CuI/L-Proline-Catalyzed Coupling Reactions of Aryl Halides with Activated Methylene Compounds

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Experimental

General procedure for CuI-catalyzed coupling reaction. A Schlenk tube was charged with aryl halide (0.5 mmol), CuI (19 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol), and cesium carbonate (645 mg, 2 mmol), evacuated and backfilled with argon. The activated methylene compound (0.6 mmol) and DMSO (1 mL) were added under argon. The tube was immersed in a preheated oil bath, and the reaction mixture was stirred at the indicated temperatures until the conversion was completed detected by TLC. The cooled mixture was partitioned between ethyl acetate and saturated NH_4Cl , the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with PE/EA = 15:1 to 10:1) to provide the desired product.

2-(4-Methoxyphenyl)acetoacetic acid ethyl ester **1¹.** ^1H NMR (CDCl_3 , 400 MHz) δ 13.09 (s, 0.4H), 7.27-6.84 (m, 4H), 4.63 (s, 0.6H), 4.24-4.13 (m, 2H), 3.81 and 3.80 (s, 1.4 and 1.6H), 2.17 (s, 1.6H), 1.85 (s, 1.4H), 1.27 (t, J = 7.3 Hz, 1.6H), 1.19 (t, J = 7.4 Hz, 1.4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 202.0, 174.0, 172.9, 168.9, 159.6, 158.5, 132.3, 130.5, 127.5, 124.8, 114.4, 113.5, 103.8, 65.0, 61.6, 60.7, 55.4, 55.2, 29.8, 28.7, 20.0, 14.3, 14.2; EI-MS m/z 236 (M^+), 194, 165, 121; MALDI-HRMS calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_4\text{Na}$ ($\text{M} +$

Na)⁺: 259.0941, found: 259.0953.

2-*p*-Tolylacetoacetic acid ethyl ester 2². ¹H NMR (CDCl₃, 400 MHz) δ 13.12 (s, 0.2H), 7.24-6.99 (m, 4H), 4.64 (s, 0.8H), 4.23-4.12 (m, 2H), 2.36 2.35 (s, 3H), 2.17 (s, 2.4H), 1.85 (s, 0.6H), 1.28-1.16 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 202.0, 173.9, 172.9, 168.8, 147.1, 136.6, 132.3, 131.1, 129.7, 129.3, 128.9, 113.8, 104.2, 99.8, 65.5, 61.7, 60.7, 52.7, 32.0, 29.8, 29.5, 28.8, 21.3, 21.2, 20.0, 14.3, 14.2; EI-MS *m/z* 220 (M⁺), 178, 132; MALDI-HRMS calcd. for C₁₃H₁₆O₃ (M⁺): 220.1105, found: 220.1100.

2-(3-methoxyphenyl)acetoacetic acid ethyl ester 3³. ¹H NMR (CDCl₃, 400 MHz) δ 13.11 (s, 0.6H), 7.27-7.23 (m, 1H), 6.92-6.70 (m, 3H), 4.65 (s, 0.4H), 4.24-4.15 (m, 2H), 3.81 (s, 3H), 2.19 (s, 1.2H), 1.86 (s, 1.8H), 1.28-1.18 (m, 3H); ¹³C NMR (CDCl₃, 100MHz) δ 201.7, 174.0, 172.6, 168.5, 159.3, 136.7, 130.0, 129.0, 123.8, 121.7, 117.1, 114.9, 113.9, 112.4, 104.3, 65.8, 61.7, 60.7, 55.4, 55.3, 29.8, 28.8, 20.0, 14.3, 14.2; EI-MS *m/z* 236 (M⁺), 194, 148, 121; MALDI-HRMS calcd. for C₁₃H₁₆O₄Na (M + Na)⁺: 259.0941, found: 259.0933.

2-(2-Fluorophenyl)acetoacetic acid ethyl ester 4. ^1H NMR (CDCl_3 , 400 MHz) δ 13.21 (s, 0.8H), 7.75-6.88 (m, 4H), 5.05 (s, 0.2H), 4.28-4.10 (m, 2H), 2.23 (s, 0.6H), 1.86 (s, 2.4H), 1.28-1.16 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.9, 172.2, 139.5, 133.3, 130.2, 130.1, 129.4, 129.3, 125.9, 125.8, 124.6, 123.8, 123.7, 115.9, 115.8, 115.7, 115.6, 115.4, 97.9, 61.9, 60.8, 57.8, 32.0, 29.8, 29.5, 29.1, 22.8, 19.8, 14.2, 14.1; EI-MS m/z 224 (M^+), 178, 154, 136; MALDI-HRMS calcd. for $\text{C}_{12}\text{H}_{13}\text{FO}_3$ (M^+): 224.0841, found: 224.0847.

2-(3-Nitrophenyl)acetoacetic acid ethyl ester 5. ^1H NMR (CDCl_3 , 400 MHz) δ 13.20 (s, 0.5H), 8.25-7.51 (m, 4H), 4.85 (s, 0.5H), 4.30-4.17 (m, 2H), 3.81 (s, 3H), 2.30 (s, 1.5H), 1.89 (s, 1.5H), 1.32-1.18 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 199.8, 174.9, 171.8, 167.6, 148.4, 148.1, 137.6, 137.1, 135.8, 134.5, 129.8, 129.0, 126.3, 124.7, 123.4, 122.1, 102.8, 64.8, 62.4, 61.2, 29.8, 29.4, 20.0, 14.2, 14.1; EI-MS m/z 251 (M^+), 205, 163, 150; MALDI-HRMS calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 274.0686, found: 274.0677.

2-(4-Acetylphenyl)acetoacetic acid ethyl ester 6. ^1H NMR (CDCl_3 , 400 MHz) δ 13.19 (s, 0.2H), 7.98-7.94 (m, 2H), 7.48-7.28 (m, 2H), 4.78 (s, 0.8H), 4.26-4.18 (m, 2H), 2.62-2.61 (s, 3H), 2.23 (s, 2.4H), 1.87 (s, 0.6H), 1.29-1.17 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 200.5, 197.9, 197.6, 174.3, 172.1, 168.0, 140.6, 137.7, 136.9, 135.9, 131.6, 129.8, 128.8, 128.2, 103.8, 65.5, 62.0, 60.9, 29.1, 26.7, 26.6, 20.0, 14.2, 14.1; EI-MS m/z 249 ($\text{M} + \text{H}$) $^+$, 206, 178, 145; MALDI-HRMS calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 271.0941, found: 271.0941.

2-(3-Methoxycarbonylphenyl)acetoacetic acid ethyl ester 7³. ^1H NMR (CDCl_3 , 400 MHz) δ 13.14 (s, 0.5H), 8.04-7.36 (m, 4H), 4.77 (s, 0.5H), 4.28-4.14 (m, 2H), 3.92 (s, 3H), 2.22 (s, 1.5H), 1.85 (s, 1.5H), 1.28-1.16 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 200.9, 174.3, 172.3, 168.2, 167.1, 166.7, 135.9, 135.7, 133.9, 133.1, 132.5, 130.9, 130.7, 130.2, 129.6, 128.3, 128.2, 103.7, 65.4, 62.0, 60.9, 52.3, 52.2, 29.8, 29.1, 20.0, 14.2, 14.1; EI-MS m/z 264 (M^+), 218, 176, 84; MALDI-HRMS calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 287.0890, found: 287.0897.

2-(3-Trifluoromethylphenyl)acetoacetic acid ethyl ester **8³.** ¹H NMR (CDCl₃, 400 MHz) δ 13.17 (s, 0.5H), 7.62-7.33 (m, 4H), 4.77 (s, 0.5H), 4.28-4.15 (m, 2H), 2.24 (s, 1.5H), 1.87 (s, 1.5H), 1.29-1.16 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 200.4, 174.5, 172.2, 167.9, 136.1, 134.7, 133.6, 132.9, 129.4, 128.5, 128.2, 126.4, 125.3, 123.8, 103.5, 65.3, 62.1, 61.0, 43.9, 29.8, 29.5, 29.2, 22.8, 20.0, 18.7, 14.2, 14.1; EI-MS *m/z* 274 (M⁺), 232, 204, 186; MALDI-HRMS calcd. for C₁₃H₁₃F₃O₃ (M⁺): 274.0801, found: 274.0808.

2-(4-Methoxyphenyl)benzoacetic acid ethyl ester **9⁴.** ¹H NMR (CDCl₃, 400 MHz) δ 13.59 (s, 0.05H), 7.97-7.94 (m, 2H), 7.57-7.30 (m, 5H), 6.90-6.87 (m, 2H), 5.55 (s, 0.95H), 4.24-4.19 (m, 2H), 3.77 (s, 3H), 1.26-1.22 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 193.6, 169.2, 159.5, 135.8, 133.5, 130.8, 129.0, 128.8, 125.1, 114.4, 61.8, 59.8, 55.3, 14.1; EI-MS *m/z* 298 (M⁺), 148, 135, 105; ESI-HRMS calcd. for C₁₈H₁₈O₄Na (M + Na)⁺: 321.1097, found: 321.1091.

2-(3-Methoxycarbonylphenyl)benzoacetic acid ethyl ester 10. ^1H NMR (CDCl_3 , 400 MHz) δ 13.65 (s, 0.2H), 8.09-7.10 (m, 9H), 5.69 (s, 0.8H), 4.24-4.19 (m, 2H), 3.90 3.87 (s, 3H), 1.26-1.22 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 192.9, 168.5, 166.7, 136.7, 135.6, 134.2, 133.8, 133.5, 133.3, 130.9, 130.8, 129.5, 129.3, 129.0, 128.9, 128.0, 127.8, 62.1, 61.4, 60.2, 52.3, 29.8, 14.2, 14.1; EI-MS m/z 326 (M^+), 280, 194, 105; ESI-HRMS calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 349.1047, found: 349.1032.

2-(3-Methoxyphenyl)benzoacetic acid ethyl ester 11. ^1H NMR (CDCl_3 , 400 MHz) δ 13.64 (s, 0.05H), 7.97-7.94 (m, 2H), 7.57-6.82 (m, 7H), 5.57 (s, 0.95H), 4.27-4.19 (m, 2H), 3.78 (s, 3H), 1.26-1.22 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 193.4, 168.8, 159.9, 135.8, 134.4, 133.6, 129.9, 129.0, 128.8, 125.1, 122.0, 115.3, 113.8, 61.9, 60.6, 55.3, 32.3, 29.8, 26.5, 23.5, 14.1; ESI-MS m/z 299 ($\text{M} + \text{H}$) $^+$; ESI-HRMS calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 321.1097, found: 321.1096.

2-(4-Acetylphenyl)benzoacetic acid ethyl ester 12. ^1H NMR (CDCl_3 , 400 MHz) δ 13.70 (s, 0.1H), 7.98-7.17 (m, 9H), 5.68 (s, 0.9H), 4.28-4.19 (m, 2H), 2.56 (s, 3H), 1.26-1.22 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 197.7, 192.7, 168.3, 138.1, 136.8, 135.5, 135.3, 133.9, 132.4, 130.0, 129.3, 129.0, 128.9, 128.8, 128.0, 127.9, 125.1, 62.1, 61.4, 60.4, 32.3, 32.0, 29.8, 29.4, 26.7, 26.5, 23.5, 22.8, 14.2, 14.1; ESI-MS m/z 311 ($\text{M} + \text{H}$) $^+$; ESI-HRMS calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 333.1097, found: 333.1094.

***p*-Tolylmalonic acid diethyl ester 13⁵.** ^1H NMR (CDCl_3 , 400 MHz) δ 7.28 (d, $J = 3.9$ Hz, 2H), 7.16 (d, $J = 3.9$ Hz, 2H), 4.57 (s, 1H), 4.24-4.13 (m, 4H), 2.34 (s, 3H), 1.25 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 168.4, 138.1, 129.9, 129.4, 129.2, 61.8, 57.7, 21.2, 14.1; EI-MS m/z 250 (M^+), 177, 149, 121; MALDI-HRMS calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$ (M^+): 250.1201, found: 250.1206.

2-(3-Methoxyphenyl)malonic acid diethyl ester **14**⁶. ¹H NMR (CDCl₃, 400 MHz) δ 7.29-7.25 (m, 1H), 6.97-6.96 (m, 2H), 6.88-6.86 (m, 1H), 4.58 (s, 1H), 4.26-4.17 (m, 4H), 3.81 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 168.2, 160.0, 134.2, 129.6, 121.7, 114.9, 114.0, 61.9, 58.0, 55.3, 14.1; EI-MS *m/z* 266 (M⁺), 193, 165, 148; MALDI-HRMS calcd. for C₁₄H₁₈O₅Na (M + Na)⁺: 289.1047, found: 289.1056.

2-(4-Methoxyphenyl)malonic acid diethyl ester **15**⁷. ¹H NMR (CDCl₃, 400 MHz) δ 7.34-7.31 (m, 2H), 6.91-6.87 (m, 2H), 4.55 (s, 1H), 4.26-4.18 (m, 4H), 3.79 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 168.5, 159.6, 130.5, 125.0, 114.1, 61.8, 57.2, 55.3, 14.1; EI-MS *m/z* 266 (M⁺), 193, 165, 137; MALDI-HRMS calcd. for C₁₄H₁₈O₅Na (M + Na)⁺: 289.1047, found: 289.1059.

o*-Tolylmalonic acid diethyl ester **16*⁸. ¹H NMR (CDCl₃, 400 MHz) δ 7.41-7.38 (m, 1H), 7.23-7.18 (m, 3H), 4.87 (s, 1H), 4.26-4.19 (m, 4H), 2.34 (s, 3H), 1.27 (t, *J* = 7.4 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 168.5, 136.6, 131.7, 130.6, 128.9, 128.2, 126.4, 61.9, 54.5, 19.8, 14.1; EI-MS *m/z* 250 (M⁺), 204, 177, 158; MALDI-HRMS calcd. for C₁₄H₁₈O₄ (M⁺): 250.1209, found: 250.1214.

2-Naphthalen-1-yl-malonic acid diethyl ester 17⁸. ¹H NMR (CDCl₃, 400 MHz) δ 7.96 (d, *J* = 4.1 Hz, 1H), 7.88-7.82 (m, 2H), 7.58-7.45 (m, 4H), 5.42 (s, 1H), 4.28-4.21 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 168.6, 134.0, 131.7, 129.4, 129.1, 129.0, 127.2, 126.8, 125.9, 125.5, 122.9, 62.0, 54.6, 14.1; EI-MS *m/z* 286 (M⁺), 213, 185, 141; MALDI-HRMS calcd. for C₁₇H₁₈O₄Na (M + Na)⁺: 309.1097, found: 309.1105.

2-(2-Fluorophenyl)malonic acid diethyl ester 18. ¹H NMR (CDCl₃, 400 MHz) δ 7.50-7.45 (m, 1H), 7.36-7.29 (m, 1H), 7.18-7.15 (m, 1H), 7.10-7.06 (m, 1H), 4.98 (s, 1H), 4.28-4.21 (m, 4H), 1.28 (t, *J* = 7.4 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 167.7, 130.6, 130.1, 130.0, 124.4, 115.6, 115.4, 62.1, 50.6, 14.1; EI-MS *m/z* 254 (M⁺), 182, 154, 136, 109; MALDI-HRMS calcd. for C₁₃H₁₅FO₄Na (M + Na)⁺: 277.0847, found: 277.0857.

2-(3-Nitrophenyl)malonic acid diethyl ester 19⁹. ¹H NMR (CDCl₃, 400 MHz) δ 8.31-8.30 (m, 1H), 8.24-8.21 (m, 1H), 7.79 (d, *J* = 3.9 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 4.72 (s, 1H), 4.29-4.21 (m, 4H), 1.29 (t, *J* = 7.3 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 167.3, 148.3, 135.7, 134.7, 129.6, 124.7, 123.4, 62.5, 57.5, 14.1; EI-MS *m/z* 282 (M + H)⁺, 236, 208, 181, 136; MALDI-HRMS calcd. for C₁₃H₁₅NO₆Na (M + Na)⁺: 304.0792, found: 304.0806.

2-(4-Acetylphenyl)malonic acid diethyl ester 20⁸. ¹H NMR (CDCl₃, 400 MHz) δ 7.96 (d, *J* = 4.1 Hz, 2H), 7.52 (d, *J* = 4.3 Hz, 2H), 4.68 (s, 1H), 4.28-4.19 (m, 4H), 2.61 (s, 3H), 1.27 (t, *J* = 7.3 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 197.7, 167.6, 137.9, 136.9, 129.7, 128.6, 62.2, 57.9, 26.8, 14.1; EI-MS *m/z* 278 (M⁺), 263, 206, 178, 145; MALDI-HRMS calcd. for C₁₅H₁₈O₅Na (M + Na)⁺: 301.1047, found: 301.1059.

2-(3-Methoxycarbonylphenyl)malonic acid diethyl ester 21. ^1H NMR (CDCl_3 , 400 MHz) δ 8.07-8.01 (m, 2H), 7.66-7.63 (m, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 4.67 (s, 1H), 4.28-4.17 (m, 4H), 3.92 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 167.9, 166.7, 133.8, 133.3, 130.7, 130.6, 129.6, 128.8, 62.1, 57.8, 52.3, 14.1; EI-MS m/z 294 (M^+), 263, 222, 190, 162; MALDI-HRMS calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 317.0996, found: 317.1010.

2-(3-Trifluoromethylphenyl)malonic acid diethyl ester 22⁹. ^1H NMR (CDCl_3 , 400 MHz) δ 7.68 (s, 1H), 7.64-7.59 (m, 2H), 7.49 (t, $J = 7.8$ Hz, 1H), 4.67 (s, 1H), 4.28-4.17 (m, 4H), 1.27 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 167.6, 133.8, 132.9, 131.0, 130.8, 129.1, 126.4, 125.2, 62.2, 57.7, 14.0; EI-MS m/z 304 (M^+), 285, 232, 204, 186; MALDI-HRMS calcd. for $\text{C}_{14}\text{H}_{15}\text{F}_3\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 327.0815, found: 327.0804.

(S)-Diethyl-2-(4-(2-(*tert*-butoxycarbonylamino)-3-methoxy-3-oxopropyl)- phenyl)malonate 23. ^1H NMR (CDCl_3 , 400 MHz) δ 7.34 (d, J = 4.1 Hz, 2H), 7.13 (d, J = 3.9 Hz, 2H), 4.98 (d, J = 3.9 Hz, 1H), 4.58 (br s, 2H), 4.28-4.17 (m, 4H), 3.70 (s, 3H), 3.14-3.01 (m, 2H), 1.42 (s, 9H), 1.29-1.24 (m, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.3, 168.2, 155.2, 136.2, 131.6, 129.6, 129.5, 80.1, 61.9, 57.7, 54.3, 52.3, 38.0, 28.4, 14.1; ESI-MS m/z 455 ($\text{M} + \text{NH}_4$) $^+$; ESI-HRMS calcd. for $\text{C}_{22}\text{H}_{31}\text{NO}_8\text{Na}$ ($\text{M} + \text{Na}$) $^+$: 460.1942, found: 460.1939.

2-Biphenyl-4-yl-malonic acid diethyl ester 24⁸. ^1H NMR (CDCl_3 , 400 MHz) δ 7.60-7.30 (m, 9H), 4.66 (s, 1H), 4.28-4.18 (m, 4H), 1.28 (t, J = 8.7 Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 168.3, 141.2, 140.7, 131.9, 129.8, 128.9, 127.5, 127.4, 127.2, 61.0, 57.8, 14.1; ESI-MS m/z 312 (M^+).

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