Aryliminodimagnesium Reagents. X. The Mild Reagent Derived from 2-Aminopyridine and Formation of Highly Reactive Azoxypyridines in the Reaction with Nitrobenzenes

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Synopsis. The reaction of iminodimagnesium reagent derived from 2-amino-4-methylpyridine with nitrobenzenes was examined. The relative yields of the azoxypyridine formed via condensation and the azopyridines via deoxygenation and oxidative dimerization were explained in terms of weak electron-donating ability of the reagent and the strong electron-accepting ability of the azoxypyridine.

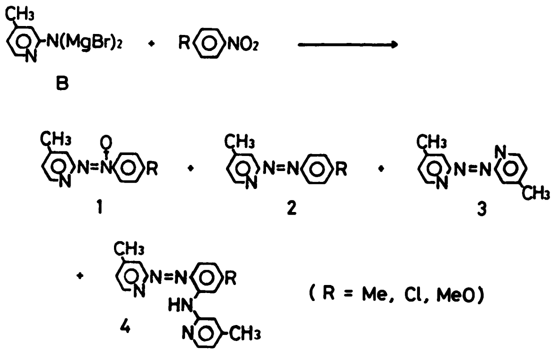
As an application of the procedure using aryliminodimagnesium reagents($ArN(MgBr)_2$, aryl-IDMg), the reaction of reagent ***A*** derived from 1,2-benzenediamine with nitrobenzenes was reported.[1] The product distribution is governed by the sterically hindered but strongly electron-donating nature of ***A***. In the preliminary study on IDMg condensation with carbonyl compounds,[2] reagent B^{H} derived from 2-aminopyridine gave low yield of anil of fluorenone but no anil of benzophenone.

In order to study the reason for the low reactivity of the reagent derived from 2-aminopyridines for the purpose of developing the IDMg procedure, the reaction of nitrobenzenes with reagent B^{Me} derived from 2-amino-4-methylpyridine was examined. The product distribution was compared with that obtained in the reaction of reagent C^{MeO} derived from *p*-methoxyaniline.[3] The result will be explained by the quite weak electron-donating ability of B^{Me} and the very strong electron-accepting ability of azoxypyridine formed in the present reaction.

Results and Discussion

The reagents B^{H} and B^{Me} were prepared without difficulty from 2-aminopyridine and its 4-methyl derivative, respectively, by treating with EtMgBr in THF.[2] Attempts to convert 3- and 4-aminopyridines into IDMg failed; a voluminous white precipitate appeared and no evolution of ethane was observed. The results are quite similar to the successful preparation of IDMg (***A***) from 1,2-benzenediamine and the failure of preparation of IDMg from 1,3- and 1,4-isomers.[1] The reagent B^{Me} was allowed to react with *p*-(Me, Cl, MeO)-substituted nitrobenzenes. Four products identified are shown in Scheme 1: **1** is formed via condensation, **2** via deoxygenation of **1**, and **3** via oxidative dimerization of reagent molecules.[3] While the formation of **1**—**3** is expected from the previous study using the reagents derived from anilines,[3] the formation of the *ortho*-substitution product **4** is observed for the first time in IDMg reactions of nitrobenzenes. Reaction conditions and yields of **1**—**4** are summarized in Table 1 (Runs 1—9).

In Runs 2—4 using small excess of B^{Me}, the yields of azopyridine **2** are higher than those of azoxypyridine **1**; the relative yield is distinct from the higher yields of symmetrical azoxybenzene than the those of azobenzene obtained by use of small excess of reagent derived from aniline.[3] For the complete consumption of the substrate, the large amount of B^{Me} and prolonged heating are needed (Runs 5—7). The azoxypyridine **1** is also consumed completely and



Scheme 1.

Table 1. Conditions and Yields of Products in the Reaction of Reagent B^{Me} with *p*-$RC_6H_4NO_2$

Run	R	$[B^{\mathrm{Me}}]$/Substr.	Reacn. time[a]/h	Yield[b]/%					
				1	2	3	4	Recovd.	Overall
1	Me	1.1	1.5	18	7	4	trace	71	100
2	Me	1.1	3.5	16	17	4	1	58	96
3	Me	2.5	1.5	16	31	7	2	39	95
4	Me	3.0	3.0	9	38	14	trace	30	91
5	Me	10.0	3.0	1	52	13	3	25	94
6	Me	10.0	5.0	0	74	13	5	0	92
7	Me	10.0	21.0[a]	10	20	5	1	63	99
8	Cl	2.5	1.5	24	29	12	3	30	98
9	MeO	2.5	1.5	22	26	5	3	37	93

a) Reaction mixtures were heated at 55 °C in Runs 1—6, 8, and 9, and at room temperature in Run 7.
b) Yields based on the amounts of substrates used.

Table 2. Correlation between EAA and Types of Products Formed in IDMg Reaction with Azoxyarenes
Ar^1-N=N(O)-Ar^2 + *p*-MeOC_6H_4-IDMg (at 55 °C for 3 h)

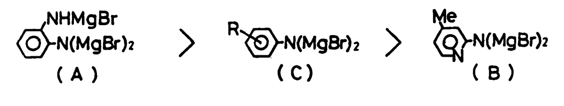
Azoxyarene				Products Formed *via*				
Ar^1	Ar^2	Redn. Pot./V	EAA	Deox. /%	Exchg. /%	Ox. Dim. /%	*ort.* Subs. /%	Decompn. /%
p-MeOC_6H_4	*p*-MeC_6H_4	−1.748	weak	○/16	—	—	—	—
C_6H_5	C_6H_5	−1.596		○/75	—	—	—	—
m-ClC_6H_4	C_6H_5	−1.423		○/75	○/21	—	—	—
2-4MPy[a]	*p*-ClC_6H_4	−1.312	strong	○/32	○/8	○/25	○/9	○/≥50

a) 2-(4-methyl)pyridyl.

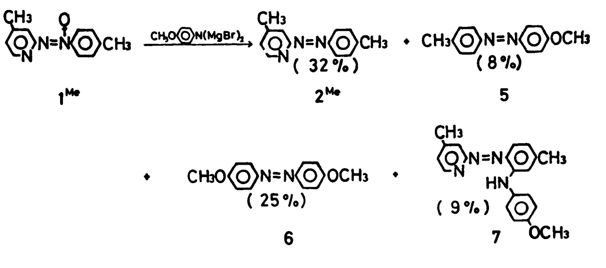
good yield of **2** is obtained (Run 6).

It was postulated previously that the distribution of "normal and abnormal" products in the reactions of organomagnesium reagents depends principally on the combination of electron-donating and -accepting abilities (EDA and EAA) of reactants.[4,5] According to the EDA–EAA concept, the mechanism of reaction of benzophenones with ArMgBr was distinguished successfully from that with IDMg.[6] In order to apply the concept to the present result, the polarographic oxidation peak potential of ***B***$^{\mathrm{Me}}$ (1.295 V) was measured in THF using ferrocene as internal standard.[5] The value higher than that of ***C***$^{\mathrm{MeO}}$ (0.921 V)[5] indicates the weak EDA of ***B***$^{\mathrm{Me}}$ which is responsible for the low reactivity shown by the large amount of recovery in Runs except 6. It is also responsible for the deoxygenation ability of ***B***$^{\mathrm{Me}}$ in the reaction with azoxyarenes. By the treatment of azoxybenzene with five molar equivalents of ***B***$^{\mathrm{Me}}$ and ***C***$^{\mathrm{MeO}}$ at 55 °C for 3 h, deoxygenation proceeds to the extents of 0.5 and 75%,[5] respectively. Taking the previous results[1,5] into account, the order of EDA of IDMg's is shown as follows.

EDA: Electron-donating Ability



The reduction potentials of *p*-substituted nitrobenzenes (MeO: −1.508 V; Me: −1.418 V; Cl: −1.254 V) and those of azoxyarenes including **1**$^{\mathrm{Cl}}$ (See Experimental) were also measured in THF using bisbiphenylchromium(I)tetraphenylborate(BCTB) as internal standard,[7] the latters being listed in Table 2. The EDA of azoxyarene is affected greatly by the aryl group locating opposite to the positive nitrogen.[8] The products and yields obtained in the reaction of **1**$^{\mathrm{Me}}$ with reagent ***C***$^{\mathrm{MeO}}$ are given in Scheme 2(**2**$^{\mathrm{Me}}$ and **5**—**7**). The product **2**$^{\mathrm{Me}}$ is formed via "normal" deoxygenation,[8] **5** via exchange,[8] **6** via oxidative dimerization of IDMg molecules, and **7** via *ortho*-substitution. Table 2 includes also the types of products obtained under the same reaction conditions in the previous[8] and present studies.



Scheme 2.

The results shown in Table 2 demonstrate that EAA of azoxyarenes are correlated to the distribution of types of products in IDMg reaction. In the reaction with ***C***$^{\mathrm{MeO}}$ having strong EDA, azoxybenzenes having weak EAA undergo mild deoxygenation and those having strong EAA undergo rapid deoxygenation and exchange.[8] The azoxypyridine **1** having extremely strong EAA undergoes, additionally, oxidative dimerization of IDMg as well as *ortho*-substitution. The former process is indicative of involvement of electron transfer and is observed usually in the IDMg reaction with nitrobenzenes[3] having strong EAA. The latter process resembles the many examples of conjugate addition of Grignard reagents having strong EDA[5] with nitrobenzenes via electron transfer reported by Bartoli.[9] The strong EAA of **1**$^{\mathrm{Me}}$ and strong EDA of ***C***$^{\mathrm{MeO}}$ are also responsible for the formation of an appreciable amount of unidentifiable black materials indicative of the decomposition via too much vigorous electron transfer.[4] Only a half amount of **1**$^{\mathrm{Me}}$ was converted into the identified products, **2**$^{\mathrm{Me}}$, **5**, and **7**.

In the reaction of Scheme 1, the large amounts of recovery in Runs except 6 are due to the weak EDA of ***B***$^{\mathrm{Me}}$. In contrast to the reactions of nitrobenzenes with ordinary IDMg derived from anilines,[3] however, the azoxy compound formed first in the present reaction has EAA comparable to or stronger than that of substrate. Thus, the strong EAA of **1** not only gives rise to the higher yield of **2** than that of **1** (Runs 2—5 and 7—9) but also is responsible for the slight dependence of product distribution on the electronic effect of substituents of substrates (Runs 3, 8, and 9). The formation of **3** and **4** corresponding to **6** and **7**, respectively, is ascribed to the interaction of ***B***$^{\mathrm{Me}}$ with **1**; the possibility of interaction with substrate is excluded from the large amount of recovery in Runs except 6.

The weak EDA of ***B***$^{\mathrm{H}}$ and ***B***$^{\mathrm{Me}}$ and also the strong EAA of **1** are ascribed to the electron-deficient pyridyl group shown by the lower reactivity of pyridines than that of benzenes toward electrophilic reagents.[10] The good yield of azopyridine (Run 6) suggests the further development of the present method.

Table 3. Melting Points, Elemental Analyses, and ^{1}H NMR Spectra of Products

No.	Mp θ_m/°C	Formula	C	H	N	^{1}H NMR/δ
			Found/(Calcd)			
$\mathbf{1}^{\mathrm{Me}}$	110—110.5	$C_{13}H_{13}N_3O$	68.73 (68.71)	5.82 (5.77)	18.58 (18.49)	8.56 and 7.08(2H, ABq), 8.30 and 7.30(4H, ABq), 8.01(1H, s), 2.44(6H, s).
$\mathbf{1}^{\mathrm{Cl}}$	121—122	$C_{12}H_{10}ClN_3O$	57.99 (58.19)	4.13 (4.07)	16.71 (16.97)	8.62 and 7.16(2H, ABq), 8.14 and 7.50(4H, ABq), 8.10(1H, s), 2.45(3H, s).
$\mathbf{1}^{\mathrm{MeO}}$	79.8—80.2	$C_{13}H_{13}N_3O_2$	63.97 (64.19)	5.33 (5.39)	17.04 (17.27)	8.58 and 7.09(2H, ABq), 8.38 and 6.98(4H, ABq), 8.00(1H, s), 3.85(3H, s), 2.40(3H, s).
$\mathbf{2}^{\mathrm{Me}}$	77—79	$C_{13}H_{13}N_3$	73.96 (73.91)	6.38 (6.20)	19.82 (19.82)	8.54 and 7.10(2H, ABq), 7.93 and 7.28(4H, ABq), 7.44(1H, s), 2.37(3H, s), 2.33(3H, s).
$\mathbf{2}^{\mathrm{Cl}}$	92.5—93.0	$C_{12}H_{10}ClN_3$	62.03 (62.21)	4.36 (4.35)	18.01 (18.14)	8.62 and 7.19(2H, ABq), 7.02 and 7.50(4H, ABq), 7.59(1H, s), 2.39(3H, s).
$\mathbf{2}^{\mathrm{MeO}}$	83.5—84.0	$C_{13}H_{13}N_3O$	68.70 (68.71)	5.87 (5.77)	18.48 (18.49)	8.59 and 7.14(2H, ABq), 8.10 and 7.04(4H, ABq), 7.60(1H, s), 3.82(3H, s), 2.36(3H, s).
3	143—146	$C_{12}H_{12}N_4$	68.01 (67.90)	5.92 (5.70)	26.43 (26.40)	8.60 and 7.30(4H, ABq), 7.84(2H, s), 2.48(6H, s).
$\mathbf{4}^{\mathrm{Me}}$	62—64	$C_{19}H_{19}N_5$	71.63 (71.90)	6.19 (6.03)	21.94 (22.07)	12.65(1H, broad s), 8.83(1H, s), 8.50 and 7.06(2H, ABq), 8.17 and 6.78(2H, ABq), 7.82 and 6.86(2H, ABq), 7.55(1H, s), 6.78(1H, s), 2.45(3H, s), 2.40(3H, s), 2.29(3H, s).
$\mathbf{4}^{\mathrm{Cl}}$	oil	$C_{18}H_{16}ClN_5$	— (64.00)	— (4.74)	— (20.74)	10.76(1H, broad s), 8.95(1H, d), 8.62 and 7.24(2H, ABq), 8.26(1H, d), 7.95(1H, d), 7.61(1H, s), 7.02 (1H, d), 6.80(1H, s), 2.51(3H, s), 2.35(3H, s).
$\mathbf{4}^{\mathrm{MeO}}$	oil	$C_{19}H_{19}N_5O$	— (68.47)	— (4.80)	— (21.02)	12.60(1H, broad s), 8.90(1H, d), 8.56 and 7.10(2H, ABq), 8.22 and 6.67(2H, ABq), 7.87 and 6.60(2H, ABq), 7.63(1H, s), 6.87(1H, s), 3.97(3H, s), 2.43(3H, s), 2.34(3H, s).
7	96—100	$C_{20}H_{20}N_4O$	72.16 (72.27)	6.06 (6.06)	16.72 (16.86)	11.28(1H, broad s), 8.57 and 7.19(2H, ABq), 7.94 and 6.74(2H, ABq), 7.63(1H, s), 7.30 and 6.98(4H, ABq), 6.90(1H, s), 3.86(3H, s), 2.46(3H, s), 2.30 (3H, s).

Experimental

Melting points are uncorrected.

Materials, Reactions, and Products. 2-Amino-4-methylpyridine and nitrobenzenes were commercially available. The solution of $\boldsymbol{B}^{\mathrm{Me}}$ in THF was prepared according to the reported procedure.[1,5] The reactions of Scheme 1 were carried out by adding the solution of nitrobenzenes (3.0 mmol) into the solution of given amount of $\boldsymbol{B}^{\mathrm{Me}}$ at 0 °C. The reaction mixtures were stirred at 55 °C or at room temperature for the given period of time (See Table 1). Using the samples of $\mathbf{1}^{\mathrm{Me}}$ formed in Runs 1—5 and 7, collected and purified, the reaction of Scheme 2 was carried out under the same conditions as those of the previous study.[8] The products formed in the reactions of Schemes 1 and 2 were separated by column and thin-layer chromatographies on silica gel.

The melting points, values of elemental analyses, and ^{1}H NMR spectra of products **1**—**4** and **7** are summarized in Table 3, those of the products **5** and **6** being reported previously.[3,8] The products $\mathbf{4}^{\mathrm{Cl}}$ and $\mathbf{4}^{\mathrm{MeO}}$ were not completely purified, and no elemental analysis was carried out.

Polarographic Measurements. The cyclic voltammetry was carried out by using a Yanaco P-1100 Model Voltammetric Analyzer. Using tetrabutylammonium perchlorate (0.2 M, 1 M=1 mol dm^{-3}) as supporting electrolyte, the oxidation peak potential of $\boldsymbol{B}^{\mathrm{Me}}$ in THF was observed and normalized according to the reported procedure.[5] The reduction potentials of nitro- and azoxy-arenes given in the text are redox potentials observed and normalized similarly; no sample of $\mathbf{1}^{\mathrm{Me}}$ was available because it had been used up for the reaction of Scheme 2. All the values of potentials are those vs. NHE. The two internal standard compounds used for the measurements of oxidation peak and reduction potentials, respectively, are given in the text.

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