Oxidative Deamination of Primary Amines: Selective Synthesis of Geminal Dihalides

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Summary Oxidative deamination of unbranched primary amines by the combination of alkyl nitrites and anhydrous copper(II) halides in acetonitrile produces geminal dihalides selectivity and in synthetically useful yields.

Selective oxidative conversion of unbranched primary amines into aldehydes or aldehyde derivatives has not previously been achieved. Two approaches to this problem are envisaged: dehydrogenation of amines, and oxidative deamination. Considerable interest has recently been focused on the dehydrogenation of amine ligands in promoting amine oxidations by transition metals.[1] However, dehydrogenation of unbranched primary amines does not terminate at the aldimine stage but continues to the formation of nitriles.[2] In contrast, we have found that primary amines are converted selectively and in high yield into masked aldehydes with the near exclusion of nitrile products through the process of oxidative deamination.

Treatment of unbranched primary amines with either anhydrous copper(II) chloride or bromide and an alkyl nitrite in acetonitrile at 65 °C resulted in the production of geminal dihalides. The stoicheiometric requirement of 2 mol. equiv. of copper(II) halide and 1 equiv. of alkyl nitrite to the amine, as described in equation (1), was established

$$R^1CH_2NH_2 + 2CuX_2 + R^2ONO \longrightarrow R^1CHX_2 + 2CuX + R^2OH + N_2 \quad (1)$$

by systematic variations of the three reactants and products

Table. Yields of geminal dihalides from reactions of amines with copper(II) halides and alkyl nitrites at 65 °C.

Amine	*gem*-Dihalide	*gem*-Dihalide (mol %) from reaction with: Isopentyl nitrite $CuCl_2$	t-Butyl nitrite $CuCl_2$	t-Butyl nitrite $CuBr_2$
$PhCH_2CH_2NH_2$	$PhCH_2CHX_2$	67[a]	79	70
$Ph[CH_2]_2CH_2NH_2$	$Ph[CH_2]_2CHX_2$	68		
$Ph[CH_2]_3CH_2NH_2$	$Ph[CH_2]_3CHX_2$	62		
$Me[CH_2]_5CH_2NH_2$	$Me[CH_2]_5CHX_2$	55	48	59[b]
$Me[CH_2]_8CH_2NH_2$	$Me[CH_2]_8CHX_2$	62	54[c]	70[b]
$HOCH_2[CH_2]_4CH_2NH_2$	$HOCH_2[CH_2]_4CHX_2$	53		
$H_2NCH_2[CH_2]_8CH_2NH_2$	$X_2CH[CH_2]_8CHX_2$	57	56	
$H_2NCH_2[CH_2]_{10}CH_2NH_2$	$X_2CH[CH_2]_{10}CHX_2$	51		
$HO_2C[CH_2]_4CH_2NH_2$	$HO_2C[CH_2]_4CHX_2$		55	
$HO_2C[CH_2]_{10}CH_2NH_2$	$HO_2C[CH_2]_{10}CHX_2$		52	
Cyclohexyl-CH_2NH_2	Cyclohexyl-CHX_2	38	43	46

[a] Isolated in 58% yield after distillation (b.p 80 °C at 3·5 Torr). [b] Reaction performed at room temperature. [c] Isolated yield of 1,1-dichlorodecane (b.p. 55 °C at 0·1 Torr).

analyses. The yields of geminal dihalides formed in these reactions are given in the Table. Substitution products, alkyl halide and alcohol, were also formed in this procedure but their combined yield was usually less than 15%. Nitrile formation amounted to less than 5% of the actual yield.

In a typical procedure β-phenylethylamine (10·0 mmol) in 2 ml of acetonitrile was slowly added by syringe to t-butyl nitrite[3] (15·0 mmol) and a suspension of anhydrous $CuCl_2$ (20·0 mmol) in 50 ml of anhydrous acetonitrile at 65 °C. The addition of amine provided immediate and nearly quantitative evolution of nitrogen and a blackening of the reaction solution. After complete addition ($<$ 1 h) the mixture was cooled, poured into ethylenediamine (80 mmol), and made alkaline with 200 ml of 3M sodium hydroxide, and then extracted with ether. Recovery procedures suitable to the isolation of reaction products were used but were not varied to optimize the yield of each geminal dihalide in the Table; the use of ethylenediamine and aqueous sodium hydroxide did not noticeably affect the product yields. After distilling off the ether under reduced pressure the reaction products were subjected to g.l.c. and ^{1}H n.m.r. analyses; 2,2-dichloro-1-phenylethane (79%), 2-chloro-1-phenylethane (10%), 2-phenylethanol ($<$ 1%), and phenylacetonitrile (5%) were identified from reactions with β-phenylethylamine. The yields of geminal dihalides reported in the Table were generally reproducible to within $\pm 2\%$. Geminal dihalides from β-phenylethylamine and 1-aminodecane were conveniently isolated by distillation under reduced pressure.

We have previously reported that copper halide nitrosyls formed from copper(II) halides and nitric oxide also react with unbranched primary amines to yield geminal dihalides.[4] However, displacement of the nitrosyl ligand by the free amine [equation (2)] in this procedure accounts for

$$2RCH_2NH_2 + (CuX_2{\cdot}NO)_2 \longrightarrow 2(RCH_2NH_2{\cdot}CuX_2) + 2NO \qquad (2)$$

a major portion of the reaction process and, consequently, the yields of geminal dihalides are relatively low (25—40%). In contrast, in reactions of these same amines with copper(II) halides and alkyl nitrites, the nitrosyl group is retained and synthetically useful yields of geminal dihalides are obtained.

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