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Iron-Catalyzed Cross-Coupling Reaction of Alkyl Halides with Biphenyl Grignard Reagent

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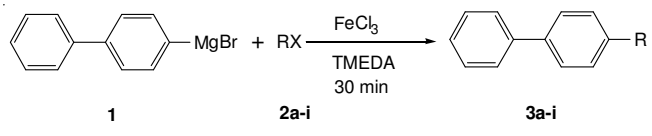
In the presence of a catalytic amount of iron salts and N,N,N',N'-tetramethylethylene diamine as additive, alkyl bromide reacted with biphenyl magnesium bromide to obtain the cross-coupling product in good yields. The suitable amount of catalyst and the additive are 5 % mol (based on alkyl bromide), 1.3 equiv(based on alkyl bromide), respectively. Under the optimal conditions, the yields of the cross-coupling could reach up to 92.3 %.

Key Words: Cross-coupling, Grignard reagent.

INTRODUCTION

The cross-coupling of Grignard reagents with alkyl halides catalyzed by metal is the important method for constructing carbon-carbon bonds in organic synthesis[1-3]. While the coupling reaction of alkyl halides with certain alkyl[4-7], phenyl or substituted phenyl[8-10] Grignard reagents is known in the literature, there have been no examples reported of this reaction using biphenyl Grignard reagents. We have recently reported that $CuCl_2$[11] and CuI[12] catalyzes the cross-coupling reaction of alkyl bromides with biphenylmagnesium bromide in THF for 6 h, the product, alkylbiphenyl, was obtained in high yield; however, shorten the reaction time, unsatisfactory results were obtained. During the course of our study on the cross-coupling reaction of biphenyl Grignard reagents, we have found that $FeCl_3$ show high catalytic reactivity for the cross-coupling reaction of alkyl halides with biphenylmagnesium bromide, the cross-coupling reaction was completed in very short time in high yields in the presence of catalytic amounts of $FeCl_3$ and N,N,N',N'-tetramethylethylene diamine (TMEDA) as an additive (**Scheme-I**).



Scheme-I

EXPERIMENTAL

Melting points were determined on a Laboratory Devices Mel-temp apparatus and uncorrected. The IR spectra (KBr) were recorded on a NICOLET 330 FT-IR spectrophotometer; the ^1H NMR spectra were measured in a $CDCl_3$ solution with TMS as internal reference on a Varian Mercury VX-400 NMR spectrometer. THF was purified by distillation from sodium prior to use.

General procedure: A mixture of biphenylmagnesium bromide **1** (0.9 M in THF, 65 mmol) and TMEDA (0.9 M in THF, 65 mmol) was added to a mixture of alkyl halide **2a-i** (50 mmol) and $FeCl_3$ (0.1 M in THF, 5 mol %) at -5 ºC. The reaction mixture was stirred at -5 ºC for 0.5 h and after the completion of the addition of biphenylmagnesium bromide and TMEDA. 1 M HCl (50 mL) were added and extracted with toluene (3 mL × 15 mL). The combined extracts were dried over anhydrous $MgSO_4$. After evaporation of the solvent under the reduced pressure and again the crude products were purified by crystallization from ethanol or distilled under the reduced pressure.

4-Ethylbiphenyl (3a): m.p. 34-35 ºC; ^1H NMR ($CDCl_3$, δ ppm): 1.40 (t, 3H, $-CH_3$), 2.52 (m, 2H, $-CH_2-$), 7.20-7.54 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3010, 2950, 1600, 1505, 1462, 1228, 805, 735; MS (50 eV) m/z (%): 182 (M^+, 100), 167 (75). Anal. calcd. (%) for $C_{14}H_{14}$: C 92.31, H 7.69; found (%) C 92.26, H 7.73.

4-Propylbiphenyl (3b): b.p. 162-165 ºC/6 mm Hg; ^1H NMR ($CDCl_3$, δ ppm): 1.06 (t, 3H, $-CH_3$), 1.58 (m, 2H, $-CH_2-$), 2.55 (t, 2H, $-CH_2-Ar$), 7.20-7.54 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3050, 2895, 1605, 1508, 1456, 1280, 835, 730; MS (50 eV) m/z (%): 196 (M^+, 100), 167 (65). Anal. calcd. (%) for $C_{15}H_{16}$: C 91.84, H 8. 16; found (%) C 91.86, H 8.11.

4-Butylbiphenyl (3c): b.p. 140-141 ºC/3 mm Hg (Lit.[12] 140 ºC/3 mmHg); ^1H NMR ($CDCl_3$, δ ppm): 0.91 (t, 3H, $-CH_3$), 1.34-1.42 (m, 2H, $-CH_2-$), 1.62-1.67 (m, 2H, $-CH_2-$),

2.65 (t, 2H, -CH_2-Ar), 7.22-7.56 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3050, 2893, 1605, 1511, 1455, 1280, 835, 745; MS (50 eV) m/z (%): 210 (M^+, 100), 167 (85). Anal. calcd. (%) for $C_{16}H_{18}$: C 91.37, H 8.63; found (%) C 91.44, H 8.66.

4-Hexylbiphenyl (3d): m.p. 29-31 ºC (Lit.[11] 29-32 ºC); ^{1}H NMR ($CDCl_3$, δ ppm): 0.83 (t, 3H, -CH_3), 1.22-1.35 (m, 6H, -$(CH_2)_3$-), 1.59 (t, 2H, -CH_2-), 2.54 (t, 2H, -CH_2-Ar), 7.15-7.58 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3045, 2923, 1605, 1501, 1438, 1240.

4-Octylbiphenyl (3e): m.p. 41-42 ºC (Lit.[11] 41-42 ºC); ^{1}H NMR ($CDCl_3$, δ ppm): 0.87 (t, 3H, -CH_3), 1.27-1.35 (m, 10H, -$(CH_2)_5$-), 1.60 (t, 2H, -CH_2-), 2.61 (t, 2H, -CH_2-Ar), 7.25-7.60 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3026, 2863, 1601, 1495, 1432, 1283.

4-Nonylbipheny (3f): m.p. 44-46 ºC (Lit.[11] 44-45 ºC); ^{1}H NMR ($CDCl_3$, δ ppm): 0.85 (t, 3H, -CH_3), 1.25-1.31 (m, 12H, -$(CH_2)_6$-), 1.57 (m, 2H, -CH_2-), 2.63 (t, 2H, -CH_2-Ar), 7.22-7.53 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3020, 2885, 1600, 1491, 1452, 1280.

4-Decylbiphenyl (3g): m.p. 52-53 ºC (Lit.[11] 52-54 ºC); ^{1}H NMR ($CDCl_3$, δ ppm): 0.86 (t, 3H, -CH_3), 1.25-1.34 (m, 14H, -$(CH_2)_7$-), 1.63 (t, 2H, -CH_2-), 2.65 (t, 2H, -CH_2-Ar), 7.25-7.53 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3045, 2945, 1601, 1495, 1455, 1281.

4-Undecylbiphenyl (3h): m.p. 52-54 ºC (Lit.[11] 53-54 ºC); ^{1}H NMR ($CDCl_3$, δ ppm): 0.85 (t, 3H, -CH_3), 1.23-1.31 (m, 16H, -$(CH_2)_8$-), 1.52 (m, 2H, -CH_2-), 2.61 (t, 2H, -CH_2-Ar), 7.21-7.48 (m, 9H, ArH); IR(KBr, ν_{max}, cm^{-1}): δ 3035, 2911, 1590, 1504, 1320, 854, 746.

4-Dodecylbiphenyl (3i): m.p. 61-62 ºC (Lit.[11] 61-62 ºC); ^{1}H NMR ($CDCl_3$, δ ppm): 0.89 (t, 3H, -CH_3), 1.26-1.36 (m, 18H, -$(CH_2)_9$-), 1.62 (t, 2H, -CH_2-), 2.64 (t, 2H, -CH_2-Ar), 7.25-7.58 (m, 9H, ArH); IR (KBr, ν_{max}, cm^{-1}): 3040, 2931, 1609, 1458, 854, 746.

RESULTS AND DISCUSSION

Initially, we performed the coupling reaction of biphenyl magnesium bromide with *n*-$C_{12}H_{25}$Br as a model reaction. Selected results are shown in Table-1. Without any additive, the product was obtained in only 2.1 % yield (Table-1, entry 1). Under similar conditions, tertiary monoamines such as triethylamine and N-methyl morpholine were ineffective (entries 2 and 3) and TMEDA showed high activity for this cross-coupling reaction (entries 4-6). Optimization of the reaction conditions using TMEDA and $FeCl_3$ revealed that use of 5 mol % $FeCl_3$ (0.1 M in THF) and 1.3 equiv of TMEDA (0.9 M in THF) based on the halides at -5 ºC afforded coupling products in highest yield (entry 5).

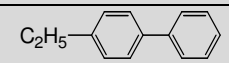
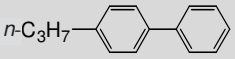
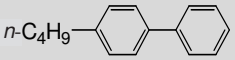
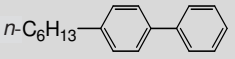
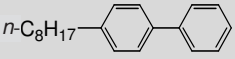
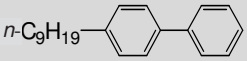
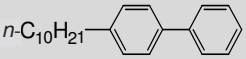
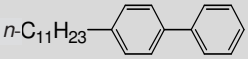
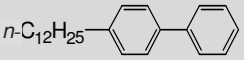
Further examination of the reaction conditions revealed that slow addition of a mixture of the Grignard reagent and the TMEDA to a solution of the halide and the iron catalyst improves the product yield significantly. The mixture of the Grignard reagent and TMEDA was added at such a rate that the temperature of the react mixture was kept at -5 ºC. The reaction mixture turns dark red and a greatly reduced yield is obtained above 0 ºC. The scope of the reaction is illustrated in Table-2.

TABLE-1
CROSS-COUPLING REACTION OF BIPHENYLMAGNESIUM BROMIDE WITH n-$C_{12}H_{25}$Br[a]

Entry	$FeCl_3$ (mol %)[b]	Additive (equiv.)[b]	Yield (%)[c]
1	5	None	2.1
2	5	Et_3N (1.3)	8.3
3	5	N-Methyl morpholine (1.3)	6.5
4	5	TMEDA(1.1)	85.2
5	5	TMEDA(1.3)	92.3
6	5	TMEDA(1.5)	88.4
7	1	TMEDA(1.3)	86.7
8	3	TMEDA(1.3)	90.1

[a]Reaction conditions: *n*-$C_{12}H_{25}$Br (50 mmol), biphenyl magnesium bromide (1.3 equiv, 0.9 M in THF), -5 ºC, 0.5 h. [b]Based on *n*-$C_{12}H_{25}$Br. [c]Isolated yield.

TABLE-2
CROSS-COUPLING REACTION OF ALKYL HALIDES WITH BIPHENYLMAGNESIUM BROMIDE[a]

Entry	Alkyl halides	Product	Yield (%)[b]
1	C_2H_5-Br	 **(3a)**	90.1
2	*n*-C_3H_7-Br	 **(3b)**	89.3
3	*n*-C_4H_9-Br	 **(3c)**	89.2
4	*n*-C_6H_{13}-Br	 **(3d)**	90.4
5	*n*-C_8H_{17}-Br	 **(3e)**	90.6
6	*n*-C_9H_{19}-Br	 **(3f)**	88.8
7	*n*-$C_{10}H_{21}$-Br	 **(3g)**	90.1
8	*n*-$C_{11}H_{23}$-Br	 **(3h)**	90.5
9	*n*-$C_{12}H_{25}$-Br	 **(3i)**	92.3

[a]Reaction conditions: alkyl halides (50 mmol), biphenylmagnesium bromide (1.3 quiv, 0.9 M in THF), TMEDA (1.3 equiv, 0.9 M in THF), $FeCl_3$ (0.1 M in THF, 5 mol %), -5 ºC, 0.5 h. [b]Isolated yield.

Conclusion

For the first time, we have developed the $FeCl_3$/TMEDA catalyzed coupling reaction of biphenylmagnesium bromide with alkyl bromide. Good to excellent yields of the coupling products were obtained.

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