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BROMOFLUORINATION OF DOUBLE BONDS USING N-BROMOIMIDES AND TETRA-n-BUTYLAMMONIUM FLUORIDE AS A SOURCE OF FLUORIDE

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SUMMARY

Bromofluorination of 4-tert-butyl-1-methylcyclohexene (**I**) using a combination of N-bromosuccinimide and tetra-n-butylammonium fluoride as a source of fluoride gave the vicinal bromofluorides in acceptable yield. Similar treatment of methyl 3α,7α-diacetoxy-5β-chol-11-ene-24-carboxylate (**IV**) afforded the 12α-bromo-11β-fluoro steroid (**V**) in good yield.

INTRODUCTION

Vicinal halofluoride compounds serve as intermediates for the preparation of monofluoroaliphatic compounds. A variety of combinations of N-haloelectrophiles such as N-bromosuccinimide (NBS) and fluoride ion sources such as the HF-pyridine complex have been utilized effectively for addition of the elements of a halogen (except fluorine) and fluorine across double bonds [1-6]. A survey of the literature reveals that the most common sources of fluoride ion are anhydrous hydrogen fluoride and elemental fluorine. The other method involving silver fluoride [5] is limited to use with the halogen, in which the use of finely powdered silver fluoride and vigorous stirring of the reaction mixture are definitely required. Recently, Heasley et al. [6] have investigated boron trifluoride-promoted reactions of N-haloelectrophiles or hypohalites with alkenes to give halofluorides.

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Tetraalkylammonium fluorides have found widespread use in synthetic chemistry as organic-soluble and potent sources of nucleophilic fluoride ion [7]. The recent preparation and successful use of anhydrous tetra-n-butylammonium fluoride (TBAF) as a fluorinating agent [8-10] led us to investigate the synthetic utility of employing this agent in conjunction with N-bromoimides for bromofluorination of alkenes.

RESULTS AND DISCUSSION

In the initial investigation, 4-tert-butyl-1-methylcyclohexene (**I**) was chosen as a suitable model of alkylated olefins, in which isomerization of the primary formed bromonium ion could be avoided when the stereochemistry of halogenation is studied [11]. When (**I**) was treated with NBS-RbF or NBS-CsF in acetonitrile, no bromofluorination occurred. However, the use of TBAF as a source of fluoride gave a reaction mixture containing two vicinal bromofluorides, which were assigned as c-2-bromo-t-4-tert-butyl-1-fluoro-r-1-methylcyclohexane (**II**) and c-2-bromo-c-4-tert-butyl-1-fluoro-r-1-methylcyclohexane (**III**) on the basis of their spectroscopic data; no fluorine-free products were identified. These adducts were identical with products obtained by the reaction of (**I**) with NBS in the presence of a mixture of HF-pyridine. In order to determine the optimal conditions for bromofluorination, reactions were carried out by adding 1.2 equivalents of NBS to a solution of (I) in dipolar aprotic solvent containing 1.2 equivalents of TBAF and allowed to proceed in the range from -20° to 80°C. The progress of the

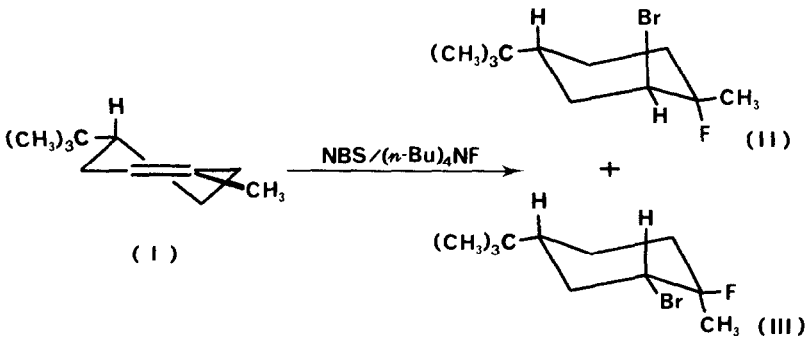


TABLE 1

Bromofluorination of 4-tert-butyl-1-methylcyclohexene (I) with N-bromoimides and TBAF in acetonitrile at room temperature[a]

Substrate concentration	N-bromoimides	Reaction time(min)	Bromo-fluoride adduct[b],%	
			(II)	(III)
9.4×10^{-2} M	NBS	10	9.2	0.7
		30	14.0	1.3
		60	14.5	1.3
		120	15.2	1.5
12.5×10^{-2} M	NBS	10	13.8	1.2
		30	18.7	1.8
		60	20.0	2.0
		120	23.0	1.9
27.8×10^{-2} M	NBS	10	21.4	2.6
		40	31.4	2.8
		120	50.9	2.4
5.3×10^{-2} M	NBPFS[c]	120	2.6	1.6
13.3×10^{-2} M	NBPFS[c]	120	6.7	4.1
6.1×10^{-2} M	NBPFG[c]	120	4.0	2.7

[a] All reactions were carried out using 1.2 molar equivalents of N-bromoimides and TBAF, respectively, with respect to the alkene.

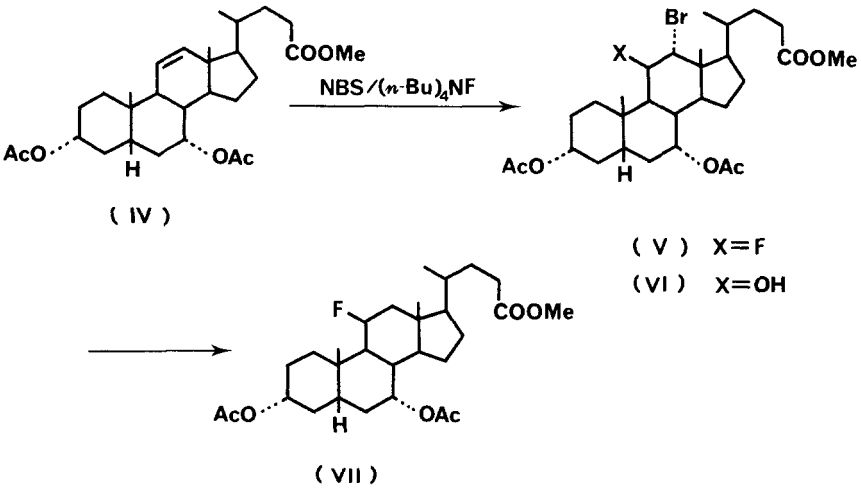
[b] Yields were determined by gas chromatographic analysis using an internal standard.

[c] NBPFS : N-bromoperfluorosuccinimide
NBPFG : N-bromoperfluoroglutarimide

reaction was monitored by gas chromatographic analysis. The most favorable conditions for bromofluorination of (I) involved use of acetonitrile as the solvent and room temperature. The amount of fluorine incorporation is greater when the concentration of (I) in acetonitrile is increased (Table 1). In changing the alkene concentration from 9.4×10^{-2} M to 27.8×10^{-2}M, the yield of the bromo-fluoride adduct (II) increased from 15.2 up to 50.9% in 2 hr; prolongation of reaction time led to no

increased formation of the bromofluorides. The use of N-bromoperfluorosuccinimide (NBPFS) and N-bromoperfluoroglutarimide (NBPFG) of higher ionic nature instead of NBS as brominating agents was disappointing, giving only few % of (**II**) and (**III**). Thus, bromofluorination of (**I**) using NBS-TBAF follows the Markovnikov-type regioselectivity and proceeded stereospecifically anti, in accord with that already observed by reaction of 1-phenyl-4-tert-butylcyclohexene with conventional NBS-HF-pyridine [11].

In order to assess the further utility of bromofluorination using the combination of NBS and TBAF, we selected methyl 3α,7α-diacetoxy-5β-chol-11-ene-24-carboxylate (**IV**) having a cis-olefinic component as substrate. Initial approach of electrophilic bromine to the C_{11}-C_{12} double bond had been expected from the α-face [12] and fluoride ion attack via 'antiparallel path' [13] would produce exclusively the 12α-bromo-11β-fluoro steroid. As expected, (**IV**) reacted with the NBS-TBAF reagent with regiospecificity to give methyl 3α,7α-diacetoxy-12α-bromo-11β-fluoro-5β-cholane-24-carboxylate (**V**) along with the bromohydrin (**VI**) in the isolated yields shown in Table 2. In particular, the use of three equivalent amounts of NBS and TBAF,



(IV)

(V) X=F

(VI) X=OH

(VII)

TABLE 2

Bromofluorination of methyl 3α,7α-diacetoxy-5β-chol-11-ene-24-carboxylate (**IV**) with NBS and TBAF in acetonitrile[a]

Equiv of NBS[b]	Equiv of TBAF[b]	Recovery %	Product %[c]	
			(**V**)	(**VI**)
1	1	23	50	13
3	1	6	63	22
3	3	-	87	11

[a] Reactions were carried out at room temperature for 1 hr with substrate concentration of 15 X 10^{-2}M.

[b] Molar equivalent with respect to the steroid (**IV**).

[c] Isolated yields based on the starting steroid (**IV**).

respectively, led to a good yield of (**V**) with the complete consumption of (**IV**). Similar treatment of (**IV**) with conventional NBS-HF-pyridine in ether at room temperature for 2 hr gave the same steroid (**V**) in 54% yield. The stereochemistry of (**V**) was conveniently determined from its ^{1}H-NMR spectrum. The structure of (**VI**) was established by comparison with a sample prepared by the reaction of (**IV**) with NBS in aqueous DMSO [14]. The monofluoro steroid (**VII**) was produced by reduction of (**V**) with tri-n-butyltin hydride generated *in situ* [15].

This work presents the first attempt to use TBAF as a source of nucleophilic fluorine for bromofluorination of the double bonds and provides satisfactory yields of bromo-fluoride adducts. The described method has the advantages of using mild conditions, readily available reagents and simplicity of procedure. It may be comparable to the conventional method using the HF-pyridine complex, although more extensive studies are needed. The present methodology may be also applied to the radiosynthesis of specially ^{18}F-labeled fluorinated analogs of bioactive molecules, because ^{18}F-labeled TBAF with high specific activity can be readily prepared from aqueous tetra-n-butylammonium hydroxide and aqueous ^{18}F-fluoride [16].

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR spectra were obtained with a JEOL PS-100 spectrometer in $CDCl_3$ solutions with Me_4Si as an internal reference. Infrared (IR) spectra were obtained with a JASCO IR-1 spectrophotometer and mass spectra (MS) were determined on a JEOL D-300 mass spectrometer. Column chromatography was carried out on silica gel (Kiesel gel-60, 70-230 mesh, Merck). Analytical gas chromatography (GC) was performed with a Hitachi 063 gas chromatograph equipped with a flame ionization detector and a stainless steel column (2m X 3mm) packed with a 5% PEG-20M on 80-100 mesh chromosorb W(AW-DMCS) was used at 140°. Commercial tetra-n-butylammonium fluoride trihydrate was kept under reduced pressure for 2 days at 40° [9] and immediately used for the fluorinations. N-Bromoperfluorosuccinimide and N-bromoperfluoroglutarimide were prepared by a published method [17].

Bromofluorination of 4-tert-butyl-1-methylcyclohexene (I) with NBS and pyridinium poly(hydrogen fluoride)

Into a mixture of pyridinium poly(hydrogen fluoride)(70%) (6.0 ml) and dry ether (6.0 ml), NBS (2.82 g) was added, cooled by an ice bath. To this mixture was added a solution of (I) (2.0 g) [18] in dry ether (4.0 ml) at 0°. After being stirred at room temperature for 1 hr, the mixture was poured into ice-water and extracted with ether. The ether was washed with 5% NaOH, 5% HCl, and water and dried over Na_2SO_4. After evaporation of the solvent at 0° under reduced pressure, the residue was chromatographed on silica gel. Elution with n-hexane gave gas chromatographically pure c-2-bromo-t-4-tert-butyl-1-fluoro-r-1-methylcyclohexane (II) (nc) (1.03 g, 31%) as an oil. MS m/e 252(M^+ + 2), 250(M^+); ^{1}H-NMR($CDCl_3$) δ: 0.88(s, 9H, 3XMe), 1.45(d, J_{HF}=23.0 Hz, 3H, Me), 1.1-2.3(m, 7H), 4.27(m, 1H, C_2-H). Further elution with the same solvent gave gas chromatographically pure c-2-bromo-c-4-tert-butyl-1-fluoro-r-1-methylcyclohexane (III) (nc) (738 mg, 22%) as an oil. MS m/e 252(M^+ + 2), 250(M^+); ^{1}H-NMR($CDCl_3$) δ: 0.89(s, 9H, 3XMe), 1.45(d,

J_{HF}=23.0 Hz, 3H, Me), 1.0-2.4(m, 7H), 4.22(ddd, J_{HF}=12.0 Hz, J=4.5, 9.5 Hz, 1H, C_2-H).

Bromofluorination of 4-tert-butyl-1-methylcyclohexene (I) with N-bromoimides and TBAF

To a 5.3 X 10^{-2}- 27.8 X 10^{-2}M solution (volume of the reaction: 2-6 ml) of (I) in dry acetonitrile containing 1.2 equivalent amounts of anhydrous TBAF was added 1.2 equivalent amounts of NBS (NBPFS or NBPFG). The stirring was continued for 3 hr at room temperature. Portions of the mixture were directly withdrawn at various time and analyzed by GC using t-4-tert-butylcyclohexanol as an internal standard. The bromo-fluoride adducts (**II** and **III**) were identified by comparison of retention times with those obtained by the reaction of (I) with NBS-HF-pyridine in ether. A summary of the yield data is presented in Table 1; there was at least one unidentified peak in the chromatogram. The use of other solvents such as dimethylformamide, dimethyl sulfoxide, and propylene carbonate, and higher temperature yielded no increasing amounts of the bromo-fluoride adducts.

Bromofluorination of methyl 3α,7α-diacetoxy-5β-chol-11-ene-24-carboxylate (**IV**)

(A) With NBS-TBAF

(a) The steroid olefin (**IV**)(156 mg, 0.319 mmol) [19] was dissolved in dry acetonitrile (2.0 ml) containing anhydrous TBAF (83 mg, 0.317 mmol). To this solution was added NBS (57 mg, 0.319 mmol). The reaction mixture was stirred for 1 hr at room temperature, quenched by addition of water, and extracted with $CHCl_3$. The $CHCl_3$ was washed with aqueous saturated NaCl and dried over Na_2SO_4. The residue, after removal of the solvent, was chromatographed on silica gel with n-hexane-ethyl acetate (15:1, v/v). The first fraction furnished starting material (**IV**)(36 mg). The second fraction gave methyl 3α,7α-diacetoxy-12α-bromo-11β-fluoro-5β-cholane-24-carboxylate (**V**) (nc) (94 mg, 50%) as colorless needles, after recrystallization from n-hexane, mp 148-149°. IR($CHCl_3$): 1735(CO)cm^{-1}; MS m/e

528(M^+ + 2 - AcOH), 526(M^+ - AcOH), 507(M^+ - Br), 468(M^+ + 2 - 2AcOH), 466(M^+ - 2AcOH); ^{1}H-NMR($CDCl_3$) δ: 0.96(d, J_{HF}=3.0 Hz, 3H, C_{18}-Me), 1.03(d, J=6.0 Hz, 3H, C_{21}-Me), 1.08(d, J_{HF}=4.0 Hz, 3H, C_{19}-Me), 0.8-2.6(m, 22H), 2.05(s, 3H, OCOMe), 2.09(s, 3H, OCOMe), 3.67(s, 3H, COOMe), 4.56(broad m, 1H, C_3-H), 4.57(dd, J=2.8 Hz, J_{HF}=12.0 Hz, 1H, C_{12}-H), 5.00(m, 1H, C_7-H), 5.15(dm, J_{HF}=48 Hz, 1H, C_{11}-H); Anal. Calcd. for $C_{29}H_{44}O_6BrF$: C, 59.28; H, 7.55. Found: C, 59.18; H, 7.55. The coupling of 11β-fluorine with both C_{18}- and C_{19}- methyl protons is consistent with that expected [20]. Further elution with n-hexane-ethyl acetate (10:1, v/v) gave methyl 3α,7α-diacetoxy-12α-bromo-11β-hydroxy-5β-cholane-24-carboxylate (**VI**) (nc) (36 mg) as colorless needles, after recrystallization from n-hexane, mp 144-145°. IR($CHCl_3$): 1735(CO)cm^{-1}; MS m/e 505(M^+ - Br), 466(M^+ + 2 - 2AcOH), 464(M^+ - 2AcOH); ^{1}H-NMR($CDCl_3$) δ: 1.07(s, 3H), 1.16(s, 3H), 0.8-2.8(m, 25H), 2.06(s, 3H, OCOMe), 2.09(s, 3H, OCOMe), 2.27(1H, OH, D_2O exchangeable), 3.67(s, 3H, COOMe), 4.60(broad m, 1H, C_3-H), 4.47(broad s, 2H, C_{11}-H and C_{12}-H), 4.92(m, 1H, C_7-H); Anal. Calcd. for $C_{29}H_{45}O_7Br$: C, 59.48; H 7.74. Found: C, 59.51; H, 7.64. The structure of the compound was further confirmed by comparison with material obtained by the reaction of (**IV**)(100 mg) with NBS (73 mg) in dimethyl sulfoxide (4 ml) containing one drop of water for 30 min at room temperature [14].

(b) The reaction of (**IV**)(0.128 mmol) in dry acetonitrile (0.83 ml) with anhydrous TBAF (3 equiv) and NBS (3 equiv) was carried out for 1 hr at room temperature by the same procedure as described in part (a); the yields of the products are shown in Table 2.

(c) The reaction of (**IV**)(0.228 mmol) in dry acetonitrile (1.5 ml) with anhydrous TBAF (1 equiv) and NBS (3 equiv) was carried out for 1 hr at room temperature. The same work-up and purification as described in part (a) gave (**V**) and (**VI**) in the yields shown in Table 2.

(B) With NBS-HF-pyridine

Into a mixture of pyridinium poly(hydrogen fluoride)(70%) (2.0 ml) and dry ether (6 ml), NBS (219 mg) was added. The

mixture was stirred for 5 min at room temperature. A solution of (**IV**)(500 mg) in dry ether (10 ml) was slowly added, and the reaction mixture was stirred for additional 2 hr at room temperature. The usual work-up and subsequent chromatography on silica gel with n-hexane-ethyl acetate (10:1, v/v) afforded the bromo-fluoride adduct (**V**)(335 mg, 55.8%) as colorless needles.

Methyl 3α,7α-diacetoxy-11β-fluoro-5β-cholane-24-carboxylate (**VII**)

The bromo-fluoride (**V**)(313 mg) was dissolved in dry benzene (1.0 ml). To this solution was added bis(tri-n-butyltin)oxide (239 mg) and polymethylhydrosiloxane (49 mg)[15]. The mixture was refluxed for 50 min, quenched by addition of water (10 ml), and extracted with $CHCl_3$. The $CHCl_3$ was washed with aqueous saturated NaCl and dried over Na_2SO_4. The residue, after removal of the solvent, was chromatographed on silica gel. Elution with n-hexane-ethyl acetate (15:1, v/v) gave (**IV**)(60 mg). Further elution with n-hexane-ethyl acetate (10:1, v/v) gave (**VII**) (nc) (182 mg, 67%) as colorless needles, after recrystallization from n-hexane, mp 188-189°. IR($CHCl_3$): 1735(CO)cm^{-1}; MS m/e 508(M^+); ^{1}H-NMR($CDCl_3$) δ: 0.79(d, J_{HF}=2.5 Hz, 3H, C_{18}-Me), 0.93(d, J=5.5 Hz, 3H, C_{21}-Me), 1.10(d, J_{HF}=3.5 Hz, 3H, C_{19}-Me), 0.8-2.7(m, 24H), 2.04(s, 3H, OCOMe), 2.06(s, 3H, OCOMe), 3.65(s, 3H, COOMe), 4.62(broad m, 1H, C_3-H), 4.99(broad d, J_{HF}=49 Hz, 1H, C_{11}-H), 4.99(m, 1H, C_7-H); Anal. Calcd. for $C_{29}H_{45}O_6F$: C, 68.48; H, 8.92. Found: C, 68.40; H, 9.05.

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