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THE INFLUENCE OF α-ARYL ETHERS ON THE ASYMMETRIC REDUCTION OF CARBONYLS

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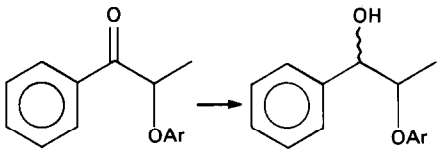
Summary The asymmetric reduction of α-aryl ethers 1 was found to be strongly influenced by the presence of ortho substituents on the aryl ring. Groups (methoxy or hydroxy) that chelate metal cations tend to stabilize a "locked" bicyclic 4 which, intermediate when reduced, yielded preferentially the erytho isomer.

During our investigation into the mechanistic details of the thermal decomposition of lignocellulosic materials, we had anticipated the preparation of a series of compounds representing the various types of bonds within lignin. Our initial interest was directed toward the preparation of 2-aryloxyphenylpropanols 2. The synthesis of similar compounds has been accomplished by the reduction of the appropriate ketone 1 with $NaBH_4$[1,2].



1 2

The latter reference indicated an erthro to threo isomer ratio of 9:1[2]. These results can be explained by the work of Cram [3] and Karabatsos [4] with cyclic rigid models bearing either oxygen or nitrogen. Work by others on the reduction of ketones, with a variety of metal hydrides, adjacent to α-alkoxyethers [5], alcohols [6], epoxides [7], and sulfoxides [8] had also indicated a high degree of asymmetric induction. Further, oxygen containing functional groups in the α position to the carbonyl have also exhibited enhanced stereoselectivity for metal hydride reduction; they include α-alcohols [9], α-alkoxy ethers [10], and α-phenoxy ethers and β-esters[11]. However, when the ketones 1a-h were subjected to $NaBH_4$ (in ethanol) reduction, selectivity was not found for all of the alcohols prepared (see Table 1). Thus, we sought to determine the reasons for this loss of selectivity in the preparation of some of the alcohols and to establish the conditions which produce stereoselectivity.

The phenoxy ketones, 1, used in this work were prepared from 2-bromopropiophenone and the respective phenol. Typically, the reducing agent was added to a flame dried flask under a nitrogen atmosphere. A sufficient volume of anhydrous solvent was added to dissolve the

TABLE 1. Reduction of 2-Phenoxypropiophenones.

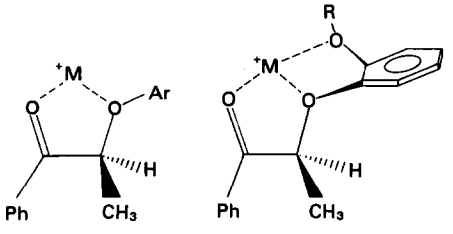
	Aryloxy Substitution	Reducing Agent (erythro:threo)[a]		
		$NaBH_4$[b]	$LiAlH_4$[c]	$Zn(BH_4)_2$[c]
a	2-methoxy	89:11	90:10	>99:1
b	2,5-dimethoxy	77:23	92:8	92:8
c	2-hydroxy	92:8	92:8	>99:1
d	none	42:58	72:28	>99:1
e	4-methoxy	55:45	77:23	>99:1
f	3-methoxy	45:55	70:30	91:9
g	2-methyl	26:74	46:54	72:28
h	2-t-butyl	<1:99	<1:99	<1:99

a Isomer ratios were determined by gas chromatography and confirmed by integration (NMR) of the methyl absorbences.
b Reductions were performed in ethanol.
c Reductions were performed in ether.

reducing agent. Then the α-phenoxy ketone was added via a syringe to the flask. The molar ratio of reducing agent to ketone was 1:1, except for ketone 1c where the ratio was increased to 1.25:1. The ratio of solvent to ketone was kept at 25mL to 1.0 mmole. The reaction mixture was stirred at 23°C for 3 hours before a minimal amount of saturated NH_4Cl solution was added. This mixture was extracted with ether, dried, and stripped of solvent. All alcohols were obtained in quantitative yield and exhibited NMR, IR, and MS data consistent with the expected products.

The initial reduction of ketones 1a-c with $NaBH_4$ suggested that the presence of an oxygen atom at the ortho position in the phenoxy ring had a greater influence on the stereochemical control than had been previously reported[1,2]. The isomer designations of erythro and threo in Table 1 have been used in accordance with the results of the previous work on the reduction of 1-(4'-benzyloxyphenyl,3'-methoxy-)-2-(2"-methoxyphenoxy)-1-propanone [2], where an isomer ratio of 9:1 was found for the reduction run with $NaBH_4$ in ethanol.

The five-membered ring rigid model 3, similar to that proposed by Cram [3], might adequately describe the course of the reduction of the ketones 1, but for several exceptions



3 4

which are apparent in Table 1. Glass [6] has shown that the sodium cation effectively chelates both oxygen atoms of the alkoxy and ketone groups in the reduction of 2-methoxy phenylpropanone and that an isomer ratio of approximately 9:1 was observed. This was not observed with the reductions of the non ortho-substituted phenoxypropriophenones 1d-f using $NaBH_4$. Rather, the results found in Table 1 indicate that there are at least three groups of compounds: ortho-methoxy and hydroxy substituted rings which show erythro selectivity (2a-c), non-ortho substituted rings which show no selectivity (2d-f), and ortho-alkyl substituted rings which show a threo or "reverse" selectivity (2g and h). These distinct groups suggest that some modification of the five membered chelate ring 3 is necessary.

The erytho-selectivity shown by 2a-c prepared from $NaBH_4$ probably involves cation chelation of the oxygens in the carbonyl, aryloxy, and o-methoxy or hydroxy groups. Molecular models suggest that a bicyclic structure such as 4 is preferred to its alternative, a convoluted, eight-membered ring. With the presumed structure 4 the aryloxy-group can be held in a non-hindering position which allows metal hydride attack to occur predominately away from the β-methyl group. The lower erythro-selectivity of 2b may be attributed to a hindrance from the O-methoxy group, that is not chelated, in a manner noted with 2g. The erythro-threo ratios approach unity in 2d-f due to the lack of the bicyclic "locked" structure. Apparently, the sodium cation does not form as rigid a ring structure 3 as either lithium, or zinc; i.e., hardness of the cation [12] allows the propanone methyl to predominate. We do caution against direct comparisons of the results obtained by $NaBH_4$ and $LiAlH_4$ reductions in Table 1 since different solvents were used due to synthetic necessity. However, the trends do appear somewhat consistent since reductions of 1a, preformed in THF gave erytro:threo of 73:27($NaBH_4$) and 81:19($LiAlH_4$), while 1d gave ratios of 50:50 for both reagents.

The predominance of the threo-diastereomers after $NaBH_4$ reduction of 1g and, 1h can be attributed to steric hindrance of the o-toluoxy and o-t-butyl-phenoxy groups. The presence of the t-butyl group is overwhelming even when strong Zn^{++} chelation can occur.

Acknowledgment

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