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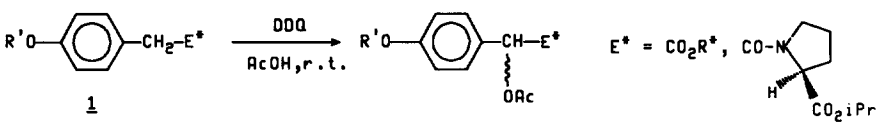
DIASTEREOSELECTIVE FLUORINATION AT BENZYLIC POSITION BY ANODIC OXIDATION

Léopold KABORE[a], *Samir CHEBLI*[a], *René FAURE*[b], *Eliane LAURENT*[a] *and Bernard MARQUET*[a]
[a]Laboratoire de Chimie Organique 3, associé au CNRS,
[b]Laboratoire de Chimie Analytique 2,
UCB-Lyon I - 43, Boulevard du 11 Novembre 1918, 69622 VILLEURBANNE Cedex (France)

Summary : By anodic oxidation of benzylic derivatives 1 in $Et_3N,3HF/CH_3CN$, diastereoselective fluorination in the α position of the electron withdrawing group is obtained. The observed stereoselectivities are discussed in connection with the inductor group. The role of the anode is also examined.

Due to their potentiality in biological applications, several synthetic routes to optically active β fluorinated aromatic aminoacids have been reported[1]. One of them involves the direct fluorination of activated benzylic derivatives[2], which can be used as precursors to this special class of aminoacids ; however the halogenation step is not stereoselective. In fact, direct enantioselective fluorination of prochiral compounds was only recently considered using an asymmetric electrophilic reagent[3]. An homochiral analogue of DAST has also been prepared in order to achieve stereoselective deshydroxy fluorination, but the enantioselectivities were low[4]. Other studies in this field were devoted to fluorination of molecules in which a chiral centre was already present (fluorodeamination of α phenylglycin[5], deshydroxyfluorination of mandelates[5,6]) or to multiple step syntheses of chiral fluorinated compounds[7].
On the other hand, Guetté and co-workers[8] have demonstrated that stereoselective acetoxylation of asymmetric benzylic derivatives 1 can be obtained using 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) as oxidant (scheme 1).

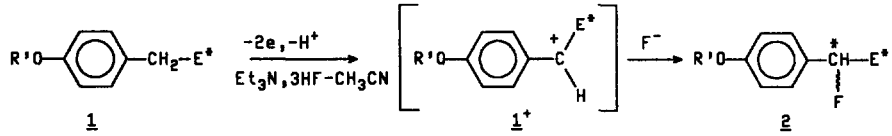


1

Scheme 1

Unfortunately, fluorination has failed when DDQ was concomitantly employed with a nucleophilic fluorinating reagent ($Et_3N,3HF$). Hence we decided to apply a previously published electrochemical process[9] which allowed the introduction of fluorine at the same position. With compounds 1, we actually found that diastereoselective fluorination occurs, without epimerization of the chiral inductor nor of the fluorinated products 2 during oxidation at the platinum anode, (scheme 2).

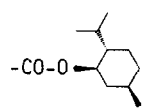
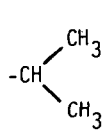
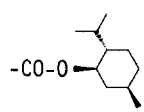
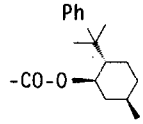
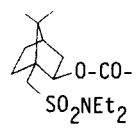
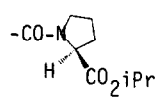
In contrast to the methodology described in ref.[3], stereoselectivity is due to the attack of an achiral nucleophilic fluorinating reagent on an intermediary chiral carbocation. Results of these electrolyses[10] are given below in the table.



Scheme 2

Except for the camphor derivative **1d**, yields of monofluorides **2** are quite the same as those observed from achiral substrates. Diastereoselective ratios of **2** can be evaluated from ^{1}H NMR (300 MHz)[11] data or more easily from a ^{19}F NMR of the crude. In the case of amide **1e**, stereoisomers were readily separated by medium pressure liquid chromatography on silica gel (5μ). The fluorine decoupled proton NMR spectrum exhibited for each one two signals of unequal intensity which indicated a conformational equilibrium.

Electrofluorination of 1 - Influence of E* structure on diastereoselectivity

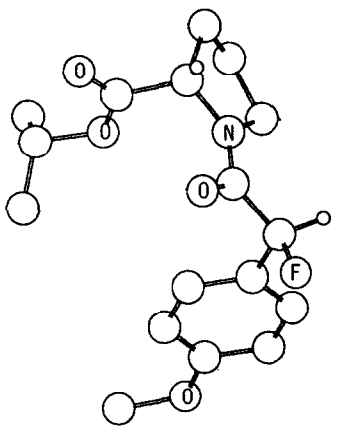
Starting compounds	R'	E*	Chemical[a] yield %	d.e.[b] %	^{19}F NMR data ($CDCl_3$) of **2**: δ ($CFCl_3$)	$^{2}J_{HF}$
1a	$-CH_3$		74	20	major -174.5 (d) minor -175.2 (d)	49.5 49.8
1b			50	20	isomeric ratios were determined by ^{1}H NMR (300 MHz)	
1c	$-CH_3$		65	60	major -173,1 (d) minor -178.8 (d)	47.7 47.6
1d	$-CH_3$		37[c]	54	major -174.9 (d) minor -173.9 (d)	48.1 48.8
1e	$-CH_3$		61	10	major -167.5(d) and -168.5(d) minor -170.0(d) and -172.9(d)	48.8 49.4 49.9 49.7

a) isolated yields (mixture of diastereoisomers) based on recovered starting material (conversion rate is always about 70 %) ;

b) diastereoisomeric excess ;

c) difluorinated benzylic product is also isolated (20 %).

In order to examine this problem in detail, an X ray diffraction analysis[12] of major isomer has been carried out (figure) and has enabled the absolute configuration (S) of the benzylic carbon to be assigned. The esters configurations have not been presently established, but this is in progress on the basis of ^{19}F NMR data of these compounds[13]. Concerning the diastereoselectivity, the best result (d.e. 60 %) was obtained when the phenylmenthyl group was used as inductor. The difference observed with 1c as against the menthyl ester derivative 1a suggests that induction might be improved by phenyl ring substituent. However it is still difficult to determine if it is related more to steric hindrance or to the specific adsorption of this group at the anode which could block the conformation of the transient cation. Other results in electrofluorination, where noticeable stereoselectivity has been obtained[14], are in favour of the adsorption hypothesis.



In summary, these preliminary result reveal that asymmetric benzylic esters or amide 1 can be electrofluorinated with an interesting degree of diastereoselectivity. We are currently studying further possible improvements of our process. Functionalization by other nucleophiles will be also examined.

References and notes

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8 - a) Lemaire M., Guy A., Imbert D. and Guetté J.P., JCS Chem. Comm., 1986, 741 ;
b) Guy A., Lemor A., Imbert D. and Lemaire M., Tetrahedron Lett., 1989, 30, 327.

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10 - Electrolyses were carried out as described before[9] at controlled potential until about 3F/mole of starting material ($5x10^{-3}$ mol.) had been passed.

11 - 2a - ^1H NMR (300 MHz, $CDCl_3$, isomeric mixture) : 0.52-0.91 (6d, 9H) ; 0.91-2.04 (m, 9H) ; 3.79 (s, 3H) ; 4.74 (m, 1H) ; 5.66 (d, 0.6H, $^2J_{HF}$=48.0) ; 5.69 (d, 0.4H, $^2J_{HF}$=48.2) ; 6.80-6.96 (m, 2H) ; 7.15-7.42 (m, 2H). MS, m/z (%) : 322 ($M^{\cdot+}$, 5), 139 (72), 83 (100), 69 (34), 57 (29), 55 (34), 43 (23).

2b - ^1H NMR (300 MHz, $CDCl_3$, isomeric mixture) : 0.51-0.92 (6d, 9H) ; 0.92-2.07 (m, 15H) ; 4.52-4.69 (m, 1H) ; 4.69-4.84 (m, 1H) ; 5.65 (d, 0.6H, $^2J_{HF}$=48.0) ; 5,69 (d, 0.4H, $^2J_{HF}$=48.3) ; 6.85-6.95 (m, 2H) ; 7.31-7.37 (m, 2H).
MS, m/z (%) : 350 ($M^{\cdot+}$, 6), 167 (34), 125 (77), 83 (100).

2c - ^1H NMR (300 MHz, $CDCl_3$, isomeric mixture) : 0.74-0.80 (2d, 3H) ; 1.00, 1.10, 1.14, 1.28 (4s, 6H) ; 0.84-1.94 (m, 8H) ; 3.73, 3.72 (2s, 3H) ; 4.38 (d, 0.2H, $^2J_{HF}$=47.6) ; 4.76-4.85 (m, 1H) ; 5.41 (d, 0.8H, $^2J_{HF}$=47.7) ; 6.75-7.34 (m, 9H).
MS, m/z (%) : 398 ($M^{\cdot+}$,0), 139 (34), 119 (100), 105 (33), 91 (35), 55 (10).

2d - ^1H NMR (300 MHz, $CDCl_3$, isomeric mixture) : 0.74-1.02 (4s, 6H) ; 1.10-1.21 (2t, 6H) ; 1.55-2.07 (m, 7H) ; 2.58-2.68 (2d, 1H) ; 3.10 (q, 4H) ; 3.17-3.25 (2d, 1H) ; 3.80 (s, 3H) ; 5.00-5.12 (2dd, 1H) ; 5.53 (d, 0.2H, $^2J_{HF}$=48.2 ; 5.71 (d, 0.8H, $^2J_{HF}$=48.0) ; 6.87-6.97 (m, 2H) ; 7.34-7.42 (m, 2H). MS, m/z (%) : 455 ($M^{\cdot+}$,0), 272 (38), 139 (100), 136 (14), 135 (99), 120 (17), 107 (32), 93 (34), 91 (12), 79 (20), 74 (17), 72 (15), 58 (14), 55 (11), 43 (14).

2e (major) - mp 114-117°C (Et_2O-acetone 95/5) ; $[\alpha]_D^{25}$=-6.79°, C=0.37 ($CHCl_3$). ^1H NMR (80 MHz, $CDCl_3$, rotameric mixture 80/20) : 1.16 (d, 3H) , 1.19 (d, 3H) ; 1.77-2.16 (m, 4H) ; 3.15-3.57 (m, 2H) ; 3.75 (s, 3H) ; 4.37-4.61 (m, 1H) ; 5.00 (sept., 1H) ; 5.63 (d, 0.2H, $^2J_{HF}$=48.8) ; 5.80 (d, 0.8H, $^2J_{HF}$=50.0) ; 6.85-7.00 (m, 2H) ; 7.22-7.50 (m, 2H). MS, m/z (%) : 323 ($M^{\cdot+}$, 1), 139 (100), 114 (90), 96 (28), 78 (32), 43 (57). Anal. Calcd for $C_{17}H_{22}NO_4F$: C, 63.16 ; H 6.81 ; N, 4.33, F, 5.88. Found : C, 62.89 ; H, 6.92 ; N 4.31 ; F, 5.70.

2e (minor) - mp 88-90°C (Et_2O-acetone 80/20) : $[\alpha]_D^{25}$=-83.72°, C=0.387 ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, rotameric mixture 80/20) : 1.15-1.25 (4d, 6H) ; 1.82-2.10 (m, 4H) ; 3.33-3.38 (m, 1H) ; 3.58-3.62 (m, 1H) ; 3.78 and 3.79 (2s, 3H) ; 4.43-4.61 (m, 1H) ; 4.91-5.05 (m, 1H) ; 5.87 (d, 1H, $^2J_{HF}$=49.9) ; 6.86-6.90 (m, 2H) ; 7.31-7.44 (m, 2H). MS, m/z (%) : 323 ($M^{\cdot+}$,5), 139 (100), 114 (63), 96 (15), 70 (21), 43 (35).

12 - Further details can be obtained upon request through the Director of Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB 1 EW.

13 - to be published in collaboration with Beguin C. and Hamman S.

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