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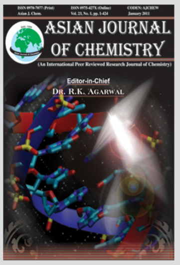

Cuprous-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Alkyl Halides

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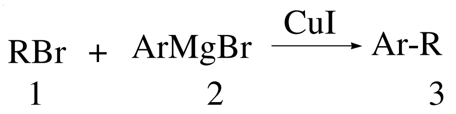
For the first time in the presence of a catalytic amount of cuprous iodide, alkyl bromide reacted with aryl magnesium bromide (Grignard reagent) to obtain the cross-coupling product in good yields. The conditions of the cross-coupling reaction were studied. The suitable amount of catalyst, reaction temperature and time are 2 % mol (based on alkyl halide), 67 ºC (reflux), 6 h, respectively. Under the optimal conditions, the yields of the cross-coupling could reach up to 90 %. Moreover, Grignard reagent with an electron-rich group reacted rapidly and with an electron-withdrawing group reacted sluggishly.

Key Words: Cross-coupling, Grignard reagent, Cuprous iodide.

INTRODUCTION

The metal-catalyzed cross-coupling of alkyl halides with Grignard reagents has become one of the most useful methods for constructing carbon-carbon bonds in organic synthesis[1-6]. A topic of current interest in this area is economical and non-pollutant metal catalyst. Important contributions have been made, for example, Nakamura and co-workers[7] described the application of the $FeCl_3$/TMEDA (N,N,N',N'-tetramethylethylenediamine) catalyst system for cross-coupling reaction of Grignard reagent with alkyl bromides and iodides. Terao and Kambe[8-9] reported $CuCl_2$ catalyzed cross-coupling reactions with various nuclephiles Grignard reagents in the presence of a 1,3-butadiene or 1-phenylpropyne as an additive. During our study on the synthetic application of alkyl halides in transition metal chemistry, we have recently revealed that $CuCl_2$ catalyzes cross-coupling reactions of alkyl bromides with Grignard reagent in the absence of any additive[10]. As an extension of this study, we describe herein the first example of a CuI catalyzed cross-coupling reaction of alkyl bromides with Grignard reagents without any additive (**Scheme-I**).



$$\underset{1}{\text{RBr}} + \underset{2}{\text{ArMgBr}} \xrightarrow{\text{CuI}} \underset{3}{\text{Ar-R}}$$

Scheme-I

EXPERIMENTAL

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 50-mL flask was charged with alkyl halide (**1a-f**) (40 mmol) and CuI (0.1 M in THF, 2 mol %), purged with argon. A solution of aryl magnesium bromide 2(0.9 M in THF, 50 mmol) was added dropwise over 10 min to the stirred mixture. After the completion of the addition of aryl magnesium bromide, the reaction mixture was stirred at reflux for 6h. 1M HCl (50 mL) were added and extracted with toluene (3 × 15 mL). The combined extracts were dried over anhydrous $MgSO_4$. After evaporation of the solvent under the reduced pressure, the products were isolated by column chromatography (silica gel, heptane) to give colourless liquids.

Butyl benzene (3a): bp 181-183 ºC (Lit.[11] 181-184 ºC); IR (KBr, cm^{-1}): ν 3050, 3020, 2960, 2880, 1610, 1498, 1450, 760, 700; ^1H NMR ($CDCl_3$, δ ppm): 7.25 (t, $^3J_{HH}$ = 7.42 Hz, 2H, Ar); 7.16 (d, $^3J_{HH}$ = 7.44 Hz, 3H, Ar); 2.59 (t, $^3J_{HH}$ = 7.74 Hz, 2H, Ar-CH_2); 1.61-1.57 (m, 2H, Ar-CH_2-CH_2); 1.37-1.32 (m, 2H, CH_2-CH_3); 0.92 (t, $^3J_{HH}$ = 7.34 Hz, 3H, CH_2-CH_3).

Amyl benzene (3b): bp 204-205 ºC (Lit.[12] 205 ºC); IR (KBr, cm^{-1}): ν 3048, 3020, 2968, 2882, 1609, 1500, 1455, 755, 700; ^1H NMR ($CDCl_3$, δ ppm): 7.26 (t, $^3J_{HH}$ = 7.48 Hz, 2H, Ar); 7.15 (d, $^3J_{HH}$ = 7.44 Hz, 3H, Ar); 2.59 (t, $^3J_{HH}$ = 7.76 Hz, 2H, Ar-CH_2); 1.65-1.57 (m, 2H, Ar-CH_2-CH_2); 1.43-1.26 (m, 4H, $(CH_2)_2$-CH_3); 0.90 (t, $^3J_{HH}$ = 6.73 Hz, 3H, CH_2-CH_3).

Hexyl benzene (3c): bp 225 ºC (Lit.[13] 226 ºC); IR (KBr, cm^{-1}): ν 3045, 3022, 2970, 2880, 1608, 1502, 1452, 750, 700; ^1H NMR ($CDCl_3$, δ ppm): 7.25 (t, $^3J_{HH}$ = 7.48 Hz, 2H, Ar);

7.16 (d, $^3J_{HH}$ = 7.32 Hz, 3H, Ar); 2.59 (t, $^3J_{HH}$ = 7.78 Hz, 2H, Ar-CH_2); 1.62-1.58 (m, 2H, Ar-CH_2-CH_2); 1.34-1.29(m, 6H, $(CH_2)3$-CH_3); 0.88 (t, $^3J_{HH}$ = 6.68 Hz, 3H, CH_2-CH_3).

1-Butyl-4-methoxybenzene (3d): bp 223-224 ºC (Lit.[14] 225 ºC); IR (KBr, cm^{-1}): ν 3020, 2957, 2929, 2857, 1601, 1510, 1458, 1222, 1157, 824; ^{1}H NMR ($CDCl_3$, δppm): 7.09 (d, $^3J_{HH}$ = 8.60 Hz, 2H, Ar); 6.82 (d, $^3J_{HH}$ = 8.60 Hz, 2H, Ar); 3.78 (s, 3H, OCH_3); 2.55 (t, $^3J_{HH}$ = 7.80Hz, 2H, Ar-CH_2); 1.58-1.54 (m, 2H, Ar-CH_2-CH_2); 1.37-1.30 (m, 2H, CH_2-CH_3); 0.92 (t, $^3J_{HH}$=7.40 Hz, 3H, CH_2-CH_3).

1-Butyl-4-fluorobenzene(3e): bp 49 ºC/1mm Hg (Lit.[15] 50 ºC/1mm Hg); IR (KBr, cm^{-1}): ν 3020, 2956, 2928, 2856, 1613, 1512, 1465, 1245, 1176, 1039, 829; ^{1}H NMR ($CDCl_3$, δppm): 7.09 (t, $^3J_{HH}$ = 8.80 Hz, $^4J_{HF}$ = 5.92 Hz, 2H, Ar); 6.93 (t, $^3J_{HH}$=8.80 Hz, $^3J_{HF}$ = 10.40 Hz, 2H, Ar); 2.56 (t, $^3J_{HH}$ = 7.74 Hz, 2H, Ar-CH_2); 1.57-1.52 (m, 2H, Ar-CH_2-CH_2); 1.35-1.30 (m, 2H, CH_2-CH_3); 0.91 (t, $^3J_{HH}$ = 7.34 Hz, 3H, CH_2-CH_3).

4-Butylbiphenyl (3f): bp 140 ºC /3mm Hg (Lit.[16] 140 ºC/3mm Hg); IR (KBr, cm^{-1}): ν 3020, 2935, 1598, 1501, 1458, 1230, 805; ^{1}H NMR ($CDCl_3$, δppm): 7.56 (d, $^3J_{HH}$ = 8.36 Hz, 2H, Ar); 7.48 (d, $^3J_{HH}$ = 8.16 Hz, 2H, Ar); 7.38 (t, $^3J_{HH}$ = 7.70 Hz, 2H, Ar); 7.27 (t, $^3J_{HH}$ = 7.46 Hz, 1H, Ar); 7.22 (d, $^3J_{HH}$ = 8.16 Hz, 2H, Ar); 2.65 (t, $_3J_{HH}$ = 7.80 Hz, 2H, Ar-CH_2); 1.67-1.62 (m, 2H, Ar-CH_2-CH_2); 1.42-1.34 (m, 2H, CH_2-CH_3); 0.91 (t, $^3J_{HH}$ = 7.20 Hz, 3H, CH_2-CH_3).

RESULTS AND DISCUSSION

Initially, we performed the coupling reaction of 1-bromo butane (**1**) with phenyl magnesium bromide (**2**) as a model reaction. Selected results are shown in Table-1.Without any catalyst, the product was obtained in only 4.2 % yield (Table-1, entry 1). However, in the presence of 1 mol % CuI based on the 1-bromo butane, the yield raised to 35.8 % (Table- 1, entry 2). On increasing the amount of CuI up to 2 mol %, the yield of butylbenzene improved to 80.4 % (Table-1, entry 3). Further increase of CuI did not lead to significant improvement of the yield. CuCl and CuBr are less effective as the catalyst (Table-1, entry 5 and 6). Further optimization of the reaction time and temperature led to excellent yield (92.6 %) of butylbenzene at reflux for 6 h.

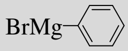
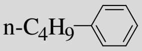
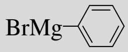
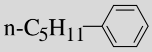
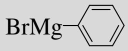
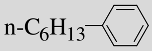
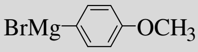
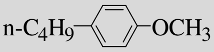
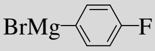
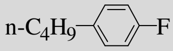
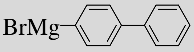
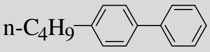
After having optimized the model reaction, we were interested in extending the scope of the coupling reaction. As shown in Table-2, the coupling reactions of phenyl magnesium bromide with different 1-bromo butane, 1-bromo pentane and 1-bromo hexane proceeded in good to excellent yields (Table-2, entry 1-3). Comparison the Grignard reagents in the reaction with 1-bromo butane indicated that the Grignard reagent with an electron-rich group reacts rapidly and with an electron-withdrawing group reacts sluggishly: (4-methoxy phenyl) magnesium bromide reacted with 1-bromo butane to give the

TABLE-1
CROSS-COUPLING REACTION OF 1-BROMOBUTANE WITH PHENYL MAGNESIUM BROMIDE[a]

Entry	Catalyst (mol %)[b]	Temperature (ºC)	Time (h)	Yield (%)[c]
1	CuI(0)	67(reflux)	5	4.20
2	CuI (1)	67(reflux)	5	35.8
3	CuI (2)	67(reflux)	5	80.4
4	CuI (3)	67(reflux)	5	80.8
5	CuCl (2)	67(reflux)	5	64.2
6	CuBr (2)	67(reflux)	5	61.9
5	CuI (2)	25	5	56.7
8	CuI (2)	25	24	68.2
9	CuI (2)	40	5	76.4
10	CuI (2)	67(reflux)	4	57.2
11	CuI (2)	67(reflux)	6	92.6
12	CuI (2)	67(reflux)	7	92.0

[a]Reaction conditions: 1-bromo butane (40 mmol), phenyl magnesium bromide (1.25 equiv, 0.9 M in THF), [b]Based on 1-bromo butane, [c]Isolated yield.

TABLE-2
CUPROUS IODIDE CATALYZED CROSS-COUPLING OF
ALKYL BROMIDE WITH ARYL GRIGNARD REAGENTS[a]

Entry	RBr	Ar Mg Br	Product		Yield (%)[b]
1	*n*-C_4H_9Br			(3a)	92.6
2	*n*-$C_5H_{11}Br$			(3b)	91.4
3	*n*-$C_6H_{13}Br$			(3c)	90.3
4	*n*-C_4H_9Br			(3d)	93.1
5	*n*-C_4H_9Br			(3e)	81.3
6	*n*-C_4H_9Br			(3f)	92.9

[a]Reaction conditions: RBr (40 mmol), Ar Mg Br (1.25 equiv, 0.9 M in THF), CuI (2 mol %), reflux, 6 h, [b]Isolated yield.

corresponding 1-butyl-4-methoxy benzene in 93.1 % yield (Table -2, entry 4), but (4-fluorophenyl) magnesium bromide gave the coupling product in 81.3 % yield (Table-2, entry 5), which was in agreement with the results reported by Nakamura[7]. Biphenyl magnesium bromide smoothly reacted with 1-bromo butane and gave 4-butylbiphenyl in 92.9 % yield (Table-2, entry 6).

Conclusion

In conclusion, the CuI catalyzed coupling reaction of alkyl bromide with arylmagnesium bromides is developed for the first time. Good to excellent yields of the coupling products were obtained. Using CuI as the catalyst not only very cheap and toxicologically benign, but also under "additive free" conditions.

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