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HALOFLUORINATION. PART II. BROMOFLUORINATION OF ARYLCYCLOHEXENES[1]

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SUMMARY

Bromofluorination of 1-phenylcyclohexene with N-bromosuccinimide-hydrogen fluoride-pyridine in ether proceeds with Markovnikov-type regioselectivity. The reaction is stereospecific anti. Bromofluorination of 2-phenyl-3-bromocyclohexene results in the formation of r-1-bromo, t-2-fluoro-2-phenyl, t-3-bromocyclohexane.

INTRODUCTION

Available data on the stereochemistry of addition of BrF species to olefins are sparse. In the steroid series[2,3,4] stereospecific anti-addition with anti-Markovnikov-type regioselectivity is observed, on the other hand, the bromofluorination of carbohydrates[5,6] is stereospecifically syn. Using hydrogen fluoride-pyridine in conjunction with N-bromosuccinimide (NBS) for fluorination of aliphatic olefins, Olah and his co-workers[7] observed typical Markovnikov-type regioselectivity.

Bromofluorination of phenyl-substituted olefins, e.g. 1,1-diphenylethylenes, β-alkylstyrenes, proceeds with Markovnikov type regioselectivity. The reaction is stereospecific anti for trans and nonstereospecific for cis olefins[1]. Previous systematic studies on the steric course of the bromination of aryl-substituted olefins were confined to acyclic derivatives in which the possibility of rotation about the carbon-carbon single bond in the intermediates (bromonium ion) made the understanding of the mechanism of the syn addition ambiguous. Such uncertainty is obviously eliminated by using cyclic compounds like arylcyclohexenes (1). We chose these olefins because the stereochemistry of their bromination is known[8,9] and so there was a possibility of drawing conclusions from the stereochemical results about the reaction pathway.

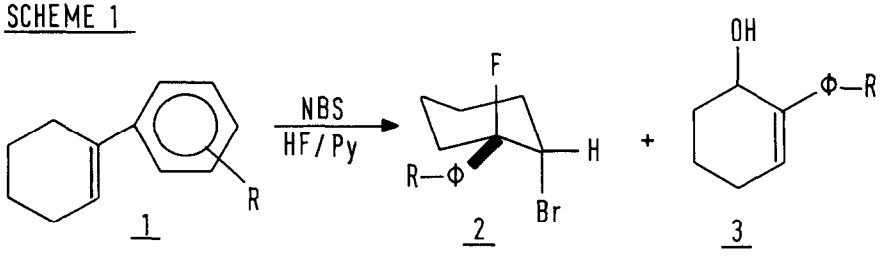
RESULTS AND DISCUSSION

The preparation of fluoroalkanes presents a different problem from that of other halogenoalkanes, and necessitates a specific method of fluorination[10]. Difficulties involve the handling of anhydrous hydrogen fluoride on the laboratory scale, the need for pressure equipment and a low temperature, and the ease of

polymerisation of alkenes. Bromofluorination with hydrogen fluoride-pyridine-NBS avoids some experimental difficulties[7], e.g. low temperature, high pressure techniques, and polymerisation of olefins.

The bromofluorination of 1-phenylcyclohexene (1a) with N-bromosuccinimide--hydrogen fluoride-pyridine in ether resulted in the formation of two products (Scheme 1). The structures of the products were determined by their, i.r., ^{1}H and ^{19}F n.m.r. and mass spectra. The major product formed (90% relative yield, determined by n.m.r.) showed a doublet signal in its ^{19}F n.m.r. spectrum at -157,3 ppm with a coupling constant of 45 Hz and in its proton n.m.r. spectrum a broad singlet signal at 4.48 ppm. On the basis of the coupling constants over three bonds we established that trans addition took place. The minor product (10%) formed in the reaction was 2-phenyl-3-hydroxycyclohexene (3a). In order to clarify the nature of the formation of the hydroxy product, we dissolved 1-bromo, t-2--fluoro-2-phenylcyclohexane (2a) in methylene chloride and the solution was treated with water for 30 min. (Scheme 2). Under these conditions we established that hydroxy product (3a) was formed. On the other hand, 2-phenyl-3-bromocyclohexene (5) remained unchanged under the conditions mentioned above. Bromofluoride (2a) was converted with sodium ethoxide or an ethanolic solution of potassium hydroxide into 2-phenyl-3-ethoxycyclohexene (4). We studied the effect of the group bonded to the phenyl ring on the course of the stereochemistry of bromofluoride addition. Bromofluorination of m-chloro derivative (1b) also resulted in the formation of trans-bromofluoride (2b) (85%) accompanied by a hydroxy derivate (3b) (15%). On the other hand, reaction with p-methoxy derivative (1c) gave the hydroxy product as the major product, the bromofluoride product being detected in traces only by n.m.r. and mass spectrometry. The formation of hydroxy compounds could be explained by the instability of the primarily formed products under the isolation conditions. Bromofluorination of 2-phenyl-3-bromocyclohexene (5) resulted in the formation of one product, which could be isolated by preparative t.l.c. (Scheme 3). The ^{19}F n.m.r. spectra shows a doublet signal at -155.5 ppm with a coupling constant of 30 Hz, indicating coupling with an axially bonded proton at the β-position. In the proton n.m.r. spectra we observed two protons at lower field, the first one as a doublet of triplet at 4.96 ppm with

SCHEME 1



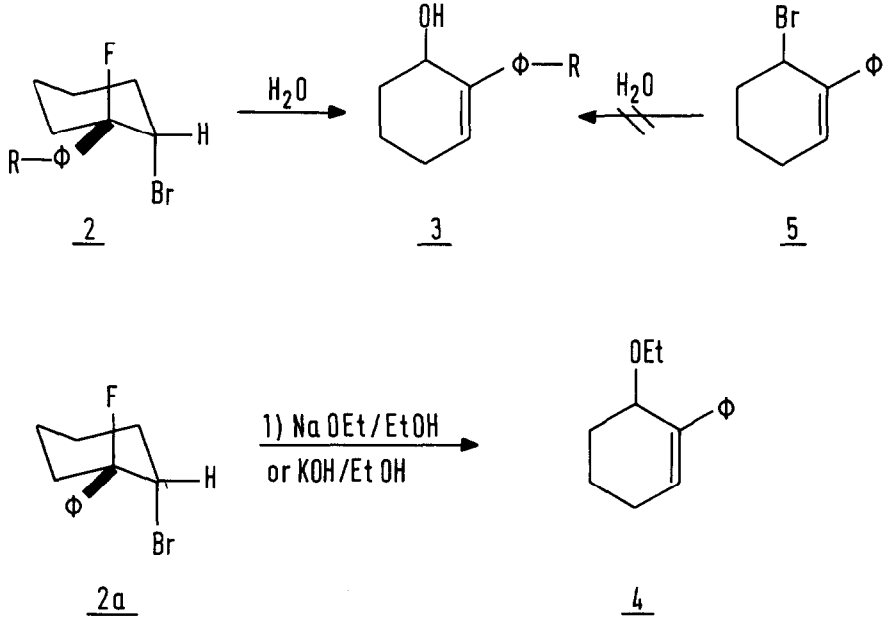
1 2 3

1a : R = H

1b : R = m—Cl

1c : R = p—OCH_3

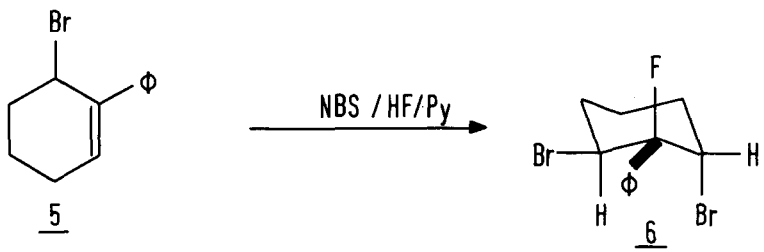
SCHEME 2



a coupling constant of 30 Hz and 9 Hz, and the second one at higher field as a broad singlet at 4.25 ppm. On the basis of the chemical shifts and the multiplicity we established that the former signal at 4.96 ppm corresponds to axially bonded hydrogen and the latter to equatorial hydrogen, indicating the formation of r-1-bromo- t-2-fluoro-2-phenyl-t-3-bromocyclohexane (6).

The mechanism of electrophilic addition of bromine to alkenes has been extensively investigated, from both kinetic and stereochemical points of view[9,11]. It is now known that the nature of the intermediates[12-21] depends on the structure

SCHEME 3



of the substrate and on the reaction medium, ranging from a strongly bridged bromonium ion of type (A) to a weakly bridged species of type (B), or an open-chain ion like (C) (Scheme 4). Whereas intermediates of type (A) involved in bromination of non-conjugated olefins, which give only anti-adducts, in the case of arylsubstituted compounds the unsymmetrical bridged (B) or open species (C) must be involved to rationalise the nonstereospecific course of the addition, which leads to syn- as well as anti-adducts. The stereochemical results of bromination reactions can be explained in terms of an intermediate more resembling an open benzylic cation (C) than a bridged bromonium ion[21] (B).

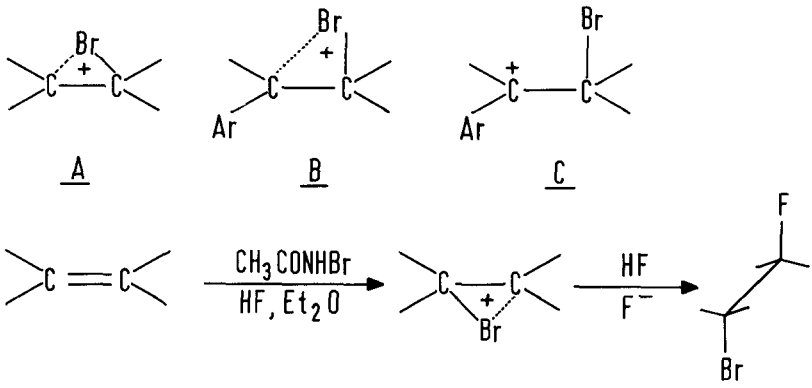
For bromofluorination with N-halogeno-amides in the presence of hydrogen fluoride, the reaction sequence shown in Scheme 4, involving a cyclic bromonium ion, has been suggested[3,4,22]. The consequences of a mechanistic pathway involving an open bromonium or partly bridged bromonium cation are presented in Scheme 5. Were such an intermediate really involved, we should observe non-stereospecific addition, accompanied by elimination products and three bromo-products as observed in bromination of phenylcyclohexene[8]. Our previous observation show a stereospecific anti-addition for trans phenylolefins and a nonstereo-specific addition for cis-phenylolefins which could be explained by the large degree of isomerisation of cis-olefins under the reaction conditions[1]. However, the solvent polarity has been considered to be the main factor affecting the extent of bridging of the intermediate, and consequently, the stereochemical results of bromination of a conjugated substrate[8,17,18]. The ability of the solvent to co-ordinate with the attacking electrophile and to solvate cationic intermediates must be also taken into account[13]. Date about the effect of hydrogen fluoride on carbocations are rather sparse and there is a possibility of a more rigid bromonium ion, which could be attacked in the anti-position. The influence of the solvent polarity on the stereochemistry of bromofluorination of phenylcyclohexene was studied by Bellucci et al.[8]

We suggest a more reasonable reaction pathway (Scheme 6) which can better explain the anti-stereoselectivity. We propose the formation of the polarised NBS-hydrogen fluoride complex (D), which reacts in a reversible step with phenyl-cyclohexene to form a complex (E), decomposing in the next step to bromofluo-rides. The reversible step in the transition state (E) could explain the high degree of isomerisation of cis olefins under the reaction conditions.[1].

A complex similar to (E) was suggested for the bromination of 1-phenylcyclo-hexene with bromine-pyridine complex[8] and has also been proposed for E2Hal elimi-nation of bromine from trans-1,2-dibromocyclohexane with benzenethiolate as base.[23]. A polarised complex of NBS with olefins has been suggested in the bromination of styrene and cyclohexene with NBS in the presence of dimethyl sulphoxide and methanol.[24].

A third interpretation of the present bromofluorination reaction involves formation of a pyridinium-bromide complex (F), reacting with 1-phenylcyclohexene with high stereoselectivity. This complex (F) is probably involved in bromofluori-nation by bromine-hydrogen fluoride-pyridine[7], which results in bromofluorides ac-companied by dibromides.

SCHEME 4



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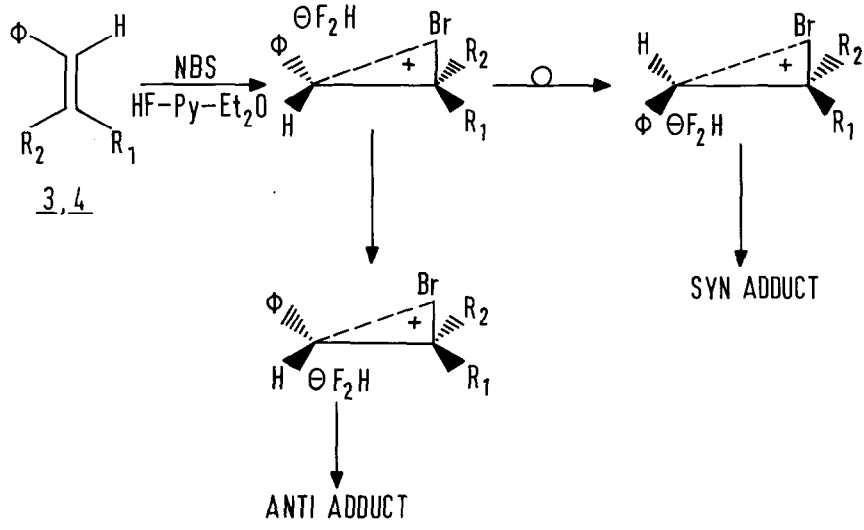
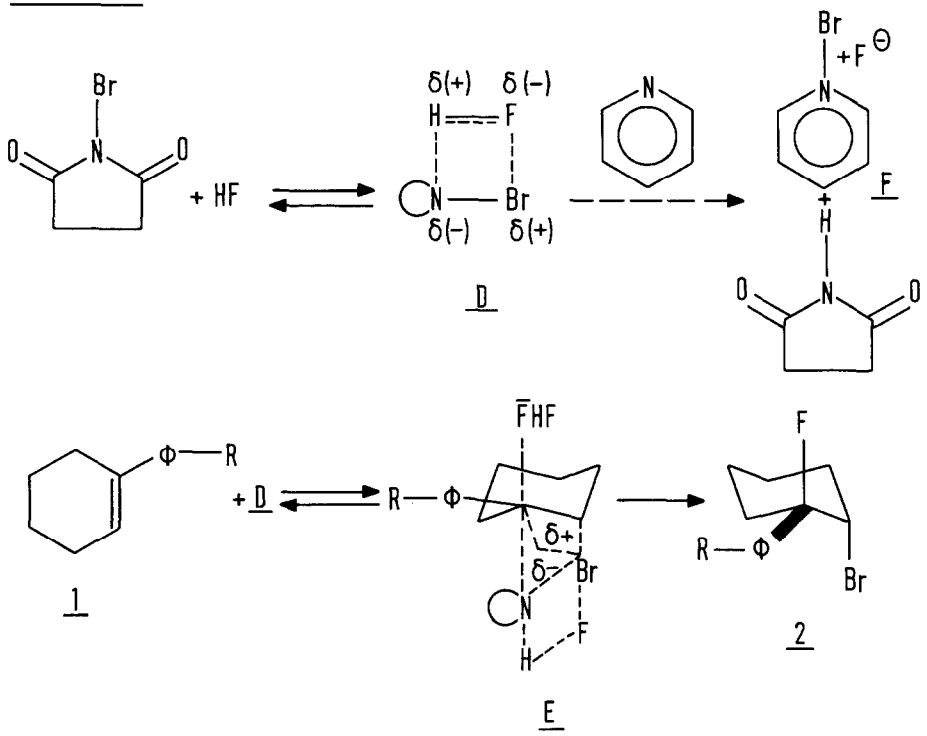


SCHEME 6



EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer, ^{1}H and ^{19}F n.m.r. spectra with a JEOL JNM-PS-100 (CCl_4 as solvent and Me_4Si or CCl_3F as internal reference). Mass spectra and high resolution measurements were obtained with a CEC-21-110 spectrometer. G.l.c. was carried out with a Varian Aerograph 1800 instrument and t.l.c. with Merck chromatoplates (PSC-fertigplatten Aluminiumoxid F-254-typ T).

Materials

A solution of pyridine in hydrogen fluoride was prepared according to Olah's procedure.[7] The pyridine used was predistilled, while hydrogen fluoride (Fluka, Purum) was used without prior purification. NBS (Fluka, Purum) was crystallised and dried (P_2O_5) before use. Diethyl ether was purified by standard methods and distilled before use. Pure samples of olefins were prepared by established methods: 1-phenyl-cyclohexenes[25], 2-phenyl-3-bromocyclohexene[8].

ADDITION AND ISOLATION PROCEDURES. In a mixture of 70% hydrogen fluoride (2 ml) and ether (2 ml), NBS (250 mg, 1.4 mmol) was dissolved with stirring at 0°C, and then the olefin (1 mmol) was added. The mixture was stirred for 1 hr at 15°C, then poured into ice-water and extracted with ether. The ether layer was washed with water, aqueous sodium hydrogen carbonate, then water again, dried (Na_2SO_4), and evaporated. After separation by preparative t.l.c. or g.l.c., n.m.r., mass, and i.r. spectra were taken.

1-bromo-t-2-fluoro-2-phenylcyclohexane (2a) n.c. and 2-phenyl-3-hydroxycyclohexene (3a) n.c.:

2a is an oily product (52%) (decomposition by heating), n.m.r.: δF-157.3 ppm (d), δCHBr =4.48 ppm (s), $J(^{19}F - ^{1}H)$=45 Hz, mass spectrum calcd. for $C_{12}H_{14}FBr$ m/e 256.0263, found m/e 256.0268, m/e: 256 (M^+, 7%), 154 (28), 91 (28), 84 (75), 66 (100), anal.calcd. for $C_{12}H_{14}FBr$: C 56.03, H 5.49%, found: C 56.02, H 5.72%.

3a is an oily product (20%) (decomposition by heating), n.m.r.: δ >CH 6.1 ppm(t), δ CHOH 4.4 ppm(s), mass spectrum calcd. for $C_{12}H_{14}O$ m/e 174.1045, found: m/e 174.1045, m/e 174 (M^+ 44%), 84(75), 66(100), anal.calcd. for $C_{12}H_{14}O$: C 82.71, H 8.10, found C 82.95, H 8.00%.

1-bromo-2-t-fluoro-2(3'-chloro)phenylcyclohexane (2b) n.c. and 2-(3'-chloro)phenyl-3-hydroxycyclohexene (3b) n.c.:

2b is an oily product (48%), (decomposition by heating), n.m.r.: δF-154.0 ppm (d), δ CHBr 4.3 ppm (s), $J(^{19}F - ^{1}H)$ = 45 Hz, mass spectrum calcd. for $C_{12}H_{13}BrClF$ m/e 289.9873, found 289.9859, m/e 292 (M^+ + 2.46%), 290 (M^+ 37%), 169(100%), 129(78), anal.calcd. for $C_{12}H_{13}BrClF$: C 49.40, H 4.49, found C 49.63, H 4.40%;

3b is an oily product (22%) (decomposition by heating), n.m.r. δ >CH 6.1 ppm(t), δ CHOH 4.7 ppm(s), mass spectrum calcd. for $C_{12}H_{13}ClO$ m/e 208.0655, found 208.0657, m/e 208 (M^+ 8%), 101(18), 86(100), 58(24), anal. calc. for $C_{12}H_{13}ClO$: C 69.04 H 6.28, found C 69.23 H 6.35%.

2-(4'-methoxy)phenyl-3-hydroxycyclohexene (3c) n.c.:

an oily product (68%), (decomposition on heating) n.m.r. δ >CH 5.9 ppm (t), δ CHOH 4.4 ppm(s), mass spectrum calcd. for $C_{13}H_{16}O_2$ m/e 204.1156, found 204.1150, m/e 204 (M^+ 42%), 186(23), 121(100), 108(20), 77(14), anal.calc. for $C_{13}H_{16}O_2$: C 76.43 H 7.90, found C 76.22 H 8.13%.

r-1-bromo-t-2-fluoro-2-phenyl-t-3-bromocyclohexane (6) n.c.:

an oily product (46%),(decomposition on heating) n.m.r. δ F -155.5 ppm(d), δ CHBr 4.25 ppm (s), δCHBr 4.96 ppm (dt), $J(^{19}F - ^{1}H)$ = 30 Hz, $J(^{1}H - ^{1}H)$ = 9 Hz, mass spectrum calcd. for $C_{12}H_{13}FBr_2$ m/e 333.9368, found 333.9358; m/e 336 (M^+ + 2,13%), 334 (M^+ 7%), 154(100), 136(32), 110(31), 87(54%), anal. calc.for $C_{12}H_{13}FBr_2$: C 42.89 H 3.90 found C 43.12 H 3.77%.

Treatment of 1-bromo-t-2-fluoro-2-phenylcyclohexane (2a)

i) with water: 1 mmol of 2a was dissolved in 5 ml of methylene chloride, 5 ml of water was added and the mixture stirred at room temperature for 30 min. The methylene chloride layer was dried (Na_2SO_4), filtered, and evaporated and the residue was analyzed by t.l.c. and n.m.r. spectroscopy. 60% of 2a were converted into hydroxy product (3a).

ii) with sodium ethoxide: 3 mmol of sodium were dissolved in 10 ml of ethanol and 2 mmol of 2a were added and stirred at room temperature for 3 hours, mixed with water, acidified with hydrogen chloride and extracted with methylene chloride. The methylene chloride layer was dried (Na_2SO_4), filtered and evaporated and residue was separated by preparative t.l.c. Yellow oily product (4) was isolated in 62% yield (decomposition on heating). N.m.r. data: δ CH 5.95 ppm (t), δ CHOEt 4.1 ppm(s), δ OCH_2 3.4 ppm(m), δ CH_3 1.0 ppm(t), mass spectrum calcd. for $C_{14}H_{18}O$ m/e 202.1353, found 202.1361, m/e 202 (M^+ 15 %), 156(100), 115(32), 91(59), anal.calcd. for $C_{14}H_{18}O$: C 83.11 H 8.97, found C 83.23 H 9.21.

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