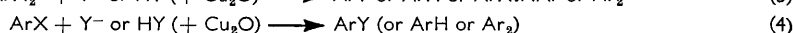
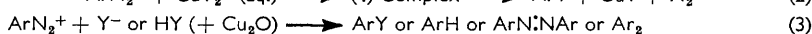
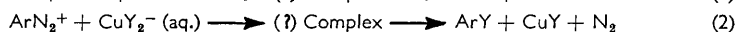
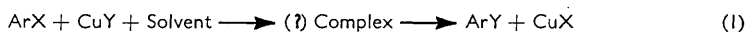


**211. Metal Ions and Complexes in Organic Reactions. Part II.<sup>1</sup>**  
*Substitution Reactions of Aryl Halides Promoted by Cuprous Oxide.*

By R. G. R. BACON and H. A. O. HILL.

A suspension of cuprous oxide promotes nucleophilic substitutions of aryl halides in aprotic polar solvents at, *e.g.*, 150—200°. Effective nucleophiles are the anions  $\text{ArO}^-$ ,  $\text{AlkO}^-$ ,  $\text{ArS}^-$ ,  $\text{AlkS}^-$ ,  $\text{CN}^-$ ,  $\text{I}^-$ ,  $\text{Br}^-$ , and  $\text{Cl}^-$ ; phenols and thiols may be used in place of their salts. Some other types of nucleophile are unreactive under the conditions examined. Some features of the reactions resemble, and others differ from, features of reactions between aryl halides and cuprous salts. Substitutions promoted by cuprous oxide are of preparative value, particularly for ethers and sulphides. Competitive reactions which may be encountered are reduction, nuclear coupling, and participation of solvent in a substitution reaction.

AROMATIC substitutions of type (1), which are effected homogeneously in organic solvents between aryl halides and cuprous salts,<sup>1</sup> show some degree of formal similarity (without necessarily being mechanistically similar) to Sandmeyer reactions (2) between diazonium salts and cuprous complexes in aqueous solution. Copper in the form of cuprous oxide also decomposes aqueous diazonium salts,<sup>2</sup> the reaction (3) in this heterogeneous system being substitution by a nucleophile, reduction, or coupling. It is shown in this Paper that a suspension of cuprous oxide in a suitable solvent may likewise promote a substitution reaction (4) between aryl halides and some nucleophiles, and that reduction or formation of a biaryl compound may be side-reactions.



Results from a preliminary survey of reactions of type (4) are summarised in Table 1, while the effects of variations in solvent and cation are shown for a reaction of the type  $\text{ArI} \longrightarrow \text{ArBr}$  in Table 2.

Nucleophiles of type  $\text{HY}$ , as well as anionic species  $\text{Y}^-$  were examined. Compounds of the former type which effected substitution were phenols and thiols, but reaction did not occur, under conditions so far tried, with methanol, piperidine, or aniline. The anions  $\text{PhO}^-$ ,  $\text{MeO}^-$ ,  $\text{PhS}^-$ ,  $\text{EtS}^-$ ,  $\text{CN}^-$ ,  $\text{I}^-$ ,  $\text{Br}^-$ , and  $\text{Cl}^-$  all effected substitution, but the following failed under the conditions tried:  $\text{F}^-$  (used as the potassium or tetrabutylammonium salt),  $\text{OH}^-$  (used as the tetrabutylammonium compound),  $\text{AcO}^-$ ,  $\text{SCN}^-$ ,  $\text{NO}_2^-$ ,  $\text{SO}_3^{2-}$ , and  $(\text{EtO}_2\text{C})_2\text{CH}^-$  (all used as sodium salts). The successful reduction of a halide by sodium borohydride, in the presence of cuprous oxide, is described in the following paper.<sup>3</sup>

In the case of substitutions effected by non-ionic nucleophiles, reaction is accompanied by consumption of cuprous oxide, 0.5 mol. of which is theoretically required:  $2\text{ArX} + 2\text{HY} + \text{Cu}_2\text{O} \longrightarrow 2\text{ArY} + 2\text{CuX} + \text{H}_2\text{O}$ . When a thiol,  $\text{RSH}$ , is the reagent  $\text{HY}$ , the first step<sup>1</sup> is the visible formation of its cuprous salt,  $\text{CuSR}$ , which then reacts with the halide. Cuprous phenoxides are unknown as stable solids, but can be postulated as reaction intermediates, present in low concentration in the solution:  $2\text{PhOH} + \text{Cu}_2\text{O} \rightleftharpoons 2\text{CuOPh} + \text{H}_2\text{O}$ . Alternatively, substitution of halides by phenols may involve catalysis by cuprous oxide of the direct reaction,  $\text{ArX} + \text{Ar}'\text{OH} \longrightarrow \text{ArOAr}' + \text{H}^+ + \text{X}^-$ , which is succeeded by dissolution of the cuprous oxide by hydrogen halide. Anions derived from reaction of cuprous oxide with the nucleophile are unlikely to be intermediates in

<sup>1</sup> Part I, Bacon and Hill, preceding paper.

<sup>2</sup> Saunders, "The Aromatic Diazo Compounds," E. Arnold and Co., London, 1949.

<sup>3</sup> Part III, Bacon and Hill, following paper.

the case of substitution by certain amines, which more recent investigations<sup>4</sup> have shown to be possible.

Catalysis without consumption of cuprous oxide is involved in reactions with anions:  $\text{ArX} + \text{M}^+\text{Y}^- \rightarrow \text{ArY} + \text{M}^+\text{X}^-$  (where  $\text{M}^+$  is an alkali-metal or tetra-alkylammonium cation). It was noted incidentally that cuprous oxide dissolved to some extent in quinoline, and to a lesser extent in benzonitrile, even before reaction occurred, giving a deep red solution; this recalls a report that copper metal dissolves in quinoline to give a red solution.<sup>5</sup> The results shown in Table 1 suggest that an anion  $\text{Y}^-$  is a good deal more effective than the corresponding compound  $\text{HY}$ . Thus, the sulphide was obtained in poor yield from the system  $\text{ArBr}-\text{Cu}_2\text{O}-\text{PhSH}-\text{pyridine}$ ,<sup>1</sup> but quantitatively from  $\text{ArBr}-$

TABLE 1.

The reaction: Aryl halides + Nucleophiles +  $\text{Cu}_2\text{O}$ , in organic solvents.

Aryl halide and concn. (M)	Nucleophile and concn. (M)	$\text{Cu}_2\text{O}$ (mol./mol. of halide)	Solvent	Temp.	Time (hr.)	Product and yield (%)
PhCl 0.25	PhOH 0.25	0.5	Collidine	170°	72	PhOPh 10
PhBr 0.25	" "	0.5	"	170	72	" 42
PhI 0.25	" "	0.5	"	170	72	" 70
" "	" "	None	"	170	72	PhPh 5
1-C <sub>10</sub> H <sub>7</sub> Br 0.25	" "	0.5	"	170	72	PhOPh 0.5
" "	" "	0.5	"	170	72	1-C <sub>10</sub> H <sub>7</sub> ·OPh 68
" "	PhOH 1.25	2.5	"	170	24	" 35
" "	" "	2.5	Quinoline	238	24	" 80
1-C <sub>10</sub> H <sub>7</sub> Br 0.08	PhOH 0.4	5	Pyridine	115	24	" 53
1-C <sub>10</sub> H <sub>7</sub> Br 0.2	None	1	Dimethyl sulphoxide	144	24	" 15
" "	PhOH 0.4	1	"	144	24	None
" "	PhOH 0.2	0.5	"	144	24	1-C <sub>10</sub> H <sub>7</sub> ·SMe 58
" "	+ PhONa 0.2	0.5	"	144	21	1-C <sub>10</sub> H <sub>7</sub> ·OPh 7
" "	PhOH 0.4	0.5	Dimethyl formamide	144	21	1-C <sub>10</sub> H <sub>7</sub> ·SMe 8
" "	PhONa 0.4	0.5	"	144	21	1-C <sub>10</sub> H <sub>7</sub> ·OPh 5
1-C <sub>10</sub> H <sub>7</sub> Br 0.4	" "	0.5	"	153	72	" 24
" "	MeOH 0.4	0.5	"	153	20	" 84
" "	MeONa 0.4	0.5	"	153	24	None
" "	PhSNa 0.4	0.5	"	153	24	1-C <sub>10</sub> H <sub>7</sub> ·OMe 45
" "	EtSNa 0.4	0.5	"	153	24	C <sub>10</sub> H <sub>8</sub> 50
" "	NaCN 0.4	0.5	"	153	24	1-C <sub>10</sub> H <sub>7</sub> ·SPh 99
" "	NaI 0.4	0.5	"	153	24	1-C <sub>10</sub> H <sub>7</sub> ·SEt 95
" "	LiCl 0.4	0.5	"	153	20	1-C <sub>10</sub> H <sub>7</sub> ·CN 41
" "	" "	" "	" "	" "	" "	1-C <sub>10</sub> H <sub>7</sub> I 7
" "	" "	" "	" "	" "	" "	1-C <sub>10</sub> H <sub>7</sub> Cl 29

$\text{Cu}_2\text{O}-\text{NaSPh}-\text{dimethylformamide}$ ; the yield of diaryl ether was better from the system  $\text{ArBr}-\text{Cu}_2\text{O}-\text{NaOPh}$  than from  $\text{ArBr}-\text{Cu}_2\text{O}-\text{PhOH}$ ; reaction in the system  $\text{ArBr}-\text{Cu}_2\text{O}-\text{NaOMe}$  proceeded readily, but failed in  $\text{ArBr}-\text{Cu}_2\text{O}-\text{MeOH}$ . The reactions are influenced by several experimental variables, the effects of which, as so far discovered, are summarised below. Both resemblances to and differences from reactions in systems  $\text{ArHal}-\text{CuY}$  have been encountered.

Experiments to ascertain the effect of varying the nucleophile were carried out with 1-bromonaphthalene, but if the halide substrate was varied the observed order of reactivity  $\text{ArI} > \text{ArBr} > \text{ArCl}$  was the same as in the reaction system  $\text{ArHal}-\text{CuY}$ .<sup>1</sup> It is known<sup>6</sup> that many factors determine relative nucleophilic reactivity. Some nucleophiles, such as  $\text{PhS}^-$ ,  $\text{MeO}^-$ , and  $\text{PhO}^-$ , which are particularly effective for uncatalysed aromatic substitutions,<sup>6</sup> were similarly effective for the reactions catalysed by cuprous oxide, but there was no such correspondence for some other nucleophiles, such as piperidine and  $\text{OH}^-$ .

<sup>4</sup> Unpublished results by O. J. Stewart.

<sup>5</sup> Dowden, *Discuss. Faraday Soc.*, 1960, **29**, 260.

<sup>6</sup> Edwards and Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 18, and references therein.

Although reaction-rate measurements have yet to be carried out on ArHal-Y<sup>-</sup>-Cu<sub>2</sub>O-solvent systems, it is evident from the available data that the relative reactivity of anions Y<sup>-</sup> is very different from that of corresponding ligands Y in ArHal-CuY-solvent systems.<sup>1</sup> When Y<sup>-</sup> is a halide, the substitutions promoted by cuprous oxide are probably equilibria. Thus, although the reaction  $1\text{-C}_{10}\text{H}_7\text{I} + \text{Br}^- \longrightarrow 1\text{-C}_{10}\text{H}_7\text{Br} + \text{I}^-$  went substantially towards completion (Table 2), the reverse reaction was also demonstrated (Table 1).

Great enhancement of rates of heterolytic organic reactions by using aprotic solvents, free from hydrogen-bonding effects, has lately been abundantly demonstrated, and particularly strikingly, in the case of bromobenzene, by the observation<sup>7</sup> that in dimethyl sulphoxide with sublimed potassium t-butoxide the reaction  $\text{PhBr} + \text{Bu}^t\text{O}^- \longrightarrow \text{PhOBu}^t + \text{Br}^-$  (for which a benzyne mechanism was postulated) occurs readily even at 25°. Effective media for the substitutions described in this Paper are polar aprotic solvents such as were used when cuprous halides were reagents,<sup>1</sup> but choice of solvent within this group had a smaller effect on ease of substitution in reactions promoted by cuprous oxide (Table 2) than in ArHal-CuY reactions. Moreover, heterocyclic bases, which are among the least effective media for the latter reactions,<sup>1</sup> gave very good results with reactions promoted by cuprous oxide.

It appears that ease of substitution may also be somewhat influenced by the nature of the cation (alkali-metal or quaternary ammonium) in a nucleophile M<sup>+</sup>Y<sup>-</sup>, but comparisons are complicated by differences in solubility of the salts in organic solvents (Table 2). Aluminium alkoxides, unlike sodium methoxide, were unreactive under the conditions

TABLE 2.  
The reaction:  $1\text{-C}_{10}\text{H}_7\text{I}$  (0.1M) + Bromides + Cu<sub>2</sub>O (mol. ratio, 1 : 1.1 : 0.5).

Bromide	Solvent	Temp.	Time (hr.)	Yield of $1\text{-C}_{10}\text{H}_7\text{Br}$ (%)
Bu <sup>n</sup> <sub>4</sub> NBr	Dimethylformamide	153°	18	64
LiBr	"	"	"	71
NaBr *	"	"	"	61
KBr *	"	"	"	23
Bu <sup>n</sup> <sub>4</sub> NBr	Hexamethylphosphoramide	144.5°	20	74
"	Quinoline	"	"	70
"	Benzonitrile	"	"	69
"	Dimethyl sulphoxide	"	"	61
"	Dimethylformamide	"	"	53
"	Diethylene glycol dimethyl ether	"	"	31

\* Incompletely dissolved.

tried. Cuprous oxide was used in its ordinary red form; the yellow form, prepared by precipitation, changed into the red in the hot solvent, and no advantage was found in using it. Increased yields of substitution product were obtained by raising the concentrations of the halide or nucleophile, or the proportion of cuprous oxide.

In three instances (Table 1) variations from the normal course of substitution were observed: iodobenzene underwent a small degree of coupling to give biphenyl; interaction between 1-bromonaphthalene and methoxide ion resulted in both reduction and ether-formation; a reaction in dimethyl sulphoxide was complicated by participation of the solvent, which yielded the thiomethyl derivative. The result with methoxide ion recalls the well-known formation of the same two kinds of product when diazonium salts are treated (sometimes in the presence of copper or cuprous oxide) with alcohols.<sup>8</sup> The participation of dimethyl sulphoxide in the reaction appears to require the presence of phenol; this may be related to the observed promotion of sulphoxide decomposition,  $\text{R}\cdot\text{SO}\cdot\text{CH}_2 \longrightarrow \text{RSH} + \text{O}=\text{C} \llcorner$ , by acidic catalysts.<sup>9</sup> By-products containing methylthio-groups have been noted for other nucleophilic aromatic substitutions in dimethyl sulphoxide.<sup>10</sup>

<sup>7</sup> Cram, Rickborn, and Knox, *J. Amer. Chem. Soc.*, 1960, **82**, 6412.

<sup>8</sup> Kornblum, *Org. Reactions*, 1944, **2**, 262.

<sup>9</sup> Kenney, Walsh, and Davenport, *J. Amer. Chem. Soc.*, 1961, **83**, 4019.

<sup>10</sup> Finger and Kruse, *J. Amer. Chem. Soc.*, 1956, **78**, 6034.

The substitution reactions promoted by cuprous oxide provide useful new preparative methods, particularly for ethers and sulphides. As shown above, the preparation of diaryl ethers can be performed with the free phenol in, *e.g.*, boiling collidine, or with the phenol plus one equivalent of alkali in, *e.g.*, boiling dimethylformamide; the former method is preferable for halogen replacements in alkali-sensitive aromatic compounds. Such procedures may be found more convenient than the traditional Ullmann technique,<sup>11</sup> in which phenol, halide, alkali, and copper are heated in the absence of a solvent. Diaryl ether formation with a suspension of cuprous oxide in boiling collidine has proved advantageous in alkaloid synthesis,<sup>12</sup> and a broad evaluation of catalysis by cuprous oxide in the preparation of aryl ethers is now being carried out.<sup>4</sup> The corresponding route to aryl sulphides represents a variation on published methods<sup>13</sup> involving copper(i) derivatives of thiols.

Mechanistically, processes with cuprous oxide belong to the little-known territory of heterogeneous catalysis at a solid-solvent interface. Presumably, adsorption of reagents at copper(i) centres is involved, as likewise in those diazonium salt decompositions and reactions of organic compounds with oxygen, which are catalysed by cuprous oxide. Further aspects of the catalytic activity of cuprous oxide are being studied.

#### EXPERIMENTAL

Purification of solvents, procedures for studying substitution reactions, and gas-chromatographic analytical methods are described in Part I.<sup>1</sup>

*Reactions with Phenol.*—Preparations were carried out in an atmosphere of nitrogen under conditions summarised in Table 1. The resulting solutions were added to 6*N*-hydrochloric acid, the product extracted with benzene, the extract washed with acid, alkali, and sodium chloride solution, and analysed by gas chromatography. The only compounds found were the diaryl ether, unchanged halide, and the by-products shown. Constituents of the solution were commonly accounted for to the extent of 95%. 1-Phenoxynaphthalene was alternatively estimated by chromatography on alumina; elution with light petroleum (b. p. 40–60°) gave unchanged 1-bromonaphthalene, followed by the ether, m. p. 55° (from ethanol). Cuprous iodide caused no ether production when used in place of cuprous oxide and did not improve the yield when used with the oxide.

For preparations in dimethyl sulphoxide, gas chromatography revealed 1-methylthionaphthalene. The reaction mixture, which contained a white solid, presumably the copper(i) methanethiolate, was filtered, added to concentrated aqueous ammonia, and the mixture extracted with ether. The extract yielded a liquid, chromatography of which, with light petroleum on alumina, gave 1-methylthionaphthalene, b. p. 116°/20 mm., in the fractions following unchanged 1-bromonaphthalene (Found: C, 75.8; H, 5.6. Calc. for C<sub>11</sub>H<sub>10</sub>S: C, 75.8; H, 5.8%). When the liquid was oxidised at 100° with 30% hydrogen peroxide in acetic acid, the peak in the gas chromatogram due to the sulphide disappeared, and chromatography on alumina yielded, with benzene-light petroleum (9:1), 1-methanesulphonylnaphthalene, m. p. 103° (from ethanol) (Found: C, 63.8; H, 4.8. Calc. for C<sub>11</sub>H<sub>10</sub>O<sub>2</sub>S: C, 64.1; H, 4.9%).

*Reactions with Thiols.*—Reaction of 1-bromonaphthalene with thiophenol and sodium hydroxide (1 equiv.) was quantitative under the conditions given in Table 1; longer periods of heating resulted in darkening and lower yields. A trace of 2-phenylthionaphthalene (~2%) in the product, shown by gas chromatography, was attributed to a similar proportion of the 2-isomer in the sample of 1-bromonaphthalene used. For a preparation of 1-ethylthionaphthalene (Table 1), the appropriate amount of sodium was dissolved in ethanethiol and, after removal of excess of the thiol, the halide, solvent, and cuprous oxide were added. After reaction, the product was treated as described for 1-phenoxynaphthalene and shown by gas chromatography to contain 1-ethylthionaphthalene (95%) and unchanged 1-bromonaphthalene (5%). Removal of benzene from the extract left the sulphide as a liquid, b. p. 101°/0.2 mm., *n*<sub>D</sub><sup>19</sup> 1.6492, which was identified by oxidation at 100° with 30% hydrogen peroxide in acetic

<sup>11</sup> Ullmann and Sponagel, *Annalen*, 1906, **350**, 83.

<sup>12</sup> Crowder, Glover, Grundon, and Kaempfen, *J.*, 1963, 4578.

<sup>13</sup> Adams and Ferretti, *J. Amer. Chem. Soc.*, 1959, **81**, 4927; Campbell, *J. Org. Chem.*, 1962, **27**, 2207.

acid, to give 1-ethanesulphonylnaphthalene, m. p. 88° (from ethanol) (Found: C, 65·6; H, 5·2. Calc. for  $C_{12}H_{12}O_2S$ : C, 65·4; H, 5·5%).

*Reaction with Other Nucleophiles* (Tables 1 and 2).—For the reaction with methoxide ion, sodium was dissolved in methanol, excess of which was removed before other reagents were added. Reactions with halide and cyanide ions were carried out under the conditions shown in the Tables and the products were analysed as described<sup>1</sup> for reactions involving the corresponding cuprous salts. No substitution products were observed, and 1-bromonaphthalene was recovered practically quantitatively, after treatment of the halide for 20 hr. in boiling dimethylformamide with cuprous oxide (0·5 mol.) and the following nucleophilic reagents (1 mol., 0·4M): aniline, methanol, piperidine, aluminium isopropoxide or t-butoxide, sodium acetate, nitrite, sulphite, or thiocyanate, potassium fluoride, tetra-n-butylammonium fluoride or hydroxide; decomposition of the tetra-n-butylammonium compounds occurred.

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