Preparation of Methoxy-substituted Diaryl Ketone Anils *via* Phenyliminodimagnesium Intermediate

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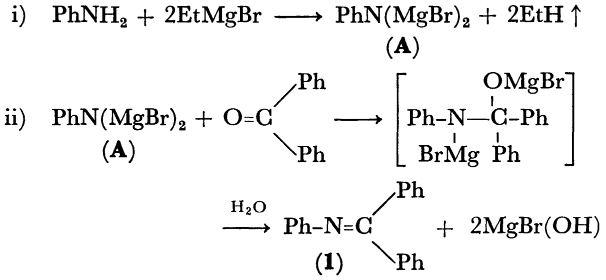
Synopsis. Phenyliminodimagnesium reagent ($PhN(MgBr)_2$) and its *o*- and *p*-methoxy derivatives, prepared in THF by treatment of anilines with EtMgBr, were found to be effective for condensation with benzophenones and fluorenone. The corresponding anils (*N*-(diarylmethylene)-anilines) were prepared in good yields.

In the course of studies on the Grignard reaction with a carbon-nitrogen double bond, it was found necessary to prepare the unknown *o*-methoxybenzophenone anil (*N*-(phenyl-2-methoxyphenylmethylene)-aniline) as a model compound for examining the S_{RN}-type reaction of the methoxyl group with phenylmagnesium bromide.[1] While benzaldehydes can be condensed with anilines without any catalyst,[2] the condensation of ketones with amines requires a catalyst such as $ZnCl_2$,[3,4] HBr,[5] $POCl_3$,[6] BF_3,[7] $TiCl_4$,[8] or molecular sieves.[9] The first four catalysts have been used for the condensation of diaryl ketones with anilines, but they can cause side reactions such as cleavage of ether linkage, making their applicability to the desired condensation of *o*-methoxybenzophenone with aniline impracticable.

The three catalytic methods gave anils in poor yields (Table 1). The very high yield of anil **4** obtained by the condensation of fluorenone with *p*-methoxyaniline(c-4)[7] might show the effectiveness of BF_3, which, however, gave no satisfactory results in other cases. None or only trace amounts of the expected anils were detected by TLC in experiments b-2, c-2, c-6, and c-7. From the results and from successful BF_3-catalysis reported on the condensation of nitro-substituted fluorenones with anilines,[7] it is apparent that the strongly electron-donating methoxyl group especially at *ortho*-position of both benzophenones and anilines is unfavorable for catalytic condensation. Since benzaldehyde and *o*-methoxybenzaldehyde can be condensed respectively with *o*-methoxyaniline and aniline,[10] the bulkiness of the carbonyl component is another obstructive factor.

In our search for some other method involving a procedure to activate the NH-bond of aniline molecule, the anilinomagnesium (PhNHMgBr) and phenyliminodimagnesium($PhN(MgBr)_2$) reagents supplied us with a clue. The former reagent and its *N*-methyl derivative have been used as catalysts for aldol condensation;[11] the latter has been used as the intermediate for preparing trimethylsilylated amino compounds[12] and for converting carboxylic esters into amides.[13] The dimagnesium intermediate seems effective for achieving dehydrative condensation. The expected reaction is shown in Scheme 1.



$$\text{i)}\quad PhNH_2 + 2EtMgBr \longrightarrow \underset{(\mathbf{A})}{PhN(MgBr)_2} + 2EtH\uparrow$$

$$\text{ii)}\quad \underset{(\mathbf{A})}{PhN(MgBr)_2} + O{=}C(Ph)_2 \longrightarrow \left[\begin{array}{c} \quad\quad OMgBr \\ Ph\text{-}N\text{—}C\text{-}Ph \\ BrMg\quad Ph \end{array}\right] \xrightarrow{H_2O} \underset{(\mathbf{1})}{Ph\text{-}N{=}C(Ph)_2} + 2MgBr(OH)$$

Scheme 1.

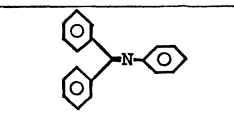
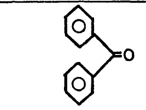
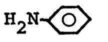
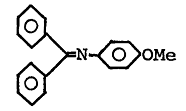
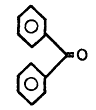
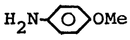
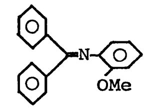
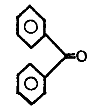
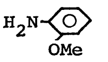
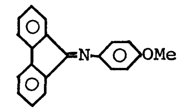
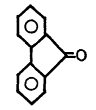
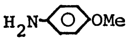
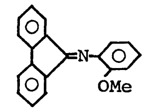
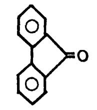
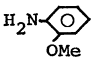
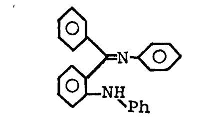
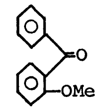
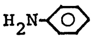
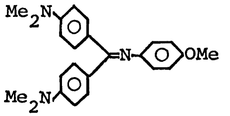
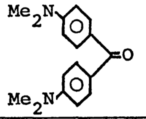
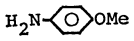
Phenyliminodimagnesium reagent(**A**) and its *o*- and *p*-methoxy derivatives were prepared according to step i) and subsequently condensed with benzophenones and fluorenone (Table 1, d-1 to d-7). The yields of anils **1**[3] and **2**[5] were markedly improved though the reaction conditions were not optimized. However, the desired preparation of *o*-methoxybenzophenone anil was not successful even by this method(d-6), since the methoxyl group was replaced by the PhN(MgBr)-group leading to the formation of **6**. This is apparently due to a S_{RN}-type reaction similar to that proposed for the Grignard reaction of hindered benzophenone derivatives.[1] The low yield of **6** is due to the consumption of two molar equivalents of **A**. The successful preparation of **7** by the condensation of 4,4′-bis(dimethylamino)benzophenone with *p*-methoxyaniline(d-7), both of which have strongly electron-donating substituents, shows the usefulness of the method. The *ortho*-effect of the methoxyl group on the aniline component was substantially overcome as indicated by the fair yields of **3** and **5**. The anils **3**, **5**, **6**, and **7** are new compounds.

The reaction conditions of the method are much milder compared to those of the previous ones requiring higher temperature for the fusion of the reaction mixtures or for the removal of the formed water. The THF solution of **A** is extremely air-sensitive, the solution turning reddish purple rapidly by only a slight intrusion of air. The mechanism of step ii) remains equivocal, since there is another possibility that the $O(MgBr)_2$ species leaves directly from the addition complex prior to treatment with water. Since it is not applicable to nitro-substituted diaryl ketones and aniline, this method and BF_3-catalysis[7] are complementary to each other.

Experimental

Procedures. The phenyliminodimagnesium reagent (**A**, 0.03 mol) in THF (35 ml) was prepared under nitrogen by the addition of aniline to a solution of ethylmagnesium bromide (0.06 mol) at room temperature. The mixture was stirred at 50—55 °C for 30 min to complete the evolution of the latter half equivalent of ethane. Slight heat evolution took place with the subsequent addition of equimolar benzophenone (0.03 mol in 10 ml THF). The reaction mixture turned yellow and then reddish brown. The colored mixture was stirred at 50—55 °C for 30 min and at room temperature overnight, and then treated with saturated aqueous NH_4Cl.

Table 1. Yields of methoxy-substituted ketone anils

Anils		Ketones	Anilines	Yields of anils			
No.	Structure			(a) $ZnCl_2$	(b) $POCl_3$	(c) BF_3	(d) $ArN(MgBr)_2$
1				28	27	—	68
2				10.1 1.3 7.5	not isolated	not isolated	72
3				—	3.6	—	36
4				—	—	81	82
5				—	—	10.2	54
6				—	—	not isolated	39
7				—	—	not isolated	59

Extraction of the resulting mixture with diethyl ether or benzene, drying of the combined extracts with $MgSO_4$, and evaporation of the solvent under reduced pressure afforded a dark yellow crystalline mass. Recrystallization from methyl alcohol afforded 5.0 g (68%) of **1** in a pure form.

The other anils were prepared similarly. Anils **3** and **6** were isolated from the respective product mixture by column chromatography on silica gel (Wakogel C-200, petroleum ether:diethyl ether:benzene=10:1:1).

Melting points (uncorrected), NMR data for methyl and NH protons, and results of the elemental analysis (for only new anils) are given below. All the aromatic protons in NMR appear in the range 6.40—7.95 ppm.

Anil **1**. Mp 116 °C (lit,[3] 116 °C), —.

Anil **2**. Mp 70—72 °C (lit,[4] 70 °C), δ=3.62(s).

Anil **3**. Mp 61—62 °C, δ=3.52(s). Found: C, 83.81; H, 5.85; N, 4.67%. Calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87%.

Anil **4**. Mp 135—138 °C (lit,[4,7] 135—136 °C), δ=3.80(s).

Anil **5**. Mp 141—142 °C, δ=3.70(s). Found: C, 83.97; H, 5.28; N, 4.81%. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91%.

Anil **6**. Oil, δ=10.02(s, NH). Found: C, 86.23; H, 5.76; N, 8.07%. Calcd for $C_{22}H_{20}N_2$: C, 86.18; H, 5.79; N, 8.04%.

Anil **7**. Mp 174—175 °C, δ=3.64 (3H, s) and 3.90 (12H, d). Found: C, 77.15; H, 7.31; N, 11.22%. Calcd for $C_{24}H_{27}N_3O$: C, 77.18; H, 7.29; N, 11.26%.

From the control experiments for measuring the volume of evolved ethane, the yield of intermediate **A** was estimated to be 85—92%.

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