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gem-Difluoro-cyclohexene and -cycloheptene derivatives through cyclization of *gem*-difluoroallyl radicals

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Abstract

6-Alkoxy-7-chloro-7,7-difluoro-5-[(*S*)-(4-methylphenyl)sulfinyl]-1,5-heptadienes have been transformed, through chlorine atom abstraction by tributyltin radical, into the corresponding difluoroallyl radicals, which, via intramolecular trapping by the vinyl group and reduction of the cyclohexenylmethyl and cycloheptenyl radicals obtained, gave *gem*-difluoro-cyclohexene and -cycloheptene derivatives. Reduction of the intermediate difluoroallyl radical afforded the corresponding dechlorinated open-chain difluoro compounds as side-products.

Keywords: Difluorocyclohexene; Difluorocycloheptene; Radical cyclization; NMR spectroscopy; Difluoroallyl radicals

1. Introduction

In connection with our programme dealing with the chemistry of β-keto- and β-hydroxyfluoro or perfluoroalkyl sulfoxides, which are versatile chiral building blocks for the asymmetric synthesis of selectively fluorinated molecules [1], we are exploring the chemical reactivity of some chlorofluoro derivatives for the generation of fluoroalkyl radicals which can be utilised for the construction of carbon–carbon bonds adjacent to fluorine.

We have performed extensive studies on the asymmetric synthesis of cyclopentane and cyclohexane derivatives **1**, containing a CHF or CF_2 group in the ring along with one to three oxygen-bearing carbons, by the route outlined on Scheme 1 [2].

To date, we have only been able to employ β-hydroxysulfoxides **2** obtained by hydride reduction from the corresponding ketones **3**, the product of the acylation of the α-lithium derivative of sulfoxide **4** by the fluorinated esters **5**. Ketones **3** are labile compounds and cannot be separated in an optically pure form and utilised in radical cyclisation [3]. In order to circumvent this problem, we have now studied the cyclisation of the corresponding enol ethers **6**, available from **3** by a procedure recently reported [4].

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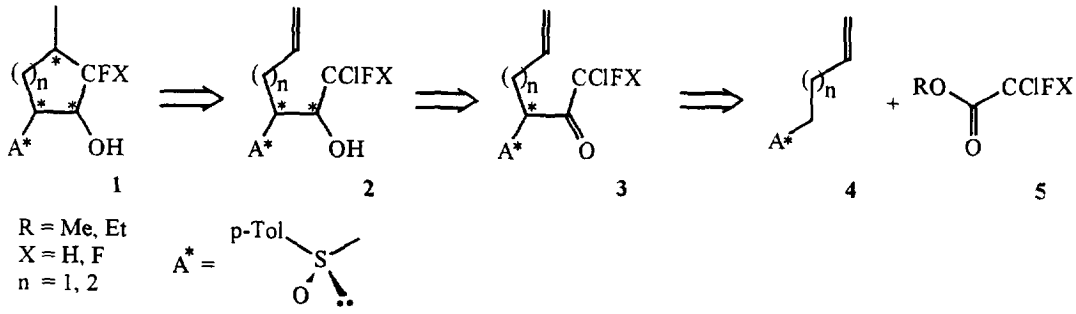
2. Results and discussion

A 1.3:1 mixture of the methyl enol ethers (*Z*)- and (*E*)-**6a** was treated with an excess of tributyltin hydride in degassed benzene. The energy required for bond breaking was supplied by irradiating the solution in the presence of AIBN as chain initiator [5] with a mercury discharge lamp having a significant emission at 350 nm.

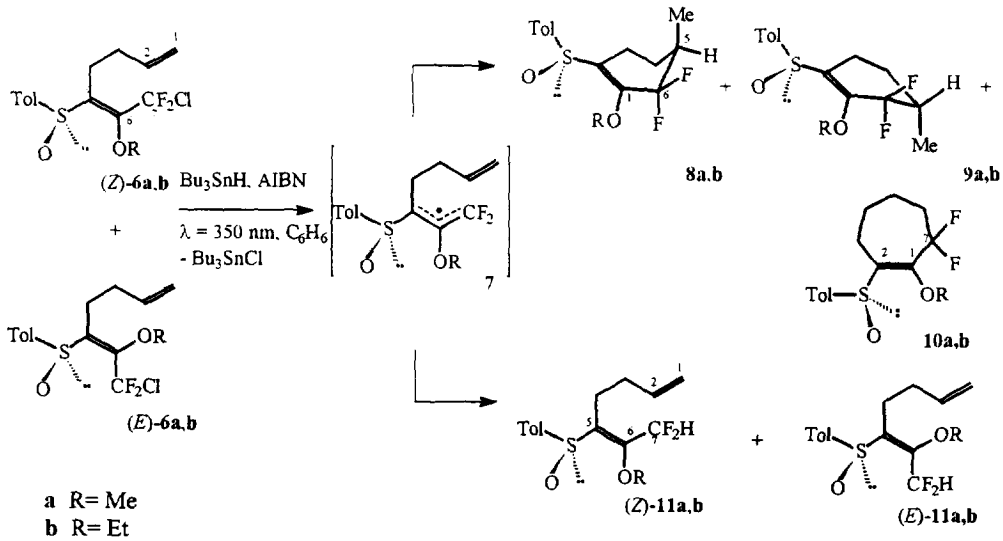
The radical-chain process occurred as shown in Scheme 2. Dissociation of AIBN followed by hydrogen abstraction from tributyltin hydride generates a tributyltin radical which, through chlorine abstraction from the chlorofluoroalkyl group, produces the difluoroallyl radical **7**. This electrophilic radical can be intramolecularly trapped by the terminal vinyl group in an *exo*– or *endo–trig* cyclization, giving the corresponding cyclic alkyl radicals. Those radicals, in turn, abstract a hydrogen atom from the stannane affording the final cyclic products, i.e. six-membered **8a** and **9a** or seven-membered **10a**, and a tributyltin radical which propagates the chain reaction.

The product mixture was more complex than expected since, besides the cyclic compounds **8a, 9a** and **10a**, the reductively dechlorinated open-chain compounds (*Z*)- and (*E*)-**11a** were present in noticeable amounts.

The corresponding ethyl enol ethers (**6b**) showed a behaviour strictly comparable with the methyl enol ethers (**6a**) (see Experimental details). Pure isomer (*Z*)-**6**, or mixtures



Scheme 1.



Scheme 2.

of (*E*)- and (*Z*)-**6**, gave comparable mixtures (**8, 9, 10** and **11**) of reaction products. This implies that the (*E*)- and (*Z*)-configurations for the intermediate allyl radical **7** interconvert in the reaction medium.

Radical **7**, which is stabilised by electron delocalisation, is a long-lived species which is less reactive than a normal difluoroalkyl radical. The presence of the double bond in the carbon chain of radical **7** makes its proper folding to give cyclohexenylmethyl and cycloheptenyl products through an *exo–trig* and *endo–trig* ring-closure more difficult. Hence, intermolecular trapping of radical **7** by tin hydride [1] and intramolecular trapping by the vinyl group should proceed at comparable rates [2].

The cyclohexene derivatives **8** and **9** possess a β- and α-methyl group, respectively, formed in a ca. 1:2 ratio (see the formulae reported in Scheme 2). The low induction observed during ring closure, relative to that experienced during cyclization of α-hydroxy radicals generated from chlorodifluoro alcohols **2** [2a], is due to the absence of stereogenic carbons on the carbocycle-forming chain and is solely a consequence of the presence of the exocyclic stereogenic sulfinyl group.

2.1. Structure determination

For the purpose of structure determination, the pure compounds, or enriched mixtures for those present in only relatively small amounts in the reaction mixture, were obtained by flash chromatography.

Evidence for the elucidation of the structure and stereochemistry of compounds **8–11** was provided by the ^1H, ^{13}C and ^{19}F NMR data reported in Tables 1 and 2 and under Experimental details. Specifically, the ^1H and ^{19}F NMR spectra of compounds (*Z*)- and (*E*)-**11a,b** were similar to those exhibited by the starting compounds (*Z*)- and (*E*)-**6a,b**, the only relevant difference being the presence in (*Z*)- and (*E*)-**11a,b** of signals attributable to a CHF_2 moiety in place of a

[1] It was not possible to use a pump-driven syringe to minimise the generation of reduction products [6].

[2] It is well known that the fluoro substitution on an alkyl radical enhances the rate of radical trapping by olefins. Unfortunately, the rate of hydrogen abstraction from tributyltin hydride is also enhanced to about the same extent [7].

Table 1
^{1}H NMR chemical shifts (δ, ppm) of compounds **8a,b** and **9a,b** in $CDCl_3$

Atom [a]	8a	8b	9a	9b	Atom	8a	8b	9a	9b
3a	2.67	2.68	2.50	2.50	Fb	−112.93	−113.33	−111.32	−112.24
3b	1.68	1.68	1.93	1.91			4.30		4.23
4a	1.70	1.72	1.85	1.86	1-OR	3.95	4.14	3.93	4.18
4b	1.62	1.63	1.47	1.47			1.42		1.41
5	1.92	1.92	2.22	2.22		7.48	7.50	7.50	7.51
Me	1.07	1.07	0.94	0.93	*p*-Tol	7.27	7.26	7.29	7.29
Fa	−105.21	−105.31	−102.77	−101.28		2.39	2.39	2.40	2.40

[a] The $^2J_{F,F}$ values ranged between 268.5 Hz and 269.0 Hz.

$CClF_2$ group [3]. Moreover, the NOE enhancements observed in (*Z*)-**11b** between H-7 and protons of the pentenyl chain (see Experimental details) established the geometry of the C-5, C-6 double bond as in the (*Z*)-configuration. Finally, the close relationship between the NMR data for (*Z*)- and (*E*)-**11b** and (*Z*)- and (*E*)-**11a** also permitted their assignment. Regarding the cyclization products **8a,b**, **9a,b** and **10a,b**, the NMR data, and in particular the two-bond C,F couplings observed in the ^{13}C NMR spectra, indicate that the vinyl carbons of the starting compounds (*Z*)- and (*E*)-**6a,b** give rise to a $\rangle$C(5)H–C(7)H_3 unit in compounds **8a,b** and **9a,b** and to a –C(5)H_2–C(6)H_2– fragment in compounds **10a,b**, implying the presence of six- and seven-membered rings, respectively.

A tentative attribution of C-5 as *S* in compounds **9a,b** followed from the higher field chemical shift exhibited by the 7-methyl protons (assumed to be pseudo-axially α-disposed in Scheme 2) relative to those in **8a,b** (δ 0.94 and 0.93 ppm versus δ 1.07 ppm). This is probably due to the anisotropic effect exerted by the tolyl ring which, in order to relieve interactions with the ethereal alkyl groupings (the two oxygen atoms being assumed as being far from each other in order to minimise dipole interactions), occupies the α-face of the molecule preferentially. This supposition is supported by the values of 6.5 Hz and 3.5 Hz, respectively, for the vicinal coupling constants exhibited by the 7-methyl carbons with the 6-fluorine atoms. In the related cyclohexane compounds [2a], similar values were observed for axially disposed methyl carbons, while values ranging between 3 and 4 Hz were observed for methyl groups disposed equatorially and gauche with respect to the fluorine atoms. The values of 7 and 3 Hz observed in **8b** indicate that the methyl group is also pseudo-axially disposed in this compound but situated on the β face of the molecule.

[3] It should be noted that the 7-proton of (*E*)-**11a,b**, which is disposed *cis* with respect to the tolylsulfinyl grouping, resonates at lower field than the corresponding *trans* disposed proton in (*Z*)-**11a,b** (δ 7.26 and 7.23 ppm versus δ 6.29 and 6.28 ppm) as observed previously in related compounds. In (*Z*)-3,3-difluoro-2-methoxy-1-[(*R*)-(4-methylphenyl)sulfinyl]-propene, the 3-proton resonates at δ 5.97 ppm, whereas in the (*E*)-isomer the same proton resonates at δ 6.83 ppm; in (*Z*)-3-fluoro-2-methoxy-1-[(*R*)-(4-methylphenyl)sulfinyl]propene, the 3-protons resonate at δ 4.77 ppm (average value) whereas in the (*E*)-isomer the same protons resonate at δ 5.27 ppm [8].

Table 2
^{13}C NMR data for compounds **8a**, **9a** and **10a** in $CDCl_3$

Carbon atom	8a		9a		10a	
	δ_C (ppm) [a]	*J*(C,F) (Hz)	δ_C (ppm)	*J*(C,F) (Hz)	δ_C (ppm)	*J*(C,F) (Hz)
1	147.63	25.5; 24.5	147.29	25.5; 24.5	151.27	26
	S dd		S dd		S t	
2	133.75	8; 7.5	134.15	8; 7.5	139.06	7.5
	S dd		S dd		S t	
3	16.25		16.59		17.12	
	T		T		T	
4	26.29	7.5	25.85	5; 2	25.18	
	T d		T dd		T	
5	38.07	22.5	37.37	22.5	21.20	5.5
	D t		D t		T t	
6	119.24	245	119.60	244.5	34.27	25
	S t		S t		T t	
7					120.53	244
					S t	
5-Me	12.01	7; 3	11.79	6; 4		
	Q dd		Q dd			
OMe	60.66	3.5	60.69	3.5	61.43	2.5
	Q d		Q d		Q t	
	140.92		140.91		140.92	
	S		S		S	
	139.95		140.03		140.39	
	S		S		S	
p-Tol	129.85		129.89		129.85	
	D		D		D	
	123.94		123.86		124.22	
	D		D		D	
	21.35		21.35		21.35	
	Q		Q		Q	

[a] Capital letters refer to the pattern resulting from one-bond (C,H) coupling constants and small letters to that from (C,F) couplings.

3. Experimental details

3.1. General

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker CXP 300 or a Bruker AC 250L spectrometer; chemical shifts are in ppm (δ); tetramethylsilane was used as internal standard (δ_H and δ_C = 0.00 ppm) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as internal standard (δ_F = −162.90 ppm) for

^{19}F nuclei. TLC controls were made on silica gel $60F_{254}$ Merck plates; column chromatography separations were performed with Silica gel 60 (60–200 μm, Merck). Benzene was distilled from calcium chloride and stored over molecular sieves (4 Å). Starting compounds (*Z*)- and (*E*)-**6a,b** were prepared [4] by room temperature reaction of a solution of β-ketosulfoxide **3** ($n=2$, X=F, see Scheme 1) in benzene/methanol or ethyl ether/ethanol mixture with potassium carbonate and dimethyl or diethyl sulfate, respectively. Careful chromatographic separation allowed (*Z*)-**6b** to be obtained as a pure compound; in the other cases, mixtures of (*Z*)- and (*E*)-isomers were isolated.

3.2. Radical cyclisation of enol ethers 6. General procedure

This is exemplified by the cyclization of methyl enol ethers (*E*+*Z*)-**6a** A 1.0:1.3 mixture of (*E*)- and (*Z*)-**6a** (538 mg, 1.6 mmol) was partitioned into four Pyrex tubes and dissolved in oxygen-free benzene (5 ml). To these solutions was added AIBN (0.04 mmol) and tributyltin hydride (141 μl, 0.52 mmol) under a nitrogen atmosphere.

The four Pyrex tubes were irradiated for 4 h at 350 nm by means of the mercury discharge lamp of a Rayonet apparatus. Since the TLC control revealed the presence of moderate amounts of the starting mixture, a further 50% amount of tributyltin hydride and AIBN relative to the starting conditions was added to each tube and the reaction mixtures further irradiated for 2 h. During such irradiation, the temperature was maintained at 35 °C.

TLC analysis (7:3 cyclohexane/ethyl acetate) of the reaction mixture showed a small amount of unreacted starting material and four spots close together at a lower R_f value. To the reaction mixture diluted with wet ethyl ether (15 ml) was added DBU [9] (0.78 mmol) and a 0.1 M solution of iodine in ethyl ether until a persistent iodine colour was obtained. The resulting mixture was loaded into a short silica gel column and eluted with ethyl ether (30 ml). Finally, the solvent was removed under reduced pressure. The residue was flash-chromatographed (gradient elution: cyclohexane/ethyl acetate from 8.5:1.5 to 6.5:3.5) to give the unreacted starting material (7%), the reduction products (*Z*)- and (*E*)-**11a** (42.2% and 14.5% conversion, respectively) and the cyclization products **8a, 9a** and **10a** (11.6%, 22.3% and 6.3% conversion, respectively).

Similarly, starting from pure (*Z*)-**6b**, 8% of the unreacted substrate was recovered and compounds **8b, 9b, 10b**, (*Z*)-**11b** and (*E*)-**11b** were obtained in 18.0%, 38.7%, 9.9%, 17.5% and 5.8% conversion, respectively. Starting from a 1.0:1.4 mixture of (*E*)- and (*Z*)-**6b**, 10% of unreacted substrate was recovered and the same products as described above were obtained in 10.7%, 23.1%, 5.8%, 36.5% and 12.9% conversion, respectively. The ^1H NMR chemical shifts of compounds **8a,b** and **9a,b** are listed in Table 1 while the ^{13}C NMR data for compounds **8a, 9a** and **10a** are listed in Table 2.

7,7-Difluoro-1-methoxy-2-[(*S*)-(4-methylphenyl)sulfinyl]cycloheptene (**10a**): ^1H NMR ($CDCl_3$) δ: 7.50, 7.26 (4H, m, ArH); 3.90 (3H, d, $J=1.5$ Hz, OMe); 2.6–1.1 (8H, m, H_2-3, -4, -5 and -6); 2.39 (3H, br s, ArMe) ppm. ^{19}F NMR ($CDCl_3$) δ: −92.12, −94.16 (2F, br d, $J=270.2$ Hz, F_2-7) ppm.

7,7-Difluoro-1-ethoxy-2-[(*S*)-(4-methylphenyl)sulfinyl]cycloheptene (**10b**): ^1H NMR ($CDCl_3$) δ: 7.52, 7.26 (4H, m, ArH); 4.22, 4.10 (2H, m, OCH_2); 2.6–1.2 (8H, m, H_2-3, -4, -5 and -6); 2.39 (3H, br s, ArMe); 1.43 (3H, t, $J=7.0$ Hz, OCH_2Me) ppm. ^{19}F NMR ($CDCl_3$) δ: −92.21, −94.09 (2F, br d, $J=270.0$ Hz, F_2-7) ppm.

(*Z*)-7,7-Difluoro-6-methoxy-5-[(*S*)-(4-methylphenyl)-sulfinyl]-1,5-heptadiene [(*Z*)-**11a**]: ^1H NMR ($CDCl_3$) δ: 7.56, 7.29 (4H, m, ArH); 6.29 (1H, dd, $J=53.2$, 52.5 Hz, H-7); 5.64 (1H, m, H-2); 4.95, 4.88 (2H, m, H_2-1); 3.92 (3H, br d, $J=1.9$ Hz, OMe); 2.46, 2.30 (2H, m, H_2-4); 2.39 (3H, br s, Me); 2.00, 1.89 (2H, m, H_2-3) ppm. ^{19}F NMR ($CDCl_3$) δ: −116.60 (1F, br dd, $J=314.5$, 53.2 Hz, F-7a); −122.50 (1F, br, dd, $J=314.5$, 52.5 Hz, F-7b) ppm.

(*E*)-7,7-Difluoro-6-methoxy-5-[(*S*)-(4-methylphenyl)-sulfinyl]-1,5-heptadiene [(*E*)-**11a**]: ^1H NMR ($CDCl_3$) δ: 7.45, 7.35 (4H, m, ArH); 7.26 (1H, dd, $J=52.9$, 51.4 Hz, H-7); 5.62 (1H, m, H-2); 4.87, 4.82 (2H, m, H_2-1); 3.94 (3H, t, $J=1.5$ Hz, OMe); 2.5–1.5 (4H, m, H_2-3 and -4); 2.42 (3H, br s, Me) ppm. ^{19}F NMR ($CDCl_3$) δ: −115.08 (1F, br dd, $J=318.0$, 52.9 Hz, F-7a); −120.25 (1F, br dd, $J=318.0$, 51.4 Hz, F-7b) ppm.

(*Z*)7,7-Difluoro-6-ethoxy-5-[(*S*)-(4-methylphenyl)-sulfinyl]-1,5-heptadiene [(*Z*)-**11b**]: ^1H NMR ($CDCl_3$) δ: 7.57, 7.28 (4H, m, ArH); 6.28 (1H, dd, $J=$ 53.6, 52.2 Hz, H-7); 5.64 (1H, m, H-2); 4.94, 4.87 (2H, m, H_2-1); 4.26 (1H, ddd, $J=9.4$, 6.8, 1.7 Hz, OCHa); 4.11 (1H, br ddd, $J=9.4$, 6.8, 1.1 Hz, OCHb); 2.47, 2.31 (2H, m, H_2-4); 2.38 (3H, br s, ArMe); 2.00, 1.88 (2H, m, H_2-3); 1.42 (3H, t, $J=6.8$ Hz, Me) ppm. ^{19}F NMR ($CDCl_3$) δ: −116.15 (1F, br dd, $J=315.0$, 53.6 Hz, F-7a); −122.90 (1F, br dd, $J=315.0$, 52.2 Hz, F-7b) ppm. Irradiation of H_2-4 in an NOE experiment enhanced, inter alia, H-7 (3%) while no NOE was observed for the 6-OEt protons. Furthermore, irradiation of H-7 enhanced H_2-3 (2%) and H_2-4 (1%) and irradiation of 6-OCHb enhanced 6-OCHa (7%) and the vicinal methyl protons (1.5%).

(*E*)-7,7-Difluoro-6-ethoxy-5-[(*S*)-(4-methylphenyl)-sulfinyl]-1,5-heptadiene [(*E*)-**11b**]: ^1H NMR ($CDCl_3$) δ: 7.45, 7.34 (4H, m, ArH); 7.23 (1H, dd, $J=53.1$, 51.6 Hz, H-7); 5.63 (1H, m, H-2); 4.86, 4.84 (2H, m, H_2-1); 4.20 (2H, m, OCH_2); 2.5–1.5 (4H, m, H_2-3 and -4); 2.40 (3H, br s, ArMe); 1.33 (3H, t, $J=6.9$ Hz, Me) ppm. ^{19}F NMR ($CDCl_3$) δ: −115.12 (1F, br dd, $J=317.5$, 51.6 Hz, F-7a); −120.46 (1F, br dd, $J=317.5$, 53.1 Hz, F-7b) ppm.

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