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HYDROFLUORINATION AND BROMOFLUORINATION OF HALOGENO-SUBSTITUTED ETHYL CINNAMATES AND RELATED COMPOUNDS

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SUMMARY

We have effected bromofluorination of six olefins (unsubstituted and α or β halogeno-substituted ethyl cinnamates) and ethyl propiolate with N-bromosuccinimide : hydrofluoric acid : pyridine and the hydrofluorination of two β halogeno-ethyl cinnamates and ethyl propiolate with hydrofluoric acid : pyridine. The bromofluorination proceeds with Markovnikov-type regioselectivity and is stereospecific (anti) for unsubstituted and α-halogeno-substituted ethyl cinnamates but faster and not stereospecific for the β-substituted ones and ethyl propiolate. This difference is interpreted for cinnamates as a change in transition state from a bridged bromonium ion to an open-chain ion.

INTRODUCTION

Several methods for the synthesis of vicinal fluorohaloalkanes have recently been developed from different fluorinating agents for fluorination [1], for bromofluorination [2] and for iodofluorination [3]. The bromofluorination of aliphatic [2], aromatic [4,5] and cyclic [6] olefins, using hydrofluoric acid : pyridine in conjunction with N-bromosuccinimide, has been extensively studied. The reaction proceeds with Markovnikov-type regioselectivity. The stereospecificity seems to depend on the structure of the substrate [4,7,8].

Because of our interest in the introduction of fluorine at the β position of α-substituted carboxylic esters, we undertook the study of the hydrofluorination and the bromofluorination of α-β unsaturated esters such as substituted ethyl cinnamates and ethyl propiolate, examining the reactivities of the substrates the regioselectivity and the stereospecificity of the reaction in the relation to the nature of the substituents and the configuration of the olefins [9]. Six substrates were studied : E-ethyl cinnamates 1a, four α or β halogeno-substituted ethyl cinnamates (Z-α-fluoro 2a, Z-α-bromo 3a, Z-β-chloro 4a, E-β-chloro 5a) and ethyl propiolate 6a.

RESULTS

The extent of the bromofluorination and hydrofluorination reactions, under comparable conditions, is given in table I. The bromofluorination of the six substrates (1a-6a) gave : ethyl α-bromo β-fluoro β-phenylpropionate 1b, ethyl α-bromo α-fluoro β-fluoro β-phenylpropionate 2b, ethyl α-dibromo β-fluoro β-phenylpropionate 3b, ethyl α-bromo β-chloro β-fluoro β-phenylpropionate 4b (or 5b) with some ethylα-bromo β-difluoro β-phenylpropionate 4d (or 5d), ethyl α-bromo β-fluorocinnamate 6b with some ethyl β-difluoro β-phenylpropionate 6c.

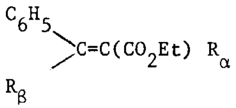
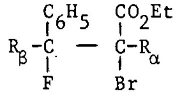
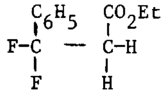
The hydrofluorination of the substrates worked only with 4a-6a. The extent of this reaction is shown on table I. With 4a (or 5a), ethyl β-difluoro β-phenylpropionate 4c (or 5c) was obtained and with 6a, 6c (= 4c = 5c) with some ethyl β-fluoro cinnamate 6d was isolated.

Several media were used : for bromofluorination, N-bromosuccinimide in hydrofluoric acid : pyridine, 70 : 30 (by weight, i.e. 0.9 : 0.1 in molar fraction) designated in table I 70% HF, or in the mixture 82 : 18 (by weight, i.e. 0.95 : 0.05 in molar fraction) designated in table I 82% HF, for hydrofluorination, hydrofluoric acid : pyridine 82 : 18. No reaction was observed using a 70% HF mixture.

Table II gives the chemical shifts of the fluorines in the α position (ϕ_{α}) and in the β position (ϕ_{β}) and of the protons in α position (δ_{α}) and β position (δ_{β}) and the two or three bond spin-spin coupling constants $^{2}J_{HF}$ and $^{3}J_{HF}$ ($^{2}J(H_{\beta}F_{\beta})$ •and

TABLE I

Extent of bromofluorination of 1a - 6a and hydrofluorination of 4a - 6a and configuration of the products

	a  $C_6H_5(R_\beta)C=C(CO_2Et)R_\alpha$			Bromofluorination b  $R_\beta-C(C_6H_5)(F)-C(CO_2Et)(Br)-R_\alpha$			Hydrofluorination c  $F-C(C_6H_5)(F)-C(CO_2Et)(H)-H$
	R_α	R_β	Configuration	Extent of the reaction (b) after 24 h with : 70% HF	82% HF	Configuration	Extent of the reaction after 24 h with (e) 82% HF
1	H	H	E	100	100	R^*S^*	0
2	F	H	Z	60	100	R^*S^*	0
3	Br	H	Z	0	5	-	0
4	H	Cl	Z	100	100 (c)	75 R^*R^* 25 R^*S^*	80
5	H	Cl	E	100	100 (c)	60 R^*R^* 40 R^*S^*	80
6(a)	-	-	-	30	100 (d)	80 E 20 Z	60 (f)

(a) 6a is $C_6H_5C\equiv C\ CO_2Et$, 6b is $C_6H_5CF=CBr\ CO_2Et$ (E and Z), 6c is $C_6H_5CF_2-CH_2CO_2Et$ (6c=5c=4c), 6d is $C_6H_5CF=CH-CO_2Et$ E.

(b) Extent of the reaction determined by NMR analysis.

(c) Total reaction : 80% of 4b and 20% of 4d ($C_6H_5CF_2-CHBrCO_2Et$).

(d) Complete reaction : 60% of 6b and 40% of 6c.

(e) No reaction with 70% HF.

(f) 60% extent of reaction = 60% of 6c and 40% of 6d.

TABLE II

^1H and ^{19}F NMR chemical shifts and coupling constants of the addition products.

	ϕ_β	δ_β	δ_α	$^2J_{HF}$	$^3J_{HF}$	homonuclear J
1b	161.4	5.7	4.4	45.7	8.0	9.75 ($^3J_{HH}$)
2b	171.5$^{(a)}$	5.9	-	44	21	21 ($^3J_{FF}$)
3b	167.6	5.9	-	37	-	-
4b	117.3	-	4.75	-	18	-
5b	122.3	-	4.65	-	20	-
4c	96.2	-	3.10	-	14	-
4d	102.5 98.8	-	4.60	-	9 14	248 ($^2J_{FF}$)
6b	69.5 E 78.5 Z	-	-	-	-	
6d	83.7	-	5.80	-	21	

(a) ϕ_α = 142.5

$^3J(H_\alpha F_\beta)$ or $^3J(H_\beta F_\alpha)$) and when appropriate $^3J_{HH}$, $^2J_{FF}$ and $^3J_{FF}$. For 1b [10], 2b and 3b, the values of the chemical shifts ϕ_β [11,12] and δ_β and the corresponding $^2J(H_\beta F_\beta)$ value are characteristic of a benzylic secondary position. The absence of β proton, and the values of the J(HF) coupling constants which are characteristic of spin-spin coupling through three bonds, make the assigment of 4b, 5b, 4c and 4d unambiguous. The structures of 6b and 6d will be discussed below along with their stereochemistry.

The configurations of 1b, 2b, 4b, 5b, 6b and 6d are given in table I. 1b with the $R^{*}S^{*}$configuration has previously been obtained by A.K. Bose and al. [10] from the bromofluorination reaction of 1a with hydrofluoric and N-bromoacetamide, a trans-addition working also with dialkyl maleate and dialkyl fumarate. We were able to prepare the diastereoisomer $R^{*}R^{*}$of 1b (1b') in hydrofluoric acid : tetrahydrofuran (see experimental part) and a close agreement was found with n.m.r. parameters of the corresponding known chloride (ethyl α-chloro β-fluoro β-phenylpropionate $R^{*}R^{*}$ described by Jullien and al. [12]). The exchanging of a chloride for a bromide introduces only minor differences in the ^{1}H and ^{19}F n.m.r. parameters. No such close comparison could be made for the configuration of 2b, but assuming the $R^{*}S^{*}$ configuration for 2b [13] , a consistent conformational analysis of the series 1b-5b could be made.

The configuration of the products from the bromofluorination of both 4a and 5a was made using elimination reactions. 4b (a mixture of two diastereoisomers 75 : 25) and 5b (the same isomers 60 : 40), in all cases form hydrochloric acid and 6b (85E : 15Z). So 4b (5b) undergoes both anti and syn-elimination. From a general point of view, open chain compounds show a distinct preference for anti-elimination [14a] . 4d under the same reaction conditions forms hydrofluoric acid and 6b with the same ratio of stereoisomer. This reaction is slightly slower for 4d than for 4b. There is a more pronounced difference in the rates and a different product ratio in the dehydrofluorination of the fluorine adducts of propenylbenzene and the dehydrochlorination of the chlorine adducts of propenylbenzene [15, 16] .

In all these reactions, the elimination seems to go through a common intermediate with a high degree of $C_{\alpha}H$ bond-breaking, with a negative charge on the α carbon stabilized by an electron-withdrawing group [17] (i.e. E1cB mechanism [14b]). This carbanion-like species could undergo inversion at the α carbon and this affords the isomeric products. Such a carbanion intermediate has already been postulated in a closely related reaction [18] : (i) the kinetics of the dehydrohalogenation of chalcone dichlorides was shown to be E1cB, (ii) this reaction occured with the R^*R^*diastereoisomer giving the Z and E olefins (2 : 1) and with the R^*S^* giving chiefly the Z olefin. These reactions could be explained by a very short-lived carbanion which gives preferentially the more stable olefin by anti-elimination. In our case, the E isomer is the major product (85 : 15) from the two mixtures of diastereoisomers (75 : 25 and 60 : 40). The prefered anti-elimination of the most abundant diastereoisomer to form the E isomer leads to the conclusion that this diastereoisomer is R^*R^* ; the R^*S^*, through the E1cB mechanism, gives more E than Z isomer.

Two isomers (80 : 20) are obtained from the bromofluorination of 6a. The hydrofluoric acid N-bromoacetamide system with 1-hexyne and phenylacetylene gives, as a very major product, the E isomer (trans addition) [19]. We can assume that the major product of 6b is the E isomer.

The configuration of 6d was E from the value $^3J_{HF}$ (21 hz). The same value has been observed on the E isomer of ethyl α-fluorocinnamate [20]. The $^3J_{HF}$ value for the Z isomer was observed to be much larger : for Z ethyl α-fluorocinnamate it was 35 hz [21] and for the other isomer of 6d, obtained from elimination of 4c (see experimental part), it was 33 hz. In both cases, the ^{13}C n.m.r. spectra of 6b and 6d were unambiguous ($^1J_{CF}$ coupling constant for the benzylic carbon) [22].

DISCUSSION

Comparative reactivity

The bromofluorination occurs much more slowly with the olefins 1a-5a and with 6a than with alkyl or aromatic olefins [2,4]. For cyclohexene [2] and for styrenes [4], the reaction times are half an hour and one hour respectively. In our work, the reaction times were 24 h or 48 h. This can be ascribed to the highly electron-withdrawing ester and halogen substituents.

The influence of α substituents on the reaction rate was more important for our compounds (the extent of the reaction decreased from 100 to 5% in going from 1a to 3a) than for the corresponding styrenes (1 h versus 3 h [4]). In certain cases no reaction was observed in the standard medium (HF : pyridine 70 : 30), and it was necessary for high yields to increase the amount of hydrofluoric acid : 2a, 3a, 6a for the bromofluorination, 4a, 5a and 6a for the hydrofluorination (the reaction being nevertheless impossible for 1a, 2a, 3a), and to obtain 4d (5d) from 4b (5b) by chlorine-fluorine exchange. With geminal electron-withdrawing substituents as in ethylbenzylidenemalonate no reaction occured.

A β substitution leads to a faster reaction (4a, 5a). Two vicinal electron withdrawing substituents do not have the same effect as two geminal ones on the desactivation of the olefin. This will be discussed further.

Regioselectivity

The ^{19}F chemical shifts in table II indicate in all cases a benzylic fluorine. The addition of "BrF" in bromofluorination and of "HF" in hydrofluorination on substituted ethylcinnamates and ethylpropiolate introduces a fluorine in the β position. So the electrophilic addition of "BrF" or "HF" occurs through a Markovnikov-type regioselectivity in agreement with what has been observed with aliphatic [2] or aromatic [4] olefins but contrarily to what Bowers and al. found in the steroid series [23].

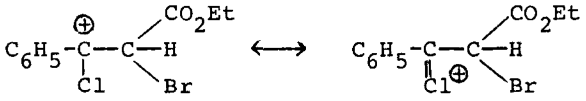
Stereospecificity

The mechanism of the electrophilic addition of brominated species to olefins has been extensively investigated from both kinetic and stereochemical points of view [24]. It is now known that the nature of the intermediate depends on the structure of the substrate and on the reaction medium, ranging from a strongly bridged bromonium ion (anti-adducts) to a weakly bridged species or an open-chain ion (anti and syn adducts).

Our results show that for unsubstituted and α-substituted cinnamates only one product is obtained for the bromofluorination

Its configuration is R*S* i.e. an anti-addition has occurred. A bridged intermediate is therefore certain.

For β-substituted cinnamates two products are obtained with the major product having the R*R* configuration i.e. also an anti-addition. This lack of stereospecificity for the ethyl β-chlorocinnamate adduct can be interpreted as either an olefin isomerisation through the reversible formation of an intermediate between the olefin and a polarized NBS-HF complex [4] or intervention of an open-chair carbonium ion stabilized by the mesomeric effect of the chlorine atom, according to the following scheme :



We prefer this second interpretation because it has been shown (vide supra) that the overall addition reaction is faster with the β chlorine atom. The β-chorosubstitution would change the mechanism from a bridged bromonium ion (without β substituent) to an open-chain ion, which would have two effects : acceleration of the reaction and loss of stereospecificity. A β-fluorocarbonium ion was assumed in the fluorination with xenon difluoride of phenyl substituted olefins [25].

With acetylenic compound <u>6a</u>, the preferred anti-addition of "BrF" that is observed is comparable to that seen with 1-hexyne (E 95 : Z 5), with 3-hexyne (E 78 : Z 22), or with phenylacetylene (E with traces of Z [19].

CONCLUSION

This reaction of bromofluorination was regioselective in all cases and had high stereospecificity for the α-substituted olefins we studied. We were able to carry out the bromofluorination of highly deactivated olefins, in spite of their decreased reactivity. We were able to introduce one or two fluorine atoms β to the ester group.

EXPERIMENTAL

Products and materials

All products were purchased from Fluka unless otherwise specified. Hydrofluoric acid was obtained from Pechiney-Ugine-Kuhlman (France).

All the 'H and ^{19}F NMR spectra were taken on a JEOL C60HL at 60 MHz (56.44 MHz). TMS was the proton reference. Trichlorofluoromethane was the fluorine reference (hexafluorobenzene was often used as a secondary reference). All new products had their molecular mass determined by mass spectroscopy on an A.E. I.MS 30 apparatus coupled with a gas liquid chromatography apparatus with a standard SE 30 column.

Starting olefins

The olefins were prepared using described methods : 2a [20], 3a [26], 4a and 5a [27]. 1a and 6a are commercial products

Bromofluorination of olefins 1a-5a [2] and alkyne 6a [19]

The olefin (0.02 mole) was added to a mixture of 25 ml of 70% (or 82%) HF-pyridine, 25 ml of ether and N-bromo succinimide (0.03 mole) in a Kel-F flask cooled to -15°C. The mixture was stirred for 1 h at 15°C and then left at room temperature for 24 h. The solution was poured into water-ice and extracted with ether. The ether layer was neutralised with saturated sodium bicarbonate solution, washed with water, and dried over anhydrous sodium sulfate. The products obtained after removal of the solvent were purified by distillation. 1b [10] : 91°C (0.4 mm) ; 2b : 94°C (0.4 mm) ; 4b-(5b) : 95°C (0.06 mm) (no separation by distillation of the two diastereoisomers could be made) ; 6b : 101°C (0.3 mm) (yield 60-70%). 3b was only observed and characterized by its 'H and ^{19}F n.m.r. parameters (table II).

Hydrofluorination of 4a - 6a

Ester (0.02 mole) was added to a mixture of 25 ml of 82% HF : pyridine and 10 ml of ether at -15°C. After one hour at -15°C and 24 h at room temperature the product was isolated as above. The compound 4c was obtained [80°C (0.1 mm)]. When the mixture was extracted after 24 h, the extent of the reaction for 6a was 60% (60% of 6c and 40% of 6d). NMR analysis of crude product gives, for 6d : 'H RMN δ_α 5.80 ppm (doublet) $^3J_{HF}$ = 21 Hz, ^{19}F RMN $^{*}\phi_\beta$ = 83.7 ppm (doublet) $^3J_{HF}$ = 21.5 Hz (E isomer see text). The other isomer is not observed in this reaction but could be prepared by elimination of hydrofluoric acid from 6c (vide infra).

Preparation of 4d

0.02 Mole of 4b was added to 50 ml of 82% HF : pyridine and 25 ml of ether at -15°C. The mixture was then stirred 36 h at room temperature and the compound isolated as above [80° (0.06 mm)].

Elimination reaction of fluorobrominated products 4b, 5b, 4d

The elimination reaction was carried out on 0.01 mole of ester 4b, 5b, or 4d in 40 ml of acetone using 1-4 diazabicyclo [2.2.2]octane (0.015 mole) as the base. Completion of the reaction was determined by g.l.c. with a SE 30 column. After two hours of stirring at room temperature for 4b and 5b, and after four hours for 4d, 150 ml of water was added. The mixture was extracted with ether, washed with 5% HCl, dried, and the solvent was evaporated. G.l.c. showed no products other than 6b, obtained by bromofluorination of 6a. ^{19}F analysis of crude product gave the proportion of the different stereoisomers. The same results were obtained by substitution of the β chlorine by fluoride anion (potassium fluoride with dibenzo-18-crown-6 in acetonitrile or potassium fluoride in N-Methyl-pyrolidone) or by azide anion (sodium azide in dimethylformamide).

Elimination reaction of the hydrofluorinated product 6c

1-4 diazabicyclo[2.2.2]octane was not strong enough to effect the elimination of hydrofluoric acid, and therefore ethanolic hydroxyde was used : 0.03 mole of sodium hydroxide dissolved in 20 ml of ethanol was added slowly to 0.03 mole of 6c in 20 ml of ethanol. After 4 h of stirring, the mixture was poured into water, extracted with ether and washed with water. Distillation gave 6d [80°, 0.1 mm], NMR analysis : 'H δ_α = 5.72 ppm (doublet), $^3J_{HF}$ = 33 Hz, ^{19}F ϕ_β = 103.2 ppm (doublet) $^3J_{HF}$ = 33 Hz.

Bromofluorination of 1a in HF : THF

HF (2 moles) was added to 40 ml of tetrahydrofuran-dichloromethane 1 : 1 at -78°C followed by 0.03 mole of N-bromoacetamid and 0.02 mole of olefin 1a. The mixture was stirred for 24 h at room temperature and worked as described above. B.P. 91°C, (0.4 mm). G.l.c. on a SE 30 column showed only one peak with the same retention time as for 1b. NMR spectra of 1b were consistent with the spectra of another product of the same type : 'H n.m.r. : δ_β = 5.65 ($^3J_{HH}$ = 8.25, $^2J_{HF}$ = 45.7), δ_α = 4.40 ppm was non resolved from the δ_α of 1b, ^{19}F n.m.r. : ϕ_β = 177.5 ($^2J_{HF}$ = 45.7 and $^3J_{HF}$ = 13.5 Hz). These spectra were similar to those of the corresponding chloro-compound [12].

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