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Electron-transfer oxidation of Organo-cuprates with Benzophenone: Synthesis of Biaryls

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Abstract

A mild and simple way to synthesize Biaryls from aryl bromides via formation of organo-cuprate complexes has been developed. The Organo-cuprates {$Ar_2CuMgBr.Mg(I)Br$}, generated from Arylmagnesium bromide and half equivalent of copper(I) iodide in dry THF at lower temperature under nitrogen, underwent electron-transfer oxidation with an aryl ketone benzophenone producing homo-coupled Biaryls in moderate yields. Aryl bromides either with electron-donating or with electron-withdrawing substituents were smoothly transformed into the corresponding Biaryls through formation of aryl Grignard reagents and Organo-cuprate complexes in a one pot reaction under this electron-transfer oxidation procedure.

Keywords: Aryl bromides, Organo-cuprates, electrons-transfer oxidation, Biaryls

1. Introduction

Transition metal mediated aryl-aryl bond formation is one of the most powerful tools in modern organic synthesis [1-3]. Biaryl skeletons and their hetertoaromatic analogues are widely distributed in dyes, natural products, bioactive compounds, functional polymers and some ligands in catalysis etc [4-5]. For the synthesis of biaryls, the transition metals that are mostly used for either homo- or cross-coupling reactions, include copper, nickel, palladium and iron [6-10]. Metallic copper which was used in the original Ullmann reaction has been followed by a number of coupling reagents including activated metallic copper, copper(I) and copper(II) salts for the construction of biaryls [11-14].

One of the favorable methods for the homo-coupling of the ligands (R) on the copper atom in an organo-cuprate is its oxidative decomposition with suitable electron acceptor. The organo-cuprates can be formed from readily accessible organolithiums or Grignard reagents and half equivalent of copper (I) salts at lower temperatures. The oxidative coupling of organo-cuprates like Gilman cuprates (R_2CuLi) [15] or Lipshutz cuprates {$R_2Cu(CN)Li_2$}[16] with molecular oxygen yielded coupling products [17-19]. Quite interestingly the Lipshutz cuprate intermediates, derived from copper(I) cyanide and two equivalents of aryllithiums, have been found to undergo electron-transfer oxidation with 1,4-benzoquinones to give homo-coupled biaryls in good to excellent yields [20-21]. However this electron-transfer oxidation procedure has found its utility in the production of symmetric macrocyclic oligoarylenes like nonaphenylenes and dodecaphenylenes from 4,4′′-dihalo-*o*-terphenyls, and pentadecaphyenylenes from 4,4′′′′-dihaloquinquephenyls [22-24]. Recently, we reported the formation of biaryls in moderate yields through electron-transfer oxidation of organo-cuprates with benzil (a 1,2-diketone) [25].

In this paper, we report the construction of biaryls through electron-transfer oxidation of organo-cuprates with an aryl ketone benzophenone. The organo-cuprate complexes were prepared from aryl magnesium bromides and copper (I) iodide at lower temperature. Electron-transfer oxidation of these cuprate-complexes with benzophenone under inert condition yielded homo-coupled biaryls in moderate yields along with the formation of benzophenone ketyl radical.

2. Experimental

2.1 General

The solvents used were dried and purified by the usual techniques: tetrahydrofuran (THF) was distilled from benzophenone ketyl under nitrogen atmosphere; *n*-hexane and dichloromethane were simply distilled without using any drying agent. The melting points of the synthesized compounds were determined with Yanaco MP-500D melting point apparatus. The NMR spectra were measured on a Bruker Biospin 400 spectrometer using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a Shimadzu GCMS-QP2010 spectrometer.

2.2 General procedure for the synthesis of biaryls through electron-transfer oxidation of Organo-cuprates

Activated Mg-turning (2 mmol) and a small magnetic stirrer bar were taken in a two neck round-bottomed flask. This is then equipped with a rubber septum at one end and a three-way stop-cock connected to a nitrogen balloon at the other end. In a similar fashion an aryl bromide 1 (2 mmol) was taken into another two-necked round-bottomed flask. Using a syringe and a needle, dry THF (2 ml) was added to the flask containing the aryl bromide and then the resulting THF solution was transferred to the flask containing Mg turning under nitrogen atmosphere. Within few minutes exothermic reaction started. To complete the formation of the Grignard reagent, the reaction mixture was stirred at room temperature for 1 hour. A 10 mL portion of dry THF was then added to the prepared Grignard reagent in order to dilute it. The resulting diluted Grignard reagent was then cooled to -5 °C when copper (I) iodide (1 mmol) was added in one portion. The reaction mixture was then vigorously stirred at -5 to 0 °C under nitrogen for 40 minutes to compete the formation of the orgno-cuprate complex. The electron-acceptor benzophenone (2.0 mmol) was added in one portion under nitrogen, and the chilling bath was then removed. The reaction mixture was then stirred at room temperature for another 3 hours to complete the reaction (TLC check up). To quench the reaction, water was added followed by the addition of dil. HCl. The resulting mixture was then transferred into a separatory funnel where a 30 mL portion of dichloromethane was added. Two layers were separated and the organic layer was collected. The aqueous layer was again extracted with more dichloromethane. Anhydrous $MgSO_4$ was added to the combined organic layer to remove any water. After the filtration, the solvent was removed in rotary vacuum evaporator to obtain the crude product. This was then chromatographed on a silica gel column eluting with *n*-hexane or *n*-hexane/dichloromethane mixed solvent system to get the pure biaryl 3.

2.3 Biphenyl (3a)

Colorless crystals (yield 36%), mp 69.0-70.0 °C (lit [26]. mp 69.0-69.5 °C); EI MS: m/z 154 (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.62 (d, *J* = 8.4 Hz, 4H), 7.46 (t, *J* = 7.8 Hz, 4H), 7.37 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 141.2, 128.7, 127.2, 127.1.

2.4 Dimethylbiphenyl (3b)

Colorless crystals (yield 47%); mp 119.0-120.0 °C, (lit [26]. mp 119.5-120.0 °C); EI-MS *m/z* 182 (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, *J* = 8.0 Hz, 4H), 7.24 (d, *J* = 8.0 Hz, 4H), 2.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 136.7, 129.4, 126.8, 21.0.

2.5 Dimethylbiphenyl (3c)

Colorless liquid (yield 38%); EI-MS *m/z* 182 (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (s, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 2.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.3, 138.2, 128.6, 127.9, 127.8, 124.2, 21.5.

2.6 Dimethoxylbiphenyl (3d)

Colorless crystals (yield 65%); mp 176.0-177.0 °C, (lit [27]. mp 176.5- 177.0 °C); EI-MS *m/z* 214 (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, *J* = 8.8 Hz, 4H), 6.96 (d, *J* = 8.8 Hz, 4H), 3.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7, 133.4, 127.7, 114.1, 55.3.

2.7 Dibromobiphenyl (3e)

Colorless crystals (yield 40%), mp 165.0-166.0 °C (lit [27]. mp 166.5-167.0 °C); EI MS: m/z 310/312/314 (1:2:1) (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.58 (d, *J* = 8.4 Hz, 4H), 7.43 (d, *J* = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.9, 132, 128.5, 121.9.

2.8 Dichlorobiphenyl (3f)

Colorless crystals (yield 38%), mp 147.0-148.0 °C, (lit [27]. mp 148.0-149.0 °C); EI-MS *m/z* 222/224/226 (9:6:1) (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, *J* = 8.4 Hz, 4H), 7.42 (d, *J* = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 133.7, 129.0, 128.2.

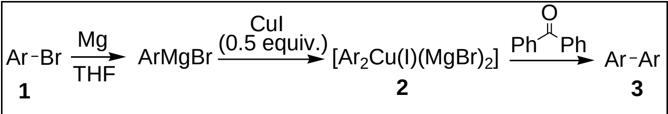
2.10 Difluorobiphenyl (3g)

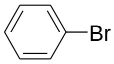
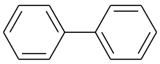
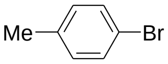
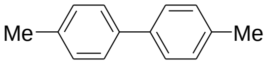
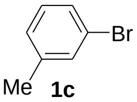
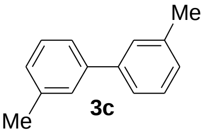
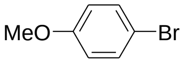
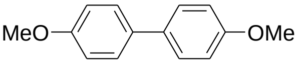
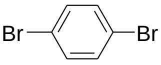
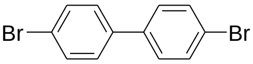
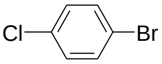
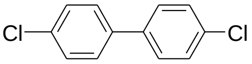
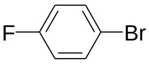
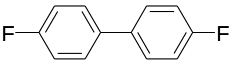
Colorless crystals (yield 38%), mp 87.0-88.0 °C, (lit [27]. mp 88.5 °C); EI-MS *m/z* 190 (M^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (dd, *J* = 8.8 and 5.2 Hz, 4H), 7.13 (t, *J* = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 161.4, 136.4, 136.3, 128.6, 128.5, 115.7, 115.6.

3. Results and Discussion

As reported, the traditional Gilman cuprates ($R_2CuLi{\cdot}LiX$) or Lipshutz cuprates ($R_2Cu(CN)Li_2$) undergo oxidative decomposition with molecular oxygen giving coupling products [17-19] and also the Lipshutz cuprates of the type $Ar_2Cu(CN)Li_2$ under electron-transfer oxidation with 1,4-benzoquinones give homo-coupled biaryls in excellent yields [20, 21]. In our previous study we found that benzil, an aryl 1,2-diketone, behaves as an electron acceptor in the electron-transfer oxidation of the organo-cuprate (derived from Grigard reagent and copper(I) iodide) leading to the formation of homo-coupled biaryls in moderate yields.[25] In this study we have tried to carry out our electron-transfer oxidation procedure with an aryl ketone like benzophenone. We chose benzophenone as an electron acceptor, as its carbonyl function is flanked by two electron withdrawing aromatic rings, which help to stabilize its anion radical after its generation by electron acceptance. We know that benzophenone forms benzophenone ketyl radical during drying of diethyl ether or tetrahydrofuran (THF) with metallic sodium under inert atmosphere. As benzophenone accepts electron from metallic sodium forming stable benzophenone ketyl radical, we believe that this reagent can also accept electron from organo-cuprate giving the stable ketyl radical and diaryl copper (II) ($Ar–Cu^{II}–Ar$) intermediate. This diaryl copper(II) may undergo reductive elimination to give the homo-coupling product biaryl.

Table 1: Homo-coupling of aryl bromides via electron-transfer oxidation of Organo-cuprates



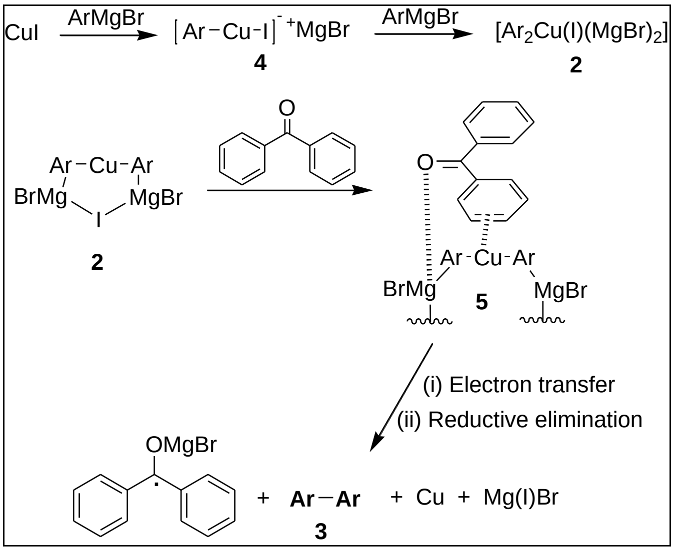
Entry	Substrate (**1**)	Product (**3**)	Yield^a (%)
1	 **1a**	 **3a**	36
2	 **1b**	 **3b**	47
3	 **1c**	 **3c**	38
4	 **1d**	 **3d**	65
5	 **1e**	 **3e**	40
6	 **1f**	 **3f**	38
7	 **1g**	 **3g**	38

^{a} Isolated yield

We prepared the aryl Grignard reagents from pure aryl bromides 1a-g and activated magnesium turnings in dry THF under nitrogen atmosphere. The Grignard reagents thus produced were then diluted with sufficient amount of dry THF before the formation of the cuprate complexes. Treatment of the diluted arylmagnesium bromide with half equivalent of copper(I) iodide at -5 °C under an inert condition produced an organo-cuprate [($Ar_2Cu(I)(MgBr)_2$] 2 within one hour. When the electron-acceptor benzophenone was added to the cuprate-complex at lower temperature, the electron-transfer oxidation took place forming biaryl as homo-coupled product along with the formation of benzophenone ketyl radical (dark blue to violet coloration).

The electron-transfer oxidation procedure to synthesize biaryl was first investigated with the organo-cuprate complex generated from phenylmagnesium bromide and copper(I) salt. For the cuprate-complex to remain soluble in the solvent, sufficient amount of dry THF is necessary for the dilution of the prepared Grignard reagent before the addition of copper(I) salt. The temperature is lowered as well before addition of CuI, because the Organo-cuprate formed may decompose even at lower temperature. When the oxidation of the cuprate complex was carried out with benzophenone, the homo-coupling product biphenyl 3a was obtained in moderate yield (36%) (Table 1, entry 1).

We chose various aryl bromides 1a-g for our homo-coupling procedure via formation of the corresponding Organo-cuprate complexes. Aryl bromides either with electron-donating groups (e.g., 4-bromotoluene 1b, 3-bromotoluene 1c, and 4-bromoanisole 1d entry 2, 3, and 4 respectively) or with electron-withdrawing substituents (e.g., 1,4-dibromobenzene 1e, 1-bromo-4-chlorobenzene 1f and 1-bromo-4-fluorobenzene 1g, entry 5, 6 and 7 respectively) smoothly transformed into the corresponding biaryls 3 in moderate yields under this electron-transfer oxidation procedure.



Scheme 1: Plausible Reaction Pathway

A plausible reaction pathway is depicted in the Scheme 1. Copper (I) iodide first reacts with one equivalent of Arylmagnesium bromide to form a lower order cuprate 4. This cuprate then combines with another equivalent of ArMgBr to give an Organo-cuprate complex 2 which on treatment with benzophenone (the electron-acceptor) forms a π-complex 5. There might involve a magnesium-carbonyl and copper-arene coordinations in the π-complex 5. The electron-transfer from the cuprate to the electron-acceptor (benzophenone), followed by reductive elimination yields the biaryls 3 as the homo-coupling products along with the formation benzophenone ketyl radical. During the work up, a disproportionation reaction of the ketyl radical might take place leading to the formation of benzophenone and diphenylmethanol. Thus a good amount of benzophenone has been recovered after each reaction.

4. Conclusion

In conclusion, a new methodology for the homo-coupling of aryl bromides through electron-transfer oxidation of the corresponding organo-cuprate with an aryl ketone has been developed. Benzophenone has been chosen as the aryl ketone, as its carbonyl function is flanked by two electron-withdarwing phenyl rings which help it to accept electron from the cuprate-complex and to stabilize the ketyl radical after its generation. The key step for the coupling of aryl groups on the copper atom is the electron-transfer from the organo cuprate-complex to the aryl ketone. Aryl bromides with either electron-donating or withdrawing substituents have smoothly been transformed into the corresponding biaryls under this electron-transfer oxidation procedure. It is noteworthy that a good amount of benzophenone is recovered after each reaction, which can be recycled.

5. Acknowledgement

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