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Iminodimagnesium Reagents. Condensation Reaction with Ketones. Direct Preparation of Anils and a Hydrazone of Xanthone

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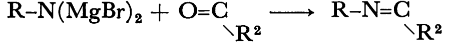
The condensation reaction of ketones with iminodimagnesium reagents (RN(MgBr)$_2$) derived from various primary amines as well as 1,1-disubstituted hydrazines was investigated. *N*-Arylimines and 1-methyl-1-phenylhydrazones of diaryl ketones were prepared, their yields being affected by the electronic and positional effects of substituents of reagent and substrate. Direct preparation of some anils of xanthone and its 1-methyl-1-phenylhydrazone was achieved by use of the corresponding iminodimagnesium reagents.

Aryliminodimagnesium reagents (ArN(MgBr)$_2$, aryl-IDMg) derived from methoxy-substituted anilines were reported recently1) to be condensed with benzophenones and fluorenone (Scheme 1, R=*o*- and *p*-MeOC$_6$H$_4$; R^1 and R^2=aryl).

$$\text{R-NH}_2 + 2\text{EtMgBr} \longrightarrow \text{R-N(MgBr)}_2 + 2\text{EtH}\uparrow$$



$$\text{R-N(MgBr)}_2 + \text{O=C}\begin{smallmatrix}\diagup R^1\\ \diagdown R^2\end{smallmatrix} \longrightarrow \text{R-N=C}\begin{smallmatrix}\diagup R^1\\ \diagdown R^2\end{smallmatrix}$$

Scheme 1.

No extensive studies have been carried out on reagents of this type.2,3) In order to find the characteristics of IDMg reaction with ketones, we carried out the reaction of diaryl ketones and acetophenone with IDMg reagents derived from arylamines and alkylamines as well as 1,1-disubstituted hydrazines, the results being reported in this paper. Xanthone, which is unreactive towards "carbonyl reagents," gives condensation products by this method.

Results and Discussion

All the experiments 1—24 were carried out in tetrahydrofuran (THF) under nitrogen atmosphere, with use of equimolar amounts of ketones and IDMg reagents except for 11 and 12. Product yields are given in Tables 1—3. The reaction time at room temperature and at 55—60 °C were not optimized and the molar ratio of reagents with ketones was fixed; the yields indicate the reactivity of both components used in individual experiments.

Effect of Alkyl Group of Reagents and Substrates. Applicability of the method to the condensation of alkylamine with benzophenone and to that of arylamine with enolizable ketone has been studied.

When benzophenone was treated with *t*-butyl-IDMg at 50 °C for 2 h, 25% yield of *N*-benzhydrylidene-*t*-butylamine **1** was detected by NMR of the product mixture obtained after quenching with aqueous ammonium chloride. When the same ketone was treated with less hindered isobutyl-IDMg at room temperature for 192 h, the yield of the corresponding imine **2** estimated by NMR after quenching with absolute methanol was *ca.* 50%. A by-product, diphenylmethanol, was formed in *ca.* 50% yield. Since **1** and **2** undergo hydrolysis easily, their isolation by column chromatography was difficult even by use of silica gel dried at 120 °C for 2 h.

An attempt to condense acetophenone with *p*-methylphenyl-IDMg by heating at 60 °C for 5 h was unsuccessful. Even by quenching with absolute methanol, TLC of the product mixture shows the presence of only trace amounts of *N*-(α-methylbenzylidene)-*p*-methylaniline **3** and the aldol condensation product, 1,3-diphenyl-2-buten-1-one: formation of the latter is reasonable since similar basic anilinomagnesium reagents (PhN(R)MgBr, R=H and Me)4) were used as catalyst for the aldol condensation. An authentic sample of **3** was also hydrolyzed during the treatment with silica gel.

The easily hydrolyzable nature of ketimines **1**—**3** can be ascribed to the insufficient conjugation system as compared with those having three aryl groups around the >C=N– groups (*vide infra*). The results indicate that the method is not suitable for preparing ketimines from alkylamines and enolizable ketones; the reported method using a Lewis acid, TiCl$_4$,5) is preferable. In the following experiments, aryl-IDMg and diaryl ketones were used.

Aryl-IDMg and Diaryl Ketones. Electronic as well as positional effects of substituents of aryl-IDMg and those of diaryl ketone were examined (Table 1).

m-Methoxyphenyl-IDMg gives anil **4** in moderate yield in the reaction with a 2-methyl-substituted benzophenone; *o*-methylphenyl-IDMg, however, gives anil **5** in poor yield in the reaction with the same ketone. Sterically much hindered 2,4,6-trimethylphenyl-IDMg does not undergo condensation with unhindered 4-methylbenzophenone, but does with planar and less hindered fluorenone; the yield of **7** is low.

p-Chlorophenyl-IDMg, which is less reactive due to the electron-attracting effect of the substituent, can be condensed with a 2-methyl-substituted benzophenone, the yield of **8** being moderate. The IDMg reagent derived from 2-aminopyridine, which is also less reactive due to chelation of the ring nitrogen atom to the Mg atom, gives no condensation product with 2-methylbenzophenone, but does with fluorenone.

Formation of by-products, diarylmethanols, should originate from the initially formed ketyl radicals, which abstract hydrogen from the solvent molecule when the subsequent addition process is slow. The initial formation of ketyl radicals due to electron-transfer from Grignard reagent to benzophenones was discussed.6)

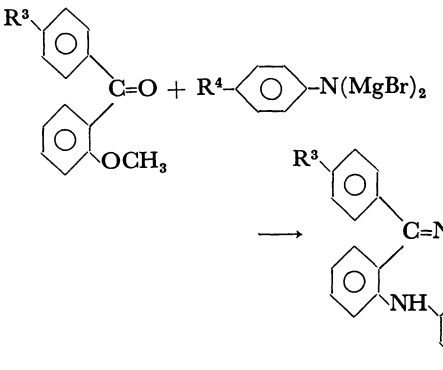
Aryl-IDMg and 2-Methoxybenzophenones. Condensation of phenyl-IDMg with 2-methoxybenzophenone was accompanied by replacement of the *o*-methoxyl

Table 1. Effect of substituents on the reaction of $ArN(MgBr)_2$ with benzophenones and fluorenone

Anil No.	$ArN(MgBr)_2$ Ar	Ar^1–CO–Ar^2		Yield of the anil/%[a]	By-product
		Ar^1	Ar^2		
4	3-$MeOC_6H_4$	2-MeC_6H_4	4-MeC_6H_4	57	
5	2-MeC_6H_4	2-MeC_6H_4	4-MeC_6H_4	20	Ar^1Ar^2CHOH
6	2,4,6-$Me_3C_6H_2$	C_6H_5	4-MeC_6H_4	0	$PhAr^2CHOH$
7	2,4,6-$Me_3C_6H_2$	Flu.[b]		11	
8	4-ClC_6H_4	2-MeC_6H_4	4-MeC_6H_4	34	
9	2-Pyridyl	2-MeC_6H_4	C_6H_5	0	$Ar^1PhCHOH$
10	2-Pyridyl	Flu.[b]		54	
11	4-MeC_6H_4[c]	2-$MeOC_6H_4$	4-MeC_6H_4	25	
12	4-MeC_6H_4[c]	2-$MeOC_6H_4$	4-MeC_6H_4	20	

a) Heated at 55 °C for 10—20 h. b) Fluorenone. c) Reaction conditions are given in the text. d) Reagent containing metallic Mg was used.

group, leading to the formation of 2-anilino-substituted anil (Scheme 2, R^3 and R^4=H).[1] However, the "normal" anil **11** (Table 1) was obtained by treating 2-methoxy-4′-methylbenzophenone with five molar equivalents of *p*-methylphenyl-IDMg at 55 °C for 10 h: **11** was recovered unchanged after treatment with three molar equivalents of the reagent at 55 °C for 6 h.



Scheme 2.

In the reaction carried out in order to examine the effect of equimolar excess of metallic magnesium, the condensation-replacement product **12** was obtained (Scheme 2, R^3 and R^4=Me) in 20% yield. The metal dissolved smoothly with intense purple coloration due to the formation of ketyl radicals developed from the metal surface. The condensation-replacement reaction[1] is thus due to the accidental presence of excess metallic magnesium after the preparation of EtMgBr.

The high radical concentration caused by the efficient electron-donor, metallic magnesium, is one reason for the methoxyl replacement. Similar methoxyl replacement in Grignard reaction *via* electron-transfer process was discussed.[7]

Aryl-IDMg and Xanthone. Xanthone does not undergo condensation with hydroxylamine and phenylhydrazine owing to the electron-releasing resonance effect of the ethereal oxygen atom. So far the oxime and the hydrazone have been obtained after the conversion of ketone into more reactive thioketone.[8] The anil was obtained indirectly from 2,2′-dihydroxybenzophenone by strong heating with aniline.[9] The nonreactivity of xanthone towards amino-functional reagents and its normal reactivity towards Grignard reagents[10] led us to examine the reaction with IDMg (Table 2).

Table 2. Reaction of $ArN(MgBr)_2$ with xanthone

Anil No.	$ArN(MgBr)_2$ Ar	Yield of the anil/%[a]
13	4-MeC_6H_4	86
14	2-MeC_6H_4	0
15	4-$MeOC_6H_4$	53
16	3-$MeOC_6H_4$	50
17	4-ClC_6H_4	0
18	2-Pyridyl	0

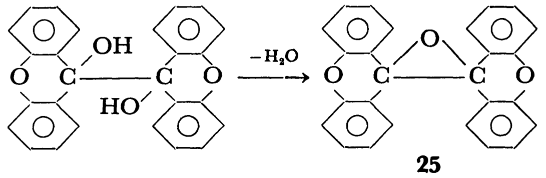
a) Heated at 55—60 °C for 10—20 h.

The ketone can be condensed satisfactorily with *p*-methyl-, *p*- and *m*-methoxyphenyl-IDMg giving anils **13**, **15**, and **16** after heating for more than 10 h. No anil **13** was formed after heating of the reaction mixture for 2 h in contrast with the moderate yields of benzophenone anils by heating for only 30 min.[1] IDMg reagents derived from *o*-methyl- and *p*-chloroaniline as well as 2-aminopyridine, less reactive in the reaction with benzophenones, gave no expected products.

In spite of the lower reactivity, anils of xanthone have been prepared directly for the first time.

IDMg Reagents Derived from 1,1-Disubstituted Hydrazines and Diaryl Ketones. The IDMg reagent derived from 1-methyl-1-phenylhydrazine was found to be useful (Table 3): diaryl ketones including xanthone give excellent yields of the hydrazones **19**, **21**, and **24** after heating for a short time except much hindered 2,3,5,6-tetramethylbenzophenone which was recovered unchanged.

The reagent derived from 1,1-dimethylhydrazine is not effective, which resembles the results obtained with



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Scheme 3.

Table 3. Reaction of IDMg reagents derived from 1,1-disubstituted hydrazines withdiaryl ketones

Hydrazone No.	$\overset{R}{R'}>N-N(MgBr)_2$		$Ar^1-CO-Ar^2$		Yield of the hydrazone/%	By-product
	R	R′	Ar^1	Ar^2		
19	Ph	Me	Xan.[a)]		93[c)]	
20	Me	Me	Xan.[a)]		0[c)]	Epoxide **25**
21	Ph	Me	$4-MeC_6H_4$	C_6H_5	87[c)]	
22	Me	Me	$4-MeC_6H_4$	C_6H_5	0[c)]	$Ar^1PhCHOH$
23	Ph	Me	Dur.[b)]	C_6H_5	0[d)]	
24	Ph	Me	$2-MeC_6H_4$	$2-MeC_6H_4$	78[e)]	

a) Xanthone. b) 2,3,5,6-Me_4C_6H. c) Heated at 55 °C for 1 h. d) Heated at 55 °C for 8 h. e) Heated at 55 °C for 5 h.

use of the reagents derived from alkylamines. By-products should be derived from the ketyl radicals. The epoxide **25** isolated from the reaction mixture with xanthone indicates the intermediate formation of the corresponding pinacol (Scheme 3).[11)]

Characteristics of IDMg Reaction with Ketones. Taking the previous results[1)] into account, characteristics of the reaction can be summarized as follows.

i) Arylamines, 1-methyl-1-phenylhydrazine, and diaryl ketones are favorable components, but not alkylamines, 1,1-dimethylhydrazine and enolizable ketones,

ii) Steric hindrance effect caused by *o*-methyl group of diaryl ketone is overcome when the IDMg reagent is unhindered, and *vice versa*,

iii) Strongly electron-donating methoxyl group, unfavorable to Lewis acid catalyzed condensation, is favorable to the IDMg method,[1)]

iv) Xanthone gives anils when reactive aryl-IDMg reagents are used,

v) IDMg reagent derived from 1-methyl-1-phenylhydrazine gives excellent yields of hydrazones of diaryl ketones including xanthone, and

vi) Initial electron-transfer from IDMg reagent to ketones is suggested.

Experimental

Melting points are uncorrected.

Materials. Commercial *t*-butylamine, isobutylamine, all the anilines, 2-aminopyridine, acetophenone, benzophenone, 4-methylbenzophenone, fluorenone, xanthone, 1,1-dimethylhydrazine, and 1-methyl-1-phenylhydrazine were used. 2-Methyl- and 2,4′-dimethylbenzophenone were prepared by the Friedel-Crafts method. 2-Methoxy-4′-methylbenzophenone (mp 64—65 °C) was prepared by the addition of 4-methylphenylmagnesium bromide to 2-methoxybenzaldehyde followed by chromium(VI) oxide oxidation in acetic acid. 2,2′-Dimethylbenzophenone (mp 72 °C) was prepared by treatment of 2-methylbenzoyl chloride with 2-methylphenylmagnesium bromide. Authentic sample of *N*-(α-methylbenzylidene)-*p*-methylaniline **3** was prepared according to the reported method.[12)]

Procedures. A typical procedure for IDMg reaction was described.[1)] All the experiments were carried out using 5—10 mmol of reagents and substrates in 40—50 ml THF: reaction conditions and yields of isolated products are given in the text and in Tables 1—3.

Column chromatography (Wakogel C-200, petroleum benzine–benzene–diethyl ether = 10 : 1 : 1) was applied to the isolation of products except **13** and **19**: all the condensation products were eluted faster than the unreacted ketones. The isolated crystalline products were recrystallized from ethanol.

Products. Presence of diarylmethanols in product mixtures was confirmed by TLC as well as the NMR signal at 5.4—5.7 ppm characteristic of their benzylic protons.

The NMR spectrum of epoxide **25** (8.48—8.52 (4H, m) and 7.12—7.92 (12H, m)) resembles closely that of xanthone. The IR spectrum, resembling also that of the ketone, has another absorption band at 1070 cm^{-1} assignable to ν(C–O–C) vibration. Found: C, 83.02; H, 4.29; O, 12.69%. Calcd for $C_{26}H_{16}O_3$: C, 82.97; H, 4.25; O, 12.76%.

Imine, anil or hydrazone, melting point, NMR data, and result of elemental analysis are as follows: Imine **2**: an oil; NMR (CCl_4): δ=7.18—7.98 (10H, m), 3.16 (2H, d), 2.00 (1H, m), 0.97 (6H, d). Found: C, 85.95; H, 7.98; N, 5.98%. Calcd for $C_{17}H_{19}N$: C, 86.07; H, 8.02; N, 5.90%. Anil **4**: an oil; NMR (CCl_4): δ=6.22—7.74 (12H, m), 3.42 (3H, s), 2.24 (3H, s), 2.00 (3H, s). Found: C, 83.90; H, 6.60; N, 4.39%. Calcd for $C_{22}H_{21}NO$: C, 83.81, H. 6.66; N, 4.44%. Anil **5**: an oil; NMR (CCl_4): δ=6.16—7.72 (12H, m), 2.34 (3H, s), 2.26 (3H, s), 2.00 (3H, s). Found: C, 88.36; H, 6.97; N, 4.61%. Calcd for $C_{22}H_{21}N$: C, 88.29, H, 7.02, N, 4.68%. Anil **7**: mp 159—162 °C; NMR ($CDCl_3$): δ= 6.75—8.32 (10H, m), 2.35 (3H, s), 2.00 (6H, s). Found: C, 88.92; H, 6.36; N, 4.76%. Calcd for $C_{22}H_{19}N$: C, 88.88; H, 6.39; N, 4.71%. Anil **8**: mp 104—105 °C; NMR (CCl_4): δ=6.65—7.80 (12H, m), 2.38 (3H, s), 2.02 (3H, s). Found: C, 79.01; H, 5.59; N, 4.40%. Calcd for $C_{21}H_{18}ClN$: C, 78.87; H, 5.63; N, 4.38%. Anil **10**: mp 79—80.5 °C; NMR (CCl_4): δ=6.18—8.52 (12H, m). Found: C, 84.40; H, 4.64; N, 11.00%. Calcd for $C_{18}H_{12}N_2$: C, 84.37; H, 4.68; N, 10.93%. Anil **11**: mp 129—131 °C; NMR (CCl_4): δ= 6.44—7.64 (12H, m), 3.56 (3H, s), 2.36 (3H, s), 2.18 (3H, s). Found: C, 84.01; H, 6.70; N, 4.48%. Calcd for $C_{22}H_{21}NO$: C, 83.81; H, 6.66; N, 4.44%. Anil **12**: an oil; NMR (CCl_4): δ=6.24—7.34 (16H, m), 3.90 (1H, broad s), 2.24 (6H, s), 2.14 (3H, s). Found: C, 85.99; H, 6.76; N, 7.25%. Calcd for $C_{28}H_{26}N_2$: C, 86.15, H, 6.66; N, 7.18%. Anil **13**: mp 111—112.5 °C; NMR ($CDCl_3$): δ=6.76—8.65 (12H, m), 2.36 (3H, s). Found: C, 84.18; H, 5.28; N, 4.93%. Calcd for $C_{20}H_{15}NO$: C, 84.21; H, 5.26; N, 4.91%. Anil **15**: mp 151—153 °C; NMR ($CDCl_3$): δ=6.72—8.64 (12H, m), 3.58 (3H, s). Found: C, 79.71; H, 5.00; N, 4.70%. Calcd for $C_{20}H_{15}NO_2$: C, 79.73; H, 4.98; N, 4.65%. Anil **16**: mp 88—90.5 °C; NMR ($CDCl_3$): δ=6.40—8.44 (12H, m), 3.78 (3H, s). Found: C, 79.68; H, 5.01; N, 4.68%. Calcd for $C_{20}H_{15}NO_2$: C, 79.73; H, 4.98; N, 4.65%. Hydrazone **19**: mp 138—139 °C; NMR ($CDCl_3$): δ=6.90—8.96 (13H, m), 3.16 (3H, s). Found: C, 80.15; H, 5.40; N, 9.40%. Calcd for $C_{20}H_{16}$-

N_2O: C, 80.00; H, 5.33, N, 9.33%. Hydrazone **21**: an oil; NMR (CCl_4): δ=6.68—7.60 (14H, m), 2.92 (3H, d), 2.44 (3H, d). Found: C, 84.10; H, 6.70; N, 9.25%. Calcd for $C_{21}H_{20}N_2$: C, 84.00; H, 6.66; N, 9.33%. Hydrazone **24**: an oil: NMR (CCl_4): δ=6.66—7.44 (13H, m), 2.84 (3H, s), 2.40 (3H, s), 2.06 (3H, s). Found: C, 84.12; H, 6.96; N, 9.01%. Calcd for $C_{22}H_{22}N_2$: C, 84.07; H, 7.00; N, 8.91%.

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