Tetrahedron. Vol. 26, pp. 3927 to 3932. Pergamon Press 1970. Printed in Great Britain

AROMATIC AZOCOMPOUNDS—VI[1]

FURTHER EXPERIMENTS PERTAINING TO THE AROMATIC ARYLATION OF *ORTHO*-SUBSTITUTED AZOBENZENES BY GRIGNARD REAGENTS

S. BOZZINI, A. RISALITI and A. STENER
Istituto di Chimica, Università, 34127 Trieste, Italy

(*Received in the UK* 3 *March* 1970; *accepted for publication* 31 *March* 1970)

Abstract—The aromatic arylation of *ortho*-substituted azobenzenes with phenylmagnesium bromide has been investigated. 2,2′-Disubstituted symmetric azobenzenes do not undergo the reaction. 2-Methoxy-6-methyl- and 2-methoxy-2′-methyl-azobenzene give 2-phenyl-6-methyl- and 2-methoxy-2′-methyl-6′-phenyl-azobenzene, respectively. Comparison of the behaviour of 2-methyl-, 2-ethyl- and 2-phenyl-azobenzenes shows that the larger the substituent in the azo derivative, the lower the reactivity of the latter towards arylation. The results obtained support the mechanism previously reported.

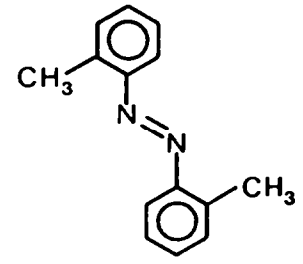
IT HAS been shown that *ortho*-substituted azobenzenes, unlike *meta* and *para* isomers, undergo aromatic arylation with aryl-magnesium bromides at the free positions *ortho* to the azo group. Thus, 2-methoxy- and 2-methyl-azobenzene give 2-methoxy-2′,6′-diaryl- and 2-methyl-6-aryl-azobenzene, respectively.[2-4] Under the same conditions azobenzene undergoes reduction at the azo bridge and this also occurs in part in the *ortho*-substituted azobenzenes and sometimes in the corresponding arylated derivatives.

A mechanism of 1,4-addition involving the azo group, followed by elimination of magnesium bromohydride, was reported for these arylation reactions.[1] Such a mechanism requires the presence of certain structural features in the substrate, e.g. a different molecular environment for the two N atoms and a high degree of coplanarity of the azo group with the reacting ring. Furthermore, in the case of *o*-methoxy-azobenzene the aromatic arylation should take place via a complex, in which the Mg is co-ordinated both with the oxygen of the OMe group and with the nitrogen linked to the substituted ring.

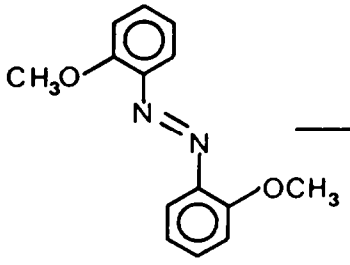
The present work was undertaken to examine whether the absence of these structural features in the *o*-substituted azobenzenes, could change the behaviour towards Grignard reagents. Thus, the reaction of 2,2′-dimethyl- (I) and 2,2′-dimethoxy-azobenzene (II) (in which the two N atoms are structurally equivalent) with phenylmagnesium bromide was investigated. No reaction was observed for I which was recovered almost quantitatively, while II furnished N-phenyl-N,N′-di-*o*-anisyl-hydrazine (III). The behaviour of II appears to be analogous to that of azobenzene, which with particular organometallic reagents yields trisubstituted hydrazines.

The most stable conformation for 2-methoxy-6-methyl-azobenzene is IV, because of the steric hindrance of the Me group. In such a conformation the possibility for the Mg to co-ordinate both with the oxygen of the OMe group and with the nitrogen linked to the substituted ring, fails. Therefore the behaviour of IV is similar to that of 1-phenylazo-2-methoxy-naphthalene,[5] stable in the analogous conformation VI, rather

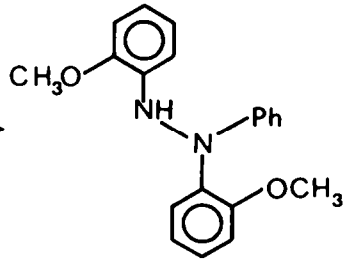
than to 2-methoxy-azobenzene.[2] Actually, the reaction of IV with phenylmagnesium bromide gave 2-phenyl-6-methyl-azobenzene (V) in high yield. From this reaction small amounts of 2-amino-3-methyl-anisole and azobenzene were also isolated.



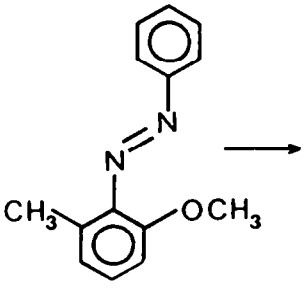
I



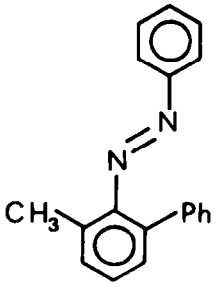
II



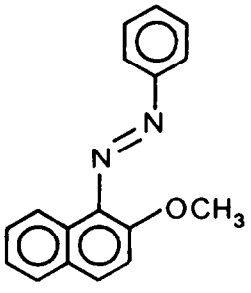
III



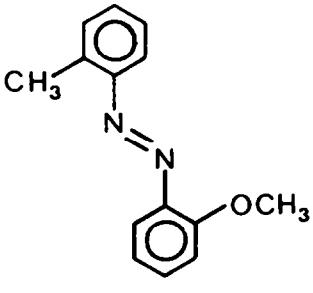
IV



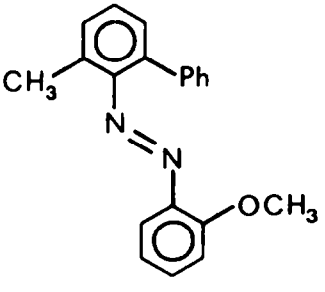
V



VI



VII



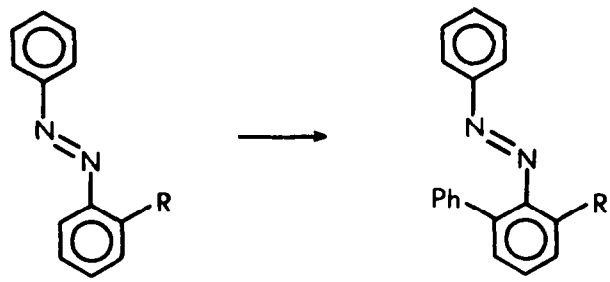
VIII

Isomeric 2-methoxy-2′-methyl-azobenzene (VII), in which both substituents assist the arylation at the 6′-position, yielded 2-methoxy-2′-methyl-6′-phenyl-azobenzene (VIII).

An increase in the steric hindrance of the *o*-substituents in azobenzene derivatives, reduces the coplanarity of the azo group with the reacting ring. This should induce reactivity changes in the aromatic arylation, and therefore 2-methyl- (IX), 2-ethyl- (X) and 2-phenyl-azobenzene (XI), reacted with phenyl-magnesium bromide yielding 2-methyl-6-phenyl- (XII), 2-ethyl-6-phenyl- (XIII) and 2,6-diphenyl-azobenzene (XIV) in 46%,[3] 29% and 5% yields respectively.

These results support the mechanism previously reported for the aromatic arylation

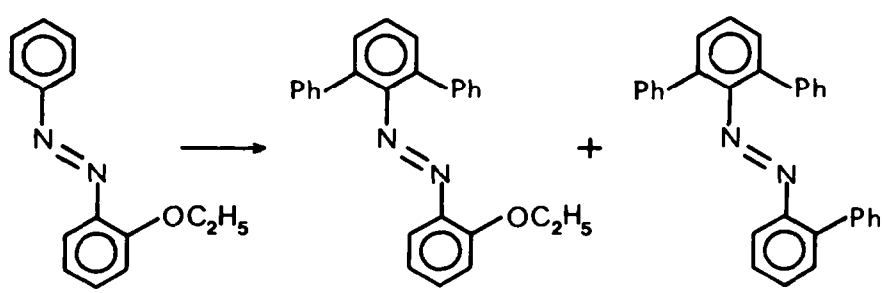
of *o*-substituted azobenzenes with Grignard reagents,[1] although this could be complicated by side reactions. Thus, 2-ethoxy-azobenzene (XV) reacts with phenylmagnesium bromide yielding besides the expected 2-ethoxy-2',6'-diphenyl-azobenzene (XVI),



IX: R = CH_3
X: R = C_2H_3
XI: R = Ph

XII: R = CH_3
XIII: R = C_2H_5
XIV: R = Ph

also 2,2',6'-triphenyl-azobenzene (XVII). Furthermore the formation of azobenzene from IV by demethoxylation and demethylation is another surprising result, which at present cannot be explained. Finally, aliphatic Grignard reagents do not give aromatic alkylation of *o*-substituted azobenzenes.[4] The failure of the reaction of *o*-methyl-azobenzene with both benzyl- and vinyl-magnesium chloride, as shown in the present work, confirmed such contrasting behaviour.



XV XVI XVII

The structures of the reaction products III, V, VIII, XIII, XIV, XVI and XVII were established by reductive cleavage into the corresponding amines.

EXPERIMENTAL

All m.ps were uncorrected. Alumina Merck, acc. to Brockmann, was used for column chromatography. Plates for analytical and preparative TLC were spread with Silica Gel G Merck, acc. to Stahl. As aromatic Grignard Reagent, PhMgBr, in a molar ratio of 2 : 1 with respect to the azo derivative, was used.

Attempted reaction of 2,2'-dimethyl-azobenzene (I). From the reaction, carried out under the conditions described for IV, the starting azo derivative I[6] was recovered in 95% yield.

Reaction of 2,2'-dimethoxy-azobenzene (II). To the ethereal soln (40 ml) of Grignard reagent, a warm soln for 2,2'-dimethoxy-azobenzene[7] (12·1 g, 50 mmoles) in anhyd benzene (260 ml) was added dropwise under vigorous stirring, to prevent the temp rising above 25–30°. At higher temp the reaction yielded

large amounts of tar. The soln was stirred at room temp for a further 5 hr, and then hydrolysed with 20% NH_4Cl aq. The organic layer was separated and repeatedly washed with 5% HCl aq and from the acidic soln *o*-anisidine (0·2 g, 1·6%) was isolated. From the organic soln, after column chromatography (elution with benzene), III (6·2 g, 39%) was obtained and recrystallized from EtOH, as white-rosy crystals, m.p. 119°. (Found: C, 74·72; H, 6·20; N, 8·67. $C_{20}H_{20}N_2O_2$ requires: C, 74·97; H, 6·29; N, 8·74%).

Reduction of N-*phenyl*-N,N'-*di*-*o*-*anisyl-hydrazine* (III). To a soln of III (3·2 g, 10 mmoles) in EtOH (150 ml), Ni-Raney T-1[8] (1 g) and 20% NaOH aq (0·2 ml) were added. The mixture was hydrogenated in a Parr apparatus at room temp and 3–4 atm. The reduction was accomplished when 10 mmoles of H_2 were absorbed. After removal of the catalyst, the soln was evaporated under reduced press and the residue was dissolved in ether. The ethereal soln, after washing with water and removal of the solvent, left an oily residue which on fractional steam distillation, gave *o*-anisidine and 2-methoxy-diphenylamine. The latter was purified by preparative TLC (development with benzene–ligroin 3 : 1) and identified by comparison on TLC and GLC with an authentic sample.[9]

2-*Methoxy*-6-*methyl-azobenzene* (IV). 2-Amino-3-methyl-anisole[10] (4·1 g, 30 mmoles), dissolved in a mixture of EtOH (10 ml) and AcOH (5 ml), was added dropwise and under cooling to a soln of nitroso-benzene (3·3 g, 30 mmoles) in EtOH (12 ml) and AcOH (6 ml). After standing at room temp for 48 hr, the soln was poured into 200 ml water and the resulting mixture was extracted with ligroin. The organic layer was repeatedly washed with 10% HCl aq, with water and then dried over Na_2SO_4. After removal of the solvent, the residual oil was purified by distillation. Red viscous oil, b.p. 160–162° (0·9 mm), (5·1 g, 75%), which proved to be 2-methoxy-6-methyl-azobenzene. (Found: C, 74·50; H, 6·05; N, 12·70. $C_{14}H_{14}N_2O$ requires: C, 74·32; H, 6·24; N, 12·39%).

Reaction of 2-*methoxy*-6-*methyl-azobenzene* (IV). A soln of IV (11·3 g, 50 mmoles) in anhyd benzene (40 ml) was added dropwise with stirring to an ethereal soln (50 ml) of PhMgBr. The stirring was carried on under gentle reflux for 3 hr and at room temp for a further 4 hr. The mixture was hydrolysed with 20% NH_4Cl aq and the organic layer extracted with 5% HCl aq. The hydrochloric extract by concentration gave 2-amino-3-methyl-anisole hydrochloride (0·8 g, 12%). The free base was identified by comparison (TLC) with an authentic sample.[10] The organic layer, after treatment with charcoal and removal of the solvent, gave a residue which on distillation under reduced press furnished two fractions. The first one by preparative TLC gave biphenyl (2 g, 26%) and azobenzene (0·5 g, 6%), both identified by comparison with authentic samples. The second fraction (7·9 g, 58%) proved to be V.[2]

2-*Methoxy*-2'-*methyl-azobenzene* (VII). To a soln of *o*-nitroso-toluene (12·1 g, 100 mmoles) in AcOH (25 ml), a soln of *o*-anisidine (12·3 g, 100 mmoles) in EtOH (25 ml) was added dropwise with cooling. The soln was heated at 40–45° for 4 hr, kept at room temp for a further 2 hr and then poured into 1 l. water. The resulting mixture was extracted with ligroin, and the organic layer was washed with 10% HCl aq, water and then dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on alumina. Elution with benzene furnished VII (16 g, 71%), which crystallized from EtOH as orange-red needles, m.p. 75–76°. (Found: C, 74·34; H, 6·01; N, 12·30. $C_{14}H_{14}N_2O$ requires: C, 74·31; H, 6·23; N, 12·38%).

Reaction of 2-*methoxy*-2'-*methyl-azobenzene* (VII). The reaction of VII (5·6 g, 25 mmoles) in anhyd benzene (20 ml) with PhMgBr in ether (25 ml) was carried out as described for IV. By concentration of the hydrochloric extract, a ppt of 2-amino-3-methyl-biphenyl hydrochloride (0·1 g, 2%), m.p. 208–211° (from 20% HCl aq) was obtained and identified as free base.[3] The mother liquors, evaporated to dryness, gave a mixture (2·2 g) of *o*-anisidine and *o*-toluidine hydrochlorides. The organic layer, by chromatography on alumina (elution with benzene), furnished biphenyl (0·9 g, 23%) and VIII (3·4 g, 45%) as a viscous red oil. (Found: C, 79·14; H, 5·86; N, 8·96. $C_{20}H_{18}N_2O$ requires: C, 79·44; H, 6·00; N, 9·26%).

Reduction of 2-*methoxy*-2'-*methyl*-6'-*phenyl-azobenzene* (VIII). Reductive cleavage of VIII, performed under the same conditions described for III, afforded *o*-anisidine and 2-amino-3-methyl-biphenyl[3] (TLC).

2-*Ethyl-azobenzene* (X). This was prepared by condensation of nitrosobenzene (21·4 g, 200 mmoles) with 2-ethyl-aniline (24·6 g, 200 mmoles), as described for VII. Pure 2-ethyl-azobenzene (32 g, 76%) was obtained by chromatography on alumina (elution with ligroin) as a red oil, b.p. 137° (0·2 mm). (Found: C, 79·75; H, 6·66; N, 13·39. $C_{14}H_{14}N_2$ requires: C, 79·97; H, 6·71; N, 13·32%).

2-*Ethyl-hydrazobenzene*. To a boiling soln of X (6 g) in EtOH (75 ml), 20% NaOH aq (25 ml) was added all at once and Zn dust (5 g) portionwise with vigorous stirring. The heating was carried on until complete decolorization of the mixture (about 1 hr). The inorganic material was filtered off and from the filtrate 2-ethyl-hydrazobenzene (4·3 g, 70%) precipitated on cooling. The product recrystallized from

EtOH as pale yellow crystals, m.p. 77–79°. (Found: C, 79·60; H, 7·80; N, 13·17. $C_{14}H_{16}N_2$ requires: C, 79·20; H, 7·60; N, 13·20%).

3-Ethyl-benzidine hydrochloride. A soln of conc HCl (1 ml) in EtOH (5 ml) was added dropwise with cooling to a soln of 2-ethyl-hydrazobenzene (2g) in ether (11 ml). A ppt of 3-ethyl-benzidine hydrochloride formed immediately and yielded white crystals from 20% HCl aq, m.p. 290°. (Found: C, 59·12; H, 6·36; N, 9·97. $C_{14}H_{18}N_2Cl_2$ requires: C, 58·95; H, 6·36; N, 9·82%). Picrate, yellow crystals (from EtOH–H_2O), m.p. 191–193°.

Reaction of 2-ethyl-azobenzene (X). The reaction was carried out as described for IV, using 12·6 g (60 mmoles) of X in anhyd benzene (40 ml). By concentration of the hydrochloric extract, 3-ethyl-benzidine hydrochloride (5·2 g, 30%) separated and was identified by comparison with an authentic sample. The organic layer, after removal of the solvent, gave a residue which was purified by chromatography on alumina (elution with benzene). Distillation under reduced press of the eluate furnished biphenyl (2 g, 11%), unchanged 2-ethyl-azobenzene (1 g, 8%) and XIII (5g, 29%) as a viscous red oil, b.p. 146° (4×10^{-4} mm). (Found: C, 83·32; H, 6·21; N, 9·47. $C_{20}H_{18}N_2$ requires: C, 83·89; H, 6·34; N, 9·78%).

Reduction of 2-ethyl-6-phenyl-azobenzene (XIII). The catalytic hydrogenation of XIII was carried out as described for III. The mixture, freed from catalyst, was steam distilled. The distillate contained aniline, identified on TLC, while from the residue, 2-amino-3-ethyl-biphenyl was isolated by column chromatography and identified as hydrochloride, m.p. 191–193°. (Found: C, 71·43; H, 7·02; N, 5·81. $C_{14}H_{16}NCl$ requires: C, 71·95; H, 6·90; N, 5·99%).

Reaction of 2-phenyl-azobenzene (XI). 2-Phenyl-azobenzene[3] (7·75 g, 30 mmoles) in anhyd benzene (35 ml) reacted with the Grignard reagent under the conditions described for IV. From the hydrochloric extract 2-amino-biphenyl (1·3 g, 21%) and aniline (1·2 g, 31%) were isolated as hydrochlorides. The organic layer, by concentration and addition of light petroleum (b.p. 30–50°), gave a ppt (0·6 g, 8%) which was identified as 2′-amino-*m*-terphenyl.[2] The filtrate, evaporated to dryness, gave a residue which after column chromatography afforded biphenyl (0·7 g, 8%) and a mixture of unchanged XI and XIV. XI (4 g, 51%) and XIV (0·5 g, 5%) were then separated by preparative TLC (development with benzene–ligroin 2 : 3). Pure 2,6-diphenyl-azobenzene was obtained by further chromatography on alumina (elution with benzene) as red needles, m.p. 75–77°. (Found: C, 85·73; H, 5·62; N, 8·16. $C_{24}H_{18}N_2$ requires: C, 86·20; H, 5·42; N, 8·37%).

Reduction of 2,6-diphenyl-azobenzene (XIV). By catalytic reduction of XIV, aniline and 2′-amino-*m*-terphenyl[2] were obtained (TLC).

Reaction of 2-ethoxy-azobenzene (XV). The reaction of 2-ethoxy-azobenzene[11] (13·5 g, 60 mmoles) in anhyd benzene (35 ml) with PhMgBr in dry ether (40 ml) was carried out as reported. The hydrochloric extract furnished 3-ethoxy-benzidine hydrochloride (6·5 g, 36%), m.p. 275–278°, from which the base, m.p. 136–138° (lit.[11] 139°), was freed and identified by comparison with an authentic sample. The organic soln, by column chromatography (elution with benzene), provided biphenyl (1·7 g, 18%) and a mixture of XVI and XVII. This mixture was further chromatographed on alumina. Ligroin eluted XVII (3·1 g, 13%) as red crystals from ligroin, m.p. 128–129°. (Found: C, 86·32; H, 5·52; N, 6·92. $C_{30}H_{22}N_2$ requires: C, 87·77; H, 5·40; N, 6·82%). The alumina was then extruded and the red coloured portion cut up and repeatedly washed with acetone. The extract, after removal of the solvent, afforded XVI (4·2 g, 19%) as red-orange crystals from ligroin, m.p. 78–80°. (Found: C, 83·29; H, 5·76; N, 7·50. $C_{26}H_{22}N_2O$ requires: C, 82·51; H, 5·86; N, 7·40%).

Reduction of 2-ethoxy-2′,6′-diphenyl-azobenzene (XVI). Cleavage of XVI by catalytic hydrogenation, furnished *o*-phenetidine and 2′-amino-*m*-terphenyl[2] (TLC).

Reduction of 2,2′,6′-triphenyl-azobenzene (XVII). Carrying out the reductive cleavage of XVII under the conditions previously described, 2-amino-biphenyl and 2′-amino-*m*-terphenyl[2] were obtained (TLC).

Reaction of 2-methyl-azobenzene (IX) *with benzylmagnesium chloride.* A soln of 2-methyl-azobenzene (11·8 g, 60 mmoles) in anhyd benzene (35 ml) was added dropwise to a stirred soln of BzMgCl (Mg turnings 2·9 g, benzyl chloride 15·1 g, 120 mmoles) in dry ether (50 ml). The stirring was carried on for 3 hr under reflux and for a 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. From the hydrochloric extract 3-methyl-benzidine hydrochloride[3] (8·3 g, 50%) was isolated. The organic soln, after chromatography on alumina (elution with benzene), provided a red oily residue from which after prolonged standing, colourless crystals of dibenzyl (2·2 g, 20%) separated. The remaining red oil (5·5 g, 46%) proved to be unchanged 2-methyl-azobenzene.

Reaction of 2-methyl-azobenzene (IX) *with vinylmagnesium chloride.* A soln of 2-methyl-azobenzene (11·8 g, 60 mmoles) in anhyd THF (20 ml) was added dropwise to a stirred soln of CH_2=$CHMgCl$[12] (Mg turnings 3·6 g, EtBr 0·2 ml, vinyl chloride 9·3 g, 150 mmoles) in the same solvent (50 ml). The reaction was carried out as described. After hydrolysis with 20% NH_4Claq, the organic layer was treated with 5% HClaq which causes rearrangement of hydrazobenzene derivatives into the corresponding benzidines. In this way 3-methyl-benzidine (10 g, 85%) was separated from the soln after alkalization with NH_4OH and removal of the solvent.

Acknowledgements—This work was supported by a grant from the Consiglio Nazionale delle Ricerche (Rome).

REFERENCES

[1] Previous paper in this series (regarded as Part V): A. Risaliti, S. Bozzini and A. Stener, *Tetrahedron* **25**, 143 (1969)
[2] A. Risaliti and S. Bozzini, *Ann. Chim. Rome* **54**, 685 (1964)
[3] A. Risaliti and A. Stener, *Ibid.* **57**, 3 (1967)
[4] S. Bozzini and A. Stener, *Ibid.* **58**, 169 (1968)
[5] A. Risaliti, *Ibid.* **47**, 1119 (1957)
[6] A. H. Cook, *J. Chem. Soc.* 876 (1938)
[7] B. M. Bogolovskii, *Zh. Obshch. Khim.* **16**, 193 (1946); *Chem. Abstr.* **41**, 105 (1947)
[8] X. A. Dominguez, J. C. Lopez and R. Franco, *J. Org. Chem.* **26**, 1625 (1961)
[9] S. P. Massie and P. K. Kadaba, *Ibid.* **21**, 347 (1956)
[10] W. Q. Beard, D. N. Van Eenam and C. R. Hauser, *Ibid.* **26**, 2310 (1961)
[11] P. Jacobson, G. Franz and F. Hönigsberger, *Ber. Dtsch. Chem. Ges.* **36**, 4069 (1903)
[12] H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint and R. Cserr, *J. Org. Chem.* **22**, 1602 (1957)