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Molecular iodine-catalyzed and air-mediated tandem synthesis of quinolines via three-component reaction of amines, aldehydes, and alkynes

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ABSTRACT

A one-pot synthesis of quinolines via molecular iodine-catalyzed and air-mediated tandem condensation/imino-Diels–Alder/isomerization/oxidation of simple readily available amines, aldehydes, and alkynes has been developed. This methodology was extended to synthesize quinazolines from two molecules of amines and two molecules of glyoxalates.

1. Introduction

Quinolines and their derivatives play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals but also as useful building blocks for various biologically active molecules and functional materials.[1] Consequently, synthesis of quinoline derivatives bearing diverse substitution patterns has received much attention[2] since Skraup reported the classical method of quinoline synthesis in 1880 for the first time.[3] Among these novel strategies for the synthesis of quinolines, multicomponent reactions (MCRs) provides an easy access to the preparation of quinoline derivatives, because multicomponent reactions (MCRs) have emerged as powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry.[4] Recently, Tu developed the $FeCl_3$-catalyzed three-component coupling-/hydroarylation/dehydrogenation of aldehydes, alkynes, and amines for the synthesis of 2, 4-disubstituted quinolines.[5a] Wang reported a sequential catalytic process for the synthesis of quinolines by $AuCl_3$/CuBr-catalyzed MCR strategy.[5b] Liu synthesized the quinoline-2-carboxylates using $Cu(OTf)_2$-catalyzed tandem Grignard-type imine addition/Friedel–Crafts alkenylation of arenes with alkynes.[5c] Guchhait described the synthesis of polysubstituted quinolines via ($HClO_4$)-modified montmorillonite-catalyzed Povarov reaction.[5d] Nagarajan reported CuI/$La(OTf)_3$ catalyzed, one-pot three-component synthesis of isomeric ellipticine derivatives in ionic liquid.[5e] All these methods are through strong acid-catalyzed or metal-catalyzed sequential intermolecular addition of alkynes onto imines and subsequent intramolecular ring closure by arylation. Considering the continued importance of the quinoline core in both biological and chemical fields, new direct approaches remain highly valuable to the contemporary collection of synthetic methods.

Recently, molecular iodine has received considerable attention as an inexpensive and readily available catalyst for various organic transformations due to its moderate Lewis acidity and water-tolerance.[6] Previously, we reported several molecular iodine-catalyzed organic reactions.[7] In continuation of our efforts to develop novel MCRs and domino reaction strategy on heterocyclic synthesis,[8] herein we report a metal-free and one-pot three-component synthesis of quinolines under mild reaction conditions. This has been done by assembling the quinoline core via molecular iodine-catalyzed and air-mediated tandem condensation/imino-Diels–Alder/isomerization/oxidation of simple readily available amines, aldehydes, and alkynes.

2. Results and discussion

Exhaustive studies of the reaction conditions for the synthesis of quinoline **4a** from *p*-methoxyphenyl amine **1a** with ethyl glyoxalate **2a** and phenylacetylene **3a** in the presence of molecular iodine were conducted (Table 1). We examined several organic solvents, which are commercially available and used without further purification or drying. We found that a remarkable solvent effect existed in 10 mol % iodine-catalyzed reaction at room temperature.

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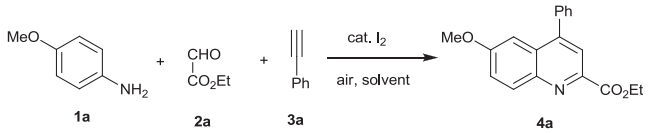
Table 1
Optimization of reaction conditions[a]



1a 2a 3a 4a

Entry	Iodine (mol %)	Solvent	T	*t*/h	Yield[b] (%)
1	10	MeCN	rt	12	75
2	10	PhMe	rt	24	65
3	10	THF	rt	24	68
4	10	DCM	rt	24	53
5	10	EtOH	rt	24	44
6	10	$MeNO_2$	rt	12	82
7	10	$MeNO_2$	Reflux	6	74
8	15	$MeNO_2$	rt	7	83
9	5	$MeNO_2$	rt	24	65
10	0	$MeNO_2$	rt	24	0

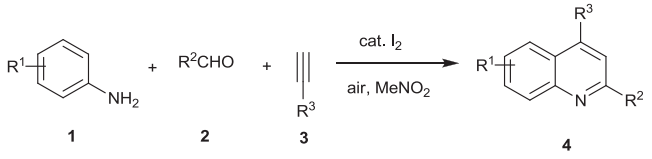
[a] All the reactions were carried out using **1a** (1 mmol), **2a** (1 mmol), and **3a** (1.5 mmol) in 2 mL solvent.
[b] Isolated yields.

These results showed that nitromethane was the most suitable solvent for this transformation among others, such as acetonitrile, toluene, THF, DCM, and EtOH (Table 1, entries 1–6). When the model reaction was carried out under reflux, reduced yield was observed (Table 1, entry 7). Furthermore, the reaction was accelerated when the amount of catalyst was increased to 15 mol %, but the yield was not improved (Table 1, entry 8). When the reaction was catalyzed by 5 mol % iodine, the reaction time was prolonged to 24 h and the desired product **4a** was obtained with only 65% (Table 1, entry 9). While no quinoline product **4a** was obtained in the absence of molecular iodine (Table 1, entry 10). Thus, the most suitable reaction conditions for the formation of **4a** were established (Table 1, entry 6). It is noteworthy that the metal-free reaction proceeded smoothly without exclusion of moisture or air.

To reveal the generality of this method, we next explored the protocol with a variety of simple readily available amines **1**, aldehydes **2**, and alkynes **3**, and the results were presented in Table 2. First, we examined the scope of alkynes in this reaction, and it was found that substituted phenylacetylenes **3a**–**c** were suitable substrates for this transformation, and the expected products were obtained in good yields (Table 2, entries 1–3). Then, the versatility of this transformation was assessed by altering aldehydes **2** (Table 2, entries 1 and 6–12). Isolated yield was tuned by the property of the substituted groups on compound **2**. In case of aromatic aldehydes, the reaction was carried out under reflux. Except in case of 4-nitrobenzaldehyde, when the aromatic aldehyde carried an electron-donating group or an electronwithdrawing group, isolated yields were comparable to those of the ethyl glyoxalate case. It is noted that hydroxyl group on aromatic ring was well tolerated (Table 2, entries 10 and 14). When aliphatic aldehyde **2h** was used instead of aromatic ones, product **4l** was isolated with low yield (32%; Table 2, entry 12).

Subsequently, we investigated the scope of aromatic amines (Table 2, entries 1, 4–5, 13, and 14). It can be seen that the reactions proceeded smoothly to give the corresponding quinolines in moderate to good yields when the aromatic amine carried an electron-donating group or an electronwithdrawing group, except that in cases of 4-nitroaniline, lower yield was obtained for **4e** (45%; Table 2, entry 5). Polycyclic aromatic amines, such as naphthalene-2-amine **1f** and 9-ethyl-carbazol-3-amine **1g** produced benzo[*f*] quinoline **4o** (70% yield) and isomeric ellipticine **4p** (68% yield), respectively in the one-pot three-component reaction (Scheme 1).

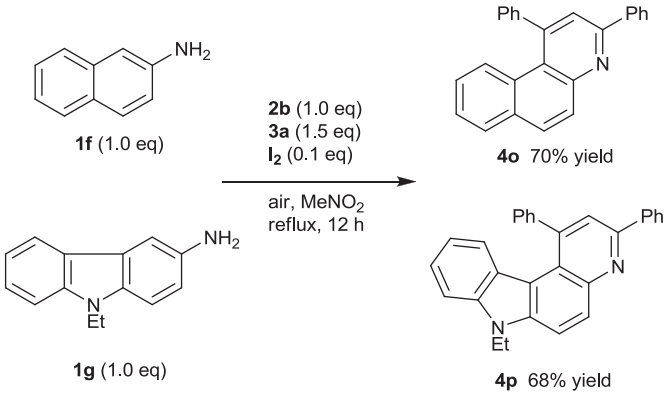
Table 2
Three-component synthesis of quinolines[a]



1 2 3 4

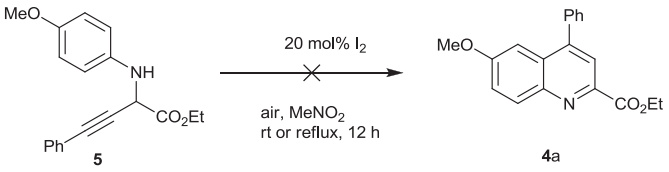
Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	4-MeO (**1a**)	CO_2Et (**2a**)	Ph (**3a**)	**4a**	82
2[c]	**1a**	**2a**	3-BrPh (**3b**)	**4b**	65
3	**1a**	**2a**	4-MePh (**3c**)	**4c**	73
4	4-Cl (**1b**)	**2a**	**3a**	**4d**	60
5	4-NO_2 (**1c**)	**2a**	**3a**	**4e**	45
6[c]	**1a**	Ph (**2b**)	**3a**	**4f**	71
7[c]	**1a**	4-MePh (**2c**)	**3a**	**4g**	75
8[c]	**1a**	4-BrPh (**2d**)	**3a**	**4h**	80
9[c]	**1a**	4-NO_2Ph (**2e**)	**3a**	**4i**	41
10[c]	**1a**	2-OHPh (**2f**)	**3a**	**4j**	70
11[c]	**1a**	3,4-(−OCH_2O−)Ph (**2g**)	**3a**	**4k**	77
12[c,d]	**1a**	H (**2h**)	**3a**	**4l**	32
13[c]	H (**1d**)	**2b**	**3a**	**4m**	61
14[c]	4-Me (**1e**)	**2f**	**3a**	**4n**	63

[a] All the reactions were carried out using **1** (1 mmol), **2** (1 mmol), **3** (1.5 mmol), and iodine (0.1 mmol) in 2 mL $MeNO_2$ at rt for 12 h.
[b] Isolated yields.
[c] Under reflux.
[d] Using Paraformaldehyde (1.5 mmol).



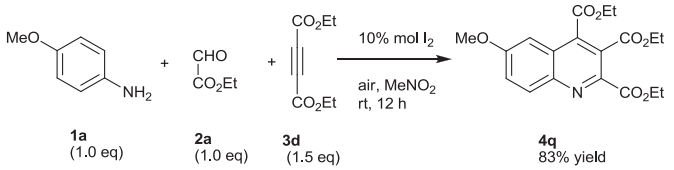
Scheme 1.

To probe the reaction mechanism of the iodine-catalyzed tandem synthesis of quinolines, propargylamine **5**, which is identified as the key intermediate in metal-catalyzed synthesis of quinolines,[5] was treated with 20 mol % iodine in $MeNO_2$ at room temperature or under reflux for 12 h, but **4a** was not observed and all of **5** was recovered (Scheme 2). Furthermore, in case of disubstituted alkyne **3d**, the 10 mol % iodine-catalyzed tandem reaction gave the desired quinoline **4q** with 83% yield at room temperature for 12 h (Scheme 3). Thus the use of alkyne as a dienophile is suitable in this reaction and the key-step of the mechanism may be an imino-Diels–Alder reaction.



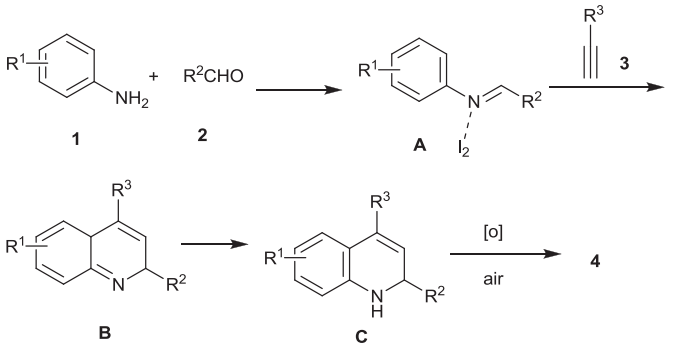
5 4a

Scheme 2.



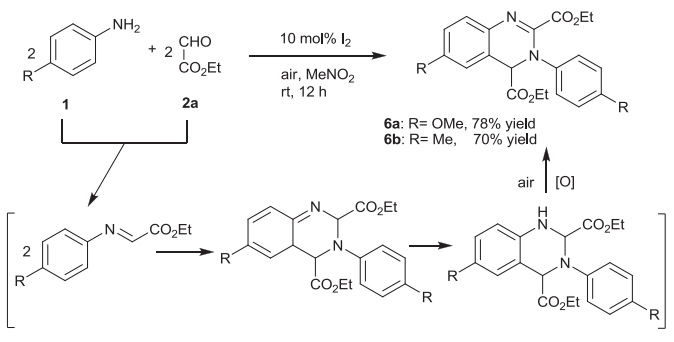
Scheme 3.

Based on the experimental results above and together with our previous work,[7] we think that molecular iodine catalyzes the reaction as a mild Lewis acid. Thus, we propose a possible mechanism as shown in Scheme 4. The first step is the formation of the intermediate identified by the experiment in the preceding course, namely Schiff base **A** formed by the condensation of amine **1** with aldehyde **2**. And then imino-Diels–Alder reaction between the iodine-activated Schiff base **A** and alkyne dienophile **3** proceeds to afford intermediate **B**, followed by isomerization to dihydroquinoline **C**, which is subsequently oxidized by O_2 in air to give the final quinoline product **4**.



Scheme 4.

One interesting extension of this methodology is the ready access to quinazoline derivatives. We investigated the possibility of iodine-catalyzed intermolecular annulation of α-iminoester generated in situ by condensation of aniline and ethyl glyoxalate, as shown in Scheme 5. When anilines **1a** and **1e** were treated with **2a** in the presence of 10 mol% iodine in $MeNO_2$ at 50 °C for 12 h, quinazolines **6a** and **6b** were obtained in 78% yield and 70% yield, respectively. The tandem reaction involves iodine-catalyzed imino-Diels–Alder cyclization and air-mediated oxidation reaction. This one-step and metal-free strategy for access substituted quinazoline, which is potentially useful scaffold for the synthesis of biologically active compounds,[9] is concise and efficient.



Scheme 5.

3. Conclusion

In conclusion, we have developed a molecular iodine-catalyzed and air-mediated tandem synthesis of quinolines starting from simple readily available amines, aldehydes, and alkynes. This has been done by assembling the quinoline core via one-pot and three-component reaction from [3+2+1] atom fragments by formation of three new bonds. This methodology is extended to the ready access to quinazoline derivatives.

4. Experimental section

4.1. General

Melting points were obtained on a microscopical instrument and uncorrected. NMR spectra were recorded at 400 MHz spectrometer and TMS as internal standard. IR spectra were recorded on an FT-IR spectrometer. Low-resolution MS was obtained using ESI ionization. HRMS data were obtained using EI ionization. All reagents and solvents used were commercially available. Column chromatography was carried out on silica gel (300–400 mesh) with mixed solvents (hexane/ethyl acetate).

4.2. General procedure for the synthesis of quinoline 4

After amine **1** (1 mmol) and aldehyde **2** (1 mmol) were dissolved in CH_3NO_2 (2 mL), alkyne **3** (1.5 mmol), and iodine (0.1 mmol) were added, and the solution was stirred at room temperature or under reflux for 12 h. Then the reaction mixture was diluted with ethyl acetate and washed with a solution of sodium thiosulfate followed by water. The organic phase was dried over anhydrous Na_2SO_4, and evaporation of the solvent followed by purification on silica gel afforded pure desired quinoline **4**.

4.3. General procedure for the synthesis of quinazoline 6

After amine **1** (1 mmol) and ethyl glyoxylate **2a** (1 mmol) were dissolved in CH_3NO_2 (2 mL), iodine (0.1 mmol) were added, and the solution was stirred at 50 °C for 12 h. Then the reaction mixture was diluted with ethyl acetate, and washed with a solution of sodium thiosulfate followed by water. The organic phase was dried over anhydrous Na_2SO_4, and evaporation of the solvent followed by purification on silica gel afforded pure desired quinazoline **6**.

4.4. Characterization data

*4.4.1. Ethyl 6-methoxy-4-phenylquinoline-2-carboxylate (**4a**)*[5c]. Yellow solid, mp 146–147 °C; IR (KBr) ν 1730, 1619, 1492, 1473, 1366, 1224, 1107, 1027, 841, 763, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J=9.2 Hz, 1H), 8.02 (s, 1H), 7.42–7.51 (m, 5H), 7.36 (dd, J=3.2 Hz, J=2.4 Hz, 1H), 7.14 (d, J=2.4 Hz, 1H), 4.48 (q, J=7.2 Hz, 2H), 3.74 (s, 3H), 1.41 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.59, 159.49, 147.99, 145.38, 144.32, 137.90, 132.68, 129.27, 129.15, 128.72, 128.58, 122.72, 121.75, 103.30, 62.02, 55.46, 14.37 ppm; MS (ESI): m/z ([M+H]$^+$): 308.

*4.4.2. Ethyl 4-(3-bromophenyl)-6-methoxyquinoline-2-carboxyl-ate (**4b**).* Yellow solid, mp 156–157 °C; IR (KBr) ν 1715, 1620, 1586, 1547, 1481, 1438, 1222, 1127, 1107, 1022, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J=9.2 Hz, 1H), 8.07 (s, 1H), 7.70–7.71 (m, 1H), 7.63–7.66 (m, 1H), 7.41–7.49 (m, 3H), 7.14 (d, J=2.8 Hz, 1H), 4.56 (q, J=6.8 Hz, 2H), 3.83 (s, 3H), 1.49 (t, J=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.39, 159.71, 146.19, 145.33, 144.27, 139.87, 132.80, 132.21, 131.66, 130.24, 128.79, 127.89, 122.89, 122.85, 121.67, 102.89, 62.10, 55.52, 14.36 ppm; MS (ESI): m/z ([M+H]$^+$): 386; HRMS (EI): m/z calcd for ($C_{19}H_{16}BrNO_3$): 385.0314; found: 385.0304.

*4.4.3. Ethyl 6-methoxy-4-p-tolylquinoline-2-carboxylate (**4c**)*[5c]. Yellow solid, mp 145–146 °C; IR (KBr) ν 1712, 1621, 1508, 1473, 1374, 1245, 1178, 1026, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J=9.2 Hz, 1H), 8.08 (s, 1H), 7.41–7.46 (m, 3H), 7.34–7.37 (m, 2H), 7.25 (d, J=2.4 Hz, 1H), 4.55 (q, J=6.8 Hz, 2H), 3.82 (s, 3H), 2.48 (s, 3H),1.48 (t, J=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.56, 159.35, 147.98, 145.34, 144.27, 138.44, 134.89, 132.59, 129.37, 129.16, 129.17, 122.59, 121.65, 103.28, 61.89, 55.39, 21.19, 14.30 ppm; MS (ESI): m/z ($[M+H]^+$): 322.

*4.4.4. Ethyl 6-chloro-4-phenylquinoline-2-carboxylate (**4d**).* White solid, mp 179–180 °C; IR (KBr) ν 1736, 1604, 1484, 1451, 1387, 1234, 1143, 1114, 1020, 840, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (m, 1H), 8.14 (d, J=5.2 Hz, 1H), 7.92 (d, J=4.4 Hz, 1H), 7.69–7.74 (m, 1H), 7.51–7.57 (m, 5H), 4.53–4.60 (q, J=7.2 Hz, 2H), 1.46–1.51 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.09, 149.01, 147.94, 146.51, 136.83, 134.76, 132.65, 131.00, 129.37, 128.95, 128.83, 128.38, 124.48, 121.96, 62.29, 14.30 ppm; MS (ESI): m/z ($[M+H]^+$): 312; HRMS (EI): m/z calcd for ($C_{18}H_{14}ClNO_2$): 311.0713; found: 311.0712.

*4.4.5. Ethyl 6-nitro-4-phenylquinoline-2-carboxylate (**4e**).* Yellow solid, mp 204–205 °C; IR (KBr) ν 1716, 1619, 1534, 1502, 1344, 1257, 1140, 1110, 848, 785, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.53 (s, 2H), 8.27 (s, 1H), 7.56–7.62 (m, 5H), 4.59 (q, J=5.2 Hz, 2H), 1.51(t, J=5.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.71, 152.32, 150.80, 150.17, 146.87, 136.02, 133.02, 129.70, 129.49, 129.25, 126.88, 123.42, 122.76, 122.65, 62.78, 14.33 ppm; MS (ESI): m/z ($[M+H]^+$): 323; HRMS (EI): m/z calcd for ($C_{18}H_{14}N_2O_4$): 322.0954; found: 322.0946.

*4.4.6. 6-Methoxy-2,4-diphenylquinoline (**4f**)*[5]. Yellow solid, mp 119–120 °C; IR (KBr) ν 2362, 2341, 1616, 1588, 1545, 1487, 1357, 1221, 1025, 836, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.16 (m, 3H), 7.76 (s, 1H), 7.48–7.58 (m, 7H), 7.37–7.44 (m, 2H), 7.18 (d, J=2.8 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.07, 155.13, 148.79, 141.09, 138.22, 131.47, 129.39, 129.22, 128.77, 128.65, 126.58, 122.32, 119.15, 118.46, 118.48, 117.87, 104.19, 55.46 ppm; MS (ESI): m/z ($[M+H]^+$): 312.

*4.4.7. 6-Methoxy-4-phenyl-2-p-tolylquinoline (**4g**).* Yellow solid; mp 136–137 °C; IR (KBr) ν 1617, 1590, 1546, 1488, 1394, 1222, 1113, 1027, 834, 781, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05–8.25(m, 3H), 7.74 (s, 1H), 7.46–7.59 (m, 5H), 7.28–7.37 (m, 3H), 7.17 (s, 1H), 3.76 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.59, 154.52, 147.59, 144.83, 138.88, 138.74, 138.86, 136.45, 131.45, 129.44, 129.29, 128.59, 128.22, 127.09, 121.60, 119.38, 103.68, 55.32, 21.23 ppm; MS (ESI): m/z ($[M+H]^+$): 326; HRMS (EI): m/z calcd for ($C_{23}H_{19}NO$): 325.1467; found: 325.1456.

*4.4.8. 2-(4-Bromophenyl)-6-methoxy-4-phenylquinoline (**4h**).* Yellow solid; mp 135–136 °C; IR (KBr) ν 1617, 1589, 1544, 1488, 1356, 1224, 1071, 1027, 827, 767, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J=9.2 Hz, 1H), 7.99 (d, J=8.8 Hz, 2H), 7.66 (s, 1H), 7.56 (d, J=8.8 Hz, 2H), 7.43–7.57 (m, 5H), 7.34 (q, J=6.8 Hz, 1H), 7.13(d, J=2.8 Hz, 1H), 3.74(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.94, 153.16, 147.93, 144.85, 138.55, 131.85, 131.56, 130.28, 129.30, 128.77, 128.70, 128.41, 126.75, 123.44, 122.00, 119.05, 103.68, 55.42 ppm; MS (ESI): m/z ($[M+H]^+$): 390; HRMS (EI): m/z calcd for ($C_{22}H_{16}BrNO$): 389.0415; found: 389.0421.

*4.4.9. 6-Methoxy-2-(4-nitrophenyl)-4-phenylquinoline (**4i**)*[3]. Light yellow solid, mp 100–101 °C; IR(KBr) ν 1707, 1602, 1512, 1342, 1244, 1196, 1105, 1034, 851, 819, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 4H), 8.16 (d, J=9.2 Hz, 1H), 7.81 (s, 1H), 7.51–7.58 (m, 5H), 7.42–7.45 (m, 1H), 7.20(d, J=2.4 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.54, 151.64, 148.33, 148.08, 145.57, 144.95, 138.27, 131.82, 129.26, 128.81, 128.62, 127.92, 127.26, 123.98, 122.56, 119.38, 103.59, 55.48 ppm; MS (ESI): m/z ($[M+H]^+$): 357; HRMS (EI): m/z calcd for ($C_{22}H_{16}N_2O_3$): 356.1161; found: 356.1146.

*4.4.10. 2-(6-Methoxy-4-phenylquinolin-2-yl)phenol (**4j**).* Yellow solid, mp 158–159 °C; IR (KBr) ν 1621, 1586, 1509, 1494, 1429, 1270, 1218, 1122, 1035, 756, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 15.13 (s, 1H), 7.99 (d, J=9.2 Hz, 1H), 7.92–7.93 (m, 2H), 7.56–758 (m, 5H), 7.33–7.41 (m, 2H), 7.17 (d, J=2.4 Hz, 1H), 7.10 (d, J=8 Hz, 1H), 6.93 (t, J=7.2 Hz, 1H), 3.80(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.78, 154.60, 147.77, 144.87, 139.72, 138.72, 138.71, 131.57, 131.56, 129.32, 128.93, 128.74, 128.65, 128.30, 127.27, 126.63, 121.76, 119.60, 103.71, 55.40 ppm; MS (ESI): m/z ($[M+H]^+$): 328; HRMS (EI): m/z calcd for ($C_{22}H_{17}NO_2$): 327.1259; found: 327.1263.

*4.4.11. 2-(Benzo[d][1,3]dioxol-5-yl)-6-methoxy-4-phenylquinoline (**4k**).* Yellow solid, mp 135–136 °C; IR (KBr) ν 1626, 1603, 1491, 1454, 1335, 1249, 1104, 1033, 968, 922, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J=9.2 Hz, 1H), 7.73 (s, 1H), 7.68 (s, 1H), 7.63 (q, J=1.6 Hz, 1H), 7.51–7.55(m, 5H), 7.37 (q, J=2.8 Hz, 1H), 7.16 (d, J=2.8 Hz, 1H), 6.91 (d, J=8 Hz, 1H), 6.02 (s, 2H), 3.78(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.63, 154.01, 148.52, 148.35, 147.71, 144.77, 138.73, 134.24, 131.40, 129.32, 128.66, 128.30, 126.43, 121.71, 121.33, 119.24, 108.41, 107.70, 103.76, 101.27, 55.42 ppm; MS (ESI): m/z ($[M+H]^+$): 356; HRMS (EI): m/z calcd for ($C_{23}H_{17}NO_3$): 355.1208; found: 355.1197.

*4.4.12. 6-Methoxy-4-phenylquinoline (**4l**)*[2o]. Yellow liquid; IR (neat) ν 3058, 2925, 1619, 1584, 1493, 1428, 1256, 1032, 1030,853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J=4.8 Hz, 1H), 8.07 (d, J=9.2 Hz, 1H), 7.46–7.55 (m, 5H), 7.38 (d, J=8.8 Hz, 1H), 7.27 (d, J=4.4 Hz, 1H), 7.19 (s, 1H), 3.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.80, 147.41, 147.01, 144.71, 138.25, 131.15, 129.20, 128.57, 128.26, 127.61, 121.65, 121.57, 103.63, 55.30 ppm; MS (ESI): m/z ($[M+H]^+$): 236.

*4.4.13. 2,4-Diphenylquinoline (**4m**)*[5a]. Light yellow liquid; IR (neat) ν 1634, 1588, 1519, 1489, 1446, 1343, 1260, 967, 768, 701, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24(d, J=8.4 Hz, 1H), 8.19 (d, J=6.8 Hz, 2H), 7.90 (d, J=8.0 Hz, 1H), 7.82 (s, 1H), 7.70–7.75 (m, 1H), 7.45–7.56 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.89, 149.18, 148.82, 139.66, 138.41, 130.12, 129.55, 129.50, 129.33, 128.81, 128.58, 128.39, 127.59, 126.31, 125.78, 125.63, 119.35 ppm; MS (ESI): m/z ($[M+H]^+$): 282.

*4.4.14. 2-(6-Methyl-4-phenylquinolin-2-yl)phenol (**4n**).* Yellow solid, mp 190–191 °C; IR (neat) ν 1587, 1546, 1492, 1418, 1355, 1295, 1246, 877, 853, 754, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=15.26 (s, 1H), 7.95 (d, J=8.8 Hz, 1H), 7.89–7.91 (m, 2H), 7.60 (s, 1H), 7.50–7.57 (m, 6H), 7.30–7.34 (m, 1H), 7.06–7.09 (m, 1H), 6.90 (t, J=8 Hz, 1H), 2.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.98, 156.49, 149.41, 143.68, 138.10, 136.69, 132.38, 131.71, 129.38, 128.63, 128.57, 127.63, 126.76, 125.24, 124.59, 119.03, 118.58, 118.51, 117.51, 21.72 ppm; MS (ESI): m/z ($[M+H]^+$): 312; HRMS (EI): m/z calcd for ($C_{22}H_{17}NO$): 311.1310; found: 311.1306.

*4.4.15. 1,3-Diphenylbenzo[f]quinoline (**4o**)*[2p]. Yellow solid, mp 148–149 °C; IR (KBr) ν 1579, 1544, 1447, 1359, 1256, 1159, 1072, 1026, 834, 748, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 8.00 (s, 1H), 7.60 (s, 1H), 7.43–7.57 (m, 13H), 7.26 (d, J=1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.39, 149.78, 149.15, 143.01, 139.00, 132.90, 131.47, 129.72, 129.29, 129.21, 129.10, 128.82, 128.60, 128.37, 128.11, 128.02, 127.38, 126.43, 125.51, 122.77, 121.80 ppm; MS (ESI): m/z ($[M+H]^+$): 332.

*4.4.16. 7-Ethyl-1,3-diphenyl-7H-pyrido[2,3-c]carbazole (**4p**)*[2q]. Yellow solid, mp 197–198 °C; IR (KBr) ν 1613, 1555, 1515, 1488, 1407, 1329, 1145, 1097, 794, 741, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J=8.8 Hz, 1H), 8.24 (d, J=7.6 Hz, 2H), 7.90(s, 1H), 7.85 (d, J=8.8 Hz, 1H), 7.48–7.56 (m, 4H), 7.33–7.43 (m, 4H), 7.34 (d, J=7.6 Hz, 1H), 7.20 (q, J=7.6 Hz, 1H), 6.64 (t, J=8.0 Hz, 1H), 6.06 (d, J=8 Hz, 1H), 4.40 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.72, 146.55, 146.37, 142.78, 139.57, 138.83, 138.40, 129.46, 129.40, 129.06, 128.72, 128.08, 127.18, 124.95, 123.72, 123.25, 122.25, 121.12, 118.53, 114.39, 114.04, 108.26, 37.54, 14.17 ppm; MS (ESI): m/z ($[M+H]^+$): 399.

*4.4.17. Triethyl 6-methoxyquinoline-2,3,4-tricarboxylate (**4q**).* Light yellow liquid; IR (neat) ν 2983, 1733, 1620, 1561, 1498, 1420, 1302, 1062, 1024, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J=7.6 Hz, 1H), 7.50 (m, 1H), 7.34 (s, 1H), 4.52–4.56 (m, 4H), 4.43 (q, J=7.2 Hz, 2H), 3.94 (s, 3H), 1.38–1.46 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.83, 165.57, 165.27, 160.35, 145.08, 143.80, 137.55, 131.95, 125.43, 124.88, 124.27, 102.69, 62.39, 62.36, 62.21, 55.59, 14.03, 13.92, 13.80 ppm; MS (ESI): m/z ($[M+H]^+$): 376; HRMS (EI): m/z calcd for ($C_{19}H_{21}NO_7$): 375.1318; found: 375.1324.

*4.4.18. Diethyl 6-methoxy-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**6a**)*[9c]. Red liquid; IR (neat) ν 2991, 1754, 1719, 1618, 1560, 1508, 1244, 1177, 1027, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J=8.0 Hz, 1H), 7.06–7.09 (m, 2H), 6.85–6.90 (m, 3H), 6.74 (d, J=2.4 Hz, 1H), 5.31 (s, 1H), 4.11–4.24 (m, 4H), 3.80 (s, 3H), 3.79 (s, 3H), 1.24 (t, J=6.8 Hz, 3H), 1.06 (t, J=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.69, 162.37, 158.61, 158.11, 145.68, 136.59, 133.49, 127.14, 125.16, 121.12, 114.90, 114.43, 111.36, 63.84, 61.85, 61.78, 55.43, 55.38, 13.92, 13.59 ppm; MS (ESI): m/z ($[M+H]^+$): 413.

*4.4.19. Diethyl 6-methyl-3-p-tolyl-3,4-dihydroquinazoline-2,4-dicarboxylate (**6b**)*[9c]. Yellow liquid; IR (neat) ν 2981, 1740, 1619, 1585, 1513, 1381, 1291, 1257, 1189, 1022, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=8.0 Hz, 1H), 7.14 (m, 3H), 7.03 (s, 1H), 6.99 (d, J=7.6 Hz, 2H), 5.32 (s, 1H), 4.12–4.27 (m, 4H), 2.33 (s, 3H), 2.31 (s, 3H), 1.23 (t, J=7.2 Hz, 3H), 1.06 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.94, 162.45, 146.53, 141.10, 137.55, 137.16, 136.18, 130.19, 129.88, 126.77, 125.79, 122.92, 120.28, 63.44, 61.93, 61.88, 21.06, 20.85, 13.94, 13.57 ppm; MS (ESI): m/z ($[M+H]^+$): 381.

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Supplementary data

Copies of the ^1H, ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.087.

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