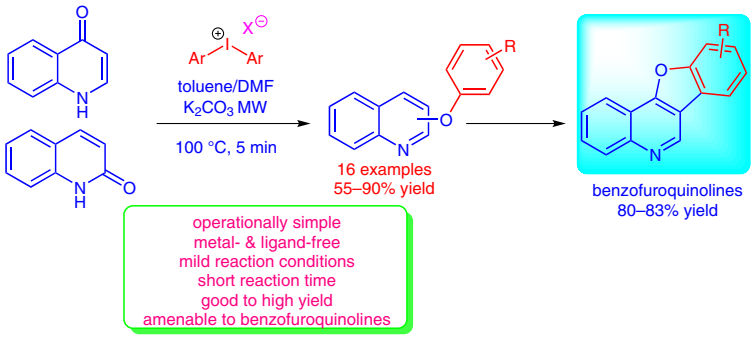
Synlett M. K. Mehra et al. Letter

Microwave-Assisted Metal- and Ligand-Free O-Arylation of Quinolones Using Diaryliodonium Salts: An Easy and Rapid Synthesis of Aryloxyquinolines

Manish Kumar Mehra
Mukund P. Tantak
Indresh Kumar
Dalip Kumar*

Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, India
dalipk@pilani.bits-pilani.ac.in



Received: 19.08.2015
Accepted after revision: 05.10.2015
Published online: 16.11.2015
DOI: 10.1055/s-0035-1560367; Art ID: st-2015-d0650-l

Abstract A microwave-assisted metal- and ligand-free direct O-arylation of quinolones has been achieved by employing easily accessible diaryliodonium salts in the presence of a base to afford various aryloxyquinolines in good yields. The operationally simple and rapid protocol has also been utilized for the construction of biologically important benzofuro[3,2-c]quinolines.

Key words quinolones, aryloxyquinolines, microwave-assisted reactions, diaryliodonium salts, metal-free reactions

The quinoline motif is present widely in natural products as well as in synthetic organic molecules of biological interest.[1,2] In particular, many compounds with this structural motif have been found to display antimalarial, antiasthmatic, antimicrobial, antituberculosis, antileishmanial, anti-HIV, and anticancer activity.[3–6] There is continuing interest in making modifications to the quinoline scaffold to furnish 'drug-like' small molecules for biological screening. For example, the C-2 and C-4 positions have been modified by introducing a number of carbon-, oxygen-, nitrogen-, and sulfur-based nucleophiles to achieve substituted quinolines. For example, aryloxyquinolines **1**–**3** were identified as potent inhibitors of HMG CoA reductase, tyrosin kinase, and thrombin, respectively (Figure 1).[7–9] For the preparation of 2- and 4-quinolinyl aryl ethers, quinolin-2(1*H*)-ones and quinolin-4(1*H*)-ones are the key precursors.

Generally, quinolinyl aryl ethers are prepared by the activation of the 2/4-positions of quinolones using $POCl_3$ followed by nucleophilic substitution with an appropriate phenol. Recently, 4-aryloxyquinolines have been synthesized by a Cu-catalyzed reaction of 4-haloquinolines with phenols in the presence of picolinic acid as a ligand.[10] Analoguous 2-aryloxy-3-substituted quinolines were synthesized through 1,4-diazabicyclo[2.2.2]octane (DABCO) mediated reactions of *O*-alkynyl arylisocyanides and phenols.[11] However, some of the existing synthetic protocols involve

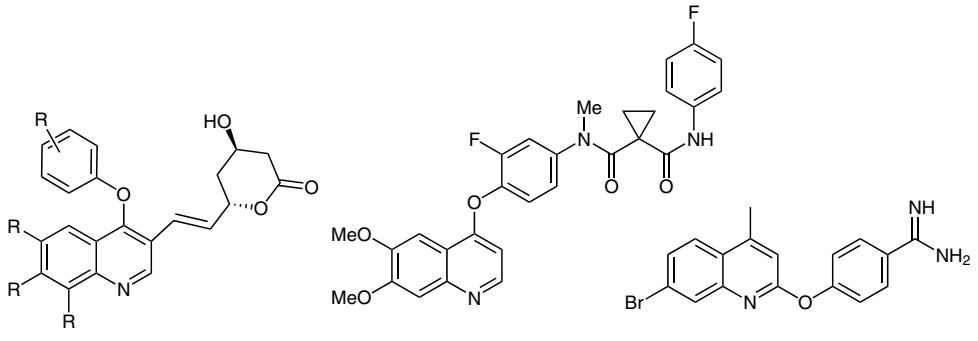
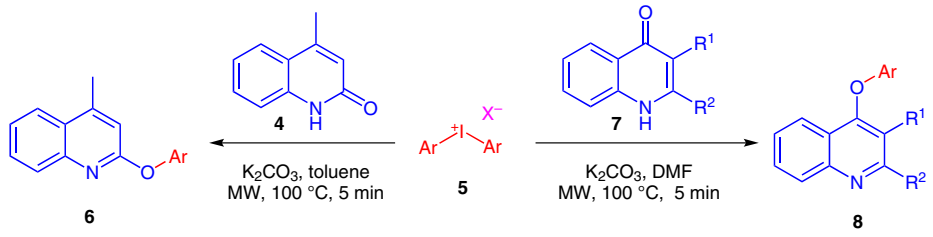


Figure 1 Representative examples of biologically important aryloxyquinolines



Scheme 1 O-Arylation of quinolones **4** and **7**

multistep sequences, use metal catalysts and ligands or harsh reaction conditions, and can give low product yields.

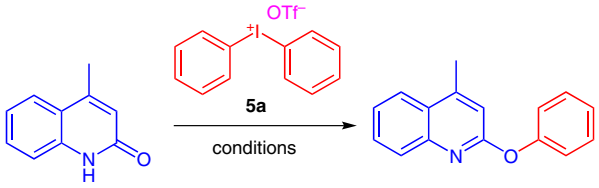
In recent years, diaryliodonium salts have received substantial attention as powerful electrophilic arylating agents due to their high reactivity, stability, and low toxicity.[12,13] They have been employed in metal-free as well as in metal-catalyzed arylation reactions leading to the formation of biologically important heterocycles.[14,15] Many transition-metal catalysts and associated ligands are normally very expensive and some of them are air- and moisture-sensitive. Most of the transition metals are toxic to different degrees, and their removal from the final products is an expensive challenge in medicinal chemistry.[16] The limitations associated with metal-based reagents, together with the biological significance of heteroaryl ethers and analogues, have stimulated us to develop an operationally simple and metal-free protocol for the O-arylation of quinolones to prepare an array of aryloxyquinolines.

Very recently, significant progress has been made by several researchers who have explored the metal-free arylation of various nucleophiles using diaryliodonium salts.[17,18] Recently, Olofsson et al. reported the metal-free arylation of phenols, alcohols, *N*-hydroxyphthalimides, and *N*-hydroxysuccinimides by employing diaryliodonium salts.[19–21] Subsequently, Karade et al. utilized diaryliodonium salts in the metal-free O-arylation of pyrimidine-2(1*H*)-one to prepare aryloxypyrimidines.[22]

By employing diaryliodonium salts, we have recently developed high-yielding syntheses of diaryl sulfones and arylated azaheterocycles.[23,24] Herein, we wish to report a novel and metal-free direct O-arylation of quinolones utilizing readily available and stable diaryliodonium salts to access aryloxyquinolines (Scheme 1).

The requisite diaryliodonium salts were prepared by following the reported protocols.[25–27] The 4-methylquinolin-2(1*H*)-one and quinolin-4(1*H*)-one precursors **4** and **7**, respectively, were synthesized from the reaction of aniline with ethyl acetoacetate or diethyl (ethoxymethylene)malonate.[28,29] To optimize reaction conditions, arylation of 4-methyl-quinolin-2(1*H*)-one (**4**) with diphenyliodonium triflate (**5a**) under conventional and microwave (MW) irradiation conditions was selected as a model reaction; the results are summarized in Table 1. To our satisfaction, the reaction of **4** with **5a** proceeded in DMF using Cs_2CO_3 as base without any metal catalyst; albeit in low yield (entry 1). To improve the yield, we screened different bases and solvents at different temperatures using conventional heating as well as MW irradiation. A slight improvement in yield was observed when K_2CO_3 was used as base (entry 2). By increasing the reaction temperature from 100 to 130 °C, the product yield improved significantly (up to 65%). Under similar conditions, the reaction of **4** with **5a** in DMSO resulted in a poor yield of **6a** (entries 4 and 5). Product **6a** was only obtained in moderate yield when the same reaction in DCE was performed using K_2CO_3 or *t*-BuOK

Table 1 Optimization of Reaction Conditions for O-Arylation of Quinolone **4**



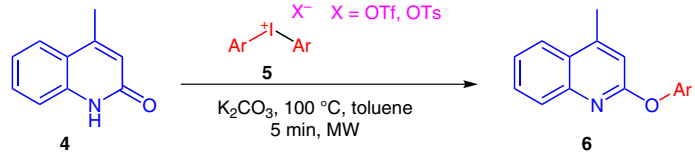
Entry	Base	Solvent	Conventional heating			MW irradiation	
			Temp (°C)[a]	Time (h)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	Cs_2CO_3	DMF	100	5.0	30	10	40
2	K_2CO_3	DMF	100	4.5	40	10	45
3	K_2CO_3	DMF	130	3.5	60	10	65
4	Cs_2CO_3	DMSO	70	8.0	25	10	30
5	K_2CO_3	DMSO	100	6.0	30	10	30
6	K_2CO_3	DCE	80	4.0	45	10	50
7	*t*-BuOK	DCE	80	3.5	50	10	50
8	K_2CO_3	toluene	100	5.0	65	5.0	85
9	K_2CO_3	toluene	100	–	–	10	85
10	K_3PO_4	THF	80	6.0	35	10	35
11	K_3PO_4	toluene	130	3.5	55	10	70
12	–	toluene	130	5.0	Trace	10	trace

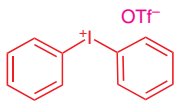
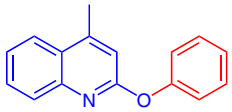
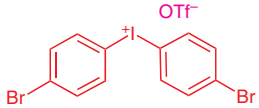
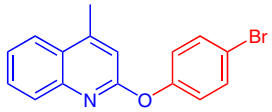
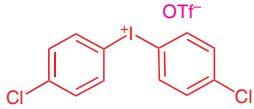
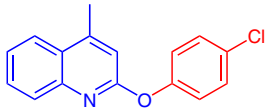
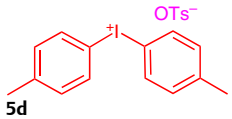
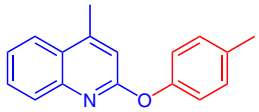
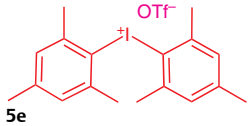
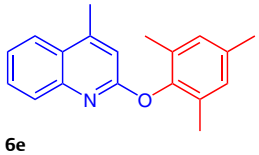
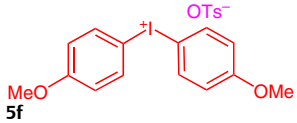
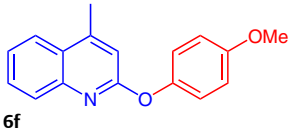
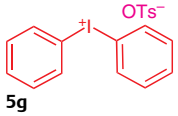
[a] We note that the stated temperatures under MW conditions are probably not the genuine reaction temperatures.
[b] Isolated yield.

as bases (entries 6 and 7). The reaction of **4** and **5a** in toluene using K_2CO_3 at 100 °C also gave **6a** in moderate yield. However, when the same reaction mixture was subjected to MW irradiation for 5 minutes, **6a** was obtained in 85% yield.

The yield of the reaction was unaffected when the time of MW exposure was extended (Table 1, entries 8 and 9). Changing the base from K_2CO_3 to K_3PO_4 led to the formation of **6a** in lower yields (entries 10 and 11). To ascertain the role of the base, reaction of **4** and **5a** was performed in toluene without any base, which afforded only a trace amount of the product even after heating to reflux for 24 hours or exposure to MW irradiation for 10 minutes (entry 12). With the use of 1.0, 2.0, and 2.5 equivalents of K_2CO_3 in the reaction of **4** and **5a**, some unchanged starting material was recovered, however, the use of 3.0 equivalents of K_2CO_3 was found to be optimum to produce **6a** in good yield. We also performed the arylation of **4** with diphenyliodonium tosylate (**5g**) using K_2CO_3 as base in toluene at 100 °C to pro-

Table 2 Synthesis of Aryloxyquinolines **6a–f**



Entry	Diaryliodonium salt	Product	Yield (%)
1	 **5a**	 **6a**	81
2	 **5b**	 **6b**	73
3	 **5c**	 **6c**	75
4	 **5d**	 **6d**	62
5	 **5e**	 **6e**	67
6	 **5f**	 **6f**	65
7	 **5g**	**6a**	65

duce **6a** in 65% yield (Table 2, entry 7). With the optimized reaction conditions in hand, the scope of the O-arylation was undertaken by employing various diaryliodonium salts **5** (Table 2).[30]

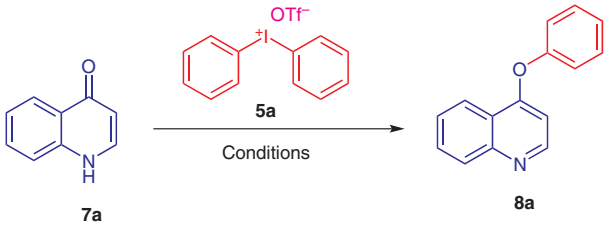
The synthesized 4-methyl-2-aryloxyquinolines **6a–f** were fully characterized based on their IR, NMR (^{1}H and ^{13}C) spectroscopic and mass spectrometric data. The ^{1}H NMR spectra of **6a–f** displayed a characteristic singlet at δ = 6.9 to 7.0 ppm, corresponding to the C-3 proton. Similarly, in the ^{13}C NMR spectra, the C-2 carbon of the quinoline ring resonated at δ = 161 to 162 ppm.

We then explored the arylation of quinolone **7a**. Reaction conditions for the O-arylation of **7a** using **5a** were optimized under conventional heating conditions as well as under MW irradiation; the results are summarized in Table 3. Initial reaction of **7a** and **5a** was performed in THF, DMF, and toluene, using Cs_2CO_3 as base, but we could isolate **8a** only in a low to moderate yield (entries 1–3). Given the good solubility of **7a** in DMF, we performed the model reaction in this solvent using various bases. No product was formed when the reaction was carried out in DMF without any base at 100 °C, even after heating to reflux for 24 h under conventional heating or heating under MW irradiation for 10 min (entry 13). Use of the bulkier base *t*-BuOK was also not satisfactory in DMF (entry 4). At low temperature, the use of K_2CO_3 in dioxane, DCE, or DMF gave **8a** in moderate yield (entries 5–7). Interestingly, when the reaction temperature was raised from 70 to 100 °C in DMF, **8a** was obtained in 75% yield. The product yield increased to 80% when the same reaction mixture was heated under MW irradiation (entry 8). Further increase in temperature (up to 120 °C) and use of DMSO and toluene as reaction solvents at 100 °C did not improve the product yield (entries 9–11). Under these optimized conditions, the influence of different diaryliodonium salts was investigated to prepare a range of aryloxyquinoline derivatives **8a–j** in good yields (Table 4).[26] Again, the synthesized products were fully characterized based on their NMR, IR spectroscopic and mass spectrometric data. In the ^{13}C NMR spectra, a characteristic peak was observed between δ values of 159 to 162 ppm, corresponding to the C-4 carbon of the quinoline ring.

Interestingly, solvents and bases were found to play an important role in the O-arylation of quinolones. Diaryliodonium salts with a triflate counter anion gave better yields of aryloxyquinolines when compared with their tosylate counterparts (Table 2, entries 1 and 7). A number of diaryliodonium salts possessing electron-withdrawing or electron-donating groups smoothly transferred their aryl rings to afford the corresponding aryloxyquinolines in good yields.

The salts **5b–c**, with electron-withdrawing groups, produced the O-arylated products in better yields compared with salts **5d–f** and **5h–i**, with electron-donating groups

Table 3 Optimization of Reaction Conditions for O-Arylation of Quinolone **7a**



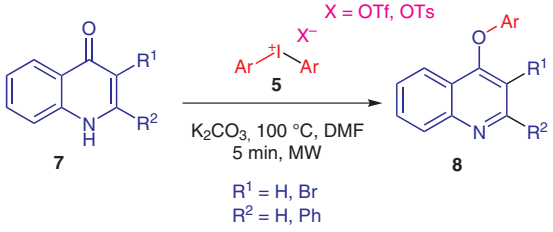
Entry	Base	Solvent	Temp (°C)[a]	Conventional heating		MW irradiation	
				Time (h)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	$CsCO_3$	THF	70	6.0	30	10	42
2	Cs_2CO_3	DMF	100	4.0	55	10	63
3	Cs_2CO_3	toluene	100	3.5	45	10	65
4	*t*-BuOK	DMF	100	5.0	25	10	25
5	K_2CO_3	dioxane	90	6.0	40	10	54
6	K_2CO_3	DCE	80	3.5	50	10	55
7	K_2CO_3	DMF	70	5.0	50	10	60
8	K_2CO_3	DMF	100	2.0	75	5.0	80
9	K_2CO_3	DMF	120	2.0	75	5.0	80
10	K_2CO_3	DMSO	100	3.5	50	10	52
11	K_2CO_3	toluene	100	4.0	55	10	60
13	–	DMF	100	24	NR	10	NR

[a] We note that the stated temperatures under MW conditions are probably not the genuine reaction temperatures.
[b] Isolated yield.

such as methyl and methoxyl. Furthermore, diaryliodonium salts possessing sterically hindered substituents such as *tert*-butyl (**5h**) and mesityl (**5e**) arylated the quinolones efficiently. Notably, the synthesized halo-substituted aryloxyquinolinesthis could be useful for the synthesis of further functionalized bioactive heterocycles.

A control experiment to detect the involvement of radical species in the reactions of **4**/**7a** with **5a** was carried out in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). The outcome of this experiment showed that the radical inhibitor TEMPO did not have any influence on the reaction rate, suggesting the formation of aryloxyquinolines through an ionic pathway. A plausible mechanism for the O-arylations of quinolones **4**/**7** is depicted in Scheme 2. Initially, the tautomeric form of quinolones **4**/**7** in the presence of K_2CO_3 is proposed to generate species **A** that, in turn, undergoes a displacement reaction with diaryliodonium salt **5** to form intermediate **B**. Finally, ligand coupling in **B** generates aryloxyquinolines **6**/**8**.

Table 4 Synthesis of Aryloxyquinolines **8a–j**



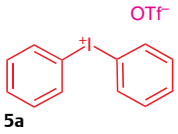
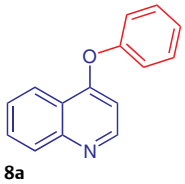
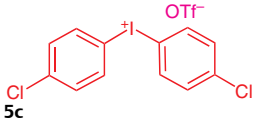
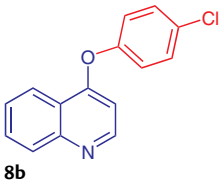
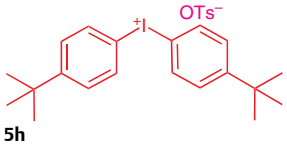
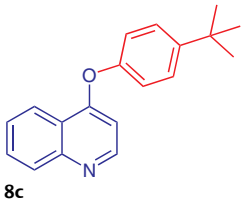
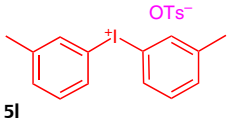
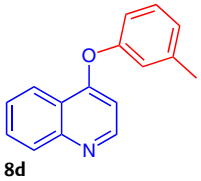
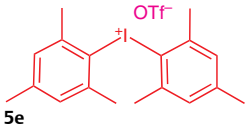
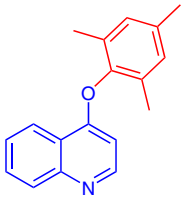
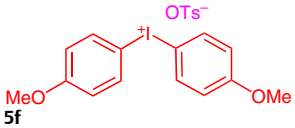
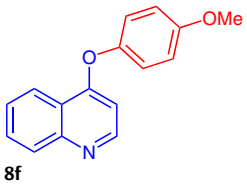
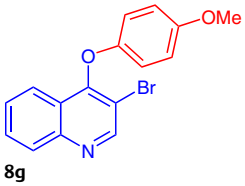
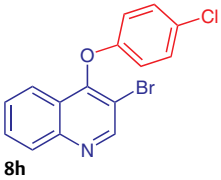
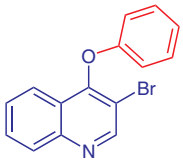
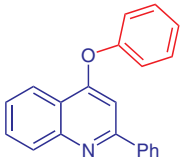
Entry	Diaryliodonium salts	Products	Yield (%)
1	 **5a**	 **8a**	80
2	 **5c**	 **8b**	70
3	 **5h**	 **8c**	55
4	 **5l**	 **8d**	58
5	 **5e**	 **8e**	74
6	 **5f**	 **8f**	55

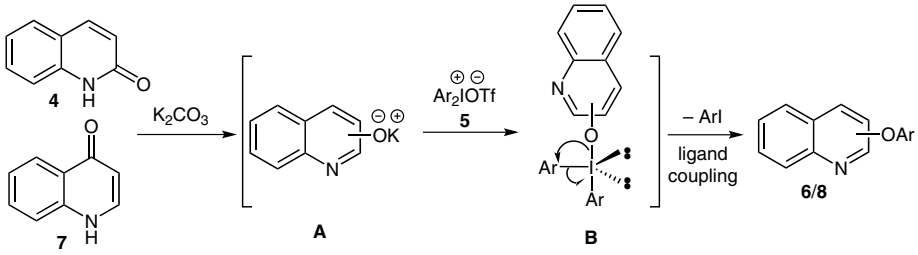
Table 4 (continued)

Entry	Diaryliodonium salts	Products	Yield (%)
7	**5f**	 **8g**	60
8	**5c**	 **8h**	70
9	**5a**	 **8i**	80
10	**5a**	 **8j**	76

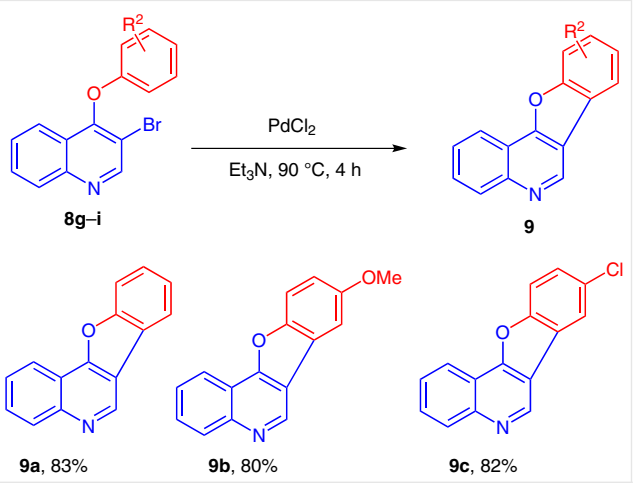
We then utilized the synthesized 4-aryloxyquinolines **8g–i** for the construction of benzofuro[3,2-*c*]quinolines **9a–c**. Fused quinoline derivatives of this nature are important because of their anticancer, antimicrobial, antiplasmodial, antiviral, and antituberculosis properties.[31,32]

Fused quinolines **9a–c** were smoothly achieved in good yields (80–83%) through the Pd-catalyzed intramolecular Heck coupling of 3-bromo-4-aryloxyquinolines **8g–i** in the presence of triethylamine, as depicted in Scheme 3. However, our attempts to convert 2-aryloxyquinolines **6** into the corresponding benzofuro[2,3-*b*]quinolines through double C–H activation were unsuccessful.

In summary, a novel and efficient MW-enhanced metal- and ligand-free synthetic protocol for the direct O-arylation of quinolones using diaryliodonium salts has been developed. Important features of this experimentally simple synthetic protocol are the use of readily available and stable diaryliodonium salts, metal- and ligand-free conditions, use of MW energy, short reaction times, and good product yields. Furthermore, the synthetic potential of the aryloxyquinolines thus synthesized was demonstrated by preparing benzofuro[3,2-*c*]quinolines in good yields.



Scheme 2 Plausible mechanism for the O-arylation of quinolones



Scheme 3 Synthesis of benzofuro[3,2-c]quinolines **9**

Acknowledgment

Financial support from the DBT, New Delhi is gratefully acknowledged. M.K.M. thanks the CSIR, New Delhi for the award of Junior Research Fellowship.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560367.

References and Notes

(1) Janz, K.; Kaila, N. *J. Org. Chem.* **2009**, *74*, 8874.
(2) Falke, H.; Chaikuad, A.; Becker, A.; Loaëc, N.; Lozach, O.; Abu Jhaisha, S.; Becker, W.; Jones, P. G.; Preu, L.; Baumann, K.; Knapp, S.; Meijer, L.; Kunick, C. *J. Med. Chem.* **2015**, *58*, 3131.
(3) Korotchenko, V.; Sathunuru, R.; Gerena, L.; Caridha, D.; Li, Q.; Kreishman-Deitrick, M.; Smith, P. L.; Lin, A. J. *J. Med. Chem.* **2015**, *58*, 3411.
(4) Soares, R. R.; da Silva, J. M. F.; Carlos, B. C.; da Fonseca, C. C.; de Souza, L. S. A.; Lopes, F. V.; de Paula Dias, R. M.; Moreira, P. O. L.; Abramo, C.; Viana, G. H. R.; de Pila Varotti, F.; da Silva, A. D.; Scopel, K. K. G. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2308.
(5) Medapi, B.; Renuka, J.; Saxena, S.; Sridevi, J. P.; Medishetti, R.; Kulkarni, P.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem.* **2015**, *23*, 2062.
(6) Pandey, A. K.; Sharma, R.; Shivahare, R.; Arora, A.; Rastogi, N.; Gupta, S.; Chauhan, P. M. S. *J. Org. Chem.* **2013**, *78*, 1534.
(7) Cai, Z.; Zhou, W.; Pan, J.; Hao, Q.; Zhang, L. *J. Chin. Pharm. Sci.* **2010**, *19*, 15.
(8) Ries, U. J.; Priepke, H. W.; Hauel, N. H.; Haaksma, E. E.; Stassen, J. M.; Wienen, W.; Nar, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2291.
(9) Qi, B.; Mi, B.; Zhai, X.; Xu, Z.; Zhang, X.; Tian, Z.; Gong, P. *Bioorg. Med. Chem.* **2013**, *21*, 5246.
(10) Maiti, D.; Buchwald, S. L. *J. Org. Chem.* **2010**, *75*, 1791.
(11) Zhao, J.; Peng, C.; Liu, L.; Wang, Y.; Zhu, Q. *J. Org. Chem.* **2010**, *75*, 7502.
(12) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052.
(13) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
(14) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269.
(15) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, *(i)*, 370.
(16) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219.
(17) Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358.
(18) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 188.
(19) Jalalian, N.; Ishikawa, E. E.; Silva, L. F.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552.
(20) Lindstedt, E.; Ghosh, R.; Olofsson, B. *Org. Lett.* **2013**, *15*, 6070.
(21) Ghosh, R.; Olofsson, B. *Org. Lett.* **2014**, *16*, 1830.
(22) Thorat, P. B.; Waghmode, N. A.; Karade, N. N. *Tetrahedron Lett.* **2014**, *55*, 5718.
(23) Kumar, D.; Arun, V.; Pilania, M.; Shekar, K. *Synlett* **2013**, *24*, 831.
(24) Kumar, D.; Pilania, M.; Arun, V.; Pooniya, S. *Org. Biomol. Chem.* **2014**, *12*, 6340.
(25) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602.
(26) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, 2521.
(27) Chun, J.-H.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2011**, *2011*, 4439.
(28) Jayashree, B. S.; Thomas, S.; Nayak, Y. *Med. Chem. Res.* **2010**, *19*, 193.
(29) Huang, L.-J.; Hsieh, M.-C.; Teng, C.-M.; Lee, K.-H.; Kuo, S.-C. *Bioorg. Med. Chem.* **1998**, *6*, 1657.
(30) **Synthesis of Aryloxyquinolines; General Procedure:** A mixture of quinolone (0.62 mmol), diaryliodonium salt (0.62 mmol) and potassium carbonate (260 mg, 1.88 mmol) in toluene (1 mL) or DMF (2–3 drops) was irradiated in a CEM Discover MW reactor (100 W power) at 100 °C for 5 min. Upon completion of the reaction, as indicated by TLC, solvent was removed and the residue was dissolved in dichloromethane (20 mL). To this solution, water (20 mL) was added and the mixture stirred at room temperature for 10 min. The organic phase was separated, washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product thus obtained was purified by silica gel (100–200) column chromatography to afford the pure aryloxyquinoline.
4-Methyl-2-phenoxyquinoline (6a): Yield: 119 mg (81%); off-white solid; mp 76–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 8.3, 1.2 Hz, 1 H), 7.80 (dd, *J* = 8.4, 0.7 Hz, 1 H), 7.66–7.62 (m, 1 H), 7.56–7.53 (m, 2 H), 7.50–7.46 (m, 1 H), 7.28 (s, 1 H), 7.18–7.15 (m, 2 H), 6.96 (d, *J* = 0.9 Hz, 1 H), 2.71 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.0, 153.0, 148.5, 146.2, 132.5, 129.7, 128.4, 126.0, 124.9, 123.7, 123.3, 117.3, 112.7, 18.9. IR (KBr): 1612, 1574, 1512, 1481, 1381, 1342, 1219, 825, 756 cm^{-1}. MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}NO$: 236.1; found: 236.2.
4-Phenoxyquinoline(8a): Yield: 122 mg (80%); yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 5.2 Hz, 1 H), 8.44–8.33 (m, 1 H), 8.12 (d, *J* = 8.5 Hz, 1 H), 7.78–7.73 (m, 1 H), 7.59–7.55 (m, 1 H), 7.49–7.44 (m, 2 H), 7.33–7.27 (m, 1 H), 7.22–7.16 (m, 2 H), 6.55 (d, *J* = 5.2 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.9, 154.4, 151.1, 149.7, 130.3, 130.1, 129.0, 126.1, 125.6, 121.8, 121.5, 121.1, 104.3. IR (KBr): 1566, 1489, 1420, 1389, 1304, 1211, 771 cm^{-1}. MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}NO$: 222.0; found: 222.1.
(31) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999.
(32) Chen, Y.-L.; Chung, C.-H.; Chen, I.-L.; Chen, P.-H.; Jeng, H.-Y. *Bioorg. Med. Chem.* **2002**, *10*, 2705.