Alkyl Nitrite–Metal Halide Deamination Reactions. 2. Substitutive Deamination of Arylamines by Alkyl Nitrites and Copper(II) Halides. A Direct and Remarkably Efficient Conversion of Arylamines to Aryl Halides[1]

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Alkyl nitrites and anhydrous copper(II) halides rapidly convert arylamines into aryl chlorides and bromides in high yield. One molar equivalent of alkyl nitrite and 0.5 molar equiv of copper(II) chloride or bromide are required for this direct substitutive deamination reaction, which results in the production of cupric oxide, nitrogen, and alcohol as well as aryl halide. Reactions of copper(II) halides and *tert*-butyl nitrite in acetonitrile with 15 representative arylamines are reported; results from this study exemplify the synthetic advantages of the direct substitution process and demonstrate the absence of side products that usually accompany similar syntheses using copper(I) halides and arenediazonium salts. A comparison of products and product yields from reactions of *tert*-butyl nitrite and aniline with copper(II) chloride and copper(I) chloride is presented; the unique role of copper(II) halides in substitutive deamination reactions with arylamines is indicated by these data. In reactions of arylamines with copper(II) bromide and *tert*-butyl nitrite a unique process that involves substitution of bromide at aromatic ring positions that are ortho or para to the original amine position competes with substitutive deamination. With arylamines that possess para substituents, orientation of bromine to the ortho position is the sole result of this competing deaminative pathway. The products from this competing process are identified and the extent of their formation is described.

The synthesis of aryl halides from arylamines by the conventional Sandmeyer procedure[3,4] involves initial diazotization of the arylamine followed by addition of the diazonium salt to the cuprous halide in an aqueous solution with the corresponding halogen acid. Although satisfactory yields of aryl halides are usually obtained, the Sandmeyer reaction (eq 1) is complicated by numerous competing reactions (eq 2–5). To minimize these side reactions prescribed procedures for the performance of the Sandmeyer reaction have been designed.

$$\mathrm{ArN_2{}^+CuX_2{}^-} \rightarrow \mathrm{ArX + N_2 + CuX} \qquad (1)$$

$$\mathrm{2ArN_2{}^+CuX_2{}^-} \rightarrow \mathrm{ArAr + 2N_2 + 2CuX_2} \qquad (2)$$

$$\mathrm{2ArN_2{}^+CuX_2{}^-} \rightarrow \mathrm{ArN{=}NAr + N_2 + 2CuX_2} \qquad (3)$$

$$\mathrm{ArN_2{}^+X^- + H_2O} \rightarrow \mathrm{ArOH + N_2 + HX} \qquad (4)$$

$$\mathrm{ArN_2{}^+X^- + SolH} \rightarrow \mathrm{ArH + N_2 + SolX} \qquad (5)$$

Since the rates of formation of biaryl and azo compounds (eq 2, 3) depend on the square of the concentration of cuprous halide[5] and the rate of aryl halide production (eq 1) is inversely proportional to the square of the chloride ion concentration,[5] the optimum conditions for the conventional Sandmeyer reaction in aqueous halogen acid appear to require equimolar amounts of copper halide and arenediazonium salt.[3] However, effective control of competing processes transcends modification of the reaction stoichiometry. The mode of addition, the reaction temperature, and the nature of the diazonium salt are also prime determinants of the yield of aryl halide. For example, when the normal addition step is reversed and a dilute acid solution of cuprous halide is added to the diazonium salt, biaryl formation effectively competes with the production of aryl halide.[3a,6] With reactive diazonium salts reaction temperatures above 10 °C generally promote phenol formation in aqueous media (eq 4);[3] subsequent coupling of the phenol with undecomposed diazonium salt produces azophenols. In addition, reduction of the diazonium compound to the corresponding arene (eq 5) often competes with aryl halide formation,[7] particularly when the Sandmeyer reaction is performed in aqueous acetone or alcohol.[8]

Numerous variations of the conventional Sandmeyer reaction have been introduced to improve the yields of substitution products. Cuprous salts have been replaced by finely divided copper metal (the Gatterman method),[9] by copper(II) salts,[10] or by iron(III), cobalt(III), and zinc(II) salts,[3a] and examples have been reported in which these replacements have resulted in comparable or improved yields of Sandmeyer products.[3] Nitrosyl complexes of anhydrous copper(II) halides have recently been reported to effect a direct conversion of arylamines to aryl halides, presumably through an intermediate diazonium dihalocuprate salt (eq 6).[11]

$$\mathrm{ArNH_2 + CuX_2\cdot NO} \xrightarrow[(-\mathrm{H_2O})]{} [\mathrm{ArN_2{}^+CuX_2{}^-}] \rightarrow \mathrm{ArX + N_2 + CuX} \qquad (6)$$

A similar direct replacement of the aromatic amino group by bromine through reactions of amine hydrobromides with dinitrogen trioxide, but without an added metal catalyst, has also been reported.[14] Although there are specific advantages to each of these methods, none of the variations has received wide application, and the preferred method for the synthesis of aryl halides from arylamines remains the conventional Sandmeyer procedure.

The recent successful uses of alkyl nitrites as nitrosating agents for alkyl-[16] and arylamines,[17] and our own observation of oxidative deamination of primary aliphatic amines by the combination of alkyl nitrites and anhydrous copper(II) halides,[18] prompted us to investigate the reactions of aromatic amines with alkyl nitrites in the presence of anhydrous copper(II) salts. In this paper we report the direct synthesis of aryl halides from arylamines by substitutive deamination.

Results

Treatment of arylamines with *tert*-butyl nitrite and anhydrous cupric halides (X = Cl, Br) in acetonitrile at 65 °C results in the rapid and quantitative evolution of nitrogen and in the formation of aryl halides, cupric oxide, and *tert*-butyl alcohol (eq 7).[19]

$$\mathrm{2ArNH_2 + 2RONO + CuX_2} \rightarrow \mathrm{2ArX + 2ROH + CuO + H_2O + 2N_2} \qquad (7)$$

The stoichiometry of this reaction, which was determined from experiments in which the molar ratios of both *tert*-butyl

Table I. Variation of Product Yields with the Molar Ratio of $CuCl_2$ to *p*-Nitroaniline in Reactions with *tert*-Butyl Nitrite at 65 °C [a]

$[CuCl_2]/$ $[p\text{-}NO_2C_6H_4NH_2]$	Relative yield, %		Isolated yield, %
	$p\text{-}NO_2C_6H_4Cl$	$C_6H_5NO_2$	
2.0	100	0	99.5
1.0	>99.9	<0.1	90
0.50	98	2	86
0.26	85[b]	15	62

[a] Reactions were performed in acetonitrile using 10 mmol of *p*-nitroaniline and 15 mmol of *tert*-butyl nitrite. [b] A 53% isolated yield of *p*-nitrochlorobenzene was obtained which quantitatively accounts for the fate of the reactant chloride.

nitrite and cupric halide to arylamine were varied independently, requires 1 molar equiv of *tert*-butyl nitrite for complete reaction but necessitates the use of only sufficient cupric halide to quantitatively produce cupric oxide and aryl halide. The stoichiometric dependence of the yield of reaction products on cupric chloride is described by the data in Table I for the deamination of *p*-nitroaniline. There is a remarkable efficiency for halide utilization in this substitutive deamination procedure.

The major process competing with aryl halide formation when the molar ratio of CuX_2 to amine is equal to or less than 0.5 (Table I) is reduction of the arylamine to the corresponding arene. In the absence of copper(II) halide reaction of *tert*-butyl nitrite with *p*-nitroaniline in acetonitrile at 65 °C results in the formation of nitrobenzene in 40% yield;[20] cupric oxide has no measurable product orienting effect on this reduction process. Reaction times for complete evolution of nitrogen increase with decreasing CuX_2:$ArNH_2$ molar ratios. For example, with *p*-nitroaniline at 65 °C gas evolution is complete within 10 min when 1.0 molar equiv of $CuCl_2$ is employed, but requires nearly 30 min for complete nitrogen evolution when 0.5 equiv of the same cupric halide is used. Reduction of *p*-nitroaniline under the same reaction conditions, but in the absence of copper salts, requires reaction times comparable to those necessitated by the use of less than 0.5 molar equiv of $CuCl_2$. Thus reduction appears to be independent of substitutive deamination and is effectively minimized by the use of sufficient copper(II) halide so that the CuX_2:$ArNH_2$ molar ratio is greater than 0.5.

Copper(II) oxide was identified as the sole copper-containing product from reactions that employed less than a stoichiometric equivalent of cupric halide based on eq 7. The nature of the reaction products and the yields of these products did not depend on the presence or absence of air. For example, when the substitutive deamination procedure was performed under nitrogen with *p*-nitroaniline, *tert*-butyl nitrite, and copper(II) chloride, the products obtained were identical with those from reactions that were performed in an atmosphere open to air (Table I). No evidence was obtained by x-ray powder analysis for the presence of either copper(I) chloride or copper(I) oxide.

The isolated yields of aryl halides from reactions of representative arylamines with *tert*-butyl nitrite and copper(II) halides are given in Table II. The uniformly exceptionally high yields of aryl halides obtained by this method are comparable or superior to those obtained by the Sandmeyer procedure or its modifications.[3,9–11,14,21]

Lower reaction temperatures generally effect an increase in the yields of aryl halides from substitutive deamination reactions of arylamines bearing electron-donating substitutents. With *p*-anisidine, for example, the isolated yields of *p*-chloroanisole from reactions at 65 and 5 °C were 32 and 66%, respectively.[22] Similarly, the yields of aryl bromides from substitutive deamination reactions that employ the more reactive copper(II) bromide[23] are generally higher when the reaction temperature is at or below room temperature than at 65 °C.

The data in Table II indicate that substitutive deamination of arylamines by *tert*-butyl nitrite and copper(II) halides is general for the formation of aryl chlorides and bromides. However, arylamines possessing methyl substituents ortho to the amino group give low yields of aryl halides. For example, deamination of 2,4,6-trimethylaniline by *tert*-butyl nitrite and copper(II) chloride at 0–5 °C gave 2,4,6-trimethylchlorobenzene in only 32% yield; mesitylene, the product of reductive deamination, was the only other observed product (14% yield). Substitutive deaminations of 2-methyl-1-aminonaphthalene resulted in similar low yields of 2-methyl-1-halonaphthalenes. Amines with *o*-nitro, -chloro, and -carboxylate functional groups show no similar limitation.

Table II. Aryl Halide Product Yields from Reactions of Arylamines with *tert*-Butyl Nitrite and Copper(II) Halides in Acetonitrile [a]

Registry no.	$ArNH_2$	ArX	% yield ArCl[b]	% yield ArBr[b]
100-01-6	$p\text{-}NO_2C_6H_4NH_2$	$p\text{-}NO_2C_6H_4X$	99.5 (92)	90[c]
99-92-3	$p\text{-}CH_3COC_6H_4NH_2$	$p\text{-}CH_3COC_6H_4X$	98	92[c]
118-92-3	$o\text{-}HOOCC_6H_4NH_2$	$o\text{-}HOOCC_6H_4X$	95	
106-47-8	$p\text{-}ClC_6H_4NH_2$	$p\text{-}ClC_6H_4X$	74	88[d]
371-40-4	$p\text{-}FC_6H_4NH_2$	$p\text{-}FC_6H_4X$	61[c]	71[c]
455-14-1	$p\text{-}CF_3C_6H_4NH_2$	$p\text{-}CF_3C_6H_4X$	94[c]	78[c]
62-53-3	$C_6H_5NH_2$	C_6H_5X	66	47[c]
106-49-0	$p\text{-}CH_3C_6H_4NH_2$	$p\text{-}CH_3C_6H_4X$	96[c]	76[c]
104-94-9	$p\text{-}CH_3OC_6H_4NH_2$	$p\text{-}CH_3OC_6H_4X$	66[c]	71[c]
634-93-5	$2,4,6\text{-}Cl_3C_6H_2NH_2$	$2,4,6\text{-}Cl_3C_6H_2X$	84 (82)	93
88-05-1	$2,4,6\text{-}(CH_3)_3C_6H_2NH_2$	$2,4,6\text{-}(CH_3)_3C_6H_2X$	32[c]	26[d]
89-62-3	$2\text{-}NO_2\text{-}4\text{-}CH_3C_6H_3NH_2$	$2\text{-}NO_2\text{-}4\text{-}CH_3C_6H_3X$	(95)	98
92-87-5	Benzidine	$p\text{-}XC_6H_4C_6H_4X\text{-}p$	95	
134-32-7	1-Aminonaphthalene	$1\text{-}C_{10}H_7X$	82	96
2246-44-8	2-Methyl-1-aminonaphthalene	$2\text{-}CH_3\text{-}1\text{-}C_{10}H_6X$	15[d]	10[d]

[a] Reactions were performed by adding 10.0 mmol of the amine in 2 mL of anhydrous acetonitrile to 15.0 mmol of *tert*-butyl nitrite and, ordinarily, 12.0 mmol of copper(II) halide in 40 mL of acetonitrile. Reaction temperature was 65 °C unless indicated otherwise. [b] Absolute yield of the aryl halide after isolation of the organic product; yields were generally determined by GLC analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±1% of the reported values. Isolated yields after recrystallization are given in parentheses. [c] The reaction solution was cooled in an ice bath to 0–5 °C and was warmed to room temperature 2 h after complete addition of the amine. [d] Reaction temperature was 25 °C.

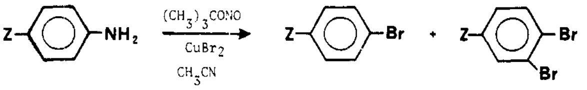
Table III. Mono- and Dibromide Products from Reactions of Arylamines with Copper(II) Bromide and *tert*-Butyl Nitrite in Acetonitrile[a]

$ArNH_2$	Relative yield, %			Isolated yield, %
	$ArBr$	o-$ArBr_2$	p-$C_6H_4Br_2$	
p-$NO_2C_6H_4NH_2$	92	8	0	98
p-$CH_3COC_6H_4NH_2$	94	6	0	98
p-$ClC_6H_4NH_2$	90	10	0	98
p-$FC_6H_4NH_2$	81	19	0	88
p-$CF_3C_6H_4NH_2$	79	21	0	99
$C_6H_5NH_2$	57	(3)[b]	40	82
p-$CH_3C_6H_4NH_2$	79	21	0	96
p-$CH_3OC_6H_4NH_2$	88	12	0	81

[a] Reaction conditions are those given in Table II for the same amines. [b] 1,2,4-Tribromobenzene; *o*-dibromobenzene is not a detectable product in the reaction with aniline.

Thorough examination of the product mixtures from reactions of *tert*-butyl nitrite and copper(II) chloride with the para-substituted arylamines reported in Table II showed a general absence of compounds that usually accompany aryl chlorides in the Sandmeyer reaction: biphenyls (eq 2), azobenzenes (eq 3), phenols (eq 4), arene reduction products (eq 5), and *N*-arylacetamides. Corresponding biphenyl, phenol, and arene compounds were not detected in the reaction mixtures from substitutive deamination of the series of arylamines: *p*-nitroaniline, *p*-aminoacetophenone, *p*-chloroaniline, *p*-fluoroaniline, *p*-trifluoromethylaniline, aniline, *p*-toluidine, and *p*-anisidine. Azobenzenes were found as minor products only from reactions with aniline (<1%), *p*-toluidine (1%), and *p*-anisidine (3%). *N*-Arylacetamides were constituents of product mixtures from reactions of copper(II) halide and *tert*-butyl nitrite with *p*-chloroaniline (5%) and *p*-toluidine (2%) but were absent in product mixtures from reactions with other amines. Identifiable side products (biphenyl, azobenzene, arene, phenol, and *N*-arylacetamide) were similarly absent in reaction mixtures from substitutive deaminations by copper(II) bromide and *tert*-butyl nitrite of those amines listed in Table II.

In reactions of arylamines with copper(II) bromide and *tert*-butyl nitrite a unique and, for the Sandmeyer process, previously unreported reaction accompanies the formation of aryl bromides. Substitution of bromide at aromatic ring positions that are ortho or para to the original amine position competes effectively with substitutive deamination (eq 7). With arylamines that possess para substituents, orientation of bromine to the ortho position is the sole result of this competing deaminative pathway (eq 8). With arylamines that do not possess para substituents, however, orientation of bromine to the para position is highly favored. The yields of mono- and dibromide products from reactions of arylamines with copper(II) bromide and *tert*-butyl nitrite in acetonitrile are given in Table III. 2-Methyl-1-aminonaphthalene, which is not listed in Table III, formed 2-methyl-1,4-dibromonaphthalene (17%) as the only identifiable dibromonaphthalene derivative.



(8)

Deamination of aniline by *tert*-butyl nitrite and copper(II) bromide yielded only bromobenzene, *p*-dibromobenzene, and 1,2,4-tribromobenzene. *o*-Dibromobenzene, biphenyl, azobenzene, and phenol were not present in detectable amounts. The absence of *o*-dibromobenzene and the inertness of aryl halides to substitution reactions under the same reaction conditions point to a mechanistic pathway for deamination of aniline that involves para substitution prior to ortho substitution. Efforts are presently being directed toward determining the mechanism of this novel aromatic substitution process and its relationship to direct substitutive deamination (eq 7).

Of the arylamines listed in Table II only 1-aminonaphthalene, 2-methyl-1-aminonaphthalene, and aniline yielded dichloro compounds in detectable quantities when treated with copper(II) chloride and *tert*-butyl nitrite in acetonitrile. 1-Aminonaphthalene gave 1,4-dichloronaphthalene in 18% isolated yield with 1-chloronaphthalene as the only other constituent of the reaction mixture. 2-Methyl-1-aminonaphthalene yielded both 2-methyl-1-chloronaphthalene (15%) and 2-methyl-1,4-dichloronaphthalene (2%). Aniline gave *p*-dichlorobenzene in 2% yield (Table IV). Reaction conditions conducive to selective formation of dihaloarenes in high yields are currently being examined.

Since copper(II) halides are reduced to copper(I) halides in the formation of by-products that accompany deamination reactions, and low concentrations of copper(I) halides catalyze the Sandmeyer reaction,[5b,c,8b,24,25] the products and their percentage yields from copper(II) chloride and copper(I) chloride reactions with aniline and *tert*-butyl nitrite were compared. The unique role of copper(II) halides in substitutive deamination reactions with arylamines is indicated by the data in Table IV. Reactions that employ copper(II) chloride form chlorobenzene with only a minor amount of *p*-dichlorobenzene and a trace amount of azobenzene as by-products. By comparison, reactions of aniline–*tert*-butyl nitrite with copper(I) chloride result in a complex mixture of products. In addition, isolated product yields are 50% greater when copper(II) chloride is the reactant than when copper(I) chloride is used.

Discussion

Substitutive deamination by *tert*-butyl nitrite and copper(II) halides is a selective, synthetically valuable method for the direct formation of aryl halides from arylamines. Unlike the previously reported direct method for the conversion of arylamines to aryl halides by the use of copper halide nitrosyls,[11] the method that employs alkyl nitrites and copper(II) halides is not limited to anilines; for example, 1-chloronaphthalene is formed from 1-aminonaphthalene in 6% yield by the former method and in 82% yield by the latter procedure. In addition, the preparation of organic halides by copper(II) halide–alkyl nitrite reactions with amine compounds is not limited to arylamines. *p*-Chlorobenzenesulfonamide, for example, yields, *p*-chlorobenzenesulfonyl chloride in 95% yield when treated with copper(II) chloride and *tert*-butyl nitrite in acetonitrile at 65 °C. The general absence of side products that usually accompany aryl halides in the Sandmeyer procedure, the required use of copper(II) halides rather than air-sensitive copper(I) halides, and the convenient direct conversion of arylamine to aryl halide are particular synthetic advantages.

The marked differences in products and product yields between the substitutive deamination procedure that is reported here and the conventional Sandmeyer procedure suggests that the process that involves copper(II) halides is not a simple variation of the Sandmeyer reaction. In his comparison of copper salts, Sandmeyer reported that copper(II) salts do not have the same effect as copper(I) salts for the substitution of nitrogen by halide.[26] Considerable controversy concerning the effectiveness of the copper salt and the mechanism of its action on diazonium ions ensued,[3a,b] due principally to Hodgson's proposal that copper(II) salts also catalyze Sandmeyer reactions[27] and to his insistence that

Table IV. Deamination of Aniline by *tert*-Butyl Nitrite and Copper(II) Chloride or Copper(I) Chloride[a]

CuX_n	Temp, °C	C_6H_5Cl	Relative yield, %[b]				Isolated yield, %
			p-$C_6H_4Cl_2$	$C_6H_4C_6H_5$	$C_6H_5{=}NC_6H_5$	$C_6H_5NHCOCH_3$	
$CuCl_2$	25	>96	3	0	<1	0	68
$CuCl_2$	65	>96	3	0	<1	0	67
$(CuCl)_2$	25	53	4	1	14	28	44
$(CuCl)_2$	65	43	2.5	2.5	7	45	42

[a] Reactions were performed by adding 10.0 mmol of the aniline in 2 ml of anhydrous acetonitrile to 15.0 mmol of *tert*-butyl nitrite and 12.0 mmol of the anhydrous copper halide in 40 mL of acetonitrile. [b] Precision of analysis is ±1% from duplicate runs.

copper(I) salts are not unique in substitutive reactions with diazonium ions.

Current understanding of the Sandmeyer reaction holds that copper(I) plays an integral role in the substitution of nitrogen by halide.[3c,d,28] The previously reported effective use of copper(II) salts is explained by reduction of a portion of the copper(II) salt to copper(I) in processes that compete with the Sandmeyer reaction.[8b,24,25,29] Indeed, copper(I) chloride has been effectively employed in catalytic amounts for the decomposition of p-nitrobenzenediazonium chloride in the Sandmeyer reaction.[8a]

Four observations in this study point to a unique role for copper(II) halides in reactions of arylamines with alkyl nitrites: (1) the stoichiometry of these reactions that result in the conversion of copper(II) halides to cupric oxide, (2) the nearly complete absence of those side products that are usually obtained in the Sandmeyer procedure, (3) the comparatively high yield of aryl halide products from reactions of arylamines with alkyl nitrites and copper(II) halides, and (4) the substitution of halide at aromatic ring positions that are para and/or ortho to the original amine position. The nature of the role of copper(II) halides in the substitutive deamination reaction that is represented by eq 7 is presently under investigation.

Experimental Section

Instrumentation. Proton magnetic resonance spectra were obtained with a Varian Model A-60A 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. Powder analyses were taken on a Norelco x-ray diffractometer. Analytical gas chromatographic analyses were performed on a Varian Aerograph Model 2720 gas chromatograph with thermal conductivity detectors; a Varian Model 485 digital integrator was used to determine peak areas. Use was made of 5–7-ft columns of 20% SE-30, 20% Carbowax 20M, and 10% DEGS, all on Chromosorb P. Melting points were obtained on a Thomas-Hoover apparatus and were uncorrected.

Materials. Anhydrous cupric chloride and cupric bromide were obtained commercially from Alfa and PCR, Inc., and were dried in an oven at 110 °C prior to use. Anhydrous cuprous chloride was prepared from cupric chloride dihydrate.[30] Reagent grade acetonitrile was distilled from calcium hydride prior to its use as a reaction solvent. 2-Methyl-1-aminonaphthalene was prepared from 2-methyl-1-bromonaphthalene by the procedure of Newman, Dhawan, and Tuncay.[31] Other amines that were used in this study were commercially available. Aniline and p-anisidine was purified prior to use. *tert*-Butyl nitrite was prepared from *tert*-butyl alcohol according to the procedure of Noyes.[32] Isoamyl nitrite was obtained commercially.

Substitutive Deamination of Arylamines. General Procedure. In the procedure employed for the reactions reported in Table II anhydrous copper(II) halide (12 mmol), *tert*-butyl nitrite (15 mmol), and anhydrous acetonitrile (40 mL) were added to a three-necked round-bottom flask that was equipped with a reflux condenser, addition funnel or solid inlet tube, and a gas outlet tube. The resulting rapidly stirred mixture was warmed (cooled) to the indicated reaction temperature (Table II). The amine (10 mmol) in 2 mL of acetonitrile (for liquid or acetonitrile-soluble amines) or as a solid was slowly added over a period of 5 min to the reaction solution. During this addition the reaction solution turned completely black from the initial green ($CuCl_2$) or black ($CuBr_2$) color as nitrogen was evolved. Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret; with the exception of reactions with 2,4,6-trimethylaniline, p-anisidine, and 2-methyl-1-aminonaphthalene, the yield of gaseous products in substitutive deamination reactions was 220 ± 20 mL (based on 10 mmol of the limiting reagent). At 65 °C gas evolution was generally complete within 10 min following the addition of the amine. After complete gas evolution the reaction temperature was allowed to reach room temperature, the reaction solution was then poured into 200 mL of 20% aqueous hydrochloric acid and extracted with 200 mL of ether, and the organic layer was washed once with 200 mL of 20% aqueous hydrochloric acid. The resulting ether solution was dried over anhydrous magnesium sulfate and the ether was removed under reduced pressure. Ether solutions containing volatile products were distilled at atmospheric pressure through a 12.5-cm Vigreux column.

Product Analyses. Structural assignments for the aryl halides produced in reactions of arylamines with alkyl nitrites and copper halides were made on the reaction solutions by ^{1}H NMR spectral comparisons and by GLC retention time and peak enhancement with authentic samples. The presence or absence of biphenyl, azobenzene, arene, phenol, and N-arylacetamide compounds in these reaction mixtures was confirmed by GLC retention time comparisons and by peak enhancement, if the compound was present, on two columns, generally 5-ft 20% SE-30 and 10% DEGS on Chromosorb P. Except for p-dichlorobenzene and p-dibromobenzene, which were identified by comparison to commercially available samples, the dihaloarenes produced from arylamines in this study were isolated by GLC separations and identified spectroscopically.

1,2-Dibromo-4-nitrobenzene: IR (KBr) 3095, 1592, 1564, 1525 (NO_2), 1448, 1370, 1340 (NO_2), 1280, 1245, 1122, 1015, 892, 871, 821, 745, and 736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.50 (J_m = 2.3 Hz, H-3), 8.08 (J_o = 8.5, J_m = 2.3 Hz, H-5), and 7.82 (J_o = 8.5 Hz, H-6); mp 53.5–54.0 °C (lit.[33] mp 58–59 °C).

3,4-Dibromoacetophenone: IR (KBr) 3092, 3024, 3008, 2966, 1687 (C=O), 1580, 1548, 1464, 1423, 1392, 1367, 1353, 1321, 1270, 1247, 1135, 1120, 1108, 1079, 1019, 1010, 954, 894, 827, 793, 693, 653, and 607 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.28–8.17 (1 H), 7.84–7.72 (2 H), and 2.60 (s, 3 H); mp 58.5–59.0 °C (lit.[34] mp 64 °C).

1,2-Dibromo-4-chlorobenzene: IR (KBr) 3080, 1560, 1487, 1450, 1407, 1365, 1248, 1090, 1072, 1013, 868, 809, and 778 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (J_m = 2.3 Hz, H-3), 7.57 (J_o = 9 Hz, H-6), and 7.15 (J_o = 9, J_m = 2.3 Hz, H-5); mp 35–36 °C (lit.[35] mp 35.5 °C).

1,2-Dibromo-4-fluorobenzene: IR (film) 3100, 1590, 1465, 1426, 1388, 1370, 1275, 1258, 1212, 1095, 1020, 889, 865, 810, 680, and 670 cm^{-1}. This IR spectrum corresponded to the similar Sadtler infrared spectrum of 1,2-dichloro-4-fluorobenzene.[36]

1,2-Dibromo-4-trifluoromethylbenzene: IR (film) 3090, 1600, 1520, 1380, 1320, 1250, 1170, 1070, 1050, 1010, 888, 820, 808, 707, and 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.90 (J_m = 2 Hz, H-3), 7.60 (J_o = 13, J_m = 2 Hz, H-5), and 7.20 (J_o = 13 Hz, H-6).

3,4-Dibromotoluene: IR (film) 3050, 2925, 1590, 1460, 1375, 1256, 1210, 1108, 1012, 860, 840, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47 (H-2), 7.50 (J_o = 8 Hz, H-5), 6.98 (J_o = 8 Hz, H-6), and 2.30 (s, 3 H).

3,4-Dibromoanisole: IR (film) 3090, 3000, 2970, 2940, 2840, 1575, 1560, 1465, 1435, 1285, 1260, 1225, 1180, 1100, 1032, 1005, 845, 800, 740, and 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (J_o = 8.8 Hz, H-5), 7.18 (J_m = 2.8 Hz, H-2), 6.75 (J_o = 8.8, J_m = 2.8 Hz, H-6), and 3.81 (s, 3 H).

1,4-Dichloronaphthalene: ^{1}H NMR ($CDCl_3$) δ 8.4–8.1 (m, 2 H), 7.8–7.5 (m, 2 H), and 7.50 (s, 2 H); mp 56–59 °C (lit.[37] mp 67–68 °C).

1,4-Dichloro-2-methylnaphthalene: ^{1}H NMR ($CDCl_3$) δ 8.5–8.15 (m, 2 H), 7.8–7.5 (m, 2 H), 7.63 (broad s, 1 H), and 2.55 (s, 3 H).

1,4-Dibromo-2-methylnaphthalene: ^{1}H NMR ($CDCl_3$) δ 8.5–8.1 (m, 2 H), 7.8–7.5 (m, 2 H), 7.69 (broad s, 1 H), and 2.60 (s, 3 H).

1,2,4-Tribromobenzene was similarly isolated from reactions of copper(II) bromide and *tert*-butyl nitrite with aniline, mp 42 °C (lit.[38] mp 44-45 °C).

Copper(II) oxide was isolated as a black, granular powder from reactions of copper(II) chloride with a stoichiometric excess of isoamyl nitrite and *p*-nitroaniline. The reaction mixture was filtered following complete gas evolution and prior to workup in aqueous acid. The isolated solid was dried in an oven for 2 h at 110 °C. The resulting black powder was subjected to x-ray analysis which confirmed its identity as copper(II) oxide and gave no evidence for the presence of either copper(I) oxide or copper(I) chloride.

The gaseous products from the reaction of copper(II) chloride and *tert*-butyl nitrite with *p*-nitroaniline were analyzed by GLC retention times on a 5-ft silica gel column and by infrared spectral analysis. Nitrogen was confirmed as the sole major product. Nitrous oxide was present as a minor constituent (<1% of the gaseous mixture) and no other gaseous product was detected.

Product yields were determined by GLC analyses for the vast majority of reactions reported in this study. Prior to workup a weighed amount of dibenzyl ether was added to the reaction mixture as an internal standard. The average integrated area ratio from at least two GLC traces was employed in each yield determination. Absolute yields were calculated with the use of experimentally determined thermal conductivities for each of the aryl halides examined by this method. Thermal conductivity ratios were determined immediately prior to product analyses to ensure accuracy in these determinations.

Product yields for naphthylamines were determined by ^{1}H NMR analyses through the use of 1,2-dibromoethane as the internal standard. Reaction products were analyzed by integration of the individual and characteristic absorption signals of each product and of the internal standard. The average values of at least five integrations were utilized in the calculation of absolute yields. Yields obtained by ^{1}H NMR analysis for reaction products from amines other than the naphthylamines confirmed those obtained by GLC methods.

4-Chloro-3-nitrotoluene. Solid 4-methyl-2-nitroaniline (15.2 g, 0.100 mol) was added slowly over 40 min to a rapidly stirred mixture of *tert*-butyl nitrite (15.5 g, 0.150 mol) and anhydrous copper(II) chloride (16.0 g, 0.120 mol) in 200 mL of acetonitrile which was heated at 65 °C in an oil bath. The rate of addition of 4-methyl-2-nitroaniline was determined by the rate of gas evolution; gas evolution was complete within 20 min following the last addition of the amine to the reaction mixture. After 16 h the black reaction mixture was cooled and then poured into 400 mL of 20% aqueous hydrochloric acid. The aqueous acetonitrile mixture was extracted twice with 200-mL portions of ether, the combined ether solution was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure. The resulting yellow liquid (16.3 g) was analyzed by ^{1}H NMR and GLC methods which showed the presence of only 4-chloro-3-nitrotoluene (0.095 mol, 95% yield).

1,2,3,5-Tetrachlorobenzene. 2,4,6-Trichloroaniline (19.65 g, 0.100 mol) was dissolved in 60 mL of acetonitrile and then added dropwise to a rapidly stirred mixture of *tert*-butyl nitrite (15.5 g, 0.150 mol) and anhydrous copper(II) chloride (13.65 g, 0.100 mol) in acetonitrile which was heated at 65 °C in an oil bath. Gas evolution was complete at 40 min following the start of addition. After 15 h the black reaction mixture was cooled and then worked up as described in the previous synthesis. Following the removal of ether, crude 1,2,3,5-tetrachlorobenzene was isolated as a brown solid (20.6 g). Recrystallization from absolute ethanol gave 17.6 g of pure 1,2,3,5-tetrachlorobenzene[39] (0.082 mol, 82% yield), mp 53.5-54.0 °C (lit.[40] mp 51 °C).

***p*-Chloronitrobenzene.** *p*-Nitroaniline (13.81 g, 0.100 mol) was dissolved in 100 mL of anhydrous acetonitrile and added dropwise over 40 min to the *tert*-butyl nitrite-copper(II) chloride mixture in acetonitrile. The reaction procedure and workup method were identical with those described in the previous syntheses. Following removal of ether, crude *p*-nitrochlorobenzene was isolated as a light yellow solid (16.8 g). Recrystallization from 50 mL of absolute ethanol gave 14.3 g of pure *p*-nitrochlorobenzene (0.092 mol, 92% yield), mp 82 °C (lit.[41] mp 83 °C).

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Registry No.—*tert*-Butyl nitrite, 540-80-7; copper(II) chloride, 7447-39-4; copper(I) chloride, 7758-89-6; $CuBr_2$, 7789-45-9; 1,2-dibromo-4-nitrobenzene, 5411-50-7; 3,4-dibromoacetophenone, 3114-30-5; 1,2-dibromo-4-chlorobenzene, 60956-24-3; 1,2-dibromo-4-fluorobenzene, 2369-37-1; 1,2-dibromo-4-trifluoromethylbenzene, 7657-08-1; 3,4-dibromotoluene, 60956-23-2; 3,4-dibromoanisole, 62415-74-1; 1,4-dichloronaphthalene, 1825-31-6; 1,4-dichloro-2-methylnaphthalene, 13577-15-6; 1,4-dibromo-2-methylnaphthalene, 62415-75-2.

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(23) In a competition experiment at 65 °C between $CuCl_2$ (7.0 mmol) and $CuBr_2$ (7.0 mmol) that employed *p*-nitroaniline (10 mmol) and *tert*-butyl nitrite (15 mmol), the recovered yield of *p*-bromonitrobenzene (57%) was twice that of *p*-chloronitrobenzene (29%).

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Alkyl Nitrite–Metal Halide Deamination Reactions. 3. Arylation of Olefinic Compounds in the Deamination of Arylamines by Alkyl Nitrites and Copper(II) Halides. A Convenient and Effective Variation of the Meerwein Arylation Reaction[1]

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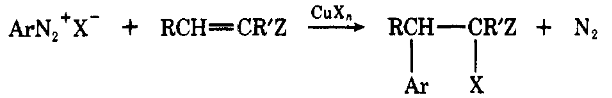
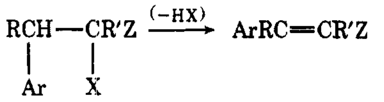
Arylation of olefinic substrates occurs when arylamines are treated with alkyl nitrites and copper(II) halides in acetonitrile or acetone solutions that contain the olefin. The corresponding β-aryl-α-halo derivatives are formed in high yields by this direct procedure. Results from direct arylation reactions of representative arylamines with acrylonitrile and styrene in the presence of copper(II) chloride are reported; isolated yields of arylation products from these reactions are comparable or superior to those obtained by the Meerwein procedure. The yields of α-chloro-β-arylpropionitriles from deamination reactions of arylamines in the presence of copper(II) chloride and acrylonitrile closely match those of substitution products that are formed by direct substitutive deamination of arylamines with *tert*-butyl nitrite and copper(II) chloride. This similarity indicates that neither the Sandmeyer reaction nor potentially competitive processes that involve arylation intermediates adversely affect this Meerwein reaction, and that reactions that compete with the Sandmeyer reaction are of comparable importance in the Meerwein reaction. Reactions with acrylonitrile that employ copper(II) bromide, however, are complicated by a preponderance of products that result from competing substitutive deamination and ring substitution by bromine. In arylation reactions that involve the deamination of *p*-nitroaniline in the presence of copper(II) chloride and selected olefins the importance of the competing Sandmeyer reaction is dependent on the nature of the olefinic substrate.

The Meerwein reaction is the copper salt catalyzed arylation of olefinic compounds by arenediazonium halides (eq 1).[3]



$$\mathrm{ArN_2^+X^-} + \mathrm{RCH{=}CR'Z} \xrightarrow{\mathrm{CuX}_n} \underset{\mathrm{Ar}}{\mathrm{RCH}}\text{—}\underset{\mathrm{X}}{\mathrm{CR'Z}} + \mathrm{N_2} \quad (1)$$

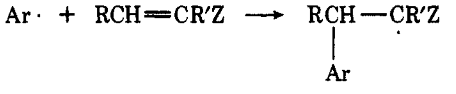
The olefinic components that are most suitable for this transformation are activated by electron-withdrawing groups or by conjugation with unsaturated functional groups (Z). Combination of the diazonium salt with the unsaturated compound and the copper salt results in the addition of the aryl component to the β carbon of the substituted olefin, with halide added to the α carbon. Elimination of hydrogen halide (eq 2) may occur under the reaction conditions of the Meerwein reaction or often results from a subsequent transformation.



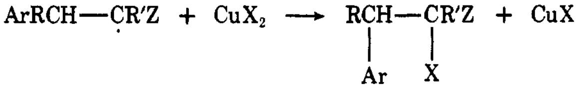
$$\underset{\mathrm{Ar}}{\mathrm{RCH}}\text{—}\underset{\mathrm{X}}{\mathrm{CR'Z}} \xrightarrow{(-\mathrm{HX})} \mathrm{ArRC{=}CR'Z} \quad (2)$$

Although cupric salts were promoted by Meerwein,[4] cuprous halides have been shown to be the effective catalysts for the arylation reaction.[5,6] However, both copper(I) and copper(II) oxidation states are utilized in the production of the Meerwein addition compound (eq 3–5).[7] Competing reactions, which in addition to formation of the Sandmeyer product include those processes that are most often associated with the Sandmeyer reaction, reinforce the widely held belief that the Meerwein reaction is initiated by copper(I)-catalyzed production of aryl radicals (eq 3).[3,7–9]

$$\mathrm{ArN_2^+} + \mathrm{CuX_2^-} \longrightarrow \mathrm{Ar\cdot} + \mathrm{N_2} + \mathrm{CuX_2} \quad (3)$$



$$\mathrm{Ar\cdot} + \mathrm{RCH{=}CR'Z} \longrightarrow \underset{\mathrm{Ar}}{\mathrm{RCH}}\text{—}\dot{\mathrm{C}}\mathrm{R'Z} \quad (4)$$



$$\mathrm{ArRCH}\text{—}\dot{\mathrm{C}}\mathrm{R'Z} + \mathrm{CuX_2} \longrightarrow \underset{\mathrm{Ar}}{\mathrm{RCH}}\text{—}\underset{\mathrm{X}}{\mathrm{CR'Z}} + \mathrm{CuX} \quad (5)$$

In the procedure normally employed for the Meerwein reaction[3] the arenediazonium halide is initially prepared in an aqueous halogen acid solution and then mixed with the unsaturated component in an appropriate solvent (water, acetone, or acetonitrile). Copper(II) halide is added to the homogeneous mixture and nitrogen evolution ensues, usually at temperatures at or below 25 °C. In this two-step procedure reaction variables, including the solution pH and the reaction solvent, are important determinants of the yield of the Meerwein arylation product. The Meerwein reaction is usually conducted in buffered solutions within the pH range of 2–4 to minimize side reactions.[10] Acetone is most often employed as the organic cosolvent but is reported to inhibit arylation in reactions with certain unsaturated compounds.[11]

The yields of arylation products are dependent on the structure of the diazonium salt and of the unsaturated compound, as well as on the previously mentioned reaction variables. For example, electron-donating substituents on the arenediazonium ion and the presence of ortho substituents generally adversely affect the yield of the Meerwein product.[3] Reactions that compete with the Meerwein reaction are often dominant and, consequently, the yield of the arylation product is low in many reactions.