The N-Heterocyclic Carbene Catalyzed Nucleophilic Substitution Reaction for Construction of Benzopyrones and Benzofuranones

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General Information

The ¹H and ¹³C NMR data were recorded on a Mercury Plus-300 or a Bruker-400 MHz spectrometer. The chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. IR spectra were recorded on a Nicolet 670 FTIR spectrophotometer and reported in wavenumbers (cm^{-1}). Mass spectral (MS) data were obtained on a V.G.ZAB-HS mass spectrometer. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEX II 47e mass spectrometer. Column chromatography was generally performed on silica gel (200—300 mesh) and TLC inspections were on silica gel GF254 plates.

Xylene was purchased at analytical pure and stored over molecular sieves, if not noted especially below, other solvents were purified and dried by standard methods

prior to use. DBU was purchased from commercial suppliers and used without further treatment. Thiazolium salts and imidazolium salt were synthesized according to the literature procedure.

General Procedure

Preparation of pre-substrates:

Salicylaldehyde (1.22 g, 10 mmol) was added dropwise over 15 min to a vigorously stirred solution of sodium hydroxide (0.4 g, 10 mmol) in water (10 ml), and then 2-chloroethanol (0.81 g, 10 mmol) was added dropwise and the resulting solution was heated at 98 °C for 16 h. The solution was cooled and maintained at about 10 °C while sodium hydroxide was added until the solution was strongly alkaline (PH=10). The reaction mixture was extracted with dichloromethane (4*20ml). The combined organic layers were dried (MgSO₄) and filtered, concentrated in vacuo, the residue was chromatographed using 5:1 petroleum ether/ EtOAc to afford 1.262 g (76%) of corresponding 2-(2-hydroxyethoxy)benzaldehyde as a yellow oil.

Other precursors of substrates were generated in the same way as above from salicylaldehyde counterpart and corresponding α -halogenated alcohol.

Synthesis of benzopyrone product (5):

A round-bottomed flask was charged with DBU (53 mg, 0.35 mmol) in 25 ml xylene, and thiazolium salt 1 (36 mg, 0.125 mmol) was added, the resulting mixture was stirred intensely at 50 °C for 15 min, and then substrate 4 (160 mg, 0.5 mmol) was added. The reaction mixture was stirred 4 h at reflux temperature. The solvent was removed under ordinary pressure, the residue was chromatographed using 2:1 dichloromethane/petroleum ether to afford 53 mg (72%) of chromanone 5 as a yellow

oil.

Synthesis of other benzopyrones and benzofuranones were following this general procedure as above.

Experimental Data

chromanone (**5**):

^1H NMR (300 MHz, CDCl_3) δ 7.90 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.48-7.45 (m, 1H), 7.05-6.96 (m, 2H), 4.54 (t, $J = 6.5$ Hz, 2H), 2.82 (t, $J = 6.5$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 191.8, 161.8, 135.9, 127.1, 121.3, 117.8, 66.9, 37.7; IR (KBr) 1688, 1647, 1602, 1475, 1457, 1036 cm^{-1} ; Ms m/z (%) 148 (M^+ , 53), 120 (100), 92 (60), 64 (14), 63 (16).

2, 3-dihydro-6-methoxychromen-4-one (**8**):

The reaction mixture was chromatographed using 2:1 dichloromethane/petroleum ether to afford 67 mg (75%) of the indicated compound as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.31 (d, $J = 3.3$ Hz, 1H), 7.08 (dd, $J = 9.0, 3.3$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 4.49 (t, $J = 6.3$ Hz, 2H), 3.81 (s, 3H), 2.79 (t, $J = 6.3$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 191.9, 156.6, 153.9, 125.2, 121.1, 119.2, 107.3, 67.1, 55.8, 37.7; IR (KBr) 1685, 1490, 1282, 1035 cm^{-1} ; Ms m/z (%) 178 (M^+ , 48), 150 (100), 135 (29), 107 (36), 79 (38).

6-bromo-2, 3-dihydrochromen-4-one (**10**):

The reaction mixture was chromatographed using 3:1 dichloromethane/petroleum ether to afford 86 mg (76%) of the indicated compound as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 8.8, 1.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.53 (t, J = 6.4 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.4, 160.7, 138.6, 129.6, 122.5, 119.9, 114.1, 67.1, 37.4; IR (KBr) 1693, 1598, 1474, 1273, 1028 cm^{-1} ; Ms m/z (%) 228 (M^+ , 58), 226 (M^+ , 58), 200 (62), 198 (70), 172 (51), 170 (46), 91 (18), 86 (25), 84 (44), 63 (100).

2, 3-dihydro-7-methoxychromen-4-one (**12**):

The reaction mixture was chromatographed using 3:1 dichloromethane/petroleum ether to afford 43 mg (48%) of the indicated compound as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (d, J = 9.0 Hz, 1H), 6.57 (dd, J = 8.7, 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 4.50 (t, J = 6.6 Hz, 2H), 3.82 (s, 3H), 2.74 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 190.5, 165.9, 163.8, 128.8, 115.2, 109.9, 100.7, 67.3, 55.6, 37.4; IR (KBr) 1679, 1608, 1256, 1158, 1116 cm^{-1} ; Ms m/z (%) 178 (M^+ , 69), 150 (100), 122 (97), 107 (64), 79 (36), 63 (26).

2-methyl-2-phenylbenzofuran-3(2H)-one (**16**):

The reaction mixture was chromatographed using 20:1 petroleum ether/EtOAc to afford 92 mg (82%) of the indicated compound as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.69-7.59 (m, 4H), 7.39-7.31 (m, 3H), 7.24 (d, J = 8.1 Hz, 1H), 7.12-7.09 (m, 1H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.5, 171.1, 138.1, 138.0, 128.5, 128.0, 125.1, 124.6, 122.0, 119.3, 113.2, 89.4, 24.2; IR (KBr) 1720, 1611, 1462, 1322, 1254, 756 cm^{-1} ; Ms m/z (%) 224 (M^+ , 100), 223 (32), 209 (16), 195 (48), 121 (69), 103 (72), 94 (74), 77 (76); HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{13}\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 225.0910, found

225.0912.

5-methoxy-2-methyl-2-phenylbenzofuran-3(2H)-one (**19**):

The reaction mixture was chromatographed using 20:1 petroleum ether/EtOAc to afford 102 mg (80%) of the indicated compound as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.57 (dd, $J = 8.1, 1.4$ Hz, 2H), 7.36-7.27 (m, 4H), 7.15 (d, $J = 8.7$ Hz, 1H), 7.04 (d, $J = 3.0$ Hz, 1H), 3.78 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.8, 166.5, 155.0, 138.3, 128.5, 128.2, 128.0, 124.6, 119.2, 114.2, 104.6, 90.2, 55.8, 24.2; IR (KBr) 1712, 1489, 1441, 1276, 1224, 1027, 747 cm^{-1} ; Ms m/z (%) 254 (M^+ , 59), 253 (26), 151 (96), 124 (62), 109 (29), 103 (67), 84 (58), 77 (100), 63 (66), 51 (63); HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$ 255.1021, found 255.1026.

5-bromo-2-methyl-2-phenylbenzofuran-3(2H)-one (**21**):

The reaction mixture was chromatographed using 20:1 petroleum ether/EtOAc to afford 130 mg (86%) of the indicated compound as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.78-7.71 (m, 2H), 7.56-7.53 (m, 2H), 7.36-7.33 (m, 3H), 7.14 (d, $J = 9.0$ Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 200.1, 169.9, 140.7, 137.6, 128.6, 128.3, 127.6, 124.6, 121.2, 115.1, 114.5, 90.6, 24.3; IR (KBr) 1727, 1605, 1462, 1273, 1160, 820, 699 cm^{-1} ; Ms m/z (%) 304 (M^+ , 11), 302 (M^+ , 11), 223 (23), 201 (16), 199 (16), 174 (17), 172 (23), 103 (100), 77 (84), 63 (53); HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{12}\text{BrO}_2$ $[\text{M}+\text{H}]^+$ 303.0020, found 303.0016.

2-(4-chlorophenyl)-6-methoxy-2-methylbenzofuran-3(2H)-one (**23**):

The reaction mixture was chromatographed using 20:1 petroleum ether/EtOAc to afford 103 mg (71%) of the indicated compound as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, $J = 8.6, 7.8$ Hz, 1H), 7.50 (d, $J = 7.4$ Hz, 2H), 7.32 (dd, $J = 8.4, 1.2$ Hz, 2H), 6.68-6.63 (m, 2H), 3.91 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.8, 173.6, 168.7, 137.2, 134.1, 128.6, 126.3, 126.2, 112.2, 112.0, 96.2, 89.9, 55.9, 24.5; IR (KBr) 1709, 1613, 1493, 1443, 1287, 1202, 831 cm^{-1} ; Ms m/z (%) 290 (M^+ , 7), 288 (M^+ , 21), 151 (100), 134 (46), 124 (31), 106 (49), 75 (34), 63 (88); HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{14}\text{ClO}_3$ $[\text{M}+\text{H}]^+$ 289.0631, found 289.0625.

2-(4-chlorophenyl)-2-methylbenzofuran-3(2H)-one (**25**):

The reaction mixture was chromatographed using 20:1 petroleum ether/EtOAc to afford 100 mg (77%) of the indicated compound as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.69-7.64 (m, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 9.0$ Hz, 1H), 7.10 (t, $J = 7.2$ Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.1, 171.0, 138.4, 136.7, 134.1, 128.7, 126.2, 125.2, 122.3, 119.2, 113.4, 88.9, 24.4; IR 1721, 1611, 1482, 1091, 757 cm^{-1} ; Ms m/z (%) 260 (M^+ , 11), 258 (M^+ , 35), 139 (36), 137 (38), 121 (100), 94 (93), 76 (60); HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{13}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 259.0526, found 259.0530.