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A Facile Synthesis of Benzo[*h*]quinolines via Silica-TsOH-P_2O_5 Promoted Condensation of 1-Naphthylamines with 1,3-Diketones under Solvent Free Conditions

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A facile synthesis of benzo[*h*]quinolines has been developed via improved Combes reaction. A combination of silica gel, *p*-toluenesulfonic acid and phosphorus pentoxide was utilized to promote the condensation of 1-naphthylamines with 1,3-diketones under solvent free conditions. In this case, silica gel was used as reaction media, *p*-toluenesulfonic acid and phosphorus pentoxide were acted as catalyst and dehydrating agent, respectively.

Keywords silica-TsOH-P_2O_5, benzo[*h*]quinoline, catalysis, synthesis, solvent free

Introduction

Benzo[*h*]quinoline and its derivatives are very important organic sketones due to their broad and important applications. They displayed excellent biological activities, including antibacterial, anti-hypertension, antimalarial, antivirus, insecticidal activities[1] and so on. Furthermore, functionalized benzo[*h*]quinoline and related metal complexes are very useful in the design of fluorescent sensors and preparation of luminescent materials, which are very attractive due to their potential applications in optoelectronics and analytical chemistry, such as preparation of organic light-emitting devices (OLED), luminescence-based sensors, detecting hazard materials, photocatalysis, and photopolymerization.[2] On the other hand, benzo[*h*]quinolines are also very important organic framework for studying the transient metal catalyzed aromatic C—H bond functionalization reactions, for example, direct nucleophilic addition of inert C(sp^2)—H bonds to aldehydes and nitriles, aromatic C(sp^2)—H bonds oxidation, nitration and halogenations, nitrogen-directed coupling reaction.[3]

By utilizing different starting materials, several methods for synthesizing benzo[*h*]quinoline derivatives have been reported, including modified Skraup reaction, classical Combes reaction, palladium catalyzed *aza*-wacker oxidative cyclization, BF_3 catalyzed [3+3] annulation reaction, iodine-mediated intramolecular electrophilic aromatic cyclization, Lewis acid catalyzed *aza*-Diels-Alder reaction, tris(4-bromophenyl) aminium-hexachloroantimonate ($TBPA^+$) catalyzed oxidative Povarov reaction, copper(I) promoted tandem reaction of azobenzenes with allyl bromides via N=N bond cleavage and iridium-catalyzed N-heterocyclization, as well as transformation from other heterocyclic compounds.[4] However, some of these methods are suffered from limitations such as poor regioselectivity, low yield, long reaction time, harsh reaction conditions, expensive substrates and catalysts, and tedious reaction procedures. Therefore, it is highly desirable to develop an efficient reaction with easily available reagents for getting benzo[*h*]quinolines.

Comparing these reaction methods, the direct condensation between 1-naphthylamines and 1,3-diketones (Combes reaction) is still the straight access for obtaining benzo[*h*]quinolines, because all reagents involved in this reaction are easily available with broad scope of substrates. On the other hand, silica gel and silica gel based catalysts[5] were broadly applied to catalyze many organic reactions due to its several advantages, such as high surface areas, excellent stability (chemical and thermo-mechanical), good mobility that is suitable for reaction media, easier work-up, good dispersion of active reagent sites associated with selectivity, and the fact that the organic groups can be robustly anchored to the silica surface to provide catalytic centers. In our previous work,[6] we have reported a silica sulfuric acid mediated acylation of amines with 1,3-diketones, most of anilines and alkylamine could be acylated by 1,3-diketones via C—C bond cleavage. However, in the case of 1-naphthylamine reacting with pentane-2,4-dione, only traces of amidation product, *N*-(naphthalen-1-yl) acetamide was obtained, while the 2,4-dimethylbenzo[*h*]-quinoline was isolated as the major product. According

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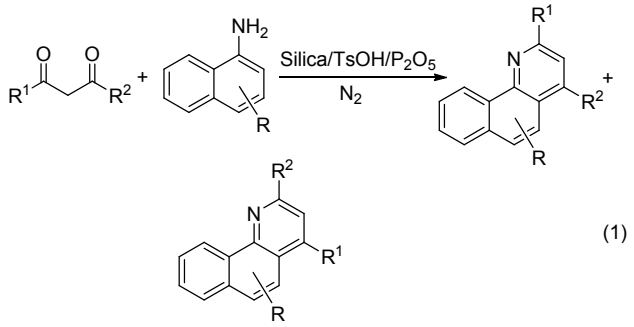
to our proposed C—C bond cleavage mechanism (both hydrolysis and oxidative cleavage), with the silica gel sulfuric acid, the water and oxygen were the main factors to promote the C—C bond cleavage. Thus, if the reaction was carried out under anhydrous and inert atmosphere, while the water formed in reaction could be removed quickly as soon as possible, the reaction should afford benzo[*h*]quinoline as the main product. Inspired by this idea, we tried to find an optimal catalytic system for synthesizing benzo[*h*]quinolines. Herein, we will describe an efficient process for the synthesis of benzo[*h*]quinolines by the condensation of 1-naphthylamines and 1,3-diketones mediated with silica gel, and the combination of TsOH and P_2O_5 as acid catalyst and water removal reagent, respectively (Eq. 1).



(1)

Experimental

1-Naphthyl amines, pentane-2,4-dione, heptane-3,5-dione, 1,3-diphenylpropane-1,3-dione, 4,4,4-trifluoro-1-(*p*-tolyl)butane-1,3-dione and 1-phenyl butane-1,3-dione were commercially available, 2,6-dimethyl-heptane-3,5-dione, 4-methylnaphthalen-1-amine, 4-methoxynaphthalen-1-amine, and *N*-(5-aminonaphthalen-1-yl)acetamide were prepared according to literature method.[7] ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400. Chemical shifts (δ) are referenced to the solvent residual peak: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) and TMS peak as an internal standard. High resolution mass spectra (HRMS) were performed using a Bruker Daltronics MicrOTOF. TLC analyses were performed on commercial aluminum sheets bearing 0.25 mm layer of silica gel. 200—300 mesh silica gel was used for column chromatography. Infrared (IR) spectra were recorded using a KBr disc or coating on a Nicolet 6700 spectrometer.

General procedure for the preparation of 2,4-disubstituted benzo[*h*]quinoline

A mixture of 1-naphthylamine (143 mg, 1 mmol), 2,4-diketopentane (1.2 mmol), TsOH•H_2O (38 mg 0.2 mmol), P_2O_5 (43 mg 0.3 mmol) and silica gel 500 mg, was stirred violently at 155 ℃ for 12 h under nitrogen atmosphere. After 1-naphthylamine was consumed out (detected by TLC), the reaction was cooled to room temperature and 10 mL ammonium (17%) and 20 mL ethyl acetate were added. Then the mixture was filtered after stirring for 30 min. The filter cake was washed with ethyl acetate (20 mL×3). The combined organic layer was dried over sodium sulfate and concentrated on a rotary evaporator to give a residue, which was purified on silica gel [*V*(PE)∶*V*(EA)=10∶1, as eluent) to afford a yellow solid in 88 % yield.

2,4-Dimethylbenzo[*h*]quinolone (3aa)[8] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.37 (d, J=8.0 Hz, 1H), 7.93—7.80 (m, 2H), 7.77 (d, J=9.0 Hz, 1H), 7.74—7.61 (m, 2H), 7.23 (s, 1H), 2.79 (s, 3H), 2.70 (s, 3H).

2,4-Diethylbenzo[*h*]quinolone (3ab) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.46 (d, J=8.1 Hz, 1H), 7.90 (d, J=9.0 Hz, 1H), 7.82—7.52 (m, 1H), 3.35—2.84 (m, 4H), 1.53 (t, J=7.6 Hz, 3H), 1.41 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.1, 148.5, 144.8, 132.2, 131.0, 126.6, 126.4, 125.5, 125.1, 123.9, 122.0, 119.9, 119.1, 31.0, 24.4, 13.4, 12.7; IR (film) v: 3048, 2968, 2933, 2874, 1622, 1594, 1561, 1505, 1461, 1385 cm^{-1}. HRMS calcd for $C_{17}H_{17}N$ [M^+] 235.1361, found 235.1359.

2,4-Diisopropylbenzo[*h*]quinolone (3ac) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, J=8.0 Hz, 1H), 7.07 (d, J=9.2 Hz, 1H), 6.98 (d, J=7.3 Hz, 1H), 6.87 (d, J=9.2 Hz, 1H), 6.83—6.66 (m, 2H), 6.44 (s, 1H), 3.12—2.64 (m, 1H), 2.56—2.15 (m, 1H), 0.59 (d, J=6.9 Hz, 6H), 0.53 (d, J=6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.81, 152.97, 144.71, 132.1, 131.3, 126.5, 126.3, 125.5, 125.0, 124.1, 121.6, 119.7, 114.7, 36.1, 27.5, 22.1, 21.8; IR (film) v: 3048, 2964, 1592, 800 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{21}N$ [M^+] 263.1674, found 263.1672.

2,4-Diphenylbenzo[*h*]quinolone (3ad)[9] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (d, J=8.1 Hz, 1H), 8.39 (d, J=7.5 Hz, 2H), 7.97 (s, 1H), 7.91 (d, J=7.7 Hz, 1H), 7.85—7.65 (m, 4H), 7.63—7.44 (m, 8H).

2,4,6-Trimethylbenzo[*h*]quinolone (3ba) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.61—9.21 (m, 1H), 8.15—7.91 (m, 1H), 7.80—7.55 (m, 3H), 7.21 (s, 1H), 2.77 (d, J=2.2 Hz, 6H), 2.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.3, 145.1, 143.1, 133.2, 132.1, 131.6, 127.7, 126.4, 125.2, 123.9, 123.6, 123.3, 121.0, 25.2, 20.2, 18.9; IR (KBr) v: 3070, 2938, 1594, 764 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{15}N$ [M^+] 221.1204, found 221.1205.

2,4-Diethyl-6-methylbenzo[*h*]quinolone (3bb) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69—9.33 (m, 1H), 8.02 (d, J=8.1 Hz, 1H), 7.84—7.48 (m, 3H), 7.25 (s, 1H), 3.44—2.84 (m, 4H), 2.74 (s, 3H), 1.49 (t, J=7.5 Hz, 3H), 1.41 (t, J=7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.3, 147.8, 144.2, 132.1, 130.9, 126.5, 125.2, 124.3, 122.8, 121.9, 119.6, 119.1, 31.0, 24.3, 19.2, 13.5, 12.8; IR (KBr) v: 3066, 2929, 1595, 759 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{19}N$ [M^+] 249.1517, found 249.1516.

2,4-Diisopropyl-6-methylbenzo[*h*]quinolone (3bc) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82—8.83 (m, 1H), 8.08—7.91 (m, 1H), 7.79 (s, 1H), 7.74—7.62 (m, 2H), 7.30 (s, 1H), 3.91—3.63 (m, 1H), 3.38—

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3.19 (m, 1H), 2.78 (s, 3H), 1.47 (d, J=6.9 Hz, 6H), 1.42 (d, J=6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.0, 153.3, 145.2, 133.0, 132.3, 131.9, 127.6, 126.2, 125.5, 123.7, 122.5, 120.4, 115.7, 37.2, 28.4, 23.2, 22.9, 20.4; IR (KBr) v: 3064, 2925, 1590, 768 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{23}N$ [M^+] 277.1830, found 277.1828.

6-Methyl-2,4-diphenylbenzo[*h*]quinolone (**3bd**) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.71 (d, J=7.9 Hz, 1H), 8.42 (d, J=7.6 Hz, 2H), 8.06 (d, J=7.8 Hz, 1H), 7.96 (s, 1H), 7.86−7.72 (m, 2H), 7.66 (s, 1H), 7.64−7.54 (m, 7H), 7.55−7.45 (m, 1H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 152.9, 147.1, 145.1, 138.7, 137.9, 132.4, 132.4, 130.9, 128.6, 127.7, 127.5, 127.1, 126.3, 125.5, 124.5, 122.9, 122.1, 121.3, 118.5, 19.0; IR (KBr) v: 3061, 3025, 2938, 2857, 1633, 1586, 1544, 1508, 1475, 1447, 1424, 1387, 735, 727 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{19}N$ [M^+] 345.1517, found 345.1519.

***N*-(2,4-Dimethylbenzo[*h*]quinolin-7-yl)acetamide** (**3ca**) Gray solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H), 9.10 (s, 1H), 8.24−7.55 (m, 4H), 7.39 (s, 1H), 2.69 (s, 6H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.0, 157.1, 144.6, 144.2, 133.9, 131.6, 127.6, 126.2, 124.2, 123.5, 123.0, 121.5, 121.3, 120.9, 24.9, 23.4, 18.3; IR (KBr) v: 3275, 3028, 2922, 1653, 1597, 773 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{16}N_2O$ [M^+] 264.1263, found 264.1262.

***N*-(2,4-Diethylbenzo[*h*]quinolin-7-yl)acetamide** (**3cb**) Gray solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H), 9.14 (d, J=8.2 Hz, 1H), 8.04 (s, 2H), 7.82 (d, J=7.5 Hz, 1H), 7.69 (t, J=7.9 Hz, 1H), 7.44 (s, 1H), 3.30−3.05 (m, 2H), 3.07−2.93 (m, 2H), 2.22 (s, 3H), 1.41 (t, J=7.6 Hz, 3H), 1.37−1.27 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.0, 161.9, 149.8, 144.8, 133.9, 132.0, 127.5, 126.2, 124.2, 122.4, 121.6, 121.0, 120.9, 120.6, 24.6, 23.4, 14.5, 13.5; IR (KBr) v: 3266, 3059, 2968, 1655, 1595, 775 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{20}N_2O$ [M^+] 292.1576, found 292.1578.

***N*-(2,4-Diisopropylbenzo[*h*]quinolin-7-yl)acetamide** (**3cc**) Gray solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H), 9.19 (d, J=8.1 Hz, 1H), 8.50−7.95 (m, 2H), 7.84 (d, J=7.4 Hz, 1H), 7.70 (t, J=7.9 Hz, 1H), 7.49 (s, 1H), 4.02−3.65 (m, 1H), 3.53 (s, 1H), 3.35 (s, 1H), 3.36−3.12 (m, 1H), 2.23 (s, 3H), 1.49−1.29 (m, 12H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.0, 165.6, 154.2, 144.7, 133.8, 132.2, 127.3, 126.2, 124.1, 121.9, 121.6, 121.1, 120.6, 116.4, 40.1, 39.9, 39.7, 39.4, 39.2, 39.0, 38.8, 36.3, 27.9, 22.5; IR (KBr) v: 3282, 3060, 2963, 1662, 1591, 774 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{24}N_2O$ [M^+] 320.1889, found 320.1888.

***N*-(2,4-Diphenylbenzo[*h*]quinolin-7-yl)acetamide** (**3cd**) Gray solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 9.35 (d, J=8.8 Hz, 1H), 8.49 (d, J=7.4 Hz, 2H), 8.19 (s, 1H), 8.04 (d, J=9.5 Hz, 1H), 7.88 (d, J=7.4 Hz, 2H), 7.80 (t, J=8.0 Hz, 2H), 7.74−7.55 (m, 7H), 7.54 (d, J=7.1 Hz, 2H), 3.38 (s, 12H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.1, 154.3, 148.7, 145.8, 138.6, 137.7, 134.2, 132.0, 129.7, 129.6, 128.9, 128.7, 128.6, 127.9, 127.3, 126.8, 124.9, 122.5, 122.4, 122.0, 121.8, 119.4, 23.4; IR (KBr) v: 3216, 3048, 2919, 1645, 1604, 780 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{20}N_2O$ [M^+] 388.1576, found 388.1574.

6-Methoxy-2,4-dimethylbenzo[*h*]quinolone (**3da**) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.33 (d, J=8.0 Hz, 1H), 8.32 (d, J=7.8 Hz, 1H), 7.92−7.49 (m, 2H), 7.15 (s, 1H), 6.90 (s, 1H), 4.05 (s, 3H), 2.75 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 153.3, 152.0, 141.3, 140.9, 131.2, 126.3, 126.2, 123.5, 123.3, 122.3, 120.4, 94.9, 53.8, 23.9, 18.2; IR (KBr) v: 3031, 2963, 1627, 1107, 778 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{15}NO$ [M^+] 227.1154, found 237.1153.

2,4-Diethyl-6-methoxybenzo[*h*]quinolone (**3db**) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.40 (d, J=8.1 Hz, 1H), 8.33 (d, J=8.0 Hz, 1H), 7.88−7.55 (m, 2H), 7.21 (s, 1H), 7.01 (s, 1H), 3.52−2.73 (m, 1H), 1.50 (t, J=7.6 Hz, 3H), 1.42 (t, J=7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.5, 152.0, 146.8, 141.1, 131.7, 126.4, 126.4, 126.1, 123.8, 122.6, 120.6, 119.0, 94.9, 54.3, 30.8, 24.5, 12.8; IR (KBr) v: 3069, 2961, 1627, 1109, 763 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{19}NO$ [M^+] 265.1467, found 265.1468.

2,4-Diisopropyl-6-methoxybenzo[*h*]quinolone (**3dc**) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.43 (d, J=8.2 Hz, 1H), 8.31 (d, J=7.8 Hz, 1H), 7.83−7.56 (m, 2H), 7.29 (s, 1H), 7.12 (s, 1H), 4.11 (s, 3H), 3.80−3.49 (m, 1H), 3.49−2.81 (m, 1H), 1.55−1.38 (m, 12H), 0.73−0.71 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.3, 152.1, 152.0, 151.3, 141.1, 132.0, 126.4, 126.4, 126.1, 124.0, 122.2, 120.5, 114.7, 94.5, 54.4, 35.9, 27.7, 21.7; IR (KBr) v: 3072, 2962, 1624, 1107, 774 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{23}NO$ [M^+] 293.1780, found 293.1779.

6-Methoxy-2,4-diphenylbenzo[*h*]quinolone (**3dd**) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (d, J=8.0 Hz, 1H), 8.54−8.17 (m, 3H), 7.92 (s, 1H), 7.82 (t, J=4.0 Hz, 1H), 7.75 (t, J=4.0 Hz, 1H), 7.67−7.51 (m, 7H), 7.48 (t, J=7.3 Hz, 1H), 7.04 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.1, 152.6, 147.5, 143.4, 139.9, 139.3, 132.8, 129.5, 128.9, 128.8, 128.7, 128.2, 128.1, 128.0, 127.5, 127.2, 125.2, 124.2, 121.9, 119.7, 97.9, 55.4; IR (KBr) v: 3057, 2934, 1623, 1118, 1103, 770 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{19}NO$ [M^+] 361.1467, found 361.1471.

2-Methyl-4-phenylbenzo[*h*]quinolone (**3ae-1**)[10] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.32 (d, J=8.0 Hz, 1H), 7.76 (d, J=7.6 Hz 1H), 7.69−7.52 (m, 4H), 7.48−7.33 (m, 5H), 7.23 (s, 1H), 2.76 (s, 3H).

4-Methyl-2-phenylbenzo[*h*]quinoline (**3ae-2**) White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (d, J=8.0 Hz, 1H), 8.35 (d, J=7.4 Hz, 2H), 7.92 (d, J=8.8 Hz, 2H), 7.88−7.78 (m, 2H), 7.78−7.62 (m, 2H), 7.57 (t, J=7.5 Hz, 2H), 7.48 (t, J=7.3 Hz, 1H), 2.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.0, 146.0, 144.6, 139. 9, 133.6, 132.2, 129.1, 128.8, 128.0, 127.7, 127.4, 127.1, 126.8, 125.2, 124.8, 121.3, 120.0, 19.5; IR (KBr) v: 3060, 2970, 1590, 1550, 751 cm^{-1}. HRMS (EI) calcd

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for $C_{20}H_{15}N$ [M^+] 269.1204, found 269.1205.

1,3-Dimethylbenzo[*f*]quinoline (**3ea**) Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (d, J=8.4 Hz, 1H), 8.02 (d, J=9.2 Hz, 1H), 7.95 (d, J=9.2 Hz, 2H), 7.69−7.63 (m, 2H), 7.27 (s, 1H), 3.10 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.6, 148.5, 145.9, 132.6, 131.4, 130.7, 129.1, 128.0, 127.2, 126.5, 126.3, 125.9, 123.9, 26.7, 24.0. HRMS (EI) calcd for $C_{15}H_{13}N$ [M^+] 207.1048, found 207.1049.

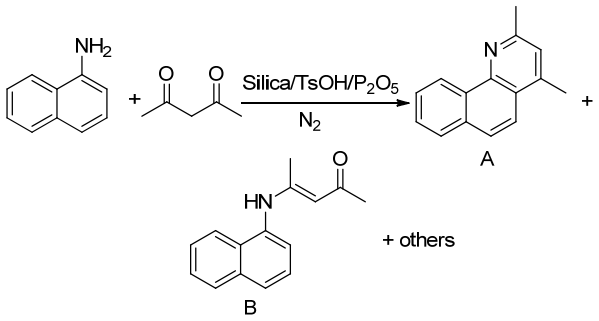
1,3-Diethylbenzo[*f*]quinoline (**3eb**) Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, J=8.4 Hz, 1H), 7.99 (d, J=9.2 Hz, 1H), 7.91 (d, J=8.8 Hz, 2H), 7.66−7.57 (m, 2H), 7.30 (s, 1H), 3.44 (q, J=7.2 Hz, 2H), 3.03 (q, J=7.6 Hz, 2H), 1.52 (t, J=7.6 Hz, 3H), 1.45 (t, J=7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.2, 151.1, 149.3, 132.7, 130.8, 130.3, 129.1, 127.2, 126.3, 126.1, 123.4, 122.3, 31.5, 30.6, 14.5, 14.2. HRMS (EI) calcd for $C_{17}H_{17}N$ [M^+] 235.1361, found 235.1355.

Results and Discussion

Under classical Combes reaction conditions,[2f] the yield of benzo[*h*]quinoline formation was usually low (about 21%), thus it is desirable to develop an efficient method for synthesizing benzo[*h*]quinolines. Herein, we would like to describe a useful and straight access for efficiently obtaining benzo[*h*]quinolines, and all of involved reagents are inexpensive and easily available. For obtaining the optimum reaction condition, the condensation reaction was initially carried out by choosing 1-naphthylamine and pentane-2,4-dione as a probe substrate under different reaction conditions (Table 1). The ratio of 1-naphthylamine (1 mmol), pentane-2, 4-dione (2 mmol) and commercial silica gel (200−300 mesh, 0.5 g) were used in all entries. When this reaction was carried out at lower temperature (40 ℃) in the presence of 20 mol% of TsOH, the dehydrate product (enaminone) between 1-naphthylamine and pentane-2,4-dione was formed quickly as the sole product and no 2,4-dimethyl benzo[*h*]quinoline was detected (Table 1, Entry 1).

Only when the temperature was increased to 155 ℃, 2,4-dimethylbenzo[*h*]quinoline was formed in higher yield (Table 1, Entry 2). In this case, small amount of side product (amide) was also detected, which might be attributed to the hydrolyzed C−C bond cleavage. Thus addition of the strong dehydrant P_2O_5 may suppress this side reaction. Then 30% P_2O_5 was added to this reaction system, and the yield was dramatically enhanced (Table 1, Entry 3). However, higher temperature lowered the yield, which may be attributed to some side reaction, such as polymerization or carbonization reaction (Table 1, Entry 4). Lower reaction temperature led to incomplete reaction, and most of the dehydrate product (enaminone) was detected (Table 1, Entry 5). Further experiments showed that silica gel and catalytic amount of TsOH is the key factor for full conversion, and poor yield was obtained in the absence of either silica gel

Table 1 Optimization of the reaction conditions[a]



Entry	*p*-TsOH/P_2O_5 (mol%)	*T*/℃	Composition[b] A/B/others
1	20/0	40	0/100/0
2	20/0	155	77/0/23
3	20/30	155	95/0/5
4	20/30	175	90/0/10
5	20/30	135	38/62/0
6[c]	20/30	155	60/40/0
7	0/30	155	14/86/0
8	10/30	155	85/0/15

[a] Reaction conditions: 1-naphthylamine (143 mg, 1 mmol) and 1,3-diketones (200 mg, 2 mmol), silica gel 500 mg, TsOH (0.2 mmol) and P_2O_5 (0.3 mmol) were heated under nitrogen atmosphere for 12 h; [b] composition was determined by GC analysis (areas of peak normalization method); [c] without using silica gel.

(Table 1, Entry 6) or TsOH (Table 1, Entry 7). Decrease in the amount of TsOH leads to the loss of yield (Table 1, Entry 8). Thus the optimum reaction conditions were selected as follows: a mixture of 1-naphthylamines (1 mmol) and substituted 1,3-diketones (2 mmol), silica gel 500 mg, TsOH (0.2 mmol) and P_2O_5 (0.3 mmol) was heated under nitrogen atmosphere at 155 ℃ for an appropriate time. With the optimized reaction condition, the substrate scope of both 1-naphthylamine derivatives and substituted 1,3-diketones was broadened. Most of these substrates could be prepared in moderate to good yields (Eq. 2). For the 1,3-diketones with more hindered substitute gave a little lower yield (**3ac**, **3bc**, **3cc** and **3dc**, Eq. 2), and aryl substituted 1,3-diketones afforded much higher yield (**3ad**, **3bd** and **3cd**, Eq. 2), though longer reaction time was required. For the 1-naphthylamines, the electron withdrawing group and donating group display weak effect on the yield (**3ca**, **3cb**, **3cc** and **3cd**, Eq. 2). Furthermore, under similar reaction conditions, the condensation between 2-naththylamine and 1,3-diketones affords benzo[*f*]quinoline derivatives as the main products in acceptable yield (**3ea** and **3eb**, Eq. 2).

Next, we applied this reaction condition to the condensation of 1-naphthylamine with unsymmetrical 1,3-diketones, such as 1-phenylbutane-1,3-dione and 4,4,4-trifluoro-1-(*p*-tolyl) butane-1,3-dione. In both cases, two region isomers were detected, and 1-phenylbutane-1,3-dione gives better regioselectivity (10∶1) than 4,4,4-tri-

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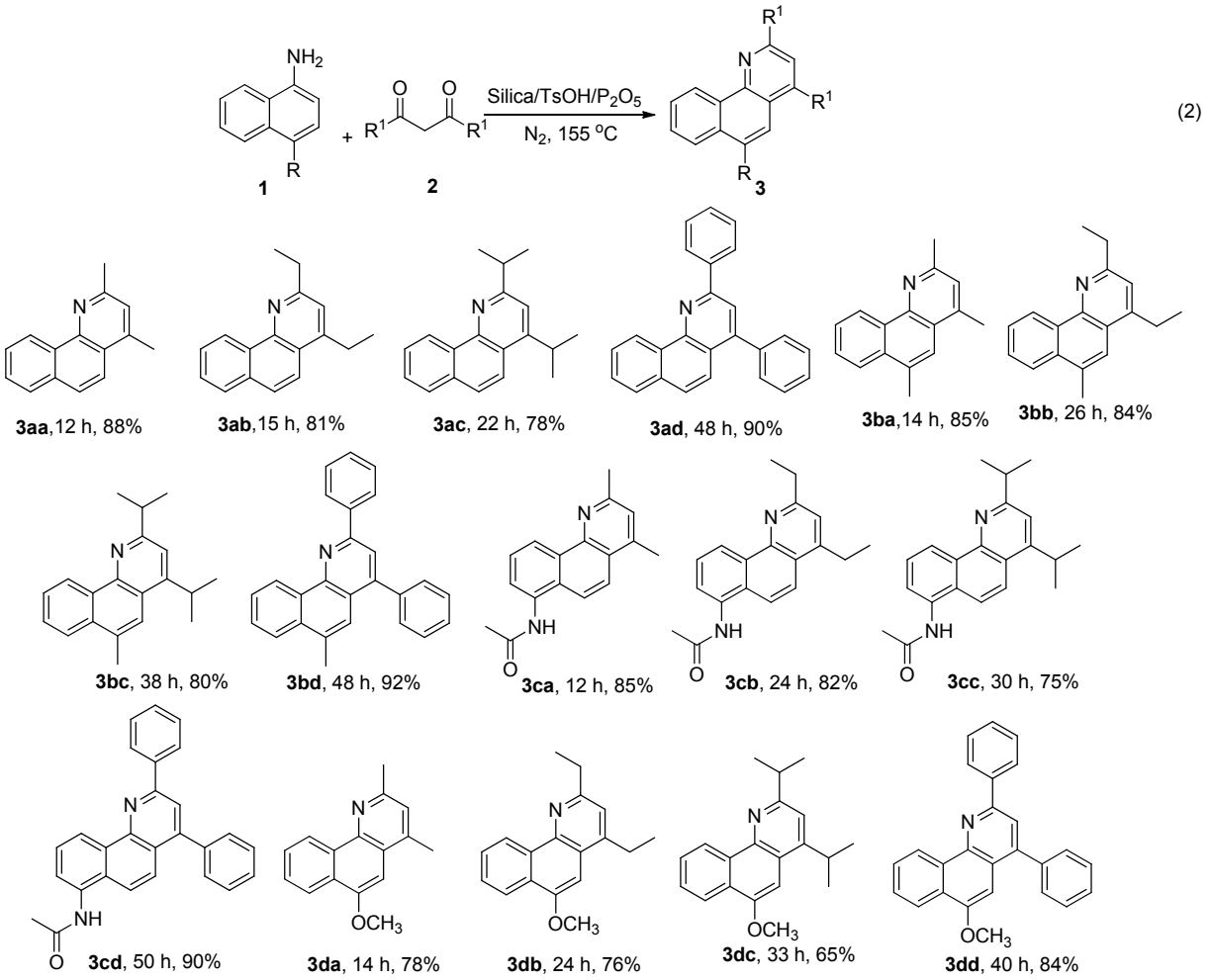
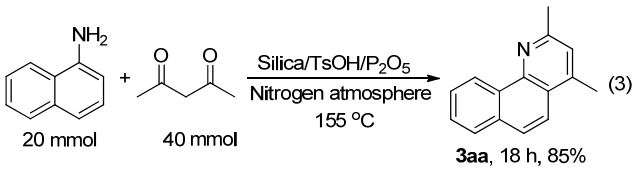
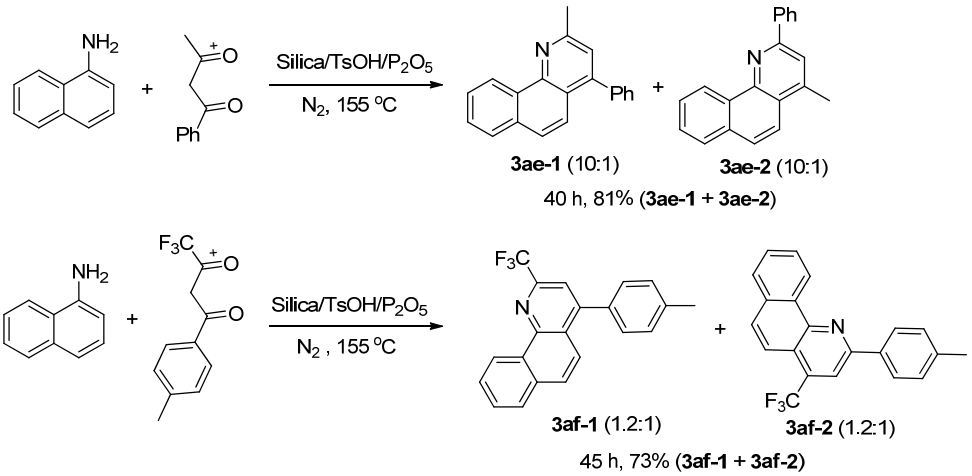


fluoro-1-(*p*-toly) butane-1,3-dione (1.2∶1), which may be attributed to the bigger difference of electronic effect between two carbonyl groups in the former than that in the latter (Scheme 1).

Finally, this condensation reaction between 1-naphthylamine and pentane-2,4-dione was scaled up, and it could proceed smoothly to afford dimethyl benzo[*h*]quinoline with a little decreased yield (85%) (Eq. 3).



Scheme 1 Reaction of 1-naphthylamines with unsymmetrical 1,3-diketones mediated by silica-TsOH-P_2O_5



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Conclusions

In conclusion, we have developed a facile and efficient method for the synthesis of benzo[*h*]quinolines via improved Combes reaction. In these cases, catalytic amount of acids in combination of silica gel were used, and all substrates and reagents were commercially or readily available. This method should be very useful for practical synthesis of benzo[*h*]quinolones.

Acknowledgement

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