Preliminary Note

F/Cl substitution with rearrangement initiated by the Lewis acid $AlCl_3$ in α,ω-[2-(*F*-alkyl)ethenyl]acyl derivatives: highly stereospecific *trans*-CF_2–CH=CH– to *trans*-CF=CH–CH(Cl)– transformation

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Abstract

The action of $AlCl_3$ on C_8F_{17}–CH=CH–$(CH_2)_8$–COCl (*E* isomer) leads, under mild conditions and after ethanolysis, to the formation of C_7F_{15}–CF=CH–CH(Cl)$(CH_2)_8$–COOEt, as a result of the –CF_2–CH=CH– to –CF=CH–CH(Cl)– transformation which proceeds in high yield (70%) and with high stereospecificity: the isolated compound consists of the *Z* isomer (H and F *trans*).

Our goal is to develop amphiphilic metal complexes which may be carried by vesicles (or liposomes) or by injectable fluorocarbon emulsions to be used simultaneously as drug delivery systems and as artificial oxygen carriers. We thus became interested in metallocene derivatives, a potent new class of organometallic antitumour agents [1]. The functionalization of their cyclopentadienyl ligands by highly perfluoroalkylated side-chains is expected to increase the hydrophobic and fluorophilic character of these complexes and therefore to facilitate their incorporation into liposomes and into oxygen-delivering fluorocarbon emulsions. The incorporation of a drug in fluorocarbon emulsions should combine the numerous advantages of liposome drug encapsulation (improvement of its therapeutic index, modification of its biodistribution, higher intravascular persistence as compared to the free drug) [2] with the capacity of the fluorocarbon to deliver oxygen in radio- [3] and chemo-resistant [4] tumours, thus enhancing the tumouricidal effects of radiations or of cytotoxic drugs [5].

During our investigations to prepare perfluoroalkylated side-chain ferrocenes through a Friedel–Crafts aromatic electrophilic substitution reaction on the ferrocene cyclopentadienyl rings by various perfluoroalkylated acyl chlorides, i.e. α,ω-(*F*-alkyl)acyl chlorides or α,ω-[2′-(*F*-alkyl)ethenyl]acyl chlorides, in the presence of $AlCl_3$, a more complex, but clean, reaction occurred with the latter derivatives [6]. In this case, mono- and 1,1′-bis-(perfluoroalkylated-acyl)ferrocenes were obtained as a result of an electrophilic sub-

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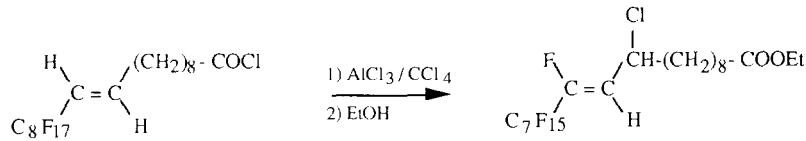
stitution reaction on the cyclopentadienyl ring. However, NMR spectroscopic analyses were not consistent with α,ω[2′-(*F*-alkyl)ethenyl]acyl side-chains. In order to gain further insight into this reaction and to characterize the compounds formed, we performed the reaction without ferrocene. We show in this paper that the action of $AlCl_3$ on the *trans* compound $C_8F_{17}-CH=CH-(CH_2)_8-COCl$ (**1**)* results, under mild conditions, in the unprecedented $-CF_2-CH=CH-$ to $-CF=CH-CH(Cl)-$ transformation [eqn. (1)] in high yield (70%) and with high stereospecificity: the isolated compound **2** consists of the *Z* isomer (H and F *trans*).



1 **2** (1)

A CCl_4 solution (10 ml) of *trans*-11-(*F*-octyl)-10-undecen-1-oyl chloride (1.66 g, 2.68 mmol)† was added dropwise to an $AlCl_3$ (0.35 g, 2.61 mmol) suspension in CCl_4 (10 ml), cooled to 0 °C and placed under dry argon. The resulting mixture was stirred over 1 h at 0 °C, then heated at 50 °C for a further hour. The reaction was then quenched by addition of ethanol‡. Usual work-up, chromatography on silica gel (eluant: petroleum ether/ethyl acetate, 9:1) and recrystallization from pentane at −18 °C led to compound **2** (1.21 g, 1.87 mmol, 70% yield) as white crystals melting at room temperature.

The elemental and spectroscopic analysis of **2**§ were consistent with the proposed formulation. Thus, the IR, ^1H and ^{13}C NMR data of **2** indicate

*To our knowledge, the action of $AlCl_3$ alone on compounds containing a $CF_2-CH=CH-$ sequence has never been reported (see ref. 12). However, several reactions could have been expected to occur between $AlCl_3$ and **1** in CCl_4: thus (i) an intra- and/or inter-molecular electrophilic addition of the $-C(O)-Cl$ link on to the double bond of **1** resulting in the formation of a ketone derivative or (ii) condensation of **1** with CCl_4 [7]; another alternative is (iii) fluorine by chlorine exchange, as shown for $CF_3-CF=CF_2$ in the presence of $AlCl_3$ [8].

†The synthesis of **1** has been performed from *trans*-11-(*F*-octyl)-10-undecylenic acid and thionyl chloride [9]. The ^1H NMR spectrum of this acid exhibits two multiplets at 5.33–5.94 ppm and 6.20–6.75 ppm for the CH=CH ethylenic protons.

‡The reaction, when quenched by the addition of water, leads to the acid corresponding to **2**.

§Compound **2** ($C_{21}H_{23}ClF_{16}O_2$): Anal. Calcd.: C, 38.99; H, 3.58%. Found: C, 39.48; H, 3.66%. IR (KBr, cm^{-1}): 1215, 1242 (CF_2, CF_3); 1738 (C=O). MS (*m/z*): 646, 648 ($M^{+\cdot}$, ^{35}Cl, ^{37}Cl); 611 $(M-Cl)^+$; 601, 603 $[(M-OEt)^+$, ^{35}Cl, $^{37}Cl]$. ^1H NMR, 80 MHz, $CDCl_3$, δ: 1.25 (t, $^3J_{H,H}=8$ Hz, 3H, CH_3); (1.35 (br s, 14H, $(CH_2)_7-CH_2CO$); 2.37 (t, 2H, $^3J_{H,H}=7$ Hz, CH_2CO); 4.14 (q, $^3J_{H,H}=8$ Hz, 2H, H_2C-O); 4.78 (dt, 1H, $^3J_{H,H}=10$ Hz, $^3J_{H,H}=7$ Hz, $-CHCl-$); 5.77 (dd, $^3J_{H,H}=10$ Hz; $^3J_{H,F}=31$ Hz, 1H, CH=) ppm. ^{19}F NMR, 188.8 MHz, $CDCl_3$, δ: −82.6 (3F, CF_3); −119.5 (2F, $-CF_2-CF=$); −123.3 and −122.2 (each 4F, $(CF_2)_4-CF_2-CF=$); −127.7 (2F, CF_3-CF_2); −128.6 (1F, $-CF=$) ppm. ^{13}C NMR, 50.3 MHz, $CDCl_3$, δ: 14.1 (s,CH_3); 25.0, 26.1, 28.8, 29.1, 29.15, 29.2 (all s, $(CH_2)_6-CH_2CO$); 34.3 (s, CH_2-CO); 38.1 (s,$CH(Cl)-CH_2$); 51.3 (d, $^3J_{C,F}=4$ Hz, CHCl); 60.1 (s, $O-CH_2$); 117.1 (dt, $^3J_{C,F}=4$ Hz, $^2J_{C,F}=7$ Hz, $-CH=$): 146.2 (dt, $^2J_{C,F}=30$ Hz, $^1J_{C,F}=266$ Hz, CF=); 173.8 (s, C=O) ppm.

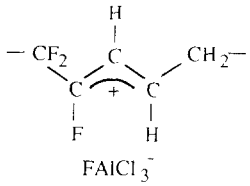
clearly that the isolated compound, after ethanolysis, converts into an ethylic ester. The presence of the molecular ($M^{+\cdot}$ = 646 and 648 for the ^{35}Cl and ^{37}Cl isotopes, respectively) and $(M-Cl)^{+\cdot}$ peaks in the mass spectrum of **2** agrees with the replacement of one fluorine by a chlorine atom. The loss of one fluorine is further confirmed by the ^{19}F NMR spectrum which exhibits, in addition to the resonances of the $CF_3-(CF_2)_6-$ chain, a signal at -128.6 ppm corresponding to one single fluorine. The transformation of the initial $CF_2-CH=CH-$ linking in **1** into the $CF=CH-CH(Cl)$ sequence in **2** is strongly supported by ^1H NMR: thus, the complex signal of the ethylenic protons of the starting material [9] is replaced by (i) a doublet ($^3J_{H,F}$ = 31 Hz) of doublets ($^3J_{H,H}$ = 10 Hz) located at 5.77 ppm corresponding to one ethylenic proton in agreement with a $CF=CH-CH$ linking in **2**, together with (ii) a doublet ($^3J_{H,H}$ = 10 Hz) of triplets ($^3J_{H,H}$ = 7 Hz) at 4.78 ppm consistent with a CH(Cl) proton in a $=CH-CH(Cl)-CH_2$ sequence. These assumptions are definitively confirmed by the ^{13}C NMR spectrum of **2** which exhibits, as expected for a $CF_2-CF=CH-CH(Cl)$ link, (i) a doublet ($^1J_{C,F}$ = 266 Hz) of triplets ($^2J_{C,F}$ = 30 Hz) for the ethylenic CF carbon at 146.2 ppm, (ii) a doublet ($^2J_{C,F}$ = 7 Hz) of triplets ($^3J_{C,F}$ = 4 Hz) for the ethylenic CH carbon at 117.1 ppm and (iii) a doublet ($^3J_{C,F}$ = 4 Hz) at 51.3 ppm for the CH(Cl) carbon. Furthermore, the presence of only one ^{19}F resonance for the CF_2 group α to the double bond and of a single $CF_2-CF=CH$ ^{13}C pattern* indicates that, as for the double bond configuration, the isolated compound **2** consists of a single isomer. The large value (30 Hz) for the $^{19}F-^1H$ coupling constant shows that the configuration of the $CF=CH$ double bond is *trans* [11] and that the isolated compound is therefore the *Z* isomer.

It should be pointed out that, under the same conditions, no reaction occurred between $AlCl_3$ and the saturated α,ω-(*F*-alkyl)acyl chloride, i.e. $C_8F_{17}-(CH_2)_{10}-COCl$. Furthermore, the fact that ethanolysis of the reaction mixture of $AlCl_3$ and **1** leads to an ethylic ester shows that acylation of the double bond in **1**, which would produce a ketone [7], if it occurs, is a minor process. Therefore, the reaction reported here, is unequivocally attributable to the presence of a $CF_2-CH=CH-$ sequence in the α,ω-[2′-(*F*-alkyl)-ethenyl]acyl chlorides, hence to the activated allylic fluorine atoms. Thus, in the presence of $AlCl_3$, intermediates **A** or **B**, either free or as an ion pair, are formed from **1** after abstraction of an allylic fluorine atom**. The observed high stereoselectivity in **2** is likely to arise from (i) the formation of the thermodynamically more stable intermediate **A** as compared to **B**, in which

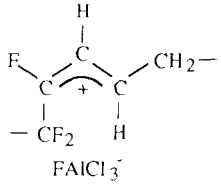
*The *cis*- and *trans*-$C_8F_{17}-CH=CH-(CH_2)_8-COOH$ derivatives exhibit different ^{19}F and ^{13}C NMR patterns for the $CF_2-CH=CH$ sequence [10].

**It has been shown that electrophilic additions of the strong acids $AlCl_3$/HCl or HSO_3Cl on $CF_3-CH=CH_2$ produce $X-CF_2CH_2CH_2Cl$ compounds (X = OSO_2Cl or Cl, F, respectively) via the postulated allylic cation $CF_2=CH-CH_2^+$, formed by solvent-assisted ionization. In the former case, it has been assumed on the basis of ^1H NMR data alone, that compound $CF_2=CH-CH_2-Cl$ (which formally results, as in our case, from the displacement of a fluorine by a chlorine atom and isomerization of the double bond) was present in the reaction mixture in 5–10% [12].

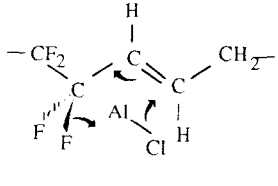
the steric hindrance effect of the CF_2 group is more important, then (ii) attack of chloride on to the more stable mesomeric carbocation, i.e. $-CF_2-CF=CH-CH(^+)-CH_2-$ because of electronic effects. Both the fluorine abstraction and chlorine entrance could also occur via a concerted six-centred mechanism as depicted in **C**.



(A)



(B)



(C)

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