Influence of Substrate Structure on Copper(I)-assisted Cyanide Substitution in Aryl Halides

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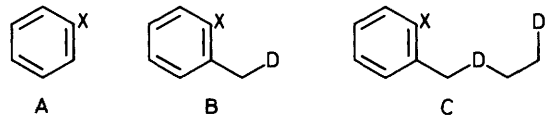
The synthesis of various aryl halides is described: these are designed to explore the structural characteristics which are sufficient to enable copper(I)-assisted substitution of the halide by cyanide to proceed. The copper ion serves to polarise the substrate; stable co-ordination complexes are not formed. The role of various heteroatoms in the substrate is assessed and the importance of intramolecular hydrogen bonding is established.

Aryl halides undergo nucleophilic substitution reactions which are assisted by copper metal, its salts, and co-ordination complexes.[1] These reactions have been reviewed recently.[2] The mode of action of the metal atom has been studied in some of these transformations, particularly the processes which may occur within the co-ordination sphere, and various possible roles have been identified. The variety of products which result in some systems suggests that more than one mechanism may operate. Following the report that the halogen in 2-halogeno-diarylazo compounds could be rapidly replaced[3] by hydroxide through the action of copper(II) sulphate, sodium hydroxide, and ammonia at 350 K, a variety of other nucleophiles including alkoxide,[4-7] phenoxide,[4,5,7,8] sulphinate,[4,9] cyanide,[10] carboxylate,[11] and nitrite[12] ions, ammonia[4] and both aromatic[4,5] and aliphatic[4,5,13] amines, and alkyl phosphites[14] have been used in copper-assisted nucleophilic substitution reactions of the same type of substrate.

Investigations of substrate reactivity have been rather restricted. Studies of the copper-assisted phosphonation[14] and carboxylation[11] of 2-halogeno-diarylazo compounds showed that the reactivity of the halogen atom in different substrates could be typified as follows: Type 1, those substrates in which the halogen does not occupy a potentially chelating position relative to any donor groups which may be present in the molecule (**A**) (see Scheme): Type 2, those in which the halogen



A B C

Scheme. D represents a donor atom.

is so located relative to one donor group in the molecule that, in principle, the possibility exists of it being involved in the formation of a six-membered chelate ring (**B**); and Type 3, those in which the halogen is so located relative to two donor groups in the molecule that, in principle, the possibility exists of it being involved in the formation of an annelated, chelated copper complex in which the halogen forms part of a six-membered ring (**C**). A sub-division of Type 2 and Type 3 can be made in that those 2-halogeno-diarylazo compounds which have substituents (NO_2 or CH_3) in the 6-position of the halogen-bearing ring react more rapidly than those without a substituent: the steric (rather than the electronic) nature of this effect has been inferred.

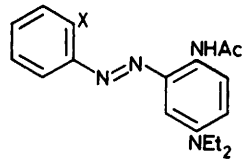
Although co-ordination complexes of the aryl halide with copper(I) are not usually isolable in these reactions, there is evidence[15] from ^{63}Cu NMR for interaction between the two components. We have examined the influence of changes in the composition and structure of the organic halide on reactivity to substitution by cyanide in the presence of copper as copper(I) cyanide.

Results and Discussion

In general, the major product of this copper-assisted nucleophilic substitution reaction, ArCN, is accompanied by small amounts (< 10%) of a biaryl coupling product, Ar_2, and a reductive substitution product, ArH, from side-reactions. For the present purposes these minor products have been ignored and the emphasis is placed on those structural features necessary for cyanide substitution to occur.

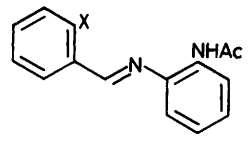
Role of the Proximal Donor Atom in Type 3 Substrates.—Compound (**1a**) reacts with copper(I) cyanide in pyridine solution at reflux temperature to give, by displacement of bromine, the corresponding nitrile (**1b**) in good (85%) yield after 3 h. 2-(2′-Bromophenylmethyleneamino)acetanilide (**2a**) also reacts with copper(I) cyanide in refluxing pyridine to give the corresponding nitrile (**2b**) although the isolated yield after 3 h was lower (60%). 2-(2-Bromophenyliminomethyl)acetanilide (**3**) failed to react with copper(I) cyanide in refluxing pyridine, no nitrile product being detected after 16 h. Other conditions were investigated: the aryl halide (**3**) was warmed with copper(I) cyanide in *N,N′*-dimethylformamide at 150 °C for 4 h, but no nitrile product was formed, and no substitution was observed when (**3**) was added to a solution of $[Cu_3(CN)_4(NCMe)_4]$ in acetonitrile and then heated at reflux for 7 h. The alkene, 2-acetylamino-2′-bromostilbene (**4**) does not react with copper(I) cyanide in refluxing pyridine, nor does it undergo substitution of the halogen by cyanide under any of the conditions outlined above. To confirm this, 2-bromo-4,6-dimethyl-2′-acetylamino-stilbene (**5**) was prepared, but this compound also failed to react with copper(I) cyanide in solution. The (bromoaryl)alkenes were recovered unchanged.

These experiments demonstrate that the presence of a heteroatom in a specific position in the *ortho* side-chain of the aryl halide substrate is necessary for substitution to occur. The heteroatom is required in a position where the possibility exists of a six-membered chelate ring involving the halogen being



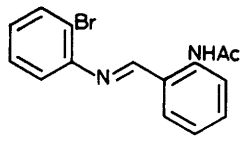
X

(1)a Br
b CN

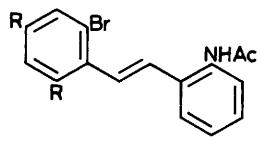


X

(2)a Br
b CN



(3)

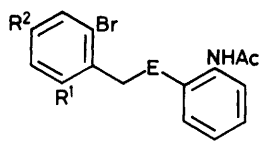


R

(4) H
(5) Me

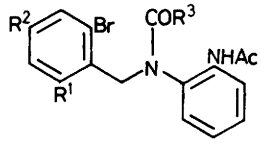
formed. The possibility of forming a five-membered chelate ring, as might occur with (**3**), does *not* assist substitution. The possibility that (**3**) might be reactive in this case, was based on the report[17] that the halogen in 2-(2′-hydroxyphenyliminomethyl)chlorobenzene is substituted by alkoxide ion in the presence of copper (II). This report could not be substantiated.[18] The specific nature of the interaction between the aryl halide and copper is emphasised both by the lack of reactivity shown by the olefins (**4**) and (**5**) in which acentric binding[19] of the π-system to the metal might have sufficed to assist the reaction, and the reaction[20] of 2-bromoacetophenone with copper(I) cyanide in pyridine to form 2-cyanoacetophenone, in which it is presumed that the carbonyl oxygen and the halogen may be involved in chelation of the copper ion.

Having established the need for a donor atom in a β-position on the *ortho* side-chain of the aryl halide, attention focussed on the specific requirement. A range of substrates (**6a–i**) were allowed to react with copper(I) cyanide in pyridine solution and in *N*,*N*-dimethylformamide, and with $[Cu_3(CN)_4(NCMe)_4]$ in acetonitrile. None of the compounds (**6a–f**) undergoes substitution of bromide by cyanide under these conditions. This suggests that the basicity of the heteroatom (O,S) or its state of hybridisation may be responsible. The secondary amine (**6g**) reacts with $[Cu_3(CN)_4(NCMe)_4]$, which is prepared[16] in acetonitrile solution from the reaction between anhydrous copper(II) acetate and acetic anhydride–formamide (1:1), to form 2-(2-cyanophenylmethylenamino)acetanilide (**2b**). This (unexpected) product is the consequence of nucleophilic displacement of bromide by cyanide and oxidation of the benzylaniline. Further investigation of the reaction showed that 2-acetylamino-N-(2-bromobenzyl)-*N*-acetylaniline (**7a**) is formed as an intermediate. It is this compound, which is formed by acetylation of (**6g**) with the acetic anhydride, which is present as a dehydrating agent for formamide in the reaction, which is converted into (**2a**) as a result of loss of the elements of ethanal, before reacting with cyanide in the manner already described to form (**2b**). Separate experiments also showed that the loss of ethanal from (**7a**) to give (**2a**) is assisted by copper(I) [in the form of copper(I) chloride or copper(I) acetate] but not by copper(II) in similar form. Reaction of (**6i**) with $[Cu_3(CN)_4(NCMe)_4]$ in acetonitrile also proceeds through the *N*-acetylated intermediate (**7b**) to form the nitrile (**8a**). In this case the rate of reaction is less than in the case of (**6g**). Copper(I) cyanide reacts with (**7b**) in acetonitrile to form (**8a**).



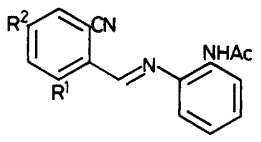
(6)

	E	R^1	R^2
a	O	H	H
b	O	H	NO_2
c	O	Me	Me
d	S	H	H
e	S	H	NO_2
f	S	Me	Me
g	NH	H	H
h	NH	H	NO_2
i	NH	Me	Me



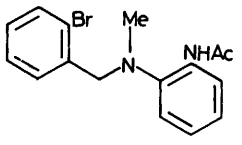
(7)

	R^1	R^2	R^3
a	H	H	Me
b	Me	Me	Me
c	H	H	Ph
d	H	NO_2	Ph
e	Me	Me	Ph

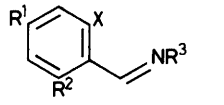


(8)

	R^1	R^2
a	Me	Me
b	H	NO_2



(9)

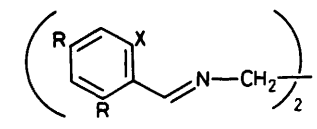


(10)X=Br (11)X=CN

	R^1	R^2	R^3
a	H	H	CH_2CH_2NHMe
b	Me	Me	CH_2CH_2NHMe
c	H	H	CH_2CH_2NHAc
d	Me	Me	CH_2CH_2NHAc
e	H	H	$(CH_2)_3NHAc$
f	H	H	$(CH_2)_4NHAc$
g	Me	Me	$CHCH(NHAc)(CH_2)_4$
h	H	H	Cyclohexyl

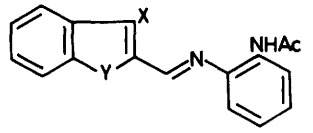
The influence of electron density on the reactivity of the aryl halide was demonstrated by the reaction of (**6h**) with copper(I) cyanide in *N*,*N*-dimethylformamide solution at 420 K which produced (**8b**) in which both substitution of bromide by cyanide and dehydrogenation have occurred. The acylation/dehydroacylation step is limited in its scope. If the benzylanilines (**6g–i**) are benzoylated at the benzylamino nitrogen atom (**7c–d**) the resulting compounds are inert to substitution of bromide by cyanide. Methylation of the benzylamino nitrogen (**9**), also inhibits the substitution of bromide by cyanide. These results emphasise the importance of the acidity of the methylene hydrogen atoms adjacent to the amino nitrogen in compounds such as (**6g–i**) and (**7a,b**), in facilitating the formation of the benzylideneimine, in which the nitrogen is planar rather than tetrahedral. Comparison of the results obtained with the benzyl ethers (**6a–c**) and benzylsulphides (**6d–f**) with those obtained with the benzylamines (**6g–i**) shows the need for conjugation between the heteroatom and the halide; where this exists, (**1a**) or (**2a**), or can be established, (**6g–i**), the halide can be activated towards nucleophilic substitution.

Role of the Second Donor Atom in Reactive Type 3 Substrates.—Previous work has established that the presence of a



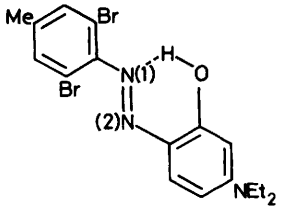
	X	R
a	Br	H
b	Br	Me
c	CN	H
d	CN	Me

(12)



	X	Y
a	Br	O
b	Br	S
c	CN	O
d	CN	S

(13)



(14)

second (distal) donor atom in the substrate in a position where it can, potentially, participate in a five-membered chelate ring involving the copper ion and the other formally sp^2 hybridised, donor atom is beneficial to activating the aryl halide substrate. It is known that the distal donor atom should be relatively acidic (for example, acetylamino rather than methylamino), but it is not known whether it needs to be part of a 1,2-di-substituted aromatic ring. A series of 2-bromobenzylideneamines (**10a–h**) has been prepared. All of these compounds are rapidly hydrolysed in (moist) air so that particular care was taken in manipulations involving them. They are all stable in solution in dry pyridine.

Reaction of these benzylideneamines with copper(I) cyanide in dry pyridine showed that whereas the 2-methylaminoethyl compounds (**10a,b**) do not undergo substitution of bromide by cyanide, their acetylamino analogues (**10c–g**) are straightforwardly converted into nitriles (**11c–g**). These results confirm the advantage of a more acidic donor atom and establish both that a second aromatic ring is not necessary and that it can be replaced by a flexible alkyl chain apparently without loss of activity. However, the presence of the distal donor atom is not crucial to the activity of the substrate because the aryl bromide (**10h**), in which R^3 is a cycloalkyl group, reacts with copper(I) cyanide in pyridine to form the nitrile (**11h**). The 1,2-diaminoethane derivatives (**12a,b**) also react with copper(I) cyanide to form the corresponding *N,N'*-bis(2-cyanobenzylidene) compounds (**12c,d**). Simple kinetic measurements using IR spectroscopy in the 2 200 cm^{-1} [aryl ν(CN) absorption] region to observe the progress of the substitution showed that conversion of (**10c**) into (**11c**) is effectively quantitative after 2 h. The rate of conversion of (**10f–h**) is similar to that (**10c**) initially, but after 0.5 h the reaction is effectively complete and the conversion of these substrates into (**11f–h**) is *ca.* 35%. These results suggest strongly that while the second (distal) nitrogen donor in (**10c**) may assist the nucleophilic displacement of bromide by cyanide in a Type 3 substrate, in (**10f–h**) it does not assist and these benzylideneamines react as Type 2 systems, even though they contain a second (potential) donor atom.

Other Substrates.—2-(2'-Acetylaminophenyliminomethyl)-3-bromo-benzofuran (**13a**) and -benzothiophene (**13b**) react with copper(I) cyanide in refluxing pyridine to form the corresponding 3-nitrile (**13c,d**). In each case, the reaction is significantly slower than that of (**2a**) or (**10c**) under identical conditions.

Conclusion.—The evidence accumulated in this and in previous work which we and others have done on this problem indicates that copper(I) is necessary to transport the entrant nucleophile to the reaction site and to receive and to remove the departing halide from the reaction. Although it has not been possible, in any of these reacting systems, to isolate a complex containing copper and the organic molecule, whether substrate or product, it is clearly established that an sp^2 hybridised electron-pair donor atom is an essential component of the substrate. The location of this donor with reference to the halogen is also important. There is limited spectroscopic evidence[15] for interaction between copper(I) and substrates of the type used here. The structure of (**14**) shows[21] that the bromine-bearing aromatic ring plane is almost perpendicular to the plane defined by the azo group and the acetamidophenyl group. If interaction with copper(I) goes through the azo-nitrogen atom (2), it appears likely that copper serves to polarise the substrate. The formation of a transient complex, in which the halide, the azo-nitrogen, and the acetamido nitrogen are co-ordinated in regular positions to the (presumed) tetrahedral copper(I) ion is unrealistic. The role of the second donor atom in a Type 3 substrate (**C**) appears to be to interact *via* an intramolecular H-bond with the sp^2 hybridised nitrogen or methine group in a six-membered ring. Evidence from the reactivity of (**10a–e**), mentioned earlier, together with the results of other work[11] indicate the importance of this intramolecular protonation in assisting the reaction. The evidence from the reactions of (**10f–h**) indicates the precise geometric requirements for a six-membered ring in this intramolecular interaction in assisting the reaction of (**10c–e**).

In this study we have sought to define the necessary structural components of a reactive substrate in the Ullmann reaction. The mechanism of the reaction has not been investigated *per se*. In connection with this, the conclusion of a recent detailed investigation of the mechanism has concluded that the active (catalytic) species is a soluble copper(I) ion.[22]

Experimental

NMR spectra were recorded (δ scale) with a JEOL JNM-PS-100 spectrometer at 100 MHz (protons), using TMS as standard and $CDCl_3$ as solvent. Mass spectra were recorded with a VG Analytical-modified AEI MS-9 spectrometer at a nominal beam energy of 70 eV. IR spectra were recorded with a Perkin-Elmer PE683 spectrometer using KBr plates (liquids as films) or discs (solids) as appropriate. Microanalyses were performed by Mr. A. J. Fassam in this Laboratory. Standard chemicals were reagent grade materials. All known compounds were prepared by established methods and characterised in accordance with published values.

2-(2-Bromophenylmethyleneamino)acetanilide (**2a**).—2-Bromobenzaldehyde (3.70 g, 20 mmol) was heated at reflux (6 h) with 2-acetylaminoaniline (3.0 g, 20 mmol) in ethanol (25 cm^3). As the solution cooled, yellow crystals formed and these were filtered off (3.42 g, 11 mmol, 54%), m.p. 137–139 °C (Found: C, 56.5; H, 4.2; Br, 25.5; N, 8.8. Calc. for $C_{15}H_{13}BrN_2O$: C, 56.7; H, 4.1; Br, 25.3; N, 8.8%); δ 2.14 (s, CH_3), 6.72–8.30 (m, 9 H), and 8.72 (s, 1 H).

2-(2-Cyanophenylmethyleneamino)acetanilide (**2b**).—Compound (**2a**) (0.65 g, 2 mmol), copper(I) cyanide (0.25 g, 2 mmol), and pyridine were heated together at reflux (5 h). The resulting dark solution was concentrated to yield a dark oil which was extracted with boiling methanol. The combined extracts (40

cm^3) yielded yellow needles on cooling (0.30 g, 1.15 mmol, 57%), m.p. 164 °C (Found: C, 72.4; H, 4.8; N, 15.6. Calc. for $C_{16}H_{13}N_3O$: C, 73.0; H, 4.9; N, 16.0%); ν_{max} 3 250m, 3 050w, 2 950w, 2 210m, 1 645s, 1 590m, 1 350ms, and 780s cm^{-1}; δ 2.05 (s, CH_3) and 6.57–8.70 (m, 10H).

2-(2-*Bromophenyliminomethyl*)*acetanilide* (**3**).—2-Bromoaniline (3.44 g, 20 mmol) was stirred with 2-acetylaminobenzaldehyde (3.26 g, 20 mmol) at 100 °C for 24 h. The resulting mixture was cooled to room temperature and diluted with diethyl ether (50 cm^3) to give a solid. This was filtered off, dried in the air, and recrystallised from methanol (1.50 g, 4.7 mmol, 24% yield), m.p. 145–147 °C (Found: C, 56.1; H, 3.9; Br, 25.1; N, 9.0. Calc. for $C_{15}H_{13}BrN_2O$: C, 56.7; H, 4.1; Br, 25.3; N, 8.8%; δ 2.03 (s, CH_3), 6.80–7.41 (m, 7 H), 8.21 (s, 1 H), 8.61–8.85 (m, 1 H), and 12.51 (br s, 1 H).

2-*Acetylamino*-2′-*bromostilbene* (**4**).—A solution of *trans*-2-bromo-2′-nitrostilbene (1.5 g, 4.9 mmol) in glacial acetic acid (100 cm^3) was heated to just below its reflux temperature, whilst zinc powder (9.6 g, 0.15 mmol) was added slowly in portions during 0.5 h. After this, the mixture was heated at reflux for 0.5 h and then allowed to cool to ambient temperature when precipitation occurred ($ZnSO_4$). The mixture was filtered and acetic anhydride (5.55 g, 54.4 mmol) added to the filtrate; the mixture was then refluxed for 0.5 h. The mixture was then poured onto water (100 cm^3) and the resulting tar was extracted with diethyl ether. The combined extracts were washed with water and then concentrated to yield a brown tar. This was purified by passage down a silica column, eluting with light petroleum (b.p. 60–80 °C)–chloroform (70:30). The slowest running fraction was collected and concentrated, and the residue recrystallised from methanol to afford white needles (0.46 g, 1.46 mmol, 30%), m.p. 183–184 °C (Found: C, 60.7; H, 4.3; Br, 24.0; N, 4.7. Calc. for $C_{16}H_{14}$ BrNO: C, 60.7; H, 4.4; Br, 25.3; N, 4.3%); ν_{max} 3 270m, 3 060w, 2 920w, 1 660s, 1 575m, 1 540m, 953m, 750m, and 728m cm^{-1}; δ 2.21 (s, CH_3), 7.13–7.60 (m, 11 H); *m/z*: 317–315 (16.8), 272 (44.3), 194 (100), 165 (47.3), 117 (19.6), and 43 (39.2). A similar procedure was used to prepare 2-*acetylamino*-2′-*bromo*-4,6′-*dimethylstilbene* (**5**) from 2-bromo-4,6-dimethyl-2′-nitrostilbene. Compound (**5**) forms white platelets, m.p. 137–138 °C (Found: C, 61.5; H, 5.2; Br, 23.0; N, 4.1. Calc. for $C_{18}H_{18}BrNO$: C, 62.8; H, 5.2; Br, 23.3; N, 4.1%); ν_{max} 3 270m, 3 020w, 2 965w, 1 650s, 1 600m, 1 295ms, 965m, and 745m cm^{-1}; δ 1.84 (s, $COCH_3$), 2.04 (s, CH_3), 2.20 (s, CH_3), and 6.30–7.62 (m, 6 H).

2-*Acetylaminophenyl* 2-*Bromobenzyl Ether* (**6a**).—2-(Acetylamino)phenol (15.1 g, 0.1 mol) was dissolved in ethanol (100 cm^3) containing sodium ethoxide (2.3 g sodium). A solution of 2-bromobenzyl bromide (25 g, 0.1 mol) in ethanol (50 cm^3) was added dropwise to this solution and then the mixture was heated at reflux (1 h). The hot mixture was filtered and the precipitate (NaBr) was washed with boiling ethanol. The filtrate and washings were combined and as they cooled gave a white crystalline solid (21.2 g, 67 mmol, 66.3%), m.p. 124–125 °C (Found: C, 56.9; H, 4.3; N, 4.2; Br, 25.6. Calc. for $C_{15}H_{14}BrNO_2$: C, 56.3; H, 4.4; Br, 25.0; N, 4.4%); δ 2.12 (s, CH_3), 5.14 (s, CH_2), 6.80–7.62 (m, 7 H), 7.64–8.00 (br s, NH), and 8.24–8.36 (t, 1 H).

2-*Acetylaminophenyl* 2-*bromo*-4-*nitrobenzyl Ether* (**6b**). A similar procedure gave this compound as white needles, m.p. 181–183 °C (Found: C, 48.8; H, 3.5; Br, 21.1; N, 7.5. Calc. for $C_{15}H_{13}BrN_2O_4$: C, 49.3; H, 3.6; Br, 21.9; N, 7.7%); ν_{max} 3 295br m, 3 100w, 2 925w, 1 660s, 1 600ms, 1 540s, 1 445m, 1 120m, 1 055m, 1 028ms, 805m, and 755ms cm^{-1}; δ 2.24 (s, CH_3), 5.22 (s, CH_2), 6.76–7.8 (m, 3 H), 7.20 (s, 1 H), and 7.42–8.33 (m, 4 H); *m/z* 366–364 (8.2), 171 (4.6), 150 (32.1), 108 (100), and 80 (20.4).

2-*Acetylaminophenyl* 2-*bromo*-4,6-*dimethylbenzyl ether* (**6c**). This compound was prepared by a method similar to that for (**6a**) as white needles, m.p. 132–135 °C (Found: C, 58.6; Br, 22.4; N, 4.2. Calc. for $C_{17}H_{18}BrNO_2$: C, 58.6; Br, 23.0; N, 4.0%); ν_{max} 3 420m, 2 960w, 1 698s, 1 605m, 1 540s, 1 450ms, 1 255ms, 1 115m, 1 000ms, 858m, and 760s cm^{-1}; δ 2.12 (s, CH_3), 2.32 (s, CH_3), 2.42 (s, CH_3), 5.16 (s, CH_2), and 6.80–8.30 (m, 7 H); *m/z* 349–347 (29.2), 303–301 (6.2), 268 (10.8), 199–197 (100), 155 (36.9), 153 (70.4), 119 (30.8), 118 (40), and 109 (19.2).

2-*Acetylaminophenyl* 2-*Bromobenzyl Sulphide* (**6d**).—This compound was prepared by acetylating 2-aminophenyl 2-bromobenzyl sulphide, itself prepared from a reaction between 2-aminothiophenol and 2-bromobenzyl bromide in the presence of sodium ethoxide. Compound (**6d**) was obtained as white crystals (85%), m.p. 73–74 °C (Found: C, 53.6; H, 4.2; N, 4.1; S, 10.3. Calc. for $C_{15}H_{14}BrNOS$: C, 53.6; H, 4.2; N, 4.2; S, 9.5%); δ 1.95 (s, CH_3), 3.86 (s, CH_2), 6.60–7.58 (m, 7 H), and 8.10–8.20 (br m, 2 H). The following compounds were similarly prepared.

2-*Acetylaminophenyl* 2-*bromo*-4-*nitrobenzyl sulphide* (**6e**). This compound was obtained as white needles, m.p. 103–104 °C (Found: C, 46.1; H, 3.3; N, 7.3; S, 8.6. Calc. for $C_{15}H_{13}BrN_2O_3S$: C, 47.2; H, 3.4; N, 7.3; S, 8.4%); δ 2.12 (s, CH_3), 4.06 (s, CH_2), and 6.80–8.32 (m, 8 H); *m/z* 382–380 (10), 149 (15), 134 (16), 124 (100), 89 (19.2), and 80 (20.8).

2-*Acetylaminophenyl* 2-*bromo*-4,6-*dimethylbenzyl sulphide* (**6f**). This compound was obtained as white crystals, m.p. 138–139 °C (Found: C, 56.2; H, 4.9; N, 4.1; S, 9.4. Calc. for $C_{17}H_{18}BrNOS$: C, 56.0; H, 5.0; N, 3.9; S, 8.8%); δ 2.06 (s, CH_3), 2.12 (s, CH_3), 2.24 (s, CH_3), 4.04 (s, CH_2), 6.8–7.56 (m, 5 H), and 8.20–8.48 (m, 2 H); *m/z* 364–362 (20), 199–197 (100), 153 (8.4), 118–116 (8.7), and 91 (6.9).

2-*Acetylamino*-N-(2-*bromobenzyl*)*aniline* (**6g**).—This was prepared from 2-(acetylamino)aniline, and obtained as a white powdery solid (66% yield), m.p. 163–165 °C (Found: C, 56.5; H, 4.8; Br, 26.6; N, 8.7. Calc. for $C_{15}H_{15}BrN_2O$: C, 56.4; H, 4.7; Br, 25.1; N, 8.8%); δ 2.18 (s, CH_3), 4.35 (s, CH_2), 4.52 (br s, NH), and 6.53–7.46 (m, 9 H); *m/z* 320–318 (41.9), 303–301 (18.6), 277–275 (23.3), 261–259 (7.0), 195 (16.3), 171–169 (20.9), 149 (15.1), 119 (25.6), 107 (100), and 80 (17.4). The following compounds were similarly prepared.

2-*Acetylamino*-N-(2-*bromo*-4-*nitrobenzyl*)*aniline* (**6h**). This compound was obtained as bright yellow platelets (62%), m.p. 197–200 °C (Found: C, 49.5; H, 3.8; Br, 21.6; N, 11.5. Calc. for $C_{15}H_{14}BrN_3O_3$: C, 49.4; H, 3.8; Br, 21.9; N, 11.5%); ν_{max} 3 430m, 3 050w, 1 660ms, 1 610m, 1 540s, 1 335s, 1 025m, and 740ms, cm^{-1}; δ 2.06 (s, CH_3), 4.54 (d, CH_2), 6.38–7.24 (m, 6 H), and 7.90–8.28 (m, 2 H); *m/z* 365–363 (57.3), 359–357 (80.0), 321–319 (29.3), 306–304 (50.7), 276–274 (46.7), 216–214 (32.0), 161 (49.3), 149 (17.3), 145 (29.3), 131 (13.3), 119 (88), 107 (90.7), 93 (36.0), 90 (85.3), and 80 (100).

2-*Acetylamino*-N-(2-*bromo*-4,6-*dimethyl*)*aniline* (**6i**). This was obtained as white needle-like crystals (12%) (Found: C, 58.8; H, 5.6; Br, 22.8; N, 8.4. Calc. for $C_{17}H_{19}BrN_2O$: C, 58.8; H, 5.5; Br, 23.0; N, 8.1%); ν_{max} 3 360wm, 3 050w, 2 950w, 1 650s, 1 610s, 1 515ms, 1 455ms, 850m, 805m, and 745s cm^{-1}; δ 2.12 (s, CH_3), 2.25 (s, CH_3), 2.38 (s, CH_3), 4.25 (d, CH_2), and 6.40–7.48 (m, 7 H).

2-*Acetylamino*-N-(2-*bromobenzyl*)*acetylaniline* (**7a**).—A solution of compound (**6g**) (3.19 g, 10 mmol) in acetonitrile (50 cm^3) was added to solution of $[Cu_3(CN)_4(NCMe)_4]$ in acetonitrile (50 cm^3) and the mixture was heated at reflux under dry, deoxygenated dinitrogen for 1 h. Water (100 cm^3) was then added and the resulting precipitate was filtered off. Ethanol extraction of the solid followed by reprecipitation with water produced a brown solid. This was refluxed in methanol and

the solution after being screened (Carbon DY 3) was cooled to produce a yellow solid (2.46 g, 6.8 mmol), m.p. 162–164 °C (Found: C, 56.3; H, 4.7; Br, 22.3; N, 7.7. Calc. for $C_{17}H_{17}BrN_2O_2$: C, 56.5; H, 4.7; Br, 22.2; N, 7.8%); δ 2.16 (s, CH_3), 2.36 (s, CH_3), 4.30 (q, CH_2), 6.58–7.10 (m, 8 H), and 7.36–7.48 (br s, NH) *m/z* 362–360 (10), 320–318 (36.2), 277–275 (20.6), 148 (12.6), 107 (100), and 80 (26.3).

2-*Acetylamino*-N-(2-*cyano*-4-*nitrobenzylidene*)*aniline* (**8b**).—Compound (**6h**) (3.64 g, 10 mmol) was stirred with copper(I) cyanide (1.97 g, 10 mmol) in *N*,*N*-dimethylformamide (25 cm^3) in a dry, deoxygenated dinitrogen atmosphere for 4 h, after which the mixture was poured onto ice–water (250 cm^3). The resulting precipitate was filtered off, dried in an oven at 80 °C, and then extracted with ethanol. The extract was screened with charcoal and on cooling gave a yellow precipitate; this was recrystallised from acetonitrile to give orange crystals of (**8b**) (0.86 g, 2.6 mmol, 29%), m.p. 226–230 °C (Found: C, 62.8; H, 3.6; N, 18.1. Calc. for $C_{16}H_{12}N_4O_3$: C, 62.3; H, 3.9; N, 18.2%); ν_{max} 3 290m, 3 095w, 2 210m, 1 680s, 1 595s, 1 520s, 1 342s, 1 294m, and 830m, cm^{-1}; δ 2.03 (s, CH_3), 6.84–8.36 (m, 8 H), and 9.24 (CH). The following was prepared in a similar manner.

2-*Acetylamino*-N-(2-*cyano*-4,6-*dimethylbenzylidene*)*aniline* (**8a**). This was obtained 25% yield from (**6i**) (Found: C, 73.3; H, 6.5; N, 14.2. Calc. for $C_{18}H_{19}N_3O$: C, 73.7; H, 6.5; N, 14.3%); δ 2.14 (s, CH_3), 2.28 (s, CH_3), 2.45 (s, CH_3), 6.82–8.23 (m, 8 H), 9.16 (s, CH).

2-*Methylamino*-N-(2-*bromobenzylidene*)*ethylamine* (**10a**).—This was obtained as a yellow liquid from the reaction between 2-bromobenzaldehyde and *N*-methyl-1,2-diaminoethane (Found: C, 49.5; H, 5.4; Br, 34.4; N, 11.7. Calc. for $C_{10}H_{13}BrN_2$: C, 49.8; H, 5.4; Br, 33.2; N, 11.6%); ν_{max}(film): 1 467s, 1 020s, and 752s cm^{-1}; δ 2.29 (s, CH_3), 2.45 (t, CH_2), 3.26 (t, CH_2), 4.41 (s, NH), and 7.02–7.72 (m, 5 H). Similarly prepared were the following.

2-*Methylamino*-N-(2-*bromo*-4,6-*dimethylbenzylidene*)*ethylamine* (**10b**) (Found: C, 54.1; H, 6.3; Br, 27.3; N, 10.5. Calc. for $C_{12}H_{17}BrN_2$: C, 53.5; H, 6.3; Br, 29.7; N, 10.4%; ν_{max}(film) 2 950s, 1 610s, 1 240m, 850s, and 800m cm^{-1}; δ 2.21 (s, CH_3), 2.42 (s, CH_3), 2.51 (s, CH_3), 3.26 (m, CH_2), 3.76 (m, CH_2), 6.92 (s, 1 H), 7.16 (1 H), and 8.46 (CH); *m/z* 270–268 (3), 254 (2), 228–226 (10), 146 (24), 132–130 (21), 105 (23), and 44 (100).

2-*Acetylamino*-N-(2-*bromobenzylidene*)*ethylamine* (**10c**).—This compound was obtained as a white crystalline solid from the reaction between 2-bromobenzaldehyde and N-acetyl-1,2-diaminoethane in refluxing ethanol (64%), m.p. 64–65 °C (Found: C, 48.9; H, 4.8; Br, 29.7; N, 10.4. Calc. for $C_{11}H_{13}BrN_2O$: C, 49.1; H, 4.8; Br, 29.7; N, 10.4%); ν_{max} 3 300m, 3 082w, 2 950w, 1 645s, 1 550s, 1 433ms, 1 300m, 1 105m, 1 028m, 952m, 748s, and 605m cm^{-1}; δ 2.01 (s, CH_3), 3.66 (m, 4 H, CH_2), 6.00 (s, NH), 7.17–7.94 (m, 4 H), and 8.53 (s, CH); *m/z* 270–268 (38), 211–209 (41), 198–196 (58), 182 (16), 172 (76), 169 (80), 130 (81), 117 (26), 87 (100), and 43 (78). A similar method was used to prepare the following.

2-*Acetylamino*-N-(2-*bromo*-4,6-*dimethylbenzylidene*)*ethylamine* (**10d**). This compound was obtained as a white crystalline solid, m.p. 109–110 °C (68%) (Found: C, 52.5; H, 5.8; Br, 26.9; N, 9.6. Calc. for $C_{13}H_{17}BrN_2O$: C, 52.5; H, 5.7; Br, 26.9; N, 9.4%); ν_{max} 3 295m, 3 090w, 2 922w, 1 635s, 1 550m, 1 115m, 845m, and 605w cm^{-1}; δ 2.02 (s, CH_3), 2.30 (s, CH_3), 2.43 (s, CH_3), 3.70 (m, 4 H, CH_2), 5.90 (br s, NH), 7.00 (s, ArH), 7.24 (s, ArH), and 8.44 (s, CH); *m/z* 298–296 (14), 236 (13), 224 (40), 210 (17), 144 (15), 130 (16), 115 (20), 87 (74), 72 (21), 43 (13), and 28 (100).

3-*Acetylamino*-N-(2-*bromobenzylidene*)*propylamine* (**10e**). M.p. 76–77 °C (76%) (Found: C, 50.3; H, 5.5; Br, 26.3; N, 10.0. Calc. for $C_{12}H_{15}BrN_2O$: C, 50.9; H, 5.3; Br, 28.3; N, 9.9%); ν_{max} 3 310m, 3 064w, 2 878m, 1 638s, 1 591m, 1 540m, 1 380m, 1 257m, 1 028m, 921m, 792w, 758s, and 600s cm^{-1}; δ 1.88 (t, CH_3), 1.95 (s, CH_3), 3.40 (q, CH_2), 3.68 (t, CH_2), 6.68 (br s, NH), 7.12–7.88 (m, 4 H), and 8.48 (s, CH); *m/z* 284–282 (2), 225–223 (37), 210 (72), 196 (21), 185 (26), 98 (40), 56 (39), and 44 (100).

4-*Acetylamino*-N-(2-*bromobenzylidene*)*butylamine* (**10f**). M.p. 51–53 °C (96%) (Found: C, 52.4; H, 5.9; Br, 27.7; N, 9.2. Calc. for $C_{13}H_{17}BrN_2O$: C, 52.5; H, 5.7; Br, 26.9; N, 9.4%); ν_{max} 3 290m, 3 080w, 2 938m, 1 640s, 1 592m, 1 565m, 1 375m, 1 212w, 1 022m, and 758s cm^{-1}; δ 1.44–1.92 (m, 4 H), 1.96 (s, CH_3), 3.26 (q, CH_2), 3.68 (m, 2 H), 6.24 (br s, NH), 7.08–7.95 (m, 4 H), and 8.52 (s, CH).

2-*Acetylamino*-N-(2-*bromo*-4,6-*dimethylbenzylidene*)*cyclohexylamine* (**10g**). M.p. 160–161 °C (23%) (Found: C, 58.3; H, 6.8; N, 8.2. Calc. for $C_{17}H_{23}BrN_2O$: C, 58.1; H, 6.6; N, 8.0%); ν_{max} 3 305m, 3 060w, 2 935m, 1 642s, 1 600w, 1 535m, 1 368m, 1 135m, and 845m cm^{-1}; δ 1.0–1.95 (m, 10 H), 2.13 (s, CH_3), 2.26 (s, CH_3), 6.70 (br s, NH), 7.15 (s, ArH), 7.26 (s, ArH), and 8.20 (s, CH).

N-(2-*Bromobenzylidene*)*cyclohexylamine* (**10h**). M.p. 36–37 °C (Found: C, 58.4; H, 6.2; Br, 29.2; N, 5.1. Calc. for $C_{13}H_{16}BrN$: C, 58.6; H, 6.0; Br, 30.1; N, 5.2%); ν_{max} 3 060w, 2 925, 2 850s, 1 632s, 1 561m, 1 450m, 1 112w, 1 020m, 850w, and 755s cm^{-1}; δ 0.80–2.24 (m, 10 H), 3.04–3.46 (m, 1 H), 7.00–8.00 (m, 4 H), and 8.54 (s, CH).

2-*Acetylamino*-N-(2-*cyanobenzylidene*)*ethylamine* (**11c**).—This compound was obtained when (**10c**) (1.40 g, 5.2 mmol) and copper(I) cyanide (0.46 g, 5.2 mmol) were heated together at reflux in pyridine (25 cm^3) for 3 h. The resulting dark solution was concentrated by evaporation under reduced pressure and then the resulting dark oil was extracted with boiling diethyl ether (6 × 50 cm^3). The ethereal extracts were concentrated (*ca.* 10 cm^3). The colourless solid product (0.16 g, 14%) was filtered off, m.p. 64–65 °C (Found: C, 66.4; H, 5.9; N, 19.2. Calc. for $C_{12}H_{13}N_3O$: C, 66.9; H, 6.0; N, 19.5%); ν_{max} 3 300m, 3 080m, 2 930w, 2 213m, 1 645s, 1 550m, 1 150m, 950m, 735m, and 608m cm^{-1}. A similar method was used to prepare the following compounds.

2-*Acetylamino*-N-(2-*cyano*-4,6-*dimethylbenzylidene*)*ethylamine* (**11d**), a white crystalline solid, m.p. 85 °C (decomp.) (53%) (Found: C, 69.2; H, 6.9; N, 17.5. Calc. for $C_{14}H_{17}N_3O$: C, 69.1; H, 7.0; N, 17.3%); ν_{max} 3 290m, 3 080w, 2 938w, 2 224m, 1 650s, 1 550m, and 768 cm^{-1}; δ 2.04 (s, CH_3), 2.28 (s, CH_3), 2.36 (s, CH_3), 2.50–3.74 (m, 4 H, CH_2), 6.32 (br s, NH), 7.00 (s, ArH), 7.24 (s, ArH), and 8.32 (s, CH); *m/z* 243 (18), 200 (16), 180 (21), 168 (33), 157 (20), 103 (15), 87 (48), 79 (91), 72 (22), 43 (62), 32 (56), and 28 (100).

3-*Acetylamino*-N-(2-*cyanobenzylidene*)*propylamine* (**11e**). A pale straw-yellow oil (24%) which was very air sensitive (Found: C, 68.3; H, 6.5; N, 18.5. Calc. for $C_{13}H_{15}N_3O$: C, 68.1; H, 6.6; N, 18.3%); ν_{max} 3 290m, 3 080m, 2 930m, 2 224m, 1 655s, 1 550ms, 1 440ms, 1 370m, 1 285m, and 705ms cm^{-1}; *m/z* 229 (2), 214 (8), 184 (11), 85 (76), and 83 (100).

4-*Acetylamino*-N-(2-*cyanobenzylidene*)*butylamine* (**11f**). A pale yellow solid (30%), m.p. 60–61 °C (Found: (C, 69.0; H, 6.9; N, 16.9. Calc. for $C_{14}H_{17}N_3O$: C, 69.1; H, 7.0; N, 17.3%); ν_{max} 3 280m, 3 065w, 2 922m, 2 220m, 1 650s, 1 600m, 1 435m, 1 284m, 980w, and 745m cm^{-1}; δ 1.72 (m, 4 H), 1.94 (s, CH_3), 3.26 (q, CH_2), 3.73 (t, CH_2), 5.86 (br s NH), 7.20–7.98 (m, 4 H), and 8.50 (s, CH).

2-*Acetylamino*-N-(2-*cyano*-4,6-*dimethylbenzylidene*)*cyclohexylamine* (**11g**). M.p. 120 °C (decomp.) (Found: C, 72.4; H, 7.5; N, 14.2. Calc. for $C_{18}H_{23}N_3O$: C, 72.7; H, 7.7; N, 14.1%); ν_{max} 3 265m, 3 085w, 2 930m, 2 225m, 1 645s, 1 605w, 1 472m, 1 442s, 1 070m, and 855 cm^{-1}; δ 0.64–2.10 (m, 10 H), 2.36 (s, CH_3), 2.50 (s, CH_3), 6.20 (br s, NH), 7.16 (s, ArH), 7.28 (s, ArH), and 8.56 (s, CH).

N-(2-*Cyanobenzylidene*)*cyclohexylamine*, (**11h**). M.p. 122–123 °C (Found: C, 79.1; H, 7.6; N, 13.1. Calc. for $C_{14}H_{16}N_2$: C, 79.2; H, 7.6; N, 13.2%); ν_{max} 3 070w, 2 915s, 2 224m, 1 680m, 1 610m, 1 445s, 1 215m, 1 070m, and 755s cm^{-1}; δ 0.64–2.16 (m, 10 H), 2.68 (m, 1 H), 7.17–8.08 (m, 4 H), and 8.52 (s, CH).

N,N′-*Bis*(2-*cyanobenzylidene*)*ethane*-1,2-*diamine* (**12c**).—Copper(I) cyanide (1 g, 10 mmol) and *N,N′*-bis(2-bromobenzylidene)-1,2-diaminoethane (2 g, 5 mmol) were heated at reflux in pyridine (20 cm^3) for 1 h. Concentration of the reaction mixture produced a viscous dark oil which was then extracted with diethyl ether. Concentration of the ethereal extract produced a yellow oil which was then boiled with ethanol to produce a white crystalline solid product (0.23 g, 16% yield), m.p. 94–96 °C (Found: C, 75.1; H, 4.7; N, 19.4. Calc. for $C_{18}H_{14}N_4$: C, 75.5; H, 4.9; N, 19.6%); ν_{max} 3 062w, 2 915w, 2 210m, 1 590m, 1 440s, 1 029m, 752s, and 670m cm^{-1}; δ 2.05 (m, CH_2), 7.16–8.08 (m, 4H), and 8.53 (s, CH); *m/z* 286 (5), 211 (4), and 158 (100).

N,N′-Bis(2-*cyano*-4,6-*dimethylbenzylidene*)*ethane*-1,2-*diamine* (**12d**). This was prepared by a similar procedure as a white solid (13%), m.p. 91–92 °C (Found: C, 76.9; H, 6.5; N, 16.6. Calc. for $C_{22}H_{22}N_4$: C, 77.2; H, 6.4; N, 16.4%); ν_{max} 3 040w, 2 925w, 2 862w, 2 224m, 1 645s, 1 610s, 1 375m, 1 288m, 862m, and 730 cm^{-1}; δ 2.34 (s, CH_3), 2.45 (s, CH_3), 4.06 (m, CH_2), 6.96 (s, ArH), 7.22 (s, ArH), and 8.60 (s, CH).

2(2-*Acetylaminophenyliminomethyl*)-3-*cyanobenzofuran* (**13c**).—This compound was a mustard-yellow crystalline solid, m.p. 191–192 °C, prepared (48%) from the corresponding 3-bromobenzofuran (Found: C, 71.4; H, 4.0; N, 13.9. Calc. for $C_{18}H_{13}N_3O_2$: C, 71.3; H, 4.3; N, 13.9%); ν_{max} 3 360m, 3 070w, 2 940w, 2 218m, 1 685s, 1 592s, 1 518s, 1 242m, 1 140w, 832w, 752s, and 605w cm^{-1}; δ 2.32 (s, CH_3), 6.92–7.88 (m, 7 H), 8.52 (s, 1 H), 8.64 (s, 1 H), and 8.94 (br s, NH).

All other compounds were characterised by microanalysis and by spectroscopic measurements which were in agreement with published values.

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