[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

The Coupling of Aryl Grignard Reagents to Benzyl Systems

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The coupling of aryl Grignard reagents to benzyl systems has been found to be a broad, useful method for the easy preparation of diarylmethane-type molecules in high yield.

In connection with the synthesis of certain polynuclear systems containing the thiophene ring,[2] we attempted to prepare 2-(2-chlorobenzyl)thiophene, a necessary intermediate. All attempts to prepare this compound in a way similar to the one used to prepare 2-chlorodiphenylmethane[3] failed. When 2-thienylmagnesium bromide was added to 2-chlorobenzaldehyde the reaction appeared to proceed smoothly but when an attempt was made to distil the product it decomposed. An attempt to reduce the hydrol, 2-chlorophenyl-2-thienylcarbinol, without prior distillation, also failed.

The Friedel-Crafts reaction between thiophene and 2-chlorobenzyl chloride in the presence of zinc chloride[4] at 40° led to recovery of starting materials. When the reaction temperature was raised to 90° there was obtained only 14% of the desired 2-(2-chlorobenzyl)thiophene and 24% of a compound whose analysis checked for 2,5-di(2-chlorobenzyl)thiophene.

According to Tiffeneau,[5] allylbenzene was obtained from phenylmagnesium bromide and allyl bromide. As the benzyl system is in certain respects similar to the allyl system, we attempted the cross coupling of 2-thienylmagnesium bromide with 2-chlorobenzyl chloride. When the condensation was attempted in an ether solution, only starting materials were recovered; however, at 60°, an excellent yield of the desired product was obtained. In view of the great simplicity of this reaction, the easy work-up of the product, and the excellent yield, we sought to extend this cross coupling reaction to the preparation of substituted diphenylmethanes and substituted naphthylphenylmethanes. These compounds, which have served[6,7] as valuable intermediates in our research program, were all readily prepared in good yields. The literature with regard to the reactions of Grignard reagents is reported thoroughly in Kharasch and Reinmuth's book.[8] Although the crossed-coupling of Grignard reagents with benzyl systems has been reported, the majority of such examples involve alkyl Grignard reagents. The available information concerning crossed-coupling with aryl Grignard reagents is misleading. Almost all such cases seem to involve the activating influence of a methoxy group in the benzyl system and one experiment,[9] apparently erroneous, reported no crossed-coupling product when phenylmagnesium bromide was treated with benzyl chloride in benzene at 60°. We obtained an essentially quantitative yield of diphenylmethane under these conditions. Excellent yields were also obtained when electron-withdrawing groups were present in the benzyl system. Contrary to what the literature suggests, the cross coupling of aryl Grignard reagents with benzyl systems proceeded in high yields and is an excellent synthetic route to the preparation of many diarylmethane-type molecules. The reaction appears to be quite broad in scope and our experiments suggest that the reaction may be used with a large variety of benzyl-type systems which may contain either electron-attracting or electron-withdrawing groups and that the aryl Grignard reagent may also be so varied and that it may be mono-, poly-, or hetero-cyclic. The data obtained with benzyl chlorides and various phenylmagnesium bromides are summarized in Table I.

Although a study of the reaction mechanism[10] was not made, the following experiments are consistent with the concept of an ionic reaction and are of interest to one concerned with the reaction as a synthetic tool.

The reaction was complete within five minutes.

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[1] This paper has been abstracted from the Doctorate thesis of Sih-gwan Quo and the Masters thesis of John Sheridan presented to the Virginia Polytechnic Institute in 1959 and 1960 respectively.

[2] A manuscript which describes the successful completion of this work is being prepared.

[3] C. K. Bradsher, *J. Am. Chem. Soc.*, **62**, 486 (1940).

[4] Stronger catalysts such as aluminum chloride gave tars.

[5] M. Tiffeneau, *Compt. rend.*, **139**, 482 (1904).

[6] F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, **77**, 3413 (1955).

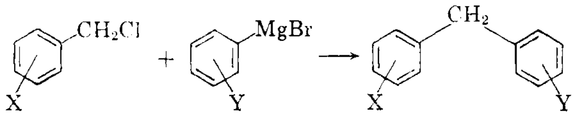
[7] F. A. Vingiello and J. G. Van Oot, *J. Am. Chem. Soc.*, **73**, 5070 (1951).

[8] M. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954.

[9] H. Gilman and H. L. Jones, *J. Am. Chem. Soc.*, **51**, 2841 (1929). Unfortunately, the error in this paper is repeated in ref. 8, p. 1060.

[10] C. D. Mukai, Ph.D. thesis, New York University, 1955, and R. T. Morrison, N. P. Loire, and F. L. Bach, Jr., Abstracts, American Chemical Society Meeting, April, 1960, p. 20. These researches are concerned with the functional exchange between Grignard reagents and benzyl halides. Again the work concerned only alkyl halides and no mention was made of the cross coupling reaction as a useful synthetic tool.

TABLE I



I II III

I	II	III	Yield, %
X = H	Y = H	X = H, Y = H	Quant.
X = H	Y = 4-Cl	X = H, Y = 4-Cl	75
X = H	Y = 4-CH$_3$	X = H, Y = 4-CH$_3$	80
X = H	Y = 4-OCH$_3$	X = H, Y = 4-OCH$_3$	75
X = 2-F	Y = H	X = 2-F, Y = H	85
X = 2-Cl	Y = H	X = 2-Cl, Y = H	88
X = 4-Cl	Y = 4-CH$_3$	X = 4-Cl, Y = 4-CH$_3$	80
X = 4-Cl	Y = 4-OCH$_3$	X = 4-Cl, Y = 4-OCH$_3$	85

Irradiation of the reaction mixture with ultraviolet light was without effect on the yield. The following reagents, when added to the Grignard reagent prior to the addition of the benzyl halide, had no effect on the yield: hydroquinone, benzoyl peroxide, cobaltous chloride, and ferric chloride.

A reaction temperature of about 60–70° was found effective. Only starting materials were recovered when reactions were run in ether at room temperature. Good yields were obtained when the reactions were run in benzene at 60–70° and no improvement was realized when the reaction temperature was raised by using toluene or *p*-xylene as the solvent.

When tetrahydrofuran was used as the solvent no crossed-coupling product was obtained but the Grignard reagent self-coupled.

No change in yield was observed when the Grignard reagent was added to the benzyl system (reverse addition).

EXPERIMENTAL[11,12]

2-Fluorodiphenylmethane (III. X = 2-F, Y = H).[13] A Grignard reagent was prepared from 7.3 g. (0.30 g.-atom) of magnesium tunings and 47 g. (0.30 mole) of bromobenzene dissolved in 150 ml. of dry ether. When the reaction was complete, the ether was replaced with dry benzene. This established a boiling point of 73° for the mixture. To this hot solution there was added 22 g. (0.15 mole) of 2-fluorobenzyl chloride dissolved in 100 ml. of dry benzene. The mixture was heated under reflux for 1 hr.[14] and then cooled and decomposed with 100 ml. of cold *4N* hydrochloric acid. The organic layer was separated, washed with water, dried over calcium chloride, concentrated, and distilled. This gave 25 g. (85%) of 2-fluorodiphenylmethane, b.p. 108–111° (3.8 mm.).

The above sample was fractionated again to give the analytical sample, b.p. 103–104° (2.3 mm.), n_D^{22} 1.5608.

Anal. Calcd. for $C_{13}H_{11}F$: C, 83.87; H, 5.91. Found: C, 84.19; H, 5.85.

4-Chloro-4'-methyldiphenylmethane (III. *X* = *4* − *Cl*, *Y* = *4* − *CH*$_3$). A Grignard reagent was prepared from 7.3 g. (0.30 mole) of magnesium turnings and 51 g. (0.30 mole) of 4-bromotoluene. This was allowed to react with 25 g. (0.15 mole) of 4-chlorobenzyl chloride in benzene at a reaction temperature of 73°. This gave 26 g. (80%) of 4-chloro-4'-methyldiphenylmethane, b.p. 120–127° (0.3 mm.).

The above sample was fractionated again to give the analytical sample, b.p. 112–114° (0.1 mm.), n_D^{27} 1.5779.

Anal. Calcd. for $C_{14}H_{13}Cl$: C, 77.49; H, 6.05; Cl, 16.35. Found: C, 77.36; H, 6.11; Cl, 16.11.

2-(2-Chlorobenzyl)thiophene (*via a crossed-coupling reaction*). The Grignard reagent from 36 g. (0.22 mole) of 2-bromothiophene and 5.3 g. (0.22 mole) of magnesium turnings was allowed to react with 36 g. (0.22 mole) of 2-chlorobenzyl chloride. The reaction temperature was 60°. This gave 33 g. (72%)[15] of 2-(2-chlorobenzyl)thiophene, b.p. 113–114° (1 mm.). The analytical sample was taken from a center-cut of this fraction.

Anal. Calcd. for $C_{11}H_9Cl$ S: C, 63.30; H, 4.34; Cl, 17.00; S, 15.36. Found: C, 62.69; H, 4.19; Cl, 17.20; S, 15.54.

2-(2-Chlorobenzyl)thiophene and 2,5-di(2-chlorobenzyl)-thiophene (*via a Friedel-Crafts reaction*). A mixture of 21 g. (0.25 mole) of thiophene, 42 g. (0.25 mole) of 2-chlorobenzyl chloride, 34 g. (0.25 mole) of zinc chloride, and 60 ml. of petroleum ether (b.p. 80–100°) was stirred and heated under reflux for 8 hr. The mixture was cooled, poured into cold water and the organic layer separated, washed with water, dried over calcium chloride, and concentrated. On distillation of the residue two fractions were obtained: first; 2-(2-chlorobenzyl)thiophene, b.p. 113–114° (1 mm.), 7.0 g. (14%), and second; a fraction assumed to be 2,5-di(2-chlorobenzyl)-thiophene, b.p. 190–192 (5 mm.), a pale yellow oil with a strong blue fluorescence, 10 g. (24%). The analytical sample was taken from a center-cut of this fraction.

Anal. Calcd. for $C_{18}H_{14}Cl_2$ S: C, 64.86; H, 4.23; Cl, 21.24; S, 9.62. Found: C, 63.98; H, 4.05; Cl, 21.99; S, 9.98.

1-Naphthylphenylmethane. The Grignard reagent from 7.3 g. (0.30 mole) of magnesium turnings and 62 g. (0.30 mole) of 1-bromonaphthalene was allowed to react with 19 g. (0.15 mole) of benzyl chloride. There was obtained 20 g. (65%) of 1-naphthylphenylmethane, b.p. 217–220° (19 mm.) (lit.[16] b.p. 217–220° (20 mm.)), white solid from ethanol, m.p. 55–56° (lit.[16] m.p. 58°), and 11 g. of naphthalene, b.p. 107–116° (20 mm.), white solid from ethanol, m.p. 80°.

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(11) All boiling points are uncorrected. All melting points are corrected.

(12) All analyses were carried out by the Geller Microanalytical Laboratories, Bardonia, N. Y.

(13) Only this experiment is described in some detail. The other cross coupling reactions were carried out in a similar way and the work-up followed usual organic laboratory procedures. The yields are given in Table I.

(14) Later experiments showed that the reaction was complete after 5–10 min.

(15) This yield could undoubtedly be increased if sufficient Grignard reagent were employed.

(16) I. Heilbron, *Dictionary of Organic Compounds*, Vol. 3, p. 432, Oxford University Press, New York, 1934.