Metal Ions and Complexes in Organic Reactions. Part XV.[1] Copper-catalysed Substitutions of Aryl Halides by Phthalimide Ion

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Copper-catalysed nucleophilic substitutions, ArHal ⟶ $ArN(CO)_2C_6H_4$ (and thence $ArNH_2$ by hydrolysis) are effective with a wide range of aromatic bromo- or iodo-derivatives; they are preferably carried out with potassium phthalimide and copper(I) iodide in refluxing dimethylacetamide. Reductive substitution, ArHal ⟶ ArH, is rarely competitive, but accompanying decarboxylation occurs in the case of halogenocarboxylic acids. Rates of halide substitution are dependent on the ratio of potassium phthalimide to copper(I) iodide. These two reagents solubilise each other and are considered to associate in cuprate complexes which react with the halides. Rates of substitution of *para*- (or *meta*-)halogeno-compounds, XC_6H_4Hal, show relatively small dependence on the polar character of X. The substitutions are however very susceptible to steric inhibition, as is evidenced by the behaviour of polycyclic halides and of compounds of the type *o*-XC_6H_4Hal, particularly if polar effects in the substituents X do not provide partial compensation.

WE have reported [2] that, with the aid of copper catalysis, application of the Gabriel reaction may be extended from alkyl halides to aryl halides. This reaction (1), followed by hydrolysis of the resulting *N*-arylphthalimide (2), provides a useful synthetic route from the halide to the corresponding primary aromatic amine. It was

$$ArHal + KN(CO)_2C_6H_4 \ (+ \text{Cu species in an organic solvent}) \longrightarrow ArN(CO)_2C_6H_4 + KHal \quad (1)$$

$$ArN(CO)_2C_6H_4 + 2KOH \longrightarrow ArNH_2 + o\text{-}C_6H_4(CO_2K)_2 \quad (2)$$

known that the most reactive aryl halides (*e.g.* those containing NO_2 or CN substituents) may be substituted by potassium phthalimide even in the absence of the catalyst; examples have been listed in a review [3] and others are given in this paper (Table 1 and Figure 2). The same review [3] reported copper-catalysed reactions of potassium phthalimide with 1-chloroanthraquinone [4] and with ω-bromostyrene.[5] Copper(II) phthalimide has been used to convert bromoferrocene into the phthalimido-derivative.[6]

We now show that under appropriate conditions the copper-catalysed reaction (1) is effective with a wide range of aryl bromides or iodides, which may contain either electron-attracting or electron-donating substituents. The polar effect of the substituents is relatively small, but the reaction is strongly subject to steric inhibition. It rarely suffers from competition from the reductive substitution process, ArHal ⟶ ArH, which often occurs with other nucleophiles, *e.g.* alkoxides.[7]

Investigation of Reaction Conditions.—When the work was initiated, it seemed, from previous experience, that the desired substitutions (1) might best be effected by employing a copper(I) halide as catalyst and an amide or heterocyclic base as solvent. Tests indicated (Table 1) that copper(I) iodide (alternatively, the bromide) in refluxing dimethylacetamide (alternatively, dimethylformamide) is a particularly effective combination. The use of copper(I) chloride has been avoided because it readily effects halogen exchange, ArBr ⟶ ArCl.[8] In subsequent series of experiments the reagents, ArBr + $KN(CO)_2C_6H_4$ + CuI, were commonly used, in dimethylacetamide, in a 1 : 1 : 1 molar ratio, but larger amounts of copper(I) iodide were found necessary (see later) for the less responsive halides.

As substrates, aryl bromides, or, occasionally, the iodides were used; the difference in reactivity between the two types of halide was not great. As expected,[8] aryl chlorides proved ineffective except when a strongly activating structural feature was present, as in 2-chloroanthraquinone (Table 7). In choosing the nucleophile, no advantage was found in using other alkali-metal phthalimides in place of the potassium salt. The data in Table 2 are illustrative.

Tests showed that whereas potassium phthalimide and copper(I) iodide are individually rather sparingly soluble

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[2] R. G. R. Bacon and Amna Karim, *Chem. Comm.*, 1969, 578.
[3] M. S. Gibson and R. W. Bradshaw, *Angew. Chem. Internat. Edn.*, 1968, **7**, 919.
[4] H. A. E. Drescher and J. Thomas, U.S.P. 1,528,470/1925.
[5] K. W. Rosenmund, M. Nothnagel, and H. Riesenfeldt, *Ber.*, 1927, **60**, 392.
[6] A. N. Nesmeyanov, W. A. Ssasonowa, and V. N. Drosd, *Chem. Ber.*, 1960, **93**, 2717; A. N. Nesmeyanov, *Pure Appl. Chem.*, 1968, **17**, 211.
[7] R. G. R. Bacon and J. R. Wright, *J. Chem. Soc.* (*C*), 1969, 1978.
[8] R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1097.

in dimethylacetamide (respectively 0·0149 and 0·0125 mol l^{-1} at 20°) each has a solubilising effect on the other (up to *ca.* ten-fold at 20°) when both are present in the solvent. This is attributed to the formation of copper(I) complexes (cuprates) of the type $n\mathrm{K}^+[\mathrm{CuIphthal}_n]^{n-}$. These would be analogous to the complexes involved in copper-catalysed, diazonium-salt (Sandmeyer) substitutions[9] and to the lithium copper-alkyls and -aryls recently used for coupling processes.[10] To provide some preliminary information on possible mechanisms of the phthalimide substitutions (1), varying proportions of copper(I) iodide and potassium phthalimide were equilibrated (at 20°) with dimethylacetamide. These solubility measurements (Figure 1) indicated that the solutes had the approximate composition $\mathrm{CuI,2KN(CO)_2C_6H_4}$ when potassium phthalimide was in excess and $\mathrm{2CuI,KN(CO)_2C_6H_4}$ when copper(I) iodide was in excess. This suggests the possibility of equilibria of types (3)—(5), in which phthal represents $\mathrm{C_6H_4(CO)_2N^-}$ and L represents other ligands on tetraco-ordinate copper. It is considered that an aryl halide molecule must enter the complex, in competition with other ligands, and associate with the metal ion, as a preliminary to nucleophilic substitution by a phthalimide ion ligand; *e.g.*, reaction may be envisaged[8] as in (I).* In view of the beneficial effects of employing reagent mixtures with the copper : phthalimide ratio >1, it is possible that copper-rich complexes, of types suggested at the beginning of the equilibria series (3)—(5), provide particularly favourable locations for reaction. Further

TABLE 1

Potassium phthalimide (0·01 mol) + *p*-bromobenzonitrile (A) (0·01 mol) or *p*-bromonitrobenzene (B) (0·01 mol) + catalyst (0·01 mol) in solvent (100 ml), 24 h under nitrogen

	Catalyst and solvent	$\mathrm{ArN(CO)_2C_6H_4}$ Yield (%)		Catalyst and solvent	Temp. (°C)	$\mathrm{ArN(CO)_2C_6H_4}$ Yield (%)
(A)	CuI, dimethylacetamide [a]	94	(B)	CuI, dimethylacetamide [a,d]	165	96
(A)	CuBr, dimethylacetamide [a]	82	(B)	CuI, 2,4,6-collidine [b]	165	51
(A)	$\mathrm{Cu_2O}$, dimethylacetamide [a]	57	(B)	CuI, quinoline [b]	165	14
(A)	$\mathrm{Cu^{2+}}$,[c] dimethylacetamide [a]	55	(B)	CuI, nitrobenzene [b]	165	12
(A)	Cu, dimethylacetamide [a]	15	(B)	CuI, diethylene glycol dimethyl ether [a]	162	5
(A)	$\mathrm{CuBr_2}$, dimethylacetamide [a]	12	(B)	CuI, dimethylformamide [a]	155	90
(A)	No catalyst, dimethylacetamide [a]	8	(B)	CuI, *p*-xylene [a]	138	0
			(B)	CuI, 2-picoline [a]	128	6

[a] Refluxing solvent. [b] Heated by vapour bath, provided by refluxing dimethylacetamide. [c] Copper(II) phthalimide used; the colour of the solution changed from blue to red-brown during reaction. [d] In dimethylacetamide, with no catalyst present, the yield was 41%.

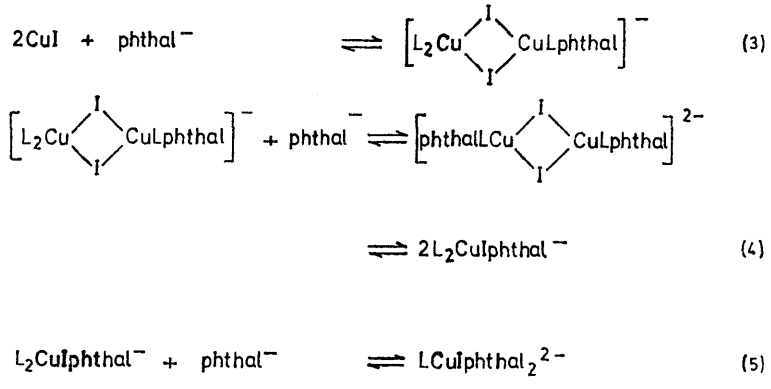
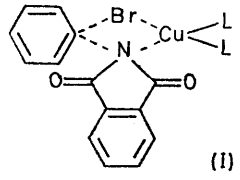


TABLE 2

Variations in halide and cation (CuI-catalysis; conditions as in Table 1)

Reaction	Variation [Yield (%) of *N*-arylphthalimide]
$p\text{-MeC}_6\mathrm{H_4Hal}$ + $\mathrm{KN(CO)_2C_6H_4}$	Hal = I, 67; Br, 60; Cl, nil; F, nil.
$p\text{-NO}_2\text{·C}_6\mathrm{H_4Hal}$ + $\mathrm{KN(CO)_2C_6H_4}$	Hal = I, 97; Br, 96; Cl, nil.
PhBr + $\mathrm{MN(CO)_2C_6H_4}$	M = K, 71; Na, 62; Li, 67.



(I)

* For recent discussions of copper-assisted nucleophilic substitutions involving perfluoro-aryl and -alkyl halides see J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *J.C.S. Perkin I*, 1972, 639, 763.

[9] W. A. Cowdrey and D. S. Davies, *Quart. Rev.*, 1952, **6**, 358.
[10] *E.g.*, H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31**, 3129; G. M. Whitesides, W. F. Fischer jun., J. S. Philippo jun., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, 1969, **91**, 4871.

investigations are needed to ascertain variations in the composition of solutes when the nature of the solvent, ratio of reactants, or temperature is varied. Solid complexes have not been isolated. Copper(I) phthalimide is unknown, but the copper(II) salt is readily prepared [11] and is reported to complex with phthalimide ions [11] and with amines.[12] Imide-containing complexes of various other transition metals have been described.[13]

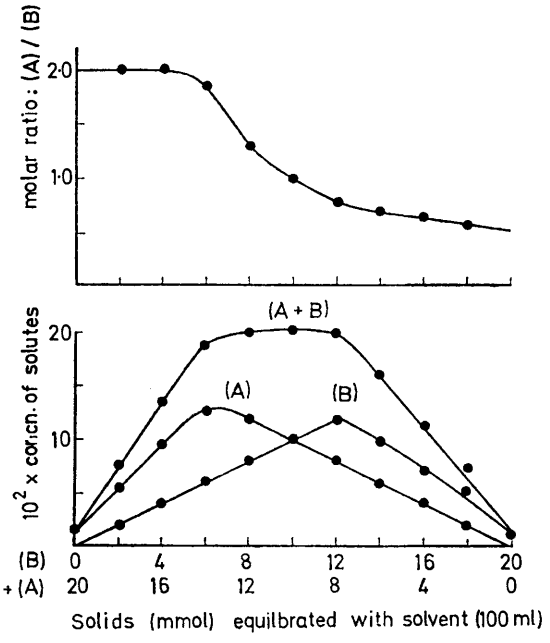


FIGURE 1 Equilibration of mixtures of potassium phthalimide (A) and copper(I) iodide (B) with dimethylacetamide at 20°: concentrations of (A) and (B) in solution; solute ratio, (A) : (B) [after deduction of solubilities found for (A) or (B) in the absence of the second solute]

Polar Effects of Nuclear Substituents in the Aryl Halide.—It is known [8] that exchange reactions (6) between aryl

$$XC_6H_4Br + CuCl \text{ (in pyridine)} \longrightarrow XC_6H_4Cl + CuBr \quad (6)$$

halides with copper(I) salts follow second-order kinetics and that nuclear substituents X have a very small effect (unless X is *o*-NO_2) on the rate. To obtain data on rates of production of *N*-arylphthalimides by reactions of type (1), a g.l.c. analytical method was used. Its precision was inadequate for ascertaining reaction kinetics, but the results served to demonstrate (Table 3) (*a*) that rates of substitution were dependent on the CuI : $KN(CO)_2C_6H_4$ ratio and (*b*) that the effects of *para*-substituents X, although in accord with their electron-attracting or -donating character, were very small. By comparison, uncatalysed substitutions of aryl halides by nucleophiles may be 10^6—10^8 times faster, when X is NO_2 or CN, than when X is OMe or NH_2.[14]

TABLE 3

Rates of reaction: ArI + $KN(CO)_2C_6H_4$ + CuI in dimethylacetamide at 165°

[reagents] / mol^{-1}	$t_{\frac{1}{2}}$ / h
[PhI], 0·10; [$KN(CO)_2C_6H_4$], 0·10; [CuI], 0·11	7
[PhI], 0·10; [$KN(CO)_2C_6H_4$], 0·10; [CuI], 0·10	14
[PhI], 0·10; [$KN(CO)_2C_6H_4$], 0·11; [CuI], 0·10	40
[*p*-XC_6H_4I], 0·10; [$KN(CO)_2C_6H_4$], 0·10; [CuI], 0·10	
X = NO_2	2
H	15
OMe	27

Polar effects are more extensively illustrated by preparations (Table 4) in which eighteen bromobenzene derivatives, *p*-XC_6H_4Br, were converted under standard conditions into phthalimido-derivatives and the products isolated chromatographically. A relatively small polar effect is again apparent, but all the halides reacting faster than bromobenzene contained electron-attracting substituents whereas most of those reacting more slowly contained electron-donating substituents. Few of these reactions produced tars and no side effects were discovered apart from the partial decarboxylation of *p*-bromobenzoic acid. Including portions of reagents recovered unchanged, 90—100% of organic materials were commonly accounted for. Two anomalous halides were ethyl *p*-bromobenzenesulphonate, which gave *N*-ethylphthalimide, and *p*-bromobenzenesulphonamide, which gave no phthalimido-compound, possibly because it competed with the phthalimide in ionic and ligand-forming equilibria.[15]

TABLE 4

p-XC_6H_4Br (0·01 mol) + $KN(CO)_2C_6H_4$ (0·01 mol) + CuI (0·01 mol) in dimethylacetamide (100 ml), 24 h at 165°

X	$XC_6H_4{\cdot}N(CO)_2C_6H_4$ (%)	X	$XC_6H_4{\cdot}N(CO)_2C_6H_4$ (%)
NO_2 [a]	96	Br	50 + 10 [c]
CO_2H	70 + 26 [b]	COMe	63
CN	94	Me	60
SO_2Ph	88	OMe	54
		NH·COPh	52
N=NPh [a]	83	SO_2Cl	51
COPh	81	Ph	47
$N(CO)_2C_6H_4$	72	OH [a]	40
CHO	71	NHCOMe	35
H	71	NH_2 [d]	33

[a] The reaction gave small amounts of tar. [b] The minor product was $PhN(CO)_2C_6H_4$. [c] The minor product was *p*-$C_6H_4[N(CO)_2C_6H_4]_2$. [d] The reaction gave a good deal of tar.

Steric Effects in Monocyclic and Polycyclic Halides; Counteracting Effects of High Copper : Phthalimide Ratios.—Marked susceptibility to steric inhibition became apparent when reaction (1) was applied to the isomeric bromonitrobenzenes, bromobenzoic acids, bromoanilines, and dibromobenzenes. A practical reason for investigating the dibromides was their potential use as a

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[12] P. Shukla, M. P. Khare, and L. N. Strivastava, *J. prakt. Chem.*, 1965, **28**, 21; 1965, **29**, 38; *Z. phys. Chem. (Leipzig)*, 1967, **234**, 153, 157; G. Narain, *Indian J. Chem.*, 1966, **4**, 248.
[13] *E.g.*, L. Cambi, L. Canonica, and R. DeLeone, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1955, **18**, 467; D. M. Roundhill, *Inorg. Chem.*, 1970, **9**, 254; W. Beck and E. Schier, *Naturforschung B*, 1970, **25**, 221.
[14] *E.g.*, W. Greizerstein, R. A. Bonelli, and J. A. Brieux, *J. Amer. Chem. Soc.*, 1962, **84**, 1026; for a general account see J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968.
[15] R. G. R. Bacon and Amna Karim, following paper.

source of diamines; likewise 1,3,5-tribromobenzene was examined (see Experimental section). Yields (Table 5) were somewhat less from the *meta*-isomers than from the *para*-isomers; reaction virtually ceased in the cases of *o*-bromoaniline and the *o*-dibromide, and likewise if a methyl group was present, *ortho* to the halogen, in *p*- or *m*-bromonitrobenzene. It appeared that polar effects of NO_2 or CO_2H counteracted steric inhibition, but yields from the *o*-nitro- or *o*-carboxy-bromides were less than from their *para*- and *meta*-isomers. By increasing the amount of copper(I) iodide two- or three-fold, reactions giving low yields could be improved, and apparently inactive halides could be brought into moderate reactivity. Reactions of the bromobenzoic acids were complicated by copper-catalysed decarboxylation, the extent of which varied in the order *ortho*- > *meta*- > *para*-isomer; it was not established whether this occurred in the bromo-acid, or in the phthalimido-acid, or in both.

In view of the strongly inhibitive effect of *o*-methyl groups (Table 5), homologues of bromobenzene provided

TABLE 5

o-, *m*-, and *p*-Substituted bromobenzenes (0·01 mol) + $KN(CO)_2C_6H_4$ (0·01 mol) + CuI (normally 0·01 mol) in dimethylacetamide (100 ml), 24 h at 165°

Yield (%) of *N*-arylphthalimide from XC_6H_4Br (or XC_6H_3MeBr)

	p-X	*m*-X	*o*-X
	4-Nitro, 96	3-Nitro, 82 [a]	2-Nitro, 57 [b]
	2-Methyl-4-nitro, 5 [c]	2-Methyl-5-nitro, 0	
	4-Amino, 33		2-Amino, 0 [d]
	4-Carboxy, 70 + 26 [e]	3-Carboxy, 58 + 37 [e]	2-Carboxy, 0 + 78 [e]
	4-Bromo:	3-Bromo:	2-Bromo:
CuI 0·020 mol	46 + 47 [f]	30 + 31 [f]	0
CuI 0·035 mol	3 + 98 [f]	6 + 68 [f]	13
CuI 0·045 mol		0 + 93 [f]	16

[a] $PhNO_2$ (17%) was a by-product. [b] Raised to 67% with 0·02 mol CuI. [c] Raised to 28% with 0·03 mol CuI. [d] Raised to 4%, 5%, respectively, with 0·02, 0·03 mol CuI. [e] The second figure refers to decarboxylated product. [f] 0·020 mol $KN(CO)_2C_6H_4$ + 0·020 mol CuI; 0·025 mol $KN(CO)_2C_6H_4$ + 0·035 mol or 0·045 mol CuI; the second yield figure refers to diphthalimido-derivatives (none obtained from the *o*-dibromide).

a suitable series for further examining how far this inhibition could be overcome by augmenting the catalyst. Reactions of fourteen mono-, di-, tri-, tetra-, and penta-methylbromobenzenes were therefore compared (Table 6). The bromides in series *A*, possessing no *ortho*-substituents, gave 40—60% yields under standard conditions (*p*-bromotoluene being the most reactive) and 80—100% yields when the amount of catalyst was doubled. The bromides in series *B*, possessing one *o*-methyl group, all failed to react under standard conditions, but 2 or 3 molar proportions of catalyst led to yields of 20—40%. The bromides in series *C*, possessing two *o*-methyl groups, all failed to react under all conditions employed. The presence of *ortho*-groups (unless they provide compensating polar effects) would be expected to hinder establishment of a transition state for the substitutions such as is indicated in (I). Previous series of experiments,[7] analogous to those in Table 6, showed that two *o*-methoxy-substituents depressed, but did not prevent, substitution of halogen by methoxide ions. The difference in susceptibility of the two types of reaction may be connected with the greater bulk of the nucleophile $C_6H_4(CO)_2N^-$ compared with that of MeO^-.

TABLE 6

Bromobenzene homologues, $C_6H_{5-n}Me_nBr$ (0·01 mol) + $KN(CO)_2C_6H_4$ (0·01 mol) + CuI (0·01—0·03 mol) in dimethylacetamide (100 ml), 24 h at 165°

CuI (mol)	Yield (%) of $C_6H_{5-n}Me_n{\cdot}N(CO)_2C_6H_4$			
	A (no *ortho*-substituent):			
	3-Methyl	4-Methyl	3,4-Dimethyl	3,5-Dimethyl
0·01	53	60	44	41
0·02	85	97		78
	3,4,5-Trimethyl			
0·01	50			
0·02	81			
	B (one *ortho*-substituent): [a]			
	2-Methyl	2,3-Dimethyl	2,4-Dimethyl	2,5-Dimethyl
0·02	17	21	17	16
0·03	32	38	27	
	2,3,4-Trimethyl	2,4,5-Trimethyl	2,3,4,5-Tetramethyl	
0·02	30	19	26	
0·03	40		31	
	C (two *ortho*-substituents)			
	No yield, with up to 0·03 mol CuI, from 2,6-dimethyl-, 2,4,6-trimethyl-, 2,3,4,6- or 2,3,5,6-tetramethyl-, or pentamethyl-bromobenzene.			

[a] No bromide in series *B* reacted when only 0·01 mol CuI was used.

In Figure 2 catalytic effects are further illustrated for one of the hindered halides, 2,3-dimethylbromobenzene (Table 6, Series *B*). As the molar proportion of copper(I) iodide was varied over the range 1—5 maximum yield was observed around 3 mol. equiv.; the mixtures became increasingly heterogeneous as the proportion of copper(I) iodide was raised. For comparison, Figure 2 includes the case of an activated, non-hindered halide; *p*-bromobenzonitrile, which is sluggishly reactive even without catalyst, responds to small proportions of copper(I) iodide, and readily undergoes practically quantitative conversion when 1 mol. equiv. is used.

Steric effects are also evident in the response of polycyclic aryl bromides (Table 7). The difference in behaviour of 1- and 2-bromonaphthalene suggests that location of halogen *ortho* to a point of ring juncture is detrimental. In the case of 9-bromoanthracene, where the bromine is flanked by two such junctures, no substitution could be achieved. This halide yielded traces of anthraquinone, which was attributed to copper-catalysed oxidation by oxygen present as an impurity in the nitrogen gas stream employed. In an atmosphere of oxygen, conversions of up to *ca.* 50% were observed; anthracene was likewise oxidised, but more slowly.

Tables 5 and 7 incidentally include the only two cases of reductive substitution, ArHal ⟶ ArH, which were encountered as a side reaction in the investigation. The

reproducibility of these effects would need checking, since adventitious impurities may be a cause of such reductions. Evidently, however, phthalimide ion, unlike many other aromatic nucleophiles,[16] has little or no capacity as a hydrogen donor for aryl halides.

TABLE 7

Polycyclic aryl halide (0·01 mol) + $KN(CO)_2C_6H_4$ (0·01 mol) + CuI (0·01—0·03 mol) in dimethylacetamide (100 ml), 24 h at 165°

CuI (mol)	Yield of *N*-phthalimido-compound from: 1-Bromonaphthalene	2-Bromonaphthalene	9-Bromophenanthrene
0·01	3	67	0
0·02	21		19
0·03			26

CuI (mol)	9-Bromofluorene	2-Chloroanthraquinone
0·01	32	89 [a]

[a] Anthraquinone (11%) was a by-product.

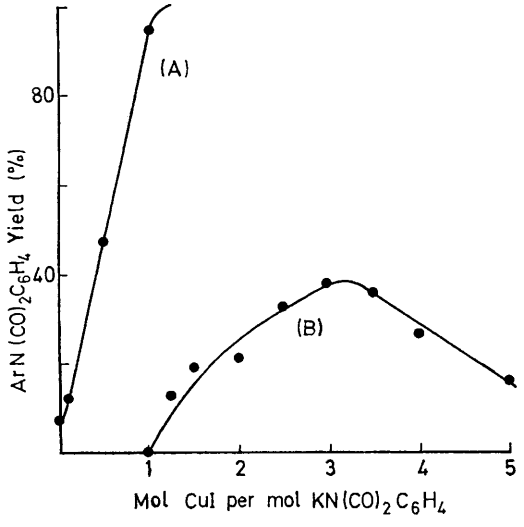

FIGURE 2 Effect of CuI concentration (other conditions as in Tables 4 and 6) on production of $ArN(CO)_2C_6H_4$: (A), Ar = *p*-cyanophenyl; (B), Ar = 2,3-dimethylphenyl

EXPERIMENTAL

Solvents and Reagents.—Dimethylacetamide was dried over calcium hydride, distilled under nitrogen at 165—166°, and stored over Linde type 5A molecular sieves. The heterocyclic bases were stirred with barium oxide, distilled under nitrogen, and stored over potassium hydroxide. Diethylene glycol dimethyl ether was refluxed with sodium and distilled at 162°. Copper(I) iodide (B.D.H.) and other copper catalysts were dried at 110° and 0·5 mmHg before use. Potassium phthalimide was prepared by treating phthalimide in pyridine with potassium hydroxide in aqueous ethanol.[17] Lithium or sodium salts (Table 2) were prepared in dimethylacetamide, immediately prior to the reaction, by treatment of phthalimide with lithium hydride or sodium hydride respectively. Copper(II) phthalimide was prepared from potassium phthalimide and copper(II) acetate.[11] Some of the aryl halides were purified commercial materials and others were prepared as follows.

Bromination of 2,6-xylidine gave 4-bromo-2,6-dimethylaniline which was converted into 1-bromo-3,5-dimethylbenzene.[18] Bromination of hemimellitene, pseudocumene, durene, and isodurene [19] gave, respectively, 1-bromo-2,3,4-trimethylbenzene, 1-bromo-2,3,5-trimethylbenzene, 1-bromo-2,3,5,6-tetramethylbenzene, and 1-bromo-2,3,4,6-tetramethylbenzene. 3,4,5-Trimethylaniline was prepared from isophorone [20] and was converted into 1-bromo-3,4,5-trimethylbenzene by diazotisation in hydrobromic acid and treatment with copper.[21] Durene was isomerised, *via* 2,3,4,5-tetramethylbenzenesulphonic acid, to 1,2,3,4-tetramethylbenzene,[22] which was brominated, yielding 1-bromo-2,3,4,5-tetramethylbenzene, m.p. 25° (lit.,[23] 24°). Bromination of pentamethylbenzene gave bromopentamethylbenzene.[24]

Ethyl *p*-bromobenzenesulphonate,[25] *p*-bromobenzenesulphonamide,[26] and phenyl *p*-bromophenyl sulphone [27] were prepared by treating *p*-bromobenzenesulphonyl chloride, respectively, with ethanol, with aqueous ammonia, and with bromobenzene (at 140—180°, in the presence of ferric chloride). *p*-Bromoazobenzene [28] was prepared by condensation [29] of nitrosobenzene with *p*-bromoaniline in ethanol–acetic acid. Phthalic anhydride and *p*-bromoaniline in refluxing acetic acid gave *N*-*p*-bromophenylphthalimide.[30]

Procedure for Copper-catalysed Substitutions.—The aryl halide, potassium phthalimide, and copper(I) iodide (0·01 mol each, or other ratios, as shown in the Tables) were added to dimethylacetamide (100 ml) and the mixture was heated to boiling under a reflux condenser while a slow stream of dry nitrogen was passed through the apparatus. Solutions were homogeneous unless higher proportions of copper(I) iodide were used; a yellow and then greenish colour generally developed during reaction. The solution was cooled and added to an excess of *ca.* 4N-hydrochloric acid (or water if halogeno-amines were used), which precipitated copper(I) iodide and organic material, generally including some unchanged phthalimide. The mixture was extracted with dichloromethane, the extract washed, dried, and evaporated, and the residue was chromatographed on a column of silica gel (Whatman, SG31; *ca.* 50 g per g of crude product), using solvents in the sequence: light petroleum (b.p. 40—60°), benzene, and ether. Unchanged halide was eluted by light petroleum and unchanged

[16] R. G. R. Bacon and O. J. Stewart, *J. Chem. Soc.* (*C*), 1969, 301.
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phthalimide (generally last in the sequence) by benzene–ether or petroleum–ether. Phthalimido-compounds resulting from the reactions were purified by recrystallisation of chromatographic fractions (from ethanol unless otherwise stated) and characterised by m.p. and spectroscopic properties.

Homologous N-*Arylphthalimides*.—The following (see Tables 4 and 6) were prepared: *N*-phenyl-, m.p. 205° (lit.,[30] 205°), *N*-*o*-tolyl-, m.p. 182° (lit.,[31] 183°), *N*-*m*-tolyl-, m.p. 176° (lit.,[31] 176°), and *N*-*p*-tolyl-phthalimide, m.p. 204° (lit.,[31] 204—205°); *N*-2,3-dimethylphenyl-, m.p. 144° (lit.,[32] 143—144°; lit.,[33] 172—174°), *N*-2,4-dimethylphenyl-, m.p. 153° (lit.,[32] 154°; lit.,[33] 202—203°), *N*-2,5-dimethylphenyl-, m.p. 162° (lit.,[31] 163°), *N*-3,4-dimethylphenyl-, m.p. 195° (lit.,[33] 193—194°), and *N*-3,5-dimethylphenyl-phthalimide, m.p. 136° (lit.,[31] 135°); N-2,3,4-*trimethylphenylphthalimide*, m.p. 194—195° (from benzene–light petroleum) (Found: C, 76·8; H, 5·5; N, 5·5. $C_{17}H_{15}NO_2$ requires C, 77·0; H, 5·7; N, 5·3%), *m/e* 265 (M^+), *N*-2,4,5-trimethylphenylphthalimide, m.p. 146° (lit.,[31] 147°), and N-3,4,5-*trimethylphenylphthalimide*, m.p. 215° (from ether–dichloromethane) (Found: C, 76·9; H, 5·5; N, 5·3%), *m/e* 265 (M^+); and N-2,3,4,5-*tetramethylphenylphthalimide*, m.p. 178° (Found: C, 77·2; H, 6·1; N, 5·0. $C_{18}H_{17}NO_2$ requires C, 77·4; H, 6·1; N, 5·0%), *m/e* 279 (M^+).

Other Nuclear-substituted N-*Phenylphthalimides*.—The following were obtained under conditions shown in Tables 4 and 5. From nitro-halides: *N*-*o*-nitro-, m.p. 203° (lit.,[34] 203—204°), *N*-*m*-nitro-, m.p. 244° (lit.,[30] 246°), *N*-*p*-nitrophenylphthalimide, m.p. 267° (lit.,[30] 268°), and *N*-(2-methyl-4-nitrophenyl)phthalimide, m.p. 198° (lit.,[30] 201°). From bromo-acids: *m*-phthalimido-, m.p. 285° (from acetic acid) (lit.,[30] 284°) and *p*-phthalimido-benzoic acid, m.p. 290° (from acetic acid) (lit.,[30] 290°); these were preceded in the chromatogram by *N*-phenylphthalimide, which was the only product obtained from *o*-bromobenzoic acid. From bromoanilines: *o*-phthalimido-, m.p. 193° (lit.,[35] 193°) and *p*-phthalimido-aniline, m.p. 250° (lit.,[36] 250°). From various *p*-halogeno-compounds: *N*-*p*-biphenylylphthalimide, m.p. 290° (from chloroform) (lit.,[30] 285°), *p*-phthalimidophenol, m.p. 294° (from acetic acid) (lit.,[30] 295°), *p*-phthalimidoanisole, m.p. 162° (lit.,[30] 162°), *p*-phthalimidobenzaldehyde, m.p. 201° (lit.,[37] 202°), *p*-phthalimidoacetophenone, m.p. 240° (from acetic acid) (lit.,[30] 240°), *p*-phthalimidobenzophenone, m.p. 183° (lit.,[38] 183°), *p*-phthalimidobenzonitrile, m.p. 188° (lit.,[39] 187°), *p*-phthalimidoacetanilide, m.p. 289—290° (from acetic acid) (lit.,[31] 283°; lit.,[40] 287—288°), p-*phthalimidobenzanilide*, m.p. 362—363° (from acetic acid) (Found: C, 73·6; H, 4·2; N, 8·2. $C_{21}H_{14}N_2O_3$ requires C, 73·7; H, 4·1; N, 8·2%), *m/e* 342 (M^+), *p*-phthalimidoazobenzene, m.p. 260° (from dichloromethane) (lit.,[31] 252°), *p*-phthalimidobenzenesulphonyl chloride, m.p. 235—237° (from dichloromethane) (lit.,[41] 234—237°), *phenyl* p-*phthalimidophenyl sulphone*, m.p. 226° (Found: C, 66·1; H, 3·7; N, 4·0; S, 8·7. $C_{20}H_{13}NO_4S$ requires C, 66·1; H, 3·6; N, 3·9; S, 8·8%), *m/e* 363 (M^+). Treatment of ethyl *p*-bromobenzenesulphonate, under conditions given in Table 4, yielded *N*-ethylphthalimide (59%), m.p. 78° (lit.,[30] 78°).

Products from Di- and Tri-bromobenzenes.—Under the conditions shown (Table 5) *o*-dibromobenzene gave *N*-*o*-bromophenylphthalimide, m.p. 150—151° (lit.,[33] 127—128°), eluted with benzene–light petroleum (9 : 1) (Found: C, 55·6; H, 2·5; Br, 26·4; N, 4·6. Calc. for $C_{14}H_8BrNO_2$: C, 55·8; H, 2·6; Br, 26·5; N, 4·6%). In the case of *m*-dibromobenzene, cooling the reaction mixture gave a crystalline precipitate of *m*-diphthalimidobenzene, m.p. 317—318° (from acetic acid) (lit.,[42] 318°) and treatment of the filtrate gave *N*-*m*-bromophenylphthalimide, m.p. 172—173° (lit.,[33] 164—165°), eluted with benzene–ether (95 : 5) (Found: C, 55·9; H, 2·5; Br, 26·5; N, 4·5%). Similarly, *p*-dibromobenzene gave *p*-diphthalimidobenzene, m.p. 361—362° (from acetic acid) (lit.,[42] 357°) as a precipitate, and *N*-*p*-bromophenylphthalimide, m.p. 204—205° (lit.,[30] 206°), eluted by light petroleum–benzene (1 : 4). Treatment of 1,3,5-tribromobenzene gave an insoluble, high-melting product (67% of theory for the triphthalimido-derivative) for which satisfactory elemental analyses were not obtained.

Polycyclic Derivatives.—The following (see Table 7) were prepared: *N*-1-naphthylphthalimide, eluted with benzene–ether (95 : 5), m.p. 182—183° (lit.,[31] 181°), *N*-2-naphthylphthalimide, m.p. 218° (from ether–dichloromethane) (lit.,[31] 216°), N-9-*phenanthrenylphthalimide*, eluted with light petroleum–benzene (1 : 9), m.p. 210° (from dichloromethane) (Found: C, 81·4; H, 4·3; N, 4·4. $C_{22}H_{13}NO_2$ requires C, 81·7; H, 4·0; N, 4·3%), *m/e* 323 (M^+), *N*-2-fluorenylphthalimide, eluted with ether–dichloromethane (1 : 1), m.p. 290° (from acetic acid) (lit.,[31] 288°), and 1-phthalimidoanthraquinone,[4,43] eluted with ether–dichloromethane (1 : 1), red leaflets, m.p. 305—306° (from dimethylacetamide) (lit. m.p. not recorded). The last-named compound was preceded on the chromatographic column by anthraquinone, eluted by light petroleum–ether (3 : 2).

Hydrolysis of N-*Arylphthalimides*.—For example, a solution of *N*-*o*-nitrophenylphthalimide (0·01 mol) in 0·5N-ethanolic potassium hydroxide (100 ml) was refluxed for 3 h, evaporated, and added to water; extraction with ether gave *o*-nitroaniline (99%).

Copper-catalysed Oxidations.—A mixture of 9-bromoanthracene (5 mmol) (*cf.* Table 7) and copper(I) iodide (15 mmol) was kept in refluxing dimethylacetamide (50 ml) for 24 h while an atmosphere of oxygen was maintained. This yielded unchanged 9-bromoanthracene (23%) and anthraquinone (50%), m.p. 284—285°, eluted by light petroleum–ether (1 : 1). When the catalyst was omitted, 86% of the anthracene was recovered and anthraquinone isolated (9%). A similar catalysed oxidation of anthracene resulted in 53% recovery and anthraquinone (22%). Similar catalysed oxidations of 1-bromonaphthalene and of 9-bromophenanthrene resulted in their partial destruction, but only tarry products were obtained.

Solubility Measurements.—Weighed amounts of potassium phthalimide (20 mmol), copper(I) iodide (20 mmol), or mixtures of these in varying proportions (20 mmol total;

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see Figure 1) were added to dimethylacetamide (100 ml), the mixtures stirred at 60°, and cooled to 20°. When the sample was a 1 : 1 molar mixture it was completely soluble, but mixtures deficient in copper(I) iodide left residues which were entirely potassium phthalimide, and mixtures deficient in potassium phthalimide left residues which were entirely copper(I) iodide. These residues were filtered off, dried, and weighed.

Rate Measurements (*Table* 3).—Dimethylacetamide solutions containing potassium phthalimide and copper(I) iodide, augmented by naphthalene or biphenyl as an internal standard for g.l.c. analysis, were maintained at the b.p. of the solvent, under a reflux condenser, in a nitrogen atmosphere. The aryl halide was introduced, in a small glass bulb, and was dissolved to start the reaction. At intervals, 5 ml portions of solution were withdrawn by a syringe inserted through a rubber seal. These samples were added to dilute hydrochloric acid, organic material was extracted by dichloromethane, and the solutions were dried and reduced in bulk. Samples were analysed for unchanged aryl halide by g.l.c.; a Celite–silicone oil column was employed.

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