s, Me), 3.58 (1H, d, 2J = 15.0 Hz, CH), 3.80 (3H, s, MeO), 4.54 (1H, br s, NH), 5.56 (1H, d, 2J = 15.0 Hz, CH), 5.57 (1H, br s, CH), 6.49 (1H, d, 3J = 8.0 Hz, CH), 6.83-6.86 (3H, m, CH), 7.12-7.27 (7H, m, CH), 8.01 (1H, d, 3J = 7.7 Hz, CH) ppm; ^{13}C NMR (CDCl_3): δ = 21.2 (Me), 46.2 (CH_2), 55.3 (MeO), 70.7 (CH), 114.0 (2CH), 114.3 (CH), 115.8 (C), 119.0 (CH), 126.5 (2CH), 128.7 (CH), 128.9 (C), 129.5 (2CH), 129.6 (2CH), 133.5 (CH), 136.6 (C), 139.2 (C), 145.2 (C), 159.0 (C), 163.2 (C=O) ppm.

3-(4-Methoxybenzyl)-2,3-dihydro-2-(3-nitrophenyl)quinazolin-4(1H)-one (4i). Yellow powder; yield 0.37 g (95%); m.p.: 189-191 °C; IR (KBr): $\bar{\nu}$ = 3270, 1618 cm^{-1} ; EI-MS: m/z = 389 (M^+ , 21), 268 (60), 267 (88), 135 (29), 121 (100); ^1H NMR (CDCl_3): δ = 3.78 (1H, d, 2J = 15.1 Hz, CH), 3.80 (3H, s, MeO), 4.59 (1H, br s, NH), 5.51 (1H, d, 2J = 15.1 Hz, CH), 5.73 (1H, s, CH), 6.57 (1H, d, 3J = 8.0 Hz, CH), 6.84 (2H, d, 3J = 8.4 Hz, CH), 6.93 (1H, t, 3J = 7.5 Hz, CH), 7.14 (2H, d, 3J = 8.4 Hz, CH), 7.30 (1H, t, 3J = 7.7 Hz, CH), 7.49 (1H, t, 3J = 8.0 Hz, CH), 7.65 (1H, d, 3J = 7.7 Hz, CH), 8.04 (1H, d, 3J = 7.8 Hz, CH), 8.12 (1H, s, CH), 8.18 (1H, d, 3J = 7.9 Hz, CH) ppm; ^{13}C NMR (CDCl_3): δ = 46.9 (CH_2), 55.3 (MeO), 69.8 (CH), 114.2 (2CH), 114.8 (CH), 116.2 (C), 120.1 (CH), 121.8 (CH), 124.0 (CH), 128.2 (C), 128.9 (CH), 129.5 (2CH), 130.0 (CH), 132.2 (CH), 133.9 (CH), 141.9 (C), 144.2 (C), 148.5 (C), 159.3 (C), 162.8 (C=O) ppm.

3-(4-Methoxybenzyl)-2,3-dihydro-2-(4-nitrophenyl)quinazolin-4(1H)-one (4j). Yellow powder; yield 0.37 g (96%); m.p.: 190-192 °C; IR (KBr): $\bar{\nu}$ = 3275, 1619 cm^{-1} ; EI-MS: m/z = 389 (M^+ , 23), 268 (58), 267 (90), 135 (25), 121 (100); ^1H NMR (CDCl_3): δ = 3.67 (1H, d, 2J = 15.1 Hz, CH), 3.81 (3H, s, MeO), 4.51 (1H, br s, NH), 5.59 (1H, d, 2J = 15.1 Hz, CH), 5.70 (1H, d, 3J = 3.1 Hz, CH), 6.55 (1H, d, 3J = 8.0 Hz, CH), 6.85 (2H, d, 3J = 8.6 Hz, CH), 6.93 (1H, t, 3J = 7.6 Hz, CH), 7.16 (2H, d, 3J = 8.6 Hz, CH), 7.30 (1H, dt, 3J = 7.6 Hz, 4J = 1.6 Hz, CH), 7.45 (2H, d, 3J = 8.7 Hz, CH), 8.05 (1H, dd, 3J = 7.8 Hz, 4J = 1.3 Hz, CH), 8.17 (2H, d, 3J = 8.7 Hz, CH) ppm; ^{13}C NMR (CDCl_3): δ = 46.8 (CH_2), 55.3 (MeO), 69.6 (CH), 114.2 (2 CH), 114.7 (C), 114.8 (CH), 120.1 (CH), 124.2 (2CH), 127.4 (2CH), 128.1 (C), 128.9 (CH), 129.5 (2CH),

133.9 (CH), 134.0 (C), 137.7 (C), 139.7 (C), 159.0 (C), 162.8 (C=O) ppm.

RESULTS AND DISCUSSION

The choice of an appropriate reaction medium is important for successful synthesis. Initially, the three-component reaction of isatoic anhydride, benzaldehyde, and aniline as a simple model was investigated to optimize the reaction conditions (Table 1). Different amounts of the catalyst were used in the model reaction. As shown in Table 1, best result was obtained with a 20 mol-% of ZnO NPs, and the desired product **4d** was obtained in 88%. Using lower amount of catalyst resulted in lower yields, while higher amount of catalyst did not affect reaction times and yields (Table 1).

After optimizing the reaction conditions, a variety of aromatic aldehydes and amines were employed under similar reaction conditions to evaluate the scope of this reaction. The results are shown in Scheme 1. These reactions proceeded smoothly and no undesirable side reactions were observed. The aromatic aldehydes carrying both electron-withdrawing and electron-releasing substituents were converted to the corresponding quinazolinones **4a-4j** in good yields.

A plausible mechanism for this reaction is shown in Scheme 2. It is conceivable that the ZnO NPs are coordinated to the oxygen atom of the carbonyl groups in different stages of the reaction activating them for the nucleophilic attack of the amine and amide nitrogen atoms. The high surface area-to-volume ratio of ZnO NPs is mainly responsible for their

Table 1. Reaction between Isatoic Anhydride, Benzaldehyde, and Aniline, under Different Conditions

Catalyst (mol%)	Time (h)	Yield (%)
None	14	50
Bulk ZnO (20)	8	70
Bulk ZnO (30)	8	72
ZnO NPs (10)	3	80
ZnO NPs (20)	3	88
ZnO NPs (30)	3	88

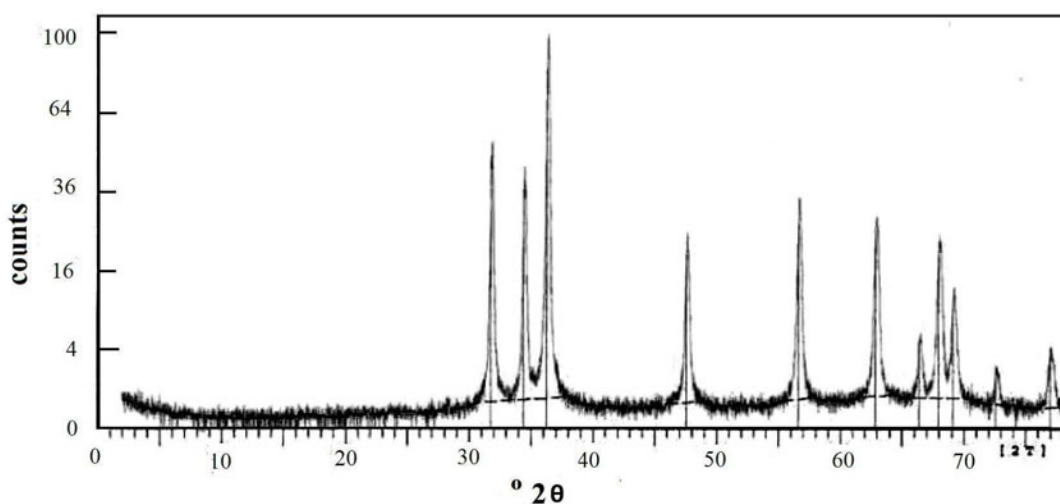
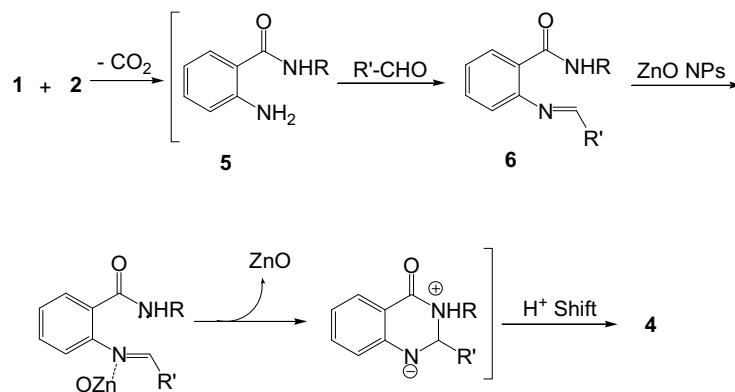


Fig. 1. XRD pattern of synthesized ZnO nanoparticles.

catalytic properties [16-18].

The ZnO NPs were prepared through a solid-state reaction [19]. Figure 1 shows XRD pattern of the ZnO NPs. All of the diffraction peaks are in agreement with the JCPDS file of ZnO (JCPDS No. 36-1451). The morphology and grain size of the ZnO NPs were investigated by SEM (Fig. 2). They have a narrow distribution of sizes, from 32 nm to 48 nm.

In Table 2, the catalytic activity of the synthesized ZnO NPs to catalyze the formation of compounds **4** is compared with other catalyst [8-14]. In most cases, the ZnO NPs are comparable or better than other catalysts.

CONCLUSIONS

In conclusion, we have developed an efficient ZnO NPs as Lewis acid catalyst for the synthesis of quinazolinones by a one-pot, three-component condensation of isatoic anhydride with amines and aldehydes in high atom economy under solvent-free conditions. The ZnO NPs would act as a catalyst to activate the substrate molecules. Moreover, the catalyst can be recovered conveniently and reused for at least three reaction cycles without appreciable loss of activity.

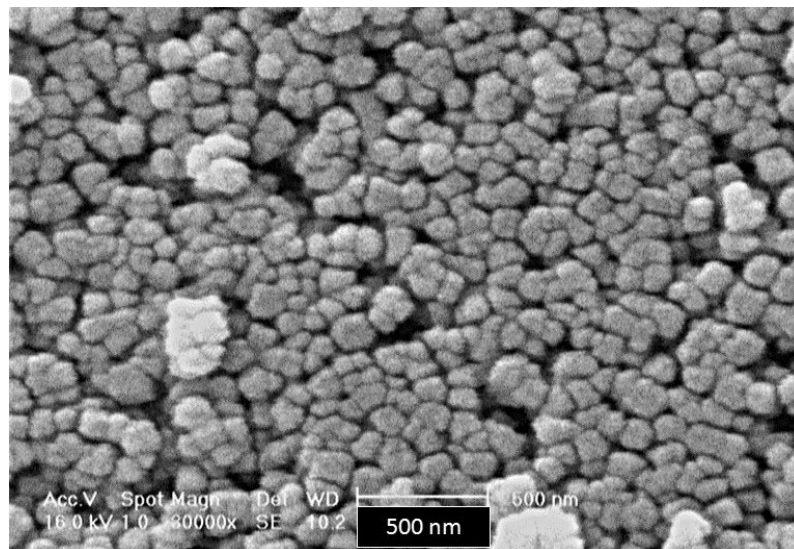


Fig. 2. SEM image of the synthesized ZnO NPs.

Table 2. A comparison of Catalytic Activity of Various Catalysts in Condensation Reaction of Isatoic Anhydride, Benzaldehyde and Aniline

Conditions	Yield (%)	Ref.
Alum, H ₂ O, reflux, 1 h	65	[8]
Alum, EtOH, reflux, 4 h	78	[8]
Amberlyst 15, solvent-free, MW, 3 min	81	[9]
Ga(OTf) ₃ , EtOH, 70 °C, 1 h	79	[10]
Zn(PFO) ₂ , H ₂ O/EtOH (1:3), reflux, 6 h	82	[11]
SSA, H ₂ O, 80 °C, 4.5 h	85	[12]
SSA, solvent-free, 80 °C, 5 h	80	[12]
[bmim]BF ₄ ⁻ , 70 °C, 1.5 h	80	[13]
Fe ₃ O ₄ NPs, H ₂ O, reflux, 2 h	80	[14]
ZnO NPs, solvent-free, 70 °C, 3 h	88	This work

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