ORTHO-PARA SELECTIVITY IN COORDINATED REACTIONS OF ALDIMINES WITH MAGNESIUM PHENOXIDES

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<u>Abstract</u>. N-Aryl imines from aromatic aldehydes react in benzene with *ortho*-tertbutylphenoxymagnesium bromide to give 4,4'-arylidenebisphenols 5 through two consecutive *para*-regiospecific processes whereas N-alkyl imines give mainly *ortho*regioselective reactions in the same conditions, producing 2,2'-arylidenebisphenols 4.

In the last few years we have reported several examples of *ortho*-regioselective reactions on metal phenolates involving weak electrophiles which were activated by highly coordinating cations (usually $MgBr^+$) in solvents of low donicity (benzene, toluene).¹

These reactions are thought to occur via the formation of 'oriented' substrate-reagent complexes (I) which explains the high *ortho*-regioselectivity observed. Evidences for the existence in solution of such complexes (I) have been recently obtained in the case of aldehydes as reagents.²



Schiff bases derived from aromatic aldehydes are weaker electrophiles compared with the parent carbonyl compounds and usually do not react with phenols.³ Only special cases of nucleophilic addition of phenols to carbon-nitrogen double bond are reported.⁴

Since aldimines are known to act as Lewis bases and to form both hydrogen bonded and metal complexes,⁵ we have explored the possibility of activating the C=N group using metal phenolates in low polarity media. The results of these studies are reported in this paper.

Initially $(PhO)_{3}Al$ and PhOZnBr were reacted with N-benzylidenemethylamine 2 and N-benzylideneaniline 3 in refluxing benzene. The reacted phenol was high in all cases (~60-70%) but the products were always resinous materials.

Using the less acidic MgBr⁺ as counterion no reactivity was observed with phenol and p-tert-butyl phenol in benzene at 80°C, while *o*-tert-butyl phenol showed high reactivity with both imines 2 and 3. This is presumably due to the high aggregation and insolubility of p-tert-butyl and phenoxymagnesium bromides, while the *o*-tert-butyl salt is soluble and is only

tetrameric in this solvent at concentration 0.1-0.15 M.⁶ However, an activating steric effect of the *o*-tert-butyl group similar to that observed in other reactions of phenolic substrates⁷ can also contribute to this observed high reactivity.

Surprisingly two completely different processes were observed with the two imines. Nbenzylidenemethylamine 2 gives a completely *ortho*-regiospecific process to produce, after quenching with saturated NH_4Cl solution, the 2,2'-benzylidenebisphenol $\frac{4a}{4A}$ in good yield, while benzylidene aniline $\frac{3}{4A}$ gives a completely *para*-regiospecific process leading to the 4,4'-benzylidenebisphenol $\frac{5a}{4A}$.



To test the influence of steric and electronic factors on the regioselectivity of these coordinated reactions we have changed the nature of the substituents both on the nitrogen and the aromatic group of the imine. The results are reported in the Table.⁸

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Table.	Reactions bet	ween 2-	-tert-butylp	henoxymagn	nesium (bromide	1 ar	nd aldimines	Ar-CH=N-F	<u>۲</u>

		Reacted phenol				
Ar	R ¹	8	4	8	5	8
Ph	Ph	98		.0	5a	95
p-MeOPh	Ph	70		0	5b	68
$p-NO_2Ph$	Ph	89		0	50	88
Ph	p-MeOPh	77		0	表	75
Ph	<i>m</i> -NO ₂ Ph	70		0	5 a	68
Ph	Cyclohexyl	0		-	÷	-
Ph	iPr	21	4a	45	5a	26
Ph	n Pr	70	4a	35	5a	18
Ph	Me	88	4 <u>æ</u>	98	रुर	0

^{α}In refluxing benzene for 24 h; [salt] = [imine] = 0.15 M.

^bBased on reacted phenol.

The reactivity and regioselectivity are very little influenced by electronic factors and with all the N-aryl imines the yield of 4,4'-arylidenebisphenols $\frac{5}{2}$ is always high (\geq 70%).

On the other hand both reactivity and regioselectivity are strongly dependent on the steric bulkiness of the alkyl substituent on the nitrogen. Increasing the steric requirement of the substituent the reactivity decreases until drops to zero with R^1 = cyclohexyl and the *ortho*-regioselectivity decreases in the same direction.

The coordination between the azomethine group and magnesium seems to be essential for the reactivity but not sufficient to obtain *ortho*-regiospecific reactions. In this case a substrate-reagent molecular complex properly arranged (6) has to be formed and the electrophilic attack takes place through an intramolecular pathway.



R = tBu $R^1 = Me, nPr, iPr$

It is also possible that an isomerization of the aldimine from the more stable E to the Z form, 5, 9 which would reduce the steric crowding inside the reacting complex (6), occurs before the electrophilic attack. It is known that the rate of E/Z interconversion in the aldimines increases in the presence of acids. 9b, 10

Mainly for steric reasons the analogous complexes with N-aryl imines have difficulty to collapse intramolecularly to give products of *ortho*-regiospecific attack. Intermolecular *para*-selective reactions between the complexed imine and the phenolic substrate are then likely to occur with the production of 4,4'-arylidenebisphenols 5.

It is noteworthy that no mixed 2,4'-arylidenebisphenols are obtained, the regioselectivity of the overall process beeing determined by the first step which leads to the Mannich base intermediate 7. This is in agreement with the known ability of *ortho*-quinone methide intermediates to form oriented complexes (8) which evolve *ortho*-regiospecifically, ^{1b,11} whereas the correspondent *para*-compounds usually give *para*-attack.^{1b}

The major evidence for the formation of oriented complexes (I) between aldehydes and aryloxymagnesium bromides has been the upfield shift experienced by the formyl proton upon complexation compared with a 'normal' downfield shift observed in complexes with other Lewis acids $(BF_3, MgBr_2)$ in the same conditions.² Similar experiments performed in Et₂O at [salt] = 0.5-1 M show that the methinic proton of N-benzylidene aniline shifts 0.15 ppm downfield from $\delta = 8.23$ to $\delta = 8.38$ ppm in the presence of 5 times excess of 2,4,6-trimethylphenoxymagnesium bromide (2,4,6-TMPOMgBr) and 0.23 ppm downfield with MgBr₂. This 'normal' behaviour indicates a difficulty for the N-aryl imines to form 'oriented' complexes of the type (I) and supports the hypothesis that *para*attack of these electrophiles proceeds intermolecularly.

Unfortunately, it was not possible to obtain the evidence that N-benzylidenemethylamine $\frac{2}{6}$ gives such oriented complexes since they are insoluble both in Et_20 and benzene-d₆, while in the more basic THF no shift has been observed for the methinic proton in the presence of both MgBr₂ and 2,4,6-TMPOMgPr.

The results obtained show that in coordinated processes which occur inside molecular complexes often small structural variations on both substrate and reagent have a great influence on the reaction course.

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