Replacement of Methoxyl Group on the Grignard Reaction of *N*-(*o*-Methoxybenzylidene)aniline

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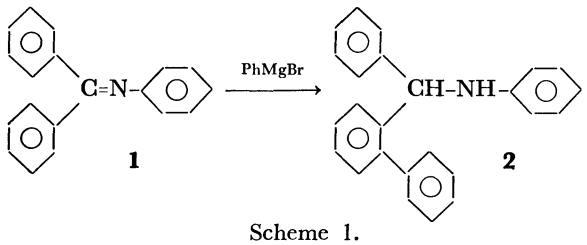
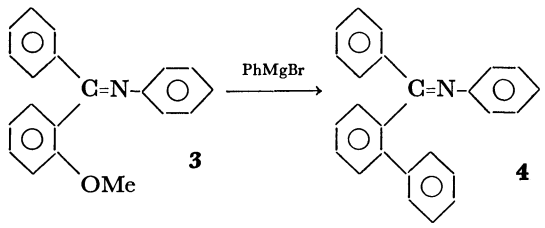
The methoxyl group of the title imine was replaced by the phenyl group on treatment with PhMgBr, the same group of *N*-benzylidene-*o*-anisidine remaining. The result was discussed on the basis of radical chain mechanism involving the initial electron-transfer.

The Grignard reaction of >C=N– compounds has not been extensively studied. Gilman and his co-workers reported that *N*-(diphenylmethylene)aniline (**1**) on the "forced" reaction with phenylmagnesium bromide (PhMgBr) affords the *o*-phenylation product (**2**) as the result of 1,4-addition (Scheme 1).[1] The characteristic deep-red coloration of the reaction mixture seems to indicate the presence of radical species. From the results of recent studies on the Grignard reaction of hindered benzophenones,[2,3] a similar, more facile *o*-phenylation is expected if the substrate has an *o*-methoxyl group. We thus attempted to realize the replacement reaction of Scheme 2.

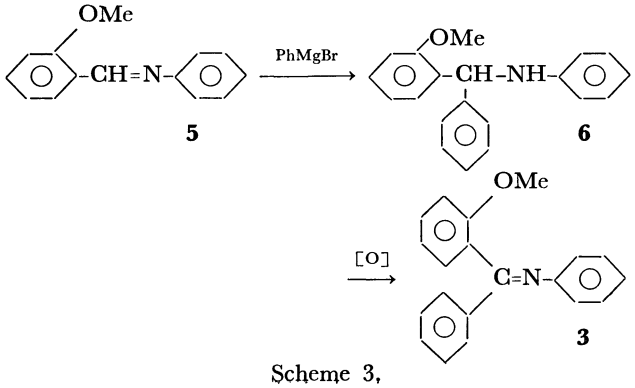


Scheme 1.



Scheme 2.

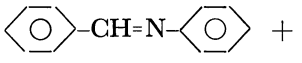
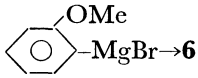
For the preparation of **3**, however, attempts to condense the benzophenone and aniline by use of some Lewis' acid catalysts ($POCl_3$,[4] $ZnCl_2$,[5] and BF_3[6]) were unsuccessful. In the course of studies on the Grignard reaction of *o*-methoxy-substituted *N*-benzylideneanilines in order to find another preparative route (Scheme 3), an interesting replacement of *o*-methoxyl group was found. The results are reported in this paper.

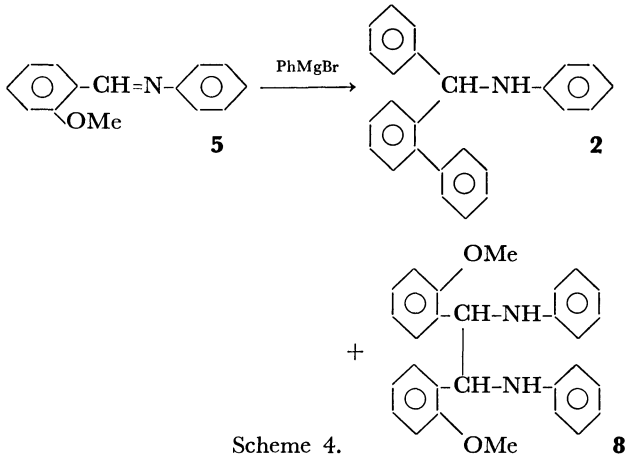


Scheme 3.

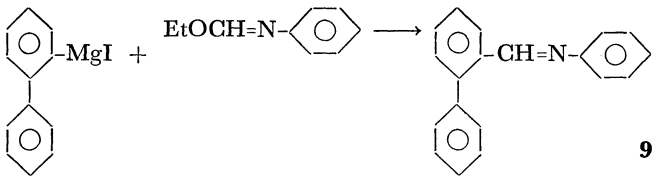
Results and Discussion

Preparation of o-*Methoxy-substituted* N-*Benzylideneanilines.* *N*-(*o*-Methoxybenzylidene)aniline (**5**) and *N*-benzylidene-*o*-anisidine (**7**) were prepared by the condensation of the corresponding benzaldehydes and anilines in methyl alcohol.[7] However, in both cases the colorless crystalline products obtained after recrystallization from the same solvent were found by NMR to be 1:1-molecular complexes, **5** with methyl alcohol and **7** with *o*-anisidine. In order to obtain purified pale-yellow imines, the alcohol combined with **5** should be removed by evacuation at 70 °C for about 1 h and **7** distilled under reduced pressure.

Grignard Reaction. The reaction was carried out in tetrahydrofuran(THF) under N_2. On reaction of **5** with five molar equivalents of PhMgBr at 50—55 °C for 5 h, the products isolated by column chromatography on silica gel (petroleum ether : diethyl ether : benzene=10 : 1 : 1) were the Gilman product **2** (58%) and the dimer **8** (0.5%) (Scheme 4). 25% of **5** recovered. Formation of **2** is obviously the result of the methoxy-replacement accompanied by 1,2-addition. Absence of the simple addition product **6** was confirmed by comparing the thin-layer chromatogram of the product mixture of this reaction with that of the independent reaction:  +  –MgBr→**6** and other products. *N*-(2-Biphenylylmethylene)aniline (**9**), prepared according to Scheme 5,[8] was not detected in the reaction mixture, nor recognized as an intermediate product. Formation of **8** suggests that the radical chain mechanism is involved.



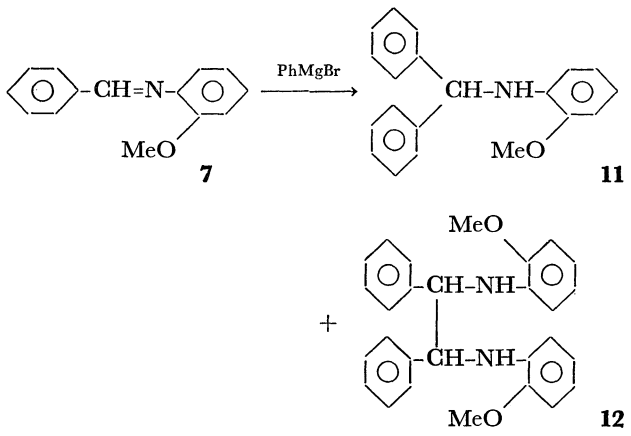
Scheme 4.



9

Scheme 5.

In contrast, the *o*-methoxyl group of **7** was not replaced at all even by treatment with five molar equivalents of PhMgBr at 50—55 °C for 5 h (Scheme 6). A fair yield of the secondary amine **11**[9] (64%) and the dimer **12** (0.8%) were isolated. 28% of **7** recovered. Two isomeric dimers giving the same TLC spot were obtained: **12a**, mp 135—138 °C, NMR ($CDCl_3$), δ=6.24—7.22 (18H, m, aromatic), 5.15 (2H, broad d, NH), 4.9 (2H, d, >CH), and 3.80 (6H, s, OCH_3); **12b**, mp 198—201 °C, NMR ($CDCl_3$), δ= 6.22—7.22 (18H, m, aromatic), 5.15 (2H, broad s, NH), 4.58 (2H, d, >CH), and 3.80 (6H, s, OCH_3). No stereochemical assignment was made. Formation of **12** suggests the intermediate formation of the radical derived from **7** *via* initial electron-transfer.



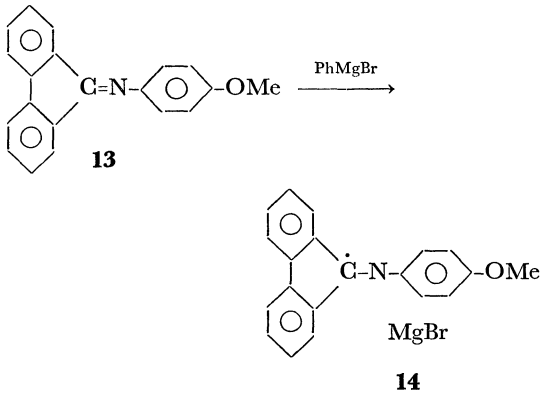
7 11 12

Scheme 6.

The low reactivity of *N*-benzylideneanilines and *N*-(diphenylmethylene)anilines towards PhMgBr should be noted. This is demonstrated by the fact that no heat evolution usually observed in the reaction of >C=O compounds was detectable in all the reactions of >C=N- compounds examined, and about 50% of **7** was recovered after it had been treated with 1.3 molar equivalents of PhMgBr at 50—55 °C for 30 min. Such a low reactivity of >C=N- compounds can be interpreted by their much lower electrophilic character as compared to that of >C=O compounds due to the lower electronegativity of nitrogen atom.

ESR Study. Attempts to detect radical species in the reaction of **5** and **7** were unsuccessful. No ESR signal was detected at lower temperatures (—20 °C and —40 °C) and at higher one (+40 °C) even by the use of concentrated reaction solutions.

However, in the reaction of Scheme 1, an ESR signal gradually became very strong at room temperature accompanied by deep purple coloration; no resolvable hyperfine splitting was observed probably because of the non-planarity of the diphenylmethylene moiety. In the reaction of *N*-fluorenylidene-*p*-anisidine(**13**) with PhMgBr (Scheme 7), a strong ESR signal accompanied by deep green coloration was detected, hyperfine splitting being observed when the reaction mixture was diluted. The well-resolved spectrum consists of 45 lines expected solely from the number of protons of the planar fluorenylidene moiety (**14**, $2p+2o+4m$). The same hyperfine splitting was observed in the reaction of *N*-fluorenylideneaniline.[6]



13 14

Scheme 7.

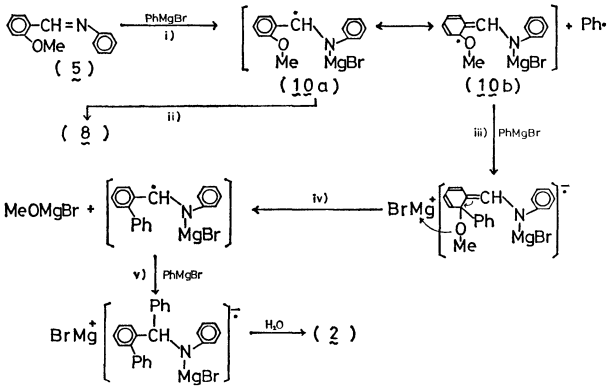
General Discussion. From the observation of strong ESR signals in the reactions of **1** and **13**, the original suggestion that Gilman's reaction of **1** (Scheme 1) proceeds *via* initial electron-transfer was verified.

On the basis of discussion on the steric hindrance effect on the amount of radicals detectable in the Grignard reaction of >C=O compounds,[2] failure to detect radical species in the reactions of **5** and **7** is attributed to their less crowded molecular structures as compared to those of **1** and **13**. The radical formed as the result of initial electron-transfer would accumulate if the subsequent reactions involving the attack of another Grignard molecule are hindered by the crowded molecular structure of substrate such as **1** and **13**. In contrast, the radicals formed from the less crowded **5** and **7** would be rapidly consumed by the subsequent reactions.

The failure to detect ESR signals in the cases of **5** and **7** is also attributable to their low electrophilicity in contrast to that of >C=O compounds. The success to detect ketyl radicals of unhindered benzophenones at lower temperatures[2] is due to their high electrophilicity and to the suppression of the subsequent reactions by the lowered temperature. In cases of much less electrophilic >C=N- compounds, it is reasonable to consider that even the application of low temperature is ineffective since the velocity of electron-transfer is retarded. The higher temperature is ineffective due to the shortened life time of radicals.

Attempts to detect CINDP signal were abandoned since a similar attempt on the reaction of hindered benzophenones failed in spite of very high radical concentrations detected by ESR. The reaction probably proceeds *via* "radical-anion" mechanism of S_{RN}-type[10,11] and not *via* "radical-pair" mechanism.

Scheme 8 could be proposed for explaining the formation of Gilman product **2** in the reaction of Scheme 4. Formation of the dimeric product **8** indi-



Scheme 8.

cates that the initial electron-transfer (step i) and the dimerization (step ii) are involved. The fate of Ph· produced by a step similar to i was discussed.[2] The step subsequent to the initial electron-transfer should be the replacement (steps iii and iv) but not the 1,2-addition. If the latter is the case, the radical chain will terminate leading to the originally expected product **6**. However, this was not the case. The release of the methoxyl anion (step iv) should be easy due to its coordination to $^{+}$MgBr species.[3] The final addition (step v) leads to the formation of the main product **2**.

The result of ESR measurement in the reaction of **13** indicates that the free spin of the radical **14** delocalizes mainly on the fluorenylidene moiety. Thus in the reaction of Scheme 1, the subsequent addition of another PhMgBr to the initially formed radical in the 1,4-manner could be facilitated by the relatively high spin-density at the *ortho*-position. Similarly, the free spin in the radical **10** and that derived from **7** are considered to delocalize mainly on the respective benzylidene moieties. This mode of spin-distribution is responsible for the effective release of the methoxyl anion from the benzylidene moiety as well as for the survival of the group on the aniline moiety.

Experimental

All melting and boiling points are uncorrected.

Materials. Commercial benzophenone, fluorenone, benzaldehyde, *o*-anisaldehyde, aniline, *o*- and *p*-anisidine (reagent grade) were used. *N*-Fluorenylidene-*p*-anisidine (**13**) was prepared by the method of Taylor and Fletcher:[6] mp 135—136 °C. *N*-(*o*-Methoxybenzylidene)aniline (**5**) was prepared by the usual method.[7] The molecular complex with methyl alcohol melted in the range 85—88 °C, and the purified imine at 42—43 °C: NMR ($CDCl_3$), δ=8.85 (1H, s, -CH=), 6.80—8.18 (9H, m, aromatic), and 3.82 (3H, s, OCH_3). *N*-Benzylidene-*o*-anisidine (**7**) was prepared by the same method. The molecular complex with *o*-anisidine melted in the range 62.5—74 °C, and the oily pure imine was obtained by distillation: bp 158—159 °C/2 mmHg; NMR ($CDCl_3$), δ=8.30 (1H, s, -CH=), 6.70—7.88 (9H, m, aromatic), and 3.78 (3H, s, OCH_3). *N*-(2-Biphenylylmethylene)aniline (**9**) was prepared by the method of Smith and Nichols.[8] The method has been established for aldehyde synthesis, but the treatment of the Grignard reaction mixture with aqueous NH_4Cl and not aqueous HCl directly afforded **9**: mp 137—138 °C; NMR ($CDCl_3$), δ=8.16 (1H, s, -CH=), and 6.86—7.36 (14H, m, aromatic). Tetrahydrofuran for the ordinary Grignard reaction was dried over sodium wire, distilled, and stored on sodium wire. The same solvent for ESR measurement was dried by sodium hydride, frozen, degassed repeatedly, and distilled into the storage vessel on a vacuum line containing sodium-potassium alloy.

Procedures. Phenylmagnesium bromide (0.05 mol) was prepared in the usual way in THF (25 ml), imine **7** (0.01 mol) dissolved in THF (20 ml) being added at room temperature. No heat evolution took place. The resulting yellow mixture was stirred at 50—55 °C for 5 h, and quenched with saturated aqueous NH_4Cl. The residue obtained after the usual work-up was chromatographed on silica gel. Appropriate fractions were combined, solvent was removed, and the residue was recrystallized from methyl alcohol: **11**, mp 90.5—92 °C; NMR ($CDCl_3$), δ=7.12—7.36 (10H, m, phenyl), 6.20—6.72 (4H, m, *o*-substd phenyl), 5.40 (1H, s, -CH), 4.65 (1H, broad s, NH), and 3.75 (3H, s, OCH_3).

The reaction of **5** and product separation were carried out in a similar way. The Gilman product **2**: mp 140 °C; NMR ($CDCl_3$), δ=6.20—7.60 (19H, m, aromatic), 5.52 (1H, s, >CH), and 4.0 (1H, s, NH). The dimeric product **8**: mp 206—209 °C; NMR ($CDCl_3$), δ=6.44—7.20 (18H, m, aromatic), 5.35 (2H, d, >CH), 4.84 (2H, broad s, NH), and 3.68 (3H, s, OCH_3).

ESR-Spectrum was recorded on JEOL ME-1X model spectrometer. The apparatus for the measurement was constructed and used as reported.[12]

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