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HALOGEN-EXCHANGE FLUORINATION OF CYCLO AND TERTIARY ALKYL HALIDES USING Cu_2O-HF-ORGANIC BASE SOLUTIONS

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Cu_2O-HF-Organic base (tetrahydrofuran or Et_2O) solutions were used successively as a highly reactive halogen-exchange fluorination reagent for the cyclo or tertiary alkyl halides without carbon skeletal rearrangement under the mild conditions.

Halogen-exchange fluorination of aliphatic halides is the most important synthetic way to obtain fluoroderivative compounds.[1)] The reaction of cyclo and tertiary alkyl halides, however, is usually subjected to the preferential eliminations of hydrogen halides to produce olefinic compounds.[2,3)] We now wish to report here the solutions of Cu_2O in anhydrous hydrogen fluoride(HF)-organic base to be a novel, highly reactive and selective halogen-exchange fluorination reagent for the cyclo alkyl and tertiary alkyl halides.

To 7 mmol Cu_2O placed in a 100 ml FEP made reaction vessel, HF(150 mmol) organic base (mainly tetrahydrofurane (THF) or Et_2O; 3 ml)[4)] was added by portion with great care under magnetic stirring at -78 °C. The resultant solution showed a purple or violet color with partially undissolved Cu_2O as a brown orange precipitate. A substrate (5 mmol) dissolved in 3 ml CCl_4 was then added dropwise into the Cu_2O-HF-organic base solution at 20-50 °C under sufficient stirring and the mixture was allowed to stand for a desired time. With the elapse of time, the solution gradually changed in color to milky or gray. The reaction mixture was then quenched with ice-water and organic substances were extracted with CCl_4 and identified by ordinary spectroscopic methods. Some of the experimental results are listed in the table together with those appearing in the literatures.

As seen in the Table, Cu_2O-HF-Organic base solutions exhibited remarkably high halogen-exchange fluorinated activity in the reaction of cyclo or tertiary alkyl halides, which give only products of elimination by using the reagents and conditions reported so far.[2,3)] HF-Organic base solutions themselves did not give any product. HF-Cu_2O solution, on the other hand, gave complicated oligocondensed products of the starting halides. These results indicate that the reaction of cyclo and tertiarly alkyl halides RX (X; Cl or Br) was initiated by cuprous cation Cu^+ to form alkyl cation R^+ and cuprous halide CuX. In the case of using an HF-Cu_2O solution, cationically induced polymerizations and rearrangements of R^+ readily occur because of the strongly acidic properties of anhydrous hydrogen fluoride solution. However, HF behaves as a weaker acid in organic base than in the pure form and the nucleophic activity of the fluoride anion is known to be much more enhanced[5)] so that undesirable reactions such as

Table 1. The Halogen-Exchange Fluorination of Alkyl Halides

Reagent	Substrate[a)]	Reaction		Conversion	Product
		Time/h	Temp/°C	%	Distribution/%[j)]
Anion-exchange resins[b)]	Bromocyclopentane	30	35	50	Cyclopentene 100
Aq-KF with phase-transfer catalyst[c)]	Chlorocyclohexane	70	125	100	Cyclohexene 100
HF-THF[d)]	"	2	50	No Reaction	
$HF\text{-}Cu_2O$[e)]	"	2	30	100	Oligomers
$HF\text{-}THF\text{-}Cu_2O$[f)]	"	2	50	84	Cyclohexene 12 Fluorocyclohexane 88
"[f)]	Bromocyclohexane	1	20	95	Cyclohexene 4 Fluorocyclohexane 96
$HF\text{-}Et_2O\text{-}Cu_2O$[g)]	Bromocyclopentane	1.5	20	87	Cyclopentene 8 Fluorocyclopentane 92
$HF\text{-}THF\text{-}Cu_2O$[f)]	Bromoadamantane	0.25	25	100	Fluoroadamantane 100
"[f)]	2-Chloro-2-methylbutane	0.5	20	97	2-Fluoro-2-methylbutane 100
$HF\text{-}Et_2O\text{-}Cu_2O$[g)]	2-Chloro-2-methylpentane	2	0	78	2-Fluoro-2-methylpentane 100
"[h)]	2-Chloro-2,4-dimethylpentane	1.5	0	83	2-Fluoro-2,4-dimethylpentane 100
"[i)]	1-Chloro-1-methylcyclopentane	0.1	0	75	1-Fluoro-1-methylcyclopentane 100

a) 5 mmol in 3 ml CCl_4. b) Ref. 2. c) Ref. 3. d) HF; 150 mmol, THF; 40 mmol. e) HF; 150 mmol, Cu_2O; 7 mmol. f) HF; 150 mmol, THF; 40 mmol, Cu_2O; 7 mmol. g) HF; 150 mmol, Et_2O; 30 mmol, Cu_2O; 7mmol. h) HF; 150 mmol, Et_2O; 40 mmol, Cu_2O 7 mmol. i) HF; 150 mmol, Et_2O; 50 mmol, Cu_2O; 7 mmol. j) Determined by GLPC.

oligocondensation of R^+ are strongly suppressed in the Cu_2O-HF-Organic base solution and the reaction of R^+ with fluoride anion occurs predominantly. Interestingly, such halogen-fluorine exchange reactions are observed to take place without the carbon skeletal rearangement in the substrate such as 2-chloro-2,4-dimethyl pentane.

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