Ionic Liquid – an Efficient Recyclable System for the Synthesis of 2,4-Disubstituted Quinolines via Meyer–Schuster Rearrangement

Rupam Sarma, Dipak Prajapati*

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

Received 4 June 2008

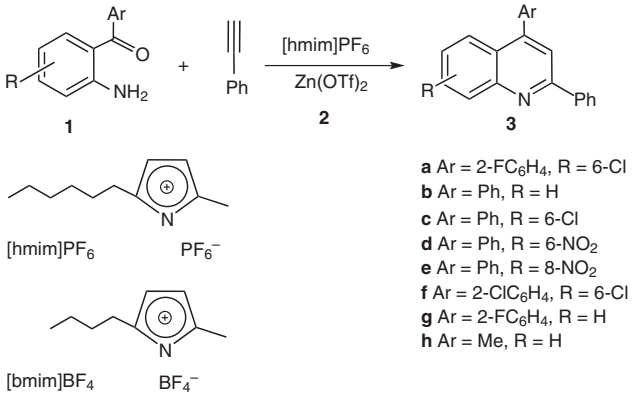
Abstract: An improved and eco-friendly method for the synthesis of 2,4-disubstituted quinolines via Meyer–Schuster rearrangement of 2-aminoaryl ketones and phenylacetylenes in the presence of zinc trifluoromethanesulfonate in [hmim]PF_6 has been developed.

Key words: ionic liquid, Meyer–Schuster rearrangement, green solvents, quinolines

In recent years, the application of ionic liquids as alternative reaction media was frequently reported in the literature.[1–4] It has attracted increasing attention and been successfully used in a variety of catalytic reactions as environmentally benign solvents and catalysts due to their relatively low viscosities, low vapor pressure, and high thermal and chemical stability.[5,6] Their nonvolatile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction solvents. They are being used as green solvents for the immobilization of transition-metal-based catalysts, Lewis acids, and enzymes.[7–9] Much attention has currently been focused on the organic reactions with ionic liquids as catalysts or solvents, and many organic reactions were performed in ionic liquids with high performances.[10–13] Many reactions such as Friedel–Crafts reactions,[14] arene hydrogenation,[15] dimerizations of alkenes,[16] allylations of aldehydes,[17] Heck reactions,[18] and Diels–Alder reactions[19] have been reported with good results, which offered some new clues indicating that use of ionic liquids as catalysts may not only be possible for those traditionally important reactions, but also practical and even highly efficient. To our knowledge, so far there is no report in the literature on the Meyer–Schuster rearrangement mediated by ionic liquids for the synthesis of 2,4-disubsituted quinolines. Herein, we wish to report an efficient, simple, and recyclable protocol with the enhancements in reaction rates for the synthesis of 2,4-disubstituted quinolines using [hmim]PF_6 as recyclable ionic liquid in the presence of 1 mol% zinc triflate.

The quinoline derivatives occur in several natural products and pharmacologically active substances displaying a broad range of biological activity.[20] They are also known for their formation of conjugated molecules and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent mechanical properties.[21] Several methods such as Skraup, Doebner–von Miller, Friedländer and Combe reactions have been developed for the preparation of quinolines,[22] 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[23] and new methods for their constructions.[24] Amongst methodologies reported for the preparation of quinolines, Friedländer annulation is the most straightforward protocol. However, various Brønsted acids employed in this reaction require harsh reaction conditions and lead to several side reactions.[25] Under thermal or base-catalysis conditions, 2-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-keto esters[26,27] Most of the reported protocols for the synthesis of quinolines suffered from the usage of harmful organic solvents, high reaction temperature, prolonged reaction time, 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[28] and an even increasing demand for selective, cheap, ecobenign, and low-cost protocols for their synthesis.[29]

To overcome the problems arising from the addition of stoichiometric amounts of the Brønsted and Lewis acidic or basic reagents, we report herein an efficient and novel synthesis of 2,4-disubstituted quinolines using [hmin]PF_6 as green solvent in presence of catalytic amount of zinc triflate via Meyer–Schuster rearrangement. Accordingly, treatment of 2-amino-5-chloro-2′-fluorobenzophenone (**1a**) with phenylacetylene (**2**) in [hmim]PF_6 and in the

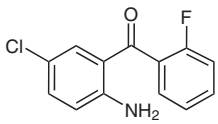
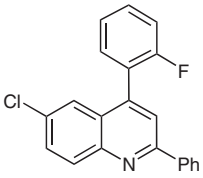
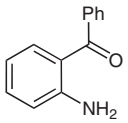
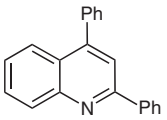
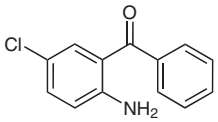
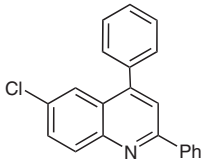
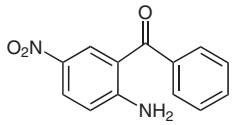
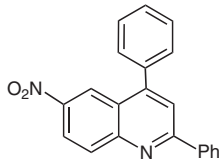
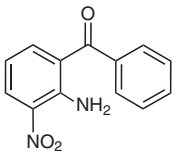
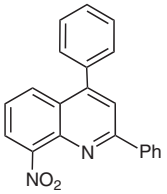
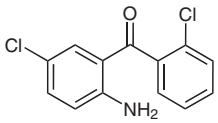
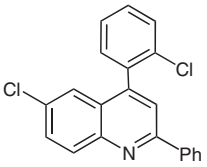
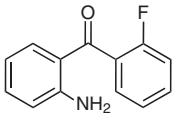
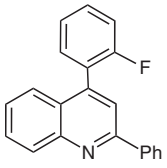
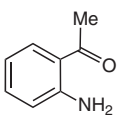
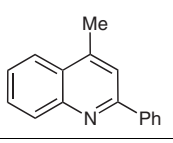


Scheme 1

SYNLETT 2008, No. 19, pp 3001–3005
Advanced online publication: 12.11.2008
DOI: 10.1055/s-0028-1087340; Art ID: D20508ST

presence of 1 mol% zinc triflate, when heated at 80–90 °C for about 2.5 hours, resulted the formation of 2-phenyl-4-(2′-fluorophenyl)-6-chloroquinoline (**3a**) mp 125 °C in 98% yield[30] (Scheme 1). Rate enhancement of the reaction was observed when 5 mol% or 10 mol% of $Zn(OTf)_2$ were used but relatively lower yield (75% or 65%) was obtained due to decomposition of the starting material. Moreover, use of lesser amount (0.5 mol%) of $Zn(OTf)_2$ led to weaker results (50–60%) in longer reaction time. In view of the current interest in environmentally benign catalytic processes, a protocol involving a lower amount of $Zn(OTf)_2$ would be more appreciable, so we decided to extend the scope of the reaction using only 1 mol% of the catalyst. Various 2-aminoaryl ketones **1b–h** were reacted similarly with phenylacetylene in the presence of 1 mol% $Zn(OTf)_2$ in $[hmim]PF_6$, and the corresponding 2,4-disubstituted quinolines **3b–h** were isolated in excellent yields. The reactions are generally clean and no side products like dihydroquinoline could be detected in the NMR spectra of the crude products.

Table 1 Synthesis of 2,4-Disubstituted Quinolines **3**

Entry	2-Aminoaryl ketones	Quinolines	Reaction time (h)	Yield (%)[a]
1			2.5	98 (95)
2			2.0	90 (89)[20]
3			2.5	95 (93)
4			2.0	94 (90)
5			2.5	90 (88)
6			2.5	92 (89)
7			2.5	90 (88)
8			2.5	90[20]

[a] Yields in parentheses indicate yields in the second run.

All the products thus obtained were characterized by spectral analyses (IR, ^{1}H NMR, and MS). 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.

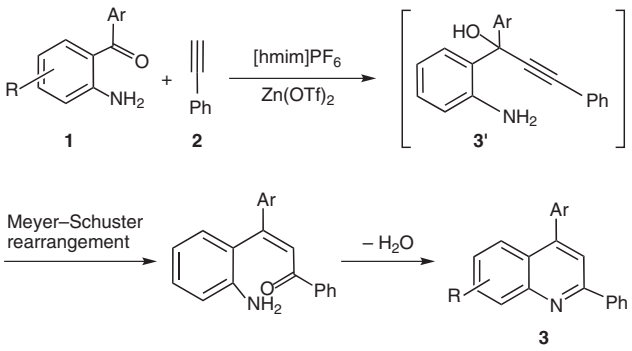
Under this reaction conditions, we then investigated the Meyer–Schuster rearrangement using three different ionic liquids, such as [bmim]PF_6, [hmim]PF_6, and [bmim]BF_4. Among these, 1-hexyl-3-methylimidazolium hexafluoro phosphate ([hmim]PF_6) was found to give excellent yields. For instance, 2-amino-5-chloro-2′-fluorobenzophenone with phenylacetylene in ionic liquids [hmim]PF_6, [bmim]PF_6, and [bmim]BF_4 gave 98%, 50%, and 35% yields, respectively. The presence of catalytic amounts of zinc triflate was found to be essential for the reaction outcome. Indeed in the absence of this catalyst, the reaction did not yield any fruitful product even after 8 hours of heating. Further increase of reaction time also did not yield any characterizable product rather decomposition of starting materials occurred. Interestingly, when zinc triflate was replaced by 1 mol% $InCl_3$ in the above reaction, the ionic liquids [hmim]PF_6 and [bmim]PF_6 both were found equally effective, and the quinoline derivatives were obtained in comparable yields, but the ionic liquid [bmim]BF_4 was very less effective. All reactions exhibited pronounced rate accelerations, and excellent yields were obtained for isolated products **3** with [hmim]PF_6. In general, the reaction is very clean, rapid, efficient, and involves simple workup procedure. Encouraged by the results obtained with ionic liquids, we turned our attention toward the possibility of recycling the ionic liquids. Since the products 2,4-disubstituted quinolines were fairly soluble in ionic phase, they could be easily separated by simple extraction with diethyl ether. The remaining ionic liquid was recovered and reused in subsequent experiments with gradual decrease in activity. For example, 5-chloro-2-aminobenzophenone **3c** with phenylacetylene gave 95%, 93%, and 80% yields over three cycles. To compare the efficiency of this method, we carried out the reaction in various organic solvents such as dichloromethane, acetonitrile, DMF, ethanol, and THF (2 mL) in the presence of catalytic amount of zinc triflate under similar reaction conditions. The reaction was found to be slow in organic solvents and afforded less yields of the desired product (Table 2).

Use of 1 mol% of zinc triflate in conjunction with [hmim]PF_6 showed rate enhancements and excellent yields in this Meyer–Schuster rearrangement. As shown in Table 1, the method appears to be quite general and under these reaction conditions nitro groups, which are sensitive to reductions by metals,[31] do survive. Although the detailed mechanism of the reaction is not clear at this stage, it seems likely that the reaction is proceeded by initial alkynylation of the 2-aminoaryl ketone **1** with phenylacetylene (**2**) to form the propargylic alcohol **3′**, followed by Meyer–Schuster rearrangement[32] to the enone, and cyclization (Scheme 2) occurs to give the products.

Table 2 Effects of Various Solvents on Meyer–Schuster Rearrangement

Entry	Product	Solvent	Reaction time (h)	Yield (%)[a]
1	**3a**	MeCN	5	30
2	**3a**	EtOH	4	15
3	**3a**	THF	6	10
4	**3a**	DMF	5	20
5	**3a**	CH_2Cl_2	6	15
6	**3a**	[bmim]BF_4	3	35
7	**3a**	[bmim]PF_6	3	50
8	**3a**	[hmim]PF_6	2.5	98

[a] Reaction conditions: 2-aminobenzophenone (1.5 mmol), phenylacetylene (3 mmol), solvent (1 g), $Zn(OTf)_2$ (15 mg), 80–90 °C.



Scheme 2

In conclusion, we have developed the use of ionic liquid [hmin]PF_6 as green and reusable reaction medium, as well as promoter for the Meyer–Schuster rearrangement of various substituted 2-aminobenzophenones and phenylacetylene to afford corresponding 2,4-disubstituted quinolines[33] utilizing catalytic amount of zinc triflate in excellent yields. 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.[34] 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.

Acknowledgment

We thank the Department of Science and Technology (DST), New Delhi for financial support and Director, North East Institute of Science & Technology (NEIST), Jorhat for his keen interest and constant encouragement.

References and Notes

(1) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23.
(2) Kitazume, T.; Kassai, K. *Green Chem.* **2001**, *3*, 30.
(3) Owens, G. S.; Abu-Omar, M. M. *Chem. Commun.* **2000**, 1165.
(4) For reviews, see: (a) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772. (b) Dupont, J.; Suarez, P. A. Z.; Umpierre, A. P.; De Souza, R. F. *J. Braz. Chem. Soc.* **2000**, *11*, 293. (c) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
(5) Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049.
(6) Du, D. M.; Chen, X. *Chin. J. Org. Chem.* **2003**, *23*, 331.
(7) Dubreuil, J. F.; Bozureau, J. P. *Tetrahedron Lett.* **2000**, *41*, 7351.
(8) Qiao, K.; Yokoyama, C. *Chem. Lett.* **2004**, *33*, 472.
(9) Dubreuil, J. F.; Bourahala, K. *Catal. Commun.* **2002**, *3*, 185.
(10) Sheldon, R. *Chem. Commun.* **2001**, 2399.
(11) Gordon, C. M. *Appl. Catal., A* **2001**, *222*, 101.
(12) Zimmermann, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205.
(13) (a) Welton, T. *Coord. Chem. Rev.* **2004**, *104*, 2459. (b) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667. (c) Li, S.; Lin, Y.; Xie, H.; Zhang, S.; Xu, J. *Org. Lett.* **2006**, *8*, 391.
(14) (a) Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480. (b) Luer, G. D.; Bartak, D. E. *J. Org. Chem.* **1982**, *47*, 1238.
(15) (a) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun.* **1999**, 25. (b) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *15*, 1217.
(16) Ellis, B.; Keim, W.; Wasserscheid, P. *Chem. Commun.* **1999**, 337.
(17) Gordon, C. M.; McCluskey, A. *Chem. Commun.* **1999**, 1431.
(18) (a) Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017. (b) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997.
(19) (a) Earle, J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23. (b) Fisher, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.
(20) (a) Larsen, R. D.; Corley, E. G.; King, A. O.; Carrol, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398. (b) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374. (c) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021. (d) Kalluraya, B.; Sreenivasa, S. *Farmaco* **1998**, *53*, 399. (e) Dube, D.; Blouin, M.; Brideau, C.; Chan, C. C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255.
(21) (a) Stille, J. K. *Macromolecules* **1981**, *14*, 870. (b) Agrawal, A. K.; Jenekhe, S. A. *Macromolecules* **1991**, *24*, 6806. (c) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1992**, *4*, 95. (d) Agrawal, A. K.; Jenekhe, A. K.; Jenekhe, S. A. *Chem. Mater.* **1993**, *28*, 895. (e) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1993**, *5*, 633. (f) Jenekhe, S. A.; Lu, L.; Alam, M. M. *Macromolecules* **2001**, *34*, 7315. (g) Agrawal, A. K.; Jenekhe, S. A.; Vanherzeele, H.; Meth, J. S. *J. Phys. Chem.* **1992**, *96*, 2837. (h) Jegou, G.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 7926. (i) Lu, L.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 6249. (j) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1996**, *8*, 579. (k) Jenekhe, S. A.; Zhang, X.; Chen, X. L.; Choong, V. E.; Gao, Y.; Hsieh, B. R. *Chem. Mater.* **1997**, *9*, 409. (l) Zhang, X.; Shetty, A. S.; Jenekhe, S. A. *Macromolecules* **1999**, *32*, 7422. (m) Zhang, X.; Shetty, A. S.; Jenekhe, S. A. *Macromolecules* **2000**, *33*, 2069.
(22) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*, Vol. 5; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: New York, **1996**, 167. (b) Cho, C. S.; Oh, B. H.; Kim, T. J.; Shim, S. C. *Chem. Commun.* **2000**, 1885. (c) Jiang, B.; Si, Y. G. *J. Org. Chem.* **2002**, *67*, 9449. (d) Skraup, H. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086. (e) Friedländer, P. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2572. (f) Mansake, R. H.; Kulka, M. *Org. React.* **1953**, *7*, 59. (g) Linderman, R. J.; Kirollos, K. S. *Tetrahedron Lett.* **1990**, *31*, 2689. (h) Theoclitou, M. E.; Robinson, L. A. *Tetrahedron Lett.* **2002**, *43*, 3907.
(23) Hoemann, M. Z.; Kumaravel, G.; Xie, R. L.; Rossi, R. F.; Meyer, S.; Sidhu, A.; Cuny, G. D.; Hauske, J. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2675.
(24) (a) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765. (b) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467. (c) Matsugi, M.; Tabusa, F.; Minamikawa, J. *Tetrahedron Lett.* **2000**, *41*, 8523. (d) Lindsay, D. M.; Dohle, W.; Jensen, A. E.; Kopp, F.; Knochel, P. *Org. Lett.* **2002**, *4*, 1819.
(25) Arcadi, A.; Chiarini, M.; Giuseppe, S. D.; Marinelli, F. *Synlett* **2003**, 203; and references cited therein.
(26) Fehnel, E. A. *J. Org. Chem.* **1996**, *31*, 2899.
(27) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109.
(28) (a) Li, A. H.; Ahmed, E.; Chen, X.; Cox, M.; Crew, A. P.; Dong, H. Q.; Jin, M. Z.; Ma, I. F.; Panicker, B.; Siu, K. W.; Steing, A. G.; Stolz, K. M.; Tavares, P. A. R.; Volk, B.; Weng, Q. H.; Werner, D.; Mulyihill, M. *Org. Biomol. Chem.* **2007**, *5*, 61. (b) Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875. (c) Jia, C. S.; Wang, G. W. *Lett. Org. Chem.* **2006**, *3*, 289.
(29) (a) Zolfogol, M. A.; Salehi, P.; Ghaderi, A.; Shiri, M.; Tanbakouchian, Z. *J. Mol. Catal. A: Chem.* **2006**, *259*, 253. (b) Li, Y. S.; Wu, C. L.; Huang, J. L.; Su, W. K. *Synth. Commun.* **2006**, *36*, 3065. (c) Selvam, N. P.; Saravan, C.; Muralidharan, D.; Perumal, P. T. *J. Heterocycl. Chem.* **2006**, *43*, 1379.

(30) **General Procedure for the Synthesis of 2,4-Disubstituted Quinoline Derivatives under Thermolytic Conditions Using Ionic Liquids**

A mixture of 2-amino-5-chloro-2′-fluoro-benzophenone (**1a**, 0.25 g, 1 mmol), and phenylacetylene (0.18 g, 1.8 mmol) in 1-hexyl-3-methylimidazolium hexafluorophosphate (1 g) was placed in a round-bottom flask (50 mL) in the presence of $Zn(OTf)_2$ (15 mg). Two phases were formed at r.t. The flask was then dipped in a pre-heated oil bath at 80–90 °C (bath temperature), the mixture becomes homogeneous, and was stirred for about 2.5 h. After completion (monitored by TLC), the reaction mixture was cooled to r.t. and extracted with Et_2O (2 × 15 mL). The ether layer was dried over anhyd Na_2SO_4 for 10 h and concentrated in a rotary evaporator to half the volume and left overnight. The yellow crystals of the products so obtained was filtered, dried, and recrystallized from $CHCl_3$–MeOH (1:1) mixture to get the pure product; mp 125 °C in 98% yield. The filtrate containing the Et_2O is evaporated to expel the Et_2O completely and ionic liquid is reused directly for the second run. Similarly other 2-aminoaryl ketones and phenylacetylene were reacted in the presence of $Zn(OTf)_2$ under thermal heating at 80–90 °C to produce the corresponding quinoline derivatives in excellent yields. The results are summarized in the Table 1.

2-Phenyl-4-(2′-fluorophenyl)-6-chloroquinoline (3a)
Mp 125 °C. IR (KBr): 1615, 1370, 1280, 1165, 1125 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 7.15–7.28 (m, 7 H), 7.72 (m, 1 H), 8.02 (m, 1 H), 8.10–8.30 (m, 4 H). Anal. Calcd for $C_{21}H_{13}ClFN$: C, 75.68; H, 3.90; N, 4.20. Found: C, 75.70; H, 4.02; N, 4.11. MS: *m/z* = 333 [M^+].

2,4-Diphenylquinoline (3b)
Mp 107 °C. IR (KBr): 1610, 1370, 1270, 1160, 1125 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): 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^+].

6-Chloro-2,4-diphenylquinoline (3c)
Mp 98 °C. IR (KBr): 1610, 1375, 1270, 1165, 1125 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 7.12–7.25 (m, 8 H), 7.65 (m, 1 H), 8.05 (m, 1 H), 8.13–8.28 (m, 4 H). Anal. Calcd for $C_{21}H_{14}ClN$: C, 80.00; H, 4.44; N, 4.44. Found: C, 80.09; H, 4.50; N, 4.35. MS: *m/z* = 315 [M^+].

2,4-Diphenyl-6-nitroquinoline (3d)
Mp 264 °C. IR (KBr): 1630, 1375, 1240, 1150, 1040 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 7.25–7.65 (m, 8 H), 7.83 (m, 1 H), 8.05–8.15 (m, 5 H). Anal. Calcd for $C_{21}H_{14}N_2O_2$: C, 77.30; H, 4.29; N, 8.59. Found: C, 77.37; H, 4.20; N, 8.68. MS: *m/z* = 326 [M^+].

2,4-Diphenyl-8-nitroquinoline (3e)
Mp 264 °C. IR (KBr): 1635, 1375, 1240, 1150, 1035 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): 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, 77.41; H, 4.35; N, 8.49. MS: *m/z* = 326 [M^+].

2-Phenyl-4-(2′-chlorophenyl)-6-chloroquinoline (3f)
Mp 112 °C. IR (KBr): 1615, 1375, 1275, 1165, 1130 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 7.30 (s, 1 H), 7.42–7.88 (m, 7 H), 8.15 (s, 1 H), 8.16–8.25 (m, 4 H). Anal. Calcd for $C_{21}H_{13}Cl_2N$: C, 72.21; H, 3.72, N, 4.01. Found: C, 72.14; H, 3.80; N, 4.10. MS: *m/z* = 349 [M^+].

2-Phenyl-4-(2′-fluorophenyl)quinoline (3g)
Mp 90 °C. IR (KBr): 1615, 1375, 1275, 1160, 1130 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 7.10–7.23 (m, 7 H), 7.65 (m, 1 H), 8.02 (m, 1 H), 8.15–8.30 (m, 4 H). Anal. Calcd for $C_{21}H_{14}FN$: C, 84.28; H, 4.68; N, 4.68. Found: C, 84.38; H, 4.58; N, 4.76. MS: *m/z* = 299 [M^+].

(31) Kalyanam, N.; Rao, G. W. *Tetrahedron Lett.* **1993**, *34*, 1647.
(32) Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 3403.
(33) For some of the most recent work on quinoline synthesis, see: (a) Ahmed, N.; Lier, E. V. *Tetrahedron Lett.* **2007**, *48*, 13. (b) Arcadi, A.; Bianchi, G.; Inesi, A.; Marinelli, F.; Rossi, I. *Synlett* **2007**, 1031. (c) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653. (d) Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811. (e) Wang, G.-W.; Jia, C. S.; Dong, Y.-W. *Tetrahedron Lett.* **2006**, *47*, 1059. (f) Subhas Bose, D.; Kumar, R. K. *Tetrahedron Lett.* **2006**, *47*, 813. (g) Lee, B. S.; Lee, J. H.; Chi, D. Y. *J. Org. Chem.* **2002**, *67*, 7884. (h) Jia, C. S.; Zhang, Z.; Tu, S. J.; Wang, G. W. *Org. Biomol. Chem.* **2006**, *4*, 104.
(34) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37; yields of 67% and 55% were reported for **3d** and **3h**, respectively.