Preliminary Note

Radical cyclisations of 2-fluoroallyl derivatives for synthesising fluorovinyl-substituted carbocycles

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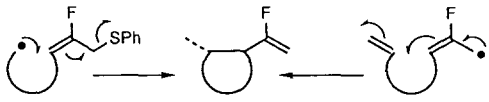
Abstract

Radical cyclisations of derivatives of 2-fluoroallyl sulphide and 2-fluoroallyl bromide provide fluorovinyl-substituted carbocycles. 2-Fluoroallyl components (−C=CF−C−) act as radical acceptors or initial radical sites in cyclisation reactions.

Radical cyclisation reactions have become recognized as useful tools in synthetic chemistry [1]. Free radical-promoted allylic rearrangement is involved in cyclisation processes via an S_H' mechanism [2] or intermediary allylic radicals [3], and contributes efficiently towards the retainment of the double-bond functionality in the cyclised products.

During the study of the radical cyclisation reactions of fluorine-substituted compounds [4], examination has also been made of the reactions of cyclisation systems containing the 2-fluoroallyl component (−C=CF−C−). Since fluorine substitution generally permits the use of the tin hydride method in the radical reaction, allylic rearrangement of the fluoroallyl component should lead to the formation of a new fluorovinyl group in the cyclised product (see Scheme 1). This paper describes radical cyclisation reactions achieved via the allylic rearrangement of 2-fluoroallyl sulphide and 2-fluoroallyl bromide producing fluorovinyl-substituted carbocycles.

Substrates **1**, **2** and **6** were readily prepared by the Emmons reaction with triethyl α-fluorophosphonoacetate [5] followed by conventional transformation of the functional group [see eqns. (1)–(3)].



Scheme 1.

0022-1139/92/$5.00

$$THPOCH_2CH_2(CH_2)_nCHPhCHO \xrightarrow[\text{ii, DIBAL; iii, MsCl, Et}_3\text{N}]{\text{i, (EtO)}_2\text{P(O)CHFCO}_2\text{Et/NaN(SiMe}_3)_2;} \xrightarrow[\text{vi, MsCl, Et}_3\text{N; vii, NaI}]{\text{iv, PhSH, NaH; v, } p\text{-TsOH, EtOH;}} ICH_2CH_2(CH_2)_nCHPhCH{=}CHFCH_2SPh \quad (1)$$

(**1**) $n = 1$
(**2**) $n = 2$

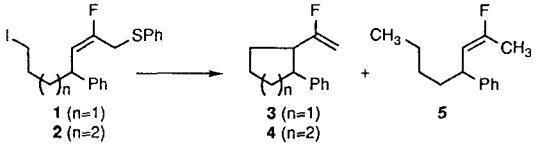
$$RCH{=}CH(CH_2)_3CHO \xrightarrow[\text{iii, MsCl, Et}_3\text{N}\ \text{iv, LiBr}]{\text{i, (EtO)}_2\text{P(O)CHFCO}_2\text{Et/NaH;}\ \text{ii, DIBAL;}} RCH{=}CH(CH_2)_3CH{=}CHFCH_2Br \quad (2)$$

(**6**) **a**: R = Ph
c: R = $PhCH_2OCH_2$

$$TBDPSO(CH_2)_4CHO \xrightarrow[\text{ii, DIBAL; iii, dihydropyran/}p\text{-TsOH}]{\text{i, (EtO)}_2\text{P(O)CHFCO}_2\text{Et/NaN(SiMe}_3)_2;} \xrightarrow[\text{vii, } p\text{-TsOH/EtOH; viii, MsCl, Et}_3\text{N; ix, LiBr}]{\text{iv, TBAF; v, PCC; vi, (MeO)}_2\text{P(O)CH}_2\text{CO}_2\text{Me/NaN(SiMe}_3)_2;} RCH{=}CH(CH_2)_3CH{=}CHFCH_2Br \quad (3)$$

(**6b**) R = CO_2Me

When fluoroallylic sulphide (**1**) was reacted with a 0.04 mol dm^{-3} solution of tributyltin hydride (Bu_3SnH, 2 equiv.) in benzene and a catalytic amount (0.2 equiv.) of azobisisobutyronitrile (AIBN) at reflux temperature for 3 h, fluorovinyl-substituted cyclopentane (**3**) was obtained in 64% yield as the only isolable product. The radical cyclisation of **1** proceeded in the selective 5-*exo* mode followed by allylic rearrangement to eject the phenylthio radical (PhS·) via the S_H' mechanism. However, under the same conditions (0.04 mol dm^{-3}), **2** gave a cyclohexane derivative **4** in low yield (16%) along with a reduction product (**5**, 13% yield). In the 6-*exo* cyclisation of **2**, the high dilution method was employed in order to increase the extent of cyclisation. In 0.004 mol dm^{-3} solution, **4** was obtained in 43% yield with the formation of **5** being less than 4%. Slow addition using a syringe pump (0.004 mol dm^{-3} final concentration) resulted in a 54% yield of **4**. Thus, slow 6-*exo* cyclisation to the fluoroallyl sulphide (compared to 5-*exo* cyclisation) occurs predominantly by lowering the concentration of tin hydride, and under such conditions, intermolecular side-reactions may be minimized to a large extent (see Scheme 2 and Table 1).



1 (n=1)
2 (n=2)
3 (n=1)
4 (n=2)
5

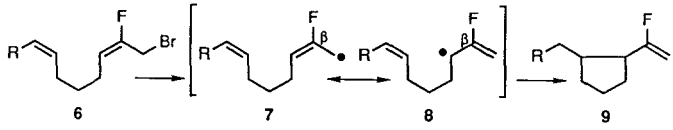
Scheme 2. Reagents and conditions: **1** or **2** (1 equiv.), Bu_3SnH (2 equiv.), AIBN (0.2 equiv.), benzene, reflux, 3 h.

TABLE 1

Radical cyclisation of **1** and **2**

Substrate[a]	[Bu_3SnH] (mol dm^{-3})	Product(s) (yield, %)
1	0.04	**3** (64)[b]
2	0.04	**4** (16)[b], **5** (13)[c]
2	0.004	**4** (43)[b], **5** (<4)[c]
2	0.004 (slow add.)	**4** (54)[b], **5** (<13)[c]

[a]Mixtures of stereoisomers were used as substrates.
[b]Only one isomer was observed. The stereochemistry of **3** was not determined. Compound **4** was a *trans* isomer.
[c]Other by-products were not characterized.



6 7 8 9

Scheme 3. Reagents and conditions: **6** (1 equiv.), Bu_3SnH (1.1 equiv.), AIBN (0.1 equiv.), benzene, reflux, 3 h.

Fluorovinyl-substituted cyclopentanes could be also synthesized by reverse-mode radical cyclisation through the allylic radical generated from the fluoroallyl bromide **6**. The tin hydride-promoted reaction of **6a** proceeded smoothly via the 5-*exo* mode cyclisation of the allylic radical **8a** to give **9a** in 74% yield. Similarly, **9b** was obtained by the allylic radical cyclisation of **6b** in 64% yield. The substituent on the acceptor double bond affects the cyclisation yield of the allylic radical. In the case of **6c**, the cyclisation yield was reduced to 48% and reduction products without cyclisation were observed in 32% yield*. However, the high dilution method improved the yield of **9c** to 68%. Intermediary allylic radicals (**7** and **8**) bearing a fluorine-substituent at the β-position may possibly be synthetically important in that the corresponding carbanion ($-C=CF-C^-$) may involve the problem of β-elimination of the fluoride anion to afford the allene derivative (see Scheme 3 and Table 2).

In summary, two types of radical cyclisations involving 2-fluoroallyl component as the acceptor and the initial radical site have been developed for the synthesis of fluorovinyl-substituted carbocycles.

Spectral data

1 (stereoisomeric mixture, $E{:}Z = 4.1{:}1.0$ determined by ^1H NMR spectroscopy): ^1H NMR $CDCl_3$ δ: 1.44–1.76 (4H, m, CH_2); 2.99–3.12 (3H, m,

*The reduction products were $PhCH_2OCH_2CH=CH(CH_2)_3CH=CFCH_3$ and $PhCH_2OCH_2CH=CH(CH_2)_4CF=CH_2$ (22% and 10% yields, respectively).

TABLE 2

Allylic radical cyclisation of **6**

Substrate[a]	[Bu_3SnH] (mol dm^{-3})	Product[b] (yield, %)
6a (R=Ph)	0.01	**9a** (74)
6b (R=CO_2Me)	0.02	**9b** (64)
6c (R=$PhCH_2OCH_2$)	0.01	**9c** (48)
6c (R=$PhCH_2OCH_2$)	0.0025 (slow add.)	**9c** (68)

[a]Mixtures of stereoisomers were used as substrates.
[b]Ratio of stereoisomers; **9a** (1.6:1), **9b** (1.4:1), **9c** [2:1 (0.01 mol dm^{-3}), 3.4:1 (0.0025 mol dm^{-3})].

CHPh and CH_2I); 3.46–3.71 (2H, m, CH_2SPh for *Z*-isomer, overlapping); 3.58 (1H, dd, $J=18.5$, 14.3 Hz, CHSPh for *E*-isomer); 3.71 (1H, dd, $J=24.1$, 14.3 Hz, CHSPh for *E*-isomer); 4.70 [1H, dd, $J=34.8$, 10.0 Hz, $CH_{(trans)}=CF$ (*trans* relationship between H and F) for *Z*-isomer]; 5.34 [1H, dd, $J=19.9$, 10.5 Hz, $CH_{(cis)}=CF$ for *E*-isomer]; 7.03–7.48 (10H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ (from benzotrifluoride): −42.10 (br for *E*-isomer); −49.38 (m, for *Z*-isomer) ppm. IR (neat): 3060; 3026; 2928; 2855; 1692 cm^{-1} MS *m/z*: 426 (M^+); 316; 147.

2 (stereoisomeric mixture, *E*:*Z*=7.2:1.0 determined by ^1H NMR spectroscopy): ^1H NMR $CDCl_3$ δ: 1.10; 1.10–1.81 (6H, m, CH_2); 3.0–3.15 (3H, m, CHPh and CH_2I); 3.52–3.69 (2H, m, CH_2SPh for *Z*-isomer, overlapping); 3.59 (1H, dd, $J=18.7$, 14.3 Hz, CHSPh for *E*-isomer); 3.72 (1H, dd, $J=23.8$, 14.3 Hz, CHSPh for *E*-isomer); 4.73 [1H, dd, $J=35.0$, 10.5 Hz, $CH_{(trans)}=CF$ for *Z*-isomer]; 5.34 [1H, dd, $J=20.1$, 10.5 Hz, $CH_{(cis)}=CF$ for *E*-isomer]; 7.02–7.47 (10H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: −42.07 (m, for *E*-isomer); −48.86 (m, for *Z*-isomer) ppm. IR (neat): 3059; 3027; 2934; 2857; 1692 cm^{-1}. High-resolution MS: $C_{20}H_{22}FIS$, 440.0446. Calcd. 440.0470.

3: ^1H NMR $CDCl_3$ δ: 1.74–1.94 (4H, m, CH_2); 2.01–2.21 (2H, m, CH_2); 2.70 (1H, dddd, $J=22.2$, 9.8, 8.5, 8.5 Hz, CHCF=C); 3.07 (1H, dt, $J=9.8$, 8.5 Hz, CHPh); 4.10 [1H, dd, $J=50.5$, 2.7 Hz, $CF=CH_{(trans)}$], 4.42 [1H, dd, $J=17.6$, 2.7 Hz, $CF=CH_{(cis)}$]; 7.18–7.32 (5H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: −41.70 (ddd, $J=50.5$, 22.2, 17.6 Hz) ppm. IR (neat): 3063; 3029; 2960; 2874; 1670 cm^{-1}. High-resolution MS: $C_{13}H_{15}F$, 190.1135. Calcd., 190.1156.

4: ^1H NMR $CDCl_3$ δ: 1.35–1.66 (4H, m, CH_2); 1.80–2.02 (4H, m, CH_2); 2.35 (1H, dddd, $J=24.7$, 11.6, 11.6, 3.4 Hz, CHCF=C); 2.62 (1H, ddd, $J=11.6$, 11.6, 3.4 Hz, CHPh); 3.91 [1H, dd, $J=50.8$, 2.7 Hz, $CF=CH_{(trans)}$]; 4.22 [1H, dd, $J=18.1$, 2.7 Hz, $CF=CH_{(cis)}$]; 7.16–7.29 (5H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: −41.32 (ddd, $J=50.8$, 24.7, 18.1 Hz) ppm. IR (neat): 3029; 2932; 2857; 1670 cm^{-1}. High-resolution MS: $C_{14}H_{17}F$, 204.1320. Calcd., 204.1313.

5 (*E*-isomer, 8%): ^{1}H NMR $CDCl_3$ δ: 0.88 (3H, t, J=7.1 Hz, CH_3); 1.14–1.37 (4H, m, CH_2); 1.56–1.77 (2H, m, CH_2), 1.91 (3H, dd, J=17.6, 0.6 Hz, C=CFCH_3); 3.21 (1H, m, CHPh); 5.21 [1H, ddd, J=21.7, 10.3, 0.6 Hz, $CH_{(cis)}$=CF]; 7.17–7.31 (5H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: −32.75 (m) ppm. IR (neat): 3028; 2958; 2930; 1704 cm^{-1}. High-resolution MS: $C_{14}H_{19}F$, 206.1445. Calcd., 206.1469.

5 (*Z*-isomer, 5%): ^{1}H NMR $CDCl_3$ δ: 0.88 (3H, t, J=7.1 Hz, CH_3); 1.12–1.37 (4H, m, CH_2); 1.57–1.73 (2H, m, CH_2); 1.88 (3H, dd, J=16.6, 0.8 Hz, C=CFCH_3); 3.70 (1H, m, CHPh); 4.65 [1H, ddd, J=36.4, 9.9, 0.8 Hz, $CH_{(trans)}$=CF]; 7.16–7.30 (5H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: −39.79 (m) ppm.

6a (mixture of two stereoisomers with respect to phenyl-substituted double bond, *E*:*Z*=1.2:1.0 determined by ^{1}H NMR spectroscopy): ^{1}H NMR $CDCl_3$ δ: 1.48–1.68 (2H, m, CH_2); 2.08–2.38 (4H, m, CH_2); 3.89 (2H, d, J=19.5 Hz, CH_2Br for one isomer); 3.94 (2H, d, J=19.5 Hz, CH_2Br for another isomer); 4.94 [1H, dt, J=34.3, 7.6 Hz, $CH_{(trans)}$=CF for one isomer]; 5.00 [1H, dt, J=34.3, 7.6 Hz, $CH_{(trans)}$=CF for another isomer]; 5.64 [1H, dt, J=11.7, 7.3 Hz, $CH_{(cis)}$=CHPh]; 6.19 [1H, dt, J=15.8, 6.9 Hz, $CH_{(trans)}$=CHPh]; 6.38–6.46 (1H, m, C=CHPh); 7.17–7.35 (5H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: −51.73–−51.97 (m) ppm. IR (neat): 3028; 2929; 2855; 1696 cm^{-1}.

6b (mixture of three stereoisomers, 19.0:1.7:1.0 determined by ^{19}F NMR spectroscopy): ^{1}H NMR $CDCl_3$ δ: 1.53–1.63 (2H, m, CH_2); 1.98–2.08 (2H, m, CH_2); 2.11–2.27 (2H, m, CH_2); 3.73 (3H, s, CH_3); 3.93 (2H, d, J=19.7 Hz, CH_2Br for second component of minor isomers); 3.98 (2H, d, J=22.0 Hz, CH_2Br for major isomer); 4.11 (2H, d, J=21.4 Hz, CH_2Br for first component of minor isomers); 4.96 [1H, dt, J=34.0, 7.6 Hz, $CH_{(trans)}$=CF for second component of minor isomers]; 5.24 [1H, dt, J=19.0, 8.2 Hz, $CH_{(cis)}$=CF for major isomer]; 5.26 [1H, dt, J=18.8, 8.2 Hz, $CH_{(cis)}$=CF for first component of minor isomers]; 5.83 (1H, dt, J=15.6, 1.5 Hz, C=$CHCO_2Me$ for first component of minor isomers); 5.85 [1H, dt, J=15.6, 1.5 Hz, C=$CHCO_2Me$ for major isomer and second component of minor isomers (overlapping)]; 6.94 [1H, dt, J=15.6, 7.0 Hz, C*H*=$CHCO_2Me$ for major isomer and minor isomers (overlapping)] ppm. ^{19}F NMR $CDCl_3$ δ: −44.48 (td, J=22.0, 19.0 Hz, for major isomers); −46.32 (td, J=21.4, 18.8 Hz, for first component of minor isomers); −49.64 (dt, J=34.0, 19.7 Hz, for second component of minor isomers) ppm. IR (neat): 2950; 2863; 1726; 1659 cm^{-1}. High-resolution MS: $C_{10}H_{14}BrFO_2$, 264.0154, 266.0159. Calcd., 264.0161, 266.0141.

6c (mixture of four stereoisomers, *E*:*Z*=1.0:2.1 with respect to fluorine-substituted double bond): ^{1}H NMR $CDCl_3$ δ: 1.43–1.55 (2H, m, CH_2); 1.98–2.16 (4H, m, CH_2); 3.89–4.08 (4H, m, CH_2); 4.50–4.52 (2H, m, CH_2); 4.94 [1H, dd, J=34.3, 7.6 Hz, $CH_{(trans)}$=CF for one isomer]; 4.97 [1H, J=34.3, 7.6 Hz, $CH_{(trans)}$=CF for one isomer]; 5.24 [1H, dd, J=18.9, 8.2 Hz, $CH_{(cis)}$=CF for one isomer]; 5.26 [1H, dd, J=18.9, 8.2 Hz, $CH_{(cis)}$=CF for one stereoisomer]; 5.56–5.74 (2H, m, CH=CH); 7.26–7.36 (5H, m, Ar) ppm. ^{19}F

NMR $CDCl_3$ δ: -45.04–-45.29 (m for *E*-fluoro-olefin isomers); -51.70–-52.0 (m for *Z*-fluoro-olefin isomers) ppm. IR (neat): 3063; 3030; 2930; 2857; 1694 cm^{-1}. MS *m/z*: 247 ($M^+ - Br$); 205; 183; 151.

9a (stereoisomeric mixture, 1.6:1.0 determined by GLC): ^1H NMR $CDCl_3$ δ: 1.24–1.98 (7H, m, CH_2 and CH); 2.12–2.45 (2H, m, CH_2); 2.73–2.96 (1H, m, CHCF=C); 4.23 [1H, dd, $J=50.4$, 2.7 Hz, $CF=CH_{(trans)}$ for major isomer]; 4.26 [1H, dd, $J=50.6$, 2.7 Hz, $CF=CH_{(trans)}$ for minor isomer]; 4.50 [1H, dd, $J=17.7$, 2.7 Hz, $CF=CH_{(cis)}$ for major isomer]; 4.59 [1H, dd, $J=18.3$, 2.7 Hz, $CF=CH_{(cis)}$ for minor isomer]; 7.16–7.28 (5H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: -31.94 (ddd, $J=50.6$, 21.3, 18.3 Hz, for minor isomer); -40.43 (ddd, $J=50.4$, 22.8, 17.7 Hz, for major isomer) ppm. IR (neat): 3064; 3028; 2959; 2874; 1667 cm^{-1}. High-resolution MS: $C_{14}H_{17}F$, 204.1323. Calcd., 204.1314.

9b (stereoisomeric mixture, 1.4:1.0 determined by GLC); ^1H NMR $CDCl_3$ δ: 1.24–2.04 (7H, m, CH_2 and CH); 2.18–2.57 (3H, m, CH_2 and CHCF=C for minor isomer); 2.82 (1H, dddd, $J=24.4$, 6.8, 6.8, 6.8 Hz, CHCF=C for major isomer); 3.66 (3H, s, CH_3); 4.22 [1H, dd, $J=50.4$, 2.7 Hz, $CF=CH_{(trans)}$ for major isomer]; 4.23 [1H, dd, $J=50.2$, 2.7 Hz, $CF=CH_{(trans)}$ for minor isomer]; 4.50 [1H, dd, $J=18.0$, 2.7 Hz, $CF=CH_{(cis)}$ for minor isomer]; 4.53 [1H, dd, $J=18.1$, 2.7 Hz, $CF=CH_{(cis)}$ for major isomer] ppm. ^{19}F NMR $CDCl_3$ δ: -33.31 (ddd, $J=50.4$, 24.4, 18.1 Hz, for major isomer); -40.93 (ddd, $J=50.2$, 21.7, 18.0 Hz, for minor isomer) ppm. IR (neat): 2955; 2876; 1741; 1670 cm^{-1}. High-resolution MS: $C_{10}H_{15}FO_2$, 186.1070. Calcd., 186.1056.

9c (stereoisomeric mixture, 2:1–3.4:1 determined by GLC): ^1H NMR $CDCl_3$ δ: 1.19–1.43 (1H, m, CH); 1.47–2.18 (8H, m, CH_2); 2.21 (1H, dddd, $J=23.1$, 8.4, 8.4, 8.4 Hz, CHCF=C for major isomer); 2.70 (1H, dddd, $J=24.3$, 7.4, 7.4, 7.4 Hz, CHCF=C for minor isomer); 3.47–3.57 (2H, m, CH_2O); 4.19 [1H, dd, $J=50.5$, 2.7 Hz, $CF=CH_{(trans)}$ for minor isomer]; 4.25 [1H, dd, $J=50.5$, 2.7 Hz, $CF=CH_{(trans)}$ for major isomer]; 4.46–4.54 (3H, m, CH_2Ph and $CF=CH_{(cis)}$]; 7.26–7.38 (5H, m, Ar) ppm. ^{19}F NMR $CDCl_3$ δ: -32.32 (ddd, $J=50.5$, 24.3, 19.5 Hz); -40.2–-40.46 (m) ppm. IR (neat): 3065; 3031; 2953; 2870; 1667 cm^{-1}. MS *m/z*: 248 (M^+); 228; 220; 205; 157; 140.

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