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Methods of replacing halogen in aromatic compounds by RS-functions

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ABSTRACT. **This review is devoted to methods of replacing aromatic halogen by RS-groups. The essential mechanisms of these reactions have been examined, and the advantages and limitations of each method noted.**

The bibliography contains 124 references.

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I. Introduction

Nucleophilic replacement of halogen in the aromatic nucleus has always been a focus of attention in view of the enormous synthetic implications. The large volume of experimental and theoretical data published in this field has been reviewed several times.[1–6] The replacement of aromatic halogen by RS-groups has been covered in part, but interest in this particular substitution has noticeably increased during the last ten years. This is partly because the theoretical aspects of this conversion have been under scrutiny, and partly because of the development of new practical routes to sulphur-containing compounds of potential use as antioxidants, polymer stabilisers, pesticides and drugs, and in the oil and petroleum industry.[7]

The replacement of aromatic halogen by organothio groups is by no means straightforward, and several key routes have been developed: 1) purely ionic processes, notably involving activation by strong bases and/or specific solvents; 2) catalytic processes, involving both metal complexes and phase transfer catalysts; 3) high-temperature, free-radical processes; and 4) photo- and electro-chemical processes, principally of an ion-radical nature.

A number of publications on the thiylation of aromatic halides prior to 1972 has been examined in a monograph.[8] However, there have been no recent surveys covering this theme in its entirety. This is a systematic review of data published in this field during the last 10–15 years.

II. Nucleophilic thiylation of aryl halides without the use of specific catalysts

In the initial attempts to replace aromatic halogen by mercaptide (RS^-) or thiyl (HS^-) anions, sodium sulphide and polysulphide were used as reagent. Unactivated aromatic halides were inert under these conditions. Thus, chlorobenzene reacts with Na_2S only at 350–360 °C under a pressure of 180–190 atm.[9] In an aqueous ethanolic solution of Na_2S, activated aromatic halides, e.g. *o*- and *p*-nitrochlorobenzene, afford a mixture of products. Here, intermediate thiophenoxide anions react with the starting halide to give the corresponding symmetrical diaryl sulphide, while, at the same time, being oxidised to the corresponding disulphide.[9] Heating *p*-nitrochlorobenzene with an excess of Na_2S_2 in an alcoholic medium for a short period of time leads to the formation of *p*-nitrothiophenol in 65% yield:[1]

$$6\,p\text{-}ClC_6H_4NO_2 + 4Na_2S_2 + 6NaOH \rightarrow 6\,p\text{-}NO_2C_6H_4SNa + 6NaCl + 3H_2O + Na_2S_2O_3.$$

2,4-Dinitrochlorobenzene has a reactivity similar to alkyl chlorides: on heating in an aqueous alcoholic medium with Na_2S it is converted to the tetranitrodiphenyl sulphide in 79% yield.[9] Treatment of activated nitroaryl halides with Na_2S results in both substitution and reduction of the nitro group to give azoxy compounds and aniline derivatives.[1]

The majority of the early syntheses of unsymmetrical thioesters were based on the reactions of halogenonitrobenzenes with methanethiol and *o*- or *p*-nitrothiophenol in the presence of alcoholic base.[1] Data published before 1970 on the reactions of halogenonitrobenzenes with MeS^- and PhS^- in alcoholic media have been surveyed in a monograph.[10]

By measuring the rate of the reaction of PhS^- with 1-halogeno-2,4-dinitrobenzenes in methanol between 0–15 °C, Bunnett and Merritt verified that the kinetic data were in accord with an S_N2 mechanism.[11] The reactivity of aryl halogen followed the order $F \gg Br > I > Cl$. The rate of replacement of Br, I and Cl was approximately the same, but that of F was approximately twice as great.

Unactivated aromatic halides interact more smoothly with mercaptide anion in the presence of a strong base. Thus, bromobenzene reacts with PhS^- in liquid ammonia in the presence of alkali metal amide.[12,13] However, as ammonia itself is weakly nucleophilic, the formation of diphenyl sulphide is accompanied by amination products:

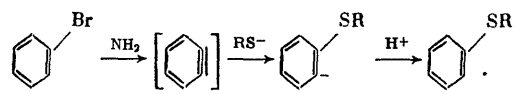
$$PhBr + PhS^- \xrightarrow{NH_3} \underset{10\%}{PhNH_2} + \underset{12\%}{Ph_2NH} + \underset{52\%}{Ph_2S}.$$

As the reaction of 1-bromonaphthalene with PhSNa yields a mixture of 1- and 2-naphthyl phenyl sulphide, it is assumed that under these conditions an elimination-addition (benzyne-type) mechanism prevails.[12]

The substitution of bromobenzene can be extended to other mercaptans if an aprotic solvent (a mixture of hexamethylphosphoramide and THF) is used in the presence of sodium amide at 35–40 °C.[14,15]

$$PhBr + RSH \xrightarrow{HMPA+THF} PhSr,$$
$$12-66\%$$
$$R = Et,\ n\text{-}Bu,\ PhCH_2,\ Ph.$$

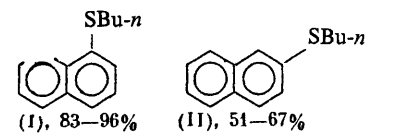
Here too, it is considered that reaction involves intermediate formation of benzyne, which undergoes subsequent nucleophilic attack by RS^-:

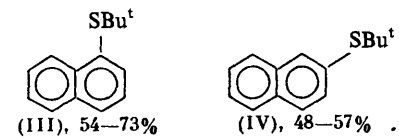


Judging by the products formed by interaction of *o*-toluyl iodide with thiophenol in DMSO containing tert-BuOK, it would appear that benzynes are also involved in the reaction of aryl iodides with aryl mercaptans:

$$PhSH + PhI \rightarrow \underset{100\%}{PhSPh}$$
$$PhSH + o\text{-}MeC_6H_4I \rightarrow \underset{50\%}{o\text{-}MeC_6H_4SPh} + \underset{50\%}{m\text{-}MeC_6H_4SPh}.$$

1-Fluoro- and 2-fluoro-naphthalene, as well as the bromine analogues, react with n-butyl and tert-butyl mercaptan on heating in DMSO (110 °C) in the presence of MeONa to give the corresponding naphthyl thioethers (I)–(IV):[17,18]





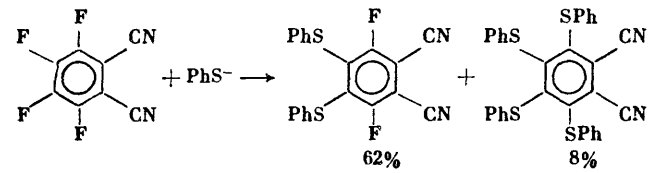
Under these conditions, butyl 2-naphthyl sulphide is not formed from 1-bromo- or 1-fluoro-naphthalene, so that the intermediate formation of the corresponding benzyne (1,2-dehydronaphthalene) can be excluded.

From a synthetic point of view, it is interesting that hexahalogenobenzenes—C_6F_6, C_6Cl_6 and C_6Br_6—react smoothly and rapidly with mercaptides on heating in a mixture of ethylene glycol and an organic base, e. g. pyridine. In the reaction of C_6Br_6 with RS^-, there is the possibility of both substitution and protodebromination, according to the following proposed scheme:[19]

$$C_6Br_6 + MeS^- \rightarrow C_6Br_5SMe,\ C_6Br_4(SMe)_2,\ C_6Br_2(SMe)_4,$$
$$C_6Br_5H,\ C_6Br_2H(SMe)_3,\ C_6H_2Br_3(SMe),$$
$$C_6Br_6 + EtS^- \rightarrow C_6Br_4H(SEt),\ C_6Br_5H,\ C_6Br_4H_2.$$

Products such as C_6Br_4HSEt and $C_6Br_2(SMe)_4$ have never previously been prepared. However, the reaction of C_6F_6 and C_6Cl_6 with RS^- (R = Me, Et, Ph, C_6F_5, CH_2CH_2SH) proceeds only by substitution (up to 4 atoms of halogen being replaced by an organothio group); there is no protodehalogenation.[20–22]

The interaction of tetrafluorophthalonitrile with PhS^- in methanol proceeds primarily by replacement of two atoms of fluorine:[23]

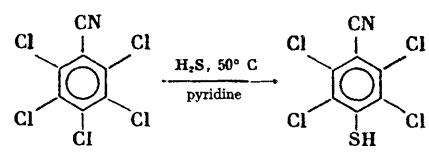


Hexafluoro- and hexachloro-benzene react with NaSH on heating in a mixture of ethylene glycol and pyridine to give the corresponding pentahalogenothiophenol:[24,26]

$$C_6Cl_6 + NaSH \rightarrow \underset{95\%}{C_6Cl_5SH} + NaCl,$$
$$C_6F_6 + NaSH \rightarrow \underset{59\%}{C_6F_5SH} + NaF.$$

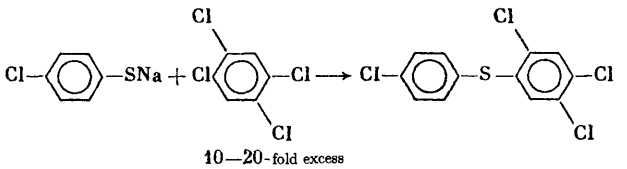
However, no such reaction takes place with hexabromobenzene.[19]

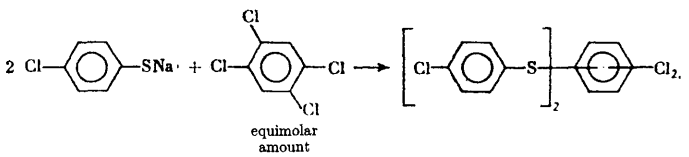
Pentachlorothiophenol can also be obtained by treatment of C_6Cl_6 with alkali metal hydrogen sulphide under 1 atm in DMF [2] or methanol.[27] Polychlorocyanobenzenes react with H_2S in pyridine in the presence of triethylamine to give the corresponding *p*-cyanothiophenol,[28] e. g.



In the 1960s it was discovered that aprotic solvents significantly enhance nucleophilic processes involving alkali metal salts by solvating the cation. Aromatic thiylation is no exception. Thus, both symmetrical and unsymmetrical diaryl sulphides have been prepared by prolonged heating of aryl mercaptides with aromatic halides in DMF—a solvent with weak dipolarophility.[29] The following thiylating agents were used: PhSNa, *p*-MeC_6H_4SNa,

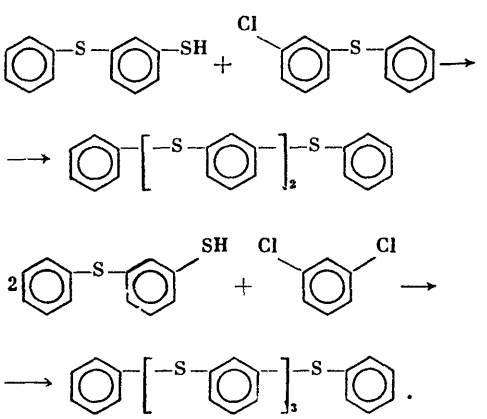
p-ClC_6H_4SNa. The reactivity of aromatic halides towards these thiophenoxides was in the following order: PhBr < bromonaphthalene < $C_6H_4Cl_2$ < $C_6H_3Cl_3$ < $C_6H_2Cl_4$. With polychlorobenzenes, the degree of substitution depends on the molar proportion of the starting materials:





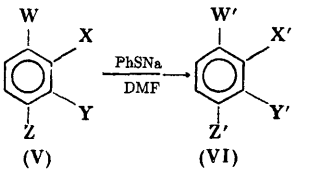
In order to extend the reaction as a preparative route to diaryl sulphides from unactivated aromatic halides, while at the same time improving the overall yield without complicating the procedure, Campbell et al. proposed the use of various amide or amine solvents: dimethylacetamide (DMA) at 170–175 °C; diethylaniline at 210–216 °C; and *N*-methyl-2-pyrrolidone at 185–190 °C.[30–32]

A thermal route is recommended for the preparation of aryl mono-, bis-, tris-, and poly-thioethers, alkyl aryl thioethers, and phenylthiobiphenyls. Thus, the conversion of bromobenzene at high temperature affords diphenyl diphenyl sulphide in ~65% yield, contrasting with 13% by the conventional route.[29] Polyphenyl thioethers with four or five aromatic nuclei were obtained for the first time as follows:[32]



It is suggested that the mechanism of the reaction is of a bimolecular, S_NAr, type,

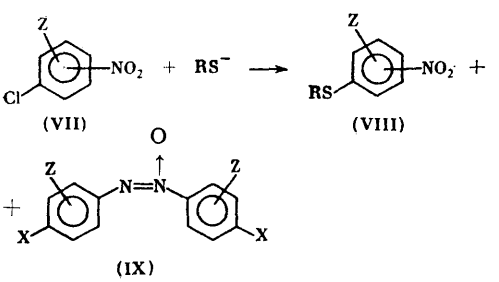
The thiylation of activated aromatic halides can be conducted at a much lower temperature by using an aprotic solvent, e. g. DMF. Thus, bis(phenylthio)benzenes (VI) were obtained from dihalogenonitrobenzenes (V) at 0 °C.[33]



(V) (VI)

(Va) W = NO_2, X = Cl, Y = H, Z = Cl; (VIa) W′ = NO_2, X′ = SPh, Y′ = H, Z′ = SPh (72%)
(Vb) W = Cl, X = NO_2, Y = H, Z = Cl; (VIb) W′ = SPh, X′ = NO_2 Y′ = H, Z′ = SPh (27%)
(Vc) W = NO_2, X = H, Y = Cl, Z = Cl; (VIc) W′ = NO_2, X′ = H, Y′ = SPh, Z′ = SPh (31%).

Another advantage of using DMF for thiylation of halogenonitrobenzenes is that side-reactions are reduced. The reaction of halogenonitrobenzenes with RS^- in alcoholic base[1] is complicated by competitive reduction of the nitro group. However, the preparation of thioethers (VIII) is significantly improved by using DMF as solvent, in which the formation of azoxybenzenes as by-product is suppressed.[34] Adjusting the order of addition of the reactants also has a beneficial effect:

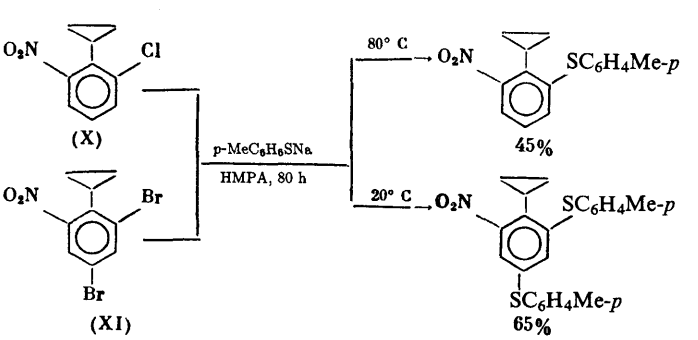


(VII) (VIII) (IX)

Z = H (a); CF_3 (b); R = Me, Pr^i, CH_2Ph, Ph; X = Cl, SPh.

As an example, the yield of (VIIIb, R = Me) and azoxybenzene (IXb) is 18% and 81%, respectively, by the conventional route.[1] However, in DMF [34] the yield of (VIIIb, R = Me) is 95%.

Replacement of halogen in (nitrohalogenophenyl)cyclopropanes (X, XI) by *p*-tolylthio groups with sodium *p*-thiocresolate can be carried out in *N*-methyl-2-pyrrolidone or hexamethylphosphoramide.[35]



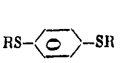
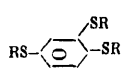
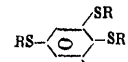
(X) (XI)

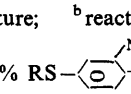
On the other hand, heating the chloride (X) with sodium *p*-thiocresolate in ethanol results in reduction of the nitro group to give 3,3'-dichloro-2,2'-dicyclopropylazobenzene.

The method described above is essentially limited to the reaction of aromatic halides with arylmercaptides (ArS^-). The same reaction with alkylmercaptides (RS^-) can be achieved in hexamethylphosphoramide, as reported by Italian chemists in a series of publications.[36-40]

Activated aryl halides, such as *o*- and *p*-nitrochlorobenzene (XIII), 1-chloro-2,4-dinitrobenzene (XIII) and picryl chloride (XIV) react at room temperature with excess of RSNa (where R = Me, Et, iso-Pr, tert-Bu) in hexamethylphosphoramide by replacement of both halogen and nitro groups (Table 1).[36] The highest yield of poly(alkylthio)benzene is obtained with sodium isopropylmercaptide in hexamethylphosphoramide. It should be noted than an alkylthio group in the *ortho*- or *para*-position activates replacement of the nitro group by RS^-.

Table 1. Reaction of *p*-nitrochlorobenzene (XII) 2,4-dinitrochlorobenzene (XIII) and picryl chloride (XIV) with RSNa in HMPA at room temperature.[36]

Substrate, *R*	Yield of product %		
	 from (XII)	 from (XIII)	 from (XIV)
Me	7 [a]	–	6 [a]
Et	14 [a]	15 [a]	68
Me_2CH	65	50	69
Me_3C	44 [b]	44 [c]	33

[a] RSSR is present in the reaction mixture; [b] reaction mixture contains unreacted (XII); [c] also isolated 17% 

Competitive reduction of the nitro group depends on the structure of the nitroaryl halide and the nature of the mercaptide. If the nitro group is not activated by an isopropylthio group in the *ortho*- or *para*-position, it is possible that a mechanism other than the S_NAr type is involved. In such instances, reaction may be initiated by a single electron transfer from RS^- to the substrate to give a nitroaryl radical anion:

$$ArNO_2 + RS^- \xrightarrow{\bar{e}} ArNO_2^{\cdot -} + RS^{\cdot},$$

$$2RS^{\cdot} \rightarrow RSSR,$$

$$ArNO_2^{\cdot -} \rightarrow \text{products of reduction}.$$

Unactivated aryl halides (PhF, PhCl, PhBr, PhI) react with sodium isopropylmercaptide in hexamethylphosphoramide at a higher temperature (80 °C) to give isopropyl phenyl sulphide in 57–81% yield.[37] By measuring the relative rates of replacement of each halogen by the isopropylthio group, the relative lability of halogen was found to decrease in the order: I > F > Br > Cl. This sequence is not that which would be anticipated for substitution of an activated aryl halide according to a S_NAr mechanism.[11] Nonetheless, the authors of this work still propose such a mechanism by taking into account the differing rates of the addition and elimination steps and their dependence on the nature of the halogen atoms.[37]

The same authors also studied the reaction of iso-PrSNa with dihalogenobenzenes in hexamethylphosphoramide.[37] Thus, *o*-, *m*- and *p*-dichlorobenzene afford mono- or bis(isopropylthio)benzenes, depending on the relative proportion of the mercaptide. Other *m*- and *p*-dihalogenobenzenes (except *p*-difluorobenzene) under these conditions are converted exclusively into the corresponding isopropyl *p*-halogenophenyl sulphides. The reaction of tri-, tetra-, penta- and hexa-chlorobenzenes with excess of iso-PrSNa (or EtSNa) proceeds readily in hexamethylphosphoramide with substitution of all the chlorine atoms in 80–95% yield.[38] Both hexachlorobenzene and hexafluorobenzene afford the corresponding hexakis(alkylthio)-benzene in hexamethylphosphoramide, while partial replacement of halogen takes place in other solvents, as indicated above.[20-22]

1,3-Dimethyl-2-imidazolidone may be used as solvent in place of hexamethylphosphoramide for the preparation of hexakis(alkylthio)-naphthalenes[41] and hexakis(arylthio)benzenes[42] in high yield. The relatively inaccessible hexakis(*p*-tert-butylphenylthio)benzene (76%) and hexakis(β-naphthylthio)benzene (72%) were also obtained under these conditions.

The reactions of polychlorobenzenes with MeSNa are complicated in certain instances by partial cleavage of the resulting methylthio groups by nucleophilic attack of mercaptide anion.[38] This leads to the formation of poly(methylthio)thiophenols,† as exemplified below:

$$C_6Cl_6 \xrightarrow{MeSNa} C_6(SMe)_6 \longrightarrow C_6(SMe)_5SH.$$

Aromatic mercaptans may also be prepared from unactivated aryl halides under the same conditions.[39] Reaction proceeeds in two steps: nucleophilic replacement of the halide according to an S_NAr mechanism, followed by dealkylation according to the more familiar S_N2 displacement at a saturated carbon:

$$ArX + MeSNa \rightarrow ArSMe + NaX,$$

$$ArSMe + MeSNa \rightarrow ArSNa + Me_2S.$$

Table 2. Reaction of aryl halides with MeSNa in HMPA at 100 °C.[39]

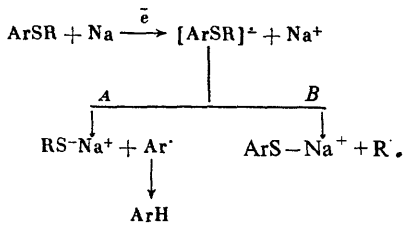
Thiol	Time, h	Yield, %	X in ArX
Thiophenol	5	90	Cl
α-Mercaptonaphthalene	3.5	90	Br
β-Mercaptonaphthalene	5	97	Br
p-Mercaptobiphenyl	2	96	Br

Some examples of this conversion are given in Table 2.

† Data on the cleavage of alkylthiobenzenes to give the corresponding thiophenols by alkali metals in liquid ammonia, ether or methylamine have been given previously.[40,43,44]

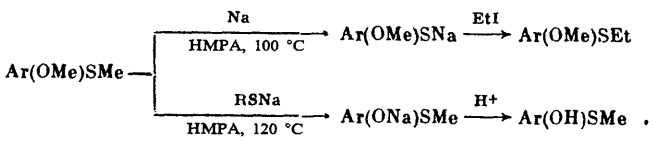
Dealkylation of alkyl aryl sulphides to give the corresponding monomercaptoarenes can be achieved with both MeSNa and EtSNa.[39] Polymercaptobenzenes may be obtained from the corresponding polychlorobenzenes via treatment of the intermediate isopropylthiobenzenes with sodium in hexamethylphosphoramide at 100 °C.[45] Alternatively, the polychlorobenzenes may be treated with NaSMe in 1,3-dimethyl-2-imidazolidone, followed by demethylation with sodium in liquid ammonia.[46] By comparison with the reaction with MeSNa, cleavage with sodium in hexamethylphosphoramide is not selective and proceeds with total dealkylation of all RS groups.

It is considered that the interaction of isopropylthiobenzenes with sodium in hexamethylphosphoramide involves an electron transfer,[45] as a result of which a thioether anion radical is formed:

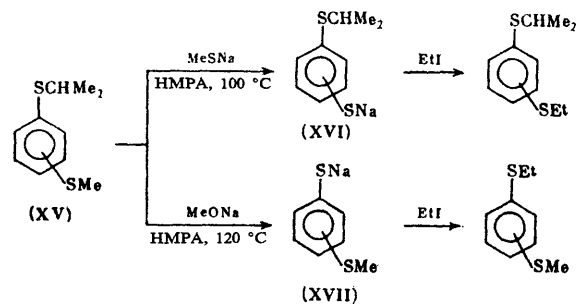


Pathway *B*, i.e. cleavage of the R–S bond, is preferred under these conditions and can only be suppressed sterically if the RS group is in an *ortho* position.

By choosing a suitable dealkylating agent (Na, MeSNa, MeONa) in hexamethylphosphoramide, selective dealkylation may be achieved. Alkoxyaryl alkyl sulphides, for example, may be selectively cleaved to give alkoxythiophenols, mercaptophenols or (alkylthio)-phenols:[47–49]

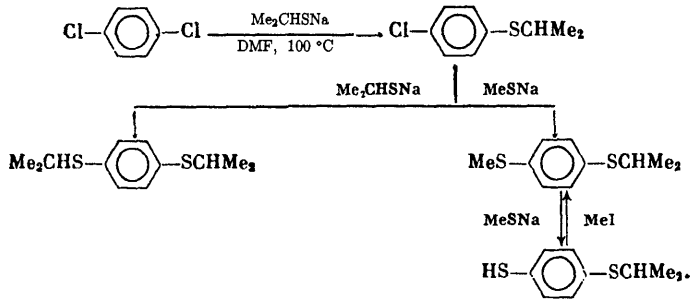


Preferential dealkylation of bis(alkylthio)benzenes having different RS-groups may also be carried out, as exemplified below.[50]



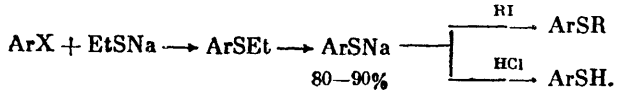
As seen above, the reaction of compound (XV) with sodium methylmercaptide involves nucleophilic aliphatic substitution by an S_N2 mechanism, which explains the selectivity towards the methyl group to give product (XVI). In contrast, sodium alkoxides in aprotic media function as strong bases, inducing elimination of the isopropyl group as propene with the formation of mercaptide (XVII).[50]

In view of the carcinogenic properties of hexamethylphosphoramide, the above-described substitution of aryl halides and the dealkylation of the resulting thioethers have been studied in DMF and dimethylacetamide.[51] Thus, nucleophilic aromatic substitution of unactivated aromatic halides by mercaptide anion proceeds smoothly in DMF at 100 °C:

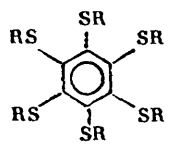


Selective monodealkylation with excess of MeSNa can be achieved at 160 °C in DMF by nucleophilic aromatic substitution. In this respect, tert-BuOK is better than MeONa for selective dealkylation in DMF. Dealkylation by electron transfer with sodium is more effective in dimethylacetamide than in DMF.

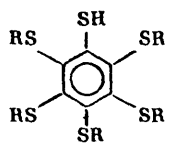
Reference has also been made[51] to the one-step synthesis of thiophenols by heating unactivated aryl halides with excess of EtSNa in DMF:



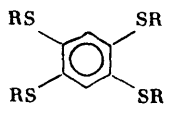
Recently, polyglymes have been used as solvents for the substitution of activated[52,53] and unactivated[54,55] aryl halides by mercaptide anion. The effectiveness of polyglymes is in the order: tetraglyme > triglyme > diglyme > monoglyme. The following products have been obtained by heating aromatic halides with RSNa at 130–200 °C in tetraglyme:



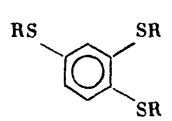
R = Ph (23%)
R = *n*-$C_{12}H_{25}$ (95%)
R = Et (30%)



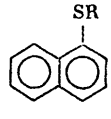
R = Et (25%)



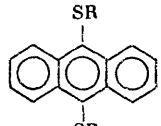
R = Et (63%)
R = *n*-C_8H_{17} (87%)
R = *n*-$C_{12}H_{25}$ (86%)
R = Ph (56%)



R = Ph (16%)
R = *n*-$C_{12}H_{25}$ (96%)



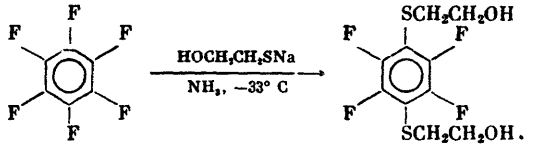
R = *n*-C_8H_{17} (67%)
R = *n*-$C_{12}H_{25}$ (81%)
R = Ph (62%)



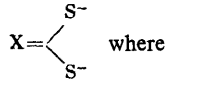
R = *n*-$C_{12}H_{25}$ (95%).

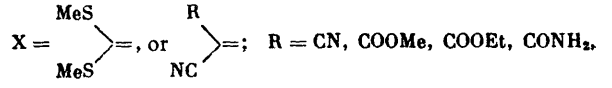
Tetraglyme is recommended as an alternative to hexamethylphosphoramide, DMF and dimethylacetamide as a solvent for the thiylation of aromatic halides.

Liquid ammonia also serves as a useful solvent, selectively solvating the cation of alkali metal mercaptides. Under these conditions it is possible to achieve thiylation of polyfluoro- and nitrohalogeno-aromatic compounds without side reactions.[56,57] This is exemplified below:

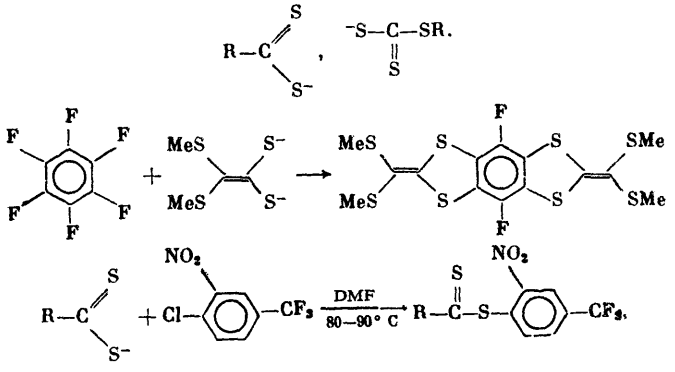


It should also be noted that activated aromatic halides react with ambident *S*-nucleophiles, such as dithiolates[58,59] of the type:





The sodium salts of dithiocarboxylic and trithiocarbonic acids, i.e. RC(S)SNa and RSC(S)SNa, are also effective nucleophiles.[60,61] The following two reactions exemplify the displacement of aromatic halogen by such *S*-nucleophiles:



where R = dimethylamino, diethylamino, and morpholino.

From the information set out in this part of the review, it is clear that the inertness of unactivated aromatic halides can only be effectively overcome by using a strong base in an aprotic, bipolar solvent. Such conditions are often used for the reactions of activated aromatic halides, and have been recommended for preparative purposes.

III. Thiylation of aryl halides in the presence of catalysts

Aromatic nucleophilic substitution is promoted by transition metals and their salts, those of copper being the most prominent.[62–64] Such catalysed thiylation of aromatic halides can be regarded as the sulphur equivalent of the classical Ullman reaction.

Copper may be used for thiylation in two ways: a) on the one hand by an exchange mechanism of the type

$$ArX + CuY \rightarrow ArY + CuX,$$

where X = halogen, and Y may be SAlk or SAr; and b) on the other hand by a nucleophilic displacement of aromatic halogen with Cu, Cu_2O, or a copper salt as catalyst:

$$ArX + Y^- (\text{or } HY) \xrightarrow{Cu} ArY + X^- (\text{or } HX).$$

As an example of method a), 1-bromonaphthalene reacts with cuprous phenylmercaptide in a polar organic solvent.[65] Thus, on heating the reactants in pyridine for 24 h, 1-naphthyl phenyl sulphide is obtained in 26% yield, while the same product is formed in 21% yield by heating in DMSO for 4 h at 144 °C, and in 31% yield in DMF.

As an example of method b) thioethers are obtained in preparatively useful yield by thiylation of aromatic halides in an aprotic solvent in the presence of a catalytic amount of suspended Cu_2O.[66] Thus, heating 1-bromonaphthalene with PhSNa or EtSNa for 24 h in the presence of Cu_2O affords 1-naphthyl phenyl sulphide and ethyl 1-naphthyl sulphide in 99% and 95% yield, respectively.

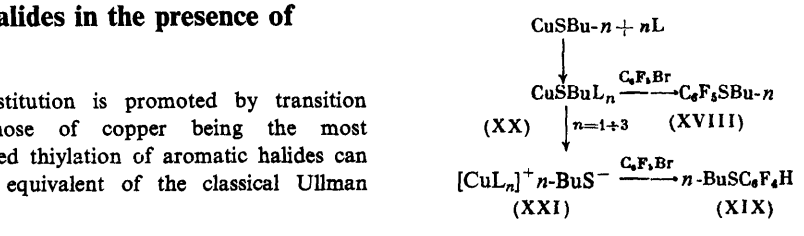
Where mercaptans (RSH) are used as substrate, reaction involves initial formation of CuSR, which then reacts with the aromatic halide. The mercaptide anion, RS^- (PhS^- or EtS^-), is more effective than the corresponding neutral mercaptan (RSH). Thus, diaryl sulphides are obtained in low yield (21%) in the system $ArBr/Cu_2O/PhSH$, but in high yield (99%) in the system $ArBr/Cu_2O/PhSNa$.

A variety of aromatic halides (ArX) may be used in the reaction with cuprous mercaptides: Ar = $C_6H_4NH_2$, C_6H_4OMe, C_6H_4Me, C_6H_4OH, C_6H_4Br, C_6H_4Cl with CuSR (R = Ph, Et, n-Bu).[67–69] The reactants are heated at 200 °C for 1–5 h in a mixture of quinoline and pyridine until the medium becomes homogeneous. It should be noted that unactivated aromatic chlorides react under these conditions with PhSCu but not AlkSCu, while both of these mercaptides react with aryl bromides and activated aryl chlorides (e.g. *o*-$ClC_6H_4NO_2$) to give the corresponding thioethers in 50–90% yield.

The replacement of bromine in bromoperfluoroaryl derivatives may be achieved with mercaptides RSCu (R = C_6F_5, Me, n-Bu):[70–72]

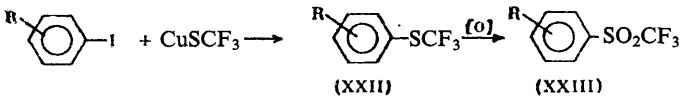
$$C_6F_5Br + CuSBu\text{-}n \rightarrow \underset{\text{(XVIII)}}{C_6F_5SBu\text{-}n} + \underset{\text{(XIX)}}{n\text{-}BuSC_6F_4H}.$$

The proportion of (XVIII) and (XIX) in the product depends on the nature of the solvent. The former predominates in DMF while the partially reduced product, (XIX), predominates in pyridine. It is thought that the reaction involves the intermediate formation of complex (XX) derived from the cuprous mercaptide and solvent:



n-Butylmercaptide anion coordinates with copper in the weakly ligating DMF to give (XVIII). However, in the strongly ligating pyridine, an ionic complex (XXI) is formed prior to reaction with C_6F_5Br to give (XIX).

Aryl trifluoromethyl sulphides (XXII) are obtained in high yield of reaction of CF_3SCu with aromatic iodides in DMF at 150 °C.[73] The products are oxidised to the corresponding sulfones (XXIII) possessing the strongly electron-withdrawing SO_2CF_3 group:



(XXII) (XXIII)

R = H, 4-Me, 2-NO_2, 4-NO_2.

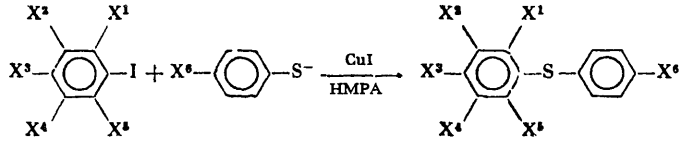
Aryl trifluoromethyl sulphides are also obtained by interaction of aromatic bromides with $HgSCF_3$ and Cu.[64]

The preliminary isolation of cuprous mercaptide, CuSr, and its insolubility are the main limitations of the above-described method. However, these may be avoided in the direct conversion of aromatic halides to alkyl aryl sulphides or diaryl sulphides with dialkyl or diaryl disulphides in dimethylacetamide containing copper at 160–170 °C:[74]

$$RSSR + PhBr \xrightarrow{Cu} PhSR,$$
$$RSSR + BrC_6H_4Br \rightarrow RSC_6H_4SR,$$
$$R = n\text{-Bu, Ph, } m\text{-}MeC_6H_4 .$$

The reaction involves copper-induced cleavage of the disulphide bond to give the corresponding cuprous mercaptide, which then reacts with the aromatic halide. Disulphides may also be reduced by other metals (Zn, Na, Al), normally in the presence of an acid, to give the corresponding mercaptan. Certain cuprous mercaptides prepared by method[67] are unstable. Thus, cuprous benzylmercaptide is converted to the corresponding benzyl sulphide and stilbene on reaction with aromatic halides. *m*-Bis(benzylthio)benzene is obtained from *m*-dibromobenzene in 46% yield via *in situ* formation of Cu(I)-benzylmercaptide from dibenzyl disulphide.[74]

The *in situ* formation of cuprous arylmercaptides from CuI and ArS^- (XXV) is considered likely during the formation of diaryl sulphides from unactivated aromatic iodides (XXIV):[75]

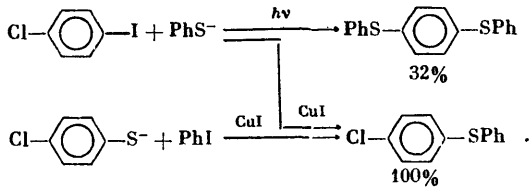


(XXIV) (XXV) (XXVI)

X^1 = Me, NO_2; X^{2-5} = H, Me; X^6 = H, Cl.

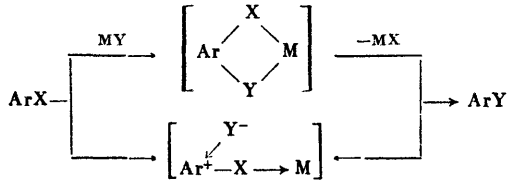
Thus, diaryl sulphides (XXVI) are obtained in 60–75% yield by heating a mixture of the appropriate aryl iodide (XXIV), alkali metal mercaptide (XXV) and CuI in hexamethylphosphoramide at 70–80 °C for 1–2 h.

Catalysis by copper(I) is recommended where processes involving an $S_{RN}1$ mechanism do not give the desired result.[76] Thus, whereas photo-initiated $S_{RN}1$ thiylation of certain dihalogenobenzenes leads exclusively to disubstitution (see also Section V), only monosubstitution takes place under Cu(I) catalysis:



Copper complexes containing P-, As- or Sb-ligands may also be used as catalyst for the thiylation of aromatic halides.[77]

The mechanism of copper-catalysed substitution of aromatic halides is thought to involve initial coordination of copper to the displaced halogen with the intermediate formation of a σ-complex:[64]

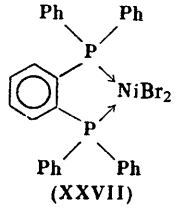


X = halogen; Y = nucleophile .

For nucleophilic substitution in the presence of copper salts, the facility of the initial addition of catalyst across the carbon-halogen bond increases with decrease in the electronegativity of the halogen and with increase in its polarisability (F < Cl < Br < I), reflecting the lability of halogen. This order is the reverse of that found for non-catalytic substitution.[1]

Copper-catalysed nucleophilic substitution may also involve coordination of the copper salt as a π-complex, in which Cu^+ serves as an acceptor.[62,63] A radical mechanism, involving a single electron transfer, has also been proposed for copper-catalysed substitution of halides.[62]

Other transition metals are reported to catalyse thiylation of aryl halides. For example, diaryl sulphides may be prepared in the presence of *o*-bis(diphenylphosphino)benzenenickel(II) bromide (XXVII).[78]



(XXVII)

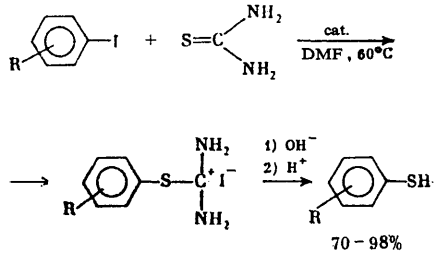
Table 3. Reaction of aryl bromides, ArBr, with NaSPh by method (200 °C, 24 h, ethylene glycol).[78]

Ar	Ph	*p*-MeC_6H_4	*o*-MeC_6H_4	*m*-MeC_6H_4	anthracene	*p*-CNC_6H_4
Yield of sulphide, %	100[a]	94	90	98	90	80

[a] In the absence of catalyst the yield of Ph_2S was 3%.

The reaction conditions and yields for this latter conversion are given in Table 3. The method is regioselective, and reaction is not suppressed by electron-donating groups in the benzene ring of the aryl bromide.

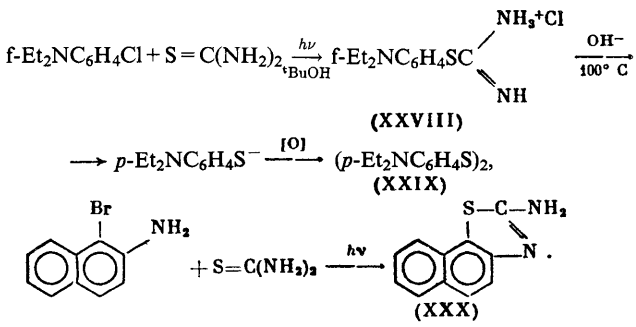
Catalysis by Ni(II) complexes has also been applied successfully to the synthesis of aromatic mercaptans from unactivated aromatic iodides and thiourea. The method is mild and involves the intermediate formation of *S*-arylisothiouronium salts.[79] It is known that unactivated aromatic halides do not form isothiouronium salts with thiourea under normal conditions.[80]



R = H, *p*-Me, *o*-Me, *p*-MeO, *p*-NH_2, *p*-Cl, *p*-Br.

In this reaction, the Ni(II) complex is formed *in situ* from bis(triethylphosphine)nickel(II) chloride and sodium trihydridocyanoborate.

S-Arylisothiouronium salts are also formed on irradiation of thiourea (or thiosemicarbazide) with *o*- or *p*-substituted aryl halides having electron-donating substituents in the benzene ring.[81] However, the mechanism of the reaction is quite different from the $S_{RN}1$ process proposed for photo-substitution of aromatic halogen by mercaptide anion, RS^- (see also Section V). Reaction ceases on formation of the arylisothiouronium salt (XXVIII). *p*-Substituted derivatives may be converted to the corresponding diaryl disulphides by basic hydrolysis at 100 °C, followed by oxidation of the resulting arylmercaptides. *o*-Substituted derivatives, however, are partially cyclised to give thiazoles, e. g. (XXX):

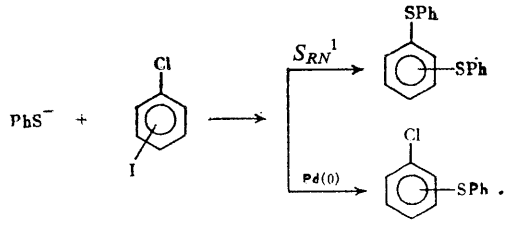


Palladium(0) complexes e.g. tetrakis(triphenylphosphine)-palladium(0), may also be used as catalyst for the reaction of unactivated aromatic halides with mercaptide anion.[82,83] Thus, phenyl and tolyl iodides or bromides react with mercaptans, RSH (R = Ph, Et, tert-Bu, *n*-Bu), in the presence of tert-BuONa as base and $Pd(PPh_3)_4$ as catalyst on heating in DMSO [82] or in alcoholic media.[83] It has been found that PhBr interacts with mercaptans more slowly than PhI. Thus Pd-catalysed reaction of PhSH with PhBr and PhI in refluxing ethanol affords diphenyl sulphide in 19% and 100% yield, respectively. There was no formation of sulphide in the absence of catalyst. Chlorobenzene is noticeably less reactive under these conditions, affording only a trace of diphenyl sulphide on heating in DMSO. Iodobenzene reacts nine times more rapidly with tert-BuS^- than with PhS^-.

It is thought that the mechanism of the substitution involves the formation of an anion radical, $ArX^{\cdot-}$. However, an $S_{RN}1$ process may be excluded for the following reasons:

1) palladium(0)-catalysed substitution is not inhibited by *p*-dinitrobenzene — a good electron acceptor, conventionally used to suppress $S_{RN}1$ reactions. Thus, there is no electron transfer initiation;

2) mono-substitution of iodochlorobenzene by PhS^- predominates under Pd(0) catalysis:



The authors propose that Pd-catalysed thiylation takes place by the following mechanism:

a) oxidative addition of the aryl halide, ArX, to Pd(0) with formation of an adduct:

$$ArX + Pd(0) \rightarrow Ar-Pd(II)-X;$$

b) nucleophilic substitution of the adduct:

$$Ar-Pd(II)-X + RS^- \rightarrow Ar-Pd-SR + X^-;$$

c) reductive elimination:

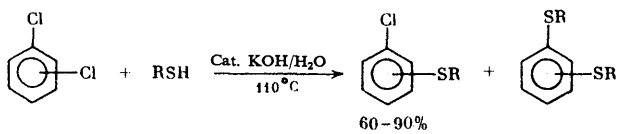
$$Ar-Pd-SR \rightarrow ArSR + Pd(0).$$

As indicated previously, the thiylation of weakly activated aryl halides requires forcing conditions: high temperatures, strong base, and a transition metal complex as catalyst. In the last five years, phase transfer catalysis, which often enhances anionic substitution, has been applied to the thiylation of aromatic halides under mild conditions.[84]

The phase-transfer catalysed thiylation of strongly activated aryl halides (by the nitro group) is worth noting.[85,86] Here, both thiophenols[85] and thiophenoxides (obtained *in situ* by reduction of the corresponding diaryl disulphide with aminoiminomethanesulphinic acid[86]) have been used as the nucleophile. Thus, diaryl sulphides have been prepared in 80–97% yield at room temperature by using a quaternary ammonium salt as phase transfer catalyst in a two-phase medium comprising aqueous base and an organic solvent (THF or toluene).

It has been reported that the rate of reaction depends on the leaving group (deceasing in the order: F > Cl > Br > I), and on the degree of activation of the aromatic ring (decreasing in the order: di-2,4-$(NO_2)_2$ > *o*-NO_2 > *p*-NO_2 > *m*-NO_2).[85] Thioethers are not formed, however, from mononitroaryl halides in the absence of catalyst; with dinitro compounds, the rate of reaction is increased 4 times in the presence of catalyst. Less activated aryl halides, e.g. *m*-BrC_6H_4Cl, are unreactive.[86]

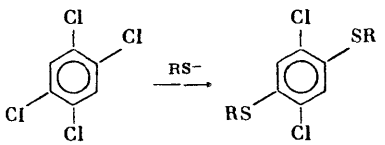
It has been found that the S_NAr reaction of dichlorobenzenes with alkylmercaptide anion is noticeably more facile under liquid-liquid phase transfer catalysis.[87] The synthesis of alkyl aryl sulphides can be carried out at 110 °C by stirring a heterogeneous mixture of the halide, catalyst and mercaptan in 60% aqueous alkali under an inert atmosphere mixture. Dicyclohexano-18-crown-6 is a suitable catalyst for this conversion:



R = Pr^i, Bu^t, *n*-Bu.

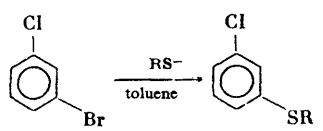
There was no reaction in the absence of catalyst. It has been shown that the rate of displacement of the first chlorine atom in dichlorobenzenes decreases in the order 1,2- > 1,3- > 1,4-dichlorobenzene. This would indicate that the inductive effect is primarily responsible for activation of the leaving group. The order of reactivity of the mercaptide anion is: n-alkyl > sec-alkyl > tert-alkyl ≫ aryl.

A wide range of chlorobenzenes has been submitted to displacement by alkylmercaptide anion.[88] Reaction proceeds in toluene at 25 °C in the presence of a phase transfer catalyst (n-Bu_4NBr, n-Bu_4PBr, 18-crown-6):



R = *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-$C_{12}H_{25}$.

Substitution of halogen in 1,2,4-trichlorobenzene proceeds more slowly than the reaction with tetrachlorobenzene, and takes place exclusively at the 2 position. All three isomeric dichlorobenzenes are less reactive still, and require heating in toluene. Aromatic bromides are substituted more rapidly than chlorides,[88] as confirmed by the following reaction:



R = *n*-C_7H_{15} (86%).

Quaternised 4-dialkylaminopyridinium salts are also effective phase transfer catalysts.[89] They are stable up to 300 °C and increase the rate of thiylation in non-polar solvents (or without solvent) at temperatures below 200 °C.

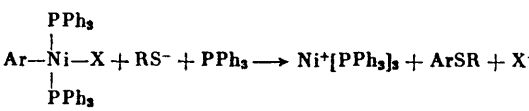
It is also reported that transition metal complexes are effective under phase transfer catalysis.[90] Thus, unactivated aryl halides interact with mercaptides in a mixture of aqueous alkali and toluene in the presence of σ-arylbis(triphenylphosphine)-nickel or -palladium complexes and triphenylphosphine (see Table 4).

Table 4. Reaction of bromobenzenes and chlorobenzene with thiophenol under conditions.[90]

PhX	Catalyst	Time, h	Temperature °C	Yield, %
Br	A	7.5	100	97
Br	A (without PPh_3)	5	100	94
Br	B	23	55	95
Cl	B (without PPh_3)	20	55	70

Key: σ-arylbis(triphenylphosphine)nickel complex (a) or palladium analogue (B).

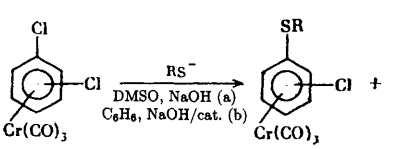
Even chlorobenzene reacts with mercaptide anion in high yield under these conditions. It is thought that the displacement involves a catalytic cycle,[90] the overall process being represented as follows:

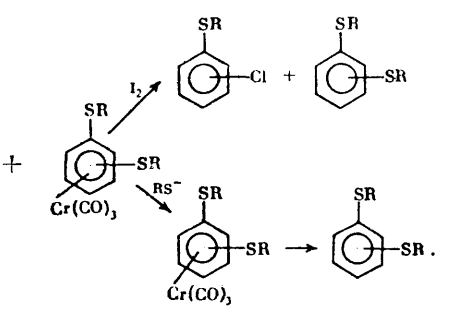


Nucleophilic substitution of halogen in aryl halides may also be activated by π-coordination with transition metal carbonyl or cyclopentadienyl complexes.[91] Reactivity increases in the order:

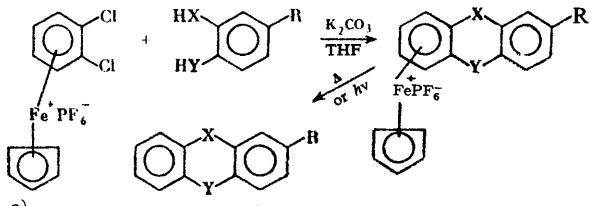
$$Cr(CO)_3 < Mo(CO)_3 \ll (\eta^5\text{–}C_5H_5)Fe^+ < Mn^+(CO)_3.$$

Particular reference has been made to S_NAr substitution of tricarbonyl(halogenobenzene)chromium complexes with alkylmercaptides ($AlkS^-$, where Alk = Me, iso-Pr, tert-Bu, n-Bu) in aprotic media either under a) phase transfer catalysis or b) solid-liquid conditions.[92,93] The following halogenobenzenes participate in this conversion: PhF, PhCl, *m*-MeC_6H_4Cl, *p*-MeC_6H_4Cl, and dichlorobenzenes, e.g.





The reaction of π-coordinated *o*-dihalogenobenzenes with binucleophiles is of potential for the synthesis of heterocyclics,[94,95] as exemplified below.



a) X = S, Y = O, R = H (76%)
b) X = Y = S, R = Me (82%)
c) X = NH, Y = S, R = H (23%).

These results confirm that activation of aryl halides by π-coordination with metals is equivalent to activation by strongly electron-accepting substituents in the aromatic ring, which facilitate thiylation under mild conditions either in aprotic solvents or under phase transfer catalysis.

Thus, specific catalysts may be used for thiylation, notably in combination with phase transfer catalysts. The only limitation of this method is the relative inaccessibility of the catalysts themselves.

IV. High-temperature thiylation

High temperature thiylation of aryl halides has been conducted at 500–700 °C with H_2S, thiophenol, alkyl mercaptans, dialkyl sulphides and disulphides. Studies in this area have been carried out systematically by M G Voronkov et al. at the Institute of Organic Chemistry of the Siberian Section of the Academy of Sciences of the USSR.

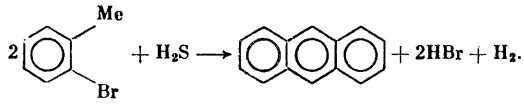
Thiophenol, diphenyl sulphide and benzene are the main products obtained by reaction of chloro-, bromo-, and iodo-benzene with H_2S.[96,98] In the high temperature conversion of halogenobenzenes with H_2S, thiophenol is formed initially and diphenyl sulphide is an intermediate, arising in the second stage:

$$PhX+H_2S\rightarrow PhSH+HX,$$
$$PhX+PhSH\rightarrow PhSPh+HX,$$
$$PhX+H_2S\rightarrow C_6H_6+HX+S.$$

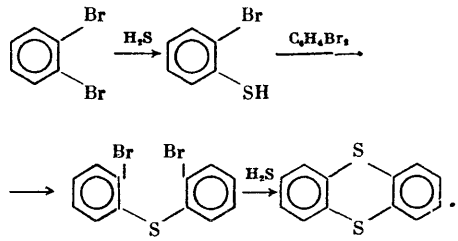
Fluorobenzene does not react with H_2S in the gas phase up to 700 °C. At this temperature and above, thermolysis takes place with cleavage of a C–H bond.

The proportion of thiol : sulphide in the reaction of PhX with H_2S increases in the following order of X; I < Br < Cl. The principal products from the reaction of iodobenzene with H_2S are benzene and diphenyl sulphide, formed also by oxidation of thiophenol with liberated iodine.[98] In comparative experiments, the reaction of bromobenzene with H_2S is more selective for the formation of diphenyl sulphide, while the reaction with chlorobenzene is more selective for the formation of thiophenol. At a fairly low ratio of H_2S : PhBr (1.25), the yield of diphenyl sulphide increases to 72% at 60% conversion.

Both electron-accepting and -donating substituents in the *para*-position (relative to halogen) accelerate the reaction with H_2S and increase the overall conversion. The distribution of electron density in the intermediate thiophenol has a pronounced effect on the ultimate thiol : sulphide ratio and is largely responsible for the rate of the reaction.[99] Thus, electron-donating groups (Me, OMe) favour formation of thiol. However, *o*-methyl groups induce side reactions by virtue of their steric effect, e.g.

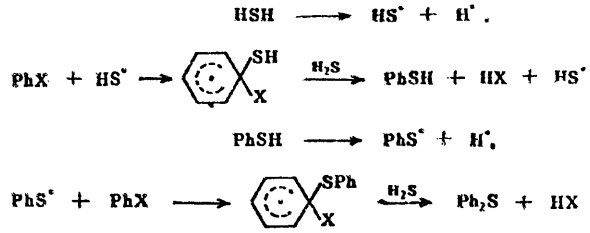


The reaction of *o*-dihalides with H_2S leads to the formation of heterocycles, e. g.



The reactions of fused halogenobenzenoid systems with H_2S have also been studied.[100] Thus, 1-chloronaphthalene reacts in the gas phase at 600 °C to give 1-thionaphthol, bis(1-naphthyl) sulphide, and naphthalene. 1-Bromonaphthalene and brominated derivatives of anthracene and phenanthrene react with H_2S in the liquid phase at 180–250 °C with the formation of symmetrical diaryl sulphides.

The authors have classified the high temperature reaction of aromatic chlorides and bromides with H_2S as a homolytic bimolecular substitution of halogen by thiyl radicals.[101] The following radical chain mechanism has been proposed:



Thiophenol interacts with aryl halides at 400–600 °C primarily with the formation of unsymmetrical sulphides:[102]

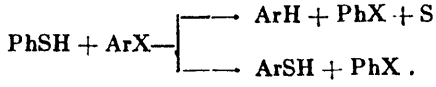
PhSH + ArX → PhSAr + HX,

X = Cl, Br; Ar = *o*-, *p*-, *m*-MeC_6H_4, 3,4-$Me_2C_5H_3$,

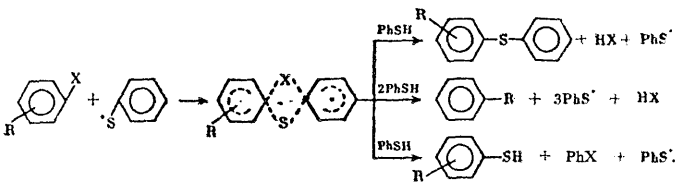
o-, *p*-OHC_6H_4, *o*-, *p*-$MeOC_6H_4$,

o-, *p*-XC_6H_4.

The reaction is more selective at low temperature and with an excess of halide. An increase in the temperature favours reduced and exchange reactions:



The mechanism of the reaction of thiophenol with aryl halides is evidently a bimolecular homolytic process involving substitution by thiyl radicals. This takes place synchronously via a transition state which reacts with the mercaptan by one of three routes depending on the temperature:



For such high temperature conversions of aryl halides, the requisite thiyl radicals may also be generated from aryl mercaptans, dialkyl sulphides or disulphides.[103,104] Alkyl mercaptans react with chlorobenzene at 600–660 °C with the formation of thiophenol, diphenyl sulphide, and benzene as side-product. Lower (C_1–C_3) mercaptans are more reactive than higher ones. By comparing reactions with H_2S and alkyl mercaptans, treatment with the latter is less facile but the thiol : sulphide proportion is greater. Co-pyrolysis of chlorobenzene with dialkyl sulphides $[Me(CH_2)_n]_2S$ (n = 0, 1, 3, 6) and disulphides affords, primarily, benzene, thiophenol, and diphenyl sulphide, together with thiophene, benzothiophene and toluene.

The high temperature thiylation of aryl halides is synthetically attractive as a one-step route to important aromatic organosulphur compounds, namely aromatic and heteroaromatic thiols and sulphides. However, such methods require much energy and are complicated by side-reactions which reduce selectivity and the yield of desired product. This clearly limits the usefulness of these routes for practical purposes.

V. Photo- and electro-chemical thiylation

As indicated above, the thiylation of unactivated aromatic halides requires relatively harsh conditions (high temperatures, aprotic solvents) to secure high yields of the desired thioether, or may be conducted in strongly basic media or under transition metal catalysis. These reactions usually take place by an anionic mechanism, involving the formation of a σ-complex (S_NAr) or aryne-type intermediates, or by a free-radical pathway.

Substitution of unactivated aromatic halides can be effected under mild conditions by photo- or electro-chemical activation. Reaction proceeds by a 'radical, nucleophilic, monomolecular' ($S_{RN}1$) mechanism, as originally proposed and reviewed by Bunnett[105,106] (recent review, see Ref. 6). The key steps of such $S_{RN}1$ substitutions are as follows:

initiation $ArX + \bar{e} \rightarrow (ArX)^{\cdot-}$,

chain propagation $(ArX)^{\cdot-} \rightarrow Ar^{\cdot} + X^-$,

$Ar^{\cdot} + Nu^- \rightarrow (ArNu)^{\cdot-}$,

$(ArNu)^{\cdot-} + ArX \rightarrow ArNu + (ArX)^{\cdot-}$.

The length of the chain depends on the reaction conditions.

The photo-induced (λ_{max} = 350 nm) reaction of aryl iodides with thiophenoxide anion in liquid ammonia is quite facile (1–3 h), affording aryl phenyl sulphides in 70–95% yield:[107]

$$ArI + PhS^- \xrightarrow{h\nu} ArSPh + I^-,$$

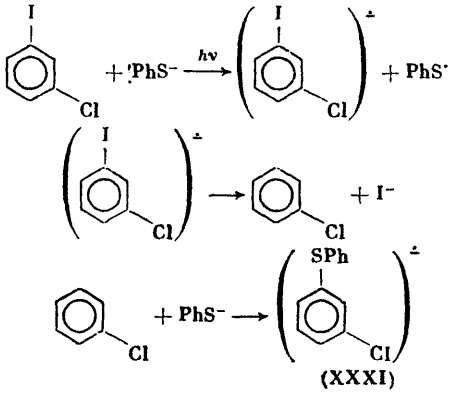
Ar = Ph, 1-naphthyl, *o*-, *p*-, *m*-MeC_4H_4,

o-, *p*-, *m*-$MeOC_6H_4$.

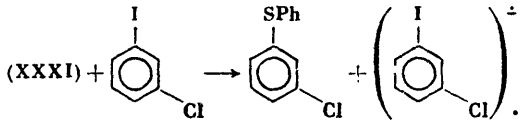
Aryl bromides also participate in this reaction, but more slowly than aryl iodides. Thus, irradiation of a mixture of PhI and PhS^- affords diphenyl sulphide in 94% yield after 70 min, but the yield from PhBr is 23% after 120 min.

The substitution is more effective in the presence of an organic base as catalyst.[108,109] Thus, the conversion of unactivated aryl bromides to diaryl sulphides can be achieved in higher yield (e.g. PhBr affording Ph_2S in 65–70% yield) by photo-initiation in the presence of tetra-n-butylammonium hydroxide or triethylamine; even chlorobenzene reacts under these conditions, Ph_2S being formed in 30% yield.[108] It is likely that such catalysts accelerate the single electron transfer in the initial formation of anion radical by the $S_{RN}1$ mechanism outlined above. The effect of tetra-n-butylammonium hydroxide on the photo-initiated reaction of aryl halides with pyridylthio anion (PyS^-) is less pronounced than its effect on the same reaction by PhS^-.[109] 2-(Phenylthio)pyridine is obtained from PhI in 68% yield, from PhBr in 19% yield, and from PhCl in 3% yield. The relatively inaccessible 3-(nitrophenylthio)pyridines may be prepared by this route under fairly mild conditions.

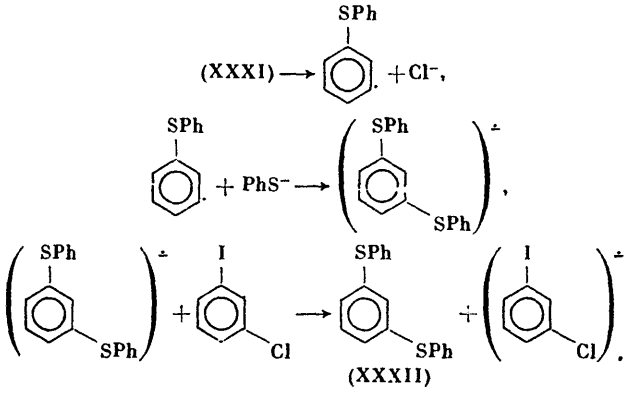
Irradiation of dihalogenobenzenes in liquid ammonia results in disubstitution.[110] Usually, the yield of mono-substitution product is poor or negligible. An $S_{RN}1$ mechanism has been proposed, the initial steps being the following:



The resulting anion radical (XXXI) may react further by two independent pathways. One involves an electron transfer:



The other is a fragmentation, leading ultimately to the disubstituted product (XXXII):



With the majority of dihalogenobenzenes (except fluorides), the formation of monosubstituted product by electron transfer from (XXXI) to the substrate is not significant, and fragmentation is the predominant process. With aromatic halogenofluorides, however, only monosubstitution takes place, i.e. electron transfer is more facile than loss of fluoride ion. This is a result of the greater strength of the C–F bond, relative to the C–Cl and C–Br bonds.

The photo-initiated reaction of alkylmercaptide anion with aryl halides affords the corresponding alkyl aryl sulphide by direct electron transfer (rate constant, k_t); fragmentation of the intermediate anion radical (rate constant k_f) results in formation of an alkyl radical which is unable to perpetuate the chain process:[111–113]

$$Ar^{\cdot} + AlkS^{-} \longrightarrow (Ar{-}S{-}Akl)^{\cdot -} \begin{cases} \xrightarrow{k_t} ArSAlk \\ \xrightarrow{k_f} ArS^{-} + Alk^{\cdot} \end{cases}$$

The relative contributions of these two processes depends on the nature of the alkyl residue and the aryl radical (Tables 5 and 6).

Table 5. The relative amount of the products of substitution and fragmentation in the reaction

$$Ph^{\cdot} + RS^{-} \xrightarrow{h\nu} PhSR + PhS^{-},$$

depending on the nucleophile.[113]

R	Ratio of the rate constants k_t, k_f	Relative yield, %		Overall yield, %
		PhSR	PhS⁻	
Ph	$k_t \gg k_f$	100	0	94
Me, Et, *n*-Bu, Bu^t	$k_t \approx k_f$	50	50	30–70
$PhCH_2$	$k_t \ll k_f$	0	100	4

Phenyl radicals react with phenylmercaptide anion to give the substitution product only (PhSPh),[107] while the interaction with alkylmercaptide anion (R = Me, Et, n-Bu, tert-Bu) affords approximately equal amounts of substitution and fragmentation product.[111,113] The reaction with benzylmercaptide anion, however, takes place only by fragmentation.[113]

Table 6. Relative amount of the products of substitution and fragmentation

$$Ar + n\text{-}BuS \xrightarrow{h\nu} ArSBu\text{-}n + ArS^{-1},$$

depending on the nature of the substrate.[113]

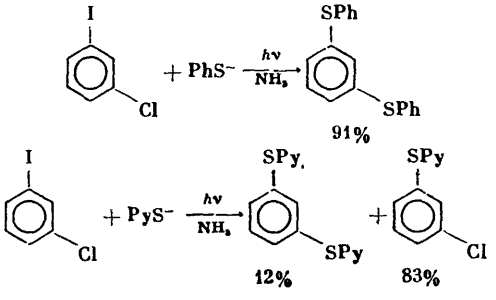
Ar	Ratio of the rate constants k_t, k_f	Relative yield, %	
		ArSBu	ArS⁻
Ph	$k_t < k_f$	50	50
1-Naphthyl	$k_t > k_f$	100	0

Since substitution proceeds as a chain reaction via electron transfer, while fragmentation is involved in the chain termination, the overall yield of substitution product will be decreased as fragmentation becomes more prominent. The relative contribution of electron transfer and fragmentation also depends on the nature of the aryl group.[112,113]

The difference between the reactivity of 1-naphthyl and phenyl radicals towards alkylmercaptide anion can be explained by the increased stability of the alkyl 1-naphthyl sulphide anion radical (relative to alkyl phenyl sulphide anion radical) and its ability to participate in the required electron transfer.

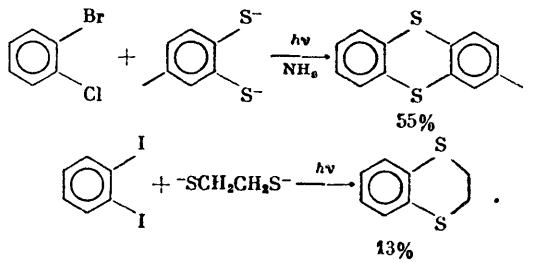
The rationale for mono- or di-substitution in the photo-initiated $S_{RN}1$ reaction of dihalogenobenzenes with RS^- anion has been studied.[114–117] The following factors affecting electron transfer or fragmentation have been identified:

a) the nature of the nucleophile[114,115]:



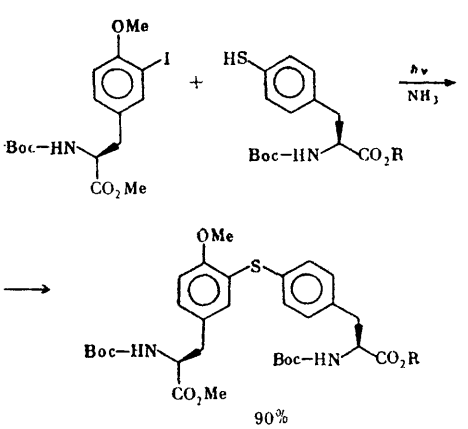
b) the structure of the substrate (in particular, the effect of electron-accepting substituents in the aromatic ring[116,117]).

Recently, heterocyclic compounds have been prepared by the $S_{RN}1$ reaction of *o*-dihalogenoarenes with dithiolate anions:[118]



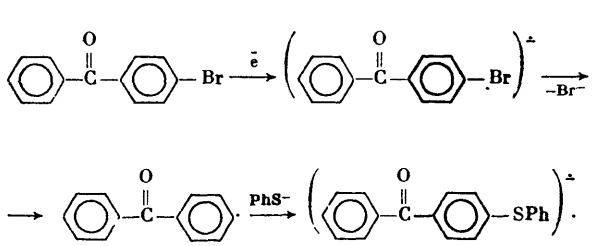
The low yield of product obtained by reaction with ethanedithiolate anion is explained by fragmentation of the intermediate anion radical.

Photo-stimulated thiylation has been applied in recent years as a mild route to complex, biologically significant, molecules. Thus, *p*-mercaptophenylalanine derivatives react effectively with iodotyrosine or iodohydroxyphenylglycine derivatives in liquid ammonia to give the corresponding diaryl sulphides by $S_{RN}1$ displacement:[119]



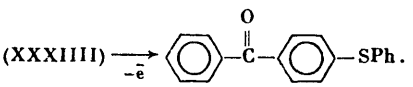
R = Me, H; Boc = ^{t}BuOCO.

It has also been shown that a number of halogenoaromatic compounds participate in electrochemically initiated $S_{RN}1$ substitution.[120–122] Thus, electrochemical reduction of 4-bromobenzophenone in DMF or acetonitrile in the presence of phenylmercaptide anion leads to 4-phenylthiobenzophenone[120] in high yield:

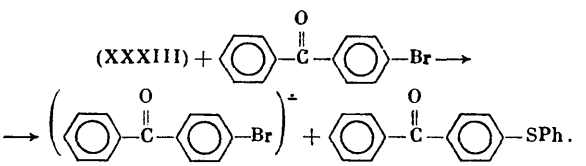


(XXXIII)

In the course of the reaction, the anion radical (XXXIII) may be oxidised at the surface of the electrode to give the desired diaryl sulphide:



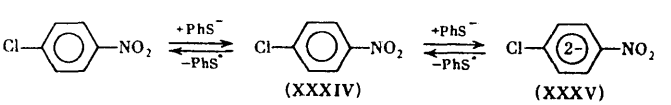
Alternatively, it may transfer its unpaired electron to another substrate molecule:



The reaction of PhS^- with 4-bromoacetophenone, *p*-bromobenzonitrile, *p*-iodobenzonitrile and 1-bromonaphthalene may, in certain instances, be complicated by competitive reduction of the aryl radical by a molecule of solvent:[122]

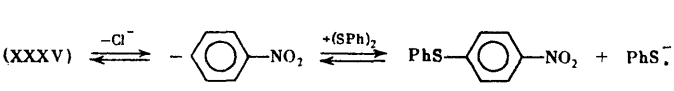
$$Ar^{\cdot} \xrightarrow{HA} ArH + A^{\cdot}.$$

From studies of electrochemical modelling,[123,124] it has been proposed that activated nucleophilic replacement of halogen in *p*-halogenonitrobenzenes can proceed via the intermediate formation of an anionic σ-complex. Thus, the formation of 4-nitrophenyl phenyl sulphide from *p*-chloronitrobenzene and phenylmercaptide anion is thought to involve intermediate formation of *p*-chloronitrobenzene anion radical (XXXIV) and dianion (XXXV), obtained as a result of sequential electron transfer from phenylmercaptide anion. However, the anion radicals themselves are not directly implicated in the displacement. Rather, the end product is formed by thiylation of *p*-nitrophenyl anion (XXXVI) with diphenyl disulphide, the latter anion arising by elimination of chloride ion from the dianion (XXXV);



(XXXIV) (XXXV)

$$2PhS^{\cdot} \longrightarrow PhS{-}SPh,$$



(XXXVI)

Photochemically and electrochemically initiated thiylation of aryl halides under mild conditions is of potential interest from the synthetical and theoretical viewpoint.

* *
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This literature survey has revealed that there is a broad spectrum of routes for the thiylation of aryl halides. Thus, the development of new methods of introducing the RS group into the aromatic ring

under mild conditions has been traced. The displacement in question is subject to a variety of activating influences, most notable from the synthesis viewpoint being transition metal catalysis, phase transfer catalysis and photochemical and electrochemical initiation. One might anticipate that further work in this area will provide more detailed information on the mechanism of these reactions as well as the nature and role of the intermediates.

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