

Radical Isomerization via Intramolecular Ipso Substitution of Aryl Ethers: Aryl Translocation from Oxygen to Carbon.

Eun Lee*, Chulbom Lee, Jin Sung Tae, Ho Sung Whang, and Kap Sok Li

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

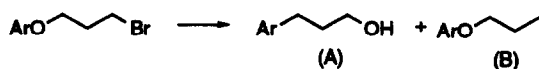
Abstract: Bromopropyl aryl ethers are converted to 3-arylpropanols under standard radical generating conditions in the presence of tributylstannane and AIBN. This rearrangement involves intramolecular ipso attack of the alkyl radicals which generates spiro cyclohexadienyl radical intermediates.

Free radical aromatic substitution played an important role in the history of free radical chemistry.¹ Aromatic ring systems serve as substrates in intermolecular free radical substitution reactions,² and more recently, annulations via intramolecular aryl ortho substitution³ of free radicals appear to serve well in the synthesis of cyclic compounds. Also well established are free radical reactions on aromatic systems which involve rearrangements⁴ triggered by intramolecular ipso attack of free radicals. These reactions proceed through spiro cyclohexadienyl radicals⁵ and result in the aryl translocation from carbon to carbon,⁶ nitrogen to carbon,⁷ sulfur to carbon,⁸ silicon to carbon,⁹ carbon to silicon,¹⁰ and oxygen to oxygen.¹¹ We report herein rearrangement of 3-aryloxypropyl radicals which effects transfer of aryl groups from oxygen to carbon.¹²

The requisite 3-aryloxypropyl bromides were prepared in good yields by alkylation of phenols with 1,3-dibromopropane in hot acetone in the presence of potassium carbonate and a catalytic amount of 18-crown-6. The substrates were reacted with tributylstannane under standard high dilution conditions: 1.2 eq. Bu₃SnH and 0.2 eq. AIBN in benzene were added to a substrate solution (0.03 M) in benzene under reflux via syringe pump for 7 hours (total reflux time 8 hours). The results are summarized in Table 1.

The simplest substrate 3-phenoxy-1-bromopropane was mainly converted into 1-phenoxypropane and only a trace amount of the rearranged product was obtained (Entry 1). When the substrate carried electron-withdrawing substituents at the aryl para or ortho position, low to moderate yield (23~43%) of the rearranged 3-aryl-1-propanol was obtained (Entries 2, 3, 5, 6, 7, 9 and 10). One exception was the substrate with 2-ethoxycarbonylvinyl substituent at the ortho position, which acted as an effective 7-*exo* intramolecular radical acceptor precluding the formation of the requisite spiro cyclohexadienyl radical (Entry 8). Methyl 3-(3'-bromopropoxy)benzoate was a poor substrate yielding a complex product mixture which contained only 4% of the normal rearrangement product (Entry 4).

Substrates with electron-donating substituents at the aryl para or ortho positions also supplied rearranged 3-aryl-1-propanols in comparable yields (24~61%). In these cases, ortho substituents (Entries 12 and 14) were more effective than para substituents (Entry 11) in promoting rearrangement. Meta



Entry	Ar	Isolated Yield (%)		Entry	Ar	Isolated Yield (%)	
		(A)	(B)			(A)	(B)
1		2	85	10		37 ^c	18
2		25	65	11		24	61
3		35 ^a	18	12		53	21
4		4	21	13		4	80
5		34	49	14		61	14
6		23	46	15		90	0
7		43	27	16		16	70
8		4	52 ^b	17		44	12
9		25	40				

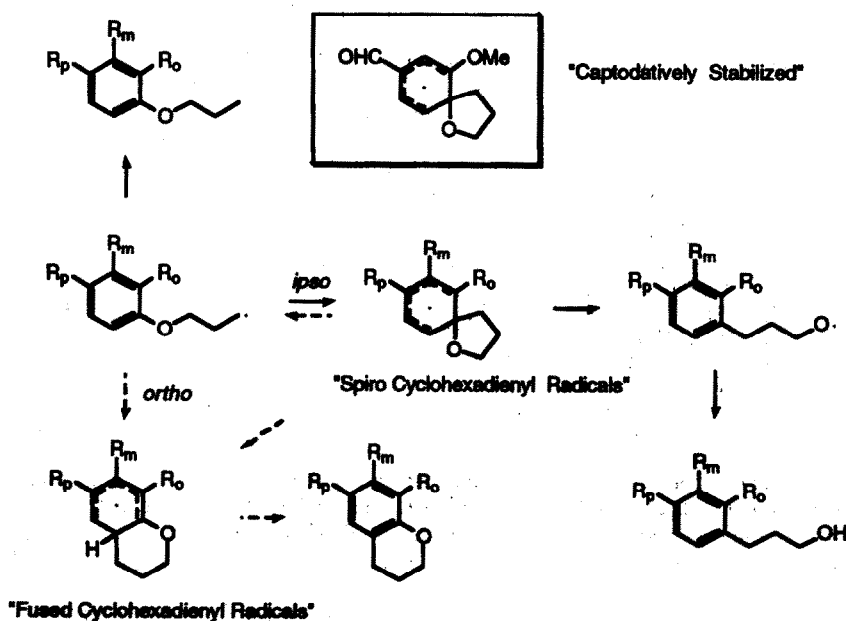
a)
b)
c)

Table 1

substituents did not increase the rearrangement yield (Entry 13).

The most efficient rearrangement was observed in the system with both electron-withdrawing and electron-donating substituents at ortho and para positions. For example, vanillin 3-bromopropyl ether was converted into the corresponding 3-aryl-1-propanol in 90% yield in a remarkably clean and efficient rearrangement reaction (Entry 15). This result is contrasted by a much lower yield (16 %) of the rearrangement product from isovanillin 3-bromopropyl ether, which features an ortho methoxy and a meta aldehydic substituent. (Entry 16). Some naphthol derivatives were also tested and the efficiency of rearrangement was found to depend mainly on the substitution pattern. For example, 44% yield of the rearrangement product was obtained from 1-methoxycarbonyl-2-(3'-bromopropoxy)naphthalene¹³ (Entry 17).

The mechanistic considerations are summarized in Scheme 1. The 3-aryloxypropyl radicals initially formed can abstract hydrogen from tributylstannane to form aryl propyl ethers, or attack ortho or ipso aryl positions intramolecularly to form fused or spiro cyclohexadienyl radicals. From the results shown in Table 1, it is clear that formation of spiro cyclohexadienyl radicals is the dominant mode of reaction for this series of substrates.¹⁴ This is analogous to the favored *5-exo* addition of alkyl radicals to intramolecular double bonds. It is interesting that both electron-withdrawing and -donating substituents on the aryl ring facilitate the ipso attack. The substituted methyl radicals in these reactions are assumed to be relatively nucleophilic in character when they react with aryl rings substituted with electron-withdrawing groups: in these cases SOMO-LUMO interaction is important. On the other hand, they are considered to be relatively electrophilic in character when they react with electron rich aryl rings: SOMO-HOMO interaction is then more important. The same type of reasoning had already been advanced by Speckamp.^{8c}



Scheme 1

The most important factor on the efficiency of the ipso attack, however, appears to be the stability of the intermediate spiro cyclohexadienyl radicals. In the case of vanilin ether derivative, the spiro cyclohexadienyl radical intermediate is strategically substituted by two groups with opposing electron demand and "captodatively" stabilized, which eventually leads to a high yield of rearrangement product. It is thus reasonable to assume that the ipso attack is irreversible under the reaction conditions employed and the fission of C-O bond is the kinetically favored pathway for re-aromatization of the spiro cyclohexadienyl radicals.

Acknowledgements : Authors thank the Ministry of Education, Republic of Korea, (BSRI-92-314), and the Organic Chemistry Research Center (KOSEF) for financial support.

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- See p.355 of the reference 4 for comments on a 1,2-shift of the phenyl group from oxygen to carbon. For an isolated example of a 1,4-shift of a phenyl group from oxygen to carbon, see: Bachi, M. D.; Bosch, E. *J. Org. Chem.* 1989, 54, 1234.
- Under the same reaction conditions, many other naphthol derivatives were converted into neither rearrangement nor reduction products efficiently and high proportion of the substrates were recovered. Similarly, 2,4-dinitrophenol derivative was also recovered in high yield after the tributylstannane reaction. These results indicate that above substrates act as radical scavengers which block the radical chain reaction.
- In only a few cases, the fused dihydropyran products originating from the ortho attack were isolated as by-products: 10% in entry 17 and 9% in entry 4. The ipso attack is most efficient with aryloxypropyl radicals: vanilin 4-iodobutyl ether was converted into 18% yield of the 4-aryl-1-butanol and 47% yield of vanilin butyl ether.