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Supporting Information for

Effect of Catalytic Alkali Metal Bromide on Hofmann-Type Rearrangement of Imides

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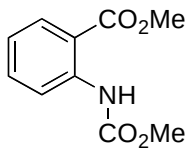
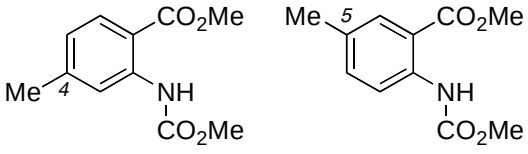
1. General Methods. ^{1}H NMR spectra were measured on a JEOL ECS-400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; sep = septet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra were recorded by Thermo Fisher Scientific Exactive Orbitrap mass spectrometers. Infrared (IR) spectra were recorded on a JASCO FT/IR 4100 spectrometer. Single crystal X-ray diffraction data were collected at 173K on a Bruker SMART APEX II CCD diffractometer with Mo Kα (λ = 0.71073) radiation and graphite monochromator. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. The products were purified by neutral column chromatography on silica gel (Kanto Chemical Co., Inc. silica gel 60N, Prod. No. 37560-84; Merck silica gel 60, Prod. No. 1.09385.9929). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. In experiments that required dry methanol was distilled in prior to use.

2. General procedure for the Hofmann-type rearrangement of imides (1) using alkali metal bromide (Table 1, entry 14).

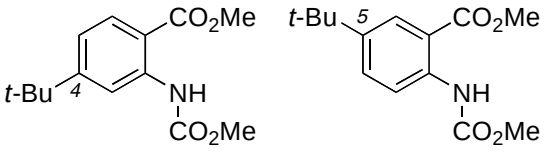
To the solution of phthalimide **1a** (36.8 mg, 0.25 mmol) in MeOH (2 mL) were added KBr (6.0 mg, 0.05 mmol), DBU (110.0 μL, 0.75 mmol), and *t*-BuOCl (84.8 μL, 0.75 mmol), and stirred at 60 ºC for 7 h under argon atomosphere. Saturated $NaHCO_3$ aqueous solution (10 mL) was added to the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed by brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: hexane/AcOEt = 5/1), to give the desired product **2a** (49.2 mg, 96% yield).



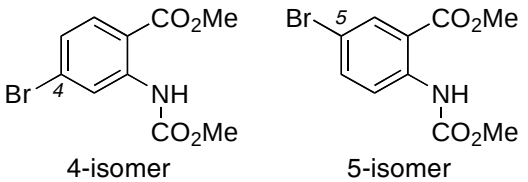
Methyl 2-((methoxycarbonyl)amino)benzoate (2a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.92 (s, 3H), 7.03 (td, *J* = 8.2, 1.2 Hz, 1H), 7.53 (td, *J* = 8.0, 1.6 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.43 (dd, *J* = 8.2, 1.2 Hz, 1H), 10.51 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2 (2C), 114.5, 118.8, 121.5, 130.8, 134.6, 141.7, 154.1, 168.5. IR (neat) 3299, 1740, 1690, 1600, 1535, 1459, 1272 cm^{-1}. MS (APCI) calcd for $C_{10}H_{12}NO_4$ $[M+H]^+$ 210.0761, found 210.0761.



Methyl 2-((methoxycarbonyl)amino)-methylbenzoate (2b, 4- and 5-isomers): In Scheme 2, 4-:5- = 38:62. The 4-isomer and 5-isomer were separeted by recrystallization. 4-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 6.84 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 8.26 (s, 1H), 10.51 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 52.1, 52.2, 112.0, 119.1, 122.6, 130.8, 141.7, 145.7, 154.1, 168.5. 5-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.78 (s, 3H), 3.91 (s, 3H), 7.34 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 10.36 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 52.2 (2C), 114.4, 118.8, 130.9, 131.0, 135.3, 139.3, 154.1, 168.5. IR (KBr) 3273, 1740, 1688, 1594, 1533, 1440, 1249 cm^{-1}. MS (APPI) calcd for $C_{11}H_{13}NO_4$ $[M]^+$ 223.0839, found 223.0841.

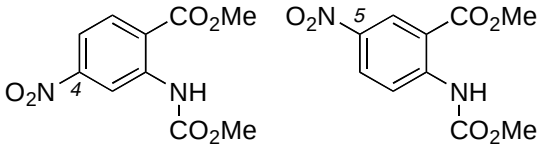


Methyl *tert*-butyl-2-((methoxycarbonyl)amino)benzoate (2c, 4- and 5-isomers): In Scheme 2, 4-:5- = 42:58. 4-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 3.79 (s, 3H), 3.89 (s, 3H), 7.05 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.91 (t, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 1.8 Hz, 1H), 10.52 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8 (3C), 35.3, 52.1 (2C), 111.8, 115.7, 118.8, 130.5, 141.6, 154.1, 158.5, 168.3. 5-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.77 (s, 3H), 3.91 (s, 3H), 7.57 (dd, *J* = 9.1, 2.5 Hz, 1H), 8.00 (d, *J* = 2.5 Hz, 1H), 8.34 (d, *J* = 9.1 Hz, 1H), 10.39 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1 (3C), 34.1, 52.0 (2C), 114.1, 118.6, 127.1, 131.8, 139.2, 144.3, 154.1, 168.5. IR (neat) 3302, 1739, 1693, 1582, 1524, 1438, 1260 cm^{-1}. MS (APCI) calcd for $C_{14}H_{20}NO_4$ $[M+H]^+$ 266.1387, found 266.1377.



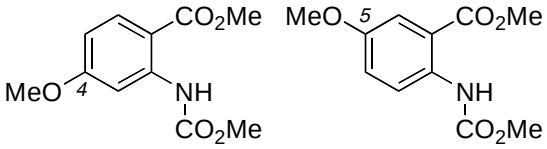
Methyl bromo-2-((methoxycarbonyl)amino)benzoate (2d, 4- and 5-isomers): In Scheme 2, 4-:5- = 47:53. 4-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.91 (s, 3H), 7.16 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 10.53 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 52.5, 113.1, 121.7, 124.8, 129.6, 131.9, 142.6, 153.9, 168.0. 5-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.92 (s, 3H), 7.61 (dd, *J* = 9.1, 2.5 Hz, 1H), 8.12 (d, *J* = 2.5 Hz, 1H), 8.36 (d, *J* = 9.1 Hz, 1H), 10.42 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.40,

52.45, 113.8, 116.0, 120.5, 133.3, 137.3, 140.8, 153.8, 167.3. IR (KBr) 3259, 1739, 1689, 1593, 1519, 1433, 1249 cm^{-1}. MS (APPI) calcd for $C_{10}H_{10}BrNO_4$ $[M]^+$ 286.9788, found 286.9789.



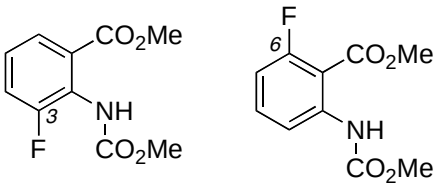
4-isomer 5-isomer

Methyl 2-((methoxycarbonyl)amino)nitrobenzoate (2e, 4- and 5-isomers): In Scheme 2, 4-:5- = 46:54. The 4-isomer and 5-isomer were separeted by column chromatography. 4-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.99 (s, 3H), 7.82 (dd, *J* = 8.9, 2.1 Hz, 1H), 8.17 (d, *J* = 8.9 Hz, 1H), 9.35 (d, *J* = 2.1 Hz, 1H), 10.57 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 53.0, 113.8, 115.6, 118.7, 132.1, 142.7, 151.3, 153.7, 167.0. 5-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 4.00 (s, 3H), 8.37 (dd, *J* = 9.4, 2.8 Hz, 1H), 8.67 (d, *J* = 9.4 Hz, 1H), 8.91 (d, *J* = 2.8 Hz, 1H), 10.87 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9, 53.0, 114.1, 118.8, 127.0, 129.3, 141.2, 146.9, 153.5, 167.0. IR (KBr) 3263, 1751, 1692, 1516, 1439, 1352, 1251 cm^{-1}. MS (APCI) calcd for $C_{10}H_9N_2O_6$ $[M–H]^–$ 253.0455, found 253.0463.



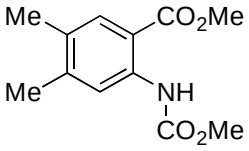
4-isomer 5-isomer

Methyl methoxy-2-((methoxycarbonyl)amino)benzoate (2f, 4- and 5-isomers): In Scheme 2, 4-:5- = 21:79. The 4-isomer and 5-isomer were separeted by column chromatography. 4-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.869 (s, 3H), 3.873 (s, 3H), 6.55 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 2.7 Hz, 1H), 10.72 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 52.2, 55.4, 102.3, 107.1, 109.0, 132.4, 143.9, 154.1, 164.5, 168.3. 5-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.81 (s, 3H), 3.92 (s, 3H), 7.12 (dd, *J* = 9.2, 3.2 Hz, 1H), 7.49 (d, *J* = 3.2 Hz, 1H), 8.33 (d, *J* = 9.2 Hz, 1H), 10.19 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 52.3, 55.6, 114.4, 115.4, 120.4, 121.3, 135.4, 153.8, 154.2, 168.1. IR (KBr) 3258, 1740, 1687, 1598, 1533, 1431, 1278 cm^{-1}. MS (APPI) calcd for $C_{11}H_{13}NO_5$ $[M]^+$ 239.0788, found 239.0790.

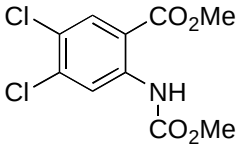


3-isomer 6-isomer

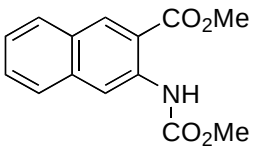
Methyl fluoro-2-((methoxycarbonyl)amino)benzoate (2g, 3- and 6-isomers): In Scheme 2, 3-:6- = 68:32. The 3-isomer and 6-isomer were separeted by column chromatography. 3-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.92 (s, 3H), 7.18 (td, *J* = 8.2, 5.0 Hz, 1H), 7.33 (t, *J* = 8.2 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.38 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 52.7, 106.0 (d, $J_{C–F}$ = 14.4 Hz), 110.1 (d, $J_{C–F}$ = 24.0 Hz), 114.8 (d, $J_{C–F}$ = 3.8 Hz), 134.4 (d, $J_{C–F}$ = 10.5 Hz), 141.8 (d, $J_{C–F}$ = 2.9 Hz), 153.9, 162.2 (d, $J_{C–F}$ = 258.7 Hz), 167.1 (d, $J_{C–F}$ = 3.8 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -116.5. 6-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.96 (s, 3H), 6.79 (ddd, *J* = 11.0, 8.2, 1.2 Hz, 1H), 7.45 (td, *J* = 8.7, 6.1 Hz, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 9.96 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 52.9, 120.9 (d, $J_{C–F}$ = 21.1 Hz), 123.7 (d, $J_{C–F}$ = 1.9 Hz), 125.1 (d, $J_{C–F}$ = 8.6 Hz), 125.9 (d, $J_{C–F}$ = 3.8 Hz), 127.5 (d, $J_{C–F}$ = 13.4 Hz), 154.0, 156.2 (d, $J_{C–F}$ = 252.9 Hz), 166.8 (d, $J_{C–F}$ = 3.8 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.4. IR (KBr) 3345, 1739, 1702, 1512, 1445, 1280, 1238 cm^{-1}. MS (APPI) calcd for $C_{10}H_{10}NO_4F$ $[M]^+$ 227.0588, found 227.0579.



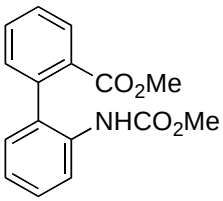
Methyl 2-((methoxycarbonyl)amino)-4,5-dimethylbenzoate (2h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.30 (s, 3H), 3.77 (s, 3H), 3.89 (s, 3H), 7.74 (s, 1H), 8.21 (s, 1H), 10.36 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 20.5, 52.0, 52.1, 112.2, 119.7, 129.9, 131.3, 139.6, 144.4, 154.1, 168.5. IR (KBr) 3253, 1733, 1690, 1592, 1524, 1432, 1226 cm^{-1}. MS (APPI) calcd for $C_{12}H_{15}NO_4$ $[M]^+$ 237.0096, found 237.0096.



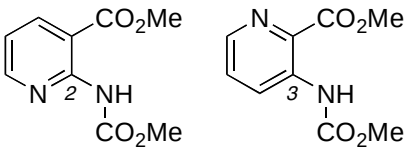
Methyl 4,5-dichloro-2-((methoxycarbonyl)amino)benzoate (2i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.93 (s, 3H), 8.07 (s, 1H), 8.66 (s, 1H), 10.43 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 52.7, 114.0, 120.5, 125.1, 132.0, 139.0, 140.7, 153.7, 166.9. IR (KBr) 3256, 1736, 1694, 1580, 1503, 1311, 1220 cm^{-1}. MS (APPI) calcd for $C_{10}H_9Cl_2NO_4$ $[M]^+$ 276.9903, found 276.9903.



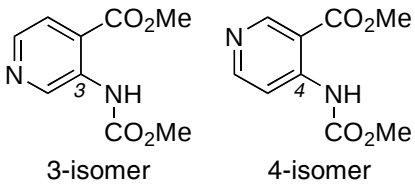
Methyl 3-((methoxycarbonyl)amino)-2-naphthoate (2j): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.97 (s, 3H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 8.59 (s, 1H), 8.79 (s, 1H), 10.42 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 52.5, 115.4, 115.5, 125.1, 127.4, 127.9, 128.9, 129.2, 133.2, 136.4, 136.6, 154.3, 168.4. IR (KBr) 3295, 1733, 1696, 1547, 1448, 1292, 1213 cm^{-1}. MS (APPI) calcd for $C_{14}H_{13}NO_4$ $[M]^+$ 259.0839, found 259.0839.



Methyl 2'-((methoxycarbonyl)amino)-[1,1'-bipheyl]-2-carboxylate (3k): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.67 (s, 3H), 6.30 (brs, 1H), 7.66 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.11 (td, *J* = 8.5, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.37 (td, *J* = 8.5, 1.7 Hz, 1H), 7.49 (td, *J* = 7.8, 1.4 Hz, 1H), 7.58 (td, *J* = 7.8, 1.4 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.93-8.06 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 52.2, 120.3, 123.3, 128.2, 128.4, 129.2, 130.4, 131.1, 131.5, 131.9, 132.1, 135.0, 138.5, 154.1, 167.6. IR (neat) 3427, 1728, 1523, 1294, 1229, 1068 cm^{-1}. MS (APPI) calcd for $C_{16}H_{15}NNaO_4$ $[M+Na]^+$ 308.0893, found 308.0887.

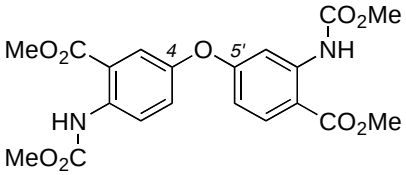


Methyl ((methoxycarbonyl)amino)pyridinecarboxylate (2l, 2- and 3-isomers): In Scheme 2, 2-:3- = 40:60. The 2-isomer and 3-isomer were separeted by column chromatography. 2-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.95 (s, 3H), 7.03 (dd, *J* = 8.0, 4.8 Hz, 1H), 8.30 (dd, *J* = 8.0, 1.9 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.9 Hz, 1H), 10.42 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 52.6, 110.6, 117.5, 139.8, 152.1, 152.6, 153.3, 167.0. 3-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.03 (s, 3H), 7.49 (dd, *J* = 8.8, 4.4 Hz, 1H), 8.36 (dd, *J* = 4.4, 1.5 Hz, 1H), 8.86 (dd, *J* = 8.8, 1.5 Hz, 1H), 10.43 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 53.1, 127.0, 128.2, 131.3, 139.4, 142.8, 154.0, 167.7. IR (KBr) 3258, 1752, 1685, 1593, 1523, 1331, 1239 cm^{-1}. MS (APPI) calcd for $C_9H_{11}N_2O_4$ $[M+H]^+$ 211.0713, found 211.0708.

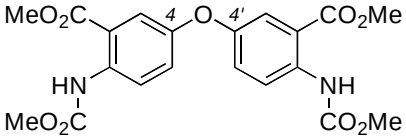


Methyl ((methoxycarbonyl)amino)nicotinate (2m, 3- and 4-isomers): In Scheme 2, 3-:4- =

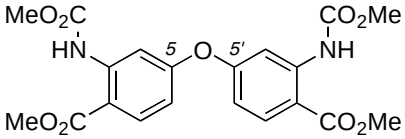
28:72. The 3-isomer and 4-isomer were separeted by column chromatography. 3-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.97 (s, 3H), 8.35 (d, *J* = 6.0 Hz, 1H), 8.58 (d, *J* = 6.0 Hz, 1H), 9.12 (s, 1H), 10.59 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 52.8, 110.3, 112.2, 148.1, 152.5, 153.4, 154.3, 167.8. 4-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.97 (s, 3H), 7.76 (d, *J* = 5.2 Hz, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 9.78 (s, 1H), 10.05 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 52.9, 120.3, 122.5, 136.3, 142.5, 143.0, 153.6, 167.2. IR (KBr) 3255, 1743, 1695, 1597, 1519, 1442, 1302, 1229 cm^{-1}. MS (APPI) calcd for $C_9H_{11}N_2O_4$ $[M+H]^+$ 211.0713, found 211.0712.



4,5'-isomer

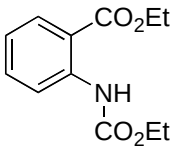


4,4'-isomer

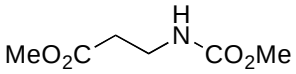


5,5'-isomer

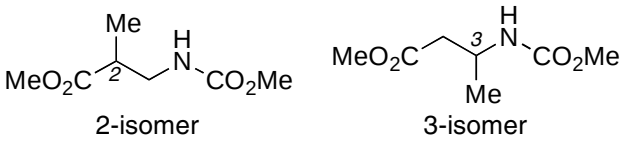
Dimethyl oxybis(2-((methoxycarbonyl)amino)benzoate) (2o, 4,5'-, 4,4'-, and 5,5'-isomers): In Scheme 2, 4,5'-:4,4'-:5,5'- = 53:20:37. 4,5'-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.80 (s, 3H), 3.89 (s, 6H), 6.53 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.29 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.73 (d, *J* = 3.0 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 2.5 Hz, 1H), 8.48 (d, *J* = 9.0 Hz, 1H), 10.42 (brs, 1H), 10.64 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.26 (2C), 52.29, 52.4, 106.8, 108.8, 110.1, 112.1, 120.5, 122.4, 127.0, 132.8, 138.6, 143.8, 148.7, 153.8 (2C), 162.9, 167.6, 168.0. 4,4'-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 6H), 3.90 (s, 6H), 6.69 (dd, *J* = 8.9, 2.3 Hz, 2H), 8.01 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 2.3 Hz, 2H), 10.64 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1 (2C), 52.4 (2C), 109.0 (2C), 110.1 (2C), 115.7 (2C), 132.9 (2C), 143.8 (2C), 154.0 (2C), 160.9 (2C), 168.0 (2C). 5,5'-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 6H), 3.88 (s, 6H), 7.21 (dd, *J* = 9.2, 3.0 Hz, 2H), 7.59 (d, *J* = 3.0 Hz, 2H), 8.41 (d, *J* = 9.2 Hz, 2H), 10.33 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1 (2C), 52.3 (2C), 110.1 (2C), 120.2 (2C), 120.6 (2C), 125.2 (2C), 137.5 (2C), 151.0 (2C), 154.1 (2C), 167.7 (2C). IR (KBr) 3290, 1741, 1694, 1595, 1526, 1436, 1249 cm^{-1}. MS (APCI) calcd for $C_{20}H_{21}N_2O_9$ $[M+H]^+$ 433.1242, found 433.1239.



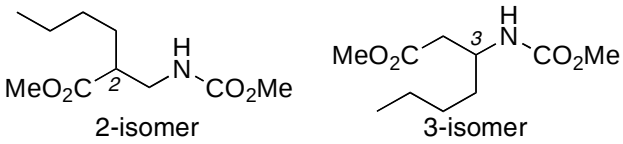
Ethyl 2-((ethoxycarbonyl)amino)-benzoate (2m): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 7.02 (td, *J* = 8.0, 1.2 Hz, 1H), 7.52 (td, *J* = 8.7, 1.6 Hz, 1H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.44 (dd, *J* = 8.7, 1.2 Hz, 1H), 10.51 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.5, 61.1, 61.2, 114.7, 118.7, 121.3, 130.8, 134.4, 141.9, 153.7, 168.1. IR (neat) 3256, 1727, 1693, 1595, 1533, 1452, 1244 cm^{-1}. MS (APPI) calcd for $C_{12}H_{15}NO_4$ $[M]^+$ 237.0096, found 237.0096.



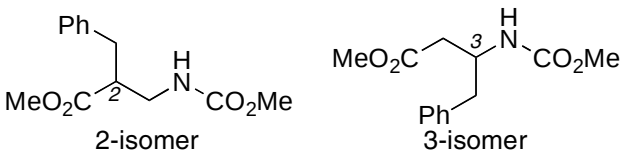
***N*-(Methoxycarbonyl)-β-alanine methyl ester (4a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (t, *J* = 6.1 Hz, 2H), 3.45 (q, *J* = 6.1 Hz, 2H), 3.66 (s, 3H), 3.70 (s, 3H), 5.23 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 36.5, 51.8, 52.1, 156.9, 172.8. IR (neat) 3346, 1725, 1533, 1441, 1256 cm^{-1}. MS (ESI) calcd for $C_6H_{11}NO_4Na$ $[M+Na]^+$ 184.0580, found 184.0580.



Methyl ((methoxycarbonyl)amino)-methyl propanoate (4b, 2- and 3-isomers): In Table 3, 2-:3- = 31:69. 2-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7.3 Hz, 3H), 2.67-2.75 (m, 1H), 3.26-3.42 (m, 2H), 3.66 (s, 3H), 3.70 (s, 3H), 5.24 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 39.8, 43.3, 51.7, 52.0, 157.0, 175.6. 3-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.8 Hz, 3H), 2.48-2.58 (m, 2H), 3.66 (s, 3H), 3.69 (s, 3H), 4.01-4.18 (m, 1H), 5.07 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 40.2, 44.0, 51.5, 51.9, 156.1, 171.8. IR (neat) 3342, 1727, 1532, 1440, 1255 cm^{-1}. MS (ESI) calcd for $C_7H_{14}NO_4$ $[M+H]^+$ 176.0917, found 176.0920.

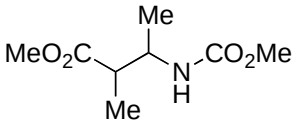


Methyl butyl-((methoxycarbonyl)amino) propanoate (4c, 2- and 3-isomers): In Table 3, 2-:3- = 41:59. 2-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.24-1.39 (m, 4H), 1.44-1.56 (m, 2H), 2.57-2.67 (m, 1H), 3.25-3.34 (m, 1H), 3.37-3.46 (m, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 5.14 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.4, 28.2, 29.1, 42.0, 45.4, 51.7, 52.0, 157.0, 175.5. 3-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.24-1.39 (m, 5H), 1.56-1.67 (m, 1H), 2.54 (t, *J* = 5.2 Hz, 2H), 3.66 (s, 3H), 3.68 (s, 3H), 3.89-4.00 (m, 1H), 5.19 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.3, 29.3, 34.0, 38.8, 48.0, 51.6, 51.9, 156.4, 172.0. IR (neat) 3342, 1729, 1533, 1441, 1254 cm^{-1}. MS (ESI) calcd for $C_{10}H_{20}NO_4$ $[M+H]^+$ 218.1387, found 218.1389.

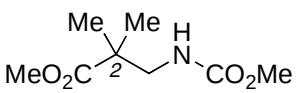


Methyl benzyl-((methoxycarbonyl)amino) propanoate (4d, 2- and 3-isomers): In Table 3,

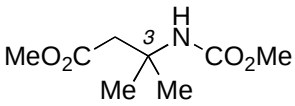
2-:3- = 27:73. 2-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77-2.84 (m, 1H), 2.90-2.99 (m, 2H), 3.27-3.35 (m, 1H), 3.36-3.46 (m, 1H), 3.61 (s, 3H), 3.65 (s, 3H), 5.32 (brs, 1H), 7.12-7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 41.7, 47.0, 51.6, 51.9, 126.4, 128.3(2C), 128.6(2C), 138.0, 156.1, 174.4. 3-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42-2.55 (m, 2H), 2.77-2.84 (m, 1H), 2.90-2.99 (m, 1H), 3.61 (s, 3H), 3.63 (s, 3H), 4.16-4.25 (m, 1H), 5.43 (brs, 1H), 7.12-7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 40.0, 49.2, 51.5, 51.8, 126.5, 128.3(2C), 129.1(2C), 137.4, 156.8, 171.8. IR (neat) 3341, 1728, 1532, 1442, 1259 cm^{-1}. MS (ESI) calcd for $C_{13}H_{18}NO_4$ $[M+H]^+$ 252.1230, found 252.1230.



Methyl 3-((methoxycarbonyl)amino)-2-methylbutanoate (4e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 7.3 Hz, 3H), 2.59-2.68 (m, 1H), 3.36 (s, 3H), 3.70 (s, 3H), 3.85-3.98 (m, 1H), 5.36 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.3, 43.9, 48.8, 51.6, 51.9, 156.6, 175.5. IR (neat) 3336, 1724, 1530, 1453, 1246 cm^{-1}. MS (ESI) calcd for $C_8H_{16}NO_4$ $[M+H]^+$ 190.1074, found 190.1075.

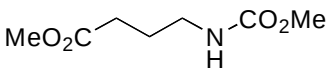


2-isomer

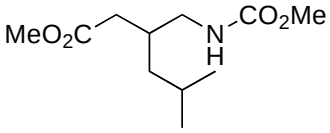


3-isomer

Methyl ((methoxycarbonyl)amino)-dimethyl propanoate (4f, 2- and 3-isomers): In Table 3, 2-:3- = 71:29. 2-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 3.30 (d, *J* = 6.6 Hz, 2H), 3.66 (s, 3H), 3.69 (s, 3H), 5.21 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9 (2C), 44.0, 48.7, 51.4, 51.9, 157.3, 177.4. 3-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 6H), 2.69 (s, 2H), 3.62 (s, 3H), 3.68 (s, 3H), 5.21 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2 (2C), 43.5, 51.2, 51.4, 52.0, 155.5, 171.6. IR (neat) 3358, 1725, 1530, 1469, 1257 cm^{-1}. MS (ESI) calcd for $C_8H_{16}NO_4$ $[M+H]^+$ 190.1074, found 190.1076.

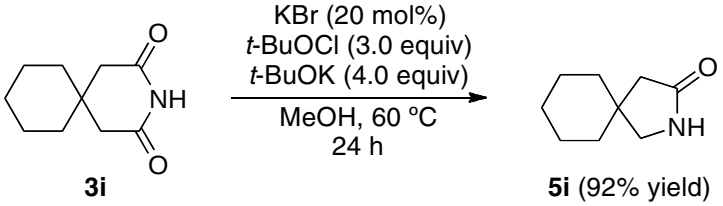


Methyl 4-((methoxycarbonyl)amino)butanoate (4g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.88 (m, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 3.23 (q, *J* = 6.5 Hz, 2H), 3.66 (s, 3H), 3.68 (s, 3H), 4.93 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 31.2, 40.3, 51.6, 52.0, 157.1, 173.7. IR (neat) 3345, 1724, 1535, 1442, 1260 cm^{-1}. MS (ESI) calcd for $C_7H_{14}NO_4$ $[M+H]^+$ 176.0917, found 176.0917.

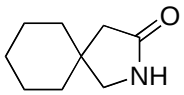


Methyl 3-(((methoxycarbonyl)amino)methyl)-5-methylhexanoate (4h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 1.07-1.23 (m, 2H), 1.65 (sep, *J* = 6.6 Hz, 1H), 2.08-2.19 (m, 1H), 2.29 (d, *J* = 6.6 Hz, 2H), 2.96-3.12 (m, 1H), 3.16-3.32 (m, 1H), 3.66 (s, 3H), 3.67 (s, 3H), 5.02 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5(2C), 25.1, 33.5, 37.1, 41.4, 44.7, 51.5, 51.9, 157.2, 173.6. IR (neat) 3347, 1731, 1536, 1439, 1254 cm^{-1}. MS (ESI) calcd for $C_{11}H_{22}NO_4$ $[M+H]^+$ 232.1543, found 232.1543.

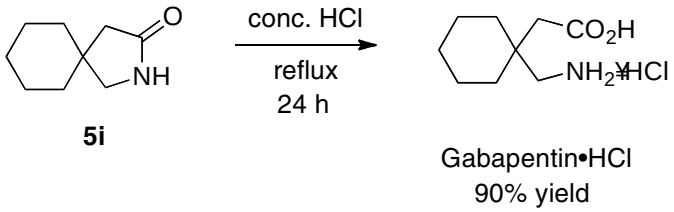
3. Synthesis of gabapentin by Hofmann-type rearrangement of cyclic imides using alkali metal bromide.



To the solution of 3-azaspiro[5,5]undecane-2,4-dione **3i** (45.3 mg, 0.25 mmol) in MeOH (2 mL) were added KBr (6.0 mg, 0.05 mmol), *t*-BuOK (112.2 mg, 1.0 mmol), and *t*-BuOCl (84.8 μL, 0.75 mmol), and stirred at 60 ºC for 24 h under argon atomosphere. The solvents were removed under reduced pressure and the crude product was purified silica gel chromatography (elute: Et_2O/MeOH = 30/1) to give desired product **5i** (35.2 mg, 92% yield).



2-Azaspiro[4,5]decan-3-one (5i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.58 (m, 10H), 2.17 (s, 2H), 3.15 (s, 2H), 6.92 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (2C), 25.5, 36.7 (2C), 39.3, 43.1, 53.6, 178.2. IR (neat) 3202, 2927, 1680 cm^{-1}. MS (ESI) calcd for $C_9H_{15}NNaO$ $[M+Na]^+$ 176.1046, found 176.1044.



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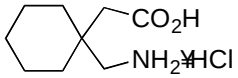
The solution of 2-azaspiro[4,5]decane-3-one **5i** (38.3 mg, 0.25 mmol) in conc. HCl aqueous (2 mL) was refluxed for 24 h. The solvents were removed under reduced pressure and the crude product was washed acetone to give gabapentine (46.7 mg, 90% yield) as its hydrochloric salt.



Gabapentin hydrochloric salt : ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15-1.50 (m, 10H), 2.40 (s, 2H), 2.82-2.92 (m, 2H), 3.44 (brs, 1H), 8.11 (brs, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7 (2C), 25.3, 32.5 (2C), 34.6, 38.5, 45.2, 172.8. IR (KBr) 3386, 2932, 1713, 1522, 1389, 1200 cm^{-1}. MS (ESI) calcd for $C_9H_{17}ClNO_2$ $[M–H]^-$ 206.0942, found 206.0944.