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4-Dimethylaminopyridine-catalyzed Cascade Reaction for Efficient Synthesis of Naphthofurans

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Abstract A convenient and efficient method was developed for the synthesis of naphtho[2,1-*b*]furans *via* 4-dimethylaminopyridine(DMAP)-catalyzed cascade reaction of 2-hydroxy-1-naphthaldehydes and *α*-halogenated ketones in moderate to good yields in the presence of Na_2CO_3 at 80 ºC for 6 h. The mechanism for this process was briefly discussed with a tentative catalytic cycle proposed. Moreover, this method features organocatalysts and high step-economy, which makes it practical and attractive.

Keywords 4-Dimethylaminopyridine; *α*-Halogenated ketone; Cascade reaction; Naphthofuran; Organocatalysis

1 Introduction

Benzofurans and naphthofurans, as important classes of heterocyclic compounds, have been found as key structural motifs in many natural products and many synthetic pharmaceutical compounds[1,2]. Among those compounds, naphthofuran derivatives have been applied in biological and medical areas, as potentially anticancer reagents, regulators of the nuclear receptor activity[3], and *in vivo/vitro* imaging agents[4]. In contrast to benzofurans[5,6], many naphthofuran derivatives are isolated from various natural sources[7], and only few efforts have been devoted on the synthesis of naphthofurans[8—11]. Therefore, the development of new synthetic method for the efficient synthesis of naphtho[2,1-*b*]furans, especially those with polysubstituents, is highly desirable.

Organocatalysis has been widely applied in organic synthesis for the new carbon-carbon/heteroatom bond formation over the last decades[12—16]. Previously, we developed an efficient synthetic approach for heterocyclic compounds *via* organocatalytic one-pot cascade and multicomponent reactions[17,18]. Recently, we have reported an efficient 4-dimethylaminopyridine(DMAP)-catalyzed cascade reaction for the syntheses of a series of 2-aroylbenzofurans and 1,4-diazabibicyclo[2.2.2]-octane(DABCO)-catalyzed multicomponent reaction for the syntheses of a series of 3,4-dihydro-2*H*-1,4-benzo[*b*]thiazines in good to excellent yields. As a part of our ongoing project into the development of efficient organocatalytic cascade reactions, herein we reported a convenient method for the efficient synthesis of a series of naphtho[2,1-*b*]furans using DMAP-catalyzed cascade reaction between 2-hydroxy-1-naphthaldehydes and *α*-halogenated ketones.

2 Experimental

2.1 Reagents and Instruments

All the reactions were carried out using standard round-bottom flask; solvents such as CH_2Cl_2, CH_3CN and EtOAc were distilled from CaH_2.

^1H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ on a Bruker AXS-300 MHz instrument with tetramethylsilane(TMS) as internal standard. Coupling constants were reported in Hz. Infrared(IR) spectra were taken on a SHIMADZU IR Prestige-21 Spectrometer with KBr plates; high resolution mass spectrum(HRMS) was obtained using electrospray ionization (ESI). Melting points were measured with micro melting point apparatus. Single crystal X-ray diffraction data were collected on a Bruker SMART APEX diffractiometer with molybdenum cathodes.

2.2 General Procedure for the Synthesis of Naphthofuran Derivatives

To DMAP(0.2 mmol) and Na_2CO_3(1.5 mmol) in CH_3CN were added halogenated ketone(**2**, 1.0 mmol) and 2-hydroxy-1-naphthaldehyde(**1**, 1.0 mmol). The resulted mixture was stirred at 80 °C for 6 h, concentrated under vacuum, washed with water, and extracted with ethyl acetate(10 mL×3). Organic layers were combined, dried over anhydrous Na_2SO_4, and

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evaporated *in vacuo*. The residue was purified by column chromatography on silica gel(200—300 mesh)[*V*(EtOAc)/*V*(petroleum)=1/15] to give the pure product **3**.

Naphtho[2,1-*b*]furan-2-yl(phenyl)methanone(**3**a)[19,20]: a faint yellow solid, yield 78%(212 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.09(d, *J*=7.8 Hz, 3H), 7.85—7.94(m, 3H), 7.55—7.71(m, 6H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 182.9, 153.4, 150.7, 136.3, 131.7, 129.4, 129.1, 128.4, 128.0, 127.5, 127.0, 126.4, 124.5, 122.3, 121.8, 114.6, 111.7. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3450, 3051, 2924, 2852, 1637, 1597, 1544, 1442, 1321, 1278, 1253, 1180, 1130, 1082, 974, 866, 752, 717, 692. m. p. 105—106 °C. HRMS(ESI), *m*/*z* calcd. for $C_{19}H_{13}O_2[M+H]^+$: 273.0916; found: 273.0916.

Naphtho[2,1-*b*]furan-2-yl(*p*-tolyl)methanone(**3**b)[20]: a faint yellow solid, yield 85%(243 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.08(d, *J*=8.1 Hz, 1H), 7.88—7.95(m, 4H), 7.83(d, *J*=9.3 Hz, 1H), 7.65(d, *J*=9.0 Hz, 1H), 7.57(d, *J*=8.7 Hz, 1H), 7.47(d, *J*=9.3 Hz, 1H), 7.27(d, *J*=8.1 Hz, 2H), 2.40(s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 182.5, 153.2, 150.7, 142.4, 133.5, 129.3, 128.7, 128.4, 128.0, 127.9, 126.9, 126.1, 124.3, 122.1, 121.6, 114.0, 113.9, 111.6, 20.5. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3115, 3039, 2920, 2854, 1631, 1606, 1583, 1539, 1519, 1452, 1319, 1278, 1132, 1082, 966, 893, 864, 808, 746, 613. m. p. 138—139 °C. HRMS(ESI), *m*/*z* calcd. for $C_{20}H_{15}O_2[M+H]^+$: 287.1072; found: 287.1071.

(4-Methoxyphenyl)(naphtho[2,1-*b*]furan-2-yl)methanone (**3**c)[20]: a white solid, yield 80%(241 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.15—8.20(m, 3H), 7.90—8.02(m, 3H), 7.76(d, *J*=9.0 Hz, 1H), 7.66(t, *J*=7.3 Hz, 1H), 7.56(t, *J*=7.3 Hz, 1H), 7.05(d, *J*=8.4 Hz, 2H), 3.93(s, 3H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 162.4, 153.2, 151.5, 130.9, 129.5, 128.9, 128.6, 128.0, 127.1, 126.3, 124.4, 122.3, 121.8, 113.5, 112.8, 111.8, 54.5; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3134, 3055, 3005, 2972, 2935, 2841, 1629, 1598, 1544, 1506, 1444, 1417, 1307, 1284, 1253, 1170, 1134, 1024, 972, 893, 812, 761, 613. m. p. 137—138 °C. HRMS(ESI), *m*/*z* calcd. for $C_{20}H_{15}O_3[M+H]^+$: 303.1021; found: 303.1021.

(4-Bromophenyl)(naphtho[2,1-*b*]furan-2-yl)methanone(**3**d)[20]: a faint yellow solid, yield 72%(252 mg). ^{1}H NMR($CDCl_3$, 300 Hz), δ: 8.18(d, *J*=7.8 Hz, 1H), 7.92—8.04(m, 5H), 7.64—7.75(m, 4H), 7.57(t, *J*=7.6 Hz, 1H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 181.6, 153.5, 150.4, 134.9, 130.8, 129.9, 129.5, 129.3, 128.1, 126.8, 126.5, 124.6, 122.3, 114.4, 111.7; IR(KBr), $\tilde{\nu}$/cm^{-1}: 3132, 3055, 2956, 2920, 2848, 1635, 1583, 1543, 1521, 1440, 1394, 1307, 1284, 1180, 1134, 1066, 974, 893, 833, 813, 750, 605. m. p. 172—173 °C. HRMS(ESI), *m*/*z* calcd. for $C_{19}H_{12}O_2Br[M+H]^+$: 351.0020; found: 351.0020.

(4-Chlorophenyl)(naphtho[2,1-*b*]furan-2-yl)methanone(**3**e): a dark green solid, yield 71%(217 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.15(d, *J*=7.8 Hz, 1H), 7.96(d, *J*=8.1 Hz, 1H), 7.66—7.76(m, 4H), 7.56—7.61(m, 3H), 7.25—7.27(m, 2H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 174.0, 159.2, 143.1, 127.6, 125.2, 124.1, 123.4, 122.3, 111.4, 104.5. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3057, 2958, 2918, 2848, 1637, 1585, 1544, 1519, 1440, 1307, 1286, 1255, 1180, 1134, 1087, 1012, 972, 893, 837, 813, 752, 692, 605. m. p. 165—166 °C. HRMS(ESI), *m*/*z* calcd. for $C_{19}H_{12}O_2Cl[M+H]^+$: 307.0526; found: 307.0526.

Naphthalen-2-yl(naphtho[2,1-*b*]furan-2-yl)methanone(**3**f): a yellow solid, yield 88%(283 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.66(s, 1H), 8.20(d, *J*=7.8 Hz, 1H), 8.14(d, *J*=7.8 Hz, 1H), 7.92—8.07(m, 6H), 7.79(d, *J*=7.8 Hz, 1H), 7.56—7.67(m, 4H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 183.7, 154.6, 152.2, 135.4, 134.7, 132.4, 131.0, 130.6, 130.1, 129.5, 129.1, 128.5, 128.4, 128.2, 127.8, 127.4, 126.9, 125.6, 125.3, 123.3, 115.5, 115.4, 112.9. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3125, 3050, 2962, 2372, 2302, 1645, 1582, 1552, 1335, 1268, 1222, 1145, 1080, 973, 845, 732. m. p. 162—163 °C. HRMS(ESI), *m*/*z* calcd. for $C_{23}H_{15}O_2[M+H]^+$: 323.1072; found: 323.1070.

Naphtho[2,1-*b*]furan-2-yl(4-nitrophenyl)methanone(**3**g): a yellow solid, yield 62%(196 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.44(d, *J*=8.7 Hz, 2H), 8.28(d, *J*=8.7 Hz, 2H), 8.21(d, *J*=8.1 Hz, 1H), 8.10(s, 1H), 7.96—8.01(m, 2H), 7.68—7.75(m, 2H), 7.59(t, *J*=7.2 Hz, 1H). ^{13}C NMR($CDCl_3$, 125 MHz), δ: 181.9, 155.4, 151.9, 150.5, 142.7, 131.4, 131.0, 129.6, 128.5, 128.2, 126.3, 124.1, 123.7, 123.3, 116.6, 113.1. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3742, 3653, 2962, 2922, 2842, 2362, 2308, 1658, 1592, 1558, 1470, 1336, 1265, 1226, 1190, 1098, 975, 878, 823, 759. m. p. 200—201 °C. HRMS(ESI), *m*/*z* calcd. for $C_{19}H_{12}NO_4[M+H]^+$: 318.0766; found: 318.0762.

Methyl naphtho[2,1-*b*]furan-2-carboxylate(**3**h): a white solid, yield 73%(164 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.17 (d, *J*=7.8 Hz, 1H), 8.03(s, 1H), 7.97(d, *J*=8.1 Hz, 1H), 7.89(d, *J*=8.7 Hz, 1H), 7.65—7.72(m, 2H), 7.55(t, *J*=8.1 Hz, 1H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 159.0, 152.9, 143.6, 129.4, 128.1, 127.9, 126.2, 124.4, 122.2, 111.9, 111.6, 51.3. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3086, 2954, 2873, 2848, 1732, 1666, 1587, 1552, 1514, 1462, 1436, 1367, 1330, 1284, 1207, 1170, 1155, 1114, 1097, 977, 819, 711. m. p. 95—96 °C. HRMS(ESI), *m*/*z* calcd. for $C_{14}H_{11}O_3[M+H]^+$: 227.0708; found: 227.0708.

Ethyl naphtho[2,1-*b*]furan-2-carboxylate(**3**i)[21]: a white solid, yield 74%(177 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.17(d, *J*=7.5 Hz, 1H), 8.02(s, 1H), 7.97(d, *J*=7.8 Hz, 1H), 7.88(d, *J*=8.4 Hz, 1H), 7.72(d, *J*=8.7 Hz, 1H), 7.62—7.67(m, 2H), 7.57(d, *J*=7.2 Hz, 1H), 4.47(q, *J*=6.3 Hz, 2H), 1.46(t, *J*=6.3, 3H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 158.6, 152.9, 143.8, 128.0, 127.9, 126.2, 124.3, 122.2, 111.7, 60.4, 13.3. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3128, 3084, 3059, 2985, 2939, 2906, 1726, 1585, 1552, 1519, 1442, 1367, 1327, 1280, 1222, 1170, 1124, 1080, 1020, 952, 823, 761, 744. m. p. 91—92 °C. HRMS(ESI), *m*/*z* calcd. for $C_{15}H_{13}O_3[M+H]^+$: 241.0865; found: 241.0865.

Isopropyl naphtho[2,1-*b*]furan-2-carboxylate(**3**j): a dark green solid, yield 74%(187 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.17(d, *J*=8.1 Hz, 1H), 7.93—7.99(m, 2H), 7.86(d, *J*=9.0 Hz, 1H), 7.63—7.71(m, 2H), 7.53(t, *J*=8.1 Hz, 1H), 5.34—5.40(m, 1H), 1.45(d, *J*=6.3 Hz, 6H). ^{13}C NMR($CDCl_3$, 75 MHz), δ: 158.0, 152.8, 144.3, 129.4, 127.9, 126.9, 126.1, 124.2, 122.2, 121.6, 111.7, 111.5, 68.1, 20.9. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3082, 3055, 2978, 2939, 2374, 1936, 1718, 1585, 1552, 1473, 1444, 1355, 1323, 1284, 1220, 1172, 1099, 910, 864, 819, 759, 744; m. p. 75—76 °C. HRMS(ESI), *m*/*z* calcd. for $C_{16}H_{15}O_3[M+H]^+$: 255.1021; found: 255.1020.

1-(Naphtho[2,1-*b*]furan-2-yl)ethanone(**3**k)[22]: a yellow solid, yield 72%(151 mg). ^{1}H NMR($CDCl_3$, 300 MHz), δ: 8.18 (d, *J*=7.5 Hz, 1H), 7.88—7.99(m, 3H), 7.66(t, *J*=9.0 Hz, 2H),

7.58(d, *J*=7.5 Hz, 1H), 2.67(s, 3H). ^{13}C NMR($CDCl_3$, 75 MHz), *δ*: 186.9, 153.2, 151.3, 129.4, 128.9, 128.0, 127.1, 126.3, 124.5, 122.2, 111.7, 110.9, 25.3. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3101, 3061, 2962, 2918, 1672, 1587, 1546, 1521, 1444, 1423, 1359, 1276, 1247, 1170, 1074, 1020, 970, 877, 812, 783, 759, 619. m. p. 109—110 °C. HRMS(ESI), *m*/*z* calcd. for $C_{14}H_{11}O_2[M+H]^+$: 211.0759; found: 211.0759.

(1-Methylnaphtho[2,1-*b*]furan-2-l)phenylmethanone(**3**m): a yellow solid, yield 76%(217 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.51(d, *J*=8.1 Hz, 1H), 8.10(d, *J*=7.2 Hz, 2H), 7.99(d, *J*=7.8 Hz, 1H), 7.89(d, *J*=9.0 Hz, 1H), 7.54—7.66(m, 6H), 3.07(s, 3H). ^{13}C NMR($CDCl_3$, 75 MHz), *δ*: 184.5, 151.9, 147.1, 137.2, 131.3, 129.8, 129.0, 128.7, 128.3, 127.7, 127.2, 126.2 124.0, 122.2, 121.3, 111.7, 11.7. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3053, 2914, 1629, 1583, 1541, 1446, 1396, 1332, 1276, 1240, 1172, 1095, 1028, 995, 923, 860, 806, 717, 690, 619. m. p. 119—120 °C. HRMS(ESI), *m*/*z* calcd. for $C_{20}H_{15}O_2[M+H]^+$: 287.1072; found: 287.1072.

(1-Methylnaphtho[2,1-*b*]furan-2-yl)(*p*-tolyl)methanone(**3**n): a yellow solid, yield 78%(234 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.53(d, *J*=8.1 Hz, 1H), 8.01(d, *J*=7.8 Hz, 3H), 7.91(d, *J*=9.3 Hz, 1H), 7.66(d, *J*=8.7 Hz, 2H), 7.58(d, *J*=7.2 Hz, 1H), 7.35(d, *J*=7.2 Hz, 2H), 3.08(s, 3H), 2.47(s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), *δ*: 184.5, 151.8, 147.2, 142.2, 134.5, 129.8, 128.9, 128.8, 128.4, 128.3, 127.9, 127.3, 126.2, 123.9, 122.2, 111.7, 20.6, 11.7. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3055, 2953, 2916, 2854, 1637, 1608, 1585, 1546, 1438, 1398, 1330, 1274, 1240, 1170, 1095, 1045, 995, 929, 860, 8081, 752, 690, 619. m. p. 128—129 °C. HRMS(ESI), *m*/*z* calcd. for $C_{21}H_{17}O_2[M+H]^+$: 301.1228; found: 301.1228.

(4-Methoxyphenyl)(1-methylnaphtho[2,1-*b*]furan-2-yl)-methanone(**3**o): a white solid, yield 78%(246 mg). ^{1}H NMR ($CDCl_3$, 300 MHz), *δ*: 8.53(d, *J*=8.1 Hz, 1H), 8.15(d, *J*=7.5 Hz, 2H), 8.01(d, *J*=8.1 Hz, 1H), 7.90(d, *J*=8.7 Hz, 1H), 7.67(d, *J*=7.5, 2H), 7.58(d, *J*=7.2 Hz, 1H), 7.04(d, *J*=7.8 Hz, 2H), 3.92(s, 3H), 3.07(s, 3H). ^{13}C NMR($CDCl_3$, 75 MHz), *δ*: 183.2, 162.1, 151.7, 147.4, 131.2, 129.8, 128.6, 128.3, 126.5, 126.1, 123.9, 122.2, 121.6, 112.5, 111.7, 54.4, 11.7. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3066, 3005, 2933, 2837, 1631, 1606, 1548, 1512, 1438, 1409, 1332, 1313, 1261, 1166, 1095, 1028, 993, 929, 842, 804, 763, 738, 690, 621. m. p. 131—132 °C. HRMS(ESI), *m*/*z* calcd. for $C_{21}H_{17}O_3[M+H]^+$: 317.1178; found: 317.1176.

(4-Bromophenyl)(1-methylnaphtho[2,1-*b*]furan-2-yl)-methanone(**3**p): a faint yellow solid, yield 70%(254 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.53(d, *J*=8.1 Hz, 1H), 7.90—8.01(m, 4H), 7.57—7.69(m, 5H), 3.11(s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), *δ*: 183.6, 151.9, 146.7, 135.8, 130.5, 130.3, 129.8, 129.3, 128.4, 128.3, 126.4, 126.3, 124.1, 122.2, 111.6, 11.7. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3064, 2949, 2920, 2852, 1631, 1587, 1541, 1438, 1400, 1330, 1276, 1238, 1174, 1070, 1029, 1010, 927, 860, 835, 798, 750, 684, 615. m. p. 159—160 °C. HRMS(ESI), *m*/*z* calcd. for $C_{20}H_{14}O_2Br[M+H]^+$: 365.0177; found: 365.0177.

Methyl 1-methylnaphtho[2,1-*b*]furan-2-carboxylate(**3**q): a white solid, yield 71%(170 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.46(d, *J*=8.1 Hz, 1H), 7.98(d, *J*=7.8 Hz, 1H), 7.87(d, *J*= 7.8 Hz, 1H), 7.64(t, *J*=7.9 Hz, 2H), 7.56(d, *J*=7.5 Hz, 1H), 4.01(s, 3H), 3.03(s, 3H). ^{13}C NMR($CDCl_3$, 75 MHz), *δ*: 159.9, 151.9, 129.8, 128.6, 128.3, 126.1, 123.8, 121.9, 111.7, 50.9, 11.2. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3022, 2949, 2922, 2846, 1716, 1597, 1570, 1436, 1371, 1330, 1278, 1234, 1193, 1149, 1080, 869, 808, 763, 692, 619. m. p. 119—120 °C. HRMS(ESI), *m*/*z* calcd. for $C_{15}H_{13}O_3[M+H]^+$: 241.0865; found: 241.0865.

Ethyl 1-methylnaphtho[2,1-*b*]furan-2-carboxylate(**3**r): a white solid, yield 73%(185 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.47(d, *J*=8.4 Hz, 1H), 7.98(d, *J*=7.8 Hz, 1H), 7.87(d, *J*=9.0 Hz, 1H), 7.65(t, *J*=6.0 Hz, 2H), 7.53(d, *J*=6.0 Hz, 1H), 4.49(q, *J*=7.2 Hz, 2H), 3.03(s, 3H), 1.47(t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), *δ*: 159.6, 152.0, 129.8, 128.4, 128.3, 128.1, 126.6, 126.0, 123.7, 121.9, 121.7, 121.3, 111.7, 59.9, 13.3, 11.2. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3084, 2978, 2927, 2906, 1710, 1560, 1477, 1367, 1340, 1282, 1226, 1159, 1124, 1083, 1024, 995, 866, 819, 769, 696, 603. m. p. 105—106 °C. HRMS(ESI), *m*/*z* calcd. for $C_{16}H_{15}O_3[M+H]^+$: 255.1021; found: 255.1020.

Isopropyl 1-methylnaphtho[2,1-*b*]furan-2-carboxylate(**3**s): a white solid, yield 73%(195 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.46(d, *J*=8.4 Hz, 1H), 7.97(d, *J*=8.1 Hz, 1H), 7.85(d, *J*= 8.7 Hz, 1H), 7.65(t, *J*=6.1 Hz, 2H), 7.55(d, *J*=7.2 Hz, 1H), 5.32—5.40(m, 1H), 3.01(s, 3H), 1.46(d, *J*=6.0 Hz, 6H). ^{13}C NMR($CDCl_3$, 75 MHz), *δ*: 159.1, 151.8, 139.6, 129.7, 128.2, 126.0, 123.7, 121.9, 111.8, 67.7, 21.0, 11.3. IR(KBr), $\tilde{\nu}$/cm^{-1}: 2989, 2922, 2873, 1705, 1624, 1597, 1568, 1523, 1440, 1409, 1355, 1323, 1282, 1240, 1161, 1107, 1076, 997, 920, 808, 769, 744, 692, 621. m. p. 81—82 °C. HRMS (ESI), *m*/*z* calcd. for $C_{17}H_{17}O_3[M+H]^+$: 269.1178; found: 269.1178.

1-(1-Methylnaphtho[2,1-*b*]furan-2-yl)ethanone(**3**t): a brown solid, yield 70%(156 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.45(d, *J*=7.8 Hz, 1H), 7.98(d, *J*=7.8 Hz, 1H), 7.89(d, *J*=9.0 Hz, 1H), 7.54—7.67(m, 3H), 3.04(s, 3H), 2.66(s, 3H). ^{13}C NMR($CDCl_3$, 75 MHz), *δ*: 190.1, 151.6, 146.9, 136.5, 129.7, 128.9, 128.5, 128.4, 128.3, 126.1, 125.2, 123.9, 122.2, 122.1, 118.8, 111.6, 26.8, 11.1. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3007, 2920, 1959, 1894, 1666, 1622, 1585, 1556, 1444, 1398, 1355, 1327, 1269, 1226, 1134, 997, 948, 860, 806, 744, 686, 638. m. p. 148—149 °C. HRMS(ESI), *m*/*z* calcd. for $C_{15}H_{13}O_2[M+H]^+$: 225.0916; found: 225.0916.

Bis(naphtho[2,1-*b*]furan-2-yl)methanone(**3**u): a yellow solid, yield 79%(285 mg). ^{1}H NMR($CDCl_3$, 300 MHz), *δ*: 8.52(s, 2H), 8.29(d, *J*=7.5 Hz, 2H), 7.97(t, *J*=8.7 Hz, 4H), 7.82(d, *J*=9.0 Hz, 2H), 7.69(t, *J*=7.2 Hz, 2H), 7.57(t, *J*=7.2 Hz, 2H). ^{13}C NMR($CDCl_3$, 75 MHz), *δ*: 170.5, 154.4, 151.4, 130.6, 130.3, 129.1, 128.2, 127.5, 125.6, 123.5, 123.1, 114.9, 112.7. IR(KBr), $\tilde{\nu}$/cm^{-1}: 3134, 3053, 2962, 2922, 2378, 2308, 1620, 1587, 1550, 1332, 1261, 1226, 1170, 1083, 983, 852, 806, 752. m. p. 224—225 °C. HRMS(ESI), *m*/*z* calcd. for $C_{25}H_{15}O_3$ $[M+H]^+$: 363.1021; found: 363.1021.

2.3 X-Ray Structure Determination of Compound 3a

The crystal data of compounds **3**a are listed in Table 1.

Single crystals of compounds **3**a suitable for X-ray structural analysis were respectively obtained from a solution of chloroform and petroleum. The diffraction data were collected at 293(2) K on a Bruker Smart CCDC APEX-2 diffractometer (graphite-monochromated Mo *Kα* radiation, λ=0.071073 nm). The structure was solved *via* the direct method and refined by means of full-matrix least-squares on F^2. All the calculation was performed *via* the SHELXTL crystallographic software package. The CCDC number of compound **3**a is 896103.

Table 1 Crystal data and details of intensity collection and refinement of compound 3a

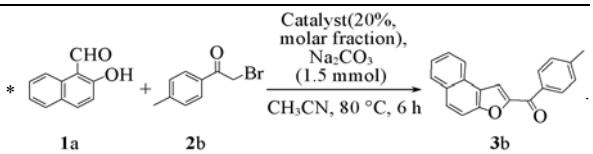
Empirical formula	$C_{19}H_{12}O_2$
Formula weight	272.29
Crystal system, space group	Monoclinic, *C*2/*c*
a/nm	1.9218(3)
b/nm	0.63397(11)
c/nm	2.1980(4)
α/(°)	90
β/(°)	92.285(2)
γ/(°)	90
Volume/nm^3	2.6759(8)
Z	8
Calculated density/(Mg·m^3)	1.352
Absorption coefficient/mm^{-1}	0.087
F(000)	1136
Crystal size	0.18 mm×0.15 mm×0.12 mm
θ range for data collection	1.85°—27.57°
Limiting index	$-24\leqslant h\leqslant 24$, $-8\leqslant k\leqslant 8$, $-28\leqslant l\leqslant 25$
Reflection collected/unique	10962/3072[*R*(int)=0.0219]
Max. and min. transmission	0.9896 and 0.9845
Datum/restraint/parameter	3072/0/191
Goodness-of-fit on F^2	1.037
Final *R* index[$I>2\sigma(I)$]	R_1=0.0394, wR_2=0.1062
R index(all data)	R_1=0.0472, wR_2=0.1128
Extinction coefficient	0.0027(4)
Largest diff. peak and hole/(e·nm^{-3})	251 and –161

3 Results and Discussion

Initially, naphtho[2,1-*b*]furan **3**b was used as a model compound for the exploration of appropriate organic base as catalyst for the cascade reaction between 2-hydroxy-1-naph-thaldehyde and 2-bromo-1-(*p*-tolyl)ethanone(Table 2). A wide range of organic base, including DMAP, quinoline, triethylamine(TEA), pyridine, 3-hydroxyquinuclidine(3-HQD) and DABCO has been used for this reaction as summarized in Table 2. Among those, DMAP gave the best result and was chosen as the catalyst for this reaction.

Table 2 Optimization of catalysts*

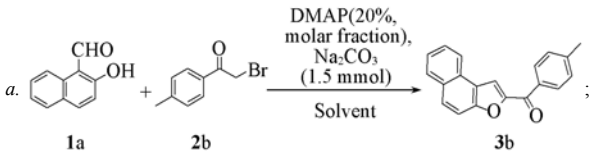
Entry	Catalyst	Isolated yield(%)
1	DMAP	85
2	DABCO	80
3	3-HQD	75
4	Pyridine	40
5	TEA	35
6	Quinoline	40
7	—	—



To determine the optimum reaction conditions, the effects of other reaction parameters such as DMAP loading, solvent, temperature and reaction time were studied. The best results, with respect to reactivity and yield were obtained with 20%(molar fraction) of DMAP in CH_3CN in the presence of Na_2CO_3 at 80 °C for 6 h as summarized in Table 3.

Table 3 Optimization of reaction conditions*a*

Entry	Solvent	Temp./°C	Time/h	Isolated yield(%)
1	DMF	80	8	82
2	DMSO	80	8	75
3	THF	80	8	81
4	H_2O	80	8	71
5	CH_3CN	80	8	86
6	CH_3CN	r.t.	24	10
7	CH_3CN	40	24	40
8	CH_3CN	80	6	85
9	CH_3CN	100	6	84
10*b*	CH_3CN	80	6	78
11*c*	CH_3CN	80	6	85



b. 10%(molar fraction) catalyst was used; *c*. 30%(molar fraction) catalyst was used.

With the optimal reaction conditions in hand, various *α*-halogenated ketones **2** and 2-hydroxy-1-naphthaldehyde or 1-(2-hydroxynaphthalen-1-yl)ethanone were examined to test the scope and limitation of this cascade reaction; the results are summarized in Table 4. Both 2-hydroxy-1-naphthaldehyde and 1-(2-hydroxynaphthalen-1-yl)ethanone were found to yield the desired products, with the former providing relatively higher yields of the products. Among various *α*-halogenated aromatic ketones **2** investigated, higher yields for those with electron-donating group attached on the benzene rings of R_2 were observed(Entries 2 and 3, Table 4). Compared with *α*-bromoacetophenone(Entry 1, Table 4), lower yield for chloroacetophenone was observed(Entry 21, Table 4). In comparison with those halogenated aromatic ketones(Entries 1—5, Table 4), lower yields were observed for halogenated aliphatic ketones(Entries 8—11, Table 4). The reaction was affected significantly by the electronic effect and the steric effect, lower yield was obtained when strongly electron-withdrawing group was at the benzene rings of R_2(Entry 6, Table 4), and no product was detected when 1-bromo-3,3-dimethylbutan-2-one was used as substrate(Entry 12, Table 4).

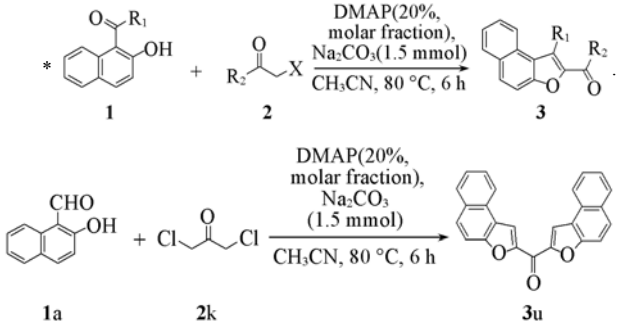
Interestingly, when 1,3-dichloroacetone was used for this reaction, compound **3**u with two naphthofuran rings attached was obtained in 79% yield under the optimized reaction conditions(Scheme 1).

The structure of product **3**a was confirmed by X-ray crystallographic analysis as shown in Fig.1.

On the basis of our experimental results and literature

Table 4 Scope of the DMAP-catalyzed cascade reaction for the formation of naphtho-furan derivatives*

Entry	R_2	X	R_1	Product	Isolated yield(%)
1	C_6H_5	Br	H	**3**a	78
2	4-$CH_3C_6H_4$	Br	H	**3**b	85
3	4-$CH_3OC_6H_4$	Br	H	**3**c	80
4	4-BrC_6H_4	Br	H	**3**d	72
5	4-ClC_6H_4	Br	H	**3**e	71
6	4-$NO_2C_6H_4$	Br	H	**3**f	60
7	2-Naphthyl	Br	H	**3**g	88
8	CH_3O	Br	H	**3**h	73
9	CH_3CH_2O	Br	H	**3**i	74
10	^{i}PrO	Br	H	**3**j	74
11	CH_3	Br	H	**3**k	72
12	^{t}Bu	Br	H	**3**l	0
13	C_6H_5	Br	CH_3	**3**m	76
14	4-$CH_3C_6H_4$	Br	CH_3	**3**n	78
15	4-$CH_3OC_6H_4$	Br	CH_3	**3**o	78
16	4-BrC_6H_4	Br	CH_3	**3**p	70
17	CH_3O	Br	CH_3	**3**q	71
18	CH_3CH_2O	Br	CH_3	**3**r	73
19	^{i}PrO	Br	CH_3	**3**s	73
20	CH_3	Br	CH_3	**3**t	70
21	C_6H_5	Cl	CH_3	**3**m	72



Scheme 1 DMAP-catalytzed cascade reaction for the formation of dinaphtho[2,1-*b*]furan-2-yl methanone(3u)

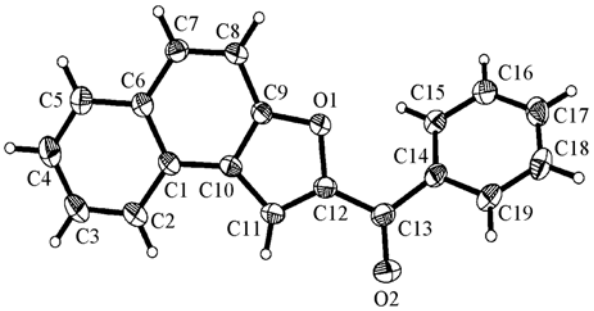
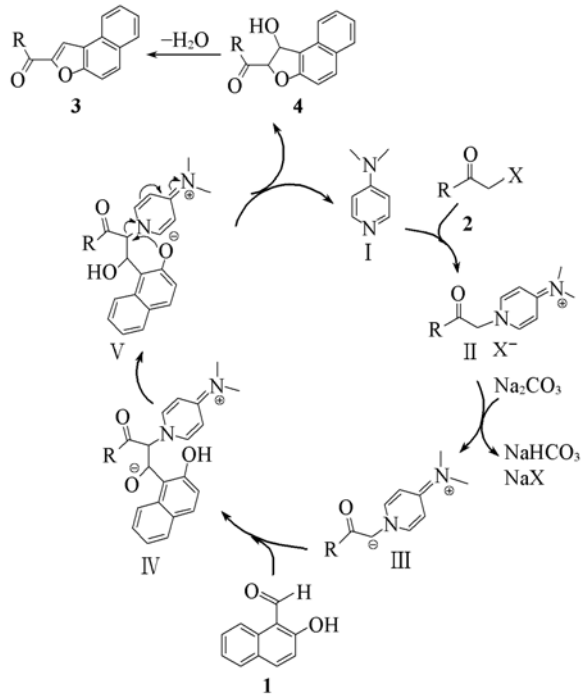


Fig.1 X-Ray crystal structure of compound 3a

reports[17,18,23], a plausible mechanism for the formation of naphtho[2,1-*b*]furans was proposed as shown in Scheme 2. Initially, the catalyst I displaces the halogen of compound **2** to generate the corresponding ammonium salt II. Subsequent nucleophilic attack at the carbonyl group of salicylaldehyde **1** by the enolate form of the ammoniumylide III generates the intermediate IV, which undergoes proton-transfer to generate the intermediate V. Subsequent intramolecular nucleophilic addition within intermediate V generates the key precursor **4**, which will be subjected to a dehydration process to give the desired target **3** and regenerate catalyst I.



Scheme 2 Plausible mechanism for the synthesis of naphthofuran derivatives

4 Conclusions

An efficient DMAP-catalyzed cascade reaction for the synthesis of naphthofurans with good yields from easily available 2-hydroxy-1-naphthaldehyde and *α*-halogenated ketones was developed. The reaction presented here provides a new strategy for the synthesis of naphthofurans under mild reaction conditions and with high catalytic efficiency, which offers an efficient approach for the preparation of synthetic and medicinal furan derivatives.

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