3. Aromatic, Heteroaromatic, and Fluoroaromatic Compounds

A variety of aromatic compounds have been prepared by various procedures in which an aryl radical substitutes in another aromatic nucleus. Usually a mixture of positional isomers results, the separation of which is often difficult. The field of study is known as homolytic aromatic substitution, and several comprehensive reviews on the subject are available [1–7]. For this reason the chapter will concentrate on the general features of the reactions that have proved to be of synthetic value.

A phenyl radical can afford biphenyl via substitution in benzene, and similarly a substituted phenyl radical can give rise to a substituted biphenyl. If a phenyl radical reacts

\[
\text{Ph}^\cdot + \text{Ph} \rightarrow \text{Ph} - [\text{H}^\cdot] \rightarrow \text{Ph}_2
\]

with a monosubstituted benzene as solvent, a mixture of \( o^- \), \( m^- \), and \( p^- \) substituted biphenyls results. The synthetic value of such schemes is dependent on the ease of separation of the individual isomers. The ortho-isomer usually predominates in the product mixture, but the early workers in the field found that in many reactions the para-isomer was sufficiently insoluble for it to be crystallised from the reaction mixture in a pure form, albeit in low yield (5%), so that in the 1930's this was a useful procedure by which \( p^- \) substituted biphenyls could be prepared [1, 8].

The synthetic value of homolytic aromatic substitution reactions in the synthesis of aromatic compounds depends on the source of aryl or phenyl radicals employed, the ease of the experimental procedures, and the yield of the substitution step.

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In the Gomberg reaction [2, 3, 9, 10] an aqueous solution of a diazonium salt is vigorously stirred with an aromatic solvent and sodium hydroxide or sodium acetate [11] is slowly added. The reaction leads to a very tarry product, and the biaryl can best be isolated by steam distillation in yields which are usually in the region of 10–20%.

\[
\text{Br-D-NH}_2 \rightarrow \text{Br-D-N}_2 \text{Cl}^- \rightarrow \text{Br-D} + [\text{H}^+] \\
(35–46\%) \quad [12]
\]

From the synthetic standpoint the Gomberg reaction is quite useful for making monosubstituted biphenyls by the substitution of monosubstituted phenyl radicals in benzene as illustrated in the reaction above. In the following example phenyl radicals substitute in nitrobenzene to form a mixture of ortho, meta, and para nitrobiphenyls.

\[
\text{ortho : meta : para} \\
60 : 10 : 30 \\
[13, 14]
\]

It is synthetically useful since p-nitrobiphenyl can be readily crystallised from the reaction mixture in a relatively pure form. In related reactions it has occasionally been possible for the three isomers to be isolated. For example in the phenylation of pyridine, 2-, 3-, and 4-phenylpyridine have all been isolated via fractional crystallisation of the picrates [15], and the 2-, 3-, and 4-methyl-p-terphenyls from the reaction between 4-nitrosoacetamidobiphenyl and toluene isolated by fractional crystallisation of the product mixture [16]. A useful tabular summary of preparative arylation reactions in the earlier literature, and the isomers obtained, has been drawn up by Augood and Williams [2]. Many of these reactions were carried out before the widespread availability