Chemistry of Novel Compounds with Multifunctional Carbon Structure. Part 3.[1] Synthesis of α-Azido-α-fluoro-α-(phenylthio and ethylthio)acetates

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The synthesis of tri- and tetra-functional carbon compounds which possess three or four different functional groups on the same carbon atom is described.

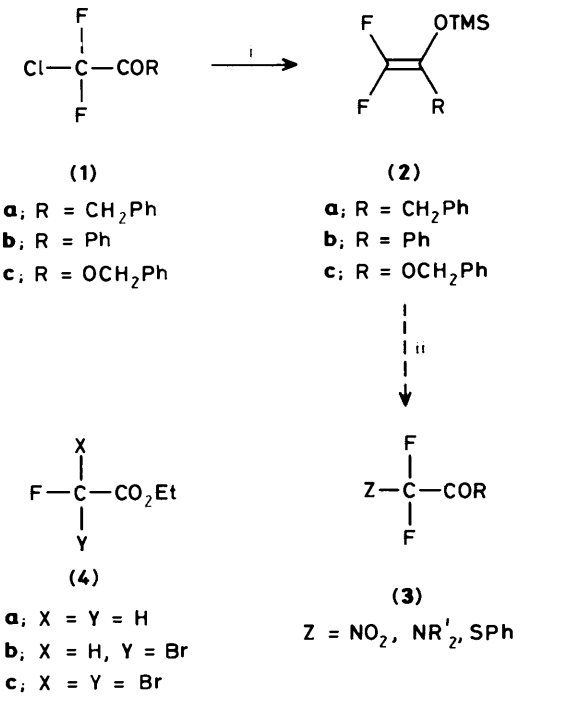
Reactions of ethyl bromofluoro- or chlorofluoro-acetate (**4b**) or (**5**) with several heteroatomic nucleophiles give the corresponding α-functionalised α-fluoroacetates (**6a—g**) in good yields. The trifunctional carbon compounds which have phenylthio and ethylthio functionalities (**6a, b**) are brominated with NBS to afford the tetrafunctional carbon compounds, ethyl bromofluoro(phenylthio and ethylthio)acetates (**8a, b**). The bromo derivatives (**8a, b**) can be converted into another type of tetrafunctional carbon compound, ethyl azidofluoro(phenylthio and ethylthio)acetates (**9a, b**) by reaction with sodium azide under phase-transfer conditions. Ethyl azidobromofluoroacetate (**12**) is prepared from the dibromo derivative (**4c**) in a similar manner.

The noticeable reactivities which are caused by the novel multifunctionalised carbon structures are also reported.

α-Functionalised carbonyl derivatives, *e.g.* α-amino acids[2] or α-hydroxyaldehydes,[3] are extremely useful compounds in organic synthesis. In addition to the versatility of the carbonyl group in functional group interconversions, those difunctional compounds have the added potential of serving as chiral auxiliaries and as useful starting materials for the synthesis of optically active natural products. Compounds containing a carbon atom bearing more than two different heteroatom-containing labile groups, therefore, should be much more significant in theoretical and synthetic chemistry although they have received little attention. We have recently succeeded in the first synthesis of such novel structures[4] and the term 'multifunctional carbon compounds' was proposed for them.[1] Herein we detail a full account of the synthetic approaches to and structural determination of various azido- and bromine-containing tetrafunctional carbon compounds. We also report the noticeable reactivities observed in the course of this work which are caused by these novel structures.

Results and Discussion

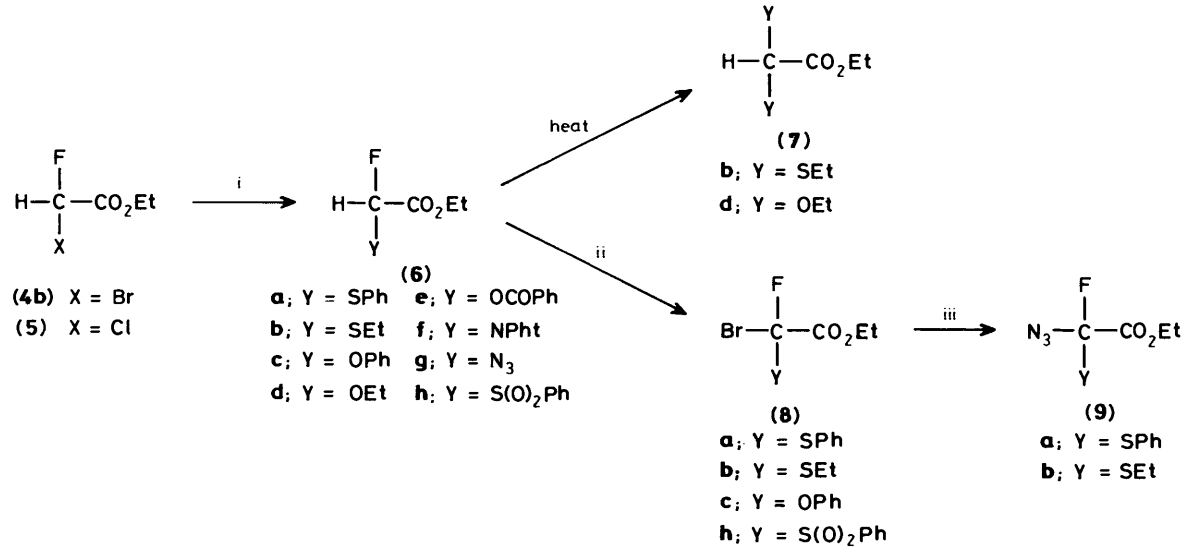
Electrophilic Functionalisation of α-Fluoro Esters.—Although fluorine is the best contributor among the halogens to the stabilisation of compounds with such unique structures, it is difficult to achieve selective fluorination of a carbon atom with plural labile functionalities. Therefore, our initial investigation was based on the strategy of stepwise introduction of functionality onto the available fluorine-bearing molecules. We first attempted functionalisation of α-fluoro esters through the corresponding enol silyl ethers (Scheme 1). Treatment of the α-fluoro ketones or esters (**1a—c**) with Zn and trimethylsilyl chloride (TMSCl) gave α-fluoro enol silyl ethers (**2a—c**) in good yields.[5] Electrophilic nitration of compounds (**2a—c**) with $PrONO_2$–Bu_4NF,[6] NH_4ONO_2–$(CF_3CO)_2O$,[7] and O_2NBF_4–HF–pyridine,[8] amination using $R^1{}_2NOR$[2,9] or sulphenylation with PhSCl or PhSSPh, did not produce any tri- or tetra-functional carbon compounds (**3**), mainly affording instead undesired complicated products. Direct electrophilic functionalisation of α-fluoro enolates was also attempted. Reaction of α-halogeno esters (**4a—c**) with NaOEt,[10] NaH,[11] BuLi, or $LiNPr^i{}_2$,[12] followed by the addition of various electrophiles mentioned above, mostly resulted in the recovery of starting materials. These facts were attributed to the concomitant side-reactions associated with the presence of plural labile groups on the same carbon atom or the poor reactivity of the α-fluoro enolate towards heteroatomic electrophiles.[13]



Scheme. 1. *Reagents:* i, Zn, TMSCl; ii, Z^+. TMS = $SiMe_3$

Nucleophilic or Radical Functionalisation of α-Fluoro Esters.—We next attempted the nucleophilic or radical introduction of heteroatom-centred functional groups. Reactions of bromo-, fluoro-, or chlorofluoro-acetates (**4b**) and (**5**) with various nucleophiles such as RS^-, RO^-, Pht=N^-,† and N_3^-, in the presence of appropriate bases and polar solvents, smoothly produced the geminally functionalised fluoro esters (**6a—g**) in

† Pht=N is phthalimido.



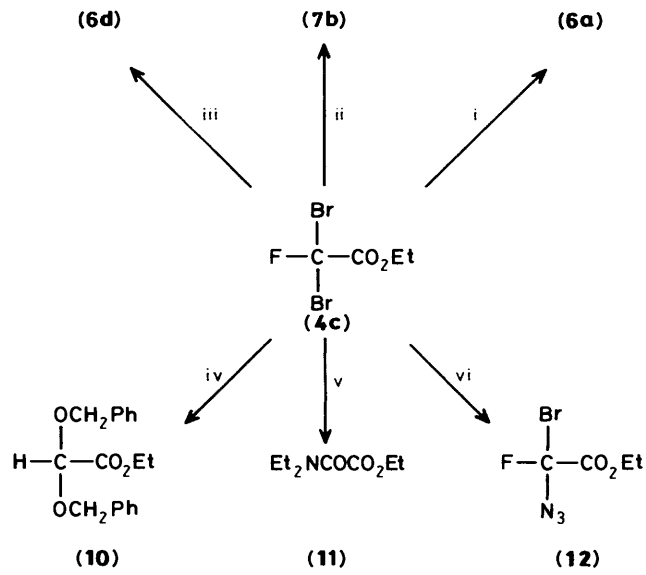
Scheme 2. *Reagents:* i, NaY or KY; ii, NBS or Br_2; iii, NaN_3. NPht = phthalimido

68—98% yield (Scheme 2). Although there are a few reports of sulphur- or oxygen-functionalised α-fluoro esters,[14] nitrogenously functionalised α-fluoro acetates, such as imidyl, or azidofluoroacetates, are unknown. The α-functionalised α-fluoro esters (**6b,d**) were thermally unstable, thereby providing disproportionated glyoxylate acetal analogues (**7b,d**) on distillation.

With the trifunctional carbon compounds (**6a—g**) now in hand, we then attempted to convert them into the tetrafunctional carbon compounds. Since the electrophilic introduction of another labile group on the chiral centre of compounds (**6a—g**) seemed infeasible as already shown in Scheme 1, bromination was attempted. After close investigation of the reaction conditions, we succeeded in isolating unstable brominated products. Thus, treatment of compounds (**6a,b**) with *N*-bromosuccinimide (NBS) in the presence of 2,2′-azoisobutyronitrile (AIBN) or benzoyl peroxide (BPO), under the controlled conditions described in the Experimental section, produced the bromides (**8a,b**) in 66 and 32% yield, respectively. α-Fluoro-α-(phenylsulphonyl)acetate (**6h**) obtained by *m*-chloroperbenzoic acid (MCPBA) oxidation of sulphide (**6a**) could be also converted into the bromide (**8h**) in a similar manner. Bromination of compound (**6c**) was achieved by the use of bromine to produce the bromide (**8c**) in 45% yield. Isolation of the bromides (**8d—g**) was not possible probably because of decomposition during attempted purification on silica gel.

Transformation of the bromides (**8a—c,h**) into another structural type of tetrafunctional carbon compounds was also attempted using various nitrogenous nucleophiles such as R_2N^-, $Pht{=}N^-$, NO_2^-, and N_3^-. Although most of the reactions resulted in the production of decomposition compounds,* only azido derivatives (**9a,b**) were obtained from (**8a,b**) in 32 and 40% yield, respectively, by reaction with NaN_3 under phase-transfer conditions (Scheme 2). The multifunctional carbon compounds are rather volatile and much less polar than expected[15] in spite of the presence of plural groups with comparatively large dipole moments.

An alternative approach to these novel tetrafunctionalised carbon structures was successive nucleophilic displacement of functionality from polyhalogenated acetate derivatives. However, the presence of plural halogens made it difficult to control



Scheme 3. *Reagents:* i, NaSPh; ii, NaSEt; iii, NaOEt; iv, $NaOCH_2Ph$; v, $HNEt_2$; vi, NaN_3

the reaction, resulting in the formation of several products derived from multiple and unexpected side-reactions. For example, reaction of dibromofluoroacetate (**4c**) with NaSPh, NaSEt, NaOEt, and $NaOCH_2Ph$ yielded, as the only isolable compound, reduced products (**6a**), (**7b**), (**6d**), and (**10**), respectively. Reaction of dibromide (**4c**) with $HNEt_2$ afforded the amide (**11**). The formation of these unexpected products can be explained in terms of either nucleophilic attack on the heteroatoms rather than on the central carbon atom or hydrolysis during work-up (Scheme 3). In contrast, reaction of dibromide (**4c**) with NaN_3 under phase-transfer conditions produced the tetrafunctional azido derivative (**12**) in 47% yield. The unsatisfactory yields of the bromo and azido derivatives can be ascribed to their instability and volatility.

All the tetrafunctional carbon compounds obtained here are new, despite their structural simplicity. A survey of the literature revealed no example of structures with a carbon atom

* Reaction of (**8a**) with proline ethyl ester gave the reduced product (**6a**).

surrounded by such labile functionalities, even as a part of a larger molecule.

From the results above and from many unsuccessful experiments, we can in general terms say that multifunctionality increases reactivity and volatility although it decreases polarity. We have found little consistency between reactivities and functional groups. Spectral analyses of this class of compounds are notable. In the ^{13}C n.m.r. spectra, multifunctionality generally lowers the central carbon shifts and raises the carbonyl carbon shifts. In their mass spectra, the first fragmentation peaks are usually derived from (M^+ − Br), (M^+ − F), or (M^+ − N_3) ions. However, these compounds give secondary fragmentation peaks, which at this time we are at a loss to explain by the conventional mechanisms for fragmentation. All the spectral analyses based on electronic properties of each heteroatom are now under investigation for some other multiply functionalised carbon compounds including nitro derivatives.[16]

Experimental

I.r. spectra were recorded on a JASCO A-102 spectrophotometer. ^1H N.m.r. spectra were measured in $CDCl_3$ with $SiMe_4$ as internal standard and recorded on JEOL PMX-60 (60 MHz) and Varian XL-200 (200 MHz) spectrometers, while ^{19}F n.m.r. spectra were measured in $CDCl_3$ with $CFCl_3$ as internal standard and taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative. ^{13}C N.m.r. spectra were measured in $CDCl_3$ with $SiMe_4$ as internal standard and recorded on Varian XL-200 (50 MHz) spectrometer. EI Mass spectra were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative t.l.c. (p.l.c.) were performed using Kieselgel 60 (Merck, Art. 9385 and Art. 7748, respectively).

Ethyl Fluoro(phenylthio)acetate (**6a**).—To a stirred solution of ethyl bromofluoroacetate (**4b**) (2.22 g, 12 mmol) in tetrahydrofuran (THF) (25 ml) were added successively triethylamine (2.5 ml, 18 mmol) and thiophenol (1.24 ml, 12 mmol) and the mixture was heated at reflux for 1 h. The precipitate was removed by filtration and the filtrate was concentrated using a rotary-evaporator below 35 °C. The residue was purified by silica gel column chromatography with hexane–ether (10:1) as eluant to afford the *title compound* (**6a**) as an oil (2.56 g, 95.6%). Distillation under reduced pressure gave an analytical sample; b.p. 125 °C/14 mmHg (Found: C, 55.9; H, 5.3. $C_{10}H_{11}FO_2S$ requires C, 56.06; H, 5.17%); $\nu_{max.}$(neat) 1 760 (CO), 1 585 (Ph), and 1 045 cm^{-1} (C–F); δ_H 1.17 (3 H, t, *J* 7 Hz, Me), 4.17 (2 H, q, *J* 7 Hz, CH_2), 6.10 (1 H, d, J_{H-F} 52 Hz, CFH), and 7.2—7.7 (5 H, m, Ph); δ_F −158.7 (d, J_{F-H} 53 Hz); δ_C 94.2 (dd, J_{C-F} 235, J_{C-H} 110 Hz, CHF) and 165.3 (d, J_{C-F} 26 Hz, CO); *m/z* 214 (M^+, 44%) and 141 (M^+ − CO_2Et, 100).

Ethyl Ethylthiofluoroacetate (**6b**).—To a suspension of sodium hydride (60% in mineral oil; 1.20 g, 30 mmol) in THF (10 ml) at 0 °C was slowly added ethanethiol (4.43 ml, 60 mmol) during 10 min. After foaming had ceased, a solution of compound (**4b**) (5.55 g, 30 mmol) in THF (19 ml) was added into the solution *via* a syringe and the mixture was stirred at 0 °C for 1 h. Evaporation of the solvent gave an oil, which was dissolved in ether (40 ml); the solution was washed with water (10 ml) and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by silica gel column chromatography with hexane–ether (1:1) as eluant to give the *title compound* (**6b**) as a pale yellow oil (4.61 g, 92.5%); $\nu_{max.}$(neat) 1 755 (CO) and 1 035 cm^{-1} (C–F); δ_H 1.33 (3 H, t, *J* 7 Hz, SCH_2Me), 1.33 (3 H, t, *J* 7 Hz, OCH_2Me), 2.57—3.07 (2 H, m, SCH_2), 4.33 (2 H, q, *J* 7 Hz, OCH_2), and 5.93 (1 H, d, J_{H-F} 52 Hz, CHF); δ_F −162.8 (d, J_{F-H} 51 Hz); δ_C 92.3 (dd, J_{C-F} 229, J_{C-H} 110 Hz, CHF) and 166.3 (d, J_{C-F} 32 Hz, CO) [Found: M^+, 166.0472. $C_6H_{11}FO_2S$ requires *M*, 166.0464; *m/z* 147.0469. $C_6H_{11}O_2S$ (M^+ − F) requires *m/z* 147.0479]. Attempted distillation for an analytical sample gave ethyl glyoxylate diethyl thioacetal (**7b**) *via* decomposition; b.p. 99 °C/38 mmHg; δ_H 1.23 (6 H, t, *J* 7 Hz, SCH_2Me × 2), 1.30 (3 H, t, *J* 7 Hz, OCH_2Me), 2.87 (4 H, q, *J* 7 Hz, SCH_2 × 2), 4.37 (2 H, q, *J* 7 Hz, OCH_2), and 4.47 (1 H, s, CH); *m/z* 208 (M^+, 17%), 147 (M^+ − SEt, 36), and 135 (M^+ − CO_2Et, 100).

Ethyl Fluoro(phenoxy)acetate (**6c**).—To a suspension of sodium hydride (60% in mineral oil; 400 mg, 10 mmol) in THF (10 ml) was added a solution of phenol (940 mg, 10 mmol) in THF (2 ml) and the mixture was stirred at 0 °C for 20 min. A solution of compound (**4b**) (1.85 g, 10 mmol) in THF (2 ml) was added slowly to the mixture, which was then stirred at room temperature for 30 min. The resultant solution was poured into a mixture of water (5 ml) and ether (20 ml) and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave the *title compoumd* (**6c**) as an oil (1.94 g, 97.8%); $\nu_{max.}$(neat) 1 760 (CO), 1 595 (Ph), and 1 025 cm^{-1} (C–F); δ_H 1.21 (3 H, t, *J* 7 Hz, Me), 4.21 (2 H, q, *J* 7 Hz, CH_2), 5.85 (1 H, d, J_{H-F} 60 Hz, CFH), and 6.95—7.30 (5 H, m, Ph); δ_F −129.8 (d, J_{F-H} 59 Hz); δ_C 102.6 (dd, J_{C-F} 232, J_{C-H} 99 Hz, CHF) and 164.0 (d, J_{C-F} 30 Hz, CO) [Found: M^+, 198.0688. $C_{10}H_{11}FO_3$ requires *M*, 198.0691; *m/z* 125.0409. C_7H_6FO (M^+ − CO_2Et) requires *m/z* 125.0403]. Attempted distillation of compound (**6c**) resulted in decomposition.

Ethyl Ethoxyfluoroacetate (**6d**).—To a mixture of sodium hydride (60% in mineral oil; 40 mg, 1 mmol) in THF (1 ml) was added ethanol (46 mg, 1 mmol) under argon. After foaming had ceased completely, a solution of compound (**4b**) (185 mg, 1 mmol) in THF (0.5 ml) was added to the mixture, which was then stirred at room temperature for 20 min. Water (10 ml) and ether (10 ml) were added and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave the *title compound* (**6d**) as an oil (138 mg, 89.8%); $\nu_{max.}$(neat) 1 760 (CO), 1 115 (C–O), and 1 030 cm^{-1} (C–F); δ_H 1.33 (3 H, t, *J* 7 Hz, $CHFOCH_2Me$), 1.37 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 3.7—4.1 (2 H, m, $CHFOCH_2$), 4.37 (2 H, q, *J* 7 Hz, CO_2CH_2), and 5.53 (1 H, d, J_{H-F} 62 Hz, CH) [Found: M^+, 150.0657. $C_6H_{11}FO_3$ requires *M*, 150.0691; *m/z* 131.0718. $C_6H_{11}O_3$ (M^+ − F) requires *m/z* 131.0707]. Attempted distillation to give an analytical sample produced ethyl glyoxylate diethyl acetal (**7d**) *via* decomposition; b.p. 78 °C/57 mmHg; δ_H 1.27 [6 H, t, *J* 7 Hz, $C(OCH_2Me)$ × 2], 1.33 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 3.70 [4 H, q, *J* 7 Hz, $C(OCH_2Me)$ × 2], 4.27 (2 H, q, *J* 7 Hz, CO_2CH_2), and 4.90 (1 H, s, CH).

Ethyl Benzoyloxyfluoroacetate (**6e**).—A mixture of compound (**4b**) (185 mg, 1 mmol) and potassium benzoate (800 mg, 1 mmol) in dimethylformamide (DMF) (2 ml) was stirred at room temperature under argon for 2 h. Water (10 ml) and ether (5 ml) were added and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by column chromatography with hexane–ether (1:1) as eluant to give the *title compound* (**6e**) as a pale yellow oil (203 mg, 90.0%); $\nu_{max.}$(neat) 1 755 (CO_2Et), 1 720 (OCOPh), and 1 015 cm^{-1} (C–F); δ_H 1.37 (3 H, t, *J* 7 Hz, Me), 4.37 (2 H, q, *J* 7 Hz, $3H_2$), 6.67 (1 H, d, J_{H-F} 52 Hz, CH), and 7.4—8.0 (5 H, m, Ph); δ_F −140.4 (d, J_{F-H} 55 Hz); δ_C 95.3 (dd, J_{C-F} 233, J_{C-H} 111 Hz, CHF) and 164.2 (d, J_{C-F} 30 Hz, CO) [Found: M^+, 226.0639. $C_{11}H_{11}FO_4$ requires *M*, 226.0640; *m/z* 181.0373. $C_9H_6FO_3$ (M^+ − OEt) requires *m/z* 181.0300]. Attempted distillation of compound (**6e**) resulted in decomposition.

Ethyl Fluoro(phthalimido)acetate (**6f**).—A mixture of compound (**5**) (16.86 g, 120 mmol) and potassium phthalimide (22.20 g, 120 mmol) in DMF (50 ml) was heated at 100 °C under argon for 5 h. To the mixture was added ether (100 ml) and the precipitate was removed by filtration. The filtrate was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was chromatographed on silica gel with benzene–ether (19:1) as eluant to afford the title compound (**6f**) as a solid (26.83 g, 89.1%). Recrystallisation from ethyl acetate gave an analytical sample; m.p. 104—105 °C (lit.,[1] 103—104 °C) (Found: C, 57.2; H, 4.0; N, 5.9. Calc. for $C_{12}H_{10}FNO_4$: C, 57.37; H, 4.01; N, 5.58%); $\nu_{max.}$(KBr) 1 765 (CO_2), 1 725 (CON), and 1 065 cm^{-1} (C–F); δ_H 1.40 (3 H, t, *J* 7 Hz, Me), 4.43 (2 H, q, *J* 7 Hz, CH_2), 6.37 (1 H, d, J_{H-F} 48 Hz, CHF), and 7.8—8.3 (4 H, m, ArH); δ_F −155.6 (d, J_{F-H} 48 Hz); δ_C 81.1 (dd, J_{C-F} 214, J_{C-H} 94 Hz, CHF) and 164.3 (d, J_{C-F} 34 Hz, CO); *m/z* 252 (M^+ + 1, 2%) and 178 (M^+ − CO_2Et, 20).

Ethyl Azidofluoroacetate (**6g**).—A solution of compound (**4b**) (0.52 g, 2.8 mmol) in ether (5 ml) and a solution of sodium azide (2.58 g, 49 mmol) in water (5 ml) were combined. To the two-layered solution was added intermittently ethanol (total 7 ml) during a period of 10 h as the reaction was monitored by n.m.r. spectroscopy of the organic layer. Insoluble materials were removed by filtration. To the filtrate were added water (5 ml) and ether (5 ml), and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave the title compound (**6g**) as an almost pure (n.m.r.) oil (0.28 g, 68.0%); $\nu_{max.}$(neat) 2 120 (N_3), 1 755 (CO), and 1 020 cm^{-1} (C–F); δ_H 1.40 (3 H, t, *J* 7 Hz, Me), 4.33 (2 H, q, *J* 7 Hz, CH_2), and 5.44 (1 H, br d, J_{H-F} 52 Hz, CHF); δ_F −147.8 (d, J_{F-H} 51 Hz); δ_C 93.7 (dd, J_{C-F} 233, J_{C-H} 95 Hz, CHF) and 164.0 (d, J_{C-F} 34 Hz, CO). The mass spectrum did not show any rational fragmentation, probably because of ready decomposition. **Cautionary note.** Attempted distillation (b.p. 83—84 °C/18 mmHg) resulted in *explosion.*

Ethyl Fluoro(phenylsulphonyl)acetate (**6h**).—To a solution of the sulphide (**6a**) (107 mg, 0.5 mmol) in CH_2Cl_2 (1 ml) was added dropwise a solution of MCPBA (80%; 216 mg, 1.0 mmol) in CH_2Cl_2 (3 ml) and the mixture was stirred for 20 min. The resulting solution was diluted with CH_2Cl_2 (6 ml) and washed successively with saturated aq. $NaHCO_3$, saturated aq. NaCl, then dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by p.l.c. to afford the *title compound* (**6h**) as an oil (41.5 mg, 33.7%); δ_H 1.33 (3 H, t, *J* 7 Hz, Me), 4.37 (2 H, q, *J* 7 Hz, CH_2), 5.63 (1 H, d, J_{H-F} 49 Hz, CHF), and 7.5—8.2 (5 H, m, Ph) (Found: M^+, 246.0351. $C_{10}H_{11}FO_4S$ requires *M*, 246.0361).

Ethyl Bromofluoro(phenylthio)acetate (**8a**).—A solution of compound (**6a**) (214 mg, 1 mmol) and benzoyl peroxide (10 mg) in CCl_4 (2 ml) was heated at reflux and irradiated with a 250 W sun-lamp for 10 h. During this period, NBS (total 89 mg) and CCl_4 (total 62 ml) were added in several portions. To the resulting mixture were added hexane (10 ml) and ether (5 ml), and the precipitate was removed by filtration. Evaporation of the solvent gave a crude product, which was purified by column chromatography with hexane–ether (9:1) as eluant to give the *title compound* (**8a**) as a pale yellow oil (194 mg, 66.2%); $\nu_{max.}$(neat) 1 755 (CO), 1 575 (Ph), and 1 060 cm^{-1} (C–F); δ_H 1.20 (3 H, t, *J* 7 Hz, Me), 4.20 (2 H, q, *J* 7 Hz, CH_2), and 7.1—7.7 (5 H, m, Ph); δ_F −83.8 (s); δ_C 98.1 (d, J_{C-F} 302 Hz, CF) and 163.7 (d, J_{C-F} 29 Hz, CO); *m/z* 292, 294 (M^+, 8%), 219, 221 (M^+ − CO_2Et, 12), and 213 (M^+ − Br, 100) (Found: M^+, 291.9603. $C_{10}H_{10}BrFO_2S$ requires *M*, 291.9570). Attempted distillation of compound (**8a**) resulted in decomposition.

Ethyl Bromo(ethylthio)fluoroacetate (**8b**).—A mixture of compound (**6b**) (391 mg, 2.36 mmol), NBS (420 mg, 2.36 mmol), and AIBN 5 mg) in CCl_4 (10 ml) was heated at reflux in an oil-bath for 8 h. More AIBN (20 mg) was added and the mixture was heated at reflux with a 250 W sun-lamp for 6 h. After the mixture had been cooled to room temperature, insoluble materials were removed by filtration. Concentration of the filtrate gave a crude product, which was purified by column chromatography with hexane–ether (9:1) as eluant to afford the *title compound* (**8b**) as a pale yellow oil (184 mg, 31.9%); $\nu_{max.}$(neat) 1 755 (CO) and 1 085 cm^{-1} (C–F); δ_H 1.33 (3 H, t, *J* 7 Hz, SCH_2Me), 1.40 (3 H, t, *J* 7 Hz, OCH_2Me), 3.05 (2 H, q, *J* 7 Hz, SCH_2), and 4.43 (2 H, q, *J* 7 Hz, OCH_2); δ_F −81.4 (s); δ_C 99.6 (d, J_{C-F} 302 Hz, CF) and 163.8 (d, J_{C-F} 24 Hz, CO) (Found: M^+, 243.955 73. $C_6H_{10}BrFO_2S$ requires *M*, 243.9570). Attempted distillation of compound (**8b**) resulted in decomposition.

Ethyl Bromofluoro(phenoxy)acetate (**8c**).—A solution of compound (**6c**) (99 mg, 0.5 mmol) and bromine (80 mg, 0.5 mmol) in CCl_4 (1.8 ml) was heated at reflux with a 250 W sun-lamp under argon for 4 h. Concentration of the mixture gave a crude product, which was purified by p.l.c. to give the *title compound* (**8c**) as an oil (63 mg, 45.4%); $\nu_{max.}$(neat) 1 770 (CO), 1 590 (Ph), 1 200 (C–O), and 1 075 cm^{-1} (C–F); δ_H 1.43 (3 H, t, *J* 7 Hz, Me), 4.46 (2 H, q, *J* 7 Hz, CH_2), and 7.37 (5 H, m, Ph); δ_F −58.0 (s); δ_C 106.4 (d, J_{C-F} 302 Hz, CF) and 161.3 (d, J_{C-F} 30 Hz, CO); *m/z* 276, 278 (M^+, 14%), and 197 (M^+ − Br, 38) (Found: M^+, 275.9769. $C_{10}H_{10}BrFO_3$ requires *M*, 275.9796). Attempted distillation of compound (**8c**) resulted in decomposition.

Ethyl Bromofluoro(phenylsulphonyl)acetate (**8h**).—A mixture of compound (**6h**) (27 mg, 0.11 mmol), NBS (20 mg, 0.11 mmol), and AIBN (2 mg) in CCl_4 (1 ml) was heated at reflux in an oil-bath under argon for 44 h. Insoluble materials were removed, and concentration of the filtrate gave a crude product, which was purified by p.l.c. to give the title compound (**8h**) as an oil (12 mg, 33.6%); δ_H 1.40 (3 H, g, *J* 7 Hz, Me), 4.43 (2 H, q, *J* 7 Hz, CH_2), and 7.2—8.2 (5 H, m, Ph); *m/z* 324, 326 (M^+, 15%), 279, 281 (M^+ − OEt, 3), and 141 (SO_2Ph, 100). Attempted distillation of compound (**8h**) resulted in decomposition.

Ethyl Azidofluoro(phenylthio)acetate (**9a**).—To a solution of compound (**8a**) (293 mg, 1 mmol) in ethyl acetate (2 ml) were successively added water (1 ml), ethanol (0.5 ml), and sodium azide (650 mg, 10 mmol), and the flask was filled with argon and sealed. The reaction mixture was stirred at 20 °C for 28 h. Water (10 ml) and ether (10 ml) were added to the mixture and the ethereal layer was dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by p.l.c. to afford the *title compound* (**9a**) as a yellow oil (81 mg, 31.8%); $\nu_{max.}$(neat) 2 135 (N_3), 1 755 (CO), and 1 045 cm^{-1} (C–F); δ_H 1.27 (3 H, t, *J* 7 Hz, Me), 4.28 (2 H, q, *J* 7 Hz, CH_2), and 7.2—7.8 (5 H, m, Ph) [Found: M^+, 255.0709. $C_{10}H_{10}FN_3O_2S$ requires *M*, 255.0478; *m/z* 213.0382. $C_{10}H_{10}FO_2S$ (M^+ − N_3) requires *m/z* 213.0384]. Attempted distillation of compound (**9a**) resulted in decomposition.

Ethyl Azido(ethylthio)fluoroacetate (**9b**).—To a solution of compound (**8b**) (130 mg, 0.53 mmol) in ethyl acetate (3 ml) were successively added water (2 ml), ethanol (1 ml), and sodium azide (650 mg, 10 mmol), and the flask was filled with argon and sealed. The reaction mixture was stirred at 20 °C for 16 h. After the same work-up as above, the *title compound* (**9b**) was obtained as a yellow oil (44 mg, 40.1%); $\nu_{max.}$(neat) 2 130 (N_3), 1 750 (CO), and 1 030 cm^{-1} (C–F); δ_H 1.33 (3 H, t, *J* 7 Hz, SCH_2Me), 1.37 (3 H, t, *J* 7 Hz, OCH_2Me), 2.87 (2 H, q, *J* 7 Hz, SCH_2), and 4.34 (2 H, q, *J* 7 Hz, OCH_2) [Found: M^+, 207.0490.

$C_6H_{10}FN_3O_2S$ requires M, 207.0501; m/z 165.0371. $C_6H_{10}FOS$ ($M^+ - N_3$) requires m/z 165.0384]. Attempted distillation of compound (**9b**) resulted in decomposition.

Ethyl Azidobromofluoroacetate (**12**).—A mixture of compound (**4c**) (520 mg, 1.97 mmol), sodium azide (1.292 g, 19.8 mmol), and tetrabutylammonium bromide (297 mg, 0.92 mmol) in CH_2Cl_2 (1 ml) and water (1 ml) was stirred in a sealed flask at 20 °C for 140 h. The mixture was diluted with water (10 ml) and extracted with CH_2Cl_2 (3 ml × 3). The combined organic layer was dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by column chromatography with hexane–ether (2:1) as eluant to give the title compound (**12**) as an oil (209 mg, 46.9%); $\nu_{max.}$(neat) 2 230 (N_3), 1 760 (CO), and 1 030 cm^{-1} (C–F); δ_H 1.37 (3 H, t, J 7 Hz, Me) and 4.37 (2 H, q, J 7 Hz, CH_2); m/z 183, 185 ($M^+ - N_3$, 18%). **Cautionary note.** Attempted distillation of compound (**12**) resulted in *explosion.*

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References

1 Part 2, Y. Takeuchi, M. Asahina, K. Nagata, and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2203.
2 J. Martens, *Top. Curr. Chem.*, 1984, **125**, 165; H. C. J. Ottenheijm, *Chimia*, 1985, **39**, 89; L. R. Smith and H. J. Williams, *J. Chem. Educ.*, 1979, **56**, 696; R. B. Silverman and M. W. Holladay, *J. Am. Chem. Soc.*, 1981, **103**, 7357; D. Seebach, M. Boes, R. Naef, and W. B. Schweizer, *ibid.*, 1983, **105**, 5390; P. J. Maurer, C. G. Knudsen, A. D. Palkowitz, and H. Rapoport, *J. Org. Chem.*, 1985, **50**, 325; S. Hanessian and S. P. Sahoo, *Tetrahedron Lett.*, 1984, **25**, 1425; K. Drauz, A. Kleeman, and J. Martens, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 584 and references therein.
3 T. R. Kelly and P. N. Kaul, *J. Org. Chem.*, 1983, **48**, 2775; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 556 and references therein; W. Waszkuć, T. Janecki, and R. Bodalski, *Synthesis*, 1984, 1025; R. M. Williams, O. P. Anderson, R. W. Armstrong, J. Josey, H. Meyers, and C. Eriksson, *J. Am. Chem. Soc.*, 1982, **104**, 6092; S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1 and references therein.
4 Y. Takeuchi, M. Asahina, A. Murayama, K. Hori, and T. Koizumi, *J. Org. Chem.*, 1986, **51**, 955.
5 M. Yamana, T. Ishihara, and T. Ando, *Tetrahedron Lett.*, 1983, **24**, 507.
6 F. E. Elfehail and W. W. Zajac, Jr., *J. Org. Chem.*, 1981, **46**, 5151.
7 P. Dampawan and W. W. Zajac, Jr., *Synthesis*, 1983, 545.
8 G. A. Olah, *Aldrichimica Acta*, 1979, **12**, 43.
9 T. Sheradsky and Z. Nir, *Tetrahedron Lett.*, 1969, 77; E. W. Colvin, G. W. Kirby, and A. C. Wilson, *ibid.*, 1982, **23**, 3835; M. Bernheim and G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 1010.
10 E. Elkik and M. Imbeaux-Oudotte, *Tetrahedron Lett.*, 1978, 3793.
11 R. L. Buchanan, F. H. Dean, and F. L. M. Pattison, *Can. J. Chem.*, 1962, **40**, 1571.
12 H. Molines, M. H. Massoudi, D. Cantacuzene, and C. Wakselman, *Synthesis*, 1983, 322; J. T. Welch and S. Eswarakrishnan, *J. Chem. Soc., Chem. Commun.*, 1985, 186; J. T. Welch, K. Seper, S. Eswarakrishnan, and J. Samartino, *J. Org. Chem.*, 1984, **49**, 4720.
13 P. Brownbridge, *Synthesis*, 1983, 1 and references therein.
14 R. Sauvetre, J. Normant, and J. Villieras, *Tetrahedron*, 1975, **31**, 897; J. F. Normant, R. Suavetre, and J. Villieras, *C.R. Acad. Sci., Ser. C*, 1973, **277**, 515; A. V. Fokin, V. I. Zimin, Y. N. Studnev, and A. I. Rapkin, *Zh. Org. Khim.*, 1971, **7**, 249; V. V. Berenblit, V. A. Nikitin, V. P. Sass, L. N. Senyushov, Y. K. Starobin, and Y. V. Tsyganov, *ibid.*, 1979, **15**, 284.
15 Y. Takeuchi, T. Hagi, A. Muruyama, T. Koizumi, and A. Ichida, *J. Liq. Chromatogr.*, 1987, **10**, 3279.
16 Y. Takeuchi, A. Murayama, T. Hagi, and T. Koizumi, *Nippon Kagaku Kaishi*, 1985, 2029.

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