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THE MECHANISM OF AN UNUSUAL REACTION OF ORTHO-SUBSTITUTED AZOBENZENES WITH GRIGNARD REAGENTS

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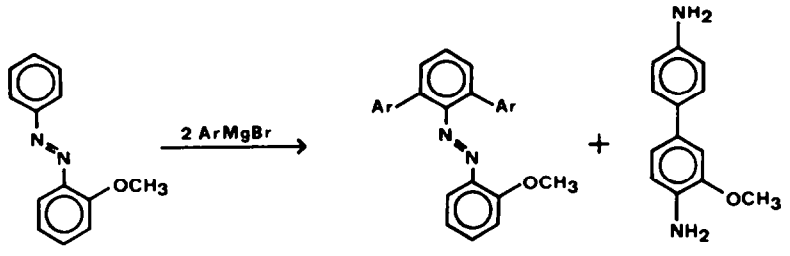
Abstract—2-Methoxy- and 2-methyl-azobenzene reacted with aromatic Grignard reagents giving 2-methoxy-2',6'-diaryl- and 2-methyl-6-aryl-azobenzene respectively. The mechanism of these arylation reactions was investigated. Evidence for a mechanism of 1,4-addition involving the azo group, followed by elimination of magnesium bromohydride is reported.

THE reactions of azobenzene with organometallic compounds have been extensively investigated. In these reactions an attack of the organometallic reagent at the azo bridge occurs and, after hydrolysis, hydrazobenzene, aniline or trisubstituted hydrazine are obtained.[1] Conjugated heterocyclic aromatic azocompounds also undergo a similar attack by Grignard reagents, giving trisubstituted hydrazines.[2]

In previous work we reported that some *o*-methoxyazo derivatives react with phenylmagnesium bromide to give aromatic arylation products by replacement of the methoxy group. Thus, 1-phenylazo-2-methoxy- and 1-methoxy-2-phenylazo-naphthalene yield 1-phenylazo-2-phenyl- and 1-phenyl-2-phenylazo-naphthalene respectively.[3] Unexpectedly, in a similar reaction carried out on 2-methoxyazobenzene, replacement of the methoxy group did not occur, whilst arylation at both the *ortho* positions of the unsubstituted ring was observed.[4] (Chart 1).

CHART 1



I

III

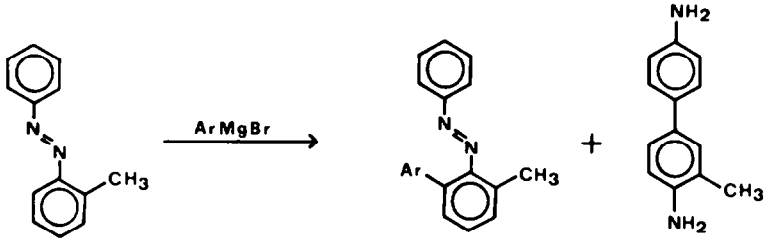
IIa : Ar = $-C_6H_5$

IIb : Ar = $-C_6H_4(CH_3)p$

IIc : Ar = $-C_6H_2(CH_3)_3$ (2,4,6)

This result is somewhat surprising, particularly as the substitution occurs at the most hindered sites of the molecule. Similarly, in 2-methyl-azobenzene, the arylation took place at the free *ortho* position of the substituted ring[5] (Chart 2). In contrast, the isomeric 3- and 4-methylazobenzene under similar reaction conditions with phenylmagnesium bromide gave only the corresponding hydrazo derivatives,[5] like the unsubstituted azobenzene.

CHART 2



IV VI

V a : Ar = $-C_6H_5$

V b : Ar = $-C_6H_4(CH_3)p$

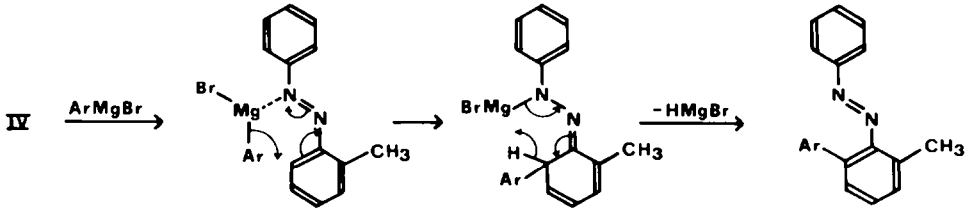
V c : Ar = $-C_6H_2(CH_3)_3(2,4,6)$

These results indicate that the aromatic arylation of azobenzenes is peculiar to the *ortho* substituted derivatives. The arylation can occur either at the unsubstituted or the substituted ring, depending on the nature of the *o*-substituent present in the molecule, but in any case the incoming group attacks only the *ortho* positions with respect to the azo grouping.

The reaction takes place with various aromatic Grignard reagents, even when the hydrocarbon residue is very bulky, as for instance a mesityl group.[6] This new method of aromatic arylation is interesting because it can be exploited to obtain polynuclear hydrocarbons, their aminic derivatives and heterocyclic compounds.[4–6]

The present work was undertaken to investigate the mechanism of the above reaction. The most stable conformation of the *trans*-2-methylazobenzene is that

CHART 3

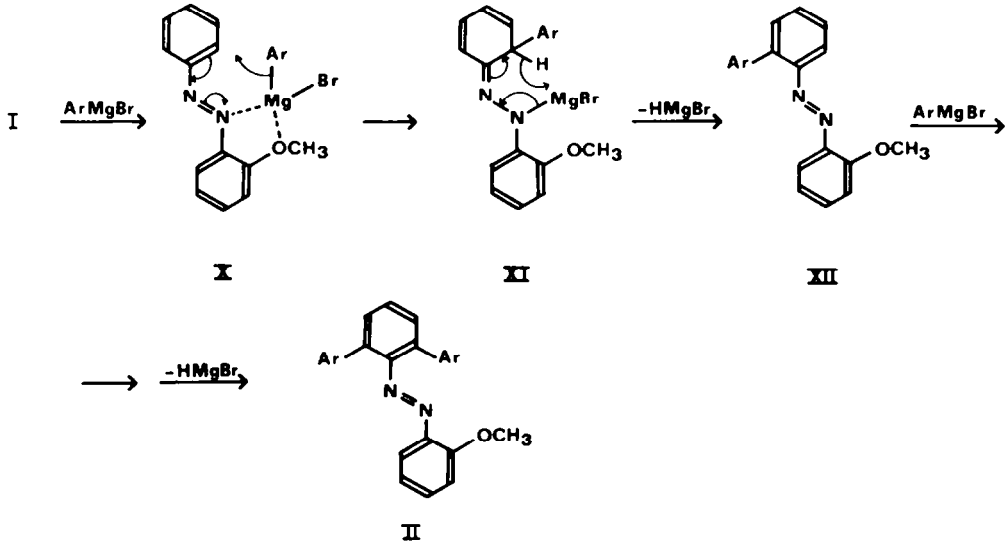


VII VIII V

indicated in IV (Chart 2), having the minimum steric interaction between the azo and Me groups.[7] The two N atoms of IV being sterically nonequivalent, the Grignard reagent would approach the less hindered one, forming the complex VII (Chart 3). A direct consequence is an electron withdrawal from the substituted ring and subsequent activation for a nucleophilic attack. Thus, the arylation at the 6 position may be explained in terms of 1,4-addition through a 6-membered cyclic transition state, leading to the compound VIII. Such a mechanism is similar to that for the reaction of the α,β-unsaturated ketones with Grignard reagents. Compound VIII is only an intermediate of the whole reaction; from which, by elimination of magnesium bromohydride, the final azo compound V is obtained. We have to assume that this elimination is an irreversible process, that is V does not react with the hydride to give either VIII or addition products at the azo bridge. In fact, if these reactions did occur, the hydrolysis of the reaction mixture would lead to the hydrazo derivative of V and not to V itself. Moreover the formation of V from its hydrazo derivative either by cross hydrogen transfer with IV or by air oxidation can be ruled out. Actually the oxidation of 2-methyl-6-phenylhydrazobenzene *via* both these ways was not achieved. On the contrary the hydride can reduce the starting azo compound IV to 2-methylhydrazobenzene. Thus, the benzidine VI (Chart 2), which is always obtained together with V, can be formed, at least in part, in this way.

Also for 2-methoxy-azobenzene the most stable conformation is that indicated in I (Chart 1), but in this case the N atom linked to the substituted ring is not as hindered as in IV. Thus, the complex X (Chart 4), where the magnesium is coordinated either

CHART 4

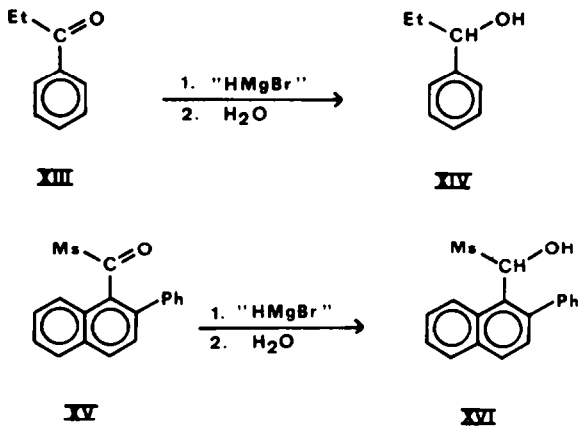


with such a nitrogen or with the oxygen of the OMe group, can be easily formed. In this situation the ring activated for a nucleophilic attack is now the unsubstituted one. Therefore, by an analogous mechanism of 1,4-addition, the mono-arylated intermediate XI is formed. At this stage the irreversible elimination of the magnesium

bromohydride with formation of XII appears to be even more evident, because the final diarylated azocompound II can arise only from XII by further reaction with the Grignard reagent. According to it, 2-methoxy-2′-phenylazobenzene (XII, Ar = Ph), prepared by independent synthesis, furnished by reaction with phenylmagnesium bromide, 2-methoxy-2′,6′-diphenylazobenzene (IIa). The hydrazo derivatives of XII and II were never isolated among the reaction products. Therefore we can assume that the arylated azocompounds XII and II do not react with the hydride.

The formation of the magnesium bromohydride as by-product was clarified by preparation of the hydride by pyrolysis under reduced pressure of ethylmagnesium bromide.[8] The grey powder obtained behaved in accordance with the usual hydrides, e.g. LAH. In fact, it reduced propiophenone (XIII) and 1-mesitoyl-2-phenylnaphthalene (XV) to the corresponding secondary alcohols XIV and XVI (Chart 5). No tertiary

CHART 5



XIII XIV XV XVI

alcohols were present among the products of these reactions, which indicated the absence of starting Grignard reagent in the pyrolysate.

The ketone XV was inert toward phenylmagnesium bromide. Exploiting this feature, we repeated the reaction of 2-methylazobenzene with phenylmagnesium bromide in presence of XV and in this case together with the arylated azo compound Va and the benzidine VI (Chart 2), the alcohol XVI was isolated. This result supports the formation of the magnesium bromohydride during the aromatic arylation of the *o*-substituted azobenzene. In fact, the alcohol XVI cannot be formed in anyway except by hydride reduction of XV.

Finally, the magnesium bromohydride and LAH reduced IV into 2-methylhydrazobenzene, whilst under similar reaction conditions Va was recovered unchanged. This result is also in agreement with the mechanism above discussed.

EXPERIMENTAL

2-Methoxy-2′-phenyl-azobenzene (XII). A soln of *o*-nitroso-anisole (5·48 g, 40 mmoles) in AcOH (7·5 ml) and EtOH (15 ml) was added dropwise and under stirring to a well cooled soln of 2-amino-biphenyl (6·76 g, 40 mmoles) in AcOH (7·5 ml) and EtOH (5 ml). After standing at room temp for 4 hr, ice-water was added and the mixture was extracted with ether. The ethereal extract was washed successively with

Na_2CO_3 aq, 10% HCl aq, to remove AcOH and the unreacted amine respectively, and then with water until neutral. The dried (Na_2SO_4) soln was evaporated and the residue dissolved in benzene. This soln, treated with charcoal and chromatographed on Al_2O_3 (Merck, acc. to Brockmann), gave XII. Orange needles (from EtOH), m.p. 96–97°. (Found: C, 78·72; H, 5·67; N, 9·96. $C_{19}H_{16}N_2O$ requires: C, 79·14; H, 5·59; N, 9·72%).

Reaction of XII *with phenylmagnesium bromide.* This reaction was carried out using the conditions reported for the reactions of I and IV with Grignard reagents.[4–6] A soln of XII (3·45 g, 12 mmoles) in dry benzene (15 ml) was added to a stirred soln of PhMgBr (Mg turnings 0·58 g, bromobenzene 3·77 g, 24 mmoles) in dry ether (20 ml). The mixture was stirred under gentle reflux for 5 hr and at room temp for further 4 hr. After hydrolysis with 20% NH_4Cl aq, the red coloured organic layer was separated, repeatedly washed with 5% HCl aq (8 × 25 ml) and water. The soln, treated with charcoal and chromatographed on alumina, furnished 3·8 g (87% yield) of IIa, m.p. 117–119°[4]. From the hydrochloric acid washings, purified on charcoal, by concentration under red. press, a solid separated which was recrystallized from 20% HCl aq. This product, m.p. 190–200°, was dissolved in water and the soln was made alkaline with NH_4OH and then extracted with ether. The ethereal extract contained only 2-aminobiphenyl and *o*-anisidine, as resulted from TLC analysis by comparison with authentic samples.

Magnesium bromohydride.[8] EtMgBr was prepared in ethereal soln, using an excess of EtBr to entirely consume the magnesium. Solvent and EtBr excess were removed under reduced press and by heating. The residue was then pyrolysed, in the same flask, at 235° for 3½ hr under 0·5 mm press. After cooling *in vacuo*, dry ether was sucked in until the grey powder was completely covered, and then the flask was closed *in vacuo*.

Reduction of 2-*methyl-azobenzene* (IV) *by hydrides.* A soln of IV (7·84 g, 40 mmoles), in dry benzene (40 ml) was added dropwise to a well stirred suspension of LAH (4·56 g, 120 mmoles) in dry ether (50 ml). The mixture was refluxed for 4 hr and then kept at room temp for further 4 hr. After standing overnight, hydrolysis was carried out with water and 10% H_2SO_4 aq. The organic layer was separated and extracted with 5% HCl aq. The hydrochloric extract, treated with charcoal and concentrated to dryness, gave 3-methylbenzidine hydrochloride (2 g). The freed base VI gave a picrate, m.p. 204°. No depression was observed in the mixed m.p. with an authentic specimen.[9]

In another run IV (2 g), dissolved in dry benzene (20 ml) was added to "HMgBr" (prepared as previously described from 6·8 g Mg turnings) in dry ether (100 ml). Carrying out the reduction and the subsequent hydrolysis as above, 3-methylbenzidine hydrochloride (0·5 g) was obtained.

Under similar reaction conditions, Va was not reduced either by LAH or by "HMgBr".

2-Methyl-6-phenylhydrazobenzene. Compound Va (8 g) was dissolved in EtOH (100 ml), and to this soln, heated under reflux with stirring, 20% NaOH aq (25 ml) at once and Zn dust (5 g) portionwise were added. After 2 hr the hot mixture was filtered and the filtrate was cooled and extracted with ether. The separated organic layer was evaporated under reduced press to dryness. The residue was washed with ether and from the ethereal washings, after removal of the solvent, a semisolid product, which crystallized by storage in refrigerator, was obtained. The product was washed with light ligroin and recrystallized from EtOH, white prisms, m.p. 108–109°. (Found: C, 83·13; H, 6·49; N, 10·29. $C_{19}H_{18}N_2$ requires: C, 83·18; H, 6·61; N, 10·21%).

2-Methyl-6-phenylhydrazobenzene by air exposure for 1 hr was recovered unchanged and only after several days was oxidized to Va.

A benzene soln of this hydrazo derivative and IV in equimolecular amounts, was kept at room temp for 1 hr. After this time the TLC analysis revealed only the presence of the starting compounds, whilst no traces of 2-methylhydrazobenzene and Va were detected.

1-Mesitoyl-2-phenyl-naphthalene (XV).[10] This compound was prepared from 1-mesitoyl-2-methoxy-naphthalene and PhMgBr, by the literature method and the purified XV did not react with the same Grignard reagent.

Mesityl-1-(2-phenyl)naphthylcarbinol (XVI). A soln of XV (2 g) in dry benzene (15 ml) was added to LAH (0·4 g) in dry ether (35 ml). The mixture was heated under reflux for 5 hr and then hydrolysed with water and 10% H_2SO_4 aq. The organic layer was separated, washed with water and dried over Na_2SO_4. After removal of the solvent, 1·9 g pure XVI (TLC analysis) were obtained as colourless prisms (from EtOH), m.p. 135–137°. (Found: C, 88·12; H, 6·85. $C_{26}H_{24}O$ requires: C, 88·65; H, 6·87%); IR spectrum (Nujol): 3375 cm^{-1} (OH); absorption bands were missing in the 2200–1600 cm^{-1} region.

Reduction of ketones by "HMgBr". (a) A soln of XV (1·5 g) in dry benzene (10 ml) was added to "HMgBr" (prepared from 2·3 g of Mg) in dry ether (50 ml). The mixture was stirred for 1 hr at room temp and for

4 hr under reflux. After this time, hydrolysis was carried out with 5% HCl aq. The separated organic layer, washed with H_2O and dried over Na_2SO_4, showed on TLC analysis only two spots corresponding to the ketone XV and the alcohol XVI. The identification was made by comparison with authentic samples.

(b) Compound XIII (3·5 g) dissolved in dry ether (20 ml) was added to "HMgBr" (from 6·8 g Mg) in the same solvent (100 ml). Carrying out the reduction and the hydrolysis as above, XIV was obtained in almost quantitative yield. It was identified by comparison on TLC analysis with an authentic specimen. No diethylphenylcarbinol was detected beside the alcohol XIV, which indicated the absence of unpyrolysed EtMgBr within the grey powder containing "HMgBr". In fact, propiophenone reacted quantitatively with EtMgBr to give the tertiary alcohol.

Reaction of 2-*methylazobenzene* (IV) *with* PhMgBr *in presence of* XV. 2-Methylazobenzene (3 g, 15 mmoles) and XV (2·5 g, 7·5 mmoles) were dissolved in dry benzene (40 ml) and the soln was added dropwise to a stirred soln of PhMgBr (Mg turnings 0·72 g, bromobenzene 4·7 g, 30 mmoles) in dry ether (20 ml). The stirring was carried on for 3 hr under reflux and for further 4 hr at room temp. The mixture was then hydrolysed with 20% NH_4Cl aq. The organic layer was separated and repeatedly washed with 5% HCl aq, in order to extract VI and with water and then dried over Na_2SO_4. The TLC analysis revealed in this soln the presence of XVI, unchanged XV, Va and traces of the starting IV. The solvent was removed and the residue, dissolved in benzene, was chromatographed on alumina. Elution with benzene yielded IV, Va and XV. The alumina was then washed with acetone. Removal of the solvent from the acetonic soln gave a residue which was submitted to a preparative TLC separation (silica gel G, Merck, acc. to Stahl, benzene–ligroin :3 :2). In this way pure XVI, identified by comparison with an authentic sample, was obtained.

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REFERENCES

[1] H. Gilman, Organic Chemistry. *An Advanced Treatise* Vol. I; p. 511. Wiley, New York (1949); M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances* pp. 117, 1249. Prentice-Hall, New York (1954); H. Zollinger, *Azo and Diazo Chemistry. Aliphatic and Aromatic Compounds* p. 307. Interscience, New York (1961).

[2] M. Colonna and A. Risaliti, *Gazz. Chim. Ital.* **86**, 698 (1956); A. Risaliti, *Ibid.* **87**, 120 (1957); H. Beyer, C. K. Kroeger and M. Zander, *Chem. Ber.* **88**, 1233 (1955); L. Pentimalli and L. Lolli, *Ann. Chim. Rome*, **47**, 34 (1957).

[3] A. Risaliti, *Ann. Chim. Rome* **47**, 1119 (1957).

[4] A. Risaliti and S. Bozzini, *Ibid.* **54**, 685 (1964).

[5] A. Risaliti and A. Stener, *Ibid.* **57**, 3 (1967).

[6] S. Bozzini and A. Stener, *Ibid.* **58**, 169 (1968).

[7] G. Favini, *Gazz. Chim. Ital.* **94**, 1287 (1964).

[8] R. A. Firestone, *Tetrahedron Letters*, 2629 (1967).

[9] J. Braun and M. Mintz, *Chem. Ber.* **50**, 1653 (1917).

[10] R. C. Fuson and S. B. Speek, *J. Am. Chem. Soc.* **64**, 2447 (1942).