The Barbier-Grignard-Type Carbonyl Alkylation using Unactivated Alkyl Halides in Water

Charlene C. K. Keh, Chunmei Wei and Chao-Jun Li*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118

General: All reagents were purchased from Aldrich and used without further purification. All reactions were carried out under an air atmosphere at room temperature. ^1H NMR and ^{13}C NMR measurements were conducted on a Varian Unity Inova 400, IR spectra were measured on a Nexus 670 Avatar FT-IR, HRMS calculations were performed at the Chemistry Institute of the Chinese Academy of Sciences. Flash chromatography employed Kiesegel 60, 230-400 mesh and preparative thin layer chromatography on precoated Kiesegel 60 F-254 plates both purchased from Sorbent Technologies.

Representative example for alkylation: To a solution of p-cyanobenzaldehyde (50 mg, 0.38 mmol) and isopropyl iodide (324 mg, 1.91 mmol) in 30 mL 0.07 M $\text{Na}_2\text{C}_2\text{O}_4$ was added InCl (0.06 mg, 0.038 mmol) and was allowed to stir for ten minutes. CuI (220 mg, 1.14 mmol) and Zn powder (150 mg, 2.29 mmol) was added in one portion and allowed to stir at room temperature for 36 hours. The aqueous layer was extracted with diethyl ether (3 x 15 mL), washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography using 4:1 hexanes: ethyl acetate to yield 4-(1-hydroxy-2-methylpropyl)-benzonitrile (57 mg, yield 85%).

4-(1-Hydroxy-2-methylpropyl)-benzonitrile: ^1H NMR (400 MHz, CDCl_3 , TMS) 7.57 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 4.43 (d, J = 6.0 Hz, 1H), 2.27 (br, 1H), 1.92-1.87 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) 149.26, 132.15, 127.45, 119.15, 111.08, 35.49, 29.01, 19.05, 17.69. IR (liquid film): max 3457(s), 2963(s), 2873(s), 2229(s), 1609(s), 1470(m), 1409(m), 1017(s), 841(s) cm^{-1} . HRMS Calculated: 176.103 Found: 176.107

4-(Cyclohexylhydroxymethyl)-benzonitrile [259672-48-5]: ^1H NMR (400 MHz, CDCl_3 , TMS) 7.57 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 4.42 (d, J = 6.4 Hz, 1H), 2.10 (br, 1H), 1.80-1.53 (m, 5H), 1.37-1.34 (m, 1H), 1.17-0.91 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) 149.29, 132.14, 127.54, 119.17, 111.04, 78.54, 45.23, 29.41, 28.33, 27.46, 26.22, 26.12. IR (liquid film): max 3453(s), 2927(m), 2853(s), 2228(s), 1609(s), 1450(s), 1410(m), 1017(s), 843(s) cm^{-1} .

4-(Hydroxy-2,2-dimethylpropyl)-benzonitrile: ^1H NMR (400 MHz, CDCl_3 , TMS) 7.61 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.42 (s, 1H), 1.98 (br, 1H), 0.89 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) 147.71, 131.55, 128.59, 119.18, 111.16, 81.82, 36.00, 25.96. IR (liquid film): max 3492(s), 2965(s), 2870(s), 2229(s), 1609(s), 1479(s), 1364(s), 1056(s), 1012(s), 850(s), 830(s), 768(s) cm^{-1} .

4-(Hydroxy-3-methylbutyl)-benzonitrile: $^1\text{H NMR}$ (400 MHz, CDCl_3 , TMS) 7.57 (d, $J = 8.0$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 4.78-4.75 (m, 1H), 2.32 (br, 1H), 1.72-1.61 (m, 2H), 1.43-1.37 (m, 1H), 0.93-0.91 (m, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 151.04, 132.49, 126.70, 119.13, 111.09, 72.14, 48.71, 24.91, 23.42, 22.19. **IR** (liquid film): ν_{max} 3454(s), 2957(m), 2229(s), 1609(s), 1468(m), 1405(m), 1061(s), 849(s) cm^{-1} . **HRMS** Calculated: 190.119 Found: 190.123

4-(Cyclopentylhydroxymethyl)-benzonitrile: $^1\text{H NMR}$ (400 MHz, CDCl_3 , TMS) 7.58 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 4.46 (d, $J = 8.0$ Hz, 1H), 2.18 (br, 1H), 1.77 (m, 1H), 1.61-1.34 (m, 6H), 1.16-1.14 (m, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 149.97, 132.35, 127.34, 119.13, 111.24, 78.16, 47.92, 29.48, 29.10, 25.59, 25.58. **IR** (liquid film): ν_{max} 3457(s), 2955(m), 2228(s), 1609(s), 1451(m), 1410(m), 1032(m), 836(m) cm^{-1} . **HRMS** Calculated: 202.119 Found: 202.122

Cyclohexylphenyl methanol [945-49-3]: $^1\text{H NMR}$ (400 MHz, CDCl_3 , TMS) 7.34-7.25 (m, 5H), 4.32 (d, $J = 7.2$ Hz, 1H), 1.98-1.95 (m, 2H), 1.76-1.73 (m, 1H), 1.65-1.57 (m, 2H), 1.37-1.33 (m, 1H), 1.23-0.89 (m, 5H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 143.84, 128.39, 127.61, 126.87, 79.59, 45.15, 29.51, 29.06, 26.64, 26.31, 26.23. **IR** (liquid film): ν_{max} 3382(s), 3028(m), 2924(s), 2851(s), 1600(m), 1492(s), 1270(m), 1016(s), 893(s), 759(s) cm^{-1} .

3-(Hydroxy-2-methylpropyl)-phenol : $^1\text{H NMR}$ (400 MHz, CDCl_3 , TMS) 7.20-6.86 (m, 1H), 6.84-6.79 (m, 2H), 6.74-6.71 (m, 1H), 4.86 (s, 1H), 4.31 (d, $J = 6.8$ Hz, 1H), 1.94-1.89 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.79 (d, $J = 6.8$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 155.70, 145.86, 129.64, 119.31, 114.53, 113.54, 78.87, 35.40, 19.26, 18.37. **IR** (liquid film): ν_{max} 3582(m), 3382(m), 2961(m), 1589(m), 1457(w), 1268(m) cm^{-1} .

(3-Chlorophenyl)-cyclohexyl methanol: $^1\text{H NMR}$ (400 MHz, CDCl_3 , TMS) 7.47-7.45 (m, 1H), 7.31-7.23 (m, 2H), 7.18-7.14 (m, 1H), 4.88 (d, $J = 6.4$ Hz, 1H), 2.01 (s, 1H), 1.86-1.83 (m, 1H), 1.75-1.63 (m, 4H), 1.42-1.40 (m, 1H), 1.19-1.08 (m, 5H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 141.33, 132.66, 129.50, 128.45, 128.40, 126.99, 75.09, 44.16, 29.26, 27.94, 26.60, 26.48, 26.22. **IR** (liquid film): ν_{max} 3380(s), 2927(m), 2852(s), 1473(m), 1449(s), 1016(m), 755(s) cm^{-1} .

Cyclohexyl-(4-methoxyphenyl)-methanol [835-68-7]: $^1\text{H NMR}$ (400 MHz, CDCl_3 , TMS) 7.18 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 4.25 (d, $J = 7.6$ Hz, 1H), 3.77 (s, 3H), 1.99-1.97 (m, 2H), 1.75-1.72 (m, 1H), 1.63-1.54 (m, 3H), 1.34-1.31 (m, 1H), 1.29-0.83 (m, 5H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 159.09, 136.05, 127.99, 113.74,

79.19, 55.45, 45.16, 29.45, 29.33, 26.65, 26.28, 26.22. **IR** (liquid film): $\max$ 3451(s), 2925(s), 2851(s), 1611(s), 1512(m), 1449(m), 1247(s), 1035(s), 831(s) cm^{-1} .

Cyclohexyl-*m*-tolyl methanol: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.23- 7.19 (m, 1H), 7.09-7.06 (m, 3H), 4.29 (d, $J = 7.2$ Hz, 1H), 2.35 (s, 3H), 2.00-1.96 (m, 1H), 1.91 (br, 1H), 1.78-1.74 (m, 1H), 1.67-1.55 (m, 3H), 1.38-1.34 (m, 1H), 1.24-0.89 (m, 5H). **^{13}C NMR** (100 MHz, CDCl_3) 143.84, 138.01, 128.36, 128.27, 127.52, 123.98, 79.65, 45.09, 29.58, 29.10, 26.65, 26.32, 26.24, 21.73. **IR** (liquid film): $\max$ 3374(s), 3024(m), 2922(s), 1608(s), 1486(s), 1262(m), 1024(s), 892(m), 783(s) cm^{-1} .

(4-Chlorophenyl)-cyclohexyl methanol [106165-42-8]: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.27 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 4.31 (d, $J = 7.2$ Hz, 1H), 1.98 (br, 1H), 1.91-1.88 (m, 1H), 1.76-1.49 (m, 4H), 1.36-1.33 (m, 1H), 1.21-0.86 (m, 5H). **^{13}C NMR** (100 MHz, CDCl_3) 142.21, 133.18, 128.49, 128.19, 78.82, 45.19, 29.38, 28.85, 26.56, 26.24, 26.16. **IR** (liquid film): $\max$ 3382(s), 2925(s), 2852(s), 1597(m), 1492(s), 1089(s), 1013(s), 832(s) cm^{-1} .

(4-Bromophenyl)-cyclohexyl methanol [106166-01-2]: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.43 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 4.30 (d, $J = 7.2$ Hz, 1H), 1.98 (br, 1H), 1.91-1.87 (m, 1H), 1.75-1.49 (m, 4H), 1.36-1.32 (m, 1H), 1.23-0.86 (m, 5H). **^{13}C NMR** (100 MHz, CDCl_3) 142.73, 131.44, 128.57, 121.31, 78.85, 45.15, 29.37, 28.81, 26.55, 26.24, 26.16. **IR** (liquid film): $\max$ 3383(s), 2924(s), 2851(s), 1592(m), 1485(s), 1071(s), 1009(s), 828(s) cm^{-1} .

4-(Hydroxyheptyl)-benzonitrile [212197-71-2]: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.59 (d, $J = 8.4$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 4.72-4.69 (m, 1H), 2.15 (s, 1H), 1.73-1.64 (m, 2H), 1.36-1.26 (m, 8H), 0.84 (t, $J = 6.8$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) 150.54, 132.45, 126.75, 119.13, 111.19, 74.03, 39.46, 31.89, 29.30, 25.71, 22.77, 14.27. **IR** (liquid film): $\max$ 3427(s), 2930(s), 2858(s), 2229(s), 1609(s), 1464(m), 1407(m), 1064(s), 842(s) cm^{-1} .

(2,4-Dimethylphenyl)-2-methylpropanol: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.28 (d, $J = 8.8$, 1H), 7.01 (d, $J = 7.2$ Hz, 1H), 6.94 (s, 1H), 4.58 (d, $J = 7.2$ Hz, 1H), 2.28 (s, 6H), 1.95 (m, 1H), 1.02 (d, $J = 6.4$, 3H), 0.81 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) 139.40, 136.83, 135.13, 131.29, 127.01, 126.23, 75.94, 34.84, 21.21, 19.66, 19.58, 18.28. **IR** (liquid film): $\max$ 3407(s), 2958(s), 2872(s), 1615(s), 1502(s), 1469(s), 1382(s), 1266(m), 1205(m), 1010(s), 819(s), 792(m) cm^{-1} .

2-Methyl-*p*-tolyl-propanol: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.18 (d, $J = 8.0$, 2H), 7.13 (d, $J = 8$, 2H), 4.29 (d, $J = 6.8$, 1H), 2.33 (s, 3H), 1.92 (m,

1H), 0.98 (d, $J = 6.8$, 3H), 0.76 (d, $J = 6.8$, 3H). **^{13}C NMR** (100 MHz, CDCl_3) 140.88, 137.26, 129.09, 126.73, 80.17, 35.41, 21.35, 19.23, 18.63. . **IR** (liquid film): max 3400(s), 2958(s), 2872(s), 1514(m), 1468(m), 1382(m), 1175(w), 1030(s), 1017(m), 810(m), 666(m) cm^{-1} .

2-Methyl-1-(4-trifluoromethylphenyl)-propanol: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.56 (d, $J = 8.0$, 2H), 7.39 (d, $J = 8.8$, 2H), 4.42 (d, $J = 6.4$, 1H), 1.92 (m, 1H), 0.93 (d, $J = 6.8$, 3H), 0.80 (d, $J = 7.2$, 3H). **^{13}C NMR** (100 MHz, CDCl_3) 147.67, 129.74, 127.04, 125.26, 79.38, 35.49, 19.03, 19.95. **IR** (liquid film): max 3389(s), 2965(s), 2876(m), 1620(m), 1469(m), 1420(m), 1327(s), 1165(s), 1126(s), 1068(s), 836(m) cm^{-1} .

(2,4-Bistrifluoromethylphenyl)-2-methylpropanol: **^1H NMR** (400 MHz, CDCl_3 , TMS) 7.86 (d, $J = 6.4$, 2H), 7.82 (d, $J = 8.8$, 1H), 4.80 (d, $J = 7.2$, 1H), 2.00 (m, 1H), 1.06 (d, $J = 6.4$, 3H), 0.77 (d, $J = 6.8$, 3H). **^{13}C NMR** (100 MHz, CDCl_3) 147.32, 129.93, 129.43, 129.04, 122.96, 122.42, 74.34, 35.22, 19.59, 17.93. . **IR** (liquid film): max 3412(s), 2971(s), 2881(s), 1630(s), 1471(s), 1347(s), 1278(s), 1132(s), 1085(s), 1056(s), 1022(s), 912(s), 856(s), 666(s) cm^{-1} .

Table 1 Further optimization conditions

Entry	Conditions ^a	Solvent	Yield (%) ^b
1	$\text{InCl}/\text{Bu}_3\text{SnH}/\text{Zn}/\text{CuBr}$	H_2O	5:27:58 ^d
2	$\text{Bu}_3\text{SnH}/\text{Zn}/\text{CuBr}$	H_2O	8:42:46 ^e
3	$(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuBr}$	H_2O	32:20:48
4	$\text{InCl}/(\text{Me}_3\text{Ge})_2/\text{Zn}/\text{CuBr}$	H_2O	25:25:50
5	$\text{InCl}/(\text{Me}_3\text{Si})_2/\text{Zn}/\text{CuBr}$	H_2O	13:30:57
6	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuBr}$	H_2O	22:14:64 ^f
7	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuBr}$	0.1 M SDS	77:12:11
8	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuBr}$	$\text{H}_2\text{O}:\text{PhMe}(10:1)$	0
9	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuBr}$	$\text{MeOH}:\text{H}_2\text{O}(1:1)$	45:17:38
10	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuBr}$	$\text{MeOH}:\text{H}_2\text{O}(2:5)$	0:58:42
11	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuI}$	H_2O	8:25:67
12	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuI}$	0.05M $\text{Na}_2\text{C}_2\text{O}_4$	0:17:83
13	$\text{InCl}/(\text{Me}_3\text{Sn})_2/\text{Zn}/\text{CuI}$	0.01M $\text{Na}_2\text{C}_2\text{O}_4$	7:22:70

^d 10% unidentified ^e 4% unidentified ^f Adding larger equivalents of hexamthyliditin did not increase desired product ratio.