Tetrahedron Vol. 48, No. 6, pp. 1109-1114, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

Solvolytic Stereoselective Coupling Reaction of *p*-Methoxyphenylmagnesium Bromide with Substituted Allylic Chlorides.

Nordin Hj. Lajis* **and Mohammad Niyaz Khan**

Chemistry Department, University Pertanian Malaysia, 43400 UPM
Serdang, Selangor, MALAYSIA.

(*Received in UK 26 November* 1991)

Abstract: The α- and γ-coupling reactions of a few substituted allylic chlorides with *p*-methoxyphenylmagnesium bromide were concluded as to involve the formation of an intimate ion-pair intermediate. The solvents used gave substantial effects both on the regio-and stereo-selectivity of the reaction.

Introduction

The mechanistic diagnosis of allylic halides with a wide variety of organometallic reagents has attracted much interest for the last several decades partly because of the common occurrence of olefinic moiety in many bioactive naturally occurring compounds. Several distinct mechanisms have been proposed to explain the interesting features of this reaction[1]. We have been interested in the synthesis of estragole analogues in order to explore a structure-activity relationship of this compound as an attractant for the oil palm pollinating weevil, *Elaeidobius kamerunicus*[2]. We report here the synthesis of some of these analogues and discuss the mechanism of the coupling reactions between allylic chlorides with *p*-methoxyphenylmagnesium bromide.

RESULTS AND DISCUSSION

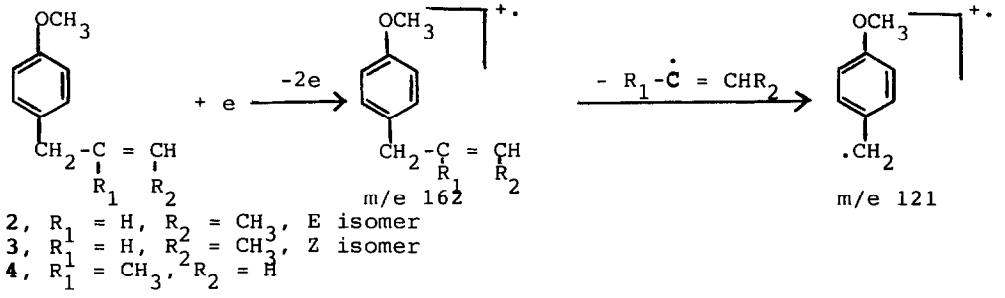
The reaction of 3-chloro-1-butene with *p*-methoxyphenylmagnesium bromide (MPMB) in tetrahydrofuran (THF) yielded approximately 28% substitution product, **1**, (i.e. 28% α-attack or α-coupling) and 72% allylic rearrangement products, **2** and **3**, (i.e. 72% γ-attack or γ-coupling) based on gas chromatography using capillary column. The percent contents of **2** and **3** in this reaction were determined as 38% and 62%, respectively. The assignment of **1**, **2** and **3** to the corresponding peaks in the chromatogram was based on the mass spectral fragmentation patterns, the proton NMR spectra of the product mixtures as well as comparison of the chromatogram with that of the products from the reaction between MPMB and crotyl chloride. The reaction of 3-chloro-1-butene with MPMB in ether gave approximately 14%

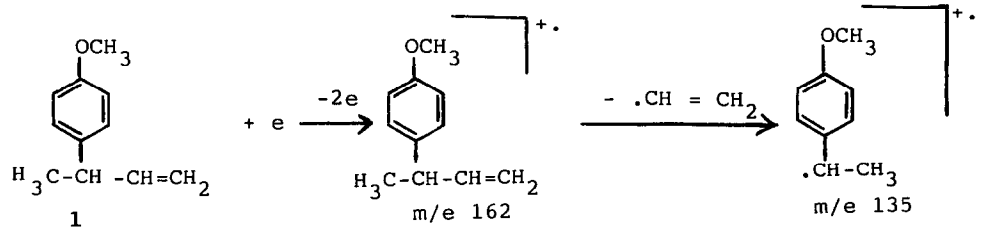
products resulted from α-attack and 86% from γ-attack consisting 2 and 3 with percent ratio of 98:2.

The coupling reaction of MPMB with 1-chloro-2-butene in ether produced approximately 17% allylic rearrangement product 1 and 83% substitution products, 2 and 3 as evidenced from the chromatogram. The ratio of 2:3 appeared to be 96:4. The commercial crotyl chloride used in the present study contained 30%, 3-chloro-1-butene. The observed 17% value of 1 should therefore be the sum of α-coupling (*ca.* 4%)[3] resulted from the reaction between MPMB with 3-choro-1-butene and γ-coupling (*ca.* 13%) of MPMB with 1-chloro-2-butene. These observations thus indicated that the percent ratio of (α/γ)-attack was approximately 81/19.

The observed respective values of *ca.* 19% γ-attack and 14% α-attack in the reaction between MPMB with 1-chloro-2-butene and with 3-chloro-1-butene, may be compared with the reported values of *ca.* 25% for both γ- and α-attack in the corresponding reaction with phenylmagnesium bromide (PhMgBr) in ether[4]. Nearly 25% for both α- and γ-attack has also been reported to occur in the reaction of 1-chloro-2-butene with phenyllithium (PhLi) using the same solvent. The observed ratio of 14/86 for (α/γ)-attack in the reaction between 3-chloro-1-butene with MPMB in ether was also comparable with the correspondig ratios of 25/75 obtained for PhMgBr[4] and 1.0/99.0 for PhLi[5], when these reagents are reacted with this chlorobutene under the same reaction condition.

Compound 4 was synthesized from the reaction of MPMB with 3-chloro-2-methylpropene. The mass spectra of 2, 3 and 4 revealed similar fragmentation patterns including the presence of a strong peak at m/e 121. The mass spectrum of 1 however differed from those of 2, 3 and 4 by the significance of the peak at m/e 135 which was almost absent in the latter three. In addition the peak at m/e 121 for 1 was almost absent. The peaks at m/e 121 and 135 were presumably due to the fragmentations depicted as in the following Scheme.





Scheme

The gas chromatographic peak at retention time 8.0-8.1 was assigned for **2** because it represented the major peak (*ca.* 80%) in the reaction of crotyl chloride with MPMB in which the crotyl chloride used was predominantly in *trans*-form. This consideration was taken in view of Magid's results which demonstrated that double bond geometry was preserved in the reaction of PhLi with *trans*- and *cis*-crotyl chloride[6].

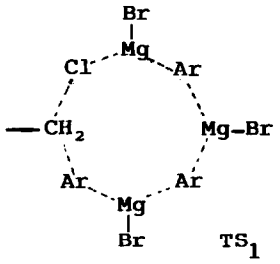
Further support on this assignment was based on the NMR spectral consideration of the products mixture resulted from the reaction between 3-chloro-1-butene and MPMB in THF. The percent ratios of 1/(2+3) (*i.e.* α/γ-attack) as derived from the integration ratios for methyl and vinyl protons of **1**, **2** and **3** were found to be 31/69 and 27/73, respectively. Similarly, the integrations for methylene protons of **2** and **3** and methine proton of **1** indicated that the α/γ-attack as 25/75 and the proportion of 1:2:3 as 25:31:44. These results were comparable with the ratio of α/γ-attack as 28/72 and the proportion of 1:2:3 as 28:27:45, obtained from gas-chromatogram.

The change of reaction solvent from THF to ether in the reaction of 3-chloro-1-butene with MPMB caused the reduction of α-attack from 28% to 14%. The value of **2**/**3** (*i.e.* *E*/*Z*-isomer) changed from 38/62 in THF to 98/2 with ether. Anderson *et al.*[7] reported that α,β-disubstituted allylic acetates gave primarily γ-attack with predominantly *E*-stereochemistry (*E*/*Z* = 96.5/3.5) when the reaction was carried out in ether, but a substantial enhancement of α-attack and reduction of *E*/*Z* stereochemical ratio (*E*/*Z* = 65.7/34.3) resulted when THF was used as solvent. It is interesting to note that the stereochemical aspects of the coupling reaction in the present study are significantly affected by the nature of the solvents. When ether and THF were used as the solvent the *E*-isomer was generated in 98% and 38% , respectively. Recently, solvolytic stereoselectivity has been observed in elimination reactions[8].

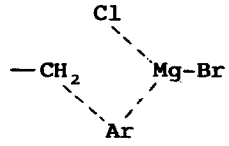
Although the distributions of coupling products appeared to be similar in the reactions of MPMB with 1-chloro-2-butene (*i.e.* 1/(2+3) = 19/81) and 3-chloro-1-butene (*i.e.* 1/(2+3) = 14/86), it is difficult to explain these results in terms of pure S_N1 and S_N1' mechanisms[5]. If these reactions were assumed to involve S_N1 and S_N1' mechanism it is then difficult to explain the formation of only 14-19% of **1** since reactions which obey S_N1 or S_N1' mechanism should not exhibit high sensitivity toward steric requirements of the reaction sites. On the other hand although it is known that reactions which followed S_N2 mechanism normally showed high sensitivity toward steric requirements of the reaction sites, consideration of such a mechanism is also less attractive for the present system. This is due to the fact that in the coupling reactions of Grignard reagent with allylic chlorides in ether or THF, both the nucleophile and leaving group (Cl^-) should be coordinated with magnesium in the transition state. It is also known that arylmagnesium bromide existed in monomeric form at all concentrations in THF and at lower than 0.1M[9] in ether. Hence, in these reactions a colinear alignment of nucleophile and leaving group in the transition state of S_N2 reaction is stereochemically impossible. However, the involvement of three or

more monomeric ArMgBr molecules in the cyclic trans (TS_1) cannot be completely ruled out.

As argued by Magid[5] in an elegant and very convincing manner, the operation of S_N1 or ion-pair mechanism with complete loss of all memory of the structure and stereochemistry of the starting reactant(s) seemed to be unlikely in these reactions. We considered that intimate ion-pair mechanism is operating in which, although dissociated leaving group (Cl^-) is not completely free from the carbon of its initial attachment, it can freely slide around the electrophilic carbon atom to coordinate with magnesium. The nucleophile may then attack the electrophilic in a transition state like TS_2.



TS_1



TS_2

Experimental:

Instruments. ^1H Nuclear Magnetic Resonance spectra were recorded on Bruker AM 500 with chemical shifts (δ) expressed in ppm downfield from tetramethylsilane (TMS). Gas chromatographic studies were carried out using Schimadzu gas chromatograph Model 9A using 508735 OV-1 capillary as stationary phase and He as the carrier gas. Gas Chromatography-Mass Spectrometry analysis was performed on Hewlett Packard 5890 gas chromatography filled with an open split capillary interface and an HP-1 (polymethylsiloxane, 0.17 μ; 25 m x 0.32 mm i.d) capillary column with He carrier gas (2 ml/min. flow rate; 15 psi). Column chromatography were carried out using Merck Kieselgel 60 (230 mesh) and thin layer chromatography was carried using Merck Kieselgel 60 PF_{254}.

Reagents. Commercial 4-bromoanisole was dried on molecular sieves (5A) and fractionally distilled to give colourless liquid and ether or THF 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 used were of reagent grade.

Preparation of 4-Methoxyphenylmagnesium Bromide (MPMB). Grignard reagent (MPMB) was prepared in a 100 ml three necked flask equipped with a condenser, dropping funnel and a magnetic stirrer. To 0.9g (40.1 Mg-atom) of magnesium turnings in 10 ml THF kept in the flask was added 3.4 ml (26.7 mmol) of 4-bromoanisole dissolved in 25ml of ether or THF dropwise for the period of *ca.* 15 min. After 5 hours, the unreacted magnesium (ca. 0.27g) was removed by filtration.

Reaction of **MPMB** *with 1-Chloro-2-butene.* Commercial 1-chloro-2-butene (2.7 ml, 27 mmol which consisted of predominantly *trans*-isomer and contained 30% of 3-chloro-1-butene was dissolved in 10 ml ether and added to the freshly prepared solution of Grignard reagent (MPMB) of *ca.* 26.7 mmol at such a rate which minimize gas evolution. The reaction mixture was stirred overnight at room temperature and then poured into an aqueous solution of *ca.* 40 ml of 2.5 M NH_4CH. The organic layer was separated and washed with 30 ml of 0.4 M NaOH and the combined organic extracts was concentrated and fractionated by column chromatography followed by preparative *tlc.* The products 1.8 g (41% yield) was obtained as a mixture containing 17% of 1-methoxy-4-(1-methyl-2-propenyl)benzene (1)[10], 80% of 1-methoxy-4-(*trans*-2-butenyl)benzene (2)[11], and 3% of 1-methoxy-4-(*cis*-2-butenyl)benzenes (3)[11].

Reaction of **MPMB** *with 3-Chloro-1-butene in Ether.* The reaction of 3-chloro-1-butene with **MPMB** was carried out as described for 1-chloro-2-butene using the same amount of reagents and solvent. The combined yield of products was approximately 40%. The products distribution obtained for **1**, **2** and **3** as determined by capillary GC was *ca.* 28%, 27%, and 45%, respectively.

Reaction of **MPMB** *with 3-Chloro-1-butene in THF.* The same procedure as in previous reaction was followed using the same amounts of reagents. The products distribution of the title reaction obtained for **1**, **2** and **3** as determined by capillary GC was 14%, 84% and 27%, respectivly.

1-Methoxy-4-(1-methyl-2-propenyl)benzene (1) MS: m/e (%)M^+ 162 (40), 147 (100), 135 (09) 131 (19), 121 (03), 115 (21), 91 (42), 77 (15), 65 (10), 51 (10). ^1H NMR ($CDCl_3$): δ 1.41 (3H, d, J = 7.0 Hz, CH_3), 3.48 (1 H, quintet, J = 7.0 Hz, CH), 3.84 (3 H, s, OCH_3), 5.07-5.13 (2 H, m, C_2 = CH), 6.00-6.12 (1 H, m, CH=C), 6.91 (2 H, d, J = 8.7 Hz, ArH), 7.20 (2 H, d, J = 8.7 Hz, ArH).

*1-Methoxy-4-(*trans*-2-butenyl)benzene* (2). MS: m/e (%)M^+ 162 (80), 147 (100), 135 (01) 131 (16), 121 (27), 115 (22), 91 (52), 77 (20), 65 (13), 51 (14). ^1H NMR ($CDCl_3$): δ 1.76 (3 H, br d, J = 6.0 Hz, CH_3), 3.33 (2 H, br d, J = 6.0 Hz, CH_2), 3.84 (3 H, s, OCH_3 5.57-5.63 (2 H, m, CH=CH), 6.90 (2 H, d, J = 8.5 Hz, ArH), 7.16 (2 H, d, J = 8.5 Hz, ArH).

*1-Methoxy-4-(*cis*-2-butenyl)benzene* (3). MS: m/e (5)M^+ 162 919), 147 (100), 135 (20), 131 (20), 121 (33), 115 (23), 91 (63), 77 (22), 65 (14), 51 (17). ^1H NMR ($CDCl_3$): δ 1.79 (3H, br d, J = 5.0 Hz, CH_3), 3.41-3.43 (2 H, br d, J = 5.0 Hz, CH_2), 3.84 (3 H, s, OCH_3), 5.64-5.67 (2 H, m, Ch=CH), 6.90 (2 H, d, J = 8.5 Hz, ArH), 7.18 (2 H, d, J = 8.5 Hz, ArH).

Reaction of MPMB with 3-Chloro-2-methylpropene. The coupling reaction of 3-chloro-2-methylpropene with MPMB was carried out following the procedure described for 1-chloro-2-butene. The same amount of reagents were used and the product 1-methoxy-4(2-methyl-2-propenyl)benzene[12-14], (**4**) was obtained in *ca.* 38% yield.

MS: m/e (5) M^+ 162 (87), 147 (100), 135 (01), 131 (18), 121 (85), 115 (16), 91 (45), 77 (28), 65 (11), 51 (16). ^1H NMR ($CDCl_3$): δ 1.70 (3 H, s, CH_3) 3.29 (2 H, s, CH_2) 3.81 (3H, s, OCH_3), 4.75 (1H, s, C = CH_2), 4.82 (1 H, s, C = CH_2), 6.87 (2 H, d, J = 9.0 Hz, ArH), 7.14 (2 H, d, J = 9.0 Hz, ArH). ^{13}C NMR ($CDCl_3$): δ, aromatic carbons, 158.00 (C-1), 129.81 (C-3 and C-5) 113.68 (C-2 and C-6), 145.54 (C-4); nonaromatic carbons, 43.75 (C-1), 131.83 (C-2), 11.53 (C-3), 21.98 (CH), 55.20 (OCH) ppm.

Acknowledge

The authors wish to thank the National Council for Scientific Research and Development for financial assistance and the Network for the Chemistry of Biologically Important Natural Products, an activity of the International Development Program of Australian Universities and Colleges for its support.

References

1. Magid, R.M., Tetrahedron **1980** *36*, 1901-1930.
2. Lajis, N.H; Hussein, M.Y; Toia, R.F. *Pertanika*, **1985** 8 105-108 and referrences cited therein.
3. It is assumed that the ratio of (α/γ)-attack for the reaction of MPMB with 3-chloro-1-butene remains the same for both the 30% and 98% 3-chloro-1-butene in reaction mixtures.
4. Wilson, K.W.; Roberts J.D.; Young W.G. *J. Amer. Chem. Soc.* **1949** *71*, 2019-2020.
5. Magid, R.M,; Nieh, E.C.; Gandour, R.D. *J. Org, Chem.*, **1971** *36*, 2099-2105.
6. Magid, R.M.; Gandour, R.D. *J. Org. Chem.* **1970** *35*, 269-270.
7. Anderson, R.J; Hendrick, C.A. Siddall, J.B. *J. Amer. Chem. Soc.* **1970** *92*, 7735-737.
8. Khurana, J.M; Maikap, G.C. *J. Org. Chem.*, **1991** *56*, 2582-2584.
9. March, J. 'Advanced Organic Chemistry: Reactions Mechanism, and Structure'. 2nd edn. McGraw-Hill Kogakusha Ltd., Tokyo **1977**, p. 168 and references cited therein.
10. Tanaka, J,; Nojima, M.; Kusabayashi, S.; Nagase, S. *J. Chem. Soc, Perkin Trans.* II, **1987**, 673-678.
11. Vdovtsova E.A.; Yanichkin L.P. *Zh. Org. Khim.*, **1969**, *5*, 510-515, Chem. Abstr. 71:12722r.
12. Couts, R.T.; Benderily, A.; Mak, A.L.C.; Taylor, W.G. *Can. J. Chem.*, **1978**, *56*, 30544-3058.
13. Bunnett, J.F.; Sridharan, S. *J. Org. Chem.*, **1979**, *44*, 1458-1463.
14. Heck, R.F. *J. Am. Chem. Soc.*, **1968**, *90*, 5531-5534.