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Note

An environmentally benign indium (III) chloride catalysed one-pot synthesis of quinolines

Mazaahir Kidwai*, Vikas Bansal, Neeraj Kumar Mishra & Divya Bhatnagar

Green Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India

E-mail: kidwai.chemistry@gmail.com

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A convenient eco-friendly procedure for the quantitative synthesis of novel quinoline derivatives has been developed by a simple one-pot reaction of substituted anilines with β-ketoesters at 60°C in ethanol using recyclable indium chloride as catalyst. The reaction proceeds smoothly under solvent free conditions with quantitative yields.

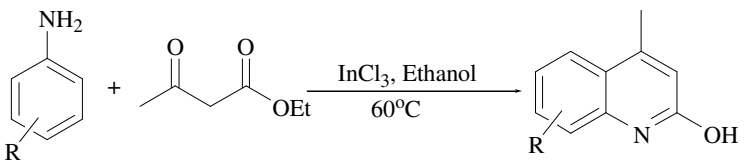
Keywords: Indium chloride, quinolines, recyclability, eco-friendly, green chemistry

Recently, Lewis acidity associated with Indium chloride (III) enhanced its usage in organic synthesis[1] and has received considerable attention as non-toxic, recyclable and readily available catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity[2]. For many years, the synthesis of quinoline and its derivatives has been of considerable interest in organic and medicinal chemistry since a large number of natural products and drugs contain this heterocyclic nucleus[3]. In addition, quinolines are valuable synthons, used for the preparation of nano and meso structures with enhanced electronic and photonic properties[4-8].

As part of the continuing effort towards the expeditious synthesis of biodynamic heterocycles[9,10], the possibility of developing a novel and efficient method to construct the quinoline scaffold became the focus of interest. This is inspite of some methods such as the Skraup, Doebner-von Miller, Combes reaction and Friedlander being available for the synthesis of quinolines[11-15]. Brønsted acids and several Lewis acids have been reported to be effective for the synthesis of quinolines[16-22]. However, many of these procedures also suffered from harsh reaction conditions, low yields, difficult work-up and in some cases high catalyst loading had to be employed in order to obtain a respectable yield. Thus, simple, eco-benign and efficient procedures for the synthesis of these important heterocycles are still in demand. Inspired by reports on catalytic applications of $InCl_3$ for organic transformations and the endeavour of this research group toward the development of new synthetic methods[23-25], it is wished to report herein a novel and efficient procedure for the synthesis of quinoline.

Results and Discussion

An initial study was performed by the treatment of aniline **1a** with ethyl acetoacetate **2** in methanol in the presence of catalytic amounts of indium chloride (10 mole %) at RT (**Scheme I**). To our delight, the formation of 2-hydroxy-4-methylquinoline **3a** was observed. Complete conversion and 93% isolated yields were obtained after 30 min. Further studies established that 5 mole % of catalyst was equally efficient to perform the reaction **(Table I)**. Moreover, it is noteworthy that this reaction could be run under normal air without loss of efficiency. Among the solvent screened, ethanol and methanol were demonstrated as the best solvent and further procedures were developed with ethanol as it is more environmentally benign as compared to methanol. This is because of high solubility of $InCl_3$ in polar solvents. Under solvent-free conditions, the reaction also proceeded smoothly to afford the corresponding



1a-h **2** **3a-h**

Scheme I — Synthesis of substituted quinolines

Table I — Evaluation of catalytic activity of $InCl_3$ on the synthesis of 6-substituted-4-methyl-quinolin-2-ol[a].

Entry	$InCl_3$ (X mole %)	Time (min)	Yield (%)[b]
1	0	4 hr	0
2	5	45	88
3	10	30	93
4	15	20	93
5	20	20	95

[a]Reaction conditions: aniline (**1a,** 1 mmole); ethyl acetoacetate (**2,** 1 mmole); $InCl_3$ (X mole %); solvent methanol; RT, 1 atm.
[b]Isolated yields.

Table II — Screening of solvent on the synthesis of 6-substituted-4-methyl-quinolin-2-ol[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	Methanol	45	88
2	Ethanol	35	86
3	Dichloromethane	70	64
4	Acetonitrile	55	72
5	Solvent-free condition	40	70

[a]Reaction conditions: aniline (**1a, 1** mmole); ethyl acetoacetate (**2**, 1 mmole); $InCl_3$ (5 mole %); RT, 1 atm.
[b]Isolated yields.

Table III — Effect of temperature on catalytic activity of $InCl_3$ on the synthesis of 6-substituted-4-methyl-quinolin-2-ol[a].

Entry	Temperature (°C)	Time (min)	Yield (%)[b]
1	RT	35	86
2	45	30	90
3	60	20	93
4	80 and above	20	94

[a]Reaction conditions: aniline (**1a**, 1 mmole); ethyl acetoacetate (**2**, 1 mmole); $InCl_3$ (5 mole %); solvent ethanol; 1 atm.
[b]Isolated yields.

product, although the yield was slightly lower (**Table II**). In order to examine the effect of temperature, concentration of $InCl_3$ was kept constant at 5 mole % and the reaction was monitored at different temperatures as compiled in (**Table III**). At elevated temperatures using 5 mole % of $InCl_3$ gave better results in terms of yield and reaction times.

Table IV — $InCl_3$ promoted synthesis 6-substituted-4-methyl-quinolin-2-ol[a].

Entry	Aniline	R	Time (min)	Product	Yield (%)[b]	m.p. (°C)
1	**1a**	H	20	**3a**	93	218-20
2	**1b**	4-F	25	**3b**	78	260-62
3	**1c**	4-CH_3	40	**3c**	84	248-50
4	**1d**	4-OCH_3	30	**3d**	91	256-58
5	**1e**	4-NO_2	65	**3e**	70	>300
6	**1f**	4-COOH	40	**3f**	73	>300
7	**1g**	2-pyridinyl	30	**3g**	80	180-82
8	**1h**	2-napthyl-amine	45	**3h**	87	270-72

[a]Reaction conditions: aromatic amines (**1a-h**, 1 mmole); ethyl acetoacetate (**2**, 1 mmole); $InCl_3$ (5 mole %); solvent ethanol; temperature 60°C; 1 atm.
[b]Isolated yields.

It is important to stress that the catalyst was recycled and reused for four or five runs with only slight drop in activity. An additional starting material was added into the reaction mixture and reaction was continued for an additional 10 hr and which resulted in the formation of **3a** in excellent yields.

To demonstrate the generality of this method, the scope of this reaction under optimized conditions was investigated and it was found that structurally diverse aromatic amines with different substitution (both electron withdrawing and electron donating group) reacted with equal ease to produce a range of quinoline derivatives in excellent yields (**Table IV**).

Experimental Section

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR-1710 spectrometer using KBr disc. ^{1}H NMR spectra were recorded on a Bruker Avance Spectrospin 300 (300 MHz) instrument using TMS as internal standard and chemical shift are in δ. Elemental analysis was performed on a Horeaus CHN Rapid analyzer. High resolution mass spectra (HRMS) were recorded on a Waters LCT Micromass and EI mass spectra were recorded on Jeol JHS-DX 303 instrument. All reactants were purchased from Sigma-Aldrich and Lancaster and used as received. Solvents used in reaction are doubled distilled using vacuum distillation.

Table V — Spectroscopic data for 6-substituted-4-methyl-quinolin-2-ol, **3a-h**

Compd	Mol. formula	HRMS $(M+Na)^+$	^{1}H NMR (δ, $CDCl_3$)
3a	$C_{10}H_9NO$	182.14	2.14 (s, 3H, CH_3), 6.15 (s, 1H, CH), 7.33-7.45 (m, 4H, ϕ), 8.43 (s, 1H, NH)
3b	$C_{10}H_8FNO$	200.20	2.28 (s, 3H, CH_3), 6.17 (s, 1H, CH), 7.22 (s, 1H, CH-ϕ), 7.53 (d, 1H, *J* = 7.7 Hz, CH-ϕ), 7.66 (d, 1H, *J* = 7.6 Hz, CH), 9.12 (s, 1H, NH)
3c	$C_{11}H_{11}NO$	195.88	2.28 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.25 (s, 1H, CH), 7.27 (s, 1H, CH-ϕ), 7.51 (d, 1H, *J* = 7.7 Hz, CH-ϕ), 7.54 (d, 1H, *J* = 7.5 Hz, CH), 9.10 (s, 1H, NH)
3d	$C_{11}H_{11}NO_2$	212.12	2.38 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.43 (s, 1H, CH), 7.52 (s, 1H, CH), 7.63 (d, 1H, *J* = 7.6Hz, CH), 7.81 (d, 1H, *J* =7.6Hz, CH) 8.82 (s, 1H, NH)
3e	$C_{10}H_8N_2O_3$	227.23	2.25 (s, 3H, CH_3), 6.14 (s, 1H, CH), 7.41 (s, 1H, CH), 7.65 (d, 1H, *J* = 7.4Hz, CH), 7.78 (d, 1H, *J* = 7.6Hz, CH), 8.42 (s, 1H, NH)
3f	$C_{11}H_9NO_3$	225.82	2.28 (s, 3H, CH_3), 6.13 (s, 1H, CH), 7.24 (s, 1H, CH), 7.48 (d, 1H, *J* = 7.8Hz, CH), 7.83 (d, 1H, *J* =7.3Hz, CH), 9.46 (s, 1H, NH), 11.36 (s,1H, COOH)
3g	$C_9H_8N_2O$	182.78	2.41 (s, 3H, CH_3), 6.44 (s, 1H, CH), 7.88-8.96 (m, 3H, CH), 9.31 (s, 1H, NH)
3h	$C_{14}H_{11}NO$	208.75	2.33 (s, 3H, CH_3), 6.03 (s, 1H, CH), 7.22-7.63 (m, 7H, CH)

General procedure for the synthesis of substituted quinolines, 3a-h

In a 50 mL round bottom flask, substituted anilines **1a-h** (1 mmole), ethyl acetoacetate **2** (1 mmole) and 5 mole % $InCl_3$ in ethanol (15 mL) were mixed and the resulting solution was stirred at 60°C for the appropriate time as mentioned in (**Table IV**). After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the crude product was subjected to purification by flash chromatography using a mixture of 20% ethyl acetate and 80% *n*-hexane as eluent to yield the quinolines **3a-h**. The purified product was recrystallized using appropriate solvent. The structure of all the products was unambiguously established on the basis of their spectral analysis (**Table V**).

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