

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

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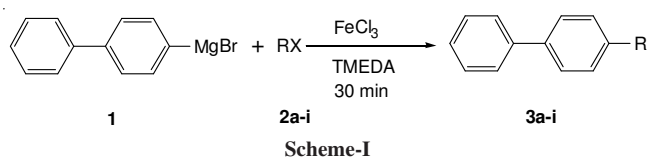
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In the presence of a catalytic amount of iron salts and N,N,N',N'-tetramethylethylene diamine as additive, alkyl bromide reacted with biphenyl magnesium bromide to obtain the cross-coupling product in good yields. The suitable amount of catalyst and 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 synthesis¹⁻³. While the coupling reaction of alkyl halides with certain alkyl⁴⁻⁷, phenyl or substituted phenyl⁸⁻¹⁰ 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 CuCl₂¹¹ and CuI¹² 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 FeCl₃ 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 FeCl₃ and N,N,N',N'-tetramethylethylene diamine (TMEDA) as an additive (**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 CDCl₃ 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 FeCl₃ (0.1 M in THF, 5 mol %) at -5 °C. The reaction mixture was stirred at -5 °C 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 MgSO₄. 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 °C; ¹H NMR (CDCl₃, δ ppm): 1.40 (t, 3H, -CH₃), 2.52 (m, 2H, -CH₂-), 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 C₁₄H₁₄: C 92.31, H 7.69; found (%) C 92.26, H 7.73.

4-Propylbiphenyl (3b): b.p. 162-165 °C/6 mm Hg; ¹H NMR (CDCl₃, δ ppm): 1.06 (t, 3H, -CH₃), 1.58 (m, 2H, -CH₂-), 2.55 (t, 2H, -CH₂-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 C₁₅H₁₆: C 91.84, H 8.16; found (%) C 91.86, H 8.11.

4-Butylbiphenyl (3c): b.p. 140-141 °C/3 mm Hg (Lit.¹² 140 °C/3 mmHg); ¹H NMR (CDCl₃, δ ppm): 0.91 (t, 3H, -CH₃), 1.34-1.42 (m, 2H, -CH₂-), 1.62-1.67 (m, 2H, -CH₂-),

2.65 (t, 2H, -CH₂-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 C₁₆H₁₈: C 91.37, H 8.63; found (%) C 91.44, H 8.66.

4-Hexylbiphenyl (3d): m.p. 29-31 °C (Lit.¹¹ 29-32 °C); ¹H NMR (CDCl₃, δ ppm): 0.83 (t, 3H, -CH₃), 1.22-1.35 (m, 6H, -(CH₂)₃-), 1.59 (t, 2H, -CH₂-), 2.54 (t, 2H, -CH₂-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 °C (Lit.¹¹ 41-42 °C); ¹H NMR (CDCl₃, δ ppm): 0.87 (t, 3H, -CH₃), 1.27-1.35 (m, 10H, -(CH₂)₅-), 1.60 (t, 2H, -CH₂-), 2.61 (t, 2H, -CH₂-Ar), 7.25-7.60 (m, 9H, ArH); IR (KBr, ν_{\max} , cm⁻¹): 3026, 2863, 1601, 1495, 1432, 1283.

4-Nonylbiphenyl (3f): m.p. 44-46 °C (Lit.¹¹ 44-45 °C); ¹H NMR (CDCl₃, δ ppm): 0.85 (t, 3H, -CH₃), 1.25-1.31 (m, 12H, -(CH₂)₆-), 1.57 (m, 2H, -CH₂-), 2.63 (t, 2H, -CH₂-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 °C (Lit.¹¹ 52-54 °C); ¹H NMR (CDCl₃, δ ppm): 0.86 (t, 3H, -CH₃), 1.25-1.34 (m, 14H, -(CH₂)₇-), 1.63 (t, 2H, -CH₂-), 2.65 (t, 2H, -CH₂-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 °C (Lit.¹¹ 53-54 °C); ¹H NMR (CDCl₃, δ ppm): 0.85 (t, 3H, -CH₃), 1.23-1.31 (m, 16H, -(CH₂)₈-), 1.52 (m, 2H, -CH₂-), 2.61 (t, 2H, -CH₂-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 °C (Lit.¹¹ 61-62 °C); ¹H NMR (CDCl₃, δ ppm): 0.89 (t, 3H, -CH₃), 1.26-1.36 (m, 18H, -(CH₂)₉-), 1.62 (t, 2H, -CH₂-), 2.64 (t, 2H, -CH₂-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*-C₁₂H₂₅Br 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 FeCl₃ revealed that use of 5 mol % FeCl₃ (0.1 M in THF) and 1.3 equiv of TMEDA (0.9 M in THF) based on the halides at -5 °C afforded coupling products in highest yield (entry 5).

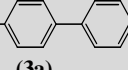
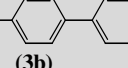
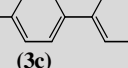
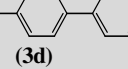
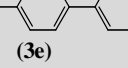
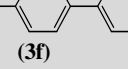
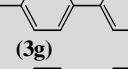
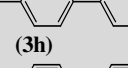
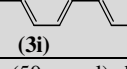
Further examination of the reaction conditions revealed that slow addition of a mixture of the Grignard reagent and the TMEDA to a solution of the halide and the iron catalyst improves the product yield significantly. The mixture of the Grignard reagent and TMEDA was added at such a rate that the temperature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

TABLE-1
CROSS-COUPLING REACTION OF
BIPHENYLMAGNESIUM BROMIDE WITH *n*-C₁₂H₂₅Br^a

Entry	FeCl ₃ (mol %) ^b	Additive (equiv.) ^b	Yield (%) ^c
1	5	None	2.1
2	5	Et ₃ N (1.3)	8.3
3	5	<i>N</i> -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

^aReaction conditions: *n*-C₁₂H₂₅Br (50 mmol), biphenyl magnesium bromide (1.3 equiv, 0.9 M in THF), -5 °C, 0.5 h. ^bBased on *n*-C₁₂H₂₅Br. ^cIsolated yield.

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

Entry	Alkyl halides	Product	Yield (%) ^b
1	C ₂ H ₅ -Br	C ₂ H ₅ -  (3a)	90.1
2	<i>n</i> -C ₃ H ₇ -Br	<i>n</i> -C ₃ H ₇ -  (3b)	89.3
3	<i>n</i> -C ₄ H ₉ -Br	<i>n</i> -C ₄ H ₉ -  (3c)	89.2
4	<i>n</i> -C ₆ H ₁₃ -Br	<i>n</i> -C ₆ H ₁₃ -  (3d)	90.4
5	<i>n</i> -C ₈ H ₁₇ -Br	<i>n</i> -C ₈ H ₁₇ -  (3e)	90.6
6	<i>n</i> -C ₉ H ₁₉ -Br	<i>n</i> -C ₉ H ₁₉ -  (3f)	88.8
7	<i>n</i> -C ₁₀ H ₂₁ -Br	<i>n</i> -C ₁₀ H ₂₁ -  (3g)	90.1
8	<i>n</i> -C ₁₁ H ₂₃ -Br	<i>n</i> -C ₁₁ H ₂₃ -  (3h)	90.5
9	<i>n</i> -C ₁₂ H ₂₅ -Br	<i>n</i> -C ₁₂ H ₂₅ -  (3i)	92.3

^aReaction conditions: alkyl halides (50 mmol), biphenylmagnesium bromide (1.3 equiv, 0.9 M in THF), TMEDA (1.3 equiv, 0.9 M in THF), FeCl₃ (0.1 M in THF, 5 mol %), -5 °C, 0.5 h. ^bIsolated yield.

Conclusion

For the first time, we have developed the FeCl₃/TMEDA catalyzed coupling reaction of biphenylmagnesium bromide with alkyl bromide. Good to excellent yields of the coupling products were obtained.

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