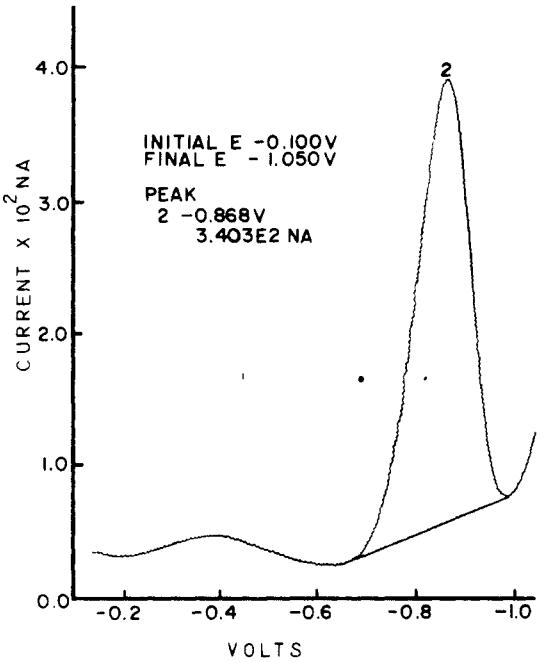

Figure 1. Cimetidine (10^{-5} M) in 0.1 M HCl.

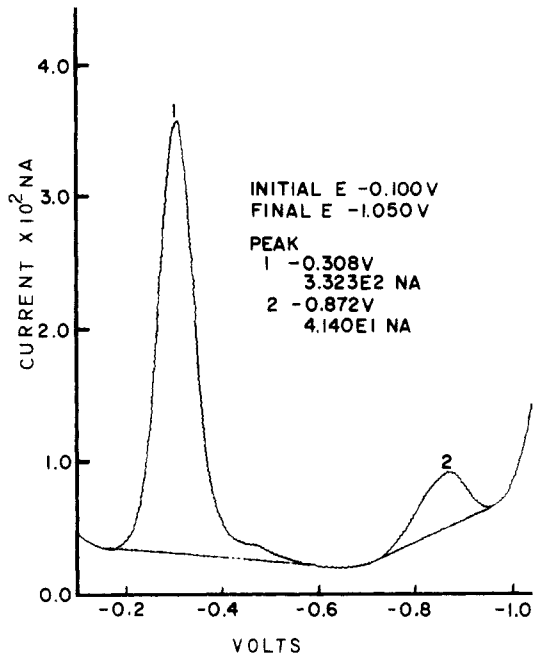

Figure 2. *N*-Nitrosocimetidine (10^{-5} M) in 0.1 M HCl.

determined in 0.1 M HCl, using usual degassing procedures. This supporting electrolyte and pH were chosen since it was found that both compounds yield maximum response and the sharpest peaks under these conditions. Nitrosocimetidine slowly decomposes at this acid concentration but at a rate of only about 5% per hour.

Over the time period of the polarographic run, about 5–10 min, no decompoisition was observed. The polarograms are shown in Figures 1 and 2. Cimetidine shows a characteristic peak potential at approximately –0.87 V; this peak is linear for concentrations ranging from 10^{-7} to 10^{-5} M. *N*-Nitrosocimetidine shows two characteristic peak potentials, the first at approximately –0.31 V and the second at approximately –0.87 V. The peak at –0.31 V is linear for nitrosocimetidine concentrations ranging from 10^{-4} to 10^{-7} M; the peak at –0.87 V is not linear over the same concentration range. The presence of the peak at –0.31 V allows one to distinguish *N*-nitrosocimetidine from cimetidine.

Experimental Section

All melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Unicam SP-1000 infrared spectrophotometer. The ^{1}H NMR spectra were determined by using a Varian XL-100 instrument and Me_4Si as internal standard. Differential pulse polarograms were determined as previously reported[7] except that an EG & G PARC Model 384 polarograph and Model 303 electrode were used. All potentials are reported vs. Ag/AgCl reference. The specific conditions were as follows: drop time, 1 s; scan rate, 4 mV/s; pulse height, 150 mV; drop size, large. [*N*-methyl-^{3}H]cimetidine (Code TRK 615) was purchased from Amersham. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

***N*-Nitrosocimetidine Hydrate (2).** To a stirred solution of cimetidine (2.25 g, 9 mmol) in 2 M hydrochloric acid (45 mL) at 0 °C was added a solution of sodium nitrite (2.1 g, 30 mmol) in water (15 mL). Stirring was continued for 40 min at 0 °C, and the yellow solution was basified to pH 10 with potassium carbonate and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed successively with saturated aqueous sodium chloride and water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, yielding a pale yellow oily residue which solidified to a yellow solid when kept at 0 °C overnight: mp 23–28 °C; IR (neat) 1440 (NO), 1630 (C=N), 2150 (C≡N), 3300 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 2.15 (s, imidazole CH_3), 2.50–2.70 (m, NCH_2CH_2S), 3.15 (s, $ONNCH_3$), 3.65 (m, NCH_2CH_2S), 3.95 (s, SCH_2-imidazole), 9.0 (s, imidazole H), 9.7 (br, NH). Anal. Calcd for $C_{10}H_{15}N_7OS{\cdot}H_2O$: C, 40.13; H, 5.68; N, 32.77; S, 10.70. Found: C, 40.15; H, 5.16; N, 32.91; S, 10.69.

[*N*-methyl-^{3}H]Nitrosocimetidine Nitrate (3b). To a solution of cimetidine (100 mg, 0.45 mmol) in 3 mL of ethanol was added [*N*-methyl-^{3}H]cimetidine (1.5 mg, 0.0067 mmol, radioactivity 1 mCi) in 1 mL of ethanol. Ethanol was removed under vacuum and to the residual white solid in a wide mouth beaker were added sodium nitrite (150 mg, 2.3 mmol) and 1 mL of water. To the stirred mixture at 0 °C was added 0.3 mL of concentrated hydrochloric acid over a period of 10 min. Stirring was continued for an additional hour at 0 °C. The white solid which separated was filtered, dried, and recrystallized from ethanol–2-propanol (1:1) to afford 100 mg (75% yield) of **3b**: mp 144–146 °C; IR (KBr) 1340 (NO_3), 1480 (NO), 1615 (C=N), 2155 (C≡N), 3310 (NH); NMR (Me_2SO-d_6) 2.3 (s, imidazole CH_3), 2.7–2.9 (m, NCH_2CH_2S), 3.25 (s, $ONNCH_3$), 3.5–3.7 (m, NCH_2CH_2S), 3.95 (s, imidazole-CH_2), 9.0 (s, imidazole H), 9.6–9.75 (br, HN); specific radioactivity 8.31 μCi/mg (2.33 μCi/mmol).

Acknowledgment. We thank the National Cancer Institute, DHEW (Grants CA-18618 and CA-09214), the Samual S. Fels Fund, and Temple University for support of this work.

Registry No. 1, 51481-61-9; 2, 73785-40-7; **3a**, 75523-16-9; **3b**, 76999-44-5.

Coupling of Aryl Grignard Reagents by Electron Transfer to Unsaturated 1,4-Dihalo Compounds

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Received November 13, 1980

The coupling of aromatic compounds has been the subject of numerous past and current investigations.[1-5] Of

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0022-3263/81/1946-2194$01.25/0

Table I. Coupling of Aromatic Grignard Reagents with Unsaturated 1,4-Dihalo Compounds

Grignard reagent from	biaryl	% yield[a] with promoter 1	2	3[b]	mp, °C	lit. mp,[c] °C
bromobenzene	biphenyl	86	92	73	69-71	70.5
4-bromotoluene	4,4'-dimethylbiphenyl	82	90	71	119-121	121
3-bromotoluene	3,3'-dimethylbiphenyl	80	83		bp 80-82 (0.05 mm)	bp 130 (1 mm)
4-bromoanisole[d]	4,4'-dimethoxybiphenyl	78	89		177-178	176-178
4-bromochlorobenzene	4,4'-dichlorobiphenyl	70	70	64	146-148	148
3-bromochlorobenzene	3,3'-dichlorobiphenyl	86	80	60	bp 318-319 (760 mm)	bp 320 (760 mm)
4-bromofluorobenzene	4,4'-difluorobiphenyl	77	63	60	87-88	91-92
1,4-dibromobenzene	4,4'-dibromobiphenyl	71			164-166	164
1-bromonaphthalene[d]	1,1'-binaphthyl	88			157-159	160
4-bromobiphenyl[d]	4,4'-quaterphenyl		85		318-320	320

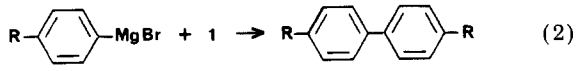
[a] Based on weight of crude solid. GC yields are slightly lower. [b] GC yields. Distilled technical grade 3 was used. [c] See ref 3. [d] Reaction solvent was tetrahydrofuran.

the modern aryl coupling methods, those involving the use of thallium salts[3] have been judged as perhaps the best.[6] However, each method has its characteristic shortcomings such as low yield,[4a] difficulty in workup,[7] or lack of generality (method will not couple *o*-aryl, secondary, and/or tertiary reagents[2-11]).

We report a new method of coupling aryl Grignard reagents which utilizes an organic coupling promotor rather than highly toxic thallium and hence is safer. Also, product workup and purification are more convenient,[3,7] yields are similar, and the procedure offers further promise because it provides a way of minimizing back electron transfer.

The procedure was serendipitously discovered while trying to prepare 1,4-diaryl-2-butynes by the reaction shown in eq 1, where Ar = *p*-$CH_3C_6H_4$. Instead of isolating the 1,4-diaryl-2-butyne, a highly crystalline biaryl was obtained (eq 2). Maximum yields were obtained when the molar ratio of Grignard to dichloro-2-butyne was 1:1 (Table I).

$$2\ ArMgBr + ClCH_2C{\equiv}CCH_2Cl \xrightarrow{\not\rightarrow} \underset{1}{ArCH_2C{\equiv}CCH_2Ar} \quad (1)$$



(2)

The cis and trans isomers of 1,4-dichloro-2-butene (**2** and **3**, respectively) were also found to promote coupling in high yields but propargyl chloride, 4-octyne, 1,2-dichloroethane, benzyl chloride, and *trans*-1,4-dibromo-2-butene did not. Previous work[8,9] has shown that high yields of the normal substitution product result when phenylmagnesium bromide is treated with 3-chloro- and 3-bromopropene ($PhCH_2CH{=}CH_2$), and two literature reviews[10,11] cite only one example of an alkyl halide coupling promoter. In that case, Korshak[12] reported that hexachloroethane promotes aryl coupling,[12] but only in low yields (approximately 35%). Thus, **1-3** exhibit novel behavior.

Levina and co-workers did treat methyl, ethyl, propyl, and butyl Grignards with **1** and **3** and reported low yields of aliphatic coupling products ($2RMgX \rightarrow RR$)[13] as a minor competitive process along with the normal halide displacement reaction products. However, they did not attempt to optimize such reactions nor did they extend the reaction to aryl Grignard reagents where the higher electron density of aromatics would facilitate higher coupling yields.

Ease of workup in our method results because when electron transfer occurs to the 1,4-dihalide, the coupling promoter is tranformed into an easily removed material. For example, **1** forms and insoluble polymer[14] which is merely filtered off to leave an ether/biaryl mixture with small amounts of $ArCH_2C{\equiv}CCH_2Cl$. The dichlorobutenes accept an electron(s) and form butadiene[12] (we are investigating the possibility of other gaseous products) which boils out of the reaction mixture, leaving little or no promoter product to remove. This facilitates product purification, but, more importantly, it assures minimized back electron transfer.

In a typical reaction[15] a solution of 2.50 g (0.02 mol) of *cis*-1,4-dichloro-2-butene in 5 mL of ether was added dropwise over 10 min to a refluxing solution of 0.02 mol of phenylmagnesium bromide in 20 mL of ether. The resulting mixture was refluxed with stirring for 3 h. Workup consisted of neutralization with 5% HCl and washing the organic layer with saturated sodium bicarbonate and water and drying over magnesium sulfate. Upon evaporation of the ether, large crystals of biphenyl resulted (1.42 g, 92%). The same reaction conducted without the dichloro-2-butene promoter added gave biphenyl in 5% yield.

Typically, the biaryl and a small quantity (9-15%) of the normal substitution product (e.g., $ArCH_2CHCH{=}$

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(7) Reference 3 described the use of column chromatography to remove the thallium salt. In our procedure, a crystalline product is obtained which requires only simple recrystallization for purification.

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(14) The polymer is similar to that obtained by treating 1,4-dichloro-2-butyne with magnesium, in which the formation and polymerization of butatriene is implicated. See: Schubert, W. M.; Liddicoet, T. H.; Lanka, W. A. *J. Am. Chem. Soc.* **1954**, *76*, 1929.

(15) Our method failed to couple ortho-substituted Grignard reagents. The thallium method did too (see ref 3).

$CHCH_2Cl$) were essentially the only compounds observed by GC analysis. For example, the reaction of 1,4-dichloro-2-butyne (1) and *m*-chlorophenylmagnesium bromide gave a product distribution of 15% *m*-$ClC_6H_4CH_2C{\equiv}CCH_2Cl$ and 85% biaryl, according to GC–MS analysis. However, the *p*-bromo- and *p*-fluoroaryl Grignards gave a significant number of side products. Apparently, these para electron-withdrawing groups repress the desired electron transfer in favor of other competitive processes. For example, the product distribution for the reaction of 2 and the Grignard made from *p*-dibromobenzene in ether was 14% $CH_2{=}CHCH(p\text{-}BrC_6H_4)CH_2Cl$ (from an S_N2'-like reaction on 1,4-dichloro-2-butene), 8% *p*-$BrC_6H_4CH_2CH{=}CHCH_2Cl$, 12% 4-bromobiphenyl, 62% 4,4′-dibromobiphenyl, and 4% of a tribromobiphenyl.

The product mixture was even more complex for the reaction between 2 and the Grignard reagent made from *p*-bromofluorobenzene. Product composition was 8% $CH_2{=}CHCH(p\text{-}BrC_6H_4)CH_2Cl$, 14% *p*-$BrC_6H_4CH_2CH{=}CHCH_2Cl$, 68% 4,4′-difluorobiphenyl, 6% of a difluorobromobiphenyl, 1.5% of a bromofluorobiphenyl, and 2% of an unidentified compound.

We believe this chemistry may be useful as a probe for electron-transfer phenomena and are therefore investigating the reaction mechanism and ways of improving the coupling yields of alkyl Grignards.[13] In a separate paper we describe the use of this chemistry to prepare aromatic polymers[16] in high yields.

Experimental Section

Infrared spectra were obtained with Perkin-Elmer 137 and Beckman IR 10 spectrophotometers. Gas chromatographic analyses were obtained on a Hewlett-Packard 5712 TC detector instrument. Integration of peak areas was done on a Hewlett-Packard 3380 A integrator-recorder. NMR spectra were recorded on a Varian EM-360 spectrometer. Low-resolution mass spectra were obtained on a Varian MAT A GC/MS. Melting points are uncorrected and were obtained on a Mel-Temp apparatus. All chemicals were commercially obtained in reagent purity.

General Procedure for Coupling of Aryl Grignard Reagents. The Grignard reagent was typically prepared in 20 mL of ether from 0.53 g of magnesium (0.022 mol) and 0.022 mol of aryl bromide. Then, to the ice-water-cooled Grignard was added a solution of 0.020 mol of the dihalobutene (2 or 3) or butyne (1) in 5 mL of dry ether. After a 3-h reflux, the mixture was cooled with an ice-water bath, and a small amount of 4% HCl was added to make the solution just acidic to litmus. The aqueous layer was separated and the organic layer (if coupler 1 was used, the organic layer was filtered) was washed with 5% sodium bicarbonate and water and dried ($MgSO_4$). Air or rotary evaporation in vacuo then normally left a solid biaryl product. Liquids obtained (3,3′-biaryls) were distilled by using a 9-in. Vigreux column (see Table I). Product comparisons were made by NMR, melting point, and GC or GC–MS (with authentic samples). Three Grignards were prepared in THF (see Table I) instead of ether.

3,3′-Dichlorobiphenyl by means of 1,4-Dichloro-2-butyne (1) Promoter. A Grignard was prepared in 20 mL of ether from 0.54 g (0.022 mol) of magnesium and 4.30 g (0.022 mol) of 3-bromochlorobenzene. Then 2.48 g (0.02 mol) of 1,4-dichloro-2-butyne in 5 mL of ether was added dropwise over 15 min. The resulting mixture was refluxed for 3 h and then workup was done as above. A brown liquid (2.26 g) was obtained, which was 15% *m*-$ClC_6H_4CH_2C{\equiv}CCH_2Cl$ and 85% 3,3′-dichlorobiphenyl (1.92 g, 86% yield). Retention times were 6.9 and 14.1 min, respectively (6 ft × 0.125 in. 10% polyphenyl ether column at 225 °C). In GC–MS (6 ft × 0.125 in. 3% OV 17 column, 100–300 °C at 10 °C/min), the former compound's retention time was 7.4 min: *m/z* (relative intensity) 202 (1), 200 (9), 198 (12), 163 (55), 128 (100), 127 (90). The 3,3′-dichlorobiphenyl eluted at 8.8 min: *m/z* (relative intensity) 226 (10), 224 (54), 222 (100), 152 (99), 76 (30), 75 (25). The product distilled at 318–319 °C (lit.[3] bp 320).

4,4′-Difluorobiphenyl by means of *cis*-1,4-Dichloro-2-butene (2) Promoter. The reaction was performed as described above only with the Grignard from *p*-bromofluorobenzene and 2 as the promoter. The solid product was recrystalized twice from ethanol [mp 87–88 (lit.[3] mp 91–92 °C)]. The crude product (1.77 g) was 68.1% pure (63%) as determined by GC–MS analysis (5% SE-30 column, 160 °C, 6.12 min). Other products were 8% $CH_2{=}CHCH(p\text{-}FC_6H_4)CH_2Cl$ (3.5 min) 14% *p*-$FC_6H_4CH_2CH{=}CHCH_2Cl$ (5.0 min), 6% unknown compound (7.2 min), 1.5% of a difluorobromobiphenyl (11.1 min), 0.5% bromofluorobiphenyl (11.8 min), and 2% unknown compound (13.2 min).

Acknowledgment. We thank Peter Kovacic, Michael P. Doyle, and the Purdue University Organic Chemistry Faculty for helpful discussions. M. Beeny provided valuable GC–MS assistance. We also thank Research Corporation (C1108) and the National Science Foundation (CDP-8006131) for supporting this work.

Registry No. 1, 821-10-3; 2, 1476-11-5; 3, 110-57-6; bromophenylmagnesium, 100-58-3; bromo-*p*-tolylmagnesium, 4294-57-9; bromo-*m*-tolylmagnesium, 28987-79-3; bromo(*p*-methoxyphenyl)magnesium, 13139-86-1; bromo(*p*-chlorophenyl)magnesium, 873-77-8; bromo(*m*-chlorophenyl)magnesium, 36229-42-2; bromo(*p*-fluorophenyl)magnesium, 352-13-6; bromo(*p*-bromophenyl)magnesium, 18620-02-5; bromo-1-naphthylmagnesium, 703-55-9; 4-biphenylylbromomagnesium, 3315-91-1; biphenyl, 92-52-4; 4,4′-dimethylbiphenyl, 613-33-2; 3,3′-dimethylbiphenyl, 612-75-9; 4,4′-dimethoxybiphenyl, 2132-80-1; 4,4′-dichlorobiphenyl, 2050-68-2; 3,3′-dichlorobiphenyl, 2050-67-1; 4,4′-difluorobiphenyl, 398-23-2; 4,4′-dibromobiphenyl, 92-86-4; 1,1′-binaphthyl, 604-53-5; 4,4′-quaterphenyl, 135-70-6; tribromobiphenyl, 51202-79-0; difluorobromobiphenyl, 77029-20-0; $CH_2{=}CHCH(p\text{-}BrC_6H4)CH_2Cl$, 77028-08-1; (*Z*)-*p*-$BrC_6H_4CH_2CH{=}CHCH_2Cl$, 77028-09-2; *m*-$ClC_6H_4CH_2C{\equiv}CCH_2Cl$, 77028-10-5; $CH_2{=}CHCH(p\text{-}FC_6H_4)CH_2Cl$, 77028-11-6; (*Z*)-*p*-$FC_6H_4CH_2CH{=}CHCH_2Cl$, 77028-12-7.

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Formation of Dioxolanes from Carbonyl Compounds: Favored 5-Trigonal Cyclizations[1a]

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Received February 3, 1981

A few years ago, a series of rules was formulated which permitted predictions to be made regarding the ease with which certain cyclizations may occur.[2] Particularly important among these, in a predictive sense, has been that, in a chain of five first row atoms, attack by a nucleophilic atom at one end (atom 1) onto atom 5 of a 4,5-double bond is a "disfavored" path to a five-membered ring. In contrast, similar attack on atom 5 of a 5,6-double bond in a six-atom chain is "favored". These processes, which were denoted 5-endo-trig and 5-exo-trig, respectively, are depicted in eq 1 and 2. The rules were based on empirical data rather than on theory, and a critical consideration was the importance of the direction of approach of a nucleophile toward a double bond that had been deduced from crystallographic studies.[3] This approach vector is dis-

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