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FLUORINATION OF HALOGENO ALCOHOLS WITH 1,1,2,3,3,3-HEXAFLUOROPROPYL DIETHYLAMINE

S. WATANABE, T. FUJITA, Y. USUI, Y. KIMURA

Department of Applied Chemistry, Faculty of Engineering, Chiba University, Yayoicho, Chiba 260 (Japan)

and T. KITAZUME

Department of Chemical Technology, Tokyo Institute of Technology, Ohokayama, Meguro-ku, Tokyo 152 (Japan)

SUMMARY

Fluorination of halogeno alcohols with 1,1,2,3,3,3-hexafluoropropyl diethylamine (PPDA) was investigated. 2-Bromo-1-fluorobutane was obtained from the reaction of PPDA and 2-bromo-1-butanol (yield 50 %). Similar results were obtained from other aliphatic and aromatic halogeno alcohols. However, the corresponding 2,3,3,3-tetra-fluoropropionate esters were obtained from the reactions of PPDA and α-halogeno cycloalkanols, such as 2-chlorocyclohexanol.

INTRODUCTION

Fluorinated compounds have been widely utilized in biochemical investigations. However, fluorinations of bromo-alcohols and chloro-alcohols by exchange of -F for -OH have not been described previously. We now wish to report a convenient fluorination of halogeno-alcohols. Recently, it was reported that 1,1,2,3,3,3-hexafluoropropyl diethyamine is useful as a fluorinating agent for alcohols [1], glycerol derivatives [2] and diols [3]. As this reagent is the adduct of perfluoropropene and diethylamine, it is abbreviated as PPDA. In this note, we describe the reaction of PPDA with a variety of halogeno-alcohols.

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RESULTS AND DISCUSSION

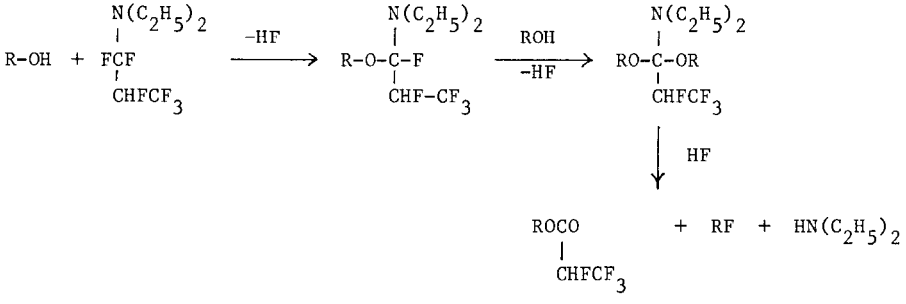
Convenient fluorinations of standard alcohols by the exchange of F for OH using PPDA have been reported [1]. This note describes an extension of this fluorination to various halogeno-alcohols using PPDA. We have found that the corresponding fluorinated halogeno-hydrocarbons are obtained from the reaction of PPDA with a range of aliphatic and aromatic halogeno-alcohols. For example, 1-chloro-6-fluorohexane (II) was obtained from 6-chloro-1-hexanol (I) and PPDA. Other fluorides were obtained in reasonable yields (Table 1).

$$ClCH_2CH_2CH_2CH_2CH_2CH_2OH\ (I) \xrightarrow{PPDA} ClCH_2CH_2CH_2CH_2CH_2CH_2F\ (II)$$

In contrast however, 2,3,3,3-tetrafluoropropionate esters were obtained from the reaction of PPDA with halogeno-cyclohexanols. For example, 3-bromobornyl 2,3,3,3-tetrafluoropropionate (IV) was produced by the reaction of PPDA with 3-bromoborneol (III). Such esters were obtained also from 2-methyl (and ethyl)-3-fluoro-3-phenylpropanol.

III IV

The undesirable side reaction of α-halogenocyclohexanols is interesting. The possible mechanism is proposed as the equation.



The examples studied are all given in Table I. Evaluation of these new fluorine compounds as bioactive substances is now in progress at our laboratory.

EXPERIMENTAL

Reaction of 6-chloro-1-hexanol (I) with PPDA

A solution of PPDA (10.0g, 45 mmol) in dry diethyl ether (15 mL) was added dropwise into a solution of 6-chloro-1-hexanol (6.8g, 50 mmol) in diethyl ether (15 mL) at room temperature. After stirring for 6hr, the reaction mixture was left overnight. It was then poured into water and the oily product was extracted with diethyl ether. The ether extract was washed with water, dried over anhydrous sodium carbonate, filtered, and evaporated to remove the solvent. The residue was distilled to give the following fractions: (i) 44-125°C/760mmHg, 2.1g; (ii) 125-130°C/760mmHg, 5.0g, and (iii) 130-160°C/760mmHg, 4.1g. Fraction (ii) was 1-chloro-6-fluorohexane (II) (purity 95% by gas chromatographic analysis using a column of Silicone DC 200 on Celite 545 at 130°C). The isolated yield was 69%. Fraction (iii) was a mixture of (II) , N,N-diethyl 2,3,3,3-tetrafluoropropionamide and unreacted (I). Compound (II) showed the following spectral data. ^{1}H NMR (δ, ppm): 1.45 (8H, broad s, $-CH_2-$), 3.50 (2H, t, J=6Hz, $-CH_2Cl$), 4.40 (2H, dt, J_{HF}=48.0, J_{HH}=6.0, $-CH_2F$). ^{19}F NMR (δ, ppm): 136.7 upfield (multiplet) from external standard CF_3COOH.

Other halogeno alcohols were fluorinated in the same manner, and the results are listed in TABLE 1.

Reaction of 3-Bromoborneol (III) with PPDA

A solution of PPDA (4.0g, 18 mmol) in dry dichloromethane (15 mL) was added dropwise into a solution of 3-bromoborneol (III)(2.0g, 8.6 mmol) in dichloromethane (20 mL) at room temperature. The reaction mixture was treated in the usual way to give following fractions;(i) b.p. 79-133°C/21 mmHg, 3.5g; (ii) b.p. 133-136°C/21 mmHg, 2.0g; (iii) residue 0.4g. Fraction (i) was a mixture of the amide and a small amount of a fluoride of (III) and ester (IV) . Fr(ii) was pure 3-bromobornyl 2,3,3,3-tetrafluoropropionate (IV) (yield 65 %). Compound (IV) showed the following spectral data. IR

TABLE 1

Fluorination of Halogen-containing Alcohols with PPDA

Alcohol	Product	Boiling Point[a] (°C/mmHg)[b] (yield%)	^{19}F NMR δ, ppm -CHF	-CH_2F	CF_3	J_{HF} Hz	J_{FF}
Aliphatic Halogeno Alcohols							
4-Chloro-1-butanol	1-Chloro-4-fluorobutane	50-60°/760mmHg (64%)		+138(m)		48	
2-Bromo-1-butanol	2-Bromo-1-fluorobutane	78-82/760 (50)		+139(m)		49	
1-Bromo-2-butanol	1-Bromo-2-fluorobutane	80-90/760 (40)	+98(d,quintet)			52	
1-Chloro-2-butanol	1-Chloro-2-fluorobutane	45-50/760 (39)	+95(d,quintet)			50	
2-Bromo-1-pentanol	2-Bromo-1-fluoropentane	90-95/760 (55)		+138(m)		48	
6-Chloro-1-hexanol	1-Chloro-6-fluorohexane	125-130/760 (69)		+136.7(m)		48	
6-Bromo-1-hexanol	1-Bromo-6-fluorohexane	140-145/760 (68)		+139(m)		49	
1-Bromo-2-hexanol	1-Bromo-2-fluorohexane	135-140/760 (65)	+98(d,m)			50	
8-Bromo-1-octanol	1-Bromo-8-fluoroctane	c (55)		+135(m)		46	
11-Bromo-1-undecanol	1-Bromo-11-fluoroundecane	c (50)		+134(m)		47	

11-Chloro-1-undecanol	1-Chloro-11-fluoroundecane	c (43)		+132(m)	48	
Cyclic Halogeno Alcohols						
3-Bromoborneol	3-Bromobornyl 2,3,3,3-tetrafluoropropionate	136/21 (65)	+124(d,q)	-3.1(d,d)	42	12
3-Chloroborneol	3-Chlorobornyl 2,3,3,3-tetrafluoropropionate	c (55)	+124(d,q)	-2.9(d,d)	39	11
2-Bromocyclohexanol	2-Bromocyclohexyl 2,3,3,3-tetrafluoropropionate	c (40)	+125(d,m)	-3.0(d,d)	41	12
2-Chlorocyclohexanol	2-Chlorocyclohexyl 2,3,3,3-tetrafluoropropionate	140/15 (50)	+123(d,m)	-2.5(d,m)	38	10
Aromatic Halogeno Alcohols						
p-Chlorobenzyl alcohol	p-Chlorobenzyl fluoride	65-68/21 (48)		+126.3(t)	46.4	
m-Chlorobenzyl alcohol	m-Chlorobenzyl fluoride	63-65/21 (50)		+128.5(t)	45	
o-Chlorobenzyl alcohol	o-Chlorobenzyl fluoride	60-63/21 (49)		+128(t)	45	
p-Bromobenzyl alcohol	p-Bromobenzyl fluoride	c (40)		+130(t)	49	
m-Bromobenzyl alcohol	m-Bromobenzyl fluoride	c (38)		+134.2(t)	48	

(continued overleaf)

TABLE 1 (cont.)

o-Bromobenzyl alcohol	o-Bromobenzyl fluoride	60-63/21 (49)	+132.3(t)		47.4	
m-Iodobenzyl alcohol	m-Iodobenzyl fluoride	c (50)	+127.0(t)		48.0	
2-Ethyl-3-phenyl-3-fluoropropanol	2-Ethyl-3-phenyl-3-fluoropropyl 2,3,3,3-tetrafluoropropionate	95-96.5/4 (70)	+123(d,q)(-$\overset{O}{\overset{\|}{C}}$CHF-) +107(d,d)(Ph-CHFCH)	-2.04	45.6 46.0	11.8 11.7
2-Methyl-3-phenyl-3-fluoropropanol	2-Methyl-3-phenyl-3-fluoropropyl 2,3,3,3-tetrafluoropropionate	90-90/4 (55)	+123(d,q)(-COCHF) +106(d,d)(ph-CHFCH)	-2.10	46.0 47.1	12.0 11.7

[a] The isolation of fluorides or esters was done by fractionation through a small Widmer column.

[b] The yield was calculated as isolated yield.

[c] These compounds were separated by liquid chromatography using a silica gel column and n-hexane containing 3% ethyl acetate as the solvent.

(cm^{-1}): 1785 (-O-C-). ^{1}H NMR (δ, ppm): 0.85 (3H, s, CH_3-), 1.00 (6H, s, CH_3x2), 1.6-2.0 (5H, m, other cyclic protons), 4.8 (2H, m, -CH-OCO and -CHBr-), 5.25 (1H, dq, J_{HF}42.0Hz, J_{HCF_3}=6.3Hz, CHF), ^{19}F NMR(δ, ppm) CF_3 at 3.1 downfield from external standard CF_3COOH (dd, J_{FF}=12.0Hz, J_{HF}=6.3Hz, CF_3) -CHF- at 124.0 upfield (dq, J_{HF}=42.0Hz, J_{FF}=12.0Hz, -CHF). Other cyclic alcohols were fluorinated in the same way, and the results are listed in Table I.

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