

단 신

Copper(II) Triflate로 유도된 Grignard 시약의 산화성 짝지음

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(2004. 10. 12 접수)

Copper(II) Triflate-Induced Oxidative Coupling of Grignard Reagents

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(Received October 12, 2004)

주제어: 바이아릴, 바이알킬, 짝지음, 구리(II) 트리플레이트, 그리니야드 시약

Keywords: Biaryls, Bialkyls, Coupling, Copper(II) triflate, Grignard reagents

The transition metal induced coupling reactions¹ of organometallic reagents are very attractive and useful methods for the preparation of biaryls and bialkyls because the reactions proceed under mild conditions as compared with the classical Ullmann reactions.² The reaction of transition metal halides (FeCl₂, NiCl₂, CoBr₂, PdCl₂)³ with Grignard reagents affords biaryls, but it requires an additive such as styrene and gives low yields when alkyl Grignard reagents are used. Biaryls are also prepared from oxidative homocoupling of arylmagnesium bromides with TIBr⁴ in refluxing benzene and TiCl₄⁵ in THF. The homocoupling of organolithium and organomagnesium reagents with oxovanadium(V) compounds⁶ proceeds effectively to give biaryls and bialkyls at -78 °C, but it requires the use of an excess of oxovanadium(V) compounds. The treatment of silver(I) triflate⁷ and triflic anhydride⁸ with Grignard reagents also provides the symmetrical coupling products at room temperature and are especially useful for the preparation of carbocyclic rings. Other methods to synthesize biaryls include the homocouplings of aryl Grignard reagents with 1,4-dichloro-2-butyne⁹ and 2,3-dichloropropene,¹⁰ which proceed *via* electron-transfer and the substitution products are essentially obtained in small

amounts. Although the treatment of copper chloride¹¹ with Grignard reagents or 2-thienyl lithium and copper(II) nitrate¹² with organotin compounds gives the symmetrical dimeric products, the yields are low to moderate and the scope of the reaction is limited to vinyl and alkynylstannanes, respectively. However, copper(II) triflate has never been utilized as a homocoupling agent of Grignard reagents. In the present paper we report that biaryls and bialkyls can be efficiently prepared from copper(II) triflate-induced oxidative coupling of Grignard reagents in high yields under mild conditions.

EXPERIMENTAL

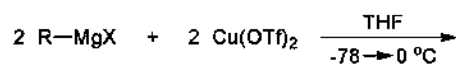
Preparation of 4,4'-dimethoxybiphenyl (typical procedure). To a stirred solution of copper(II) triflate (868.0 mg, 2.4 mmol) in tetrahydrofuran (15 mL) precooled to -78 °C was slowly added *p*-methoxyphenylmagnesium bromide (8.0 mL, 0.3 M in THF, 2.4 mmol) under argon. The resulting brownish yellow solution was allowed to warm to 0 °C over 1 h and then 4 mL of 10% NH₄OH/sat. NH₄Cl was added to the reaction mixture. After evaporation of THF, the reaction mixture was extracted with methylene chloride (3×20 mL) and washed

with 10% $\text{NH}_4\text{OH}/\text{sat. NH}_4\text{Cl}$ (30 mL). The combined organic phases were dried over anhydrous MgSO_4 , filtered, and evaporated to dryness *in vacuo*. The crude product was purified by short pathway silica gel column chromatography using 20% EtOAc/n -hexane as an eluant to afford 4,4'-dimethoxybiphenyl (244.3 mg, 95%). M.p. 174-175 °C (lit.¹⁰ 175-176 °C); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.47 (d, $J=9.0$ Hz, 4H), 6.95 (d, $J=9.0$ Hz, 4H), 3.84 (s, 6H); FT-IR (KBr) 3056, 2957, 1608, 1510, 1455, 1251, 1041, 824 cm^{-1} ; Ms $m/z(\%)$ 214(M^+ , 100), 199(92), 171(34), 128(18). Spectral data, **Hexadecane**: B.p. 105-110 °C/0.8 mm Hg (lit.¹³ 149 °C/10 mm Hg); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 0.88 (t, $J=6.0$ Hz, 6H), 1.22-1.30 (m, 28H); FT-IR (film) 2923, 2854, 1466, 1378, 721 cm^{-1} ; Ms $m/z(\%)$ 226(M^+ , 9), 113(10), 99(20), 85(63), 71(81), 57(100). **1,2-Diphenylethane**: M.p. 51-52 °C (lit.¹³ 52.2 °C); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.25-7.30 (m, 4H), 7.16-7.21 (m, 6H), 2.92 (s, 4H); FT-IR (KBr) 3059, 3026, 2942, 2856, 1601, 1493, 1452, 1064, 752, 698 cm^{-1} ; Ms $m/z(\%)$ 182(M^+ , 48), 92(10), 91(100), 65(16). **Bicyclohexyl**: B.p. 68-73 °C/0.6 mm Hg (lit.¹³ 238 °C/760 mm Hg); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.57-1.72 (m, 10H), 0.88-1.24 (m, 12H); FT-IR (film) 2922, 2861, 1448, 895 cm^{-1} ; Ms $m/z(\%)$ 166(M^+ , 41), 83(47), 82(100), 67(49), 55(42). **1,4-Diphenyl-1,3-butadiyne**: M.p. 83-85 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.52-7.55 (m, 4H), 7.29-7.38 (m, 6H); FT-IR (KBr) 3049, 2150, 1593, 1485, 916, 756, 687 cm^{-1} ; Ms $m/z(\%)$ 202(M^+ , 100), 201(17), 200(33), 150(9), 101(8). **Biphenyl**: M.p. 69-70 °C (lit.¹⁰ 69-70 °C); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.50-7.54 (m, 4H), 7.33-7.39 (m, 4H), 7.24-7.30 (m, 2H); FT-IR (KBr) 3034, 1597, 1481, 1429, 1091, 729, 697 cm^{-1} ; Ms $m/z(\%)$ 154(M^+ , 100), 153(47), 152(33), 76(11). **2,2'-Dimethylbiphenyl**: B.p. 85-90 °C/0.8 mm Hg (lit.¹³ 256 °C/760 mm Hg); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.25-7.32 (m, 6H), 7.16 (d, $J=6.3$ Hz, 2H), 2.11 (s, 6H); FT-IR (film) 3060, 3017, 2922, 1600, 1478, 1453, 1379, 1008, 754 cm^{-1} ; Ms $m/z(\%)$ 182(M^+ , 68), 167(100), 166(23), 165(48), 152(22). **4,4'-Dimethylbiphenyl**: M.p. 120-121 °C (lit.⁹ 119-121 °C); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.51-7.54 (m, 4H), 7.27-7.29 (m, 4H), 2.44 (s, 6H); FT-IR

(KBr) 3025, 2919, 1501, 1449, 1265, 804 cm^{-1} ; Ms $m/z(\%)$ 182(M^+ , 100), 181(31), 167(52), 166(17), 165(39), 152(15). **4,4'-Dichlorobiphenyl**: M.p. 145-147 °C (lit.⁹ 146-148 °C); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.40 (d, $J=8.7$ Hz, 4H), 7.33 (d, $J=8.7$ Hz, 4H); FT-IR (KBr) 3051, 1647, 1388, 1090, 814 cm^{-1} ; Ms $m/z(\%)$ 226(M^+ +4, 11), 224(M^+ -2, 65), 222(M^+ , 100), 152(56), 151(16), 111(9). **2,2',4,4',6,6'-Hexamethylbiphenyl**: M.p. 96-97 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.93 (s, 4H), 2.32 (s, 6H), 1.86 (s, 12H); FT-IR (KBr) 3025, 2915, 1609, 1471, 1375, 1003, 852 cm^{-1} ; Ms $m/z(\%)$ 238(M^+ , 79), 224(20), 223(100), 208(46), 193(33), 178(11). **1,1'-Binaphthyl**: M.p. 158-160 °C (lit.¹⁰ 158-160 °C); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.90-7.97 (m, 4H), 7.53-7.60 (m, 2H), 7.40-7.51 (m, 4H), 7.35-7.40 (m, 2H), 7.20-7.29 (m, 2H); FT-IR (KBr) 3049, 1589, 1504, 1383, 802, 778 cm^{-1} ; Ms $m/z(\%)$ 254(M^+ , 89), 253(100), 252(84), 239(27), 126(31). **2,2'-Bithiophene**: B.p. 87-92 °C/0.9 mm Hg (lit.¹³ 103 °C/3.0 mm Hg); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.14-7.19 (m, 4H), 6.98 (dd, $J_1=5.0$ Hz, $J_2=3.7$ Hz, 2H); FT-IR (film) 3075, 1500, 1415, 1049, 827, 816 cm^{-1} ; Ms $m/z(\%)$ 167(M^+ +1, 12), 166(M^+ , 100), 165(10), 134(15), 121(27).

RESULTS AND DISCUSSION

To investigate the relative effectiveness of copper (II) salts for the oxidative coupling of Grignard reagents we added *p*-methylphenylmagnesium bromide to a solution of copper(II) bromide, copper(II) chloride, and copper(II) nitrate in THF at -78 °C. 4,4'-Dimethylbiphenyl was obtained in 67%, 47%, and 32% yield, respectively, after 1 h between -78 °C and 0 °C. However, the reaction of copper(II) triflate with *p*-methylphenylmagnesium bromide in THF proceeded well to give 4,4'-dimethylbiphenyl in 81% yield after 1 h between -78 °C and 0 °C (Scheme 1). The addition of Grignard reagents to a solution of copper(II) triflate



Scheme 1

Table 1. Preparation of bialkyls and biaryls from Grignard reagents and copper(II) triflate

Entry	RMgX	Products	Isolated yield, %
1	<i>n</i> -C ₈ H ₁₇ MgCl		73
2	C ₆ H ₅ CH ₂ MgCl	C ₆ H ₅ CH ₂ CH ₂ C ₆ H ₅	94
3	<i>c</i> -C ₆ H ₁₁ MgCl		81
4	C ₆ H ₅ -C≡C-MgBr	C ₆ H ₅ -C≡C-C≡C-C ₆ H ₅	70
5	C ₆ H ₅ MgBr		75
6	<i>o</i> -CH ₃ -C ₆ H ₄ MgCl		77
7	<i>p</i> -ClC ₆ H ₄ MgBr		81
8	<i>p</i> -ClC ₆ H ₄ OMeMgBr		95
9	<i>p</i> -Cl-C ₆ H ₄ MgBr		75
10	2,4,6-(CH ₃) ₃ -C ₆ H ₂ MgBr		79
11	α -NaphthylMgBr		76
12	2-ThienylMgBr		90

in THF at -78 °C resulted in color changes starting with brownish yellow and proceeding through deep brown at 0 °C. Aqueous work-up with 10% NH₄OH/sat. NH₄Cl and purification by short pathway silica gel column chromatography or vacuum distillation with a Kugelrohr apparatus gave only the symmetrical coupling products without side products.

The catalytic effect of copper(II) triflate for the oxidative coupling of *p*-methylphenylmagnesium bromide was also briefly studied. The addition of *p*-methylphenylmagnesium bromide to a THF solution of 0.5 equiv and 0.75 equiv of copper(II) triflate afforded 4,4'-dimethylbiphenyl in 60% and 71% yield, respectively, after 1 h between -78 °C and 0 °C. Thus,

copper(II) triflate did not nearly play a catalytic effect and, therefore, 1 equiv of copper(II) triflate was requisite for the high yield formation of the dimeric products.

Table 1 summarized the results of the oxidative coupling reaction of alkyl, alkynyl, and aryl Grignard reagents with an equimolar amount of copper(II) triflate in THF. The reaction worked well both for aliphatic and aromatic Grignard reagents and thus it showed somewhat wider applicability than the reported methods. The treatment of copper(II) triflate with primary and secondary alkyl Grignard reagents (entry 1-3) afforded the corresponding bialkyls in high yields (73-94%). Furthermore, the

reaction of phenylethynylmagnesium bromide (entry 4) with copper(II) triflate proceeded smoothly to give 1,4-diphenyl-1.3-butadiyne in 70% yield. Similarly, aryl Grignard reagents (entry 5-12) gave the coupled biaryls in high yields (75-95%). The reaction of aryl Grignard reagents having electron donating group (entry 7, 8) in 4-position gave somewhat higher yield than that of aryl Grignard reagent having electron withdrawing group (entry 9) in 4-position. This reaction was also applicable to the coupling of 2-methylphenylmagnesium chloride (entry 6) and 2,4,6-trimethylphenylmagnesium bromide (entry 10) with copper(II) triflate, producing the corresponding biaryls in 77% and 79% yield, respectively. The presence of *o*-methyl substituent in aryl Grignard reagents did not affect the efficiency of the oxidative coupling with copper(II) triflate under the present reaction conditions.

Acknowledgment. We are very grateful to Dukung Women's University for its financial support (2004).

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