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HALOGEN EXCHANGE REACTIONS BETWEEN ALKYL HALIDES AND AQUEOUS HYDROGEN HALIDES. A NEW METHOD FOR PREPARATION OF ALKYL HALIDES.

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Abstract

Alkyl fluorides and chlorides are efficiently converted to their corresponding alkyl bromides and iodides by using readily available aqueous HBr and HI. The application of the same method for the conversion of some alkyl fluorides to the corresponding alkyl chlorides with conc. HCl is also described.

Alkyl bromides and iodides are generally more reactive and synthetically useful than the correspondingly cheaper and readily available alkyl chlorides. Examples include the preparation of alkyl lithiums, Grignard reagents, and copper-catalyzed alkylations.[1-3] Classically, the halogen exchange reaction between alkyl chlorides and various bromide and iodide salts,[4] and the transhalogenation of alkyl chloride with alkyl bromide[5] are the two processes used for conversion of alkyl chlorides to alkyl iodides or bromides. However, formation of undesired side products due to elimination reactions limit the synthetic utility of these methods. The preparation of iodoalkanes from the corresponding fluoro- or chloroalkanes with iodotrimethylsilane has also been reported.[6] This technique is effective only for converting tertiary fluoro- or chloro- and secondary fluoroalkanes to the corresponding iodoalkanes. Sluggish reaction with primary fluoralkanes and unreactivity of primary and secondary chloroalkanes in these reactions have been noted. Halogen exchange reactions between tertiary alkyl and benzylic chlorides and sodium iodide catalyzed by ferric chloride were also shown not to be effective for primary or secondary alkyl chlorides.[7] More recently, halogen exchange reactions between alkyl chlorides and gaseous HBr or HI to alkyl bromides and iodides in the presence of a ferric halide as a catalyst have been reported for the conversion of secondary and tertiary alkyl chlorides to bromides or iodides.[8] However, the preparation of anhydrous $FeBr_3$ and FeI_3 catalysts is difficult and the extreme labile nature of ferric iodide[9] is partly responsible for low yields obtained with alkyl chlorides[8]. Interestingly, halogen exchange reactions of fluoroalkanes with HI, HBr or HCl have not been studied. We now address the application of such reactions for the synthesis of bromo- or iodoalkanes from the corresponding fluoro- or chloroalkanes, conveniently using the readily available aqueous hydrogen halides.

We have found that conversion of fluoro-, chloro- or bromoalkanes to the corresponding iodoalkanes can be achieved at 105-130 °C in the presence of aqueous hydrogen iodide (Table I).

Table I. Synthesis of Iodoalkanes

$$RX + HI \xrightarrow{105-130^\circ C} RI + HX$$

Alkyl halide		Reaction condition		
R	X	time, h	temp, °C	Yield,[a] %
1-heptyl	F[b]	1.5	105	(21)
		10	105	85
	Cl	1.5	105	(17)
		8	130	84
	Br	1.5	105	(38)
		5	130	90
benzyl	F[b]	0.2	105	95
	Cl	0.2	105	92
	Br	0.2	105	94
cyclohexyl	F	0.2	105	(64)
		1	105	90
	Cl	0.2	105	(18)
		2.5	105	85
	Br	0.2	105	(45)
		1.5	105	92
1-adamantyl	F[b]	0.2	105	95
	Cl	0.2	105	(30)
		2	130	92
	Br	0.2	105	(83)
		0.5	105	90
exo-2-norbornyl	F[b]	0.5	105	93[c]
	Cl	2.5	130	90[d]
	Br	0.5	105	91[e]

[a] Isolated yields unless otherwise noted. The products were identified by physical and spectral data. Yields in parentheses are based on GLC. [b] Alkyl fluorides were synthesized according to ref. 10. [c] The exo/endo isomer ratios were determined by integration of the C-2 methine protons at δ 3.95 (exo) and δ 4.20 (endo) exo/endo = 9.4/1. [d] exo/endo = 5.8/1. [e] exo/endo = 4/1.

Table II. Synthesis of Bromoalkanes

$$RX + HBr \xrightarrow{105-130°C} RBr + HX$$

alkyl halide		reaction condition		
R	X	time, h	temp, °C	yield,[a] %
1-heptyl	F	8	130	87
	Cl	20	130	84
benzyl	F	1	130	95
	Cl	1	130	93
cyclohexyl	F	2	105	96
	Cl	4	105	90
1-adamantyl	F	0.5	105	92
	Cl	2	130	90
exo-2-norbornyl	F	1	105	93[b]
	Cl	3	130	91[b]

[a]Isolated yields. [b]Mixture of exo and endo.

In a typical experiment, the alkyl halide (RX) was treated with four molar excess of aqueous hydrogen iodide (57% in H_2O containing 0.5% H_3PO_2 as stabilizer) and heated at 105-130°C. After the given period of time (see Table I) the reaction mixture was quenched with cold water and the product was extracted with dichloromethane. The dichloromethane layer was washed with aqueous sodium bisulfite, water and dried ($MgSO_4$). Pure iodoalkane (RI) was obtained upon evaporation of solvent. Similarly, fluoro- or chloroalkanes were converted to the respective bromoalkanes using aqueous hydrogen bromide (47% in H_2O) (Table II).

Finally, alkyl fluorides were also converted to the corresponding alkyl chlorides with 12N HCl at 105°C. For example, fluorocyclohexane and 1-fluoroadamantane were converted to their corresponding chloroderivatives in 3 and 1 h, respectively, in yields > 90%.

$$RF + HCl \xrightarrow{105°C} RCl + HF$$

R = 1-heptyl, benzyl, cyclohexyl
1-adamantyl or exo-2-norbornyl

In summary, the salient features of these halogen exchange reactions are (a) their broad scope and experimental simplicity, (b) the excellent yields of alkyl halides, (c) the easy synthesis of fluoroalkane precursors, and (d) the commercial availability of hydrogen halides.

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References and Notes

1. M.S. Kharash and O. Reinmth, Grignard Reactions of Nonmetallic Substances; Prentice-Hall, New York 1954.
2. a) B.J. Wakefield, The Chemistry of Organolithium Compounds; Pergamon Press, New York, 1974. b)G. Wittig, In Newer Methods of Preparative Organic Chemistry; Interscience Publishers, New York, 1948; pp 572-575.
3. a) E.J. Corey and G.H. Posner, J. Am. Chem. Soc., 89, 3911 (1967). b) E.J. Corey and G.H. Posner, J. Am. Chem. Soc., 90, 5615 (1968).
4. H.A. Finkelstein, Ber. Dtsch. Chem. Ges., 43, 1528 (1910).
5. W.E. Willy, D.R. McKean, B.A. Garcia, Bull. Chem. Soc. Japan., 49, 1989 (1976).
6. a)G.A. Olah, S.C. Narang and L.D. Field, J. Org. Chem. 46, 3727 (1981). b)E.C. Friedrich and G. De Lucca, J. Organometal. Chem. 226, 143 (1982).
7. J.A. Miller and M.J. Nunn, Tetrahedron Lett. 31, 2691 (1974).
8. K.B. Yoon and J.K. Kochi, J. Org. Chem. 54, 3028 (1989).
9. K.B. Yoon and J.K. Kochi, Anorg. Allg. Chem. 561, 174 (1988).
10. W.J. Middleton, J. Org. Chem., 40, 574 (1975).

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