TLC (5% diethyl ether/hexane) R_f 0.22 (product), 0.04 (starting material reference); IR (neat) no OH, 1090 cm^{-1} (C–O); NMR (neat) 0.2–0.4 (m, 4, CH_2CH_2), 0.8–1.25 (m, 1, CH of cyclopropyl group), 3.08 (s, 3, CH_3), 3.59 (d, 1, J = 6 Hz, CHO), and 7.2 ppm (br s, 5, aromatic H).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.69. Found: C, 81.54; H, 8.76.

Treatment of Cyclopropylmethoxyphenylmethane (3) with Magnesium Iodide in Diethyl Ether. By use of the standard procedure 0.157 g (0.97 mmol) of ether **3** was treated with 0.640 g (2.3 mmol) of MgI_2 in diethyl ether. After 127 h at reflux, **3** was 70% converted into **2d** (1:24 Z/E by GC, retention times 15.9 and 16.6 min, 11.6 min for **3**). Workup afforded 0.243 g of a mixture of iodides **2d**, together with some **3** (by NMR).

Registry No. 1a, 930-39-2; **1b**, 765-42-4; **1c**, 2516-33-8; **1d**, 31729-66-5; **1e**, 4435-58-9; **2a** (X = Br), 2270-59-9; **2a** (X = Cl), 7712-60-9; **2a** (X = I), 43161-11-1; (*E*)-**2b** (X = I), 56399-98-5; (*Z*)-**2b** (X = I), 66688-64-0; (*E*)-**2b** (X = Br), 7515-62-0; (*Z*)-**2b** (X = Br), 50273-84-2; **2c** (X = I), 7766-51-0; (*E*)-**2d** (X = I), 56399-99-6; (*Z*)-**2d** (X = I), 73611-77-5; (*E*)-**2d** (X = Br), 7515-41-5; (*Z*)-**2d** (X = Br), 73611-78-6; (*E*)-**2d** (X = Cl), 7515-46-0; (*Z*)-**2d** (X = Cl), 35123-84-3; (*E*)-**2e** (X = Br), 51861-86-0; (*Z*)-**2e** (X = Br), 38351-81-4; (*E*)-**2e** (X = I), 56400-00-1; (*Z*)-**2e** (X = I), 56400-01-2; **3**, 5558-08-7; *cis*-**4**, 822-58-2; *trans*-**4**, 822-59-3; **5** (X = Br), 3540-84-9; **5** (X = I), 2566-56-5; **7**, 7432-49-7; **8** (X = Br), 73611-79-7; **8** (X = Cl), 32446-16-5; **8** (X = I), 62914-11-8; **9** (X = Br), 34825-93-9; **9** (X = Cl), 19509-49-0; **9** (X = I), 34825-94-0; magnesium iodide, 10377-58-9; magnesium bromide, 7789-48-2; 1-phenylethanol, 98-85-1; 1-phenyl-1-iodoethane, 10604-60-1.

Supplementary Material Available: Spectral and analytical data for the homoallylic halides **2a–e** shown in Table II. IR, NMR, and mass spectral data for **5** (X = Br, I), **8** (X = Br, I), and **9** (X = Br, I) (3 pages). Ordering information is given on any current masthead page.

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(25) Data obtained from a mixture of 8 and 9.

Alkyl Nitrite–Metal Halide Deamination Reactions. 7. Synthetic Coupling of Electrophilic Bromination with Substitutive Deamination for Selective Synthesis of Multiply Brominated Aromatic Compounds from Arylamines[1a]

Michael P. Doyle,* Michael A. Van Lente,[1b] Rex Mowat, and William F. Fobare

Department of Chemistry, Hope College, Holland, Michigan 49423

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Aromatic amines undergo oxidative substitution with copper(II) bromide that is in competition with substitutive deamination when these reactions are performed with *tert*-butyl nitrite. Except for the exceptionally reactive 4-substituted 1-aminonaphthalenes, which undergo selective bromine substitution at the 1- and 2-positions in relatively high isolated yields, rates for oxidative bromination and substitutive deamination are not sufficiently different that selective multiple bromination can be achieved. Oxidative bromination of *N*,*N*-dimethylaniline by copper(II) bromide occurs with partial dealkylation, and nitration products are observed from reactions performed with copper(II) bromide and *tert*-butyl nitrite. Implications of these results for the successful utilization of copper(II) bromide/*tert*-butyl nitrite combinations in substitutive deamination reactions of aromatic amines are discussed. Multiply brominated aromatic compounds are produced from aromatic amines in high yield through treatment of the aromatic amine with the combination of molecular bromine and catalytic quantities of copper(II) bromide and, following a normally brief time delay, with *tert*-butyl nitrite. All unsubstituted aromatic ring positions ortho and para to the amino group, as well as the position of the amino group, are substituted by bromine. The only observed byproducts from use of this procedure (usually ≤2% yield) are the partially brominated benzene derivatives.

We have recently reported that di- and tribromoarenes are formed as byproducts during nitrosative substitution reactions of arylamines with *tert*-butyl nitrite and copper(II) bromide in acetonitrile.[2] Although relatively low yields of these products were described, the uniqueness of this process in methodologies for the Sandmeyer reaction,[3,4] the observed orientation of bromine substitution ortho and/or para to the original position of the amino group, apparently independent of the activating influence of a spectrum of para-substituted ring substituents, and the potential suggested by these observations for directed multiple bromination of arylamines prompted this investigation.

The amino group has long been recognized for its pronounced directive influence in electrophilic halogenation reactions.[5] When electrophilic halogenation is coupled to the Sandmeyer reaction, directed multiple halogenation can be achieved (e.g., eq 1). However, such processes generally require a minimum of three sequential reactions and are subject to the experimental limitations of each reaction.[6] In this paper we report an efficient direct

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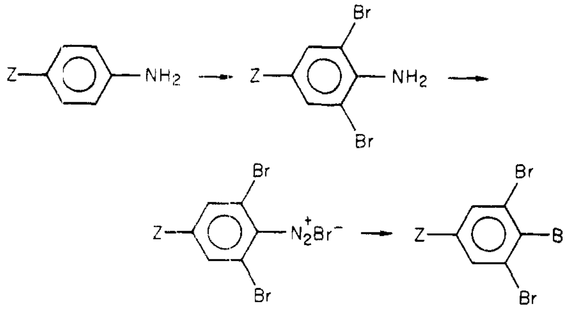


(1)

procedure that combines these reactions within one synthetic operation and affords multiply brominated aromatic compounds in nearly quantitative yields. The activity of copper(II) bromide in the oxidative bromination of arylamines is described, and the cause of the reported success of copper(II) halide/*tert*-butyl nitrite combinations in effecting substitutive deamination of arylamines[2] is explained.

Results and Discussion

Copper(II) Bromide/*tert*-Butyl Nitrite. Copper(II) halides are known to effect aromatic nuclear halogenation, particularly with compounds whose substituents strongly activate the aromatic ring toward electrophilic substitution (eq 2).[7] Chlorination of phenols by copper(II) chloride

$$ArH + 2CuX_2 \rightarrow ArX + 2CuX + HX \qquad (2)$$

occurs in both water and nonhydroxylic solvents[8] and, although relatively high temperatures are required for this transformation, the use of cupric chloride is attractive because of its orientation selectivity.[8a] Although similar in reactivity to phenols, anilines have received scant attention in their reactions with copper(II) halides. The ability of anilines to form complexes with copper(II) halides and, more importantly, their sensitivity to oxidation[9] have limited studies of effective halogenation of aromatic amines.

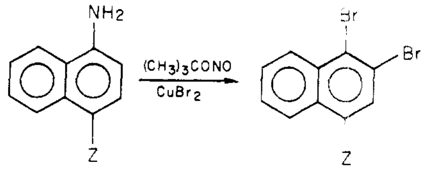
Prompted by consideration of the potential for selective bromination by copper(II) bromide under reaction conditions conducive to substitutive deamination, the reactions of representative substituted anilines with *tert*-butyl nitrite and variable amounts of $CuBr_2$ in acetonitrile were investigated. These reactions can be considered to operate in three sequential steps: oxidative bromination by $CuBr_2$, diazotization by *tert*-butyl nitrite, and substitutive denitrogenation catalyzed by copper(I) bromide[10] (eq 1). Since substitutive deamination terminates oxidative bromination, diazotization must occur at a slower rate than oxidative bromination in order to achieve multiple bromination. However, since copper(II) halides readily form stable complexes with anilines,[11] use of the additional amounts of $CuBr_2$ required for oxidative bromination might be expected to inhibit diazotization.

Table I. Aryl Halide Product Yields from Reactions of Aromatic Amines with *tert*-Butyl Nitrite and Copper(II) Bromide[a]

arylamine	$[CuBr_2]^b$ / $[ArNH_2]$	relative yield, %[c] Ar-Br	Ar-Br_2	Ar-Br_3	isolated yield, %
p-$NO_2C_6H_4$-NH_2	1.0	94	6	0	86
	3.0	51	47	2	95
p-ClC_6H_4-NH_2	1.0	80	16	4	82
	3.0	47	43	10	98
$C_6H_5NH_2$	1.0	39	54	7	59
	3.0	13	71	16	63
p-$CH_3C_6H_4$-NH_2	1.0	62	34	4	69
	3.0	29	46	25	98
4-$NO_2C_{10}H_6$-1-NH_2	1.0	33	67		92
	3.0	8	92		96
4-$ClC_{10}H_6$-1-NH_2	1.0	6	94		61
	3.0	0	100		83

[a] Reactions were performed by adding 10.0 mmol of the amine in acetonitrile to 15.0 mmol of *tert*-butyl nitrite and the indicated amount of copper(II) bromide in acetonitrile. Reaction temperature was 65 °C. [b] Reactions performed with a molar ratio of 2.0 gave product distributions and isolated yields that were intermediate to those recorded here for 1.0 and 3.0 molar equiv of copper(II) bromide. [c] Precision of analysis is ± 2% from duplicate runs.

Results from the reactions of representative aromatic amines with *tert*-butyl nitrite and both 1.0 and 3.0 molar equiv of $CuBr_2$ are given in Table I. Except for the exceptionally reactive 4-substituted 1-aminonaphthalenes, which undergo selective bromine substitution at the 1- and 2-positions (eq 3, Z = NO_2, Cl) in relatively high isolated



(3)

yields, rates for oxidative bromination and substitutive deamination are not sufficiently different that selective multiple bromination can be achieved. Furthermore, the reactivity of the reactant aniline toward oxidative bromination is comparable to that of the derivative monobromoaniline if activated positions on the aromatic ring remain available for substitution.[12] Thus, although high product recovery is generally observed, obviating the conclusion that oxidative dimerization and polymerization are not important competing reactions, the use of copper(II) bromide in combination with *tert*-butyl nitrite is not uniformly adaptable to the selective synthesis of multiply brominated aromatic compounds.

The consistently low yields of bromination products obtained from aniline in this study (Table I) are reminiscent of the similar low yields that were obtained with this amine in our earlier study of substitutive deamination with copper(II) halides and alkyl nitrites.[2] To investigate the cause of the yield disparity with substituted anilines, *N*,*N*-dimethylaniline was reacted with 2.0 molar equiv of $CuBr_2$ and with $CuBr_2$/*tert*-butyl nitrite under the same reaction conditions as were employed for the reactions reported in Table I. Surprisingly, in addition to the expected 4-bromo- and 2,4-dibromo derivatives of *N*,*N*-di-

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(6) In select cases the bromination of acetanilides by a mixture of hydrobromic acid and nitric acid results in the replacement of the acetamido group by bromine: Bell, F.; Buck, K. R. *J. Chem. Soc.* **1965**, 4601.

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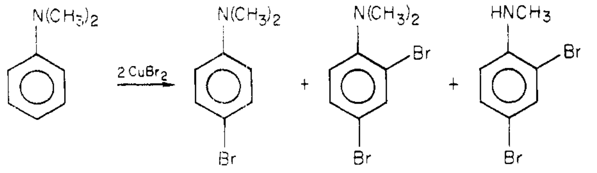
(12) Under the same reaction conditions but without *tert*-butyl nitrite, *p*-chloroaniline is converted to 2-bromo-4-chloroaniline in >95% yield when 2.0 molar equiv of $CuBr_2$ is employed. The absence of the dibromination product 2,6-dibromo-4-chloroaniline (<1%) contrasts with the data given in Table I ($ArBr_3$) and suggests that the $CuBr_2$/*tert*-butyl nitrite combination is a less selective reagent for oxidative bromination than is $CuBr_2$ alone.

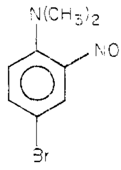
methylaniline, the reaction with $CuBr_2$ also yielded 2,4-dibromo-*N*-methylaniline (eq 4: **1**, 85%; **2**, 5%; **3**, 10%).



(4)

1 2 3

These same products were produced in the reaction of *N,N*-dimethylaniline with $CuBr_2$/*tert*-butyl nitrite (**1**, 53%; **2**, 16%; **3**, 6%), but in this latter reaction the nitration products **4**, **5**, and **6** were formed in 12%, 8%, and



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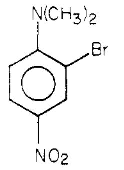

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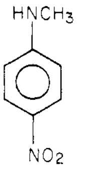

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5% yield, respectively. Dealkylation of *N,N*-dimethylaniline has been previously observed in the products from the complex reactions of this tertiary amine with copper(II) chloride in ethanol.[13] However, the observation of nitration products with the use of *tert*-butyl nitrite is unprecedented in prior limited investigations of the reactions of alkyl nitrites, but can be explained as occurring by initial *C*-nitrosation of the reactive aniline followed by oxidative conversion to the stable nitro derivative. *C*-Nitrosation would also account for the relatively low yield of bromo derivatives formed from aniline by the $CuBr_2$/*tert*-butyl nitrite combination; the observation of **5** and **6** indicates that *C*-nitrosation is competitive with oxidative bromination.

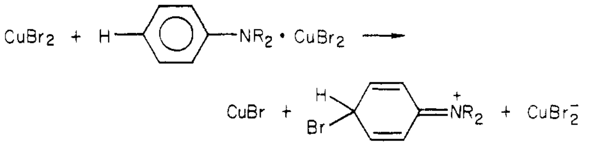
The results presented here allow us to provide further details relating to the mechanism and operation of substitutive deamination reactions of aromatic amines by alkyl nitrites and copper(II) halides. The effectiveness of copper(II) halides and the surprising ineffectiveness of copper(I) halides in promoting this process have been described.[2] The unique role of the copper(II) halides appears to be associated with their activity as Lewis acids in promoting nitrosation of the amine and with their effective utilization as the source of halogen in the product-forming step[10,14] (eq 5 and 6). The copper(I) halide catalyst for

$$ArNH_2 + CuX_2 + RONO \rightarrow ArN_2{}^+CuX_2(OH)^- + ROH \quad (5)$$

$$ArN_2{}^+CuX_2(OH)^- \xrightarrow{Cu^IX} ArX + N_2 + CuX(OH) \quad (6)$$

the substitutive denitrogenation steps in this mechanism can now be identified as arising, at least in part, from oxidative halogenation (eq 6). Although our current investigation has been restricted to reactions with the more reactive $CuBr_2$, oxidative chlorination has been previously observed to occur during substitutive deamination reactions performed with $CuCl_2$ and *tert*-butyl nitrite.[2] As has been indicated by prior results and demonstrated here, electron-donating substituents accelerate the relative rate for oxidative halogenation; however, lowering the reaction temperature from 65 to 0 °C[2] has only a minor effect on the relative rates for oxidative halogenation and substitutive deamination. *C*-Nitrosation at unsubstituted ortho or para positions of aromatic amines, particularly when excess alkyl nitrite is employed, is also a plausible competing reaction and, in the oxidative conversion of the *C*-nitroso to the *C*-nitro derivative,[15] can also serve as a generative source of copper(I) halide. Similar statements can be made for any of a growing number of processes that employ anhydrous copper(II) halides in substitutive deamination procedures[4b,16] and for the Meerwein arylation reaction in procedures that employ copper(II) halides and alkyl nitrites.[17]

The requirement of copper(II) bromide association with aromatic amines in order to accomplish oxidative bromination is suggested by the effect of bromide salts on the yields of aryl bromide reaction products in the multiple bromination procedure. For reactions performed with anhydrous $CuBr_2$, the addition of tetrabutylammonium bromide to the reaction solution has the same effect on the reaction products as does decreasing the molar amount of $CuBr_2$. Thus, for example, use of 2.0 molar equiv of tetrabutylammonium bromide with 3.0 molar equiv of $CuBr_2$ provides the same aryl bromide product distribution as if only 1.0 molar equiv of $CuBr_2$ had been employed. The total isolated yields of aryl bromides, however, are similar to those observed when 3.0 molar equiv of $CuBr_2$ is used (>93% from reactions with para-substituted anilines, Table I). Thus, for processes in which the product from substitutive deamination is desired, copper(II) tribromide salts can be effectively employed in order to inhibit oxidative bromination. The inhibition of oxidative bromination caused by formation of copper(II) tribromide salts suggests that oxidative bromination occurs through bromine transfer from copper(II) bromide to an aromatic ring position of a copper(II) bromide associated aniline (eq 7 and 8). A similar mechanistic understanding of the role



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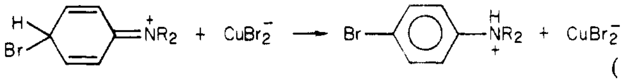

(8)

of copper(II) chloride in the chlorination of phenols and ketones has been presented.[8b]

Bromine/Copper(II) Bromide/*tert*-Butyl Nitrite. The combination of anhydrous copper(II) bromide and *tert*-butyl nitrite is of marginal effectiveness for selective oxidative bromination–substitutive deamination of aromatic amines because CuX_2 promotes *N*-nitrosation of aromatic amines at rates comparable to those for oxidative bromination. Although this drawback could be circumvented by procedural modifications in which the introduction of *tert*-butyl nitrite is delayed, the relatively high cost of $CuBr_2$ precludes its use for the synthesis of multiply brominated aromatic compounds. As an inexpensive alternative to copper(II) bromide, molecular bromine is well-known as an effective aromatic nuclear brominating agent, although numerous procedural modifications are employed in order to minimize oxidation and achieve se-

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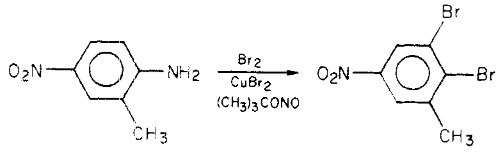
Table II. Synthesis of Multiply Brominated Aromatic Compounds from Arylamines[a]

arylamine	$[Br_2]$[b] / $[ArNH_2]$	time, min[c]	aryl bromide	isolated yield, %[d]
p-nitroaniline	4.1	30	1,2,3-tribromo-5-nitrobenzene	94
p-bromoaniline	3.9	15	1,2,3,5-tetrabromobenzene	99
p-chloroaniline	3.8	15	1,2,3-tribromo-5-chlorobenzene	86[e]
p-toluidine	3.7	30	3,4,5-tribromotoluene	99
p-anisidine[f]	3.6	180	3,4,5-tribromoanisole	67[g]
2,5-dichloroaniline	3.9	15	1,3,4-tribromo-2,5-dichlorobenzene	95[h]
3,4-dichloroaniline	3.9	30	1,2,3-tribromo-4,5-dichlorobenzene	92[i]
4-methyl-2-nitroaniline	2.7	30	3,4-dibromo-5-nitrotoluene	97
2-methyl-4-nitroaniline	2.5	30	2,3-dibromo-5-nitrotoluene	98
2-chloro-4-nitroaniline	2.6	30	1,2-dibromo-3-chloro-5-nitrobenzene	99

[a] Reactions were performed by adding the amine in acetonitrile to copper(II) bromide in anhydrous acetonitrile; *tert*-butyl nitrite was then added after the indicated time period. Unless indicated otherwise, reactions were performed at 50 °C. [b] A 25% molar excess of bromine was employed in order to compensate for bromination of the reaction solvent. [c] Time in minutes between the last addition of the amine and initiation of addition of *tert*-butyl nitrite. [d] Generally obtained as weight yield with purity analysis performed by NMR and/or GC analysis; unless indicated otherwise, the listed aryl bromide was the sole isolated product (≥99%). [e] Reaction performed without copper(II) bromide. [f] Reaction performed at 0 °C with heating at 45 °C following the introduction of *tert*-butyl nitrite. [g] 3,4-Dibromoanisole was also formed in 12% yield. [h] The dibromo product, assumed to be 1,4-dibromo-2,5-dichlorobenzene [^{1}H NMR ($CDCl_3$) δ 7.71 (s)], was formed in 2% yield. [i] The dibromo product, assumed to be 1,2-dibromo-4,5-dichlorobenzene [^{1}H NMR ($CDCl_3$) δ 7.71 (s)], was formed in 5% yield.

lectivity in reactions with aromatic amines.[5b] Bromine has also been employed for the direct replacement of the aromatic amino group through reactions of amine hydrobromides with dinitrogen trioxide; however, aromatic nuclear bromination does not readily occur in this procedure and product yields from substitutive deamination are markedly dependent on the nature of aromatic ring substituents.[18]

We have found that the combination of molecular bromine and catalytic quantities of copper(II) bromide can be directly employed for selective multiple bromination of aromatic amines and that substitutive deamination can be successfully coupled to the bromination reaction following a normally brief time delay in the addition of *tert*-butyl nitrite. This procedure provides direct and convenient entry to multiply brominated aromatic compounds which are generally produced in nearly quantitative yields (Table II). The advantage of using $CuBr_2$ in this procedure can be described through a comparison of product yields from reactions of 2-methyl-4-nitroaniline with bromine, *tert*-butyl nitrite, and variable amounts of anhydrous copper(II) bromide (eq 9): at constant initial concentrations of the reactant aniline, bromine, and *tert*-butyl nitrite, the yields of 7 at $[CuBr_2]/[ArNH_2]$ equals 0.20, 0.05, and 0.00 were 98, 87, and 79%, respectively. Reaction times for substitutive deamination, as measured by the extent of nitrogen evolution, increased markedly with decreasing concentrations of $CuBr_2$: from 20 min with 0.20 equiv of $CuBr_2$ to 4 h with 0.05 equiv of $CuBr_2$. Similarly, in the absence of $CuBr_2$, 4-methyl-2-nitroaniline yielded 3,4-dibromo-5-nitrotoluene in only 65% yield after a reaction time of 4 h. As only one product is usually observed to be formed from these reactions following acid extraction, we assume that the principal advantage of $CuBr_2$ is associated with the substitutive deamination process.



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(9)

When *tert*-butyl nitrite is added with the amine to the $Br_2/CuBr_2$ reaction solution, substitutive deamination competes with bromination and mixtures of brominated products are obtained. Therefore, the addition of *tert*-butyl nitrite must be delayed until bromination of the aniline is complete, and at 50 °C bromination is usually complete within 30 min. The only observed byproducts from use of this procedure are the partially brominated derivatives, indicative of incomplete bromination. Low product yields from the use of this procedure are generally due to incomplete substitutive deamination since product analysis following acid workup gives no evidence of products other than those that we have described in Table II.

Expectedly, multiple bromination of *p*-anisidine proved difficult to achieve in high yield. Treatment of *p*-anisidine at 50 °C with an equivalent amount of *tert*-butyl nitrite, 0.2 equiv of $CuBr_2$, and 2.5 equiv of bromine resulted in the production of *p*-bromoanisole (13%), 3,4-dibromoanisole (21%), and 3,4,5-tribromoanisole (21%).[19] However, pretreatment of *p*-anisidine with 3.6 molar equiv of bromine at 0 °C for 1.0 h followed by the addition of *tert*-butyl nitrite and warming to room temperature produced 3,4,5-tribromoanisole in 31% yield, but 3,4-dibromoanisole was also formed in relatively high yield (50%). Extending the time for bromination at 0 °C from 1.0 to 2.0 h provided a decrease in the yield of 3,4-dibromoanisole to 22% and markedly increased the yield of 3,4,5-tribromoanisole to 65%. Similarly, extending the time for bromination at 0 °C to 3.0 h and then heating the reaction solution with *tert*-butyl nitrite to 45 °C provided 3,4,5-tribromoanisole in 67% yield and 3,4-dibromoanisole in 12% yield. Several minor products were observed in these reaction mixtures and, although they were not separately isolated and identified, are presumed to be formed by oxidation, nitrosation, and/or bromination at positions ortho to the methoxy group of *p*-anisidine.[21] However, even with such a sensitive reactant, bromination–substi-

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(18) Newman, M. S.; Fones, W. S. *J. Am. Chem. Soc.* **1947**, *69*, 1221.

(19) 3,5-Dibromoanisole, the product of reductive deamination[20] of 2,6-dibromo-4-methoxyaniline, was formed as a minor product from reactions performed with less than the stoichiometrically required amount of bromine.

(20) Doyle, M. P.; Dellaria, J. F., Jr.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494.

(21) NMR accountability of methoxy units is greater than 95% for all reactions initiated at 0 °C. Absorptions observed at δ 7.8–8.2 are presumed to be derived from nitro derivatives.

Table III. ^{13}C NMR Chemical Shifts of Isomeric Bromobenzene Derivatives[a] (δ [b])

aryl bromide	C-1	C-2	C-3	C-4	C-5	C-6	CH_3
1,3,4-tribromo-2,5-dichlorobenzene[c]	122.0	135.0	128.0	126.3	134.4	132.6	
1,2,3-tribromo-4,5-dichlorobenzene[c]	123.7	127.7	128.1	133.9	133.0	132.7	
3,4-dibromo-5-nitrotoluene[d]	142.0	137.8	127.3	113.2	152.8	125.0	20.4
2,3-dibromo-5-nitrotoluene[d]	143.5	135.0	126.4	124.6	147.7	124.6	25.2

[a] Obtained from a Varian FT-80A spectrometer at 30 °C. [b] Relative to internal Me_4Si. [c] In $CDCl_3$. [d] In acetone-d_6.

tutive deamination is effective in producing multiply brominated products in relatively high yield.

Structural assignments for the previously unknown isomeric tribromodichlorobenzenes and dibromonitrotoluenes were based on ^{13}C NMR analyses (Table III) which provided definitive structural identification for the pentahalobenzenes that could not be obtained by more conventional methods. Chemical-shift assignments were made with the use of additive empirical parameters for substituted benzenes.[22] A surprisingly good correlation between observed and calculated chemical shifts was found to exist (generally ±1 ppm) except for the chlorine-substituted carbons of the pentahalobenzenes (−3 to −6 ppm from calculated values).

Experimental Section

Instrumentation. Proton magnetic resonance spectra were obtained with Varian Models A-60A and FT-80A spectrometers; ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer. Chemical shifts are reported in δ units, using tetramethylsilane as the internal standard. Infrared spectra were obtained on a Perkin-Elmer Model 621 grating spectrophotometer. Analytical gas chromatographic analyses were performed on a Varian Aerograph Model 2720 gas chromatograph with thermal-conductivity detectors; peak areas were determined with the use of a Hewlett-Packard Model 3380A integrator. Use was made of 5-ft columns of 10% DEGS on Chromosorb P and 20% SE-30 on Chromosorb W. A Finnigan Model 1015 GC/MS spectrometer operated at 70 eV was employed for mass spectral analyses. Melting points were obtained on a Thomas-Hoover apparatus and were uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Materials. Anhydrous cupric bromide was obtained commercially from PCR, Inc., and was stored in a desiccator prior to use. *tert*-Butyl nitrite was prepared from *tert*-butyl alcohol according to the procedure of Noyes.[23] Reagent-grade acetonitrile was distilled from calcium hydride prior to its use as a reaction solvent. The aromatic amines employed for this study were commercially available and, if necessary, were purified by distillation or recrystallization prior to use.

Reactions of Aromatic Amines with *tert*-Butyl Nitrite and Copper(II) Bromide. General Procedure. In the procedure employed for the reactions reported in Table I, anhydrous copper(II) bromide (10.0, 20.0, and 30.0 mmol), *tert*-butyl nitrite (15 mmol), and anhydrous acetonitrile (50 mL) were added to a three-necked round-bottom flask that was equipped with a reflux condenser, addition funnel, and a gas outlet tube. The resulting rapidly stirred mixture was heated at 65 °C, and the amine (10.0 mmol) dissolved in 15 mL of acetonitrile (or 25 mL in the case of *p*-nitroaniline) was then slowly added over a period of 5 min to the reaction solution. Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret; the yield of gaseous products reflected the isolated yield of aryl bromide products (±15%). Gas evolution was usually complete within 10 min following the addition of the amine, and reaction times extended beyond this period did not lead to measurable increases in product yields. After complete gas evolution, the reaction solution was cooled and then poured into 200 mL of 20% aqueous sodium hydroxide. The resulting solution was extracted with 200 mL of ether, the organic layer was washed once with 200 mL of 20% aqueous sodium hydroxide containing 10% ethylenediamine, and, after drying the ether solution over anhydrous magnesium sulfate, ether was removed under reduced pressure.

Structural assignments for the aryl halides produced in reactions of arylamines with alkyl nitrites and copper(II) bromide were made on the reaction mixtures through ^{1}H NMR spectral comparisons and by GC retention time and peak enhancement with authentic samples.[2] Product yields were determined by GC analyses. Prior to workup a weighed amount of dibenzyl ether was added to the reaction mixture as an internal standard. The average integrated area ratios from at least two GC traces were employed in each yield determination. Absolute yields were calculated with the use of experimentally determined relative thermal-conductivity ratios for each of the aryl halides examined by this method.

Oxidative Bromination of *N*,*N*-Dimethylaniline. Reactions were performed as previously described by adding 5.0 mmol of *N*,*N*-dimethylaniline in 10 mL of acetonitrile to an acetonitrile solution (40 mL) containing 10.0 mmol of copper(II) bromide and, in alternate reactions, 6.0 mmol of *tert*-butyl nitrite that was heated at 60 °C. After 2.0 h at this temperature, the reaction mixture was cooled and then added to 200 mL of ether. The ether solution was washed twice with 100-mL portions of 20% aqueous sodium hydroxide, once with 100 mL of 2% aqueous ethylenediamine, and once with 100 mL of water. The resulting organic layer was dried over anhydrous magnesium sulfate, and the ether was then removed under reduced pressure. GC (20% SE-30 column) and NMR analyses of the reaction mixtures relative to an internal standard, 1,2-dibromoethane, were employed to determine the yields of individual products from reactions with $CuBr_2$ (92% total yield) and with $CuBr_2$/*tert*-butyl nitrite (86% total yield). Duplicate reactions confirmed the reported results. Individual products were separated by GC and identified by spectral analyses.

***p*-Bromo-*N*,*N*-dimethylaniline (1):** ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J_o = 9.0 Hz, 2 H), 6.59 (d, J_o = 9.0 Hz, 2 H), 2.91 (s, 6 H); mass spectrum, *m/e* (relative intensity) 202 (9, M + 3), 201 (85, M + 2), 200 (87, M + 1), 199 (86, M), 198 (85, M − 1), 187 (11), 186 (12), 185 (24), 184 (21), 183 (13), 182 (9), 157 (10), 155 (10), 118 (45).

2,4-Dibromo-*N*,*N*-dimethylaniline (2): ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J_m = 2.2 Hz, H-3), 7.36 (d of d, J_o = 8.6 Hz, J_m = 2.2 Hz, H-5), 6.96 (d, J_o = 8.6 Hz, H-6), 2.78 (s, 6 H); mass spectrum, *m/e* (relative intensity) 281 (56, M + 4), 280 (64, M + 3), 279 (100, M + 2), 278 (62, M + 1), 277 (56, M), 276 (28, M − 1), 198 (19), 197 (33), 196 (21), 195 (27), 184 (22), 183 (29), 182 (30), 181 (29), 156 (20), 154 (23).

2,4-Dibromo-*N*-methylaniline (3): ^{1}H NMR δ 7.53 (d, J_m = 2.2 Hz, H-3), 7.30 (d of d, J_o = 8.6 Hz, J_m = 2.2 Hz, H-5), 6.48 (d, J_o = 8.6 Hz, H-6), 2.91 (s, 3 H); mass spectrum, *m/e* (relative intensity) 267 (25, M + 4), 266 (25, M + 3), 265 (50, M + 2), 264 (37, M + 1), 263 (28, M), 262 (25, M − 1), 249 (8), 247 (7), 105 (29), 104 (48), 93 (25), 92 (27), 91 (22), 90 (27).

4-Bromo-2-nitro-*N*,*N*-dimethylaniline (4): ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J_m = 2.4 Hz, H-3), 7.47 (d of d, J_o = 9.0 Hz, J_m = 2.4 Hz, H-5), 6.90 (d, J_o = 9.0 Hz, H-6), 2.88 (s, 6H); mass spectrum *m/e* (relative intensity) 246 (22, M + 2), 244 (20, M), 229 (26), 227 (27), 200 (13), 198 (28), 196 (18), 184 (28), 183 (27), 182 (26), 181 (25), 170 (43), 168 (44), 119 (23), 118 (58), 117 (25).[24]

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(22) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: Philadelphia, 1978; p 47.

(23) Noyes, W. A. "Organic Syntheses", Collect. Vol. II; Wiley: New York, 1943; p 108.

(24) The relatively low chemical shift for the hydrogen absorption that is ortho to the nitro group (H-3), suggesting that the nitro group is not planar with the benzene ring, and the unique mass-spectral fragmentation of this compound substantiate the structure assignment.

2-Bromo-4-nitro-*N*,*N*-dimethylaniline (5): ^{1}H NMR (CDCl$_3$) δ 8.43 (d, J_m = 2.6 Hz, H-3), 8.11 (d of d, J_o = 9.1 Hz, J_m = 2.6 Hz, H-5), 6.99 (d, J_o = 9.1 Hz, H-6), 2.98 (s, 6H); mass spectrum *m/e* (relative intensity) 246 (83, M + 2), 245 (78, M + 1), 244 (83, M), 243 (72, M − 1), 232 (7), 230 (7), 216 (9), 214 (18), 212 (8), 199 (31), 197 (28), 185 (14), 184 (8), 183 (12), 182 (6), 165 (22), 119 (61), 118 (83), 117 (17).

***p*-Nitro-*N*-methylaniline (6)**: ^{1}H NMR (CDCl$_3$) δ 8.13 (d, J_o = 9.4 Hz, 2 H), 6.60 (d, J_o = 9.4 Hz, 2 H), 3.11 (s, 3 H).

Reactions of Aromatic Amines with Bromine and *tert*-Butyl Nitrite in the Presence of Copper(II) Bromide. General Procedure. In the procedure employed for the reactions described in Table II, anhydrous copper(II) bromide (2.0 mmol) was added to 40 mL of acetonitrile in a round-bottom flask that was fitted with a reflux condenser, addition funnel, and a gas outlet tube. The resulting solution was heated to 50 °C and, after 5 min at that temperature, the measured amount of bromine dissolved in 10 mL of acetonitrile was added directly to the reaction solution followed by the amine (10.0 mmol) in a minimum volume of the reaction solvent. After the indicated reaction period, *tert*-butyl nitrite (12.0 mmol) in 20 mL of acetonitrile was added dropwise to the reaction solution over a 15-min period. Heating was continued at 50 °C until a quantitative yield of evolved nitrogen was measured, normally less than 30 min.

Bromination of *p*-anisidine was performed at 0 °C with an optimum reaction time of 3 h. *tert*-Butyl nitrite was then added and the reaction solution was allowed to warm to room temperature. The reaction solution was maintained at 25 °C or heated at 45 °C until a limiting volume of nitrogen was measured.

After the normally dark brown reaction solution was cooled to room temperature, saturated aqueous sodium sulfite was added in sufficient quantity to reduce excess bromine, as indicated by the immediate and distinct lightening in the color of the reaction solution. The resulting solution was then poured into 200 mL of 3 M hydrochloric acid and extracted with 200 mL of ether. The aqueous layer was washed with 100 mL of ether, and the combined ether solution was washed with 100 mL of 3 M hydrochloric acid. After the organic layer was dried over anhydrous magnesium sulfate, ether was removed under reduced pressure.

Product yields were determined as weight yields of the isolated product and also through NMR analyses relative to an internal standard, dibenzyl ether, which was introduced into the reaction solution prior to extraction with acid and ether. GC analyses were employed to determine product purity. If obtained as a mixture or required for analysis, reaction products were purified by recrystallization or obtained by GC collection for structural identification.

1,2,3-Tribromo-5-nitrobenzene: ^{1}H NMR (CDCl$_3$) δ 8.41 (s); mp 107–109 °C without recrystallization (lit.[25] mp 111.9 °C).

1,2,3,5-Tetrabromobenzene: ^{1}H NMR (CDCl$_3$) δ 7.72 (s); mp 95–97 °C without recrystallization (lit.[26] mp 98 °C).

1,2,3-Tribromo-5-chlorobenzene: ^{1}H NMR (CDCl$_3$) δ 7.60 (s); mp 97–99 °C without recrystallization (lit.[6] mp 98–100 °C).

3,4,5-Tribromotoluene: ^{1}H NMR (CDCl$_3$) δ 7.39 (s, 2 H), 2.26 (s, 3 H); mp 85–89 °C without recrystallization (lit.[27] mp 90.5–91.5 °C).

3,4,5-Tribromoanisole: ^{1}H NMR (CDCl$_3$) δ 7.15 (s, 2 H), 3.77 (s, 3 H). Spectral data for 3,4-dibromoanisole has been previously presented.[2]

3,5-Dibromoanisole: ^{1}H NMR (CDCl$_3$) δ 7.24 (t, J_m = 1.6 Hz, 1 H), 6.99 (d, J_m = 1.6 Hz, 2 H), 3.78 (s, 3 H).

1,3,4-Tribromo-2,5-dichlorobenzene: ^{1}H NMR (CDCl$_3$) δ 7.76 (s); IR (KBr) 3095 (m), 3050 (w), 1510 (m), 1426 (m), 1380 (s), 1307 (s), 1196 (m), 1165 (s), 1050 (s), 1040 (m), 865 (s), 760 (m), 625 cm^{-1} (m); mass spectrum, *m/e* (relative intensity) 391 (3, M + 10), 389 (16, M + 8), 387 (59, M + 6), 385 (96, M + 4), 383 (73, M + 2), 381 (23, M), 310 (1), 308 (8), 306 (21), 304 (32), 302 (12), 273 (0.4), 271 (3), 269 (3), 267 (2), 229 (4), 227 (16), 225 (40), 223 (25), 146 (17), 144 (24), 111 (32), 109 (96), 73 (100); mp 128.0–128.2 °C.

Anal. Calcd for $C_6HBr_3Cl_2$: C, 18.78; H, 0.26; Br, 62.48; Cl, 18.48. Found: C, 18,80; H, 0.28; Br, 62.09; Cl, 18.44.

1,2,3-Tribromo-4,5-dichlorobenzene: ^{1}H NMR (CDCl$_3$) δ 7.76 (s); IR (KBr) 3090 (w), 3050 (w), 1510 (m), 1430 (w), 1380 (s), 1305 (s), 1200 (m), 1174 (s), 1168 (s), 1051 (s), 1042 (m), 865 (s), 761 (m), 620 cm^{-1} (m); mass spectrum, *m/e* (relative intensity) 391 (2, M + 10), 389 (11, M + 8), 387 (34, M + 6), 385 (56, M + 4), 383 (45, M + 2), 381 (14, M), 310 (1), 308 (7), 306 (17), 304 (26), 302 (9), 273 (0.3), 271 (2), 269 (3), 267 (2), 229 (3), 227 (14), 225 (30), 223 (19), 146 (18), 144 (26), 111 (34), 109 (89), 73 (100); mp 130.9 °C.

Anal. Calcd for $C_6HBr_3Cl_2$: C, 18.78; H, 0.26; Br, 62.48; Cl, 18.48. Found: C, 18.50; H, 0.21; Br, 62.04; Cl, 18.53.

3,4-Dibromo-5-nitrotoluene: ^{1}H NMR (CDCl$_3$) δ 7.66 (J_m = 2.5 Hz, 1 H), 7.43 (J_m = 2.5 Hz, 1 H), 2.37 (s, 3 H); IR (KBr) 3064 (m), 2927 (m), 2882 (w), 1590 (m), 1517 (s), 1437 (s), 1352 (s), 1266 (s), 1228 (w), 1200 (m), 1138 (m), 1030 (s), 934 (s), 896 (w), 854 (s), 838 (m), 742 (w), 722 (s), 692 cm^{-1} (m); yellow prisms; mp 63.6–65.0 °C.

Anal. Calcd for $C_7H_5Br_2NO_2$: C, 28.51; H, 1.71; Br, 54.19. Found: C, 28.70; H, 1.77; Br, 54.35.

2,3-Dibromo-5-nitrotoluene: ^{1}H NMR (CDCl$_3$) δ 8.31 (J_m = 2.6 Hz, 1 H), 8.03 (J_m = 2.6 Hz, 1 H), 2.59 (s, 3 H); IR (KBr) 3080 (m), 2928 (w), 2850 (w), 1590 (w), 1500 (s), 1450 (w), 1435 (w), 1382 (w), 1340 (s), 1280 (w), 1228 (w), 1170 (w), 1038 (s), 938 (m), 891 (s), 836 (m), 750 (m), 738 (m), 685 cm^{-1} (w); light yellow needles; mp 106.4 °C.

Anal. Calcd for $C_7H_5Br_2NO_2$: C, 28.51; H, 1.71; Br, 54.19. Found: C, 28.42; H, 1.87; Br, 54.09.

1,2-Dibromo-3-chloro-5-nitrotoluene: ^{1}H NMR (CDCl$_3$) δ 8.39 (J_m = 2.6 Hz), 8.27 (J_m = 2.6 Hz); mp 98–100 °C without recrystallization (lit.[25] mp 99.5 °C).

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Registry No. **1**, 586-77-6; **2**, 64230-27-9; **3**, 73557-58-1; **4**, 829-02-7; **5**, 64230-23-5; **6**, 100-15-2; *p*-nitroaniline, 100-01-6; *p*-bromoaniline, 106-40-1; *p*-chloroaniline, 106-47-8; *p*-toluidine, 106-49-0; *p*-anisidine, 104-94-9; 2,5-dichloroaniline, 95-82-9; 3,4-dichloroaniline, 95-76-1; 4-methyl-2-nitroaniline, 89-62-3; 2-methyl-4-nitroaniline, 99-52-5; 2-chloro-4-nitroaniline, 121-87-9; 1,2,3-tribromo-5-nitrobenzene, 3460-20-6; 1,2,3,5-tetrabromobenzene, 636-28-2; 1,2,3-tribromo-5-chlorobenzene, 3460-25-1; 3,4,5-tribromotoluene, 73557-59-2; 3,4,5-tribromoanisole, 73557-60-5; 1,3,4-tribromo-2,5-dichlorobenzene, 73557-61-6; 1,2,3-tribromo-4,5-dichlorobenzene, 73557-62-7; 3,4-dibromo-5-nitrotoluene, 73557-63-8; 2,3-dibromo-5-nitrotoluene, 73557-64-9; 1,2-dibromo-3-chloro-5-nitrobenzene, 73557-65-0; 3,4-dibromoanisole, 62415-74-1; 1,4-dibromo-2,5-dichlorobenzene, 4571-24-8; 1,2-dibromo-4,5-dichlorobenzene, 73557-66-1; aniline, 62-53-3; 1-amino-4-nitronaphthalene, 776-34-1; 1-amino-4-chloronaphthalene, 4684-12-2; 2-bromo-4-nitroaniline, 13296-94-1; 2,6-dibromo-4-nitroaniline, 827-94-1; 2-bromo-4-chloroaniline, 873-38-1; 2,6-dibromo-4-chloroaniline, 874-17-9; 2-bromoaniline, 615-36-1; 2,6-dibromoaniline, 608-30-0; 1,2,3-tribromobenzene, 608-21-9; 2-bromo-4-methylaniline, 583-68-6; 2,6-dibromo-4-methylaniline, 6968-24-7; 1,2,3-tribromo-5-methylbenzene, 73557-59-2; 1-amino-2-bromo-4-nitronaphthalene, 63240-26-6; 1,2-dibromo-4-nitronaphthalene, 73557-67-2; 1-amino-2-bromo-4-chloronaphthalene, 73557-68-3; 1,2-dibromo-4-chloronaphthalene, 73557-69-4.

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