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62

Synthetic and Mechanistic Organic Chemistry

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Synthetic and Mechanistic Organic Chemistry

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This series presents critical reviews of the present position and future trends in modern chemical research. It is addressed to all research and industrial chemists who wish to keep abreast of advances in their subject.

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Recent Aspects of Homolytic Aromatic Substitutions

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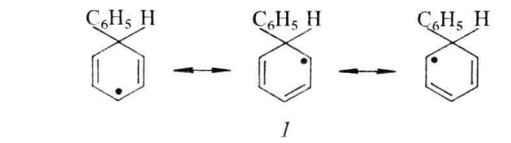
I. Introduction

Among the free radical reactions, homolytic aromatic substitution has an undoubted theoretical interest for the understanding of the reactivity of the aromatic compounds and of the free radicals. However it was considered till recent years a secondary aspect of the general problem of the aromatic substitution. It is difficult to find a modern text book of general organic chemistry in which this subject is only mentioned.

The poor interest of the organic chemists concerning the homolytic aromatic substitution mainly arose from the discouraging characteristics of the most studied reaction: the homolytic arylation [1]. A very low positional and substrate selectivity is in fact the most qualifying characteristic of this reaction. That clearly appears from the results of homolytic phenylation shown in Table 1. The fact that the partial rate factors (a measure of both positional and substrate selectivity) of the *meta* positions are all very close to unity and, in the absence of steric effects, those of *ortho* and *para* positions are slightly higher independently of the polar character of the substituent, is best explained by the stability of the intermediate cyclohexadienyl radical (*1*), which is affected by the delocalization of the odd electron into the substituent groups in *ortho* (*2*) and *para* (*3*), but not in *meta* positions



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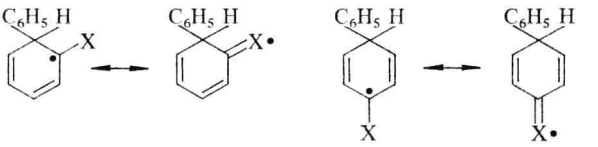

2 *3*

This point of view is supported by the unusually high values of the partial rate factors of the α- and γ-positions in the homolytic phenylation of pyridine-N-oxide [8] (α 139, β 1.5, γ 31.2) compared with those of pyridine (α 1.8, β 1.0, γ 1.2). This behavior can in fact be ascribed to the higher stability of the σ-complex which has a nitroxide type structure (*4*)

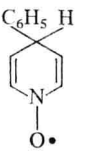

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Table 1. Partial rate factors for homolytic phenylation of benzene derivatives with benzoyl peroxide

Aromatic substrate	Partial rate factors			Refs.
	f_o	f_m	f_p	
Ph—Me	2.4	0.74	1.1	2,3)
Ph—Et	1.4	0.76	1.0	2)
Ph—Pr^i	0.60	0.81	1.0	2)
Ph—Bu^t	0.46	0.94	1.0	2)
Ph—Ph	2.1	1.0	2.5	2)
Ph—Cl	1.8	0.81	1.1	2,3)
Ph—CO_2Me	3.0	0.93	2.7	4)
Ph—CN	6.5	1.1	6.1	5)
Ph—NO_2	—5.5	0.86	4.9	2)
Ph—OMe	4.2	0.87	1.9	6)
Pyridine	1.7	1.0	0.87	7)

The results of Table 2 show that the presence of substituents in the phenyl radical modifies only slightly the whole picture. This very low selectivity affects the synthetic interest of the homolytic arylation. Generally all the free positions of an aromatic substrate are substituted, giving complex mixtures of isomers. Moreover, if the conversions are not too low, the mixtures of the reaction products become much more complex because polysubstitution occurs in all the aromatic positions.

Table 2. Partial rate factors for homolytic arylation of nitrobenzene with X-substituted phenyl radicals [1)]

X	Partial rate factors		
	f_o	f_m	f_p
m—Me	5.5	1.2	4.7
p—Me	6.1	1.2	5.8
H	5.5	0.86	4.9
m—Cl	2.2	0.58	2.2
p—Cl	2.7	0.63	2.5
m—NO_2	0.68	0.23	0.75
p—NO_2	1.64	0.43	1.6

Recently we realized that polar factors could play a much more important role in homolytic aromatic substitutions than that foreseen only few years ago and the possibility of substitutions of much greater synthetic potential became apparent [9,10)].

The extensive investigation of the polar effects in homolytic aromatic substitutions has led to two important developments:

i) New free radical substitutions in homocyclic and heterocyclic aromatic series, characterized by very high positional and substrate selectivity, were found. The consequent synthetic interest is sometimes not lower than that of the main ionic substitutions, so that the homolytic substitution can now be considered a much more significant aspect of the aromatic substitution also from a synthetic point of view.

ii) Very useful models were developed for investigating the influence of the polar factors on the reactivity of free radicals, even moderately polar, such as carbon free radicals. These models are far the most general and sensitive used till now for determining the relative nucleophilicities of the carbon free radicals.

These two aspects are strictly connected because the causes determinig the synthetic interest of the new homolytic substitutions are the same as determine the interest of the ionic substitutions. The synthetic interest in fact becomes prominent when the polar effects significantly contribute in determining the global reactivity of the homolytic substitution.

At first the polarity of the radical was considered pre-eminent over all the other factors in determining the sensitivity to the polar effects, but soon it was realized that the polarity of the substrate is no less important, so that strong polar effects were observed not only with strongly polar radicals, but also with moderately polar radicals, if the aromatic substrate has a marked polar nature.

In this review the two developments concerning the synthetic aspects and the causes of the selectivity will be discussed in some homolytic substitutions with electrophilic and nucleophilic radicals.

II. Aromatic Substitution with Electrophilic Radicals. Homolytic Amination by N-Chloroamines

Very strongly electrophilic radicals are the amino radical cations, $R_2\overset{+}{\dot{N}}H$, which can be easily obtained from N-chloroamines; they are very versatile and react differently with alkanes [9], alkenes [11], alkynes and aromatics [11], involving potentially most of the organic compounds and showing in all cases an exceptional sensitivity to polar effects.

A. Products of Amination

The homolytic amination by N-chloroamines is of great synthetic interest, with a selectivity and versatility comparable to those of the most selective electrophilic substitutions. The overall stoichiometry is shown by Eq. (1)

$$Ar{-}H + R_2\overset{+}{N}HCl \longrightarrow Ar{-}\overset{+}{N}HR_2 + HCl \qquad (1)$$

Several factors contribute to the synthetic success of this substitution.

i) The ready availability and the relative stability of N-chloramines, which can be obtained in high yields by chlorination of the corresponding amines, make them convenient reagents for the aromatic amination.

ii) The experimental conditions are very simple; under the best conditions, the reaction is carried out at room temperature in the presence of a catalytic amount of metal salts (Fe^{2+}, Ti^{3+}, Cu^{+}, Cr^{2+}). Concentrated sulphuric acid, aqueous solutions of sulphuric acid and mixtures of sulphuric acid and organic solvents (acetic acid, methanol, nitroalkanes) are generally used as reaction media. The solubility of the aromatic substrate is not a severe limitation; a very low solubility, such as that of benzene, alkyl benzenes or byphenyl in sulphuric acid is sufficient for the reaction to be completed in a few minutes.

iii) The yields based on N-chloroamine are often high and those based on the aromatic substrate are for the most part quantitative. The side products come from the electrophilic chlorination of the aromatic substrates activated by strongly electron-releasing groups (OH, OR, NHCOR) and from benzylic chlorination of alkylbenzenes.

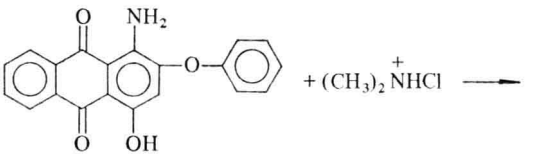
iv.) A variety of monoalkyl and dialkyl-N-chloroamines can be used. The reaction did not succeed with NH_2Cl owing to its lower stability in a strongly acidic medium. The main limitation, concerning the structure of N-chloroalkylamines, is due to steric effects. Thus yields based on N-chloramines decrease by increasing the bulk of the alkyl groups. No substitution takes place with N-chlorodiisobutylamine or N-chloro-di-*n*-butylamine; in this last case the Hofman-Löffler [12] reaction occurs. The competition of intramolecular hydrogen abstraction is not, however, the only cause of the lack of aromatic amination; in fact N-chloroalkylamines with less steric hindrance, but still capable of Hofman-Löffler rearrangement, such as N-chloro-*n*-butylamine and N-chloro-*n*-butylmethylamine also lead to aromatic amination.

v) A large variety of aromatic substrates can be readily aminated. The only limitation concerns aromatic rings with strong electron deficiency due to the presence of electron-withdrawing groups.

vi) The substrate selectivity is very high. This selectivity is exclusively due to polar effects and it is very advantageous from a synthetic point of view. Thus protonated anilines do not react under conditions in which benzene is easily aminated in a few minutes, so that the reaction does not generally lead to polysubstitution of an aromatic ring, even with total conversion of the aromatic substrate. The reaction is in fact carried out in acidic medium and the protonation of the amine formed completely deactivates the ring against subsequent attack. No other homolytic aromatic substitution in homocyclic series has this valuable synthetic characteristic.

vii) The positional selectivity is also very high, comparable with that of highly selective ionic electrophilic substitutions. The sensitivity to polar effects is mainly responsible for the positional selectivity. The great sensitivity to steric effects can contribute to further increasing the selectivity of the isomer distribution.

The amination of the anthraquinone dye **5** by N-chlorodimethylamine is a significant example of the versatility of this reaction also with complex molecules and of the exceptional substrate and positional selectivity. In fact **5** has 8 non equivalent free aromatic positions, but only the isomer **6** is formed in quantitative yield [13], with complete conversion of *5* by using only a light excess of N-chloroamine, and without formation of polysubstituted compounds [Eq. (2)].



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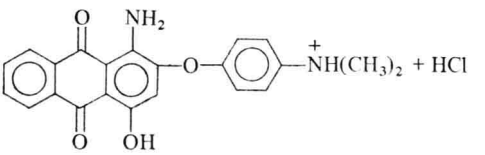

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(2)

The only exceptions, so far as orientation is concerned, are alkylbenzenes, which are attacked with poor selectivity at the meta and para positions.

The scope and the limitations of the general process will be illustrated by the behavior of the main classes of aromatic compounds.

1. Phenols, Phenol Ethers and Anilides

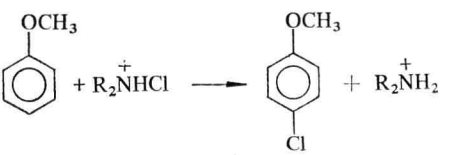
Since the reactivity of the homolytic aromatic amination is mainly determined by the electrophilic character of the amino radical cations, this class of aromatic compounds is strongly activated. Exclusive *o,p* orientation occurs without

formation of traces of the *m* isomers; the *o*:*p* ratio changes with the experimental conditions, but the *p*-isomer always prevails over the *o*-isomer. Aromatic amines cannot be aminated in the ring containing the amino group, whose protonation prevents further attack; with primary and secondary amines this limitation is easily overcome by acetylating the amine.

Table 3. Homolytic amination of phenols, phenol ethers and anilides

Aromatic substrate	N-chloro-amine	Orientation (%)	Yield (%)	Refs.
Phenol	Piperidine	*o* (9); *p* (91)	87	14)
Phenol	Dimethyl-amine	*p* *o*	59	14)
o—Cl-phenol	Piperidine	4 (80) + other isomers	92	14)
Anisole	Piperidine	*o* (8.9); *p* (91.1)	65	15)
Anisole	Dimethyl-amine	*o* (37); *p* (63)	54	15)
8-Methoxyquinoline	Dimethyl-amino	5 (100)	89	15)
Acetanilide	Dimethyl-amine	*p*, traces of *o*	93	16)
Acetanilide	Piperidine	*p*, traces of *o*	98	16)
Acetanilide	Methyl-benzyl-amine	*p* (100)	88	16)
Oxindole	Dimethyl-amine	5 (100)	86	16)

Table 3 shows some results obtained with these aromatic compounds, which require particular experimental conditions to overcome the competitive electrophilic chlorination [(Eq. (3)].



(3)

This side reaction can in fact be minimized or eliminated by working with a relatively high concentration of reducing metal salt and a low concentration of N-chloroamine. Since a too-high concentration of metal salt is not recommended, because it can increase the reduction of the N-chloroamine [Eq. (4)], the best experimental conditions are always a compromise between these opposite requirements depending on the ease of the electrophilic chlorination of each aromatic substrate

$$\overset{+}{R_2NHCl} + 2\,Fe^{2+} \longrightarrow R_2NH + 2\,Fe^{3+} + Cl^- \qquad (4)$$

2. Polycyclic Aromatic Compounds

The results reported in Table 4 were obtained without performing optimization experiments; with the most reactive substrates, yields can probably be further increased by using the same experimental expedients employed with strongly

Table 4. Homolytic amination of polycyclic aromatic compounds

Aromatic substrate	N-chloroamine	Orientation (%)	Yield (%)	Refs.
Biphenyl	Dimethyl-amine	4 (100)	71	17)
4-Nitrobiphenyl	Dimethyl-amine	4′ (100)	86	18)
4-Nitrobiphenyl	Piperidine	4′ (100)	85	18)
4-Biphenyl-sulfonic	Dimethyl-amine	4′ (100)	86	18)
4-Dimethylacidamino-biphenyl	Dimethyl-amine	4′ (100)	90	18)
4-Chlorobiphenyl	Dimethyl-amine	4′ (100)	84	18)
Naphtalene	Dimethyl-amine	1 (97); 2 (3)	68	19)
1-Bromonaphtalene	Dimethyl-amine	5 (92) + other isomers	97	19)
Fluorene	Dimethyl-amine	2 (100)	63	17)
Fluorenone	Dimethyl-amine	2 (100)	98	18)

activated substrates. However, also in these cases, yields and selectivity are generally very high. The disubstitution observed with biphenyl and fluorene is only the result of the experimental conditions used: the hydrocarbons have a very low solubility, while the monosubstituted derivatives are completely soluble in the reaction medium. In both cases however, only one disubstituted isomer was obtained, even with total conversion of the aromatic substrates. This is another significant example of the exceptional selectivity of the reaction, because fluorene and biphenyl can give rise respectively to 16 and 9 different disubstituted isomers.

3. Aromatic Compounds with Strongly Electron-Withdrawing Groups

Substituents such as NO_2, CN, COR, $\overset{+}{N}R_3$ strongly deactivate the aromatic ring towards homolytic amination. The presence of electron-releasing groups in these compounds can counterbalance the deactivating effect of the electron-withdrawing group and allow the aromatic substrate to be easily aminated. Thus fluorenone is aminated with high yield and complete selectivity (Table 4) under conditions in which benzophenone does not react; the phenyl group in a biphenyl system strongly activates the *p*-position of the other phenyl group (the partial-rate factor of the *p*-position of biphenyl is 600). The presence of electron-withdrawing groups in polycyclic aromatic substrates (naphthalene or biphenyl derivatives of Table 4 or compound *5*) leads to amination of the unsubstituted rings.

4. Heteroaromatic Compounds

The homolytic amination is of less use with heterocyclic than with homocyclic aromatic compounds because either the heteroccylic compounds are too deactivated (protonated heteroaromatic bases) or they are unstable in the strongly acidic medium usually required by the reaction. Thus, quinoline cannot be aminated because the protonated heterocyclic nitrogen deactivates both rings. In the

8-methoxyquinoline, however, the electron-releasing effect of the methoxyl counterbalances the electron-withdrawing effect of the heterocyclic nitrogen and the homolytic amination leads in high yield to only one of the 6 possible isomers (Table 3). Heteroaromatics activated towards electrophilic species, such as furan and pyrrole, are not suitable for homolytic amination owing to their low stability under the reaction conditions. Thiophene, however, has been aminated to 2-alkylamino derivatives [13].

5. Halobenzenes and Cinnamic Esters

The halogens and the ω-substituted vinyl groups, Ar—CH=CH—X, where X is an electron-withdrawing group, deactivate the benzene ring but the orientation is prevalent in *o* and *p* positions, as for the ionic electrophilic substitutions (Table 5) Yields based on N-chloroamine are not very high with halobenzenes, owing to the deactivation of the aromatic ring and to a more marked reduction of the N-chloroamines [Eq. (4)]. Yields based on halobenzenes are always very high, the only side products being small amounts of anilines arising from the substitution of the halogen by the amino group.

Table 5. Orientation in the homolytic amination of halobenzenes [20] and methyl cinamate [21] by N-chlorodimethylamine

Aromatic substrate	*ortho*	*meta*	*para*
Chlorobenzene	18.5	5.5	76
Bromobenzene	21.6	3.4	75
Iodobenzene	6	8	86
Methyl cinnamate	—	—	100

With cinnamic esters, the addition of N-chloroamines to the double bond competes with the aromatic attack [Eq. (5)]

$$C_6H_5{-}CH = CH{-}COOR + R_2\overset{+}{N}HCl \longrightarrow C_6H_5{-}CHCl{-}\underset{\overset{+}{N}HR_2}{\underset{|}{CH}}{-}COOR \qquad (5)$$

The ratio of attack at the double bond and at the aromatic ring is strongly affected by the reaction medium; the nuclear attack increases with the acidity of the medium. The sensitivity to steric effects reduces or prevents the substitution in the ortho positions.

6. Intramolecular Amination

High yields of tetrahydroquinolines were obtained by intramolecular amination of N-chloro-3-phenylpropylamines [22,32] [Eq. (6)].