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Molecular iodine-catalyzed one-pot synthesis of substituted quinolines from imines and aldehydes

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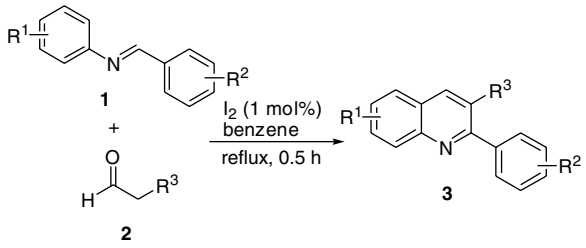
Abstract—A mild, efficient, and general method for the synthesis of substituted quinolines via a molecular iodine-catalyzed one-pot domino reaction of imines with enolizable aldehydes has been described.

Quinoline and their derivatives, which usually possess diverse biological activities, play important roles as versatile building blocks for the synthesis of natural products and as therapeutic agents.[1] In particular, 2-arylquinolines are biologically active and occur in structures of a number of antimalarial compounds and antitumor agents.[2] Therefore, the synthesis of quinolines has attracted much attention in organic synthesis. The classic methods for the synthesis of quinolines include Skraup, Doebner–von Miller, Conrad–Limbach, Combes, and Pfitzinger quinoline syntheses.[3] A number of general synthetic methods have also been reported.[4] However, some of these methods suffer from several disadvantages such as harsh reaction conditions, multisteps, a large amount of promoters, and/or long reaction time. Therefore, the development of new synthetic approaches using mild reaction conditions remains an active research area.

Iodine has been used as a mild and efficient catalyst for various organic transformations.[5] In continuation of our efforts to develop new synthetic routes of heterocycles,[6] herein we report a molecular iodine-catalyzed one-pot synthesis of substituted quinolines from imines and enolizable aldehydes (Scheme 1).

In a preliminary experiment, refluxing a solution of imine **1a**, decyl aldehyde (**2a**), and iodine (10 mol %) in benzene under an air atmosphere for 1 h afforded 2-phenyl-3-octylquinoline (**3a**) in 80% isolated yield. The product **3a** was fully characterized by spectroscopic analysis.



Scheme 1.

We have examined the conditions for the reaction of **1a** with **2a**. Among the solvents tested, benzene gave the best result (Table 1, entries 7 and 8). CH_3CN, $ClCH_2CH_2Cl$, MeOH, THF, or DMSO gave the product **3a** in lower yields (Table 1, entries 1–5). When the

Table 1. Screening for the reaction conditions[a]

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	1	THF	Reflux	0.5	60
2	1	CH_3CN	Reflux	0.5	65
3	1	$ClCH_2CH_2Cl$	Reflux	0.5	72
4	10	MeOH	Reflux	12	15
5	10	DMSO	80	2	45
6	10	Benzene	rt	12	Trace
7	1	Benzene	Reflux	0.5	79
8	10	Benzene	Reflux	0.1	80
9	0	Benzene	Reflux	12	0

[a] All reactions were performed using **1a** (1.2 mmol), **2a** (1.0 mmol), and a solvent (5 mL) under an air atmosphere.
[b] Isolated yield.

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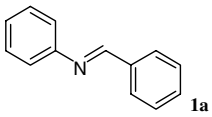
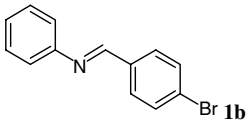
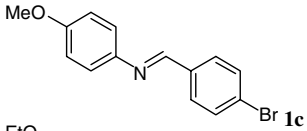
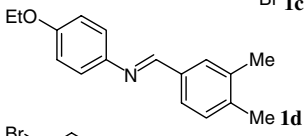
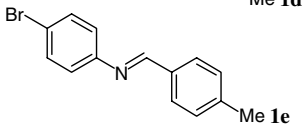
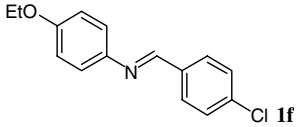
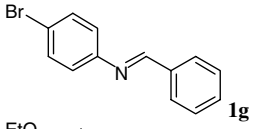
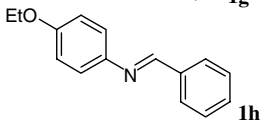
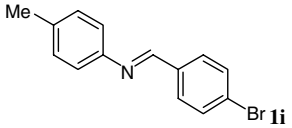
reaction was performed at room temperature (Table 1, entry 6) or in the absence of iodine (Table 1, entry 9), no product was obtained. Furthermore, the reaction time and the catalyst concentration can be reduced to 0.5 h and 1 mol %, respectively (Table 1, entries 7 and 8).

Table 2. Iodine-catalyzed reaction of imines **1** with aldehydes **2**[a]

Entry	Imine	Aldehyde	Product	Yield (%)[b]
1	 **1a**	*n*-$C_8H_{17}CH_2CHO$ **2a**	**3a**	79
2	**1a**	*n*-$C_7H_{15}CH_2CHO$ **2b**	**3b**	75
3	**1a**	*n*-$C_6H_{13}CH_2CHO$ **2c**	**3c**	80
4	**1a**	*n*-$C_5H_{11}CH_2CHO$ **2d**	**3d**	72
5	**1a**	*n*-$C_4H_9CH_2CHO$ **2e**	**3e**	70
6	**1a**	*i*-$C_3H_7CH_2CHO$ **2f**	**3f**	75
7	**1a**	$PhCH_2CHO$ **2g**	**3g**	65
8	 **1b**	**2a**	**3h**	86
9	 **1c**	**2a**	**3i**	80
10	 **1d**	**2a**	**3j**	63
11	 **1e**	**2a**	**3k**	68
12	 **1f**	**2b**	**3l**	81
13	**1b**	**2c**	**3m**	82
14	 **1g**	**2c**	**3n**	75
15	 **1h**	**2c**	**3o**	77
16	**1f**	**2d**	**3p**	75
17	 **1i**	**2f**	**3q**	82
18	**1b**	**2g**	**3r**	69

[a] All reactions were performed using **1a** (1.2 mmol), **2a** (1.0 mmol), and I_2 (0.01 mmol) in benzene (5 mL) under an air atmosphere and reflux for 0.5 h.

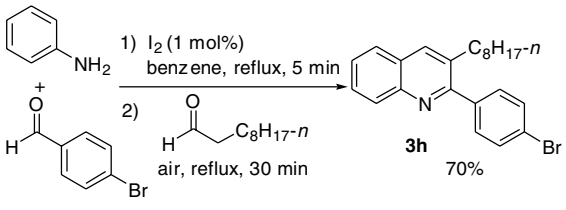
[b] Isolated yields.

Under the optimized reaction conditions, a variety of imines **1a**–**i** and enolizable aldehydes **2a**–**g** were tested (Table 2).[7] Diphenylimine **1a** reacted with aldehydes **2a**–**g** to afford the corresponding 3-substituted 2-phenyl quinolines **3a**–**g** in moderate to good yields (Table 2, entries 1–7). Substituted imines **1b**–**i** bearing functional groups such as Br, Me, or MeO, also reacted smoothly with various aldehydes to afford the desired substituted 2-arylquiniolines **3h**–**r** (Table 2, entries 8–18). It is noteworthy that bromoquinolines may be subjected to further transformation via a C–C bond coupling reaction. However, when using enolizable acetophenone instead of the aliphatic aldehydes, no quinoline product was isolated.

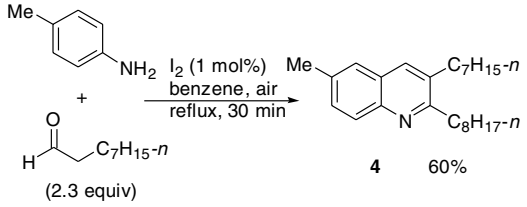
To expand the preparative utility, a two-step, one-pot synthesis of 2-arylquinolines from an arylamine, an aromatic aldehyde and an aliphatic aldehyde was examined (Scheme 2). Using 1 mol % of iodine as catalyst, the imine generated in situ from aniline and 4-bromobenzaldehyde (1 equiv) in benzene reacted with decanal (**2a**) under reflux and an air atmosphere conditions to afford the quinoline **3h** in 70% yield. The addition of anhydrous $MgSO_4$ or 4 Å molecular sieve powder did not help to improve the yield.

We also examined the in situ generated alkylimines, which are hygroscopic, unstable, and difficult to be purified by distillation, recrystallization, or column chromatography. When *p*-tolylamine (1.0 equiv) was treated with nonanal (**2b**) (2.3 equiv) in the presence of iodine (1 mol %) in benzene under reflux and an air atmosphere, the resulting alkylimine further reacted with excess aldehyde **2b** to give the corresponding 3,4-dialkyl-substituted quinoline **4** in 60% yield (Scheme 3).[8]

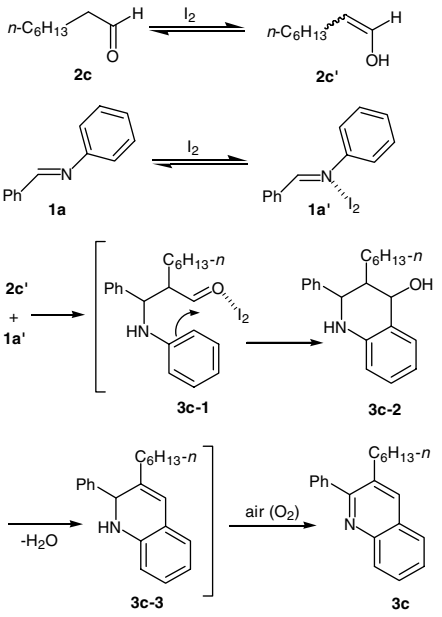
According to the literatures,[5e,9] we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was proposed as shown in Scheme 4. In the presence of iodine, octanal (**2c**) is in equilibrium with the enol form **2c**′, in the presence of iodine, which was confirmed by ^{1}H NMR experiment.[10] The in situ generated enol



Scheme 2.



Scheme 3.



Scheme 4.

immediately reacts with the iodine-activated imine **1a**′ to form intermediate **3c-1**,[11] followed by an intramolecular Friedel–Crafts cyclization to give **3c-2**. The subsequent dehydration of **3c-2** results in dihydroquinoline **3c-3**, which is further oxidized by air to give an aromatized quinoline **3c**. These reactions take place in a one-flask domino manner.

In summary, we have developed a new and general route to substituted quinolines from imines and enolizable aldehydes. A catalytic amount of molecular iodine (1 mol %) effectively initiates the reaction in a one-pot domino process to give the products. The procedure offers several advantages including mild and metal-free reaction conditions, operational simplicity, inexpensive reagents, and short reaction time.

Acknowledgments

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7. General procedure for the synthesis of quinolines **3**. The appropriate imines **1** (1.2 mmol), enolizable aldehydes **2** (1.0 mmol), and iodine (0.01 mmol, 2.5 mg) were mixed in 5 mL of benzene. The mixture was vigorously stirred in an open flask under reflux for 30 min and the reaction was monitored by TLC. After completion, the reaction mixture was directly evaporated and quinoline derivatives **3** were obtained by silica gel column chromatography with hexane–EtOAc (40:1, v/v). All products gave satisfactory spectroscopic and analytical data. Spectral data of the selective new compounds are followed.

Compound **3a**: Liquid; IR (neat): 2953, 2924, 2854, 1486, 1456, 1418, 767, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, $J = 8.4$ Hz, 1H), 8.05 (s, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.70–7.72 (m, 1H), 7.45–7.57 (m, 6H), 2.78 (t, $J = 8.0$ Hz, 2H), 1.52–1.56 (m, 2H), 1.20–1.27 (m, 10H), 0.88 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.71, 146.29, 140.89, 135.66, 134.08, 129.21, 128.73, 128.70, 128.22, 127.99, 127.60, 126.85, 126.30, 32.79, 31.74, 30.53, 29.22, 29.16, 29.05, 22.58, 14.06. MS (ESI): $m/z = 318$ ($[M+H]^+$). Anal. Calcd for $C_{23}H_{27}N$: C, 87.02; H, 8.57; N, 4.41. Found: C, 87.00; H, 8.61; N, 4.35.

Compound **3c**: Liquid; IR (neat): 2954, 2924, 2853, 1486, 1457, 1419, 767, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, $J = 8.4$ Hz, 1H), 8.04 (s, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.65–7.69 (m, 1H), 7.44–7.57 (m, 6H), 2.77 (t, $J = 8.0$ Hz, 2H), 1.52–1.56 (m, 2H), 1.17–1.27 (m, 6H), 0.85 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.70, 146.29, 140.89, 135.63, 134.06, 129.21, 128.71, 128.67, 128.21, 127.97, 127.57, 126.84, 126.28, 32.77, 31.39, 30.48, 29.65, 22.40, 13.98. MS (ESI): $m/z = 290$ ($[M+H]^+$). Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.08; H, 8.10; N, 4.77.

Compound **3k**: White solid, mp 104–106 °C; IR (neat): 2954, 2919, 2853, 1467, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, $J = 8.4$ Hz, 1H), 7.94 (d, $J = 2.0$ Hz, 1H), 7.90 (s, 1H), 7.70 (dd, $J = 2.4$, 2.0 Hz, 1H), 7.31 (s, 1H), 7.23–7.24 (m, 2H), 2.77 (t, $J = 8.0$ Hz, 2H), 2.33 (s, 6H), 1.50–1.57 (m, 2H), 1.19–1.26 (m, 10H), 0.87 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.34, 144.85, 138.03, 136.62, 136.53, 135.25, 134.38, 131.98, 130.97, 129.81, 129.35, 128.82, 128.59, 125.93,119.87, 32.74, 31.76, 30.42, 29.66, 29.16, 29.06, 22.59, 19.84, 19.10, 14.06. MS (ESI): $m/z = 424$ ($[M+H]^+$). Anal. Calcd for $C_{25}H_{30}NBr$: C, 70.75; H, 7.12; N, 3.30. Found: C, 70.71; H, 7.21; N, 3.23.
8. Spectral data of compound **4**: Liquid; IR (neat): 2954, 2924, 2854, 1490, 1465, 824 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, $J = 8.4$ Hz, 1H), 7.74 (s, 1H), 7.46 (s, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 2.94 (t, $J = 8.0$ Hz, 2H), 2.75 (t, $J = 7.6$ Hz, 2H), 2.49 (s, 3H), 1.72–1.80 (m, 2H), 1.61–1.70 (m, 2H), 1.25–1.45 (m, 18H), 0.85–0.91 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.30, 145.02, 135.11, 134.20, 134.02, 130.49, 128.07, 127.19, 125.70, 35.88, 32.37, 31.86, 31.78, 30.56, 29.95, 29.85, 29.67, 29.53, 29.50, 29.25, 29.16, 22.63, 21.48, 14.05, 14.07. MS (ESI): $m/z = 354$ ($[M+H]^+$). Anal. Calcd for $C_{25}H_{39}N$: C, 84.92; H, 11.12; N, 3.96. Found: C, 84.86; H, 11.19; N, 3.87.
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10. To a NMR tube containing a solution of octanal (0.1 mmol) in benzene-d_6 (0.5 mL) was added iodine (1.0 mg) and subject to a ^1H NMR spectroscopy. When the temperature was increased to 40 °C, new signals corresponding to the enol **2c′** appeared. The chemical shifts of the two protons of CH=CH and the proton of OH in **2c′** were δ 6.01, 4.81, and 3.75, respectively. The ratio of enol form (13%) was determined by the integration of the ^1H NMR chemical shifts.
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