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An Efficient Method for the Synthesis of Indolo[3,2-*c*]quinoline Derivatives Catalyzed by Iodine

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The reaction of Schiff base and indole catalyzed by iodine in DMA, subsequently treated with DDQ, gave indolo[3,2-*c*]quinoline derivatives in good yields. The structure of **3e** was confirmed by X-ray diffraction analysis.

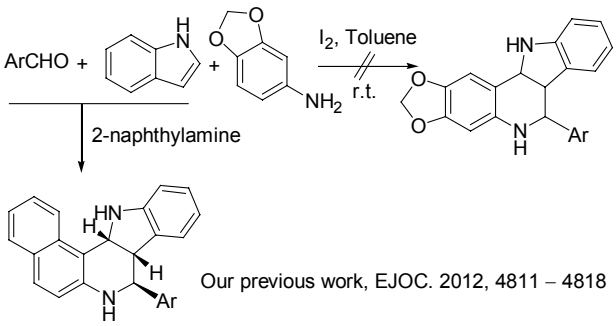
Keywords indolo[3,2-*c*]quinoline, Schiff base, iodine, indole

Introduction

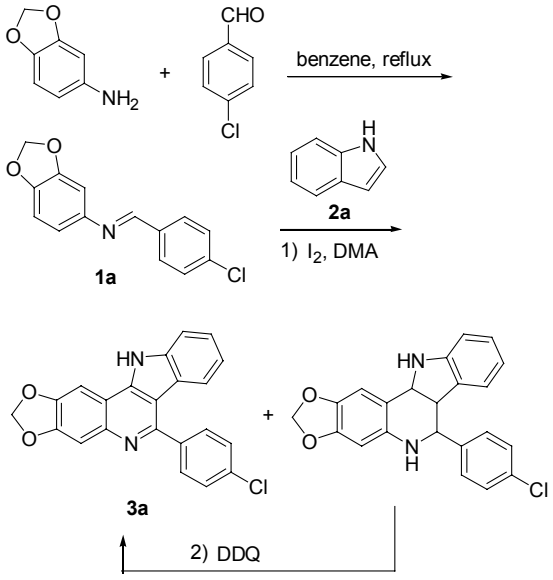
Indoloquinoline is a very important class of heterocyclic compounds, some of which are useful alkaloids, such as Cryptolepine and *iso*-Cryptolepine, which are used traditionally to treat a variety of health disorders, including clinical therapy of rheumatism, urinary tract infections, malaria, and other diseases.[1] In addition, they are also reported to possess various kinds of biological and pharmacological activities, for example, phosphodiesterase inhibitors,[2] antitumor activity,[3] calcium channel blockers,[4] antifungals & parasiticides[5] and antiplasmodial activity.[6] Therefore, novel strategies for the synthesis of indoloquinolines continue to receive considerable attention in the field of synthetic organic chemistry.[7]

In our previous study,[8] we have described that *exo*-tetrahydroindolo[3,2-*c*]quinoline derivatives could be obtained in good yields and high stereo-selectivity at r.t. catalyzed by iodine. However, this reaction was only limited to active amines, such as 2-naphthylamine and indazole-5-amine. It failed to give desired products using ordinary aromatic amine as reactant (Scheme 1), such as piperonylamine and 3,4-dimethoxyaniline. In our recent study, we further improved the reaction temperature (80 ℃) in order to facilitate the reaction, it was found that it was carried out smoothly, however, it gave a complicated system. We tried to separate them by column chromatography, but failed. In order to simplify the reaction and prevent the aromatic aldehydes to react with indole to produce bis-indolylmethane derivatives,[9] the Schiff base was synthesized and separated first, and then was allowed to react with indole in *N*,*N*-dimethylacetamide (DMA) at 80 ℃ (Scheme 2).

Scheme 1 The designed reaction



Scheme 2 The model reaction



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We found in delight that the main product was aromatized indolo[3,2-*c*]quinoline, along with the tetrahydroindolo[3,2-*c*]quinoline isomers as byproducts in low stereo-selectivity, which is also hard to be separated. In order to obtain the single aromatization product, DDQ was added to the mixture (Scheme 2), it was found that it was a good oxidant to promote the dehydrogenation to give final aromatized indolo[3,2-*c*]quinoline in good yield. Herein, we would like to report the synthesis of indolo[3,2-*c*]quinoline derivatives catalyzed by iodine and subsequent dehydrogenation by DDQ.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellet. ^{1}H NMR spectra were obtained from a solution in DMSO-d_6 or $CDCl_3$ with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

General procedure for the synthesis of indolo[3,2-*c*]-quinoline (3)

Schiff base (1.0 mmol), indole (1.0 mmol), I_2 (0.013 g), and DMA (10 mL) were added into a 50 mL flask. The reaction mixture was stirred at 80 ℃ for 16－22 h until all the Schiff base was consumed which was monitored by TLC. And then DDQ (0.114 g, 0.5 mmol) was added to the mixture for another 2－4 h at the same temperature. The solvent of DMA was recovered under reduced pressure, the residue was purified by column chromatography using ethyl acetate and petroleum ether (1∶5) as eluent to give the product **3**.

6-(4-Chlorophenyl)-11*H*-[1,3]dioxolo[4,5-*g*]indolo-[32-*c*]quinoline (3a) m.p.: ＞300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.42 (s, 2H, CH_2), 7.30－7.34 (m, 1H, ArH), 7.41 (d, J=8.0 Hz, 1H, ArH), 7.62－7.64 (m, 2H, ArH), 7.84 (d, J=8.0 Hz, 1H, ArH), 7.91－7.95 (m, 2H, ArH), 8.00 (d, J=8.0 Hz, 2H, ArH), 8.07 (s, 1H, ArH), 13.67 (s, 1H, NH); IR (KBr) v: 3446, 3086, 3019, 2917, 1646, 1624, 1598, 1509, 1498, 1472, 1441, 1326, 1272, 1223, 1102, 1035, 1018, 936, 858, 786, 757, 721 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{22}H_{12}ClN_2O_2$ $[M-H]^-$ 371.0586, found 371.0575.

8-Bromo-(4-bromophenyl)-11*H*-[1,3]dioxolo[4,5-*g*]indolo[3,2-*c*]quinoline (3b) m.p.: ＞300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.43 (s, 2H, CH_2), 7.43 (d, J=1.6 Hz, 1H, ArH), 7.63 (s, 1H, ArH), 7.74－7.81 (m, 2H, ArH), 7.92－7.94 (m, 2H, ArH), 8.04 (s, 1H, ArH), 8.08 (d, J=8.4 Hz, 2H, ArH), 13.74 (s, 1H, NH); IR (KBr) v: 3440, 3047, 3030, 1645, 1607, 1590, 1469, 1446, 1390, 1377, 1271, 1251, 1102, 1059, 1037, 1010, 938, 903, 860, 840, 819, 789, 724, 710 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{22}H_{13}Br_2N_2O_2$ $[M+H]^+$ 494.9344, found 494.9342.

8-Methoxy-(4-bromophenyl)-11*H*-[1,3]dioxolo[4,5-*g*]indolo[3,2-*c*]quinoline (3c) m.p.: ＞300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.65 (s, 3H, CH_3O), 6.25 (s, 2H, CH_2), 6.90 (s, 1H, ArH), 7.11 (d, J=8.4 Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.59 (d, J=8.4 Hz, 1H, ArH), 7.76 (d, J=8.0 Hz, 2H, ArH), 7.86 (b, 3H, ArH), 12.60 (s, 1H, NH); IR (KBr) v: 3389, 3066, 2896, 1656, 1607, 1488, 1468, 1460, 1437, 1388, 1298, 1216, 1174, 1102, 1035, 1010, 944, 914, 852, 838, 805, 748, 715 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{23}H_{16}BrN_2O_3$ $[M+H]^+$ 447.0344, found 447.0343.

8-Methoxy-(4-chlorophenyl)-11*H*-[1,3]dioxolo[4,5-*g*]indolo[3,2-*c*]quinoline (3d) m.p.: ＞300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.66 (s, 3H, CH_3O), 6.39 (s, 2H, CH_2), 6.79 (s, 1H, ArH), 7.24 (d, J=8.4 Hz, 1H, ArH), 7.59 (s, 1H, ArH), 7.71 (d, J=8.8 Hz, 1H, ArH), 7.91－7.95 (m, 5H, ArH), 13.45 (s, 1H, NH); IR (KBr) v: 3401, 3061, 3014, 2964, 1649, 1610, 1578, 1498, 1474, 1436, 1390, 1272, 1222, 1206, 1153, 1097, 1029, 937, 875, 819, 728, 670 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{23}H_{16}ClN_2O_3$ $[M+H]^+$ 403.0849, found 403.0850.

10-Methyl-(4-chlorophenyl)-11*H*-[1,3]dioxolo[4,5-*g*]indolo[3,2-*c*]quinoline (3e) m.p.: ＞300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 2.67 (s, 3H, CH_3), 6.24 (s, 2H, CH_2), 7.03 (t, J=7.6 Hz, 1H, ArH), 7.22 (d, J=8.4 Hz, 1H, ArH), 7.31 (d, J=8.0 Hz, 1H, ArH), 7.48 (s, 1H, ArH), 7.66 (d, J=8.0 Hz, 2H, ArH), 7.80 (d, J=8.0 Hz, 2H, ArH), 8.20 (s, 1H, ArH), 12.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C: 17.2, 98.4, 101.8, 106.2, 111.6, 111.7, 118.3, 120.2, 121.0, 121.1, 125.9, 128.4, 130.8, 133.3, 138.3, 139.5, 141.3, 142.4, 146.7, 149.3, 151.6; IR (KBr) v: 3252, 3051, 2963, 1653, 1616, 1499, 1488, 1463, 1388, 1323, 1250, 1212, 1190, 1154, 1087, 1039, 947, 911, 853, 783, 745 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{23}H_{16}ClN_2O_2$ $[M+H]^+$ 387.0900, found 387.0901.

6-(4-Chlorophenyl)-2,3-dimethoxy-11*H*-indolo[3,2-*c*]quinoline (3f) m.p.: 271－274 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.98 (s, 3H, CH_3O), 4.04 (s, 3H, CH_3O), 7.25－7.28 (m, 1H, ArH), 7.45 (d, J=8.0 Hz, 2H, ArH), 7.55－7.59 (m, 2H, ArH), 7.80－7.85 (m, 3H, ArH), 7.94－7.96 (m, 1H, ArH), 8.08 (s, 1H, ArH), 13.37 (s, 1H, NH); IR (KBr) v: 3440, 3063, 2998, 2962, 1639, 1604, 1562, 1509, 1460, 1433, 1386, 1325, 1284, 1265, 1228, 1181, 1136, 1113, 1091, 1016, 998, 854, 751, 739 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{23}H_{18}ClN_2O_2$ $[M+H]^+$ 389.1057, found 389.1056.

8-Bromo-6-(4-chlorophenyl)-2,3-dimethoxy-11*H*-indolo[3,2-*c*]quinoline (3g) m.p.: ＞300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.98 (s, 3H, CH_3O), 4.03 (s, 3H, CH_3O), 7.45 (d, J=2.0 Hz, 1H, ArH), 7.57 (s, 1H, ArH), 7.68 (dd, J=8.4 Hz, J'=2.0 Hz, 1H, ArH), 7.75 (d, J=8.4 Hz, 1H, ArH), 7.87 (d, J=8.4 Hz, 2H, ArH), 7.95 (d, J=8.4 Hz, 1H, ArH), 7.96 (s, 1H, ArH), 8.02 (s, 1H, ArH), 13.50 (s, 1H, NH); IR (KBr) v: 3127, 3058, 2997, 1638, 1608, 1561, 1542, 1498, 1459, 1441, 1423, 1377, 1285, 1265, 1229, 1092, 998, 969, 911, 854, 807, 770 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{23}H_{17}BrClN_2O_2$ $[M+H]^+$ 467.0162, found 467.0161.

10-Methoxy-8-(4-methylphenyl)-13*H*-benzo[*f*]-

indolo[3,2-*c*]quinoline (3h) m.p.: >300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 2.51 (s, 3H, CH_3), 3.71 (s, 3H, CH_3O), 7.11−7.16 (m, 2H, ArH), 7.42 (d, J=8.0 Hz, 2H, ArH), 7.61 (d, J=8.8 Hz, 1H, ArH), 7.68−7.72 (m, 1H, ArH), 7.81−7.85 (m, 3H, ArH), 8.01 (d, J=8.8 Hz, 1H, ArH), 8.08 (d, J=8.0 Hz, 1H, ArH), 8.25 (d, J=9.2 Hz, 1H, ArH), 8.81 (d, J=8.8 Hz, 1H, ArH), 9.54 (s, 1H, NH); IR (KBr) *v*: 3419, 3020, 2936, 1586, 1561, 1503, 1468, 1438, 1354, 1303, 1282, 1223, 1203, 1178, 1159, 1109, 1035, 1005, 870, 825, 793, 752, 691 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{27}H_{19}N_2O$ $[M-H]^-$ 387.1496, found 387.1509.

8-(4-Chlorophenyl)-10-methoxy-13*H*-benzo[*f*]-indolo[3,2-*c*]quinoline (3i) m.p.: >300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.66 (s, 3H, CH_3O), 6.83 (s, 1H, ArH), 7.19−7.21 (m, 1H, ArH), 7.70−7.96 (m, 7H, ArH), 8.11−8.20 (m, 3H, ArH), 9.19 (d, J=8.0 Hz, 1H, ArH), 12.56 (s, 1H, NH); IR (KBr) *v*: 3338, 3022, 2938, 1589, 1560, 1504, 1486, 1468, 1439, 1385, 1354, 1303, 1282, 1223, 1203, 1175, 1161, 1109, 1086, 1036, 1005, 866, 825, 802, 794, 753 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{16}ClN_2O$ $[M-H]^-$ 407.0950, found 407.0949.

8-(4-Methoxyphenyl)-13*H*-benzo[*f*]indolo[3,2-*c*]-quinoline (3j) m.p.: 271−272 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 3.96 (s, 3H, CH_3O), 7.27−7.33 (m, 3H, ArH), 7.57 (d, J=8.4 Hz, 1H, ArH), 7.62 (t, J=7.6 Hz, 1H, ArH), 7.87−7.96 (m, 3H, ArH), 8.02−8.07 (m, 2H, ArH), 8.25−8.29 (m, 2H, ArH), 8.36 (d, J=9.2 Hz, 1H, ArH), 9.333 (d, J=8.0 Hz, 1H, ArH), 13.25 (s, 1H, NH); IR (KBr) *v*: 3064, 2933, 2836, 1612, 1548, 1510, 1460, 1442, 1425, 1375, 1332, 1301, 1252, 1180, 1125, 1029, 998, 863, 829, 799, 772, 747 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{19}N_2O$ $[M+H]^+$ 397.1317, found 397.1318.

8-(4-Bromophenyl)-13*H*-benzo[*f*]indolo[3,2-*c*]-quinoline (3k) m.p.: 239−240 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 7.33−7.39 (m, 2H, ArH), 7.64−7.67 (m, 1H, ArH), 7.90−7.95 (m, 4H, ArH), 8.01−8.06 (m, 3H, ArH), 8.19−8.22 (m, 1H, ArH), 8.28 (d, J=6.8 Hz, 1H, ArH), 8.41 (d, J=7.2 Hz, 1H, ArH), 9.19−9.21 (m, 1H, ArH), 13.32 (s, 1H, NH); IR (KBr) *v*: 3091, 3043, 2978, 2916, 2846, 1622, 1602, 1585, 1516, 1479, 1464, 1402, 1340, 1279, 1246, 1205, 1183, 1096, 1042, 1004, 955, 929, 817, 754 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{16}BrN_2$ $[M+H]^+$ 423.0497, found 423.0494.

8-(4-Chlorophenyl)-13*H*-benzo[*f*]indolo[3,2-*c*]-quinoline (3l) m.p.: >300 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 7.36−7.41 (m, 2H, ArH), 7.69−7.74 (m, 1H, ArH), 7.93−8.00 (m, 3H, ArH), 8.05−8.10 (m, 3H, ArH), 8.12−8.16 (m, 1H, ArH), 8.29 (d, J=9.2 Hz, 1H, ArH), 8.38 (d, J=8.0 Hz, 1H, ArH), 8.52 (d, J=9.2 Hz, 1H, ArH), 9.32 (d, J=8.4 Hz, 1H, ArH), 13.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C: 108.5, 111.6, 112.7, 113.8, 115.6, 120.2, 120.5, 120.9, 123.0, 125.6, 126.8, 128.2, 128.3, 128.6, 129.3, 129.4, 129.9, 131.4, 131.5, 133.7, 136.5, 141.4, 142.5; IR (KBr) *v*: 3032, 1915, 1665, 1649, 1638, 1618, 1611, 1594, 1578, 1561, 1543, 1523, 1509, 1491, 1476, 1459, 1439, 1380, 1364, 1324, 1092 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{16}ClN_2$ $[M+H]^+$ 379.1002, found 379.1003.

8-(4-Fluorophenyl)-13*H*-benzo[*f*]indolo[3,2-*c*]-quinoline (3m) m.p.: >300 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 7.18−7.22 (m, 1H, ArH), 7.50−7.52 (m, 4H, ArH), 7.77−7.82 (m, 1H, ArH), 7.92 (b, 4H, ArH), 8.11−8.22 (m, 3H, ArH), 9.23 (d, J=8.0 Hz, 1H, ArH), 12.58 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C: 111.6, 112.7, 114.9, 115.3, 115.5, 120.6, 120.7, 120.8, 125.6, 126.0, 126.5, 127.5, 128.1, 128.7, 128.9, 129.4, 131.15, 131.24, 131.4, 140.4, 140.5, 145.1, 153.4, 161.3, 163.8; IR (KBr) *v*: 3050, 1604, 1562, 1498, 1454, 1390, 1352, 1327, 1240, 1226, 1154, 1123, 999, 841, 828, 748 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{16}FN_2$ $[M+H]^+$ 363.1298, found 363.1333.

6-(4-Chlorophenyl)-11*H*-benzo[*h*]indolo[3,2-*c*]-quinoline (3n) m.p.: 260−261 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 7.28 (t, J=7.6 Hz, 1H, ArH), 7.56−7.60 (m, 2H, ArH), 7.80−7.84 (m, 5H, ArH), 8.04 (d, J=8.0 Hz, 2H, ArH), 8.17 (d, J=8.0 Hz, 1H, ArH), 8.22 (d, J=8.4 Hz, 1H, ArH), 8.58 (d, J=8.8 Hz, 1H, ArH), 9.32 (d, J=7.2 Hz, 1H, ArH), 13.33 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C: 112.4, 112.6, 113.7, 114.0, 119.5, 120.3, 121.1, 121.3, 121.4, 124.0, 127.0, 127.5, 127.6, 128.4, 128.5, 128.8, 131.3, 133.2, 134.8, 140.1, 142.80, 142.81, 156.7; IR (KBr) *v*: 3160, 3056, 1635, 1607, 1570, 1561, 1513, 1490, 1456, 1445, 1433, 1380, 1343, 1324, 1267, 1230, 1176, 1155, 1123, 1091, 1015, 963, 837, 823, 801, 773, 752, 724, 716, 672 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{16}ClN_2$ $[M+H]^+$ 379.1002, found 379.1002.

6-(4-Fluorophenyl)-11*H*-benzo[*h*]indolo[3,2-*c*]-quinoline (3o) m.p.: 220−221 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 7.27 (t, J=7.6 Hz, 1H, ArH), 7.52−7.63 (m, 4H, ArH), 7.82−7.84 (m, 3H, ArH), 8.05−8.09 (m, 2H, ArH), 8.17−8.25 (m, 2H, ArH), 8.59 (d, J=9.2 Hz, 1H, ArH), 9.33−9.35 (m, 1H, ArH), 13.32 (s, 1H, NH); IR (KBr) *v*: 3233, 3160, 3056, 2973, 2894, 2811, 2769, 1633, 1606, 1565, 1506, 1486, 1445, 1434, 1408, 1379, 1323, 1268, 1229, 1154, 1082, 1048, 843, 820, 802, 791, 773, 752, 673 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{16}FN_2$ $[M+H]^+$ 363.1298, found 363.1297.

6-(4-Bromophenyl)-11*H*-benzo[*h*]indolo[3,2-*c*]-quinoline (3p) m.p.: 273−274 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 7.16−7.30 (m, 2H, ArH), 7.58 (t, J=7.6 Hz, 2H, ArH), 7.82−7.83 (m, 3H, ArH), 7.97 (s, 3H, ArH), 8.16−8.23 (m, 2H, ArH), 8.57−8.59 (m, 1H, ArH), 9.32 (t, J=1.2 Hz, 1H, ArH), 13.42 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C: 112.4, 112.6, 113.6, 119.5, 121.1, 121.2, 123.39, 123.42, 124.0, 125.3, 126.9, 127.4, 127.5, 128.2, 128.3, 128.5, 128.9, 131.5, 131.7, 133.2, 140.0, 142.7, 150.9; IR (KBr) *v*: 3214, 3161, 3052, 2973, 2866, 1606, 1570, 1561, 1512, 1490, 1482, 1457, 1446, 1323, 1231, 1013, 773, 750 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{16}BrN_2$ $[M+H]^+$ 423.0497, found 423.0498.

6-(4-Methoxyphenyl)-11*H*-benzo[*h*]indolo[3,2-*c*]-

quinoline (3q) m.p.: 189－190 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 3.93 (s, 3H, CH_3O), 7.19－7.26 (m, 3H, ArH), 7.50 (t, J=7.6 Hz, 1H, ArH), 7.72－7.77 (m, 3H, ArH), 7.82 (d, J=8.0 Hz, 1H, ArH), 7.96 (d, J=8.8 Hz, 2H, ArH), 8.06－8.08 (m, 2H, ArH), 8.53 (d, J=8.8 Hz, 1H, ArH), 9.32 (d, J=7.6 Hz, 1H, ArH), 12.85 (s, 1H, NH); IR (KBr) v: 3216, 2973, 2866, 1609, 1589, 1576, 1565, 1509, 1488, 1456, 1443, 1322, 1295, 1269, 1239, 1179, 1022, 797, 775, 752, 742 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{26}H_{19}N_2O$ $[M+H]^+$ 375.1497, found 375.1488.

6-(3,4-Dimethoxyphenyl)-11*H*-benzo[*h*]indolo[3,2-*c*]quinoline (3r) m.p.: 175－176 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H: 3.88 (s, 3H, CH_3O), 3.97 (s, 3H, CH_3O), 7.28－7.35 (m, 2H, ArH), 7.59－7.61 (m, 2H, ArH), 7.65 (s, 1H, ArH), 7.71 (d, J=7.6 Hz, 1H, ArH), 7.83－7.85 (m, 3H, ArH), 8.17－8.25 (m, 2H, ArH), 8.60 (d, J=8.8 Hz, 1H, ArH), 9.38 (d, J=8.0 Hz, 1H, ArH), 13.46 (s, 1H, NH); IR (KBr) v: 3153, 3061, 2956, 2932, 2905, 2834, 1661, 1634, 1603, 1582, 1565, 1510, 1488, 1455, 1434, 1407, 1385, 1337, 1322, 1262, 1240, 1214, 1182, 1156, 1138, 1021, 824, 802, 753 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{27}H_{21}N_2O_2$ $[M+H]^+$ 405.1603, found 405.1610.

6-(3-Bromophenyl)-11*H*-benzo[*h*]indolo[3,2-*c*]quinoline (3s) m.p.: 212－213 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.21－7.25 (m, 2H, ArH), 7.48－7.54 (m, 7H, ArH), 7.69 (d, J=8.0 Hz, 1H, ArH), 7.73 (d, J=8.0 Hz, 1H, ArH), 7.80－7.82 (m, 2H, ArH), 8.05 (d, J=8.8 Hz, 1H, ArH), 9.06 (s, 1H, NH); IR (KBr) v: 3060, 1610, 1592, 1560, 1542, 1514, 1473, 1457, 1446, 1435, 1418, 1404, 1376, 1325, 1260, 1229, 1171, 1125, 1071, 1032, 824, 792, 765, 753 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{25}H_{16}BrN_2$ $[M+H]^+$ 423.0497, found 423.0521.

6-(4-Methylphenyl)-11*H*-benzo[*h*]indolo[3,2-*c*]quinoline (3t) m.p.: 185－187 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.24－7.28 (m, 1H, ArH), 7.57 (d, J=7.6 Hz, 4H, ArH), 7.82 (d, J=7.6 Hz, 3H, ArH), 7.89 (d, J=8.0 Hz, 2H, ArH), 8.18 (d, J=8.0 Hz, 1H, ArH), 8.23 (d, J=8.8 Hz, 1H, ArH), 8.57 (d, J=8.8 Hz, 1H, ArH), 9.34 (d, J=8.4 Hz, 1H, ArH), 13.39 (s, 1H, NH); IR (KBr) v: 3395, 3055, 2914, 1648, 1614, 1562, 1508, 1445, 1384, 1323, 1268, 1229, 1179, 1101, 1020, 823, 800, 772, 752, 724 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{26}H_{19}N_2$ $[M+H]^+$ 359.1548, found 359.1566.

Results and Discussion

Treatment of (*E*)-*N*-(4-chlorobenzylidene) piperonyl amine **1a** with indole **2a** in DMA at 80 ℃ catalyzed by iodine, and further dehydrogenation by DDQ, gave 6-(4-chlorophenyl)-11*H*-[1,3]dioxolo[4,5-*g*]indolo[3,2-*c*]-quinoline **3a** in 82% yield (Scheme 2).

Initially, the reaction conditions, including reaction temperature, amount of iodine, and solvents, were optimized in our lab. 1, 5 and 10 mol% iodine were used to mediate the reaction, it was found that 5 mol% I_2 at 80 ℃ in DMA was sufficient to initiate the reaction (Table 1, Entries 1－3). To find the optimum reaction temperature, the reaction was carried out with 5 mol% of I_2 at 50, 80 and 100 ℃, resulting in the isolation of **3a** in 74%, 82% and 82% yields (Table 1, Entries 2, 4 and 5), respectively. In addition, THF, benzene, toluene and DMF (Table 1, Entries 6－9) were also tested as the solvents. In these cases, product **4a** was formed in slightly lower yields. In order to promote aromatization, oxygen was tried to use as oxidant instead of DDQ, but failed. The model reaction was heated under O_2 for 48 h, and un-aromatized product was still found clearly by TLC.

Table 1 Yields of **3a** under various conditions[a]

Entry	Solvent	Iodine/mol%	T/℃	Isolated yield/%
1	DMA	1	80	75
2	**DMA**	**5**	**80**	**82**
3	DMA	10	80	82
4	DMA	5	50	74
5	DMA	5	100	82
6	THF	5	Reflux	38
7	Benzene	5	Reflux	42
8	Toluene	5	80	45
9	DMF	5	80	78

[a] Reaction condition: 10 mL solvent, **1a** (0.259 g, 1.0 mmol), **2a** (0.117 g, 1.0 mmol), DDQ (0.114 g, 0.5 mmol).

According to the optimized reaction conditions, various kinds of aromatic aldehydes, different amines, for example, piperonylamine, 2-naphthylamine, 3,4-dimethoxyaniline and 1-naphthylamine, were selected as reactants to produce Schiff base first; and then, they were put forward to react with substituted indoles, which included indole, 5-bromoindole, 5-methoxyindole and 7-methylindole (Scheme 3). The reactions all gave desired aromatized indolo[3,2-*c*]quinoline in good yields (Table 2). The structures were characterized by IR, ^{1}H NMR and HRMS, and their data were in good agreement with corresponding structures. The product of **3e** was confirmed by X-ray diffraction analysis.[10] Its crystal structure is shown in Figure 1.

Scheme 3 Iodine-catalyzed reaction of Schiff base and indole

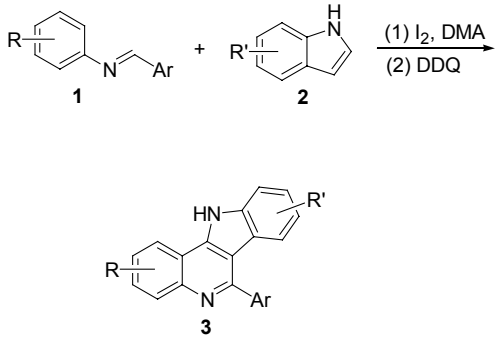

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Table 2 Synthetic results of **3a**—**3t** in DMA[a]

Entry	R	Ar	R'	*t*/h	Product	Yield/%
1	3,4-OCH_2O	4-ClC_6H_4	H	21	**3a**	82
2	3,4-OCH_2O	4-BrC_6H_4	5-Br	18	**3b**	81
3	3,4-OCH_2O	4-BrC_6H_4	5-CH_3O	16	**3c**	86
4	3,4-OCH_2O	4-ClC_6H_4	5-CH_3O	17	**3d**	90
5	3,4-OCH_2O	4-ClC_6H_4	7-CH_3	22	**3e**	78
6	3,4-$(MeO)_2$	4-ClC_6H_4	H	20	**3f**	82
7	3,4-$(MeO)_2$	4-ClC_6H_4	5-Br	20	**3g**	80
8	3,4-CH=CH−CH=CH	4-MeC_6H_4	5-CH_3O	16	**3h**	90
9	3,4-CH=CH−CH=CH	4-ClC_6H_4	5-CH_3O	16	**3i**	86
10	3,4-CH=CH−CH=CH	4-$MeOC_6H_4$	H	19	**3j**	72
11	3,4-CH=CH−CH=CH	4-BrC_6H_4	H	20	**3k**	76
12	3,4-CH=CH−CH=CH	4-ClC_6H_4	H	19	**3l**	80
13	3,4-CH=CH−CH=CH	4-FC_6H_4	H	19	**3m**	72
14	2,3-CH=CH−CH=CH	4-ClC_6H_4	H	20	**3n**	85
15	2,3-CH=CH−CH=CH	4-FC_6H_4	H	18	**3o**	82
16	2,3-CH=CH−CH=CH	4-BrC_6H_4	H	18	**3p**	89
17	2,3-CH=CH−CH=CH	4-$MeOC_6H_4$	H	20	**3q**	79
18	2,3-CH=CH−CH=CH	3,4-$(MeO)_2C_6H_3$	H	22	**3r**	86
19	2,3-CH=CH−CH=CH	3-BrC_6H_4	H	22	**3s**	75
20	2,3-CH=CH−CH=CH	4-MeC_6H_4	H	19	**3t**	86

[a] Reaction condition: 10 mL DMA, **1** (1.0 mmol), **2** (1.0 mmol), and iodine (0.013 g), DDQ (0.114 g, 0.5 mmol), 80 ℃.

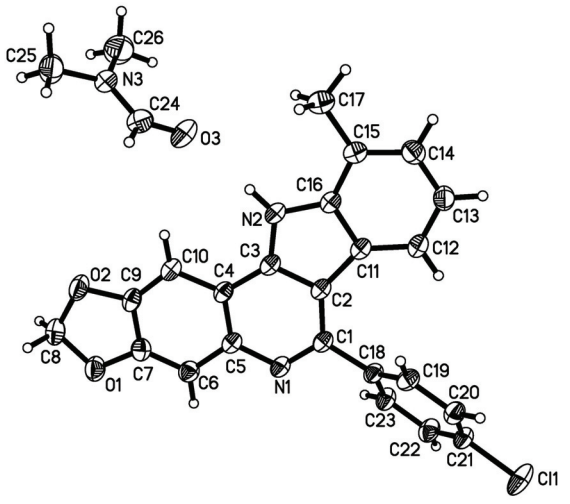
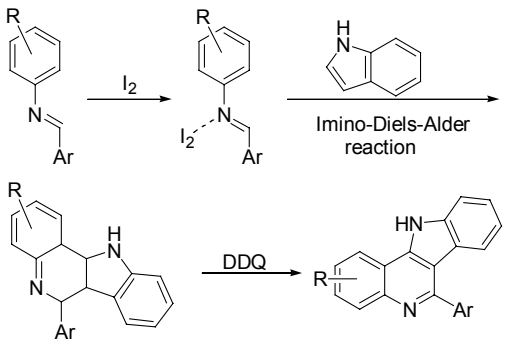


Figure 1 Crystal structure of the product **3e** DMF solvent.

According to the structure of product, we think the imino-Diels-Alder reaction and aromatization may occur subsequently. The Schiff base is used as a conjugated diene, while indole is dienophile in the imino-Diels-Alder reaction. It is also named Povarov reaction,[11] which is a well known method to the synthesis of quinoline derivatives. The possible reaction mechanism is outlined in Scheme 4.

Scheme 4 Possible reaction mechanism



Conclusions

In summary, an efficient iodine-catalyzed reaction of Schiff base with indole in DMA is described in this paper. It gives aromatized indolo[3,2-*c*]quinoline derivatives in good yields via subsequent dehydrogenation by DDQ.

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[10] Crystal data for **3e** DMF solvent: $C_{26}H_{22}ClN_3O_3$; M_r=459.92, pale-yellow block crystals, 0.26 nm×0.20 nm×0.13 mm, triclinic, space group *P*-1, a=9.4529(15) Å, b=10.0575(15) Å, c=12.5093(19) Å, α=71.006(2)°, β=85.428(2)°, γ=83.096(2)°, V=1115.3(3) Å^3, Z=2, D_c=1.369 g•cm^{-3}. F(000)=480, μ(Mo Kα)=0.206 mm^{-1}. Intensity data were collected on Bruker SMART APEXII CCD area-detector diffractometer using π and ω scan mode with 3.45°<θ<25.20°. 3939 unique reflections were measured and 3338 reflections with $I>2\sigma(I)$ were used in the refinement. Structure was solved by direct methods and expanded using Fourier techniques. R=0.0397, wR=0.1030

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