The Reaction of ω-Ethoxyalkyl Bromides with Silver(I) Cyanide and Nitrite. The Participation of an Oxonium Ion

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The reaction of ω-ethoxyalkyl bromides (C_n: n=2—5) with silver(I) cyanide or nitrite in less polar solvents to give the corresponding isocyanide or a mixture of the corresponding alkyl nitrite and nitroalkane respectively, proceeded with ease only when n=4. In the latter reaction, the ratios of O- and N-attack (O/N) were 16—18/82—84 and 31—46/54—69 when $n \neq 4$ and n=4 respectively. The facile reaction in both cases when n=4 and the increasing O-attack in the case of silver(I) nitrite may suggest that the reaction proceeds through the initial formation of a five-membered oxonium ion, the *O*-ethyltetrahydrofuranium ion, and a subsequent attack by CN^- and NO_2^- or their silver(I) bromide complex.

Previously, we have shown that various alkyl halides reacted with mercury(II) thiocyanate to give an isomeric mixture of alkyl thiocyanate and isothiocyanate.[1] This ambident behavior of the mercury(II) salt has also been observed in the reaction with 4-alkoxybutyl halide where the isomer ratio (N/S) of the products is nearly 1, in contrast to the results for unsubstituted primary halides (N/S=*ca.* 1/4).[2] This difference has been explained by considering the attack of an ambident anion of the mercury(II) salt upon a tetrahydrofuranium ion intermediate. In order to establish further examples of the ambident reaction of metal salt with such an oxonium ion, we have carried out the reactions of ω-alkoxyalkyl halides (C_n: n=2—5) with silver(I) cyanide and nitrite, both metal salts being well known to have an ambident reactivity on alkyl halide.[3] As a result, it was found that the reaction proceeded smoothly when n=4 and that silver(I) nitrite showed a different ambident behavior on the halide of n=4 and the halides of $n \neq 4$.

Results and Discussion

The reaction of ω-alkoxyalkyl halides or butyl bromide with silver(I) cyanide was carried out by stirring a heterogeneous mixture of both reagents in dichloromethane or without a solvent at 75—85 °C for appropriate times. At least under these conditions, the reaction proceeded only in the case of 4-ethoxybutyl bromide to give the corresponding isocyanide, the formation of the cyanide being scarcely observed (Table 1 and Scheme 1).[4] Although we have already found

$$EtO(CH_2)_4Br + AgCN \longrightarrow EtO(CH_2)_4NC \qquad (1)$$

that mercury(II) thiocyanate, acetate, and chloride reacted with alkyl halides in tetrahydrofuran (THF) to give the THF-incorporated compounds,[2,5] no such reaction has been observed by stirring mercury(II) or silver(I) cyanide and ethyl iodide in THF at a reflux temperature for 24 h.

Table 1. Reaction of RX with AgCN[a)]

RX (10 mmol)	Solvent (10 ml)	React. temp (°C)	React. time (h)	Yield[b)] of RNC
$EtO(CH_2)_2Br$	$(CH_2Cl)_2$	80	24	0
$EtO(CH_2)_3Br$	$(CH_2Cl)_2$	80	32	0
$EtO(CH_2)_4Br$	$(CH_2Cl)_2$	85	48	90
$EtO(CH_2)_4Br$[c)]	—	80	24	75
$EtO(CH_2)_5Br$	$(CH_2Cl)_2$	85	32	trace
n-$BuO(CH_2)_4Cl$	$(CH_2Cl)_2$	85	96	0
n-BuBr	—	80	24	trace

a) AgCN, 10 mmol. b) Determined by GLC. c) RX, 30 mmol. AgCN, 20 mmol.

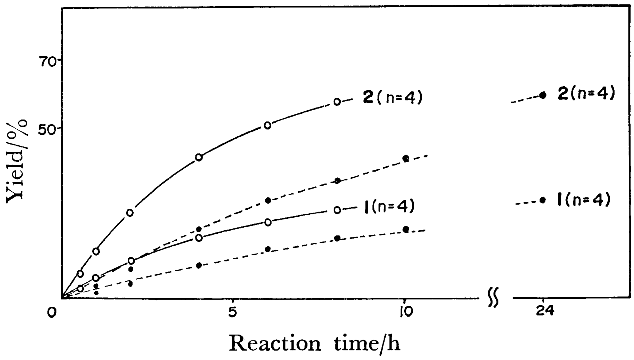

Fig. 1. The yield of **1** (n=4) and **2** (n=4) against reaction time.[a)]
a) Determined by GLC using tetralin as internal standard. The reaction in 1,2-dichloroethane solvent is represented by a solid line, while that in diethyl ether by a dashed line.

The reaction of ω-ethoxyalkyl or butyl bromide with silver(I) nitrite was also carried out by stirring them in 1,2-dichloroethane, diethyl ether, or THF at 15—25 °C for 1—7 days, the mixture being heterogeneous. The products were the corresponding alkyl nitrite(**1**) and nitroalkane (**2**), the ambident character of the metal salt being clearly observed (Table 2 and Scheme 2). Here also, the reaction proceeded smoothly when

$$EtO(CH_2)_nBr + AgNO_2 \longrightarrow$$
$$EtO(CH_2)_nONO + EtO(CH_2)_nNO_2 \qquad (2)$$
$$\mathbf{1}(n=2-5) \qquad \mathbf{2}(n=2-5)$$

n=4. The isomer ratio (O/N) depended on the kind of alkyl bromide, an increase of the O-attack being observed in the case of n=4: namely, 31—46/54—69 from 4-ethoxybutyl bromide and 16—19/81—84 from the other halides. In contrast to the reaction with mercury(II) thiocyanate,[2] the reaction in THF as

TABLE 2. REACTION OF RBr WITH $AgNO_2$ a)

R in RBr (10 mmol)	Solvent (10 ml)	React. time (day)	Yield b) of **1**+**2** (%)	Isomer ratio b) of **1**/**2** (O/N)
$EtO(CH_2)_2$	Et_2O	7	2	16/84
$EtO(CH_2)_3$	Et_2O	7	14	16/84
$EtO(CH_2)_3$	$(CH_2Cl)_2$	7	14	16/84
$EtO(CH_2)_4$	Et_2O	1	87	33/67
$EtO(CH_2)_4$	$(CH_2Cl)_2$	0.33	83	31/69
$EtO(CH_2)_4$	THF	3	54	46/54
$EtO(CH_2)_5$	Et_2O	7	8	17/83
n-C_6H_{13}	Et_2O	4	40	19/81 c)
n-C_6H_{13}	$(CH_2Cl)_2$	4	13	18/82 c)
n-C_6H_{13}	THF	4	9	16/84 c)

a) $AgNO_2$, 10 mmol. React. temp, 20—25 °C. b) Determined by GLC. c) n-$C_6H_{13}ONO$/n-$C_6H_{13}NO_2$.

TABLE 3. BOILING POINTS AND NMR AND ANALYTICAL DATA OF NEW COMPOUNDS

Compound	Bp (°C/mmHg)	^{1}H-NMR (δ)	Found (Calcd) C(%)	H(%)	N(%)
1(n=2)	45—46/50 a)	1.10(t. 3H), 3.45(q. 2H), 3.61(t. 2H), 4.78(t. 2H)			
1(n=3)	51—53/50	1.13(t. 3H), 1.92(quintet 2H), 3.42(q. 2H), 3.43(t. 2H), 4.71(t. 2H)	45.81(45.10)	8.70(8.33)	10.01(10.52)
1(n=4)	50—51/22	1.12(t. 3H), 1.35—2.1(m. 4H), 3.36(t. 2H), 3.39(q. 2H), 4.68 (t. 2H)	49.23(48.79)	9.27(8.90)	9.26(9.52)
1(n=5)	67—68/14	1.07(t. 3H), 1.28—2.0(m. 6H), 3.30(t. 2H), 3.36(q. 2H), 4.61(t. 2H)	52.25(52.16)	9.69(9.38)	8.97(8.69)
n-$C_6H_{13}ONO$	50—51/40 b)	0.92(t. 3H), 1.1—2.0(m. 8H), 4.61(t. 2H)			
2(n=3)	100—102/48	1.16(t. 3H), 2.17(quintet 2H), 3.43(q. 2H), 3.48(t. 2H), 4.38(t. 2H)	44.63(45.10)	8.09(8.33)	9.88(10.52)
2(n=4)	93—95/19	1.15(t. 3H), 1.4—2.4(m. 4H), 3.42(t. 2H), 3.42(q. 2H), 4.39(t. 2H)	48.35(48.97)	8.62(8.90)	9.00(9.52)
2(n=5)	105—107/11	1.14(t. 3H), 1.3—2.3(m. 6H), 3.35(t. 2H), 3.38(q. 2H), 4.35(t. 2H)	51.91(52.16)	9.61(9.38)	8.64(8.69)
n-$C_6H_{13}NO_2$	120—140/45 c)	0.90(t. 3H), 1.1—2.2(m. 8H), 4.30(t. 2H)			
$EtO(CH_2)_4NC$	90/30	1.13(t. 3H), 1.5—2.2(m. 4H), 2.9—3.9(m. 4H), 3.42(q. 2H)	65.49(66.11)	9.99(10.30)	10.71(11.01)

a) Lit,8) bp 30—33 °C/15—20 mmHg. b) Lit,9) bp 45 °C/30 mmHg. c) Lit,9) bp 80°C/12 mmHg.

a solvent did not show any THF-incorporation.

It is generally known, in the reaction of alkyl halide with silver(I) nitrite, that a side reaction producing alkyl nitrate ester, alcohol, ketone, *etc.* occurs in some cases.6) We observed, however, the formation of only a small amount of the corresponding nitrate ester and alcohol, even in the reactions continued for several days or a week. Further, when we plotted the yields of both alkyl nitrite and nitroalkane against the reaction time in the reaction with 4-ethoxybutyl bromide, the ratio between the two isomeric products was almost constant with an increase in the yield of the products (Fig. 1). These facts show that no further reaction of the initially produced alkyl nitrite occurs under these conditions and, consequently, that the O/N ratio is the kinetically controlled one in these reactions. When the reaction of ethyl iodide with silver(I) nitrite was carried out in THF at 25 °C for 6 h, an isomeric mixture of 4-ethoxybutyl nitrite and 4-ethoxy-1-nitrobutane was obtained in a 4% yield (O/N=55/45). Although the yield was low because of the rapid formation of ethyl nitrite and nitroethane, this finding shows that the THF-incorporation reaction occurs as in the cases of similar reactions with various mercury(II) salts.2,5)

Because the silver(I) salts are almost completely insoluble in any solvent used, the reactions are generally quite slow. However, the reactions of 4-ethoxybutyl bromide proceeded smoothly. The reason for the comparatively facile reaction of this halide can be ascribed to the involvement of the *O*-ethyltetrahydrofuranium ion intermediate, as has been found in the cases of the reactions of similar halides with various mercury(II) salts.2,5) The formation of **1** (n=4) and **2** (n=4) in the reaction of ethyl iodide in THF, though the yield was low, also supports this assumption. As to the isomer ratio of the products from the reaction of 4-ethoxybutyl bromide with silver(I) nitrite, the ratio for the O-attack was higher than that from other primary halides. This can be understood by considering that the isomer ratio is determined by the step of the attack on the intermediate oxonium ion;2) that is, the carbon bearing a harder ligand as the leaving group (R_2O in R_3O^+) is more apt to be attacked by a harder atom in an ambident ion, the O atom being harder than the N atom in the attacking species of NO_2^- or $AgBr(ONO)^-$. At present, the question of which is the more likely species must be left unresolved.

Experimental

The O/N ratios in mixtures of alkyl nitrites and nitroalkanes were determined by GLC. The GLC analyses were carried out on a Shimadzu 4BMPF and a Yanagimoto G800-T apparatus, using EGSS-X (1 or 3 m), Apiezon-L (1 m), and SE-30(1 m) columns(carrier gases, N_2 and H_2 respectively). The ^{1}H-NMR spectra (60 MHz) were recorded with a Varian EM-360 and a Hitachi R-24 spectrometer in CCl_4, using TMS as the internal standard.

Materials. The diethyl ether (dried over Na), 1,2-dichloroethane (over K_2CO_3), and THF (over KOH) were used after distillation, while the other organic and inorganic substances were used without further purification. The ω-alkoxyalkyl halides were prepared by a previously reported method.[6] Authentic samples of alkyl nitrite were prepared from the corresponding alcohols by a previously reported method,[7] while nitroalkanes and 4-ethoxybutyl isocyanide were separated from the reaction products by distillation and then analyzed. All the compounds except **1**(n=2), **2**(n=2), hexyl nitrite, and 1-nitrohexane are new; their boiling points and ^{1}H-NMR and analytical data are summarized in Table 3. Although **2**(n=2) could not be isolated in a pure state, the retention time in the GLC and the NMR spectrum support the assigned structure.

Reaction of 4-Ethoxybutyl Bromide with $AgNO_2$. A suspension of $AgNO_2$(1.52 g, 10 mmol) and 4-ethoxybutyl bromide(1.82 g, 10 mmol) in diethyl ether or 1,2-dichloroethane(10 ml) containing tetralin (1.07 g) as an internal standard for GLC analysis was stirred at 15—20 °C in the dark. At appropriate time intervals an aliquot was analyzed by GLC to determine the amounts of **1**(n=4) and **2**(n=4) produced (see Fig. 1). In order to isolate the products, a similar reaction was carried out without the addition of tetralin. After the precipitated AgBr had been filtered off, the filtrate was distilled to give a mixture of **1**(n=4) and **2**(n=4).

Reaction of 4-Ethoxybutyl Bromide with AgCN. A suspension of 4-ethoxybutyl bromide (3.60 g, 20 mmol) and AgCN(2.65 g, 20 mmol) in 1,2-dichloroethane (10 ml) was kept at 80—85 °C for 24 h under stirring. After being cooled down to room temperature, an aqueous KCN solution was added, the separated oil layer was extracted with ether, and the ether extract was dried over $MgSO_4$. Subsequent distillation gave 1.53 g(60% yield) of 4-ethoxybutyl isocyanide.

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3) See, for example, J. March, "Advanced Organic Chemistry," 3rd ed, McGraw-Hill-Kogakusha, Tokyo (1977), p. 338.

4) It has been known in the reaction of ethyl iodide with AgCN that the relative amounts of the corresponding isocyanide and cyanide depend very much on the reaction temperature; only the isocyanide was formed at 80 °C. See, for example, P. Kurz, "Methoden der Organischen Chemie (Houben-Weyl)," ed by E. Müller, Georg Thieme Verlag, Stuttgart (1952), Vol VIII, p. 291.

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