Indium(III) Trifluoromethanesulfonate: An Efficient Reusable Catalyst for the Alkynylation–Cyclization of 2-Aminoaryl Ketones and Synthesis of 2,4-Disubstituted Quinolines

Kushal C. Lekhok, Dipak Prajapati,* Ramesh C. Boruah

Department of Medicinal Chemistry, North East Institute of Science & Technology, Jorhat 785 006, Assam, India
Fax +91(376)2370011; E-mail: dr_dprajapati2003@yahoo.co.uk

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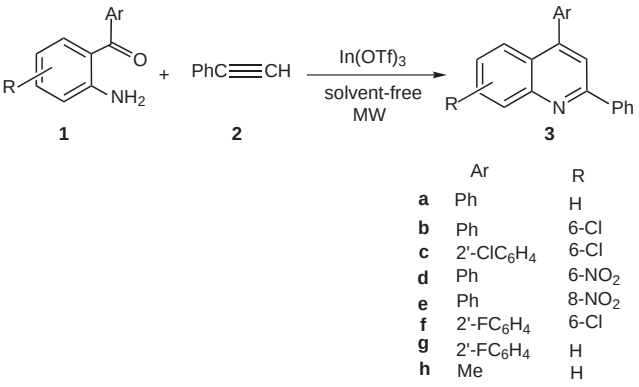
Abstract: An environmentally friendly and highly efficient procedure for the preparation of 2,4-disubstituted quinoline derivatives has been developed by a simple alkynylation–cyclization reaction of 2-aminoaryl ketones with phenylacetylenes in the presence of indium(III) trifluoromethanesulfonate $In(OTf)_3$ under microwave irradiation and solvent-free conditions. This catalyst can be recovered after the reaction and reused efficiently in subsequent runs.

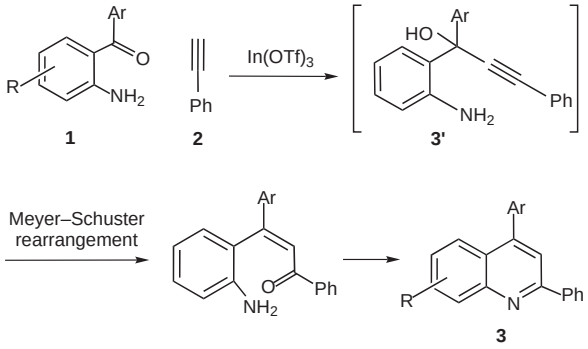
Key words: 2,4-disubstituted quinolines, solvent-free conditions, microwave irradiations, indium triflate

Quinolines and their derivatives are important scaffolds because of their wide spectrum of biological activities[1] and formation of conjugated molecules and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent medicinal properties.[2] In addition to medicinal applications, quinoline derivatives have been employed in the study of bioorganic and bioorganometallic processes.[3] In spite of their importance from industrial, pharmacological, and synthetic points of view, relatively few methods of their preparation have been reported. Although other methods such as Skraup, Doebner–von Miller, Friedländer, Combes reactions have been developed for the preparation of quinolines,[4] but due to their importance as substructures in a broad range of natural and designed products, significant effort continues to be directed into the development of new quinoline-based structures[5] and new methods for their constructions.[6] Amongst methodologies reported for the preparation of quinolines, Friedländer annulation is the most straightforward protocol, but the harsh reaction conditions can lead to several side reactions.[7] Under thermal or base-catalysis conditions, 2-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-keto esters.[8] Recently, Rh(I)-complex-catalyzed coupling cyclization of *N*-aryl trifluoroacetylimidoyl chloride with alkynes[9] and $InBr_3$-promoted dimerization of 2-ethynylaniline[10] to give polysubstituted quinoline have been reported. However, most of the reported protocols for the synthesis of quinolines suffer from the use of harmful organic solvents, high reaction temperatures, prolonged reaction times, low yields, tedious workup procedures and the use of stoichiometric and/or relatively expensive reagents. Consequently, there is great current interest in assembling quinoline systems from acyclic precursors[11] and an ever-increasing demand for selective and low-cost protocols for their synthesis.[12]



	Ar	R
a	Ph	H
b	Ph	6-Cl
c	2'-ClC_6H_4	6-Cl
d	Ph	6-NO_2
e	Ph	8-NO_2
f	2'-FC_6H_4	6-Cl
g	2'-FC_6H_4	H
h	Me	H

Scheme 1



Scheme 2

In recent years indium salts have received increasing attention both as reagents and catalysts for organic reactions.[13] We have studied the application and catalytic effect of indium trifluoromethanesulfonate and indium chloride in various carbon–carbon bond-forming reactions.[14]

To overcome the problems arising from the addition of stoichiometric amounts of the Brønsted and Lewis acidic or basic reagents, and in continuation to our studies on metal catalysts,[14] we report herein an efficient synthesis of 2,4-disubstituted quinolines using catalytic amount of $In(OTf)_3$, under microwave irradiation and solvent-free conditions. Accordingly, treatment of 5-chloro-2-ami-

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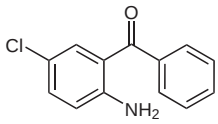
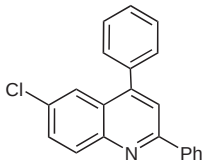
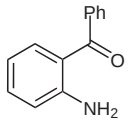
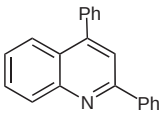
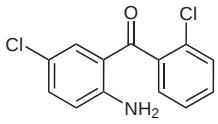
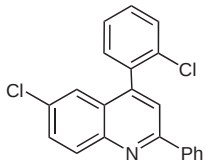
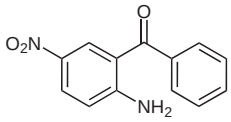
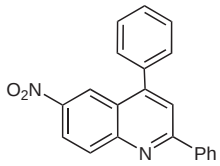
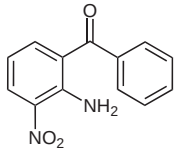
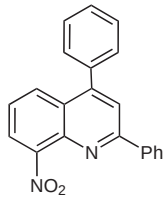
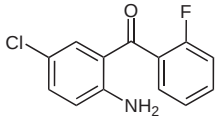
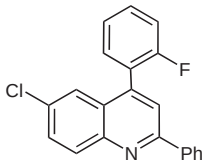
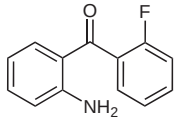
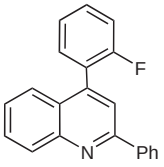
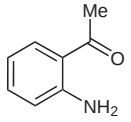
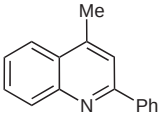
Table 1 $In(OTf)_3$-Catalyzed Synthesis of Quinolines **3**

Entry	2-Aminoaryl ketones **1**	Quinolines **1**	Reaction time [min, $In(OTf)_3$]	Yield [%,$In(OTf)_3$]
1		 **3a**	4.5	93
2		 **3b**	5.0	90[20]
3		 **3c**	4.5	96
4		 **3d**	5.0	87
5		 **3e**	4.5	86
6		 **3f**	3.5	92
7		 **3g**	4.0	90
8		 **3h**	5.0	90[20]

nobenzophenone (**1a**, R = 5-Cl, Ar = Ph) with phenylacetylene (**2**) in the presence of 1 mol% $In(OTf)_3$ under microwave irradiation and solvent-free conditions, resulted in the formation of 6-chloro-2,4-diphenylquinoline (**3a**) in 93% yield (Scheme 1). The reaction was carried out in a Synthwave 402 Monomod reactor from Prolabo and the automatic mode stirrer helps in mixing and uniform heating of the reactants. The reaction proceeds efficiently in excellent yields within a few minutes at 110 °C and at 2450 MHz frequency. Complete conversion and 93% isolated yield was obtained after 4.5 minutes of microwave irradiations. Rate enhancement of the reaction was observed when 5 mol% or 10 mol% of $In(OTf)_3$ were used but relatively lower yields (85% or 80%) were obtained due to decomposition of the starting material. Moreover, use of a lesser amount 0.5 mol% of $In(OTf)_3$ led to lower yields (60–70%) in longer reaction times. In view of our current interest in environmentally benign catalytic processes, we decided to extend the scope of the reaction using only 1 mol% of the catalyst (1 mol%, 4.5 min, 93% yield). It is noteworthy that this reaction can be run without an inert atmosphere without loss of efficiency. Similarly, various 2-aminoaryl ketones **1b**–**h** were reacted with phenylacetylene in the presence of 1 mol% $In(OTf)_3$ and the corresponding 2,4-disubstituted quinolines **3b**–**h** were obtained in excellent yields. The reactions are generally clean and no side products such as dihydroquinolines could be detected in the NMR spectra of the crude products. To be conclusive and for direct comparison, parallel reactions have also been investigated under conventional heating at 85 °C in solvent-free conditions. The reaction proceeded, but not so effectively, requiring several hours and the corresponding quinoline derivatives were obtained in 75–83% yields. To demonstrate the generality of this reaction, we next studied the scope of this reaction under the optimized conditions and the results are summarized in Table 1 (Scheme 2).[15] In the absence of a catalyst, the reaction did not yield any product even after 10 minutes of microwave irradiation. Further increase of reaction time led only to decomposition of starting materials. The advantage of $In(OTf)_3$ as a Lewis acid catalyst is that it can be quantitatively recovered after the reaction and the recovered catalyst is effective in subsequent experiments.

It should be noted that the yields in second and even third runs are comparable to that of the first run. As shown in the Table 1 the method appears to be quite general and the reaction conditions are tolerant of nitro groups.[16] Although the detailed mechanism of the reaction is not clear at this stage, it seems likely that the reaction is preceded by initial alkynylation of the 2-aminoaryl ketone **1** with phenyl acetylene **2** to form the propargylic alcohol **3′** followed by Meyer–Schuster rearrangement[17] to the enone and cyclization.

In conclusion, we describe a mild and efficient route for the synthesis of 2,4-disubstituted quinolines[18] utilizing indium triflate as a new catalyst. This method not only provides an excellent complement to substituted quinoline synthesis, but also avoids the use of hazardous acids or bases and harsh reaction conditions. The yields obtained by this method are superior to the corresponding Friedländer synthesis, which uses *o*-acylanilines and ketones.[19] In addition to its simplicity and selectivity, this reaction shows the ability to tolerate a variety functional groups (nitro, chloro, fluoro, and amino) and will constitute a useful alternative to the commonly utilized procedures.

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(15) **General Procedure for the Synthesis of 2,4-Disubstituted Quinoline Derivatives under Microwave Irradiations**
A mixture of 5-chloro-2-aminobenzophenone (**1a**, 1.65 g, 5 mmol), phenylacetylene (0.52 g, 5 mmol), and $In(OTf)_3$ (0.03 g) was placed in a quartz reaction vessel of a Prolabo Synthwave Microwave Reactor 402 and allowed to react under microwave irradiation at 110 °C for 4.5 min. After completion (monitored by TLC), the reaction mixture was cooled to r.t. and cold MeOH (15 mL) added. The residue was filtered and the filtrate was evaporated to obtain the crude product which was then recrystallized from hot MeOH to afford quinoline **3a** in 93% yield, mp 98 °C. The residue obtained after filtration contains $In(OTf)_3$ which was used as such in another experiment and the corresponding 6-chloro-2,4-diphenylquinoline was isolated in 90% yield.
6-Chloro-2,4-diphenylquinoline (**3a**): mp 98 °C. IR (KBr): 1610, 1375, 1270, 1160, 1125 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.10–7.23 (m, 8 H), 7.65 (m, 1 H), 7.95 (m, 1 H), 8.10–8.25 (m, 4 H). Anal. Calcd for $C_{21}H_{14}ClN$: C, 80.00; H, 4.44; N, 4.44. Found: C, 80.11; H, 4.52; N, 4.36. MS: *m/z* = 315 [M^+].
2,4-Diphenyl-quinoline (**3b**): mp 107 °C. IR (KBr): 1610, 1375, 1270, 1160, 1125 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.10–7.23 (m, 9 H), 7.65 (m, 1 H), 7.95 (m, 1 H), 8.10–8.25 (m, 4 H). Anal. Calcd for $C_{21}H_{15}N$: C, 89.69; H, 5.34; N, 4.98. Found: C, 89.75; H, 5.42; N, 4.88. MS: *m/z* = 281 [M^+].
2-Phenyl-4-(2′-chlorophenyl)-6-chloroquinoline (**3c**): mp 112 °C. IR (KBr): 1610, 1375, 1270, 1160, 1125 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.27 (s, 1 H), 7.39–7.84 (m, 7 H), 8.18 (s, 1 H), 8.19–8.21 (m, 4 H). Anal. Calcd for $C_{21}H_{13}Cl_2N$: C, 72.21; H, 3.72, N, 4.01. Found: C, 72.13; H, 3.82; N, 4.12. MS: *m/z* = 349 [M^+].
2,4-Diphenyl-6-nitroquinoline (**3d**): mp 264 °C. IR (KBr): 1625, 1370, 1240, 1150, 1035 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.30–7.65 (m, 8 H), 7.80 (m, 1 H), 8.10–8.15 (m, 5 H). Anal. Calcd for $C_{21}H_{14}N_2O_2$: C, 77.30; H, 4.29; N, 8.59. Found: C, 77.39; H, 4.19; N, 8.66. MS: *m/z* = 326 [M^+].
2,4-Diphenyl-8-nitroquinoline (**3e**): mp 264 °C. IR (KBr): 1630, 1375, 1235, 1150, 1030 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.25–7.60 (m, 8 H), 7.75 (m, 1 H), 8.12–8.20 (m, 5 H). Anal. Calcd for $C_{21}H_{14}N_2O_2$: C, 77.30; H, 4.29; N, 8.59. Found: C, 77.42; H, 4.35; N, 8.48. MS: *m/z* = 326 [M^+].
2-Phenyl-4-(2′-fluorophenyl)-6-chloroquinoline (**3f**): mp 124 °C. IR (KBr): 1610, 1375, 1270, 1160, 1125 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.10–7.23 (m, 7 H), 7.65 (m, 1 H), 7.95 (m, 1 H), 8.10–8.25 (m, 4 H). Anal. Calcd for $C_{21}H_{13}ClFN$: C, 75.68; H, 3.90; N, 4.20. Found: C, 75.75; H, 3.98; N, 4.13. MS: *m/z* = 333 [M^+].
2-Phenyl-4-(2′-fluorophenyl)quinoline (**3g**): mp 90 °C. IR (KBr): 1610, 1375, 1270, 1160, 1125 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.10–7.23 (m, 7 H), 7.65 (m, 1 H), 7.95 (m, 1 H), 8.10–8.25 (m, 4 H). Anal. Calcd for $C_{21}H_{14}FN$: C, 84.28; H, 4.68; N, 4.68. Found: C, 84.36; H, 4.59; N, 4.78. MS: *m/z* = 299 [M^+].

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