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AROMATIC FLUORO DERIVATIVES
XLIX. SYNTHESIS OF CARBOCYCLIC COMPOUNDS BY INTRAMOLECULAR NUCLEOPHILIC SUBSTITUTION REACTIONS

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SUMMARY

Interaction of a compound of the type $Ar_F\text{-}\underset{R}{\underset{|}{C}}H\text{-}_nCH(COOEt)_2$ with sodium hydride results in the formation of the Na salt of the carbanion $Ar_F\text{-}\underset{R}{\underset{|}{C}}H\text{-}_n\bar{C}(COOEt)_2\ Na^+$ (where Ar_F represents a polyfluorinated group), which can enter into an intramolecular nucleophilic substitution reaction with the formation of the corresponding polyfluorinated carbocyclic compound. This reaction may serve as a general method for producing such compounds.

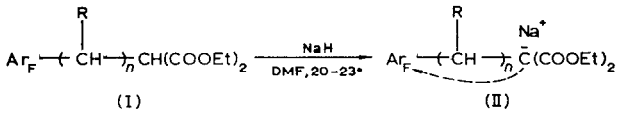
INTRODUCTION

Intramolecular nucleophilic substitution of fluorine atoms in polyfluorinated aromatic compounds has found a wide application in the synthesis of polyfluorinated heterocyclic compounds. The nucleophilic function is usually performed by the grouping containing a heteroatom[1] or an unstable carbanion generated at an unsaturated carbon atom in the course of the reaction[2]. This reaction has not been employed practically for producing polyfluorinated carbocyclic compounds, though its applicability in principle for such purposes has been established[3,4]. In this case the role of the nucleophile was played by a stable carbanion at a saturated carbon atom.

RESULTS AND DISCUSSION

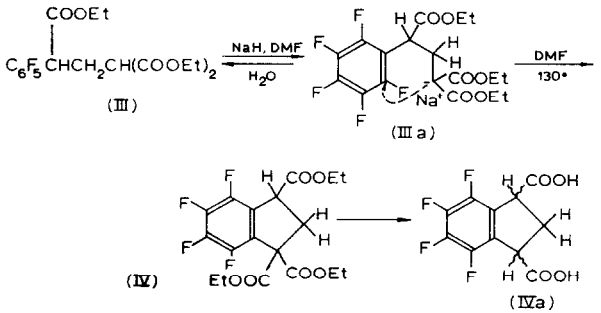
In the present paper a reasonably general method of producing polyfluorinated carbocyclic compounds is suggested, involving intramolecular nucleophilic

substitution of a fluorine atom in an aralkyl-substituted malonic ester containing a polyfluorinated aromatic group, under the action of a stable carbanion generated in the course of the reaction:



(I) (II)

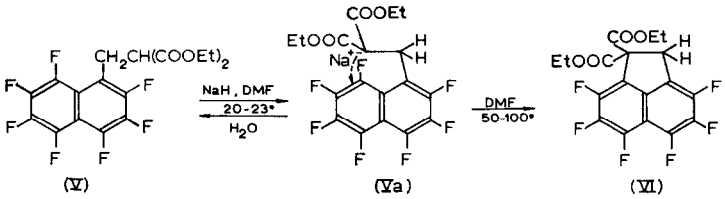
It is essential here that the equilibrium acidity of the C–H bond which is in the α position with respect to Ar_F is considerably lower than that for the mono-substituted malonic ester[5], this factor conditioning the predominant formation of the carbanion of type (II). Depending on the nature of the polyfluorinated aromatic group Ar_F and the number of carbon atoms n found between the carbanion centre and Ar_F, the cyclization reaction can result in the formation of five-, six- or seven-membered rings. Some examples of this cyclization reaction leading to 5-membered rings have been studied by us for different Ar_F and n. Thus in the case of (β-pentafluorophenyl-β-carbethoxy)ethylmalonic ester(III) ($Ar_F = C_6F_5$ and $n = 2$), a derivative of 4,5,6,7-tetrafluoroindane, namely, 1,1,3-tris(carbethoxy)-4,5,6,7-tetrafluoroindane(IV) is smoothly produced. From the latter, 1,3-dicarboxy-4,5,6,7-tetrafluoroindane(IVa) is produced by hydrolysis and subsequent decarboxylation.



(III) (IIIa) (IV) (IVa)

The structure of the salt of carbanion (IIIa) has been proved by the use of ^{19}F NMR spectroscopy and by chemical transformations. In the ^{19}F NMR spectrum of a solution of this salt, the intensity and position of the signals are similar to those in the ^{19}F NMR spectrum of the isoelectronic β-pentafluorophenylethylamine. Neutralization of the solution of the salt (IIIa) allows the isolation of the starting compound (III) in a quantitative yield.

The reaction can also be employed for producing polyfluorinated derivatives of acenaphthene. Thus from (α-heptafluoronaphthyl)methylmalonic ester (V) ($Ar_F = \alpha$-$C_{10}F_7$ and $n = 1$), 1,1-dicarbethoxy-3,4,5,6,7,8-hexafluoroacenaphthene (VI) is produced.

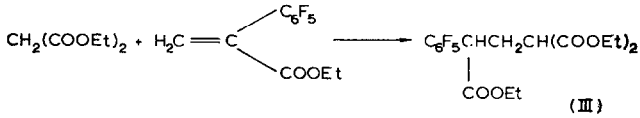


In the course of generation of the salt of the carbanion (Va) partial cyclization also occurs with the formation of compound (VI). This has been demonstrated by ^{19}F NMR spectroscopy and also by the analysis of the IR spectrum of the neutralization product of a solution of the salt (Va).

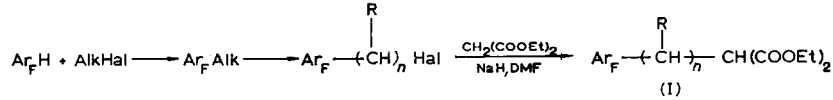
Filler *et al.* have shown[3] that the interaction of 2-carbethoxymethyl-nonafluorobiphenyl (VII) with sodium hydride in DMF gives 9-carbethoxy-1,2,3,4,5,6,7,8-octafluorofluorene. Although in this case the starting compound is a derivative of a polyfluoroarylacetic acid (VII) and not a derivative of a polyfluoroarylmalonic ester, the former compound may also be regarded as being related to compounds of type (I) in which Ar_F is a nonafluoro-*o*-biphenylyl group and $n = 0$. However, the use of polyfluoroaralkyl derivatives of acetic acid diminishes the reaction potentialities of the synthesis, since with $n \geqslant 1$ the equilibrium acidity of the compounds drops sharply, and therefore the generation of carbanions from them during reaction with sodium hydride is considerably hindered.

Presumably when Ar_F is a nonafluoro-*o*-biphenylyl group and $n = 1$ in compound (I), the formation of a corresponding polyfluorinated derivative of 9, 10-dihydrophenanthrene may be expected, while if Ar_F is an *o*-(2,3,4,5,6-pentafluorobenzyl)tetrafluorophenyl group and $n = 1$, a corresponding derivative of polyfluorinated dibenzocycloheptadiene should be formed.

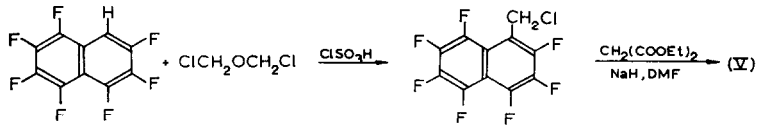
The availability of the cyclization reaction products will, obviously, be determined by the availability of the starting compounds of type (I). One of the ways for producing such compounds is *via* the Michael reaction of 1,1-disubstituted ethylenes with a malonic ester or mono-substituted malonic ester. Thus, the interaction of malonic ester with 1-pentafluorophenyl-1-carbethoxyethylene gave compound (III) [*cf.* ref.6]:



Another method for the preparation of compounds of type (I) is through the introduction of a malonic ester residue into the molecule of a polyfluoroaromatic compound in accordance with the scheme



By this method α-heptafluoronaphthylmalonic ester (V) has been produced from α-chloromethylheptafluoronaphthalene*.



EXPERIMENTAL

^1H and ^{19}F NMR spectra were recorded on a Varian A56–60A apparatus at frequencies of 60 and 56.4 MHz respectively, the internal standards being hexamethyldisiloxane and hexafluorobenzene (the shift into the weak field was negative); concentrations of the specimens are specified in the text. The IR spectra were recorded on a UR-20 apparatus using a 5% solution in CCl_4. The UV spectra were recorded on a Unicam SP700 apparatus. Molecular weights were determined by the method of isothermal distillation.

(β-Pentafluorophenyl-β-carbethoxy)ethylmalonic ester (III)

Method A

To a suspension of freshly calcined potassium fluoride (3 g) in anhydrous 1,2-dimethoxyethane (20 ml), malonic ester (2.7 g) and a solution of 1-pentafluorophenyl-1-carbethoxyethylene[6] (3.7 g) in 1,2-dimethoxyethane (5 ml) were added in succession. The mixture was stirred for 24 h at 60°, allowed to cool and first diethyl ether (30 ml) and then a 5% solution of hydrochloric acid (20 ml) added. The organic layer was separated, washed with water (5 × 10 ml), dried with $MgSO_4$, filtered and a major portion of the diethyl ether distilled off. The residue was distilled *in vacuo* when 2.7 g (45%) of compound (III) was isolated as a colourless liquid, b.p. 165–168°/0.3 mmHg, n_D^{20} 1.4468. (Found: C, 51.0; H, 4.53; F, 22.5%. Mol. wt., 423. $C_{18}H_{19}F_5O_6$ requires C, 50.6; H, 4.45; F, 22.3%. Mol. wt., 426.) IR spectrum: $\nu_{max.}$ 2995(m), 2950(w), 2920(w), 2885(w), 1763–1750(s) (doublet), 1535–1518(s) (doublet), 1485(w), 1475(w), 1455(m), 1400(w), 1380(m), 1335(m), 1312(s), 1295–1120(s) (multiplet), 1105(m), 1075(w), 1045–950(m) (multiplet), 920(w), 865(w), 820(w) and 645(w) cm^{-1}. The ^1H NMR spectrum (15% in CCl_4) contained signals at 1.18 (3H in $COOCH_2\underline{CH_3}$, triplet, $J(CH_3–CH_2) = 7.2$ Hz), 1.21 (6H in two $COOCH_2\underline{CH_3}$, triplet, $J(CH_3–CH_2) = 7.2$ Hz), 2.4 (3H in $\geqslant CH$ and $>CH_2$, multiplet), 3.2 (1H in $\geqslant CH$, multiplet), 4.06 (2H in $COO\underline{CH_2}CH_3$, quartet, $J(CH_2–CH_3) = 7.2$ Hz), 4.12 (4H in two $COO\underline{CH_2}CH_3$, quartet, $J(CH_2–CH_3) = 7.2$ Hz) ppm. ^{19}F NMR spectrum (15% in CCl_4) contained three signals at −0.1 ($2F_m$, multiplet), −6.9 ($1F_p$, triplet of triplets, $J(3,4) = 20.5$ Hz, $J(2,4) = 1.3$ Hz), −20.6 ppm ($2F_o$, multiplet).

* This compound has been prepared by O. I. Osina and V. D. Steingarts in our laboratory.

Method B

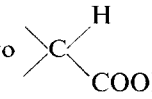
To a suspension of sodium hydride (0.012 g) in anhydrous dimethylformamide (0.47 g), compound (III) was added (0.21 g) in a stream of dry argon at 20–23°. After bubbles of hydrogen had ceased to be evolved, the solution was kept for 5 h at 20–23° and the ^{19}F NMR spectrum of the carbanion (IIIa) recorded. The ^{19}F NMR spectrum contained three signals at +2.3 ($2F_m$, multiplet), −3.6 ($1F_p$, triplet, $J(3,4) = 21$ Hz), −22.6 ppm ($2F_o$, multiplet). The solution was diluted with diethyl ether (4 ml), neutralized with a 5% solution of HCl (3 ml), the extract separated, washed with water (3 × 1 ml) and dried with $MgSO_4$. After filtration, the solution was evaporated when 0.18 g of the starting compound (III) was isolated. The IR spectrum of the product was identical to that of the initial compound.

1,1,3-Tris(carbethoxy)-4,5,6,7-tetrafluoroindane(IV)

To a suspension of sodium hydride (0.45 g) in anhydrous dimethylformamide (35 ml), a solution of compound (III) (7.1 g) in anhydrous dimethylformamide (10 ml) was added dropwise with stirring in a stream of dry argon at 20–23°. After bubbles of hydrogen had ceased to be evolved, the resulting dark red solution was heated to 130° for 30 min and kept at this temperature for 4.5 h. After this time the solution was allowed to cool, and diluted first with diethyl ether (40 ml) and then with a 5% solution of HCl (40 ml). The organic layer was separated, washed with water (5 × 10 ml), dried with $MgSO_4$, filtered and a major portion of the diethyl ether distilled off. The residue was distilled *in vacuo* when 2.71 g (49%) of compound (IV) was obtained as a colourless liquid, b.p. 137–139°/0.6 mmHg, n_D^{20} 1.4660. (Found: C, 53.3; H, 4.77; F, 18.9%. Mol. wt., 395. $C_{18}H_{18}F_4O_6$ requires C, 53.2; H, 4.43; F, 18.7%. Mol. wt., 406.) IR spectrum: $\nu_{max.}$ 2995(m), 2950(w), 2920(w), 2885(w), 1756(s), 1518(s), 1456(w), 1380(m), 1338(m), 1310(m), 1275–1250(m) (multiplet), 1200(s), 1154(m), 1105(m), 1086(m), 1050–1025(m) (multiplet), 986(m), 945(w), 895–870(s) (multiplet), 655(w) and 555(w) cm^{-1}. UV spectrum: $\lambda_{max.}$ (petroleum ether, boiling range 70–100°) 263 nm (log ε 2.75). The ^1H NMR spectrum (15% in benzene) contained signals at 0.93 (9H in three $COOCH_2\underline{CH_3}$, triplet, $J(CH_3\text{–}CH_2) = 7$ Hz), 3.1 (2H in $>\underline{CH_2}$, part AB of an ABX system, $J(gem\text{-}HH) = 14$ Hz), 3.94 (2H in $COO\underline{CH_2}CH_3$, quartet, $J(CH_2\text{–}CH_3) = 7$ Hz), 3.99 (4H in two $COO\underline{CH_2}CH_3$, quartet, $J(CH_2\text{–}CH_3) = 7$ Hz), 3.9 (1H in $>\underline{CH}$, signal in region of quartets). The ^{19}F NMR spectrum (15% in CCl_4) contained three multiplet signals at −7.5 (2F), −20.8 (1F) and −24.6 ppm (1F).

1,3-Dicarboxy-4,5,6,7-tetrafluoroindane (nc) (IVa)

Compound (IV) (0.2 g), glacial acetic acid (0.8 ml), water (0.2 ml) and concentrated sulphuric acid (0.2 ml) were heated with stirring over a period of 27 h at 110°. The mixture was poured into ice water (4 ml), the solution filtered

and extracted with diethyl ether. The ethereal solution was dried with $MgSO_4$ and the ether distilled off. After distillation of the diethyl ether, the residue was treated with petroleum ether (boiling range 70–100°) when 0.11 g (74%) of compound (IVa) was obtained, the product being purified by sublimation at 200% 80 mmHg. The product was hygroscopic, m.p. 185–195° (in a sealed capillary). (Found: C, 47.9; H, 2.41; F, 27.5%. $C_{11}H_6F_4O_4$ requires C, 47.4; H, 2.16; F, 27.3%.) IR spectrum: $\nu_{max.}$ (KBr) 3300–2600 (broad band), 1735(s), 1645(m), 1520(s), 1415(s), 1335(m), 1295(m), 1235–1190(s), 1142(m), 1105(m), 987(s) and 960(m) cm^{-1}. The ^1H NMR spectrum (5% in CF_3COOH) contained two multiplet signals at 2.40 (2H in $>CH_2$) and 4.05 ppm (2H in two ) with a 1:1 intensity ratio. The ^{19}F NMR spectrum (5% in CF_3COOH) contained two multiplet signals at −9.4 and −23.6 ppm with a 1:1 intensity ratio.

(α-Heptafluoronaphthyl)methylmalonic ester (nc) (V)

Method A

To a suspension of sodium hydride (0.45 g) in anhydrous dimethylformamide (20 ml), freshly distilled malonic ester (2.56 g) was added with stirring. After evolution of hydrogen had ceased, the solution was heated to 60°, allowed to cool and then stirred over a period of 1.5 h at 20–25°. α-Chloromethylheptafluoronaphthalene (4.85 g) was added and the reaction mixture stirred for 3 h at 40–45°, allowed to cool, diluted with diethyl ether (50 ml) and neutralized with a 5% solution of HCl (30 ml). The ethereal layer was separated, washed with water (5 × 10 ml), dried with $MgSO_4$, filtered and a major portion of the diethyl ether distilled off. The residue was distilled *in vacuo* when 2.46 g (36%) of compound (V) was isolated, m.p. 54–55° (from petroleum ether, boiling range 40–60°). (Found: C, 50.7; H, 3.15; F, 31.5%. Mol. wt., 424. $C_{18}H_{13}F_7O_4$ requires C, 50.7; H, 3.05; F, 31.2%. Mol. wt., 426.) IR spectrum: $\nu_{max.}$ 2995(m), 2950(w), 2920(w), 1767–1750(s) (doublet), 1663(s), 1547(m), 1495(s), 1463(s), 1411(s), 1380(m), 1355(w), 1340(w), 1310(m), 1278(m), 1253(m), 1205(s), 1160(m), 1120(s), 1090(w), 1063(m), 1040(s), 930(s) and 867(w) cm^{-1}. The ^1H NMR spectrum (15% in CCl_4) contained signals at 1.18 (6H in two $COOCH_2\underline{CH_3}$, triplet, $J(CH_3–CH_2) = 7.0$ Hz), 3.6 (3H in $\geqslant CH$ and $>CH_2$, multiplet), 4.08 ppm (4H in two $COO\underline{CH_2}CH_3$, quartet, $J(CH_2–CH_3) = 7.0$ Hz). The ^{19}F NMR spectrum (15% in CCl_4) contained six multiplet signals at −6.01 ($1F_6$, $1F_7$), −7.5 ($1F_3$), −17.5 ($1F_5$, J(*peri*-FF) = 65 Hz), −18.4 ($1F_8$), −22.0 ($1F_4$, J(*peri*-FF) = 65 Hz) and −32.6 ppm ($1F_2$).

Method B

To a suspension of sodium hydride (0.012 g) in anhydrous dimethylformamide (0.47 g), compound (V) was added (0.21 g) in a stream of dry argon at 20–23°. After bubbles of hydrogen ceased to be evolved, the solution was kept for 5 h at

20–23° when the ^{19}F NMR spectrum was recorded. The spectrum contained eight multiplet signals at −5.9 (4F), −7.5 (1F), −16.9 (1F), −18.8 (1F), −20.6 (1F), −22.0 (2F), −26.7 (1F) and −33.4 ppm (2F). The position and intensity of the signals confirmed the presence in the solution of compound (VI) and anion (Va) in approximately equal quantities. The solution was then diluted with diethyl ether (4 ml), neutralized with a 5% solution of HCl (3 ml) and the extract separated, washed with water (3 × 10 ml), and dried with $MgSO_4$. After filtering, the solution was evaporated when 0.13 g of a product was isolated which, from its IR spectroscopy data, contained approximately equal quantities of compounds (V) and (VI). Analytical bands in the IR spectrum: 930 cm^{-1} for compound (V) and 670 and 968 cm^{-1} for compound (VI).

1,1-Dicarbethoxy-3,4,5,6,7,8-hexafluoroacenaphthene (nc) (VI)

To a suspension of sodium hydride (0.04 g) in anhydrous dimethylformamide (6 ml), (α-heptafluoronaphthyl)methylmalonic ester (V) was added (0.43 g) and the mixture stirred for 1 h at 20–25° and then, successively, for 1 h at 50° and 2 h at 100–110°. It was then allowed to cool, diluted with diethyl ether (15 ml) and neutralized with a 5% solution of HCl (10 ml). The ethereal layer was separated, washed with water (4 × 5 ml), dried with $MgSO_4$, filtered and a major portion of the diethyl ether distilled off. The residue (0.33 g), which was a dark brown viscous material, was purified by chromatographic techniques on a column (1.0 × 15 cm) packed with Al_2O_3, the product being eluted with a mixture of n-hexane:CCl_4 = 1:1 (by volume). After this procedure, 0.16 g (39.4%) of compound (VI) was isolated, m.p. 72–73.5° (from petroleum ether, boiling range 70–100°). (Found: C, 53.5; H, 3.16; F, 27.8%. Mol. wt., 408. $C_{18}H_{12}F_6O_4$ requires C, 53.2; H, 2.95; F, 28.1%. Mol. wt., 406.) IR spectrum: $\nu_{max.}$ 2995(m), 2950(w), 2920(w), 2885(w), 1753(s), 1656–1640(m) (doublet), 1530(w), 1505(w), 1465(s), 1427(m), 1400(m), 1378(m), 1350(w), 1320(m), 1310(m), 1280(s), 1256(s), 1218(s), 1192(s), 1120(m), 1085(m), 1062(m), 1035(w), 1020(w), 968(m), 875(m), 840(w), 670(m), 560(w) and 530 (broad) cm^{-1}. UV spectrum: $\lambda_{max.}$ (EtOH) 274 and 282 nm (log ε 3.658 and 3.730). The ^1H NMR spectrum (15% in CCl_4) contained signals at 1.26 (6H in two $COOCH_2\underline{CH_3}$, triplet, $J(CH_3\text{–}CH_2)$ = 7.0 Hz), 3,9 (2H in $>CH_2$, multiplet), 4.21 ppm (4H in two $COO\underline{CH_2}CH_3$, quartet, $J(CH_2\text{–}CH_3)$ = 7.0 Hz). The ^{19}F NMR spectrum (15% in CCl_4) contained six multiplet signals of equal intensity at −5.5, −6.6, −19.1, −22.4, −26.6 and −32.9 ppm.

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