NH_4Cl/Zn powder: An efficient, chemoselective reducing catalyst for the microwave-assisted synthesis of 2,3-disubstituted quinolines *via* tandem Knoevenagel condensation

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Abstract

An efficient, a hitherto unreported, sustainable, and environmentally friendly microwave-assisted synthesis of 2,3-disubstituted quinolines by reductive cyclization of 2-nitrobenzaldehydes and various active methylene compounds *via* tandem Knoevenagel condensation promoted by an efficient eco-friendly, chemoselective reducing catalyst ammonium chloride (NH_4Cl) and zinc powder was developed. This present methodology is a mild, green, efficient, and environmentally benign process as it eliminates the harsh reaction conditions, non-volatile solvents, relatively expensive reagents, high catalyst loading, and also provides a number of other benefits like fast synthesis, simple reaction set-up, and good to the excellent yield of the products.

Key words

Microwave assisted synthesis; Knoevenagel condensation and reductive cyclization; NH_4Cl/Zn a chemoselective catalyst; quinoline derivatives

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INTRODUCTION

Quinoline moiety exists in numerous natural products, especially in alkaloids, and is often used for the synthesis of many pharmacologically active compounds.[1] A number of quinoline derivatives are pharmacologically important because of their wide spectrum of biological activities.[2] Quinoline moieties have attracted both synthetic chemists and biologists as they are crucial components of various naturally existing pharmacologically active compounds.[3]

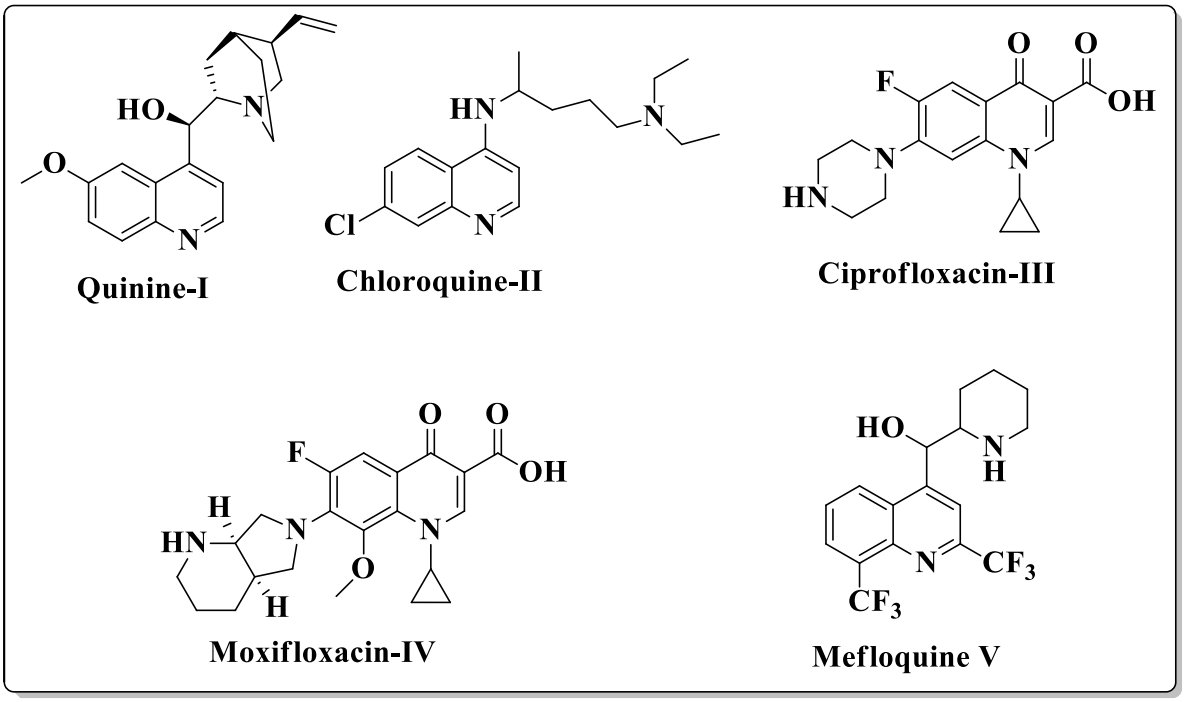


Fig. 1. Chemical structures of pharmacologically active quinolone moieties

Some promising quinoline derivatives are shown in **Figure 1**. It was found that quinoline moieties possess a wide range of pharmacological properties like antibacterial,[4] antifungal,[5] anticancer,[6] antiviral,[7] and antimalarial.[8] Therefore, the construction of pharmacologically active quinoline moieties has gained enough interest in synthetic organic chemists. Various methods were established for designing the quinoline derivatives including the Skraup,[9] Conrad-Limpach-Knorr,[10] Pfitzinger,[11] Friedlander,[12] and Friedlander condensation.[13-18]

For the synthesis of quinoline moieties, different new strategies were set up which utilizes metallic or organometallic chemicals such as CuCN, LiCl,[19] $RuCl_3.nH_2O/3PPh_3$,[20] $Yb(OTf)_3$,[21] $W(CO)_5(THF)$,[22] $BF_3.OEt_2$,[23,24] Benzotriazoleiminium salts,[25] etc. Notwithstanding the numerous merits detailed by these strategies be that as it may be, they are too tormented by impediments like destitute yields, troublesome work-up, and gushing contamination.

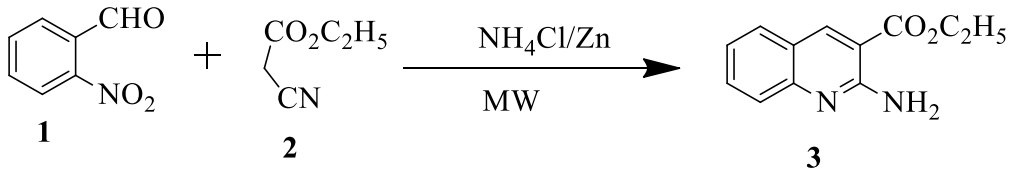
These days, sustainable reactions are the challenge for chemists in zones like health, social concern, environment and to beat these problems it's aimed to develop straightforward and simple strategies to conduct organic reactions under gentle conditions.[26] Reactions performed under microwave oven offers various benefits such as short reaction time, good to the excellent yield of the product, eco-friendly in nature, and consumes less heat (thermal energy).[27,28]

In the radiance of the above-mentioned facts, and as part of our continuing investigation about committed to the improvement of a facile, simple, and commercially affordable methods for the synthesis of various organic compounds,[29,30] an attempt has been through to carry out a highly atom-economic synthesis of 2,3-disubstituted quinoline derivatives by reductive cyclization of 2-nitrobenzaldehydes and various active methylene compounds *via* tandem Knoevenagel condensation under microwave irradiation in NH_4Cl and zinc powder. In the literature, it has been reported that there is growing interest in ammonium chloride as a catalyst due to its soft, most diligent activities, eco-friendly property, commercially accessible, and affordable.[31] Very recently ammonium chloride is effectively used in the chemoselective reduction of nitro compounds to aromatic amines with samarium metal,[32] reduction of azides to amines or amides,[33] reductive cleavage of azo compounds to Amines.[34] Thus we planned to develop a new method for synthesis of quinoline derivatives by using ammonium chloride as a mild acid catalyst that can avoid the restriction of functionally substituted substrates.

RESULTS AND DISCUSSION

At the initial stage of reaction, we evaluated the most favorable requirements with respect to the volume of solvent, the quantity of catalyst, reaction time, and watt power of microwave radiations. For this cause, the reaction of 2-nitrobenzaldehyde (**1**) and ethyl cyanoacetate (**2**) under microwave irradiation in the presence of NH_4Cl/Zn powder catalyst was chosen as a model

reaction (Scheme 1). When the reaction was conducted under solvent-free conditions in the absence of a catalyst (Table 1, entry 1), only a 10% yield of the desired product (**3a**) was observed. Next, we investigated the effect of solvents on the reaction rate and yield of the product. It is to be noted here that, the yield of the product obtained under solvent-free condition is higher than the yield of the product obtained with various solvents like EtOH, H_2O, $C_6H_5CH_3$, CH_3CN, and DMF (Table 1, entries 2,3,4,5,6).



Scheme 1: Synthesis of 2,3-disubstituted quinoline.

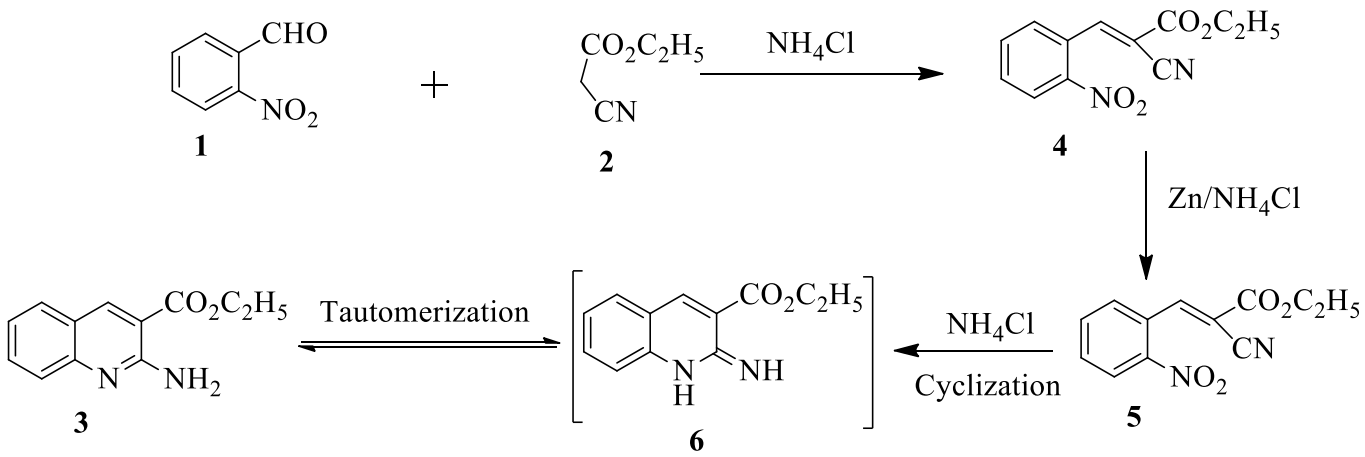
Table 1: Investigation of reaction conditions for the synthesis of quinoline derivatives[a]

Entry	Solvent	NH_4Cl/Zn-Catalyst (mole %)	Temp (Watt)	Time (min)	Yield (%)
1	-	-	400	10	10
2	EtOH	10	400	10	80
3	H_2O	10	400	10	60
4	$C_6H_5CH_3$	10	400	10	60
5	CH_3CN	10	400	10	60
6	DMF	10	400	10	50
7	-	10	200	10	50
8	-	10	300	10	80
9	-	10	400	4	98
10	-	2.5	400	4	60
11	-	5	400	4	70
12	-	8	400	4	85
13	-	10	400	4	98
14	-	15	400	4	95

[a]Reaction condition: 2-nitrobezaldehyde (10 mmol), ethyl cyanoacetate (10 mmol).
[b]Yields of the isolated products.

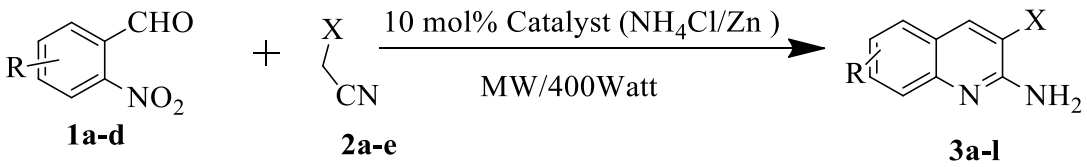
The most extreme power of the microwave radiation was optimized by conducting the above model scheme at distinctive watt powers (200, 300, 400 W). Microwave radiations at 400 W and reaction time 4 min gave the highest yield of the desired product (Table 1, entries 7, 8, 9). Next, we investigated the impact of the sum of catalyst the (NH_4Cl/Zn). The optimized condition shows that 1.5 mmol Zn powder (10 mol%) and 1 mmol NH_4Cl (10 mol%) was sufficient to get a maximum yield of the desired product. The optimum amount of catalyst (NH_4Cl/Zn) required in the above reaction was studied by changing the amount of catalyst from 2.5, 5, 8, 10, and 15 mol% in the presence of microwave radiations at 400 W (Table 1, entries 10, 11, 12, 13, 14). The corresponding product was obtained in 60%, 70%, 90%, 98%, and 95% yield respectively. Thus, the above results showed that the most excellent results were gotten when the reaction was carried out with 10 mol% of NH_4Cl/Zn catalyst in a microwave oven at 400 W for 4 min under solvent-free conditions.

To investigate the possible reaction pathway controlled experiment was carried out. A possible reaction mechanism (Scheme 2) has been described on the basis of controlled reaction and experimental study. Initially, Knoevenagel adduct was obtained by the reaction of 2-nitrobenzaldehyde and ethyl cyanoacetate which further undergo nucleophilic attack of the amino group on cyano and subsequent intramolecular cyclization and tautomerization lead to obtain the final product.



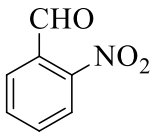
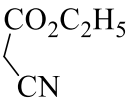
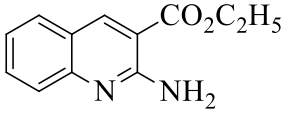
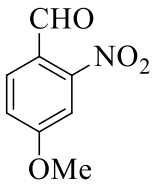
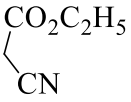
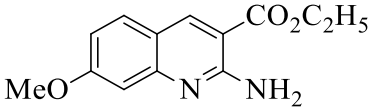
Scheme 2: A plausible mechanism for the synthesis of ethyl 2-aminoquinoline 3-carboxylate.

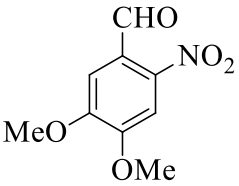
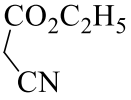
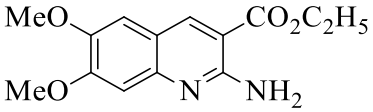
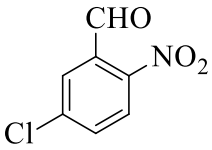
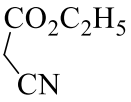
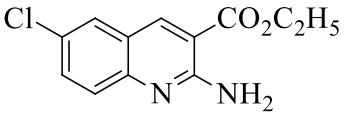
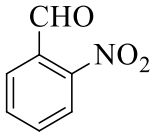
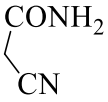
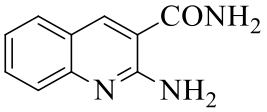
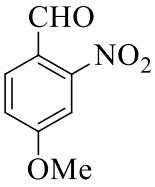
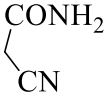
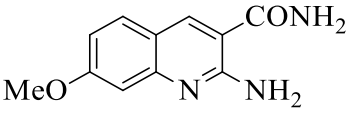
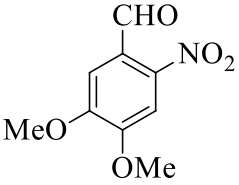
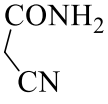
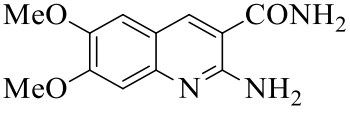
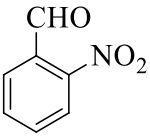
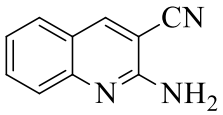
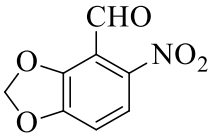
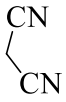
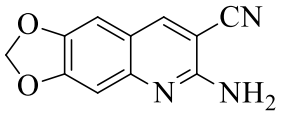
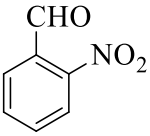
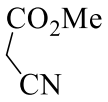
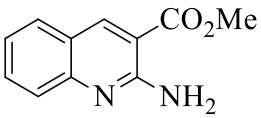
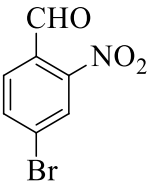
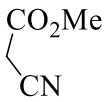
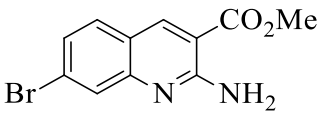
In the light of the above results, and to show the universality of the reaction (Scheme 1), the upgraded reaction circumstances were subjected to a variety of benzaldehydes and active methylene compounds (Scheme 3), and the results were reported (Table 2). It is to be noted that in all cases, the reaction proceeds smoothly with 10 mol% NH_4Cl/Zn catalyst under solvent-free microwave-assisted condition (Scheme 3). Next, we evaluated the reactivity of various benzaldehydes bearing electron-withdrawing and electron-donating groups. It was observed that the condensation of benzaldehydes with electron-withdrawing groups with active methylene compounds, can be carried out in relatively less time than the benzaldehydes with electron-donating groups.

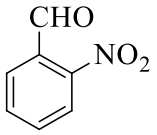
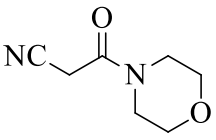
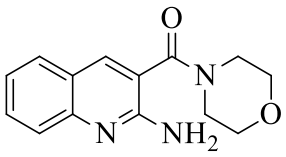


Scheme 3: Synthesis of 2,3-disubstituted quinolines.

Table 2: NH_4Cl/Zn catalyzed synthesis of 2,3-disubstituted quinoline derivatives[a]

Comp no	1 (Reactant)	2 (Reactant)	3 (Product)	Time (min)	Yield[b] (%)
3a				4	98
3b				4.5	97

3c				6	95
3d				4	98
3e				4.5	97
3f				4.5	95
3g				6	90
3h				4.5	97
3i				6	90
3j				4.5	95
3k				4.5	90

3l				6	90

[a]Reaction condition: reaction of **1** (10 mmol), **2** (10 mmol) in (NH_4Cl/Zn) catalyst (10 mol %) under microwave-assisted solvent-free condition.
[b]Yields of the isolated products.

To show the superiority of the catalyst (NH_4Cl/Zn), the above synthesis (Scheme 1) was performed with other catalysts and the results are reported (Table 3). Thus, it is concluded that NH_4Cl/Zn (10 mol%) is the most excellent catalyst for the synthesis of the title compound.

Table 3: Investigation of efficiency of various catalyst for the synthesis of quinoline derivatives

Entry	Catalyst & Reaction condition	Solvent	Time (min)	Yield[a] (%)	Reference
1	Et_3N – heat/150 ^oC	EtOH	30 min	80	[35]
2	PEG-400 – heat/110 ^oC	No solvent	240 min	88	[36]
3	PEG-OSO_3H – MW	No solvent	12 min	81	[37]
4	$HClO_4$-SiO_2 – heat/ 60 ^oC	CH_3CN	120 min	90	[38]
5	NH_4Cl/Zn - MW	No solvent	4 min	98	present work

[a]Yields of the isolated products.

CONCLUSION

Finally, we have demonstrated an eco-friendly, simple, sustainable, economical, and efficient solvent-free protocol for the preparation of 2,3-disubstituted quinolines by reductive cyclization of 2-nitrobenzaldehydes and various active methylene compounds *via* tandem Knoevenagel condensation under microwave irradiation conditions promoted by NH_4Cl/Zn catalyst. This environmentally acceptable synthetic method provides various benefits like less reaction time,

green condition, product yield is good to excellent, utilizing non-hazard chemicals and all the chemicals used in the above reactions are commercially affordable. Furthermore, the results suggest that our environmentally green and sustainable approach by using a solvent-free microwave-assisted technique leads to higher yields within a very short reaction time.

EXPERIMENTAL

Materials and reagents applied in our experiment were commercially available. Glass TLC plates coated with Silica Gel-G were used to check the progress of the reaction. The newly synthesized compounds were purified by column chromatography wherever needed. Open capillary tubes and a sulfuric acid bath was used to determine the melting points of the synthesized compounds. FT-IR spectra were obtained with a Shimadzu 8000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian spectrometer. Chemical shifts (δ) are reported in ppm. The microwave-assisted reactions were carried out in a scientific microwave oven (Catalyst System, Model No-CATA 2R).

General procedure for the synthesis of Ethyl 2-aminoquinoline-3-carboxylate (3a-l):

In a 50 mL Erlenmeyer Flask a mixture of **1** (2 mmol), **2** (2 mmol), and NH_4Cl/Zn (10 mol%) were taken and the reaction was performed in a microwave oven at 400 W level for a period of 4 min at 5-sec intervals. The confirmation of completion of the reaction was ascertained by TLC using ethyl acetate-hexane (8:2) as a solvent system. Finally, the reaction mixture was cooled to room temperature and poured in crushed ice with continuous stirring. The solid product thus obtained was further, dried, and recrystallized with ethyl acetate-hexane in a volume ratio of (10:10 mL). The compounds 3b-l were also synthesized by using this same procedure. The synthesized compounds were subjected to elemental and spectra analysis for the confirmation of their structures.

Ethyl 2-aminoquinoline-3-carboxylate (3a): Yellow colored solid; mp 133–135 °C; IR (ν_{max}/cm^{-1}): 3418, 1697, 1628, 1288, 1080; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 7.85

(dd, *J* = 8.2, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.3, 6.7, 1.6 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.25 (bs, 2H), 7.24 – 7.22 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 166.5, 156.7, 150.0, 142.8, 133.0, 129.9, 125.1, 122.7, 122.0, 110.5, 61.6, 14.6. LCMS: m/z 216 [M^+]; Anal. calc. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.69; found: C, 66.69; H, 5.62; N, 12.72.

^{1}H and ^{13}C NMR spectral data have been provided in supporting information.

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CONFLICT OF INTEREST The authors confirm that they have no conflict of interest.

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