Tetrahedron Vol. 49, No. 16, pp. 3405-3410, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

Evidence for the Occurrence of Substitution Side Products in Grignard Reactions

Nordin Hj. Lajis*, Mohammad Niyaz Khan, and Hazimah A. Hassan

Department of Chemistry, Universiti Pertanian Malaysia,
43400 UPM Serdang, Selangor Darul Ehsan, Malaysia.

(*Received in UK* 1 *February* 1993)

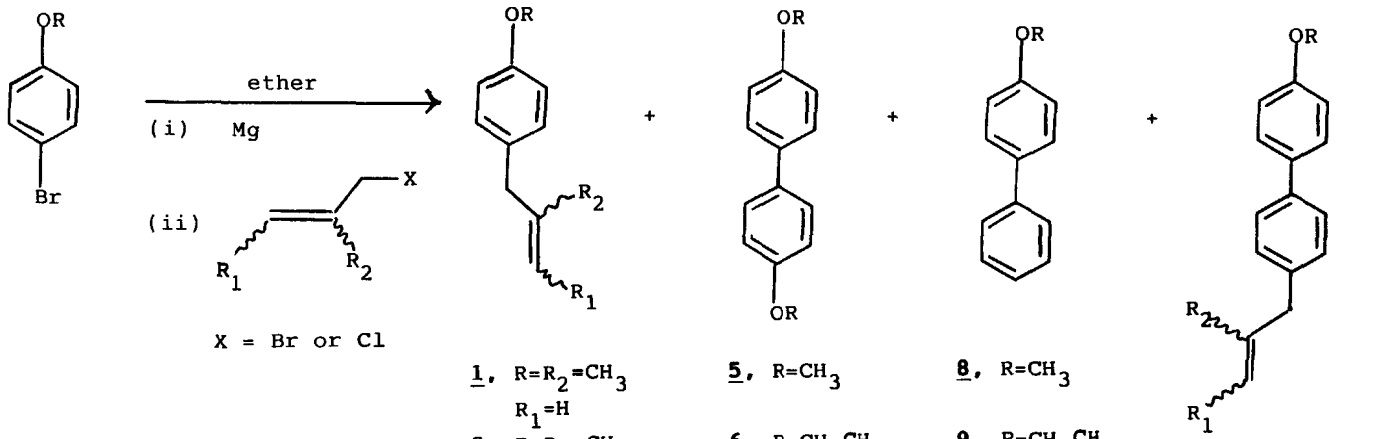
Abstract: **In the formation of Grignard reagents from 4-bromoalkoxybenzene and their subsequent coupling reactions with allylic halides, the unusual minor side products, 8 - 14 have been obtained.**

Introduction

Although the Grignard reagents have been known and are the most useful synthetically since 1900, the mechanism of its formation is still not well understood[1]. The adsorption model mechanism proposed by Kharasch and Reinmuth[2] and substantiated by Walborsky[3] presumes that the intermediate radicals which involved during the formation and various side products remain adsorbed on the Mg surface. Garst *et al.*[4] have recently questioned the validity of this model and have suggested that all radicals produced in Grignard reagent formation diffuse freely through the solution (the diffusion model). The side products obtained during the Grignard reagent formation are due to radical isomerization, attack on solvent, and dimerization[3]. To synthesize the analogues of estragole (an attractant for the oil palm pollinating weevil, *Elaeidobius kamerunicus*[5]), we synthesized the Grignard reagents of 4-alkoxybromobenzenes. Besides the normal dimer side product, unusual side products were also formed by substitution reaction between two molecules of Grignard reagent. The details are described in this paper.

RESULTS AND DISCUSSION

In our attempt to synthesize compounds **1 - 4**, we carried out the reactions shown in Scheme 1. The apparent experimental yields of the major products, **1 - 4** and **5 - 7**, were 20 - 40% and 5 - 11%, respectively; while those of minor products, **8 - 14** ranged from 0.1 to 0.8%. Compounds **1 - 8** were obtained in pure form whereas compounds **9 - 14** were detected from the analysis of the spectra of the products



1, $R=R_2=CH_3$, $R_1=H$

2, $R=R_1=CH_3$, $R_2=H$

3, $R=CH_2CH_3$, $R_1=R_2=H$

4, $R=CH(CH_3)_2$, $R_1=R_2=H$

5, $R=CH_3$

6, $R=CH_2CH_3$

7, $R=CH(CH_3)_2$

8, $R=CH_3$

9, $R=CH_2CH_3$

10, $R=CH(CH_3)_2$

11, $R=R_2=CH_3$, $R_1=H$

12, $R=R_1=CH_3$, $R_2=H$

13, $R=CH_2CH_3$, $R_1=R_2=H$

14, $R=CH(CH_3)_2$, $R_1=R_2=H$

Scheme 1

mixtures. The estimated proportions of each compound in the product mixture were calculated from the integrals of characteristic proton signals in the NMR spectrum. To the best of our knowledge, no reports have appeared showing the existence of products similar to **8** - **14** in reactions involving Grignard reagents. Even though no conclusive evidence of the mechanism for their formation could be established, possible involvement of free radicals might have taken place in these reactions[1-4].

Table 1: Apparent Experimental Yields of the Major and Minor Coupling Products.

$RMgBr + R_1X \longrightarrow$	$R-R_1$	$R-R$	$R-Ph$	$1,4-RC_6H_4R_1$
$R = 4\text{-}C_6H_4OMe$	**1**	**5**	**8**	**11**
$R_1X = CH_2{=}C(CH_3)CH_2Cl$	38%	11%	0.3%	≤ 0.8%
$R = 4\text{-}C_6H_4OMe$	**2**	**5**	**8**	**12**
$R_1X = \textit{trans}\text{-}CH_3CH{=}CHCH_2Cl$	41%	≤ 5%	0.6%	≤ 0.04%
$R = 4\text{-}C_6H_4OEt$	**3**	**6**	**9**	**13**
$R_1X = CH_2{=}CHCH_2Br$	20%	> 5%	0.4%	0.1%
$R = 4\text{-}C_6H_4OCH(CH_3)_2$	**4**	**7**	**10**	**14**
$R_1X = CH_2{=}CHCH_2Br$	36%	> 5%	0.3%	0.1%

Experimental

Instruments. ^1H NMR spectra were recorded with either a Bruker AM 300 or a JNM-GSX 270 with chemical shifts (δ) expressed in ppm downfield from tetramethylsilane (TMS). Low resolution mass spectra were measured on Varian MAT CH7 and Finnigan Mat GC-MS SSQ 710. Column chromatography was carried out using Merck Kieselgel 60 (230 mesh) and thin layer chromatography was carried out using Merck Kieselgel 60 PF_{254}.

Reagents. Commercial 4-bromoanisole was dried on molecular sieves (5A) and fractionally distilled to give colourless liquid. Ether was dried on sodium wire before use. Allylic chlorides were obtained from Aldrich and were used without further purification. Magnesium turnings and all other reagents were of reagent grade.

Preparation of 4-Bromoethoxybenzene. To 10.0 g (58 mmol) of 4-bromophenol was added 12 ml of 20% NaOH and 48 ml distilled water in a 250 ml two necked flask. The pH of the reaction mixture was *ca.* 10. To the clear ice-cooled alkaline aqueous solution of 4-bromophenol was added dropwise 3.0 g (35 mmol) of diethyl sulfate. The reaction mixture was then gently refluxed for 4-5 hours and then left overnight at room temperature. The pH of the reaction mixture remained *ca.* 10. The reaction mixture was extracted with ether. The crude product (7.3 g) obtained from the ether-extract was purified by column chromatography (petroleum ether/ether, 80:20) to give 3.8 g (19 mmol; 33% yield) of 4-bromoethoxybenzene.

^{1}H NMR (300 MHz, $CDCl_3$): 7.32 (2H, AA' of AA'BB'), 6.73 (2H, BB' of AA'BB'), 3.94 (2H, q, J = 7.0 Hz, CH_2), 1.38 (3H, t, J = 7.0 Hz, CH_3).

Preparation of 4-Bromoisopropoxybenzene. To an ethanolic solution (100 ml) of 0.24 mol of sodium ethoxide was added 10.4 g (0.06 mol) of 4-bromophenol. After complete dissolution, 33 ml of isopropyl bromide was added. The reaction mixture was refluxed for 4 hours and left overnight at room temperature. The reaction mixture was filtered and the solvent was removed by vacuum evaporator. The crude reaction mixture was treated with 30 ml of 0.4 M NaOH, extracted with ether and fractionated by column chromatography to produce 7.4 g (34.4 mmol, 57% yield) of 4-bromoisopropoxybenzene.

^{1}H NMR (300 MHz, $CDCl_3$): 7.32 (2H, AA' of AA'BB'), 6.73 (2H, BB' of AA'BB'), 4.44 (1H, hept., J = 6.1 Hz, CH), 1.29 (6H, d, J = 6.1 Hz, 2 x CH_3).

Reaction of Allylic Halides with 4-Alkoxyphenylmagnesium Bromides in Ether.

4-Alkoxyphenylmagnesium bromides were prepared as described elsewhere[6]. The coupling reaction of a typical allylic halide with 4-alkoxyphenylmagnesium bromide and workup procedures were carried out according to the usual procedure[6]. The apparent yields are shown in Table 1. The spectral data for the coupled compounds **1** - **2** are shown elsewhere[6] and for **3** - **14** are summarized as below.

3:

^{1}H NMR (300 MHz, $CDCl_3$): 7.08 (2H, AA' of AA'BB'), 6.82 (2H, BB' of AA'BB'), 5.88 - 5.99 (1H, m, vinylic CH), 5.06 (1H, m-d, J = 8.2 Hz, vinylic CH_2), 5.02 (1H, t, J = 1.4 Hz, vinylic CH_2), 3.99 (2H, q, J = 6.9 Hz, OCH_2), 3.31 (2H, br-d, J = 6.7 Hz, CH_2), 1.39 (3H, t, J = 6.9 Hz, CH_3).

4:

^{1}H NMR (300 MHz, $CDCl_3$): 7.07 (2H, AA' of AA'BB'), 6.80 (2H, BB' of AA'BB'), 5.90-5.99 (1H, m, vinylic CH), 5.05 (1H, m-d, J = 8.3 Hz, vinylic CH_2), 5.02 (1H, m, vinylic CH_2), 4.51 (1H, hept, J = 6.0 Hz, CH), 3.31 (2H, br-d, J = 6.7 H_2, CH_2), 1.32 (6H, d, J = 6.0 Hz, 2 x CH_3).

5:

^{1}H NMR (300 MHz, $CDCl_3$): 7.48 (4H, AA' of AA'BB'), 6.96 (4H, BB' of AA'BB'), 3.84 (6H, s, 2 x OCH_3).

MS, m/z (%) : 214(M^+, 100), 199(76), 171(24), 156(10), 139(7), 128(16), 107(7).

6:

^{1}H NMR (270 MHz, $CDCl_3$): 7.46 (4H, AA' of AA'BB'), 6.93 (4H, BB' of AA'BB'), 4.04 (4H, q, J = 6.8 Hz, 2 x OCH_2), 1.43 (6H, t, J = 6.8 Hz, 2 x CH_3).

MS, m/z (%): 242(M^+, 100), 213(27), 185(43), 186(43), 157(28), 139(7), 128(14).

7:

^{1}H NMR (270 MHz, $CDCl_3$): 7.45 (4H, AA' of AA'BB'), 6.92 (4H, BB' of AA'BB'), 4.52 - 4.61 (2H, m, 2 x OCH), 1.35 (12 H, d, J = 5.9 Hz, 4 x CH_3).

MS, m/z (%): 270(M^+, 27), 226(45), 211(24), 186(100), 157(10), 139(4), 128(9).

8:

^{1}H NMR (300 MHz, $CDCl_3$): 7.50 - 7.56 (4H, m, H_3, H_5, $H_{3'}$, $H_{5'}$), 7.38 - 7.44 (2H, m, $H_{2'}$, $H_{6'}$), 7.29 (1H, m, $H_{1'}$), 6.97 (2H, m, H_2, H_6), 3.84 (3H, s, OCH_3).

MS, m/z (%): 184 (M^+, 100), 169(40), 152(6), 141(29), 139(9), 115(24).

9:

^{1}H NMR (270 MHz, $CDCl_3$): 7.50 - 7.57 (4H, m, H_3, H_5, $H_{3'}$, $H_{5'}$), 7.40 (2H, m, $H_{2'}$, $H_{6'}$), 7.29 (1H, m, $H_{1'}$), 6.96 (2H, m, H_2, H_6), 3.99 (2H, q, J = 6.8 Hz, OCH_2), 1.39 (3H, t, J = 6.8 Hz, CH_3).

MS, m/z (%) : 198(M^+, 58), 170(100), 152(5), 141(22), 115(24).

10:

^{1}H NMR (270 MHz, $CDCl_3$): 7.46 - 7.56 (4H, m, H_3, H_5, $H_{3'}$, $H_{5'}$), 7.40 (2H, m, $H_{2'}$, $H_{6'}$), 7.29 (1H, m, $H_{1'}$), 6.94 (2H, m, H_2, H_6), 4.56 - 4.61 (1H, m, OCH), 1.36 (6H, d, J = 5.9 Hz, 2 x CH_3).

MS, m/z (%): 212(M^+, 36), 170(100), 152(4), 141(11), 115(9).

11:

^{1}H NMR (300 MHz, $CDCl_3$): 7.49 - 7.54 (6H, m, H_3, H_5, $H_{3'}$, $H_{5'}$, $H_{2'}$, $H_{6'}$), 6.97 (2H, m, H_2, H_6), 4.83 (1H, br-s, vinylic CH), 4.77 (1H, br-s, vinylic CH), 3.83 (3H, s, OCH_3), 3.34 (2H, s, CH_2), 1.71 (3H, s, CH_3).

MS, m/z (%): 238(M^+, 27), 223(6), 208(4), 197(6).

12:

MS, m/z (%): 238(M^+, 9), 223(3), 208(2).

^{1}H NMR signals could not be assigned because of its content of ≤ 7% in the mixture with **8**.

13:

^{1}H NMR (270 MHz, $CDCl_3$): 7.50 - 7.57 (6H, m, H_3, H_5, $H_{3'}$, $H_{5'}$, $H_{2'}$, $H_{6'}$), 6.96 (2H, m, H_2, H_6), 6.00 (1H, m, vinylic CH), 5.02 - 5.08 (2H, m, vinylic CH_2), 3.99 (2H, q, J = 6.8 Hz, OCH_2), 3.32 (2H, br-d, J = 6.7 Hz, CH_2), 1.39 (3H, t, J = 6.8 Hz, CH_3).

MS, m/z (%): 238(M^+, 100), 209(32), 181(13), 165(22), 152(14), 139(9), 115(20).

14:

^{1}H NMR (270 MHz, $CDCl_3$): 7.46 - 7.56 (6H, m, H_3, H_5, $H_{3'}$, $H_{5'}$, $H_{2'}$, $H_{6'}$), 6.94 (2H, m, H_2 , H_6), 6.00 (1H, m, vinylic CH), 5.03 - 5.13 (2H, m, vinylic CH_2), 4.56 - 4.61 (1H, m, OCH), 3.38 (2H, br-d, J = 6.7 Hz, CH_2), 1.36 (6H, d, J = 5.9 Hz, 2 x CH_3).

MS, m/z (%): 252(M^+, 59), 210(100), 183(10), 181(10), 165(18), 152(11), 139(5), 115(10).

Acknowledgement We would like to thank the National Council for Scientific Research and Development for financial assistance and the Network for Chemistry of Biologically Important Natural Products (under the International Development Program of Australian Universities and Colleges) for its support. We also would like to thank Dr. L. T. Byrne for assistance to obtain ^{1}H NMR and MS spectra for some of the compounds.

References

1. Walling, C. *Acc. Chem. Res.* 1991, **24**, 255 - 256.
2. Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*, Prentice-Hall : New York, 1954.
3. Walborsky, H.M. *Acc. Chem. Res.* 1990, **23**, 286 - 293. Walborsky, H.M.; Zimmermann, C. *J. Am. Chem. Soc.*, 1992, **114**, 4996-5000.
4. (a) Garst, J.F. *Acc. Chem. Res.* 1991, **24**, 95-97. (b) Garst, J.F.; Dentch, J.E.; Whitesides, G.M. *J. Am. Chem. Soc.* 1986, **108**, 2490-2491. Garst, J.F.; Swift, B.L.; Smith, D.W. *J. Am. Chem. Soc.* 1989, **111**, 234-241.
5. Lajis, N.H.; Hussein, M.Y. ; Toia, R.F. *Pertanika.* 1985, **8**, 105 - 108.
6. Lajis, N.H.; Khan, M.N. *Tetrahedron.* 1992, **48**, 1109-1114.