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Coupling Reaction of Grignard Reagents with α,ω-Dibromoalkanes in the Presence of Copper(I) Bromide–HMPA: Preparation of α,ω-Bis(vinylaryl)alkanes

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Synopsis. The coupling reaction of Grignard reagents with α,ω-dibromoalkanes took place smoothly in THF/HMPA (12:1) in the presence of a catalytic amount of copper(I) bromide and gave the products in 60—100% yields. Several α,ω-bis(vinylaryl)alkanes were prepared in reasonable yields by the application of this reaction.

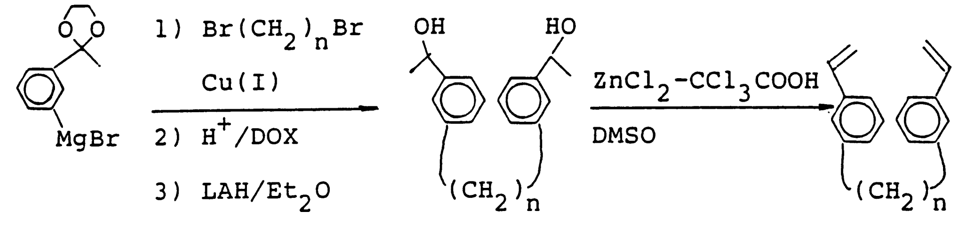
The coupling reaction of Grignard reagents with alkyl halides has been known to be induced by many transition metal halides[1–5] and sometimes to proceed without catalysts.[6] Recently we have found a facile coupling reaction of Grignard reagents with α,ω-dibromoalkanes in THF in the presence of a catalytic amount of copper(I) bromide and a small amount of HMPA. Our method gives comparable or even better yields in some cases than those using Tamura-Kochi's catalyst Li_2CuCl_4,[5,7] and we have successfully applied it to the preparation of several α,ω-bis(vinylaryl)alkanes of recent interest.[8,9]

$$\mathrm{ArMgBr} \xrightarrow[\mathrm{CuBr/HMPA,\ THF}]{\mathrm{Br(CH_2)_{\mathit{n}}Br}} \mathrm{Ar(CH_2)_{\mathit{n}}Br} + \mathrm{Ar(CH_2)_{\mathit{n}}Ar} \qquad (1)$$

Results are summarized in Table 1. The reverse addition of the Grignard reagent and the use of copper(I)–HMPA as catalyst are essential for this coupling. Without the catalyst, the reaction gave products in much poorer yields. In the present method, only a small amount of HMPA is enough for dissolving copper(I) bromide and the recommended volume ratio of THF/HMPA is 12. Although the copper-catalyzed Grignard coupling is wellknown,[1,4,5,7] the present procedure seems to be more useful than the previous ones for the coupling of arylmagnesium halide because of its simplicity, comparatively high yields of products, and easy availability of necessary chemicals.

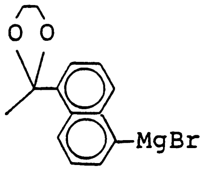
The reaction was successfully applied to the synthesis of several styrene derivatives which are less easily accessible by other methods based on Friedel–Crafts acylation of diarylalkanes.[8] The reaction sequence for the synthesis of α,ω-bis(*m*-vinylphenyl)alkanes **5** and **6** is shown in Eq. 2, and results of the preparations of diolefins **5** to **9** from the corresponding Grignard reagents **1** to **4** are summarized in Table 2.

Although compound **9** may be prepared through



(2)

1 **5** n=3 **6** n=6



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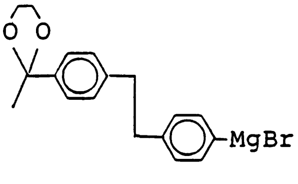

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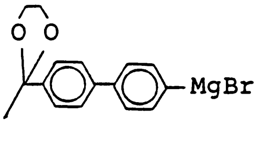

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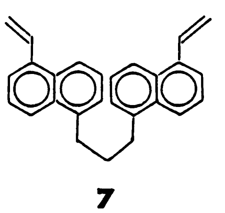

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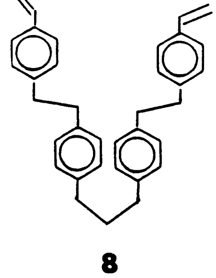

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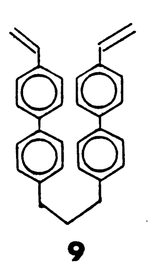

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Table 1. Coupling Reaction of Grignard Reagents with α,ω-Dibromoalkanes[a]

RMgBr	$Br(CH_2)_nBr$ n	Yield/%			
		R-R[b]	$R(CH_2)_nBr$	$R(CH_2)_nR$	Total[c]
PhMgBr	3	3	81	16	100
1	3	tr (2)[d]	81 (43)[d]	11 (8)[d]	92 (53)[d]
1	4	tr	79	21	100
1	5	tr	76	18	94
1	6	tr	77	23	100
2-NaphMgBr	3	6	53	29	88
i-PrMgBr[e]	6	—[f]	44	16	60

a) Reaction conditions: RX, 10 mmol; dibromoalkane, 12 mmol; CuBr, 0.5 mmol; THF, 12 ml; HMPA, 1 ml; reflux for 4 h. b) Kharasch reaction products. c) Determined by GLC, using internal standards (based on RX). d) A solution of CuBr and 1,3-dibromopropane in HMPA was added to a THF solution of the Grignard reagent, free from any Mg turnings. e) At r.t. f) Not determined.

Table 2. Preparation of α,ω-Bis(vinylaryl)alkanes

RMgBr	$Br(CH_2)_n$-Br n	Mole ratio[a]	Yield/%		Product	Mp θ_m/°C	MS(M+·) Found (Calcd)	¹H NMR chem, shift δ (intensity, multiplicity, J in Hz)
			Glycol[b]	Diene[c]				
1	3	2:1	58	78	**5**	—[d]	248.1555 (248.1566 for $C_{19}H_{20}$)	1.91 (2H, m), 2.60 (4H, bt), 5.12 (2H, dd, 10.0 and 1.5), 5.62 (2H, dd, 18.1 and 1.5), 6.62 (2H, dd, 10.0 and 18.1), 7.10 (8H, m).
1	6	2:1	75	50	**6**	—[d]	290.2033 (290.2036 for $C_{22}H_{26}$)	1.50 (8H, m), 2.53 (4H, bt, 7.0), 5.10 (1H, dd, 10.8 and 2.0), 5.60 (1H, dd, 17.6 and 2.0), 6.62 (1H, dd, 10.8 and 17.6), 7.12 (8H, m).
2	3	2:0.7	73	79	**7**	79—80	348.1869 (348.1879 for $C_{27}H_{24}$)	2.22 (2H, quin, 7.1), 3.20 (4H, t, 7.1), 5.46 (2H, dd, 10.7 and 1.2), 5.76 (2H, dd, 17.9 and 1.2), 7.30—7.64 (10H, m), 7.91 (2H, d, 7.9), 7.99 (2H, d, 7.9).
3	3	2:0.7	81	81	**8**	152—154	456.2811 (456.2819 for $C_{35}H_{36}$)	1.94 (2H, m), 2.63 (4H, t, 7.1), 2.90 (8H, s), 5.20 (2H, dd, 11.2 and 1.2), 5.72 (2H, dd, 17.7 and 1.3), 6.72 (2H, dd, 17.7 and 11.2), 7.13 (8H, s), 7.25 (8H, A_2B_2).
4	3	2:0.7	63	75	**9**	162—164	400.2188 (400.2192 for $C_{31}H_{28}$)	2.02 (2H, quin, 7.1), 2.72 (4H, t, 7.1), 5.26 (2H, dd, 10.3 and 0.8), 5.78 (2H, dd, 17.1 and 0.8), 6.76 (2H, dd, 17.1 and 10.3), 7.22—7.64 (16H, m).

a) Grignard reagent vs. dibromide. b) Isolated yield of glycol (based on dibromoalkane). c) Isolated yield (based on glycol). d) Thick oil.

the Friedel–Crafts acetylation of 1,3-bis(4-biphenylyl)propane derived from a poorly soluble aldol condensation product, 1,3-bis(4-biphenylyl)propenone, the present sequence allows its synthesis more conveniently, being carried out in a homogeneous system.

Experimental

¹H NMR spectra were recorded on Varian T-60A and XL-200 NMR spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi M-80A mass spectrometer. GLC analyses were done by a Shimadzu GC-4CIT gas chromatograph (OV-17, 3%, 2 m, 250—300 °C). Melting points were not corrected. Tetrahydrofuran was dried with benzophenone ketyl and distilled just before use. HMPA was heated over calcium hydride for prolonged time under a nitrogen atmosphere, then distilled in vacuo and stored over molecular sieves (3A) under the same atmosphere. Commercial copper(I) bromide of highest grade was used without purification.

Coupling Reaction of Arylmagnesium Bromide with α,ω-Dibromides (General Procedure). Grignard reagent **1** was prepared in dry THF (600 ml) from *m*-bromoacetophenone ethylene acetal (130 g, 0.552 mol) and Mg turnings (16.1 g, 0.662 mol) under a nitrogen atmosphere.[10] After the completion of reaction excess Mg turnings were removed[11] and the solution was added dropwise over 1 h to a vigorously stirred mixture of dry HMPA (50 ml), 1,3-dibromopropane (55.7 g, 0.552 mol),[12] and copper(I) bromide (1.98 g, 5 mol% to the Grignard reagent) under reflux. The dark green mixture was refluxed for further 4 h with stirring, then poured into ice–HCl mixture (500 ml) to decompose organometallic compounds. The aqueous phase was extracted with benzene three times. The combined extracts were washed successively with water three times, with aq NaOH, and again with water. The mixture was dried over Na_2SO_4 and then condensed by evaporation. The residue was distilled in vacuo; *m*-(3-bromopropyl)acetophenone ethylene acetal was obtained as a thick oil in a 33.8% yield (45.4 g, 103 °C/0.05 mmHg) and 1,3-bis(*m*-acetylphenyl)propane bis(ethylene acetal) as a solid residue (mp, 95—96 °C) in a 60.4% yield (59.0 g).

Preparation of 1,3-Bis(*m*-vinylphenyl)propane 5 (Typical Procedure). The above bis-adduct (59.0 g) was dissolved in dioxane (500 ml) without further purification. To this solution 10% aq HCl (500 ml) was added and the mixture was stirred overnight at room temperature. The reaction mixture was extracted with benzene three times, then the combined extracts were washed with aq $NaHCO_3$ followed by water three times, dried over Na_2SO_4, and condensed by evaporation to give 1,3-bis(*m*-acetylphenyl)propane. The diketone was reduced by $LiAlH_4$ in ether and the glycol obtained was purified by column chromatography (SiO_2, cyclohexane/AcOEt=4:1—1:1). The overall yield was 43.1 g (95.5%). The glycol (4.00 g) was dehydrated by the reported method[13] to afford 1,3-bis(*m*-vinylphenyl)propane **5**, which was purified by column chromatography (SiO_2, petroleum ether/cyclohexane).[14] Yield was 2.31 g (78.0%).

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11) Since the remaining Mg turnings readily react with 1,3-dibromopropane to afford cyclopropane, we used head-to-head connected hypodermic needles (ϕ 1.0 mm) to transfer the Grignard reagent by appling a nitrogen pressure.

12) Dibromomethane and 1,2-dibromoethane did not undergo the coupling reaction efficiently (see also Ref. 1a).

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14) For the purification of compounds **7**, **8**, and **9**, a cyclohexane–benzene mixture was used as an eluent.