Indium Catalyzed Friedel-Crafts Benzylation of Aromatic Compounds with Benzyl Halides

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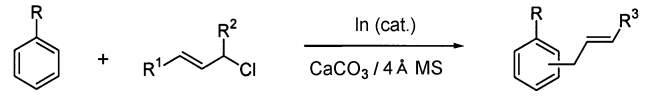
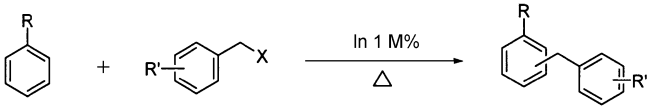
Treatment of the aromatic compounds with benzyl halides in the presence of a catalytic amount of indium gave the corresponding diarylmethane products in good to excellent yields.

The Friedel-Crafts alkylation reaction is one of the most powerful methods to form the carbon-carbon bond in organic reactions[1-3] and especially the Friedel-Crafts benzylation reaction is of great synthetic significance in industrial processes.[4-8] The Friedel-Crafts benzylation reaction is generally carried out by employing a benzyl halide and a catalytic amount of Lewis acid such as $AlCl_3$ under strictly anhydrous conditions due to the extreme moisture sensitivity of the catalyst. But these reaction conditions often induced production of many by-products by isomerization, disproportionation or overalkylation.[9-11] To avoid this drawback, several reaction procedures under the atmospheric circumstances using benzyl halide with K10 supported zinc chloride under sonication[12] or with mild Lewis acid,[9,11] benzyl alcohol,[13] trimethylsilyl benzyl ether,[14] arene carboxaldehyde,[15] or arene carboxaldehyde acetals[16,17] as benzylating agents have been developed.

Metal catayzed reactions have gained wide prosperity in organic synthesis because of their simple and practical procedure, high selectivity, economic consideration, and environmental concern. Among them, the chemistry of indium is of current interest in organic synthesis due to its meditation ability for many organic transformations and its exceptional stability to air and water.[18,19] In the course of our extensive study[20-22] on utilizing indium metal, we reported that indium metal catalyzed the Friedel-Crafts allylation reaction of the aromatic compounds with allylic chlorides (Scheme 1).[21] To explore further the generality and scope of this indium catalyzed reaction, we have tried to apply this new method to other Friedel-Crafts alkylation reactions and found that benzyl halides upon treatment with a catalytic amount of indium underwent smoothly Friedel-Crafts benzylation with various aromatic compounds (Scheme 2).



Scheme 1



Scheme 2

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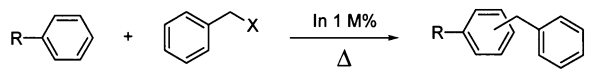
Results and Discussions

Thus reactions of aromatic compounds with benzyl halides in the presence of 1 M% of indium metal at 60-110 °C under air for 1-3 h gave the corresponding benzylated products in good to excellent yields. The results concerning the preparation of diphenylmethane derivatives from benzyl halides and arenes are listed in the Table 1.

For the reaction with benzyl chloride, a higher temperature was required. Indium catalyzed benzylations of the aromatic compounds were carried out using the aromatic compound

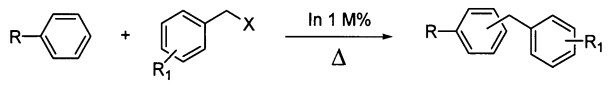
Table 1. Indium Catalyzed Benzylation of Aromatic Compounds



Entry	R	X	Arene/BnX (eq.)	Temp. (°C)	Time (h)	Yields (%)[a] (*ortho* : *para*)
1	H	Br	30/1	70	3	80
2	H	Cl	30/1	110	3	80
3	Me	Br	30/1	70	3	99[b] (1:0.2:1.3)[c]
4	Me	Cl	30/1	110	3	97 (1:0.2:1.1)[c]
5	1,4-dimethyl	Br	30/1	70	3	98
6	1,4-dimethyl	HCl	30/1	110	3	94
7	OMe	Br	15/1	70	2.5	96 (1 : 1.5)
8	OMe	Cl	15/1	110	3	95 (1 : 1)
9	OH	Br	10/1	60	1.5	96 (1 : 1.5)
10	OH	Cl	10/1	90	1.5	96 (1: 1)
11	F	Br	50/1	70	3	90 (1 : 1.5)
12	F	Cl	50/1	110	3	89 (1 : 1.5)
13	Cl	Br	50/1	70	3	92 (1 : 1.5)
14	Cl	Cl	50/1	110	3	85(1:0.05:1.3)[c]

[a]The yield was determined by GC and all products gave satisfactory spectral and analytical data. [b]The preparative synthesis was also applicable: To a solution of benzyl bromide (7.45 g, 43.6 mmol) in toluene (120.3 g, 1308 mmol) was added 1 M% of indium powder (0.05 g, 0.436 mmol). The product was isolated in 88% yield by vacuum distillation (116°C/3 mmHg). [c]The ratio of *ortho* : *meta* : *para*

Table 2. Indium Catalyzed Benzylation with Substituted Benzyl Halides



Entry	R	R_1	X	Arene/ BnX (eq.)	Temp (°C)	Time (hr)	Yield (%)[a] (*ortho* : *para*)
1	F	4-F	Br	15/1	40	24	95 (1:3.6)
2	F	4-F	Br	15/1	70	2.5	93 (1:3.5)
3	F	2-Br	Br	30/1	60	12	97 (1:4.4)
4	H	4-Me	Br	50/1	70	3	85
5	H	4-Cl	Cl	15/1	95	3	92
6	Me	4-F	Br	15/1	50	24	95 (1:0.2:1.1)[b]
7	1,4-dimethyl	4-F	Br	15/1	40	12	97
8	1,4-dimethyl	2-Br	Br	15/1	40	12	93
9	OH	4-F	Br	5/1	40	24	91 (1:2)
10	OH	4-NO_2	Cl	10/1	110	3	96 (1:1.5)

[a]The yield was determined by GC and all products gave satisfactory spectral and analytical data. [b]The ratio of *ortho*:*meta*:*para*.

as a solvent and no acidic solvent like nitromethane was involved. In some cases, dibenzylated products in small amounts were formed by the subsequent reaction of the benzylation products. To suppress this side reaction, the reaction was performed using arenes in excess. The reaction rate and yield enhanced to some extent with the stronger electron-releasing ability of the substituent. The regioselectivity of the benzylation of substituted arenes showed an *ortho-para* preference in agreement well with the typical electrophilic aromatic substitution. In cases of chlorobenzene and toluene, a small amount of *meta*-substituted products was observed. It is noteworthy that not only anisole but also phenol could be successfully benzylated without contamination of any by-product in excellent yield, which was poorly obtained by the previously known method.[23] The indium powder (−100 mesh) was used with no pretreatment before using and the recovered indium after workup could be reused without loss of its activity.

The result of reaction using substituted benzyl halides with various aromatic compounds at 40-110 °C for 3-24 h is shown in the Table 2. Particularly, the reactions of benzene with 4-methylbenzyl bromide and 4-chlorobenzyl chloride at 70 °C and 95 °C respectively for 3 h proceeded well with no detection of any side product by the isomerization or disproportionation reaction.[9,24] Even, 4-nitrobenzyl chloride was reacted with phenol to afford the corresponding benzylated phenol in excellent yield without formation of benzyl ether.[15] The reaction time could be reduced at the elevated temperature.

In conclusion, we demonstrate that indium could catalyze the Friedel-Crafts benzylation efficiently and this present simple, convenient, and practical reaction procedure using less amount of the catalyst has an advantage over the already reported methods. Studies on the mechanism of this reaction and further applications of the present method to organic synthesis are in progress.

Experimental Section

All reactions were performed under atmospheric condition with $CaCl_2$ drying tube on the top of reflux condenser, and monitored by Hewlett Packard 5890 Gas Chromatography. Infrared spectra (IR) were recorded on a Perkin Elmer 16F PC FT-IR spectrophotometer and frequencies are given in reciprocal centimeters. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Varian Gemini 300 or Bruker Avance 300 spectrometer. Chemical Shifts are given in δ scale with TMS as an internal reference in $CDCl_3$. Electron-impact mass spectra (EIMS) were recorded in the form of *m/z* (intensity relative to base=100) on a Hewlett Packard GC-MSD (5890II-5972) system. High-resolution mass spectral analyses were carried out at Korea Basic Science Institute, Taejon, Korea.

Typical procedure for indium catalyzed Friedel-Crafts benzylation of aromatic compounds with benzyl halides. A typical procedure is as followings: To a solution of benzyl bromide (0.4 g, 2.4 mmol) in toluene (6.6 g, 72 mmol) was added 1 M% of indium powder (2.8 mg, 0.024 mmol). The reaction mixture was heated at 70 °C for 3 h until the benzyl bromide was disappeared. The solution was cooled to room temperature and filtered off the residue. The yield was determined by GC with an internal standard.

1-Bromo-2-|(2- and 4-fluorophenyl)methyl|benzene. IR (cm^{-1}) 1510, 1470, 1440, 1224, 1158, 1092, 1026, 772, 746; ^{1}H NMR ($CDCl_3$) δ 7.57 (dd, J = 8.0, 1.0 Hz, 1H), 7.34-7.20 (m, 1H), 7.16-7.04 (m, 4H), 7.02-6.93 (m, 2H), 4.13 (s, 2H for *ortho* isomer), 4.08 (s, 2H for *para* isomer); ^{13}C NMR ($CDCl_3$) δ 163.50, 160.26, 140.57, 135.53, 135.48, 133.35, 133.24, 131.37, 131.23, 130.80, 130.70, 128.43, 127.93, 125.20, 115.79, 115.51, 41.33; GC-MS *m/z* (%) 266 (M^++2, 39), 264 (M^+, 39), 185 (100), 184 (33), 183 (89), 165 (55), 109 (14); HRMS *m/z* calcd for $C_{13}H_{10}BrF$ (M^+): 263.9950; found: 263.9950.

2-|(4-Fluorophenyl)methyl|-1,4-dimethylbenzene. IR (cm^{-1}) 1602, 1506, 1446, 1222, 1156, 812, 770; ^{1}H NMR ($CDCl_3$) δ 7.10-7.06 (m, 3H), 7.03-6.80 (m, 4H), 3.90 (s, 2H), 2.29 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.30, 160.07, 138.93, 136.57, 135.89, 133.77, 131.05, 130.69, 130.47, 130.37, 127.64, 115.65, 115.37, 39.02, 21.39, 19.55; GC-MS *m/z* (%) 215 (M^+−1, 11), 214 (M^+, 69), 199 (100), 184 (26), 183 (30), 118 (31), 109 (15); HRMS *m/z* calcd for $C_{15}H_{15}F$ (M^+): 214.1158; found: 214.1158.

2-|(2-Bromophenyl)methyl|-1,4-dimethylbenzene. IR (cm^{-1}) 1502, 1466, 1440, 1024, 804, 746, 662; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 7.07 (m, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.81 (s, 1H), 4.01 (s, 2H), 2.27 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.23, 137.63, 135.92, 134.03, 132.99, 130.96, 130.57, 128.05, 127.80, 127.72, 125.42, 39.88, 21.41, 19.47; GC-MS *m/z* (%) 276 (M^+−2, 53), 274 (M^+, 55), 261 (12), 259 (12), 196 (17), 1195 (100), 180 (81), 179 (51), 178 (44), 165 (60), 152 (12), 118 (19), 105 (21), 89 (25); HRMS *m/z* calcd for $C_{15}H_{15}Br$ (M^+): 274.0357; found: 274.0357.

2- and 4-|(4-Fluorophenyl)methyl|phenol. IR (cm^{-1})

3382 (br. s), 1600, 1508, 1454, 1222, 1156, 1100, 820, 756; ^{1}H NMR ($CDCl_3$) δ 7.20-7.05 (m, 3H), 7.05-6.85 (m, 4H), 6.81-6.75 (m, 1H), 4.69 (s, 1H), 3.95 (s, 2H for *ortho* isomer), 3.87 (s, 2H for *para* isomer); ^{13}C NMR ($CDCl_3$) δ 163.00, 159.77, 153.85, 153.51, 137.17, 135.91, 135.67, 133.29, 130.88, 130.20, 130.14, 130.09, 130.04, 129.99, 127.91, 126.98, 121.06, 115.66, 115.45, 115.36, 115.31, 115.17, 115.03, 40.16 (*ortho*), 35.42 (*para*); GC-MS of *ortho* isomer *m/z* (%) 203 (M+1, 15), 202 (M+, 100), 201 (25), 183 (46), 181 (20), 170 (10), 153 (13), 152 (15), 133 (9), 109 (24), 106 (63), 78 (50); GC-MS of *para* isomer *m/z* (%) 203 (M^-+1, 14), 202 (M^-, 100), 201 (52), 183 (28), 181 (15), 170 (12), 165 (6), 153 (12), 152 (13), 133 (8), 109 (21), 107 (34), 106 (32), 78(15), 77 (15); HRMS *m/z* calcd for $C_{13}H_{11}FO$ (M^-): 202.0794; found: 202.0794.

Diphenylmethane. ^{1}H NMR ($CDCl_3$) δ 7.36-7.05 (m, 10H), 3.95 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 141.21, 129.67, 128.40, 126.03, 42.13; GC-MS *m/z* (%) 167 (M^-, 100), 152, 139, 128, 115, 91, 77, 65, 51.

1-Methyl-2-(phenylmethyl)benzene. ^{1}H NMR ($CDCl_3$) δ 7.21-7.06 (m, 9H), 3.93 (s, 2H), 2.19 (s, 3H).

1-Methyl-3-(phenylmethyl)benzene. ^{1}H NMR ($CDCl_3$) δ 7.39-7.03 (m, 9H), 3.94 (s, 2H), 2.31 (s, 3H).

1-Methyl-4-(phenylmethyl)benzene. ^{1}H NMR ($CDCl_3$) δ 7.24-7.14 (ABq, 4H), 7.06 (s, 5H), 3.91 (s, 2H), 2.28 (s, 3H); GC-MS *m/z* (%) 182 (M^-, 100), 167, 152, 139, 128, 115, 104, 91, 77, 65, 51.

1,4-Dimethyl-2-(phenylmethyl)benzene. ^{1}H NMR ($CDCl_3$) δ 7.39-6.89 (m, 8H), 3.93 (s, 2H), 2.21 (s, 6H); GC-MS *m/z* (%) 196 (M^-, 100), 181, 165, 152, 139, 118, 115, 91, 77, 65, 51.

2-(Phenylmethyl)phenol and 4-(phenylmethyl)phenol. ^{1}H NMR ($CDCl_3$) δ 7.16-6.77 (m, 9H), 5.54 (s, 1H), 3.39 (s, 2H for *ortho* isomer), 3.88 (s, 2H for *para* isomer); GC-MS *m/z* (%) 184 (M^-, 100), 165, 152, 139, 128, 115, 107, 91, 77, 63, 51.

1-Methoxy-2-(phenylmethyl)benzene and 1-methoxy-4-(phenylmethyl)benzene. ^{1}H NMR ($CDCl_3$) δ 7.13-6.65 (m, 9H), 3.93 (s, 2H for *ortho* isomer), 3.86 (s, 2H for *para* isomer), 3.69 (s, 3H); GC-MS *m/z* (%) 198 (M^-, 100), 183, 167, 153, 139, 128, 121, 107, 91, 77, 63, 51.

1-Chloro-2- and 4-(phenylmethyl)benzene. ^{1}H NMR ($CDCl_3$) δ 7.60-7.21 (m, 9H), 3.81 (s, 2H for *ortho* isomer), 3.93 (s, 2H for *para* isomer); GC-MS *m/z* (%) 202 (M^+), 167 (100), 152, 139, 125, 115, 99, 89, 82, 63, 51.

1-[(4-Fluorophenyl)methyl]-2-methylbenzene and 1-fluoro-4-[(4-methylphenyl)methyl]benzene. ^{1}H NMR ($CDCl_3$) δ 7.43-6.91 (m, 8H), 3.92 (s, 2H for *ortho* isomer), 3.88 (s, 2H for *para* isomer), 2.20 (s, 3H for *ortho* isomer), 2.13 (s, 3H for *para* isomer); GC-MS *m/z* (%) 200 (M^+), 185 (100), 170, 165, 146, 133, 125, 109, 91, 77, 63, 51.

2-[(4-Nitrophenyl)methyl]phenol. ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.17-7.10 (m, 2H), 6.90 (dt, J = 7.5, 0.9 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 5.12 (s, 1H), 4.06 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 153.85, 149.27, 146.66, 131.43, 129.95, 128.74, 126.16, 124.06, 121.59, 116.00, 36.47; GC-MS *m/z* (%) 229 (M^+, 100), 212, 199, 182, 165, 152, 128, 115, 107, 77, 63, 51.

4-[(4-Nitrophenyl)methyl]phenol. ^{1}H NMR ($CDCl_3$, CD_3COCD_3) δ 8.11 (d, J = 8.6 Hz, 2H), 7.56 (s, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.98 (s, 2H); ^{13}C NMR ($CDCl_3$, CD_3COCD_3) δ 155.62, 150.10, 146.62, 130.96, 130.42, 129.90, 124.00, 116.07, 41.18; GC-MS *m/z* (%) 229 (M^+, 100), 212, 199, 182, 165, 152, 128, 115, 107, 77, 63, 51.

Preparative synthesis of 1-chloro-4-(phenylmethyl) benzene. To a solution of 4-chlorobenzyl chloride (10.0 g, 62.1 mmol) in benzene (83 ml, 93.1 mmol), 1 M% of indium powder (71.5 mg, 0.62 mmol) was added. The reaction mixture was heated at 95 °C for 3 h until the 4-chlorobenzyl chloride was disappeared. The solution was cooled to room temperature and filtered off the indium. The filtrate was concentrated under reduced pressure, and the product was isolated in 88% yield (11.08 g, 54.7 mmol) by vacuum distillation: bp 130-135 °C (3 mmHg); ^{1}H NMR ($CDCl_3$) δ 7.32-7.07 (m, 9H), 3.93 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 140.97, 140.00, 132.30, 130.68, 129.28, 128.99, 126.71, 41.65; GC-MS *m/z* (%) 202 (M^-), 167 (100), 152, 139, 125, 115, 99, 89, 82, 63, 51.

Preparative synthesis of 1-methyl-2, 3 and 4-(phenylmethyl)benzene. To a solution of benzyl bromide (7.45 g, 43.6 mmol) in toluene (120.3 g, 1308 mmol) was added 1 M% indium powder (0.05 g, 0.436 mmol). The reaction mixture was heated at 70 °C for 3 h until the benzyl bromide was disappeared. The solution was cooled to room temperature and filtered off the indium. The filtrate was concentrated under reduced pressure, and the product was isolated in 88% yield (7.02 g, 38.5 mmol) by vacuum distillation [bp 116 °C (3 mmHg)] as a mixture of *ortho*, *meta* and *para* isomers.

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