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NITROSATIVE OXIDATION OF ARYLHYDRAZINES BY ALKYL NITRITES AND COPPER(II) HALIDES[1]

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Nitrosation reactions of monosubstituted hydrazines generally are of little synthetic value except in the synthesis of aryl and acyl azides.[3] Monosubstituted hydrazines possess two unlike basic sites; the site of nitrosation on these dibasic substrates is dependent on the nature of the substituent and on the acidity of the reaction medium.[4] Azide formation generally results from nitrosation at the terminal nitrogen; however, nitrogen rearrangement in the formation of these stable products is suggested by labeling experiments.[5] The removal of the hydrazine functional group as an oxidized nitrogen compound, although desireable as a substitution process analogous to nitrosative deamination of primary amines, does not occur in nitrosation reactions of monosubstituted hydrazines. Such a process has, however, been possible through oxidations by copper(II).[6,7] Oxidations of arylhydrazines by copper(II) salts that occur under midly acidic conditions result in the replacement of the hydrazine functional group by hydrogen with concurrent formation of nitrogen.[8] Our prior identification of oxidative deamination in reactions of primary alkylamines with copper(II) halides and alkyl nitrites,[9] together with known contrasting hydrogen substitution processes in arylamine nitrosation reactions[10] and in copper(II) oxidations of arylhydrazines,[6,7] suggested that azide production could be effectively bypassed in nitrosation reactions of monosubstituted hydrazines through oxidative substitution by copper(II) halides.

We have found that arylhydrazines react efficiently with alkyl nitrites in the presence of copper(II) chloride or copper(II) bromide to form the corresponding aryl halides in high yield (eq 1). In a typical procedure 2,5-dichlorophenylhydrazine (10.0 mmol) in 6 ml of acetonitrile

$$ArNHNH_2 + RONO + CuX_2 \xrightarrow{CH_3CN} ArX + ROH + CuX + H_2O + {}^3\!/\!_2N_2 \qquad (1)$$

was added dropwise over a 5-min period to *tert*-butyl nitrite (15 mmol) and a suspension of anhydrous copper(II) chloride (12 mmol) in 50 ml of acetonitrile at 65°C. The addition of the hydrazine produced an immediate and, according to eq 1, quantitative evolution of nitrogen. Gas evolution was complete within 10 min following complete addition of the hydrazine. After cooling, the reaction solution was poured into 200 ml of 20% aqueous hydrochloric acid and extracted with

200 ml of ether. Reaction products, which included 1,2,4-trichlorobenzene (90%) and 2,4-dichlorophenyl azide (3%) were analyzed following evaporation of the ether under reduced pressure. The yields of aryl halides from similar reactions with representative arylhydrazines are presented in Table I.

Table I. Yields of Aryl Halides from Reactions of Arylhydrazines with *tert*-Butyl Nitrite and Copper(II) Halides in Acetonitrile at 65°C.

	Reaction with $CuCl_2$		Reaction with $CuBr_2$	
$ArNHNH_2$	ArCl	Yield,%[a]	ArBr	Yield,%[a]
$2,4\text{-}(NO_2)_2C_6H_3NHNH_2$	$2,4\text{-}(NO_2)_2C_6H_3Cl$	74[b]	$2,4\text{-}(NO_2)_2C_6H_3Br$	78
$p\text{-}NO_2C_6H_4NHNH_2$	$p\text{-}NO_2C_6H_4Cl$	84	$p\text{-}NO_2C_6H_4Br$	82
$2,4\text{-}Cl_2C_6H_3NHNH_2$	$1,2,4\text{-}Cl_3C_6H_3$	82	$2,4\text{-}Cl_2C_6H_3Br$	93
$2,5\text{-}Cl_2C_6H_3NHNH_2$	$1,2,4\text{-}Cl_3C_6H_3$	90	$2,5\text{-}Cl_2C_6H_3Br$	82
$C_6H_5NHNH_2$	C_6H_5Cl	42[c,d]	C_6H_5Br	49[c]
$p\text{-}CH_3C_6H_4NHNH_2$	$p\text{-}CH_3C_6H_4Cl$	84	$p\text{-}CH_3C_6H_4Br$	71

[a] As determined from duplicate runs, percentage yields were accurate to within ± 2% of the reported values. [b] Isolated in 75% yield as a crystalline solid from a separate reaction. [c] Reaction was performed at 5°C. [d] At 65°C the yield of chlorobenzene was 46%.

The stoichiometric requirement of one equivalent of copper(II) halide and one equivalent of alkyl nitrite per arylhydrazine that is described in eq 1 was established by systematic variations of the three reactants together with quantitative product analyses. Nitrogen, the only gaseous product as determined by IR and GLC analyses, quantitatively accounted for the nitrogen content of the reactants. Copper(I) halide was identified as the sole copper product by x-ray powder analysis. Organic reaction products were identified by GLC and spectroscopic methods, and their yields were determined by GLC and/or ^1H NMR analyses through comparisons with authentic samples.

Nitrosative oxidations of arylhydrazines by alkyl nitrites and copper(II) halides are remarkably free of competing processes. Phenol production is significant only in reactions of 2,4-dinitrophenylhydrazine with *tert*-butyl nitrite and $CuCl_2$ (16%) or $CuBr_2$ (20%); the yields of phenol products in reactions with other hydrazines listed in Table I are less than 3%. Similarly, aryl azides are formed as minor products in yields ranging from less than 2% (2,4-dinitrophenylhydrazine) to less than 10% (phenylhydrazine and *p*-toluidine). No other products are observed in greater than 3% yield.

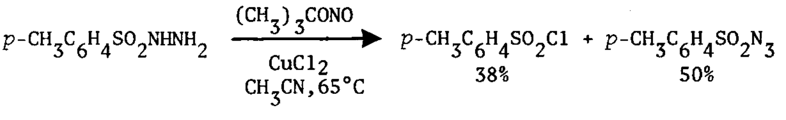
In the absence of CuX_2 arylhydrazines react slowly with alkyl nitrites to form a complex mixture of products. Aryl azides, although the major identifiable constituents of the reaction mixtures, are formed in low yield (< 20%); reduction of arylhydrazines to the corresponding aromatic hydrocarbons is also observed in reactions with alkyl nitrites in acetonitrile at 65°C.[11] Thus, as in reactions of arylamines with alkyl nitrites,[12] copper(II) halides modify the reaction pathway for nitrosative decomposition of arylhydrazines and direct halide substitution onto the aromatic nucleus. Copper(II) halide is not reduced in nitrosation reactions with arylamines,[12] whereas nitrosation reactions with arylhydrazines that yield the same halide substitution products require reduction of copper(II) to copper(I).[13]

In the absence of alkyl nitrite, oxidative loss of nitrogen in reactions of arylhydrazines with copper(II) halides in acetonitrile proceeds at rates that are comparable to those for nitrosative oxidation. However, the stoichiometric requirement for CuX_2 is greater than 2:1 in this alternate process for aryl halide production,[14] which suggests that reduction of copper(II) halides by arylhydrazines is more complicated than either one of the processes represented by eq 2 or 3. Aryl halide yields that are comparable to those in Table I are observed only when a 4-fold molar excess of copper(II) halide is employed. Isolated yields of aryl halides (in parentheses) from reactions of representative arylhydrazines with 4.2 equiv of CuX_2 in acetonitrile at 65°C are comparable to those from oxidative nitrosation: 2,4-dinitrophenylhydrazine (Cl, 82%; Br, 69%), 2,5-dichlorophenylhydrazine (Cl, 91%; Br, 59%), *p*-nitrophenylhydrazine (Cl, 93%; Br, 68%) and phenylhydrazine (Br, 55%). As expected from these reactions, which are performed under anhydrous conditions and in which water is not produced, phenol formation does not compete with the production of aryl halides. Although fewer processes compete with aryl halide formation in the oxidative substitution reaction (eq 2 or 3), the nitrosative oxidation reaction (eq 1) is unique with respect to its economy and efficiency in the use of copper(II) halides.

$$\mathrm{ArNHNH_2 + 4CuX_2 \longrightarrow ArX + 4CuX + 3HX + N_2} \qquad (2)$$

$$\mathrm{ArNHNH_2 + 2CuX_2 \longrightarrow ArX + 2Cu + 3HX + N_2} \qquad (3)$$

Although azide formation is a relatively minor process in nitrosative oxidations of arylhydrazines, the production of *p*-toluenesulfonyl azide effectively competes with the formation of *p*-toluenesulfonyl chloride (eq 4) in reactions of *p*-toluenesulfonyl hydrazine with *tert*-butyl nitrite and copper(II) chloride. By comparison, *p*-toluenesulfonyl chloride is formed in 67% yield by reaction of the corresponding hydrazine with 4.2 equiv of $CuCl_2$ in the absence of alkyl nitrite. We may infer from these observations that one role of copper(II) halides in nitrosative oxidations of monosubstituted hydrazines is that of electron transfer to the nitrosated hydrazine along the pathway for azide production.[15] Furthermore, the sole production of nitrogen in these reactions suggests that the mechanism for product formation involves hexazadiene[16] or hexazatriene intermediates. The observation that nitrous oxide is not produced demonstrates that sequential nitrosative decomposition resulting in the formation of arylamines[15] is not involved



$$p\text{-}\mathrm{CH_3C_6H_4SO_2NHNH_2} \xrightarrow[\substack{\mathrm{CuCl_2}\\ \mathrm{CH_3CN,65°C}}]{\mathrm{(CH_3)_3CONO}} \underset{38\%}{p\text{-}\mathrm{CH_3C_6H_4SO_2Cl}} + \underset{50\%}{p\text{-}\mathrm{CH_3C_6H_4SO_2N_3}} \qquad (4)$$

in reactions between arylhydrazines and alkyl nitrites that occur in the presence of copper(II) halides. Work is continuing in our laboratories to determine the scope and mechanism of the unique copper(II) halide - promoted nitrosative oxidation and oxidative substitution reactions of hydrazines and hydrazine derivatives.

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11. This process is the dominant pathway for nitrosative decomposition of arylhydrazines in dimethylformamide. A similar transformation of phenylhydrazines that are substituted with strong electron-donating groups occurs in the absence of alkyl nitrites: *p*-methoxyphenylhydrazine, for example, undergoes rapid and quantitative conversion to anisole at 25°C in an oxygenated atmosphere.
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13. Neither copper(I) nor copper(II) halide react with *tert*-butyl nitrite under the reaction conditions employed for nitrosative oxidation.
14. For example, from reactions of *p*-nitroaniline with 1.2, 2.4, and 4.2 molar equiv of $CuCl_2$ in acetonitrile at 65°C, the yields of *p*-chloronitrobenzene were 45, 71, and 93%, respectively. In contrast, reactions between *tert*-butyl nitrite and either 2,4-dinitrophenylhydrazine or 2,5-dichlorophenylhydrazine in the presence of 1.2 and 2.4 molar equiv of $CuCl_2$ produced the corresponding aryl halides in invarient yields (74%, 75% from 2,4-dinitrophenylhydrazine; 90%, 87% from 2,5-dichlorophenylhydrazine).
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