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SYNTHETICALLY USEFUL MONO-FUNCTIONALIZATIONS OF DIHALOARENES VIA RIEKE METALS

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Abstract: Reaction of dihalobenzenes and 2, 5-dibromothiophene with Rieke magnesium, Rieke zinc, and Rieke calcium at low temperature affords a monoorganometallic intermediate which upon subsequent treatment with an electrophile provides a mono-functionalized aromatic product in excellent chemical yield.

The preparation of polymers having π -conjugated systems along the polymer chains is a subject of great interest because of their potential utility as organic conductors or semiconductors.¹ Furthermore, the formation of aryl-aryl bonds continues to be an important problem in organic synthesis, and a substantial number of methods for effecting this construction are known.² A common route for producing this class of polymer involves the coupling of Grignard reagents with aryl halides catalyzed by transition metals such as palladium or nickel.³ Any

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methodology which controls the formation of the Grignard reagent would produce a polymer which is more desirable because other deleterious coupling modes would be eliminated. For example, if the aryl dihalide is unsymmetrically substituted, high regioselectivity in the oxidative addition step ultimately induces high regioregularity in the resulting polymer.⁴ Higher molecular weight polymers can be achieved by ensuring the presence of excess mono-Grignard precursor. Thus, the formation of mono-Grignard intermediates leading to these valuable polymers is indeed a worthwhile endeavor.

The reaction of ordinary magnesium with 2,5-dibromothiophene (1 : 1)leads to a mixture of products. The formation of the mono-Grignard, di-Grignard, and unreacted dibromothiophene are detected in a 2 : 1 : 1 ratio, respectively. It should be noted that when the ratio of magnesium to 2.5-dibromothiophene deviated from unity, the yield of the polymer was considerably decreased.⁵ Thus, the polymerization is considered to proceed through the coupling between these intermediates. Similarly, the reaction of ordinary magnesium with 1,4dibromobenzene (1 : 1) again leads to a mixture of Grignard products.⁶ It is obvious that the formation of mono-Grignard intermediates is difficult to achieve in a one-pot process. One approach for the cross-coupling of arvl Grignard reagents which uses bromochlorobenzenes to achieve halogen selectivity was reported by Ikoma, et al.⁷ Friederich, et al. recently reported the formation of the mono-Grignard from para-dibromobenzene and magnesium (1:1) under refluxing conditions.⁸ We wish to report here a one-pot, low temperature formation of mono-organometallic intermediates derived from the incorporation of (1 : 1) Rieke magnesium, Rieke zinc, and Rieke calcium with meta- and para-dihalobenzenes and 2,5-dibromothiophene. The ability of Rieke magnesium, Rieke zinc, and Rieke calcium to undergo formal oxidative addition reactions with aryl-chlorides and aryl-bromides at low temperature is possible owing to the high reactivity of the metal.⁹ Importantly, the oxidative addition at low temperature enhances the selectivity for the mono-organometallic intermediate. Although the formation of the mono-organometallic intermediate was possible with both meta- and para-dihalobenzenes, attempts with ortho-dihalobenzenes were fruitless.

The mono-organometallic intermediates were generated and treated with either CO_2 or benzaldehyde followed by acidic hydrolysis and afforded the monofunctionalized products in excellent chemical yields. Table 1, entry 1 shows the formation of the mono-organomagnesium intermediate and subsequent reaction with carbon dioxide and acidic hydrolysis to afford para-bromobenzoic acid in 99% isolated yield. Also, Table 1, entry 3 shows the high chemical yield conversion of 1,4-dichlorobenzene into 4-chlorobenzoic acid. Similarly, Table 1, entry 8 demonstrates the high reactivity of Rieke calcium to undergo oxidative addition with an aryl fluoride in excellent yield, as shown by the high yield of 4-fluorobenzhydrol. In all of the reactions shown in Table 1, the ratio of Rieke metal to dihalide was (1: 1).

Entry	Dihaloarene	Electrophile	Product ^a	%Yield ^b
1	Br	CO ₂		99
2	Br	С	HO HPh	85
3		CO ₂	COOH	95 ^c
4	Br Br	CO ₂	COOH Br	88
5	Br Br	С Ч Н	HO, H Ph Br	79

 Table I.
 Reactions of Rieke Metals with Dihaloarenes

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Table I Continued



a) Spectral analysis of the synthesized known compounds were consistent with data already reported. b) Isolated yields. c) Reflux, 30 min. d) Rieke calcium was used at -78 °C, 30 min. e) Rieke zinc was used at room temperature, 1h. Cross coupling was performed following standard literature procedure.¹⁰ Also, elemental analysis, ¹H NMR, ¹³C NMR, and FTIR were all consistent with the indicated formulation of all new products.

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This one-pot preparation of mono-organomagnesium, mono-organozinc, and mono-organocalcium intermediates in excellent chemical yields could certainly be applicable in the synthesis of many types of conducting polymers as well as many unsymmetrical aryl molecules. Further studies to expand the scope of this methodology are currently under investigation in our laboratories.

Representative Procedure

4-Bromobenzhydrol: Lithium (10.00 mmol) and naphthalene (10.80 mmol) in freshly distilled THF (10 mL) were stirred under argon for 2 h at room The resulting dark green lithium naphthalenide was added via temperature. cannula to a THF (10 mL) suspension of MgCl₂ (4.80 mmol). The mixture was stirred at room temperature for 30 min. The solution containing the Rieke magnesium (black powder) was cooled to -78 °C, 1,4-dibromobenzene was added via syringe and stirred for 30 min. Benzaldehyde was then added to the dark orange mono-organomagnesium intermediate at -78 °C and stirred for 30 minutes with subsequent warming to 0 °C. The reaction was guenched with 3 N HCl (10 mL) at 0 °C and allowed to warm to room temperature. The reaction was worked up by extracting with diethyl ether (3 X 20 mL). The combined organic phases were washed with NaHCO₃ (2 X 20 mL) and water (1 X 20 mL). The reaction mixture was dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was purified by flash chromatography (EtOAc/Hexanes) providing 4bromobenzhydrol in 85% yield.

- Product 1: p-Bromobenzoic Acid; Sadtler ¹H 6755; IR 4564.
- Product 2: 4-Bromobenzhydrol; Sadtler ¹³C 6018; ¹H 20409; IR 47734.
- Product 3: *p*-Chlorobenzoic Acid; Sadtler ¹³C 4621; ¹H 10266.
- Product 4: *m*-Bromobenzoic Acid; Sadtler ¹H 17210; IR 20984.
- Product 5: 3-Bromobenzhydrol; for IR and ¹H; see Synthesis, 1989, 291.
- Product 6: *m*-Chlorobenzoic Acid; Sadtler ¹H 10952; IR 6617.

Product 7: **5-Bromo-2-Thiophenecarboxylic Acid**; IR (KBr) 3300 (br), 3099, 1689, 1664, 1531, 1433, 1327, 1277 cm⁻¹; ¹H NMR (CDCl₃) δ 11.7 (br. s, 1H), 7.64 (d, J=4.2 Hz, 1H), 7.11 (d, J=3.6 Hz, 1H); ¹³C NMR δ 166.7, 135.3, 133.8, 131.29, 122.3; mp 137-138 °C.

Product 8: **4-Fluorobenzhydrol**; IR (neat) 3363 (br), 3062, 3029, 2879, 1604, 1510, 1494, 1225, 1157, 1014, 812, 698 cm⁻¹; ¹H NMR (CDCl₃) δ 7.37-7.24 (m, 9H), 7.04-6.98 (m, 2H), 5.81 (s, 1H), 2.30-2.20 (br. s, 1H); ¹³C NMR δ 162.2 (d, J_{CF}=246), 143.7, 139.6, 128.6, 128.2 (d, J_{CF}=7.4), 115.3 (d, J_{CF}=22.1), 75.6. HRMS (EI) calcd for C₁₃H₁₁FO 202.0794, found 202.0792.

Product 9: **2-Allyl-5-Bromothiophene**; IR (neat) 3080, 2898, 1639, 1541, 1444, 966, 920, 793 cm⁻¹; ¹H NMR (CDCl₃) δ 6.87 (d, J=3.6 Hz, 1H) 6.56 (dt, J=1.2, 3.6 Hz, 1H), 6.00-5.87 (m, 1H), 5.19-5.09 (m, 2H), 3.51-3.47 (m, 2H); ¹³C NMR δ 144.6, 135.7, 129.6, 125.0, 116.8, 109.6, 34.5. Anal. Calcd for C₇H₇BrS: C, 41.40; H, 3.45. Found: C, 41.50; H, 3.41.

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