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Synthesis, characterisation and mass spectrometric fragmentation of *O*-(chlorodifluoroacylated) alcohols

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Abstract

An indirect and uncatalysed esterification of chlorodifluoroacetic acid with polyfluoro and hydrocarbon alcohols has been developed. The method which involves the reaction between sodium chlorodifluoroacetate and alcohols in dimethylformamide (DMF) is particularly facile with polyfluorinated alcohols resulting in esters in 71–85% yield. The esters have been characterised on the basis of ^{1}H and ^{19}F NMR and mass spectral data. The electron impact (EI) mass spectrometric fragmentation of these polyfluorinated esters have shown some interesting features which have been substantiated by using tandem mass spectrometry.

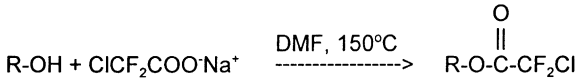
Keywords: Sodium chlorodifluoroacetate; Polyfluorinated alcohols; Esterification; Mass spectrometric fragmentation; Tandem mass spectrometry; ^{19}F NMR

1. Introduction

Decarboxylation of the sodium salt of chlorodifluoroacetic acid takes place in the presence of tertiary phosphines [1,6]. However, the salt alone when heated at elevated temperatures or subjected to pyrolysis [2] undergoes decarboxylation and serves as a source of difluorocarbene (CF_2). This salt has in fact been reacted with a number of substrates at higher temperatures as a possible source of difluorocarbene [3]. When used in dimethylformamide (DMF), it can be converted as a soluble source of fluoride ion [4] or a combination of fluoride ion and proton source [1]. This property of DMF has, however, not been made use of for preparative work. As a first report of its synthetic use, we have synthesised a series of alkyl/polyfluoroalkyl esters of chlorodifluoroacetic acid by heating alcohols with sodium chlorodifluoroacetate in DMF.

2. Results and discussion

The esterification of carboxylic acids by reactions with alkyl halides is the most common method of indirect esterification which is generally promoted by catalysts [5]. We have developed an unusual and uncatalysed method of esterification of chlorodifluoroacetic acid by the reaction of sodium chlorodifluoroacetate and alcohols in a neutral medium. The esterification reaction which occurs only in the solvent DMF particularly works well with polyfluorinated alcohols.



Compound no.	R	Isolated yield (%)
I	CF_3CH_2	82
II	$CF_3CF_2CH_2$	85
III	$(CF_3)_2CH$	71
IV	CH_3	09
V	CH_3CH_2	19
VI	n-C_8H_{17}	31

In this paper, synthesis of a series of esters of polyfluorinated and hydrocarbon alcohols has been achieved by heating 1 mol of alcohols with 2.5 mol of sodium chlorodifluoroacetate in DMF under nitrogen atmosphere at a temperature of >150 °C.

The formation of polyfluorinated esters has been shown in Scheme 1. Under the influence of difluorocarbene, obtained by heating sodium chlorodifluoroacetate in DMF, a proton source is probably generated which in turn converts the alcohols into a strong leaving group, thereby facilitating the S_N2 displacement by excess acetate anion. The conversion

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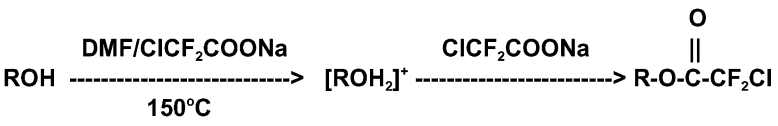


Scheme 1. Synthesis of *O*-(chlorodifluoroacylated) alcohols.

Table 1
NMR and mass spectral data of esters I–VI

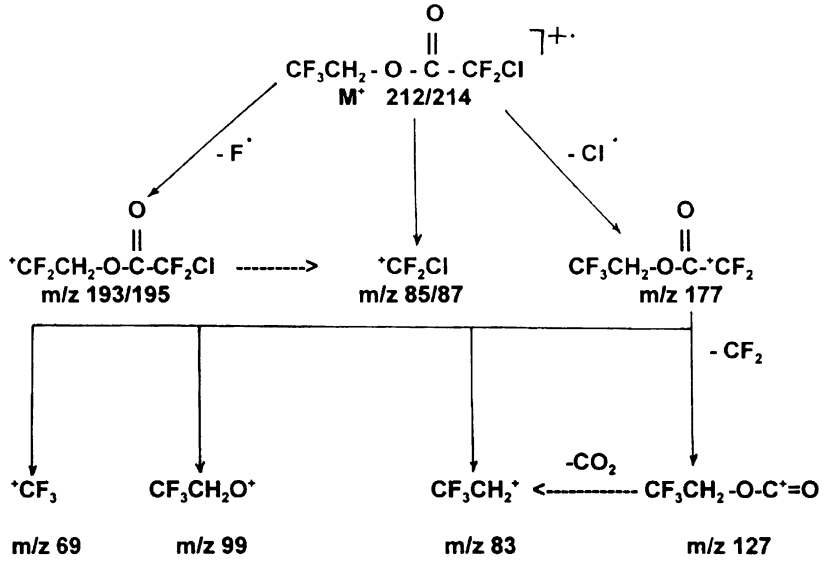
Compound no.	^{1}H NMR δ (ppm)	^{19}F NMR δ (ppm)	EI–MS (*m*/*z*)	CI–MS
I	CH_2 4.80 (q)	CF_3 −76.5 (t) CF_2Cl −62.5 (s)	213/215, 193/195, 173, 127, 99, 85/87, 83, 69, 50	213/215
II	CH_2 4.85 (t)	CF_3 −124.3 (t) CF_2 −84.7 (m) CF_2Cl −64.8 (s)	263/265, 243/245, 227, 215, 177, 143/145, 133, 113, 85/87, 69, 51	263/265
III	CH 5.75 (m)	CF_3 −73.4 (d) CF_2Cl −64.7 (s)	281/283, 261/263, 245, 241/243, 225, 195, 157, 151, 129, 113, 99, 85/87, 69, 51	281/283
IV	–	CF_2Cl −63.1 (s)	145/147, 131/133, 109, 85/87, 59	145/147
V	–	CF_2Cl −63.4 (s)	159/161, 131/133, 123, 115, 95, 85/87, 78, 59, 50	159/161
VI	–	CF_2Cl −64.0 (s)	243/245, 224, 187, 173, 157, 143, 115/117, 99, 85/87, 69, 56.	243/245

of the solvent DMF into a proton donor source under similar conditions has been observed earlier [1]. As with any other S_N2 displacement, the reactions are more facile with electron deficient polyfluorinated alcohols where the creation of a positive centre is possible at the carbon atom attached to an alcoholic OH group. With normal hydrocarbon alcohols, the reactions are sluggish and do not occur at all even with a secondary alcohol like isopropanol. As with most other S_N2 displacements, the reaction fails to take place with polyfluorinated tertiary alcohols, such as 2-(4-fluorophenyl)-1,1,1,3,3,3-hexafluoro-2-propanol probably due to steric factors. It should also be noted that the esterification reaction does not occur in other media, such as diglyme, triglyme, acetonitrile and dimethylsulphoxide and only alcohols but not organohalides can undergo this reaction. The esters obtained have been characterised on the basis of ^{1}H and ^{19}F NMR spectra and mass spectral data in both electron impact (EI) and CI modes (Table 1). The NMR data correspond to the assigned structures. The mass spectral data were obtained for total identification of the compounds. The interesting features observed in the EI–MS data obtained led us to investigate the fragmentation mechanism by using tandem mass spectrometry.

The mass spectra of all the esters showed $(M + H)^+$ ions rather than M^+ ions as the highest mass peaks. In order to confirm this observation and the molecular weight of the compounds, chemical ionisation MS was also performed using methane as the reagent gas. All the compounds gave the expected pseudomolecular ions in CI. The EI mass spectra of all the *O*-(chlorodifluoroacylated) alcohols showed some interesting fragmentation due to the loss of F, Cl, CF_2Cl, and CO_2CF_2Cl from their respective molecular ions. All the esters showed a prominent ion—base peak at *m*/*z* 85/87 in most of the cases due to the formation of a highly stabilised CF_2Cl^+ ion. The esters formed from polyfluorinated alcohols also showed a prominent ion at *m*/*z* 69 corresponding to the CF_3^+ ion (Table 2). In certain esters, specific ions were also observed due to the loss of HF from different fragment ions and ions corresponding to fluorinated hydrocarbon/hydrocarbon moieties. The genesis of the formation of various ions is shown in Scheme 2. In order to confirm the mechanism of fragmentation, tandem mass spectrometric experiments in daughter ion and parent ion modes were also performed. The daughter ions obtained from various parent ions in MS/MS experiments are shown in Table 3.

Table 2
Fragment ions observed in I and corresponding ions in esters II–VI

Compound no.	Molecular weight	$(M + H)^+$ (i)	$(M^+ - F)$ (ii)	$(M^+ - Cl)$ (iii)	(iii − CF_2) (iv)	$(M^+ - CO_2CF_2Cl)$ (v)	$(CF_2Cl)^+$ (vi)	$(CF_3)^+$ (vii)
I	212/214	213/215	193/195	177	127	83	85/87	69
II	262/264	263/265	243/245	227	177	133	85/87	69
III	280/282	281/283	261/263	245	195	151	85/87	69
IV	144/146	145/147	–	109	59	–	85/87	–
V	158/160	159/161	–	123	73	–	85/87	–
VI	242/244	243/245	–	–	157	113	85/87	–



Scheme 2. Probable fragmentation pathway for ester I under EI–MS.

Table 3
Daughter ion scans for esters I–VI

Compound no.	Parent ions (*m/z*)	Daughter ions (*m/z*)
I	213/215, 177	193/195, 177, 85/87, 127, 99, 83, 69
II	263/265, 227	243/245, 227, 85/87, 177, 135, 111, 69
III	281/283, 245	261/263, 245, 85/87, 195, 151, 69
IV	145/147, 109	131/133, 109, 85/87, 59
V	159/161, 123	131/133, 123, 85/87, 73
VI	243/245	157, 115, 85/87

Taking compound I as the model, the molecular ion (*m/z* 213/215) gave only three daughter ions, viz. *m/z* 193/195 ($M^+ - F$), 177 ($M^+ - Cl$) and 85/87 (CF_2Cl^+). The daughter ion scan of *m/z* 193/195 showed only one daughter at *m/z* 85/87 (CF_2Cl^+). The fact that *m/z* 85/87 is a daughter of both the molecular ion (*m/z* 213/215) and *m/z* 193/195 ($M^+ - F$) clearly indicates that the fluoride radical loss from the molecular ion to give the ion *m/z* 193/195 occurs from the CF_3 group rather than CF_2Cl group, otherwise the ion *m/z* 85/87 will be difficult to account for from *m/z* 193/195. All the other ions (*m/z* 127, 99, 83 and 69) arise from *m/z* 177 which was confirmed by studying the daughter ion scan of this ion. The ion *m/z* 127 which was expected to arise from the molecular ion by the loss of CF_2Cl, was shown to arise from *m/z* 177 rather than from the molecular ion. This observation confirms a sequential loss of a chlorine radical followed by CF_2 radical from the molecular ion. Parent ion experiments demonstrated that the ion *m/z* 83 $(CF_3CH_2)^+$ arises from two different parent ions, viz. *m/z* 177 and *m/z* 127. The parent ion experiments also confirmed that the ions *m/z* 69 and 99 arise from *m/z* 177 and not from the molecular ion. Compounds II–VI also showed corresponding daughter and parent ions when subjected to tandem mass spectrometric experiments.

3. Conclusion

A method has been described wherein a facile esterification of chlorodifluoroacetic acid has been achieved with certain electron deficient alcohols in neutral DMF medium. Mass spectrometry data are helpful in the total identification of such esters as they result in characteristic fragment ions confirmed by MS/MS experiments.

4. Experimental details

4.1. Synthesis of O-(chlorodifluoroacylated) alcohols

Sodium salt of chlorodifluoroacetic acid [6] {$\delta CF_2 \rightarrow -57$ ppm (acetone d_6)} (7.6 gm; 0.05 mol) and DMF (50 ml) were heated together at 150 °C under a nitrogen atmosphere in a three-necked round bottomed flask. Alcohol (0.02 mol) was then added dropwise into the reaction mixture when an exothermic reaction ensued. The reaction is instantaneous with electron-deficient fluorinated alcohols. Initially, the salt was soluble making a homogenous solution in DMF. The reaction mixture turned brown with the deposition of solid at the bottom of the flask indicating thereby the completion of the reaction. Highly volatile esters (III and IV), were distilled off directly from the reaction mixtures by the heat of reaction and collected in a liquid N_2/MeOH cooled trap by entrainment in a stream of dry nitrogen. For relatively less volatile esters (I, II and V) the reaction mixture after filtration was subjected to distillation under vacuum. For non-volatile compounds (VI), the reaction mixture after filtration was washed with excess water and extracted into dichloromethane. The compounds were identified by ^1H, ^{19}F NMR spectra and mass spectral data in both EI and CI modes.

4.2. Instrumental analysis

The details of monitoring of reaction by GLC and characterisation of compounds by ^{1}H and ^{19}F NMR spectra have been reported earlier [7]. The mass spectra were recorded on a TSQ 7000 mass spectrometer (Finnigan Mat) using a GC inlet with a BP-5 column (30 m × 2.5 mm i.d. × 0.25 μm thickness) with a temperature program of 30 °C (2 min)—5 °C/min—120 °C—20 °C/min—200 °C (5 min) using helium as the carrier gas at a flow rate of 1.2 ml/s. The injector temperature was 150 °C and the transfer line was heated to 200 °C. EI–MS was performed at 70 eV with the ion source temperature 150 °C and an emission current of 400 mA. CI–MS experiments were performed using methane as the reagent gas at a pressure of 4000 mT, source temperature 150 °C and an emission current 300 mA. MS/MS experiments were performed using argon as the collision gas at such a pressure as to attenuate the parent ion beam intensity by 50%. The collision energy was 20 eV (laboratory frame of reference).

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